2,3-DIHYDROIMIDAZO[1,2-A]PYRIDINES: A NEW CLASS OF ENANTIOSELECTIVE ACYL TRANSFER CATALYSTS AND THEIR USE IN KINETIC RESOLUTION OF ALCOHOLS

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SUPPORTING INFORMATION: Experimental procedures (11 pages), ¹H NMR and ¹³C NMR spectra (20 pages).

EXPERIMENTAL PART.

A) General. All reagents used for the preparation of the catalysts were obtained commercially and were used as received. Reactions involving higher than atmospheric pressures were carried out in 25 mL Cajon® Airfree® storage vessels available from Chemglass. The substrates used in the kinetic resolution experiments were either purchased or prepared (either by borohydride reduction of the corresponding ketones or by reacting aromatic aldehydes with Grignard reagents) and were purified as necessary. Chloroform (OmniSolv® grade, stabilized with nonpolar hydrocarbons) was used as received from EM Science. Deuterated chloroform was used as received from Cambridge Isotope Laboratories, Inc. Solvents used for chromatography were ACS or HPLC grade, as appropriate. Reactions were monitored by thin layer chromatography (TLC) using EM Science 60F silica gel plates. Flash column chromatography was performed over ICN Ecochrom silica gel (32-63 μm). Melting points were measured on a Mel-Temp II capillary melting point apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded on a Unity 300 MHz Varian spectrometer. The chemical shifts are reported as δ values (ppm) relative to TMS. High-Resolution mass spectral analyses were performed at Washington University MS Center on a Kratos MS-50TA spectrometer using the fast atom bombardment method (FAB). Methods used for kinetic resolution experiments, determination of ee's and calculation of conversions and selectivities were adopted from previously published work.^{3b,4a} HPLC analyses were performed using a Breeze LC system (Waters Corporation) using isopropanol-hexanes mobile phase at a flow rate of 1 mL/min and UV detection at 254 nm. Specific optical rotations were measured using a Perkin-Elmer 241 polarimeter. The absolute chirality of the esters and alcohols obtained by kinetic resolution was determined by the sign of the optical rotation of the unreacted alcohol.

B) Preparation of the catalysts

2, 3-Dihydroimidazo[1,2-a]pyridine hydrochloride

A combination of several existing procedures was adapted for the preparation of DHIP hydrochloride.^{6a-c} The following protocol was used only once and is unoptimized. A mixture of 2-bromopyridine (3.16 g, 20.0 mmol) and ethanolamine (4.88 g, 80.0 mmol) was heated at 160 °C under reflux in an oil bath for 15 hours. The reflux condenser was replaced with a distillation condenser and most of the unreacted ethanolamine was removed under reduced pressure (bath temperature 150 °C). The remaining oil (5.37 g) was triturated with CH₂Cl₂ and left to crystallize. The crystalline ethanolamine hydrobromide was filtered off and rinsed with CH₂Cl₂ on the filter. The filtrate was evaporated to give 3.34 g of yellow oil. The oil was diluted with 20 mL of chloroform, cooled to 0 °C and treated with thionyl chloride (3.0 mL, 41 mmol) added cautiously dropwise. The resulting solution was heated under reflux (bath temperature 75 °C) for 1 hour. The solvent was evaporated, and the residue was treated with 1 mL of MeOH. The resulting beige, crystalline mass was dissolved in 15 mL of water and 25 mL of benzene was added. The two-phase mixture was cooled in an ice bath and then basified with aqueous NaOH (2 g/5 mL H₂O) with vigorous magnetic stirring. The organic layer was separated and the aqueous layer was extracted twice with benzene (2x25 mL). The combined organic extract was washed with brine, dried over Na₂SO₄ and kept at room temperature for 1.5 hours. The light-yellow solution was decanted off the dark-brown oil that had precipitated and heated under reflux (bath temperature 85 °C). Light-beige crystals precipitated slowly. After two hours, the reaction was complete by TLC. The precipitate was filtered off and dried over Drierite® overnight to give 2.535 g of the crude product (81% yield) which was sufficiently pure for subsequent experiments.

¹H NMR (300 MHz, D₂O, HOD peak at δ 4.80 ppm used as reference) δ 7.97 (d; J = 6.6 Hz, 1H), 7.88 (ddd; J₁ = 8.8 Hz, J₂ = 7.4 Hz, J₃ = 1.4 Hz, 1H), 7.00 (d; J = 9.0 Hz, 1H), 6.89 (ddd; J₁ = 7.4 Hz, J₂ = 7.1 Hz, J₃ = 1.1 Hz, 1H), 4.70 (dd; J₁ = 10.1 Hz, J₂ = 9.6 Hz, 2H), 4.01 (dd; J₁ = 10.1 Hz, J₂ = 9.6 Hz, 2H); ¹³C NMR (75 MHz, D₂O, CH₃OH added and used as reference peak at δ 49.50 ppm) δ 145.1, 137.0, 114.3, 110.0, 51.6, 43.3 (quaternary carbon C7a not observed).

2, 3-Dihydroimidazo[1,2-a]pyridine base

The hydrochloride obtained as described above (156 mg, 1.00 mmol) was dissolved in 1 mL of water and treated with 2 mL of 33% aqueous NaOH. The dark-yellow oil that separated out

was extracted with CH₂Cl₂ several times until the aqueous phase became pale-yellow. The organic extract was dried over NaOH pellets and rotary evaporated leaving 121 mg of oil (quantitative yield), which was dissolved in CDCl₃, evaporated again to remove traces of CH₂Cl₂, dissolved in CDCl₃, filtered through a plug of cotton wool and diluted to 5.0 mL with CDCl₃ in a volumetric flask.

¹H NMR (300 MHz, CDCl₃) δ 6.94 (dd; $J_1 = 6.9$ Hz, $J_2 = 0.8$ Hz; 1H), 6.78 (ddd; $J_1 = 9.6$ Hz, $J_2 = 6.3$ Hz, $J_3 = 1.4$ Hz; 1H), 6.30 (dd; $J_1 = 9.6$ Hz, $J_2 = 0.8$ Hz; 1H), 5.59 (ddd; $J_1 = 6.6$ Hz, $J_2 = 6.3$ Hz, $J_3 = 1.1$ Hz; 1H), 3.88-4.03 (m, 4H); **¹³C NMR** (75 MHz, CDCl₃) δ 158.5, 136.3, 133.7, 114.8, 102.4, 52.0, 49.6.

(R)-N-(Pyridyl-2)-2-Hydroxy-1-phenylethylamine

A 25-mL medium-pressure tube charged with 2-bromopyridine (158 mg, 1.00 mmol), (R)-phenylglycinol (137 mg, 1.00 mmol), N, N-diisopropylethylamine (150 mg, 1.16 mmol) and a stir bar was flushed with nitrogen several times, stoppered and heated at 160 ± 5 °C for 2 days. The tube was allowed to cool to room temperature, the contents was diluted with a small amount of CH₂Cl₂ and chromatographed (hexanes-EtOAc 2:1 $\rightarrow$ 1:1 $\rightarrow$ neat EtOAc) to afford 137 mg of the product, which crystallized quickly (64% yield).

¹H NMR (300 MHz, CDCl₃) δ 8.02 (dd; $J_1 = 5.2$ Hz, $J_2 = 0.8$ Hz; 1H), 7.26-7.40 (m, 6H), 6.57 (ddd; $J_1 = 7.2$ Hz, $J_2 = 5.2$ Hz, $J_3 = 0.8$ Hz; 1H), 6.29 (d, $J = 8.5$ Hz; 1H), 5.51 (d, $J = 4.4$ Hz, 1H), 5.28 (s, br, 1H), 4.78 (ddd, $J_1 = J_2 = 4.0$ Hz, $J_3 = 8.0$ Hz, 1H), 3.95 (m, 1H), 3.86 (dd; $J_1 = 11.0$ Hz, $J_2 = 7.4$ Hz; 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 158.7, 147.6, 140.5, 138.1, 129.1, 127.9, 127.0, 113.7, 108.3, 68.0, 59.6; **MS**: HR-FAB calculated for C₁₃H₁₄N₂O₂ (M + H⁺) m/z: 215.1184, measured m/z: 215.1181, error = -1.5 ppm; **mp** 104-106 °C; $[\alpha]_D^{25} = -21^\circ$ (c = 1.05, MeOH).

(R)-2-Phenyl-2,3-dihydroimidazo[1,2-a]pyridine

A solution of **4a** (214 mg, 1.00 mmol) in 2 mL of CHCl₃ was treated with SOCl₂ (0.150 mL, 2.06 mmol) added dropwise at room temperature, then heated to reflux in an oil bath kept at 70 °C. After 1 hour, the flask was taken out of the bath, allowed to cool and treated cautiously with 2-3 drops of MeOH (vigorous gas evolution!), then heated again for 5-10 minutes. The solvent was removed under reduced pressure, and the semicrystalline, gummy residue was extracted with warm water. The aqueous extract was filtered from gummy particles through a cotton plug, basified with concentrated NaOH and extracted with benzene (ca. 25 mL). The benzene solution

was dried briefly over Na_2SO_4 and then heated under reflux in an oil bath at 80-85 °C. After 2 hours, the reaction mixture was cooled to room temperature and extracted with water 3 times. The aqueous extract was made strongly basic with concentrated NaOH and extracted with CH_2Cl_2 . The organic extract was dried over Na_2SO_4 and evaporated to give bright-yellow, crystalline product (121 mg, 62% yield). Recrystallization from boiling hexanes gave thin plates. **^1H NMR** (300 MHz, CDCl_3) δ 7.24-7.35 (m, 5H), 6.90-6.93 (m, 1H), 6.82-6.88 (m, 1H), 6.42 (ddd, $J_1 = 9.34$ Hz, $J_2 = 1.38$ Hz, $J_3 = 0.28$ Hz, 1H), 5.66 (m, 1H), 5.23 (m, 1H), 4.36 (m, 1H), 3.84 (m, 1H); **^{13}C NMR** (75 MHz, CDCl_3) δ 158.4, 145.0, 137.0, 133.8, 128.8, 127.3, 126.8, 115.0, 103.2, 67.3, 57.6; **MS**: HR-FAB calculated for $\text{C}_{13}\text{H}_{13}\text{N}_2$ ($\text{M} + \text{H}^+$) m/z : 197.1079, measured m/z : 197.1070, error = -4.4 ppm; **mp** 101-103 °C; $[\alpha]_{\text{D}}^{25} = +412^\circ$ ($c = 1.03$, MeOH).

(R)-N-(5-Bromopyridyl-2)-2-Hydroxy-1-phenylethylamine

To a solution of **4a** (214 mg, 1.00 mmol) in 5 mL of MeCN was added, in several portions, NBS (178 mg, 1.00 mmol). The mixture was stirred at room temperature, then concentrated and chromatographed (hexanes-EtOAc 3:1 $\rightarrow$ 2:1) to afford 273 mg of white solid (93% yield).

^1H NMR (300 MHz, CDCl_3) δ 8.07 (d, 2.47 Hz, 1H), 7.41 (dd, $J_1 = 8.79$ Hz, $J_2 = 2.47$ Hz; 1H), 7.26-7.37 (m, 5H), 6.24 (d, $J = 9.07$ Hz, 1H), 5.36 (d, $J = 5.49$ Hz, 1H), 4.79 (m, 2H), 3.92 (m, 2H), 3.02 (s, br, 1H); **^{13}C NMR** (75 MHz, CDCl_3) δ 157.1, 148.5, 140.3, 139.9, 129.2, 128.2, 127.0, 109.7, 108.0, 67.8, 59.2; **MS**: HR-FAB calculated for $\text{C}_{13}\text{H}_{13}\text{BrN}_2\text{O}$ ($\text{M} + \text{H}^+$) m/z : 293.0281, measured m/z : 293.0275, error = -4.9 ppm; **mp** 100-102 °C; $[\alpha]_{\text{D}}^{25} = -73^\circ$ ($c = 1.07$, MeOH).

(R)-5-Bromo-2-phenyl-2,3-dihydroimidazo[1,2-a]pyridine

A procedure analogous to the cyclization of **4a** was carried out on 0.5 mmol scale (147 mg of **4b**, 0.075 mL SOCl_2 , 1 mL CHCl_3) and produced 126 mg (91% yield) of yellow oil which crystallized quickly.

^1H NMR (300 MHz, CDCl_3) δ 7.26-7.37 (m, 5H), 7.07 (d, $J = 1.37$ Hz, 1H), 6.86 (dd, $J_1 = 9.89$ Hz, $J_2 = 2.20$ Hz, 1H), 6.37 (dd, $J_1 = 11.70$ Hz, $J_2 = 0.55$ Hz, 1H), 5.25 (dd, $J = 11.54$ Hz, 1H), 4.35 (t, $J = 10.98$, 1H), 3.86 (dd, $J_1 = 9.07$ Hz, $J_2 = 10.80$ Hz, 1H); **^{13}C NMR** (75 MHz, CDCl_3) δ 156.5, 144.3, 140.0, 133.7, 129.0, 127.6, 126.8, 116.3, 94.3, 67.7, 57.8; **MS**: HR-FAB calculated for $\text{C}_{13}\text{H}_{12}\text{BrN}_2$ ($\text{M} + \text{H}^+$) m/z : 275.0184, measured m/z : 275.0172, error = -4.3 ppm; **mp** 86-87.5 °C; $[\alpha]_{\text{D}}^{25} = +353^\circ$ ($c = 1.03$, MeOH).

(R)-N-(5-Nitropyridyl-2)-2-Hydroxy-1-phenylethylamine

A solution of 2-chloro-5-nitropyridine (316 mg, 2.00 mmol), (R)-phenylglycinol (274 mg, 2.00 mmol) and NEt₃ (0.280 mL, 2.00 mmol) in 3.5 mL of absolute EtOH was refluxed under nitrogen for 2 days. EtOH was removed on a rotary evaporator and the residue was chromatographed (hexanes-EtOAc 3:1 → 1:1) to afford 480 mg of the product as orange, viscous oil, which crystallized after long standing (92% yield).

¹H NMR (300 MHz, CDCl₃) δ 8.96 (d, J = 2.7 Hz, 1H), 8.12 (dd, J_1 = 9.1 Hz, J_2 = 2.7 Hz, 1H), 7.26-7.41 (m, 5H), 6.31 (d, J = 9.1 Hz, 2H), 5.00 (s, br, 1H), 4.04 (dd, J_1 = 11.3 Hz, J_2 = 3.8 Hz, 1H), 3.95 (dd, J_1 = 11.3 Hz, J_2 = 5.8 Hz, 1H), 2.38 (s, br, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 160.2, 145.9 (q, J = 4.5 Hz), 139.5, 134.9 (q, J = 1.5 Hz), 129.3, 128.3, 126.9, 124.6 (q, J = 270 Hz), 116.4 (q, J = 33.2 Hz), 107.4, 67.5, 58.8; **MS**: HR-FAB calculated for C₁₃H₁₃BrN₂O (M + H⁺) m/z : 260.1035, measured m/z : 260.1057, error = -4.4 ppm; **mp** 109-110 °C; $[\alpha]_D^{25}$ = -165° (c = 0.96, MeOH).

(R)-5-Nitro-2-phenyl-2,3-dihydroimidazo[1,2-a]pyridine

A solution of 4c (347 mg, 1.34 mmol) in 7 mL of CHCl₃ was treated with SOCl₂ (0.250 mL, 3.43 mmol) added dropwise at room temperature, then heated to reflux in an oil bath kept at 65 °C. After 1.5 hours, the flask was taken out of the bath, allowed to cool somewhat and treated cautiously with 2-3 drops of MeOH (vigorous gas evolution!), then heated again for 5 minutes. The mixture was rotary evaporated and the evaporation residue was extracted with water. The aqueous extract was decanted from the gummy residue, brought to pH 7-8 with aqueous NaHCO₃ and extracted with CH₂Cl₂ 3 times. More aqueous NaHCO₃ / NaOH was added to the aqueous phase to pH 12 and extraction was continued until organic extracts were pale-yellow (4 times). The organic phase was dried over NaOH pellets and then rotary evaporated. The crude mixture was chromatographed (20% *i*-PrOH + 2% NEt₃ in hexanes) to give 318 mg of light-orange, non-crystalline mass (98%).

¹H NMR (300 MHz, CDCl₃) δ 8.38 (d, J = 2.20 Hz, 1H), 7.59 (dd, J_1 = 10.44 Hz, J_2 = 7.97 Hz, 1H), 7.26-7.38 (m, 5H), 6.38 (d, J = 10.44 Hz, 1H), 5.37 (dd, J_1 = 10.71 Hz, J_2 = 8.24 Hz, 1H), 4.46 (t, J = 11.54, 1H), 3.94 (dd, J_1 = 11.82 Hz, J_2 = 8.24 Hz, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 155.2, 142.5, 137.8, 130.9, 129.5, 129.1, 128.1, 126.7, 113.4, 68.8 57.1; **MS**: HR-FAB calculated for C₁₃H₁₂N₃O₂ (M + H⁺) m/z : 242.0930, measured m/z : 242.0930, error = 0.2 ppm; $[\alpha]_D^{25}$ = +173° (c = 0.94, MeOH).

(R)-N-(5-Trifluoromethylpyridyl-2)-2-Hydroxy-1-phenylethylamine

A 25 mL medium-pressure tube charged with 2-chloro-5-trifluoromethylpyridine (1.502 g, 8.270 mmol), (R)-phenylglycinol (1.102 g, 8.030 mmol), N, N-diisopropylethylamine (1.200 g, 9.300 mmol) and a stir bar was flushed with nitrogen several times, stoppered and heated at $105 \pm 5^\circ\text{C}$ for 2 days. The tube was allowed to cool to room temperature, the contents was diluted with a small amount of CH_2Cl_2 and chromatographed (isopropanol-hexanes 5% $\rightarrow$ 10%) to afford 1.503 g of the product, which crystallized quickly (66% yield).

^1H NMR (300 MHz, CDCl_3) δ 8.28 (s, 1H), 7.52 (dd, $J_1 = 8.79$ Hz, $J_2 = 2.20$ Hz, 1H), 7.26-7.37 (m, 5H), 6.33 (d, $J = 8.79$ Hz, 1H), 5.80 (d, $J = 5.50$ Hz, 1H), 4.89 (dd, $J_1 = 9.89$ Hz, $J_2 = 6.05$ Hz, 1H), 3.99 (dd, $J_1 = 11.26$ Hz, $J_2 = 3.84$ Hz, 1H), 3.91 (dd, $J_1 = 10.99$ Hz, $J_2 = 6.60$ Hz, 1H), 3.28 (s, br, 1H); **^{13}C NMR** (75 MHz, CDCl_3) δ 161.0, 146.9, 138.7, 136.5, 133.4, 129.4, 128.5, 126.8, 106.7, 66.9, 58.3; **MS**: HR-FAB calculated for $\text{C}_{13}\text{H}_{13}\text{BrN}_2\text{O}$ ($\text{M} + \text{H}^+$) m/z : 283.1058, measured m/z : 283.1069, error = 3.8 ppm; **mp** $105\text{--}105.5^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} = -57^\circ$ ($c = 1.09$, MeOH).

(R)-5-Trifluoromethyl-2-phenyl-2, 3-dihydroimidazo[1,2-a]pyridine

A procedure analogous to the cyclization of **4c** was carried out on 5.24 mmol scale (1.499 g of **4d**, 1.05 mL SOCl_2 , 30 mL CHCl_3) and produced after chromatography (isopropanol-hexanes 5% $\rightarrow$ 10%) 1.176 g (85% yield) of yellow oil which crystallized quickly.

Recrystallization from hexanes produced yellow needles (78% recovery). **Note**: for the sake of consistency, all the data for kinetic resolution experiments shown in the table were obtained using the recrystallized material. However, the difference between it and the unrecrystallized product becomes appreciable only at selectivity levels of 25:1 and above.

^1H NMR (300 MHz, CDCl_3) δ 7.26-7.38 (m, 6H) 6.93 (dd, $J_1 = 10.01$ Hz, $J_2 = 2.20$ Hz, 1H) 6.46 (d, $J = 9.77$, 1H) 5.29 (dd, $J_1 = 11.48$ Hz, $J_2 = 8.79$ Hz, 1H), 4.36 (t, $J = 11.23$ Hz, 1H), 3.86 (t, $J = 9.74$ Hz, 1H); **^{13}C NMR** (75 MHz, CDCl_3) δ 156.7, 143.8, 133.8 (q, $J = 5.54$ Hz), 132.5 (q, $J = 2.51$ Hz), 129.0, 127.8, 126.8, 124.0 (q, $J = 268$ Hz), 115.6, 106.9 (q, $J = 34.8$ Hz), 67.9, 57.2; **MS**: HR-FAB calculated for $\text{C}_{14}\text{H}_{12}\text{F}_3\text{LiN}_2$ ($\text{M} + \text{Li}^+$) m/z : 271.1034, measured m/z : 271.1029, error = -1.9 ppm; **mp** $128\text{--}129^\circ\text{C}$ (from hexanes); $[\alpha]_{\text{D}}^{25} = +277^\circ$ ($c = 0.99$, MeOH).

C) Kinetic resolution experiments.

All kinetic resolution experiments were carried out according to Procedures A, B, C, and D described below. Selectivities and conversions were determined as described in Procedure E.

Procedure A. Variation of substituent X in DHIP catalysts.

To a solution of 0.25 mmol of phenylethylcarbinol (34 μ L, 34 mg) and 0.050 mmol of the catalyst (**1a-d**) in 0.250 mL CDCl_3 was added 0.25 mmol of acetic anhydride (24 μ L, 26 mg). The mixture was swirled, left at room temperature for 1 hour, quenched by rapid addition of 0.25 mL of methanol, and left for one more hour. The reaction mixture was diluted with CH_2Cl_2 , washed twice with 1 M HCl, then twice with saturated aqueous NaHCO_3 , and dried over Na_2SO_4 . The solution was concentrated on a rotary evaporator at room temperature and chromatographed (5 – 20% Et_2O in hexanes) to separate the ester from the unreacted alcohol.

Table 1.

Entry	X	t(h)	#	ee _E %	ee _A %	C _{HPLC} %	s	C _{AVG} %	s _{AVG}
1	H	1.0	1	49.0	12.8	20.7	3.3	21	3.3
			2	49.5	13.4	21.1	3.36		
2	Br	1.0	1	74.4	25.2	25.3	8.7	25	8.6
			2	74.0	24.4	24.8	8.5		
3	NO_2	1.0	1	81.7	13.4	14.1	11.3	14	11
			2	81.5	12.0	12.9	11.1		
4	CF_3	1.0	1	79.5	51.9	39.5	14.6	38	14
			2	79.4	46.3	36.8	13.7		

Procedure B. Variation of the substrate and the acylating agent.

1) The stock solution of the catalyst was prepared by dissolving 0.100 mmol of **1d** (26.4 mg) and 3.75 mmol of *N,N*-diisopropylethylamine (654 μ L, 485 mg) in CHCl_3 in a 5 mL volumetric flask and bringing the volume to the mark.

2) A one-dram vial was charged with 0.5 mmol of the racemic secondary alcohol and 0.500 mL of the stock solution of **1d**, and cooled in an ice bath. After 15 minutes, 0.375 mmol of the anhydride was added. The mixture was swirled and left in the ice bath for a specified period of time, at the end of which it was quenched by rapid addition of 0.5 mL of methanol, allowed to warm slowly and left for one more hour at room temperature. The workup and chromatography were carried out as described in Procedure A.

Table 2.

Entry	R ¹	R ²	R'	t(h)	#	ee _E %	ee _A %	C _{HPLC} %	s	C _{AVG} %	s _{AVG}
1	Phenyl	Me	Me	8	1	72.9	20.0	21.5	7.75	21	7.7
					2	73.0	18.9	20.6	7.70		
2	“	Et	Me	8	1	80.7	60.6	42.9	17.2	43	17
					2	81.0	59.6	42.4	17.4		
3	“	<i>i</i> -Pr	Me	30	1	82.4	79.2	49.0	24.8	47	24
					2	82.9	70.3	45.9	22.4		
4	“	Me	Et	8	1	89.3	42.7	32.3	26.8	32	26
					2	89.2	40.3	31.1	26.0		
5	“	Et	Et	8	1	90.4	60.8	40.2	36.8	39	36
					2	90.6	57.2	38.7	36.0		
6	“	<i>i</i> -Pr	Et	30	1	80.9	97.6	54.7	41.1	55	41
					2	78.7	98.9	55.7	41.8		
7	“	<i>t</i> -Bu	Et	52	1	93.5	88.2	48.6	87.1	48	85
					2	93.8	83.6	47.1	82.5		
8	1-Naphthyl	Me	Et	8	1	90.1	89.1	49.7	57.8	51	56
					2	87.8	94.0	51.7	54.4		
9	<i>m</i> -MeC ₆ H ₄	Me	Et	8	1	88.1	51.7	37.0	26.3	36	27
					2	88.7	48.8	35.5	27.1		
10	<i>m</i> -MeOC ₆ H ₄	Me	Et	8	1	89.8	57.8	39.2	33.2	40	34
					2	89.4	63.2	41.4	34.2		
11	<i>m</i> -BrC ₆ H ₄	Me	Et	8	1	88.1	69.1	44.0	32.6	44	32
					2	87.8	69.7	44.2	32.0		
12	<i>o</i> -MeC ₆ H ₄	Me	Et	8	1	86.4	66.3	43.4	27.3	44	26
					2	85.5	66.0	43.6	25.3		
13	2,4,6-Me ₃ C ₆ H ₂	Me	Et	30	1	76.2	85.1	52.8	19.8	53	20
					2	76.0	88.1	53.7	21.0		
14	Cyclohexyl	Me	Et	50	n/a	nd ^a	nd ^a	nd ^a	nd ^a	<4 ^b	nd ^a
15	1-Indanol		Et	50	n/a	□0	□0	nd ^a	□1	16 ^b	□1

^a) Not determined ^b) Determined by ¹H NMR

Procedure C. Variation of the solvent.

1) The stock solution of the catalyst was prepared by dissolving 0.040 mmol of **1d** (10.6 mg) and 1.5 mmol of N,N-diisopropylethylamine (262 μ L, 194 mg) in the reaction solvent in a 2 mL volumetric test tube and bringing the volume to the mark.

2) A one-dram vial was charged with 0.5 mmol of (±)-phenylethylcarbinol and 0.500 mL of the stock solution of **1d**, and cooled in an ice bath. After 15 minutes, 0.375 mmol of propionic anhydride was added. The mixture was swirled and left in the ice bath for 8 hours, at the end of which it was quenched by rapid addition of 0.5 mL of methanol, allowed to warm slowly and left for one more hour at room temperature. The workup and chromatography were carried out as described in Procedure A.

Table 3.

Entry	Solvent	#	ee _E %	ee _A %	C _{HPLC} %	s	C _{AVG} %	s _{AVG}
1	Diethyl ether	1	93.5	35.8	27.7	42.0	27	40
		2	92.9	34.6	27.1	38.3		
2	Toluene	1	92.8	36.7	28.3	38.3	30	36
		2	91.6	41.7	31.3	34.5		
3	Dichloromethane	1	88.4	40.3	31.3	24.2	30	24
		2	89.2	34.7	28.0	24.5		
4	t-Amyl alcohol	1	90.4	21.4	19.2	24.3	18	23
		2	89.9	18.7	17.2	22.5		
5	Acetonitrile	1	81.5	19.5	19.3	11.8	20	11
		2	79.3	19.6	19.8	10.5		

Procedure D. Preparative scale resolution of (±)-1-(1-naphthyl)-1-ethanol.

The same proportions were used as in Procedure B described above. A solution of the substrate (2.416 g, 14.0 mmol), DIPEA (1.93 mL, 10.5 mmol) and CF₃-PIP **2d** (74 mg, 0.28 mmol) in 14 mL of chloroform was stirred magnetically in an ice bath for 15 minutes, then

treated with propionic anhydride (1.35 mL, 10.5 mmol). The mixture was stirred at 0 °C for 10 hours, at which time it was quenched with methanol (10 mL), allowed to warm slowly and left for one more hour at room temperature. The reaction mixture was diluted with CH₂Cl₂, washed twice with 1 M HCl, then twice with saturated aqueous NaHCO₃, and dried over Na₂SO₄. The solution was concentrated on a rotary evaporator at room temperature and chromatographed (5 – 20% Et₂O in hexanes). The ester was eluted first (1.672 g, 7.32 mmol, 52% yield), followed by the unreacted alcohol (1.091 g, 6.33 mmol, 45% yield). The enantiomeric excess of the ester was determined by HPLC (*vide infra*) to be 82.5%, and that of the alcohol, 98.8%. Based on these ee values, the conversion was calculated to be 54.5% (*cf.* 53.6% conversion based on the isolated materials), and the selectivity factor, 52.3. The aqueous phase obtained during the workup was basified with 0.5 M NaOH and extracted with CH₂Cl₂ several times until the aqueous phase was pale-yellow. The extract was dried over Na₂SO₄, evaporated, and chromatographed to give 50 mg of pure CF₃-PIP (68% recovery).

Procedure E. Determination of Enantiomeric Excesses, Conversions and Selectivities.

All the alcohols recovered from kinetic resolutions were found to be enriched in the S-enantiomer according to the negative sign of optical rotation. Accordingly, the esters were concluded to be enriched in the R-enantiomer.

The enantiomeric excesses of the alcohols were determined by HPLC using a CHIRALCEL OD-H analytical column (4.6x250 mm, Chiral Technologies, Inc.) and 3% isopropanol in hexanes as mobile phase, except for 1-(1-naphthyl)-1-ethanol, which required 10% isopropanol in hexanes.

The enantiomeric excesses of the esters were determined, in most cases, by hydrolysis to the parent alcohols (2 mL of 2 M KOH in methanol, at room temperature until complete by TLC), which were analyzed as described above. 1-(1-naphthyl)-1-ethyl propionate was analyzed directly on CHIRALCEL OD-H analytical column using 3% isopropanol in hexanes.

The enantioselectivity was calculated according to the equation:

$$s = \ln((1-C_{\text{HPLC}})(1-ee_A)) / \ln((1-C_{\text{HPLC}})(1+ee_A)),$$

The conversion C_{HPLC} used in the above equation was calculated as $C_{\text{HPLC}} = ee_A / (ee_E + ee_A)$, where ee_E is the enantiomeric excess of the ester and ee_A is the enantiomeric excess of the unreacted alcohol. The conversion values thus obtained were generally within 1-2% of the values obtained by NMR integration of crude reaction mixtures.

D) NMR study of DHIP.

The following 0.2 M stock solutions in CDCl_3 were prepared: DHIP free base (see Section B), acetic acid, acetic anhydride, and methanol. Using aliquots of these stock solutions, the following mixtures were prepared and their ^1H NMR spectra recorded (Figure S1).

- a) 0.1 mL 0.2 M DHIP + 0.5 mL CDCl_3 (0.033 M DHIP base) – bright-yellow solution;
- b) 0.1 mL 0.2 M DHIP + 0.15 mL 0.2 M AcOH + 0.35 mL CDCl_3 (0.033 M H-DHIP $^+$ AcO $^-$) – the solution of DHIP faded somewhat upon addition of AcOH;
- c) 0.1 mL 0.2 M DHIP + 0.2 mL 0.2 M Ac_2O + 0.3 mL CDCl_3 (0.033 M Ac-DHIP $^+$ AcO $^-$ and 0.033 M unreacted Ac_2O) – the solution faded almost completely upon addition of 2 equivalents of Ac_2O ; Only the acylated form of DHIP was observed by NMR.
- d) 0.1 mL 0.2 M DHIP + 0.2 mL 0.2 M Ac_2O + 0.3 mL 0.2 M MeOH ($[\text{Ac}_2\text{O}]_0 = 0.066$ M; $[\text{MeOH}]_0 = 0.1$ M; $[\text{DHIP}]_0 = 0.033$ M). After 40 minutes at room temperature, no Ac_2O remained unreacted and comparable amounts of Ac-DHIP $^+$ AcO $^-$ and AcOMe were observed. After 7 hours, the acyl transfer was essentially complete.
- e) 0.1 mL CDCl_3 + 0.2 mL 0.2 M Ac_2O + 0.3 mL 0.2 M MeOH ($[\text{Ac}_2\text{O}]_0 = 0.066$ M; $[\text{MeOH}]_0 = 0.1$ M) – No reaction between Ac_2O and MeOH was observed in the absence of DHIP after 50 minutes.

Figure S1.

INDEX	FREQUENCY PPM	HEIGHT
1	2394.610	7.979
2	2388.017	7.957
3	2372.633	7.906
4	2371.260	7.901
5	2365.491	7.882
6	2363.843	7.876
7	2362.469	7.872
8	2356.426	7.852
9	2355.052	7.847
10	2106.447	7.019
11	2097.381	6.989
12	2076.229	6.918
13	2075.131	6.914
14	2068.812	6.893
15	2062.769	6.873
16	2061.670	6.870
17	1445.238	4.816
18	1440.568	4.800
19	1420.240	4.732
20	1410.625	4.700
21	1400.461	4.666
22	1210.367	4.033
23	1203.500	4.010
24	1201.577	4.004
25	1200.203	3.999
26	1190.589	3.967

H₂O (4.80 ppm)

INDEX	FREQUENCY	PPM	HEIGHT
1	10947.040	145.062	35.0
2	10336.966	136.977	21.5
3	8623.260	114.269	33.7
4	8302.906	110.024	33.8
5	3895.826	51.624	39.6
6	3736.079	49.508	11.1
7	3271.151	43.347	45.8

INDEX	FREQUENCY	PPM	HEIGHT
1	10288.284	136.333	56.4
2	10091.892	133.730	38.1
3	8661.609	114.777	44.9
4	7725.741	102.376	58.4
5	5842.841	77.425	45.6
6	5810.777	77.000	47.0
7	5778.999	76.579	46.4
8	3927.018	52.038	62.9
9	3745.799	49.636	53.8

¹³C OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl₃

Ambient temperature

UNITYplus-300 "baloo"

PULSE SEQUENCE

Pulse 50.0 degrees

Acq. time 1.815 sec

Width 16501.7 Hz

2832 repetitions

OBSERVE C13, 75.4208588 MHz

DECOUPLE H1, 299.9450942 MHz

Power 38 dB

continuously on

GARP-1 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 2 hr, 1 min, 43 sec

STANDARD 1H OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3

Ambient temperature

Mercury-300 "m300"

PULSE SEQUENCE

Relax. delay 1.000 sec

Pulse 39.6 degrees

Acq. time 1.998 sec

Width 4500.5 Hz

16 repetitions

OBSERVE H1, 300.1176004 MHz

DATA PROCESSING

FT size 32768

Total time 0 min, 0 sec

13C OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3

Ambient temperature

Mercury-300 "m300"

PULSE SEQUENCE

Pulse 43.3 degrees

Acq. time 1.815 sec

Width 18761.7 Hz

688 repetitions

OBSERVE C13, 75.4646127 MHz

DECOUPLE H1, 300.1190554 MHz

Power 43 dB

continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 131072

Total time 36 min, 0 sec

STANDARD 1H OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3

Ambient temperature

Mercury-300 "m300"

PULSE SEQUENCE

Relax. delay 1.000 sec

Pulse 39.6 degrees

Acq. time 1.998 sec

Width 4500.5 Hz

16 repetitions

OBSERVE H1, 300.1176007 MHz

DATA PROCESSING

FT size 32768

Total time 0 min, 49 sec

INDEX	FREQUENCY	PPM	HEIGHT
1	2514.662	8.379	55.7
2	2288.308	7.625	33.1
3	2277.869	7.590	32.1
4	2208.369	7.358	59.3
5	2201.502	7.335	64.4
6	2187.217	7.288	111.4
7	2180.350	7.265	54.7
8	1925.700	6.416	38.9
9	1915.262	6.382	34.4
10	1618.308	5.392	30.8
11	1352.946	4.508	20.8
12	1341.683	4.471	37.9
13	1330.420	4.433	20.9
14	1197.464	3.990	24.7
15	1189.223	3.963	31.5
16	1185.927	3.952	23.0

STANDARD 1H OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3

Ambient temperature

UNITYplus-300 "balco"

PULSE SEQUENCE

Pulse 51.4 degrees

Acq. time 3.744 sec

Width 4000.0 Hz

16 repetitions

OBSERVE H1, 299.9436023 MHz

DATA PROCESSING

FT size 32768

Total time 1 min, 0 sec