Nanomole-scale assignment and one-use kits for determining the absolute configuration of secondary alcohols

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SUPPORTING INFORMATION

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I. Kinetic Resolution of 3 via salt 2

Salt 2b ¹H and ¹³C Spectral Data
$^1$H NMR spectra were collected for the reaction mixtures in Table 1 as well as for both the $R$-HBTM and $S$-HBTM reactions in Figure 6, Table 5, Table 6, Table 7, and Figure 9. The percent conversion for a reaction was measured according to the integrals of a peak corresponding to the
starting material and to the product after phase correction and baseline correction of the $^1$H NMR spectrum (Formula 1).

Formula 1.

$$\text{Percent Conversion} = \frac{\text{^1H NMR integral}_{\text{ESTER}}}{\text{^1H NMR integral}_{\text{ESTER}} + \text{^1H NMR integral}_{\text{ALCOHOL}}} \times 100$$

$^1$H NMR Spectrum and Chiral HPLC Trace for Equation 1
Data File C:\HPChem\DATA\ALEX\M-283-0H2-D
Sample Name: SMM-283-OH2-NO3
Chiralcel OD with OD guard 5% iPrOH/n-Hexane 1.0 mL/min
23 bar 254 NM UV

Injection Date : 10/23/2013 11:51:42 AM
Sample Name : SMM-283-OH2-NO3 Location : Vial 51
Acq. Operator : SHAWN Inj Volume : 20 µl
Acq. Method : C:\HPChem\DATA\METHODS\ALEX.M
Last changed : 10/7/2013 3:56:21 PM by Alex
Analysis Method : C:\HPChem\DATA\METHODS\ALEXB.M
Last changed : 12/16/2015 6:21:14 PM by ALEXB

ADC1 A, ADC1 CHANNEL A (ALEX-283-OH2-D)

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 10.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: ADC1 A, ADC1 CHANNEL A

Signal 2: VWD1 A, Wavelength=254 nm

Peak RetTime Type Width Area Height Area
# [min] [min] mAU ² [mAU ] %
---|---|---|---|---|---
1 11.471 FB 0.5349 2234.44751 63.18405 18.2971
2 14.061 BV 0.6685 9977.60840 224.47878 81.7029

Totals : 1.22121e4 287.66283

Results obtained with enhanced integrator!

*** End of Report ***

1100 LC 1/19/2016 9:29:44 AM ALEXB
$^1$H NMR Spectra and Chiral HPLC Traces for Table 1

**Entry 1**

![Chemical Structures](image-url)
Data File C:\HPCHEM\DATA\ALEX\SM-289AA.D

Chiralcel OD with OD guard 5m iPrOH/n-Hexane 1.0 mL/min
23 bar 254 NM UV

Injection Date : 11/11/2013 5:17:11 PM
Sample Name : SMM-289-A-ALC
Location : Vial 32
Acq. Operator : SHAWN
Inj Volume : 20 µl

Acq. Method : C:\HPCHEM1\METHODS\ALEX.M
Last changed : 11/11/2013 4:53:38 PM by SHAWN
(modified after loading)
Analysis Method : C:\HPCHEM1\METHODS\ALEXE.M
Last changed : 12/16/2015 6:21:14 PM by ALEXB

Area Percent Report

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Dilution : 1.0000
Sample Amount : 10.000000 [ng/µl] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: ADC1 A, ADC1 CHANNEL A

Signal 2: VWD1 A, Wavelength=254 nm

Peak RetTime Type Width Area Height Area
--- --- ---- ------- ------ ------- ------- -------
1 10.417 VB 0.5332 2591.86916 76.29269 28.8143
2 12.543 PB 0.6197 6403.20410 161.55348 71.1857

Totals : 8995.07227 237.84818

Results obtained with enhanced integrator!

*** End of Report ***
Entry 2

\[
2a + R\text{-HBTM}
\]
Data File C:\HPChem\DATA\ALEX\SM-289BA.D  
Sample Name: SMM-289-B-ALC

Chiralcel OD with OD guard 50 iPrOH/n-Hexane 1.0 mL/min
23 bar 254 NM UV

Injection Date: 11/11/2013 5:49:07 PM
Sample Name: SMM-289-B-ALC  Location: Vial 62
Acq. Operator: SHAWN  Inj Volume: 20 µl

Acq. Method: C:\HPChem\METHODS\ALEX.M
Last changed: 11/11/2013 4:53:38 PM by SHAWN
(modified after loading)

Analysis Method: C:\HPChem\METHODS\ALEXB.M
Last changed: 12/15/2015 6:21:14 PM by ALEXB

ADC1 A, ADC1 CHANNEL A (ALEXSM-289BA.D)

Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Sample Amount: 10.0000 [ng/µl] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: ADC1 A, ADC1 CHANNEL A

Signal 2: VWD1 A, Wavelength=254 nm

Peak RetTime  Type  Width  Area  Height  Area
# [min]  [min]  [mAU]  [s]  [mAU]  [%]
---|------|------|------|------|------|
1 10.324 VV 0.5396 5358.06152 155.79208 46.9017
2 12.458 VB 0.6280 6085.95459 151.26903 53.0983

Totals: 1.14240e4 307.06111

Results obtained with enhanced integrator!

*** End of Report ***
**Experimental Data for Kinetic Resolution of 3 with other Salts**

**BF₄ counterion.** 1-phenylethanol (25.8 mg, 0.211 mmol) was added to a 20 mL scintillation vial with a stirbar. CDCl₃ (600. µL) and N,N-diisopropylethylamine (36.4 µL, 0.209 mmol) were added and the reaction mixture was stirred at 0 °C (ice bath). BF₄ salt (52.0 mg, 0.127 mmol) was added and the reaction was stirred for 1 h at 0 °C. The reaction was halted with the addition of methanol (85.9 µL). ¹H NMR spectral data of the crude reaction mixture revealed a reaction conversion to ester of 42.6%. The unreacted alcohol was recovered by column chromatography (9:1 hexanes/ethyl acetate) and analyzed by chiral HPLC (Chiralcel OD with OD guard, 10% i-PrOH in n-hexane, 25 bar, 1.0 mL/min, UV detection at 254 nm, tᵣ = 6.90 min, tₛ = 8.01 min) 61.4% e.e.

**PF₆ counterion.** 1-phenylethanol (19.3 mg, 0.158 mmol) was added to a 20 mL scintillation vial with a stirbar. CD₃CN (600. µL) and N,N-diisopropylethylamine (27.5 µL, 0.158 mmol) were added and the reaction mixture was stirred at 25 °C. PF₆ salt (50.8 mg, 0.108 mmol) was added and the reaction was stirred for 14 h. The reaction was halted with the addition of methanol (63.9 µL). ¹H NMR spectral data of the crude reaction mixture revealed a reaction conversion to ester of 26.0%. The unreacted alcohol was recovered by column chromatography (9:1 hexanes/ethyl acetate) and analyzed by chiral HPLC (Chiralcel OD with OD guard, 5% i-PrOH in n-hexane, 23 bar, 1.0 mL/min, UV detection at 254 nm, tᵣ = 10.36 min, tₛ = 12.40 min) 15.2% e.e.

**SbF₆ counterion.** 1-phenylethanol (26.2 mg, 0.214 mmol) was added to a 20 mL scintillation vial with a stirbar. CDCl₃ (600. µL) and N,N-diisopropylethylamine (37.5 µL, 0.215 mmol) were
added and the reaction mixture was stirred at 25 °C. Salt 2b (60.4 mg, 0.108 mmol) was added and the reaction was stirred for 14 h. The reaction was halted with the addition of methanol (87.0 µL). 1H NMR spectral data of the crude reaction mixture revealed a reaction conversion to ester of 30.8%. The unreacted alcohol was recovered by column chromatography (9:1 hexanes/ethyl acetate) and analyzed by chiral HPLC (Chiralcel OD with OD guard, 5% i-PrOH in n-hexane, 23 bar, 1.0 mL/min, UV detection at 254 nm, tR = 10.34 min, tS = 12.61 min) 28.8% e.e.

**BF₄ Salt**
PF₆ Salt
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 10.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with TSTDs

Signal 1: ADC1 A, ADC1 CHANNEL A

Signal 2: VW1 A, Wavelength=254 nm

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<thead>
<tr>
<th>Peak RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
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<tbody>
<tr>
<td># [min]</td>
<td>[min]</td>
<td>mAU</td>
<td>s [mAU]</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>1 10.362</td>
<td>BB</td>
<td>0.530</td>
<td>21353</td>
<td>2.386</td>
<td>0.035</td>
</tr>
<tr>
<td>2 12.400</td>
<td>BB</td>
<td>0.604</td>
<td>7532</td>
<td>201.57</td>
<td>57.558</td>
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</tbody>
</table>

Totals : 1.37866e4 378.14433

Results obtained with enhanced integrator!

*** End of Report ***
SbF₆ Salt

![Chemical Structure](image)
Data File: C:\HPCHEM\DATA\ALEX\M-285-OH.D
Sample Name: SMM-285-OH2-SBF6
Chiralcel OD with OD guard 5% iPrOH/n-Hexane 1.0 mL/min
23 bar 254 NM UV

Injection Date: 10/28/2013 10:42:17 AM
Sample Name: SMM-285-OH2-SBF6
Acq. Operator: SRAMM
Location: Vial 61
Acq. Method: C:\HPCHEM\METHODS\ALEX.M
Last changed: 10/7/2013 3:56:21 AM by Alex
Analysis Method: C:\HPCHEM\METHODS\ALEXB.M
Last changed: 12/16/2015 6:21:14 PM by ALEXB

ADC1 A, ADC1 CHANNEL A (ALEX/M-285-OH.D)

---

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Sample Amount: 10.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISIDs

Signal 1: ADC1 A, ADC1 CHANNEL A

Signal 2: VWD1 A, Wavelength=254 nm

Peak RetTime Type Width Area Height Area
# [min] [min] mAU *s [mAU] %
---|-------|--------|--------|--------|----|--------|--------|
1 10.345 VP 0.3539 5129.94238 142.03905 35.5690
2 12.600 BP 0.6679 2992.67913 219.35796 64.4310

Totals: 1.44225e4 360.39700

Results obtained with enhanced integrator!

*** End of Report ***

1100 LC 1/19/2016 9:30:20 AM ALEXB
II. Additional Data for Tables 3 and 4

Table SI.1. Masses, TLC solvent systems, and TLC plate staining solutions used for compounds in Tables 3 and 4 with the CEC microscale protocol

<table>
<thead>
<tr>
<th>table</th>
<th>entry</th>
<th>mass in 1 mL volumetric flask (mg)</th>
<th>TLC solvent conditions</th>
<th>TLC stain</th>
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<tbody>
<tr>
<td>3</td>
<td>1</td>
<td>2.5</td>
<td>7:3 hexanes/ethyl acetate</td>
<td>PMA</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2.5</td>
<td>7:3 hexanes/ethyl acetate</td>
<td>PMA</td>
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<tr>
<td>3</td>
<td>3</td>
<td>2.9</td>
<td>3:1 hexanes/ethyl acetate</td>
<td>PMA</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>2.9</td>
<td>3:1 hexanes/ethyl acetate</td>
<td>PMA</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>2.2</td>
<td>3:1 hexanes/ethyl acetate</td>
<td>PMA</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>3.0</td>
<td>6:1 hexanes/ethyl acetate</td>
<td>Dragendorf-Munier&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>2.6</td>
<td>6:1 hexanes/ethyl acetate</td>
<td>PMA</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>2.0</td>
<td>6:1 hexanes/ethyl acetate</td>
<td>PMA</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>5.9</td>
<td>6:1 hexanes/ethyl acetate</td>
<td>KMnO4</td>
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<td>PMA</td>
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<td>4.3</td>
<td>6:1 hexanes/ethyl acetate</td>
<td>PMA</td>
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<td>4</td>
<td>3.0</td>
<td>ethyl acetate</td>
<td>Dragendorf-Munier&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>4</td>
<td>5</td>
<td>4.5</td>
<td>6:1 hexanes/ethyl acetate</td>
<td>KMnO4</td>
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<tr>
<td>4</td>
<td>6</td>
<td>4.0</td>
<td>6:1 hexanes/ethyl acetate</td>
<td>PMA</td>
</tr>
<tr>
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<td>7</td>
<td>3.4</td>
<td>3:1 hexanes/ethyl acetate</td>
<td>PMA</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>3.6</td>
<td>6:1 hexanes/ethyl acetate</td>
<td>PMA</td>
</tr>
</tbody>
</table>

(a) plate was allowed to dry at room temperature over a period of 3-5 min before a photograph of the image was captured
III. Calibration Curves of \((R)-5\) and \((R)-6\) with GC-MS for Figure 6

Stock Solutions

\((R)-5\). To a 10 mL volumetric flask was added \((R)-5\) (5.0 mg, 0.029 mmol) and the flask was filled to the line with dichloromethane, preparing a solution of \((R)-5\) (2.9 mM).

\((R)-6\). To a 10 mL volumetric flask was added \((R)-6\) (6.6 mg, 0.029 mmol) and the flask was filled to the line with dichloromethane, preparing a solution of \((R)-6\) (2.9 mM).

Calibration Solutions

All solutions are summarized in Table SI.2.

Solution 1. To a GC-MS vial was added stock solutions of \((R)-5\) (909 \(\mu\)L) and \((R)-6\) (91.0 \(\mu\)L), preparing a solution ratio for \((R)-5:(R)-6\) of 10:1 at 2.6 mM and 0.26 mM.

Solution 2. To a GC-MS vial was added stock solutions of \((R)-5\) (833 \(\mu\)L) and \((R)-6\) (167 \(\mu\)L), preparing a solution ratio for \((R)-5:(R)-6\) of 5:1 at 2.4 mM and 0.48 mM.

Solution 3. To a GC-MS vial was added stock solutions of \((R)-5\) (667 \(\mu\)L) and \((R)-6\) (333 \(\mu\)L), preparing a solution ratio for \((R)-5:(R)-6\) of 2:1 at 1.9 mM and 0.97 mM.

Solution 4. To a GC-MS vial was added stock solutions of \((R)-5\) (500 \(\mu\)L) and \((R)-6\) (500 \(\mu\)L), preparing a solution ratio for \((R)-5:(R)-6\) of 1:1 at 1.5 mM and 1.5 mM.
**Solution 5.** To a GC-MS vial was added stock solutions of \((R)-5\) (333 µL) and \((R)-6\) (667 µL), preparing a solution ratio for \((R)-5:(R)-6\) of 1:2 at 0.97 mM and 1.9 mM.

**Solution 6.** To a GC-MS vial was added stock solutions of \((R)-5\) (167 µL) and \((R)-6\) (833 µL), preparing a solution ratio for \((R)-5:(R)-6\) of 1:5 at 0.48 mM and 2.4 mM.

**Solution 7.** To a GC-MS vial was added stock solutions of \((R)-5\) (91.0 µL) and \((R)-6\) (909 µL), preparing a solution ratio for \((R)-5:(R)-6\) of 1:10 at 0.26 mM and 2.6 mM.

**Table S1.2.** Mixed ratios of \((R)-5\) and \((R)-6\) in solutions used for GC-MS calibration curves

<table>
<thead>
<tr>
<th>solution</th>
<th>concentration (mM)</th>
<th>ratio</th>
<th>simulated conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>((R)-5)</td>
<td>((R)-6)</td>
<td>((R)-5)</td>
</tr>
<tr>
<td>1</td>
<td>2.6</td>
<td>0.26</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>2.4</td>
<td>0.48</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
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<td>4</td>
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<td>1.5</td>
<td>1</td>
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<td>5</td>
<td>0.97</td>
<td>1.9</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
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<td>7</td>
<td>0.26</td>
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<td>1</td>
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</table>

Vials of solutions 1-7 were capped and subsequently analyzed via GC-MS with a programmed method increasing from 50 °C to 290 °C at a rate of 5 °C per min. Solutions 1-7 were compared to pure samples of \((R)-5\) and \((R)-6\) at concentrations of 2.9 mM to match retention times.

Integration of peak intensities in solutions 1-7 was collected and compared to the concentrations of \((R)-5\) and \((R)-6\) within each solution to develop calibration curves (Table S1.3). GC-MS peak
Intensities were divided by 100,000,000 to simply the resulting graphs for (R)-5 (Figure SI.1) and (R)-6 (Figure SI.2).

**Table SI.3.** GC-MS integration of peak intensities of (R)-5 and (R)-6 for solutions 1-7.

<table>
<thead>
<tr>
<th>Solution</th>
<th>GC-MS integration</th>
<th>GC-MS integration (100000000)</th>
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</thead>
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<td>(R)-6</td>
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<td></td>
<td>1669713607</td>
<td>474853025</td>
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<tr>
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<td>1308193746</td>
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<td>642913949</td>
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<td>0.45344897</td>
<td>42.72364606</td>
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**Figure SI.1.** Calibration curve for concentration of (R)-5 relative to GC-MS peak intensity
Figure S1.2. Calibration curve for concentration of \((R)-6\) relative to GC-MS peak intensity.
IV. Additional Data for Figure 6

Testing Reaction Conversion by Varied Initial Concentrations of (R)-5 with the CEC Kit conditions

CEC Protocol
Substrate (R)-5 was solvated in CDCl₃ in a 1 dram vial. Masses and the volume of CDCl₃ added are included in Table SI.4. The resulting alcohol solution (100. µL) was dispensed to both the R-HBTM and S-HBTM CEC kit vials via microsyringe with a one-minute gap between additions. A needle was inserted to the CEC kit vial to equalize the pressure before addition of the alcohol solution. The solutions were agitated to ensure homogeneity and let sit for 30 min. Methanol- d₄ (50. µL) was added via microsyringe and the solution was again agitated to ensure homogeneity, halting reaction progress.

TLC Analysis
To a TLC plate with 2 lanes was spotted the R-HBTM reaction (4.0 µL), and the S-HBTM reaction (4.0 µL) via micropipette. The plate was run (30 % ethyl acetate in hexanes), dried, stained (PMA), heated by oven (160 °C, ~ 1 min), and photographed. Images are included in Figure SI.3.

1H NMR Analysis
The quenched solution was then analyzed by 1H NMR spectroscopy to assess reaction conversion via measurement of peak integration of the proton germinal to the alcohol and ester
functional groups on the substrate and product respectively. Spectra from entries 1-6 are included starting on page SI.31.

**GC-MS Analysis**

The $R$-HBTM and $S$-HBTM CEC kit solutions were concentrated under reduced pressure. The mixture was then resolvolated in methylene chloride (2 mL), washed with saturated aqueous NaHCO$_3$ (2 × 2 mL) and brine (1 × 2 mL). The organic layer was dried (MgSO$_4$), filtered, and concentrated under reduced pressure to afford the crude reaction mixtures for each entry. Each crude mixture was then solvated with methylene chloride in order to give an assumed additive concentration between $(R)$-5 and $(R)$-6 of 2.5 mM based on the initial amount of substrate added to the reaction kit. If the total solution was in excess of 1.0 mL, then a portion of the solution (1.0 mL) was transferred to a GC-MS vial and capped under air for subsequent analysis via GC-MS with a programmed method increasing from 50 °C to 290 °C at a rate of 5 °C per min. Volumes and the resulting GC-MS integration data are included below. The GC-MS integration data for $(R)$-5 and $(R)$-6 was utilized with previously developed calibration curves to calculate concentrations in each reaction mixture and the reaction conversion for each entry. Data are summarized for $R$-HBTM and $S$-HBTM reactions with entries 1-6 in Table SI.5 and Table SI.6.
Table SI.4. CEC Kit substrate loadings analyzed for \((R)-5\) in Figure 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>substrate (mg)</th>
<th>CDCl(_3) added to substrate (µL)</th>
<th>substrate added to each reaction (µmol)</th>
<th>substrate stock solution (nmol)</th>
<th>conc. (M)</th>
<th>(M)</th>
<th>(mM)</th>
<th>[KIT]</th>
</tr>
</thead>
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<td>0.079</td>
<td>0.014</td>
</tr>
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Figure SI.3. TLC plate images of CEC kit conditions for entries 1-6 in Table SI.4, plotted in Figure 6. The left lane of each TLC plate contains \(R\)-HBTM and the right lane contains \(S\)-HBTM. Plates were eluted in 30% ethyl acetate in hexanes. Visualization was achieved by UV lamp (bottom row) and staining with PMA stain (top row). Plate numbers correlate to entry numbers in Table SI.4.
Table SI.5. *R*-HBTM GC-MS integration data and reaction conversion for entries 1-6 of Table SI.4 plotted in Figure 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Volume (mL)</th>
<th>GC-MS integration (R-5)</th>
<th>GC-MS integration (R-6)</th>
<th>calculated conc. (mM)</th>
<th>rxn conv.</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
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<tr>
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<td>4.54000294</td>
<td>2.31883693</td>
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<td>3</td>
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<tr>
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Table SI.6. *S*-HBTM GC-MS integration data and reaction conversion for entries 1-6 of Table SI.4 plotted in Figure 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Volume (mL)</th>
<th>GC-MS integration (R-5)</th>
<th>GC-MS integration (R-6)</th>
<th>calculated conc. (mM)</th>
<th>rxn conv.</th>
</tr>
</thead>
<tbody>
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<td>0.03540546</td>
<td>13.74798635</td>
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</table>
$^1$H NMR Spectra CEC Analysis for entries 1-6 of Table SI.4 plotted in Figure 6

Table SI.4 Entry 1. 29 mM (R)-5 CEC $^1$H NMR spectra
Table SI.4 Entry 2. 14 mM (R)-5 CEC $^1$H NMR spectra
Table SI.4 Entry 3. 7.2 mM (R)-5 CEC $^1$H NMR spectra
Table SI.4 Entry 4. 4.8 mM (R)-5 CEC $^1$H NMR spectra

$^1$H NMR in CDCl$_3$ at 500 MHz with R-HBTM substrate 4.8 mM
Table SI.4 Entry 5. 2.9 mM (R)-5 CEC $^1$H NMR spectra

$^1$H NMR in CDCl$_3$ at 500 MHz

with R-HBTM substrate 2.9 mM

$^1$H NMR in CDCl$_3$ at 500 MHz

with S-HBTM substrate 2.9 mM
Table SI.4 Entry 6. 1.4 mM (R)-5 CEC $^1$H NMR spectra

$^1$H NMR in CDCl$_3$ at 500 MHz with R-HBTM substrate 1.4 mM

$^1$H NMR in CDCl$_3$ at 500 MHz with S-HBTM substrate 1.4 mM
V. Additional Data for Table 5

Testing Reaction Conversion by Varied Solvent to Solvate (R)-5 with the CEC Kit in CDCl₃

Preparation of Solutions

**Substrate.** Substrate (R)-5 (3.4 mg, 0.020 mmol) was solvated in a deuterated solvent varying between entries 1-7 of Table 5 (250. µL) in a 1 dram vial.

**CEC Kit.** Prepared as previously described in the Experimental Section.

**CEC Protocol**

The resulting alcohol solution (100. µL) was dispensed to both the R-HBTM and S-HBTM CEC kit vials via microsyringe with a one-minute gap between additions. A needle was inserted to the CEC kit vial to equalize the pressure before addition of the alcohol solution. The solutions were agitated to ensure homogeneity and let sit for 30 min. Methanol-d₄ (50. µL) was added via microsyringe and the solution was again agitated to ensure homogeneity, halting reaction progress. Deuterated solvents tested are included below in Table SI.7.

**TLC Analysis**

To a TLC plate with 2 lanes was spotted the R-HBTM reaction (4.0 µL), and the S-HBTM reaction (4.0 µL) via micropipette. The plate was run (30 % ethyl acetate in hexanes), dried, stained (PMA), heated by oven (160 °C, ~ 1 min), and photographed. Images are included in Figure SI.4.

**¹H NMR Analysis**

The quenched solution was then analyzed by ¹H NMR spectroscopy to assess reaction conversion via measurement of peak integration of the proton germinal to the alcohol and ester
functional groups on the substrate and product respectively. Spectra and a graph of dielectric constant compared to reaction conversion for both HBTM reactions for entries 1-7 are included below starting on S39.

Table SI.7. Deuterated solvents used in solvating (R)-5 for use in the CEC kit in CDCl₃

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate loading solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene-&lt;i&gt;d&lt;/i&gt;&lt;sub&gt;8&lt;/sub&gt;</td>
</tr>
<tr>
<td>2</td>
<td>CDCl₃</td>
</tr>
<tr>
<td>3</td>
<td>THF-&lt;i&gt;d&lt;/i&gt;&lt;sub&gt;8&lt;/sub&gt;</td>
</tr>
<tr>
<td>4</td>
<td>acetone-&lt;i&gt;d&lt;/i&gt;&lt;sub&gt;6&lt;/sub&gt;</td>
</tr>
<tr>
<td>5</td>
<td>MeCN-&lt;i&gt;d&lt;/i&gt;&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>6</td>
<td>DMF-&lt;i&gt;d&lt;/i&gt;&lt;sub&gt;7&lt;/sub&gt;</td>
</tr>
<tr>
<td>7</td>
<td>DMSO-&lt;i&gt;d&lt;/i&gt;&lt;sub&gt;6&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

Figure SI.4. TLC plate images of CEC kit conditions for entries 1-7 in Table SI.5. The left lane of each TLC plate contains <i>R</i>-HBTM and the right lane contains <i>S</i>-HBTM. Plates were eluted in 30% ethyl acetate in hexanes. Visualization was achieved by UV lamp (bottom row) and staining with PMA stain (top row). Plate numbers correlate to entry numbers in Table SI.5
$^1$H NMR Spectra CEC Analysis of Entries 1-7 from Table 5

**Table 5. Entry 1**
Table 5. Entry 2

$^1$H NMR in CDCl$_3$ at 500 MHz with R-HBTM substrate in CDCl$_3$

$^1$H NMR in CDCl$_3$ at 500 MHz with S-HBTM substrate in CDCl$_3$
Table 5. Entry 3

$^1$H NMR in CDCl$_3$ at 500 MHz with $R$-HBTM substrate in THF-d$_8$

$^1$H NMR in CDCl$_3$ at 500 MHz with $S$-HBTM substrate in THF-d$_8$
Table 5. Entry 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>NMR Conditions</th>
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<td>MeOH</td>
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</tr>
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<tr>
<td></td>
<td>MeOH</td>
<td>$^1$H NMR in CDCl$_3$ at 500 MHz with S-HBTM substrate in acetone-d$_6$</td>
</tr>
</tbody>
</table>
**Table 5. Entry 5**

$^1$H NMR in CDCl$_3$ at 500 MHz with $R$-HBTM substrate in MeCN-d$_3$

$^1$H NMR in CDCl$_3$ at 500 MHz with $S$-HBTM substrate in MeCN-d$_3$
Table 5. Entry 6

<table>
<thead>
<tr>
<th>Entry 6</th>
<th>MeOH</th>
<th>1H NMR in CDCl₃ at 500 MHz with R-HBTM substrate in DMF-d7</th>
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</thead>
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<tr>
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<td>MeOH</td>
<td>1H NMR in CDCl₃ at 500 MHz with S-HBTM substrate in DMF-d7</td>
</tr>
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</table>

[Image of NMR spectra]

[Image of NMR spectra]
Table 5. Entry 6 – after vacuum removal of solvent and resolvation in CDCl$_3$
Table 5. Entry 7

\[^1H\] NMR in CDCl\textsubscript{3} at 500 MHz with R-HBTM substrate in DMSO-d\textsubscript{6}

\[^1H\] NMR in CDCl\textsubscript{3} at 500 MHz with S-HBTM substrate in DMSO-d\textsubscript{6}
Table 5. Entry 7 – after vacuum removal of solvent and resolvation in CDCl₃

\[ ^1H \text{NMR in CDCl}_3 \text{ at 500 MHz} \]

\[
\begin{array}{c}
\text{with } R\text{-HBTM} \\
\text{substrate in DMSO-}d_6
\end{array}
\]

\[ ^1H \text{NMR in CDCl}_3 \text{ at 500 MHz} \]

\[
\begin{array}{c}
\text{with } S\text{-HBTM} \\
\text{substrate in DMSO-}d_6
\end{array}
\]
Figure S1.5. Comparison of reaction conversion (%) after 30 minutes of \((R)-5\) to \((R)-6\) relative to the dielectric constant of the solvent \((R)-5\) was loaded into the CEC kit that contained CDCl₃.
**VI. Additional Data for Tables 6, Table 7, and Figure 9**

**Table SI.8.** Masses, TLC solvent systems, and TLC plate staining solutions used for compounds in Tables 6 and 7 with the CEC kit protocol

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<thead>
<tr>
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<td>Dragendorf-Munier&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>3.2</td>
<td>ethyl acetate</td>
<td>Dragendorf-Munier&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>11&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>ethyl acetate</td>
<td>Dragendorf-Munier&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>2.8</td>
<td>6:1 hexanes/ethyl acetate</td>
<td>KMnO4&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>3.4</td>
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<td>3:1 hexanes/ethyl acetate</td>
<td>PMA</td>
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</table>

(a) substrate solvated in DMSO-<sub>d6</sub> before injection into CEC kit in CDCl<sub>3</sub>  
(b) plate was allowed to dry at room temperature over a period of 3-5 min before a photograph of the image was captured
Figure SI.6. TLC images corresponding to each entry tested in Table 6. Left TLC lane: \textit{R}-HBTM; Right TLC lane: \textit{S}-HBTM. TLC conditions and stains are listed in Table SI.8.
Figure SI.7. TLC images corresponding to each entry tested in Table 7. Left TLC lane: $R$-HBTM; Right TLC lane: $S$-HBTM. TLC conditions and stains are listed in Table SI.8.
\(^1\)H NMR Spectra CEC Analysis for Tables 6 and 7

Table 6. Entry 1
Table 6. Entry 2

$^1$H NMR in CDCl$_3$ at 500 MHz with R-HBTM

$^1$H NMR in CDCl$_3$ at 500 MHz with S-HBTM
A peak from HBTM (1H) overlaps with the starting material peak (1H) at 4.75 ppm. The integrated starting material peak in the reaction mixture was calculated by subtracting the integrated catalyst peak (1H) at 6.81 ppm before calculating percent conversion.
Table 6. Entry 4

A peak from HBTM (1H) overlaps with the starting material peak (1H) at 4.77 ppm. The integrated starting material peak in the reaction mixture was calculated by subtracting the integrated catalyst peak (1H) at 7.03 ppm before calculating percent conversion.
Table 6. Entry 5

$^1$H NMR in CDCl$_3$ at 500 MHz

with R-HBTM

with S-HBTM
Table 6. Entry 5 – after vacuum removal of solvent and resolvation in CDCl₃
Table 6. Entry 6
**Table 6. Entry 7**

$^1$H NMR in CDCl$_3$ at 500 MHz

with $R$-HBTM

$^1$H NMR in CDCl$_3$ at 500 MHz

with $S$-HBTM
Table 6. Entry 7 – after vacuum removal of solvent and resolvation in CDCl$_3$

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<tr>
<th>Entry</th>
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<td>1H NMR in CDCl$_3$ at 500 MHz with R-HBTM</td>
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<tr>
<td>2</td>
<td>1H NMR in CDCl$_3$ at 500 MHz with S-HBTM</td>
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</table>
Table 6. Entry 8

Peaks are integrated, but not used for conversion in Table 7; $R$-HBTM 81%, $S$-HBTM 36%.
Table 6. Entry 8 – after vacuum removal of solvent and resolvation in CDCl₃

A peak from HBTM (1H) overlaps with the starting material peak (1H) at 4.57 ppm. The integrated starting material peak in the reaction mixture was calculated by subtracting the integrated catalyst peak (1H) at 6.77 ppm before calculating percent conversion.
Table 6. Entry 9

$^1$H NMR in CDCl$_3$ at 500 MHz with R-HBTM

$^1$H NMR in CDCl$_3$ at 500 MHz with S-HBTM
Table 6. Entry 10

1H NMR in CDCl3 at 500 MHz with R-HBTM

1H NMR in CDCl3 at 500 MHz with S-HBTM
Table 6. Entry 11

<table>
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<th>Compound</th>
<th>Spectrum 1</th>
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<td><img src="image2" alt="Spectrum 2" /></td>
</tr>
<tr>
<td>S-HBTM</td>
<td><img src="image3" alt="Spectrum 1" /></td>
<td><img src="image4" alt="Spectrum 2" /></td>
</tr>
</tbody>
</table>
Peaks at 8.15 and 8.41 ppm were used for calculation of reaction conversion. Other notable peaks are also highlighted in the reaction mixture between 5 and 7 ppm.
Additional analysis for Table 6, Entry 12.

HRMS (TOF MS ES, CH$_2$Cl$_2$) m/z calcd for C$_{31}$H$_{32}$N$_2$O$_5$Na (M+Na)$^+$ 535.2209, found 535.2214.

HRMS (TOF MS ES, CH$_2$Cl$_2$) m/z calcd for C$_{28}$H$_{28}$N$_2$O$_4$Na (M+Na)$^+$ 479.1947, found 479.1966.

TLC in 9:1 ethyl acetate/hexanes
Table 7. Entry 1

$^1$H NMR in CDCl$_3$ at 500 MHz

with $\text{R-HBTM}$

$^1$H NMR in CDCl$_3$ at 500 MHz

with $\text{S-HBTM}$
Table 7. Entry 1 – after vacuum removal of solvent and resolvation in CDCl₃
Table 7. Entry 2

\[ ^1H \text{NMR in } \text{CDCl}_3 \text{ at 500 MHz} \]

with \( S \)-HBTM

\[ ^1H \text{NMR in } \text{CDCl}_3 \text{ at 500 MHz} \]

with \( R \)-HBTM
Table 7. Entry 2 – after vacuum removal of solvent and resolvation in CDCl₃
Table 7. Entry 3

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<tr>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>$^1$H NMR in CDCl$_3$ at 500 MHz with S-HBTM</td>
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</table>
Table 7. Entry 3 – after vacuum removal of solvent and resolvation in CDCl₃
Table 7. Entry 4

1H NMR in CDCl₃ at 500 MHz

with R-HBTM

1H NMR in CDCl₃ at 500 MHz

with S-HBTM
Table 7. Entry 4 – after vacuum removal of solvent and resolvation in CDCl₃

<table>
<thead>
<tr>
<th>Entry</th>
<th>After Vacuum Removal</th>
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<tbody>
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<td>1H NMR in CDCl₃ at 500 MHz</td>
<td></td>
</tr>
</tbody>
</table>

![NMR Spectra](image)

with R-HBTM

![NMR Spectra](image)

with S-HBTM
Table 7. Entry 5

$^1$H NMR in CDCl$_3$ at 500 MHz

with R-HBTM

$^1$H NMR in CDCl$_3$ at 500 MHz

with S-HBTM
Table 7. Entry 5 – after vacuum removal of solvent and resolvation in CDCl₃

<table>
<thead>
<tr>
<th>Compound</th>
<th>Spectrum 1</th>
<th>Spectrum 2</th>
</tr>
</thead>
<tbody>
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<td>S⁻-HBTM</td>
<td><img src="image1" alt="S⁻-HBTM Spectra" /></td>
<td><img src="image2" alt="S⁻-HBTM Spectra" /></td>
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<tr>
<td>R⁻-HBTM</td>
<td><img src="image3" alt="R⁻-HBTM Spectra" /></td>
<td><img src="image4" alt="R⁻-HBTM Spectra" /></td>
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**Table 7. Entry 6**

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<th>Spectroscopy Details</th>
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<tr>
<td>![Chemical Structure 1]</td>
<td>$^1$H NMR in CDCl$_3$ at 500 MHz with R-HBTM</td>
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<tr>
<td>![Chemical Structure 2]</td>
<td>$^1$H NMR in CDCl$_3$ at 500 MHz with S-HBTM</td>
</tr>
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</table>
Table 7. Entry 6 – after vacuum removal of solvent and resolvation in CDCl₃
Table 7. Entry 6 – after vacuum removal of solvent, resolvation in CDCl$_3$, and basic workup
Table 7. Entry 7

$^1$H NMR in CDCl$_3$ at 500 MHz with $\cdot$HBTM

$^1$H NMR in CDCl$_3$ at 500 MHz with $\cdot$HBTM
Table 7. Entry 7 – after vacuum removal of solvent and resolvaion in CDCl₃

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>NMR Spectrum</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="R-HBTM" alt="Chemical Structure" /></td>
<td><img src="R-HBTM" alt="NMR Spectrum" /></td>
<td>1H NMR in CDCl₃ at 500 MHz with R-HBTM</td>
</tr>
<tr>
<td><img src="S-HBTM" alt="Chemical Structure" /></td>
<td><img src="S-HBTM" alt="NMR Spectrum" /></td>
<td>1H NMR in CDCl₃ at 500 MHz with S-HBTM</td>
</tr>
</tbody>
</table>
Table 7. Entry 8
Table 7. Entry 8 – after vacuum removal of solvent and resolvation in CDCl₃

^1H NMR in CDCl₃ at 500 MHz

\[
\begin{align*}
\text{with } & R-\text{HBTM} \\
\text{with } & S-\text{HBTM}
\end{align*}
\]
Peaks at 7.56 (sm) and 7.52 (pdt) ppm were used to calculate conversion in Table 7. Alternatively, the starting material peak at 3.71 ppm (which overlaps with catalyst) can be subtracted by the catalyst peak at 3.84 ppm and then used with the product peak at 4.99 ppm to calculation reaction conversion (R-HBTM 51%; S-HBTM 31%).
Table 7. Entry 10

$^1$H NMR in CDCl$_3$ at 500 MHz

with R-HBTM

with S-HBTM
Table 7. Entry 11

1H NMR in CDCl₃ at 500 MHz with R-HBTM

1H NMR in CDCl₃ at 500 MHz with S-HBTM
Table 7. Entry 12
$^1$H NMR Spectra for Figure 9

**Figure 9. Plate 1**
Figure 9. Plate 2

$^1$H NMR in CDCl$_3$ at 500 MHz

with R-HBTM
6 month old CEC kit

$^1$H NMR in CDCl$_3$ at 500 MHz

with S-HBTM
6 month old CEC kit
VII. Additional Manipulations of Microscale Systems and Data for Figure 10

Figure 10 CEC Microscale Procedure, Purposeful Error, and Equivalents of Base Studies

Preparation of Solutions

(R)-1-(naphthalen-2-yl)ethanol ((R)-5). To a 5 mL volumetric flask was added (R)-1-(naphthalen-2-yl)ethanol (12.5 mg, 0.0726 mmol). The flask was filled with toluene to the line and mixed, generating solution 1 of (R)-5 (0.0145 M). To a 2 mL volumetric flask was added solution 1 of (R)-5 (1.00 mL). The flask was filled with toluene to the line and mixed, generating the solution 2 of (R)-5 (0.00726 M). To a new 2 mL volumetric flask was added solution 2 of (R)-5 (1.00 mL). The flask was filled with toluene to the line and mixed, generating the solution 3 of (R)-5 (0.00363 M). To a new 2 mL volumetric flask was added solution 3 of (R)-5 (1.00 mL). The flask was filled with toluene to the line and mixed, generating the solution 4 of (R)-5 (0.00181 M). To a new 2 mL volumetric flask was added solution 4 of (R)-5 (1.00 mL). The flask was filled with toluene to the line and mixed, generating the solution 5 of (R)-5 (0.000907 M).

R-HBTM. To a 10 mL volumetric flask was added R-HBTM (7.7 mg, 0.029 mmol). The flask was filled with toluene to the line and mixed, generating the solution of R-HBTM (0.0029 M).

S-HBTM. To a 10 mL volumetric flask was added S-HBTM (7.7 mg, 0.029 mmol). The flask was filled with toluene to the line and mixed, generating the solution of S-HBTM (0.0029 M).

Propionic anhydride + N,N-diisopropylethylamine. To a 10 mL volumetric flask was added propionic anhydride (279 µL, 2.18 mmol) and N,N-diisopropylethylamine (75.9 µL, 0.436 mmol) via micropipette. The flask was filled with toluene to the line and mixed, generating solution 1 of propionic anhydride (0.218 M) and N,N-diisopropylethylamine (0.0436 M). To a
new 10 mL volumetric flask was added propionic anhydride (279 µL, 2.18 mmol) and \(N,N\)-diisopropylethylamine (50.6 µL, 0.290 mmol) via micropipette. The flask was filled with toluene to the line and mixed, generating solution 2 of propionic anhydride (0.218 M) and \(N,N\)-diisopropylethylamine (0.0290 M). To a new 10 mL volumetric flask was added propionic anhydride (279 µL, 2.18 mmol) and \(N,N\)-diisopropylethylamine (25.3 µL, 0.145 mmol) via micropipette. The flask was filled with toluene to the line and mixed, generating solution 3 of propionic anhydride (0.218 M) and \(N,N\)-diisopropylethylamine (0.0145 M).

**CEC Method**

A 50 µL syringe was used to draw up, in sequence, air (5 µL), (R)-5 stock solution (varied µL), air (5 µL), HBTM stock solution (varied µL), air (5 µL), propionic anhydride and \(N,N\)-diisopropylethylamine stock solution (varied µL), and air (5 µL). The contents of the syringe were then mixed in a 500 µL amber glass vial placed inside a 1 dram vial, initiating the reaction. The mixed reaction solution was drawn back into the microsyringe and allowed to sit for 1 h. Then, the reaction solution in the microsyringe was ejected into methanol (10. µL). Specific solutions of (R)-5 and of propionic anhydride/\(N,N\)-diisopropylethylamine used per entry, as well as specific volumes for all stock solutions, are outlined in each study utilizing these solutions below.

**Combinations for Figure 10:**

All entries used 10. µL of each stock solution used.

**Entry 1:** (R)-5 stock solution 2, the solution of each enantiomer of HBTM, solution 1 of propionic anhydride/\(N,N\)-diisopropylethylamine
**Entry 2:** (R)-5 stock solution 3, the solution of each enantiomer of HBTM, solution 1 of propionic anhydride/N,N-diisopropylethylamine

**Entry 3:** (R)-5 stock solution 4, the solution of each enantiomer of HBTM, solution 1 of propionic anhydride/N,N-diisopropylethylamine

**Entry 4:** (R)-5 stock solution 5, the solution of each enantiomer of HBTM, solution 1 of propionic anhydride/N,N-diisopropylethylamine

**TLC Analysis**

To a TLC plate with 2 lanes was spotted the R-HBTM reaction (4.0 µL), and the S-HBTM reaction (4.0 µL) via micropipette. The plate was run (30 % ethyl acetate in hexanes), dried, stained (PMA), heated by oven (160 °C, ~ 1 min), and photographed.

**Purposeful Error in Microsyringe Volumes**

All entries display a clear qualitative assessment of the fast reaction as the S-HBTM reaction despite both positive and negative variations of 5 µL from the standard volumes of carbinol solution 1, HBTM solutions, and anhydride/base solution 1 (Figure SI.8). This data supports the reliability of the 10 µL measurement for each stock solution and displaces concern about a misguided conclusion based on minor differences in volume pulled from stock solutions.
Figure SI.8. Variation of volume utilized from (R)-5 solution 1, HBTM solutions, and anhydride/base solution 1. The left lane of each TLC plate contains R-HBTM and the right lane contains S-HBTM. Plates were eluted in 30% ethyl acetate in hexanes. Visualization was achieved by staining with PMA stain.
Studies on Effect of Base Equivalents

All entries display clear qualitative assessment of the fast reaction as the \( S \)-HBTM reaction and no noticeable qualitative difference in reaction progress, providing supporting evidence that reaction progress is independent of base concentration (Figure SI.9). Based on this outcome, the equivalents of base was set at five relative to the standard carbinol concentration of 0.0145 M for future experiments in order to assure an excess of base for a wider substrate scope.

Figure SI.9. Variation of equivalents of base utilized from anhydride/base solutions 1, 2 and 3. The left lane of each TLC plate contains \( R \)-HBTM and the right lane contains \( S \)-HBTM. Plates were eluted in 30% ethyl acetate in hexanes. Visualization was achieved by staining with PMA stain.