Supporting Information

Systematically Probing the Effect of Catalyst Acidity in a Hydrogen Bond Catalyzed Enantioselective Reaction: Observation of Linear Free Energy Relationships

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General methods:
Unless otherwise noted all reactions were performed under a nitrogen atmosphere with stirring. Dichloromethane was distilled from CaH₂. Methanol was distilled from magnesium methoxide.¹ Triethylamine was distilled from CaH₂. Trifluoroacetic anhydride was purchased from Lancaster and used without further purification. Trichloroacetic anhydride and chloroacetic anhydride were purchased from Aldrich and used without further purification. Sodium fluoroacetate was purchased from Fluka and used without further purification. Dichloroacetic anhydride, N-methyl morpholine, and isobutyl chloroformate were purchased from Acros and used without further purification. DMAP was recrystallized from toluene.¹ Toluene was dried by filtration through alumina. Benzaldehyde was washed with saturated NaCO₃ and brine, dried over MgSO₄, and distilled under reduced pressure prior to use. Acetyl chloride was distilled under atmospheric pressure prior to use. Flash chromatography was performed using EM Reagent silica 60 (230-400 mesh). Analytical thin layer chromatography was performed with Whatman K6F Silica 60 Å plates. In situ IR was monitored using an ASI React IR 1000 with a diamond tipped probe. IR spectra were recorded using a Mattson Satellite FTIR instrument. NMR spectra were recorded in CD₂Cl₂ using one of the following: (i) Varian Unity-300 Spectrometer, or (ii) Varian XL-300 Spectrometer. MS were recorded using a Micromass Quattro II Triple Quadrupole Mass Spectrometer. Optical rotations were recorded on Perkin Elmer Model 343 Polarimeter. Concentrations for optical rotations are reported in g/100 mL. All melting points are uncorrected and recorded on Thomas Hoover Unimelt capillary melting point apparatus. The Cbz-protected oxazoline amine 6 was prepared by the method reported previously.² 1-Amino-3-siloxy-1,3-butadiene was prepared and purified according to literature procedure.³ The pyranone product has been reported previously.⁴

Synthesis of catalysts:

Cbz-Deprotection.⁵
A 100 mL round bottom flask was charged with 44 mg of 10% Pd/C and the flask was flushed with nitrogen. In a separate 100 mL flask, 442.3 mg of oxazoline 6 (0.873 mmol) was dissolved in 6 mL of dry MeOH and cannulated into the flask containing Pd/C (on occasions when this is difficult, gentle warming or addition of excess MeOH is helpful and has no discernible effect on overall yield). A further 4 mL of MeOH (2 x 2 mL) was used for rinsing. The flask was then evacuated under water aspirator pressure and filled with H₂ from a balloon. The cycle was repeated thrice more, and the reaction mixture was stirred under a H₂ balloon atmosphere. On completion of reaction (7-8 h, by disappearance of oxazoline 6 on TLC, Rₓ = 0.6 with 1:1 ethyl acetate:hexanes), the reaction mixture was filtered through a pad of celite. The filtrate was concentrated under reduced pressure, dissolved in benzene and concentrated under reduced pressure to
remove exogenous water (2 x 30 mL benzene). The residue was dried overnight under high vacuum and used without further purification.

**Acetamidation:**
The following general procedure was followed for the synthesis of 1, 2, 3, and 5. The residue from deprotection (7, 0.873 mmol, 1 equiv.) was dissolved in 5 mL of dry dichloromethane under nitrogen along with 10.7 mg of DMAP (0.087 mmol, 10 mol%). To this solution, 490 μL of freshly distilled triethylamine (3.49 mmol, 4 equiv.) was added. The reaction mixture was cooled to 0 °C in an ice bath. In a separate flask, 123 μL of trifluoroacetic anhydride (95%, 0.873 mmol, 1 equiv.) was dissolved in 3 mL of dichloromethane. This solution was cannulated into the flask containing 7. An additional 2 mL of dichloromethane was used for rinsing. The reaction mixture was stirred for 4 hours, then diluted with 30 mL of dichloromethane and washed with 30 mL of saturated aqueous NaHCO₃ followed by 30 mL of brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated.

**Column Chromatography:**
Approximately 50 mL of silica was packed into a column with 20% ether in hexanes as the solvent. The residue from workup was dissolved in minimum amount of dichloromethane and loaded onto the column. After an initial elution of 10 fractions (13 x 100 test tubes) with 20% ether in hexanes as the solvent, the eluting mixture was switched to 25% ether in hexanes for 20 fractions, followed by 30% ether in hexanes. Fractions 19-36 were concentrated to yield 178.8 mg of the oxazoline acetamide as a white solid (yield: 43%).

(1): Rᵣ = 0.7 with 1:1 ethyl acetate:hexanes; mp: 50-52 °C; [α]ᵣ²⁰ = -20.4° (c = 0.28, CHCl₃); IR (KBr) 3482, 3393, 3062, 3030, 2360, 2343, 1721, 1668, 1543, 1496, 1449, 1210, 1173, 749, 700 cm⁻¹; ¹H NMR (300 MHz CD₂Cl₂, 25 °C) δ 2.50 (s, 1H), 3.10 (dd, J = 6.6 Hz, J = 14.0, 1H), 3.23 (dd, J = 6.0 Hz, J = 14.0, 1H), 4.26 (d, J = 8.9 Hz, 1H), 4.27 (d, J = 8.9 Hz, 1H), 4.81 (ddd, J = 6.0 Hz, J = 6.5 Hz, J = 6.5, 1H), 5.25 (dd, J = 8.9 Hz, J = 8.9 Hz, 1H), 6.79 (br d, J = 6.0 Hz, 1H), 7.13-7.37 (m, 11H), 7.41-7.46 (m, 4H); ¹³C NMR {¹H} (75 MHz CD₂Cl₂, 25 °C) δ 37.5, 50.0, 70.8, 73.2, 78.6, 115.8 (q, J = 288 Hz), 126.0, 126.5, 127.3, 127.5, 127.8, 128.4, 128.7, 129.1, 129.6, 135.3, 144.2, 145.9, 157.0 (q, J = 38 Hz), 167.1; MS (ES, 2:5 CHCl₃:MeOH) m/z (M+H)⁺ calcd. 469.2, obsd. 469.1.

(2): Synthesized following the general procedure described above using trichloroacetic anhydride. Yield: 37%; white solid; Rᵣ = 0.7 with 1:1 ethyl acetate:hexanes; column chromatography: 20% ether in hexanes (20 fractions), 25% (20 fractions), 30%, collected fractions 26-38; mp: 58-61 °C; [α]ᵣ²⁰ = -32.0° (c = 0.30, CHCl₃); IR (KBr) 3474, 3412, 3060, 3029, 2962, 2935, 2362, 2344, 1711, 1666, 1510, 1448, 1388, 1209, 1031, 984, 823, 751, 700 cm⁻¹; ¹H NMR (300 MHz CD₂Cl₂, 25 °C) δ 2.66 (s, 1H), 3.11 (dd, J = 7.0 Hz, J = 14.0, 1H), 3.27 (dd, J = 5.6 Hz, J = 14.0, 1H), 4.27 (d, J = 8.4 Hz, 1H), 4.29 (d, J = 8.4 Hz, 1H), 4.69 (ddd, J = 6.5 Hz, J = 6.5 Hz, J = 6.5 Hz, 1H), 5.25 (dd, J = 8.6 Hz, J = 8.6 Hz, 1H), 7.13-7.37 (m, 12 H), 7.43-7.46 (m, 4H); ¹³C NMR {¹H} (75 MHz CD₂Cl₂, 25 °C) δ 37.4, 51.2, 70.8, 73.0, 78.7, 126.1, 126.7, 127.2, 127.4, 127.8, 128.3, 128.7, 129.1,
129.7, 135.5, 144.2, 146.1, 161.8, 167.5; MS (ES, 2:5 CHCl₃:MeOH) m/z (M+H)⁺ calcd. 517.1, obsd. 517.0.

(3): Synthesized following the general procedure described above using dichloroacetic anhydride. Yield: 30%; white solid; Rₖ = 0.6 with 1:1 ethyl acetate:hexanes; column chromatography: 20% ether in hexanes (20 fractions), 30% (20 fractions), 40%, collected fractions 43-55; mp: 52-54 °C; [α]D²⁰ = -25.7° (c = 0.30, CHCl₃); IR (KBr) 3407, 3060, 3028, 2966, 2933, 1664, 1525, 1495, 1449, 1195, 985, 810, 749, 700, 636 cm⁻¹; ¹H NMR (300 MHz, CD₂Cl₂, 25 °C) δ 2.74 (s, 1H), 3.08 (dd, J = 7.3 Hz, J = 13.9, 1H), 3.23 (dd, J = 5.7 Hz, J = 14.0 Hz, 1H), 4.25 (d, J = 8.5, 1H), 4.25 (d, J = 8.5, 1H), 4.69 (ddd, J = 6.7 Hz, J = 6.7 Hz, J = 6.7 Hz, 1H), 5.25 (dd, J = 8.5 Hz, J = 8.5 Hz, 1H), 5.80 (s, 1H), 6.90 (br d, J = 6.4), 7.15-7.37 (m, 11H), 7.43-7.49 (m, 4H); ¹³C NMR {¹H} (75 MHz, CD₂Cl₂, 25 °C) δ 37.6, 42.8, 50.2, 70.5, 73.2, 78.8, 126.1, 126.5, 127.1, 127.3, 127.6, 128.3, 128.6, 128.7, 129.1, 129.7, 135.7, 144.2, 146.2, 164.2, 167.8; MS (ES, 2:5 CHCl₃:MeOH) m/z (M+H)⁺ calcd. 483.1, obsd. 483.0.

(5): Synthesized following the general procedure described above using chloroacetic anhydride. Yield: 32%; white solid; Rₖ = 0.5 with 1:1 ethyl acetate:hexanes; column chromatography: 30% ether in hexanes (10 fractions), 40% (20 fractions), 50% (20 fractions), 60%, collected fractions 36-45; mp: 61-64 °C; [α]D²⁰ = 25.5° (c = 0.20, CHCl₃); IR (KBr) 3403, 3060, 3028, 2960, 2936, 1657, 1529, 1495, 1448, 1390, 1384, 984, 749, 701 cm⁻¹; ¹H NMR (300 MHz, CD₂Cl₂, 25 °C) δ 3.06 (dd, J = 7.3 Hz, J = 13.9 Hz, 1H), 3.19 (dd, J = 5.9 Hz, J = 13.9 Hz, 1H), 3.74 (d, J = 15.1 Hz, 1H), 3.86 (d, J = 15.1 Hz, 1H), 4.23 (d, J = 7.3 Hz, 1H), 4.66 (ddd, J = 6.3 Hz, J = 6.7 Hz, J = 6.7 Hz, 1H), 5.25 (dd, J = 7.3 Hz, J = 9.3 Hz, 1H), 6.84 (br d, J = 6.1 Hz, 1H), 7.16-7.46 (m, 11H), 7.43-7.49 (m, 4H); ¹³C NMR {¹H} (75 MHz, CD₂Cl₂, 25 °C) δ 37.6, 42.8, 50.2, 70.5, 73.2, 78.8, 126.1, 126.5, 127.1, 127.3, 127.6, 128.3, 128.7, 129.1, 129.6, 136.1, 144.4, 146.5, 166.8, 168.1; MS (ES, 2:5 CHCl₃:MeOH) m/z (M+H)⁺ calcd. 449.2, obsd. 449.1.

**Fluoroacetamidation:**

In a round bottom flask, 81.0 mg of sodium fluoroacetate (0.770 mmol, 1.3 equiv.) was dissolved in 3 mL of dry dichloromethane under nitrogen. To this solution, 103 µL of N-methylmorpholine (99%, 0.924 mmol, 1.56 equiv.) was added. The reaction mixture was cooled to -15 °C using a NaCl/ice cooling bath, and 120 µL of isobutylchloroformate (97%, 0.894 mmol, 1.51 equiv.) was added dropwise. The contents are stirred at this temperature for 45 minutes, after which the residue from deprotection (0.592 mmol, 1 equiv.) dissolved in 1 mL of dry dichloromethane along with 128 µL of N-Methylmorpholine (1.154 mmol, 1.95 equiv.) was added via cannula. An additional 1 mL of dichloromethane was used for rinsing. The reaction mixture was allowed to warm to room temperature, stirred for 8 hours, then diluted with 10 mL of dichloromethane and extracted with 10 mL of water followed by 10 mL of brine. The organic layer was dried over Na₂SO₄ and concentrated.
Column Chromatography:
Approximately 50 mL of silica was packed into a column with 30% ether in hexanes as the solvent. The residue from workup was dissolved in minimal amount of dichloromethane and loaded onto the column. After an initial elution of 20 fractions (13 x 100 test tubes) with 30% ether in hexanes as the solvent, the eluting mixture was switched to 40% ether in hexanes for 20 fractions, followed by 50% ether in hexanes. Fractions 47-60 were concentrated to yield 78.2 mg of the oxazoline acetamide as a white solid (31%).

\[
\text{RF} = 0.4 \text{ with 1:1 ethyl acetate:hexanes; mp: 69-72 °C; } [\alpha]_{D}^{20} = 26.0^\circ \text{ (c = 0.32, CHCl}_3); \text{ IR (KBr) } 3413, 3060, 3029, 2959, 1662, 1533, 1495, 1448, 1185, 1043, 749, 701 \text{ cm}^{-1}; \text{ }^{1}H \text{ NMR (300 MHz, CD}_2\text{Cl}_2, 25 \text{ °C) } \delta 3.06 \text{ (dd, } J = 7.5 \text{ Hz, } J = 14.0 \text{ Hz, 1H), 3.17 (s, 1H), 3.20 (dd, } J = 5.9 \text{ Hz, } J = 14.0 \text{ Hz, 1H), 4.22 (d, } J = 9.5 \text{ Hz, 1H), 4.24 (d, } J = 7.2 \text{ Hz, 1H), 4.45 (dd, } J = 14.4 \text{ Hz, } J = 42.6 \text{ Hz, 1H), 4.61 (dd, } J = 14.4 \text{ Hz, } J = 42.8 \text{ Hz, 1H), 4.73 (dd, } J = 6.6 \text{ Hz, } J = 6.6 \text{ Hz, } J = 6.6 \text{ Hz, 1H), 5.26 (dd, } J = 7.3 \text{ Hz, } J = 9.5 \text{ Hz, 1H), 6.62 (br d, } J = 4.6 \text{ Hz, 1H), 7.16-7.36 (m, 11H), 7.43-7.50 (m, 4H); }^{13}C \text{ NMR (75 MHz, CD}_2\text{Cl}_2, 25 \text{ °C) } \delta 37.9, 49.4, 70.4, 73.2, 78.7, 80.5 \text{ (d, } J = 173 \text{ Hz), 126.0, 126.5, 127.1, 127.2, 127.6, 128.3, 128.7, 129.0, 129.6, 136.1, 144.4, 146.6, 168.1, 168.4 \text{ (d, } J = 18 \text{ Hz); MS (ES, 2:5 CHCl}_3:MeOH) m/z (M+H)^{+} \text{ calcd. 433.2, obsd. 433.1.}
\]

Hetero Diels-Alder Reaction:
To a vial with a septum cap containing 20.6 mg of 1 (0.044 mmol, 0.20 equiv.) under nitrogen, 500 μL of toluene was added followed by 45 μL of benzaldehyde (0.440 mmol, 2 equiv.). The vial was cooled to -40 °C and 50 mg of diene (0.220 mmol, 1 equiv.) dissolved in 500 μL of toluene was cannulated into it. An additional 200 μL of toluene was used for rinsing. After stirring for 48 h at -40 °C, the reaction mixture was cooled to -78 °C, diluted with 2 mL of CH₂Cl₂, and 31 μL of acetyl chloride (0.440 mmol, 2 equiv.) was added. After stirring for 30 minutes the contents are directly transferred to column for chromatography.

Column Chromatography:
Approximately 25 mL of silica was packed into a column with 5% ethyl acetate in hexanes as the solvent. After an initial elution of 15 fractions (13 x 100 test tubes), the eluting solvent was switched to 15% ethyl acetate in hexanes. Fractions 26-40 were concentrated to yield 26.1 mg of the pyranone as a yellow oil (67%). The enantiomeric excess was determined to be 91% by HPLC analysis (Chiralcel OD, Hexane/iPrOH = 90/10, flow rate: 1 mL/min.): t_major = 12.8 min (S), t_minor = 15.4 min (R).

Standard in situ FTIR protocol:
The ASI React IR 1000 with a diamond tipped probe was used to analyze reaction progress in situ. For each reaction, the probe was cleaned and a background spectrum was taken. Disappearance of benzaldehyde was observed by recording the absorbance at
maximum peak height of the carbonyl stretch (1706.1 cm⁻¹) which was related to a baseline point. Additionally, disappearance of diene was observed by recording the absorbance at maximum peak height (1648.2 cm⁻¹) which was related to a baseline point. The absorbances were converted to concentration units dividing by the constant (ε = 0.5862 for benzaldehyde, ε = 1.0885 for diene) relating absorbance to concentration determined by constructing calibration curves of the starting materials (Beer’s Law). The apparatus used was a 50 mL Schlenk flask with a side arm and a jacketed neck for probe insertion. An ice water bath was used for reactions performed at 0 ºC. A dry ice/acetonitrile bath was used for reactions performed at -45 ºC.

Each kinetic experiment was conducted similar to this example procedure. Standard solutions of catalyst, benzaldehyde, and diene were prepared. To a 10 mL Schlenk tube 107.5 mg of 1 (0.229 mmol) was added. The tube was flushed with nitrogen, and 3 mL of toluene was added. To a 25 mL volumetric flask fitted with a septum 6.35 mL of benzaldehyde (62.5 mmol) was added under a nitrogen atmosphere. Toluene was added to the 25 mL mark. The solution was stirred and cannulated into a Schlenk flask. To a 10 mL volumetric flask 2.5015 g of diene (11.000 mmol) was added, the flask was fitted with a septum and the flask was purged with nitrogen. Toluene was added to the 10 mL mark. The solution was stirred and cannulated into a Schlenk flask. The probe was equipped with a 50 mL Schlenk flask fitted with a stirbar, and the flask was flushed with nitrogen. To the apparatus are added 241 μL of 0.076 M solution of 1 (0.018 mmol), 400 μL of 2.50 M solution of benzaldehyde (1.000 mmol), and 192 μL of toluene. The reaction flask was placed in an ice bath and allowed to stir for 20 minutes before reaction collection was started on the IR. The IR was programmed to collect spectra every 30 seconds. After the second scan, 167 μL of 1.10 M solution of diene (0.183 mmol) was added and the reaction was allowed to proceed for 6 hours. Initial rates where determined after 5% conversion of diene.

|Catalyst] Dependence:|

\[
\text{[Catalyst]} = 0.076 \text{ M of 1,}\quad \text{[diene]} = 0.183 \text{ M,}\quad \text{[benzaldehyde]} = 0.366 \text{ M} \\
\begin{array}{ccc}
\text{mol\% 1} & \text{[1] (M)} & \text{initial rate (M/s)} \\
0.5 & 7.33E-4 & 1.20E-5 \\
1 & 1.88E-3 & 2.12E-5 \\
2 & 3.67E-3 & 3.35E-5 \\
5 & 7.33E-3 & 6.08E-5 \\
\end{array}
\]

Note: based on observation of uncatalyzed reaction at room temperature, all further kinetic measurements were performed at reduced temperatures.
[Benzaldehyde] Dependence:

\[
\text{TBSO} + \text{H}^+\text{Ph} \rightarrow \text{TBSO} \text{Ph} \text{O} + \text{diene}
\]

\[
\begin{array}{c|c}
\text{[benzaldehyde] (M)} & \text{initial rate (M/s)} \\
\hline
0.05 & 1.96E-5 \\
0.10 & 3.11E-5 \\
0.25 & 4.72E-5 \\
0.50 & 4.78E-5 \\
1.00 & 4.91E-5 \\
1.00 & 4.72E-5 \\
\end{array}
\]

\[
\begin{array}{c|c}
\text{[benzaldehyde] (M)} & \text{initial rate (M/s)} \\
\hline
0.00 & 0.20 & 0.40 & 0.60 & 0.80 & 1.00 & 1.20 \\
\end{array}
\]

\[
\begin{array}{c|c}
\text{initial rate/Ms}^1 & \\
\hline
0.0 & 2.0e-6 & 4.0e-6 & 6.0e-6 & 8.0e-6 & 1.0e-4 & 1.2e-4 & 1.4e-4 & 1.6e-4 \\
\end{array}
\]
[Diene] Dependence:

![Chemical structure](image)

<table>
<thead>
<tr>
<th>[diene] (M)</th>
<th>initial rate (M/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>6.54E-5</td>
</tr>
<tr>
<td>0.14</td>
<td>9.54E-5</td>
</tr>
<tr>
<td>0.18</td>
<td>1.30E-4</td>
</tr>
<tr>
<td>0.21</td>
<td>1.51E-4</td>
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</table>

Rate of reaction at -46 ºC:

![Chemical structure](image)

<table>
<thead>
<tr>
<th>catalyst</th>
<th>$pK_a$ of RCO$_2$H$^+$</th>
<th>rate (M/s) (1st run)</th>
<th>rate (M/s) (2nd run)</th>
<th>average rate (M/s)</th>
<th>log(rate)</th>
<th>error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.25</td>
<td>9.94E-5</td>
<td>6.98E-5</td>
<td>8.46E-5</td>
<td>-4.08</td>
<td>0.11</td>
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<tr>
<td>2</td>
<td>0.65</td>
<td>3.04E-5</td>
<td>1.92E-5</td>
<td>2.48E-5</td>
<td>-4.62</td>
<td>0.14</td>
</tr>
<tr>
<td>3</td>
<td>1.29</td>
<td>2.43E-5</td>
<td>1.53E-5</td>
<td>1.98E-5</td>
<td>-4.72</td>
<td>0.14</td>
</tr>
<tr>
<td>4</td>
<td>2.66</td>
<td>3.69E-6</td>
<td>3.52E-6</td>
<td>3.61E-6</td>
<td>-5.44</td>
<td>0.02</td>
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<tr>
<td>5</td>
<td>2.86</td>
<td>2.15E-6</td>
<td>3.47E-6</td>
<td>2.81E-6</td>
<td>-5.56</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Rates are average of initial rate of disappearance of benzaldehyde and initial rate of disappearance of diene.

**Determination of rate of formation of each enantiomer:**

![Graph](image)
Rate of formation of each enantiomer calculated as the absolute initial rate of product formation times the percent of each enantiomer of isolated product determined by HPLC.

**Derivation of rate law:**

\[
\begin{align*}
C + A & \xrightarrow{\kappa_1} C:A & D & \xrightarrow{\kappa_2} P
\end{align*}
\]

assuming the second step is rate determining:

\[
v = \frac{d[P]}{dt} = k_2[C : A][D]
\]

\[
[C] = [C]_r - [C : A] \quad \text{where} \quad [C]_r \quad \text{is the total concentration of catalyst.}
\]

Using the steady state approximation:

\[
\frac{d[C : A]}{dt} = k_1([C]_r - [C : A])[A] - k_{-1}[C : A] - k_2[C : A][D] = 0
\]

\[
k_1[C]_r[A] = [C : A](k_1[A] + k_{-1} + k_2[D])
\]

\[
[C : A] = \frac{k_1[C]_r[A]}{k_1[A] + k_{-1} + k_2[D]}
\]

\[
v = \frac{d[P]}{dt} = \frac{k_2[C]_r[A][D]}{k_1[A] + k_{-1} + k_2[D]} \quad \text{or} \quad v = \frac{d[P]}{dt} = \frac{k_2[C]_r[A][D]}{[A] + \frac{k_{-1} + k_2[D]}{k_1}}
\]
References:


(7) pK$_a$ values are for the carboxylic acid measured in water and were extracted from the table at http://daecr1.harvard.edu/pKa/pka.html.