Enantioselective Claisen Rearrangement with a Hydrogen-Bond Donor Catalyst

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Supporting Information

1. General Information

General Procedure. Unless specified otherwise, all reactions were performed under a nitrogen atmosphere in a flame-dried round-bottom flask sealed with a rubber septum. Air- and moisture-sensitive liquids were transferred using stainless steal syringes or cannulae. Flash chromatrography was performed using silica gel 60 (230-300 mesh) from EM science.

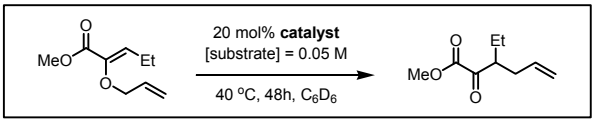
Materials. Commercial reagents were purchased from Sigma Aldrich, VWR, and Acros and used as received. Oxygen- and moisture-free diethyl ether, tetrahydrofuran, dichloromethane, dimethylformamide, methanol, and toluene were obtained from a Glass Contour solvent purification system consisting of columns packed with alumina, Q5 reactant, and molecular sieves as appropriate to the solvent. Commercially available HPLC grade hexanes and anhydrous dimethylsulfoxide were used without purification. Et_3N was freshly distilled over CaH_2 prior to use. 1,2-*trans*-diaminocyclohexane,[1] Cbz-NCS,[2] sodium BArF,[3] and diazomethane[4] were prepared according to procedures found in the literature.

Instrumentation. Proton nuclear magnetic resonance (^{1}HNMR) spectra and carbon nuclear magnetic resonance (^{13}CNMR) spectra were recorded on a Varian Mercury-400 (400 MHz) or Inova-500 (500 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak ($CHCl_3$: δ7.26, CD_3OD: δ3.31). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ77.16, CD_3OD: δ49.00). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), and coupling constants in Hertz (Hz). The mass spectroscopic data were obtained at the Harvard University mass spectrometry facility using an Agilent 6120 Quadrupole LC/MS instrument. Infrared (IR) spectra were obtained using a Mattson Galaxy Series FTIR 3000 spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm–1), intensity of absorption (s = strong, m = medium, w = weak).

Abbreviations used: ee = enantiomeric excess, GC = gas chromatography, HPLC = high-performance liquid chromatography, TLC = thin-layer chromatography, BArF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, THF = tetrahydrofuran, DMSO = dimethylsulfoxide, Cbz = benzyloxycarbonyl, Ms = methanesulfonyl, KHMDS = potassium bis(trimethylsilyl)amide, EDC = 1-(3-(dimethyl-amino)propyl)-3-ethyl-carbodiimide hydrochloride

2. Reaction and Catalyst Optimization

Screen of Hydrogen-Bond Donors



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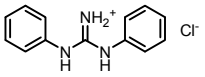
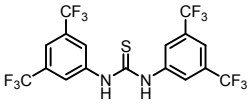


11% Conversion



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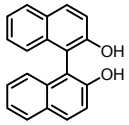

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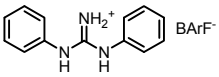

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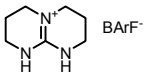

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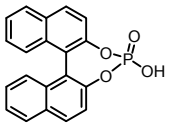
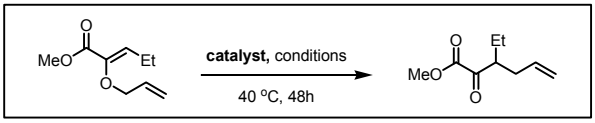
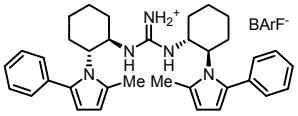


12% Conversion

Optimization of Reaction Parameters

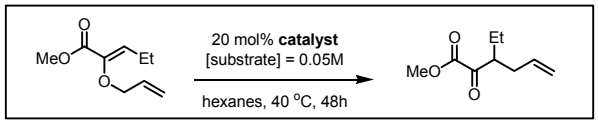


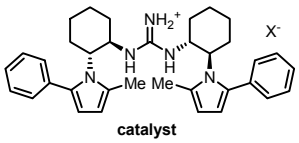


catalyst

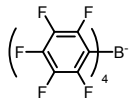
catalyst Loading	concentration	solvent	conversion	ee
0 mol%	0.05 M	hexane	6%	-
5 mol%	0.05 M	hexane	20%	+ 42%
10 mol%	0.05 M	hexane	32%	+ 48%
20 mol%	**0.05 M**	**hexane**	**66%**	**+ 58%**
50 mol%	0.05 M	hexane	94%	+ 63%
20 mol%	neat	hexane	73%	+ 23%
20 mol%	1.0 M	hexane	69%	+ 39%
20 mol%	0.5 M	hexane	71%	+ 47%
20 mol%	0.025 M	hexane	50%	+ 55%
20 mol%	0.05 M	pentane	50%	+ 56%
20 mol%	0.05 M	heptane	60%	+ 53%
20 mol%	0.05 M	cyclohexane	58%	+ 55%
20 mol%	0.05 M	dichloromethane	52%	+ 40%
20 mol%	0.05 M	1,2-dichloroethane	48%	+ 37%
20 mol%	0.05 M	chloroform	46%	+ 30%
20 mol%	0.05 M	benzene	50%	+ 46%
20 mol%	0.05 M	toluene	49%	+ 47%
20 mol%	0.05 M	trifluorotoluene	53%	+ 49%
20 mol%	0.05 M	TBME	13%	N.D.

Counterion Screen

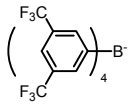




X^- : Cl^-	6% Conversion
BF_4^-	8% Conversion
SbF_6^-	8% Conversion
$[(CF_3)_3CO]_4Al^-$	8% Conversion

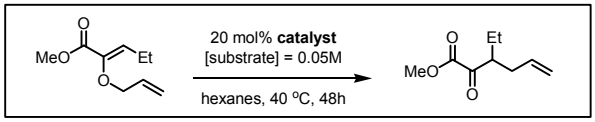


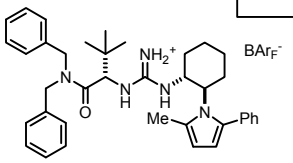
7% Conversion



66% Conversion (58% ee)

Screen of Chiral Guanidinium BArF Catalysts





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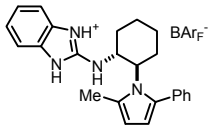
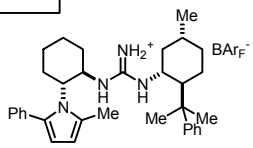
+ 36% ee



66% Conversion
+ 10% ee



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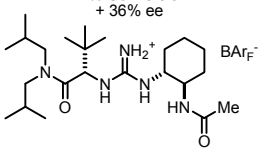

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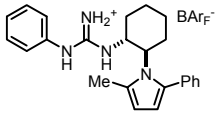

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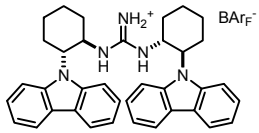

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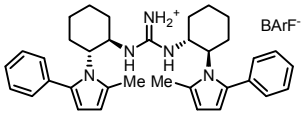

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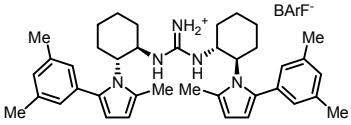

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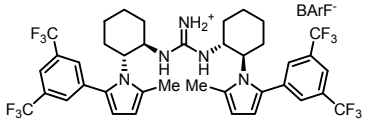

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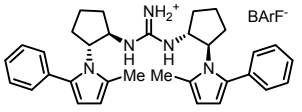

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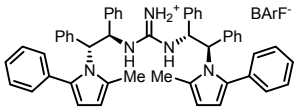

33% Conversion
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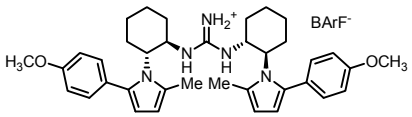
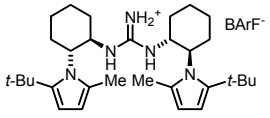


54% Conversion
+ 61% ee



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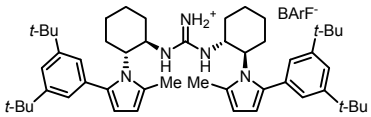

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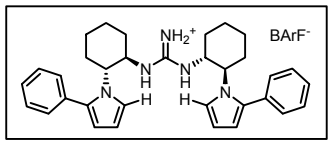

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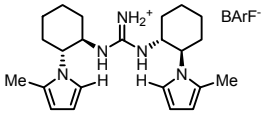

43% Conversion
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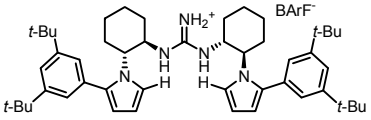
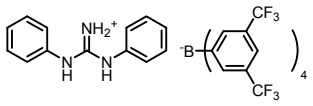


73% Conversion
+ 73% ee

Conversions measured by ^{1}HNMR integration. Enantiomeric excesses determined by chiral GC (γ-TA, 80 °C, t_r(major) = 23.3 min, t_r(minor) = 25.9 min).

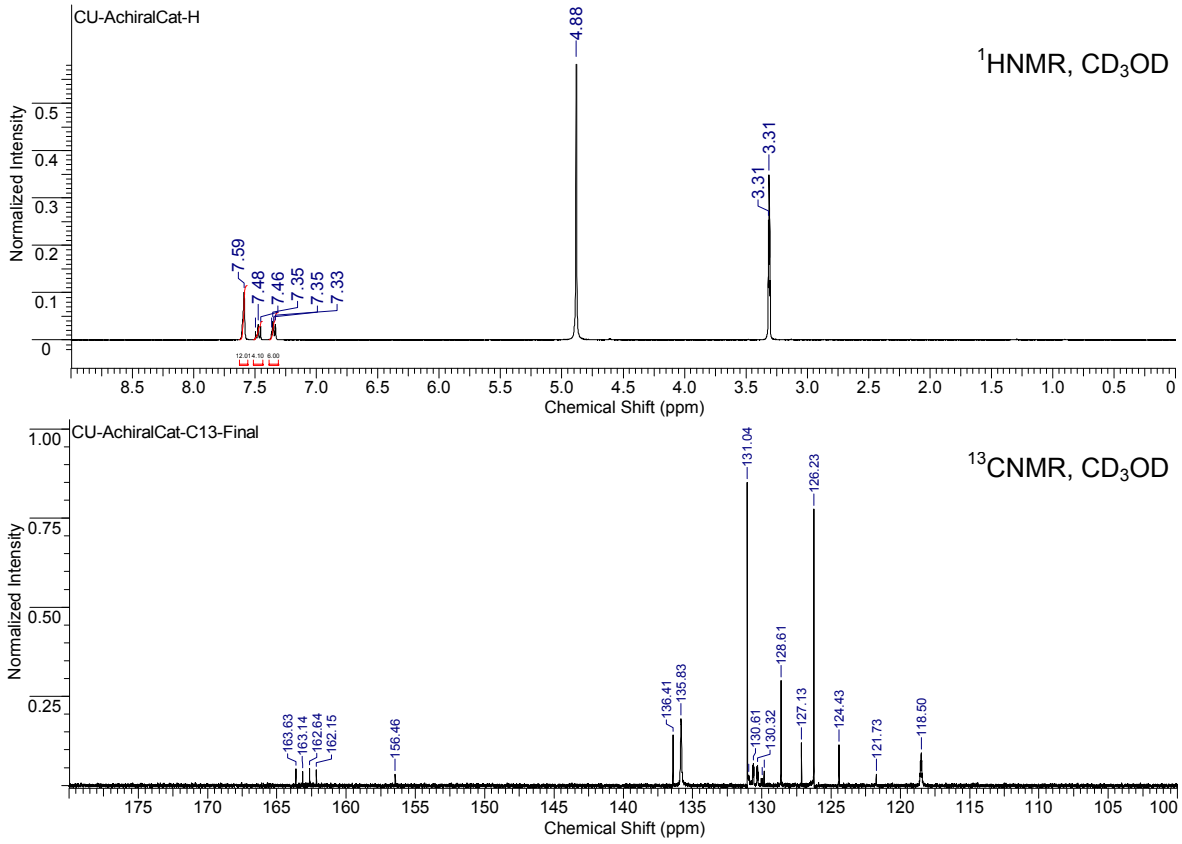
3. Catalyst Preparation and Characterization Data

Preparation of Achiral Guanidinium Catalyst 1

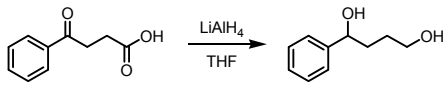


1

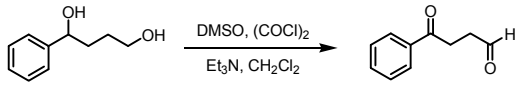
N,N'-diphenylguanidine (422.5 mg, 2.0 mmol, 1.0 eq) was suspended in 20 mL of Et_2O. 1M HCl in Et_2O (4.0 mL, 4.0 mmol, 2.0 eq) was added dropwise with stirring at room temperature. The solvent was removed under reduced pressure, and the residue was taken up in 10 mL of CH_2Cl_2. NaBArF (1.7724 g, 2.0 mmol, 1.0 eq) was added in one portion, and the mixture was stirred for 15 min at room temperature. The precipitated sodium chloride was removed by filtration through a celite plug (eluting with CH_2Cl_2), and the filtrate was concentrated. The crude product was purified by flash chromatography to remove any trace amounts of residual starting materials (eluting with a solvent mixture of 4% MeOH in CH_2Cl_2). The product obtained after column chromatography was dissolved in 2 mL of benzene, frozen at -78 ^oC, and placed under vacuum to remove the benzene, yielding a white solid. ^{1}HNMR (400 MHz, CD_3OD): δ7.59 (12H, m), 7.48 (4H, t, J = 7.9 Hz), 7.35 (6H, m); $^{13}C\{^1H\}$NMR (100 MHz, CD_3OD): δ162.9 (q, $^1J_{B-C}$ = 49.6 Hz), 156.5, 136.4, 135.8, 131.1, 130.5 (q, $^2J_{C-F}$ = 31.8 Hz), 128.6, 125.8 (q, $^1J_{C-F}$ = 270.0 Hz), 118.5; ^{11}BNMR (96 MHz, CD_3OD): δ-6.71 (s); ^{19}FNMR (282 MHz, CD_3OD): δ-64.7 (s); HRMS (ESI) $[M\text{-BArF}]^+$ calculated for $C_{45}H_{26}BF_{24}N_3$: 212.11822, found: 212.11872; FTIR (neat, cm^{-1}): 3500 (w), 3424 (w), 3400 (w), 1628 (m), 1590 (m), 1356 (s), 1278 (s), 1122 (s).



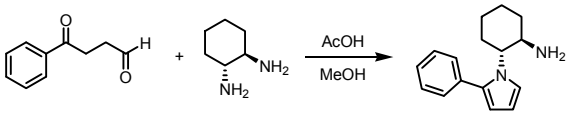
Preparation of Guanidinium Catalyst 2



Reduction. $LiAlH_4$ (3.036 g, 80.0 mmol, 4.0 eq) was suspended in 40 mL of THF, and the mixture was cooled to 0 °C. Benzoylpropionic acid (3.5638 g, 20.0 mmol, 1.0 eq) in 50 mL of THF was added dropwise. The reaction mixture was stirred overnight, allowing to warm to room temperature. After 24 h, the reaction mixture was cooled to 0 °C and quenched by successive dropwise addition of 3 mL H_2O, 3 mL 15% NaOH (aq), and 9 mL H_2O. After stirring at room temperature for 1 h, $MgSO_4$ was added, and the mixture was filtered through a plug of celite (washing with THF). The filtrate was concentrated under reduced pressure to give a clear oil that solidified upon standing. 2.77 g of a white solid (83% yield) was isolated and carried forward without purification.

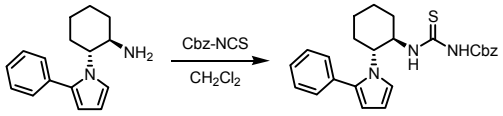


Swern Oxidation. Oxalyl chloride (6.44 mL, 73.81 mmol, 4.0 eq) was added dropwise to a stirred solution of DMSO (7.79 mL, 110.72 mmol, 6.0 eq) in 200 mL of CH_2Cl_2 cooled to -78 °C. After stirring at -78 °C for 10 min, the diol (3.0672 g, 18.45 mmol, 1.0 eq) in 100 mL of CH_2Cl_2 was added dropwise. Stirring was continued at -78 °C for 10 min. Et_3N (25.7 mL, 184.53 mmol, 10.0 eq) was added, and the reaction mixture was allowed to warm to room temperature. The reaction solution was diluted with 400 mL of Et_2O and poured into a separatory funnel. The organic phase was washed successively with 3 x 200 mL of water and 200 mL of brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with a solvent gradient of 4:1 to 2:1 hexane/EtOAc, to yield 2.6753 g of a clear oil (89% yield). ^{1}HNMR (500 MHz, $CDCl_3$): δ9.91 (1H, s), 7.99 (2H, d, J = 8.2 Hz), 7.57 (1H, t, J = 7.6 Hz), 7.48 (2H, t, J = 7.9 Hz), 3.33 (2H, t, J = 6.4 Hz), 2.94 (2H, t, J = 6.2 Hz); ^{13}C{^{1}H }NMR (100 MHz, $CDCl_3$): δ200.8, 197.9, 136.6, 133.5, 128.8, 128.2, 37.8, 31.2.

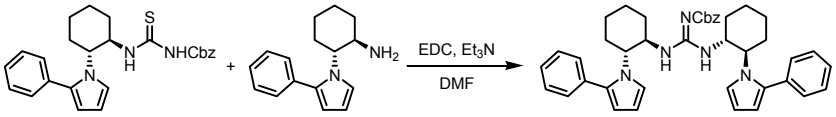


Paal-Knorr Pyrrole Synthesis. (*R,R*)-1,2-*trans*-diaminocyclohexane[1] (2.2603 g, 19.79 mmol, 1.2 eq) was added to a solution of the keto-aldehyde (2.6753 g, 16.49 mmol, 1.0 eq) in 80 mL of MeOH. The reaction flask was sealed with a rubber septum, evacuated, and back-filled with N_2 three times. Acetic acid (1.133 mL, 19.79 mmol, 1.2 eq) was added, and the reaction was stirred at 50 °C for 14 h. The reaction mixture was cooled to room temperature and poured into 400 mL of 15% NaOH (aq). The product was extracted with 4 x 200 mL of CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography, eluting with 5% MeOH in CH_2Cl_2 to yield 2.1128 g of a pale brown oil (53% yield). ^{1}HNMR (500 MHz, $CDCl_3$): δ7.30–7.45 (5H, m), 6.88 (1H, m), 6.31 (1H, m), 6.17 (1H,

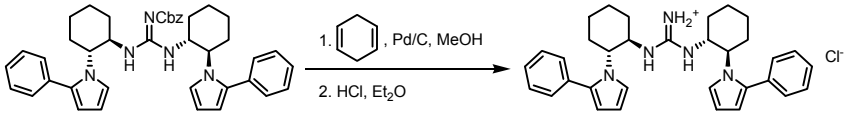
m), 3.72 (1H, m), 2.95 (1H, dt, J = 4.1, 10.5 Hz), 2.08 (1H, br d, J = 13.3 Hz), 1.97 (1H, br d, J = 11.9 Hz), 1.82 (1H, br d, J = 13.3 Hz), 1.68–1.75 (1H, m), 1.25–1.42 (2H, m), 1.11 (1H, m), $^{13}C\{^{1}H\}$NMR (125 MHz, CDCl3): δ135.9, 133.8, 129.5, 128.6, 127.0, 117.5, 109.1, 108.3, 63.0, 56.5, 34.8, 33.9, 25.8, 25.1.



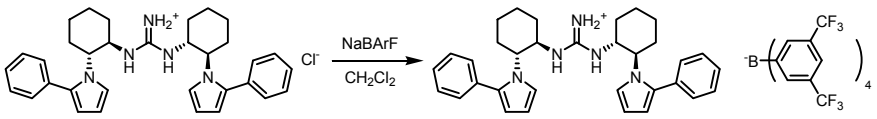
Thiourea Formation. The amine (1.0564 g, 4.40 mmol, 1.0 eq) was dissolved in 50 mL of CH_2Cl_2. Cbz-NCS[2] (~70 wt%, 1.215g, 4.40 mmol, 1.0 eq) was added dropwise at ambient temperature. After stirring for 15 min, the solvent was evaporated under reduced pressure. The oily residue was washed with 3 x 5 mL portions of hexanes to remove trace amounts of Cbz-NCS. Drying under vacuum gave in quantitative yield a light brown oil that was carried forward without purification. ^{1}HNMR (400 MHz, $CDCl_3$): δ9.32 (1H, d, J = 8.8 Hz), 7.78 (1H, s), 7.28–7.43 (10H, m), 6.94 (1H, m), 6.23 (1H, m), 6.09 (1H, m), 5.12 (2H, s), 4.72 (1H, m), 4.02 (1H, dt, J = 3.9, 11.3 Hz), 2.38 (1H, br d, J = 12.4 Hz), 2.16 (1H, br d, J = 13.5 Hz), 1.84–1.74 (3H, m), 1.32–1.48 (1H, m), 1.13–1 .30 (2H, m), $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ135.9, 133.8, 129.5, 128.6, 127.0, 117.5, 109.1, 108.3, 63.0, 56.5, 34.8, 33.9, 25.8, 25.1.



Guanidine Formation. The amine and thiourea were dissolved in 50 mL of DMF. Et_3N (3.07 mL, 22.0 mmol, 5.0 eq) and EDC (1.687 g, 8.80 mmol, 2.0 eq) were added, and the reaction was stirred at 50 ^{o}C. After 14 h, the reaction mixture was diluted with 250 mL of EtOAc and successively washed with 3 x 200mL 1M HCl (aq), sat $NaHCO_3$ (aq), and brine. The organic phase was dried over Na_2SO_4 and concentrated to yield 2.5724 g of a pale brown solid (91% yield), which was carried forward without purification.

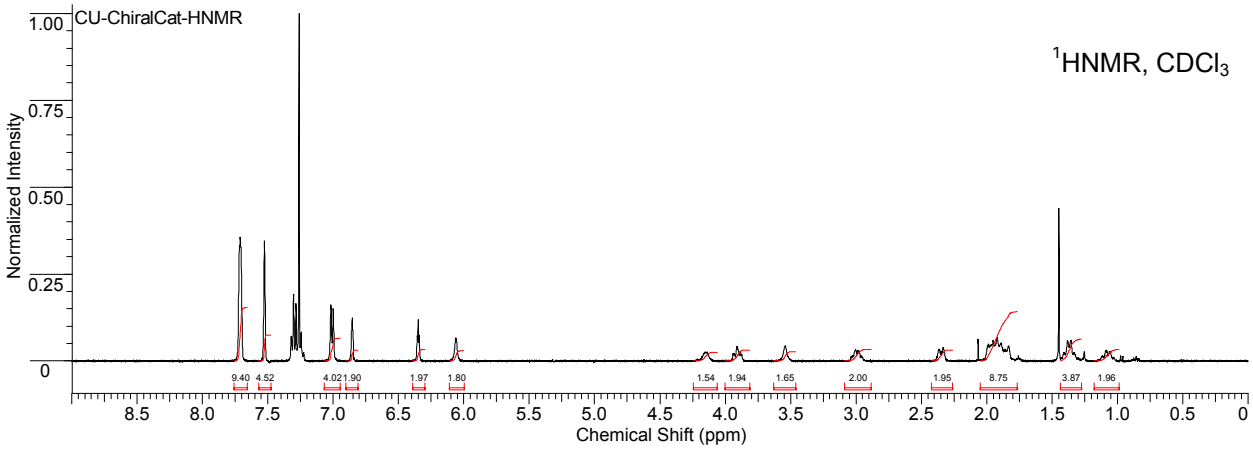


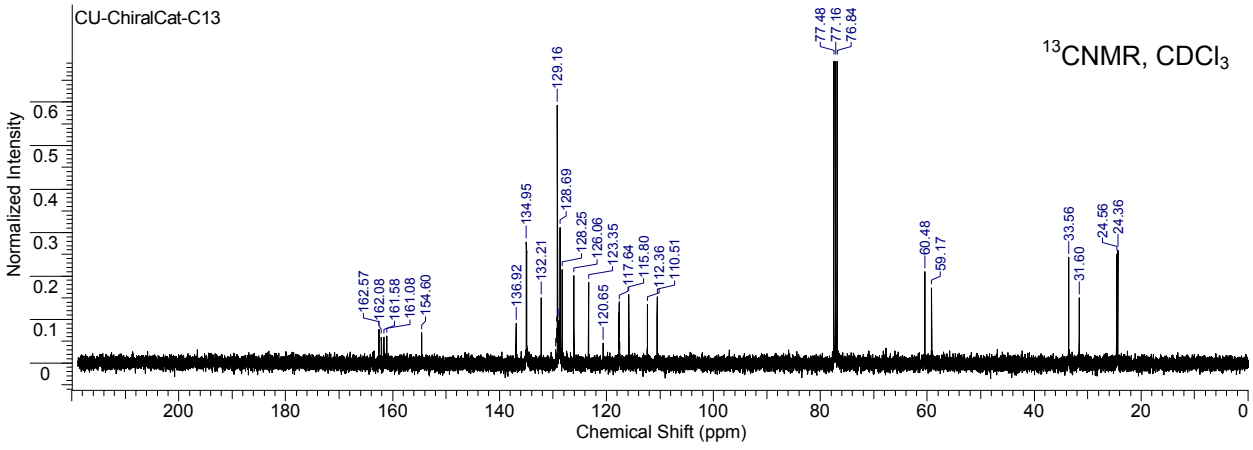
Transfer Hydrogenolysis. The Cbz-protected guanidine (2.5724 g, 4.02 mmol, 1.0 eq) was suspended in 160 mL of MeOH. The reaction flask was evacuated and back-filled with N_2 three times, and 10 wt% Pd/C (5.1448 g, 200 wt% relative to substrate) was added. The reaction flask was placed in an ambient temperature water bath, and 1,4-cyclohexadiene (7.6 mL, 80.41 mmol, 20.0 eq) was added dropwise. The reaction was stirred at room temperature and monitored by TLC (after the reaction was complete only baseline material remained in 1:1 hexanes/EtOAc). After 24 h, the reaction mixture was filtered through a celite plug (washing with MeOH), and the filtrate was cooled to -78 ^{o}C. 1M HCl in Et_2O (10 mL, 10.0 mmol, 2.5 eq) was added dropwise with stirring. The solution was allowed to warm to room temperature, and the solvent and excess HCl were removed under reduced pressure to yield 1.7317 g of pale red solid (79% yield).



2

Counterion Metathesis. The guanidinium chloride (1.7317 g, 3.194 mmol, 1.0 eq) was dissolved in 60 mL of CH_2Cl_2. $NaBArF^3$ (3.194 g, 3.194 mmol, 1.0 eq) was added, and the reaction was stirred at room temperature for 15 min during which time sodium chloride precipitated from solution. The mixture was filtered through a plug of celite (washing with CH_2Cl_2), and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 4% MeOH in CH_2Cl_2, to yield 3.559 g of an off-white solid (81% yield). $[\alpha]_D^{27}$ +33.7° (c = 1.0, $CHCl_3$); ^{1}HNMR (500 MHz, $CDCl_3$): δ7.72 (8H, s), 7.53 (4H, s), 7.30 (4H, t, J = 7.3 Hz), 7.25 (2H, t, 6.8 Hz), 7.00 (4H, d, J = 7.3 Hz), 6.86 (2H, s), 6.35 (2H, t, J = 2.9 Hz), 6.06 (2H, br s), 4.15 (2H, br s), 3.91 (2H, t, J = 9.5 Hz), 3.55 (2H, br s), 3.00 (2H, br m), 2.35 (2H, br d, J = 13.2 Hz), 1.99–1.84 (8H, m), 2.37 (4H, m), 1.07 (2H, br q, J = 12.0 Hz); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ161.8 (q, $^1J_{B-C}$ = 49.3 Hz), 154.6, 136.9, 135.0, 132.2, 129.2, 129.0 (q, $^2J_{C-F}$ = 30.0 Hz), 128.7, 128.3, 124.7 (q, $^1J_{C-F}$ = 270.5 Hz), 117.6, 115.8, 112.4 110.5, 60.5, 59.2, 33.6, 31.6, 24.6, 24.4; ^{11}BNMR (96 MHz, CDCl3): δ-6.56 (s); ^{19}FNMR (282 MHz, CDCl3): δ-62.67 (s); HRMS (ESI) $[M\text{-}BArF]^+$ calculated for $C_{65}H_{52}BF_{24}N_5$: 506.32782, found: 212.328528; FTIR (neat, cm^{-1}): 3379 (br), 2948 (w), 2869 (w), 1617 (m), 1355 (s), 1278 (s), 1125 (br).



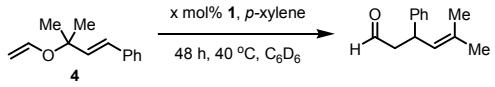


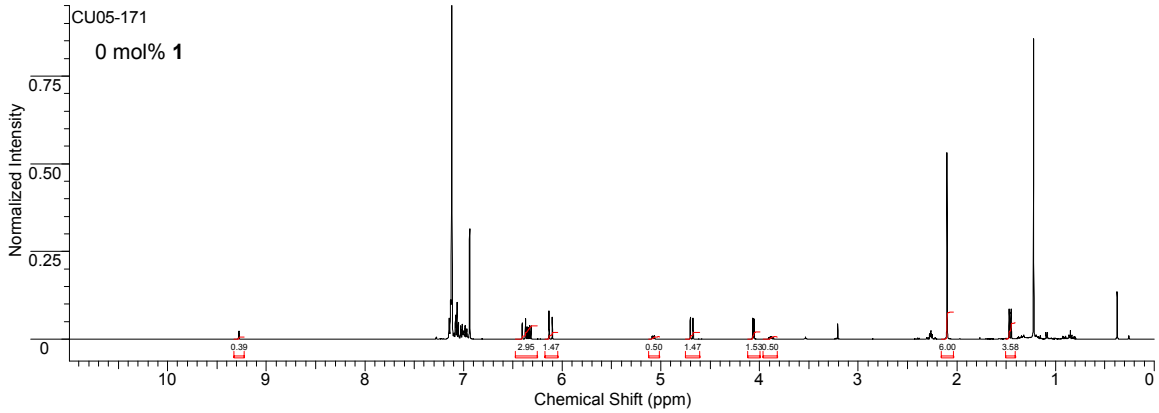
4. General Procedure and Data for the Achiral Claisen Rearrangement

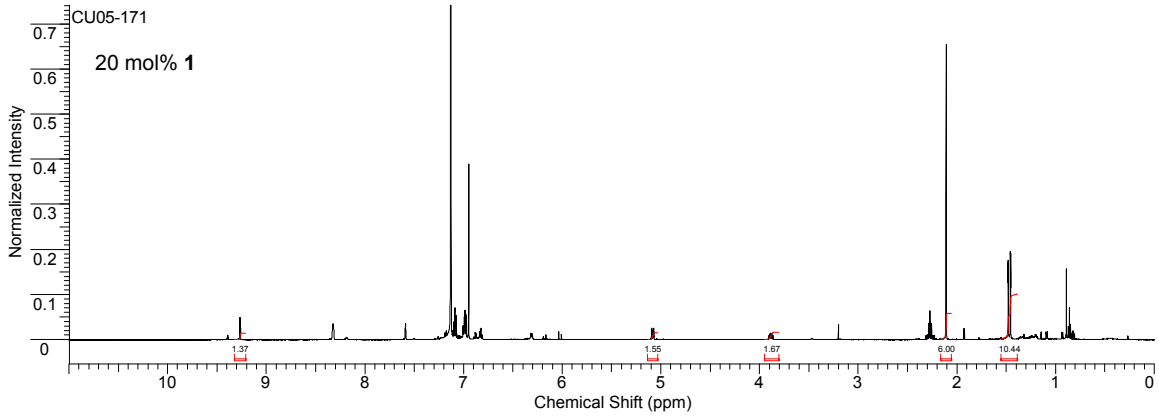
General Procedure for the achiral Claisen rearrangement

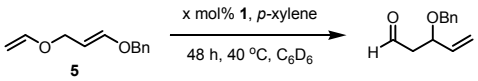
A stock solution of the Claisen substrate (0.2 M) and *p*-xylene as an internal standard in C_6D_6 was prepared. The initial relative concentration of the substrate to the internal standard was determined by ^{1}HNMR integration. The stock solution was either added to a vial containing 20 mol% of **1** or added to a vial without **1**, and stirred at the indicated temperature. After the specified amount of time, the crude reaction mixture was analyzed by ^{1}HNMR.

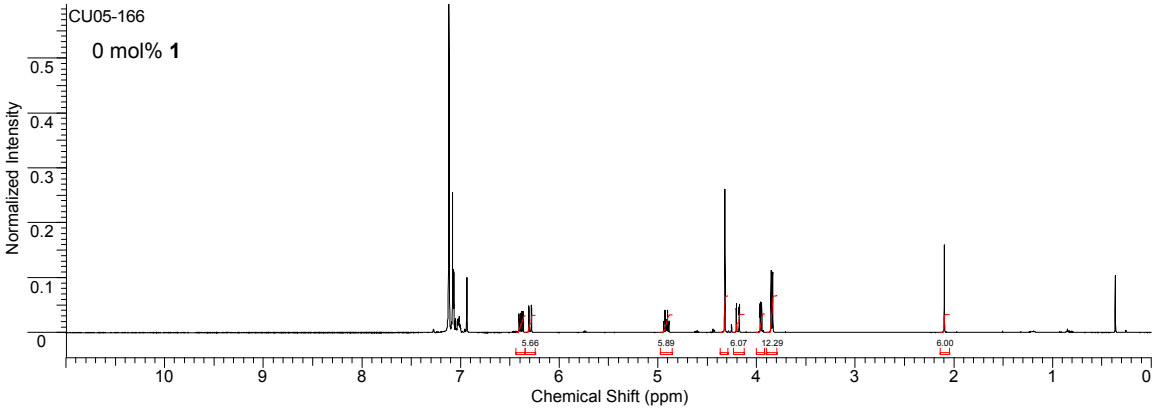
Data for the achiral Claisen rearrangement

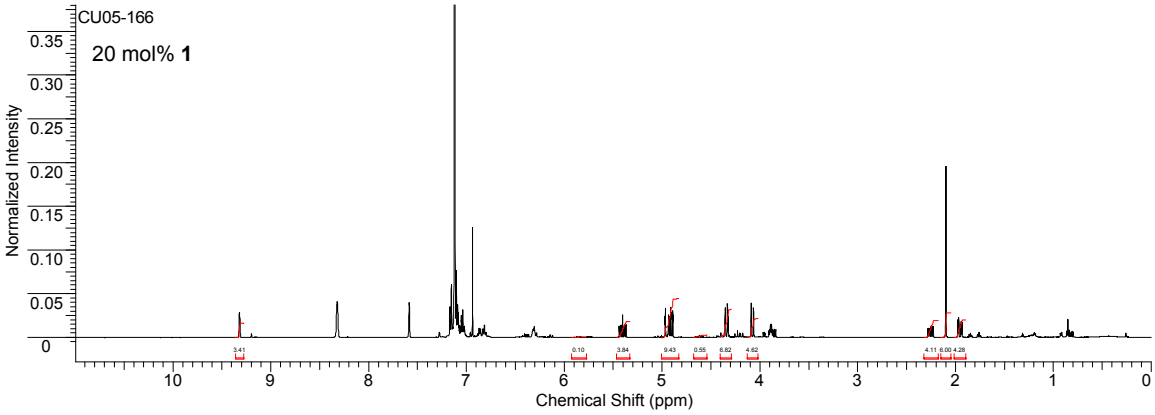


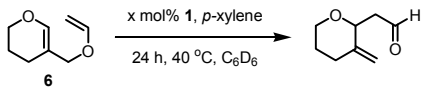


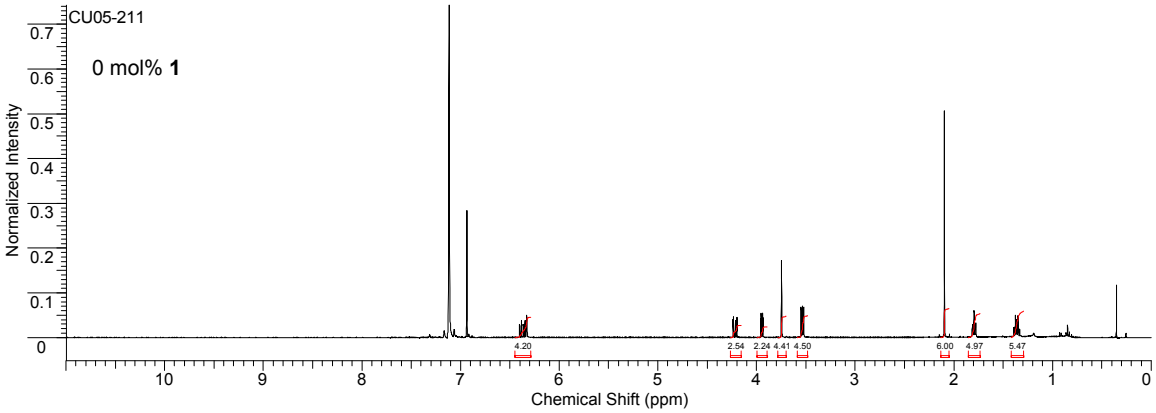


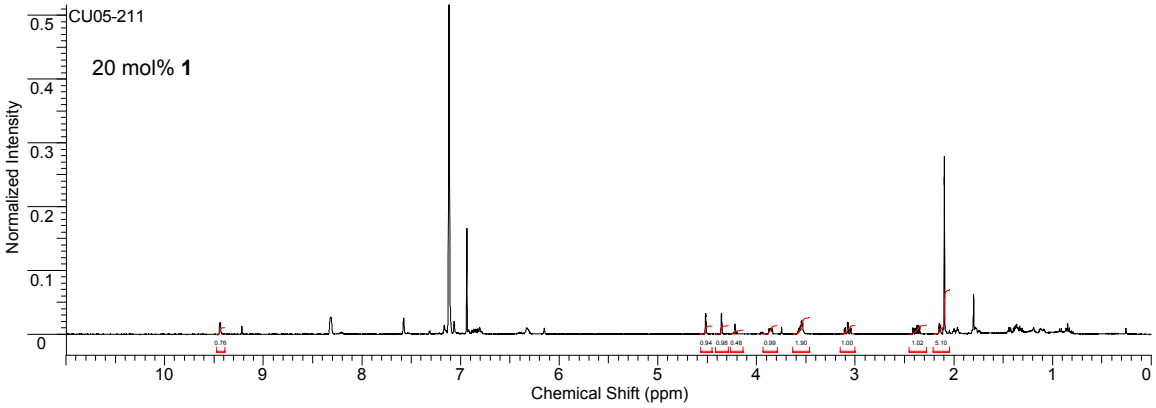

x mol% 1, p-xylene
48 h, 40 °C, C6D6
OBn
O
OBn
H
5

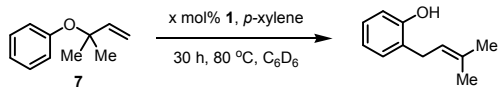

CU05-166
0 mol% 1
Normalized Intensity
Chemical Shift (ppm)
5.66
5.89
6.07
12.29
6.00


CU05-166
20 mol% 1
Normalized Intensity
Chemical Shift (ppm)

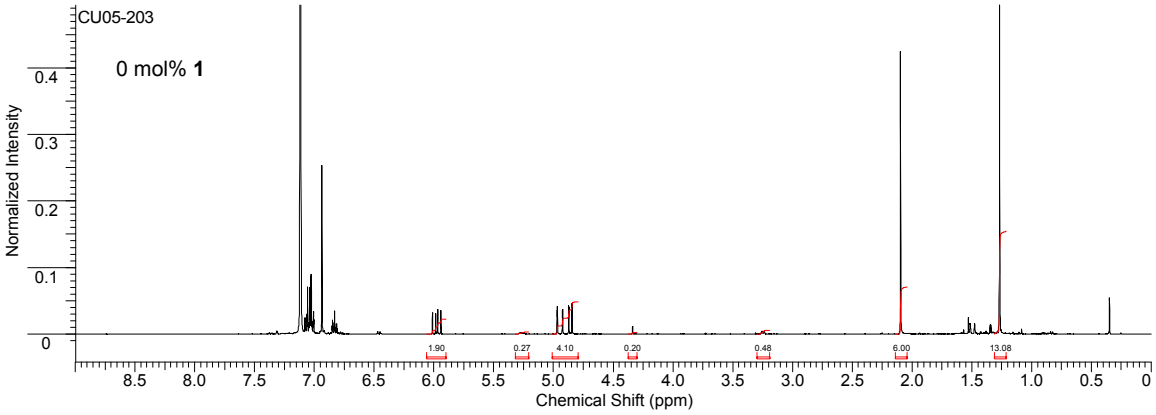

x mol% 1, p-xylene
24 h, 40 °C, C6D6
6

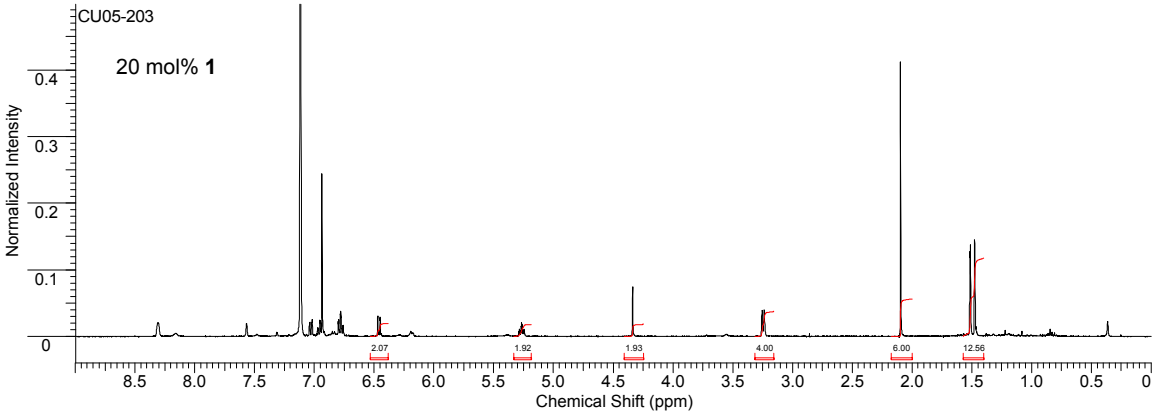

CU05-211
0 mol% 1
Normalized Intensity
Chemical Shift (ppm)

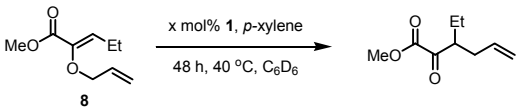

CU05-211
20 mol% 1
Normalized Intensity
Chemical Shift (ppm)

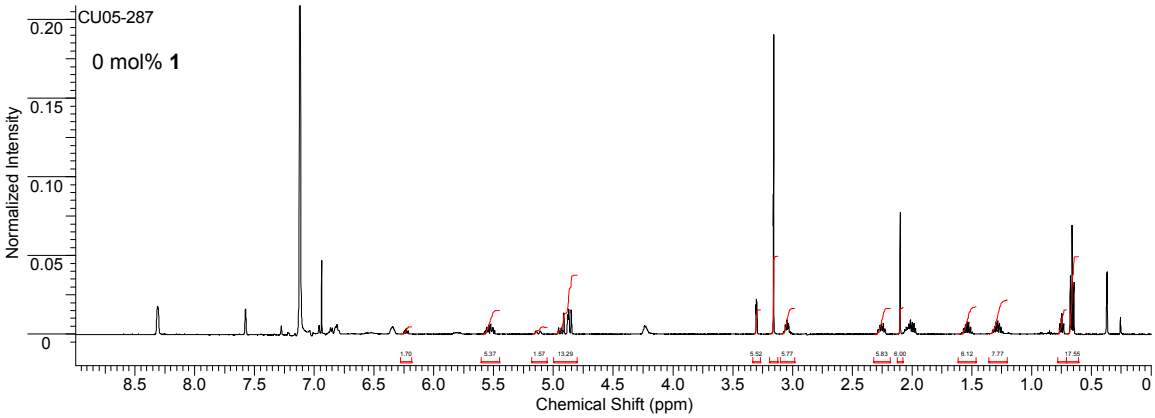

x mol% 1, p-xylene
30 h, 80 °C, C6D6
OH
Me
Me
O
Me
Me

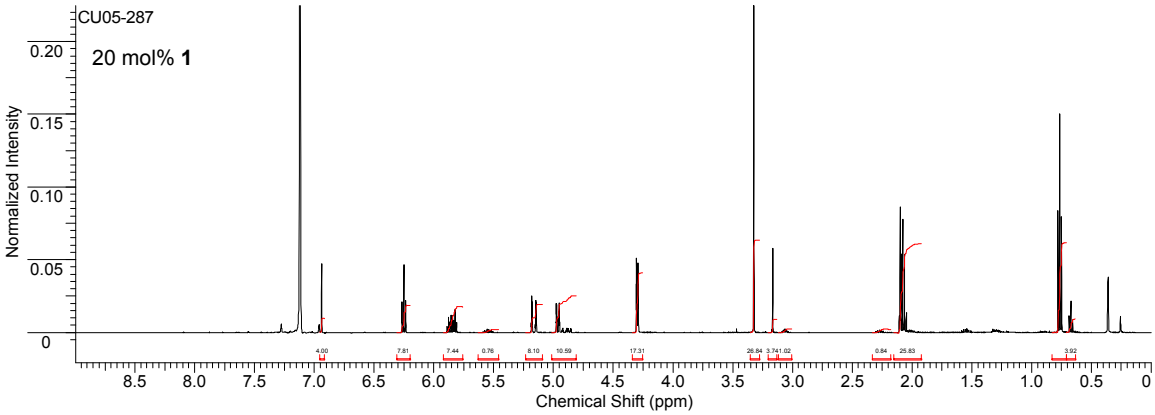
7


CU05-203
0 mol% 1
Normalized Intensity
Chemical Shift (ppm)
1.90
0.27
4.10
0.20
0.48
6.00
13.08


CU05-203
20 mol% 1
Normalized Intensity
Chemical Shift (ppm)
2.07
1.92
1.93
4.00
6.00
12.56

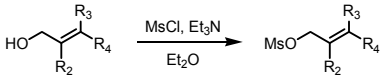

MeO
Et
O
O
8
x mol% 1, p-xylene
48 h, 40 °C, C6D6
MeO
Et
O
O


CU05-287
0 mol% 1
Normalized Intensity
0.20
0.15
0.10
0.05
0
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

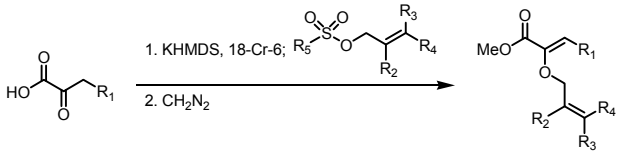

CU05-287
20 mol% 1
Normalized Intensity
0.20
0.15
0.10
0.05
0
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

5. Substrate Preparation and Characterization Data

General Procedure for Substrate Preparation

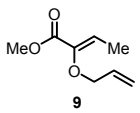


Allyl mesylates were generally prepared by dropwise addition of 1.0 eq of MsCl to a solution of 1.0 eq of the corresponding allyl alcohol and 1.0 eq of Et_3N in Et_2O (1.0 M reaction concentration) at -78 ^oC. Following addition, the reaction was warmed to 0 ^oC in an ice bath and stirred at that temperature for 15 min. The resulting slurry was filtered through a glass fritted funnel. Some of the allyl mesylates (crotyl, prenyl, and geranyl mesylate in particular) were found to decompose rapidly at room temperature when concentrated. These compounds should be handled and stored as dilute solutions in Et_2O at –78 ^oC. These allyl mesylate stock solutions could be directly added to the enolate solutions in the subsequent O-alkylation step without need for solvent removal or swapping.



18-Crown-6 (2.4 eq) was dissolved in THF (10 mL/mmol of α-ketoacid). The solution was cooled to -78 ^oC, and KHMDS solution (2.4 eq, 0.5 M in toluene) and α-ketoacid (1.0 eq) were successively added. α -ketoacids that were solids were added as a solution in THF (5 mL/mmol of α-ketoacid). After stirring at -78 ^oC for 1 h, the allyl sulfonate (1.4 eq) was added neat or as a stock solution in Et_2O. Stirring was continued at -78 ^oC for 2 h. The reaction mixture was quenched by dropwise addition of 1 M NaOH (aq) and allowed to warm to room temperature. The mixture was diluted with Et_2O and extracted with 4 x 1 M NaOH (aq). The combined aqueous phases were acidified to pH < 2.0 with 1 M HCl (aq) with cooling in an ice bath. The aqueous phase was extracted with 5 x CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4. The solvent was concentrated under reduced pressure, and the residue was taken up in Et_2O (20 mL/mmol of α-ketoacid). CH_2N_2[4] was added as a solution in Et_2O (approximately 1 M) until the yellow color persisted. N_2 was bubbled through the solution until the yellow color disappeared, and the remainder of the solvent was evaporated under reduced pressure. The product was purified by flash chromatography. Typically, CH_2Cl_2/hexanes and Et_2O/pentane solvent systems were effective in separating the desired products from any reaction byproducts.

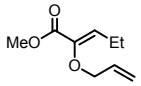
Substrate Characterization Data



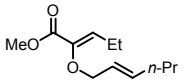
9

2-ketobutyric acid (102.1 mg, 1.0 mmol) was reacted with allyl tosylate (252 μL, 1.4 mmol) to afford 86.1 mg of the desired methyl ester as a clear oil (55% yield). ^{1}HNMR (400 MHz, $CDCl_3$): δ6.37 (1H, q, J = 7.1 Hz), 6.00 (H, ddt, J = 10.4, 17.0, 6.0 Hz), 5.33 (1H, d, J = 17.2

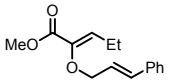
Hz), 5.22 (1H, d, J = 10.6 Hz), 4.33 (2H, d, J = 5.9 Hz), 3.77 (3H, s), 1.78 (3H, d, J = 7.0 Hz); $^{13}C\{^{1}H\}$NMR (100 MHz, CDCl3): δ164.5, 145.7, 133.9, 124.9, 118.3, 73.2, 52.0, 11.5; HRMS (ESI) $[M+Na]^+$ calculated for $C_8H_{12}O_3$: 179.06787, found: 179.06822; FTIR (neat, cm^{-1}): 2953 (w), 1726 (s), 1651 (m), 1438 (w), 1323 (m), 1267 (s), 1132 (m), 1080 (m), 1033 (m), 774 (w).



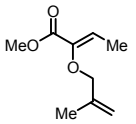
2-oxovaleric acid (105 μL, 1.0 mmol) was reacted with allyl tosylate (252 μL, 1.4 mmol) to afford 159.1 mg of the desired methyl ester as a clear oil (93% yield). ^{1}HNMR (500 MHz, $CDCl_3$): δ6.29 (1H, t, J = 7.6 Hz), 5.99 (1H, ddt, J = 17.1, 10.3, 5.9 Hz), 5.32 (1H, d, J = 17.1 Hz), 5.22 (1H, d, J = 10.3 Hz), 4.32 (2H, d, J = 5.9 Hz), 3.77 (3H, s), 2.25 (2H, apparent p, J = 7.6 Hz), 1.03 (3H, t, J = 7.6 Hz); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): d164.7, 144.1, 133.9, 131.6, 118.3, 73.4, 52.0, 19.3, 13.4; HRMS (ESI) $[M+Na]^+$ calculated for $C_9H_{14}O_3$: 193.08352, found: 193.08276; FTIR (neat, cm^{-1}): 2969 (w), 2953 (w), 1726 (s), 1650 (w), 1368 (w), 1302 (m), 1246 (m), 1144 (m), 1090 (m), 996 (w).



2-oxovaleric acid acid (105 μL, 1.0 mmol) was reacted with 2-hexenyl mesylate (1.4 mmol) to afford 99.9 mg of the desired methyl ester as a clear oil (47% yield). ^{1}HNMR (400 MHz, $CDCl_3$): δ6.26 (1H, t, J = 7.7 Hz), 5.67 (2H, m), 4.25 (2H, d, J = 6.6 Hz), 3.75 (3H, s), 2.23 (2H, apparent p, J = 7.6 Hz), 2.02 (2H, apparent q, J = 6.7 Hz), 1.39 (2H, apparent sextet, J = 7.3 Hz), 1.01 (3H, t, J = 7.5 Hz), 0.89 (3H, t, J = 7.3 Hz); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ164.8, 144.1, 136.3, 131.6, 125.5, 73.3, 52.0, 34.5, 22.2, 19.4, 13.8, 13.4; HRMS (ESI) $[M+Na]^+$ calculated for $C_{12}H_{20}O_3$: 235.13047, found: 235.12964; FTIR (neat, cm^{-1}): 2961 (m), 2934 (w), 2874 (w), 1728 (s), 1649 (w), 1436 (w), 1300 (m), 1273 (m), 1245 (m), 1144 (m), 1086 (m), 971 (w).

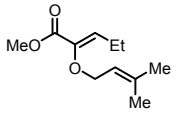


2-oxovaleric acid (105 μL, 1.0 mmol) was reacted with cinnamyl mesylate (1.4 mmol) to afford 127.6 mg of the desired methyl ester as a clear oil (56% yield). ^{1}HNMR (500 MHz, $CDCl_3$): δ7.40 (2H, d, J = 7.6 Hz), 7.32 (2H, t, J = 7.6 Hz), 7.25 (1H, t, J = 7.6 Hz), 6.64 (1H, d, J = 16.0 Hz), 6.30-6.39 (2H, m), 4.50 (2H, d, J = 6.4 Hz), 3.79 (3H, s), 2.29 (2H, p, J = 7.6 Hz), 1.03 (3H, t, J = 7.6 Hz). ; $^{13}C\{^{1}H\}$NMR (125 MHz, $CDCl_3$): δ164.7, 144.1, 136.6, 133.7, 131.8, 128.7, 128.0, 126.7, 124.9, 73.1, 52.0, 19.4, 13.4; LRMS (ESI): 269.1 (100%) $[M+Na]^+$; FTIR (neat, cm^{-1}): 2968 (m), 2874 (w), 1724 (s), 1651 (m), 1435 (m), 1343 (m), 1301 (m), 1273 (m), 1246 (s), 1145 (s), 1081 (m), 967 (m), 777 (m), 746 (m), 692 (m).

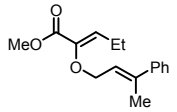


2-ketobutyric acid (102.1 mg, 1.0 mmol) was reacted with 2-methallyl mesylate (1.4 mmol) to afford 67.2 mg of the desired methyl ester as a clear oil (39% yield). ^{1}HNMR (500 MHz, $CDCl_3$): δ6.33 (1H, q, J = 7.2 Hz), 5.04 (1H, s), 4.93 (1H, s), 4.22 (2H, s), 3.76 (3H, s), 1.83 (3H,

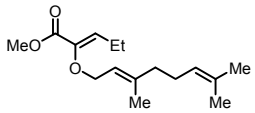
s), (3H, d, J = 6.9 Hz). ^{13}CNMR (125 MHz, $CDCl_3$): δ164.5, 145.8, 141.6, 124.3, 113.5, 76.0, 51.9, 19.8, 11.4. HRMS (ESI) $[M+Na]^+$ calculated for $C_9H_{14}O_3$: 193.08352, found: 193.08410; FTIR (neat, cm^{-1}): 2952 (w), 2919 (w), 1727 (s), 1655 (m), 1438 (w), 1325 (m), 1266 (s), 1134 (s), 1084 (m), 1033 (w), 772 (w).



2-oxovaleric acid (105 μL, 1.0 mmol) was reacted with prenyl mesylate (1.4 mmol) to afford 49.2 mg of the desired methyl ester as a clear oil (25% yield). ^{1}HNMR (500 MHz, $CDCl_3$): δ6.25 (1H, t, J = 7.8 Hz), 5.42 (1H, t, J = 7.3 Hz), 4.31 (2H, d, 7.3 Hz), 3.76 (3H, s), 2.24 (2H, p, J = 7.6 Hz), 1.75 (3H, s), 1.68 (3H, s), 1.01 (3H, t, 7.6 Hz); ^{13}C{^{1}H }NMR (125 MHz, $CDCl_3$): δ164.9, 144.2, 138.8, 131.5, 120.2, 68.7, 51.9, 25.9, 19.3, 18.1, 13.4; HRMS (ESI) $[M+Na]^+$ calculated for $C_{11}H_{18}O_3$: 221.11482, found: 221.11561; FTIR (neat, cm^{-1}): 2968 (m), 1727 (s), 1649 (w), 1436 (w), 1299 (m), 1272 (m), 1245 (m), 1144 (m), 1087 (m).



2-oxovaleric acid (105 μL, 1.0 mmol) was reacted with 3-phenyl-2-butenyl mesylate (1.4 mmol) to afford 62.9 mg of the desired methyl ester as a clear oil (24% yield). ^{1}HNMR (500 MHz, $CDCl_3$): δ7.41 (2H, d, J = 6.9 Hz), 7.33 (2H, t, 7.6 Hz), 7.27 (1H, t, 7.1 Hz), 6.31 (1H, t, J = 7.6 Hz), 6.00 (1H, t, J = 7.3 Hz), 4.56 (2H, d, J = 6.9 Hz), 3.79 (3H, s), 2.29 (2H, p, J = 7.6 Hz), 2.09 (3H, s), 1.03 (3H, t, 7.6 Hz); ^{13}C{^{1}H }NMR (125 MHz, $CDCl_3$): δ164.8, 144.2, 142.9, 138.8, 131.8, 128.4, 127.3, 126.0, 123.1, 69.1, 52.0, 19.4, 16.3, 13.4; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{20}O_3$: 283.13047, found: 283.13189; FTIR (neat, cm^{-1}): 2968 (m), 2874 (w), 1723 (s), 1648 (m), 1436 (m), 1346 (m), 1299 (m), 1272 (m), 1244 (s), 1144 (s), 1085 (s), 1037 (m), 758 (m), 695 (m).



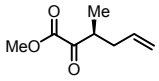
2-oxovaleric acid (105 μL, 1.0 mmol) was reacted with geranyl mesylate (1.4 mmol) to afford 83.7 mg of the desired methyl ester as a clear oil (31% yield). ^{1}HNMR (500 MHz, $CDCl_3$): δ6.26 (1H, t, J = 7.6 Hz), 5.42 (1H, t, J = 7.2 Hz), 5.09 (1H, t, J = 6.6 Hz), 4.34 (2H, d, J = 7.1 Hz), 3.76 (3H, s), 2.25 (2H, apparent p, J = 7.6 Hz), 2.02-2.11 (4H, m), 1.67 (6H, s), 1.60 (3H, s), 1.02 (3H, t, J = 7.6 Hz); ^{13}CNMR (125 MHz, $CDCl_3$): δ164.9, 144.2, 142.0, 131.8, 131.5, 124.0, 119.8, 68.7, 51.9, 39.7, 26.5, 25.8, 19.4, 17.8, 16.5, 13.4; HRMS $[M+Na]^+$ calculated for $C_{16}H_{26}O_3$: 289.17742, found: 289.17837; FTIR (neat, cm^{-1}): 2968 (m), 2931 (m), 2877 (w), 1727 (s), 1649 (w), 1436 (m), 1299 (m), 1279 (m), 1244 (s), 1144 (s), 1086 (s), 1039 (w).

6. General Procedure for the Asymmetric Claisen Rearrangement and Product Characterization

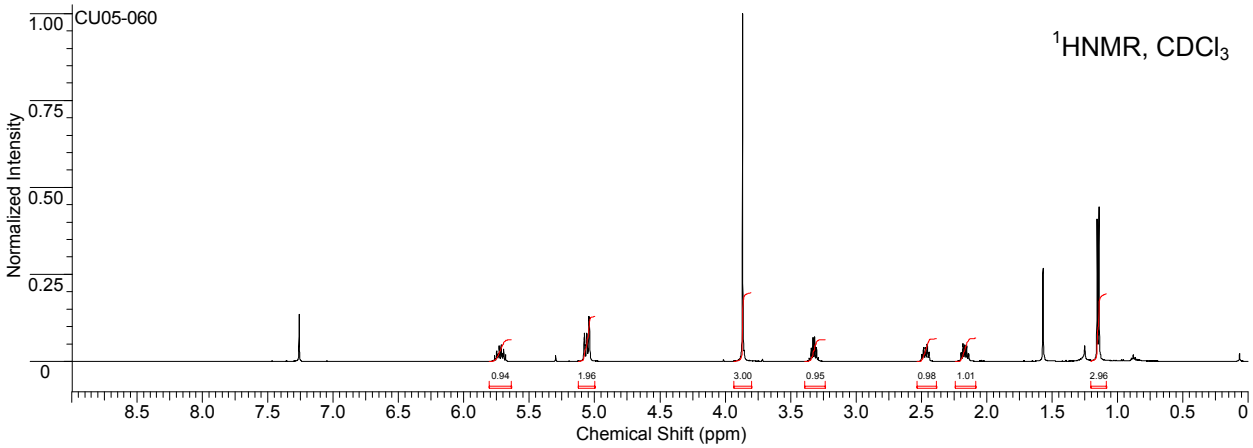
General Procedure for the Asymmetric Claisen Rearrangement

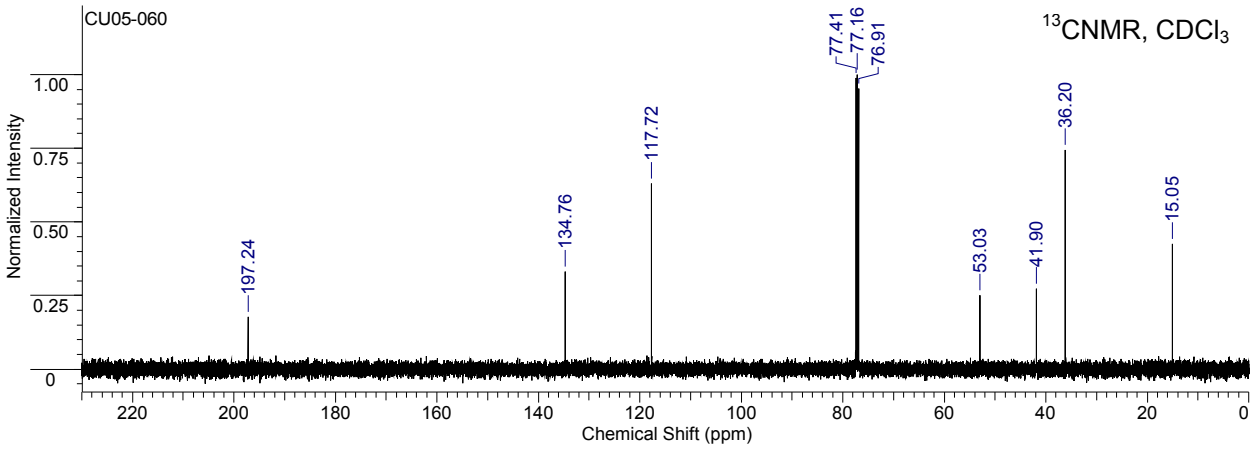
In a screw-top vial equipped with a magnetic stir bar, 0.1 mmol of the allyl vinyl ether substrate was dissolved in 2.0 mL of hexanes. 0.02 mmol of **2** was added as a solid, and the vial was sealed under air. The reaction was allowed to stir at the specified temperature and monitored by TLC. After the indicated time, the reaction mixture was concentrated to 0.5 mL, and loaded directly onto a silica gel column with 1:1 CH_2Cl_2/hexanes.

Product Characterization

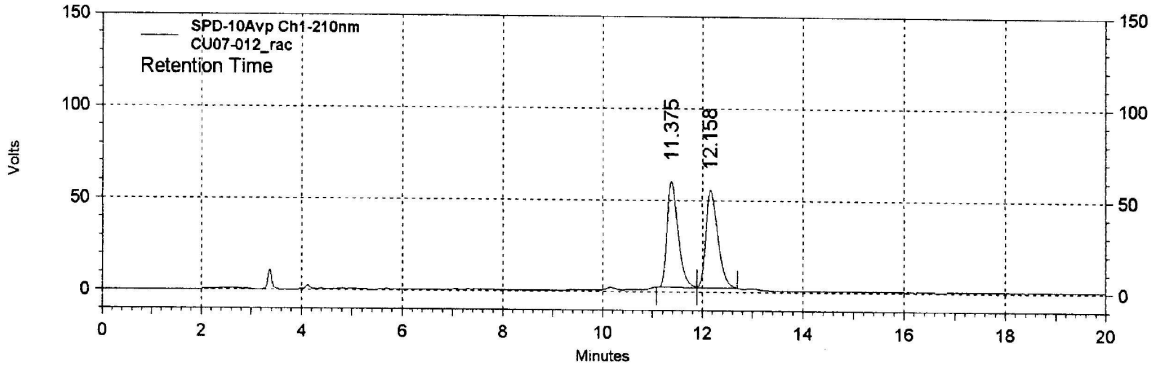


According to the general procedure, the substrate (15.6 mg, 0.1 mmol) and catalyst (27.4 mg, 0.02 mmol) in 2.0 mL of hexanes were stirred at 22 °C for 14 days. After column chromatography (eluting with 1:1 hexanes/CH_2Cl_2), 23.5 mg of product (80% yield) was obtained. This material was determined to be 92% ee by chiral HPLC analysis (OD-H, 0.1% IPA in hexanes, 1.0 mL/min, 210 nm, t_r(major)= 11.2 min, t_r(minor) = 12.2 min); $[\alpha]_D^{29}$ +20.6° (c = 0.100, $CHCl_3$); ^{1}HNMR (500 MHz, $CDCl_3$): δ5.72 (1H, m), 5.06 (2H, m), 3.87 (3H, s), 3.32 (1H, apparent sextet, J = 6.9 Hz), 2.47 (1H, m), 2.17 (1H, m), 1.15 (3H, d, J = 6.9 Hz). $^{13}C\{^1H\}$NMR (125 MHz, $CDCl_3$): δ197.2, 162.1, 134.8, 117.7, 53.0, 41.9, 36.2, 15.1; HRMS (ESI) $[M+Na]^+$ calculated for $C_8H_{12}O_3$: 179.06787, found: 179.06737; FTIR (neat, cm^{-1}): 2958 (m), 2921 (m), 1728 (s), 1282 (m), 1038 (m).





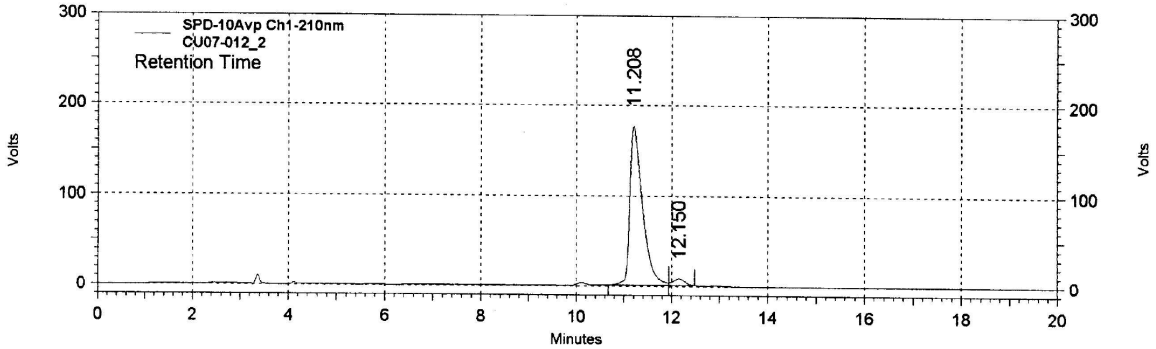
Racemic Sample: HPLC (OD-H, 0.1% IPA in hexanes, 1.0 mL/min, 210 nm)



SPD-10Avp
Ch1-210nm
Results

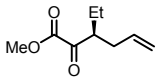
Retention Time	Area	Area %	Height	Height %
11.375	881030	49.93	57685	52.07
12.158	883498	50.07	53107	47.93

Enantioselective Sample: HPLC (OD-H, 0.1% IPA in hexanes, 1.0 mL/min, 210 nm) **92% ee**

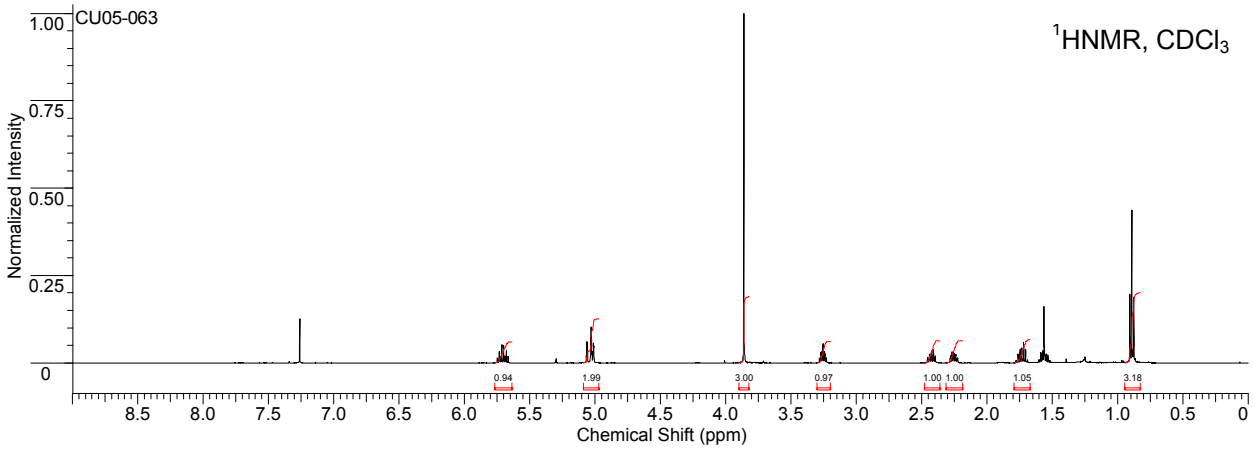


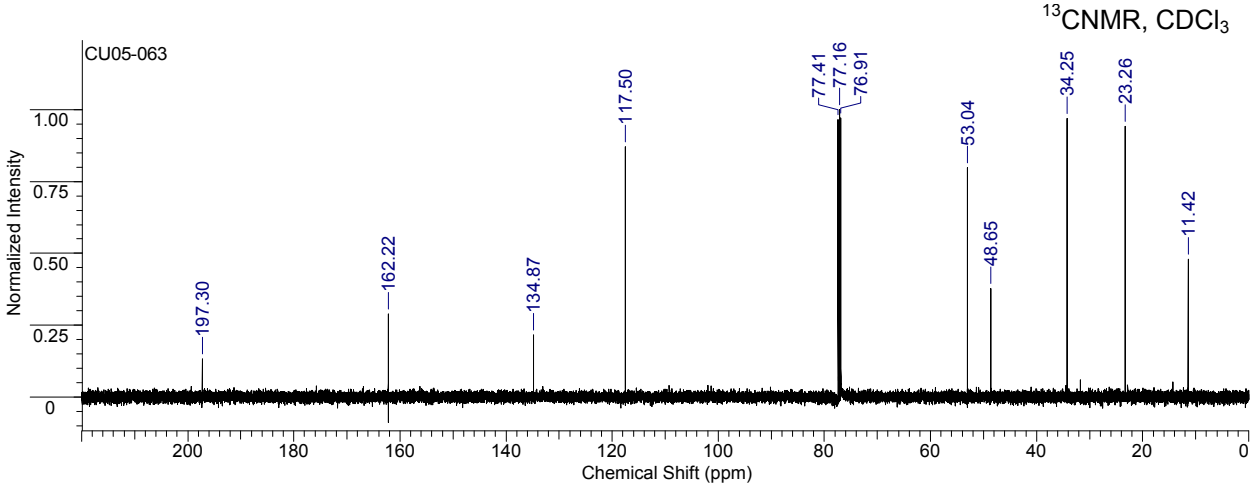
SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
11.208	3258801	96.05	176004	95.81
12.150	134027	3.95	7699	4.19

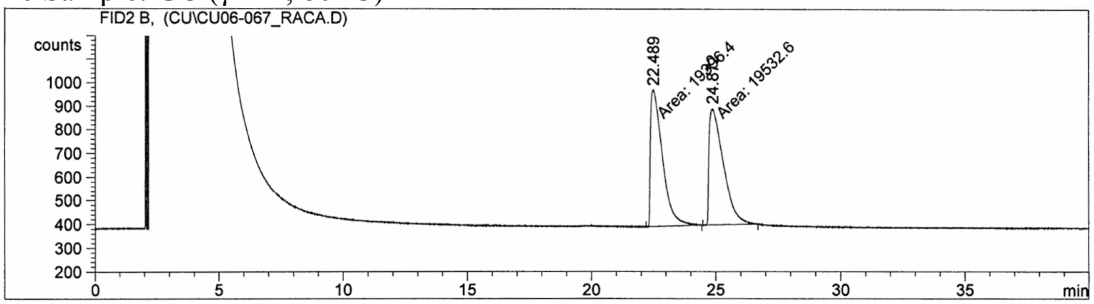


The substrate (17.2 mg, 0.1 mmol) and catalyst (27.4 mg, 0.02 mmol) in 2.0 mL of hexanes were stirred at 22 ^{o}C for 9 days. After column chromatography (eluting with 1:1 hexanes/CH_2Cl_2), 14.6 mg of product (86% yield) was obtained. This material was determined to be 92% ee by chiral GC analysis (γ-TA, 80 ^{o}C, t_r(major) = 23.3 min, t_r(minor) = 25.9 min); $[\alpha]_D^{29}$ -9.1^{o} (c = 0.600, $CHCl_3$); ^{1}HNMR (500 MHz, $CDCl_3$): δ5.71 (1H, m), 5.05 (1H, d, J = 16.9 Hz), 5.02 (1H, d, J = 7.3 Hz), 3.86 (3H, s), 3.26 (1H, tt, J = 6.0, 7.3 Hz), 2.42 (1H, m), 2.26 (1H, m), 1.73 (1H, m), 1.56 (1H, m), 0.89 (3H, t, J = 7.3 Hz) ^{13}C{^{1}H }NMR (125 MHz, $CDCl_3$): δ197.3, 162.2, 134.9, 117.5, 53.0, 48.7, 34.3, 23.3, 11.4; HRMS (ESI) $[M+Na]^+$ calculated for $C_9H_{14}O_3$: 193.08352, found: 193.08285; FTIR (neat, cm^{-1}): 2968 (m), 1730 (s), 1439 (w), 1288 (m), 1244 (w), 1052 (m), 919 (w).



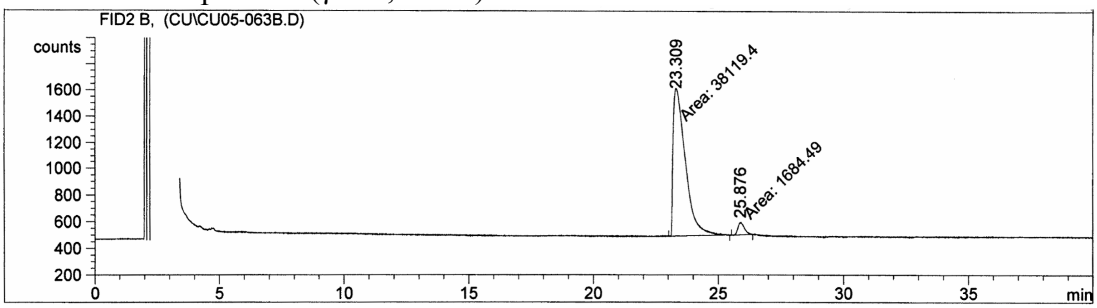


Racemic Sample: GC (γ-TA, 80 °C)

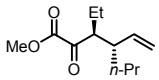


Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	22.489	MM	0.5563	1.93964e4	581.13910	49.82511
2	24.872	MM	0.6588	1.95326e4	494.16528	50.17489

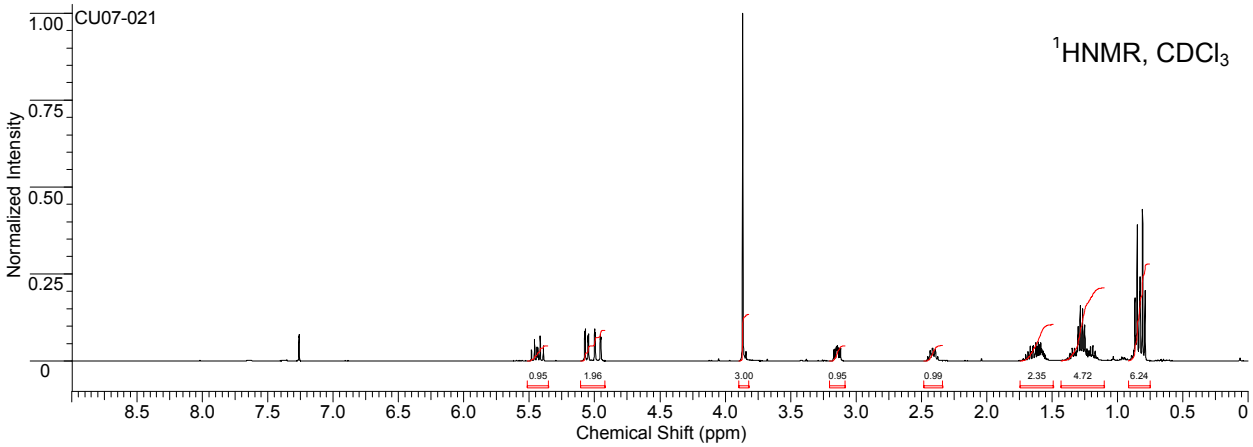
Enantioselective Sample: GC (γ-TA, 80 °C) **92% ee**

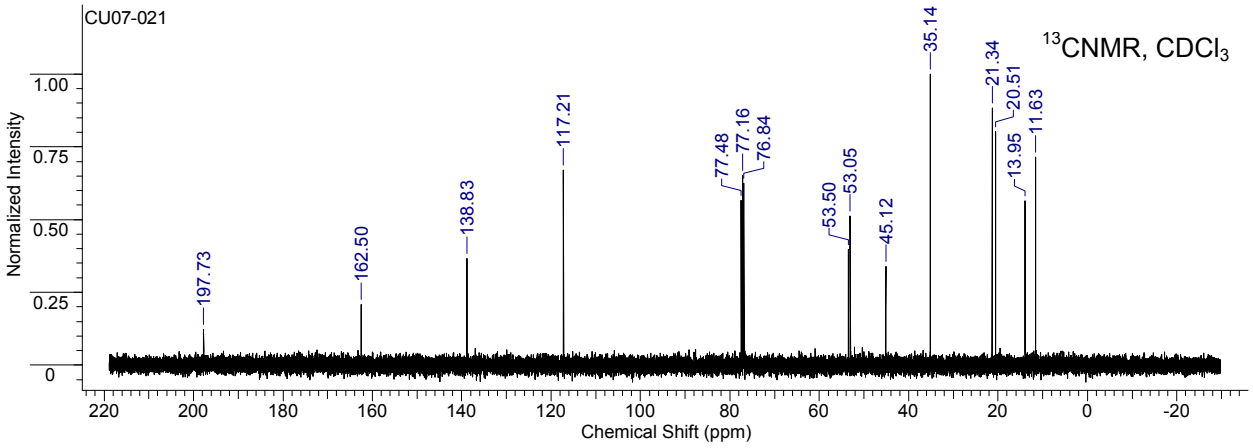


Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	23.309	MM	0.5633	3.81194e4	1127.95044	95.76803
2	25.876	MM	0.2993	1684.48694	93.79235	4.23197

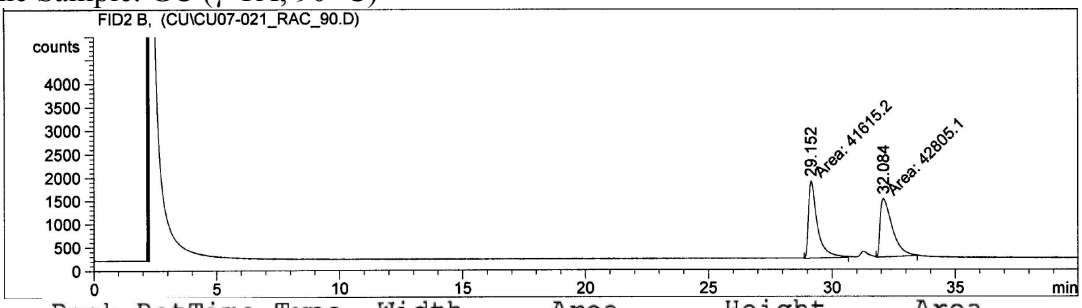


The substrate (21.2 mg, 0.1 mmol) and catalyst (27.4 mg, 0.02 mmol) in 2.0 mL of hexanes were stirred at 22 ^{o}C for 14 days. After column chromatography (eluting with 1:1 hexanes/CH_2Cl_2), 19.5 mg of product (92% yield) was obtained. This material was determined to be 85% ee by chiral GC analysis (γ-TA, 90 ^{o}C, t_r(major) = 31.6 min, t_r(minor) = 28.8 min); $[\alpha]_D^{26}$ +15.9^{o} (c = 0.74, $CHCl_3$); ^{1}HNMR (400 MHz, $CDCl_3$): δ5.44 (1H, td, J = 9.9, 16.8 Hz), 5.06 (1H, d, J = 9.9 Hz), 4.98 (1H, d, J = 17.2 Hz), 3.87 (3H, s), 3.14 (1H, m), 3.41 (1H, apparent p, J = 7.9 Hz), 1.62 (2H, m), 1.1–1.4 (4H, m), 0.87 (3H, t, J = 7.1 Hz), 0.81 (3H, t, J = 7.5 Hz); ^{13}C{^{1}H }NMR (100 MHz, $CDCl_3$): d197.7, 162.5, 138.8, 117.2, 53.5, 53.1, 45.1, 35.1, 21.3, 20.5, 14.9, 11.6; HRMS $[M+Na]^+$ calculated for $C_{12}H_{20}O_3$: 235.13047, found: 235.13091; FTIR (neat, cm^{-1}): 2961 (m), 2635 (w), 2875 (w), 1728 (s), 1461 (w), 1285 (m), 1248 (m), 1050 (m), 918 (w).



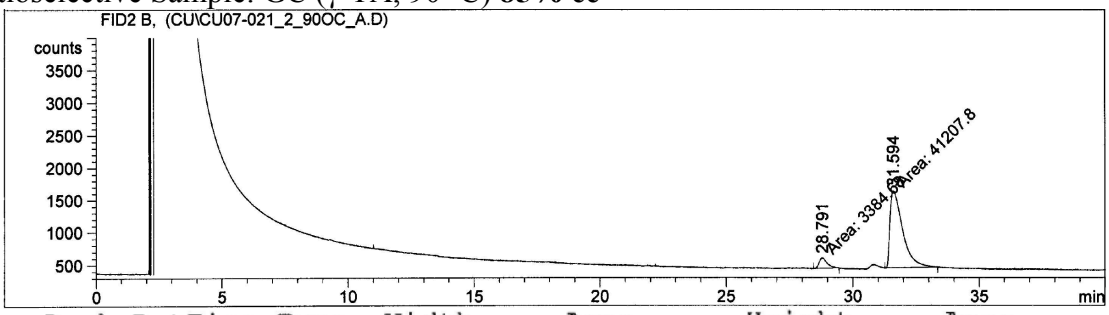


Racemic Sample: GC (γ-TA, 90 °C)

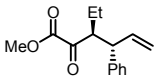


Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	29.152	MM	0.4168	4.16152e4	1663.96021	49.29524
2	32.084	MM	0.5667	4.28051e4	1258.95178	50.70476
Totals :				8.44203e4	2922.91199	

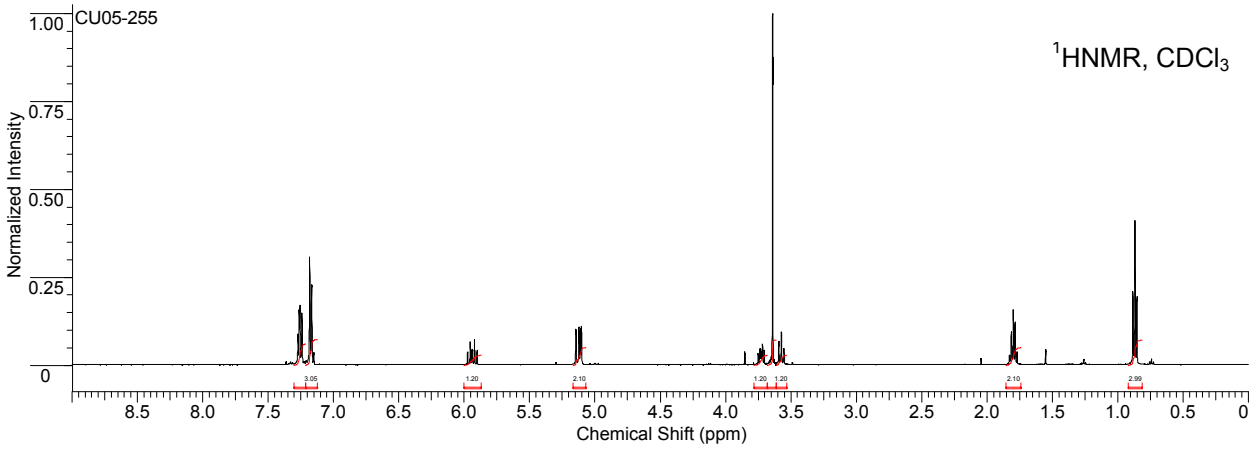
Enantioselective Sample: GC (γ-TA, 90 °C) **85% ee**

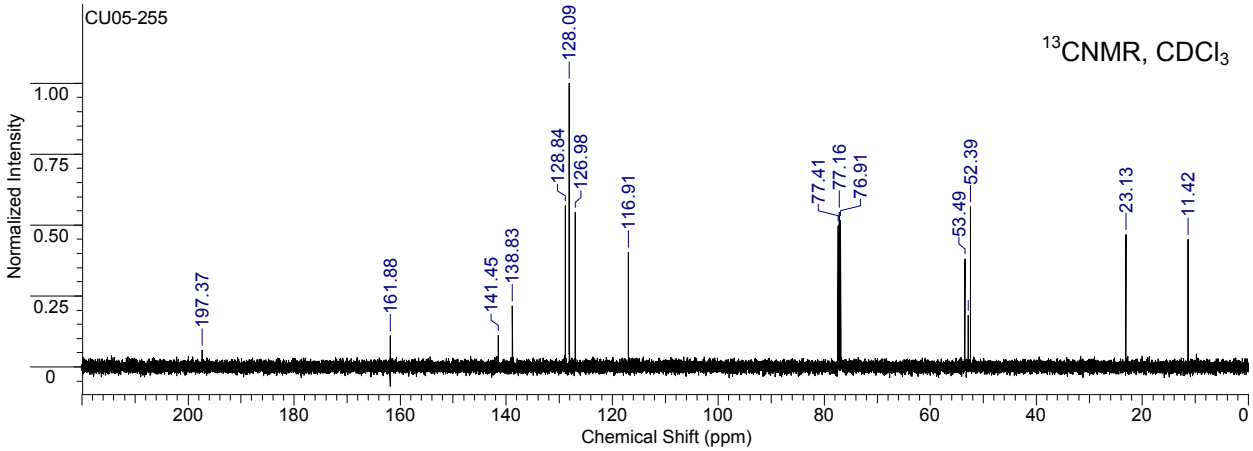


Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	28.791	MM	0.3552	3384.67676	158.82344	7.59025
2	31.594	MM	0.5768	4.12078e4	1190.72717	92.40975
Totals :				4.45924e4	1349.55061	

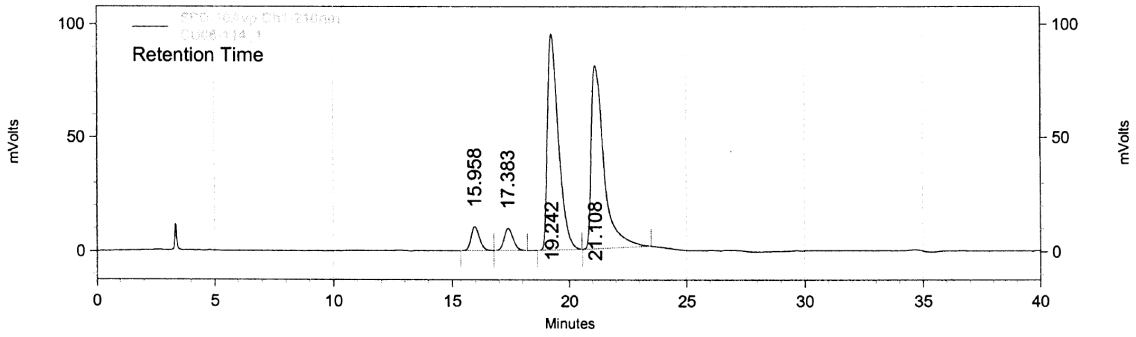


The substrate (24.6 mg, 0.1 mmol) and catalyst (27.4 mg, 0.02 mmol) in 2.0 mL of hexanes were stirred at 22 ^{o}C for 5 days. After column chromatography (eluting with 1:1 hexanes/CH_2Cl_2), 22.4 mg of product (91% yield) was obtained as a mixture of 19:1 anti/syn diastereomers. This material was determined to be 81% ee by chiral HPLC analysis (OD-H, 0.1% IPA in hexanes, 1.0 mL/min, t_r(major)= 19.5 min, t_r(minor) = 21.9 min). The minor diastereomer was produced in 78% ee (t_r(major)= 16.4 min, t_r(minor) = 18.0 min); $[\alpha]_D^{27}$ =-63.2^{o} (c = 0.865, $CHCl_3$); ^{1}HNMR (500 MHz, $CDCl_3$): δ7.26 (2H, m), 7.15-7.18 (3H, m), 5.94 (1H, td, J = 9.6, 16.9 Hz), 5.13 (1H, d, J = 10.8 Hz), 5.10 (1H, d, J = 3.9 Hz), 3.73 (1H, td, J = 6.6, 10.3 Hz), 3.64 (3H, s), 3.57 (1H, t, J = 9.7 Hz), 1.80 (2H, p, J = 7.1 Hz), 0.87 (3H, t, J = 7.4 Hz). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ197.4, 161.9, 141.5, 138.8, 128.8, 128.1, 127.0, 116.9, 53.5, 52.9, 52.4, 23.1, 11.4; LRMS (ESI): 269.1 (100%) $[M+Na]^+$; FTIR (neat, cm^{-1}): 2968 (w), 1727 (s), 1453 (w), 1286 (w), 1247 (w), 1053 (m), 921 (w), 760 (w), 701 (m).





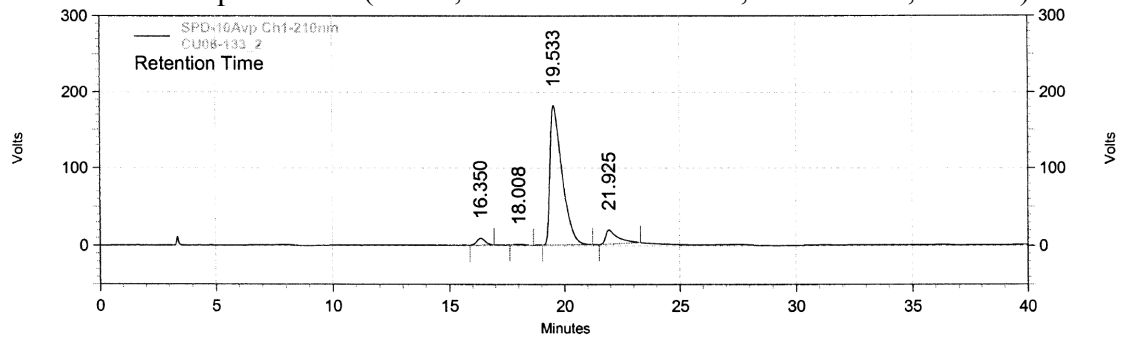
Racemic Sample: HPLC (OD-H, 0.1% IPA in hexanes, 1.0 mL/min, 210 nm)



SPD-10Avp
Ch1-210nm
Results

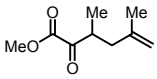
Retention Time	Area	Area %	Height	Height %
15.958	259112	3.90	10414	5.32
17.383	255524	3.84	9584	4.90
19.242	3083886	46.36	95038	48.57
21.108	3053097	45.90	80620	41.20

Enantioselective Sample: HPLC (OD-H, 0.1% IPA in hexanes, 1.0 mL/min, 210 nm) **81% ee**

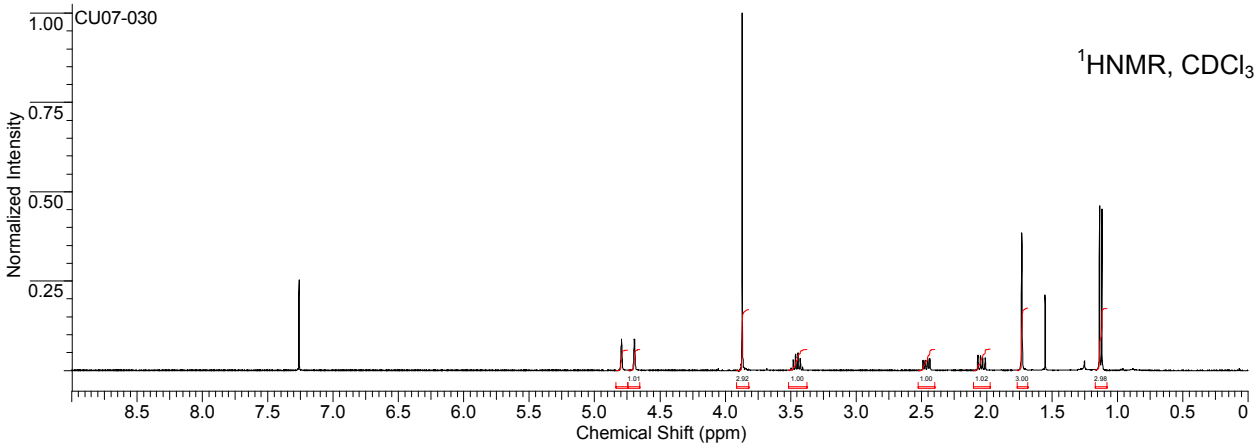


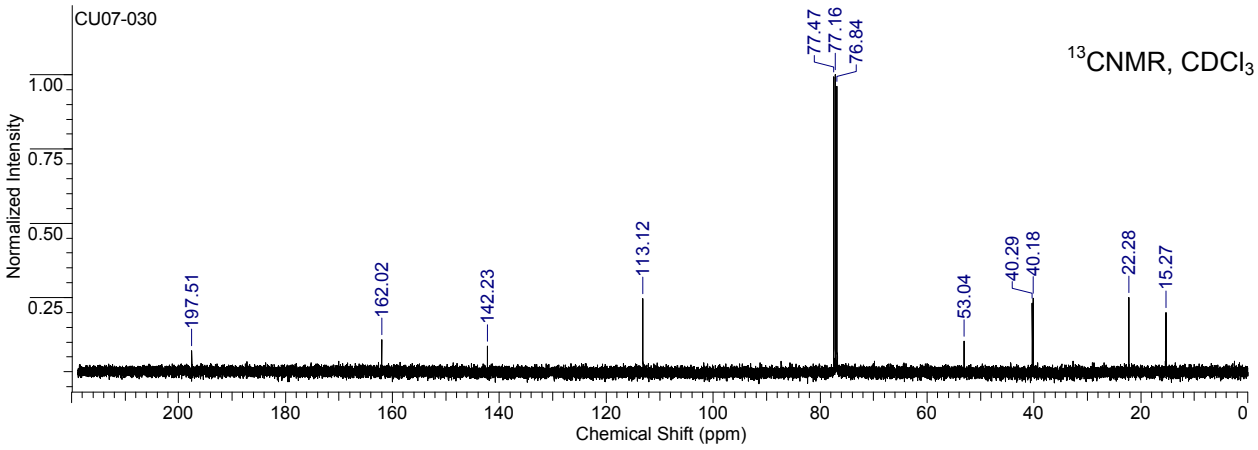
SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
16.350	213064	2.86	8639	4.13
18.008	27132	0.36	1098	0.52
19.533	6532430	87.69	180997	86.51
21.925	676596	9.08	18494	8.84

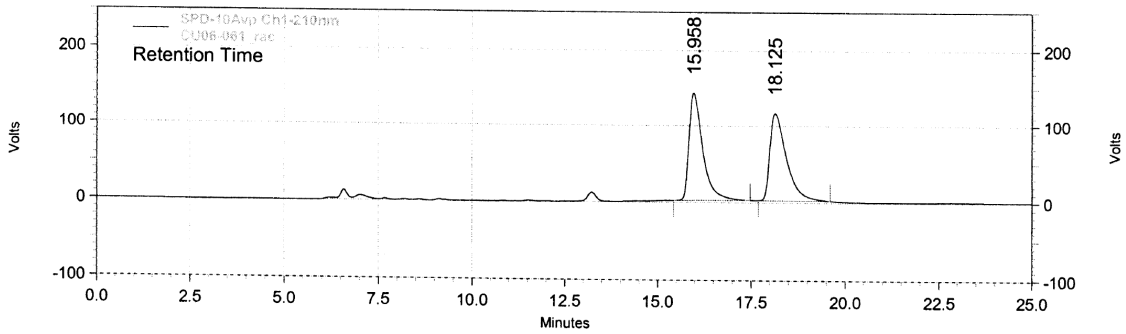


The substrate (17.0 mg, 0.1 mmol) and catalyst (27.4 mg, 0.02 mmol) in 2.0 mL of hexanes were stirred at 35 ^{o}C for 8 days. After column chromatography (eluting with 1:1 hexanes/CH_2Cl_2), 12.4 mg of product (73% yield) was obtained. This material was determined to be 96% ee by chiral HPLC analysis (AS-H, 0.1% IPA in hexanes, 0.5 mL/min, 210 nm, t_r(major)= 16.0 min, t_r(minor) = 18.3 min); $[\alpha]_D^{26}$ +9.5^{o} (c = 0.525, $CHCl_3$); ^{1}HNMR (500 MHz, $CDCl_3$): δ4.79 (1H, s), 4.69 (1H, s), 3.87 (3H, s), 3.45 (1H, apparent sextet, J = 7.2 Hz), 2.46 (1H, dd, J = 6.4, 14.0 Hz), 2.04 (1H, dd, J = 8.2, 14.0 Hz), 1.73 (3H, s), 1.13 (3H, d, J = 7.1 Hz); ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ197.5, 162.0, 142.2, 113.1, 53.0, 40.3, 40.2, 22.3, 15.3; HRMS $[M+Na]^+$ calculated for $C_9H_{14}O_3$: 193.08352, found: 193.08304; FTIR (neat, cm^{-1}): 2975 (w), 2939 (w), 1732 (s), 1455 (w), 1438 (w), 1277 (m), 1256 (m), 1041 (m), 1022 (w)





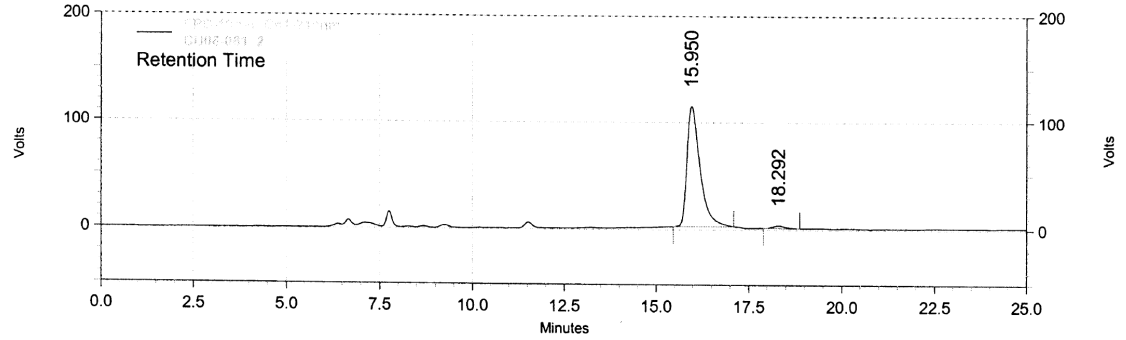
Racemic Sample: HPLC (AS-H, 0.1% IPA in hexanes, 0.5 mL/min, 210 nm)



SPD-10Avp
Ch1-210nm
Results

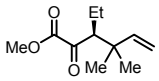
Retention Time	Area	Area %	Height	Height %
15.958	3588466	50.79	141112	55.26
18.125	3476877	49.21	114231	44.74

Enantioselective Sample: HPLC (AS-H, 0.1% IPA in hexanes, 0.5 mL/min, 210 nm) **96% ee**

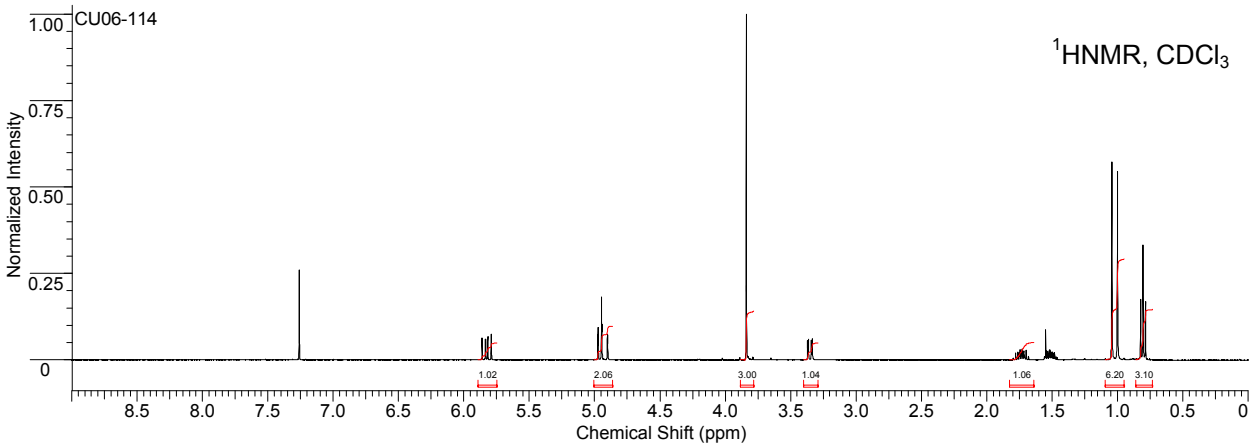


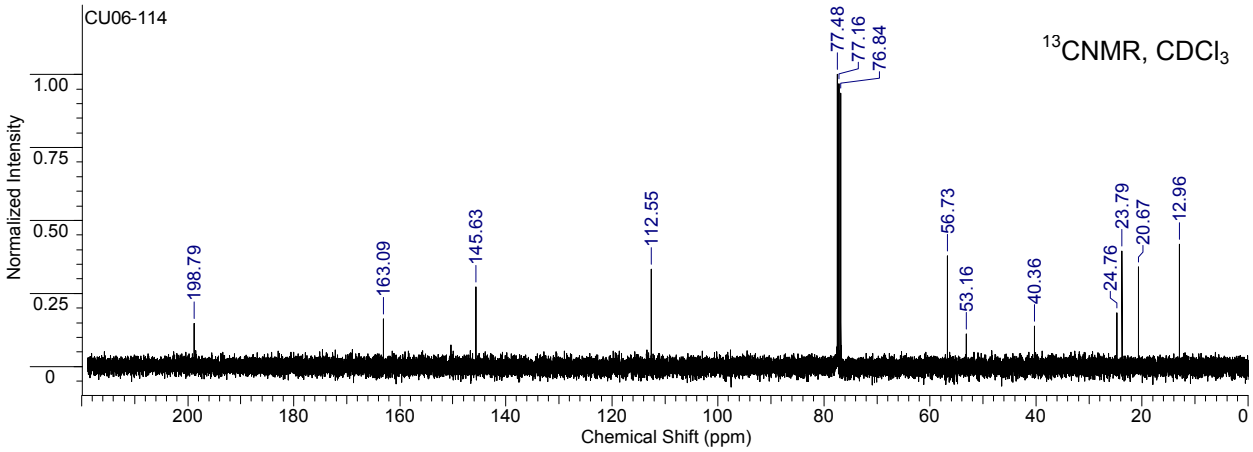
SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
15.950	2748792	98.02	112737	97.87
18.292	55621	1.98	2459	2.13

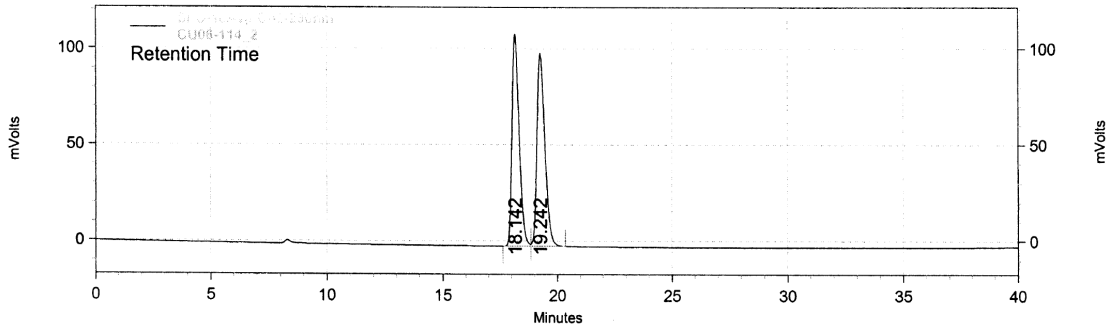


The substrate (19.8 mg, 0.1 mmol) and catalyst (27.4 mg, 0.02 mmol) in 2.0 mL of hexanes were stirred at 40 ^{o}C for 4 days. After column chromatography (eluting with 1:1 hexanes/CH_2Cl_2), 17.6 mg of product (89% yield) was obtained. This material was determined to be 81% ee by chiral HPLC analysis (OD-H, 0.1% IPA in hexanes, 0.4 mL/min, 230 nm, t_r(major)= 17.2 min, t_r(minor) = 18.7 min); $[\alpha]_D^{27}$ +84.2^{o} (c = 0.615, $CHCl_3$); ^{1}HNMR (500 MHz, $CDCl_3$): δ5.82 (1H, dd, J = 11.0, 17.4 Hz), 4.96 (1H, d, J = 11.0 Hz), 4.92 (1H, d, J = 17.4 Hz), 3.85 (3H, s), 3.35 (1H, dd, J = 2.7, 11.9 Hz), 1.74 (1H, m), 1.51 (1H, m), 1.04 (3H, s), 1.00 (3H, s), 0.80 (3H, t, J = 7.3 Hz). ^{13}C{^{1}H }NMR (100 MHz, $CDCl_3$): δ198.8, 163.1, 145.6, 112.6, 56.7, 53.2, 40.4, 24.8, 23.8, 20.7, 13.0; LRMS (ESI): 221.1 (95%) $[M+Na]^+$; FTIR (neat, cm^{-1}): 2069 (s), 1727 (s), 1461 (w), 1281 (m), 1256 (m), 1057 (s), 918 (w).





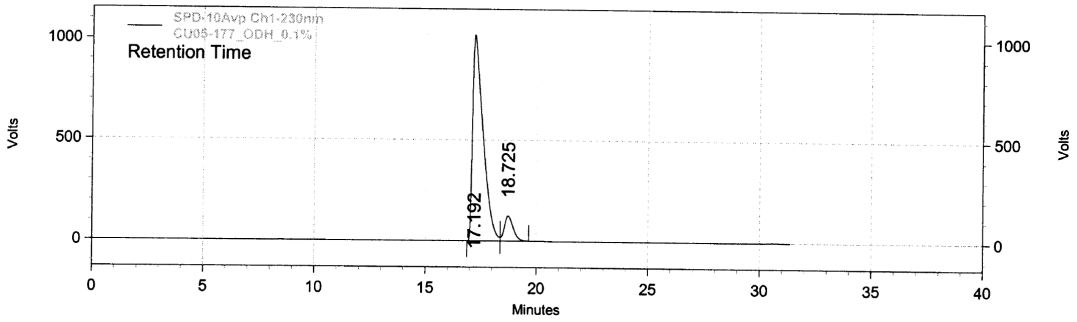
Racemic Sample: HPLC (OD-H, 0.1% IPA in hexanes, 0.4 mL/min, 230 nm)



SPD-10Avp
Ch2-230nm
Results

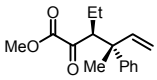
Retention Time	Area	Area %	Height	Height %
18.142	2395863	49.89	110066	52.29
19.242	2406419	50.11	100415	47.71

Enantioselective Sample: HPLC (OD-H, 0.1% IPA in hexanes, 0.4 mL/min, 230 nm) **81% ee**

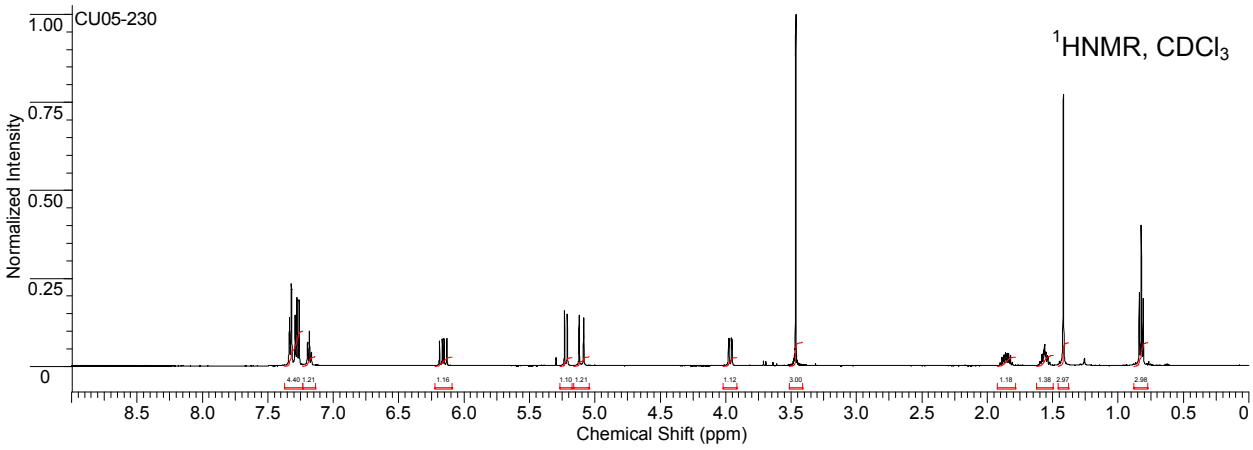


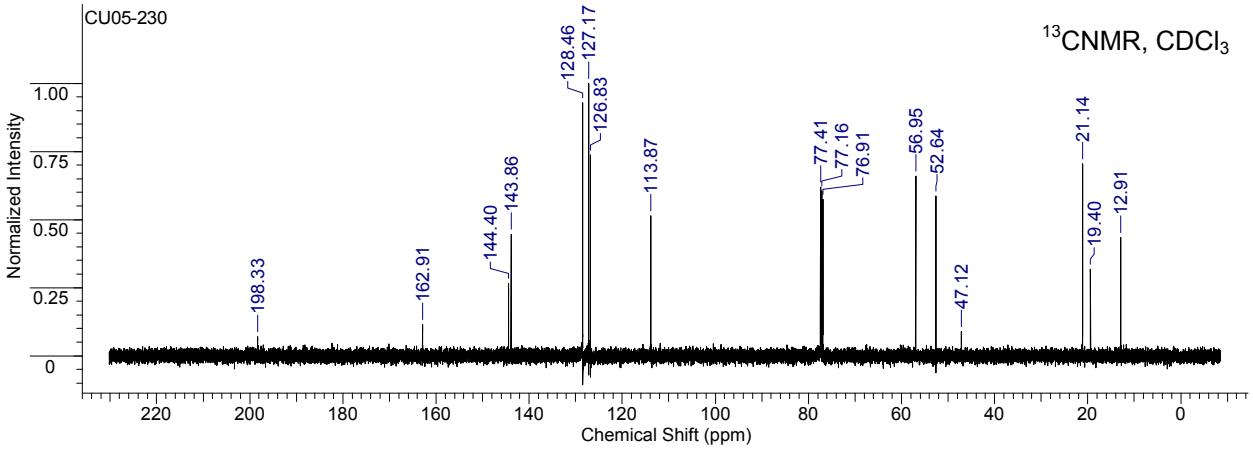
SPD-10Avp
Ch1-230nm
Results

Retention Time	Area	Area %	Height	Height %
17.192	33442046	90.74	1025306	89.25
18.725	3414452	9.26	123534	10.75

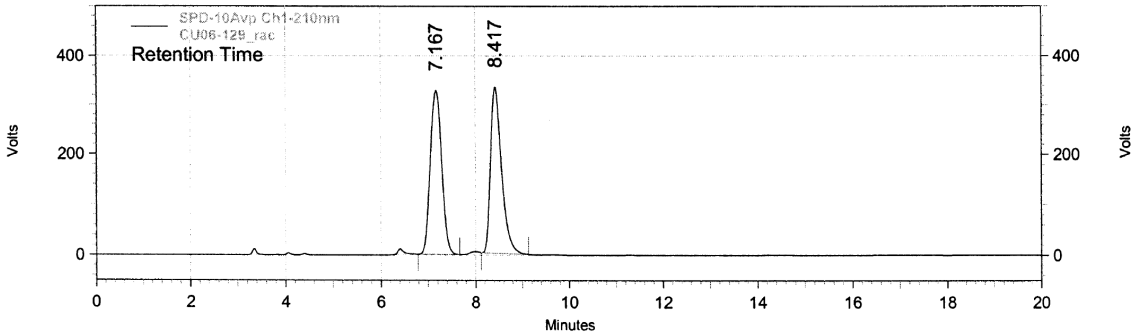


The substrate (26.0 mg, 0.1 mmol) and catalyst (27.4 mg, 0.02 mmol) in 2.0 mL of hexanes were stirred at 40 ^{o}C for 12 days. After column chromatography (eluting with 1:1 hexanes/CH_2Cl_2), 23.5 mg of product (89% yield) was obtained. This material was determined to be 82% ee by chiral HPLC analysis (OD-H, 0.5% IPA in hexanes, 1.0 mL/min, 210 nm, t_r(major)= 7.2 min, t_r(minor) = 8.5 min); $[\alpha]_D^{27}$ +69.0^{o} (c = 0.84, $CHCl_3$); ^{1}HNMR (500 MHz, $CDCl_3$): δ7.33 (2H, d, J = 8.5 Hz), 7.28 (2H, t, J = 7.6 Hz), 7.18 (1H, t, J = 7.2 Hz), 6.16 (1H, dd, J = 17.4, 10.8 Hz), 5.22 (1H, d, J = 10.8 Hz), 5.10 (1H, d, J = 17.4 Hz), 3.96 (1H, d, J = 11.4 Hz), 3.46 (3H, s), 1.85 (1H, m), 1.56 (1H, m), 1.42 (3H, s), 0.82 (3H, t, J = 7.3 Hz). ^{13}C{^{1}H}NMR (125 MHz, $CDCl_3$): δ198.3 162.9, 144.4, 143.9, 128.5, 127.2, 126.8, 113.9, 57.0, 52.6, 47.1, 21.1, 19.4, 12.9; LRMS (ESI): 283.1 (100%) $[M+Na]^+$; FTIR (neat, cm^{-1}): 2968 (m), 1731 (s), 1446 (w), 1286 (w), 1256 (m), 1055 (m), 762 (w), 701 (m).





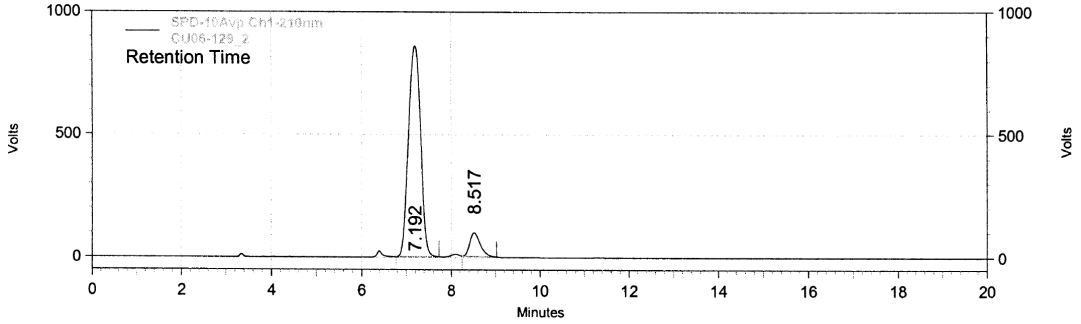
Racemic Sample: HPLC (OD-H, 0.5% IPA in hexanes, 1.0 mL/min, 210 nm)



SPD-10Avp
Ch1-210nm
Results

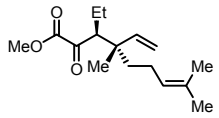
Retention Time	Area	Area %	Height	Height %
7.167	5486863	50.54	328477	49.65
8.417	5369641	49.46	333120	50.35

Enantioselective Sample: HPLC (OD-H, 0.5% IPA in hexanes, 1.0 mL/min, 210 nm) **82% ee**

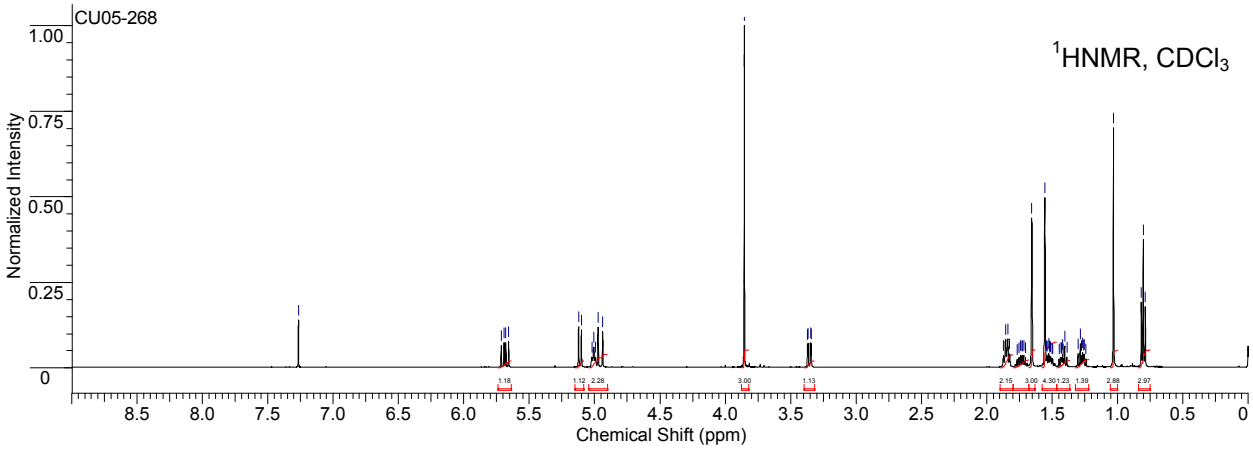


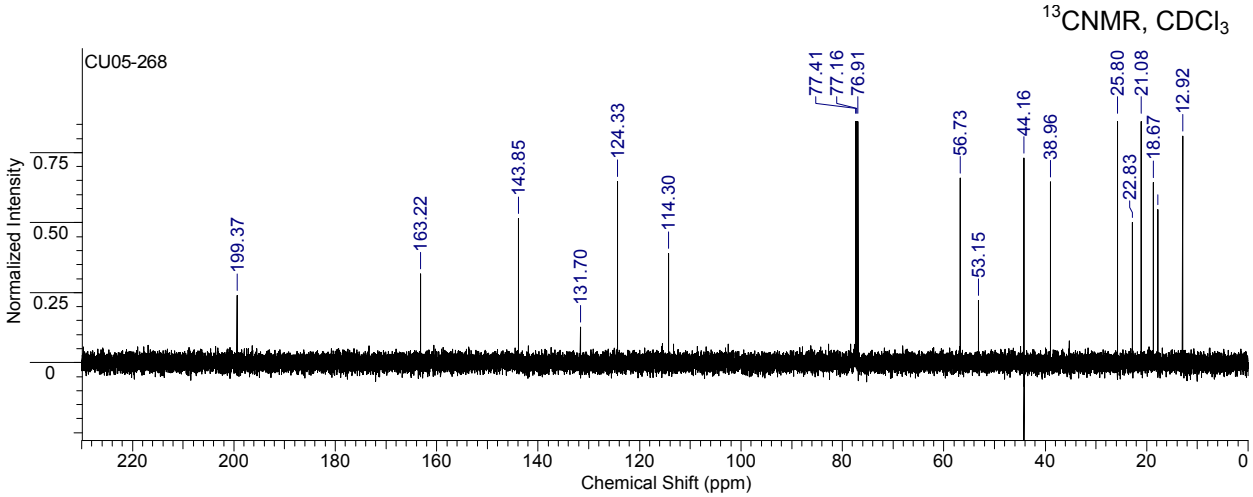
SPD-10Avp
Ch1-210nm
Results

Retention Time	Area	Area %	Height	Height %
7.192	16272743	91.12	861527	89.94
8.517	1586297	8.88	96332	10.06

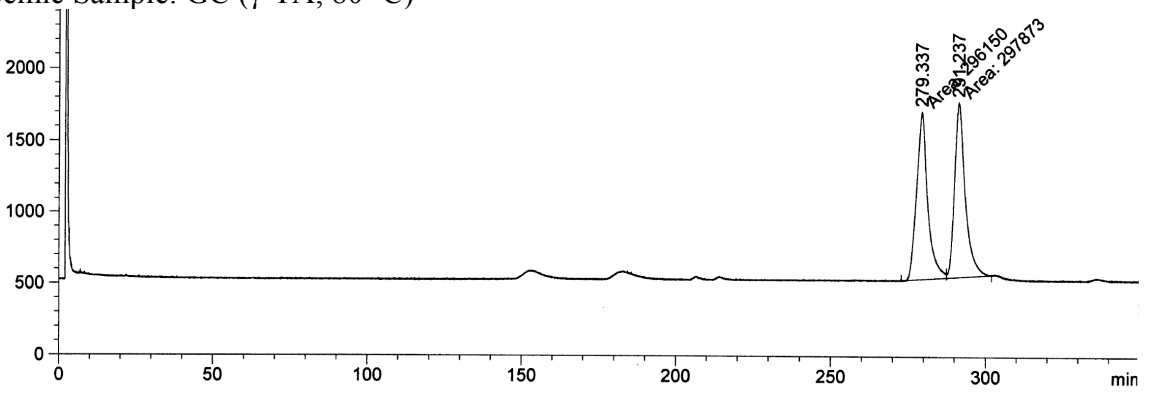


The substrate (26.6 mg, 0.1 mmol) and catalyst (27.4 mg, 0.02 mmol) in 2.0 mL of hexanes were stirred at 40 ^{o}C for 14 days. After column chromatography (eluting with 1:1 hexanes/CH_2Cl_2), 19.4 mg of product (74% yield) was obtained. This material was determined to be 84% ee by chiral GC analysis (γ-TA, 80 ^{o}C, t_r(major) = 290.7 min, t_r(minor) = 277.7 min); $[\alpha]_D^{27}$ +33.1^{o} (c = 0.392, $CHCl_3$); ^{1}HNMR (500 MHz, $CDCl_3$): δ5.68 (1H, dd, J = 10.9, 17.4 Hz), 5.11 (1H, d, J = 10.8 Hz), 5.00 (1H, t, J = 7.1 Hz), 4.95 (1H, d, J = 17.4 Hz), 3.85 (3H, s), 3.35 (1H, dd, J = 2.5, 11.7 Hz), 1.85 (2H, apparent q, J = 8.0 Hz), 1.72 (1H, m), 1.65 (3H, s), 1.55 (3H, s), 1.52 (1H, m), 1.42 (1H, m), 1.26 (1H, m), 1.03 (3H, s), 0.80 (3H, t, 7.4 Hz); ^{13}C{^{1}H }NMR (125 MHz, $CDCl_3$): δ199.4, 163.2, 143.9, 131.7, 124.3, 114.3, 56.7, 53.2, 44.2, 39.0, 25.8, 22.8, 21.1, 18.7, 17.9, 12.9; HRMS $[M+Na]^+$ calculated for $C_{16}H_{26}O_3$: 289.17742, found: 289.17599; FTIR (neat, cm^{-1}): 2967 (m), 2932 (w), 2878 (w), 1732 (s), 1460 (w), 1379 (w), 1278 (w), 1255 (m), 1054 (m), 917 (w).



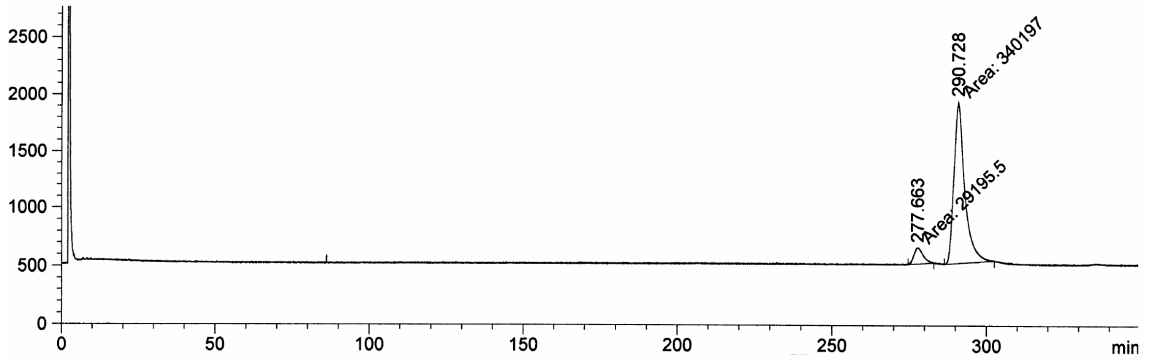


Racemic Sample: GC (γ-TA, 80 °C)



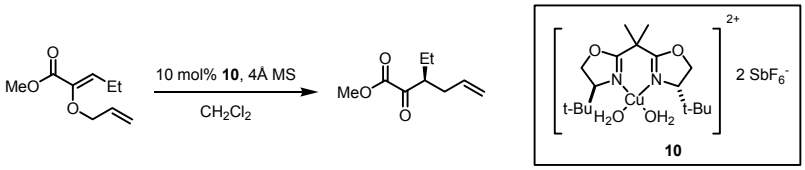
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	279.337	MF	4.1577	2.96150e5	1187.15271	49.85495
2	291.237	FM	4.0006	2.97873e5	1240.96448	50.14505

Enantioselective Sample: GC (γ-TA, 80 °C) **84% ee**



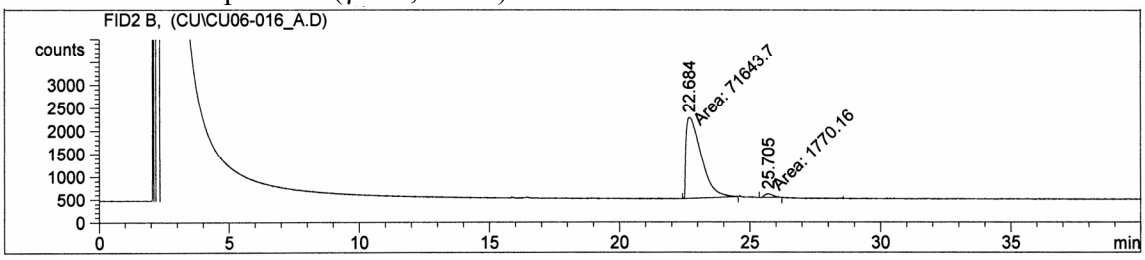
Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	277.663	MM	3.3853	2.91955e4	143.73730	7.90365
2	290.728	MM	3.9673	3.40197e5	1429.17505	92.09635

7. Determination of the Absolute Stereochemistry



According to Hiersemann's general procedure,[5] **10** (4.3 mg, 0.005 mmol) was dissolved in 250 μL of CH_2Cl_2, and stirred under N_2 at ambient temperature for 5 min. 12.5 mg of powdered 4A molecular sieves was added, and stirring was continued for 5 min. Substrate (8.5 mg, 0.05 mmol) in 250 uL of CH_2Cl_2 was added, and the reaction was stirred at ambient temperature for 24 h. The reaction mixture was diluted with 1 mL of hexanes and loaded directly onto a column (eluting with 1:1 hexanes/CH_2Cl_2). The product was determined to be 95% ee, and the major enantiomer was that obtained with **2** derived from the (R,R)-enantiomer of *trans*-1,2-diaminocyclohexane.

Enantioselective Sample: GC (γ-TA, 80 °C) **95% ee**



Peak #	RetTime [min]	Type	Width [min]	Area counts*s	Height [counts]	Area %
1	22.684	MM	0.6748	7.16437e4	1769.55237	97.58879
2	25.705	MM	0.3723	1770.16443	79.23978	2.41121

8. X-Ray Structure of 2

Experimental

The compound was crystallized from a water/isopropanol solution as colorless prisms. A crystal 0.150 mm x 0.175 mm x 0.300 mm in size was selected, mounted on a glass fiber with Paratone-N oil, and transferred to a Bruker SMART APEX II diffractometer equipped with an Oxford Cryosystems 700 Series Cryostream Cooler and Mo Kα radiation (λ = 0.71073 Å). A total of 1613 frames were collected at 193 (2) K to θ_{max} = 27.50° with an ω oscillation range of 0.5°/frame, and an exposure time of 30 s/frame using the APEX2 suite of software. (Bruker AXS, 2006a) Unit cell refinement on all observed reflections, and data reduction with corrections for Lp and decay were performed using SAINT. (Bruker AXS, 2006b) Scaling and a multi-scan absorption correction were done using SADABS. (Bruker AXS, 2004) The minimum and maximum transmission factors were 0.9629 and 0.9812, respectively. A total of 50675 reflections were collected, 16387 were unique (R_{int} = 0.0273), and 13214 had I > 2σ(I). Systematic absences were consistent with the compound having crystallized in the monoclinic space group $P2_1$ or $P2_1/m$. The chiral space group $P2_1$ (No. 4) was selected based on an observed mean $|E^2-1|$ value of 0.771 (versus the expectation values of 0.968 and 0.736 for centric and noncentric data, respectively).

The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using SHELXTL. (Bruker AXS, 2001) The asymmetric unit was found to contain one bis[(1*R*,2*R*)-2-(2-phenyl-1*H*-pyrrol-1-yl)cyclohexylamino]methaniminium cation, one tetrakis[3,5-bis(trifluoromethyl)phenyl]borate anion, and two isopropanol solvent molecules. All of the nonhydrogen atoms were refined with anisotropic displacement coefficients. The hydrogen atoms were assigned isotropic displacement coefficients U(H) = 1.2U(C), 1.5U(C_{methyl}), 1.5U(N) or 1.5U(O), and their coordinates were treated as follows: (1) The coordinates for the N-bound hydrogens H(2A), H(2B), H(3) and H(4) and for the hydroxy hydrogen H(1SO) for the ordered isopropanol were free to vary, and (2) the coordinates for all other hydrogens were allowed to ride on their respective carbons or oxygens. Two-site disorder models were used for six of the eight trifluoromethyl groups and for one of the isopropanol molecules. All of the partials atoms were assigned fixed site occupancy factors of a half based on initial population tests. Distance, isotropic and similar U_{ij} restraints were also employed. The refinement converged to R(F) = 0.0436, $wR(F^2)$ = 0.1028, and S = 1.014 for 13214 reflections with I > 2σ(I), and R(F) = 0.0590, $wR(F^2)$ = 0.1119, and S = 1.014 for 16387 unique reflections, 1145 parameters and 220 restraints. The maximum $|\Delta/\sigma|$ in the final cycle of least-squares was 0.001, and the residual peaks on the final difference-Fourier map ranged from -0.237 to 0.274 $eÅ^{-3}$. Scattering factors were taken from the International Tables for Crystallography, Volume C. (Maslen et al., 1992, and Creagh & McAuley, 1992)

The Flack parameter refined to -0.1 (4) [versus the expectation values of 0 for the correct hand and 1 for the wrong hand]. Due to the large standard uncertainty associated with the Flack parameter, and in the absence of an anomalous scatterer, the absolute structure of the cation could not be ascertained from the collected intensity data. Hence, the coordinates used here were arbitrarily fixed to the (1*R*,2*R*) enantiomer desired by the researchers. (Flack, 1983)

References

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Bruker AXS (2006b). *SAINT V7.34A*. Bruker Analytical X-ray Systems Inc., Madison, Wisconsin, USA.
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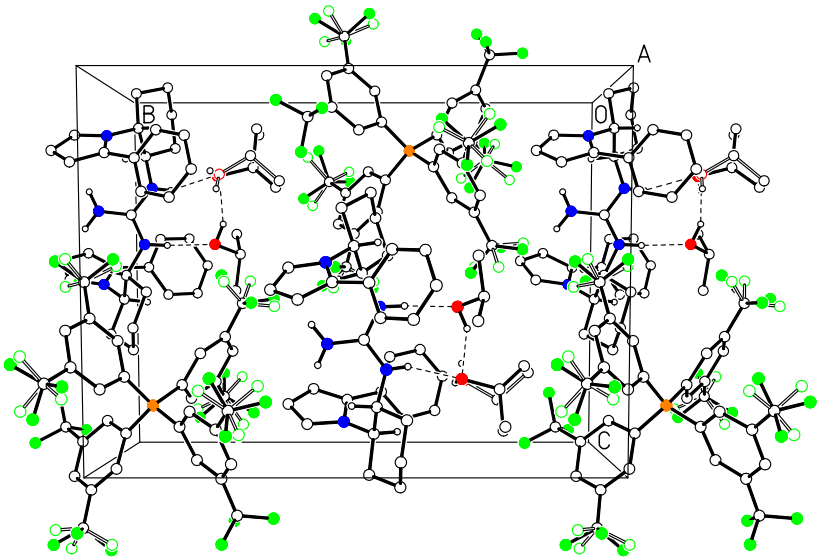
Flack, H. D. (1983). *Acta Crystallographica*, *Section A*, 39, 876-881.
Maslen, E. N., Fox, A. G. & O'Keefe, M. A. (1992). *International Tables for Crystallography: Mathematical, Physical and Chemical Tables*, Vol C, edited by A. J. C. Wilson, pp. 476-516. Dordrecht, The Netherlands: Kluwer.

$R(F) = R1 = \Sigma ||F_o|-|F_c|| / \Sigma|F_o|$, $wR(F^2) = wR2 = [\Sigma w (F_o^2-F_c^2)^2 / \Sigma w (F_o^2)^2]^{1/2}$, and S = Goodness-of-fit on $F^2 = [\Sigma w (F_o^2-F_c^2)^2 / (n-p)]^{1/2}$, where n is the number of reflections and p is the number of parameters refined.

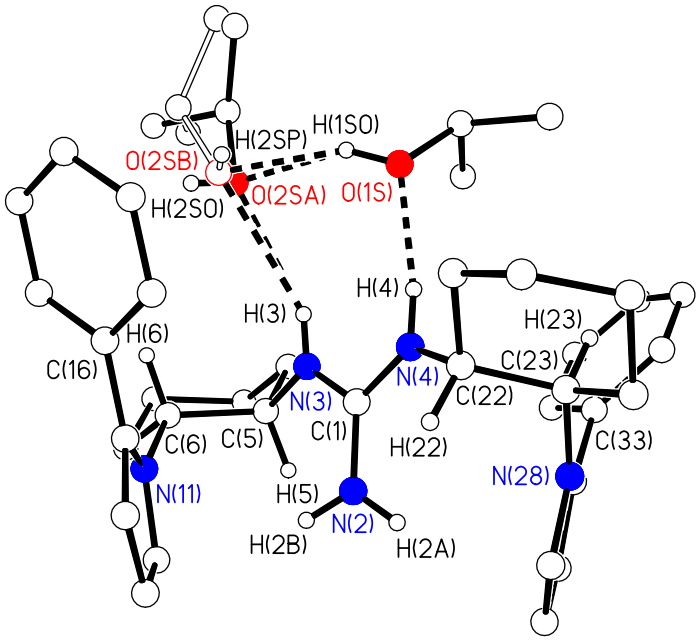
Crystal data and structure refinement.

Identification code	enj078	
Empirical formula	C71 H68 B F24 N5 O2	
Formula weight	1490.11	
Temperature	193(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$ (No. 4)	
Unit cell dimensions	a = 13.4974(1) Å	α= 90°
	b = 18.8077(2) Å	β= 96.092(1)°
	c = 14.1387(1) Å	γ = 90°
Volume	3568.91(5) $Å^3$	
Z	2	
Density (calculated)	1.387 Mg/m^3	
Absorption coefficient	0.127 mm^{-1}	
F(000)	1532	
Crystal size	0.300 x 0.175 x 0.150 mm^3	
Theta range for data collection	1.81 to 27.50°.	
Index ranges	-16<=h<=17, -24<=k<=24, -18<=l<=18	
Reflections collected	50675	
Independent reflections	16387 [R(int) = 0.0273]	
Completeness to theta = 27.50°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9812 and 0.9629	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	16387 / 220 / 1145	
Goodness-of-fit on F^2	1.014	
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.1028	
R indices (all data)	R1 = 0.0590, wR2 = 0.1119	
Absolute structure parameter	-0.1(4)	
Largest diff. peak and hole	0.274 and -0.237 $e.Å^{-3}$	

Unit Cell Diagram Viewed down the Crystallographic α-axis

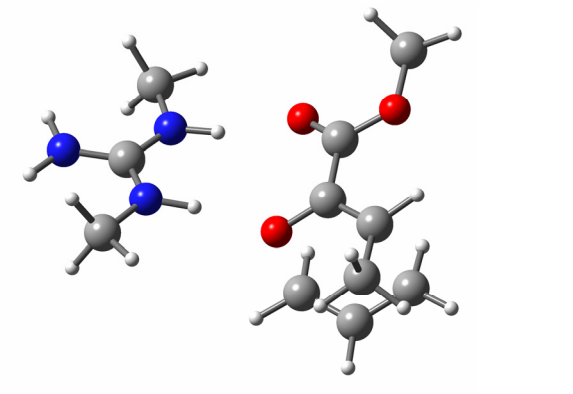


Hydrogn-bonding Interactions Between the Guanidinium Ion and Two Isopropanol Molecules



9. Computational Modeling of the Guanidinium-Bound Transition State

Calculations were performed using Gaussian 98[6] at the B3LYP[7] level of density functional theory with the 6-31G(d)[8] basis set. The transition structure was fully optimized and verified to be a first-order saddle point by the existence of a single imaginary frequency. Qualitatively, this imaginary frequency corresponds to the simultaneous C-O bond breaking and C-C bond making events expected for the Claisen rearrangement.



E(RB+HF-LYP): -822.09356485

Zero-point correction=	0.335591 (Hartree/Particle)
Thermal correction to Energy=	0.357709
Thermal correction to Enthalpy=	0.358653
Thermal correction to Gibbs Free Energy=	0.282051

Cartesian Coordinates for the Optimized Structure

C	0.00000000	0.00000000	0.00000000
C	2.47106143	0.00000000	0.00000000
H	3.22944366	0.78327466	0.00000000
H	2.60120287	-0.60071997	0.90775920
H	2.63531299	-0.62980925	-0.88384343
C	-2.46957132	0.09171687	-0.04287683
H	-2.68284370	-0.48031900	0.86916579
H	-3.19672502	0.90142115	-0.11025566
H	-2.59977061	-0.55471452	-0.91894916
N	-0.02405621	-1.34676121	0.04698941
N	-1.14274985	0.69234596	-0.01320294
N	1.16715096	0.64983053	-0.02590515
H	-1.07477783	1.71779285	0.03052776
H	1.14587814	1.66483482	-0.17571502
H	-0.89364357	-1.85239357	0.10875975
H	0.82462091	-1.88708080	-0.01239403
H	-2.22938366	5.37583189	2.59811359
C	-1.21268197	5.25937449	2.23162906
C	-0.66190941	3.97770489	2.18379970
C	-0.62720328	6.29794050	1.53326515
H	0.39867107	3.84229096	1.99935903
H	-1.16417241	3.14454777	2.66376932
H	0.42470734	6.27068202	1.26745555
H	-1.09636326	7.27587730	1.47987046
O	-1.10469211	3.49302404	0.26010255
C	-0.66586022	4.46198431	-0.47903426
C	-1.37600681	5.64026807	-0.66779040
C	0.77297692	4.35316193	-0.92720992
H	-0.90017654	6.41329273	-1.26445091
C	-2.86138597	5.73978794	-0.48326022
O	1.48364054	3.38791544	-0.66986294
O	1.20056477	5.39984704	-1.63323405
H	-3.23755395	4.96576107	0.18797364
H	-3.16313445	6.72346079	-0.11004691
H	-3.35056921	5.61046401	-1.45911552
C	2.56058836	5.34501804	-2.12171584
H	2.70487169	6.27401525	-2.67100436
H	3.25956502	5.27540730	-1.28543403
H	2.68749789	4.48206732	-2.77890569

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