

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

Alexander J. Wagner, Shawn M. Miller, Ryan P. King, and Scott D. Rychnovsky*

Department of Chemistry, 1102 Natural Sciences II, University of California,

Irvine, California 92697-2025

srychnov@uci.edu

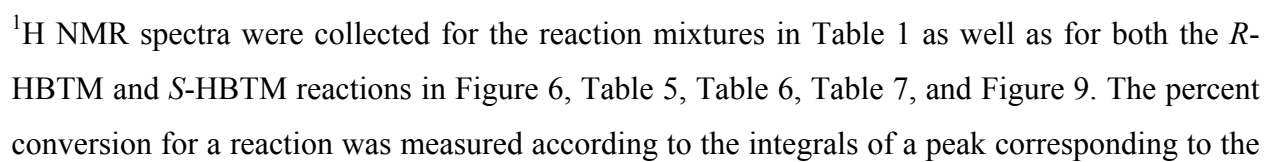
SUPPORTING INFORMATION

TABLE OF CONTENTS

Salt 2b ¹ H and ¹³ C Spectral Data.....	S2
¹ H NMR Spectrum and Chiral HPLC Trace for Equation 1.....	S3
¹ H NMR Spectra and Chiral HPLC Traces for Table 1.....	S5
Experimental Data for Kinetic Resolution of 3 with other Salts.....	S9
Additional Data for Tables 3 and 4.....	S16
Calibration Curves of (<i>R</i>)- 5 and (<i>R</i>)- 6 with GC-MS for Figure 6.....	S17
Additional Data for Figure 6.....	S21
Additional Data for Table 5.....	S31
Additional Data for Tables 6, Table 7, and Figure 9.....	S43
Additional Manipulations of Microscale Systems and Data for Figure 10.....	S85

I. Kinetic Resolution of **3** via salt **2**

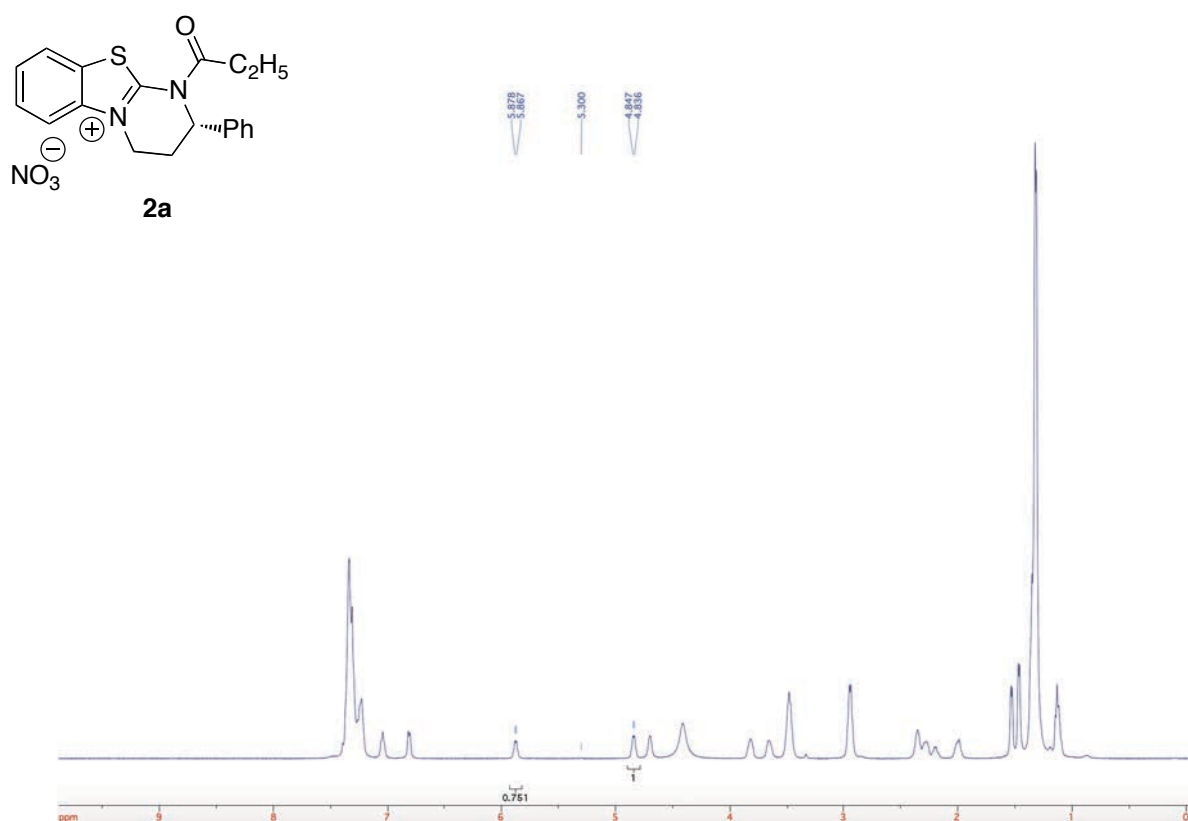
Salt **2b** ¹H and ¹³C Spectral Data



starting material and to the product after phase correction and baseline correction of the ^1H NMR spectrum (Formula 1).

Formula 1.

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

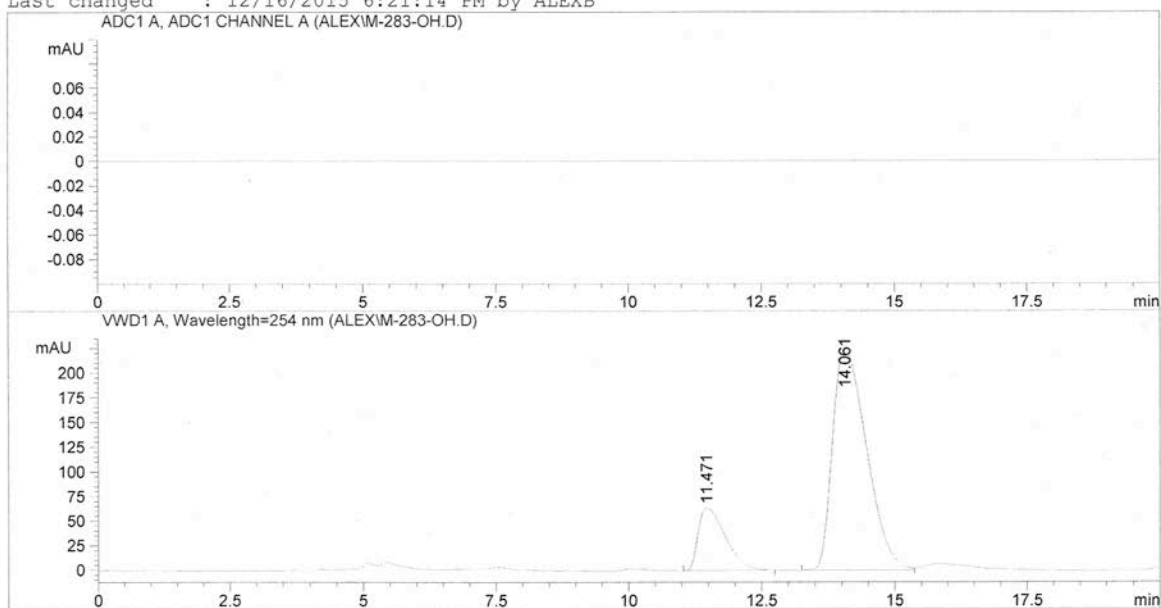
 ^1H NMR Spectrum and Chiral HPLC Trace for Equation 1

Data File C:\HPCHEM\1\DATA\ALEX\M-283-OH.D

Sample Name: SMM-283-OH2-NO3

Chiralcel OD with OD guard 5% iPrOH/n-Hexane 1.0 mL/min
23 bar 254 NM UVInjection 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\1\METHODS\ALEX.M
Last changed : 10/7/2013 3:56:21 PM by Alex
Analysis Method : C:\HPCHEM\1\METHODS\ALEXB.M
Last changed : 12/16/2015 6:21:14 PM by ALEXB

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

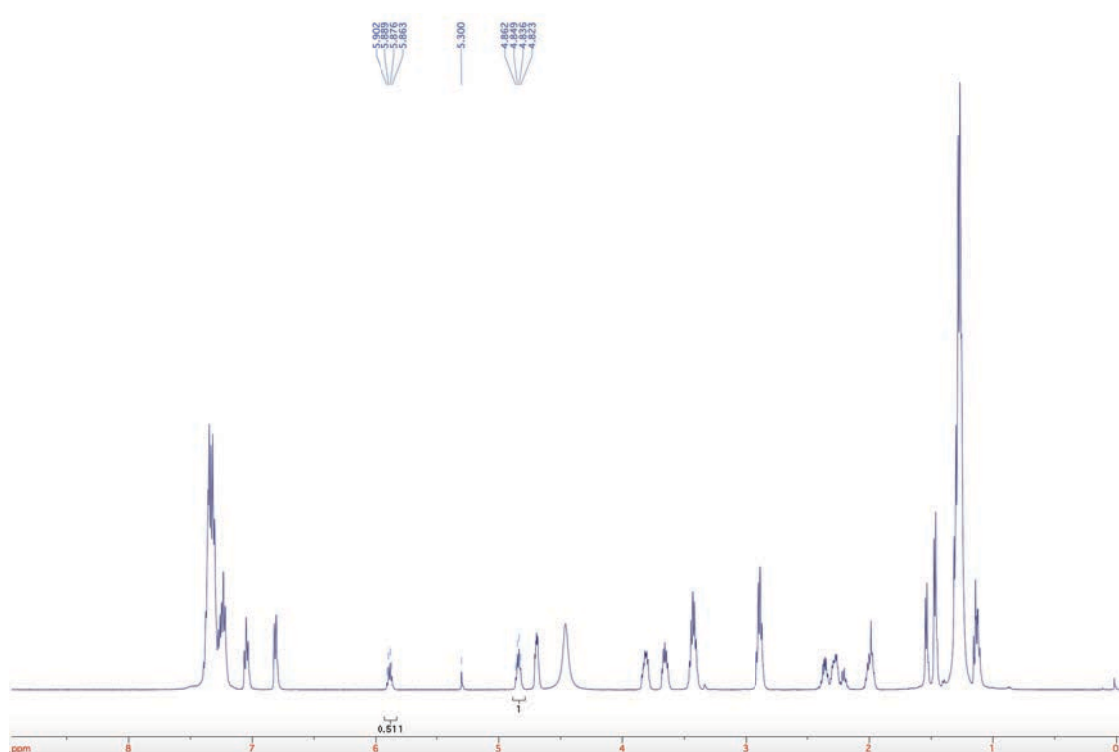
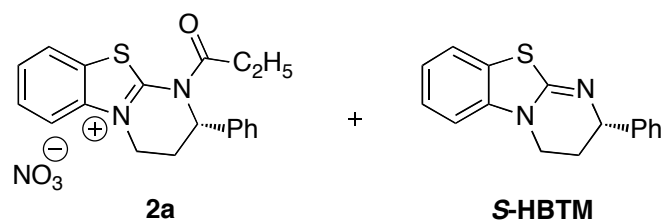
Signal 2: WVD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU	Height [mAU]	Area %
1	11.471	PB	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 ***

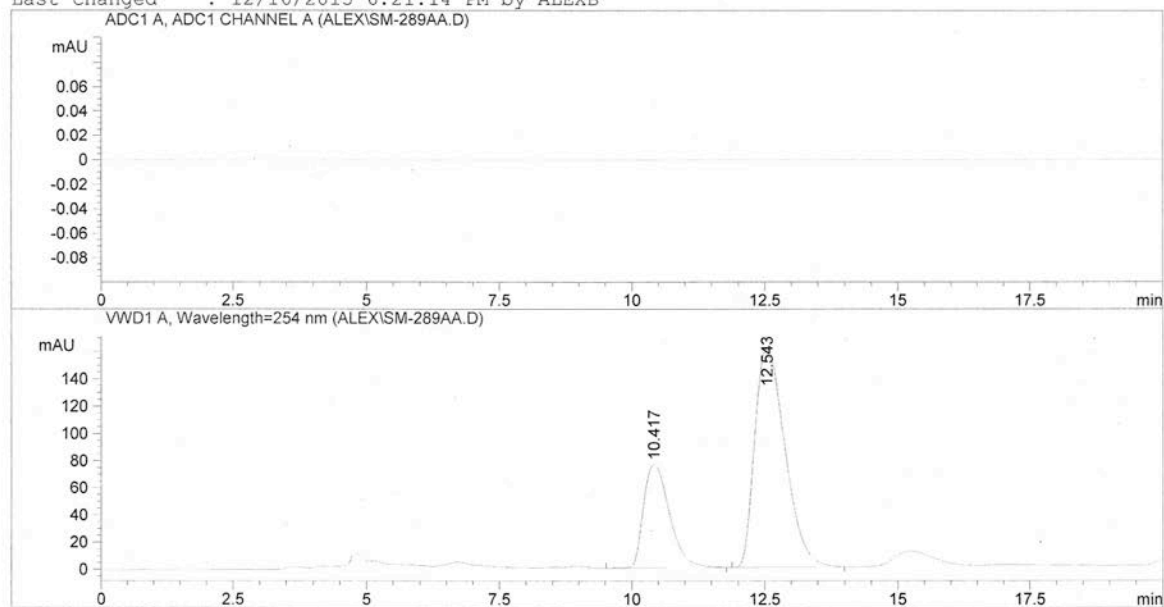
¹H NMR Spectra and Chiral HPLC Traces for Table 1**Entry 1**

Data File C:\HPCHEM\1\DATA\ALEX\SM-289AA.D

Sample Name: SMM-289-A-ALC

Chiralcel OD with OD guard 5% 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:\HPCHEM\1\METHODS\ALEX.M
Last changed : 11/11/2013 4:53:38 PM by SHAWN
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\ALEXB.M
Last changed : 12/16/2015 6:21:14 PM by ALEXB
=====
ADC1 A, ADC1 CHANNEL A (ALEX\SM-289AA.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

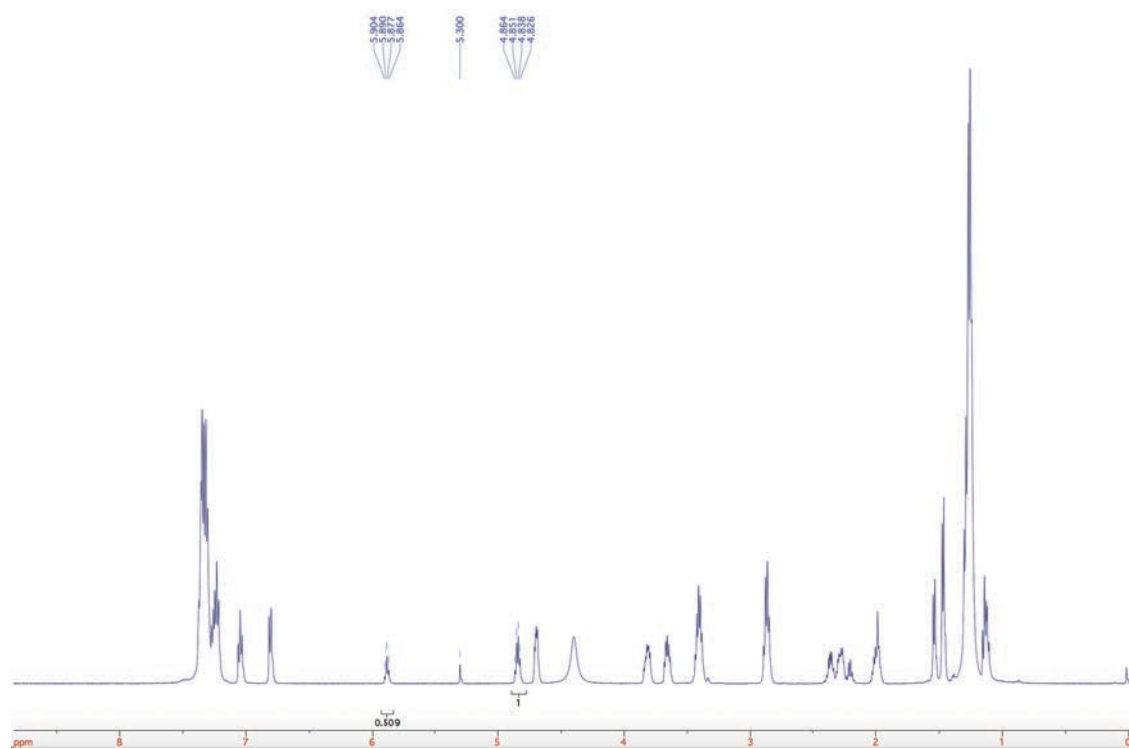
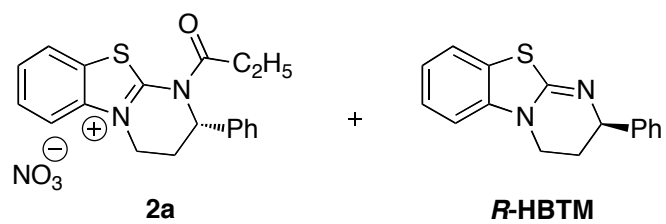
Peak #	RetTime [min]	Type	Width [min]	Area mAU*s	Height [mAU]	Area %
1	10.417	VB	0.5332	2591.86816	76.29269	28.8143
2	12.543	PB	0.6197	6403.20410	161.55348	71.1857

Totals : 8995.07227 237.84618

Results obtained with enhanced integrator!

*** End of Report ***

Entry 2

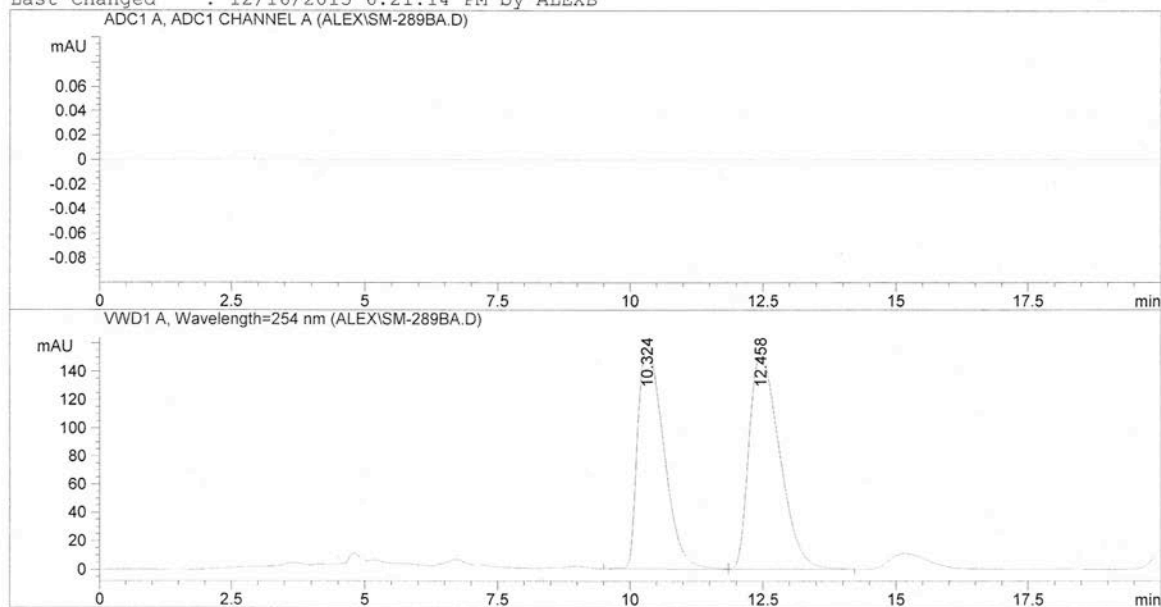


Data File C:\HPCHEM\1\DATA\ALEX\SM-289BA.D

Sample Name: SMM-289-B-ALC

Chiralcel OD with OD guard 5% 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\1\METHODS\ALEX.M
Last changed     : 11/11/2013 4:53:38 PM by SHAWN
                  (modified after loading)
Analysis Method  : C:\HPCHEM\1\METHODS\ALEXB.M
Last changed     : 12/16/2015 6:21:14 PM by ALEXB
=====
```



```
=====
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: WVD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU*s	Height [mAU]	Area %
1	10.324	VV	0.5396	5358.06152	155.79208	46.9017
2	12.458	VB	0.6280	6065.95459	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

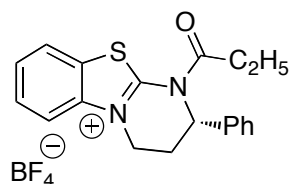
BF₄ counterion. 1-phenylethanol (25.8 mg, 0.211 mmol) was added to a 20 mL scintillation vial with a stirbar. CDCl₃ (600. μ L) and *N,N*-diisopropylethylamine (36.4 μ L, 0.209 mmol) were added and the reaction mixture was stirred at 0 °C (ice bath). BF₄ salt (52.0 mg, 0.127 mmol) was added and the reaction was stirred for 1 h at 0 °C. The reaction was halted with the addition of methanol (85.9 μ L). 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, *t_R* = 6.90 min, *t_S* = 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. μ L) and *N,N*-diisopropylethylamine (27.5 μ L, 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 μ L). 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, *t_R* = 10.36 min, *t_S* = 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. μ L) and *N,N*-diisopropylethylamine (37.5 μ L, 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 μ L). ^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, t_R = 10.34 min, t_S = 12.61 min) 28.8% e.e.

BF₄ Salt



Data File C:\HPCHEM\1\DATA\ALEX\SM-2-263.D

Sample Name: SM-2-263-KR-OH

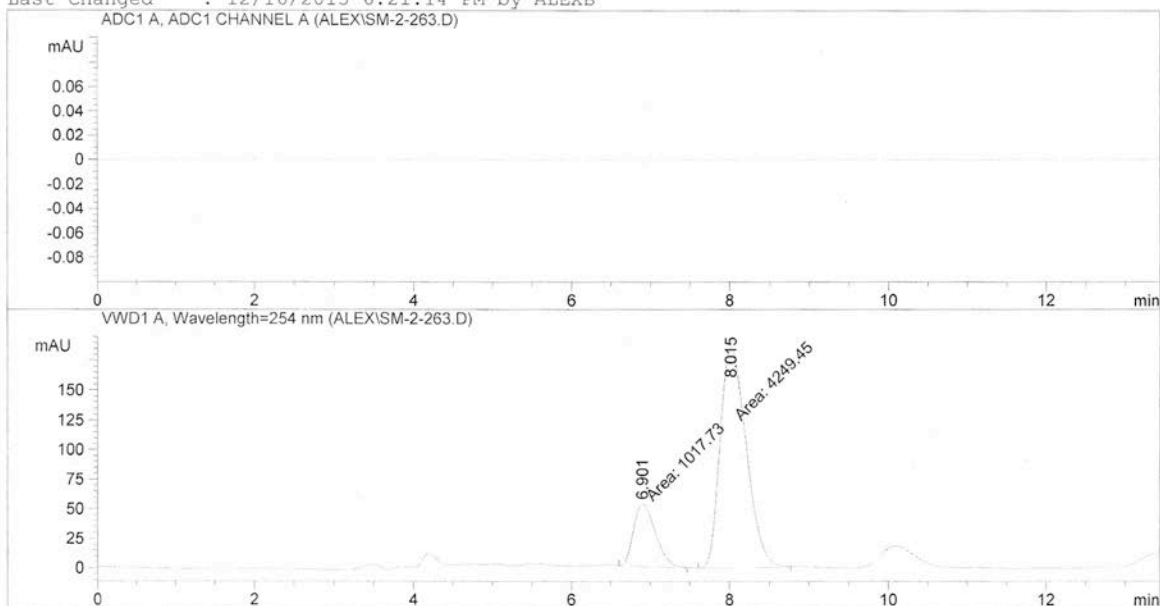
Chiralcel OD with OD guard 10% iPrOH/n-Hexane 1.0 mL/min
25 bar 254 NM UV

=====

Injection Date : 7/1/2013 1:11:08 PM
Sample Name : SM-2-263-KR-OH Location : Vial 42
Acq. Operator : ALEX Inj Volume : 10 µl

Acq. Method : C:\HPCHEM\1\METHODS\ALEX.M
Last changed : 7/1/2013 12:32:31 PM by ALEX
(modified after loading)

Analysis Method : C:\HPCHEM\1\METHODS\ALEXB.M
Last changed : 12/16/2015 6:21:14 PM by ALEXB



=====

Area Percent Report

=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 5.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: ADC1 A, ADC1 CHANNEL A

Signal 2: WVD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU*s	Height [mAU]	Area %
1	6.901	MM	0.3216	1017.73035	52.74073	19.3221
2	8.015	MM	0.3824	4249.45020	185.19360	80.6779

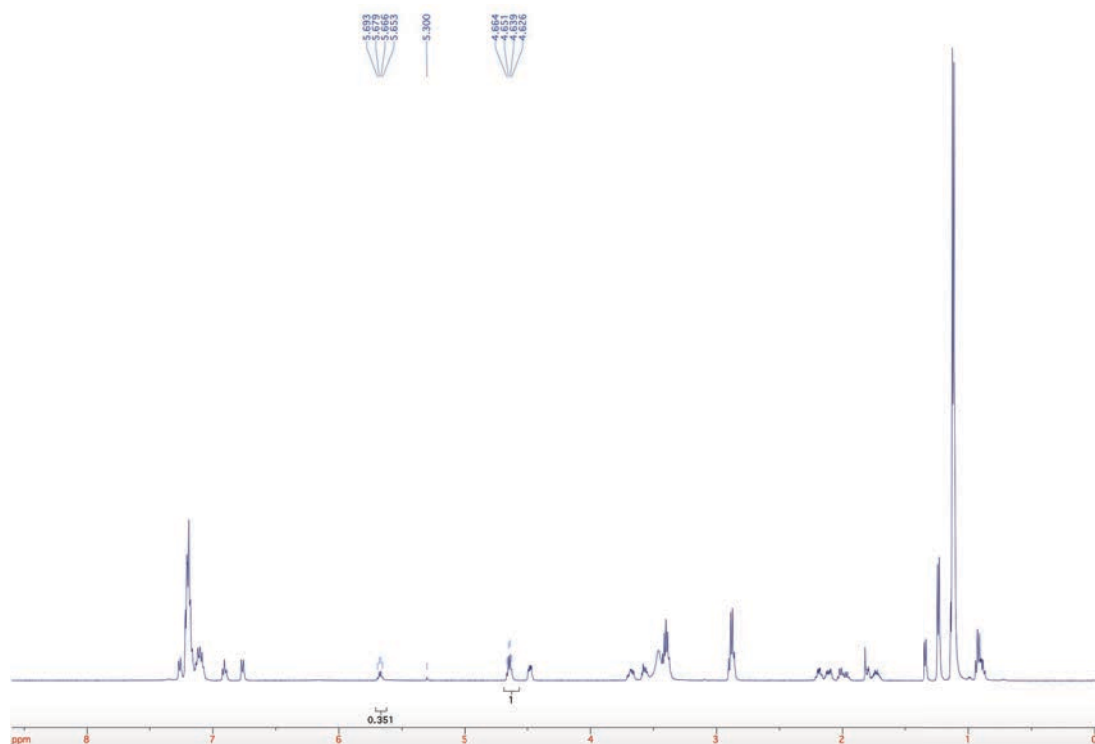
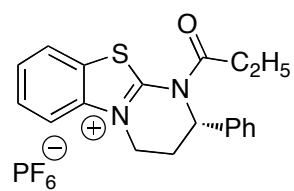
Totals : 5267.18054 237.93433

Results obtained with enhanced integrator!

=====

*** End of Report ***

=====



Data File C:\HPCHEM\1\DATA\ALEX\M-278-O2.D

Sample Name: SMM-278-OH2-PF6

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

=====

Injection Date : 10/7/2013 3:07:38 PM

Sample Name : SMM-278-OH2-PF6

Location : Vial 41

Acq. Operator : Alex

Inj Volume : 20 µl

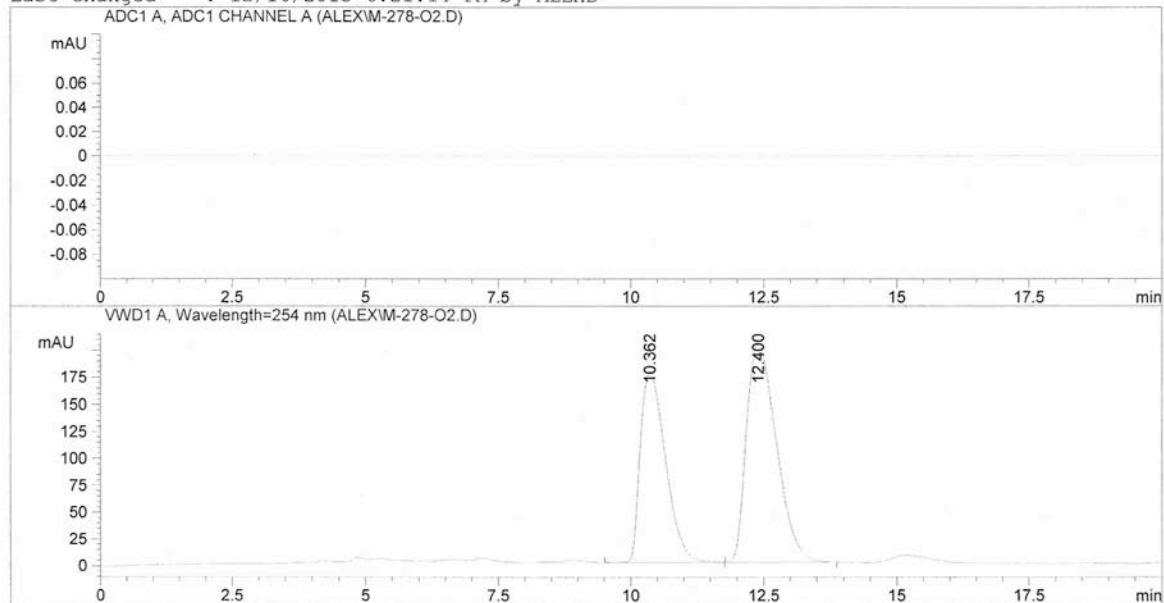
Acq. Method : C:\HPCHEM\1\METHODS\ALEX.M

Last changed : 10/7/2013 2:40:34 PM by Alex

(modified after loading)

Analysis Method : C:\HPCHEM\1\METHODS\ALEXB.M

Last changed : 12/16/2015 6:21:14 PM by ALEXB



=====

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

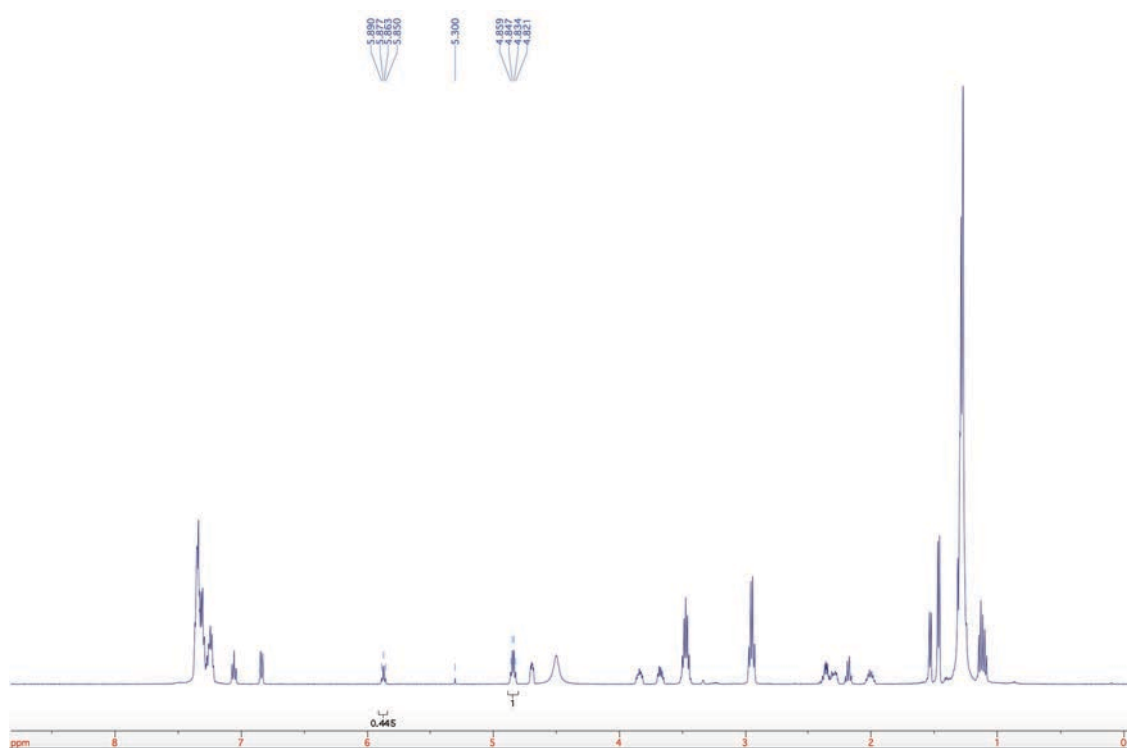
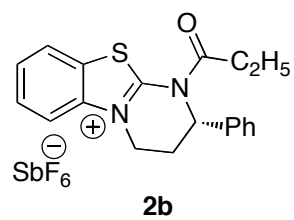
Signal 2: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Height [mAU]	Area %
1	10.362	VB	0.5300	5851.21777		176.25667	42.4415
2	12.400	BB	0.6042	7935.34326		201.88766	57.5585

Totals : 1.37866e4 378.14433

Results obtained with enhanced integrator!

*** End of Report ***

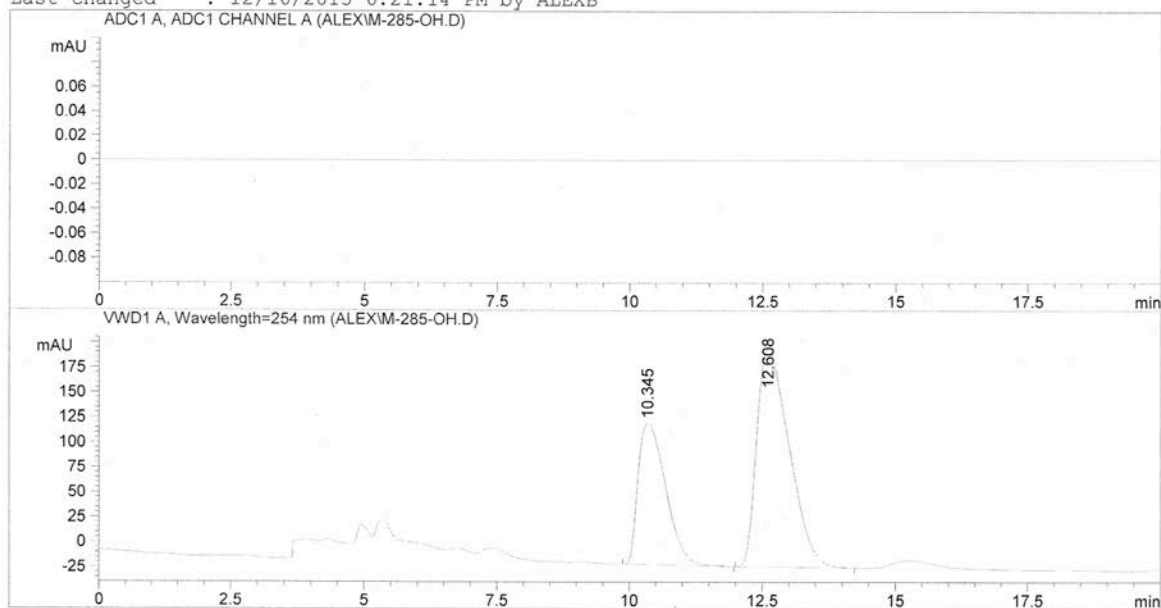
SbF₆ Salt

Data File C:\HPCHEM\1\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 Location : Vial 61
Acq. Operator : SHAWN Inj Volume : 20 µl
Acq. Method : C:\HPCHEM\1\METHODS\ALEX.M
Last changed : 10/7/2013 3:56:21 PM by Alex
Analysis Method : C:\HPCHEM\1\METHODS\ALEXB.M
Last changed : 12/16/2015 6:21:14 PM by ALEXB



=====
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 [min]	Type	Width [min]	Area mAU	Height [mAU]	Area %
1	10.345	VP	0.5539	5129.94238	142.03905	35.5690
2	12.608	BP	0.6479	9292.57813	218.35796	64.4310

Totals : 1.44225e4 360.39700

Results obtained with enhanced integrator!

=====
*** End of Report ***

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	entry	mass in 1 mL volumetric flask (mg)	TLC solvent conditions	TLC stain
3	1	2.5	7:3 hexanes/ethyl acetate	PMA
3	2	2.5	7:3 hexanes/ethyl acetate	PMA
3	3	2.9	3:1 hexanes/ethyl acetate	PMA
3	4	2.9	3:1 hexanes/ethyl acetate	PMA
3	5	2.2	3:1 hexanes/ethyl acetate	PMA
3	6	3.0	6:1 hexanes/ethyl acetate	Dragendorf-Munier ^a
3	7	2.6	6:1 hexanes/ethyl acetate	PMA
3	8	2.0	6:1 hexanes/ethyl acetate	PMA
4	1	5.9	6:1 hexanes/ethyl acetate	KMnO ₄
4	2	4.3	6:1 hexanes/ethyl acetate	PMA
4	3	4.3	6:1 hexanes/ethyl acetate	PMA
4	4	3.0	ethyl acetate	Dragendorf-Munier ^a
4	5	4.5	6:1 hexanes/ethyl acetate	KMnO ₄
4	6	4.0	6:1 hexanes/ethyl acetate	PMA
4	7	3.4	3:1 hexanes/ethyl acetate	PMA
4	8	3.6	6:1 hexanes/ethyl acetate	PMA

(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 μ L) and (*R*)-6 (91.0 μ 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 μ L) and (*R*)-6 (167 μ 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 μ L) and (*R*)-6 (333 μ 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. μ L) and (*R*)-6 (500. μ 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 SI.2. Mixed ratios of **(R)-5** and **(R)-6** in solutions used for GC-MS calibration curves

solution	concentration (mM)		ratio		simulated conversion
	(R)-5	(R)-6	(R)-5	(R)-6	(%)
1	2.6	0.26	10	1	9.1
2	2.4	0.48	5	1	17
3	1.9	0.97	2	1	33
4	1.5	1.5	1	1	50
5	0.97	1.9	1	2	67
6	0.48	2.4	1	5	83
7	0.26	2.6	1	10	91

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 SI.3). GC-MS peak

intensities were divided by 100,000,000 to simplify 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.

Solution	GC-MS integration		GC-MS integration (/100000000)	
	(R)-5	(R)-6	(R)-5	(R)-6
1	1669713607	474853025	16.69713607	4.74853025
2	1392970981	706776467	13.92970981	7.06776467
3	1014542369	1308193746	10.14542369	13.08193746
4	642913949	1819330621	6.42913949	18.19330621
5	397478401	2730191225	3.97478401	27.30191225
6	122986457	3572101899	1.22986457	35.72101899
7	45344897	4272364606	0.45344897	42.72364606

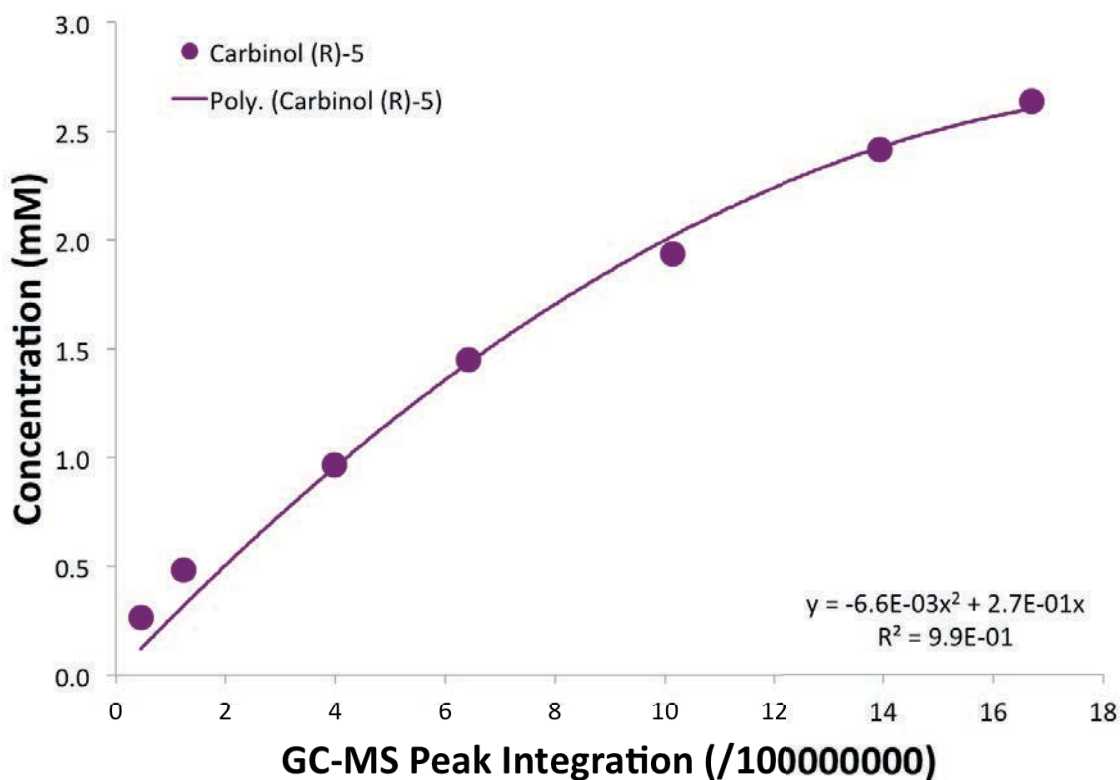


Figure SI.1. Calibration curve for concentration of **(R)-5** relative to GC-MS peak intensity

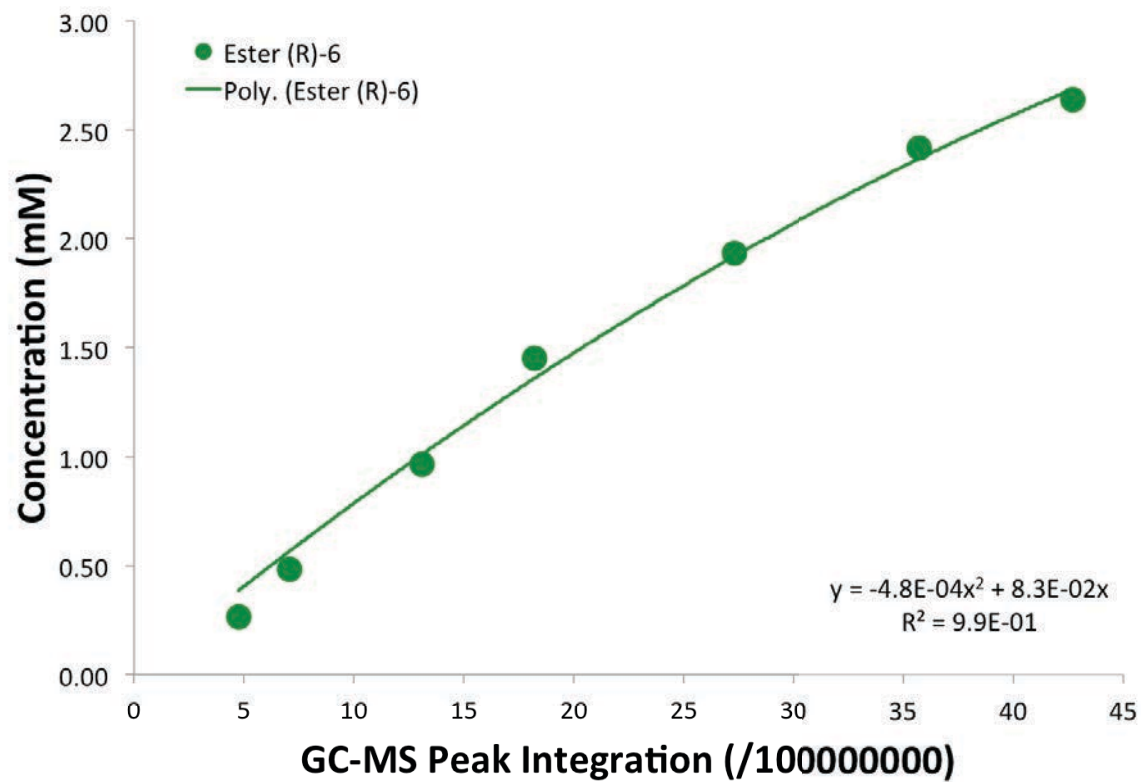


Figure SI.2. Calibration curve for concentration of (*R*)-6 relative to GC-MS peak intensity

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-*d*₄ (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 resolvated in methylene chloride (2 mL), washed with saturated aqueous NaHCO₃ (2 × 2 mL) and brine (1 × 2 mL). The organic layer was dried (MgSO₄), 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

Entry	substrate		CDCl ₃ added to substrate		substrate added to each reaction		substrate stock solution	reaction concentration		
	(mg)	(μ mol)	(μ L)	(mL)	(μ mol)	(nmol)	conc. (M)	(M)	(mM)	[KIT]
1	6.8	40	250	0.250	16	16000	0.16	0.029	29	2x
2	3.4	20	250	0.250	8.0	8000	0.079	0.014	14	same
3	3.4	20	500	0.500	4.0	4000	0.039	0.0072	7.2	1/2
4	3.4	20	750	0.750	2.7	2700	0.027	0.0048	4.8	1/3
5	3.4	20	1250	1.250	1.6	1600	0.016	0.0029	2.9	1/5
6	3.4	20	2500	2.500	0.80	800	0.0079	0.0014	1.4	1/10

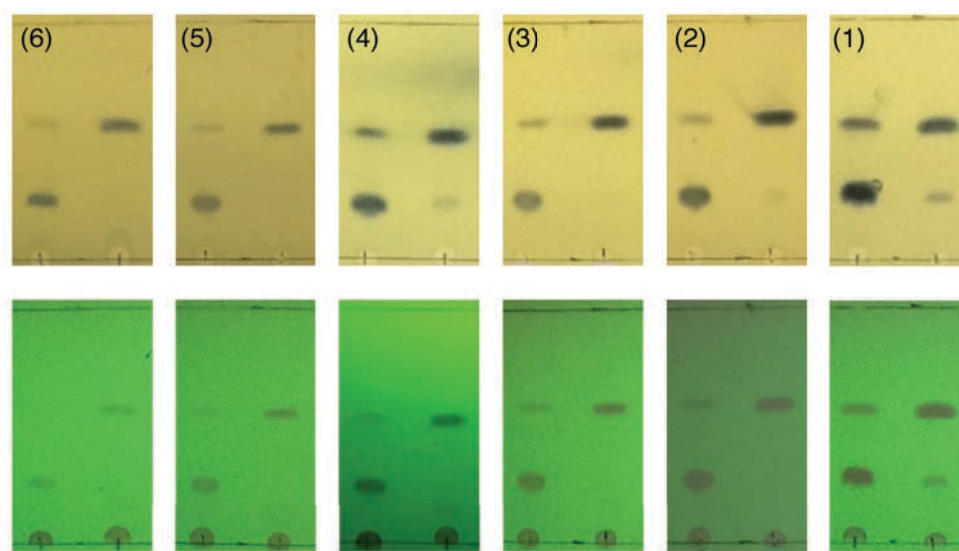
**Figure SI.3.** TLC plate images of CEC kit conditions for entries 1-6 in Table SI.4, plotted in Figure 6. The left lane of each TLC plate contains *R*-HBTM and the right lane contains *S*-HBTM. Plates were eluted in 30% ethyl acetate in hexanes. Visualization was achieved by UV lamp (bottom row) and 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

Entry	volume for 2.5 mM	GC-MS integration		GC-MS integration (/100000000)		calculated conc. (mM)		rxn conv.
	(mL)	(<i>R</i>)-5	(<i>R</i>)-6	(<i>R</i>)-5	(<i>R</i>)-6	(<i>R</i>)-5	(<i>R</i>)-6	(%)
1	11.49	454669679	206664466	4.54669679	2.06664466	1.1	0.17	13
2	5.74	454000294	231883693	4.54000294	2.31883693	1.1	0.19	15
3	2.87	533763819	298020674	5.33763819	2.98020674	1.3	0.24	16
5	1.15	627156689	337632800	6.27156689	3.376328	1.4	0.27	16
6	0.57	628174270	353906743	6.2817427	3.53906743	1.4	0.29	17

Table SI.6. *S*-HBTM GC-MS integration data and reaction conversion for entries 1-6 of Table SI.4 plotted in Figure 6

Entry	volume for 2.5 mM	GC-MS integration		GC-MS integration (/100000000)		calculated conc. (mM)		rxn conv.
	(mL)	(<i>R</i>)-5	(<i>R</i>)-6	(<i>R</i>)-5	(<i>R</i>)-6	(<i>R</i>)-5	(<i>R</i>)-6	(%)
1	11.49	7044090	858842838	0.0704409	8.58842838	0.019	0.68	97
2	5.74	2194404	1042526810	0.02194404	10.4252681	0.0059	0.81	99
3	2.87	3228511	1038670941	0.03228511	10.38670941	0.0087	0.81	99
5	1.15	3530036	1351621465	0.03530036	13.51621465	0.0095	1.0	99
6	0.57	3540546	1374798635	0.03540546	13.74798635	0.0096	1.1	99

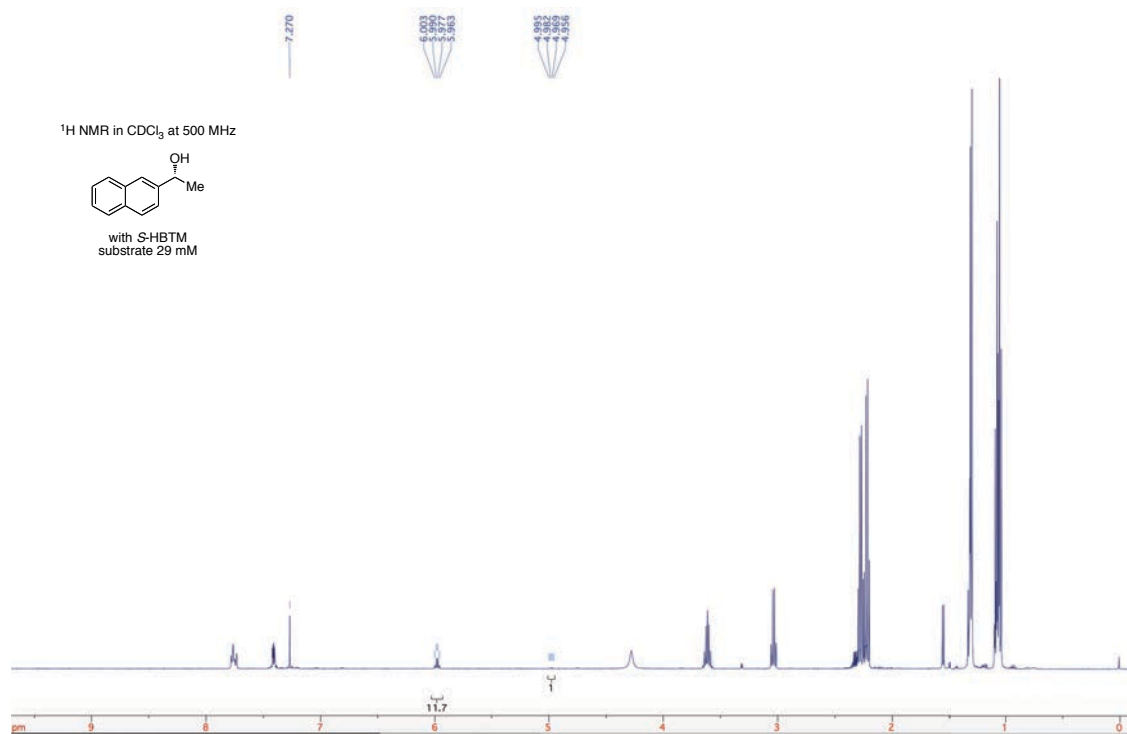
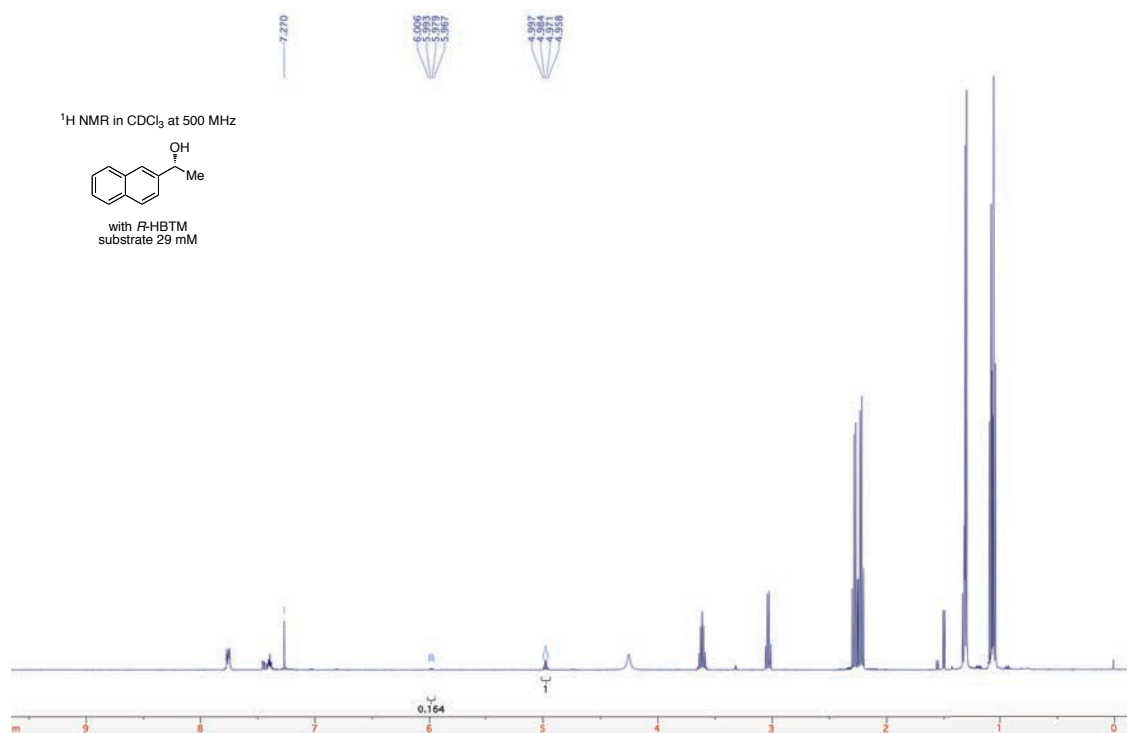
^1H NMR Spectra CEC Analysis for entries 1-6 of Table SI.4 plotted in Figure 6**Table SI.4 Entry 1. 29 mM (*R*)-5 CEC ^1H NMR spectra**

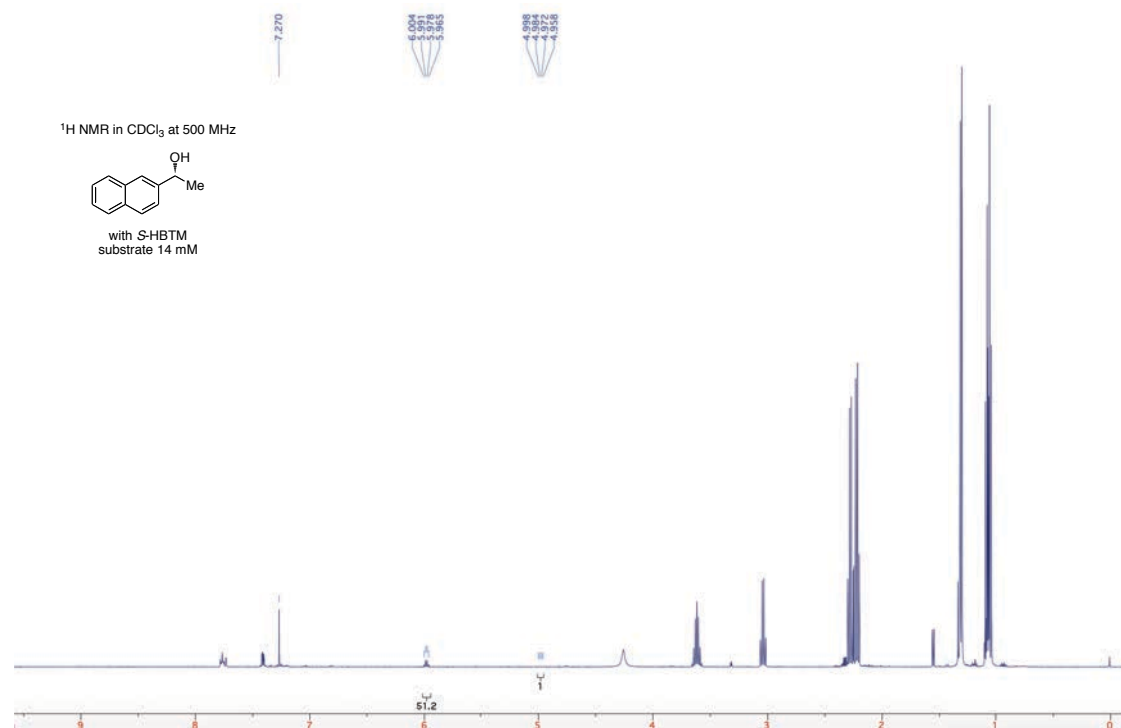
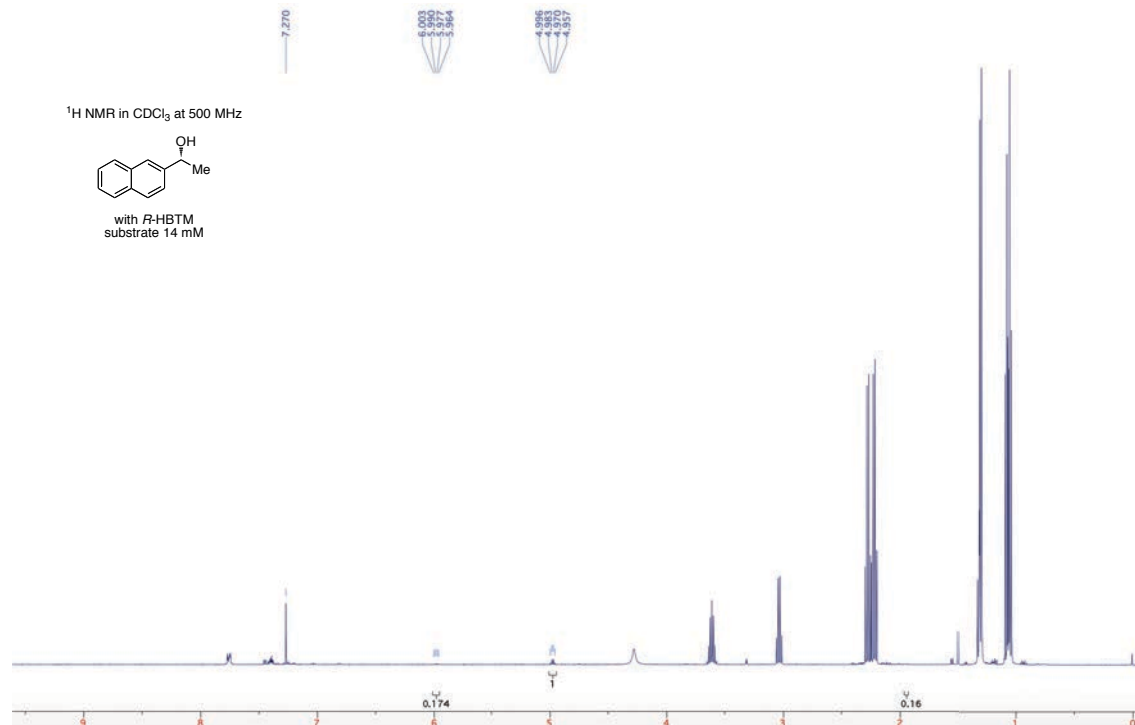
Table SI.4 Entry 2. 14 mM (*R*)-5 CEC ¹H NMR spectra

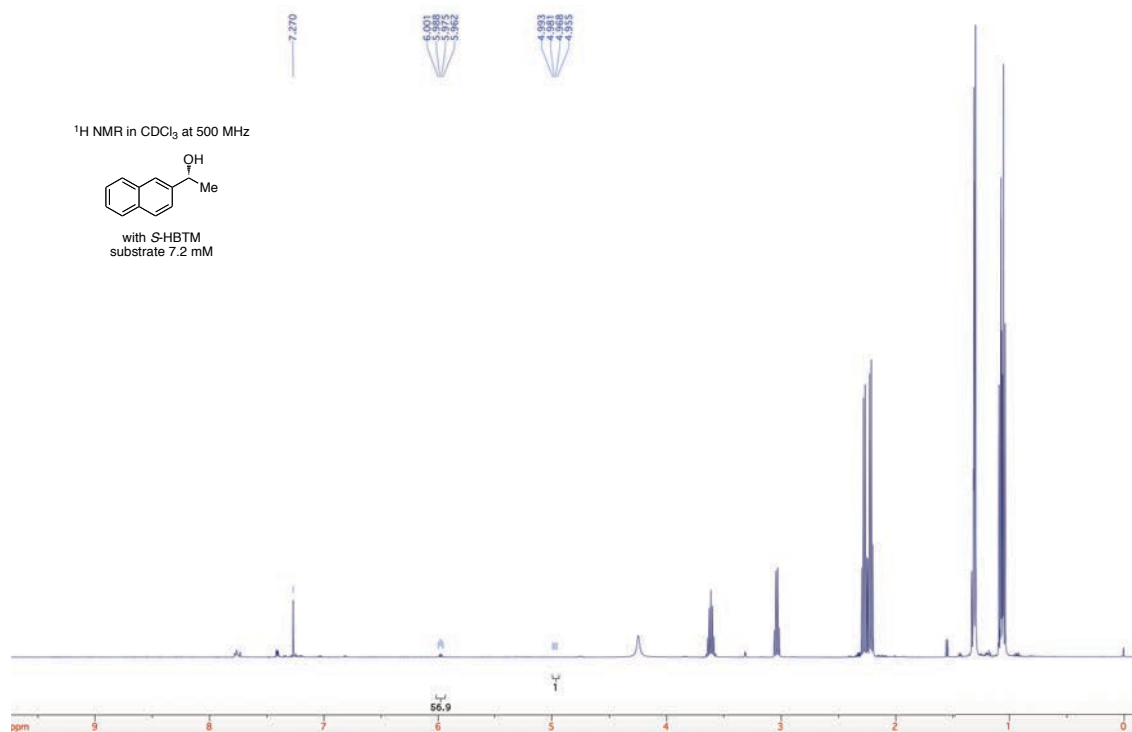
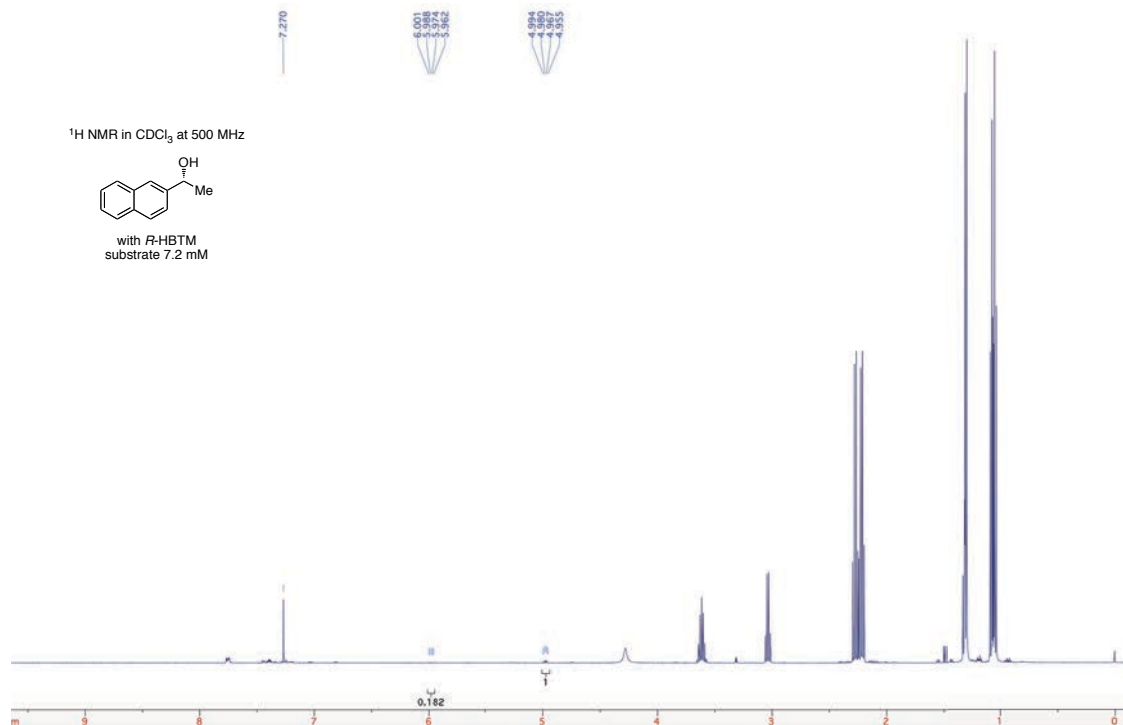
Table SI.4 Entry 3. 7.2 mM (*R*)-5 CEC ^1H NMR spectra

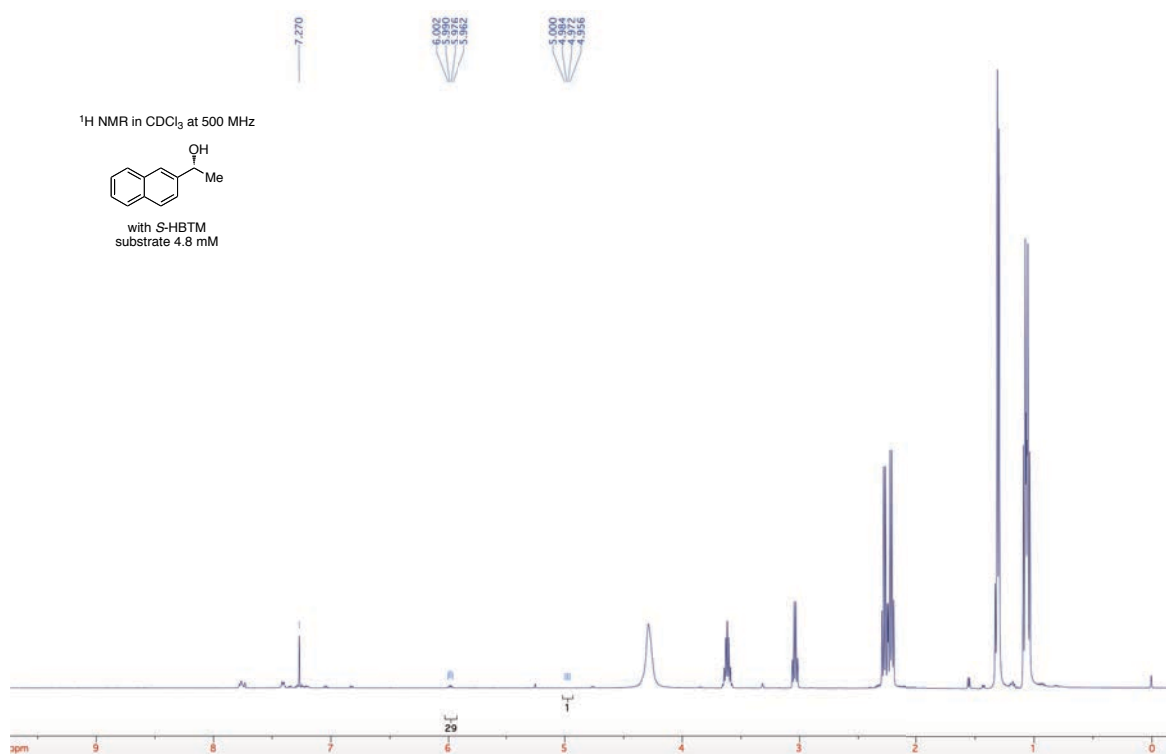
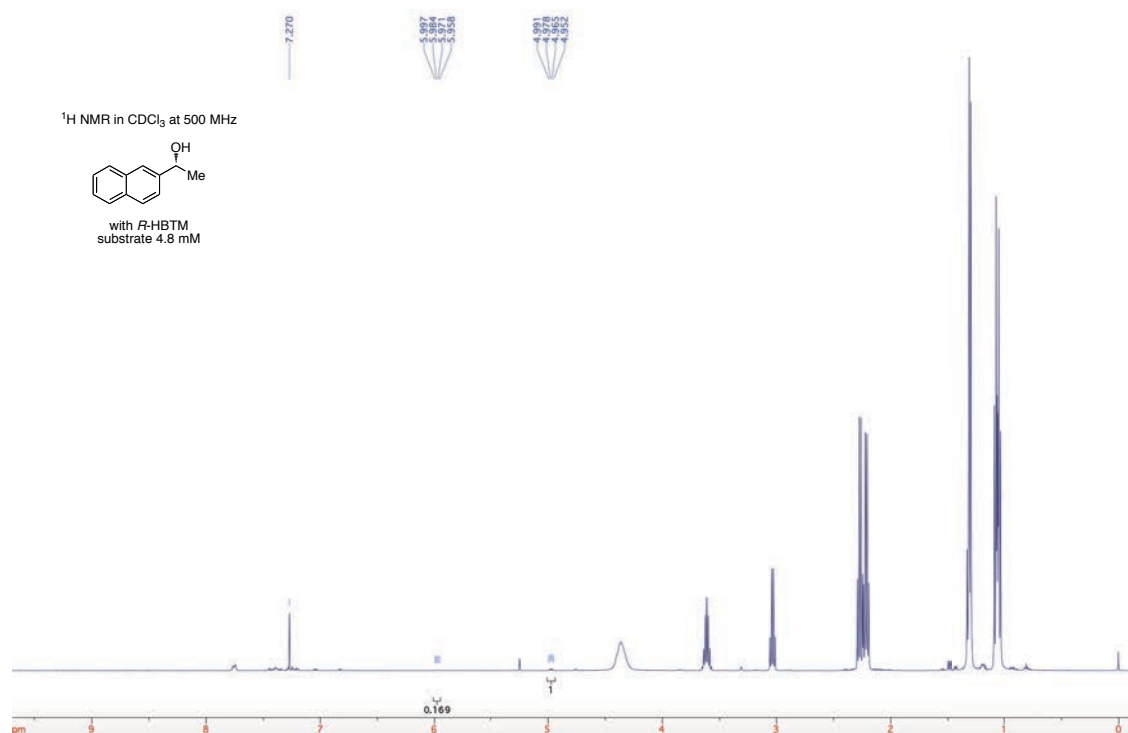
Table SI.4 Entry 4. 4.8 mM (*R*)-5 CEC ^1H NMR spectra

Table SI.4 Entry 5. 2.9 mM (*R*)-**5** CEC ¹H NMR spectra

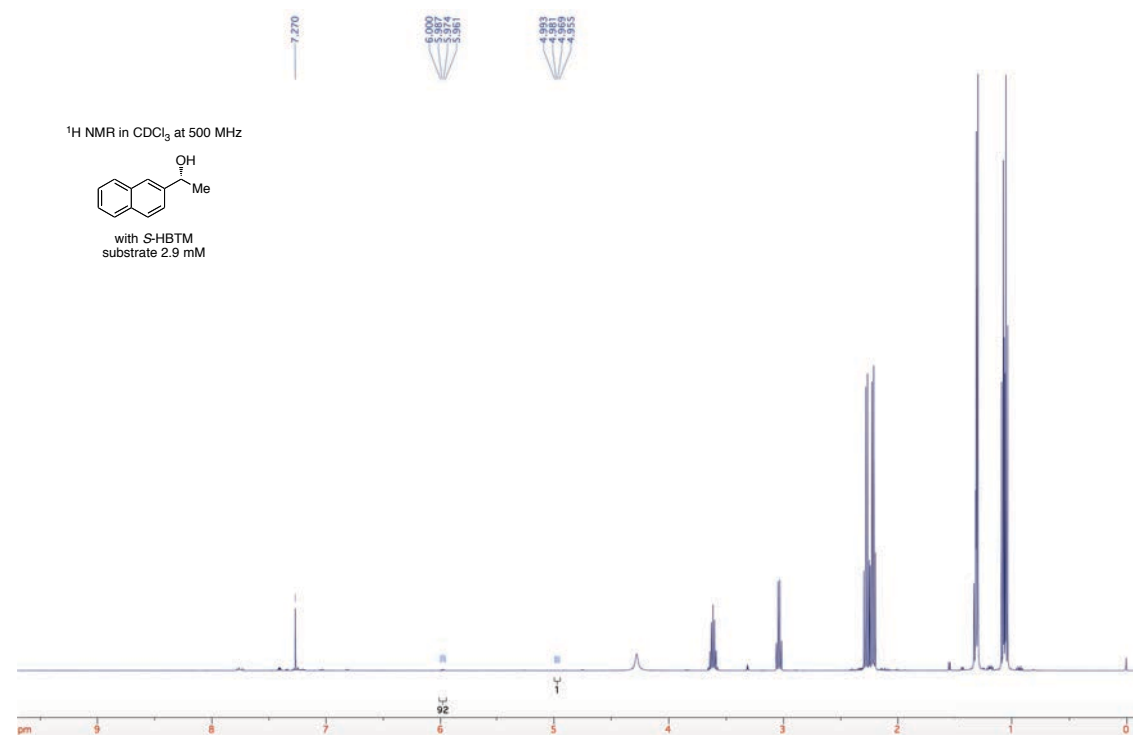
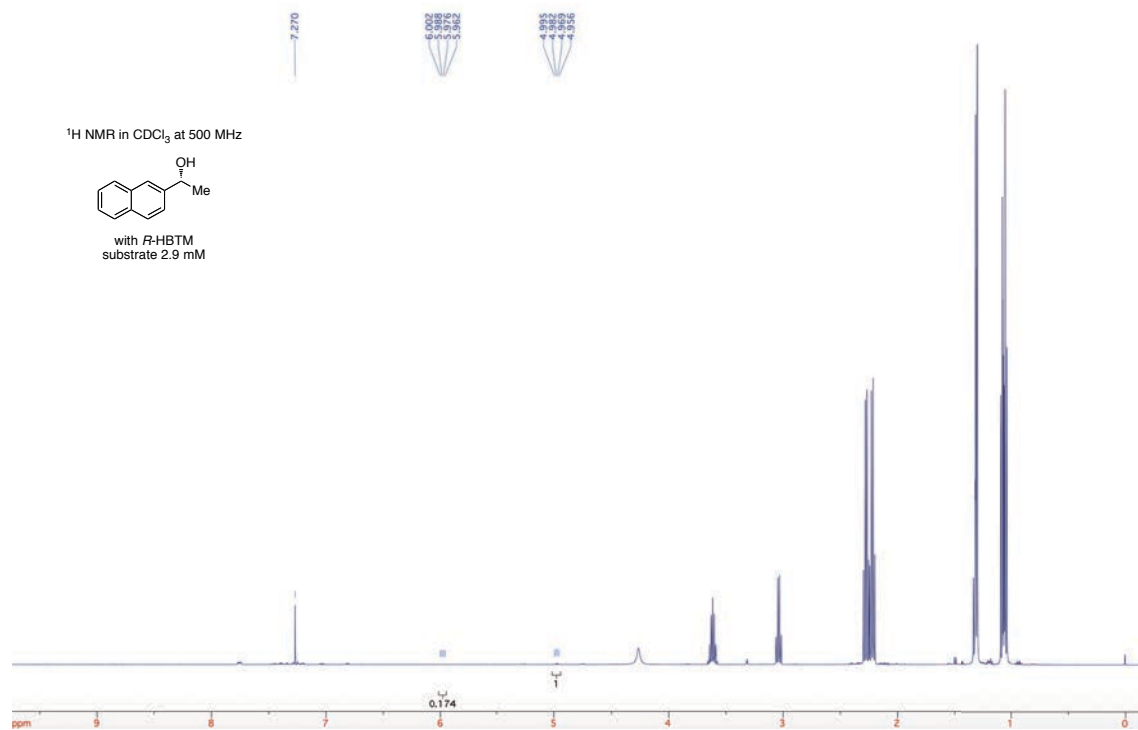
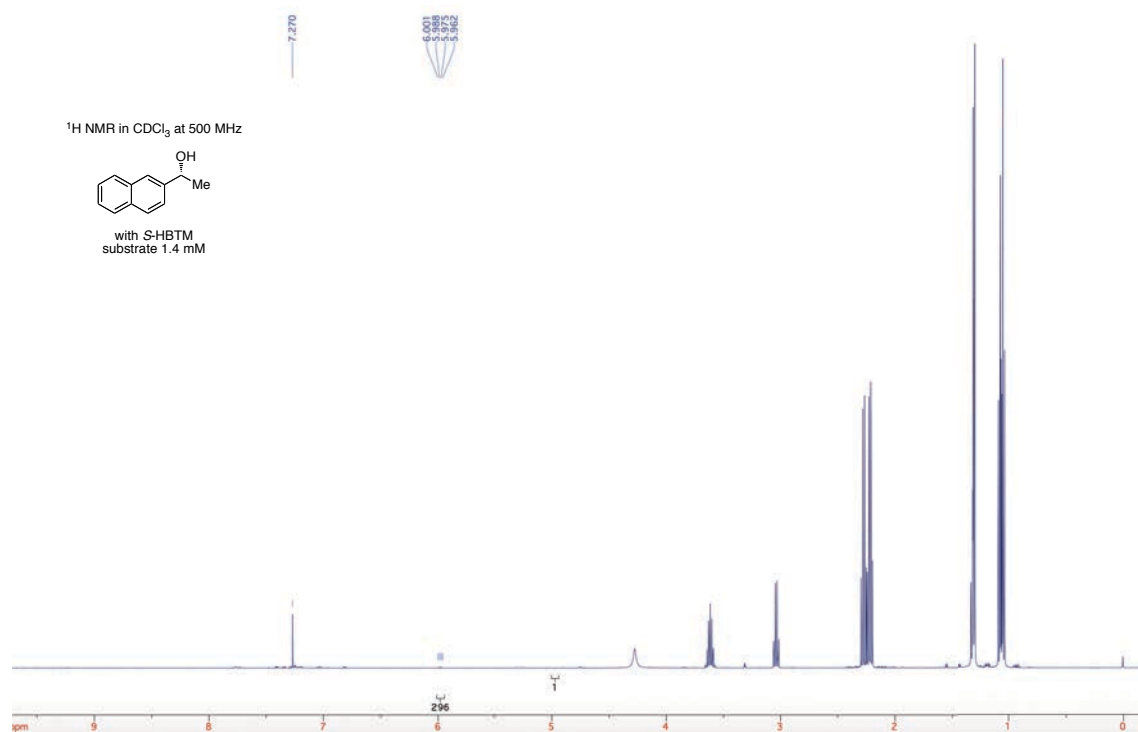
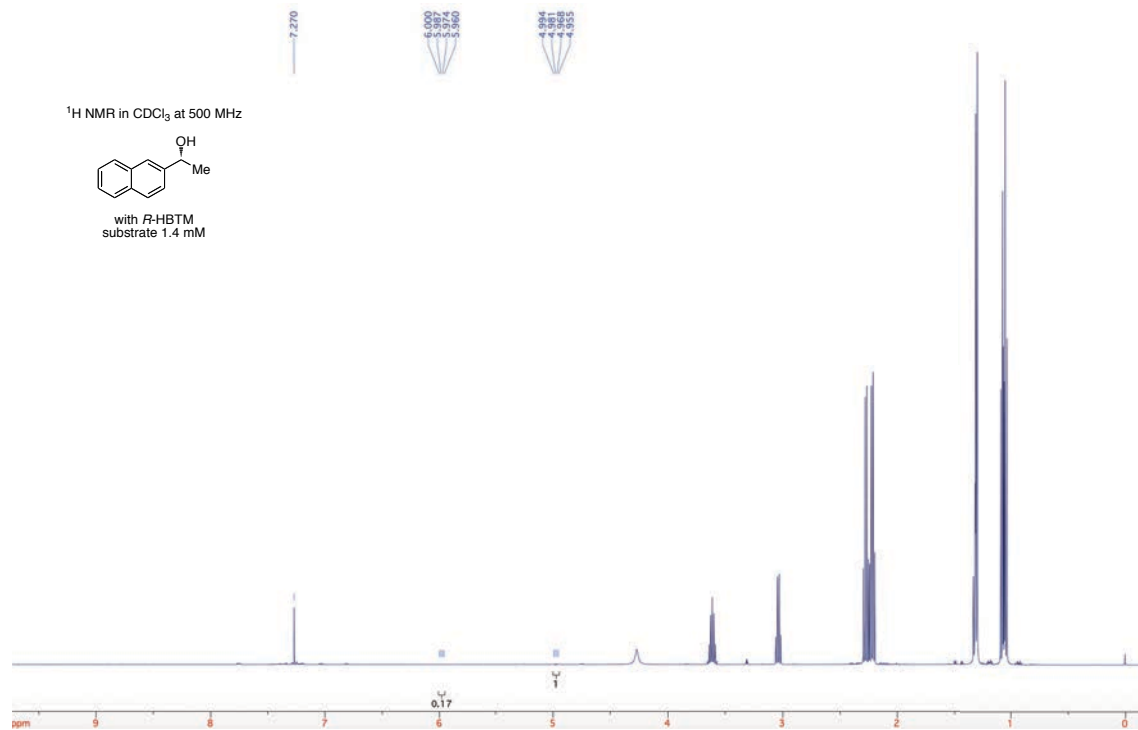


Table SI.4 Entry 6. 1.4 mM (*R*)-5 CEC ¹H NMR spectra

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. μ L) in a 1 dram vial.

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

CEC Protocol

The resulting alcohol solution (100. μ L) 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-*d*₄ (50. μ L) 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 μ L), and the *S*-HBTM reaction (4.0 μ L) 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

entry	substrate loading solvent
1	toluene- <i>d</i> ₈
2	CDCl ₃
3	THF- <i>d</i> ₈
4	acetone- <i>d</i> ₆
5	MeCN- <i>d</i> ₃
6	DMF- <i>d</i> ₇
7	DMSO- <i>d</i> ₆

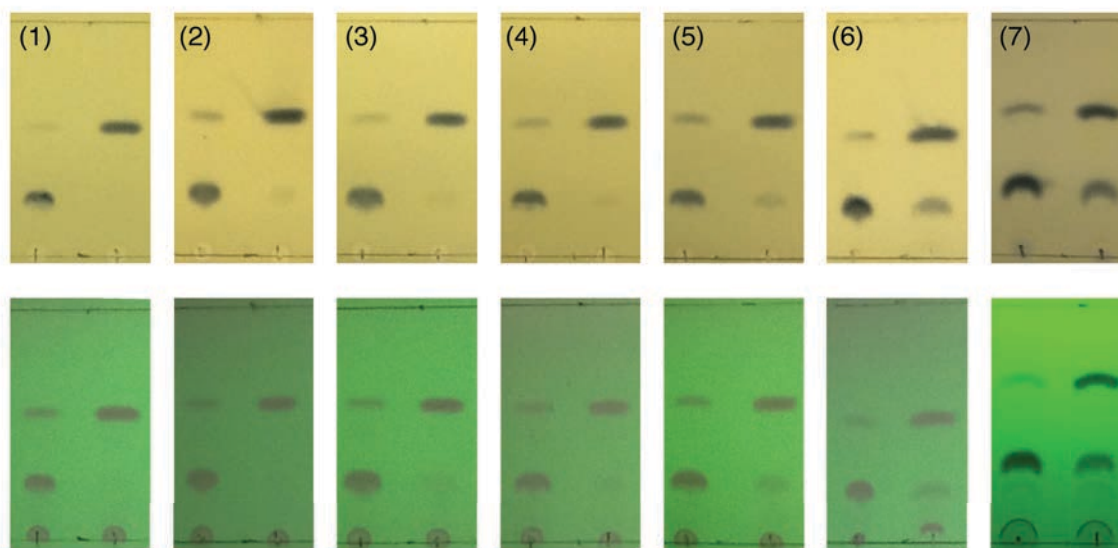


Figure SI.4. TLC plate images of CEC kit conditions for entries 1-7 in Table SI.5. The left lane of each TLC plate contains *R*-HBTM and the right lane contains *S*-HBTM. Plates were eluted in 30% ethyl acetate in hexanes. Visualization was achieved by UV lamp (bottom row) and staining with PMA stain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

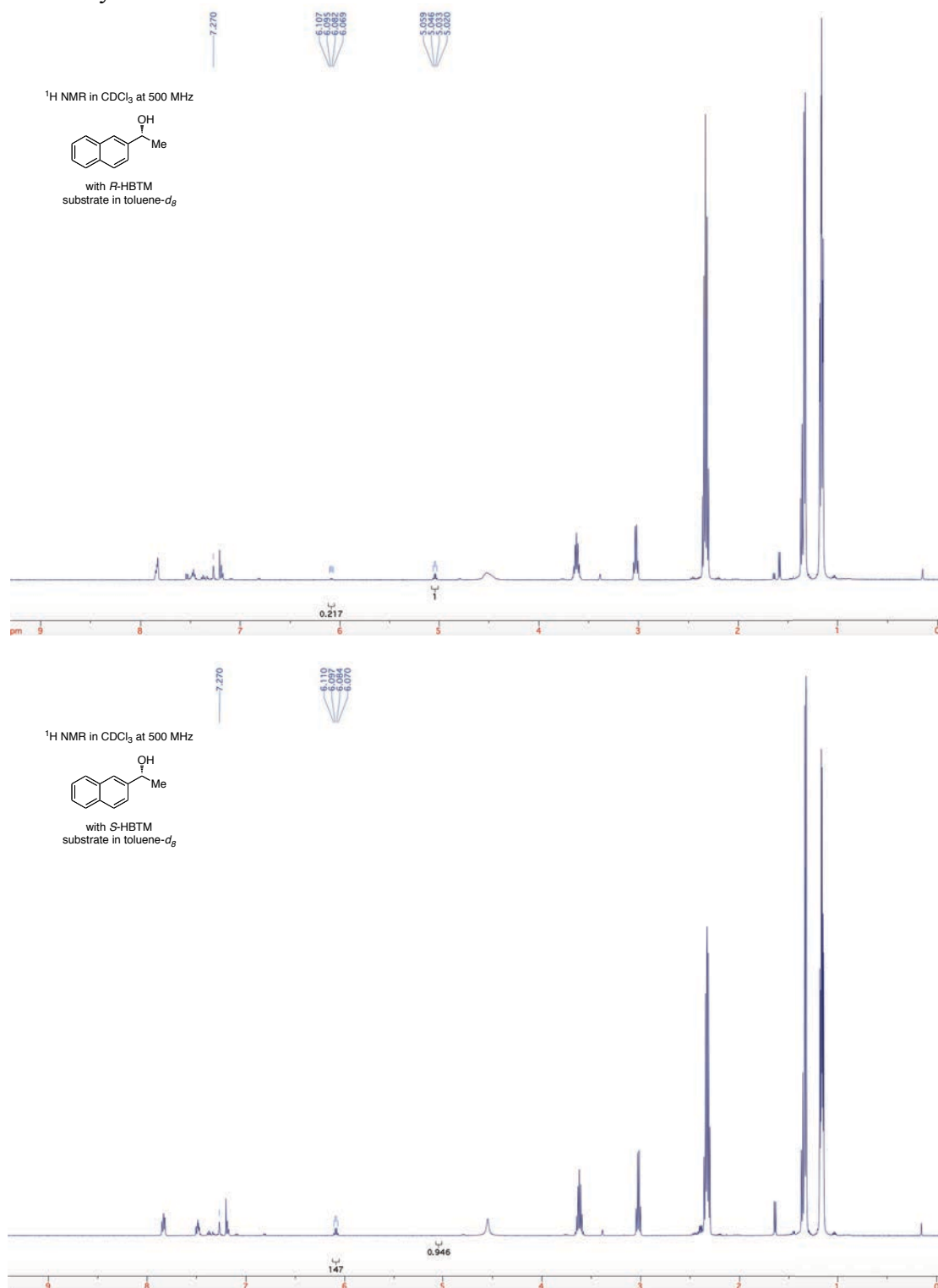
^1H NMR Spectra CEC Analysis of Entries 1-7 from Table 5**Table 5.** Entry 1

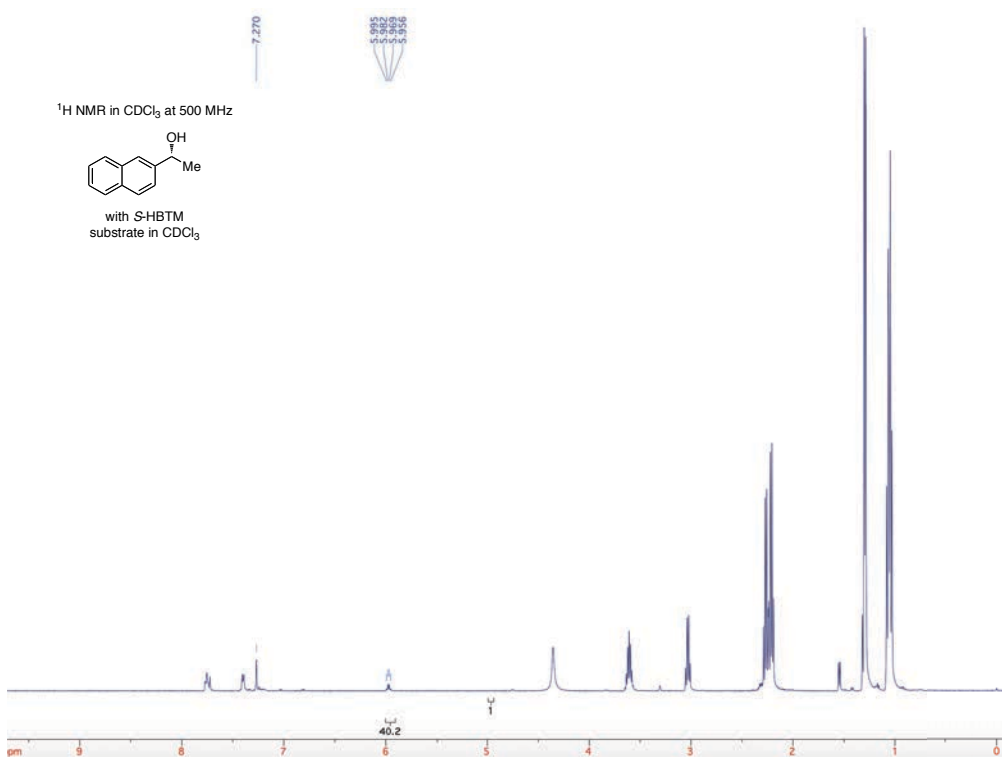
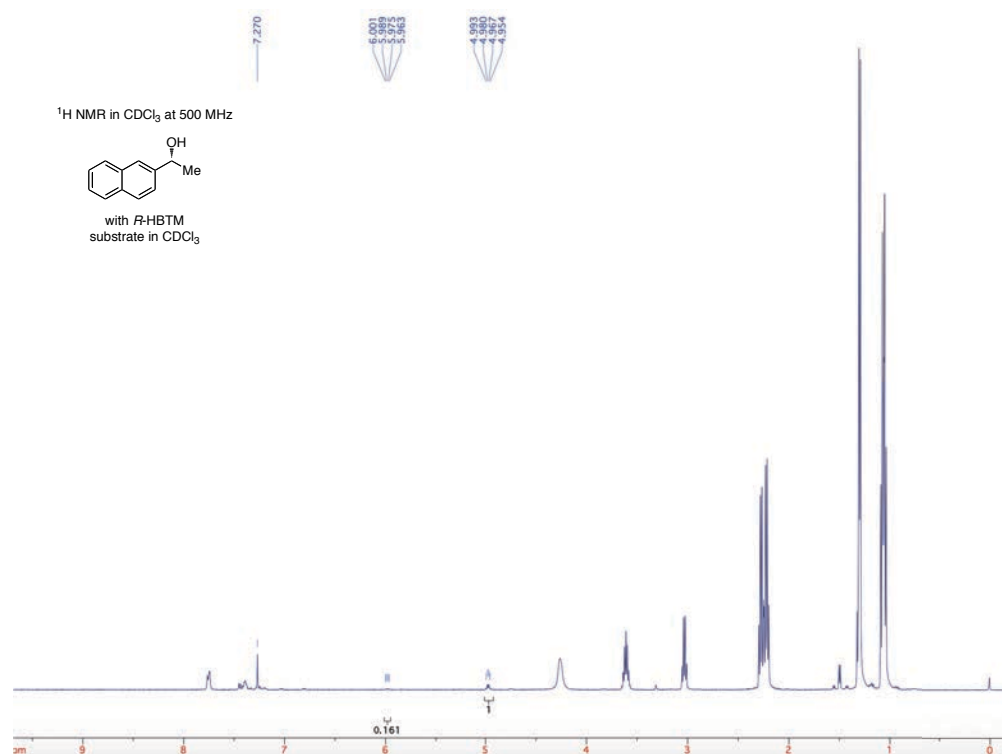
Table 5. Entry 2

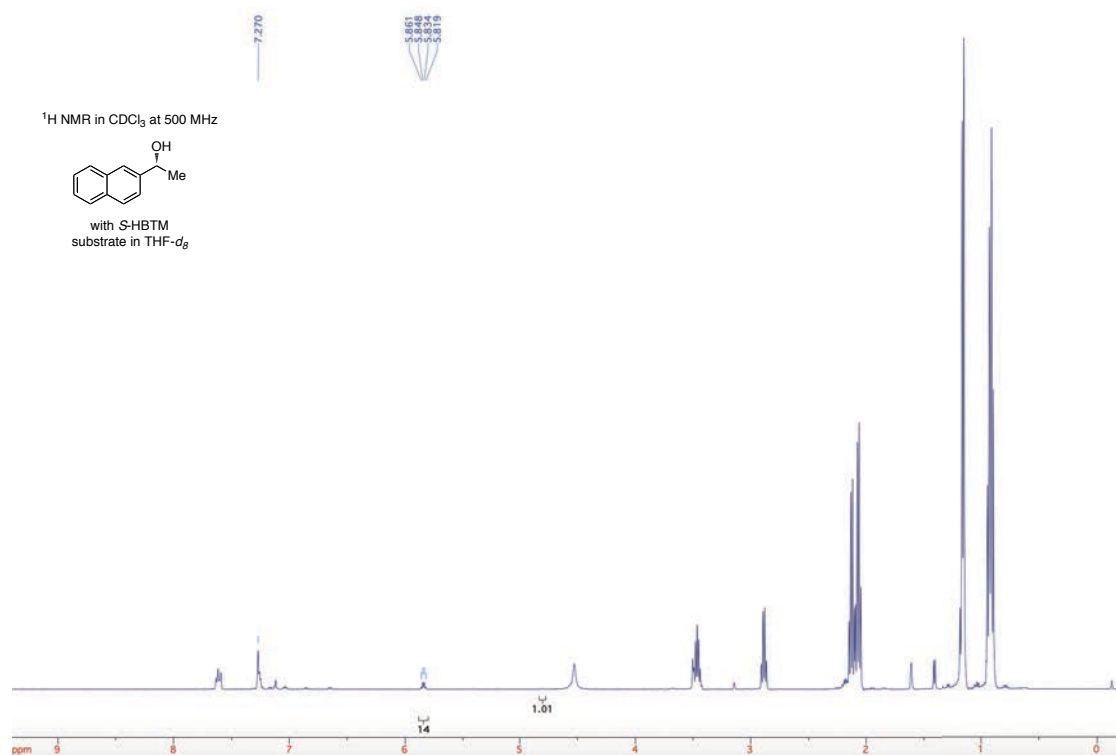
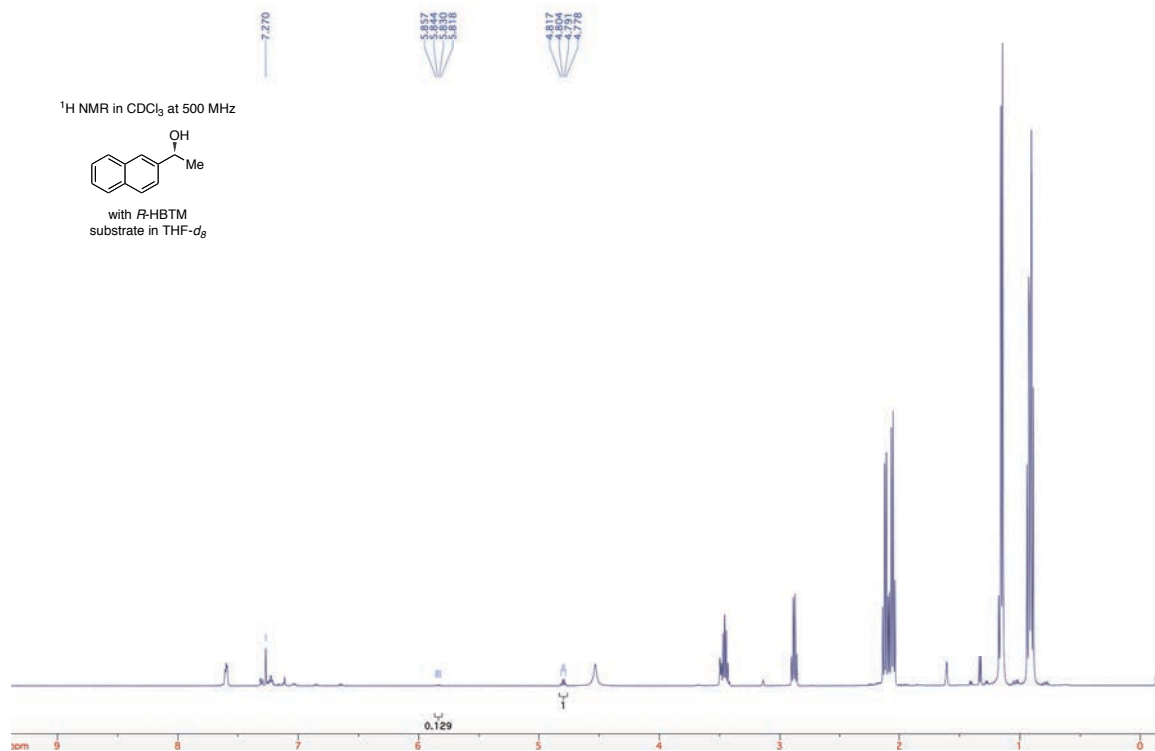
Table 5. Entry 3

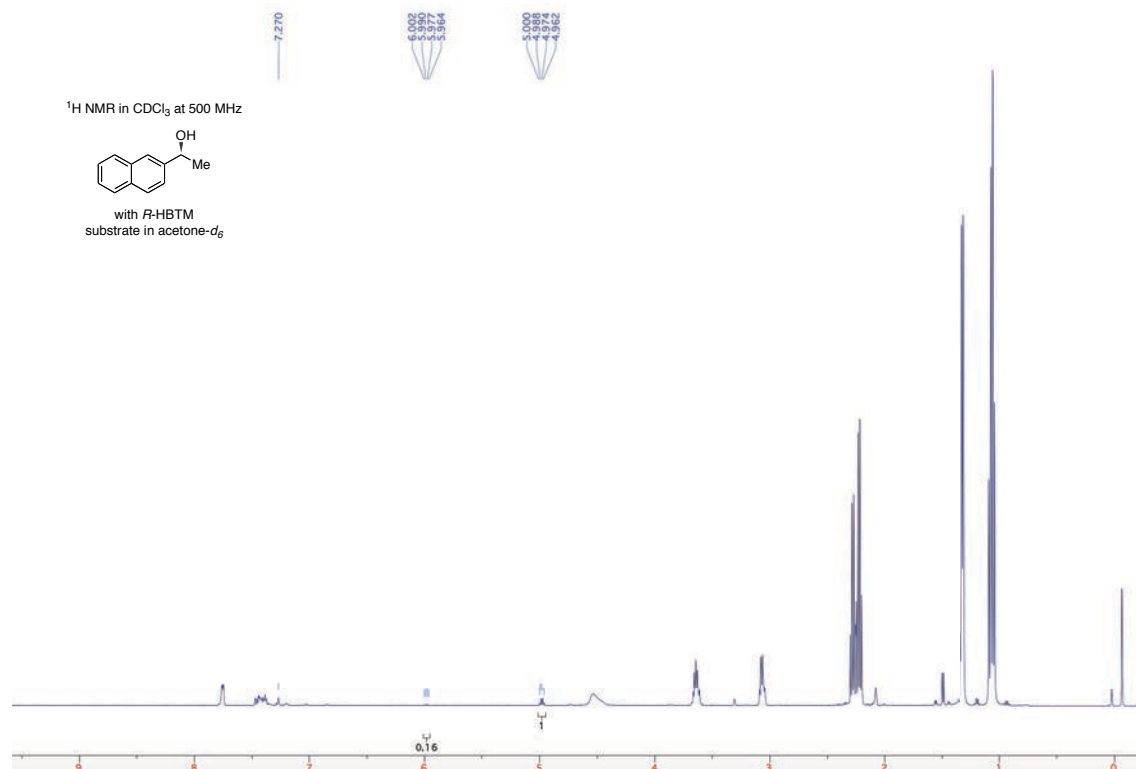
Table 5. Entry 4

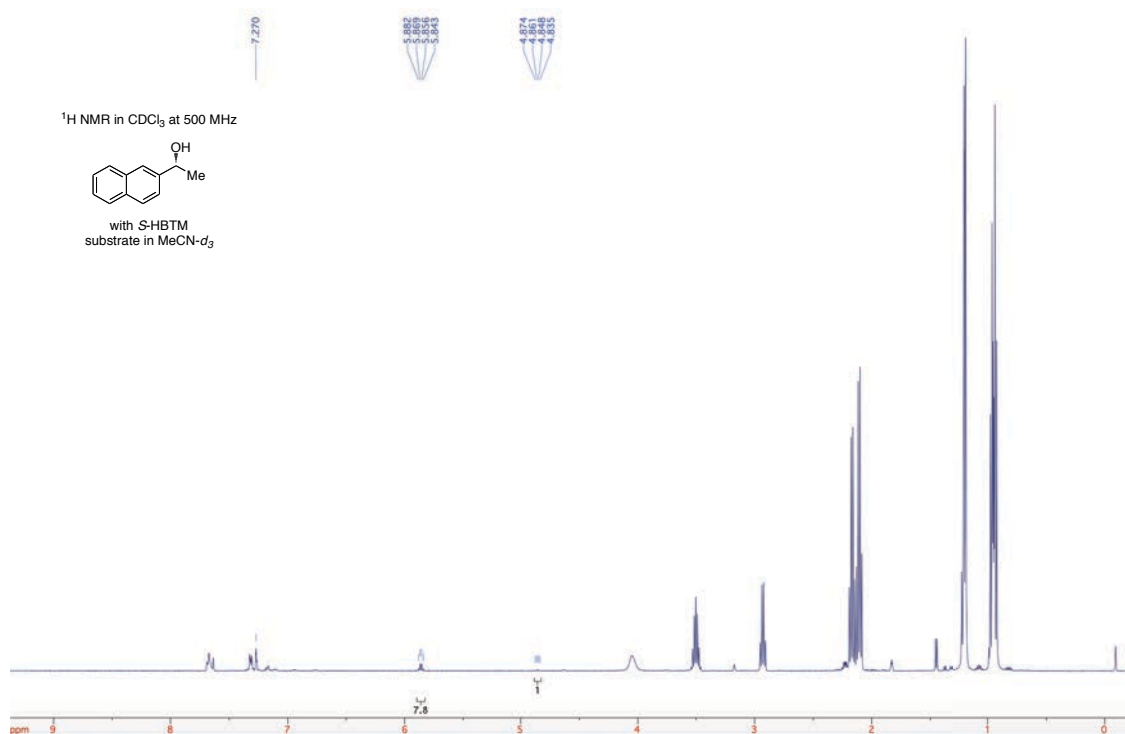
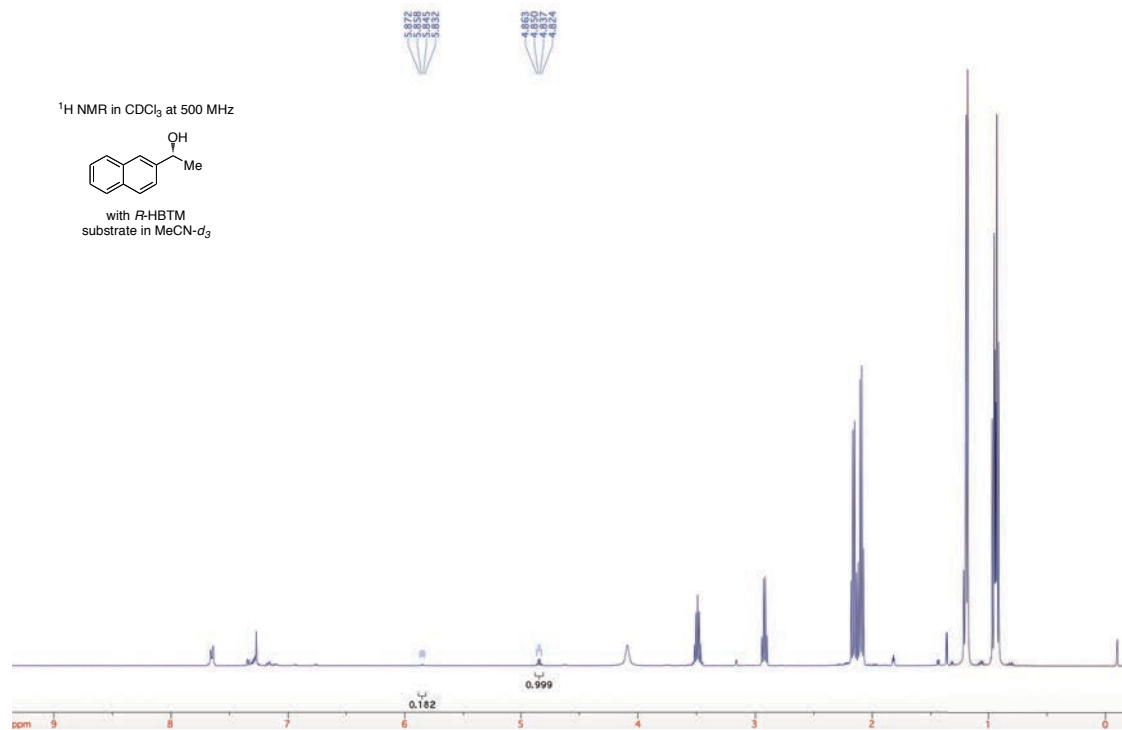
Table 5. Entry 5

Table 5. Entry 6

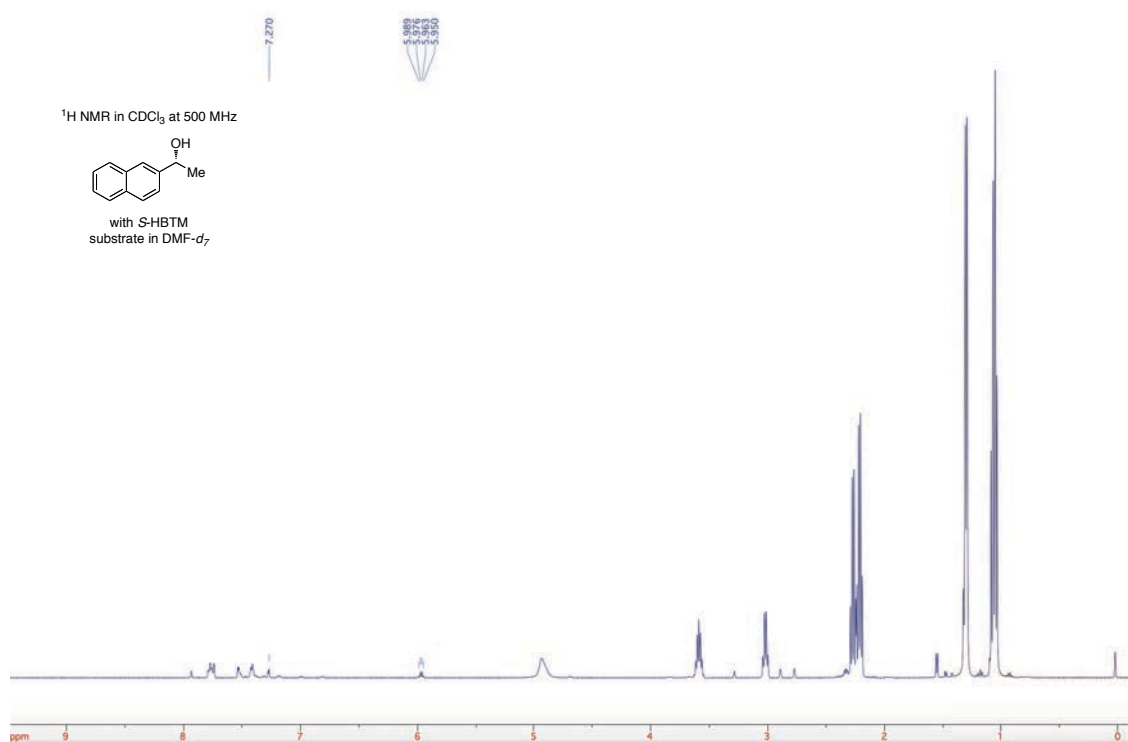
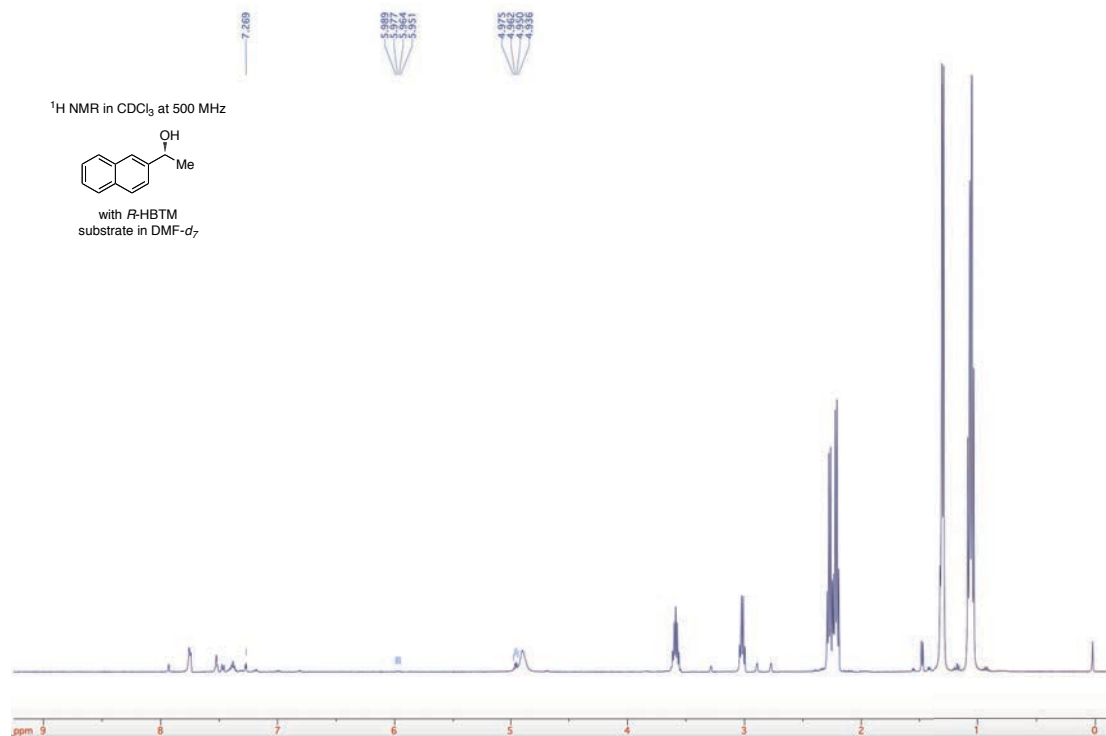


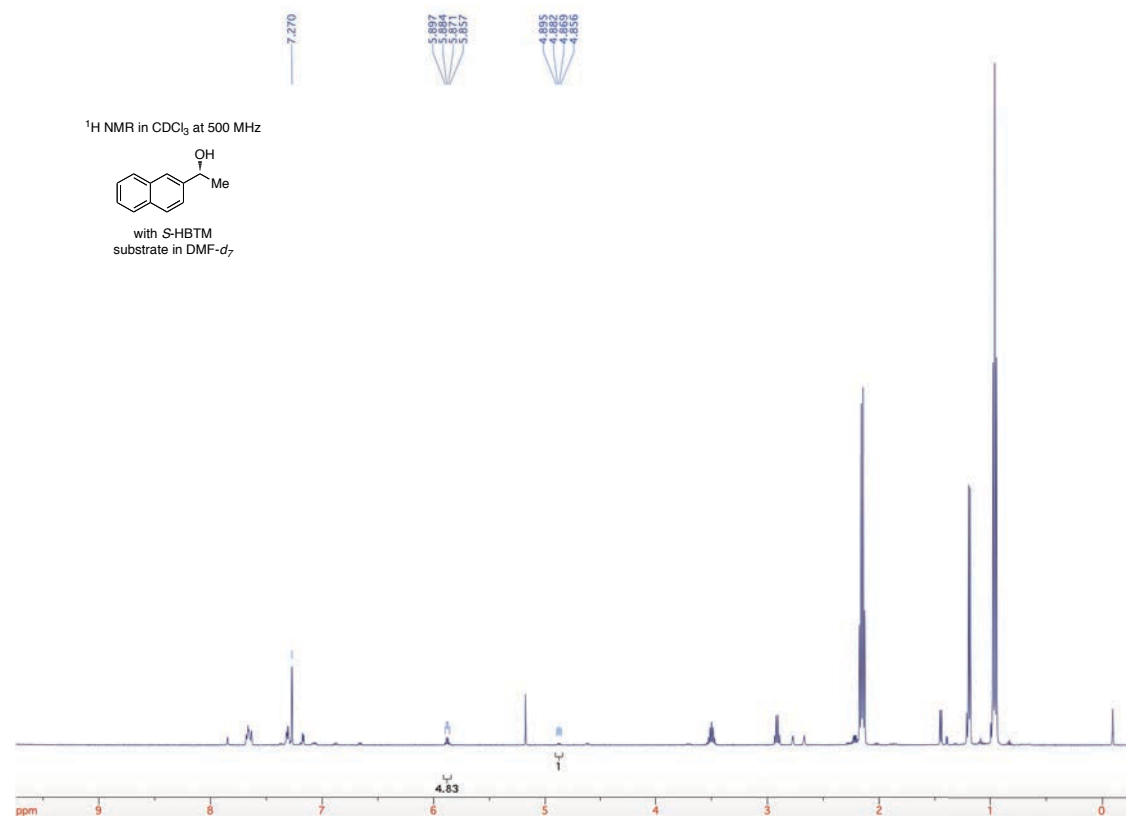
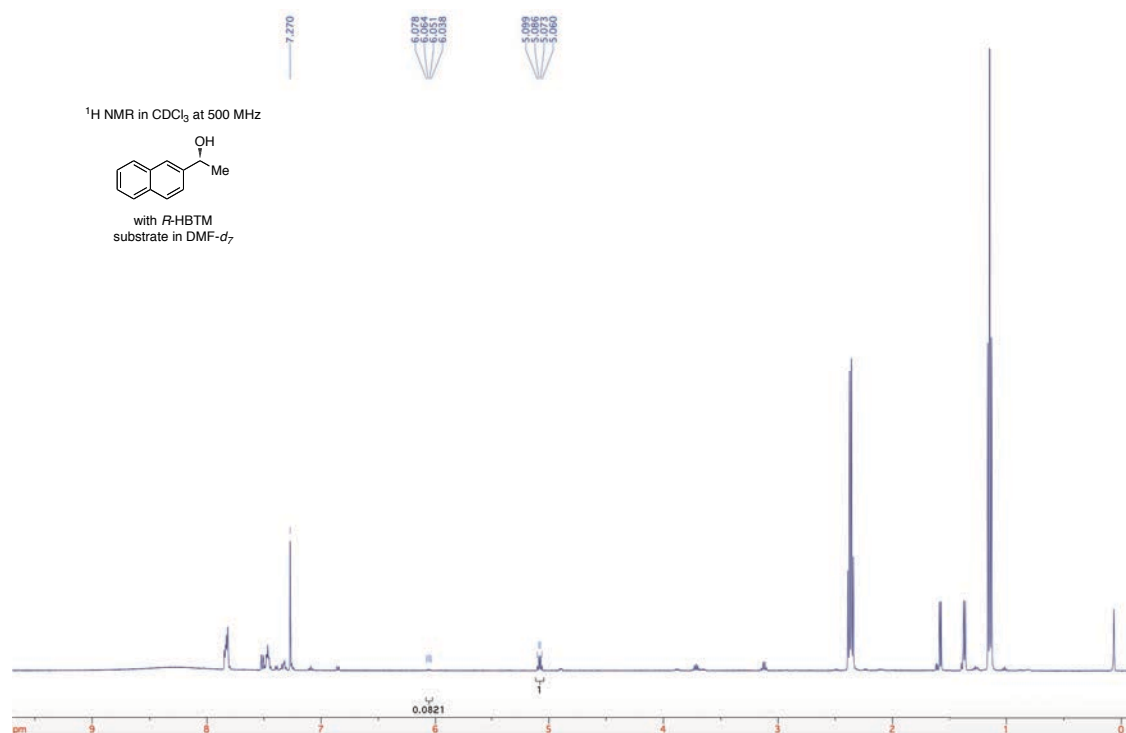
Table 5. Entry 6 – after vacuum removal of solvent and resolution in CDCl_3 

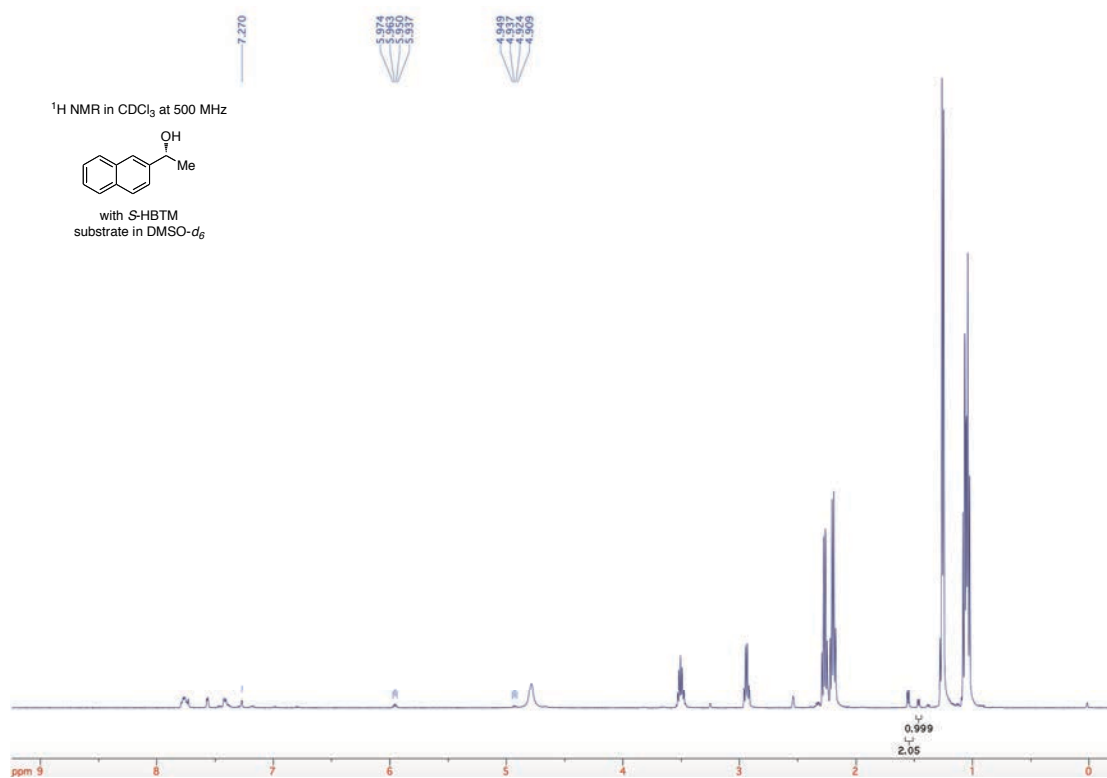
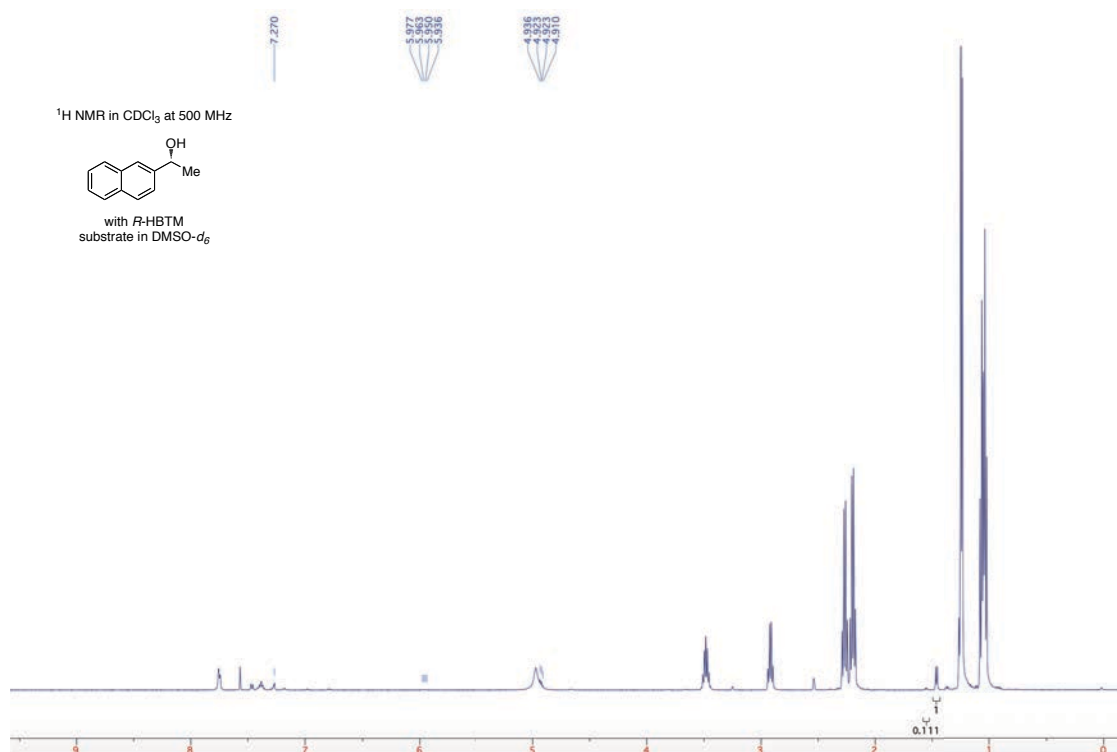
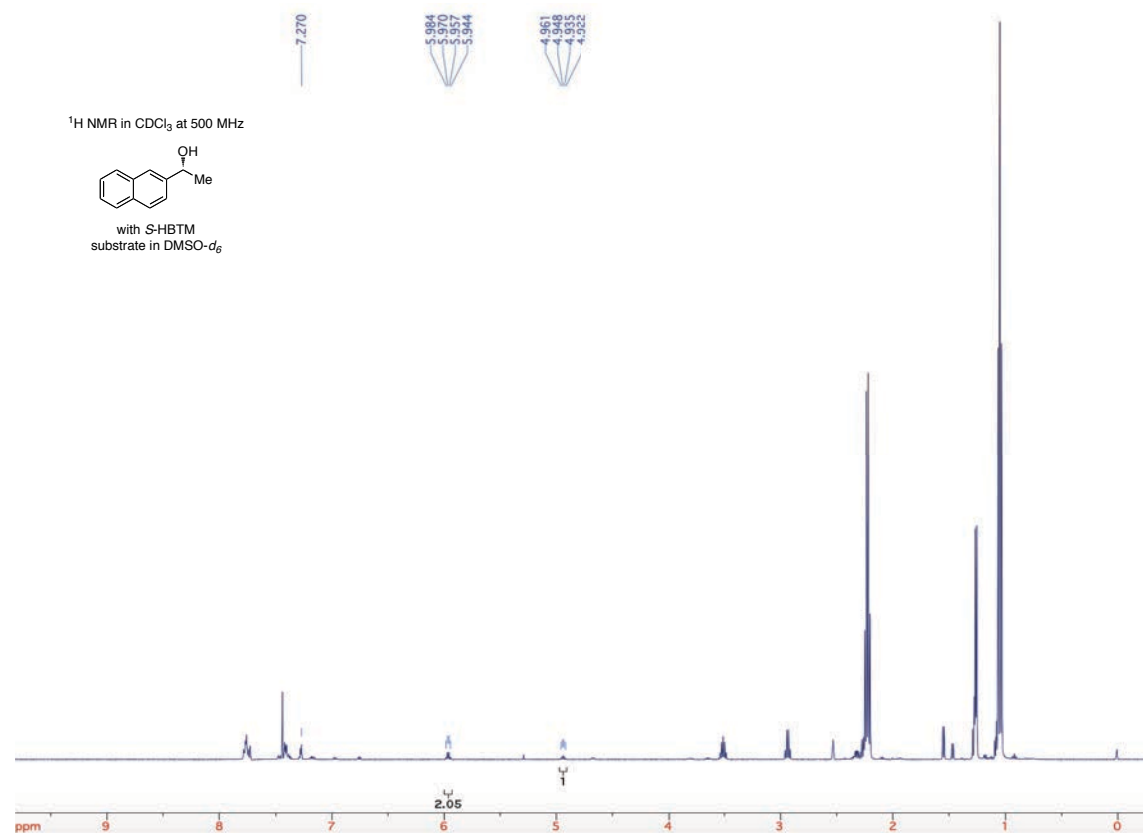
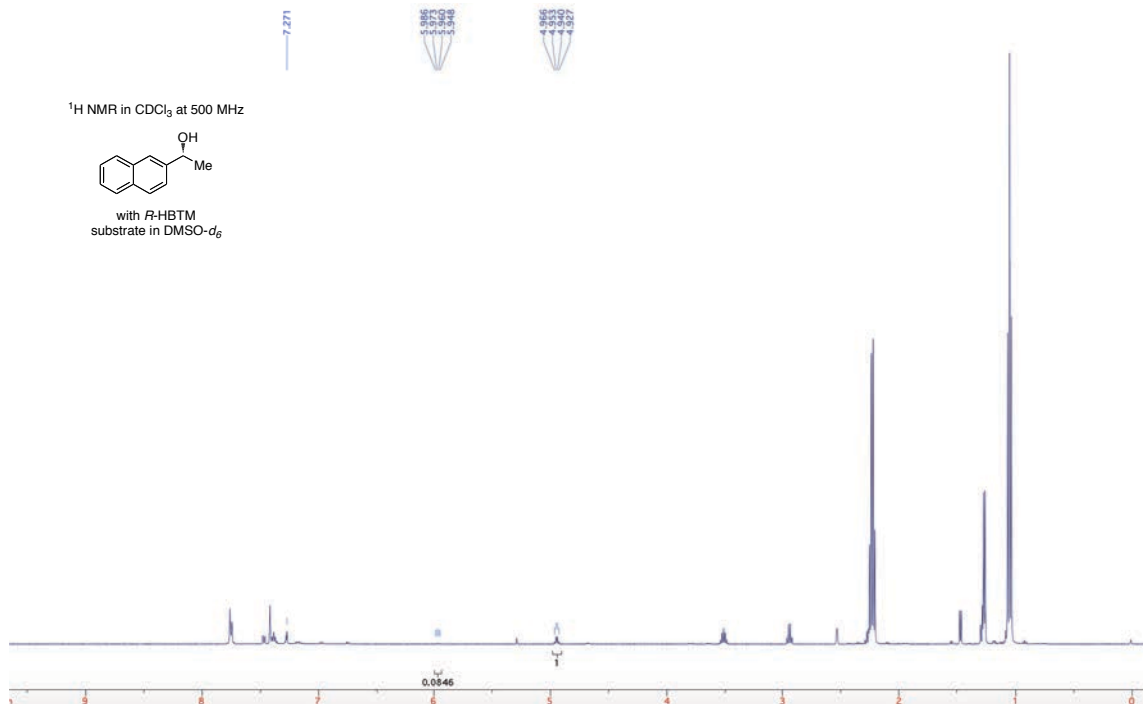
Table 5. Entry 7

Table 5. Entry 7 – after vacuum removal of solvent and resolution in CDCl_3 

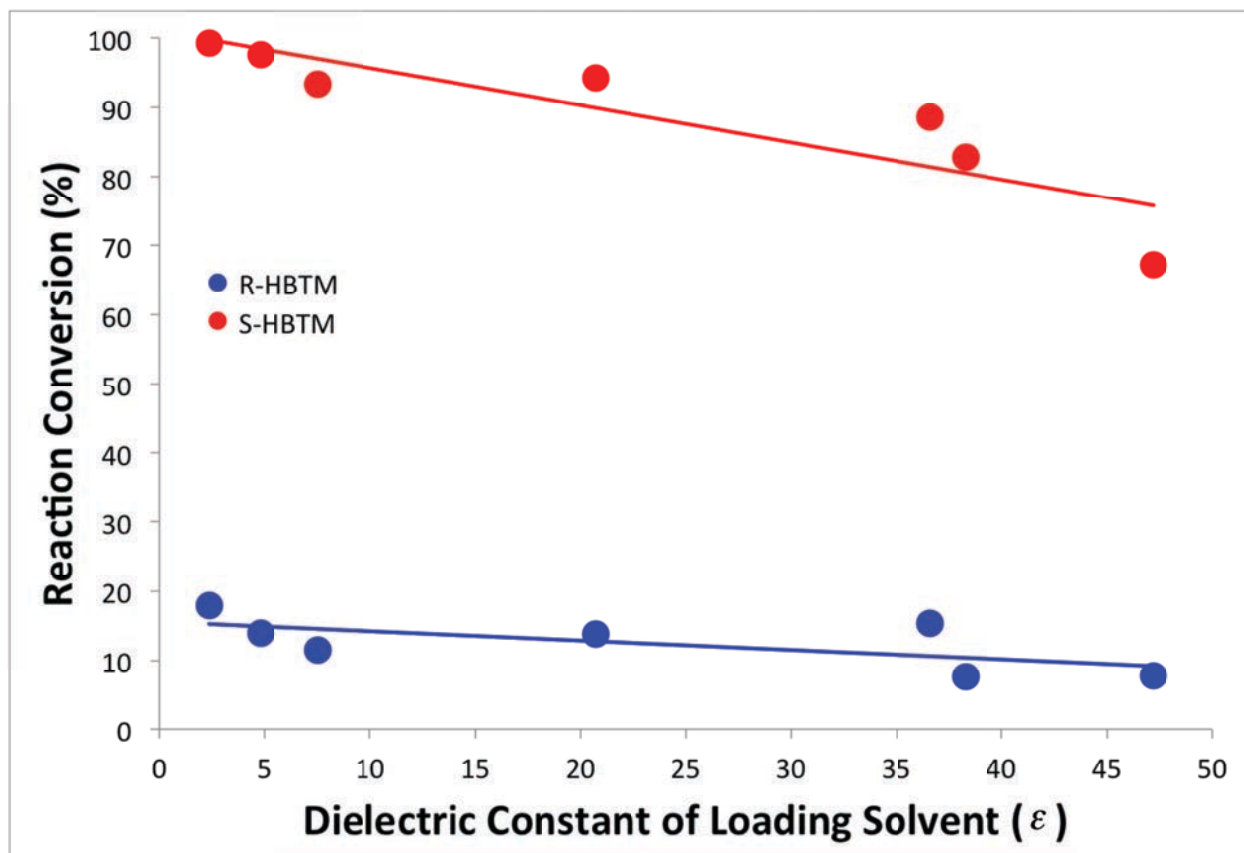


Figure SI.5. Comparison of reaction conversion (%) after 30 minutes of (*R*)-**5** to (*R*)-**6** relative to the dielectric constant of the solvent (*R*)-**5** was loaded into to the CEC kit that contained CDCl_3 .

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

table	entry	mass in 1 dram vial (mg)	TLC solvent conditions	TLC stain
6	1	3.4	3:1 hexanes/ethyl acetate	PMA
6	2	3.4	3:1 hexanes/ethyl acetate	PMA
6	3	4.0	3:1 hexanes/ethyl acetate	PMA
6	4	3.0	3:1 hexanes/ethyl acetate	PMA
6	5	4.4	ethyl acetate	Dragendorf-Munier ^b
6	6	4.2	6:1 hexanes/ethyl acetate	Dragendorf-Munier ^b
6	7	3.6	6:1 hexanes/ethyl acetate	PMA
6	8 ^a	2.5	ethyl acetate	Hannesian
6	9	2.5	1:2 hexanes/ethyl acetate	Dragendorf-Munier ^b
6	10 ^a	3.2	ethyl acetate	Dragendorf-Munier ^b
6	11 ^a	3.2	ethyl acetate	Dragendorf-Munier ^b
6	12	8.0	1:9 hexanes/ethyl acetate	KMnO ₄
7	1	2.8	6:1 hexanes/ethyl acetate	PMA
7	2	2.8	6:1 hexanes/ethyl acetate	KMnO ₄ ^b
7	3	3.4	3:1 hexanes/ethyl acetate	KMnO ₄
7	4	2.2	1:1 hexanes/ethyl acetate	Hannesian
7	5	2.4	1:1 hexanes/ethyl acetate	Hannesian ^b
7	6	3.6	2:1 hexanes/ethyl acetate	PMA
7	7	2.9	ethyl acetate	KMnO ₄
7	8	2.9	ethyl acetate	KMnO ₄
7	9	4.1	ethyl acetate	Dragendorf-Munier ^b
7	10	6.2	6:1 hexanes/ethyl acetate	KMnO ₄
7	11	5.5	6:1 hexanes/ethyl acetate	PMA
7	12	4.7	3:1 hexanes/ethyl acetate	PMA

(a) substrate solvated in DMSO-*d*₆ before injection into CEC kit in CDCl₃ (b) plate was allowed to dry at room temperature over a period of 3-5 min before a photograph of the image was captured

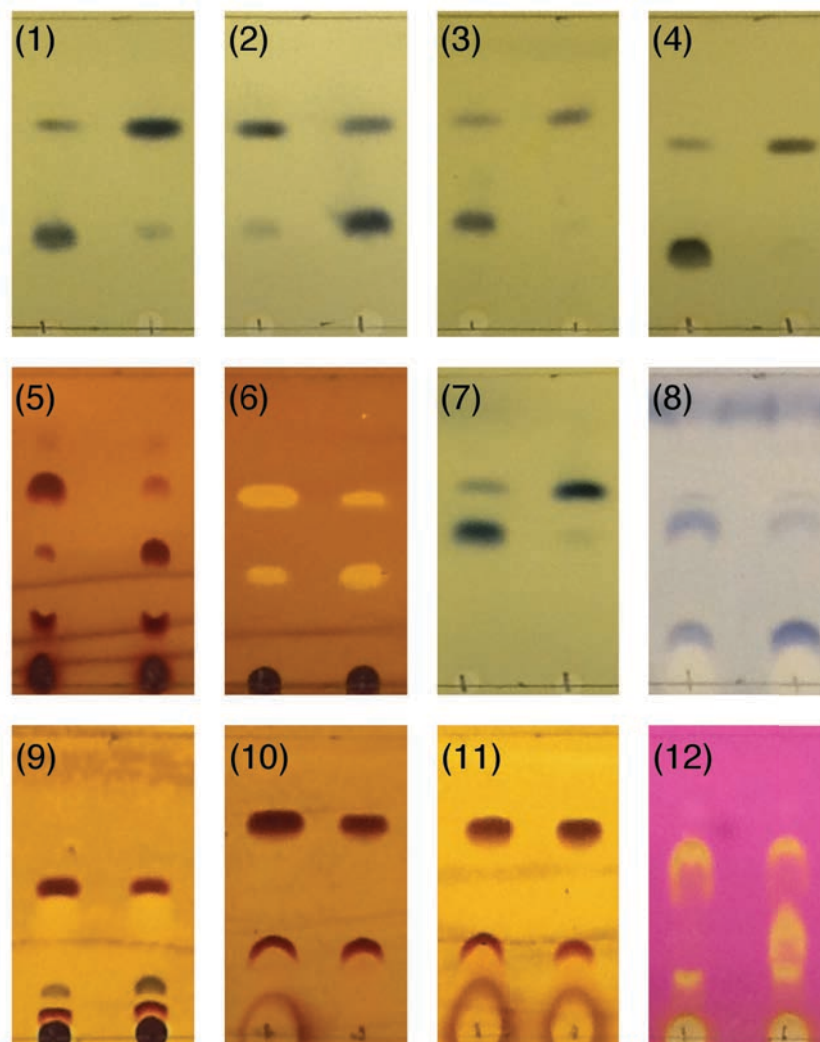


Figure SI.6. TLC images corresponding to each entry tested in Table 6. Left TLC lane: *R*-HBTM; Right TLC lane: *S*-HBTM. TLC conditions and stains are listed in Table SI.8.

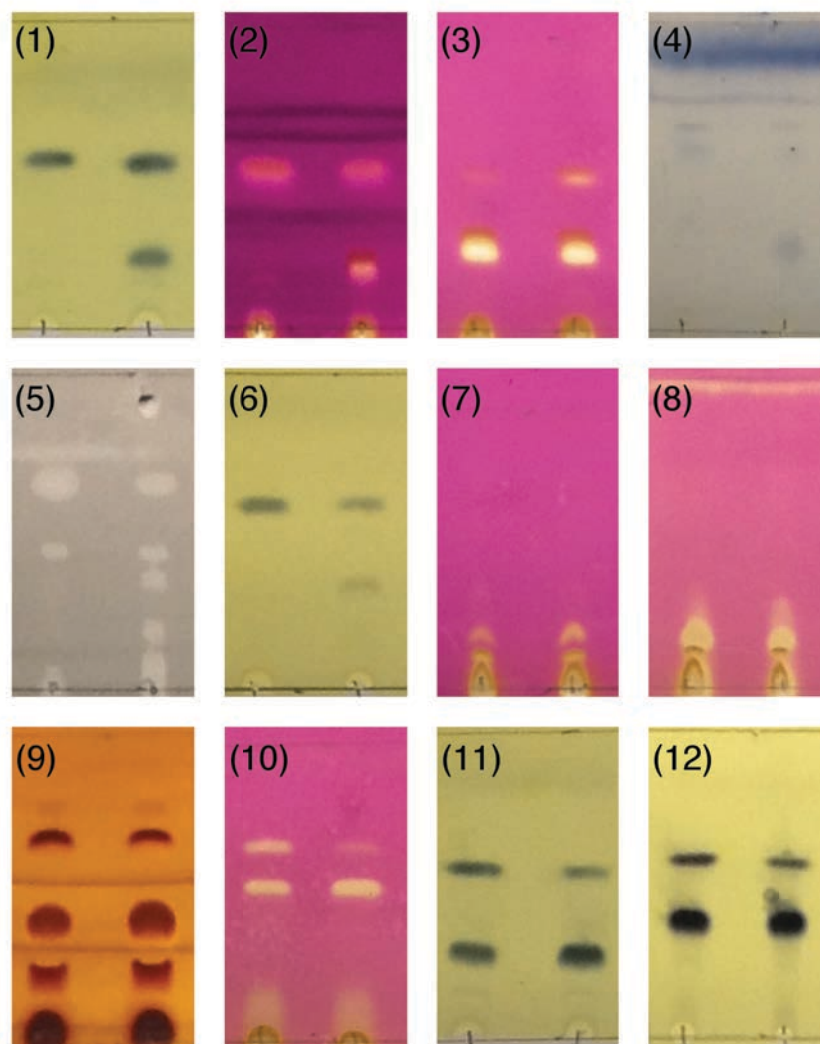


Figure SI.7. TLC images corresponding to each entry tested in Table 7. Left TLC lane: *R*-HBTM; Right TLC lane: *S*-HBTM. TLC conditions and stains are listed in Table SI.8.

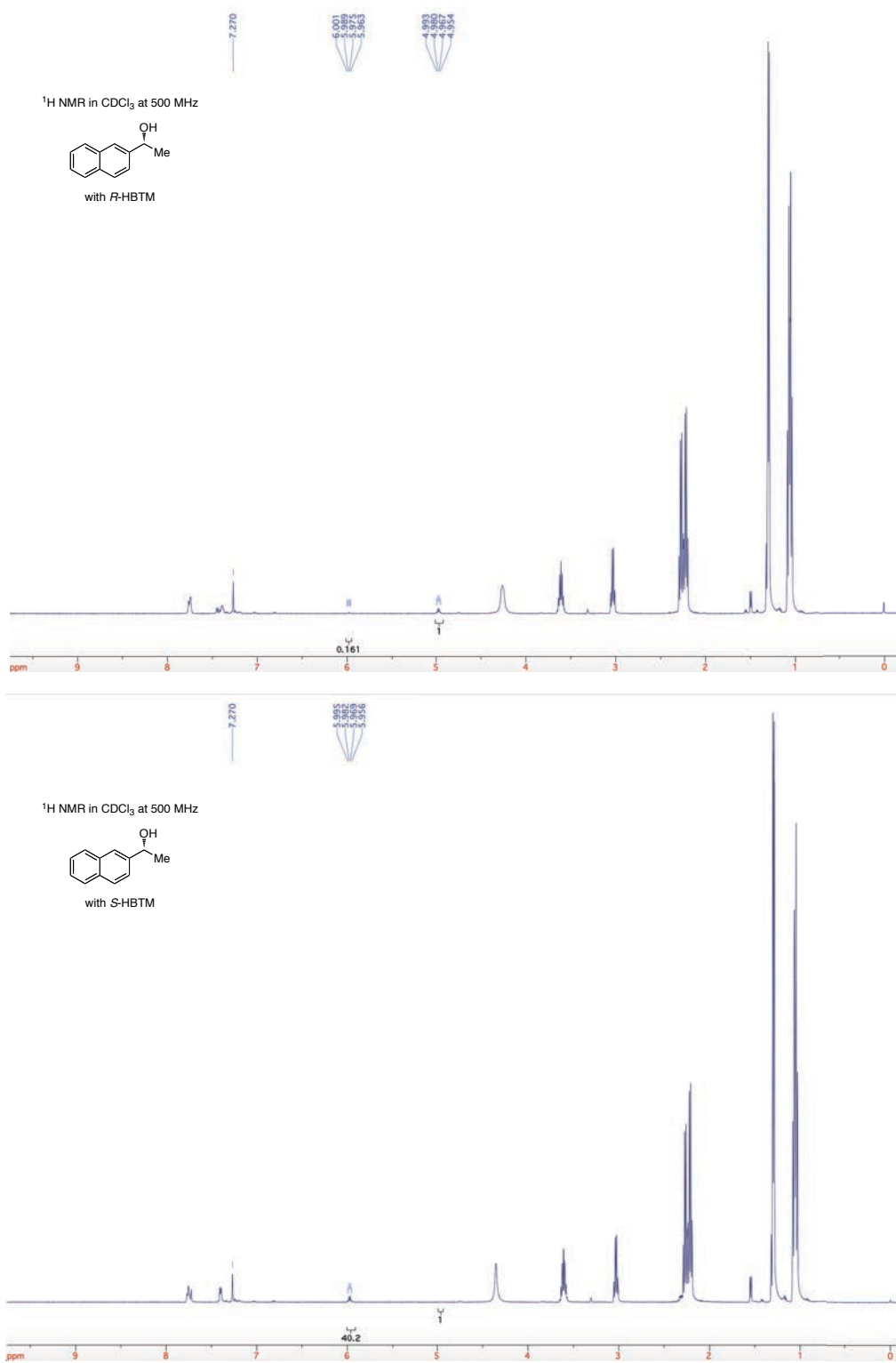
¹H NMR Spectra CEC Analysis for Tables 6 and 7**Table 6. Entry 1**

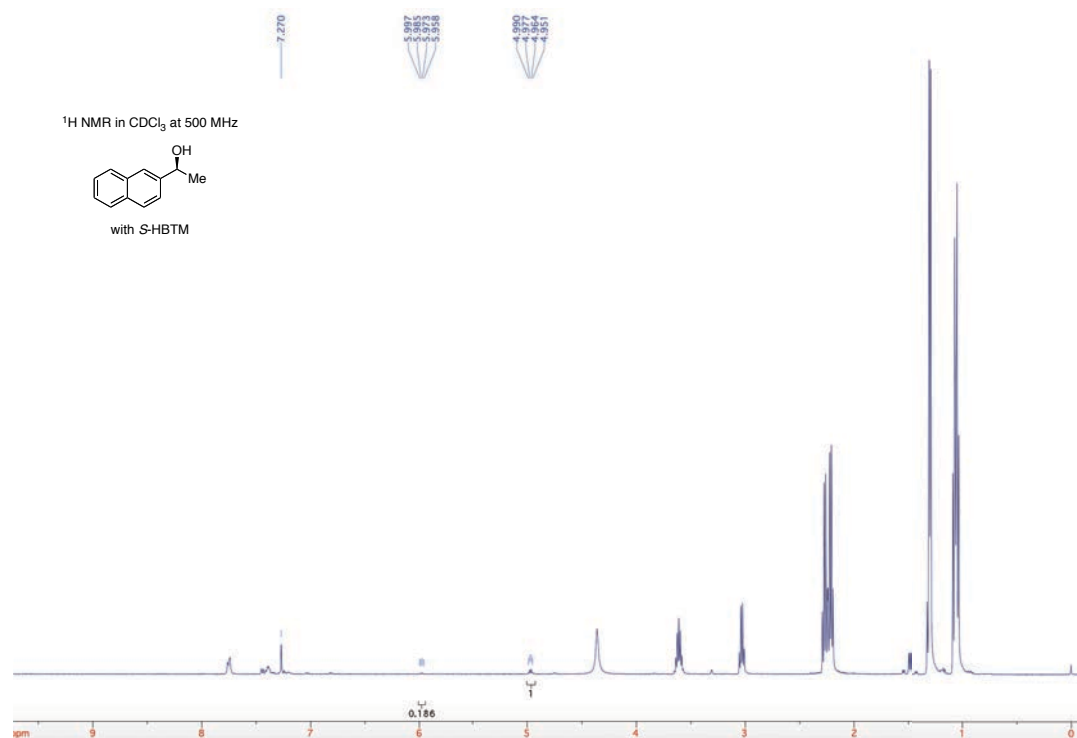
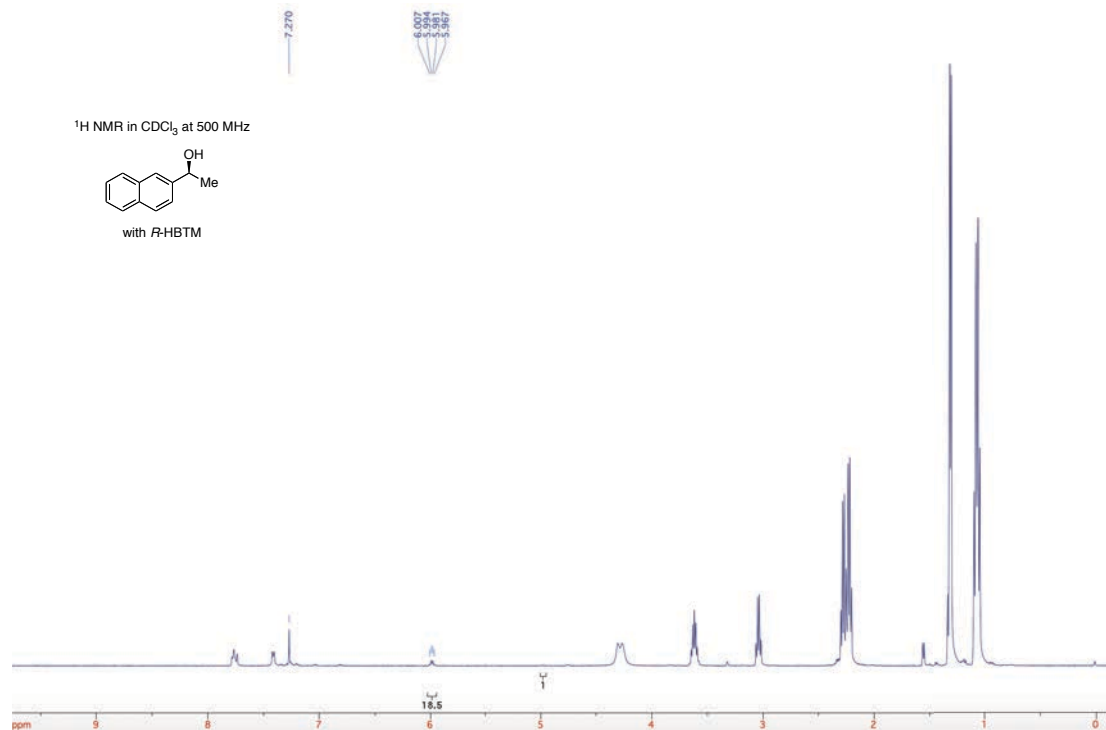
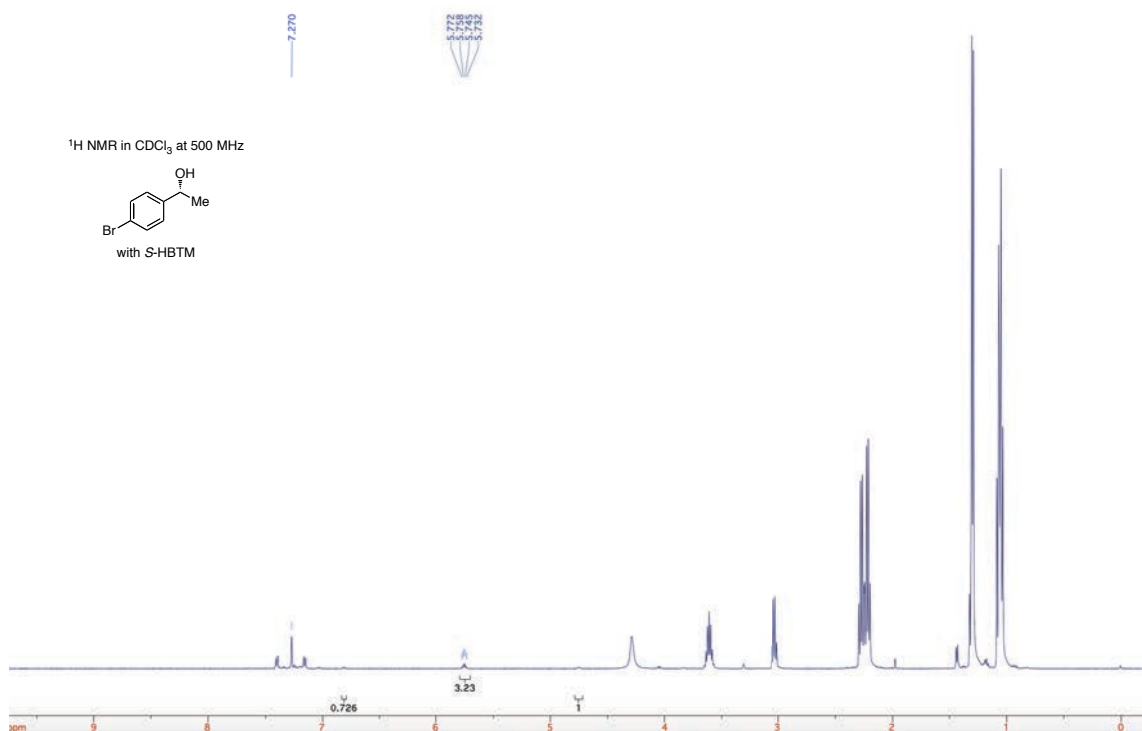
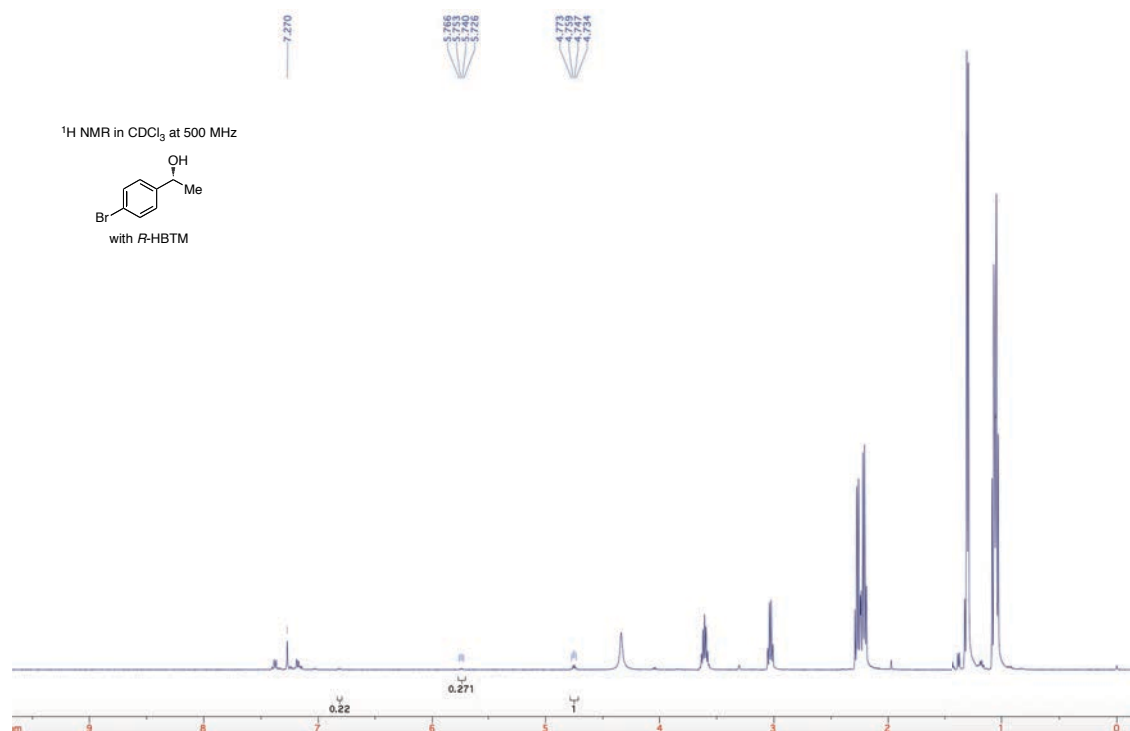
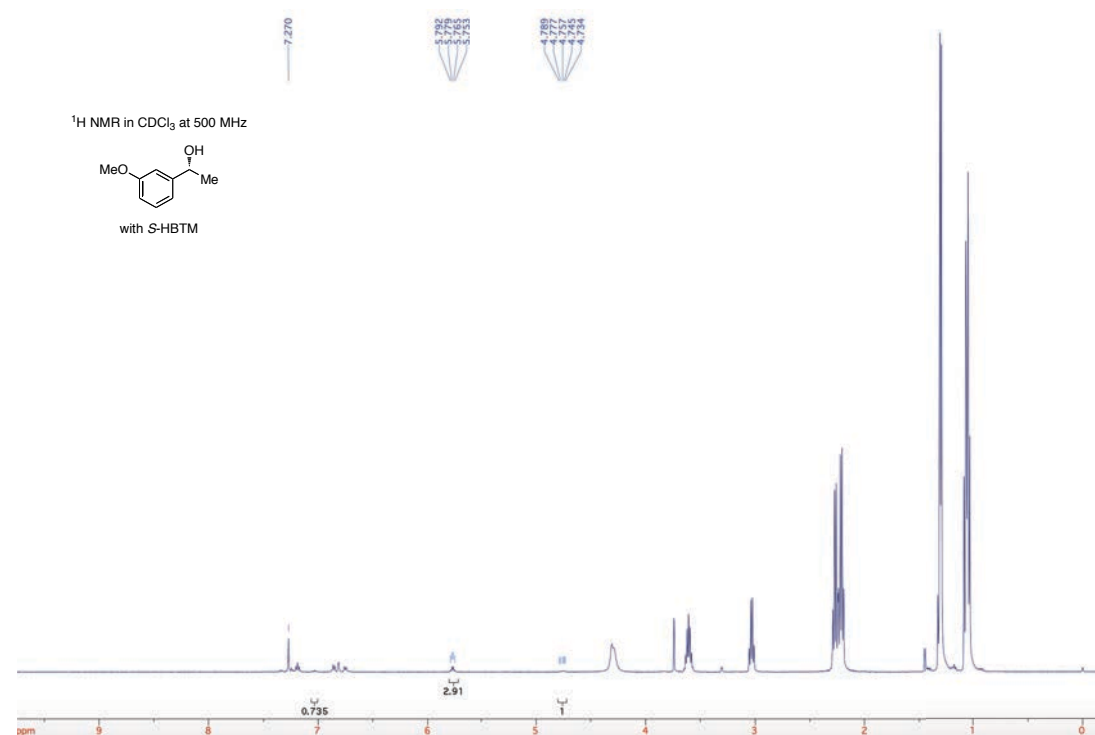
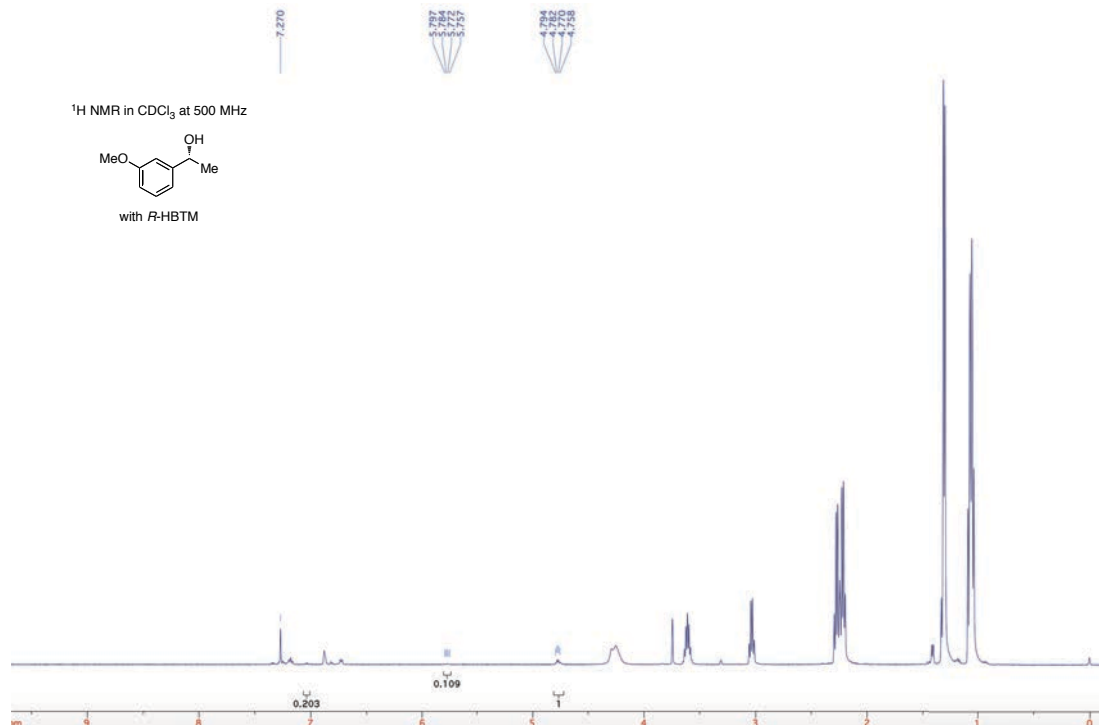
Table 6. Entry 2

Table 6. Entry 3

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.

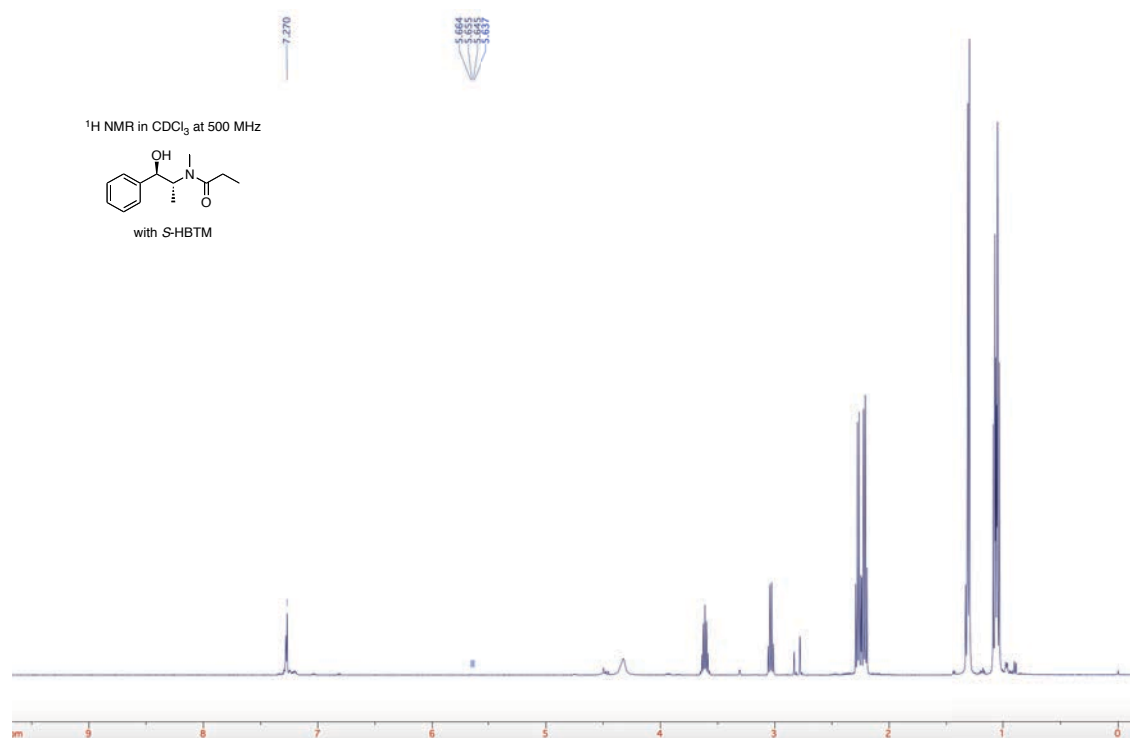
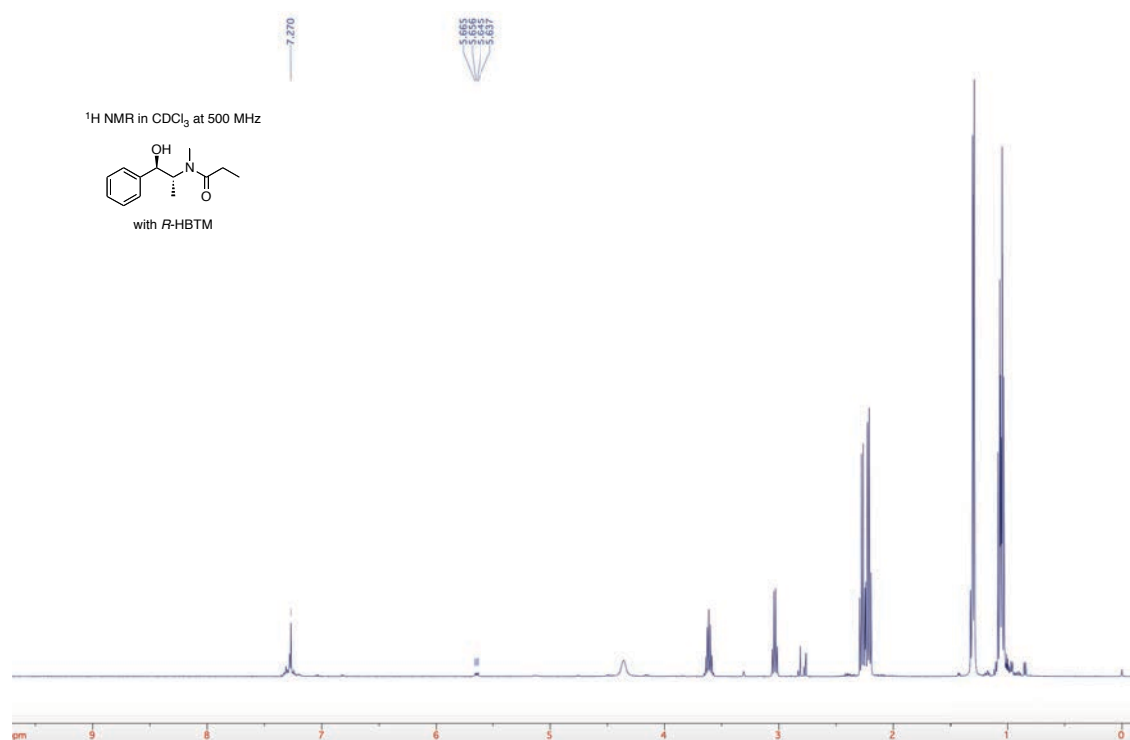
Table 6. Entry 5

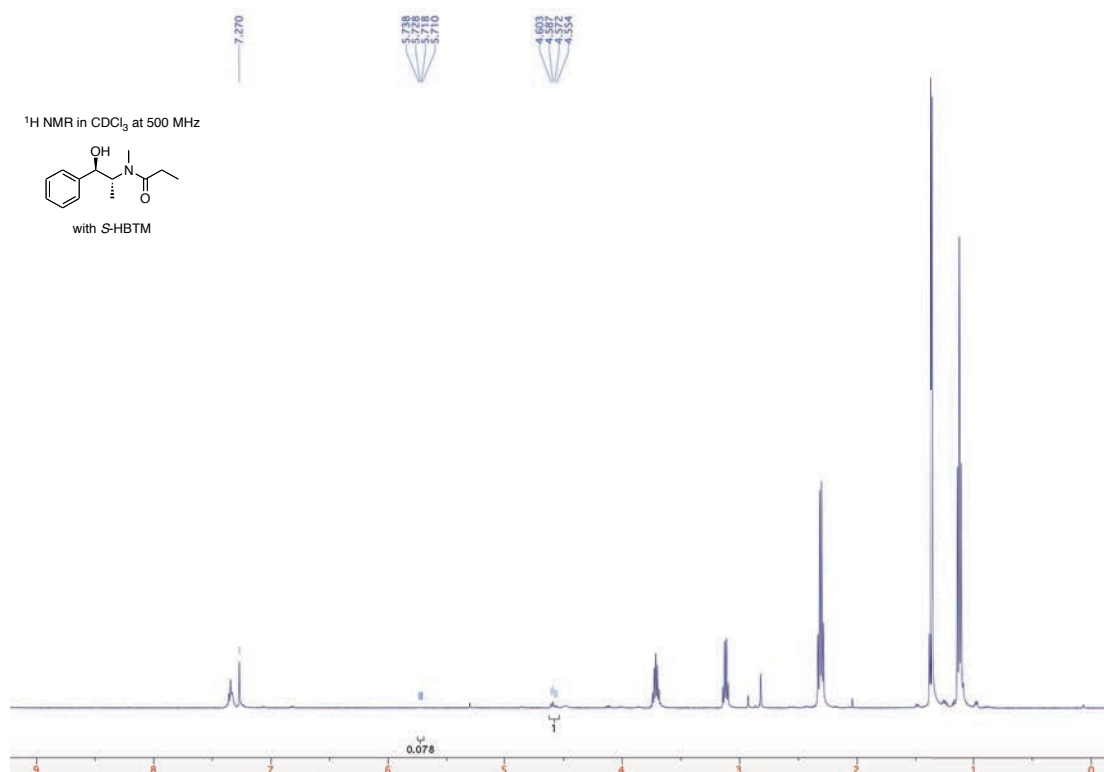
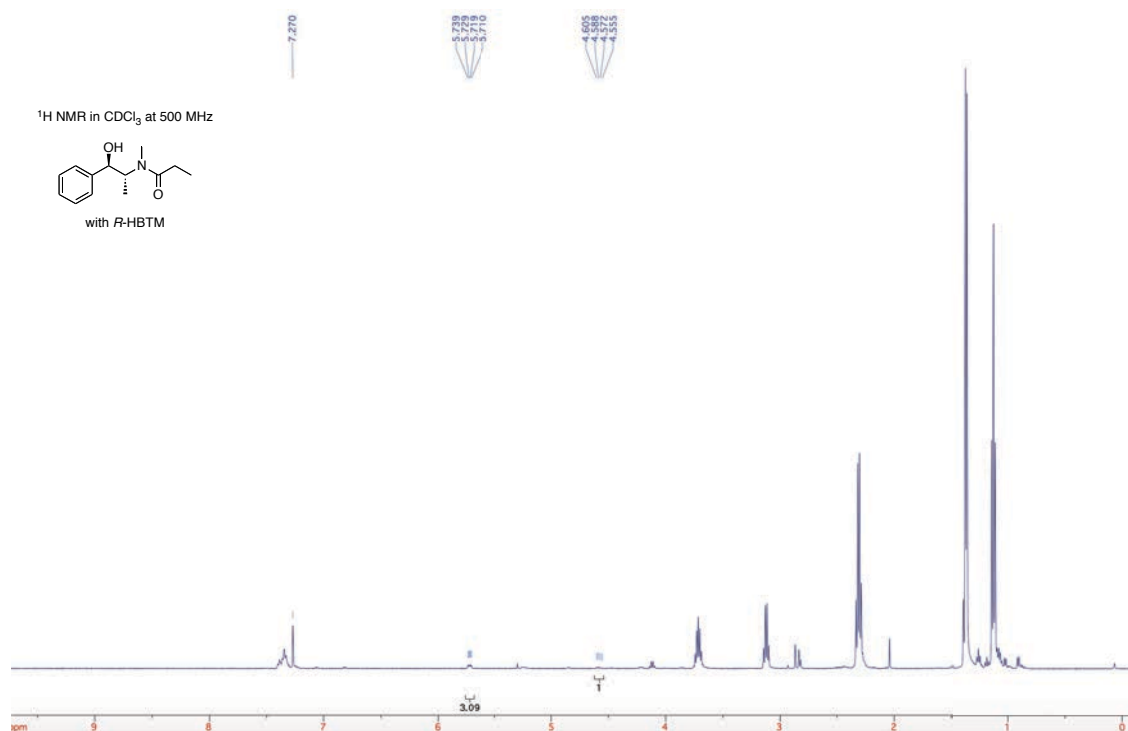
Table 6. Entry 5 – after vacuum removal of solvent and resolution in CDCl_3 

Table 6. Entry 6

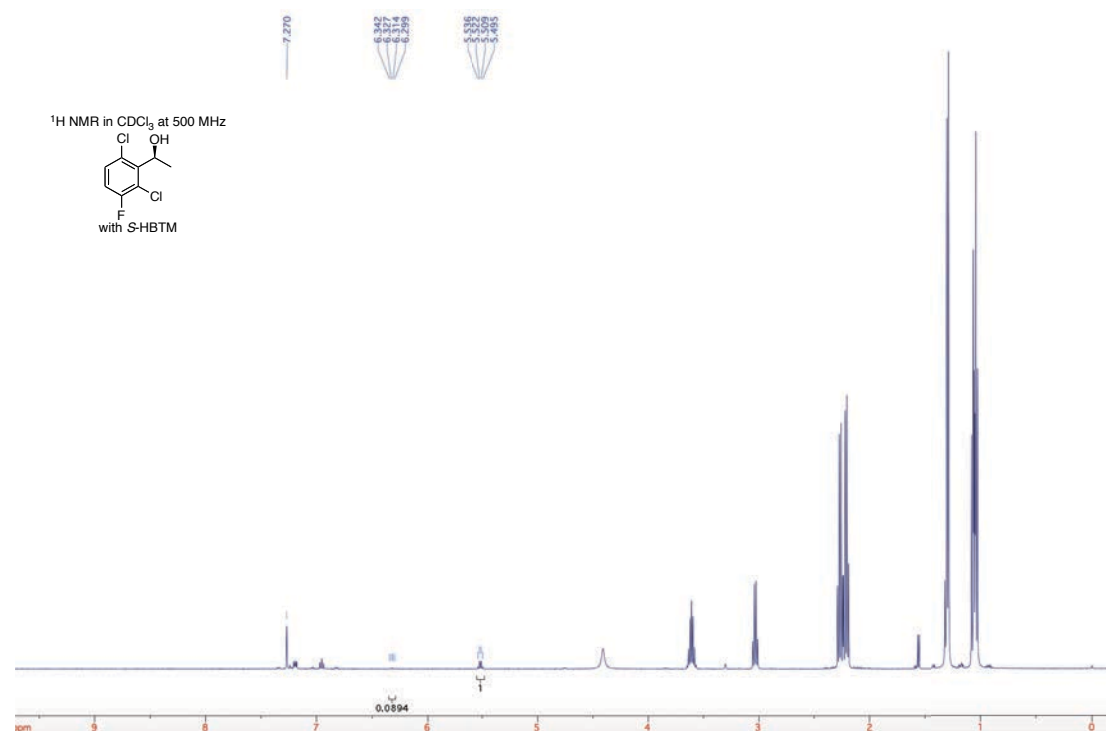
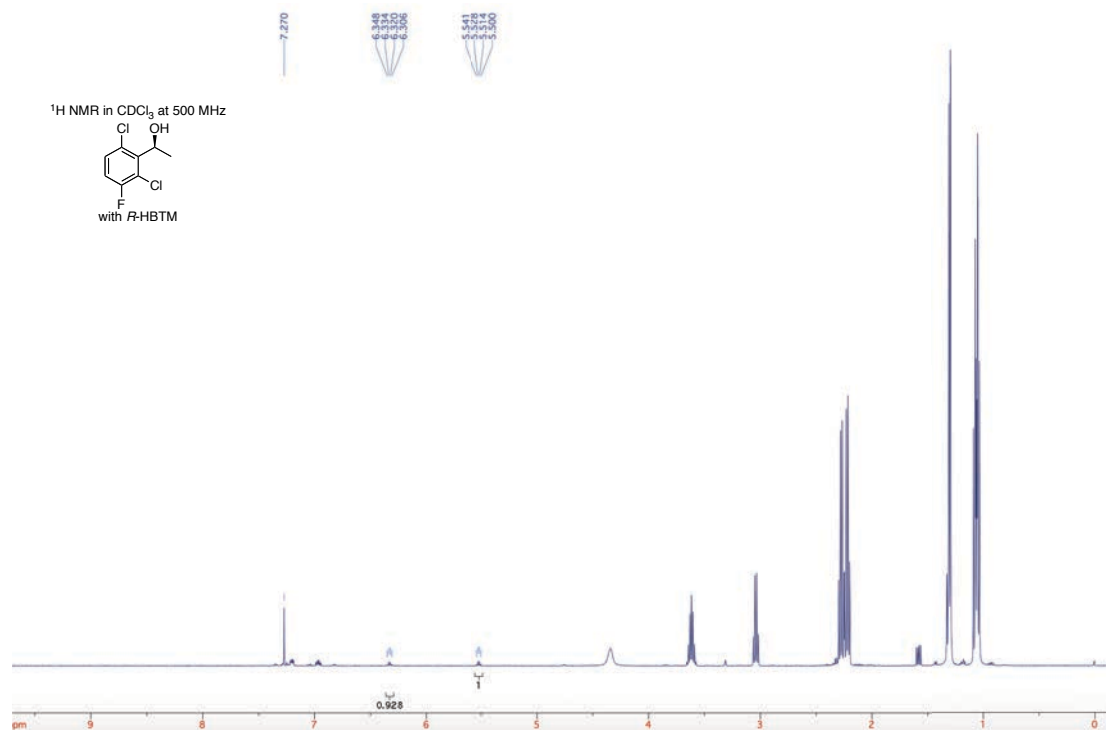


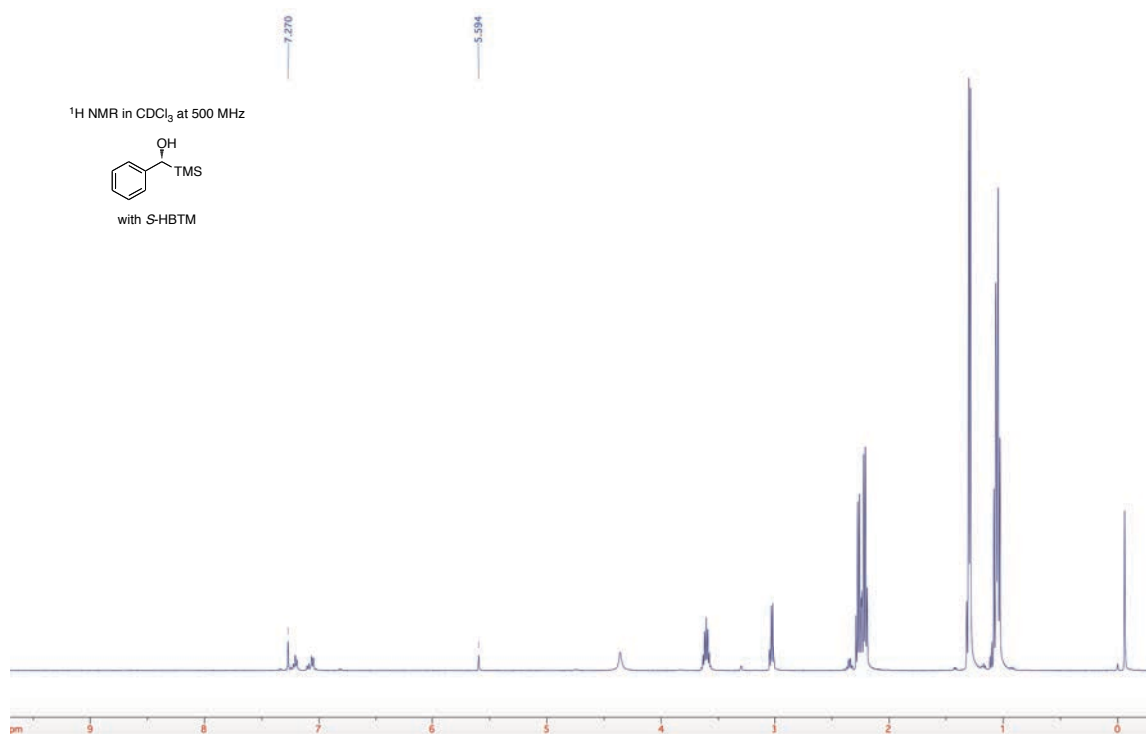
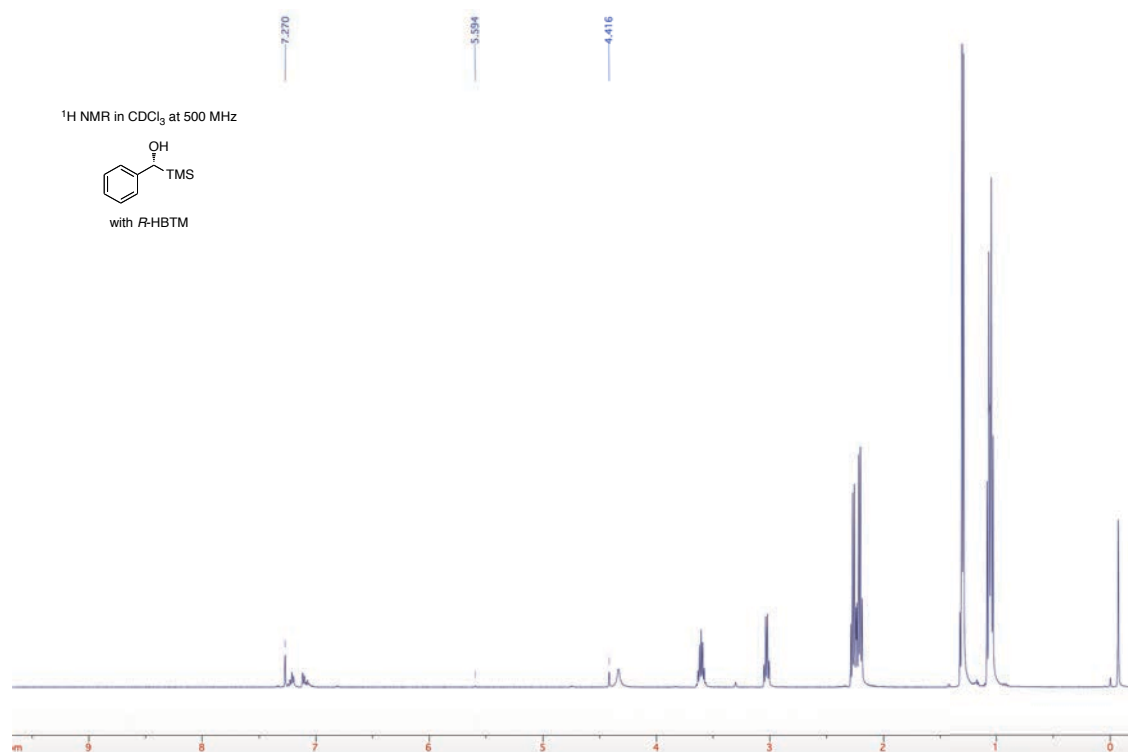
Table 6. Entry 7

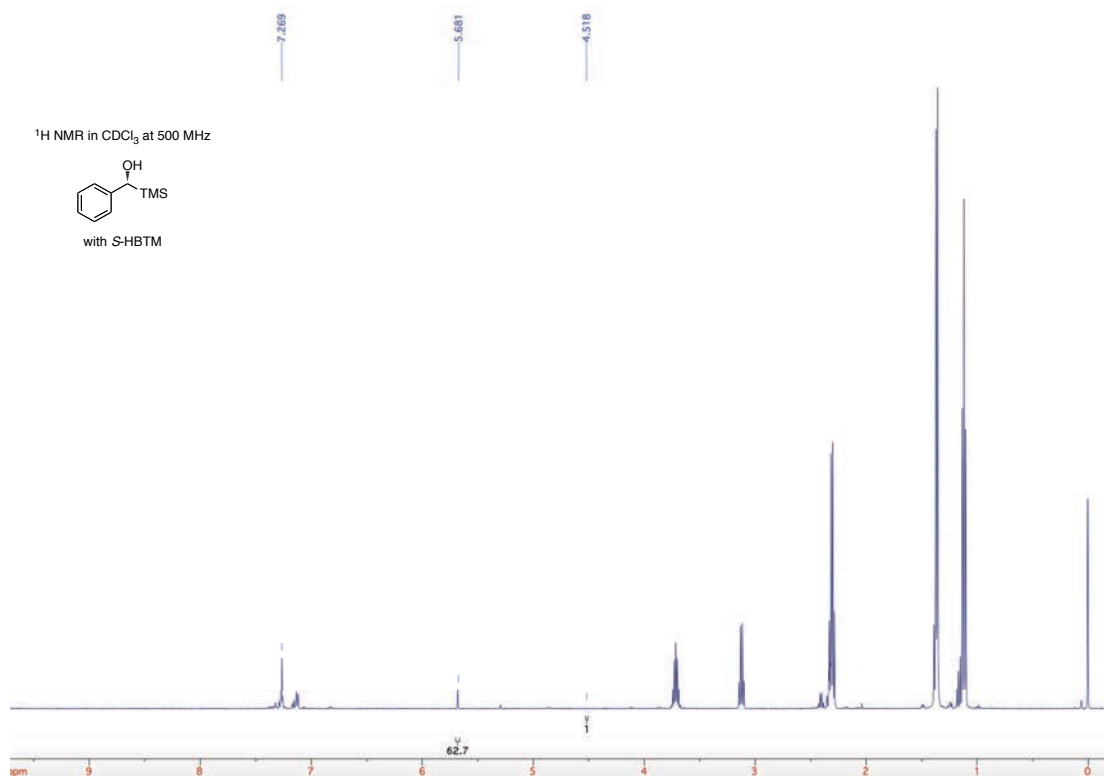
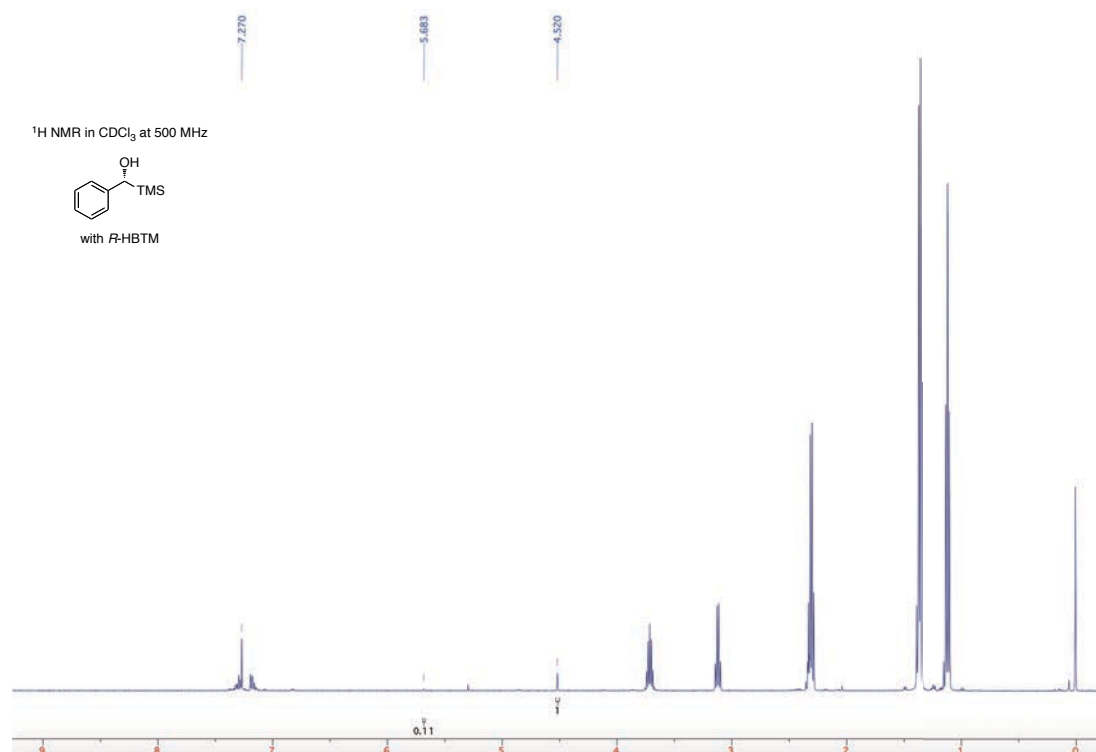
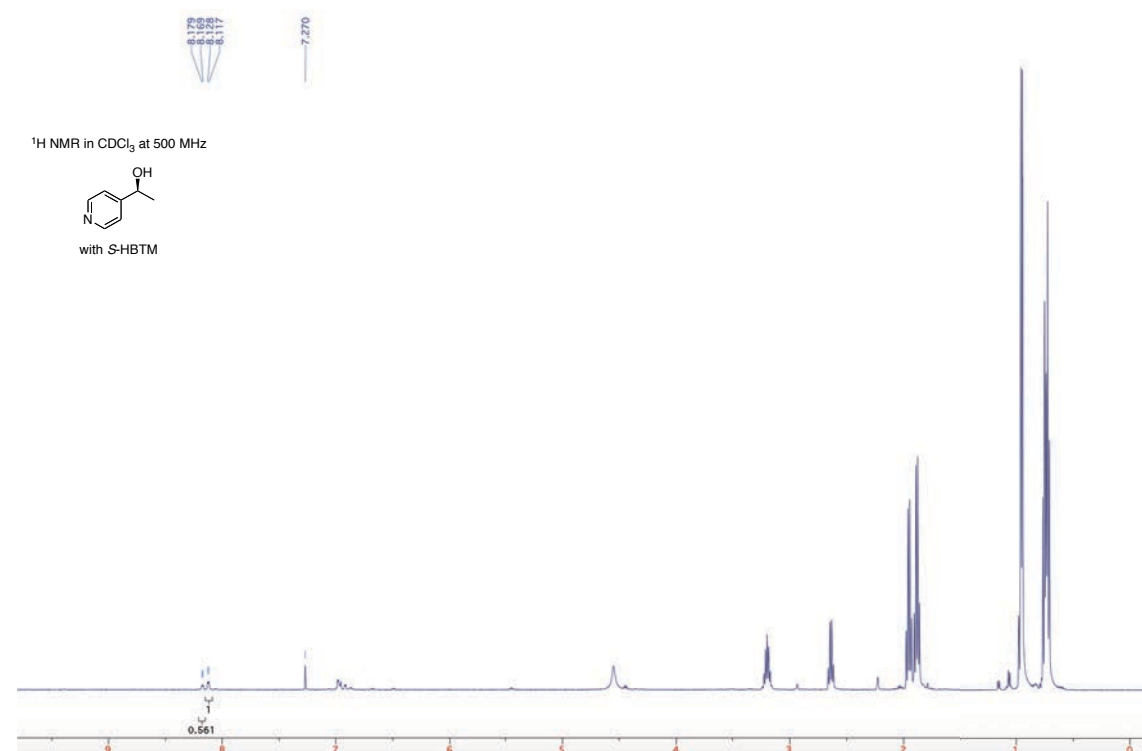
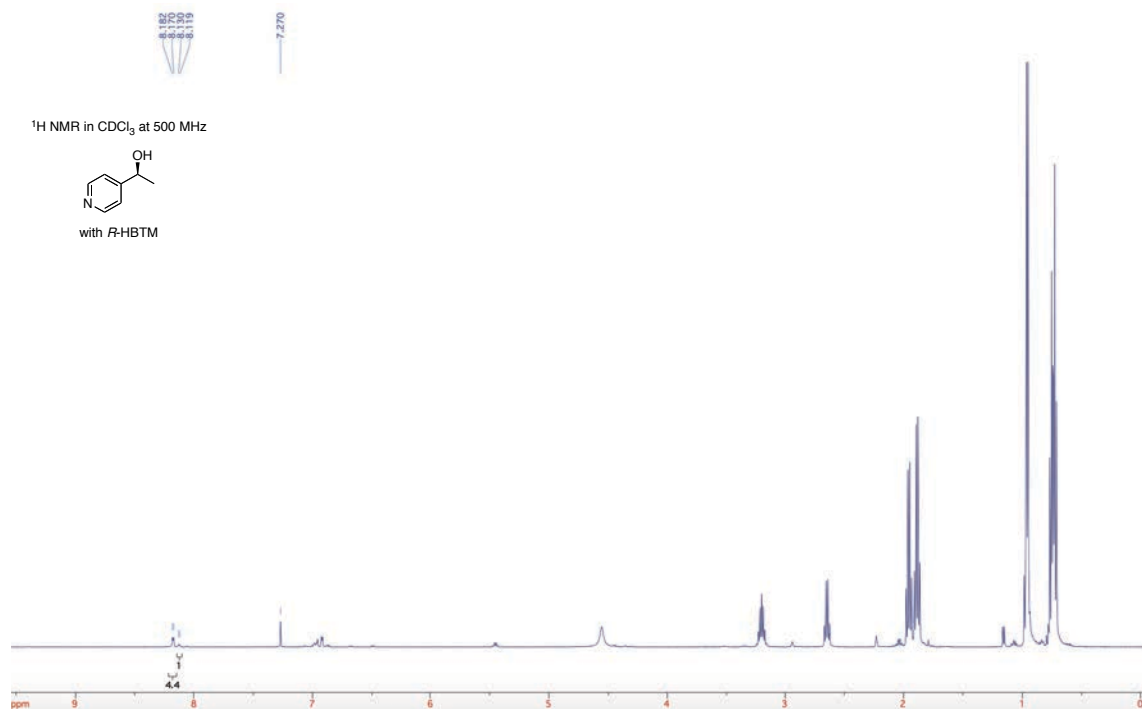
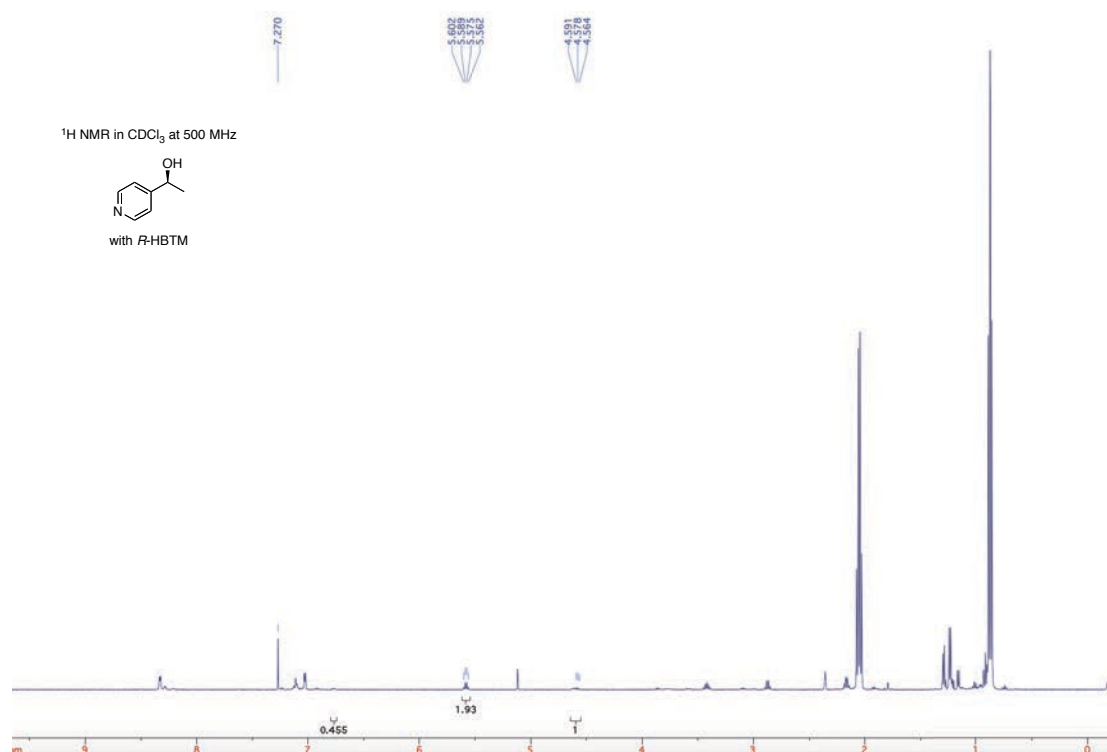
Table 6. Entry 7 – after vacuum removal of solvent and resolution in CDCl_3 

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 resolution 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.

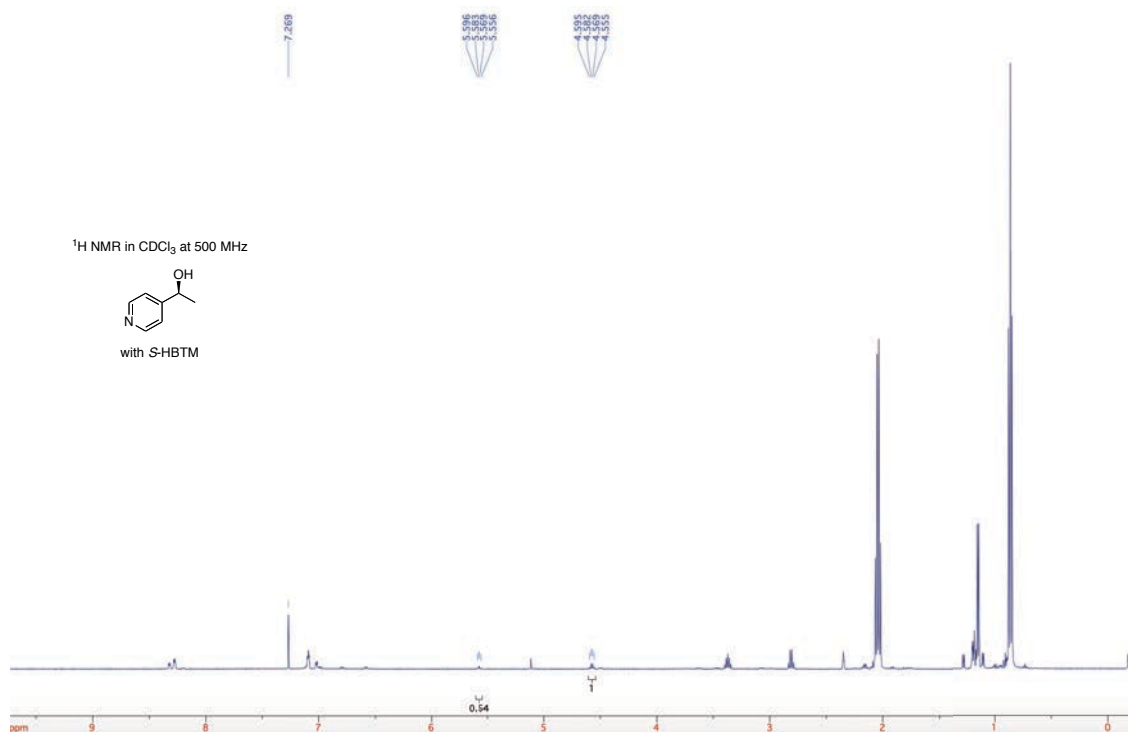


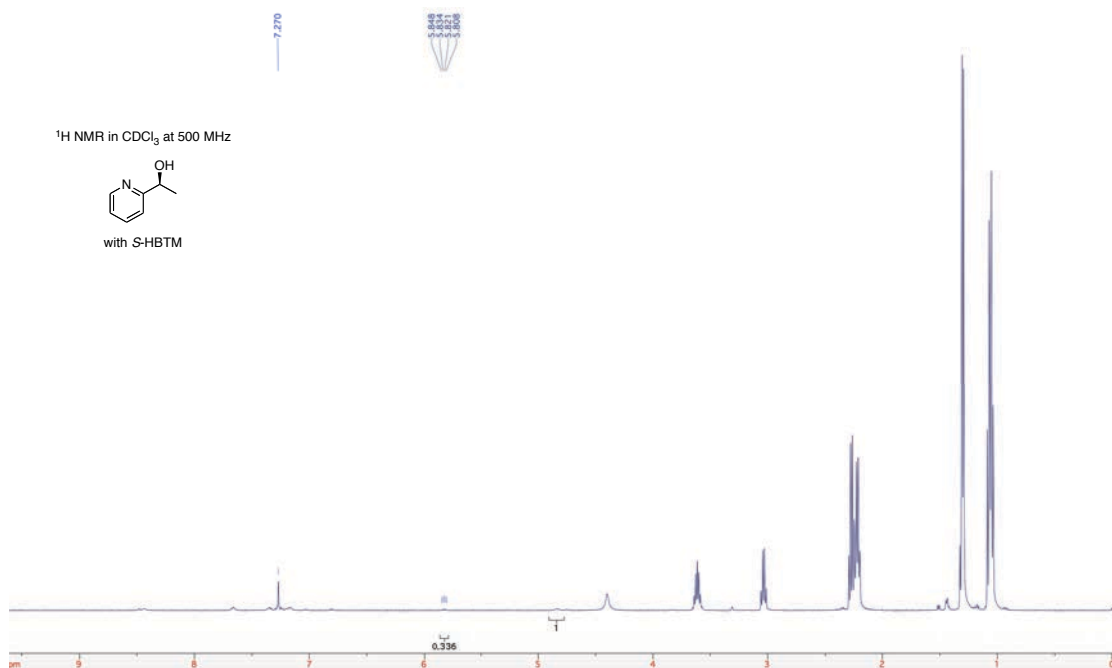
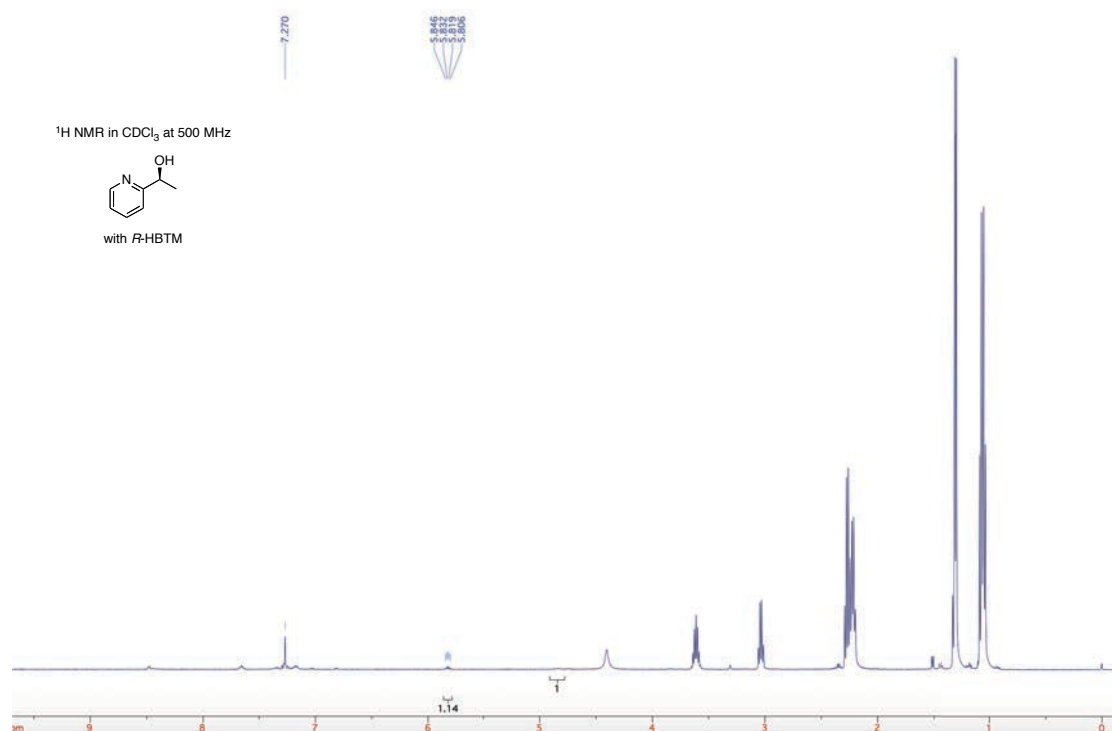
Table 6. Entry 9

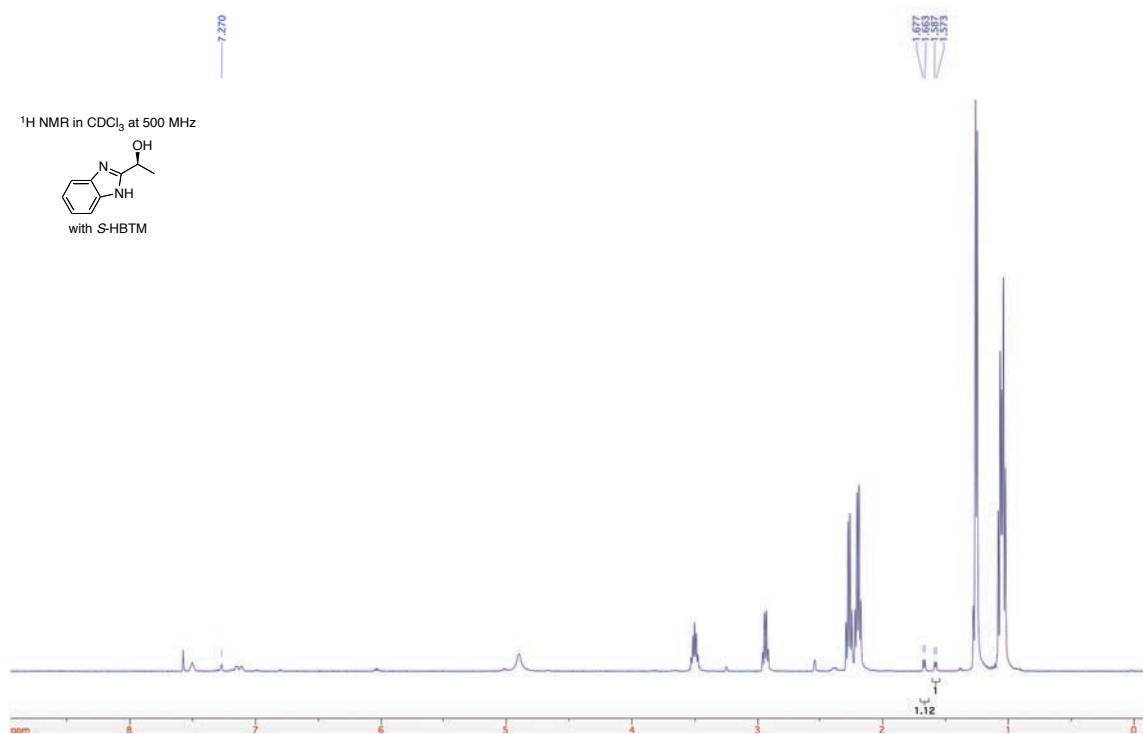
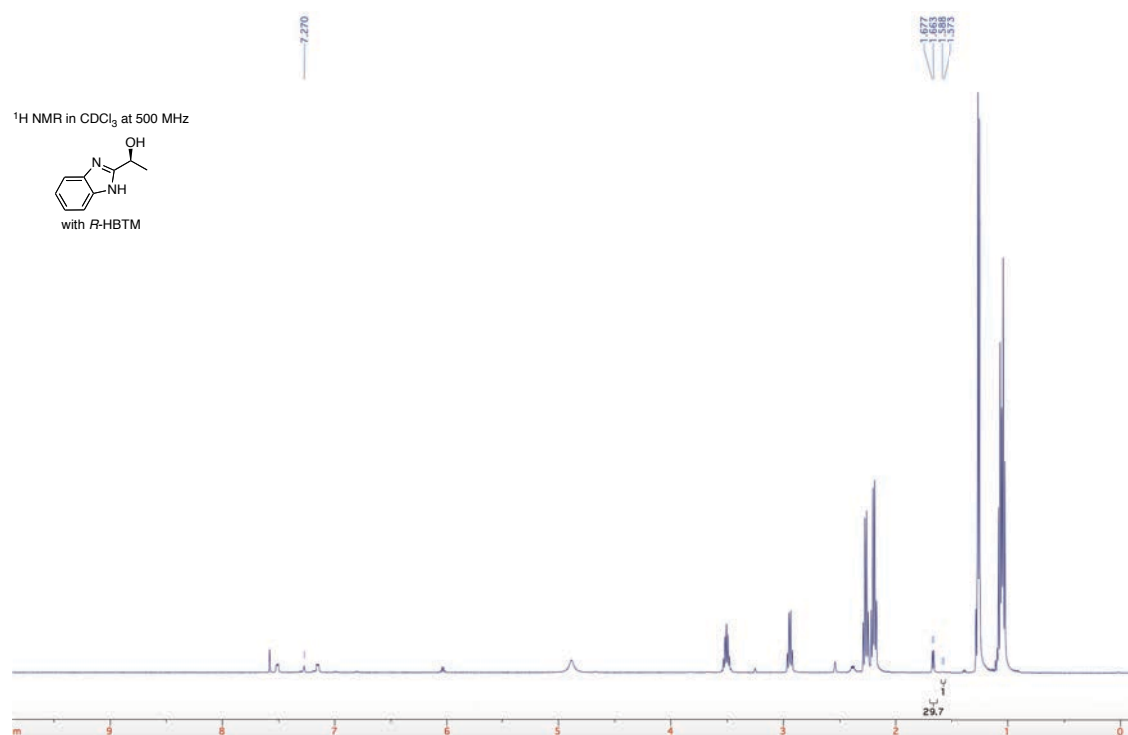
Table 6. Entry 10

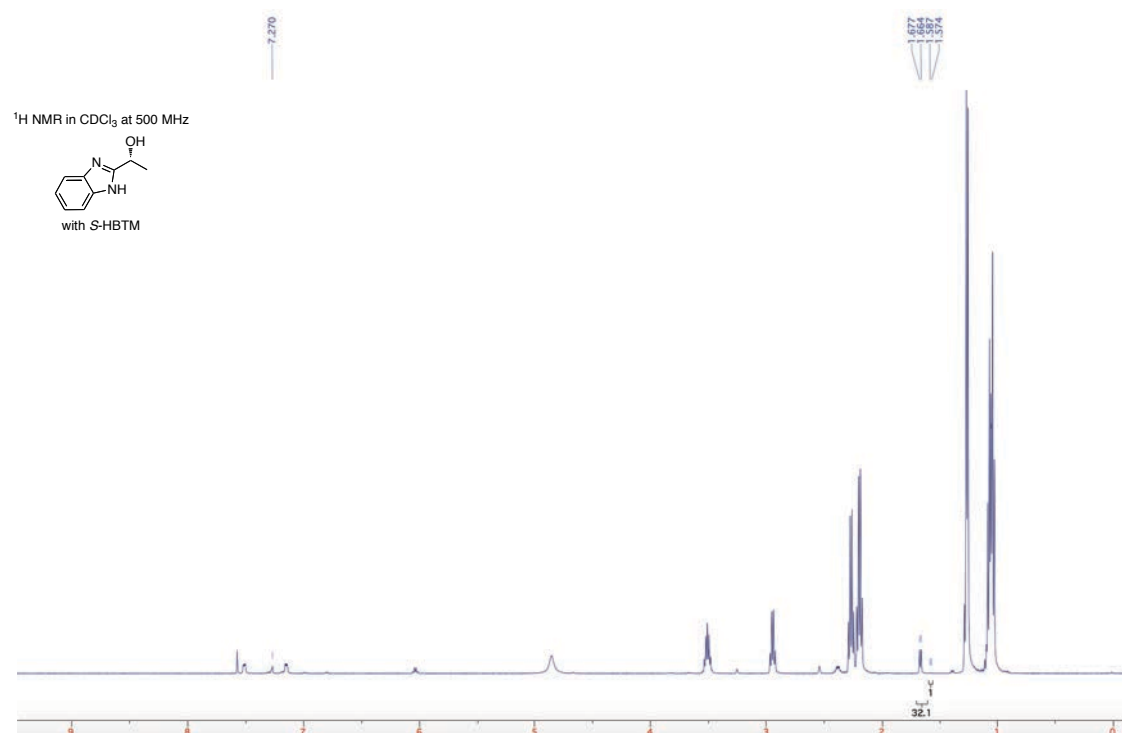
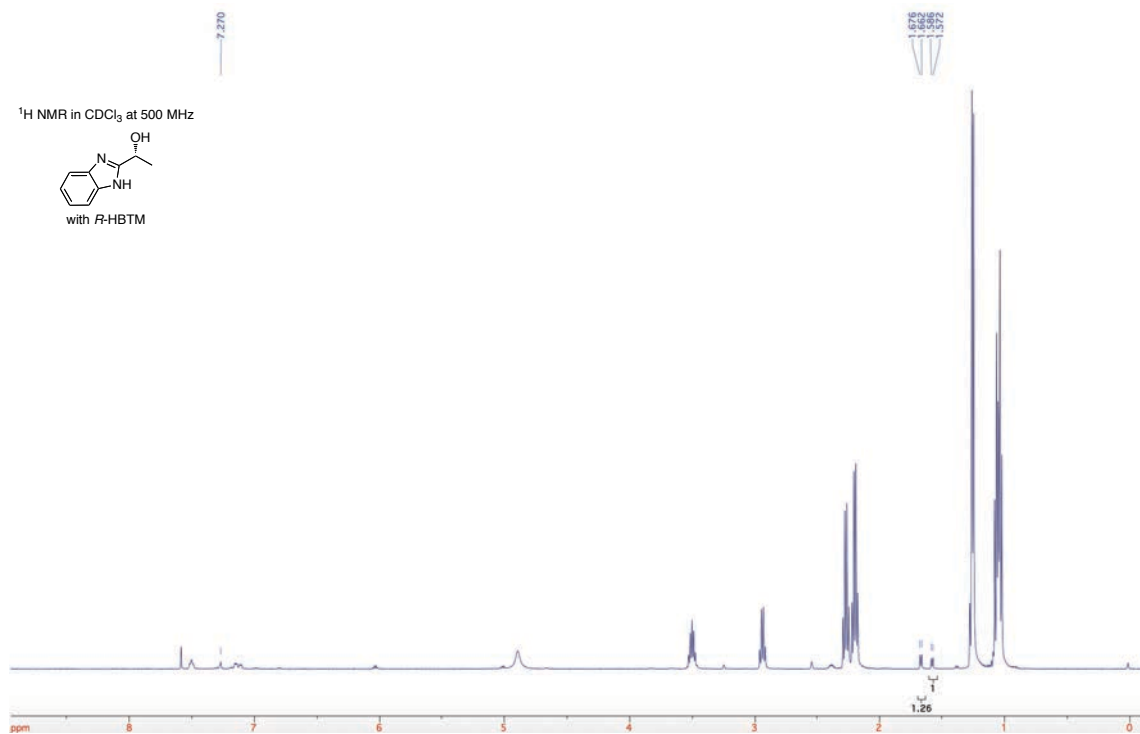
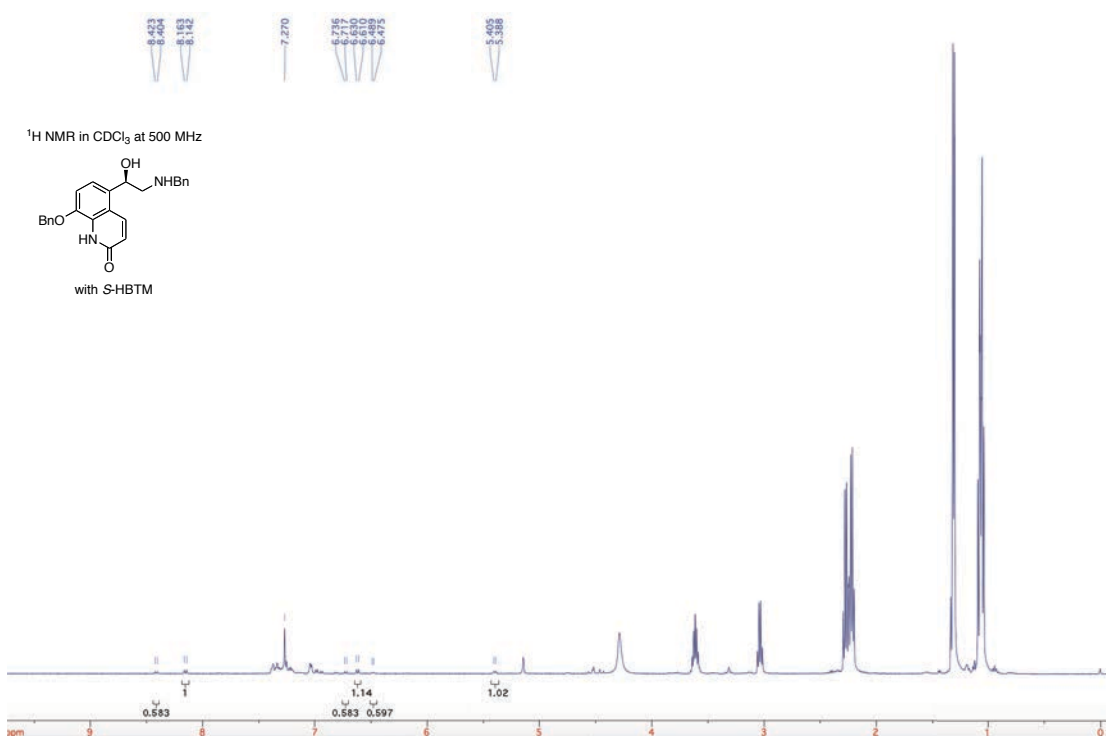
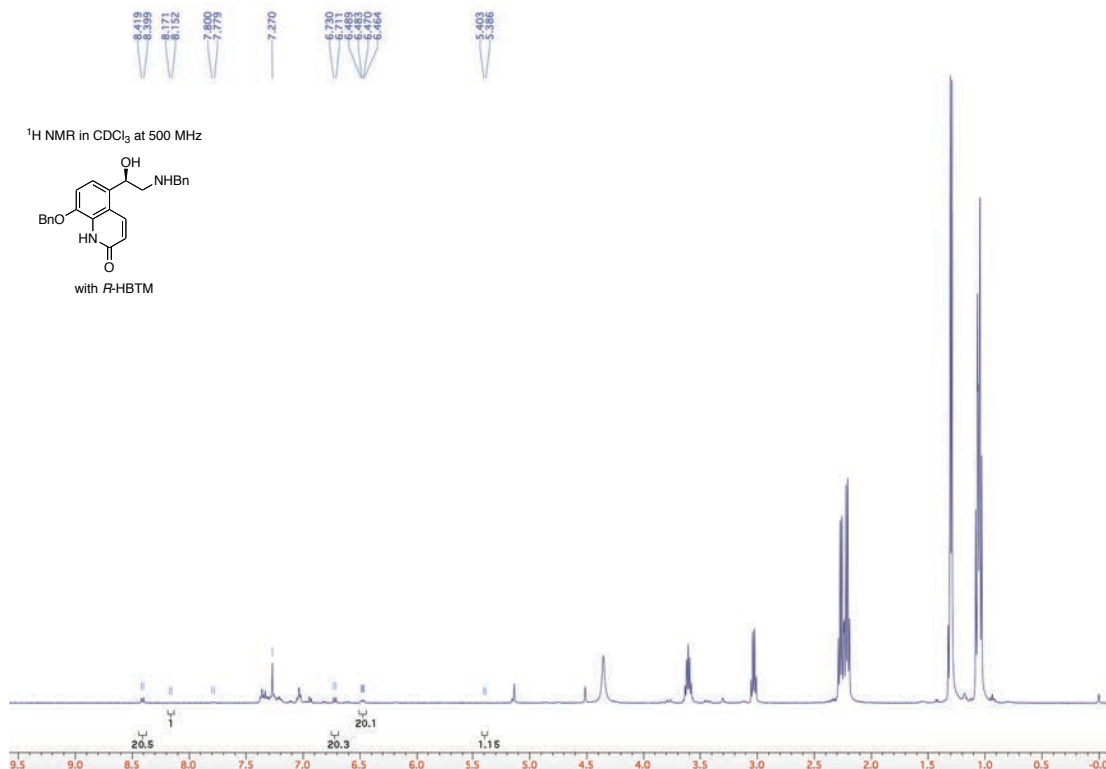
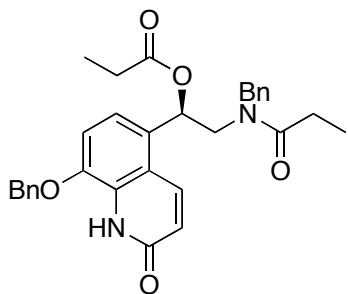
Table 6. Entry 11

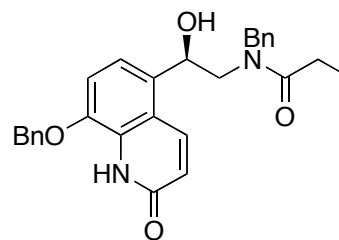
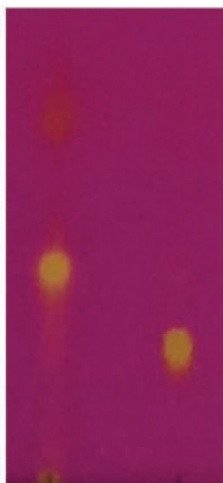
Table 6. Entry 12

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, CH₂Cl₂) *m/z* calcd for C₃₁H₃₂N₂O₅Na (M+Na)⁺ 535.2209, found 535.2214.



HRMS (TOF MS ES, CH₂Cl₂) *m/z* calcd for C₂₈H₂₈N₂O₄Na (M+Na)⁺ 479.1947, found 479.1966.

TLC in 9:1 ethyl acetate/hexanes

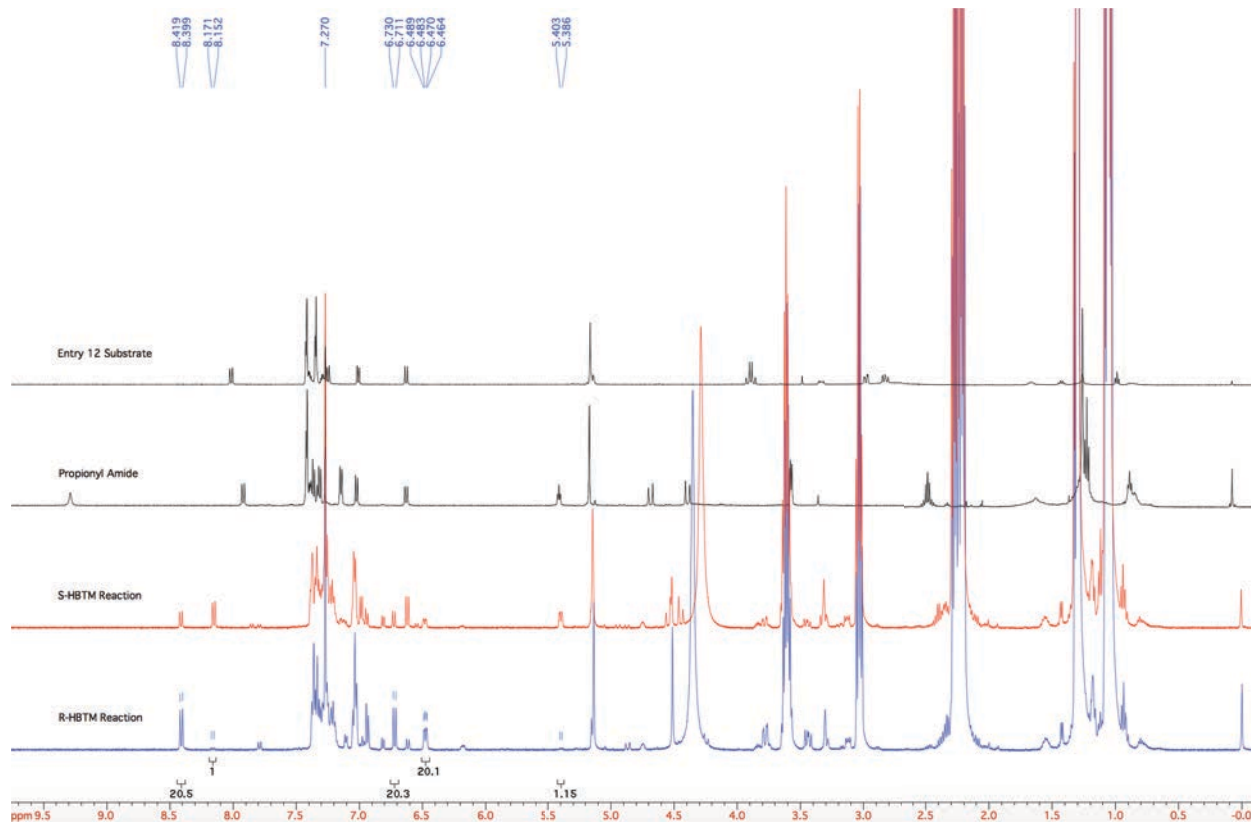


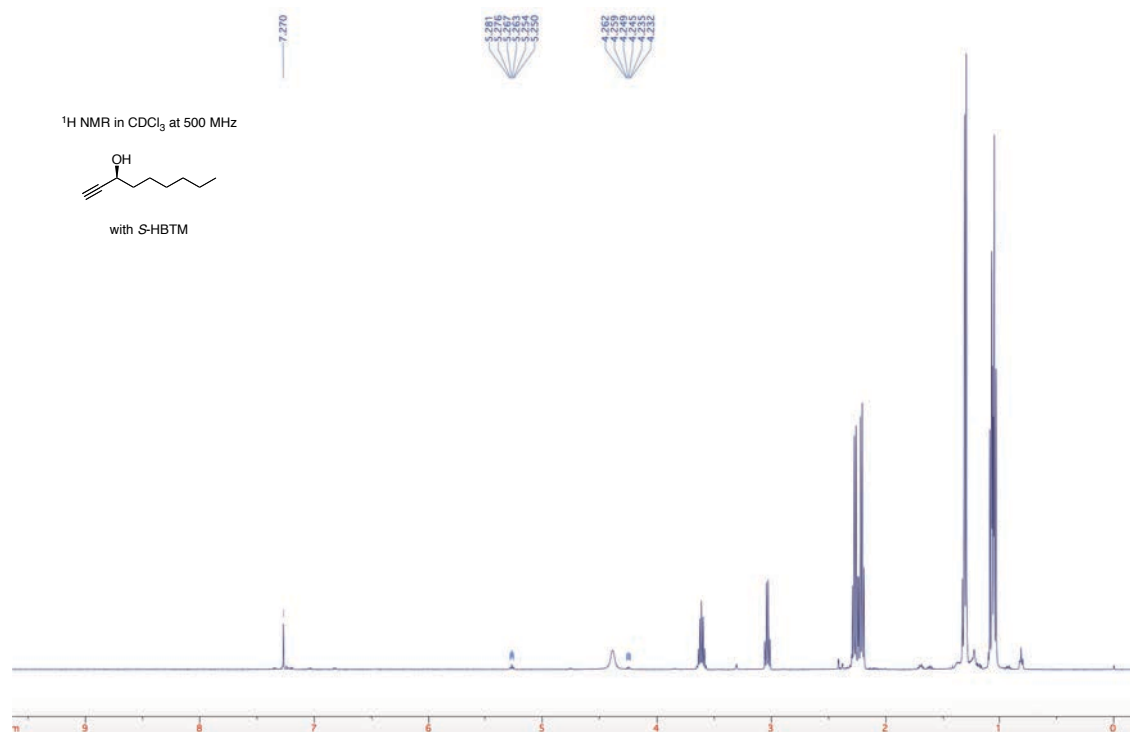
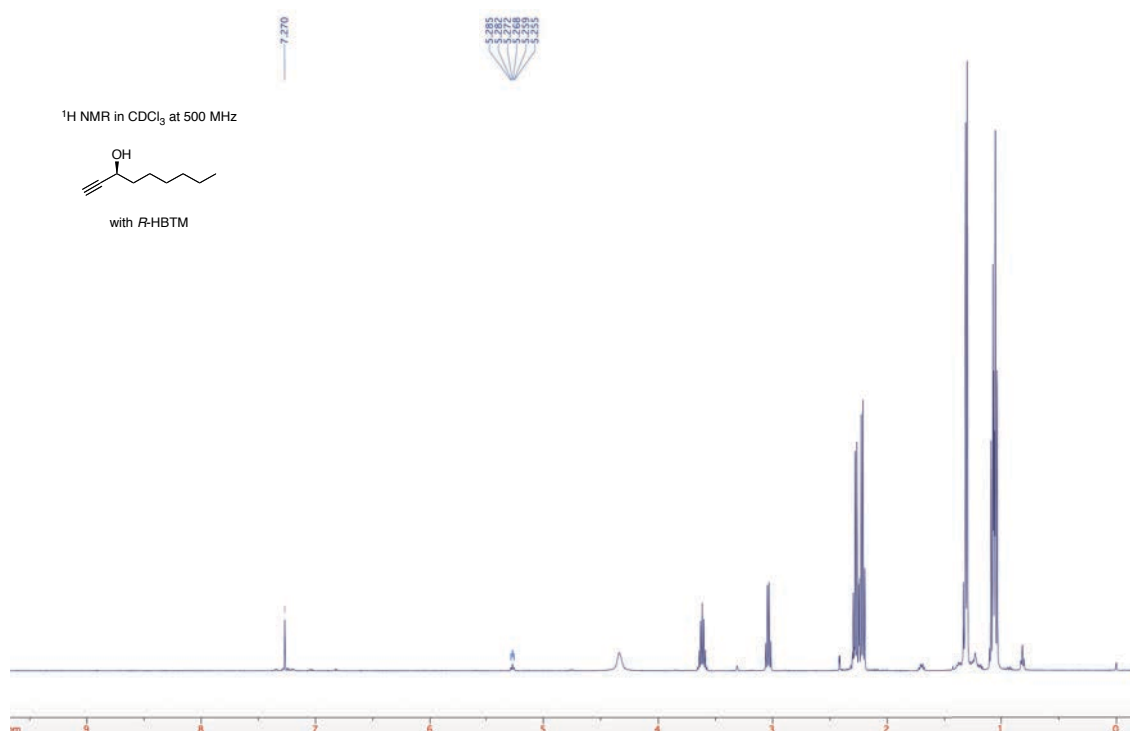
Table 7. Entry 1

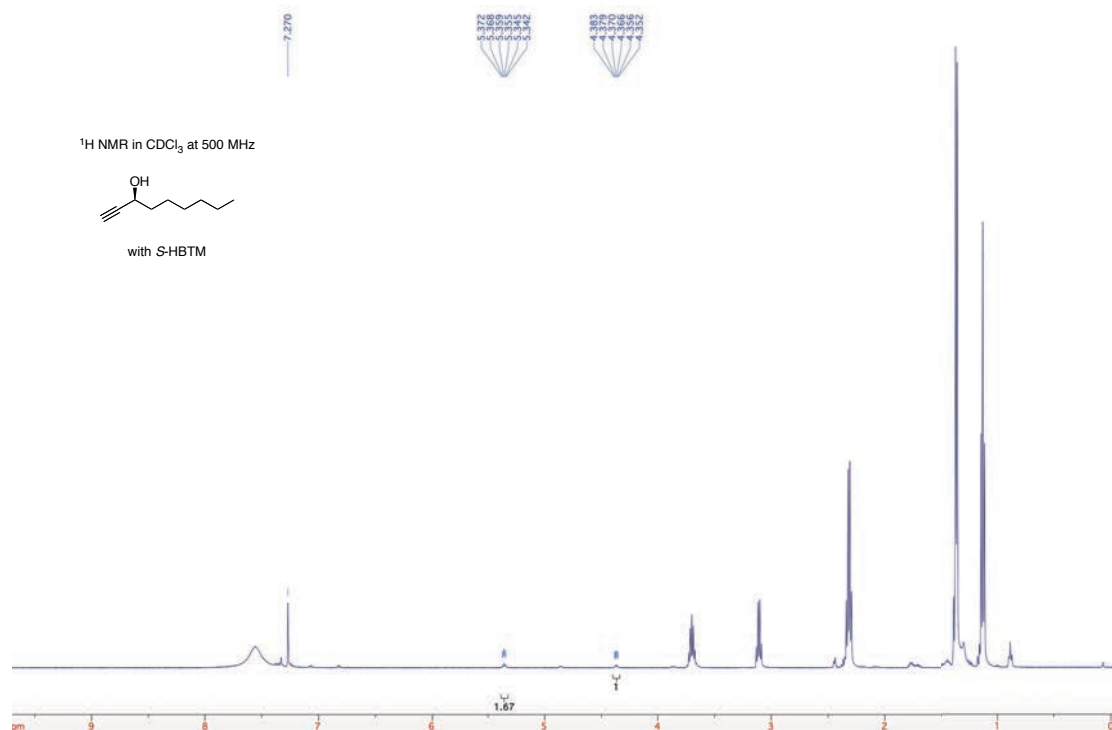
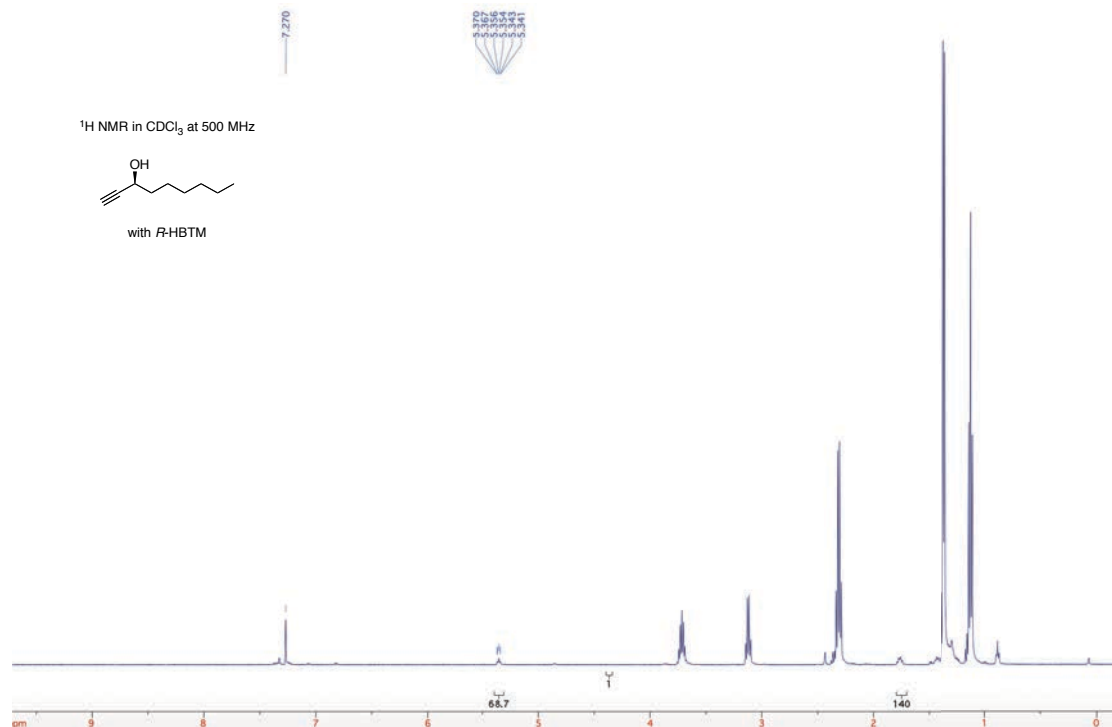
Table 7. Entry 1 – after vacuum removal of solvent and resolution in CDCl_3 

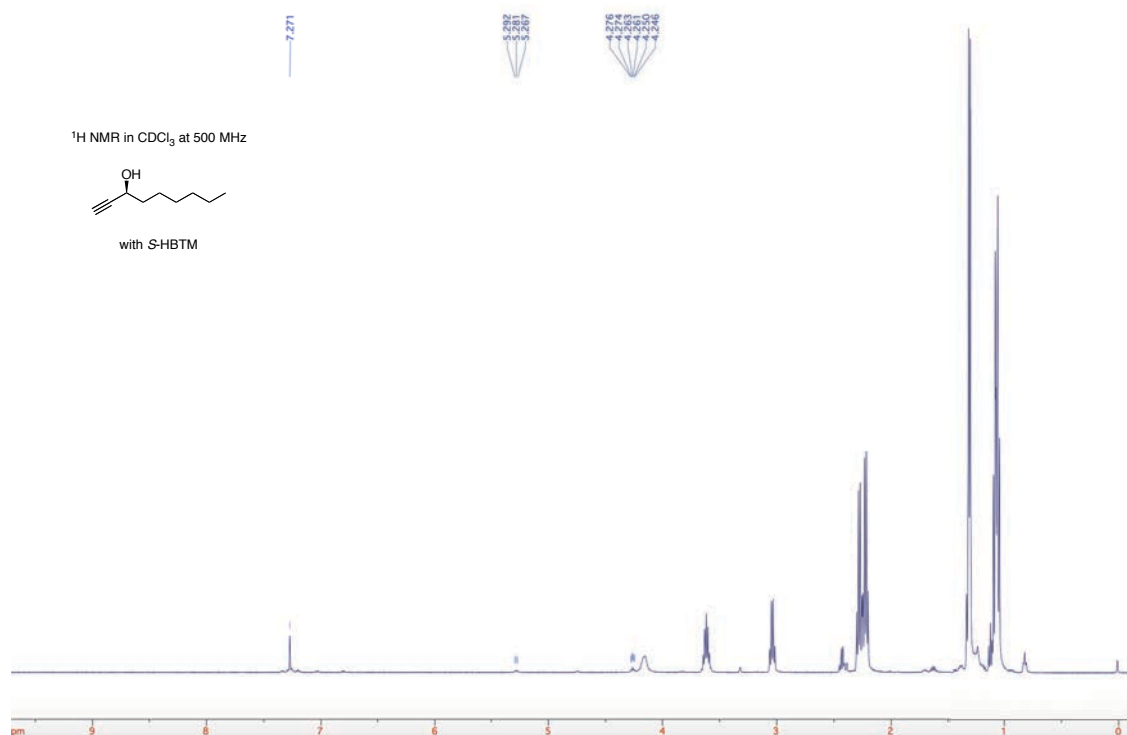
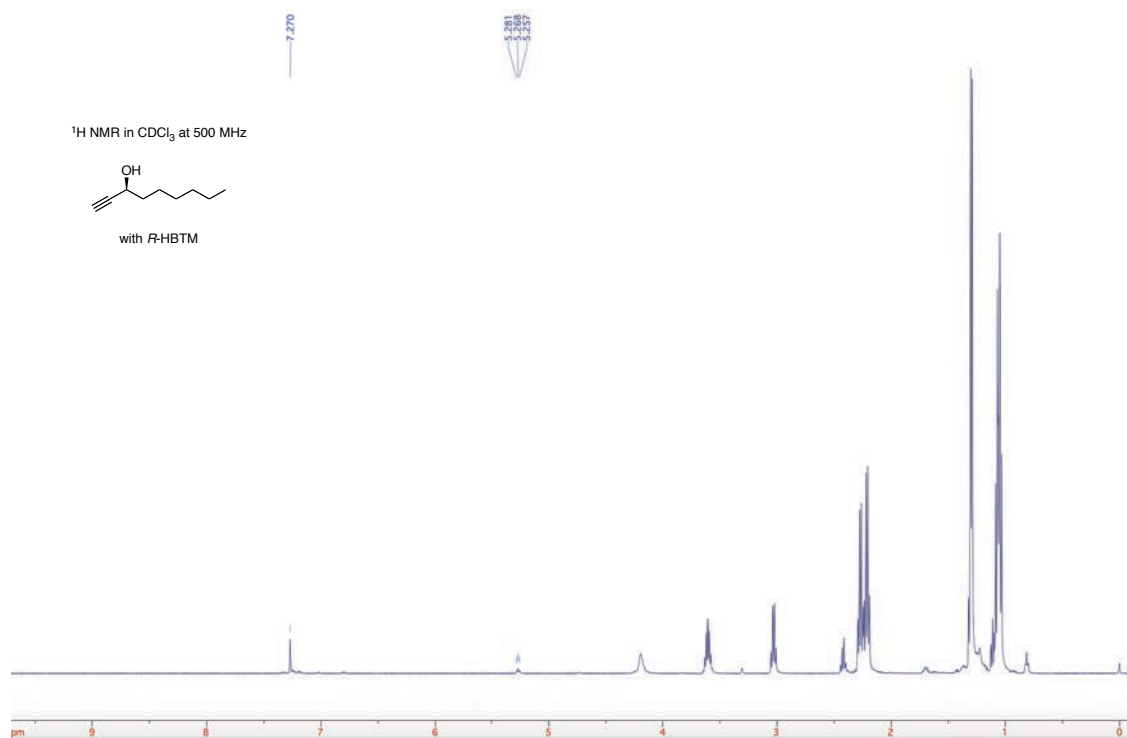
Table 7. Entry 2

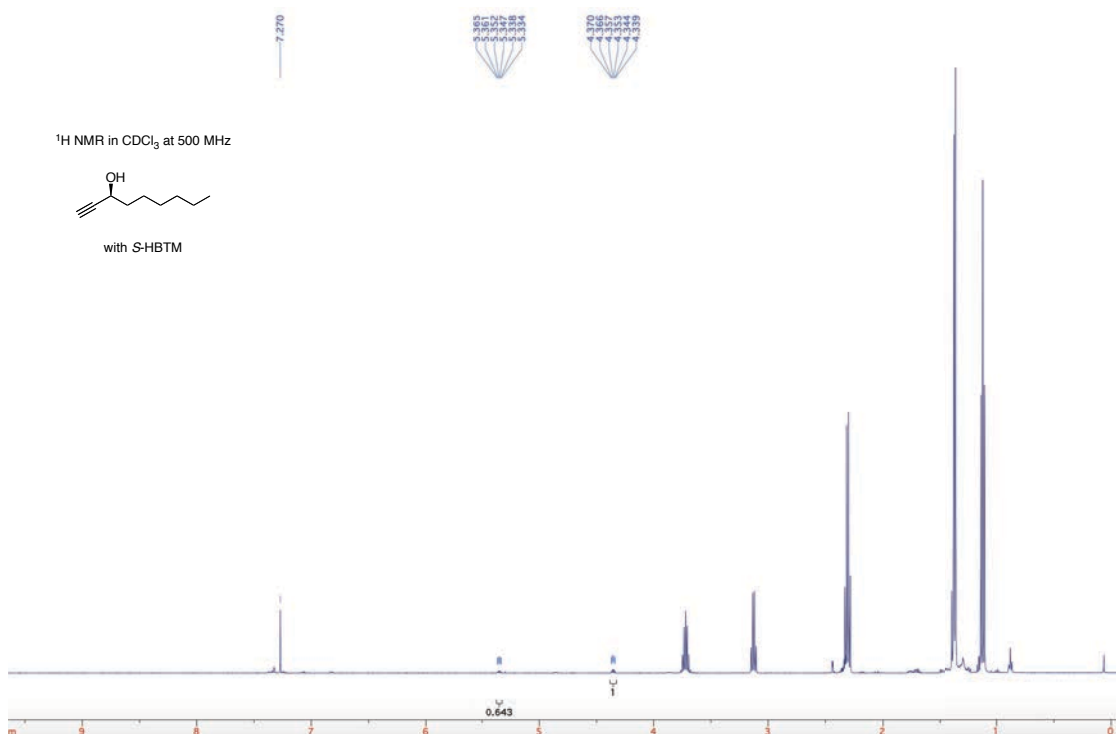
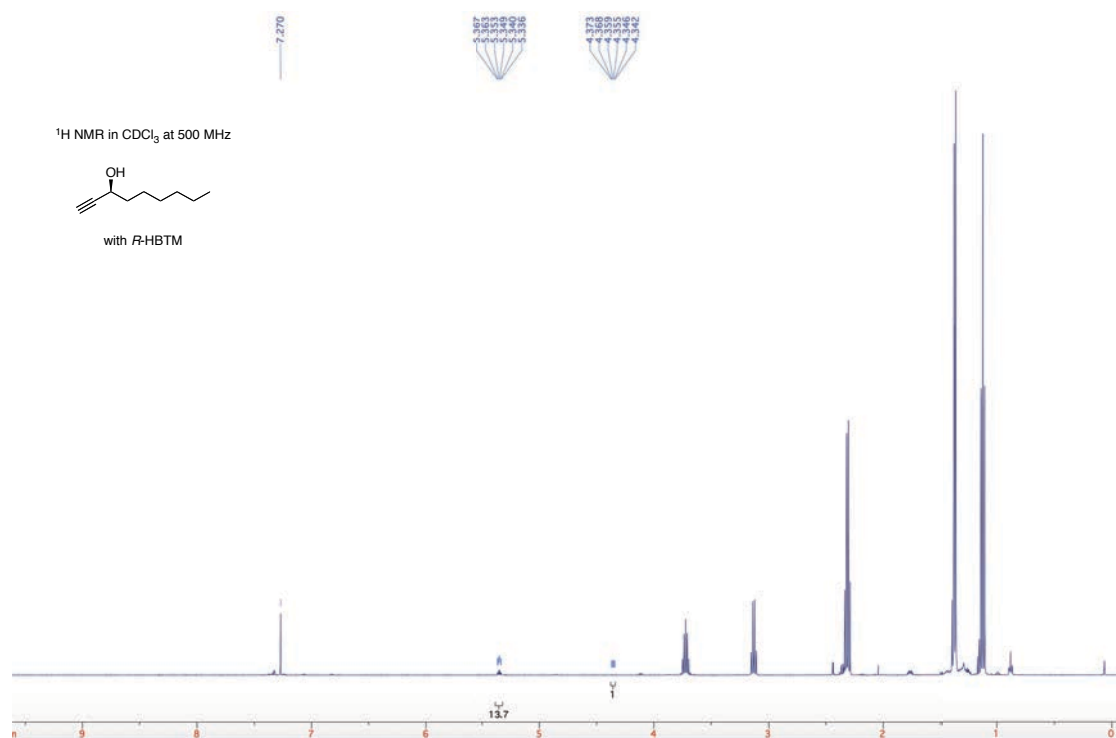
Table 7. Entry 2 – after vacuum removal of solvent and resolution in CDCl_3 

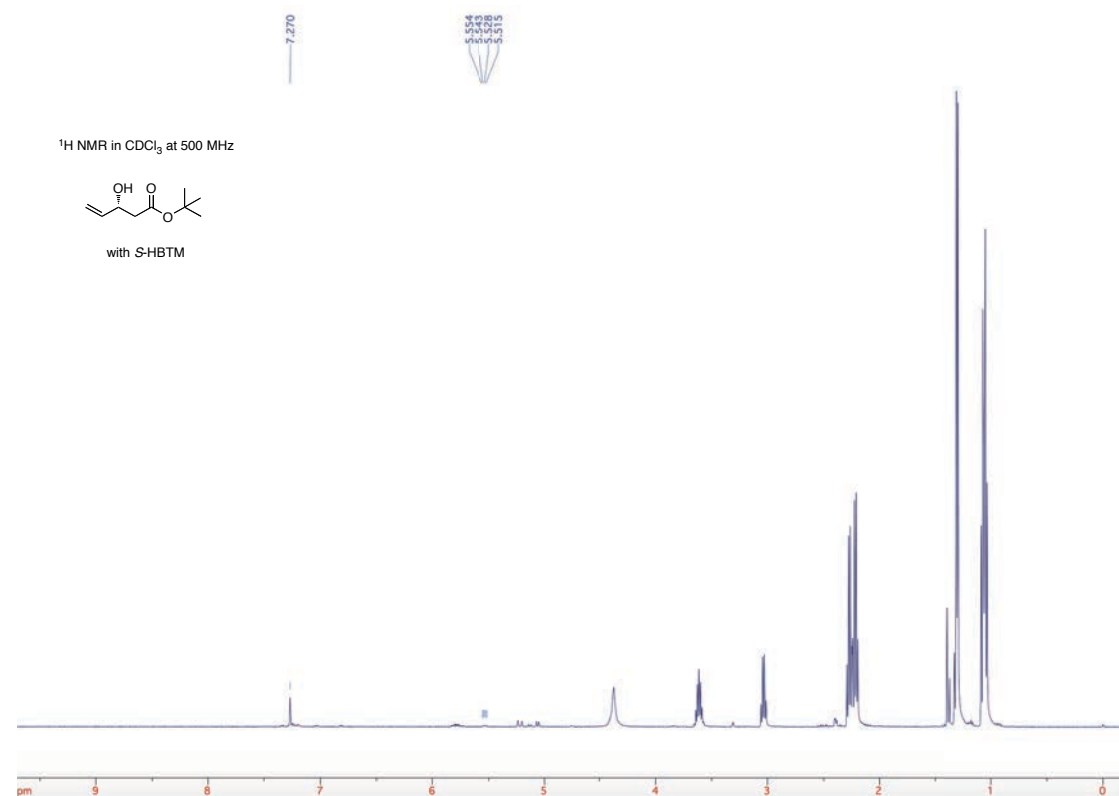
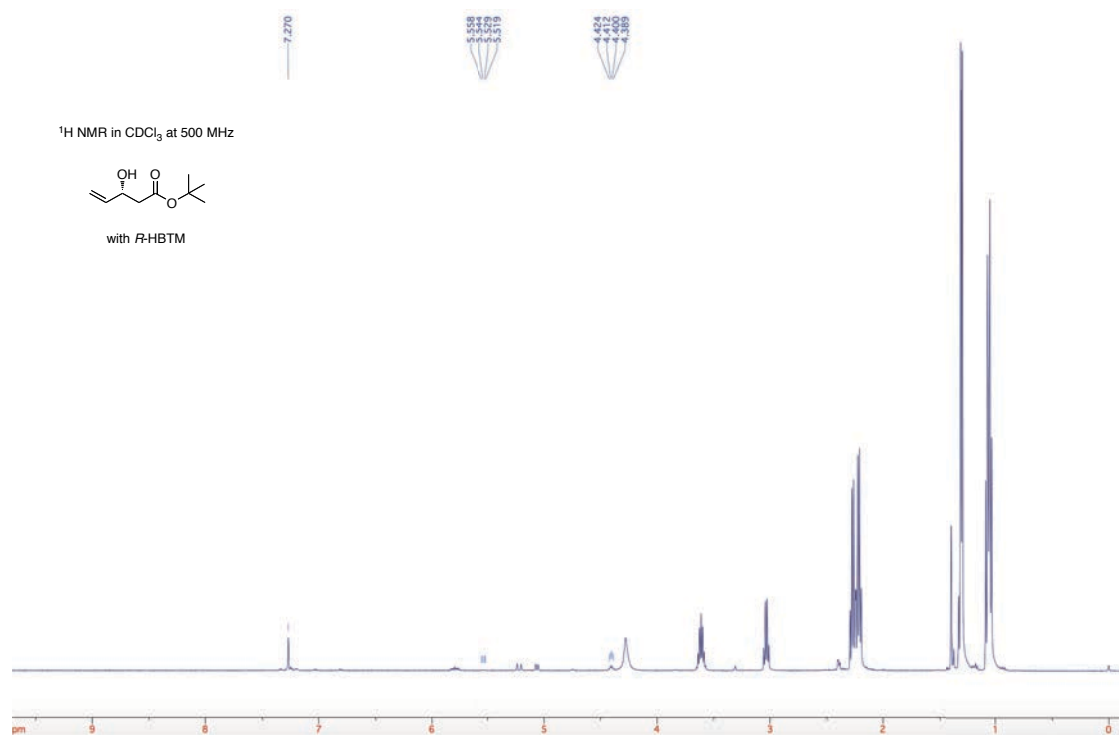
Table 7. Entry 3

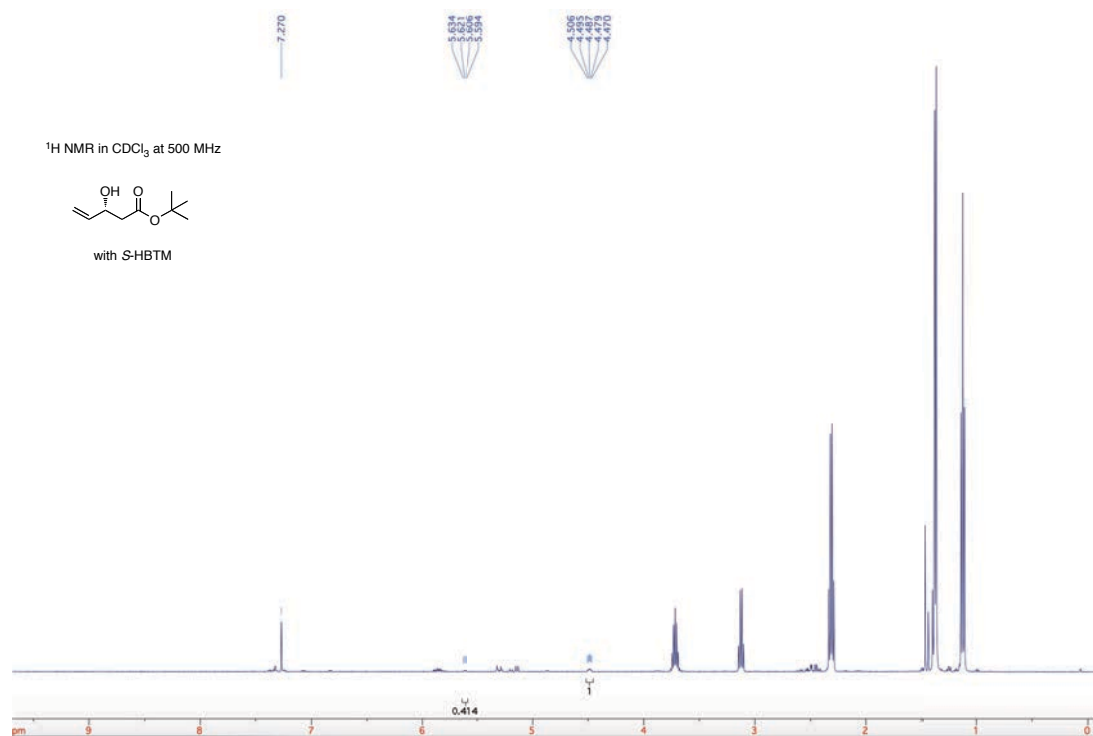
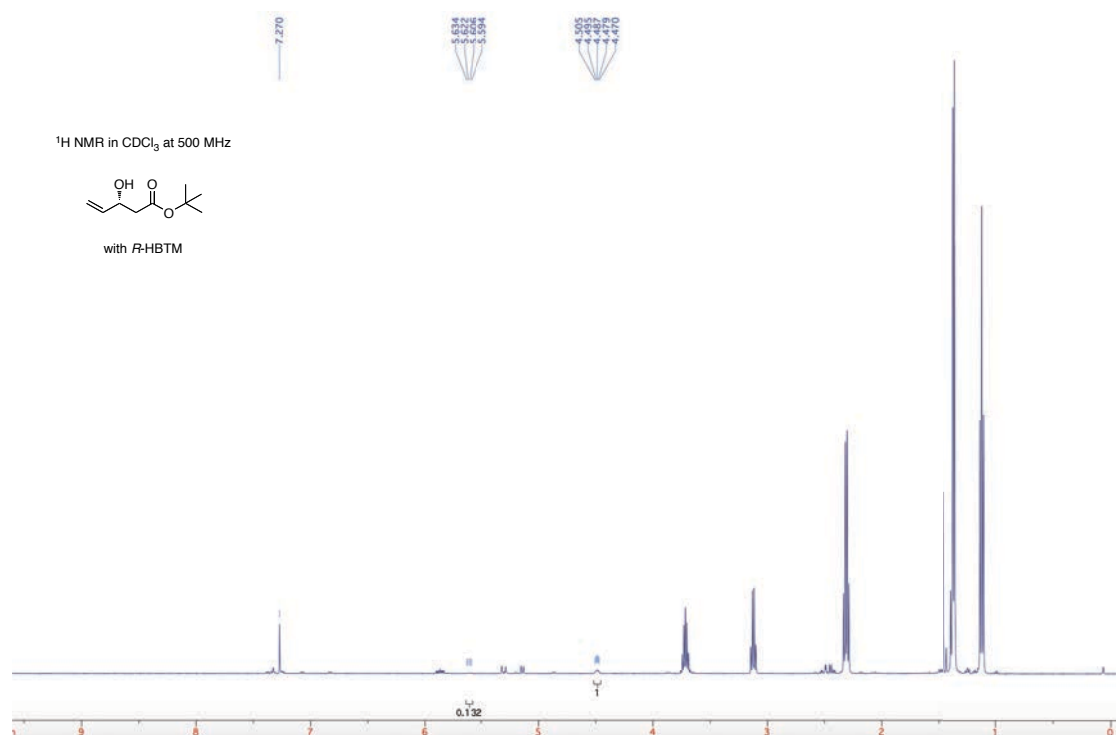
Table 7. Entry 3 – after vacuum removal of solvent and resolution in CDCl_3 

Table 7. Entry 4

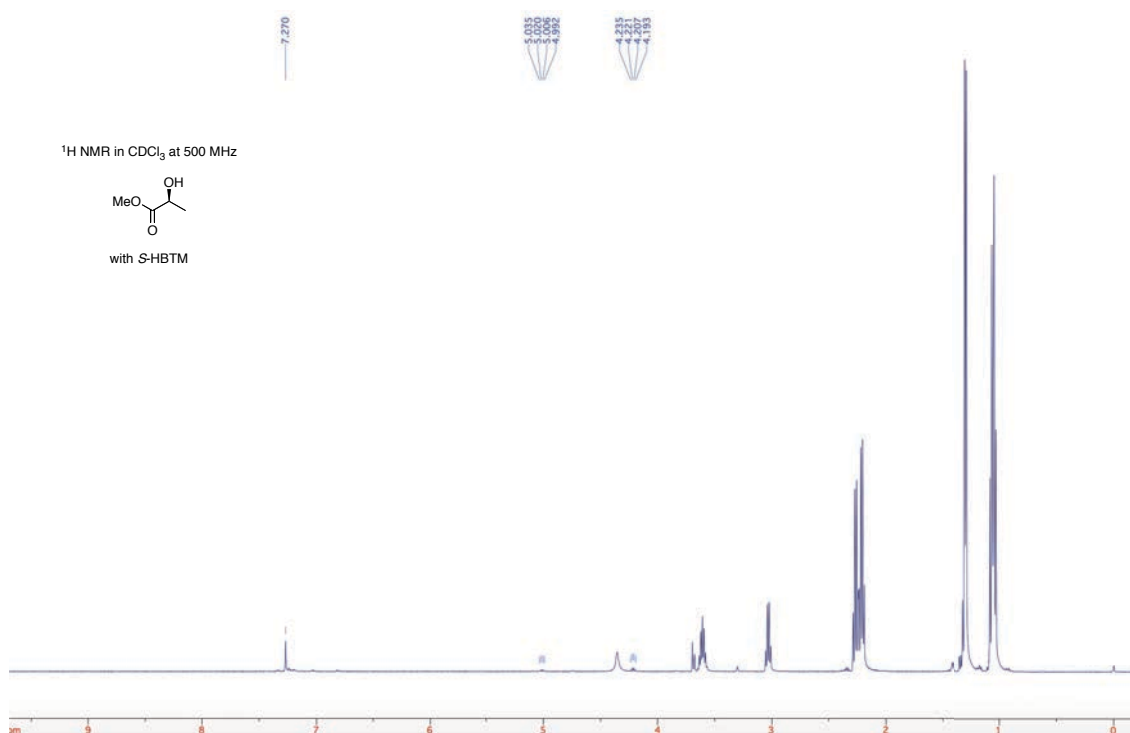
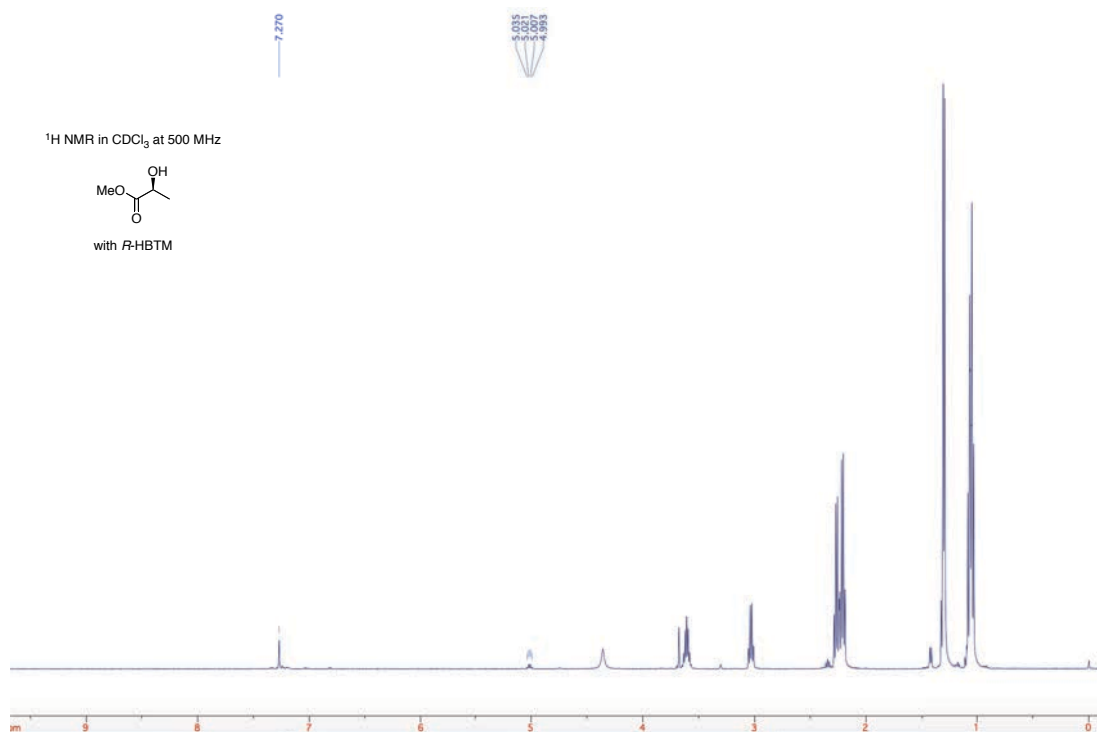


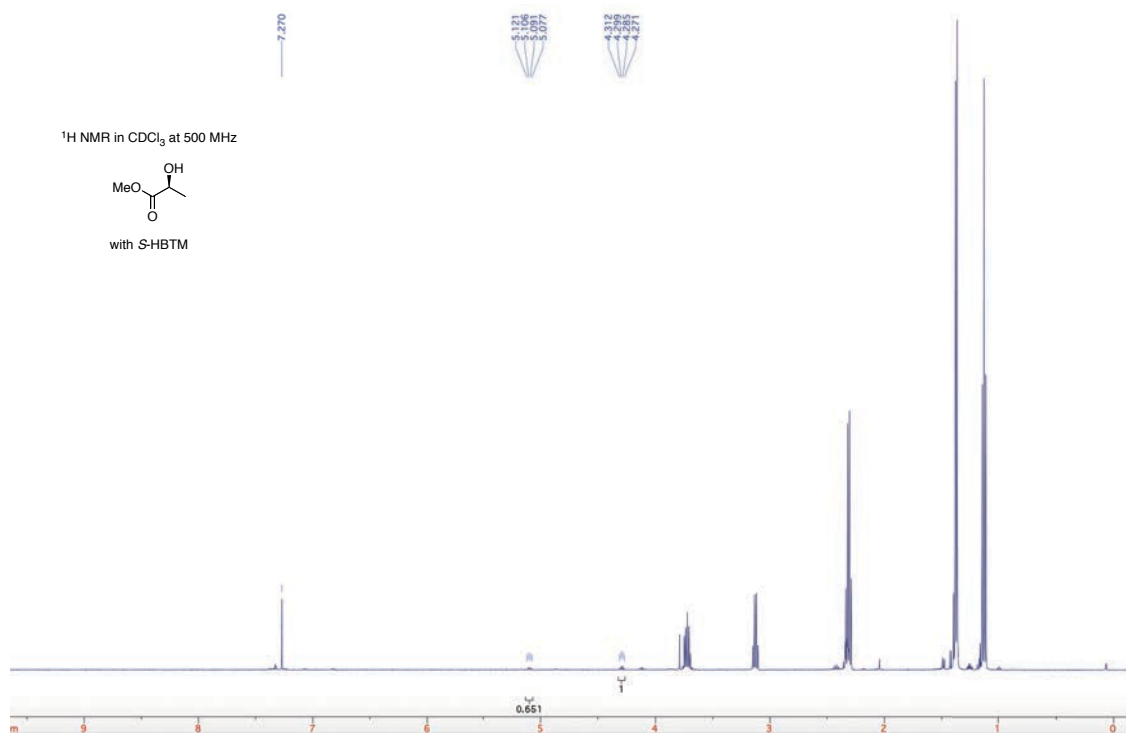
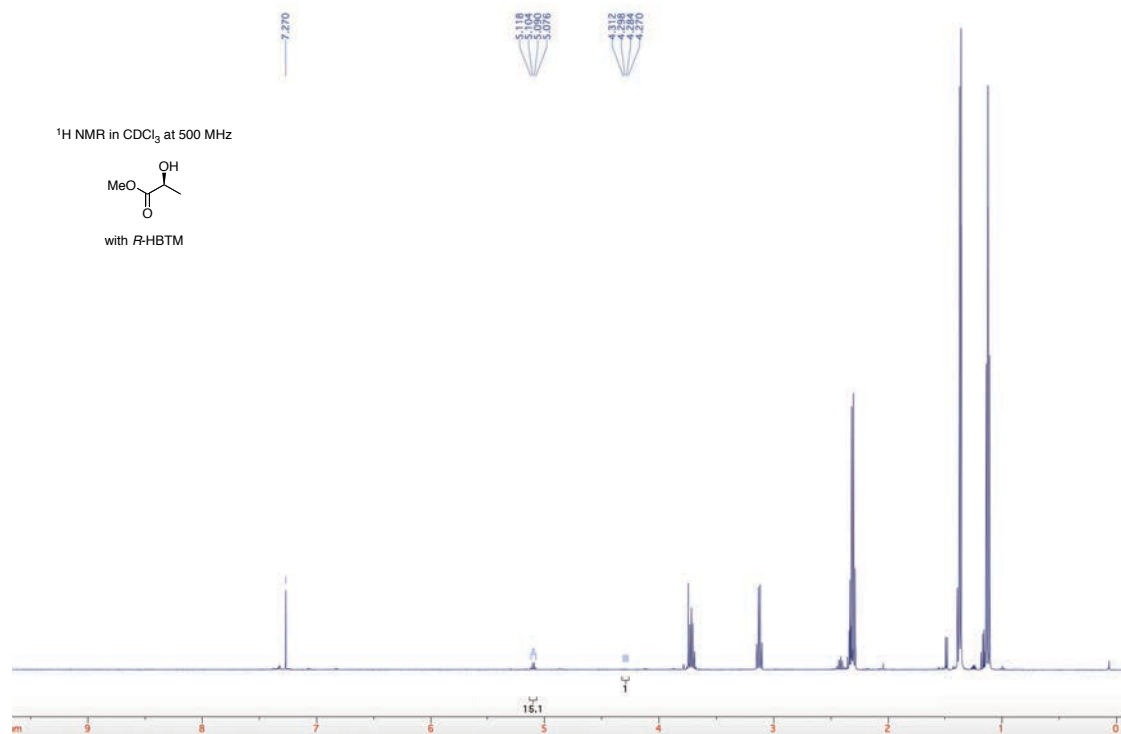
Table 7. Entry 4 – after vacuum removal of solvent and resolution in CDCl_3 

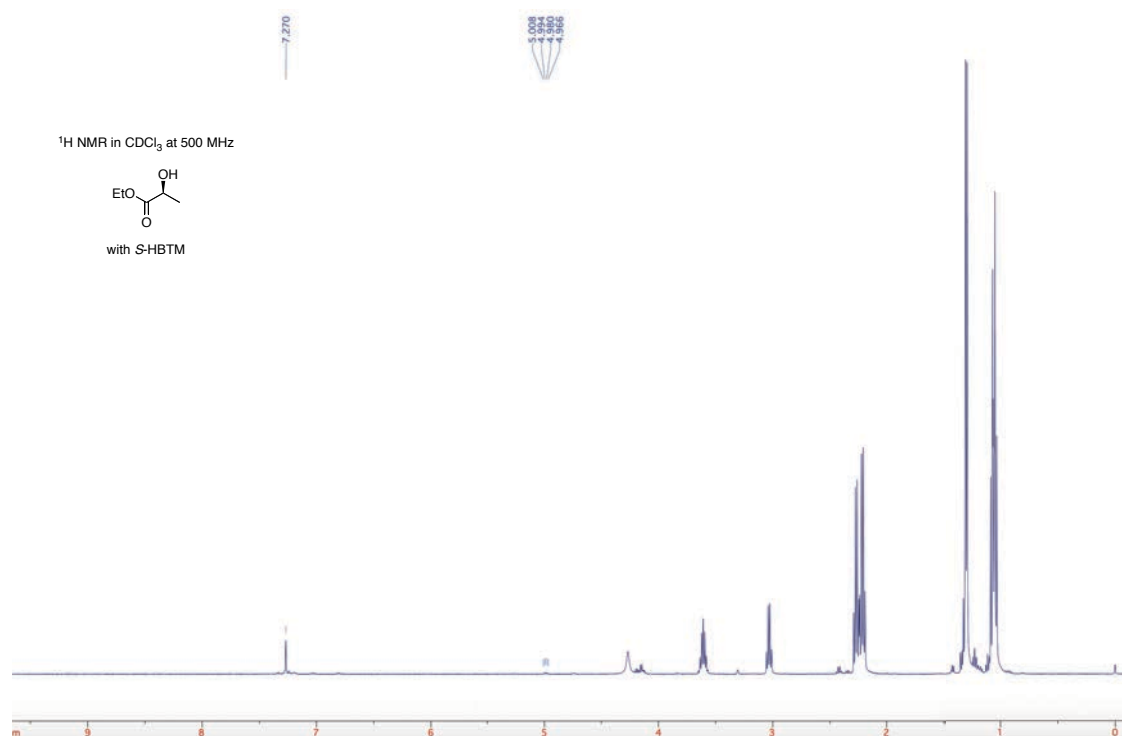
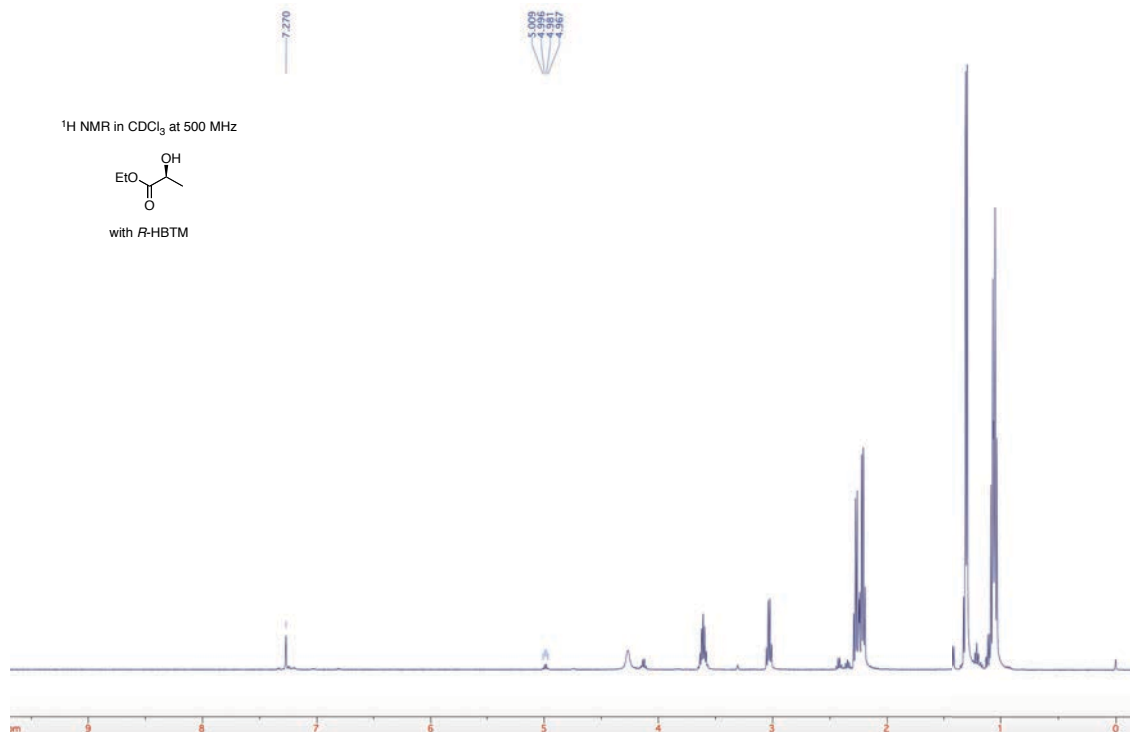
Table 7. Entry 5

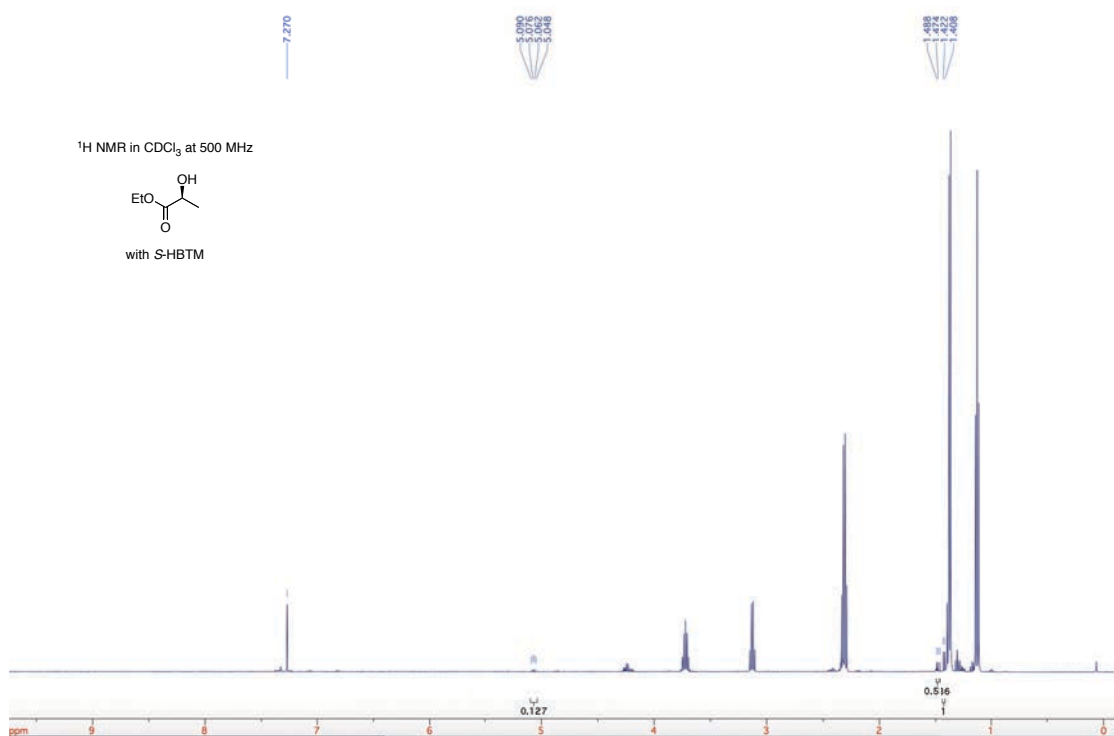
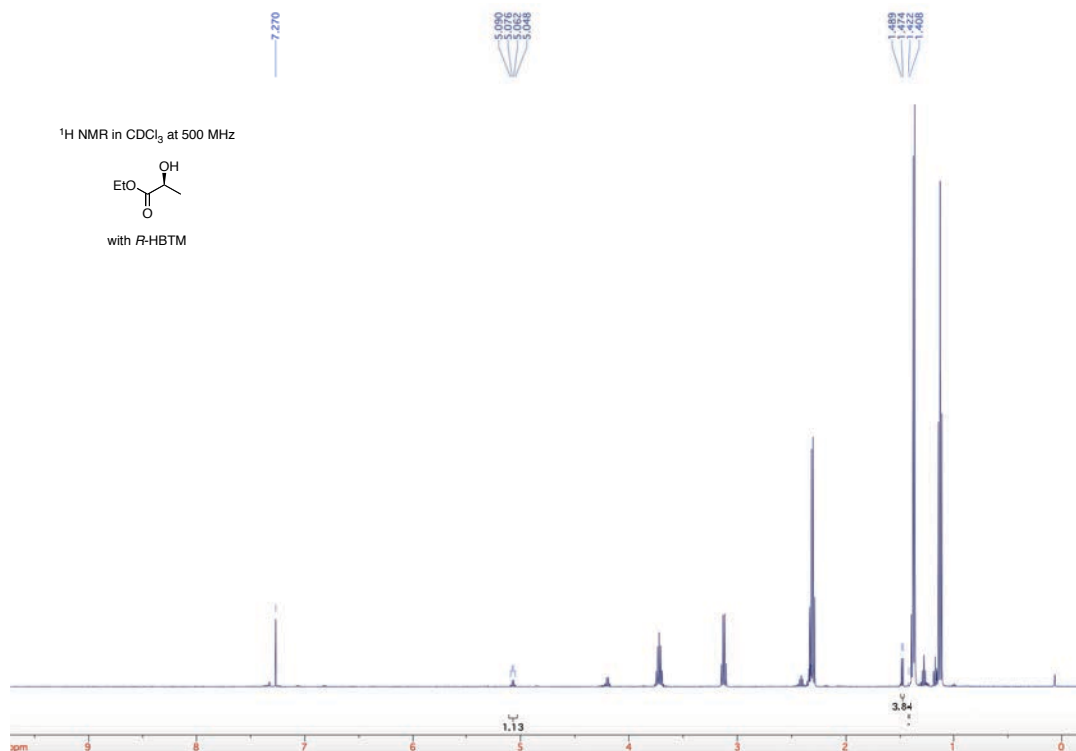
Table 7. Entry 5 – after vacuum removal of solvent and resolution in CDCl_3 

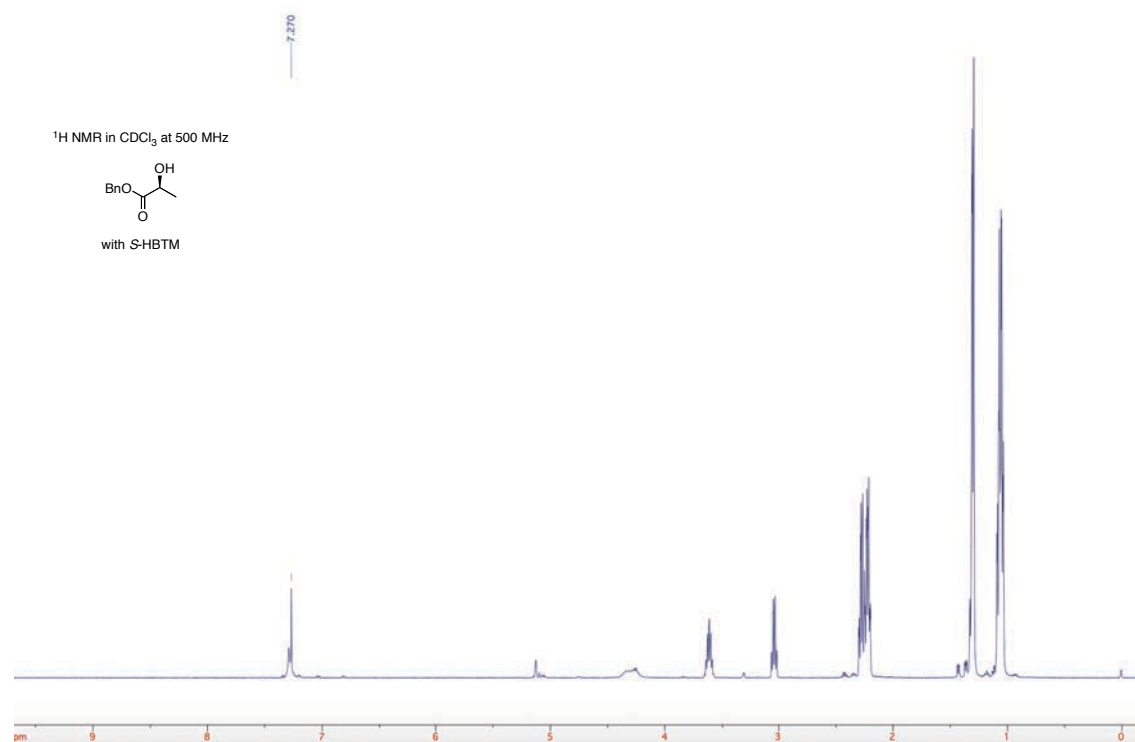
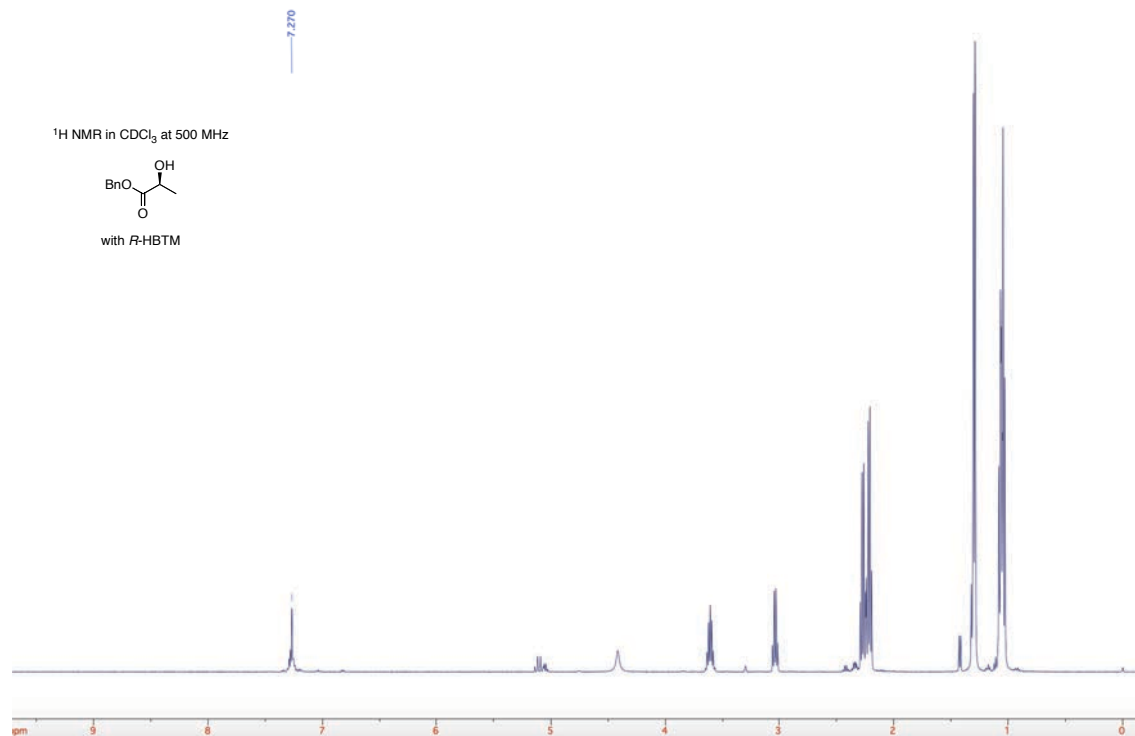
Table 7. Entry 6

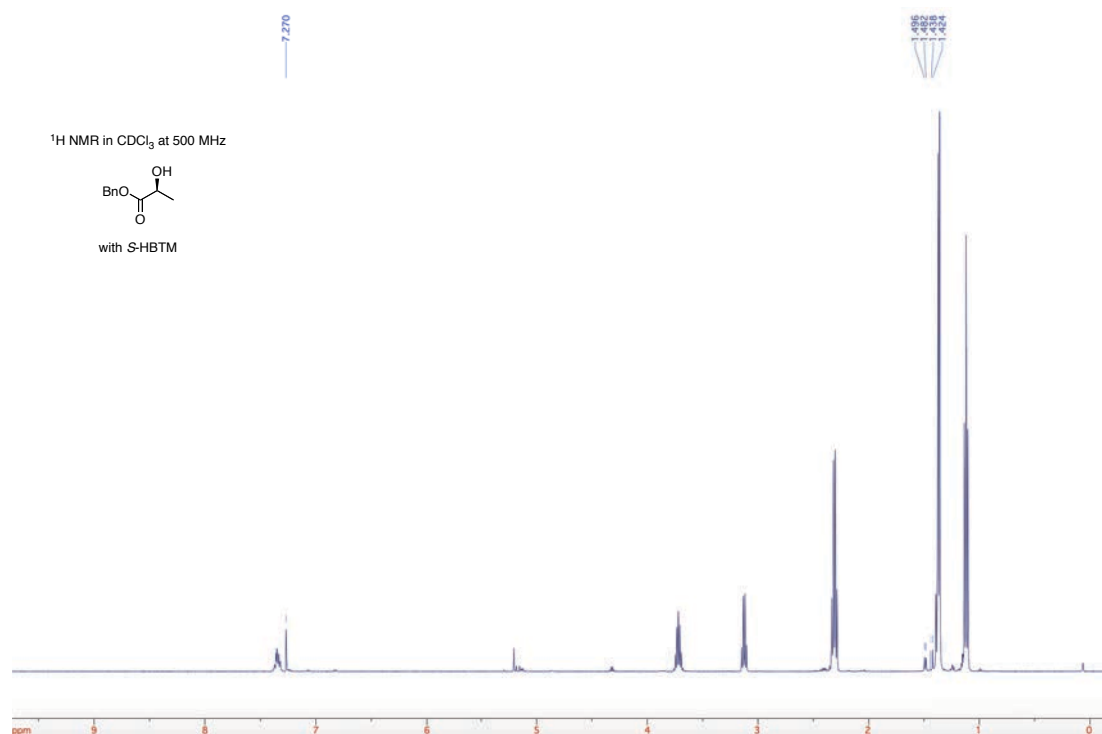
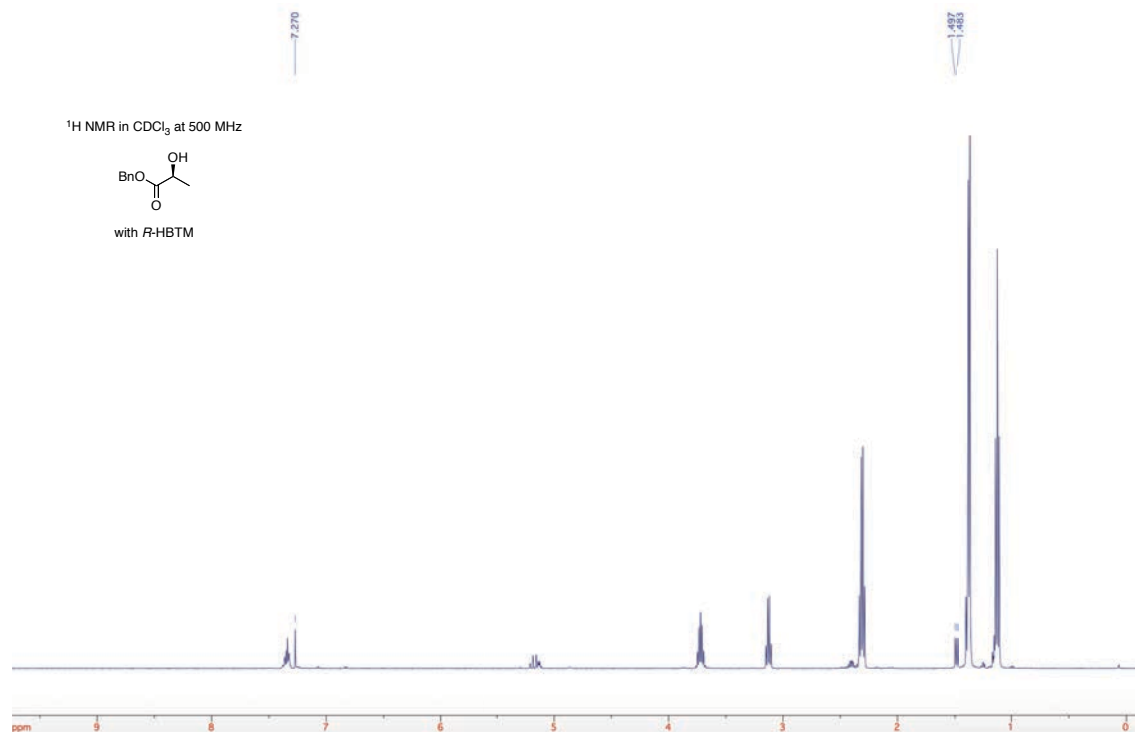
Table 7. Entry 6 – after vacuum removal of solvent and resolution in CDCl_3 

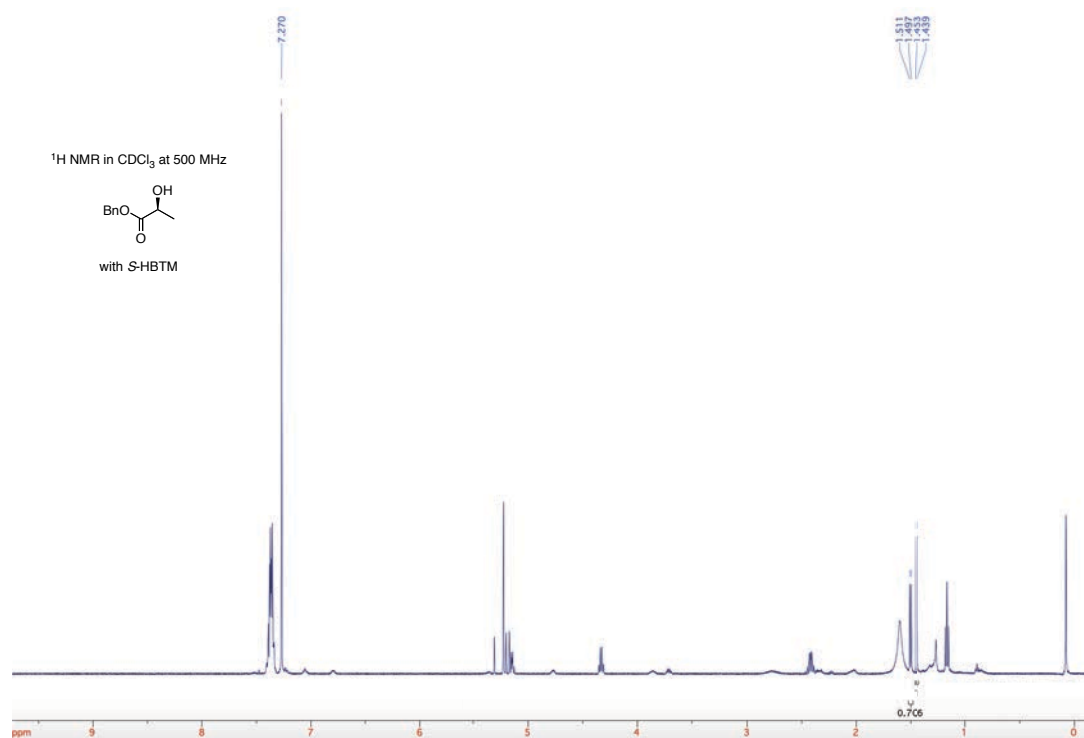
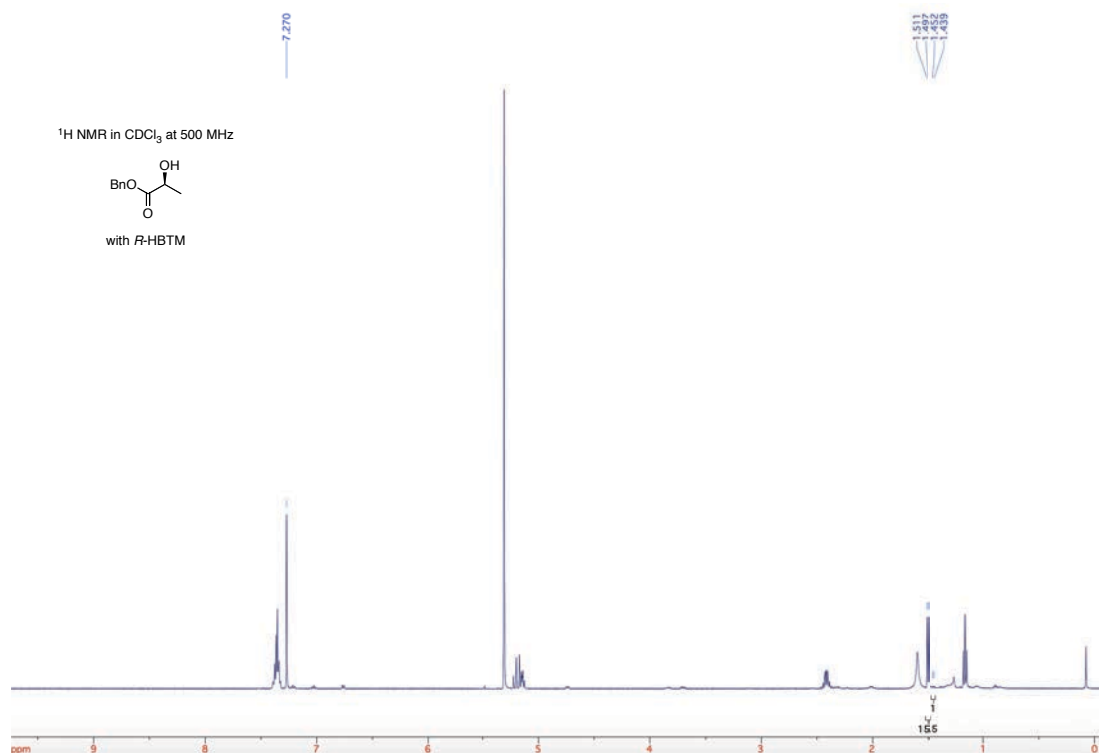
Table 7. Entry 6 – after vacuum removal of solvent, resolution in CDCl_3 , and basic workup

Table 7. Entry 7

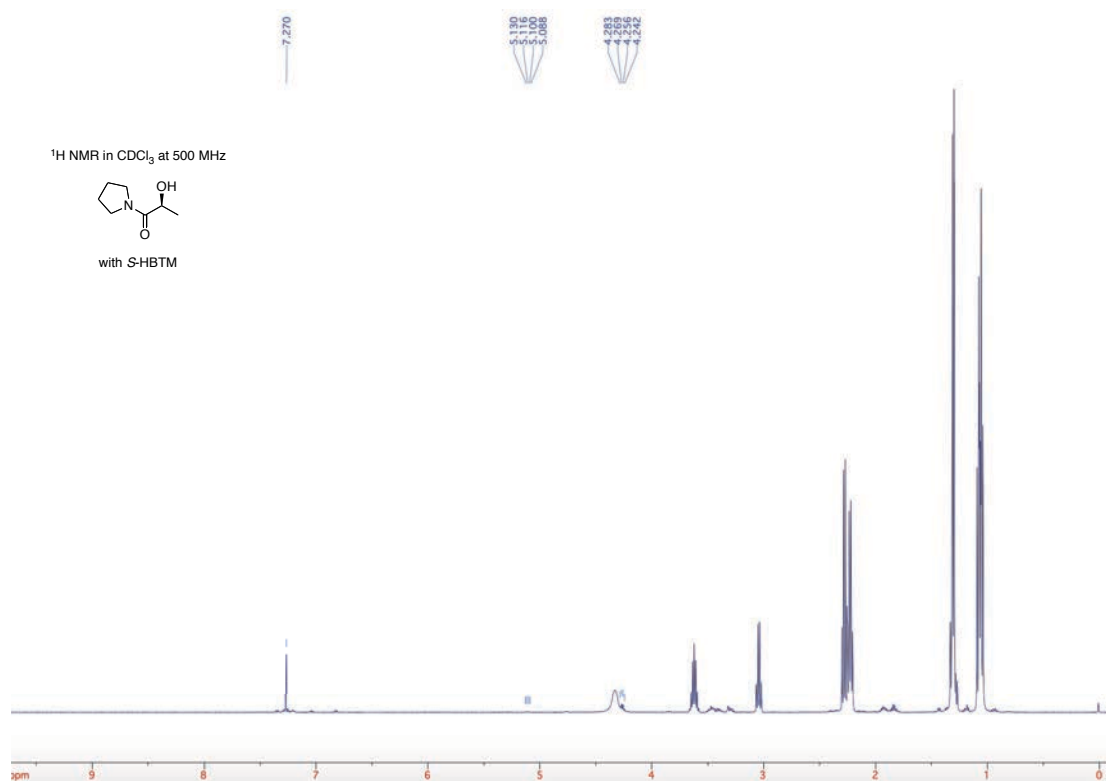
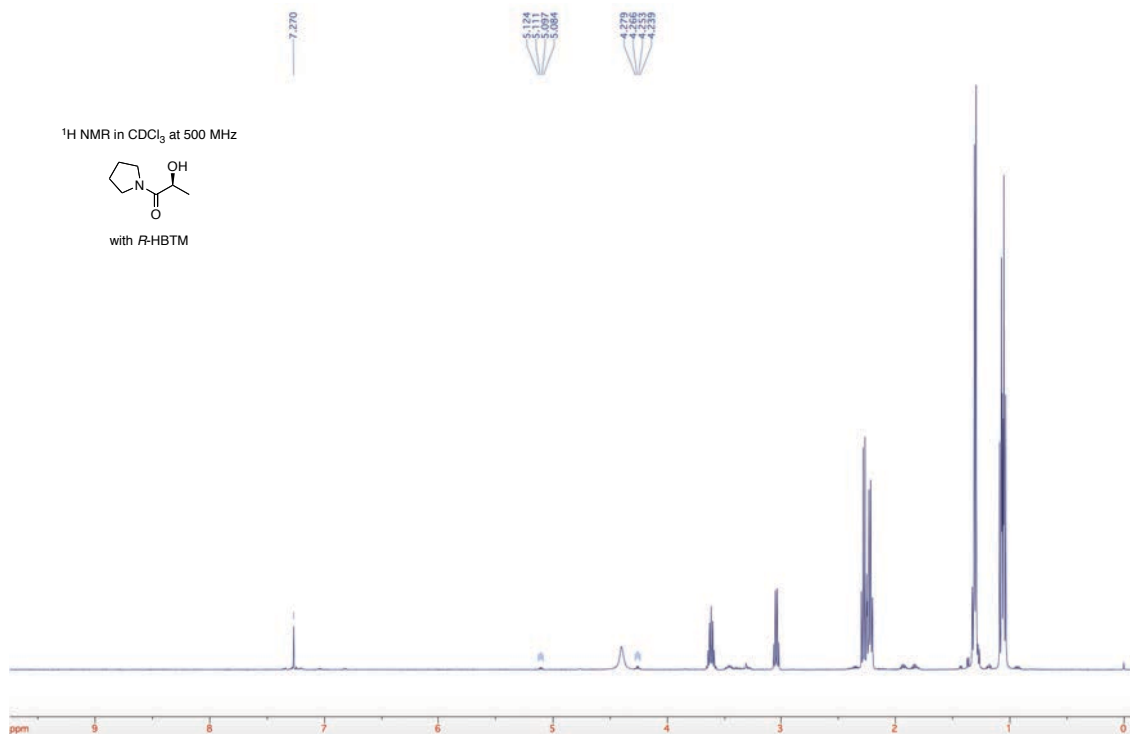


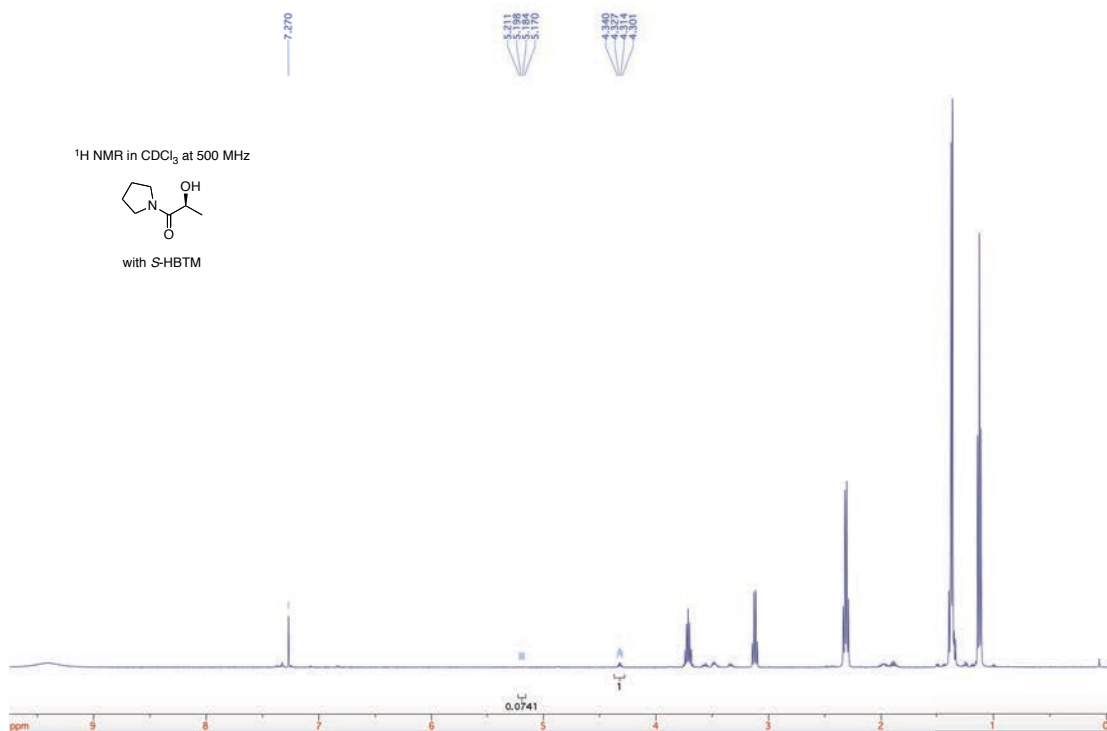
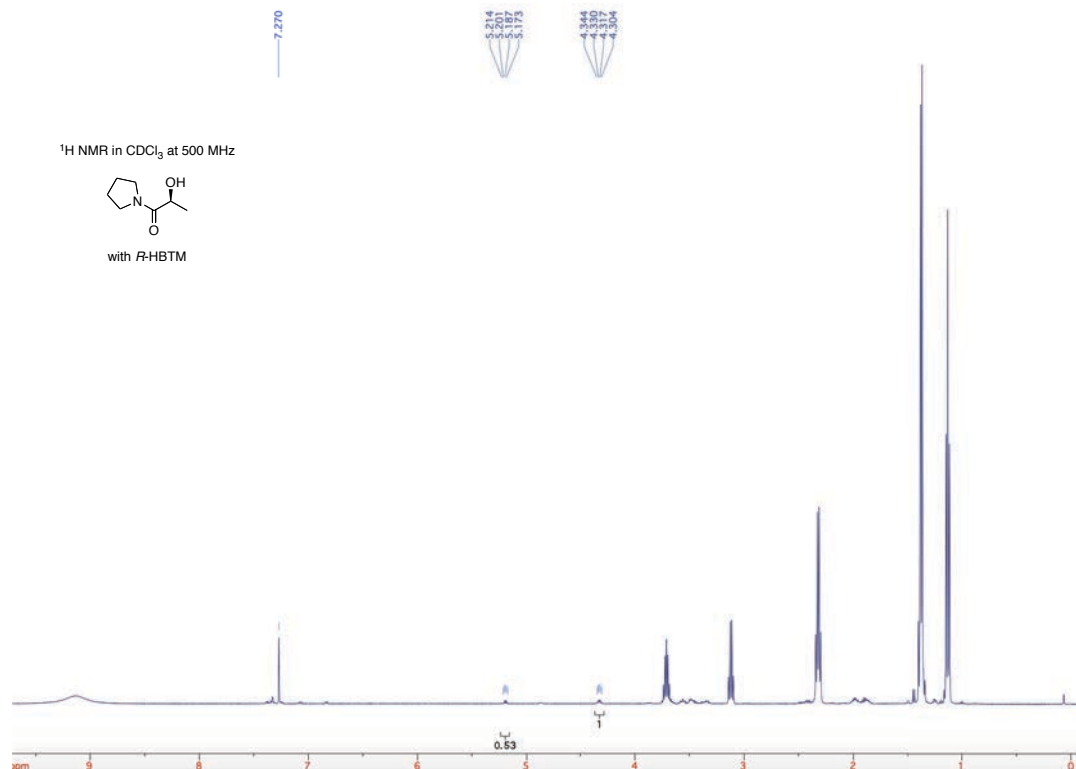
Table 7. Entry 7 – after vacuum removal of solvent and resolution in CDCl_3 

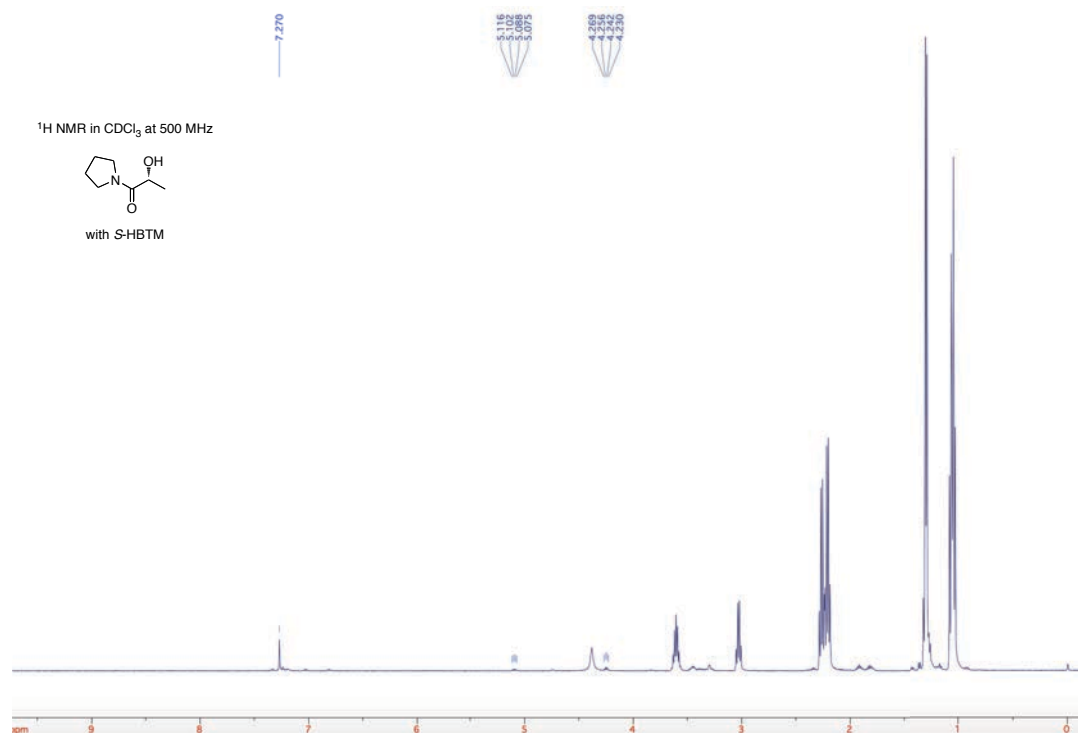
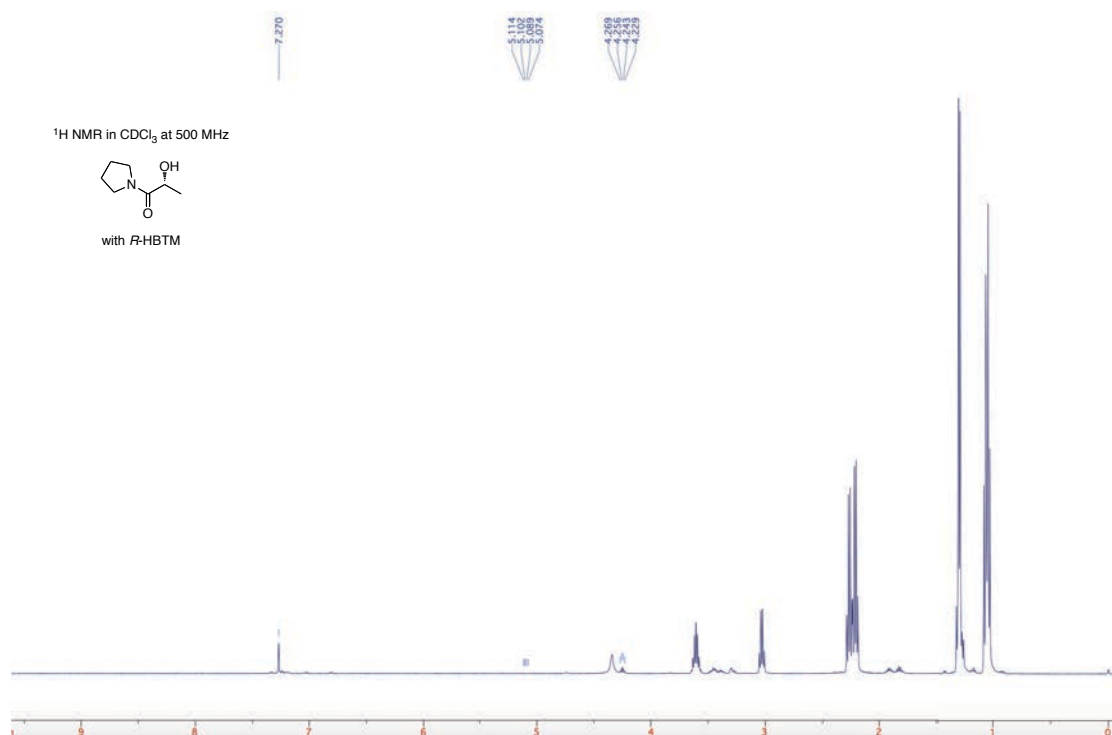
Table 7. Entry 8

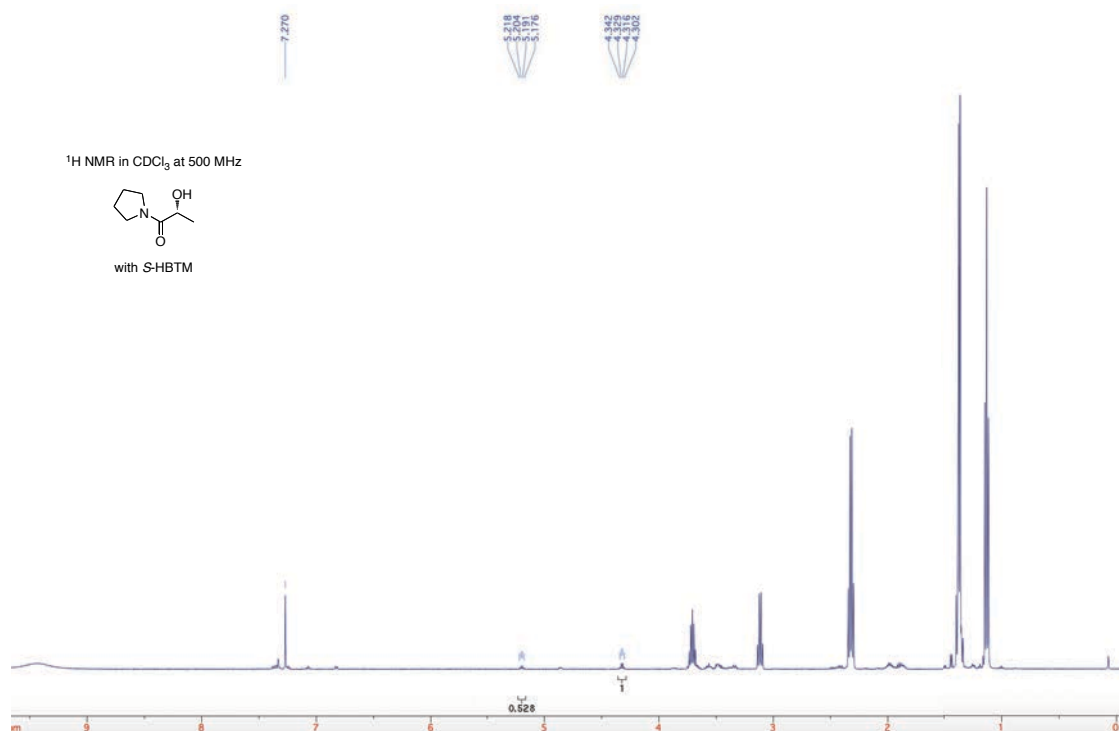
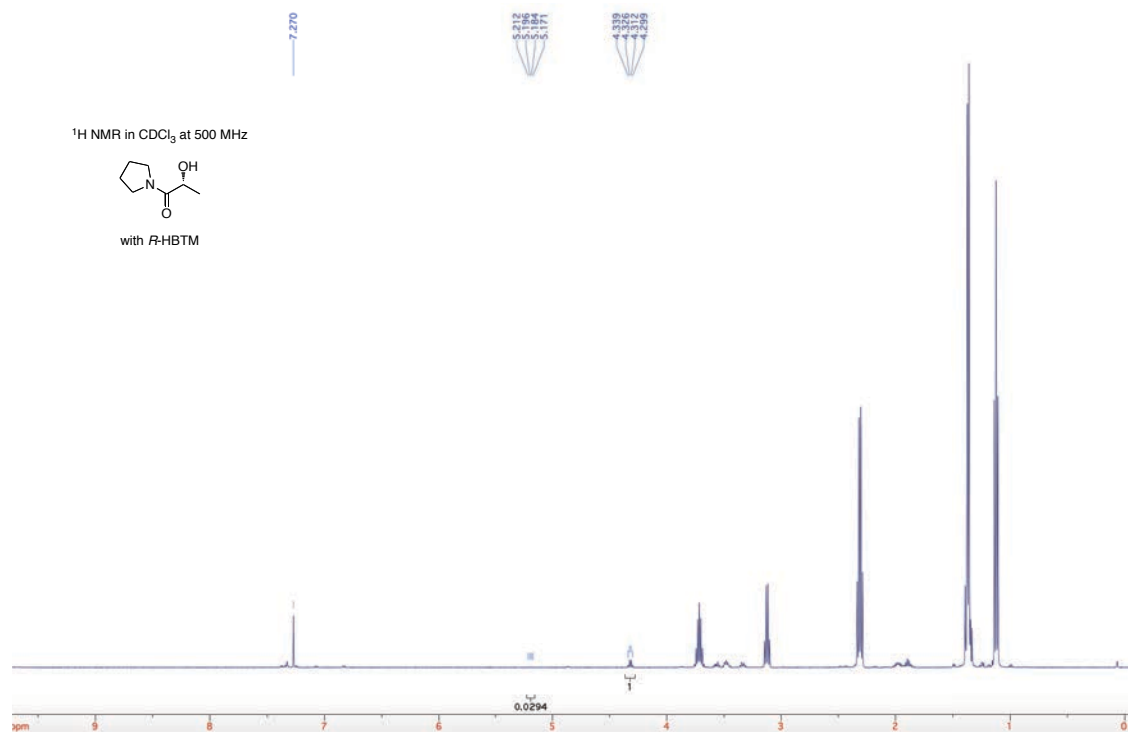
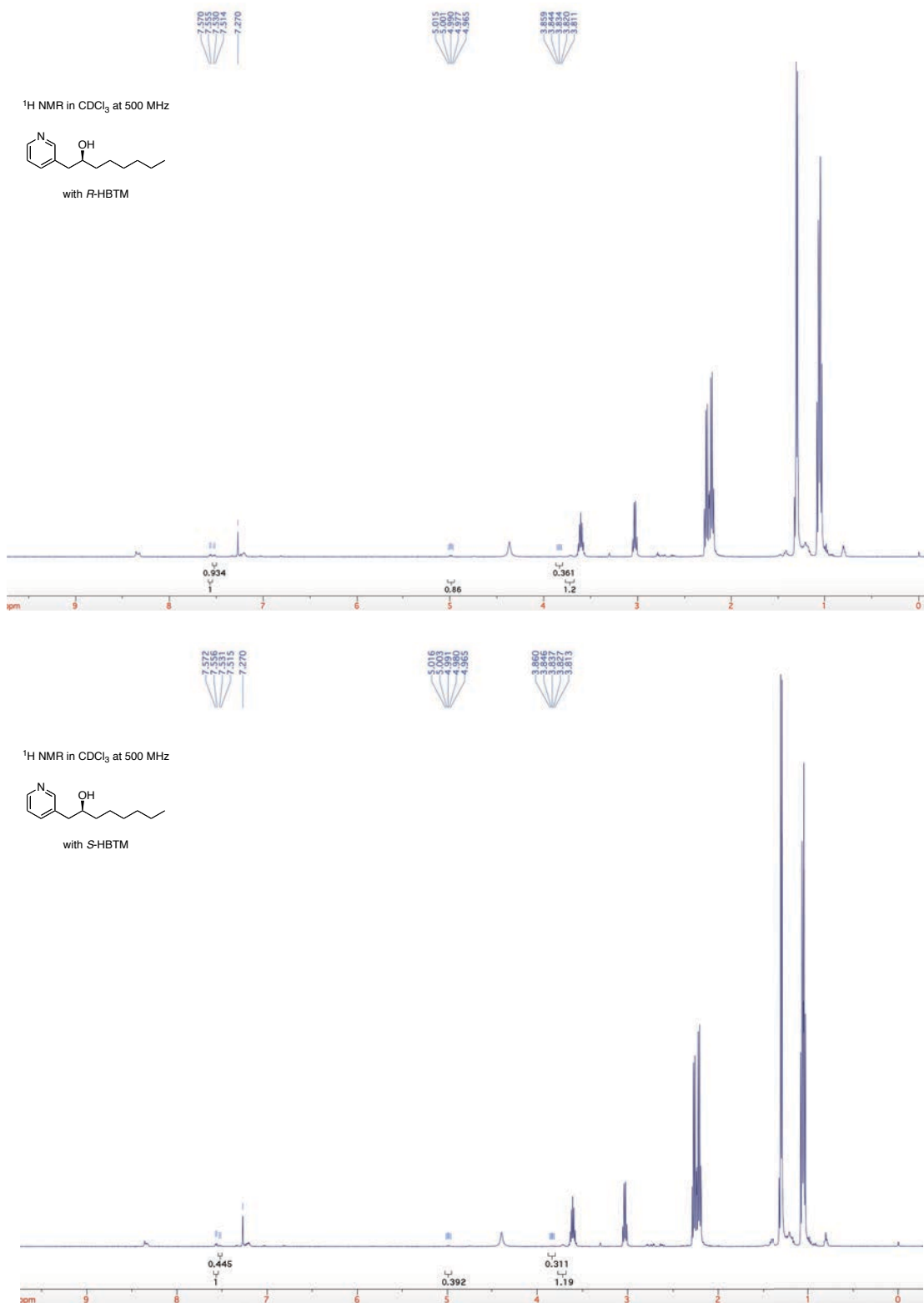
Table 7. Entry 8 – after vacuum removal of solvent and resolution in CDCl_3 

Table 7. Entry 9

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%).

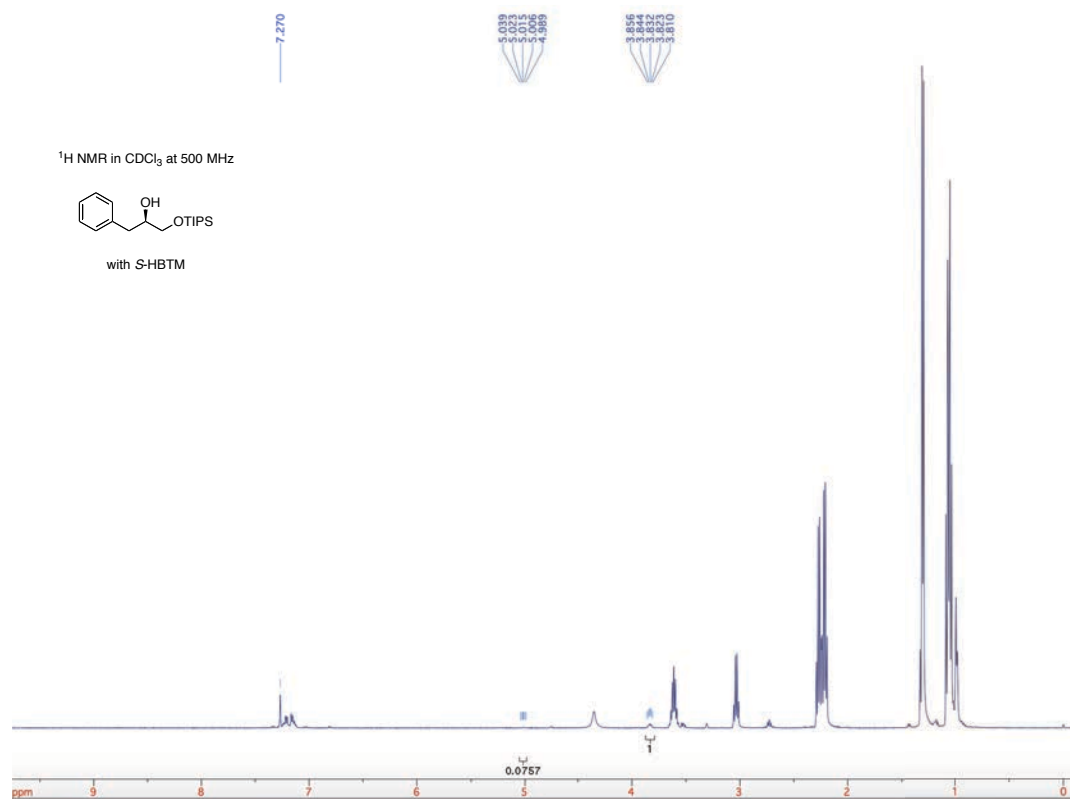
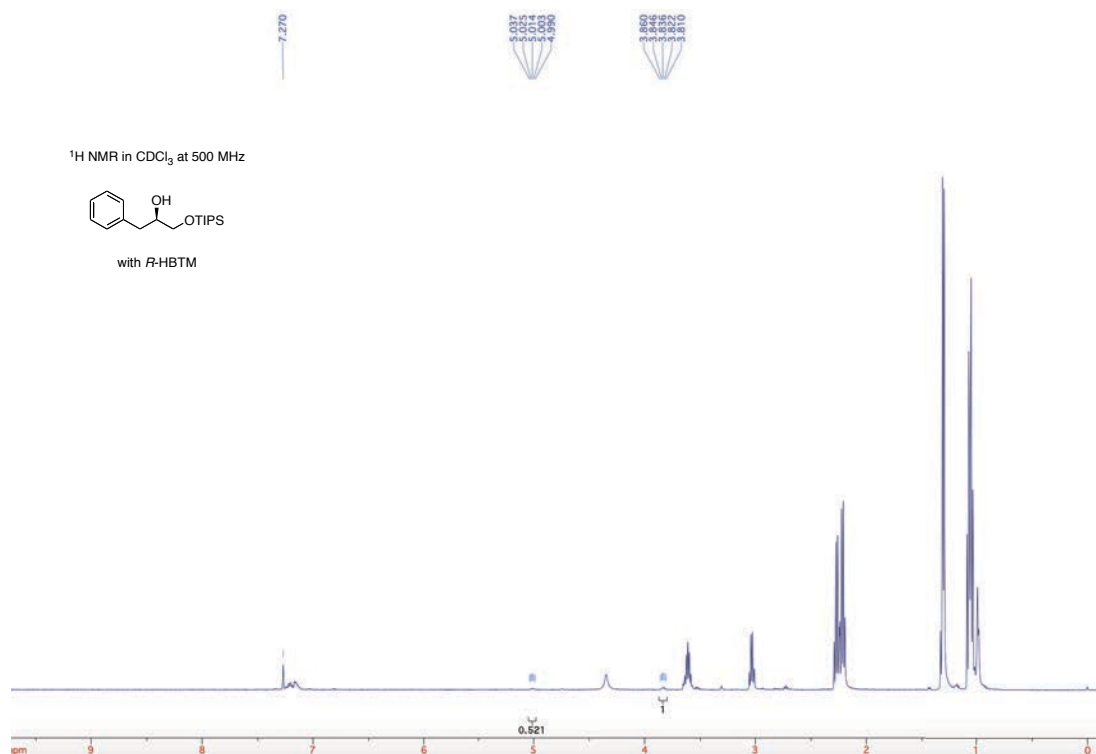
Table 7. Entry 10

Table 7. Entry 11

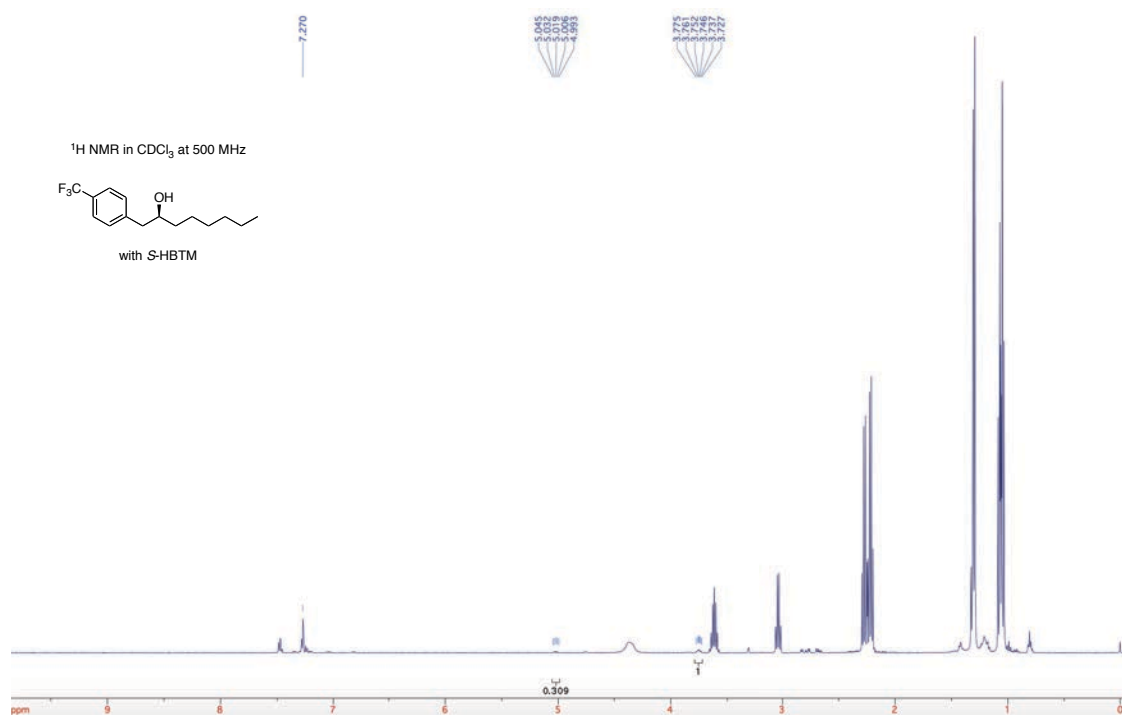
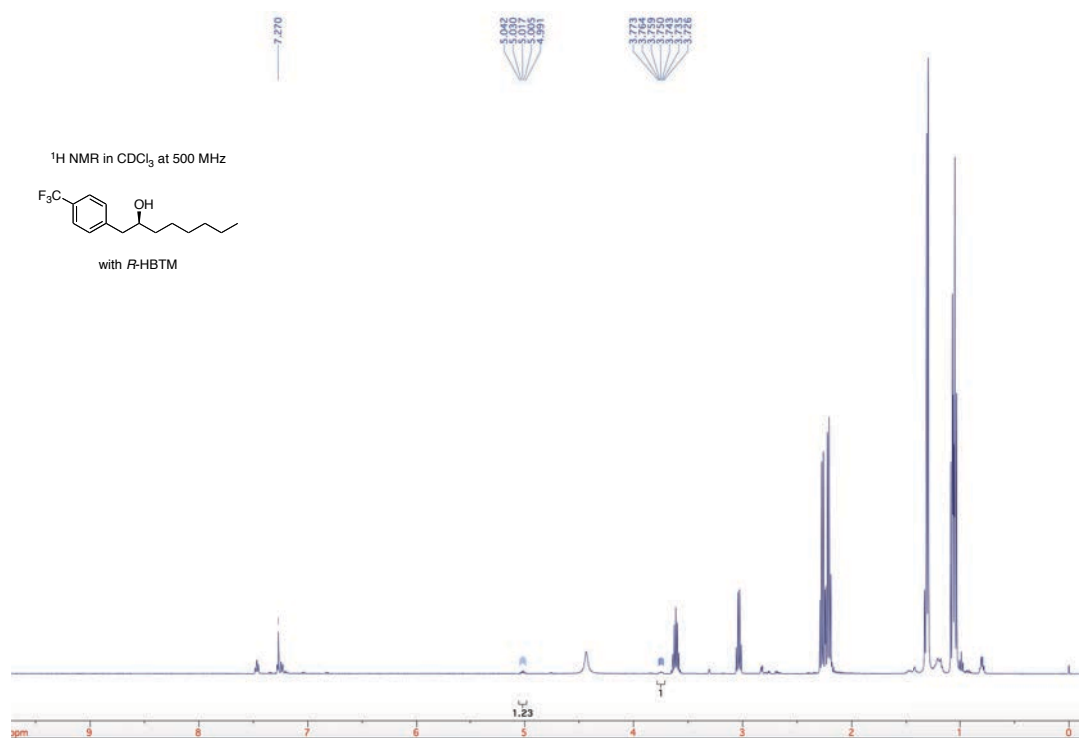
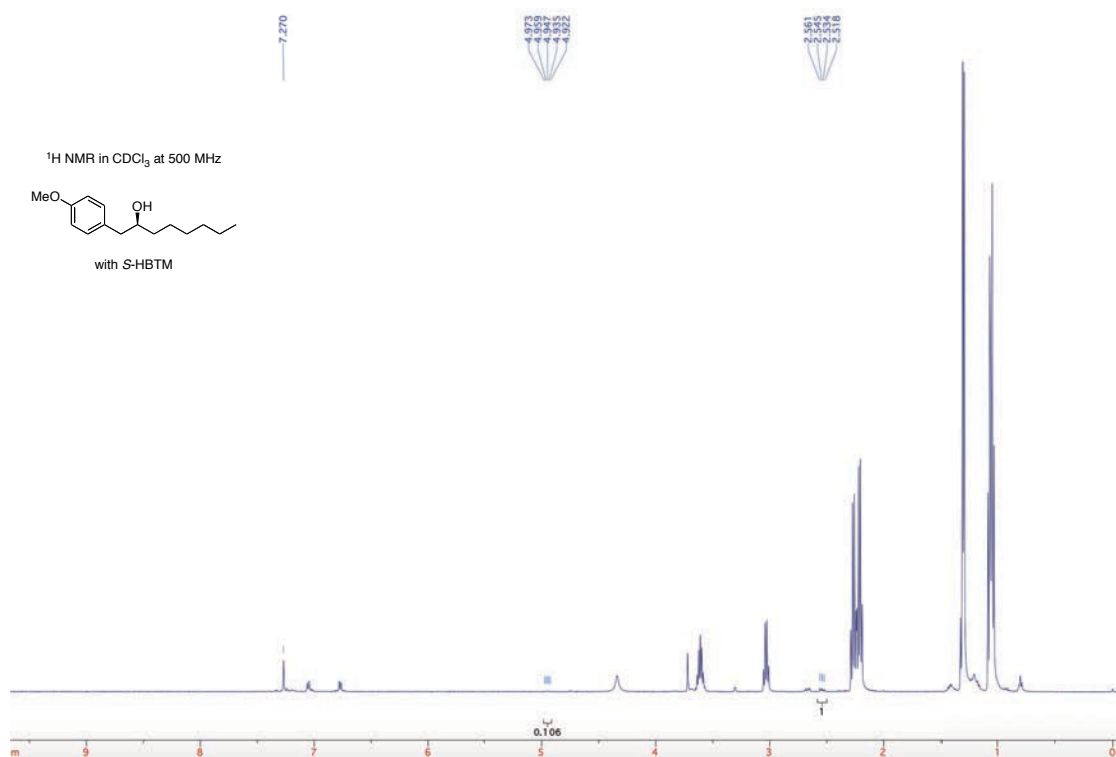
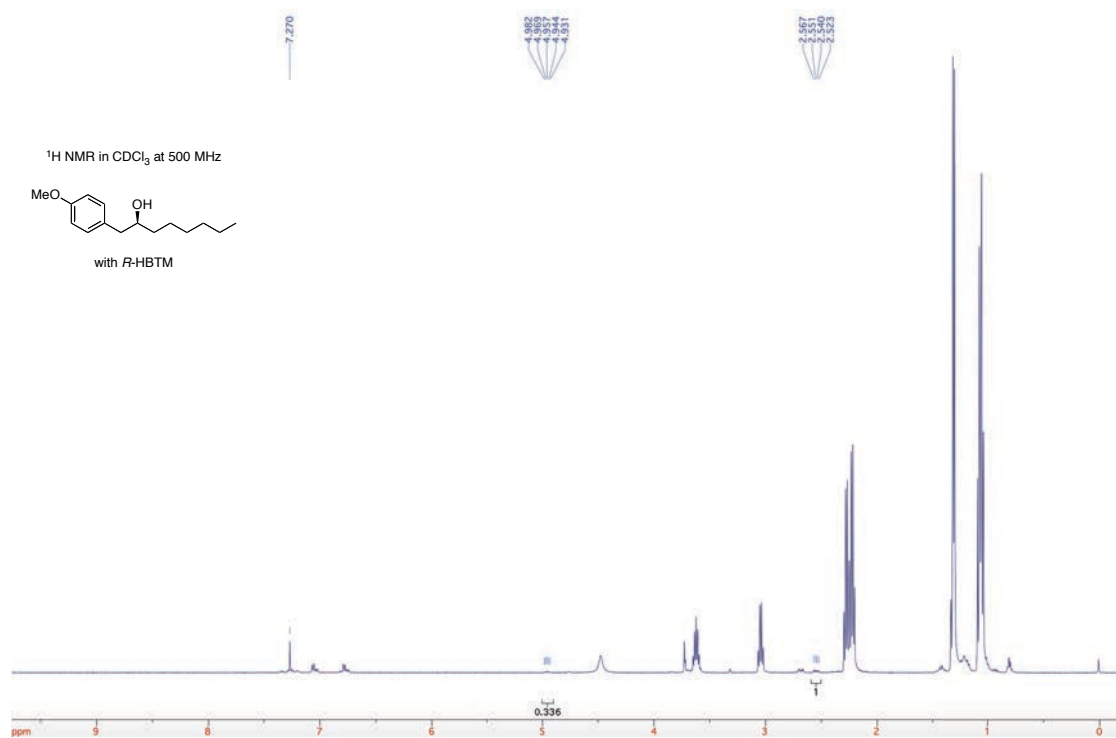
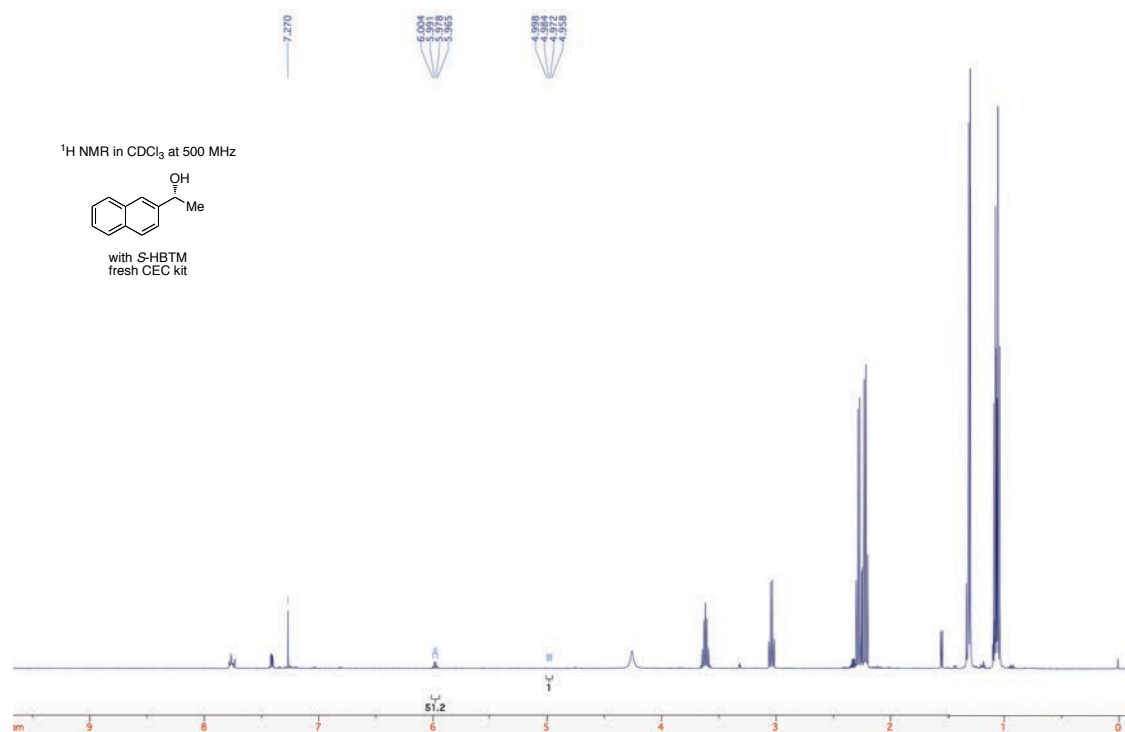
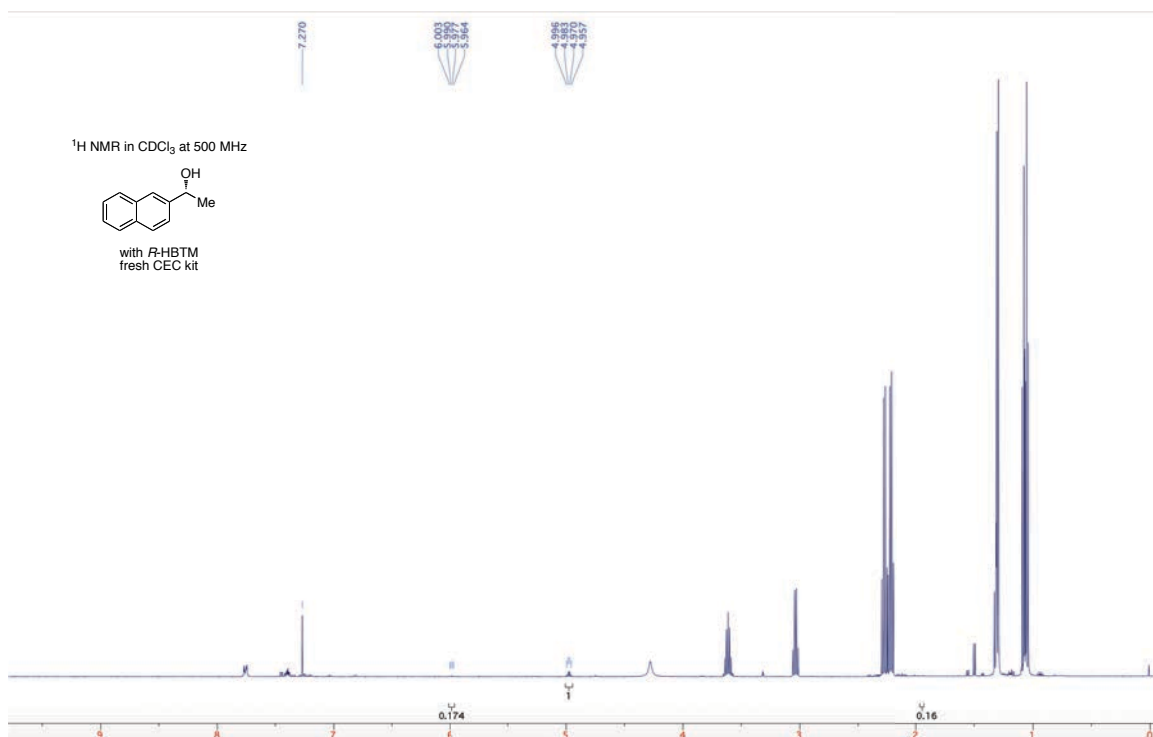


Table 7. Entry 12

¹H NMR Spectra for Figure 9**Figure 9. Plate 1**

¹H NMR in CDCl₃ at 500 MHz

CC(O)c1ccc2ccccc2c1

with *R*-HBTM
6 month old CEC kit

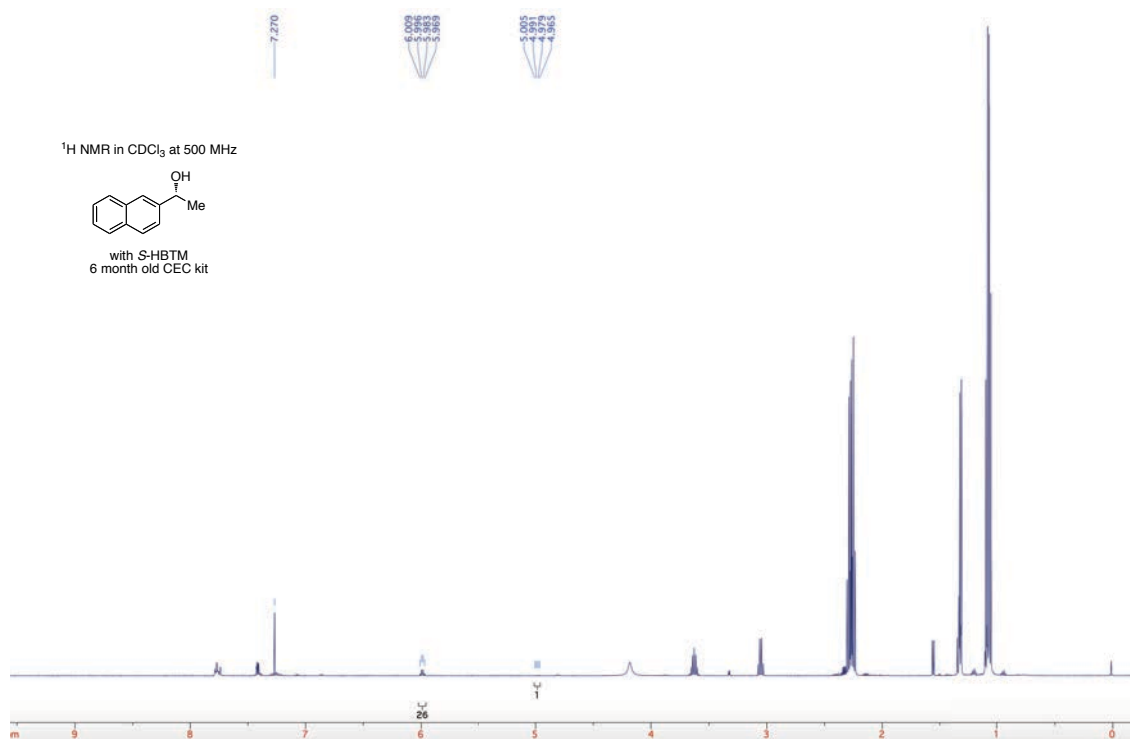
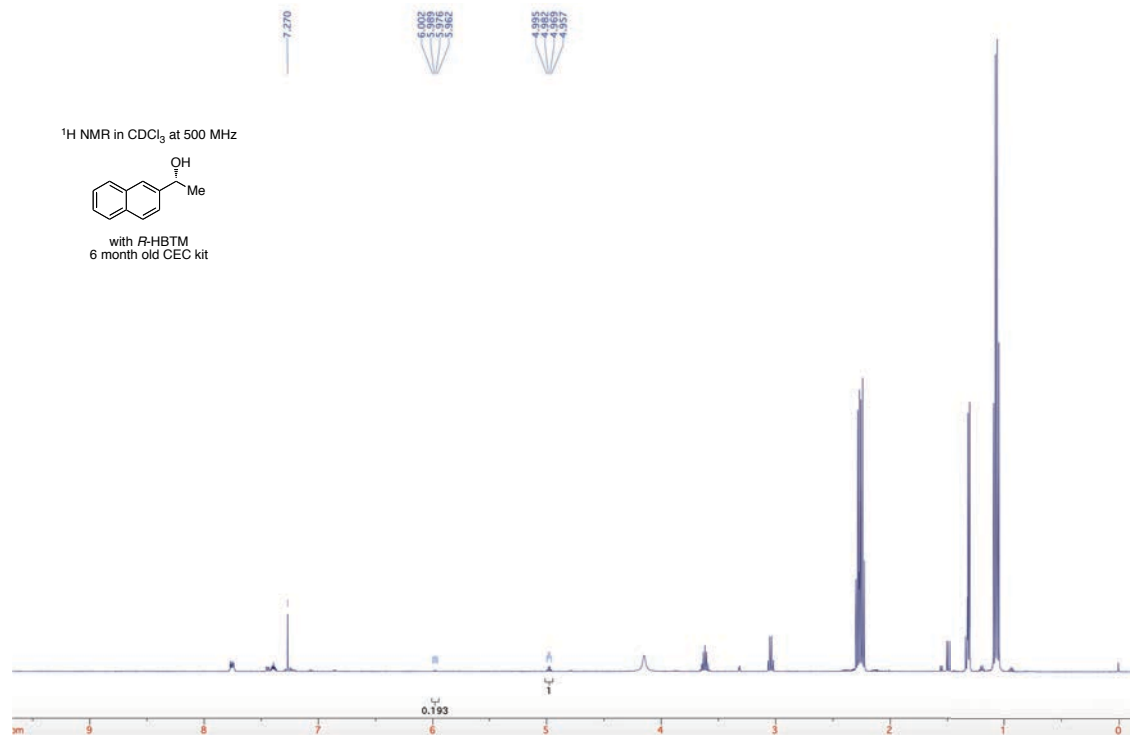
7.270
6.002
5.992
5.982
5.972
5.962
5.005
4.995
4.985
4.975
4.965
0.193
1

¹H NMR in CDCl₃ at 500 MHz

CC(O)c1ccc2ccccc2c1

with *S*-HBTM
6 month old CEC kit

7.270
6.002
5.992
5.982
5.972
5.962
5.005
4.995
4.985
4.975
4.965
0.193
1



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 μ L, 2.18 mmol) and *N,N*-diisopropylethylamine (75.9 μ L, 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 μ L, 2.18 mmol) and *N,N*-diisopropylethylamine (50.6 μ L, 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 μ L, 2.18 mmol) and *N,N*-diisopropylethylamine (25.3 μ L, 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 μ L syringe was used to draw up, in sequence, air (5 μ L), (**R**)-**5** stock solution (varied μ L), air (5 μ L), HBTM stock solution (varied μ L), air (5 μ L), propionic anhydride and *N,N*-diisopropylethylamine stock solution (varied μ L), and air (5 μ L). The contents of the syringe were then mixed in a 500 μ L 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. μ L). 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. μ L 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 μ L), and the *S*-HBTM reaction (4.0 μ L) via micropipette. The plate was run (30 % ethyl acetate in hexanes), dried, stained (PMA), heated by oven (160 $^{\circ}$ C, \sim 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 μ L 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 μ L measurement for each stock solution and displaces concern about a misguided conclusion based on minor differences in volume pulled from stock solutions.

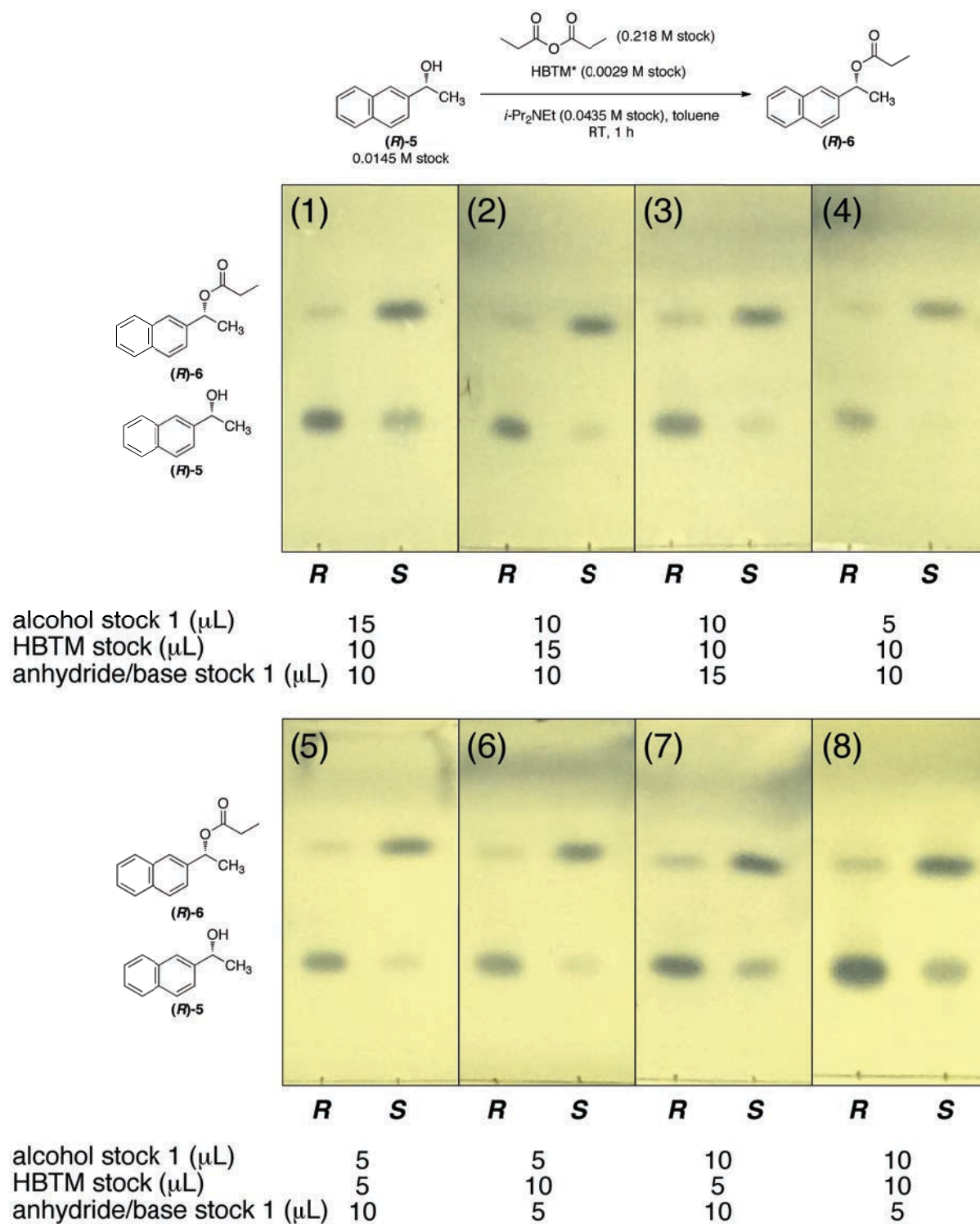


Figure SI.8. Variation of volume utilized from (*R*)-5 solution 1, HBTM solutions, and anhydride/base solution 1. The left lane of each TLC plate contains *R*-HBTM and the right lane contains *S*-HBTM. Plates were eluted in 30% ethyl acetate in hexanes. Visualization was achieved by staining with PMA 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.

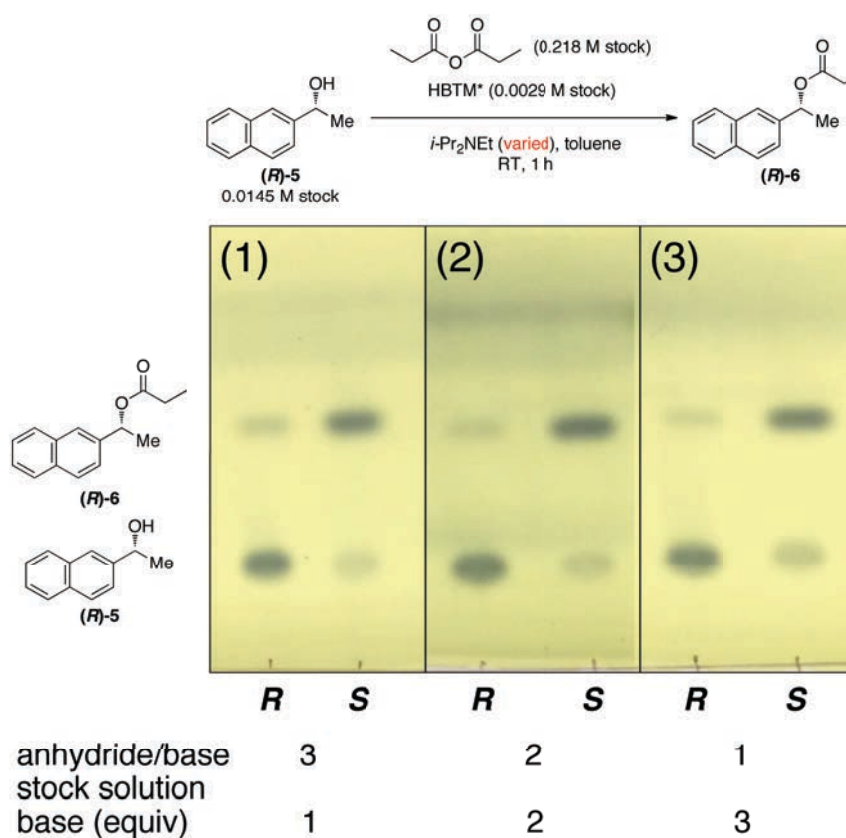


Figure SI.9. Variation of equivalents of base utilized from anhydride/base solutions 1, 2 and 3. The left lane of each TLC plate contains *R*-HBTM and the right lane contains *S*-HBTM. Plates were eluted in 30% ethyl acetate in hexanes. Visualization was achieved by staining with PMA stain.