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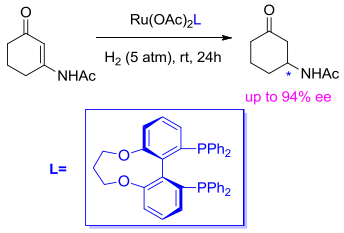

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Synthesis of chiral cyclic β-Amino ketones by Ru-catalyzed asymmetric hydrogenation

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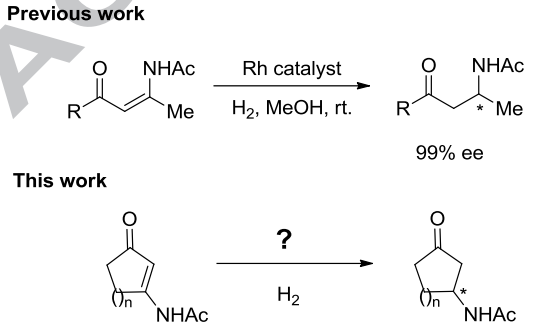
ABSTRACT

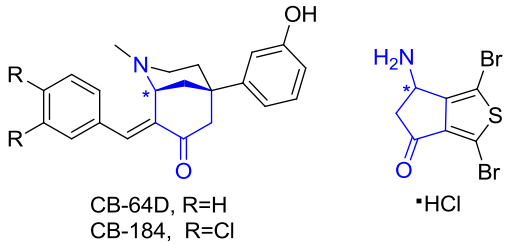
Synthesis of chiral cyclic β-Amino ketones has been first reported via Ru-catalyzed asymmetric hydrogenation. High enantioselectivities were achieved by using (*S*)-C_3-TunePhos chiral ligand (up to 94% ee).

Chiral amines and their derivatives are important synthetic targets and powerful pharmacophores for defining new pharmaceutical drugs.[1] Over the past few decades, enantioselective hydrogenation has proven to be an efficient method for chiral amine synthesis.[2] Our group has recently developed a Rh-catalyzed enantioselective hydrogenation of β-keto enamides as an efficient way to prepare optically pure β-amino ketones and their derivatives (Scheme 1).[3] We later envisioned that chiral cyclic β-Amino ketones are also interesting structural motifs. For example, these amino ketones can serve as key synthetic precursors for some antitumor agents (Scheme 2).[4,5] To the best of our knowledge, there is no report on synthesis of optically pure cyclic β-amino ketones through catalytic asymmetric hydrogenation.



Scheme 1.

Herein, we present a Ru-catalyzed highly enantioselective hydrogenation of cyclic β-keto enamides to afford chiral cyclic β -amino ketones.



Scheme 2. Examples of commercial available antitumor agents.

Preparation of cyclic β-keto enamide substrates were tried though the direct condensation of commercial available cyclic 1,3-diketones with acetamide.[6] However, all attempts afforded low yields (< 30%). Thus, a two-step procedure was applied. Cyclic 1,3 -diketones were first converted to the corresponding cyclic β-enaminones,[7] followed by acylation with acyl chloride to give the enamide substrates in moderate to good yields (up to 87%, scheme 3). We have to mention that aromatic cyclic 1,3-diketones such as 1,3-indanediones didn't give any desired products following this procedure, which dramatically narrowed the substrate scope.

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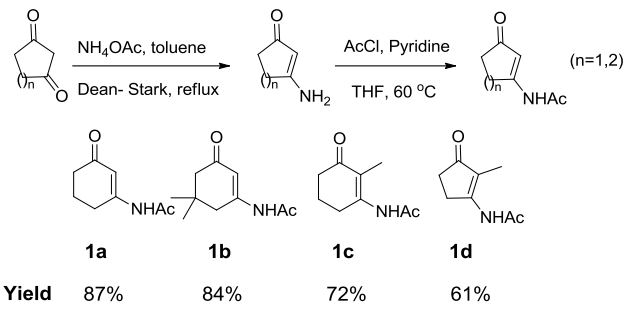
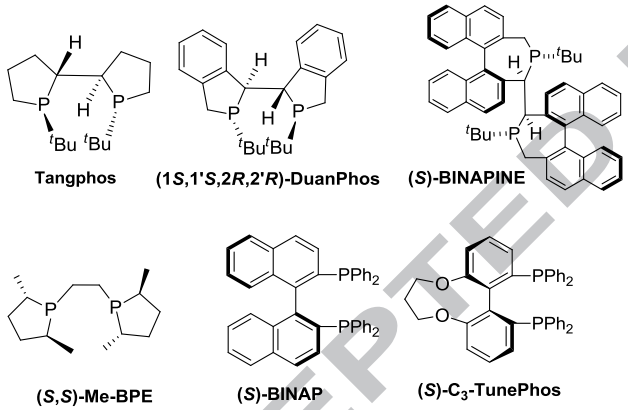


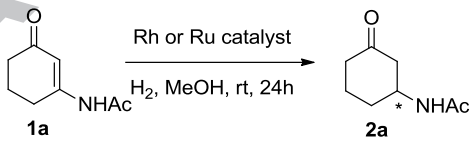
Scheme 3. Preparation of cyclic *β*-keto enamide substrates.

We began our study by investigating the asymmetric hydrogenation of **1a** as the model substrate. Rh/TangPhos and Rh/DuanPhos catalysts were initially tested since they have been previously proved efficient for enantioselective hydrogenation of acyclic *β*-ketoenamides.[3] However, neither of them gave satisfactory enantioselectivities under various reaction conditions (Table 1, entries 1-2). Other commercial available Rh complexes such as Rh/DuPhos and Rh/BINAPINE were also tested to give lower than 60% ee's (Table 1, entries 3-4). After catalyst screening, to our surprise, we found that commercial available $Ru(OAc)_2$/Binap catalyst gave the highest 92% ee. Later on, our results showed that $Ru(OAc)_2$/C_3-Tunephos give better enantioselectivities as well as good conversions (94% ee, Table 1, entries 6-7).



Picture 1. Selected structure of screened phosphine ligands.

Table 1. Selected results from initial screening of catalysts for hydrogenation of **1a**[a]

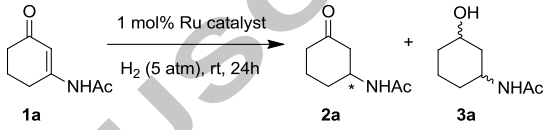


Entry	Catalyst	Conv[b] (%)	ee[c] (%)
1	TangPhos-Rh(cod)BF_4	90	61
2	DuanPhos-Rh(cod)BF_4	86	44
3	BINAPINE- Rh(cod)BF_4	68	35
4	Me-BPE-Rh(cod)BF_4	76	52
5	BINAP-$Ru(OAc)_2$	70	92
6	C_3-TunePhos- $Ru(OAc)_2$	53	94
7[d]	C_3-TunePhos- $Ru(OAc)_2$	86	94

[a] Unless otherwise mentioned, reaction conditions: Catalyst/substrate =1:100, at room temperature, under 1 atm of hydrogen for 24 h.
[b] Conversions were determined by ^{1}H NMR of the crude product.
[c] Determined by GC on a chiral phase.
[d] Under 5 atm of hydrogen.

Thus, different Ru precursors were systematically investigated. [8] As showed in Table 2, $Ru(OAc)_2$/C_3-TunePhos complex still gave the highest enantioselectivities (Table 2, entries 1-4). Further solvent screening indicated that MeOH served as the best solvent (Table 2, entries 5-11). Increasing the hydrogen pressure or catalyst loading would cause more formation of the corresponding amino-alcohol **3a** as side product.

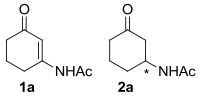
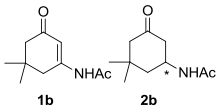
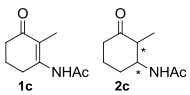
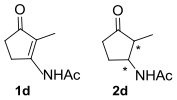
Table 2. Selected results from initial screening of Ru-catalysts for hydrogenation of **1a**[a]



Entry	{Ru}	Solvent	Yield of **2a** (%)[b]	ee of **2a** (%)[c]
1	$[NH_2Me_2][\{RuCl(L)\}_2(\mu\text{-}Cl)_3]$	MeOH	22	42
2	[RuCl(*p*-pymene)L]Cl	MeOH	36	51
3	[RuCl(benzene)L]Cl	MeOH	31	55
4	$RuCl_2L(DMF)_n$	MeOH	<5	n.d.
5	$Ru(OAc)_2L$	THF	31	82
6	$Ru(OAc)_2L$	1,4-dioxane	34	83
7	$Ru(OAc)_2L$	toluene	29	42
8	$Ru(OAc)_2L$	ethyl acetate	47	75
9	$Ru(OAc)_2L$	EtOH	69	91
10	$Ru(OAc)_2L$	^{i}PrOH	63	85
11	$Ru(OAc)_2L$	**MeOH**	**73**	**94**

[a] Unless otherwise mentioned, reaction conditions: Catalyst/substrate =1:100, at room temperature, under 5 atm of hydrogen for 24 h. L= (*S*)-C_3-TunePhos. Ru complexes were prepared according to reported procedure. [8]
[b] Conversions were determined by ^{1}H NMR of the crude product.
[c] Determined by GC on a chiral phase.

Table 3. Substrate scope and limitations[a]

Entry	Substrate	Product	Yield[b]	ee[c]
1			73	94
2			68	88
3			36	67
4			45	61

[a] Unless otherwise mentioned, reaction conditions: $Ru(OAc)_2/C_3$-TunePhos as catalyst, Catalyst/substrate =1:100, Methanol as solvent, at room temperature, under 5 atm of hydrogen for 24 h.

[b] Conversions were determined by ^1H NMR of the crude product.

[c] Determined by GC on a chiral phase.

With the optimized reaction conditions, 5,5-dimethyl substituted substrate **1b** was tested to give moderate hydrogenation results (Table 3, entry 2). However, hydrogenation of tetra-substituted olefin substrates **1c** showed dramatic loss of reactivities and enantioselectivities (Table 3, entry 3). Low reactivity and enantioselectivity were also observed when cyclopentyl substrate **1d** was tested (Table 3, entry 4).

In conclusion, we reported a Ru-catalyzed asymmetric hydrogenation of cyclic *β*-keto enamides to afford chiral cyclic *β*-amino ketones, which afforded a new approach for the synthesis of optically pure cyclic *β*-amino ketones. Further studies focusing on expanding the substrate scope and improving the reactivities and enantioselectivities are ongoing.

Experimental section

General Procedure for Asymmetric Hydrogenation

In a glovebox filled with nitrogen, Ru catalyst (0.02 mmol) was dissolved in MeOH (5 mL). 0.5 mL of this solution (0.002 mmol) was added into a solution of 0.2 mmmol substrate in 3 mL of degassed MeOH. The resulting solution was then transferred into an autoclave and charged with 5 atm of hydrogen. The hydrogenation was performed at room temperature for 24 h. After carefully releasing the hydrogen, the reaction mixture was passed through a short silica gel column to remove the catalyst. The ee values of all compounds were determined by GC on a chiral stationary phase.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version

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Support information

Synthesis of chiral cyclic β-amino ketones by Ru-catalyzed asymmetric hydrogenation

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General Methods. Starting materials, reagents and solvents were purchased from commercial sources and were used as received**.** All reactions and manipulations that were

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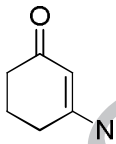
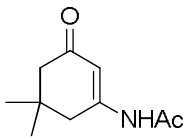
sensitive to moisture or air were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise noted. Solvents were dried with standard procedures and degassed with N_2. Column chromatography was performed using 200-400 mesh silica gel supplied by Natland International Corp. Thin-layer chromatography (TLC) was performed on EM reagents 0.25 mm silica 60-F plates. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 MHz spectrometers and a Varian VNMRS-500 MHz instrument. GC analysis was carried out on Hewlett-Packard 7890 gas chromatography using chiral capillary columns.

General Procedure for substrate synthesis

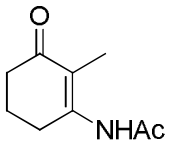
10 mmol cyclic 1,3-diketone was added to a mixture of 10 mmol ammonium acetate in dry toluene (20 mL). The mixture was heated for 3 h under reflux using a Dean–Stark water separator. The resulting oily product was separated and recrystallized with ethyl acetate to give the corresponding enaminone as crystals. The enaminone product was dissolved in 50ml THF and 2 equiv. of pyridine were added. To the mixed solution, acetyl chloride (2 equiv.) in 5ml THF was added dropwise at 0 °C. The reaction mixture was warmed up to ambient temperature and stirred additional 5 h at 60°C. The solvent was removed under vacuum and the crude product purified by flash chromatography.



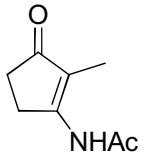
***N*-(3-oxocyclohex-1-en-1-yl)acetamide (1a)** ^{1}H NMR (400 MHz, CDCl3) δ 7.61 (1H, br), 6.49 (1H, s), 2.51 (2H, t, *J* = 6.0), 2.30 (2H, t, *J* = 6.3), 2.07 (3H, s), 1.96 (2H, q, *J* = 6.4); ^{13}C NMR (100 MHz, CDCl3) δ 21.4, 24.7, 28.2, 36.6, 111.2, 158.9, 170.1, 201.1



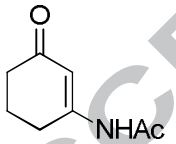
***N*-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)acetamide (1b)** ^{1}H NMR (400 MHz, CDCl3) δ 8.67 (1H, br), 6.74 (1H, s), 2.51 (2H, t, *J* = 6.0), 2.37 (2H, s), 2.19 (2H, s), 2.11 (3H, s), 1.05 (6H, s); ^{13}C NMR (100 MHz, CDCl3) δ 24.7, 28.1, 32.7, 42.1, 50.5, 110.1, 154.7, 170.1, 201.0



***N*-(2-methyl-3-oxocyclohex-1-en-1-yl)acetamide (1c)** ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.24 (1H, br), 2.77 (2H, t, *J* = 6.0), 2.33 (2H, t, *J* = 6.2), 2.10 (3H, s), 1.88 (2H, q, *J* = 6.4), 1.67 (3H, s); ^{13}C NMR (100 MHz, CDCl3) δ 7.95, 23.72, 23.75, 26.9, 36.04, 117.1, 152.0, 167.9, 197.8



***N*-(2-methyl-3-oxocyclopent-1-en-1-yl)acetamide (1d)** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (1H, br), 3.13 (2H, t, *J* = 2.4), 2.34 (2H, t, *J* = 2.5), 2.16 (3H, s), 1.59 (3H, s); ^{13}C NMR (100 MHz, CDCl3) δ 6.69, 24.5, 27.7, 33.6, 118.3, 165.1, 168.9, 206.7



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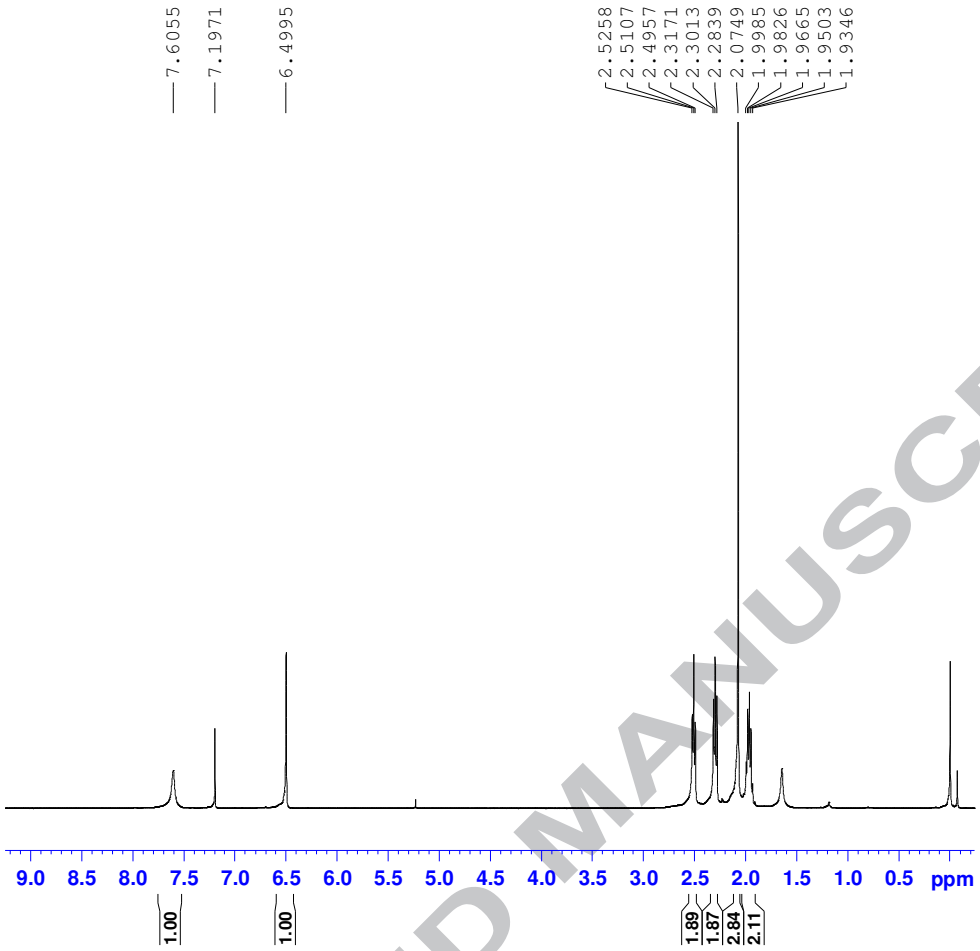

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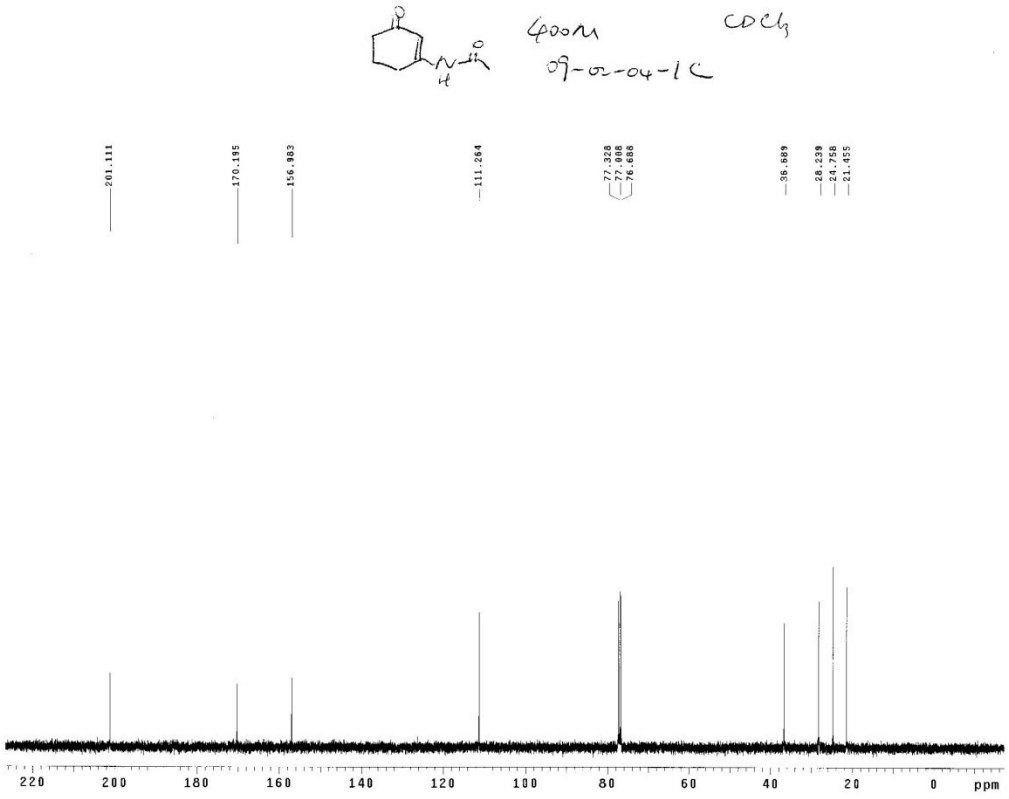

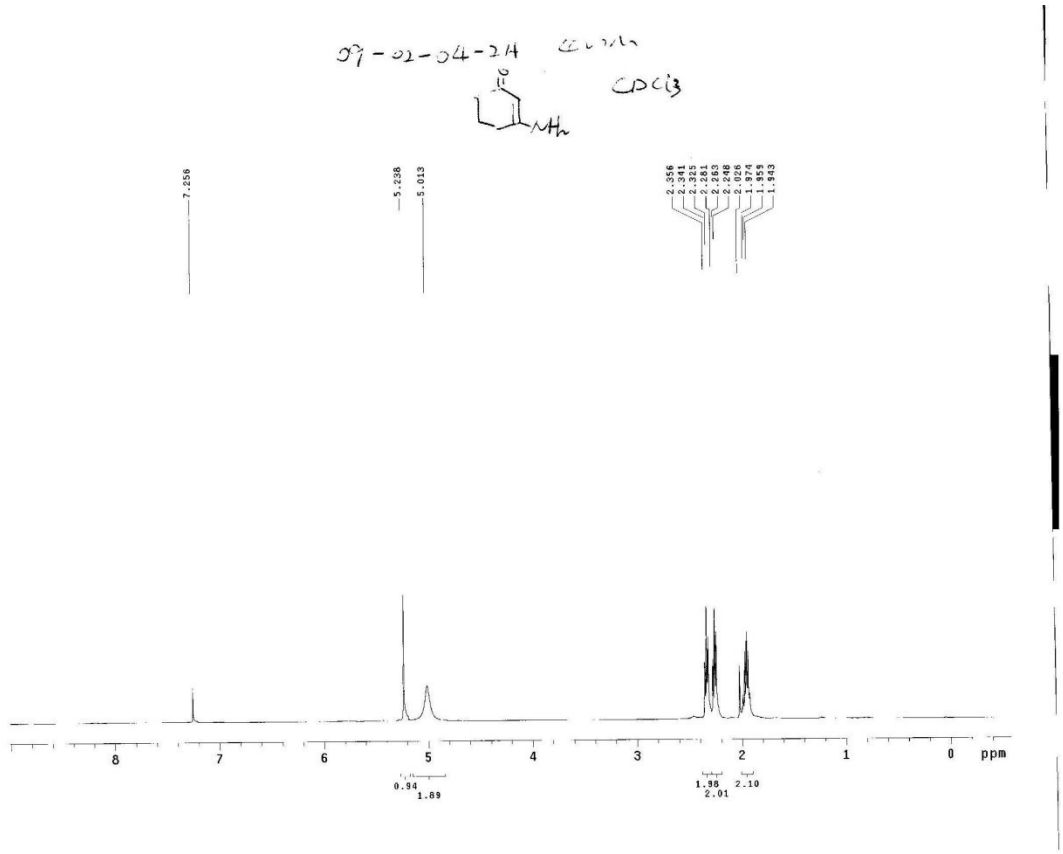

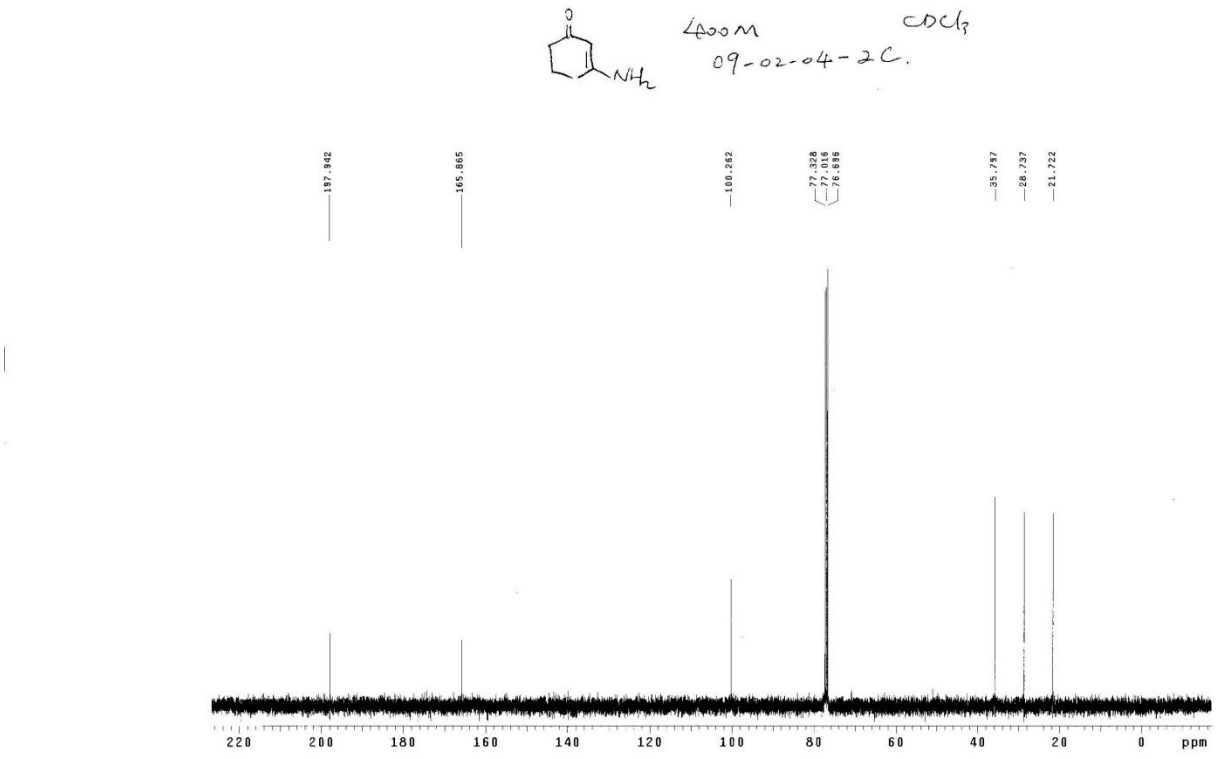

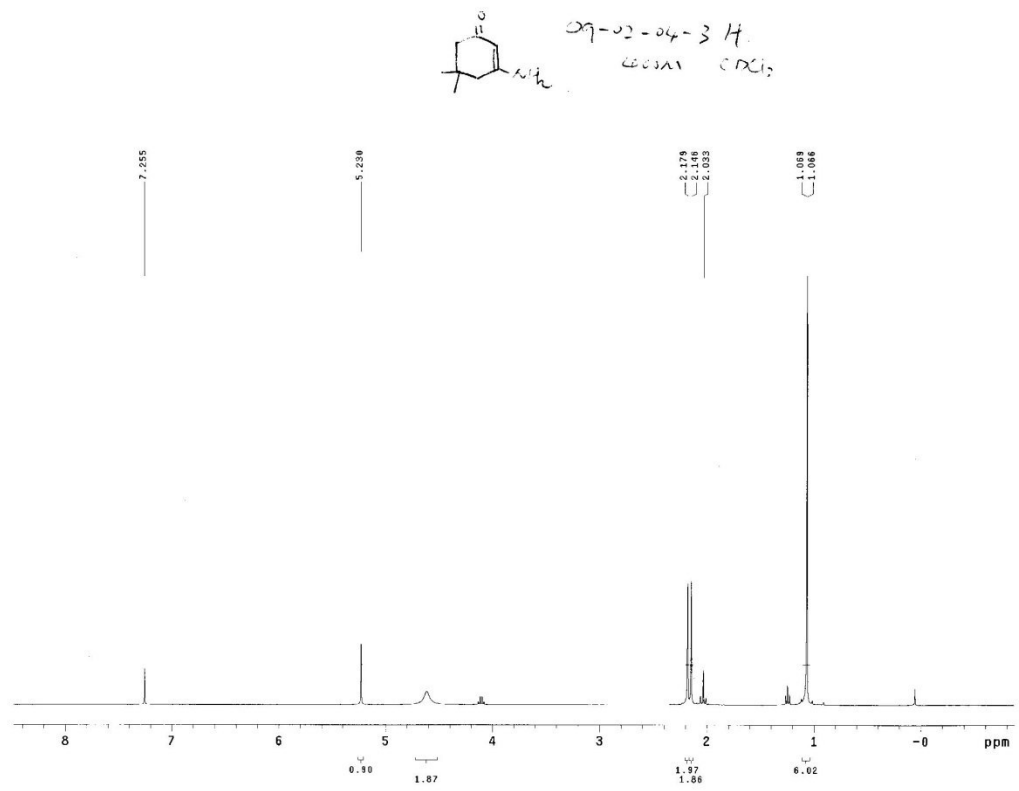

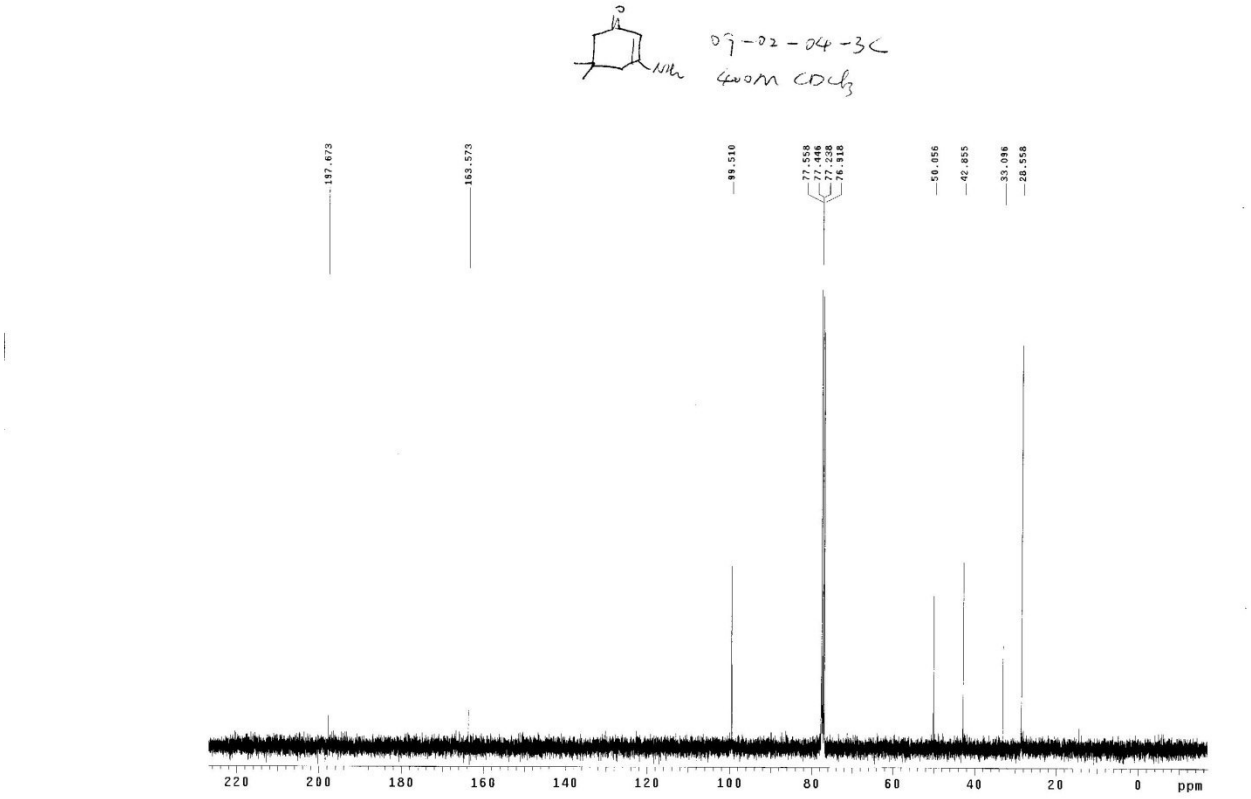
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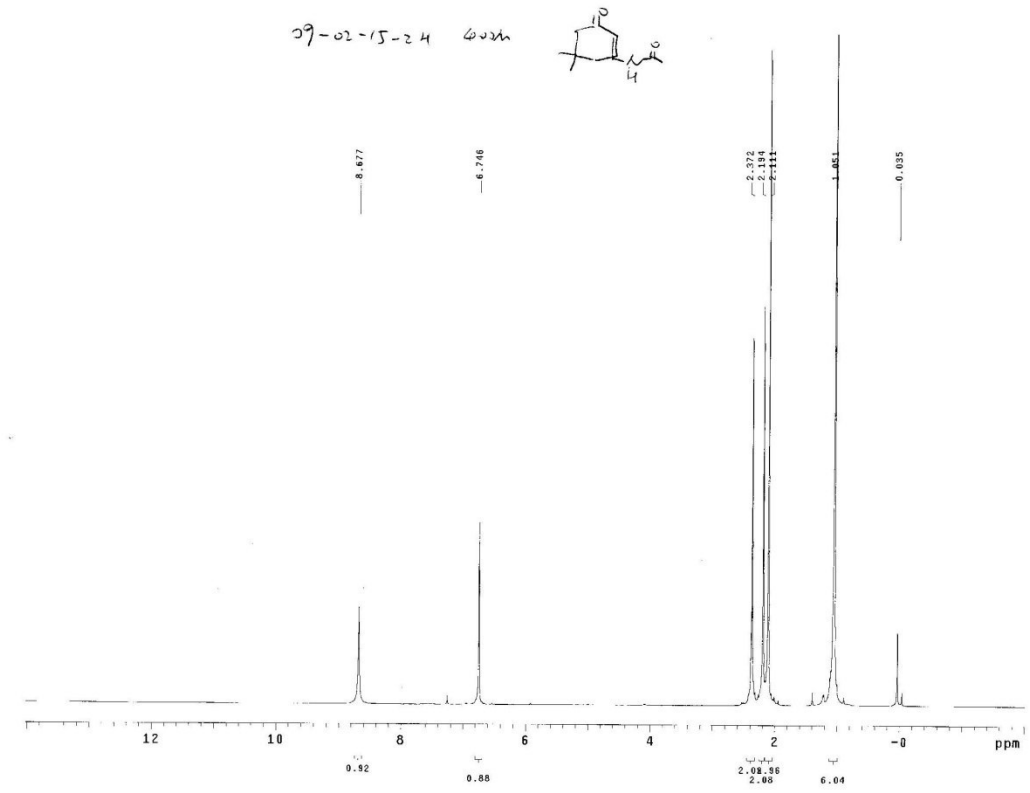
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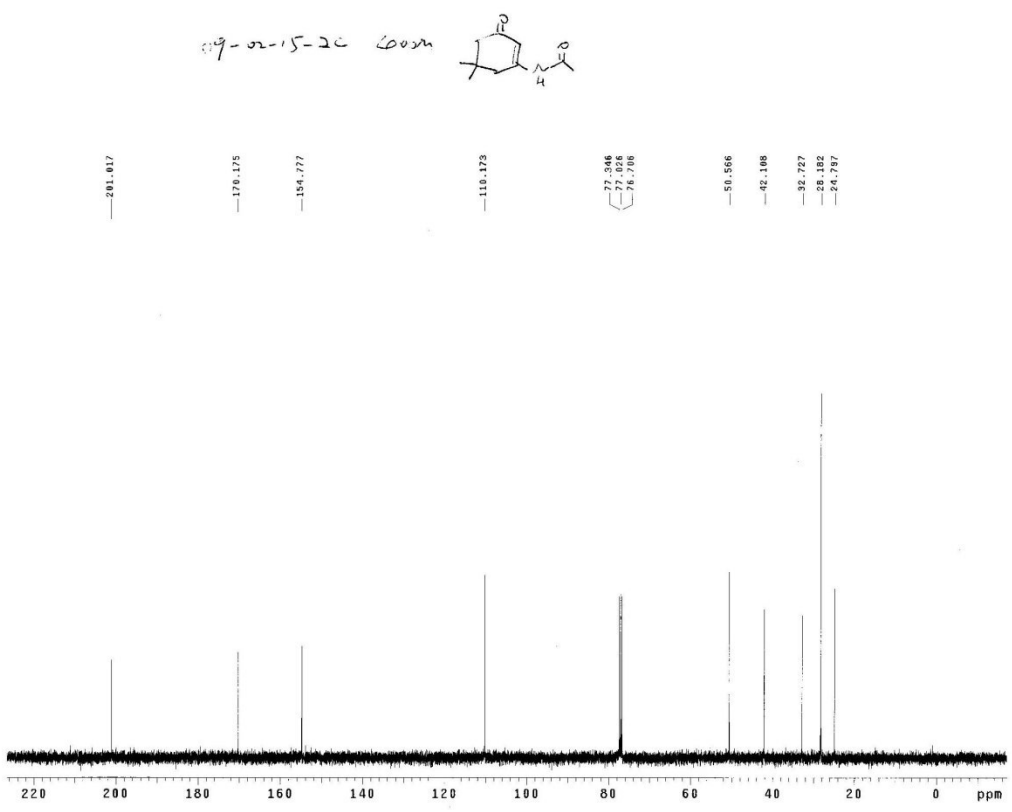
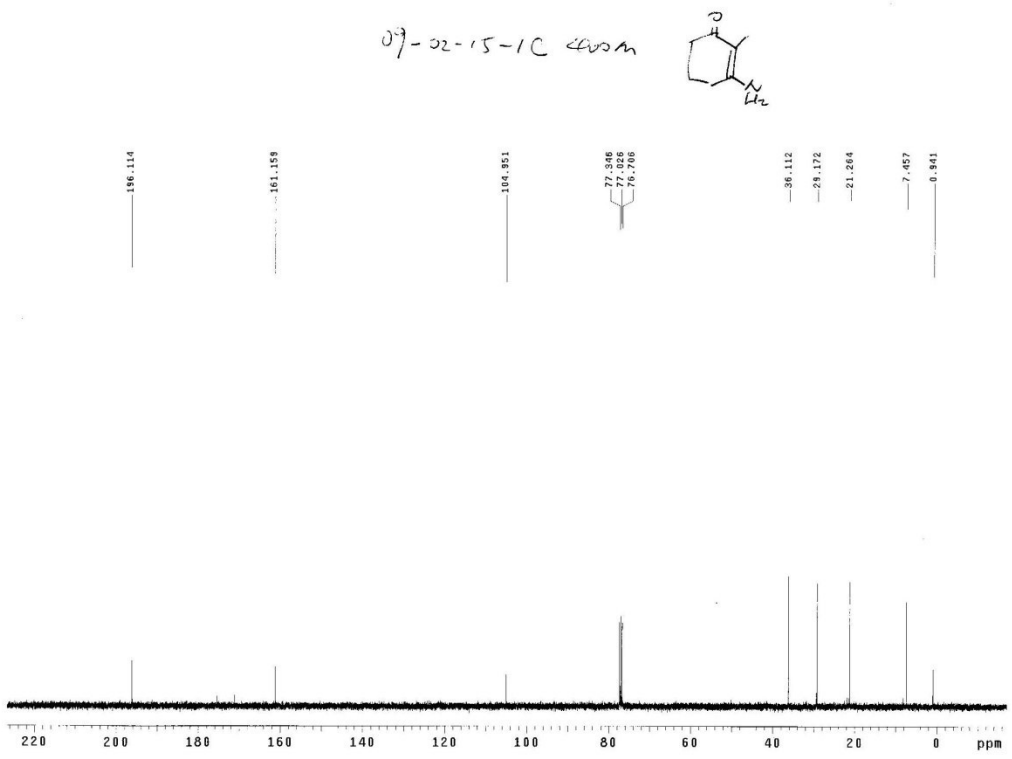
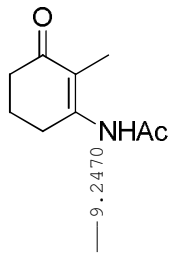
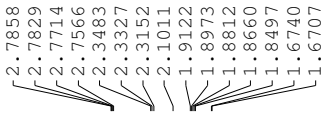
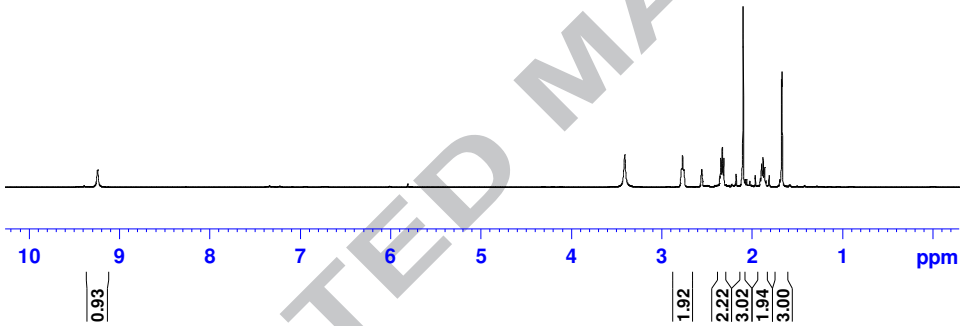
2.08
6.04



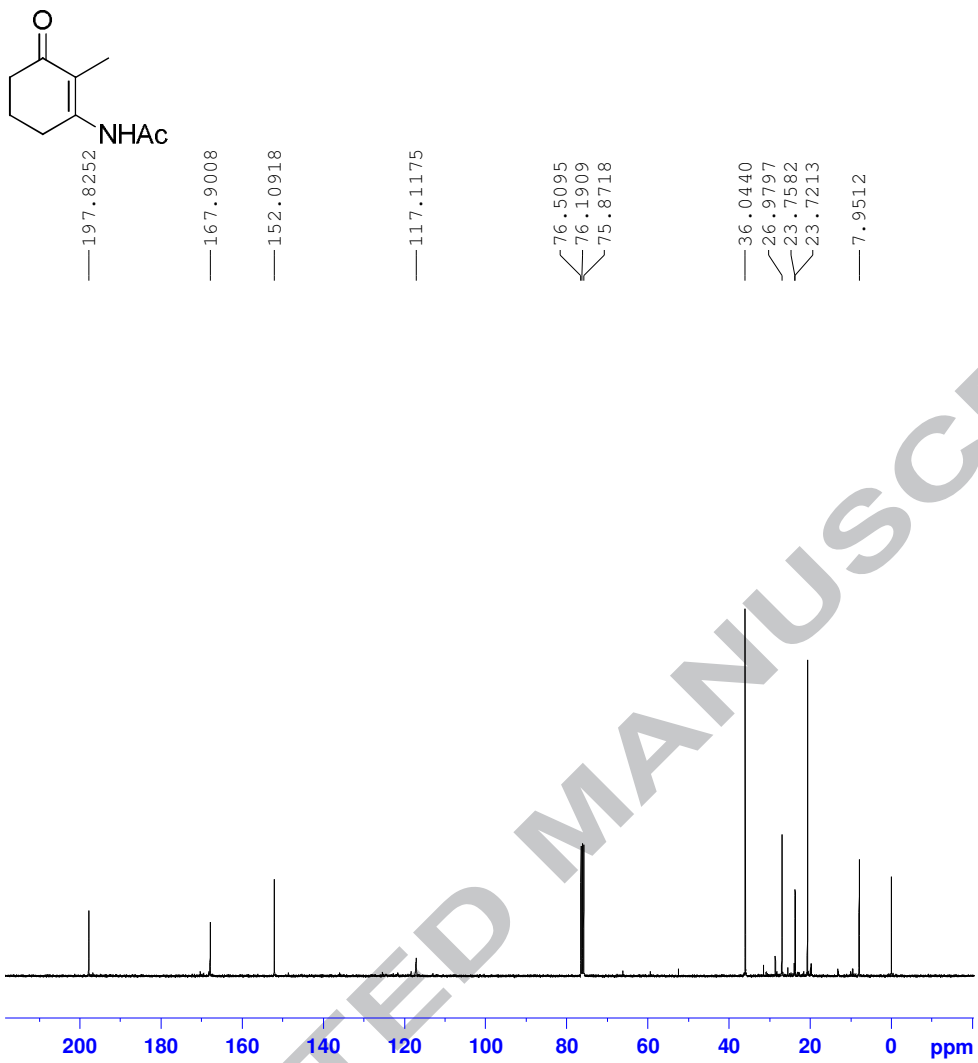




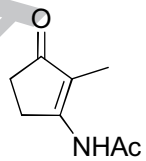


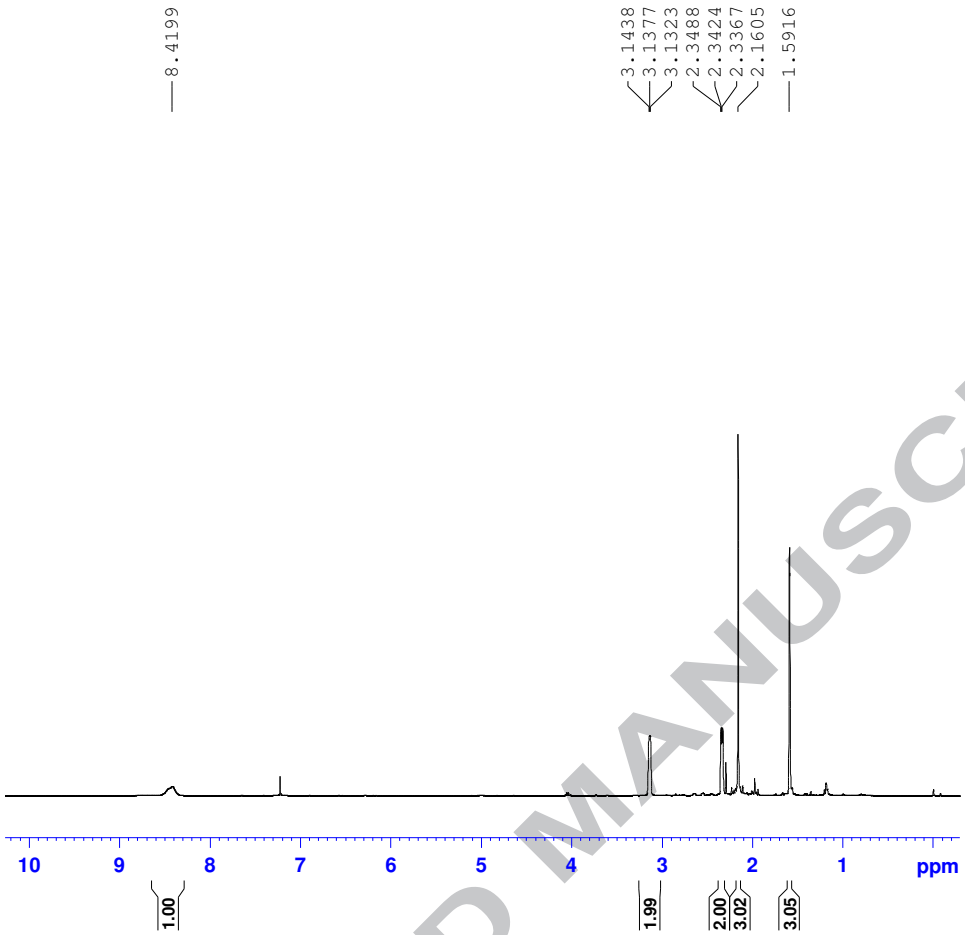



```
NAME          Feb17-2009-kh
EXPNO                    1
PROCNO                   1
Date_             20090217
Time                 12.55
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT               DMSO
NS                      16
DS                       2
SWH               8223.685 Hz
FIDRES            0.125483 Hz
AQ                3.9846387 sec
RG                     161
DW                  60.800 usec
DE                   6.50 usec
TE                  297.3 K
D1             1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   8.76 usec
PL1                 -2.00 dB
PL1W          31.17179108 W
SFO1          400.1324710 MHz
SI                   32768
SF            400.1299794 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



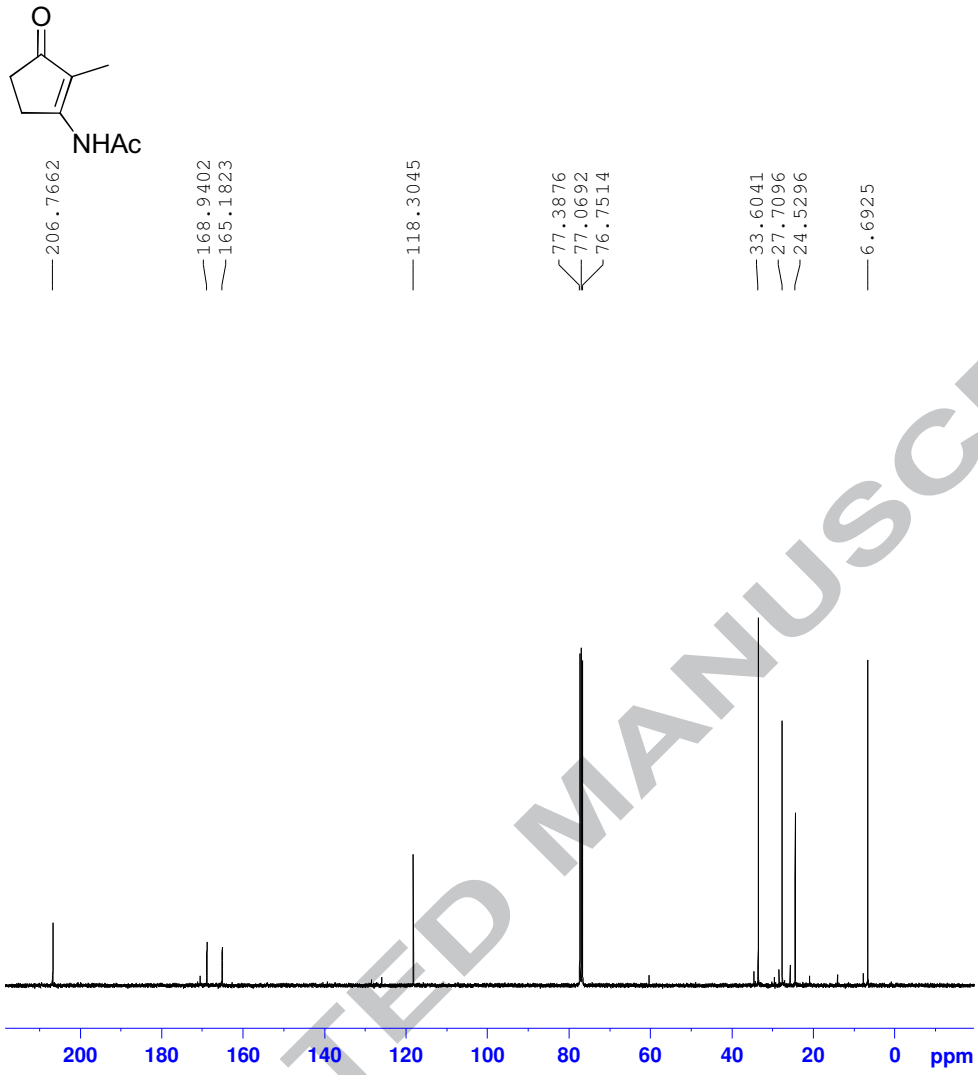

```
NAME          Feb19-2009-kh
EXPNO                    1
PROCNO                   1
Date_             20090220
Time                 1.37
INSTRUM             spect
PROBHD  5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    1024
DS                       4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631988 sec
RG                    2050
DW                  20.800 usec
DE                   6.50 usec
TE                  300.2 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    8.50 usec
PL1                   1.00 dB
PL1W          75.02186584 W
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2                90.00 usec
PL2                  -2.00 dB
PL12                 18.23 dB
PL13                 19.00 dB
PL2W          31.17179108 W
PL12W          0.29563907 W
PL13W          0.24760634 W
SFO2          400.1316005 MHz
SI                   32768
SF            100.6128640 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```





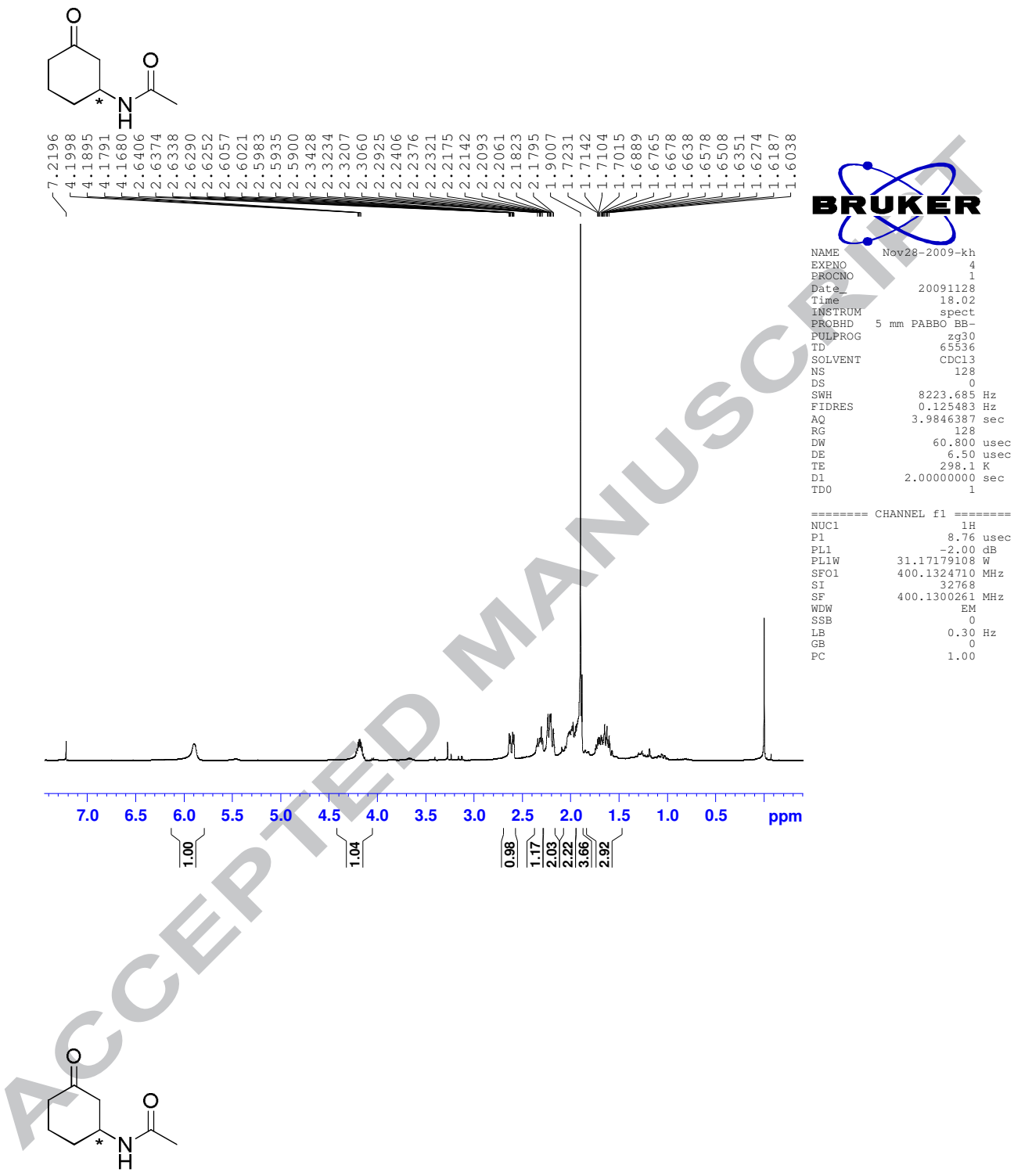
BRUKER

NAME	Feb26-2009-kh	
EXPNO	2	
PROCNO	1	
Date_	20090226	
Time	12.56	
INSTRUM	spect	
PROBHD	5 mm PABBO BB-	
PULPROG	zg30	
TD	65536	
SOLVENT	CDCl3	
NS	16	
DS	2	
SWH	8223.685	Hz
FIDRES	0.125483	Hz
AQ	3.9846387	sec
RG	71.8	
DW	60.800	usec
DE	6.50	usec
TE	297.4	K
D1	1.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	8.76	usec
PL1	-2.00	dB
PL1W	31.17179108	W
SFO1	400.1324710	MHz
SI	32768	
SF	400.1300235	MHz
WDW	EM	
SSB	0	
LB	0.30	Hz
GB	0	
PC	1.00	



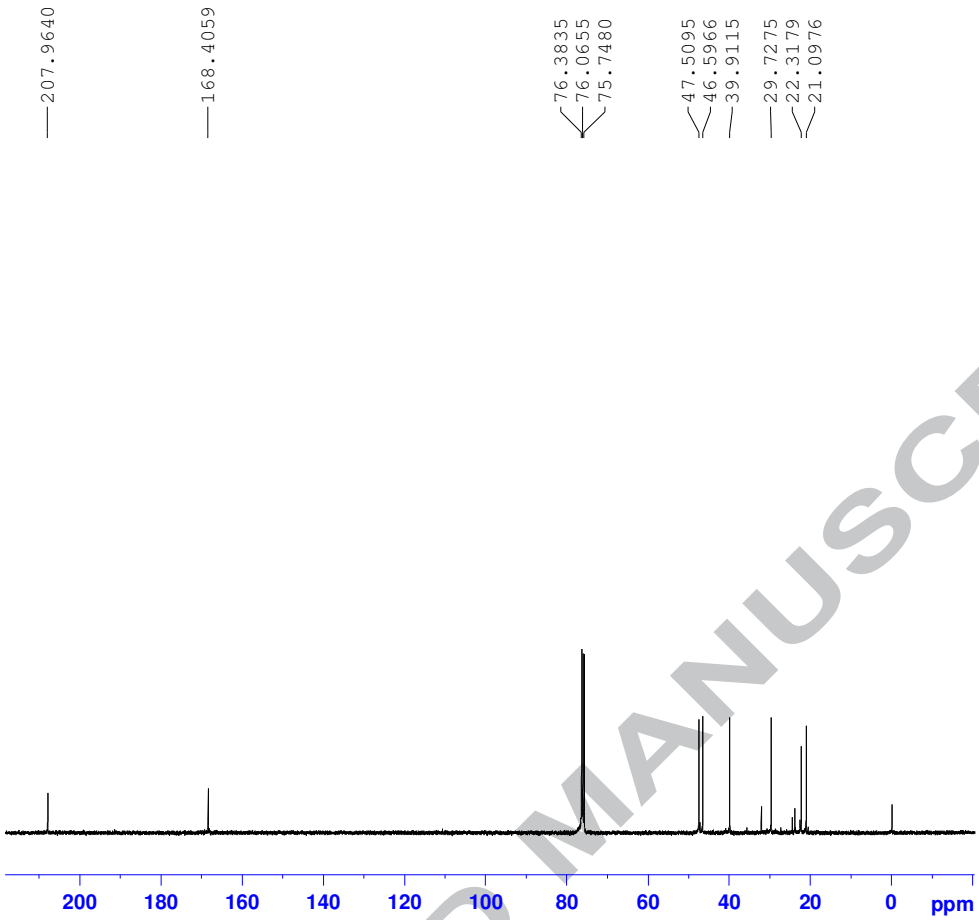
BRUKER

```
NAME          Feb26-2009-kh
EXPNO                    3
PROCNO                   1
Date_             20090226
Time                 23.20
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT              CDC13
NS                    1024
DS                       4
SWH              24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631988 sec
RG                    2050
DW                 20.800 usec
DE                  6.50 usec
TE                 300.3 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                   8.50 usec
PL1                  1.00 dB
PL1W          75.02186584 W
SFO1         100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2               90.00 usec
PL2                 -2.00 dB
PL12                18.23 dB
PL13                19.00 dB
PL2W          31.17179108 W
PL12W          0.29563907 W
PL13W          0.24760634 W
SFO2         400.1316005 MHz
SI                  32768
SF           100.6127690 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```



BRUKER

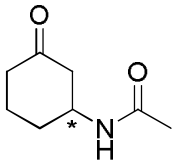
NAME	Nov28-2009-kh
EXPNO	4
PROCNO	1
Date_	20091128
Time	18.02
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	128
DS	0
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 sec
RG	128
DW	60.800 usec
DE	6.50 usec
TE	298.1 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	8.76 usec
PL1	-2.00 dB
PL1W	31.17179108 W
SFO1	400.1324710 MHz
SI	32768
SF	400.1300261 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



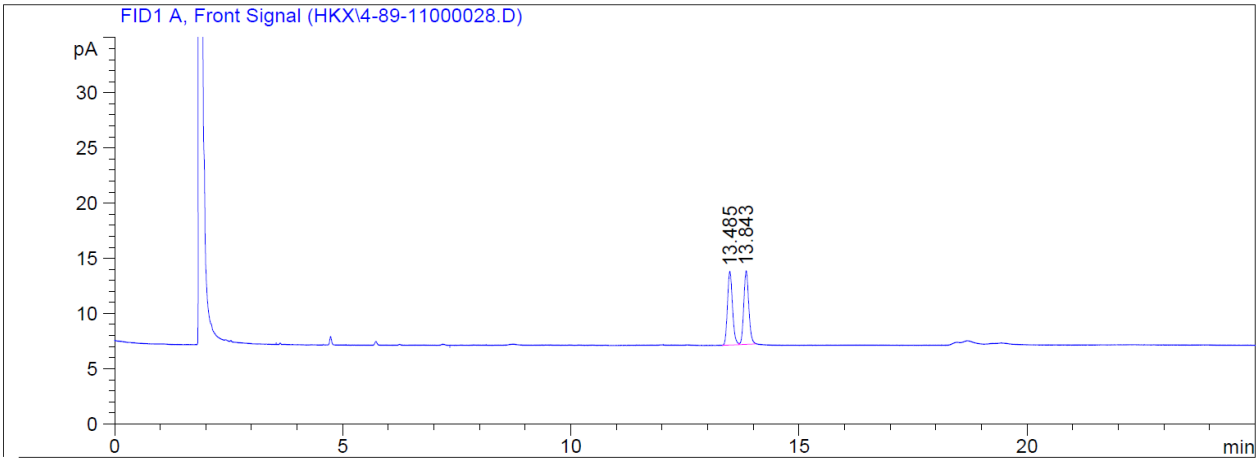

```
NAME          Nov28-2009-kh
EXPNO                    1
PROCNO                   1
Date_             20091128
Time                 16.18
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1024
DS                     4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ             1.3631988 sec
RG                  2050
DW               20.800 usec
DE                6.50 usec
TE                299.7 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 13C
P1                 8.50 usec
PL1                1.00 dB
PL1W         75.02186584 W
SFO1        100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             90.00 usec
PL2               -2.00 dB
PL12              18.23 dB
PL13              19.00 dB
PL2W         31.17179108 W
PL12W         0.29563907 W
PL13W         0.24760634 W
SFO2        400.1316005 MHz
SI                32768
SF          100.6128688 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

General Procedure for Asymmetric Hydrogenation

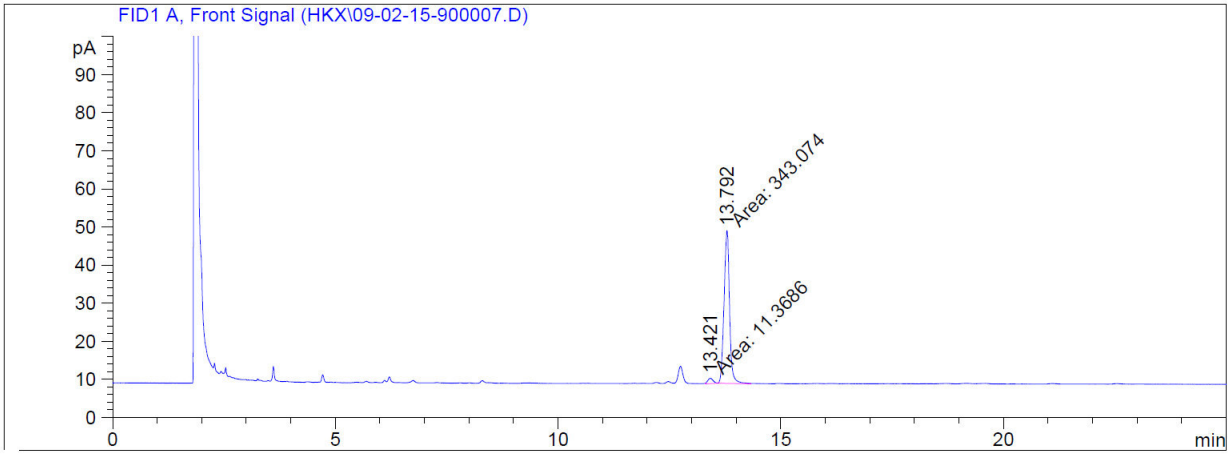
In a glovebox filled with nitrogen, Ru catalyst (0.02 mmol) was dissolved in MeOH (5 mL). 0.5 mL of this solution (0.002 mmol) was added into a solution of 0.2 mmmol substrate in 3 mL of degassed MeOH. The resulting solution was then transferred into an autoclave and charged with 5 atm of hydrogen. The hydrogenation was performed at room temperature for 24 h. After carefully releasing the hydrogen, the reaction mixture was passed through a short silica gel column to remove the catalyst. The ee values of all compounds were determined by GC on Supelco beta Dex^{TM} 390 column.



Supelco beta Dex^{TM} 390 column (30 m ×0.25 mm × 0.25 μm), He 1.0 mL/min, column temperature: 180 ^{o}C; t_R = 13.4 min (minor), t_R = 13.7 min (major). (2a)




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A, Front Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  13.485 BB    0.1178   50.71112    6.64493 50.12302
   2  13.843 BB    0.1173   50.46220    6.65246 49.87698

Totals :                   101.17332   13.29738
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A, Front Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  13.421 MM    0.1365   11.36856    1.38859  3.20744
   2  13.792 MM    0.1430  343.07437   39.98597 96.79256

Totals :                   354.44293   41.37456
```