

3-Trifluoromethanesulfonamido-pyrrolidine: A General Organocatalyst for *anti*-Selective Mannich Reactions.

Mickael Pouliquen, Jérôme Blanchet,* Marie-Claire Lasne, Jacques Rouden

Laboratoire de Chimie Moléculaire et Thio-organique, ENSICAEN, Université de Caen Basse-Normandie, CNRS ; 6 boulevard du Maréchal Juin, 14050 Caen, France

jerome.blanchet@ensicaen.fr

Supporting Information

Contents

General remarks	S2
Procedures for the preparation of 5a-d	S2
Procedures for the preparation of 6a-d	S4
General procedure for the catalytic enantioselective Mannich reactions	S6
Copies of HPLC profiles of new Mannich products	S14
Copies of ¹ H NMR and ¹³ C NMR of new Mannich products	S21
Copies of ¹ H NMR and ¹³ C NMR of precursors 5a-d and catalysts 6a-d	S24

General remarks

Commercially available compounds were used without further purification. Solvents (THF, CH₂Cl₂, MeCN, Et₂O, DMF, toluene) were dried and purified from Pure-SolvTM 400 Solvent Purification System. All aldehydes were distilled from MgSO₄ prior to use. 2-(4-Methoxyphenylimino)-acetic acid ethylester **1** was prepared according to a described procedure.¹

Melting points were determined on a K ofler bench apparatus and are uncorrected.

¹H NMR, ¹³C NMR and ¹⁹F NMR spectra were recorded on a Bruker Avance DPX 250 or Bruker Avance DPX 400 spectrometers. Chemical shifts are reported in parts per million (δ) relative to TMS or to solvent as the internal standard.

Thin layer chromatography was performed on silica gel 60 F-254 plates (0.1 mm, Merck). Detection was accomplished by irradiation with a UV lamp or staining with KMnO₄ or ninhydrin solutions. Chromatographic separations were achieved on silica gel columns (Kieselgel 60, 40–63 μ m, Merck).

Analytical high performance liquid chromatography (HPLC) was carried out with a Waters instrument [detector M996 (200–400 nm) and pump 600]. The conditions are precised for each compound.

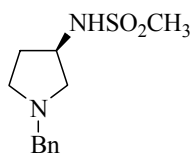
Mass spectra and high resolution mass spectra (HRMS) were obtained on a Waters-Micromass Q-ToF micro instrument. IR spectra were recorded on a Perkin–Elmer 16 PC FTIR spectrometer. Optical rotations were measured, at room temperature, on a Perkin–Elmer 241 LC polarimeter in a 10 cm cell. [α]_D Values are given in units of 10⁻¹ deg cm².g⁻¹.

General procedure for the synthesis of 5a-5d:

To a solution of (*R*)-1-benzyl-3-aminopyrrolidine **4** (338 mg, 2.0 mmol) in dry CH₂Cl₂ (5 mL) was added successively at –78 °C, NEt₃ (310 μ L, 2.2 mmol, 1.1 equiv.) and a solution of the appropriate sulfonic anhydride or sulfonyl chloride (2.0 mmol, 1.0 equiv.) in dry CH₂Cl₂ (2 mL). The reaction mixture was stirred at this temperature for 1 h. After 12 h at room temperature, Et₂O (30 mL) and H₂O (20 mL) were added. The aqueous layer was extracted with CH₂Cl₂. The crude residue was purified by flash chromatography (CH₂Cl₂/MeOH, 99:1) to afford sulfonamide **5a-5d** as a colourless oil or as a solid.

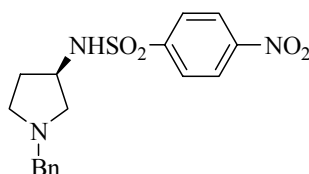
¹ Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575-580.

(R)-1-Benzylpyrrolidin-3-ylmethanesulfonamide 5a



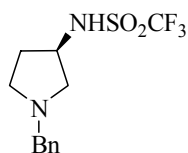
Prepared according to the general procedure from methanesulfonyl chloride as a colourless oil (63% yield). $[\alpha]_D$: +8.3 (*c* 1.0, CHCl₃). $^1\text{H NMR}$ (250 MHz, CDCl₃) δ 1.71-1.81 (m, 1H), 2.27-2.35 (m, 2H), 2.62 (dd, *J* = 6.0 Hz ; *J* = 9.9 Hz, 1H), 2.67 (dd, *J* = 3.4 Hz ; *J* = 9.9 Hz, 1H), 2.78-2.87 (m, 1H), 2.92 (s, 3H), 3.59 and 3.63 (AB, *J* = 13.0 Hz, 2H), 3.99 (br s, 1H), 4.92 (br s, 1H), 7.25-7.38 (m, 5H). $^{13}\text{C NMR}$ (62.9 MHz, CDCl₃) δ 33.2, 41.5, 52.2, 52.9, 59.8, 61.0, 127.3, 128.4, 128.8, 138.3. **IR** (neat, cm⁻¹): 3271, 2802, 1604, 1495, 1454, 1312, 1145, 1027, 973. **GC/MS** (ESI) (*m/z*) 255 (42, M+H⁺), 91 (100). **HRMS** (M+H⁺) Calcd for C₁₂H₁₉N₂O₂S: 255.1167. Found: 255.1163.

(R)-N-(1-Benzyl-pyrrolidin-3-yl)-4-nitrophenylsulfonamide 5b



Prepared according to the general procedure from 4-nitrobenzenesulfonyl chloride as a colourless solid (74% yield). **Mp**: 90 °C (CH₂Cl₂/MeOH). $[\alpha]_D$: +14.7 (*c* 1.5, CHCl₃). $^1\text{H NMR}$ (250 MHz, CDCl₃) δ 1.55-1.65 (m, 1H), 2.10-2.14 (m, 2H), 2.31 (dd, *J* = 10.0 Hz, *J* = 5.7 Hz, 1H), 2.35 (dd, *J* = 10.0 Hz, *J* = 2.7 Hz, 1H), 2.78-2.86 (m, 1H), 3.42 and 3.60 (AB, *J* = 13.0 Hz, 2H), 3.88-3.95 (m, 1H), 5.15 (br s, 1H), 7.19-7.31 (m, 5H), 8.00 (d, *J* = 8.7 Hz, 2H), 8.28 (d, *J* = 8.7 Hz, 2H). $^{13}\text{C NMR}$ (62.9 MHz, CDCl₃) δ 32.6, 52.0, 53.1, 59.6, 59.9, 124.4, 127.3, 128.2, 128.4, 128.8, 138.1, 146.9, 149.9. **IR** (neat, cm⁻¹): 3287, 3110, 2794, 1607, 1524, 1348, 1305, 1156, 1089. **GC/MS** (ESI) (*m/z*) 362 (65, M+H⁺), 270 (6), 91 (100). **HRMS** (M+H⁺) Calcd for C₁₇H₂₀N₃O₄S: 362.1175. Found: 362.1167.

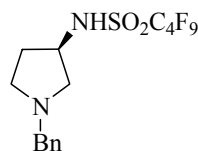
(R)-1-Benzylpyrrolidin-3-yltrifluoromethanesulfonamide 5c



Prepared according to the general procedure from trifluoromethanesulfonic anhydride as a colourless solid (94% yield). **Mp**: 133 °C (CH₂Cl₂/MeOH). $[\alpha]_D$: +14.2 (*c* 0.5, CHCl₃). $^1\text{H NMR}$ (250 MHz, CDCl₃) δ 1.87 (ddt, *J* = 12.7 Hz, *J* = 8.5 Hz, *J* = 3.8 Hz, 1H), 2.29 (q, *J* = 8.5 Hz, 1H), 2.34-2.42 (m, 1H), 2.52 (dd, *J* = 10.6 Hz, *J* = 6.4 Hz, 1H), 2.63 (d, *J* = 10.1 Hz, 1H), 3.12 (dt, *J* = 8.8 Hz, *J* = 2.8 Hz, 1H), 3.57 and 3.82 (AB, *J* = 13.0 Hz, 2H), 4.13-4.20 (m, 1H), 4.79 (br s, 1H), 7.25-7.38 (m, 5H). $^{13}\text{C NMR}$ (62.9 MHz, CDCl₃) δ 33.3, 52.2, 54.4, 59.4, 60.6, 119.8 (q, *J* (C-F) = 321 Hz), 127.8, 128.6, 129.1, 136.9. $^{19}\text{F NMR}$ (376.5 MHz, CDCl₃) δ -78.2 (s, 3F). **IR** (neat, cm⁻¹): 2990, 2362, 1486, 1458, 1446, 1365, 1276, 1191, 1176, 1089, 1047. **GC/MS** (ESI)

(*m/z*) 309 (21, M+H⁺), 91 (100). **HRMS** (M+H⁺) Calcd for C₁₂H₁₆F₃N₂O₂S: 309.0885. Found: 309.0886.

(*R*)-1-Benzylpyrrolidin-3-ylnonafluorobutanesulfonamide **5d**

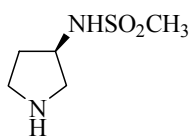


Prepared according to the general procedure from nonafluorobutanesulfonic anhydride as a colourless solid (88% yield). **Mp**: 166 °C (CH₂Cl₂/MeOH). [α]_D: +14.4 (*c* 1.0, MeOH). **¹H NMR** (400 MHz, CDCl₃) δ 1.82-1.91 (m, 1H), 2.28 (q, *J* = 8.5 Hz, 1H), 2.34-2.42 (m, 1H), 2.52 (dd, *J* = 10.4 Hz, *J* = 6.1 Hz, 1H), 2.69 (d, *J* = 10.4 Hz, 1H), 3.00-3.08 (m, 1H), 3.48 (br s, 1H), 3.57 and 3.72 (AB, *J* = 13.0 Hz, 2H), 4.18 (br s, 1H), 7.20-7.39 (m, 5H). **¹³C NMR** (100.6 MHz, CDCl₃) δ 33.7, 52.4, 55.1, 59.8, 61.1, 128.1, 129.0, 129.3, 137.4. C₄F₉ signals are not detectable. **¹⁹F NMR** (376.5 MHz, CDCl₃) δ -126.5 (m, 2F), -121.8 (m, 2F), -113.7 (t, *J* (F-F) = 13.1 Hz, 2F), -81.1 (t, *J* (F-F) = 10.2 Hz, 3F). **IR** (neat, cm⁻¹): 1458, 1351, 1284, 1234, 1208, 1193, 1176, 1131, 1098, 1024. **GC/MS** (ESI) (*m/z*) 459 (79, M+H⁺), 367 (9), 91 (100). **HRMS** (M+H⁺) Calcd for C₁₅H₁₆F₉N₂O₂S: 459.0789. Found: 459.0781.

General procedure for the debenylation of **6a-6d**

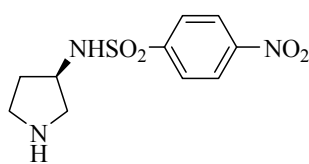
A suspension of 3-sulfonylaminopyrrolidine **5a-5d** (1.0 mmol) and Pd/C 10% (108 mg, 0.1 mmol, 0.1 equiv.) in degassed MeOH (10 mL) was stirred at room temperature under hydrogen (balloon) for 24 h. The solid was removed by filtration through celite and the cake was washed with MeOH. The filtrate was evaporated under reduced pressure to give **6a-6d** as a colourless oil or as a solid which can be used without any purification.

(*R*)-*N*-Pyrrolidin-3-ylmethanesulfonamide **6a**



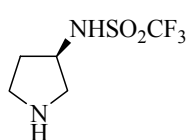
Prepared according to the general procedure from **5a** as a colourless oil (100% yield). [α]_D: +6.5 (*c* 1.0, MeOH). **¹H NMR** (400 MHz, MeOD) δ 1.92-2.02 (m, 1H), 2.21-2.32 (m, 1H), 2.95-3.05 (m, 1H), 3.12 (dd, *J* = 12.0 Hz, *J* = 4.9 Hz, 1H), 3.17-3.30 (m, 2H), 3.31-3.38 (m, 2H), 4.05-4.12 (m, 1H). **¹³C NMR** (100.6 MHz, MeOD) δ 31.7, 39.4, 47.4, 51.8, 53.2. **IR** (neat, cm⁻¹): 3162, 2931, 1652, 1451, 1307, 1143, 1019, 974. **HRMS** (M+H⁺) Calcd for C₅H₁₃N₂O₂S: 165.0698. Found: 165.0681.

(R)-Pyrrolidin-3-yl-4-nitrophenylsulfonamide **6b**



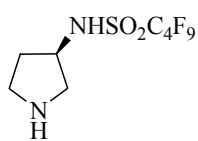
Prepared according to the general procedure from **5b** as a colourless oil (92% yield). $[\alpha]_D$: +33.7 (*c* 1.5, MeOH). $^1\text{H NMR}$ (400 MHz, MeOD) δ 1.52-1.62 (m, 1H), 1.84-1.95 (m, 1H), 2.61 (dd, $J = 11.8$ Hz, $J = 5.3$ Hz, 1H), 2.75-2.84 (m, 1H), 2.87-2.93 (m, 2H), 3.60 (quint, $J = 6.2$ Hz, 1H), 6.71 (d, $J = 8.7$ Hz, 2H), 7.54 (d, $J = 8.7$ Hz, 2H). $^{13}\text{C NMR}$ (100.6 MHz, MeOD) δ 32.6, 44.8, 52.5, 54.0, 113.5, 126.6, 129.1, 153.2. **IR** (neat, cm^{-1}): 3369, 3224, 2877, 1628, 1594, 1502, 1419, 1300, 1143, 1089. **HRMS** ($\text{M}+\text{H}^+$) Calcd for $\text{C}_{10}\text{H}_{14}\text{N}_3\text{O}_4\text{S}$: 271.0705. Found: 271.0698.

(R)-Pyrrolidin-3-yltrifluoromethanesulfonamide **6c**



Prepared according to the general procedure from **5c** as a colourless solid (100% yield). **Mp**: 196 °C (MeOH). $[\alpha]_D$: +15.4 (*c* 0.5, MeOH). $^1\text{H NMR}$ (250 MHz, MeOD) δ 1.81-2.01 (m, 1H), 2.20-2.32 (m, 1H), 3.09 (dd, $J = 12.2$ Hz, $J = 6.0$ Hz, 1H), 3.22-3.35 (m, 2H), 3.36-3.52 (m, 1H), 4.18-4.29 (m, 1H). $^{13}\text{C NMR}$ (100.6 MHz, MeOD) δ 32.2, 45.3, 51.5, 54.5, 121.5 (q, $J = 321.3$ Hz). $^{19}\text{F NMR}$ (376.5 MHz, MeOD) δ -79.8 (s, 3F). **IR** (neat, cm^{-1}): 3256, 2981, 2360, 1598, 1444, 1382, 1296, 1284, 1190, 1150, 1104, 948. **GC/MS** (ESI) (*m/z*) 219 (100, $\text{M}+\text{H}^+$), 202 (18), 98 (11), 86 (27), 85 (53). **HRMS** ($\text{M}+\text{H}^+$) Calcd for $\text{C}_5\text{H}_9\text{F}_3\text{N}_2\text{O}_2\text{S}$: 219.0415. Found: 219.0416.

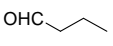
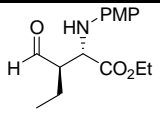

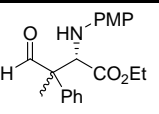
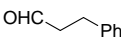
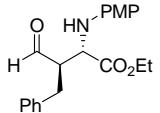
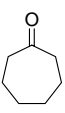
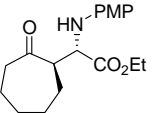
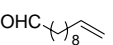
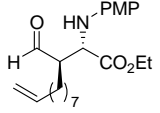
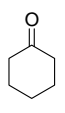
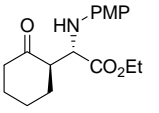
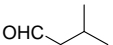
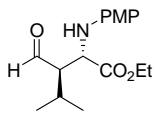
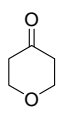
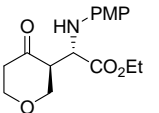

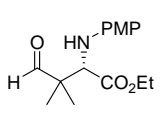
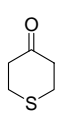
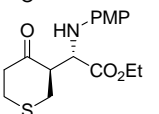

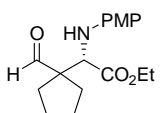

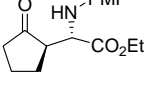

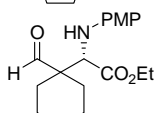

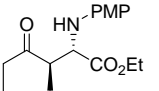
(R)-Pyrrolidin-3-ylnonafluorobutanesulfonamide **6d**



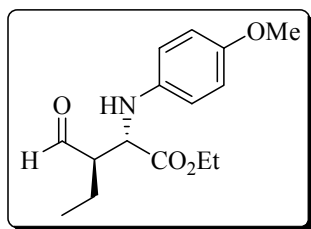
Prepared according to the general procedure from **5d** as a colourless solid (100% yield). **Mp**: 248 °C (MeOH). $[\alpha]_D$: +11.5 (*c* 1.0, MeOH). $^1\text{H NMR}$ (250 MHz, MeOD) δ 2.08 (sext, $J = 7.2$ Hz, 1H), 2.42 (sext, $J = 6.8$ Hz, 1H), 3.20 (dd, $J = 12.3$ Hz, $J = 6.3$ Hz, 1H), 2.30-2.52 (m, 2H), 3.63 (dd, $J = 12.3$ Hz, $J = 7.2$ Hz, 1H), 4.41 (quint, $J = 6.8$ Hz, 1H). $^{13}\text{C NMR}$ (100.6 MHz, MeOD) δ 30.9, 44.3, 50.1, 53.5. C_4F_9 signals are not detectable. $^{19}\text{F NMR}$ (376.5 MHz, MeOD) δ -127.7 (m, 2F), -122.8 (m, 2F), -114.4 (t, J (F-F) = 13.4 Hz, 2F), -82.9 (t, J (F-F) = 10.0 Hz, 3F). **IR** (neat, cm^{-1}): 3039, 1477, 1392, 1376, 1353, 1294, 1240, 1178, 1140, 1072, 1044. **HRMS** ($\text{M}+\text{H}^+$) Calcd for $\text{C}_8\text{H}_{10}\text{F}_9\text{N}_2\text{O}_2\text{S}$: 369.0319. Found: 369.0305.

General procedure for the asymmetric Mannich reaction:

To a solution of imine **1** (63 mg, 0.3 mmol) in DMF (2 mL) was added the aldehyde or the ketone (0.9 mmol, 3.0 equiv.) and catalyst **6a-d** (0.015 mmol, 5 mol %). The mixture was stirred at a given temperature for a given time (see tables). Disappearance of the imine **1** in the reaction mixture was monitored by TLC. At the end of the reaction, water was added and the aqueous layer was extracted with Et₂O. The combined organic extracts were dried over MgSO₄ and evaporated under reduced pressure. The residue was purified by flash column chromatography (cyclohexane/EtOAc, 96:4 for aldehyde adducts and 92:8 for ketone adducts).

donor	temp. time (°C, h)	product	yield (%) (anti:syn) ^c	ee (%) anti 2 <i>S</i> ,3 <i>R</i>	donor	temp. time (°C, h)	product	yield (%) (anti:syn) ^c	ee (%) anti 2 <i>S</i> ,3 <i>R</i>
	-40, 2		3a 86 (12:1)	98		0, 24		3h 82 (4:1)	20
	-20, 1		3b 88 (12:1)	98		20, 72		3i 56 (13:1)	98
"	-40, 2	"	85 (13:1)	99	"	20, 48 ^f	"	84 (>20:1)	98
	-40, 2		3c 77 (15:1)	> 99		20, 2		3j 95 (>20:1)	> 99
	-20, 6		3d 86 (13:1)	> 99		20, 20		3k 87 (20:1)	96
	0, 8		3e 76	92 (2 <i>S</i>)		20, 24		3l 85 (10:1)	99
	0, 3		3f 92	99 (2 <i>S</i>)		20, 72		3m 0	-
	0, 8		3g 73	60 (2 <i>S</i>)		20, 48		3n 62 (4:1)	99
"	-10, 20	"	79	97 (2 <i>S</i>)	"	20, 12 ^f	"	70 (9:1)	> 99

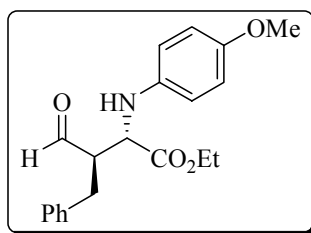
Known^{2,3} ethyl (2*S*,3*R*)-3-formyl-2-(4-methoxyphenylamino)-pentanoate 3a



Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (96:4) as eluent (97% yield of the mixture of stereoisomers, dr. 15:1). The ee was determined by chiral HPLC on Daicel Chiralpak AS-H column (99% heptane, 1% *i*PrOH, 15 °C, 0.5 mL/min, 235 nm, $t_1 =$

119.9 (major *anti*), $t_2 = 130.2$ (major *syn*), $t_3 = 138.8$ (minor *anti*), $t_4 = 155.3$ min (minor *syn*)). $[\alpha]_D^{25}$: -28.8 (c 3.2, CHCl₃, ee 99%), [litt.³ $[\alpha]_D^{25}$: -43.3 (c 1.0, CHCl₃, ee 94%, dr 80:20)]. ¹H NMR (250 MHz, CDCl₃) δ 1.00 (t, $J = 7.5$ Hz, 3H), 1.21 (t, $J = 7.1$ Hz, 3H), 1.56-1.82 (m, 2H), 2.63-2.75 (m, 1H), 3.73 (s, 3H), 4.04 (br s, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 4.26 (d, $J = 6.5$ Hz, 1H), 6.65 (d, $J = 9.0$ Hz, 2H), 6.77 (d, $J = 9.0$ Hz, 2H), 9.65 (d, $J = 2.5$ Hz, 1H). ¹³C NMR (62.9 MHz, CDCl₃) δ 11.9, 14.2, 19.1, 55.5, 55.7, 58.0, 61.5, 114.9, 115.8, 140.4, 153.2, 172.3, 202.3.

Known⁴ ethyl (2*S*,3*R*)-3-formyl-2-(4-methoxyphenylamino)-4-phenylbutanoate 3b



Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (96:4) as eluent (88% yield of the mixture of stereoisomers, dr 13:1). The ee was determined by chiral HPLC on Daicel Chiralpak AS-H column (99% heptane, 1% *i*PrOH, 15 °C, 1 mL/min, 235

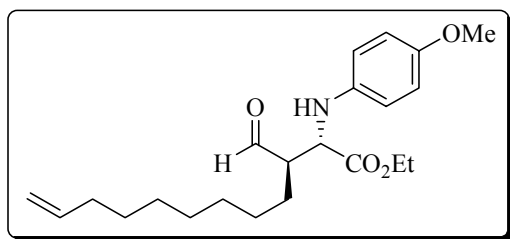
nm, $t_1 = 76.2$ (major *anti*), $t_2 = 84.4$ (minor *anti*), $t_3 = 93.6$ (major *syn*), $t_4 = 143.4$ min (minor *syn*)). $[\alpha]_D^{25}$: -17.3 (c 0.8, CHCl₃, ee 99%), [litt.⁴ $[\alpha]_D^{25}$: -16.4 (c 0.3, CHCl₃, ee > 99%, dr 11:1)]. ¹H NMR (250 MHz, CDCl₃) δ 1.14 (t, $J = 7.1$ Hz, 3H), 2.86 (dd, $J = 13.9$ Hz, $J = 7.8$ Hz, 1H), 3.07 (dd, $J = 13.9$ Hz, $J = 7.1$ Hz, 1H), 3.16-3.27 (m, 1H), 3.67 (s, 3H), 3.97-4.17 (m, 4H), 6.41-6.51 (d, $J = 8.9$ Hz, 2H), 6.63-6.71 (d, $J = 8.9$ Hz, 2H), 7.10-7.28 (m, 5H), 9.66 (s, 1H). ¹³C NMR (62.9 MHz, CDCl₃) δ 14.2, 31.8, 55.3, 55.7, 57.5, 61.7, 114.9, 115.8, 126.9, 128.5, 128.9, 137.9, 140.6, 153.2, 172.3, 202.0.

² Cordova, A.; Watanabe, S.-I.; Tanaka, F.; Notz, W.; Barbas III, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1866-1877.

³ Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjaersgaard, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296-18304.

⁴ Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408-16409.

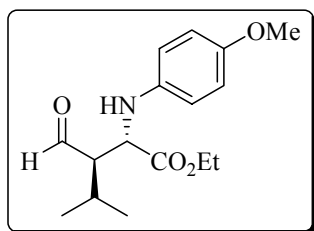
Ethyl (2*S*,3*R*)-3-formyl-2-(4-methoxyphenylamino)-dodec-11-enoate **3c**



Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (96:4) as eluent (77% yield of the mixture of stereoisomers, dr 15:1). The ee was determined by chiral HPLC on Daicel

Chiralpak AS-H column (90% heptane, 10% *i*PrOH, 15 °C, 1 mL/min, 235 nm, $t_1 = 20.8$ (minor *anti*), $t_2 = 23.4$ (major *anti*), $t_3 = 26.7$ (minor *syn*), $t_4 = 32.9$ (major *syn*) min). $[\alpha]_D^{25}$: -33.5 (*c* 1.5, CHCl₃, ee > 99%). $^1\text{H NMR}$ (250 MHz, CDCl₃) δ 1.15 (t, $J = 7.1$ Hz, 3H), 1.16-1.35 (m, 10H), 1.42-1.56 (m, 1H), 1.60-1.74 (m, 1H), 2.00-2.04 (m, 2H), 2.72-2.78 (m, 1H), 3.73 (s, 3H), 4.03 (br d, $J = 7.9$ Hz, 1H), 4.17 (dq, $J = 7.1$ Hz, $J = 1.7$ Hz, 2H), 4.22-4.28 (m, 1H), 4.93-4.97 (m, 1H), 5.01 (dq, $J = 17.1$ Hz, $J = 1.9$ Hz, 1H), 5.76-5.87 (m, 1H), 6.64 (d, $J = 8.9$ Hz, 2H), 6.77 (d, $J = 8.9$ Hz, 2H), 9.65 (d, $J = 3.5$ Hz, 1H). $^{13}\text{C NMR}$ (62.9 MHz, CDCl₃) δ 14.3, 25.8, 27.4, 28.9, 29.0, 29.2, 29.5, 33.8, 54.0, 55.8, 58.2, 61.6, 114.3, 114.9, 115.8, 139.2, 140.4, 153.3, 172.3, 202.4. **IR** (neat, cm⁻¹): 3369, 2925, 2854, 1727, 1640, 1513, 1464, 1240, 1181, 1037. **GC/MS** (ESI) (m/z) 376 (48, M+H⁺), 358 (67), 330 (15), 284 (35), 262 (100). **HRMS** (M+H⁺) Calcd for C₂₂H₃₄NO₄: 376.2488. Found: 376.2480.

Known⁵ ethyl (2*S*,3*R*)-3-formyl-2-(4-methoxyphenylamino)-4-methylpentanoate **3d**

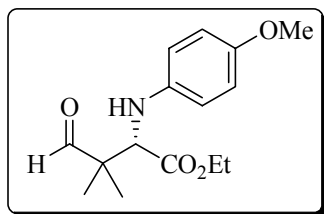


Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (96:4) as eluent (86% yield of the mixture of stereoisomers, dr 13:1). The ee was determined by chiral HPLC on Daicel Chiralpak

AS-H column (99% heptane, 1% *i*PrOH, 15 °C, 0.5 mL/min, 235 nm, $t_1 = 68.1$ (major *anti*), $t_2 = 89.5$ (major *syn*), $t_3 = 128.0$ (minor *anti*), $t_4 = 145.6$ (minor *syn*) min). $[\alpha]_D^{25}$: -33.2 (*c* 0.4, CHCl₃, ee > 99%), [litt.⁵ $[\alpha]_D^{25}$: -35.4 (*c* 1.8, CHCl₃, ee 99%, dr 98:2)]. $^1\text{H NMR}$ (250 MHz, CDCl₃) δ 1.07 (d, $J = 6.9$ Hz, 3H), 1.11 (d, $J = 6.9$ Hz, 3H), 1.19 (t, $J = 7.1$ Hz, 3H), 2.02-2.15 (m, 1H), 2.54-2.62 (m, 1H), 3.72 (s, 3H), 3.96 (br s, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 4.35 (d, $J = 7.6$ Hz, 1H), 6.65 (d, $J = 9.0$ Hz, 2H), 6.75 (d, $J = 9.0$ Hz, 2H), 9.73 (d, $J = 3.4$ Hz, 1H). $^{13}\text{C NMR}$ (62.9 MHz, CDCl₃) δ 14.2, 19.2, 21.3, 27.6, 55.6, 57.3, 59.6, 61.4, 114.8, 115.9, 140.5, 153.3, 172.9, 203.3.

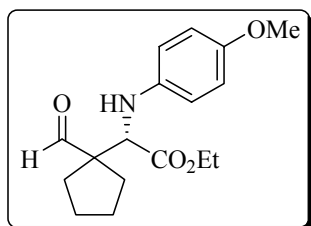
⁵ Zhang, H.; Mitsumori, S.; Tanaka, F.; Cheong, P. H.-Y.; Houk, K. N.; Barbas III, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 1040-1041.

Ethyl (S)-3-formyl-2-(4-methoxyphenylamino)-3-methylbutanoate 3e



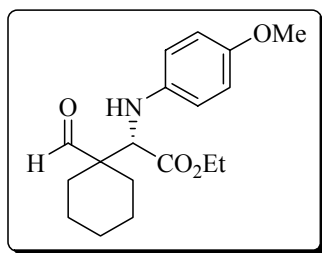
Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (96:4) as eluent (96% yield). The ee was determined by chiral HPLC on Daicel Chiralpak AS-H column (90% heptane, 10% *i*PrOH, 20 °C, 0.5 mL/min, 235 nm, $t_1 = 32.3$ (2*S*), $t_2 = 55.2$ (2*R*) min). $[\alpha]_D^{25}$: -31.0 (*c* 0.5, CHCl₃, ee 92%). $^1\text{H NMR}$ (250 MHz, CDCl₃) δ 1.14 (s, 3H), 1.22 (s, 3H), 1.23 (t, $J = 7.1$ Hz, 3H), 3.74 (s, 3H), 3.93 (br d, $J = 9.1$ Hz, 1H), 4.09-4.22 (m, 3H), 6.68 (d, $J = 9.1$ Hz, 2H), 6.77 (d, $J = 9.1$ Hz, 2H), 9.60 (s, 1H). $^{13}\text{C NMR}$ (62.9 MHz, CDCl₃) δ 14.3, 18.3, 19.3, 49.1, 55.7, 61.5, 63.2, 114.9, 116.5, 140.9, 153.6, 171.9, 202.9. **IR** (neat, cm⁻¹): 3372, 2978, 2834, 1725, 1511, 1464, 1236, 1151, 1031, 822. **GC/MS** (ESI) (m/z) 280 (13, M+H⁺), 262 (100), 234 (32), 208 (100), 188 (13), 134 (11). **HRMS** (M+H⁺) Calcd for C₁₅H₂₂NO₄: 280.1549. Found: 280.1535.

Ethyl (S)-3-formyl-2-(4-methoxyphenylamino)-3-cyclopentylpropanoate 3f



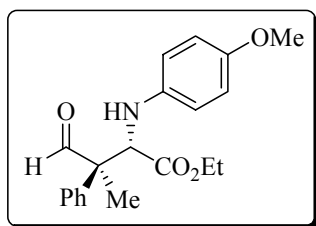
Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (96:4) as eluent (92% yield). The ee was determined by chiral HPLC on Daicel Chiralpak AS-H column (99% heptane, 1% *i*PrOH, 20 °C, 0.5 mL/min, 235 nm, $t_1 = 83.1$ (2*S*), $t_2 = 103.3$ (2*R*) min). $[\alpha]_D^{25}$: -34.0 (*c* 0.5, CHCl₃, ee 99%). $^1\text{H NMR}$ (250 MHz, CDCl₃) δ 1.17 (t, $J = 7.1$ Hz, 3H), 1.60-2.10 (m, 8H), 3.74 (s, 3H), 4.00 (br s, 1H), 4.14 (dq, $J = 7.1$ Hz, $J = 1.2$ Hz, 2H), 4.20-4.26 (m, 1H), 6.65 (d, $J = 9.0$ Hz, 2H), 6.77 (d, $J = 9.0$ Hz, 2H), 9.60 (s, 1H). $^{13}\text{C NMR}$ (62.9 MHz, CDCl₃) δ 14.2, 25.4, 25.8, 29.1, 29.9, 55.7, 60.5, 61.5, 61.7, 114.9, 115.9, 141.0, 153.3, 172.2, 202.1. **IR** (neat, cm⁻¹): 3369, 2955, 2871, 2833, 1722, 1511, 1452, 1235, 1144, 1105, 1032. **GC/MS** (ESI) (m/z) 306 (10, M+H⁺), 288 (100), 260 (13), 214 (35), 208 (55). **HRMS** (M+H⁺) Calcd for C₁₇H₂₄NO₄: 306.1705. Found: 306.1710.

Ethyl (*S*)-3-formyl-2-(4-methoxyphenylamino)-3-cyclohexylpropanoate **3g**



Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (96:4) as eluent (79% yield). The ee was determined by chiral HPLC on Daicel Chiralpak AS-H column (99% heptane, 1% (50% MeOH + 50% EtOH), 15 °C, 0.3 mL/min, 235 nm, t_1 = 68.5 (2*R*), t_2 = 73.2 (2*S*) min). $[\alpha]_D^{25}$: -35.4 (c 0.5, CHCl₃, ee 97%). ¹H NMR (250 MHz, CDCl₃) δ 1.22 (t, J = 7.1 Hz, 3H), 1.23-1.49 (m, 4H), 1.55-1.76 (m, 4H), 1.98-2.10 (m, 2H), 3.72 (s, 3H), 4.00 (br s, 2H), 4.15 (dq, J = 7.1 Hz, J = 0.7 Hz, 2H), 6.63 (d, J = 9.0 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 9.65 (s, 1H). ¹³C NMR (62.9 MHz, CDCl₃) δ 14.3, 22.5, 25.3, 28.6, 52.0, 55.8, 61.5, 64.3, 114.9, 115.9, 141.0, 153.3, 171.9, 205.4. IR (neat, cm⁻¹): 3368, 2955, 2871, 2833, 1721, 1511, 1452, 1234, 1181, 1032, 821. GC/MS (ESI) (m/z) 320 (8, M+H⁺), 302 (100), 274 (28), 228 (7), 208 (51). HRMS (M+H⁺) Calcd for C₁₈H₂₆NO₄: 320.1862. Found: 320.1866.

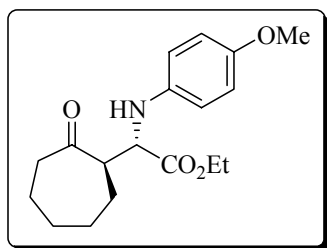
Known⁶ ethyl (2*S*,3*R*)-3-formyl-2-(4-methoxyphenylamino)-3-phenylbutanoate **3h**



Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (96:4) as eluent (82% yield of the mixture of stereoisomers, dr 4:1). The ee was determined by chiral HPLC on Daicel Chiralpak AS-H column (99% heptane, 1% (50% MeOH + 50% EtOH), 15 °C, 0.5 mL/min, 235 nm, t_1 = 46.7 (major *syn*), t_2 = 62.9 (major *anti*), t_3 = 68.2 (minor *anti*), t_4 = 75.0 (minor *syn*) min). Ee. 20% (*anti* stereoisomer). ¹H NMR (250 MHz, CDCl₃) minor diastereomer δ 1.15 (t, J = 7.1 Hz, 3H), 1.60 (s, 3H), 3.73 (s, 3H), 3.91 (br s, 1H), 4.05-4.15 (m, 2H), 4.64 (br s, 1H), 6.62 (d, J = 8.9 Hz, 2H), 6.73 (d, J = 8.9 Hz, 2H), 7.32-7.42 (m, 5H), 9.80 (s, 1H); major diastereomer δ 0.82 (t, J = 7.1 Hz, 3H), 1.71 (s, 3H), 3.74 (s, 3H), 3.80 (q, J = 7.1 Hz, 2H), 3.91 (br s, 1H), 4.75 (s, 1H), 6.77-6.79 (m, 4H), 7.33-7.41 (m, 5H), 9.70 (s, 1H). ¹³C NMR (62.9 MHz, CDCl₃) δ major diastereomer 14.1, 16.9, 55.6, 56.7, 61.4, 63.7, 114.7, 116.5, 117.1, 127.6, 127.9, 128.7, 128.8, 136.8, 140.7, 153.4, 171.7, 199.6.

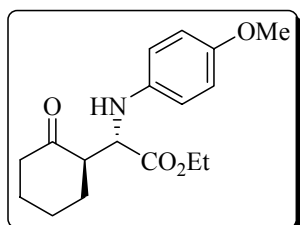
⁶ Chowdari, N. S.; Suri, J. T.; Barbas III, C. F. *Org. Lett.* **2004**, *6*, 2507-2510.

Ethyl (2*S*,3*R*)-2-(4-methoxyphenylamino)-2-(2'-oxocycloheptyl)acetate 3i



Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (92:8) as eluent (84% yield of the mixture of stereoisomers, dr >20:1). The ee was determined by chiral HPLC on Daicel Chiralpak AS-H column (90% heptane, 10% *i*PrOH, 20 °C, 0.5 mL/min, 235 nm, t_1 = 24.2 (major *anti*), t_2 = 32.3 (major *syn*), t_3 = 45.3 (minor *syn*), t_4 = 50.2 (minor *anti*) min). $[\alpha]_D^{25}$: +29.2 (*c* 1.0, CHCl₃, ee 98%). ¹H NMR (400 MHz, CDCl₃) δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.30-1.37 (m, 2H), 1.48-1.62 (m, 2H), 1.82-2.03 (m, 4H), 2.45-2.60 (m, 2H), 3.03 (dt, *J* = 7.5 Hz, *J* = 3.6 Hz, 1H), 3.74 (s, 3H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.25-4.33 (m, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 6.77 (d, *J* = 9.0 Hz, 2H). ¹³C NMR (62.9 MHz, CDCl₃) δ 14.3, 24.3, 27.3, 29.1, 30.0, 44.0, 54.5, 55.9, 60.8, 61.4, 115.0, 115.3, 141.1, 152.3, 172.7, 214.3. IR (neat, cm⁻¹): 3381, 2927, 2855, 1733, 1695, 1512, 1454, 1238, 1032. GC/MS (ESI) (*m/z*) 320 (33, M+H⁺), 208 (100). HRMS (M+H⁺) Calcd for C₁₈H₂₆NO₄: 320.1862. Found: 320.1873.

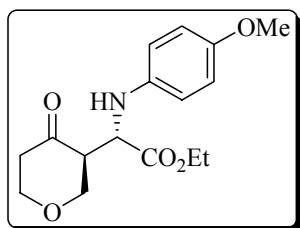
Known ethyl⁷ (2*S*,3*R*)-2-(4-methoxyphenylamino)-2-(2'-oxocyclohexyl)acetate 3j



Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (92:8) as eluent (96% yield of the mixture of stereoisomers, dr >20:1). The ee was determined by chiral HPLC on Daicel Chiralpak AS-H column (90% heptane, 10% *i*PrOH, 20 °C, 0.5 mL/min, 235 nm, t_1 = 32.1 (major *anti*), t_2 = 39.6 (major *syn*), t_3 = 46.7 (minor *anti*), t_4 = 67.9 (minor *syn*) min). $[\alpha]_D^{25}$: +29.8 (*c* 0.5, CHCl₃, ee >99%), [litt.⁷ $[\alpha]_D^{25}$: +29.1 (*c* 2.0, CHCl₃, ee 96%, dr > 99:1)]. ¹H NMR (250 MHz, CDCl₃) δ 1.20 (t, *J* = 7.1 Hz, 3H), 1.60-1.78 (m, 2H), 1.80-2.00 (m, 2H), 2.01-2.16 (m, 2H), 2.25-2.48 (m, 2H), 3.06-3.15 (m, 1H), 3.72 (s, 3H), 3.97 (d, *J* = 4.1 Hz, 1H), 4.13 (dq, *J* = 7.1 Hz, *J* = 1.5 Hz, 2H), 4.14 (br s, 1H), 6.60-6.65 (d, *J* = 9.0 Hz, 2H), 6.73-6.78 (d, *J* = 9.0 Hz, 2H). ¹³C NMR (62.9 MHz, CDCl₃) δ 14.2, 24.6, 26.9, 30.6, 41.9, 53.6, 55.7, 59.1, 61.2, 114.8, 115.7, 142.2, 152.8, 173.1, 211.0.

⁷ Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 9630-9631.

Known⁷ ethyl (2*S*,3*R*)-2-(4-methoxyphenylamino)-2-(4'-oxotetrahydrothiopyran-3'-yl)acetate 3k

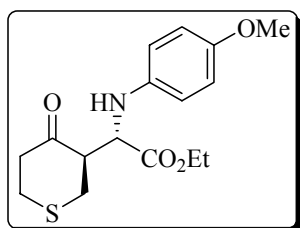


Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (92:8) as eluent (87% yield of the mixture of stereoisomers, dr 20:1). The ee was determined by chiral HPLC on Daicel Chiralpak OJ-H column (95% heptane, 5% *i*PrOH, 20 °C, 1 mL/min, 235 nm, $t_1 =$

86.2 (major *syn*), $t_2 = 93.6$ (major *anti*), $t_3 = 101.7$ (minor *syn*), $t_4 = 112.8$ (minor *anti*) min).

$[\alpha]_D^{25}$: +8.2 (*c* 1.0, CHCl₃, ee 96%). No Litt value available⁷ (ee 86%, dr > 95:5) **¹H NMR** (250 MHz, CDCl₃) δ 1.22 (t, $J = 7.1$ Hz, 3H), 2.48 (dt, $J = 14.8$ Hz, $J = 4.0$ Hz, 1H), 2.56-2.69 (m, 1H), 3.21-3.28 (m, 1H), 3.74 (s, 3H), 3.81 (ddd, $J = 11.5$ Hz, $J = 9.8$ Hz, $J = 4.0$ Hz, 1H), 3.90 (dd, $J = 11.2$ Hz, $J = 9.0$ Hz, 1H), 4.02-4.27 (m, 6H), 6.62 (d, $J = 8.9$ Hz, 2H), 6.77 (d, $J = 8.9$ Hz, 2H). **¹³C NMR** (62.9 MHz, CDCl₃) δ 14.1, 42.1, 53.8, 55.7, 56.4, 61.5, 67.8, 70.1, 114.8, 115.9, 141.3, 153.2, 172.1, 206.2.

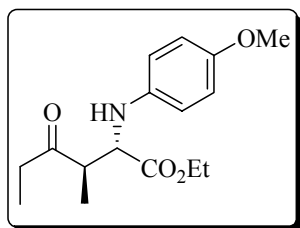
Known⁷ (2*S*,3*R*)-2-(4-methoxyphenylamino)-2-(4'-oxotetrahydrothiopyran-3'-yl)acetate 3l



Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (92:8) as eluent (84% yield of the mixture of stereoisomers, dr 10:1). The ee was determined by chiral HPLC on Daicel Chiralpak AS-H column (98% heptane, 2% *i*PrOH, 20 °C, 0.5 mL/min, 235 nm, $t_1 =$

134.9 (major *anti*), $t_2 = 201.3$ (major *syn*), $t_3 = 230.8$ (minor *anti*), $t_4 = 252.0$ (minor *syn*) min). $[\alpha]_D^{25}$: +45.5 (*c* 0.4, CHCl₃, ee 99%), [litt.⁷ $[\alpha]_D^{25}$: +48.0 (*c* 2.6, CHCl₃, ee 99%, dr > 99:1)]. **¹H NMR** (250 MHz, CDCl₃) δ 1.22 (t, $J = 7.1$ Hz, 3H), 2.62-2.82 (m, 2H), 2.89-3.03 (m, 3H), 3.09-3.15 (m, 1H), 3.38 (dt, $J = 9.8$ Hz, $J = 4.8$ Hz, 1H), 3.73 (s, 3H), 4.10-4.20 (m, 3H), 4.24 (d, $J = 4.8$ Hz, 1H), 6.65 (d, $J = 9.0$ Hz, 2H), 6.72 (d, $J = 9.0$ Hz, 2H). **¹³C NMR** (62.9 MHz, CDCl₃) δ 14.2, 29.9, 32.9, 43.8, 55.4, 55.8, 59.1, 61.5, 114.9, 116.0, 141.5, 153.2, 172.3, 208.1.

Known⁷ ethyl (2*S*,3*R*)-2-(4-methoxyphenylamino)-3-(oxoethyl)butanoate 3n



Prepared according to the general procedure and purified by silica gel column chromatography using cyclohexane:ethyl acetate (92:8) as eluent (70% yield of the mixture of stereoisomers, dr 9:1). The ee was determined by chiral HPLC on Daicel Chiralpak OJ-H column (99% heptane, 1% *i*PrOH, 12 °C, 0.3 mL/min, 235 nm, $t_1 = 162.6$ (minor *anti*), $t_2 = 171.0$ (major *anti*), $t_3 = 184.1$ (minor *syn*), $t_4 = 204.6$ (major *syn*) min). $[\alpha]_D$: -26.5 (*c* 1.0, CHCl₃, ee > 99%), [litt.⁷ $[\alpha]_D$: -27.8 (*c* 2.9, CHCl₃, ee 95%, dr > 99:1)]. ¹H NMR (250 MHz, CDCl₃) δ 1.05 (t, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 2.53 (q, *J* = 7.2 Hz, 2H), 3.02 (quint, *J* = 7.1 Hz, 1H), 3.73 (s, 3H), 4.08-4.22 (m, 4H), 6.63 (d, *J* = 8.9 Hz, 2H), 6.76 (d, *J* = 8.9 Hz, 2H). ¹³C NMR (62.9 MHz, CDCl₃) δ 7.6, 13.5, 14.2, 35.1, 48.5, 55.8, 60.9, 61.3, 114.9, 115.9, 140.9, 153.2, 172.9, 212.3.

Figure 1. HPLC chart of racemic **3a** generated by the racemic proline catalyzed reaction.

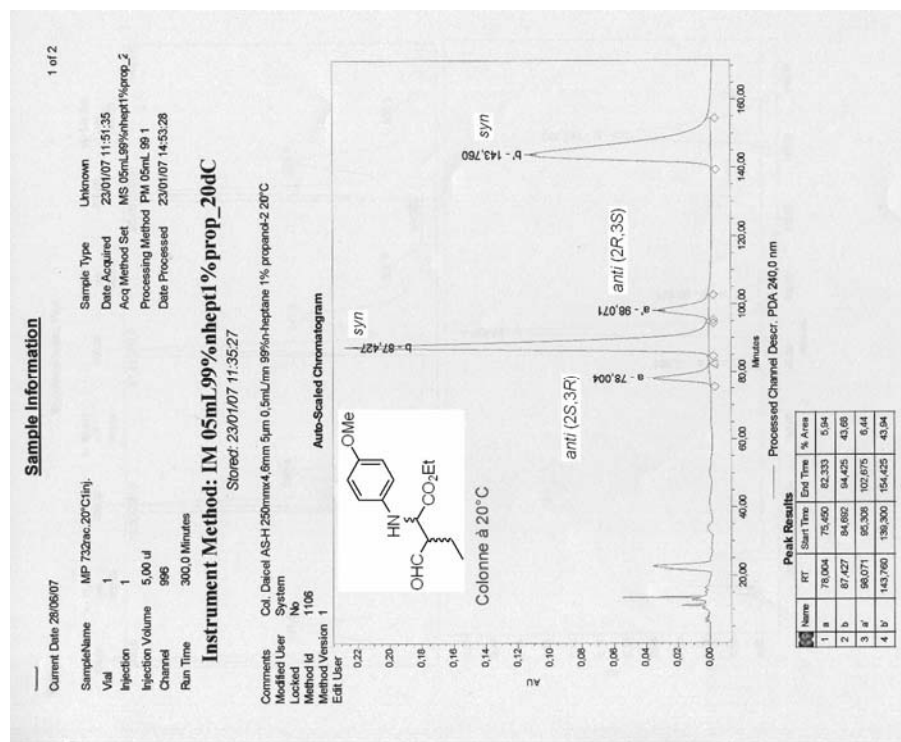


Figure 2. HPLC chart of (2*S*,3*R*) **3a** generated by the **6c** catalyzed reaction.

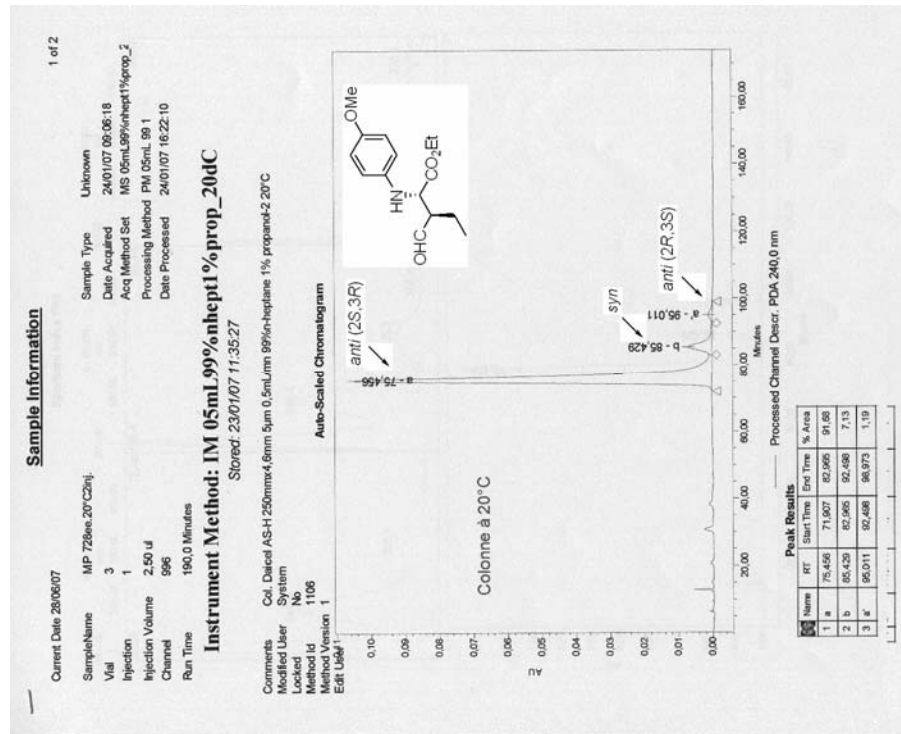


Figure 3. HPLC chart of racemic **3e** generated by the racemic proline catalyzed reaction.

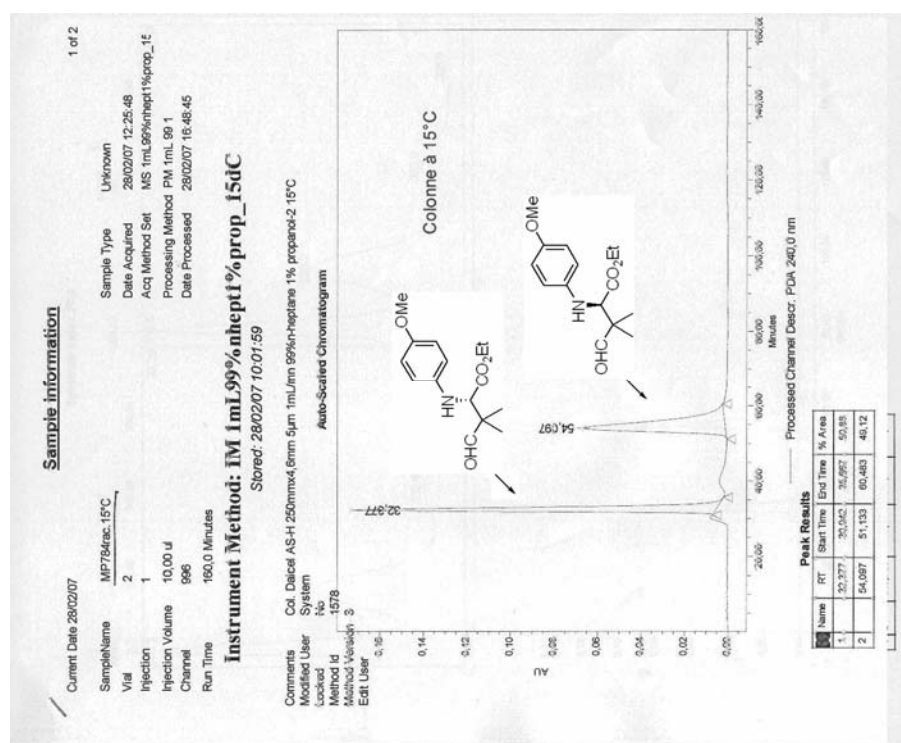


Figure 4. HPLC chart of (2*S*)-**3e** generated by the **6c** catalyzed reaction.

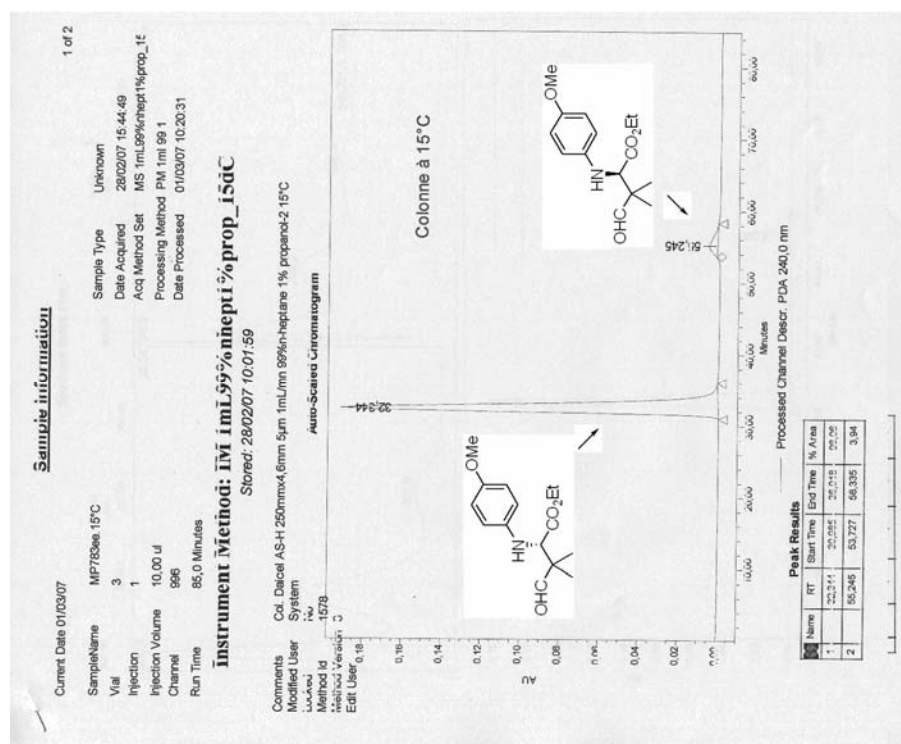


Figure 5. HPLC chart of racemic **3f** generated by the racemic proline catalyzed reaction.

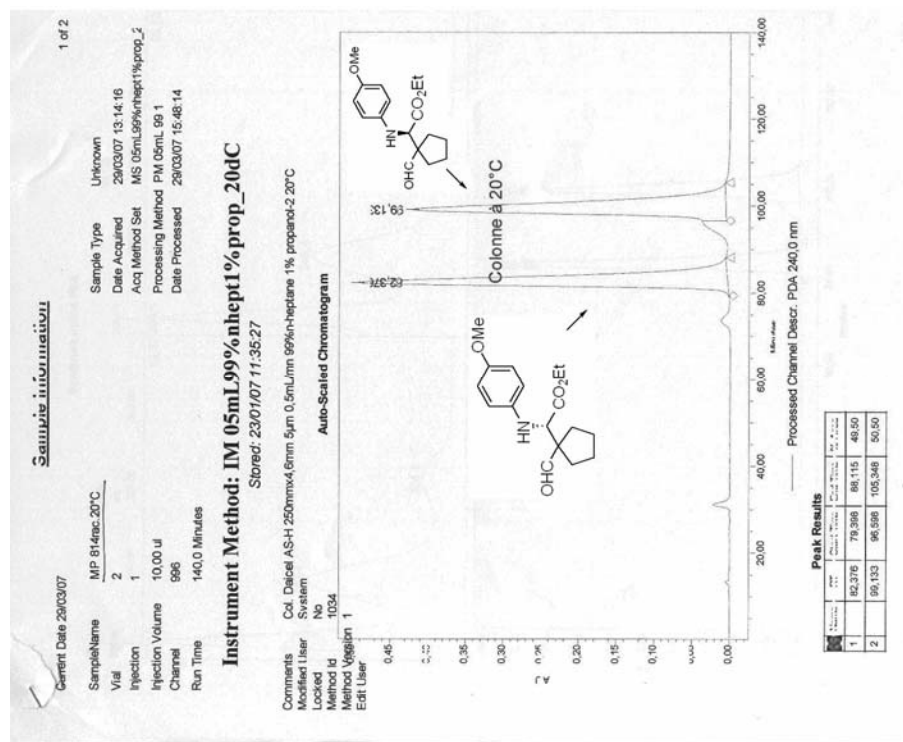


Figure 6. HPLC chart of (2*S*)-**3f** generated by the **6c** catalyzed reaction.

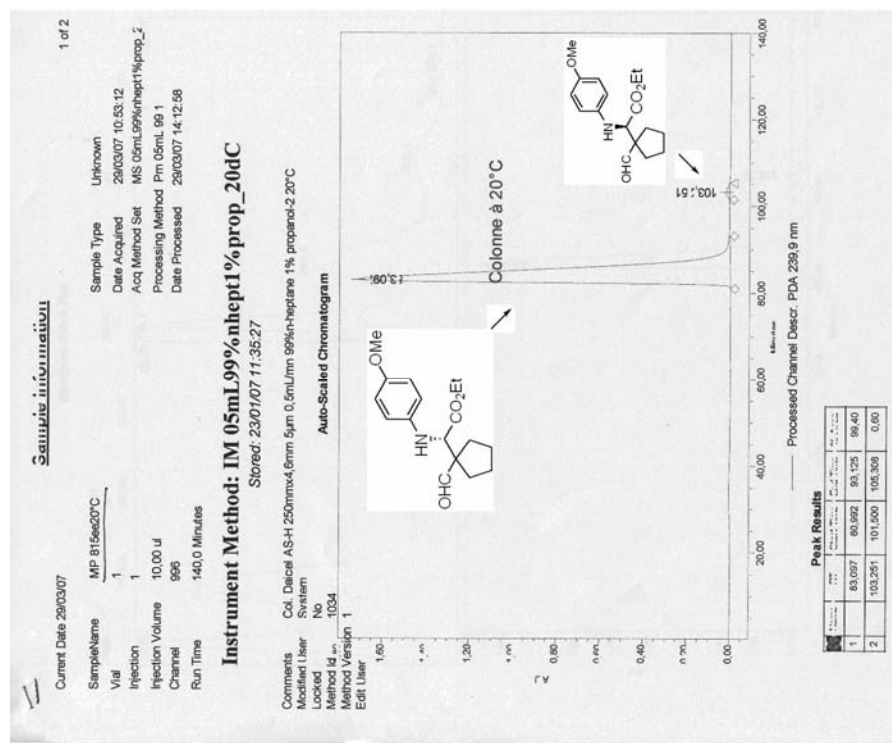


Figure 7. HPLC chart of racemic **3g** generated by the racemic proline catalyzed reaction.

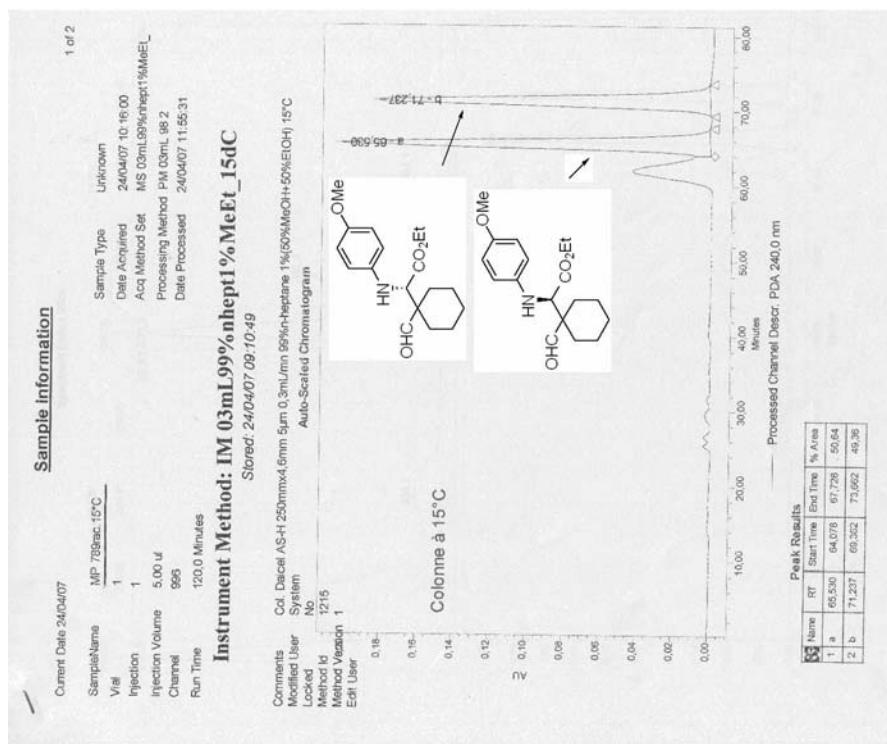


Figure 8. HPLC chart of (2S)-**3g** generated by the **6c** catalyzed reaction.

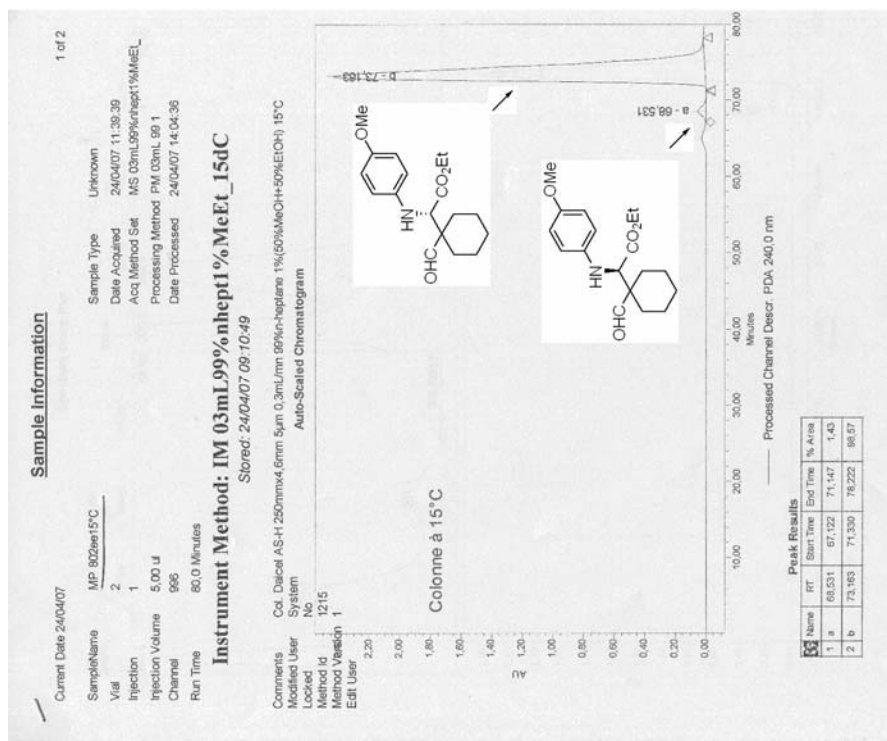


Figure 9. HPLC chart of racemic **3j** generated by the racemic proline catalyzed reaction.

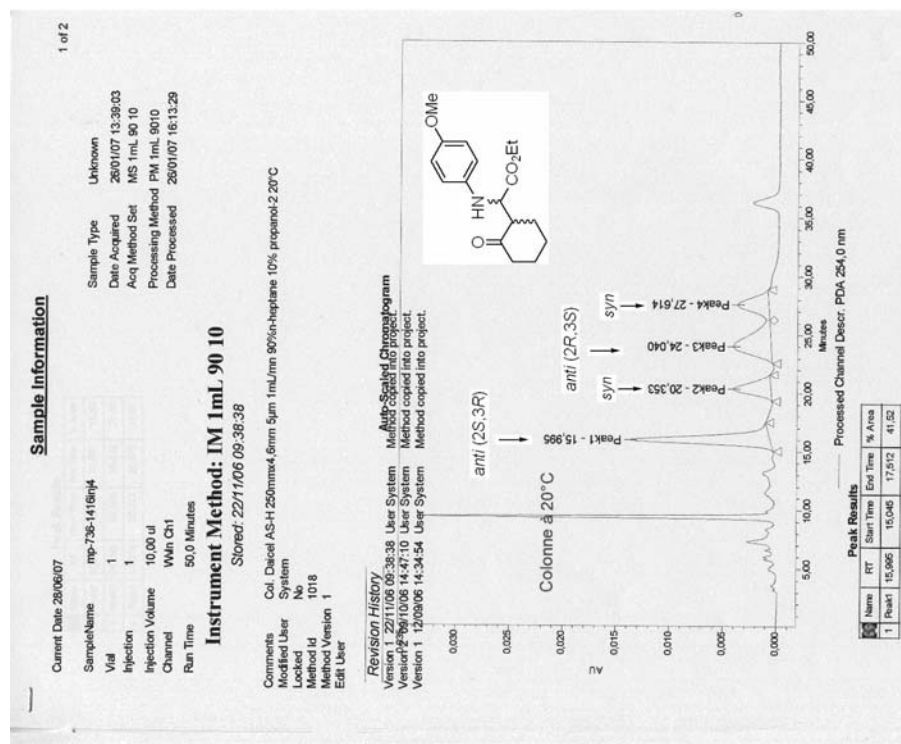


Figure 10. HPLC chart of (2*S*,3*R*)-**3j** generated by the **6c** catalyzed reaction.

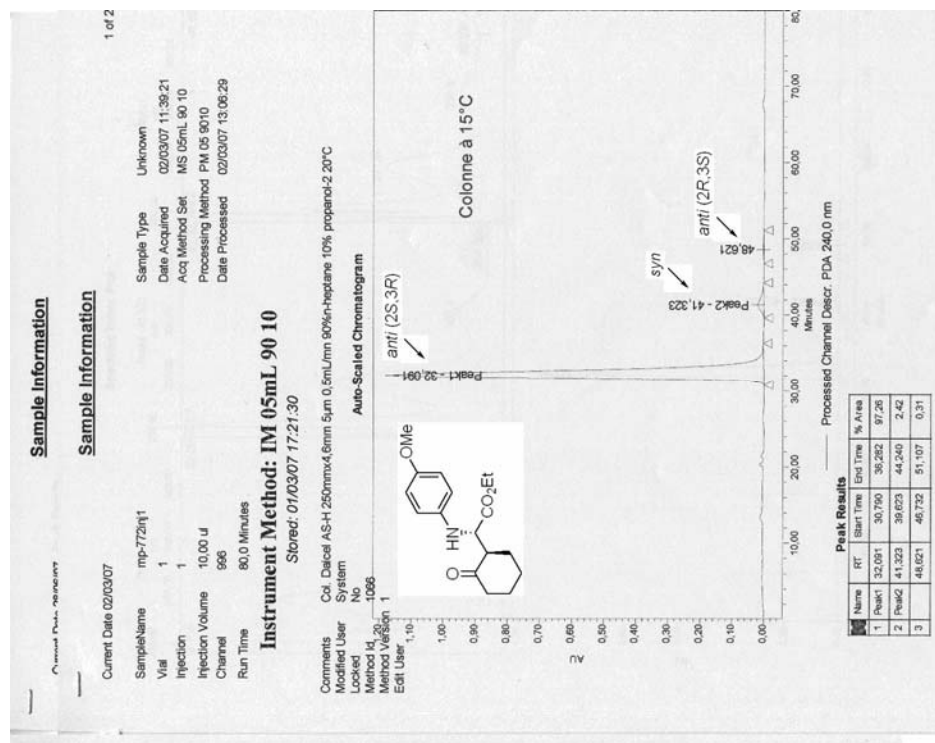


Figure 11. HPLC chart of racemic **3i** generated by the racemic proline catalyzed reaction.

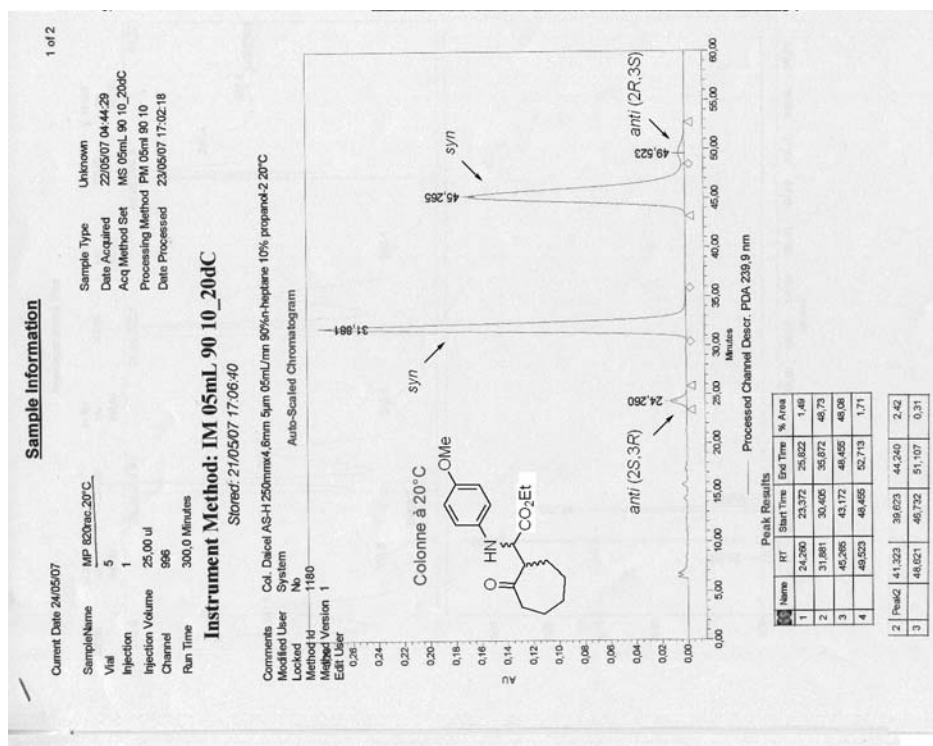
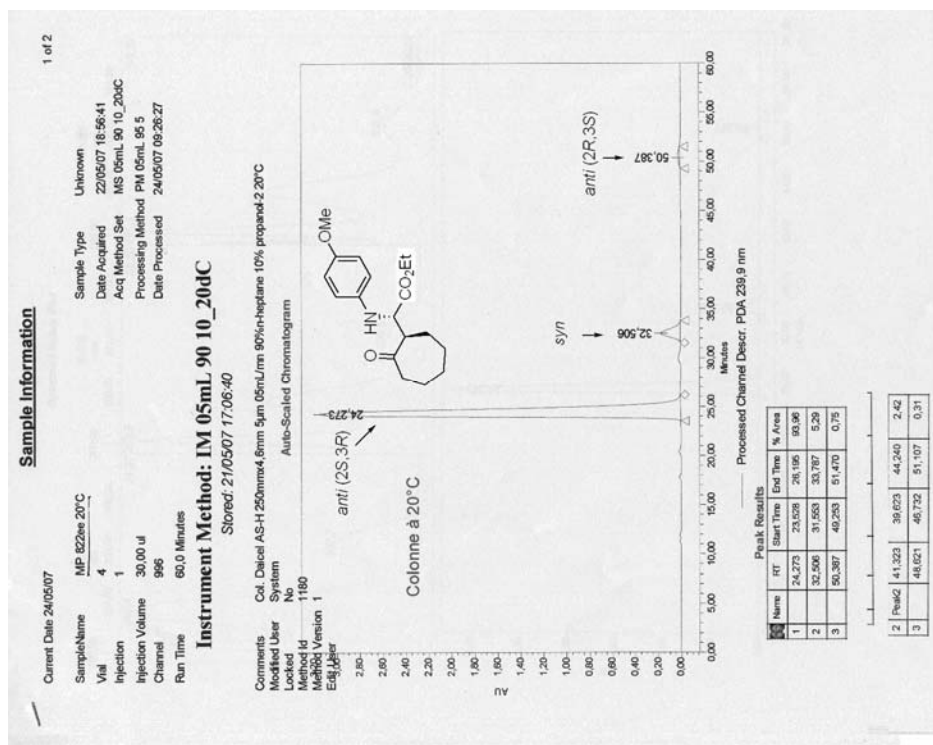
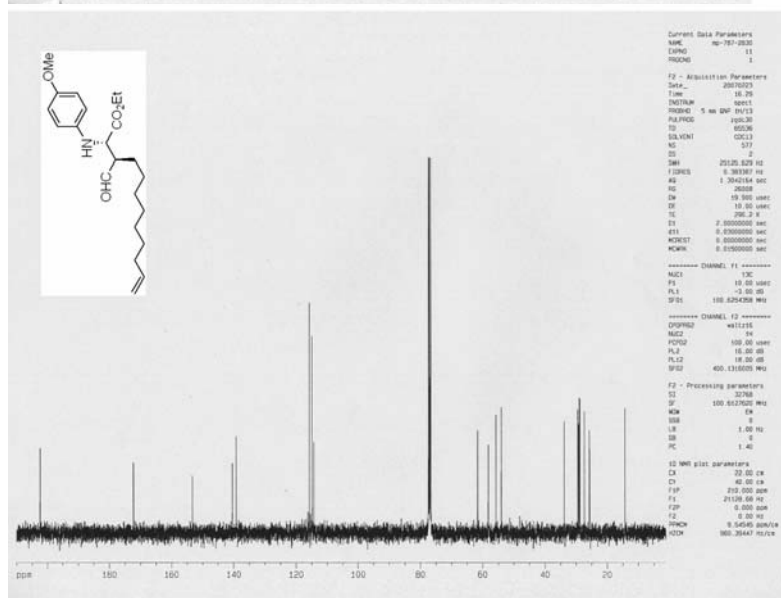
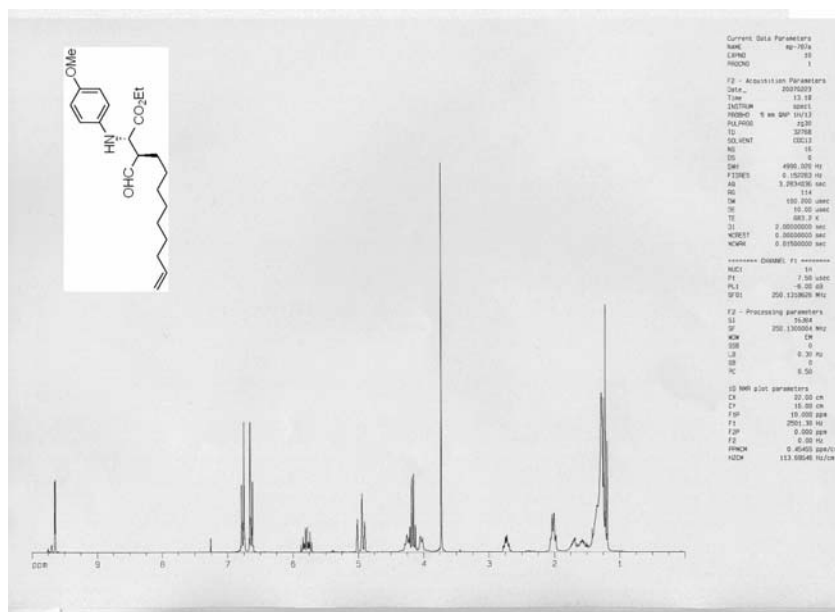


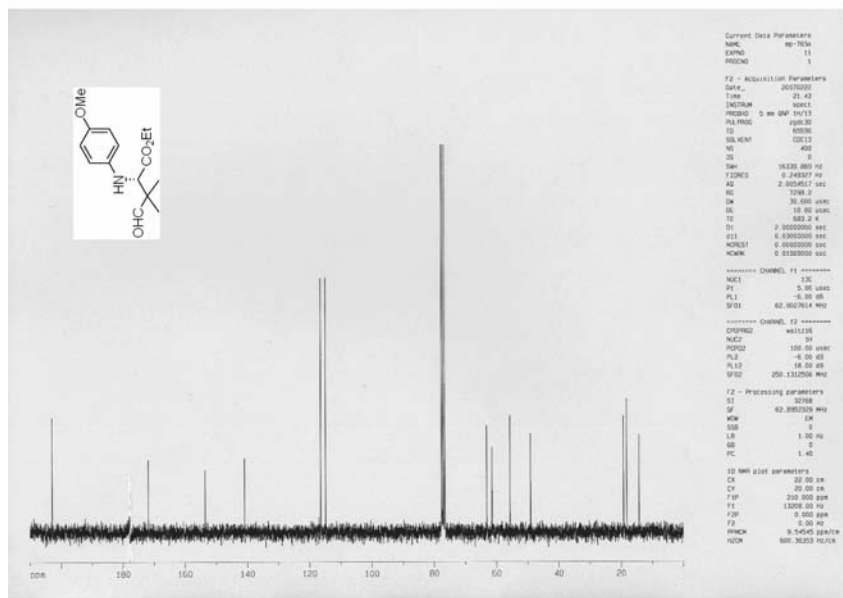
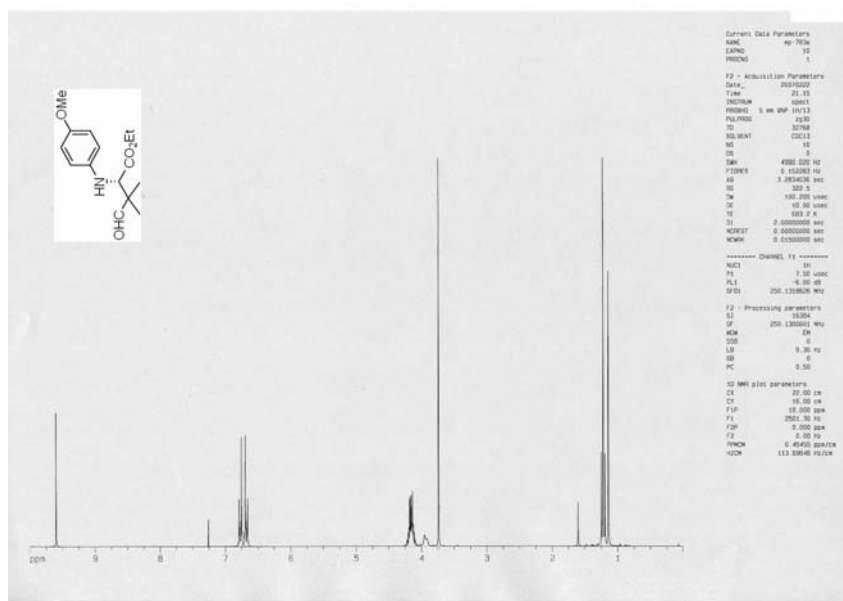
Figure 12. HPLC chart of (2*S*)-**3i** generated by the **6c** catalyzed reaction.



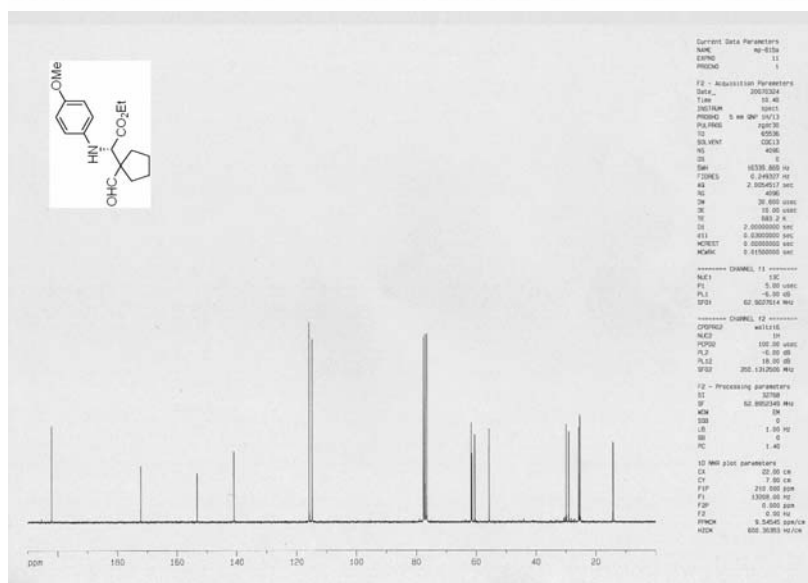
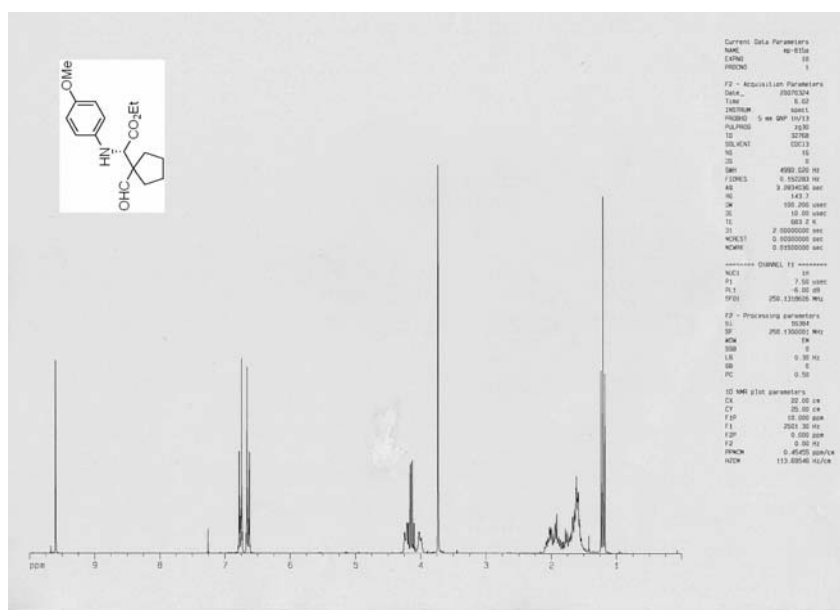
S20. NMR of 3c.



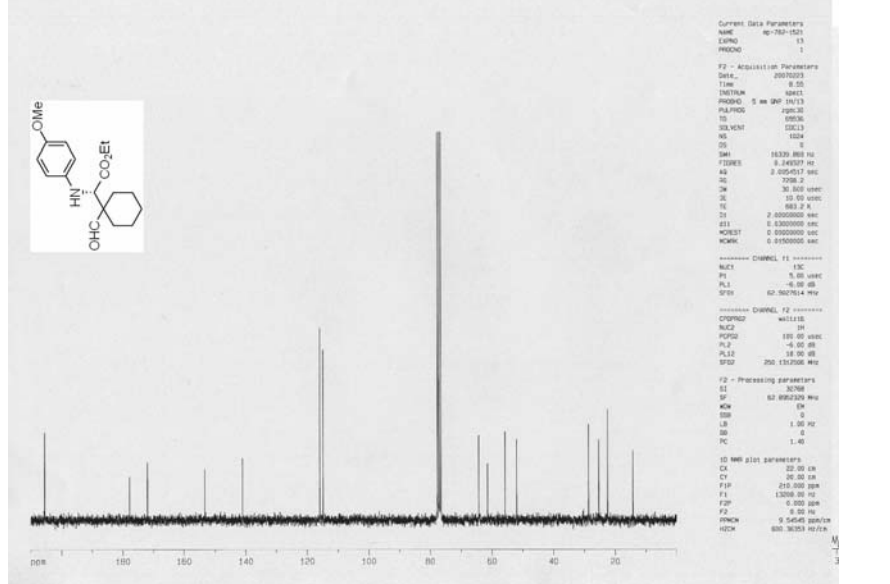
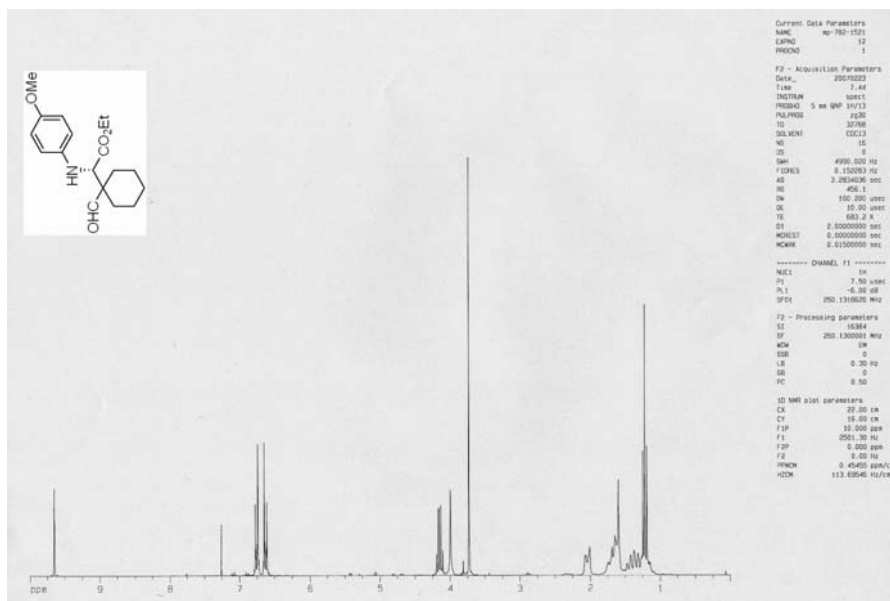
S21. NMR of 3e.



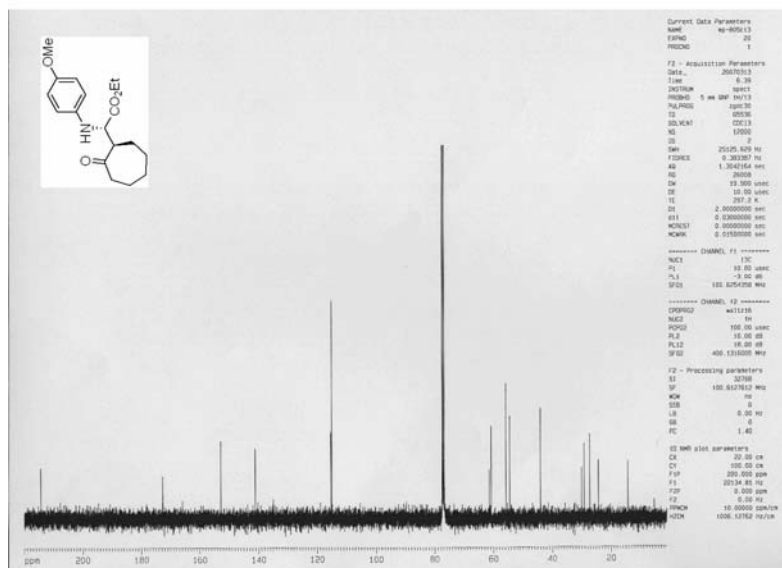
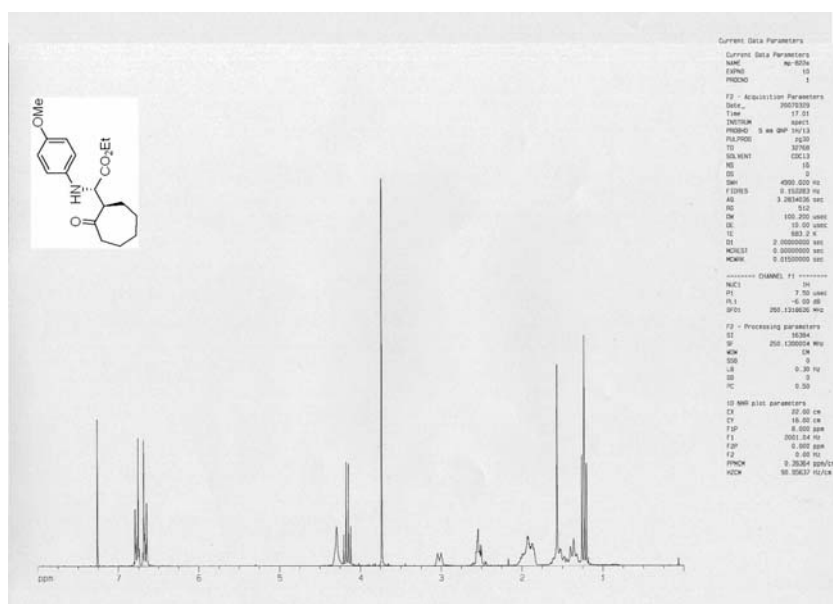
S22. NMR of **3f**.



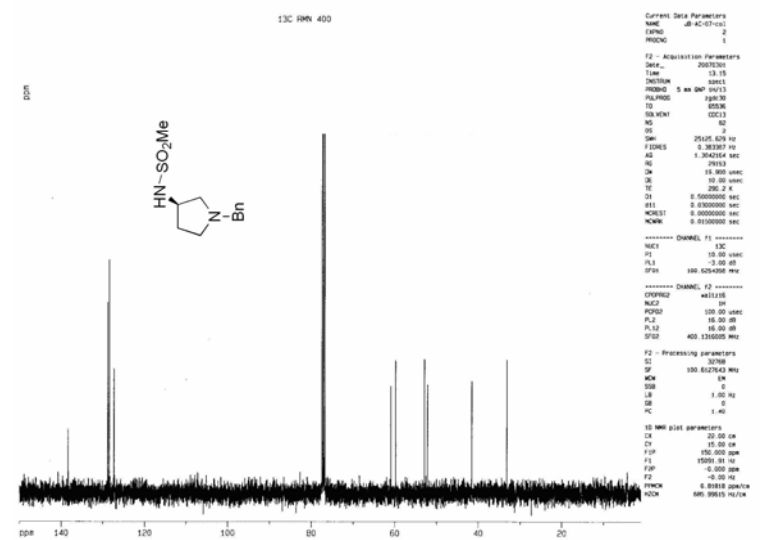
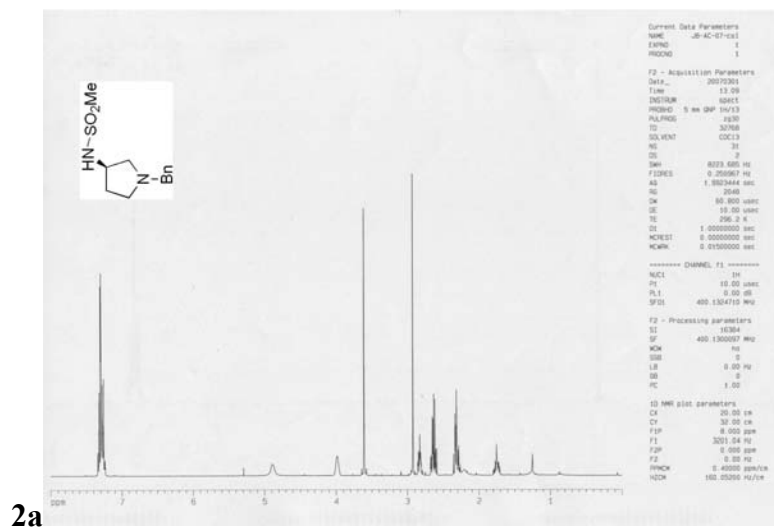
S23. NMR of 3g.



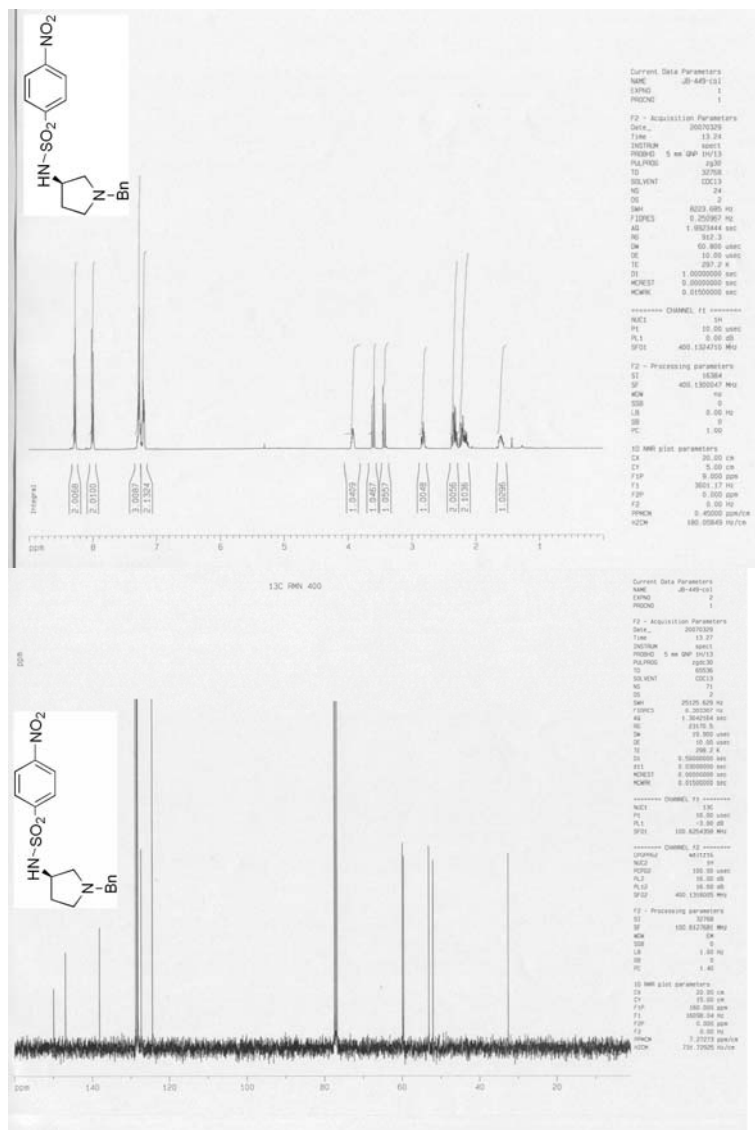
S24. NMR of **3i**.



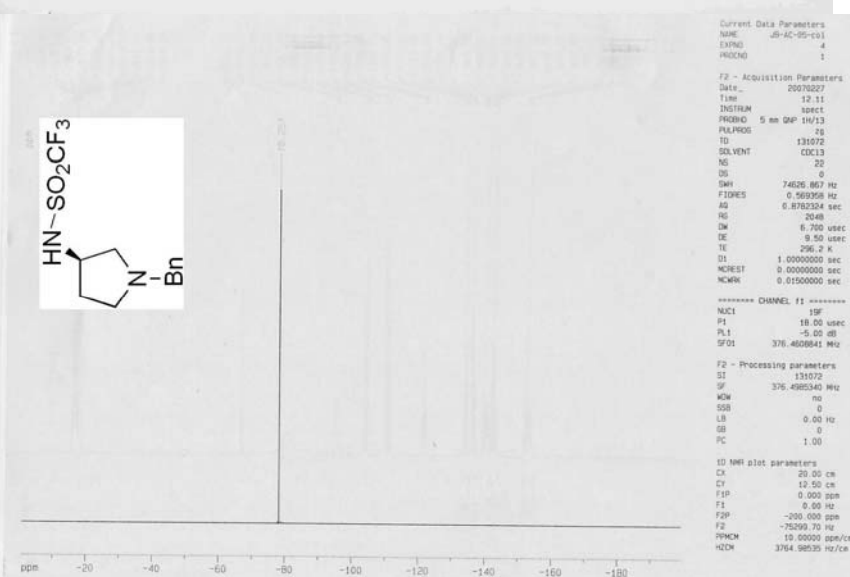
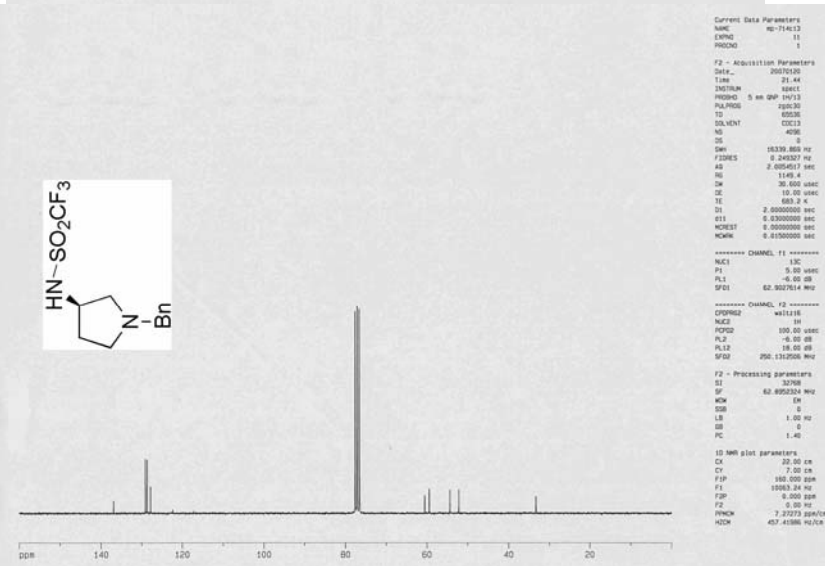
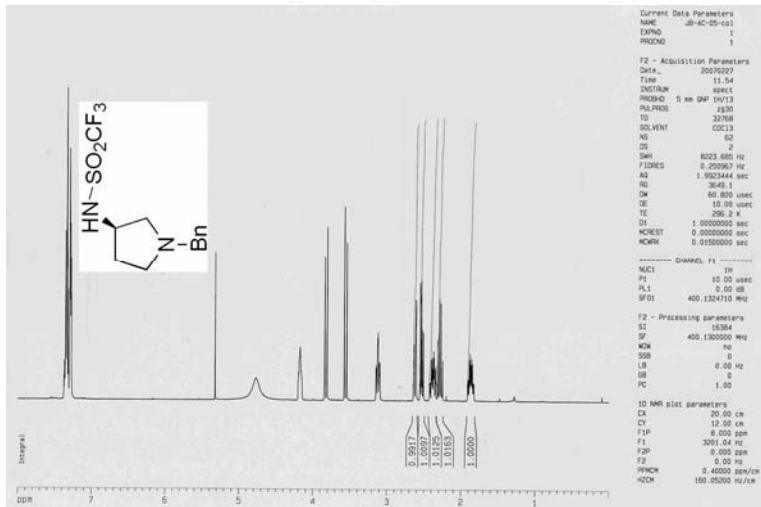
S25. NMR of precursor **5a**



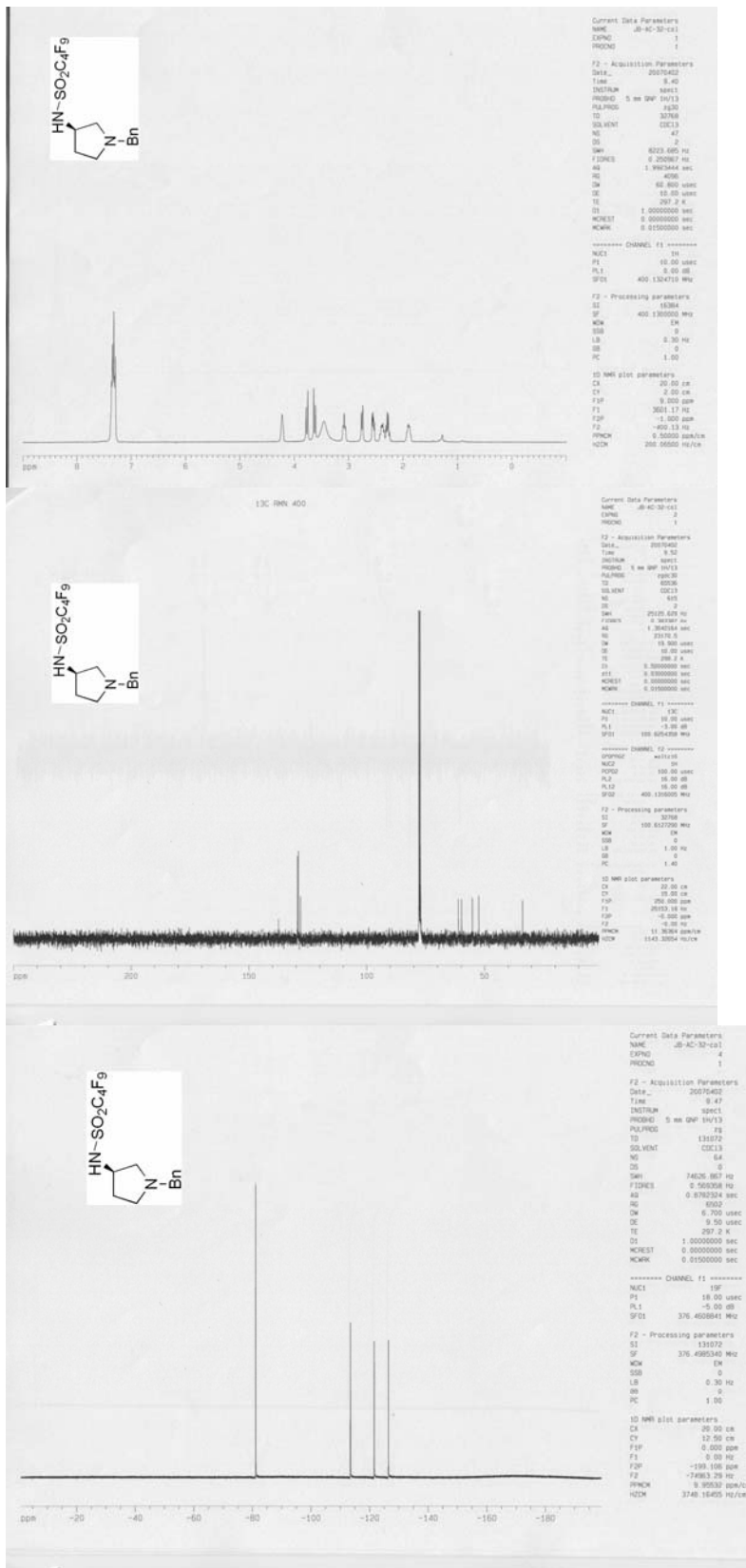
S26. NMR of precursor **5b**



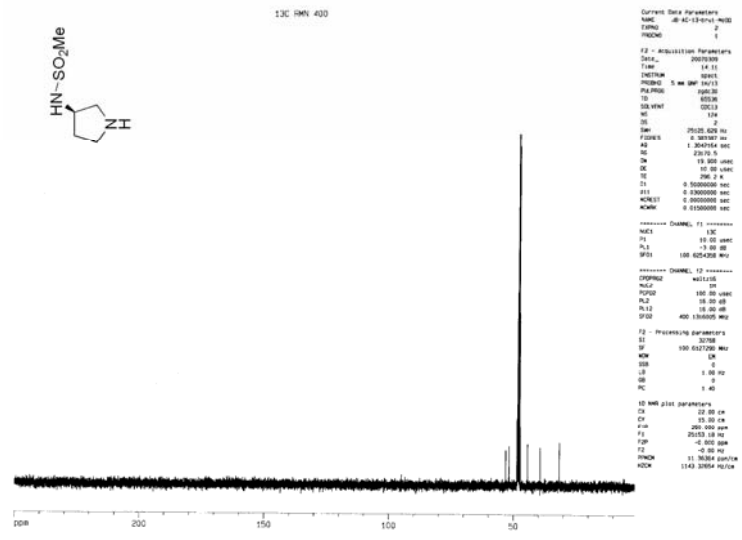
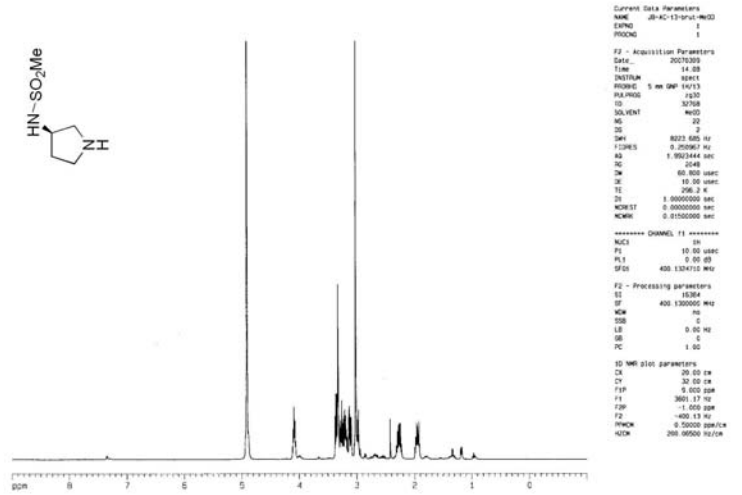
S27. NMR of precursor **5c**



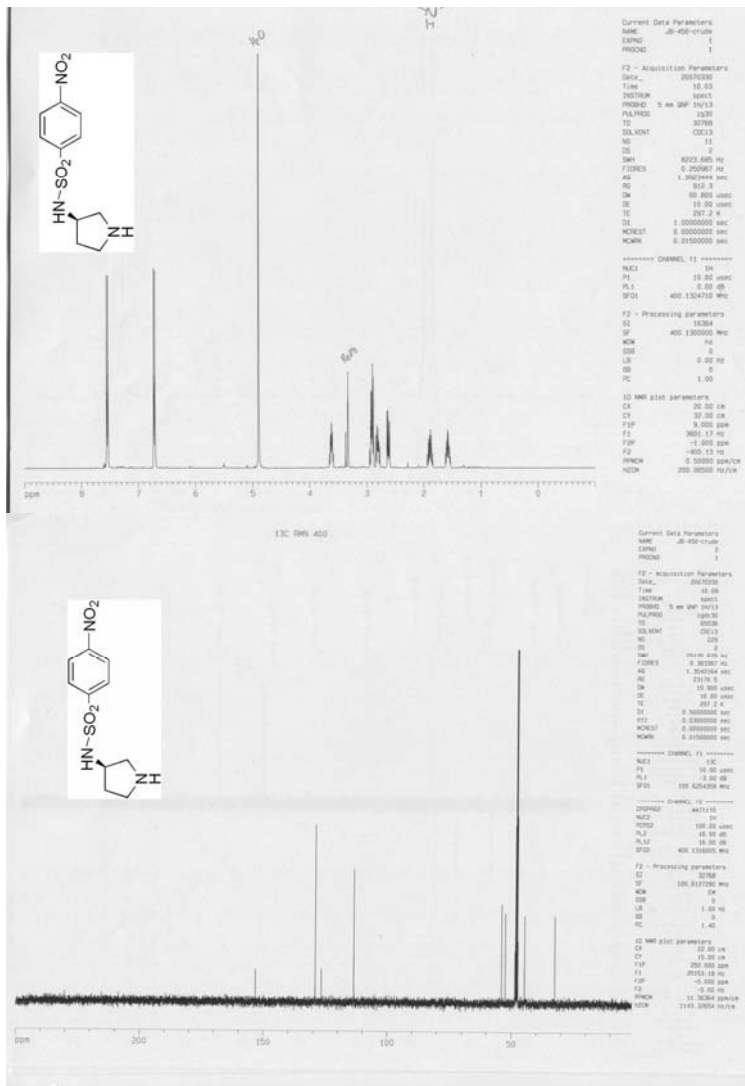
S28. NMR of precursor 5d



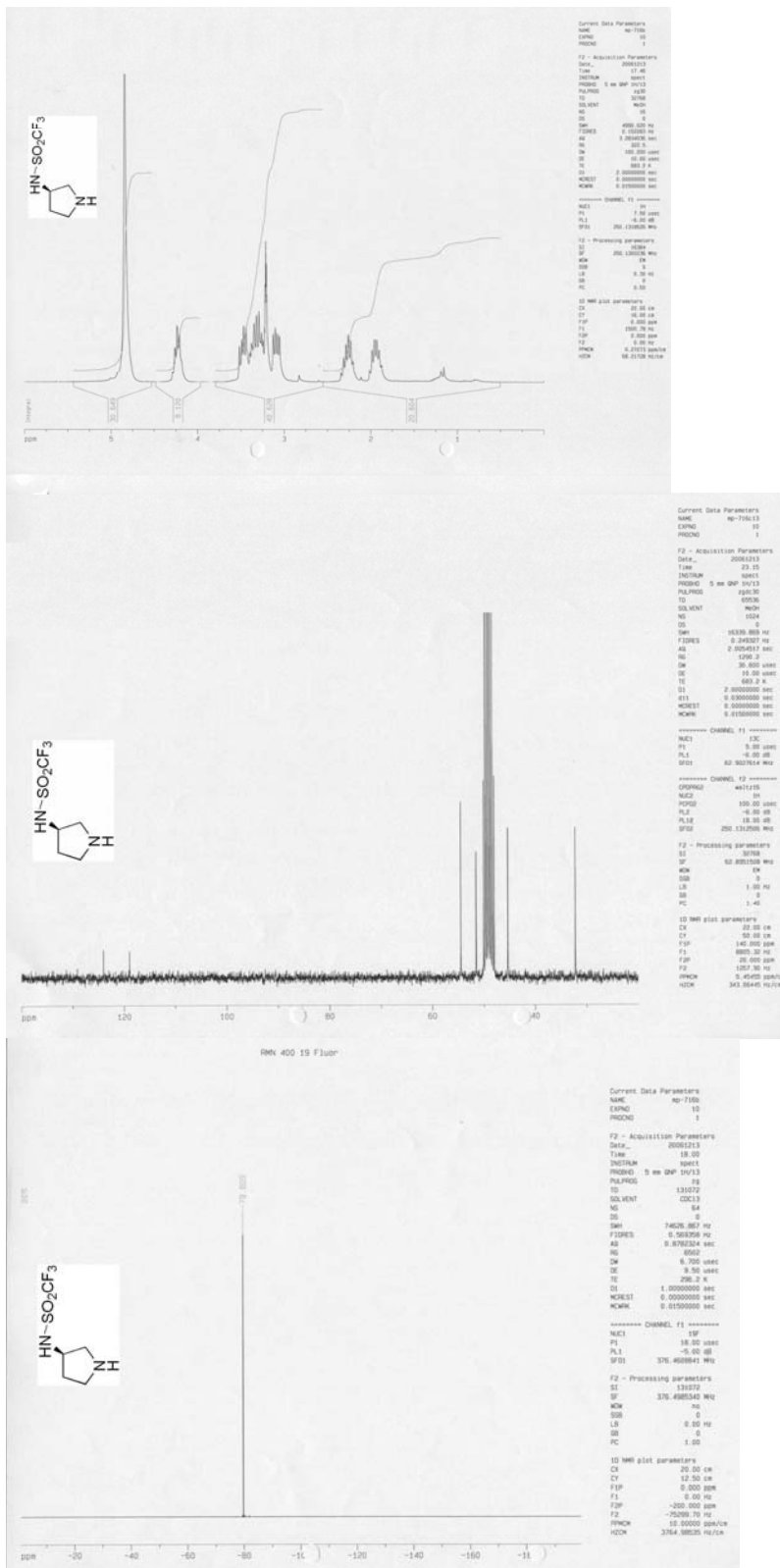
S29. NMR of the catalys 6a



S30. NMR of the catalys **6b**



S31. NMR of the catalys 6c



S32. NMR of the catalys 6d

