Supplementary Material (ESI) for Chemical Communications

Efficient Separation of a Trifluoromethyl Substituted Organocatalyst: Just Add Water

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Supporting Information

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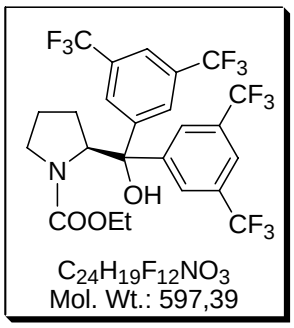
Contents

General Information. Nuclear Magnetic Resonance spectra (NMR) were acquired on a Varian UNITY INOVA (400 MHz) instrument using $CDCl_3$ as internal standard and Varian Gemini 2000 (200 MHz) instrument using $CDCl_3$ as internal standard. Chemical shifts are given in ppm, coupling constants (*J*) are given in hertz (Hz). IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrophotometer and are reported in wavenumbers (cm^{-1}). Mass spectra were recorded on a PE Sciex API 2000 triple-quadrupole mass spectrometer equipped with a Turbo Ion Spray source and Waters Quattro Micro triple quadrupole mass spectrometer (Manchester, UK). For column chromatography, Merck Silica gel 60 was employed. Enantiomer ratios were determined by a chiral HPLC analysis on a Waters 600 with Waters 996 Photodiode Array Detector using Chiracel OD or OJ column (0.46×25 cm). The product purity was also determined by GC analysis using Agilent 6850 with HP-5 column (30 m×0.25 mm×0.25 μm). Elemental analyses were performed on the Vario EL III. For product sublimation Büchi Glass Oven B-585 was used.

Materials. Trimethyl borate, 3-Acetylpyridine (**5d**) and C-18 reverse phase silica gel (DSC-18 SPE cartridge 0.5 grams) were purchased from Aldrich. The nonstabilizated BH_3•THF 1.0 M in THF and BH_3•DMS were obtained from Fluka. LiCl was purchased from Riedel-de-Haën. Fluorous reverse phase silica gel (FluoroFlash^{TM} SPE cartridge 2 grams, 8 ccm tube) was purchased from Fluorous Technologies Inc. THF and diethyl-ether were distilled from sodium/benzophenone prior to use. Corundum (EKF-100) was obtained from MOTIM Ltd. Diphenyl-prolinols **IIa**, **2** were prepared as described in the literature.[1] Diaryl prolinols **3**[2] and **4**[3] are known compounds, but we modified their synthesis, so their synthetic intermediates are novel compounds.

General procedure for the synthesis of protected fluorinated diphenyl-prolinols IIb,c. 2-[Bis-(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid ethyl ester as an example (IIc, Procedure A)

A thoroughly dried two-necked round-bottom flask was equipped with reflux condenser, additional funnel and argon inlet. Then magnesium powder (2.08 g, 85.6 mmol, activated by iodine) and 80 mL of dry diethyl-ether were placed into this apparatus. The solution of 1-bromo-3,5-bis-trifluoromethyl-benzene (21.54 g, 73.5 mmol) in dry diethyl-ether (20 mL) was slowly added over a period of 30 min at such a rate that maintain a gentle reflux. ***Safety:*** *Trifluoromethyl Aryl-Grignards can result in an uncontrollable exotherm reaction with the potential for detonation!*[4] When the addition was complete the mixture was refluxed for an additional 2 h (the Grignard solution was reddish brown). After it was cooled down to 0°C, a solution of the L-proline derivative **I**[1] (5.69 g, 28.28 mmol) in dry diethyl-ether (20 mL) was introduced at 0°C and the reaction mixture was stirred overnight. The reaction was quenched with 100 mL saturated aqueous NH_4Cl. The aqueous and organic-phase was separated and the aqueous-phase was extracted three times with 100 mL $CHCl_3$. Combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by crystallization from methyl-cyclohexane to give **IIc** as an off white solid (15.88 g, 94 %, m.p. 126-128 °C). TLC (Merck Aluminium oxide 60 F_{254}, hexanes : EtOAc = 9:1, R_f = 0.63). Highly pure **IIc** can be obtained via sublimation.



$C_{24}H_{19}F_{12}NO_3$
Mol. Wt.: 597,39

^{1}H-NMR (400 MHz, $CDCl_3$, δ_{TMS} = 0 ppm) 7.89 (s, 1H), 7.86 (s, 3H), 7.82 (s, 2H), 6.98 (br s, 1H), 4.86 (dd, *J* = 8.6, 3.2 Hz, 1H), 4.14 (m, 2H), 3.55 (m, 1H), 2.94 (m, 1H), 2.10 (m, 1H), 1.79 (m, 1H), 1.64 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.03 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ_{CDCl_3} = 77.16 ppm) 158.9 (C=O), 147.3 (C), 145.3 (C), 131.9 (q, *J* = 39 Hz, C), 131.6 (q, *J* = 39 Hz, C), 128.1 (q, *J* = 2 Hz, CH), 127.7 (q, *J* = 2 Hz, CH), 123.3 (q, J = 272.4 Hz, CF_3) 122.2 (*J* = 4 Hz, CH), 122.1 (*J* = 4 Hz, CH), 80.9 (C), 66.9 (CH), 62.9 (CH_2), 48.2

(CH_2), 30.4 (CH_2), 23.4 (CH_2), 14.6 (CH_3); IR (KBr) ν cm^{-1}; 3365, 2991, 2361, 1666, 1278, 1170, 1125, 704, 682; $[\alpha]_D^{27}$ = –45 (*c* = 1.0, $CHCl_3$). Anal. Calcd. For $C_{24}H_{19}F_{12}NO_3$: N, 2.34; C, 48.25; H, 3.21. Found N, 2.29; C, 48.21; H, 2.99

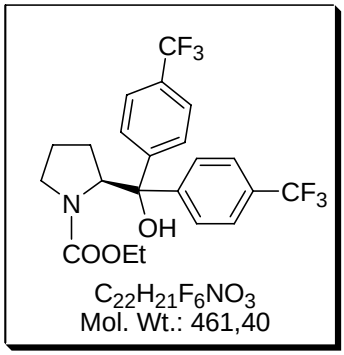
General procedure for the synthesis of protected fluorinated diphenyl-prolinols IIb,c Safe, scaleable, trans-Grignard approach. 2-[Bis-(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid ethyl ester as an example (IIc, Procedure B).

A thoroughly dried two-necked round-bottom flask was equipped with reflux condenser, additional funnel and argon inlet. Then magnesium powder (4.37 g, 0.18 mol, activated by iodine) and 80 mL of dry THF were placed into this apparatus. The solution of 2-bromopropane (20.90 g, 0.17 mol) in dry THF (20 mL) was slowly added over a period of 30 min at such a rate that maintain a gentle reflux. When the addition was complete the mixture was refluxed for an additional 2 h. Then it was cooled to 20°C and LiCl (7.20 g 0.17 mol) was added in parts. After 30 min it was transfered to the solution of 1-bromo-3,5-bis-trifluormethyl-benzene (0.17 mol, 49.81 g) in 100 mL dry THF at 0 °C. Then a the solution of the L-proline derivative **I**[1] (12.7 g, 68.0 mmol) in dry THF (20 mL) was introduced at 0°C and the reaction mixture was stirred overnight. The reaction was quenched with 200 mL saturated aqueous solution of NH_4Cl. The aqueous and organic-phase was separated and the aqueous-phase was extracted three times with 100 mL $CHCl_3$. Combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was friction by a little amount of hexane to give **IIc** as a white solid (15.88 g, 94.0 %). TLC (Merck Aluminium oxide 60 F_{254}, hexanes : EtOAc = 9:1, R_f = 0.63).

2-[Bis-(4-trifluoromethyl-phenyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid ethyl ester (IIb)

This compound was prepared using 4-bromo-trifluoromethyl-benzene (16.54 g, 73.5 mmol) and magnesium (2.08 g, 85.56 mmol, activated by iodine) following the procedure A as above described. The crude product was purified again by crystallization from

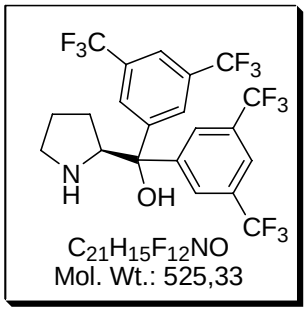
methyl-cyclohexane to give **IIb** as a white solid (11.97 g, 92 %, m.p. 124-125 °C). TLC (Merck Aluminium oxide 60 F_{254}, hexane : EtOAc = 9:1, R_f = 0.44).



^{1}H-NMR (400 MHz, $CDCl_3$, δ_{TMS} = 0 ppm) 7.54 (m, 8H), 6.40 (br s, 1H), 4.90 (dd, *J* = 8.8, 4.4 Hz, 1H), 4.13 (m, 2H), 3.49 (m, 1H), 2.99 (m, 1H), 2.10 (m, 1H), 1.90 (m, 1H), 1.57 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.95 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ_{CDCl_3} = 77.16 ppm) 158.7 (C=O), 149.6 (C), 147.4 (C), 129.95 (q, *J* = 32.4 Hz, C), 129.87 (q, *J* = 32.4 Hz, C) 128.5 (CH), 128.0 (CH), 125.2 (q, *J* = 3.4 Hz, CH), 124.7 (q, *J* = 3.6 Hz, CH), 124.3 (q, J = 270.6 Hz, CF_3) 81.4 (C), 66.3 (CH), 62.4 (CH_2), 48.0 (CH_2), 29.9 (CH_2), 23.3 (CH_2), 14.6 (CH_3); IR (KBr) ν cm^{-1} 3434, 2994, 2890, 1675, 1469, 1413, 1384, 1326, 1165, 1131, 1072, 1018, 832; $[\alpha]_D^{27}$ = –92 (*c* = 1.0, $CHCl_3$) Anal. Calcd. For $C_{22}H_{21}F_6NO_3$: N, 3.04; C, 57.27; H, 4.59. Found N, 2.81; C, 57.24; H, 4.48.

General procedure for the synthesis of fluorinated diphenyl-prolinols. Bis-(3,5-bis-trifluoromethyl-phenyl)-pyrrolidin-2-yl-methanol as an example (4)

To a mixture of 400 mL of 2.0 M KOH in MeOH was added fluorous prolinol derivative **IIc** (14.44 g, 24.2 mmol) and stirred under reflux for 5 h. The solution was concentrated in vacuoo, mixed with 200 mL of distilled water and extracted four times with 100 mL CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to furnish **4** as a pure white solid (12.16 g, 96 %). TLC (Merck Aluminium oxide 60 F_{254}, hexane : EtOAc = 9:1, R_f = 0.59).

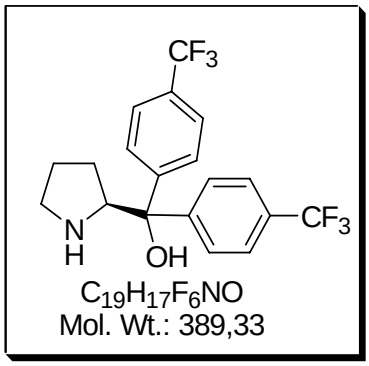


^{1}H-NMR (400 MHz, $CDCl_3$, δ_{TMS} = 0 ppm) 8.06 (s, 2H), 7.98 (s, 2H), 7.77 (s, 1H), 7.76 (s, 1H), 5.09 (br s, 1H), 4.36 (t, *J* = 7.6 Hz, 1H), 3.06 (m, 2H), 1.66 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ_{CDCl_3} = 77.16 ppm) 149.6 (C), 146.7 (C), 132.3 (q, *J* = 33.1 Hz, C), 132.0 (q, *J* = 33.1 Hz, C), 126.2 (q, *J* = 2.4 Hz,

CH), 125.8 (q, *J* = 2.5 Hz, CH), 123.4 (q, *J* = 271.1 Hz, CF_3), 121.7 (*J* = 3.5 Hz, CH), 121.5 (*J* = 3.7 Hz, CH) 76.8 (C), 64.4 (CH), 47.1 (CH_2), 26.9 (CH_2), 25.7 (CH_2); IR (KBr) ν cm^{-1}; 3419, 2988, 2924, 2880, 1628, 1468, 1377, 1281, 1167, 1133, 901, 892, 844, 713, 704, 683; $[\alpha]_D^{27}$ = –55 (*c* = 1.0, $CHCl_3$). Anal. Calcd. For $C_{21}H_{15}F_{12}NO$: N, 2.67; C, 48.01; H, 2.88. Found N, 2.46; C, 47.99; H, 2.68.

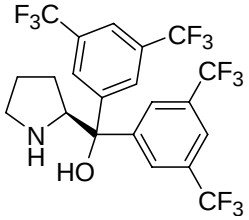
Pyrrolidin-2-yl-bis-(4-trifluoromethyl-phenyl)-methanol (3)

This compound was prepared using fluorous prolinol derivative **IIb** (5.58 g, 12.1 mmol) and 200 mL of 2.0 M KOH in MeOH following the procedure as above described to furnish **3** as a white solid (4.34 g, 92 %, m.p. 64-66 °C) TLC (Merck Aluminium oxide 60 F_{254}, hexane: EtOAc = 9:1, R_f = 0.12).



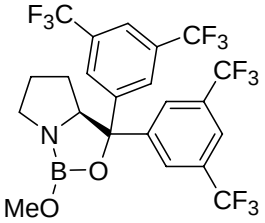
^{1}H-NMR (400 MHz, $CDCl_3$, δ_{TMS} = 0 ppm) 7.62 (m, 8H), 4.90 (br s, 1H), 4.30 (t, *J* = 8 Hz, 1H), 3.01 (m, 2H), 1.67 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ_{CDCl_3} = 77.16 ppm) 151.5 (C), 148.6 (C), 129.3 (q, *J* = 32.2 Hz, C), 129.2 (q, *J* = 32.2 Hz, C) 126.4 (CH), 126.0 (CH), 125.5 (q, J = 3.6 Hz, CH), 125.3 (q, J = 3.6 Hz, CH), 77.16 (C), 64.4 (CH), 47.0 (CH_2), 26.6 (CH_2), 25.6 (CH_2); IR (KBr) ν cm^{-1}; 3340, 2976, 2891, 2834, 1616, 1417, 1325, 1166, 1127, 1068, 1018, 830; $[\alpha]_D^{27}$ = –59 (*c* = 1.0, $CHCl_3$) Anal. Calcd. For $C_{19}H_{17}F_6NO$: N, 3.60; C, 58,94; H, 4.40. Found N, 3,3; C, 58.79; H, 4.19.

Procedure for asymmetric reduction of acetophenone (5a) with nonstabilized BH_3•THF complex. The precatalyt 4 was recovered by fluorous solid-phase extraction. (Table 1, entry 3).



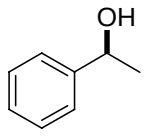
The precatalyst **4** (105.0 mg, 0.2 mmol) was dissolved in 2 mL 1M nonstabilized BH_3•THF complex. The mixture was stirred at room temperature for one hour, followed by slow addition of acetophenone (**5a**) (2.0 mmol) in 2 mL of dry THF over a period of one hour with syringe pump under argon atmosphere at room temperature. The reaction mixture was stirred for additional one hour to complete. Then it was cooled to 0°C and slowly quenched with 2 mL of MeOH. (Vigorous hydrogene gas evolution was observed). Then 2.0 g γ-Al_2O_3 was added to the reaction mixture and the whole was evaporated to dryness. Then this supported material was loaded onto fluorous silica gel cartridges and rinsed with MeOH-H_2O 1:1 (5×2 mL) to elute non-tagged product. Then the combined filtrates were extracted (3×10 mL) chloroform. The combined organic phases was dried over Na_2SO_4 and evaporated in vacuo to give **6a** as a pure product. The leaching of the **4** was determined by GC and MS experiments. Then the fluorinated precatalyst **4** was recovered by washing the fluorous silica gel with 10 mL diethyl-ether (85% efficiency, precatalyst **4** remained intact according to NMR).

Procedure for asymmetric reduction of ketones (5a-d) using in situ generated catalyst, (Table 1, entries 4, 6, 9, 10). The precatalyst 4 was recovered by different solid-phase extractions.



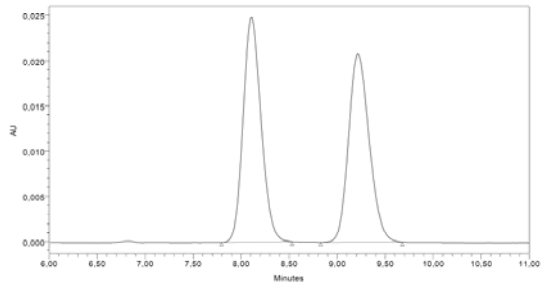
The precatalyst **4** (105.0 mg, 0.2 mmol) was dissolved in 2 mL of dry THF and trimethyl borate (25 mg, 28μL, 0.24 mmol) was added. The mixture was stirred at room temperature for one hour. Then 0.21 mL of BH_3•DMS (2 mmol, 1 equiv BH_3) was introduced under argon atmosphere at room temperature, followed by slow addition of ketones (**5a-d**) (2.0 mmol) in 2 mL of dry THF over a period of one hour with syringe pump. The reaction mixture was stirred for additional one hour to complete. Then it was cooled to 0°C and slowly quenched with 2 mL of MeOH.

(Vigorous hydrogene gas evolution was observed). Then 2.0 g γ- or α-Al_2O_3 was added to the reaction mixture and the whole was evaporated to dryness. Then this supported material was loaded onto filled cartridges (500mg DSC-18 or 1.0 g corrundum) and rinsed with MeOH-H_2O 1:1 (5×2 mL) (DMF: H_2O 1:1 for **6c)** to elute all non-tagged products. Then the combined filtrates were extracted (3×10 mL) chloroform. The combined organic phases was dried over Na_2SO_4 and evaporated in vacuo to give **6a-d** as a pure product. The leaching of the **4** was determined by GC and MS experiments. Then the fluorous precatalyst **4** was recovered by washing the cartridge with 10 mL diethyl-ether (precatalyst **4** remained intact according to NMR).



$C_8H_{10}O$
Mol. Wt.:
122,16

1-Phenyl-ethanol (6a)[5]: ^{1}H-NMR (200 MHz, $CDCl_3$) 7.40–7.25 (m, 5H, ArH), 4.88 (q, *J* = 6.3 Hz, 1H, C*H*OH), 2.10 (br s, 1H, OH), 1.49 (d, *J* = 6.3 Hz, 3H, C*H*$_3$CH); ^{13}C-NMR (50 MHz, $CDCl_3$) 145.9 (C), 128.6 (CH), 127.6 (CH), 125.5 (CH), 70.5 (CH), 25.2 (CH_3); ee = 94% Enantioselectivity was determined by HPLC analysis with a Chiracel OJ column, (hexane : i-PrOH = 90:10), 1 mL/min, λ = 210, retention times major: 9.1 min, retention times minor: 8.1 min. The product purity was determined with GC analysis using Agilent 6850 with HP-5 column (30 m×0.25 mm×0.25 μm), 160°C/2min, 5°C/min/200°C, retention time 2.86 min.



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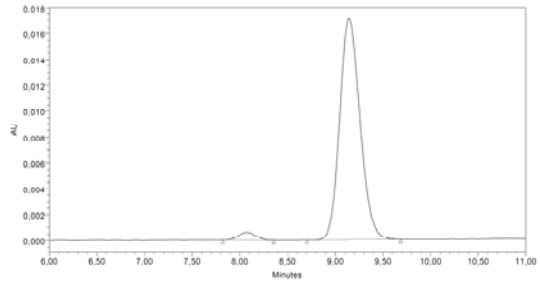
2	9,216	312289	49,12	20859



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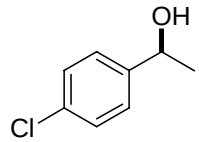
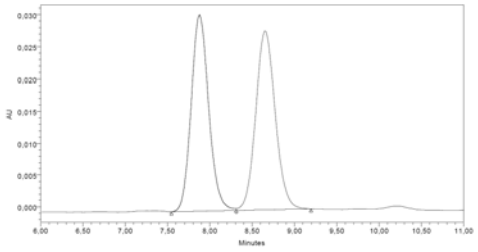
2	9,145	253323	97,01	17149



C_8H_9ClO
Mol. Wt.: 156,61

1-(4-Chloro-phenyl)-ethanol (6b)[6]: ^{1}H-NMR (200 MHz, $CDCl_3$) 7.28 (br s, 4H, ArH), 4.83 (q, *J* = 6.6 Hz, 1H, C*H*OH), 2.33 (br s, 1H, OH), 1.44 (d, *J* = 6.6 Hz, 3H, C*H*$_3$CH); ^{13}C-NMR (APT) (50 MHz, $CDCl_3$) 144.3 (C), 133.1 (C), 128.7 (CH), 126.9 (CH), 69.8

(CH), 25.3 (CH_3); ee = 95% Enantioselectivity was determined by HPLC analysis with a Chiracel OD column, (hexane : i-PrOH = 95:5), 1 mL/min, λ = 254, retention times minor: 7.8 min, retention times major: 8.5 min. The product purity was determined with GC analysis using Agilent 6850 with HP-5 column (30 m×0.25 mm×0.25 µm), 160°C/2min, 5°C/min/200°C, retention time 3.83 min.



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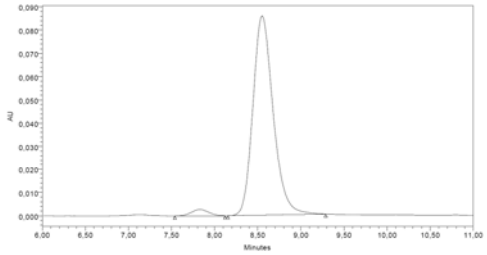
1	7,877	444213	49,64	30672
2	8,652	450673	50,36	27978



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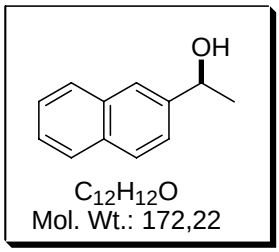
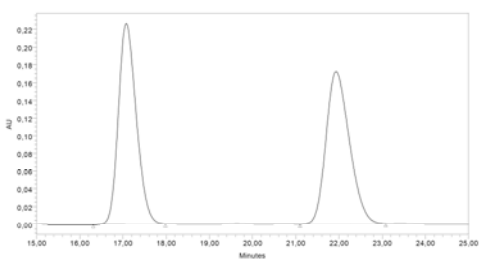
1	7,828	37401	2,59	2715
2	8,550	1405781	97,41	85894



1-Naphthalen-2-yl-ethanol (6c)[7]: ^{1}H-NMR (200 MHz, $CDCl_3$) 7.87–7.78 (m, 4H, ArH), 7.54–7.45 (m, 3H, ArH), 5.02 (q, *J* = 6.4 Hz, 1H, C*H*OH), 2.43 (br s, 1H, OH), 1.57 (d, *J* = 6.6 Hz, 3H, CH_3CH) ^{13}C-NMR (APT) (50 MHz, $CDCl_3$) 143.3 (C), 133.4 (C), 133.0 (C), 128.4 (CH), 128.0 (CH), 127.8 (CH), 126.2 (CH), 125.9 (CH), 123.94 (CH), 123.90 (CH), 70.5 (CH), 25.2 (CH_3); ee = 94 % Enantioselectivity was determined by HPLC analysis with a Chiralcel OJ column, (hexane : i-PrOH = 90:10), 1 mL/min, λ = 254, retention times minor 17.3 min, retention times major 22.1 min. The product purity was determined with GC analysis using Agilent 6850 with HP-5 column (30 m×0.25 mm×0.25 µm), 160°C/2min, 5°C/min/200°C, retention time 7.9 min.



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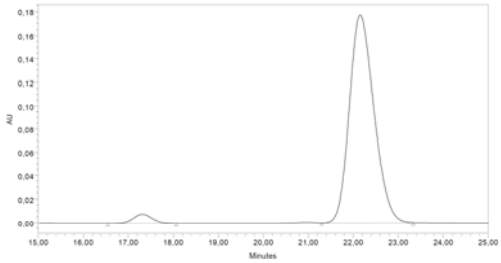
2	21,931	6485160	49,90	171814



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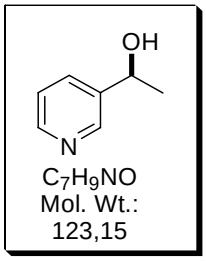
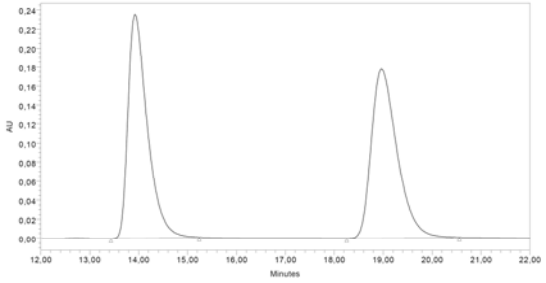
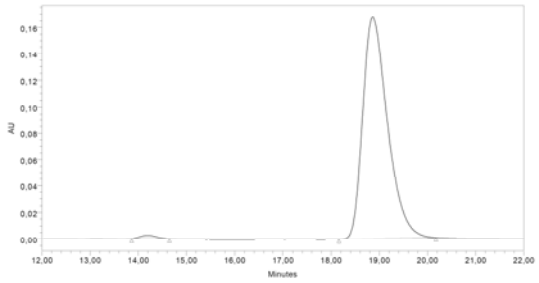
1	17,317	220589	3,17	7706
2	22,154	6727787	96,83	177083



1-(pyridin-3-yl)ethanol (6d)[8]: ^{1}H-NMR (200 MHz, $CDCl_3$) 8.53 (s, 1H, ArH), 8.41 (d, *J* = 5.4 Hz, 1H, ArH), 7.93 (d, *J* = 7.6 Hz, 1 H, ArH), 7.46 (dd, *J* = 7.8 Hz, *J* = 5.6 Hz, 1H, ArH), 4.97 (q, *J* = 6.2 Hz, 1H, C*H*OH), 2.93 (br s, 1H, OH), 1.49 (d, *J* = 6.2 Hz, 3H, C*H*$_3$CH) ^{13}C-NMR (APT) (50 MHz, $CDCl_3$) 146.1 (CH), 145.2 (CH), 144.1 (C), 136.5 (CH), 125.2 (CH), 67.2 (CH), 25.3 (CH_3); ee = 98% Enantioselectivity was determined by HPLC analysis with a Chiralcel OJ column, (hexane : i-PrOH = 95:5), 1 mL/min, λ = 254, retention times minor 14.2 min, retention times major 18.8 min. The product purity was determined with GC analysis using Agilent 6850 with HP-5 column (30 m×0.25 mm×0.25 μm), 160°C/2min, 5°C/min/200°C, retention time 3.26 min.

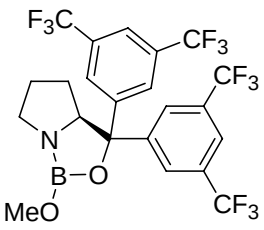


	RT	Area	% Area	Height
1	13,928	6470788	49,90	235554
2	18,966	6496944	50,10	178014



	RT	Area	% Area	Height
1	14,192	67139	1,11	2801
2	18,864	5989752	98,89	167817

Procedure for asymmetric synthesis of pyridinol 6d using in situ generated catalyst. The precatalyst 4 was recovered by liquid-liquid extraction.

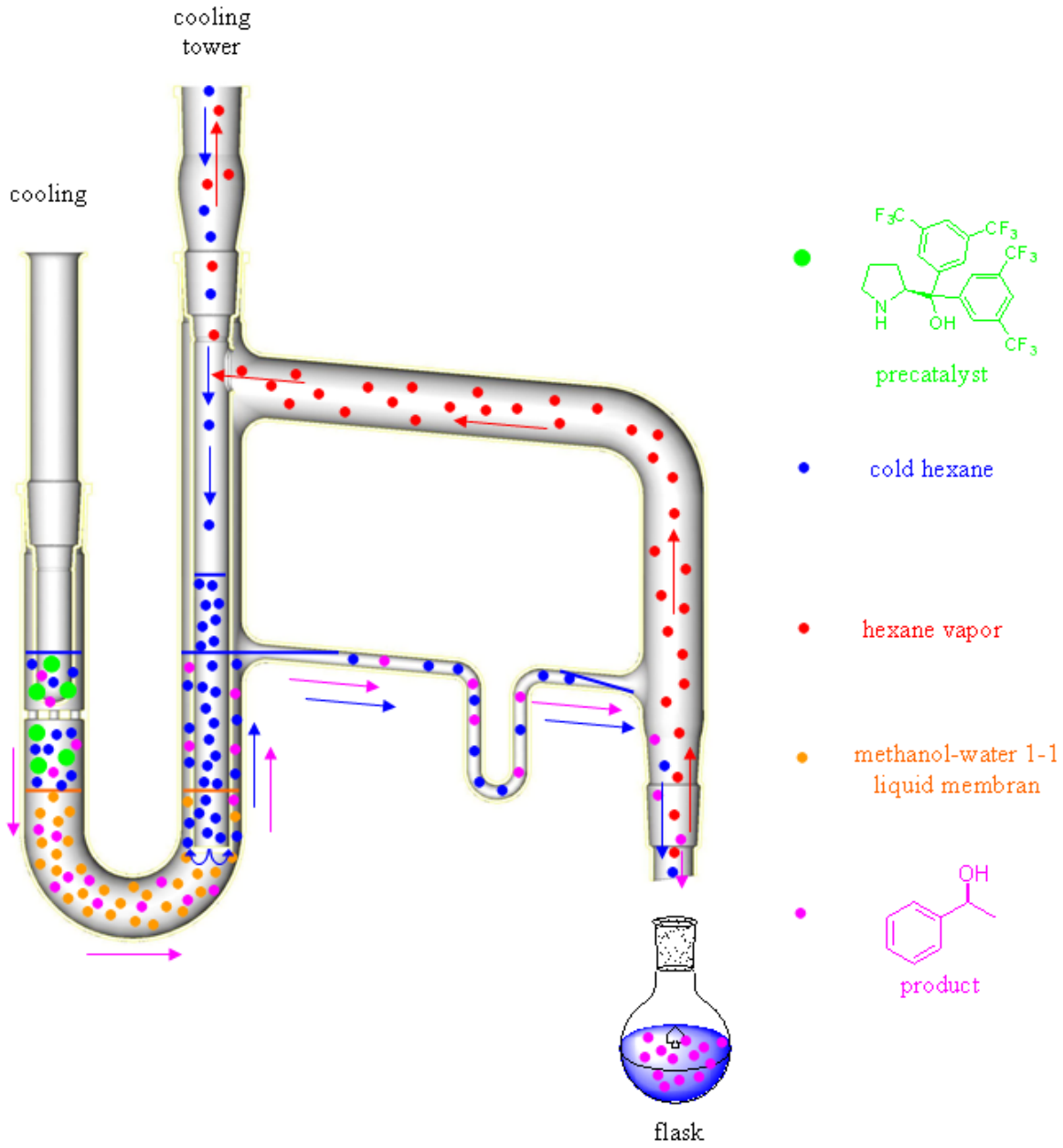


The precatalyst **4** (1315 mg, 2.5 mmol) was dissolved in 25 mL of dry THF and trimethyl borate (312 mg, 351μL, 3.0 mmol) was added. The mixture was stirred at room temperature for one hour. Then 5.3 mL of BH_3•DMS (50 mmol, 2 equiv. BH_3) was introduced under argon atmosphere at room temperature, followed by slow addition of **5d** (3.05 g, 25 mmol) in 25 mL of dry THF over a period of one hour with syringe pump. The reaction mixture was stirred for additional one hour to complete. Then it was cooled to 0°C and slowly quenched with 25 mL of MeOH. (Use well

ventilled fume hood, vigorous hydrogene gas evolution was observed). Then the quenched reaction mixture was concentrated and partitioned between 80 mL hexane and 10mL CH_3CN and 40 mL water mixture. The aqueous phase was extracted with chloroform, dried over Na_2SO_4 and evaporated in vacuo to give 2.95g **6d** (96% yield) as an opalescue oil. The upper phase was concentrated to give 1308 mg of precatalyst **4** (99.5% recovery efficiency) without any contaminant (checked by GC and NMR). Finally, this catalyst was recycled two more times without any deleterious effect on yields and enantioselectivities.

Procedure for asymmetric synthesis of 6a,b using in situ generated catalyst. The precatalyst 4 was recovered by continuous U-tube extractor with methanol-water (1:1 vol ratio) liquid membran.

These compounds were prepared using the above procedure in a 25 mmol scale. However, the quenched and concentrated reaction product was purified by the following continuous U-tube extractor. After 8h distillation this approach yielded the pure **6a** and **6b** in 89% and 90% after the evaporation of the hexanes from the distillation pot. The precatalyst **4** was recovered by >99% efficiency after the concentration of the feeding solution without any contaminant (checked by GC and NMR).



Picture and Schematic Illustration of the Continuous U-tube extraction

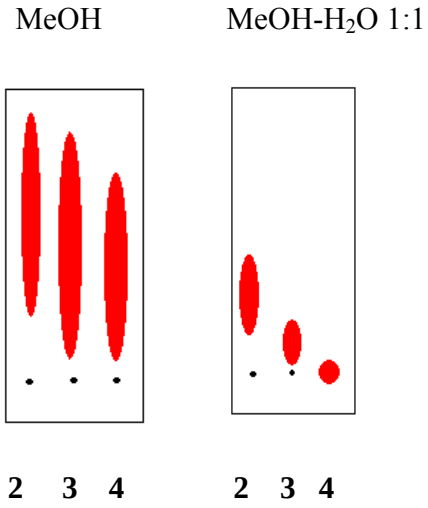
The principle element of the above apparatus is its ability to sustain a chemical potential gradient of the extracted materials until the feeding solution is depleted. The constantly redestilled extracting phase in the receiver arm facilitates the passive diffusion of the extracted material and syphones into a distillation pot. Moreover, by appropriate tuning of the liquid membrane, it is possible to retain a certain chemicals (e.g. tagged **4**) in the

feeding solution and allow the transfer of the other entity into the receiver solution. Continuous heating of the distillation pot generate renewed extracting phase and finally lead to the concentration of the target molecule in the flask. Of course, this set up is functioning only, if the boiling point of the extracted molecule and the extracting solvent (e.g. hexanes) are markedly different.

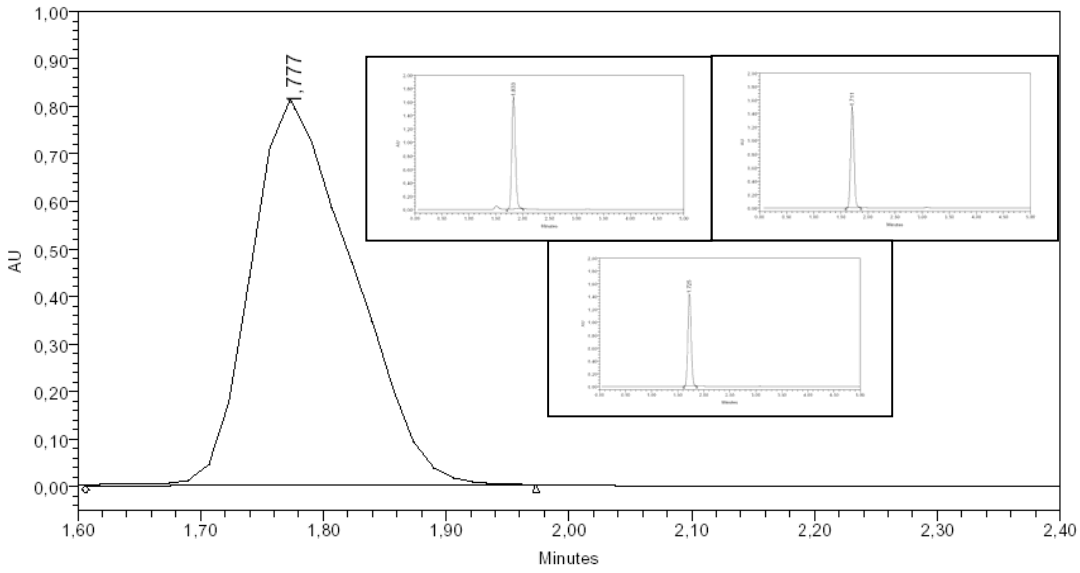
This apparatus is able to direct the hexanes vapor (because of the syphone) into the condenser and the inner-tube. This inner tube contains a porous frit at the bottom and immerses a little bit into the liquid membrane. During the extraction, the condensed hexanes fill up the inner tube until it reaches certain height when the hydrostatic pressure of hexanes is enough big to press the hexane trhough the frit and form small bubbles. Their increased surface area is also beneficial and increases the efficiency of the extraction.

Reversed phase TLC and HPLC experiments

Solvent tuning in TLC experiments



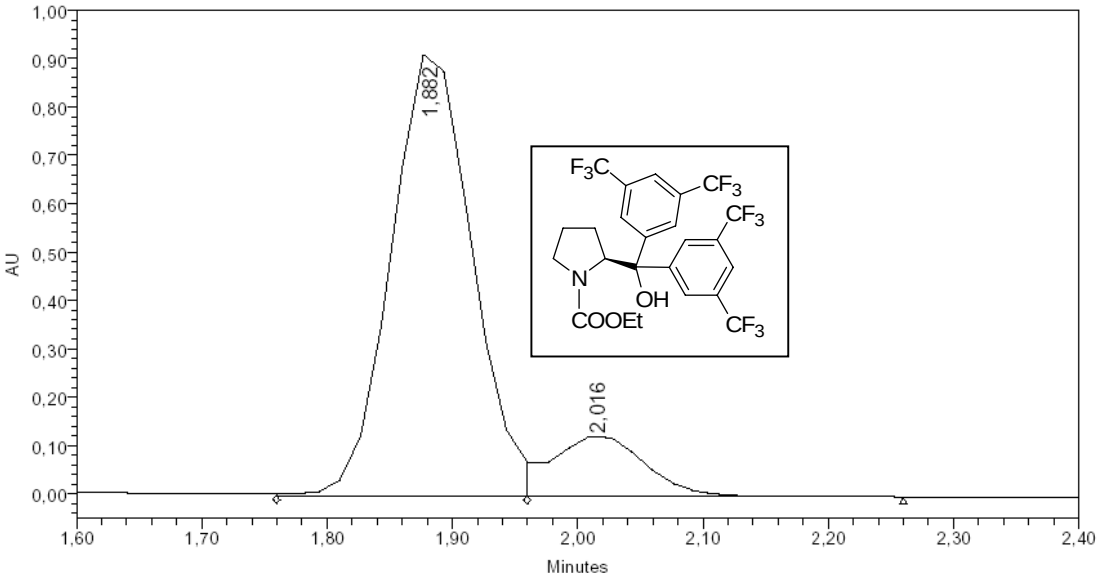
Solvent tuning in HPLC using Nucleosil 100 C-18 reversed phase column 5µm, 15x 0.4 cm.



CH_3CN-H_2O 100-0

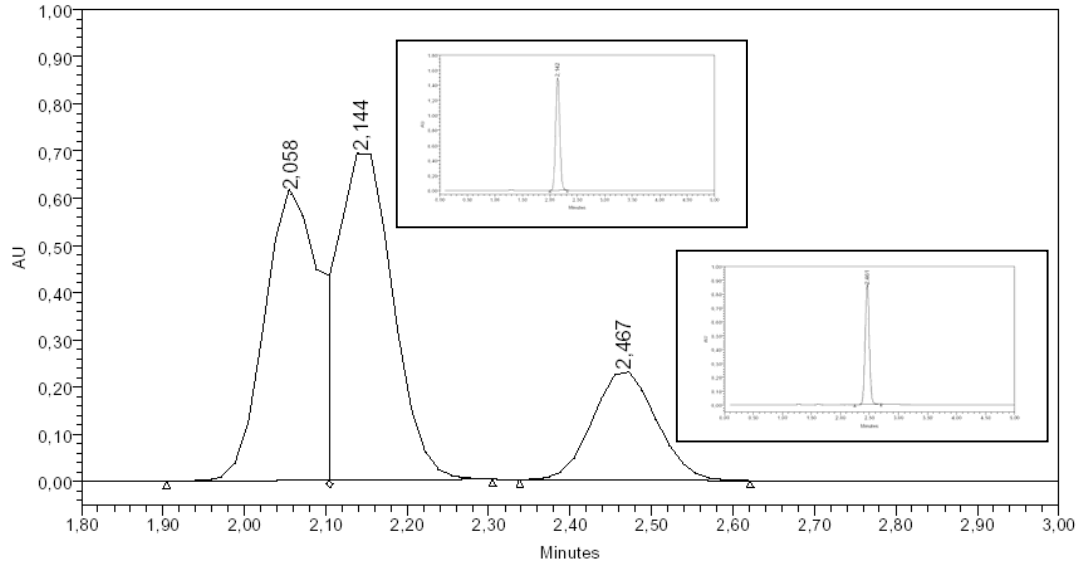
The retention times are the following:

2-(Diphenyl-Hydroxy-methyl)-pyrrolidine-1-carboxylic acid ethyl ester (**IIa**).: 1.83 min
2-[bis-(4-trifluoromethyl-hydroxy-phenyl)-methyl]-pyrrolidine-1-carboxylic acid ethyl ester (**IIb**): 1.71 min
2-[Bis-(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid ethyl ester (**IIc**): 1.73



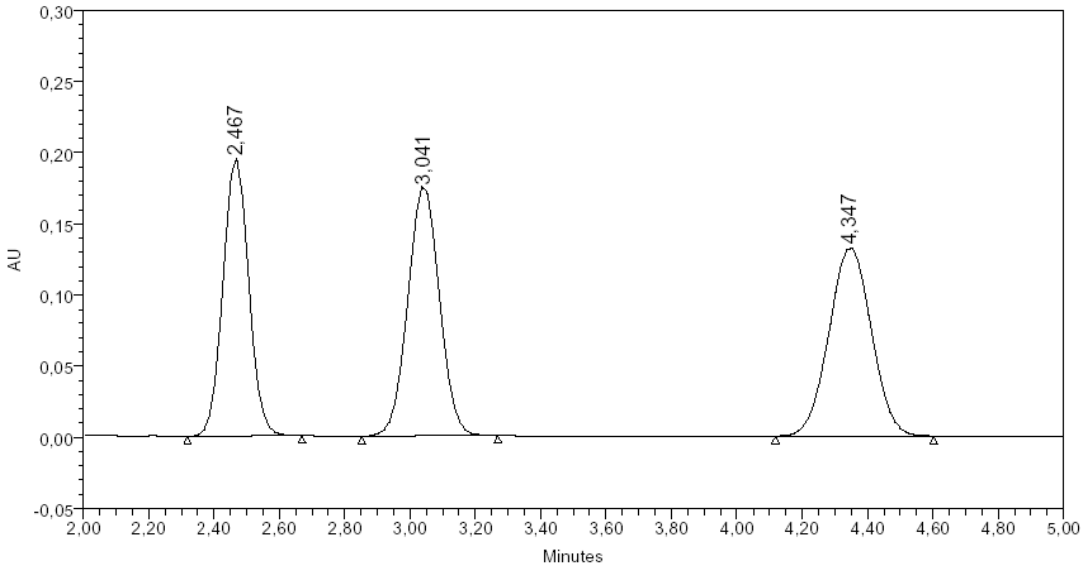
CH_3CN-H_2O 95-5

The 2-[Bis-(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid ethyl ester has already started to differentiated.

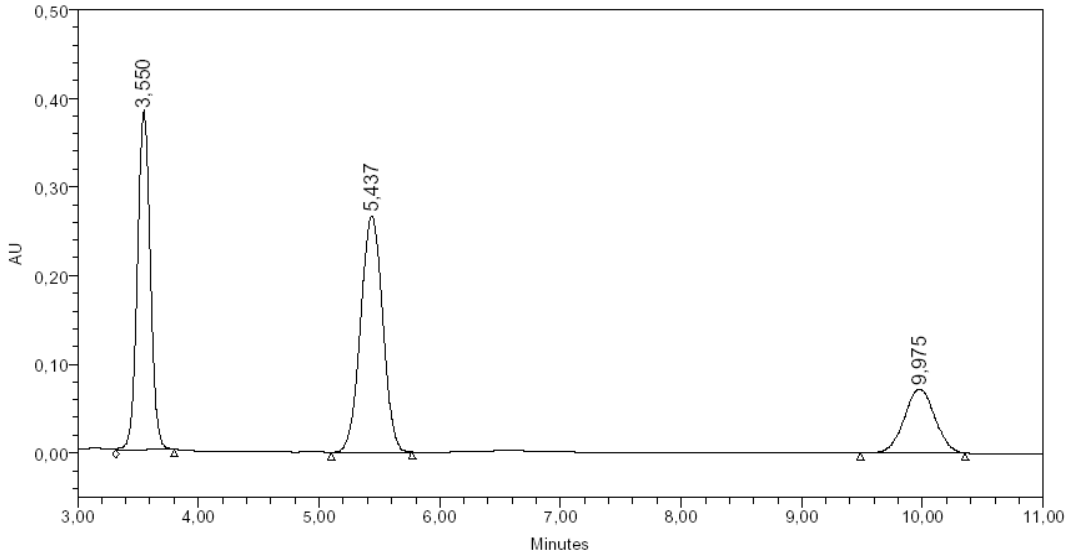


CH_3CN-H_2O 90-10
The retention times are the following:

2-(Diphenyl-hydroxy-methyl)-pyrrolidine-1-carboxylic acid ethyl ester (**IIa**).: 2.06 min
2-[Bis-(4-trifluoromethyl-phenyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid ethyl ester (**IIb**).: 2.14 min
2-[Bis-(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid ethyl ester (**IIc**).: 2.47 min



CH_3CN-H_2O 80-20
The retention times are the following:
2-(Diphenyl-hydroxy-methyl)-pyrrolidine-1-carboxylic acid ethyl ester (**IIa**): 2.47 min
2-[Bis-(4-trifluoromethyl-phenyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid ethyl ester (**IIb**): 3.04 min
2-[Bis-(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid ethyl ester (**IIc**): 4.35 min



CH_3CN-H_2O 70-30

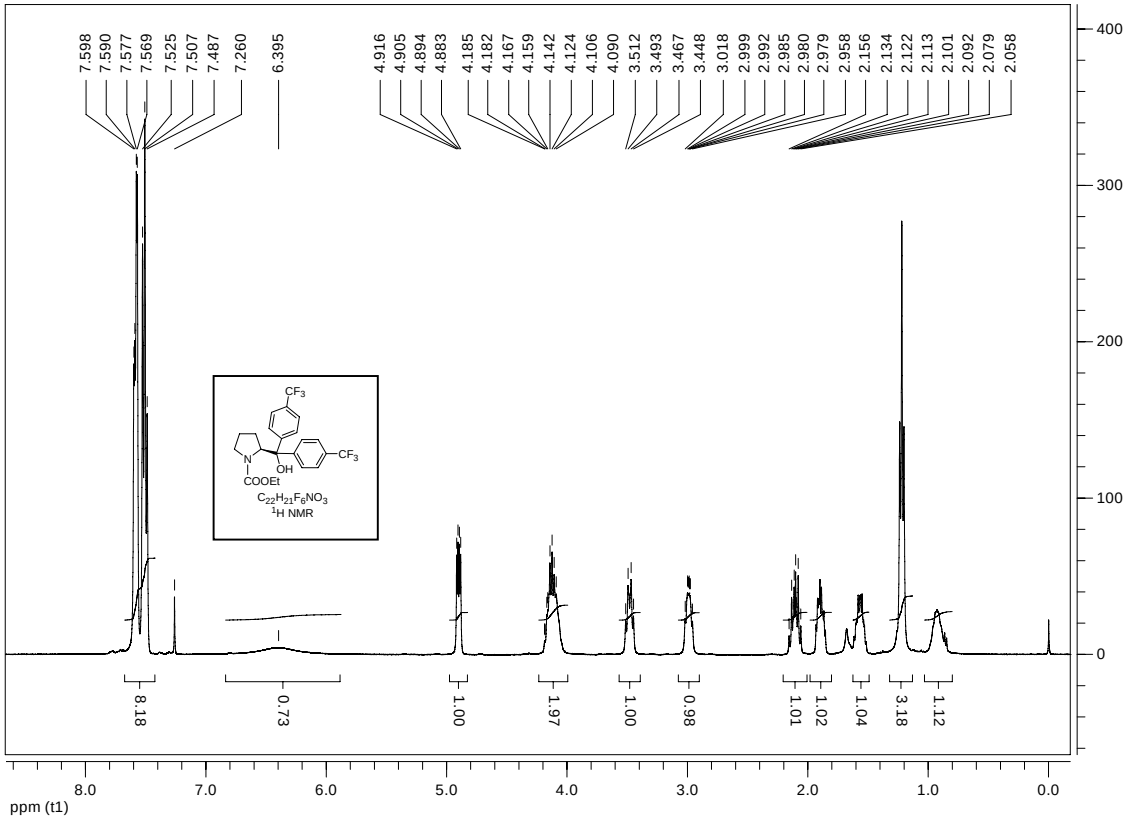
The retention times are the following:

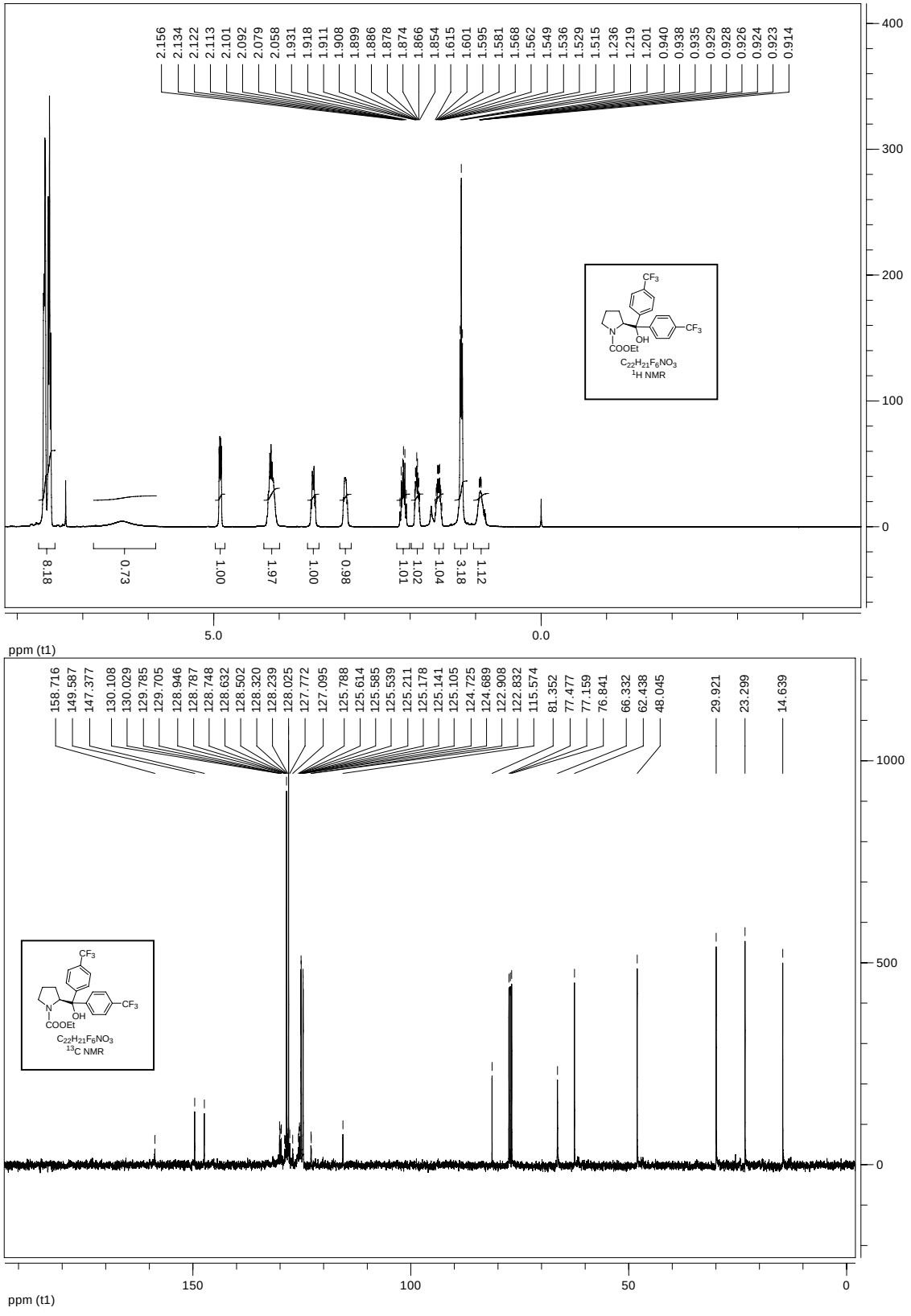
2-(Diphenyl- Hydroxy-methyl)-pyrrolidine-1-carboxylic acid ethyl ester (**IIa**).: 3.55 min

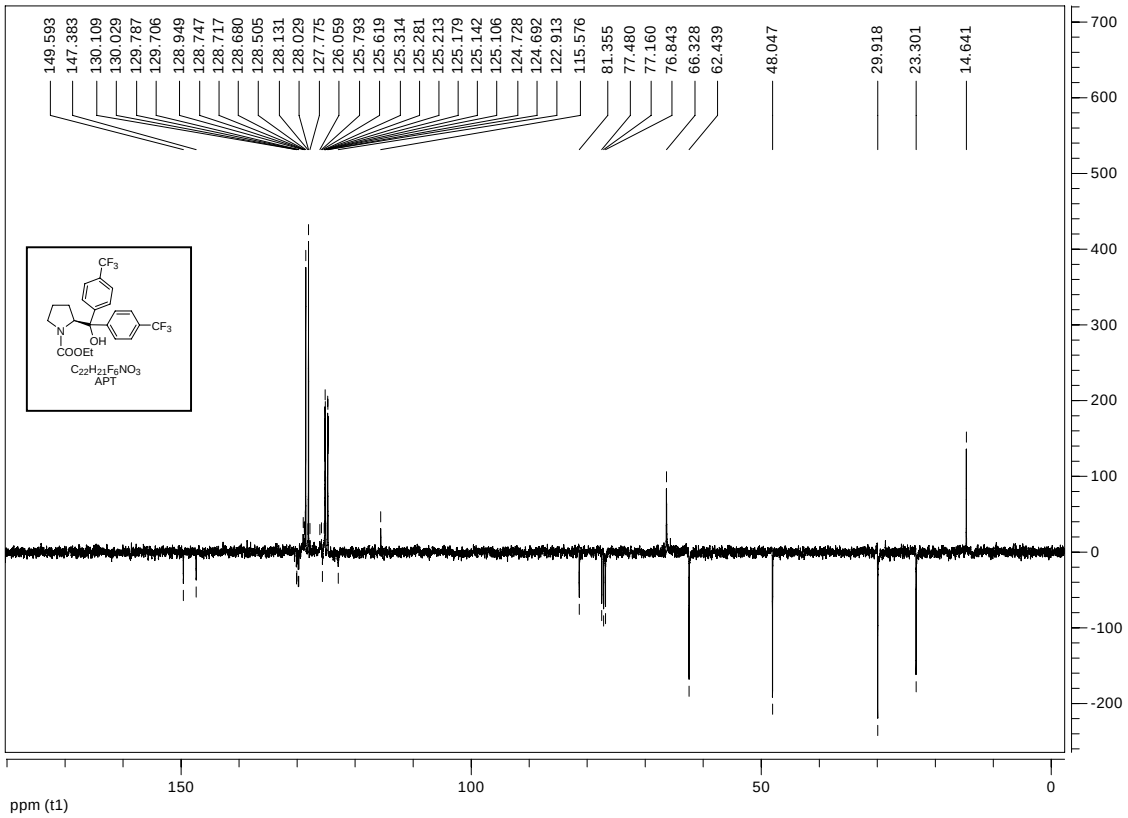
2-[Bis-(4-trifluoromethyl-phenyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid 5ethyl ester (**IIb**): 5.44 min

2-[Bis-(3,5-bis-trifluoromethyl-phenyl)-hydroxy-methyl]-pyrrolidine-1-carboxylic acid ethyl ester (**IIc**): 9.98 min

NMR spectras




2.156
2.134
2.122
2.113
2.101
2.092
2.079
2.058
1.931
1.918
1.911
1.908
1.899
1.886
1.878
1.874
1.866
1.854
1.615
1.601
1.595
1.581
1.568
1.562
1.549
1.536
1.529
1.515
1.236
1.219
1.201
0.940
0.938
0.935
0.929
0.928
0.926
0.924
0.923
0.914
8.18
0.73
1.00
1.97
1.00
0.88
1.01
1.02
1.04
3.18
1.12
5.0
0.0
ppm (t1)
$C_{22}H_{21}F_6NO_3$
^{1}H NMR
158.716
149.587
147.377
130.108
130.029
129.785
129.705
128.946
128.787
128.748
128.632
128.502
128.320
128.239
128.025
127.772
127.095
125.788
125.614
125.585
125.539
125.211
125.178
125.141
125.105
124.725
124.689
122.908
122.832
115.574
81.352
77.477
77.159
76.841
66.332
62.438
48.045
29.921
23.299
14.639
150
100
50
0
ppm (t1)
$C_{22}H_{21}F_6NO_3$
^{13}C NMR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130.029
129.787
129.706
128.949
128.747
128.717
128.680
128.505
128.131
128.029
127.775
126.059
125.793
125.619
125.314
125.281
125.213
125.179
125.142
125.106
124.728
124.692
122.913
115.576
81.355
77.480
77.160
76.843
66.328
62.439
48.047
29.918
23.301
14.641
CF3
CF3
N
COOEt
OH
C22H21F6NO3
APT
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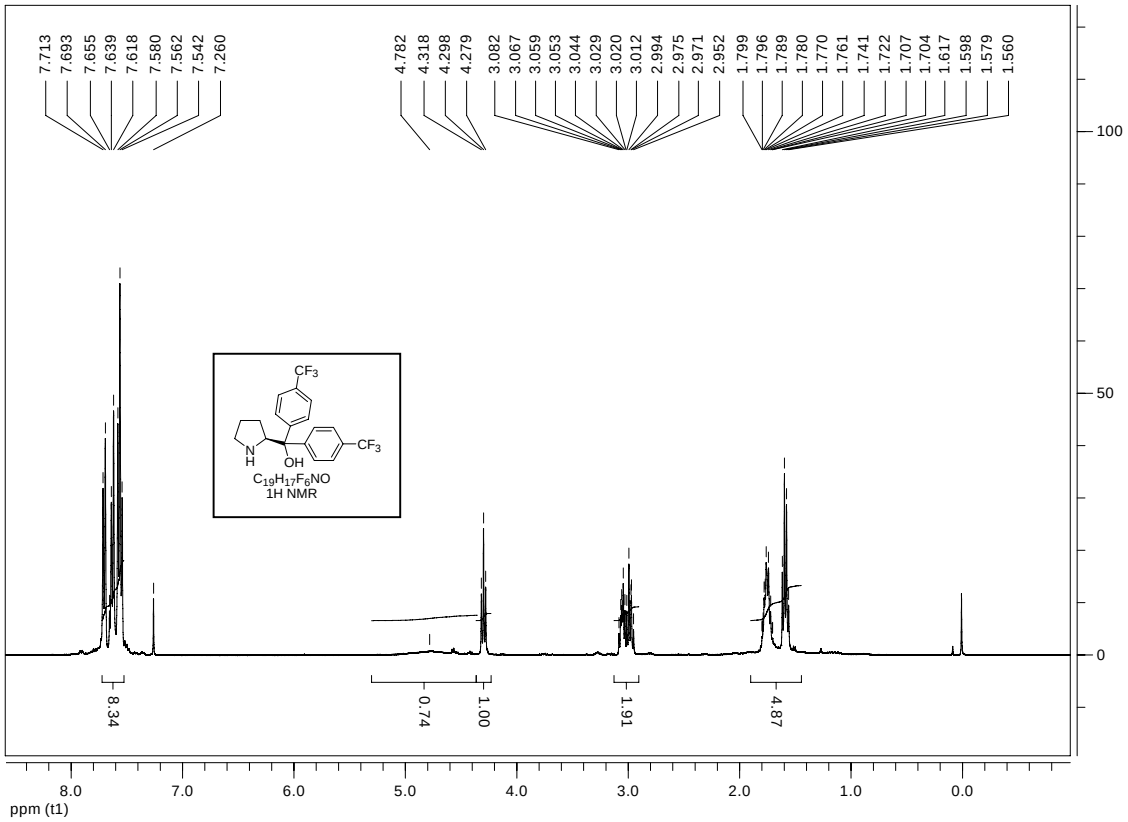
600
500
400
300
200
100
0
-100
-200
150
100
50
0
ppm (t1)


7.713
7.693
7.655
7.639
7.618
7.580
7.562
7.542
7.260
4.782
4.318
4.298
4.279
3.082
3.067
3.059
3.053
3.044
3.029
3.020
3.012
2.994
2.975
2.971
2.952
1.799
1.796
1.789
1.780
1.770
1.761
1.741
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1.704
1.617
1.598
1.579
1.560
CF3
CF3
N
H
OH
C19H17F6NO
1H NMR
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1.00
1.91
4.87
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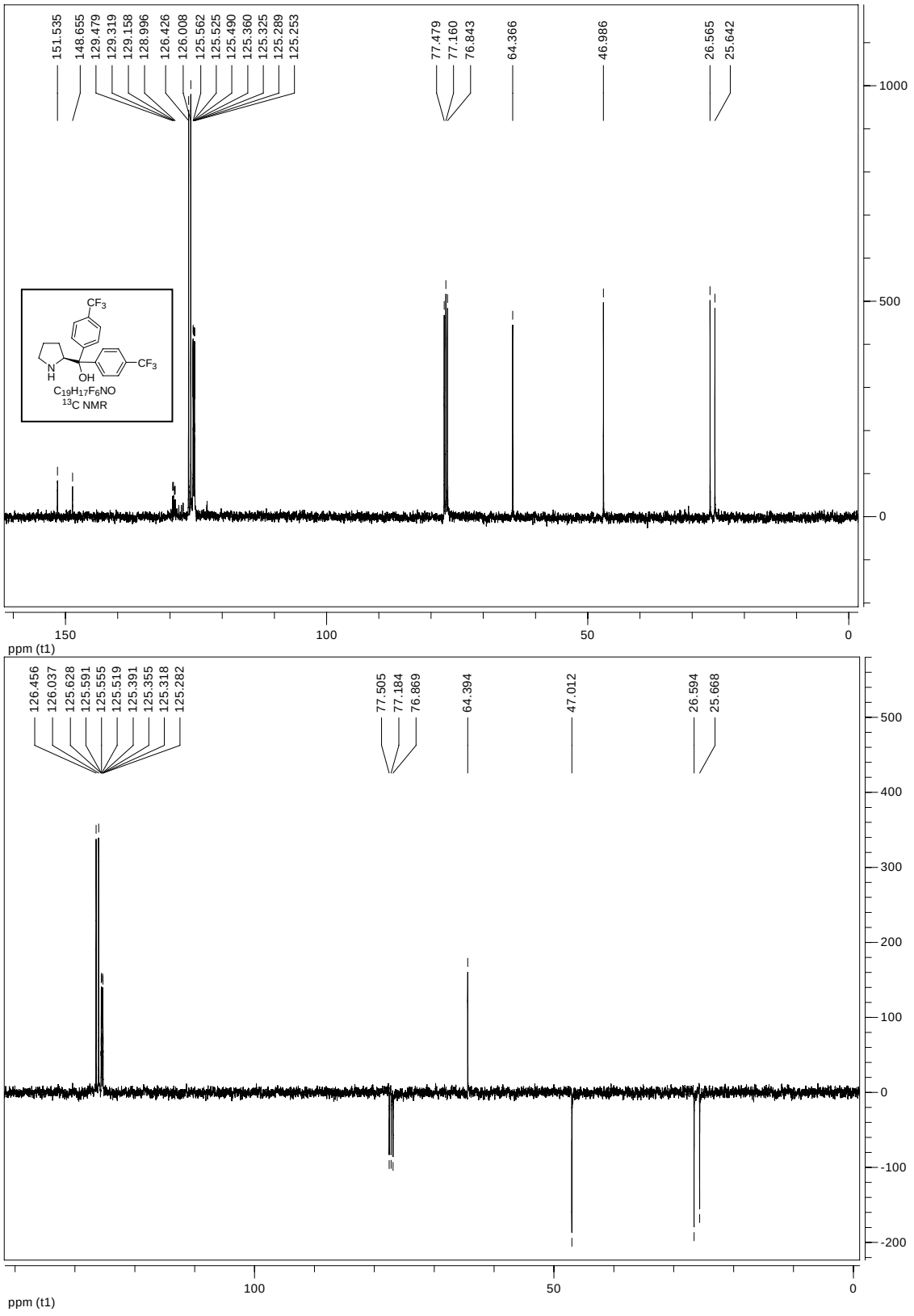
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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128.996
126.426
126.008
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125.525
125.490
125.360
125.325
125.289
125.253
77.479
77.160
76.843
64.366
46.986
26.565
25.642
CF3
CF3
N
H
OH
C19H17F6NO
13C NMR
1000
500
0
150
100
50
0
ppm (t1)
126.456
126.037
125.628
125.591
125.555
125.519
125.391
125.355
125.318
125.282
77.505
77.184
76.869
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25.668
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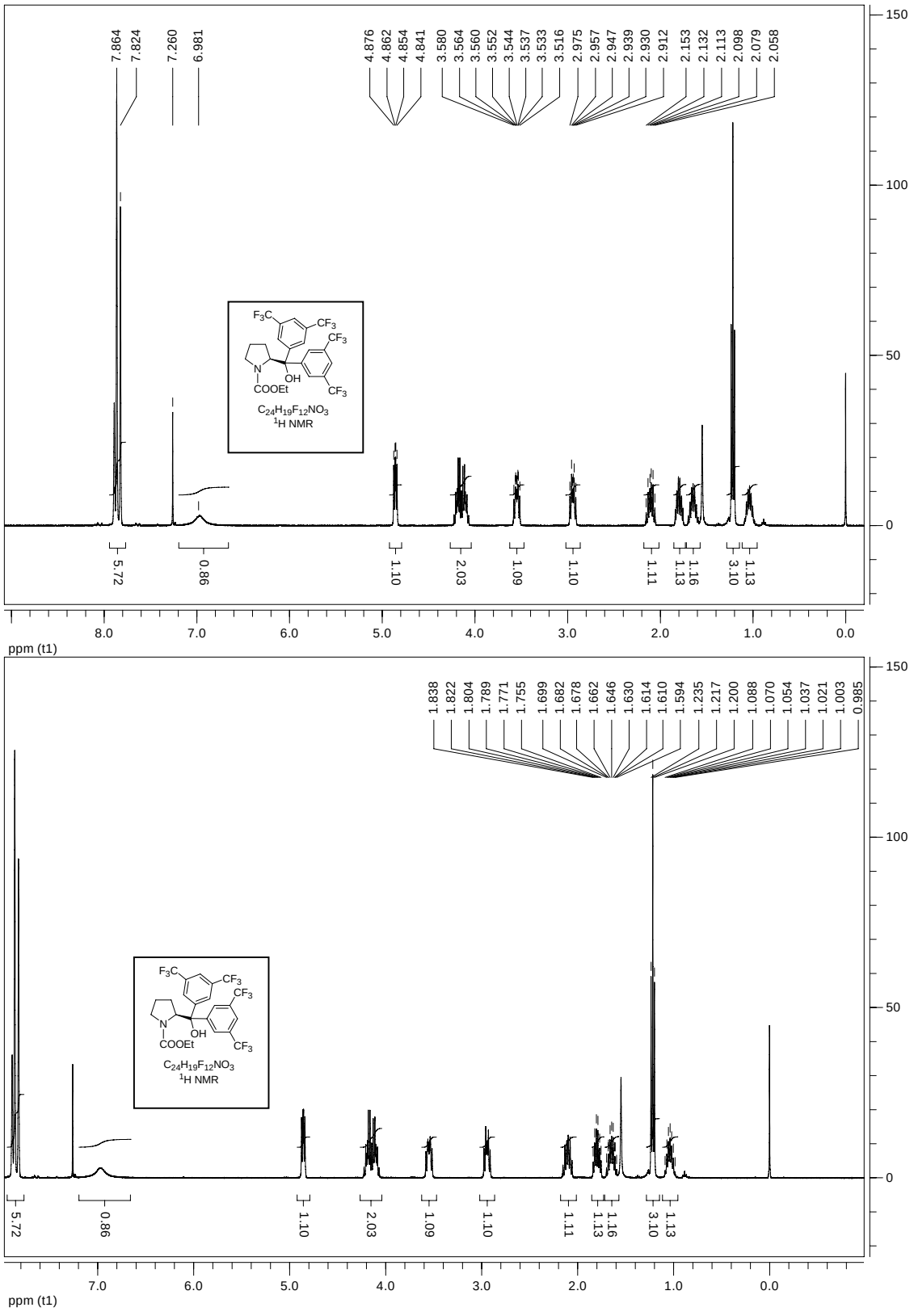
400
300
200
100
0
-100
-200
100
50
0
ppm (t1)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7.824
7.260
6.981
4.876
4.862
4.854
4.841
3.580
3.564
3.560
3.552
3.544
3.537
3.533
3.516
2.975
2.957
2.947
2.939
2.930
2.912
2.153
2.132
2.113
2.098
2.079
2.058
F3C
CF3
CF3
N
OH
COOEt
CF3
C24H19F12NO3
1H NMR
5.72
0.86
1.10
2.03
1.09
1.10
1.11
1.13
1.16
3.10
1.13
150
100
50
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)
1.838
1.822
1.804
1.789
1.771
1.755
1.699
1.682
1.678
1.662
1.646
1.630
1.614
1.610
1.594
1.235
1.217
1.200
1.088
1.070
1.054
1.037
1.021
1.003
0.985
F3C
CF3
CF3
N
OH
COOEt
CF3
C24H19F12NO3
1H NMR
5.72
0.86
1.10
2.03
1.09
1.10
1.11
1.13
1.16
3.10
1.13
150
100
50
0
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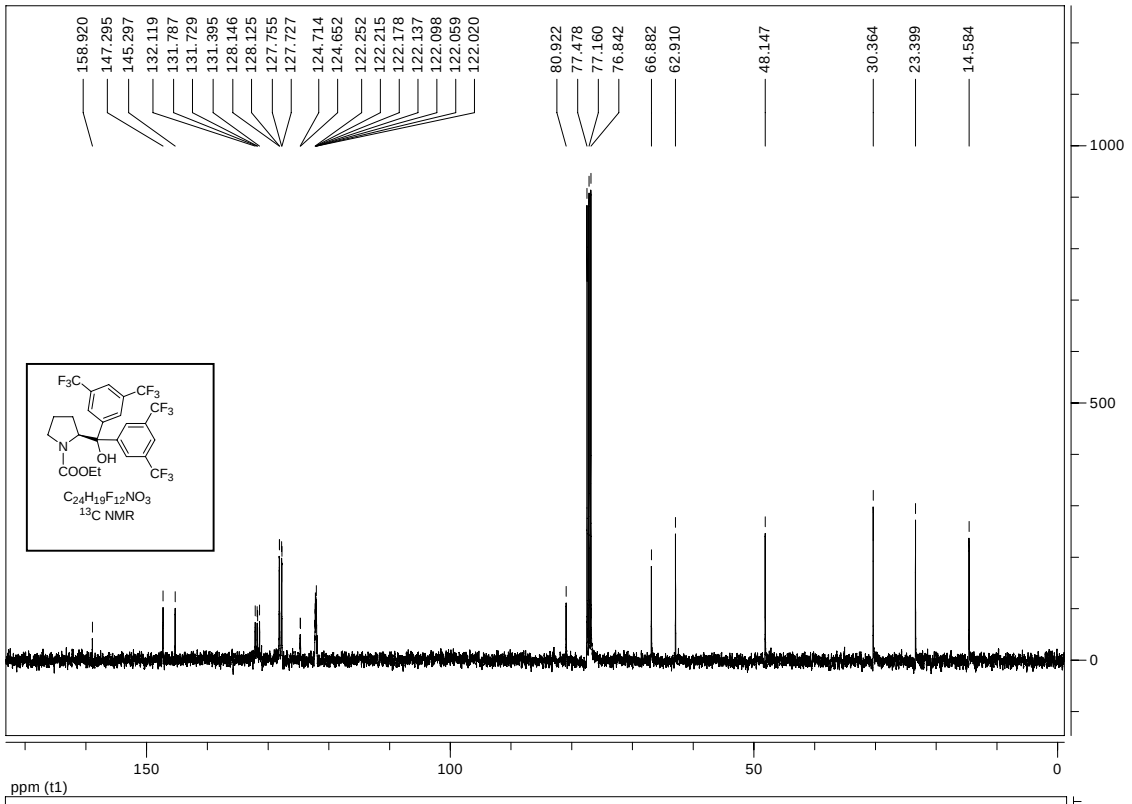
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


158.920
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131.395
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124.652
122.252
122.215
122.178
122.137
122.098
122.059
122.020
80.922
77.478
77.160
76.842
66.882
62.910
48.147
30.364
23.399
14.584
1000
500
0
150
100
50
0
ppm (t1)
F3C
CF3
CF3
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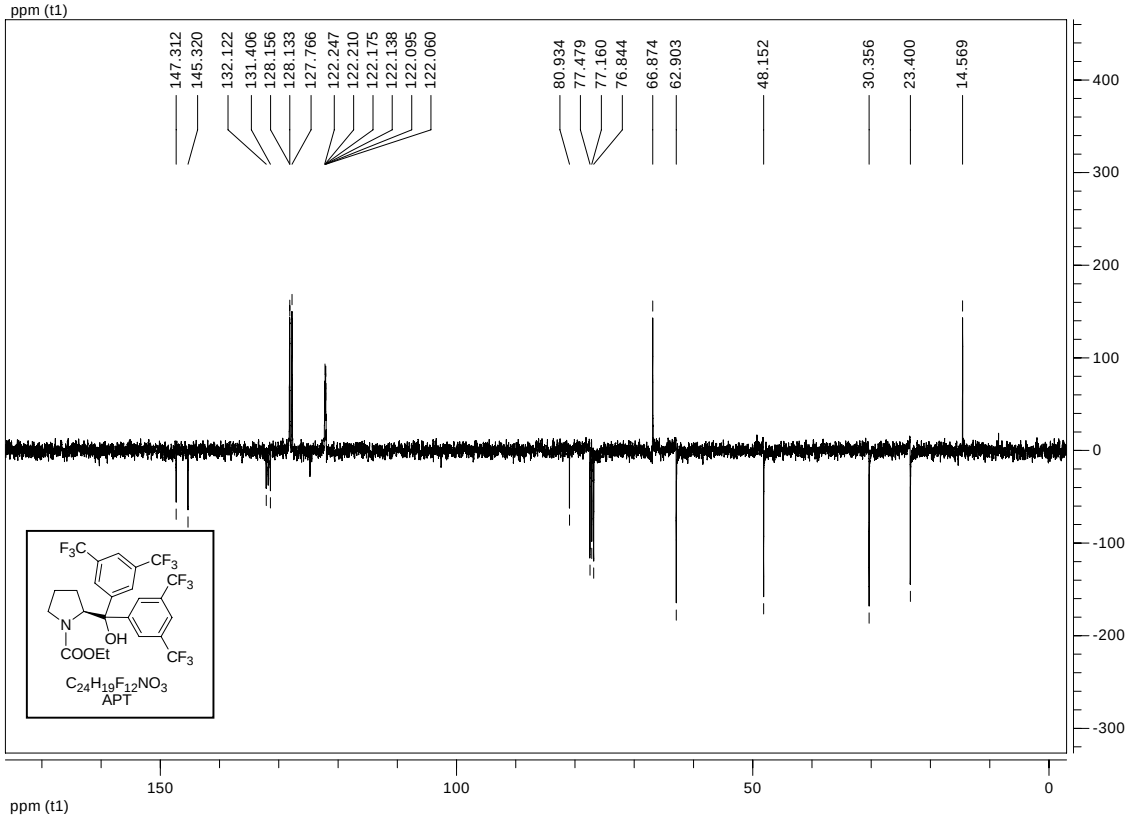
OH
COOEt
CF3
C24H19F12NO3
13C NMR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128.133
127.766
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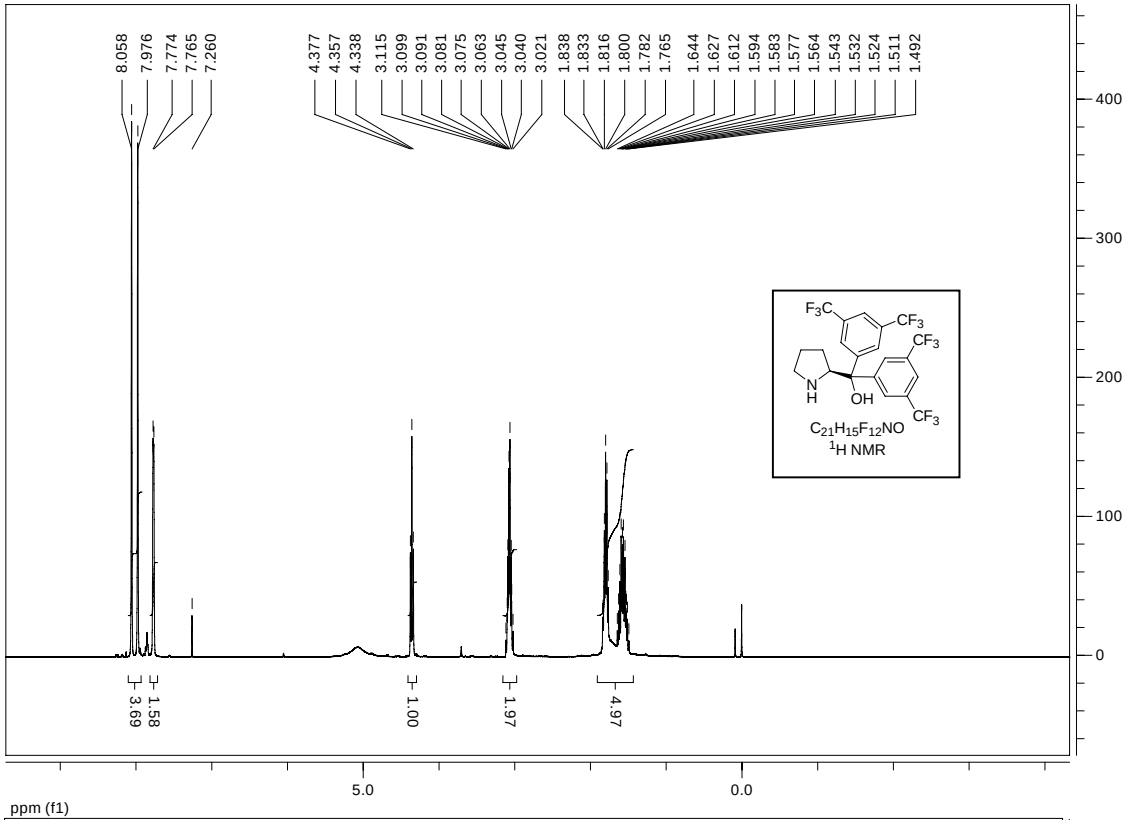
122.210
122.175
122.138
122.095
122.060
80.934
77.479
77.160
76.844
66.874
62.903
48.152
30.356
23.400
14.569
400
300
200
100
0
-100
-200
-300
150
100
50
0
ppm (t1)
F3C
CF3
CF3
N
OH
COOEt
CF3
C24H19F12NO3
APT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4.338
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3.091
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3.075
3.063
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3.040
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1.833
1.816
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1.765
1.644
1.627
1.612
1.594
1.583
1.577
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1.524
1.511
1.492
3.69
1.58
1.00
1.97
4.97
400
300
200
100
0
5.0
0.0
ppm (f1)
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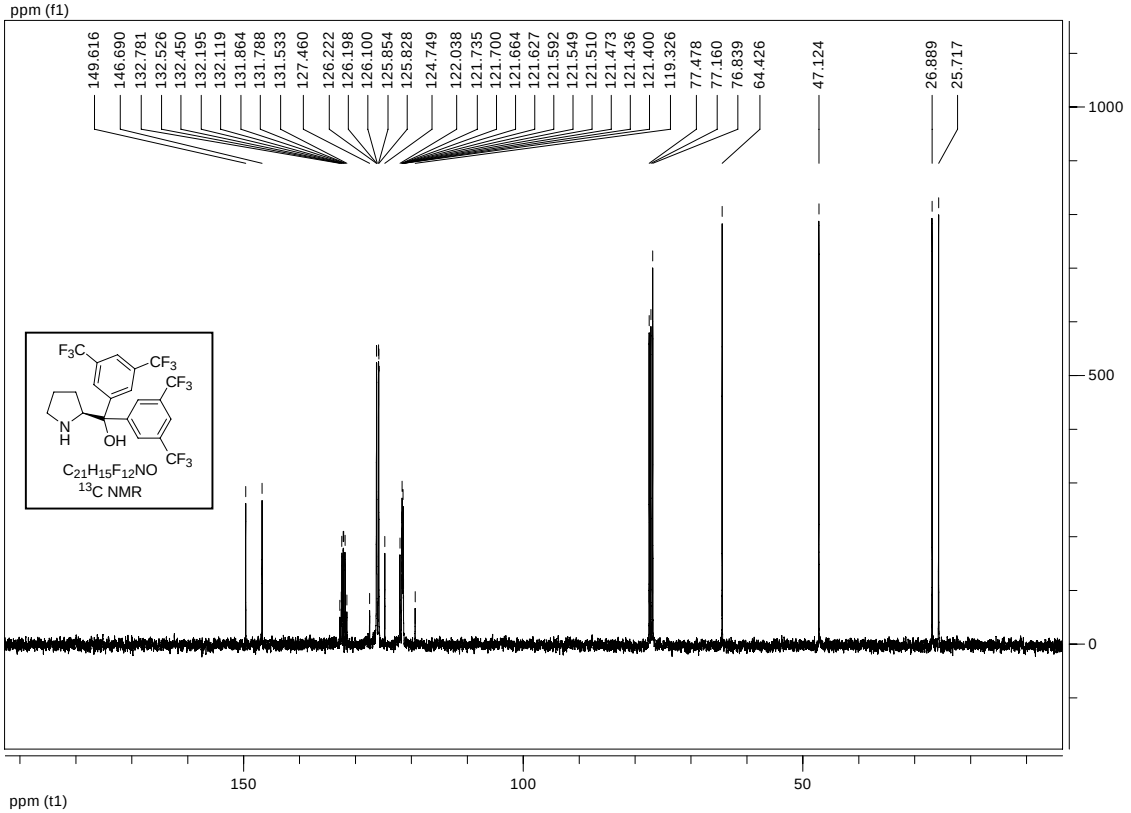
CF3
CF3
CF3
N
H
OH
C21H15F12NO
1H NMR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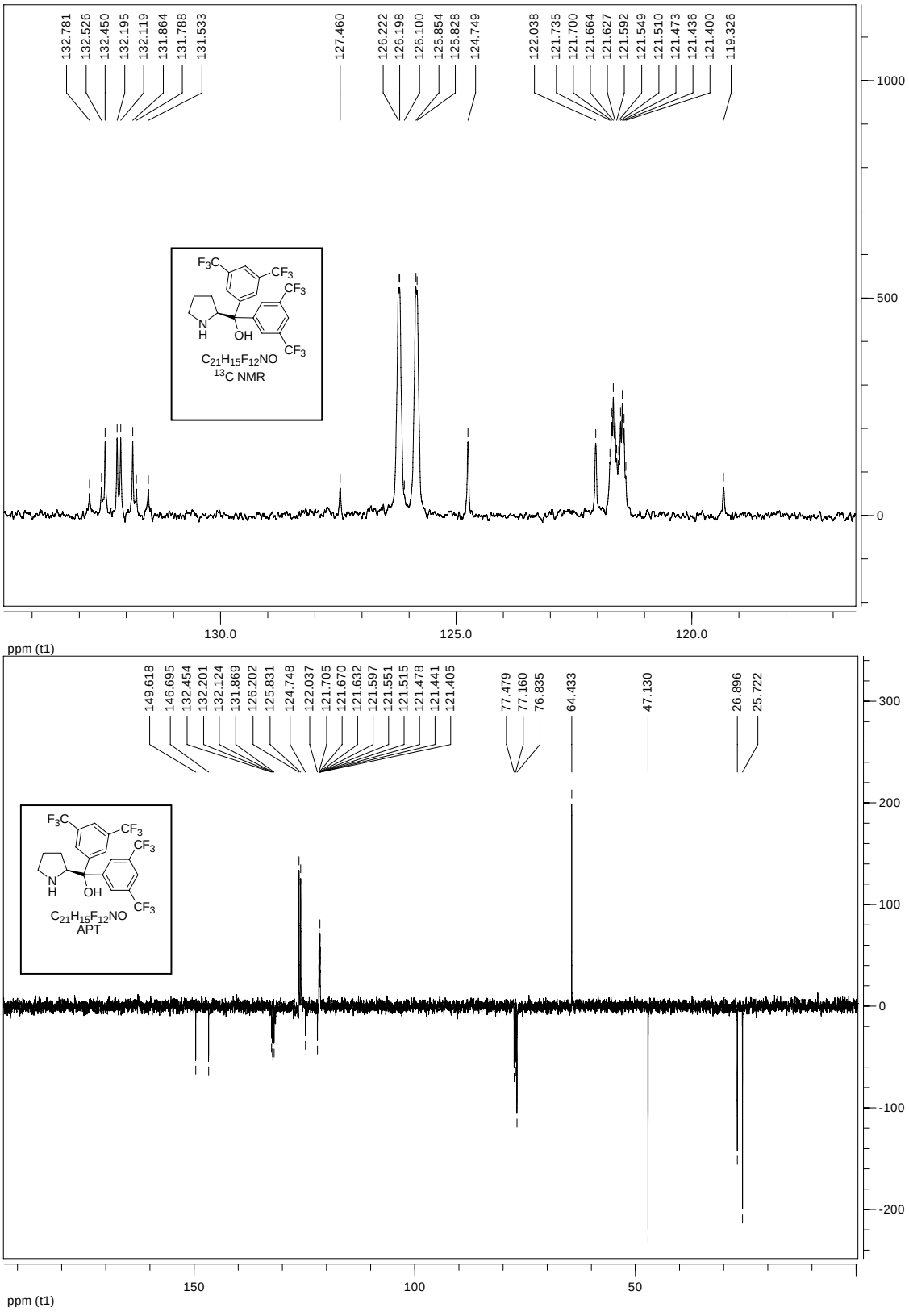
126.198
126.100
125.854
125.828
124.749
122.038
121.735
121.700
121.664
121.627
121.592
121.549
121.510
121.473
121.436
121.400
119.326
77.478
77.160
76.839
64.426
47.124
26.889
25.717
1000
500
0
150
100
50
ppm (t1)
F3C
CF3
CF3
CF3
N
H
OH
C21H15F12NO
13C NMR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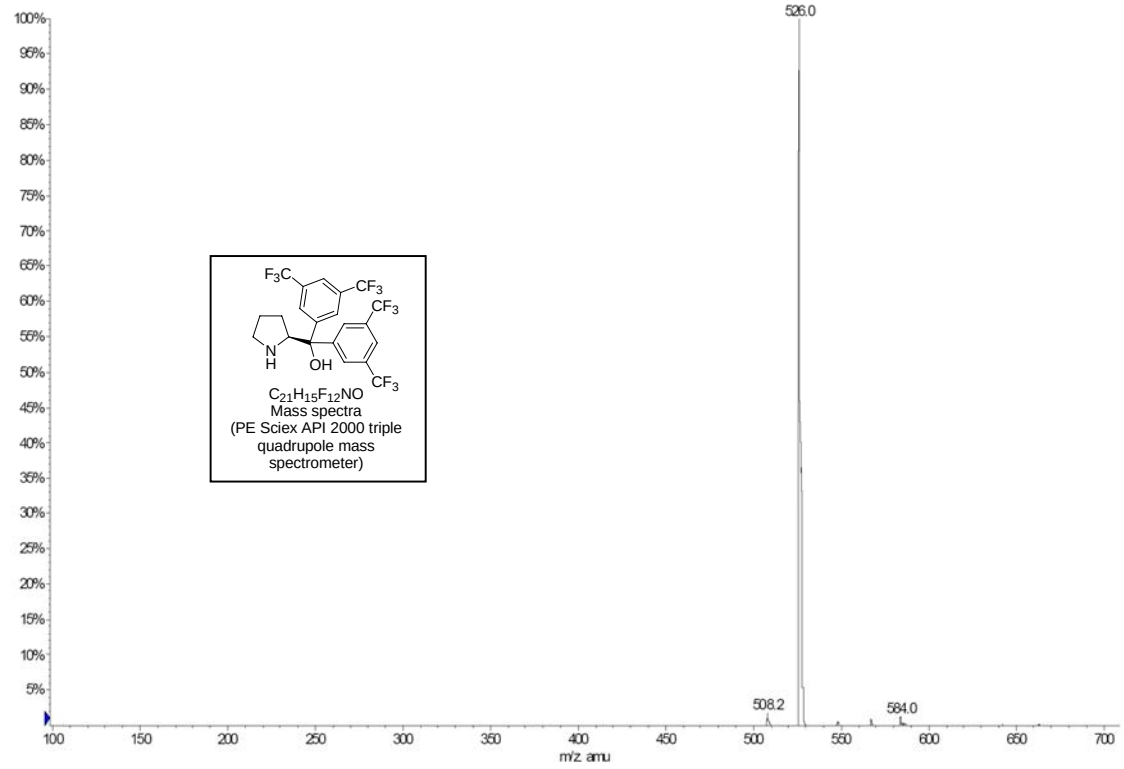
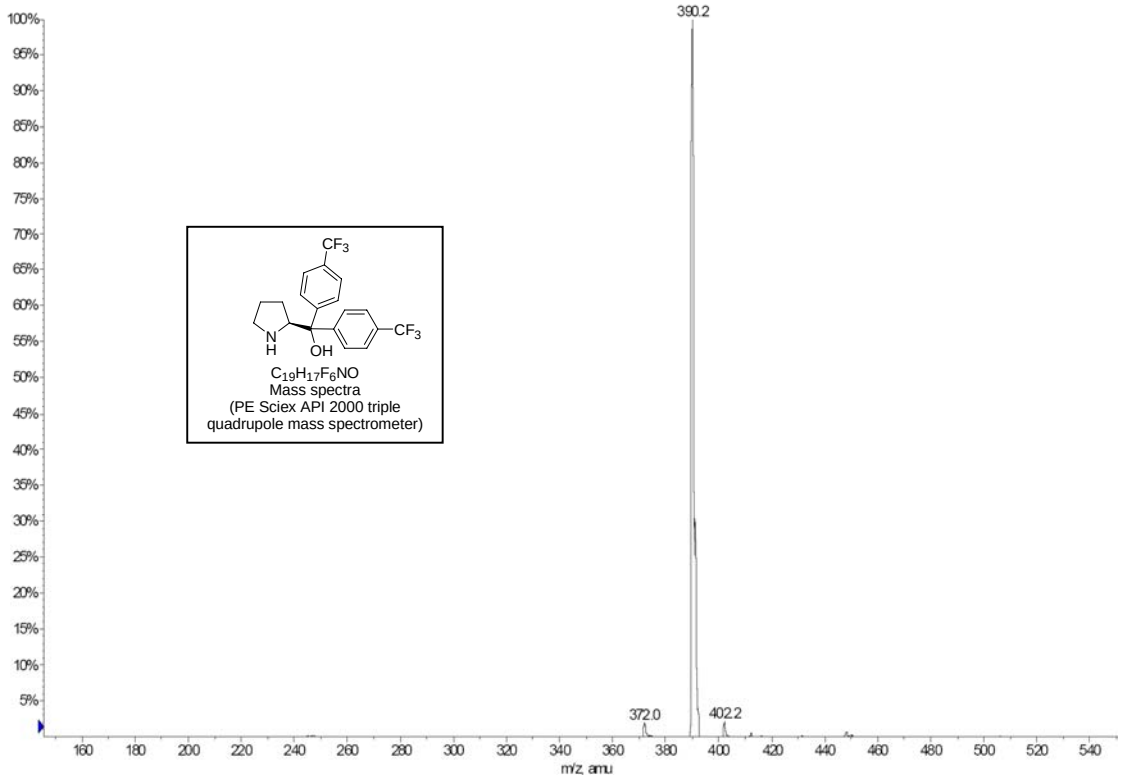
132.195
132.119
131.864
131.788
131.533
127.460
126.222
126.198
126.100
125.854
125.828
124.749
122.038
121.735
121.700
121.664
121.627
121.592
121.549
121.510
121.473
121.436
121.400
119.326
1000
500
0
F3C
CF3
CF3
CF3
N
H
OH
C21H15F12NO
13C NMR
130.0
125.0
120.0
ppm (t1)
149.618
146.695
132.454
132.201
132.124
131.869
126.202
125.831
124.748
122.037
121.705
121.670
121.632
121.597
121.551
121.515
121.478
121.441
121.405
77.479
77.160
76.835
64.433
47.130
26.896
25.722
300
200
100
0
-100
-200
F3C
CF3
CF3
CF3
N
H
OH
C21H15F12NO
APT
150
100
50
ppm (t1)

MS experiments and calibration data to determine precatalyst 4 leaching





Quantitation of catalyst leaching by mass spectrometry

Catalyst traces were quantitatively determined in the reaction products after purification by various SPE methods (as described above). This quantification were unstatisfacory using conventional GC-FID technique when the leaching was less then 5%, so a more specific/accurate ES-MS technique has been developed for this purpose.

Method and equipment: The MeOH/H_2O (1:1, v/v) calibration solutions containing the product and the precatalysts were diluted with MeOH 4000 fold because of the high sensitivity of MS. Thus calibration solutions were prepared in the concentration range of 5nM-250nM for the precatalyst **4**. To take into account the matrix effect, 50μM concentration of the appropriate alcohol was adjusted in each calibration solution. Analyses were performed on a Waters Quattro Micro triple quadrupole mass spectrometer (Manchester, UK) equipped with ESCi ion source and MassLynx 4.1 software was used for data analyis. The ESCi ion source was operated in positive electrospray (ES) mode, spectra were recorded in continuum mode by scanning the quadrupole form m/z 100-600 with a 1.0 sec scan time. High purity MeOH (Sigma-Aldrich, Hungary) eluent was used with 0.1 mL/min flow rate and 10uL loop was applied to sample injection. For the quantitative analysis peak areas of the reconstructed ion chromatograms of m/z 526.1 ($[M+H]^+$)were used.

Calibration and leaching measurement: Following SPE the purified MeOH/H_2O solution was further diluted 4000 times with MeOH before the mass spectrometric analysis. Catalyst traces were detected using ES-MS in positive ion mode, the mass spectrum showed $[M+H]^+$ and $[M+H-H_2O]^+$ ions at m/z 526.1 and 508.1 respectively. Ion chromatogram of m/z 526.1 was recostructed from the spectra and the peak areas were used for quantitative analysis. It was also observed that signal intensity of the catalyst in the aqueous MeOH solution showed significant dependence on the type of reaction product (eg. 1-Phenyl-ethanol, 1-Naphthalen-2-yl-ethanol, 1-(pyridin-3-yl)ethanol, 1-(4-Chloro-phenyl)-ethanol). (Note, that the concentration of reaction products in MeOH/H_2O solution is ca. 3 orders of magnitude greater than the catalyst concentration.)

For accurate quantitation the matrix effect had to be taken into account. Calibration solutions containing the appropriate amount of the reaction product (50μM) in MeOH were prepeared which contained a varying amount of catalyst (in the 5-250nM range). The calibration curves are shown in Fig.X and demonstrate good linearity and illustrate the surprising large matrix effect. Calibration curves and analysis were always measured on the same day. Results are shown in Table X, Y.

SPE-cartridge	1-Phenyl-ethanol	1-Naphthalen-2-yl-ethanol	1-(pyridin-3-yl)ethanol	1-(4-Chloro-phenyl)-ethanol
γAl_2O_3-FSPE	14.9			
γAl_2O_3-C18	4.0			
αAl_2O_3-C18	3.3	Not detected	Not detected	1.6
αAl_2O_3- αAl_2O_3	5.7	0.2	2.8	2.7

Table 1. Catalyst leaching (mg /10mL MeOH/H_2O 1:1 solution), originally 105 mg was applied

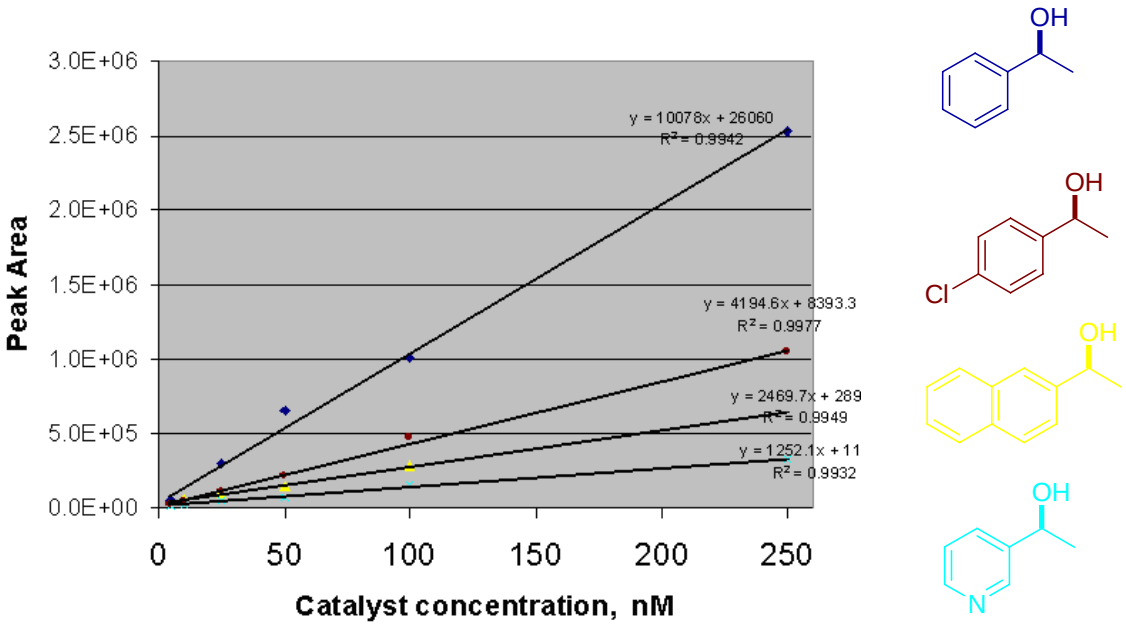


Figure1. Calibration curves for 1-Phenyl-ethanol (**6a**), 1-Naphthalen-2-yl-ethanol (**6c**), 1-(pyridin-3-yl)ethanol (**6d**), 1-(4-Chloro-phenyl)-ethanol (**6b**).

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