Efficient Separation of a Trifluoromethyl Substituted Organocatalyst: Just Add Water

Zoltán Dalicsek, Ferenc Pollreisz and Tibor Soós*

Supporting Information

Chemical Research Center of Hungarian Academy of Sciences, P. O. Box 17, H-1525, Budapest, Hungary
tibor.soos@chemres.hu

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**General Information.** Nuclear Magnetic Resonance spectra (NMR) were acquired on a Varian UNITY INOVA (400 MHz) instrument using CDCl₃ as internal standard and Varian Gemini 2000 (200 MHz) instrument using CDCl₃ 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 nonstabilized BH₃•THF 1.0 M in THF and BH₃•DMS were obtained from Fluka. LiCl was purchased from Riedel-de-Haën. Fluorous reverse phase silica gel (FluoroFlash™ 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** and **4** 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!* 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 (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 NH₄Cl. The aqueous and organic-phase was separated and the aqueous-phase was extracted three times with 100 mL CHCl₃. Combined organic phases were dried over Na₂SO₄ 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 F₂₅₄, hexanes : EtOAc = 9:1, Rf = 0.63). Highly pure IIc can be obtained via sublimation.

\[ \text{C}_{24}\text{H}_{19}\text{F}_{12}\text{NO}_3 \]

Mol. Wt.: 597.39

\[ \delta^\text{TMS} = 0 \text{ ppm} \]

\[ \text{H-NMR (400 MHz, CDCl}_3 \] (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); \[ \text{C-NMR (100 MHz, CDCl}_3 \] (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, CF₃) 122.2 (J = 4 Hz, CH), 122.1 (J = 4 Hz, CH), 80.9 (C), 66.9 (CH), 62.9 (CH₂), 48.2
(CH₂), 30.4 (CH₂), 23.4 (CH₂), 14.6 (CH₃); IR (KBr) ν cm⁻¹; 3365, 2991, 2361, 1666, 1278, 1170, 1125, 704, 682; [α]D²⁷ = −45 (c = 1.0, CHCl₃). Anal. Calcd. For C₂₄H₁₉F₁₂NO₃: 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 solution of the L-proline derivative I¹ (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 NH₄Cl. The aqueous and organic-phase was separated and the aqueous-phase was extracted three times with 100 mL CHCl₃. Combined organic phases were dried over Na₂SO₄ 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 F₂₅₄, hexanes : EtOAc = 9:1, Rf = 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 F254, hexane : EtOAc = 9:1, Rf = 0.44).

![Image](image.png)

\[^1\text{H-NMR (400 MHz, CDCl}_3, \delta_{\text{TMS}} = 0 \text{ ppm) 7.54 (m, 8H), 6.40 (br s, 1H), 4.90 (dd, } J = 8.8, 4.4 \text{ 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 \text{ Hz, 3H), 0.95 (m, 1H); } ^{13}\text{C-NMR (100 MHz, CDCl}_3, \delta_{\text{CDCl}_3} = 77.16 \text{ ppm) 158.7 (C=O), 149.6 (C), 147.4 (C), 129.95 (q, } J = 32.4 \text{ Hz, C), 129.87 (q, } J = 32.4 \text{ Hz, C) 128.5 (CH), 128.0 (CH), 125.2 (q, } J = 3.4 \text{ Hz, CH), 124.7 (q, } J = 3.6 \text{ Hz, CH), 124.3 (q, } J = 270.6 \text{ Hz, CF}_3 \text{) 81.4 (C), 66.3 (CH), 62.4 (CH), 48.0 (CH), 29.9 (CH), 23.3 (CH), 14.6 (CH), 32.9 (q, } J = 270.6 \text{ Hz, CF}_3 \text{); IR (KBr) } \nu \text{ cm}^{-1} = 3434, 2994, 2890, 1675, 1469, 1413, 1384, 1326, 1165, 1131, 1072, 1018, 832; [\alpha]_D^{27} = -92 (c = 1.0, CHCl}_3 \text{ Anal. Calcd. For } \text{C}_{22}\text{H}_{21}\text{F}_{12}\text{NO}_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 vacuo, mixed with 200 mL of distilled water and extracted four times with 100 mL CH₂Cl₂. The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo to furnish 4 as a pure white solid (12.16 g, 96 %). TLC (Merck Aluminium oxide 60 F254, hexane : EtOAc = 9:1, Rf = 0.59).

![Image](image.png)

\[^1\text{H-NMR (400 MHz, CDCl}_3, \delta_{\text{TMS}} = 0 \text{ 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 \text{ Hz, 1H), 3.06 (m, 2H), 1.66 (m, 5H); } ^{13}\text{C-NMR (100 MHz, CDCl}_3, \delta_{\text{CDCl}_3} = 77.16 \text{ ppm) 149.6 (C), 146.7 (C), 132.3 (q, } J = 33.1 \text{ Hz, C), 132.0 (q, } J = 33.1 \text{ Hz, C), 126.2 (q, } J = 2.4 \text{ Hz, C).}
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 F254, hexane: EtoAc = 9:1, Rf = 0.12).

\[
\begin{align*}
\text{1H-NMR (400 MHz, CDCl}_3, \delta_{\text{TMS}} &= 0 \text{ ppm}) &: 7.62 (m, 8H), 4.90 (br s, 1H), 4.30 (t, J = 8 \text{ Hz}, 1H), 3.01 (m, 2H), 1.67 (m, 5H) ; \text{13C-NMR (100 MHz, CDCl}_3, \delta_{\text{CDCl}_3} &= 77.16 \text{ ppm}) &: 151.5 (C), 148.6 (C), 129.3 (q, J = 32.2 \text{ Hz}, C), 129.2 (q, J = 32.2 \text{ Hz}, C) 126.4 (CH), 126.0 (CH), 125.5 (q, J = 3.6 \text{ Hz}, CH), 125.3 (q, J = 3.6 \text{ Hz}, CH), 77.16 (C), 64.4 (CH), 47.0 (CH2), 26.6 (CH2), 25.6 (CH2); \text{IR (KBr) } \nu \text{ cm}^{-1} &: 3340, 2976, 2891, 2834, 1616, 1417, 1325, 1166, 1127, 1068, 1018, 830; [\alpha]_D^{27} &= -59 (c = 1.0, \text{ CHCl}_3) \text{ Anal. Calcd. For C}_{19}\text{H}_{17}\text{F}_{6}\text{NO: N, 3.3; C, 58.79; H, 4.19. Found N, 3.3; C, 58.79; H, 4.19.}
\end{align*}
\]
Procedure for asymmetric reduction of acetophenone (5a) with nonstabilized BH$_3$•THF complex. The precatalyst 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 hydrogen gas evolution was observed). Then 2.0 g γ-Al$_2$O$_3$ 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$_2$O 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$_2$SO$_4$ 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 hydrogen gas evolution was observed). Then 2.0 g γ- or α-Al₂O₃ 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 corundum) and rinsed with MeOH-H₂O 1:1 (5×2 mL) (DMF: H₂O 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 Na₂SO₄ 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).

1-Phenyl-ethanol (6a): 

![1-Phenyl-ethanol (6a)](image)

1H-NMR (200 MHz, CDCl₃) 7.40–7.25 (m, 5H, ArH), 4.88 (q, J = 6.3 Hz, 1H, CH(OH)), 2.10 (br s, 1H, OH), 1.49 (d, J = 6.3 Hz, 3H, CH₃CH); 13C-NMR (50 MHz, CDCl₃) 145.9 (C), 128.6 (CH), 127.6 (CH), 125.5 (CH), 70.5 (CH), 25.2 (CH₃); 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.

1-(4-Chloro-phenyl)-ethanol (6b): 

![1-(4-Chloro-phenyl)-ethanol (6b)](image)

1H-NMR (200 MHz, CDCl₃) 7.28 (br s, 4H, ArH), 4.83 (q, J = 6.6 Hz, 1H, CH(OH)), 2.33 (br s, 1H, OH), 1.44 (d, J = 6.6 Hz, 3H, CH₂CH); 13C-NMR (APT) (50 MHz, CDCl₃) 144.3 (C), 133.1 (C), 128.7 (CH), 126.9 (CH), 69.8...
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.

**1-Naphthalen-2-yl-ethanol (6c)**

$^1$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, CH$_2$OH), 2.43 (br s, 1H, OH), 1.57 (d, $J$ = 6.6 Hz, 3H, CH$_3$CH) $^{13}$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 Chiralecel 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.
1-(pyridin-3-yl)ethanol (6d): $^1$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, 1H, ArH), 7.46 (dd, $J = 7.8$ Hz, $J = 5.6$ Hz, 1H, ArH), 4.97 (q, $J = 6.2$ Hz, 1H, CH$_2$OH), 2.93 (br s, 1H, OH), 1.49 (d, $J = 6.2$ Hz, 3H, CH$_3$CH); ee = 98% Enantioselectivity was determined by HPLC analysis with a Chiralcel OJ column, (hexane : i-PrOH = 95:5), 1 mL/min, $\lambda = 254$, 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.

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, 351 µL, 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 hydrogen gas evolution was observed). Then the quenched reaction mixture was concentrated and partitioned between 80 mL hexane and 10mL CH$_3$CN and 40 mL water mixture. The aqueous phase was extracted with chloroform, dried over Na$_2$SO$_4$ and evaporated in vacuo to give 2.95g 6d (96% yield) as an opalescule 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).
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 redistilled extracting phase in the receiver arm facilitates the passive diffusion of the extracted material and syphons 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 through 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

MeOH

MeOH-H₂O 1:1

2 3 4

2 3 4

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

CH₃CN-H₂O 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 min

CH$_3$CN-H$_2$O 95-5

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

CH$_3$CN-H$_2$O  90-10

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$_3$CN-H$_2$O  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
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 spectra
Supplementary Material (ESI) for Chemical Communications
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S23
MS experiments and calibration data to determine precatalyst 4 leaching

![Mass spectra (PE Sciex API 2000 triple quadrupole mass spectrometer)](image)

Supplementary Material (ESI) for Chemical Communications
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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 unsatisfactory using conventional GC-FID technique when the leaching was less than 5%, so a more specific/accurate ES-MS technique has been developed for this purpose.

Method and equipment: The MeOH/H$_2$O (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 analysis. 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$_2$O 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$_2$O]$^+$ ions at m/z 526.1 and 508.1 respectively. Ion chromatogram of m/z 526.1 was reconstructed 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$_2$O 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 prepared 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.

<table>
<thead>
<tr>
<th>SPE-cartridge</th>
<th>1-Phenyl-ethanol</th>
<th>1-Naphthalen-2-yl-ethanol</th>
<th>1-(pyridin-3-yl)ethanol</th>
<th>1-(4-Chloro-phenyl)-ethanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>γAl₂O₃-FSPE</td>
<td>14.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>γAl₂O₃-C18</td>
<td>4.0</td>
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</tr>
<tr>
<td>αAl₂O₃-C18</td>
<td>3.3</td>
<td>Not detected</td>
<td>Not detected</td>
<td>1.6</td>
</tr>
<tr>
<td>αAl₂O₃-αAl₂O₃</td>
<td>5.7</td>
<td>0.2</td>
<td>2.8</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Table 1. Catalyst leaching (mg /10mL MeOH/H₂O 1:1 solution), originally 105 mg was applied

Figure 1. 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).
References:


