Highly diastereoselective synthesis of quaternary $\alpha$-trifluoromethyl $\alpha$-amino acids from chiral imines of trifluoropyruvate

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**General information:** Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). For 19F NMR, CFCl3 was used as outside standard and low field is positive. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. NMR yield was determined by 19F NMR using benzotrifluoride as an internal standard before working up the reaction.

**Materials:** All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. All reagents were weighed and handled in air, and refilled with an inert atmosphere of N2 at room temperature. THF was distilled from sodium and benzophenone immediately before use.

**Preparation of Chiral Imino Ester 1a.**

(R)-Ethyl 3,3,3-trifluoro-2-(2-methoxy-1-phenylethylimino)propanoate (1a). To a stirred solution of ethyl trifluoropyruvate (2.806 g, 16.5 mmol, 1.1 equiv) in toluene (150 mL) was slowly added the (R)-2-methoxy-1-phenylethanamine (2.268 g, 15 mmol, 1.0 equiv) at room temperature, followed by pyridinium p-toluenesulfonate (378 mg, 1.5 mmol, 0.1 equiv). After stirring for 2.0 h at room temperature, the reaction mixture was heated to reflux with a Dean-Stark apparatus for 20 h. Then the reaction mixture was cooled to 0 °C with an ice-bath, and toluene was evaporated. The residue was isolated with silica gel by flash chromatography (Petroleum ether /Ethyl Acetate = 80:1) to give 1a (4.0 g, 88% yield) as a yellow oil. 1H NMR (300 MHz, CDCl3) δ 7.37-7.22 (m, 5H), 5.20 (dd, J = 8.7 Hz, 4.5 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.57-3.48 (m, 2H), 3.23 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 158.4, 149.3 (q, J = 36.4 Hz), 138.2, 128.7, 128.0, 127.2, 118.3 (q, J = 276.8 Hz), 76.7, 66.5, 62.4, 59.0, 13.9. 19F NMR (282 MHz, CDCl3) δ -70.5 (s, 3F). IR (thin film): v_max 3034, 1743, 1682 cm⁻¹. MS (EI): m/z (%) 258 (M⁺ -C₂H₅O, 100), 135, 91. HRMS: Calculated for C₁₄H₁₆NO₃F₃ (M⁺): 303.1082; Found: 303. 1077.
Preparation of Chiral Imino Ester 1b.

\[
\text{(R)-2-(Trimethylsilyl)ethyl 3,3,3-trifluoro-2-(2-methoxy-1-phenylethylimino)propanoate(1b).}
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According to Uneyama’s procedure,\(^1\) imino ester 1b (2.62 g) was prepared from TFA (1.43 g, 12.5 mmol) in 56% overall yield (3 steps) as a yellow oil. The product was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 80:1). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.33-7.20 (m, 5H), 5.19 (dd, \(J = 8.1\) Hz, 4.5 Hz, 1H), 4.30 (m ,2H), 3.55-3.48 (m, 2H), 3.22 (s, 3H), 1.03-0.97 (m, 2H), -0.02 (s, 9H). \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 158.6, 149.5 (q, \(J = 35.6\) Hz), 138.2, 128.6, 128.0, 127.3, 118.3 (q, \(J = 276.8\) Hz), 76.7, 66.5, 65.1, 59.0, 17.3, -1.7. \(^19\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) -70.2 (s, 3F). IR (thin film): \(\nu_{\text{max}}\) 3035, 1740, 1683, 1604 cm\(^{-1}\). MS (ESI): \(m/z\) (%) 398 (M\(^+\) + Na\(^+\)), 376 (M\(^+\) + H\(^+\)), 348. HRMS: Calculated for C\(_{17}\)H\(_{24}\)F\(_3\)NO\(_3\)SiNa (M\(^++\)Na\(^+\)): 398.13698; Found: 398.13732.

General procedure for the preparation of imino esters 1c-e.

The preparation of imino esters 1c-e was according to literature.\(^2\) To a stirred solution of silylated imino ester 1b (1 mmol) in THF (10 mL) were added corresponding electrophile R-X (2 mmol), followed by dropwise TBAF (1 M in THF, 1.1 mL, 1.1 mmol) at 0 \(^\circ\)C. The reaction mixture was then warmed to room temperature and stirred until the starting material was consumed. The solvents were removed under reduced pressure and the residue was purified by flash column chromatography.
(R)-Allyl 3,3,3-trifluoro-2-(2-methoxy-1-phenylethylimino)propanoate (1c). Imino ester 1c (220 mg, 70% yield) was prepared as above described from 1b (375 mg) as a yellow oil. The product was purified with silica gel chromatography (Petroleum ether/Ethyl Acetate = 50:1). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.43-7.24 (m, 5H), 5.99-5.88 (m, 1H), 5.44-5.28 (m, 3H), 4.79 (d, $J = 5.4$ Hz, 2H), 3.67-3.56 (m, 2H), 3.31 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 158.0, 148.9 (q, $J = 36.4$ Hz), 138.1, 130.4, 128.7, 128.1, 127.3, 119.7, 118.2 (q, $J = 276.8$ Hz), 76.6, 66.6, 59.0. $^{19}$F NMR (282 MHz, CDCl$_3$) δ -70.2 (s, 3F). IR (thin film): $\nu_{\text{max}}$ 3090, 1745, 1683, 1604 cm$^{-1}$. MS (ESI): $m/z$ (%) 316 ($M^+ + H^+$). HRMS: Calculated for C$_{15}$H$_{16}$NO$_3$F$_3$Na ($M^+ + Na^+$): 338.09745; Found: 338.09810.

(R)-prop-2-ynyl 3,3,3-trifluoro-2-(2-methoxy-1-phenylethylimino)propanoate (1d). Imino ester 1d (330 mg, 52% yield) was prepared as above described from 1b (750 mg) as a yellow oil. The product was purified with silica gel chromatography (Petroleum ether/Ethyl Acetate = 50:1). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.46-7.33 (m, 5H), 5.33 (dd, $J = 9.3$ Hz, 4.2 Hz, 1H), 4.90 (d, $J = 2.4$ Hz, 2H), 3.69-3.55 (m, 2H), 3.34 (s, 3H), 2.60 (t, $J = 2.4$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 157.5, 148.2 (q, $J = 36.4$ Hz), 137.9, 128.7, 128.1, 127.3, 118.1 (q, $J = 268.0$ Hz), 76.5, 76.3, 75.9, 66.6, 59.0, 53.3. $^{19}$F NMR (282 MHz, CDCl$_3$) δ -69.9 (s, 3F). IR (thin film): $\nu_{\text{max}}$ 2964, 1749, 1261 cm$^{-1}$. MS (ESI): $m/z$ (%) 314 ($M^+ + H^+$). HRMS: Calculated for C$_{15}$H$_{14}$NO$_3$F$_3$ ($M^+$): 313.0926; Found: 313.0923.

(R)-benzyl 3,3,3-trifluoro-2-(2-methoxy-1-phenylethylimino)propanoate (1e). Imino ester 1e (245 mg, 67% yield) was prepared as above described from 1b (375 mg) as a yellow oil. The
product was purified with silica gel chromatography (Petroleum ether/Ethyl Acetate = 50:1). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.37-7.28 (m, 10H), 5.32 (d, $J = 5.1$ Hz, 2H), 5.25 (m, 1H), 3.56 (m, 2H), 3.22 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.2, 148.9 (q, $J = 35.6$ Hz), 138.0, 134.2, 128.8, 128.6, 128.5, 128.4, 128.0, 127.2, 118.2 (q, $J = 276.9$ Hz), 76.5, 67.9, 66.5, 58.8. $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -70.1 (s, 3F). IR (thin film): $\nu_{\text{max}}$ 3068, 1745, 1682, 1604 cm$^{-1}$. MS (ESI): $m/z$ (%) 366 (M$^+ + H^+$). HRMS: Calculated for C$_{19}$H$_{18}$NO$_3$F$_3$Na (M$^+ + Na^+$): 388.11310; Found: 388.11420.

General procedure for the preparation of $\alpha$-allyl $\alpha$-Tfm $\alpha$-amino acids 3.

To a 10 mL of Schlenk tube were added chiral imino ester 1 (0.3 mmol) and In powder (69 mg, 0.6 mmol) under N$_2$ at room temperature. After standing for 5 min, THF (3 mL) was added. The resulting mixture was stirred for 15 min at 27-30 °C, and then fresh distilled allyl bromide 2 (0.66 mmol) was added. The reaction mixture was stirred at the same temperature until the starting material was totally consumed, as confirmed by means of TLC. The reaction mixture was quenched with HCl (1 M, 2 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (3 x 7 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash column chromatography.

(R)-Ethyl 2-((R)-2-methoxy-1-phenylethylamino)-2-(trifluoromethyl)pent-4-enoate (3a). Compound 3a (104 mg, 98% yield) was prepared as above described from 1a (91 mg, 0.3 mmol) as a yellow oil. The product was purified with silica gel chromatography (Petroleum ether/Ethyl Acetate = 50:1). $[\alpha]_D^{25} = -49.8$ (c 1.0, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.39-7.22 (m, 5H),
5.80-5.71 (m, 1H), 5.11-5.06 (m, 2H), 4.18-4.07 (m, 2H), 4.05-3.95 (m, 1H), 3.38 (d, \( J = 6.6 \) Hz, 2H), 3.33 (s, 3H), 2.83 (br, 1H), 2.65 (dd, \( J = 14.7 \) Hz, 6.6 Hz, 1H), 2.45 (dd, \( J = 14.7 \) Hz, 7.8 Hz, 1H), 1.21 (t, \( J = 7.2 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 168.0, 141.6, 131.2, 128.2, 127.5, 124.9 (q, \( J = 286.0 \) Hz), 119.4, 77.5, 67.9 (q, \( J = 25.0 \) Hz), 61.7, 58.6, 56.9, 36.7, 13.7. \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \( \delta \) -72.5 (s, 3F). IR (thin film): \( \nu_{max} \) 3339, 3084, 1740, 1642, 1603 cm\(^{-1}\). MS (EI): \( m/z \) (%) 300 (M\(^{+}\)-C\(_2\)H\(_5\)O, 100), 135, 131, 91. HRMS: Calculated for C\(_{15}\)H\(_{17}\)NO\(_2\)F\(_3\) (M\(^{+}\)-C\(_2\)H\(_5\)O): 300.1211; Found: 300.1217.

(R)-2-(Trimethylsilyl)ethyl 2-((R)-2-methoxy-1-phenylethylamino)-2-(trifluoromethyl)pent-4-enoate (3b). Compound 3b (118 mg, 94% yield) was prepared as above described from 1b (113 mg, 0.3 mmol) as a yellow oil. The product was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 80:1). \([\alpha]_D^{25} = -38.6 \) (c 1.9, CHCl\(_3\)); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.34-7.21 (m, 5H), 5.71 (m, 1H), 5.07-5.03 (m, 2H), 4.15-3.94 (m, 3H), 3.34 (d, \( J = 6.3 \) Hz, 2H), 3.30 (s, 3H), 2.80 (br, 1H), 2.61 (dd, \( J = 15.0 \) Hz, 6.5 Hz, 1H), 2.41 (dd, \( J = 15.0 \) Hz, 7.5 Hz, 1H), 0.91 (t, \( J = 8.1 \) Hz, 2H), -0.03 (s, 9H). \(^{13}\)C NMR (75.4 MHz, CDCl\(_3\)) \( \delta \) 168.2, 141.7, 131.3, 128.1, 127.3, 124.9 (q, \( J = 286.9 \) Hz), 119.3, 77.6, 67.9 (q, \( J = 25.3 \) Hz), 64.3, 58.7, 56.9, 36.7, 17.0, -1.7. \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \( \delta \) -72.1 (s, 3F). IR (thin film): \( \nu_{max} \) 3343, 3085, 1739, 1643 cm\(^{-1}\). MS (ESI): \( m/z \) (%) 418 (M\(^{+}\)+H\(^+\)). HRMS: Calculated for C\(_{20}\)H\(_{31}\)NO\(_3\)F\(_3\)Si (M\(^{+}\)+H\(^+\)): 418.20198; Found: 418.20255.

(R)-Allyl 2-((R)-2-methoxy-1-phenylethylamino)-2-(trifluoromethyl)pent-4-enoate (3c). Compound 3c (104 mg, 97% yield) was prepared as above described from 1c (95 mg, 0.3 mmol) as a yellow oil. The product was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 80:1). \([\alpha]_D^{25} = -54.7 \) (c 0.3, CHCl\(_3\)); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.37-7.23 (m, 5H), 5.71 (m, 1H), 5.07-5.03 (m, 2H), 4.15-3.94 (m, 3H), 3.34 (d, \( J = 6.3 \) Hz, 2H), 3.30 (s, 3H), 2.80 (br, 1H), 2.61 (dd, \( J = 15.0 \) Hz, 6.5 Hz, 1H), 2.41 (dd, \( J = 15.0 \) Hz, 7.5 Hz, 1H), 0.91 (t, \( J = 8.1 \) Hz, 2H), -0.03 (s, 9H). \(^{13}\)C NMR (75.4 MHz, CDCl\(_3\)) \( \delta \) 168.2, 141.7, 131.3, 128.1, 127.3, 124.9 (q, \( J = 286.9 \) Hz), 119.3, 77.6, 67.9 (q, \( J = 25.3 \) Hz), 64.3, 58.7, 56.9, 36.7, 17.0, -1.7. \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \( \delta \) -72.1 (s, 3F). IR (thin film): \( \nu_{max} \) 3343, 3085, 1739, 1643 cm\(^{-1}\). MS (ESI): \( m/z \) (%) 418 (M\(^{+}\)+H\(^+\)). HRMS: Calculated for C\(_{20}\)H\(_{31}\)NO\(_3\)F\(_3\)Si (M\(^{+}\)+H\(^+\)): 418.20198; Found: 418.20255.
5.82-5.75 (m, 2H), 5.33-5.21 (m, 2H), 5.11-5.06 (m, 2H), 4.49 (dd, $J = 13.2$ Hz, 5.3 Hz, 1H), 4.37 (dd, $J = 13.2$ Hz, 5.4 Hz, 1H), 4.16 (t, $J = 6.3$ Hz, 1H), 3.37 (d, $J = 6.9$ Hz, 2H), 3.32 (s, 3H), 2.66 (br, 1H), 2.65 (dd, $J = 14.3$ Hz, 6.2 Hz, 1H), 2.45 (dd, $J = 14.3$ Hz, 7.4 Hz, 1H). $^{13}$C NMR (75.4 MHz, CDCl$_3$) δ 167.7, 141.6, 131.2, 128.2, 127.3, 124.8 (q, $J = 287.7$ Hz), 119.7, 118.7, 77.4, 68.0 (q, $J = 25.6$ Hz), 66.2, 58.6, 57.0, 36.8. $^{19}$F NMR (282 MHz, CDCl$_3$) δ -72.1 (s, 3F). IR (thin film): $\nu_{\text{max}}$ 3340, 3086, 1744, 1644, 1604 cm$^{-1}$. MS (ESI): $m/z$ (%) 358 (M$^+$ + H$^+$). HRMS: Calculated for $\text{C}_{18}\text{H}_{22}\text{NO}_{3}\text{F}_3\text{Na}$ (M$^+$ + Na$^+$): 380.14440; Found: 380.14610.

(R)-Prop-2-ynyl 2-((R)-2-methoxy-1-phenylethylamino)-2-(trifluoromethyl)pent-4-enoate (3d). Compound 3d (104 mg, 98% yield) was prepared as above described from 1d (94 mg, 0.3 mmol) as a yellow oil. The product was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 80:1). $[\alpha]_D^{25} = -51.7$ (c 0.5, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.37-7.25 (m, 5H), 5.74 (m, 1H), 5.15-5.09 (m, 2H), 4.53 (dd, $J = 15.6$ Hz, 2.1 Hz, 1H), 4.36 (dd, $J = 15.6$ Hz, 2.7 Hz, 1H), 4.18 (t, $J = 6.6$ Hz, 1H), 3.38 (d, $J = 6.6$ Hz, 2H), 3.34 (s, 3H), 2.81 (br, 1H), 2.66 (dd, $J = 14.4$ Hz, 6.6 Hz, 1H), 2.57 (br, 1H), 2.50-2.44 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.4, 141.1, 130.7, 128.2, 127.4, 124.7 (q, $J = 288.4$ Hz), 120.0, 77.5, 75.5, 67.9 (q, $J = 25.2$ Hz), 58.7, 56.9, 52.9, 37.0. $^{19}$F NMR (282 MHz, CDCl$_3$) δ -72.7 (s, 3F). IR (thin film): $\nu_{\text{max}}$ 3306, 3034, 2136, 1750, 1642 cm$^{-1}$. MS (ESI): $m/z$ (%) 378 (M$^+$ + Na$^+$), 356 (M$^+$ + H$^+$). HRMS: Calculated for $\text{C}_{18}\text{H}_{20}\text{NO}_{3}\text{F}_3\text{Na}$ (M$^+$ + Na$^+$): 378.12875; Found: 378.12982.

(R)-Benzyl 2-((R)-2-methoxy-1-phenylethylamino)-2-(trifluoromethyl)pent-4-enoate (3e). Compound 3e (55 mg, 45% yield) was prepared as above described from 1e (110 mg, 0.3 mmol) as a yellow oil. The product was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 80:1). $[\alpha]_D^{25} = -50.4$ (c 2.8, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.39-7.21 (m, 10H),
5.70 (m, 1H), 5.07-4.99 (m, 3H), 4.91 (d, J = 12.9 Hz, 1H), 4.15 (t, J = 6.3 Hz, 1H), 3.34 (d, J = 6.6 Hz, 2H), 3.27 (s, 3H), 2.86 (br, 1H), 2.64 (dd, J = 15.0 Hz, 6.6 Hz, 1H), 2.44 (dd, J = 15.0 Hz, 8.1 Hz, 1H). 13C NMR (75.4 MHz, CDCl3) δ 168.0, 141.4, 134.9, 131.0, 128.5, 128.3, 128.2, 128.0, 127.3, 124.8 (q, J = 288.0 Hz), 119.6, 77.4, 68.1 (q, J = 25.6 Hz), 67.4, 58.6, 57.0, 36.8. 19F NMR (282 MHz, CDCl3) δ -72.0 (s, 3F). IR (thin film): νmax 3340, 3036, 1743 cm⁻¹. MS (ESI): m/z (%) 408 (M⁺ + H⁺). HRMS: Calculated for C22H24NO3F3Na (M⁺ + Na⁺): 430.16005; Found: 430.16018.

(R)-Ethyl 2-((R)-2-methoxy-1-phenylethylamino)-4-methyl-2-(trifluoromethyl)pent-4-enoate (3f). Compound 3f (103 mg, 96% yield) was prepared as above described from 1a (91 mg, 0.3 mmol) as a yellow oil. The product was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 80:1). [α]D 25 = -36.3 (c 1.4, CHCl3); 1H NMR (300 MHz, CDCl3) δ 7.36-7.20 (m, 5H), 4.88 (s, 1H), 4.84 (s, 1H), 4.23 (t, J = 6.0 Hz, 2H), 4.09-4.04 (m, 1H), 3.94-3.88 (m, 1H), 3.42-3.38 (m, 2H), 3.30 (s, 3H), 2.79 (br, 1H), 2.63 (d, J =15.0 Hz, 1H), 2.54 (d, J =15.0 Hz, 1H), 1.70 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 168.4, 142.2, 139.4, 128.0, 127.3, 127.1, 125.0 (q, J = 289.0 Hz), 115.6, 77.6, 67.5 (q, J = 25.5 Hz), 61.8, 58.8, 56.8, 39.8, 23.5, 13.6. 19F NMR (282 MHz, CDCl3) δ -72.5 (s, 3F). IR (thin film): νmax 3370, 1742 cm⁻¹. MS (ESI): m/z (%) 360 (M⁺ + H⁺). HRMS: Calculated for C18H24NO3F3Na (M⁺ + Na⁺): 382.16005; Found: 382.15994.

(R)-2-(Trimethylsilyl)ethyl 2-((R)-2-methoxy-1-phenylethylamino)-4-methyl-2-(trifluoromethyl)pent-4-enoate (3g). Compound 3g (110 mg, 85% yield) was prepared as above described from 1b (113 mg, 0.3 mmol) as a yellow oil. The product was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 80:1). [α]D 25 = -45.7 (c 3.5, CHCl3); 1H NMR (300 MHz, CDCl3) δ 7.33-7.19 (m, 5H), 4.86 (s, 1H), 4.81 (s, 1H), 4.23 (t, J = 5.7 Hz, 1H), 4.08-4.05 (m, 1H),
3.92-3.89 (m, 1H), 3.39-3.35 (m, 2H), 3.30 (s, 3H), 2.81 (br, 1H), 2.60 (d, \( J = 14.9 \) Hz, 1H), 2.51 (d, \( J = 14.9 \) Hz, 1H), 1.67 (s, 3H), 0.88-0.81 (m, 2H), -0.02 (s, 9H). \(^{13}\)C NMR (75.4 MHz, CDCl\(_3\)) \( \delta \) 168.5, 142.2, 139.4, 128.0, 127.3, 127.1, 125.0 (q, \( J = 288.0 \) Hz), 115.5, 77.5, 67.3 (q, \( J = 25.6 \) Hz), 64.4, 58.7, 56.7, 39.5, 23.5, 16.9, -1.7. \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \( \delta \) -72.5 (s, 3F). IR (thin film): \( \nu \)\(_{\text{max}}\) 3344, 3031, 1739, 1651 cm\(^{-1}\). MS (ESI): \( m/z \) (%) 432 (M\(^+\) + H\(^+\)). HRMS: Calculated for C\(_{21}\)H\(_{32}\)NO\(_3\)F\(_3\)SiNa (M\(^+\) + Na\(^+\)): 454.19958; Found: 454.20001.

\((R)-\text{Diethyl 2-((R)-2-methoxy-1-phenylethylamino)-4-methylene-2-(trifluoromethyl)pentane Dioate (3h)}\) Compound 3h (110 mg, 88% yield) was prepared as above described from 1a (91 mg, 0.3 mmol) as a yellow oil (Note: The reaction was quenched with water instead of HCl (1 M, 2 mL)). The product was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 80:1). \([\alpha]_D^{25} = -38.3 \) (c 5.9, CHCl\(_3\)); \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.29-7.20 (m, 5H), 6.28 (s, 1H), 5.68 (s, 1H), 4.25-4.17 (m, 3H), 3.95-3.89 (m, 1H), 3.78-3.72 (m, 1H), 3.42 (d, \( J = 6.3 \) Hz, 2H), 3.29 (s, 3H), 2.95 (s, 2H), 2.88 (br, 1H), 1.30 (t, \( J = 7.2 \) Hz, 3H), 0.99 (t, \( J = 7.1 \) Hz, 3H). \(^{13}\)C NMR (75.4 MHz, CDCl\(_3\)) \( \delta \) 167.6, 167.0, 142.3, 134.9, 128.7, 127.8, 127.1, 126.9, 125.1 (q, \( J = 289.6 \) Hz), 77.4, 68.2 (q, \( J = 25.3 \) Hz), 61.6, 61.0, 58.7, 57.0, 33.8, 14.0, 13.3. \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \( \delta \) -71.9 (s, 3F). IR (thin film): \( \nu \)\(_{\text{max}}\) 3350, 2986, 1744 cm\(^{-1}\). MS (EI): \( m/z \) (%) 372 (M\(^+\) -C\(_2\)H\(_5\)O, 100), 157, 135, 131, 91. HRMS: Calculated for C\(_{20}\)H\(_{28}\)NO\(_5\)F\(_3\) (M\(^+\)): 417.1763; Found: 417.1754.

\((2R,3S)-\text{Ethyl 2-((R)-2-methoxy-1-phenylethylamino)-3-methyl-2-(trifluoromethyl)pent-4-ENOate (3i)}\) Compound 3i (90 mg, 82% yield) was prepared as above described from 1a (91 mg, 0.3 mmol) as a yellow oil. The product was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 80:1). \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.33-7.19 (m, 5H), 5.90 (m, 1H), 5.20-5.15 (m, 2H), 4.17 (t, \( J = 5.4 \) Hz, 1H), 3.94-3.88 (m, 1H), 3.65-3.60 (m, 1H), 3.59-3.43 (m,
(2R,3R)-Ethyl 2-((R)-2-methoxy-1-phenylethylamino)-3-phenyl-2-(trifluoromethyl)pent-4-enoate (3j). Compound 3j (110 mg, 92% yield) was prepared as above described from 1a (91 mg, 0.3 mmol) as a yellow oil. The product was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 100:1). $[\alpha]_D^{25} = -48.1$ (c 2.0, CHCl₃); $^1$H NMR (300 MHz, CDCl₃) δ 7.38-7.17 (m, 10H), 6.37 (m, 1H), 5.29-5.16 (m, 2H), 4.11 (t, $J = 5.1$ Hz, 1H), 4.03 (d, $J = 9.6$ Hz, 1H), 3.69-3.63 (m, 1H), 3.58-3.41 (m, 3H), 3.26 (s, 3H), 2.81 (d, $J = 5.1$ Hz 1H), 0.69 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl₃) δ 167.2, 142.4, 137.3, 134.6, 129.4, 127.9, 127.6, 127.3, 127.1, 126.6, 125.3 (q, $J = 291.0$ Hz), 119.5, 76.5 71.7 (q, $J = 23.0$ Hz), 61.1, 58.7, 57.2, 54.9, 12.8. $^{19}$F NMR (282 MHz, CDCl₃) δ -65.2 (s, 3F). IR (thin film): $\nu_{\text{max}}$ 3375, 3088, 1740, 1638, 1603 cm⁻¹. MS (ESI): $m/z$ (%) 422 (M⁺ + H⁺). HRMS: Calculated for C₂₃H₂₇NO₃F₃ (M⁺ + H⁺): 422.19375; Found: 422.19471.

(2R,3S)-Diethyl 2-((R)-2-methoxy-1-phenylethylamino)-2-(trifluoromethyl)-3-vinylsuccinate (3k). Compound 3k (75 mg, 60% yield) as a yellow oil was prepared as above described with utilization of In powder (96 mg, 0.84 mmol) and allyl bromide 2f (0.96 mmol) from 1a (91 mg, 0.3 mmol) The product was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 80:1). (Note: The reaction was quenched with water instead of HCl (1 M, 2 mL)). $^1$H NMR (300 MHz, CDCl₃) δ 7.30-7.23 (m, 5H), 6.11 (m, 1H), 5.34-5.26 (m, 2H), 4.18-4.10 (m, 3H), 3.88-3.82
(m, 1H), 3.66 (d, J = 9.6 Hz, 2H), 3.56-3.49 (m, 2H), 3.46-3.40 (m, 1H), 3.30 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (75.4 MHz, CDCl$_3$) δ 169.5, 166.6, 141.4, 130.7, 127.9, 127.4, 127.2, 124.8 (q, J = 290.2 Hz), 121.7, 77.4, 69.0 (q, J = 24.7 Hz), 61.5, 58.8, 57.3, 54.7, 13.7, 13.3. $^{19}$F NMR (282 MHz, CDCl$_3$) δ -68.8 (s, 3F). IR (thin film): $\nu_{\text{max}}$ 3360, 3034, 1747, 1637 cm$^{-1}$. MS (EI): m/z (%) 372 (M$^+$ -C$_2$H$_5$O, 100), 135, 58, 43. HRMS: Calculated for C$_{18}$H$_{21}$NO$_4$F$_3$ (M$^+$ - C$_2$H$_5$O): 372.1423; Found: 372.1422.

Preparation of (3R, 5R)-4b.

$^{3R,5R}$-3-allyl-5-phenyl-3-(trifluoromethyl)morpholin-2-one (4b). To a solution of 3b (84 mg, 0.2 mmol) in CH$_2$Cl$_2$ (2 mL) was added dropwise BBr$_3$ (2 M in CH$_2$Cl$_2$, 0.5 mL, 1 mmol) at -78 °C. After stirring for 1 h at the same temperature, the reaction mixture was warmed to -25 °C and stirred for 4 h. The reaction was quenched with brine, extracted with CH$_2$Cl$_2$, washed with water, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated to provide crude amino alcohol which was used to do the next step without further purification. The crude amino alcohol was dissolved in anhydrous THF (4 mL) under N$_2$. Concentrated H$_2$SO$_4$ (15 μL) was added, and the resulting mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with ethyl acetate, washed with saturated NaHCO$_3$, brine, dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 50:1) to give (3R,5R)-4b 50 mg (88% overall yield, 2 steps) as a white solid. This compound is known.$^3$ [$\alpha$]$_D$$^{25}$ = 13.7 (c 1.8, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.43-7.37 (m, 5H), 5.82 (m, 1H), 5.33-5.25 (m, 2H), 4.37-4.26 (m, 3H), 3.16 (dd, J = 13.6 Hz, 6.6 Hz, 1H), 2.54 (dd, J = 13.6 Hz, 7.8 Hz, 1H), 2.08 (br, 1H). $^{19}$F NMR (282 MHz, CDCl$_3$) δ -76.9 (s, 3F).
Preparation of optically pure 4j.

(3R,5R)-5-phenyl-3-((R)-1-phenylallyl)-3-(trifluoromethyl)morpholin-2-one (4j). To a solution of 3j (66 mg, 0.16 mmol) in CH₂Cl₂ (2 mL) was added dropwise BBr₃ (4 M in CH₂Cl₂, 0.2 mL, 0.8 mmol) at -78 °C. After stirring for 2 h at the same temperature, the reaction mixture was warmed to -25 °C and stirred for 4 h. The reaction was quenched with brine at same temperature, extracted with CH₂Cl₂, washed with water, dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified with silica gel chromatography ((Petroleum ether /Ethyl Acetate = 20:1) to give 3j’ (51 mg, 78%). ¹H NMR (300 MHz, CDCl₃) δ 7.34-7.25 (m, 10H), 6.42 (m, 1H), 5.33-5.23 (m, 2H), 4.08-4.00 (m, 2H), 3.80-3.64 (m, 3H), 3.54-3.44 (m, 1H), 2.32 (br, 2H), 0.73 (t, J = 7.5 Hz, 3H). ¹⁹F NMR (282 MHz, CDCl₃) δ -65.5 (s, 3F).

3j’ (20 mg, 0.05 mmol) was dissolved in THF (2 mL), a solution of NaOH (3 mg, 0.075 mmol) in H₂O (2 mL) was added. The resulting mixture was stirred at room temperature for 36 h. The reaction was quenched with 1N HCl and adjusted pH value to 1-2. The resulting mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated. The residue was purified with silica gel chromatography (Petroleum ether /Ethyl Acetate = 50:1) to give (3R,5R)-4j 11 mg (60% yield) as a white solid. [α]D²⁵ = -49.6 (c 0.91, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.36 (m, 8H), 7.24 (m, 2H), 6.24 (m, 1H), 5.40-5.30 (m, 2H), 4.65 (d, J = 9.9 Hz, 1H), 4.22 (t, J = 10.8 Hz, 1H), 3.95 (dd, J = 10.5 Hz, 3.0 Hz, 1H), 3.29 (dd, J = 10.5 Hz, 2.4 Hz, 1H), 2.43 (br, 1H). ¹³C NMR (100.6 MHz, CDCl₃) δ 164.7, 137.5, 136.5, 131.5, 129.3, 129.1, 129.0, 128.0, 127.3, 124.0 (q, J = 285.7 Hz), 120.4, 73.9, 70.4 (q, J = 24.1 Hz), 54.1, 53.3. ¹⁹F NMR (282 MHz, CDCl₃) δ -72.8 (s, 3F). IR (thin film): νₘₐₓ 3350, 1735 cm⁻¹. MS (ESI): m/z (%) 384 (M⁺ + Na⁺), 362 (M⁺ + H⁺). HRMS: Calculated for C₂₀H₁₉NO₂F₃ (M⁺ + H⁺): 362.13624; Found: 362.13701.
(R)-2-(Trimethylsilyl)ethyl 2-amino-4-methyl-2-(trifluoromethyl)pentanoate (5). To a solution of 3g (50 mg, 0.116 mmol) in MeOH (5 mL) was added Pd(OH)\textsubscript{2}/C (20%, 21.5 mg). The resulting mixture was stirred under H\textsubscript{2} (5 atm) for 24 h at room temperature. The mixture was filtered with celite and the filtrate was concentrated without further purification to give (R)-\(\alpha\)-Tfm-Leu 5 28 mg (80% yield) as a light yellow oil. \([\alpha]_D^{25} = -4.85 \ (c \ 0.75, \text{CHCl}_3).\) \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 4.29 (m, 2H), 2.03 (dd, \(J = 13.8 \text{ Hz}, 7.8 \text{ Hz}, 1\text{H}), 1.82 \text{ (m, 2H}), 1.65 \text{ (dd, } J = 13.8 \text{ Hz, 5.4 Hz, 1H}), 1.05 \text{ (dd, } J = 10.8 \text{ Hz, 7.2 Hz, 2H}), 1.00 \text{ (d, } J = 6.9 \text{ Hz, 3H}), 0.87 \text{ (d, } J = 6.9 \text{ Hz, 3H}), 0.06 \text{ (s, 9H}).\) \(^{13}\)C NMR (75.4 MHz, CDCl\textsubscript{3}) \(\delta\) 169.6, 125.2 (q, \(J = 285.9 \text{ Hz}), 64.9, 64.3 (q, J = 26.1 \text{ Hz}), 40.0, 24.4, 23.7, 22.4, 17.1, -1.7. \(^{19}\)F NMR (282 MHz, CDCl\textsubscript{3}) \(\delta\) -78.3 (s, 3F). IR (thin film): \(\nu_{\text{max}} \text{ 2959, 1747, 1253 cm}^{-1}.\) MS (ESI): \(m/z\) (%) 256 (M\textsuperscript{+} - C\textsubscript{3}H\textsubscript{7}), 154, 73 (100). HRMS: Calculated for C\textsubscript{9}H\textsubscript{17}NO\textsubscript{2}F\textsubscript{3}Si (M\textsuperscript{+} - C\textsubscript{3}H\textsubscript{7}): 256.0981; Found: 256.0976.
(R)-2-((R)-2-methoxy-1-phenylethlamino)-2-(trifluoromethyl)pent-4-en-1-ol (6). To a solution of 3a (103 mg, 0.3 mmol) in CH$_2$Cl$_2$ (3 mL) was added dropwise DIBAI-H (1 M in toluene, 0.9 mL, 0.9 mmol) at – 78 °C. After stirring for 1 h at the same temperature, the reaction mixture was warmed to room temperature and stirred for 1.5 h. The reaction was quenched with 1N HCl, and extracted with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified with Al$_2$O$_3$ chromatography (CH$_2$Cl$_2$/MeOH = 60:1) to give 6 87 mg (96% yield). [α]$_D^{25}$ = -59.8 (c 1.56).

1H NMR (300 MHz, CDCl$_3$) δ 7.44-7.28 (m, 5H), 5.76 (m, 1H), 5.12-5.06 (m, 2H), 4.23 (dd, $J$ = 8.7 Hz, 3.6 Hz, 1H), 3.49 (d, $J$ = 6.3 Hz, 2H), 3.44-3.31 (m, 5H), 2.43 (t, $J$ = 7.4 Hz, 1H), 2.39 (dd, $J$ = 14.7 Hz, 8.1 Hz), 2.29 (dd, $J$ = 14.7 Hz, 7.5 Hz, 1H). 13C NMR (100.6 MHz, CDCl$_3$) δ 142.2, 131.6, 128.6, 127.8, 127.1 (q, $J$ = 288.8 Hz), 126.9, 119.4, 77.7, 63.2 (q, $J$ = 22.7 Hz), 61.1, 58.7, 55.7, 36.8. 19F NMR (282 MHz, CDCl$_3$) δ -71.8 (s, 3F). IR (thin film): $\nu_{max}$ 3450, 3355, 1640 cm$^{-1}$.

MS (ESI): m/z (%) 304 (M$^+$ + H$^+$), 326 (M$^+$ + Na$^+$). HRMS: Calculated for C$_{15}$H$_{20}$NO$_2$F$_3$Na (M$^+$ + Na$^+$): 326.13383; Found: 326.13403.

(R)-2-allyl-1-((R)-2-methoxy-1-phenylethyl)-2-(trifluoromethyl)aziridine (7). To a solution of 6 (45 mg, 0.15 mmol) in CH$_2$Cl$_2$ (1.5 mL) was added Et$_3$N (56 μL, 0.30 mmol), followed by MsCl (18 μL, 0.225 mmol) at 0 °C. The resulting mixture was then warmed to room temperature and stirred for 12 h. The reaction mixture was directly purified with Al$_2$O$_3$ chromatography (pure CH$_2$Cl$_2$) to give 7 40 mg (93% yield). [α]$_D^{25}$ = -100.0 (c 1.6). 1H NMR (300 MHz, CDCl$_3$) δ
7.42-7.27 (m, 5H), 5.56 (m, 1H), 5.03-4.97 (m, 2H), 3.68 (dd, \( J = 9.6 \) Hz, 8.1 Hz, 1H), 3.50 (dd, \( J = 9.6 \) Hz, 3.9 Hz, 1H), 3.37 (m, 1H), 3.35 (s, 3H), 2.42 (s, 1H), 2.34 (dd, \( J = 15.6 \) Hz, 6.3 Hz, 1H), 2.20 (dd, \( J = 15.6 \) Hz, 7.5 Hz, 1H). 13C NMR (75.4 MHz, CDCl\(_3\)) \( \delta \) 139.7, 133.8, 128.4, 127.6, 127.2, 125.2 (q, \( J = 276.9 \) Hz), 117.6, 78.9, 66.1, 59.1, 35.1, 28.9. 19F NMR (282 MHz, CDCl\(_3\)) \( \delta \) -73.2 (s, 3F). IR (thin film): \( \nu \) max 1643, 1454, 1123 cm\(^{-1}\). MS (ESI): \( m/z \) (%) 286 (M\(^+\) + H\(^+\)). HRMS: Calculated for C\(_{15}\)H\(_{19}\)NO\(_3\)F (M\(^+\) + H\(^+\)): 286.14133; Found: 286.14184.

References:


Proposed transition state for Brigaud's method
(R)-Ethyl 3,3,3-trifluoro-2-(2-methoxy-1-phenylethylimino)propanoate (1a).
(R)-2-(Trimethylsilyl)ethyl 3,3,3-trifluoro-2-(2-methoxy-1-phenylethylimino)propanoate (1b).
(R)-Allyl 3,3,3-trifluoro-2-(2-methoxy-1-phenylethylimino)propanoate(1c).
(R)-prop-2-ynyl 3,3,3-trifluoro-2-(2-methoxy-1-phenylethylimino)propanoate (1d).
(R)-benzyl 3,3,3-trifluoro-2-(2-methoxy-1-phenylethylimino)propanoate (1e).
(R)-Ethyl 2-((R)-2-methoxy-1-phenylethylamino)-2-(trifluoromethyl)pent-4-enoate (3a).
(R)-2-(Trimethylsilyl)ethyl 2-((R)-2-methoxy-1-phenylethylamino)-2-(trifluoromethyl)pent-4-enoate (3b).
(R)-Allyl 2-((R)-2-methoxy-1-phenylethylamino)-2-(trifluoromethyl)pent-4-enoate (3c).
(R)-Prop-2-ynyl 2-((R)-2-methoxy-1-phenylethylamino)-2-(trifluoromethyl)pent-4-enoate (3d).
(R)-Benzyl 2-((R)-2-methoxy-1-phenylethylamino)-2-(trifluoromethyl)pent-4-enoate (3e).
(R)-Ethyl 2-((R)-2-methoxy-1-phenylethylamino)-4-methyl-2-(trifluoromethyl)pent-4-enoate (3f).
\((R)-2-(\text{Trimethylsilyl})\text{ethyl 2-}\((R)\)-2-methoxy-1-phenylethylamino\)-4-methyl-2-(trifluoromethyl)pent-4-enoate (3g).\)
(R)-Diethyl 2-((R)-2-methoxy-1-phenylethylamino)-4-methylene-2-(trifluoromethyl)pentane Dioate (3h).
(2R,3S)-Ethyl 2-((R)-2-methoxy-1-phenylethylamino)-3-methyl-2-(trifluoromethyl)pent-4-Enoate (3i).
(2R,3R)-Ethyl 2-((R)-2-methoxy-1-phenylethylamino)-3-phenyl-2-(trifluoromethyl)pent-4-enoate (3j).
(2R,3S)-Diethyl 2-((R)-2-methoxy-1-phenylethylamino)-2-(trifluoromethyl)-3-vinylsuccinate (3k).
(3R,5S)-3-allyl-5-phenyl-3-(trifluoromethyl)morpholin-2-one (4b).
(2R,3R)-ethyl 2-((R)-2-hydroxy-1-phenethylamino)-3-phenyl-2-(trifluoromethyl)pent-4-enoate (3j′)
(3R,5R)-5-phenyl-3-((R)-1-phenylallyl)-3-(trifluoromethyl)morpholin-2-one (4j).
(R)-2-(Trimethylsilyl)ethyl 2-amino-4-methyl-2-(trifluoromethyl)pentanoate (5).
(R)-2-((R)-2-methoxy-1-phenylethlamino)-2-(trifluoromethyl)pent-4-en-1-ol (6).
(R)-2-allyl-1-((R)-2-methoxy-1-phenylethyl)-2-(trifluoromethyl)aziridine (7).