# Supporting Information for

# "The Rate of Elimination of a β-Amino Zinc Reagent is *Reduced* by using a *Better* Leaving Group"

**Richard F.W. Jackson,*[a] Ian Rilatt[a] and P. John Murray[b]**

## Experimental Details

**4-Iodo-3-(2,2,2-trifluoro-acetylamino)-butyric acid methyl ester (5b)**
To a stirred solution of **4** (15.00 g, 61.7 mmol) in ethyl acetate (80 mL) was added solid N-hydroxysuccinimide (7.10 g, 61.7 mmol) at 0°C. A solution of dicyclohexylcarbodiimide (12.74 g, 61.7 mmol) in ethyl acetate (30 mL) was added slowly. The reaction was allowed to attain room temperature and left overnight. The precipitate of dicyclohexylurea was filtered off, and the filtrate was washed successively with saturated aqueous sodium hydrogen carbonate then brine, dried ($MgSO_4$) and evaporated under reduced pressure to give crude succinimide ester as a white solid (21 g, 79 %). The crude succinimide ester (21 g, 61.7 mmol, 1.0 eq.) was dissolved in the minimun amount of THF and added to a suspension of sodium borohydride (3.74 g, 98.9 mmol, 1.6 eq.) in THF (170 mL) at 0°C. The reaction was left for 5 minutes before quenching by the addition of water (100 mL). The product was extracted into ethyl acetate (3 x 50 mL) and the combined organic fractions washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography on silica with DCM-ethyl acetate (1:1) to give the alcohol as a white crystalline solid (10 g, 71 %).

Triphenylphosphine (12.0 g, 19.5 mmol), imidazole (3.1 g, 19.5 mmol) and iodine (11.6 g, 19.5 mmol) were added to dry DCM (130 mL) with stirring. The reaction flask was purged with nitrogen and a solution of the starting alcohol (10.0 g, 18.6 mmol) in dry DCM (40 mL) added under nitrogen via syringe. The reaction was monitored by TLC (DCM) and observed to have gone to completion after 5 min. The mixture was filtered before washing with saturated sodium thiosulfate solution (1 x 50 mL) and brine (50mL) and drying ($MgSO_4$). The DCM was evaporated under reduced pressure and the crude product purified by column chromatography on silica with DCM to give iodide **5b** as white crystals (12.8 g, 86 %), m.p. 71 - 72 °C. $\nu_{max.}/cm^{-1}$ 3287 (N-H); 1731 (C=O); 1705 (C=O); 1182 (C-O). Found C, 25.02; H, 2.67; N, 4.01; I, 36.98. $C_7H_9O_3NF_3I$ requires C, 24.80; H, 2.68; N, 4.13; I, 37.43. $\delta_H$ 2.72 (1H, dd, *J* = 17.0 and 5.5), 2.91 (1H, dd, *J* = 17.0 and 5.0), 3.39 (1H, dd, *J* = 10.5 and 6.5), 3.44 (1H, dd, *J* = 10.5 and 5.5), 3.73 (3H, s), 4.22 – 4.38 (1H, m) and 7.21 (1H, d, *J* = 5.5); $\delta_C$ 6.9, 37.2, 47.4, 52.3, 115.5 (q, *J* = 287), 156.6 (q, *J* = 39), and 170.9; m/z (TOF MS ES$^+$) 339.9653 (12 %, $MH^+$, $C_7H_{10}O_3NF_3I$ requires 339.9658), 308(5) and 295(5); $[\alpha]_D^{22.5}$ + 6.9 (c 1.01 in $CHCl_3$).

**4-Iodozinc-3-(2,2,2-trifluoro-acetylamino)-butyric acid methyl ester (1b)**
$\delta_H$ (400 MHz, DMF) 0.49 (2H, d, *J* = 7.9), 2.59 (1H, dd, *J* = 15.0 and 9.0), 2.74 (1H, dd, *J* = 15.0 and 5.0), 3.56 (3H, s), 4.47 - 4.59 (1H, m) and 8.71 (1H, d (br), *J* = 8.0). $\delta_C$ (100 MHz, DMF) 18.1, 42.8, 49.7, 51.2, 116.8 (q, *J* = 288), 155.3 (q, *J* = 35) and 172.3.

**Methyl but-3-enoate (2)**

Accurate mass analysis of this material was obtained from a GC-MS spectrum of a solution of decomposed organozinc reagent **1b** in DMSO. An NMR spectrum of **2** was obtained by heating the solution and condensing the material onto a cold finger cooled by liquid nitrogen; $\delta_H$ (250 MHz, DMSO) 3.15 (2H, dt, *J* = 7.0 and 1.5), 3.62 (3H, s), 5.10 - 5.24 (2H, m) and 5.78 - 5.97 (1H, m). m/z (TOF MS ES$^+$) 100.0526 (60 %, $M^+$, $C_5H_8O_2$ requires 100.0524), 72(40), 69(56) and 59(100).

**General procedure for the Coupling Reactions of Iodide 5b with Aryl Iodides**

Zinc dust (0.236 g, 3.6 mmol, 6.0 eq.) was placed in a dry 25 mL round bottom flask, with sidearm, containing a rugby ball shaped stirrer. The flask was flushed with nitrogen and dry DMF (0.75mL) and TMSCl (100μL, 0.8 mmol) were added under nitrogen *via* syringe. The solution was observed to effervesce and the mixture was vigorously stirred at room temperature for 5 min (the DMF occasionally changes to a yellow colour during this period). The zinc was allowed to settle and the supernatant solution was removed *via* syringe, followed by drying of the zinc under vacuum by heating with a hot air gun. The iodide **5b** (204 mg, 0.6 mmol, 1.0 eq.) was dissolved in DMF (0.75 mL) under nitrogen, and transferred to the zinc *via* syringe. The solution was stirred at 0 $^oC$ and the insertion judged by TLC (dichloromethane) to be complete within 5 min. $Pd_2(dba)_3$ (17.9 mg, 0.02 mmol), P(*o*-tol)$_3$ (23.8 mg, 0.08 mmol) and the aryl iodide (1.3 eq relative to the iodide **5b**) were added to the flask. The flask was covered with aluminium foil, and left at room temperature overnight. The reaction was diluted with EtOAc (50 mL), filtered and evaporated under reduced pressure. The residue was warmed at 40 $^oC$ under high vacuum to remove the DMF. The crude product was purified by column chromatography.

**4-*p*-Tolyl-3-(2,2,2-trifluoro-acetylamino)-butyric acid methyl ester (7a)**

This product was prepared following the procedure outlined above, using 4-iodotoluene as the aryl iodide (171 mg, 0.78 mmol, 1.3 eq.). Purification of the crude product by column chromatography on silica with DCM yielded a white solid (118 mg, 64 %), m.p. 80 – 83. $\nu_{max.}/cm^{-1}$ 3303 (N-H); 1732 (C=O); 1705 (C=O); 1563 (N-H). Found C, 55.41; H, 5.34; N, 4.52. $C_{14}H_{16}O_3NF_3$ requires C, 55.44; H 5.32; N 4.62. $\delta_H$ 2.32 (3H, s), 2.56 (2H, d, *J* = 5.0), 2.83 (1H, dd, *J* = 13.5 and 8.0), 2.96 (1H, dd, *J* = 13.5 and 6.5), 3.73 (3H, s), 7.05 (2H, d, *J* = 8.0), 7.13 (2H, d, *J* = 8.0) and 7.27 (1H, d(br), *J* = 6.0). $\delta_C$ 21.0, 35.7, 38.9, 48.1, 52.0, 115.7 (q, *J* = 286), 129.0, 129.4, 133.2, 136.7, 156.5 (q, *J* = 37) and 172.0. m/z (EI$^+$) 303.1088 (2 %, $M^+$, $C_{14}H_{16}O_3NF_3$ requires 303.1082); $[\alpha]_D^{22.5}$ –1.0 (c 1.03 in $CHCl_3$).

**4-(4-Methoxy-phenyl)-3-(2,2,2-trifluoro-acetylamino)-butyric acid methyl ester (7b)**

This product was prepared following the procedure outlined above, using 4-iodoanisole as the aryl iodide (183 mg, 0.78 mmol, 1.3 eq.). Purification of the crude product by column chromatography on silica with DCM yielded a white solid (133 mg, 69 %), m.p. 80 – 82 $^oC$. νν$max./cm^{-1}/cm^{-1}$ 3296 (N-H); 1732 (C=O); 1706 (C=O); 1515 (N-H). Found C, 52.82; H 5.02; N 4.46. $C_{16}H_{16}O_4$ $NF_3$ requires C, 52.67; H 5.05; N 4.39. $\delta_H$ 2.56 (2H, d, *J* = 5.0), 2.58 (1H, dd, *J* = 8.5 and 4.5), 2.81

(1H, dd, *J* = 14.0 and 8.0), 2.93 (1H, dd, *J* = 14.0 and 6.5), 3.73 (3H, s), 3.79 (3H, s), 4.34 - 4.50 (1H, m), 6.85 (2H, d, *J* = 9.0), 7.08 (2H, d, *J* = 9.0) and 7.27 (1H, d, *J* = 7.0). $\delta_C$ 35.7, 38.4, 48.1, 51.9, 55.1, 114.1, 115.6 (q, *J* = 286), 128.2, 130.1, 156.4 (q, *J* = 37), 158.6 and 171.9. m/z (EI) 319.1036 (8 %, $M^+$, $C_{14}H_{16}O_4NF_3$ requires 319.1031), 206 (72), 175 (11), 147 (19), 122 (11) and 121 (100); $[\alpha]_D^{22.5}$ –2.0 (c 1.02 in $CHCl_3$).

**4-Phenyl-3-(2,2,2-trifluoro-acetylamino)-butyric acid methyl ester (7c)**

This product was prepared following the procedure outlined above, using iodobenzene as the aryl iodide (88 μL, 0.78 mmol, 1.3 eq.). Purification of the crude product by column chromatography on silica with DCM yielded a white solid (126 mg, 72 %), m.p. 88 – 90 $^oC$. $\nu_{max.}/cm^{-1}$ 3305 (N-H); 1731 (C=O); 1702 (C=O); 1179 (C-O). Found C, 53.73; H, 4.71; N, 4.91. $C_{13}H_{14}NO_3F_3$ requires C, 53.98; H, 4.88; N, 4.84. $\delta_H$ 2.50 – 2.69 (2H, m), 2.84 (1H, dd, *J* = 13.5 and 6.5), 2.98 (1H, dd, *J* = 13.5 and 8.0), 4.38 – 4.56 (1H, m), 5.16 (2H, app q, *J* = 12.0), 7.18 – 7.33 (5H, m) and 7.33 – 7.44 (5H, m). m/z (TOF MS $ES^+$) 366.1305 (13 %, $MH^+$, $C_{19}H_{19}NO_3F_3$ requires 366.1317), 348 (6), 276 (13) 235 (100); $[\alpha]_D^{22.3}$ + 1.9 (c 1.05 in $CHCl_3$).

**4-(4-Cyano-phenyl)-3-(2,2,2-trifluoro-acetylamino)-butyric acid methyl ester (7d)**

This product was prepared following the procedure outlined above, using 4-iodobenzonitrile as the aryl iodide (179 mg, 0.78 mmol, 1.3 eq.). Purification of the crude product by column chromatography on silica with DCM yielded a white solid (146 mg, 77 %), m.p. 159 – 161 $^oC$. $\nu_{max.}/cm^{-1}$ 3292 (N-H); 2230 (C≡N); 1732 (C=O); 1703 (C=O). Found C, 53.67; H, 4.12; N, 8.73. $C_{14}H_{13}O_3N_2F_3$ requires C, 53.51; H, 4.17; N, 8.97. $\delta_H$ 2.56 (1H, dd, *J* = 17.0 and 4.5), 2.66 (1H, dd, *J* = 17.0 and 4.0), 2.94 (1H, dd, *J* = 13.5 and 7.5), 3.07 (1H, dd, *J* = 13.5 and 7.0), 3.75 (3H, s), 4.40 - 4.56 (1H, m), 7.30 (2H, d, *J* = 8.0), 7.40 (1H, d, *J* = 9.0), 7.62 (1H, d, *J* = 8.0); $\delta_C$ 36.0, 39.5, 47.7, 52.3, 111.2, 115.6 (q, *J* = 286), 118.6, 130.0, 132.6, 142.2, 156.7 (q, *J* = 37) and 171.8. m/z (EI) 314.0870 (2 %, $M^+$, $C_{14}H_{13}O_3N_2F_3$ requires 314.0878), 283 (16), 241 (18), 201 (100), 198 (62), 156 (82) and 117 (91); $[\alpha]_D^{22.5}$ +4.0 (c 1.00 in $CHCl_3$).

**4-(4-Nitro-phenyl)-3-(2,2,2-trifluoro-acetylamino)-butyric acid methyl ester (7e)**

This product was prepared following the procedure outlined above, except that after the zinc insertion was complete, the zinc was allowed to settle and the supernatant organozinc solution was transferred *via* syringe to a clean, dry flask under nitrogen. This was to avoid possible reduction of the aryl iodide with metallic zinc. The catalyst, ligand and 4-iodonitrobenzene (195 mg, 0.78 mmol, 1.3 eq.) were added to the flask and the reaction left overnight. Purification of the crude product by column chromatography on silica with DCM yielded a pale yellow solid (130 mg, 65 %), m.p. 173 - 175 $^oC$. $\nu_{max.}/cm^{-1}$ 3289 (N-H); 1735 (C=O); 1703 (C=O); 1346 (N=0). Found C, 46.87; H, 3.84; N, 8.34. $C_{13}H_{13}O_5N_2F_3$ requires C, 46.71; H, 3.92; N, 8.38. $\delta_H$ 2.58 (1H, dd, *J* = 17.0 and 4.5), 2.67 (1H, dd, *J* = 17.0 and 5.0), 2.99 (1H, dd, *J* = 13.5 and 7.5), 3.12 (1H, dd, *J* = 13.5 and 7.5), 3.75 (3H, s), 4.43 - 4.61 (1H, m), 7.36 (2H, d, *J* = 9.0), 7.46 (1H, d(br), *J* = 8.5) and 8.18 (2H, d, *J* = 9.0); $\delta_C$ 35.9, 39.2, 52.1, 115.6 (q, *J* = 286), 124.0, 130.0, 144.2, 147.2, 156.7 (q, *J* = 37) and 171.7. m/z (TOF MS

$ES^+$) 335.0845 (18 %, $MH^+$, $C_{13}H_{14}O_5N_2F_3$ requires 335.0855), 321 (100) and 303 (8); $[\alpha]_D^{22.9}$ +8.3 (c 0.85 in $CHCl_3$).

**4-Naphthalen-1-yl-3-(2,2,2-trifluoro-acetylamino)-butyric acid methyl ester (7f)**

This product was prepared following the procedure outlined above, except on a larger scale, using **5b** (1.2 g, 3.0 mmol, 1 eq.), $Pd_2(dba)_3$ (89.5 mg, 0.09 mmol), P(*o*-tol)$_3$ (119.0 mg, 0.39 mmol) and 2-iodonaphthalene as the aryl iodide (570 μL, 3.9 mmol, 1.3 eq.). Purification of the crude product by column chromatography on silica with DCM-petrol (4:1) yielded a white solid (711 mg, 70 %), m.p. 128 – 130 $^oC$. $\nu_{max.}/cm^{-1}$ 3306 (N-H); 1726 (C=O); 1698 (C=O); 1564 (N-H). Found C, 60.03; H, 4.75; N, 4.01. $C_{17}H_{16}O_3NF_3$ requires C, 60.18; H 4.75; N 4.13. $\delta_H$ 2.55 (2H, d, *J* = 4.5) 3.24 (1H, dd, *J* = 13.5 and 9.0) 3.59 (1H, dd, *J* = 13.5 and 6.0) 3.76 (3H, s) 4.57 - 4.73 (1H, m) 7.26 (1H, d, *J* = 9.0) 7.40 (1H, t, *J* = 8.0) 7.47 - 7.66 (3H, m) 7.79 (1H, d, *J* = 8.0) 7.87 (1H, d, *J* = 6.5) 8.21 (1H, d, *J* = 8.5). $\delta_C$ 35.5, 36.6, 47.5, 52.0, 115.7 (q, *J* = 286), 123.4, 125.2, 125.9, 126.5, 127.6, 128.0, 128.8, 131.8, 132.6, 133.9, 156.8 (q, *J* = 37) and 172.2. m/z (TOF MS $ES^+$) 340.1152 (100 %, $MH^+$, $C_{17}H_{16}O_3NF_3$ requires 340.1161); $[\alpha]_D^{22.5}$ +14.7 (c 1.02 in $CHCl_3$).

**4-(4-Bromo-phenyl)-3-(2,2,2-trifluoro-acetylamino)-butyric acid methyl ester (7g)**

This product was prepared following the procedure outlined above, using 1-bromo-4-iodobenzene as the aryl iodide (221 mg, 0.67 mmol, 1.3 eq.). Purification of the crude product by column chromatography on silica with DCM-petrol (4:1) yielded a white solid (118 mg, 53 %), m.p. 110 – 113 $^oC$. $\nu_{max.}/cm^{-1}$ 3296 (N-H); 1728 (C=O); 1702 (C=O); 1073 (C-Br). Found C, 42.61; H, 3.51; N, 3.72; Br 21.55. $C_{13}H_{13}O_3$ $NF_3Br$ requires C, 42.41; H 3.56; N 3.80; Br 21.70. $\delta_H$ 2.53 (1H, dd, *J* = 17.0 and 4.5), 2.61 (1H, dd, *J* = 17.0 and 5.0), 2.83 (1H, dd, *J* = 13.5 and 8.0), 2.97 (1H, dd, *J* = 13.5 and 6.5), 3.74 (3H, s), 4.35 - 4.51 (1H, m), 7.05 (2H, d, *J* = 8.5), 7.33 (1H, d, *J* = 8.5), 7.44 (2H, d, *J* = 8.5). $\delta_C$ 36.0, 39.2, 48.2, 52.6, 116.1 (q, *J* = 287), 131.2, 132.3, 135.8, 157.0 (q, *J* = 37) and 172.3. m/z (TOF MS $ES^+$) 368.0122 (100 %, $M^+$, $C_{13}H_{13}O_3NF_3Br$ requires 368.0109) and 336 (4); $[\alpha]_D^{22.5}$ –1.0 (c 1.01 in $CHCl_3$).

**4-(4-Fluoro-phenyl)-3-(2,2,2-trifluoro-acetylamino)-butyric acid methyl ester (7h)**

This product was prepared following the procedure outlined above, except on a smaller scale, using **5b** (175 mg, 0.5 mmol, 1 eq.), $Pd_2(dba)_3$ (15.4 mg, 0.02 mmol), P(*o*-tol)$_3$ (20.4 mg, 0.08 mmol) and 1-fluoro-4-iodobenzene as the aryl iodide (77 μL, 0.67 mmol, 1.3 eq.). Purification of the crude product by column chromatography on silica with DCM-petrol (4:1) yielded a white solid (117 mg, 74 %), m.p. 108 – 110. $\nu_{max.}/cm^{-1}$ 3291 (N-H); 1735 (C=O); 1705 (C=O); 1509 (N-H). Found C, 50.67; H, 4.18; N, 4.80. $C_{13}H_{13}O_3NF_4$ requires C, 50.82; H 4.26; N 4.56. $\delta_H$ 2.54 (1H, dd, *J* = 17.0 and 4.5), 2.62 (1H, dd, *J* = 17.0 and 5.0), 2.85 (1H, dd, *J* = 14.0 and 8.0), 2.97 (1H, dd, *J* = 14.0 and 7.0), 3.73 (3H, s), 4.36 - 4.51 (1H, m), 6.94 - 7.06 (2H, m), 7.09 - 7.18 (2H, m) and 7.32 (1H, d, *J* = 7.0). $\delta_C$ 36.2, 39.0, 46.6, 52.5, 116.1 (d, *J* = 22), 116.1 (q, *J* = 286), 131.0 (d, *J* = 8), 132.6 (d, *J* = 3), 157.0 (q, *J* = 37), 162.4 (d, *J* =

244) and 172.3. m/z (TOF MS $ES^+$) 308.0895 (100 %, $MH^+$, $C_{14}H_{16}O_3NF_3$ requires 308.091) and 275(5); $[\alpha]_D^{22.5}$ +5.8 (c 1.04 in $CHCl_3$).

**3-tert-Butoxycarbonylamino-4-naphthalen-1-yl-butyric acid methyl ester (8f)**

This product was synthesised by the deprotection of the trifluoroacetamide group and subsequent re-protection of the free amine as the N-Boc Derivative; Trifluoroacetamide **7f** (100 mg, 0.29 mmol, 1 eq.) and sodium methoxide (100mg, 1.85 mmol) were refluxed for 2 days in dry methanol (10 mL). After this time the solvent was evaporated to leave an off-white solid, which was shown to contain 100% of the free amine by $^1$H-NMR in MeOH. The amine was then converted to the hydrochloride salt to remove any sodium methoxide, which might interfere with the Boc protection, by dissolving the crude product in a solution of dry HCl in MeOH (generated by the reaction of methanol (20mL) and acetyl chloride (3.8 mL)). The solvent was evaporated and the crude product dissolved in dioxane (4.5 mL) at 0$^o$C. Triethylamine (82 μL, 0.59 mmol, 2 eq.) was added, followed by di-*tert*-butyl dicarbonate (64 mg, 0.29 mmol, 1 eq.) as a solution in dioxane (0.5 mL), and the solution stirred overnight at room temperature. The solvent was evaporated and the crude product purified by column chromatography on silica with DCM-ethyl acetate (20:1) to yield **8f** as colourless oil which crystallised upon standing, 94 mg (93%) m.p. 92 – 95 $^o$C (lit. m.p. 93 – 96 $^o$C), $[\alpha]_D^{21.9}$ +34.9 (c 4.01 in DCM), literature value $[\alpha]_D^{22}$ +37.5 (c 4.07 in DCM).[1]

1 C. S. Dexter and R. F. W. Jackson, *Journal of Organic Chemistry*, 1999, **64**, 7579.