Lipase-Catalysed Enzymatic Kinetic Resolution of Aromatic Morita-Baylis-Hillman Derivatives by Hydrolysis and Transesterification

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1. General procedure for the preparation of Morita-Baylis-Hillman adducts 4a–d

![Scheme S1](image)

The MBH adducts were prepared by dissolving DABCO (1 eq.) and the relevant aldehyde (1-1.5 eq.) in excess acrylonitrile (10-12 ml) in a 50 ml round-bottomed flask and stirring at room temperature (Scheme S1). After reaction completion, as determined by TLC, ethyl acetate (30 ml) and water (30 ml) were added to the reaction mixture. The organic layer was separated from the aqueous layer, and the aqueous layer was extracted twice more with ethyl acetate. The organic medium was dried over anhydrous MgSO$_4$ and purified by column chromatography (30% ethyl acetate/hexane) using normal silica gel (150 g). The reaction products were then concentrated under reduced pressure to afford the desired product.

1.1 Synthesis of 2-[(4-fluorophenyl) (hydroxy)methyl]acrylonitrile 4a

Acrylonitrile (10 ml, 153 mmol, 6 eq), DABCO (2.82 g, 25.14 mmol, 1 eq) and 4-fluorobenzaldehyde (3.12 g, 25.14 mmol, 1 eq) were left to stir for 18 h to afford 4a as a yellow oil (3.12 g, 71%). R$_f$ = 0.34 (30% ethyl acetate/hexane); IR (neat, cm$^{-1}$) 3432, 2896, 2230, 1509, 1015; $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.36 – 7.32 (m, 2H, H3 & H5), 7.10 – 7.04 (m, 2H, H2 & H6), 6.08 (d, $J_{C-F} = 1.2$ Hz, 1H, H10a), 6.02 – 6.01 (m, 1H, H10b), 5.25 (s, 1H, H7), 3.04 (d, $J = 3.4$ Hz, 1H, OH). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 162.8 (d, $J_{C-F} = 247.7$ Hz, C1), 134.9 (d, $J_{C-F} = 3.2$ Hz, C4), 130.0 (C10), 128.3 (d, $J_{C-F} = 8.4$ Hz, C3& C5), 126.0 (C8), 116.8 (C9), 115.8 (d, $J_{C-F} = 21.7$ Hz, C2& C6), 73.3 (C7). Chiral HPLC: Lux 3 immobilised Amylose-1 (250 x 4.6 mm); mobile phase, hexane: IPA (90:10); flow rate = 1 mL/min; $t_R = 6.25$ min, $t_R = 6.73$ min.
1.2 Synthesis of 2-[(4-bromophenyl) (hydroxy)methyl]acrylonitrile 4b

Acrylonitrile (12 ml, 183 mmol, 15 eq), DABCO (1.36 g, 12.15 mmol, 1 eq) and 4-bromobenzaldehyde (3.31 g, 17.89 mmol, 1.5 eq) were left to stir for 20 h to afford 4b as a yellow oil (3.57 g, 82%). Rf = 0.31 (30% ethyl acetate/hexane); IR (neat, cm⁻¹) 3435, 2883, 2228, 1592, 1010; ¹H NMR (300 MHz, Chloroform-d) δ 7.55 – 7.50 (m, 2H, H2 & H6), 7.29 – 7.23 (m, 2H, H3 & H5), 6.10 (d, J = 1.3 Hz, 1H, H10a), 6.03 (d, 1H, J = 0.9 Hz, H10b), 5.26 (s, 1H, H7), 2.81 (s, 1H, OH). ¹³C NMR (75 MHz, CDCl₃) δ 138.1 (C4), 132.0 (C2 & C6), 130.2 (C10), 128.1 (C3 & C5), 125.8 (C8), 122.9 (C1), 116.6 (C9), 73.5 (C7). Chiral HPLC: Lux 3 immobilised Amylose-1 (250 x 4.6 mm); mobile phase, hexane: IPA (90:10); flow rate = 1 mL/min); tR = 8.88 min, tR = 9.66 min.

1.3 Synthesis of 2-[(4-cyanophenyl) (hydroxy)methyl]acrylonitrile 4c

Acrylonitrile (10 mL, 153 mmol, 24 eq), DABCO (0.71 g, 6.33 mmol, 1 eq) and 4-cyanobenzaldehyde (1.04 g, 7.93 mmol, 1.25 eq) were left to stir for 1.5 h to afford 4c as a white precipitate (1.21 g, 82%), mp 72-74 ºC. Rf = 0.34 (40% ethyl acetate/hexane); IR (neat, cm⁻¹) 3430, 2888, 2233, 1506, 1020; ¹H NMR (300 MHz, Chloroform-d) δ 7.71 – 7.67 (m, 2H, H2 & H6), 7.57-7.52 (m, 2H, H3 & H5), 6.17 (d, J = 1.3 Hz, 1H, H10a), 6.09 (d, J = 0.9 Hz, 1H, H10b), 5.39 (s, 1H, H7), 3.09 (s, 1H, OH). ¹³C NMR (75 MHz, CDCl₃) δ 144.2 (C4), 132.6 (C2 & C6), 130.8 (C10), 127.1 (C3 & C5), 125.4 (C8), 118.3 (C11), 116.3 (C9), 112.4 (C1), 73.3 (C7). Chiral HPLC: Lux 3 immobilised Amylose-1 (250 x 4.6 mm); mobile phase, hexane: IPA (90:10); flow rate = 1 mL/min); tR = 15.49 min, tR = 17.44 min.

1.4 Synthesis of 2-[(4-chlorophenyl) (hydroxy)methyl]acrylonitrile 4d
Acrylonitrile (12 ml, 183 mmol, 8.5 eq), DABCO (2.42 g, 21.57 mmol, 1 eq) and 4-chlorobenzaldehyde (3.51 g, 24.97 mmol, 1.2 eq) were left to stir for 3 h to afford t4d as a yellow oil (4.16 g, 86%). Rf = 0.36 (30% ethyl acetate/hexane); IR (neat, cm⁻¹) 3430, 2879, 2228, 1597, 1014; ¹H NMR (400 MHz, Chloroform-d) δ 7.42 – 7.38 (m, 2H, H2 & H6), 7.37 – 7.34 (m, 2H, H3 & H5), 7.32 – 6.06 (m, 1H, 10Hb), 5.29 (s, 1H, H7), 2.60 (s, 1H, OH). ¹³C NMR (101 MHz, CDCl₃) δ 137.6 (C4), 134.9 (C1), 130.1 (C10), 129.1 (C2& C6), 127.9 (C3& C5), 125.9 (C8), 116.6 (C9), 73.5 (C7). Chiral HPLC: Lux 3 immobilised Amylose-1 (250 x 4.6 mm); mobile phase, hexane: IPA (90:10); flow rate = 1 mL/min); tᵣ = 8.37 min, tᵣ = 9.10 min.

2. General procedure for the preparation of Morita-Baylis-Hillman acetates 5a–d

Scheme S2

The MBH acetates were prepared by initially stirring the corresponding MBH adduct (4a-d) (1eq.) in 2-methyltetrahydrofuran (20-25 ml) for 5 min, followed by the addition of trimethylamine (1.1-1.25 eq.), acetic anhydride (1.1-1.25 eq.) and DMAP (1-2 mol %) to the solution (Scheme S2). The resulting mixture was stirred at room temperature for 30 min – 1 h. The organic layer was washed with an aqueous saturated solution of NaHCO₃ (2 x 25 ml) and then dried over anhydrous MgSO₄, concentrated in vacuo and purified by column chromatography (30% ethyl acetate/hexane) to afford the desired products.

2.1. Synthesis of (±)-2-cyano-1-(4-fluorophenyl)allyl acetate 5a
Compound 4a (3.06 g, 17.27 mmol, 1 eq.), triethylamine (3 ml, 21.52 mmol, 1.25 eq.), acetic anhydride (2 ml, 21.16 mmol, 1.25 eq.) and DMAP (24.28 mg, 0.20 mmol, 1 mol%) were stirred in 2-methyltetrahydrofuran (25 ml) to afford 5a as a yellow oil (3.1 g, 83%). Rf = 0.39 (30% ethyl acetate/hexane). IR (neat, cm⁻¹) 3035, 2967, 2229, 1746, 1218; ¹H NMR (300 MHz, Chloroform-d) δ 7.43 – 7.35 (m, 2H, H3 & H5), 7.13 – 7.05 (m, 2H, H2 & H6), 6.32 (s, 1H, H7), 6.08 (d, J = 1.0 Hz, 1H, H10a), 6.02 (d, J = 1.3 Hz, 1H, H10b), 2.17 (s, 3H, H11). ¹³C NMR (75 MHz, CDCl₃) δ 169.0 (C=O), 162.9 (d, ¹J C-F = 248.6 Hz, C1), 131.9 (C10), 131.5 (d, ²J C-F = 3.3 Hz, C4), 128.8 (d, ³J C-F = 8.5 Hz, C3 & C5), 122.9 (C8), 115.9 (C9), 115.8 (d, ⁴J C-F = 21.8 Hz, C2 & C6), 73.5 (C7), 20.7 (C11). Chiral HPLC: Lux 3 immobilised Amylose-1 (250 x 4.6 mm); mobile phase, hexane: IPA (90:10); flow rate = 1 mL/min; tR = 6.4 min, tR = 6.8 min.

2.2. Synthesis of (±)-2-cyano-1-(4-bromophenyl)allyl acetate 5b

Compound 4b (2.17 g, 9.11 mmol, 1 eq.), triethylamine (1.5 ml, 10.76 mmol, 1.2 eq), acetic anhydride (1 ml, 10.58 mmol, 1.2 eq.) and DMAP (24.28 mg, 0.20 mmol, 2 mol%) were stirred in 2-methyltetrahydrofuran (20 ml) to afford 5b as a colourless oil (1.86 g, 74%). Rf = 0.48 (30% ethyl acetate/hexane). IR (neat, cm⁻¹) 3034, 2966, 2229, 1746, 1218; ¹H NMR (400 MHz, Chloroform-d) δ 7.54 (d, J = 8.2 Hz, 1H, H2 & H6), 7.28 (d, J = 8.1 Hz, 1H, H3 & H5), 6.28 (s, 1H, H7), 6.10 (s, 1H, H10a), 6.03 (s, 1H, H10b), 2.18 (br s, 3H, H11). ¹³C NMR (101 MHz, CDCl₃) δ 169.0 (C=O), 134.6 (C4), 132.2 (C10), 132.1 (C2 & C6), 128.5 (C3 & C5), 123.3 (C8), 122.6 (C1), 115.8 (C9), 73.6 (C7), 20.8 (C11). Chiral HPLC: Lux 3 immobilised Amylose-1 (250 x 4.6 mm); mobile phase, hexane: IPA (90:10); flow rate = 1 mL/min; tR = 7.18 min, tR = 8.11 min.

2.3. Synthesis of (±)-2-cyano-1-(4-cyanophenyl)allyl acetate 5c
Compound 4c (1.76 g, 9.56 mmol, 1 eq.), triethylamine (1.5 ml, 10.76 mmol, 1.13 eq.), acetic anhydride (1 mL, 10.58 mmol, 1.1 eq.) and DMAP (24.28 mg, 0.20 mmol, 2 mol%) were stirred in 2-methyltetrahydrofuran (20 ml) to afford 5c as a yellow precipitate (1.80 g, 83%), mp 48-50 ºC. Rf = 0.41 (30% ethyl acetate/hexane). IR (neat, cm⁻¹) 3072, 2964, 2225, 1611, 1371; ¹H NMR (500 MHz, Chloroform-d) δ 7.74 – 7.71 (m, 2H, H2 & H6), 7.55 – 7.52 (m, 2H, H3 & H5), 6.36 (s, 1H, H7), 6.15 (s, 1H, H10a), 6.11 (d, J = 0.9 Hz, 1H, H10b), 2.21 (s, 3H, H11). ¹³C NMR (126 MHz, CDCl₃) δ 168.9 (C=O), 140.6 (C4), 133.0 (C10), 132.7 (C2 & C6), 127.5 (C3 & C5), 122.1 (C8), 118.0 (C12), 115.5 (C9), 113.2 (C1), 73.6 (C7), 20.8 (C11). Chiral HPLC: Lux 3 immobilised Amylose-1 (250 x 4.6 mm); mobile phase, hexane: IPA (90:10); flow rate = 1 mL/min); tᵣ = 18.44 min, tᵣ = 20.21 min.

2.4. Synthesis of (±)-2-cyano-1-(4-chlorophenyl)allyl acetate 5d

Compound 4d (3.18 g, 16.42 mmol, 1 eq.), triethylamine (1.5 ml, 10.76 mmol, 1.13 eq.), acetic anhydride (1 mL, 10.58 mmol, 1.1 eq.) and DMAP (24.28 mg, 0.20 mmol, 1 mol%) were stirred in dichloromethane (25 ml) to afford 5d as a colourless oil (2.78 g, 81%). Rf = 0.80 (30% ethyl acetate/hexane). IR (neat, cm⁻¹) 3113, 2890, 2229, 1624, 1371; ¹H NMR (300 MHz, Chloroform-d) δ 7.41 – 7.37 (m, 2H, H6& H2), 7.36 – 7.32 (m, 2H, H3& H5), 6.30 (s, 1H, H7), 6.10 (d, J = 1.0 Hz, 1H, H10a), 6.03 (d, J = 1.3 Hz, 1H, H10b), 2.18 (s, 3H, H11). ¹³C NMR (75 MHz, CDCl₃) δ 169.2 (C=O), 135.3 (C4), 134.1 (C1), 132.2 (C10), 129.2(C2& C6), 128.3 (C3& C5), 122.8 (C8), 115.9 (C9), 73.7 (C7), 20.9 (C11). Chiral HPLC: Lux 3 immobilised Amylose-1 (250 x 4.6 mm); mobile phase, hexane: IPA (90:10); flow rate = 1 mL/min); tᵣ = 7.29 min, tᵣ = 8.08 min.

3. General procedure for the preparation of Morita-Baylis-Hillman butyrates 6a–d and propionate 11b

Scheme S3
MBH adducts 4a-4d were dissolved in 2-methyltetrahydrofuran (10-20 ml) and trimethylamine (1-1.6 eq.), butyric anhydride (1-1.3 eq.) and 4-dimethylaminopyridine DMAP (2-4 mol %) were added to these stirring solutions (Scheme S3). The resulting mixture was stirred at room temperature for 40 min – 1 h. The organic layer was washed with aqueous saturated NaHCO₃ (2 x 25 ml) and then dried over anhydrous MgSO₄. After removal of the solvent, the product was purified by column chromatography (30% ethyl acetate/hexane) using normal silica gel (150 g).

3.1. Synthesis of (±)-2-cyano-1-(4-fluorophenyl)allyl butyrate 6a

![Image of 6a structure]

Triethylamine (0.794 mL, 5.70 mmol, 1 eq.), butyric anhydride (0.93 mL, 5.68 mmol, 1 eq.) and DMAP (24.28 mg, 0.20 mmol, 3.5 mol%) were added to a stirred solution of 4a (1.01 g, 5.70 mmol, 1 eq.) in 2-methyltetrahydrofuran (10.00 mL) to afford 6a as a yellow oil (0.861 g, 61%). Rᵢ = 0.78 (30% ethyl acetate/hexane). IR (neat, cm⁻¹) 2969, 2229, 1744, 1510, 1006; ¹H NMR (300 MHz, Chloroform-d) δ 7.42 – 7.35 (m, 2H, H3 & H5), 7.13 – 7.05 (m, 2H, H2 & H6), 6.33 (br s, 1H, H7), 6.08 (d, J = 0.9 Hz, 1H, H10a), 6.01 (d, J = 1.3 Hz, 1H, H10b), 2.41 (td, J = 7.4, 1.9 Hz, 2H, H11), 1.76 – 1.63 (m, 2H, H12), 0.95 (t, J = 7.4 Hz, 3H, H13). ¹³C NMR (75 MHz, CDCl₃) δ 171.8 (C=O), 163.0 (d, ¹J_{C,F} = 248.6 Hz, C1), 131.9 (C10), 131.6 (d, ²J_{C,F} = 3.3 Hz, C4), 128.9 (d, ³J_{C,F} = 8.5 Hz, C3 & C5), 123.1 (C8), 116.0 (C9), 115.9 (d, ²J_{C,F} = 21.9 Hz, C2 & C6), 73.4 (C7), 36.0 (C11), 18.3 (C12), 13.5 (C13). HRMS m/z calcd for C₁₄H₁₅FNO₂ [M+H]⁺: 248.1081, found: 248.1096. Chiral HPLC: Lux 3 immobilised Amylose-1 (250 x 4.6 mm); mobile phase, hexane: IPA (90:10); flow rate = 1 mL/min); tᵣ = 6.23 min, tᵣ = 7.06 min.

3.2. Synthesis of (±)-1-(4-bromophenyl)-2-cyanoallyl butyrate 6b

![Image of 6b structure]

Triethylamine (1 mL, 7.17 mmol, 1.6 eq.), butyric anhydride (1.4 mL, 8.56 mmol, 0.76 eq.) and DMAP (24.28 mg, 0.20 mmol, 1.8 mol%) were added to a stirred solution of 4b (2.68 g, 11.26 mmol, 1 eq.) in 2-methyltetrahydrofuran (12 mL) to afford 6b as yellow oil (2.36 g, 68%). Rᵢ = 0.34 (30% ethyl acetate/hexane). IR (neat, cm⁻¹) 2961, 2229, 1743,
3.3. Synthesis of (±)-2-cyano-1-(4-cyanophenyl)allyl butyrate 6c

Triethylamine (1.5 mL, 10.76 mmol, 1.6 eq.), butyric anhydride (1.4 mL, 8.56 mol, 1.3 eq.) and DMAP (24.28 mg, 0.20 mmol, 3 mol%) were added to a stirred solution of 4c (1.2040 g, 6.54 mmol, 1 eq.) in 2-methyltetrahydrofuran (20 ml) to afford 6c as an orange oil (1.07 g, 64%). Rf = 0.30 (20% ethyl acetate/hexane). IR (neat, cm⁻¹) 2968, 2231, 1745, 1506, 1011; ¹H NMR (400 MHz, Chloroform-d) δ 7.73 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 6.38 (s, 1H), 6.15 (s, 1H), 6.11 (m, 1H), 2.46 (td, J = 7.4, 3.4 Hz, 1H), 1.73 (sxt, 1H), 0.98 (t, J = 7.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.6, 140.7, 132.9, 132.7, 127.5, 122.2, 118.0, 115.5, 113.2, 73.3, 35.9, 18.2, 13.5. HRMS m/z calcd for C₁₅H₁₄N₂O₂ [M+H]: 255.1128, found: 255.1124. Chiral HPLC: Lux 3 immobilised Amylose-1 (250 x 4.6 mm); mobile phase, hexane: IPA (90:10); flow rate = 1 mL/min; tₐ = 6.97 min, tᵣ = 8.12 min.

3.4. Synthesis of (±)-1-(4-chlorophenyl)-2-cyanoallyl butyrate 6d

Triethylamine (0.73 mL, 5.24 mmol, 1 eq.), butyric anhydride (0.86 mL, 5.26 mmol, 1 eq) and DMAP (24.28 mg, 0.20 mmol, 3.8 mol%) were added to a stirred solution of 4d (1.02 g, 5.27 mmol, 1 eq.) in 2-methyltetrahydrofuran (10 ml) to afford 6d as a yellow oil (672 mg, 49%). Rᵣ = 0.80 (30% ethyl acetate/hexane). IR (neat, cm⁻¹) 2967, 2228, 1744, 1598, 1013; ¹H NMR (300 MHz, Chloroform-d) δ 7.40 – 7.36 (m, 2H, H2 & H6), 7.36 – 7.32 (m, 2H, H3 & H5), 6.31 (s, 1H, H7), 6.09 – 6.08 (m, 1H, H10a), 6.02 (d, J
= 1.3 Hz, 1H, H10b), 2.41 (td, J = 7.3, 1.9 Hz, 2H, H11), 1.69 (sxt, J = 7.4 Hz, 2H, H12), 0.95 (t, J = 7.4 Hz, 3H, H13); 13C NMR (75 MHz, CDCl3) δ 171.7 (C=O), 135.1 (C1), 134.2 (C4), 132.1 (C10), 129.1 (C2& C6), 128.2 (C3 &C5), 122.9 (C8), 115.9 (C9), 73.4 (C7), 35.9 (C11), 18.2 (C12), 13.5 (C13). C14H15ClNO2 [M+H]⁺: 264.0786, found: 264.0780. Chiral HPLC: Lux 3 immobilised Amylose-1 (250 x 4.6 mm); mobile phase, hexane: IPA (90:10); flow rate = 1 mL/min); tR = 6.26 min, tR = 7.16 min.

Synthesis of (±)-1-(4-bromophenyl)-2-cyanoallyl propionate 11b

Triethylamine (1.00 mL, 9.88 mmol, 1 eq.), propionic anhydride (1.40 mL, 10.76 mmol, 1 eq.) and DMAP (24.28 mg, 0.20 mmol, 3.5 mol%) were added to a stirred solution of 4a (1.01 g, 4.26 mmol, 1 eq.) in 2-methyltetrahydrofuran (20.00 mL) to afford 6a as a light yellow oil (1.03 g, 82%). R f = 0.68 (30% ethyl acetate/hexane). IR (neat, cm⁻¹) 2984, 2200, 1744, 1593, 1155; 1H NMR (400 MHz, CDCl3) δ 7.56 (d, J = 8.1 Hz, 2H, H2 & H6), 7.30 (d, J = 8.1 Hz, 2H, H3 & H5), 6.31 (s, 1H, H7), 6.11 (s, 1H, H10a), 6.04 (s, 1H, H10b), 2.57 – 2.37 (hept, J = 8.0 Hz, 7.2 Hz 2H, H11), 1.20 (t, J = 7.5 Hz, 3H, H12). 13C NMR (101 MHz, CDCl3) δ 172.5 (C=O), 134.7 (C4), 132.2 (C10), 132.1 (C2 & C6), 128.5 (C3 & C5), 123.3 (C1), 122.8 (C8), 115.9 (C9), 73.5 (C7), 27.5 (C11), 8.8 (C12). C13H13BrNO2 [M+H]⁺: 294.0124, found: 294.0156. Chiral HPLC: Lux 3 immobilised Amylose-1 (250 x 4.6 mm); mobile phase, hexane: IPA (90:10); flow rate = 1mL/min); tR = 9.43 min, tR = 11.25 min.

4. General procedure for Enzymatic kinetic resolution reactions

To a mixture of enzyme (8 mg) in phosphate buffer (0.1 M, pH=7, 950 µl) in an Eppendorf tube was added substrate (8 mg) dissolved in acetone (50 µl) (Scheme S4).
Reactions were incubated at 25-30 °C and were monitored using TLC then analysed by chiral HPLC when hydrolysis was observed.

4.1 Chromatograms for EKR of compounds 4a, 5a and 6a
MBH acetate and MBH adduct starting material (Fig S1)

![Chromatograms for EKR of compounds 4a, 5a and 6a](image)

**Figure S1**

Enzymatic reaction using PCL (Fig S2)
OAc peaks: 13 & 14; OH peaks: 15 & 16

Results: eeₚ = 92%, eeₑ = 74%, c = 45, E = 53

MBH butyrate and MBH adduct starting material (Fig S3)
Enzymatic reaction using Novozyme 435 (Fig S4)

Figure S4

OBut peaks: 7 & 8; OH peaks: 11 & 12

Results: ee_p=84%, ee_e=54%, c=39, E=20

4.2 Chromatograms for compound 4b, 5b and 6b

MBH acetate starting material and MBH adduct (Fig S5)
Enzymatic reaction using Novozyme 435 (Fig S6)

OAc peaks: 7 & 8; OH peaks: 9 & 10

Results: eeₚ= 98%, eeₛ= 40%, c=29, E=147

MBH butyrate starting material and MBH adduct (Fig S7)
Figure S7

Enzymatic reaction using Novozyme 435 (Fig S8)

Figure S8

OBut peaks: 11 & 13; OH peaks: 15 & 16
Results: eep = 95%, eeα = 67%, c = 41, E = 79

4.3 Chromatograms for compounds 4c, 5c, and 6c
MBH adduct (Fig S9)

Figure S9

MBH acetate (Fig S10)
Figure S10

Enzymatic reaction using Novozyme 435 (Fig S11)

OAc peaks: 15 & 17; OH peaks: 14 & 16

Results: $e_{e_{p}} = 93\%$, $e_{e_{s}} = 93\%$, $c=50$, $E=94$

MBH butyrate and MBH adduct starting material (Fig S12)
Enzymatic reaction using CALB (Fig S13)

Figure S12

Figure S13

OBut peaks: 18 & 20; OH peaks: 19 & 21
Results: $e_{p} = 99.2\%$, $e_{c} = 53\%$, $c = 35$, $E = 424$

4.4 Chromatograms for compounds 4d, 5d and 6d

MBH adduct (Fig S14)

![MBH adduct](Figure S14)

MBH acetate (Fig S15)

![MBH acetate](Figure S15)
Figure S15

Enzymatic reaction using *P. fluorescens* (Fig S16)

Figure S16

OAc peaks: 14 & 15; OH peaks: 18 & 19

Results: eeₚ = 91%, eeₛ = 66%, c = 42, E = 42

MBH butyrate starting material and MBH adduct (Fig S17)
**Figure S17**

Enzymatic reaction using Novozyme 435 (Fig S18)

**Figure S18**
OBut peaks: 11 &12; OH peaks: 15 &16

Results: eep= 96%, ee= 53%, c=36, E=83

5. General procedure for the preparation of Enzymatic kinetic resolution scaled-up reactions

Isolation of the (+)-4b enantiomer

A phosphate buffer solution (21 ml) containing Novozyme 435 (0.730 g) at pH 7 was added to a stirred solution of acetone (3 ml) and 5b (0.73g) at room temperature and the reaction was followed by chiral HPLC (Fig S19). The mixture was left to stir for 97 hrs, the product was then extracted using ethyl acetate. Further purification by column chromatography (30% ethyl acetate/hexane) afforded the products light yellow oil products (+)-4b [253 mg, c= 44%, ee= 98% (Fig S20); [βD] = +50.5 (c 0.5, MeOH)] as a single enantiomer and (-)-5b as an enantio-enriched product [296 mg, c=44%, ee= 77%].

SCALED-UP REACTION (Fig S19)
OH ISOLATION (Fig S20)

Isolation of the (-)-5b enantiomer

A phosphate buffer solution (18.5 ml) containing *Pseudomonas cepacia* lipase (0.295 g) at pH 7 was added to a stirred solution of acetone (1.5 ml) and 5b (0.295 g) at room temperature and the reaction was followed by chiral HPLC (Fig S21). The mixture was left to stir for 34 hrs 30 min, the product was then extracted using ethyl acetate. Further purification by column chromatography (30% ethyl acetate/hexane) afforded the products as light yellow oils: (+)-4b [trace amount, c= 55%, ee= 78%] and (-)-5b [168 mg, c=55%, ee= 99%; [α]D = -28.0 (c 0.5, MeOH)] (Fig S22).

SCALED-UP REACTION (Fig S21)
Isolated product (Fig S22)

**Figure S22**

ees = 99%

SECOND OH ISOLATION (From hydrolysis of original acetate, Fig S23)

**Isolation of the (-)-4b enantiomer**

A phosphate buffer solution (10 ml) containing non-selective lipase (117 mg) at pH 7 was added to a stirred solution of acetone (1 ml) and (-)-5b (117 mg) at room temperature and the reaction was followed by chiral HPLC (Fig S23). The mixture was left to stir for 26 hrs 30 min, the product was then extracted using ethyl acetate. Further purification by column chromatography (30% ethyl acetate/hexane) afforded the two products as light yellow oils: (-)-4b [c= 49%, ee= 95%] and (-)-5b [c=49%, ee= 93%].

**Figure S23**
6. General procedure for the preparation of Mosher products

A mixture of DCC (1.9 – 2.2 eq.), DMAP (0.2 – 0.4 eq.), (+) or (-) alcohol (1 eq.) and (R)- or dried (S)-MPTA (2.7 – 3.4 eq.) in DCM (5 ml) was stirred at room temperature for 6 h. DCM (2 x 5 ml) and water (2 x 5ml) were added to a separating funnel and shaken. The DCM layer was isolated and over magnesium sulphate and purified using column chromatography (30% ethyl acetate/hexane).

6.1. Preparation \((S)\)-\((S)\)-2-cyano-4-bromo-1-phenylallyl]3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 7

\[
\begin{align*}
\text{Br} & \quad \text{H} \\
\text{NC} & \quad \text{O} \\
\text{O} & \quad \text{Ph} \\
\text{CF}_3 & \quad \text{OMe}
\end{align*}
\]

\((+)-4b\) (9.1 mg, 1 eq), DMAP (1.5 mg, 0.3 eq), DCC (15.2 mg, 1.9 eq) and (S)-MPTA (25.3 mg, 2.8 eq) were stirred in 5 ml DCM to afford compound 7 as a light yellow oil (17 mg, 91%). \(R_f = 0.45\) (30% ethyl acetate/hexane). \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.48 (d, \(J = 8.2\) Hz, 2H), 7.44 – 7.34 (m, 5H), 7.10 (d, \(J = 8.3\) Hz, 2H), 6.44 (s, 1H), 6.13 (s, 1H), 5.98 (s, 1H), 3.58 (d, \(J = 0.9\) Hz, 3H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 165.1, 139.3, 133.3, 133.1, 132.2, 131.5, 129.9, 128.7, 128.5, 127.2 – 127.1 (m), 123.1 (q, \(J_{C-F} = 289\) Hz), 115.7, 114.1, 84.7 (q, \(J_{C-F} = 27.8\) Hz), 75.6, 55.86 – 55.85 (m). Calculated for C\(_{20}\)H\(_{15}\)F\(_3\)NO\(_3\)\(_{79}\)BrNa [M+Na\(^+\): 476.0080, found: 476.0062.

6.2. Preparation \((S)\)-\((R)\)-2-cyano-4-bromo-1-phenylallyl]3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 8

\[
\begin{align*}
\text{Br} & \quad \text{H} \\
\text{NC} & \quad \text{O} \\
\text{O} & \quad \text{Ph} \\
\text{CF}_3 & \quad \text{MeO}
\end{align*}
\]

\((+)-4b\) (9 mg, 1 eq), DMAP (1.1 mg, 0.2 eq), DCC (15.7 mg, 2.0 eq) and (R)-MPTA (24.1 mg, 2.7 eq) were stirred in 5 ml DCM to afford compound 8 as a light yellow oil (16 mg, 86%). \(R_f\)
= 0.46 (30% ethyl acetate/hexane). $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.55 (d, $J = 8.4$ Hz, 2H), 7.43 – 7.33 (m, 5H), 7.25 (d, $J = 8.2$ Hz, 2H), 6.47 (s, 1H), 6.06 (s, 1H), 5.94 (s, 1H), 3.46 (d, $J = 0.6$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 165.1, 139.2, 133.3, 132.4, 132.3, 131.5, 129.9, 129.0, 128.6, 127.3 – 127.2 (m), 123.1 (q, $J_{C-F} = 289$ Hz), 115.4, 114.1, 84.7 (q, $J_{C-F} = 28$ Hz), 75.2, 55.52 – 55.51 (m). Calculated for C$_{20}$H$_{16}$F$_3$NO$_3$Br$^+$: 454.0260, found: 454.0265.

6.3 Preparation (R)-[(S)-2-cyano-4-bromo-1-phenylallyl]3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 9

\[
\begin{align*}
\text{NC} & \quad \text{O} \quad \text{Ph} \\
\text{Br} & \quad \text{CF}_3 \\
9 & \quad \text{OMe}
\end{align*}
\]

(-)-4b (5.6 mg, 1 eq), DMAP (1.2 mg, 0.4 eq), DCC (10.8 mg, 2.2 eq) and (S)-MPTA (18.5 mg, 3.4 eq) were stirred in 5 ml DCM to afford compound 9 as a light yellow oil (trace amount). Rf = 0.47 (30% ethyl acetate/hexane). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.59 – 7.52 (m, 2H), 7.45 – 7.36 (m, 5H), 7.29 – 7.23 (m, 2H), 6.48 (s, 1H), 6.08 (s, 1H), 5.95 (d, $J = 1.2$ Hz, 1H), 3.46 (s, 3H). Calculated for C$_{20}$H$_{15}$F$_3$NO$_3$BrNa$^+$: 476.0080, found: 476.0081.

6.4 Preparation (R)-[(R)-2-cyano-4-bromo-1-phenylallyl]3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 10

\[
\begin{align*}
\text{NC} & \quad \text{O} \quad \text{Ph} \\
\text{Br} & \quad \text{CF}_3 \\
10 & \quad \text{MeO}
\end{align*}
\]

(-)-4b (6.2 mg, 1 eq), DMAP (1 mg, 0.2 eq), DCC (10.7 mg, 2.0 eq) and (R)-MPTA (18.5 mg, 3.0 eq) were stirred in 5 ml DCM to afford compound 10 as a light yellow oil (trace amount). Rf = 0.46 (30% ethyl acetate/hexane). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.51 – 7.47 (m, 2H), 7.45 – 7.35 (m, 5H), 7.13 – 7.08 (m, 2H), 6.44 (s, 1H), 6.15 (d, $J = 0.9$ Hz, 1H), 5.99 (d, $J = 1.3$ Hz, 1H), 3.59 (d, $J = 1.2$ Hz, 3H). Calculated for C$_{20}$H$_{16}$F$_3$NO$_3$Br$^+$: 454.0260, found: 454.0274.
7. EKR reaction by transesterification

Enzyme screening

Acetic anhydride (15 mg) and enzyme (3 mg) were added to a solution of 4b (12 mg, 0.25mmol) in dry diethyl ether (1 ml) in a 2.5 ml Eppendorf tube and stirred at 30°C. Reactions were monitored by TLC and then analysed by chiral HPLC once reaction was observed.

Transesterification using *P. fluorescens* (Fig S24)

![Figure S24](image)

Ester peaks: 13 & 14

Adduct peaks: 16 & 17

\[ \text{ee}_p = 71\%, \text{ ee}_s = 6\%, c = 8\% \]

Transesterification using PCL (Fig S25)
Figure S25

Ester peaks: 13 & 14
Adduct peaks: 15 & 16

$ee_p = 29\%$, $ee_e = 16\%$, $c = 36\%$

Transesterification using CAL-A (Fig S26)

Figure S26

Ester peaks: 15 & 16
Adduct peaks: 17 & 18

$ee_p = 78\%$, $ee_e = 52\%$, $c = 40\%$
Transesterification using Novozyme 435 (Fig S27)

Ester peaks: 15 & 16
Adduct peaks: 18 & 19
\[ \text{ee}_{R} = 22\%, \text{ ee}_{S} = 6\%, c = 21\% \]

CAL-A transesterification reaction

Acetic anhydride (15 mg) and CAL-A (3 mg) were added to a solution of 4b (12 mg, 0.25mmol) in various organic solvents (1 ml) for 3-4 days. The reaction was set in a 2.5 ml Eppendorf tube and stirred at 30°C. Chiral HPLC analysis was performed using an Amylose 1 column, elution 92:8 hexane: IPA, flow rate @ 0.8 ml/min.)

Reaction in THF (Fig S28)
OAc peaks: 4 & 5
OH peaks: 6 & 7
ee_e= 93%, ee_c= 26%, c= 22%

8. NMR, HRMS and FTIR data

Morita-Baylis-Hillman adducts 4a–d

Compound 4a
Figure S29. FTIR spectrum of 4a

Figure S30. $^1$H NMR spectrum of 4a
Figure S31. $^{13}$C NMR spectrum of 4a

Compound 4b
Figure S32. FTIR spectrum of 4b

Figure S33. $^1$H NMR spectrum of 4b
Figure S34. $^{13}$C NMR spectrum of 4b

Compound 4c
Figure S35. FTIR spectrum of 4c

Figure S36. $^1$H NMR spectrum of 4c
Figure S37. $^{13}$C NMR spectrum of 4c

Compound 4d
Figure S38. FTIR spectrum of 4d

Figure S39. $^1$H NMR spectrum of 4d
Figure S40. $^{13}$C NMR spectrum of 4d

Morita-Baylis-Hillman acetates 5a–d

Compound 5a

![Chemical Structure of Compound 5a]
Figure S41. FTIR spectrum of 5a

Figure S42. $^1$H NMR spectrum of 5a
Figure S43. $^{13}$C NMR spectrum of 5a

**Compound 5b**

![Chemical Structure of Compound 5b](image)
Figure S44. FTIR spectrum of 5b

Figure S45. $^1$H NMR spectrum of 5b
Figure S46. $^{13}$C NMR spectrum of $5b$

Compound 5c
Figure S47. FTIR spectrum of 5c

Figure S48. $^1$H NMR spectrum of 5c
Figure S49. $^{13}$C NMR spectrum of 5c

Compound 5d

Figure S50. FTIR spectrum of 5d
Figure S51. $^1$H NMR spectrum of 5d

Figure S52. $^{13}$C NMR spectrum of 5d
Morita-Baylis-Hillman butyrates 6a–d

Compound 6a

Figure S53. FTIR spectrum of 6a
Figure S54. $^1$H NMR spectrum of 6a

Figure S55. $^{13}$C NMR spectrum of 6a

Compound 6b
Figure S56. FTIR spectrum of 6b

Figure S57. $^1$H NMR spectrum of 6b
Compound 6c

Figure S58. $^{13}$C NMR spectrum of 6b
Figure S59. FTIR spectrum of 6c

Figure S60. ¹H NMR spectrum of 6c
Figure S61. $^{13}$C NMR spectrum of 6c

Compound 6d
Figure S62. FTIR spectrum of 6d

Figure S63. $^1$H NMR spectrum of 6d
Figure S64. $^{13}$C NMR spectrum of 6d

Compound 11b

Figure S65. FTIR spectrum of 11b
Figure S66. $^1$H NMR spectrum of 11b
Figure S67. $^{13}$C NMR spectrum of 11b
Mosher products

Compound 7

Figure S68. $^1$H NMR spectrum of 7
**Compound 8**

Figure S69. $^{13}$C NMR spectrum of 7

Figure S70. $^1$H NMR spectrum of 8
Figure S71. $^{13}$C NMR spectrum of 8
Compound 9

Figure S72. 1H NMR spectrum of 9
Compound 10

Figure S73. $^1$H NMR spectrum of 10