



Supporting Information

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Highly Enantioselective One-Pot, Three-Components Imino-Reformatsky Reaction

Pier Giorgio Cozzi,* Eleonora Rivalta

General: ^1H NMR spectra were recorded on Varian 200 MHz or Varian 300 MHz spectrometers. chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuteriochloroform: δ 7.27 ppm). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian 50 MHz, Varian 75 MHz or Varian 100 MHz spectrometers with complete proton decoupling. ^{19}F spectra were recorded with Varian VXR spectrometer at 282.208 MHz. ^{19}F spectra were referenced to CFCl_3 as the external standard. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuteriochloroform: δ 77.0 ppm). Mass spectra were performed at an ionizing voltage of 70 eV. Chromatographic purification was done with 240-400 mesh silica gel. Analytical gas chromatography (GC) was performed on a Hewlett-Packard HP 6890 gas chromatograph with a flame ionization detector and split mode capillary injection system, using a Crosslinked 5% PH ME Siloxane (30 m) column or a Megadex5 chiral (25 m) column. Analytical high performance liquid chromatograph (HPLC) was performed on a HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190-600 nm), using a Daicel ChiralcelTM OD column (0.46 cm I.D. x 25 cm) (Daicel Inc.). HPLC grade isopropanol and hexane were used as the

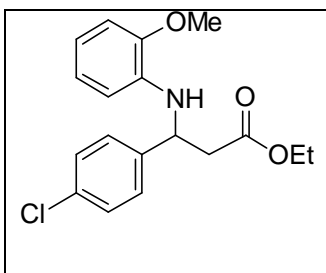
eluting solvents. LC were obtained with HPLC Agilent technologies HP1100 series equipped with diode array detector. Only a pre-column was used for purifying the products. The binary mobile phase consisted in (A) water (B) acetonitrile in isocratic conditions (A)20% (B)80% with a flow rate of 0.3 ml/min. The Mass detector consist in a Hewlett Packard 1100 MSD series equipped with API-ES interface and single quadrupole. The API-ES conditions for analysis in positive mode were performed with drying gas flow: x l/min, nebulizer pressure: x psig, drying gas temperature: x °C, capillary voltage: x V, fragmentor: x V. All the reactions were carried out under a nitrogen atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents. All aldehydes were distilled prior to use. 2-Methoxy aniline was distilled and stored under nitrogen. All the other commercially obtained reagents were used as received. Bistriphenylphosphine nickel(II) dichloride was purchased by Stream. Commercially available Me₂Zn 2M in toluene (Fluka) was used for all the reactions. Anhydrous toluene and CH₂Cl₂ were purchased from the Fluka. All racemic β-amino esters were prepared by a three component imino-Reformatsky reaction run at room temperature without the presence of *N*-methylephedrine.¹

¹ J. C. Adrian, M. L. Snapper, *J. Org. Chem.* **2003**, *68*, 2143-2150.

General procedure for the Enantioselective Imino-Reformatsky reaction

To a stirred solution of aldehyde (0.2mmol) in toluene (2mL) at room temperature 2-methoxyaniline (0.2mmol) was added. After 30min, a solution of dimethylzinc (0.4mL, 2M, 0.8mmol) in toluene was added all at once. After 10 min (1*S*, 2*R*)-*N*-methylephedrine (0.060g, 0.33mmol) was added and the resulting solution was stirred at room temperature. After 60 min the reaction was cooled down to -30°C and ethylbromoacetate (0.24mmol) was added, followed immediately by tris-triphenylphosphine nickel(II) dichloride (10mg, 0.015mmol) and was stirred at the same temperature for 23-48 h, then quenched by the addition of HCl 1M (3mL). The reaction was stirred for 3-10 min then the organic phase was separated, washed with saturated NaHCO₃ and brine, then dried with Na₂SO₄, and concentrated in *vacuo* to afford a crude product, purified by chromatography (cyclohexane:Et₂O, 8:2-95:5).

3-(4-chlorophenyl)-3-(2-methoxyphenylamino)-ethylpropanoate


 $C_{18}H_{20}ClNO_3$ Fw = 333.81

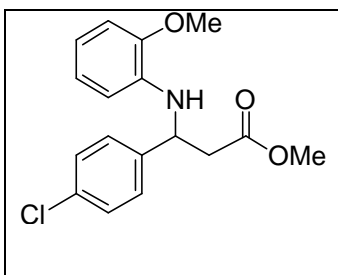
 $[\alpha]_D = -11$ (c 0.5, $CHCl_3$)

1H NMR ($CDCl_3$, 300 MHz) δ : 1.24 (t, 3H, $J = 7.2$ Hz); 2.88-2.80 (m, 2H); 3.91 (s, 3H); 4.14 (q, 2H, $J = 7.2$ Hz); 4.84 (t, 1H, $J = 6.9$ Hz); 5.05 (brs, 1H); 6.39 (d, 1H, $J = 7.5$ Hz); 6.81-6.67 (m, 3H); 7.37-7.29 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ : 14.36; 43.35; 54.58; 55.76; 61.09; 109.78; 111.50; 117.43; 121.36; 127.99; 129.13; 133.29; 136.63; 141.21; 147.20; 170.96.

GCMS: 333(18); 246(100); 120(17); 108(18); 92(17); 77(11); 55(17).

HPLC analysis OD: isocratic, flux 0.6mL/m (hexane: *i*-PrOH) 90:10. tm: 10.96 min; TM: 14.20 min ee 90%.

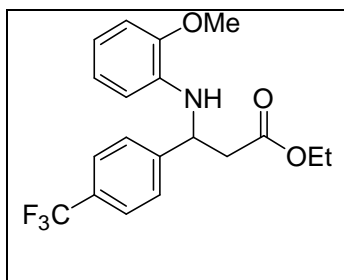
3-(4-chlorophenyl)-3-(2-methoxyphenylamino)-methylpropanoate ¹
 $C_{17}H_{18}ClNO_3$ Fw = 319.78

 $[\alpha]_D = -14$ (c 1, $CHCl_3$)

Analytical data: see ref. 1

HPLC analysis OD: isocratic, flux 0.8mL/m (hexane: *i*-PrOH) 90:10. tm: 14.90 min; TM: 16.31 min ee 90%.

3-(trifluoromethylphenyl)-3-(2-methoxyphenylamino)-
ethylpropanoate



$C_{19}H_{20}F_3NO_3$ Fw = 367.36

$[\alpha]_D = -17$ (c 1.7, $CHCl_3$)

1H NMR ($CDCl_3$, 200 MHz) δ : 1.22 (t, 3H, $J = 7.3$ Hz); 2.86 (d, 2H, $J = 6.9$ Hz); 3.91 (s, 3H); 4.13 (q, 2H, $J = 7.3$ Hz); 4.94 (t, 1H, $J = 6.9$ Hz); 5.20 (brs, 1H); 6.37-6.32 (m, 1H); 6.82-6.66 (m, 3H); 7.62-7.50 (m, 4H).

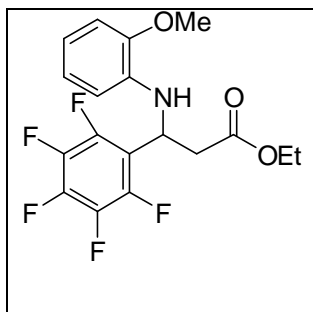
^{13}C NMR ($CDCl_3$, 100 MHz) δ : 14.30; 43.20; 54.77; 55.70; 61.17; 109.76(s); 111.38(s); 117.56(s); 121.33(s); 124.39(q, $J = 271.8$ Hz); 125.87(q, $J = 3.6$ Hz); 129.85(q, $J = 32.7$ Hz); 126.98; 136.49; 146.89; 147.19; 170.83.

GCMS: 367(18); 348(2); 280(100); 264(7); 159(2); 151(2); 120(17); 92(8); 65(8); 51(4).

^{19}F NMR($CDCl_3$, 282 MHz): δ : -62.8.

HPLC analysis OD: isocratic, flux 0.6mL/m (hexane: *i*-PrOH) 85:15. tm: 14.22 min; TM: 20.63 min ee 90%.

3-(pentafluorophenyl)-3-(2-methoxyphenylamino)-
ethylpropanoate



$C_{18}H_{16}F_5NO_3$ Fw = 389.11

$[\alpha]_D = +20$ (c 1, $CHCl_3$)

1H NMR ($CDCl_3$, 300 MHz) δ : 1.26 (t, 3H, $J = 6.83$ Hz); 3.05-2.97 (A, part of ABX, 1H, $J = 7.8, 15.6$ Hz); 3.20-3.12 (B part of ABX, 1H; $J = 6.8, 15.6$ Hz); 3.87 (s, 3H); 3.95 (q,

2H, $J = 6.83\text{Hz}$); 5.0 (brs, 1H); 5.44-5.40 (m, 1H); 6.90-6.71 (m, 4H).

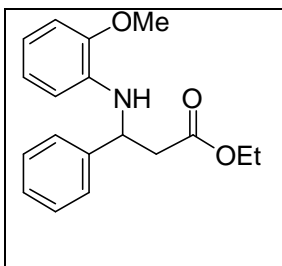
^{13}C NMR (CDCl_3 , 100 MHz) δ : 14.29; 40.25, 45.64; 55.83; 61.33; 110.15; 110.91; 115.53; 118.49; 121.51; 135.53; 137.71(d, $J = 253\text{Hz}$); 140.73(d, $J = 254\text{Hz}$); 145.32(d, $J = 247\text{Hz}$); 147.63; 170.08.

^{19}F NMR(CDCl_3 , 282 MHz) δ : -144.14(dd, 2F, $J = 9, 27.0\text{Hz}$); -155(t, 1F, $J = 21.0\text{Hz}$); -161.87(ddd, 2F, $J = 6, 21, 27\text{Hz}$).

GCMS: 389(22); 344(1); 316(1); 302(100); 268(1); 252(1); 221(1); 194(2); 181(2); 151(2); 120(22); 92(9); 65(8); 52(3).

HPLC analysis OD: isocratic, flux 0.6mL/m (hexane: *i*-PrOH) 85:15. tm: 10.90 min; TM: 12.74 min ee 90%.

3-(phenyl)-3-(2-methoxyphenylamino)-ethylpropanoate



$\text{C}_{18}\text{H}_{21}\text{NO}_3$ Fw = 299.36

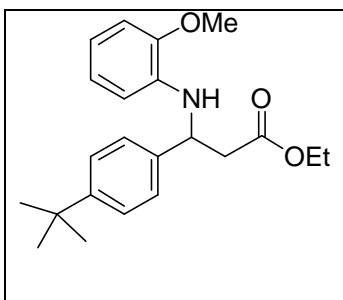
$[\alpha]_{\text{D}}$ = -19 (c 1.2, CHCl_3)

^1H NMR (CDCl_3 , 300 MHz) δ : 1.26 (t, 3H, $J = 7\text{Hz}$); 2.90-2.88 (m, 2H); 3.92 (s, 3H); 4.15 (q, 2H, $J = 7\text{Hz}$); 4.90 (t, 1H; $J = 6\text{Hz}$); 5.1 (brs, 1H); 6.47 (d, 1H, $J = 7.8\text{Hz}$); 6.83-6.65 (m, 3H); 7.44-7.22 (m, 5H).

^{13}C NMR (CDCl_3 , 50 MHz) δ : 14.21; 43.35; 54.98; 55.61; 60.83; 109.58; 111.34; 116.98; 121.24; 126.40; 127.48; 128.81; 136.78; 142.48; 147.03; 171.13.

GCMS: 299(20); 254(1); 222(1); 212(100); 196(9); 167(2); 150(2); 135(4); 120(14); 105(12); 77(12); 65(11); 52(4).

HPLC analysis OD: isocratic, flux 0.6mL/m (hexane: *i*-PrOH) 85:15. TM: 13.96 min; tm: 15.56 min ee 83%.

3-(4-*t*Butylphenyl)-3-(2-methoxyphenylamino)-ethylpropanoate

$C_{22}H_{29}NO_3$ Fw = 355.47

$[\alpha]_D = +2.0$ (c 1.1, $CHCl_3$)

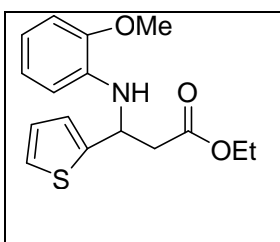
1H NMR ($CDCl_3$, 300 MHz) δ : 1.22 (t, 3H, $J = 7.3$ Hz); 1.33 (s, 9H); 2.88-2.85 (m, 2H); 3.91 (s, 3H); 4.14 (q, 2H, $J = 7.3$ Hz); 4.88-4.83 (m, 1H); 5.11 (brs, 1H); 6.53-6.50 (m, 1H); 6.80-6.61 (m, 3H); 7.38-7.31 (m, 4H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ : 14.37; 31.63; 34.73; 43.45; 54.71; 55.76; 60.92; 109.71; 111.38; 116.97; 121.41; 125.85; 126.18; 137.08; 138.51; 147.16; 150.39; 171.46.

GCMS: 355(14); 311(2); 268(100); 252(6); 236(3); 207(1); 191(16); 163(3); 145(9); 123(20); 91(4); 77(4); 57(17).

HPLC analysis OD: isocratic, flux 0.6mL/m (hexane: *i*-PrOH 85:15). tm: 11.70 min; TM: 12.52 min ee 82%.

3-(2-thienyl)-2-(2-methoxyphenylamino)-ethylpropanoate



$C_{16}H_{19}NO_3S$ Fw = 305.39

$[\alpha]_D = -6$ (c 1.5, $CHCl_3$)

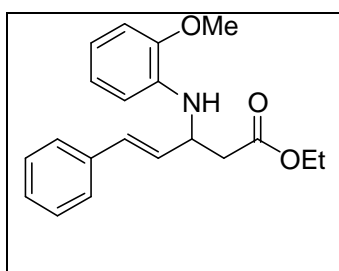
1H NMR ($CDCl_3$, 300 MHz) δ : 1.26 (t, 3H, $J = 7.3$ Hz); 2.91-3.06 (m, 2H); 3.89 (s, 3H); 4.17 (q, 2H, $J = 7.3$ Hz); 5.11 (brs, 1H); 5.21 (t, 1H, $J = 6.8$ Hz); 6.81-6.67 (m, 4H); 6.97 (dd, 1H, $J = 3.9, 5.3$ Hz); 7.03 (d, 1H, $J = 2.9$ Hz); 7.21 (dd, 1H, $J = 1.0, 4.9$ Hz).

^{13}C NMR (CDCl_3 , 50 MHz) δ : 14.40; 43.34; 51.08; 55.80; 61.11; 109.94; 111.59; 117.58; 121.26; 123.94; 124.35; 126.91; 136.45; 147.16; 147.24; 171.00.

GCMS: 305(44); 218(100); 202(13); 183(14); 141(39); 123(80); 111(49); 92(11); 65(22); 52(11).

HPLC analysis OD: isocratic, flux 0.6mL/m (hexane: *i*-PrOH) 85:15. tm: 14.33 min; TM: 15.59 min ee 92%.

3-(cinnamyl)-3-(2-methoxyphenylamino)-ethylpropanoate



$\text{C}_{20}\text{H}_{23}\text{NO}_3$ Fw = 325.40

$[\alpha]_{\text{D}} = +26$ (c 3, CHCl_3)

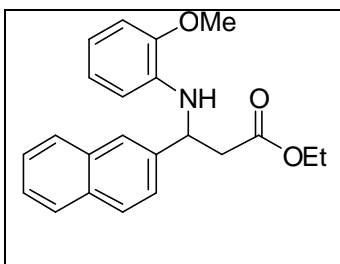
^1H NMR (CDCl_3 , 300 MHz) δ : 1.28 (t, 3H, $J = 6.9\text{Hz}$); 2.9–2.7 (m, 2H); 3.90 (s, 3H); 4.19 (q, 2H, $J = 6.9\text{Hz}$); 4.56–4.40 (m, 1H); 4.67 (brs, 1H); 6.29–6.22 (m, 1H); 6.87–6.59 (m, 5H); 7.39–7.22 (m, 5H).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 14.39; 40.98; 52.35; 55.64; 60.88; 109.75; 111.32; 117.15; 121.41; 126.65; 127.75; 128.68; 129.30; 130.21; 131.03; 136.83; 147.16; 171.31.

GCMS: 325(37); 238(100); 207(27); 129(100); 123(33); 115(33); 91(22); 77(3); 51(17).

HPLC analysis OD: isocratic, flux 0.6mL/m (hexane: *i*-PrOH) 85:15. tm: 20.69min; TM: 22.75 min ee 85%.

3-(2-naphtyl)-3-(2-methoxyphenylamino)-ethylpropanoate


 $C_{22}H_{23}NO_3$ Fw = 349.42

 $[\alpha]_D = -10$ (c 0.5, $CHCl_3$)

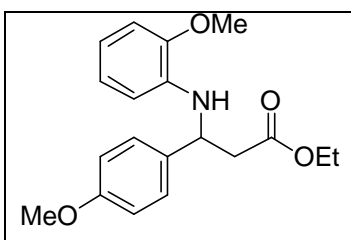
1H NMR ($CDCl_3$, 300 MHz) δ : 1.22 (t, 3H, $J = 6.8$ Hz); 2.96 (d, 2H, $J = 7.3$ Hz); 3.93 (s, 3H); 4.12 (q, 2H, $J = 6.8$ Hz); 5.06 (brs, 1H); 5.13 (t, 1H, $J = 6.3$ Hz); 6.8–6.4 (m, 4H); 7.56–7.44 (m, 3H); 7.89–7.82 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ : 14.36; 43.49; 55.45; 55.79; 61.04; 109.74; 111.63; 117.22; 121.42; 124.71; 125.36; 126.02; 126.34; 127.92; 128.20; 128.88; 133.20; 133.74; 137.00; 140.21, 147.23; 171.25.

GCMS: 349(22); 262(100); 246(10); 207(7); 185(19); 154(19); 123(19); 108(10); 77(11); 65(8).

HPLC analysis OD: isocratic, flux 0.6mL/m(hexane: *i*-PrOH) 85:15. tm: 11.70 min; TM: 12.52 min ee 84%.

3-(4-methoxyphenyl)-3-(2-methoxyphenylamino)-ethylpropanoate


 $C_{19}H_{23}NO_4$ Fw = 329.39

 $[\alpha]_D = -3$ (c 2.6, $CHCl_3$)

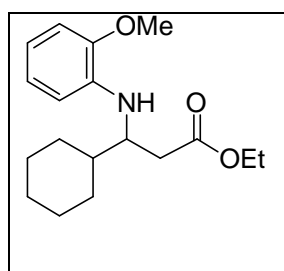
1H NMR ($CDCl_3$, 300 MHz) δ : 1.24 (t, 3H, $J = 6.8$ Hz); 2.90–2.82 (m, 2H); 3.80 (s, 3H); 3.90 (s, 3H); 4.16 (q, 2H, $J = 6.8$ Hz); 4.75 (brs, 1H); 4.82 (t, 1H, $J = 6.9$ Hz); 6.47 (d, 1H, $J = 7.2$ Hz); 6.66 (d, 1H, $J = 7.8$ Hz); 6.74 (d, 1H, $J = 7.8$ Hz); 6.79 (d, 1H, $J = 7.8$ Hz); 6.88 (d, 1H, $J = 8.7$ Hz); 7.32 (d, 1H, $J = 8.7$ Hz).

^{13}C NMR (CDCl_3 , 75 MHz) δ : 14.07; 43.24; 54.20; 55.18; 55.41; 60.65; 109.33; 111.13; 114.00; 116.71; 121.06; 127.33; 134.30; 136.65; 146.82; 158.73; 171.09.

GCMS: 329(33); 284(2); 267(1); 242(100); 226(11); 207(27); 184(2); 165(55); 123(36); 121(30); 91(5); 77(5); 51(3).

HPLC analysis OD: isocratic, flux 0.6mL/m(hexane: *i*-PrOH) 85:15. tm: 17.74 min; TM: 18.85 min ee 66%.

3-(cyclohexyl)-3-(2-methoxyphenylamino)-ethylpropanoate



$\text{C}_{18}\text{H}_{27}\text{NO}_3$ Fw = 305.41

$[\alpha]_{\text{D}} = -3$ (c 4, CHCl_3)

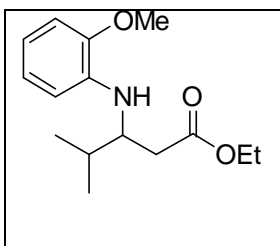
^1H NMR (CDCl_3 , 300 MHz) δ 1.23 (t, 3H, $J = 7.3\text{Hz}$); 2.0-1.0 (m, 11H); 2.58-2.21 (m, 2H); 3.78 (q, 1H, $J = 5.8\text{Hz}$); 3.87 (s, 3H); 4.11 (q, 2H, $J = 7.3\text{Hz}$); 4.30 (brs, 1H); 6.69 (t, 1H, $J = 7.8\text{Hz}$); 6.80-6.69 (m, 2H); 6.81 (t, 1H, $J = 7.8\text{Hz}$).

^{13}C NMR (CDCl_3 , 50 MHz) δ : 14.21; 26.41; 29.18; 29.49; 37.64; 42.32; 54.98; 55.61; 60.47; 109.82; 110.41; 116.09; 121.41; 139.08; 146.90; 172.48.

GCMS: 305(11); 222(100); 194(1); 176(8); 161(2); 134(31); 121(30); 120(3); 93(3); 77(3); 55(3).

HPLC analysis OD: isocratic (hexane: *i*-PrOH) 93:7. TM: 9.93 min; tm: 10.85 min ee 80%.

3-(isopropyl)-3-(2-methoxyphenylamino)-ethylpropanoate


 $C_{15}H_{23}NO_3$ Fw = 265.35

 $[\alpha]_D = -10$ (c 1, $CHCl_3$)

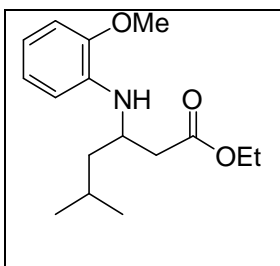
1H NMR ($CDCl_3$, 300 MHz) δ : 0.97(d, 3H, $J = 6.8Hz$); 1.03 (d, 3H, $J = 7.1Hz$); 1.23 (t, 3H; $J = 7.1Hz$); 1.99-1.94 (m, 1H); 2.51-2.54 (m, 2H); 3.79 (q, 1H, $J = 6.1Hz$); 3.87(s, 3H); 4.12 (q, 2H, $J = 7.1Hz$); 4.30 (brs, 1H); 6.66 (t, 1H, $J = 7.8Hz$); 6.71-6.50 (m, 2H); 6.88 (t, 1H, $J = 7.8Hz$).

^{13}C NMR ($CDCl_3$, 75 MHz) δ : 14.35; 24.19; 33.97; 43.47; 54.84; 55.76; 60.91; 109.72; 111.42; 116.99; 121.41; 137.07; 147.17; 171.43.

GCMS: 265(24); 222(100); 194(2); 178(22); 161(3); 148(4); 134(47); 120(3); 106(3); 92(3); 77(2); 65(3); 52(2).

HPLC analysis OD: isocratic, flux 0.5mL/m (hexane: *i*-PrOH) 93:7. TM: 9.90 min; tm: 10.82 min ee 64%.

3-(3-methylbutyl)-3-(2-methoxyphenylamino)-ethylpropanoate


 $C_{16}H_{25}NO_3$ Fw = 279.37

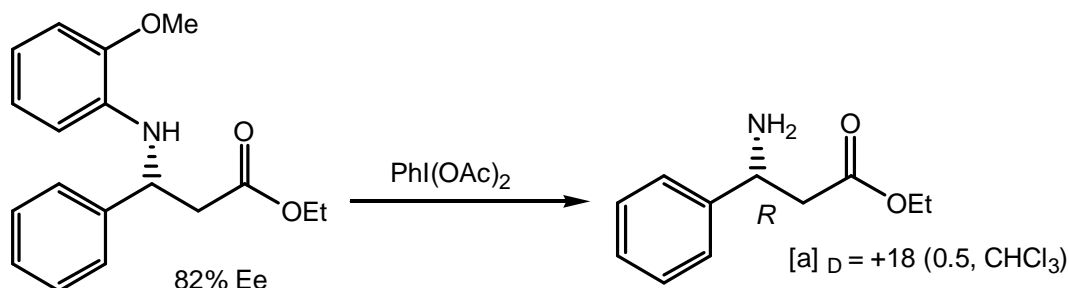
 $[\alpha]_D = -8$ (c 1, $CHCl_3$)

1H NMR ($CDCl_3$, 200 MHz) δ : 0.99 (t, 6H, $J = 6.8Hz$); 1.23 (t, 3H; $J = 7.2 Hz$); 1.84-1.56 (m, 2H); 1.96-1.90 (m, 1H); 2.51-2.48 (m, 2H); 3.80-3.76 (m, 1H); 3.86 (s, 3H); 4.11 (q, 2H, $J = 7.2Hz$); 4.30 (brs, 1H); 6.66-6.88 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ : 14.39; 18.69; 18.93; 32.02; 37.57; 55.66; 55.76; 60.71; 109.94; 110.70; 116.37; 121.56; 137.77; 147.10; 172.69.

GCMS: 265(27); 250(1); 222(100); 194(2); 178(22); 161(3); 148(4); 134(47); 120(3); 106(3); 92(3); 77(2); 65(3); 55(1).

HPLC analysis OD: isocratic (hexane: *i*-PrOH) 95:5. TM: 13.72 min.; tm: 15.16 min. ee 74%.



In a two-necked round bottom flask PhI(OAc)₂ (400 mg, 1.2 mmol) was dissolved in MeOH (2 mL) and glacial acetic acid (0.200 mL). A solution of 3-(phenyl)-3-(2-methoxyphenylamino)-ethylpropanoate (90 mg, 0.3 mmol) in MeOH (1 mL) was added by a pressure equalising addition funnel over 30 min at rt. The resulting black solution was stirred 6 hours, then a 10% HCl solution (3 mL) was added and a white precipitate immediately formed, which gradually dissolved with stirring over 30 min. A 10% aq. Na₂S₂O₃ solution (3 mL) was added and the mixture stirred for an additional 20 min. As the solution reached pH = 12, with the addition of solid Na₂CO₃, it was immediately diluted with 10 mL of water, and the methanol was distilled off under reduced pressure. The resulting solution was extracted with CH₂Cl₂ (2 x 15 mL) and the combined organic layers were dried over Na₂SO₄, the solvent was evaporated under reduced pressure to afford a brown oil which was purified by flash chromatography (SiO₂, eluent AcOEt). The solid obtained was further purified by extraction with

pentane. The deprotected aminoacid was obtained as a pale oil in 79% yield (46 mg).

^1H NMR (200 MHz, CDCl_3) δ : 1.26 (t, 3H, $J = 7.08$ Hz), 2.67 (d, 2H, $J = 7.25$ Hz), 4.16 (q, 2H, $J = 7.08$ Hz), 4.44 (m, 1H), 7.18 (m, 5H,).