Supporting Information

Protecting-Group-Free Mechanosynthesis of Amides from Hydroxycarboxylic Acids: Application to the Synthesis of Imatinib

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General information

All reagents were purchased from commercial suppliers (Fluorochem, BLD pharm, Sigma-Aldrich and Alfa Aesar) and used without further purification. Amine **16** is commercially available from BLDpharm (65 €/mol). Inorganic salts (e.g., K₂HPO₄, K₄P₂O₇) were dried prior to use by heating under reduced pressure. Mechanochemical experiments were carried out in a FTS-1000 shaker mill at 30 Hz frequency by using 14 mL ZrO₂-coated milling jars with 10 mm ZrO₂ milling balls.

Silica gel 40 – 63 µm was used for column chromatography; silica gel 60 F₂₅₄ plates were used for TLC. Visualization of TLC plates was performed by ninhydrin stain. ¹H NMR (400 MHz) and ¹³C NMR (100.6 MHz) spectra were recorded on Bruker Avance III spectrometer. Chemical shifts were referenced to residual protio solvent peaks and solvent resonances (δ ¹H 7.26 and δ ¹³C 77.16 measured in CDCl₃, δ ¹H 2.50 and δ ¹³C 39.52 measured in DMSO-*d*₆; δ ¹H 3.31 and δ ¹³C 49.00 measured in CD₃OD) as internal standards for ¹H NMR and ¹³C NMR spectra, respectively. All chemical shifts are reported in ppm units. HPLC analysis was carried out on Agilent 1200 Series HPLC system equipped with a multiple wavelength detector (MWD) and a single quadrupole mass detector (MSD). HRMS data was obtained on Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS system using AJS-ESI method in positive ion detection mode. Single crystal X-ray diffraction data was collected at 123K on Rigaku Compact HomeLab diffractometer, equipped with a Saturn 944 HG CCD detector and Oxford Cryostream cooling system using monochromatic Cu-*K*a radiation (1.54178Å) from a MicroMaxTM-003 sealed tube microfocus X-ray source. Melting points were determined with Stuart SMP40 apparatus.

1. Screening experiments



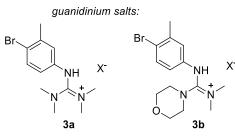
Reaction conditions: 4-(hydroxymethyl)benzoic acid **1** (100 mg, 0.657 mmol), amine **3** (110–122 mg, 0.592–0.657 mmol, 0.9–1 equiv.) and 1,3,5-trimethoxybenzene (~11 mg) as a standard were used in the reactions performed according to the published protocols.^{1–4} Ethyl ester of 4-(hydroxymethyl)benzoic acid **S1** was prepared according to the literature procedure.⁵ All the reactants (acid, amine, base and coupling reagent) and LAG additive (the latter) were placed into a 14 mL ZrO₂-coated jar charged with a single 10 mm ZrO₂ milling ball. The jar was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was analysed by ¹H NMR using CD₃OD as a solvent, after separation of insoluble inorganic material (Table S1).

Entry	Coupling reagent	Base	LAG (η, μL·mg ⁻¹)	Yield of 4 , % ^a	References
1	EDC (1 equiv.)	-	CH ₃ NO ₂ (0.25)	88 (87) ^b	
2	EDC (1 equiv.)	-	Sulfolane (0.25)	92 (87) ^b	- Č. 11 . 11
3	EDC (1 equiv.)	-	EtOAc (0.25)	90 (89) ^b	- Štrukil et al. ¹
4	EDC (1 equiv.)	DMAP (2 equiv.)	CH ₃ NO ₂ (0.25)	0 ^e	-
5	COMU (1.1 equiv.)	K ₂ HPO ₄ (3 equiv.)	EtOAc (0.19)	83 ^f	
6	TCFH (1.1 equiv.)	K ₂ HPO ₄ (3 equiv.)	EtOAc (0.19)	26 ^g	- Dalidovich et al. ²
7	TCFH (1.1 equiv.)	NMI (3 equiv.)	without	74 ^h	-
8	CDI (1 equiv.) ^c	-	without	10 ⁱ	Métro et al. ³
9	-	<i>t</i> -BuOK ^d (0.85 equiv.)	without	Oj	Nicholson et al. ⁴

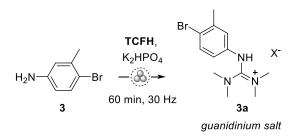
Table S1. Screening experiments

^a Conversion of **1** into amide **4**, as determined by ¹H NMR (characteristic signals of aromatic CH protons from 1,3,5-trimethoxybenzene standard at δ 6.06 ppm and aromatic CH proton from amide **4** at δ 7.65 ppm were integrated). ^b In parenthesis, the yield of isolated amide **4** is given (after washing with water and further drying in air). ^c Acid **1** was pre-milled with CDI for 5 minutes, then amine was added, followed by milling for 60 minutes (according to the published conditions).^{3 d} Ethyl 4-(hydroxymethyl)benzoate **S1** (0.789 mmol, 1.2 equiv., 142 mg) was used instead of **1** according to the published protocol.^{4 e} Mixture of by-products and the starting materials was obtained. ^f Ester-type by-products derived from self-condensation of **1** (characteristic signals of benzylic CH₂

at δ 5.5–5.3 ppm in ¹H NMR) and guanidinium derivative **3b** (ca. 12% yield) were observed. ^g Guanidinium salt **3a** was formed as the main product (ca. 75% yield). ^h Incomplete conversion of starting amine **3** and generation of **3a** were observed. ⁱ Ester-type by-products derived from **1** and unreacted amine **3** were observed. ^j Unreacted starting materials.

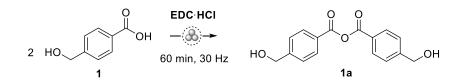


The reaction of amine 3 with $TCFH/K_2HPO_4$.



Amine **3** (122 mg, 0.657 mmol), TCFH (203 mg, 0.723 mmol, 1.1 equiv.), K₂HPO₄ (343 mg, 1.972 mmol, 3 equiv.), 1,3,5-trimethoxybenzene (~11 mg) and EtOAc (127 μ L) were placed into a 14 mL ZrO₂-coated jar charged with a single 10 mm ZrO₂ milling ball. The jar was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was analysed by ¹H NMR using CD₃OD as a solvent, after separation of insoluble inorganic material. Characteristic signals of guanidinium salt **3a** in ¹H NMR (CD₃OD, 400 MHz): δ 7.57 (d, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = 2.7 Hz, 1H), 6.79 (ddd, *J* = 8.5, 2.7, 0.7 Hz, 1H), 2.98 (s, 12H), 2.40 (s, 3H).

The reaction of 4-(hydroxymethyl)benzoic acid 1 with EDC.



Acid **1** (100 mg, 0.657 mmol), EDC·HCl (126 mg, 0.657 mmol, 1 equiv.) and EtOAc (57 μ L) were placed into a 14 mL ZrO₂-coated jar charged with a single 10 mm ZrO₂ milling ball. The jar was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was analysed by ¹H NMR using CD₃OD as a solvent, after separation of insoluble inorganic material. Characteristic signals of anhydride **1a** in ¹H NMR (CD₃OD, 400 MHz): δ 8.13 (d, *J* = 7.9 Hz, 4H), 7.57 (d, *J* = 7.9 Hz, 4H), 4.73 (s, 4H). HRMS (AJS-ESI) calcd. for C₁₆H₁₄O₅Na⁺ [M+Na]⁺ 309.0733, found *m/z* 309.0734.

The reaction of amide 4 with 4-(hydroxymethyl)benzoic acid 1.



Reaction conditions: amide **4** (0.19 mmol, 60 mg), 4-(hydroxymethyl)benzoic acid **1** (29 mg, 0.19 mmol), coupling reagent (36–88 mg, 1–1.1 equiv.), base (45–98 mg, 3 equiv.) and LAG additive ($\eta = 0.19-0.25 \ \mu L \cdot mg^{-1}$) were placed into a 14 mL ZrO₂-coated jar charged with a single 10 mm ZrO₂ milling ball. The jar was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was analysed by ¹H NMR using CD₃OD as a solvent, after separation of insoluble inorganic material (Table S2).

Entry	Coupling reagent	Base	LAG $(\eta, \mu L \cdot mg^{-1})$	Yield of 5 , % ^a
1	TCFH	K ₂ HPO ₄	EtOAc (0.19)	5 ^b
2	COMU	K ₂ HPO ₄	EtOAc (0.19)	31
3	TCFH	NMI	-	40
4	EDC	-	EtOAc (0.25)	<1°

Table S2. Screening experiments

^a Conversion of **4** into ester **5**, as determined by ¹H NMR (characteristic signals of aromatic CH protons from **4** at δ 7.90 ppm and aromatic CH protons from **5** at δ 7.61 ppm were integrated). ^b Anhydride **1a** was formed in 70% yield. ^c Starting materials are left and anhydride **1a** was formed in 30% yield.

Characteristic signals of ester **5** in ¹H NMR (CD₃OD, 400 MHz): δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 2.3 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.52–7.46 (m, 4H), 5.45 (s, 2H), 4.69 (s, 2H), 2.40 (s, 3H). ¹³C NMR (CD₃OD, 100.6 MHz): δ 168.39, 167.60, 148.90, 141.82, 139.37, 139.35, 135.92, 133.49, 130.73, 129.97, 129.04, 128.97, 127.70, 124.32, 121.30, 120.41, 66.95, 64.52, 23.16. MS calcd. for C₂₃H₂₁BrNO₄⁺ [M+H]⁺ 454.1, found *m*/*z* 454.0.

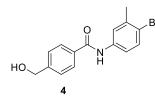
2. General procedure and characterization of products

General procedure. A hydroxy acid (1 equiv.), amine (1 equiv.), EDC·HCl (1 equiv.) and EtOAc as a LAG additive ($\eta = 0.25 \,\mu L \cdot mg^{-1}$) were placed into a 14 mL ZrO₂-coated jar charged with a single 10 mm ZrO₂ milling ball. The jar was then set to mill at 30 Hz for 60 minutes.

<u>Work-up procedure I:</u> water (10 mL) was added to the crude reaction mixture, followed by transferring to a glass filter and washing with water (3×10 mL). The obtained solid product was dried in air. If required, further purification by silica gel chromatography (petroleum ether/acetone) was performed.

<u>Work-up procedure II:</u> the crude reaction mixture was mixed with water (15 mL) and extracted with ethyl acetate (3×15 mL). The combine organic layers were washed with 10% aq. NaHSO₄ (5 mL), sat. NaHCO₃ (5 mL), brine (10 mL), and dried over Na₂SO₄, then filtered, and concentrated under reduced pressure. If required, further purification by silica gel chromatography (petroleum ether/acetone) was performed.

N-(4-bromo-3-methylphenyl)-4-(hydroxymethyl)benzamide (4). Prepared from 1 (100 mg,



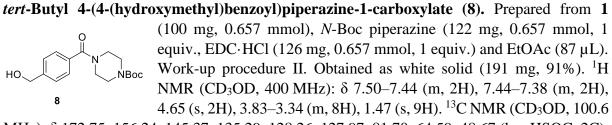
0.657 mmol), amine **3** (122 mg, 0.657 mmol, 1 equiv.), EDC·HCl (126 mg, 0.657 mmol, 1 equiv.) and EtOAc (87 μ L). Work-up procedure I. Obtained as white solid (187 mg, 89%). Analytically pure sample was prepared by recrystallization (petroleum ether/ethyl acetate = 1:1). mp = 156–157 °C. ¹H NMR (CD₃OD, 400 MHz): δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 2.2 Hz, 1H), 7.54-7.42 (m, 4H),

4.69 (s, 2H), 2.39 (s, 3H). ¹³C NMR (CD₃OD, 100.6 MHz): δ 168.61, 147.18, 139.39, 139.30, 134.84, 133.45, 128.73, 127.74, 124.34, 121.31, 120.34, 64.56, 23.16. HRMS (AJS-ESI) calcd. for C₁₅H₁₅BrNO₂⁺ [M+H]⁺ 320.0281, found *m/z* 320.0276.

Ethyl 4-(4-(hydroxymethyl)benzamido)benzoate (6). Prepared from 1 (100 mg, 0.657 mmol, 1 equiv.), O_{1} mmol), ethyl 4-aminobenzoate (109 mg, 0.657 mmol, 1 equiv.), EDC·HCl (126 mg, 0.657 mmol, 1 equiv.) and EtOAc (84 µL) in 76% yield by ¹H NMR. Characteristic signals of amide 6 in ¹H NMR (CD₃OD, 400 MHz): δ 8.01 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 4.70 (s, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H). HRMS (AJS-ESI) calcd. for C₁₇H₁₈NO₄⁺ [M+H]⁺ 300.1230, found *m/z* 300.1233.

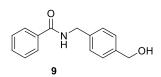
4-(Hydroxymethyl)-*N*-mesitylbenzamide (7). Prepared from 1 (100 mg, 0.657 mmol), 2,4,6trimethylaniline (89 mg, 0.657 mmol, 1 equiv.), EDC·HCl (126 mg, 0.657 mmol, 1 equiv.) and EtOAc (60 μ L) in 77% yield by ¹H NMR. Work-up procedure II. Purified by silica gel chromatography with petroleum ether/acetone (25 to 30%) as eluent and obtained as white solid (136 mg, 77%). Analytically pure sample was prepared by

recrystallization (petroleum ether/ethyl acetate = 1:2). mp = 157–158 °C. ¹H NMR (CD₃OD, 400 MHz): δ 7.96 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 6.95 (s, 2H), 4.70 (s, 2H), 3.35 (s, 1H), 2.29 (s, 3H), 2.21 (s, 6H). ¹³C NMR (CD₃OD, 100.6 MHz): δ 169.09, 147.10, 138.17, 136.84, 134.34, 133.15, 129.75, 128.70, 127.80, 64.59, 21.05, 18.32. HRMS (AJS-ESI) calcd. for C₁₇H₂₀NO₂⁺ [M+H]⁺ 270.1489, found *m/z* 270.1491.



MHz): δ 172.75, 156.24, 145.37, 135.29, 128.26, 127.97, 81.70, 64.59, 48.67 (br., HSQC, 2C), 44.72 (br., HSQC), 43.27 (br., HSQC), 28.59. HRMS (AJS-ESI) calcd. for C₁₇H₂₅N₂O₄⁺ [M+H]⁺ 321.1809, found *m*/*z* 321.1809. Spectral data are in agreement with previously reported.⁶

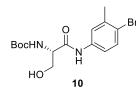
N-(4-(hydroxymethyl)benzyl)benzamide (9). Prepared from benzoic acid (100 mg, 0.819



mmol), (4-(aminomethyl)phenyl)methanol (112 mg, 0.819 mmol, 1 equiv.), EDC·HCl (157 mg, 0.819 mmol, 1 equiv.) and EtOAc (92 μ L). Work-up procedure II. Obtained as yellowish oil, which crystallizes upon standing (191 mg, 91%). Following work-up procedure I, amide **9** was obtained in 61% yield (120 mg). ¹H NMR

(CD₃OD, 400 MHz): δ^{1} H NMR (CD₃OD, 400 MHz): $\delta^{7.87-7.82}$ (m, 2H), 7.56–7.50 (m, 1H), 7.49–7.43 (m, 2H), 7.37–7.29 (m, 4H), 4.58 (s, 2H), 4.57 (s, 2H). ¹³C NMR (CD₃OD, 100.6 MHz): $\delta^{170.15}$, 141.66, 139.27, 135.65, 132.71, 129.59, 128.56, 128.32, 128.23, 64.96, 44.27. HRMS (AJS-ESI) calcd. for C₁₅H₁₆NO₂⁺ [M+H]⁺ 242.1176, found *m/z* 242.1175. Spectral data are in agreement with previously reported.⁷

tert-Butyl



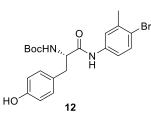
(S)-(1-((4-bromo-3-methylphenyl) amino)-3-hydroxy-1-oxopropan-2-yl) carbamate (10). Prepared from (*tert*-butoxycarbonyl)-L-serine (100 mg, 0.487 mmol), amine 3 (91 mg, 0.487 mmol, 1 equiv), EDC·HCl (94 mg, 0.487 mmol, 1 equiv.) and EtOAc (71 μL). Work-up procedure II. Purified by silica gel chromatography with petroleum ether/acetone (15 to 20%) as eluent and obtained as colourless oil, which crystallizes upon

standing (150 mg, 82%). mp = 133–134 °C. ¹H NMR (CD₃OD, 400 MHz): ¹H NMR (CD₃OD, 400 MHz): δ 7.53 (d, *J* = 2.6 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.34 (dd, *J* = 8.6, 2.6 Hz, 1H), 4.25 (t, *J* = 5.4 Hz, 1H), 3.80 (d, *J* = 5.4 Hz, 2H), 2.35 (s, 3H), 1.46 (s, 9H). ¹³C NMR (CD₃OD, 100.6 MHz): 171.55, 157.79, 139.29, 138.94, 133.43, 123.59, 120.56, 120.11, 80.90, 63.36, 58.58, 28.66, 23.12. HRMS (AJS-ESI) calcd. for C₁₅H₂₁BrN₂O₄Na⁺ [M+Na]⁺ 395.0577, found *m/z* 395.0573.

Methyl (*tert*-butoxycarbonyl)-L-seryl-L-phenylalaninate (11). Prepared from (*tert*-butoxycarbonyl)-L-serine (100 mg, 0.487 mmol, 1 equiv.), methyl L-phenylalaninate (87 mg, 0.487 mmol, 1 equiv.), EDC·HCl (94 mg, 0.487 mmol, 1 equiv.), EDC·HCl (94 mg, 0.487 mmol, 1 equiv.) and EtOAc (70 μ L). Work-up procedure II. Obtained as colourless oil, which could crystallize upon standing (150 mg, 84%). ¹H NMR (CDCl₃, 400 MHz): δ 7.32–7.22 (m, 3H), 7.15–7.10 (m, 2H), 7.02 (d, *J* = 6.0 Hz, 1H), 5.48 (d, *J* = 6.5 Hz, 1H), 4.85 (q, *J* =

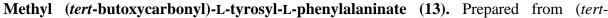
6.9 Hz, 1H), 4.20–4.08 (m, 1H), 3.99 (d, J = 9.7 Hz, 1H), 3.73 (s, 3H), 3.60 (dd, J = 11.3, 5.5 Hz, 1H), 3.18 (dd, J = 13.9, 5.6 Hz, 1H), 3.05 (dd, J = 14.0, 6.9 Hz, 1H), 1.44 (s, 9H). ¹³C NMR (CDCl₃, 100.6 MHz): δ 171.97, 171.19, 156.04, 135.83, 129.31, 128.77, 127.35, 80.60, 63.04, 55.11, 53.52, 52.64, 37.83, 28.39. HRMS (AJS-ESI) calcd. for C₁₈H₂₇N₂O₆⁺ [M+H]⁺ 367.1864, found *m*/*z* 367.1865. Spectral data are in agreement with previously reported.⁸

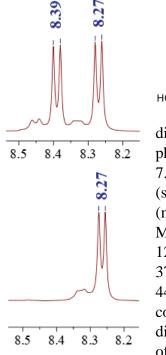
tert-Butyl (S)-(1-((4-bromo-3-methylphenyl) amino)-3-(4-hydroxyphenyl)-1-oxopropan-



2-yl) carbamate (12). Prepared from (*tert*-butoxycarbonyl)-L-tyrosine (100 mg, 0.355 mmol), amine **3** (66 mg, 0.355 mmol, 1 equiv.), EDC·HCl (68 mg, 0.355 mmol, 1 equiv.) and EtOAc (59 μ L). Work-up procedure I. Purified by silica gel chromatography with petroleum ether/acetone (20 to 25%) as eluent and obtained as white solid (144 mg, 90%). mp = 169–170 °C. ¹H NMR (CD₃OD,

400 MHz): δ 7.47–7.36 (m, 2H), 7.23 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 4.33 (t, *J* = 7.4 Hz, 1H), 2.99 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.84 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.33 (s, 3H), 1.40 (s, 9H). ¹³C NMR (CD₃OD, 100.6 MHz): δ 172.94, 157.63, 157.31, 139.25, 138.79, 133.39, 131.40, 128.87, 123.66, 120.63, 120.15, 116.20, 80.68, 58.34, 38.86, 28.67, 23.11. HRMS (AJS-ESI) calcd. for C₂₁H₂₆BrN₂O₄⁺ [M+H]⁺ 449.1070, found *m*/*z* 449.1068.



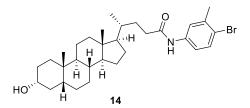


previously reported.¹⁰

BocHN_{7/2} HO 13 butoxycarbonyl)-L-tyrosine (100 mg, 0.355 mmol), methyl L-phenylalaninate (64 mg, 0.355 mmol, 1 equiv.), EDC·HCl (68 mg, 0.355 mmol, 1 equiv.) and EtOAc (58 μ L). Work-up procedure I. Obtained as white solid (130 mg, 83%). mp = 139–140 °C; lit. mp = 140–141 °C.⁹ Mixture of (*S*,*S*)- and (*S*,*R*)-13

diastereomers was obtained analogously from methyl D,Lphenylalaninate. ¹H NMR (CDCl₃, 400 MHz): δ 7.26–7.20 (m, 3H), 7.05–6.95 (m, 4H), 6.74–6.69 (m, 2H), 6.25 (d, *J* = 4.87 Hz, 1H), 4.98 (s, 1H), 4.77 (d, *J* = 7.2 Hz, 1H), 4.26 (s, 1H), 3.66 (s, 3H), 3.11–2.99 (m, 2H), 2.94 (d, *J* = 6.8 Hz, 1H), 1.41 (s, 9H).¹³C NMR (CDCl₃, 100.6 MHz): δ 171.54, 171.22, 155.57, 155.30, 135.70, 130.56, 129.37, 128.71, 128.03, 127.29, 115.73, 80.56, 56.07, 53.45, 52.47, 38.10, 37.67, 28.39. HRMS (AJS-ESI) calcd. for C₂₄H₃₁N₂O₆⁺ [M+H]⁺ 443.2177, found *m*/*z* 443.2175. The diastereomeric purity (99:1 dr) was confirmed by characteristic resonances in ¹H NMR: (*S*,*S*)diastereormer, 8.27 ppm; (*S*,*R*)-diastereomer, 8.39 ppm (see a fragment of ¹H NMR spectra in DMSO-*d*₆). Spectral data are in agreement with

(4R)-N-(3-bromo-4-methylphenyl)-4-((3R, 5R, 10S, 13R, 17R)-3-hydroxy-10,



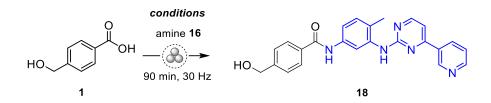
dimethylhexadecahydro-1*H*-cyclopenta $[\alpha]$ phenanthren-17-yl) pentanamide (14). Prepared fromlithocholic acid (100 mg, 0.266 mmol), amine 3 (49 mg,0.266 mmol, 1 equiv.), EDC·HCl (51 mg, 0.266 mmol,1 equiv) and EtOAc (50 µL). Work-up procedure I.Obtained as white solid (134 mg, 93%). Analytically pure

13-

sample was prepared by recrystallization (dichloromethane/methanol = 3:1). mp = 240–241 °C. ¹H NMR (DMSO- d_6 , 400 MHz): δ 9.90 (s, 1H), 7.58 (d, J = 2.5 Hz, 1H), 7.46 (d, J = 8.7 Hz, 1H), 7.36 (dd, J = 8.7, 2.5 Hz, 1H), 4.44 (d, J = 4.5 Hz, 1H), 3.43–3.33 (m, 1H), 2.37–2.26 (m, 1H), 2.29 (s, 3H), 2.24–2.15 (m, 1H), 1.93 (d, J = 8.8 Hz, 1H), 1.86–1.46 (m, 7H), 1.41–0.99

(m, 17H), 0.91 (d, J = 6.5 Hz, 3H), 0.94–0.88 (m, 1H), 0.87 (s, 3H), 0.61 (s. 3H). ¹³C NMR (DMSO- d_6 , 100.6 MHz): δ 171.77, 138.89, 137.27, 132.12, 121.29, 118.47, 116.94, 69.85, 56.09, 55.55, 42.27, 41.51, 39.97, 39.70, 36.30, 35.37, 35.14, 34.95, 34.20, 33.35, 31.23, 30.38, 27.73, 26.88, 26.16, 23.85, 23.27, 22.66, 20.40, 18.31, 11.88. HRMS (AJS-ESI) calcd. for C₃₁H₄₇BrNO₂⁺ [M+H]⁺ 544.2785, found *m*/*z* 544.2785.

3. Preparation of intermediate 18: optimization studies



Reaction condition for the optimization studies: Acid **1** (54.9 mg, 0.36 mmol,), amine **16** (100.0 mg, 0.36 mmol, 1 equiv.), coupling reagent (0.36–0.40 mmol, 1–1.3 equiv.), base (1.08 mmol, 3 equiv.), triphenylmethane (in entries 5 and 6, Table S2) and LAG additive (0.19–0.25 μ L·mg⁻¹) were placed into a 14 mL ZrO₂-coated jar charged with a single 10 mm ZrO₂ milling ball. The jar was then set to mill at 30 Hz for 90 minutes.

- A. The resulting crude reaction mixture was transferred to a beaker, diluted with distilled water (10–15 mL), stirred for 2 hours, then filtered through a glass filter and dried under vacuum (Table S2, Entries 1–4).
- B. The resulting crude reaction mixture was analysed by ¹H NMR in DMSO- d_6 , after separation of insoluble inorganic material (Table S3, Entries 5 and 6).

Entry	Coupling reagent	Base	LAG $(\eta, \mu L \cdot mg^{-1})$	Yield of 18 , %
1	EDC (1 equiv.)	-	CH ₃ NO ₂ (0.25)	86
2	EDC (1 equiv.)	-	Sulfolane (0.25)	83
3	EDC (1 equiv.)	-	EtOAc (0.25)	93
4	COMU (1.1 equiv.)	K ₂ HPO ₄ (3 equiv.)	EtOAc (0.19)	81
5	TCFH (1.1 equiv.)	K ₂ HPO ₄ (3 equiv.)	EtOAc (0.19)	36 ^a
6	TCFH (1.3 equiv.)	NMI (3 equiv.)	without	63 ^a

Table S3. Optimization studies.

^a Conversion of **1** into **18**, as determined by ¹H NMR in DMSO- d_6 using an internal standard (characteristic signals of triphenylmethane CH proton at δ 5.61 ppm and CH₂-OH protons from amide **18** at δ 4.59 ppm were integrated).

HPLC-UV-MS analysis of amide 18.

The chromatographic separation was performed on Phenomenex Kinetex XB-C18 column (150 mm \times 4.6 mm, 2.6 µm). Eluents A (water / 0.1% formic acid) and B (methanol) were used in A:B 60:40 (v/v) isocratic mode for 3 minutes, followed by a 10-minute gradient from A:B 60:40 (v/v) to A:B 30:70 (v/v) and a 17-minute isocratic stage with the flow rate of 0.5 mL/min. The column temperature was set at 30 °C, injection volume at 1 µL and detection wavelength at 270 nm. The peaks were characterized by ESI-MS with the following spray chamber parameters: drying gas flow 5 L/min, drying gas temperature 300 °C, nebulizer pressure 60 psig, vaporizer temperature 150 °C, capillary voltage 2000 V and charging electrode voltage 2000 V. Mass spectra were acquired in positive mode within *m/z* 100 – 2000 range and fragmentor voltage 100 V.

Sample preparation: ~0.5 mg/ml in acetonitrile: methanol 1:1 (v/v).

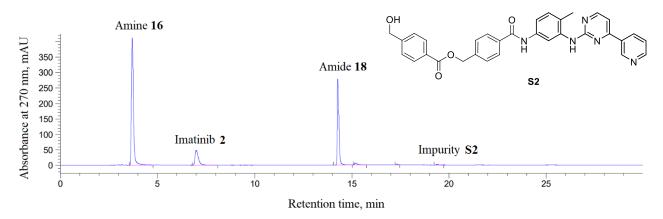


Figure S1. HPLC-UV chromatogram of the mixture of amine **16**, imatinib **2**, amide **18** and impurity **S2** at 270 nm.

MS data:

Amine **16**, calcd. for $C_{16}H_{16}N_5^+$ [M+H]⁺ 278.1, found *m/z* 278.1.

Imatinib **2**, calcd. for $C_{29}H_{32}N_7O^+$ [M+H]⁺ 494.3, found *m/z* 494.2.

Amide **18**, calcd. for $C_{24}H_{22}N_5O_2^+$ [M+H]⁺ 412.2, found *m/z* 412.1.

Impurity **S2**, calcd. for $C_{32}H_{28}N_5O_4^+$ [M+H]⁺ 546.2, found *m*/*z* 546.2.

Table S4. HPLC purity of amide 18 prepared under different conditions.

Entry	Coupling reagent / Base	LAG	HPLC a	rea percent	age, %
Lintry	Coupling reagent / Dase	$(\eta, \mu L \cdot mg^{-1})$	18	16	S2
1	EDC (1 equiv.)	CH ₃ NO ₂ (0.25)	98.3	1.5	0.2
2	EDC (1 equiv.)	Sulfolane (0.25)	97.3	1.3	1.3
3	EDC (1 equiv.)	EtOAc (0.25)	98.0	0.9	1.1
4	COMU (1.1 equiv.) / K ₂ HPO ₄ (3 equiv.)	EtOAc (0.19)	94.3	0.2	4.8

The final protocol: Two identical reactions were performed simultaneously in two jars.

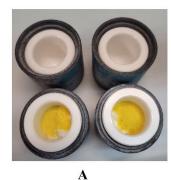








Figure S2. Synthesis of amide 18.

Amine **16** (300 mg, 1.08 mmol), acid **1** (173 mg, 1.14 mmol, 1.05 equiv.), EDC HCl (228 mg, 1.19 mmol, 1.1 equiv.) and EtOAc (350 μ L) were placed into a 14 mL ZrO₂-coated jar charged with one 10 mm ZrO₂ ball (Figure S2, A). The second jar was loaded with the same amount of chemicals and the two jars were set to mill at 30 Hz for 90 min. The resulting crude reaction mixtures (yellowish solid, Figure S2, B) were combined and transferred to a beaker, diluted with water (ca. 40 mL), stirred for 2 hours (Figure S2, C), then filtered through a glass filter (Figure S2, D) and dried first in air ant then under vacuum. Product **18** was obtained as a yellowish solid (835 mg, 94% yield, 98% HPLC purity, Figure S3). mp = 197–198 °C (CH₃OH). ¹H NMR (DMSO-*d*₆, 400 MHz): δ 10.16 (s, 1H, NH), 9.28 (d, *J* = 2.3 Hz, 1H), 8.98 (s, 1H, NH), 8.68 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.51 (d, *J* = 5.1 Hz, 1H), 8.48 (d, *J* = 8.1 Hz, 1H), 8.10 (d, *J* = 2.3 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.56-7.39 (m, 3H), 7.21 (d, *J* = 8.3 Hz, 1H), 5.35 (t, *J* = 5.7 Hz, 1H, OH), 4.59 (d, *J* = 5.7 Hz, 12, 12, 123 (s, 3H). ¹³C NMR (DMSO-*d*₆, 100.6 MHz): δ 165.23, 161.62, 161.20, 159.49, 151.40, 148.22, 146.27, 137.80, 137.23, 134.43, 133.35, 132.23, 130.04, 127.57, 127.52, 126.05, 123.79, 117.23, 116.76, 107.52, 62.48, 17.67. HRMS (AJS-ESI) calcd. for C₂₄H₂₂N₅O₂⁺ [M+H]⁺ 412.1768, found *m*/z 412.1766.

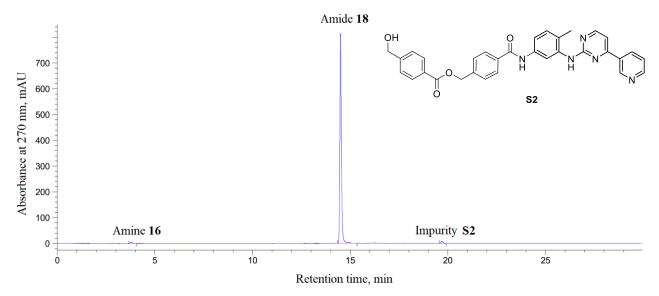


Figure S3. HPLC-UV chromatogram of amide 18 (98.0%), containing amine 16 (0.9%) and impurity S2 (1.1%).

The confirmation of the structure of impurity S2 by synthesis and alkaline hydrolysis

Amide **18** (50.0 mg, 0.12 mmol), acid **1** (19 mg, 0.12 mmol, 1 equiv.), TCFH (38 mg, 0.13 mmol, 1.1 equiv.), NMI (30 mg, 0.36 mmol, 3 equiv.) were placed into a 14 mL ZrO₂-coated jar charged with a single 10 mm ZrO₂ milling ball. The jar was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was transferred to a beaker, diluted with distilled water (5 mL), stirred for 2 hours, then filtered through a glass filter, dried under vacuum and analysed by HPLC (Figure S4) that shows generation of **S2** and unreacted **18**. Characteristic signals of benzylic CH₂OC(O) of **S2** in ¹H and ¹³C NMR (DMSO-*d*₆): $\delta_{\rm H} = 5.44$ ppm, $\delta_{\rm C} = 65.4$ ppm. The treatment of amide **18**, containing 1.1% of **S2**, with 1M aq. NaOH at 40°C for 2 hours (in methanol) resulted in the hydrolysis of ester **S2** and its disappearance from the HPLC chromatogram (Figure S5).

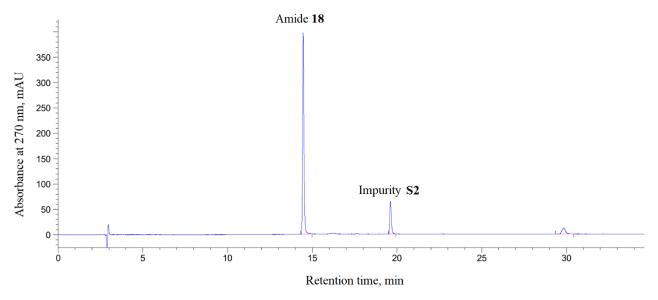


Figure S4. HPLC-UV chromatogram of amide 18, containing impurity S2.

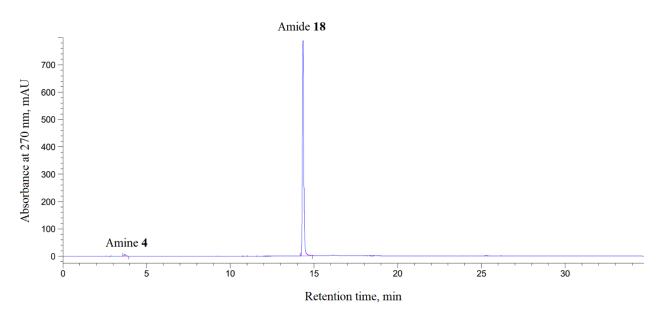
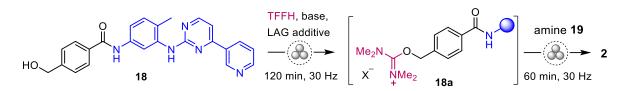


Figure S5. HPLC-UV chromatogram of amide 18 after hydrolysis with 1M NaOH solution.

4. Preparation of Imatinib 2 from amide 18: optimization studies.

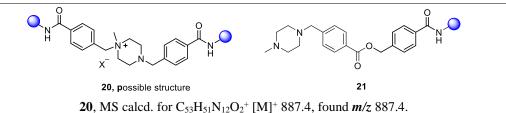


Reaction condition for the optimization studies: Amide **18** (100 mg, 0.24 mmol), TFFH (0.49 mmol, 2 equiv.) and a base (0.49–0.61 mmol, 2–2.5 equiv.) were placed into a 14 mL ZrO₂-coated jar charged with a single 10 mm ZrO₂ milling ball. Then LAG additive was added to the jar ($\eta = 0.2$ – 0.75 µL·mg⁻¹), which was then set to mill at 30 Hz for 120 min. 1-Methylpiperazine **7** (0.36–2.43 mmol, 1.5–10 equiv.) was added to the resulting mixture, and the jar was set to mill at 30 Hz for additional 60 min. The resulting crude reaction mixture was transferred to a beaker, diluted with cold distilled water (20–30 mL), stirred overnight, then filtered through a glass filter, dried in air and analysed by HPLC-UV-MS (Table S5).

Entres	Dage (conin)	LAG	A main a 7	Н	IPLC area p	ercentage, %	6
Entry	Base (equiv.)	$(\eta, \mu L \cdot mg^{-1})$	Amine 7	2	18	20	21
1 ⁶	K ₂ HPO ₄	EtOAc (0.2)	1.5 equiv.	66 ^a	_	_	-
	(2.0 equiv.)		1.5 equit.				
2	K ₂ HPO ₄	Sulfolane (0.5)	2.5 equiv.	74.6	8.1	13.5	_
	(2.5 equiv.)		2.0 040111	,			
3	K_2HPO_4	EtOAc (0.5)	5.0 equiv.	89.1	6.5	2.9	0.5
	(2.5 equiv.)						
4	K ₂ HPO ₄	Sulfolane (0.5)	5.0 equiv.	91.8	1.9	5.5	0.8
	(2.5 equiv.)	~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~					
5	$K_4P_2O_7$	DMI (0.6)	5.0 equiv.	94.2	0.9	3.8	1.1
	(2.0 equiv.)	(0.0)		,	•		
6	$K_4P_2O_7$	EtOAc (0.5)	5.0 equiv.	84.9	13.7	0.7	0.7
	(2.0 equiv.)		I				
7	K ₂ HPO ₄	DMI (0.65)	5.0 equiv.	93.2	0.6	5.2	1.0
	(2.5 equiv.)						
8	$K_4P_2O_7$	DMI (0.6)	10.0 equiv.	94.9	0.4	3.2	1.5
	(2.0 equiv.)	(0.0)					
9	K ₂ HPO ₄	DMI (0.65)	10.0 equiv.	95.6	0.6	2.4	1.5
	(2.5 equiv.)						
10 ^b	K ₂ HPO ₄	DMI(0.65)	10.0 equiv.	95.3	1.3	2.0	1.4
	(2.5 equiv.)	2			2.0	2.0	

 Table S5. Optimization studies.

^a With 1.5 equiv. of TFFH, conversion of amide **18** into product **2**, as determined by ¹H NMR in DMSO- d_6 (characteristic signals of NH proton from amide **18** at δ 10.15 ppm and from product **2** at δ 10.16 ppm were integrated). ^b The reaction was performed starting from 300 mg of **18** in a 14 mL ZrO₂-coated jar charged with two 10 mm ZrO₂ milling balls.



21, MS calcd. for C₃₇H₃₈N₇O₃⁺ [M+H]⁺ 628.3, found *m/z* 628.3.

The final protocol: Two identical reactions were performed simultaneously in two jars.

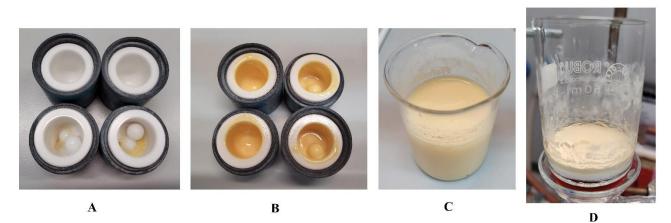


Figure S6. Preparation of Imatinib 2 from intermediate 18.

Amide 18 (300 mg, 0.73 mmol, 98% purity, crude material obtained in the previous step and used without any additional purification), TFFH (385 mg, 1.46 mmol, 2 equiv.) and K₂HPO₄ (318 mg, 1.82 mmol, 2.5 equiv.) were placed into a 14 mL ZrO₂-coated jar charged with two 10 mm ZrO₂ milling balls. Dimethyl isosorbide was added (655 µL) as a LAG additive. The second jar was loaded with the same amount of chemicals (Figure S6, A) and the two jars were set to mill at 30 Hz for 120 minutes. Then 1-methylpiperazine 7 (810 µL, 7.30 mmol, 10 equiv.) was added to each jar to the formed reaction mixture. The two jars were set to mill at 30 Hz for additional 60 minutes. The resulting crude reaction mixtures (yellowish viscous paste, Figure S6, B) were combined and transferred to a beaker, diluted with distilled water (100 mL), stirred overnight (Figure S6, C), then filtered through a glass filter (Figure S6, D), dried first in air and then under vacuum. Imatinib 2 was obtained as off-white solid (690 mg, 96% yield, 95% HPLC purity, Figure S7). Analytically pure sample was obtained by crystallization from methanol/ethyl acetate (1:1) to give Imatinib 2 with 99% HPLC purity (Figure S8). ¹H NMR (DMSO- d_6 , 400 MHz): δ 10.16 (s, 1H), 9.28 (dd, J = 2.3, 0.9 Hz, 1H), 8.98 (s, 1H), 8.68 (dd, J = 4.8, 1.6 Hz, 1H), 8.51 (d, J = 5.1 Hz, 1H), 8.48 (dt, J = 8.0, 1.9 Hz, 1H), 8.09 (d, J = 1.9 Hz, 1H), 7.91 (d, J = 8.3 Hz, 2H), 7.55-7.46 (m, 2H), 7.45-7.39 (m, 3H), 7.20 (d, J = 8.4 Hz, 1H), 3.52 (s, 2H), 2.47-2.20 (m, 8H), 2.22 (s, 3H), 2.14 (s, 3H). ¹³C NMR (DMSO*d*₆, 100.6 MHz) δ 165.25, 161.60, 161.19, 159.47, 151.39, 148.21, 142.11, 137.80, 137.21, 134.42, 133.77, 132.22, 130.03, 128.62, 127.58, 123.78, 117.20, 116.72, 107.51, 61.62, 54.71, 52.58, 45.74, 17.67. HRMS (AJS-ESI) calcd. for C₂₉H₃₂N₇O⁺ [M+H]⁺ 494.2663, found *m/z* 494.2665. Spectral data are in agreement with previously reported.¹¹

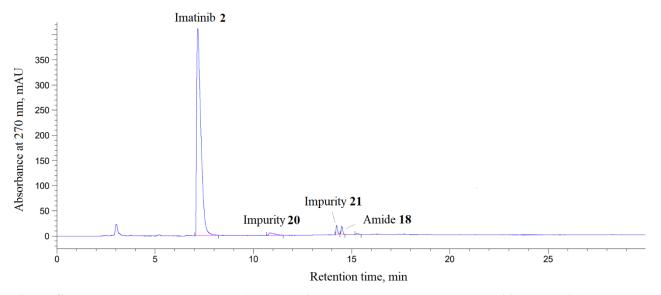


Figure S7. HPLC-UV chromatogram of Imatinib **2** (95.3%), containing impurities **20** (1.4%), **21** (2.0%) and amide **18** (1.3%).

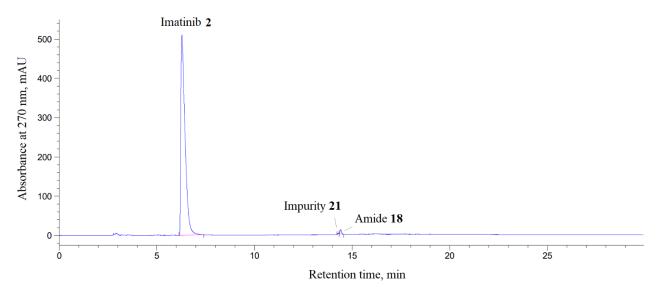


Figure S8. HPLC-UV chromatogram of Imatinib **2** (99.2%), containing impurity **21** (0.1%) and amide **18** (0.7%).

5. SC-XRD characterization of 18.

Single crystal X-ray diffraction data was collected at 123K on Rigaku Compact HomeLab diffractometer, equipped with a Saturn 944 HG CCD detector and Oxford Cryostream cooling system using monochromatic Cu- $K\alpha$ radiation (1.54178Å) from a MicroMaxTM-003 sealed tube microfocus X-ray source. The data was solved by intrinsic phasing (SHELXT)¹² and refined by full-matrix least squares on F^2 using Olex2¹³ utilising the SHELXL module.¹² Anisotropic displacement parameters were assigned to non-H atoms and isotropic displacement parameters for all H atoms were constrained to multiples of the equivalent displacement parameters of their parent atoms with U_{iso}(H) = 1.2 U_{eq} (methylene, methine) or U_{iso}(H) = 1.5 Ueq(methyl, hydroxy) of their respective parent atoms. Appropriate restraints were applied to the geometry and thermal displacement parameters of the atoms involved in the disordered parts of the structures. Restrain DFIX was used to fix the distance between carbon and oxygen atoms (C1A O1A bond distance was fixed to be 1.43) to be equal within the standard uncertainty s value 0.02. Terminal OH-group was modelled as a 60:40% disorder model.

The crystallographic data is deposited with the Cambridge Crystallographic Data Centre (CCDC 2287665) and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Single-crystal XRD analysis unambiguously revealed that we obtained a crystal structure of amide **18** with methanol coordinated to it (Figure S9).

Crystallographic details for amide 18

 $[C_{24}H_{21}N_5O_2] \cdot [C_1H_4O_1]$: Single crystals of the compound were obtained from a methanol solution of amide **18** by slow evaporation of the solvent.

C₂₅H₂₅N₅O₃, M = 426.71 g/mol 1, colorless blocks, 0.06 × 0.20 × 0.20, monoclinic, $P2_1/c$, a = 14.3819(4) Å, b = 15.9349(5) Å, c = 9.4755(3) Å, α = 90°, β = 99.199(3)°, γ = 90°, V = 2143.61(11) Å³, Z = 4, Cu-Kα radiation (λ = 1.54184 Å), at *T* = 123.0(1) K, μ(Cu-*Kα*) = 0.701 mm⁻¹, 13786 reflections measured (6.208° ≤ 2Θ ≤ 129.382°), R_{int} = 0.028, 314 parameters, 1 restraints, $R_1[F^2>2\sigma(F^2)] = 0.061$, wR_2 (all data) = 0.188, *S* = 1.095, 0.21 < dΔρ < - 0.30 eÅ⁻³.

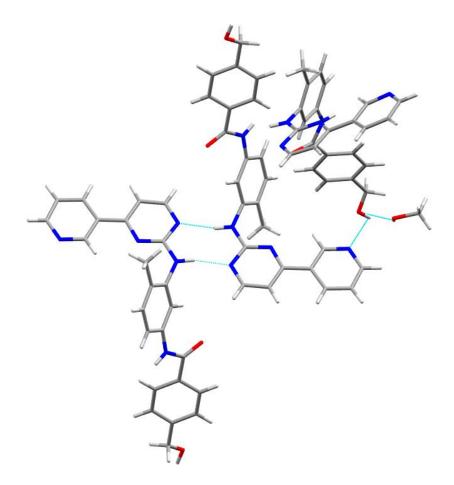
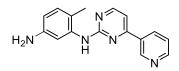


Figure S9. Crystal structure of amide 18.

6. Determination of Amine 16 (Impurity F) according to the European Pharmacopoeia and optimization studies for its content reduction.

6.1. Quantification of Amine 16.



Amine 16 (Impurity F)

Determination of genotoxic impurity **F** (amine **16**) was carried out according to the method established by European Pharmacopoeia 9.2, 07/2017:2736 used in analysis of Imatinib mesylate. The allowed limit is maximum 20 ppm.

Imatinib **2** with 99% HPLC purity was analysed (the synthetic procedure is described in the section 4, p. S14).

Sample preparation:

0.5 mg/ml in acetonitrile: methanol 1:1 (v/v).

Reference solution of impurity F:

0.00001 mg/ml in acetonitrile: methanol 1:1 (v/v). The concentration of impurity **F** corresponds to 20 ppm in test solution.

General HPLC-MS conditions:

The chromatographic separation was performed on Macherey-Nagel RP18 column (150 mm \times 3.0 mm, 2.7 µm). Eluents A (1.26 g/L solution of ammonium formate in water adjusted to pH 3.5 with formic acid) and B (0.05% formic acid in acetonitrile) were used in a gradient mode starting with A:B 80:20 (v/v) isocratic stage for 6 minutes, followed by a 4-minute gradient from A:B 80:20 (v/v) to A:B 20:80 (v/v) and holding the latter as 5-minute isocratic stage, with the flow rate of 0.5 mL/min. The column temperature was set at 40 °C and injection volume at 10 µL. Impurity **F** was followed by mass detector operated in single ion monitoring (SIM) mode with the following parameters: ESI, positive polarity, detection *m*/*z* 278.2, gas temperature 350 °C, drying gas flow 12 L/min, nebulizer pressure 60 psig, capillary voltage 3000 V. MS acquisition was started at 3.5 min and stopped at 6 min.

The content of impurity $\mathbf{F}(X, ppm)$ was calculated via formula (1):

$$X = \frac{S_{i} \cdot m_{0} \cdot A_{0} \cdot V_{i} \cdot 10^{6}}{S_{0} \cdot m_{i} \cdot V_{0} \cdot 100}$$
(1)

where S_i – peak area of impurity **F** on the chromatogram of test solution, ion counts; S_0 – peak area of impurity **F** on the chromatogram of reference solution, ion counts; m_i – weight of the sample, mg; m_0 – weight of the reference standard, mg; A_0 – reference standard purity or assay, %; V_0 – total volume of reference solution; V_i – total volume of test solution.

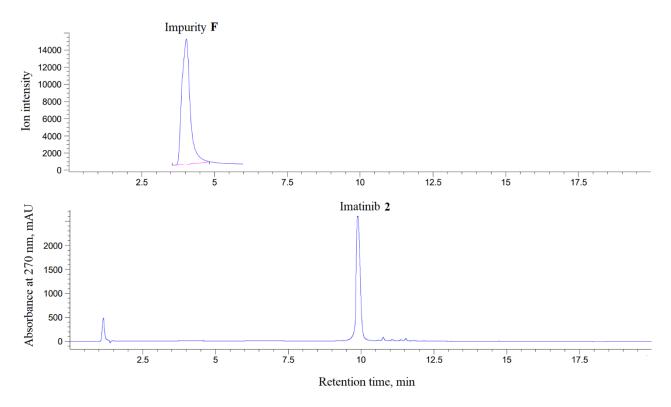


Figure S10. Upper: HPLC monitored ion count chromatogram of impurity F, lower: HPLC-UV chromatogram of Imatinib 2 at 270 nm.

 $X = 556 \pm 25 \text{ ppm}$

6.2. Optimization studies for reducing the content of amine 16.

In order to decrease the content of impurity F, slight modifications in the previously described protocol for the synthesis of amide **18** (see section 3, p. S11) were performed (modifications are underlined):

Amine **16** (300 mg, 1.08 mmol), acid **1** (214 mg, 1.41 mmol, 1.3 equiv.), EDC HCl (228 mg, 1.19 mmol, 1.1 equiv.) and EtOAc (375 μ L) were placed into a 14 mL ZrO₂-coated jar charged with one 10 mm ZrO₂ ball. The second jar was loaded with the same amount of chemicals and the two jars were set to mill at 30 Hz for 90 min. The resulting crude reaction mixtures were combined and transferred to a beaker, diluted with 5% KOH solution (ca. 20 mL), stirred for 2 hours, then filtered through a glass filter, washed with water (2×10 mL) and dried first in air ant then under vacuum. Product **18** was obtained as a yellowish solid (840 mg, 94% yield, 99% HPLC purity, Figure S11). Next, dichloromethane (ca. 25 mL) was added to the obtained solid amide **18**, and the resulting suspension was stirred for 1 hour, then filtered through a glass filter, washed with dichloromethane (2×10 mL) and dried first in air ant then under vacuum. Product **18** was obtained as a yellowish solid (805 mg, 90% yield, 99.6% HPLC purity, Figure S12).

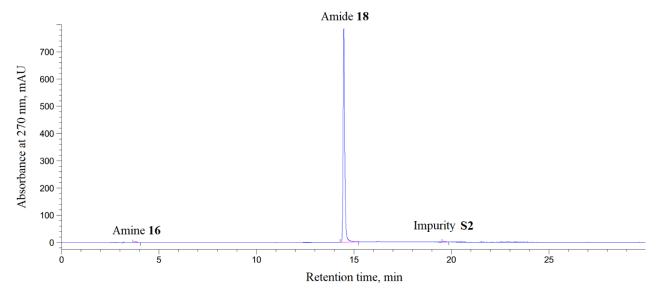


Figure S11. HPLC-UV chromatogram of amide **18** (99.0%), containing impurity **S2** (0.46) and amine **16** (0.51).

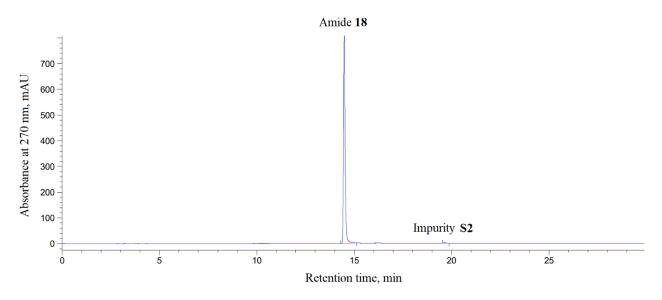


Figure S12. HPLC-UV chromatogram of amide 18 (99.6%), containing impurity S2 (0.44).

Imatinib **2** was synthesised according to the previously described protocol (see section 4, p. S14). Further assay of impurity F was determined in the crude product **2** prior to the recrystallization.

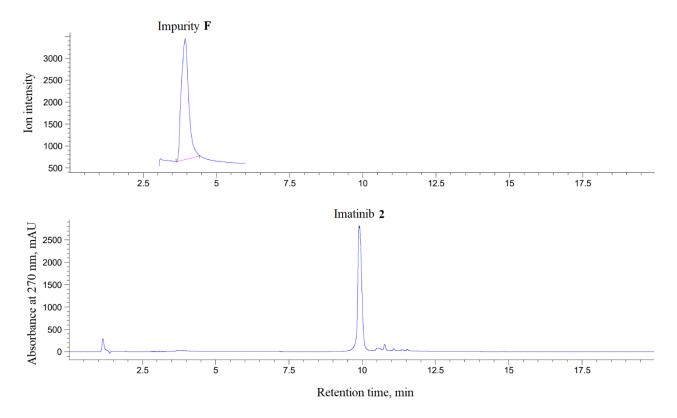
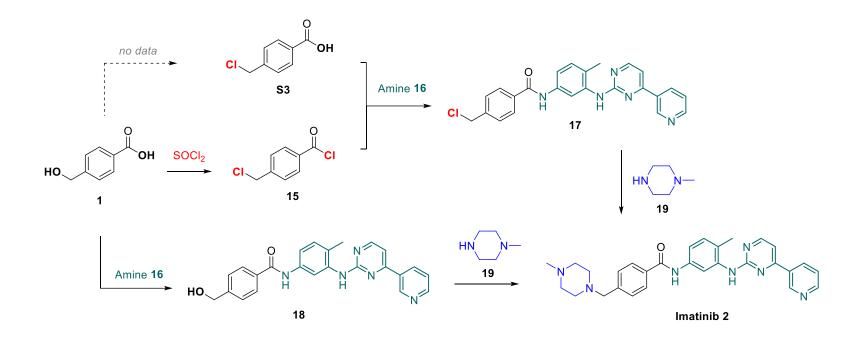


Figure S13. Upper: HPLC monitored ion count chromatogram of impurity **F**, lower: HPLC-UV chromatogram of Imatinib **2** at 270 nm.

 $X = 86 \pm 3 \text{ ppm}$

7. Green Chemistry metrics

Green chemistry metrics analysis have been performed for the developed mechanochemical procedure and six previously published protocols,^{14–19} including three patents and three research articles (Table S6). The described protocols start from 4-(chloromethyl)benzoic acid **S3** (Table S6, entry 1), or 4-(chloromethyl)benzoil chloride **15** (Table S6, entries 2, 5 and 6), or 4-(hydroxylmethyl)benzoic acid **1** (Table S6, entries 3, 4 and 7). The metrics were evaluated for the total process (2 or 3 steps).



Ent	Manufacturer or	St.	№ of constru	Mass of	Total			Total	PMI	PMI	PMI			Ha	azards	
ry	Publication	mat erial	ctive/tot al steps	product	yield	AE	RME	PMI	r-n	r-n solvents	work-up solvents	Solvents	Ther mal	Reagent	Produc ts	Genotoxic intermediates
1	ACTAVIS GROUP PTC EHF ¹⁴	S 3	2/2	240g	 78	58.3	9.5	131.9	20.1	9.6	110.5	1,4-dioxane, DMF, THF, Acetone, EtOAc, H2O	► 65- 70°C	1,4-dioxane (H350), DMF (H360D)	SO ₂ , HCl	16, 17
2	Y. Heo et al. ¹⁵	15	2/2	0.51 g	P 84	68.8	38.4	>36.8	36.8	34.1		DMF, THF, H2O	 ⊂ 90°C	DMF (H360D)		16, 17
3	Liu et al. 2008 ¹⁶	1	2/3	0.45 g	8 5	50.9	3.8	563.5	43.5	17	520	CH2Cl2, THF, H2O	► 140°C		SO ₂ , HCl	16, 17
4	NATCO Pharma LTD ¹⁷	1	2/3	9.8 kg	4 3	50.9	13.2	192.2	46.6	39.0	144.6	DMF, CHCl ₃ , Toluene, EtOAc, H ₂ O	№ 60°C	DMF (H360D), CHCl ₃ H372)	SO ₂ , HCl	16, 17
5	Z. Szakács et al. ¹⁸	15	2/2	1.25 g	4 1	74.1	17.0	>364.8	158.4	152.5	206.4	DMF, ACN, EtOH, H ₂ O	80°C	DMF (H360D)		16, 17
6	W. Szczepek et al. ¹⁹	15	2/2	60.6 g	9 5	74.1	44.0	42.6	12.1	9.2	30.4	THF, H2O	► 140°C			16, 17
7	This work	1	2/2	0.66 g	86 ^a	39.1	17.0	221.0	8.9	3.0	212.1	EtOAc, DMI, H ₂ O	r.t.	EDC (H410)	TMU (<mark>H360</mark>)	16, -

Table S6. Comparison of green metrics for mechanochemical and solution-based key-step synthesis of Imatinib 2.

^aYield is adjusted considering HPLC purity (95%) of obtained product.

Among the described protocols,^{14–19} the shortest routes for which the complete data were available for calculations, was an early-stage development described by Liu et al.¹⁶ and an example of kilo-scale preparation patented by NATCO Pharma LTD.¹⁷ Activation of hydroxy acid **1** by its conversion into the corresponding chloride by the reaction with SOCl₂ was used in both approaches as an additional non-constructive step.

The mass-based metrics have been calculated considering all steps of the respective preparation route combined. In terms of total yield (86%), the mechanochemical approach delivered comparable or superior results as the benchmark solution-state approaches. Atom economy (AE), which reflects the theoretical efficiency of reactant utilization, is lower in the mechanochemical route (AE = 39.1) due to the higher molecular weight of the reagents involved. However, reaction mass efficiency (RME), which represents the actual maximum efficiency of reactant utilization,²⁰ is noticeably better (RME = 17.0) compared to the solution-based protocols, in which larger excesses of chemicals was used. Finally, total process mass intensity (total PMI), which reflects the amount of waste generated per unit of product, is about 2.5 times lower than in a similar early-stage development solution route (PMI = 563.5 vs 221.0) and is comparable with PMI of a kilo-scale preparation (PMI = 192.2). It is important to note that the main contributor to PMI in the case of mechanochemical synthesis was work-up solvent (water, PMI = 212.1) rather than chemicals (PMI = 8.9) and reactions solvents (PMI = 3.0). In terms of two former, the mechanochemical route greatly surpasses the benchmarking solution approaches, in which excess of reactants and use of bulk solvents increase the PMI significantly. Furthermore, the mechanochemical protocol relies on the use of green and sustainable solvents for work-up (water) and as LAG additives (ethyl acetate, dimethyl isosorbide). This contrasts a larger portfolio of solvents which was involved in the solution-based preparations and includes several toxic compounds (DMF, CH₂Cl₂, chloroform). It worth also noting a room temperature operation as an additional benefit of mechanochemistry, in contrast to the solution methods which rely on thermal activation and involve heating up to 140 °C. The streamlined isolation protocol of **18** and **2** by filtration and washing with water brings an additional advantage. Although the solvent-related and thermal hazards have been greatly attenuated in our approach, it still relies on a use of stoichiometric amide coupling reagents (EDC and TFFH) which themselves, or their reaction products (e.g., tetramethyl urea, TMU), could pose environmental or health hazards,²¹ thus representing a disadvantage. On the other hand, TFFH is an air-stable and non-hygroscopic solid that offer a better safety profile^{21,22} than other amide couplers.

Exclusion of the genotoxic intermediate **17** was another important advantage which is especially relevant to pharma synthesis. Since intermediate **18** with unknown properties was involved instead, additional *in silico* assessment was performed for the designed route to evaluate the safety profile of all known chemical entities involved. Knowledge-based and statistical systems were used to predict potential mutagenicity following the recommendations of the ICH M7 (R1) (2018) guideline. The knowledge-based system Derek Nexus and the statistical system Sarah Nexus were used to predict mutagenicity. Derek Nexus (Lhasa Ltd. Leeds, UK), is a rule-based expert system, which has been designed on the basis of open accessible and proprietary data. It generates predictions based on the knowledge about the relationship of substructures and biological activity in a given molecule. Sarah Nexus (Lhasa Ltd. Leeds, UK) is a statistical-based system. Structures submitted for processing were fragmented and these fragments are reviewed for activity vs inactivity. The model then arranges those 'interesting' fragments into a network of hypotheses (or nodes) and relevant hypotheses are used to inform an overall prediction of toxicity. Sarah Nexus predicts activity or inactivity in the Ames test and provides information on coverage of a query compound. As a result, intermediate **18** displayed no structural concern for mutagenicity.

					Summary	of First	t Pass Metric	cs Toolkit										
-	Yield, AE, RME, MI/PMI and																	
toichiometry	Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml ⁻¹)	Mass (
1	Amine	173.30	277.00	0.63					1,4 - dioxane	590.00	1.03	607.70	K₂CO₃	173.00	Water	19561.00	1.00	19561.0
1	4-chloromethyl benzoic acid	118.00	170.59	0.69					DMF	251.00	0.94	236.94	AcOH	129.00	Acetone	2673.00	0.78	2095.
1	Thionyl chloride	280.80	118.97	2.36					THF	1651.00	0.89	1467.74			EtOAc	3875.00	0.90	3495.
2	N-methylpiperazine	1580.00	100.17	15.77								0.00			aq. NH3	1500.00	0.91	1365.
1	Pyridine	370.60	79.00	4.69								0.00						0.0
												0.00						0.0
	Total	2522.70	845.89			0.00		0.00				2312.38		302.00				26516
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	total mass of read	ctants 1						RME	9.5	OE	16.3		110	1000	mass	400.00	0.40	
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	total molecular well	gnt of real	cunts					PMI Reaction	20.1									
	total ma	ass in a pro	ocess or pr	ocess st	ep			reactants,		— ———————————————————————————————————								
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	Solvents (First Pass)							chemical PMI workup solvents List solv			→`_N_\		(L)	Ç +	SO ₂ + HCI	+ 🖓 cr	+ -N	
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		5		BnOH, eth		, acetone	²hOMe, MeOH, ≥, MEK, MIBK,	chemical PMI workup solvents List solv	110.5		•``\\`\			Ç) +	SO ₂ + HCI	+	+ -N	
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H4	120		1													
H4 nvironmer		ern			st subs	tances of v	ery high con	се								
	Amber Flag Green Flag 70°C 0 or 70 to 0 or 7	colour element Red Flag	colour element Red Flag I Amber Flag + Green Flag I Green Flag I I I	Colour element H Red Flag	Colour element H Red Flag	Colour element H utility Amber + -	Colour element H util depeters of nown recovers based examples Amber Flag + Image: Second conditioned and the second	Colour element H util depletion of koosen reserves Amber Flag + H util depletion of koosen reserves Band flag Amber Flag + H </td <td>Tick Tick <th< td=""><td>Colour element H Junct Head Eduction of Monocity Head Head Head Head Head Head Head Head</td><td>Amber Flag Hereinen (mitorial production) Hereinen (mitorial producti</td><td>Colour Clement H <t< td=""><td>Colour element I <thi< th=""> I <thi< th=""> I <thi< th=""> I I <thi<< td=""><td>Colour element N <t< td=""><td>color element (Ref Flag is <th< td=""><td>color i</td></th<></td></t<></td></thi<<></thi<></thi<></thi<></td></t<></td></th<></td>	Tick Tick <th< td=""><td>Colour element H Junct Head Eduction of Monocity Head Head Head Head Head Head Head Head</td><td>Amber Flag Hereinen (mitorial production) Hereinen (mitorial producti</td><td>Colour Clement H <t< td=""><td>Colour element I <thi< th=""> I <thi< th=""> I <thi< th=""> I I <thi<< td=""><td>Colour element N <t< td=""><td>color element (Ref Flag is <th< td=""><td>color i</td></th<></td></t<></td></thi<<></thi<></thi<></thi<></td></t<></td></th<>	Colour element H Junct Head Eduction of Monocity Head Head Head Head Head Head Head Head	Amber Flag Hereinen (mitorial production) Hereinen (mitorial producti	Colour Clement H <t< td=""><td>Colour element I <thi< th=""> I <thi< th=""> I <thi< th=""> I I <thi<< td=""><td>Colour element N <t< td=""><td>color element (Ref Flag is <th< td=""><td>color i</td></th<></td></t<></td></thi<<></thi<></thi<></thi<></td></t<>	Colour element I <thi< th=""> I <thi< th=""> I <thi< th=""> I I <thi<< td=""><td>Colour element N <t< td=""><td>color element (Ref Flag is <th< td=""><td>color i</td></th<></td></t<></td></thi<<></thi<></thi<></thi<>	Colour element N <t< td=""><td>color element (Ref Flag is <th< td=""><td>color i</td></th<></td></t<>	color element (Ref Flag is is <th< td=""><td>color i</td></th<>	color i

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					Summary													
	Yield, AE, RME, MI/PMI and (DE																
toichiometry	Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml ⁻¹)	Mass (g
1	1 Amine	0.34	277.00	0.00123					THE	14.00	0.89	12.45			water			0.00
	1 Chloromethyl-benzoyl chloride	0.28	188.00	0.00149					DMF	5.00	0.99	4.97			"der			0.00
1	N-methylpiperazine	0.23	100.17	0.00230					2.1.1	0.00	0.00	0.00						0.00
1	1 Triethylamine	0.25	101.19	0.00244								0.00						0.00
0.5		0.23	100.09	0.00230								0.00						0.00
0.0	, cace,	0.20	100.00	0.002.00					+ +		+ +	0.00						0.00
									+ +			0.00						0.00
	Total	1.33	716.41			0.00		0.00				17.42		0.00				0.00
	Total	1.00	110.41			0.00		0.00		Flag		11.42		0.00				0.00
								Yield	83.8		5							
								r ieia Conversion	100.0	-								
									83.8	-					Mass	MW	Mol	
	$RME = \frac{mass of isolated pr}{total mass of reac}$	oduct _ 1	00					Selectivity AE	68.8	03.	,		Prode	uat	0.51	493.00	0.00	
	total mass of reac	tants ^ 1	00					RME	38.4	05	55.8		Prod	16(0.51 mass	433.00	0.00	
								RIME	30.4	UE	55.0		Unread		mass			
	molecular weigh	t of prodi	ict					PMI total	36.8						0.00			
	$AE = \frac{molecular weigh}{total molecular weig}$	ht of read	tants × 1	00									limiting re	actant	0.00			
		-						PMI Reaction	30.0									
	mass intensity = $\frac{total}{r}$	nass in a	process o	r process st	ep			reagents,		Stoichiomet	ic equation							
	mass intensity =	mas	s of prod	uct	-			catlyst	2.6		0							
								PMI reaction			Ĭ							
	$OE = \frac{RME}{AE} \times 100$							solvents	34.1		Y 0						\square	
	AE									LCI LCI L	J +	$H_2N^2 \sim N^2$	$N' \gamma >$	+ Et ₃ N	+ 1/2 CaC	0. + —	J NH —	-
												- н				• <u>,</u> · ·	1 /	
								PMI Workup	0.0			- н	L N	- 4.		•, •		
								PMI Workup PMI Workup	0.0			- н		- •		o,		
									0.0 0.0							•, •		
								PMI Workup				i (1				•, •		
								PMI Workup chemical				i "				1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H⊰
								PMI Workup chemical PMI workup	0.0			ji (j			,ÑH CI¯ +	1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ (
	Solvents (First Pass)							PMI Workup chemical PMI workup	0.0			ji (j				1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ (
	Solvents (First Pass) Preferred solvents		water, EtO	H, nBuOH, AcC	ipr, AcOnBu,	, PhOMe, M	1eOH, tBuOH,	PMI Workup chemical PMI workup solvents List solve	0.0			ji ti				1/2 CaCl ₂	+ 1/2 CO2	+ 1/2 H ₂ /
				H, nBuOH, AcC	· · · · · · · · · · · · · · · · · · ·			PMI Workup chemical PMI workup solvents List solve	0.0		2.0	j h				1/2 CaCl ₂	+ 1/2 CO2	+ 1/2 H ₂ 4
					· · · · · · · · · · · · · · · · · · ·			PMI Workup chemical PMI workup solvents List solve	0.0		<u>).(</u>	ji ti				1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ 4
	Preferred solvents		BnOH, eth		cetone, MEK,	, MIBK, AcC	DEt, sulfolane	PMI Workup chemical PMI workup solvents List solve	0.0).(ji (j				1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ 4
	Preferred solvents Problematic solvents: (accept	table only if	BnOH, eth	nylene glycol, a cyclohexanone	cetone, MEK,	, MIBK, AcC) <mark>H, Ac2O, A</mark>	DEt, sulfolane Acetonitrile,	PMI Workup chemical PMI workup solvents List solve	0.0 0.0 nts belov			ji fi				1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ 0
	Preferred solvents	table only if	BnOH, eth DMSO, J AcOMe,	nylene glycol, a cyclohexanone , THF, heptane,	cetone, MEK, , DMPU, AcC Me-cyclohe	, MIBK, AcC)H, Ac2O, A xane, tolue	DEt, sulfolane Acetonitrile, me, xylene,	PMI Workup chemical PMI workup solvents List solve	0.0			JIN H				1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ 4
	Preferred solvents Problematic solvents: (accept	table only if	BnOH, eth DMSO, J AcOMe,	nylene glycol, a cyclohexanone	cetone, MEK, , DMPU, AcC Me-cyclohe	, MIBK, AcC)H, Ac2O, A xane, tolue	DEt, sulfolane Acetonitrile, me, xylene,	PMI Workup chemical PMI workup solvents List solve	0.0 0.0 nts belov			J. H				1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ ¢
	Preferred solvents Problematic solvents: (accep substitution does not offer adve	otable only if antages)	BnOH, eth DMSO, - AcOMe, MTBE, cyc	nylene glycol, a cyclohexanone , THF, heptane, klohexane, chło	, DMPU, AcC Me-cyclohe robenzene, fi THF	, MIBK, AcC)H, Ac2O, 4 xane, tolue ormic acid,	DEt, sulfolane Acetonitrile, ene, sylene, . pyridine, Me-	PMI Workup chemical PMI workup solvents List solve	0.0 0.0 nts belov							1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ 4
	Preferred solvents Problematic solvents: (accep substitution does not offer adva Hazardous solvents: These	otable only if antages) • solvents	BnOH, eth DMSO, - AcOMe, MTBE, cyc	vylene glycol, a cyclohexanone , THF, heptane, dohexane, chło , pentane, TEA,	, DMPU, AcC Me-cyclohe robenzene, fr THF diisopropyl e	, MIBK, AcC DH, Ac2O, A xane, tolue ormic acid, ther, DME,	DEt, sulfolane Acetonitrile, ene, xylene, pyridine, Me- . DCM, DMF,	PMI Workup chemical PMI workup solvents List solve	0.0 0.0		<u>).(</u>					1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ 4
	Preferred solvents Problematic solvents: (accep substitution does not offer adva Hazardous solvents: These have significant health and/or	otable only if antages) • solvents	BnOH, eth DMSO, - AcOMe, MTBE, cyc	nylene glycol, a cyclohexanone , THF, heptane, klohexane, chło	, DMPU, AcC Me-cyclohe robenzene, fr THF diisopropyl e	, MIBK, AcC DH, Ac2O, A xane, tolue ormic acid, ther, DME,	DEt, sulfolane Acetonitrile, ene, xylene, pyridine, Me- . DCM, DMF,	PMI Workup chemical PMI workup solvents List solve	0.0 0.0 nts belov			ц Ц				1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ 4
	Preferred solvents Problematic solvents: (accept substitution does not offer advance) Hazardous solvents: These have significant health and/or concerns.	otable only if antages) solvents rsafety	BnOH, etł DMSO, AcOMe, MTBE, cyc dioxane,	ylene glycol, a cyclohexanone , THF, heptane, dohexane, ohlo , pentane, TEA, DMA, NMP, 1	cetone, MEK, , DMPU, AcC Me-cyclohe robenzene, fr THF diisopropyl e nethoxyethar	, MIBK, AcC DH, Ac2O, A xane, tolue ormic acid, ormic acid, ther, DME, nol, hexane	DEt, sulfolane Acetonitrile, ene, xylene, . pyridine, Me- . DCM, DMF,	PMI Workup chemical PMI workup solvents List solve	0.0 0.0 nts belov			jî (j				1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ 4
	Preferred solvents Problematic solvents: (accep substitution does not offer adva Hazardous solvents: These have significant health and/or concerns. Highly hazardous solvents	solvents solvents safety ts: The	BnOH, etł DMSO, AcOMe, MTBE, cyc dioxane,	vylene glycol, a cyclohexanone , THF, heptane, dohexane, chło , pentane, TEA,	, DMPU, AcC Me-cycloher robenzene, f THF diisopropyl e nethoxyethar	, MIBK, AcC DH, Ac2O, A xane, tolue ormic acid, ormic acid, ther, DME, nol, hexane	DEt, sulfolane Acetonitrile, ene, xylene, . pyridine, Me- . DCM, DMF,	PMI Workup chemical PMI workup solvents List solve	0.0 0.0 nts belov							1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ 4
	Preferred solvents Problematic solvents: (accep substitution does not offer adv Hazardous solvents: These have significant he alth and/or concerns. Highly hazardous solvent solvents which are agreed not to	solvents solvents safety ts: The	BnOH, etł DMSO, AcOMe, MTBE, cyc dioxane,	ylene glycol, a cyclohexanone , THF, heptane, dohexane, ohlo , pentane, TEA, DMA, NMP, 1	cetone, MEK, , DMPU, AcC Me-cyclohe robenzene, fr THF diisopropyl e nethoxyethar	, MIBK, AcC DH, Ac2O, A xane, tolue ormic acid, ormic acid, ther, DME, nol, hexane	DEt, sulfolane Acetonitrile, ene, xylene, . pyridine, Me- . DCM, DMF,	PMI Workup chemical PMI workup solvents List solve	0.0 0.0 nts belov			J H				1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ 4
	Preferred solvents Problematic solvents: (accep substitution does not offer adva Hazardous solvents: These have significant health and/or concerns. Highly hazardous solvents	solvents solvents safety ts: The	BnOH, etł DMSO, AcOMe, MTBE, cyc dioxane,	ylene glycol, a cyclohexanone , THF, heptane, dohexane, ohlo , pentane, TEA, DMA, NMP, 1	, DMPU, AcC Me-cycloher robenzene, f THF diisopropyl e nethoxyethar	, MIBK, AcC DH, Ac2O, A xane, tolue ormic acid, ormic acid, ther, DME, nol, hexane	DEt, sulfolane Acetonitrile, ene, xylene, . pyridine, Me- . DCM, DMF,	PMI Workup chemical PMI workup solvents List solve	0.0 0.0							1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ /
	Preferred solvents Problematic solvents: (accept substitution does not offer adva Hazardous solvents: These have significant health and/or concerns. Highly hazardous solvent solvents which are agreed not to even in screening	solvents solvents rsafety ts: The be used,	BnOH, etł DMSO, AcOMe, MTBE, cyc dioxane,	ylene glycol, a cyclohexanone , THF, heptane, dohexane, ohlo , pentane, TEA, DMA, NMP, 1	cetone, MEK, , DMPU, AcC Me-cycloher robenzene, fr THF diisopropyl e nethoxyethar hloroform, DO HMPA	, MIBK, AcC DH, Ac2O, A xane, tolue ormic acid, ormic acid, ther, DME, nol, hexane	DEt, sulfolane Acetonitrile, ene, xylene, . pyridine, Me- . DCM, DMF,	PMI Workup chemical PMI workup solvents List solve	0.0 0.0		Tick					1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ (
	Preferred solvents Problematic solvents: (accept substitution does not offer adve Hazardous solvents: These have significant health and/or concerns. Highly hazardous solvent solvents which are agreed not to even in screening Catalyst/enzyme (First Pass)	solvents solvents safety ts: The be used,	BnOH, etf DMSO, (AcOMe, MTBE, cyc dioxane, Et ₂ O, Be	vylene glycol, a cyclohexanone , THF, heptane, kohexane, chło , pentane, TEA, DMA, NMP, i cnzene, CCl ₄ , oł	, DMPU, AcC Me-cycloher robenzene, f THF diisopropyl e nethoxyethar	, MIBK, AcC DH, Ac2O, A xane, tolue ormic acid, ormic acid, ther, DME, nol, hexane	DEt, sulfolane Acetonitrile, sne, xylene, pyridine, Me- DCM, DMF, e	PMI Workup chemical PMI workup solvents List solve	0.0 0.0		Tick					1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ (
	Preferred solvents Problematic solvents: (accept substitution does not offer adv Hazardous solvents: These have significant health and/or concerns. Highly hazardous solvent solvents which are agreed not to even in screening Catalyst/enzyme (First Pass) Catalyst or enzyme used, or react	stable only if antages) solvents rsafety ts: The be used, iton takes pl	BnOH, et/ DMSO, / AcOMe, MTBE, cyc dioxane, Et ₂ O, Be	ylene glycol, a cyclohexanone THF, heptane, lohexane, chlo pentane, TEA DMA, NMP, 1 enzene, CCl ₄ , cl Green Flag	cetone, MEK, , DMPU, AcC Me-cycloher robenzene, fr THF diisopropyl e nethoxyethar hloroform, DO HMPA	, MIBK, AcC DH, Ac2O, A xane, tolue ormic acid, ormic acid, ther, DME, nol, hexane	DEt, sulfolane Acetonitrile, ne, xylene, pyridine, Me- DCM, DMF, c thane, CS ₂ , Facile reco	PMI Workup chemical PMI workup solvents List solve	0.0 0.0	GreenFlag	Tick					1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂ 4
	Preferred solvents Problematic solvents: (accept substitution does not offer adve Hazardous solvents: These have significant health and/or concerns. Highly hazardous solvent solvents which are agreed not to even in screening Catalyst/enzyme (First Pass)	stable only if antages) solvents rsafety ts: The be used, iton takes pl	BnOH, et/ DMSO, / AcOMe, MTBE, cyc dioxane, Et ₂ O, Be	vylene glycol, a cyclohexanone , THF, heptane, kohexane, chło , pentane, TEA, DMA, NMP, i cnzene, CCl ₄ , oł	cetone, MEK, , DMPU, AcC Me-cycloher robenzene, fr THF diisopropyl e nethoxyethar hloroform, DO HMPA	, MIBK, AcC DH, Ac2O, A xane, tolue ormic acid, ormic acid, ther, DME, nol, hexane	DEt, sulfolane Acetonitrile, ne, xylene, pyridine, Me- DCM, DMF, c thane, CS ₂ , Facile reco	PMI Workup chemical PMI workup solvents List solve	0.0 0.0	Green Flag Amber Flag	Tick					1/2 CaCl ₂	+ 1/2 CO ₂	+ 1/2 H ₂

Critical elements									1			
Supply remaining	Flag	Note	н	Ren	aining years I depletion of			He				
	colour	element	1.00794	kno	in reserves	_		A DECIMAL				
5-50 years	RedFlag		Li Be		extraction)	r i	B C N	O F Ne				
50-500 years	Amber Flag		11 12 Na Mg	· 3	0-100 years 0-500 years		10 12-0507 14-05674 34 15 AJ SI P	15.000 18.0000 20.000 16 17 18 5 Cl Ar				
+500 years	Green	+	21.96077 24.909 29 20	a 11 1	a a a a	20 20 20	455 28.005 26.075	10.000 35.4527 39.548 36 25 36				
	Flag		K Ca	Sc Ti	V Cr Mn Fe Co	Ni Cu Zn G	la Ge As	Se Br Kr				
			37 44	10 40 4	40 40 40 40 40 40 40 40 40 40 40 40 40 4		90 91	90 90 94				
			Rb Sr	Y 2r	Nb Mo Tc Ru Rh	Pd Ag Cd I	in Sn Sb	Te I Xe				
			S Ba	La* Hf	Ta W Re Os Ir	Pt Au He	ті <mark>Рь</mark> ві	Po At Rn				
			1123054 11232	7 114.9055 114.40 3	0.5475 141.46 146.207 146.21 110.212 11	100 100 200 100 200	100 270.2 200 Mills	0199 0198 0205 114 117 118				
			Fr Ra	Ac # Rf	Db Sg Bh Hs Mt	Ds Rq Uub U	lut Uuq Uup	Lv Uus Uuo				
			0111 234.02	5 0275 0757 0	40) Dell Dell Dell Dell Dell Dell	ni ani awi aw	6 (Jam) (Jam)	0101				
					10 40 41 42 40	64 65 66	y Ho Er	0 N N				
				Lanthanides *	Pr Nd Pm Sm E 007 044.34 (140) 010.36 010.36 010.36	u Gd Tb D	y Ho Er 9 984 9869 987 28	Tm Yb Lu sacsac creat creat				
				Actinides I T	n Pa U Np Pu A	m Cm Bk C	f Es Fm	Md No Lr				
				312.0	an 221.0349 210.0389 (210) (240) (240)	045 045 055	010 017	D146 0156 D120				
Energy (First Pass)			Tick					Tick	1			
Reaction run between 0 to	70°C	Green	TICK				_					
		Flag			Reaction run at	reflux	Red Flag	+				
Reaction run between -20 to 1	Jor 70 to	Amber	+									
140°C		Flag			Reaction run 5°C or m		Green					
Reaction run below -20 or abo	ve 140°C	Red Flag			solvent boiling	point	Flag					
Batch/flow			Tick		Work Up			List	1			
Flow	Gree	n Flag			quenchin	g						
Batch	Ambe	er Flag	+		filtration							
					centrifugati		Green	+				
					crystallisati		Flag					
					Low tempera distillation/evaporation/							
					solvent exchange, qu		Amber					
					aqueous solv		Flag					
					chromatographylion	n exchange						
					high tempera		Red Flag					
					multiple recrysta	llisation						
						List substa	nces and	List substan	ces and			
Health & safety						H-co		H-cod		List substan	ces and H-	-codes
		Flag	Amber		Green Flag							
Highly explosive		201, H202,	H205, H2:	20, H224	If no red or amber							
Explosive thermal runaway		203 240, H250	H2	41	flagged Hoodes present then green							
Toxic		310, H330	H301, H3		flag							
Long Term toxicity	H340, H3	50, H360, 1, H372	H341, H351, H H3	H361, H371,		DM	F	THF				
Environmental		, no rz 410, H411,	H401,									
implications		120	1100						1			
Use of chemicals of	environm	iental cor	ncern		st substances of ver	y high conce						
Chemical identified as Subs			oncern by	Red Flag	DMF							
ChemSec w	hich are ut	ilised		Hearlag	DIAL							

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					Summary	of First	Pass Metrics	5 I oolkit										
	Yield, AE, RME, MI/PMI and (DE																
toichiometry	Reactant (Limiting Reactant First)	Mass (g)	MV	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml ⁻¹)	Mass (g
1	Amine	0.30	277.00	0.00108					CH2CI2	0.71	1.33	0.94			Water	234.00	1.00	234.00
1	4-hydroxymethyl benzoic acid	0.22	152.00	0.00141					THF	7.55	0.89	6.71			in dicit	201.00		0.00
2	Thionyl chloride	1.16	118.97	0.00975						1.00	0.00	0.00						0.00
2	N-methylpiperazine	10.00	100.17	0.09984								0.00						0.00
1	Triethylamine	0.23	101.19	0.00223								0.00						0.00
	mediyiamine	0.20	101.10	0.00220							+	0.00						0.00
												0.00						0.00
	Total	11.90	968.46			0.00		0.00				7.66		0.00				234.0
		11.00	000.10			0.00		0.00	-	Flag		1.00		0.00				201.0
								Yield	84.8		3							
								Conversion	100.0	-								
								Selectivity	84.8	-					Mass	MW	Mol	
	$RME = \frac{mass of isolated pr}{total mass of read}$	oduct	00					AE	50.9	04.0	, 		Prod	uat	0.45	493.00	0.00	
	total mass of reac	tants × 1	100					RME	3.8	OF	7.4		FIUU	aci	mass	433.00	0.00	
								INPIE .	3.0	UE	1.4		Unrea	otod	mass			
	molecular weigh	t of produ	uct .					PMI total	563.5						0.00			
	$AE = \frac{molecular weigh}{total molecualr weig}$	ht of rea	ctants × 1	.00				PMIReaction	43.5				limiting re	eactant	0.00			
									43.5									
	total	mass in o	process	or process st	ep			reagents,		Stoich	niometric equi	ation						
	$mass intensity = \frac{total}{t}$	ma	ss of prod	duct	-			catlyst	26.4	3000	nometric equa	0						
								PMI reaction				ĭ .		~ N≤				
	$OE = \frac{RME}{AE} \times 100$							solvents	17.0		\sim	∼он й		Ιï			\frown	
	AE × 100									н		↓ 0 + 2 CI - 5	CI + H₂N ~~	~1/~		Et₃N + 2 —	v() ін —	+
								PMI Workup	520.0		* *			н	L.		\Box	
								PMI Workup							IN IN			
								chemical	0.0			° ľ	^^ Ŋ^					
								PMIworkup	0.0				₅∽⊾⊸,	\sim	2 SO ₂ + 2			\frown
								solvents	520.0		–⇒ĩ "	I I H	H H	•	2 SO2 + 2	HCI + Et ₃ ÑI	⊣cī + — I	n ()ÑH₂ C
								Solvents	020.0	L	$\overline{}$	<u>~~</u>		<u>_N</u> ~				
	Solvents (First Pass)							List solver	te below									
1	Preferred solvents		water EtC	DH, nBuOH, AcO	ior AcOoBu	DLOM-		LISC SOIVER	It's Delow									
	Fielened solvents			thylene glycol, ac														
	Problematic solvents: (accep	u a bla a blu if	DMSO	, cyclohexanone		H 0-20	0. ootopitrilo											
	substitution does not offer adva			HF, heptane, Me														
	substitution does not oner adva	antages)		xane, chloroben				í +										
			Cyclone	sane, chioroben	izene, ronnio -	aciu, pyrit	une, ne-mi											
		1		TEA III	1.1	DME D	ON DMC DMA											
	Hazardous solvents: These so		dioxane, p				ICIM, DIME, DIMA											
	significant health and/or safety o	concerns.		NIMP, met	hoxyethanol,	hexane		+										
	Highly hazardous solvents: T		Et ₂ O, Benz	zene, CCl ₄ , chlor	oform, DCE, n	itrometha	ane, CS ₂ , HMPA	1										
	which are agreed not to be used	d, even in																
,	screening																	
					Tick						Tick							
	Catalyst/enzyme (First Pass)				TICK													
	Catalyst/enzyme (First Pass) Catalyst or enzyme used, or react		lace without		TICK			overy of catalyst		Green Flag								
		tion takes pl		Green Flag Amber Flag				overy of catalyst lenzyme not reco		Green Flag Amber Flag								

Critical elements				1		1						
Supply remaining	Flag colour	Note element	1 H 1.007H	until d	ining years lepletion of n reserves			Не				
5-50 years	Red Flag		LI Be	(based or ex	n current rate of traction)	· · ·	° c ′ N	0 F Ne				
50-500 years	Amber Flag	+	11 11 Na Mg		50 years 100 years 500 years	La contra	12-25027 14-20624 14 15	L.mmi Lk.manb 24.000 5 Cl Ar				
+500 years	Green Flag		221.580077 20. 279 20 K Ca	sc Ti V	r Cr Mn Fe Co	Ni Cu Zn Ga	a alan ana ana ana ana ana ana ana ana a	Nome 11.4527 10.548 N 25 26 Se Br Kr				
			21.0161 40.078 37 40	44.90340 47.867 50.54 79 40 41	15 11.9%2 14.0000 15.945 14.0000 42 43 44 41 41	4.0104 43.546 49.899 49.799 4. 37 49 49	TEAN PERSON NO NI	PE-N6 71:30H 81.80				
			Rb Sr HLALTH BT 62	Y Zr N	Mo Tc Ru Rh	Pd Ag Cd In	Sn Sb transit	Te I Xe				
			Cs Ba	La* H T	W Re Os W	Pt Au Hg Ti	РБ ВІ	Po At Rn				
			132-3054 132-337 87 88 Fr Ra	134.9055 174.00 9400 80 304 305	No. No. <td>10 111 112 113</td> <td>118 115</td> <td>000 000 0000 116 117 118 Lv Uus Uus</td> <td></td> <td></td> <td></td> <td></td>	10 111 112 113	118 115	000 000 0000 116 117 118 Lv Uus Uus				
			Fr Ra (221) 224.005	Ac # Rf D	b Sg Bh Hs Mt Dell Dell Dell OH	Ds Rq Uub Uu artii artii artii artii artii	t Uuq Uup	Lv Uus Uuo				
					19 60 61 62 60	64 85 66	0 00 I	0 20 21				
			L	anthanides * Ce	Pr Nd Pm Sm 194234 (147) Vision Vision (1	Eu Gd Tb Dy	Ho Er 964.9300 567.95	Tm Yb Lu				
				Actinides I Th	Pa U Np Pu	Am Cm Bk Cf	Es Fm	Md No Lr				
				112-3080	231.6340 236.040 2303 0441 D	00 0405 0405 0540	(nu) (nn)	2146 (2144 (2425				
Energy (First Pass)			Tick					Tick				
Reaction run between 0 to 70°C Green Flag					Reaction run	at reflux	Red Flag	+				
	Reaction run between -20 to 0 or 70 to Amber											
140°C Flag			+		Reaction run 5°C or solvent boilir		Green Flag					
Reaction run below -20 or above 140°C Red Fla		Red Flag			Solveric Dollin	ig point	riag					
Batch/flow			Tick		Work Up			List				
Flow		n Flag			quench							
Batch	Amber Flag		+		filtratio centrifug		Green					
					crystallis;		Flag	+				
					Low tempe		1					
					distillation/evaporationsolvent exchange,		Amber					
					aqueouss	olvent	Flag	+				
					chromatography/i high tempe		Red Flag					
					multiple recrys		heariag					
						List substa	and and	List substan	non and			
Health & safety						H-co		H-cod		List substar	nces and H	-codes
		Flag	Amber		Green Flag							
Highly explosive	H200, H2	201, H202, 203	H205, H22	20, H224	If no red or amber flagged H codes							
Explosive thermal runa v ay		203 240, H250	H2	41	present then green							
Toxic H300, H310, H330		H301, H31		flag			SOC	2				
Long Term toxicity		50, H360, - , H372	H341, H351, H361, H371, H373			DM	DMF					
Environmental implications		410, H411, 120	H401,	H412								
Use of chemicals of Chemical identified as Substanc					st substances of v	ery high conce						
	es of very f are utilised		n by Chember	Red Flag	DMF							
										-		

Summary of First Pass Metrics Toolkit Yield, AE, RME, MI/PMI and OE Stoichiometry Reactant (Limiting Mass (g) MW Mol Catalyst Mass Reagent Mass Reaction Volume Density Mass (g) Work up | Mass (g) Workup Volume Density (g ml⁻¹) Reactant First) (q) (q) solvent (cm³) chemical solvent (cm3) (g ml⁻¹) Amine 12800.00 277.00 46.21 CHCI 230850.00 343966.50 NaOH 10000.00 Toluene 40430.00 1.49 0.87 8410.00 152.00 DMF 40810.00 0.94 38524.64 Water 795000.00 1.00 4-hydroxymethyl benzoic acid Thionyl chloride 24300.00 118.97 204.25 0.00 EtOAc 155000.00 0.90 19700.00 100.17 196.68 0.00 CHCI₃ 300000.00 1.49 N-methylpiperazine Triethylamine 9300.00 101.19 91.91 0.00 0.00 0.00 Total 74510.00 968.46 0.00 0.00 382491.14 10000.00 Flag 43.0 100.0 🔘 100.0 MW 43.0 Mol Mass $\frac{mass of isolated product}{total mass of reactants} \times 100$ ectivity 50.9 RME =Product 9800.00 493.00 19.88 25.8 mass OE Unreacted limiting molecular weight of product $AE = \frac{AE}{total \ molecular \ weight \ of \ product} \times 100$ PMI total reactant PMI Reaction 46.6 $mass\ intensity = \frac{total\ mass\ in\ a\ process\ or\ process\ step}{mass\ of\ product}$ reactants, reagents, 7.6 Stoichiometric equation PMI reaction $\begin{array}{c} OH \\ + 2 CI \overset{\circ}{\longrightarrow} CI + H_2 N \overset{\circ}{\longrightarrow} H_1 \overset{\circ}{\longrightarrow} H_2 \overset{\circ}$ $OE = \frac{RME}{AE} \times 100$ 39.0 solvents PMI Workup 145.6 PMI Workup chemical 1.0 PMI workup 144.6 solvents Solvents (First Pass) List solvents below Preferred solvents water, EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Problematic solvents: (acceptable only if substitution does not offer advantages) Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF dioxane, pentane, TEA, diisopropyl ether, DME, DCM, Hazardous solvents: These solvents have significant health and/or safety DMF, DMA, NMP, methoxyethanol, hexane + concerns. Highly hazardous solvents: The Et₂O, Benzene, CCl₄, chloroform, DCE, nitromethane, solvents which are agreed not to be used, CS₂, HMPA even in screening Tick Catalyst/enzyme (First Pass) Tick Catalyst or enzyme used, or reaction takes place without Green Facile recovery of catalyst/enzyme Green Flag any catalyst/reagents. Flag Amber Use of stoichiometric quantities of reagents Amber Flag catalyst/enzyme not recovered Flag

Mass (g)

35052.81

795000.00

139810.00

447000.00

0.00

0.00

0.00

1416862.81

Use of reagents in excess

Red Flag

+

Note elemen g g f g f f g f f g f f g f f g f g f	nt Harrison	Set Set <th>21/1 DHS DH.II DH.II DH.II DH.II C 5* Ce Pr Nd Pr Nd Pr S 100-000 HAL3 DHHI DHI DHI DHI DHI DHI 5* Ce Pr Nd Pre S HAL3 DHI S 100-000 MAL3A DHHI DHI DHI S HAL3A</th> <th>B B B B B Cu 2 Co N Cu 2 2 2 R Pd Ag Cu 2 R Pd Ag Cu 2 R Pd Ag Cu 2 N Cu Ag Cu 2 N R N Ag Cu Mt Ds Rq U 2 Mt Ds GG 18 2 Mt Ds GG 19 2 Mt Cu GG 19 2 Mt Cu GG 19 2 Mt Cu GT 19 2 Mt Cu GT 19 2</th> <th></th> <th>N O F 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 1000000 1000000 100000 100000 1000000 1000000 1000000 1000000 1000000 1000000 1000000 1000000 1000000 1000000 10000000 10000000 1000000 10000000 10000000 10000000 10000000 10000000000</th> <th>Kr</th> <th></th> <th></th> <th></th>	21/1 DHS DH.II DH.II DH.II DH.II C 5* Ce Pr Nd Pr Nd Pr S 100-000 HAL3 DHHI DHI DHI DHI DHI DHI 5* Ce Pr Nd Pre S HAL3 DHI S 100-000 MAL3A DHHI DHI DHI S HAL3A	B B B B B Cu 2 Co N Cu 2 2 2 R Pd Ag Cu 2 R Pd Ag Cu 2 R Pd Ag Cu 2 N Cu Ag Cu 2 N R N Ag Cu Mt Ds Rq U 2 Mt Ds GG 18 2 Mt Ds GG 19 2 Mt Cu GG 19 2 Mt Cu GG 19 2 Mt Cu GT 19 2 Mt Cu GT 19 2		N O F 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 100000 1000000 1000000 100000 100000 1000000 1000000 1000000 1000000 1000000 1000000 1000000 1000000 1000000 1000000 10000000 10000000 1000000 10000000 10000000 10000000 10000000 10000000000	Kr			
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Flag Amber Flag			Limitation Sec.34. Careline Sec.36. Careline Sec.36.	No. UD. 21 TEANDOL DOLLOG V0 M 00 02 V0 Am Cm Bk V Am Cm Bk V DHE DHT DHT	RL 14236 394.4366 98 99 4 Cf Es 0740 DUS	MO 20 MO 4000 170-300 M DO DE NO DE Fm Md NO DE OUT DEE DE DE Tick DE DE	1967			
Flag Amber Flag			Limitation Sec.34. Careline Sec.36. Careline Sec.36.	No. UD. 21 TEANDOL DOLLOG V0 M 00 02 V0 Am Cm Bk V Am Cm Bk V DHE DHT DHT	RL 14236 394.4366 98 99 4 Cf Es 0740 DUS	MO 20 MO 4000 170-300 M DO DE NO DE Fm Md NO DE OUT DEE DE DE Tick DE DE	1967			
Flag Amber Flag		Actinides	210388 211.000 000 000 000	0 (p48) (p47) (p49)	\$54\$ (718)	on me on p				
Flag Amber Flag			Reaction run a	treflux						
Flag Amber Flag			Reaction run a	treflux						
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Flag	+		I		Red Flag	+				
			Reaction run 5°C or m solvent boiling		Green Flag					
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_	Tick		Work Up			List				_
Green Flag			quenchir							
er Flag	+		filtration centrifugat		Green					
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			Low tempera	ature						
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			aqueous so		Flag	+				
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			high temper multiple recrysta		неогіад					
				List substar H-coo		List substan H-cod		List subs	tances and	H-code:
l Flag	Amt	ber Flag	Green Flag	11 00	ues	iii cou				
201, H202, 1203	H205, I	H220, H224	If no red or amber							
1203 1240, H250		H241	flagged H codes present then green							
1310, H330		H311, H331,	flag			SOCI ₂ , C	HCI3			
	H341, H351, H361, H371, H373			DMF, C	HCI3	CHCl ₃ , to	luene			
H370, H372 H400, H410, H411,						Tohuo	20			
						Toldel				
1410, H411,	cern		st substances of ve	y high conce						
1410, H411, 1420		RodElan	DME CHCL							
Ľ	350, H360, 0, H372 H410, H411, H420 ental cond	350, H360, H341, 0, H372 H3 H410, H411, H4 H420 ental concern ery High Concern by	350, H360, H341, H351, H361, 0, H372 H371, H373 H410, H411, H401, H412 H20 ental concern	350, H360, H341, H351, H361, 0, H372 H371, H373 1410, H411, H401, H412 1420 st substances of ver ental concern st substances of ver ery High Concern by Bad Else DME_CHCL	Image: State	3350, H360, H341, H351, H361, 0, H372 H371, H373, 1410, H411, H401, H412, 1420 Ft substances of very high conce ental concern Ft substances of very high conce ery High Concern by Badeler	350, H360, H341, H351, H361, 0, H372 H371, H373, 1410, H411, H401, H412, 1420 Toluer ental concern st substances of very high conce erry High Concern by Red Files PME_CHCI Red Files	Bits Bits BMF, CHCl ₃ CHCl ₃ , toluene 0, H372 H371, H373 H401, H412 Toluene 1410, H411, H401, H412 Toluene Toluene ental concern st substances of very high conce Ental concern Ental concern	Bits Bits BMF, CHCl ₃ CHCl ₃ , toluene 0, H372 H371, H373 H401, H412 Toluene 1410, H411, H401, H412 Toluene Toluene ental concern st substances of very high conce Ental concern Ental concern	Image: Display Stress of Very high conce DMF, CHCl3 CHCl3, toluene Image: Display Stress of Very high conce Image: Stress of Very High Conce Image: Display Stress of Very High con

Z. Szakács et al.

					Summary	of First Pas	ss Metrics	Toolkit										
	Yield, AE, RME, MI/PMI and	OE																
Stoichiometry	Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass F (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml ⁻¹)	Mass (g)
	1 Amine	1.70	277.00	0.00615					DMF	77.40	0.94	72.76	NaHCO ₂		water	258.00	1.00	258.00
-	1 Chloromethyl-benzoyl chloride		188.00	0.00931					Acetonitrile	150.00	0.79	117.90			EtOH			0.00
2	2 N-methylpiperazine	3.88	100.17	0.03876					rioe containe	100.00	0.10	0.00			Acetonitrile			0.00
												0.00						0.00
												0.00						0.00
												0.00						0.00
												0.00						0.00
	Total	7.34	665.34			0.00		0.00				190.66		0.00				258.00
										Flag								
								Yield	41.2	41.:	2							
								Conversion	100.0	100.1	0							
	mass of isolated m					Selectivity	41.2		2				Mass	MX	Mol			
	$RME = \frac{mass of isolated p}{total mass of read}$	tants ×1	100					AE	74.1				Prod	uct	1.25	493.00	0.00	
	total mass of real	cunto						RME	17.0	OE	23.0				mass			
	molecular weigh	t of mod	uct										Unrea					
	$AE = \frac{molecular weight}{total molecular weight}$	aht of rea	$\frac{1}{ctants} \times 1$.00				PMI total	364.8				limiting re	eactant	0.00			
								PMI Reaction	158.4									
	mass intensity = $\frac{total}{t}$	mass in a	process	r process st	ep			reagents,										-
	mass intensity =	mas	s of prod	uct	-			catlyst	5.9	Stoi	chiometric eq	uation						
								PMI reaction				°.	~ /					
	$OE = \frac{RME}{AE} \times 100$							solvents	152.5		6		ſ ĭ	N		_		
	AE										a, L	+ H	2N - N-	\sim	↑ + 2	м [′] мн —		
								PMI Workup	206.4		\sim \sim		н	Ų	N#	\smile		
								PMI Workup										
								chemical	0.0						'N			
								PMI workup				ĭ	í í I	11				
								solvents	206.4		_N_	$ \land \land$	J. N.	$\sim \sim$		V NH- CI	. нст	
											- (Ň	пп	L L			1 10	
	Solvents (First Pass)							List solve	nts below	L					N.			
	Preferred solvents	•)H, nBuOH, Ac(hylene glycol, a														
	Problematic solvents: (acce	entable oplu	DMSO	oyolohexanon	e. DMPLL Act	OH, Ac2O, Ac	etonitrile											
	if substitution does not offer ad			, THF, heptane														
		-		olohexane, chl				-	•									
				THF		·····												
	Hazardous solvents: These	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF,																
	have significant health and/o			methoxyetha			4	F .										
	concerns. Highly hazardous solvents: The																	
				enzene, CCl _a , o	chloroform, D	CE, nitrometha	ane, CS ₂ ,											
	solvents which are agreed not to be used,		Et ₂ D, Benzene, CCl ₄ , chloroform, DCE, nitromethane, CS ₂ , HMPA															
	even in screening																	
	Catalyst/enzyme (First Pass	5)			Tick						Tick							
	Catalyst or enzyme used, or r	eaction tak	es place	Green Flag			Facile reco	overy of catalys	tlenzyme	Green Flag								
	Use of stoichiometric quan	itities of rea	gents	Amber Flag				enzyme not rec		Amber Flag								
	Line of the second			Ded Elem														
	Use of reagents in	rexcess		Red Flag	+													

Critical elements			Г		1	1			1		1	-							
Supply remaining	Flag colour	Note element		1 H 1.00794		until	ining years depletion of m reserves						Не						
5-50 years	Red Flag			u '	Be		n current rate of straction)			· .	° c N	° 0 ° 1	Ne						
50-500 years	Amber Flag			1.945 9 11 1	Mg		50 years 300 years -500 years			10.411 Al	12-2507 14-26674 14 85	15.000 IA.00 15.00 5.00	840 20.12%2 18						
+500 years	Green Flag	+		21.96977 J	0 21 22	TI	v "cr 1	a a a a a a a a a a a a a a a a a a a	Ni Cu	* 11 Zn Ga	A3 28.005 28.0050 28 20 20	новы (н.н.)н (н.) Se (В	27 39.348						
				31.0960 4	44.0000 47.0 2 29 40	41	415 51.9962 94 42 43	11.445 14.4500 55 51	58.0004 62.546 46 67	41.00 44.755 44 45		18.86 75.95 19 19 19	54						
				Rb 81.4478		Zr N	16 Mo	Tc Ru Rh	Pd Ag	Cd In	Sn Sb	Te I	Xe 110.29						
				Cs III III III III III	Ba La*	н	a w	te Os kr	Pt Au	Hg T	Pb Bi	Po A	t Rn						
				Fr	Ra Ac‡ I	Rf D	b 5g 1	h Hs Mt	110 111 Ds Rq	Uub Uut	t Uuq Uup	Lv Ut	118 JS Uuo						
				014 1	04.005 0.071 01/	n DH	1 Dell De	n Dell Dell	anı anı	10 14 0H	Casel 0wel	(783) (# 79	2		_				
					Lanthanides	• Ce	Pr Nd	Pm Sm tracing the second	Eu Gd	Tb Dy	Ho Er 104-000 107-26	Tm ¥1	Lu there						
					Actinides I	Th	Pa U	Νρ Ρυ ειμή (244)	Am Cm (243) (245)	Bk Cf (247) (250)	Es Fm (710) (717)	Md No	D Lr						
Energy (First Pass)				Tick								1	lick (
Reaction run between 0 to	70°C		TIOK				Reaction rur	n at reflux		Red Flag		+							
Reaction run between -20 to 0) or 70 to	Flag Amber		+															
140°C		Flag			_		Reactio	on run 5°C oi		ow the	Green								_
Reaction run below -20 or abo	ve 140°C	Red Flag						solvent boili	ing point		Flag								
Batch/flow				Tick			Work Up)					List						
low	Green Flag							quencl											
latch	Amber Flag		+				filtration				Green								
							crystallisatio				Flag		+						
								Low temps			_								
						distillation/evaporation/ s solvent exchange, que aqueous solve													
										ng into	Amber Flag								
							obror	aqueous : natography/		onde	гіад								
							Chilo	high temp		inge	Red Flag								
							п	ultiple recry:		n									
lealth & safety					_				List	List substances H-codes				substances and H-codes		List sub	stanc	es and H	l-code
reakti u sarety	Bed	Flag		Amb	er Flag		Gre	en Flag		11-000	les		11-00	ues					
Highly explosive	H200, H2	01, H202, 203	F		1220, H224	4	lf no re	ed or amber ed H codes											
xplosive thermal runa v ay	H230, H2	240, H250			H241			hen green fl	ag										
Тохіс		H300, H310, H330		H301, H311, H331, H341, H351, H361, H371, H373															
Long Term toxicity	H370					371,				DMF									
Environmental implications	H400, H4 H4	410, H411, 420		H40	1, H412														
Use of chemicals of	environm	ental co	ncer	۰ ۱			st subst	ances of v	ery hiak	conce									
Chemical identified as Subs									any mgr	- Contract									
ChemSec w			5,1561		RedF	lag		DMF											

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					Summary	of Firs	t Pass Metric	s Toolkit										
	Yield, AE, RME, MI/PMI and	OE																
Stoichiometry	Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml ⁻¹)	Mass (g)
	1 Amine	35.84	277.00	0.12939			K2CO3	38.52	THF	628.10	0.89	558.38	NaOH	5.12	Water	1844.00	1.00	1844.00
	1 Chloromethyl-benzoyl chloride	26.88	188.00	0.14296								0.00						0.00
2	2 N-methylpiperazine	74.95	100.17	0.74822								0.00						0.00
												0.00						0.00
												0.00						0.00
												0.00						0.00
												0.00						0.00
	Total	137.67	665.34			0.00		38.52				558.38		5.12				1844.00
										Flag								
								Yield	95.0	95.0	D							
								Conversion	100.0	100.0	D							
	mass of isolated m	mass of isolated product						Selectivity	95.0	95.0	D				Mass	MW	Mol	
	$RME = \frac{mass of isolated pr}{total mass of read}$	tants ×1	00					AE	74.1				Prod	uct	60.60	493.00	0.12	
		- units						RME	44.0	OE	59.4				mass			
	molecular weigh	t of produ	uct										Unrea					
	$AE = \frac{motecular weight}{total molecular weight}$	aht of real	$\frac{1}{ctants} \times 1$.00				PMI total	42.6				limiting re	eactant	0.00			
	corat motocular moto	,	ceurres					PMI Reaction	12.1									
	total 7	nass in a	process o	r process st	tep			reagents,		Stoichiomet	ric equation							
	mass intensity = 1000000000000000000000000000000000000		s of prod		<u>.</u>			catlyst	2.9			°.	~ ~ ~					
								PMI reaction			\sim	- CI	ĨĬĬ)		,	_	
	$OE = \frac{RME}{AE} \times 100$							solvents	9.2			+ H ₂ N	S~R~n.	\sim	+ 1/2 K ₂ CO ₃	;+ 2 — N)vн ——•	-
	AE										* *		п	Ľ _N ≉∕	+ 1/2 K ₂ CO ₃	```		
								PMI Workup	30.5									
								PMI Workup				° (Y N					
								chemical	0.1	I ·	\sim		失ݕ५╗失	\sim	t	-		
								PMI workup			Ϊ.N.	L H	н	1	· _N_ NH	2 CI + KCI	+ 1/2 CO ₂	+ 1/2 H ₂ O
								solvents	30.4		~ ~	×		'N'				
	Solvents (First Pass)																	
	Preferred solvents		EtOH, nBuOH, i	A-0: A-0	- D DL .		List solve	nts below										
	Preferred solvents		nOH, ethylene															
	Problematic solvents: (acce	ptable only	DMSO. d	yclohexanone		DH. Ac20). Acetonitrile.											
	if substitution does not offer adv		THF, heptane,															
						id, pyridine, Me		•										
				THF														
	Hazardous solvents: These	dioxane,	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF,															
	have significant health and/o concerns.		DMA, NMP, r															
	Highly hazardous solven	ts: The	Et ₂ O, Be	nzene, CCl ₄ , cł	hloroform, D(CE, nitrom	ethane, CS ₂ ,											
	solvents which are agreed not to		HMPA															
	even in screening																	
	Catalyst/enzyme (First Pass	;)			Tick						Tick							
	Catalyst or enzyme used, or re	eaction tak	es place	Green Flag			Facile reco	overy of catalys	t/enzyme	Green Flag								
			<u> </u>					enzyme not red										
	Use of stoichiometric quan	tities of read	gents	Amber Flag			catalystr	renzyme not red	overed	Amber Flag								
	Use of stoichiometric quan Use of reagents in		gents	Amber Flag Red Flag	+		catalysti	enzyme not red	overed	Amberhlag								

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Energy (First Pass)			Tick					Tick				
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Reaction run between -20 to () or 70 to	Amber	+									
140°C F		Flag	т		Reaction run 5°C or more t		Green					
Reaction run below -20 or above 140°C Red Fla		Red Flag		solvent boiling			Flag					
Batch/flow			Tick		Work Up			List				
low		Green Flag			quenching							
Batch	Amber Flag		+		filtration							
					centrifugation			+				
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lealth & safety						st substand H-code				List substar	ices and H	l-code
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		H205, H22	0, H224	If no red or amber								
xplosive thermal runaway			H24	1	flagged H codes							
Тохіс	H300, H3	310, H330	H301, H31	1, H331, 👘	flag 🔤							
Long Term toxicity H340, H350, H360,			H341, H351, H H37				THF					
Long Term toxicity	H370, H372 H373 Environmental H400, H410, H411, H401, H4											
Environmental	H400, H4		H401, H	1412								
	H400, H4	410, H411, 420	H401, F	1412					1			
Environmental	H400, H4 H4	120			st substances of very hi	gh co <u>nce</u>						
Environmental implications	H400, H4 H4 environm tances of V	<mark>ental co</mark> /ery High C	ncern		st substances of very hi	gh conce						

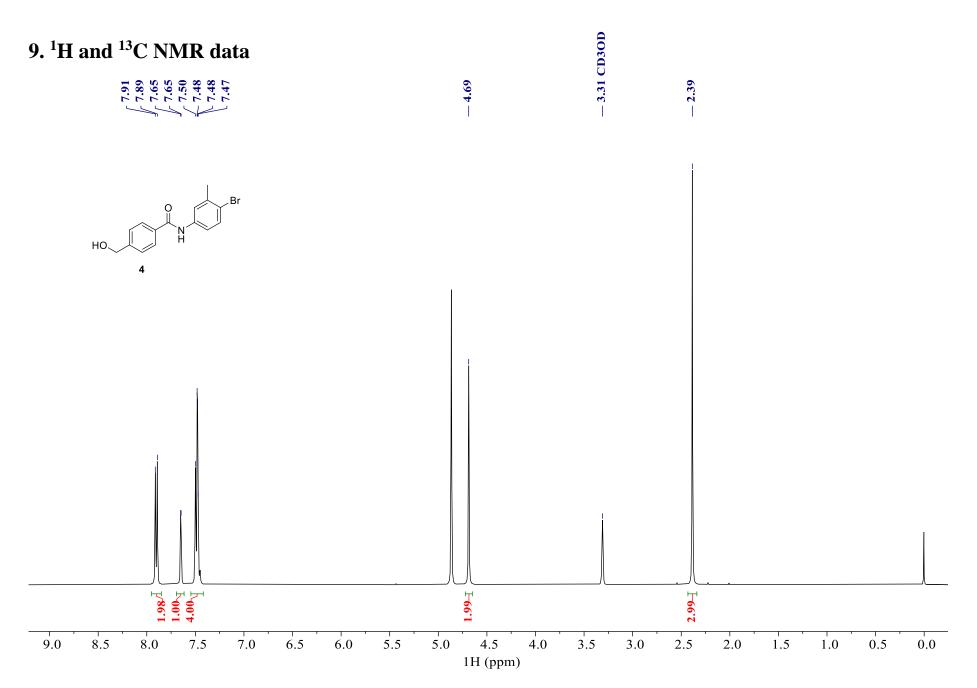
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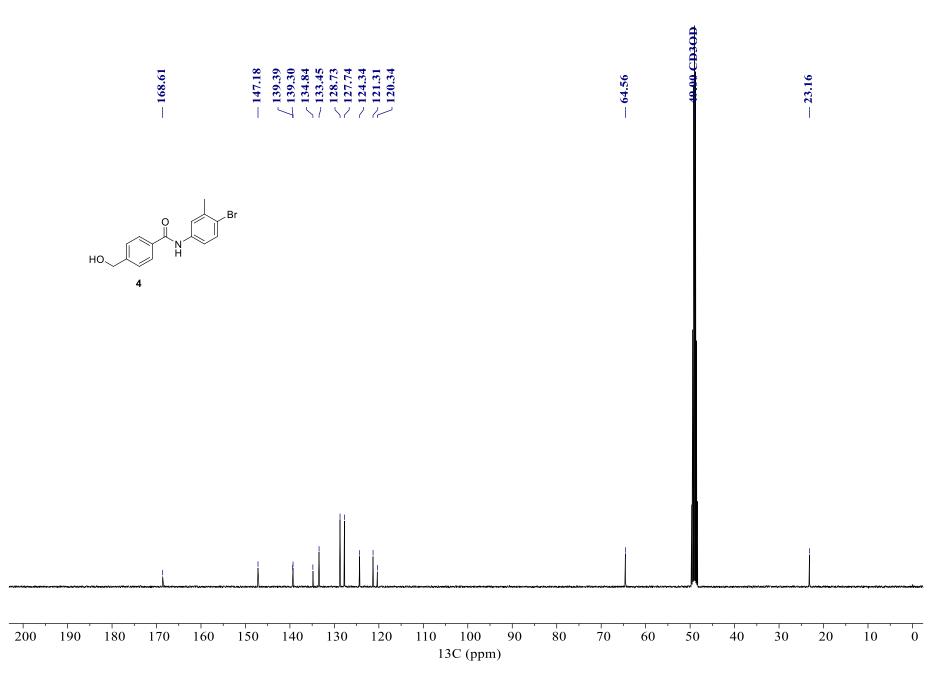
					Summary	of First Pa	ss Metrics 1	loolkit 🛛										
	Yield, AE, RME, MI/PMI and	OE																
Stoichiometry	Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density (g ml ⁻¹)	Mass (g)
1	Amine	0.43	277.00	0.00156					EtOAc	0.51	0.90	0.46			Water	140.00	1.00	140.00
1	4-hydroxymethyl benzoic acid	0.25	152.00	0.00163					DMI	1.30	1.15	1.50						0.00
1	EDC HCI	0.33	191.70	0.00174								0.00						0.00
2	N-methylpiperazine	1.46	100.17	0.01460								0.00						0.00
1	TFFH	0.77	264.12	0.00292								0.00						0.00
1	K₀HPO₄	0.64	174.20	0.00365								0.00						0.00
												0.00						0.00
	Total	3.88	1259.35			0.00		0.00				1.96		0.00				140.00
										Flag								
								Yield	86.0	6.0	0							
								Conversion	100.0	100.0)							
	man of independent	a du at						Selectivity	86.0	86.0)				Mass	MW	Mol	
	$RME = \frac{mass of isolated pr}{total mass of reac}$	vauet × 1	00					AE	39.1				Prod	uct	0.66	493.00	0.00	
	total mass of reac	tants						RME	17.0	OE	43.4				mass			
	m al anulan wat ab	famada											Unreacte	d limiting				
	$AE = \frac{molecular weight}{total molecular weight}$	t of proat	tents ×1	00				PMI total	221.0				reac	tant	0.00			
	total molecuair welg	nii oj rea	ctants					PMI Reaction	8.9									
	mass intensity = $\frac{total}{mass}$		a process ass of pro	or process st	tep			reagents, catlyst	5.9	Stoichiom	etric equation					·		
	$OE = \frac{RME}{AE} \times 100$							PMI reaction solvents PMI Workup PMI Workup chemical	3.0 212.1 0.0	но	, O ⁱ	OH NSCSN + ,H ,H ,CI	+ H ₂ N			N + K₂H + K₂H	≈04 + 2 —N	_лн —
	Solvents (First Pass)							PMI workup solvents	212.1		N N	j.		° Ni		< . VI P	VE .	
	Preferred solvents		water F	tOH, nBuOH, Act	Dipr. AcOpBu	PhOMe Me	OH BUOH	LISCOUVE	its below				' Ľ _N S	-	+ _N _N	- + KH2PC	24 + KP +	
	BnOH,		, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane			4						사이				PF ₆		
	Problematic solvents: (acception if substitution does not offer adv		THF	clohexanone, DN , heptane, Me-cy nexane, chlorober	clohexane, to	luene, xylen	e, MTBE,											
	Hazardous solvents: These solvents dioxane, j have significant health and/or safety concerns.		, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane															
	Highly hazardous solven solvents which are agreed not to even in screening		Et₂O, Be	nzene, CCI₄, chlo	roform, DCE, r	nitromethane	≥, CS₂, HMPA											
	Catalyst/enzyme (First Pass	1			Tick						Tick							
	Catalyst or enzyme used, or re		es place	Green Flag			Facile rec	overy of catalys	lenzume	Green Flag	. ISR							
	Use of stoichiometric quant			Amber Flag				lenzyme not red		Amber Flag								
	Use of reagents in			Red Flag	+					- meening								

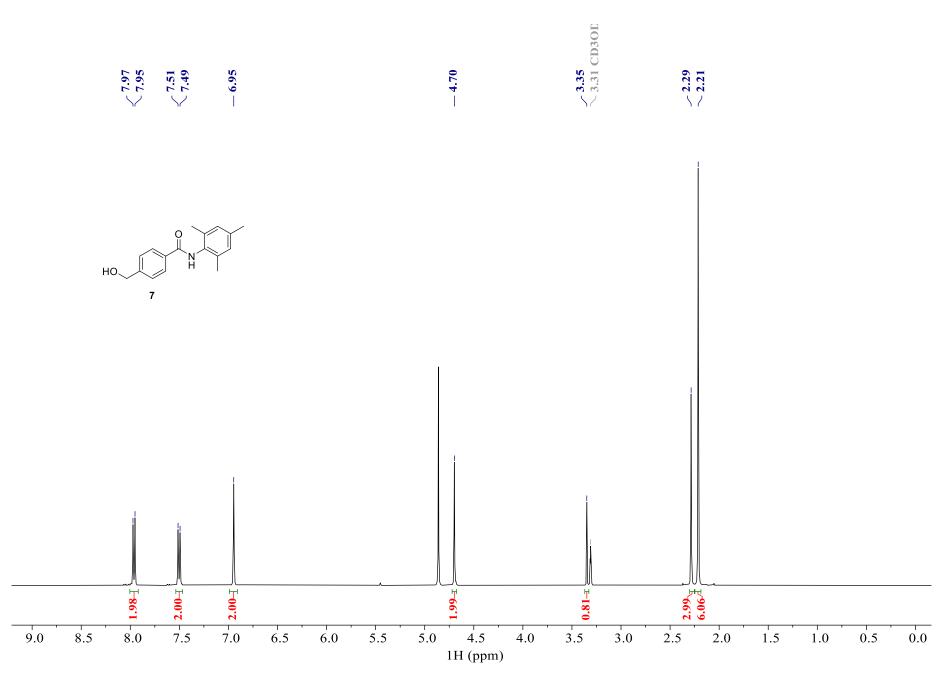
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g Creen Flag Red Flag	Be even Na Mg From P 4 Me Rest R	V Landon Constantial Constantia Cons	ment date of test of	The second and second	Image Image <th< td=""><td>veri Lange in the sector of th</td><td>NAMBER ALL NUML 1 16 C Ar Start Reg R Reg R Reg R Reg R Reg N Reg R Reg</td><td></td><td></td><td></td><td></td></th<>	veri Lange in the sector of th	NAMBER ALL NUML 1 16 C Ar Start Reg R Reg R Reg R Reg R Reg N Reg R Reg				
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	0-6-6	FI				des		codes			
Highly explosive H200, H201, H202, H205,			If no red or amber flagged								
H240, H250											
		H301, H311, H331,									
0, H372	H37	73			TMU						
	H401, H	H412			EDC	нсі					
ry High Conce				TMU, EDC HCI							
	H203 H240, H250 H310, H330 H350, H360, 70, H372 H410, H411, H420	H201, H202, H203 H205, H22 H240, H250 H24 H310, H330 H301, H31 H350, H360, H341, H351, H 70, H372 H31 H410, H411, H401, H420 H410, H411, H401, H420 H410, H411, H401, H401, H420	H201, H202, H203, H205, H220, H224 H240, H250 H310, H330 H310, H330 H350, H360, H341, H351, H361, H371, H350, H372 H373 H410, H411, H420 H420 H420 H420 H420 H420 H420 H420	Image: Constant State Sta	Image: Second	d Flag Amber Flag Green Flag H-co H201, H202, H205, H220, H224 If no red or amber flagged H H201, H202, H205, H220, H224 If no red or amber flagged H H201, H202, H205, H220, H224 If no red or amber flagged H H201, H202, H301, H311, H331, H green flag H H310, H330 H301, H311, H331, H H H H300, H301, H311, H373, H373 H TM H410, H411, H401, H412 EDC EDC pommental concern ist substances of very high concel M	Amber Flag Amber Flag Green Flag List substances and H-codes H201, H202, H205, H220, H224 If no red or amber flagged H codes present then green flag H codes present then green flag H310, H330 H301, H311, H331, H371, H371, H371, H371, H372 H H410, H412 EDC HCI H410, H411, H420 ist substances of very high concer EDC HCI	High temperature multiple recrystallisation Red Flag Hag Amber Flag Image: State Sta	High temperature multiple recrystallisation Red Flag High temperature multiple recrystallisation Red Flag High temperature multiple recrystallisation Red Flag High temperature multiple recrystallisation List substances and the codes High temperature multiple recrystallisation List substances of very high concer	Image: style in the style	Image: Second

8. References

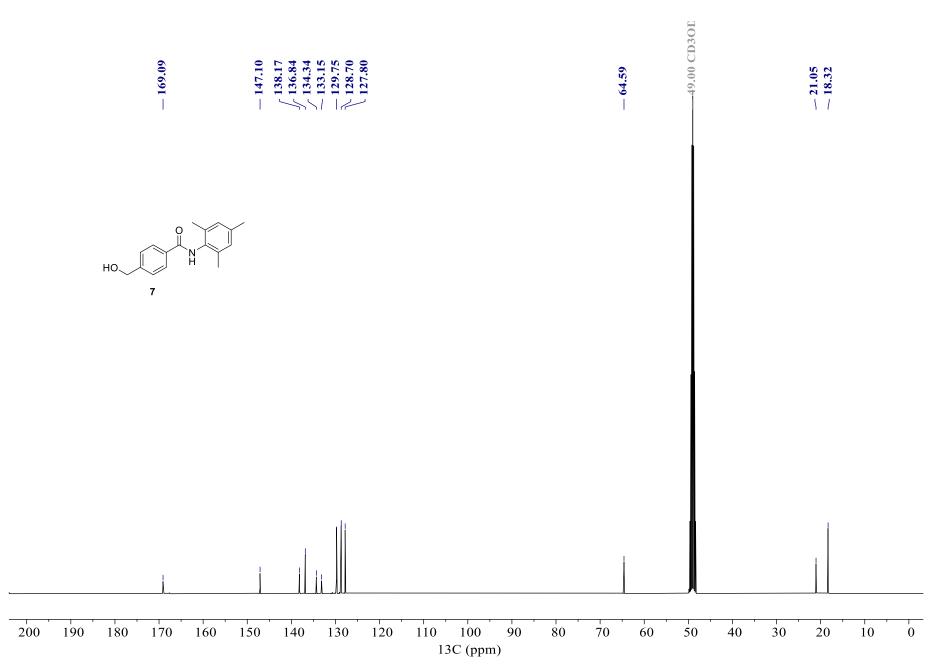
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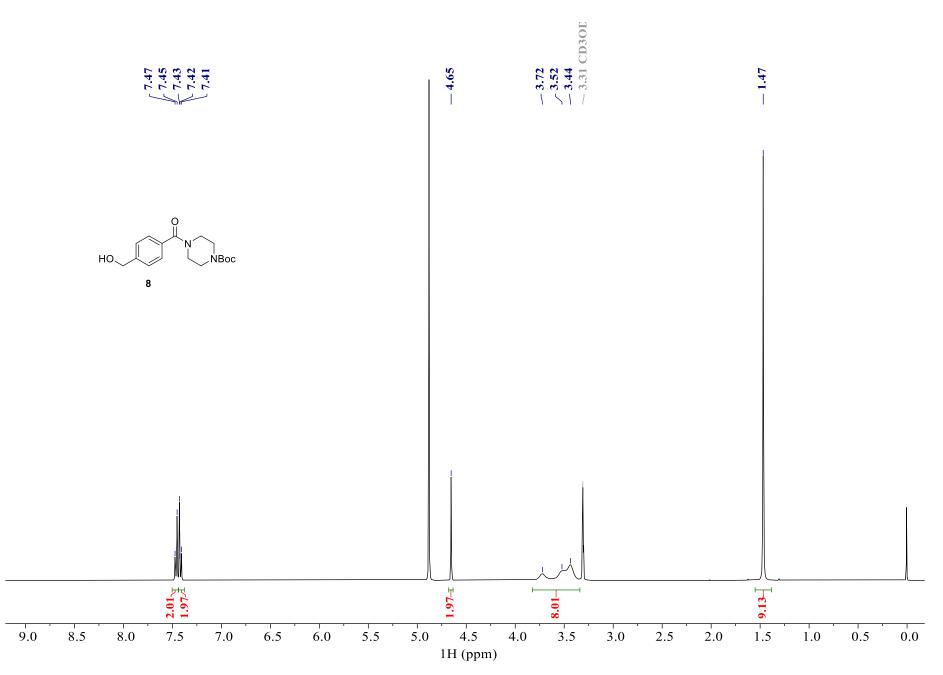




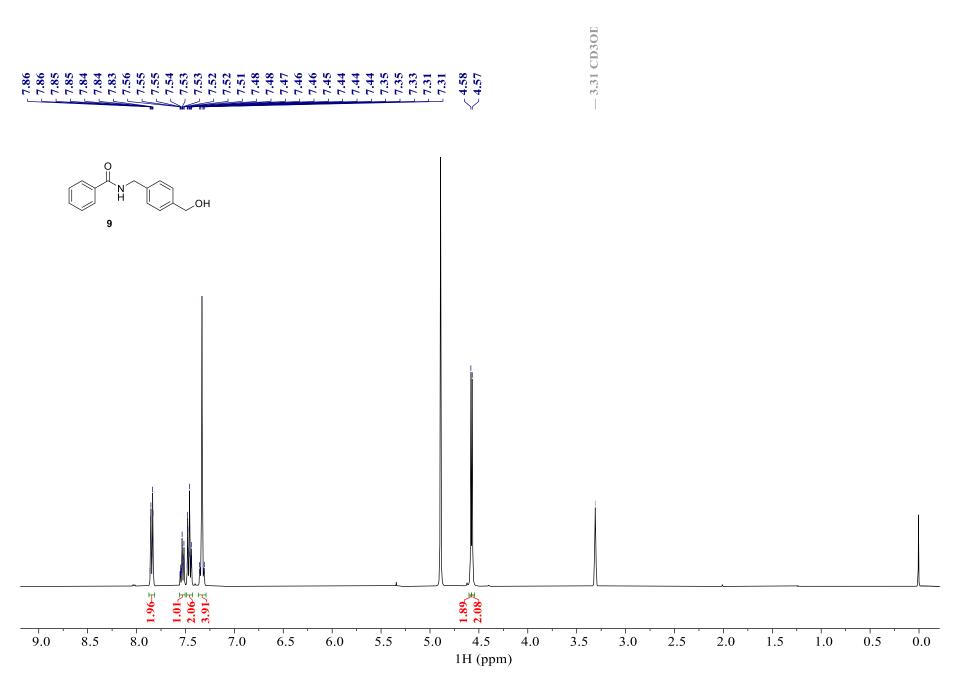


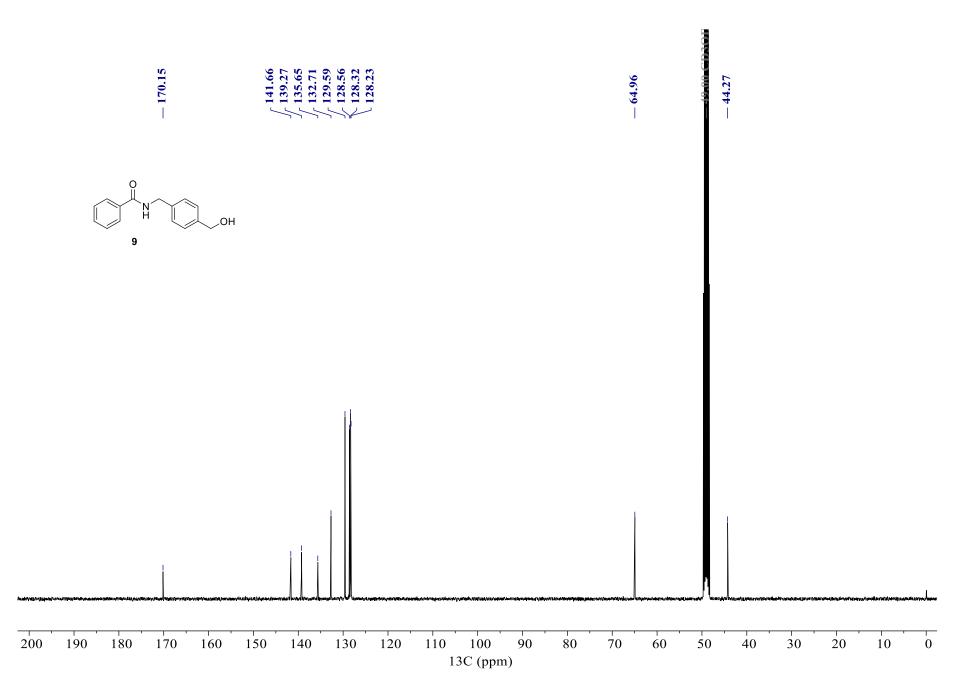
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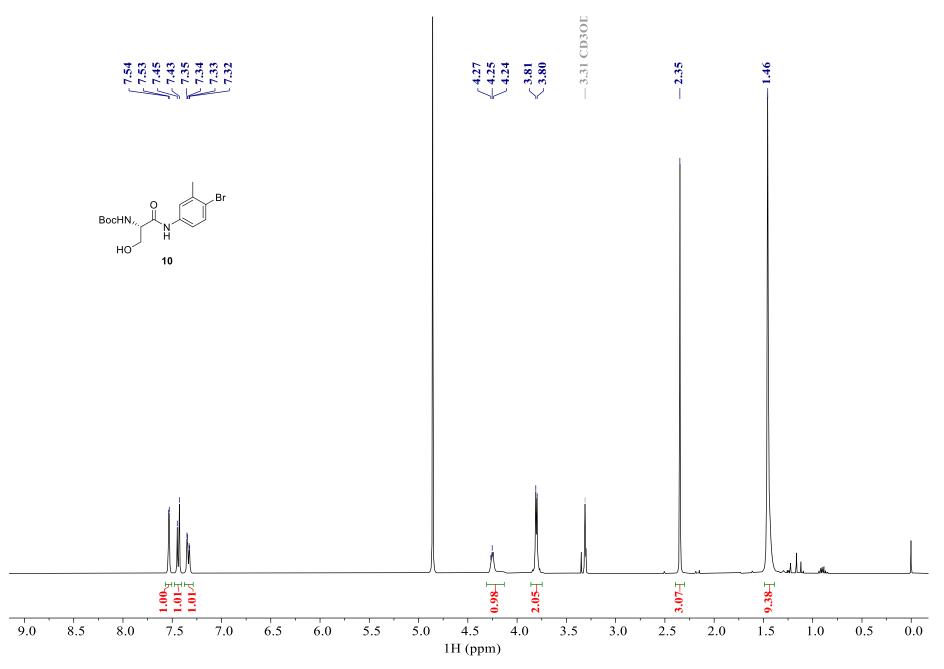


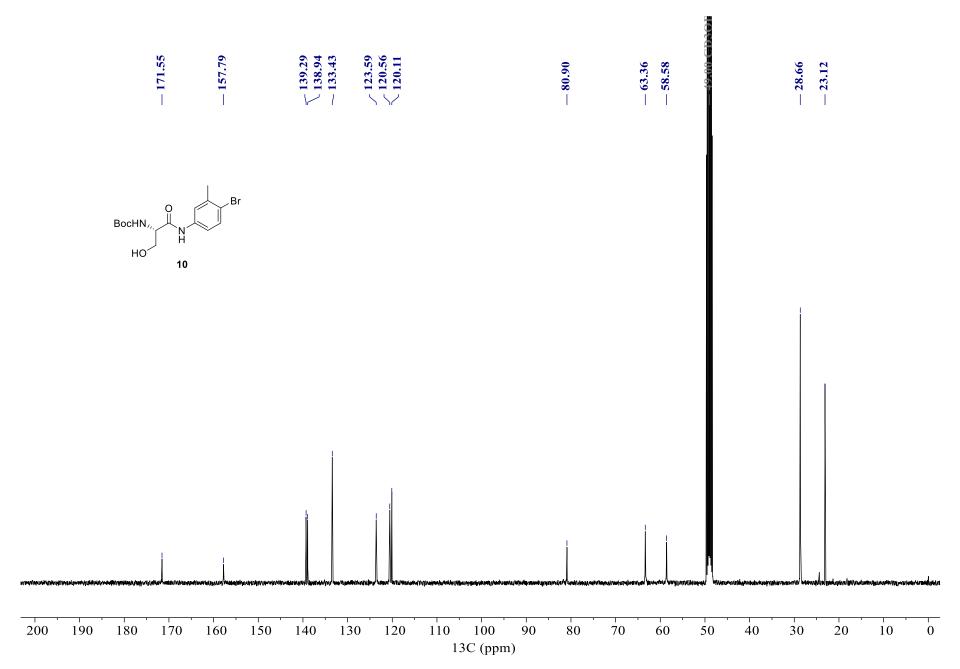


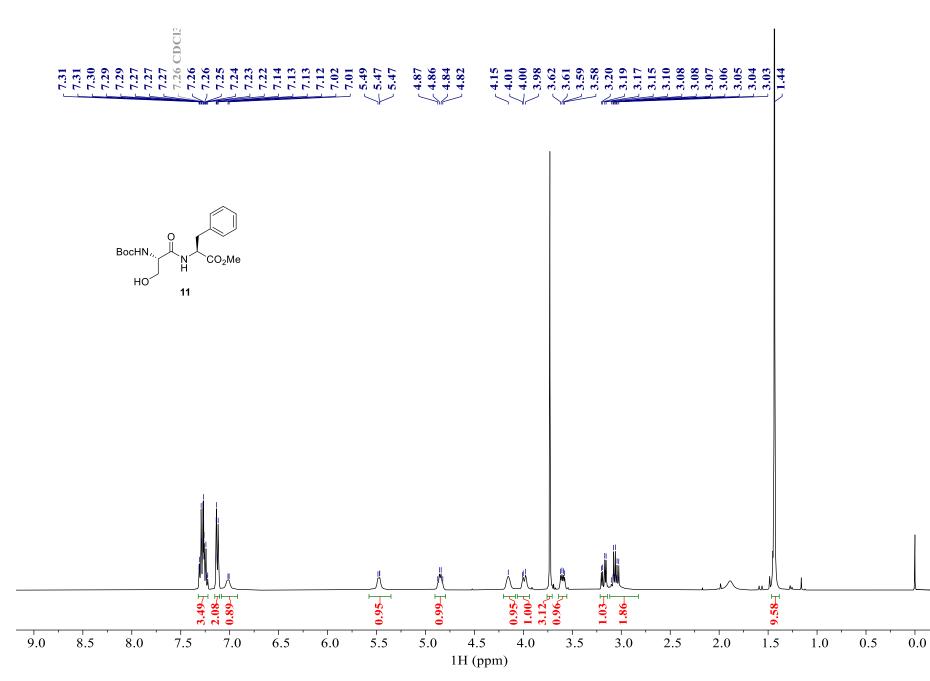
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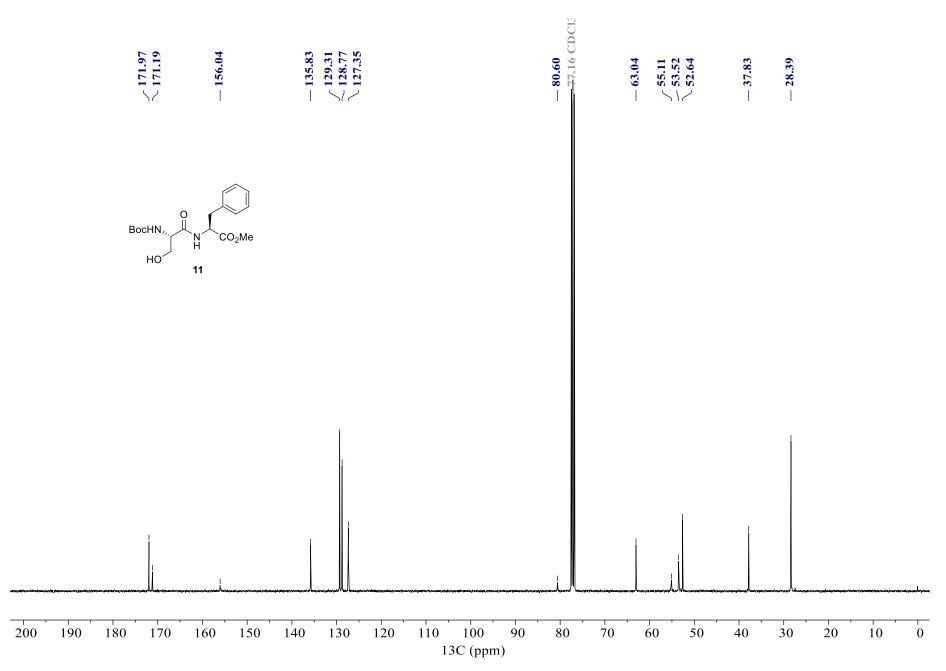


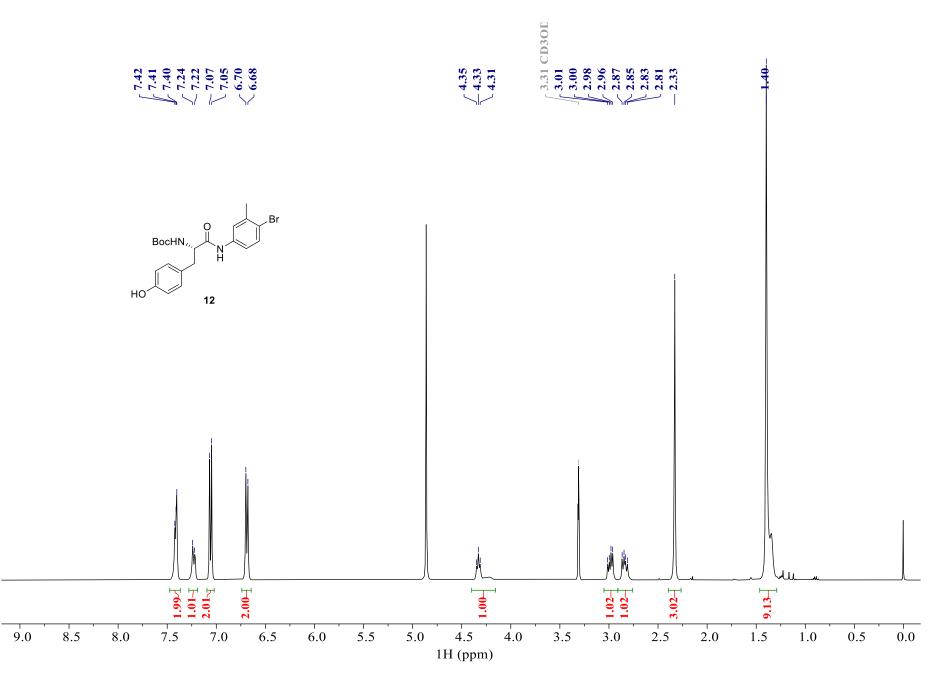


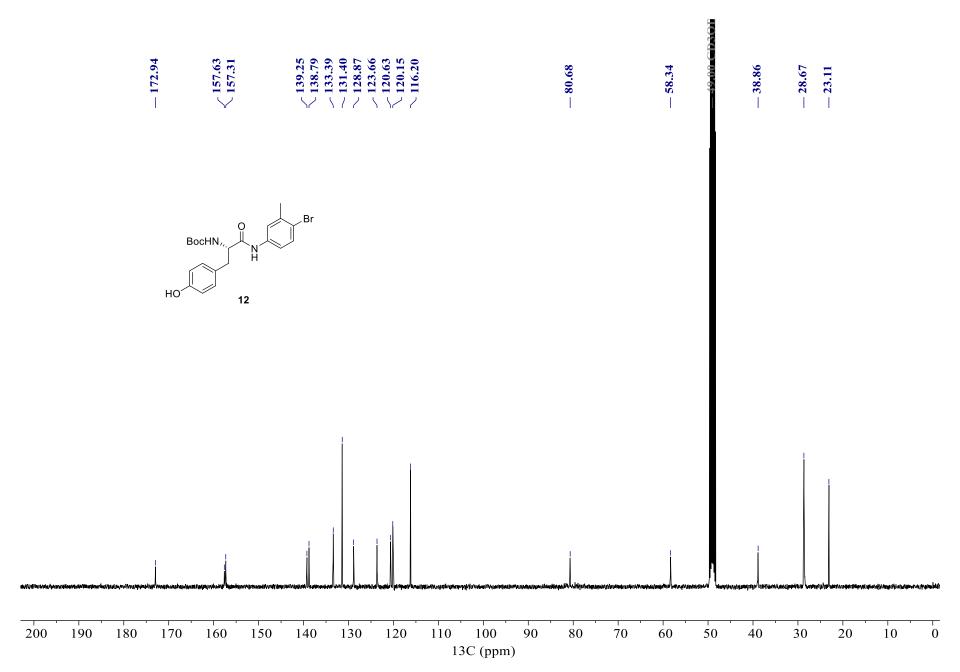


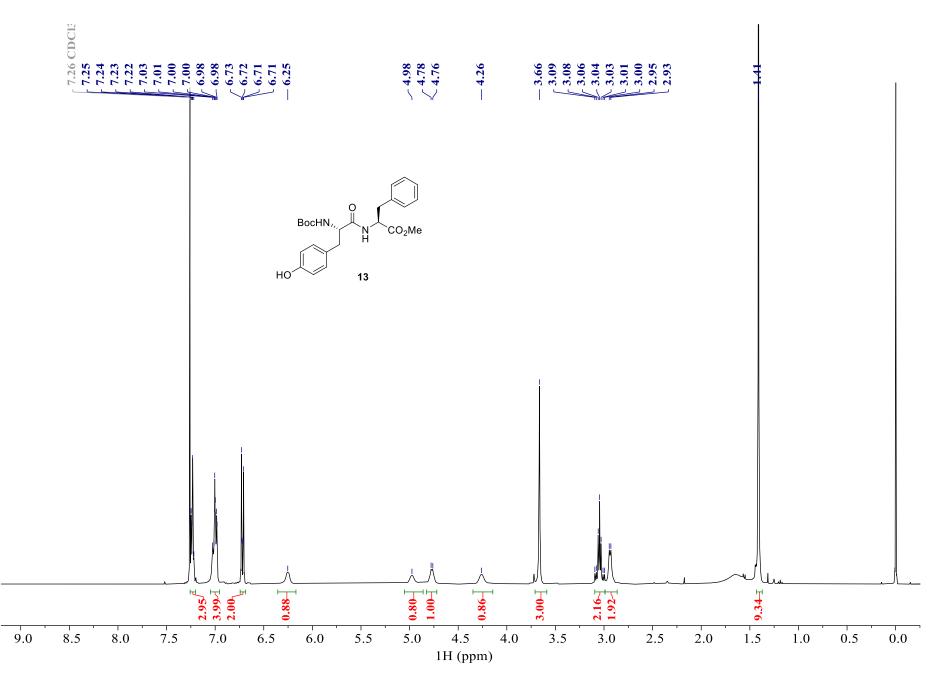


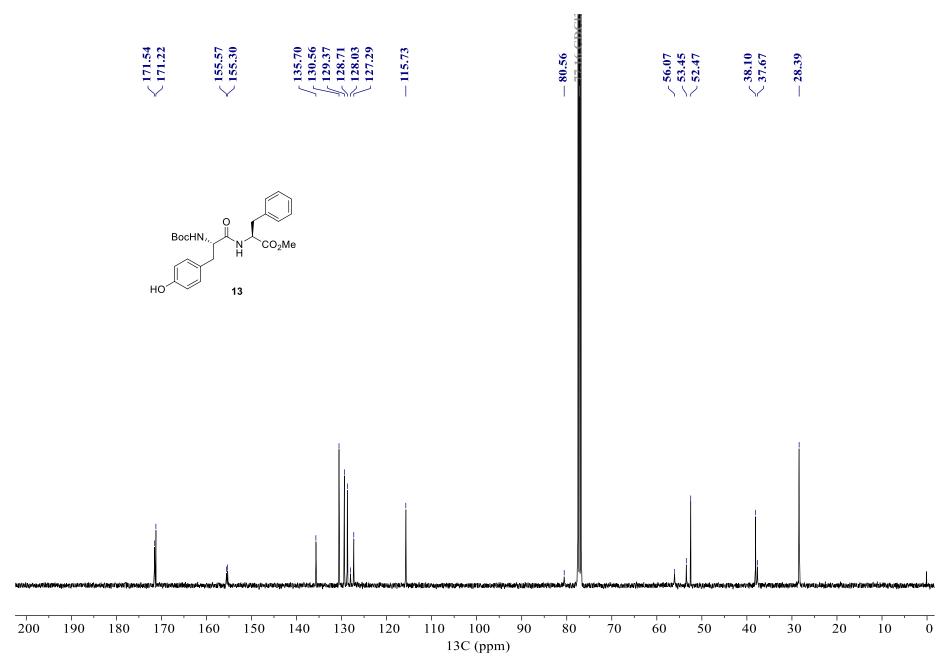












S56

