Reductive Cleavage of N-O Bonds Using Samarium(II) Iodide in a Traceless Release Strategy in Solid Phase Synthesis

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SUPPORTING INFORMATION

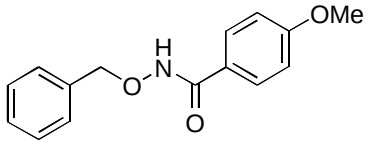
General Procedures

LCMS spectra were recorded on a Micromass Platform LC. Samples are introduced into the source *via* a Hewlett Packard 1050 HPLC, where the samples are ionized (via +ve and -ve ESI). The ions are filtered according to their mass-to-charge ratio, detected and then the signal is amplified and processed by the MassLynx NT data system. Solvent A = 10 mmol solution of ammonium acetate in milliQ water + 0.1% formic acid. Solvent B = 95% acetonitrile/5% milliQ water + 0.05% formic acid. The column was a Supercosil ABZ+PLUS (3 micron), 3.3cm x 4.6mm ID. Flow rate: 1 mL / min from a HP 1050 LC, then split 50:1 (therefore 20 µL/min into the ESI source). Run time 8 min. Gradient from 100% A to 100% B by 4.2 min then back to 100% A by 8 min. The UV detection on the LCMS is over a range of 215 - 330 nm which provides a diode array trace for each sample. Mass spectra were recorded on a Micromass Q-TOF Spectrometer or Fourier-Transform Ion Cyclotron Resonance Mass Spectrometer (FTICR). Proton NMR spectra were recorded on either a Bruker AVANCE 500 DPX, Bruker 400 DPX or a Bruker AC 250. Infra-red Spectra were recorded on an ATI Mattson Genesis FTIR spectrometer. Flash column chromatography was performed using Kieselgel 60, with mesh size 230-400 ASTM. All reactions were carried out under anhydrous conditions using oven-dried glassware and under argon unless otherwise stated. Solvents were freshly distilled prior to use. HPLC was performed on Gilson apparatus detecting at either 220 nm or 254 nm and using a gradient of 5 - 95% solvent A over 15 minutes. Solvent A = acetonitrile + 0.1% TFA, solvent B = milliQ water + 0.1% TFA. The column was a TSK gel Oligo DNA RP column. Flow rate 1 mL/min.

Abbreviations

DCM	Dichloromethane	DIPEA	*N*,*N*-diisopropylethylamine
DIAD	Diisopropylazodicarboxylate	HOBt	*N*-hydroxybenzotriazole
DIC	Diisopropylcarbodiimide	DBU	1,8-diazabicyclo-[5.4.0]undec-7-ene

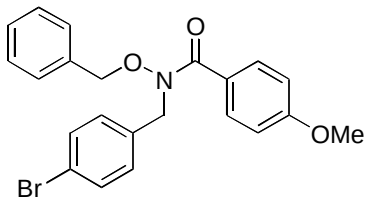
N-Benzyloxy-4-methoxy-benzamide (2)[1]



O-Benzylhydroxylamine hydrochloride (0.65 g, 4.1 mmol) was added to a solution of DIPEA (1.46 mL, 8.2 mmol) in DCM (10 mL). The resulting pale yellow solution was cooled to 0 ^{o}C and *p*-anisoyl chloride (0.70 g, 4.1 mmol) dissolved in DCM (3 mL) was added. After 45 min an additional portion of DCM (5 mL) was added, and the reaction mixture was partitioned against water (20 mL) and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layers were washed with water (25 mL), brine (25 mL) then dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a white powder that was purified by flash column chromatography (40-80% EtOAc/heptane) to give the benzamide **2** (0.76 g, 72%) as a white solid.

R_f 0.28 [ethyl acetate/heptane (1:1)]; ν_{max}/cm^{-1} 1634 (C=O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.82 (3H, s, OC**H**$_3$), 5.01 (2 H, s, C**H**$_2$O), 6.88 (2H, d, *J* 9.5, Ar-**H**), 7.35 – 7.45 (5 H, m, Ph), 7.64 (2H, d, *J* 9.5, Ar-**H**), 8.52 (1 H, br, s, N**H**); LRMS Found: 258.1 (M + H^{+}); HRMS Found: 280.0962 (M + Na); $C_{15}H_{15}NaNO_3$ requires 280.0950.

N-Benzyloxy-*N*-(4-bromobenzyl)-4-methoxy-benzamide (3)

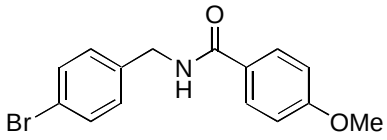


DBU (0.47 mL, 3.16 mmol) was added to a solution of benzyloxy-4-methoxy-benzamide **2** (0.68 g, 2.63 mmol) in THF (20 mL) and stirred at 0 ^{o}C for 80 min. 4-Bromobenzyl bromide (0.67 g, 2.68 mmol) was added as a solution in THF (1.5 mL). After stirring at 0 ^{o}C for 2 hours the crude reaction mixture was diluted with ethyl acetate (50 mL) then partitioned against water (30 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers washed with water (25 mL), brine (25 mL) then dried over sodium sulfate. The residue obtained on evaporation was purified by flash column

chromatography (20% ethyl acetate/heptane) to afford the b*enzamide* **3** (0.45 g, 40%) as an oil.

R_f 0.45 [ethyl acetate/heptane (1:1)]; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.85 (3 H, s, OC**H**$_3$), 4.56 (2 H, s, C**H**$_2$-N), 4.84 (2 H, s, C**H**$_2$O), 6. 86 (2 H, d, *J* 9.5, Ar-**H**), 7.04 (2 H, d, *J* 9.5, Ar-**H**), 7.27 - 7.33 (5 H, m, Ph), 7.47 (2 H, d, *J* 9.5, Ar-**H**), 7.74 (2H, d, *J* 9.5, Ar-**H**); LRMS 426.1 ($M^{79}Br + H^+$, 100%), 428.1 ($M^{81}Br + H^+$, 97%]; HRMS Found: 448.0514 (M + Na); $C_{22}H_{20}NaNO_3{}^{79}Br$ requires 448.0524.

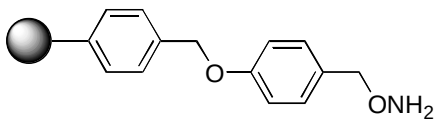
N-(4-Bromobenzyl)-4-methoxy-benzamide (solution phase synthesis) (4)



Samarium(II) iodide (0.1 M in THF) (2.12 mL, 0.21 mmol) was added drop-wise to a solution of *N*-benzyloxy-*N*-(4-bromobenzyl)-4-methoxy-benzamide **3** (43 mg, 0.1 mmol) dissolved in THF (1 mL) at rt. After 5 min DCM (10 mL) was added and the reaction quenched with 10% aq sodium thiosulfate (2 mL). The organic layer was collected, washed with water (10 mL), brine (10 mL) then dried over magnesium sulfate. The residue obtained on evaporation was dissolved in DCM (ca. 5 mL) and filtered through a short pad of silica and re-concentrated to afford the *benzamide* **4** (29 mg, 92%).

R_f 0.23 [ethyl acetate/heptane (1:1)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (3 H, s, OC**H**$_3$); 4.59 (2 H, d, *J* 6, C**H**$_2$-NH), 6.35 (1 H, br, N**H**), 6.92 (2 H, d, *J* 9, Ar-**H**), 7.22 (2 H, d, *J* 9, Ar-**H**), 7.47 (2 H, s, *J* 9, Ar-**H**), 7.75 (2 H, d, *J* 9, Ar-**H**); LRMS 320.1 ($M^{79}Br + H^+$, 100%], 322.0 ($M^{81}Br + H^+$, 97%).

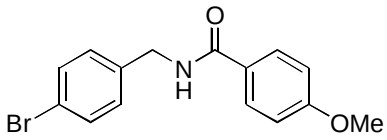
4-*O*-(Methylhydroxylamine)phenoxymethyl-copolymer(styrene-1%-dvb)resin (100-200 mesh)[2] (7)



Wang resin (100-200 mesh, 1.29 mmol/g, 25 g, 32.3 mmol) was suspended in THF (250 mL) and the suspension was cooled to 0 ^{o}C. Triphenylphosphine (16.9 g, 64.5 mmol, 2 eq.) was then added followed by *N*-hydroxyphthalimide (26.1 g, 161.3 mmol, 5 eq.). After stirring at 0 ^{o}C for 15 min DIAD, (12.7 mL, 64.5 mmol, 2 eq.) was added slowly. The suspension was allowed to warm to rt and stirring for a further 12 h. The suspension was filtered through a sintered funnel and the resin was washed with methanol, water, ethyl acetate and DCM (minimum of 2 x 100 mL of each) then dried under high vacuum. ν_{max}/cm^{-1} (gel) 1789 (C=O), 1727 (C=O). The moist resin was transferred to a 1 L conical flask and stirred in a solution of THF (500 mL) and 40% aq methylamine solution (250 mL) for 16 h. The resin was washed as described and dried under high vacuum for 4 h. A cream coloured resin was obtained (24.9 g).

ν_{max}/cm^{-1} (gel) 3323 (ONH_2). Calcd. N; 1.74% Analysis N; 1.95%. Loading 1.18 mmol/g (based on N anal.). Yield 91% (based on N anal.).

N-(4-Bromo-benzyl)-4-methoxy-benzamide (8)

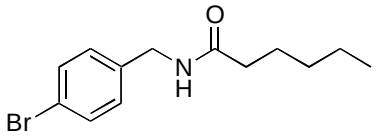


Hydroxylamine resin (0.50 g, 0.55 mmol) was suspended in a solution of DIPEA (0.14 mL, 0.76 mmol) and *p*-anisoyl chloride (0.13 g, 0.76 mmol) in DCM (5 mL). The suspension was shaken at 25 ^{o}C for 3 h. The resin was washed with methanol, ethyl acetate and DCM (5 x 25 mL of each) and then dried under high vacuum for 16 h. ν_{max}/cm^{-1} (gel) 3214 (NH), 1660 (C=O). The resin was then suspended in a solution of DBU (0.94 mL, 6.3 mmol) in toluene (15 mL) and 4-bromobenzyl bromide (3.15 g, 12.2 mmol) was added. The suspension was shaken at 25 ^{o}C for 48 h. The resin was washed and dried as before. ν_{max}/cm^{-1} 1664 (C=O).

The resin (0.66 g, 0.57 mmol) was pre-swollen with THF (2.3 mL) and samarium(II) iodide (0.1 M in THF, 11.5 mL, 1.14 mmol) was added. The suspension was shaken at 25 ^{o}C for 3 h. The resin was filtered off and rinsed with DCM (5 x 10 mL) and the cleavage solution and washings collected. The filtrate was evaporated under reduced pressure giving a dark yellow residue, this was re-dissolved in a solution of diethyl ether (25 mL), 1 M HCl (20 mL) and 10% aq sodium thiosulfate (5 mL). The mixture was transferred to a separating funnel and shaken until it became colourless. The organic layer was collected and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL) and dried over magnesium sulfate. The solid obtained after evaporation was dissolved in the minimum of DCM (*ca.* 0.3 - 0.5 mL) and filtered through a short pad of silica (*ca.* 3 cm in a 1.5 cm diameter column, eluting with 30% ethyl acetate in hexanes). The filtrate was collected and evaporated to afford the *benzamide* **8** as a white crystalline solid (97 mg, 54%).

R_f 0.43 [vis. UV, ethyl acetate/hexanes (1:1)]; ν_{max}/cm^{-1} 3292 (NH), 1633 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (3 H, s, C**H**$_3$), 4.58 (2 H, *J* 6, C**H**$_2$), 6.30 (1 H, br, s, N**H**), 6.91 (2 H, d, *J* 9, Ar-**H**), 7.23 (2 H, d, *J* 8.5, Ar-**H**), 7.45 (2 H, d, *J* 8.5, Ar-**H**), 7.73 (2 H, d, *J* 9, Ar-**H**); ^{13}C NMR (500 MHz, $CDCl_3$) δ 43.1 (CH_2), 55.2 (CH_3), 113.8 (CH), 121.4 (C), 126.1 (C), 128.5 (CH), 129.3 (CH), 131.6 (CH), 137.3 (C), 162.1 (C=O); MS (ES) *m/z* = 320.1 ($M^{79}Br + H^+$, 100%), 322.1 ($M^{81}Br + H^+$, 87%); LCMS t_R 5.0 min. HPLC t_R 14.6 min, purity 99.1% (254 nm, TSK gel Oligio DNA RP, solvent A: acetonitrile + 0.1% TFA, solvent B: milliQ water + 0.1% TFA, gradient 5 - 95% solvent A over 15 min. Flow rate 1 mL/min.)

Hexanoyl 4-bromo-benzylamide (9)

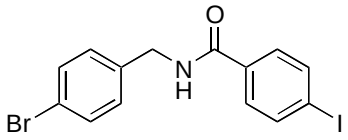


Hydroxylamine resin (1.00 g, 1.18 mmol) was suspended in a solution of DIPEA (0.67 mL, 3.78 mmol) and hexanoyl chloride (0.58 mL, 3.78 mmol) in DCM (10 mL). The suspension was shaken at 25 ^{o}C for 16 h. The resin was washed with methanol, ethyl acetate and DCM (5 x 25 mL of each) and then dried under high vacuum for 16 h. ν_{max}/cm^{-1} (gel) 3396 (NH), 1711 (C=O). The resin was suspended in a solution of DBU (0.94 mL, 6.3 mmol) and toluene (15 mL) and 4-bromobenzyl bromide (3.15 g, 12.2 mmol) was added. The suspension was shaken

at 25 ^{o}C for 48 h. The resin was washed and dried as described above. ν_{max}/cm^{-1} (gel) 1724 (C=O). The resin (659 mg, 0.82 mmol) was pre-swollen with THF (1.6 mL) and samarium(II) iodide (0.1 M in THF, 16.34 mL, 1.64 mmol) was added. The reaction suspension was shaken at 25 ^{o}C for 3 h. The resin was filtered off and rinsed with DCM (5 x 10 mL) and the cleavage solution and washings collected. The filtrate was evaporated to give a dark yellow residue. The residue was re-dissolved in a solution of diethyl ether (25 mL), 1 M HCl (20 mL) and 10% aq sodium thiosulfate (5 mL). The mixture was transferred to a separating funnel and shaken until it became colourless. The organic layer was collected and the aqueous layer was extracted diethyl ether (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL) and dried over magnesium sulfate. The solid obtained after evaporation was dissolved in the minimum amount of DCM (*ca.* 0.3 - 0.5 mL) and was filtered through a short pad of silica (*ca.* 3 cm in a 1.5 cm diameter column eluting with 50% ethyl acetate/hexanes). The filtrate was collected and evaporated to afford the *bromobenzylamide* **9** as a white solid (49 mg, 30%).

R_f 0.40 [vis. $KMnO_4$, ethyl acetate/hexanes (1:1)]; ν_{max}/cm^{-1} 3286 (NH), 1643 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3 H, t, *J* 7, $CH_2C\mathbf{H}_3$), 1.25 - 1.35 (4 H, m, $C\mathbf{H}_2C\mathbf{H}_2CH_3$), 1.61 - 1.67 (2 H, m, $OCCH_2C\mathbf{H}_2$), 2.19 (2 H, m, $OCC\mathbf{H}_2$), 4.38 (2 H, d, *J* 6, Ar-$C\mathbf{H}_2$N), 5.71 (1 H, br s, N**H**), 7.14 (2 H, d, *J* 8.5, Ar-**H**), 7.44 (2 H, d, *J* 8.5, Ar-**H**); ^{13}C NMR (500 MHz, $CDCl_3$) δ 13.6 (CH_3), 22.1 (CH_2), 25.1 (CH_2), 31.2 (CH_2), 36.5 (CH_2), 42.6 (CH_2), 121.1 (C), 129.2 (CH), 131.5 (CH), 137.3 (C), 172.2 (CO); MS (ES) *m/z* = 284.2 ($M^{79}Br + H^+$, 100%), 286.2 ($M^{81}Br$ + H, 90%), 306.2 ($M^{79}Br + Na^+$, 13%), 284.2 ($M^{81}Br + H^+$, 15%); LCMS t_R 5.1 min. HPLC t_R 15.4 min, purity 97% (220 nm, TSK gel Oligio DNA RP, solvent A: acetonitrile + 0.1% TFA, solvent B: milliQ water + 0.1% TFA, gradient 5 - 95% solvent A over 15 min. Flow rate 1 mL/min.).

N-(4-Bromo-benzyl)-4-iodo-benzamide (10)

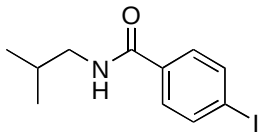


Hydroxylamine resin (1.00 g, 1.18 mmol) was suspended in a solution of DIC (0.58 mL, 3.78 mmol) and HOBt (0.59 g, 3.78 mmol) in DMF (10 mL). The suspension was shaken at 25 ^{o}C for 16 h. The resin was washed with methanol, ethyl acetate and DCM (5 x 25 mL of each)

and then dried under high vacuum for 16 h. ν_{max}/cm^{-1} (gel) 1662 (C=O). The resin was suspended in a solution of DBU (0.94 mL, 6.3 mmol) and toluene (15 mL) and 4-bromobenzyl bromide (3.15 g, 12.2 mmol) was added. The suspension was shaken at 25 ^{o}C for 48 h. The resin was washed and dried as before. ν_{max}/cm^{-1} (gel) 1666 (C=O). The resin (1.41 g, 1.11 mmol) was pre-swollen with THF (2.3 mL) and samarium(II) iodide (0.1 M in THF, 22.25 mL, 2.23 mmol) was added and the reaction suspension was shaken at 25 ^{o}C for 3 h. The resin was filtered off and rinsed with DCM (5 x 10 mL) and the cleavage solution and washings collected. The filtrate was evaporated under reduced pressure giving a dark yellow residue which was re-dissolved in a solution of diethyl ether (25 mL), 1 M HCl (20 mL) and 10% aqueous sodium thiosulfate (5 mL). The mixture was transferred to a separating funnel and shaken until it became colourless. The organic layer was collected and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL) and dried over magnesium sulfate. The solid obtained after evaporation was dissolved in the minimum amount of DCM (*ca*. 0.3 - 0.5 mL). The solution was filtered through a short pad of silica (*ca*. 3 cm in a 1.5 cm diameter column, eluting with 50% ethyl acetate/hexanes). The filtrate was collected and evaporated to the *benzamide* **10** (134 mg, 32%).

R_f 0.46 [vis. $KMnO_4$, ethyl acetate/hexanes (1:1)]; ν_{max}/cm^{-1} 3311 (NH), 1639 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.57 (2 H, d, *J* 6, C**H**$_2$), 6.37 (1 H, br, N**H**), 7.42 (2 H, d, *J* 8.5, Ar-**H**), 7.48 (2 H, d, *J* 8.5, Ar-**H**), 7.52 (2 H, d, *J* 8.5, Ar-**H**), 7.68 (2 H, d, *J* 8.5, Ar-**H**); ^{13}C NMR (500 MHz, $CDCl_3$) δ 43.50 (CH_2), 124.15, 128.47, 128.53, 128.99, 129.56, 131.59, 131.89, 131.98, 137.84, 137.92, 166.50 (C=O); (ES) *m/z* = 413.9 ($M^{79}Br + H^+$, 100%), 415.9 ($M^{81}Br + H^+$, 82%); HRMS (FTICR) Found: 437.89448 (M + Na); $C_{14}H_{11}NaNO^{79}BrI$ requires 437.91667; LCMS t_R 5.4 min. HPLC t_R 11.8 min, purity 46% (254 nm, TSK gel Oligio DNA RP, solvent A: acetonitrile + 0.1% TFA, solvent B: milliQ water + 0.1% TFA, gradient 5 - 95% solvent A over 15 min. Flow rate 1 mL/min.).

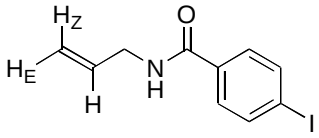
4-Iodo-*N*-isobutyl-benzamide (11)



Hydroxylamine resin (1.00 g, 1.18 mmol) was suspended in a solution of 4-iodobenzoic acid (0.94 g, 3.78 mmol), DIC (0.58 mL, 3.78 mmol) and HOBt (0.59 g, 3.78 mmol) in DMF (10 mL). The suspension was shaken at 25 ^{o}C for 16 h. The resin was washed with methanol, ethyl acetate and DCM (5 x 25 mL of each) and then dried under high vacuum for 16 h. ν_{max}/cm^{-1} (gel) 1668 (C=O). The resin was then suspended in a solution of DBU (0.94 mL, 6.3 mmol) in toluene (15 mL) and isobutyl bromide (1.33 g, 12.2 mmol) was added. The suspension was shaken at 25 ^{o}C for 48 h. The resin was washed and dried as described above. The resin (1.21 g, 1.05 mmol) was pre-swollen with THF (2.1 mL) and samarium(II) iodide (0.1 M in THF, 21 mL, 2.10 mmol) was added. The reaction suspension was shaken at 25 ^{o}C for 3 h. The resin was filtered off and rinsed with DCM (5 x 10 mL) and the cleavage solution and washings collected. The filtrate was evaporated giving a dark yellow residue, this was re-dissolved in a solution of diethyl ether (25 mL), 1 M HCl (20 mL) and 10% aq sodium thiosulfate (5 mL). The mixture was transferred to a separating funnel and the flask shaken until it became colourless. The organic layer was collected and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL) and dried over magnesium sulfate. The solid obtained after evaporation was re-dissolved in the minimum amount of DCM (*ca*. 0.3 - 0.5 mL) and filtered through a short pad of silica (*ca.* 3 cm in a 1.5 cm diameter column, eluting with 20% ethyl acetate in hexanes). The filtrate was collected and evaporated to afford the *benzamide* **11** (49 mg, 33%)

R_f 0.63 [vis. UV, ethyl acetate/hexanes (1:1)]; ν_{max}/cm^{-1} 3305 (NH), 1633 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (6 H, d, *J* 6.5, (C**H**$_3$)$_2$C), 1.86 - 1.91 (1 H, m, (CH$_3$)$_2$C**H**), 3.27 (2 H, d, *J* 6.5, C**H**$_2$), 6.06 (1 H, s, br, N**H**), 7.74 (2 H, d, *J* 8.5, Ar-**H**), 7.77 (2 H, d, *J* 8.5, Ar-**H**); ^{13}C NMR (500 MHz, $CDCl_3$) δ 19.9 (CH_3), 28.3 (CH), 47.2 (CH_2), 128.2 (CH), 137.5 (CH), 163.4 (C=O); MS (ES) *m/z* = 304.0 (M + H$^+$, 100%), 326.0 (M + Na, 12%); LCMS t_R 5.0 min. HPLC t_R 14.4 min, purity 99.2% (254 nm, TSK gel Oligio DNA RP, solvent A: acetonitrile + 0.1% TFA, solvent B: milliQ water + 0.1% TFA, gradient 5 - 95% solvent A over 15 min. Flow rate 1 mL/min.).

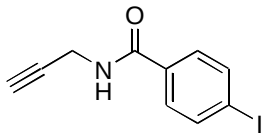
N-Allyl-4-iodo-benzamide (12)



Hydroxylamine resin (1.00 g, 1.18 mmol) was suspended in a solution of 4-iodobenzoic acid (0.94 g, 3.78 mmol), DIC (0.58 mL, 3.78 mmol) and HOBt (0.59 g, 3.78 mmol) in DMF (10 mL). The suspension was shaken at 25 ^{o}C for 16 h. The resin was washed with methanol, ethyl acetate and DCM (5 x 25 mL of each) and then dried under high vacuum for 16 h. ν_{max}/cm^{-1} (gel) 1668 (C=O). The resin was then suspended in a solution of DBU (0.94 mL, 6.3 mmol) in toluene (15 mL) and allyl bromide (1.06 mL, 12.2 mmol) was added. The suspension was shaken at 25 ^{o}C for 48 h. The resin was washed and dried as before. The resin (1.16 g, 1.02 mmol) was pre-swollen with THF (2.0 mL) and samarium(II) iodide (0.1 M in THF, 20.5 mL, 2.05 mmol) was added. The reaction suspension was shaken at 25 ^{o}C for 3 h. The resin was filtered off and rinsed with DCM (5 x 10 mL) and the cleavage solution and washings collected. The filtrate was evaporated to give a dark yellow residue, this was re-dissolved in a solution of diethyl ether (25 mL), 1 M HCl (20 mL) and 10% aq sodium thiosulfate (5 mL). The mixture was transferred to a separating funnel and the flask shaken until it became colourless. The organic layer was collected and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL) and dried over magnesium sulfate. The solid obtained after evaporation was re-dissolved in the minimum amount of DCM (*ca.* 0.3 - 0.5 mL) and filtered through a short pad of silica (*ca.* 3 cm in a 1.5 cm diameter column, eluting with 20% ethyl acetate in hexanes). The filtrate was collected and evaporated to afford the *benzamide* **12** (89 mg, 31%).

R_f 0.82 [vis. UV, ethyl acetate/hexanes (1:1)]; ν_{max}/cm^{-1} 3307 (NH), 1635 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (2 H, m, (C**H**$_2$N), 5.18 (1H, dd, *J* 10, 1.5, **H**$_E$) 5.25 (1 H, dd, *J* 17, 1.5, **H**$_Z$), 5.92 (1H, ddt, *J* 17, 10, 5.5, C**H**CH$_2$), 6.12 (1H, s, br, N**H**), 7.49 (2H, d, *J* 8.5, Ar-**H**), 7.78 (2H, d, *J* 8.5, Ar-**H**); ^{13}C NMR (500 MHz, $CDCl_3$) δ 42.2, 98.2, 116.7, 133.6, 133.8, 137.6, 166.4; MS (ES) *m/z* = 287.9 (M + H$^+$, 100%); LCMS t_R 5.1 min. HPLC t_R 12.9 min, purity 84% (254 nm, TSK gel Oligio DNA RP, solvent A: acetonitrile + 0.1% TFA, solvent B: milliQ water + 0.1% TFA, gradient 5 - 95% solvent A over 15 min. Flow rate 1 mL/min.).

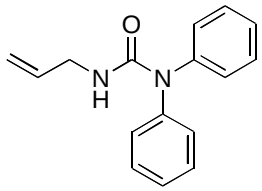
4-Iodo-*N*-prop-2-ynyl-benzamide (13)



Hydroxylamine resin (1.00 g, 1.18 mmol) was suspended in a solution of 4-iodobenzoic acid (0.94 g, 3.78 mmol), DIC (0.58 mL, 3.78 mmol) and HOBt (0.59 g, 3.78 mmol) in DMF (10 mL). The suspension was shaken at 25 ^{o}C for 16 h. The resin was washed with methanol, ethyl acetate and DCM (5 x 25 mL of each) and then dried under high vacuum for 16 h. The resin was then suspended in a solution of DBU (0.94 mL, 6.3 mmol) in toluene (15 mL) and propargyl bromide (80% in toluene, 1.36 mL, 12.2 mmol) was added. The suspension was shaken at 25 ^{o}C for 48 h. The resin was washed and dried as described above. The resin (1.16 g, 1.02 mmol) was pre-swollen with THF (2.0 mL) and samarium(II) iodide (0.1 M in THF, 20.5 mL, 2.05 mmol) was added. The reaction suspension was shaken at 25 ^{o}C for 3 h. The resin was filtered off and rinsed with DCM (5 x 10 mL) and the cleavage solution and washings collected. The filtrate was evaporated giving a dark yellow residue which was re-dissolved in a solution of diethyl ether (25 mL), 1 M HCl (20 mL) and 10% aq sodium thiosulfate (5 mL). The mixture was transferred to a separating funnel and the flask shaken by hand until it became colourless. The organic layer was collected and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL) and dried over magnesium sulfate. The solid obtained after evaporation was re-dissolved in the minimum amount of DCM (*ca*. 0.3 - 0.5 mL) and filtered through a short pad of silica (*ca*. 3 cm in a 1.5 cm diameter column, eluting with 20% ethyl acetate in hexanes). The filtrate was collected and evaporated to afford the *benzamide* **13** (120 mg, 40%).

R_f 0.61 [vis. $KMnO_4$, ethyl acetate/hexanes (1:1)]; ν_{max}/cm^{-1} 3284 (C≡**C**-**H**), 1643 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (1 H, t, *J* 2.5, C≡C-**H**), 4.28 (2 H, dd, *J* 5, 2.5, C**H**$_2$) 6.24 (1 H, s, br, N**H**), 7.49 (2 H, d, *J* 8.5 Ar-**H**), 7.85 (2 H, d, *J* 8.5, Ar-**H**); ^{13}C NMR (500 MHz, $CDCl_3$) δ 29.8, 72.1, 79.1, 98.8, 128.5, 133.1, 137.8, 166.2; MS (ES) *m/z* = 286.0 (M + H^+, 100%), 308.6 (M + Na, 100%); LCMS t_R 5.1 min. HPLC t_R 12.8 min, purity 79% (254 nm, TSK gel Oligio DNA RP, solvent A: acetonitrile + 0.1% TFA, solvent B: milliQ water + 0.1% TFA, gradient 5 - 95% solvent A over 15 min. Flow rate 1 mL/min.)

3-Allyl-1,1-diphenylurea[3] (14)

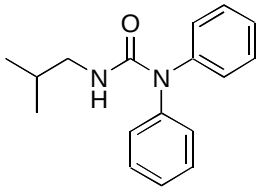


Hydroxylamine resin (1.00 g, 1.18 mmol) was suspended in a solution of diphenylcarbamyl chloride (0.84 g, 3.78 mmol) and DIPEA (0.67 mL, 3.78 mmol) in DCM (10 mL). The suspension was shaken at 25 ^{o}C for 16 h. The resin was washed with methanol, ethyl acetate and DCM (5 x 25 mL of each) and then dried under high vacuum for 16 h. ν_{max}/cm^{-1} (gel) 3373 (NH), 1697 (C=O). The resin was then suspended in a solution of DBU (0.94 mL, 6.3 mmol) and toluene (15 mL) and allyl bromide (1.06 mL, 12.2 mmol) was added. The suspension was shaken at 25 ^{o}C for 48 h. The resin was washed and dried as before. ν_{max}/cm^{-1} 1660 (C=O). The resin (0.91 g, 1.12 mmol) was pre-swollen with THF (2.2 mL). Samarium(II) iodide (0.1 M in THF, 22.5 mL, 2.24 mmol) was added and the reaction suspension was shaken at 25 ^{o}C for 3 h. The resin was filtered off and rinsed with DCM (5 x 10 mL) and the cleavage solution and washings collected. The solution was then evaporated under reduced pressure to give a dark yellow residue which was re-dissolved in a solution of diethyl ether (25 mL), 1 M HCl (20 mL) and 10% aq sodium thiosulfate (5 mL). The mixture was transferred to a separating funnel and shaken until it became colourless. The organic phase was collected and the aqueous phase was extraced with diethyl ether (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL) then dried over magnesium sulfate. The solid obtained after evaporation was dissolved in the minimum amount of DCM (*ca.* 0.3 - 0.5 mL) was filtered through a short pad of silica (*ca.* 3 cm in a 1.5 cm diameter column, eluting with 50% ethyl acetate / hexanes). The filtrate was collected and evaporated to afford the diphenylurea **14** (67 mg, 32%).

R_f 0.48 [ethyl acetate/hexanes (1:1)]. ν_{max}/cm^{-1} 3286 (NH), 1647 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) (2 rotamers in a ratio of 0.2 : 0.3 based on amide protons.) δ 3.87 (2 H, m, C**H**$_2$-N), 4.59 (0.6 H, s, N**H**), 5.05 - 5.20 (2 H, m, **H**$_2$C=C), 5.79 - 5.88 (1 H, m, H$_2$C=C**H**), 6.33 (0.4 H, s, N**H**), 7.13 - 7.36 (10 H, m, Ar); ^{13}C NMR (500 MHz, $CDCl_3$) (According to HMQC spectrum all carbons except the aromatic ones are seen as two rotamers) δ 42.9 (CH_2N), 54.4 (CH_2N), 115.3 (C=**C**H$_2$), 118.6 (C=**C**H$_2$), 125.7 (Ar), 125.9 (Ar), 126.1 (Ar), 127.2 (Ar), 129.1 (Ar), 131.5 (**C**H=CH$_2$), 134.9 (**C**H=CH$_2$), 142.5 (N-**C**-C$_5$H$_6$), 143.6 (N-**C**-C$_6$H$_5$), 155.7

(C=O), 161.9 (C=O); MS (ES) *m/z* = 253.2 (M + H^+, 100%); LCMS t_R 4.7 min. The HPLC trace has one peak that splits into two near the top, one for each rotamer. HPLC t_R 13.4 (rotamer 1), t_R 13.7 (rotamer 2), purity 94% (44.5% + 49.1%) (254 nm, TSK gel Oligio DNA RP, solvent A: acetonitrile + 0.1% TFA, solvent B: milliQ water + 0.1% TFA, gradient 5 - 95% solvent A over 15 min. Flow rate 1 mL/min.).

3-Isobutyl-1,1-diphenylurea (15)



Hydroxylamine resin (1.00 g, 1.18 mmol) was suspended in a solution of diphenylcarbamyl chloride (0.84 g, 3.78 mmol) and DIPEA (0.67 mL, 3.78 mmol) in DCM (10 mL). The suspension was shaken at 25 ^oC for 16 h. The resin was washed with methanol, ethyl acetate and DCM (5 x 25 mL of each) and then dried under high vacuum for 16 h. ν_{max}/cm^{-1} (gel) 3372 (NH), 1697 (C=O). The resin was suspended in a solution of DBU (0.94 mL, 6.3 mmol) and toluene (15 mL). Isobutyl bromide (1.33 mL, 12.2 mmol) was added and the suspension was shaken at 25 ^oC for 48 h. The resin was washed and dried as before. ν_{max}/cm^{-1} (gel) 1690 (C=O). The resin (0.78 g, 0.97 mmol) was pre-swollen with THF (1.9 mL) and samarium(II) iodide (0.1 M in THF, 19.3 mL, 1.93 mmol) was added. The reaction suspension was shaken at 25 ^oC for 3 h. The resin was filtered off and rinsed with DCM (5 x 10 mL) and the cleavage solution and washings collected. The solution was evaporated under reduced pressure to give a dark yellow residue which was re-dissolved in a solution of diethyl ether (25 mL), 1 M HCl (20 mL) and 10% aq sodium thiosulfate (5 mL). The mixture was transferred to a separating funnel and shaken until it became colourless. The organic layer was collected and the aqueous layer extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL) then dried over magnesium sulfate. The solid obtained after evaporation was dissolved in the minimum amount of DCM (*ca*. 0.3 - 0.5 mL) then filtered through a short pad of silica (*ca.* 3 cm in a 1.5 cm diameter column, eluting with 50% ethyl acetate/hexanes). The filtrate was collected and evaporated to afford the *diphenylurea* **15** (58 mg, 31%).

R_f 0.55 [vis. UV, ethyl acetate/hexanes (1:1)]. ν_{max}/cm^{-1} 3288 (NH), 1643 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$) (2 rotamers in a ratio of 0.2 : 0.3 assigned using HMQC as A and B where possible) δ 0.78 (3 H, d, *J* 7, C**H**$_3$), 0.86 (3 H, d, *J* 7, C**H**$_3$), 1.70 - 1.77 (0.8 H, m, CH_3-C**H**, A), 1.90 - 1.98 (1.2 H, m, CH_3-C**H**, B), 3.05 (0.4 H, m, C**H**$_2$-N, A), 3.11 (0.6 H, d, *J* 7, C**H**$_2$-N, B), 4.56 (0.6 H, s, N**H**, A), 6.52 (0.4 H, s, N**H**, B), 7.10 - 7.38 (10 H, m, Ar-**H**); ^{13}C NMR (500 MHz, $CDCl_3$) (According to the HMQC and APT spectra all carbon atoms except the aromatic carbons are seen as two rotamers and have been assigned as A and B where possible in relation to A and B in the proton spectrum) δ 19.7 (CH_3, A), 19.8 (CH_3, B), 25.9 (CH, B), 28.5 (CH, A), 47.9 (CH_2, A), 58.8 (CH_2, B), 125.4 (Ar), 125.6 (Ar), 125.8 (Ar), 127.1 (Ar). 129.0 (Ar), 142.6 (N-C-C_5H_6), 143.7 (N-C-C_5H_6,), 156.0 (C=O), 161.7 (C=O); MS (ES) *m/z* = 269.2 ($M + H^+$, 100%); LCMS t_R 5.0 min, purity 99% determined from peak area in LC trace (UV 215-330 nm, details as specified in general procedure).

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