Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Flow synthesis of organic azides and the multistep synthesis of imines and amines using a new monolithic triphenylphosphine reagent

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General Information

Unless specified, reagents were obtained from commercial sources and used without further purification. Divinylbenzene (80% technical grade) and 4-vinylbenzene chloride (90% purity) were obtained from Sigma-Aldrich®, and diphenyl(4-vinylphenyl)phosphine (90% purity) was obtained from Hokko Chemical Industry Co., Ltd. QuadraPure™ sulfonic acid resin (QP-SA) and QuadraPure™ dimethylamine resin (QP-DMA) were obtained from Johnson Matthey and used without further purification. 4-Nitroaniline was dissolved in MeCN and filtered through a plug of silica before use.

Solvents were obtained from Fisher Scientific, and H_2O was deionised before use. MeOH (analytical reagent grade) and MeCN (HPLC grade) were used as supplied, without further purification. EtOAc, PhMe, CH_2Cl_2 and petroleum ether (all technical grade) were distilled before use. PE 30–40 refers to petroleum distillate collected between 30 and 40 °C, and PE 40–60 refers to petroleum distillate collected between 40 and 60 °C. Dry THF refers to either analytical grade THF dried over calcium hydride and lithium aluminium hydride with triphenylmethane as an indicator and distilled under an atmosphere of dry argon, or unstabilised HPLC grade THF passed through activated alumnia under an atmosphere of dry argon immediately before use. Dry MeCN refers to HPLC grade MeCN dried over calcium hydride and distilled under an atmosphere of dry argon immediately before use.

Stock solutions of starting materials for aryl azide syntheses were made up in dry MeCN, though these reactions could be carried out with similar results using either HPLC grade MeCN (without further purification) or dry MeCN as the system solvent. Staudinger and aza-Wittig reactions were carried out with dry MeCN and/or THF.

Flow reactions and polymerisation of monolithic reagents were carried out using commercially available Vapourtec R2+/R4 flow systems, and automated flow sequences were controlled by Flow Commander™ software. Monolithic reagents were formed and used in glass Omnifit® columns, sealed for polymerisation with end seals from Vapourtec, and otherwise connected to the flow system with standard tubing connectors. Convective flow coils (CFC), glass heating jackets for columns and CFCs, and column end seals for monolith polymerisation are commercially available from Vapourtec.

Flash column chromatography was carried out on silica gel [Breckland 60 (0.040–0.063 mm)].

Melting points were measured with a SRS OptiMelt apparatus.

Elemental analysis was performed by the Microanalytical Laboratories at the Department of Chemistry, University of Cambridge. Limit: ±0.3%.

IR spectra were recorded neat on a Perkin-Elmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Letters in parentheses refer to the relative absorbency of the peak: w – weak (<40% of the most intense peak), m – medium (40–75% of the most intense peak), s – strong (>75% of the most intense peak).

^{1}H NMR spectra were recorded on a Bruker DPX-400 (400 MHz), a Bruker Avance 400 (400 MHz) QNP Ultrashield, a Bruker DRX-600 (600 MHz) or a Bruker Avance 700 (700 MHz) Ultrashield with TXI Cryoprobe spectrometer using the deuterated solvent as internal deuterium lock. Chemical shift data are given in units δ relative to tetramethylsilane (external standard), calibrated based on residual monoprotic solvent. The multiplicity of a signal is indicated as: br – broad, app – apparent, s – singlet, d – doublet, t – triplet, q – quartet, sept – septet, m – multiplet, dd – doublet of doublets, dt – doublet of triplets, etc. Coupling constants (J) are recorded to the nearest 1 Hz.

^{13}C NMR spectra were recorded on a Bruker DPX-400 (100 MHz), a Bruker Avance 400 (100 MHz) QNP Ultrashield, a Bruker Avance 500 (125 MHz) with Dual Cryoprobe, or a Bruker DRX-600 (150 MHz) spectrometer with broadband proton decoupling using the deuterated solvent as internal deuterium lock. Chemical shift data are given in units δ relative to tetramethylsilane (external standard), calibrated based on deuterated solvent. Coupling constants (*J*) are recorded to the nearest 1 Hz.

^{19}F NMR spectra were recorded on a Bruker Avance 400 (376 MHz) QNP Ultrashield spectrometer with broadband proton decoupling using the deuterated solvent as internal deuterium lock. Chemical shift data are given in units δ relative to $CFCl_3$ (external standard).

^{15}N NMR spectra were recorded on a Bruker Avance 500 (50 MHz) BroadBand spectrometer using the deuterated solvent as internal deuterium lock. Chemical shift data are given in units δ relative to liquid NH_3 (external standard).

Gas chromatography-mass spectrometry (GCMS) was performed on a Perkin Elmer Turbomass Autosystem XL with a Supelco SLB-5ms column (30 m × 0.25 mm × 0.25 μm film thickness) and positive electron ionisation (EI^+). Run parameters: injector temperature = 200 ºC, injection volume = 1 μL, split ratio 10:1, gas = He, flow rate = 1 mL/min, start temperature = 80 ºC (hold 5 min), ramp = 10 ºC/min, end temperature = 240 ºC (hold 1 min), total run time = 22 min. Retention times are reported as Rt. Masses are reported with assignment, followed by relative intensity, in parentheses.

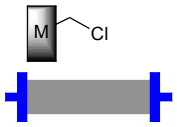
Liquid chromatography-mass spectrometry (LCMS) was performed on an Agilent HP 1100 series chromatograph (Mercury Luna 3μ C18 (2) column) attached to a Waters ZQ2000 mass spectrometer with ESCi ionisation source in ESI mode. Elution was carried out at a flow rate of 0.6 mL/min using a reverse phase gradient of MeCN–water containing 0.1% formic acid. Gradient = 0–1 min: hold MeCN 5%, 1–4 min: ramp MeCN 5–95%, 4–5 min: hold MeCN 95%, 5–7 min: ramp MeCN 95–5%, 7–8 min: hold MeCN 5%. Retention times are reported as Rt.

High resolution mass spectra (HRMS) were recorded on a Waters Micromass LCT Premier spectrometer using time of flight with positive electrospray ionisation (ESI^+), an ABI/MDS Sciex Q-STAR Pulsar with ESI^+, or a Bruker BioApex II 4.7e FTICR utilising either ESI^+ or a positive electron ionisation (EI^+) source equipped with a direct insertion probe. The mass reported is that containing the most abundant isotopes (^{35}Cl and ^{79}Br). Limit: ±5 ppm.

X-Ray crystal structure determination was performed by Dr John E. Davies at the Department of Chemistry, University of Cambridge using a Nonius Kappa CCD detector.

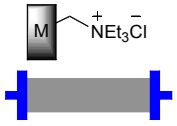
***Safety Warning*:** While flow processing does address many of the safety concerns associated with azide synthesis, these reactions should still be carried out with caution, and with the awareness that starting materials and product mixtures may contain hazardous components.
Sodium azide is unstable, toxic and absorbed through the skin. Trimethylsilyl azide is more thermally stable, but is still toxic, volatile, latex-permeable and absorbed by the skin. Furthermore, both of these azide sources may be hydrolised to hydrazoic acid, which is volatile, highly toxic and extremely explosive. Use of these azide sources (including the azide exchange monolith) with CH_2Cl_2 or $CHCl_3$ should be avoided, due to the potential formation of explosive $CH_2(N_3)_2$ or $CH(N_3)_3$. Alkyl and aryl azide products may also be explosive and/or toxic.

Monolithic Reagents



Merrifield-type monolith[1]

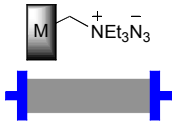
A stock solution of divinylbenzene (5.2 mL, 36.5 mmol), 4-vinylbenzene chloride (7.8 mL, 55.3 mmol), 1-dodecanol (13.0 mL, 63.5 mmol) and AIBN (130 mg, 0.8 mmol) was prepared. A 15 mm i.d. × 10 cm length glass column was filled to 7 cm height with this stock solution, and both ends of the column were sealed using column plugs from Vapourtec. The Vapourtec R4 convection heater was used to heat the column at 80 ºC for 20 h, resulting in a rigid white monolith. The monolith was allowed to cool to room temperature, and the column end seals were replaced with standard Omnifit® tubing connectors. In order to remove the porogen and any residual non-polymeric material, the monolith was then heated to 60 ºC and washed with THF at 1.0 mL/min for 2 h using the Vapourtec R2+/R4 flow system. Pressure drop (THF, 1.0 mL/min, 60 ºC) = 0.1 bar; Elemental analysis found C 78.7, H 6.8, Cl 12.5% (Loading = 3.5 mmol Cl per g monolith).



Quaternary ammonium chloride ion-exchange monolith[1]

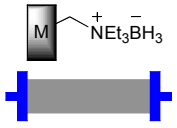
The Merrifield-type monolith was heated to 60 ºC, and a 100 mL stock solution of triethylamine (25 mL) in PhMe (75 mL) was recycled through the monolith at 0.2 mL/min for 48 h. The monolith was then washed with CH_2Cl_2 at 1.0 mL/min for 30 min, during which the system pressure steadily increased to 12 bar. Subsequent washing with MeOH (1.0 mL/min for 30 min) allowed the system pressure to return to 0.1 bar. Pressure drop (MeOH, 1.0 mL/min, 60 ºC) = 0.1 bar; Elemental analysis found C 74.4, H 8.4, N 3.2% (Loading = 2.3 mmol $R_4\mathbf{N}^+Cl^-$ per g monolith).

Finally, the monolith was washed with H_2O (1.0 mL/min, 30 min) before being subjected to further ion-exchange functionalisation.



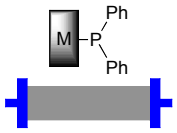
Azide exchange monolith[1]

A stock solution of sodium azide (2.5 g, 38.5 mmol) in H_2O (40 mL) was passed through the quaternary ammonium chloride ion-exchange monolith at 0.25 mL/min (room temperature). The column was then washed sequentially with H_2O, H_2O–MeCN (1:1) and MeCN, each at 1.0 mL/min for 1 h. Pressure drop (MeCN, 1.0 mL/min, RT) = 0 bar; Elemental analysis found C 77.2, H 6.5, N 10.8% (Loading = 1.9 mmol $R_4\mathbf{N}^+\mathbf{N_3}^-$ per g monolith); Dry weight = 7 g.



Borohydride exchange monolith

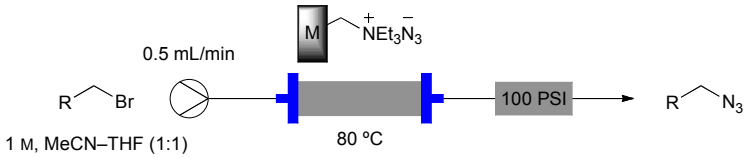
A 10 mL injection loop was filled with a solution of $NaBH_4$ (100 mg/mL) in H_2O. This solution was pumped (0.25 mL/min) through the quaternary ammonium chloride ion-exchange monolith at room temperature over 40 min, during which the system pressure rose to 3.3 bar, then dropped gradually to 1.7 bar. This procedure was repeated with another 10 mL of $NaBH_4$ solution, then the monolith was washed with H_2O (75 mL, 1.0 mL/min, system pressure = 4.5 bar). Finally, the monolith was washed sequentially with 30 mL each of MeOH–H_2O (1:1), MeOH–H_2O (3:1) and MeOH at 1.0 mL/min. Pressure drop (MeOH, 1.0 mL/min, RT) = 2.5 bar.



Triphenylphosphine monolith

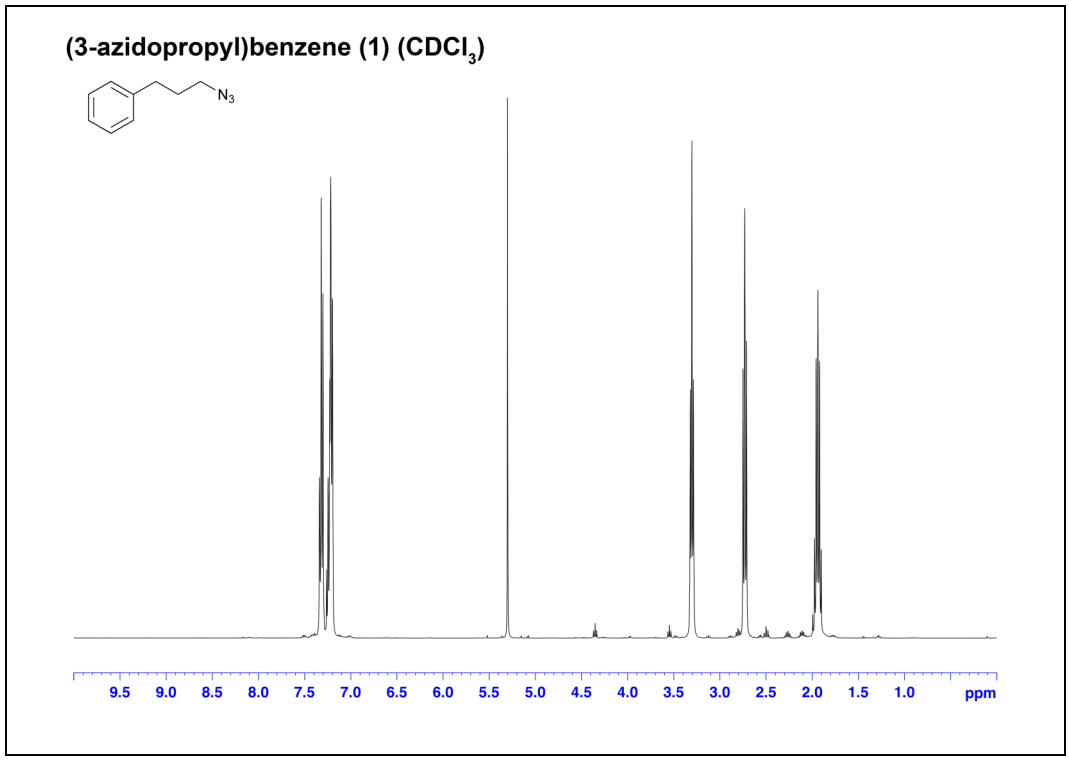
A stock solution was prepared by dissolving diphenyl(4-vinylphenyl)phosphine (1.76 g, 6.1 mmol) in 1-dodecanol (2.85 mL, 2.37 g, 12.7 mmol) with gentle heating (>50 ºC), then adding divinylbenzene (1.51 mL, 1.38 g, 10.6 mmol), and 4,4'-azo*bis*(4-cyanovaleric acid) (40 mg, 0.14 mmol). A 10 mm i.d. × 10 cm length glass column was filled to 7 cm height with this stock solution, and both ends of the column were sealed with plugs (Vapourtec). The column was heated at 90 ºC for 20 h using the Vapourtec R4 convection heater, resulting in a rigid white monolith. Following polymerisation, the monolith was allowed to cool to room temperature, and the end seals were exchanged for standard tubing connectors. In order to remove the porogen and any residual non-polymeric material, the monolith was then heated to 60 ºC and washed with THF at 1.0 mL/min for 2 h using the Vapourtec R4/R2+ flow system. Average pressure drop (THF, 1.0 mL/min, 60 ºC) = 2–4 bar; Elemental analysis found C 82.1, H 6.5, P 5.2% (Loading = 1.7 mmol P per g monolith); Dry weight = 3 g.

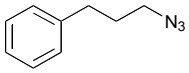
Alkyl Azides



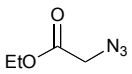
Flow synthesis of alkyl azides:
A solution of alkyl bromide (1 M in a 1:1 mixture of MeCN–THF) was pumped at 0.5 mL/min through an azide-exchange monolith heated at 80 ºC, followed by a 100 psi backpressure regulator. Washing with MeCN–THF (1:1) was continued until the output stream ran clear. Alkyl azide products were isolated by evaporation of solvent.

A representative spectrum is shown below: (3-azidopropyl)benzene (1) was isolated following only evaporation of solvent.



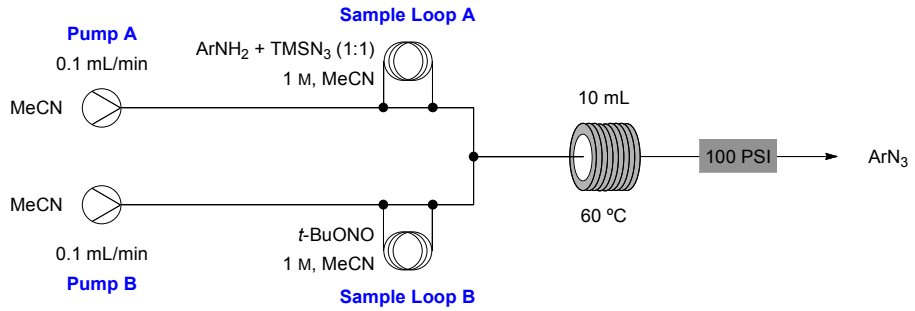


(3-azidopropyl)benzene[2] (1)
6 mmol scale, 99% yield (159 mg) as a clear oil. IR (neat) ν_{max}/cm^{-1} 2940 (w), 2091 (s), 1497 (w), 1454 (m), 1256 (m), 1030 (w), 911 (w), 744 (m), 699 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.32 (2H, dd, J = 7 and 7 Hz), 7.25–7.19 (3H, m), 3.30 (2H, t, J = 7 Hz), 2.73 (2H, t, J = 7 Hz), 1.94 (2H, tt, J = 7 and 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 141.3 (C), 128.9 (2 × CH), 128.9 (2 × CH), 126.6 (CH), 51.1 (CH_2), 33.2 (CH_2), 30.9 (CH_2).



ethyl azidoacetate[3] (2)
6 mmol scale, 97% yield (125 mg) as a clear oil. IR (neat) ν_{max}/cm^{-1} 2986 (w), 2105 (s), 1740 (s), 1372 (w), 1285 (m), 1193 (s), 1025 (m), 948 (w), 856 (w), 732 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 4.14 (2H, q, J = 7 Hz), 3.76 (2H, s), 1.20 (3H, t, J = 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 168.6 (C), 62.1 (CH_2), 50.6 (CH_2), 14.4 (CH_3).

Aryl Azides (Table 1)

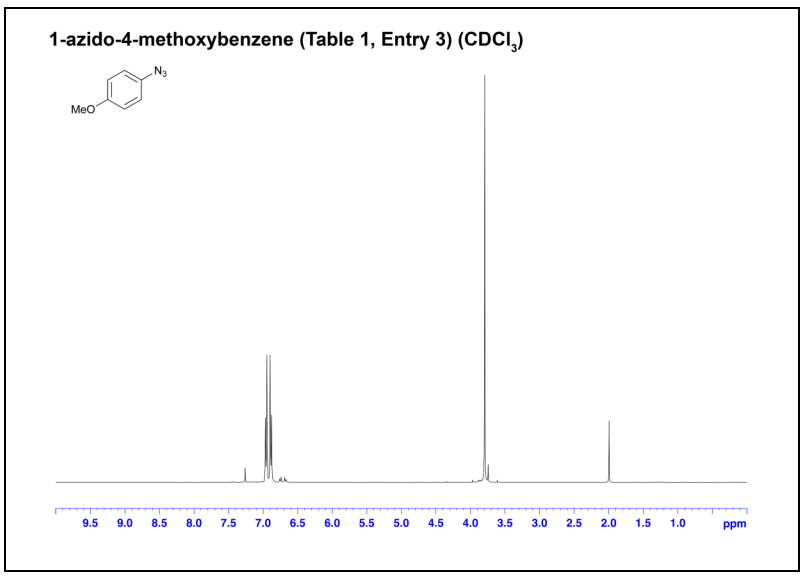


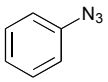
Flow synthesis of aryl azides:
Sample Loop A (1 mL, 1 mmol scale) was filled with a stock solution of aniline starting material and trimethylsilyl azide (1:1, 1 M in MeCN) and Sample Loop B (1 mL, 1 mmol scale) was filled with a stock solution of *tert*-butyl nitrite (1 M in MeCN). The two sample loops were simultaneously switched into line and the starting material solutions were pumped through the system at 0.1 mL/min each, driven by Pumps A and B with a constant stream of MeCN. The starting materials mixed in a T-piece and the reaction solution (at a combined flow rate of 0.2 mL/min) passed through a 10 mL CFC heated at 60 ºC, then exited the flow system through a 100 psi backpressure regulator.

In order to determine the overall conversion to the desired azide product during the flow reaction, the output stream was collected in a flask cooled to –78 ºC, where the crude product solution was frozen solid until all the material was collected. When all of the product had been collected, this output solution was melted rapidly by stirring in a room temperature water bath, then an aliquot was taken for immediate analysis by ^{1}H NMR. (Control experiments indicated that this temperature quench/analysis protocol was sufficient to prevent any significant further conversion to the desired product in the collection flask before analysis.) Conversions reported are based on the ratio of azide product to starting aniline by ^{1}H NMR analysis of the crude (non-evaporated) aliquot.

Many of these aryl azide products are volatile, as well as potentially toxic and/or explosive. Therefore azide products previously characterised in the literature were not isolated, but the identity of the product confirmed by GCMS, ^{1}H and ^{13}C NMR. Novel or previously uncharacterized azides were isolated as described in the individual procedures below for full characterization.

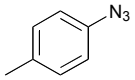
A representative spectrum is shown below: the crude reaction output containing 1-azido-4-methoxybenzene (Table 1, Entry 3) was subjected to ^{1}H NMR analysis following only evaporation of solvent.





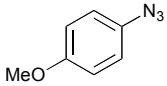
azidobenzene[4] (Table 1, Entry 1)

1 mmol scale, 94% conversion. IR (thin film from $CDCl_3$) ν_{max}/cm^{-1} 2127 (m), 2095 (m), 1594 (w), 1493 (m), 1455 (w), 1343 (w), 1295 (m), 1282 (w), 1175 (w), 1130 (w), 1076 (w), 1026 (w), 688 (m), 670 (w); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.36 (2H, dd, J = 8 and 8 Hz), 7.14 (1H, t, J = 8 Hz), 7.04 (2H, d, J = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 140.2 (C), 129.9 (2 × CH), 125.0 (CH), 119.2 (2 × CH); GCMS Rt 5.33 min, *m/z* (EI^+) 119 ($M^{+\bullet}$, 58%), 91 ($[M–N_2]^{+\bullet}$, 93), 64 ($[M–N_2–HCN]^{+\bullet}$, 100); HRMS *m/z* (EI^+) found 119.0480 ($M^{+\bullet}$, $C_6H_5N_3$ requires 119.0478).



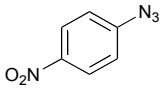
1-azido-4-methylbenzene[5] (Table 1, Entry 2)

1 mmol scale, 94% conversion. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.17 (2H, d, J = 8Hz), 6.95 (2H, d, J = 8 Hz), 2.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 137.3 (C), 134.7 (C), 130.4 (2 × CH), 119.0 (2 × CH), 20.9 (CH_3); GCMS Rt 7.90 min, *m/z* (EI^+) 133 ($M^{+\bullet}$, 47%), 105 ($[M–N_2]^{+\bullet}$, 100), 78 ($[M–N_2–HCN]^{+\bullet}$, 94).



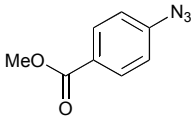
1-azido-4-methoxybenzene[4] (Table 1, Entry 3)

1 mmol scale, 95% conversion. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 6.96 (2H, d, J = 9 Hz), 6.89 (2H, d, J = 9 Hz), 3.79 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 157.2 (C), 132.5 (C), 120.1 (2 × CH), 115.3 (2 × CH), 55.7 (CH_3); GCMS Rt 10.85 min, *m/z* (EI^+) 149 ($M^{+\bullet}$, 18%), 121 ($[M–N_2]^{+\bullet}$, 100), 106 ($[M–N_2–(CH_3)^\bullet]^+$, 43).



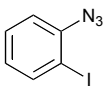
1-azido-4-nitrobenzene[4] (Table 1, Entry 4)

1 mmol scale, 93% conversion. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 8.25 (2H, d, J = 9 Hz), 7.14 (2H, d, J = 9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 147.0 (C), 144.7 (C), 125.7 (2 × CH), 119.5 (2 × CH); GCMS Rt 13.69 min, *m/z* (EI^+) 164 ($M^{+\bullet}$, 17%), 136 ($[M–N_2]^{+\bullet}$, 34), 90 ($[M–N_2–(NO_2)^\bullet]^+$, 49), 63 ($[M–N_2–(NO_2)^\bullet–HCN]^+$, 100).



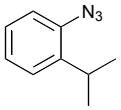
methyl 4-azidobenzoate[2] (Table 1, Entry 5)

1 mmol scale, 86% conversion. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.96 (2H, d, J = 9 Hz), 7.00 (2H, d, J = 9 Hz), 3.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 166.2 (C), 144.7 (C), 131.3 (2 × CH), 126.7 (C), 118.8 (2 × CH), 52.0 (CH_3); GCMS Rt 13.61 min, *m/z* (EI^+) 177 ($M^{+\bullet}$, 29%), 149 ($[M–N_2]^{+\bullet}$, 100), 117 ($[M–N_2–CH_3OH]^{+\bullet}$, 63), 90 ($[M–N_2–CH_3OH–HCN]^{+\bullet}$, 77).



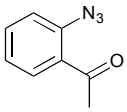
1-azido-2-iodobenzene[6] (Table 1, Entry 6)

1 mmol scale, 86% conversion. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.78 (1H, dd, J = 8 and 1 Hz), 7.38 (1H, ddd, J = 8, 8 and 1 Hz), 7.13 (1H, dd, J = 8 and 1 Hz), 6.86 (1H, ddd, J = 8, 8 and 1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 141.8 (C), 140.1 (CH), 129.6 (CH), 126.4 (CH), 118.5 (CH), 87.9 (C); GCMS Rt 13.28 min, *m/z* (EI^+) 245 ($M^{+\bullet}$, 30%), 217 ($[M–N_2]^{+\bullet}$, 81), 90 ($[M–N_2–(I)^\bullet]^+$, 100), 63 ($[M–N_2–(I)^\bullet–HCN]^+$, 88).



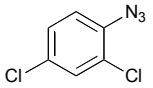
1-azido-2-(propan-2-yl)benzene[7] (Table 1, Entry 7)

1 mmol scale, 93% conversion. After determination of conversion, the product solution was concentrated *in vacuo* to a brown oil, which was purified by column chromatography (PE 30–40) to afford 72% yield (116 mg) as a yellow oil. IR (neat) ν_{max}/cm^{-1} 2964 (w), 2872 (w), 2121 (s), 2092 (s), 1581 (w), 1488 (m), 1446 (w), 1383 (w), 1363 (w), 1349 (w), 1290 (s), 1159 (w), 1141 (w), 1110 (w), 1077 (w), 1036 (w), 935 (w), 893 (w), 853 (w), 814 (w), 747 (s), 656 (m); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 7.32–7.27 (2H, m), 7.23 (1H, d, J = 7 Hz), 7.16 (1H, dd, J = 7 and 7 Hz), 3.14 (1H, sept, J = 7 Hz), 1.16 (6H, d, J = 7 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 139.1 (C), 136.4 (C), 127.3 (CH), 126.5 (CH), 125.2 (CH), 118.3 (CH), 27.4 (CH), 22.7 (2 × CH_3); GCMS Rt 10.44 min, *m/z* (EI^+) 161 ($M^{+\bullet}$, 40%), 133 ($[M–N_2]^{+\bullet}$, 29), 118 ($[M–N_2–(CH_3)^\bullet]^+$, 100), 91 ($[M–N_2–(CH_3)^\bullet–HCN]^+$, 94); HRMS *m/z* ($EI^+$) found 161.0947 ($M^{+\bullet}$, $C_9H_{11}N_3$ requires 161.0947).



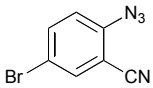
1-(2-azidophenyl)ethanone[8] (Table 1, Entry 8)

1 mmol scale, 89% conversion. After determination of conversion, the product solution was concentrated *in vacuo* to a brown oil, which was purified by column chromatography (EtOAc–PE 40–60 (1:9)) to afford 75% yield (120 mg) as a yellow oil. IR (neat) ν_{max}/cm^{-1} 2119 (s), 2090 (s), 1677 (s), 1594 (m), 1573 (m), 1479 (m), 1444 (m), 1415 (w), 1358 (m), 1291 (s), 1276 (s), 1240 (s), 1166 (w), 1148 (w), 1110 (w), 1068 (w), 1043 (w), 1019 (w), 965 (w), 862 (w), 820 (w), 755 (s), 654 (m); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.71 (1H, dd, J = 8 and 1 Hz), 7.52 (1H, ddd, J = 8, 8 and 1 Hz), 7.24 (1H, d, J = 8 Hz), 7.20 (1H, dd, J = 8 and 8 Hz), 2.64 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 199.3 (C), 138.9 (C), 133.2 (CH), 131.3 (C), 130.6 (CH), 124.9 (CH), 119.3 (CH), 31.3 (CH_3); GCMS Rt 12.52 min, *m/z* (EI^+) 133 ($[M–N_2]^{+\bullet}$, 100%); HRMS *m/z* (EI^+) found 133.0518 ($[M–N_2]^{+\bullet}$, $C_8H_7N_1O$ requires 133.0522).



1-azido-2,4-dichlorobenzene[9] (Table 1, Entry 9)

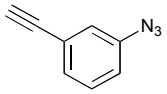
1 mmol scale, 91% conversion. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.40 (1H, d, J = 2 Hz), 7.27 (1H, dd, J = 9 and 2 Hz), 7.10 (1H, d, J = 9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 136.2 (C), 130.7 (CH), 130.6 (C), 128.2 (CH), 126.0 (C), 120.6 (CH); GCMS Rt 12.46 min, *m/z* (EI^+) 191/189/187 ($M^{+\bullet}$, 1/8/12%), 163/161/159 ($[M–N_2]^{+\bullet}$, 8/36/51%), 126/124 ($[M–N_2–(Cl)^\bullet]^+$, 53/100%).



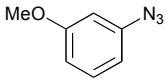
2-azido-5-bromobenzonitrile (Table 1, Entry 10)

1 mmol scale, 87% conversion. After determination of conversion, the product solution was concentrated *in vacuo* to a brown solid, which was purified by column chromatography (EtOAc–PE 40–60 (1:9)) to afford 88% yield (196 mg) as a light yellow solid. mp 103–105 ºC (from EtOAc–PE 40–60); Elemental analysis found C 37.7, H 1.3, N 25.0, Br 35.6% ($C_7H_3N_4Br$ requires C 37.7, H 1.4, N 25.1, Br 35.8%); IR (neat) ν_{max}/cm^{-1} 3097 (w), 3065 (w), 2454 (w), 2416 (w), 2233 (w), 2124 (s), 1929 (w), 1771 (w), 1667 (w), 1587 (w), 1563 (w), 1483 (s), 1465 (m), 1388 (m), 1303 (s), 1269 (m), 1203 (m), 1185 (m), 1158 (m), 1113 (m), 1078 (w), 966 (w), 888 (m), 851 (m), 831 (s), 790 (m), 770 (m), 715 (m), 664 (m); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 8.12 (1H, d, J = 2 Hz), 7.92 (1H, dd, J = 9 and 2 Hz), 7.50 (1H, d, J = 9 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 142.6 (C), 137.4 (CH), 135.8 (CH), 122.0 (CH), 116.5 (C), 114.4 (C), 104.3 (C); GCMS Rt 15.65 min, *m/z* (EI^+) 224/222

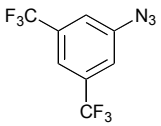
($M^{+\bullet}$, 5/5%), 196/194 ($[M–N_2]^{+\bullet}$, 36/21), 115 ($[M–N_2–(Br)^{\bullet}]^+$, 100), 88 ($[M–N_2–(Br)^{\bullet}–HCN]^+$, 44); HRMS *m/z* ($EI^+$) found 221.9540 ($M^{+\bullet}$, $C_8H_3N_4Br$ requires 221.9536); X-ray crystallography: File reference CCDC 791581; Formula: $C_7H_3Br_1N_4$; Unit cell parameters: a 7.4355(1) b 8.5948(2) c 13.7214(3) α 88.715(1) β 89.784(1) γ 68.818(1) space group P-1.



1-azido-3-ethynylbenzene[4] (Table 1, Entry 11)
1 mmol scale, 92% conversion. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.32–7.25 (2H, m), 7.15 (1H, m), 7.02 (1H, ddd, *J* = 8, 2 and 2 Hz), 3.11 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 140.5 (C), 129.9 (CH), 128.8 (CH), 123.9 (C), 122.6 (CH), 119.8 (CH), 82.7 (C), 78.3 (CH); GCMS Rt 9.67 min, *m/z* (EI^+) 143 ($M^{+\bullet}$, 29%), 115 ($[M–N_2]^{+\bullet}$, 100), 88 ($[M–N_2–HCN]^{+\bullet}$, 75), 62 ($[M–N_2–HCN–C_2H_2]^{+\bullet}$, 61).

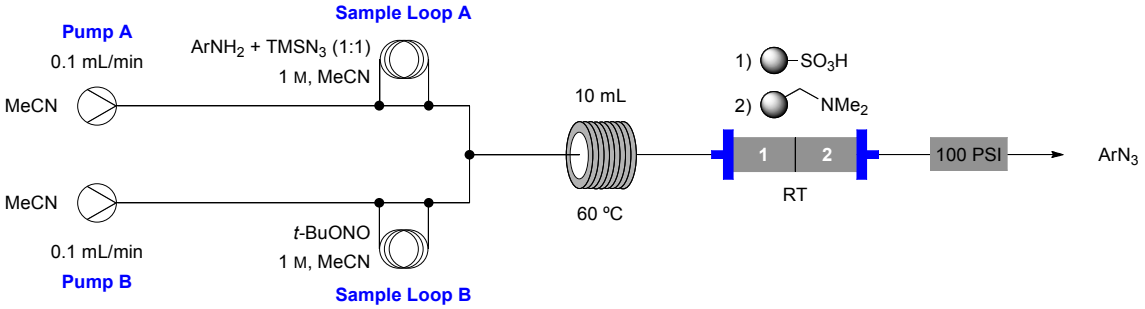


1-azido-3-methoxybenzene[4] (Table 1, Entry 12)
1 mmol scale, 91% conversion. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.26 (1H, dd, *J* = 8 and 8 Hz), 6.70 (1H, ddd, *J* = 8, 2 and 1 Hz), 6.65 (1H, ddd, *J* = 8, 2 and 1 Hz), 6.56 (1H, dd, *J* = 2 and 2 Hz), 3.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 161.0 (C), 141.5 (C), 130.6 (CH), 111.5 (CH), 110.9 (CH), 105.1 (CH), 55.5 (CH_3); GCMS Rt 10.57 min, *m/z* (EI^+) 149 ($M^{+\bullet}$, 24%), 121 ($[M–N_2]^{+\bullet}$, 56), 106 ($[M–N_2–(CH_3)^{\bullet}]^+$, 100).



1-azido-3,5-bis(trifluoromethyl)benzene[10] (Table 1, Entry 13)
1 mmol scale, 89% conversion. ^1H NMR (400 MHz, C_6D_6): δ_H = 7.35 (1H, s), 6.82 (2H, s); ^{13}C NMR (100 MHz, C_6D_6): δ_C = 142.5 (C), 133.1 (2 × C, q, *J* = 34 Hz), 123.2 (2 × CF_3, q, *J* = 273 Hz), 119.2 (2 × CH, m), 118.2 (CH, m); ^{19}F NMR (376 MHz, C_6D_6): δ_F = –63.2; GCMS Rt 3.71 min, *m/z* (EI^+) 255 ($M^{+\bullet}$, 10%), 227 ($[M–N_2]^{+\bullet}$, 66); HRMS *m/z* (EI^+) found 255.0219 ($M^{+\bullet}$, $C_8H_3F_6N_3$ requires 255.0226).

Mechanistic Investigation

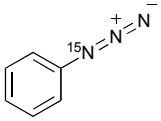


Flow synthesis of labelled azides:
Labelled azides were prepared using the same general procedure as described above, modified only by the inclusion of an in-line purification sequence (described in detail in the following publication[11]) to remove any unreacted starting materials.

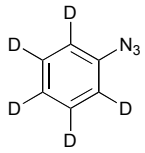
Sample Loop A (1 mL, 1 mmol scale) was filled with a stock solution of aniline starting material and trimethylsilyl azide (1:1, 1 M in MeCN) and Sample Loop B (1 mL, 1 mmol scale) was filled with a stock solution of *tert*-butyl nitrite (1 M in MeCN). The two sample loops were simultaneously switched into line and the starting material solutions pumped through the system at 0.1 mL/min each, driven by Pumps A and B with a constant stream of MeCN. The starting materials mixed in a T-piece and the reaction solution (at a combined flow rate of 0.2 mL/min) passed through a 10 mL CFC heated at 60 ºC. Upon exiting the CFC, the flow stream entered a 10 mm i.d. glass column packed with QP-SA (1.3 g) followed by QP-DMA (1.3 g), then exited the flow system through a 100 psi backpressure regulator.

The output stream was collected in a flask cooled to –78 ºC, where the crude product solution was frozen solid until all the material was collected. When all of the product had been collected, this output solution was melted rapidly by stirring in a room temperature water bath, then an aliquot was taken for immediate analysis by ^{1}H NMR and GCMS. The output solution was then concentrated for further analysis.

All labelled azide syntheses were performed using this procedure on 1 mmol scale. As described in the text, carrying out this reaction with (^{15}N)aniline starting material provided (1-^{15}N)azidobenzene as a single product. Correspondingly, d_5-azidobenzene was prepared from d_5-aniline by the same method for comparison purposes. Finally, this azide synthesis procedure was repeated with Sample Loop A filled with a mixed solution of d_5-aniline (0.5 mmol), (^{15}N)aniline (0.5 mmol), and trimethylsilyl azide (1 mmol) in MeCN (1 M). (1-^{15}N)azidobenzene and d_5-azidobenzene were identified as the only products.



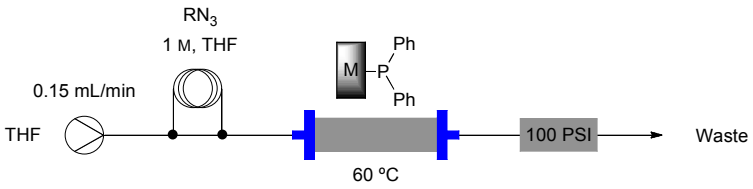
(1-^{15}N)azidobenzene[12]
IR (thin film from $CDCl_3$) ν_{max}/cm^{-1} 2114 (m), 1594 (w), 1492 (m), 1271 (w), 1255 (w), 1122 (w), 1076 (w), 688 (m), 668 (w); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.29 (2H, dd, J = 8 and 8 Hz), 7.08 (1H, t, J = 8 Hz), 6.97 (2H, d, J = 8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 139.7 (C), 129.6 (2 × CH, d, J = 2 Hz), 124.8 (CH), 118.8 (2 × CH, d, J = 5 Hz); ^{15}N NMR (50 MHz, $CDCl_3$): δ_N = 91.5; GCMS Rt 5.27 min, *m/z* (EI$^+$) 120 ($M^{+\bullet}$, 30%), 92 ($[M–N_2]^{+\bullet}$, 100), 64 ($[M–N_2–HC^{15}N]^{+\bullet}$, 63); HRMS *m/z* (EI$^+$) found 120.0452 ($M^{+\bullet}$, $C_6H_5N_2{}^{15}N$ requires 120.0448). HSQC experiments and comparison with literature IR and NMR data[12] confirmed the position of the labelled nitrogen as N-1.



d_5-azidobenzene[13]

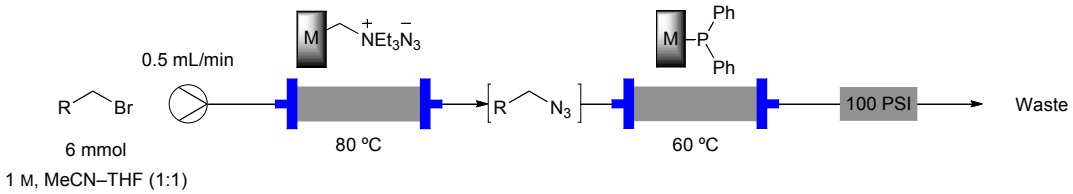
IR (thin film from $CDCl_3$) ν_{max}/cm^{-1} 2114 (m), 2098 (w), 1563 (w), 1374 (w), 1262 (w), 1099 (w), 819 (w); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 139.6 (C), 129.1 (2 × CH, t, J = 25 Hz), 124.2 (CH, t, J = 25 Hz), 118.4 (2 × CH, t, J = 25 Hz); GCMS Rt 5.11 min, *m/z* (EI^+) 124 ($M^{+\bullet}$, 36%), 96 ($[M–N_2]^{+\bullet}$, 100), 68 ($[M–N_2–DCN]^{+\bullet}$, 84); HRMS *m*/*z* (EI^+) found 124.0794 ($M^{+\bullet}$, $C_6D_5N_3$ requires 124.0792).

Staudinger aza-Wittig Reactions (Table 2)



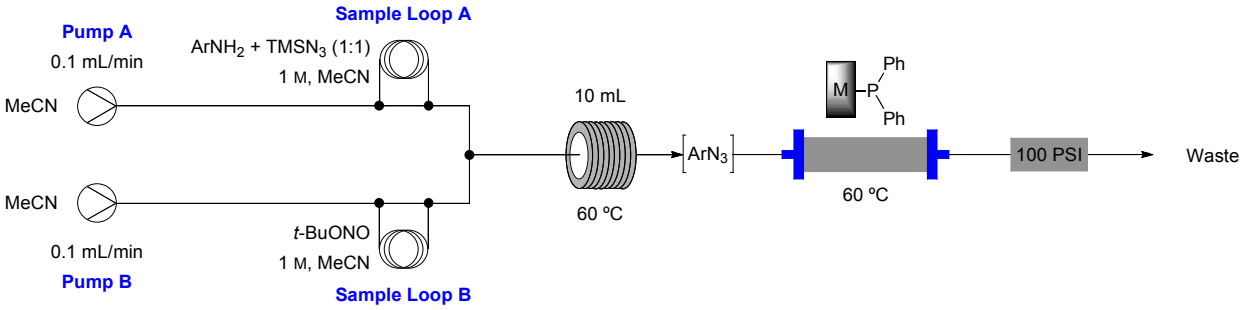
Staudinger reaction, Method A:

A 5 mL sample loop was filled with a solution of alkyl or aryl azide (1 M in THF). This solution was introduced to the flow system in a constant stream of THF at a flow rate of 0.15 mL/min. The azide solution was pumped through a triphenylphosphine monolith heated to 60 ºC followed by a 100 psi backpressure regulator. The output exiting the flow system was collected as toxic waste. The system was washed with MeCN until no further material was detected in the output, and the resulting iminophosphorane monolith could be used immediately for aza-Wittig reaction (after washing in the appropriate solvent) as described below or cooled to room temperature, then sealed and stored for later use.



Staudinger reaction, Method B:

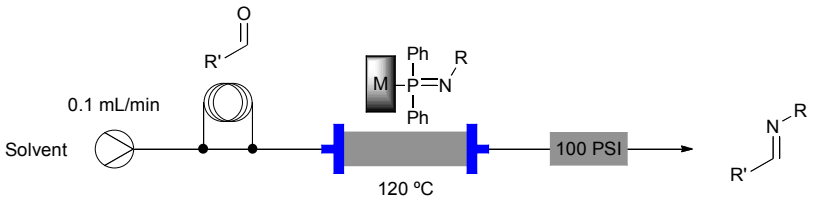
A solution of the starting alkyl bromide (6 mmol, 1 M in MeCN–THF (1:1)) was pumped at 0.2 mL/min through an azide-exchange monolith heated to 80 °C. The resulting alkyl azide intermediate then passed through a triphenylphosphine monolith heated to 60 ºC. The output stream exited the flow system through a 100 psi backpressure regulator and was collected as toxic waste. The system was washed with MeCN–THF (1:1) until no further material was detected in the output, and the resulting iminophosphorane monolith could be used immediately for aza-Wittig reaction (after washing in the appropriate solvent) as described below or cooled to room temperature, then sealed and stored for later use.



Staudinger reaction, Method C:

Sample Loop A (10 mL, 10 mmol scale) was filled with a stock solution of aniline starting material and trimethylsilyl azide (1:1, 1 M in MeCN) and Sample Loop B (10 mL, 10 mmol scale) was filled with a stock solution of *tert*-butyl nitrite (1 M in MeCN). The two sample loops were simultaneously switched into line and the starting material solutions pumped through the system at 0.1 mL/min each, driven by Pumps A and B with a constant stream of MeCN. The starting materials mixed in a T-piece and the reaction solution (at a combined flow rate of 0.2 mL/min) passed through a 10 mL CFC heated at 60 ºC, followed by a triphenylphosphine monolith heated at 60 ºC. The output stream then exited the flow system through a 100 psi backpressure regulator and was collected as toxic waste. The system was washed with MeCN (0.2 mL/min) until no further material was detected in the output, and the resulting iminophosphorane monolith could be used immediately for aza-Wittig reaction (after

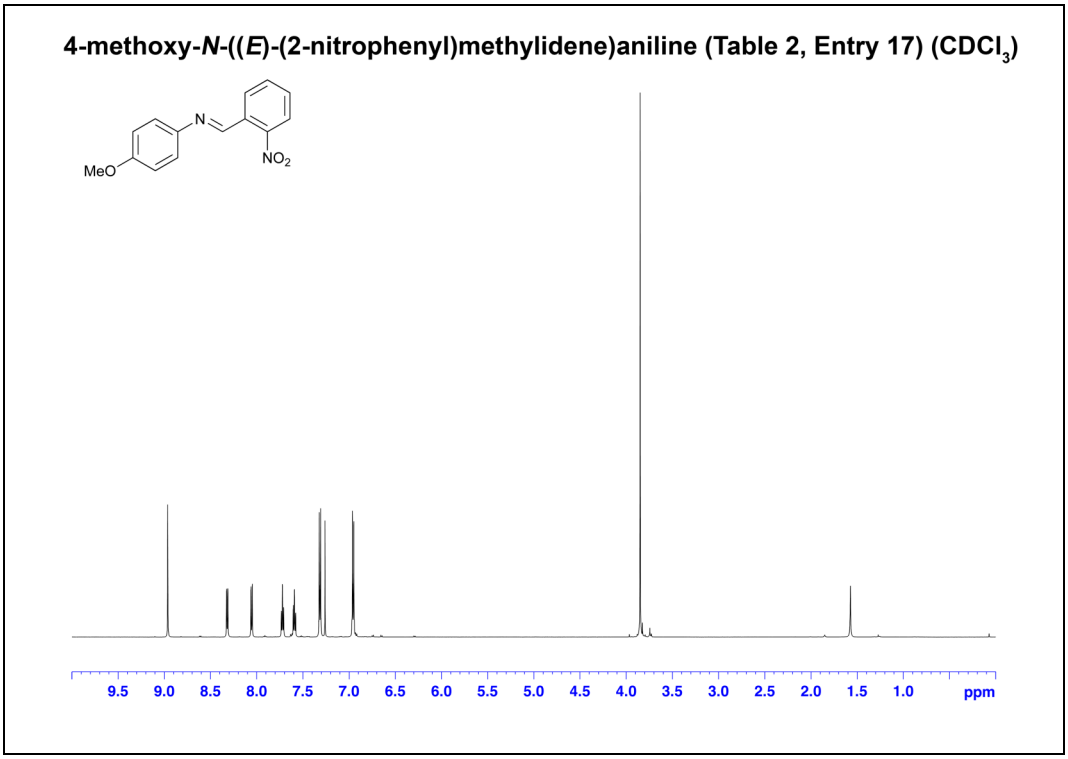
washing in the appropriate solvent) as described below or cooled to room temperature, then sealed and stored for later use.

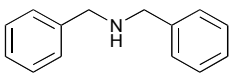


Aza-Wittig reaction:
A sample loop was filled with a solution of aldehyde or ketone starting material (0.1–1.0 M in THF or MeCN–THF 1:1, as specified for each example below). This solution was then pumped at 0.1 mL/min through an iminophosphorane monolith (prepared by Method A, B or C above) heated to 120°C, followed by a 100 psi backpressure regulator. Washing was continued until no further material was detected in the output. The iminophosphorane monolith could then be used for reaction with another aza-Wittig partner or cooled to room temperature, then sealed and stored for later use. As specified in the individual procedures below, reaction products were either directly isolated as the imines following only evaporation of solvent, or reduced to the corresponding amines.

For reduction, the reaction output was concentrated, and the imine intermediate was redissolved in a sufficient volume of MeOH, with MeCN added if necessary to obtain a homogeneous solution. This solution was cooled on an ice bath, then $NaBH_4$ (3 equivalents) was added portion-wise, and the resulting solution was allowed to warm to room temperature with stirring under Ar overnight. The reaction was then quenched with an equal volume of H_2O and concentrated to remove most of the organic solvents. The resulting aqueous mixture was then extracted with CH_2Cl_2, and the organic phase was treated with 3 equivalents of QP-SA and stirred for 30 min. The beads were washed with CH_2Cl_2 and MeOH to remove any impurities, then the desired product was released by washing with NH_3 in MeOH (2 M). Amine products were isolated following removal of solvent *in vacuo*.

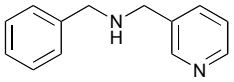
A representative spectrum is shown below: 4-methoxy-*N*-((*E*)-(2-nitrophenyl)methylidene)aniline (Table 2, Entry 17) was isolated from the flow aza-Wittig reaction following only evaporation of solvent.





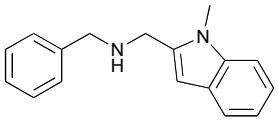
***N*-benzyl-1-phenylmethanamine[14] (Table 2, Entry 1)**

0.5 mmol scale (0.5 M in THF), 93% yield (92 mg, over 2 steps) as a clear oil. IR (neat) ν_{max}/cm^{-1} 3027 (m), 2811 (m), 1495 (s), 1452 (s), 1362 (m), 1107 (m), 1074 (m), 827 (m), 731 (s), 695 (s); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.40–7.35 (8H, m), 7.31–7.28 (2H, m), 3.85 (4H, s), 1.72 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 140.8 (2 × C), 128.8 (4 × CH), 128.6 (4 × CH), 127.4 (2 × CH), 53.6 (2 × CH_2); LCMS Rt 3.61 min, *m*/*z* (ESI^+) 198 ($[M+H]^+$); HRMS *m*/*z* (ESI^+) found 198.1284 ($[M+H]^+$, $C_{14}H_{16}N$ requires 198.1283).



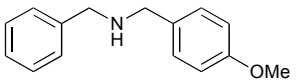
1-phenyl-*N*-(pyridin-3-ylmethyl)methanamine[15] (Table 2, Entry 2)

0.5 mmol scale (0.5 M in THF), 95% yield (94 mg, over 2 steps) as a yellow oil. IR (neat) ν_{max}/cm^{-1} 3271 (m), 3027 (m), 2826 (m), 1576 (m), 1495 (m), 1478 (m), 1453 (s), 1424 (s), 1362 (m), 1186 (m), 1103 (s), 1027 (s), 789 (m), 737 (s), 714 (s), 700 (s); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 8.58 (1H, s), 8.52–8.49 (1H, m), 7.70–7.67 (1H, m), 7.35–7.33 (4H, m), 7.28–2.22 (2H, m), 3.80 (4H, s), 1.89 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 150.2 (CH), 149.1 (C), 148.9 (CH), 140.4 (C), 136.2 (CH), 128.5 (2 × CH), 127.5 (2 × CH), 127.4 (CH), 123.8 (CH), 53.6 (CH_2), 50.9 (CH_2); LCMS Rt 0.24 min, *m*/*z* (ESI^+) 199 ($[M+H]^+$); HRMS *m*/*z* (ESI^+) found 199.1242 ($[M+H]^+$, $C_{13}H_{15}N_2$ requires199.1235).



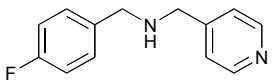
***N*-benzyl-1-(1-methyl-1*H*-indol-2-yl)methanamine[16] (Table 2, Entry 3)**

0.5 mmol scale (0.5 M in THF), 72% yield (90 mg, over 2 steps) as a yellow oil. IR (neat) ν_{max}/cm^{-1} 3026 (m), 2924 (m), 1610 (m), 1550 (m), 1495 (m), 1468 (s), 1453 (s), 1399 (m), 1360 (m), 1334 (m), 1316 (m), 1233 (m), 1140 (m), 1099 (s), 1028 (m), 1010 (m), 906 (m), 843 (m), 777 (s), 732 (s), 698 (s); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.65 (1H, d, *J* = 8 Hz), 7.44–7.42 (4H, m), 7.38–7.33 (2H, m), 7.27 (1H, ddd, *J* = 7, 7 and 1 Hz), 7.17 (1H, ddd, *J* = 7, 7 and 1 Hz), 6.48 (1H, s), 4.00 (2H, s), 3.93 (2H, s), 3.82 (3H, s), 1.75 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 140.7 (C), 138.9 (C), 138.4 (C), 128.9 (2 × CH), 128.7 (2 × CH), 128.0 (C), 127.5 (CH), 121.7 (CH), 120.7 (CH), 119.8 (CH), 109.4 (CH), 101.4 (CH), 53.7 (CH_2), 42.7 (CH_2), 30.2 (CH_3); HRMS *m*/*z* (ESI^+) found 251.1557 ($[M+H]^+$, $C_{17}H_{19}N_2$ requires 251.1548).



***N*-benzyl-1-(4-methoxyphenyl)methanamine[14] (Table 2, Entry 4)**

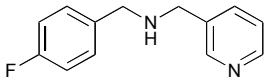
0.5 mmol scale (0.5 M in THF), 81% yield (92 mg, over 2 steps) as a yellow oil. IR (neat) ν_{max}/cm^{-1} 3062 (w), 3027 (w), 2908 (m), 2834 (m), 1611 (m), 1585 (m), 1510 (s), 1495 (m), 1453 (s), 1361 (m), 1301 (m), 1243 (s), 1173 (s), 1104 (m), 1033 (s), 809 (s), 734 (s), 697 (s); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.40–7.38 (4H, m), 7.34–7.30 (3H, m), 6.93 (2H, d, *J* = 8 Hz), 3.86 (2H, s), 3.85 (3H, s), 3.81 (2H, s), 1.81 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 159.1 (C), 140.9 (C), 133.0 (C), 129.8 (2 × CH), 128.9 (2 × CH), 128.6 (2 × CH), 127.3 (CH), 114.3 (2 × CH), 55.7 (CH_3), 53.6 (CH_2), 53.1 (CH_2); HRMS *m*/*z* (ESI^+) found 228.1391 ($[M+H]^+$, $C_{15}H_{18}NO$ requires 228.1388).



1-(4-fluorophenyl)-*N*-(pyridin-4-ylmethyl)methanamine (Table 2, Entry 5)

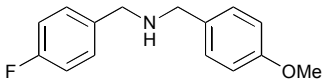
0.5 mmol scale (0.5 M in THF), 81% yield (87 mg, over 2 steps) as a yellow oil. IR (neat) ν_{max}/cm^{-1} 3292 (w), 3031 (m), 2824 (m), 1601 (s), 1560 (m), 1508 (s), 1451 (m), 1414 (s), 1363 (m), 1218 (s),

1156 (m), 1118 (m), 1094 (m), 1065 (m), 1015 (m), 994 (m), 822 (s), 795 (s), 762 (m), 729 (m), 668 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.46 (2H, d, J = 6 Hz), 7.23–7.19 (4H, m), 6.93 (2H, dd, J = 8 and 8 Hz), 3.72 (2H, s), 3.68 (2H, s), 1.87 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 162.4 (C, d, J = 244 Hz), 150.3 (2 × CH), 149.7 (C), 136.0 (C), 130.1 (2 × CH, d, J = 8 Hz), 123.4 (2 × CH), 115.7 (2 × CH, d, J = 21 Hz), 52.9 (CH_2), 52.2 (CH_2); LCMS Rt 0.30 min, m/z (ESI$^+$) 217 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 217.1140 ([M+H]$^+$, $C_{13}H_{14}N_2F$ requires 217.1141).



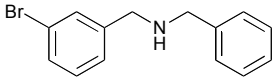
1-(4-fluorophenyl)-*N*-(pyridin-3-ylmethyl)methanamine (Table 2, Entry 6)

0.5 mmol scale (0.5 M in THF), 73% yield (79 mg, over 2 steps) as a yellow oil. IR (neat) ν_{max}/cm^{-1} 3277 (m), 3036 (w), 2916 (m), 2831 (m), 1648 (m), 1602 (m), 1577 (m), 1508 (s), 1472 (m), 1455 (m), 1424 (s), 1362 (m), 1219 (s), 1156 (m), 1094 (m), 1028 (m), 1016 (m), 984 (m), 822 (s), 789 (s), 763 (m), 712 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.51–8.49 (1H, m), 8.45–8.42 (1H, m), 7.63–7.61 (1H, m), 7.27–7.14 (3H, m), 6.94 (2H, dd, J = 9 and 9 Hz), 3.73 (2H, s), 3.70 (2H, s), 1.75 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 162.4 (C, d, J = 243 Hz), 150.1 (CH), 149.1 (CH), 135.9 (CH), 135.3 (C), 135.2 (C), 130.1 (2 × CH, d, J = 8 Hz), 123.9 (CH), 115.7 (2 × CH, d, J = 21 Hz), 52.9 (CH_2), 50.8 (CH_2); LCMS Rt 0.48 min m/z (ESI$^+$) 217 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 217.1150 ([M+H]$^+$, $C_{13}H_{14}N_2F$ requires 217.1141).



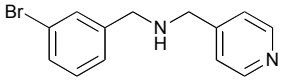
1-(4-fluorophenyl)-*N*-(4-methoxybenzyl)methanamine (Table 2, Entry 7)

0.5 mmol scale (0.5 M in THF), 78% yield (95 mg, over 2 steps) as a yellow oil. IR (neat) ν_{max}/cm^{-1} 3000 (w), 2908 (m), 2835 (m), 1611 (s), 1585 (m), 1509 (s), 1455 (m), 1360 (m), 1301 (m), 1246 (s), 1220 (s), 1175 (m), 1155 (m), 1105 (m), 1035 (m), 825 (s), 699 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.32 (2H, dd, J = 8 and 6 Hz), 7.28 (2H, d, J = 8 Hz), 7.03 (2H, dd, J = 8 and 8 Hz), 6.90 (2H, d, J = 8 Hz), 3.83 (3H, s), 3.78 (2H, s), 3.76 (2H, s), 1.83 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 162.3 (C, d, J = 243 Hz), 159.1 (C), 136.5 (C), 132.7 (C), 130.1 (2 × CH, d, J = 8 Hz), 129.8 (2 × CH), 115.6 (2 × CH, d, J = 21 Hz), 114.3 (2 × CH), 55.7 (CH_3), 53.0 (CH_2), 52.7 (CH_2); HRMS m/z (ESI$^+$) found 246.1293 ([M+H]$^+$, $C_{15}H_{17}NOF$ requires 246.1294).



***N*-benzyl-1-(3-bromophenyl)methanamine[17] (Table 2, Entry 8)**

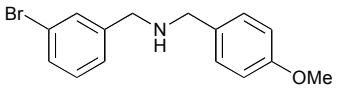
0.5 mmol scale (0.5 M in THF), 98% yield (134 mg, over 2 steps) as a yellow oil. IR (neat) ν_{max}/cm^{-1} 3062 (m), 3026 (m), 2826 (m), 1595 (m), 1568 (s), 1495 (m), 1472 (m), 1453 (s), 1426 (s), 1359 (m), 1195 (m), 1112 (m), 1068 (s), 1028 (m), 996 (m), 882 (m), 775 (s), 734 (s), 668 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.55 (1H, s), 7.42 (1H, d, J = 8 Hz), 7.38 (2H, s), 7.36 (2H, s), 7.32–7.28 (2H, m), 7.24–7.22 (1H, m), 3.83 (2H, s), 3.81 (2H, s), 1.75 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 143.4 (C), 140.5 (C), 131.6 (CH), 130.5 (CH), 130.4 (CH), 128.9 (CH), 128.6 (2 × CH), 127.5 (2 × CH), 127.1 (CH), 123.0 (C), 53.6 (CH_2), 53.0 (CH_2); LCMS Rt 3.40 min, m/z (ESI$^+$) 276 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 276.0398 ([M+H]$^+$, $C_{14}H_{15}NBr$ requires 276.0388).



1-(3-bromophenyl)-*N*-(pyridin-4-ylmethyl)methanamine (Table 2, Entry 9)

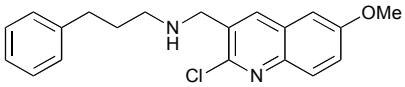
0.5 mmol scale (0.5 M in THF), 80% yield (110 mg, over 2 steps) as a yellow oil. IR (neat) ν_{max}/cm^{-1} 3264 (m), 3028 (m), 2919 (m), 2832 (m), 1600 (s), 1569 (s), 1473 (s), 1414 (s), 1363 (m), 1196 (m), 1120 (m), 1069 (s), 995 (m), 797 (s), 693 (m), 668 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.47 (2H, d, J = 6 Hz), 7.43 (1H, s), 7.31 (1H, d, J = 8 Hz), 7.20–7.17 (3H, m), 7.11 (1H, dd, J = 8 and 8 Hz), 3.72 (2H, s), 3.69 (2H, s), 1.84 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 150.5 (2 × CH), 149.5 (C),

142.7 (C), 131.5 (CH), 130.7 (CH), 130.5 (CH), 127.1 (CH), 123.4 (2 × CH), 123.1 (C), 53.0 (CH_2), 52.2 (CH_2); LCMS Rt 0.48 min, *m*/*z* (ESI^+) 277 ($[M+H]^+$); HRMS *m*/*z* (ESI^+) found 277.0347 ($[M+H]^+$, $C_{13}H_{14}N_2Br$ requires 277.0340).



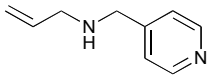
1-(3-bromophenyl)-*N*-(4-methoxybenzyl)methanamine (Table 2, Entry 10)

0.5 mmol scale (0.5 M in THF), 80% yield (123 mg, over 2 steps) as a clear oil. IR (neat) ν_{max}/cm^{-1} 3336 (w), 3001 (w), 2906 (w), 2833 (m), 1611 (m), 1595 (m), 1585 (m), 1568 (m), 1510 (s), 1463 (s), 1441 (s), 1426 (m), 1301 (m), 1243 (s), 1173 (s), 1106 (m), 1068 (m), 1033 (s), 997 (m), 814 (s), 772 (s), 685 (s), 667 (s); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.54 (1H, s), 7.40 (1H, d, *J* = 8 Hz), 7.29–7.26 (3H, m), 7.21 (1H, dd, *J* = 8 and 8 Hz), 6.90 (2H, d, *J* = 9 Hz), 3.83 (3H, s), 3.79 (2H, s), 3.76 (2H, s), 1.73 (1H, s, br); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 159.2 (C), 143.2 (C), 132.6 (C), 131.6 (2 × CH), 130.4 (CH), 130.4 (CH), 129.8 (CH), 127.1 (CH), 123.0 (C), 114.3 (2 × CH), 55.7 (CH_3), 53.0 (CH_2), 52.8 (CH_2); HRMS *m*/*z* (ESI^+) found 306.0499 ($[M+H]^+$, $C_{15}H_{17}NOBr$ requires 306.0494).



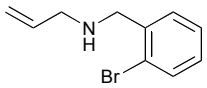
***N*-((2-chloro-6-methoxyquinolin-3-yl)methyl)-3-phenylpropan-1-amine (Table 2, Entry 11)**

1 mmol scale (1 M in MeCN–THF 1:1), 91% yield (308 mg) of the imine. Reduced to the corresponding amine (white solid) *via* the standard procedure above for characterisation. IR (neat) ν_{max}/cm^{-1} 2934 (w), 1623 (m), 1598 (w), 1496 (s), 1453 (m), 1349 (m), 1331 (m), 1226 (s), 1162 (m), 1118 (m), 1036 (s), 909 (m), 828 (s), 730 (s), 698 (s); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 8.01 (1H, s), 7.88 (1H, d, *J* = 9 Hz), 7.33 (1H, d, *J* = 9 Hz), 7.27 (2H, dd, *J* = 8 and 8 Hz), 7.21–7.16 (3H, m), 7.03 (1H, s), 3.96 (2H, s), 3.90 (3H, s), 2.71 (4H, m), 1.90 (2H, tt, *J* = 7 and 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 158.6 (C), 148.3 (C), 143.1 (C), 142.4 (C), 136.6 (CH), 132.5 (C), 130.0 (CH), 128.9 (C), 128.8 (2 × CH), 128.8 (2 × CH), 126.2 (CH), 122.9 (CH), 105.5 (CH), 56.0 (CH_3), 51.3 (CH_2), 49.2 (CH_2), 34.0 (CH_2), 32.1 (CH_2); LCMS Rt 3.60 min, *m*/*z* (ESI^+) 341 ($[M+H]^+$); HRMS *m*/*z* (ESI^+) found 341.1406 ($[M+H]^+$, $C_{20}H_{22}N_2OCl$ requires 341.1415).



***N*-(pyridin-4-ylmethyl)prop-2-en-1-amine (Table 2, Entry 12)**

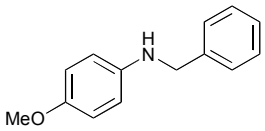
1 mmol scale (1 M in MeCN–THF 1:1), quantitative yield (146 mg) of the imine. Reduced to the corresponding amine (brown oil) *via* the standard procedure above for characterisation. IR (neat) ν_{max}/cm^{-1} 3002 (w), 2837 (w), 1666 (w), 1443 (w), 1400 (m), 1388 (w), 1251 (w), 1180 (w), 1122 (w), 1002 (w), 972 (m), 765 (s), 705 (s); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 8.50 (2H, d, *J* = 6 Hz), 7.23 (2H, d, *J* = 6 Hz), 5.87 (1H, m), 5.17 (1H, dd, *J* = 17 and 2 Hz), 5.09 (1H, dd, *J* = 10 and 2 Hz), 3.77 (2H, s), 3.23 (2H, d, *J* = 6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 149.8 (2 × CH), 149.3 (C), 136.3 (CH), 122.9 (2 × CH), 116.2 (CH_2), 56.8 (CH_2), 51.6 (CH_2); LCMS Rt 0.59 min, *m*/*z* (ESI^+) 149 ($[M+H]^+$).



***N*-(2-bromobenzyl)prop-2-en-1-amine[18] (Table 2, Entry 13)**

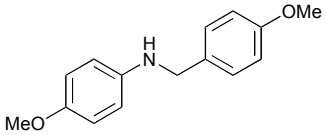
1 mmol scale (1 M in MeCN–THF 1:1), 88% yield (197 mg) of the imine. Reduced to the corresponding amine (brown oil) *via* the standard procedure above for characterisation. IR (neat) ν_{max}/cm^{-1} 3068 (w), 2924 (w), 2824 (w), 1643 (w), 1466 (m), 1438 (m), 1356 (w), 1197 (w), 1121 (w), 1102 (w), 1024 (m), 993 (w), 918 (m), 823 (w), 746 (s), 656 (w); ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.53 (1H, d, *J* = 8 Hz), 7.39 (1H, d, *J* = 8 Hz), 7.27 (1H, m), 7.11 (1H, dd, *J* = 8 and 8 Hz), 5.94 (1H, ddt, *J* = 17, 10 and 6 Hz), 5.21 (1H, dd, *J* = 17 and 2 Hz), 5.12 (1H, dd, *J* = 10 and 2 Hz), 3.86 (2H, s),

3.27 (2H, d, J = 6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 139.2 (C), 136.7 (CH), 132.8 (CH), 130.4 (CH), 128.6 (CH), 127.4 (CH), 124.0 (C), 116.2 (CH_2), 53.1 (CH_2), 51.6 (CH_2); LCMS Rt 3.54 min, m/z (ESI$^+$) 226 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 226.0241 ([M+H]$^+$, $C_{10}H_{13}NBr$ requires 226.0231).



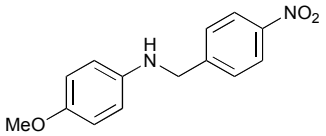
_N_-benzyl-4-methoxyaniline[19] (Table 2, Entry 14)

0.5 mmol scale (0.5 M in THF), 97% yield (103 mg, over 2 steps) as a brown solid. IR (neat) ν_{max}/cm^{-1} 3375 (m), 2998 (m), 2949 (m), 2833 (m), 1509 (s), 1455 (s), 1440 (m), 1406 (m), 1354 (m), 1294 (s), 1265 (m), 1235 (s), 1180 (s), 1119 (m), 1076 (m), 1035 (s), 941 (m), 821 (s), 767 (s), 740 (s), 704 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.46–7.40 (3H, m), 7.37–7.34 (2H, m), 6.87 (2H, d, J = 9 Hz), 6.68 (2H, d, J = 9 Hz), 4.35 (2H, s), 3.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 152.7 (C), 143.0 (C), 140.3 (C), 129.1 (2 × CH), 128.0 (2 × CH), 127.7 (CH), 115.4 (2 × CH), 114.6 (2 × CH), 56.3 (CH_3), 49.7 (CH_2); LCMS Rt 3.48 min, m/z (ESI$^+$) 214 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 214.1240 ([M+H]$^+$, $C_{14}H_{16}NO$ requires 214.1232).



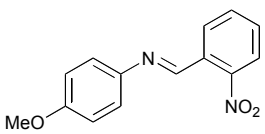
4-methoxy-_N_-(4-methoxybenzyl)aniline (Table 2, Entry 15)

0.5 mmol scale (0.5 M in THF), 95% yield (115 mg, over 2 steps) as a yellow solid. IR (neat) ν_{max}/cm^{-1} 3374 (m), 3015 (m), 2952 (m), 2908 (m), 2837 (m), 1610 (s), 1582 (m), 1509 (s), 1460 (s), 1439 (s), 1406 (s), 1360 (m), 1292 (s), 1247 (s), 1178 (s), 1113 (m), 1080 (m), 1029 (s), 940 (m), 876 (m), 820 (s), 775 (m), 732 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.32 (2H, d, J = 8 Hz), 6.91 (2H, d, J = 9 Hz), 6.81 (2H, d, J = 8 Hz), 6.64 (2H, d, J = 9 Hz), 4.24 (2H, s), 3.83 (3H, s), 3.77 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 159.3 (C), 152.6 (C), 143.0 (C), 132.1 (C), 129.3 (2 × CH), 115.4 (2 × CH), 114.6 (2 × CH), 114.4 (2 × CH), 56.3 (CH_3), 55.7 (CH_3), 49.2 (CH_2); HRMS m/z (ESI$^+$) found 244.1344 ([M+H]$^+$, $C_{15}H_{18}NO_2$ requires 244.1338).



4-methoxy-_N_-(4-nitrobenzyl)aniline[20] (Table 2, Entry 16)

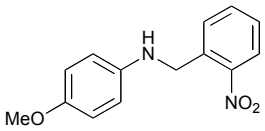
0.5 mmol scale (0.5 M in THF), 62% yield (80 mg, over 2 steps) as an orange solid. IR (neat) ν_{max}/cm^{-1} 3378 (m), 3075 (m), 2936 (m), 2838 (m), 1602 (m), 1509 (s), 1459 (s), 1410 (m), 1340 (s), 1317 (m), 1285 (m), 1232 (s), 1172 (m), 1122 (m), 1084 (m), 1035 (s), 1007 (m), 991 (m), 966 (m), 876 (m), 847 (s), 819 (s), 739 (s), 690 (m), 655 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.19 (2H, d, J = 9 Hz), 7.55 (2H, d, J = 9 Hz), 6.78 (2H, d, J = 9 Hz), 6.56 (2H, d, J = 9 Hz), 4.44 (2H, s), 3.76 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 153.0 (C) 148.3 (C), 147.6 (C), 141.9 (C), 128.2 (2 × CH), 124.3 (2 × CH), 115.4 (2 × CH), 114.6 (2 × CH), 55.2 (CH_3), 48.9 (CH_2); HRMS m/z (ESI$^+$) found 259.1076 ([M+H]$^+$, $C_{14}H_{15}N_2O_3$ requires 259.1083).



4-methoxy-_N_-((_E_)-(2-nitrophenyl)methylidene)aniline[21] (Table 2, Entry 17)

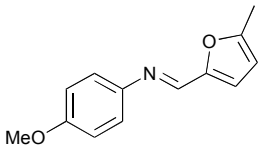
0.5 mmol scale (0.5 M in THF), quantitative yield (128 mg) as a brown solid. Elemental analysis found P 0, C 65.9, H 4.8, N 10.7% ($C_{14}H_{12}N_2O_3$ requires C 65.6, H 4.7, N 10.9%); IR (neat) ν_{max}/cm^{-1} 2967 (w), 2839 (w), 1979 (w), 1674 (w), 1618 (w), 1605 (w), 1590 (w), 1568 (w), 1521 (s), 1502 (s), 1457

(m), 1439 (m), 1376 (m), 1350 (m), 1300 (m), 1273 (m), 1248 (s), 1190 (m), 1163 (m), 1110 (m), 1079 (w), 1023 (s), 964 (m), 954 (m), 925 (w), 891 (w), 861 (m), 823 (s), 806 (m), 778 (m), 767 (s), 739 (s), 719 (s), 700 (m), 677 (m); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.96 (1H, s), 8.32 (1H, dd, J = 8 and 1 Hz), 8.06 (1H, dd, J = 8 and 1 Hz), 7.72 (1H, dd, J = 8 and 8 Hz), 7.59 (1H, ddd, J = 8, 8 and 1 Hz), 7.32 (2H, d, J = 9 Hz), 6.96 (2H, d, J = 9 Hz), 3.85 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 159.3 (C), 153.4 (CH), 149.4 (C), 144.1 (C), 133.6 (CH), 131.5 (C), 131.0 (CH), 129.7 (CH), 124.7 (CH), 122.9 (2 × CH), 114.7 (2 × CH), 55.7 (CH_3); HRMS m/z (ESI$^+$) found 257.0936 ([M+H]$^+$, $C_{14}H_{13}N_2O_3$ requires 257.0926).



4-methoxy-*N*-(2-nitrobenzyl)aniline[22] (Table 2, Entry 18)

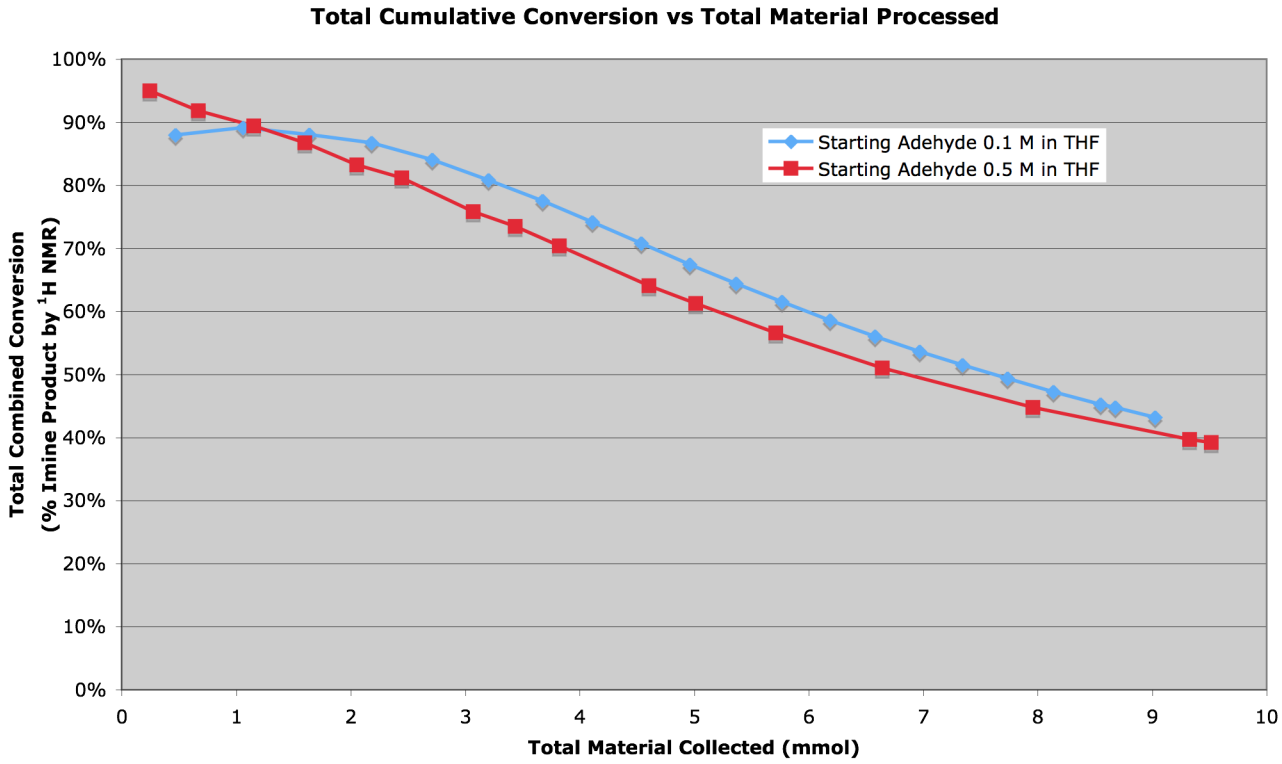
0.5 mmol scale (0.5 M in THF), 94% yield (122 mg, over 2 steps) as a red oil. IR (neat) ν_{max}/cm^{-1} 3420 (m), 2932 (m), 2832 (m), 1609 (m), 1509 (s), 1464 (m), 1443 (m), 1340 (s), 1301 (m), 1233 (s), 1179 (m), 1118 (m), 1067 (m), 1034 (s), 909 (m), 857 (m), 819 (s), 787 (s), 731 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.06 (1H, dd, J = 8 and 1 Hz), 7.69 (1H, d, J = 8 Hz), 7.57 (1H, ddd, J = 8, 8 and 1 Hz), 7.43 (1H, ddd, J = 8, 8 and 1 Hz), 6.78 (2H, d, J = 9 Hz), 6.55 (2H, d, J = 9 Hz), 4.67 (2H, s), 3.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 153.0 (C), 148.7 (C), 142.0 (C), 136.3 (C), 134.0 (CH), 130.6 (CH), 128.4 (CH), 125.7 (CH), 115.4 (2 × CH), 114.7 (2 × CH), 56.2 (CH_3), 47.1 (CH_2); LCMS Rt 4.27 min, m/z (ESI$^+$) 259 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 259.1094 ([M+H]$^+$, $C_{14}H_{15}N_2O_3$ requires 259.1083).

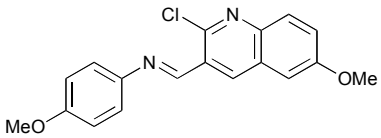


4-methoxy-*N*-((*E*)-(5-methylfuran-2-yl)methylidene)aniline[23] (Table 2, Entry 19)

3 mmol scale (0.5 M in THF). The reaction stream was recycled through the monolith (120 ºC) for 4.5 h at 0.1 mL/min, then the monolith was washed with THF at 0.5 mL/min until no further material was recovered. The reaction proceeded with 95% conversion, as determined by the ratio of imine product to aldehyde starting material by ^{1}H NMR. Recrystallisation from EtOAc–PE 40–60 provided a sample of pure 4-methoxy-*N*-((*E*)-(5-methylfuran-2-yl)methylidene)aniline as a brown crystalline solid. mp 66–68 ºC (from EtOAc–PE 40–60) (lit.,[23] 67 ºC from EtOH); Elemental analysis found C 72.5, H 6.1, N 6.5% ($C_{13}H_{13}NO_2$ requires C 72.5, H 6.1, N 6.5%); IR (neat) ν_{max}/cm^{-1} 2966 (w), 2837 (w), 1979 (w), 1624 (m), 1596 (w), 1578 (m), 1531 (w), 1499 (s), 1466 (m), 1454 (w), 1438 (m), 1369 (m), 1289 (m), 1239 (s), 1187 (m), 1178 (m), 1164 (m), 1109 (m), 1022 (s), 1011 (m), 966 (m), 948 (m), 867 (m), 833 (s), 794 (s), 733 (m), 721 (m), 660 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.17 (1H, s), 7.22 (2H, d, J = 9 Hz), 6.89 (2H, d, J = 9 Hz), 6.78 (1H, d, J = 3 Hz), 6.14 (1H, d, J = 3 Hz), 3.80 (3H, s), 2.41 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 158.3 (C), 156.5 (C), 151.0 (C), 145.8 (CH), 144.8 (C), 122.3 (2 × CH), 118.0 (CH), 114.4 (2 × CH), 108.8 (CH), 55.5 (CH_3), 14.1 (CH_3); HRMS m/z (ESI$^+$) found 216.1021 ([M+H]$^+$, $C_{13}H_{14}NO_2$ requires 216.1024); X-ray crystallography: File reference CCDC 791578; Formula: $C_{13}H_{13}N_1O_2$; Unit cell parameters: a 8.8940(3) b 8.4670(3) c 15.2509(6) α 90.00 β 90.00 γ 90.00 space group Pca21.

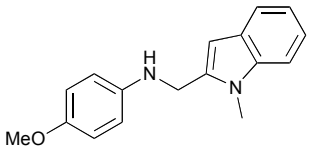
This reaction was also carried out in a single pass fashion under the standard aza-Wittig reaction conditions (120 ºC, 0.1 mL/min), starting with an excess (10 mmol) of 5-methylfuraldehyde (0.1 M or 0.5 M in THF). The reaction output was collected in fractions and examined by ^{1}H NMR. The total cumulative conversion of the reaction output (ratio of imine product to aldehyde starting material as determined by ^{1}H NMR) as a function of total material processed is plotted below.





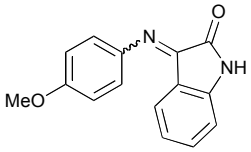
***N*-((*E*)-(2-chloro-6-methoxyquinolin-3-yl)methylidene)-4-methoxyaniline (Table 2, Entry 20)**

0.5 mmol scale (0.1 M in THF), quantitative yield (163 mg) as a yellow solid. Elemental analysis found P 0, C 66.1, H 4.7, N 8.6, Cl 11.1% ($C_{18}H_{15}ClN_2O_2$ requires C 66.2, H 4.6, N 8.6, Cl 10.9%); IR (neat) ν_{max}/cm^{-1} 2945 (w), 2832 (w), 1617 (w), 1595 (w), 1578 (w), 1499 (m), 1452 (w), 1411 (w), 1381 (w), 1339 (w), 1298 (m), 1252 (m), 1234 (s), 1179 (w), 1162 (m), 1128 (w), 1109 (w), 1037 (m), 1021 (m), 958 (w), 917 (w), 876 (w), 823 (s), 786 (w), 759 (m), 732 (m), 687 (w); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.97 (1H, s), 8.90 (1H, s), 7.92 (1H, d, J = 9 Hz), 7.41 (1H, dd, J = 9 and 3 Hz), 7.34 (2H, d, J = 9 Hz), 7.17 (1H, d, J = 3 Hz), 6.98 (2H, d, J = 9 Hz), 3.93 (3H, s), 3.85 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C = 159.2 (C), 158.6 (C), 153.6 (CH), 147.9 (C), 144.7 (C), 144.3 (C), 136.0 (CH), 129.9 (CH), 128.5 (C), 128.0 (C), 124.7 (CH), 122.8 (2 × CH), 114.7 (2 × CH), 106.0 (CH), 55.8 (CH_3), 55.7 (CH_3); HRMS m/z (ESI$^+$) found 349.0728 ($[M+Na]^+$, $C_{18}H_{15}ClN_2O_2Na$ requires 349.0719).



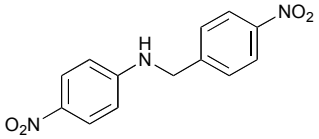
4-methoxy-*N*-((1-methyl-1*H*-indol-2-yl)methyl)aniline (Table 2, Entry 21)

0.5 mmol scale (0.5 M in THF), 65% yield (86 mg, over 2 steps) as a brown solid. IR (neat) ν_{max}/cm^{-1} 3371 (m), 2932 (m), 2831 (m), 1612 (m), 1509 (s), 1467 (s), 1409 (m), 1314 (m), 1232 (s), 1179 (m), 1115 (m), 1076 (m), 1035 (s), 910 (m), 819 (s), 782 (m), 749 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.63 (1H, d, J = 8 Hz), 7.35 (1H, d, J = 8 Hz), 7.27 (1H, dd, J = 8 and 8 Hz), 7.16 (1H, dd, J = 8 and 8 Hz), 6.87 (2H, d, J = 9 Hz), 6.72 (2H, d, J = 9 Hz), 6.51 (1H, s), 4.40 (2H, s), 3.80 (3H, s), 3.78 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 152.7 (C), 142.2 (C), 138.0 (C), 137.6 (C), 127.5 (C), 121.6 (CH), 120.5 (CH), 119.6 (CH), 115.1 (2 × CH), 114.5 (2 × CH), 109.1 (CH), 101.2 (CH), 55.9 (CH_3), 42.1 (CH_2), 29.9 (CH_3); HRMS m/z (ESI$^+$) found 267.1487 ($[M+H]^+$, $C_{17}H_{19}N_2O$ requires 267.1497).



3-((4-methoxyphenyl)imino)-1,3-dihydro-*2H*-indol-2-one[24] (Table 2, Entry 22)

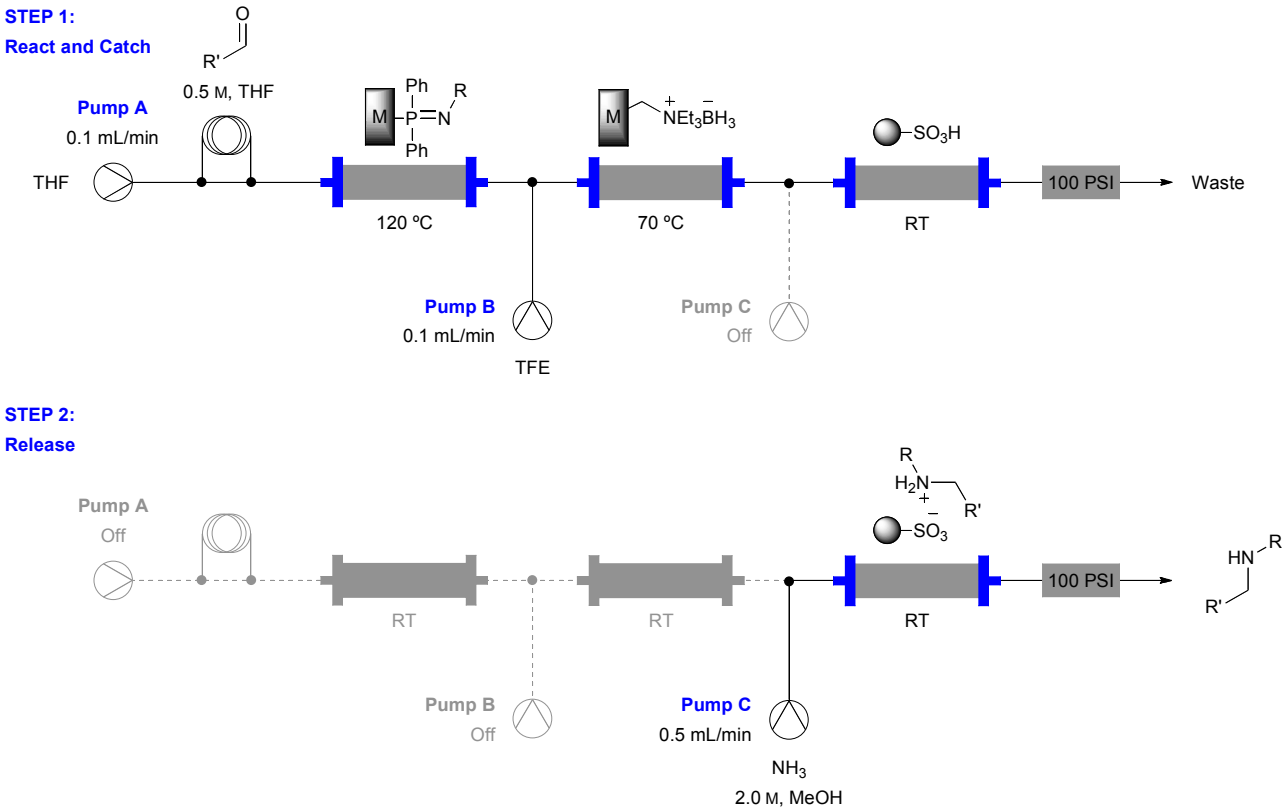
0.5 mmol scale (0.25 M in THF), quantitative yield (126 mg) as an orange solid. Mixture of isomers; 8:2 of *E*:*Z* by ^{1}H NMR analysis and comparison with previously reported[24] NMR data. ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 10.94 (1H^{E}, s, br), 10.83 (1H^{Z}, s, br), 7.55 (1H^{Z}, d, J = 8 Hz), 7.42 (1H^{Z}, ddd, J = 8, 8 and 1 Hz), 7.33 (1H^{E}, dd, J = 8 and 8 Hz), 7.18 (2H^{Z}, d, J = 9 Hz), 7.03 (2H^{E} + 1H^{Z}, d, J = 9 Hz), 6.98 (2H^{E}, d, J = 9 Hz), 6.90 (1H^{E} + 2H^{Z}, d, J = 8 Hz), 6.85 (1H^{Z}, d, J = 8 Hz), 6.74 (1H^{E}, dd, J = 8 and 8 Hz), 6.66 (1H^{E}, d, J = 8 Hz), 3.79 (3H^{E}, s), 3.77 (3H^{Z}, s); ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 163.7 (C^{E}), 158.8 (C^{Z}), 157.6 (C^{Z}), 157.2 (C^{E}), 154.6 (C^{E}), 151.7 (C^{Z}), 146.8 (C^{E}), 145.0 (C^{Z}), 143.1 (C^{E}), 141.1 (C^{Z}), 134.2 (CH^{E}), 133.6 (CH^{Z}), 125.0 (CH^{E}), 122.8 (2 × CH^{Z}), 122.4 (CH^{Z}), 122.2 (CH^{Z}), 122.2 (C^{Z}), 121.7 (CH^{E}), 119.5 (2 × CH^{E}), 115.8 (C^{E}), 114.8 (2 × CH^{E}), 113.5 (2 × CH^{Z}), 111.5 (CH^{E}), 110.6 (CH^{Z}), 55.3 (CH$_3^{E}$), 55.3 (CH$_3^{Z}$); HRMS m/z (ESI$^+$) found 275.0796 ([M+Na]$^+$, $C_{15}H_{12}N_2O_2Na$ requires 275.0796).



4-nitro-*N*-(4-nitrobenzyl)aniline[25] (Table 2, Entry 26)

1 mmol scale (0.1 M in THF), 51% conversion to the imine by ^{1}H NMR. In order to obtain pure material for characterisation, the crude reaction mixture was subjected to the general reduction procedure described above. Attempts to purify the desired amine by catch-and-release with either QP-SA or Nafion® NR50 were unsuccessful, due to the electron-poor nature of this amine product. The remaining material was purified by column chromatography (CH_2Cl_2) to provide a pure sample of 4-nitro-*N*-(4-nitrobenzyl)aniline as a yellow solid. IR (neat) ν_{max}/cm^{-1} 3355 (w), 1591 (m), 1539 (w), 1515 (m), 1493 (m), 1449 (m), 1339 (m), 1322 (m), 1303 (m), 1273 (s), 1185 (m), 1108 (s), 1000 (m), 857 (m), 847 (m), 826 (s), 784 (m), 752 (m), 732 (s), 694 (m), 666 (m); ^{1}H NMR (600 MHz, DMSO-d_6): δ_H = 8.22 (2H, d, J = 9 Hz), 7.99 (2H, d, J = 9 Hz), 7.94 (1H, t, J = 6 Hz), 7.60 (2H, d, J = 9 Hz), 6.67 (2H, d, J = 9 Hz), 4.60 (2H, d, J = 6 Hz); ^{13}C NMR (150 MHz, DMSO-d_6): δ_C = 154.1 (C), 147.0 (C), 146.6 (C), 136.4 (C), 128.1 (2 × CH), 126.2 (2 × CH), 123.7 (2 × CH), 111.3 (2 × CH, br), 45.2 (CH_2); LCMS Rt 4.83 min, m/z (ESI$^+$) 274 ([M+H]$^+$); HRMS m/z (ESI$^+$) found 274.0830 ([M+H]$^+$, $C_{13}H_{12}N_3O_4$ requires 274.0828).

Automated aza-Wittig, Reduction, and Purification Sequence (Table 3)



Automated aza-Wittig, reduction, and purification:

Step 1:

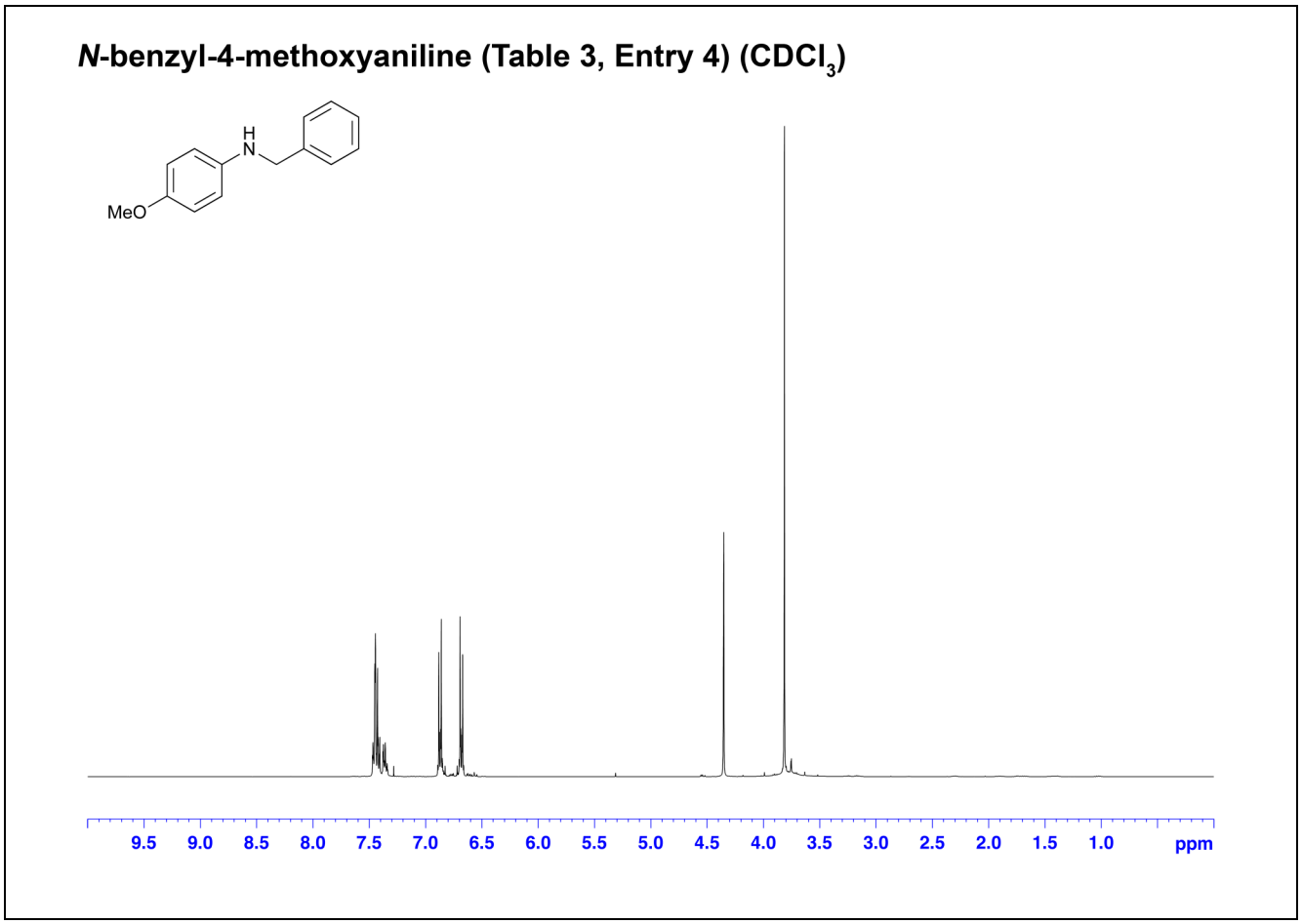
A 1 mL sample loop was filled by the autosampler with a solution of aldehyde starting material (0.5 M in THF), which was introduced to the system and pumped 0.1 mL/min in a constant stream of THF by Pump A. This aldehyde solution passed through a pre-loaded iminophosphorane monolith heated to 120 ºC to effect the aza-Wittig reaction. Upon exiting the iminophosphorane monolith, the flow stream containing the imine intermediate in THF met a second stream of trifluoroethanol (TFE), which was constantly pumped at a flow rate of 0.1 mL/min (Pump B). These two streams mixed in a T-piece and the resulting TFE–THF solution passed through a borohydride monolith heated to 70 ºC at a combined flow rate of 0.2 mL/min to effect reduction of the imine to the corresponding amine. The flow stream exiting the borohydride monolith then passed through a column packed with 0.5 g of QP-SA at room temperature, trapping the desired amine product onto solid support. The entire system was maintained under constant pressure using a 100 psi backpressure regulator (BPR). The output from Step 1 was directed to waste, and Pumps A and B operated constantly for 120 min from the beginning of the reaction sequence to allow adequate time for reaction and thorough washing of the QP-SA column. The iminophosphorane and borohydride monoliths were then cooled to room temperature and Pumps A and B were stopped.

Step 2:

Pump C pumped a solution of NH_3 in MeOH (2.0 M) through the QP-SA column at 0.5 mL/min to release the desired amine product. The output from Step 2 was directed to a fraction collector, and Pump C was operated for 60 min to ensure full collection of the product.

The entire flow sequence described above was run in a fully automated fashion using Flow Commander™ software, and following the automated sequence, the desired amine products were isolated following only evaporation of solvent. (Isolated yields in Table 3.)

A representative spectrum is shown below: *N*-benzyl-4-methoxyaniline (Table 3, Entry 4) was isolated following only evaporation of solvent.



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