Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Continuous-flow copper hydride-catalyzed reduction of 2,1-benzoisoxazoles.

Cristian Cavedon, [a] Sarah Jane Mear, [a] Austin Croke [a] and Timothy F. Jamison *[a]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, United States.
Correspondence to: tfj@mit.edu

Table of contents

1. General remarks

When not otherwise indicated, reagents and solvents were purchased from commercial suppliers and used without further purification. Polymethylhydrosiloxane was purchased as polymer with MW distribution 1700-3200 (Sigma-Aldrich, product No. 176206) and stoichiometry was calculated on the monomer molecular weight MW(CH_4OSi) = 60.13 g/mol.

For all procedures described, “room temperature” refers to a temperature range of 20–24 °C, solvents were dried and sparged with Argon using a solvent purification system prior to use and reactions were run under Argon atmosphere.

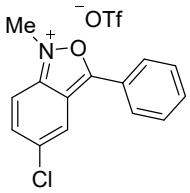
Analytical thin layer chromatography (TLC) was performed on pre-coated TLC-sheets, ALUGRAM Xtra SIL G/UV254 sheets (Macherey-Nagel) and visualized with 254 nm light or staining solutions followed by heating.
Purification by column chromatography over silica gel was performed on a Biotage Selekt flash chromatography system using Isco RediSep Rf Gold silica gel columns.
All NMR spectra were collected using a two-channel Bruker Avance-III HD Nanobay spectrometer operating at 400.09 MHz equipped with a 5 mm liquid-nitrogen cooled Prodigy broad band observe (BBO) cryoprobe. Chemical shifts (δ) are reported in units of ppm, relative to the residual solvent peak, which was adjusted to match reported values. Peaks are reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, with coupling constants in Hz.
High resolution mass spectra (HRMS) were acquires using a JEOL AccuTOF 4G LC-plus instrument equipped with an ionSense DART source.

2. Preparation of reagents and substrates

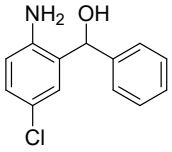
Iodosobenzene was prepared according to literature.[1]

1b, **1c**, **1e** and **1f** were prepared by oxidative cyclization with iodosobenzene, according to literature.[2]

1g, **1h**, **1i** and **1j** were prepared by palladium-catalyzed cross-coupling of anthranil and aryl bromides, according to literature.[3]

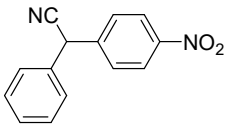


5-Chloro-1-methyl-3-phenylbenzo[*c*]isoxazol-1-ium trifluoromethanesulfonate (1d) was prepared adapting a protocol previously reported for the methylation of 3-phenylisoxazoles[4] as follows:
5-Chloro-3-phenylbenzo[*c*]isoxazole (**1a**, 918.6 mg, 4 mmol) was loaded in a 100 mL, oven-dried, round-bottomed flask, which was sealed with a septum and purged with argon for 10 minutes. Dichloromethane (10 mL) was added and after cooling the solution to 0 °C, methyl triflate (475 µL, 4.2 mmol) was added dropwise. The resulting solution was stirred for 30 minutes at 0 °C, then at room temperature. After 20 hours, additional methyl triflate (226 µL, 2 mmol) was added. After additional 5 hours, the reaction was quenched by addition of diethyl ether (50 mL), followed by filtration of the resulting suspension to obtain **1d** as a yellow solid (1.191 g, 3.03 mmol, 76%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.09 (m, 3H), 8.03 – 7.93 (m, 2H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.73 (t, *J* = 7.9 Hz, 2H), 4.74 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 168.72, 168.37, 148.11, 142.01, 135.59, 135.10, 130.60, 129.29, 123.55, 120.74, 116.60, 116.60, 112.97, 39.81. ^{19}F-NMR (471 MHz, $CDCl_3$) δ -78.37. HRMS (ESI) m/z calcd for $C_{14}H_{11}ClNO$ [(M-OTf)$^+$] 244.0524, found 244.0532.



(2-amino-5-chlorophenyl)(phenyl)methanol (3a) was prepared by exposing commercial **2a** to the copper hydride reduction conditions:
In a nitrogen-filled glovebox, copper(II) acetate (5 mg, 0.03 mmol, 5 mol%) and racemic BINAP (19 mg, 0.03 mmol, 6 mol%) were added to an oven-dried 20 mL vial equipped with a magnetic stirrer. The vial was capped and removed from the glovebox. THF (0.5 mL) was added and the mixture was stirred for 10 minutes. Dimethoxymethylsilane (185 µL, 1.50 mmol) was added and the mixture was stirred for 10 minutes. (2-amino-5-chlorophenyl)(phenyl)methanone (**2a**, 116 mg, 0.50 mmol) was dissolved in THF (0.5 mL) and added and the reaction mixture was stirred overnight. The reaction vessel was vented by inserting a needle through the septum cap. A solution of 0.3 M ammonium fluoride in MeOH (10 mL) was added and the resulting mixture was stirred for 30 minutes at room temperature. TLC analysis of the crude reaction mixture showed full conversion of starting material to a single product (R*f* = 0.1, 10% EtOAc/hexanes). Silica gel was added to the quenched reaction mixture and the solvent was removed under reduced pressure. The material was purified by column chromatography (5–60% EtOAc/hexanes) to yield **3a** as a white solid (99.5 mg, 0.43 mmol, 86%).

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 5H), 7.07 (dd, J = 8.4, 2.5 Hz, 1H), 7.05 – 7.03 (m, 1H), 6.58 (d, J = 8.4 Hz, 1H), 5.77 (s, 1H), 3.46 (br. s, 2H). ^{13}C-NMR (101 MHz, DMSO-*d6*) δ 144.6, 143.6, 129.9, 128.0, 127.1, 126.9, 126.8, 126.5, 119.2, 116.7, 70.9.
These data are in full agreement with those previously published in the literature.[5]



2-(4-nitrophenyl)-2-phenylacetonitrile (4a) was isolated as a side-product in the synthesis of **1a**.
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.7 Hz, 2H), 7.43 – 7.37 (m, 3H), 7.36 – 7.32 (m, 2H), 5.24 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 142.9, 134.6, 129.8, 129.1, 128.9, 127.9, 124.6, 118.6, 42.5.
These data are in full agreement with those previously published in the literature.[6]

3. Optimization of the N,O-reduction of 1a using copper hydride catalysis

3.1 General Experimental Procedures

#1

In a nitrogen-filled glovebox, copper(II) acetate (4.5 mg, 0.025 mmol, 5 mol%) and the ligand (0.03 mmol, 6 mol%) were added to an oven-dried 20 mL vial equipped with a magnetic stirrer. The vial was sealed with a septum cap and removed from the glovebox. The solvent (1.0 mL) and, if indicated, the alcohol were added and the mixture was stirred for 10 minutes, then the silane (1.5 mmol, 3 equiv) was added. **1a** (1.0 mL of 0.5 M solution in reaction solvent) was added and the resulting reaction mixture was stirred for 8 (day reaction) or 16 hours (overnight). Reaction vessels were vented by puncturing the septum, then a 0.3 M ammonium fluoride solution in MeOH (10 mL) was added. The mixture was stirred for 30 minutes at room temperature then subjected to analysis by HPLC (dilution in MeOH, filtration and reverse phase HPLC) or qNMR (^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard).

#2

In a nitrogen-filled glovebox, copper(II) acetate (4.5 mg, 0.025 mmol, 5 mol%) and the ligand (0.06 mmol, 12 mol%) were added to an oven-dried 20 mL vial equipped with a magnetic stirrer. The vial was sealed with a septum cap and removed from the glovebox. t-BuOH (0.5 mL of 3 M solution in THF) was added and the mixture was stirred for 10 minutes, then poly(methylhydrosiloxane) (70 μL, 1.1 mmol) was added. **1a** (0.5 mL of 1 M solution in THF) was added and the resulting reaction mixture was stirred for 16 hours. Reaction vessels were vented by puncturing the septum, then a 0.3 M ammonium fluoride solution in MeOH (10 mL) was added. The mixture was stirred for 30 minutes at room temperature then passed through a Pasteur pipette filled with silica gel and equilibrated with methanol. 1,3,5-Trimethoxybenzene was added to the filtered solution and ^{1}H-NMR analysis in DMSO-*d6* was performed.

#3

In a nitrogen-filled glovebox, copper(II) acetate (4.5 mg, 0.025 mmol, 5 mol%) and tricyclohexylphosphine (corresponding amount) were added to an oven-dried 20 mL vial equipped with a magnetic stirrer. The vial was sealed with a septum cap and removed from the glovebox. t-BuOH (0.5 mL of 3 M solution in THF) was added and the mixture was stirred for 10 minutes, then poly(methylhydrosiloxane) (95 μL, 1.5 mmol, 3 equiv) was added. **1a** (0.5 mL of 1 M solution in THF) was added and the resulting reaction mixture was stirred for 16 hours. Reaction vessels were vented by puncturing the septum, then a 0.3 M ammonium fluoride solution in MeOH (10 mL) was added. The mixture was stirred for 30 minutes at room temperature then diluted with EtOAc and washed with a saturated solution of sodium bicarbonate (2 mL). 1,3,5-Trimethoxybenzene was added to the organic phase, an aliquot was removed, concentrated under reduced pressure and analyzed by ^{1}H-NMR in DMSO-*d6*.

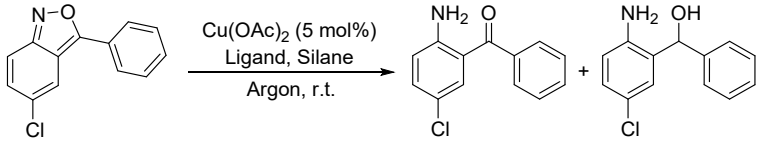
#4

In a nitrogen-filled glovebox, copper(II) acetate (4.5 mg, 0.025 mmol, 5 mol%) and the tricyclohexylphosphine (0.03 mmol, 6 mol%) were added to an oven-dried 20 mL vial equipped with a magnetic stirrer. The vial was sealed with a septum cap and removed from the glovebox. The corresponding alcohol (0.5 mL of 3 M solution in THF) was added and the mixture was stirred for 10 minutes, then poly(methylhydrosiloxane) (corresponding amount) was added. **1a** (0.5 mL of 1 M solution in THF) was added and the resulting reaction mixture was stirred for the corresponding time. Reaction vessels were vented by puncturing the septum, then methanol (0.5 mL) was added followed by stirring for 10 minutes. A saturated solution of sodium bicarbonate (1 mL) was added and the mixture was further stirred for 10 minutes. The mixture was diluted with water (1 mL) and diethyl ether (2 mL), then phases were separated and the organic one was concentrated and analyzed by ^{1}H-NMR in DMSO-*d6*.

3.2 Initial result and screening of bidentate phosphine ligands

Initial screening efforts showed that reduction of benzo[c]isoxazole **1a** to benzophenone **2a** with copper hydride is possible using precedented conditions for copper hydride reduction (Table S1, entry 1 and Table 1, entry 1).[7]
Further studies focusing on identified the best combination of silane and phosphine ligand to achieve conversion of **1a** to **2a** while minimizing overreduction to **3a**.

Table S1: Screening experiments for reaction optimization



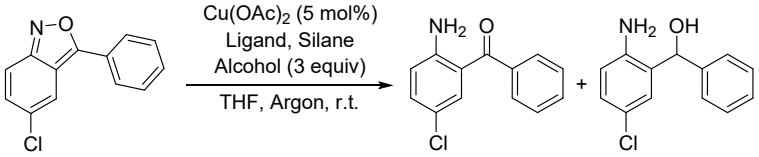
1a (0.5 mmol) **2a** **3a**

Entry	Solvent	Ligand (mol%)	Silane (equiv)	Alcohol (equiv)	Time	**1a** (%)[a]	**2a** (%)[a]	**3a** (%)[a]
1	toluene	*rac*-BINAP (6)	DMMS (3)	none	16 h	12	13	59
2	toluene	*rac*-BINAP (6)	$PhMe_2SiH$ (3)	none	16 h	56	22	n.d.
3	THF	*rac*-BINAP (6)	DMMS (3)	none	16 h	17	19	51
4	THF	*rac*-BINAP (6)	$PhMe_2SiH$ (3)	none	16 h	59	26	n.d.
5	THF	*rac*-BINAP (6)	DMMS (3)	none	8 h	64	17	19
6	THF	*rac*-BINAP (6)	PMHS (3)	none	8 h	83	12	5
7	THF	*rac*-BINAP (6)	PMHS (3)	*t*-BuOH (3 equiv)	8 h	6	15	79
8	THF	*rac*-BINAP (6)	$PhMe_2SiH$ (3)	none	8 h	88	11	1
9	THF	*rac*-BINAP (6)	$PhMe_2SiH$ (3)	*t*-BuOH (3 equiv)	8 h	39	52	10
10	THF	*rac*-BINAP (6)	TMDS (3)	none	8 h	92	5	4
11	THF	*rac*-BINAP (6)	Et_3SiH (3)	none	8 h	99	1	n.d.
12	THF	*rac*-BINAP (6)	$PhSiH_3$ (3)	none	8 h	79	2	19
13	THF	*rac*-BINAP (6)	$PhMe_2SiH$ (3)	none	16 h	59	26	n.d.
14	THF	DCyPE (6)	$PhMe_2SiH$ (3)	none	16 h	77	16	n.d.
15	THF	DPPP (6)	$PhMe_2SiH$ (3)	none	16 h	69	27	2
16	THF	P(*o*-Tol)$_3$ (12)	DMMS (3)	none	16 h	84	9	n/a

Prepared according to Experimental Procedure #1. [a]Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. n.d. = not detected. DMMS = dimethoxymethylsilane. PMHS = poly(methylhydrosiloxane). TMDS = tetramethyldisiloxane. DCyPE = 1,2-bis(dicyclohexylphosphino)ethane. DPPP = 1,3-bis(diphenylphosphino)propane.

Addition of *t*-BuOH improved conversion of **1a**, likely by accelerating turnover of the copper catalyst.
Since monodentate ligands are known to be more selective for N,O- vs 1,2-reduction,[8] we further investigated the use of monodentate phosphine ligands for our protocol and ultimately optimized the stoichiometry of PCy_3 needed in the reaction.

Table S2. Screening experiments for reaction optimization



1a (0.5 mmol) **2a** **3a**

Entry	Ligand (mol%)	Silane (equiv)	Alcohol	Time	**1a** (%)[a]	**2a** (%)[a]	**3a** (%)[a]
1 [b]	PCy_3 (12)	PMHS (2.2)	*t*-BuOH	16 h	21	74	1
2 [b]	P(*t*-Bu)$_3$ (12)	PMHS (2.2)	*t*-BuOH	16 h	53	52	n.d.
3 [b]	P(*n*-Bu)$_3$ (12)	PMHS (2.2)	*t*-BuOH	16 h	10	56	30
4 [b]	P(*n*-Oct)$_3$ (12)	PMHS (2.2)	*t*-BuOH	16 h	43	52	1
5 [b]	P(OEt)$_3$ (12)	PMHS (2.2)	*t*-BuOH	16 h	28	28	39
6 [b]	P(OPh)$_3$ (12)	PMHS (2.2)	*t*-BuOH	16 h	10	17	64
7 [c]	PCy_3 (12)	PMHS (3)	*t*-BuOH	16 h	63	36	2
8 [c]	PCy_3 (6)	PMHS (3)	*t*-BuOH	16 h	15	83	2
9 [c]	PCy_3 (1)	PMHS (3)	*t*-BuOH	16 h	35	66	2
10 [d]	PCy_3 (6)	PMHS (6)	*t*-BuOH	3 h	2	83	7
11 [d]	PCy_3 (6)	PMHS (6)	*t*-BuOH	1 h	7	90	3
12 [d]	PCy_3 (6)	PMHS (6)	*i*-PrOH	1 h	44	56	n.d.
13 [d]	PCy_3 (6)	PMHS (6)	*t*-AmOH	1 h	9	88	3
14 [d]	PCy_3 (6)	PMHS (4)	*t*-AmOH	4 h	5	87	8

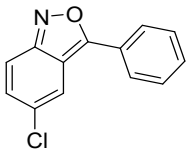
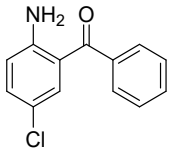
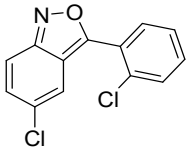
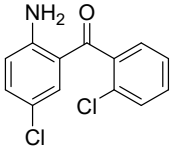
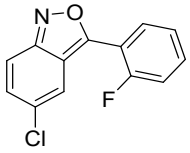
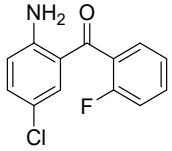
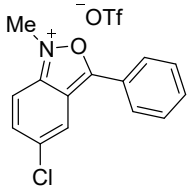
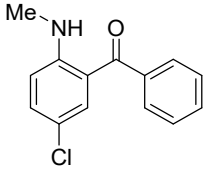
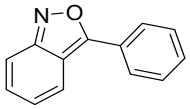
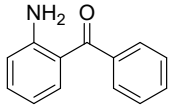
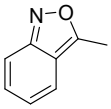
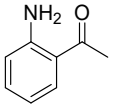
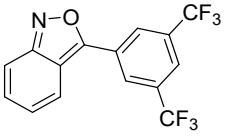
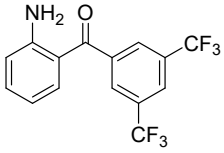
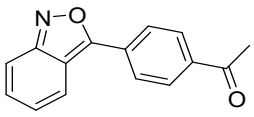
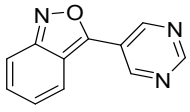
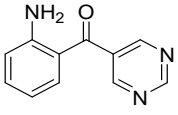
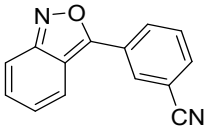
[a]Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [b]Prepared according to Experimental Procedure #2. [c]Prepared according to Experimental Procedure #3. [d]Prepared according to Experimental Procedure #4. n.d. = not detected. n/a = not available due to peaks overlap in qNMR analysis.

While attempting to reduce reaction time, we observed that:

- performing the reaction at 40 °C didn't increase conversion;
- lower amounts of *t*-BuOH resulted in lower selectivity (higher amounts of **3a**).

We tried to drive reactivity by using a larger silane excess. 14 equivalents of PMHS reduce reactions selectivity. 6 equivalents were found to work best, with 90% formation of **2a** detected (entry 11, 98% conversion) over 1 hour.

4. Control experiments and substrate scope using optimized reaction conditions

Substrate	Product	Scale	Reaction time	Analytical yield	Isolated yield
1a 	2a 	1 mmol	4 hours	87	85%
		10 mmol	8 hours	-	92%
1b 	2b 	1 mmol	3 hours	99%	85%
1c 	2c 	1 mmol	4 hours	71%	64%
1d 	2d 	1 mmol	24 hours	no conversion	
1e 	2e 	1 mmol	21 hours	96%	91%
1f 	2f 	1 mmol	2 hours	98%	98%
1g 	2g 	1 mmol[a]	4 hours	31%	-
		1 mmol[b]	48 hours	73%	72%
1j 	unselective	1 mmol	7 hours	-	-
1i 	2i 	1 mmol	48 hours	product not detected	-
1h 	unselective	1 mmol	6 hours	43% prod & 32% subs	-

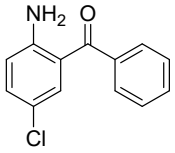
4.1 Experimental procedure for control experiments as reported in Table 2 of the manuscript

In a nitrogen-filled glovebox, copper(II) acetate (4.5 mg, 0.025 mmol, 5 mol%) and tricyclohexylphosphine (8.5 mg, 0.03 mmol, 6 mol%) were added to an oven-dried 8 mL vial equipped with a magnetic stirrer. The vial was sealed with a septum cap and removed from the glovebox. Anhydrous, degassed THF (0.5 mL) was added to the vial under Argon, followed by tert-amyl alcohol (165 µL, 1.5 mmol, 3 equiv) and the mixture was stirred for 10 minutes, observing formation of a homogeneous, light blue solution. Poly(methylhydrosiloxane) (131 µL of 1700-3200 MW polymer, 2 mmol, 4 equiv) was added and the mixture was stirred for additional 10 minutes observing a colour shift from blue/green to brown/red. **1a** (0.5 mL of 1 M solution THF) was added and the resulting reaction mixture was stirred for 4 hours. Reaction vessels were vented by puncturing the septum, then a saturated ammonium fluoride solution in MeOH (2 mL) was added. The mixture was stirred for 30 minutes at room temperature then 1,3,5-trimethoxybenzene was added. An aliquot of the reaction mixture was diluted in DMSO-*d6* and analyzed by ^{1}H-NMR .

4.2 Experimental procedure for isolation products isolation in substrate scope

In a nitrogen-filled glovebox, copper(II) acetate (9 mg, 0.05 mmol, 5 mol%) and tricyclohexylphosphine (17 mg, 0.06 mmol, 6 mol%) were added to an oven-dried, 20 mL vial equipped with a magnetic stirrer. The vial was sealed with a septum cap and removed from the glovebox. Anhydrous, degassed THF (1 mL) was added to the vial under Argon, followed by tert-amyl alcohol (325 µL, 3 mmol, 3 equiv) and the mixture was stirred for 10 minutes, observing formation of a homogeneous, light blue solution. Poly(methylhydrosiloxane) (262 µL of 1700-3200 MW polymer, 4 mmol, 4 equiv) was added and the mixture was stirred for additional 10 minutes observing a colour shift from blue/green to brown/red. **1a** (1.0 mL of 1 M solution THF) was added and the resulting reaction mixture was stirred, monitoring consumption of starting material by TLC. After the indicated time, reaction vessels were vented by puncturing the septum and a saturated ammonium fluoride solution in MeOH (5 mL) was added. The mixture was stirred for 30 minutes at room temperature then 1,3,5-trimethoxybenzene was added and an aliquot (50 µL) of the solution was diluted in DMSO-d6 and analyzed by ^{1}H-NMR.
The remaining reaction mixture was diluted in ethyl acetate (circa 10 mL) and filtered through a short plug of celite (5 mm). Silica gel (700 mg) was added to the filtrate, then the suspension was concentrated and purified by flash chromatography (gradient gradients of ethyl acetate/hexane) to afford the desired product.

4.3 Experimental data for isolated products

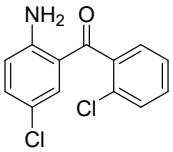


(2-Amino-5-chlorophenyl)(phenyl)methanone (2a)

5-Chloro-3-phenylbenzo[c]isoxazole (**1a**, 229.7mg, 1 mmol) reacted in 4 hours under standard conditions to give **2a** as a bright yellow solid (197.3 mg, 0.85 mmol, 85%). Purity of isolated product was 95% by qNMR.
qNMR analysis of crude: 3% of **1a**; 87% of **2a**; 6% of **3a**
purification: gradient 10-40% ethyl acetate/hexane

5-Chloro-3-phenylbenzo[c]isoxazole (**1a**, 2.297 g, 10 mmol) reacted in 8 hours under standard conditions to give **2a** as a bright yellow solid (2.120 g, 9.15 mmol, 92%).
purification: gradient 5-40% ethyl acetate/hexane

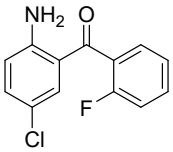
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.3 Hz, 2H), 7.42 (d, J = 2.5 Hz, 1H), 7.24 (dd, J = 8.7, 2.4 Hz, 1H, contains $CDCl_3$ residual signal), 6.71 (d, J = 8.8 Hz, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 198.10, 149.26, 139.42, 134.30, 133.37, 131.68, 129.25, 128.46, 120.26, 119.09, 118.70.
These data are in full agreement with those previously published in the literature.[9]



(2-Amino-5-chlorophenyl)(2-chlorophenyl)methanone (2b)

5-Chloro-3-(2-chlorophenyl)benzo[c]isoxazole (**1b**, 264.1 mg, 1 mmol) reacted in 3 hours under standard conditions to give **2b** as a bright yellow solid (226.5 mg, 0.85 mmol, 85%).
qNMR analysis of crude: no **1b**; 99% of **2b**; 1% of **3b**
purification: gradient 5-15% ethyl acetate/hexane

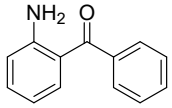
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 1H), 7.42 (t, J = 6.6 Hz, 1H), 7.37 (t, J = 6.5 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.23 (dd, J = 8.9, 2.5 Hz, 1H), 7.11 (d, J = 2.5 Hz, 1H), 6.68 (d, J = 8.8 Hz, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 196.52, 149.95, 139.12, 135.38, 133.29, 130.87, 130.84, 130.18, 128.52, 126.92, 120.22, 118.69, 118.13.
These data are in full agreement with those previously published in the literature.[10]



(2-Amino-5-chlorophenyl)(2-fluorophenyl)methanone (2c)

3-(2'-Fluorophenyl)-5-fluorobenzo[c]isoxazole (**1c**, 247.7 mg, 1 mmol) reacted in 4 hours under standard conditions to give **2c** as a bright yellow solid (160.3 mg,0.64 mmol, 64%).
qNMR analysis of crude: 15% of **1c**; 71% of **2c**; 3% of **3c**
purification: gradient 5-15% ethyl acetate/hexane

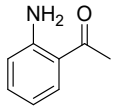
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.25 (dd, J = 15.4, 2.4 Hz, 3H), 7.17 (t, J = 9.0 Hz, 1H), 6.69 (d, J = 8.7 Hz, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 194.56, 160.44, 157.95, 149.59, 135.21, 133.27 (d, J = 1.9 Hz), 132.36 (d, J = 8.2 Hz), 129.83 (d, J = 3.1 Hz), 128.04 (d, J = 16.1 Hz), 124.46 (d, J = 3.5 Hz), 120.35, 118.87, 118.66, 116.40 (d, J = 21.5 Hz). ^{19}F-NMR (376 MHz, $CDCl_3$) δ -113.33.
These data are in full agreement with those previously published in the literature.[9]



(2-Aminophenyl)(phenyl)methanone (2e)

3-Phenylbenzo[c]isoxazole (**1e**, 195.2 mg, 1 mmol) reacted in 21 hours under standard conditions to give **2e** as a bright yellow solid (180.2 mg, 0.91 mmol, 91%).
qNMR analysis of crude: no **1e**; 96% of **2e**; 5% of **3e**
purification: gradient 5-20% ethyl acetate/hexane

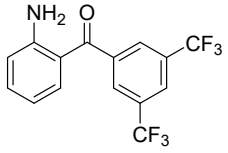
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.5 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.49 – 7.43 (m, 3H), 7.30 (t, J = 6.9 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 6.62 (t, J = 7.0 Hz, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 199.21, 150.80, 140.19, 134.72, 134.37, 131.21, 129.27, 128.22, 118.45, 117.26, 115.83.
These data are in full agreement with those previously published in the literature.[9, 10]



1-(2-Aminophenyl)ethan-1-one (2f)

3-Methylbenzo[c]isoxazole (**1f**, 133.2 mg, 1 mmol) reacted in 2 hours under standard conditions to give **2f** as an off-white oil (132.4 mg, 0.98 mmol, 98%).
qNMR analysis of crude: no **1f**; 98% of **2f**
purification: gradient 5-20% ethyl acetate/hexane

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 6.7 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 6.67 – 6.62 (m, 2H), 2.57 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 200.86, 150.33, 134.48, 132.14, 118.38, 117.33, 115.88, 27.96.
These data are in full agreement with those previously published in the literature.[10]

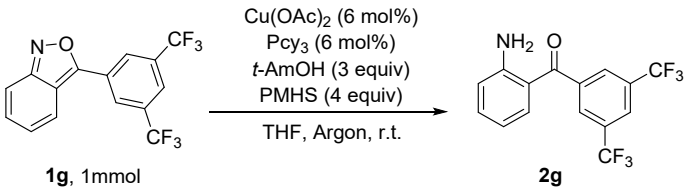


(2-Aminophenyl)(3,5-bis(trifluoromethyl)phenyl)methanone (2g)

3-(3,5-Bis(trifluoromethyl)phenyl)benzo[c]isoxazole (**1g**, 331.2 mg, 1 mmol) reacted in 48 hours using only 1.5 mmol of PMHS to give **2g** as a yellow solid (241.3 mg, 0.72 mmol, 72%).
qNMR analysis of crude: 12% of **1g**; 73% of **2g**; 13% of **3g**
purification: gradient 2-20% ethyl acetate/hexane

1H-NMR (400 MHz, CDCl3) δ 8.06 (s, 2H), 8.03 (s, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H). 13C-NMR (101 MHz, CDCl3) δ 195.52, 151.70, 142.12, 135.51, 133.95, 131.87 (q, J = 34.0 Hz), 129.09 (d, J = 4.0 Hz), 124.48 – 124.31 (m), 123.15 (d, J = 275.6 Hz), 117.58, 116.68, 116.15. 19F-NMR (376 MHz, CDCl3) δ -62.86.
These data are in full agreement with those previously published in the literature.[11]

Table S3. Optimization of stoichiometry for the reduction of **1g**



1g, 1mmol **2g**

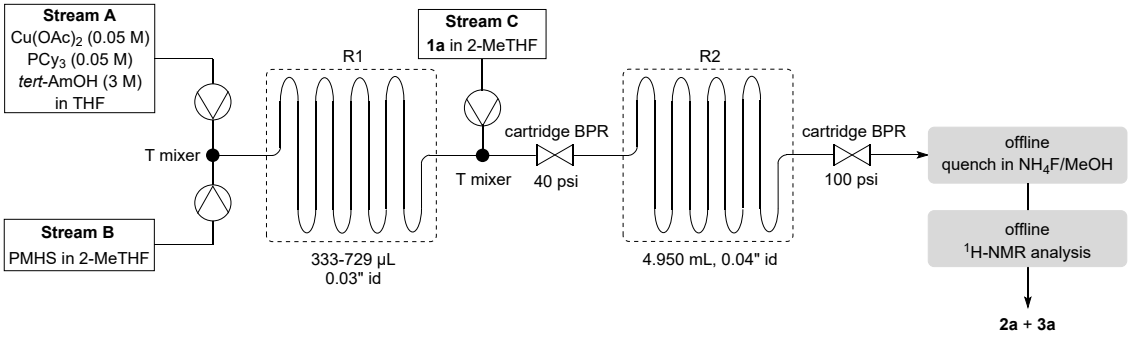
Entry	PMHS stoichiometry	Time	**1g** (%)[a]	**2g** (%)[a]	**Others** (%)[a]
1	4 equiv	1 h	42	37	20
2	4 equiv	4 h	1	31	52
3	2 equiv	30 h	10	62	23
4	1.5 equiv	48 h	12	73	13
5	1.2 equiv	4 h	48	47	5
6	1.2 equiv	48 h	22	70	9

[a]Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard.

5. Optimization of the N,O-reduction of 1a in continuous flow

Results reported here expand what discussed in Table 3 and relative text of the manuscript.

Table S4: Screening experiments for reaction optimization in flow



Entry	Flow rate (µL/min)			[PMHS]	PMHS : **1a**	[**1a**] in C	Residence time		Temp	NMR analysis[a]		
	A	B	C	in B			R1	R2	in R2	**1a**	**2a**	**3a**
1	40.0	40.0	80	4.0 M	4 equiv	0.50 M	6.6 min	30.9 min	80 °C	n.d.	78%	34%
2	52.7	26.3	81	8.0 M	4 equiv	0.65 M	6.6 min	30.9 min	80 °C	n.d.	68%	34%
3	52.7	26.3	81	8.0 M	4 equiv	0.65 M	6.6 min	30.9 min	60 °C	traces	75%	24%
4	78.0	39.0	120	8.0 M	4 equiv	0.65 M	6.2 min	20.9 min	60 °C	7%	54%	15%
5	78.0	39.0	120	8.0 M	4 equiv	0.65 M	6.2 min	20.9 min	60 °C	traces	66%	20%
6	84.5	21.1	130	8.0 M	2 equiv	0.65 M	6.9 min	21.0 min	60 °C	32%	64%	5%
7	86.5	16.2	133	8.0 M	1.5 equiv	0.65 M	7.1 min	21.0 min	80 °C	31%	60%	4%
8	84.5	21.1	130	8.0 M	2 equiv	0.65 M	6.9 min	21.0 min	80 °C	27%	70%	5%
9	84.5	21.1	130	8.0 M	2 equiv	0.65 M	5.0 min	21.0 min	80 °C	28%	69%	5%
10	52.0	13.0	80	8.0 M	2 equiv	0.65 M	5.1 min	34.1 min	80 °C	6%	84%	10%
11	54.0	10.1	83	8.0 M	1.5 equiv	0.65 M	5.2 min	33.7 min	80 °C	18%	77%	6%
12	54.0	10.1	83	8.0 M	1.5 equiv	0.65 M	5.2 min	33.7 min	95 °C	8%	87%	4%

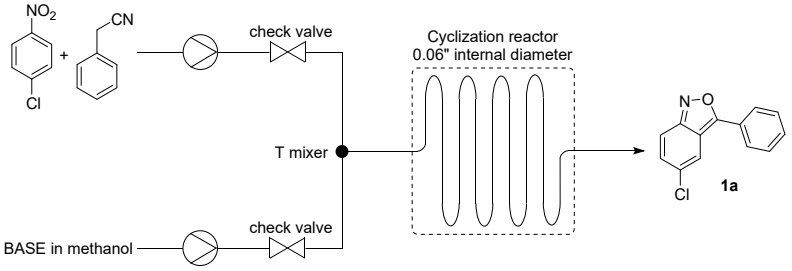
[a]For each entry, the system was equilibrated for 3 times the corresponding total residence time, then a sample was collected in NH_4F (0.5 M solution in MeOH) for quenching of residual silane, 1,3,5-trimethoxybenzene was added as internal standard, and an aliquot was diluted in DMSO-*d6* and analyzed by ^{1}H-NMR. n.d. = not detected.

6. VNS-cyclization/N,O-reduction sequence in continuous flow for the synthesis of 2a

6.1 Screening experiments for optimization of VNS reaction step

A 2-feed configuration was used to study the synthesis of **1a**, solutions of 4-chloronitrobenzene and benzyl cyanide, mixing with a base in methanol. Due to thickening of the mixture once the reaction starts, a check valve (3 psi, IDEX CV-3315) was placed on each feed before mixing them, to avoid backflow of the reacting mixture into the pumps. Reaction mixture was processed through a heated plug-flow reactor and collected in a stirred emulsion of water and ethyl acetate.
Results reported here expand what discussed in Table 4 and relative text of the manuscript.

Table S5: Screening experiments for reaction optimization

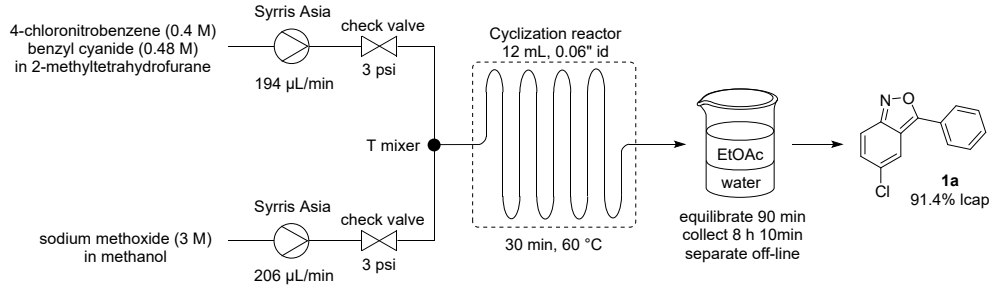


Entry	Solvent	[Ar-NO_2]	[Bn-CN]	Base (equiv)	Temp.	Time	**Ar-NO_2** (lcap)	**4a** (lcap)	**1a** (lcap)
1	MeOH	0.5 M	0.5 M	KOH (8)	50 °C	50 min	-	10%	n.d.
2	2-MeTHF	0.5 M	0.5 M	KOH (8)	50 °C	50 min	11.0%	15.4%	70.2%
3	2-MeTHF	0.3 M	0.45 M	KOH(8)	50 °C	50 min	23.2%	18.6%	37.7%
4	2-MeTHF	0.4 M	0.6 M	NaOMe (4)	60 °C	50 min	0.6%	-	82.0%
5	2-MeTHF	0.4 M	0.6 M	NaOMe (4)	60 °C	25 min	43.2%	11.0%	41.6%
6	2-MeTHF	0.4 M	0.6 M	NaOMe (8)	60 °C	25 min	2.1%	7.5%	87.6%
7	2-MeTHF	0.4 M	0.48 M	NaOMe (8)	60 °C	25 min	4.7%	7.5%	84.6%

For each entry, the system was equilibrated for 3 times the corresponding total residence time, then a sample was collected in emulsion of ethyl acetate and water (1:1) under stirring, and an aliquot (50µL) of the organic phase was diluted in acetonitrile (1mL) and analyzed by reverse phase HPLC. Results are not corrected for Bn-CN area.

6.2 Scale up run and isolation of 1a

Scheme S1: Experimental setup and equipment list for the large-scale synthesis of **1a**



Reciprocating syringe pumps	Syrris Asia	Mounting 250/500 µL syringes
Check valves	IDEX CV-3315	Open pressure 3 psi
T mixer	IDEX P-713	
Reactor loop	PFA tubing from Zeus Inc.	inner diameter 0.063” ±0.004
Heating bath	Büchi B-491	

Reagent solutions

Solutions were prepared in oven-dried volumetric flasks. Solids were loaded first, followed by sealing the flasks with rubber septa and purging with nitrogen before loading liquid phases under nitrogen pressure.

Solution	Reagents	Dilution
A (2x)	4-chloronitrobenzene (6.30 g, 40 mmol) benzyl cyanide (55.4 mL, 480 mmol)	100 mL with anhydrous 2-MeTHF
B (2x)	sodium methoxide (55.56 mL of 5.4 M solution in MeOH)	100 mL with anhydrous MeOH

Flow reactor operation

Setup described in Scheme S1 was used. Stoichiometry and conditions refer to Table S5, entry 7.

Heating bath was set to 60 °C, pumps 1 and 2 were operated using solutions A and B respectively. After equilibrating the reactor loop for 90 minutes and discarding the output, the reaction mixture was collected in a mix of ethyl acetate and water, under stirring, for 8 hours and 10 minutes (490 min*0.194 mL/min*0.4 M = 38.0 mmol of Ar-NO_2).

The reaction mixture was moved into a separatory funnel. After phase separation, the aqueous one was drained and the organic one was further washed with water (500 mL), dried over sodium sulfate, passed through a plug of active charcoal and celite[‡] and concentrated under vacuum. The residue was dissolved in acetone (40 mL) and triturated with water, then the solid was filtered on a glass frit and washed with abundant water (yellow solid, 6.923 g, 88.6% HPLC purity). The product was solved in boiling hexane, then cooled to 5 °C to obtain 5-chloro-3-phenylbenzo[*c*]isoxazole (**1a**) as yellow needle-shaped crystals (4.033 g, 17.6 mmol, 46%, 99.5% HPLC purity).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 6.9 Hz, 2H), 7.82 (s, 1H), 7.60 – 7.47 (m, 4H), 7.25 (dd, J = 9.3, 1.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.41, 156.42, 132.59, 130.71, 130.41, 129.49, 128.00, 126.66, 119.11, 117.28, 114.63.

These data are in full agreement with those previously published in the literature.[12]

Figure S1: **1a** after trituration (left) and crystallization (right).

[‡] Filtration through active charcoal and celite was used to remove a tar-like substance detected in previous experiments.

6.3 Implementation of in-line quenching and phase separation after VNS reaction step

In-line quenching of the VNS reaction and extraction of **1a** was studied starting from conditions as reported in Table S5, entry 7. Residence time was extended to 31 minutes to maximize conversion.

Two additional pumps were used to mix an emulsion of water and organic solvents with the reaction mixture. A check valve (3 psi) was added upstream of the emulsion mixing point to avoid backflow into the reactor loop.

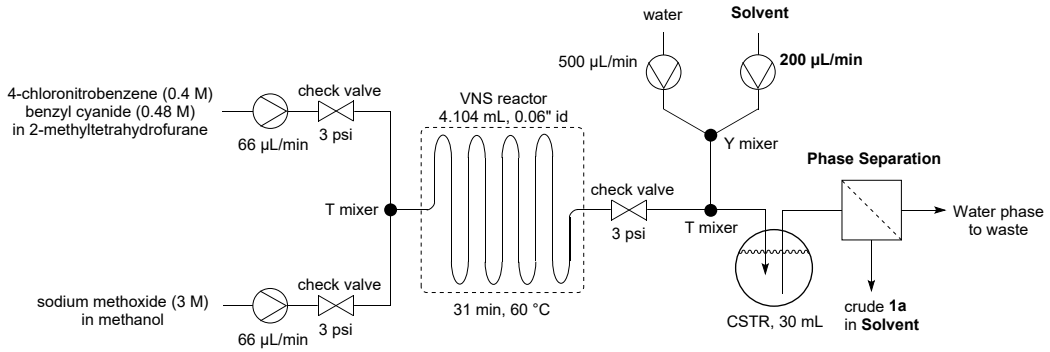
Mixing was tested first offline, using a separatory funnel (Table S6, entry 1-2), then in-line using a continuous stirred tank reactor (CSTR, entry 3-6). Mixing in-line by using a simple tubing segment led to poor partition of the product between aqueous and organic phase.

Good results were obtained using a CSTR assembled from a glass, 30 mL microwave vessel containing a football-shaped magnetic stirbar and sealed with a crimped, septum cap. The pressure which built up by loading the reaction mixture was sufficient to discharge the content through a needle connected to downstream elements.

Phase separation was studied offline using gravity (separatory funnel) and in-line, with a membrane permeation-based device[13] (Zaiput SEP10 phase separator with 0.5 µm PTFE membrane). Pressurization of the lines downstream of the phase separator was not necessary.

Using dichloromethane and ethyl acetate, similar ratios were detected of Ar-NO_2/**1a**/**4a** (entry 5-6). 2-MeTHF and diethyl ether were found to give poor phase separation.

Table S6: Screening experiments to improve in-line extraction of crude **1a**



Entry	Solvent		Mixing	Phase Separation	**Ar-NO_2** (lcap)	**1a** (lcap)	**4a** (lcap)
1	EtOAc	150 µL/min	offline	offline/gravity	1.4%	86.5%	5.2%
2	2-MeTHF	150 µL/min	offline	offline/gravity[a]	3.2%	75.9%	20.9%
3	EtOAc	150 µL/min	CSTR	offline/gravity	1.4%	85.8%	5%
4	EtOAc	150 µL/min	CSTR	in-line/membrane	1.3%	86.1%	5.4%
5	EtOAc	200 µL/min	CSTR	in-line/membrane	1.3%	85.1%	5.3%
6	DCM	200 µL/min	CSTR	in-line/membrane	1.4%	87.1%	5.6%

Reactor system was equilibrated for 3 times the corresponding total residence time, then for each entry, the corresponding mixing and separation conditions were implemented. After filling of the CSTR and/or the membrane phase separator, reaction mixture was discarded for one residence time before collecting an aliquot (50µL) of the organic phase, diluting it in acetonitrile (1mL) and analysing it by reverse phase HPLC. Results are not corrected for Bn-CN area. [a]Poor phase separation observed.

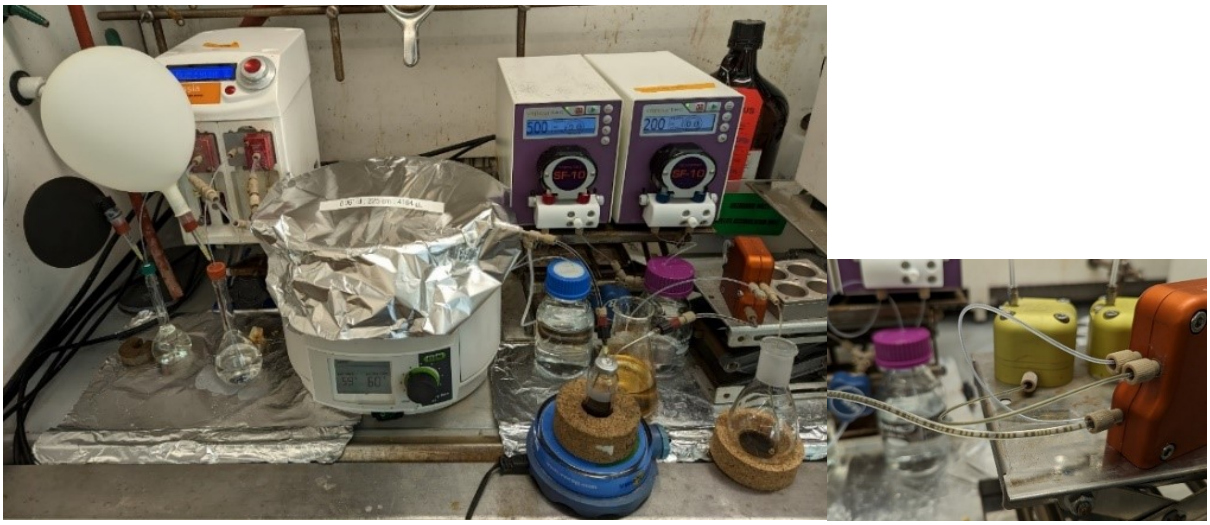
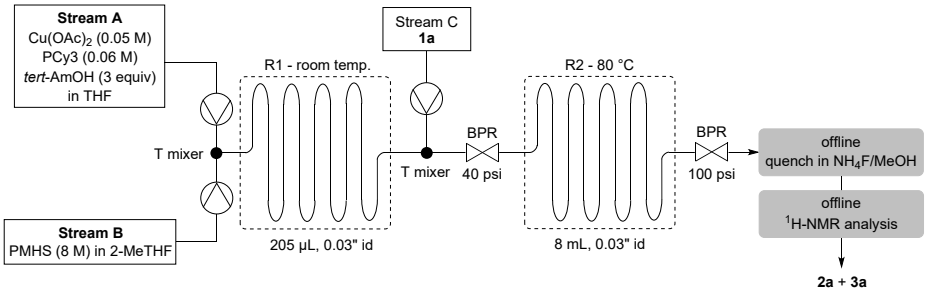


Figure S2: Experimental setup for Table 6, entry 6 and detail of the membrane phase separator.

6.4 Screening experiments for the N,O-reduction of crude 1a

N,O-Reduction conditions as optimized in Table S4 were applied to mixtures of crude 1a obtained from experiments of Table S6, entry 5 (crude in EtOAc) and entry 6 (crude in DCM).
These results are discussed in the main text of the manuscript.

Table S7: Screening experiments to test N,O-reduction of crude **1a**

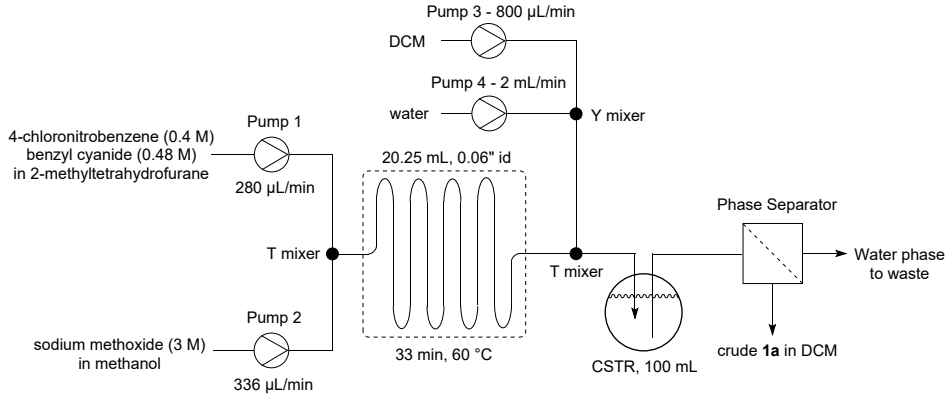


Entry	Stream C		Residence time		NMR analysis[a]		
	Description	[**1a**]	R1	R2	**1a**	**2a**	**3a**
1	pure **1a** in 2-MeTHF	0.650 M	5.1 min	34.1 min	6	84	10
2	pure **1a** in DCM	0.650 M	6.7 min	31.3 min	28	67	4
3	crude **1a** in DCM	0.284	7.0 min	31 min	72	26	2
4	crude **1a** in DCM	0.115 M	14.8 min	32.8 min	82	13	5
5	crude **1a** in DCM	0.040 M	6.9 min	29.9 min	n/a	n.d.	n/a
6	crude **1a** in EtOAc	0.258 M	5.9 min	31.9 min	62	36	2

[a]For each entry, the system was equilibrated for 3 times the corresponding total residence time, then a sample was collected in NH_4F (0.5 M solution in MeOH) for quenching of residual silane and an aliquot was diluted in DMSO-*d6* and analyzed by ^{1}H-NMR. Data are expressed as relative ratios of **1a**/**2a**/**3a**. n.d. = not detected. n/a = not calculated.

6.5 Final telescoped sequence on large scale

Scheme S2: Experimental setup and equipment list for the large-scale synthesis and extraction of **1a**



Pumps 1 and 2	Vapourtech SF-10	
Pumps 3 and 4	Syrris Asia	Mounting 250/500 µL syringes
Y mixer	IDEX P-514	
T mixers	IDEX P-713	
Reactor loop	PFA tubing from Zeus Inc.	Inner diameter 0.063" ±0.004
Heating bath	Büchi B-491	
CSTR	Sealed round-bottom flask	With magnetic stirrer and rubber septum seal
Phase separator	Zaiput SEP-10	Mounting PTFE membrane with 1µm pores

Reagent solutions

Solutions were prepared in oven-dried volumetric flasks. Solids were loaded first, followed by sealing the flasks with rubber septa and purging with nitrogen before loading liquid phases under nitrogen pressure.

Solution	Reagents	Dilution
A	4-chloronitrobenzene (15.755 g, 100 mmol) benzyl cyanide (13.85 mL, 120 mmol)	250 mL with anhydrous 2-MeTHF
B	sodium methoxide (138.9 mL of 5.4 M solution in MeOH)	250 mL with anhydrous MeOH

Experimental Procedure

Setup described in Scheme S2 was used.

Heating bath was set to 60 °C, pumps 1 and 2 were operated using solutions A and B respectively. Reaction mixture was collected right after the reactor loop in an emulsion of water and dichloromethane under stirring. After 100 minutes the collected mixture was discarded, a sample (200 µL) was collected in fresh DCM/water (circa 2 mL) for HPLC analysis, then the output of the reactor was connected to the CSTR and pumps 3 and 4 activated.

50 more minutes were used to fill the CSTR and prime the phase separator, while output of the system was discarded. After this time, organic phase was collected in a 1 liter round-bottom flask, while discarding the aqueous phase. The system was operated this way for 8 hours and 6 minutes (486 min*0.280 mL/min*0.4 M = 54.4 mmol of Ar-NO_2) then the setup was washed by flowing methanol through the reactor and emptying the CSTR and phase separator with a nitrogen flow.

Crystallization

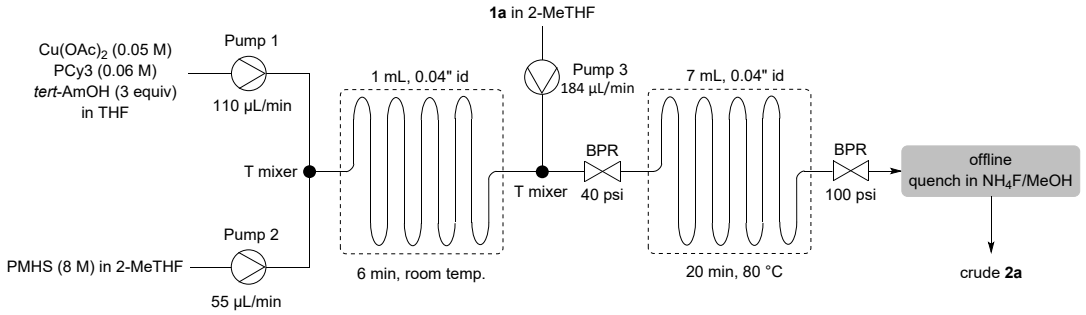
Collected organic phase was concentrated under vacuum and the residue (27.28 g) was solved in toluene (12 mL) at 40 °C. Crystallization initiated upon addition of hexanes (5-10 mL) and cooling to 5 °C. The slurry was transferred to a büchner filter, washed with hexanes and dried to obtain **1a** as yellow crystals (7.703 g, 33.5 mmol, 61.6%).

Analytical data of the product were in full agreement with those previously recorded and those published in literature.[12]

HPLC Analysis

Sample	Ar-NO_2 (lcap)	**1a** (lcap)	**4a** (lcap)
Reaction mixture before CSTR	4.5%	88.2%	7.2%
Collected organic phase	4.2%	86.7%	6.1%
Crystalline **1a**	n.d.	99.0%	0.7%

Scheme S3: Experimental setup and equipment list for the large-scale reduction of **1a** in flow



Pumps 1 and 2	Syrris Asia	Mounting 50/100 µL syringes
Pump 3	Syrris Asia	Mounting 250/500 µL syringes
T mixers	IDEX P-713	
Reactor loops	PFA tubing from IDEX	Inner diameter 0.04”
Heating bath	Büchi B-491	
BPR 100 psi	IDEX P-465 and P-763	
BPR 40 psi	IDEX P-465 and P-761	

Reagent solutions

Solutions were prepared in oven-dried volumetric flasks. Solids were loaded first, followed by sealing the flasks with rubber septa and purging with nitrogen before loading liquid phases under nitrogen pressure. Copper(II) acetate and tricyclohexylphosphine were handled in a glove box. Solution F was prepared open to air, in a round-bottom flask.

Solution	Reagents	Dilution
C	Copper(II) acetate (227 mg, 1.25 mmol) tricyclohexylphosphine (421 mg, 1.5 mmol) *tert*-amyl alcohol (8.21 mL, 75 mmol)	25 mL with anhydrous THF
D	PMHS (4.78 mL, 80 mmol)	10 mL with anhydrous 2-MeTHF
E1	Crystalline **1a** from previous step (3.445 g, 15 mmol)	25 mL with anhydrous 2-MeTHF
E2	Crystalline **1a** from previous step (1.378 g, 5.7 mmol)	10 mL with anhydrous 2-MeTHF
F	Ammonium fluoride (1.85 g, 50 mmol)	100 mL with anhydrous MeOH

Experimental Procedure

Setup described in Scheme S3 was used.

Heating bath for the second reactor was set to 80 °C, pumps 1 and 2 were operated using solutions C and D respectively. After 6 minutes (equilibration of first reactor loop), pump 3 was turned on and operated using solutions E1 and E2. Reaction mixture was collected in a flask containing methanol.

After 20 minutes (equilibration of second reactor loop), the reaction mixture was collected in a flask containing 0.5 M NH4F (solution F). The system was operated this way for 114 minutes (114 min*0.184 mL/min*0.6 M = 12.6 mmol of **1a**) then the setup was washed by flowing methanol through the reactors.

An aliquot (50 µL) of the quenched reaction mixture was diluted in DMSO-*d6* and analyzed by ^{1}H-NMR, indicating presence of **1a**/**2a**/**3a** in the relative ratios 9 : 78 : 13.

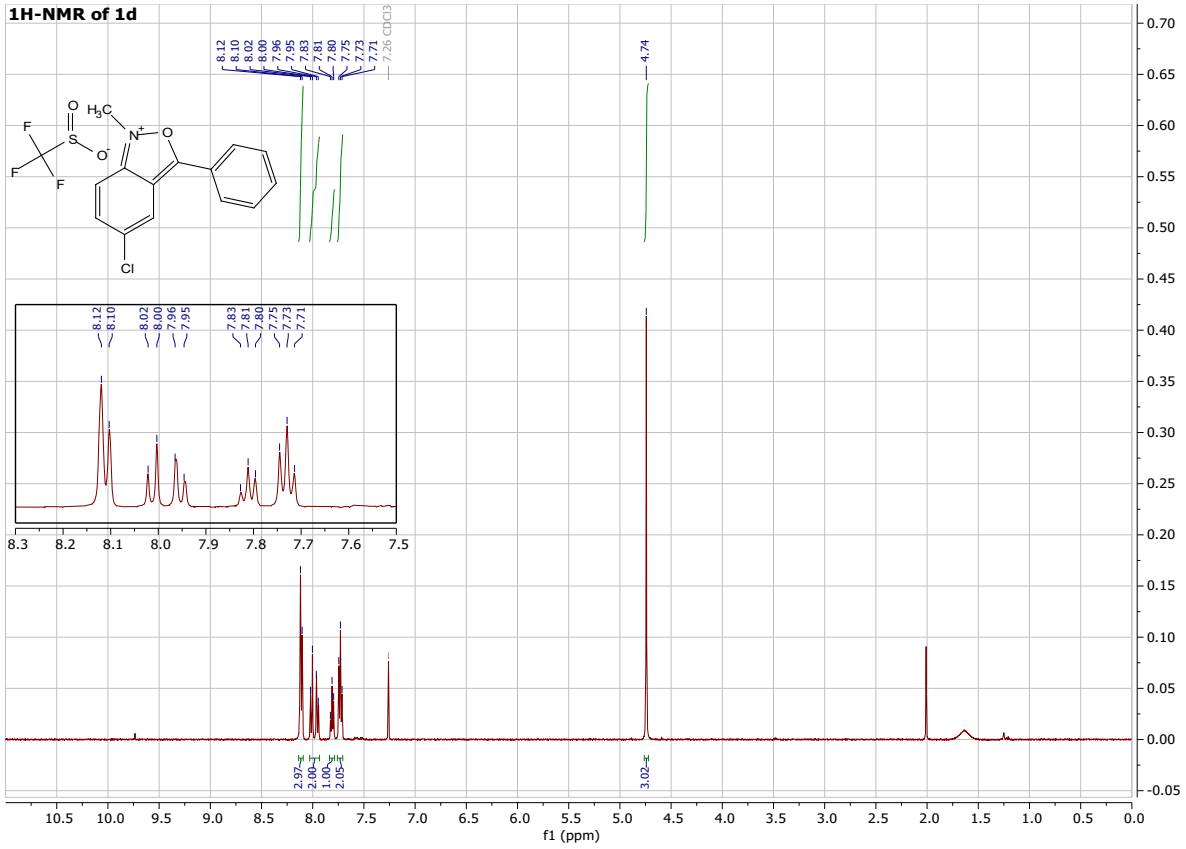
The remaining reaction mixture was diluted in ethyl acetate (20 mL) and filtered through a plug of celite (15 mm) and concentrated. The residue was purified by chromatography (gradient 2-30% ethyl acetate/hexanes) to afford the **2a** as a bright yellow solid (2.487 g, 10.7 mmol, 85%).

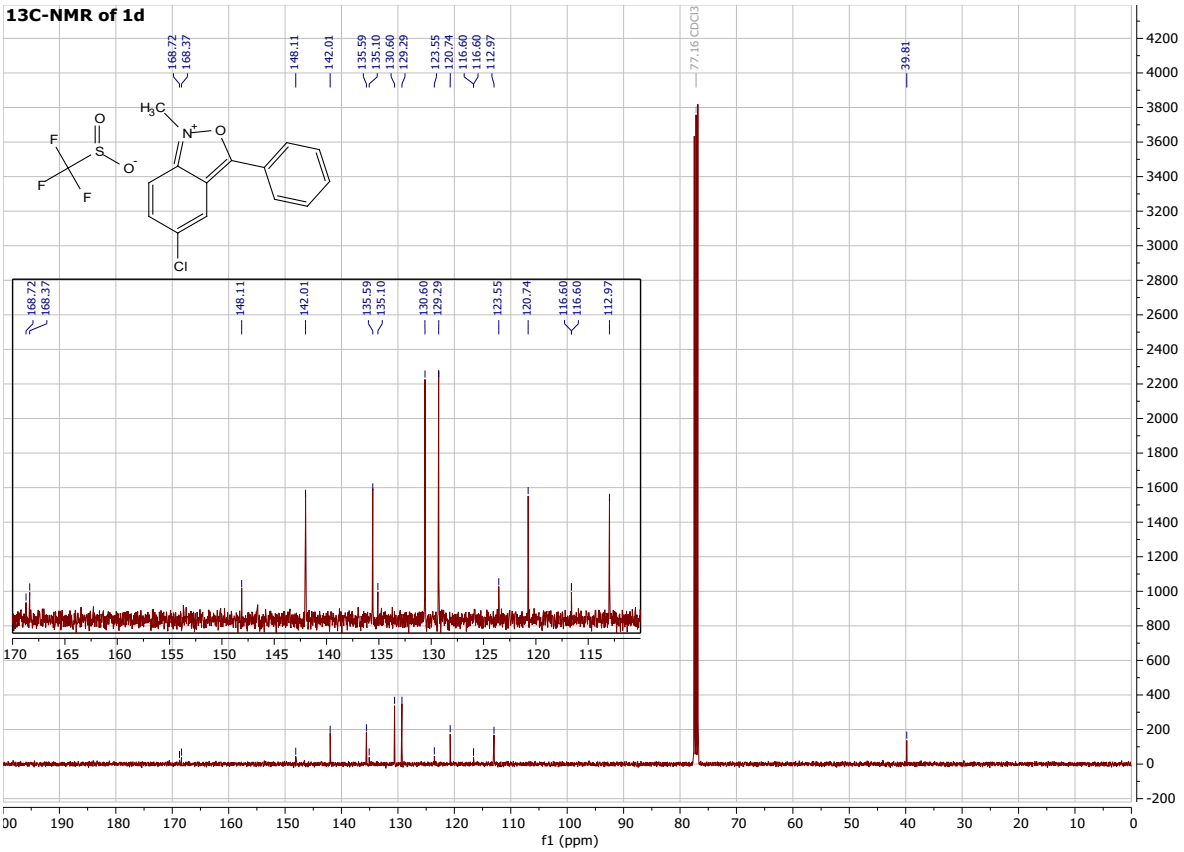
Analytical data of the product were in full agreement with those previously recorded and those published in literature.[9]

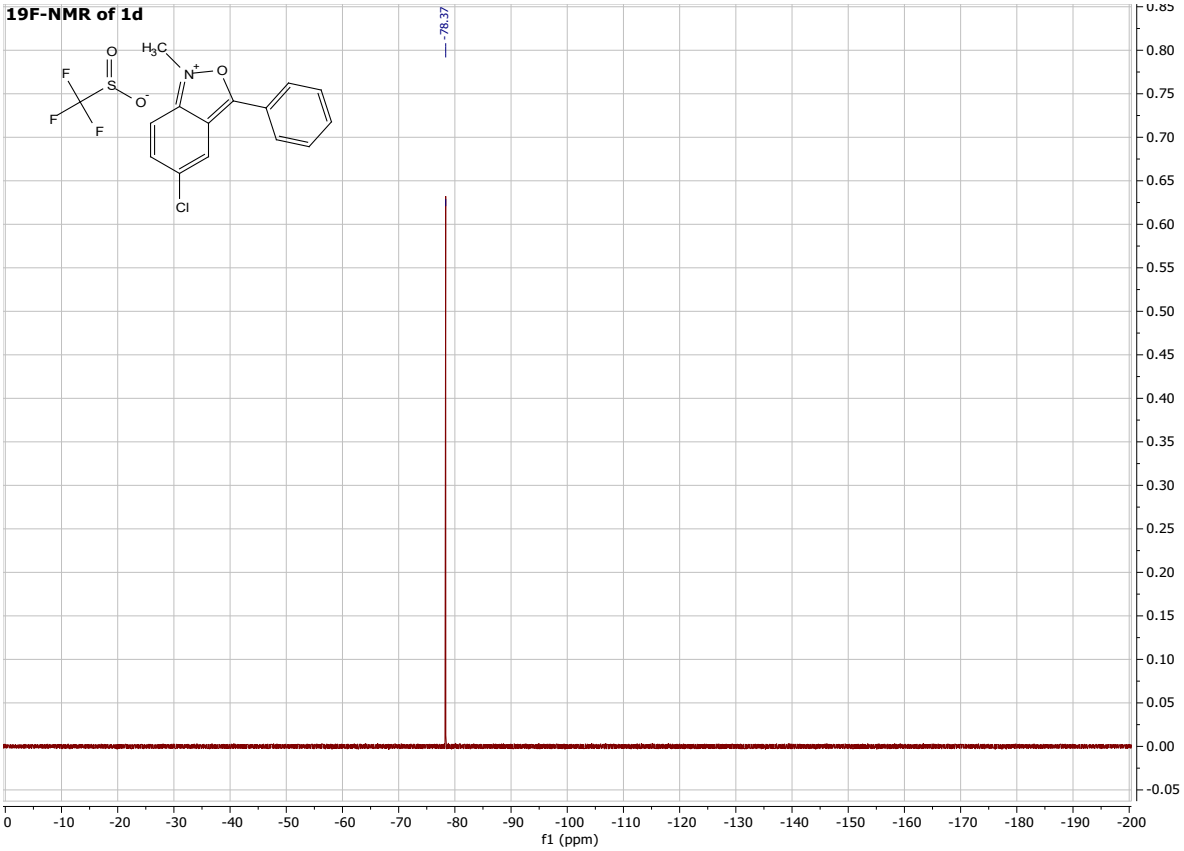
7. References

1. H. Saltzman, J. G. Sharefkin, M. S. Newman and N. Gill, *Organic Syntheses*, 1963, **43**, 60-61.
2. A. Garia, J. Grover and N. Jain, *European Journal of Organic Chemistry*, 2021, **2021**, 4125-4131.
3. M. Aidene, F. Belkessam, J.-F. Soulé and H. Doucet, *ChemCatChem*, 2016, **8**, 1583-1590.
4. R. Ikeda and R. Kuwano, *Chemistry – A European Journal*, 2016, **22**, 8610-8618.
5. J. Fan, C. Wan, G. Sun and Z. Wang, *The Journal of Organic Chemistry*, 2008, **73**, 8608-8611.
6. N. Rad and M. Mąkosza, *European Journal of Organic Chemistry*, 2018, **2018**, 376-380.
7. E. Y. Tsai, R. Y. Liu, Y. Yang and S. L. Buchwald, *Journal of the American Chemical Society*, 2018, **140**, 2007-2011.
8. B. H. Lipshutz and P. Papa, *Angewandte Chemie International Edition*, 2002, **41**, 4580-4582.
9. J. Chen, L. Ye and W. Su, *Organic & Biomolecular Chemistry*, 2014, **12**, 8204-8211.
10. K. G. Thakur, K. S. Srinivas, K. Chiranjeevi and G. Sekar, *Green Chemistry*, 2011, **13**, 2326-2329.
11. A. Boelke, L. D. Caspers and B. J. Nachtsheim, *Organic Letters*, 2017, **19**, 5344-5347.
12. B. J. Stokes, C. V. Vogel, L. K. Urnezis, M. Pan and T. G. Driver, *Organic Letters*, 2010, **12**, 2884-2887.
13. Z. F. Technologies, Development-scale, liquid-liquid and gas-liquid separators, https://www.zaiput.com/product/liquid-liquid-gas-separators/, (accessed 2023-07-10, 2023).

8. Copies of NMR spectra of new, isolated compounds.




13C-NMR of 1d
168.72
168.37
148.11
142.01
135.59
135.10
130.60
129.29
123.55
120.74
116.60
116.60
112.97
77.16 CDCl3
39.81
f1 (ppm)


19F-NMR of 1d
-78.37
f1 (ppm)