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Note

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Chemoselective Synthesis of Amines from Ammonium Hydroxide and Hydroxylamine in Continuous Flow

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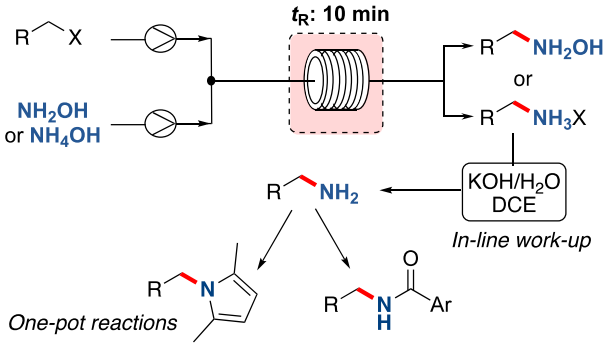
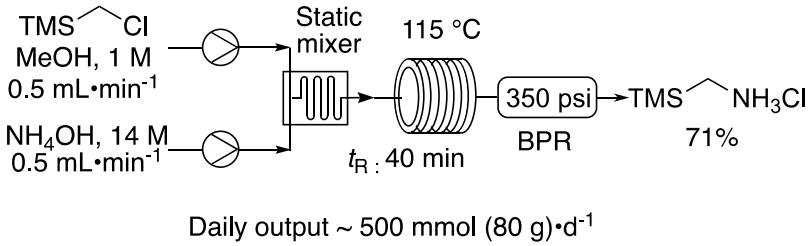
Abstract. The chemoselective amination of alkyl bromides and chlorides with aqueous ammonia and hydroxylamine was achieved in continuous flow to produce primary ammonium salts and hydroxylamines in high yields. An in-line work-up was designed to isolate the corresponding primary amine, which was also telescoped in further reactions, such as acylation and Paal–Knorr pyrrole synthesis. Monosubstituted epoxides are also compatible with the reaction conditions.



Nitrogen-containing compounds are essential for the pharmaceutical, agrochemical, and food additive industries.[1] Consequently, numerous methods have been investigated over the years to form carbon-nitrogen bonds. Among them, displacement reactions with nitrogen nucleophiles are versatile transformations allowing the synthesis of a large variety of amine products.[2] Unfortunately the simplest displacement reaction with ammonia and an electrophile is complicated by the formation of polyalkylated by-products. To overcome this problem, ammonia equivalents

have been developed, such as azides and phthalimides (Gabriel Synthesis).[3] In these cases, an additional step is necessary to reveal the amine moiety. The reductive amination of aldehydes and ketones is an alternative method to efficiently prepare amines, but again it is a two-steps synthesis, although it could be performed in a one-pot process.[4] Alternatively, special techniques were reported, such as microwave irradiation to promote the amination of alkyl halides using 7M ammonia solution in methanol at 130 °C for 0.25 to 2.5 h.[5] However, the scale up of such techniques is often limited. Furthermore, an amination process using commercially available cheap aqueous ammonia (and other amines such as hydroxylamine) is highly desirable. Recently, we delineated the synthesis of trimethylsilylmethylammonium chloride from trimethylsilylmethylchloride and ammonium hydroxide in a continuous flow process (scheme 1).[6]



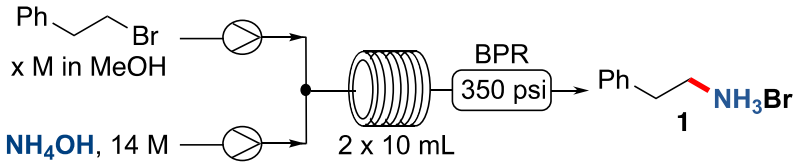
Scheme 1. Continuous-flow synthesis of $TMSCH_2NH_2$.[6]

Continuous flow technologies enable rapid reactions with excellent heat transfer, facilitate the manipulation of gas, and often decrease the formation of by-products.[7,8,9,10] Herein, we report a general amination procedure in flow, applicable to various electrophiles (alkyl halides and epoxides) with ammonia and hydroxylamine. In addition, we describe in-line processes whereby the amination reaction was combined to an additional step.

We first investigated the amination of phenethyl bromide with ammonia under the previously developed reaction conditions.[6] Low yields were obtained with the formation of the secondary ammonium salt (resulting from the double addition of ammonia to the bromide) as the major by-product (Table 1, entry 1). When the concentration of the bromide was decreased to 0.25 M (thus

increasing the number of equiv of ammonium hydroxide from 28 to 56 equiv) with a 30 min residence time, the yield increased to 74% (entry 2). To improve the mixing, a faster flow rate was then tested using a T-mixer; the same yield was obtained with a residence time (t_R) of 10 min at 160 °C (entry 5). Finally, a 0.1 M solution of phenethyl bromide produced the desired ammonium salt **1** in 94% yield (entry 6, 93% isolated yield, Table 2, entry 1).

Table 1. Amination of Phenethyl Bromide with Ammonia

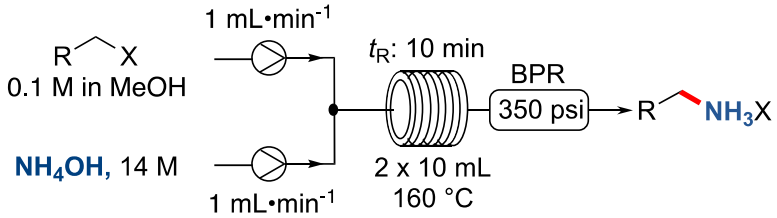


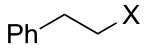
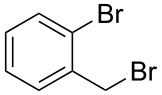
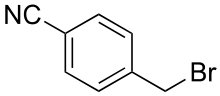
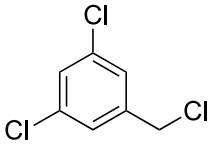
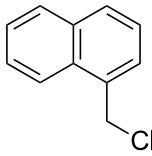
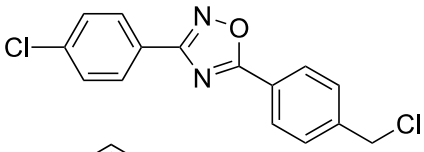
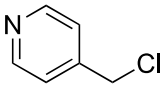
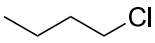
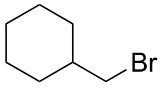
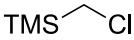
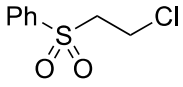
entry	[bromide]	rate (mL•min^{-1})	t_R	temp	yield[a]
1	0.50 M	0.50	40 min	130 °C	44%
2	0.25 M	0.67	30 min	120 °C	74%
3	0.25 M	1.00	20 min	140 °C	72%
4	0.25 M	2.00	10 min	140 °C	71%
5	0.25 M	2.00	10 min	160 °C	74%
6	**0.10 M**	**2.00**	**10 min**	**160 °C**	**94%**

[a] NMR yield using maleic acid as an internal standard

High yield was observed with phenethyl iodide (Table 2, entry 2). Benzyl bromides and chlorides afforded the corresponding ammonium salts in excellent yields (entries 3–7). When the halide was not fully soluble in methanol, a mixture of methanol/THF was used (entries 4–6). The reaction is also compatible with heterocycles (entries 7–8). Primary and secondary chlorides and bromides were successfully reacted, furnishing the corresponding ammonium salt in high yields (entries 9–12). Similar yield for the synthesis of $TMSCH_2NH_3Cl$ was obtained under these conditions (entry 13). Despite the high temperature, product **14** was also isolated in high yield (entry 14).

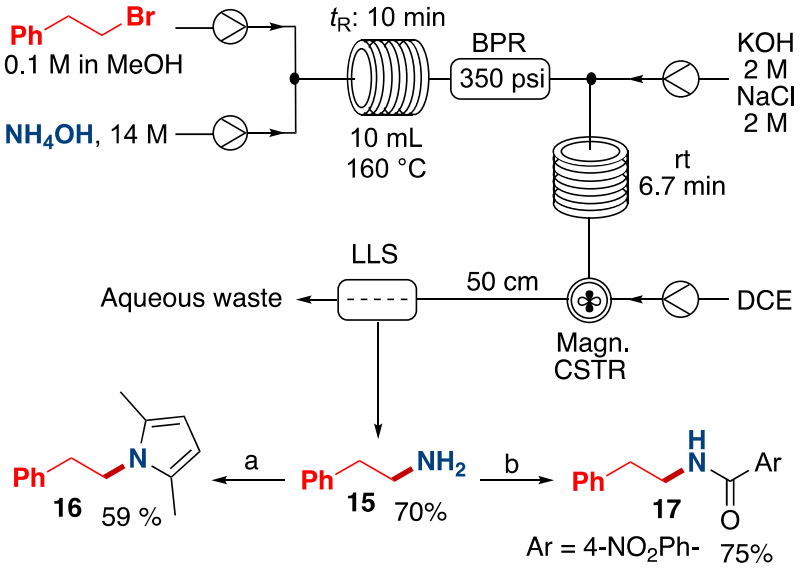
Table 2. Amination of Halides with Ammonia



Entry	R X	R NH$_3$X
1	 X = Br	93% (**1**)
2	X = I	91% (**2**)
3		90% (**3**)
4		90%[a] (**4**)
5		91% (**5**)
6		81%[a] (**6**)
7		97%[a] (**7**)
8		85% (**8**)
9		98%[b] (**9**)
10		97%[b] (**10**)
11		86%[c] (**11**)
12		86%[b,c] (**12**)
13		73% (**13**)
14		81% (**14**)

[a] 0.1 M in MeOH/THF (1:1). [b] 0.25 M in MeOH. [c] t_R: 5 min (rate : 2 mL/min)

An in-line neutralization of the ammonium salt was considered to free-base the amine (Scheme 2). A mixture of aqueous potassium hydroxide and sodium chloride was injected after the back-pressure regulator, and the resulting mixture was passed through a 10 mL-PFA loop. The reaction mixture was then combined with dichloroethane (DCE) in a Continuous Stirred Tank Reactor (CSTR). The organic layer was separated from the aqueous waste using a Zaiput liquid-liquid separator and evaporation of the solvent afforded the pure amine **15** in 70% yield.

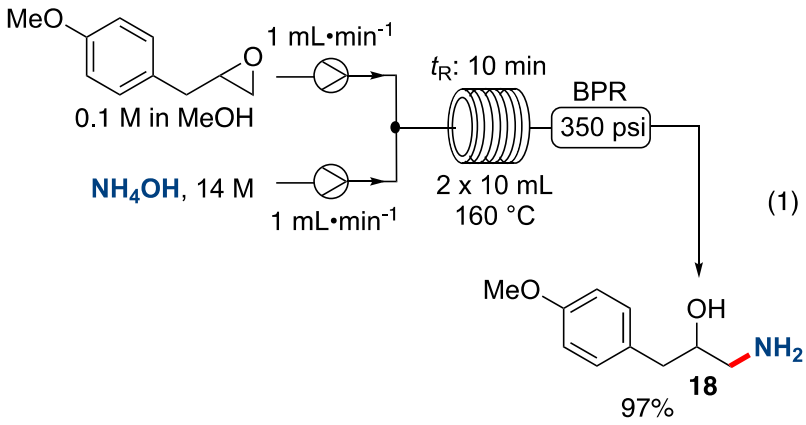


All flow pump are fixed to 0.5 mL•min^{-1}; Magn.CSTR: Magnetic Continous Stirred Tank Reactor; LLS: Liquid-Liquid Separator; a) Acetylacetone (1.05 equiv), 100 °C, 1 h; b) 4-Nitrobenzoyl chloride (2.4 equiv), NEt_3 (2.4 equiv), 25 °C, 1 h.

Scheme 2. In-line Work-up and One-pot Reactions

One of the advantages of continuous flow syntheses is the ability to telescope a series of reactions. In this vein, the stream of amine solution **15** (without isolation) was further reacted in an acylation and a Paal–Knorr pyrrole synthesis. Pyrrole **16** was isolated in 59% yield, whereas the addition of 4-nitrobenzoyl chloride afforded amide **17** in 75% yield (Scheme 2).

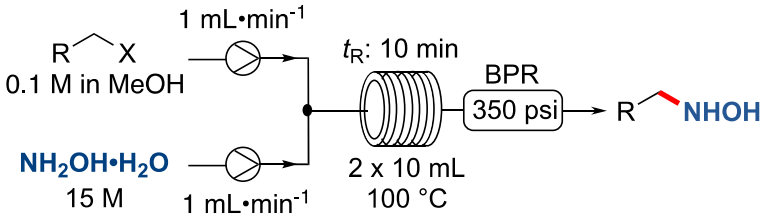
Monosubstituted epoxides are compatible with the reaction conditions: it underwent a ring opening reaction with ammonium hydroxide, affording the corresponding amino alcohol **18** in high yields (Eq 1).

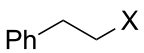
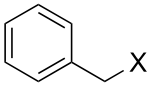
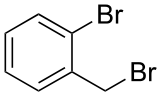
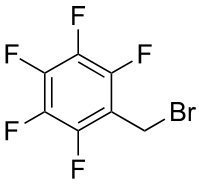
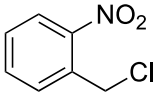
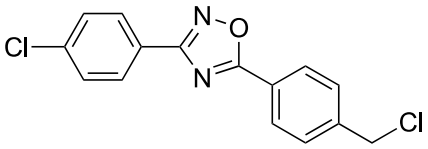
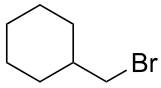
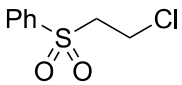


(1)

The reaction was then tested with another nucleophile, hydroxylamine, also known to afford multiple products with halides.[11] Typically *N*-alkylhydroxylamines are prepared by reduction of oximes in mild conditions[12] or by reduction of a nitro group.[13,14] The reaction of commercially available 50% hydroxylamine solution with phenethyl bromide in continuous flow afforded the corresponding *N*-alkylhydroxylammonium salt. To separate the desired product from the remaining hydroxylamine, the resulting salt was treated with a saturated aqueous solution of sodium bicarbonate, affording the corresponding *N*-alkylhydroxylamine (Table 3). The optimal temperature for the amination of alkyl bromide was 100 °C, as lower yields resulting from overreaction was observed at higher temperature. Furthermore, decreasing the number of equiv of hydroxylamine also afforded lower yields of the desired product. Under the optimal reaction conditions with a residence time of 10 min, *N*-alkylhydroxylamine **19** was isolated from phenethyl bromide and iodide in 97% and 88% yields respectively (Table 3, entries 1, 2). Various benzyl chlorides and bromides were successfully reacted producing the desired *N*-alkylhydroxylamine with good to excellent yields (entries 3-8).

Table 3. Amination of Halides with Hydroxylamine



Entry	R X	R NHOH
1	 X = Br	>99% (**19**)
2	X = I	88% (**19**)
3	 X = Cl	65% (**20**)
4	X = Br	76% (**20**)
5		86 (**21**)
6[a]		97 (**22**)
7		70 (**23**)
8[a]		80 (**24**)
9[b]		71 (**25**)
10		50 (**26**)

[a] 0.1 M in MeOH/THF (1:5). [b] 0.1 M in NMP

The reaction is compatible with various functional groups, including heterocycles and nitro groups (entries 7, 8). Alkylhydroxylamines **25** and **26** were also isolated in moderate to good yields (entries 9, 10).

In conclusion, the amination of alkyl halides and monosubstituted epoxides with nucleophilic amine derivatives in continuous flow produced the corresponding amine products in good to high yields. The process is fast and safe and can be easily combined with in-line purification or further derivatization.

Experimental Section.

General Information. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by UV absorbance, cerium ammonium molybdate, aqueous potassium permanganate or ninhydrin. Flash chromatography was performed using silica gel (230−400 mesh) with the indicated solvent system. Infrared spectra are reported in reciprocal centimeters (cm−1). Only the most important and relevant frequencies are reported. ^{1}H NMR spectra were recorded in $CDCl_3$, unless otherwise noted. Chemical shifts for ^{1}H NMR spectra were recorded in parts per million with the solvent resonance as the reference $CDCl_3$ (δ = 7.26 ppm), DMSO-d_6 (δ = 2.50 ppm) and D_2O (δ = 4.79 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for $^{13}C\{^{1}H\}$ NMR spectra are recorded in parts per million using the central peak of $CDCl_3$ (δ = 77.16 ppm) or DMSO-d_6 (39.52 ppm) as the reference. All ^{13}C NMR spectra were obtained with complete proton decoupling. When ambiguous, proton and carbon assignments were

established through COSY, HSQC, and/or DEPT experiments. All NMR yields were determined using quantitative ^{1}H NMR spectra using maleic acid as an internal standard with a 10-sec relaxation time. High resolution mass spectra analysis was performed by the Centre régional de spectroscopie de masse de l'Université de Montréal.

General Procedure A for the Amination of Alkyl Halides with Ammonia. Amination reactions were performed in a Vapourtec R-series continuous flow system equipped with two high temperature tube reactors (10 mL, stainless steel, 1.00 mm i.d). A stock solution of the halide (0.100 or 0.250 M in MeOH) was prepared in a 100 mL volumetric flask. The solution of the halide (0.100 M, 5.00-20.0 mL, 0.500-2.00 mmol) and saturated ammonium hydroxide (14.0 M, 5.00-20.0 mL, 70.0-280 mmol) were pumped at equal flow rates (1.00 or 2.00 mL/min) and directed into two successive 10 mL-stainless steel reactor heated at 160 °C, after being combined with a T-mixer. Upon exiting the second flow reactor, the combined reaction stream passed a back-pressure regulator (350 psi) before being collected into a flask. The solvent was evaporated and the residue was dried under high vacuum. If necessary, the product was triturated in AcOEt/Hexanes (3/7, 10 mL/1 mmol) for 30 min, filtered, and washed (2 x 10 mL AcOEt/Hexanes [3:7]) to afford the ammonium salt product.

2-Phenylethan-1-ammonium bromide (1). The title compound was prepared from (2-bromoethyl)benzene (1.00 mmol, 0.100 M in MeOH) according to the general procedure **A**, with a residence time of 10 min. The desired ammonium salt was obtained as a white solid (188 mg, 93%) after trituration. mp 248–250 °C (lit. 256–259 °C);[15] ^{1}H NMR (400 MHz, DMSO) δ 7.79 (s (br), 3H), 7.35–7.31 (m, 2H), 7.26–7.23 (m, 3H), 3.04 (t, J = 8.4, 2H), 2.88 (t, J = 8.7, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 137.3, 128.6, 128.6, 126.7, 39.9, 32.9; IR (neat) 2989, 1593, 1496, 1461,

1390, 1257, 1135, 1012, 934, 904, 779, 744, 693, 591, 494; HRMS (ESI +) calcd. for $C_8H_{12}N$ $[M]^+$: 122.0964; found 122.0968 (ESI -) calcd. for Br $[M]^-$: 78.9194; found: 78.9204.

2-Phenylethan-1-ammonium iodide (2). The title compound was prepared from (2-iodoethyl)benzene (0.500 mmol, 0.100 M in MeOH) according to the general procedure **A**, with a residence time of 10 min. The desired ammonium salt was obtained as a white solid (113 mg, 91%) after trituration. mp 262–265 °C (lit. 267 °C);[16] ^{1}H NMR (400 MHz, DMSO) δ 7.73 (s (br), 3H), 7.35–7.22 (m, 5H), 3.04 (t, J = 8.8 Hz, 2H), 2.88 (t, J = 8.8 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 137.3, 128.6, 128.6, 126.7, 39.9, 32.9; IR (neat) 2989, 1593, 1496, 1461, 1390, 1257, 1135, 1012, 934, 904, 779, 744,693, 591, 494; HRMS (ESI +) calcd. for $C_8H_{12}N$ $[M]^+$: 122.0964; found: 122.0965 (ESI -) calcd. for I $[M]^-$: 126.9050, found: 126.9062.

(2-Bromophenyl)methanammonium bromide (3). The title compound was prepared from 1-bromo-2-(bromomethyl)benzene (0.500 mmol, 0.100 M in MeOH) according to the general procedure **A**, with a residence time of 10 min. The desired ammonium salt was obtained as a white solid (240 mg, 90%) after trituration. mp 159–161 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.74 (dd, J = 8.0, 1.1 Hz, 1H), 7.54–7.44 (m, 2H), 7.40–7.35 (m, 1H), 4.35 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 133.2, 131.9, 131.2, 131.1, 128.4, 123.8, 43.2; IR (neat) 2886, 1493, 1434, 1026, 757, 657, 450, 427, 408; HRMS (ESI +) calcd. for C_7H_9BrN $[M]^+$: 185.9912; found: 185.9917 (ESI -) calcd. for Br $[M]^-$: 78.9189; found: 78.9193.

(4-Cyanophenyl)methanammonium bromide (4). The title compound was prepared from 4-(bromomethyl)benzonitrile (0.200 mmol, 0.100 M in MeOH:THF (5:1)) according to the general procedure **A**, with a residence time of 10 min. The desired ammonium salt was obtained as a white

solid (38.4 mg, 90 %). mp 220–223 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.25 (s (br), 3H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 4.15 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 139.5, 132.5, 129.8, 118.5, 111.2, 41.7; IR (neat) 2977, 2880, 2031, 1991, 1589, 1460, 1378, 1215, 1101, 960, 874, 522; HRMS (ESI +) calcd. for $C_8H_9N_2$ $[M]^+$: 133.0766; found: 133.0761.

(3,5-Dichlorophenyl)methanammonium chloride (5). The title compound was prepared from 1,3-dichloro-5-(chloromethyl)benzene (2.00 mmol, 0.100 M in MeOH) according to the general procedure **A**, with a residence time of 10 min. The desired ammonium salt was obtained as a white solid (288 mg, 91%) after trituration. mp 240–242 °C (lit. 267–269 °C);[17] ^{1}H NMR (400 MHz, DMSO) δ 8.32 (s (br), 3H), 7.64 (s, 3H), 4.04 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 138.8, 134.4, 128.4, 128.3, 41.4; IR (neat) 2924, 1573, 1524, 1431, 1209, 1100, 904, 879, 858, 836, 795, 667, 433; HRMS (ESI +) calcd. for $C_7H_8Cl_2N$ $[M]^+$: 176.0028; found: 176.0021.

Naphthalen-1-ylmethanammonium chloride (6).[18] The title compound was prepared from 1-(chloromethyl)naphthalene (2.25 mmol, 0.100 M in MeOH:THF (1:1)) according to the general procedure **A**, with a residence time of 10 min. The desired ammonium salt was obtained as a white solid (353 mg, 81%) after trituration. mp 243–245 °C (lit. 249–250 °C);[19] ^{1}H NMR (400 MHz, DMSO) δ 8.26 (s (br), 3H) 8.14 (d, *J* = 7.8 Hz, 1H), 7.97 (t, *J* = 9.6 Hz, 2H), 7.66–7.52 (m, 4H) 4.49 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 133.2, 130.7, 130.0, 129.0, 128.6, 127.3, 126.7, 126.2, 125.4, 123.5, 38.8; IR (neat) 2887, 1572, 1493, 1403, 1140, 917, 858, 797, 772, 667, 434, 409; HRMS (ESI +) calcd. for $C_{11}H_{12}N$ $[M]^+$: 158.0964; found: 158.0956.

4-(3-(4-(Chloromethyl)phenyl)-1,2,4-oxadiazol-5-yl)benzenammonium chloride (7). The title compound was prepared from 5-(4-(chloromethyl)phenyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole

(0.200 mmol, 0.100 M in MeOH:THF (1:1)) according to the general procedure **A**, with a residence time of 5 min. The desired ammonium salt was obtained as an orange solid (63 mg, 97 %). mp 215–218 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.24 (d, *J* = 8.4 Hz, 2H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.94 (s (br), 3H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.70, (d, *J* = 8.4 Hz, 2H), 4.14 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 175.8, 168.0, 140.1, 136.9, 130.4, 130.0, 129.4, 128.6, 125.4, 123.6, 42.4; IR (neat) 2964, 2170, 2043, 1991, 1596, 1466, 1409, 1094, 835, 758; HRMS (ESI +) calcd. for $C_{15}H_{13}ClN_3O$ $[M]^+$: 286.0742; found: 286.0734.

Pyridin-4-ylmethanammonium chloride (8). The title compound was prepared from 4-(chloromethyl)pyridine hydrochloride (0.500 mmol, 0.100 M in MeOH) according to the general procedure **A**, with a residence time of 10 min. The desired ammonium salt was obtained as a white solid (123 mg, 85%) after trituration. mp 188–190 °C; ^{1}H NMR (300 MHz, D_2O) δ 8.61 (d, *J* = 6.1 Hz, 2H), 7.52 (d, *J* = 6.1 Hz, 2H), 4.29 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, D_2O) δ 149.2, 143.0, 123.6, 41.7; IR (neat) 2824, 1610, 1524, 1392, 1223, 1125, 987, 837, 797, 590, 505; HRMS (ESI +) calcd. for $C_6H_9N_2$ $[M]^+$: 109.0760; found: 109.0764.

Propan-1-ammonium bromide (9). The title compound was prepared from 1-bromopropane (0.500 mmol, 0.250 M in MeOH) according to the general procedure **A**, with a residence time of 10 min. The desired ammonium salt was obtained as a white solid (69 mg, 98%). mp 157–160 °C (lit. 169–172 °C);[20] ^{1}H NMR (400 MHz, D_2O) δ 2.99 (t, *J* = 7.4 Hz, 2H), 1.70 (sex, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, D_2O) δ 41.1, 20.2, 10.1; IR (neat) 2966, 1499, 1393, 988, 753, 446; HRMS (ESI +) calcd. for $C_3H_{10}N$ $[M]^+$: 60.08078; found 60.0810 (ESI -) calcd. for Br $[M]^-$: 78.9194; found: 78.9185.

Butan-1-ammonium chloride (10). The title compound was prepared from 1-chlorobutane (0.500 mmol, 0.250 M in MeOH) according to the general procedure **A**, with a residence time of 10 min. The desired ammonium salt was obtained as a white solid (106 mg, 97%). mp 205-207 °C (lit. 208-209 °C);[21] ^{1}H NMR (400 MHz, D_2O) δ 2.95 (t, *J* = 7.5 Hz , 2H), 1.59 (qn, *J* = 7.6 Hz , 2H), 1.34 (sex, *J* = 7.5 Hz, 2H) 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, D_2O) δ 39.3, 28.8, 19.0, 12.9; IR (neat) 2959, 2929, 2871, 1602, 1510, 1399, 1161, 1075, 1025, 914, 741, 479, 434; HRMS (ESI+) calcd. for $C_4H_{12}N$ $[M]^+$: 74.0964; found: 74.0966.

Cyclohexylmethanammonium bromide (11). The title compound was prepared from (bromomethyl)cyclohexane (1.00 mmol, 0.100 M in MeOH) according to the general procedure **A**, with a residence time of 5 min. The desired ammonium salt was obtained as a white solid (166 mg, 86%) after trituration. mp 262–265 °C; ^{1}H NMR (400 MHz, DMSO) δ 7.66 (s (br), 3H), 2.63 (d, *J* = 6.9 Hz, 2H), 1.73–1.48 (m, 6H), 1.22–1.07 (m, 3H), 0.95–0.86 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 44.3, 35.4, 29.7, 25.6, 25.0; IR (neat) 2920, 2850, 1597, 1503, 1393, 990, 470; HRMS (ESI +) calcd. for $C_{11}H_{12}N$ $[M]^+$: 158.0964; found: 158.0956; (ESI -) calcd. for Br $[M]^-$: 78.9194; found: 78.9203.

Propan-2-ammonium bromide (12). The title compound was prepared from 2-bromopropane (5.00 mmol, 0.250 M in MeOH) according to the general procedure **A**, with a residence time of 5 min. The desired ammonium salt was obtained as a yellowish solid (600 mg, 86%). mp > 230 °C; ^{1}H NMR (400 MHz, D_2O) δ 3.53 (sep, *J* = 6.6 Hz, 1H) 1.32 (d, *J* = 6.6 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, D_2O) δ 44.1, 19.8; IR (neat) 2977, 1620, 1504, 1396, 1213; HRMS (ESI +) calcd. for $C_3H_{10}N$ $[M]^+$: 60.0808; found: 60.0800; (ESI -) calcd. for Br $[M]^-$: 78.9189, found: 78.9185.

(Trimethylsilyl)methanammonium chloride (13). The title compound was prepared from (chloromethyl)trimethylsilane (2.50 mmol, 0.100 M in MeOH) according to the general procedure **A**, with a residence time of 10 min. The desired ammonium salt was obtained as a white solid (254 mg, 73% yield). mp 240-242 °C (lit. 240–241 °C);[22] ^{1}H NMR (300 MHz, D_2O) δ 2.45 (s, 2H), 0.17 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, D_2O) δ 28.4, -3.9.

2-(Phenylsulfonyl)ethan-1-ammonium chloride (14). The title compound was prepared from 2-chloroethyl phenyl sulfone (0.500 mmol, 0.100 M in MeOH) according to the general procedure **A**, with a residence time of 10 min. The desired ammonium salt was obtained as a white solid (90 mg, 81%) after trituration. mp 155–158 °C (lit. 155–155.5 °C);[23] ^{1}H NMR (400 MHz, DMSO) δ 8.25 (s (br), 3H), 7.94 (d, J = 7.8 Hz, 2H), 7.81 (t, J = 7.5 Hz, 1H), 7.71 (t, J = 7.8 Hz, 2H), 3.72 (t, J = 7.6 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO) δ 138.0, 134.5, 129.8, 50.0, 33.1; IR (neat) 2833**,** 1562, 1447, 1400, 1298, 1144, 1084, 827, 803, 750, 689, 533; HRMS (ESI+) calcd. for $C_8H_{12}NO_2S$ $[M]^+$: 186.0583; found: 186.0583.

2-Phenylethan-1-amine (15).[24] The reaction was performed in a Vapourtec R-series continuous flow system equipped with a high temperature tube reactor (10 mL, stainless steel, 1.00 mm i.d). A stock solution of 2-bromoethylbenzene (0.100 M in MeOH) was prepared in a 25 mL volumetric flask. The solution of the halide (0.100 M, 10.00 mL, 1.00 mmol) and saturated ammonium hydroxide (14.0 M, 10.00 mL, 140.0 mmol) were pumped at equal flow rates (0.5 mL/min) and directed into a 10 mL stainless steel reactor heated at 160 °C, after being combined with a T-mixer. Upon exiting the second flow reactor, the combined reaction stream passed a back-pressure regulator (350 psi). A continuous stream of KOH/NaCl 2M was injected at 0.5 mL/min after the BPR in a 10 mL PFA reactor. The reaction was combined in a magnetic CSTR with a stream of

DCE (0.5 mL/min), then passed by a 50 cm PFA tubing. The organic layer was then separated using a Zaiput liquid-liquid separator. A solution of free amine was collected in a round bottom flask and the solvent was evaporated to afford the amine as a colorless liquid (85.1 mg, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.26 (m, 2H), 7.23–7.17 (m, 3H), 2.95 (t, J = 6.9 Hz, 2H), 2.73 (t, J = 6.9 Hz, 2H), 1.26 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 140.0, 129.0, 128.6, 126.3, 43.8, 40.3.

2,5-Dimethyl-1-phenethyl-1H-pyrrole (16).[25] The reaction was performed in a Vapourtec R-series continuous flow system equipped with a high temperature tube reactor (10 mL, stainless steel, 1.00 mm i.d). A stock solution of 2-bromoethylbenzene (0.100 M in MeOH) was prepared in a 500 mL volumetric flask. The solution of the halide (0.100 M, 5.00 mL, 0.500 mmol) and saturated ammonium hydroxide (14.0 M, 5.00 mL, 70.0 mmol) were pumped at equal flow rates (0.5 mL/min) and directed into a 10 mL-stainless steel reactor heated at 160 °C, after being combined with a T-mixer. Upon exiting the second flow reactor, the combined reaction stream passed a back-pressure regulator (350 psi). A continuous stream of KOH/NaCl 2M was injected at 0.5 mL/min after the BPR in a 10 mL PFA reactor. The reaction was combined in a magnetic CSTR with a stream of DCE (0.5 mL/min). The organic layer was separated using a Zaiput liquid-liquid separator and collected in a round bottom flask. To this solution was added acetonylacetone (70 µL, 0.60 mmol, 1.2 equiv) and the reaction was heated at reflux during 1 h. The reaction was quenched with aq. NH_4Cl (25 mL), then the layers were separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, affording the desired pyrrole (58.9 mg, 0.295 mmol, 59%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (m, 3H), 7.18–7.11 (m,

2H), 5.81 (s, 2H), 4.05–3.93 (m, 2H), 2.97–2.88 (m, 2H), 2.19 (s, 6H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 138.7, 129.0, 128.7, 127.5, 126.7, 105.3, 45.4, 37.7, 12.5.

4-nitro-*N*-phenethylbenzamide (17).[26] The reaction was performed in a Vapourtec R-series continuous flow system equipped with a high temperature tube reactor (10 mL, stainless steel, 1.00 mm i.d). A stock solution of 2-bromoethylbenzene (0.100 M in MeOH) was prepared in a 500 mL volumetric flask. The solution of the halide (0.100 M, 5.00 mL, 0.500 mmol) and saturated ammonium hydroxide (14.0 M, 5.00 mL, 70.0 mmol) were pumped at equal flow rates (0.5 mL/min) and directed into a 10 mL-stainless steel reactor heated at 160 °C, after being combined with a Y-mixer. Upon exiting the second flow reactor, the combined reaction stream passed a back-pressure regulator (350 psi). A continuous stream of KOH/NaCl 2M was injected at 0.5 mL/min after the BPR in a 10 mL PFA reactor. The reaction was combined in a magnetic CSTR with a stream of DCE (0.5 mL/min). The organic layer was separated using a Zaiput liquid-liquid separator and collected in a round bottom flask. To this solution was added was added triethylamine (174 µL, 1.25 mmol, 2.50 equiv), 4-(dimethylamino)pyridine (6 mg, 0.05 mmol, 0.1 equiv) and 4-nitrobenzoyl chloride (118 µL, 1.25 mmol, 2.50 equiv) and the reaction was stirred 1 h at 25 °C. The reaction was quenched with aq NH_4Cl (25 mL), then the layers were separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography on silica gel using 80/20 to 70/30 Hexanes/AcOEt. The desired compound (102 mg, 0.377 mmol, 75%) was obtained as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38-8.16 (m, 2H), 7.97–7.75 (m, 2H), 7.45–7.30 (m, 2H), 7.30–7.20 (m, 3H), 6.37 (s (br), 1H), 3.75 (app. q, J = 6.9 Hz, 2H), 2.96 (t, J = 6.9 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 165.6, 149.6, 140.3, 138.6, 128.9, 128.9, 128.1, 126.9, 123.9, 41.5, 35.6.

1-Amino-3-(4-methoxyphenyl)propan-2-ol (18). The ring opening reaction was performed in a Vapourtec R-series continuous flow system equipped with two high temperature tube reactors (10 mL, stainless steel, 1.00 mm i.d). A solution of 2-(4-methoxybenzyl)oxirane (5.00 mL, 0.500 mmol, 0.100 M in MeOH) and saturated ammonium hydroxide (14.0 M, 5.00 mL, 70.0 mmol) were pumped at equal flow rates (2.00 mL/min) and directed into two successive 10 mL-stainless steel reactor heated at 160 °C, after being combined with a T-mixer. Upon exiting the second flow reactor, the combined reaction stream passed a back-pressure regulator (350 psi) before being collected into a flask. The solvent was evaporated and the residue was dried under high vacuum. The title amino alcohol was isolated (87.9 mg, 97%) as a colorless oil which crystalize over time. mp 182-183 °C; ^{1}H NMR (500 MHz, DMSO) δ 7.15–7.08 (m, 2H), 6.85–6.79 (m, 2H), 3.71 (s, 3H), 3.55–3.47 (m, 1H), 2.61 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.54 (dd, *J* = 12.6, 6.0 Hz, 1H), 2.43–2.35 (m, 1H).; ^{13}C{^{1}H} NMR (125 MHz, DMSO) δ 157.4, 131.4, 130.2, 113.4, 73.1, 54.9, 47.0, 40.0; IR (neat) 3255, 2931, 2835, 1655, 1610, 1509, 1462, 1243, 1107, 1082, 1031, 811; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{10}H_{15}NaNO_2$ 205.0976; Found 205.0875.

General Procedure B for the Amination of Alkyl Halides with Hydroxylamine. Amination reactions were performed in a Vapourtec R-series continuous flow system equipped with two high temperature tube reactors (10 ml, stainless steel, 1 mm i.d). A solution of halide (0.10 M in MeOH) was prepared in a 25 ml volumetric flask. The solution of halide (0.10 M, 1.0 mmol, 10 ml) and hydroxylamine in water (15 M, 150 mmol, 10 ml) were pumped with two separate pumps at equal flow (1 ml/min) and directed into two successive 10 ml stainless steel reactors heated at 100 °C, after being combined with a T-mixer. After exiting the second flow reactor, the combined reaction stream passed through a back-pressure regulator (350 psi) before being collected. The collected

mixture was then treated with $NaHCO_3$ (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. Purification by flash chromatography furnish the desired product.

***N*-Phenethylhydroxylamine (19).**[13] The title compound was prepared from (2-bromoethyl)benzene (1.00 mmol, 0.100 M in MeOH) according to the general procedure **B**, with a residence time of 10 min. The desired *N*-alkylhydroxylamine was obtained as a white solid (137 mg, >99%) after purification by flash chromatography using Hexanes/EtOAc 8:2 then 0:100. R_f 0.26 (Hexane/EtOAc 4:6); mp 83-85 °C (lit. 85 °C);[13] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H), 7.23–7.20 (m, 3H), 5.67 (s (br), 2H), 3.19 (t, J = 7.1 Hz, 2H), 2.88 (t, J = 7.1 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 139.4, 129.0, 128.7, 126.5, 55.1, 33.5; FTIR (neat) 3262, 2906, 2828, 1634, 1012, 695, 459, 436, 421; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_8H_{12}NO$ 138.0913, found 138.0917.

***N*-Phenethylhydroxylamine (19).**[13] The title compound was prepared from (2-iodoethyl)benzene (1.00 mmol, 0.100 M in MeOH) according to the general procedure **B**, with a residence time of 10 min. The desired *N*-alkylhydroxylamine was obtained as a white solid (121 mg, 88%) after purification by flash chromatography using Hexanes/EtOAc 8:2 then 0:100. R_f 0.26 (Hexane/EtOAc 4:6); mp 83–85 °C (lit. 85 °C);[13] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.29 (m, 2H), 7.23–7.20 (m, 3H), 5.67 (s (br), 2H), 3.19 (t, J = 7.1 Hz, 2H), 2.88 (t, J = 7.1 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 139.4, 129., 128.7, 126.5, 55.1, 33.5; FTIR (neat) 3262, 2906, 2828, 1634, 1012, 695, 459, 436, 421; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_8H_{12}NO$ 138.0913, found 138.0917.

***N*-Benzylhydroxylamine (20).**[27] The title compound was prepared from (chloromethyl)benzene (1.00 mmol, 0.1 M in MeOH) according to the general procedure **B**, with a residence time of 10 min. The desired *N*-alkylhydroxylamine was obtained as an off-white solid (79.6 mg, 65%) after purification by flash chromatography using hexane/EtOAc 5:5 then 0:100. R_f 0.37 Hexane/EtOAc 5:5); mp 55–56 °C (lit. 54–56 °C);[28] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5H), 5.9 (s (br), 2H), 3.99 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 137.1, 129.3, 128.7, 127.8, 58.4; FTIR (neat): 3257, 2911, 2864, 2359, 1454, 1018, 746, 696, 491; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_7H_{10}NO$ 124.0756; found 124.0755.

***N*-Benzylhydroxylamine (20).**[27] The title compound was prepared from (bromomethyl)benzene (1.00 mmol, 0.1 M in MeOH) according to the general procedure **B**, with a residence time of 10 min. The desired *N*-alkylhydroxylamine was obtained as an off-white solid (94 mg, 76%) after purification by flash chromatography using hexane/EtOAc 5:5 then 0:100. R_f 0.37 Hexane/EtOAc 5:5); mp 55–56 °C (lit. 54–56 °C);[28] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.28 (m, 5H), 5.9 (s (br), 2H), 3.99 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 137.1, 129.3, 128.7, 127.8, 58.4; FTIR (neat): 3257, 2911, 2864, 2359, 1454, 1018, 746, 696, 491; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_7H_{10}NO$ 124.0756; found 124.0755.

***N*-(2-Bromobenzyl)hydroxylamine (21).** The title compound was prepared from 1-bromo-2-(bromomethyl)benzene (1.00 mmol, 0.1 M in MeOH) according to the general procedure **B**, with a residence time of 10 min. The desired *N*-alkylhydroxylamine was obtained as a white solid (173 mg, 86%) after purification by flash chromatography using Hexane/EtOAc 7:3 then 0:100. R_f 0.37 (Hexane/EtOAc 6:4); mp 79–81°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, J = 7.7, 1.1 Hz, 1H), 7.38 (dd, J = 7.6, 1.6 Hz, 1H), 7.28 (dt, J = 7.7, 1.6 Hz, 1H), 7.16 (dt, J = 7.6, 1.2 Hz, 1H), 5.71 (s

(br), 2H), 4.12 (s, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 136.3, 133.1, 131.9, 129.5, 127.6, 124.6, 58.1; FTIR (neat): 3260, 2921, 1470, 1439, 1024, 749; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for C_7H_9BrNO 201.9862, found 201.9869.

***N*-((perfluorophenyl)methyl)hydroxylamine (22).** The title compound was prepared from 1-(bromomethyl)-2,3,4,5,6-pentafluorobenzene (1.00 mmol, 0.1 M in MeOH) according to the general procedure **B**, with a residence time of 10 min. The desired *N*-alkylhydroxylamine was obtained as a white solid (206 mg, 97%) after purification by flash chromatography using Hexane/EtOAc 0:100. R_f 0.37 (Hexane/EtOAc 6:4); mp 111–113 °C (lit. 110–111 °C);[29] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s (br), 1H), 5.39 (s (br), 1H), 4.16 (s, 2H); $^{13}C\{^{1}H\}$ NMR (176 MHz, $CDCl_3$) δ 145.7 (dm, J = 248 Hz), 140.9 (dm, J = 249 Hz), 137.4 (dm, J = 250 Hz), 110.8 (td, J = 14, 3 Hz), 45.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -144.8–-144.9 (m), -156.1 (t, J = 21 Hz), -163.5 – -163.7; FTIR (neat) 3268, 3252, 3186, 2904, 2361, 1505, 1123, 1020, 926; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_7H_5F_5NO$ 214.0285; found 214.0295.

***N*-(2-nitrobenzyl)hydroxylamine (23).** The title compound was prepared from 1-(chloromethyl)-2-nitrobenzene (1 mmol, 0.1 M in MeOH) according to the general procedure **B**, with a residence time of 10 min. The desired *N*-alkylhydroxylamine was obtained as a pale yellow solid (118 mg, 70%) after purification by flash chromatography using Hexane/EtOAc 7:3 then 0:100. R_f 0.37 (Hexane/EtOAc 5:5); mp 66–67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, J = 8.2, 1.1 Hz, 1H), 7.62–7.55 (m, 2H), 7.47–7.44 (m, 1H), 6.28 (s (br), 1H), 4.27 (s, 2H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 149.5, 133.3, 133.1, 132.6, 128.8, 125.0, 55.1; FTIR (neat):

3271, 2942, 2878, 2360, 2342, 1519, 1342, 1018, 729; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_7H_9N_2O_3$ 169.0609; found 169.0616.

***N*-(4-(3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)benzyl)hydroxylamine (24).** The title compound was prepared from 5-(4-(chloromethyl)phenyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (1 mmol, 0.1M in MeOH:THF (1:5)) according to the general procedure **B**, with a residence time of 10 min. The desired *N*-alkylhydroxylamine was obtained as a white solid (240 mg, 80%) after purification by flash chromatography using Hexane/EtOAc 6:4 then 0:100. R_f 0.35 (Hexane/EtOAc 2:8); mp 165–167 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.13 (d, J = 8.5 Hz, 2H), 8.10 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.36 (s (br), 1H), 6.27 (s (br), 1H), 3.99 (s, 2H); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ 176.17, 167.92, 146.21, 136.85, 129.98, 129.92, 129.37, 128.12, 125.54, 122.00, 57.33; FTIR (neat): 3267, 2359, 2342, 1636, 1414, 1368, 1355, 1014, 757; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}ClN_3O_2$ 302.0690, found 302.0696.

***N*-(Cyclohexylmethyl)hydroxylamine (25).** The title compound was prepared from (bromomethyl)cyclohexane (1 mmol, 0.1 M in MeOH) according to the general procedure **B**, with a residence time of 20 min. The desired *N*-alkylhydroxylamine was obtained as a white solid (92 mg, 71%) after purification by flash chromatography using Hexane/EtOAc 8:2 then 0:100. R_f 0.32 (Hexane/EtOAc 5:5); mp 59–60 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (s (br), 2H), 2.78 (d, J = 6.5 Hz, 2H), 1.78–1.63 (m, 5H), 1.62–1.53 (m, 1H), 1.30–1.13 (m, 3H), 0.97–0.87 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 60.6, 35.2, 31.3, 26.6, 25.9; FTIR (neat): 3251, 3225, 3160, 2915, 2849, 2361, 2342, 1446, 1027, 959; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_7H_{16}NO$ 130.1226; found 130.1230.

***N*-(2-(Phenylsulfonyl)ethyl)hydroxylamine (26).** The title compound was prepared from 2-chloroethyl phenyl sulfone (1.00 mmol, 0.100 M in MeOH) according to the general procedure **B**, with a residence time of 10 min. The desired *N*-alkylhydroxylamine was obtained as a white solid (100 mg, 50 %) after purification by flash chromatography using Hexane/EtOAc 7:3 then 0:100. R_f 0.35 (Hexane/EtOAc 2:8); mp 68–70 °C (lit. 67–68 °C);[12b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.92 (m, 2H), 7.69–7,66 (m, 1H), 7.60–7.57 (m, 2H), 5.68 (s (br), 2H), 2.43 (t, J = 6.1 Hz, 2H), 3.33 (t, J = 6.1 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 139.3, 134.1, 129.6, 128.1, 53.2, 47.4; FTIR (neat) 3277, 1447, 1286, 1142, 1085, 1039, 734, 689, 578, 535; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_8H_{12}NO_3S$ 202.0532, found 202.0527.

Supporting Information Available: Characterization spectra (^{1}H and ^{13}C{^{1}H} NMR) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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