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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.0c00193 • Publication Date (Web): 25 Aug 2020

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Convenient Continuous Flow Synthesis of *N*-Methyl Secondary Amines from Alkyl Mesylates and Epoxides

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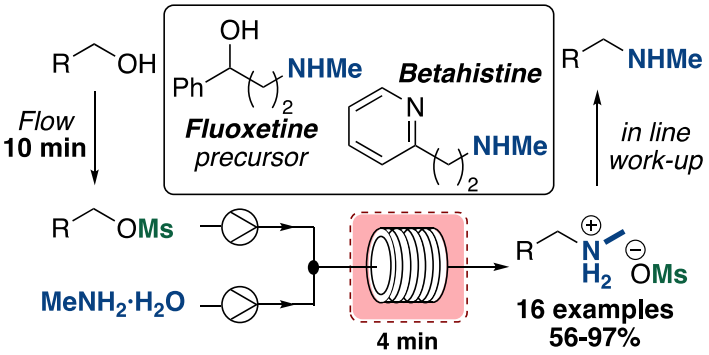

R
OH
Flow
10 min
R
OMs
MeNH2·H2O
OH
Ph
NHMe
2
Fluoxetine
precursor
Betahistine
N
NHMe
2
4 min
R
NHMe
in line
work-up
R
N
H2
OMs
16 examples
56-97%

ABSTRACT. The first continuous flow process was developed to synthesize *N*-methyl secondary amines from alkyl mesylates and epoxides via a nucleophilic substitution using aqueous methylamine. A variety of *N*-methyl secondary amines were produced in good to excellent yields, including a number of bioactive compounds, or their precursors. Up to 10.6 g (88% yield) of a *N*-methyl secondary amine was produced in 140 min process time. The amination procedure included an in-line workup, and the starting mesylate material was also produced in continuous flow from the corresponding alcohol. Finally, an in-line process combining the mesylate synthesis and nucleophilic substitution was developed.

KEYWORDS. Substitution, Methylamine, Mesylation, *N*-methylamino alcohol, Betahistine, Fluoxetine.

INTRODUCTION. Nitrogen-containing molecules are an important class of compounds[1] as they are ubiquitous components of biologically active molecules.[2] Among them, *N*-methyl secondary amines[3] are found in many important drugs, such as fluoxetine (Prozac),[4] duloxetine,[5] desipramine,[6] betahistine[7] or L-epinephrine[8] (Figure 1).[9]

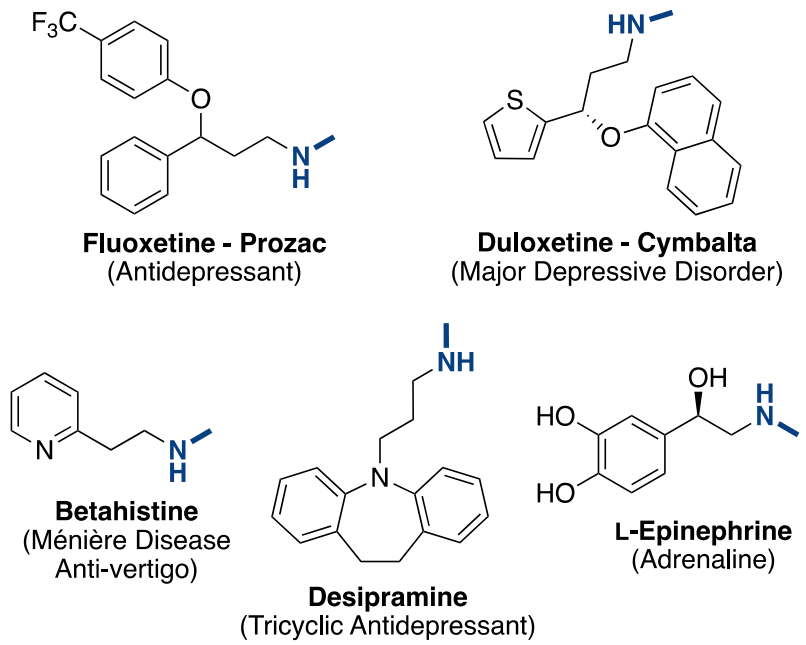


Figure 1. *N*-Methyl Secondary Amine-Containing Drugs.

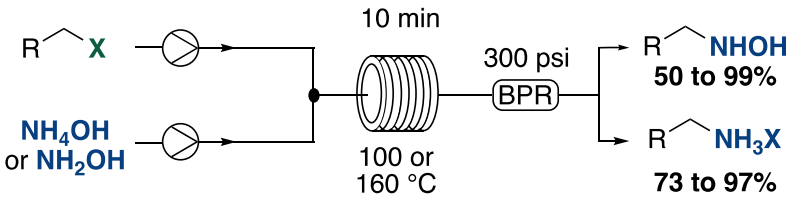
A number of methods have been delineated for the synthesis of *N*-methyl secondary amines,[10] including the reductive amination of aldehydes and ketones,[11] and the nucleophilic displacement of halides[12] or sulfonates,[13] as well as the ring opening of epoxides[14] with methylamine.[15] In general, THF or MeOH solutions of the later reagent were used,[12,13,14] whereas exploiting the less expensive aqueous methylamine reagent was not as common.[16] In addition, reaction times are typically in the order of 12 to 24 h. Due to the low boiling point of methylamine, it is often required to perform the reaction under pressure in a sealed tube. Alternatively, a continuous flow process would be a powerful alternative, as shown in the synthesis of fluoxetine, whereby an alkyl iodide was converted into a *N*-methyl secondary amine.[17,18]

Many advantages would be associated with the development of a general method combining the use of the aqueous methylamine reagent with the displacement of mesylates derived from alcohols. Not only would such a process take advantages of an inexpensive source of methylamine, but alcohols are also readily available and versatile reagents.

Continuous flow is a technique that provides several advantages over traditional batch chemistry.[19] First, safety is significantly improved, namely due to the small reactor size. Mixing, heat and mass transfers are also positively affected by the small diameter of the tubing. As a result, the reaction rate is often improved, and the reaction time is typically shorter in continuous flow vs batch process, thus avoiding by-product formation. In addition, the use of gaseous reagents is impressively simplified (with the use of a back-pressure regulator), allowing the development of novel synthetic processes. In 2018, our group has reported a novel procedure capitalizing on a continuous flow process for the amination of halides using aqueous ammonia and hydroxylamine to produce primary ammonium salts and alkylated hydroxylamines in high yields (Scheme 1).[20] The process was extended to ring openings of epoxides[20] and the absence of headspace in the continuous flow microreactor,[21] combined with the use of water solution of the amine,[22] appeared as key elements to avoid polyalkylation

reactions. Other aqueous solution of amine, for instance methylamine, may be suitable for such amination reactions.

Scheme 1. Continuous Flow Amination of Halides.

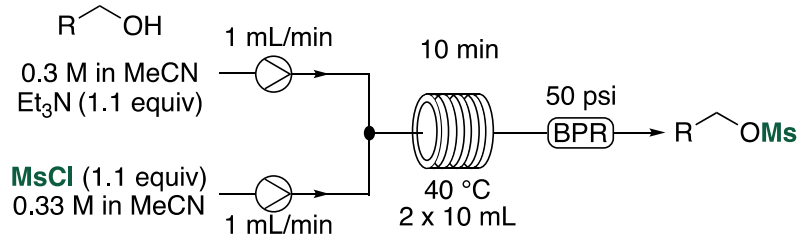


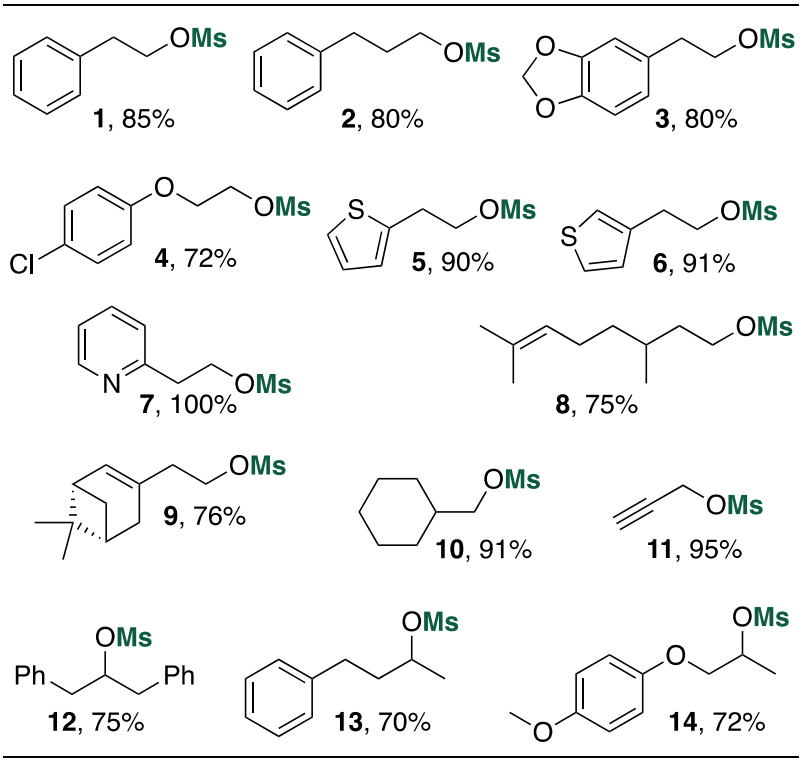
The use of sulfonates as leaving groups shows many advantages over halides. Not only are they suitable electrophiles for nucleophilic substitutions, but they are also easily prepared from the widely available alcohols. Herein, we report a general continuous flow process to react alkyl mesylates with aqueous methylamine, producing *N*-methyl secondary amines with a 4 min residence time. An in-line work-up has been developed and the process is applicable to gram scale production. In addition, the starting alkyl mesylates are also produced in continuous flow and an in-line process, combining the mesylation and nucleophilic substitution has been achieved.

RESULTS AND DISCUSSION. Alkyl mesylates are often prepared from the corresponding alcohol, mesyl chloride, and an amine as a base. In batch reactions, precipitation of the ammonium chloride salt is typically observed. Consequently, only few examples of mesylation processes are described in continuous flow.[23] Given the need for

alkyl mesylates as substrates in the current investigation, an opportunity was seen to develop their preparation in flow. The reaction of 2-phenylethanol and mesyl chloride in the presence of various amine bases and solvents was thus investigated.[24] Heating the reactor at 40 °C was key to avoid the formation of solid and clogging of the reactor. Whereas dichloromethane or ether could be used as solvents at a concentration of 0.1M, only acetonitrile was suitable at higher concentration (0.3M). Quite surprisingly, there was no advantage using bases that form ionic liquids (such as DBU, *n*-butylimidazole and tributylamine),[25] as higher yields were observed with triethylamine.[24] Under the optimized reaction conditions, with 2 reactors of 10 mL at a total flow rate of 2 mL/min, mesyltate **1** was isolated in 85% yield (Scheme 2). The reaction was performed on 30 mmol of 2-phenylethanol to produce 5.11 g of mesylate **1** in 120 min process time. Other alkyl mesyltates containing ether (mesylate **3** & **4**), chloride (mesylate **4**), thiophene (mesylate **5** & **6**), pyridine (mesylate **7**), alkene (mesylate **8** & **9**) and alkyne (mesylate **11**) functional groups were successfully synthesized in good to excellent yields. The reaction conditions are also compatible with the preparation of mesylates derived from secondary alcohols (mesylate **12**, **13** & **14**), and no elimination reaction was observed. Only a few substrates could not be prepared under these reaction conditions, primarily due to solubility issues.[26]

Scheme 2. Continuous Flow Mesylation of Primary and Secondary Alcools.[a]



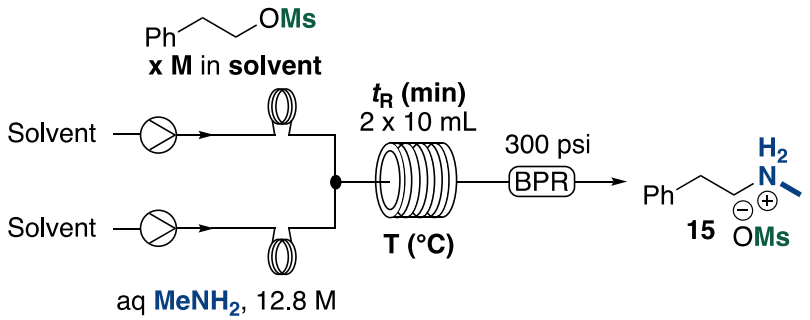


[a] 5 mL of alcohol and Et_3N solution, and 5 mL of mesyl chloride solution were injected (1.50 mmol of alcohol), followed by a steady stream of pure acetonitrile. The entire reactor contents were collected (process time: 20 min, $V_{collection}$ = 24 mL). Isolated yields are reported.

With the alkyl mesylate substrates in hand, the synthesis of *N*-methyl secondary amines using aqueous methylamine in continuous flow was investigated. At the outset, a 0.1 M solution of mesylate

1 in methanol was used, based on the reaction conditions previously developed with ammonia.[20] The commercially available aqueous methylamine solution has a concentration of 12.8 M and was applied neat in the process (Table 1). Two distinct 0.5 mL injection loops[27] were charged with respectively the mesylate solution and the aqueous methylamine solution, then pumped at an equal flow rate in the T-mixer, before being injected in the reactor. With a total rate of 2 mL/min (1 mL/min per pump) corresponding to a residence time of 10 min, 74% and 87% yield of the desired *N*-methyl ammonium salt **15** was observed at respectively 120 °C and 140 °C (entries 1, 2). Increasing the total flow rate to 5 mL/min improved the yield slightly at 140 °C (entry 5). Decreased or equivalent yields were obtained when using respectively THF, $MeNO_2$ or MeCN as solvents, known to favor nucleophilic substitutions (entries 6–8).

Table 1. Amination of Mesylate **1** with Aqueous Methylamine



entry	[OMs] (M)	Solvent	Rate (mL/min)	t_R (min)	Temp (°C)	Yield[a] (%)
1	0.1	MeOH	2.0	10	120	74
2	0.1	MeOH	2.0	10	140	87
3	0.1	MeOH	5.0	4	100	71

4	0.1	MeOH	5.0	4	120	69
5	0.1	MeOH	5.0	4	140	90
6	0.1	THF	5.0	4	140	78
7	0.1	$MeNO_2$	5.0	4	140	88
8	0.1	MeCN	5.0	4	140	86
9	**0.25**	**MeOH**	**5.0**	**4**	**140**	**94**
10	0.5	MeOH	5.0	4	140	45
11	0.25	MeCN	5.0	4	140	95
12	0.5	MeCN	5.0	4	140	60[b]
13[c]	0.25	MeOH	5.0	4	120	84

[a] Yield determined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b] Isolated yield of amine **16**. [c] NH_4OH, 14 M, was used to produce $PhCH_2CH_2NH_3OMs$.

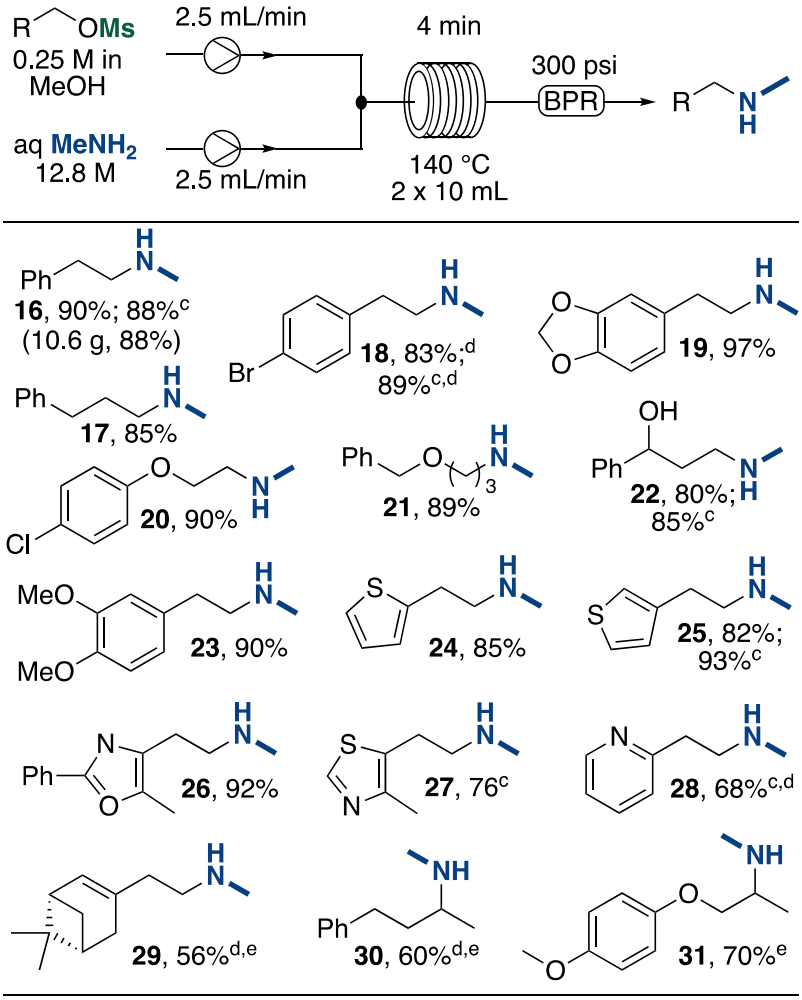
Methanol was favored as a solvent, due of its low cost, although acetonitrile proved also suitable (entries 9–12). The yield was not affected when the amount of methylamine was decreased by a factor of 2.5 (from 128 equiv to 51 equiv), as *N*-methyl ammonium salt **15** was produced in 94–95% yield when starting with a 0.25 M solution of mesylate **1** in methanol or acetonitrile (entries 9 and 11). However, using a more concentrated solution (0.5 M, ~26 equiv of $MeNH_2$) was detrimental for the yield of the desired product, as a result of a lower conversion (entries 10 and 12). In all cases, no polyalkylation product was detected. Ammonium hydroxide was also compatible with the reaction conditions, and $PhCH_2CH_2NH_3OMs$ was produced in 84% yield (entry 13).

The reaction conditions were probed with various alkyl mesylates to produce the corresponding *N*-methyl secondary amine, after a basic work-up (Scheme 3). The reaction was performed on 90 mmol of

mesylate **1** to produce 10.6 g of *N*-methyl amine **16** in 140 min process time. A variety of aryl derivatives containing an ether linkage, a bromide, a chloride, and an alcohol were successfully reacted to afford the desired *N*-methyl secondary amines **17**–**23** in excellent yields. Of note, amine **22** is a precursor in the synthesis of fluoxetine and was prepared in very good yields. The mesylate precursor was synthesized at low temperature by the chemoselective mesylation of the diol (see Sup. Info for details). Giving that the mesylation is tolerant with alcohol functional groups (the reaction is run in methanol), it was not necessary to protect the secondary alcohol, for the primary mesylate to undergo the nucleophilic substitution with methylamine, producing amine **22**. Thiophene and oxazole were found compatible with the reaction conditions and *N*-methyl secondary amines **24**–**26** were isolated in excellent yields. Good yields were observed for the synthesis of thiazole-containing amine **27** and betahistine **28** in acetonitrile. The substrates of these two products are susceptible to degradation, via ipso attack of the methylamine for mesylate **S6** and polymerization for mesylate **7**. The *N*-methyl amine derived from nopol (**29**) was produced in 56% yield: it was necessary to treat the free amine with HCl to isolate the amine•HCl salt. *N*-Methyl amines **30** and **31** derived from secondary mesylates **13** and **14** were synthesized in good yields. It was, however, necessary to use 128

equiv of $MeNH_2$ (mesylate concentration of 0.1 M) and a small amount of elimination by-product was observed.

Scheme 3. Continuous Flow Amination of Alkyl Mesylates with Aqueous Methylamine.[a,b]



[a] 5 mL of mesylate solution, and 5 mL of methylamine solution were injected (1.25 mmol of mesylate), followed by a steady stream of pure methanol. The entire reactor contents were collected (process time: 10 min, $V_{collection}$ = 34 mL). Isolated yields are reported. [b] KOH was used to produce the free amine. [c] 0.25 M in MeCN. [d] Isolated as an HCl salt. [e] 0.1 M in MeOH.

One of the advantages of continuous flow synthesis is the possibility of developing a fully automated process that includes

the in-situ work-up and purification of the product. Such a process was elaborated for the preparation of *N*-methyl amine **16** (Scheme 4, Figure 2). Two Vapourtec R-series were connected to the same computer to control four different pumps for the complete automatization of the process. After the formation of *N*-methyl ammonium salt **15**, a mixture of aqueous KOH/NaCl was added after the back-pressure regulator, and the combined streams passed through a 10 mL PFA reactor. Dichloromethane was added next, and the reaction mixture was then passed through a homemade column magnetic stirrer. The organic layer was separated from the aqueous with a gravity liquid-liquid separator.[28] The organic layer was pumped through a drying column (4Å MS/Celite) to afford the desired *N*-methyl amine **16** in 70% yield.

Scheme 4. In-Line Workup to Synthesize *N*-Methyl Amine **16**.

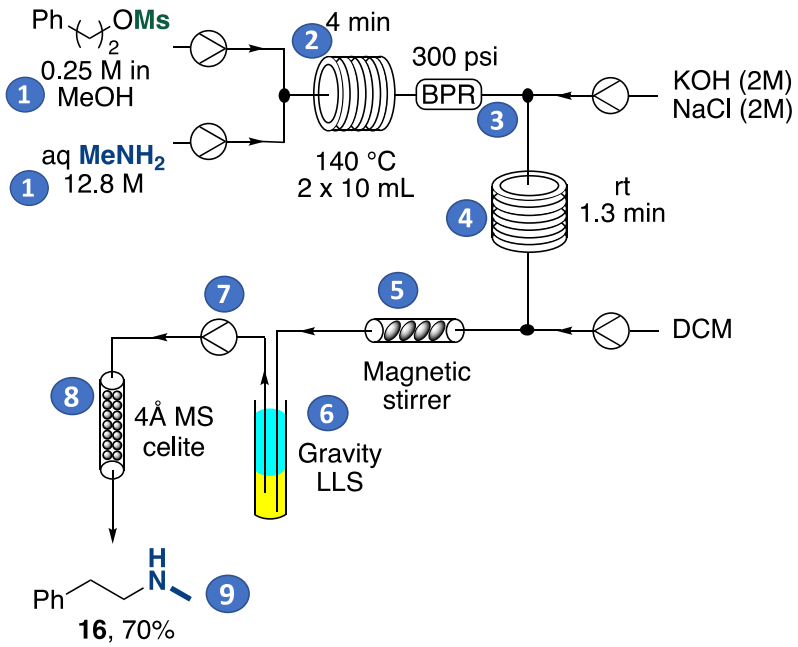
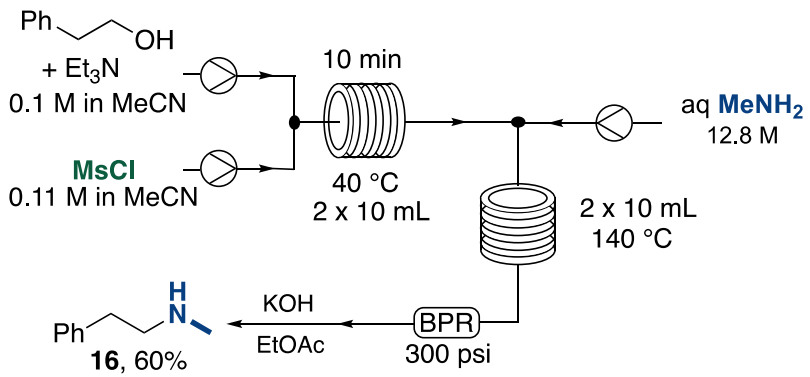


Figure 2. Reactor setup for the automated in-line work-up to synthesize methylamine **16**: 1. Reagent bottles; 2. Stainless steel reactors; 3. Back pressure regulator (BPR); 4. PFA reactor; 5. Homemade column magnetic stirrer; 6. Gravity liquid-liquid separator; 7. Syrris Pump; 8. Drying column; 9. Collecting flask.

An in-line process to perform the mesylation reaction, followed by the nucleophilic substitution was then developed (Scheme 5).

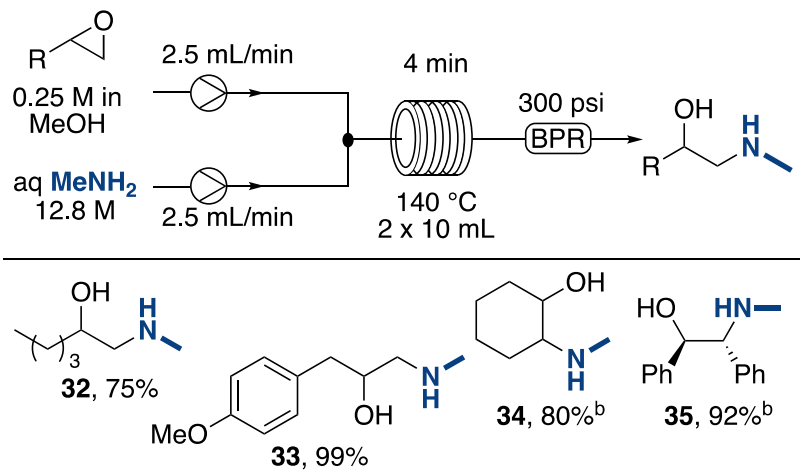
Scheme 5. In-line Process to Synthesize *N*-Methyl Amine **16** from 2-Phenylethanol.



Acetonitrile was used as solvent and the concentration was decreased to 0.1 M for the alcohol to achieve a reasonably good conversion in the nucleophilic substitution. The desired *N*-methyl amine **16** was isolated in 60%. Side reactions between the trialkylammonium salt and methylamine may explain the slightly lower yield obtained in comparison with the 2-step process.

Other suitable electrophiles for nucleophilic substitution include epoxides. Using the same reaction conditions as the alkyl mesylates, the corresponding *N*-methylamino alcohol was produced in good to excellent yields (Scheme 6). The reaction was compatible with terminal and disubstituted epoxides.

Scheme 6. Epoxide Ring Opening with Aqueous Methylamine.[a]



[a] 5 mL of epoxide solution, and 5 mL of methylamine solution were injected (1.25 mmol of epoxide), followed by a steady stream of pure methanol. The entire reactor contents were collected (process time: 10 min, $V_{collection}$ = 34 mL). Isolated yields are reported. [b] Isolated as an HCl salt.

CONCLUSION. In conclusion, a highly efficient continuous flow process to synthesize *N*-methyl secondary amines and substituted *N*-methylamino alcohol from alkyl mesylates and epoxides in good to excellent yields was developed. This process features good functional group compatibility, the use of inexpensive aqueous methylamine and a very short reaction time. An in-line work-up was also developed, thus a fully automated process is also possible. In addition, it is possible to combine, both the mesylation step and the nucleophilic substitution in one in-line process. Considering the importance of *N*-methyl secondary amines in biologically active products, this process will be of interest for industrial researchers.

EXPERIMENTAL SECTION.

General Information. Commercially available reagents were used without further purification, unless noted. Analytical thin-layer chromatography was performed using 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by UV absorbance, cerium ammonium molybdate or aqueous potassium permanganate. Flash chromatography was performed using silica gel (230–400 mesh) with the indicated solvent system. Infrared spectra are reported in wavenumbers (cm^{-1}). Only the most important and relevant frequencies are reported. 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) or D_2O (δ = 4.79 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextuplet, m = multiplet, and br = broad), coupling constants in hertz, 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) 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 1,1,2,2-tetrachloroethane as an internal standard with a 10s relaxation time. High-resolution mass spectra analysis was performed by the Centre Régional de Spectroscopie de Masse de l'Université de Montréal. Continuous

flow experiments were run on the Vapourtec® R-Series flow system (R2+ pump and R4 heating module) using a 2 mL injection loop, a 10 mL stainless steel or PFA reactor coil (1/16 OD x 0.04 ID tubing) and a spring back-pressure regulator.

General Continuous Flow Procedure for the Preparation of Alkyl Mesylates (Scheme 2). *NB. The continuous flow system was flushed with anhydrous acetonitrile prior to running the reaction.* A solution of the alcohol (3.00 mmol) and NEt_3 (460 µL, 3.30 mmol) in anhydrous MeCN (0.3M), and a solution of mesyl chloride (255 µL, 3.30 mmol) in anhydrous MeCN (0.33 M) were independently prepared in two 10 mL volumetric flasks. These stock solutions (5 mL, 1.50 mmol of alcohol; 1.65 mmol of NEt_3 and 5 mL, 1.65 mmol MsCl) were pumped using the bottle reagent mode at 1 mL/min (total flow rate is 2 mL/min), combined in a T-mixer and injected into two successive 10 mL PFA reactors heated at 40 °C. Upon exiting the second flow reactor, the combined reactor stream passed a back-pressure regulator (50 psi) before being collected into a 100 mL opened flask (process time: 20 min). After all reagents were pumped, the system was purged with MeCN until collection volume was reached ($V_{collection}$ = 24 mL). Sat. aq. $NaHCO_3$ was added, followed by EtOAc. The two layers were separated, and the organic layer was washed with brine, then dried over Na_2SO_4. The solvent was removed

under reduced pressure and the residue was passed through a pad of silica gel to afford the corresponding pure mesylate.

*Phenethyl methanesulfonate (**1**).* The title compound was prepared according to the general procedure from 2-phenylethanol (180 μL, 1.50 mmol or 3.60 mL, 30 mmol) and was obtained as a light-yellow liquid (255 mg or 5.11 g, 85%) after purification by flash chromatography on silica gel using hexane/EtOAc (7:3). Spectral data matched those reported in the literature.[29] R_f 0.28 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2H), 7.30–7.25 (m, 3H), 4.42 (t, *J* = 6.8 Hz, 2H), 3.06 (d, *J* = 6.8 Hz, 2H), 2.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 128.9, 128.6, 126.9, 70.4, 37.1, 35.5.

*3-Phenylpropyl methanesulfonate (**2**).* The title compound was prepared according to the general procedure from 3-phenyl-1-propanol (204 μL, 1.50 mmol) and was obtained as a light-yellow liquid (257 mg, 80%) after purification by flash chromatography on silica gel using Hexane/EtOAc (7:3). Spectral data matched those reported in the literature.[29] R_f 0.36 (Hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H), 7.23-7.19 (m, 3H), 4.22 (t, *J* = 8 Hz, 2H), 2.98 (s, 3H), 2.75 (t, *J* = 8 Hz, 2H), 2.11 (q, *J* = 8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 128.6, 128.5, 126.3, 69.2, 37.3, 31.6, 30.7.

*2-(Benzo[d][1,3]dioxol-5-yl)ethyl methanesulfonate (**3**).* The title compound was prepared according to the general procedure from 2-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-ol (249 mg, 1.50 mmol) and was obtained as a yellow liquid (293 mg, 80%) after purification by flash chromatography on silica gel using hexane/EtOAc (7:3). Spectral data matched those reported in the literature.[29] R_f 0.5 (hexane/EtOAc 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76–6.66 (m, 3H), 5.92 (s, 2H), 4.35 (t, *J* = 6.8 Hz, 2H), 2.95 (t, *J* = 6.8 Hz, 2H), 2.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 146.7, 130.0, 122.1, 109.4, 108.5, 101.1, 70.5, 37.4, 35.4.

*2-(4-Chlorophenoxy)ethyl methanesulfonate (**4**).* The title compound was prepared according to the general procedure from 2-(4-chlorophenoxy)ethan-1-ol (259 mg, 1.5 0mmol) and was obtained as a white crystalline solid (271 mg, 72%) after purification by flash chromatography on silica gel using hexane/EtOAc (7:3). R_f 0.29 (hexane/EtOAc 7:3); mp 76–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.23 (m, 2H), 6.83–6.81(m, 2H), 4.55–4.53 (m, 2H), 4.21–4.19 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 129.6, 126.6, 115.9, 67.8, 66.2, 37.8; FTIR (neat) 1595, 1489, 1452, 1343, 1243, 1169, 1030, 968, 811, 527; HRMS (ESI+) m/z $[M + Na]^+$ calcd for $C_9H_{11}ClO_4S$ 272.9958 found 272.9957.

*2-(Thiophen-2-yl)ethyl methanesulfonate (**5**).* The title compound was prepared according to the general procedure from 2-thiopheneethanol (167 μL, 1.50 mmol), and was obtained as a light-yellow liquid (282 mg, 90%) after purification by flash chromatography on silica gel using hexane/EtOAc (7:3). Spectral data matched those reported in the literature.[30] R_f 0.28 (hexane/EtOAc 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.17 (m, 1H), 6.96–6.94 (m, 1H), 6.91–6.90 (m, 1H), 4.39 (t, *J* = 6.5 Hz, 2H), 3.25 (t, *J* = 6.5 Hz, 2H), 2.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 127.1, 126.2, 124.5, 69.9, 37.2, 29.7.

*2-(Thiophen-3-yl)ethyl methanesulfonate (**6**).* The title compound was prepared according to the general procedure from 3-thiopheneethanol (166 μL, 1.50 mmol) and was obtained as a light-orange liquid (282 mg, 91%) after purification by flash chromatography on silica gel using hexane/EtOAc (7:3). R_f 0.28 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.27 (m, 1H), 7.08–7.07 (m, 1H), 6.99–6.97 (m, 1H), 4.39 (t, *J* = 6.8 Hz, 2H), 3.97 (t, *J* = 6.8 Hz, 2H), 2.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 128.1, 126.0, 122.3, 69.8, 37.1, 30.0; FTIR (neat) 2931, 1439, 1380, 1247, 1116, 1034, 849, 821, 689; HRMS (ESI+) m/z $[M + Na]^+$ calcd for $C_7H_{10}O_3S_2$ 228.9963 found 228.9963.

*2-(Pyridin-2-yl)ethyl methanesulfonate (**7**).* The title compound was prepared according to the general procedure from 2-pyridineethanol (169 μL, 1.50 mmol) and was obtained as an orange liquid (302 mg, 100%) after purification by flash chromatography on silica gel using hexane/EtOAc (5:5). Spectral data matched those reported in the literature.[30] R_f 0.20 (hexane/EtOAc 5:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50–8.49 (m, 1H), 7.60–7.56 (m, 1H), 7.18–7.11 (m, 2H), 4.62–4.58 (m, 2H), 3.18–3.14 (m, 2H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 149.4, 136.6, 123.9, 122.1, 69.1, 37.4, 36.1.

*3,7-Dimethyloct-6-en-1-yl methanesulfonate (**8**).* The title compound was prepared according to the general procedure from (+/-) citronellol (274 μL, 1.50 mmol) and was obtained as a colorless liquid (264 mg, 75%) after purification by flash chromatography on silica gel using hexane/EtOAc (7:3). Spectral data matched those reported in the literature.[31] R_f 0.4 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07–5.04 (m, 1H), 4.29–4.19 (m, 2H), 2.98 (s, 3H), 2.01–1.91 (m, 2H), 1.82–1.74 (m, 1H), 1.69 (s, 3H), 1.62–1.48 (m + s, 5H), 1.38–1.29 (m, 1H), 1.23-1.14 (m, 1H), 0.91 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.6, 124.3, 68.6, 37.4, 36.9, 35.9, 29.0, 25.8, 25.3, 19.2, 15.7.

*2-((1R,5S)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl methanesulfonate (**9**).* The title compound was prepared according to the general procedure from (1*R*)-(-)-nopol (258 μL, 1.50 mmol) and was obtained as a light-yellow liquid (279 mg, 76%) after purification by flash chromatography on silica gel using hexane/EtOAc (7:3). Spectral data matched those reported in the literature.[32] R_f 0.28 (hexane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (s, 1H), 4.21–4.17 (m, 2H), 2.97 (s, 3H), 2.41–2.33 (m, 3H), 2.27–2.15 (m, 2H), 2.07–2.01 (m, 2H), 1.26 (s, 3H), 1.13 (d, *J* = 8.8 Hz, 1H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 120.0, 68.0, 45.6, 40.6, 38.1, 37.5, 36.4, 31.6, 31.4, 26.3, 21.2.

*Cyclohexylmethyl methanesulfonate (**10**).* The title compound was prepared according to the general procedure from cyclohexylmethyl alcohol (185 μL, 1.50 mmol), and was obtained as a colorless liquid (262 mg, 91%) after purification by flash chromatography on silica gel using hexane/EtOAc (8:2). R_f 0.35 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (d, *J* = 6 Hz, 2H), 2.95 (s, 3H), 1.72–1.66 (m, 6H), 1.24–1.11 (m, 3H), 1.01–0.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.0, 37.4, 37.1, 29.1, 26.1, 25.4; FTIR (neat) 2925, 2853, 1450, 1347, 1170, 967, 936, 830, 519; HRMS (ESI+) m/z [M + Na]$^+$ calcd for $C_8H_{16}O_3S$ 215.01512 found 215.0711.

*Prop-2-yn-1-yl methanesulfonate (**11**).* The title compound was prepared according to the general procedure from propargyl alcohol (87.3 μL, 1.50 mmol) and was obtained as a colorless liquid (291 mg, 95%) after purification by flash chromatography on silica gel using hexane/EtOAc (7:3). Spectral data matched those reported in the literature.[33] R_f 0.21 (hexane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (d, *J* = 2.4 Hz, 2H), 3.10 (s, 3H), 2.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.0, 75.8, 75.3, 39.0.

*1,3-Diphenylpropan-2-yl methanesulfonate (**12**).* The title compound was prepared according to the general procedure from 1,3-diphenylpropan-2-ol (318 mg, 1.50 mmol) and was obtained as a white solid (327 mg, 75%) after purification by flash chromatography on silica gel using hexane/EtOAc (7:3). R_f 0.53 (hexane/EtOAc 7:3); mp 76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.22 (m, 10H), 4.91 (qn, *J* = 6.6 Hz, 1H), 3.01 (d, *J* = 6.6 Hz, 4H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 129.8, 128.8, 127.2, 86.1, 41.2, 37.2; FTIR (neat) 3030, 2932, 1603, 1495, 1365, 1169, 970, 894, 689; HRMS (ESI+) m/z $[M + Na]^+$ calcd for $C_{16}H_{18}O_3S$ 313.0868 found 313.0872.

*4-Phenylbutan-2-yl methanesulfonate (**13**).* The title compound was prepared according to the general procedure from 4-phenylbutan-2-ol (225 mg, 1.50 mmol) and was obtained as a colorless liquid (240

mg, 70%) after purification by flash chromatography on silica gel using hexane/EtOAc (7:3). Spectral data matched those reported in the literature.[34] R_f 0.57 (hexane/EtOAc 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.26 (m, 2H), 7.22-7.19 (m, 3H), 4.84 (sext, *J* = 6.3 Hz, 1H), 2.99 (s, 3H), 2.82–2.65 (m, 2H), 2.13–1.87 (m, 2H), 1.46 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 128.7, 128.4, 126.3, 79.6, 38.8, 38.4, 31.5, 21.4.

*1-(4-Methoxyphenoxy)propan-2-yl methanesulfonate (**14**).* The title compound was prepared according to the general procedure from 1-(4-methoxyphenoxy)propan-2-ol (273 mg, 1.50 mmol), and was obtained as a white solid (281 mg, 72%) after purification by flash chromatography on silica gel using hexane/EtOAc (7:3). R_f 0.31 (hexane/EtOAc 7:3); mp 70–71 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85–6.81 (m, 4H), 5.05 (m, 1H), 4.04 (dd, *J* = 10.5, 7.5 Hz, 2H), 4.97 (dd, *J* = 10.5, 3.5 Hz, 2H), 3.76 (s, 3H), 3.07 (s, 3H), 1.50 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 152.2, 115.6, 114.9, 77.9, 71.2, 55.8, 38.6, 18.1; FTIR (neat) 2941, 1508, 1460, 1341, 1230, 1171, 1077, 975, 743, 530; HRMS (ESI+) m/z $[M + Na]^+$ calcd for $C_{11}H_{16}O_5S$ 283.0610 found 283.0610.

General Continuous Flow Procedure for the Amination of Alkyl Mesylates with Aqueous Methylamine (Scheme 3). *NB. The continuous flow system was successively flushed with aqueous ammonia, water,*

and the reaction solvent, prior to running the reaction. A stock solution of the alkyl mesylate (5.00 mL, 1.25 mmol, 0.25 M in MeOH of in CH_3CN) and the aqueous methylamine solution (12.8 M, 5.00 mL, 51.2 mmol) were pumped using the bottle reagent mode at 2.5 mL/min (total flow rate: 5 mL/min), combined in a T-mixer and injected into two successive 10 mL SS reactors heated at 140 °C. Upon exiting the second flow reactor, the combined reaction stream passed a back-pressure regulator (300 psi) before being collected into a 100 mL opened flask (process time:10 min). After all reagents were pumped, the system was purged with MeOH until collection volume was reached ($V_{collection}$ = 34 mL). The solvent and the excess of aqueous methylamine were removed under reduced pressure. The crude residue was treated with aq. KOH (2M) and extracted with EtOAc (3x). The two layers were separated, and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the analytically pure *N*-methyl secondary amine.

*N-Methyl-2-phenylethan-1-amine (**16**).* The title compound was prepared according to the general procedure from phenethyl methanesulfonate (**1**) (250 mg, 1.25 mmol, 0.25 M in MeOH or MeCN or 18 g, 90 mmol, 0.25 M in MeOH). The desired amine was obtained as a pale-yellow liquid (90%, 152 mg (in MeOH); 88%, 149 mg (in MeCN); 88%, 10.6 g (in MeOH), after Kugelrohr distillation). Spectral

data matched those reported in the literature.[35] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.22–7.19 (m, 3H), 4.0 (m, 4H), 2.44 (s, 3H), 1.40 (s (br), 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 128.8, 128.5, 126.2, 53.2, 36.4, 36.2.

*N-Methyl-3-phenylpropan-1-amine (**17**).* The title compound was prepared according to the general procedure from 3-phenylpropyl methanesulfonate (**2**) (268 mg, 1.25 mmol, 0.25 M in MeOH). The desired amine was obtained as a pale-yellow liquid (85%, 159 mg). Spectral data matched those reported in the literature.[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 1.81 (q, J = 7.2 Hz, 2H), 1.11 (s (br), 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 128.5, 128.4, 125.8, 51.7, 36.6, 33.7, 31.7.

*2-(4-Bromophenyl)-N-methylethan-1-amine (**18**).* The title compound was prepared according to the general procedure from 4-bromophenethyl methanesulfonate (**S1**) (349 mg, 1.25 mmol, 0.25 M in MeOH or in MeCN). The crude mixture was diluted in ether and treated with HCl (0.320 mL, 4.0 M in dioxane) to produce the corresponding ammonium salt. A filtration afforded the desired amine•HCl as a solid (83%, 260 mg (in MeOH); 89%, 279 mg (in MeCN)). Spectral data matched those reported in the literature.[37] mp 196–197 °C (litt. 196 °C);[39] ^{1}H NMR (400 MHz, D_2O) δ 7.57 (d, *J*

= 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 3.31 (t, *J* = 7.2 Hz 2H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.72 (s, 3H). ^{13}C NMR (100 MHz, D_2O) δ 135.4, 131.9, 130.7, 120.5, 49.7, 32.8, 31.1. FTIR (neat) 2935, 2779, 2712, 2451, 1591, 1481, 1445, 1073, 816; HRMS (ESI+) m/z [M + H]$^+$ calcd for $C_9H_{12}BrN$ 214.0226 found 214.0224.

2-(Benzo[d][1,3]dioxol-5-yl)-N-methylethan-1-amine (***19***). The title compound was prepared according to the general procedure from 2-(benzo[d][1,3]dioxol-5-yl)ethyl methanesulfonate (**3**) (305 mg, 1.25 mmol, 0.25 M in MeOH). The desired amine was obtained as a yellow liquid (97%, 217 mg). Spectral data matched those reported in the literature.[38] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72–6.67 (m, 2H), 6.64–6.62 (m, 1H), 5.89 (s, 2H), 2.77 (t, *J* = 6.4 Hz, 2H), 2.69 (t, *J* = 6.4 Hz, 2H), 2.40 (s, 3H), 1.14 (s (br), 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 145.9, 133.8, 121.5, 109.1, 108.2, 100.8, 53.4, 36.3, 35.9.

2-(4-Chlorophenoxy)-N-methylethan-1-amine (***20***). The title compound was prepared according to the general procedure from 2-(4-chlorophenoxy)ethyl methanesulfonate (**4**) (313 mg, 1.25 mmol, 0.25 M in MeOH:THF, 1:1). The desired amine was obtained as a yellow liquid (90%, 209 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 9 Hz, 2H), 6.81 (d, *J* = 9 Hz, 2H), 4.02 (t, *J* = 5 Hz, 2H), 2.95 (t, *J* = 5 Hz, 2H), 2.49 (s, 3H), 1.51 (s (br), 1H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 157.6, 129.4, 125.7, 115.8, 67.6, 50.8, 36.5; FTIR (neat) 2932, 1596, 1489, 1282, 1239, 1092, 1040, 821, 665; HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_9H_{12}ClNO$ 186.0680 found 186.0682.

*3-(Benzyloxy)-N-methylpropan-1-amine (**21**).* The title compound was prepared according to the general procedure from 3-(benzyloxy)propyl methanesulfonate (**S2**) (305 mg, 1.25 mmol, 0.25 M in MeOH). The desired amine was obtained as a yellow liquid (89%, 199 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 4.49 (s, 2H), 3.53 (t, *J* = 6.6 Hz, 2H), 2.67 (t, *J* = 6.6 Hz, 2H), 2.41 (s, 3H), 1.79 (q, *J* = 6.6 Hz, 2H), 1.32 (s (br), 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 128.4, 127.6, 127.5, 72.9, 68.9, 49.5, 36.6, 30.0; FTIR (neat) 2850, 1453, 1362, 1098, 1027, 733, 695, 610; HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{11}H_{17}NO$ 180.1382 found 180.1378.

*3-(Methylamino)-1-phenylpropan-1-ol (**22**).* The title compound was prepared according to the general procedure from 3-hydroxy-3-phenylpropyl methanesulfonate (**S3**) (288 mg, 1.25 mmol, 0.25 M in MeOH or in MeCN). The desired amine was obtained as a light-yellow liquid (80%, 165 mg (in MeOH); 85%, 176 mg (in MeCN)). Spectral data matched those reported in the literature.[39] ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.30 (m, 4H), 7.26–7.21 (m, 1H), 4.93 (m, 1H), 4.77 (s (br), 2H), 2.99–2.85 (m, 2H), 2.47 (s, 3H), 1.98–1.80 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 128.4, 127.1, 125.7, 74.9, 50.0, 36.5, 35.6.

*2-(3,4-Dimethoxyphenyl)-N-methylethan-1-amine (**23**).* The title compound was prepared according to the general procedure from 3,4-dimethoxyphenethyl methanesulfonate (**S4**) (325 mg, 1.25 mmol, 0.25 M in MeOH). The desired amine was obtained as a yellow liquid (90%, 220 mg). Spectral data matched those reported in the literature.[40] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81–6.73 (m, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 2.87–2.83 (m, 4H), 2.45 (s, 3H), 2.07 (s (br), 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 147.6, 132.4, 120.7, 112.1, 111.4, 56.0, 55.9, 53.3, 36.3, 35.7.

*N-Methyl-2-(thiophen-2-yl)ethan-1-amine (**24**).* The title compound was prepared according to the general procedure from 2-(thiophen-2-yl)ethyl methanesulfonate (**5**) (258 mg, 1.25 mmol, 0.25 M in MeOH). The desired amine was obtained as a light-yellow liquid (85%, 150 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.12 (m, 1H), 6.93–6.92 (m, 1H), 6.83–6.82 (m, 1H), 3.02 (t, J = 6.8 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H), 2.44 (s, 3H), 1.29 (s (br), 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 149.4, 136.6, 123.9, 122.1, 69.1, 37.4, 27.1; FTIR (neat) 2931, 1439, 1380, 1247, 1116, 1034, 849, 821, 689; HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_7H_{11}NS$ 142.0685 found 142.0681.

*N-Methyl-2-(thiophen-3-yl)ethan-1-amine (**25**).* The title compound was prepared according to the general procedure from 2-(thiophen-3-yl)ethyl methanesulfonate (**6**) (258 mg, 1.25 mmol, 0.25 M in MeOH or in MeCN). The desired amine was obtained as an off-white semi-solid (82%, 145 mg (in MeOH); 93%, 164 mg (in MeCN)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (s (br), 1H), 7.27–7.25 (m, 1H), 7.08 (s, 1H), 6.95 (d, *J* = 5 Hz, 1H), 3.23–3.15 (m, 4H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 127.7, 126.5, 122.4, 49.9, 33.2, 27.0; FTIR (neat) 2931, 1439, 1380, 1247, 1116, 1034, 849, 821, 689; HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_7H_{11}NS$ 142.0685 found 142.0681.

*N-Methyl-2-(5-methyl-2-phenyloxazol-4-yl)ethan-1-amine (**26**).* The title compound was prepared according to the general procedure from 2-(5-methyl-2-phenyloxazol-4-yl)ethyl methanesulfonate (**S5**) (352 mg, 1.25 mmol, 0.25 M in MeOH:THF, 1:1). The desired amine was obtained as a yellow liquid (92%, 249 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97–7.96 (m, 2H), 7.43–7.37 (m, 3H), 2.91 (t, *J* = 7 Hz, 2H), 2.69 (t, *J* = 7 Hz, 2H), 2.48 (s, 3H), 2.33 (s, 3H), 2.20 (s (br), 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 144.3, 134.3, 129.8, 128.7, 127.9, 126.0, 50.9, 36.3, 26.0, 10.3; FTIR (neat) 2921, 1636, 1553, 1485, 1447, 1335, 1143, 773, 690; HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{13}H_{16}N_2O$ 217.1335 found 217.1332.

*N-Methyl-2-(4-methylthiazol-5-yl)ethan-1-amine (**27**).* The title compound was prepared according to the general procedure from 2-(4-methylthiazol-5-yl)ethyl methanesulfonate (**S6**) (221 mg, 1.25 mmol, 0.25 M in MeCN). The desired amine was obtained as a brownish liquid (76%, 148 mg) after purification by flash chromatography on silica gel using hexane/EtOAc (7:2) + 10% (DCM/MeOH/NH_4OH (55:45:5)). ^1H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 2.93 (t, *J* = 7 Hz, 2H), 2.82 (t, *J* = 7 Hz, 2H), 2.44 (s, 3H), 2.39 (s, 3H), 1.08 (s (br), 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 149.3, 129.3, 52.9, 36.4, 26.8, 15.1; FTIR (neat) 2923, 1662, 1542, 1444, 1413, 1167, 1036, 840, 612; HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_7H_{12}NS$ 157.0794 found 157.0794.

*N-Methyl-2-(pyridin-2-yl)ethan-1-amine (**28**).* The title compound was prepared according to the general procedure from 2-(pyridin-2-yl)ethyl methanesulfonate (**7**) (252 mg, 1.25 mmol, 0.25 M in MeCN). The crude mixture was diluted in ether and treated with HCl (0.320 mL, 4.0 M in dioxane) to produce the corresponding ammonium salt. A filtration afforded the desired amine•HCl as a white solid (68%, 147 mg). mp 140-142 °C; ^1H NMR (400 MHz, D_2O) δ 8.75–8.73 (m, 1H), 8.58 (dt, *J* = 10.8, 2.4 Hz, 1H), 8.04–7.97 (m, 2H), 3.54 (s, 4H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 150.8, 147.5, 141.6, 127.6, 126.1, 46.7, 33.0, 29.5; FTIR (neat) 3298, 3066, 2935, 2852,

2801, 1653, 1592, 1474, 1300, 735; HRMS (ESI+) m/z $[M-Cl]^+$ calcd for $C_8H_{13}N_2$ 137.1073 found 137.1067.

*2-((1S,5R)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-3-yl)-N-methylethan-1-amine (**29**).* The title compound was prepared according to the general procedure from 2-((1*S*,5*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl)ethyl methanesulfonate (**9**) (244 mg, 1.00 mmol, 0.1 M in MeOH, 10 mL) and aqueous methylamine (12.8 M, 10 mL, 128 mmol). The crude mixture was diluted in ether and treated with HCl (0.250 mL, 4.0 M in dioxane) to produce the corresponding ammonium salt. A filtration afforded the desired amine•HCl a white solid (56%, 120 mg). mp 188–189 °C; ^{1}H NMR (300 MHz, D_2O) δ 5.45–5.43 (m, 1H), 3.11–3.05 (m, 2H), 2.72 (s, 3H), 2.45–2.33 (m, 3H), 2.26–2.23 (m, 2H), 2.11–2.05 (m, 2H), 1.28 (s, 3H), 1.12 (d, *J* = 8.7 Hz, 1H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 142.8, 120.0, 47.1, 45.0, 40.1, 37.3, 32.7, 32.6, 30.9, 30.8, 25.3, 20.3; FTIR (neat) 2923, 2830, 2746, 2447, 1602, 1459,1218, 1058, 803; HRMS (ESI+) m/z $[M]^+$ calcd for $C_{12}H_{22}N$ 180.1746 found 180.1751.

*N-Methyl-4-phenylbutan-2-amine (**30**).* The title compound was prepared according to the general procedure from 4-phenylbutan-2-yl methanesulfonate (**13**) (228 mg, 1.00 mmol 0.1 M in MeOH, 10 mL) and aqueous methylamine (12.8 M, 10 mL, 128 mmol). The crude mixture was diluted in ether and treated with HCl (0.250 mL, 4.0

M in dioxane) to produce the corresponding ammonium salt. A filtration afforded the desired amine•HCl as off-white solid (60%, 120 mg). mp = 86-87 °C; ^{1}H NMR (400 MHz, D_2O) δ 7.42–7.38 (m, 2H), 7.34–7.29 (m, 3H), 3.25–3.20 (m, 1H), 2.85–2.78 (ddd, J = 5.5, 10, 15 Hz, 1H), 2.73–2.65 (m, 2H), 2.67 (s, 3H), 2.12–2.04 (m, 1H), 1.92–1.83 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, D_2O) δ 140.8, 128.8, 128.4, 126.4, 54.8, 33.9, 30.6, 29.6, 14.9; FTIR (neat) 2964, 2928, 2789, 2721, 2458, 1591, 1426, 1181, 1047, 699; HRMS (ESI+) m/z $[M]^+$ calcd for $C_{11}H_{18}N$ 164.1438 found 164.1437.

*1-(4-Methoxyphenoxy)-N-methylpropan-2-amine (**31**).* The title compound was prepared according to the general procedure from 1-(4-methoxyphenoxy)propan-2-yl methanesulfonate (**14**) (260 mg, 1.00 mmol, 0.1 M in MeOH, 10 mL) and aqueous methylamine (12.8 M, 10 mL, 128 mmol). The desired amine was obtained as a light-yellow liquid (70%, 137 mg) after purification by flash chromatography on silica gel using hexane/EtOAc (7:2) + 10% (DCM/MeOH/NH_4OH (55:45:5)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86–6.78 (m, 4H), 4.08 (s (br), 1H), 3.92–3.81 (m, 2H), 3.74 (s, 3H), 3.12-3.02 (m, 1H), 2.49 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 152.8, 115.6, 114.7, 71.5, 55.8, 54.2, 32.9, 15.9; FTIR (neat) 2933, 1505, 1460, 1226, 1175, 1035, 926, 822, 743; HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{11}H_{17}NO_2$ 196.1332 found 196.1328.

In-Line Workup to Synthesize *N*-Methyl Amine 16 (Scheme 4 & Figure 2). *NB. The continuous flow system was flushed with aqueous ammonia, prior to running the reaction.* A stock solution of phenethyl methanesulfonate (**1**) (10.0 mL, 2.50 mmol, 0.25 M in MeOH) and the aqueous methylamine solution (10 mL, 12.8 M, 51.2 mmol) were pumped using the bottle reagent mode at 2.5 mL/min (total flow rate: 5 mL/min), combined in a T-mixer and injected into two successive 10 mL PFA reactors heated at 40 °C. Upon exiting the second flow reactor, the combined reaction stream passed a back-pressure regulator (300 psi). A continuous stream of KOH/NaCl (2M) was pumped at 2.5 mL/min after the BPR in a 10 mL PFA reactor (total flow rate: 7.5 mL/min, t_R = 1.3 min). After exiting the PFA reactor, a stream of DCM was pumped at 2.5 mL/min and the mixture was passed through a homemade magnetic column stirrer (V = 12.4 mL). The stream passed by an 82 cm PFA tubing and was inserted deep-down in the gravity liquid-liquid separator (a graduated cylinder previously filled with 20 mL of DCM). After the organic and aqueous layers started to get separated, an Asian Syrris pump was used to pump at 2.5 mL/min the organic layer into a column filled with crushed 4Å molecular sieves in celite. A solution of free amine was obtained in a round-bottomed flask and was evaporated to afford the desired secondary amine **16** (237 mg, 70%).

Homemade Magnetic Column Stirrer. An OmniFit column (V = 12.4 mL), three round stir bars and three cross-shaped stir bars were used to assemble the homemade magnetic stirrer. The stir bars were introduced in alternance, a cross-shaped stir bar, followed by a round stir bar. The column was filled with MeOH, while removing air bubbles. A magnetic stir plate is used next to the column.

In-line Process to Synthesize *N*-Methyl Amine 16 from 2-Phenylethanol (Scheme 5). *NB. The continuous flow system was flushed with anhydrous acetonitrile prior to running the reaction.* A solution of 2-phenylethanol (1.00 mmol) and triethylamine (153 µL, 1.10 mmol) in anhydrous MeCN (0.1 M), and a solution of mesyl chloride (85.1 µL, 1.10 mmol) in anhydrous MeCN (0.11 M) were independently prepared in two 10 mL volumetric flasks. These stock solutions (5 mL, 0.5 mmol of alcohol + 0.55 mmol of NEt_3 and 5 mL, 0.55 mmol MsCl) were pumped using the bottle reagent mode at 1 mL/min (total flow rate is 2 mL/min), combined in a T-mixer and injected into two successive 10 mL PFA reactors heated at 40 °C. After exiting the second flow reactor, a stream of aqueous methylamine (22 mL, 12.8 M, 281 mmol) was pumped at 3 mL/min using bottle reagent mode (total flow rate is 5 mL/min) and combined in a second T-mixer and injected into two successive 10 mL SS reactors heated at 140 °C. Upon exiting the fourth flow reactor, the stream passed a back-pressure regulator (300 psi) before being collected

into a 100 mL opened flask (process time: 27 min). After all reagents were pumped, the system was purged with MeCN until collection volume was reached ($V_{collection}$ = 65 mL). The solvent and the excess of aqueous methylamine were removed under reduced pressure. The crude residue was treated with aq. KOH (2M) and extracted with EtOAc (3x). The two layers were separated, and the organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the analytically pure *N*-methyl secondary amine **16** (88 mg, 60%).

General Continuous Flow Procedure for the Epoxide Ring Opening with Aqueous Methylamine (Scheme 6). *NB. The continuous flow system was successively flushed with aqueous ammonia, water, and the reaction solvent, prior to running the reaction.* A stock solution of the epoxide (5.00 mL, 1.25 mmol, 0.25 M in MeOH) and the aqueous methylamine solution (12.8 M, 5 mL, 51.2 mmol) were pumped using the bottle reagent mode at 2.5 mL/min (total flow rate: 5 mL/min), combined in a T-mixer and injected into two successive 10 mL SS reactors heated at 140 °C. Upon exiting the second flow reactor, the combined reaction stream passed a back-pressure regulator (300 psi) before being collected into a 100 mL opened flask (process time:10 min). After all reagents were pumped, the system was purged with MeOH until collection volume was reached ($V_{collection}$ = 34 mL).

The solvent and the excess of aqueous methylamine were removed under reduced pressure to afford the *N*-methylamino alcohol.

1-(Methylamino)hexan-2-ol (**32**). The title compound was prepared according to the general procedure from 1,2-epoxyhexane (151 μL, 1.25 mmol). The desired *N*-methylamino alcohol was obtained as a white solid (75%, 123 mg) after a few hours under high vacuum. mp 32–34 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64–3.59 (m, 1H), 2.67–2.62 (m, 3H), 2.47–2.40 (m, 4H), 1.43–1.30 (m, 6H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 69.1, 57.4, 36.1, 34.9, 27.9, 22.9, 14.2; FTIR (neat) 3295, 3162, 2921, 2856, 2789, 1462, 1280, 1134, 1077, 834; HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_7H_{17}NO$ 132.1382 found 132.1377.

*1-(4-Methoxyphenyl)-3-(methylamino)propan-2-ol (**33**).* The title compound was prepared according to the general procedure from 2-(4-methoxybenzyl)oxirane (205 mg, 1.25 mmol). The desired *N*-methylamino alcohol was obtained as a brownish off-solid (99%, 242 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 3.85–3.79 (m, 1H), 3.78 (s, 3H), 2.73–2.63 (m, 3H), 2.61–2.45 (m, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 130.5, 130.4, 113.9, 70.5, 56.9, 55.3, 40.9, 36.; FTIR (neat) 2835, 1611, 1510, 1460, 1350, 1242, 1138, 1029, 838; HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{11}H_{17}NO_2$ 196.1332 found 196.1326.

*2-(Methylamino)cyclohexan-1-ol (**34**).* The title compound was prepared according to the general procedure from cyclohexene oxide (126 μL, 1.25 mmol). The crude mixture was diluted in ether and treated with HCl (0.320 mL, 4.0 M in dioxane) to produce the corresponding ammonium salt. A filtration afforded the desired amine•HCl as a white solid (80%, 166 mg). mp 113–115 °C; ^{1}H NMR (300 MHz, D_2O) δ 3.63–3.54 (m, 1H), 2.96–2.89 (m, 1H), 2.72 (s, 3H), 2.19–2.03 (m, 2H), 1.83-1.73 (m, 2H), 1.42-1.31 (m, 4H); ^{13}C NMR (100 MHz, D_2O) δ 70.1, 63.3, 33.4, 29.5, 25.7, 23.3, 23.2; FTIR (neat) 3325, 2945, 2741, 2498, 1587, 1465, 1205, 1070; HRMS (ESI+) m/z $[M]^+$ calcd for $C_7H_{16}NO$ 130.1226 found 130.1232.

(1R,2R*)-2-(Methylamino)-1,2-diphenylethan-1-ol (**35**).* The title compound was prepared according to the general procedure from *trans*-stilbene oxide (245 mg, 1.25 mmol, 0.25 M in MeOH:THF, 1:1). The crude mixture was diluted in ether and treated with HCl (0.320 mL, 4.0 M in dioxane) to produce the corresponding ammonium salt. A filtration afforded the desired amine•HCl as a white solid (92%, 303 mg). mp > 220 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.48–7.19 (m, 10H), 5.37 (d, J = 5.1 Hz, 1H), 4.53 (d, J = 5.1 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 138.3, 130.4, 129.6, 129.0, 128.8, 128.6, 126.4, 72.5, 67.8, 31.2; FTIR (neat) 3374, 2936, 2794, 1477, 1404, 1210, 1056, 771, 698; HRMS (ESI+) m/z $[M]^+$ calcd for $C_{15}H_{18}NO$ 228.1282 found 228.1383.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Additional experimental information, supporting tables and ^{1}H and ^{13}C NMR spectra (PDF).

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The authors declare no competing financial interest.

ACKNOWLEDGMENT

This research was supported by the Natural Science and Engineering Research Council of Canada (NSERC) under the CREATE Training Program in Continuous Flow Science, a discovery grant from NSERC (Canada), the Canada Foundation for Innovation, the Université de Montréal and the Centre in Green Chemistry and

Catalysis (CGCC). We thank Vanessa Kairouz and Dr. James J. Mousseau for fruitful discussions.

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27. Injection loops are more convenient for rapid optimization with small volumes (Table 1). There was no issue translating the chemistry to a bottle reagent set-up when a larger scale was required (Scheme 3).
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