

Continuous-Flow Electrophilic Amination of Arenes and Schmidt Reaction of Carboxylic Acids Utilizing the Superacidic Trimethylsilyl Azide/Triflic Acid Reagent System

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13 Continuous-Flow Electrophilic Amination of
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17 Arenes and Schmidt Reaction of Carboxylic Acids
18
19
20
21 Utilizing the Superacidic Trimethylsilyl
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25 Azide/Triflic Acid Reagent System
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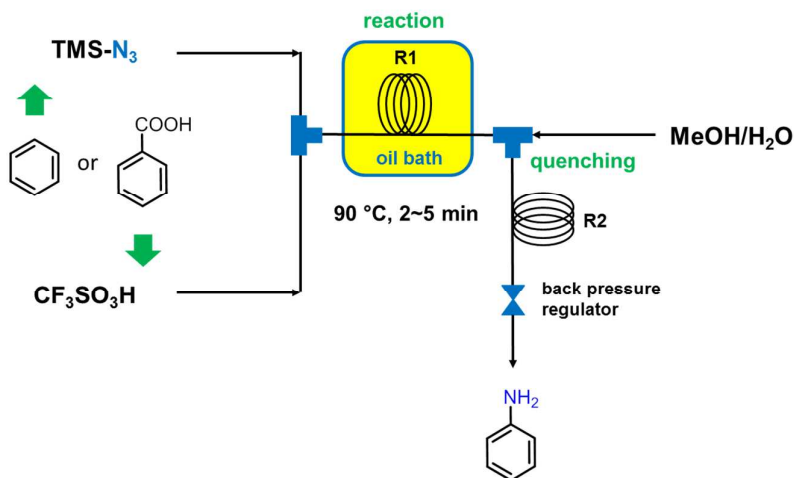
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TABLE OF CONTENTS GRAPHICS



ABSTRACT: A continuous flow protocol for the direct stoichiometric electrophilic amination of aromatic hydrocarbons and the Schmidt reaction of aromatic carboxylic acids using the superacidic trimethylsilyl azide/triflic acid system is described. Optimization of reagent stoichiometry, solvent, reaction time and temperature led to an intensified protocol at elevated temperatures that allows the direct amination of arenes to be completed within 3 min at $90\text{ }^\circ\text{C}$. In order to improve the selectivity and scope of this direct amination protocol, aromatic carboxylic acids were additionally chosen as substrates. Selected carboxylic acids could be converted to their corresponding amine counterparts in good to excellent yields (11 examples, 55-83%) via Schmidt reaction employing similar flow reaction conditions (<5 min at $90\text{ }^\circ\text{C}$) and a similar reactor setup as for the amination. The safety issues derived from the explosive, toxic and volatile hydrazoic acid intermediate, the corrosive nature of triflic acid and the exothermic quenching were addressed by designing a suitable continuous flow reaction set-up for both types of transformations.

INTRODUCTION

Since the discovery of aniline in the early nineteenth century, aromatic amines have become useful intermediates in the fine chemical industry, including the synthesis of dyes, pharmaceuticals and agrochemicals.¹ In most cases, anilines are prepared via nitration of arenes followed by a reduction step, or by nucleophilic substitution of aryl halides with ammonia.² Alternatively, transition-metal catalyzed coupling transformations,³ the electrophilic amination of boronic acids,⁴ and the reaction of aryl lithium species with hydroxylamine derivatives⁵ can be utilized for the introduction of amino groups onto an aromatic ring system. In principle, the direct amination of arenes is the simplest and the most straightforward method for the preparation of anilines. Due to the strength of the N-H bond in ammonia (107 kcal/mol),⁶ the amination of benzene with gaseous ammonia fails to provide a synthetically useful product yield, even under high-temperature and high-pressure conditions.⁷ To circumvent the challenging N-H bond activation, hydroxylamine derivatives have been used in the past as electrophilic aminating agents in the presence of an acid catalyst and excess amount of substrate as solvent, providing the desired aromatic amines in rather poor yields (with respect to the aminating agent).⁸

The acid-catalyzed direct amination of benzene by hydrazoic acid (HN₃) was discovered by Karl-Friedrich Schmidt in 1924.⁹ Since that time significant progress has been made with respect to the electrophilic amination of arenes using a variety of different azide sources.¹⁰⁻¹² In general, anilines can be obtained in moderate to good yields (with respect to the aminating agent) employing either NaN₃/AlCl₃/HCl or trimethylsilyl azide (TMSN₃)/trifluoromethanesulfonic acid (TfOH) amination systems whereby the arene substrate is used as solvent.¹⁰ The above-mentioned amination methods exhibit a certain degree of selectivity for the formation of *ortho*- and *para*-amino compounds, but all of these methods typically require a large excess of the arene substrate. Genuinely stoichiometric amination methods were not realized until recently. For example, Shubin and coworkers described the amination of activated arenes using 1 equiv of NaN₃ and 3 equiv of TfOH exposing the reaction mixture to ultrasonic irradiation for 8-11 h followed by 4 days standing at room temperature.¹¹ Very recently, Prakash and coworkers reported similar aromatic aminations utilizing 1 equiv of NaN₃ and 30 equiv of boron trifluoride monohydrate at 55 °C requiring 12-72 h reaction time.¹² These reactions follow an S_EAr mechanism, where the protonated hydrazoic acid (H₂N₃⁺) serves as electrophile.^{10b,12} The low selectivity of these

amination protocols, however, typically restricts the substrate scope to highly symmetric and activated arenes.

Aromatic carboxylic acids are widely available from the petroleum industry and natural sources.¹³ The carboxylic group can be converted to an amino group via several well-known rearrangement reactions involving electron deficient nitrogen intermediates (Figure 1).¹⁴ Among those rearrangements, the Schmidt reaction (named after Karl Friedrich Schmidt, the discoverer of this reaction and the direct amination of arenes with hydrazoic acid)⁹ is the only transformation in this family that allows *the direct conversion of carboxylic- to amino-groups* using hydrazoic acid under acid catalysis.¹⁴ Its mechanism¹⁵ guarantees that the amino group is introduced to the same carbon atom where the carboxylic group was. In addition, the reaction conditions of the atom- and step-economic Schmidt reaction (azide/acid) are very similar to those of the stoichiometric amination.^{11,12} Therefore, the Schmidt reaction of carboxylic acids can be seen as a very useful and highly selective alternative to the amination protocol.

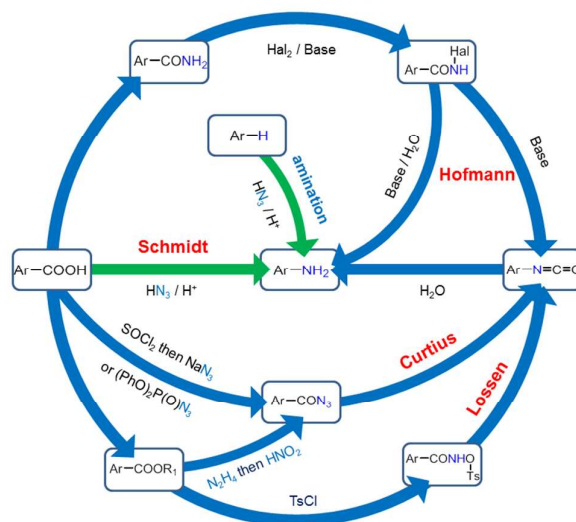


Figure 1. Name reactions converting aromatic carboxylic acids to anilines involving azides or electron deficient nitrogen intermediates.

Notably, hydrazoic acid, the common reagent for both the direct electrophilic amination and the Schmidt reaction, generated from the reaction of an azide source and acid, is a highly explosive, toxic and volatile substance (b.p. = 37 °C).¹⁶ In the case of stoichiometric amination,^{11,12} an extremely corrosive superacid is employed in large excess. The reaction heat and the produced gas (amination: 1 equiv N₂; Schmidt reaction: 1 equiv N₂ and 1 equiv CO₂) can give rise to thermal runaway and additional pressure build-up, especially on larger scales. Hence, a robust reactor system withstanding corrosion with high heat exchange

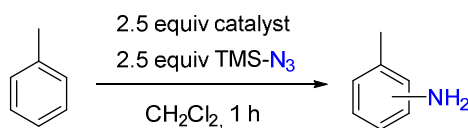
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3 efficiency is required. In the past decade, continuous flow technologies have received
4 increasing popularity among organic chemists, in particular for transformations involving
5 hazardous reagents or intermediates.¹⁷ In a continuous flow approach, the volumes processed
6 at any time are kept very small and the total hazard present is thus kept to a minimum. The
7 characteristics of microreaction technology (i.e. fast heat and mass transfer, high pressure
8 resistance of capillaries with small inner diameters) often allow temperatures to be used which
9 would be unsafe in traditional batch reactors. Synthetic intermediates can be generated,
10 consumed and finally quenched inside a closed, pressurized system by combining multiple
11 reagent streams, without the need to handle or store toxic, reactive, or explosive
12 intermediates.¹⁷ Not surprisingly, a broad spectrum of hazardous chemistries has therefore
13 been performed in continuous flow reactors,¹⁷ including transformations involving hydrazoic
14 acid.¹⁸⁻²¹ Following on our experience in safely handling hydrazoic acid in continuous flow
15 mode,^{18,19} including its recent use in combination with superacids,¹⁸ we herewith describe a
16 safe and scalable intensified continuous-flow protocol for the rapid stoichiometric
17 electrophilic amination of arenes and the Schmidt reaction of carboxylic acids using the
18 superacidic trimethylsilyl azide/triflic acid system.

32 RESULTS AND DISCUSSION

35 **Direct Amination - Reaction Optimization in Batch.** We started our investigation using the
36 amination of toluene as model reaction, since this transformation has been used frequently as
37 a model in previous studies on stoichiometric amination reactions.^{11,12} In order to search for
38 other possible catalysts and shorten the reaction time, toluene (0.2 mmol) was subjected to
39 reaction with excess amounts of azide and a series of strong acids at room temperature or 60
40 °C in sealed HPLC vials for one hour (Table 1).

46 **CAUTION:** *Risk of explosion and poisoning! All the batch experiments in this article must be*
47 *performed in a fume cupboard with sash door closed! Quenching of the reaction involves*
48 *dilution of concentrated strong acid; operate carefully under cooling and stirring!).*

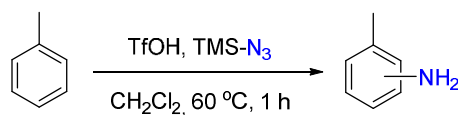
51
52 As can be seen from the data presented in Table 1, trifluoromethanesulfonic acid (triflic acid,
53 CF₃SO₃H, TfOH) was the only acid which provided the desired toluidines. Concentrated or
54 fuming sulfuric acid led to sulfonation of toluene in a competing pathway, whereas aluminum
55 trichloride catalyzed a Friedel-Crafts reaction with the solvent dichloromethane, ultimately
56 forming diarylmethane species.²²

Table 1. Acid Screening for the Direct Amination of Toluene^a

acid	room temperature	60 °C
fuming H ₂ SO ₄ (20% SO ₃)	sulfonation	sulfonation
conc. H ₂ SO ₄	no reaction	sulfonation
CH ₃ SO ₃ H	no reaction	no reaction
CF ₃ SO ₃ H (TfOH)	no reaction	amination, 28% ^b
BF ₃ OEt ₂		no reaction
AlCl ₃	Friedel-Crafts reaction with CH ₂ Cl ₂	

^aReactions were carried out with 0.2 mmol of toluene in 500 μ L of solvent; the reaction mixtures were quenched with methanol for HPLC and LC-MS analysis (for more details, see the Experimental Section). ^bHPLC peak area integration at 254 nm.

Optimization of the relative reagent amount (Table 2) demonstrated that 1 equiv of azide and a large excess of TfOH favored the amination reaction. Notably, a small amount (ca. 5%) of chlorotoluenes was detected in the reaction mixture by GC-MS analysis. We suspect that these chlorides are formed via an electrophilic attack of the protonated dichloromethane (see Scheme S1 in the Supporting Information for a proposed mechanism).

Table 2. Optimization of Reagent Ratios^a

TfOH	TMSN ₃		
	1.0 equiv	2.0 equiv	3.0 equiv
1.0 equiv	0	0	0
2.0 equiv	20 %	0	0
3.0 equiv	47 %	20 %	0

^aReactions were carried out with 0.2 mmol of toluene in 500 μ L of solvent; the reaction mixtures were quenched with methanol for HPLC analysis. Conversions were obtained by HPLC peak area integration at 254 nm.

We further hypothesized that this side reaction could be diminished by employing a less basic solvent. Based on those considerations, further optimization work with a larger excess of acid was carried out in parallel using dichloromethane and chloroform as solvents (Table 3). High

conversions were achieved in both solvents within one hour using 9 equiv of TfOH. Gratifyingly, no byproducts were formed using chloroform as solvent, whereas chlorotoluenes were detected using dichloromethane as solvent (Figure S3, Supporting Information). Therefore, chloroform was employed as the solvent of choice for all subsequent transformations in this study.

Table 3. Further Optimizations of Catalyst Amount and Solvent^a

solvent		CH ₂ Cl ₂		CHCl ₃	
reaction time		1 h	2 h	1 h	2 h
TfOH	3.0 equiv	47 % ^b	54 %	27 %	29 %
	6.0 equiv	85 %	90 %	76 %	83 %
	9.0 equiv	95 %	93 %	99 %	93 %

^aReactions were carried out with 0.2 mmol of toluene in 500 μ L of solvent; the reaction mixtures were quenched with methanol for HPLC analysis. Conversions were obtained by HPLC peak area integration at 254 nm.

Having identified an optimized reagent ratio and solvent system, the kinetic behavior of the model reaction was investigated. At 60 °C, the conversion of toluene exceeded 95% after 30 min, providing a mixture of toluidine isomers. Although *o*- and *p*-toluidines are formed preferentially, the observed selectivities were not preparatively useful (Figure 2).

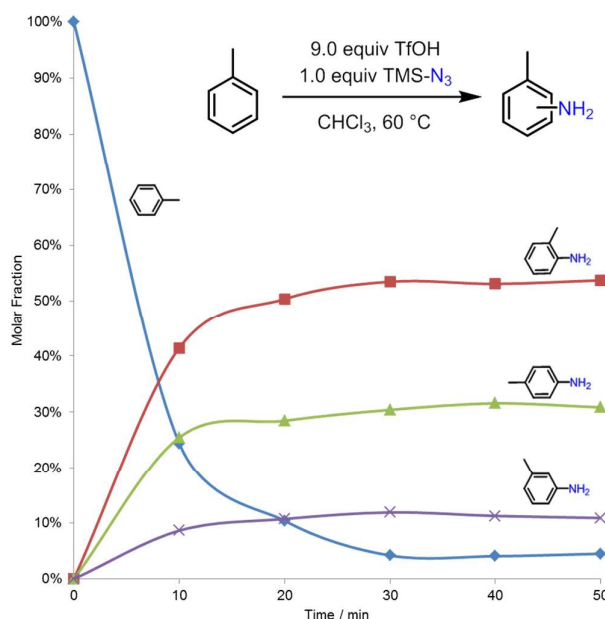
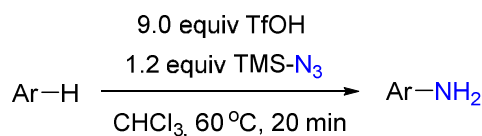
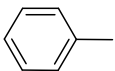
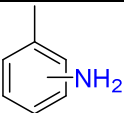

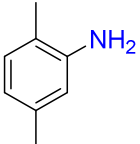
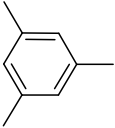
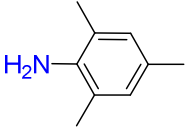
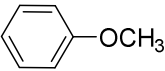
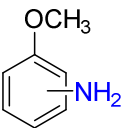
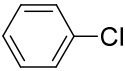
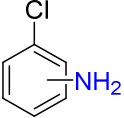


Figure 2. Influence of reaction time on conversion and selectivity (60 °C).

A limited screening of the substrate scope at 60 °C (20 min, Table 4) showed that anilines can be obtained in good yields from alkyl benzenes, whereas anisole and chlorobenzenes provided only unsatisfactory conversions. In addition to the selectivity issue, the TMSN₃/TfOH system, in accordance with previous research,¹¹ will only aminate electron-rich arenes. Triflic acid is apparently strong enough to catalyze the retro-Friedel-Crafts alkylation of *p*-xylene (Table 4, entry 2) which gave rise to the formation of toluene, toluidines and isomers of xylidine. Not unsurprisingly, good results were obtained for mesitylene, which cleanly provided the corresponding aniline derivative (Table 4, entry 3). Although anisole is considered to be an electron-rich aromatic compound it reacted slower than alkylbenzenes (Table 4, entry 4). The protonation on the ethereal oxygen by triflic acid is likely to be responsible for the low reactivity of the benzene ring, since the positively charged oxonium group (-O⁺HMe) is electron-withdrawing.

Table 4. Direct Amination of Arenes - Batch Screening Experiments^a



entry	substrate	conversion (%)	product	product (%)	remarks
1		95		95	<i>o:m:p</i> = 56:13:31
2		99		86	toluidines 4% other xylidine isomers 5%
3		99		99	
4		43		22	diarylamines detected
5		4		4	9.6 % after 1 h

^aReactions were carried out with 0.2 mmol of substrate in 500 μL of solvent; the reaction mixtures were quenched with methanol for GC analysis. Conversions and product fraction were obtained by GC-FID analysis (peak area integration).

In order to investigate the temperature dependence of the conversion, a small excess of TMSN_3 (0.2 mmol) was added to compensate the possible loss arising from thermal decomposition.^{15d} The reaction mixture was heated in a sealed vessel microwave reactor for 5 min to 60-100 °C, and then quenched for GC-FID analysis (Figure 3). In the temperature range that was screened (60-100 °C) an increase in temperature did not markedly affect selectivity. The high reactivity of the reagent H_2N_3^+ is likely to be responsible for the formation of these isomer mixtures.^{10b} Under optimized conditions, a 97% toluene conversion could be reached after 5 min at 90 °C, a significant reduction in reaction time and increase in yield compared to previously reported room temperature protocols.¹¹ These conditions were then translated to a flow protocol following the so-called microwave-to-flow paradigm.²³ With reaction temperatures far above the boiling point of hydrazoic acid (37 °C) and chloroform (61 °C) upscaling in a batch environment would clearly be challenging from a safety standpoint.

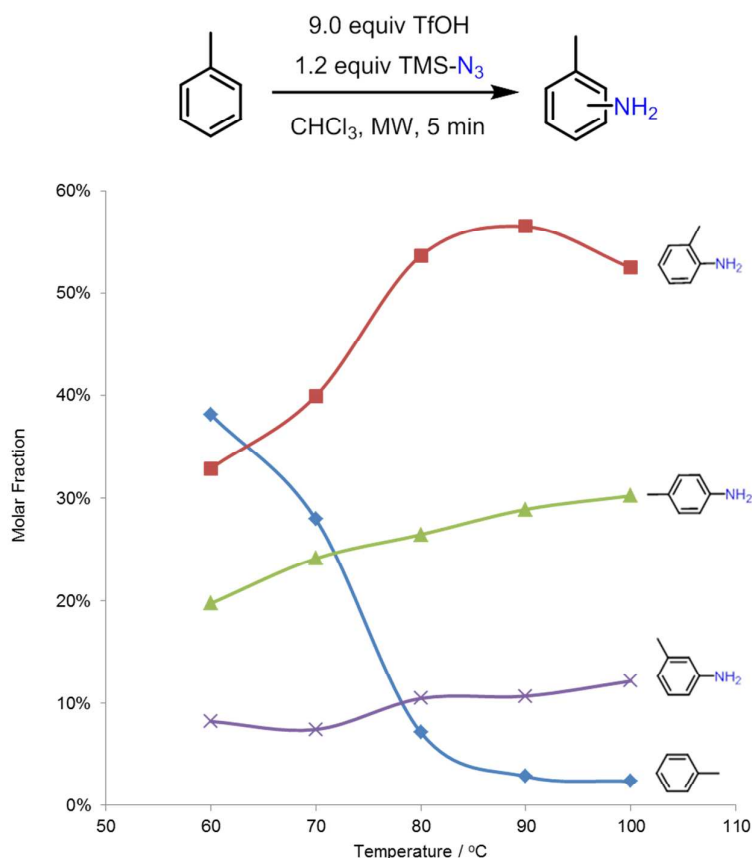


Figure 3. Influence of reaction temperature on conversion and selectivity (5 min).

Direct Amination – Continuous Flow Conditions. A continuous flow setup for the amination reaction was constructed utilizing commercially available PTFE tubing (0.8 mm inner diameter) as outlined in Figure 4. The reaction coil (R1) was made of PTFE tubing wrapped up and tied as a coil (residence volume $V_R = 6$ mL) which was immersed into an oil bath for temperature control. Each end of R1 was connected to a T-mixer for feeding (M1) and quenching (M2). A back pressure regulator (BPR) was installed at the exit to maintain pressure in the flow system. The solution of arene and TMSN_3 in CHCl_3 (stream 1) and neat TfOH (stream 2) were pumped into a T-mixer (M1) from injection loops; the mixture then entered the reaction coil (R1) where the amination took place. The flow pattern in R1 and downstream was a gas-liquid segmented flow owing to the formation of N_2 gas during the reaction. The resulting stream was then quenched with methanol in a second T-mixer (M2), forming a homogeneous solution at the outlet of the reactor for analysis or product isolation. The hazards associated with the highly exothermic quenching process and the corrosion of the BPR material by concentrated TfOH were avoided by inline quenching of the reaction mixture (for more details of the setup see the Supporting Information).

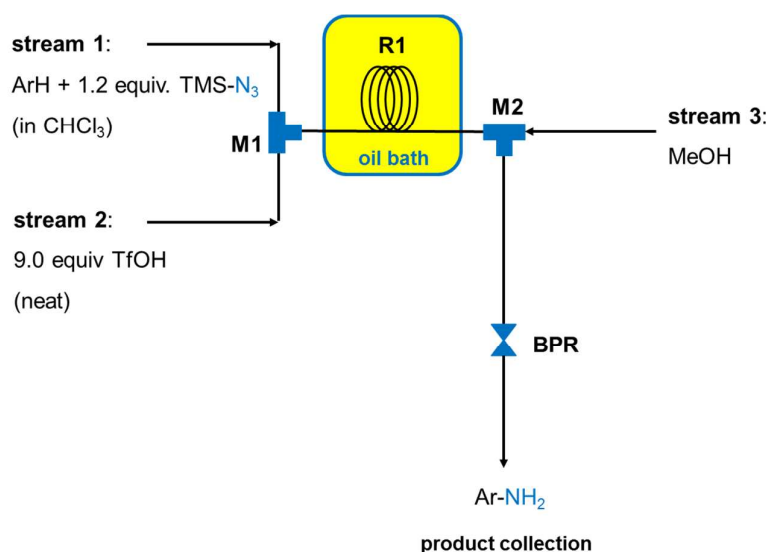
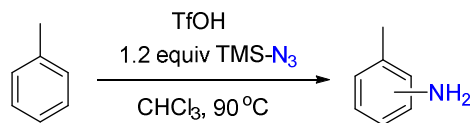


Figure 4. Continuous-flow microreactor set-up for amination

The optimization experiments in the flow reactor were started with a reagent ratio (1.2 equiv TMSN_3 and 9 equiv TfOH) and at the same concentration (0.4 mol/L) as for the batch experiments. A good yield was achieved within 2.2 min (Table 5, entry 1). Higher pressure did not increase the conversion further (entry 2), but was still used to enable the handling of larger amounts of gas in case of higher substrate concentrations. A reduction of the amount of TfOH reagent led to a decrease in yield (entries 3 and 4), similar to the batch experiments

described above (see Table 3). In the presence of 9 equiv of TfOH, high conversions were attained for 0.8 and 1.6 mol/L substrate feed solution within 3 min (Table 5, entries 5 and 6).

Table 5. Optimization of Direct Amination in a Flow Reactor (Figure 4)



entry	flow rate of the pumps ^a		ArH conc. ^b (mol/L)	TfOH (equiv)	conv ^c (%)	t_R ^d (min)	P^e (bar)
	F_1 (μL/min)	F_2 (μL/min)					
1	500	150	0.4	9	96	2.2	3
2	500	150	0.4	9	97	3.0	7
3	500	150	0.8	4.5	58	2.5	7
4	464	186	0.8	6	88	2.4	7
5	406	244	0.8	9	99	2.3	7
6	295	355	1.6	9	95	2.9	7

^a $F_3 = 2.35$ mL/min. ^bConcentration in feed solution. ^cMeasured by GC-FID analysis. ^dExperimentally determined residence time in **R1** (determined by a stopwatch). ^ePressure display on pump 1 at steady state.


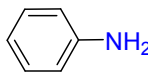
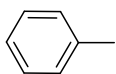
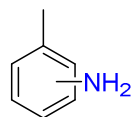
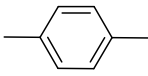
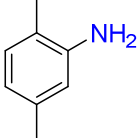
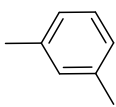
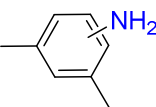
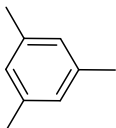
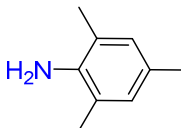
During the flow optimization, the sum of the flow rates of streams 1 and 2 were kept the same in order to minimize the residence time variation. The generation of gas and the difference of reaction rates made the accurate control of the residence time quite difficult, but ultimately did not impair the reproducibility of the results. Methanol was fed with a flow rate of 2.35 mL/min to quench the reaction, dissolve the ammonium salts and dilute the acid. Lower methanol flow rates led to the blockage of the BPR by salt crystals. Using the optimized conditions described in Table 5 entry 6, five aromatic hydrocarbons were aminated with good yields (Table 6). Among the chosen substrates, the amination of benzene (Table 6, entry 1) and mesitylene (Table 6, entry 5) led to single isolable amination products of potential preparative value. In particular, the amination of mesitylene provides a direct approach to mesidine (2,4,6-trimethylaniline), which is often used as a building block in the synthesis of bulky NHC ligands in coordination chemistry.²⁴ *p*-Xylene (Table 6, entry 3) was converted to 2,5-xylidine (containing trace impurities of toluidines and other xylidine isomers, see the Supporting Information for details). When the azide was removed from the feed of the experiment corresponding to entry 3, a mixture of toluene, xylene, mesitylene and tetramethylbenzene was obtained, confirming the tendency of methyl group migrations in these arenes under the superacidic conditions employed (see Figure S4 in the Supporting

Information).²⁵ While the continuous flow conditions described above allow the safe and direct amination of arenes within less than 3 min at 90 °C, the poor regioselectivity and the disability to aminate electron-deficient substrates led us to investigate an alternative approach.

Table 6. Continuous Flow Direct Amination of Arenes

$$\text{Ar-H} \xrightarrow[\text{CHCl}_3, 90^\circ\text{C}]{\begin{matrix} 9.0 \text{ equiv TfOH} \\ 1.2 \text{ equiv TMS-N}_3 \end{matrix}} \text{Ar-NH}_2$$

1a-e **2a-e**

entry	substrate (1)	product (2)	yield ^a (%)	<i>t_R</i> ^b (min)	remarks
1 (a)			86	2.8	
2 (b)			78	2.9	<i>o</i> : <i>m</i> : <i>p</i> = 53:11:36 ^c
3 (c)			89	2.9	toluidines and other xylydine isomers trace
4 (d)			89	2.7	2,4-methylaniline/ 2,6-methylaniline = 77:23 ^c
5 (e)			75	2.8	

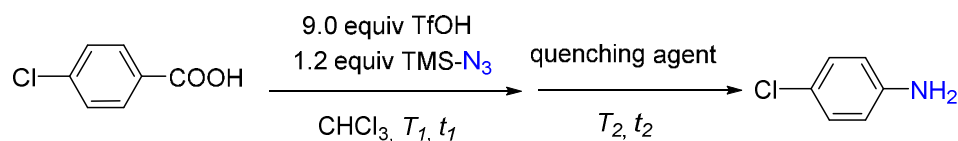
^aIsolated yield. ^b*F*₁ = 295 μL/min (ArH + TMSA), *F*₂ = 355 μL/min (TfOH), *F*₃ = 2.35 mL/min (MeOH); experimentally determined residence time in **R1** (determined by a stopwatch). ^cDetermined by ¹H NMR.

Schmidt Reaction - Reaction Optimization in Batch. The Schmidt reaction of carboxylic acid is normally carried out in a NaN₃/conc. H₂SO₄/CHCl₃ system at 40-60 °C for several hours.^{9,26} Other kinds of halogenated solvents (e.g. 1,2-dichloroethane²⁷ or trichloroethene^{15d}) and different acid catalysts²⁸ are sometimes applied as solvents. Triflic acid has been previously employed in Schmidt chemistry of aldehydes and ketones for the introduction of nitrogen moieties.²⁹ As NaN₃ is not soluble in the unpolar solvents typically used in Schmidt reactions, TMSN₃^{21a} and TBAA^{21b} (tetrabutylammonium azide) often serve as azide sources in continuous flow Schmidt reactions instead of NaN₃. Our investigations on the Schmidt reaction started with 4-chlorobenzoic acid, whose direct amination counterpart, i.e., chlorobenzene could not be aminated in synthetically significant yield. Although chloroform

is a good solvent for the Schmidt reaction,^{15c} the low solubility of carboxylic acids makes the use of this unpolar solvent problematic for a continuous flow process. As shown in Table S1 in the Supporting Information, 1.2 equiv of TMSN₃ and 9 equiv of triflic acid again proved to be the optimum conditions for performing the Schmidt reaction, triflic acid being able to dissolve the aromatic carboxylic acids at room temperature. Nearly full conversion was achieved at 70 °C after a reaction time of 1 h.

In a subsequent optimization cycle the conditions for the hydrolysis of the isocyanate intermediates using alcohols as quenching reagents were studied (Table 7). Depending on the quality of the chloroform (in particular on the presence of ethanol as stabilizer) varying amounts of byproducts (i.e., carbamates) were found to be present in the crude reaction mixture, regardless of the quenching agent used (Table 7, entries 1 to 4). Using alcohol-free chloroform as solvent provided nearly quantitative yields of the desired 4-chloroaniline product after a reaction time of 30 min at 70 °C and a quenching period of 5 min using MeOH (Table 7, entries 7 and 8). As expected, higher temperatures did increase the yield within 5 min, but the formation of urea byproducts became increasingly apparent (Table 7, entries 9-12).

Table 7. Optimization of Reaction Conditions for the Schmidt Reaction^a



entry	solvent	T ₁ (°C)	t ₁ (min)	quenching agent	T ₂ (°C)	t ₂ (min)	yield (%)
1	CHCl ₃	70	20	MeOH	70	60	78
2	CHCl ₃	70	20	EtOH	70	60	80
3	CHCl ₃	70	20	<i>n</i> -PrOH	70	60	85
4	CHCl ₃	70	20	<i>i</i> -PrOH	70	60	81
5	CHCl ₃	70	30	MeOH	rt	~ 5	85
6	CHCl ₃	70	60	MeOH	rt	~ 5	96
7	EtOH-free CHCl ₃ ^b	70	30	MeOH	rt	~ 5	>99
8	EtOH-free CHCl ₃ ^b	70	60	MeOH	rt	~ 5	>99
9 ^c	CHCl ₃	70	5	MeOH	rt	~ 5	43

10 ^c	CHCl ₃	80	5	MeOH	rt	~ 5	71
11 ^c	CHCl ₃	90	5	MeOH	rt	~ 5	75
12 ^c	CHCl ₃	100	5	MeOH	rt	~ 5	81

^aReactions were carried out with 0.2 mmol of substrate in 500 μ L of solvent; the reaction mixtures were quenched with methanol for HPLC analysis. Yields were calculated from HPLC peak area % using an external standard. Technical chloroform, purity > 99.3%, stabilizer 0.6 % ethanol was used.

^bChloroform, purity 99.5 %, stabilizer 2-methyl-2-butene. ^cSealed vessel microwave reaction.

Schmidt Reaction – Continuous Flow Experiments. The subsequent flow optimization was performed at 90 °C in a setup similar to the one used for the amination, the only difference being the (optional) residence time coil R2 (Figure 5). The carboxylic acid was dissolved in TfOH as feed solution (1 mol/L, containing 9 equiv TfOH). Since the Schmidt reaction generates 2 equiv of gas, the overall flow rate in R1 was set to a lower value compared to that used with the amination process in order to provide for the necessary residence times. As observed in the flow amination, the flow pattern in R1 and downstream was a gas-liquid segmented flow.

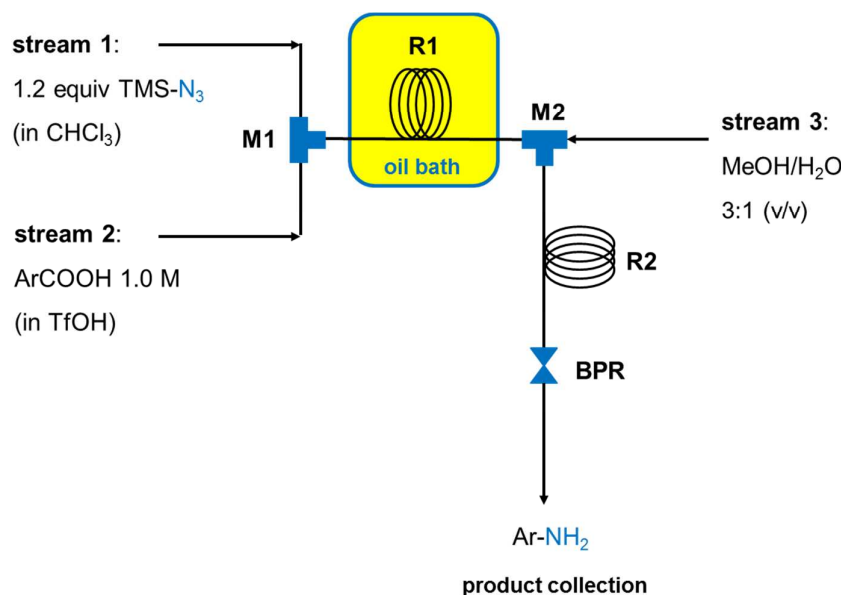
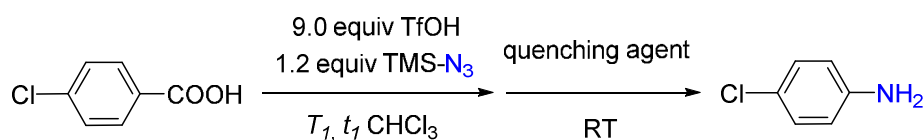


Figure 5. Continuous-flow microreactor set-up for the Schmidt reaction.

Although satisfactory yields were attained for the first few trials (Table 8, entries 1 to 3), the back pressure regulator (BPR) occasionally got blocked due to the accumulation of solids when pure methanol was used as quenching agent. Slower flow rates did not improve the yield any further (Table 8, entries 4 and 5). The poor solubility of some polar reaction components (urea, carboxylic acid and ammonium salts) and incomplete mixing probably

caused the blockage. Based on these considerations, the tube between M2 and the BPR was replaced by a 2nd residence time coil R2 (residence volume $V_R = 5$ mL). The introduction of R2 not only improved the mixing performance by prolonging the mixing time, but also featured a flow system with more stability against pressure fluctuation. In order to increase the solubility of polar components, a mixture of MeOH and water was utilized as quenching agent. With a MeOH/H₂O ratio = 1:1 (v/v), a biphasic discharge was formed and the BPR was blocked before the reaction completed (Table 8, entry 6). This might reflect the poor solubility of the polar components in either of the two phases. As the MeOH/H₂O ratio was adjusted to 3:1 (v/v), the discharge became homogeneous and no blocking occurred (Table 8, entry 7).

Table 8. Optimization of Schmidt Reaction in a Flow Reactor (Figure 5)



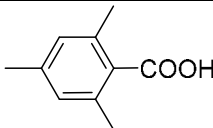
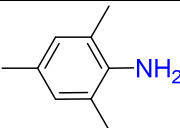
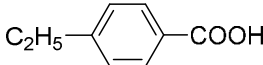
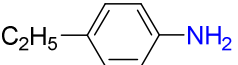
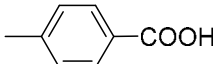
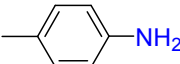
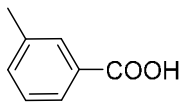
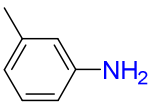
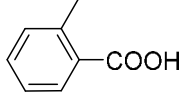
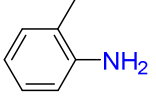
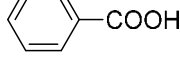
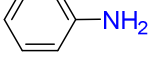
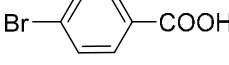
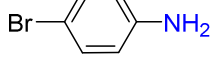
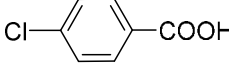
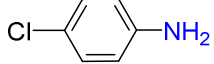
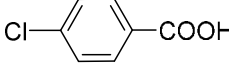
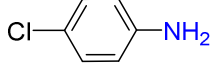
entry	F_1 ($\mu\text{L}/\text{min}$)	F_2 ($\mu\text{L}/\text{min}$)	T_1 ($^{\circ}\text{C}$)	t_1^d (min)	quenching agent	F_3 (mL/min)	yield ^a (%)	remarks
1	275	275	90	3.0	MeOH	2.35	67	without R2
2 ^b	275	275	90	3.0	MeOH	2.35	68	without R2
3 ^b	275	275	90	2.0	MeOH	2.35	63	without R2
4 ^c	137	137	90	7.6	MeOH	1.17	67	without R2
5 ^c	137	137	90	5.3	MeOH	1.17	55	without R2
6	275	275	90	2.7	MeOH/H ₂ O 1:1 (v/v)	2.35	blocked	with R2
7	250	250	90	3.8	MeOH/H ₂ O 3:1 (v/v)	2.00	73	with R2

^aIsolated yields. ^{b,c}The difference in residence time arose from small variations of back pressure. ^dExperimentally determined residence time in **R1** (determined by a stopwatch).

Using the optimized conditions (Table 8, entry 7), an array of substituted benzoic acids was converted to their corresponding anilines at 90 $^{\circ}\text{C}$ within 3-5 min (Table 9). Alkyl- and halogen-substituted anilines were obtained with modest to good yields. *p*-, *m*- and *o*-Toluidines (**4c-e**) and chloroanilines (**4h-j**) were prepared individually as pure compounds from their corresponding benzoic acids. No formation of other isomers was observed. The

carboxylic groups of benzoic acids possessing strong electron-withdrawing groups, such as nitro- (**3k** and **3l**) and trifluoromethyl- (**3m**), were more difficult to activate by protonation.^{15d} Therefore, their respective anilines were generated in only poor yields. A small yield increase was observed during the upscaling from 1.0 mmol to 2.0 mmol scale (Table 9, entries 8 and 9). This is because the operation time at steady state was longer at larger scale, so that the influence of dead volume and diffusion became smaller. The modified setup (Figure 5 with R2) for the Schmidt reaction could also be used for the amination. All amination reactions shown in Table 6 could be duplicated in this setup using the following conditions: $F_1 = 295 \mu\text{L/min}$ (ArH + TMSA); $F_2 = 355 \mu\text{L/min}$ (TfOH); $F_3 = 2.35 \text{ mL/min}$ (MeOH or MeOH/H₂O 3:1).

Table 9. Continuous Flow Schmidt Reaction of Aromatic Carboxylic Acids

$\text{Ar-COOH} \xrightarrow[\text{90 } ^\circ\text{C, CHCl}_3]{\begin{matrix} 9.0 \text{ equiv TfOH} \\ 1.2 \text{ equiv TMS-N}_3 \end{matrix}} \xrightarrow[\text{rt}]{\begin{matrix} \text{MeOH-H}_2\text{O} \\ 3:1 \text{ (v/v)} \end{matrix}} \text{Ar-NH}_2$ 3a-m 4a-m					
entry	acid (3)	aniline (4)	scale (mmol)	t_R^c (min)	yield ^a (%)
1 (a)			1.0	3.6	71
2 (b)			2.0	4.0	69
3 (c)			2.0	3.5	77
4 (d)			2.0	3.2	79
5 (e)			2.0	3.4	83
6 (f)			2.0	3.6	55
7 (g)			1.0	4.3	60
8 (h)			1.0	3.1	73
9 (h)			2.0	3.7	78

10 (i)			2.0	3.3	79
11 (j)			2.0	3.8	79
12 (k)			2.0	3.4	28 ^b
13 (l)			1.0	3.6	18 ^b
14 (m)			2.0	3.5	24

^aIsolated yields. ^bProducts not isolated, conversion determined by HPLC-UV at 254 nm.

^cExperimentally determined residence time in **R1** (determined by a stopwatch).

Compared to the continuous Schmidt reaction of ketones,²¹ where moderately strong acids (CF₃COOH or CH₃SO₃H) and non-protic polar solvents (MeCN or DME) were employed, the current flow protocol for the Schmidt reaction of carboxylic acid required a superacid (TfOH) and non-polar solvent (CHCl₃) combination, in order to trigger the reaction by protonation of the carboxylic acids. Under continuous flow conditions both types of Schmidt reactions provided products in a few minutes residence time in good isolated yields.

CONCLUSION

A continuous-flow protocol for the stoichiometric amination of aromatic hydrocarbons and the Schmidt reaction of aromatic acids was developed. The reaction time for amination was shortened from days to a few minutes using an elevated temperature regime allowing the preparation of specific anilines from highly symmetric arenes. The intrinsic poor selectivity of this amination method, however, restricts its general scope and applicability. The Schmidt reaction of aromatic carboxylic acids was introduced as a regioselective alternative applying the same reaction condition. Both reactions were performed at 90 °C within 2-5 min residence time using 1.2 equiv of TMSN₃ and 9.0 equiv of triflic acid. Substituted anilines were obtained in generally good yields after a simple work-up.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded on a 300 MHz instrument (75 MHz for ^{13}C). Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q and m stand for singlet, doublet, triplet, quadruplet and multiplet. HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (150 \times 4.6 mm, particle size 5 μm) at 37 $^{\circ}\text{C}$ using a mobile phase A (water/MeCN 90:10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear increase from solution 30% B to 100% B within 10 min. GC-FID analysis was performed using a HP5 column (30 m \times 0.250 mm \times 0.025 μm). After 1 min at 50 $^{\circ}\text{C}$ the temperature was increased in 2 $^{\circ}\text{C min}^{-1}$ stepped up to 80 $^{\circ}\text{C}$, then in 25 $^{\circ}\text{C min}^{-1}$ stepped up to 300 $^{\circ}\text{C}$ and kept at 300 $^{\circ}\text{C}$ for 4 minutes. The detector gas for the flame ionization is H_2 and compressed air (5.0 quality). GC-MS spectra were recorded using a HP5-MS column (30 m \times 0.250 mm \times 0.25 μm) with helium as carrier gas (1 mL/min constant flow) coupled with a mass spectrometer (EI, 70 eV). After 1 min at 50 $^{\circ}\text{C}$, the temperature was increased in 25 $^{\circ}\text{C/min}$ steps up to 300 $^{\circ}\text{C}$ and kept at 300 $^{\circ}\text{C}$ for 1 min. All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification. Products were characterized by ^1H NMR and identified by comparison of the spectra with those reported in the literature. All compounds synthesized herein are known in the literature. Proof of purity was obtained by ^1H NMR and HPLC-UV or GC-FID spectroscopy.

General Methods for Batch Reactions

Amination of Arenes (Table 4). A sample of the arene (0.20 mmol), TMSN_3 (0.24 mmol), CHCl_3 (500 μL) and TfOH (1.8 mmol) were added into an HPLC vial (1.5 mL / 11.6 \times 32 mm, Macherey-Nagel GmbH, internal volume 2 mL) with a magnetic stir bar inside. The vial was then sealed with an 11 mm cap and then heated at the given temperature for the given time. After the reaction, the vial was then cooled in an ice bath. An injection needle was carefully pierced through the septum to release the gas inside. After removing the cap, 500 μL methanol were carefully added under stirring (**CAUTION: the quenching is exothermic! It involves dilution of concentrated strong acid. The first few drops of methanol must be added slowly under continuous stirring!**). The resulting solution was subjected to the work-up methods given below for different purposes.

Amination of Aromatic Carboxylic Acids (Table 8). A 1.0 mol/L solution of the aromatic carboxylic acid in TfOH (contains 9 equiv TfOH) (200 μL), CHCl_3 (500 μL) and TMSN_3

(0.24 mmol) was added into an HPLC vial with a stirring bar inside. The subsequent procedures are identical to the amination protocol given above.

Microwave Reactions. A sample of arene or carboxylic acid (0.20 mmol), TMSN₃ (0.24 mmol), CHCl₃ (500 μ L) and TfOH (1.8 mmol) (or 1.0 mol/L solution of aromatic carboxylic acid in TfOH (200 μ L), CHCl₃ (500 μ L) and TMSN₃ (0.24 mmol) for Schmidt reaction) was added into a microwave vessel (0.5 ~ 2.0 mL filling volume) with a magnetic stir bar inside. The microwave vessel was permanently sealed with a septum fitted in an aluminum crimp top, then placed in the microwave cavity of a Biotage Initiator+ reactor: Instrument settings: reaction time 5 min (hold time mode), high absorption mode, 10 s pre-stirring. After the reaction, an injection needle was carefully pierced through the septum to release the gas inside. After removing the cap, 500 μ L methanol was carefully (!) added to the vessel with stirring. The resulting solution was transferred to an HPLC vial and subjected to the work-up methods given below for different purposes.

Work-up method A: The vial was filled with methanol and recapped for HPLC analysis.

Work-up method B: The quenched solution was transferred to a test tube, neutralized with 4 mL saturated NaHCO₃ solution, then extracted with 1 mL of CHCl₃; 0.5 mL of the CHCl₃ layer was transferred to another HPLC vial. The vial was then filled with CHCl₃, recapped for GC-FID or GC-MS analysis. *Work-up method C:* For the isolation of the product the reaction mixtures of 4 experiments (4 \times 0.2 mmol scale) were combined and subsequently dissolved in 7 mL 1 mol/L HCl solution. The solution was extracted with 3 \times 5 mL of CHCl₃ to remove all non-amine organics. The aqueous layer was neutralized with saturated NaHCO₃ solution and extracted with 3 \times 5 mL CHCl₃. The chloroform layer was dried over anhydrous Na₂SO₄, evaporated *in vacuo* to afford the product.

General Procedure for the Continuous Flow Direct Amination of Arenes. The complete reactor setup (for more detailed information, see the Supporting Information) was flushed with pure solvents by pumping CHCl₃ (P1 and P2) and MeOH (P3) with flow rates $F_1 = 295$ μ L/min, $F_2 = 355$ μ L/min and $F_3 = 2.35$ mL/min until the temperature of the oil bath stabilized at 90 $^{\circ}$ C (this process took ca. 30 min). The corresponding arenes (3.20 mmol) and TMSN₃ (3.84 mmol, 1.2 equiv) were dissolved in CHCl₃ and diluted to 2.00 mL in a volumetric flask (feed of stream 1). Neat TfOH (2.8 mL) was used as feed for stream 2. Both feeds were loaded into their corresponding feeding loops (L1 and L2). Pumping of the reactants and timing was started at the same time. Stream 1 and 2 were pumped into a T-

mixer (M1) by two syringe pumps. The combined mixture then passed through the reaction coil R1 (1/16 in. o.d.; 0.8 mm i.d.; residence volume $V_I = 6.0$ mL) in the 90 °C oil bath. The resulting reaction mixture stream was brought to contact with MeOH (stream 3) in the second T-mixer (M2), passed through the back pressure regulator (BPR) and was then directed into the collection vessel. Hydrochloric acid (1mol/L aq, 10 mL) was added to the collection vessel and the resulting mixture was concentrated *in vacuo* to ca. 10 mL. The mixture was extracted with 3×7 mL CHCl_3 to remove all non-amine organics. The aqueous phase was collected and the organic phase was extracted with 10 mL HCl (1 mol/L, aq). In a 250 mL beaker, the combined aqueous phase was neutralized with saturated NaHCO_3 (aq) to liberate the amine. The neutralized mixture was extracted with 3×7 mL CHCl_3 . The organic phase containing amine was dried over anhydrous Na_2SO_4 and then evaporated *in vacuo* to afford the product.

Aniline (2a): 257.2 mg (86%); light yellow oil; ^{30a} ^1H NMR (300 MHz, CDCl_3) δ 7.28 (t, $J = 7.8$ Hz, 1H), 6.93 – 6.85 (m, 2H), 6.80 – 6.73 (m, 2H), 3.69 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 146.6, 129.4, 118.6, 115.2.

Mixture of o-, m- and p-Toluidine (2b): 275.7 mg (78%); brown oil; (lit.^{30a} for the spectra of each component) (for spectra see the Supporting Information)

2,5-Dimethylaniline (2c): 346.4 mg (89%);^{30f} light brown oil; ^1H NMR (300 MHz, CDCl_3) δ 7.15 (d, $J = 7.6$ Hz, 1H), 6.76 (d, $J = 7.7$ Hz, 1H), 6.66 (s, 1H), 2.48 (s, 3H), 2.32 (s, 3H).

Mixture of 2,4-methylaniline^{30e} and 2,6-dimethylaniline^{30b} (2d): 347.0 mg (89%); green oil. (Spectra see the Supporting Information)

Mesidine (2e): 322.2 mg (75%); light brown oil; ^{30d} ^1H NMR (300 MHz, CDCl_3) δ 7.07 (s, 2H), 3.67 (s, 2H), 2.54 (s, 3H), 2.43 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 140.6, 129.2, 127.2, 122.0, 20.7, 17.8.

General Procedure for the Continuous Flow Schmidt Reaction of Aromatic Carboxylic Acids. The complete reactor setup (for more detailed information, see the Supporting Information) was flushed with pure solvents by pumping CHCl_3 (P1 and P2) and MeOH/ H_2O 3:1(v/v) (P3) with the flow rates $F_1 = 250$ $\mu\text{L}/\text{min}$, $F_2 = 250$ $\mu\text{L}/\text{min}$ and $F_3 = 2.00$ mL/min until the temperature of the oil bath stabilized at 90 °C (this process took ca. 30 min). A TMSN_3 (1.2 mol/L, 2.5 mL) solution in CHCl_3 was used as feed of stream 1. The corresponding aromatic carboxylic acid (2.00 mmol) was dissolved in neat TfOH and diluted to 2.00 mL in a volumetric flask with TfOH (feed of stream 2). Both feeds were loaded to

their corresponding feeding loops (L1 and L2). Pumping of the reactants and timing were started at the same time. Stream 1 and 2 were pumped into a T-mixer (M1) by two syringe pumps. The combined mixture then passed through the reaction coil R1 (1/16 in. o.d.; 0.8 mm i.d.; residence volume $V_I = 6.0$ mL) in the 90 °C oil bath. The resulting reaction mixture stream was brought to contact with MeOH/H₂O 3:1(v/v) (stream 3) in the second T-mixer (M2), passed through the buffer coil R2 and the back pressure regulator (BPR) and was then directed to the collection vessel. Hydrochloric acid (1 mol/L aq, 10 mL) was added into the discharge and the resulting mixture was concentrated *in vacuo* to ca. 10 mL. The mixture was extracted with 3 × 7 mL CHCl₃ to remove all non-amine organics. The aqueous phase was collected and the organic phase was extracted with 10 mL HCl (1 mol/L, aq). In a 250 mL beaker, the combined aqueous phases were neutralized with saturated NaHCO₃ (aq) to release the amine. The neutralized mixture was extracted with 3 × 7 mL CHCl₃. The organic phase containing amine was dried over anhydrous Na₂SO₄ and then evaporated *in vacuo* to afford the product.

Mesidine (4a = 2e): 95.6 mg (71%); light brown oil; ^{30d} ¹H NMR (300 MHz, CDCl₃) δ 6.88 (s, 2H), 3.50 (s, 2H), 2.33 (s, 3H), 2.26 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 140.2, 128.9, 127.2, 121.9, 20.5, 17.7.

4-Ethylaniline (4b): 167.5 mg (69%); light brown oil; ^{30e} ¹H NMR (300 MHz, CDCl₃) δ 7.12 (d, *J* = 8.1 Hz, 2H), 6.80 – 6.66 (m, 2H), 3.61 (s, 2H), 2.68 (q, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 144.3, 134.4, 128.7, 115.4, 28.1, 16.1.

p-Toluidine (4c): 164.6 mg (77%); red brown oil; ^{30a} ¹H NMR (300 MHz, CDCl₃) δ 7.07 – 7.00 (m, 2H), 6.73 – 6.61 (m, 2H), 3.49 (s, 2H), 2.32 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 143.9, 129.8, 127.8, 115.3, 20.5.

m-Toluidine (4d): 168.2 mg (79%); red brown oil; ^{30a} ¹H NMR (300 MHz, CDCl₃) δ 7.16 – 7.07 (m, 1H), 6.69 – 6.61 (m, 1H), 6.60 – 6.51 (m, 2H), 3.52 (s, 2H), 2.33 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 146.4, 139.2, 129.2, 119.5, 116.0, 112.3, 21.5.

o-Toluidine (4e): 179.2 mg (83%); green oil; ^{30a} ¹H NMR (300 MHz, CDCl₃) δ 7.20 – 7.07 (m, 2H), 6.87 – 6.70 (m, 2H), 3.56 (s, 2H), 2.25 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 144.7, 130.5, 127.0, 122.4, 118.7, 115.0, 17.4.

Aniline (4f = 2a): 102.9 mg (55%); red brown oil; ^{30a} ¹H NMR (300 MHz, DMSO) δ 7.08 – 6.97 (m, 2H), 6.63 – 6.55 (m, 2H), 6.55 – 6.47 (m, 1H), 5.00 (s, 2H); ¹³C NMR (75 MHz, DMSO) δ 149.0, 129.3, 116.1, 114.4.

4-Bromoaniline (4g): 103.3 mg (60%); light brown solid;^{30c} ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.57 (d, *J* = 8.8 Hz, 2H), 3.55 (2H); ¹³C NMR (75 MHz, CDCl₃) δ 145.5, 132.0, 116.8, 110.1.

4-Chloroaniline (4h): 199.7 mg (78%);^{30a} light red crystals; ¹H NMR (300 MHz, CDCl₃) δ 7.18 – 7.07 (m, 2H), 6.67 – 6.55 (m, 2H), 3.68 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 145.0, 129.1, 123.0, 116.3.

3-Chloroaniline (4i): 201.4 mg (79%);^{30a} light yellow oil; ¹H NMR (300 MHz, CDCl₃) δ 7.08 (t, *J* = 8.0 Hz, 1H), 6.80 – 6.67 (m, 2H), 6.56 (ddd, *J* = 8.1, 2.2, 0.9 Hz, 1H), 3.57 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 147.6, 134.9, 130.3, 118.5, 114.9, 113.2.

2-Chloroaniline (4j): 201.4 mg (79%); red oil; ^{30a} ¹H NMR (300 MHz, CDCl₃): δ 7.29 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.11 (td, *J* = 8.0, 1.4 Hz, 1H), 6.83 – 6.65 (m, 2H), 4.01 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 143.0, 129.4, 127.7, 119.3, 119.0, 115.9.

4-(Trifluoromethyl)aniline (4m): 77.5 mg (24%); light yellow oil;^{30b} ¹H NMR (300 MHz, CDCl₃) δ 7.42 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 8.3 Hz, 2H), 3.96 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 149.4, 126.7 (q, *J* = 3.8 Hz), 124.8 (q, *J* = 268.7 Hz), 120.1 (q, *J* = 32.6 Hz), 114.2.

Supporting Information Available. Images of the reactors and ¹H and ¹³C NMR spectra of all isolated compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

REFERENCES

- (1) (a) Ricci, A. *Amino Group Chemistry: From Synthesis to the Life Sciences*, Wiley-VCH, Weinheim, **2008**. (b) Rappoport, Z., Ed; *The Chemistry of Anilines*, Part 1 and 2, John Wiley & Sons, New York, **2007**. (c) Lawrence, S. A., Ed; *Amines: Synthesis Properties and Applications*, Cambridge University Press, Cambridge, **2004**.
- (2) Weissrermel, K.; Arpe, H.-J. *Industrial Organic Chemistry*, 3rd ed., VCH, Weinheim **1997**.
- (3) Romero, M.; Harrak, Y.; Basset, J.; Orúe, J. A.; Pujol, M. D. *Tetrahedron* **2009**, 65, 1591.
- (4) Coeffard, V.; Moreau, X.; Thomassigny, C.; Greck, C. *Angew. Chem. Int. Ed.* **2013**, 52, 5684.
- (5) Genet, J. P.; Mallart, S.; Greck, C.; Piveteau, E. *Tetrahedron Lett.* **1991**, 32, 2359.

- (6) Klinkenberg, J. L.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 86.
- (7) Backer, J.; Höderlich, W. F. *Catal. Lett.* **1998**, *54*, 125.
- (8) (a) Graebe, C. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 1778. (b) Kovacic, P.; Bennet, R. P.; Foote, J. L. *J. Am. Chem. Soc.* **1962**, *84*, 759. (c) Kovacic, P.; Bennet, R. P.; Foote, J. L. *J. Am. Chem. Soc.* **1961**, *83*, 743. (d) Keller, R. N.; Smith, P. A. S. *J. Am. Chem. Soc.* **1944**, *66*, 1122.
- (9) Schmidt, K. F. *Ber. Dtsch. Chem. Ges.* **1924**, *57*(4), 704.
- (10) (a) Kovacic, P.; Bennet, R. P.; Foote, J. L. *J. Am. Chem. Soc.* **1964**, *86*, 1588. (b) Mertens, A.; Lammertsma, K.; Arvanighi, M.; Olah, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 5657. (c) Borodkin, G. I.; Elanov, I. R.; Popov, S. A.; Pokrovskii, L. M.; Shubin, V. G. *Russ. J. Org. Chem.* **2003**, *39*, 718. (d) Olah, G. A.; Ernst, T. D. *J. Org. Chem.* **1989**, *54*, 1203.
- (11) Borodkin, G. I.; Elanov, I. R.; Shubin, V. G. *Russ. J. Org. Chem.* **2009**, *45*, 946.
- (12) Prakash, G. K. S.; Gurung, L.; Marinez, E. R.; Mathew, T.; Olah, G. A. *Tetrahedron Lett.* **2016**, *57*, 288.
- (13) (a) Weaver, J. D.; Recio III, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846. (b) Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030.
- (14) (a) Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, *35*, 146. (b) Wroblewski, A.; Coombs, T. C.; Huh, C. W.; Li, S.-W.; Aubé, J. *Org. React.* **2011**, *78*, 1.
- (15) (a) Woodroffe, C. C.; Zhong, B.; Lu, X.; Silverman, R. B. *J. Chem. Soc., Perkin Trans. 2* **2000**, 55. (b) Schuerch, C.; Hunstress, E. H. *J. Am. Chem. Soc.* **1949**, *71*, 2233. (c) Wolff, H. *Org. React.* **1946**, *3*, 308. (d) Briggs, L. H.; Lyttleton, J. W. *J. Chem. Soc.* **1943**, 421.
- (16) For a discussion of safety aspects handling HN_3 , see: (a) Kopach, M. E.; Murray, M. M.; Braden, T. M.; Kobierski, M. E.; Williams, O. L. *Org. Process Res. Dev.* **2009**, *13*, 152 and references cited therein. For further safety and general chemical properties of HN_3 , see: (b) Encyclopedia of Inorganic Chemistry, 2nd Edition, (Ed.: King, R. B.) Wiley-VCH, Weinheim, **2005**. (c) Hagenbuch, J.-P. *Chimia* **2003**, *57*, 773. (d) *Organic Azides: Syntheses and Applications* (Eds.: Bräse, S.; Banert, K.), Wiley-VCH, Weinheim, **2010**.
- (17) For selected reviews on flow chemistry with a focus on handling hazardous transformations, see: (a) Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E.

T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. *Chem. Soc. Rev.* **2016**, *45*, 4892. (b) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2015**, *54*, 6688. (c) Jensen, K. F.; Reizmana, B. J.; Newman, S. G. *Lab Chip* **2014**, *14*, 3206. (d) Poechlauer, P.; Braune, S.; Dielemans, B.; Kaptein, B.; Obermüller, R.; Thathagar, M. *Chim. Oggi/Chem. Today* **2013**, *30*(4), 51. (e) Gemoets, H. P. L.; Su, Y.; Shang, M.; Hessel, V.; Luque, R.; Noël, T. *Chem. Soc. Rev.* **2016**, *45*, 83.

(18) Gutmann, B.; Elsner, P.; O’Kearney-McMullan, A.; Goundry, W.; Roberge, D. M.; Kappe, C. O. *Org. Process Res. Dev.* **2015**, *19*, 1062.

(19) (a) Gutmann, B.; Roduit, J.-P.; Roberge, D.; Kappe, C. O. *J. Flow Chem.* **2012**, *2*, 8. (b) Gutmann, B.; Roduit, J.-P.; Roberge, D.; Kappe, C. O. *Chem. Eur. J.* **2011**, *17*, 13146. (c) Gutmann, B.; Roduit, J.-P.; Roberge, D.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2010**, *122*, 7255.

(20) (a) Smith, C. J.; Nikbin, N.; Ley, S. V.; Lange, H.; Baxendale, I. R. *Org. Biomol. Chem.* **2011**, *9*(6), 1938. (b) Kupracz, L.; Hartwig, J.; Wegner, J.; Ceylan, S.; Kirschning, A. *Beilstein J. Org. Chem.* **2011**, *7*, 1441. (c) Baxendale, I.; Ley, S. V.; Mansfield, A.; Smith, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4017. (d) Palde, P. B.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 3525. (e) Bogdan, A.; Sach, N. W. *Adv. Synth. Catal.* **2009**, *351*, 849.

(21) For references on the Schmidt reaction of ketones in continuous flow, see: (a) Painter, T. O.; Thornton, P. D.; Orestano, M.; Santini, C.; Organ, M. G.; Aube, J. *Chem. Eur. J.* **2011**, *17*, 9595. (b) Chen, Y.; Liu, B.; Liu, X.; Yang, Y.; Ling, Y.; Jia, Y. *Org. Process Res. Dev.* **2014**, *18*, 1589.

(22) (a) Qiao, K.; Deng, Y. *J. Mol. Catal. A: Chem.* **2001**, *171*, 81. (b) Cai, X.; Cui, S.; Qu, L.; Yuan, D.; Lu, B.; Cai, Q. *Catal. Comm.* **2008**, *9*, 1173.

(23) Glasnov, T. N.; Kappe, C. O. *Chem. Eur. J.* **2011**, *17*, 11956.

(24) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Ison, E. A.; Ison, A. *J. Chem. Educ.* **2012**, *89*, 1575.

(25) Amblès, A.; Baudet, N.; Jacquesy, J.-C.; Kribii, A. *Tetrahedron Lett.* **1992**, *33*, 5193.

(26) (a) Kvaskoff, D.; Lüerssen, H.; Bednarek, P.; Wentrup C. *J. Am. Chem. Soc.* **2014**, *136*, 15203. (b) Oesterlin, M. *Angew. Chem.* **1932**, *45*, 536.

(27) Wang, J.; Zou, Y. *J. Appl. Polym. Sci.*, **2013**, *127*, 4850.

(28) Stockel, R. F.; Hall, D. M. *Nature* **1963**, 197, 787.

(29) (a) Motiwala, H. F.; Charaschanya, M.; Day, V. W.; Aube, J. *J. Org. Chem.* **2016**, 81, 1593. (b) Rokade, B. V.; Prabhu, K. R. *J. Org. Chem.* **2012**, 77, 5364.

(30) (a) Shi, Q.; Lu, R.; Jin, K.; Zhang, Z.; Zhao, D. *Green Chem.* **2006**, 8, 868. (b) Rahaim, R. J.; Maleczka, R. E. *Org. Lett.* **2005**, 7, 5087. (c) Orlandi, M.; Tosi, F.; Bonsignore, M.; Benaglia, M. *Org. Lett.* **2015**, 17, 3941. (d) Rao, H.; Fu, H.; Jiang, Y. *Angew. Chem. Int. Ed.* **2009**, 48, 1114. (e) Lv, M.-F.; Lu, G.-P.; Cai, C. *Asian J. Org. Chem.* **2015**, 4, 141. (f) Green, R. A.; Hartwig, J. F. *Org. Lett.* **2014**, 16, 4388.