JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

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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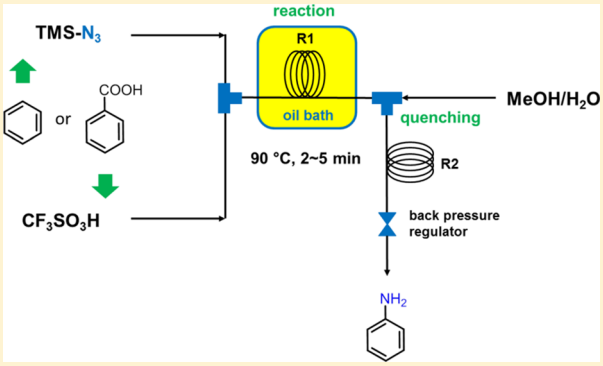
Supporting Information

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 °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 a Schmidt reaction employing similar flow reaction conditions (<5 min at 90 °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 setup for both types of transformations.



INTRODUCTION

Since the discovery of aniline in the early 19th 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 derivatives[5] 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 (HN_3) 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 $NaN_3/AlCl_3/HCl$ or trimethylsilyl azide ($TMSN_3$)/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 co-workers described the amination of activated arenes using 1 equiv of NaN_3 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 co-workers reported similar aromatic aminations utilizing 1 equiv of NaN_3 and 30 equiv of boron trifluoride monohydrate at 55 °C requiring a 12−72 h reaction time.[12] These reactions follow an S_EAr mechanism, where the protonated hydrazoic acid ($H_2N_3^+$) serves as an electrophile.[10b,12] The low selectivity of these amination protocols, however, typically restricts the substrate scope to highly symmetric and activated arenes.

Received: August 24, 2016
Published: September 20, 2016

DOI: 10.1021/acs.joc.6b02085
J. Org. Chem. 2016, 81, 9372−9380

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

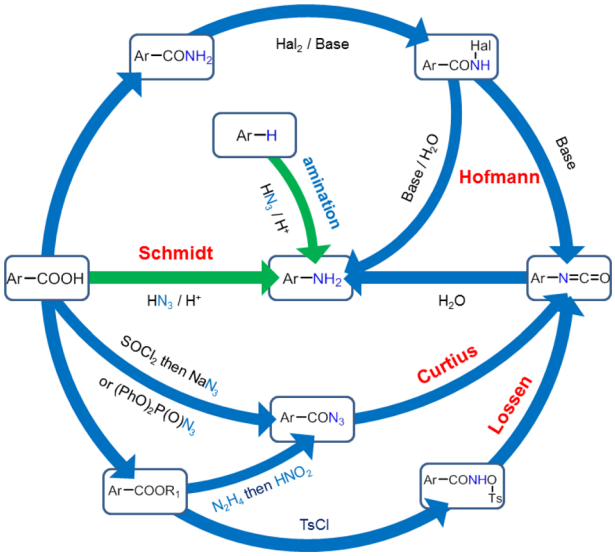


Figure 1. Name reactions converting aromatic carboxylic acids to anilines involving azides or electron-deficient nitrogen intermediates.

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 mechanism[15] 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.

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 (bp = 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 N_2; Schmidt reaction: 1 equiv N_2 and 1 equiv CO_2) 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 efficiency is required. In the past decade, continuous flow technologies have received increasing popularity among organic chemists, in particular for transformations involving hazardous reagents or intermediates.[17] In a continuous flow approach, the volumes processed at any time are kept very small and the total hazard present is thus kept to a minimum. The characteristics of microreaction technology (i.e., fast heat and mass transfer, high pressure resistance of capillaries with small inner diameters) often allow temperatures to be used which would be unsafe in traditional batch reactors. Synthetic intermediates can be generated, consumed, and finally quenched inside a closed, pressurized system by combining multiple reagent streams, without the need to handle or store toxic, reactive, or explosive intermediates.[17] Not surprisingly, a broad spectrum of hazardous chemistries has therefore been performed in continuous flow reactors,[17] including transformations involving hydrazoic acid.[18−21] Following on our experience in safely handling hydrazoic acid in continuous flow mode,[18,19] including its recent use in combination with superacids,[18] we herewith describe a safe and scalable intensified continuous-flow protocol for the rapid stoichiometric electrophilic amination of arenes and the Schmidt reaction of carboxylic acids using the superacidic trimethylsilyl azide/triflic acid system.

RESULTS AND DISCUSSION

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

Table 1. Acid Screening for the Direct Amination of Toluene

acid	room temperature	60 °C
fuming H_2SO_4 (20% SO_3)	sulfonation	sulfonation
conc. H_2SO_4	no reaction	sulfonation
CH_3SO_3H	no reaction	no reaction
CF_3SO_3H (TfOH)	no reaction	amination, 28%[b]
BF_3OEt_2		no reaction
$AlCl_3$		Friedel–Crafts reaction with CH_2Cl_2

[a]Reactions were carried out with 0.2 mmol of toluene in 500 μL of solvent; the reaction mixtures were quenched with methanol for HPLC and LC-MS analysis (for more details, see the Experimental Section). [b]HPLC peak area integration at 254 nm.

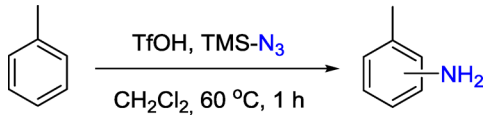
CAUTION: *Risk of explosion and poisoning! All the batch experiments in this article must be performed in a fume cupboard with sash door closed! Quenching of the reaction involves dilution of concentrated strong acid; operate carefully under cooling and stirring!*

As can be seen from the data presented in Table 1, trifluoromethanesulfonic acid (triflic acid, CF_3SO_3H, TfOH) was the only acid which provided the desired toluidines. Concentrated or fuming sulfuric acid led to sulfonation of toluene in a competing pathway, whereas aluminum trichloride catalyzed a Friedel–Crafts reaction with the solvent dichloromethane, ultimately forming a diarylmethane species.[22]

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

DOI: 10.1021/acs.joc.6b02085
J. Org. Chem. 2016, 81, 9372−9380

Table 2. Optimization of Reagent Ratios



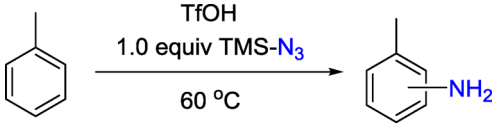
	TMSN$_3$		
TfOH	1.0 equiv	2.0 equiv	3.0 equiv
1.0 equiv	0%	0%	0%
2.0 equiv	20%	0%	0%
3.0 equiv	47%	20%	0%

[a]Reactions were carried out with 0.2 mmol of toluene in 500 μL of solvent; the reaction mixtures were quenched with methanol for HPLC analysis. Conversions were obtained by HPLC peak area integration at 254 nm.

Scheme S1 in the Supporting Information for a proposed mechanism).

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

Table 3. Further Optimizations of Catalyst Amount and Solvent



solvent		CH_2Cl_2		$CHCl_3$	
reaction time		1 h	2 h	1 h	2 h
TfOH	3.0 equiv	47%	54%	27%	29%
	6.0 equiv	85%	90%	76%	83%
	9.0 equiv	95%	93%	99%	93%

[a]Reactions were carried out with 0.2 mmol of toluene in 500 μL of solvent; the reaction mixtures were quenched with methanol for HPLC analysis. Conversions were obtained by HPLC peak area integration at 254 nm.

achieved in both solvents within 1 h 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.

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).

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 TMSN$_3$/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

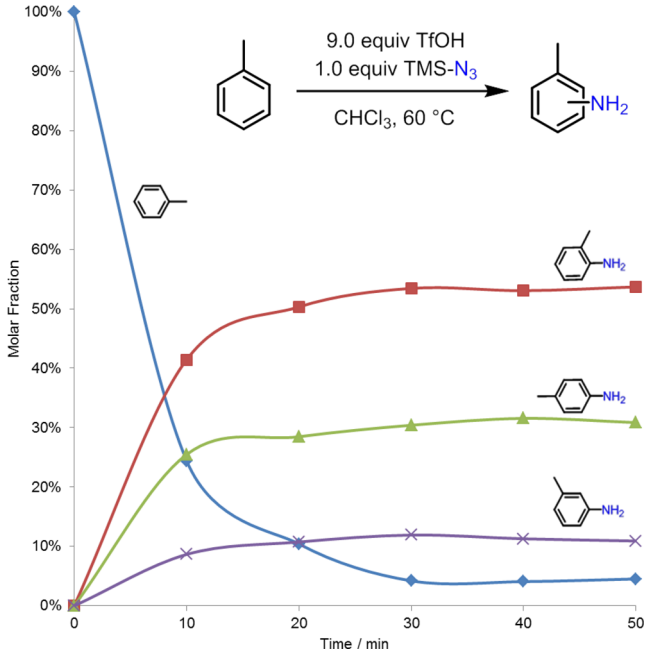
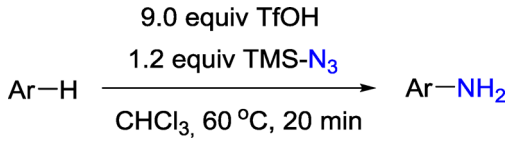
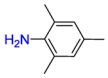
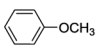


Figure 2. Influence of reaction time on conversion and selectivity (60 °C).

Table 4. Direct Amination of Arenes: Batch Screening Experiments



entry	substrate	conversion (%)	product	product (%)	remarks
1		95		95	*o*:*m*:*p* = 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

[a]Reactions 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).

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.

In order to investigate the temperature dependence of the conversion, a small excess of TMSN$_3$ (0.2 mmol) was added to

DOI: 10.1021/acs.joc.6b02085
J. Org. Chem. 2016, 81, 9372–9380

compensate for 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

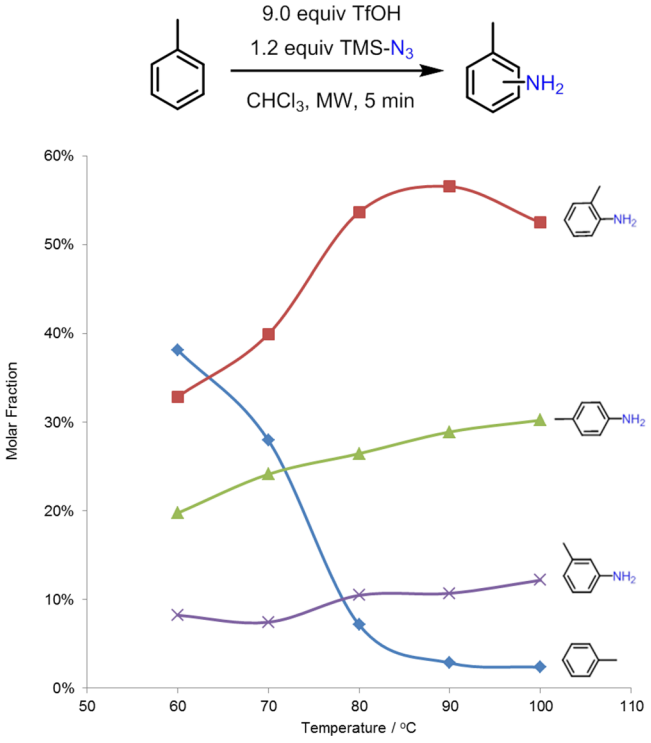


Figure 3. Influence of reaction temperature on conversion and selectivity (5 min).

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.

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_1 = 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

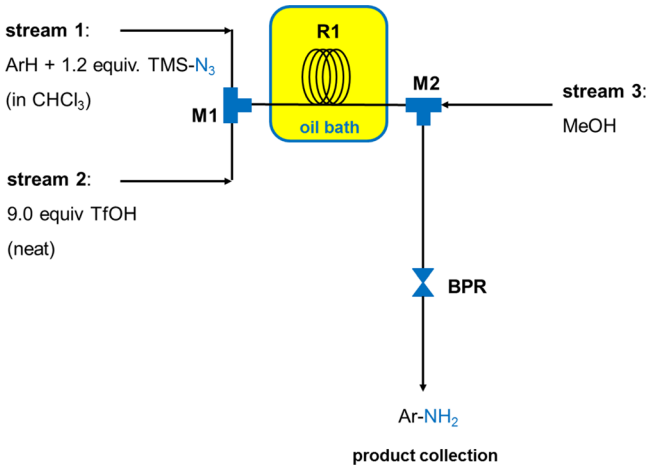
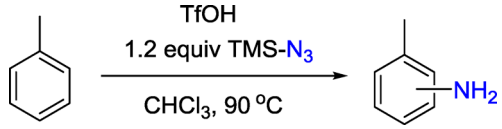


Figure 4. Continuous-flow microreactor setup for amination.

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).

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

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



	flow rate of the pumps[a]						
entry	F_1 (μL/min)	F_2 (μL/min)	ArH conc.[b] (mol/L)	TfOH (equiv)	conv[c] (%)	t_R[d] (min)	P[e] (bar)
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

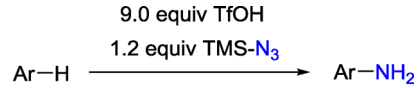
[a] F_3 = 2.35 mL/min. [b] Concentration in feed solution. [c] Measured by GC-FID analysis. [d] Experimentally determined residence time in **R1** (determined by a stopwatch). [e] Pressure display on pump 1 at steady state.

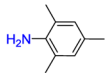
conversion further (entry 2), but was still used to enable the handling of larger amounts of gas in the case of higher substrate concentrations. A reduction of the amount of TfOH reagent led to a decrease in yield (entries 3 and 4), similar to the batch experiments described above (see Table 3). In the presence of 9 equiv of TfOH, high conversions were attained for the 0.8 and 1.6 mol/L substrate feed solution within 3 min (Table 5, entries 5 and 6).

DOI: 10.1021/acs.joc.6b02085
J. Org. Chem. 2016, 81, 9372−9380

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. Continuous Flow Direct Amination of Arenes



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

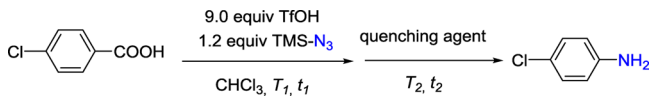
[a]Isolated yield. [b]F_1 = 295 μL/min (ArH + TMSA), F_2 = 355 μL/min (TfOH), F_3 = 2.35 mL/min (MeOH); experimentally determined residence time in **R1** (determined by a stopwatch). [c]Determined by ^{1}H NMR.

(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.

Schmidt Reaction: Reaction Optimization in Batch. The Schmidt reaction of carboxylic acid is normally carried out in a NaN_3/conc. H_2SO_4/$CHCl_3$ system at 40−60 °C for several hours.[9,26] Other kinds of halogenated solvents (e.g., 1,2-dichloroethane[27] or trichloroethene[15d]) and different acid catalysts[28] 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 NaN_3 is not soluble in the nonpolar solvents typically used in Schmidt reactions, $TMSN_3$[21a] and TBAA[21b] (tetrabutylammonium azide) often serve as azide soures in continuous flow Schmidt reactions instead of NaN_3. 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 $TMSN_3$ 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

Table 7. Optimization of Reaction Conditions for the Schmidt Reaction



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	*n*-PrOH	70	60	85
4	$CHCl_3$	70	20	*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

[a]Reactions were carried out with 0.2 mmol of substrate in 500 μL 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. [b]Chloroform, purity 99.5%, stabilizer 2-methyl-2-butene. [c]Sealed vessel microwave reaction.

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).

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

DOI: 10.1021/acs.joc.6b02085
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difference being the (optional) residence time coil R2 (Figure 5). The carboxylic acid was dissolved in TfOH as feed solution

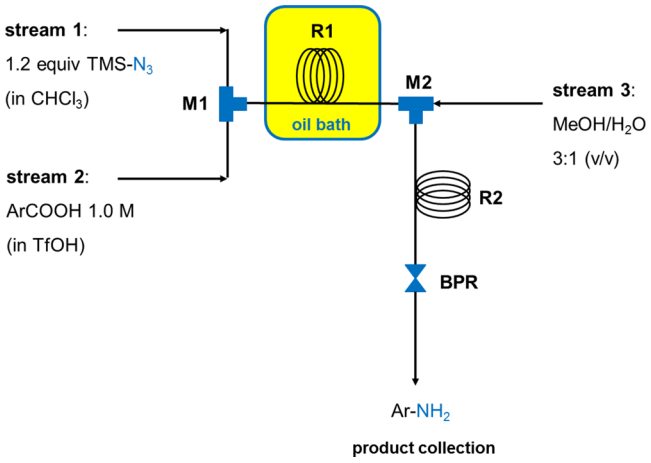


Figure 5. Continuous-flow microreactor setup for the Schmidt reaction.

(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.

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 second residence time coil R2 (residence volume V_2 = 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 the quenching agent. With a MeOH/H_2O 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/H_2O ratio was adjusted to 3:1 (v/v), the discharge became homogeneous and no blocking occurred (Table 8, entry 7).

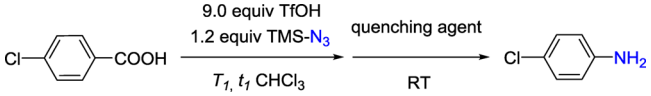
Using the optimized conditions (Table 8, entry 7), an array of substituted benzoic acids was converted to their corresponding anilines at 90 °C within 3–5 min (Table 9). Alkyl- and halogen-substituted anilines were obtained with modest to good yields. *p*-, *m*-, and *o*-Toluidines (**4c–e**) and chloroanilines (**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 the 1.0 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 μL/min (ArH + TMSA); F_2 = 355 μL/min (TfOH); F_3 = 2.35 mL/min (MeOH or MeOH/H_2O 3:1).

Compared to the continuous Schmidt reaction of ketones,[21] where moderately strong acids (CF_3COOH or CH_3SO_3H) and nonprotic polar solvents (MeCN or DME) were employed, the current flow protocol for the Schmidt reaction of carboxylic acid required a superacid (TfOH) and nonpolar solvent ($CHCl_3$) 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 nearly the same reaction condition. Both reactions were performed at

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



entry	F_1 (μL/min)	F_2 (μL/min)	T_1 (°C)	t_1[c] (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[b]	137	137	90	7.6	MeOH	1.17	67	without R2
5[b]	137	137	90	5.3	MeOH	1.17	55	without R2
6	275	275	90	2.7	MeOH/H_2O 1:1 (v/v)	2.35	blocked	with R2
7	250	250	90	3.8	MeOH/H_2O 3:1 (v/v)	2.00	73	with R2

[a]Isolated yields. [b]The difference in residence time arises from small variations of back pressure. [c]Experimentally determined residence time in **R1** (determined by a stopwatch).

DOI: 10.1021/acs.joc.6b02085
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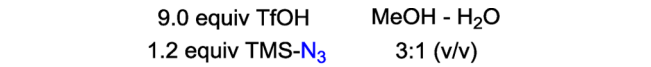
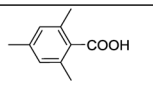
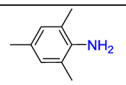
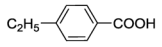
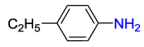
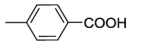
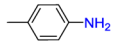
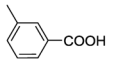
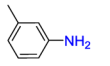
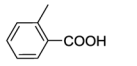
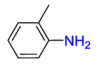
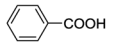
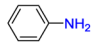
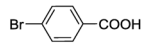
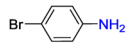
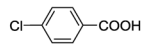
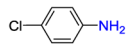
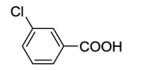
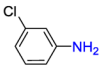
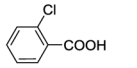
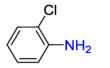
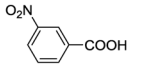
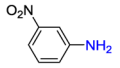
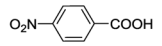
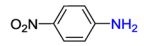
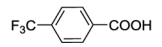
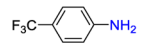
Table 9. Continuous Flow Schmidt Reaction of Aromatic Carboxylic Acids



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

[a]Isolated yields. [b]Products not isolated, conversion determined by HPLC-UV at 254 nm. [c]Experimentally determined residence time in **R1** (determined by a stopwatch).

90 °C within 2−5 min residence time using 1.2 equiv of $TMSN_3$ and 9.0 equiv of triflic acid. Substituted anilines were obtained in generally good yields after a simple workup.

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 mm × 4.6 mm, particle size 5 μm) at 37 °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 an HP5 column (30 m × 0.250 mm × 0.025 μm). After 1 min at 50 °C the temperature was increased in 2 °C min^{-1} stepped up to 80 °C, then in 25 °C min^{-1} stepped up to 300 °C, and kept at 300 °C for 4 min. The detector gas for the flame ionization is H_2 and compressed air (5.0 quality). GC−MS spectra were recorded using an HP5-MS column (30 m × 0.250 mm × 0.25 μm) with helium as the carrier gas (1 mL/min constant flow) coupled with a mass spectrometer (EI, 70 eV). After 1 min at 50 °C, the temperature was increased in 25 °C/min steps up to 300 °C and kept at 300 °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 mm × 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 of 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 workup 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 of TfOH) (200 μL), $CHCl_3$ (500 μL), and $TMSN_3$ (0.24 mmol) was added into an HPLC vial with a stir 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), $TMSN_3$ (0.24 mmol), $CHCl_3$ (500 μL), and TfOH (1.8 mmol) (or 1.0 mol/L solution of aromatic carboxylic acid in TfOH (200 μL), $CHCl_3$ (500 μL) and $TMSN_3$ (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 prestirring. After the reaction, an injection needle carefully pierced through the septum to release the gas inside. After removing the cap, 500 μL of methanol was carefully (**!**) added to the vessel with stirring. The resulting solution was transferred to an HPLC vial and subjected to the workup methods given below for different purposes.

Workup Method A. The vial was filled with methanol and recapped for HPLC analysis. *Workup method B:* The quenched solution was transferred to a test tube, neutralized with 4 mL of saturated $NaHCO_3$ solution, and then extracted with 1 mL of $CHCl_3$; 0.5 mL of the $CHCl_3$ layer was transferred to another HPLC vial. The vial was then filled with $CHCl_3$ and recapped for GC-FID or GC-MS analysis. *Workup method C:* For the isolation of the product the reaction mixtures of four experiments (4 × 0.2 mmol scale) were combined and subsequently dissolved in 7 mL of 1 mol/L HCl solution. The solution was extracted with 3 × 5 mL of $CHCl_3$ to remove all nonamine organics. The aqueous layer was neutralized with saturated $NaHCO_3$ solution and extracted with 3 × 5 mL $CHCl_3$. The chloroform layer was dried over anhydrous Na_2SO_4 and 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 $CHCl_3$ (P1 and P2) and MeOH (P3) with flow rates F_1 = 295 μL/min, F_2 = 355 μL/min, and F_3 = 2.35 mL/min until the temperature of the oil bath stabilized at 90 °C (this process took ca. 30 min). The corresponding arenes (3.20 mmol) and $TMSN_3$ (3.84 mmol, 1.2 equiv) were dissolved in $CHCl_3$ 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 were started at the same time. Streams 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_1 = 6.0 mL) in the 90 °C oil bath. The resulting reaction mixture stream was brought to contact with MeOH

DOI: 10.1021/acs.joc.6b02085
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(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 (1 mol/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 of $CHCl_3$ to remove all nonamine organics. The aqueous phase was collected, and the organic phase was extracted with 10 mL of 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 of $CHCl_3$. 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] ^{1}H 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; ^{1}H 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] ^{1}H 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 Armatic 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 μL/min, F_2 = 250 μL/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. Streams 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_1 = 6.0 mL) in the 90 °C oil bath. The resulting reaction mixture stream was brought to contact with MeOH/H_2O 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 $CHCl_3$ to remove all nonamine organics. The aqueous phase was collected, and the organic phase was extracted with 10 mL of HCl (1 mol/L, aq). In a 250 mL beaker, the combined aqueous phases were neutralized with saturated $NaHCO_3$ (aq) to release the amine. The neutralized mixture was extracted with 3 × 7 mL of $CHCl_3$. The organic phase containing amine was dried over anhydrous Na_2SO_4 and then evaporated *in vacuo* to afford the product.

Mesidine (**4a = 2e**). 95.6 mg (71%); light brown oil;[30d] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (s, 2H), 3.50 (s, 2H), 2.33 (s, 3H), 2.26 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 128.9, 127.2, 121.9, 20.5, 17.7.

4-Ethylaniline (**4b**). 167.5 mg (69%); light brown oil;[30e] ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 134.4, 128.7, 115.4, 28.1, 16.1.

p-Toluidine (**4c**). 164.6 mg (77%); red brown oil;[30a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07−7.00 (m, 2H), 6.73−6.61 (m, 2H), 3.49 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 129.8, 127.8, 115.3, 20.5.

m-Toluidine (**4d**). 168.2 mg (79%); red brown oil;[30a] ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.07 (m, 2H), 6.87−6.70 (m, 2H), 3.56 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 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] ^{1}H 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); ^{13}C NMR (75 MHz, DMSO) δ 149.0, 129.3, 116.1, 114.4.

4-Bromoaniline (**4g**). 103.3 mg (60%); light brown solid;[30c] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 8.8 Hz, 2H), 3.55 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 132.0, 116.8, 110.1.

4-Chloroaniline (**4h**). 199.7 mg (78%);[30a] light red crystals; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.07 (m, 2H), 6.67−6.55 (m, 2H), 3.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 129.1, 123.0, 116.3.

3-Chloroaniline (**4i**). 201.4 mg (79%);[30a] light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 134.9, 130.3, 118.5, 114.9, 113.2.

2-Chloroaniline (**4j**). 201.4 mg (79%); red oil;[30a] ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 8.3 Hz, 2H), 6.71 (d, J = 8.3 Hz, 2H), 3.96 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02085.

Images of the reactors and ^{1}H and ^{13}C NMR spectra of all isolated compounds (PDF)

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Notes

The authors declare no competing financial interest.

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DOI: 10.1021/acs.joc.6b02085
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