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Lewis Acid Activation | *Very Important Paper* |

Direct and Selective C-H Carbamoylation of (Hetero)aromatics with TMSOTf-Activated Carbamoyl Chloride

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Abstract: Exploiting trimethylsilyltrifluoromethanesulfonate as Lewis acid, (hetero)aromatics underwent regioselective and direct carbamoylation. The method is based on the in situ generation of a highly electrophilic carbamoyl triflate active species.

Introduction

Amide functionality is ubiquitously found, in particular in pharmaceuticals, natural products, insecticides, polymers and peptides (Figure 1).[1] Amide bond formation, which is identified as one of the most used reactions for the preparation of drug candidates,[2] is traditionally performed through the condensation of amines with acids or acylation of amines with acyl chlorides or anhydrides. To generate aromatic amides, these methods are thus limited by the necessity to pre-install the amine or the carboxylic functions into the (hetero)aromatic derivative. Metal-catalyzed aminocarbonylation emerged as a particularly versatile method to generate aromatic carboxamides.[3] The direct Pd-catalyzed carbamoylation has also been reported, but both synthetic routes need pre-activated aryl halide precursors.[4]

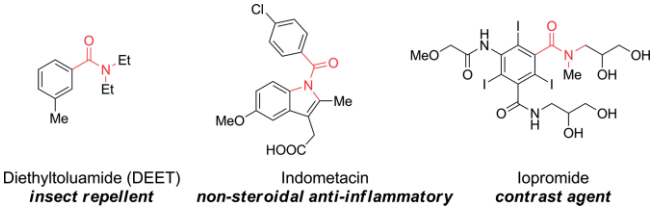
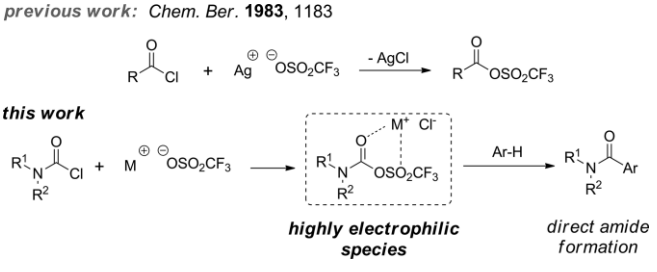


Figure 1. Examples of pharmaceutical and agrochemical commercialized aryl amide containing products.

As a complement to these substitution-based strategies, the direct C(sp^2)-H carbamoylation can be considered as an interesting alternative. Indirect methods to generate substituted aryl and heteroaryl carbamates and amides are the directed-*ortho*-metalation, as long as a well-adapted directing group is present on the target.[5] Ruthenium-catalyzed *ortho*-carbamoylation of arylpyridines[6] and the recently reported use of hydrazinecarboxamides or formamide as agents for copper-catalyzed or radical-based carbamoylation in *ortho* position of the nitrogen of heteroarenes, respectively, are also specific methods.[7] A general route to aromatic carboxamides would reside in the direct Friedel–Crafts type carbamoylation of aromatic rings.[8] However, this strategy is rather limited to a few stoichiometric examples, thus probably due to the low reactivity of the carbamoyl chloride reagents. To overcome this difficulty, related urea derivatives activated by trifluoromethanesulfonic anhydride led to the formation of the corresponding electron-rich arenecarboxamides.[9] Trifluoromethanesulfonic acid was also reported to activate carbamates and generate the required reactive isocyanate cations, allowing the introduction of the amide functionality into aromatic compounds,[10] a process that can also be used from nitroaryl ureas.[11] In this context, our attention was turned to the thirty-years-ago reported reaction of carbonyl chloride with silver trifluoromethanesulfonate, delivering an active carboxylic trifluoromethanesulfonic anhydride at –30 °C (Scheme 1).[12] In addition, the solvolysis of carbamoyl chloride was recently shown to occur at the carbonyl carbon, with replacement of the chloride ion.[13] It was also previously shown that carbamoyl fluoride could be activated by the strong antimony pentafluoride Lewis acid, enhancing the partial double bond character between carbon and nitrogen.[14] Consider-



Scheme 1. Direct synthesis of aromatic amides by metal triflate activation of carbamoyl chloride.

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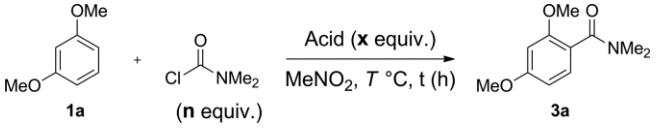
ing these precedents, we hypothesize that carbamoyl chloride could be efficiently activated by metal triflate Lewis acids to generate an active carbamoyl triflate intermediate in situ, with enhanced electrophilicity due to the presence of both the triflate electron withdrawing effect and the metal cation. The carbamoyl triflate intermediate should thus favor the direct carbamoylation of aromatic derivatives (Scheme 1).

Results and Discussion

To test this hypothesis, resorcinol dimethyl ether **1a** was selected as the model substrate and submitted to reaction with dimethylcarbamoyl chloride **2** in nitromethane (Table 1). The reaction in the presence of bismuth(III) triflate as the Lewis acid (25 mol-%) allowed to generate the corresponding amide **3a** in 24 % yield at 84 °C (Table 1, entry 1). A series of metal triflate Lewis acids was then scrutinized (Table 1, entries 2–7), but only copper(II) and zinc(II) triflates allowed to convert **1a** into amide **3a**. We next evaluated the impact of carbamoyl chloride loading on the reaction efficiency (Table 1, entries 8–12), revealing that 2.5 equivalents of carbamoyl chloride after one-hour reaction at refluxing nitromethane was the best conditions to obtain amide **3a** in 79 % yield. Moreover, any tentative carbamoylation performed without promoters was unsuccessful. Unfortunately, when these conditions were further applied to the carbamoylation of the isomer 1,4-dimethoxybenzene **1b**, only 39 % of amide **3b** were obtained.

Table 1. Optimization of the reaction conditions for the direct carbamoylation of resorcinol dimethyl ether.

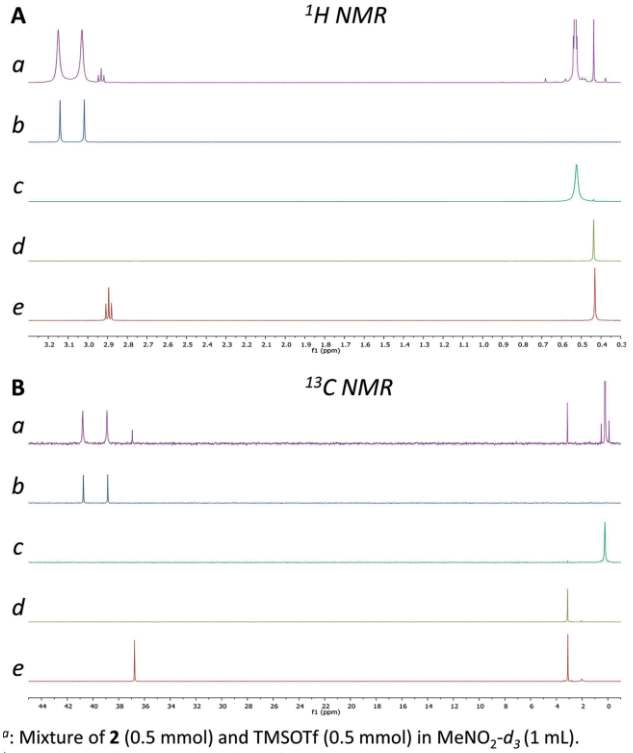


Entry	*n*	Catalyst	*x*	*T* [°C]	*t* [h]	Yield [%][a]
1	4	$Bi(OTf)_3$	0.25	84	1	24
2	4	$Yb(OTf)_3$	0.25	84	1	–
3	4	$Y(OTf)_3$	0.25	84	1	–[b]
4	4	$Fe(OTf)_2$	0.25	84	1	–
5	4	$Ba(OTf)_2$	0.25	84	1	–
6	4	$Cu(OTf)_2$	0.25	84	1	8[c]
7	4	$Zn(OTf)_2$	0.25	84	1	46
8	4	$Zn(OTf)_2$	0.25	reflux	1	39
9	3.1	$Zn(OTf)_2$	0.25	reflux	1	60
10	2.5	$Zn(OTf)_2$	0.25	reflux	1	79
11	1.7	$Zn(OTf)_2$	0.25	reflux	1	44
12	1.3	$Zn(OTf)_2$	0.25	reflux	1	18
13	2.5	HOTf	1	reflux	3	32[d]
14	2.5	AgOTf	1	reflux	3	21[d]
15	2.5	TMSOTf	1	reflux	3	80

[a] Determined by GC analysis using 1,4-dichlorobenzene as internal standard. [b] Traces. [c] Along with other regioisomers. [d] Determined by ^{1}H-NMR analysis of the crude product using *p*-anisaldehyde as internal standard.

With the aim to find a more general method to perform the direct carbamoylation of a large series of aryl derivatives, trifluoromethanesulfonic acid was also tested to verify if a protic acid could promote the reaction. The possibility of the presence of traces of water in the metal triflates has previously been proposed to generate Brønsted acids,[15] the system thus acting as a hidden Brønsted acid.[16] In the presence of one equivalent of triflic acid, only 32 % yield of amide **3a** was obtained from **1a** after 3 h in refluxing nitromethane (Table 1, entry 13). This result indicates the necessity to activate the carbamoyl chloride with a strong Lewis acid instead of a strong protic acid. Considering the generation of chloride ions after carbamoyl chloride activation by a metal triflate (Scheme 1), these ions could be detrimental to the desired process, the chloride ions being competitive to triflate ones. The in situ trapping of chloride ions could have a positive impact on the reaction. Silver triflate was thus tested as the promoter, but it led only to 21 % yield of **3a** (Table 1, entry 14). In a different alternative, when trimethylsilyl triflate was tested as the promoter, the amide **3a** was obtained in 80 % yield from **1a** (Table 1, entry 15). The reactivity of TMSOTf with isomer **1b** afforded this time the amide **3b** in 73 % yield, indicating that these conditions could be applied to other substrates. While triflic acid is known to cleave aromatic and aliphatic amide bonds, thus limiting its use as catalyst in carbamoylation reactions,[17] no cleavage of the generated aryl-amide bond was observed under the TMSOTf conditions, confirming the potential of the methodology.

To verify that a triflate-containing active species was generated in these conditions after chloride-triflate ion exchange, the reaction of dimethylcarbamoyl chloride **2** with TMSOTf was followed by in situ NMR spectroscopy (Figure 2A and Figure 2B). The ^{1}H NMR spectrum (Figure 2A) reveals the presence of two



[a]: Mixture of **2** (0.5 mmol) and TMSOTf (0.5 mmol) in $MeNO_2$-d_3 (1 mL).
[b]: **2** (0.5 mmol) in $MeNO_2$-d_3 (1 mL).
[c]: TMSOTf (0.5 mmol) in $MeNO_2$-d_3 (1 mL).
[d]: TMSCl (0.5 mmol) in $MeNO_2$-d_3 (1 mL).
[e]: Mixture of Me_2NH_2Cl (0.5 mmol) and TMSOTf (0.5 mmol) in $MeNO_2$-d_3 (1 mL).

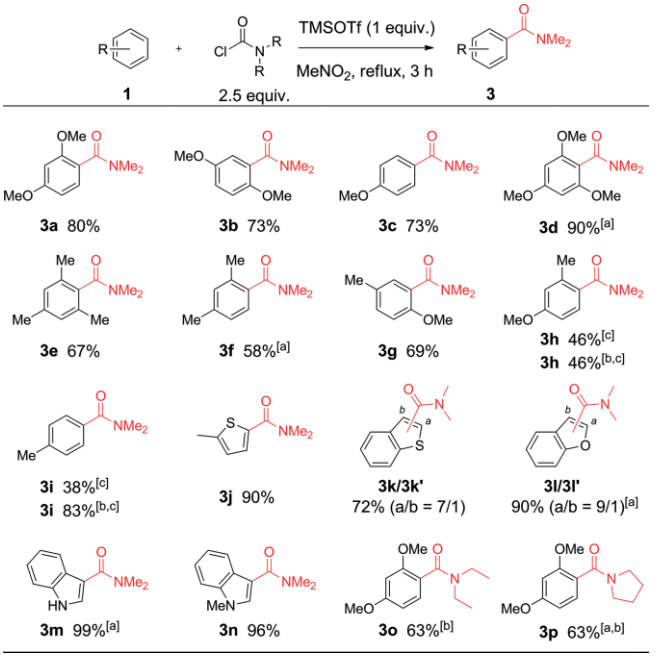
Figure 2. Evaluation of the formation of an active carbamoyl triflate intermediate by in situ NMR monitoring **A**: ^{1}H NMR spectra; **B**:^{13}C NMR spectra.

singlets at δ = 3.15 and 3.03 ppm attributed to the remaining dimethyl carbamoyl chloride. This was also confirmed by the presence of two singlets at δ = 40.8 ppm and 38.9 ppm in addition to the carbonyl signal at δ = 150.5 ppm in the ^{13}C NMR spectrum corresponding to the signals observed from a solution of carbamoyl chloride (Figure 2Ab and 2B*b*). In addition, one singlet at δ = 0.52 ppm in the ^{1}H NMR spectrum and one signal at 0.2 ppm in the ^{13}C NMR spectrum were attributed to the remaining trimethylsilyltriflate reactant, as compared with the data obtained from a solution of TMSOTf in deuterated nitromethane (Figure 2Ac and 2B*c*).

In the ^{1}H NMR spectrum a singlet is also observed at δ = 0.44 ppm correlating with a carbon NMR signal at 3.1 ppm. These signals were attributed to the in situ generation of a trimethylsilyl chloride species, an hypothesis which was further reinforced by comparing these data with the one obtained from a solution of TMSCl in CD_3NO_2 (Figure 2Ad and Figure 2Bd). This result confirmed our initial hypothesis, with the concomitant formation of the trimethylsilyl chloride species. Interestingly, a nice triplet was also observed at δ = 2.93 ppm in the ^{1}H NMR spectrum in a 2:3 ratio compared to the signal of TMSCl. This signal could be correlated to a carbon signal at δ = 36.9 ppm in the ^{13}C NMR spectrum. At this stage we hypothesized that this species must be formed from the "active" carbamoyl triflate in solution. Considering that traces of water could be present in these solutions, the formation of dimethylammonium triflate after water nucleophilic attack on the highly electrophilic dimethylcarbamoyl triflate active intermediate and further decarboxylation was envisaged. To evaluate this aspect, a solution of dimethyl ammonium chloride (0.5 mmol) and trimethylsilyltriflate (0.5 mmol) in $[D_3]MeNO_2$ was prepared and analyzed by NMR spectroscopy (Figure 2Ae and Figure 2Be). The ^{1}H NMR and ^{13}C NMR signals of this solution perfectly fit with the previously observed signals, confirming the formation of dimethylammonium triflate in solution. All these data further reinforced our initial hypothesis, with the in situ generation of a highly electrophilic carbamoyl triflate active species, prone to be trapped by aromatic nucleophiles.[18]

The use of TMSOTf in nitromethane was therefore selected to further evaluate the potential of the direct carbamoylation of several electron-rich aromatic and heteroaromatic substrates (Table 2). As mentioned above, substrates **1a** and **1b**, bearing two methoxy activating groups on the aryl moiety, could be efficiently converted into their amide analogues in 80 % and 73 % yield, respectively. Anisole **1c**, under the same conditions, was also selectively transformed into 4-methoxy-*N*,*N*-dimethylbenzamide **3c** in 73 % yield. When the aromatic ring was strongly activated for electrophilic substitution with three methoxy groups as in **1d**, 90 % of the desired amide **3d** could be obtained by using only a slight excess of carbamoyl chloride. Analogously, mesitylene **1e** was carbamoylated in 67 % yield, and its dimethylated analogue **3f** could also be prepared. While 4-methylanisole **1g** could be converted into its amide analogue **3g** in 69 % yield, only 46 % of the amide **3h** was formed from 3-methylanisole. Similarly, a modest yield was obtained when toluene **1i** was submitted to carbamoylation. Any tentative reaction with strongly deactivated nucleophiles, such as 1,4-dichlorobenzene and dimethyl carbamoyl chloride **2**, were unsuccessful. The targeted amide from 2-methylthiophene **1j** could be generated in 90 % yield, confirming the compatibility of this transformation with heteroaromatic substrates. The conditions could also be applied to the synthesis of 2- and 3-substituted benzothiophene isomers **3k** and **3k′**, obtained in 72 % yield. Analogously, the amides **3l** and **3l′** derived from benzofurane were obtained in 90 % yield. The conditions were also effective to directly convert indole derivatives to their amide analogues, as shown by the formation of both **3m** and **3n** in excellent yields of 96–99 %. In some cases, it has been reported that the synergistic combination of different Lewis acids could increase the favorability of recalcitrant acid-catalyzed processes.[19] We thus considered evaluating a similar strategy to favor the reaction of substrates **1h** and **1i**, which had been converted into their amide analogues in modest yields. When the same reaction was performed by adding a catalytic amount of zinc(II) triflate (5 mol-%) to TMSOTf, the yield of **3i** enhanced from 38 % to 83 % when similar yields were obtained from **1h**.

Table 2. Direct carbamoylation of (hetero)aromatic derivatives in the presence of trimethylsilyl triflate.



[a] Only 1.2 equiv. of dimethylcarbamoyl chloride were necessary to fully convert substrates **1** to the corresponding amides 3. [b] 5 mol-% of $Zn(OTf)_2$ was added. [c] Traces of side products regioisomers could not be separated from the desired major regioisomer.

These conditions were then briefly explored for the insertion of other amide moieties to **1a**, by modulating the alkyl substituents of carbamoyl chloride.[20] Using diethyl carbamoyl chloride and pyrrolidinyl carbamoyl chloride, resorcinol dimethyl ether **1a** could be efficiently converted into the corresponding amides **3o** and **3p**, confirming the ability to use this methodology to directly generate a variety of amides from aromatic derivatives.

Conclusions

The Lewis acid activation of carbamoyl chloride by trimethylsilyl triflate generates in situ a highly electrophilic carbamoyl triflate intermediate, which allows for the direct and selective formation of benzamide from (hetero)aromatic derivatives.

Experimental Section

General Procedure for the Direct Carbamoylation of (Hetero)-aromatic Derivatives: Aromatic compounds (1 mmol) and 1,4-dichlorobenzene (74 mg, 0.5 mmol) were dissolved in dry nitromethane (15 mL) with stirring at room temperature under nitrogen atmosphere. *N*,*N*-dialkylcarbamoyl chloride (1.1 or 2.5 mmol), and TMSOTf (181 μL, 1 mmol) were added to the solution. The reaction mixture was heated at reflux and left for 3 h. The reaction mixture was washed with a saturated $NaHCO_3$ solution, extracted with dichloromethane, dried on $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was submitted to column chromatography on SiO_2 with mixture of dichloromethane/methanol or pentane/ethyl acetate as eluents to afford the expected amide products (oils or powders).

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Keywords: Carbamoyl chloride · Lewis acids · Amides · Electrophilic substitution · Aromatic substitution

[1] a) G. Kouraklis, S. Theocharis, *Oncol. Rep.* **2006**, *15*, 489–494; b) J. M. Humphrey, A. R. Chamberlain, *Chem. Rev.* **1997**, *97*, 2243–2266; c) D. Ma, A. K. Bhattacharjee, R. K. Gupta, J. M. Karle, *Am. J. Trop. Med. Hyg.* **1999**, *60*, 1–6; d) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479; e) H. Li, F. S. Kim, G. Ren, E. C. Hollenbeck, S. Subramaniyan, S. A. Jenekhe, *Angew. Chem. Int. Ed.* **2013**, *52*, 5513–5517; *Angew. Chem.* **2013**, *125*, 5623.

[2] a) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347; b) D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443–4458.

[3] a) K. Kumar, A. Zapf, D. Michalik, A. Tillack, T. Heinrich, H. Böttcher, M. Arlt, M. Beller, *Org. Lett.* **2004**, *6*, 7–10; b) W. Tong, P. Cao, Y. Liu, J. Chen, *J. Org. Chem.* **2017**, *82*, 11603–11608; c) L. Ren, X. Li, N. Jiao, *Org. Lett.* **2016**, *18*, 5852–5855; d) W. Ren, M. Yamane, *J. Org. Chem.* **2010**, *75*, 3017–3020.

[4] a) R. F. Cunico, B. C. Maity, *Org. Lett.* **2002**, *4*, 4357–4359; b) R. F. Cunico, B. C. Maity, *Org. Lett.* **2003**, *5*, 4947–4949.

[5] a) M. A. Jalil Miah, M. P. Sibi, S. Chattopadhyay, O. B. Familoni, V. Snieckus, *Eur. J. Org. Chem.* **2018**, 447–454; b) K. Groom, S. M. Shakil Hussain, J. Morin, C. Nilewski, T. Rantanen, V. Snieckus, *Org. Lett.* **2014**, *16*, 2378–2381.

[6] T. Kochi, S. Urano, H. Seki, E. Mizushima, M. Sato, F. Kakiuchi, *J. Am. Chem. Soc.* **2009**, *131*, 2792–2793.

[7] a) Z.-Y. He, C.-F. Huang, S.-K. Tian, *Org. Lett.* **2017**, *19*, 4850–4853; b) T. B. Mete, A. Singh, R. G. Bhat, *Tetrahedron Lett.* **2017**, *58*, 4709–4712.

[8] a) S. Huang, X. Shi, D. Li, B. Luo, CN 105017058, **2015**; b) J. F. K. Wilshire, *Aust. J. Chem.* **1967**, *20*, 575–582; c) Y. A. Naumov, A. P. Isakova, A. N. Kost, N. F. Moiseikina, S. V. Nikeryasova, *Zh. Obshch. Khim.* **1975**, *45*, 2065–2068; d) A. P. Isakova, Y. A. Naumov, S. V. Nikeryasova, A. A. Fomichev, L. A. Murugova, *Zh. Org. Khim.* **1980**, *16*, 639–642; e) J. F. Stambach, L. Jung, *Tetrahedron* **1985**, *41*, 169–172.

[9] W. Ying, L. S. R. Gamage, L. R. Lovro, J. W. Herndon III, N. W. Jenkins, J. W. Herndon, *Tetrahedron Lett.* **2014**, *55*, 4541–4544.

[10] a) A. Sumita, H. Kurouchi, Y. Otani, T. Ohwada, *Chem. Asian J.* **2014**, *9*, 2995–3004; b) A. Sumita, Y. Otani, T. Ohwada, *Org. Biomol. Chem.* **2016**, *14*, 1680–1693.

[11] E. K. Raja, S. O. Nilsson Lill, D. A. Klumpp, *Chem. Commun.* **2012**, *48*, 8141–8143.

[12] F. Effenberger, G. Epple, J. K. Eberhard, U. Bühler, E. Sohn, *Chem. Ber.* **1983**, *116*, 1183–1194.

[13] a) M. J. D'Souza, D. N. Kevill, *Int. J. Mol. Sci.* **2016**, *17*, 111; b) K.-T. Liu, H.-I. Chen, Y.-S. Lin, B.-Y. Jin, *J. Phys. Org. Chem.* **2000**, *13*, 322–329.

[14] G. A. Olah, J. Nishimura, P. Kreienbüehl, *J. Am. Chem. Soc.* **1973**, *95*, 7672–7680.

[15] a) K. Y. Koltunov, S. Walspurger, J. Sommer, *Eur. J. Org. Chem.* **2004**, 4039–4047; b) K. Y. Koltunov, S. Walspurger, J. Sommer, *Tetrahedron Lett.* **2004**, *45*, 3547–3549; c) R. K. Nandi, A. Perez-Luna, D. Gori, R. Beaud, R. Guillot, C. Kouklovsky, V. Gandon, G. Vincent, *Adv. Synth. Catal.* **2018**, *360*, 161–172.

[16] a) T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem.* **2011**, *76*, 9353–9361; b) P. Ondet, A. Joffrin, I. Diaf, G. Lemière, E. Duñach, *Org. Lett.* **2015**, *17*, 1002–1005; c) G. Lemière, B. Cacciuttolo, E. Belhassen, E. Duñach, *Org. Lett.* **2012**, *14*, 2750–2753.

[17] a) K. W. Anderson, J. J. Tepe, *Tetrahedron* **2002**, *58*, 8475–8481; b) E. K. Raja, D. J. DeSchepper, S. O. Nilsson Lill, D. A. Klumpp, *J. Org. Chem.* **2012**, *77*, 5788–5793.

[18] As postulated in ref.[10a], the formation of an isocyanate cation in a contact ion pair with triflate anion cannot be ruled out.

[19] E. L. Myers, C. P. Butts, V. K. Aggarwal, *Chem. Commun.* **2006**, 4434–4436.

[20] Any tentative carbamoylation with aryl-containing carbamoyl chlorides was unsuccessful in these conditions.

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Lewis Acid Activation

TMSOTf acts as Lewis acid to activate carbamoyl chlorides and generates highly electrophilic carbamoyl triflates in situ; these are active species for late-stage aromatic carbamoylation.

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