Letter

eFluorination for the Rapid Synthesis of Carbamoyl Fluorides from Oxamic Acids

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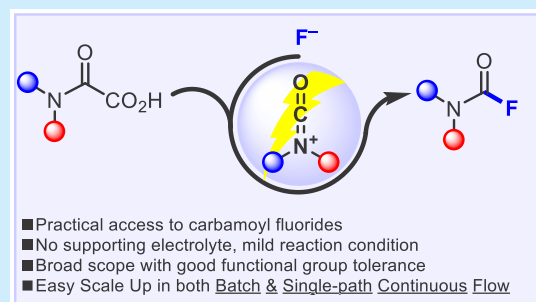
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ABSTRACT: In this letter, we disclose the anodic oxidation of oxamic acids in the presence of $Et_3N \cdot 3HF$ as a practical, scalable, and robust method to rapidly access carbamoyl fluorides from readily available and stable precursors. The simplicity of this method also led us to develop the first flow electrochemical preparation of carbamoyl fluorides, demonstrating scale-up feasibility as a proof of concept.

■ Practical access to carbamoyl fluorides
■ No supporting electrolyte, mild reaction condition
■ Broad scope with good functional group tolerance
■ Easy Scale Up in both Batch & Single-path Continuous Flow

■ INTRODUCTION

Fluorine has long held a special place in many areas of chemistry as a result of its ability to impart or enhance remarkable physical and chemical properties to a molecule when present in its framework.[1−7] Carbamoyl fluorides have attracted much attention for their use as insecticides and esterase inhibitors.[8−10] In addition, because carbamoyl fluorides exhibit greater stability and selectivity than carbamoyl chlorides, they represent exceptional building blocks in the synthesis of hydrazines,[11] isocyanates,[12] carbamates, thiocarbamates, ureas,[13] and amides.[8−10,13,14] Unfortunately, their synthesis can remain a challenge (Figure 1).[15,16] The primary preparation method is to treat a carbamoyl chloride with nucleophilic sources of fluoride.[17,18] While this method seems straightforward, it still requires the preparation of the highly reactive and often unstable chloride analogue, which is usually produced using expensive and highly toxic phosgene derivatives.[19,20] The past decade has seen a rapid increase in the development of novel methods for preparing carbamoyl fluorides, confirming the growing interest of the synthetic community in this fluorinated motif.[21−24] However, most use impractical conditions, often combined with highly air- and water-sensitive, toxic, hazardous, and expensive reagents, such as carbonyl difluoride,[13,25−28] carbon disulfide,[29] highly reactive and unstable carbamoyl chlorides,[28] or explosive diethylaminosulfur trifluoride (DAST)-type reagents.[30,31] Some other methods need expensive Ag salts,[32] significant excess of reagents leading to time-consuming chromatographic purifications,[33,34] or high temperatures.[35] Although some early work has yielded the desired products in single-step reactions, using DAST and silver salts presents a significant challenge to scale up the reaction, especially under process-friendly conditions.[13,25−28] There is an urgent need to develop a novel, practical, sustainable, inexpensive, and milder way to access carbamoyl fluorides rapidly. Herein, we disclose an unprecedented practical and robust anodic synthesis of carbamoyl fluorides from readily available stable oxamic acids in the presence of a fluoride salt.

■ RESULTS AND DISCUSSION

Optimization

On the basis of our previous experience with the anodic oxidation of oxamic acids,[36] we started our investigations with electrolysis substrate **1a** in CH_2Cl_2 using 2 equiv of the mild and less corrosive fluorinating reagent $Et_3N \cdot 3HF$,[37,38] at a current density of 8.9 mA cm^{-2}. We used carbon graphite (C_{gr}) as the anode as a result of its low cost and ability to perform multiple electron transfers. For the cathode, we chose a platinum foil electrode, known to have a low hydrogen overpotential, favoring the benign reduction of protons. To our delight, desired carbamoyl fluoride **2a** was obtained with a yield of 95% under these conditions. The reaction parameters were then further investigated (Table 1).

Each optimization experiment was followed by high-performance liquid chromatography−mass spectrometry (HPLC−MS) until complete consumption of starting oxamic
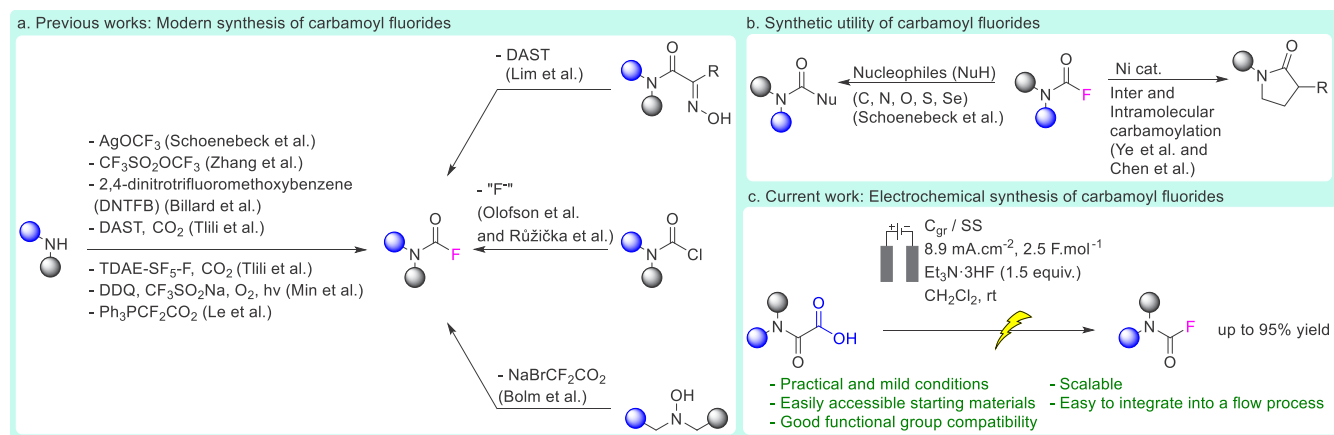
Figure 1. Syntheses and uses of carbamoyl fluorides.

Table 1. Optimization Results[a]

entry	+	−	F⁻ source	equiv	F mol⁻¹	yield (%)[b]
1	C_{gr}	Pt	Et$_3$N·3HF	2	3	95
2	C_{gr}	C_{gr}	Et$_3$N·3HF	2	2.5	89
3	C_{gr}	Ni	Et$_3$N·3HF	2	2	94
4	C_{gr}	SS	Et$_3$N·3HF	2	2.5	96
5[c]	C_{gr}	SS	Et$_3$N·3HF	2	2	60
6[d]	Pt	SS	Et$_3$N·3HF	2	2	0
7[c]	C_{gr}	Pt	CsF	2	2.5	32
8[c]	C_{gr}	Pt	KF and 18-Crown-6	5.5	4	67
9	C_{gr}	Pt	Bu$_4$N·H$_2$F$_3$	1	3	97
10	C_{gr}	SS	TMAF	1.5	2.5	
11[b]	C_{gr}	SS	TMAF	1.5	2.5	19
12[e]	C_{gr}	SS	Et$_3$N·3HF	1.5	2.5	96
13[f]	C_{gr}	SS	Et$_3$N·3HF	1.5	2	93
14	C_{gr}	Pt	Et$_3$N·3HF	3	3	69
15	C_{gr}	Pt	Et$_3$N·3HF	2	3.5	92
16	C_{gr}	SS	Et$_3$N·3HF	1	3	82

[a]Conditions: Unless otherwise stated, the solvent is CH$_2$Cl$_2$ with 0.4 mmol of oxamic acid and current density = 8.9 mA cm^{-2}. [b]^{1}H nuclear magnetic resonance (NMR) yield was calculated from the NMR ratio product and bromoform used as an internal standard, with MeCN as the solvent. [c]MeCN as the solvent. [d]No conversion of starting material was observed. [e]Current density = 4.45 mA cm^{-2}. [f]Current density = 13.35 mA cm^{-2}.

acid, which in most cases occurred after 2.5−3.0 F mol^{-1}, revealing a highly efficient anodic oxidation with average faradaic yields ranging from 66 to 80%. As expected, the electrode material proved to be an important factor (entries 1−4 for the cathode and entries 5 and 6 for the anode). While the use of carbon graphite as a cathode, which has a higher hydrogen overpotential, did not affect the yield of the reaction (entry 2), the use of less noble metals with low hydrogen overpotentials, such as Ni and stainless steel, not only performed as well as a platinum cathode but also gave very clean transformations without significant byproducts (entries 3 and 4). Therefore, cheap and readily available stainless steel

was chosen as the cathodic material. Carbon graphite was superior to platinum for the anode (entries 5 and 6). In terms of solvents, CH$_2$Cl$_2$ was shown to be better than MeCN (entries 5, 7, and 8), probably as a result of the formation of tighter ion pairs, which facilitate the addition of fluoride. With regard to the nature of the fluoride source (entries 6−9), surprisingly, even weaker nucleophilic fluorides, such as KF/18-Crown-6 or CsF, led to the formation of desired carbamoyl fluoride, albeit in modest yields along with numerous byproducts. While Bu$_4$N·H$_2$F$_3$ was found to be as efficient as Et$_3$N·3HF in achieving the desired fluorination (entry 9), the tetrabutylammonium salt led to the formation of significant amounts of tributylamine via cathodic Hofmann elimination, contaminating final carbamoyl fluoride. Interestingly, the use of tetramethylammonium fluoride (TMAF), a better nucleophilic fluoride donor than Et$_3$N·3HF as a result of the lack of hydrogen bonding, did not result in any improvement.

TMAF is poorly soluble in CH$_2$Cl$_2$ and did not provide the necessary conductivity for the electrolysis to proceed (entry 10). At the same time, only 19% yield was obtained in MeCN, together with many unidentified byproducts (entry 11). The effect of current density on the course of the reaction was also investigated. On the one hand, a lower current density of 4.45 mA cm^{-2} led to similarly excellent yields (entry 12) but surprisingly required a longer electrolysis time as a result of a lower faradaic efficiency. On the other hand, a higher current density of 13.35 mA cm^{-2} resulted in lower yields (entry 13). Using a significant excess of Et$_3$N·3HF was detrimental to the reaction (entry 14). Finally, the ideal amount of Et$_3$N·3HF was found to be 1.5 equiv (entries 15 and 16).

Substrate Scope

With the optimal reaction conditions in hand, the scope and limitations of the novel fluorination reaction were investigated, focusing on motifs that may be relevant to medicinal chemistry applications. The main results are summarized in Scheme 1. The oxamic acid precursors were all readily prepared from corresponding secondary amine, often without the need for chromatographic purification (see the Supporting Information). Notably, the reaction is compatible with a wide range of functional groups, including alkenes (**2c** and **2d**) and internal and terminal alkynes (**2e** and **2z**), in acceptable yields. Unfortunately, highly activated and redox-active alkenes, such as the nortriptyline drug derivative **1s**, gave only modest yields of the desired fluorinated compound **2s** with unidentified byproducts. Electrolysis of the biologically active tetrahydroi-

Scheme 1. Substrate Scope[e]
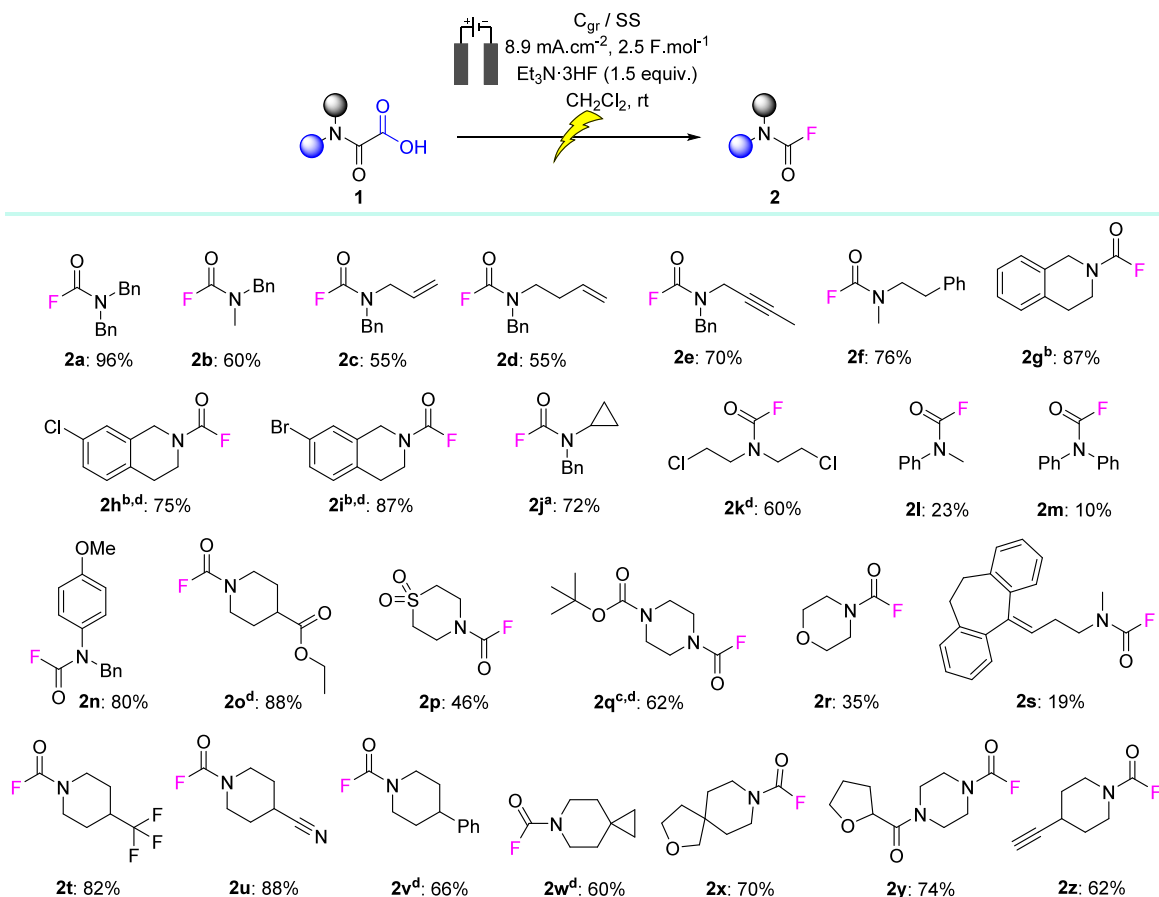
[a]Obtained using a 13.35 mA cm^{−2} current density. [b]Obtained using 2 equiv of Et$_3$N·3HF. [c]Obtained using 3 F mol^{−1}. [d]Purified through a silica pad. [e]Conditions: oxamic acid (0.4 mmol), Et$_3$N·3HF (0.6 mmol, 1.5 equiv), CH$_2$Cl$_2$ (5 mL), electrodes: carbon graphite (anode)/stainless-steel (cathode), 8.9 mA cm^{−2}, and 2.5 F mol^{−1}.

soquinoline−oxamic derivatives gave excellent yields of up to 87% of carbamoyl fluorides (2g−2i) highlighting the efficency of the method.[27,39−41] The novel methodology was shown to be compatible with both aliphatic and aromatic halides (2h, 2i, and 2k), providing the desired products in 60−87% yields. Spiro-type compounds, used in medicinal chemistry for their three-dimensional (3D) properties, were compatible with the electrolytic conditions, providing compounds 2w and 2x in 60 and 70% yields, respectively.[42] Furthermore, the successful preparation of compound 2j in 72% yield confirms the compatibility of cyclopropanes, which are redox-active moieties, with the electrolytic conditions. Numerous other functional groups, such as esters (2o),[34] sulfones (2p), tetrahydropyrans (THPs, 2r), trifluoromethyls (2t), nitriles (2u), and amides (2y), were compatible and led to the formation of functionalized carbamoyl fluorides in average to excellent yields. Interestingly, Et$_3$N·3HF is close to neutral and, therefore, did not deprotect the Boc carbamates,[38] allowing for the formation of compound 2q in 62% yield. Lower yields of carbamoyl fluorides were obtained with aniline derivatives. For example, 2l and 2m were obtained in only 23 and 10%, respectively. However, when an electron-rich methoxy group was present on the aromatic ring, compound 2n was obtained in 80%, highlighting the importance of the availability of the nitrogen lone pair in the formation of the N-centered cation (IV; Figure 2). For all reported transformations, the pure
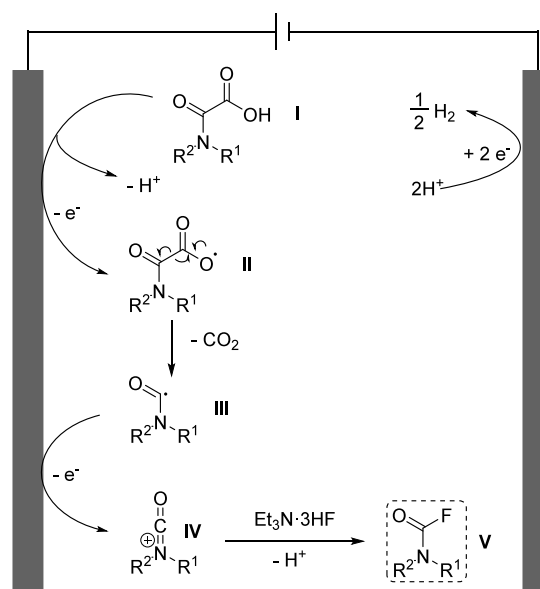

Figure 2. Proposed reaction mechanism.

product was obtained in most cases without chromatographic purification.

On the rare occasions when the product required further purification, rapid filtration through a silica pad proved

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sufficient to avoid the need for a detrimental flash chromatographic separation. In fact, we found that purification by standard column chromatography methods to obtain pure carbamoyl fluoride dramatically reduced its isolated yield.

Scale-up of the Anodic Fluorination

As mentioned in the Introduction, to our knowledge, the large-scale synthesis of carbamoyl fluorides remains a challenge. Therefore, as a proof of concept, we investigated whether the developed anodic oxidation could be transferred to flow electrochemistry to establish a continuous manufacturing process of carbamoyl fluoride using mild, safe, and inexpensive reagents (Scheme 2). Flow chemistry has proven to be a particularly successful method for rapidly scaling up electro-organic reactions.[43] The smaller interelectrode gap in a flow system compared to a batch process allows for a lower ohmic drop and better mass transfer, which usually leads to better performance. Focusing on the fluorination of compound **1a**, we started our flow optimization study (Table 2) using similar conditions (i.e., a current density of 8.9 mA cm^{-2}) to the batch reactions, resulting in the use of a flow rate of 0.5 mL min^{-1} to achieve the transfer of 2.5 F mol^{-1}. Simply pumping a mixture of starting material and Et$_3$N·3HF in CH$_2$Cl$_2$ into the electrochemical cell yielded 80% of desired carbamoyl fluoride (entry 1). Decreasing the current density to 5.6 mA cm^{-2} and using a 0.31 mL min^{-1} flow rate led to an identical result (entry 2). Additional decreases of the current density to 2.8 and 1.4 mA cm^{-2} (with flow rates of 9.28 and 18.56 mL min^{-1}, respectively) provided an increased yield of 95% (entries 3 and 4). Notably, these conditions allowed for a greater amount of product to be produced in a shorter time than in the previous batch process (Table 2), as shown by the respective space–time yields of the processes: 60 g h^{-1} L^{-1} versus 11 g h^{-1} L^{-1}, providing further evidence of the benefits of flow chemistry. However, it should be noted that a lower current density would also induce a lower flow rate and a longer residence time, thus suppressing one of the benefits of this flow process.
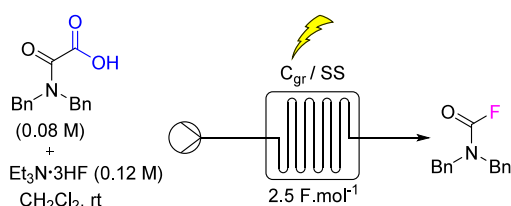
Scheme 2. Flow Chemistry Process

Table 2. Flow Process Results

entry	current density (mA cm^{-2})	pressure (bar)	flow rate (mL min^{-1})	t_R ($t_{collect}$ for 5 mL) (min)	yield (%)
1	8.9	1	0.5	2.97	80
2	5.6	1	0.31	4.79 (16.12)	80
3	2.8	4.5	0.16	9.28 (31.25)	95
4	1.4	4.5	0.08	18.56 (62.5)	95

Finally, we performed the anodic oxidation on a 1.0 g scale to show that our fluorination could withstand the change in scale without adverse effects (see the Supporting Information). As a result of the slower conversion observed on a large scale, the current density of the reaction was increased to 13.4 mA cm^{-2}, and pure carbamoyl fluoride was obtained in 98% yield

after passing 3.5 F mol^{-1}, demonstrating that scale-up in batch and flow processes is feasible.

Plausible Mechanism

On the basis of our previous work,[36,44] a plausible mechanism for the electrochemical transformation is shown in Figure 2. Cyclic voltammetric experiments have confirmed that a chemically irreversible EC-type (electrochemical event followed by a chemical event) anodic oxidation of oxamic acid (**I**) occurs at E_{pa}= 1.54 V versus Fc$^+$/Fc in CH$_2$Cl$_2$ (see Figure S1 of the Supporting Information), leading to the formation of the unstable carboxyl radical (**II**), which rapidly loses carbon dioxide to give the acyl radical (**III**). A rapid second electron transfer then occurs to form the highly electrophilic cationic isocyanate derivative (**IV**), which is finally captured by nucleophilic fluoride from Et$_3$N·3HF, leading to the formation of desired carbamoyl fluoride (**V**).

■ CONCLUSION

In conclusion, we have developed a novel mild, practical, robust, and safe electrochemical synthesis of carbamoyl fluorides from oxamic acids using Et$_3$N·3HF as both an inexpensive nucleophilic fluoride source and supporting electrolyte. The reaction can be carried out at room temperature with high faradaic efficiency using solvents straight from the bottle under non-strictly anhydrous and degassed conditions. In addition, the complete synthetic sequence starting from the amine can be achieved in most cases without chromatographic purification. Finally, taking advantage of the simplicity of our method, we have also demonstrated, as a proof of concept, the feasibility of scale-up both in batch and by transferring the methodology to flow electrochemistry. Further studies on the electrochemical synthesis of potential derivatives of carbamoyl fluorides are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c01605.

Optimization tables, synthetic procedures, and characterization data (PDF)

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Notes

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Smart, B. E. Fluorine Substituent Effects (on Bioactivity). *J. Fluorine Chem.* **2001**, *109*, 3−11.

(2) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. Organic Fluorine Compounds: A Great Opportunity for Enhanced Materials Properties. *Chem. Soc. Rev.* **2011**, *40*, 3496−3508.

(3) Ogawa, Y.; Tokunaga, E.; Kobayashi, O.; Hirai, K.; Shibata, N. Current Contributions of Organofluorine Compounds to the Agrochemical Industry. *iScience* **2020**, *23*, No. 101467.

(4) *Modern Synthesis Processes and Reactivity of Fluorinated Compounds*; Groult, H., Leroux, F., Tressaud, A., Eds.; Elsevier: Amsterdam, Netherlands, 2016.

(5) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822−5880.

(6) Xing, L.; Honda, T.; Fitz, L.; Ojima, I. Case studies of fluorine in drug discovery. In *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*; Haufe, G., Leroux, F. R., Eds.; Academic Press: Cambridge, MA, 2019; Chapter 4, pp 181−211, DOI: 10.1016/B978-0-12-812733-9.00004-0.

(7) Kirsch, P. Halofluorocarbons, Hydrofluorocarbons, and Related Compounds. *Modern Fluoroorganic Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2013; Chapter 8, pp 245−298, DOI: 10.1002/9783527651351.ch8.

(8) Kaufman, H.; Erlanger, B. F. An Investigation of the Peptic Activation of Acetylated Trypsinogen. *Biochemistry* **1967**, *6*, 1597−1606.

(9) Metzger, H. P.; Wilson, I. B. Evidence for an Electrophilic Mechanism in Catalysis by Hydrolytic Enzymes. *Biochemistry* **1964**, *3*, 926−931.

(10) Myers, D. K.; Kemp, A. Inhibition of Esterases by the Fluorides of Organic Acids. *Nature* **1954**, *173*, 33−34.

(11) Bouayad-Gervais, S.; Scattolin, T.; Schoenebeck, F. N-Trifluoromethyl Hydrazines, Indoles and Their Derivatives. *Angew. Chem., Int. Ed.* **2020**, *59*, 11908−11912.

(12) Quan, H.; Zhang, N.; Zhou, X.; Qian, H.; Sekiya, A. Syntheses of Isocyanates Via Amines and Carbonyl Fluoride. *J. Fluorine Chem.* **2015**, *176*, 26−30.

(13) Scattolin, T.; Bouayad-Gervais, S.; Schoenebeck, F. Straightforward Access to N-Trifluoromethyl Amides, Carbamates, Thiocarbamates and Ureas. *Nature* **2019**, *573*, 102−107.

(14) Zivkovic, F. G.; D.-T. Nielsen, C.; Schoenebeck, F. Access to N−Cf₃ Formamides by Reduction of N−Cf₃ Carbamoyl Fluorides. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202213829.

(15) Cadwallader, D.; Shevchuk, D.; Tiburcio, T. R.; Le, C. M. Fluoride-Catalyzed Cross-Coupling of Carbamoyl Fluorides and Alkynylsilanes. *Org. Lett.* **2023**, *25*, 7369−7373.

(16) McKnight, E. A.; Arora, R.; Pradhan, E.; Fujisato, Y. H.; Ajayi, A. J.; Lautens, M.; Zeng, T.; Le, C. M. Bf₃-Catalyzed Intramolecular Fluorocarbamoylation of Alkynes Via Halide Recycling. *J. Am. Chem. Soc.* **2023**, *145*, 11012−11018.

(17) Kirk, K. L. Fluorination in Medicinal Chemistry: Methods, Strategies, and Recent Developments. *Org. Process Res. Dev.* **2008**, *12*, 305−321.

(18) Yin, G.; Kalvet, I.; Schoenebeck, F. Trifluoromethylthiolation of Aryl Iodides and Bromides Enabled by a Bench-Stable and Easy-to-Recover Dinuclear Palladium(I) Catalyst. *Angew. Chem.* **2015**, *127*, 6913−6917.

(19) Hendriks, C. M. M.; Penning, T. M.; Zang, T.; Wiemuth, D.; Gründer, S.; Sanhueza, I. A.; Schoenebeck, F.; Bolm, C. Pentafluorosulfanyl-Containing Flufenamic Acid Analogs: Syntheses, Properties and Biological Activities. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4437−4440.

(20) Kalvet, I.; Guo, Q.; Tizzard, G. J.; Schoenebeck, F. When Weaker Can Be Tougher: The Role of Oxidation State (I) in P- Vs N-Ligand-Derived Ni-Catalyzed Trifluoromethylthiolation of Aryl Halides. *ACS Catal.* **2017**, *7*, 2126−2132.

(21) Bonnefoy, C.; Chefdeville, E.; Tourvieille, C.; Panossian, A.; Hanquet, G.; Leroux, F.; Toulgoat, F.; Billard, T. Study of Carbamoyl Fluoride: Synthesis, Properties and Applications. *Chem. - Eur. J.* **2022**, *28*, No. e202201589.

(22) Scattolin, T.; Deckers, K.; Schoenebeck, F. Direct Synthesis of Acyl Fluorides from Carboxylic Acids with the Bench-Stable Solid Reagent (Me₄n)Scf₃. *Org. Lett.* **2017**, *19*, 5740−5743.

(23) Zivkovic, F. G.; Wycich, G.; Liu, L.; Schoenebeck, F. Access to N-Difluoromethyl Amides, (Thio)Carbamates, Ureas, and Formamides. *J. Am. Chem. Soc.* **2024**, *146*, 1276−1281.

(24) Liu, L.; Gu, Y.-C.; Zhang, C.-P. Recent Advances in the Synthesis and Transformation of Carbamoyl Fluorides, Fluoroformates, and Their Analogues. *Chem. Rec.* **2023**, *23*, No. e202300071.

(25) Chang, S. C.; DesMarteau, D. D. Fluoride-Catalyzed Reactions of Perfluoromethanimine. Novel Chemistry of the Perfluoromethanamine Ion. *J. Org. Chem.* **1983**, *48*, 771−774.

(26) Allenstein, E.; Schrempf, G. Darstellung Und Untersuchung Von Difluormethylsubstituierten Aminen. *Z. Anorg. Allg. Chem.* **1981**, *474*, 7−17.

(27) Cadwallader, D.; Tiburcio, T. R.; Cieszynski, G. A.; Le, C. M. Synthesis of Carbamoyl Fluorides Using a Difluorophosgene Surrogate Derived from Difluorocarbene and Pyridine N-Oxides. *J. Org. Chem.* **2022**, *87*, 11457−11468.

(28) Cuomo, J.; Olofson, R. A. Efficient and Convenient Synthesis of Fluoroformates and Carbamoyl Fluorides. *J. Org. Chem.* **1979**, *44*, 1016−1017.

(29) Taponard, A.; Jarrosson, T.; Khrouz, L.; Médebielle, M.; Broggi, J.; Tlili, A. Metal-Free Sf₆ Activation: A New Sf₅-Based Reagent Enables Deoxyfluorination and Pentafluorosulfanylation Reactions. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202204623.

(30) Onida, K.; Tlili, A. Direct Synthesis of Carbamoyl Fluorides by Co₂ Deoxyfluorination. *Angew. Chem.* **2019**, *131*, 12675−12678.

(31) Song, J. W.; Lim, H. N. Synthesis of Carbamoyl Fluorides Via a Selective Fluorinative Beckmann Fragmentation. *Org. Lett.* **2021**, *23*, 5394−5399.

(32) Xin, J.; Deng, X.; Tang, P. Silver-Catalyzed Trifluoromethoxylation of Aziridines. *Org. Lett.* **2022**, *24*, 881−885.

(33) Cho, H.; Jang, S.; Lee, K.; Cha, D.; Min, S.-J. Visible-Light-Induced Ddq-Catalyzed Fluorocarbamoylation Using Cf$_3$so$_2$na and Oxygen. *Org. Lett.* **2023**, *25*, 8558−8563.

(34) Tang, H.-J.; Shi, X.-M.; Zhu, X.-Y.; Wang, C.-Q.; Feng, C. Oxidation of Difluorocarbene by Pyridine N-Oxide and Ensuing Access to Carbamoyl Fluorides†. *Chin. J. Chem.* **2023**, *41*, 2981−2987.

(35) Baars, H.; Engel, J.; Mertens, L.; Meister, D.; Bolm, C. The Reactivity of Difluorocarbene with Hydroxylamines: Synthesis of Carbamoyl Fluorides. *Adv. Synth. Catal.* **2016**, *358*, 2293−2299.

(36) Petti, A.; Fagnan, C.; van Melis, C. G. W.; Tanbouza, N.; Garcia, A. D.; Mastrodonato, A.; Leech, M. C.; Goodall, I. C. A.; Dobbs, A. P.; Ollevier, T.; Lam, K. Supporting-Electrolyte-Free Anodic Oxidation of Oxamic Acids into Isocyanates: An Expedient Way to Access Ureas, Carbamates, and Thiocarbamates. *Org. Process Res. Dev.* **2021**, *25*, 2614−2621.

(37) Yoneda, N. The Combination of Hydrogen Fluoride with Organic Bases as Fluorination Agents. *Tetrahedron* **1991**, *47*, 5329−5365.

(38) Haufe, G. Et$_3$N·3HF Complex Fluorination for Preparing Alkyl Fluorides. In *Fluorination*; Hu, J., Umemoto, T., Eds.; Springer: Singapore, 2019; pp 1−44, DOI: 10.1007/978-981-10-1855-8_26-1.

(39) Ghosh, S.; Biswas, K. Metal-Free Multicomponent Approach for the Synthesis of Propargylamine: A Review. *RSC Adv.* **2021**, *11*, 2047−2065.

(40) Mitchenson, A.; Nadin, A. Saturated Nitrogen Heterocycles. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862−2892.

(41) Scott, J. D.; Williams, R. M. Chemistry and Biology of the Tetrahydroisoquinoline Antitumor Antibiotics. *Chem. Rev.* **2002**, *102*, 1669−1730.

(42) Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. A Synthon Approach to Spiro Compounds. *Tetrahedron* **2006**, *62*, 779−828.

(43) Noël, T.; Cao, Y.; Laudadio, G. The Fundamentals Behind the Use of Flow Reactors in Electrochemistry. *Acc. Chem. Res.* **2019**, *52*, 2858−2869.

(44) Ogbu, I. M.; Lusseau, J.; Kurtay, G.; Robert, F.; Landais, Y. Urethanes Synthesis from Oxamic Acids under Electrochemical Conditions. *Chem. Commun.* **2020**, *56*, 12226−12229.