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Synthesis of *N*-trifluoromethyl amides from carboxylic acids

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SUMMARY

Found in biomolecules, pharmaceuticals, and agrochemicals, amide-containing molecules are ubiquitous in nature, and their derivatization represents a significant methodological goal in fluorine chemistry. Trifluoromethyl amides have emerged as important functional groups frequently found in pharmaceutical compounds. To date, there is no strategy for synthesizing *N*-trifluoromethyl amides from abundant organic carboxylic acid derivatives, which are ideal starting materials in amide synthesis. Here, we report the synthesis of *N*-trifluoromethyl amides from carboxylic acid halides and esters under mild conditions via isothiocyanates in the presence of silver fluoride at room temperature. Through this strategy, isothiocyanates are desulfurized with AgF, and then the formed derivative is acylated to afford *N*-trifluoromethyl amides, including previously inaccessible structures. This method shows broad scope, provides a platform for rapidly generating *N*-trifluoromethyl amides by virtue of the diversity and availability of both reaction partners, and should find application in the modification of advanced intermediates.

Graphical Abstract

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AUTHOR CONTRIBUTIONS

F.D.T. and D.M.W. supervised the project; J.L. developed the reaction system, conducted the experiments, and analyzed the data; J.L., M.P., S.W., and R.R.F. conducted the mechanistic studies; and J.L., F.D.T., and D.M.W. wrote the manuscript with input from all other authors.

SUPPLEMENTAL INFORMATION

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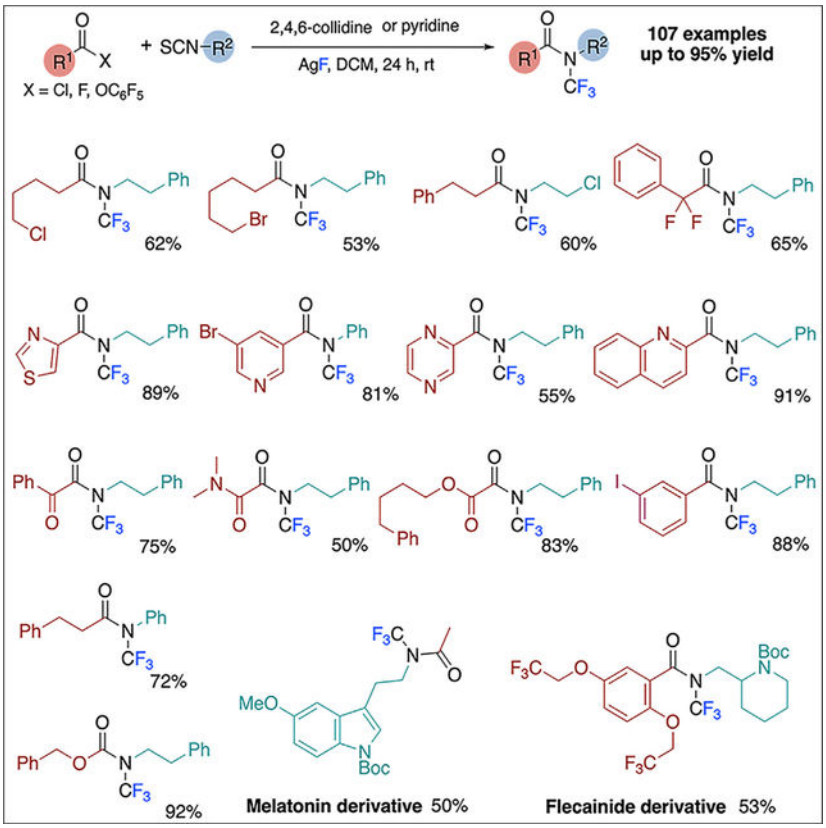
DECLARATION OF INTERESTS

The authors declare no competing interests.



Amide bonds in pharmaceuticals and other applications are generally formed through amination of carboxylic acid derivatives. However, access to *N*-trifluoromethyl amides via a procedure analogous to this most common strategy for amide-bond formation has yet to be described. Here, the synthesis of *N*-trifluoromethyl amides from carboxylic acid derivatives and isothiocyanates is achieved and markedly expands the diversity of *N*-trifluoromethyl amides and their biological and industrial applications, affording previously inaccessible structures containing alkyl bromide, alpha-heteroaryl, and alpha-carbonyl functional groups.

INTRODUCTION

The development of efficient and convenient methods for the preparation of amides has been a central goal in synthetic chemistry because of their prevalence in synthetic chemistry and the life sciences.[1–5] The introduction of the trifluoromethyl group into organic molecules has also been of major interest because this moiety can significantly alter physical and chemical properties (solubility, lipophilicity, conformation, pK_a, and membrane permeability), metabolic stability, and bioavailability of these molecules in numerous applications.[6–8] As relatively new chemical building blocks, *N*-trifluoromethyl amides combining these two important structures have naturally attracted the attention of scientists.[9–11] Compared with their N–Me and N–H amide counterparts, *N*-trifluoromethyl amides appear to be especially stable in that they possess the longest C–N bond with minimal restriction on rotation.[11] Many *N*-trifluoromethyl-amide-derived molecules show potential value as materials, pharmaceuticals, and agrochemicals.[12,13] The interest in

fluorinated molecules has also been driven by the unique availability to detect fluorine either via ^{19}F nuclear magnetic resonance (NMR) or via ^{18}F positron emission tomography. However, until recently, only a few minimally functionalized N–CF_3 amides had been reported by Rozen and coworkers,[9] motivating subsequent interest in wider N–CF_3 carbonyl families.

Synthetic access to *N*-trifluoromethyl amides is presumably limited by the instability of the parent N–CF_3 amine resulting from the n(N)→σ*(C–F) electron donation facilitating fluorine elimination,[14] thus limiting access to coupling methods traditionally employed in amide syntheses. As a result, alternative synthetic strategies have been developed for N-acyl analogs that circumvent the intermediacy of the N–CF_3 amide (Figure 1A). A strategy recently reported by Fang and Li provides an efficient and chemoselective approach to N–CF_3 amides that involves the silver-mediated electrophilic *N*-trifluoromethylation of N–H amides.[10] This method enabled the chemoselective *N*-trifluoromethylation of di- and tri-peptides with retention of configuration. The Schoenebeck group reported a major breakthrough in the field of N–CF_3 amide synthesis in the discovery that isothiocyanates can be transformed in a one-pot procedure with AgF and a carbonyl electrophile to the corresponding N–CF_3 carbamoyl fluorides, which subsequently were reacted with Grignard reagents to furnish the corresponding *N*-trifluoromethyl amides.[11] Because of the reactivity of Grignard reagents, especially the alkyl ones, the introduction of functional groups in the carboxylic acid side of amides (R^1) was partially limited.

Despite these advances, access to N–CF_3 amides via a procedure analogous to the most common strategy for amide-bond formation, namely coupling an amine with a carboxylic acid derivative, has yet to be described.[15] Amide bonds in pharmaceuticals and other applications are generally formed through amination of carboxylic acid derivatives (acyl chloride, acid anhydride, activated ester, etc.).[1] This disconnection would enable access to a greater variety of N–CF_3 amides from readily available carboxylic acids, many of which are found in nature, straightforward to obtain, stable, and often highly functionalized such that many are produced industrially on a large scale. Therefore, the use of organic carboxylic acid derivatives to directly synthesize N–CF_3 amide could markedly expand the diversity of *N*-trifluoromethyl amides and their biologic and industrial applications.

RESULTS AND DISCUSSION

Investigation of reaction conditions

Initially, we investigated the synthesis of N–CF_3 amides through the reactions of an acyl chloride ($PhCH_2CH_2COCl$ or PhCOCl) with a stable trifluoromethylated amine, $PhNH(CF_3)$[16,17] (Figure S1A). Whereas the reagent $PhNH(CF_3)$ was consumed, *N*-trifluoromethyl amides were not detected. Presumably, H–N(R)(CF_3) possesses a much lower activity than non-alpha-fluoro-substituted amines as a result of the strong electron-withdrawing nature and steric bulk of the trifluoromethyl moiety; therefore, we surmised that because of the lower reactivity, isolated *N*-trifluoromethylated secondary amines were unlikely to provide general access to N–CF_3 amides via standard amide-bond-forming protocols.

Inspired by the work of the Schoenebeck group, we generated the proposed Ag–N(R)(CF_3) **E**[11] from isothiocyanates R-NCS **B** and silver fluoride and reacted it with acyl halide **A** (prepared directly from the organic carboxylic acid *in situ*) with the goal of producing *N*-trifluoromethyl amide **C** (Figure 1B). Initially, hydrocinnamoyl chloride **1A** was added to trap the proposed Ag–N(R)(CF_3) **E** generated from phenethyl isothiocyanates **1B** in various solvents (Table S1, entries 1–4). Unfortunately, N–CF_3 amide **1** was not detected under any conditions, including acetonitrile, which had been previously identified as the ideal solvent for the formation of N–CF_3 amino-formyl fluoride.[11] An extensive evaluation of the reaction conditions (Table S1, entries 5–10) revealed that the addition of a base that could serve as a ligand to activate the proposed Ag–N(R)(CF_3) **E** accelerated the desired coupling. Notably, compared with the use of pyridine (Table S1, entry 5), 2,4,6-collidine (Table S1, entry 10) was found to nearly double the yield of the desired amide. Moreover, neither strongly basic (4-dimethylaminopyridine and Et_3N; Table S1, entries 7 and 8) nor weakly basic (2-fluoropyridine; Table S1, entry 6) ligands were effective. DCM (dichloromethane; Table S1, entry 13) was identified as a more effective solvent than THF (tetrahydrofuran; Table S1, entry 10) and MeCN (acetonitrile; Table S1, entry 14). Finally, employing 5 equiv rather than 4 equiv of AgF (silver fluoride) nearly doubled the yield of amide **1** (96%; Table S1, entry 16), most likely because of the increase in the rate of fluoride intercepting the proposed intermediate, R–N=CF_2 **D** (Figure 1B).

The amide-bond formation is expected to be affected by the steric hindrance and the low nucleophilicity of the proposed Ag–N(R)(CF_3) **E**. As a result, when different acyl halides or esters and isothiocyanates were used as substrates, the optimum conditions for amide-bond formation were somewhat different. Therefore, we developed several general procedures (reaction conditions a–d, f, h, and i in Schemes 1, 2, and 3) to access the *N*-trifluoromethyl amides at room temperature (RT) in dichloromethane. Ideally, the activity of the carboxylate-derived electrophile and the proposed Ag–N(R)(CF_3) **E** must be matched to facilitate amide-bond formation. There are two main variables for the optimization of the latter conditions: (1) the choice of additives such as pyridine or 2,4,6-collidine and (2) the activity of acyl halide or esters and the proposed Ag–N(R)(CF_3) **E** nucleophile. A more in-depth discussion of notable trends observed for these conditions is presented in Table S3. More specifically, reaction conditions (a) and (b) were consolidated into two general ones and used for the synthesis of up to 43 and 31 amides, respectively. On one hand, the typical reaction conditions when acyl halides were used as reactants were (a), the optimization process of which is shown in Table S1. For pentafluorophenyl esters as reactants, on the other hand, conditions (c) were typically employed (Table S2).

Substrate scope for the synthesis of *N*-trifluoromethyl amides

Applying the optimized conditions, we first evaluated the scope of the reaction by exploring the combination of the alkyl carboxylic acid derivative component with the more active alkyl isothiocyanate partner (Scheme 1). A wide range of acyl halides **A** were prepared *in situ* from commercially available organic carboxylic acids, reflecting their high availability, and used directly in the *N*-trifluoromethyl amide formation. Aliphatic acyl halide substrates (**1–5**, **11**, **12**, and **14**–**25**), including cycloalkyl acyl halides (**15**–**19**), generally performed well, although the yields of the cyclic variants tended to decrease with ring size. Although

a range of primary isothiocyanates performed well in the amide-bond formation, secondary isothiocyanates were incompatible with the reaction conditions to afford N–CF_3 amide, presumably because of the decreased reactivity resulting from larger R-groups in the proposed substituted (Ag–N(R)(CF_3) **E** intermediate. The incorporation of an array of functional groups on both partners, including various halo groups (Cl [**2** and **21**], Br [**3**]), a carboalkoxy (**4** and **20**) and an alkenyl group (**5** and **22**), was well tolerated despite the possibility that these groups can react with organic silver salts. Moreover, the method provided access to *N*-trifluoromethyl alpha-ketoamides (**7** and **8**),[18–20] an oxalamide (**9**), an alpha-esteramide (**10**), and an aryldifluoroamide (**11**), the latter of which is a structural unit present in several biologically active compounds.[21] The activated acyl derivatives of alpha-ether acids (**12** and **13**) and *trans*-cinnamic acid (**6**) were also smoothly converted into the corresponding N–CF_3 amides.

In order to further evaluate the scope of the reaction beyond aliphatic carboxylic acyl halides, we examined the various aryl and heteroaryl carboxylic acyl halides as coupling partners in amide-bond formation. In particular, amides derived from heteroaryl carboxylic acids are prevalent in pharmaceuticals, such as avanafil, bortezomib, meloxicam, and raltitrexed,[22] and many routes rely on the use of carboxylic acid starting materials;[23,24] however, reports related to the systematic preparation of *N*-trifluoromethyl amides are rare. Thus, a general procedure for forming *N*-trifluoromethyl heteroaryl amides—by leveraging activated acyl donors that can be accessed from heteroaryl carboxylic acids—under mild conditions with simple reagents would provide an important tool for synthetic and medicinal chemistry. Initial studies with benzoyl chlorides produced *N*-trifluoromethyl amides by using the silver-fluoride-promoted coupling with alkyl isothiocyanate, although substituting pyridine for 2,4,6-collidine was required for improved yields in some cases. In general, electron-deficient (hetero)aroyl chlorides gave better yields than those that were substituted with electron-donating groups, most likely because of the faster relative rate of reaction between the proposed (Ag–N(R)(CF_3) **E** and the more electrophilic acyl chlorides. The transformation proved to be very general (Scheme 1), and numerous functional groups were tolerated, including various halo (**27**–**30** and **42**), carboalkoxy (**31** and **71**), nitro (**32**), nitrile (**33**), carbonyl (**34**), vinyl (**35**), sulfonyl (**36**), trifluoromethyl (**37**), trifluoromethylthio (**38**), trifluoromethoxy (**39**), and ether (**40** and **41**) groups. Multi-substituted arenes, which include halogen-substituted benzoyl chlorides, were also effective coupling partners (**45**–**50**). Importantly, a number of heteroaroyl chlorides, such as those derived from furan (**51** and **52**), thiophene (**53** and **54**), thiazole (**55**), pyridine (**56**), pyrazine (**57**), pyrimidine (**58** and **59**), pyridazine (**60**), benzo[*b*]furan (**61**), and quinoline (**62**–**64**), were well tolerated (40%~95% yields). The related acyl chlorides containing halogen substituents at different positions on the ring maintained excellent results (**65**–**70**). Additionally, secondary isothiocyanate (**74**–**76**) underwent the desired reaction in reasonable chemical yields when reacting with electron-deficient aroyl chlorides. The smooth reaction with Lewis basic heterocycles is particularly noteworthy because the potential of these heterocycles to act as ligands for the proposed Ag–N(R)(CF_3) **E**, in analogy to pyridine or 2,4,6-collidine, did not impede the reaction.

Having established the scope of the reaction with respect to the acyl halide coupling component, we turned our efforts toward the thiocyanate coupling partner. More specifically, in addition to the alkyl thiocyanates described above, aryl isothiocyanates reacted smoothly with hydrocinnamoyl chloride to afford the corresponding N–CF_3 amides (Scheme 2). A variety of functional groups, including various halo (**78**–**81**, **85**, and **87**–**89**), ether (**82** and **88**), trifluoromethyl (**83**), nitro (**84**), and pyrimidinyl (**86**) groups, were tolerated. Whereas the carbamimidic fluoride **F1** was isolated in 41% yield from the silver-mediated reaction of 4-iodophenyl isothiocyanate with benzoyl chloride, arylthiocyanates underwent successful amide coupling with electro-deficient aryl- and heteroaroyl halides. In light of the successful amide couplings with aliphatic acyl chlorides, we were initially surprised by the failed coupling with benzoyl chloride; however, further studies (see below) suggest that the intermediacy of ketene intermediates could account for this unexpected observation.

Pentafluorophenyl esters of *N*-protecting amino acids, including glycine (**90**–**92**), sarcosine (**93**–**95**), beta-alanine (carboxylic acyl chloride as reaction reagent; **96**), alanine (**97** and **98**), and phenylalanine (**99**), were also converted to the corresponding *N*-trifluoromethyl amides (Scheme 3). General protecting groups including *t*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), and phthalyl (Pht) were tolerated, allowing for the generation of alpha-amino amide (**100**) after deprotection. Reaction of the generated proposed Ag–N(R)(CF_3) **E** with chloroformates instead of the acyl chloride enabled the syntheses of the corresponding carbamates. Benzyl (**101** and **106**), methyl (**102**), allyl (**103**), and phenyl chloroformate (**105**) underwent efficient transformation (Scheme 3) at RT with both alkyl and aryl isothiocyanates (**106**).

Mechanistic insights and applications

We note that amide **97** was produced as a racemate (50:50 enantiomeric ratio [er]) from the silver-mediated coupling with the protected enantiopure amino acid pentafluorophenyl ester. Moreover, a crossover experiment between L-alanine derivative-*d* **107A** and L-phenylalanine derivative **99A** showed that deuterium and hydrogen exchanged between the pentafluorophenyl esters **107A** and **99A** (Figure 2A), consistent with racemization of L-alanine amide (**97**). This information suggests that the a-proton of alkyl carboxylate ester derivatives is easily abstracted by Ag–N(R)(CF_3) **E** to form intermediate **I**, which could be reprotonated to return the racemized starting ester (Figure 2B). However, although base-promoted racemization of the chiral pentafluorophenyl esters has been previously reported, rate constants for this process are low.[25] Alternatively, intermediate **I** could proceed to products via ketene **J**.[26,27] This pathway accounts for the formation of racemic product, and the increased electrophilicity of the ketene intermediate is most likely responsible for the observed higher reactivity of alkyl acyl chlorides than of benzoyl chlorides, especially when reacting with weakly nucleophilic Ag–N(R)(CF_3) **E** derived from aryl isothiocyanates. In light of these findings, we surmise that the proposed Ag–N(R)(CF_3) **E** might undergo side reactions (Figure S1) other than the targeted amide-bond formation with the carboxylic acid derivative (Figure 1B). As discussed, it can act as a base to generate inert H–N(R)(CF_3) (Figure S1C) and, in some cases, concomitant formation of ketene intermediates. Additionally, it can react with its proposed active precursor R–N=CF_2 **D** to generate byproduct **F**[11] (Figure S1B), as observed in the attempted coupling of benzoyl chloride.

Finally, the proposed Ag–N(R)(CF_3) **E** could add to the electrophilic C=S bond of the starting isothiocyanates **B**, although this pathway seems to be mitigated under the current reaction conditions (Figure S1D).[28]

In order to further explore the utility of this synthetic methodology, we synthesized two pharmaceutically relevant molecules by using these reaction conditions (Figure 2C). Melatonin (5-methoxy-*N*-acetyl tryptamine) has been widely used in health supplements and cosmetics.[29] The acetylation of the primary amine in the synthesis of melatonin can be replaced by successive desulfurative fluorination and acylation of isothiocyanate **109B** to successfully yield the N–CF_3 amide (**109**) in one pot. Similarly, a N–CF_3 amide derivative (**110**) of flecainide,[30] a membrane-stabilizing antiarrhythmic agent, was prepared in 53% yield by desulfurative fluorination and acylation of isothiocyanate **110B**. These results show the potential of this mild procedure for the complex N–CF_3 amides synthesis from carboxylic acid derivatives and isothiocyanates via amide-bond formation.

Comparison of our method with prior methods

Finally, we provide a clearer and more direct comparison of our method of synthesizing *N*-trifluoromethyl amides with prior methods[9–11] on a sufficient number of representative examples for better assessment of methodological diversity (Table S4). The Schoenebeck group reported a strategy[11] wherein carbamoyl fluorides are readily diversified to the corresponding N–CF_3 amides in high yields and excellent functional-group tolerance at R^2 (Figure 1A); however, R^1 is introduced via a Grignard reagent. Here, we report the direct synthesis of *N*-trifluoromethyl amides from carboxylic acid derivatives. The process allows for the synthesis of 20 heteroaryl examples (**51**, **52**, **55–70**, **86**, and **87**); tolerates alkyl halides (**2**, **3**, and **21**), esters (**4**), and amides (**90**–**96**); and is amenable to the synthesis of products bearing functional groups at the alpha position (**6**–**13**). These examples suggest that our reported system complements previous systems by enabling access to *N*-trifluoromethyl amides whose synthesis might be challenging via Grignard introduction of R^1. However, it is worth noting that although Schoenenbeck reported excellent retention of stereo-chemistry at R^2, the racemization of the alpha-stereocenter of natural amino acid esters (at R^1) is a limitation of our process (**97**). With respect to the Fang-Li method, our results also expand the scope of N–CF_3 amide structures especially at R^2. When R^2 is an aryl group, only one example with 34% yield was synthesized, and compatibility of heteroaromatic rings might also be limited given that one example is provided. The product-type distribution of the N–CF_3 amides with various strategies is described in Table S4.

Conclusion

In conclusion, we have described a method for the direct transformation of simple available acyl halides (or activated esters) into their corresponding N–CF_3 amides via successive fluorination and acylation of isothiocyanates. Key to the success of the silver-fluoride-mediated amide-bond-forming reaction is the use of the ligand 2,4,6-collidine or pyridine. This approach provides access to a wide range of different N–CF_3 amides with various substituents at both the amine and carboxylic acid components. Many of these structures are likely to be inaccessible through previously described methods, especially those products containing alkyl bromide, alpha-heteroaryl, and alpha-carbonyl functional groups.

Moreover, the syntheses of *N*-trifluoromethyl derivatives of several medicinally relevant compounds, such as melatonin and flecainide, were successfully achieved. Most importantly, this platform enables the formation of N–CF_3 amides through the traditional amide-bond-forming disconnection. Given the prevalence of amides in pharmaceutical molecules and the life sciences and the diversity of available carboxylic acid derivatives and isothiocyanates, the synthesis of N–CF_3 amides directly from these components is likely to inspire numerous applications.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact—Further information and requests for resources should be directed to and will be fulfilled by the lead contact, David M. Wilson (david.m.wilson@ucsf.edu).

Materials availability—This study did not generate new unique reagents.

Data and code availability—There is no dataset or code associated with the paper.

METHODS

Full experimental procedures are provided in the supplemental information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Synthesis from carboxylic acids enables access to a great variety of N–CF_3 amides
- The process tolerates alkyl bromide, α-heteroaryl, and α-carbonyl functional groups
- The use of the ligand 2,4,6-collidine or pyridine is key to the reaction
- Amide-bond formation implies the simplest retrosynthetic disconnection of N–CF_3 amides

The bigger picture

Found in biomolecules, pharmaceuticals, and agrochemicals, amide-containing molecules are ubiquitous in nature. The trifluoromethyl group has emerged as an important fluorine-containing functional group frequently found in pharmaceutical compounds. Although elegant methods of synthesizing N–CF_3 amides have been previously reported, none have used the simplest retrosynthetic disconnection, namely amide-bond formation through amination of carboxylic acid derivatives. The new approach presented here is based on this disconnection and enables access to a greater variety of N–CF_3 amides from readily available carboxylic acids. This strategy can achieve successive desulfurative fluorination and acylation of isothiocyanates in one pot to obtain N–CF_3 amides. Given the prevalence of amides and the diversity of available carboxylic acid derivatives and isothiocyanates, the synthesis of N–CF_3 amides directly from these components is likely to inspire numerous applications.

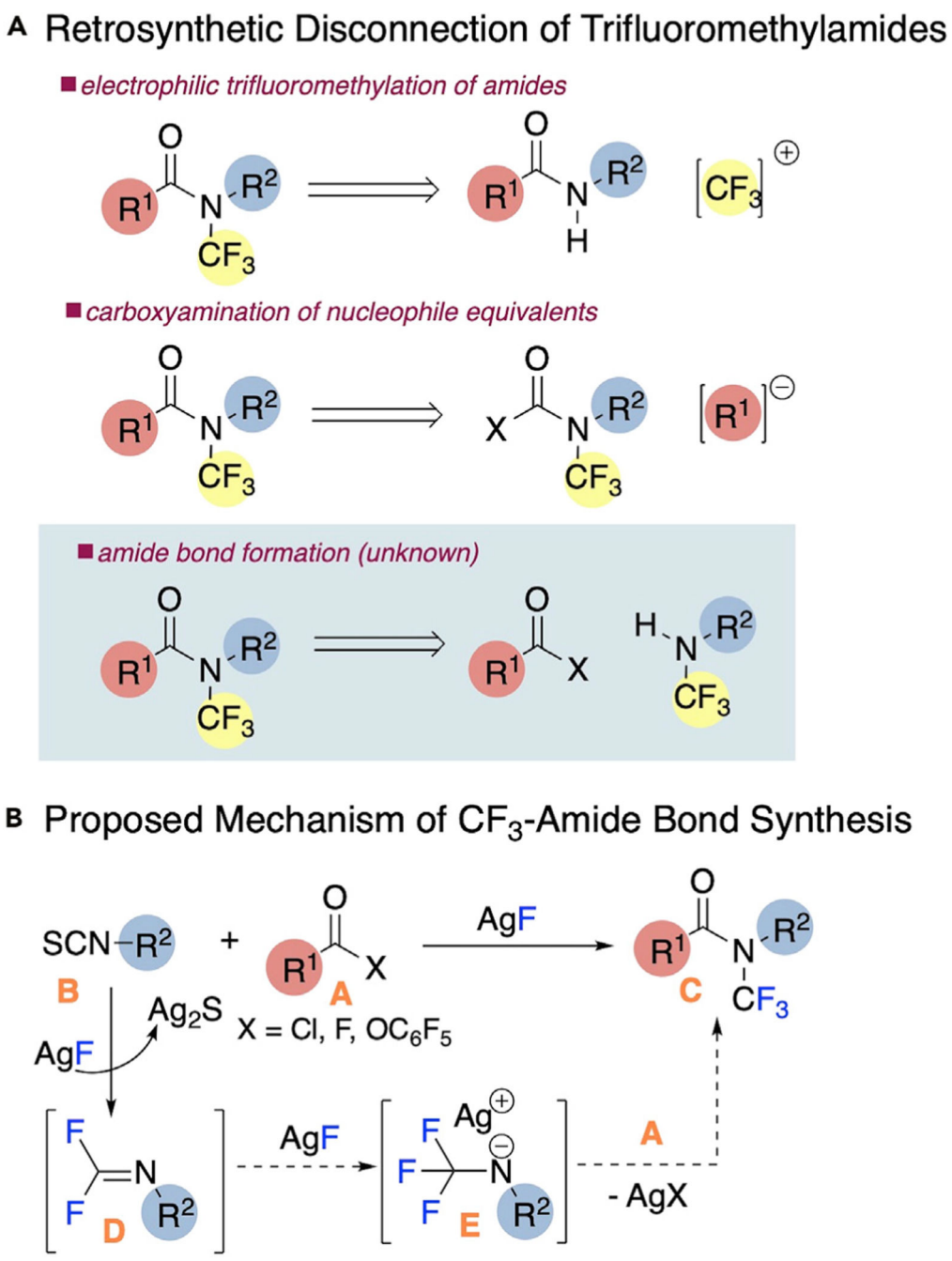


Figure 1. Direct synthesis of *N*-trifluoromethyl amides from carboxylic acid derivatives

(A) Retrosynthetic disconnection of trifluoromethylamides: electrophilic trifluoromethylation of amides, carboxyamination of nucleophile equivalents, and amide-bond formation (this manuscript).

(B) Putative mechanism of CF_3-amide-bond synthesis via successive fluorination and acylation of isothiocyanates.

See also Figure 2.

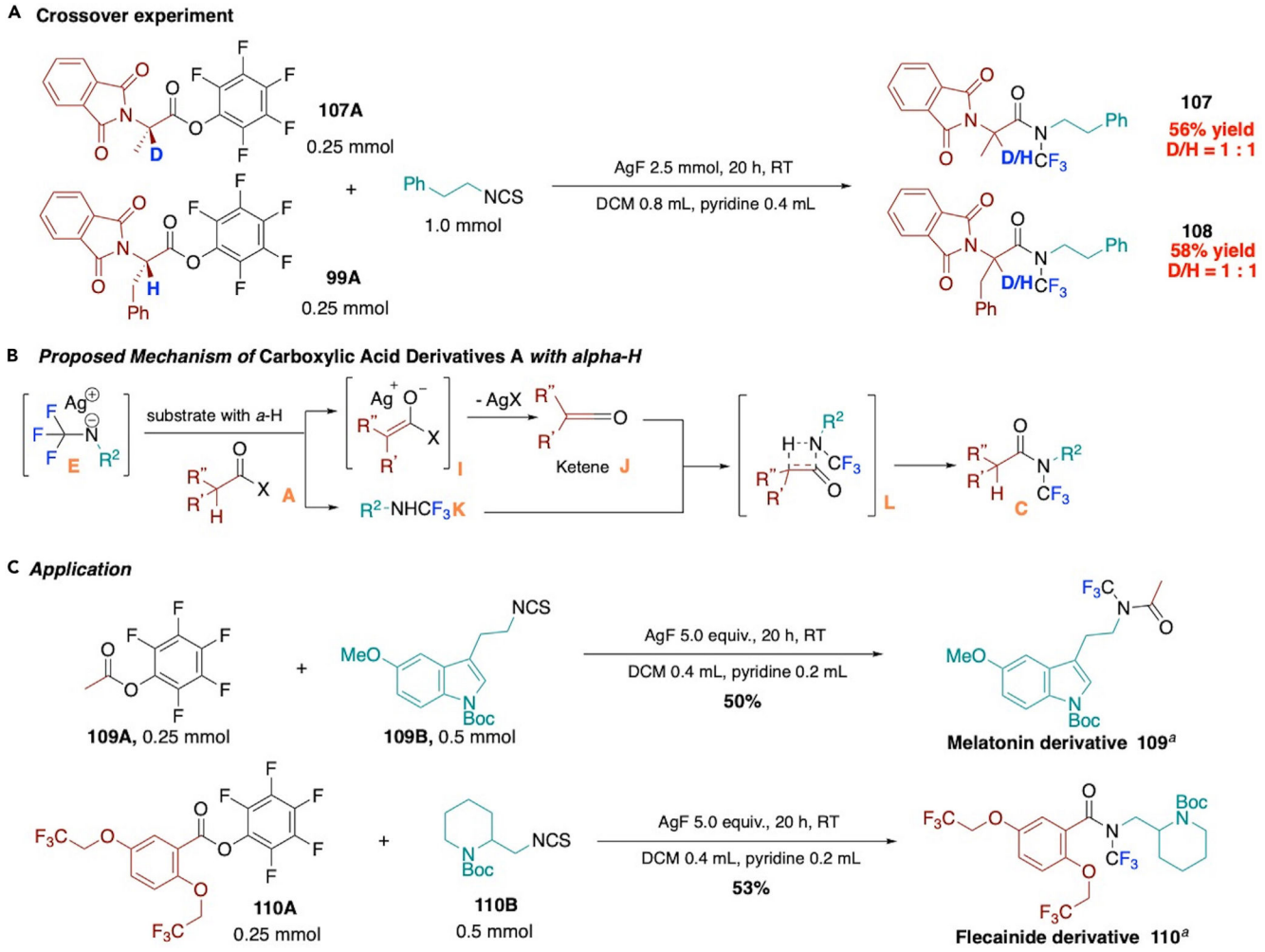


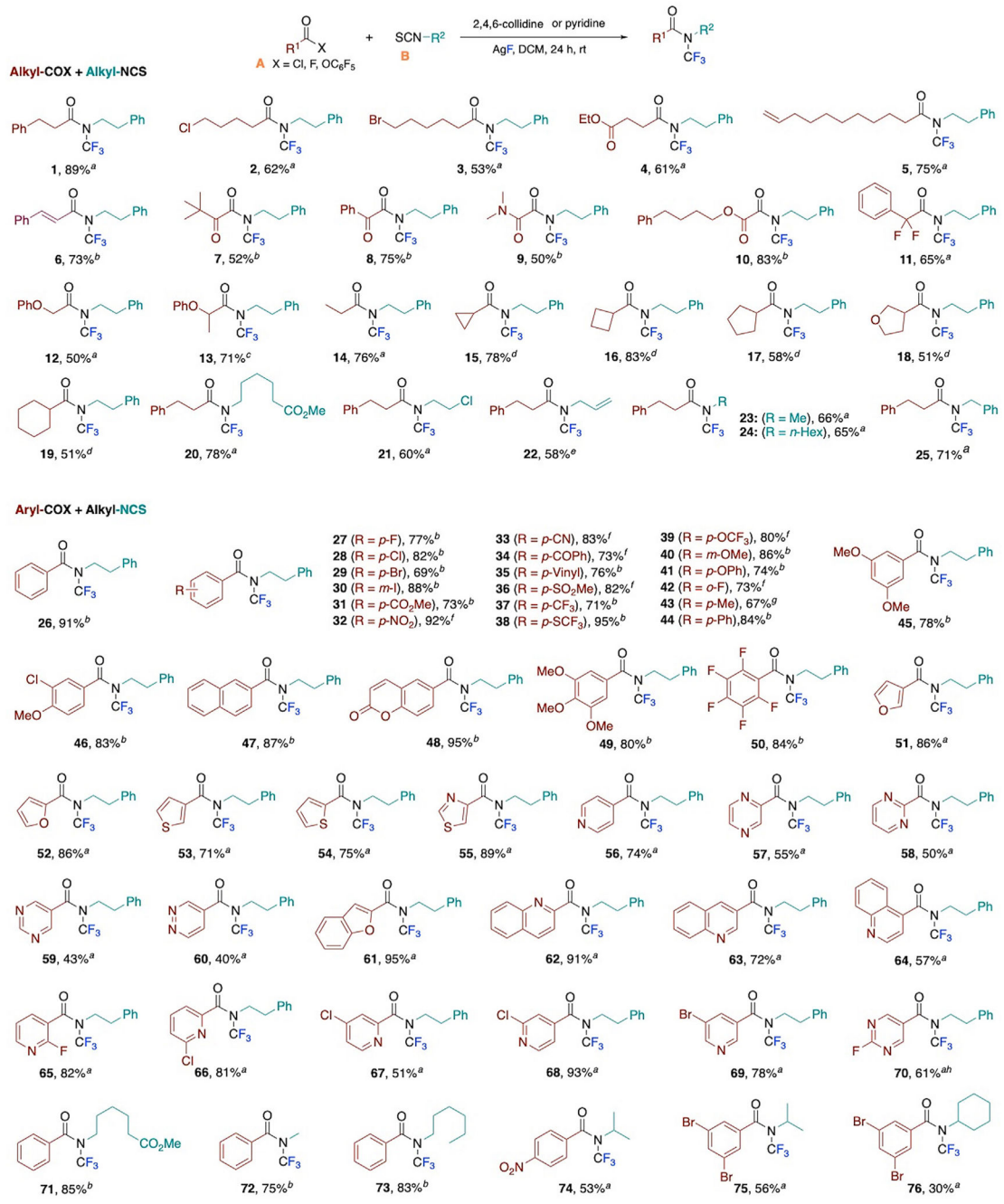
Figure 2. Crossover experiment, proposed mechanism of ketene intermediates, and applications

(A) Crossover experiment: pentafluorophenyl ester 109A (0.25 mmol, 1.0 equiv) and 100A (0.25 mmol, 1.0 equiv), alkyl isothiocyanate B (1.0 mmol), AgF (2.5 mmol), pyridine (0.4 mL), DCM (0.8 mL), RT, 24 h.

(B) Proposed mechanism of carboxylic acid derivatives A with alpha-H through the addition of ketene and amine.

(C) Applications include two pharmaceutically relevant molecules, melatonin and flecainide, and *N*-trifluoromethyl peptide synthesis.

[a]Pentafluorophenyl ester A (0.25 mmol), alkyl isothiocyanate B (2.0 equiv), AgF (5.0 equiv), pyridine (0.2 mL), DCM (0.4 mL), RT, 20 h.



Scheme 1. Scope of alkyl isothiocyanates for the synthesis of N–CF_3 amides

Reaction conditions: carboxylic acid derivative A (x mmol), alkyl isothiocyanate B (y mmol), AgF (z mmol), 2,4,6-collidine or pyridine (p mmol or p mL), DCM (s mL), RT, 24 h.

[a]Acyl chloride A and 2,4,6-collidine (3.0 mmol), x:y:z = 0.5:0.7:2.5, s = 1.6.

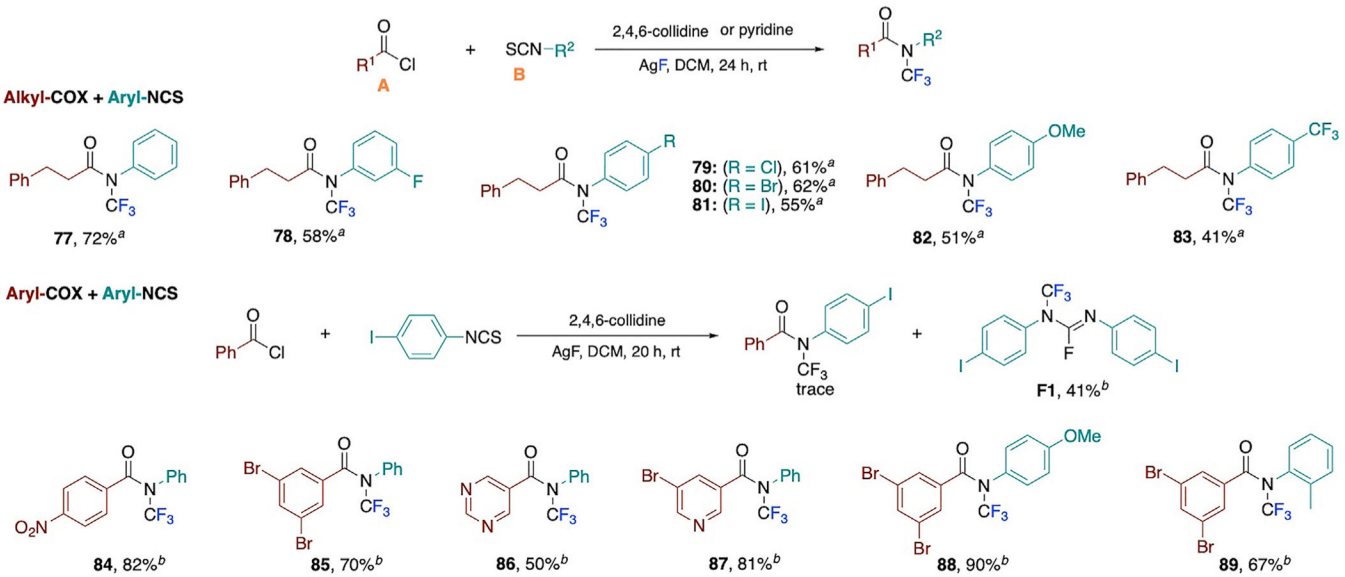
[b]Acyl chloride A and pyridine (1.0 mL), x:y:z = 0.7:0.5:2.0, s = 1.0.

[c]Pentafluorophenyl ester A and pyridine (0.4 mL), x:y:z = 0.5:1.0:2.5, s = 1.6.

[d]Acyl chloride A and pyridine (0.8 mL), x:y:z = 0.9:0.5:2.5, s = 0.4.

[e]Acyl fluoride A and 2,4,6-collidine (3.0 mmol), x:y:z = 0.5:0.8:2.5, s = 1.6.

[f]Acyl chloride A and 2,4,6-collidine (3.0 mmol), x:y:z = 0.7:0.5:2.0, s = 1.6.
[g]Acid chloride A and pyridine (1.0 mL), x:y:z = 0.5:0.7:2.5, s = 1.0.
[h]2-chloro-pyrimidine-5-carbonyl chloride was added as carboxylic acid derivative A.

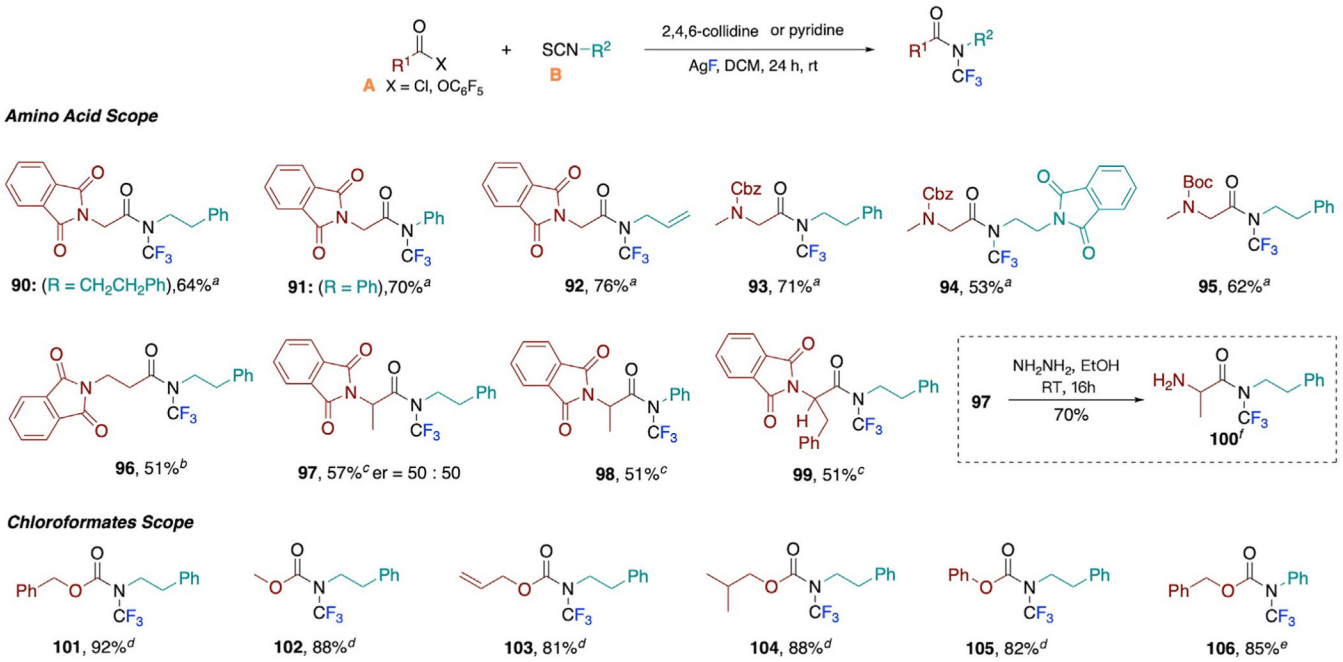


Scheme 2. Scope of aryl isothiocyanates for the synthesis of N–CF_3 amides

Reaction conditions: carboxylic acid derivative A (x mmol), alkyl isothiocyanate B (y mmol), AgF (z mmol), 2,4,6-collidine or pyridine (p mmol or p mL), DCM (s mL), RT, 24 h.

[a]Acyl chloride A and 2,4,6-collidine (3.0 mmol), x:y:z = 0.5:0.7:2.5, s = 1.6.

[b]Acyl chloride A and 2,4,6-collidine (0.6 mL), x:y:z = 0.5:0.7:2.5, s = 0.6.



Scheme 3. Scopes of aryl amino acids and chloroformates for the synthesis of N–CF_3 amides

Reaction conditions: carboxylic acid derivative A (x mmol), alkyl isothiocyanate B (y mmol), AgF (z mmol), 2,4,6-collidine or pyridine (p mmol or p mL), DCM (s mL), RT, 24 h.

[a]Acyl chloride A and 2,4,6-collidine (3.0 mmol), x:y:z = 0.5:0.7:2.5, s = 1.6.

[b]Acyl chloride A and pyridine (1.0 mL), x:y:z = 0.7:0.5:2.0, s = 1.0.

[c]Pentafluorophenyl ester A and pyridine (0.4 mL), x:y:z = 0.5:1.0:2.5, s = 1.6.

[d]Acyl chloride A and 2,4,6-collidine (0.6 mL), x:y:z = 0.5:0.7:2.5, s = 0.6.

[e]Pentafluorophenyl ester A and pyridine (0.4 mL), x:y:z = 0.5:1.0:2.5, s = 0.8.

[f]97 (0.2 mmol), dry EtOH (3.0 mL), NH_2NH_2 (g, 0.5 mmol, 2.5 equiv), RT, N_2, 16 h.