Introducing CF_3 Groups on Nitrogen Atoms

Literature Seminar

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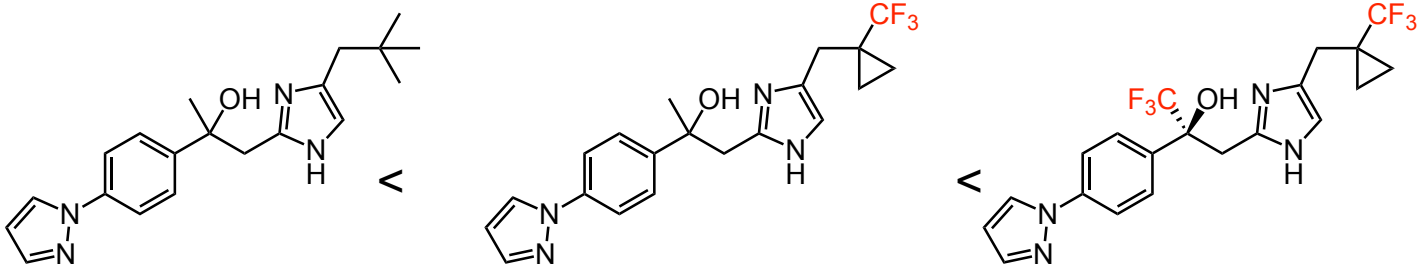
2022/10/21

Contents

- Introduction
  - Background
  - Electrophilic trifluoromethylation reagent
- Constructing *N*-CF_3 via prefucnctionalization
  - Schohenebeck's work
  - Xu's work
- Summary

Importance of F atom in medicinal chemistry

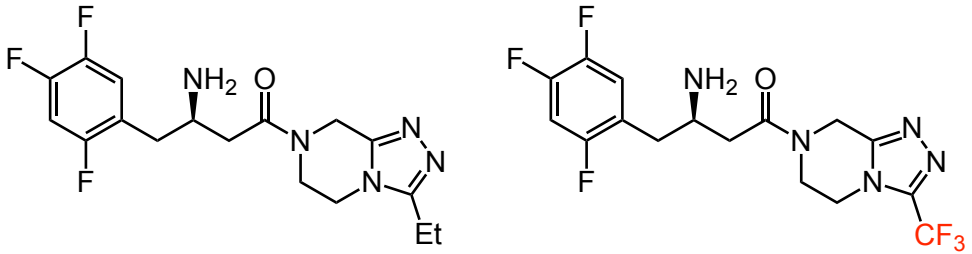
- Improvement of metabolic stability



CL_p = 110 mL/min/kg CL_p = 52 mL/min/kg CL_p = 20 mL/min/kg

Lin, S. L., *et al., ACS Med. Chem. Lett.* **2011**, *2*, 43–47

- Improvement of inhibitory activity



DPP4 IC_{50} = 37 nM DPP4 IC_{50} = 18 nM

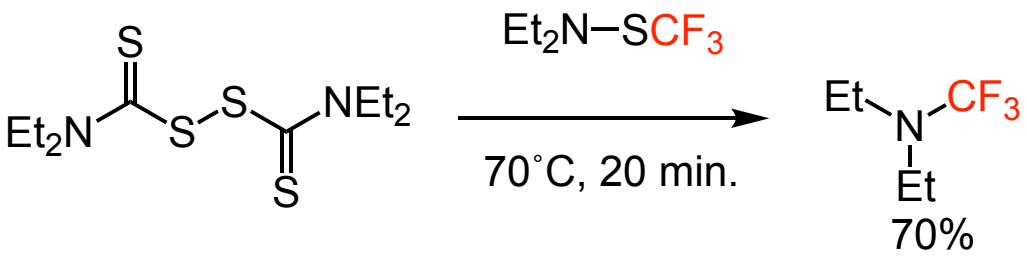
Weber, A. E., *et al*., *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3373– 3377

Meanwell, N. A., *J. Med. Chem.* **2018**, *61*, 5822−5880

Introducing F atom improves affinity, lipophilicity, metabolic stability, and other properties of drug molecules.

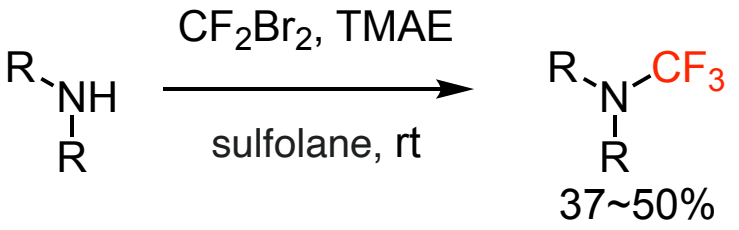
Demand for synthetic methodology is growing.

Conventional *N*-trifluoromethylation



Kirsanov, A. V., *et al*., *Synthesis* **1973**,*12*, 787-789

Dmowski, W., & Kamiński, M., *J. Fluor. Chem*. **1983**, *23*, 207-218

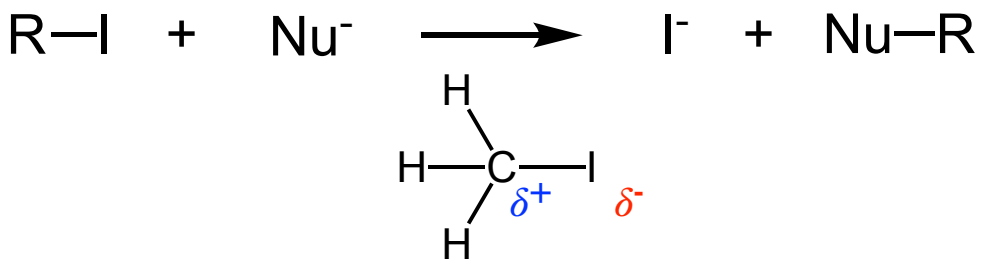


Pawelke, G., *J. Fluor. Chem*. **1991**, *52*, 229-234

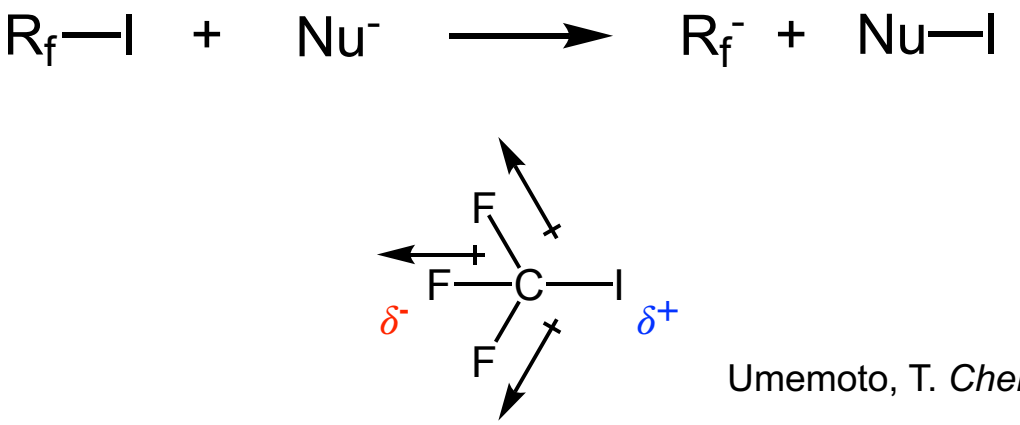
- Lacking safe, general and high yielding methodology

Electrophilic *N*-trifluoromethylation

- Typical alkylation



- Perfluorolkylation

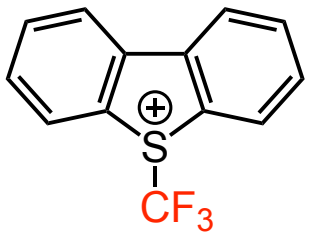


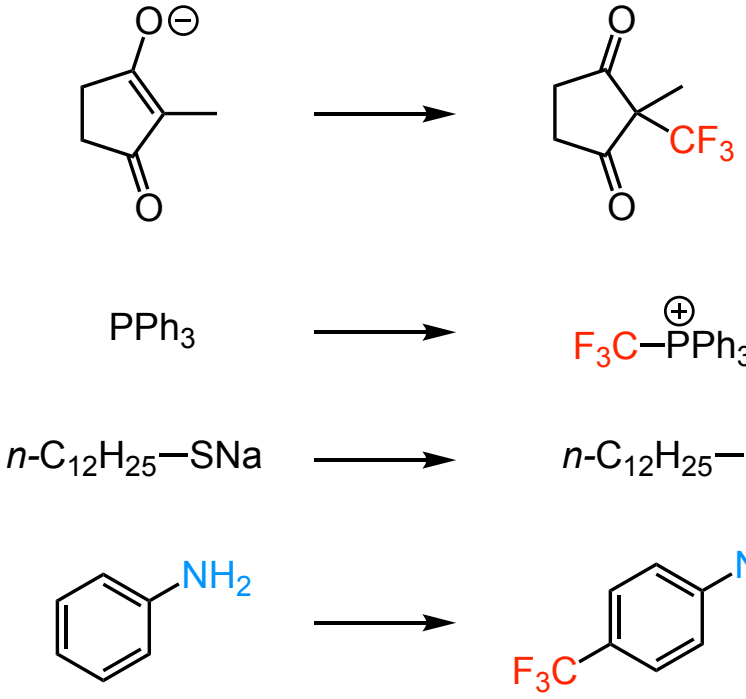
Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757–1778

➢ Trimethylation(perfluoroalkylation) does not proceed like non-fluorinated alkylation.

Electrophilic *N*-trifluoromethylation: Umemoto's reagent

- *S*-CF_3 dibenzothiophene



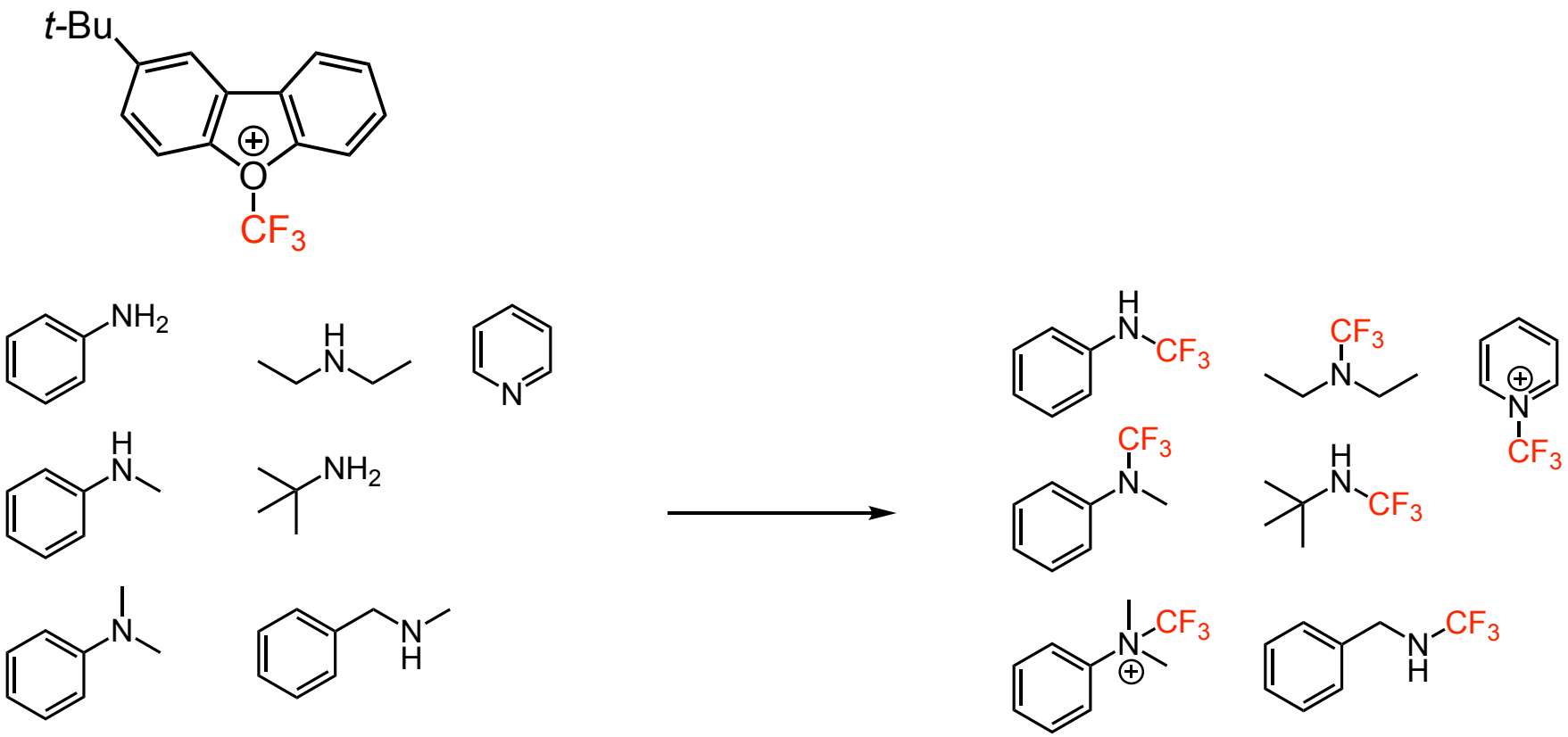


- *N*-CF_3 bond formation was not reported

Umemoto, T. & Ishihara, S., *J. Am. Chem. Soc.* **1993**, *115*, 2156–2164

Electrophilic *N*-trifluoromethylation: Umemoto's reagent

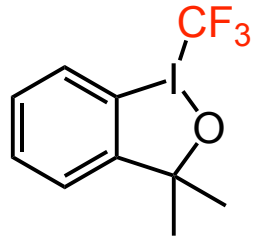
- Thermally unstable CF_3-oxionium salt



➢ Unstable above room temperature

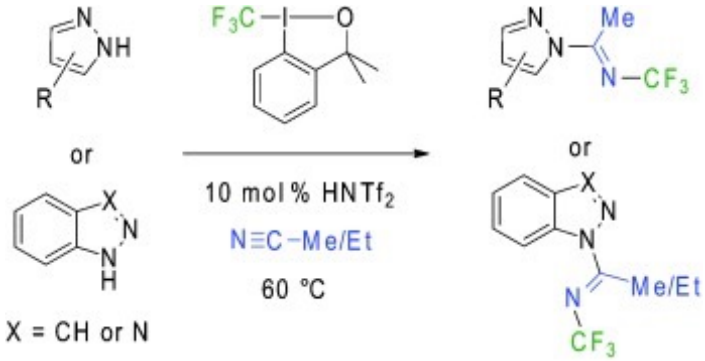
Umemoto, T., *et al., J. Org. Chem.* **2007**, *72*, 6905–6917

Electrophilic *N*-trifluoromethylation: Togni's reagent



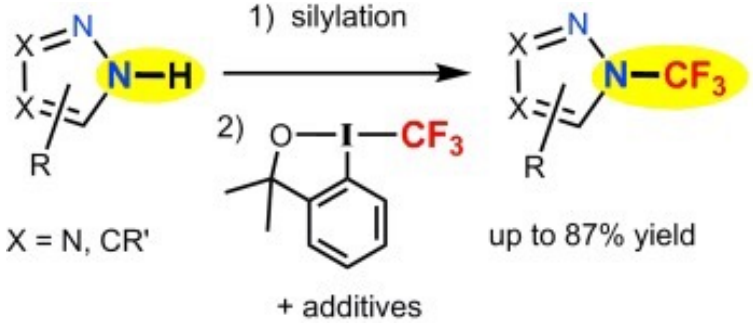
Togni's reagent

- Ritter-type trifluoromethylation



Togni. A., *et al., Angew. Chem., Int. Ed.* **2011**, *50*, 1059-1063

- Synthesizing *N*-CF_3 azoles



Togni. A., *et al., Angew. Chem., Int. Ed.* **2012**, *51*, 6511-6515

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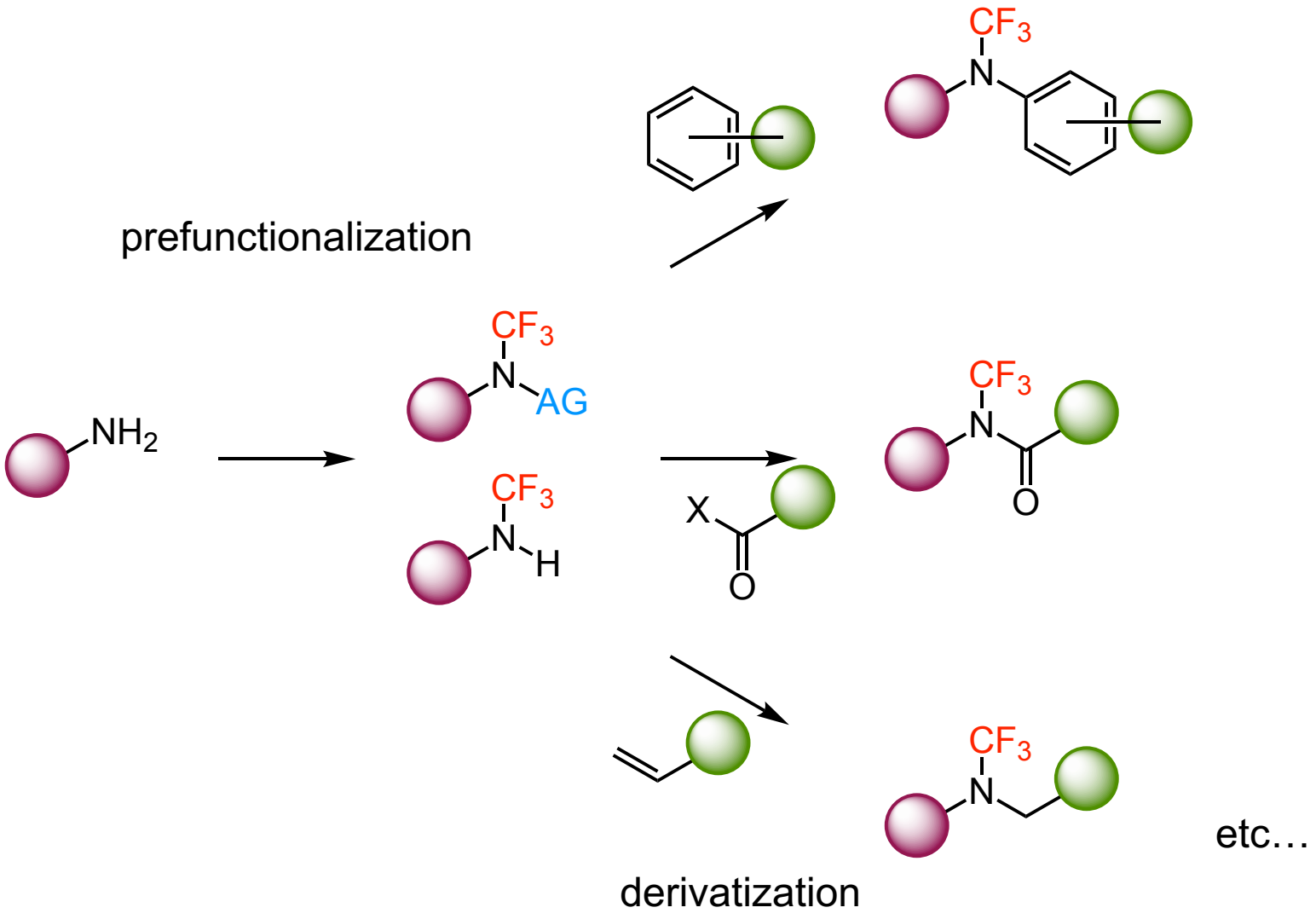
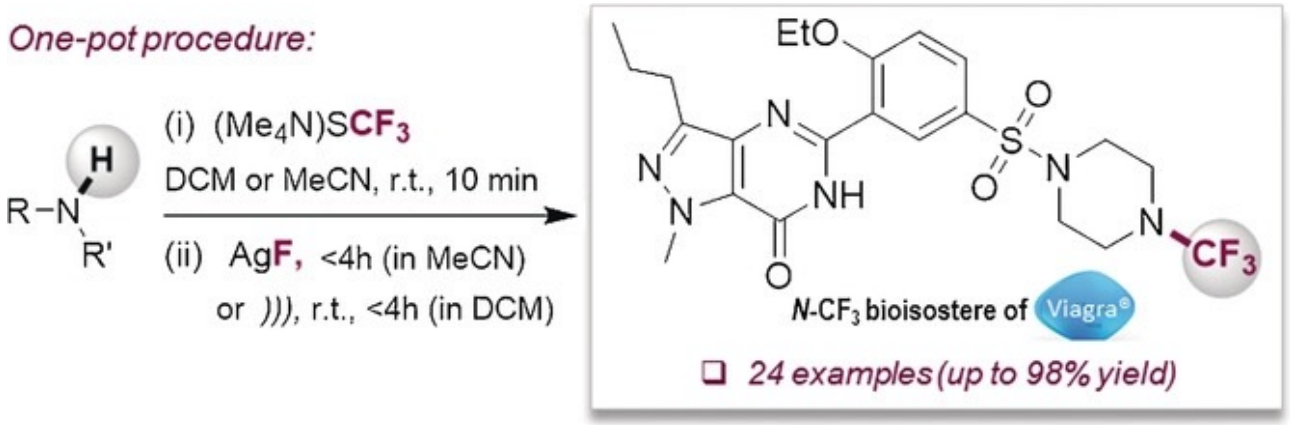
N-trifluoromethylation via prefunctionalization



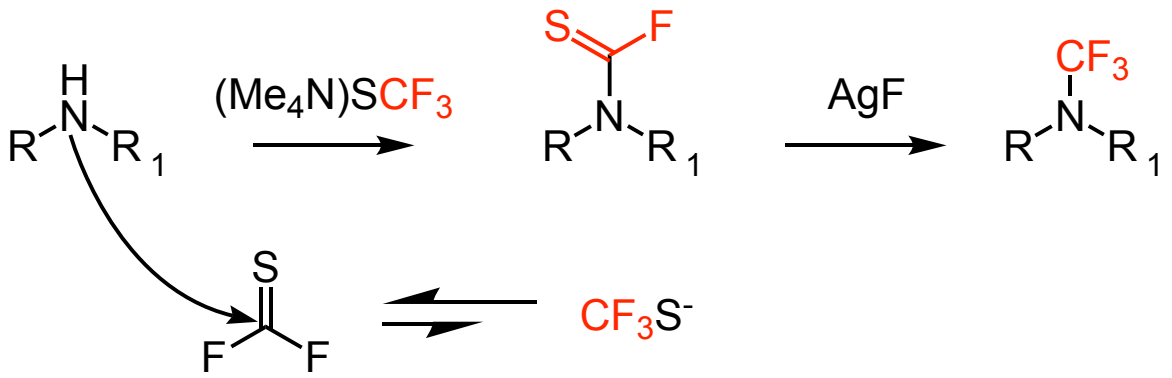
N-trifluoromethylation via prefunctionalization

- Functionalization of amine under mild conditions (Schohenebeck's work)

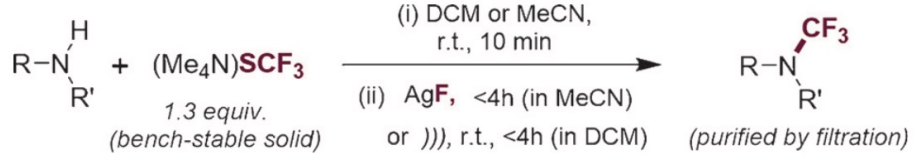


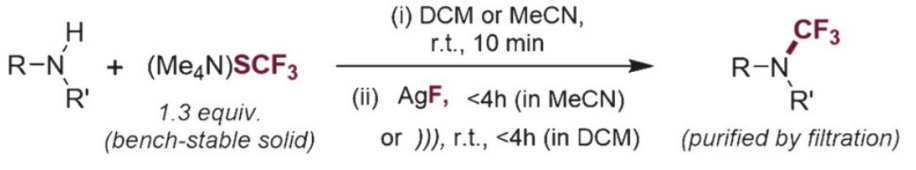
Schohenebeck, F., *et al., Angew. Chem., Int. Ed.* **2017**, *56*, 221-224

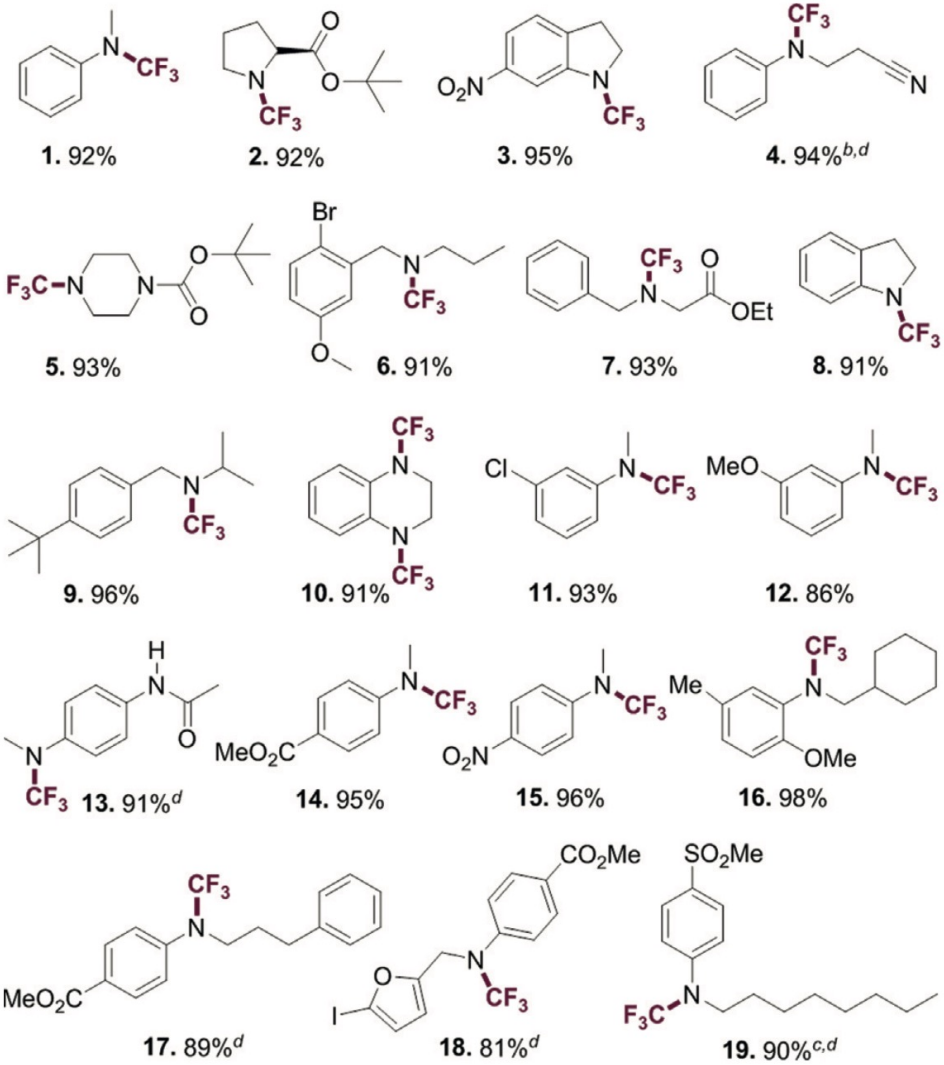
➢ Proposed mechanism

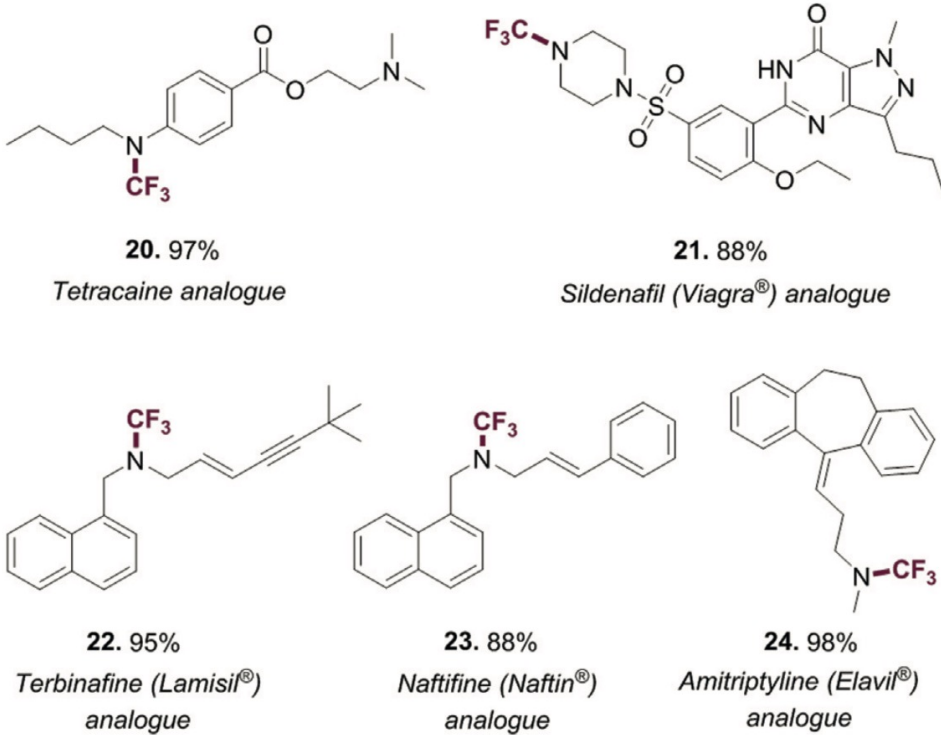


Schohenebeck's work: Substrate scope









- Tolerant to various functional group

Schohenebeck, F., *et al., Angew. Chem., Int. Ed.* **2017**, *56*, 221-224

Synthesis of *N*-CF_3 amide

LETTER

https://doi.org/10.1038/s41586-019-1518-3

Straightforward access to *N*–trifluoromethyl amides, carbamates, thiocarbamates and ureas

Thomas Scattolin[1], Samir Bouayad-Gervais[1] & Franziska Schoenebeck[1]*

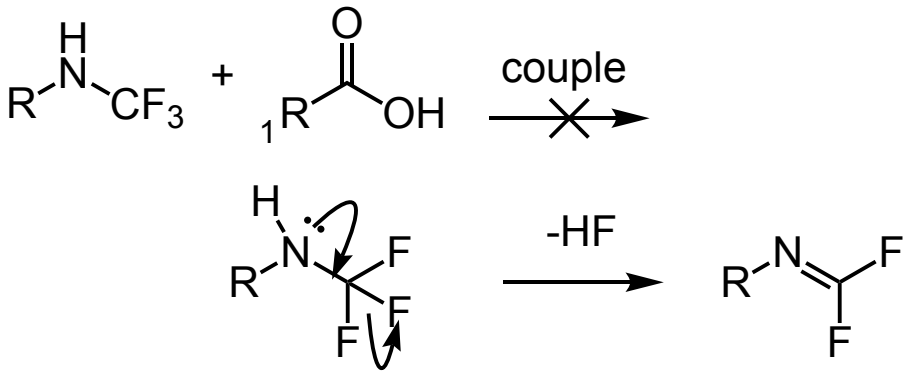
Amides and related carbonyl derivatives are of central importance across the physical and life sciences[1,2]. As a key biological building block, the stability and conformation of amides affect the structures a lack of efficient methodology to synthesize it. Here we report a straightforward method to access *N*-trifluoromethyl analogues of amides and related carbonyl compounds. The strategy relies on

- Safer, more robust and versatile methodology.

- Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

Drawbacks in constructing *N*-CF_3 amide

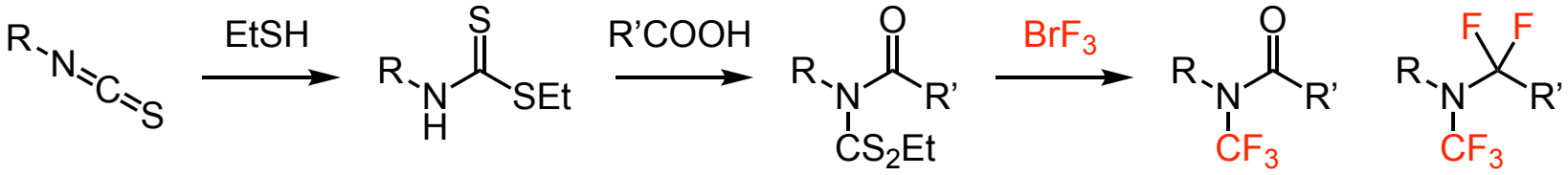
- Coupling is not applicable due to instability of secondary *N*-CF_3 amine.



Kloeter, G. & Seppelt, K. *J. Am. Chem. Soc.* **1979**, *101*, 347–349

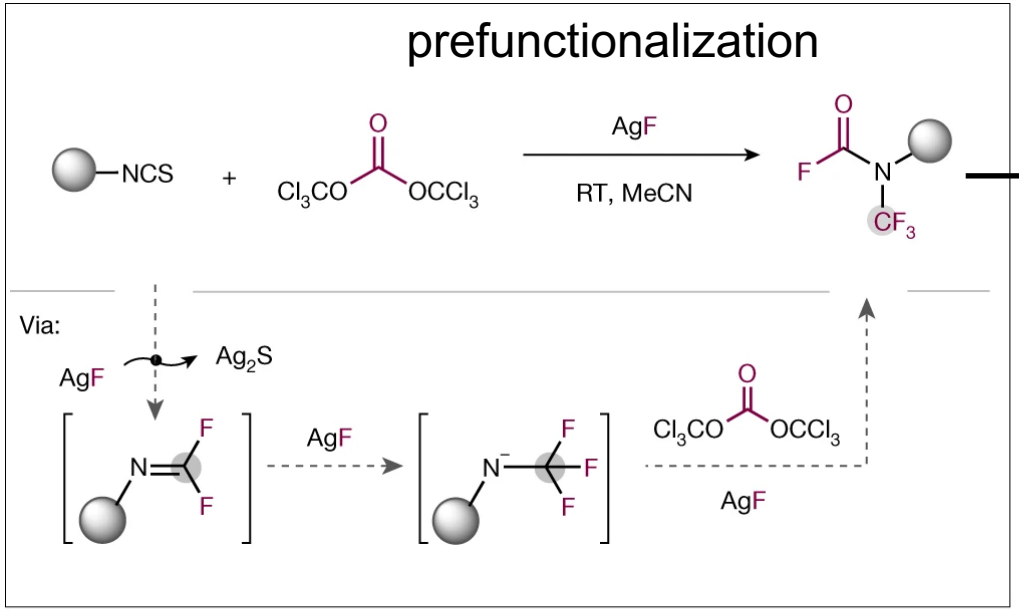
Burger, H. & Pawelke, G., *J. Chem. Soc., Chem. Commun.* **1988**, 105–106

- Conventional methods need hazardous reagent.



Rozen, S., *et al., J. Org. Chem.* **2009**, *74*, 8578-8582

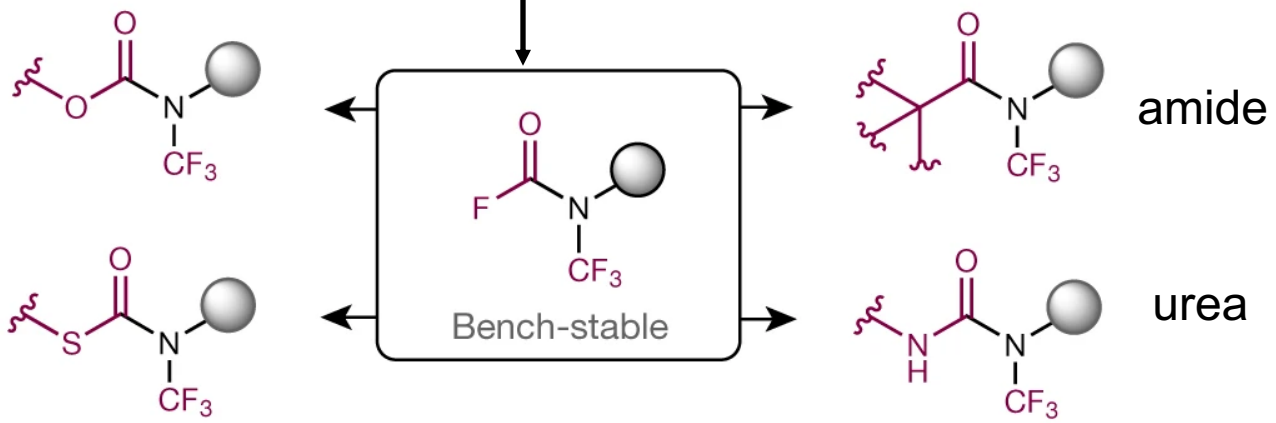
Strategy



derivatization

carbamate

thiocarbamate

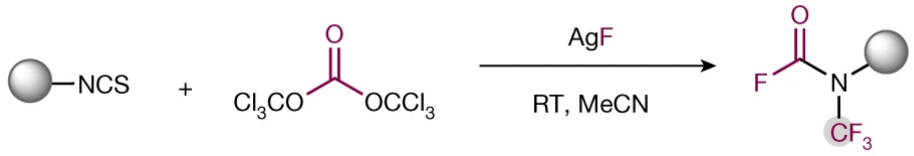


amide

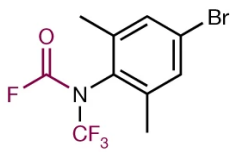
urea

Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

Substrate Scope: Carbamoyl fluoride



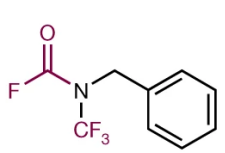
1, 98%



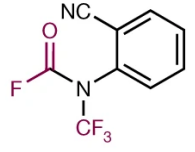
2, 91%

3, 80%

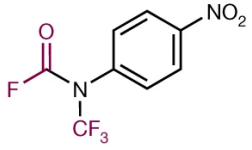
4, 95%[b]



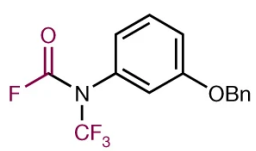
5, 86%



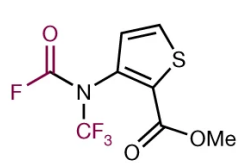
6, 96%



7, 96%

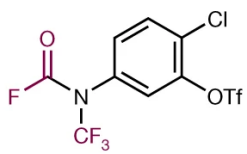


8, 99%

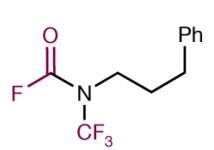


9, 92%

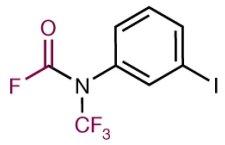
10, 93%



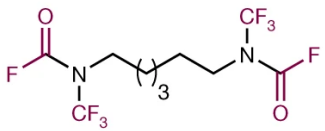
11, 95%



12, 97%

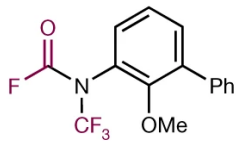


13, 92%

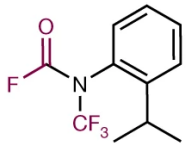


14, 81%

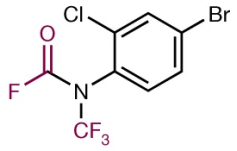
15, 93%



16, 97%

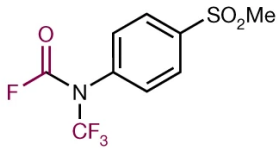


17, 93%[b]

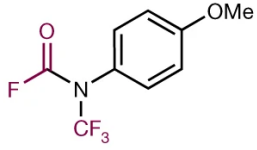


18, 90%

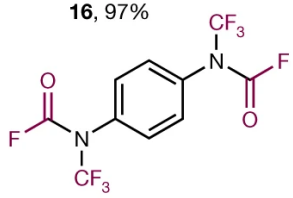
19, 99%



20, 94%

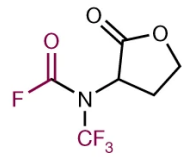


21, 91%



22, 96%

23, 93%

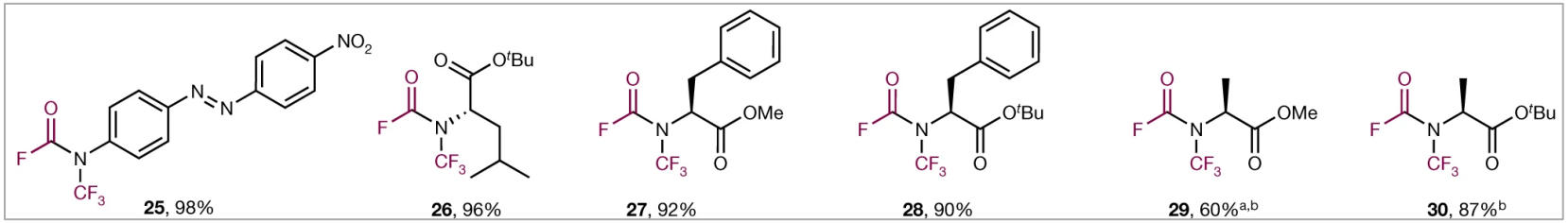


24, 80%

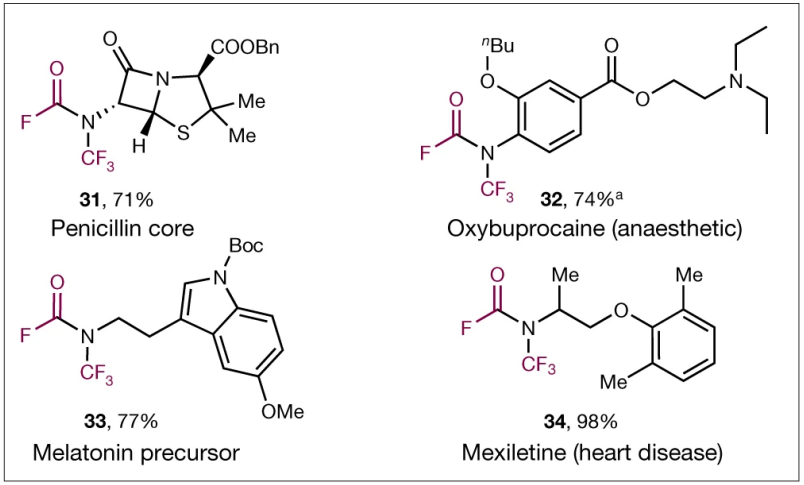
Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

Substrate Scope: Carbamoyl fluoride

chiral amino acids



drug molecules



- High functional group tolerance was shown.
- Stereochemistry was also retained.

Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

Mechanistic studies: Proposed mechanism

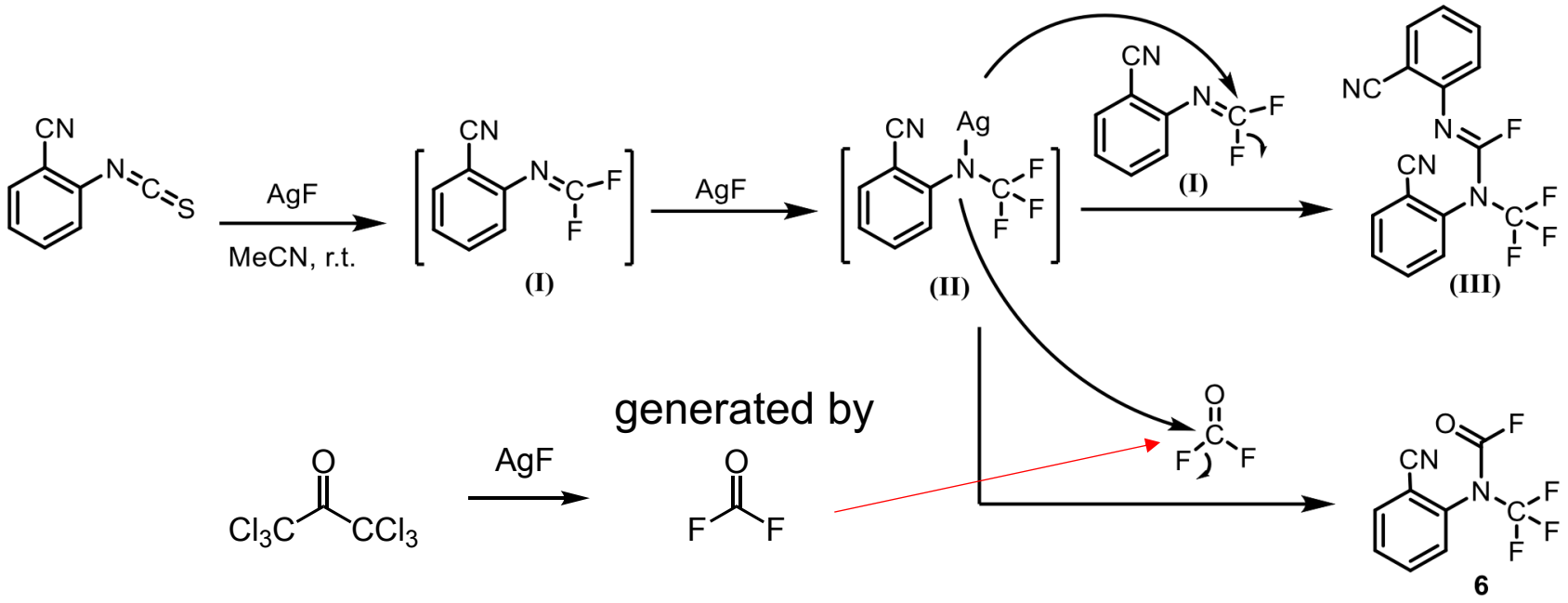
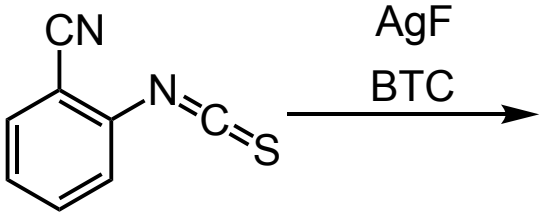


Fig. S55. Proposed mechanism for desulfurization and formation of R-N(CF_3)COF.

Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

Mechanistic studies: IR spectra



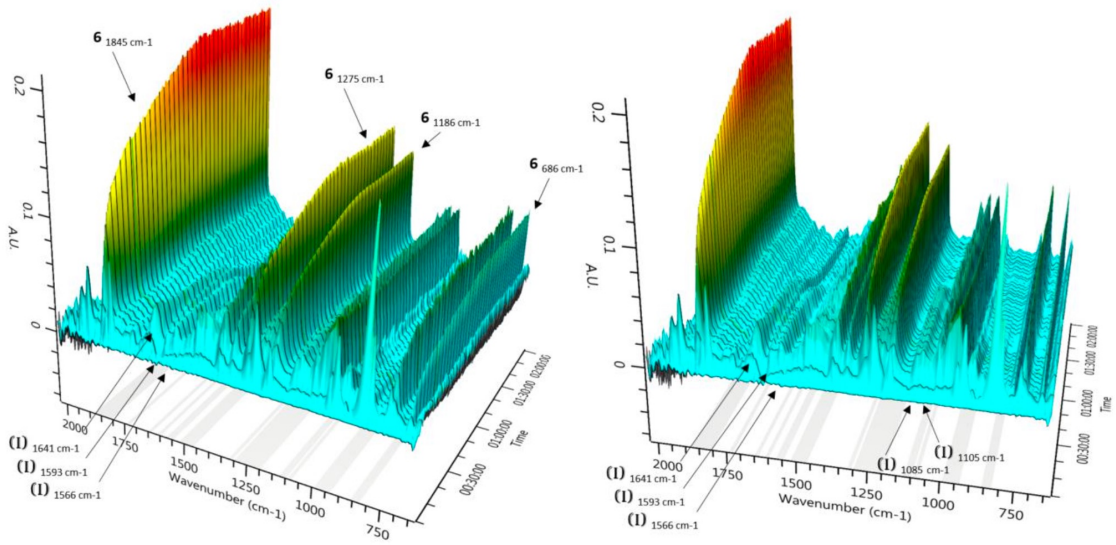
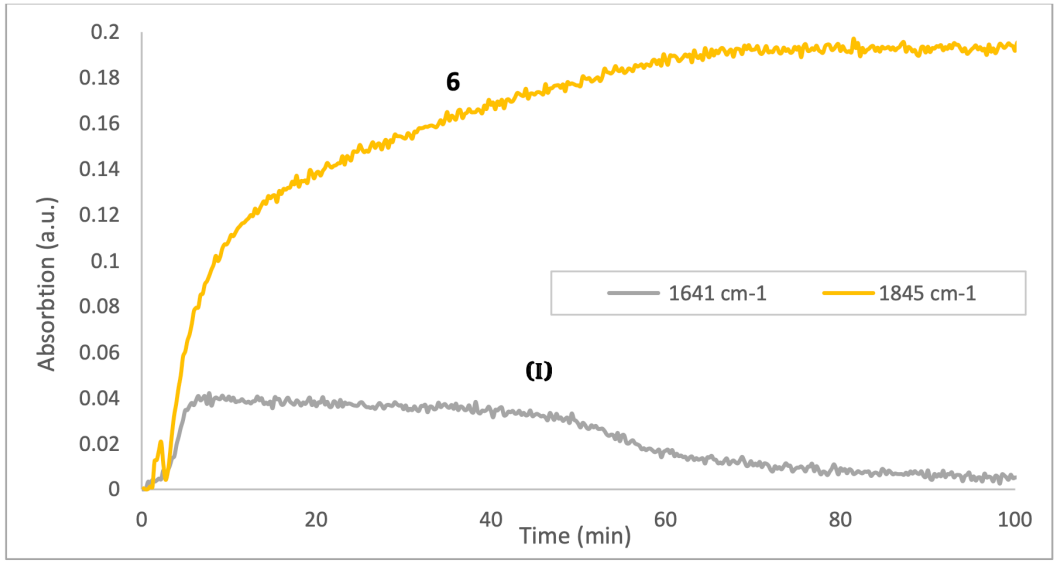
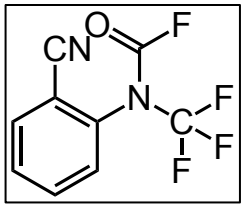


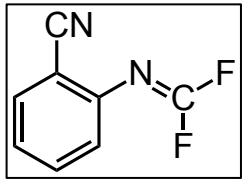
Fig. S56. 3D surface (two perspectives) of ReactIR during synthesis of R-N(CF_3)COF **6.**

Fig. S57. Main IR bands observed during R-N(CF_3)COF synthesis.





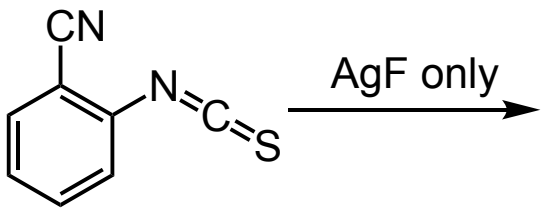
6



(I)

Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

Mechanistic studies: IR spectra



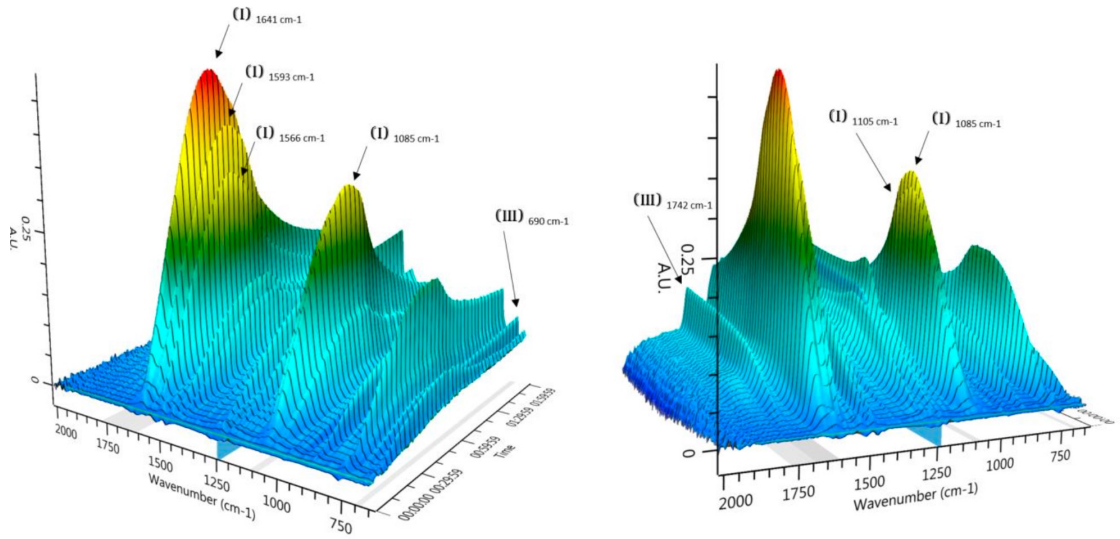
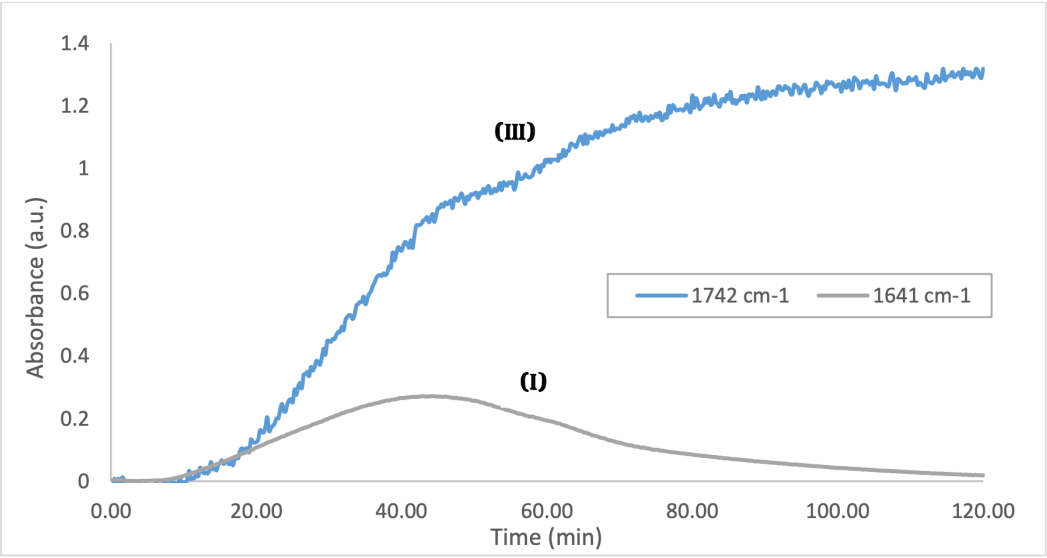
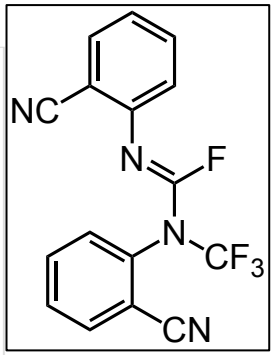


Fig. S58. IR bands of (**I**) & (**III**) on 3D surface (two perspectives), reaction of R-NCS with AgF.

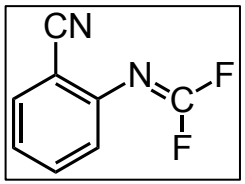
Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

Fig. S59. Main IR bands during reaction of R-NCS with AgF only.



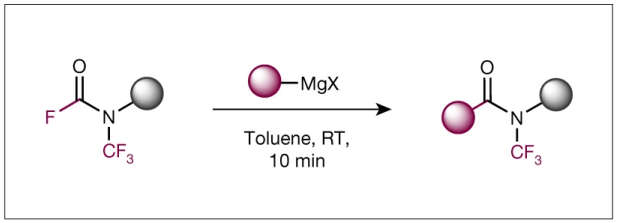


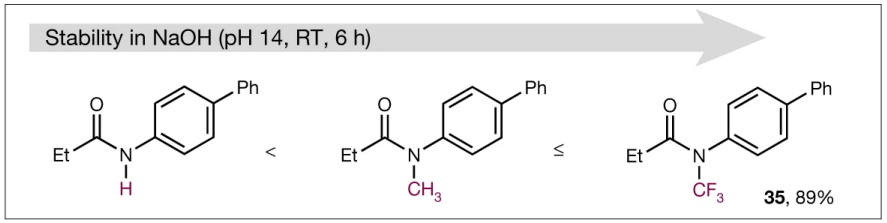
(III)

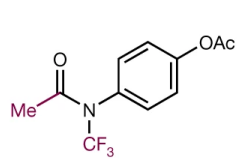


(I)

Substrate Scope: Constructing amide

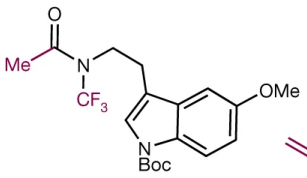






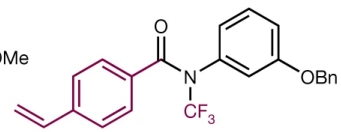
36, 41%

Paracetamol derivative

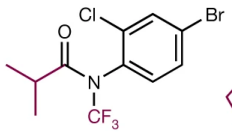


37, 30%

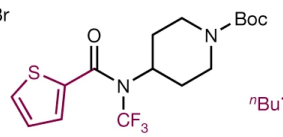
Melatonin derivative



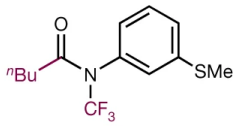
38, 86%



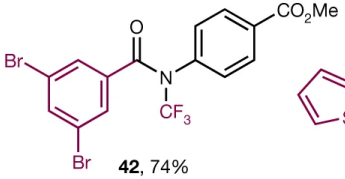
39, 75%



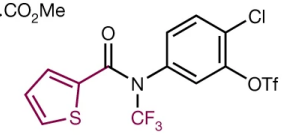
40, 93%



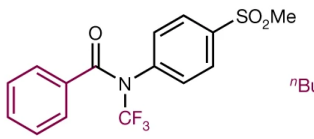
41, 74%



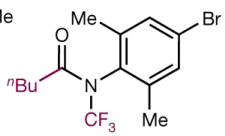
42, 74%



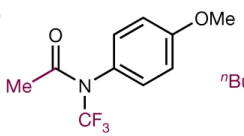
43, 97%



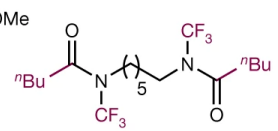
44, 83%



45, 71%

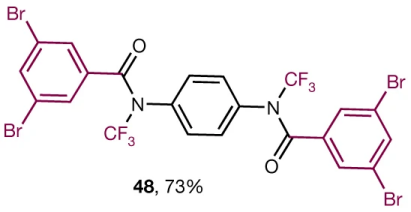


46, 68%



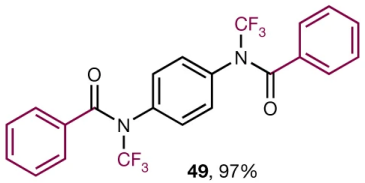
47, 82%

Nylon (6,6) derivative



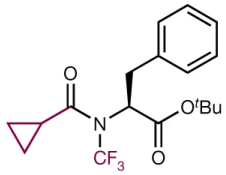
48, 73%

Microporous organic polymer derivative

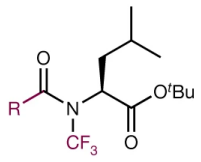


49, 97%

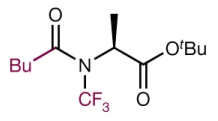
Kevlar derivative



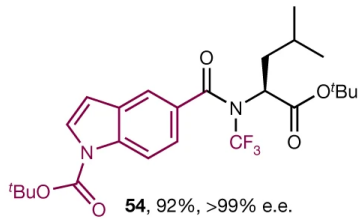
50, 69%, 96% e.e.



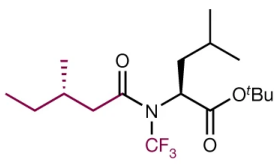
51, 97%, >99% e.e. (R = Ph)
52, 79% (R = ^{n}Bu)



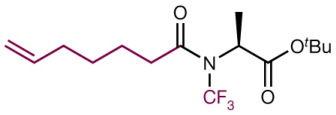
53, 72%, >99% e.e.



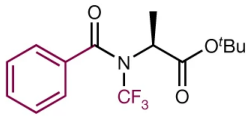
54, 92%, >99% e.e.



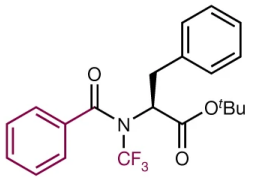
55, 39%



56, 65%, >99% e.e.



57, 91%, 99% e.e.

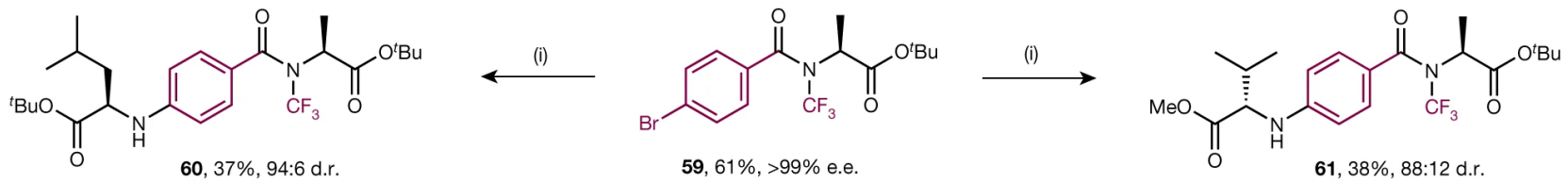


58, 87%, 98% e.e.

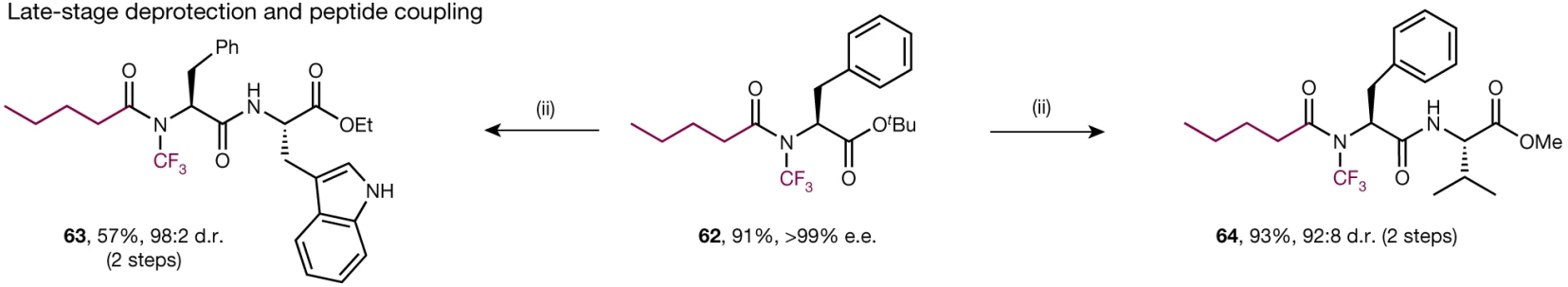
Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

Substrate Scope: Constructing amides

Pd-catalysed late-stage amination



Late-stage deprotection and peptide coupling

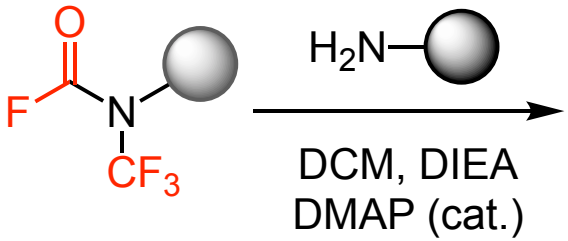


i) $Pd(OAc)_2$ (10 mol%)/ BINAP (15 mol%), Cs_2CO_3, toluene, 110 °C, 3 h; (ii) step 1: trifluoroacetic acid, dichloromethane, RT, 2 h; step 2: HBTU, DIPEA, amino acid, RT, 16 h.

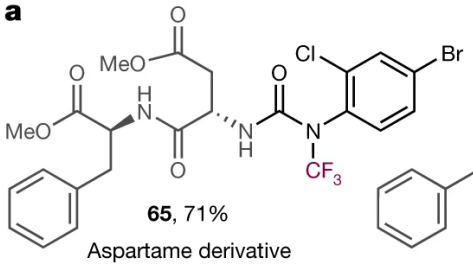
- Stereochemistry was retained.
- Compatible with further derivatization

Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

Substrate Scope: Constructing urea

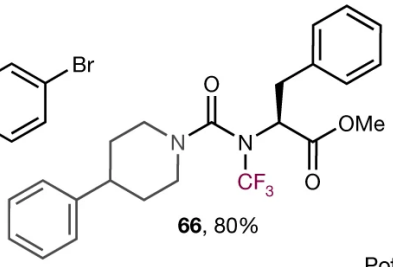


a



65, 71%

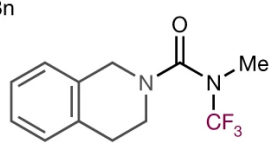
Aspartame derivative



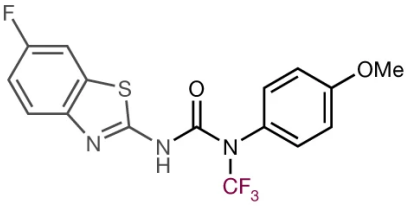
66, 80%

67, 81%

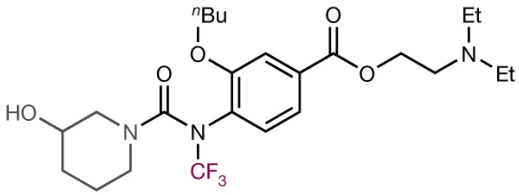
Potential antibiotic (penicillin core)



68, 63% (2 steps)

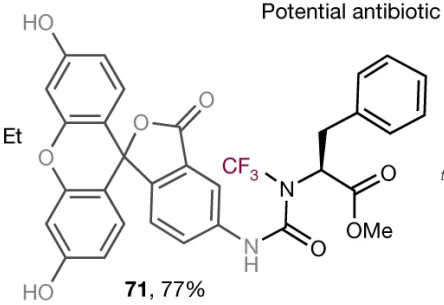


69, 94%

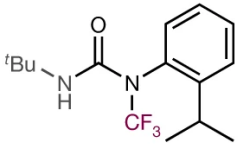


70, 61%[a]

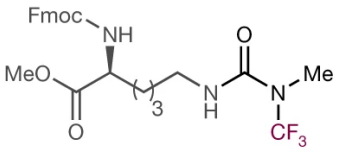
Oxybuprocaine derivative



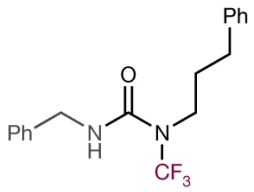
71, 77%



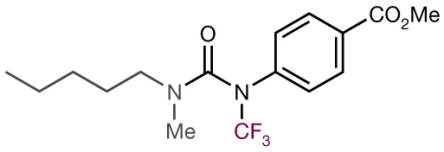
72, 80%



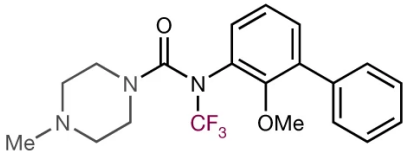
73, 67% (2 steps)



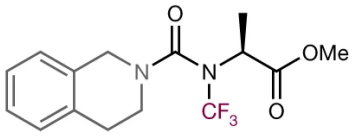
74, 87%



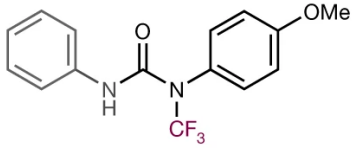
75, 89%



76, 97%



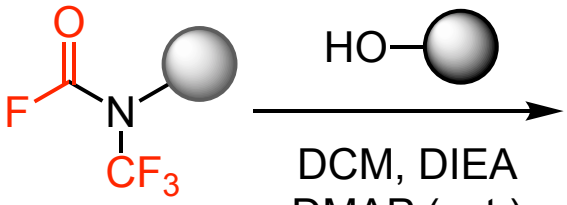
77, 79%



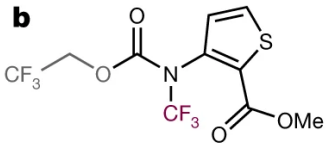
78, 92%

Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

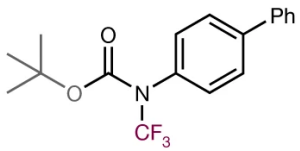
Substrate Scope: Constructing carbamate



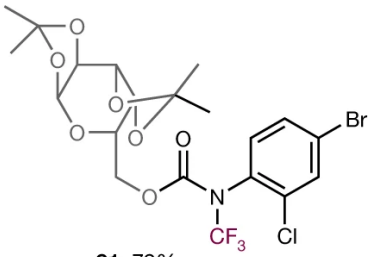
b



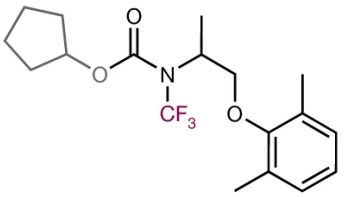
79, 99%



80, 79%[b]

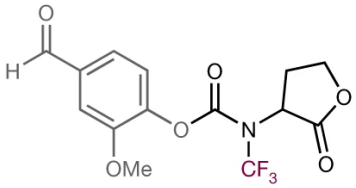


81, 79%

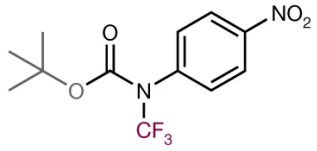


82, 67%

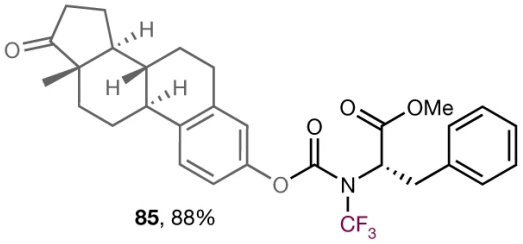
Mexiletine derivative
(heart disease)



83, 98%

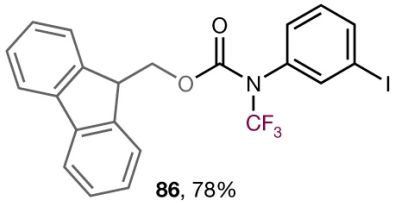


84, 74%[b]



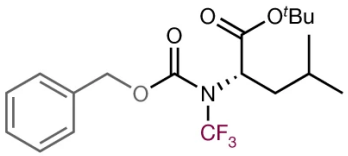
85, 88%

Oestrone derivative



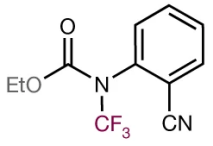
86, 78%

Fmoc protection

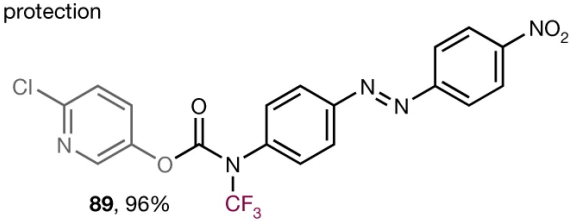


87, 83%

Cbz protection



88, 85%

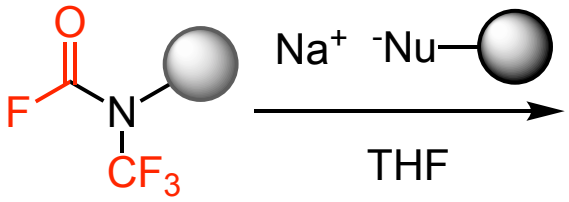


89, 96%

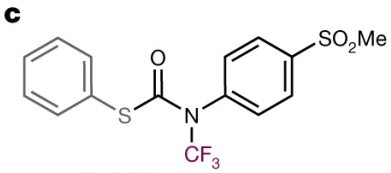
Nonlinear optical material (dye) derivative

Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

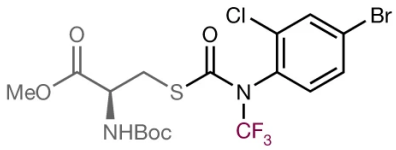
Substrate Scope: Constructing thio- and selenocarbamate



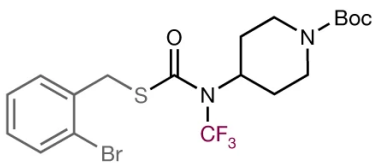
c



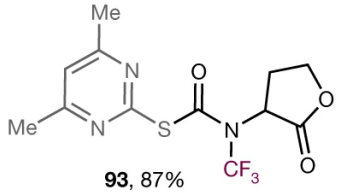
90, 86%



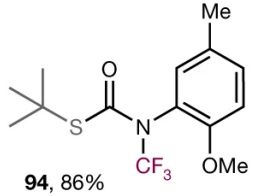
91, 74%



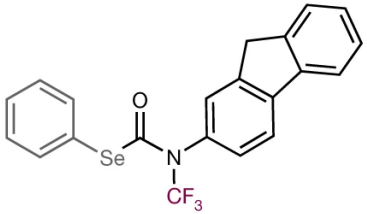
92, 88%



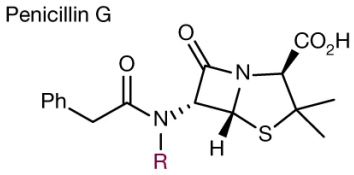
93, 87%



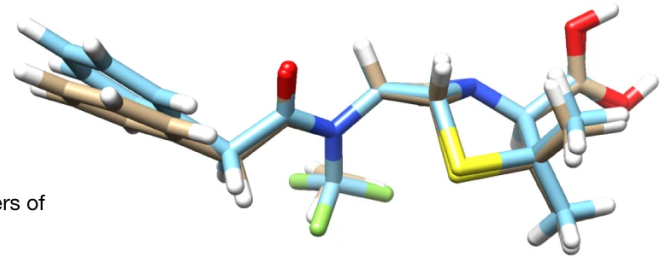
94, 86%



95, 86%



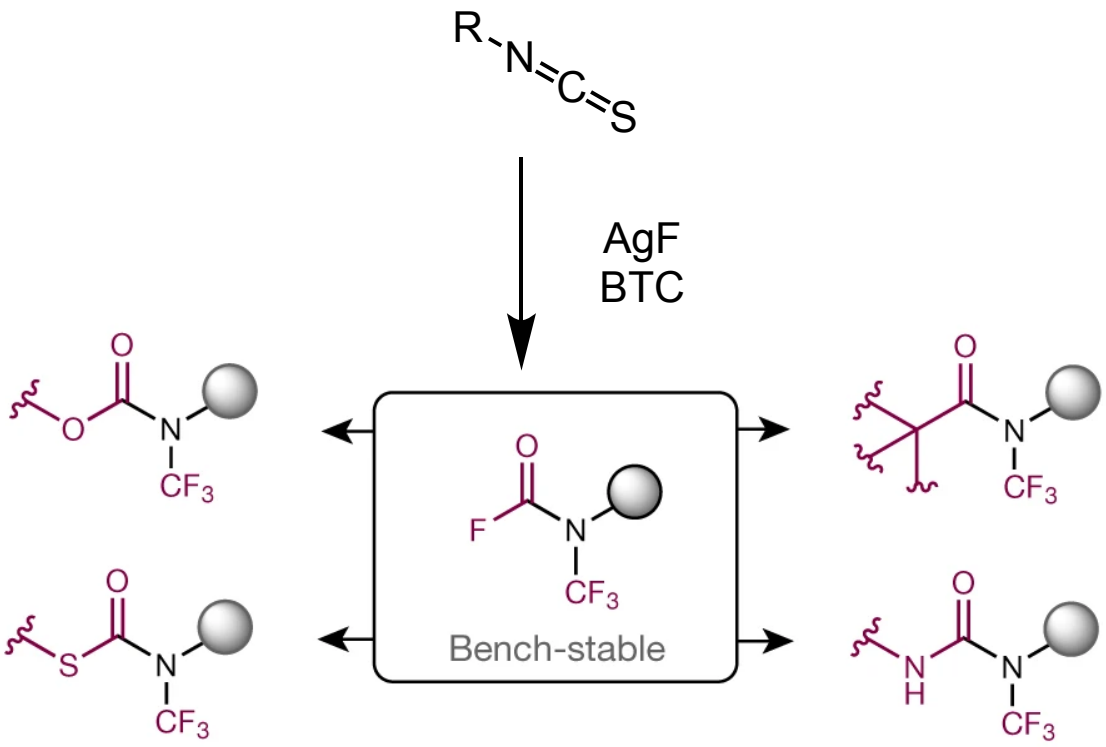
Overlay of minimum energy conformers of *N*–Me vs *N*–CF_3 penicillin G



- Carbamoylfluoride could be transformed to urea, carbamate, and thio(seleno-)carbamate

Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

Short summary

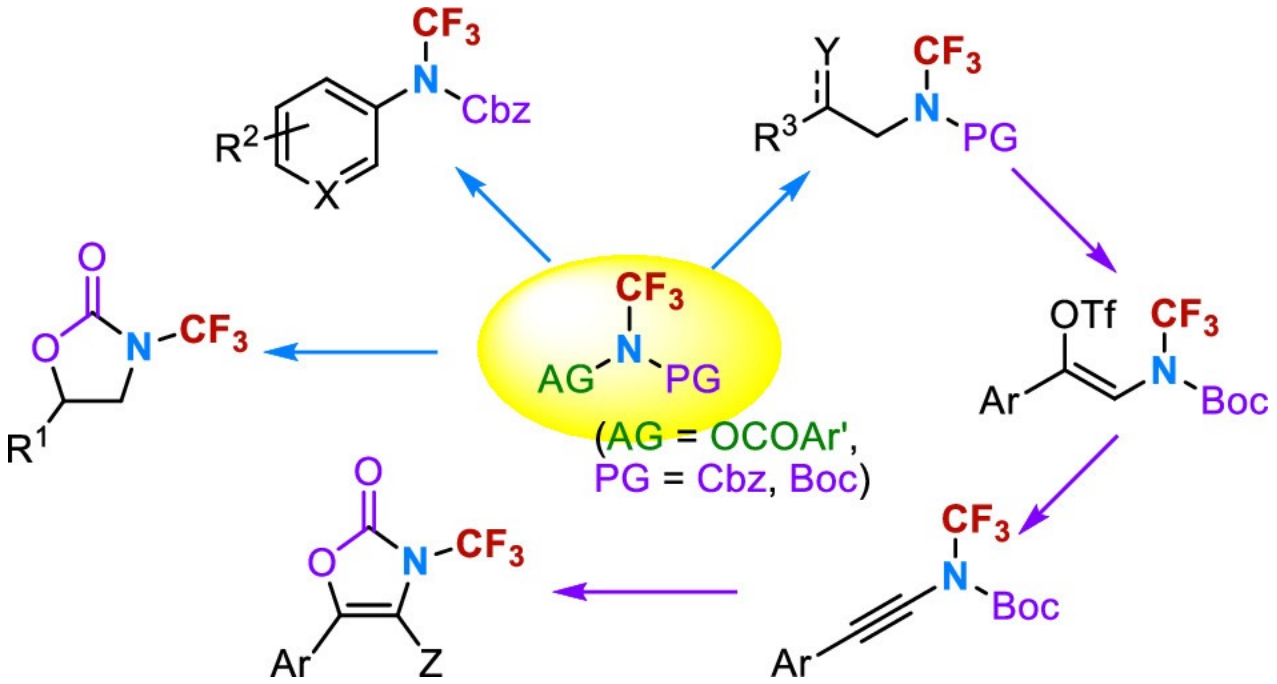


- Safe and simple methodology to construct *N*-CF3 amide
- Accessible to urea, carbamate and thiocarbamate

Contents

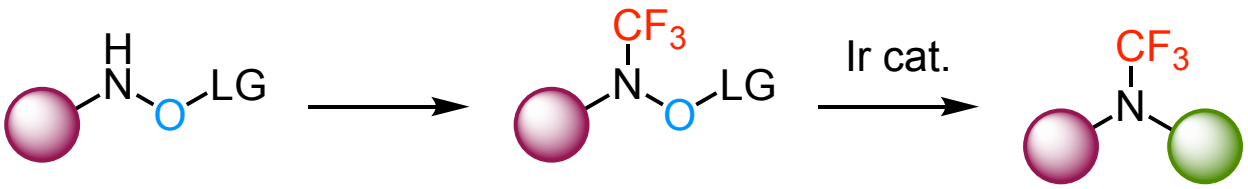
- Introduction
  - Background
  - Electrophilic trifluoromethylation reagent
- Constructing *N*-CF_3 via prefucnctionalization
  - Schohenebeck's work
  - Xu's work
- Summary

Constructing *N*-CF_3 by Prefunctionalizing hydroxylamine derivatives



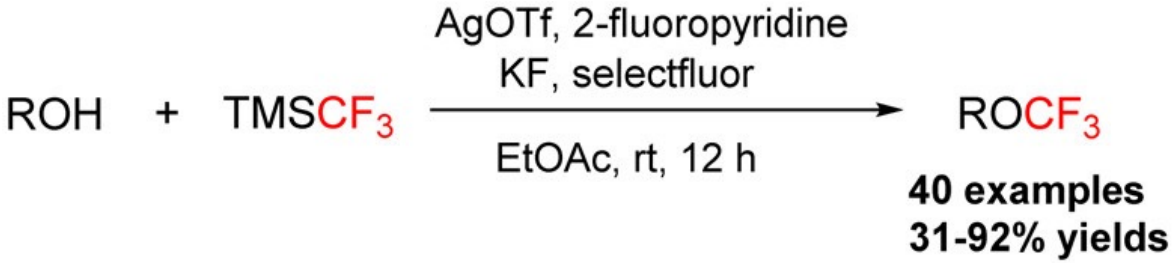
Xu, X., *et al., J. Am. Chem. Soc.* **2022**, *144*, 1962−1970

- Strategy



Constructing *N*-CF_3 hydroxylamine

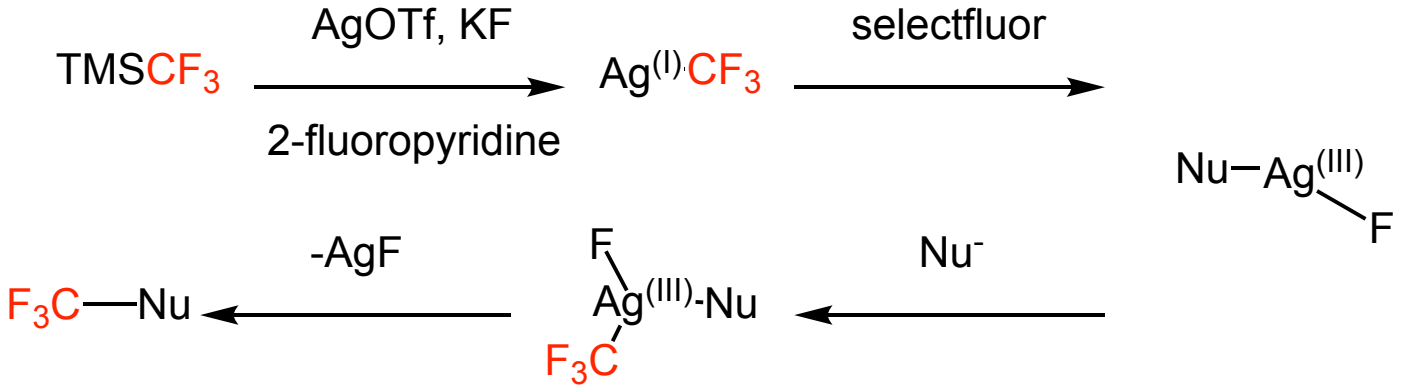
- Previous work



Xu, X., *et al., Org. Lett.* **2015**, *17*, 5048–5051

➢ Applied to *N*-trifluoromethylation of hydroxylamine

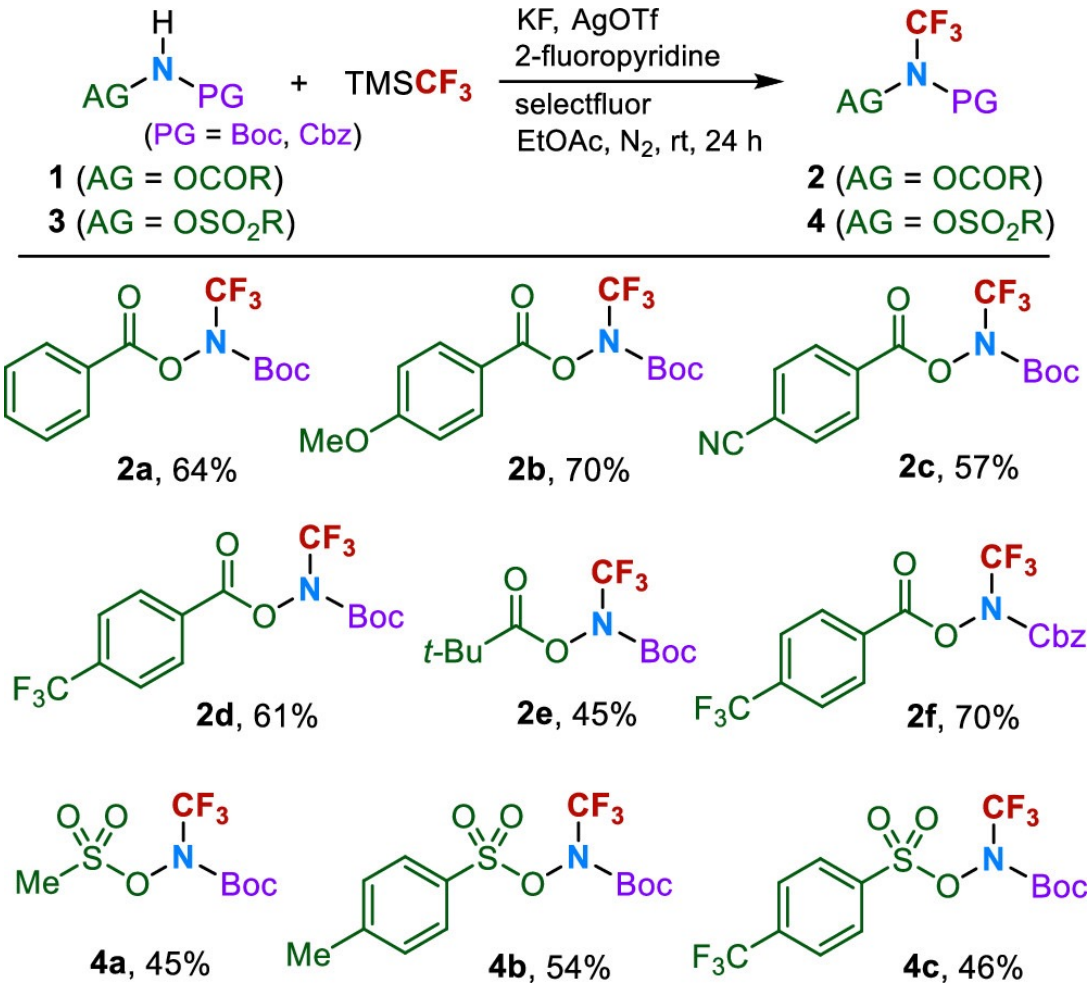
- Proposed mechanism



Xu, X., *et al., Angew. Chem., Int. Ed.* **2015**, *54,* 11839-11842

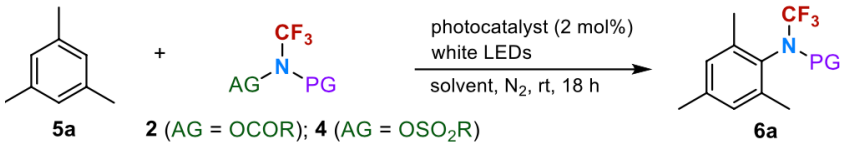
Xu, X., *et al., J. Org. Chem.* **2017**, *82*, 3702–3709

Constructing *N*-CF_3 hydroxylamine

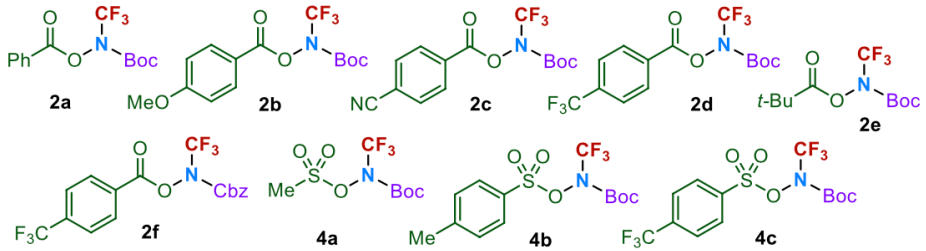


- Conversion proceeded in moderate ~ good yield.

Inserting *N*-CF_3 to C-H: Optimization



2 (AG = OCOR); 4 (AG = OSO_2R)



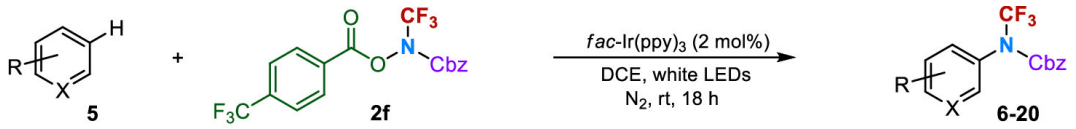
entry	reagent	photocatalyst	solvent	product	^{19}F NMR (%)[b]
1	**2a**	*fac*-Ir(ppy)$_3$	DCE	**6a** (PG = Boc)	62
2	**2b**	*fac*-Ir(ppy)$_3$	DCE	**6a** (PG = Boc)	0
3	**2c**	*fac*-Ir(ppy)$_3$	DCE	**6a** (PG = Boc)	53
4	**2d**	*fac*-Ir(ppy)$_3$	DCE	**6a** (PG = Boc)	67
5	**2e**	*fac*-Ir(ppy)$_3$	DCE	**6a** (PG = Boc)	0
6	**2f**	*fac*-Ir(ppy)$_3$	DCE	**6a** (PG = Cbz)	55
7	**4a**	*fac*-Ir(ppy)$_3$	DCE	**6a** (PG = Boc)	26
8	**4b**	*fac*-Ir(ppy)$_3$	DCE	**6a** (PG = Boc)	23
9	**4c**	*fac*-Ir(ppy)$_3$	DCE	**6a** (PG = Boc)	13
10	**2d**	Ru(bpy)$_3$Cl$_2$	DCE	**6a** (PG = Boc)	0
11	**2d**	*fac*-Ir(ppy)$_3$	MeCN	**6a** (PG = Boc)	14
12[c]	**2d**	*fac*-Ir(ppy)$_3$	DCE	**6a** (PG = Boc)	89
13[c,d]	**2f**	*fac*-Ir(ppy)$_3$	DCE	**6a** (PG = Cbz)	85
14[c,e]	**2f**	*fac*-Ir(ppy)$_3$	DCE	**6a** (PG = Cbz)	0
15[c]	**2f**	—	DCE	**6a** (PG = Cbz)	0

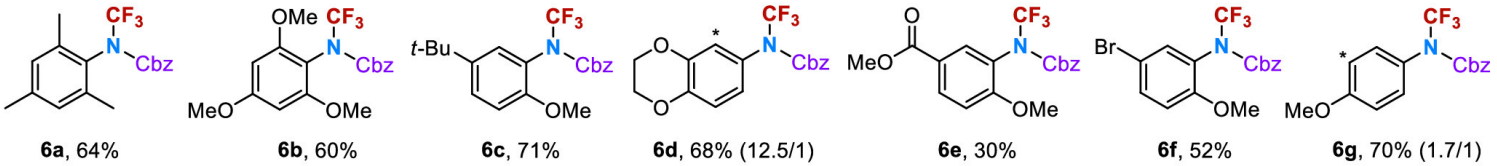
a Reaction conditions: **5a** (0.1 mmol), reagent **2** or **4** (0.15 mmol), photocatalyst (0.002 mmol), solvent (1.0 mL), white LEDs, under N2, rt, 18 h. *b* Yields were determined by 19F NMR spectroscopy using trifluoromethylbenzene as an internal standard. *c* **5a** (0.15 mmol), reagent **2** (0.1 mmol). *d* Note: reagent **2f** was selected because the Cbz is easily deprotected under mild conditions. *e* No light.

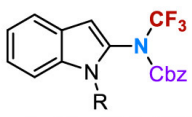
Xu, X., *et al., J. Am. Chem. Soc.* **2022**, *144*, 1962−1970

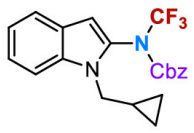
Substrate scope

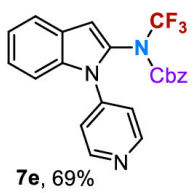
Xu, X., *et al., J. Am. Chem. Soc.* **2022**, *144*, 1962−1970

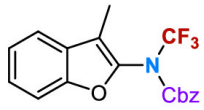


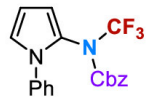


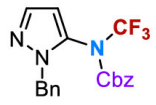


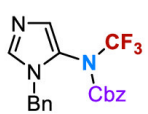


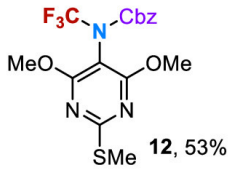


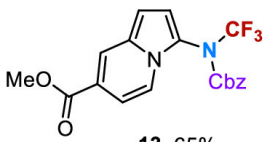


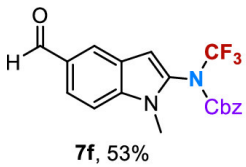


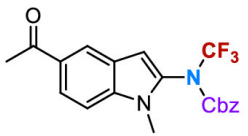


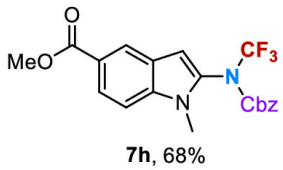


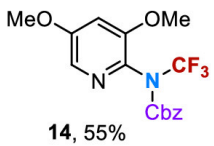


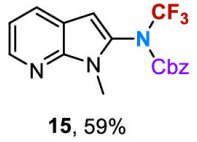


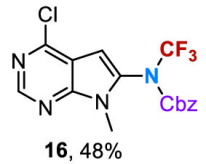


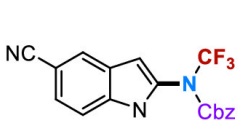


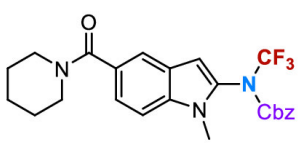


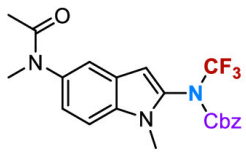


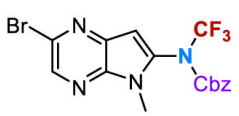


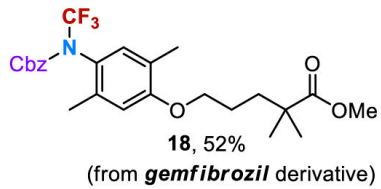


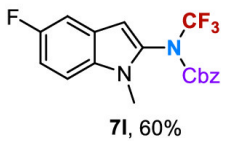


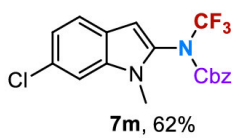


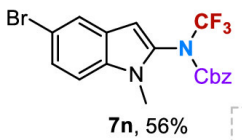


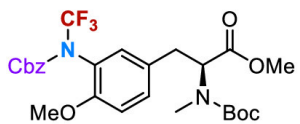


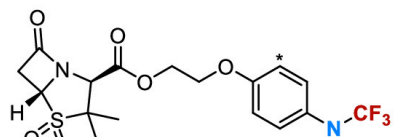


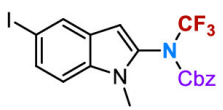


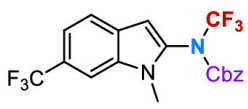


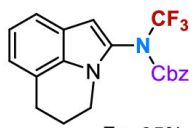




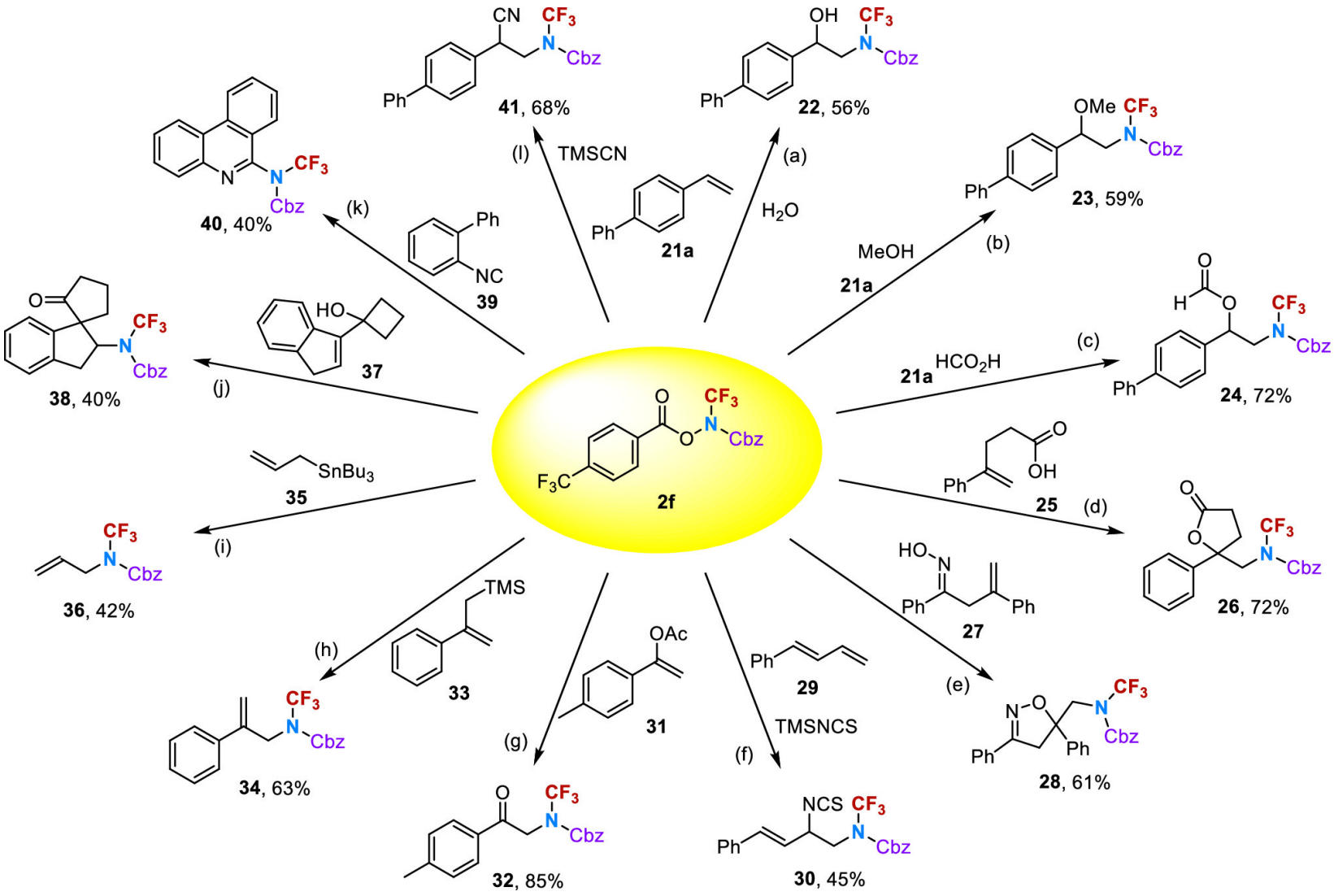






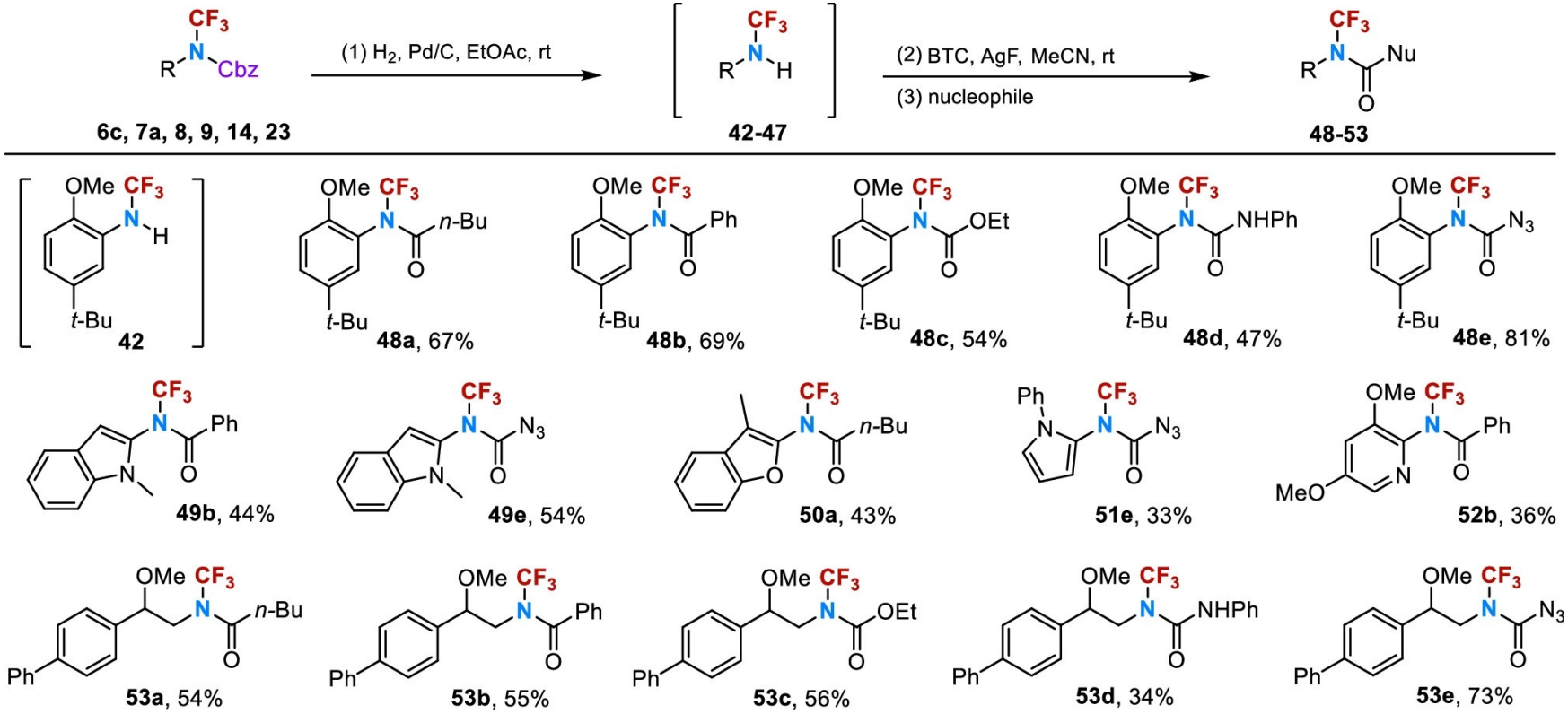


Substrate scope



Xu, X., *et al., J. Am. Chem. Soc.* **2022**, *144*, 1962−1970

Substrate scope

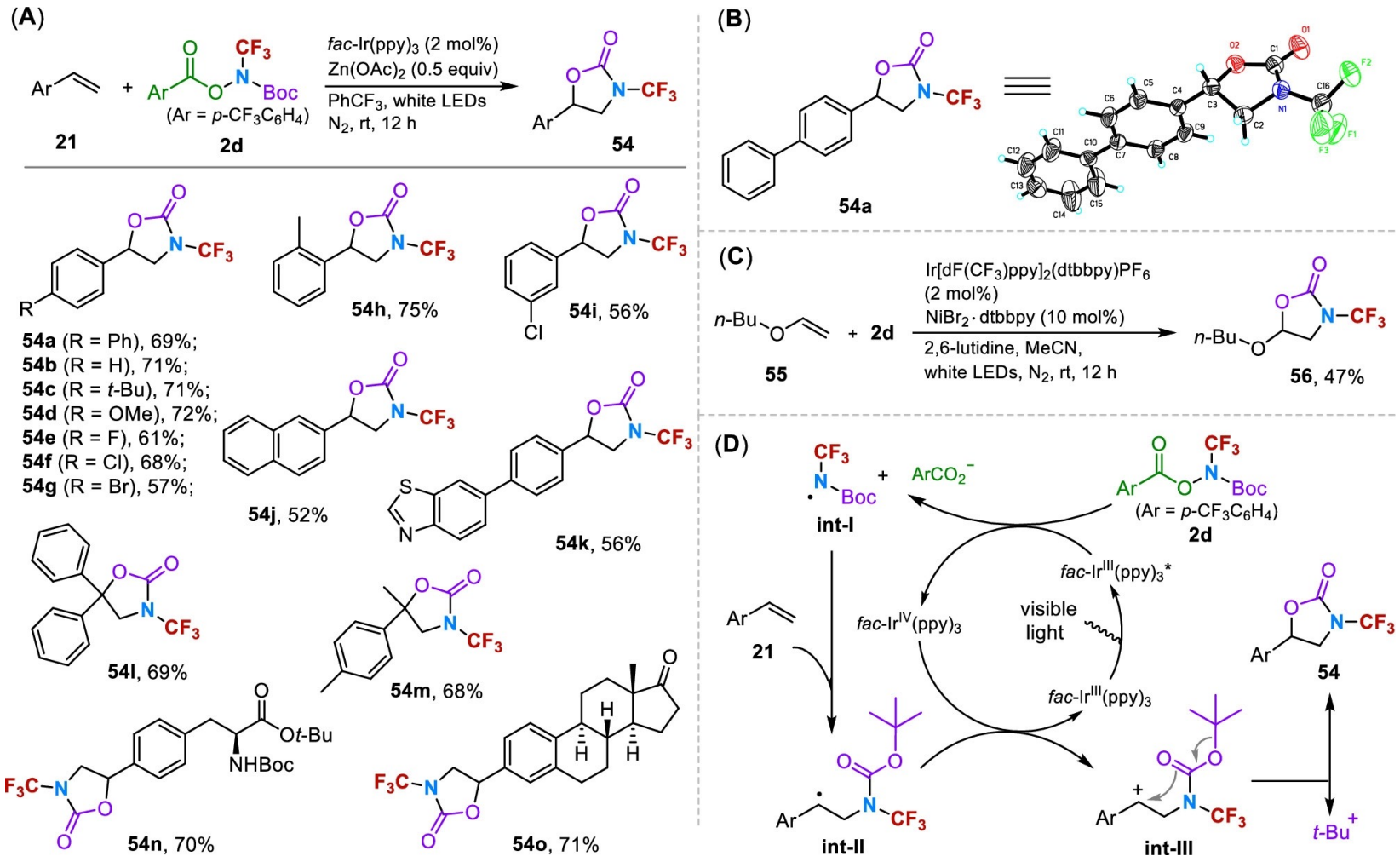


- Deprotection and further functionalization with Schoenebeck's system*.

Xu, X., *et al., J. Am. Chem. Soc.* **2022**, *144*, 1962−1970

* Schoenebeck, F., *et al., Nature* **2019**, *573*, 102−107.

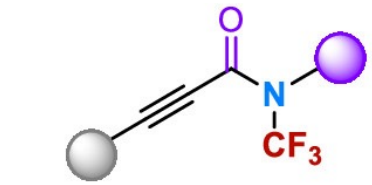
Constructing *N*-CF_3 amide



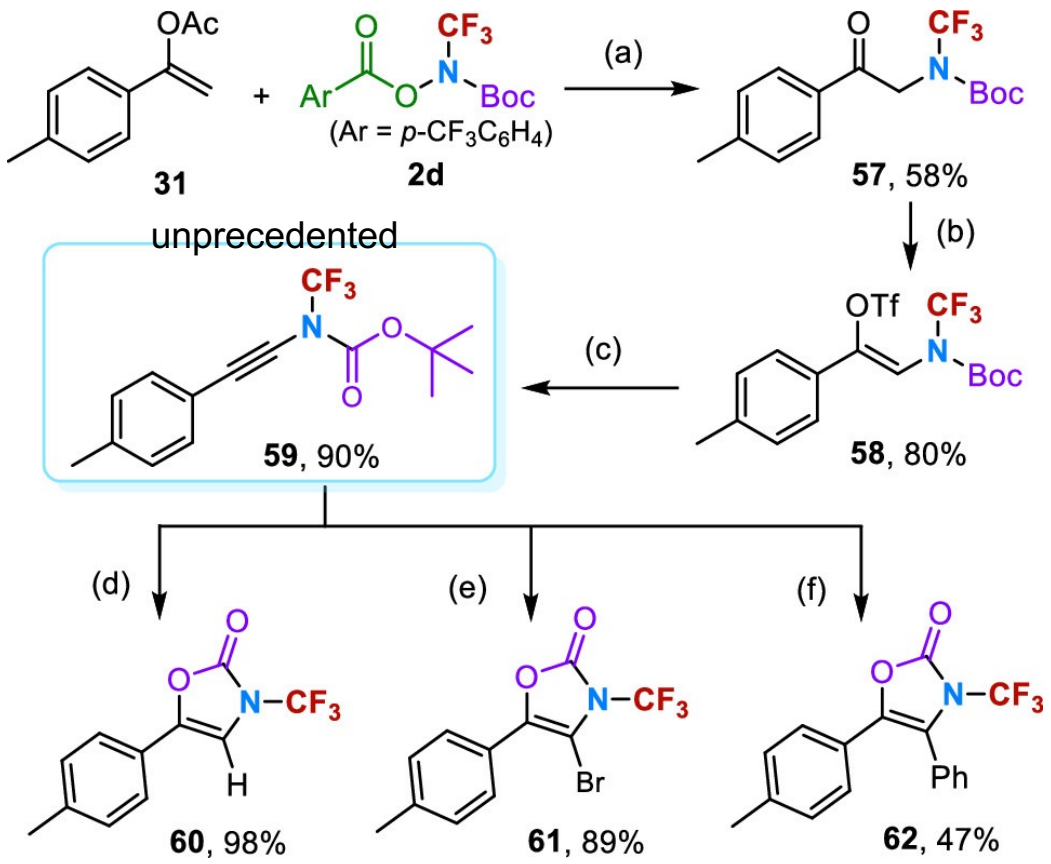
- Boc-protected amine afforded cyclized compound

Xu, X., *et al., J. Am. Chem. Soc.* **2022**, *144*, 1962−1970

Constructing unprecedented ynamide



N-CF_3 alkynamide (reported)



- Succeeded in synthesizing unprecedented ynamide

Xu, X., *et al., J. Am. Chem. Soc.* **2022**, *144*, 1962−1970

N-CF_3 alkynamide: Schoenebeck, F., *et al., J. Am. Chem. Soc.* **2021**, *143*,13029–13033

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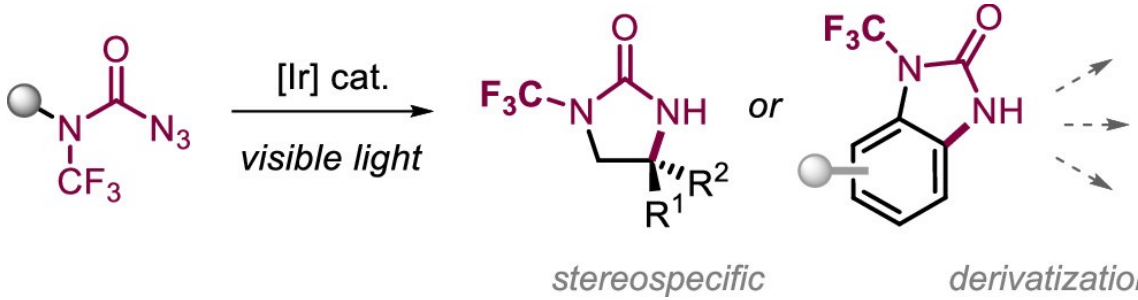
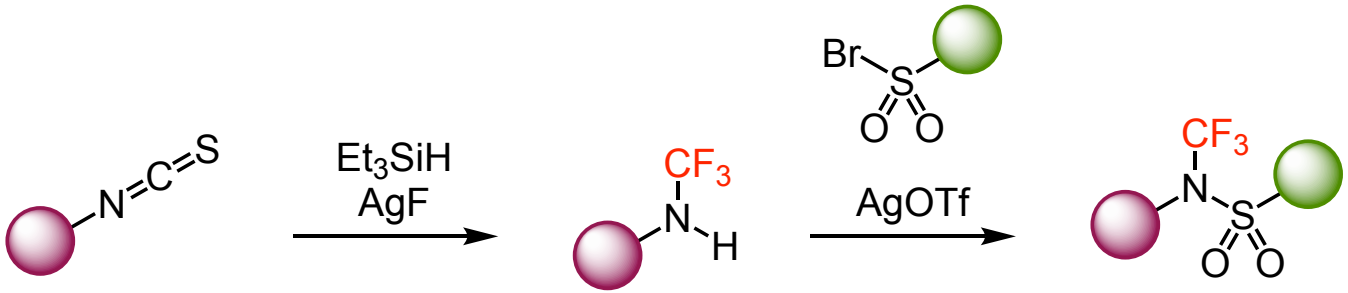


Schohenebeck, F., *et al., J. Am. Chem. Soc.* **2022**, *144*, 6100–6106



Yi. W., *et al., Angew. Chem., Int. Ed.* **2022**, accepted

Synthetic methodologies for various *N*-CF_3 compounds are now developed.

Lead to elucidating unique bioactivity

Summary

- Electrophilic direct *N*-trifluoromethylation is still difficult.

- CF_3 incorporation and derivatization is major strategy to construct *N*-CF_3 moiety.

- More simple and versatile methodology for *N*-CF_3 is emerging.

- Biological activity of *N*-CF_3 molecule will be elucidated in the future.