Chinese Journal of Chemistry
中国化学 - An International Journal

Accepted Article

Title: Silver-Mediated N-Trifluoromethylation of Amides and Peptides

Authors: Zhenzhen Zhang, Jiayan He, Lin Zhu, Haiwen Xiao, Yewen Fang,* and Chaozhong Li*

This manuscript has been accepted and appears as an Accepted Article online.

This work may now be cited as: *Chin. J. Chem.* **2020**, *38,* 10.1002/cjoc.202000132.

The final Version of Record (VoR) of it with formal page numbers will soon be published online in Early View: http://dx.doi.org/10.1002/cjoc.202000132.

WILEY-VCH SIOC CCS

ISSN 1001-604X • CN 31-1547/O6
mc.manuscriptcentral.com/cjoc
www.cjc.wiley-vch.de

Report

Keyword 1, Keyword 2, Keyword 3, Keyword 4, Keyword 5, Keyword 6

CJC Chinese Journal of Chemistry 中国化学 - An International Journal

Silver-Mediated N-Trifluoromethylation of Amides and Peptides

Zhenzhen Zhang,[a] Jiayan He,[a] Lin Zhu,[a] Haiwen Xiao,[a] Yewen Fang,*[, b] and Chaozhong Li*[, a, b]

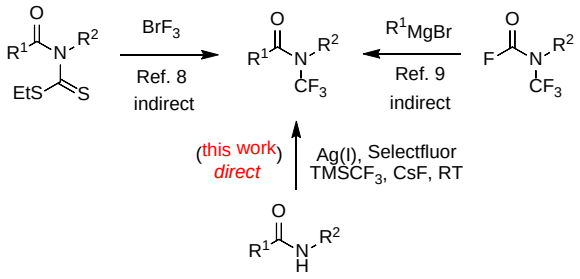
[a] *Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032*
[b] *School of Materials and Chemical Engineering, Ningbo University of Technology, 201 Fenghua Road, Ningbo 315211*

Cite this paper: *Chin. J. Chem.* **2019**, *37*, XXX—XXX. **DOI: 10.1002/cjoc.201900XXX**

We report herein the direct N-trifluoromethylation of *N*-H amides. Promoted by AgOTf and 2-fluoropyridine, the reaction of a variety of amides with Selectfluor, $TMSCF_3$ and CsF proceeds smoothly at room temperature leading to the corresponding N-trifluoromethylated products in satisfactory yields. The protocol is also applicable to amino acid derivatives, resulting in efficient and chemoselective N-trifluoromethylation of di- and tri-peptides with retention of configuration. A mechanism involving reductive elimination of Ag(III) intermediates to form N–CF_3 bonds is proposed.

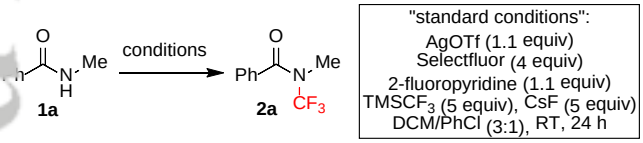
Trifluoromethyl groups exhibit a profound effect in properties such as lipophilicity, permeability and metabolic stability, and thus serve as important structural motifs in pharmaceuticals, agrochemicals and materials. Trifluoromethylation of organic molecules has therefore received considerable attention in the past decades.[1] However, the research in this field mainly focuses on C–CF_3 bond formations.[1] As a comparison, construction of N–CF_3 bonds remains challenging. *N*-Trifluoromethyl amines are typically prepared indirectly by reaction of dithiocarbamates, thiocarbamoyl fluorides, formamides or related compounds with fluorinating reagents such as SF_4, dialkylaminosulfur trifluorides or AgF.[2, 3] These approaches suffer from either harsh reaction conditions, the use of toxic reagents or poor functional group compatibility. Meanwhile, methods for direct introduction of CF_3 groups onto nitrogen atoms are rare and limited to electrophilic[4] or radical[5] N-trifluoromethylation of pyridines, azoles, imines or sulfoximines. The underdevelopment of N–CF_3 chemistry may also be attributed to the low stability of *N*-CF_3 amines that are prone to fluorine elimination because of the n(N)→σ*(C–F) electron donation. Aromatic and/or electron-withdrawing substitutions are generally required to make the amines isolable. However to our surprise, *N*-CF_3-substituted amides that are far more stable than *N*-CF_3 amines are far less explored. Yet, among the known *N*-(trifluoromethyl)amides, some exhibit important biological activities such as high anti-fungal or anti-HIV properties,[6] or serve as useful electrolyte additives for batteries.[7] Of the few relevant synthetic reports, Rozen and coworkers described the synthesis of *N*-(trifluoromethyl)amides by fluorination of *N*-acyldithiocarbamates with BrF_3 (Scheme 1).[8] Very recently, the Schoenebeck group introduced the reaction of isothiocyanates, bis(trichloromethyl) carbonate and AgF to generate *N*-trifluoromethylcarbamoyl fluorides, which then engaged in the reaction with Grignard reagents to provide N-trifluoromethylated amides.[9] These indirect syntheses are not suitable for late-stage modification of amides. Direct N-trifluoromethylation of *N*-H amides should be highly desirable given the low cost and easy availability of amides. However, there have been no reports to date of methods in his aspect. The few available procedures of electrophilic or radical N-trifluoromethylation mentioned above[4, 5] are not applicable to amides either. Also note that *N*-CF_3 amides are unlikely to be prepared from secondary *N*-CF_3 amines due to the instability and fast HF extrusion of the later. Herein we report the silver-mediated, direct N-trifluoromethylation of *N*-H amides and peptides (Scheme 1).

Scheme 1 Synthesis of *N*-(trifluoromethyl)amides



As a start, we selected *N*-methylbenzamide (**1a**) as the model substrate to explore the N-trifluoromethylation. After an extensive search of reaction conditions (see Tables S1–S7 in the Supporting Information for details), we were pleased to find that the reaction of **1a**, AgOTf (1.1 equiv), 2-fluoropyridine (1.1 equiv), Selectfluor (1-chloromethyl-4-fluorodiazoniabicyclo[2,2,2]octane bis(tetrafluoroborate))[10] (4 equiv), Ruppert–Prakash reagent[11] ($TMSCF_3$, 5 equiv) and CsF (5 equiv) in dichloromethane – chlorobenzene (3:1) solution at room temperature furnished the expected N-trifluoromethylation product **2a** in 74% isolated yield (entry 1, Table 1). Lowering the amount of Selectfluor to two equivalents led to a lower yield of **2a**, while no **2a** could be observed without Selectfluor (entries 2 and 3, Table 1). Switching the oxidant Selectfluor to *N*-fluorobis(benzenesulfonyl)imide (NFSI)[12] resulted in a sharp drop in product yield (entry 4, Table 1). Changing the CF_3 source to (bpy)$Zn(CF_3)_2$ (bpy = 2,2'-bipyridine)[13] or (bpy)$Cu(CF_3)_3$[14] yielded no desired product (entries 5 and 6, Table 1). The silver salt AgOTf proved to be essential for the transformation, as evidenced by control experiments (entries 7 and 8, Table 1). As a comparison, the use of $Cu(OTf)_2$ in place of AgOTf failed to give any product **2a** (entry 9, Table 1). In addition, a suitable ligand was also required for the reaction (entry 10, Table 1), and 2-fluoropyridine turned out to be superior over other ligands screened (see Table S2 in SI). Finally, reducing the loading of $TMSCF_3$ or CsF decreased the yield of **2a** (see Table S7 in SI).

Table 1 Optimization of reaction conditions

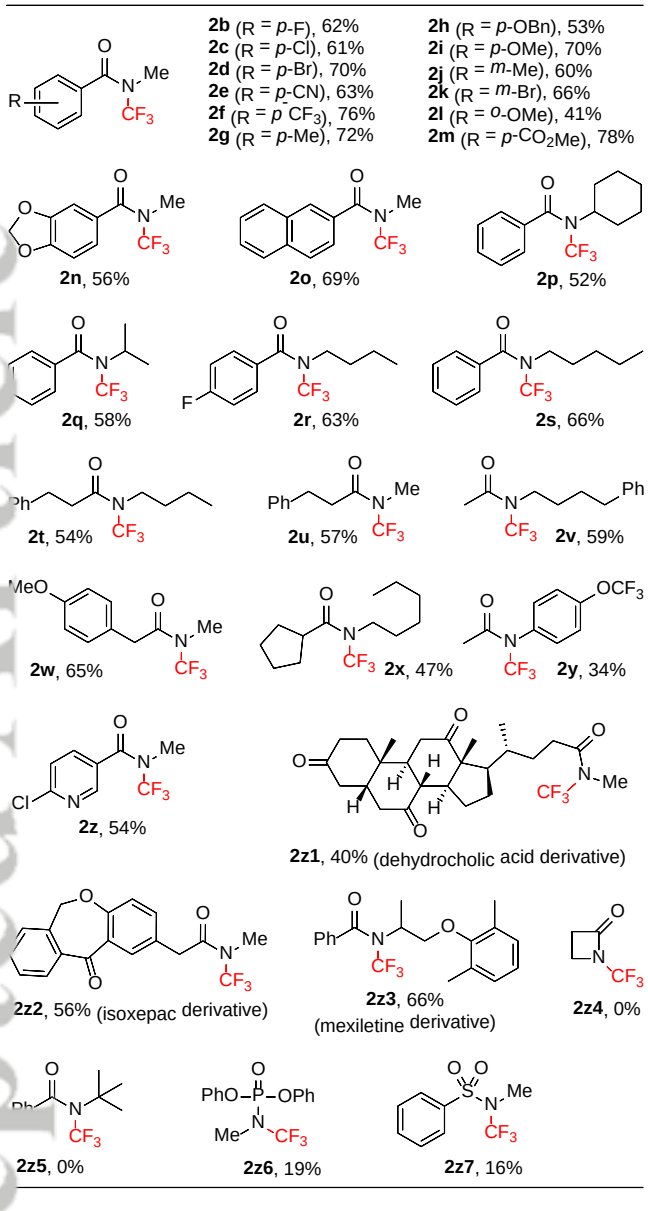


Entry[a]	Conditions	Yield (%)[b]
1	None	74
2	Less Selectfluor (2 equiv) used	58
3	Without Selectfluor	0
4	NFSI in place of Selectfluor	14
5	(bpy)$Zn(CF_3)_2$ in place of $TMSCF_3$/CsF	0
6	(bpy)$Cu(CF_3)_3$ in place of $TMSCF_3$/CsF	0
7	Less AgOTf (0.5 equiv) used	25
8	Without AgOTf	0
9	$Cu(OTf)_2$ in place of AgOTf	0
10	Without 2-fluoropyridine	< 5

[a] The reaction was carried out at 0.20 mmol scale in DCM (3.0 mL)–PhCl (1.0 mL) solution. [b] Isolated yield based on **1a**.

With the optimized conditions in hand (entry 1, Table 1), we set out to examine the scope of the method. As shown in Scheme 2, a number of *N*-methylbenzamides with either electron-withdrawing or electron-donating substituents on the aromatic ring all underwent N-trifluoromethylation, providing the expected products **2b–2o** in satisfactory yields. Benzamides with different *N*-alkyl-substitutions also participated in the reaction to afford the corresponding products **2p–2s**. The protocol was also applicable to a variety of *N*-alkylalkanamides, as exemplified by the synthesis of **2t–2x**. *N*-Arylamides could also be used as substrates to give *N*-CF_3 amides such as **2y**, albeit in a low efficiency. The presence of a range of functional group was tolerated by the process. For example, ethers, ketones, esters, nitriles and aryl halides (F, Cl, Br) all proved to be compatible with the reaction. The broad substrate scope enabled late-stage modification of complex molecules, as evidenced by the efficient synthesis of **2z1–2z3**. Nevertheless, the method had its limitation in that *N*-*tert*-butyl-substituted amides or lactams failed to produce the corresponding products (such as **2z4** and **2z5**) under the optimized conditions, and the reason remained unclear. However, a brief survey on N-nucleophiles other than amides revealed that N-trifluoromethylation of phosphonamides and sulfonamides (to give **2z6** and **2z7**) could also be achieved under the same conditions as above without further optimization. These results further expanded the substrate scope of the reaction.

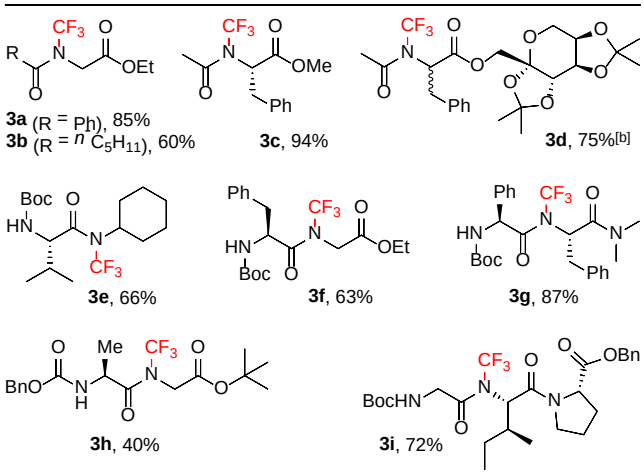
Scheme 2 N-Trifluoromethylation of amides[a]



[a] Reaction conditions: **1** (0.20 mmol), AgOTf (0.22 mmol), 2-fluoropyridine (0.22 mmol), Selectfluor (0.80 mmol), $TMSCF_3$ (1.00 mmol), CsF (1.00 mmol), DCM (3.0 mL), PhCl (1.0 mL), rt, 24 h. Isolated yield based on **1**.

We then extended the method to the N-trifluoromethylation of α-amino acid derivatives. Given the vital role of α-amino acids and peptides in life sciences, their *N*-CF_3 derivatives should be an interesting target in biological and medicinal chemistry. As illustrated in Scheme 3, ethyl *N*-Benzoylglycinate underwent smooth N-trifluoromethylation furnishing the corresponding product **3a** in a high yield. The *N*-hexanoyl analog **3b** could also be produced similarly. The reaction of methyl *N*-acyl-L-phenylalaninate proceeded nicely providing the *N*-CF_3 amide **3c** in an excellent yield with retention of configuration. Moreover, when glycosyl *N*-acylphenylalaninate as a diastereomeric mixture (37:63) was subjected to the optimized conditions, the corresponding product **3d** was obtained in the same diastereomeric ratio, thus confirming that the N-trifluoromethylation had no influence on the stereochemistry. Interestingly, *N*-Boc-protected *N*'-cyclohexyl-valinamide engaged in the trifluoromethylation leading to the exclusive formation of *N*'-CF_3 amides **3e** while the NHBoc moiety remained intact. The inertness of carbamates in the reaction was further demonstrated by the failure of naphthalene-1-yl methylcarbamate towards N-trifluoromethylation under the above optimized conditions. This unique chemoselectivity paved the road for selective N-trifluoromethylation of peptides. For example, the reaction of dipeptide Boc-Phe-Gly-OEt afforded the trifluoromethylated product **3f** in 63% yield. Analogously, Boc-Phg-Phe-NMe_2 was transformed into Boc-Phg-*N*-CF_3-Phe-NMe_2 (**3g**) highly efficiently. In a similar fashion, *N*-Cbz-protected Ala-Gly-O^{t}Bu was converted to Cbz-Ala-*N*-CF_3-Gly-O^{t}Bu (**3h**). The strategy could be further applied to the N-trifluoromethylation of tripeptides. As an example, *N*-CF_3 tripeptide **3i** was readily achieved from Boc-Gly-Ile-Glu-OBn in a high efficiency. Thus the method offers a convenient route to late-stage modification of polypeptides.

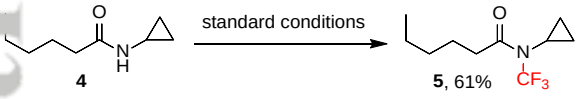
Scheme 3 N-Trifluoromethylation of α-amino acid derivatives[a]



[a] See Scheme 2. [b] d.r. = = 37:63 for both **3d** and its precursor.

To gain further insight into the N-trifluoromethylation, the following mechanistic experiments were carried out. The reaction of *N*-cyclopropylhexanamide (**4**) under the optimized conditions afforded the N-trifluoromethylated product **5** in 61% yield while no ring-opening products could be detected (eq 1). This radical clock experiment pointed out that amidyl radicals were unlikely to be involved in the N-trifluoromethylation. A careful examination on the reactions of *N*-alkylamides leading to **2s** and **2v** showed that no remote aliphatic or benzylic C–H trifluoromethylation[13b]

byproducts could be observed, also suggesting that amidyl radicals capable of 1,5-H abstraction were not generated under the experimental conditions. Furthermore, control experiments revealed that, in the absence of an amide substrate, the reaction produced the complex[15] $[(CF_3)_4Ag(III)]^-$ exclusively, as demonstrated by ^{19}F NMR analysis. Subsequent addition of amide **1a** into the resulting solution yielded no product **2a**, indicating that the stable $[(CF_3)_4Ag(III)]^-$ complex was not the active species responsible for the N-trifluoromethylation. On the other hand, ^{19}F NMR monitoring on the N-trifluoromethylation of **1a** showed that, along with the increasing formation of product **2a**, the $[(CF_3)_4Ag(III)]^-$ complex was also accumulated, implying that the two processes were competing with each other (see SI for details).



(1)

A plausible mechanism is then proposed as depicted in Figure 1. Interaction of AgOTf with 2-fluoropyridine and CF_3^- anion derived from $TMSCF_3$/CsF generates Ag(I)–CF_3 intermediate[16] that is then oxidized by Selectfluor to give the Ag(III)–CF_3 species **A**.[17, 18] In the meantime, deprotonation of an amide by CF_3^- anion gives the corresponding amidyl anion. Ligand exchange of **A** with the amidyl anion produces the Ag(III)-complex **B**, which undergoes reductive elimination to provide the N-trifluoromethylated amide. Alternatively, ligand exchange of intermediate **A** with CF_3^- anions may also take place to form the unreactive $[(CF_3)_4Ag(III)]^-$ complex. This competing process accounts for the requirement of stoichiometric amount of AgOTf. The inability of *N-tert*-butyl amides (such as **1z4**) in N-trifluoromethylation might be attributed to the steric effect in retarding the formation of key intermediate **B**. While the reason is unclear for the no-reaction of lactams and carbamates, the conformational difference between lactams and ordinary amides might play a role. Our best guess is that the coordination of a lactam or carbamate to **A** should lead to intermediate **C** that is destabilized by the possible lone pair–lone pair electron repulsion[19] between the carbonyl oxygen and the fluorine atoms of the adjacent CF_3 group. Such an interaction is not present in intermediate **B**. More mechanistic investigation is certainly required to have a detailed understanding on the mechanism.

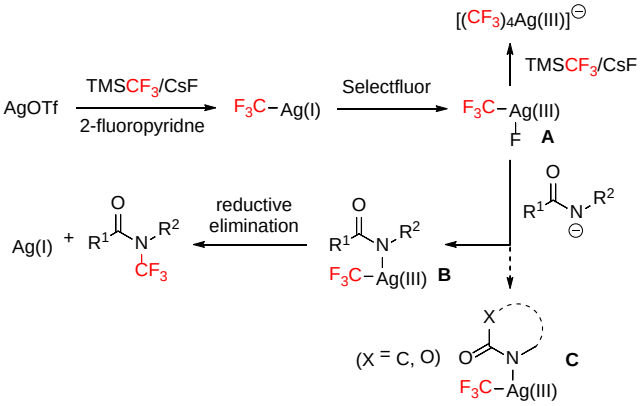


Figure 1 Proposed mechanism.

In conclusion, we have successfully developed the silver-mediated N-trifluoromethylation of *N*-H amides, providing a straightforward access to *N*-CF_3 amides. The unprecedented protocol also enables the efficient and chemoselective N-trifluoromethylation of polypeptides. As the procedure is operationally simple and the conditions are mild, the method should find application in the synthesis of important N-trifluoromethylated molecules.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement

This project was supported by the National Natural Science Foundation of China (Grants 21421002, 21532008, 21871285 and 21971253), by the Chinese Academy of Sciences (Grants XDB20020000 and ZDBS-LY-SLH026) and by Zhejiang Provincial Natural Science Foundation of China (Grant LY20B020008).

References

[1] (a) Koike, T.; Akita, M. Fine Design of Photoredox Systems for Catalytic Fluoromethylation of Carbon-Carbon Multiple Bonds. *Acc. Chem. Res.* **2016**, *49*, 1937–1945. (b) Charpentier, J.; Fruh, N.; Togni, A. Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents. *Chem. Rev.* **2015**, *115*, 650–682. (c) Alonso, C.; de Marigorta, E. M.; Rubiales, G.; Palacios, F. Carbon Trifluoromethylation Reactions of Hydrocarbon Derivatives and Heteroarenes. *Chem. Rev.* **2015**, *115*, 1847–1935. (d) Egami, H.; Sodeoka, M. Trifluoromethylation of Alkenes with Concomitant Introduction of Additional Functional Groups. *Angew. Chem. Int. Ed.* **2014**, *53*, 8294–8308. (e) Koike, T.; Akita, M. Trifluoromethylation by Visible-Light-Driven Photoredox Catalysis. *Top. Catal.* **2014**, *57*, 967–974. (f) Merino, E.; Nevado, C. Addition of CF_3 Across Unsaturated Moieties: A Powerful Functionalization Tool. *Chem. Soc. Rev.* **2014**, *43*, 6598–6608. (g) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of Fluorine and Fluoro-Containing Functional Groups. *Angew. Chem.*

Int. Ed. **2013**, *52*, 8214–8264. (h) Studer, A. A "Renaissance" in Radical Trifluoromethylation. *Angew. Chem. Int. Ed.* **2012**, *51*, 8950–8958. (i) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. Asymmetric Construction of Stereogenic Carbon Centers Featuring a Trifluoromethyl Group from Prochiral Trifluoromethylated Substrates. *Chem. Rev.* **2011**, *111*, 455–529. (j) Shibata, N.; Matsnev, A.; Cahard, D. Shelf-Stable Electrophilic Trifluoromethylating Reagents: A Brief Historical Perspective. *Beilstein J. Org. Chem.* **2010**, *6*, 65. (k) Schlosser, M. CF_3-Bearing Aromatic and Heterocyclic Building Blocks. *Angew. Chem. Int. Ed.* **2006**, *45*, 5432–5446. (l) Umemoto, T. Electrophilic Perfluoroalkylating Agents. *Chem. Rev.* **1996**, *96*, 1757–1778. (l) Xie, Q.; Hu, J. Chen's Reagent: A Versatile Reagent for Trifluoromethylation, Difluoromethylenation, and Difluoroalkylation in Organic Synthesis. *Chin. J. Chem.* **2020**, *38*, 202–212. (m) Zhu, L.; Fang, Y.; Li, C. Trifluoromethylation of Alkyl Radicals: Breakthrough and Challenges. *Chin. J. Chem.* **2020**, *38*, DOI: 10.1002/cjoc.202000095.

[2] (a) Harder, R. J.; Smith, W. C. Chemistry of Sulfur Tetrafluoride. VI. Fluorination of Thiocarbonyl Compounds. *J. Am. Chem. Soc.* **1961**, *83*, 3422–3424. (b) Markovskij, L. N.; Pashinnik, V. E.; Kirsanov, A. V. Application of Dialkylaminosulfur Trifluorides in the Synthesis of Fluoroorganic Compounds. *Synthesis* **1973**, 787–789. (c) Kuroboshi, M.; Hiyama, T. A Facile Synthesis of Trifluoromethylamines by Oxidative Desulfurization-Fluorination of Dithiocarbamates. *Tetrahedron Lett.* **1992**, *33*, 4177–4178. (d) Kanie, K.; Mizuno, K.; Kuroboshi, M.; Hiyama, T. A Facile Synthesis of Trifluoromethylamines by Oxidative Desulfurization-Fluorination of Dithiocarbamates. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1973–1991. (e) Tyrra, W. Die Desulfonierung–Fluorierung von Thiuramdisulfiden, $[R_2NC(S)S]_2$ und Silberdithiocarbamaten, $Ag[SC(S)NR_2]$ (R = CH_3, CH_3CH_2, $C_6H_5CH_2$), mit Silber(I)fluorid, AgF – ein Einfacher Zugang zu Diorgano(trifluoromethyl)aminen, R_2NCF_3, und Thiocarbamoylfluoriden, $R_2NC(S)F$. *J. Fluorine Chem.* **2001**, *109*, 189–194. (f) Hagooly, Y.; Rozen, S. Pyridine•BrF_3, the Missing Link for Clean Fluorinations of Aromatic Derivatives. *Org. Lett.* **2012**, *14*, 1114–1117. (g) Yu, J.; Lin, J.-H.; Xiao, J.-C. Reaction of Thiocarbonyl Fluoride Generated from Difluorocarbene with Amines. *Angew. Chem. Int. Ed.* **2017**, *56*, 16669–16673. (h) Scattolin, T.; Deckers, K.; Schoenebeck, F. Efficient Synthesis of Trifluoromethyl Amines through a Formal Umpolung Strategy from the Bench-Stable Precursor $(Me_4N)SCF_3$. *Angew. Chem.* **2017**, *129*, 227–230.

[3] (a) Klauke, E. Preparation and Properties of Substances with *N*- or *S*-Perhalogenmethyl Groups. *Angew. Chem. Int. Ed.* **1966**, *5*, 848. (b) Dmowski, W.; Kaminski, M. Reaction of Tertiary Formamides with Sulfur Tetrafluoride. Direct Synthesis of (Trifluoromethyl)amines. *J. Fluorine Chem.* **1983**, *23*, 207–218. (c) Abe, T.; Hayashi, E.; Baba, H.; Fukaya, H. The Electrochemical Fluorination of Nitrogen-Containing Carboxylic Acids. Fluorination of Dimethylamino- or Diethylamino-Substituted Carboxylic Acid Derivatives. *J. Fluorine Chem.* **1990**, *48*, 257–279. (d) Pawelke, G. Reaction of Tetrakis(dimethylamino)ethylene with CF_2Br_2 in the Presence of Secondary Amines, Formation of *N*-Trifluoromethyl-Dialkylamines. *J. Fluorine Chem.* **1991**, *52*, 229–234.

[4] (a) Umemoto, T.; Adachi, K.; Ishihara, S. CF_3 Oxonium Salts, *O*-(Trifluoromethyl)dibenzofuranium Salts: in situ Synthesis, Properties, and Application as a Real CF_3^+ Species Reagent. *J. Org. Chem.* **2007**, *72*, 6905–6917. (b) Niedermann, K.; Fruh, N.; Vinogradova, E.; Wiehn, M. S.; Moreno, A.; Togni, A. A Ritter-type Reaction: Direct Electrophilic Trifluoromethylation at Nitrogen Atoms Using Hypervalent Iodine Reagents. *Angew. Chem. Int. Ed.* **2011**, *50*, 1059–1063. (c) Niedermann, K.; Fruh, N.; Senn, R.; Czarniecki, B.; Verel, R.; Togni, A. Direct Electrophilic N-Trifluoromethylation of Azoles by a Hypervalent Iodine Reagent. *Angew. Chem. Int. Ed.* **2012**, *51*, 6511–6515. (d) Zheng, G.; Ma, X.; Li, J.; Zhu, D.; Wang, M. Electrophilic *N*-Trifluoromethylation of N–H Ketimines. *J. Org. Chem.* **2015**, *80*, 8910–8915.

[5] Teng, F.; Cheng, J.; Bolm, C. Silver-Mediated *N*-Trifluoromethylation of Sulfoximines. *Org. Lett.* **2015**, *17*, 3166–3169.

[6] (a) Vuettner, G.; Klaude, E.; Oehlmann, L.; Kaspers, H. *Ger. Offen. DE 2218362 19731108*, **1973** [*Chem. Abstr.* **1974**, *80*, 27280]. (b) Sahu, K. K.; Ravichandran, V.; Mourya, V. K.; Agrawal, R. K. QSAR Analysis of Caffeoyl Naphthalene Sulfonamide Derivatives as HIV-1 Integrase Inhibitors. *Med. Chem. Res.* **2007**, *15*, 418–430.

[7] Yoon, S.; Cho, J.; Lee, H. *PCT Int. Appl. WO 2008010665*, **2008** [*Chem. Abstr.* **2008**, *148*, 195277].

[8] Hagooly, Y.; Gatenyo, J.; Hagooly, A.; Rozen, S. Toward the Synthesis of the Rare *N*-(Trifluoromethyl)amides and the *N*-(Difluoromethylene)-*N*-(trifluoromethyl)amines $[RN(CF_3)CF_2R']$ Using BrF_3. *J. Org. Chem.* **2009**, *74*, 8578–8582.

[9] Scattolin, T.; Bouayad-Gervais, S.; Schoenebeck, F. Straightforward Access to *N*-Trifluoromethyl Amides, Carbamates, Thiocarbamates and Ureas. *Nature* **2019**, *573*, 102–107.

[10] (a) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. 1-Alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane Salts: a Novel Family of Electrophilic Fluorinating Agents. *J. Chem. Soc., Chem. Commun.* **1992**, 595–596. (b) Singh, R. P.; Shreeve, J. M. Recent Highlights in Electrophilic Fluorination with 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane Bis(tetra-fluoroborate). *Acc. Chem. Res.* **2004**, *37*, 31–44. (c) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. Selectfluor: Mechanistic Insight and Applications. *Angew. Chem. Int. Ed.* **2005**, *44*, 192–212.

[11] (a) Ruppert, I.; Schlich, K.; Volbach, W. Die Ersten CF_3-substituierten Organyl(chlor)silane. *Tetrahedron Lett.* **1984**, *25*, 2195–2198. (b) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. Synthetic Methods and Reactions. 141. Fluoride-induced Trifluoromethylation of Carbonyl Compounds with Trifluoromethyltrimethylsilane (TMS-CF_3). A Trifluoromethide Equivalent. *J. Am. Chem. Soc.* **1989**, *111*, 393–395. (c) Shibata, N.; Mizuta, S.; Kawai, H. Recent Advances in Enantioselective Trifluoromethylation Reactions. *Tetrahedron: Asymmetry* **2008**, *19*, 2633–2752.

[12] Differding, E.; Ofner, H. *N*-Fluorobenzenesulfonimide: A Practical Reagent for Electrophilic Fluorinations. *Synlett* **1991**, 187–189.

[13] (a) Aikawa, K.; Toya, W.; Nakamura, Y.; Mikami, K. Development of (Trifluoromethyl)zinc Reagent as Trifluoromethyl Anion and Difluorocarbene Sources. *Org. Lett.* **2015**, *17*, 4996–4999. (b) Liu, Z.; Xiao, H.; Zhang, B.; Shen, H.; Zhu, L.; Li, C. Copper-Catalyzed Remote C(sp^3)–H Trifluoromethylation of Carboxamides and Sulfonamides. *Angew. Chem. Int. Ed.* **2019**, *58*, 2510–2513. (c) Xiao, H.; Liu, Z.; Shen, H.; Zhang, B.; Zhu, L.; Li, C. Copper-Catalyzed Late-Stage Benzylic C(sp^3)–H Trifluoromethylation. *Chem* **2019**, *5*, 940–949. (d) Xiao, H.; Shen, H.; Zhu, L.; Li, C. Copper-Catalyzed Radical Aminotrifluoromethylation of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 11440–11445.

[14] (a) Romine, A. M.; Nebra, N.; Konovalov, A. I.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. Easy Access to the Copper(III) Anion $[Cu(CF_3)_4]^-$. *Angew. Chem. Int. Ed.* **2015**, *54*, 2745–2749. (b) Shen, H.; Liu, Z.; Zhang, P.; Tan, X.; Zhang, Z.; Li, C. Trifluoromethylation of Alkyl Radicals in Aqueous Solution. *J. Am. Chem. Soc.* **2017**, *139*, 9843–9846. (c) Tan, X.; Liu, Z.; Shen, H.; Zhang, P.; Zhang, Z.; Li, C. Silver-Catalyzed Decarboxylative Trifluoromethylation of Aliphatic Carboxylic Acids. *J. Am. Chem. Soc.* **2017**, *139*, 12430–12433. (d) Paeth, M.; Carson, W.; Luo, J.-H.; Tierney, D.; Cao, Z.; Cheng, M.-J.; Liu, W. Copper-Mediated Trifluoromethylation of Benzylic Csp^3–H Bonds. *Chem. Eur. J.* **2018**, *24*, 11559–11563. (e) Guo, S.; AbuSalim, D. I.; Cook, S. P. Aqueous Benzylic C–H Trifluoromethylation for Late-Stage Functionalization. *J. Am. Chem. Soc.* **2018**, *140*, 12378–12382. (f) Zhang, Z.; Zhu, L.; Li, C. Copper-Catalyzed Carbotrifluoromethylation of Unactivated Alkenes Driven by Trifluoromethylation of Alkyl Radicals. *Chin. J. Chem.* **2019**, *37*, 452–456.

[15] (a) Eujen, R.; Hoge, B.; Brauer, D. J. Preparation and NMR Spectra of the (Trifluoromethyl)argentates(III) $[Ag(CF_3)_nX_{4-n}]^-$, with X = CN (*n* = 1–3), CH_3, $C{\equiv}CC_6H_{11}$, Cl, Br (*n* = 2, 3), and I (*n* = 3), and of Related Silver(III) Compounds. Structures of $[PPh_4][trans\text{-}Ag(CF_3)_2(CN)_2]$ and $[PPh_4][Ag(CF_3)_3(CH_3)]$. *Inorg. Chem.* **1997**, *36*, 1464–1475. (b) Joven-Sancho, D.; Baya, M.; Martin, A.; Menjon, B. Homoleptic Trifluoromethyl Derivatives of Ag(I) and Ag(III). *Chem. Eur. J.* **2018**, *24*, 13098–13101.

[16] Tyrra, W.; Naumann, D. Perfluoroorganosilver(I) Compounds. *J Fluorine Chem.* **2004**, *125*, 823–830.

[17] (a) Yin, F.; Wang, Z.; Li, Z.; Li, C. Silver-Catalyzed Decarboxylative Fluorination of Aliphatic Carboxylic Acids in Aqueous Solution. *J. Am. Chem. Soc.* **2012**, *134*, 10401–10404. (b) Li, Z.; Song, L.; Li, C. Silver-Catalyzed Radical Aminofluorination of Unactivated Alkenes in Aqueous Media. *J. Am. Chem. Soc.* **2013**, *135*, 4640–4643. (c) Zhang, C.; Li, Z.; Zhu, L.; Yu, L.; Wang, Z.; Li, C. Silver-Catalyzed Radical Phosphonofluorination of Unactivated Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 14082–14085. (d) Li, Z.; Wang, Z.; Zhu, L.; Tan, X.; Li, C. Silver-Catalyzed Radical Fluorination of Alkylboronates in Aqueous Solution. *J. Am. Chem. Soc.* **2014**, *136*, 16439–16443.

[18] (a) Liu, J.-B.; Chen, C.; Chu, L.; Chen, Z.-H.; Xu, X.-H.; Qing, F.-L. Silver-Mediated Oxidative Trifluoromethylation of Phenols: Direct Synthesis of Aryl Trifluoromethyl Ethers. *Angew. Chem. Int. Ed.* **2015**, *54*, 11839–11842. (b) Liu, J.-B.; Xu, X.-H.; Qing, F.-L. Silver-Mediated Oxidative Trifluoromethylation of Alcohols to Alkyl Trifluoromethyl Ethers. *Org. Lett.* **2015**, *17*, 5048–5051.

[19] For selected examples of the effect of lone-pair electron repulsion in organic synthesis, see: (a) Yuan, X.; Liu, K.; Li, C. Development of Highly Regioselective Amidyl Radical Cyclization Based on Lone Pair – Lone Pair Repulsion. *J. Org. Chem.* **2008**, *73*, 6166–6171. (b) Hu, T.; Liu, K.; Shen, M.; Yuan, X.; Tang, Y.; Li, C. O-Attack Versus N-Attack: Electrophilic Halocyclization of Unsaturated Amides with Vinylic Halogen Substitution. *J. Org. Chem.* **2007**, *72*, 8555–8558. (c) Lu, H.; Chen, Q.; Li, C. Control of the Regioselectivity of Sulfonamidyl Radical Cyclization by Vinylic Halogen Substitution. *J. Org. Chem.* **2007**, *72*, 2564–2569. (d) Hu, T.; Shen, M.; Chen, Q.; Li, C. Pushing Radical Cyclization from Regioselective to Regiospecific: Cyclization of Amidyl Radicals Controlled by Vinylic Halogen Substitution. *Org. Lett.* **2006**, *8*, 2647 –2650.

(The following will be filled in by the editorial staff)

Manuscript received: XXXX, 2019

Manuscript revised: XXXX, 2019

Manuscript accepted: XXXX, 2019

Accepted manuscript online: XXXX, 2019

Version of record online: XXXX, 2019

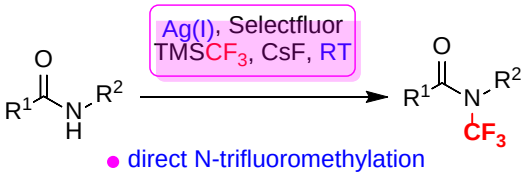
Entry for the Table of Contents

Page No.

Silver-Mediated N-Trifluoromethylation of Amides and Peptides

Zhenzhen Zhang, Jiayan He, Lin Zhu, Haiwen Xiao, Yewen Fang,* Chaozhong Li*

Max. Table height 6 cm



- direct N-trifluoromethylation
- retention of configuration
- applicable to peptides
- chemoselective

Direct and chemoselective N-trifluoromethylation of amides and peptides was achieved under mild conditions with retention of configuration.

[a] *Department, Institution, Address 1*
E-mail:

[b] *Department, Institution, Address 2*
E-mail:

[c] *Department, Institution, Address 3*
E-mail: