Nucleophilic trifluoromethoxylation of alkyl halides without silver

Yan Li¹, Yang Yang¹, Jinrui Xin¹ & Pingping Tang¹*  

The biological properties of molecules containing the trifluoromethoxy group have made these compounds important targets in pharmaceuticals and agrochemicals, yet their preparation is still a substantial challenge. Herein, we present a practical nucleophilic trifluoromethoxylation of alkyl halides with (E)-O-trifluoromethyl-benzaldoximes (TFBO) as a trifluoromethoxylation reagent in the absence of silver under mild reaction conditions. The trifluoromethoxylation reagent TFBO is easily prepared and thermally stable, and can release CF₃O⁻ species in the presence of a base. Furthermore, broad scope and good functional group compatibility are demonstrated by application of the method to the late-stage trifluoromethoxylation of alkyl halides in complex small molecules.
A growing number of fluorine-containing organic compounds have widespread application in the fields of pharmaceuticals, pesticides and materials because of irreplaceable properties of fluoriode. The incorporation of fluorine-containing groups has been an efficient strategy for the design of new drugs and agrochemical. In recent years, the late-stage and selective fluorination reaction of organic molecules has received significant attention, especially the trifluoromethylation reaction, which is one of the most important research hotspots, as the trifluoromethoxy group’s electron-withdrawing effects and high lipophilicity (Hansch parameter π_x = 1.04)6–10. However, the trifluoromethylation reaction remains limitations and challenges, such as limited trifluoromethylation reagents and instability of trifluoromethoxide anion, which impedes its development and application.11–14

The synthesis of trifluoromethyl ethers can be achieved by indirect strategies and direct strategies. The indirect strategies include the nucleophilic fluorination of ether groups15–17 and electrophilic trifluoromethylation of hydroxyl groups18–23 which suffered from poor substrate scope, harsh reaction conditions and use of highly toxic reagents. The direct strategies are the direct introduction of the trifluoromethoxy group into organic compounds with trifluoromethylation reagents.24 For example, tris(dimethylamino)sulfonium trifluoromethoxide (TASOCF₃) was used as a trifluoromethylation reagent by Ritter’s group to achieve the direct trifluoromethylation of aryl stannanes and aryl boronic acids with equivalent silver.25 Liu group reported a palladium-catalyzed intramolecular aminotrifluoromethylation of alkenes with AgOCF₃ or CsOCF₃ as the trifluoromethylation reagent.26,27 The catalytic C(sp³)–H trifluoromethylation of arynes with the new N-OCF₃ reagents under photocatalytic conditions had been reported by Ngai and Togni, respectively.28–30 One of the simplest methods for the formation of the C(sp³)-OCF₃ group is the nucleophilic substitution because of widely available leaving groups and inexpensive starting materials.31–37 However, due to the poor nucleophilicity and instability of trifluoromethoxide anion, most of the known nucleophilic trifluoromethylation methods require to use activated electrophiles such as allylic halides, benzylic halides or α-halo carbonyl compounds with few exceptions, and available trifluoromethoxide anion (“OCF₃“) sources are scarce and usually suffer from disadvantages (Fig. 1a).38 For example, direct nucleophilic trifluoromethylation of alkyl iodides or bromides with trifluoromethyl triflate (TFMT)39,40, 2,4-dinitro(trifluoromethoxy)benzene (DNTFB)33 or trifluoromethyl benzoate (TFBz)37 were reported. However, less than 10% yield of desired products were achieved.

---

**Fig. 1 Reaction design.** a) Trifluoromethylation reagents. b) Preparation of (E)-O-trifluoromethyl-benzaldoximes (TFBO). c) The current method for nucleophilic trifluoromethylation of alkyl halides without silver.
obtained with unactivated alkyl iodide such as citronellyl iodide in the absence of silver, and trifluoromethoxide anion (CF$_3$O$^-$) was generated from these reagents under the activation of a fluoride salt, which might form the fluorinated byproduct. Furthermore, only one example of trifluoromethylation of benzyl chloride with AgOCF$_3$ was reported to generate the desired product in 29% yield$^{32}$, and no method is reported to achieve the trifluoromethylation of unactivated alkyl halides in the absence of silver. Therefore, the development of an efficient method for nucleophilic trifluoromethylation of unactivated alkyl halides with a trifluoromethylation reagent in the absence of silver is highly desirable.

We envisioned developing a trifluoromethylation reagent which is active enough to readily release CF$_3$O$^-$ without the activation of nucleophiles such as fluoride salts. Inspired by alkoxy anion generated from the base-promoted elimination reactions of (E)-O-alkyl-benzaldoximes$^{41}$, we were wondering whether (E)-O-trifluoromethyl-benzaldoximes (TFBO) can be prepared and used as a trifluoromethylation reagent if a suitable base is found to activate the reagent to generate trifluoromethoxide anion in situ, which would react with unactivated alkyl halides. (Fig. 1b) Herein, we report the development of (E)-O-trifluoromethyl-benzaldoximes (TFBO) as a trifluoromethylation reagent, which can be easily prepared from benzyl aldehydes and N-trifluoromethoxy phthalimide$^{42}$ in modest yields. TFBO is shelf-stable and can be easily activated by the base to release CF$_3$O$^-$ species (Fig. 1b). With (E)-O-trifluoromethyl-benzaldoximes (TFBO) as a trifluoromethylation reagent, an efficient nucleophilic trifluoromethylation of unactivated alkyl halides in the absence of silver is reported. This reaction is operationally simple, scalable, and which shows potential value in the field of drug synthesis (Fig. 1c).

**Results**

**Investigations of reaction conditions and scope.** The initial efforts were focused on the reaction of 5-iodopentyl 4-fluorobenzoate 2 with various (E)-O-trifluoromethyl-benzaldoximes (TFBO) in the presence of a base. As briefly illustrated in Fig. 2a, the use of a base was crucial for achieving an efficient transformation in the presence of TFBO, and Cs$_2$CO$_3$ was found to give the highest yield. Changing the base to other organic bases Et$_3$N, DBU or inorganic bases KO'Bu, CsF, Na$_2$CO$_3$, K$_2$CO$_3$ resulted in lower yields. Next, a thorough evaluation of different TFBOs revealed that substituents on the aromatic rings influenced the reaction yields, and the (E)-O-trifluoromethyl-4-tert-butyl-benzaldoximes 1a was found to be particularly effective. The control experiments were performed and no desired product was observed in the absence of a base. Monitoring of the reaction between TFBO (1a) and Cs$_2$CO$_3$ by $^{19}$F NMR spectroscopy indicated that CsOCF$_3$ (−20.9 ppm) and aryl nitrile were generated in the reaction (Fig. 2b)$^{31}$. After thoroughly optimizing the reaction conditions, reactions with 3.5 equiv. of Cs$_2$CO$_3$, 5.0

![Reaction development](https://example.com/reaction-development.png)

**Fig. 2 Reaction development.** a Optimization of the reaction conditions. Standard reaction conditions: alkyl halide (1.0 equiv.), base (3.5 equiv.), TFBO (5.0 equiv.), DMA, 70 °C, N$_2$. Yields were determined by $^{19}$F NMR with benzotrifluoride as a standard. b Monitoring of the reaction between TFBO (1a) and Cs$_2$CO$_3$ by $^{19}$F NMR spectroscopy.
equiv. of TFBO (1a) in DMA under N₂ atmosphere were found to produce high yields of the desired product.

With the optimized conditions in hand, we explored the substrate scope of the transformation (Fig. 3). First, a wide range of unactivated alkyl iodides was successfully converted to the corresponding trifluoromethyl ethers with yields ranging from 49 to 98% (3 to 34). Substrates bearing electron-donating and electron-withdrawing substituents on aryl rings proceeded well. This transformation was also compatible with excellent functionalities, such as ester, ether, ketone, aldehyde, imide, amide,

\[
\begin{align*}
1a & \quad \text{X} = \text{I}, \text{Br}, \text{Cl} \\
& \quad \text{R-OCF}_3 \\
\end{align*}
\]

Alkyl iodide

| R-OCF₃ | Yield (%) |
|--------|-----------|
| 3      | 92%       |
| 4      | 88%       |
| 5      | 98%       |
| 6      | 91%       |
| 7      | 90%       |
| 8      | 94%       |
| 9      | 86%       |
| 10     | 93%       |
| 11     | 86%       |
| 12     | 90%       |
| 13     | 90%       |
| 14     | 91%       |
| 15     | 90%       |
| 16     | 95%       |
| 17     | 90%       |
| 18     | 91%       |
| 19     | 93%       |
| 20     | 92%       |
| 21     | 95%       |
| 22     | 89%       |
| 23     | 93%       |
| 24     | 86%       |
| 25     | 86%       |
| 26     | 94%       |
| 27     | 86%       |
| 28     | 89%       |
| 29     | 62% (X = I)\(\uparrow\) 69% (X = Br)\(\uparrow\) |
| 30     | 98%       |
| 31     | 54% (X = I)\(\uparrow\) 46% (X = Br)\(\uparrow\) |
| 32     | 65%       |
| 33     | 71%       |
| 34     | 49%       |

Alkyl bromide/alkyl chloride

| R-OCF₃ | Yield (%) |
|--------|-----------|
| 3      | 93% (X = Br)\(\uparrow\) 71% (X = Cl)\(\uparrow\) |
| 4      | 93% (X = Br)\(\uparrow\) 71% (X = Cl)\(\uparrow\) |
| 5      | 95% (X = Br)\(\uparrow\) 69% (X = Cl)\(\uparrow\) |
| 6      | 97% (X = Br)\(\uparrow\) 73% (X = Cl)\(\uparrow\) |
| 7      | 91% (X = Br)\(\uparrow\) 66% (X = Cl)\(\uparrow\) |
| 8      | 91% (X = Br)\(\uparrow\) 66% (X = Cl)\(\uparrow\) |
| 9      | 91% (X = Br)\(\uparrow\) 66% (X = Cl)\(\uparrow\) |
| 10     | 93% (X = Br)\(\uparrow\) 66% (X = Cl)\(\uparrow\) |
| 11     | 93% (X = Br)\(\uparrow\) 66% (X = Cl)\(\uparrow\) |

Fig. 3 Substrates scope for trifluoromethoxylation of simple alkyl halides. Standard reaction conditions: alkyl halide (1.0 equiv.), Cs₂CO₃ (3.5 equiv.), TFBO (5.0 equiv.), DMA, 70 °C, N₂. \(\uparrow\)90 °C. \(\uparrow\)Cs₂CO₃ (4.0 equiv.), TFBO (6.0 equiv.), HMPA. \(\uparrow\)Cs₂CO₃ (4.0 equiv.), TFBO (6.0 equiv.), TBAI (0.2 equiv.), HMPA. Yields were determined by \(^{19}\)F NMR with benzotrifluoride as a standard.
cyano, nitro, aryl chloride, bromide, and iodide groups. Notably, heteroaromatic substrates and amino acid derivative were also successfully employed to provide the corresponding products.\textsuperscript{17,18,30} Generally, the reactions of a variety of primary alkyl iodides gave rise to the desired trifluoromethoxylated products in high yields (3 to 30), while secondary alkyl iodides gave slightly lower yields (31 to 34). Next, we turned our attention to expanding the substrate scope to alkyl bromides and alkyl chlorides. To our great delight, the alkyl halides were smoothly with alkyl chlorides. To our great delight, the trifluoromethoxylation of alkyl bromides and alkyl chlorides proceeded smoothly with yields ranging from 30 to 97%. Furthermore, the allyl, propargyl, alkyl bromides and alkyl chlorides. To our great delight, the trifluoromethoxylation of alkyl bromides in the presence of alkyl chlorides were observed. For example, the alkyl iodide or alkyl bromide was selectively converted into a trifluoromethoxylated products (35 to 39). It is worth mentioning that chemoselectivity trifluoromethoxylation of alkyl iodides or alkyl bromides in the presence of alkyl chlorides were observed. For example, the alkyl iodide or alkyl bromide was selectively converted into a trifluoromethoxylated group while the alkyl chloride remained intact.\textsuperscript{29} The yields of fluorination byproducts were less than 10% in all cases. In addition, the product 33 with 8% ee was observed when the chiral substrate was used, which gave slightly lower yields (31 to 34).

For example, the alkyl iodide or alkyl bromide was selectively converted into the desired trifluoromethoxylated products in good yields (30 to 34). Next, we turned our attention to expanding the substrate scope to alkyl bromides and alkyl chlorides. To our great delight, the trifluoromethoxylation of alkyl bromides and alkyl chlorides proceeded smoothly with yields ranging from 30 to 97%. Furthermore, the allyl, propargyl, alkyl bromides and alkyl chlorides. To our great delight, the trifluoromethoxylation of alkyl bromides in the presence of alkyl chlorides were observed. For example, the alkyl iodide or alkyl bromide was selectively converted into a trifluoromethoxylated products (35 to 39). It is worth mentioning that chemoselectivity trifluoromethoxylation of alkyl iodides or alkyl bromides in the presence of alkyl chlorides were observed. For example, the alkyl iodide or alkyl bromide was selectively converted into a trifluoromethoxylated group while the alkyl chloride remained intact.\textsuperscript{29} The yields of fluorination byproducts were less than 10% in all cases. In addition, the product 33 with 8% ee was observed when the chiral substrate was used, which gave slightly lower yields (31 to 34).

Due to the ubiquity of the trifluoromethoxy group in small-molecule drugs and preclinical candidates, it would be more significant to achieve the late-stage trifluoromethoxylation of complex small molecules with our trifluoromethoxylation reagents. To confirm this strategy, we selected ten meaningful small molecules as the substrates of trifluoromethoxylation. (Fig. 4). Each of these architecturally complex molecules underwent trifluoromethoxylation of alkyl halides to achieve the corresponding trifluoromethoxylated products in moderate to excellent yields (40 to 49, 40–97% yield). For example,
pentacyclic diterpene giberellin acid is a plant hormone that promotes growth and influences developmental processes, including cell germination and elongation. Cyclosporin A is an immunosuppressant medication and natural product, which is a macrocyclic peptide of 11 amino acids. To our delight, the trifluoromethoxylation reaction with the giberellin acid derivative and cyclosporin A derivative proceeded smoothly to provide the corresponding products (46, 48) in good yields, which illustrates the ability to conduct the late-stage trifluoromethoxylation of complex structures.

Discussion

In conclusion, we have developed (E)-O-trifluoromethyl-benzaldoximes (TFBO) as a trifluoromethoxylation reagent for nucleophilic trifluoromethoxylation of alkyl halides without silver. The method offers direct access to trifluoromethyl ethers from various alkyl halides and α-fluorinated ethers, thioethers, and amines: anemonically biased species. Chem. Rev. 105, 827–856 (2005).

Jeschke, P., Baston, E. & Leroux, F. R. alpha-fluorinated ethers as "exotic" entity in medicinal chemistry. Mini-Rev. Med. Chem. 7, 1027–1034 (2007).

Menteau, B., Pazenok, S., Vors, J. P. & Leroux, F. R. New trends in the chemistry of a-fluorinated ethers, thioethers, amines and phosphines. J. Fluor. Chem. 131, 140–158 (2010).

Landelle, G., Panossian, A. & Leroux, F. R. Trifluoromethyl ethers and thioethers as tools for Medicinal chemistry and drug discovery. Curr. Top. Med. Chem. 14, 941–951 (2014).

Tlili, A., Toudgoat, F. & Billard, T. Synthetic approaches to trifluoromethoxy-substituted compounds. Angew. Chem. Int. Ed. 55, 11726–11735 (2016).

Basset, T., Joubaut, P., Pannecocke, X. & Poisson, T. New entries toward the synthesis of OCFO₂-containing molecules. Org. Chem. Front. 3, 1004–1010 (2016).

Lee, J., Lee, K. & Ngai, M. Synthesis of tri- and difluoromethoxy-substituted compounds by visible-light photoredox catalysis. Angew. Chem. Int. Ed. 58, 11171–11181 (2019).

Hardy, M. A., Chachignon, H. & Cahard, D. Advances in asymmetric di- and trifluoromethylthiolation and di- and trifluoromethoxylation reactions. Asian J. Org. Chem. 8, 591–609 (2019).

Yagupolski, I. M. Dokl. Akad. Nauk SSR 105, 108–102 (1955).

Umemoto, T. Electrophi...
35. Guo, S., Cong, F., Guo, R., Wang, L. & Tang, P. Asymmetric silver-catalysed intermolecular bromotrifluoromethoxylation of alkenes with a new trifluoromethoxylation reagent. Nat. Chem. 9, 546–551 (2017).
36. Jiang, X., Deng, Z. & Tang, P. Direct dehydroxytrifluoromethoxylation of alcohols. Angew. Chem. Int. Ed. 57, 292–295 (2018).
37. Zhou, M., Ni, C., Zeng, Y. & Hu, J. Trifluoromethyl benzoate: a versatile trifluoromethoxylation reagent. J. Am. Chem. Soc. 140, 6801–6805 (2018).
38. Zhang, X. & Tang, P. Recent advances in new trifluoromethoxylation reagents. Sci. Chi. Chem. 62, 525–532 (2019).
39. Nofte, R. E. & Cady, G. H. Preparation and properties of bis (trifluoromethylsulfonyl) peroxide and trifluoromethyl trifluoromethanesulfonate. Inorg. Chem. 4, 1010–1012 (1965).
40. Taylor, S. L. & Martin, J. C. Trifluoromethyl triflate: synthesis and reactions. J. Org. Chem. 52, 4147–4156 (1987).
41. Mauleón, D., Granados, R. & Mingullón, C. 4-alkoxybenzonitriles from O-alkyl-4-nitrobenzaldoximes: an elimination-aromatic substitution reaction. J. Org. Chem. 48, 3106–3108 (1983).
42. Matoušek, V., Pietrasák, E., Sigrist, L., Czarniecki, B., Togni, A. O-Trifluoromethylation of N,N-Disubstituted Hydroxylamines with Hypervalent Iodine Reagents. Eur. J. Org. Chem. 2014, 3087–3092 (2014).

Acknowledgements
The authors are grateful for the financial support from the National Key Research and Development Program of China (2016YFA0602900), NFSC (21672110, 21925105), the Natural Science Foundation of Tianjin (Grant No. 18JCQJJC47000), and the Fundamental Research Funds for the Central Universities.

Author contributions
Y.L., Y.Y., and J.X. performed the experiments and analyzed the data. P.T. designed and directed the project. P.T. wrote the manuscript. All the authors discussed the results and commented on the manuscript.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information is available for this paper at https://doi.org/10.1038/s41467-020-14598-1.

Correspondence and requests for materials should be addressed to P.T.

Peer review information Nature Communications thanks the anonymous reviewer(s) for their contribution to the peer review of this work.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2020