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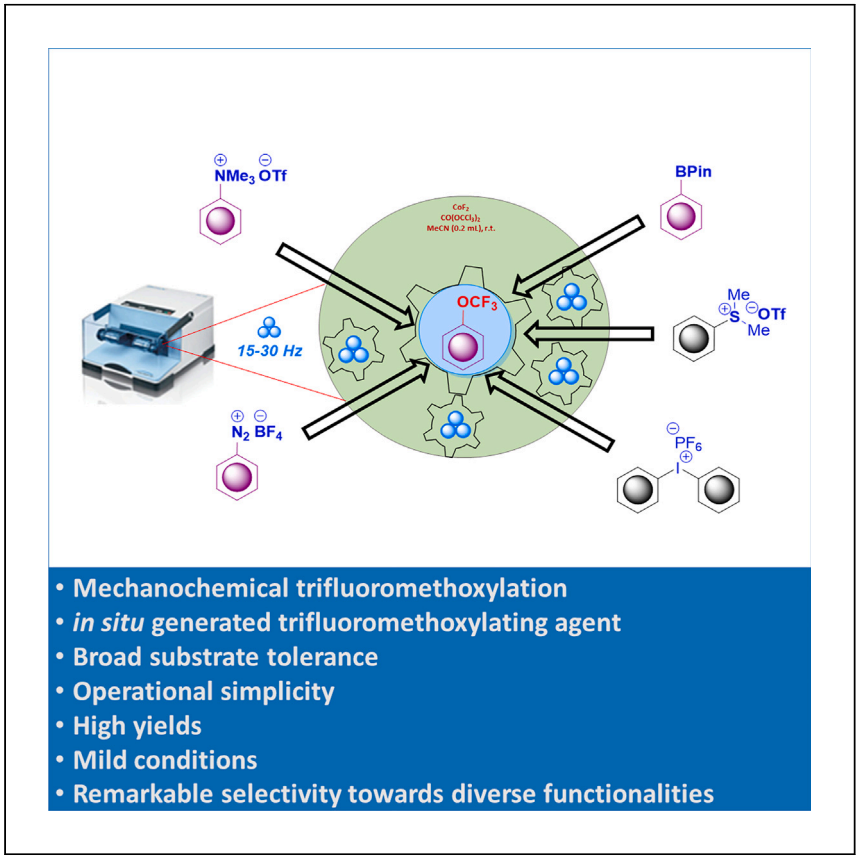

Here, Mkrtchyan and Iaroshenko et al. report a highly efficient and alternative approach for the selective mechanochemical transformation of aryldiazonium tetrafluoroborates and aryltrimethylammonium triflates to aryl trifluoromethyl ethers via *in situ*-generated OCF_3 source.

Satenik Mkrtchyan, Vishal B. Purohit, Jiří Zapletal, ..., Elena Kupcová, Barbora Benická, Viktor O. Iaroshenko

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Highlights

Mechanochemical *in situ* trifluoromethoxylation

Highly efficient functional group transformation under mild conditions

Remarkable selectivity toward diverse functionalities

Wide substrate scope and operational simplicity

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Mechanochemical trifluoromethoxylation of aryltrimethylammonium triflates, aryldiazonium tetrafluoroborates, and aryl pinacolboranes

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SUMMARY

Aryl trifluoromethyl ethers ($ArOCF_3$) are important structural motifs in pharmaceuticals, agrochemicals, and functional materials. However, the methods reported for the efficient synthesis of these scaffolds are extremely underdeveloped and limited. Here, we report a highly efficient mechanochemical approach for the selective transformation of aryltrimethylammonium triflates, aryldiazonium tetrafluoroborates, and aryl pinacolboranes to aryl trifluoromethyl ethers via *in situ*-generated OCF_3 source using triphosgene and Co(II) fluoride (CoF_2). The proposed synthetic protocol also shows potential for the selective transformation of other groups such as arylsulfonium and diaryliodonium functionalities. The present trifluoromethoxylation strategy exhibited a broad functional group tolerance and found to be superior over other existing protocols in terms of substrate scope, yields, operational simplicity, and reaction times.

INTRODUCTION

The unique properties of fluorine-containing organic molecules arise from its small atom size (covalent radius of fluorine being only slightly higher than that of the hydrogen atom) and high electronegativity. As a result, the C–F bond length (1.32–1.43 Å) is comparable to that of C–H (1.06–1.10 Å),[1] but its dissociation enthalpy is much higher (440 vs. 547 kJ/mol for methane vs. tetrafluoromethane).[2] Polyfluorinated compounds are thus unusually stable, making them an attractive platform for applications in agrochemicals and materials chemistry.[3,4] Fluorine-containing skeletons are also prominent among the drugs since replacement of hydrogen with fluorine does not change the size of the molecule, but makes it significantly more metabolically stable. Moreover, due to high electronegativity, it introduces additional polarization affecting hydrophilicity of the compound and may also act as a weak hydrogen bond acceptor.[5,6]

The most commercially or synthetically available fluorine-containing molecules are aryl fluorides,[7–9] trifluoromethyl compounds, or perfluorinated alkanes.[10–14] Organic compounds bearing chalcogenated trifluoromethyl functionality constitute a broad array of pharmaceuticals, natural products, agrochemicals, and other synthetic analogs (Figure 1). Among the trifluoromethyl compounds, aryl trifluoromethyl ethers ($ArOCF_3$) have gained considerable attention in both academia and

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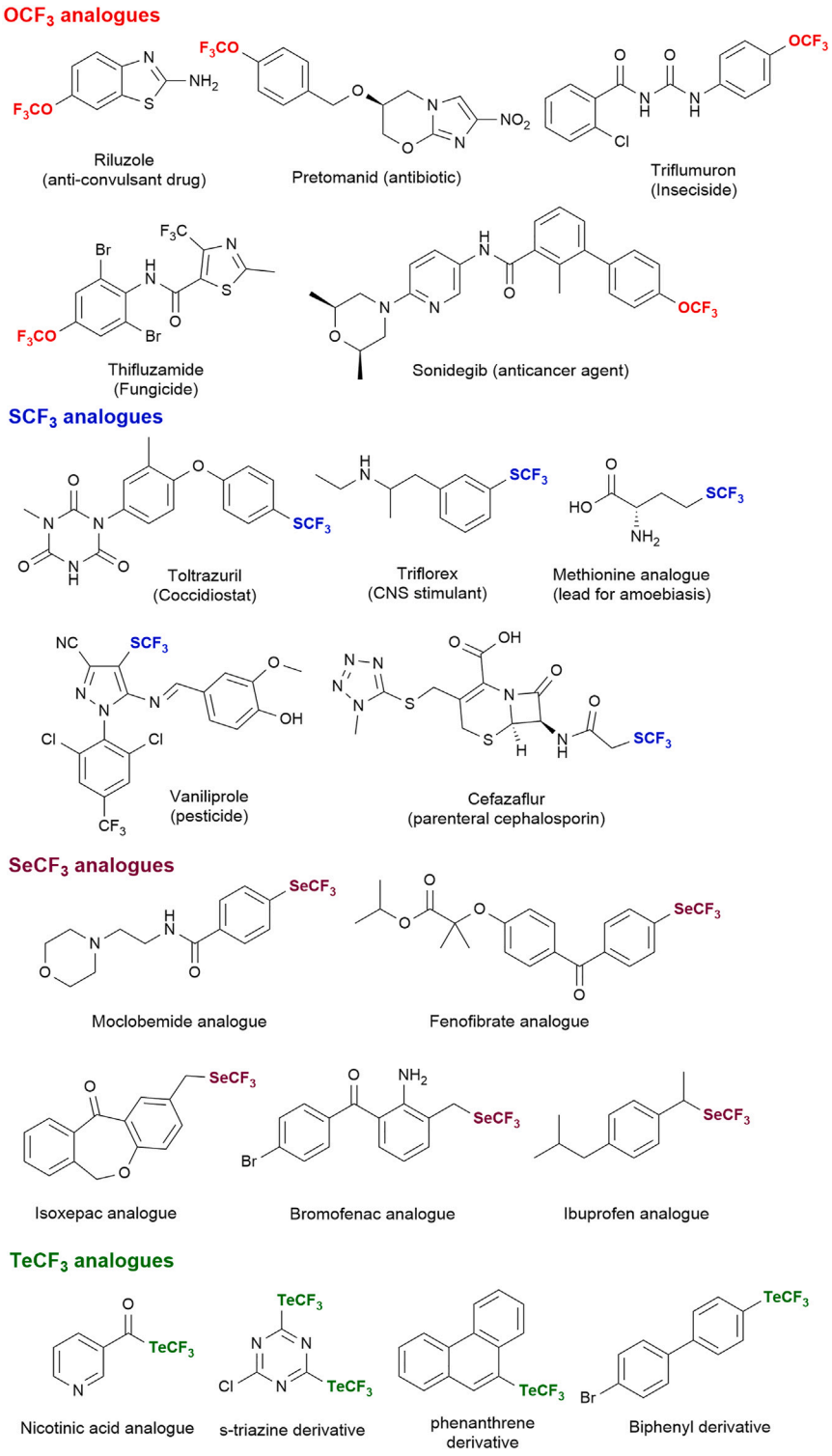
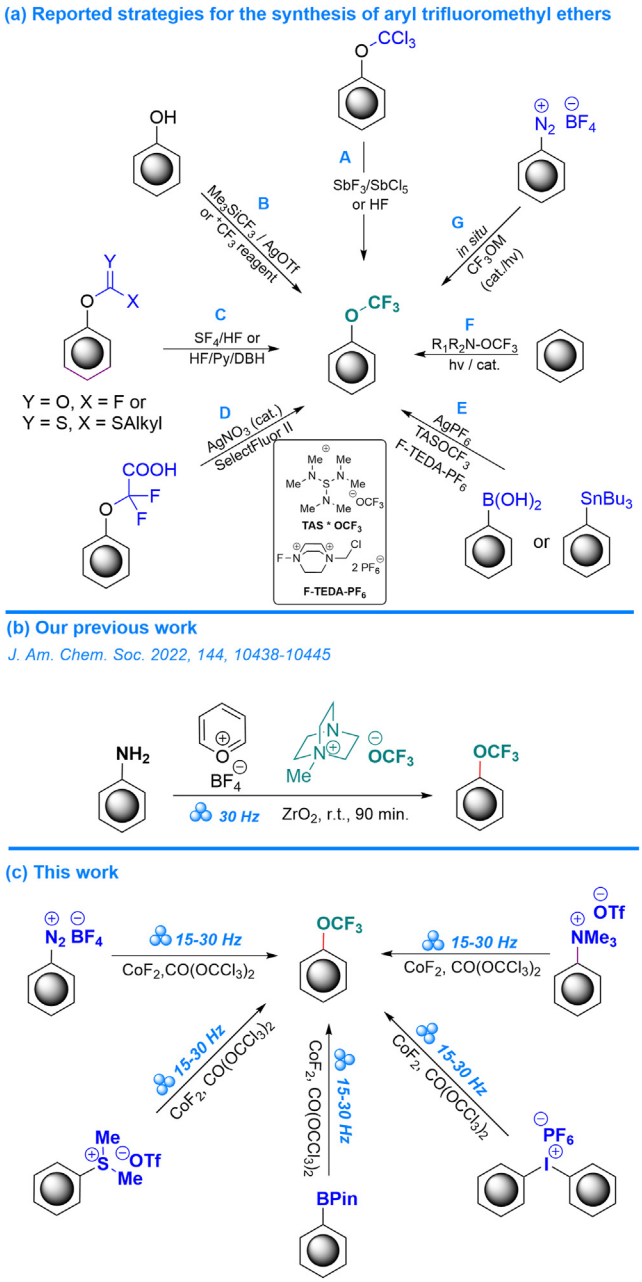


Figure 1. Representative (O, S, Se, Te)CF_3-containing compounds used in pharmaceuticals, agrochemicals, and related synthetic analogs



Scheme 1. Previous and current approaches for the synthesis of aryl trifluoromethyl ethers

industry owing to the unique properties of the trifluoromethoxy (OCF_3) group. With the Hansch parameter of 1.04 and Hammett constants of σ_p = 0.35 and σ_m = 0.38, the OCF_3 group has been of particular interest to pharmaceutical research, due to its high electronegativity (χ = 3.7), unique orthogonal conformation relative to the aromatic ring, high lipophilicity, and metabolic stability.[15] Despite the significant biological properties of these compounds, direct syntheses of aryl trifluoromethyl ethers are still rare.[16] Difficulties in the formation C_{aryl}—OCF_3 bond can be attributed to the reversible decomposition of the trifluoromethoxide anion (CF_3O^-) in solution above room temperature to afford the carbonic difluoride.[17,18]

Known methods for the synthesis of aryl trifluoromethyl ethers involve the formation of a C–F, C–OCF_3, or O–CF_3 bond or a combination thereof. As shown in Scheme 1, most of these methods utilized phenol and its derivatives as the key precursors. In 1955, Yagupolskii led the pioneering work to synthesize the first Ar–OCF_3 compounds by a chlorine–fluorine exchange on the trichloroanisole, which was obtained by the chlorination of anisole (Scheme 1a, path A).[19] Other methods include direct trifluoromethylation of phenols, either via Qing's oxidative trifluoromethylation with the Ruppert-Prakash reagent (Me_3SiCF_3) under the influence of an Ag-salt[20] or via electrophilic trifluoromethylation with Umemoto's oxonium or Togni's hypervalent iodine reagents (Scheme 1a, path B).[21–23] The fluorination of "phenol-derived" fluoroformates,[24,25] as well as dithiocarbonates,[26] have also been reported to synthesize OCF_3-containing arenes (Scheme 1a, path C). Additionally, a two-step procedure catalyzed by $AgNO_3$ was reported by Hu and coworkers through O-carboxydifluoromethylation of phenol, followed by subsequent decarboxylative fluorination using SelectFluor II (Scheme 1a, path D).[27,28] However, these phenol-based methods suffered from some drawbacks such as harsh reaction conditions, medium yields, and a long synthetic route precluding their applicability in late-stage modifications of drug candidates. In context to one of the green chemistry principles, it is obviously better to plan the direct introduction of the OCF_3 group to the aryl ring in a single step. In this regard, a series of new strategies for the direct synthesis of aryl trifluoromethyl ethers has been reported in recent years.

For example, in 2011, Ritter's group developed a highly efficient strategy for Ag-mediated trifluoromethoxylation of aryl boronic acids and stannanes using tris(dimethylamino)-sulfonium trifluoromethoxide ($TASOCF_3$) as the trifluoromethoxy reagent (Scheme 1a, path E).[29] The radical trifluoromethoxylation of the arene C–H bond was also achieved independently by Ngai and Togni with novel N–OCF_3 reagents under transition metal-based photocatalytic conditions (Scheme 1a, path F).[30–32] Later, an electrochemical C–H trifluoromethoxylation of (hetero)aromatics has also been reported by Qing and coworkers combining trifluoromethyl 2-pyridyl sulfone with oxygen as a convenient trifluoromethoxy source.[33] Nevertheless, most of these direct trifluoromethoxylation approaches either suffer from poor substrate scope or require the use of highly toxic, corrosive, expensive, and/or thermally labile reagents. Two interesting approaches to the trifluoromethoxylation of aryl or (hetero)aryldiazonium tetrafluoroborates have also been published describing the construction of aryl–OCF_3 bond via *in situ*-generated CF_3OM species (M = Cu or Ag) as the trifluoromethoxylating reagents (Scheme 1a, path G).[34,35] Initially, these methods seemed quite promising; however, the requirement of extremely low temperature (−40°C), inert atmosphere, photoredox catalysts, and prolonged reaction times along with moderate yields limit their applicability in pharmaceutical industries. In 2022, our group developed a mechanochemical one-pot approach to access aryl trifluoromethyl ethers via nucleophilic substitution (S_NAr) of an aromatic amino group with an OCF_3 substituent using a combination of pyrylium tetrafluoroborate and 1-methyl-1,4-diazabicyclo[2.2.2]-octan-1-ium trifluoromethoxide as the OCF_3 source (Scheme 1b).[36] From the aforementioned literature, it is clear that the trifluoromethoxylation approach is still in its infancy from the synthetic viewpoint, and it is therefore critical to develop a convenient strategy for the direct introduction of the OCF_3 group into structurally diverse molecules.

With the growing emphasis on the environmental impact, mechanochemical transformations using ball milling have moved to the forefront of organic synthesis as cleaner, greener and sustainable synthetic alternatives.[37–39] Apart from the environmental benefits, mechanochemistry has the potential to access the novel chemical

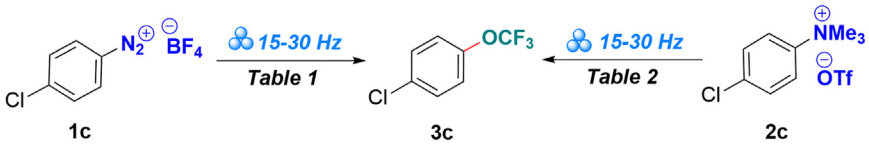
space in terms of selectivities and reactivities compared to those of classical solution-based synthetic methods.[40–43] During mechanochemical ball milling, the substrates are subjected to mechanical forces, such as shear and non-hydrostatic compression forces, and combinations thereof.[44] As a result, solid reactants undergo several associated physical processes, including particle size reduction (comminution), with a consequent surface area increase, and the formation of lattice defects of various types, wherein the reactivity is enhanced due to the reduction of the strength of the attractive interactions that hold the solid together, which also ultimately leads to amorphization. Furthermore, the mechanical energy acts synergistically with the internal energy of the chemical system due to its temperature, further increasing the chemical reactivity of the matter.

In continuation of our long-standing interest dedicated to the development of novel, efficient, and sustainable transformations for the synthesis of organofluorine compounds,[45–52] here, we report a convenient mechanochemical approach for the selective transformation of aryltrimethylammonium triflates, aryldiazonium tetrafluoroborates, and aryl pinacolboranes to aryl trifluoromethyl ethers via an *in situ*-generated OCF_3 source using triphosgene and Co(II) fluoride (CoF_2) (Scheme 1c). Furthermore, the proposed synthetic protocol also shows potential for the selective transformation of the other groups, including arylsulfonium and diaryliodonium functionalities. To the best of our knowledge, this is the first ever report disclosing selective trifluoromethoxylation of the aforementioned functionalities using cheap and readily available substrates and/or reagents. The present trifluoromethoxylation strategy is found to be superior over other existing protocols in terms of substrate scope, yields, operational simplicity, and short reaction times. Moreover, the protocol is characterized by a broad functional group tolerance, thus permitting the construction of a direct C_{aryl}-OCF_3 bond onto complex pharmaceuticals, agrochemicals, and natural products in a late-stage modification.

RESULTS AND DISCUSSION

Optimization of reaction conditions for the trifluoromethoxylation of aryldiazonium tetrafluoroborate 1c and aryltrimethylammonium triflete 2c

Inspired by our recently developed approach to deaminative trifluoromethoxylation of aromatic amines, we envisioned that a similar method could be applied to introduce the trifluoromethoxy group into amine derivatives such as aryltrimethylammonium and aryldiazonium salt precursors. In line with Hu and colleagues' work,[53] Schoenebeck et al. reported the *ex situ* synthesis of $AgOCF_3$ by the reaction of triphosgene [$CO(OCCl_3)_2$] and AgF, and used the stock solution of $AgOCF_3$ salt for trifluoromethoxylation and other reactions[54]; however, a glovebox was required for the preparation and isolation/filtration of insoluble Ag salt. With intentions to overcome the operational difficulties in the aforementioned protocols and to develop an alternative route for trifluoromethoxylation, we envisioned that metal-trifluoromethoxide (CF_3OM) precursors could be synthesized *in situ* by the reactions of triphosgene and a suitable metal fluoride. The *in situ*-generated CF_3OM salt can lead the nucleophilic trifluoromethoxylation of a variety of substrates during the course of reaction. With this idea in mind, we began our investigations choosing 4-chlorobenzenediazonium tetrafluoroborate **1c** as a model substrate in the presence of triphosgene and various metal fluorides in MeCN (0.2 mL) using a molecular ball mill with a working frequency of 15 Hz initially for 30 min, and then an increased frequency of 30 Hz for 60 min at room temperature (Scheme 2). The reaction vessel was first kept at 15 Hz for 30 min, and then the same vessel was subjected to milling at 30 Hz for 60 min



1c 3c 2c

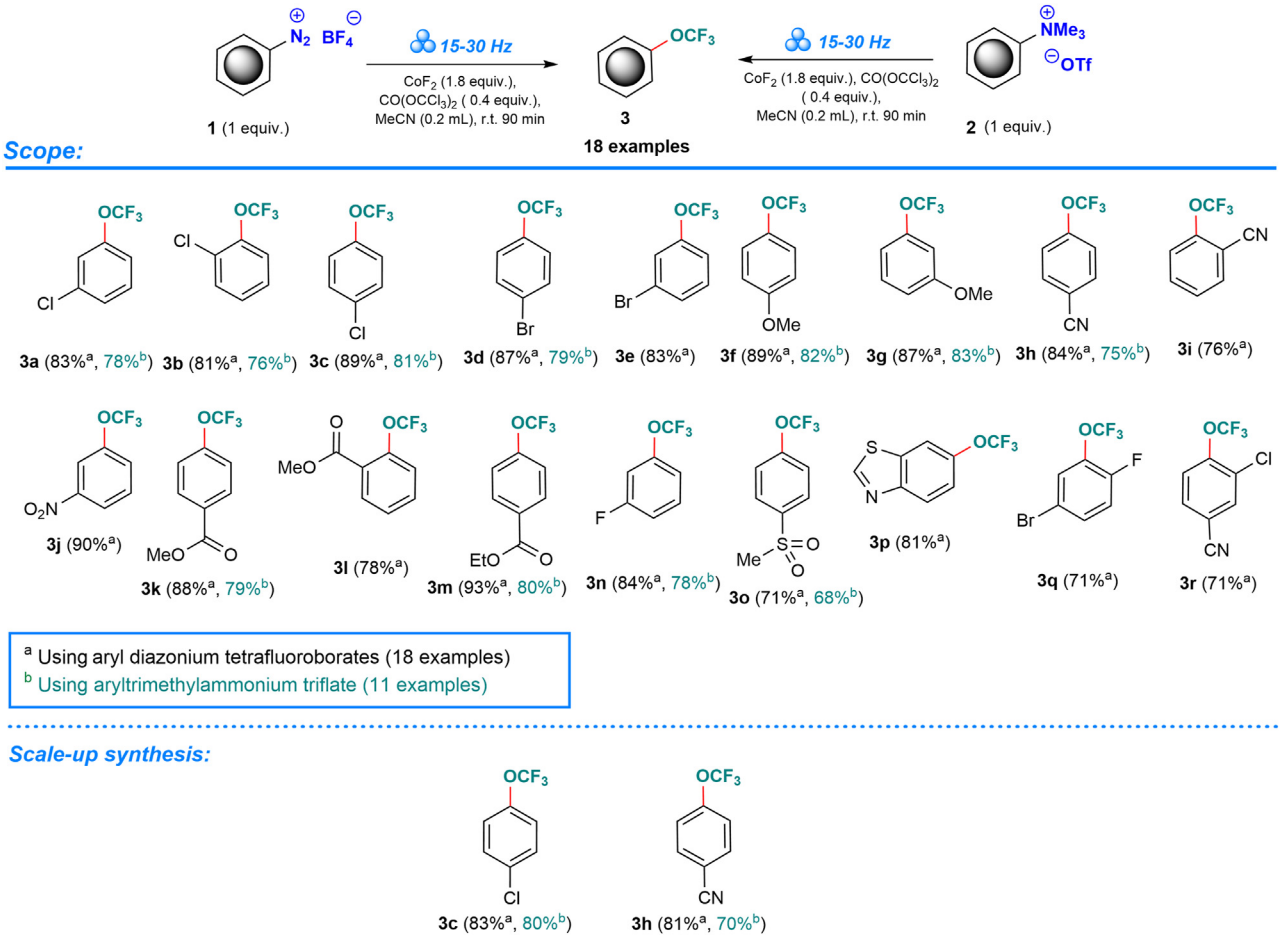
Scheme 2. Study of reaction conditions for the trifluoromethoxylation on model substrates 1c and 2c

Following the previously reported conditions to generate $AgOCF_3$ salt, initially, we employed 0.33 equiv of triphosgene and 3 equiv of AgF for the trifluoromethoxylation of the model substrate **1c**. To our delight, the targeted aryl trifluoromethyl ether **3c** was obtained with 70% yield (Table S1, entry 1). These promising results prompted us to investigate the model reaction using other transition metal fluorides (1.8 equiv) such as CoF_2, CuF_2, and PdF_2. The best results were obtained using (CoF_2) under the applied milling conditions yielding the expected product **3c** with 89% isolated yield (Table S1, entry 2), while the presence of CuF_2 and PdF_2 in the model reaction led to the formation of compound **3c**, with 42% and 49% yields, respectively (Table S1, entries 3 and 4). Furthermore, the screening of the model reaction using CoF_2 at one frequency of 15 or 30 Hz only led to the remarkable decrease in the yields of compound **3c** (Table S1, entries 5 and 6).

Apart from the solid-phase reactions, the above-mentioned model reactions have also been screened in solution phase under the normal stirring conditions in MeCN for 24 h at room temperature (Table S1, entries 7–10). Of note, moderate yields of compound **3c** were obtained in the presence of AgF and PdF_2 (Table S1, entries 8 and 10), while only traces of the product **3c** have been detected using CoF_2 and CuF_2 (Table S1, entries 7 and 9). From the above results, the optimum reaction conditions for the mechanochemical trifluoromethoxylation of aryldiazonium substrate **1c** have been set as shown in entry 2 of Table S1.

Encouraged by the above results, we then directed our efforts to optimize the reaction conditions for the trifluoromethoxylation of aryltrimethylammonium triflates, choosing compound **2c** as the model substrate (Scheme 2; Table S2). Initially, we decided to screen the conditions that were found to be quite promising in the case of aryldiazonium substrate **1c** (Table S1, entry 2). Delightfully, testing the above optimal conditions (mechano-milling, CoF_2 [1.8 equiv], $CO(OCCl_3)_2$ [0.4 equiv], MeCN [0.2 mL], room temperature) with the model substrate **2c**, the targeted aryl trifluoromethyl ether **3c** was obtained in an 81% yield (Table S2, entry 5). These results suggested that the previously optimized conditions for the trifluoromethoxylation of aryldiazonium substrate **1c** (Table S1, entry 2) were also compatible in the case of substrate **2c** with good consistency.

Besides CoF_2, other metal fluorides such as AgF, CrF_2, MnF_2, FeF_2, NiF_2, CuF_2, and PdF_2 have been been screened, maintaining the fixed amount (0.4 equiv) of triphosgene (Table S2, entries 1–4 and 6–8). As expected, good yields of the targeted aryl trifluoromethyl ether **3c** were obtained using AgF (Table S2, entry 1). The desired compound **3c** was formed with a 19% yield in the presence of CrF_2 (Table S2, entry 2), while the model reactions have failed using MnF_2, and FeF_2 as the fluoride salts (Table S2, entries 3 and 4). Additionally, two fluoride salts of the first transition series metals succeeding that of cobalt have been tested (Table S2, entries 6 and 7). However, the model reaction did not proceed in the presence of NiF_2 (Table S2, entry 6), while only a 34% yield of **3c** was observed using CuF_2 (Table S2, entry 7). Lastly, the efficacy of the model reaction has been

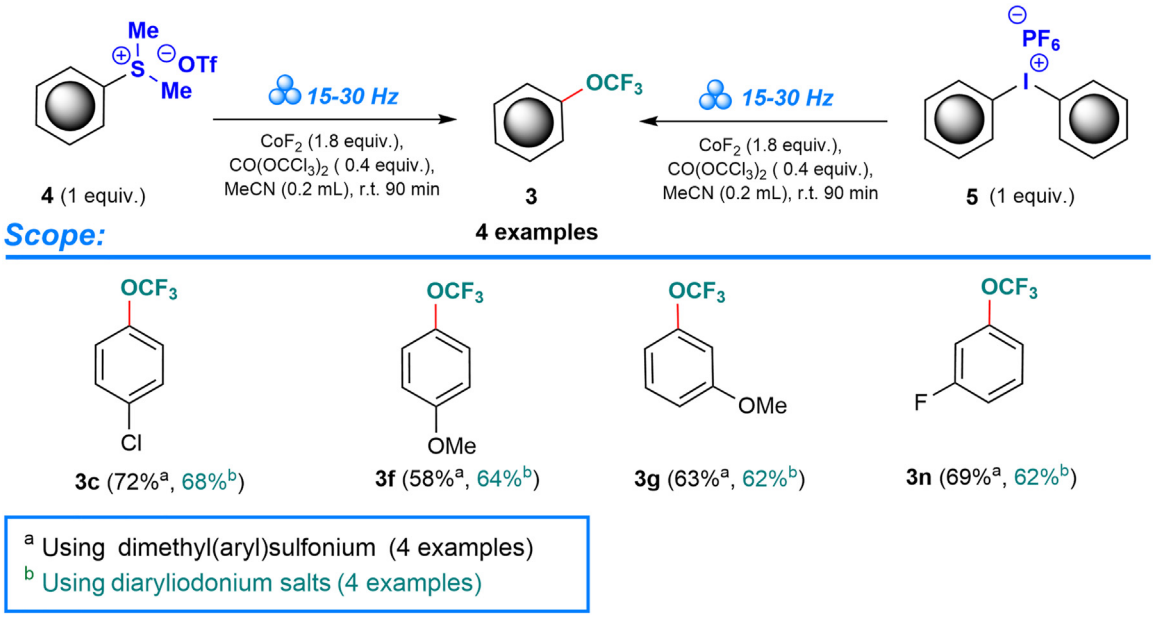


Scheme 3. Substrate scope for the synthesis of aryl trifluoromethyl ethers (3a-r)

tested against the fluoride salt of the widely used transition metal in coupling reactions. Delightedly, the reaction proceeded well in the presence of PdF_2, delivering the desired aryl trifluoromethyl ether **3c** with a 75% yield (Table S2, entry 8). A significant decrease in the yields of product **3c** has been observed with CoF_2 applying only one working frequency (i.e., 15 or 30 Hz for 90 min in the model reaction) (Table S2, entries 9 and 10). To validate the demand for the present mechanochemical approach, the model reaction has also been performed under conventional stirring conditions using MeCN as a solvent (Table S2, entries 11–14). With AgF, the model reaction proceeded smoothly, yielding the targeted product **3c** only with a 33% yield (Table S2, entry 12), while 28% and 38% yields of compound **3a** have been observed in the presence of CoF_2 and PdF_2, respectively (Table S2, entries 11 and 14). However, the reaction failed with CuF_2 delivering only traces of the expected product **3c** (Table S2, entry 13).

Substrate scope for the trifluoromethoxylation of aryldiazonium tetrafluoroborates 1 and aryltrimethylammonium triflets 2

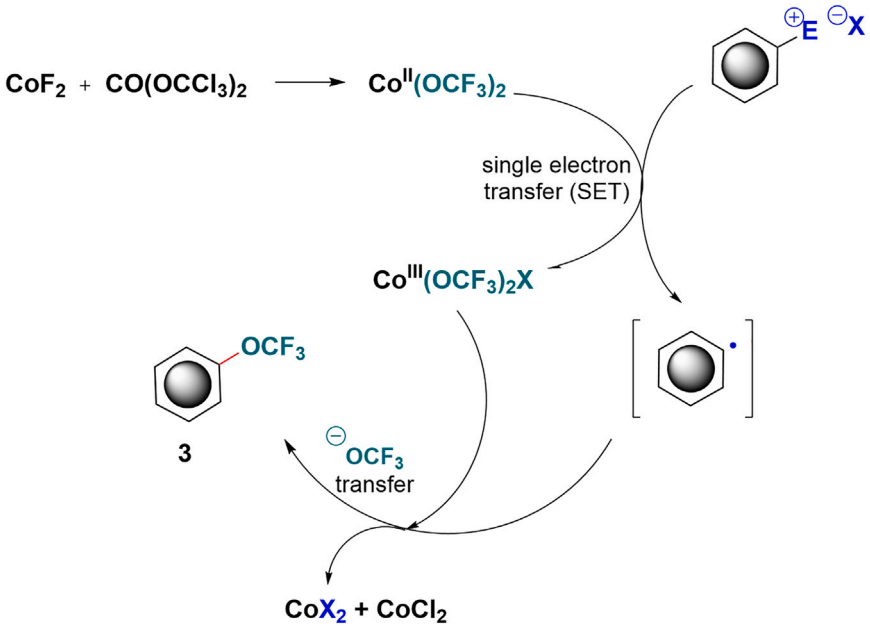
With the above optimized conditions in mind, the scope and generality of the present trifluoromethoxylation strategy have been explored (Scheme 3). Trifluoromethoxylation of 18 aryldiazonium tetrafluoroborates **1** and 11 such aryltrimethylammonium triflets **2** led to the development of a small library of 18 aryl



Scheme 4. Trifluoromethoxylation of dimethyl(aryl)sulfonium and diaryliodonium salts

trifluoromethyl ether derivatives (**3a–3r**). The careful investigation of the synthesized aryl trifluoromethyl ethers revealed that the aryldiazonium and aryltrimethylammonium substrates bearing electron withdrawing and donating substituents in the aromatic ring at different positions were susceptible to undergoing trifluoromethoxylation, providing the targeted products in good to excellent yields. It has been revealed that comparatively low yields (68%–83%) of aryl trifluoromethyl ethers were obtained using aryltrimethylammonium salts **2**, while 71%–93% yields of the same were observed utilizing the respective aryldiazonium substrates **1**. Of note, the aryltrimethylammonium/aryldiazonium functionalities have displayed an exclusive chemoselectivity in the presence of the other nucleophile-sensitive functionalities such as ester, nitrile, and sulfoxide groups tethered in the same molecule. Furthermore, the present trifluoromethoxylation strategy was successfully extended to the heteroaromatic system—in other words,-benzo[*d*]thiazole-6-diazonium tetrafluoroborate **1p** providing the respective heteroaryl trifluoromethyl ether **3p** with an 81% yield. Additionally, the scale-up synthesis of the two representative aryl trifluoromethyl ethers (**3c** and **3h**) have been carried out with a 10-mmol scale of the respective aryldiazonium/aryltrimethylammonium substrates to establish the synthetic utility of the current protocol (Scheme 3). From these results, it is clear that the present protocol can also be applied for the gram-scale synthesis of the targeted trifluoromethyl ether analogs. Of note, the aryldiazonium salts are explosive, shock sensitive, and temperature unstable; thus, careful precautions are obligatory while handling in a synthetic laboratory.

To validate the synthetic relevance of the present strategy, the optimized conditions have been screened further for the trifluoromethoxylation of other classes of organic salts, including dimethyl(aryl)sulfonium trifletes **4** and diaryliodinium hexafluorophosphates **5**. Four such representative aryl trifluoromethyl ethers (**3c**, **3f**, **3g**, and **3n**) have been synthesized in moderate to good yields using the respective dimethyl(aryl)sulfonium and diaryliodonium salt precursors (Scheme 4).



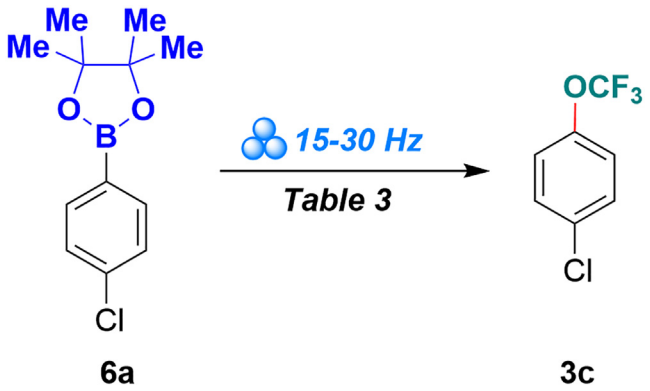
Scheme 5. Proposed mechanism for the trifluoromethoxylation of aryltrimethylammonium, aryldiazonium, arylsulfonium and diaryliodonium substrates

Reaction mechanism elucidation of the trifluoromethoxylation of substrates 1/2/4/5

Based on the reported literature and our observations, a plausible mechanism for the present trifluoromethoxylation approach has been proposed (Scheme 5).[28,29,31,32] We believe that trifluoromethoxylation might be proceeded through the Sandmeyer-type $S_{RN}1$(Ar) (radical nucleophilic aromatic substitution) mechanism. The first step involves the *in situ* generation of $Co(OCF_3)_2$ by the reaction of $CO(OCCl_3)_2$ and CoF_2. A single electron transfer from $Co(OCF_3)_2$ to the substrate **1/2/4/5** led to the formation of an aryl radical and $Co^{III}(OCF_3)_2X$ intermediate species. Finally, the sequential OCF_3 group transfer from the Co(III) species to the aryl radical yielded the desired product **3** via formation of the aryl−OCF_3 bond.

Optimization of reaction conditions for the trifluoromethoxylation of aryl pinacolborane 6a

Inspired by the above success, we noted that apart from the aforementioned organic salts, the present optimized reaction conditions could also be suitable for the trifluoromethoxylation of the other class of organic substrates. Thus, on top of that, we decided to screen the same conditions for the same synthetic scenarios by replacing the organic salts with aryl pinacolboranes, choosing compound **6a** as the model substrate (Scheme 6; Table S3). Conceivably, the reaction proceeded well enough to afford the targeted aryl trifluoromethyl ether **3c** with a 91% yield (Table S3, entry 2), confirming the superiority of CoF_2 in the present protocol. A slow decrement in the yield of **3c** was observed when replacing CoF_2 with the respective palladium analog (Table S3, entry 4), while the model reactions failed in the presence of AgF and CuF_2 (Table S3, entries 1 and 3). Of note, the conduction of model reaction at only one frequency (15 or 30Hz) resulted in the decrement in the yield of product **3c** (Table S3, entries 5 and 6). Moreover, all the solution phase reactions of the aryl pinacolborane **6a** failed to deliver the targeted product **3c** (Table S3, entries 7–10), citing the superiority of the mechanochemical ball milling over the conventional solution-based methods. Fifteen such aryl trifluoromethyl



Scheme 6. Model reaction for the trifluoromethoxylation of aryl pinacolborane 6a

ether derivatives (**3c, 3m, 3o, 3p, 3s–3z** and **3aa–3ac**) have been synthesized from the respective aryl pinacolboranes **6** (Scheme 7) using the present optimization conditions (Table S3, entry 2). Examination of the substrate scope of aryl pinacolboranes **6** revealed that the presence of electron donating, withdrawing, or fused substituents in the aryl ring did not make any observable impact in the yields of the respective products.

Reaction mechanism elucidation in the trifluoromethoxylation of aryl pinacolboranes 6

From the reported literature, it is expected that the trifluoromethoxylation of aryl pinacolboranes might proceed through the oxidative addition-reductive elimination cycle (Scheme 8).[29] As discussed earlier, the first step involves *in situ* generation of $Co^{II}(OCF_3)_2$ by the reaction of $CO(OCCl_3)_2$ and CoF_2. Meanwhile, the reaction of aryl pinacolborane **6** with CoF_2 generates the fluoro pinacolborate intermediate **Int1**. Next, the **Int1** undergoes transmetalation with $Co^{II}(OCF_3)_2$ precursor to form the Co^{II} intermediate species **Int2**. Finally, the targeted aryl trifluoromethyl ether **3** was formed via reductive elimination from **Int2** generating the Co^0 species **Int3**. The higher efficiency of trifluoromethoxylation of aryl pinacolboranes **6** might be anticipated due to the formation of borate intermediate **Int1**, which facilitates the smooth transmetalation of the aryl group from B to Co(II) species.

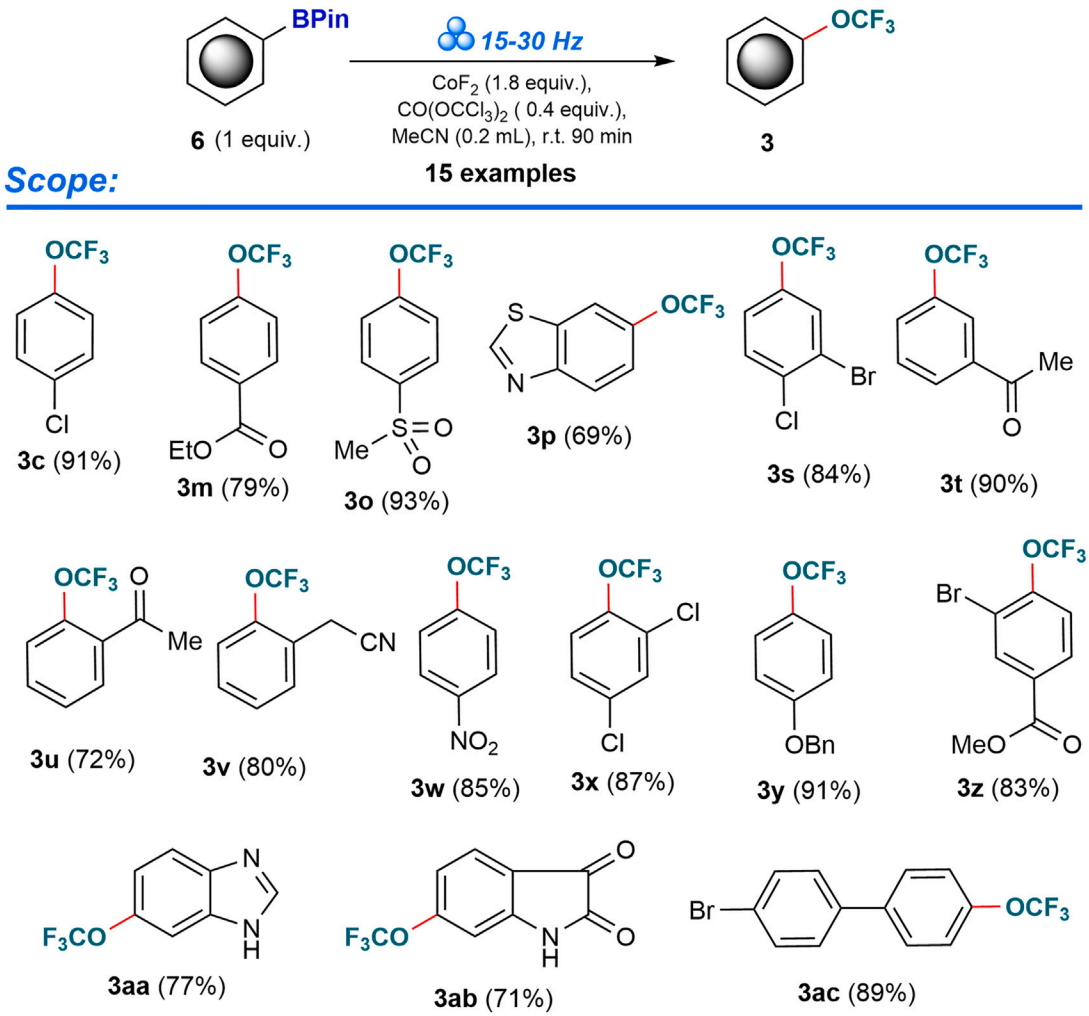
In conclusion, we have developed a highly efficient and alternative approach for the selective mechanochemical transformation of aryldiazonium tetrafluoroborates and aryltrimethylammonium triflates to aryl trifluoromethyl ethers via an *in situ*-generated OCF_3 source using triphosgene and Co(II) fluoride (CoF_2). Furthermore, the proposed synthetic method is successfully applied for the selective transformation of other groups such as arylsulfonium, diaryliodonium, and aryl pinacolborane functionalities. The present trifluoromethoxylation strategy exhibited a broad functional group tolerance and was found to be superior over other existing protocols in terms of substrate scope, yields, operational simplicity, and reaction times. Moreover, the construction of a direct C_{aryl}-OCF_3 bond in a single step would have great significance in the late-stage modification of complex pharmaceuticals, agrochemicals, and natural products.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Viktor O. Iaroshenko (iva108@gmail.com).



Scheme 7. Substrate scope for trifluoromethoxylation of aryl pinacolboranes 6

Materials availability

Experimental section, substrate scope, and optimization are found in Tables S1–S3. Reaction procedures with optimized reaction conditions, characterization of products, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra are provided in the supplemental information. All materials generated in this study are available from the lead contact without restriction.

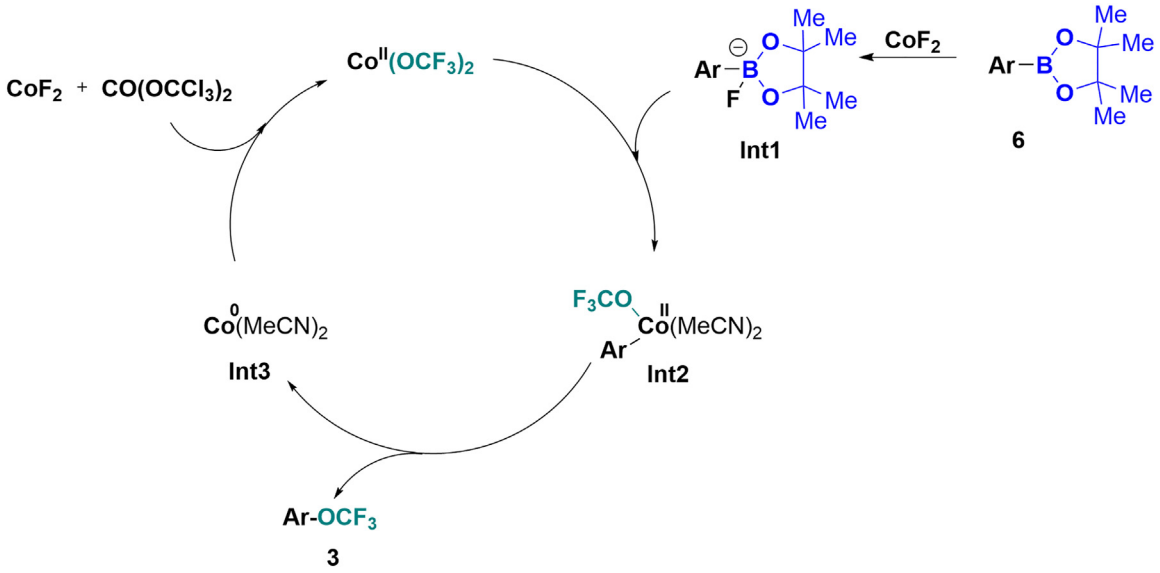
Data and code availability

The authors declare that the data supporting the findings of this study are available within the article and the supplemental information. Additional requests for data or information will be fulfilled by the lead contact.

Reaction procedure with optimized reaction conditions

General procedure for the synthesis of trifluoromethyl ethers 3 starting from aryl diazonium salts 1

Inside a glovebox, to a 5-mL grinding vessel (made of stainless steel) equipped with two balls (made of stainless steel, diameter: 5 mm) was placed consequently appropriate aryl diazonium salt (1.0 mmol, 1 equiv), dry CoF_2 (174 mg, 1.8 mmol, 1.8 equiv), and triphosgene (119 mg, 0.4 mmol, 0.4 equiv); finally, 0.2 mL acetonitrile



Scheme 8. Plausible mechanism for trifluoromethoxylation of aryl pinacolboranes 6

was added and the reaction vessel was properly capped. Afterward, the reaction vessel was installed on the mill and subjected to milling at 15 Hz for 30 min and then at 30 Hz for 60 min. After completion of the reaction, the content of the vessel, without pre-treatment, was directly subjected to gradient flash chromatography on silica gel to isolate the desired product. The gram-scale synthesis was performed on 10 mmol of the starting salts in a 25-mL grinding vessel using two 10-mm balls.

General procedure for the synthesis of trifluoromethyl ethers 3 starting from aryltrimethylammonium salts 2

Inside a glovebox, to a 5-mL grinding vessel (made of stainless steel) equipped with two balls (made of stainless steel, diameter: 5 mm) was placed consequently appropriate aryltrimethylammonium salt (1.0 mmol, 1 equiv) dry CoF_2 (174 mg, 1.8 mmol, 1.8 equiv), and triphosgene (119 mg, 0.4 mmol, 0.4 equiv); finally, 0.2 mL acetonitrile was added and the reaction vessel was properly capped. Afterward, the reaction vessel was installed on the mill and subjected to milling at 15 Hz for 30 min and then at 30 Hz for 60 min. After completion of the reaction, the content of the vessel, without pre-treatment, was directly subjected to gradient flash chromatography on silica gel to isolate the desired product. The gram-scale synthesis was performed on 10 mmol of the starting salts in a 25-mL grinding vessel using two 10-mm balls.

General procedure for the synthesis of trifluoromethyl ethers 3 starting from dimethyl(aryl)sulfonium salts 4

Inside a glovebox, to a 5-mL grinding vessel (made of stainless steel) equipped with two balls (made of stainless steel, diameter: 5 mm) was placed consequently appropriate dimethyl(aryl)sulfonium salt (1.0 mmol, 1 equiv) dry CoF_2 (174 mg, 1.8 mmol, 1.8 equiv), and triphosgene (119 mg, 0.4 mmol, 0.4 equiv); finally, 0.2 mL acetonitrile was added and the reaction vessel was properly capped. Afterward, the reaction vessel was installed on the mill and subjected to milling at 15 Hz for 30 min and then at 30 Hz for 60 min. After completion of the reaction, the content of the vessel, without pre-treatment, was directly subjected to gradient flash chromatography on silica gel to isolate the desired product.

General procedure for the synthesis of trifluoromethyl ethers 3 starting from diaryliodonium salts 5

Inside a glovebox, to a 5-mL grinding vessel (made of stainless steel) equipped with two balls (made of stainless steel, diameter: 5 mm) was placed consequently appropriate diaryliodonium salt (1.0 mmol, 1 equiv) dry CoF_2 (174 mg, 1.8 mmol, 1.8 equiv), and triphosgene (119 mg, 0.4 mmol, 0.4 equiv); finally, 0.2 mL acetonitrile was added, and the reaction vessel was properly capped. Afterward, the reaction vessel was installed on the mill and subjected to milling at 15 Hz for 30 min and then at 30 Hz for 60 min. After completion of the reaction, the content of the vessel, without pre-treatment, was directly subjected to gradient flash chromatography on silica gel to isolate the desired product. The gram-scale synthesis was performed on 10 mmol of the starting salts in a 25-mL grinding vessel using two 10-mm balls.

General procedure for the synthesis of trifluoromethyl ethers 3 starting from aryl pinacolboranes 6

Inside a glovebox, to a 5-mL grinding vessel (made of stainless steel) equipped with two balls (made of stainless steel, diameter: 5 mm) was placed consequently appropriate aryl pinacolborane (1.0 mmol, 1 equiv) dry CoF_2 (174 mg, 1.8 mmol, 1.8 equiv), and triphosgene (119 mg, 0.4 mmol, 0.4 equiv); finally, 0.2 mL acetonitrile was added, and the reaction vessel was properly capped. Afterward, the reaction vessel was installed on the mill and subjected to milling at 15 Hz for 30 min and then at 30 Hz for 60 min. After completion of the reaction, the content of the vessel, without pre-treatment, was directly subjected to gradient flash chromatography on silica gel to isolate the desired product.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrp.2024.102118.

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AUTHOR CONTRIBUTIONS

Conceptualization, S.M. and V.O.I.; methodology, S.M., V.O.I., and O.S.; investigation, S.M., O.S., J.Z., V.B.P., J.N., J.F., G.A., M.G.G., E.K., B.B., and V.O.I.; writing – original draft, V.B.P., S.M., and V.O.I.; writing – review & editing, V.B.P., S.M., and V.O.I.; funding acquisition, S.M. and V.O.I.; resources, V.O.I.; supervision, S.M. and V.O.I.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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