# General and Scalable Approach to Trifluoromethyl-substituted Cyclopropanes

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*Dedicated to the brave people of Ukraine*

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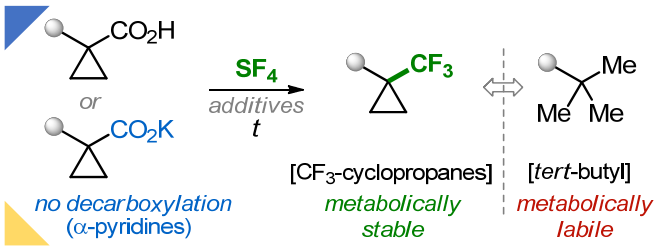



**ABSTRACT:** $CF_3$-cyclopropanes were prepared on a multigram scale by deoxyfluorination of cyclopropane carboxylic acids or their salts with sulfur tetrafluoride. For labile α-pyridine acetic acids, only the use of salts allowed to obtain the needed products. Derivatization of $CF_3$-cyclopropanes into building blocks ready for the direct use in medicinal chemistry was performed.

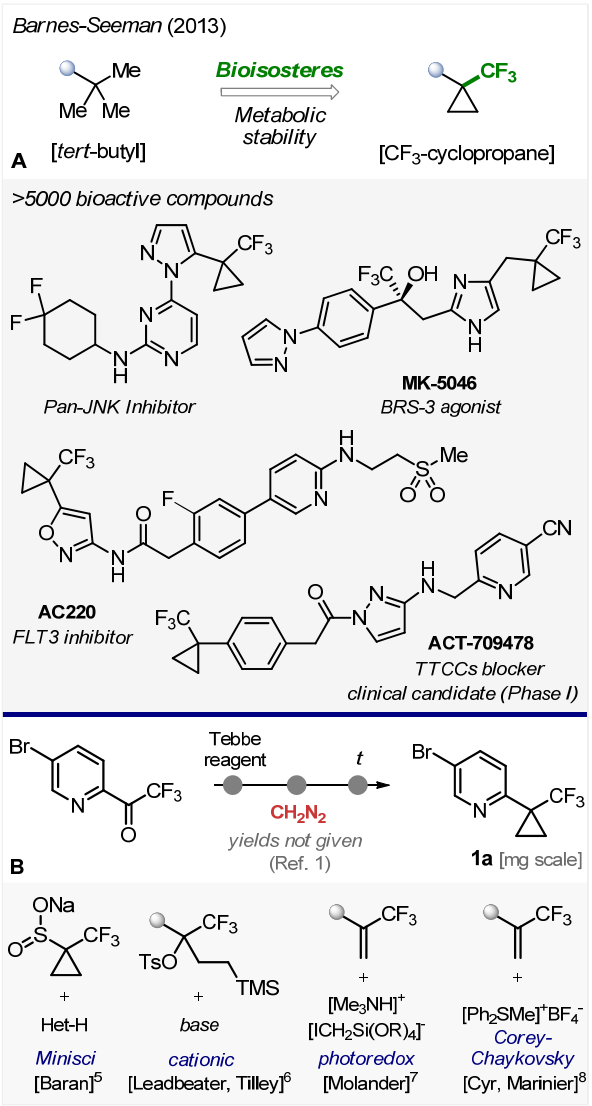
**Introduction**. In 2013, Barnes-Seeman with colleagues at Novartis showed that 1,1-disubstituted trifluoromethyl cyclopropanes could be used as metabolically stable bioisosteres of the *tert*-butyl group (Scheme 1A).[1] Since that time, the popularity of trifluoromethyl cyclopropanes in drug discovery programs started growing. More than five thousand bioactive compounds bearing the $CF_3$-cyclopropane substituent appeared in patent literature already.[2,3] Especially worth mentioning the brain-penetrating T-type calcium channel blocker ACT-709478 that recently entered Phase I clinical trials (Scheme 1).[3d]

The chemistry of $CF_3$-cyclopropanes has been the subject of at least four synthetic reviews already.[4] However, the specific class of 1,1-disubstituted trifluoromethyl cyclopropanes outlined above has been much less studied. In the original publication,[1] the authors synthesized compound **1a** with the help of diazomethane (Scheme 1B). The need from the industrial community prompted diverse academic groups to develop alternative approaches to $CF_3$-cyclopropanes. The comprehensive contributions of Baran;[5] Leadbeater, Tilley;[6] Molander;[7] and Cyr, Marinier[8] are especially worth noting (Scheme 1B). Also, several manuscripts on other topics that appeared recently contained 2-3 examples of the needed $CF_3$-cyclopropanes in the substrate scope.[9]

**Results and Discussion**. A couple of years ago, we received a request from a pharmaceutical company on the multigram synthesis of bromide **1a**. That compound was described in the literature.[1] However, the reported synthetic scheme required the use of diazomethane and had no yields. We, therefore, needed to develop another method that would be scalable and would rely on the available starting materials.

Previously, we developed a general deoxyfluorination of aliphatic carboxylic acids using a sulfur tetrafluoride/water combination.[9c] In that work, two examples of aromatic cyclopropane carboxylic acids were also used (Scheme 2). In the beginning, we were confident that compound **1a** could also be synthesized analogously. Unexpectedly, under identical conditions, the deoxyfluorination of acid **1** did not proceed. Increasing the reaction time or temperature did not help either (entries 1-5). We understood that the initially formed catalytic hydrogen fluoride (needed to initiate the deoxyfluorination) was immediately consumed by the basic pyridine nitrogen atom that stopped the reaction. Next, we decided to switch to the combination sulfur tetrafluoride/hydrogen fluoride that we used previously for the deoxyfluorination of less active (hetero)aromatic carboxylic acids and problematic carbonyl groups.[10] The plan was to block a basic nitrogen atom in pyridine with an excess of hydrogen fluoride. Unexpectedly,

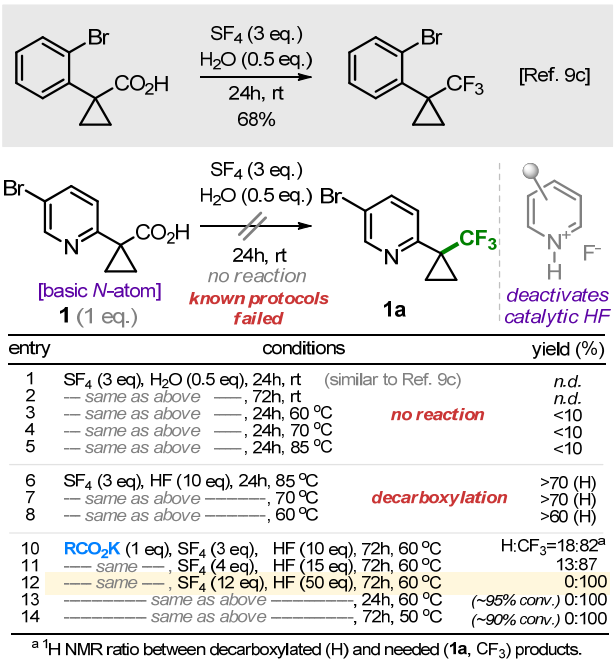
**Scheme 1**. A) $CF_3$-cyclopropanes as metabolically stable bioisosteres of the *tert*-butyl group; B) Chemical approaches to $CF_3$-cyclopropanes.




however, we faced another problem: α-pyridine carboxylic acids decarboxylated under the above-mentioned conditions (entries 6-8). At this point we were almost ready to give up on that approach, until a serendipitous observation happened.

Carboxylic acid **1** is obtained by alkali hydrolysis of the corresponding nitrile. During the work-up, acidification and isolation, temperature must be carefully controlled to avoid decarboxylation that is common for α-pyridine carboxylic acids.[11] Therefore, out of curiosity, we simply evaporated the reaction mixture after the hydrolysis (containing $RCO_2K$ and the residual KOH) and used the crude residue in the deoxyfluorination step. Surprisingly, we did observe the formation of the needed product **1a** (Scheme 2, entry 10). Decarboxylation still took place, but it was not a dominant process anymore. At this point, we easily optimized the procedure further (entries 11-15). Increasing the amount of sulfur tetrafluoride and hydrogen fluoride allowed to completely suppress the decarboxylation (entry 12).

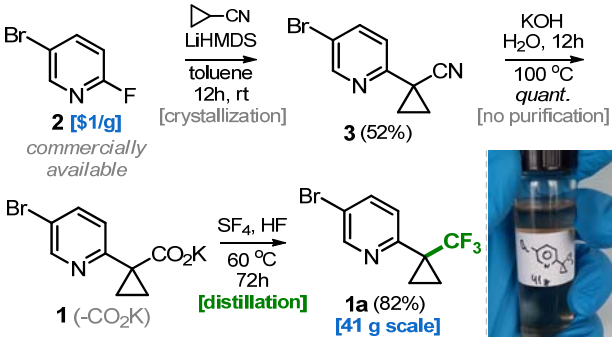
**Scheme 2**. Optimization of the synthesis of $CF_3$-cyclopropane **1** with a basic nitrogen atom.




| entry | conditions | | yield (%) |
|---|---|---|---|
| 1 | $SF_4$ (3 eq), $H_2O$ (0.5 eq), 24h, rt | (similar to Ref. 9c) | *n.d.* |
| 2 | — same as above —, 72h, rt | | *n.d.* |
| 3 | — same as above —, 24h, 60 °C | ***no reaction*** | <10 |
| 4 | — same as above —, 24h, 70 °C | | <10 |
| 5 | — same as above —, 24h, 85 °C | | <10 |
| 6 | $SF_4$ (3 eq), HF (10 eq), 24h, 85 °C | | >70 (H) |
| 7 | — same as above ————, 70 °C | ***decarboxylation*** | >70 (H) |
| 8 | — same as above ————, 60 °C | | >60 (H) |
| 10 | $RCO_2K$ (1 eq), $SF_4$ (3 eq), HF (10 eq), 72h, 60 °C | | H:$CF_3$=18:82[a] |
| 11 | —— same ——, $SF_4$ (4 eq), HF (15 eq), 72h, 60 °C | | 13:87 |
| 12 | —— same ——, $SF_4$ (12 eq), HF (50 eq), 72h, 60 °C | | 0:100 |
| 13 | ———— same as above ————, 24h, 60 °C | | *(~95% conv.)* 0:100 |
| 14 | ———— same as above ————, 72h, 50 °C | | *(~90% conv.)* 0:100 |

[a] $^1$H NMR ratio between decarboxylated (H) and needed (**1a**, $CF_3$) products.

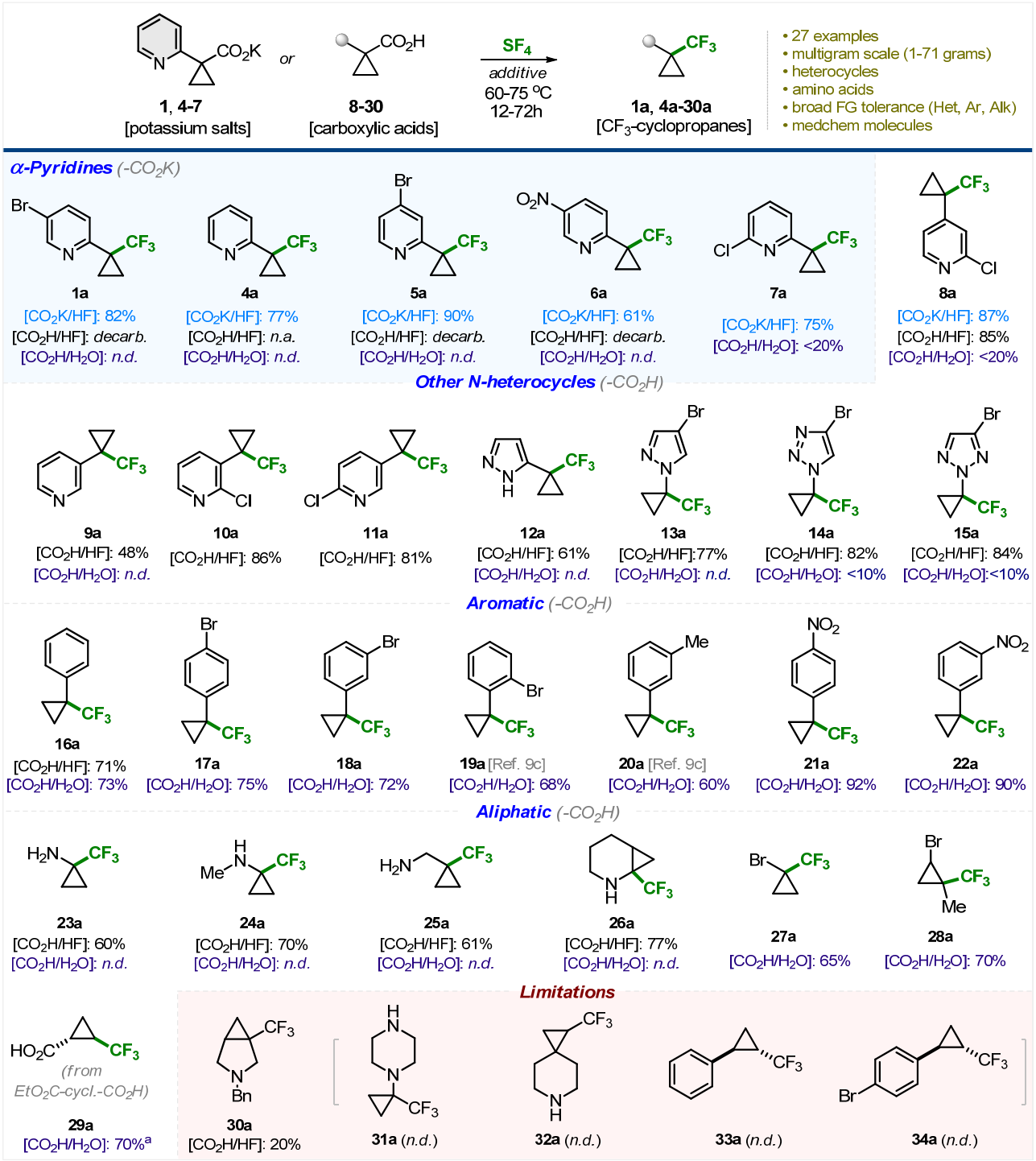
**Scheme 3**. Gram-scale synthesis of $CF_3$-cyclopropane **1**.




The whole synthetic sequence to compound **1a** is depicted in Scheme 3. The commercially available 2-fluoropyridine **2** reacted with cyclopropyl nitrile in the presence of LiHMDS in toluene to give the pure nitrile **3** in 52% yield after crystallization from hexane/chloroform mixture. The hydrolysis of the nitrile group was performed with potassium hydroxide in water under reflux overnight. Evaporation of that mixture gave a crude solid residue ($RCO_2K$+KOH) that was directly used in the next step. Treatment of the latter with sulfur tetrafluoride/hydrogen fluoride at 60 °C for three days allowed isolation of the pure $CF_3$-cyclopropane **1a** in 82% yield after distillation. The developed synthetic route allowed to obtain 41 grams of the product in one run. Moreover, the whole synthetic sequence was optimized to avoid any column chromatography.

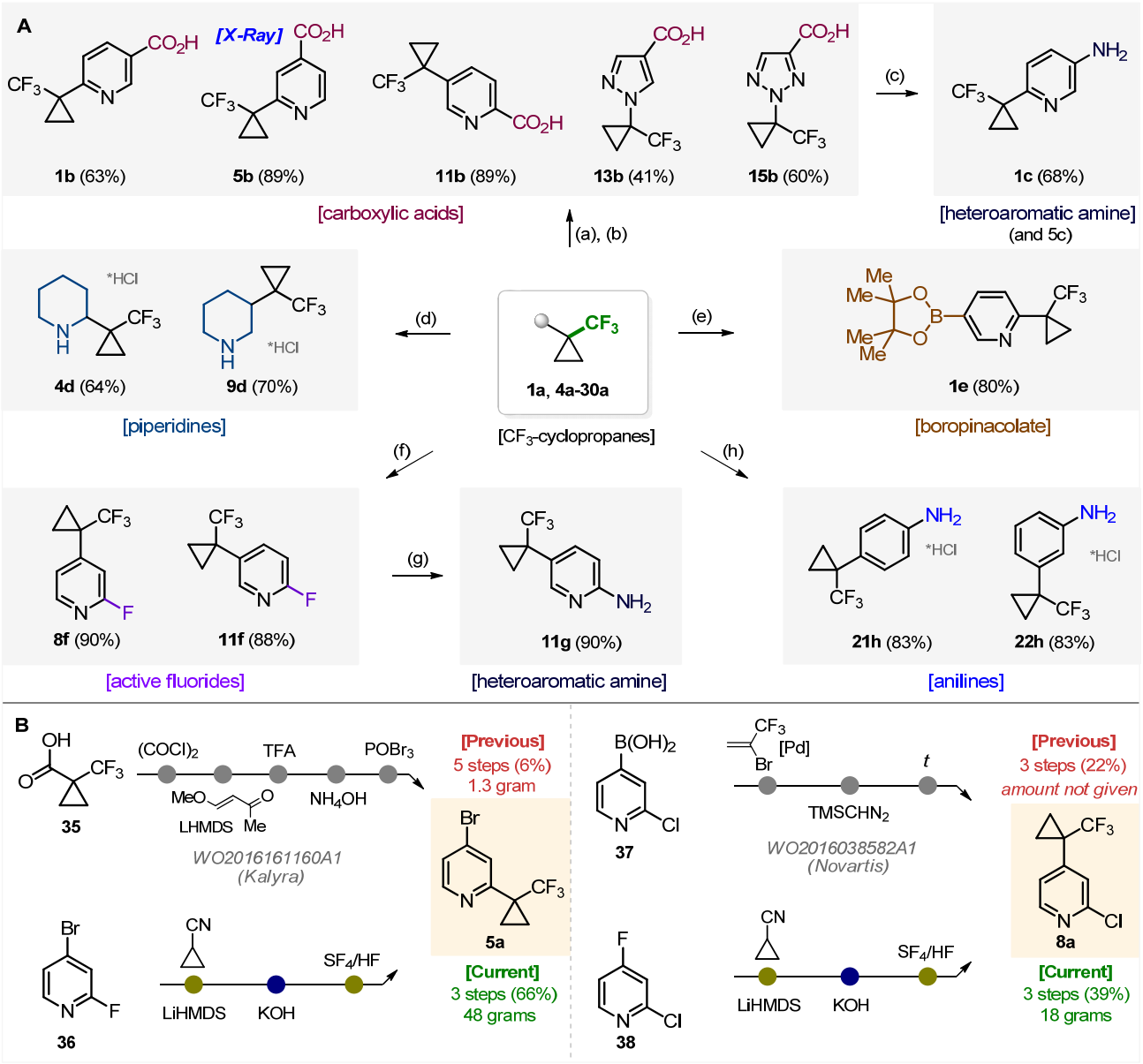
Next, we wondered if the developed protocol was general. Indeed, using the same tactic, we could easily convert the crude potassium salts of α–pyridine acetic acids **4-7** into the trifluoromethyl cyclopropanes **4a-7a** in 61-82% yield (Scheme 4). Again, the previously known protocols did not work for these compounds. Basic pyridine atom was not compatible

**Scheme 4**. Scope of the reaction. *Reaction conditions*. [$CO_2K$/HF]: $RCO_2K$ (1 eq.), $SF_4$ (12 eq.), HF (50 eq.), 60 °C, 72h. [$CO_2H$/HF]: $RCO_2H$ (1 eq.), $SF_4$ (3-4 eq.), HF (12-26 eq.), 60-75 °C, 12-72h (please, see SI for details). [$CO_2H/H_2O$]: $RCO_2H$ (1 eq.), $SF_4$ (3 eq.), $H_2O$ (cat.), 60-75 °C, 12-72h (please, see SI for details). [a]After the subsequent alkali hydrolysis of the ester group.




with sulfur tetrafluoride/water procedure, while decarboxylation was observed when treating carboxylic acids with sulfur tetrafluoride/hydrogen fluoride. For γ–pyridine derivative **8** we could use both potassium salt and the free carboxylic acid in the reaction. Presumably, α–chlorine atom reduced basicity of the pyridine nitrogen, making thereby the carboxylic acid **8** stable to thermal decarboxylation. Pyridine β-acetic acids are stable, and we could easily convert substrates **9-11** into trifluoromethyl cyclopropanes **9a-11a** in 48-86%. Pyrazole- (**12**, **13**) and triazole-acetic acids **14**, **15** were also converted into the desired products **12a-15a**[12] in 61-84% yield with sulfur tetrafluoride/hydrogen fluoride. In all cases, the basic nitrogen atom prevented the use of sulfur tetrafluoride/water procedure.

**Scheme 5**. Modifications of $CF_3$-cyclopropanes. (A) *Reaction conditions.* (a) $PdCl_2(dppf)\cdot CH_2Cl_2$, $NEt_3$, CO, MeOH, 25 atm, 120 °C, 16 h. (b) NaOH, MeOH, $H_2O$, 12 h, rt. (c) i) DPPA, $NEt_3$, *t*BuOH, 80 °C, 12 h; ii) HCl, rt, 12 h. (d) $Pd(OH)_2/C$, $H_2$, HCl, MeOH, rt, 12 h. (e) $B_2Pin_2$, KOAc, $Pd(dppf)Cl_2$, dioxane, 95 °C, 12 h. (f) CsF, DMSO, 120 °C, 72 h. (g) $NH_3$, 100 °C, 12 h. (h) Al/Ni, $H_2$, MeOH, rt, 12 h. (B) Comparison of approaches to $CF_3$-cyclopropanes **5a** and **8a**.




Next, we tried common aromatic substrates with no basic nitrogen atoms. Acid **16** was equally well converted into the product **16a** (71-73%) using both protocols: sulfur tetrafluoride/water and sulfur tetrafluoride/hydrogen fluoride. Therefore, we next converted aromatic substrates **17-22** into the corresponding fluorinates derivatives **17a-22a** in 60-90% yield using the easiest protocol: sulfur tetrafluoride water (Scheme 4).

Amino acids **23-26** with basic nitrogen atoms were not compatible with sulfur tetrafluoride/water, and we converted them into products **23a-26a** using sulfur tetrafluoride/hydrogen fluoride in 60-77% yield. Aliphatic bromides **27**, **28** and ester **29** were also smoothly converted into medchem-relevant products **27a-29a** in 65-70% yield using sulfur tetrafluoride/water (Scheme 4).[13]

We also would like to disclose limitations of the current method. Although, we could isolate the pure product **30a**, the best yield was only 20% (Scheme 4). Cyclopropane carboxylic acids **31-34**, however, failed to give the needed trifluoromethyl derivatives **31a-34a** under all conditions that we tried due to decomposition.

In short summary, all cyclopropane carboxylic acids studied here could be subdivided into three classes:

(a) simple aromatic (**16-22**) and aliphatic (**28-31**) derivatives. For these substrates, we recommend the use of the easiest protocol reported before: sulfur tetrafluoride with catalytic amount of water, [$CO_2H/H_2O$].

(b) substrates with basic nitrogen atoms: *N*-heterocycles (**9-15**) and amino acids (**23-26**). For these substrates, the previous protocol does not work, because the nitrogen atom traps the

formed catalytic hydrogen fluoride. A combination sulfur tetrafluoride/hydrogen fluoride, [$CO_2H$/HF], must be used.

(c) α-Pyridine acetic acids. This is the most problematic class. Basic nitrogen atom and the innate tendency to decarboxylation prevented the use of all previously known protocols, [$CO_2H/H_2O$] or [$CO_2H$/HF]. We have discovered here that the crude potassium salts (from the alkali hydrolysis of nitriles) could be directly used in the deoxyfluorination step with sulfur tetrafluoride/hydrogen fluoride, [$CO_2K$/HF].

Representative modifications of the obtained $CF_3$-cyclopropanes into building blocks ready for the direct use in medicinal chemistry campaigns was undertaken next. [Pd]-catalyzed carbonylation of bromide **1a** followed by saponification of the intermediate ester gave carboxylic acid **1b** (Scheme 5A). Analogously, acids **5b**, **11b**, **13b** and **15b** were synthesized. Structure of product **5b** was confirmed by X-Ray crystallographic analysis.[14] Curtius reaction of acid **1b** gave heteroaromatic amine **1c**. Similarly, amine **5c** was synthesized. [Pd]-catalyzed hydrogenation of pyridines **4a** and **9a** gave the substituted piperidines **4d** and **9d** (Scheme 5A). Bromide **1a** was also easily converted into Bpin derivative **1e** in 80% yield. Chloropyridines **8a**, **11a** reacted with CsF to provide fluorides **8f** and **11f**. Reaction of the latter with liquid ammonia gave 2-aminopyridine **11g** in 90% yield. Finally, reduction of the nitro group in compounds **21a**, **22a** gave interesting anilines **21h** and **22h**.

The protocol described here could be used not only to make new molecules but also to facilitate the synthesis of the known ones (Scheme 5B). Alternative improved synthesis of compound **1a** was discussed earlier (Schemes 1-3). Also, previously the synthesis of bromide **5a** was realized in five steps in 6% overall yield from carboxylic acid **36**.[15] In this work, we could obtain product **5a** (48 g) in three steps and 66% yield from pyridine **36**. Chloride **8a** was previously obtained in three steps from boronic acid **37** in 22% combined yield.[16] Here, we synthesized **8a** (18 g) in three steps and 39% yield from pyridine **38**.

**Summary**. In this work, we developed a general and scalable approach to $CF_3$-cyclopropanes. The protocol relies on the one-step deoxyfluorination of various cyclopropane-carboxylic acids or their salts with sulfur tetrafluoride. For labile α-pyridine acetic acids, all previous protocols failed; and only salts of carboxylic acids afforded the needed products **1a**-**7a**. All compounds described here were obtained on a gram-to-multigram scale.

We hope that the results described in this work will be of interest to practitioner medicinal chemists and agrochemists, and that the bioisosteric replacement of the metabolically labile *tert*-butyl groups with $CF_3$-cyclopropanes will become even more popular soon.

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**Keywords:** cyclopropanes • trifluoromethyl • *tetr*-butyl • bioisosteres • medicinal chemistry

**Data Availability Statement**

The data underlying this study are available in the published article and its online Supporting Information.

**Supporting Information.**

Experimental procedures, characterization data, Copies of $^{1}H$, $^{19}F$, $^{13}C$ nuclear magnetic resonance (NMR) spectra (PDF) FAIR data, including the primary NMR FID files.

**Accession Codes**

CCDC 2226167 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

**Notes**

The authors declare the following competing financial interest(s): Authors are employees of a chemical supplier Enamine.

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