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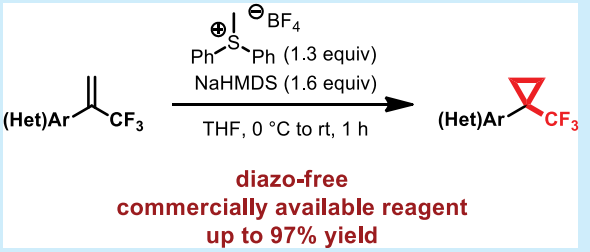
Mild and Diazo-Free Synthesis of Trifluoromethyl-Cyclopropanes Using Sulfonium Ylides

Patrick Cyr,*[,†] Joël Flynn-Robitaille,[†] Patrick Boissarie,[†] and Anne Marinier*[,†,‡,§]

[†]Medicinal Chemistry, Institute of Research in Immunology and Cancer, Université de Montréal, Montreal, QC H3C 3J7, Canada
[‡]Département de chimie, Faculté des Arts et Sciences, Université de Montréal, Montreal, QC H3C 3J7, Canada
[§]Département de pharmacologie, Faculté de Médecine, Université de Montréal, Montreal, QC H3C 3J7, Canada

Supporting Information

ABSTRACT: The synthesis of several 1,1-disubstituted trifluoromethyl-cyclopropanes (TFCPs), known as *tert*-butyl bioisosteres, has been achieved from the reaction between trifluoromethylalkenes and unstabilized sulfonium ylides in yields of ≤97%. This method offers practical access to this cyclopropyl moiety of pharmacological interest, employing a commercially available reagent at low temperatures. The synthesis of cyclopropanes bearing other electron-withdrawing groups as well as trisubstituted TFCPs was also accomplished.



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The cyclopropyl moiety is widely used in drug discovery and found in numerous pharmaceutical products.[1] Within this family, the 1,1-disubstituted trifluoromethyl-cyclopropane (TFCP) motif recently emerged as a useful bioisostere of *tert*-butyl substitutents, as it generally provides increased metabolic stability, leading to improved overall pharmacokinetic properties.[2] Such a benefit inspired the incorporation of the TFCP surrogate in many pharmaceutical lead compounds displaying biological activities in various therapeutic areas, including autoimmune diseases [I (Figure 1)],[3a] epilepsy (II),[3b] cancer (III),[3c] and chronic neurodegenerative disorders (IV).[3d] As a result of the increased use of TFCPs in biologically relevant compounds, a need to develop a general and efficient method for their synthesis arose.

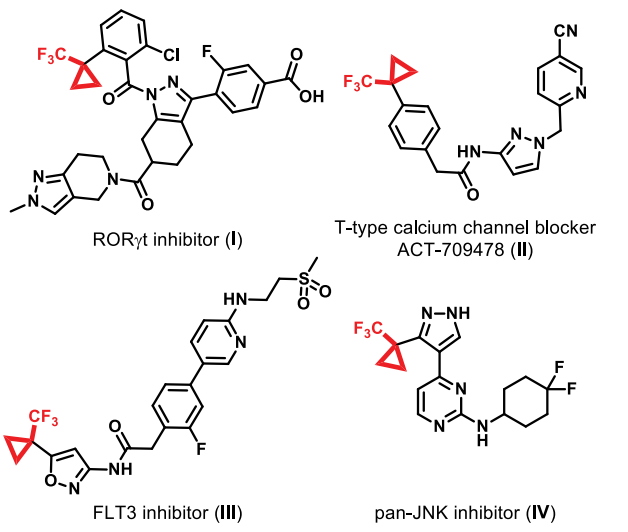
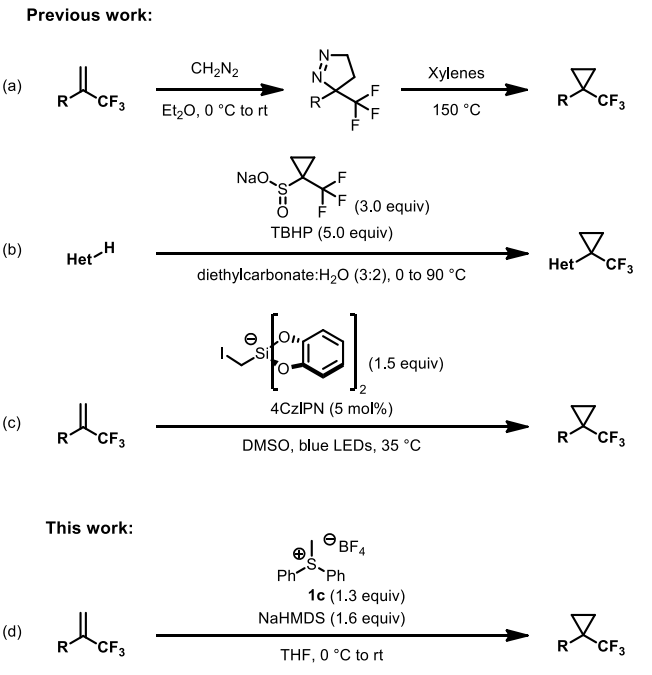


Figure 1. Bioactive pharmaceutical leads bearing the TFCP motif.

The classical way to synthesize TFCPs consists of a [3+2] cycloaddition between a trifluoromethylalkene and diazomethane, followed by nitrogen extrusion (Scheme 1a).[2b,4]

Scheme 1. Synthesis of TFCPs



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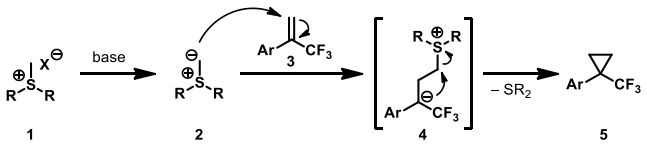
While this stepwise approach successfully produced several therapeutic leads,[2b,3a] the synthetic community has been engaged in the development of a milder and more direct method.[5] Another key improvement would consist of the use of a bench-stable reagent that would allow safer and easier manipulation. More precisely, Baran used a sulfinate as a radical precursor to directly generate TFCPs from heterocycles (Scheme 1b).[6] An alternative approach was developed by Molander; he used photoredox catalysis to generate a radical that could subsequently add on a trifluoromethylalkene (Scheme 1c).[7] These new strategies facilitated access to trifluoromethyl-cyclopropyl groups; however, the former is limited to specific heterocyclic structures, and the latter requires the use of a photochemical reactor setup and a reagent that is not commercially available.

Therefore, we sought to develop mild and robust conditions that could provide the desired TFCP substitution starting from the corresponding, easily accessible,[8] 1,1-disubstituted trifluoromethylalkene. For that purpose, we envisioned using a Corey–Chaykovsky cyclopropanation strategy (Scheme 1d).[9] Such a reaction was first described by scientists at Merck Sharp & Dohme Corp., although no yield was reported.[9b] On the basis of previous studies,[10] this transformation requires a sufficiently nucleophilic sulfur ylide **2** to add to alkene **3** (Scheme 2). Intermediate **4** must then contain a leaving group

Scheme 2. Cyclopropanation of Trifluoromethylalkenes with Sulfonium Ylide 2

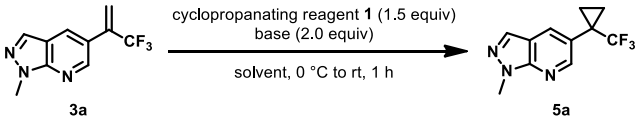


favoring an intramolecular cyclization toward TFCP **5** instead of undergoing fluoride elimination.[9c] Hence, our efforts focused on the identification of such a reagent.

Different reagents known to be reactive in the standard Corey–Chaykovsky cyclopropanation reaction were tested on the medicinal chemistry-relevant scaffold **3a** using NaHMDS as the base and THF as the solvent (Table 1, entries 1–3). Trimethylsulfoxonium iodide (Me_3SOI, **1a**) gave no reaction (Table 1, entry 1), whereas the trimethylsulfonium iodide (Me_3SI, **1b**) induced decomposition of the starting material while providing small quantities of TFCP **5a** (Table 1, entry 2). Only methyl(diphenyl)sulfonium tetrafluoroborate (Ph_2SMeBF_4, **1c**)[9b,d] furnished the desired TFCP-containing product in significant quantities (Table 1, entry 3). Cherishing the idea of developing a method using a commercially available reagent, we selected sulfonium **1c** for further optimization of the reaction conditions. Other solvents for this reaction failed to provide an increase in yield compared to that found with THF (Table 1, entries 4–6). Similarly, the screening of other bases for the cyclopropanation reaction confirmed NaHMDS as being optimal (Table 1, entries 7–10). Decreasing the amount of reagent **1c** and base used to 1.3 and 1.6 equiv, respectively, afforded TFCP **5a** in 65% yield (Table 1, entry 11).

Once the optimized reaction conditions were established, the substrate scope of the cyclopropanation reaction was studied (Scheme 3). To our delight, the methodology appeared to be quite general to a variety of heterocycles,

Table 1. Optimization of Reaction Conditions[a]



entry	cyclopropanating reagent **1**	base	solvent	yield (%)[b]
1	Me_3SOI, **1a**	NaHMDS	THF	0[c]
2	Me_3SI, **1b**	NaHMDS	THF	<10[c]
3	Ph_2SMeBF_4, **1c**	NaHMDS	THF	57[d]
4	Ph_2SMeBF_4, **1c**	NaHMDS	DCM	48[d]
5	Ph_2SMeBF_4, **1c**	NaHMDS	toluene	54[d]
6	Ph_2SMeBF_4, **1c**	NaHMDS	DME	42[d]
7	Ph_2SMeBF_4, **1c**	LiHMDS	THF	52
8	Ph_2SMeBF_4, **1c**	KHMDS	THF	19
9	Ph_2SMeBF_4, **1c**	NaH	THF	32
10	Ph_2SMeBF_4, **1c**	*t*-BuONa	THF	51
11	Ph_2SMeBF_4, **1c**	NaHMDS	THF	65[e]

[a]Reactions were run on a 0.066 mmol scale. [b]Yields determined from analysis of the crude ^1H NMR spectrum using triphenylmethane as an internal standard. [c]With 2.0 equiv of reagent, 4.0 equiv of base, and a temperature gradient from −78 °C to rt. [d]A temperature gradient from −78 °C to rt. [e]With 1.3 equiv of reagent and 1.6 equiv of base.

affording the desired TFCP products in yields ranging from 36% to 81% (Scheme 3, products **5a**–**5g**). This demonstrates the applicability of the method to relevant systems in medicinal chemistry. When using the more electron-rich indole **3h**, no reaction occurred, most likely due to its reduced electrophilicity. To test the necessity of having a heteroatom in the ring attached to the trifluoromethylalkene, substituted phenyls were also examined, displaying moderate to good yields (Scheme 3, products **5i**–**5n**, 50–97% yields). Gratifyingly, electron-neutral rings **3k** and **3l**, as well as electron-rich ring **3n**, afforded their corresponding TFCP products in good yields (Scheme 3, **5k**, **5l**, and **5n**, respectively), indicating that an electron-withdrawing group is not required for the reaction to proceed. A particularity of naphthyl product **5l** is that it could not be separated from the diphenyl sulfide byproduct using flash chromatography. To facilitate its separation, we decided to methylate back the diphenyl sulfide using methyl trifluoromethanesulfonate (MeOTf) to create a salt. This successful procedure opens the possibility of recycling the cyclopropanating reagent, something that could be of interest in large scale processes.

To broaden the scope of our methodology, we investigated the applicability of the method to the synthesis of cyclopropanes presenting different substitution patterns. We began by testing the cyclopropanation reaction on alkenes bearing electron-withdrawing groups other than CF_3. As could be expected, pentafluoroethyl (**7a**)- and cyano (**7b**)-substituted cyclopropanes (Table 2, entries 1 and 2, respectively) were accessed with yields in the same range as those obtained for TFCPs. On the other hand, when nitro-substituted alkene **6c** was exposed to the same reaction conditions (Table 2, entry 3), it resulted in a poor yield, probably due to the high reactivity of the substrate.[9a] The cyclopropanation with vinylsulfone **6d** appeared to be less efficient than when stabilized sulfonium ylides were employed[10a] but still provided 37% of **7d** (Table 2, entry 4), whereas this substrate was unreactive under Molander's cyclopropanation conditions (Scheme 1c).[7] An interesting observation was also that 3-nitrostyrene **6e** proved to be completely unreactive to the

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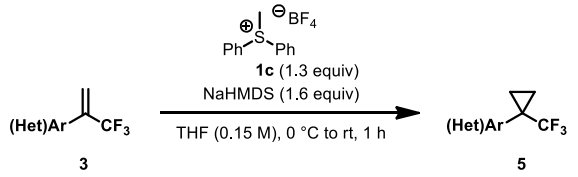
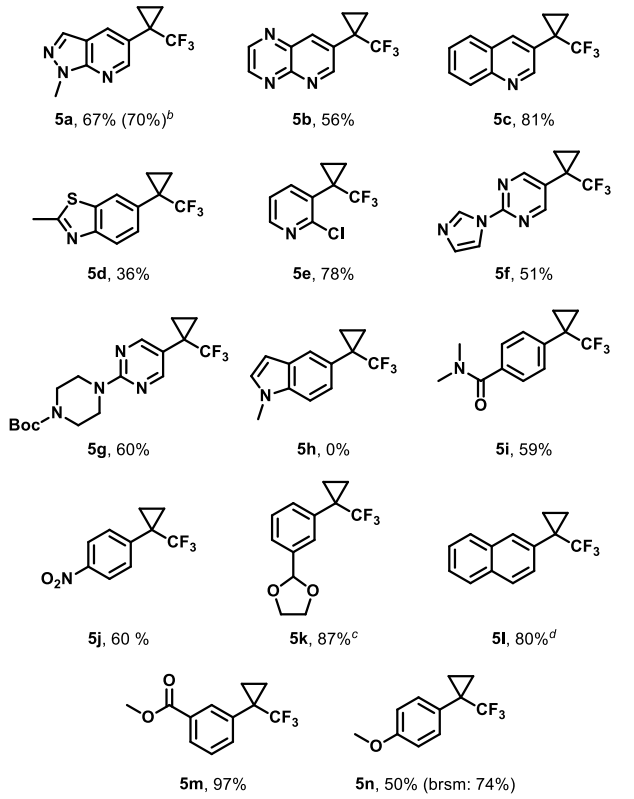
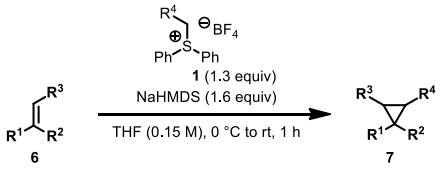
Scheme 3. Substrate Scope of Trifluoromethylalkenes[a]

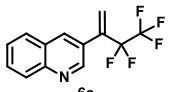
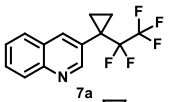
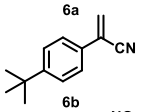
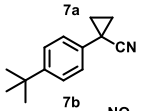
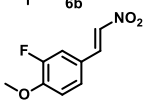
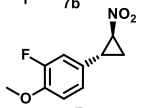
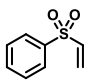
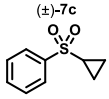
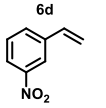
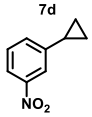
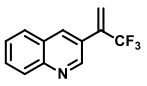
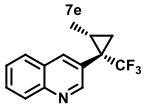
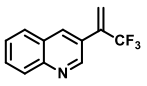
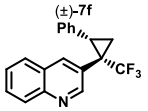




[a]Reactions were run on a 0.44 mmol scale. [b]The reaction was run on a 1.00 mmol scale. [c]With 2.0 equiv of Ph_2SMeBF_4 and 2.3 equiv of NaHMDS. [d]Following the standard reaction conditions, the solvent was removed and the resulting mixture was treated with 10 equiv of MeOTf in THF at rt for 2 days.

Table 2. Application to Other Substitutions on Cyclopropanes[a]



entry	alkene	reagent	cyclopropane	yield
1	 6a	R^4 = H 1c	 7a	59%
2	 6b	R^4 = H 1c	 7b	70%[b]
3	 6c	R^4 = H 1c	 (±)-7c	18%
4	 6d	R^4 = H 1c	 7d	37%
5	 6e	R^4 = H 1c	 7e	0%
6	 3c	R^4 = Me 1d	 (±)-7f	90%, anti/syn dr 1:1.6
7	 3c	R^4 = Ph 1e	 (±)-7g	12% (brsm: 98%)

[a]Reactions were run on a 0.44 mmol scale. [b]Following the standard reaction conditions, the solvent was removed and the resulting mixture was treated with 10 equiv of MeOTf in THF at rt for 16 h.

reaction conditions (Table 2, entry 5). This result suggests the possibility of chemoselectively performing the reaction on a trifluoromethylalkene when using a substrate bearing several alkenes.

To investigate the synthesis of trisubstituted TFCPs, various sulfonium salts were tested. Ethyl(diphenyl)sulfonium tetrafluoroborate **1d** (Table 2, entry 6) enabled the formation of **7f** in good yield as a mixture of stereoisomers, with a slight selectivity toward the *syn* isomer. However, when benzyl(diphenyl)sulfonium tetrafluoroborate **1e** was employed (Table 2, entry 7), cyclopropane **7g** was obtained in low yield but with complete selectivity in favor of the *syn* isomer, and most of the unreacted starting material could be cleanly recovered (98% brsm). Both of these results display the impacts of steric hindrance on the sulfonium reagent, which are to decrease the reaction rate and to affect the orientation of the sulfonium ylide during the addition.

In summary, we have developed a straightforward methodology for the formation of TFCPs from readily accessible trifluoromethylalkenes. The disclosed process allows the use of a commercially available reagent without the need for high temperatures. Moreover, substituted cyclopropanes with a broad substitution pattern, including a variety of heterocyclic molecules, could be synthesized using the optimized reaction conditions. We anticipate that this new method of forming TFCPs will facilitate the incorporation of this key *tert*-butyl bioisostere in drug discovery campaigns.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00557.

Optimization table, experimental procedures, characterization data, and copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: p.cyr@umontreal.ca.
*E-mail: anne.marinier@umontreal.ca.

ORCID

Patrick Cyr: 0000-0001-5320-3483

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Notes

The authors declare no competing financial interest.

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