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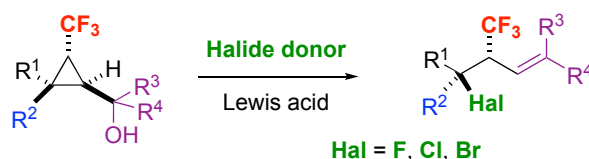
# Stereoselective Nucleophilic Halogenation at CF<sub>3</sub>-Substituted Non-Classical Carbocation

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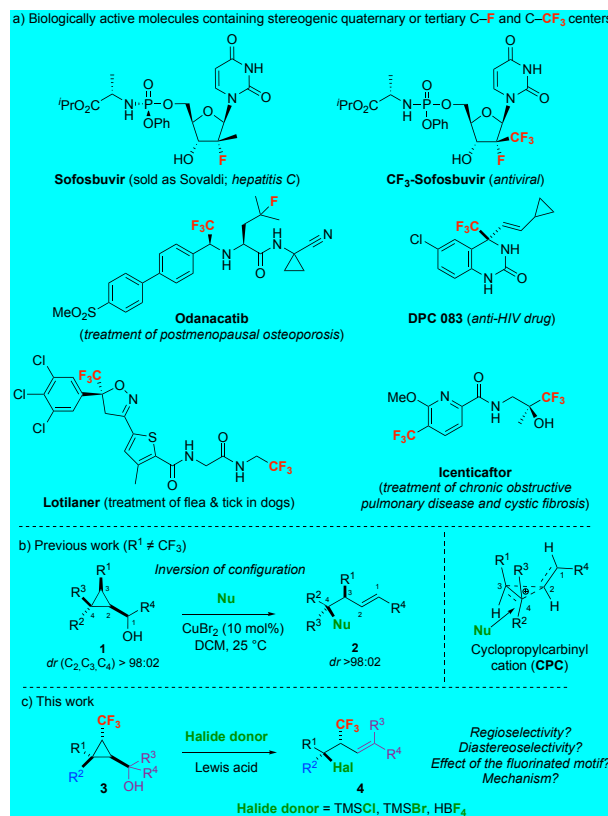
Supporting Information Placeholder



**ABSTRACT:** CF<sub>3</sub>-substituted cyclopropyl carbinol derivatives undergo regio- and diastereoselective nucleophilic halogenation at the quaternary carbon center to provide acyclic products as a single diastereomer. The selectivity of the substitution is rationalized by the formation of a non classical cyclopropylcarbinyl cation intermediate, reacting at the most substituted carbon center. Tertiary alkyl chlorides, bromides, and fluorides, adjacent to a stereogenic C–CF<sub>3</sub>-motif are diastereomerically pure, and can be obtained in few catalytic steps from commercially available alkynes.

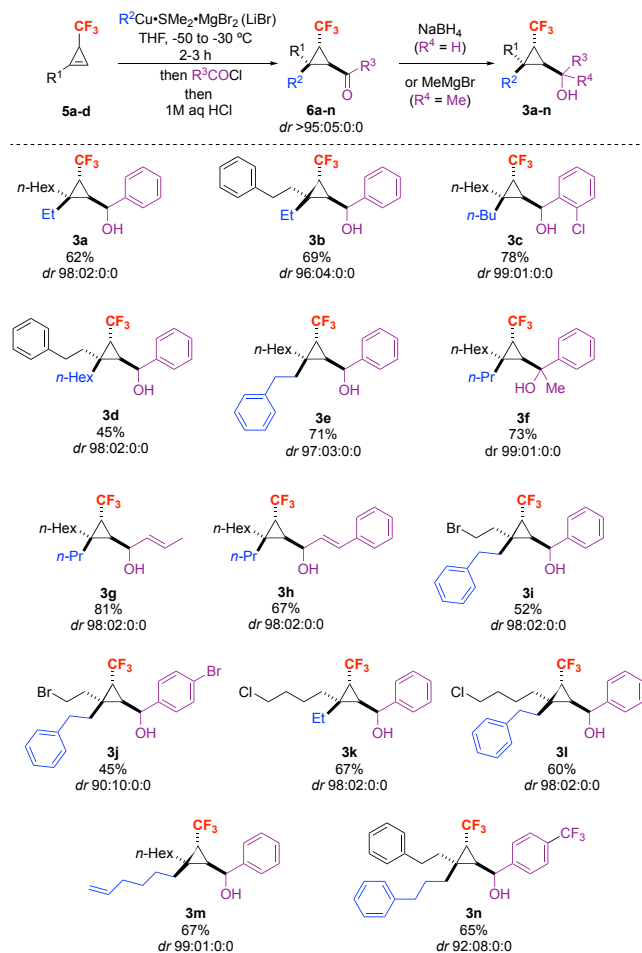
Fluorine containing compounds have shown a remarkable history of success in various fields such as agrochemicals, functional materials, polymers and notably in medicinal chemistry as 20-25 % of all pharmaceutical drugs incorporate at least one fluorine atom.<sup>1</sup> Within the spectrum of fluorine subunits, the trifluoromethyl group (CF<sub>3</sub>) stands out for its significant application in drug design, as it can modulate the solubility, lipophilicity, metabolic stability, bioavailability, and binding affinity of drug candidates.<sup>2</sup> Hence, molecules containing one or more fluorine atoms, including the CF<sub>3</sub> unit, are crucial in drug discovery (Scheme 1a).<sup>3</sup> Therefore, the development of efficient methodologies for synthesizing stereogenic fluorinated building blocks remains an important objective in organic chemistry.<sup>4</sup> Inspired by previous results from our group in controlling the stereochemistry of S<sub>N</sub>1 reactions involving non-classical carbocations (Scheme 1b),<sup>5</sup> we wondered whether we could employ a similar strategy to prepare acyclic molecular backbones containing the CF<sub>3</sub> groups with adjacent stereocenters, alongside additional halogens including fluorine (Scheme 1c). Indeed, we have recently reported that cyclopropyl carbinol derivatives **1**<sup>5a</sup> featuring a quaternary carbon stereocenter at C<sub>4</sub> undergo a smooth Lewis acid-catalyzed ring-opening, resulting in the formation of the non-classical cyclopropylcarbinyl carbocation intermediate CPC.<sup>6</sup> Given the asymmetrical substitution pattern at C<sub>3</sub> and C<sub>4</sub> of CPC, the C<sub>2</sub>–C<sub>4</sub> bond exhibits a slightly longer bond length as compared to the C<sub>2</sub>–C<sub>3</sub> bond.<sup>5e</sup> Consequently, the nucleophile is expected to preferentially react at C<sub>4</sub>, resulting in the stereospecific formation of **2** with a complete inversion of configuration with a very high diastereoselectivity as a single *E*-isomer (Scheme 1b).<sup>5e</sup>

## Scheme 1. State-of-the-art and research proposal



Given these findings, we questioned whether such an approach could be extended to the formation of adjacent polyhalogenated compounds **4** (Nu = halide) and therefore applicable to CF<sub>3</sub>-containing cyclopropyl substrates **3**, while maintaining both regio- and diastereoselectivity of the reaction. The preparation of starting materials was achieved by employing our previously reported carbocupration reaction on trifluoromethyl-substituted cyclopropenes **5**,<sup>7</sup> followed by trapping the resulting cyclopropyl copper species with various acyl chlorides. The resulting cyclopropyl ketones **6** were subsequently reduced to yield the corresponding CF<sub>3</sub>-substituted cyclopropyl carbinol derivatives **3a-n** (Scheme 2).

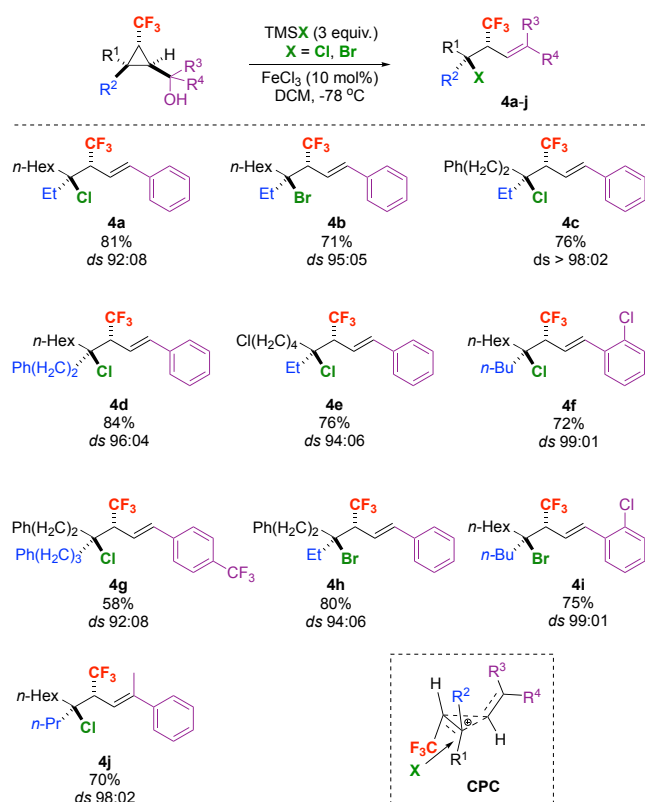
**Scheme 2.** CF<sub>3</sub>-substituted cyclopropyl carbinols



The reaction sequence exhibits a broad versatility, as it accommodates various substituted aromatics as well as  $\alpha,\beta$ -unsaturated aldehydes and ketones, which were successfully added to the cyclopropyl copper intermediates. Furthermore, alkyl halide or terminal double bond as functional groups may be present on the initial cyclopropene substrates without impeding either the carbocupration reaction or the subsequent transformations (**3i-m**, Scheme 2). With a range of CF<sub>3</sub>-substituted cyclopropyl carbinols **3a-n** in hand, we initiated our research by developing the Lewis acid-catalyzed nucleophilic halogenation reactions at non-classical cyclopropyl carbinyl carbocation intermediates, utilizing TMSCl and TMSBr as halide donors, respectively on our model compound **3a**. Following a comprehensive

investigation (see the Supporting Information for all details), we were pleased to discover that employing 10 mol% of FeCl<sub>3</sub> in dichloromethane at temperature ranging from -78 °C to room temperature for 12 h yielded the tertiary chloride **4a** and bromide **4b** in 81% and 71% yields, respectively, with outstanding diastereospecificities (Scheme 3). Globally, the outcome of the reaction can be influenced by the nature of the Lewis acid. It is essential to find a proper balance and ensure compatibility between the activation of the leaving group (to form the cyclopropyl carbinyl cation) and the nature of the nucleophile for effective nucleophilic substitution. While many Lewis acids provide the expected product, achieving the best yields often requires precise tuning. The products **4a,b** were obtained with a complete inversion of configuration at the tertiary halide center as a single *E*-isomer.

**Scheme 3.** Chlorination and bromination of CF<sub>3</sub>-substituted cyclopropyl carbinols

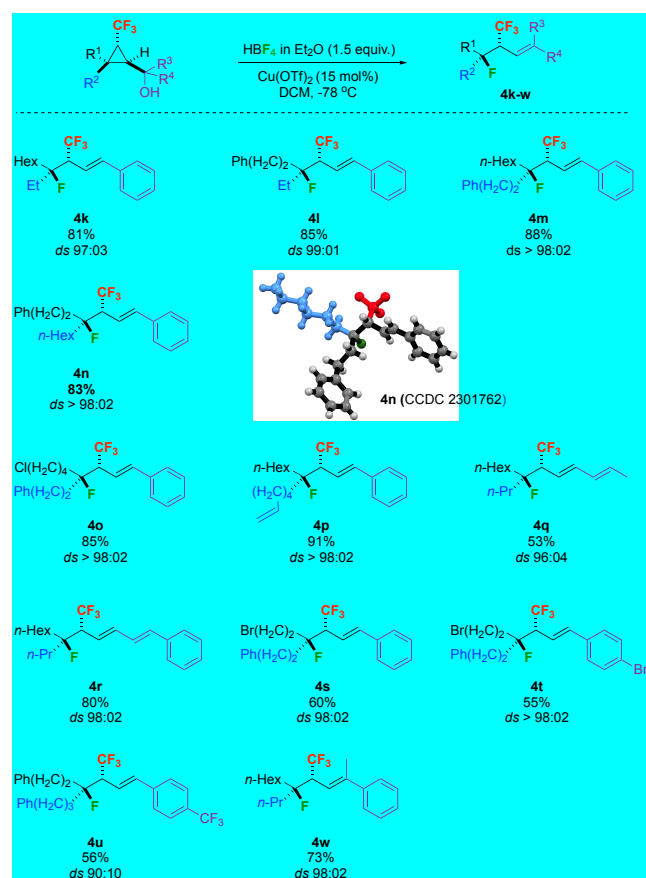


Substituent such as Ph(CH<sub>2</sub>)<sub>2</sub>- can be situated either on the initial cyclopropene or on the Grignard reagent, resulting in analogous products of opposite stereochemistry with comparable yields and diastereospecificities (**4c** and **4d**, Scheme 3). The substituent R<sup>1</sup> can have functionality such as chlorine (**4e**, Scheme 3) underlining that the reaction proceeds selectively at the quaternary carbon stereocenter by cleaving a C–C bond in the presence of what is typically considered as a more reactive functional group towards nucleophilic substitution, highlighting the efficacy of the formation and reactivity of cyclopropyl carbinyl cation intermediate CPC. In such case, the nucleophile reacts at the carbon center possessing the highest positive charge density, namely the quaternary carbon stereocenter. Moreover, ring-strain release of the cyclopropyl unit also

contributes to the regioselective substitution. Derivatives of cyclopropyl carbinol featuring electron-withdrawing CF<sub>3</sub> group or Cl atom at *para* and *ortho* positions, respectively, were transformed into the corresponding tertiary alkyl chlorides (Scheme 3, **4f** and **4g**) and bromide (**4i**, Scheme 3) in good yields with excellent diastereospecificity (*ds* > 95:05).<sup>8</sup> Finally, the reaction also proceeded smoothly with a cyclopropyl carbinol bearing a tertiary alcohol, yielding **4j** with excellent diastereospecificity and as the sole trisubstituted *E*-isomer.

With a solid ability to synthesize adjacent polyhalogenated acyclic molecular fragments, we then proceeded in our research towards the preparation of polyfluorinated compounds. Following a swift screening of various experimental parameters, we quickly found that the copper-catalyzed addition of fluoride from HBF<sub>4</sub> in Et<sub>2</sub>O provided the desired products in good to excellent yields with excellent diastereospecificities (Scheme 4).

#### Scheme 4. Fluorination of CF<sub>3</sub>-substituted cyclopropyl carbinols



The two opposite diastereomers **4m** and **4n** were readily synthesized by simply permuting the nature of the two substituents at the quaternary carbon stereocenter of the starting cyclopropyl carbinols, yielding the products with similar diastereospecificity (Scheme 4). The reaction could be scaled-up as the transformation of 350 mg of **3b** afforded **4l** with the same level of diastereoselectivity (*dr* > 95:05), demonstrating the practicability of this procedure. The relative configuration was established by single-crystal X-ray diffraction analysis of **4n**, while all other

configurations were assigned by analogy, reaffirming the complete inversion of configuration at the quaternary carbon center during the substitution. The nature of the substituent R<sup>1</sup> exhibits broad compatibility as alkyl chloride and alkyl bromide chains are well-tolerated within the reaction conditions (**4o** and **4s,t**, Scheme 3). Variation of substituents at the carbinol center provides products possessing a dienyl framework or a trisubstituted double bond, without altering the outcome of the transformation (**4q,r** and **4w**, Scheme 4).

In summary, we have established an efficient method for synthesizing tertiary alkyl halides via a stereoinvertive nucleophilic substitution at quaternary carbon stereocenter of CF<sub>3</sub>-containing cyclopropyl carbinols, through the formation of non-classical cyclopropylcarbinyl cation intermediate (CPC). This straightforward approach enables the preparation of tertiary alkyl fluorine, bromine, chlorine species, adjacent to a stereogenic C–CF<sub>3</sub> moiety. In all cases, products were obtained in good yields with excellent diastereospecificities.

#### ASSOCIATED CONTENT

##### Data Availability Statement

The data underlying this study are available in the published article and its supporting information.

##### Supporting Information Statement

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization data for all new compounds, along with copies of spectra. Computational methods and data, geometries of computed intermediates and transition states (PDF).

##### Accession Codes

CCDC 2301762 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto: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

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##### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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- (8) The term diastereospecificity (ds), represented by the formula  $[ds = \frac{dr_{\text{product}}}{dr_{\text{starting material}}} \times 100\%]$  provides a convenient method of describing the conservation of the diastereo-purity throughout the reaction.