Stereoselective Preparation of CF 3 -Containing Cyclopropanes

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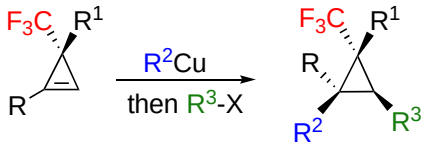
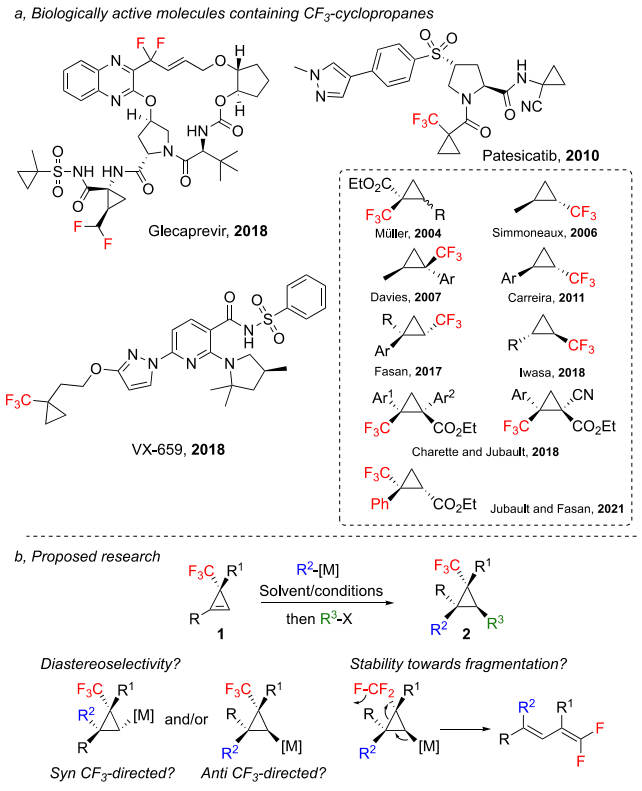
Supporting Information Placeholder



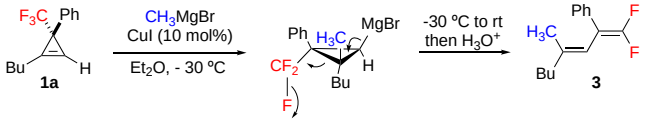
ABSTRACT: A regio- and diastereoselective carbometalation of easily accessible CF_3-substituted cyclopropenes is developed with a diastereoselectivity of the addition opposite to the CF_3 group. This simple strategy allows the preparation of polysubstituted (up to penta-) cyclopropyl rings possessing two adjacent quaternary carbon stereocenters with excellent diastereoselectivities.

The unique properties of fluorine atoms incorporated into organic molecules have created a lot of interests from the synthetic, physical and biological communities.[1,2] Similarly, cyclopropyl ring is a basic structural subunit, widespread both in natural and synthetic bioactive molecules.[3] It was therefore natural that combining cyclopropane and fluorine moieties (CH_2F, CHF_2 or CF_3) in the same molecular structure would attract the curiosity of chemists.[4] Indeed, extensive studies have appeared in the last few years,[5] leading to several bioactive approved drug candidates such as Glecaprevir,[6] Petesicatib[7] and VX-659[8] (Scheme 1a). It became rapidly clear that CF_3-substituted cyclopropanes as synthetic scaffold is of a constant interest giving rise to several powerful stereoselective approaches.[9] Among the most prominent strategies reported in the literature (Scheme 1a),[10] the metal-catalyzed (Fe, Ru, Rh, Co)[9a, 11] and the bioengineered myoglobin-catalyzed[12] addition of diazo compounds to variously substituted alkenes represent certainly the best routes to these important potential drugs subunits. In recent years, we have developed several approaches to the synthesis of polysubstituted cyclopropanes by diastereoselective carbometalation reaction of cyclopropenyl ester and achiral cyclopropenes.[13] In this vein, we questioned if we could use this strategy for the diastereoselective preparation of these important polysubstituted trifluoromethyl cyclopropyl cores. Although the synthetic scheme looks straightforward, several important questions arise such as the effect of the CF_3 group as potential chemical handle to control (or not) the diastereoselectivity of the addition[14] as well as the stability of a cyclopropyl metal species towards ring-fragmentation containing a CF_3 group (Scheme 1b). Trifluoromethyl-substituted cyclopropenes **1** have already been described in the literature[15] and are therefore easily accessible, even in enantiomerically enriched form (see supporting information for all details).[16] Having in hand various cyclopropenes **1**, we started our study by performing the copper-catalyzed carbomagnesiation on our model compound **1a** (R= Bu, R^1 = Ph).



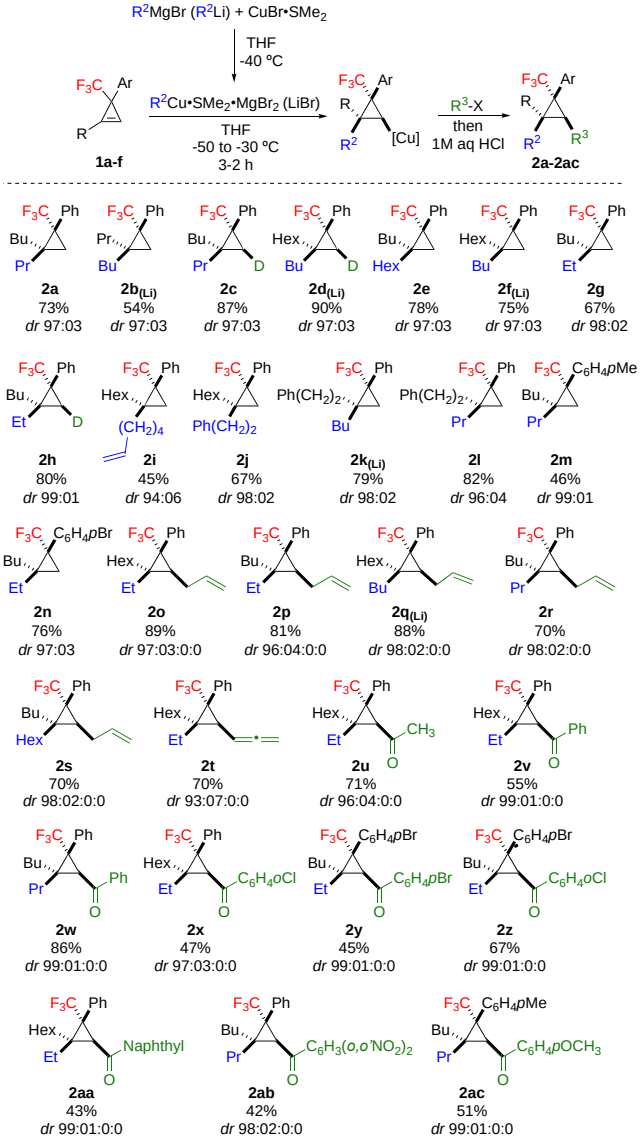
Scheme 1. CF_3-containg cyclopropanes: state-of-the-art and research proposal.

When the reaction was performed in Et_2O at low temperature, we were gratified to realize that the addition proceeded very rapidly but an instantaneous ring-fragmentation occurred to provide the diene **3** (Scheme 2).[17] Interestingly, from the stereochemistry of **3**, it appeared that the carbometalation reaction proceeded from the opposite face of the CF_3 moiety, *syn* to the aryl group.



Scheme 2. Copper-catalyzed carbomagnesiation of trifluoromethyl cyclopropene 1a

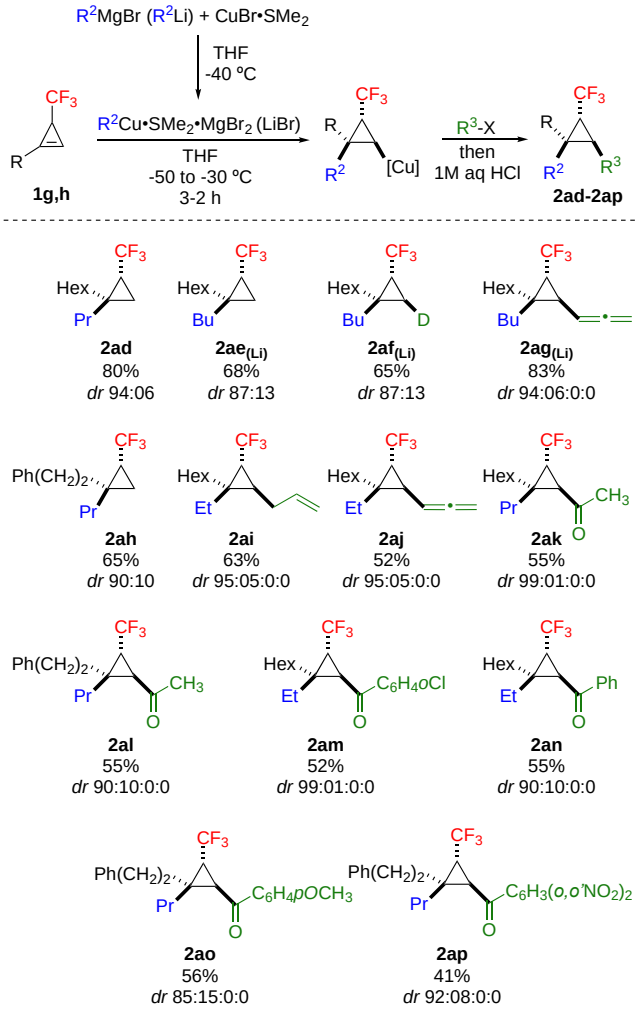
To avoid the ring-fragmentation, we surmised that a more covalent cyclopropyl metal species should be less prone towards this β-elimination reaction. We therefore considered that the addition of an organocopper, easily prepared by addition of alkyllithium or alkylmagnesium bromide to a stoichiometric amount of copper salt, would lead to a stable cyclopropyl copper species.[18] Indeed, when 1 equiv. of alkylmagnesium bromide (or alkyllithium) was added to 1 equiv. of CuBr•Me_2S in THF at -40 °C, the resulting organocopper reacted smoothly with **1a** to provide after hydrolysis, the expected trifluoromethyl cyclopropane **2a** in 73% yield with an excellent diastereoselectivity (*dr* 97:03, Scheme 3). The opposite diastereomer can easily be prepared by simply permuting the nature of the alkyl groups on the organocopper and cyclopropene. In this case, the opposite diastereomer **2b** was obtained with a similar diastereomeric ratio (Scheme 3). The organocopper could similarly be generated from an alkyllithium instead of the alkylmagnesium halide with similar diastereoselectivity; a subscript (**Li**) is indicated in those cases after the compound numbers to indicate the nature of the initial organocopper. The formation of a discrete organometallic species was proved by reaction with DCl (**2c**, Scheme 3). The reaction proceeds with various R^2 group on the organocopper as well as various R group on the cyclopropene (**2d-l**, Scheme 3). The electronic nature of the aromatic group can also be varied as shown for the examples **2m** and **2n**. The resulting configurationally stable cyclopropyl copper could react with various carbon electrophiles such as allyl and propargyl bromide or acyl chlorides to provide pentasubstituted cyclopropanes (**2o**-**2ac** respectively) possessing two adjacent quaternary carbon stereocenters including the desired trifluoromethyl group with excellent diastereomeric ratios (Scheme 3). The relative configuration was established by X-ray analysis of **2ab** and the configurations of all other products were assigned by analogy. It is interesting to note that the CF_3 group is not coordinating to the copper complex, and therefore the latter reacts *anti* to the trifluoromethyl group. The diastereoselectivity of the addition diverges completely from all the additions on cyclopropene that has a methyl group instead of the CF_3.[19] Following the positive results for the diastereocontrol of the carbometalation reaction of sp^3-disubstituted **1** (possessing an aryl group geminated to the CF_3 unit), we then further continued our investigation on the diastereoselectivity of sp^3-*mono*substituted trifluoromethyl cyclopropenes (R^1 = H, Scheme 1). The synthesis of the starting material was again performed by using reported procedures (see supporting information for all details)[15a] and two sp^2-*mono*substituted cyclopropenes **1g,h** were easily prepared (Scheme 4). Having in hand, these two sp^2-substituted cyclopropenes **1g,h**, the same experimental conditions as above were tested for the carbometalation reaction.



Scheme 3. Diastereoselective carbocupration of sp^3-disubstituted CF_3-cyclopropenes 1a-f

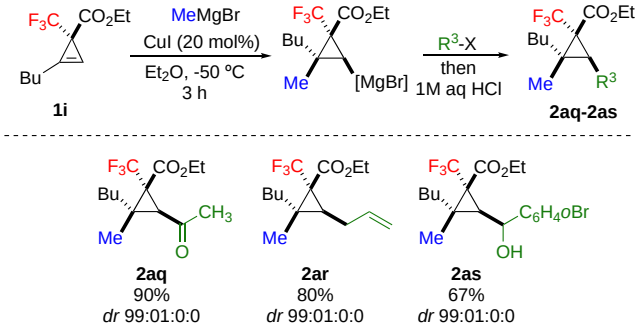
We were again pleased to observe a smooth addition of the organocopper to the strained double bond of trifluoromethyl cyclopropene but surprisingly, final acidic hydrolysis needed to be performed with 1 M HCl to get reproducible results (most probably MeOH or H_2O were not acidic enough to quantitatively quench the copper salt leading to potential side reactions). We then generalized this reaction to our two substrates and in all cases, the carbometalation proceeds with an *anti* diastereofacial preference towards the CF_3 group (Scheme 4). The relative configurations were assigned by analysis of the coupling constants (observed value J = 5.8 - 6 Hz, litera-

ture values for J_{trans} = 4 - 7.5 Hz and for J_{cis} = 7.5 - 9 Hz).[20] It is interesting to note that although one of the two diastereotopic faces of the cyclopropenes **1g,h** is now unshielded as compared to **1a-f**, the level of diastereoselectivity of the carbometalation reaction for the formers are intriguingly lower than that the latter (compare **2f$_{(Li)}$** with **2ae$_{(Li)}$**, **2l** with **2ah** or **2o** with **2ai**, Schemes 3 and 4 respectively), underlining the positive influence of an aryl group on the diastereoselectivity of the carbometalation reaction.



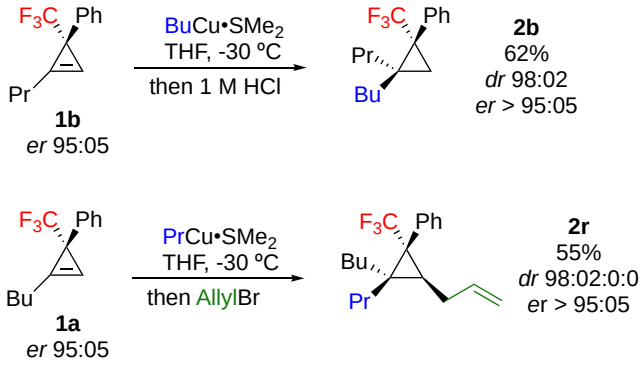
Scheme 4. Diastereoselective carbocupration of sp^3-monosubstituted CF$_3$-cyclopropenes 1g,h

An alternative group that would exert a strong diastereocontrol for a *syn*-addition reaction should be an ester. Indeed, when the easily accessible cyclopropenyl ester **1i** possessing a CF_3 group,[21] was treated with a methyl Grignard reagent in the presence of a substoichiometric amount of CuI, the carbometalation reaction proceeded at low temperature to give a thermally stable cyclopropyl metal species that could further react with carbon electrophile to provide the corresponding products **2aq-2as** in excellent yields and diastereoselectivities (Scheme 5). It should be noted that although the stereochemistry at the carbinol center of **2as** is formed in a 1:1 ratio, the cyclopropyl magnesium species is stable towards β-fragmentation, most probably due to the intramolecular chelation from the ester.



Scheme 5. Diastereoselective carbocupration of CF$_3$-cyclopropenyl ester 1i

Finally, the use of chiral ligand in the cyclopropenation of alkynes provided the cyclopropenes **1a,b** with high enantiomeric ratios (*er* 95:05, Scheme 6, see Supporting Information).[16] After carbocupration reaction and eventually reaction with an electrophile, the corresponding tetra- and penta-substituted cyclopropanes **2b and 2r**, respectively, were obtained with excellent diastereomeric and enantiomeric ratios (Scheme 6).



Scheme 6. Enantio- and diastereoselective preparation of trifluoromethyl cyclopropanes

In conclusion, we have developed a regio- and diastereoselective carbometalation of easily accessible CF$_3$-substituted cyclopropenes. The diastereoselectivity of the addition is opposite to the CF_3 group and the exact reasons still need to be fully clarified. This simple strategy allows the preparation of polysubstituted (penta-) cyclopropanes possessing two quaternary carbon stereocenters with excellent diastereoselectivities.

ASSOCIATED CONTENT

Supporting Information

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 2176014 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

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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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