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COMMUNICATION

Diastereoselective synthesis of cyclopropanes bearing trifluoromethyl-substituted all-carbon quaternary centers from 2-trifluoromethyl-1,3-enynes beyond fluorine elimination

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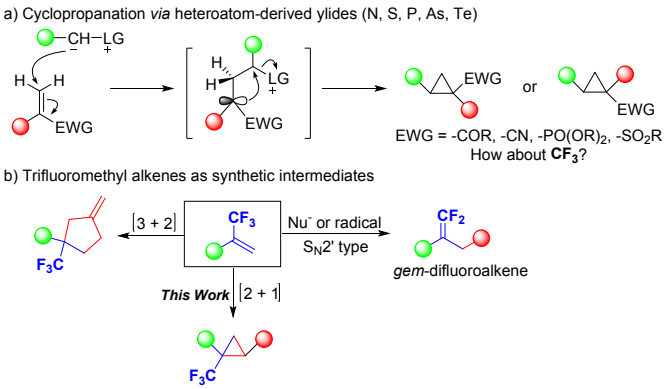
Here, a one-pot two-step procedure for the diastereoselective synthesis of cyclopropanes bearing trifluoromethyl-substituted all-carbon quaternary centers was described. Trifluoromethyl-activated 1,3-enynes undergo cyclopropanation reactions with sulfur ylides under mild reaction conditions without fluoride elimination, which affords the *cis*-isomer mainly. Interestingly, sequential TBAF-mediated deprotection of the triisopropylsilyl group results in diastereoenriched epimerization which gives rise to the *trans*-cyclopropanes as the sole isomer.

Cyclopropane is a basic structural subunit found in a diverse range of naturally occurring secondary metabolites,[1] as well as many therapeutic agents,[2] in which the cyclopropane plays an important role in biological activity. Furthermore, the high strain energy of three-membered ring makes them versatile synthetic intermediates for the synthesis of more complex (hetero)cyclic systems and acyclic alkanes.[3] Over the years, increasingly synthetic efforts have been focused on the development of new strategies and methodologies to generate functionalized cyclopropanes stereo-selectively, as well as employing them as key intermediates to access challenging target molecules.[4] Among the existing methods for cyclopropane generation, cyclopropanations of olefins represent the most common strategies, such as Simmons–Smith reactions, carbenoid-mediated reactions with electron-neutral/-rich alkenes,[5] and Michael-initiated ring closure reactions with electron-deficient alkenes. Ylide acting as cyclopropanation reagent undergoing Michael-initiated ring closure reactions with enones was firstly showcased by Corey and Chaykovsky.[6] Since then, great progress has been made in this field.[7] In current approaches, incorporating a strong electron-withdrawing group (e.g., ketone, cyano, sulfone) to the alkenes was necessary in order to decrease the LUMO energy level of the olefins (Scheme 1, a). Due to the highly electron-withdrawing effects of the trifluoromethyl group,[8] we question whether the CF_3-substituted alkenes are capable of undergoing ylide cyclopropanation.



Scheme 1 Typical ylide cyclopropanation reactions and background of trifluoromethyl alkenes

Molecules incorporating fluorine always fascinate chemists owing to the positive effects of fluorine in biochemical sciences.[9] Due to their ready availability and unique reactivity, trifluoromethyl alkenes have received considerable attention and become promising fluorine-containing building blocks in past years. Typically, trifluoromethyl alkenes are subjected to addition reactions with nucleophiles or radicals concomitant with cleavage of a C-F bond to afford *gem*-difluoroalkenes (S_N2'-type reaction) (Scheme 1, b, right side).[10] By contrast, transformations incorporating a trifluoromethyl group from trifluoromethyl alkenes into products were still rare. Preliminary experimental results from Béguéet and co-workers proved the reactivity of trifluoromethyl alkenes in Diels-Alder reactions with Danishefsky's diene, as well as in 1,3-dipolar cycloadditions with azomethine ylide or nitrone.[11] Furthermore, Trost *et al*. also realized a palladium-catalyzed [3+2]-

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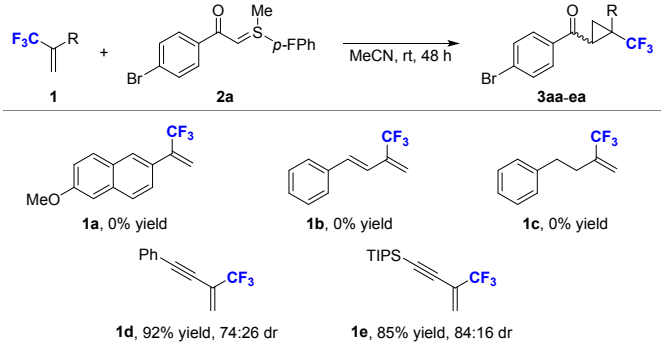
cycloaddition of trimethylenemethane with trifluoromethyl alkenes to furnish cyclopentanes bearing CF_3 group (Scheme 1, b, left side).[12] To the best of our knowledge, trifluoromethyl olefins engaging in Michael-initiated ring closure reactions with ylides has never been reported. Here, we report a mild one-pot procedure for the diastereoselective cyclopropanation of trifluoromethyl-enynes using sulfur ylide reagents.[13] The key to our success is to figure out the relationship between the reactivity and the substitution fashion of trifluoromethyl olefins.

In initial experiments, we performed the cyclopropanation reaction of benzoyl sulfur ylide **2a** with different types of 2-(trifluoromethyl)-1-alkenes **1a**-**e** in MeCN at room temperature for 2 days (Table 1). Among the tested 2-(trifluoromethyl)-1-alkenes, substrates bearing aryl (**1a**), styryl (**1b**), and alkyl (**1c**) substituents all failed to afford the desired product under the reaction condition and even at elevated temperature (for more details, see the Table S1). To our delight, trifluoromethyl-enyne **1d** displayed enhanced reactivity towards cyclopropanation reaction, which yielded the desired cyclopropane product **3da** in 92% yield with 74:26 dr. No defluorinative byproduct was detected by GC-MS analysis. We speculated that the high level of s-orbital character enhanced the electron-withdrawing character of the alkynyl group which further lowered the LUMO energy level of trifluoromethyl-enyne. Similarly, the reaction of triisopropylsilyl (TIPS)-protected trifluoromethyl-enyne **1e** with **2a** occurred smoothly to form **3ea** in 85% yield, 84:16 dr. Quite unexpectedly, an attempt to remove the TIPS group by *in situ* treatment with TBAF gave rise to a terminal alkyne with greatly diastereoselectivity enhancement (>20:1 dr). Similarly, **3da** was also obtained as a sole isomer by treating the corresponding reaction mixture with TBAF (for more details, see the Table S1). Further optimization of the reaction solvents showed that MeCN and THF were both appropriate reaction solvents, while alcoholic solvents proved to be unfavorable (for more details, see the Table S2).

With the optimal conditions in hand, the scope of the sulfur ylides was explored. As summarized in Table 2, moderate to good yields and excellent diastereoselectivity were obtained using sulfur ylides with various arene substitution patterns. Substrates bearing bromo, chloro, and isopropyl at the *para*-position were converted into the cyclopropanes smoothly (**3ea**-**3ed**: 76-85% yields, and >20:1 dr). Those with electron-withdrawing substituents (e.g., CN, NO_2) also tolerated the mild cyclopropanation conditions with excellent stereocontrol, albeit in decreased yield (**3ee** and **3eg**). The relative configuration of **3eg** was determined by single crystal X-ray diffraction analysis, which showed the *trans*-relationship between the CF_3 and the carbonyl group. Notably, the transformation of naphthyl sulfur ylide with **1e** ran smoothly even at 2 mmol scale (**3ef**). Introducing a fluorine atom to the 2-position of benzene ring did not impact on the reaction's efficiency and selectivity (**3eh**). In the case of substrates with electron donating groups, transformations also proceeded well and yielded the products **3ej** and **3ek** in 70% and 83% yields respectively in a completely stereoselective fashion. Aromatic hetereocyclic precursor **2l** was also tolerated and gave the corresponding product in high yield and with excellent diastereoselectivity (**3el**, 82% yiled, and >20:1 dr). Aliphatic sulfur ylides bearing cyclopropyl and *i*-butyl proved to be less reactive, delivering the corresponding cyclopropanes in decreased yields, both with >20:1 dr (**3em** and **3en**).

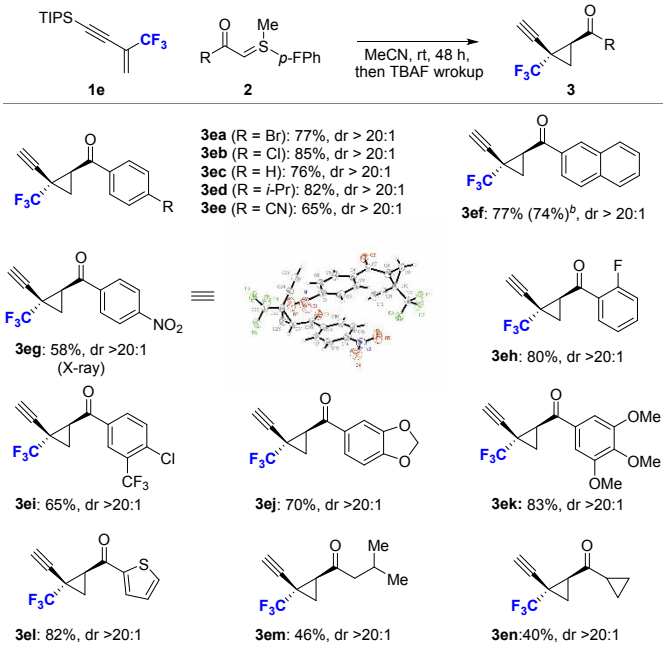
To prove the generality of the present method, other types of trifluoromethylenynes were evaluated (Table 3).[14] Gratifyingly, aromatic (**1d**, **i**) and heteroaromatic (**1j**) trifluoromethylenynes underwent cyclopropanation reactions and subsequent diastereoenriched process smoothly to afford the products in moderate to good yields, again with excellent

Table 1 Substituent effects for cyclopropanation reactions of trifluoromethyl alkenes[a]



[a] Reaction conditions: **1** (0.33 mmol), **2a** (0.30 mmol) in 2 mL of MeCN at room temperature for 48 h; Isolated yields; dr values were determined by ^{1}H NMR.

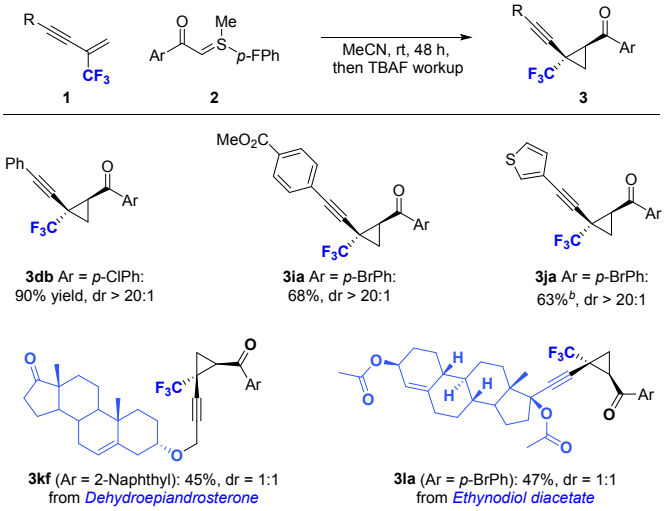
Table 2 Scope of sulfur ylides[a]



[a] Reaction conditions: **1e** (0.33 mmol), **2** (0.30 mmol) in 2 mL of MeCN at room temperature for 48 h, then TBAF (0.33 mmol, 1 M in THF), 0.5 h; Isolated yields; dr values were determined by ^{1}H NMR. [b] Reaction was performed at 2 mmol scale.

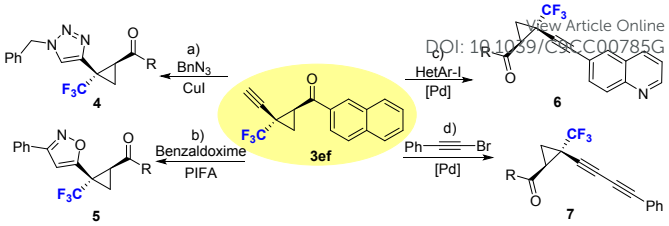
diastereoselectivity (**3db**, **3ia** and **3ja**). Noteworthily, this protocol was successfully used in late-stage functionalization of drug-scaffolds. For example, dehydroepiandrosterone (**1k**) and ethynodiol diacetate-derived 1,3-enynes (**1l**) could undergo cyclopropanations under standard conditions, affording compounds of particular interest for the medicinal chemistry.

Table 3 Scope of 2-Trifluoromethyl-1,3-enynes[a]



[a] Reaction conditions: **1** (0.30 mmol), **2** (0.33 mmol) in 2 mL of MeCN at room temperature for 48 h, then TBAF (0.33 mmol, 1 M in THF), 0.5 h; Isolated yields; dr values were determined by ^{1}H NMR. [b] 0.6 mmol TBAF and 2 h was required in the workup procedure.

To further demonstrate the synthetic utility of the resulting products, compound **3ef** was subjected to a series of chemical transformations. Obviously, functional group manipulation of the terminal triple bond is straightforward. The **3ef** can act as a good dipolarophile undergoing 1,3-dipolar cycloaddition with 1,3-dipolar compounds. For instance, the CuI-catalyzed azide-alkyne Huisgen cycloaddition of benzyl azide with **3ef** generated 1,2,3-triazole-containing CF_3-quaternary center in high yield, which was not easy to access previously (Scheme 2a).[15] Similarly, isoxazole **5** can be prepared by the addition of **3ef** to oxime, which proceed *via* a nitrile oxide intermediate (Scheme 2b).[16] In addition, the terminal alkynyl moiety can undergo transition metal-catalyzed cross-coupling reactions. For example, a typical Sonogashira reaction of **3ef** with 6-iodoquinoline delivered the heterocycle-containing product **6** in almost quantitative yield (Scheme 2c). Furthermore, a palladium-catalyzed cross-coupling reaction allowed for the introduction of a unsymmetrical 1,3-diyne **7** (Scheme 2d).[17] These transformations furnished various cyclopentanes bearing CF_3-substituted quaternary center. Owing to the beneficial effect of CF_3 group on many bioactive pharmaceuticals, the present transformations will raise the interest of medicinal chemists.[18]



Scheme 2. The synthetic transformations of product **3ef**. Reagents and conditions: a) CuI (0.5 equiv), benzyl azide (4 equiv), MeOH, 80 °C, Ar, 48 h, 95%; b) benzaldehyde oxime (4 equiv), PIFA (4 equiv), MeOH/H_2O (5:1 v/v), rt, 24 h, 61%; c) 6-iodoquinoline (1.2 equiv), $PdCl_2(PPh_3)_2$ (0.05 equiv), CuI (0.1 equiv), *i*-Pr_2NH (10 equiv), THF, 50 °C, Ar, 24 h, 98%; d) (bromoethynyl)benzene (2 equiv), $Pd(dba)_2$ (0.05 equiv), CuI (0.05 equiv), Et_3N (2 equiv), THF, rt, Ar, 12 h, 63%. PIFA = (bis(trifluoroacetoxy)iodo)benzene.

Finally, to gain further insight into the process of stereoselectivity enrichment, several common bases were evaluated for their ability in such transformation, including KOH, K_2CO_3 and Et_3N. Inorganic base KOH and K_2CO_3 delivered the cyclopropane **3da** in 77% and 85% isolated yields, respectively, both as the sole isomer. However, Et_3N failed to facilitate such process (for more details, see the Table S3). In addition, such a desilylation of TIPS-protected alkyne was conducted by treatment with AgF instead of TBAF, which selectively delivered the terminal alkyne without deprotonation on the carbon α to the carbonyl group.[19] Such conversion gave rise to diastereosiomeric mixtures, in which the major isomer could be isolated by common column chromatography in 69% yield (eq 1). Quite unexpectedly,

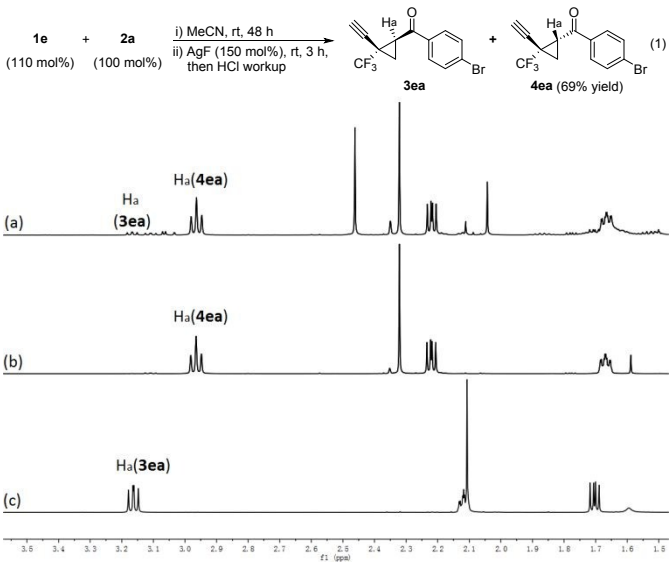


Figure 1. ^{1}H NMR studies of the stereochemistry (illustrating from 1.5-3.5 ppm). Spectrum (a) refers to the diastereoisomeric mixture resulting from eq 1; Spectrum (b) refers to major isomer from eq 1 after flash column chromatography; Spectrum (c) refers to the product **3ea** resulting from standard conditions.

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an epimerization was observed by ^{1}H NMR spectroscopy analysis of the diastereoisomeric mixtures, major isomer **4ea** and **3ea** (Figure 1a, 1b, 1c, respectively). Combined with the X-ray crystallographic analysis of **3eg**, we may reasonably come to the conclusion that the cyclopropanation reactions delivered the *cis*-cyclopropane as the major isomer originally, and then a base-promoted thermodynamic epimerization took place, driving the carbonyl group from *cis*-position to the *trans*-position relative to the CF_3 group (Figure 2). Such type of epimerization was also observed in the case of **1d** (for more details, see the Figure S1).

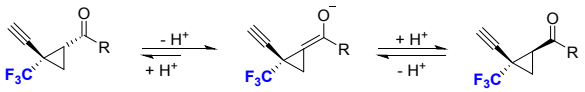

Figure 2. The mechanism of thermodynamic epimerization.

In summary, we have developed the first highly diastereoselective cyclopropanation reactions of trifluoromethyl-enynes with sulfur ylides *via* a maneuverable one-pot, two-step procedure, in which the CF_3 group acts as a novel electron-withdrawing group to enhance the nucleophilicity of the olefin. A base-triggered thermodynamic epimerization took place during the process, resulting stereoselectivity enrichments. This approach allows for the access of cyclopropanes bearing CF_3-substituted all-carbon quaternary centers. The resulting CF_3-substituted cyclopropanes incorporating an alkynyl group could also contribute to the diversity-oriented synthesis of fluoroalkylated compounds. The successful application of trifluoromethyl olefins as Michael-type acceptors in this work improves the scope of typical cyclopropanation reactions of ylides. Further studies including exploring chiral sulfur ylides as well as new methodology based on trifluoromethyl olefins are in progress.

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Conflicts of interest

There are no conflicts to declare.

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