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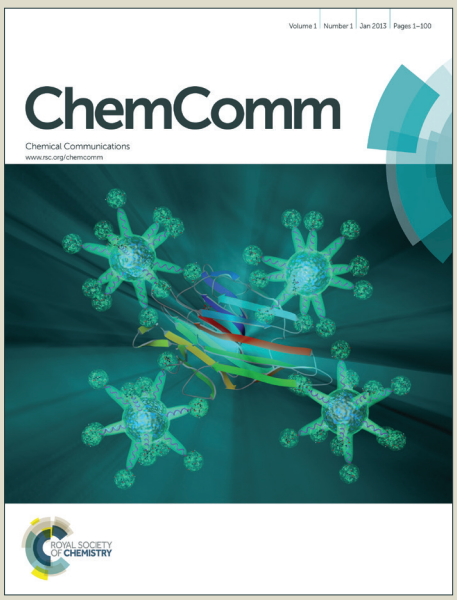




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# Diastereoselective Johnson-Corey-Chaykovsky Trifluoroethylidenation

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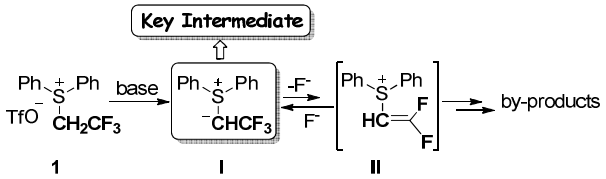
**(2,2,2-Trifluoroethyl)diphenylsulfonium triflate was found to be an efficient ylide reagent for the Johnson-Corey-Chaykovsky reaction to afford trifluoromethyl-epoxides, -cyclopropanes and -aziridines. Interestingly, excellent but different diastereoselectivity was observed for these transformations. Both trifluoromethyl-epoxides and -cyclopropanes were obtained with *trans*-selectivity, but aziridines were given in *cis*-selectivity.**

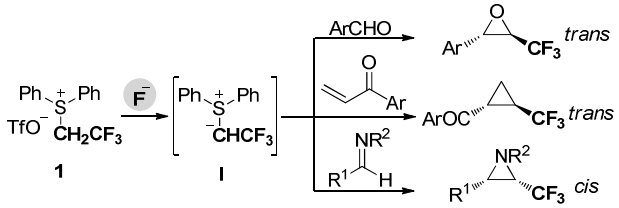
The metabolism *in vivo* is an important issue in the development of pharmaceutical chemistry. A prominent strategy to slow down the *in vivo* metabolism of a drug is to introduce electron-withdrawing group(s) into the drug molecule.[1] Trifluoromethyl group ($CF_3$) has proved to be a good choice due to its strong electron-withdrawing power and its potential in modifying the physicochemical and biological properties of organic molecules. As a result, considerable efforts have been directed towards the exploration of efficient methods for the incorporation of trifluoromethyl group.[2] Although cyclization-type trifluoroethylidenation reaction can not only incorporate trifluoromethyl group into molecules, but also construct two new C-X (X = O, C, N, etc) bonds and a ring structure, this chemistry remains a significant challenge, partially due to the fact that the commonly used methods suffer from the use of potentially explosive reagent.[3]

Johnson-Corey-Chaykovsky (JCC) reaction is a well-known cyclization protocol for the construction of three-membered rings.[4] The JCC reaction of C=X bonds (X = O, C, N) with (2,2,2-trifluoroethylidene) sulfonium ylide may be able to introduce the trifluoromethyl moiety into molecules to furnish the corresponding trifluoromethyl-epoxides, -cyclopropanes and -aziridines respectively, which are valuable ring structures and have received much attention in pharmaceuticals, agrochemicals and synthetic chemistry.[5] However, this method has never been realized despite the fact that sulfonium salt **1** ($Ph_2S^+CH_2CF_3$ $OTf^-$) has already been known for over twenty years,[6] probably owing to the instability of the corresponding ylide **I**.[7] It is well known that the β-fluorine elimination is very easy to happen simultaneously with the deprotonation of the trifluoroethyl group, leading to the formation of alkene **II**. But this tendency might be offset by the presence of fluoride ion, driving the equilibrium from **II** to ylide **I** (Scheme 1). Therefore, if the fluoride ion is employed as the base for the deprotonation of **1**, the formation of sulfonium ylide **I** may be facilitated.




**Scheme 1.** The Decomposition Process of The Ylide Reagent **1**.

In continuation of our research interest in the chemistry of fluorinated ylides,[8] we have now investigated the use of sulfonium salt **1** as a sulfonium ylide reagent in the Johnson-Corey-Chaykovsky trifluoroethylidenation reactions with the use of fluoride as the base to afford the trifluoromethyl-epoxides, -cyclopropanes and -aziridines. It was found that all of these reactions proceeded rapidly with excellent diastereoselectivity (Scheme 2).




**Scheme 2.** Johnson-Corey-Chaykovsky Trifluoroethylidenation with reagent **1**.

Serious drawbacks such as multi-step synthetic procedure existed in the reported synthesis of salt **1**,[6] which prompted us to explore a convenient and scalable method for its preparation. After screening various conditions for the reaction of different sulfides with 2,2,2-

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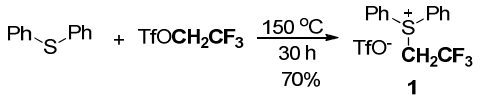
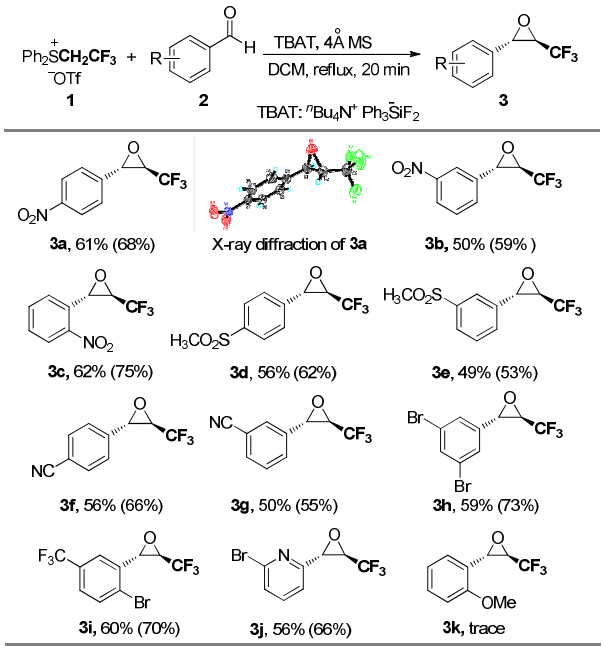
trifluoroethyl trifluoromethane -sulfonate (See ESI, Table S2.1), we finally found that diphenyl sulfide can be quarternized smoothly to give **1** at high temperature (150 °C) under neat conditions (Scheme 3).



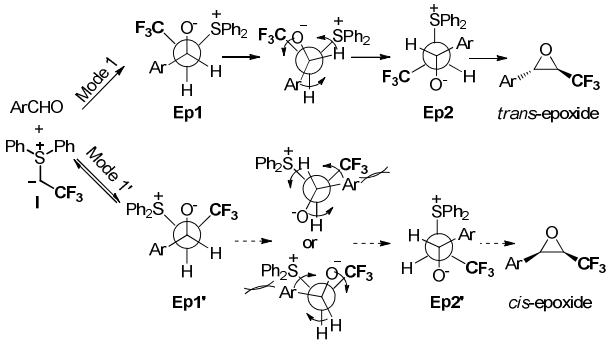

**Scheme 3.** The Synthesis of Salt **1**

Using the fluoride as the base, the reaction of sulfonium salt **1** with 4-nitrobenzaldehyde was initially investigated. TBAT (tetra-*n*-butylammonium difluorotriphenylsilicate) was shown to be the suitable base for the formation of the ylide **I** (See ESI, Table S3.1). After being refluxed in $CH_2Cl_2$ for 20 min in the presence of 4 Å MS, 61% yield of the trifluoromethyl-epoxide (**3a**) could be obtained with excellent *trans* diastereoselectivity (*trans/cis* > 99/1). Its structure was further confirmed by single crystal X-ray analysis[9] and the relative configuration of other products was surmised by analogy. The reaction with other aldehydes also proceeded smoothly, giving the corresponding trifluoromethyl-epoxides with a diastereoselectivity of above 99:1. In the case of **3k**, only trace amount of product could be detected, suggesting that the electron-donating groups on the aryl ring reduced the electrophilicity of the aldehyde carbon toward the ylidic carbon. The substitution position made no difference to the yield, indicating that the steric hindrance didn't significantly influence the epoxidation (Scheme 4). Compared with the previously reported 2,2,2-trifluoroethyl phosphonium and sulfone reagents which react with aldehydes to produce trifluoromethyl-olefins, sulfonium salt **1** shows completely different reactivity.[7b-e]



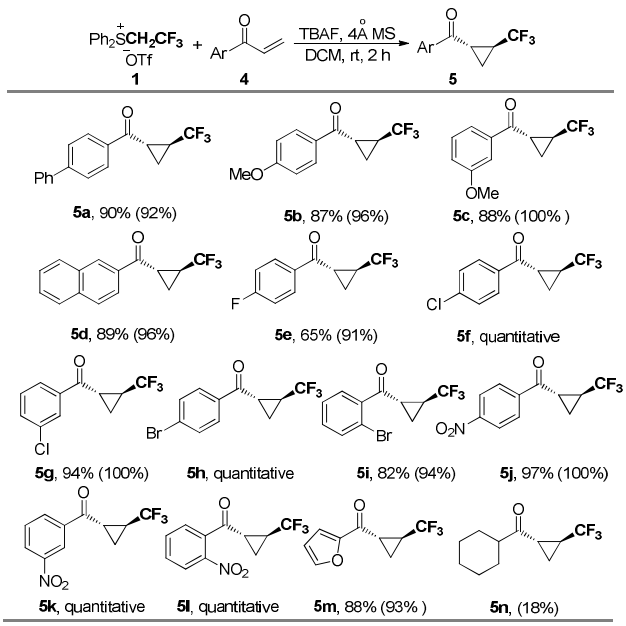

**Scheme 4.** Substrate scope of epoxidation reaction. Isolated yields. Yields in parentheses were determined by $^{19}F$ NMR.

It is believed that the ylide epoxidation proceeds via two steps, *C-C* bond formation and ring closure via $S_N2$-like intramolecular nucleophilic substitution (Scheme 5). In the *C-C* bond formation step, the intermediate **Ep1** and **Ep1'** might both be generated, owing to the Coulombic interaction between the negative oxygen and positive sulphur.[10] To realize the subsequent intramolecular nucleophilic substitution, the bond rotation from **Ep1** to **Ep2** or from **Ep1'** to **Ep2'** must be achieved first. However, the bond rotation from **Ep1'** to **Ep2'** would undergo an eclipsed interaction between the aryl group and the $Ph_2S$ or $CF_3$ group, thus leading to the collapse of **Ep1'** and the regeneration of ylide intermediate **I** (**mode 1'**). Therefore, the reaction would be very likely to proceed via **mode 1**, giving *trans*-trifluoromethyl-epoxides predominantly.




**Scheme 5.** The Mechanism of Epoxidation Reaction.

To our delight, the ylide **I** was also applicable to the trifluoromethyl-cyclopropanation of vinyl ketones (Scheme 6). Since both TBAT and TBAF were effective for this cyclopropanation, cheaper TBAF was chosen as the suitable base (See ESI, Table S3.2). After being stirred at room temperature for 2 h, the corresponding cyclopropanes could be achieved in almost quantitative yield. The relatively lower isolated yield of **5e** might result from its high volatility. The substituent on the aryl ring had no effect on the reaction. Similar to the above epoxidation, excellent *trans* diastereoselectivity (*trans/cis* > 99/1) could be also obtained for this cyclopropanation. Alphatic α,β-unsaturated ketone such as cyclohexyl vinyl ketone shows low reactivity (**5n**). *E*-Phenyl propenyl ketone is inert under these conditions, meaning that the reaction might be sensitive to steric effects. The *trans*-configuration was determined by $^1H$-$^1H$ NOESY analysis of product **5a** (See ESI).




**Scheme 6.** Substrate scope of cyclopropanation reaction. Isolated yields. Yields in parentheses were determined by $^{19}F$ NMR.

In the initial C-C bond formation step of the cyclopropanation, the Coulombic interaction between the enolate anion and sulfonium would favor the generation of the intermediate **Cy1** and **Cy1'** (Scheme 7). To realize the intramolecular nucleophilic substitution, the strong eclipsed interaction similar to the above epoxidation

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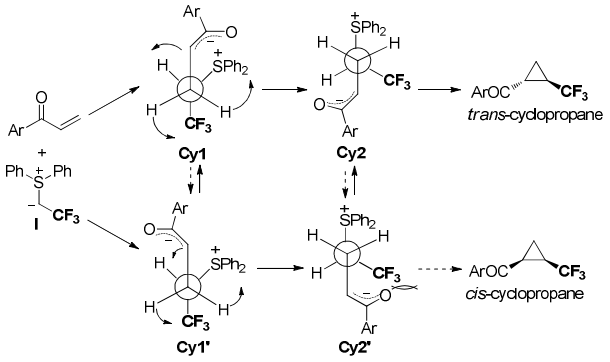
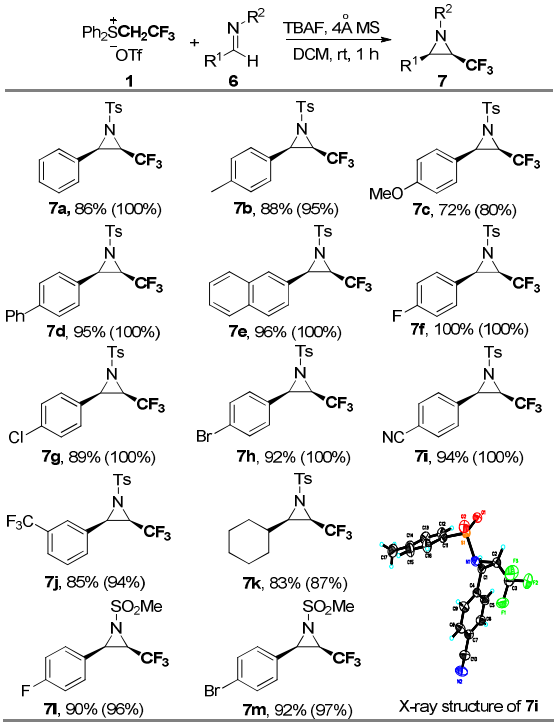
might not exist during the course of the bond rotation from **Cy1** to **Cy2** or from **Cy1'** to **Cy2'**. Nevertheless, the Coulombic interaction in **Cy1'** was weaker than that in **Cy1**, leading to the conversion from **Cy1'** to **Cy1** via C-C bond rotation in the enolate ($H_2C$-CHCOAr). In addition, the steric interaction between $CF_3$ and ArCO groups in **Cy2'** might also bring about the same C-C bond rotation in the enolate, resulting in the conversion from **Cy2'** to **Cy2**. Therefore, the intramolecular nucleophilic substitution of **Cy2** would become the predominant pathway of this ylide cyclopropanation.[11]



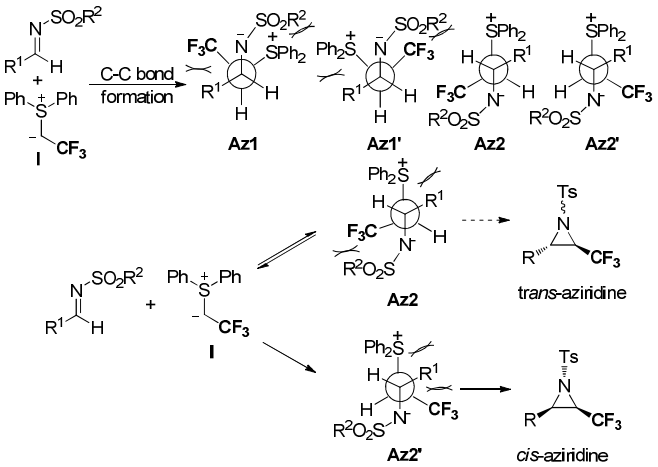

**Scheme 7.** The Mechanism of Cyclopropanation Reaction.

The successful ylide epoxidation and cyclopropanation prompted us to further investigate the possibility of the aziridination (Scheme 8). Using TBAF as the base, the reaction of salt **1** with various *N*-tosyl benzaldimines proceeded very well, giving the trifluoromethyl-aziridine in high yields (**7a**-**7k**, Scheme 8). Aliphatic imine can also be converted well into the desired product (**7k**). *N*-Mesyl imines were also suitable substrates for this transformation (**7l**-**7m**), but *N*-Boc and *N*-Cbz imines show almost no reactivity toward the aziridination under these conditions. Contrary to the above epoxidation and cyclopropanation, the aziridination demonstrated high *cis* diastereoselectivity (*cis*/*trans* > 97/3). The relative configuration was further confirmed by the X-ray analysis of **7i**.[12]




**Scheme 8.** Substrate scope of aziridination reaction. Isolated yields. Yields in parentheses were determined by $^{19}F$ NMR.

Four different intermediates **Az1**, **Az1'**, **Az2** and **Az2'** might be generated during the nucleophilic attack of the ylide **I** on the imine carbon (Scheme 9).[13] However, the negative charge developed on the nitrogen will be dispersed by the strong electron-withdrawing group $SO_2R^2$, thus leading to weak Coulombic interaction between the positive sulfonium and the negative nitrogen in **Az1** and **Az1'**. Besides, strong steric interaction exists in both **Az1** and **Az1'**, and neither of these intermediates can readily undergo bond rotation to form **Az2** and **Az2'** respectively due to strong eclipsed interaction, meaning that intramolecular nucleophilic substitution of **Az1** or **Az1'** to form products wouldn't occur easily. Therefore, only **Az2** and **Az2'** are considered for this aziridination reaction. Apparently, strong steric interaction also exists in both **Az2** and **Az2'**. Excellent *cis* diastereoselectivity was observed, which should be because the activation barrier for ring closure of **Az2'** to afford *cis*-product is lower, and the ring closure of **Az2'** is more rapid than that of **Az2**, a hypothesis which is supported by the crossover experiments performed by the group of Aggarwal[13a] and DFT calculation carried out by the group of Sunoj.[13c]




**Scheme 9.** The Mechanism for Aziridination Reaction.

## Conclusions

In summary, trifluoroethylsulfonium triflate **1** has been developed into a versatile and convenient sulfur ylide reagent for Johnson-Corey-Chaykovsky trifluoroethylidenation reactions. The reactions proceeded smoothly to afford the final products with excellent diastereoselectivity. Interestingly, trifluoromethyl-epoxides, -cyclopropanes were obtained as *trans*-diastereomers, while trifluoromethyl-aziridines were found to be *cis*-diastereomers. Different diastereoselectivity observed in this ylide reaction might result from the Coulombic interaction and steric hindrance generated in the transition state.

## Notes and references

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‡ Electronic Supplementary Information (ESI) available: Experimental procedures, characterization of data for all compounds. CCDC reference numbers 1048211 (**3a**), 1048213 (**7i**). See DOI: 10.1039/b000000x/

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