

Asymmetric Construction of Chiral Carbon Centers Featuring the SCF₃ Motif: Direct Trifluoromethylthiolation versus Building Block Approach

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Abstract: The recent advances in the field of asymmetric synthesis of chiral organofluorine molecules bearing a SCF₃ motif attached to a chiral carbon center are presented in this mini-review. Both direct trifluoromethylthiolation and the use of fluorinated building blocks are described.

Keywords: Fluorine – Trifluoromethylthiolation – Asymmetric synthesis – Chirality

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1. Introduction

Organofluorine chemistry is a research field of tremendous expansion because the scope of applications of fluorinated molecules is impressively large, impacting all domains of society from pharmaceutical and agrochemical sciences to materials science and energy. In the life sciences area, the role of chirality is crucial for interaction of molecules with the biological target. As a consequence, the stereocontrol at carbon centers featuring a fluorinated motif is an imperative to market enantiomerically pure drugs.^[1] From a chemical point of view, the asymmetric synthesis of chiral nonracemic fluorinated compounds is a highly challenging task. Methods for the direct introduction of a fluorine atom and a trifluoromethyl group are manifold and allow high level of stereoselectivity.^[2] On the other hand, the asymmetric introduction of emergent fluorochemotypes is still in its infancy. Of the fluorinated motifs exhibiting recent interest, it may be noted that the SCF₃ group occupies a place of choice.^[3] Indeed, the exceptional lipophilicity that the SCF₃ group confers to molecules (Hansch hydrophobic parameter: $\pi = 1.44$ versus 0.88 for CF₃) and its high electron-withdrawing character (Hammett substituent constants: $\sigma_m = 0.40$, $\sigma_p = 0.50$ versus 0.43, 0.54, respectively for the CF₃ group) make it attractive to build novel chemical architectures for the conception of new pharmaceuticals with enhanced capacity to pass cell membranes. Most of the current trifluoromethylthiolated biologically active compounds feature a C(sp²)-SCF₃ group mainly

on aromatics and two SCF₃ molecules are on the market for veterinary use only: Toltrazuril or Baycox[®] from Bayer and Monepantel or Zolvix[®] from Novartis. None of the SCF₃ compounds is currently marketed for human medication. The development of compounds featuring a C(sp³)-SCF₃ group with emphasis for enantiopure ones is of growing interest. In this context, it appears to us timely to review the synthetic approaches for the asymmetric construction of chiral carbon centers featuring the SCF₃ motif. This short yet exhaustive review compiled all the papers on this topic till end of June 2017.

2. Direct trifluoromethylthiolation

The most widespread approach for the construction of chiral carbon centers featuring the SCF₃ motif is the direct introduction of the SCF₃ group on various substrates. Among the strategies employed, most are focused on enantioselective trifluoromethylthiolation by means of chiral catalysts or chiral reagents. Diastereoselective trifluoromethylthiolation is clearly underdeveloped with a single published example. These methods utilize electrophilic trifluoromethylthiolation reagents among those depicted in figure 1.^[4]

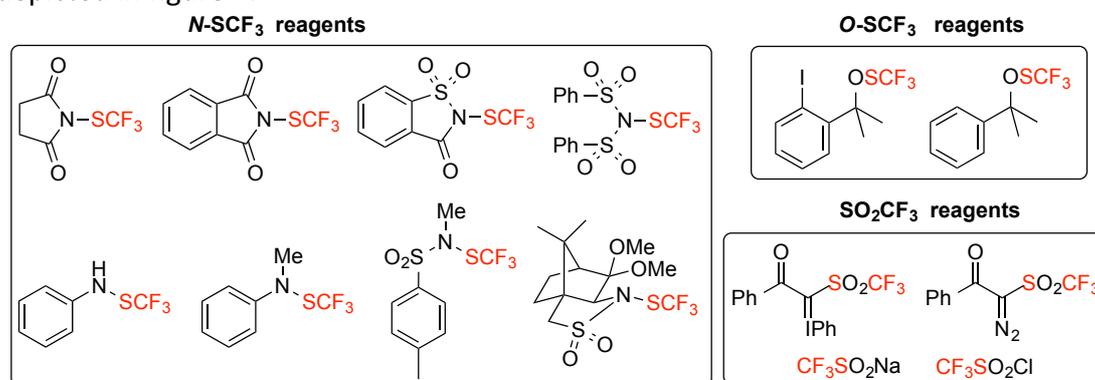
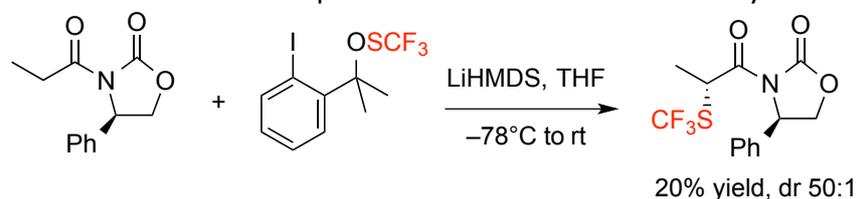


Figure 1. Classes of electrophilic trifluoromethylthiolation reagents

2.1 Diastereoselective trifluoromethylthiolation

The first asymmetric introduction of the SCF₃ motif was reported in 2013 by Shen and coworkers. This group proposed the diastereoselective trifluoromethylthiolation of a lithium enolate bearing a chiral Evans phenyloxazolidin-2-one, using a trifluoromethylated thioperoxide as the SCF₃ source (Scheme 1).^[5] The expected product was obtained with high diastereoselectivity (dr 50:1), albeit in a low yield (20%). However, no further investigation was performed on the reaction conditions. No other example of similar reaction was reported in the literature to this day.



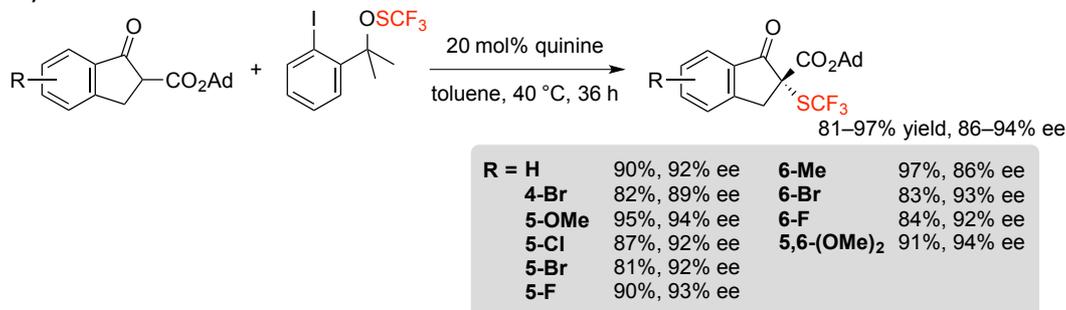
Scheme 1. Diastereoselective trifluoromethylthiolation of a carbonyl compound

2.2 Enantioselective trifluoromethylthiolation

As opposed to diastereoselective trifluoromethylthiolation, reports concerning the enantioselective introduction of the SCF₃ moiety on various substrates are more numerous.

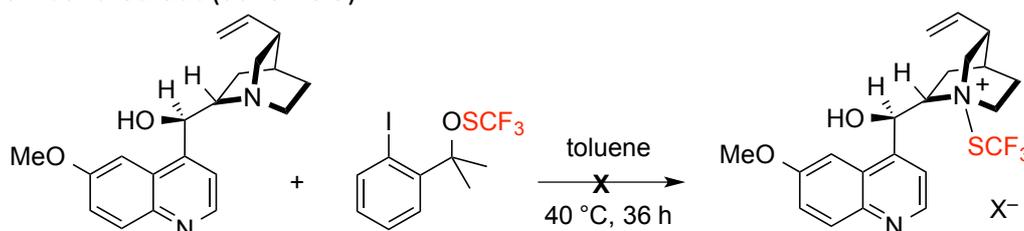
Trifluoromethylthiolation of β-ketoesters

In 2013, Shen and coworkers described the first asymmetric organocatalyzed trifluoromethylthiolation of β -ketoesters mediated by quinine-based catalysts. A variety of indanone-derived adamantyl β -ketoesters were readily converted into their (*R*)-trifluoromethylthiolated derivatives in high yields and excellent enantioselectivities using 20 mol% of quinine as well as 1.2 equivalents of Shen's trifluoromethylsulfenate reagent in toluene at 40 °C (Scheme 2).^[6]



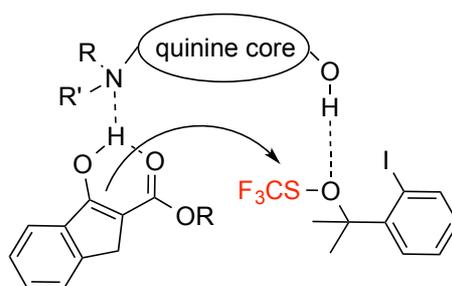
Scheme 2. Asymmetric trifluoromethylthiolation of indanone-based adamantyl β -ketoesters

The enantioselectivity proved to be particularly sensitive to the steric hindrance of the ester group; indeed, ee values dropped dramatically when performing the reaction on methyl or ethyl esters. On the contrary, the nature and position of the benzene ring substituents appeared to have little impact on the proceeding of the reaction as similar results were obtained with substrates bearing electron-withdrawing or electron-donating groups. The conditions showed as well good compatibility with a cyclopentanone-derived β -ketoester, which furnished the corresponding product in 95% yield with 94% ee. On the other hand, in the case of tetralone-derived substrates, very low conversions (<5%) were observed. Mechanistic studies were carried out in order to rationalize this phenomenon. Preliminary formation of a *N*-SCF₃ quaternary ammonium produced from quinine and the SCF₃ source was first considered by the authors. However, no newly formed species could be observed when monitoring the reaction of these two reagents by ¹⁹F NMR in the standard conditions, so this hypothesis was ruled out (Scheme 3).



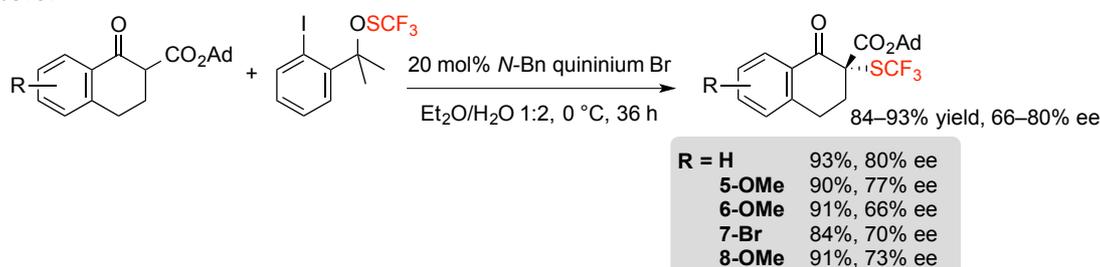
Scheme 3. Expected reaction between quinine and the trifluoromethylthiolation reagent

Consequently, a dual activation of both the substrate and the trifluoromethylthiolation agent by means of hydrogen bonding with the quinine was proposed (Scheme 4). Such hypothesis is consistent with the fact that the use of other cinchona alkaloids, which do not feature a hydroxyl group, resulted in extremely low conversions. Moreover, considering that tetralone-derived β -ketoesters form non-planar enolates, which probably cannot fit in this restrictive model nor, therefore, generate the dual-activated intermediate, this mechanism can justify their lack of reactivity.



Scheme 4. Dual activation of the substrate and the trifluoromethylthiolation reagent

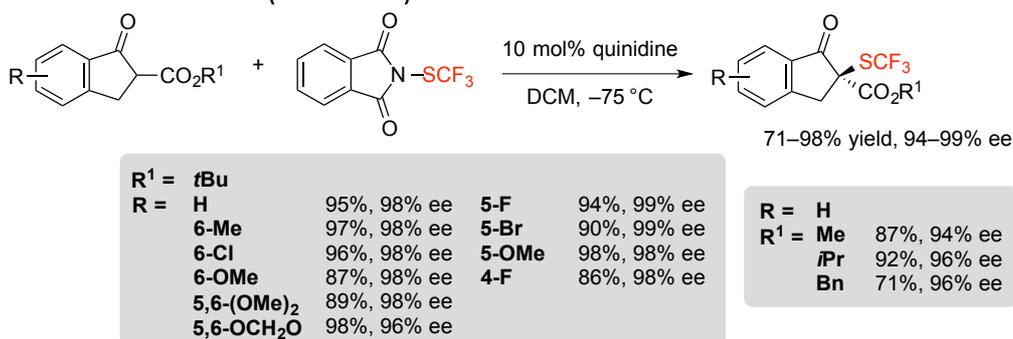
As a result, some modifications of the reaction conditions were necessary to address this issue. Among others, replacing quinine by a quinium based phase-transfer catalyst greatly contributed to reach higher yields. Hence, five SCF₃ tetralone-based β -ketoesters could be obtained in excellent yields and moderate enantioselectivities (Scheme 5). 1-Benzosuberone derivatives as well as cyclohexanone-based substrates were also compatible with the modified reaction conditions. Interestingly enough, said conditions did not allow a satisfying conversion of five-membered ring β -ketoesters.



Scheme 5. Asymmetric trifluoromethylthiolation of tetralone-based adamantyl β -ketoesters

Acyclic substrates proved to be the main limitation of these reactions, as they showed poor reactivity when using either of the two proposed quinine-based catalysts.

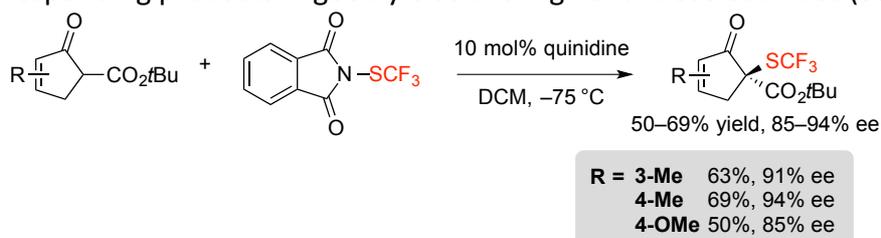
The asymmetric trifluoromethylthiolation of β -ketoesters did not only attract the interest of Shen's group. Indeed, Rueping and coworkers simultaneously reported a similar methodology, also based on the use of cinchona alkaloid catalysis.^[7] This time, *N*-(trifluoromethylthio)phthalimide was employed as the electrophilic SCF₃ source. Using 10 mol% of quinidine in dichloromethane at -75 °C, various (*S*)-indanone-derived trifluoromethylthiolated β -ketoesters were produced in excellent yields and enantioselectivities (Scheme 6).



Scheme 6. Asymmetric trifluoromethylthiolation of indanone-based β -ketoesters

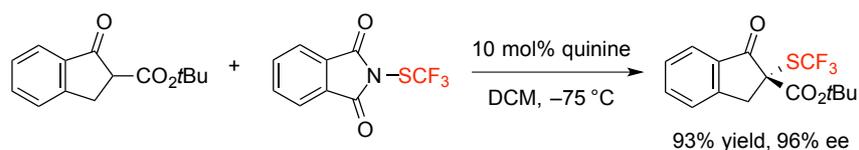
It is worth underlining that, in this case, the size of the ester group had a very limited influence on both the yield and the enantioselectivity of the reaction. Furthermore, a tetralone-based substrate could also be converted into its SCF₃ analogue, albeit in moderate yield (46% yield, 95% ee), by increasing the temperature to 0 °C and lengthening the reaction time to seven days.

Cyclopentenone-derived *tert*-butyl β -ketoesters were also compatible with the reaction conditions, offering the corresponding products in good yields and high enantioselectivities (Scheme 7).



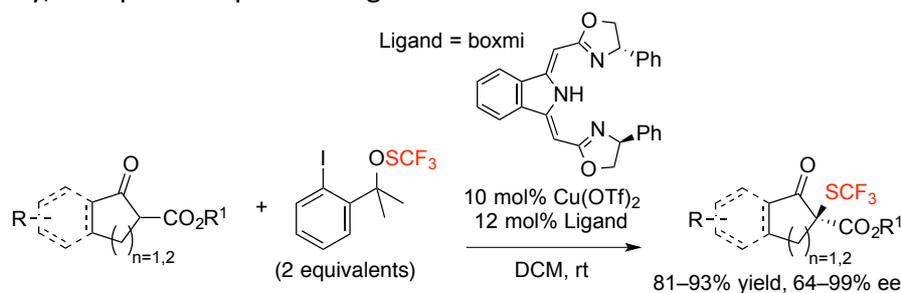
Scheme 7. Asymmetric trifluoromethylthiolation of cyclopentenone-based β -ketoesters

Finally, it was also possible to efficiently access the (*R*)-enantiomer by switching quinidine for its pseudo enantiomer quinine (Scheme 8).



Scheme 8. Access to (*R*)-SCF₃ indanone-based β -ketoester

In addition to these organocatalyzed approaches, Gade and coworkers described a method based on metal-catalysis for conducting the same kind of reaction. The association of a copper-boxmi complex and Shen's trifluoromethylsulfenate reagent allowed to obtain numerous trifluoromethylthiolated cyclic β -ketoesters in excellent yields and with high enantioselectivities (Scheme 9).^[8] The reaction was compatible with indanone-, tetralone-, cyclopentenone- as well as cyclohexenone-derived β -ketoesters, and diverse functional groups such as methoxy, methyl or halogens were well-tolerated. Once again, the bulkiness of the ester group had little impact on the enantioselectivity, except when performing the reaction on tetralone derivatives.



Indanone derivatives

R = 5,6-(OMe)₂

R¹ = Me 92%, 96% ee
Et 93%, 95% ee
***i*Pr** 90%, 98% ee
***t*Bu** 81%, >99% ee
Bn 89%, 96% ee
CH₂CHCH₂ 92%, 76% ee

R¹ = Me

R = H 90%, 93% ee
5-OMe 86%, 96% ee
5-Me 89%, 95% ee
5-Cl 92%, 91% ee
5-Br 91%, 90% ee
6-CF₃ 89%, 90% ee

Cyclopentenone derivatives

R = 3-OMe 88%, >99% ee
3-Me 92%, 99% ee
4-Me 89%, >99% ee
3,4-Me₂ 93%, >99% ee

Cyclohexenone derivative

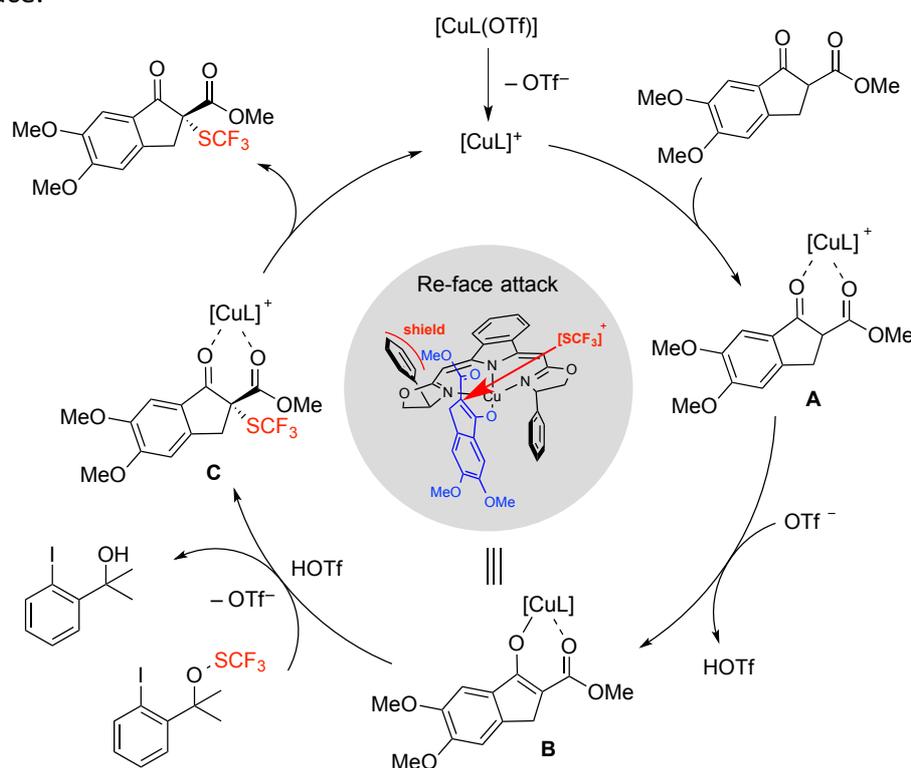
R = 4-Me 91%, 99% ee

Tetralone derivatives

R¹ = Me R = H 92%, 64% ee
***t*Bu H** 81%, 99% ee
7-F 83%, 99% ee
7-Br 82%, >99% ee
7-OMe 85%, >99% ee

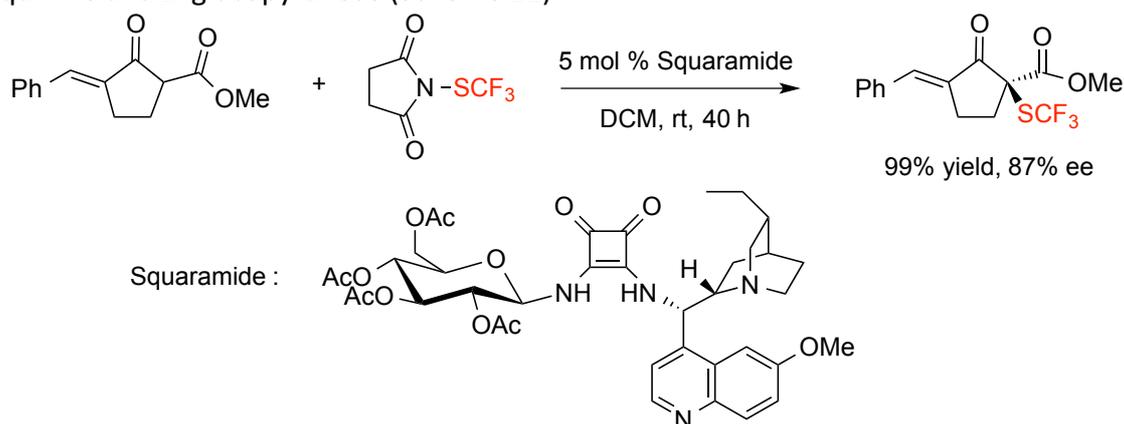
Scheme 9. Copper-catalyzed trifluoromethylthiolation of various β -ketoesters

As for the mechanism of the reaction, organocatalysis by the sole action of the ligand was quickly excluded, as no product was formed in absence of copper salts. Moreover, a potential direct reaction between the SCF_3 reagent and the copper complex was not witnessed either by EPR spectroscopy nor by ^{19}F NMR spectroscopy. Considering these information experiments, the authors proposed the pathway described in Scheme 10. In the first place, both carbonyl oxygen atoms of the β -ketoester coordinate to the copper-boxmi complex. The obtained intermediate **A** is then deprotonated by triflate anion to afford the ester enolate **B**, on which the SCF_3 group can be introduced from the trifluoromethylthiolation reagent via a triflic acid activation. The final product is produced from intermediate **C** after an ultimate step of de-coordination. The enantioselectivity of the process supposedly emerges from the fact that the *Si* face of enolate **B** is shielded by the phenyl ring of the boxmi ligand, and that, consequently, electrophilic SCF_3 preferentially approaches from the *Re* face.



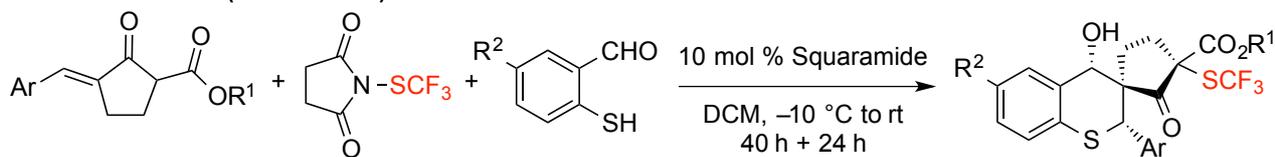
Scheme 10. Mechanism of the Cu-catalyzed trifluoromethylthiolation of cyclic β -ketoesters

Du and coworkers were also interested in the asymmetric introduction of the SCF_3 motif on 1,3-dicarbonyls. In 2017, they proposed the enantioselective trifluoromethylthiolation of a cycloalkenone thanks to *N*-trifluoromethylthiosuccinimide and a squaramide catalyst derived from hydroquinine and *D*-glucopyranose (Scheme 11).^[9]



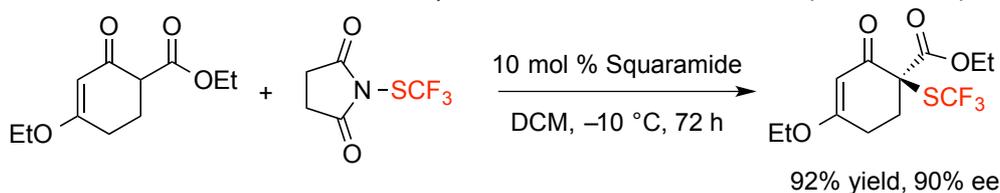
Scheme 11. Enantioselective trifluoromethylthiolation of a cycloalkenone by a squaramide catalyst

Such substrates could also be reacted with 2-mercaptobenzaldehyde derivatives in a one-pot procedure to furnish SCF₃ spiro cyclopentanone-thiochromanes through a sulfur-Michael/aldol cascade reaction (Scheme 12).



Scheme 12. One-pot synthesis of SCF₃ spiro cyclopentanone-thiochromanes

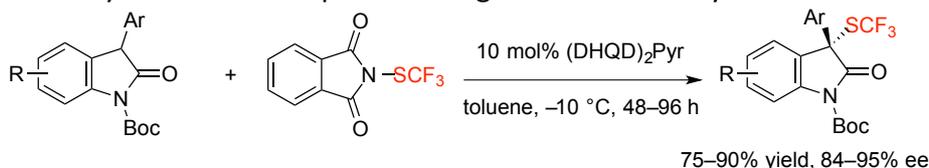
Interestingly, a cyclohexenone derivative was efficiently converted into its SCF₃ analogue using slightly tuned conditions but could not take part in the cascade reaction (Scheme 13).



Scheme 13. Enantioselective trifluoromethylthiolation of a cyclohexenone derivative

Trifluoromethylthiolation of oxindoles

Oxindoles were also privileged substrates for the enantioselective introduction of the SCF₃ moiety. Rueping and coworkers first reported a procedure allowing the asymmetric trifluoromethylthiolation of oxindoles using similar conditions as those they proposed for β -ketoesters (Scheme 14).^[10] Nonetheless, quinidine had to be replaced by a bis-cinchona alkaloid catalyst, (DHQD)₂Pyr, to obtain high enantioselectivities. Various 3-aryl Boc-protected oxindoles, substituted by different motifs on the aryl as well as on the fused-phenyl ring of the heterocycle, furnished indifferently the associated products in good to excellent yields and enantioselectivities.

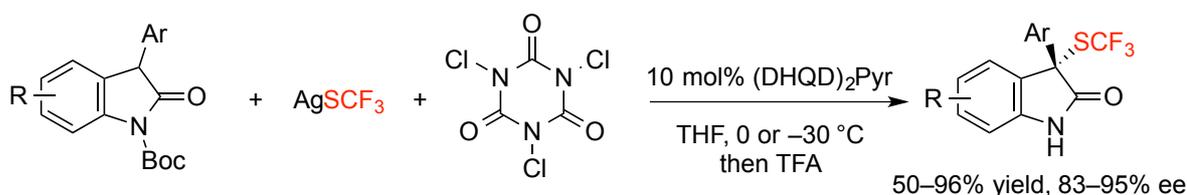


| R = H | |
|------------------------------------|-------------|
| Ar = C ₆ H ₅ | 85%, 92% ee |
| 4-MeC ₆ H ₄ | 84%, 95% ee |
| 4-tBuC ₆ H ₄ | 88%, 94% ee |
| 4-nBuC ₆ H ₄ | 75%, 94% ee |
| 4-PhC ₆ H ₄ | 85%, 91% ee |
| 4-OEtC ₆ H ₄ | 81%, 94% ee |
| 4-FC ₆ H ₄ | 77%, 92% ee |
| 4-ClC ₆ H ₄ | 90%, 84% ee |
| 3-MeC ₆ H ₄ | 76%, 92% ee |
| 3-OMeC ₆ H ₄ | 75%, 90% ee |
| 3-BrC ₆ H ₄ | 80%, 88% ee |
| 2-Naphthyl | 87%, 88% ee |

| Ar = Ph | |
|----------|-------------|
| R = 5-Me | 80%, 94% ee |
| 5-tBu | 83%, 93% ee |
| 5-OMe | 84%, 94% ee |
| 5-F | 80%, 90% ee |
| 5-Cl | 81%, 86% ee |
| 5-Br | 82%, 85% ee |

Scheme 14. Asymmetric trifluoromethylthiolation of 3-aryl oxindoles

Shortly after, Tan, Liu and coworkers described a closely related methodology, although based on the *in situ* generation of an electrophilic trifluoromethylthiolation reagent from readily available AgSCF₃ and trichloroisocyanuric acid (TCCA) (Scheme 15).^[11] The reaction conditions were compatible with 3-aryl oxindoles with various substitution patterns, and offered the expected products in moderate to excellent yields and with high enantioselectivities after a step of one-pot deprotection.



R = H

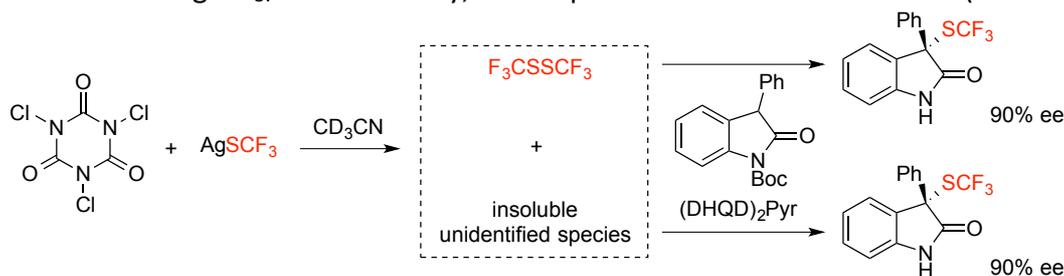
| | | | |
|---|-------------|---|-------------|
| Ar = C₆H₅ | 78%, 90% ee | 4-FC₆H₄ | 88%, 95% ee |
| 4-MeC₆H₄ | 82%, 90% ee | 3-FC₆H₄ | 96%, 92% ee |
| 3-MeC₆H₄ | 65%, 86% ee | 4-ClC₆H₄ | 95%, 93% ee |
| 3,5-Me₂C₆H₄ | 61%, 84% ee | 3-ClC₆H₄ | 85%, 90% ee |
| 4-OMeC₆H₄ | 87%, 83% ee | 4-CF₃C₆H₄ | 95%, 91% ee |

Ar = 4-ClC₆H₄

| | |
|-----------------|-------------|
| R = 5-Cl | 75%, 95% ee |
| 6-Cl | 87%, 88% ee |
| 7-Cl | 50%, 90% ee |
| 5-Br | 85%, 90% ee |
| 6-Br | 93%, 88% ee |
| 5-F | 84%, 93% ee |
| 5-Me | 85%, 93% ee |
| 5-OMe | 71%, 94% ee |

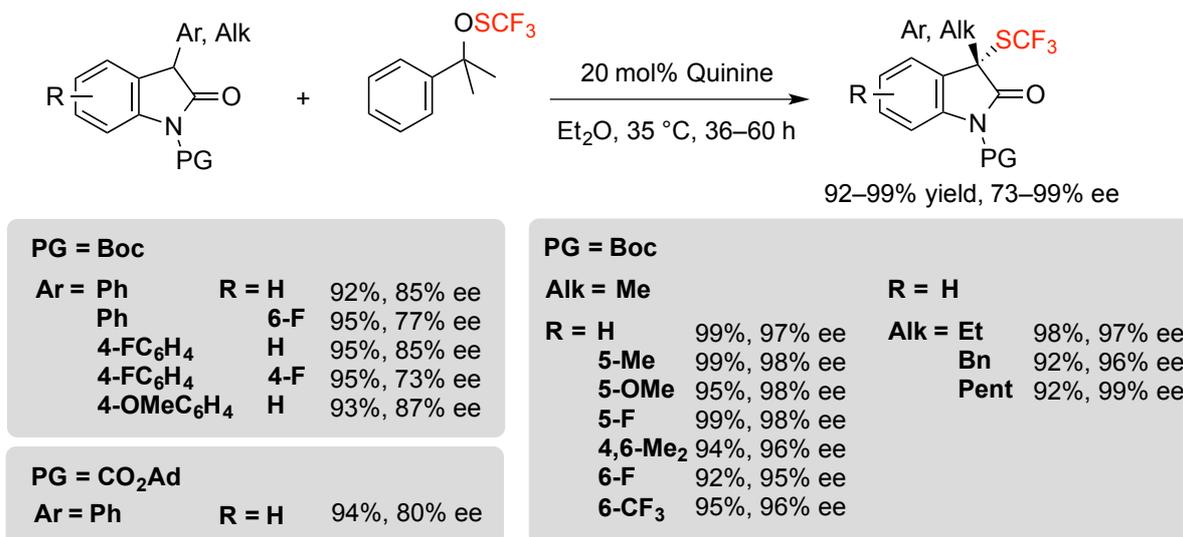
Scheme 15. Asymmetric trifluoromethylthiolation of 3-aryl oxindoles with in situ generation of the electrophilic SCF₃ donor

Experiments carried out for the identification of the reactive electrophilic SCF₃ showed that bis(trifluoromethyl)disulfide was generated *in situ*, and took part in the conversion of the substrate. However, formation of the trifluoromethylthiolated product also occurred with similar enantioselectivity without said disulfide, albeit in presence of insoluble species issued from the reaction of TCCA and AgSCF₃. Unfortunately, these species could not be identified (Scheme 16).



Scheme 16. Investigation on the active species of the reaction

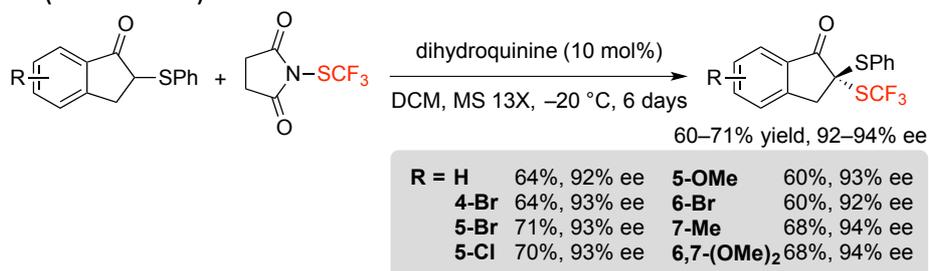
Shen and coworkers finally proposed an alternative methodology, although based on a similar concept, with the noteworthy advantage of giving access to unprecedented trifluoromethylthiolated 3-alkyl oxindoles in excellent yields and with high enantioselectivities (Scheme 17).^[12] To achieve such results, it was necessary to use 1.2 equivalents of Shen's trifluoromethylsulfonate reagent along with 20 mol% of quinine, in diethyl ether, at 35 °C. The nature of the trifluoromethylthiolation reagent proved to be truly influential on the reaction; indeed, replacing it by *N*-(trifluoromethylthio)phthalimide triggered an important decrease of the enantioselectivity. Unfortunately, the reaction proceeded less efficiently with 3-aryloxindoles, offering the associated products with slightly lower enantioselectivities. On the bright side, it was found that other protecting groups than Boc, such as CO₂Ad, could be tolerated without impacting drastically the ee values.



Scheme 17. Asymmetric trifluoromethylthiolation of 3-aryl and 3-alkyl oxindoles

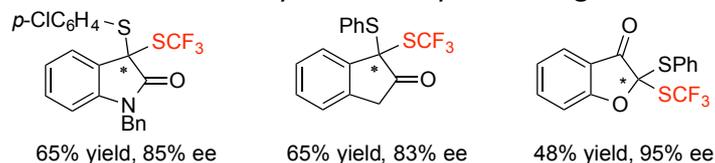
Trifluoromethylthiolation reactions toward dithioketals

The group of Zhou has been interested in the synthesis of dithioketal motifs, as they display promising potential in biopharmaceutical chemistry. In this context, they described the asymmetric introduction of the SCF₃ group onto 1-indanone-derived thioethers using 1.2 equivalents of *N*-(trifluoromethylthio)succinimide and 10 mol% dihydroquinine in dichloromethane at –20 °C. After six days, the corresponding SCF₃ products were isolated with excellent enantioselectivities, albeit in moderate yields (Scheme 18).^[13]



Scheme 18. Asymmetric trifluoromethylthiolation of 1-indanone-derived thioethers

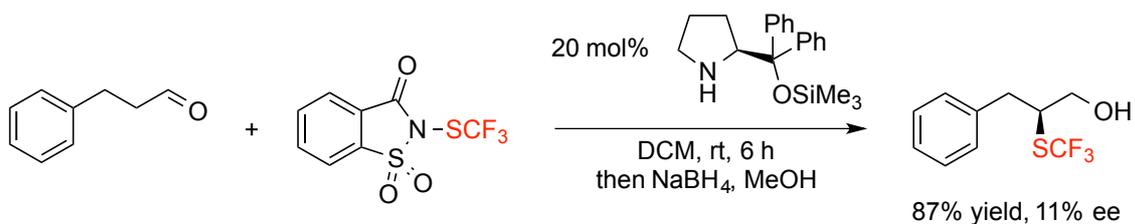
Interestingly, it was also possible to access more diverse dithioketals issued from oxindole, 2-indanone or 3-benzofuranone with similarly moderate yields and good ee values (Scheme 19).



Scheme 19. Access to structurally diverse dithioketals

Trifluoromethylthiolation of aldehydes

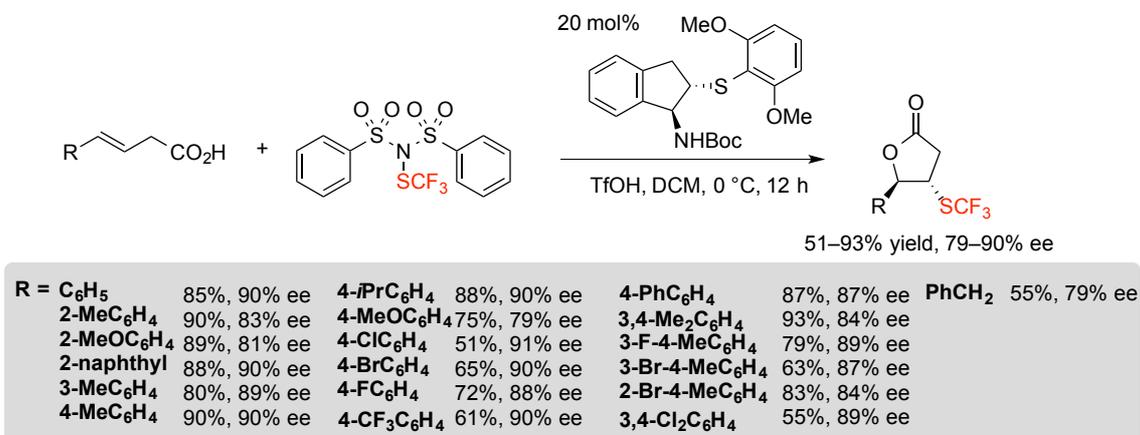
During their research focusing on the trifluoromethylthiolation of aldehydes, Wu, Sun and coworkers attempted to extend their methodology by developing an asymmetric version of it (Scheme 20).^[14] Disappointingly, only 11% ee value was measured when performing the reaction in the presence of the Hayashi-Jørgensen catalyst. To this day, no further investigation on this reaction has been reported.



Scheme 20. Asymmetric α -trifluoromethylthiolation of an aldehyde

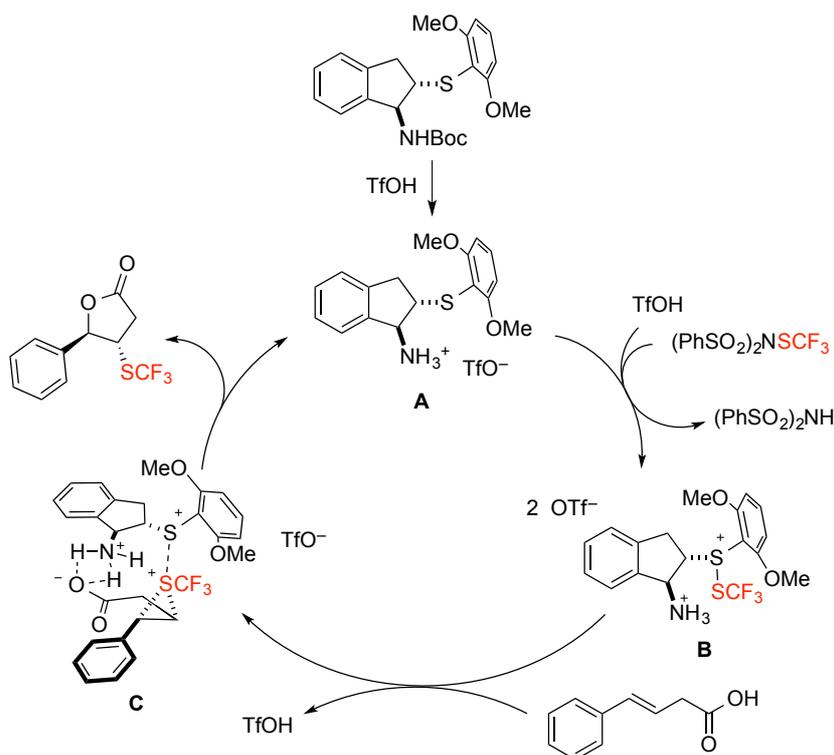
Cascade trifluoromethylthiolation / cyclization from functionalized alkenes

Recently, Zhao and coworkers studied the challenging enantioselective trifluoromethylthiolation of alkenes followed by a cyclization step for the synthesis of chiral lactones. For this purpose, a bifunctional chiral sulfide or selenide catalyst was used with a newly developed trifluoromethylthiolation reagent, $(\text{PhSO}_2)_2\text{N}-\text{SCF}_3$, analogue of the well-known fluorinating agent NFSI. Thus, using 1.5 equivalents of said reagent, 0.5 equivalents of triflic acid and 20 mol% of a chiral indane-based sulfide in dichloromethane at 0°C , a variety of 4-aryl substituted (*E*)-but-3-enoic acids could be converted into the corresponding lactones through a cascade trifluoromethylthiolation / lactonization reaction (Scheme 21).^{[15], [16]} A slight decrease of enantioselectivity was observed for substrates with aryls carrying an electron-donating group in *para* position. Similarly, hindered alkenes, with 2-substituted aryl moiety, led to lesser ee values. On the other hand, when electron-withdrawing groups were introduced on *para* or *meta* positions of the aryl, the yield was the most impacted and decreased down to 55%. The aryl substituent could be switched to a benzyl group without much consequence; however, replacing it by long alkyl chains led to mixture of diastereoisomers and moderate enantioselectivities.



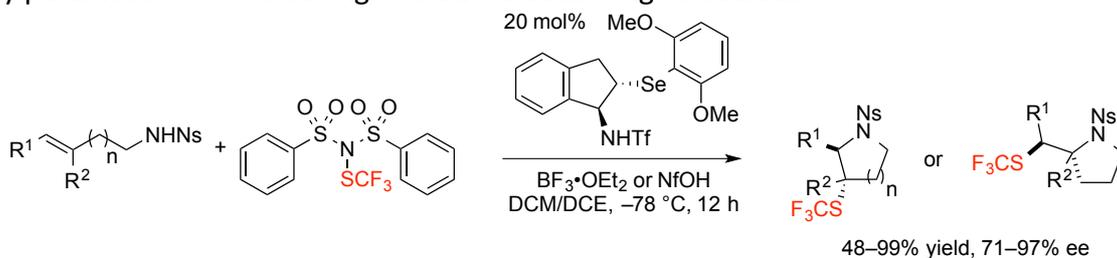
Scheme 21. Asymmetric trifluoromethylthiolating lactonization of alkenes

As for the mechanism of the reaction, the authors proposed the pathway represented on scheme 22. The Boc-protected catalyst first reacts with triflic acid to form the corresponding triflate **A**. The SCF_3 cation is then bound to the catalyst to form the intermediate sulfenylium ion **B** via a triflic acid activation. In the presence of an olefinic carboxylic acid, intermediate **B** is readily converted into the trifluoromethylthiiranium ion **C**, which is finally attacked by the oxygen of the carboxylic group to yield the expected product and regenerating the catalyst in the process. This mechanism enlightens the utility of the bifunctional catalyst, which is not only able to bind to the SCF_3 cation through the sulfur atom but also to dispose the carboxylic group for the cyclisation step. Interestingly, structurally close catalysts featuring a selenium instead of a sulfur atom could also be used, but lower enantioselectivities were achieved. This can be explained by the smaller size of the sulfur atom, which led to enhanced steric hindrance around the SCF_3 cation, and consequently resulted in better stereocontrol.



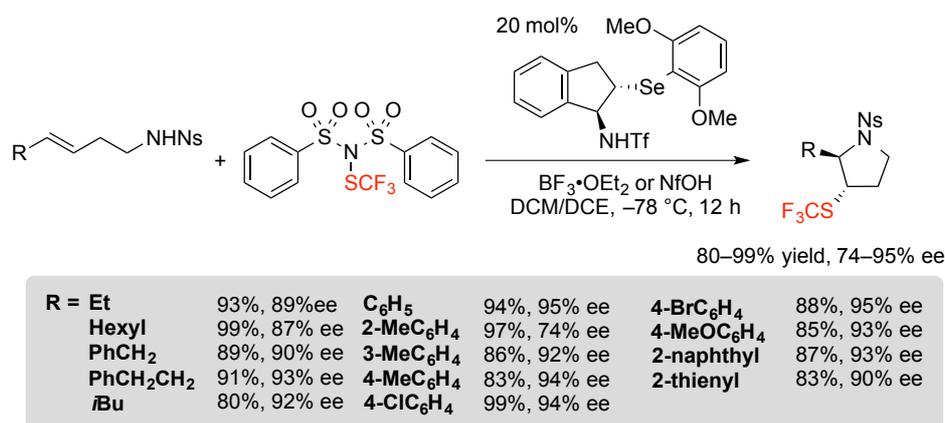
Scheme 22. Mechanism of the asymmetric trifluoromethylthiolating lactonization of alkenes

In the context of their work on trifluoromethylthiolating cyclization of alkenes, Zhao and coworkers also described an access to saturated SCF_3 azaheterocycles based on a similar concept (Scheme 23).^[17] To serve this purpose, the same trifluoromethylthiolation reagent, $(\text{PhSO}_2)_2\text{N}-\text{SCF}_3$, was selected and an indane-based chiral selenide catalyst bearing a triflyl group was used. As it was already the case in Zhao's previous work, steric hindrance and electronic effects of the catalyst were the key parameters for fine tuning in order to obtain high ee values.



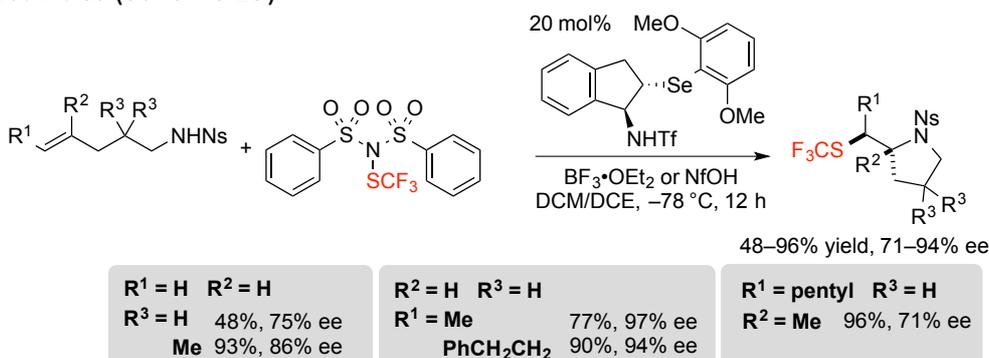
Scheme 23. Asymmetric trifluoromethylthiolating cyclization of (*E*)-alkenes toward saturated SCF_3 azaheterocycles

Thus, using 1.5 equivalents of $(\text{PhSO}_2)_2\text{N}-\text{SCF}_3$, 20 mol% of the selenide catalyst and 1.0 equivalent of $\text{BF}_3 \cdot \text{OEt}_2$ in a 1:1 mixture of dichloromethane and dichloroethane at -78°C , various (*E*)-alk-3-ene-1-sulfonamides furnished the associated products in high yields, dr and ee values (Scheme 24). Alkyl- and aryl-substituted alkenes were equally well-tolerated. Arylalkenes with electron-withdrawing groups like halogens were, however, less easily converted and necessitated a rise of the reaction temperature to afford high yields. On the other hand, (*Z*)-isomers did not react.



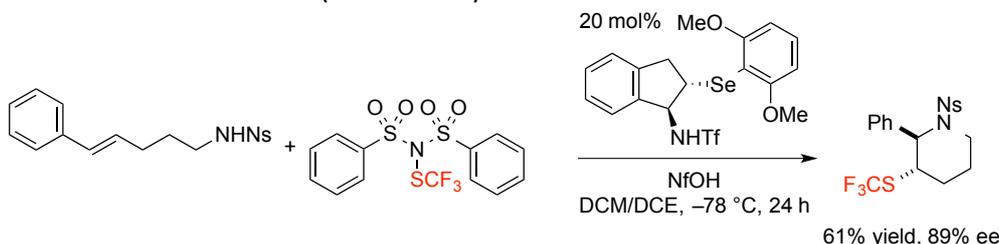
Scheme 24. Asymmetric trifluoromethylthiolating cyclization of (*E*)-alkenes toward saturated five-membered SCF₃ azaheterocycles

Alk-4-ene-1-sulfonamides proved to be more challenging substrates; indeed, competition between *endo* and *exo* cyclization was observed and the nature of the obtained product was more dependent on the substitution of the starting material. The *exo* product was predominantly obtained in the case of terminal, alkyl, and trisubstituted alkenes in moderate to excellent yields and enantioselectivities (Scheme 25).



Scheme 25. Asymmetric trifluoromethylthiolating *exo* cyclization of (*E*)-alk-4-enes toward pyrrolidines

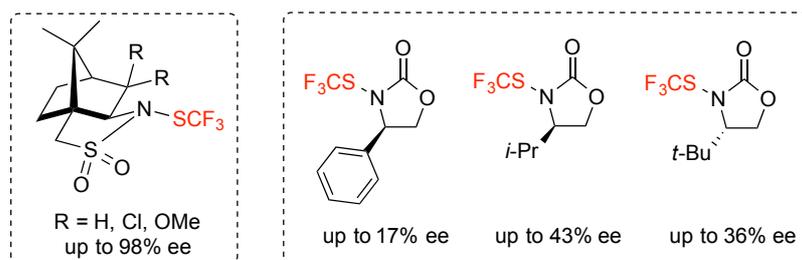
The formation of the *exo* product occurred as the main pathway when performing the reaction with a phenyl substituent on the alkene (Scheme 26).



Scheme 26. Asymmetric trifluoromethylthiolating *endo* cyclization of a (*E*)-alk-4-ene toward a saturated six-membered SCF₃ azaheterocycle

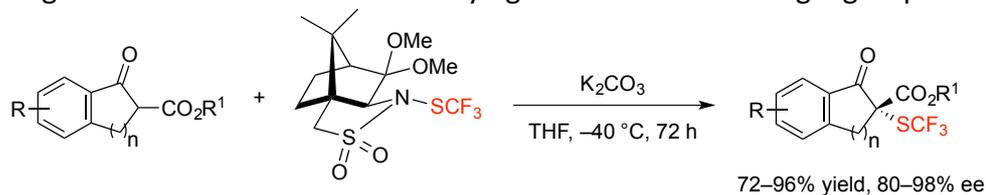
2.3 Chiral trifluoromethylthiolation reagents

In 2017, Shen and coworkers proposed the use of optically pure trifluoromethylthiolation reagents for the enantioselective trifluoromethylthiolation.^[18] (1*S*)-(-)-*N*-Trifluoromethylthio-2,10-camphorsultam derivatives proved to be the best candidates to perform this type of reaction. *N*-Trifluoromethylthio-oxazolidinone derivatives were also evaluated, but gave lower enantioselectivities (Scheme 27).



Scheme 27. Chiral trifluoromethylthiolation reagents (ee values for the reaction with β -ketoesters)

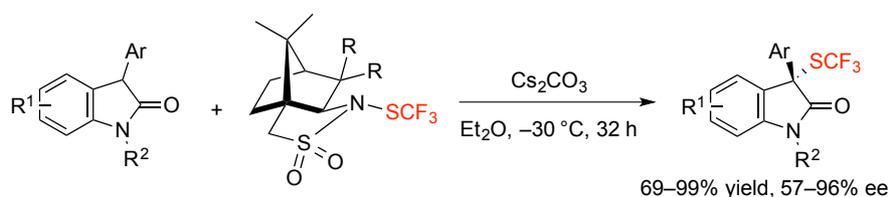
These reagents were compatible with various substrates. For example, in the presence of 0.1 equivalents of K_2CO_3 in tetrahydrofuran at $-40^\circ C$, five and six-membered ring β -ketoesters afforded the corresponding SCF_3 products in good to excellent yields with high enantioselectivities, up to 98% (Scheme 28). Several functional groups (R) and diverse ester groups (R^1) were well tolerated. However, it was necessary to increase the temperature to reach a satisfying conversion when performing the reaction on substrates carrying electron-withdrawing R groups.



| n = 1 | | R ¹ = Me | | n = 2 | |
|---------------------|-------------|---------------------|-------------|------------------------|-------------|
| R = H | | R = 6-Me | 91%, 91% ee | R ¹ = Me | |
| R ¹ = Me | 94%, 88% ee | R = 6-OMe | 77%, 91% ee | R = H | 82%, 89% ee |
| Et | 90%, 90% ee | 5-F | 81%, 86% ee | 8-OMe | 90%, 98% ee |
| iPr | 95%, 89% ee | 5-Cl | 72%, 80% ee | 7-OMe | 87%, 95% ee |
| Ad | 93%, 92% ee | | | 7-Br | 84%, 96% ee |
| | | | | 6-OMe | 92%, 94% ee |
| | | | | 5-OMe | 96%, 96% ee |
| | | | | 6,7-(OMe) ₂ | 95%, 95% ee |

Scheme 28. Asymmetric trifluoromethylthiolation of indanone- and tetralone-based cyclic β -ketoesters

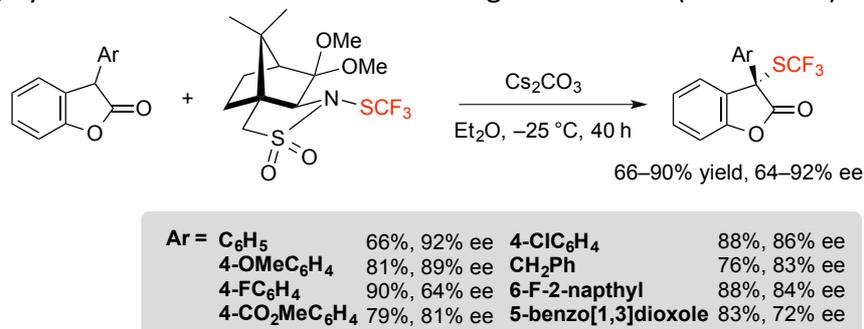
Similarly, a variety of 3-aryloxindoles were readily converted into their trifluoromethylthiolated analogues after a slight modification of the reaction conditions. Notably, K_2CO_3 was replaced by Cs_2CO_3 and tetrahydrofuran by diethyl ether (Scheme 29). Generally, the reaction conditions were once again efficient regardless of the functional groups carried by the aryl group or the nature of the protecting group linked to the nitrogen. However, in the unique case of the oxindole carrying a cyanomethyl substituent at the *para* position of its 3-aryl ring, a drop of enantioselectivity was observed. This issue could nonetheless be solved by replacing the trifluoromethylthiolating reagent to another camphorsultam analogue. Said reagent also allowed to reach higher ee values for already evaluated substrates, and even permitted to perform the reaction on a 3-methyl oxindole with moderate enantioselectivity.



| R = OMe | | | |
|--|------------------------------------|----------------------|---|
| R ¹ = H | R ² = Me | | |
| Ar = C ₆ H ₅ | | 76%, 93% ee | 4-CO ₂ MeC ₆ H ₄ 86%, 94% ee |
| 4-OMeC ₆ H ₄ | | 86%, 92% ee | 4-C(O)MeC ₆ H ₄ 95%, 89% ee |
| 4-ClC ₆ H ₄ | | 72%, 88% ee | 2-naphthyl 85%, 95% ee |
| 4-tBuC ₆ H ₄ | | 94%, 92% ee | 3-CNC ₆ H ₄ 88%, 93% ee |
| 4-CNC ₆ H ₄ | | 97%, 94% ee | 4-CNCH ₂ C ₆ H ₄ 97%, 57% ee |
| R ¹ = H Ar = C ₆ H ₅ R ² = Boc 98%, 93% ee | | | |
| R = Cl | | | |
| R ¹ = H | R ² = Me | | |
| Ar = C ₆ H ₅ | | 69%, 96% ee | R ¹ = H R ² = Boc |
| 4-ClC ₆ H ₄ | | 95%, 93% ee | Ar = C ₆ H ₅ 92%, 91% ee |
| 4-CNCH ₂ C ₆ H ₄ | | 97%, 94% ee | 4-OMeC ₆ H ₄ 94%, 93% ee |
| | | | 4-ClCH ₂ C ₆ H ₄ 99%, 91% ee |
| | | | 4-tBuC ₆ H ₄ 96%, 93% ee |
| R ¹ = 7-F | Ar = C ₆ H ₅ | R ¹ = H | Ar = Me |
| R ² = Boc | 75%, 89% ee | R ² = Boc | 76%, 79% ee |

Scheme 29. Asymmetric trifluoromethylthiolation of 3-aryloxindoles

Finally, it was also possible to access structurally new chiral 2-SCF₃-2-aryl benzofuran-2(3*H*)-ones in moderate to high yields and with ee values in the range 64–92% ee (Scheme 30).



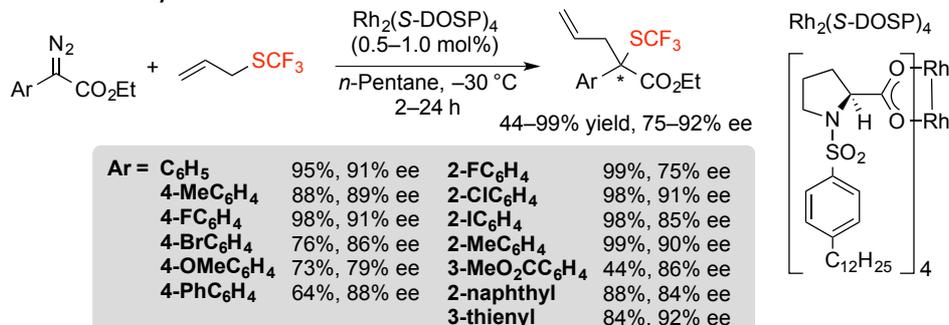
Scheme 30. Asymmetric trifluoromethylthiolation of 2-aryl benzofuran-2(3*H*)-ones

3. Building block approach

In comparison with direct enantioselective trifluoromethylthiolation methods, the building block approach for construction of chiral centers bearing the SCF₃ group is little widespread. At the present time, only two recent reports describing stereocontrolled formation of chiral SCF₃ compounds can be found.

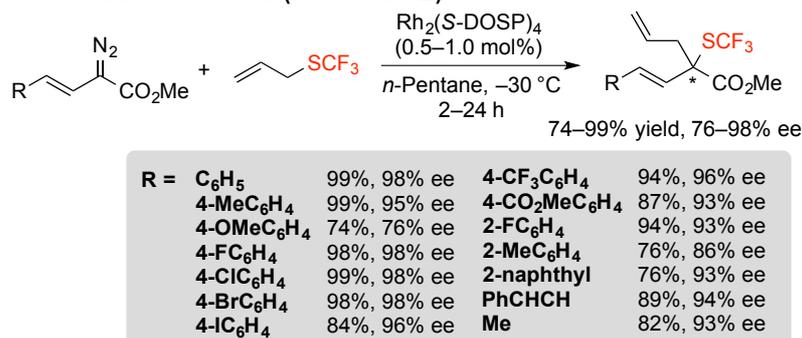
The first approach, implemented by Wang and coworkers is a variation of the Doyle-Kirmse reaction.^[19] It proceeds through an enantioselective [2,3]-sigmatropic rearrangement of a sulfonium ylide that is generated from allyl or propargyl trifluoromethyl sulfides and a metal carbene species issued from the reaction of a diazoester and a metal catalyst bearing chiral ligands. This methodology was first developed using a rhodium (II) catalyst, Rh₂(*S*-DOSP)₄, in *n*-pentane, at –30 °C. A wide range of aromatic diazoesters were submitted to these reaction conditions, giving access

to the corresponding chiral (*R*)-trifluoromethyl sulfides in good to excellent yields with high ee values (Scheme 31). Interestingly, the bulkiness of the ester group displayed an important influence on the enantioselectivity of the reaction; indeed, ee values dropped as the steric bulk of the ester increased. Electronic effects also proved to be of importance; diazoesters bearing aryls with electron-donating groups were converted with diminished yields and enantioselectivities. This phenomenon may be related to the lesser stability of such compounds, which therefore are more prone to be consumed by side-reactions like dimerization.



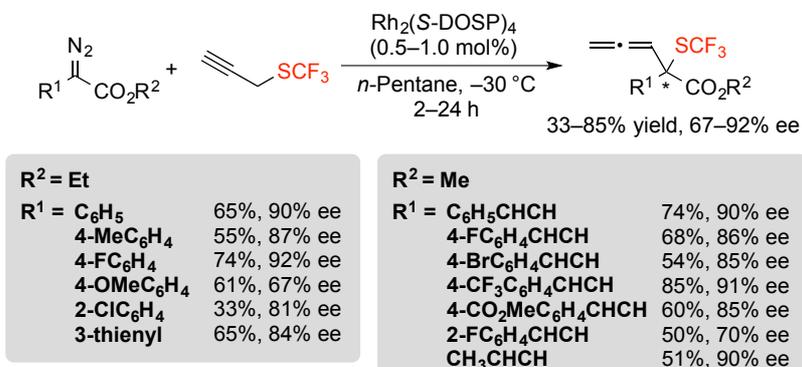
Scheme 31. Rh-catalyzed [2,3] sigmatropic rearrangement from aryl diazoesters and allyl trifluoromethyl sulfide

The reaction could also be performed efficiently on vinyl-diazoacetates and higher ee values were actually achieved with these substrates (Scheme 32).



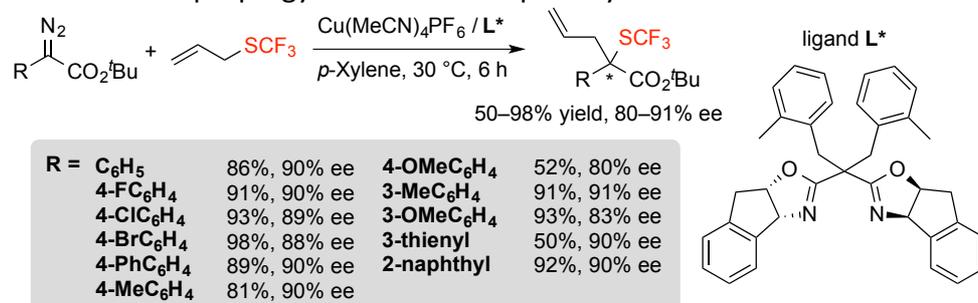
Scheme 32. Rh-catalyzed [2,3] sigmatropic rearrangement from vinyl diazoesters and allyl trifluoromethyl sulfide

Finally, it was also possible to replace the allyl trifluoromethyl sulfide by propargyl trifluoromethyl sulfide and to react it with similar aryl- and vinyl-diazoesters in order to access the corresponding allenyl sulfides. The reaction proceeded in moderate to good yields as well as enantioselectivities (Scheme 33).



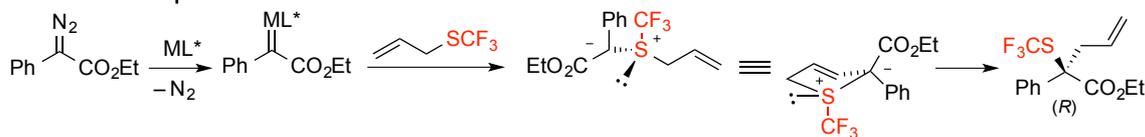
Scheme 33. Rh-catalyzed [2,3] sigmatropic rearrangement from diazoesters and propargyl trifluoromethyl sulfide

Copper(I) catalysts, which present the advantage to be more cost-effective than rhodium complexes, were also evaluated. When using $\text{Cu}(\text{MeCN})_4\text{PF}_6$ associated with a chiral ligand, the reaction showed good efficiency and afforded the expected products with essentially identical enantioselectivity (Scheme 34). The reaction suffered from similar limitations as with rhodium catalysis: diazoesters bearing electron-rich aromatic rings gave low yields and moderately high enantioselectivities. On the other hand, in these conditions, vinyl-diazoacetates furnished low ee values, and conversion of propargyl sulfides was especially slow.



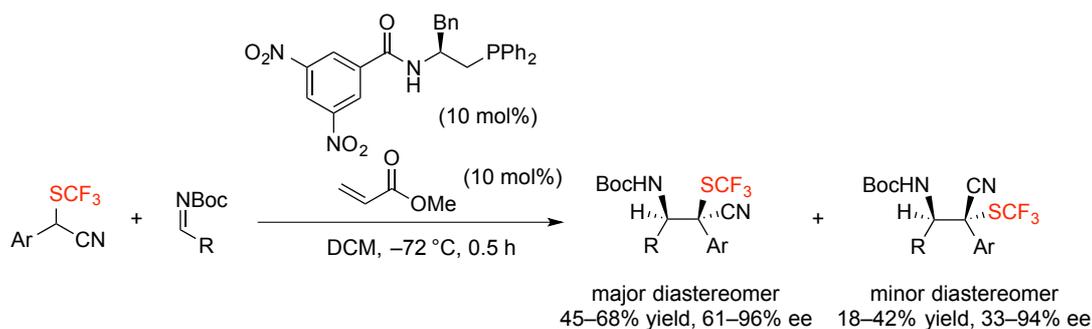
Scheme 34. Cu-catalyzed [2,3] sigmatropic rearrangement from diazoesters and allyl trifluoromethylsulfide

As mentioned earlier in the text, the considered reaction is an asymmetric example of Doyle-Kirmse reaction. The first step of said reaction consists in the formation of a chiral metal carbene, followed by its coordination with the sulfur atom of the allyl sulfide. The obtained sulfonium ylide then underwent a concerted [2,3]-sigmatropic rearrangement, transferring the chirality from sulfur to carbon (Scheme 35). The key step in respect to enantioselectivity is the formation of the free ylide. The hypothesis that the reaction might process through a Rh(II)-associated ylide was ruled out by several control experiments.



Scheme 35. Reaction mechanism

Zhao and coworkers focused on a different type of building block and described asymmetric organophosphine-catalyzed Mannich-type reactions on *N*-Boc imines giving access to tetrasubstituted carbon stereocenters featuring a cyano and a SCF_3 group.^[20] In this study, aryl 2-(trifluoromethylthio)acetonitriles were selected as substrates. The best results were obtained when using 1.0 equivalent of SCF_3 building block, 2.0 equivalents of Boc-protected imines, 10 mol% of chiral phosphine and 10 mol% of methyl acrylate. The expected products were obtained with moderate dr (up to 78:22) and moderate to high ee values, consequently the yields related to both diastereomers were limited, up to 68% for the major diastereomer (Scheme 36). Similar yields were obtained indifferently to the substitution pattern of the substrates. As for enantioselectivity, electron-donating groups carried by the Ar group of the imine contributed to increase perceptibly the obtained ee values, while electron-withdrawing groups such as halogens gave more disappointing results. The imine protecting group also proved to be quite influential. Indeed, the reaction did not proceed when using *p*-methoxyphenyl, *p*-toluenesulfonyl, 1,1-diphenylmethyl or diphenylphosphinyl, while it worked well with *N*-Cbz imine, although with lower ee value.

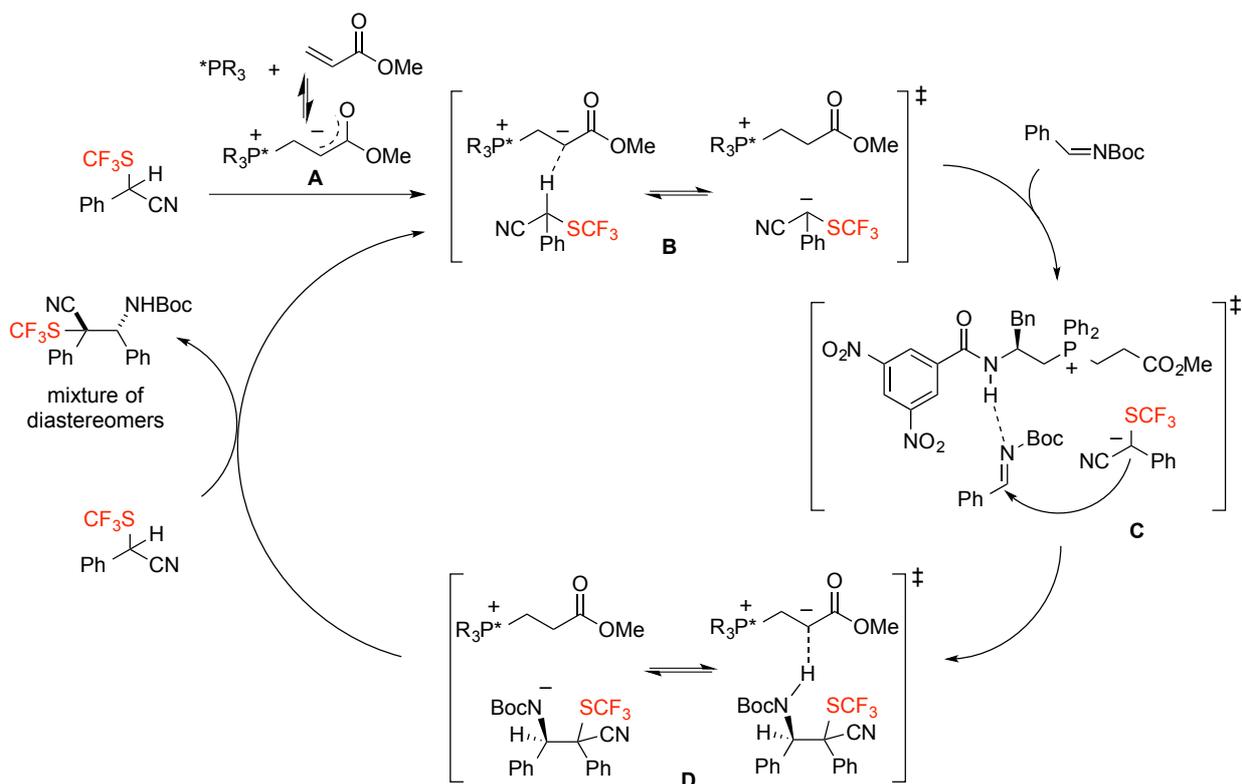


| Ar = Ph | dr | major diastereomer | minor diastereomer |
|---|-------|--------------------|--------------------|
| R = C ₆ H ₅ | 78:22 | 64%, 90% ee | 18%, 73% ee |
| 4-MeC ₆ H ₄ | 70:30 | 60%, 84% ee | 26%, 73% ee |
| 4-EtC ₆ H ₄ | 68:32 | 56%, 90% ee | 27%, 90% ee |
| 4- <i>i</i> PrC ₆ H ₄ | 74:26 | 65%, 91% ee | 23%, 91% ee |
| 4- <i>t</i> BuC ₆ H ₄ | 66:34 | 56%, 84% ee | 29%, 84% ee |
| 2-MeC ₆ H ₄ | 62:38 | 53%, 90% ee | 33%, 88% ee |
| 3-MeC ₆ H ₄ | 77:23 | 68%, 94% ee | 20%, 88% ee |
| 3,4-Me ₂ C ₆ H ₄ | 69:31 | 58%, 93% ee | 26%, 82% ee |
| 4-FC ₆ H ₄ | 64:36 | 57%, 62% ee | 32%, 76% ee |
| 4-ClC ₆ H ₄ | 62:38 | 54%, 66% ee | 33%, 76% ee |
| 4-BrC ₆ H ₄ | 61:39 | 54%, 61% ee | 34%, 76% ee |
| 2-ClC ₆ H ₄ | 57:43 | 49%, 69% ee | 37%, 75% ee |
| 3-ClC ₆ H ₄ | 64:36 | 58%, 70% ee | 32%, 85% ee |
| 3,5-Br ₂ C ₆ H ₄ | 59:41 | 53%, 63% ee | 37%, 76% ee |
| 2-furyl | 52:48 | 45%, 69% ee | 42%, 71% ee |
| 2-thienyl | 64:36 | 56%, 83% ee | 32%, 33% ee |
| 1-naphthyl | 57:43 | 51%, 92% ee | 38%, 94% ee |
| 2-naphthyl | 59:41 | 50%, 84% ee | 35%, 85% ee |
| cyclohexyl | 70:30 | 60%, 96% ee | 25%, 67% ee |

| R = Ph | dr | major diastereomer | minor diastereomer |
|--|-------|--------------------|--------------------|
| Ar = 4-MeC ₆ H ₄ | 65:35 | 55%, 72% ee | 29%, 85% ee |
| 3-MeC ₆ H ₄ | 68:32 | 58%, 82% ee | 27%, 70% ee |
| 4-FC ₆ H ₄ | 62:38 | 56%, 69% ee | 35%, 85% ee |
| 4-ClC ₆ H ₄ | 66:34 | 57%, 83% ee | 30%, 78% ee |
| 4-BrC ₆ H ₄ | 66:34 | 59%, 76% ee | 30%, 79% ee |
| 2-naphthyl | 68:32 | 59%, 82% ee | 27%, 70% ee |

Scheme 36. Formation of CF₃S-containing tetrasubstituted carbon stereocenters through enantioselective Mannich-type reactions

Concerning the mechanism of the reaction, the authors proposed the pathway represented on scheme 37. First, the two components of the catalytic system – the chiral phosphine and methyl acrylate – form the zwitterionic adduct **A**, as confirmed by ESI-MS, that acts as mild chiral Brønsted base. This phosphonium enolate **A** deprotonates the SCF₃-substrate to generate the ion-pair **B**, which is then able to attack the Boc-imine, furnishing intermediate **D** via transition-state **C**. A proton exchange then occurs between the SCF₃ building block and intermediate **D** producing the mixture of diastereomers and regenerating the species **B**. This mechanism enlightens the importance of the nitrile group on the SCF₃ substrate. Indeed, the nitrile is necessary for the efficient processing of the reaction because it favours greatly the deprotonation of the substrate. It is noteworthy that the reaction could not proceed when replacing this cyano group by an ester moiety.



Scheme 37. Proposed mechanism for the enantioselective Mannich-type reaction

4. Perspectives

The asymmetric synthesis of trifluoromethylthiolated molecules is a fledgling area of research in organofluorine chemistry. Since 2013, approaches for the direct introduction of the electrophilic SCF₃ motif through organocatalysis, metal-catalyzed reactions, or by means of chiral reagents were described in high-impact publications. More recently, the use of building blocks featuring the SCF₃ motif were reported for the stereocontrolled formation of chiral SCF₃ compounds. At this stage, research efforts still need to be made in two directions: (i) the discovery of alternative more efficient, cheap, and easy to handle reagents acting as SCF₃ donors; (ii) the development of new asymmetric syntheses by innovative approaches. These new tools will allow to reach new SCF₃ molecular architectures and ever higher stereoselectivities. We are confident that the current state-of-the-art detailed in this review should stimulate further developments in the field of chiral trifluoromethylthiolated molecules in medicinal applications, material sciences, and other domains of our daily life.

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