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Fluorinated Substrates as Michael Acceptors Towards Fine Chemicals

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Abstract: Michael addition reaction, known since the 19th century, appeared as a relevant method with a great potential to design new organofluorinated fine chemicals and enlarged their structural diversity. In the Michael addition reaction for the synthesis of organofluorine compounds, the fluorinated blocks can be both used as the Michael donors and acceptors, but the latter is relatively rare. This review aims to provide a comprehensive summary of the use of fluorinated substrates as Michael acceptors in Michael reactions.

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Keywords: Organofluorine compounds; Michael addition reaction; Fluorinated α,β -unsaturated carbonyl compounds; Fluorinated nitroalkenes; Fluorinated sulfoxides and sulfones; fluorinated alkenes

1. Introduction

Owing to the highest electronegativity and the small size of the fluorine atom, the introduction of a fluorine or a fluorinated moiety into an organic molecule can alter its physical, chemical, and biological activities.^[1] The wild applications of organic fluorinated compounds have been witnessed in many fields including the material science, pharmaceutical, and agrochemical industries.^[2] However, organic fluorinated compounds are very rare in nature (less than 20)^[3] and most of them are synthesized by chemists. In various synthetic strategies, the use of fluorinated building-block strategy, *i.e.*, starting from fluorine-containing raw materials, to access more complex fluorinated molecules through the C–C or C-heteroatom bond formation, is

becoming more and more popular.^[4] One of the most classical approaches for these bond constructions is the Michael addition reaction. Since its discovery more than hundred years ago,^[5] Michael reaction has received much attention from organic chemists because the use of different nucleophiles allows to enlarge the scope of the reaction and to go beyond the sole formation of C–C bond by the constructions of C–N, C–S, C–O, C–P, and other C-heteroatom bonds. These derived aza-,^[6] sulfa-,^[7] oxa-,^[8] phospho-^[9] Michael addition reactions are also known as hetero-Michael addition reactions. Due to the significant atom economy for diastereoselective and enantioselective bond formation in asymmetric synthesis, Michael reactions are widely used alone or in tandem with other reactions in contemporary organic synthesis to afford various



Xin Huang was born in Sichuan, China. He received his Bachelor's degree in chemistry in 2015 from Zhengzhou University, China. From 2015 to 2018, he joined Prof. Guanyu Yang's research group to continue his studies and obtained his master's degree in organic chemistry in 2018 from Zhengzhou University, China. In 2018, he started his doctoral study in

INSA Rouen Normandie under the mentorship of Dr. Samuel Couve-Bonnaire and Dr. Tatiana Besset in the "Fluorinated Biomolecules Synthesis" team at the laboratory COBRA and obtained his Ph.D. in 2022. His main research interests are dealing with the use of fluorinated alkenes as building blocks to construct new fluorine-containing molecules.



Tatiana Besset obtained her PhD in organic chemistry (2009) at Grenoble University with Dr. Greene. She then moved to the WWU Münster as a postdoctoral fellow in the group of Prof. Glorius. In 2011, she joined the group of Prof. Reek at Amsterdam University as an industrial postdoctoral fellow (Eastman company). Since 2012, she is a CNRS

Researcher in the 'Fluorinated Biomolecules Synthesis' group at the laboratory COBRA (UMR 6014, Rouen, France). Her research involves the design of new transformations involving transition-metal catalysis (C–H bond functionalization) and the development of new strategies in organofluorine chemistry.



Prof. Philippe Jubault received his Engineer Diploma in « Chemistry and Process » from the National Institute of Applied Sciences of Rouen. In 1992, he joined the research group of Prof. Collignon and Prof. C. Feasson at the INSA of Rouen where he obtained his Ph.D. in January 1996. After one year as a post-doctoral student at Hydro-Québec (Shawinigan, Québec, Canada), he was a Marie Curie research fellow in the laboratory of Prof. V. K. Aggarwal at the University of Sheffield. In 1998, he returned to the INSA of Rouen and assumed in 2000 an assistant professor position, becoming full professor in 2008. His research interests include the development of new methodologies for the synthesis of original fluorinated building blocks bearing CF₂, SF₅ groups, fluorinated cyclopropanes and new heterocyclic scaffolds for medicinal chemistry.



Samuel Couve-Bonnaire received his PhD in 2001 under the supervision of Pr. Y. Castanet and J.-F. Carpentier at the Laboratory of Catalysis of Lille. Then he carried out his postdoctoral studies in the laboratory of Pr. P. Arya at the Steacie Institute for Molecular Sciences (Canada). Back to France, he was post-doctoral researcher with Sanofi-Aventis

as industrial partner. Since February 2005, he is assistant professor in the group "Fluorinated Biomolecules Synthesis" in COBRA laboratory. His main thematic research deals with fluorinated alkenes, from their synthesis using radical or organometallic chemistry to their application as analogues of biomolecules and fluoropeptidomimetics.

functionalized products starting from inexpensive and simple starting materials.

Considering the power of Michael reaction in organic synthesis as well as the importance of organofluorine compounds, the use of fluorinated building-blocks in Michael reaction to access fine organofluorinated compounds appears as an appealing strategy, but little attention has been paid in this area.^[10] In the related reports, the fluorine atom or fluorinated moieties are generally part of the nucleophile, also called Michael donors.^[11] Although the number of examples of fluorinated Michael acceptors is far less than fluorinated Michael donors, this approach to

access the organofluorinated compounds is evolving. In the past years, many conjugated fluorinated compounds like fluorinated α,β -unsaturated carbonyl compounds, fluorinated nitroalkenes, and fluorinated α,β -unsaturated sulfoxides/sulfones have been used as the Michael acceptors. In this review, we aim to discuss the advances made on the Michael reaction using different types of fluorinated Michael acceptors.

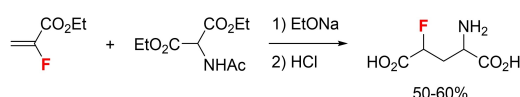
2. Fluorinated α,β -Unsaturated Carbonyl Michael Acceptors

α,β -Unsaturated carbonyl compounds refer to organic compounds with the general structure $R^1-C^{\beta}=C^{\alpha}-(C(=O)R^2)$. The corresponding fluorinated α,β -unsaturated carbonyl Michael acceptors can be classified by the different fluorinated moieties (F, CF_3 , perfluoro moiety and so on) on the double bond.

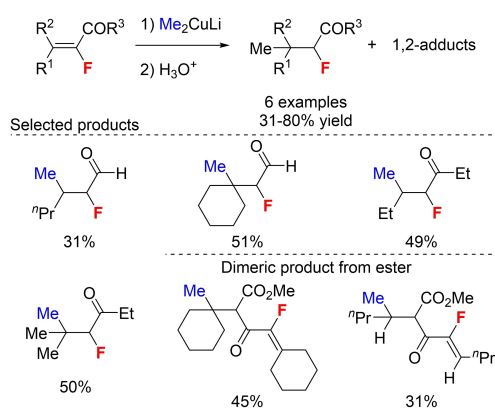
2.1. (Poly)Fluoroalkenes Michael Acceptors

The use of fluorinated substrates as Michael acceptors can be traced back to 60s. Indeed, in 1960, Hudlický described the synthesis of the γ -fluoroglutamic acid, a compound of biological interest (Scheme 1).^[12] In the presence of sodium ethoxide, a Michael addition reaction took place between ethyl 2-fluoroacrylate and diethyl 2-acetylaminomalonate. After hydrolyzing the corresponding Michael adduct, the desired γ -fluoroglutamic acid was obtained in 50–60% yield. In 1988, Tsushima and co-workers reported the same reaction and obtained the desired product γ -fluoroglutamic acid in 70% yield.^[13]

In 1979, Normant and co-workers studied the addition of lithium dimethylcuprate to α -fluoro- α,β -unsaturated carbonyl compounds including the aldehydes, ketones, and esters (Scheme 2).^[14] The use of these fluorinated Michael acceptors with cuprates could form both 1,2- and 1,4-adducts. The ratio of 1,2- and 1,4-adducts was affected by the steric hindrance at β -position of the Michael acceptor. Compared to aldehydes and ketones, the esters (R^1 , R^2 =Cy and



Scheme 1. The synthesis of γ -fluoroglutamic acid.



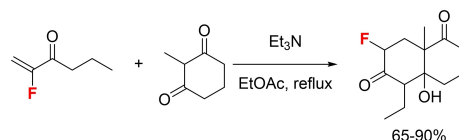
Scheme 2. The addition of Me_2CuLi to α -fluoro- α,β -unsaturated Michael acceptors.

R^1 = n Pr, R^2 =H) proved to be less reactive and the reaction has to be performed at room temperature. Nevertheless, at this temperature, a mixture of 1,2-adduct with another compound was obtained. Surprisingly, the latter was not the desired 1,4-adduct but came from the enolate resulting from 1,4-addition which immediately underwent a Claisen reaction to form a dimeric product with loss of the fluorine atom.

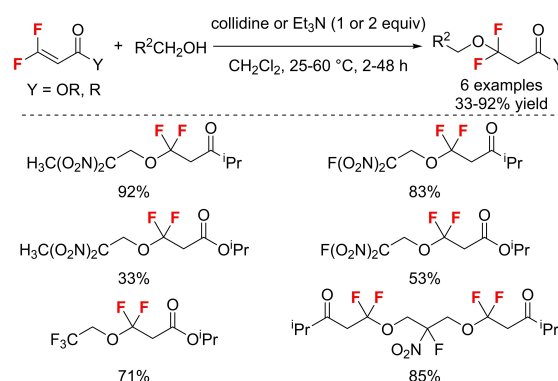
In 1981, Elkik and co-workers described the reaction between 2-fluorohex-1-en-3-one and 2-methylcyclohexane-1,3-dione. The new fluorinated cyclic product was formed by the Michael addition and a subsequent aldol reaction, but there was no characterization for this product (Scheme 3).^[15]

In 1990, Archibald and co-workers described an oxa-Michael addition on β,β -difluoroacrylates or β,β -difluorovinyl ketones (Scheme 4).^[16] The alcohols bearing electron-withdrawing substituents such trifluoromethyl or nitro groups generally afforded the corresponding fluoro ethers in moderate to high yields. Moreover, when the 2-fluoro-2-nitro-1,3-propanediol was used, a bis-adduct was obtained in 85% yield.

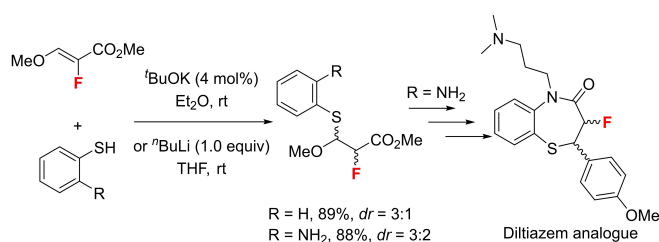
In 1996, Schlosser and co-workers described a sulfa-Michael addition on methyl (*Z*)-2-fluoro-3-methoxyacrylate. In the presence of t -BuOK or n -BuLi, the sulfa-Michael adducts were obtained as a mixture of diastereoisomers in good yields with moderate diastereoselectivities. The adduct of 2-aminothiophenol could be further used in the synthesis of fluorinated analogue related to the pharmaceutical agent Diltiazem (Scheme 5).^[17]



Scheme 3. 2-Fluorohex-1-en-3-one as the Michael acceptor.

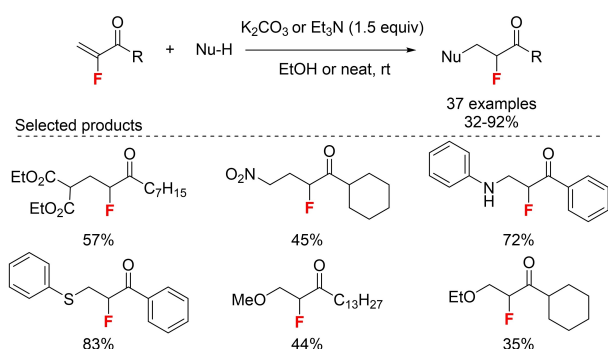


Scheme 4. The addition of alcohols bearing electron-withdrawing substituents to β,β -difluorinated α,β -unsaturated ketones and esters.

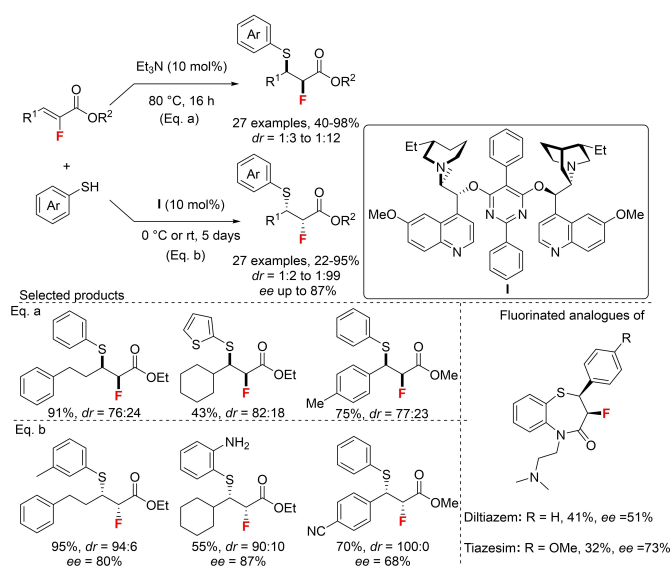


Scheme 5. The addition of thiophenol and 2-aminothiophenol to methyl (Z)-2-fluoro-3-methoxyacrylate.

More recently, Haufe and co-workers investigated the Michael addition of various nucleophiles (malonates, nitro compounds, anilines, thiolates, alkoxides) to α -fluoro- α,β -unsaturated ketones and observed their behavior in the formation of C–C and C–heteroatom bonds (Scheme 6).^[18] In the constructions of C–C, C–N, and C–S bond, all the fluorinated ketones were



Scheme 6. The addition of nucleophiles to α -fluoro- α,β -unsaturated ketones.



Scheme 7. Sulfa-Michael addition reaction of arylthiols on trisubstituted α -fluoroacrylates.

successfully converted into the desired β -substituted- α -fluoro ketones which could be isolated in moderate to very good yields. The formation of C–O bond was possible with MeOH or EtOH. The use of other bulky alcohols led to complex inseparable product mixtures.

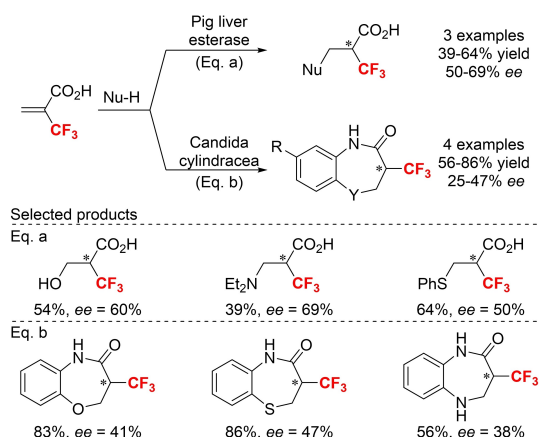
Last year, our group developed a sulfa-Michael addition reaction on α -fluoro- α,β -unsaturated esters in both racemic and enantioselective versions; fluorinated analogues of Diltiazem and Tiazesim have also been successfully synthesized (Scheme 7).^[19] In the racemic version, the use of 10 mol% of triethylamine in neat thiophenol led to moderate to excellent yields and fair to very good diastereomeric ratios. In the enantioselective version, commercially available catalyst **I**, an aryl ether of a bis-cinchona alkaloid (DHQ)₂PYR, was used as the organocatalyst. The chiral products were obtained in fair to excellent yields. Some products can be produced as a sole diastereoisomer. The enantiomeric excess of major diastereoisomer was strongly affected by the position of substituent on aryl thiols. The use of *para*-substituted thiophenols or 2-naphthalenethiol had no significant influence on the diastereoisomeric ratio but led to very low *ee* values. This could be explained by a steric hindrance in the pocket-like of the organocatalyst whereas *ortho*- or *meta*-substituted thiophenol did not hamper the approach of the reagent leading to better results in terms of enantioselectivities.

2.2. Michael Acceptors Containing CF₃, CHF₂ or CH₂F Moiety

Compared to other fluorinated Michael acceptors, Michael acceptors bearing a CF₃ moiety are the most used in Michael reactions. This family includes the acrylic acid, acrylate, enone, and acrylamide derivatives. The trifluoromethylated enone is a very important fluorine-containing building block^[20] and is also widely used as the Michael acceptor for the synthesis of trifluoromethyl-containing molecules. These reactions have already been summarized in a recent review,^[20b] hence they are not mentioned in this manuscript although they are equally important.

In 1986, Kitazume and co-workers reported enzyme-catalyzed enantioselective conjugate additions of a series of nucleophiles to commercially available 2-(trifluoromethyl)acrylic acid (Scheme 8).^[21] Various nucleophiles including water, thiophenol and diethylamine were applied in this reaction, giving the corresponding 1,4-adducts in moderate yields and enantioselectivities. From *o*-substituted anilines, a chiral Michael addition reaction followed by a condensation reaction allowed the formation of the optically active heterocycles in good yields but moderate enantioselectivities.

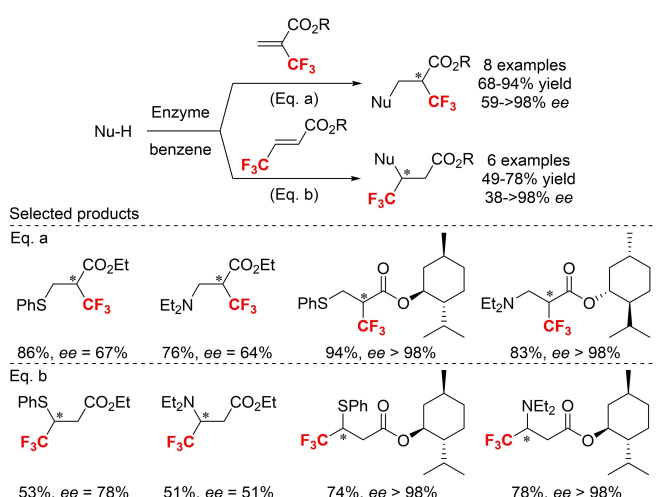
Two years later, the same group also developed an enzyme-catalyzed conjugate addition reaction to syn-



Scheme 8. Biocatalytic Michael addition reaction on the 2-(trifluoromethyl)acrylic acid.

thesize optically active compounds containing trifluoromethyl group but starting from the trifluoromethylacrylates (Scheme 9).^[22] In the described work, the α - and β -trifluoromethylacrylates were both used as the Michael acceptors, giving the corresponding products in moderate to excellent enantioselectivities. In the case of acrylates bearing a chiral menthol moiety on the ester group, the corresponding products were obtained with an excellent enantioselectivity in each case (>98% ee).

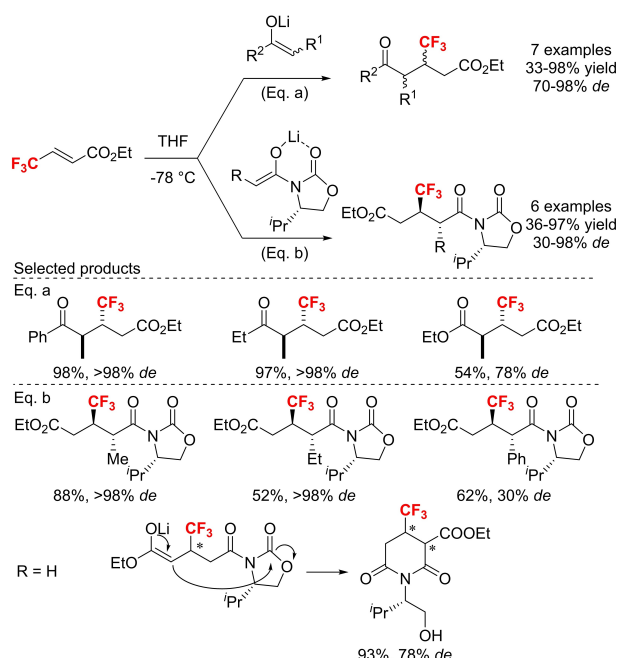
These α - and β -trifluoromethylacrylates are also found as the Michael acceptors in the conjugate addition reaction of lithium enolates, for the diastereoselective construction of new C–C bonds. Compared to the non-fluorinated acrylates, the trifluoromethylated acrylates showed a better reactivity due to the electron-withdrawing effect of trifluoromethyl group.



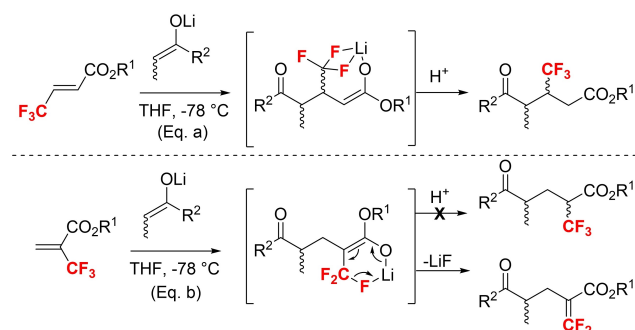
Scheme 9. Biocatalytic Michael addition reaction on α - and β -trifluoromethylacrylates.

In 1991, Yamazaki and co-workers reported the Michael reactions of lithium enolates to ethyl (*E*)-4,4,4-trifluorobut-2-enoate, these reactions were found to proceed smoothly in moderate to excellent yields as well as with high diastereoselectivities (Scheme 10, Eq. a).^[23] The same year, they described the addition of lithium enolates derived from chiral acylated oxazolidinones to the same Michael acceptors. The adducts were obtained in good to excellent yields with moderate to high level of diastereoselectivities (Scheme 10, Eq. b).^[24] The cyclic compound was obtained as the final product, which was possibly formed by a nucleophilic attack of the resulting ester enolate to the carbonyl carbon of oxazolidinone moiety, when unsubstituted enolate ($R = H$) was used.

For Michael reaction of various types of lithium enolates to (*E*)- β -trifluoromethylacrylate, the intramolecular Li–F interaction played an important role to stabilize the intermediate and allowed the Michael addition reaction to occur (Scheme 11, Eq. a).^[23] In 1994, the same authors proposed that the formation of Michael adducts of lithium enolates from α -trifluoromethylacrylates may go through a similar six-membered intermediate. Nevertheless, instead of the expected 1,4-adduct, only polymerized products, coming from the polymerization of substrates and/or byproduct, obtained from the LiF elimination, were produced (Scheme 11, Eq. b).^[25] Taking into account the high reactivity of such α -trifluoromethylacrylates, the authors suggested that the employment of much weaker nonmetallic nucleophiles could limit or avoid



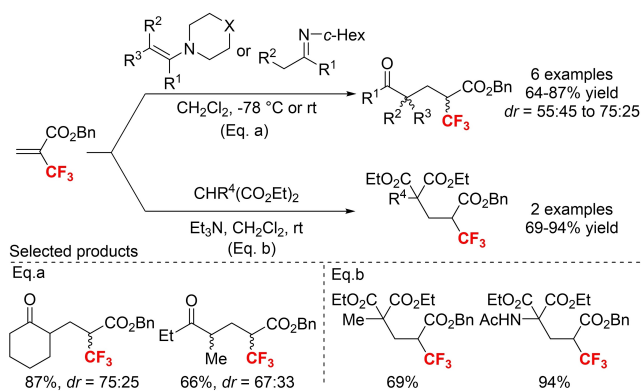
Scheme 10. The addition of lithium enolates to ethyl (*E*)-4,4,4-trifluorobut-2-enoate.



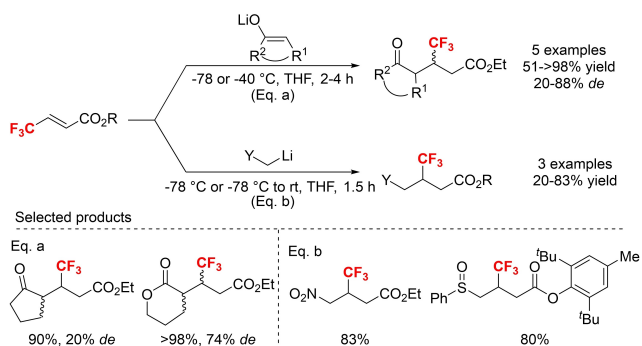
Scheme 11. Possible explanation for the stabilization of intermediates during Michael reaction of lithium enolates to α - and β -trifluoromethylated acrylates.

the polymerization reaction as well as the formation of defluorinated byproducts. In this context, they described the Michael reaction of enamines, imines, and active methylenes to benzyl 2-(trifluoromethyl)acrylate (Scheme 12).^[25]

One year later, building on their previous work, Yamazaki and co-workers extended the range of lithium enolates, employing cyclic enolates or enolates



Scheme 12. The addition of enamines, imines, and active methylenes to benzyl 2-(trifluoromethyl)acrylate.

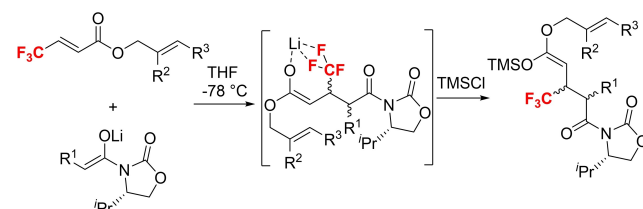


Scheme 13. The addition of various lithium enolates and nucleophiles to β -trifluoromethylated acrylates.

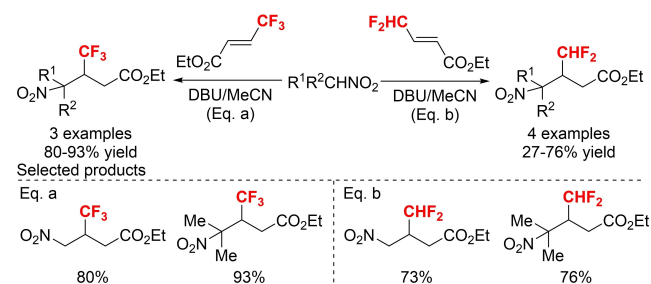
with functionalities stabilizing anion (Scheme 13, Eq. a and b), to react with the (*E*)- β -trifluoromethylacrylate.^[26] Interestingly, In their subsequent work on sequential Michael addition-Ireland Claisen reactions, the key intermediates were trapped with TMSCl (Scheme 14).^[27]

In 2003, Kitazume and co-workers employed the ethyl (*E*)-4,4,4-trifluorobut-2-enoate as a Michael acceptor for the synthesis of trifluoromethylated materials by using a microreactor. In the presence of DBU, the reaction between ethyl (*E*)-4,4,4-trifluorobut-2-enoate with nitroalkanes proceeded smoothly to afford the corresponding 1,4-adducts in the microreactor, which provided a new approach to access the CF_3 -containing compounds (Scheme 15).^[28] Two years later, they also used the ethyl (*E*)-4,4-difluorobut-2-enoate as a Michael acceptor to react with nitroalkanes in the microreactor. This ethyl (*E*)-4,4-difluorobut-2-enoate showed lower reactivity, which was reflected in the corresponding products obtained in lower yields compared to the ethyl (*E*)-4,4,4-trifluorobut-2-enoate (Scheme 15).^[29]

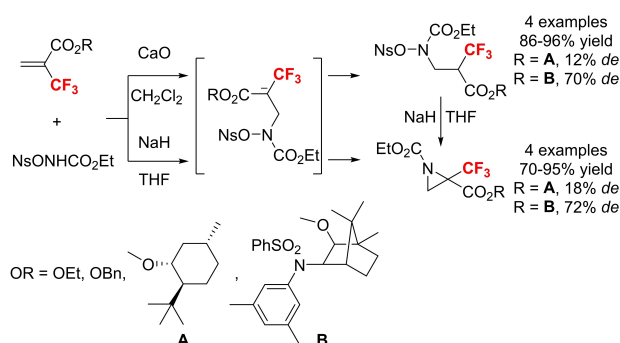
In 2004, Pellacani and co-workers reported an aza-Michael Addition of nosyloxycarbamates to four α -trifluoromethylacrylates, two of them containing chiral auxiliaries (Scheme 16).^[30] The use of different bases led to two products. A weak base as CaO led to the β -amino ester by immediate protonation, whereas with the NaH, the absence of water might favor the ring closure reaction forming the aziridine. The α -trifluoromethylacrylate bearing the menthol chiral



Scheme 14. Trapping of the key Michael adduct with TMSCl from the addition of lithium enolates to trifluoromethylated acrylates.



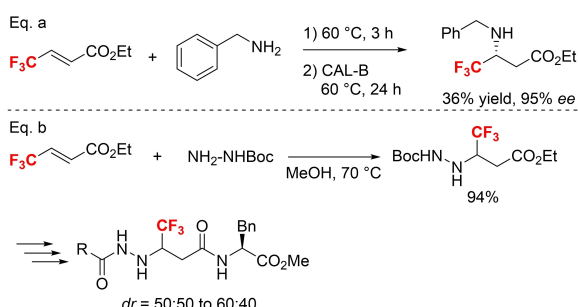
Scheme 15. The addition of nitroalkanes to ethyl (*E*)-4,4,4-trifluorobut-2-enoate and ethyl (*E*)-4,4-difluorobut-2-enoate.



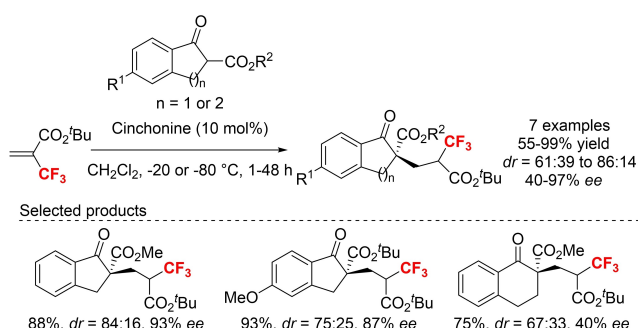
Scheme 16. The addition of nosyloxycarbamates to α -trifluoromethylacrylates.

auxiliary induced a low diastereoselectivity, giving only 12% and 18% of *de* for β -amino ester and aziridine respectively. Better results were obtained by using the bulkier Helmchen's auxiliary, giving 70% and 72% of *de* respectively.

Gröger and co-workers described a one-pot process to synthesize the short-chain aliphatic β -amino acid esters in 2009.^[31] The desired chiral amino acid ester was obtained in a two-step, one-pot process. Firstly, a racemic aza-Michael addition of benzylamine to the ethyl (*E*)-4,4,4-trifluorobut-2-enoate occurred to form the 1,4-adduct. Then, an addition of a lipase catalyzed



Scheme 17. The addition of benzylamine and Boc-protected carbamate to ethyl (*E*)-4,4,4-trifluorobut-2-enoate.



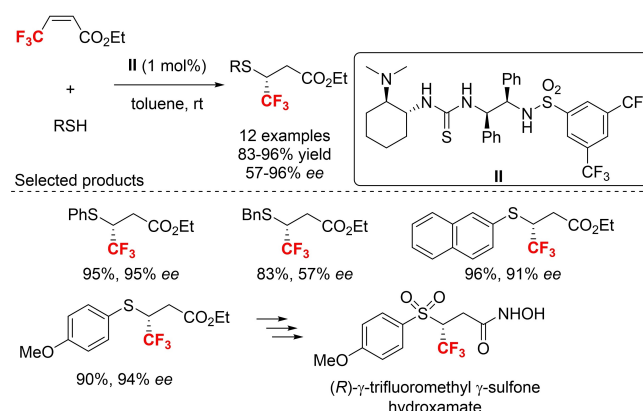
Scheme 18. The addition of β -ketoesters to *tert*-butyl 2-(trifluoromethyl)acrylate.

an enantioselective aminolysis reaction leading to enantioenriched adduct in 36% yield with high enantioselectivity (Scheme 17, Eq. a). The same year, Ongeri and co-workers selected the same ethyl (*E*)-4,4,4-trifluorobut-2-enoate as Michael acceptor to react with Boc-protected carbamate, giving an interesting β -trifluoromethyl- β -hydrazino ester scaffold used to design various inhibitors of rabbit (20S) proteasome (Scheme 17, Eq. b).^[32]

In the same year, Shibata and co-workers constructed nonadjacent quaternary stereocenters by the organocatalyzed Michael addition of cyclic β -ketoesters to *tert*-butyl 2-(trifluoromethyl)acrylate (Scheme 18).^[33] Several commercially available cinchona alkaloids were tested and among them, cinchonine gave the best results, furnishing the corresponding adducts in moderate to excellent yields as well as in moderate to very good diastereo- and enantioselectivities.

In 2011, Wang and co-workers developed a highly efficient asymmetric sulfa-Michael addition of thiols to ethyl (*Z*)-4,4,4-trifluorobut-2-enoate under the catalysis of the bifunctional amine-thiourea catalyst **II**, furnishing the corresponding 1,4-adducts in high yields and good to excellent enantioselectivities (Scheme 19).^[34] The subsequent transformation led to the convenient preparation of (*R*)- γ -trifluoromethyl γ -sulfone hydroxamate which is the key intermediate of a potent inhibitor of the matrix metalloproteinase-3 enzyme (MMP-3).

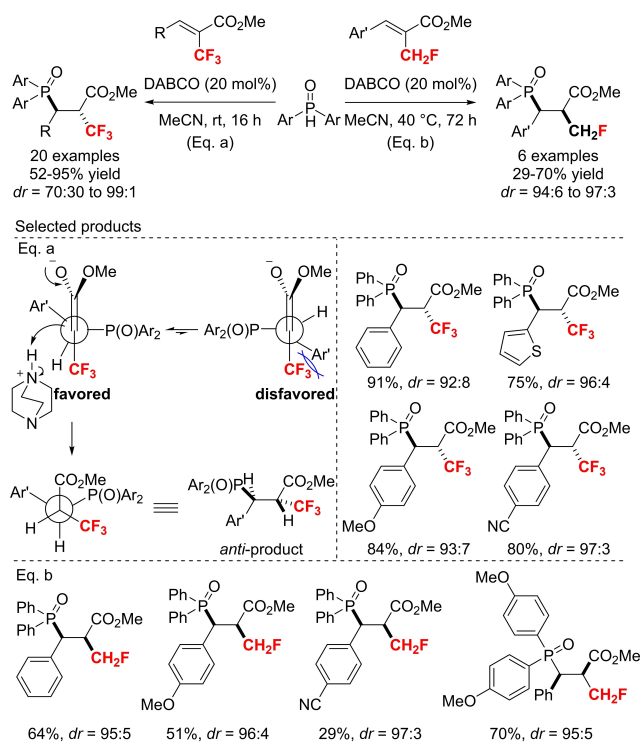
In the described Michael addition reactions of trifluoromethylated acrylate, we can point out that most of them have been done on unsubstituted α - or β -trifluoromethylacrylate whereas two concomitant stereogenic centers could be obtained directly from α,β -disubstituted trifluoromethyl acrylate. Recently, our group reported the first phospho-Michael addition reaction with α -trifluoromethyl- β -substituted-acrylates.^[35] The reaction provided a series of products



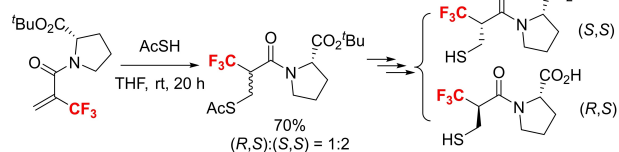
Scheme 19. The addition of thiols to ethyl (*Z*)-4,4,4-trifluorobut-2-enoate.

containing two concomitant C–P and C–CF₃ bonds in good to excellent yields and diastereoselectivities. A plausible mechanism was proposed for the formation of *anti*-favored diastereoisomer regardless of starting the reaction with (*Z*)- or (*E*)-acrylate isomers (Scheme 20, Eq. a). Furthermore, this methodology was also applicable to α -fluoromethyl- β -substituted-acrylates, giving the corresponding products in low to moderate yields but excellent diastereoselectivities with *syn*-favored configuration. (Scheme 20, Eq. b).

Trifluoromethylated acrylamides Michael acceptors also caught the attention of chemists and especially for the asymmetric synthesis. Indeed, in 1991, Ojima and co-workers described the preparation of fluorinated captopril analogues by conjugate addition of thioacetic acid to *tert*-butyl (2-(trifluoromethyl)acryloyl)-*L*-proline (Scheme 21).^[36] The diastereomeric adducts were obtained with a ratio of 1:2 (*R,S*:*S,S*) and were



Scheme 20. The phospha-Michael addition of diaryl phosphine oxides to α,β -disubstituted α -trifluoromethyl/ α -fluoromethyl acrylates.

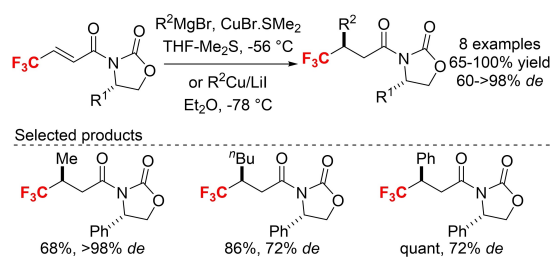


Scheme 21. The addition of thioacetic acid to *tert*-butyl (2-(trifluoromethyl)acryloyl)-*L*-proline.

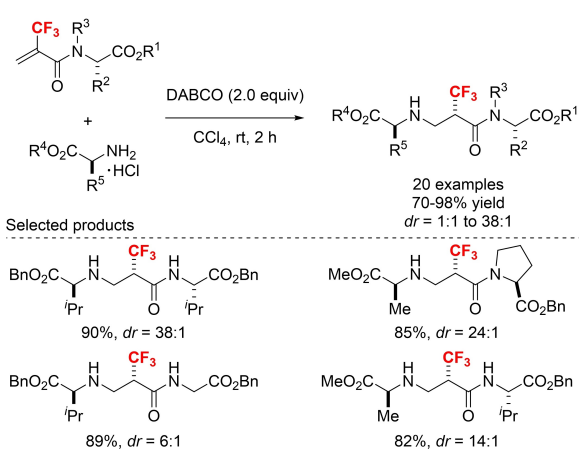
separated by medium pressure liquid chromatography. Then, subsequent reactions (removal of *tert*-butyl and thioacetyl groups) gave the trifluoromethylated analogues of captopril in (*R,S*) and (*S,S*) configurations.

In 1996, Yamazaki and co-workers also employed the chiral β -trifluoromethylacrylamides as Michael acceptors with a series of organocopper reagents. The optically active molecules bearing a CF₃ group at the stereogenic center were obtained in fair to good yields and medium to high levels of diastereoselectivity (Scheme 22).^[37] The stereochemical results of the reaction showed that organocopper approached the β -position of the Michael acceptor from the less hindered *Si*-face of the alkene.

The use of peptides in drug development is limited due to their rapid degradation and poor bioavailability.^[38] The modification of peptide backbones appeared as an attractive strategy to overcome these disadvantages. The group of Fustero and Zanda described a methodology for the synthesis of partially modified retro Ψ [NHCH₂]-peptides containing a chemically stable and stereo-defined trifluoroalanine unit. The key reaction was a stereo-controlled aza-Michael addition of α -amino ester to α -trifluoromethylacrylamides (Scheme 23).^[39] A mechanistic study showed that this type of reaction is a two-step process. Firstly, the



Scheme 22. The addition of organocopper reagents to chiral β -trifluoromethylacrylamides.



Scheme 23. The addition of α -amino ester to α -trifluoromethylacrylamides.

amide enol intermediate was generated by the initial aza-Michael addition of α -amino esters to α -trifluoromethylacrylamide acceptors; then, a stereoselective intramolecular hydrogen transfer occurred delivering the final products.^[40] The highly efficient aza-Michael addition of different amines to α -trifluoromethylacrylamide acceptors can afford other families of peptidomimetics: dipeptides, tripeptides, and structures containing an urea moiety or two units of α -trifluoromethyl- β^2 -alanine. With the help of X-ray analysis and NMR techniques, Fustero and co-workers studied the conformation of some newly synthesized peptidomimetics and the results showed a β -turn-like conformation for these structures both in the solid-state and in solution.^[41] They also developed the stereocontrolled solid^[42] and fluorous-phase^[43] syntheses of partially modified retropeptides by using Wang resin-supported Michael acceptors and ^FTMSE tagged Michael acceptors respectively. (Figure 1)

Like the α -trifluoromethylacrylamides, the modification of the peptide backbone could also start from the β -trifluoromethylacrylamides. In 2000, Zanda and co-workers exploited the asymmetric conjugate additions of chiral α -amino esters to β -trifluoromethylacrylamide acceptors. Several partially modified Ψ [NHCH(CF₃)] retropeptides were prepared as possible mimics of the usual Ψ (NHCO) retropeptides.^[44] These retropeptides containing a Ψ [NHCH(CF₃)] unit were

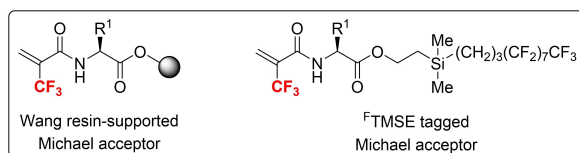
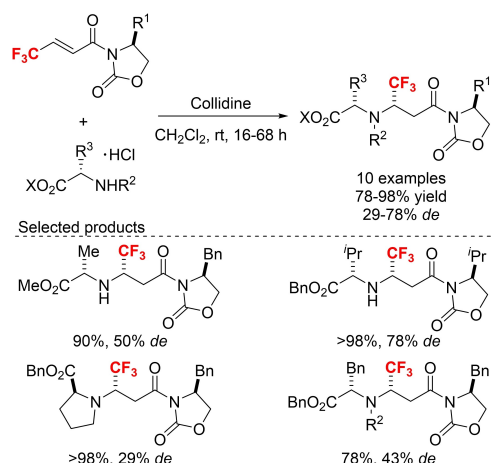


Figure 1. Designed Michael acceptors for specific studies.



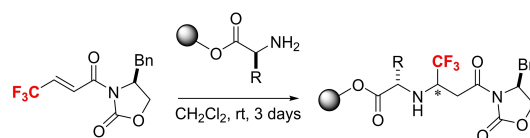
Scheme 24. The addition of α -amino ester to β -trifluoromethylacrylamides.

produced in nearly quantitative yields and moderate to good diastereoselectivities (Scheme 24).

Subsequently, the first example of solid-phase synthesis of the partially modified retro- Ψ [NHCH(CF₃)] peptides was also developed with the reaction between resin-bound α -amino hydroxamate (derived from Wang resin) and the (*S,E*)-4-benzyl-3-(4,4,4-trifluorobut-2-en-1-yl)oxazolidin-2-one as the key step (Scheme 25).^[45] Later, this strategy was applied to the design of a novel matrix metalloprotease (MMP) inhibitor (Figure 2).^[46]

Zanda and co-workers also reported a Michael addition of amines and amino alcohols to (*S,E*)-4-isopropyl-3-(4,4,4-trifluorobut-2-en-1-yl)oxazolidin-2-one in 2007 (Scheme 26).^[47] These reactions generally occurred in good to excellent yields, but with low diastereocontrol, even when some chiral nucleophilic sources were used.

In 2012, Wang and co-workers reported an efficient sulfa-Michael addition on the (*E*)-1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4,4,4-trifluorobut-2-en-1-one that was easily synthesized from commercially available ethyl 4,4,4-trifluoro-3-oxobutanoate after a synthetic se-



Scheme 25. The addition of α -amino ester to (*S,E*)-4-benzyl-3-(4,4,4-trifluorobut-2-en-1-yl)oxazolidin-2-one in solid-phase.

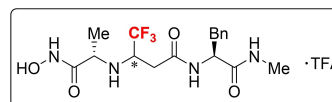
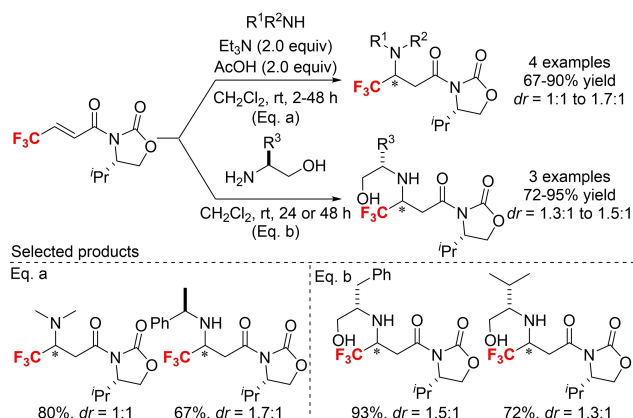


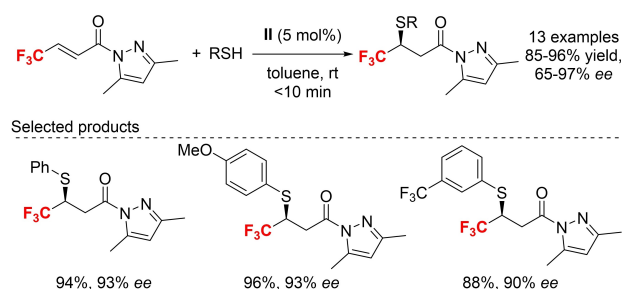
Figure 2. MMP inhibitor synthesized by Zanda *et al.*



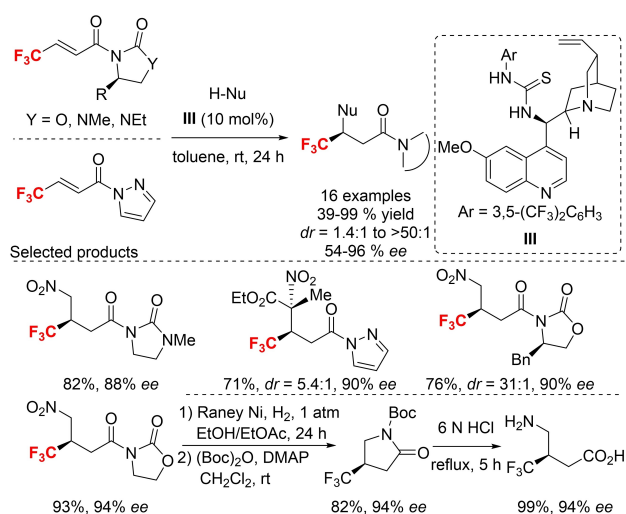
Scheme 26. The addition of amines and amino alcohols to (*S,E*)-4-isopropyl-3-(4,4,4-trifluorobut-2-en-1-yl)oxazolidin-2-one.

quence of reduction, dehydration, hydrolysis and condensation of substituted pyrazole. The corresponding sulfa-Michael adducts were obtained in a very short time in excellent yields and good to excellent enantioselectivities with a low catalyst loading of the bifunctional amine-thiourea catalyst **II** (Scheme 27).^[48] Another feature of this protocol is that all the products were provided as solids due to the incorporation of pyrazole moiety, and could be easily obtained in enantioenriched form by simple crystallization of the crude.

In 2013, Lu and co-workers described an enantioselective organocatalytic Michael addition reaction of different nucleophiles including nitroalkanes, malonates, and malononitrile to β -trifluoromethylated acrylamides. Different trifluoromethylated acrylamides were chosen as the Michael acceptors, under the catalysis of cinchona-alkaloid-thiourea catalyst **III**, affording the corresponding adducts in moderate to excellent yields, diastereoselectivities, and enantioselectivities. Furthermore, the enantioenriched trifluoromethylated γ -aminobutyric acid could be



Scheme 27. The sulfa-Michael addition of thiols to (*E*)-1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4,4,4-trifluorobut-2-en-1-one.



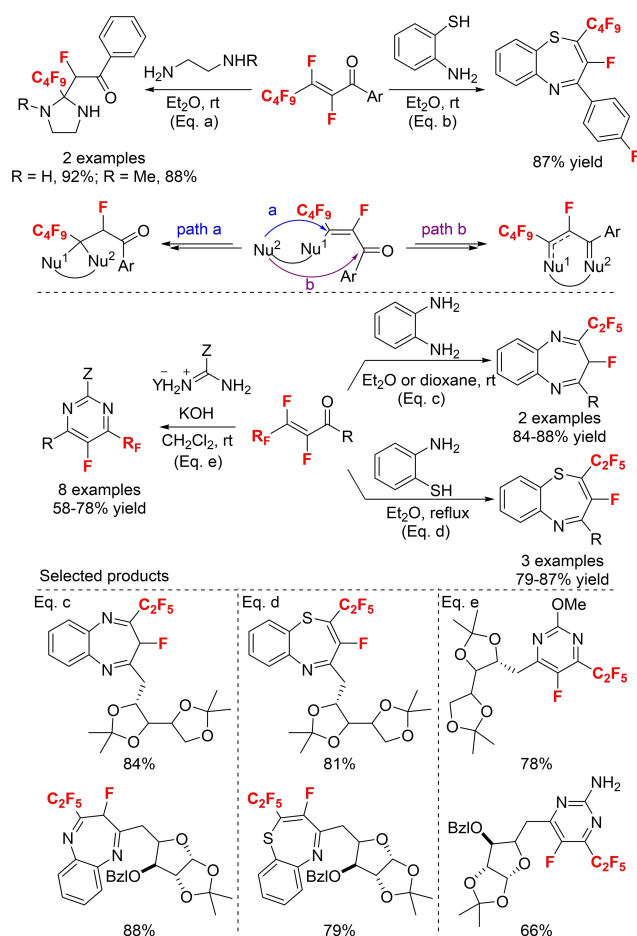
Scheme 28. The addition of nucleophiles to β -trifluoromethylacrylamides developed by Lu *et al.*

easily obtained from the corresponding Michael adducts in high yields without loss of enantioselectivities. (Scheme 28).^[49]

2.3. Michael Acceptors Containing Perfluorinated Moiety

Beside the alkene substituted by fluorine atom(s), CF_3 -, CHF_2 - or CH_2F -group, the fluorinated substituent bearing at α - or β -position of the alkene could also be perfluoro moieties, like C_2F_5 -, C_4F_9 -, C_6F_{13} -groups.

In 1994, Portella and co-workers reported a reaction using the β -perfluorinated α -fluoro- β -fluoro-unsaturated ketone to prepare heterocycles by reacting with bis-nucleophiles.^[50] For this type of Michael acceptor, the bis-nucleophiles initially attacked at the β -carbon atom of the ketone with the formation of a carbanion at the α -position, subsequently followed by the elimination of the fluorine atom present at the β -position, forming fluoride ion. Then the intramolecular nucleophilic cyclization could take place in two directions: at the β -carbon (Scheme 29, Eq. a, path a: Michael type

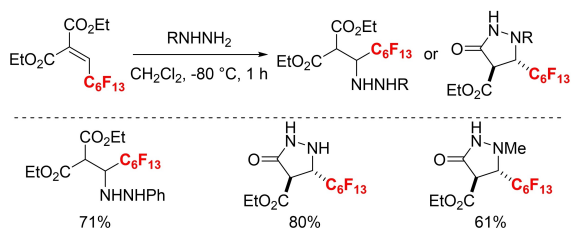


Scheme 29. The addition of bis-nucleophiles to α,β -difluoro- β -perfluorinated ketones.

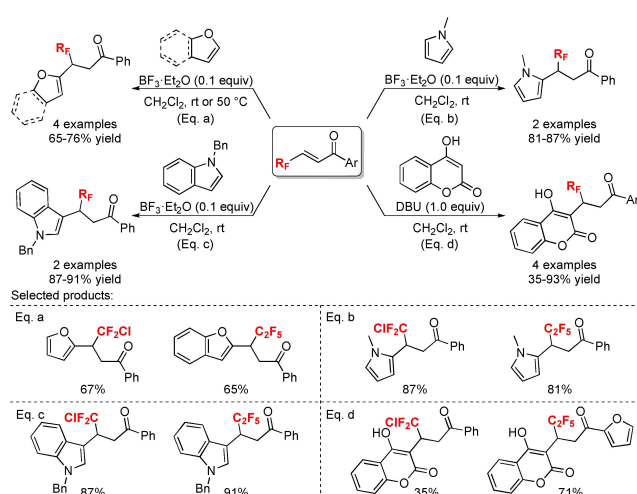
addition) for flexible nucleophiles or at the carbonyl carbon (Scheme 29, Eq. b, path b: condensation) for more constrained nucleophiles. Indeed, the use of a rigid bis-nucleophile will inhibit the formation of the Michael type product and favor the formation of the condensation product. This regioselectivity of cyclization has also been observed later when they reported the use of constrained nucleophiles, such as *o*-phenylenediamine, 2-amino-thiophenol or amidinium salts (Scheme 29, Eq. c, d and e).^[51]

In 2011, Yamazaki and co-workers described an addition of hydrazines to β -perfluorinated methylene malonate.^[52] This type of substrate was expected to be an excellent Michael acceptor due to the three electron-withdrawing substituents installed on the ethylene unit. The conjugate addition of hydrazine was very quick at low temperature in CH_2Cl_2 . The normal 1,4-adduct or the cyclic product generated by an intramolecular cyclization after the initial 1,4-addition, were obtained depending on the nature of hydrazines. The use of less nucleophilic phenylhydrazine only produced the Michael adduct (Scheme 30).

In the same year, Langlois and co-workers described the Michael addition of various electron-rich *O*- and *N*-containing heterocycles such as furans,



Scheme 30. The addition of hydrazines to β -perfluorinated dicarbonyl Michael acceptor.



Scheme 31. The addition of electron-rich heterocycles to β -perfluorinated enones.

benzofurans, pyrroles, and indoles to fluorinated enones bearing CF_2Cl and C_2F_5 at the β -position. These reactions were promoted by Lewis acid $\text{BF}_3\cdot\text{Et}_2\text{O}$ or carried out under basic reaction conditions. The corresponding products were isolated in moderate to good yields (Scheme 31).^[53]

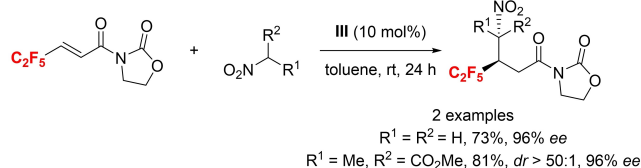
In the Michael addition to β -trifluoromethylated acrylamides reported by Lu in 2013 (see Scheme 28), the fluorinated acrylamide containing C_2F_5 group at the β -position instead of CF_3 group could also serve as a good Michael acceptor. Under the optimized conditions, the products were obtained as efficiently as those from β -trifluoromethylated acrylamides, *i.e.* in good yields with high diastereo- and enantioselectivities (Scheme 32).^[49]

2.4. Other Fluorinated α,β -Unsaturated Carbonyl Michael Acceptors

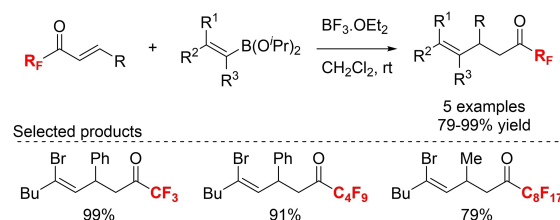
In this section we will focus on the use of α,β -unsaturated carbonyl compounds where the fluorinated group is not located on the double bond but directly connected to the carbonyl group moiety.

As early as 1993, in the work of Suzuki and co-workers, the addition of alkenyldiisopropoxyboranes to fluorinated α,β -unsaturated ketones occurred smoothly, and the desired products were obtained in good yields without the formation of 1,2-adducts (Scheme 33).^[54]

In 2007, Kondratov and co-workers reported the reaction between the ethyl triphenylphosphoranylideneacetate and β -alkoxyvinyl polyfluoroalkyl ketones.^[55] The reaction offered a mixture of two products, which can be easily separated, in high overall yields. Surprisingly, the unusual major process is an initial ylide addition to β -carbon with the subsequent



Scheme 32. The addition of nitroalkanes to β -perfluorinated acrylamides.



Scheme 33. The addition of boronate esters to the α,β -unsaturated ketones bearing a fluorinated moiety at carbonyl carbon.

EtOH elimination to form Michael adducts instead of ylide addition to carbonyl moiety of the enone. Worthy of note that the increase of R_F group bulkiness favored the formation of the Michael adduct (Scheme 34).

In 2013, an organocatalytic asymmetric sulfa-Michael addition reaction on hexafluoroisopropyl α,β -unsaturated esters has been developed by Wang and co-workers. The introduction of two trifluoromethyl groups on the ester moiety was crucial to increase the electrophilicity of α,β -unsaturated ester as Michael acceptor as well as to hinder the carbonyl moiety. The catalytic system performed well over a broad substrate scope with excellent yields and enantioselectivities (Scheme 35, Eq. a).^[56] In the same year, Duan and co-workers described an asymmetric phospho-Michael addition reaction of diphenylphosphine to the similar substrates.^[57] Under the catalysis of a chiral palladium complex catalyst **IV**, the reaction of 2,2,2-trifluoroethyl cinnamate furnished the adduct with good yield and enantioselectivity. More electrophilic Michael acceptor 1,1,1,3,3,3-hexafluoroisopropyl cinnamate gave product in better yield and enantioselectivity (Scheme 35, Eq. b).

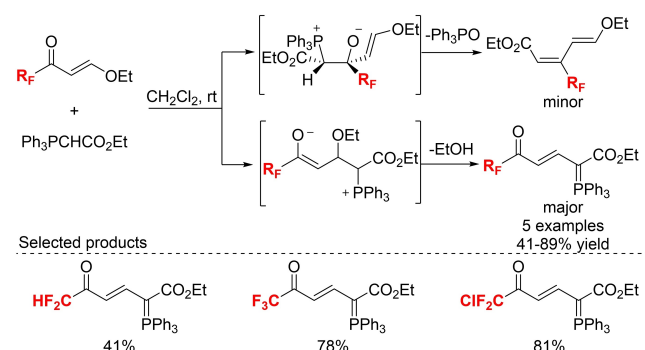
In 2018, a protocol for the synthesis of *O*, *S*-containing heterocycles has been reported by Mloston

and co-workers. The desired products were obtained in fair yields by the sequentially sulfa-Michael addition and heterocyclization starting from the β -fluorinated α -bromo enones (Scheme 36).^[58] A proposed mechanism showed that the initial step of this reaction sequence was the formation of a sulfa-Michael adduct, which easily underwent intramolecular nucleophilic substitution to give sulfonium salt intermediate. Then, the latter underwent a deprotonation and a ring-opening to give the intermediate which could form the desired heterocycle product by an intramolecular hemiacetalization.

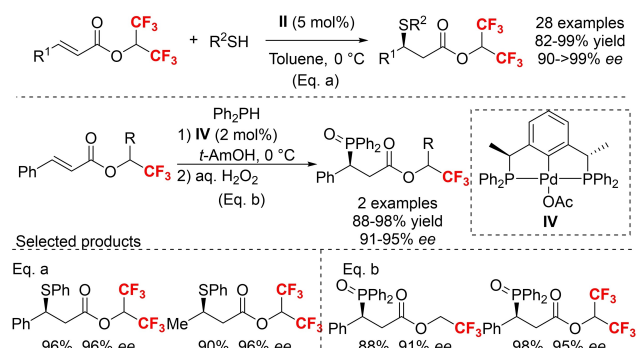
3. Fluorinated Nitroalkene Michael Acceptors

The fluorinated nitroalkene represents a highly reactive, easily handled fluorinated building block, which is very promising in the synthesis of functionalized organofluorinated compounds.^[59] The (*E*)-3,3,3-trifluoro-1-nitropropene is the most common substrate having a structure of a double bond bearing both CF_3 - and NO_2 -groups with (*E*)-configuration. The fluorinated nitroalkenes have been used in Friedel-Crafts,^[60] Diels-Alder,^[61] 1,3-dipolar^[62] reactions. There were also some examples, discussed hereafter, using this substrate as Michael acceptor.

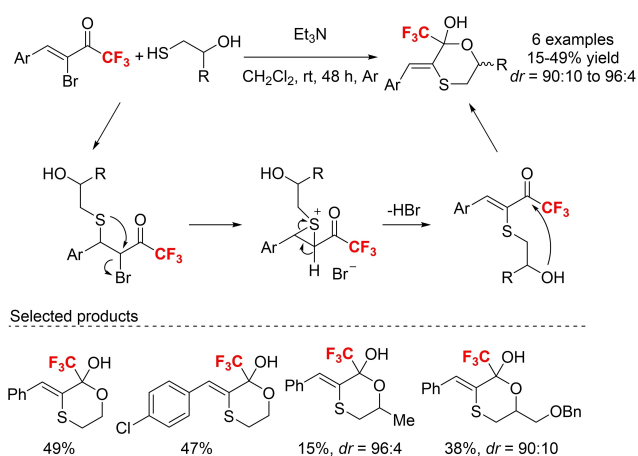
In 2003 and 2009, Zanda and co-workers described the modification of the peptide backbone with a stereogenic $\Psi[CH(CF_3)NH]$ unit.^[63] The key step was an aza-Michael reaction between (*E*)-3,3,3-trifluoro-1-nitropropene and a series of chiral α -amino acid esters which delivered two pur diastereoisomers by flash chromatography. The stereoselectivity was strongly dependent on several experimental parameters, like the solvent, the bulkiness of the nucleophile, and the base (Scheme 37, Eq. a). Later, Zanda and co-workers also



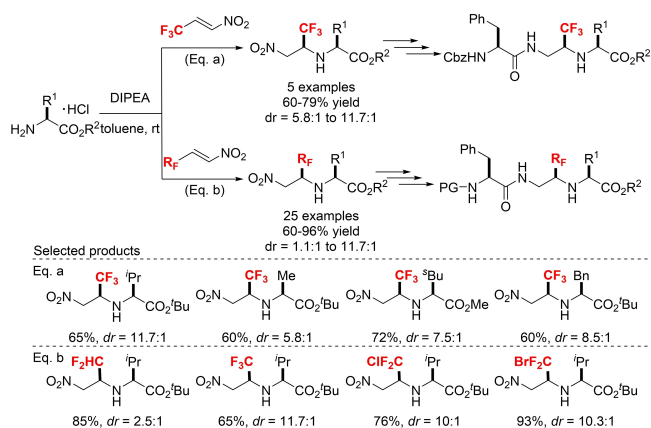
Scheme 34. The addition of Ph_3PCHCO_2Et to fluorinated β -ketoaldehyde derivatives.



Scheme 35. The addition of thiols and diphenylphosphine to fluorinated isopropyl α,β -unsaturated esters.



Scheme 36. The addition of β -Mercaptoalcohols to fluorinated α -bromo enones.



Scheme 37. The addition of chiral α -amino acid esters to fluorinated nitroalkenes.

synthesized new peptide mimics featuring $\Psi[\text{CH}(\text{R}_\text{F})\text{NH}]$ units as peptide-bond surrogates, with different degrees of fluorination.^[64] The diastereoselectivity of this process was more influenced by the electro-negativity, rather than by the bulkiness of R_F group of the fluorinated nitroalkenes (Scheme 37, Eq. b). A possible transition state for the formation of the major diastereomers was proposed (Figure 3). The (*E*)-nitroalkenes reacted from *Re* face of the α -amino acid ester and a dual hydrogen bonding exists between the upward hydrogen of amino group with carbonyl oxygen and the nitro oxygen respectively, transferring the hydrogen from the amino group to the α -position of nitroalkene with the assistance of the *N,N*-diisopropylethylamine (DIPEA).

Then, the same authors reported Michael addition reactions of ketone-derived enamines, methylene active compounds, and methylated pyrroles/indoles to (*E*)-fluorinated nitroalkenes, providing the corresponding adducts in moderate to good yields (Scheme 38).^[65]

Sosnovskikh and co-workers also used the (*E*)-3,3,3-trifluoro-1-nitropropene as Michael acceptor to construct various interested fluorinated polycycles. They first synthesized, in one step, trifluoromethylated 2H-chromenes from two salicylaldehydes in the presence of catalytic amount of triethylamine in good yields (Scheme 39, Eq. a)^[66] Few years later, they reported the synthesis of the same type of trifluoromethyl-2H-chromenes starting from *N*-unsub-

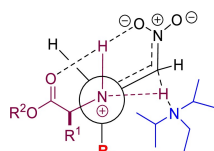
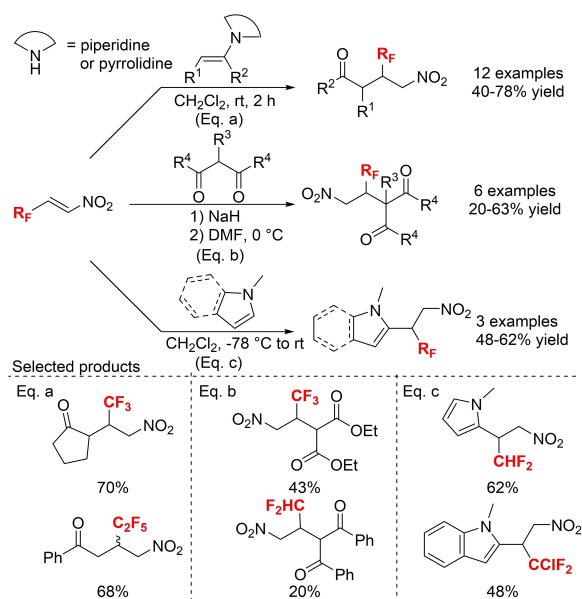
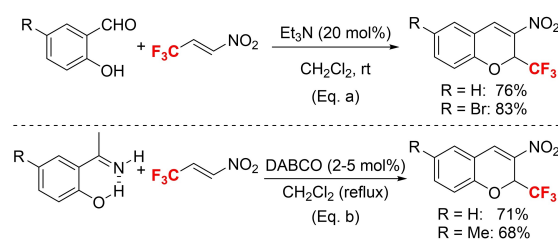


Figure 3. A possible transition state leading to the major diastereoisomers.



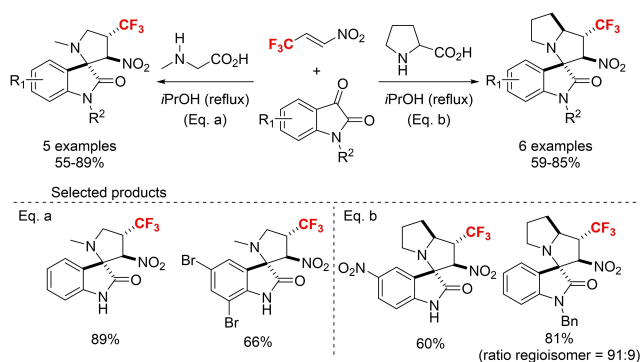
Scheme 38. The addition of C-nucleophiles to fluorinated nitroalkenes.



Scheme 39. The addition of salicylaldehydes and *N*-unsubstituted imines of 2-hydroxyacetophenones to the (*E*)-3,3,3-trifluoro-1-nitropropene.

stituted ketimines prepared from the corresponding 2-hydroxyacetophenones; the ortho-hydroxy group stabilizing the imine function by intramolecular hydrogen bonding.^[67] These substrates, in presence of a catalytic amount of DABCO, reacted with the (*E*)-3,3,3-trifluoro-1-nitropropene to afford the corresponding 2H-chromenes in good yields (Scheme 39, Eq. b).

Finally, the same group developed a three-component reaction between the (*E*)-3,3,3-trifluoro-1-nitropropene, isatins and aminoacids to obtain complex polycycle structures with high regio- and stereo-selectivities.^[68] Indeed, the reaction with sarcosine led to tricyclic trifluoromethylated spiro[indoline-3,2'-pyrrolidin]-2-ones in medium to very good yields (Scheme 40, Eq. a). When the three-components reaction was carried out with proline, the tetracyclic spiro[indoline-3,3'-pyrrolizin]-2-ones were obtained in very good yields (Scheme 40, Eq. b). The high regio- and stereo-selectivity was explained by the formation of transient azomethine ylides, derived from isatins

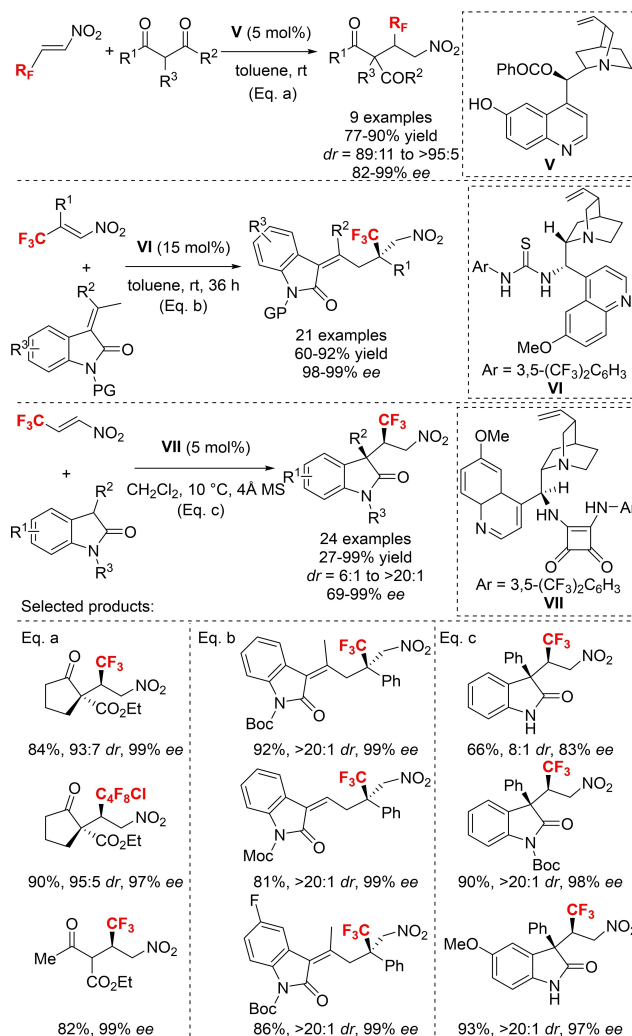


Scheme 40. Three component-reaction between the (*E*)-3,3,3-trifluoro-1-nitropropene, isatins and aminoacids towards polycyclic products.

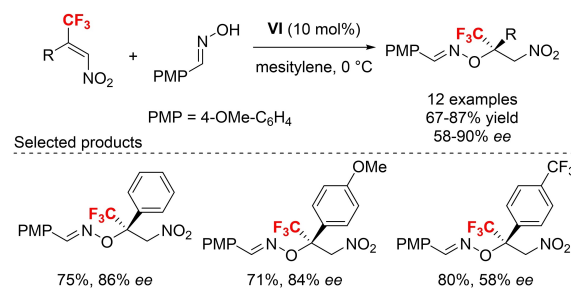
and aminoacids, and the endo addition of nitroalkenes resulted in the formation of endo-adducts with trans-arrangement of the CF₃ and NO₂ groups. When substituted *N*-alkyl isatins were used, a minor regioisomer where the position of CF₃ and NO₂ groups were reversed could also be observed in little amount.

In 2014, Liu and co-workers also investigated a Michael addition reaction of 1,3-dicarbonyl compounds to the similar substrates.^[69] The cinchona alkaloid catalyst **V** showed high efficiency with a broad substrate scope and the desired products were generally obtained in good to high yields, high diastereo- and enantioselectivities under mild conditions (Scheme 41, Eq. a). The same year, some other enantioselective Michael addition reactions of *C*-nucleophiles to fluorinated nitroalkenes have been reported. Wang and co-workers described a highly enantioselective Michael addition of oxindole derivatives to fluorinated nitroalkenes.^[70] A series of biologically important chiral oxindoles, bearing a trifluoromethyl group at the newly formed quaternary chiral center, were obtained in good yields with excellent enantioselectivities under the use of catalyst **VI** (Scheme 41, Eq. b). Shi and co-workers described a Michael addition reaction between 3-substituted oxindoles and trifluoromethylated nitroolefins catalyzed by a quinine-derived squaramide catalyst **VII**.^[71] The corresponding adducts bore a trifluoromethylated chiral carbon center and a contiguous quaternary stereocenter at the C3 position of the oxindoles (Scheme 41, Eq. c).

Some additional reactions of other nucleophiles to trifluoromethylated nitroalkenes have also been reported. For example, in 2014, Xiao and co-workers developed a catalyzed oxa-Michael addition of oximes to β-trifluoromethyl-β-disubstituted nitroalkenes using the cinchona alkaloid-based thiourea catalyst **VI**.^[72] A variety of oxime ethers with a trifluoromethylated chiral center were obtained in good yields and fair to high enantioselectivities (Scheme 42).

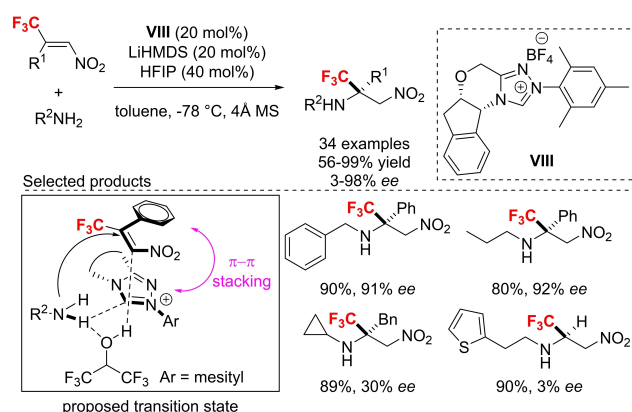


Scheme 41. The enantioselective Michael addition of *C*-nucleophiles to fluorinated nitroalkenes.



Scheme 42. The addition of oximes to β-trifluoromethyl-β-disubstituted nitroalkenes.

In 2015, a chiral *N*-heterocyclic carbene (NHC) catalyst **VIII** promoted aza-Michael reaction between primary alkyl amines and β-trifluoromethyl-β-aryl nitroalkenes (Scheme 43).^[73] In this reaction, a dual role of the NHC was proposed. Indeed, the NHC is implied in H-bonding with amines and HFIP, enhanc-



Scheme 43. The addition of primary alkyl amines to β -trifluoromethyl- β -aryl nitroalkenes.

ing the nucleophilicity of the nitrogen atom. Meanwhile, a weak π - π interaction between the β -aryl substituent and positively charged NHC heterocycle was suggested by linear free-energy relationship (LFER) study, which might be an explanation for the poor enantioselectivities when $R^1 = \text{H}$ or Bn.

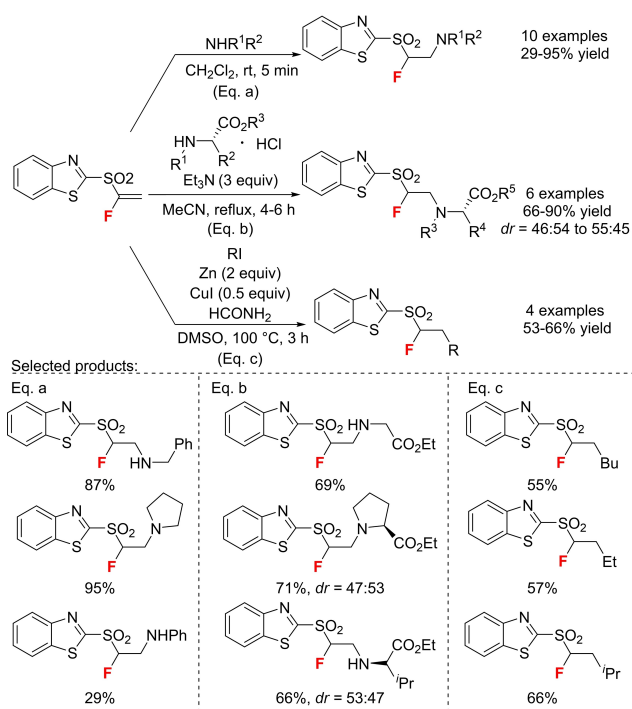
4. Fluorinated α,β -Unsaturated Sulfoxide/Sulfone Michael Acceptors

Because of the strong inductive electron-withdrawing effect of the sulfonyl or sulfinyl group, a double bond with such moieties could be considered as a suitable Michael acceptor.^[74] Meanwhile, some fluorinated Michael acceptors containing the sulfoxide or sulfone group have been investigated, providing a straightforward route to many building blocks bearing both a sulfur atom and a fluorinated moiety.

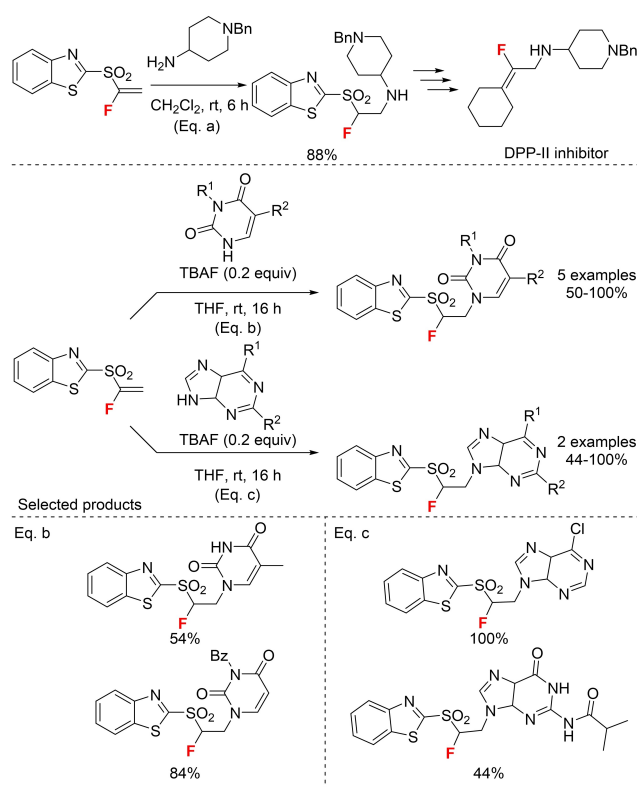
In 2009, Lequeux and co-workers described the synthesis of 2-[(1-Fluorovinyl)sulfonyl]-1,3-benzothiazole which could be functionalized by the aza-Michael addition reaction of aliphatic/aromatic amines, and amino acid alkyl esters (Scheme 44, Eq. a and b). Additionally, some fluoroalkylsulfones were prepared from alkyl iodides in the presence of Zn/CuI (Scheme 44, Eq. c).^[75]

In another report, the same authors described an aza-Michael addition reaction on the 2-[(1-Fluorovinyl)sulfonyl]-1,3-benzothiazole, provided an expeditious and efficient access to DPP-II inhibitor (Scheme 46, Eq. a). A similar method was extended to the aza-Michael addition of other nucleic bases to the same fluorovinyl sulfone (Scheme 45, Eq. b and c).^[76]

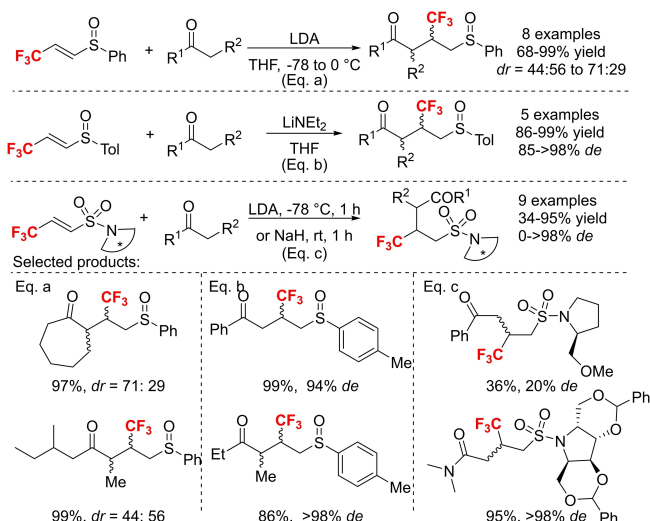
In early reports from Ichikawa and co-workers, β -trifluoromethyl vinyl sulfoxides have been treated with a variety of lithium enolates, producing the corresponding adducts in good to excellent yields and diastereoselectivities (Scheme 46, Eq. a and b).^[77]



Scheme 44. The addition of nucleophiles to 2-[(1-Fluorovinyl)sulfonyl]-1,3-benzothiazole.



Scheme 45. The addition of nucleic bases to the 2-[(1-Fluorovinyl)sulfonyl]-1,3-benzothiazole.

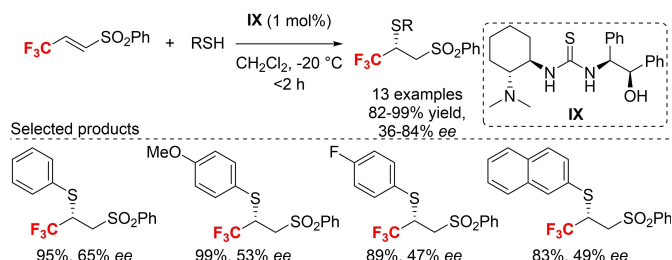


Scheme 46. The addition of lithium enolates to fluorinated sulfone derivatives.

Then, in 1997, Eguchi and co-workers reported a similar addition of enolates to chiral β -trifluoromethyl vinyl sulfonamides.^[78] The corresponding products were obtained in moderate diastereoselectivities except for the one obtained with tetrasubstituted bulky pyrrolidine sulfonamide (>98% *de*). Based on these results, the reaction of some other enolates with tetrasubstituted bulky pyrrolidine sulfonamide was performed and all the products were obtained in excellent diastereoselectivities (>98% *de*) (Scheme 46, Eq. c).

Furthermore, in 2013, Wang and co-workers reported the first asymmetric sulfa-Michael addition of thiols to (*E*)-3,3,3-trifluoropropenyl phenyl sulfone. This reaction proceeded with 1 mol% of bifunctional amine-thiourea catalyst **IX** in a short time. The desired sulfa-Michael adducts, bearing a trifluoromethyl group and a sulfur atom at the chiral center, were obtained in high yields and moderate to good enantioselectivities (Scheme 47).^[79]

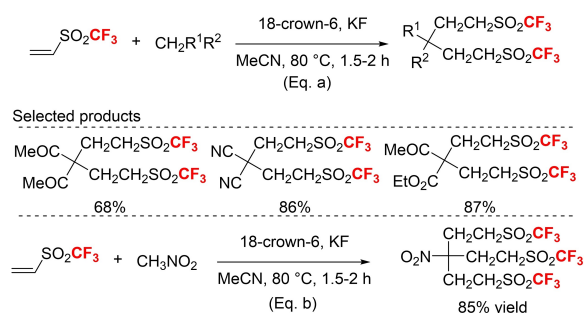
There were also some examples of fluorinated sulfoxides/sulfones where the fluorinated moiety was



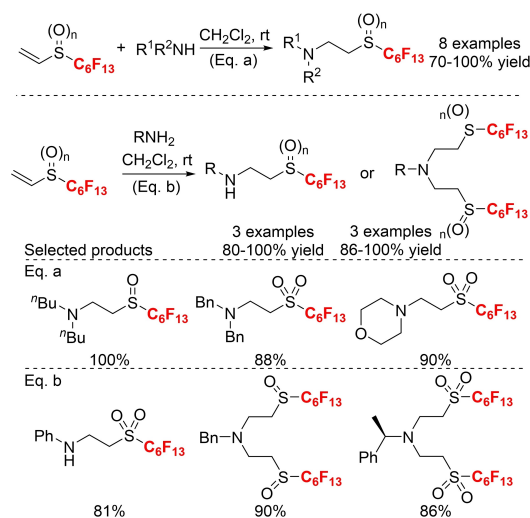
Scheme 47. The addition of thiols to *trans*-3,3,3-trifluoropropenyl phenyl sulfone.

bearing the sulfur atom. In 1982, Popov and co-workers reported the Michael addition of active methylene derivatives (malonate derivatives, β -diketones) to trifluoromethyl vinyl sulfone.^[80] Due to the powerful electronegative inductive effect of the CF_3SO_2 moiety, two Michael acceptors was reacted with the nucleophiles in the presence of KF and 18-crown-6-ether, furnished the bis-adducts in good yields (Scheme 48, Eq. a). When the nitromethane was used as the nucleophile, the corresponding tris-adduct was obtained in 85% yield (Scheme 48, Eq. b).

More recently, in the Michael addition of amines to perfluoroalkylated sulfoxides and sulfones developed by Magnier and co-workers, some examples of double addition were also described.^[81] The secondary amines only occurred mono addition, affording the corresponding product in good to high yields (Scheme 49, Eq. a). When primary amines were used as the nucleophile, there were some different results. Poor nucleophilic aniline only produced monoadduct regardless of the equivalent of Michael acceptor, whereas



Scheme 48. The double or triple addition of nucleophiles to trifluoromethyl vinyl sulfone.



Scheme 49. The addition of amines to perfluoroalkylated sulfoxides and sulfones.

more nucleophilic benzyl amine and (*R*)-1-phenylethan-1-amine produced bis-adducts when the reaction was carried out with an excess of perfluoroalkylated sulfoxide and sulfone (Scheme 49, Eq. b)

In 2010, Sokolenko and co-workers reported the Michael addition of different nucleophiles (*S*-, *O*-, *N*-) on the trifluoromethyl vinyl sulfoxide providing a series of compounds containing the (trifluoromethylsulfinyl)ethyl moiety in moderate to very good yields (Scheme 50).^[82]

The carbocycles bearing a trifluoromethyl sulfone are also constituted potentially valuable building blocks for further syntheses. In 1999, Billard and co-workers reported a Michael addition of *n*-hexylamine to a pentacyclic trifluoromethyl vinylsulfone, which occurred in a complete diastereoselective fashion affording only the *trans*-adduct (Scheme 51, Eq. a).^[83] Then, this kind of substrates has been further studied in 2008 by the same group. Surprisingly, instead of the expected β -fluoro-adduct, two inseparable diastereoisomers in a 70:30 ratio were obtained in good yield when the substrate was reacted in the presence of TBAF. Owing to the fact that the SO_2CF_3 is a strong

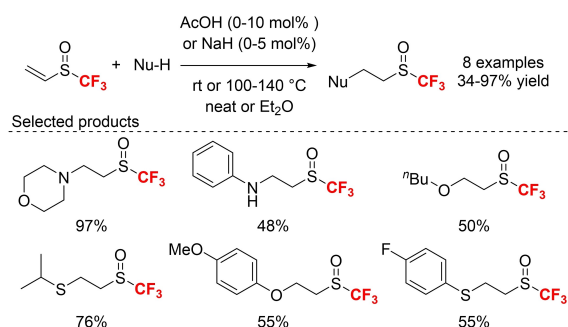
electron-withdrawing group as well as a good leaving group and the fluoride anion can behave as a base, a probable mechanism was proposed (Scheme 51, Eq. b).^[84] The same reaction occurred starting from hexacyclic trifluoromethyl sulfone, albeit in a low yield (Scheme 51, Eq. c).

5. Summary and Outlook

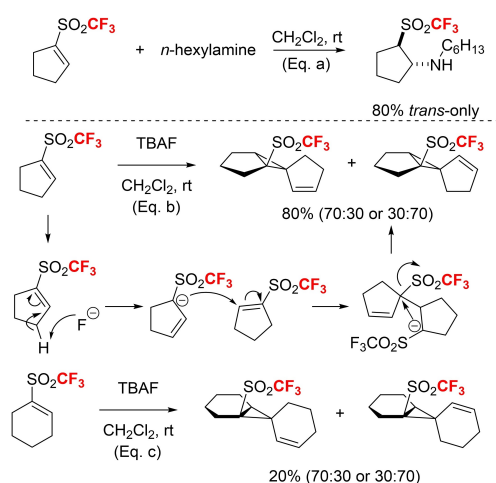
This review reported the major advances made for Michael addition reactions with fluorinated Michael acceptors, including α,β -unsaturated carbonyl compounds, fluorinated nitroalkenes, and fluorinated α,β -unsaturated sulfoxides/sulfones. The reactivity and selectivity of fluorinated Michael acceptors are substrate-dependent as in usual Michael reaction. Nevertheless, the Michael reactions with these fluorinated substrates have been less studied compared to their non-fluorinated congeners whereas the Michael reaction could lead to interesting fine fluorinated chemicals. Indeed, as highlighted in this review, some Michael reactions could be undertaken with fluorinated Michael acceptors to create C–C, C–O, C–N, C–S and C–P bonds. Hence, taking into account this current state of the art regarding the Michael addition reaction toward the formation of various relevant adducts, there is still room for improvement and strategic developments. For instance, the scope of these Michael reactions still have to be broadened to fulfil the synthetic utility criterion and will probably require the development of original catalysts as well as the use of more elaborated fluorinated Michael acceptors such as polysubstituted acrylates and derivatives. Indeed, if we focused on trifluoromethylalkenes, most of the studies have been done on disubstituted alkenes probably because of the steric hindrance of the trifluoromethyl moiety limiting the efficiency of Michael reaction with polysubstituted substrates. Nevertheless, we showed that this kind of reaction was possible to make C–P formation starting with trisubstituted trifluoromethylacrylates paving the way to the creation of other C–C or C-heteroatom bond in the future with more bulky fluorinated alkenes. In conclusion, we hope that this review will contribute to help the community to use the Michael reaction and to reach significant milestones that will push the Michael addition reaction with fluorinated Michael acceptor at the forefront of the synthetic methods to build up complex and highly functionalized fluorinated fine chemicals.

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Scheme 50. The addition of different nucleophiles to trifluoromethyl vinyl sulfoxide.



Scheme 51. The addition to cyclic trifluoromethyl sulfones.

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