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Minireview

Recent Advances in the Synthesis of CF_3- or HCF_2-Substituted Cyclopropanes

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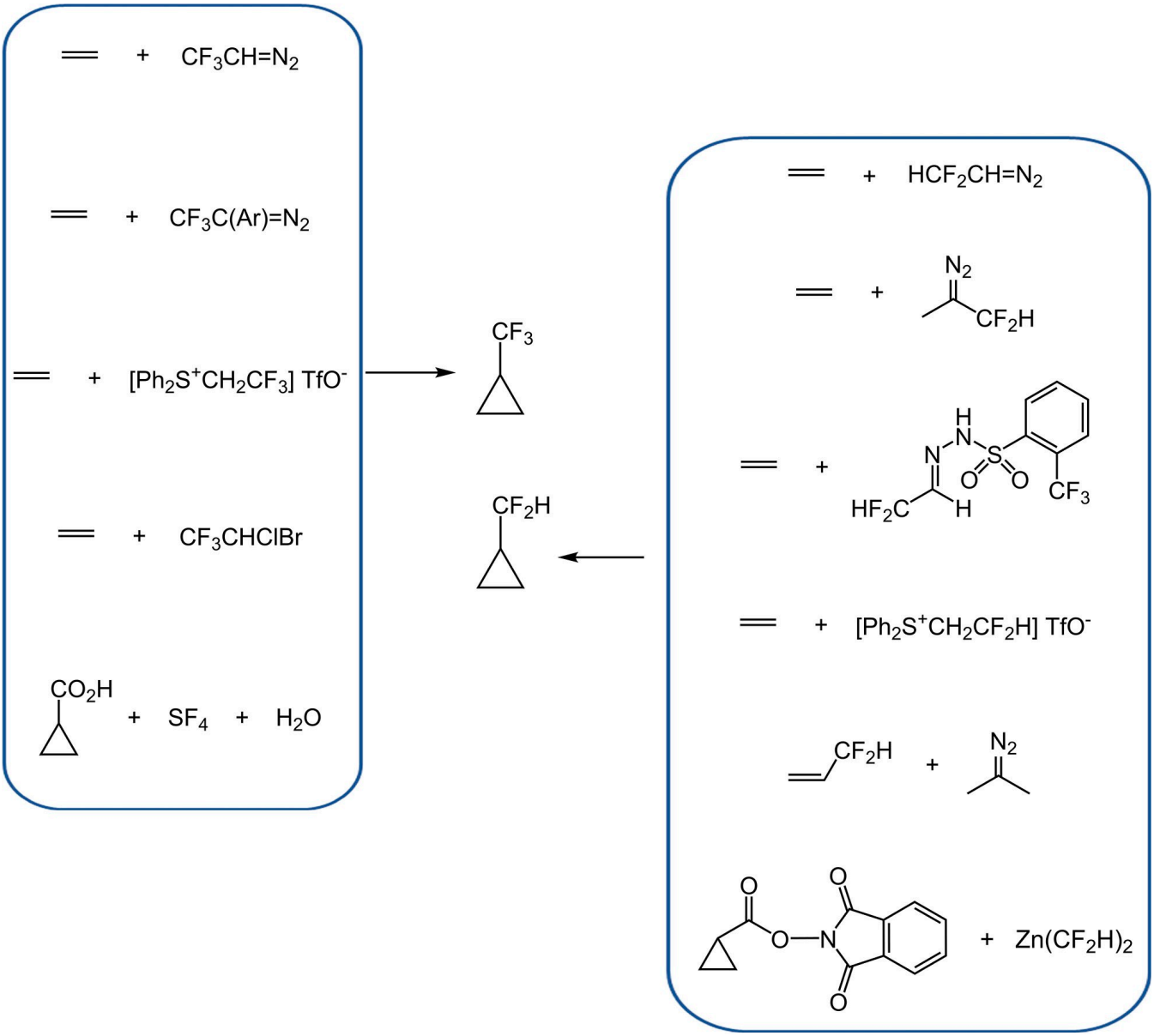

Abstract: CF_3- or HCF_2-substituted cyclopropanes are of great interest in pharmaceutical chemistry and agrochemistry, and thus significant efforts have been directed towards the development of efficient methods for the installation of these motifs. This Minireview summarizes recent efforts for the construction of CF_3- or HCF_2-substituted cyclopropanes. CF_3-cyclopropanes are usually synthesized by a transition-metal-catalyzed cyclopropanation of alkenes with a trifluoromethylcarbene generated in situ from a diazocompound, CF_3CHN_2 or $CF_3C(Ar)N_2$. The synthesis of HCF_2-cyclopropanes remains largely unexplored. Some difluoromethylcarbene reagents have been developed, such as HCF_2CHN_2, $Ph_2S^+CH_2CF_2H$ TfO^-, and difluoroacetaldehyde *N*-triftosylhydrazone (DFHZ-Tfs), and cyclopropanation of alkenes with these reagents could also occur by transition metal catalysis. These protocols may find great utility in the synthesis of biologically active molecules.

1. Introduction

The top right position of fluorine in the periodic table of chemical elements implies that fluorine atom possesses many special properties, such as highest electronegativity, small atomic radius and low polarizability. The incorporation of fluorine atoms into organic molecules usually would lead to changes of their physical, chemical, and biological properties. Therefore, fluorine-containing compounds have found widespread applications in many areas, such as pharmaceutical/agrochemical developments and material sciences.[1] It has been estimated that about 40% of agrochemicals contain at least a fluorine atom, and over 200 fluorinated drugs, occupying 30% of all pharmaceuticals, have been developed for therapeutic uses.[2]

HCF_2- or CF_3-substituted cyclopropanes have served as important structural motifs in many biologically active molecules, such as Voxilaprevir,[3] Glecaprevir,[4] Petesicatib[5] and VX-659[6] (Figure 1). Voxilaprevir is a hepatitis C virus (HCV) nonstructural protein 3/4 A protease inhibitor that is used in combination with sofosbuvir and velpatasvir, and the combination has the trade name Vosevi, which is one of the most recently approved combination therapies for the treatment of HCV.[7] Glecaprevir is an important component of Mavyret, which is a trade name of a medicine used for the treatment of chronic HCV.[8] Petesicatib is a cathepsin S inhibitor, which is currently under investigation in clinical trial.[9] The combination of VX-659 and tezacaftor/ivacaftor was developed to restore the function of Phe508del CFTR protein in patients with cystic fibrosis.[6]

HCF_2- or CF_3-substituted cyclopropane derivatives have found widespread applications in drug/agrochemical developments. Therefore, determined efforts have been directed towards the development of efficient methods for their synthesis. Effective synthetic approaches have been developed, and previous efforts have been reviewed by the groups of Grygorenko/Mykhailiuk[10] and Charette/Jubault,[11] respectively. Cyclization of alkenes with CF_3CHN_2 and HCF_2CHN_2 is one of the most commonly used strategy for the synthesis of CF_3-cyclopropanes and HCF_2-cyclopropanes, respectively. The synthetic utility of CF_3CHN_2[12] and HCF_2CHN_2[13] has recently been reviewed by Mykhailiuk and/or Koenigs.[14] Many new methods have continued to be developed, especially for the synthesis of HCF_2-substituted cyclopropanes. The current MiniReview describes the literature on the topic since 2011. The synthetic methods appearing in the previous review may be introduced as background when necessary. During the preparation of this manuscript, Charette, Jubault and co-workers reported a review on the synthesis of fluoro-, monofluoromethyl-, difluoromethyl-, and trifluoromethyl-substituted three-membered rings.[15]

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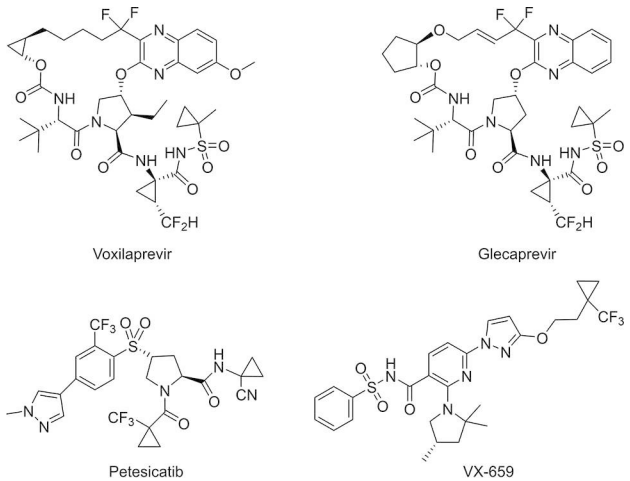


Figure 1. HCF_2- or CF_3-substituted-cyclopropane-containing biologically active molecules.

2. CF_3-Cyclopropanes

2.1. Cyclopropanation of alkenes with trifluoromethylcarbene

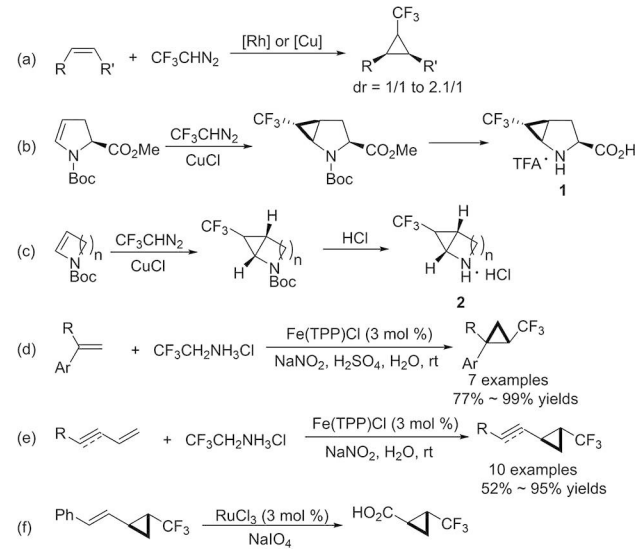
2.1.1. CF_3CHN_2 as a trifluoromethylcarbene source

Trifluoromethylcarbene (CF_3CH:) was first reported by Fields and Haszeldine in 1960.[16] It was found that this carbene can be in situ generated from a diazo compound, CF_3CHN_2, developed by Gilman and Jones in 1943,[17] under photochemical conditions. Photochemical reactions then became a commonly used method for the generation of trifluoromethylcarbene.[10] CF_3CHN_2, which is usually generated in situ from $CF_3CH_2NH_3Cl$, is an explosive gas, and thus safety cautions must be taken when handling it.

In 2006, Simonneaux and co-workers described the first report on transition-metal catalyzed generation of trifluoromethylcarbene from CF_3CHN_2 for cyclopropanation of alkenes.[18] The products were obtained with high diastereoselectivity and moderate enantioselectivity. Both Fe- and Ru-catalysts catalysts were found to be active, but only three substrates were examined. Since then, transition metal-catalyzed cyclopropanation of alkenes with trifluoromethylcarbene has become a widely used approach. The ground state of trifluoromethylcarbene is a triplet state,[10] but high diastereoselectivity would be observed for transition metal catalyzed cyclopropanation with trifluoromethylcarbene. Reasonably, the formation of a M=$CHCF_3$ double bond (M = transition metal) leads to the loss of the triplet character of trifluoromethylcarbene.

Mykhailiuk, Komarov and co-workers described that cyclopropanation with CF_3CHN_2 could be catalyzed by a Rh or Cu catalyst (Scheme 1a).[19] Low diastereoselectivity was observed in this case. They applied this approach to the synthesis of CF_3-Substituted proline analogue **1** as ^{19}F NMR labels for peptides in the polyproline II conformation (Scheme 1b).[20] The group of Mykhailiuk further discovered the synthetic utility of CF_3CHN_2.[21] and synthesized various CF_3-substituted bridged-rings **2** (Scheme 1c).[21c] The group of Carreira also focused on the transition-metal-catalyzed reactions with CF_3CHN_2.[22] When investigating the cyclopropanation of aryl alkenes, they found that Fe(TPP)Cl (TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine), which had been demonstrated to be a robust catalyst in carbene-transfer processes,[23] was able to efficiently catalyse the reactions with CF_3CHN_2 to give the desired products with high diastereoselectivity (Scheme 1d).[24] On the basis of this work, they further developed a cyclopropanation of conjugated alkenes with CF_3CHN_2 (Scheme 1e).[25] In order to demonstrate the utility of this approach, they converted a CF_3-cyclopropyl alkene into a CF_3-cyclopropyl carboxylic acid, which had been used in the preparation of insecticides[26] (Scheme 1f).

Shortly afterwards, Carreira and co-workers disclosed an asymmetric cyclopropanation of aryl alkenes (Scheme 2).[27] Instead of a Fe catalyst, a Co complex was found to be highly

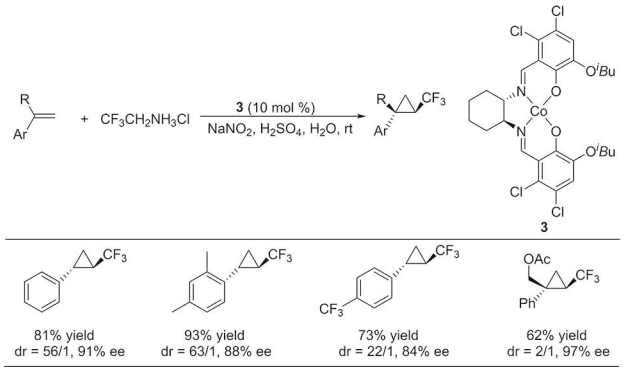


Scheme 1. Transition-metal-catalyzed cyclopropanation.

Feng-Wen Wu was born in Hunan, China in 1984. He received his Ph.D. degree in organic chemistry from Hunan Normal University in 2014. In May 2015, he joined the group of Ji-Chang Xiao at Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS) as a post-doctoral researcher. Since August 2019, he has worked in Guiyang University as an associate professor. His current research interests focus on visible light catalytic oxidation and the development of fluorinated salts as reagents.

Jin-Hong Lin obtained his Bachelor's degree from Donghua University in 2005. He received his Ph.D. from SIOC-CAS, under the supervision of Prof. Ji-Chang Xiao in January 2011. In March 2011, he joined the group of Prof. John T. Welch at State University of New York at Albany as a postdoctoral researcher. In February 2013, he left Welch's group and joined Prof. Xiao's group at SIOC as an associate professor. His current research interests focus on the development of fluorinated salts as reagents.

Ji-Chang Xiao received his Ph.D. in 2003 from SIOC-CAS under the supervision of Prof. Qing-Yun Chen. Then he conducted his postdoctoral research with Prof. Jean'ne M. Shreeve at Universiy of Idaho. In 2005, he began his independent career as a professor at SIOC. His current research interests include fluorine-containing compounds, molten salts, and extraction materials.

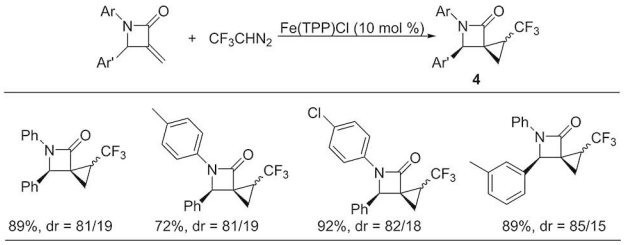


Scheme 2. Co-catalyzed asymmetric cyclopropanation.

effective. Although Co^{III}-salen catalysts were described in the literature for enantioselective cyclopropanation with diazoacetates,[28] no reaction with CF_3CHN_2 was observed by using these Cobalt-sources. Co^{II}-complexes were able to catalyse this process and the substituents in the ligands plays an important role for the enantioselectivity. The O^{i}Bu substituent is an electron-donating group with strong steric effects, and the combination of this group with four electron-withdrawing Cl substituents could smoothly transfer the chirality from catalyst **3** to products. High yields and excellent stereoselectivity were obtained for the conversions of monosubstituted alkenes. In the case of disubstituted alkenes, dramatically lower diastereoselectivity was observed.

The group of Ma also discovered some new synthetic utility of CF_3CHN_2.[29] They disclosed facile access to spirocyclic β-lactams **4** via a Fe-catalyzed cyclopropanation of α-methylene-β-lactams (Scheme 3).[30] A brief survey of catalysts revealed that Fe(TPP)Cl was a suitable choice. In this case, CF_3CHN_2 was not generated in situ, but prepared in advance. It was stored as a DMF solution and the solution was added to the reaction system slowly via a syringe pump. Compared with Carreira's Fe(TPP)Cl-catalyzed reactions, lower diastereoselectivity was obtained. Interestingly, if no catalyst is used, [3+2] cycloaddition occurs, and the cyclopropanation compound is the minor product.

The oxygen-binding metalloprotein myoglobin, containing a heme (iron-protoporphyrin IX) cofactor coordinated at the proximal side through a histidine residue, was found by Fasan and co-workers to be able to catalyse the transfer non-fluorinated carbene for asymmetric cyclopropanation. They

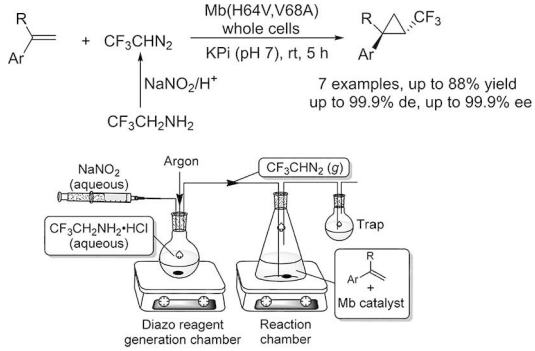


Scheme 3. The synthesis of CF_3-substituted spirocyclic β-Lactams.

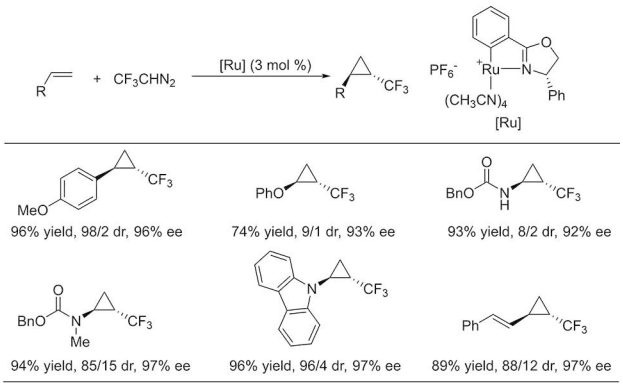
screened various sperm whale myoglobin (Mb) and disclosed that Mb(H64V,V68A) exhibits high activity for excellent diastereoselectivity and enantioselectivity.[31] Recently, they further described the Mb(H64V,V68A)-catalyzed stereoselective cyclopropanation of aryl alkenes with trifluoromethylcarbene (Scheme 4).[32] The conditions for the *in situ* generation of CF_3CHN_2 are too hash for protein-based catalysts, and thus CF_3CHN_2 was *ex situ* generated and then imported to the reaction system by an inert gas. The Fe center in Mb(H64V,V68A) was the real catalyst for this process. The biocatalytic reactions proceeded smoothly and high enantioselectivity was obtained.

Catalytic asymmetric cyclopropanation with trifluoromethylcarbene continues to be challenging. Besides the above Co- and Fe-complexes, a Ru-source was also found to be able to catalyse the asymmetric reactions, which was reported by Iwasa and co-workers (Scheme 5).[33] CF_3CHN_2 was first generated and added to the reaction system. Although the process can only be extended to monosubstituted alkenes, various alkenes show high reactivity under these conditions, including aryl alkenes, vinyl ferrocene, vinyl ethers, vinyl amines, vinyl carbamates and dienes. Interestingly, the presence of a N–H moiety in a vinyl carbamate did not lead to the decrease in enantioselectivity, although a lower diastereoselectivity was obtained.

A two-step procedure involving the synthesis of CF_3-cyclopropylboronates and then a subsequent coupling reaction offers another route to CF_3-cyclopropane derivatives



Scheme 4. Mb-catalyzed asymmetric cyclopropanation.



Scheme 5. Ru-catalyzed asymmetric cyclopropanation.

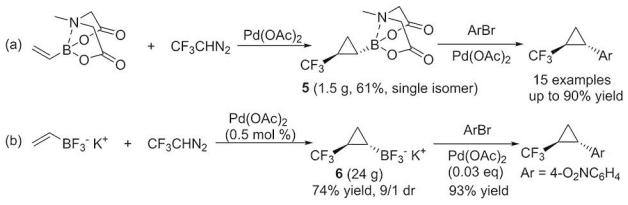
(Scheme 6).[34] The first step involves the catalytic cyclopropanation of vinylborates with CF_3CN_2, and the cyclopropanation products can then be used as building blocks for the subsequent coupling. The low diastereoselectivity obtained in the case of vinylborates (CH_2=CHB(OR)$_2$) by the group of Duncton[34a] prompted them to use another vinylborate containing a tertiary amino group, which could smoothly undergo cyclization to exclusively give the *trans* isomer **5** (Scheme 6a).[34b] The severe steric effect induced by the boronic ester moiety may be the reason for the high diastereoselectivity. The coupling of the borate building block with other partners gave various CF_3-cyclopropanes. Recently, Grygorenko and coworkers found the cyclopropanation of a vinyltrifluoroborate with CF_3CHN_2 catalyzed by $Pd(OAc)_2$ could proceed smoothly to provide **6** on a large scale (Scheme 6b).[34c] Although only one CF_3-substituted coupling product was shown in the paper, this work still deserves attention because of the successful large-scale cyclopropanation.

Thermal cyclopropanation of alkenes with CF_3CHN_2 remains largely unexplored, probably because thermal conditions may easily lead to explosion of CF_3CHN_2. Interestingly, Ma and coworkers disclosed that saturated brine could stabilize CF_3CHN_2, and thus thermal cyclopropanation of alkenes with CF_3CHN_2 was achieved to deliver products **7** (Scheme 7).[35] In contrast to other methods, this process could be extended to trisubstituted alkenes. Moderate to high yields were obtained, and high diastereoselectivity was observed. The cyclization products could be used for efficient access to functionalized CF_3-substituted α-cyclopropane amino acids **8** and relative dipeptide derivatives **9**.

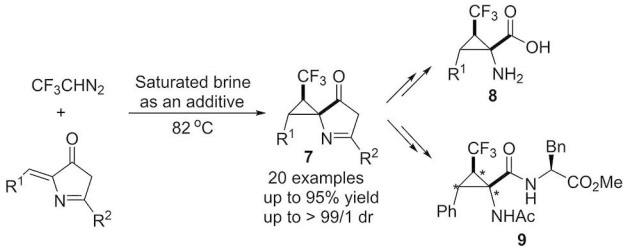
2.1.2. $CF_3C(N_2)Ar$ as a carbene source

Compared with CF_3CHN_2, $CF_3C(N_2)Ar$ exhibits enhanced thermal stability due to the presence of an Ar group. Ghanem and coworkers described a Rh-catalyzed asymmetric cyclopropanation of styrene with the CF_3-diazo compound, $CF_3C(N_2)Ph$ (Scheme 8a).[36] In this work, the authors aimed to design and synthesize rhodium catalysts, and thus the substrate scope was not investigated. They found that many Rh-catalysts could well catalyse the reaction to afford the expected product in a high yield and a good ee value. The group of Che synthesized various Fe- and Ru-mono(dialkylcarbene) complexes and used the Fe-complexes to catalyze cyclopropanation of alkenes with carbene generated from diazo compounds.[37] The also reported one example for cyclization with $CF_3C(N_2)Ph$ (Scheme 8b). In this case, low diastereoselectivity was observed. Koenigs disclosed a cyclopropanation reactions of acyl-protected D-glucal with $CF_3C(N_2)Ph$ (Scheme 8c).[38] Three examples were demonstrated, and up to 90% yield was obtained. Surprisingly, CF_3CHN_2 is inert under these conditions.

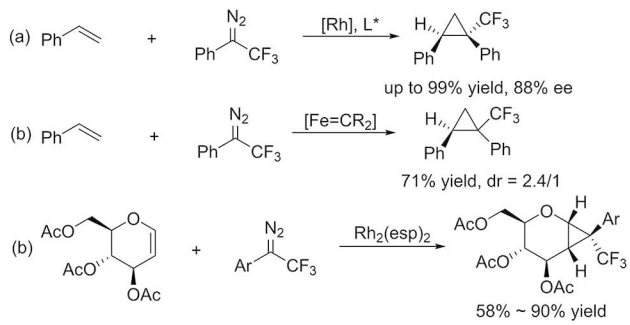
Dearomatization occurred for the reaction of indoles with $CF_3C(N_2)Ph$ in the presence of a Pd catalyst, and cyclopropanation proceeded smoothly to give the desired products in moderate yields, which was recently described by the group of Koenigs (Scheme 9).[39] It was found that aryl C–I bond remained intact under these conditions (the second example in the table),



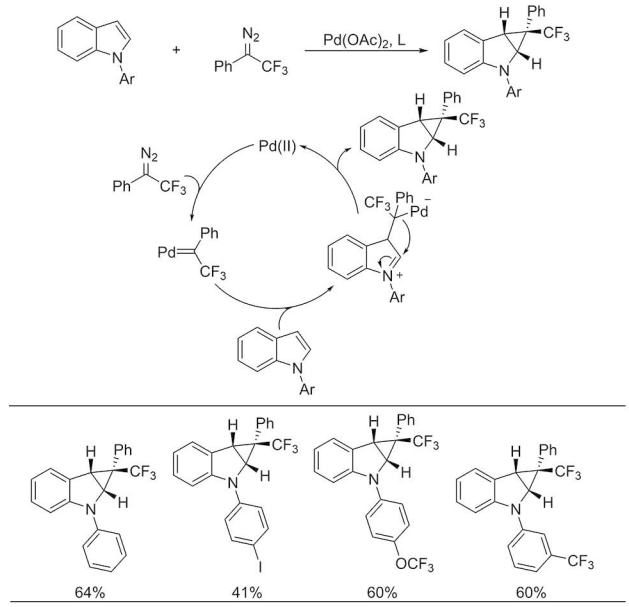
Scheme 6. A two-step procedure for the synthesis of CF_3-cyclopropanes.



Scheme 7. Thermal cyclopropanation.



Scheme 8. Catalytic cyclopropanation with $CF_3C(N_2)Ar$.



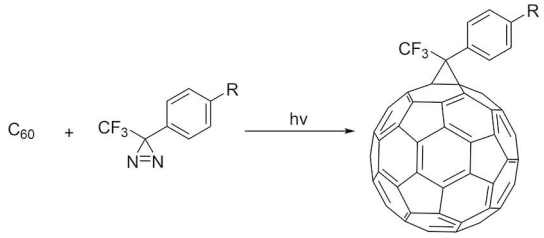
Scheme 9. Cyclopropanation of indoles.

and thus Pd(0) was proposed to be not involved. They proposed that the diazo compound first reacts with the Pd catalyst to form a Pd-carbene complex. The carbene complex attacks indole and the subsequent cyclization affords the final product and releases the catalyst.

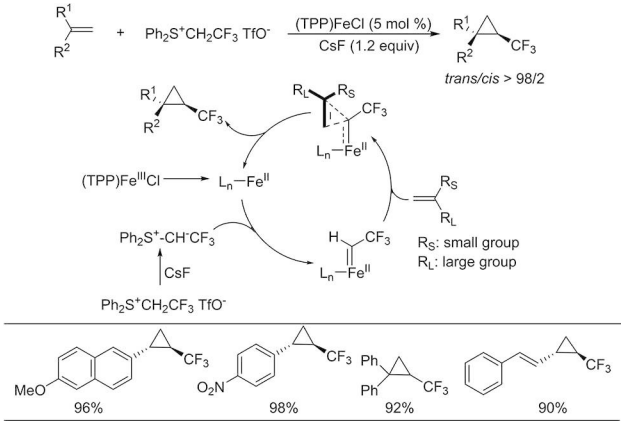
Besides diazo compounds, diazirines have also served as useful precursors of carbenes. Yamada, Hasegawa, and co-workers disclosed a cyclization of [60]fullerene (C60) with CF_3-diazirine under photolysis conditions, allowing access to the functionalised methanofullerenes in reasonable yields (Scheme 10).[40] The reaction is believed to take place via the photolytic generation of CF_3-carbene and the addition of the carbene intermediate to a [6,6] double bond of C60.

2.1.3. $[Ph_2S^+CH_2CF_3]$ TfO^- as a trifluoromethylcarbene source

Due to the explosive nature of CF_3CHN_2, it is desirable to develop a safe and convenient trifluoromethylcarbene reagent. We have been interested in the development of fluorinated phosphonium/sulfonium salts as fluorinated carbene reagents.[41] Based on our previous observation that phosphonium ylide Ph_3P^+–CF_2^- could directly undergo a P–C bond cleavage to release difluorocarbene,[42] we originally thought that sulfonium ylide Ph_2S^+–CH^-CF_3 may also be able to generate trifluoromethylcarbene via a S–C bond cleavage. However, deep investigations revealed that the bond cleavage cannot directly occur. We found that a Fe-complex, (TPP)FeCl (TPP = 5,10,15,20-tetraphenyl-21H,23H-porphine), could turn the sulfonium ylide into a Fe-carbene (Fe=$CHCF_3$), and thus Fe-catalyzed cyclopropanation of alkenes with the sulfonium ylide, in situ generated from $[Ph_2S^+CH_2CF_3]$ TfO^-, was achieved (Scheme 11).[43] A wide substrate scope was observed, and high diastereoselectivity was obtained. $[Ph_2S^+CH_2CF_3]$ TfO^- is shelf-stable and easily prepared, which makes this cyclopropanation protocol attractive. Notably, atom efficiency is an issue with the use of the sulfonium salt since Ph_2S generated from this salt turns out to be a waste.



Scheme 10. Cyclopropanation of C60.

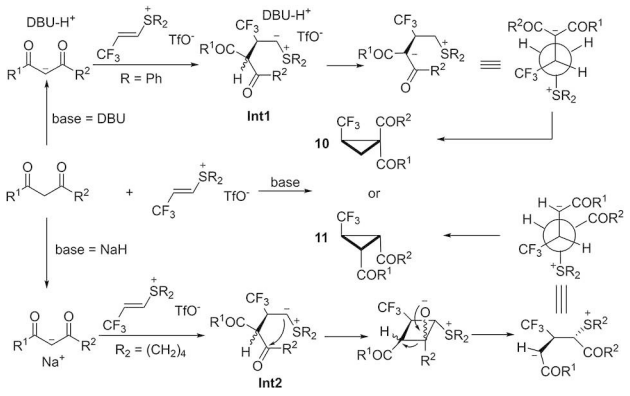


Scheme 11. Fe-catalyzed cyclopropanation with $[Ph_2S^+CH_2CF_3]$ X^-.

2.1.4. Step-wise cyclization involving a sulfonium ylide

The group of Lu developed two β-trifluoromethyl-substituted vinylsulfonium salts ($CF_3CH{=}CHS^+R_2$ X^-), and found that these two salts could react with active methylene compounds containing electron-withdrawing groups via a Michael addition to give trifluoromethyl-substituted cyclopropanes (Scheme 12).[44] Interestingly, different cyclopropanes would be obtained with different substituents (R group) on the sulfur atom and the use of different bases. The first step is a Michael addition to give sulfonium ylides (**Int1** or **Int2**). When DBU as the base, DBU may act as a proton transfer reagent via the formation of DBU-H^+, and thus protonation/deprotonation of **Int1** would readily occur, giving compounds **10** as final products. When NaH is used as the base, protonation/deprotonation does not occur. Instead, the carbanion in ylide **Int2** prefers to attack the carbonyl group to form a four-member ring, and the subsequent ring-opening and ring-closing gives the final product **11**. The carbanion in **Int1** would not attack the carbonyl group, probably because of strong steric effects induced by the two Ph groups. Although various functionalized CF_3-cyclopropanes could be synthesized, this protocol may suffer from the tedious synthesis of CF_3-vinylsulfonium salts. Almost at the same time, the group of Hanamoto reported a similar process for the synthesis of CF_3-cyclopropanes.[45] They used K_2CO_3 as the base and products **10** were obtained as major products.

Although sulfonium salt $[Ph_2S^+CH_2CF_3]$ TfO^- was reported in the 1990s,[46] it had never been developed as a sulfonium ylide reagent. This may be because the corresponding ylide (Ph_2S^+ CH^-CF_3) is highly unstable due to β-defluorination. As described



Scheme 12. Cyclization of CF_3-vinylsulfonium salts with active methylene compounds.

in Scheme 11, $[Ph_2S^+CH_2CF_3]$ TfO^- can act as a trifluoromethylcarbene source because this sulfonium salt could be easily transformed into sulfonium ylide ($Ph_2S^+CH^-CF_3$) via deprotonation. Our examination revealed that the use of fluoride as the base is favourable for the suppression of β-defluorination of the sulfonium ylide. We thus investigated the cyclization of aldehydes, α,β-unsaturated alkenes and imines with the sulfonium ylide.[47] All cyclization reactions proceeded smoothly to give the expected products in high yields and excellent diastereoselectivity. The cyclization of α,β-unsaturated alkenes almost exclusively gave *trans*-products (Scheme 13).[47] Terminal alkenes shows high reactivity, but internal alkenes are inert under these conditions. Compared with aryl-containing substrates ($ArCOCH{=}CH_2$), the alkyl couterparts ($RCOCH{=}CH_2$, R = alkyl group) exhibit much lower reactivity (**12f**).

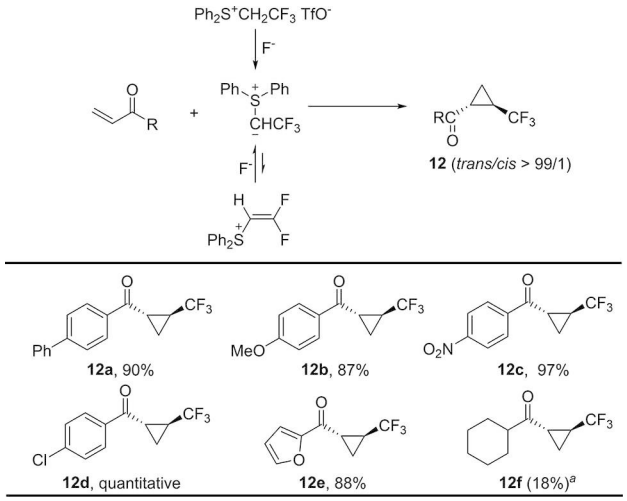
2.1.5. Miscellaneous methods

Transition-metal-catalyzed cyclization with trifluoromethylcarbene can be applied not only to alkenes, but also to alkynes. Carreira disclosed that the cyclization of alkynes catalyzed by a Rh complex occurred smoothly to give CF_3-cyclopropenes in moderate yields (Scheme 14a).[22a] Both terminal alkynes and internal alkynes were found to be reactive under these conditions. The cyclopropene could be reduced by Pd/H_2 to give CF_3-cyclopropane **13** in a high yield with high diastereoselectivity. The double bond could also smoothly undergo a Diels-Alder reaction with a diene to afford fused-ring product **14** (Scheme 14b).

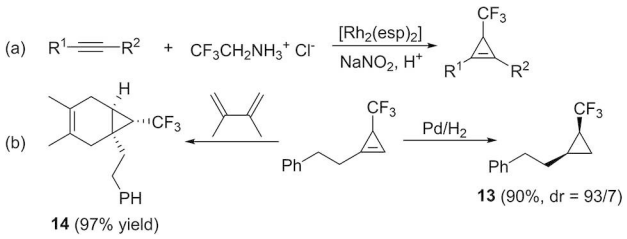
CF_3CHN_2 could generate trifluoromethylcarbene by releasing a nitrogen molecule, and it can also act as a 1,3-dipole without releasing the nitrogen molecule. Lu, Xiao and coworkers found that a [3 + 2] cyclization of trisubsituted alkenes with CF_3CHN_2 generated in situ gave highly functionalized spirooxindoles **15**, and the subsequent ring contraction afforded CF_3-containing 3,3′-cyclopropyl spirooxindoles **16** (Scheme 15).[48] High overall yields were obtained, and high diastereoselectivity was observed in both cyclization and ring contraction. The trisubstituted alkenes with *N*-protected or without being protected could all participate in this reaction very well.

The group of Severin described a two-step procedure for the synthesis of CF_3-cyclopropanes (Scheme 16).[49] $CF_3CHClBr$ could be easily reduced by a Ru complex to generate a $CF_3CHCl^•$ radical. The first step is the radical addition of $CF_3CHCl^•$ to a terminal alkene to give **17**. Since a catalytic amount of Ru complex was used, another reducing agent, Mg, was necessary to be used in a stoichiometric amount. As no solvent was used in the first step, the addition products **17** were stable in the presence of Mg. After the unreacted $CF_3CHClBr$ was removed, the cyclization occurred by using THF as a solvent at a low temperature. High diastereoselectivity was obtained for the reactions of aryl alkenes. But in the case of alkyl alkenes, almost no stereoselectivity was observed (**18b**–**18c**).

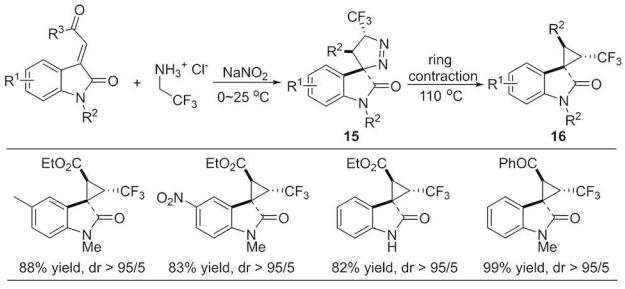
In 1960, Engelhardt found that SF_4 was able to conver a CO_2H moiety into a CF_3 group at 150 °C in liquid hydrogen



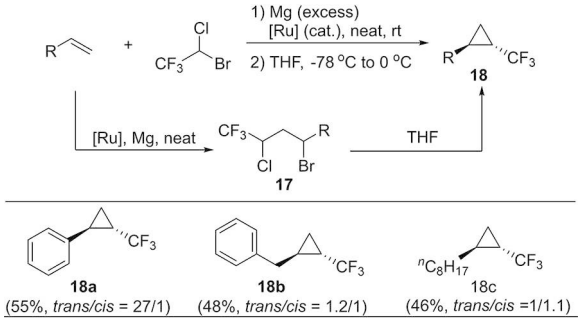
Scheme 13. Cyclopropanation of alkenes with a CF_3-sulfonium ylide. [a]The yield was determined by ^{19}F NMR spectroscopy.



Scheme 14. Cyclopropenation and the subsequent transformation.



Scheme 15. [3 + 2] cyclization and the subsequent ring contraction.



Scheme 16. Sequential Kharasch-addition/dehalogenative-cyclization.

fluoride.[50] The use of liquid hydrogen fluoride at high temperatures may limit a wide application of this approach. In 2019, Mykhailiuk described a mild approach for the deoxofluorination of carboxylic acids with SF_4.[51] The reaction occurred smoothly at 55 °C by using H_2O as a key additive. They examined three cyclopropyl acids and found that the desired products could be obtained on gram scales (Scheme 17).

3. HCF_2-Cyclopropanes

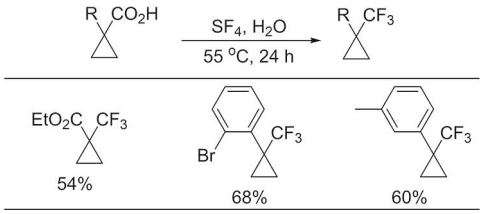
3.1. Cyclopropanation of alkenes with a carbene

Although CF_3CHN_2 was developed as a trifluoromethylcarbene source in the 1960s,[16] it took over 50 years for the development of HCF_2CHN_2 as a difluoromethylcarbene source. Since CF_3CHN_2 could be generated in situ from $CF_3CH_2NH_2/NaNO_2/H^+$, a similar reagent system, $HCF_2CH_2NH_2/NaNO_2/H^+$, appeared an appropriate approach to generate HCF_2CHN_2. However, the first reported attempt in 1971[52] and the following attempts[53] all failed. It is quite surprising that HCF_2CHN_2 remained unknown until recently. Mykhailiuk alone developed a convenient synthetic route.[54] It was found that a catalytic amount of HOAc can promote the reaction of $HCF_2CH_2NH_2$ with ^{t}BuONO to in situ generate HCF_2CHN_2. HCF_2CHN_2 was then used as a 1,3-dipole to achieve [3 + 2] cyclization with alkynes to give HCF_2-pyrazoles.[54]

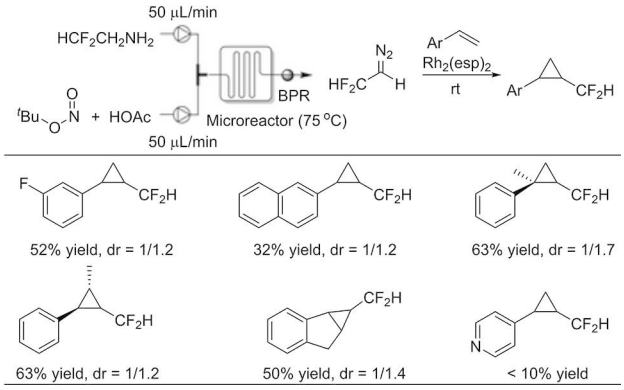
HCF_2CHN_2 exhibits very different reactivity with CF_3CHN_2. Koenigs and co-workers found that the addition of a solution of HCF_2CHN_2 generated in situ into a styrene solution could not give any cyclopropanation product at all in the presence of a transition metal catalyst which can catalyze cyclopropanation of alkenes with CF_3CHN_2.[55] They then used a continuous-flow procedure. Solutions of $HCF_2CH_2NH_2$ and HOAc/tBuOH were combined by syringe pumps into a microreactor at a constant flow rate. The microreactor was heated to 75 °C and the outlet of the microreactor was connected to a back pressure regulator. The reaction solution in the microreactor was added to a standard reaction flask under Ar atmosphere containing an alkene and a Rh catalyst. The desired products were obtained in moderate yields by using this continuous-flow procedure (Scheme 18).[55] Terminal alkenes and internal alkenes could all be converted, but almost no diastereoselectivity was observed.

N-Tosylhydrazones have proved to be efficient precursors of various diazo compounds.[56] The group of Bi recently described that a bench-stable difluoroacetaldehyde *N*-triftosylhydrazone (DFHZ-Tfs) could act as an operationally convenient HCF_2CHN_2 surrogate to achieve Fe-catalyze cyclopropanation of alkenes (Scheme 19).[57] They found that alkaline aqueous conditions would convert DFHZ-Tfs into diazoacetaldehyde ($CHOCHN_2$), and non-aqueous basic conditions is favorable for the generation of HCF_2CHN_2 from DFHZ-Tfs. High yields and excellent diastereoselectivity were observed in most cases.

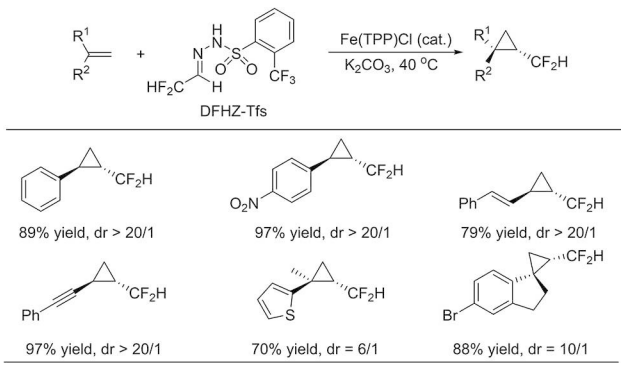
On the basis of our previous studies that sulfonium salt $[Ph_2S^+CH_2CF_3]$ TfO^- can act as a trifluoromethylcarbene source,[43] we then speculated that difluoromethyl counterpart, $[Ph_2S^+CH_2CF_2H]$ TfO^-, may act as a difluoromethylcarbene precursor.[58] A series of studies revealed that these two sulfonium salts exhibits quite different reactivities. The cyclization of aldehydes, α,β-unsaturated alkenes or imines with ylide $Ph_2S^+CH^-CF_3$ generated in situ from $[Ph_2S^+CH_2CF_3]$ TfO^-proceeded smoothly to give the desired products in high diastereoselectivity.[47] In the case of $[Ph_2S^+CH_2CF_2H]$ TfO^-, cyclization under similar conditions did occur, but low diastereoselectivity was observed. Furthermore, under the same conditions for Fe-catalyzed cyclopropanation with trifluoromethylcarbene generated from $[Ph_2S^+CH_2CF_3]$ TfO^-, no expected product was observed by using $[Ph_2S^+CH_2CF_2H]$ TfO^- instead of $[Ph_2S^+CH_2CF_3]$ TfO^-. A detailed survey of reaction conditions revealed that a reducing agent was necessary. The use of Zn as a reductant gave the cyclopropanation product in high yields and with excellent diastereoselectivity (dr > 20/1) (Scheme 20).[58] A moderate yield was obtained on a gram scale



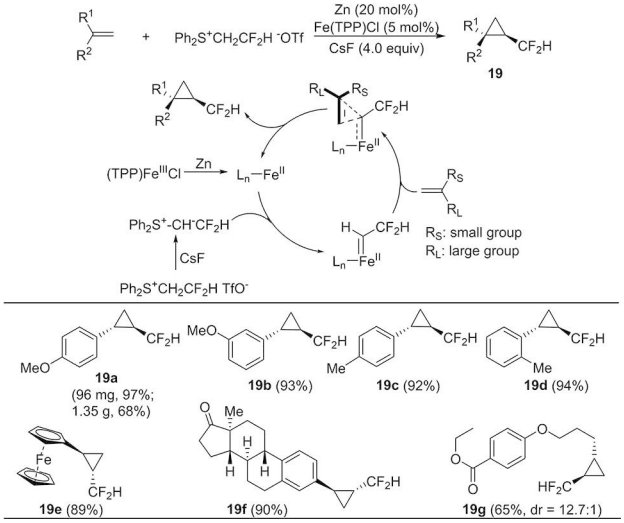
Scheme 17. Deoxofluorination of carboxylic acids with SF_4.



Scheme 18. Rh-catalyzed Cyclopropanation with HCF_2CHN_2.



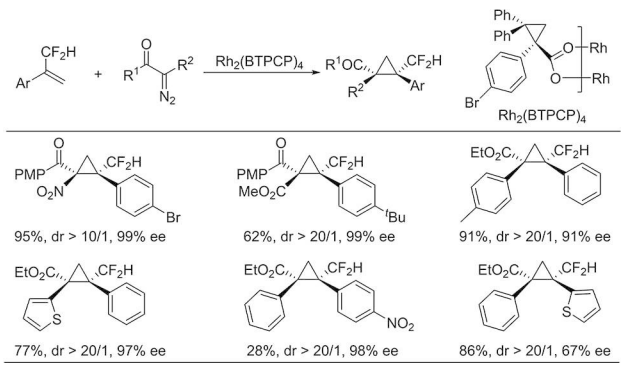
Scheme 19. Fe-catalyzed cyclopropanation with DFHZ-Tfs.



Scheme 20. Fe-catalyzed cyclopropanation with $[Ph_2S^+CH_2CF_2H]$ TfO^-.

(**19a**, 1.35 g, 68%), and a lower diastereoselectivity was observed in the case of alkyl alkenes (**19g**). The atom efficiency is also an issue by using this reagent since Ph_2S is produced as a waste.

In the above methods, HCF_2-cyclopropanes are synthesized by cyclization of alkenes with difluoromethylcarbene. Instead, cyclization of HCF_2-alkenes with a carbene could also provide HCF_2-cyclopropanes. Jubault and co-workers reported a Rh-catalyzed asymmetric cyclopropanation of HCF_2-alkenes with diazo compounds, which is the first protocol for the asymmetric synthesis of HCF_2-cyclopropanes (Scheme 21).[59] Excellent diastereoselectivity and enantioselectivity were observed by using Rh_2(*S*-BTPCP)$_4$ as a catalyst. Various carbonyl-substituted diazo compounds were found to be reactive, and many functional groups could be tolerated under these conditions. This protocol could provide highly functionalized HCF_2-cyclopropanes with excellent stereoselectivity, demonstrating its synthetic utility.



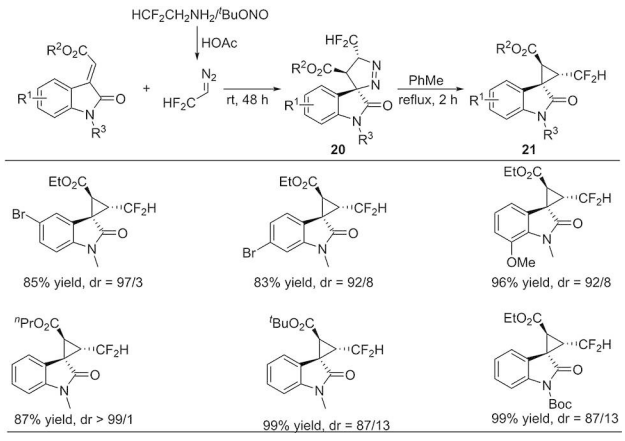
Scheme 21. Rh-catalyzed cyclopropanation of HCF_2-alkenes.

3.2. Miscellaneous methods

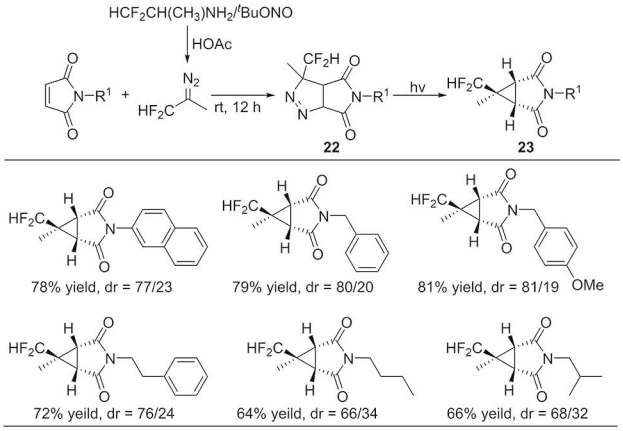
HCF_2CHN_2 can also be used as a 1,3-dipole for [3 + 2] cyclization. Han, Chen and co-workers found that the addition of alkenes into the solution of HCF_2CHN_2 generated in situ could give [3 + 2] cyclization products **20**. After the reactions were completed, elevating the reaction temperature afforded HCF_2-substituted spirocyclopropyloxindoles **21** (Scheme 22).[60] High yields were obtained and high diastereoselectivity was observed. This method was applied to the synthesis of an analogue of an HIV-1 non-nucleoside reverse transcriptase inhibitor. The cytotoxic activities of several CF_2H-containing spirocyclopropyloxindoles on normal human prostate cancer cells and human lung cancer cells were investigated by MTT-based assays, in which the commercially available cancer therapy drug, *cis*-platin, was used as a positive control. Compared with cis-platin, CF_2H-containing spirocyclopropyloxindoles, showing a low toxicity, may provide a clue for scaffold-inspired synthesis and the development of new candidates for future cancer therapy.

In a HCF_2-cyclopropyl ring synthesized by using HCF_2CHN_2, one of the three carbons contains a HCF_2 group and a H atom. It would be quite challenging to functionalize this C–H bond. Instead, if using a $HCF_2C(R)N_2$ reagent, two functional groups, HCF_2 and R, would be attached to the same carbon in the cyclopropyl ring. The group of Wu recently reported that $HCF_2C(CH_3)N_2$, in situ generated from $HCF_2CH(CH_3)NH_2$ under similar conditions as described by Mykhailiuk[54] for the in situ preparation of HCF_2CHN_2, could also be used as a 1,3-diple for [3 + 2]cyclization (Scheme 23).[61] For the subsequent ring contraction from **22** to **23**, both thermal and photochemical conditions could work, but a higher yield was obtained under photochemical conditions. As shown in the table of substrate scope, only moderate diastereoselectivity was observed.

Although difluoromethylation is an attractive and straightforward strategy for HCF_2 installation,[62] difluoromethylation for the incorporation of a HCF_2 group into a cyclopropyl ring remained challenging until recently. Liu and co-workers developed a copper-catalyzed decarboxylative difluoromethylation, a method which was successfully applied to the



Scheme 22. [3 + 2] cyclization with HCF_2CHN_2 and the subsequent ring contraction.

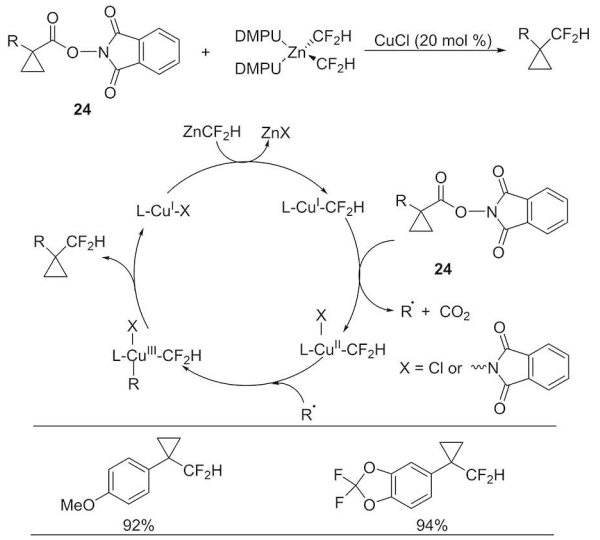


Scheme 23. [3 + 2] cyclization with $HCF_2C(CH_3)N_2$ and the subsequent ring contraction.

synthesis of HCF_2-cyclopropanes (Scheme 24).[63] This decarboxylative method involves a difluoromethylation of carbon-centered radical, which is also a challenging process. The carbon radical is in situ generated via a redox reaction of Cu^I with a redox-active ester, **24**, which is prepared from a corresponding carboxylic acid. The combination of the radical with Cu^{II} produces a $RCu^{III}CF_2H$ species, which undergoes a reductive elimination to afford the final product and releases the catalyst. Only two examples of HCF_2-cyclopropanes were shown in the article, and both of them were obtained in high yields.

4. Conclusions

CF_3- and HCF_2-substituted cyclopropyl rings are emerging of great interest in pharmaceutical chemistry and agrochemistry, and therefore the installation of these structural motifs is receiving increasing attention. The commonly used strategy is transition-metal-catalyzed cyclization of alkenes with carbene generated in situ from diazo compounds, including CF_3CHN_2 and HCF_2CHN_2. Both CF_3CHN_2 and HCF_2CHN_2 are potentially explosive and toxic chemicals, and thus safety precautions must be taken during handling them. A diversity of methods have been developed for the synthesis of CF_3-cyclopropanes, and excellent diastereoselectivity could usually be obtained. In sharp contrast, the synthesis of HCF_2-cyclopropanes has been much less explored, probably because no efficient difluoromethyl carbene reagent was developed until recently. Like CF_3CHN_2, HCF_2CHN_2 could serve as a difluoromethylcarbene reagent, but almost no diastereoselectivity was observed in the cyclopropanation. DFHZ-Tfs and $[Ph_2S^+CH_2CF_3]$ TfO^- were found to be effective difluoromethylcarbene source for diastereoselective cyclopropanation. Although significant accomplishments have been made in the past few years, further developments are still necessary. It is highly desirable to develop general protocols for the asymmetric catalytic installation of CF_3- or HCF_2-cyclopropanes, especially HCF_2-cyclopropanes. Besides, the development of safe difluoromethylcarbene and trifluoromethylcarbene reagents should also receive more attention.



Scheme 24. Cu-catalyzed decarboxylative difluoromethylation.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Trifluoromethyl · Difluoromethyl · Cyclopropanes · Carbenes · Fluorine

[1] P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, Wiley-VCH: Weinheim, Germany, **2013**.
[2] a) A. M. Thayer, *Chem. Eng. News* **2006**, *84*, 15–24; b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; c) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422–518.
[3] M. Bourliere, O. Pietri, P. Castellani, V. r Oules, X. Adhoute, *Ther. Adv. Gastroenterol.* **2018**, *11*, 1–15.
[4] A. Abutaleb, S. Kottilil, E. Wilson, *Hepatology* **2018**, *12*, 214–222.

[5] R. A. Sánchez, D. Banner, S. M. Ceccarelli, U. Grether, W. Haap, P. Hartman, G. Hartmann, H. Hilpert, H. Kuehne, H. Mauser, J.-M. Plancher, in Novel Proline Derivatives, **2010**, US2010/0267722 A1.
[6] J. C. Davies, S. M. Moskowitz, C. Brown, A. Horsley, M. A. Mall, E. F. McKone, B. J. Plant, D. Prais, B. W. Ramsey, J. L. Taylor-Cousar, E. Tullis, A. Uluer, C. M. McKee, S. Robertson, R. A. Shilling, C. Simard, F. Van Goor, D. Waltz, F. Xuan, T. Young, S. M. Rowe, *N. Engl. J. Med.* **2018**, *379*, 1599–1611.
[7] R. Besandre, H.-w. Liu, *Biochemistry* **2018**, *57*, 479–480.
[8] A. N. Matthew, N. Kurt Yilmaz, C. A. Schiffer, *Biochemistry* **2018**, *57*, 481–482.
[9] C. P. Mavragani, H. M. Moutsopoulos, *J. Autoimmun.* **2020**, *110*, 102364.
[10] O. O. Grygorenko, O. S. Artamonov, I. V. Komarov, P. K. Mykhailiuk, *Tetrahedron* **2011**, *67*, 803–823.
[11] M. Bos, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Chem. Eur. J.* **2017**, *23*, 4950–4961.
[12] P. K. Mykhailiuk, *Chem. Rev.* **2020**, *120*, 12718–12755.
[13] P. K. Mykhailiuk, R. M. Koenigs, *Chem. Eur. J.* **2019**, *25*, 6053–6063.
[14] L. Mertens, R. M. Koenigs, *Org. Biomol. Chem.* **2016**, *14*, 10547–10556.
[15] J. Decaens, S. Couve-Bonnaire, A. B. Charette, T. Poisson, P. Jubault, *Chem. Eur. J.* **2021**, *27*, 2935–2962.
[16] R. Fields, R. N. Haszeldine, *Proc. Chem. Soc. London* **1960**, *22*.
[17] H. Gilman, R. G. Jones, *J. Am. Chem. Soc.* **1943**, *65*, 1458–1460.
[18] P. Le Maux, S. Juillard, G. Simonneaux, *Synthesis* **2006**, 1701–1704.
[19] I. Komarov, P. Mykhailiuk, S. Afonin, A. Ulrich, *Synthesis* **2008**, 1757–1760.
[20] P. K. Mykhailiuk, S. Afonin, G. V. Palamarchuk, O. V. Shishkin, A. S. Ulrich, I. V. Komarov, *Angew. Chem. Int. Ed.* **2008**, *47*, 5765–5767; *Angew. Chem.* **2008**, *120*, 5849–5851.
[21] a) O. S. Artamonov, P. K. Mykhailiuk, N. M. Voievoda, D. M. Volochnyuk, I. V. Komarov, *Synthesis* **2010**, 443–446; b) O. S. Artamonov, E. Y. Slobodyanyuk, O. V. Shishkin, I. V. Komarov, P. K. Mykhailiuk, *Synthesis* **2013**, *45*, 225–230; c) O. S. Artamonov, E. Y. Slobodyanyuk, D. M. Volochnyuk, I. V. Komarov, A. A. Tolmachev, P. K. Mykhailiuk, *Eur. J. Org. Chem.* **2014**, *2014*, 3592–3599.
[22] a) B. Morandi, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 4294–4296; *Angew. Chem.* **2010**, *122*, 4390–4392; b) B. Morandi, E. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 9085–9088; *Angew. Chem.* **2011**, *123*, 9251–9254; c) B. Morandi, E. M. Carreira, *Org. Lett.* **2011**, *13*, 5984–5985; d) B. Morandi, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 9085–9088; *Angew. Chem.* **2011**, *123*, 9251–9254; e) S. A. Kuenzi, B. Morandi, E. M. Carreira, *Org. Lett.* **2012**, *14*, 1900–1901; f) J. Y. Hamilton, B. Morandi, E. M. Carreira, *Synthesis* **2013**, *45*, 1857–1862.
[23] J. R. Wolf, C. G. Hamaker, J.-P. Djukic, T. Kodadek, L. K. Woo, *J. Am. Chem. Soc.* **1995**, *117*, 9194–9199.
[24] B. Morandi, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 938–941; *Angew. Chem.* **2010**, *122*, 950–953.
[25] M. Bill, C. Jeremy, M. C. Erick, *Org. Lett.* **2011**, *13*, 3080–3081.
[26] T. Mori, K. Ujihara, O. Matsumoto, K. Yanagi, N. Matsuo, *J. Fluorine Chem.* **2007**, *128*, 1174–1181.
[27] B. Morandi, B. Mariampillai, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 1101–1104; *Angew. Chem.* **2011**, *123*, 1133–1136.
[28] Y. Chen, J. V. Ruppel, X. P. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 12074–12075.
[29] a) C.-B. Liu, W. Meng, F. Li, S. Wang, J. Nie, J.-A. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 6227–6230; *Angew. Chem.* **2012**, *124*, 6331–6334; b) F. Li, J. Nie, L. Sun, Y. Zheng, J.-A. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 6255–6258; *Angew. Chem.* **2013**, *125*, 6375–6378.
[30] S. Li, W.-J. Cao, J.-A. Ma, *Synlett* **2017**, *28*, 673–678.
[31] M. Bordeaux, V. Tyagi, R. Fasan, *Angew. Chem. Int. Ed.* **2015**, *54*, 1744–1748; *Angew. Chem.* **2015**, *127*, 1764–1768.
[32] A. Tinoco, V. Steck, V. Tyagi, R. Fasan, *J. Am. Chem. Soc.* **2017**, *139*, 5293–5296.
[33] M. Kotozaki, S. Chanthamath, T. Fujii, K. Shibatomi, S. Iwasa, *Chem. Commun.* **2018**, *54*, 5110–5113.
[34] a) M. A. J. Duncton, L. Ayala, C. Kaub, S. Janagani, W. T. Edwards, N. Orike, K. Ramamoorthy, J. Kincaid, M. G. Kelly, *Tetrahedron Lett.* **2010**, *51*, 1009–1011; b) M. A. J. Duncton, R. Singh, *Org. Lett.* **2013**, *15*, 4284–4287; c) O. V. Hryschuk, Y. Yurov, A. V. Tymtsunik, V. O. Kovtunenko, I. V. Komarov, O. O. Grygorenko, *Adv. Synth. Catal.* **2019**, *361*, 5428–5439.
[35] C.-L. Zhu, L.-J. Yang, S. Li, Y. Zheng, J.-A. Ma, *Org. Lett.* **2015**, *17*, 3442–3445.
[36] F. G. Adly, M. G. Gardiner, A. Ghanem, *Chem. Eur. J.* **2016**, *22*, 3447–3461.
[37] C.-M. Che, J.-S. Huang, K.-H. Low, Q. Wan, H.-X. Wang, J.-L. Zhang, C.-Y. Zhou, *Chem. Sci.* **2020**, *11*, 2243–2259.
[38] Y. Guo, R. M. Koenigs, C. Pei, *ChemCatChem* **2020**, *12*, 4014–4018.
[39] R. M. Koenigs, M. Möller, Z. Yang, *Angew. Chem. Int. Ed.* **2020**, *59*, 5572–5576.
[40] M. Yamada, K. Harada, Y. Maeda, T. Hasegawa, *New J. Chem.* **2013**, *37*, 3762–3769.
[41] J.-H. Lin, J.-C. Xiao, *Acc. Chem. Res.* **2020**, *53*, 1498–1510.
[42] X.-Y. Deng, J.-H. Lin, J. Zheng, J.-C. Xiao, *Chem. Commun.* **2015**, *51*, 8805–8808.
[43] Y. Duan, J.-H. Lin, J.-C. Xiao, Y. C. Gu, *Org. Lett.* **2016**, *18*, 2471–2474.
[44] H. Lin, Q. Shen, L. Lu, *J. Org. Chem.* **2011**, *76*, 7359–7369.
[45] N. Kasai, R. Maeda, H. Furuno, T. Hanamoto, *Synthesis* **2012**, *44*, 3489–3495.
[46] T. Umemoto, Y. Gotoh, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2008–2010.
[47] Y. Duan, B. Zhou, J.-H. Lin, J.-C. Xiao, *Chem. Commun.* **2015**, *51*, 13127–13130.
[48] T.-R. Li, S.-W. Duan, W. Ding, Y.-Y. Liu, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, *J. Org. Chem.* **2014**, *79*, 2296–2302.
[49] J. Risse, M. A. Fernandez-Zumel, Y. Cudre, K. Severin, *Org. Lett.* **2012**, *14*, 3060–3063.
[50] W. R. Hasek, W. C. Smith, V. A. Engelhardt, *J. Am. Chem. Soc.* **1960**, *82*, 543–551.
[51] M. Bugera, S. Trofymchuk, K. Tarasenko, O. Zaporozhets, Y. Pustovit, P. K. Mykhailiuk, *J. Org. Chem.* **2019**, *84*, 16105–16115.
[52] J. H. Atherton, R. Fields, R. N. Haszeldine, *J. Chem. Soc. C* **1971**, 366–371.
[53] P. K. Mykhailiuk, *Org. Biomol. Chem.* **2015**, *13*, 3438–3445.
[54] P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2015**, *54*, 6558–6561; *Angew. Chem.* **2015**, *127*, 6658–6661.
[55] K. J. Hock, L. Mertens, R. M. Koenigs, *Chem. Commun.* **2016**, *52*, 13783–13786.
[56] Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2013**, *46*, 236–247.
[57] Y. Ning, X. Zhang, Y. Gai, Y. Dong, P. Sivaguru, Y. Wang, B. R. P. Reddy, G. Zanoni, X. Bi, *Angew. Chem. Int. Ed.* **2020**, *59*, 6473–6481.
[58] Y. Duan, J.-H. Lin, J.-C. Xiao, Y. C. Gu, *Chem. Commun.* **2017**, *53*, 3870–3873.
[59] M. Bos, W.-S. Huang, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Angew. Chem. Int. Ed.* **2017**, *56*, 13319–13323; *Angew. Chem.* **2017**, *129*, 13504–13508.
[60] W.-Y. Han, J. Zhao, J.-S. Wang, B.-D. Cui, N.-W. Wan, Y.-Z. Chen, *Tetrahedron* **2017**, *73*, 5806–5812.
[61] Y. Zheng, X. Yu, S. Lv, P. K. Mykhailiuk, Q. Ma, L. Hai, Y. Wu, *RSC Adv.* **2018**, *8*, 5114–5118.
[62] a) C.-P. Zhang, Q.-Y. Chen, Y. Guo, J.-C. Xiao, Y.-C. Gu, *Coord. Chem. Rev.* **2014**, *261*, 28–72; b) Y. Lu, C. Liu, Q. Y. Chen, *Curr. Org. Chem.* **2015**, *19*, 1638–1650; c) D. E. Yerien, S. Barata-Vallejo, A. Postigo, *Chem. Eur. J.* **2017**, *23*, 14676–14701; d) J. Rong, C. Ni, J. Hu, *Asian J. Org. Chem.* **2017**, *6*, 139–152; e) S. Krishnamoorthy, G. K. S. Prakash, *Synthesis* **2017**, *49*, 3394–3406.
[63] X. Zeng, W. Yan, S. B. Zacate, T.-H. Chao, X. Sun, Z. Cao, K. G. E. Bradford, M. Paeth, S. B. Tyndall, K. Yang, T.-C. Kuo, M.-J. Cheng, W. Liu, *J. Am. Chem. Soc.* **2019**, *141*, 11398–11403.

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