Tetrahedron 113 (2022) 132694

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of fluoroalkenes via Julia and Julia-Kocienski olefination reactions

Qinyu Luo, Xiu Wang, Jinbo Hu*

Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai, 200032, China

ARTICLE INFO

Article history:
Received 24 November 2021
Received in revised form
19 February 2022
Accepted 21 February 2022
Available online 21 March 2022

Keywords:
Fluoroalkene
Julia olefination
Julia-Kocienski olefination
Fluoroalkyl sulfone
Heteroaryl sulfone

ABSTRACT

The introduction of one or two fluorine atoms into a carbon-carbon double bond often brings about profound changes of physical, chemical and/or biological properties of the target molecule. Fluorinated alkenes are a class of important compounds and widely used in medicinal chemistry and materials science. Julia and Julia-Kocienski reactions could be used in the synthesis of fluorinated alkenes by employing α-fluorinated sulfones. In this review, the synthesis of fluorinated alkenes through Julia and Julia-Kocienski reactions are summarized, and the contents are categorized by target molecules and sulfone reagents. The difference between the reaction conditions for monofluoromethyl sulfones and difluoromethyl sulfones reflects the unique effect of fluorine substituents.

1. Introduction

The efficient construction of carbon-carbon double bonds is of high importance in synthetic organic chemistry [1]. Specifically, double bonds involving fluorinated carbon atom(s) have received much attention due to the unique characters and utilities of fluoroalkenes [2]. It has been known that some fluoroalkenes possess bioactivities [3–5] and serve as homeostasis regulators [6,7] or as inhibitors of enzymes [8–10], while monofluoroalkenes are considered as bioisosteres with amides more specifically [11]. Polymerized fluoroalkenes (fluoropolymers) have been widely used in our everyday life, such as poly (tetrafluoroethylene) (also known as PTFE or Teflon) [12], poly (vinylidene difluoride) (PVDF) [13] and Nafion [14]. On the other hand, synthetic elaborations of fluoroalkenes provide access to diversified structural scaffolds of functional materials including liquid crystals and nonlinear optical materials [15]. Owning to their important applications, various approaches have been developed for the preparation of fluoroalkenes, such as the electrophilic fluorination of vinyl silanes [16–18], nucleophilic fluorination of alkynes [19,20], and fluoroolefination of carbonyl compounds [21–26], etc.

Among various methods in the olefination of carbonyl compounds, Julia reaction plays an important role. In 1973, the French chemist Marc Julia developed a new protocol for the synthesis of alkenes [27] from sulfones and carbonyl compounds under basic conditions, followed by reductive 1,2- elimination of the resulting β-hydroxy sulfones or their derivatives (Scheme 1). After a few years, Lythgoe and Kocienski improved the elimination step and expanded this reaction [28–31].

18 years later, Sylvestre Julia, brother of Marc Julia, developed a new method by replacing phenyl sulfones with heteroaryl sulfones [32] (Scheme 2). This new method, together with its subsequent development made by Kocienski [33,34], which is now called Julia-Kocienski reaction, curtails the previous multi-step procedure to a one-pot protocol. Until now, both Julia and Julia-Kocienski reactions are frequently employed in the synthesis of alkenes. Many reviews on the history, mechanism, development and application of Julia and Julia-Kocienski reactions have been reported [35–41]. In this review article, we aim to focus on the synthesis of *fluoroalkenes* through Julia reactions or Julia-Kocienski reactions.

2. Synthesis of fluoroalkenes via Julia reaction

2.1. General consideration

The Julia reaction is a condensation reaction between a carbonyl

* Corresponding author.
E-mail address: jinbohu@sioc.ac.cn (J. Hu).

https://doi.org/10.1016/j.tet.2022.132694
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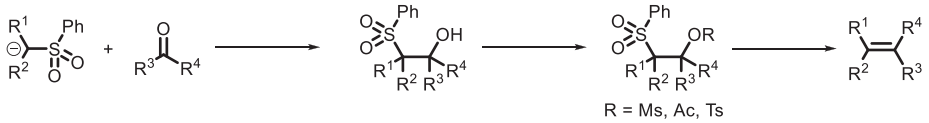
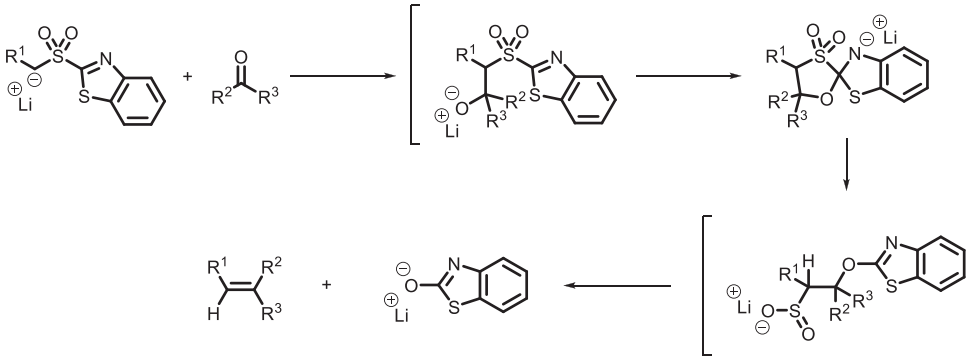


Scheme 1. Marc Julia's original olefination reaction.



Scheme 2. The original report by Sylvestre Julia.

compound and a sulfone, followed by 1,2-elimination to give an alkene. In this transformation, the sulfone is deprotonated by a Brønsted base, and then adds to a carbonyl compound to afford a β-hydroxy sulfone. The reductive 1,2-elimination converts the β-hydroxy sulfone or its derivative into a desired alkene. In Julia reaction, two or three steps are required. The stereochemistry of the generated carbon-carbon double bond depends on the reductive 1,2-elimination step, and an *E*-alkene is generally obtained.

For each step in Julia reaction, problems are encountered which lower the efficiency of the whole reaction. In the addition step, the equilibrium may favor the starting materials instead of the addition products. In addition, metalated sulfones can deprotonate the carbonyl compounds with α-H (Scheme 3).

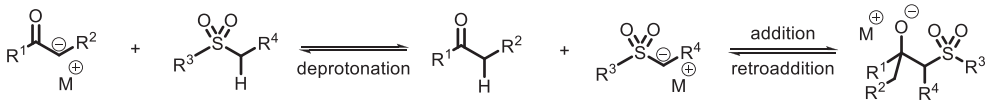
The 1,2-reductive elimination is another key step in Julia reaction. Three pathways of elimination and a pathway of side reaction [41] were shown in Scheme 4. When the free hydroxyl groups were protected with acyl groups, the mechanism of 1,2-reductive elimination can vary with structure of substrates (pathway a-c in Scheme 4). For example, when the 1,2-elimination of a β-acetoxyl sulfone was carried out in the presence of CD_3OD (Scheme 5), deuterated alkene was obtained in the presence of Na(Hg), which indicated a process via a vinyl sulfone intermediate [42] (Scheme 5 and pathway a in Scheme 4). The protected β-hydroxy sulfone was converted to the corresponding vinyl sulfone under basic conditions. When SmI_2 was used as the reductant, no deuterated alkene was yielded, and the reductive cleavage of C—S was proposed [43] (Scheme 5 and pathway b in Scheme 4). For some β-hydroxy sulfones protected by different acyl groups exhibited different stereoselectivity and efficiency in 1,2-reductive elimination, a mechanism involving the reductive cleavage of C—O bonds for the benzoyl substituted substrates was proposed [30,44] (pathway c in Scheme 4). When unprotected β-hydroxy sulfone (R = H) was treated with Na(Hg), deprotonation of partial hydroxyl groups was unavoidable, possible retroaddition of the generating alkoxide can lead to the decreasing of yield (pathway d in Scheme 4).

When the fluoroalkene was choosen as the target molecule, it can be disconnected into a sulfone moiety and carbonyl moiety with two possible strategies in retrosynthetic analysis (Scheme 6). One strategy is the reaction between a fluorinated sulfone and a carbonyl compound (path a), and the other is the reaction between a sulfone and an acyl fluoride (path b). Only the first strategy (the reaction between fluorinated sulfones and carbonyl compounds to give fluoroalkenes) is discussed in this review, owing to the fact that the second strategy (the reaction between acyl fluoride and carbonyl compound) has never been reported.

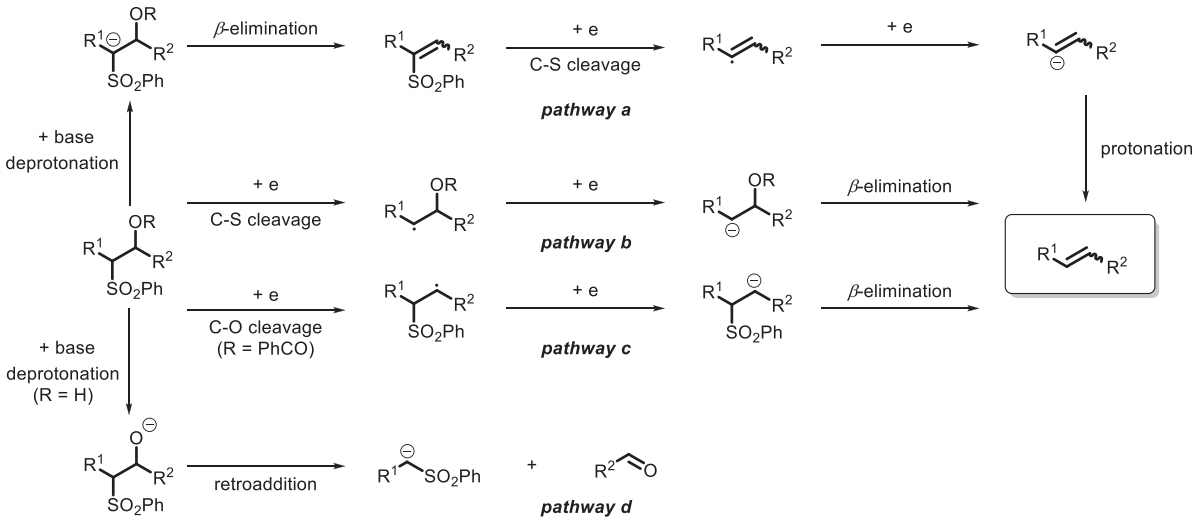
In Julia reaction, the incorporation of fluorine atom(s) at the α-carbon of sulfone often results in reactivity change of the sulfone compound. The fluorine substituent at the carbanion center influences the nucleophilicity of the sulfone anion. Monofluorinated sulfone behaves similarly to the non-fluorinated counterpart except in some special cases. However, the nucleophilicity of (phenylsulfonyl)difluoromethyl anion decreases dramatically comparing to its non-fluorinated or monofluorinated counterparts in the ring-opening reactions of epoxides. The negative role of fluorine substitution in nucleophilic fluoroalkylation is called “negative fluorine effect” (NFE) [45]. Substitution of fluorine atom at negative charged carbons can increase the “hardness” and decrease the stability of the carbanions. The instability may derived from the facile α-elimination occurs at the (phenylsulfonyl) difluoromethyl anion, since difluorocarbene and benzenesulfinate anion were detected when difluoromethyl phenyl sulfone was treated with base [46].

2.2. Synthesis of monofluoroalkenes via Julia reaction

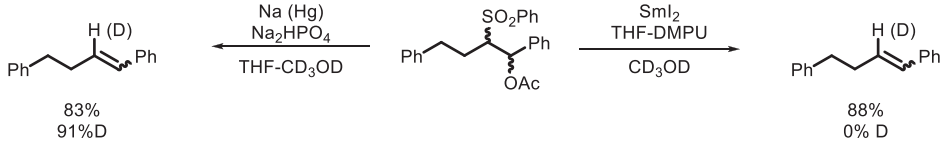
Only sporadic cases of the synthesis of monofluoroalkenes



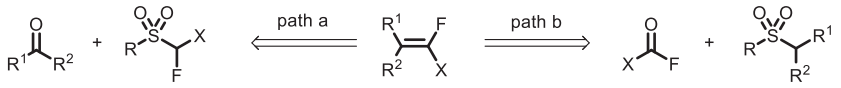
Scheme 3. Possible reaction between anion of sulfone and carbonyl compound.



Scheme 4. Possible transformations in 1,2-reductive elimination step.



Scheme 5. 1,2-reductive elimination with different reductants.



Scheme 6. Retrosynthetic analysis for the preparation of a fluoroalkene.

through Julia reaction have been reported. Both fluoromethyl phenyl sulfones and the corresponding *N*-methyl fluoromethyl phenyl sulfoximines are good monofluoroolefination reagents. The addition of the anion of fluoromethyl phenyl sulfone to the carbonyl compounds exhibits high efficiency. The reductive 1,2-elimination of the β-hydroxy sulfones or their derivatives may suffer from unexpected desulfonylation, and a result, the alkene products are obtained as a mixture of *Z*/*E* isomers in low yields.

2.2.1. Reactions with $PhSO_2CH_2F$ reagent

The fluoromethyl phenyl sulfone (**1**) and its monoalkylated derivatives could be employed in the Julia reaction. **1** is a commercially available reagent, and it could also be easily prepared in laboratory on a large scale. The treatment of the sulfone reagent with *n*-BuLi at −78 °C affords the α-sulfonyl anion. This α-sulfonyl anion could add to a carbonyl compound and give a β-hydroxy sulfone as a mixture of stereoisomers. There are many conditions available for the reductive 1,2-elimination of the β-hydroxy sulfone, but some are ineffective in specific cases. In the synthesis of (10*Z*)- and (10*E*)-19-fluoro-1α,25-dihydroxyvitamin D3 [47], β-hydroxy sulfone **2** could not be transferred to the desired alkene product **3** after the common used mesylation-elimination sequence. When **2** is submitted to 10% Na−Hg, 32% yield of alkene product **3** and 56% yield of desulfonylated side product **4** are produced (Scheme 7).

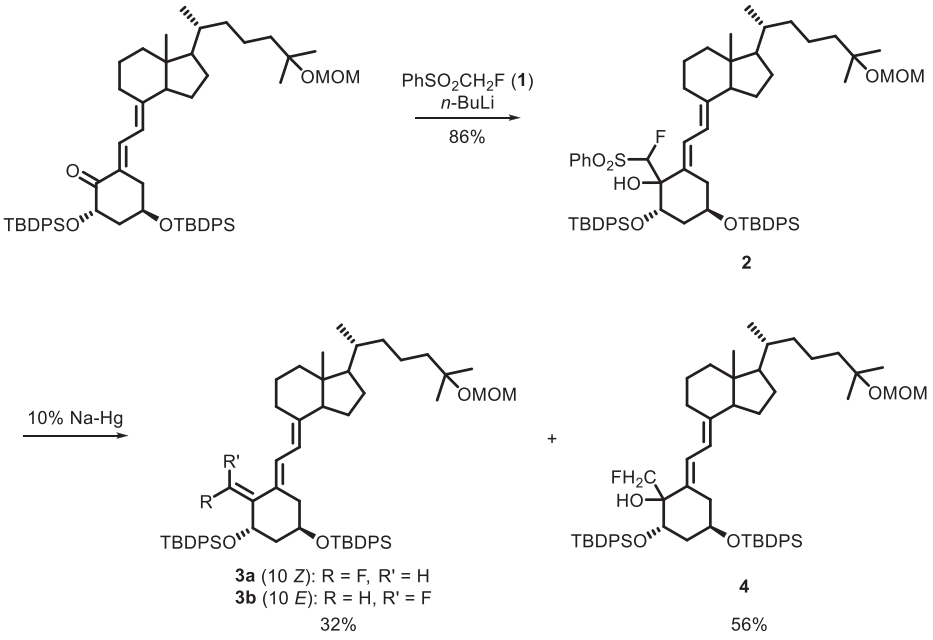
For the synthesis of γ-fluoro-β, γ-unsaturated acids [48], two derivatives of β-hydroxy sulfone, vicinal acetyl- and benzoyl sulfones (7**a** and **7b**), which remained intact in the presence of SmI_2, could be converted into the desired alkene products **8** when treated with Na−Hg amalgam (Table 1). In both examples above, the *Z*/*E* selectivities of the Julia reaction are poor.

2.2.2. Reactions with $PhS(O)(NMe)CH_2F$ reagent

α-Fluoromethyl-*N*-methyl-phenylsulfoximine (**9**) is another type of reagent for monofluoroolefination [49]. This sulfoximine reagent could be prepared in four steps (Scheme 8). **9** could be deprotonated with LDA at low temperature, and the resulting anion could add to carbonyl compounds, affording the β-hydroxy sulfoximines. In the presence of Al−Hg amalgam, the β-hydroxy sulfoximines could afford fluoroalkene products (Table 2), while the desulfonylated products are obtained when Al−Hg is replaced by Na−Hg.

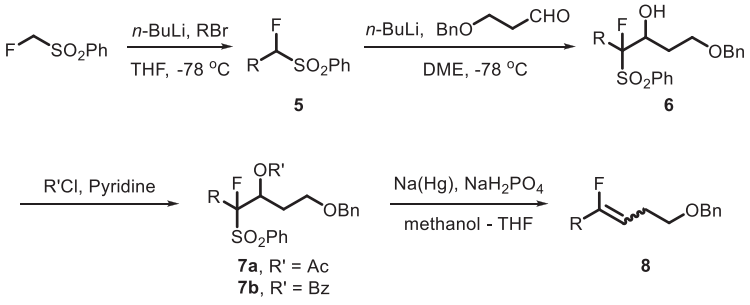
2.3. Synthesis of gem-difluoroalkenes via Julia reaction

Similar to the synthesis of monofluoro alkenes, only few reports on the synthesis of difluoroalkenes through Julia reaction have been reported. Difluoromethyl phenyl sulfone (**12**) and bromodifluoromethyl phenyl sulfone (**13**) are employed to the Julia reaction to afford the difluoroalkenes. These two sulfones generate (phenylsulfonyl)difluoromethyl anion in different ways. The reaction to produce difluoroalkenes is different from that producing monofluoroalkenes, since the poor stability of (phenylsulfonyl)difluoromethyl anion requires the Barbier-type of one-pot reaction conditions. The β-hydroxy sulfones generated from addition



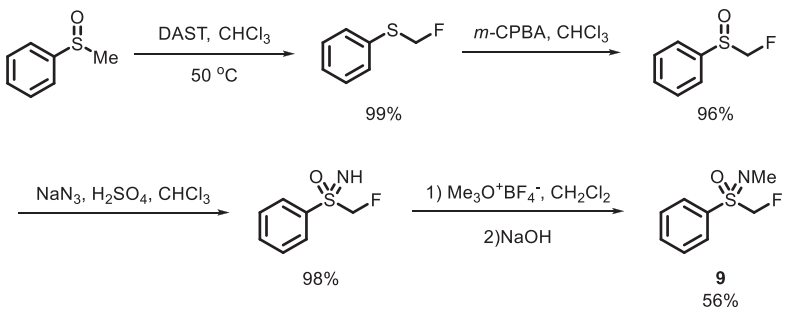
Scheme 7. Julia olefination in the synthesis of (10*Z*)- and (10*E*)-19-fluoro-1α,25-dihydroxyvitamin D3.

Table 1
Synthesis of γ-fluoro-β, γ-unsaturated acids via Julia reaction.



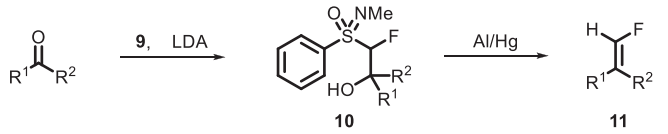
Entry	R	R′	5 (%)	6 (%)	7 (%)	8 (%)	Ratio (*E*:*Z*)	Ref
1	*n*-C_4H_9	Ac	78	70	74	80	1:3	[48]
2	*n*-C_4H_9	Bz	78	70	54	43	1:3	[48]
3	*n*-C_8H_{17}	Ac	74	83	74	77	1:2	[48]
4	*n*-$C_{13}H_{27}$	Ac	70		83[a]	86	1:2	[48]
5	*n*-$C_{15}H_{31}$	Ac	88		34[a]	46	1:2.4	[48]

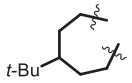
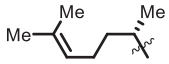
[a] Reactions were quenched by Ac_2O in one-pot.



Scheme 8. Preparation of PhS(O) (NMe)CH_2F.

Table 2
Julia monofluoroolefination with PhS(O) (NMe)CH_2F reagent.



Entry	R^1	R^2	10 (%)	11 (%)	Ref
1	*p*-$MeOC_6H_4$	H	79	61[a]	[49]
2			95	68	[49]
3		H	83	91[a]	[49]
4	$PhCH_2CH_2$	Me	91	76[a]	[49]
5	Ph	Ph	86	40	[49]

[a] 1:1 mixture of *E*:*Z* isomers.

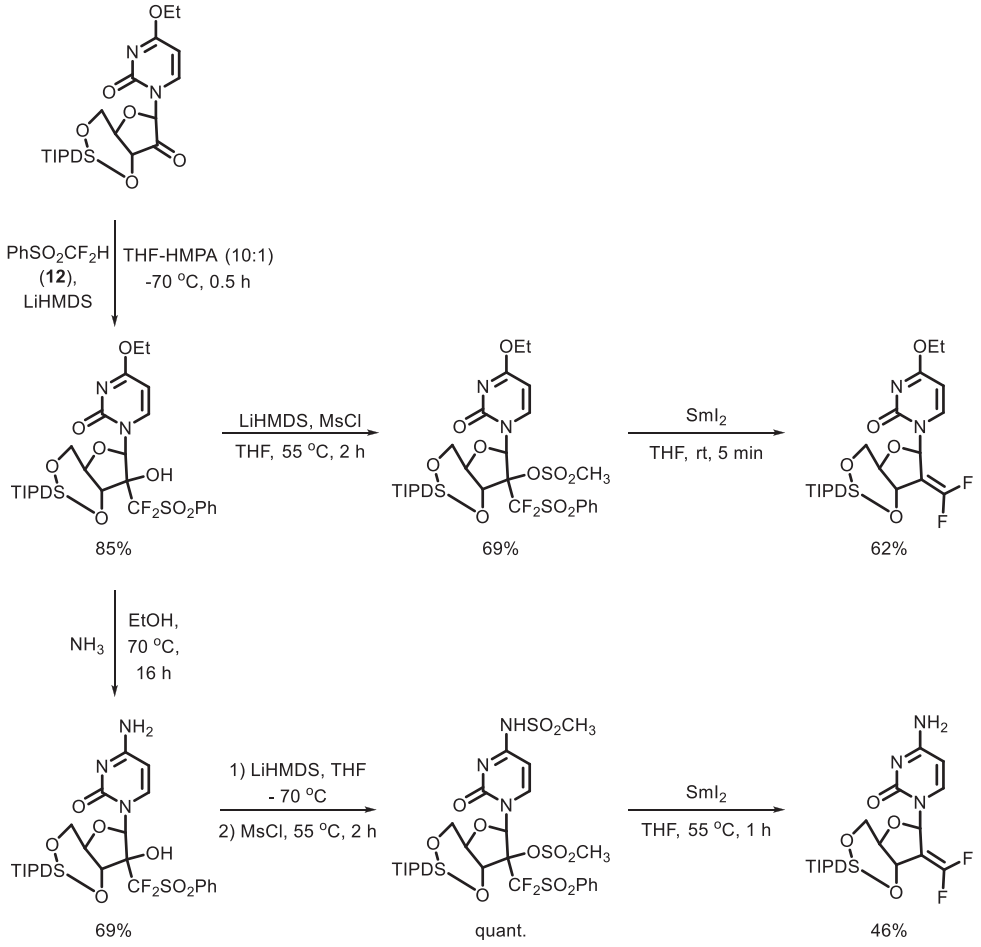
reaction should be transferred to mesylate before reductive 1,2-elimination, because the direct reduction of the β-hydroxy sulfones is prone to give the desulfonylated CF_2H-containing products instead of the desired alkenes.

2.3.1. Reactions with $PhSO_2CF_2H$ reagent

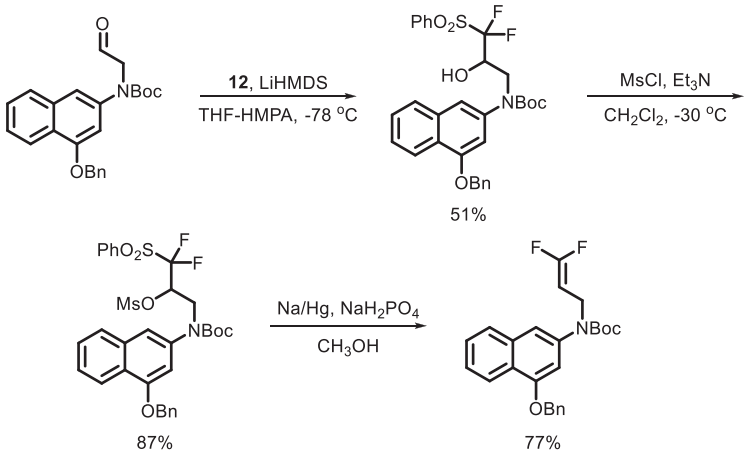
Difluoromethyl phenyl sulfone (**12**) is commercially available and could be prepared on a large scale in laboratory. In 1992, McCarthy reported a procedure [50] to convert ketones into difluoroalkenes using **12** (Scheme 9). To a solution of **12** and a ketone, LiHMDS was added to deprotonate the sulfone. The resulting (phenylsulfonyl)difluoromethyl anion was added to the ketone, affording the β-hydroxy sulfone in good yield. The β-hydroxy sulfone was mesylated and then reducted to form the difluoroalkene product by 2 equivalent of SmI_2. **12** was used to introduce a difluoromethylene in Boger's synthesis of 9,9-difluoro-1,2,9,9a-tetrahydrocyclopropa [*c*]benzo [*e*]indol-4-one (Scheme 10). The addition step is less efficient with enolizable aldehydes, and the treatment of the β-mesylate sulfone or the β-tosylate sulfone with Na—Hg afforded the product [51]. In the reductive 1,2-elimination step, SmI_2, which was used in the McCarthy's procedure, is inefficient in Boger's synthesis [51].

2.3.2. Reactions with $PhSO_2CF_2Br$ reagent

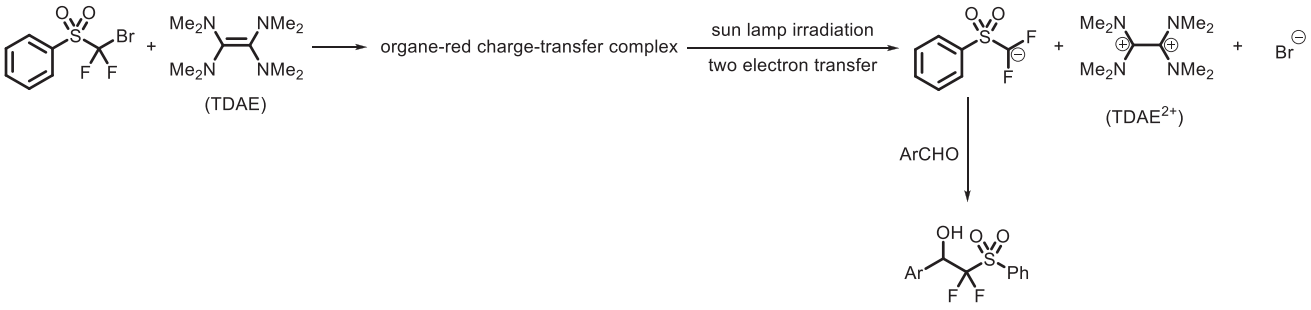
Fluoroalkyl halides are more prone to accept an electron from a reductant to yield a fluoroalkyl radical than common alkyl halide, and the fluoroalkyl radical could be further reducted to give a fluoroalkyl anion. Bromodifluoromethyl phenyl sulfone (**13**) could be used as a precursor of (phenylsulfonyl)difluoromethyl anion, in the presence of a reductant such as tetrakis (dimethylamino)ethylene (TDAE) and under the irradiation of a light source [52]. An orange-red charge-transfer complex was generated from TDAE and



Scheme 9. Synthesis of 2′-deoxy-2′-difluoromethylene nucleosides via Julia-type difluoroolefination.



Scheme 10. Synthesis of 9,9-difluoro-1,2,9,9a-tetrahydrocyclopropa [*c*]benzo [*e*]indol-4-one via Julia-type difluoroolefination.



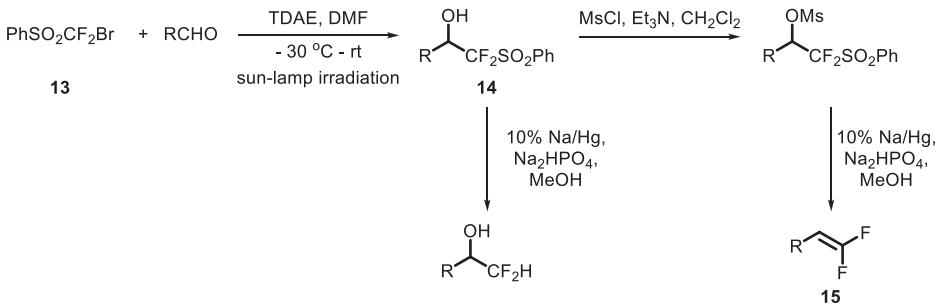
Scheme 11. Effect of TDAE in the addition of $PhSO_2CF_2Br$ to aldehydes.

$PhSO_2CF_2Br$. After the irradiation from sun lamp, the complex can release a bromide anion, $TDAE^{2+}$ cation and (phenylsulfonyl) difluoromethyl anion. This in situ generated (phenylsulfonyl) difluoromethyl anion could add to the aldehyde and give a β-hydroxy sulfone (Scheme 11). The conversion of the β-hydroxy sulfone to the difluoroalkene could be accomplished after the mesylation and reduction 1,2-elimination by Na−Hg amalgam (Table 3).

3. Synthesis of fluoroalkenes via Julia-Kocienski reaction

When phenyl sulfones are replaced with heteroaryl sulfones in Julia reaction, the reaction proceeds in a different pathway and is often called Julia-Kocienski reaction. This reaction was developed by Sylvester Julia [32] and extended by Kocienski [33,34] and others. 1,3-Benzothiazol-2-yl (BT), 1-phenyl-1*H*-tetrazol-5-yl (PT) and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT) sulfones are frequently

Table 3
Julia difluoroolefination with $PhSO_2CF_2Br$ reagent.



Entry	R	14 (%)	15 (%)	Ref
1	Ph	74	60	[52]
2	$PhCH_2CH_2$	53	84	[52]
3	*p*-BrC_6H_4	55	70	[52]

employed while there are also some reports about the Julia-Kocienski reaction with 2-pyridyl (Py), pyrimidin-2-yl (Pym) and 3,5-bis(trifluoromethyl)phenyl (BTFP) sulfones [35] (Scheme 12). Different heteroaryl sulfones show different reactivities. In the nonfluorinated Julia-Kocienski reaction, the BT sulfones are prone to self-condensation [53] under the basic conditions. Tetrazol-5-yl sulfones give less self-condensation product [33,34] due to the steric effect of the substituent on the tetrazol-5-yl ring. For the 2-pyridyl sulfone, the Smiles rearrangement and fragmentation are relatively difficult which hampers its application.

3.1. General consideration

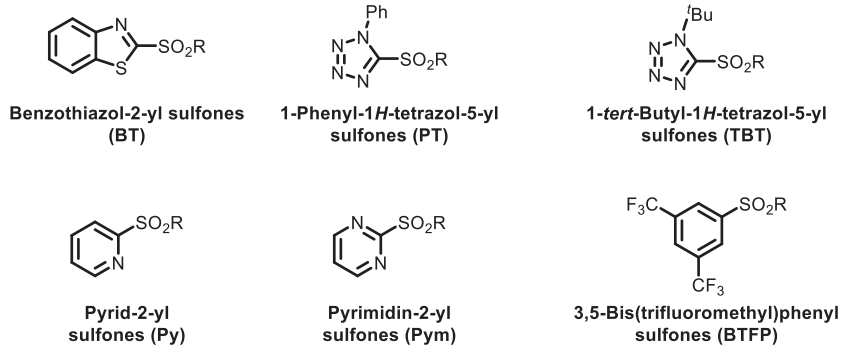
Despite the variety of heteroaryl sulfone reagents, reactions are proposed to share similar mechanism. Taking 1, 3-benzothiazol-2-yl (BT) sulfone as an example, the first step is the nucleophilic addition of the sulfone anion (**16**) to the carbonyl compound (**17**). Then a spontaneous Smiles rearrangement [54] converts the generated β-hydroxy sulfone anion (**18**) into a sulfinate salt (**20**) via a spiro cyclic intermediate (**19**) (Scheme 13). In this rearrangement, the heteroaryl transfers from S atom to the O atom. An elimination of the sulfinate salt leads to the expected alkene (**21**) with the release of SO_2 and metalated benzothiazolone (**22**).

For the Julia-Kocienski reaction with monofluoromethyl sulfones, the configuration of the double bonds is supposed to be influenced by the nature of substrates, counterions, solvents, additives as well as reaction temperatures.

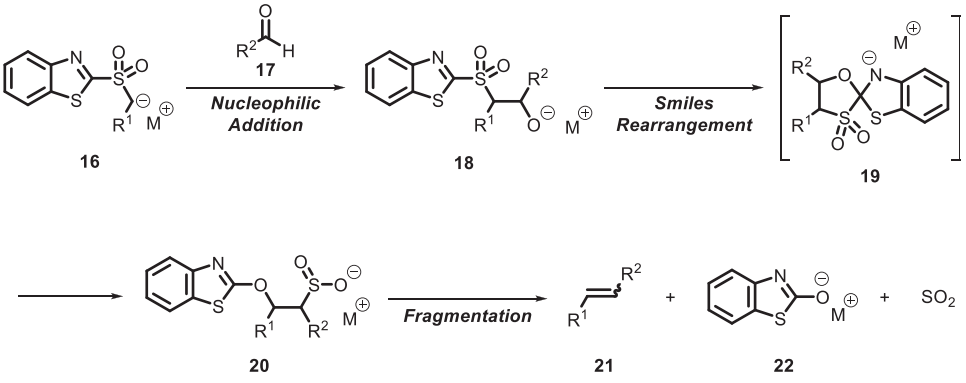
The analysis of stereochemistry of fluorinated Julia-Kocienski reaction is based on the analysis of its non-fluorinated counterpart [38]. Addition of fluorinated sulfone anion (**23**) to the carbonyl compound (illustrated by an aldehyde (**24**)) affords the *syn*-**25** and *anti*-**25**. It is known that the Smiles rearrangement is stereospecific. The *syn*-**25** will be converted to *syn*-**26** and *anti*-**25** will be converted to *anti*-**26**. The fragmentation of the resulting sulfinate salt is also generally stereospecific, which means the SO_2 and the heteroaryloxy group have an antiperiplanar alignment in the transition state and the elimination is a concerted process similar to E2 elimination (Scheme 14). Thus, the stereochemistry of the whole reaction is decided by the addition step under the simplest conditions.

Some other factors influenced by the nature of substrates could not be ignored. For the first step, the addition could be reversible for some conjugated substrates [35,55,56] according to the analysis of non-fluorinated Julia-Kocienski reactions (Scheme 15). The configuration of the sulfinate salt **26′** is decided not only by the ratio of *syn*-**25′** and *anti*-**25′,** but also by the relative rate of Smiles rearrangement of addition product **25'**. If the Smiles rearrangement is much slower than the addition process to reach the equilibrium, the configuration of sulfinate salt will be controlled by the Curtin-Hammett principle.

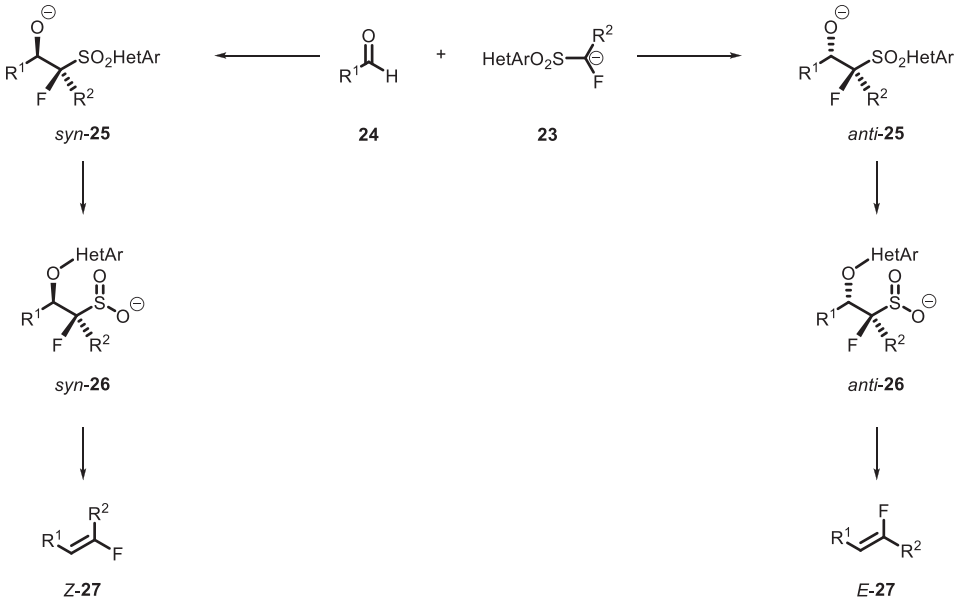
Furthermore, the fragmentation of sulfinate salts may be influenced by the specific structure of substrates. In some cases, the elimination is not stereospecific. The elimination may proceed via a zwitterion intermediate [36,53] when R^1 could stabilize a cation (Scheme 16a). The E1cb process is proposed when R^2 is a strong electron-withdrawing group [36,57,58] (Scheme 16c). Both of these two ways of elimination are not stereospecific, which is in contrast of the scenario discussed above [55] (Scheme 16b). The deviation of simplest conditions makes the prediction of stereochemistry difficult in non-fluorinated Julia-Kocienski reaction, and the



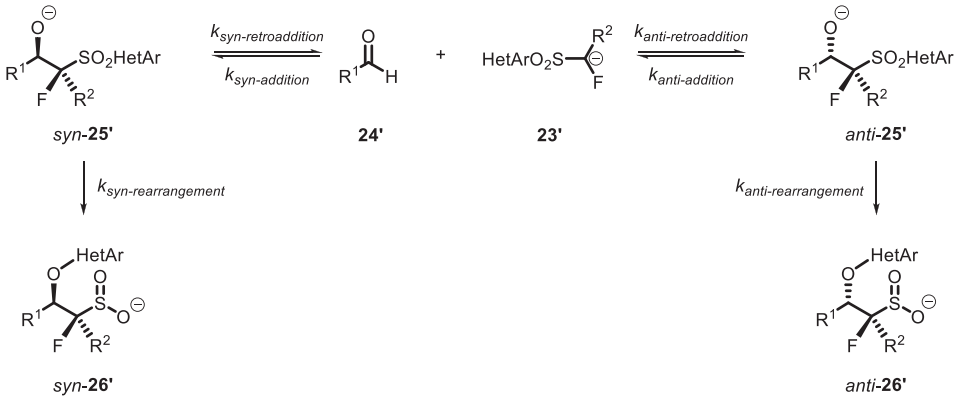
Scheme 12. Various sulfone reagent employed in Julia-Kocienski reaction.



Scheme 13. Proposed mechanism of Julia-Kocienski reaction using 1, 3-Benzothiazol-2-yl sulfone.



Scheme 14. Stereochemistry of Julia-Kocienski fluoroolefination.



Scheme 15. Impact of the first step on the stereochemistry.

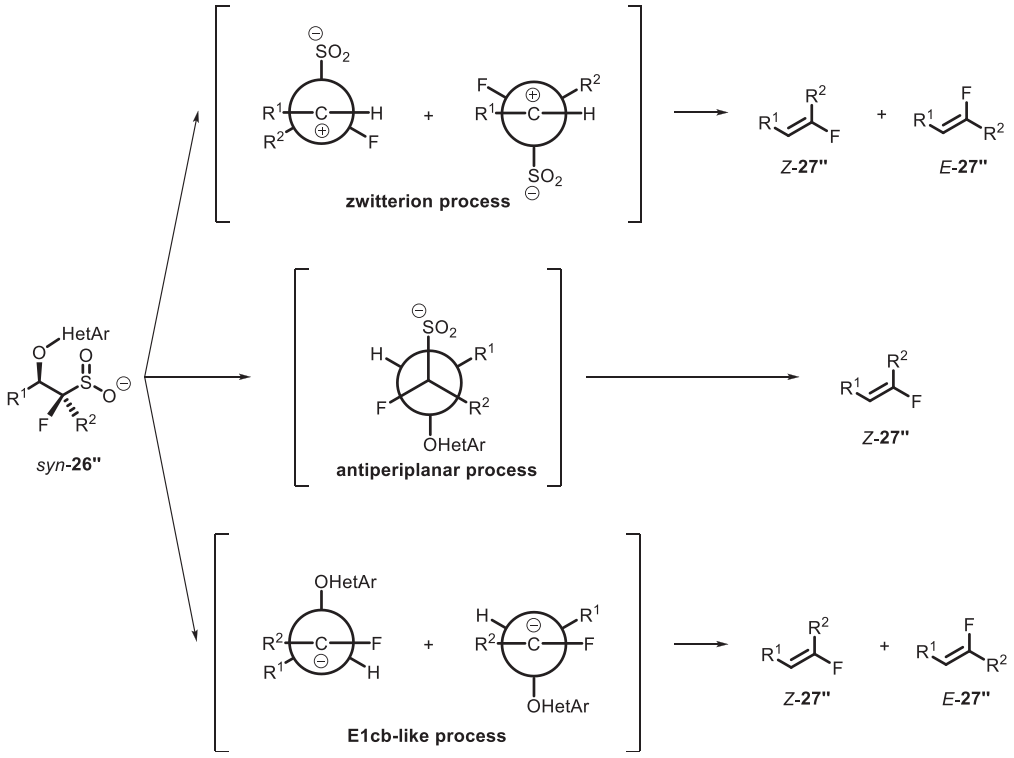
substitution of fluorine atom makes the understanding of stereochemistry even more obscure.

Comparing to the monofluoromethyl heteroaryl sulfone and difluoromethyl phenyl sulfone anions, the stabilities of difluoromethyl heteroaryl sulfone anions are lower, which indicates nucleophilic addition of the latter should be carried out under Barbier-type conditions. Until today, most reports are focused on the difluoromethyl 2-pyridyl sulfone (**28**) [59] and its derivatives. The mechanism was proposed (Scheme 17) according to the non-fluorinated Julia-Kocienski reaction.

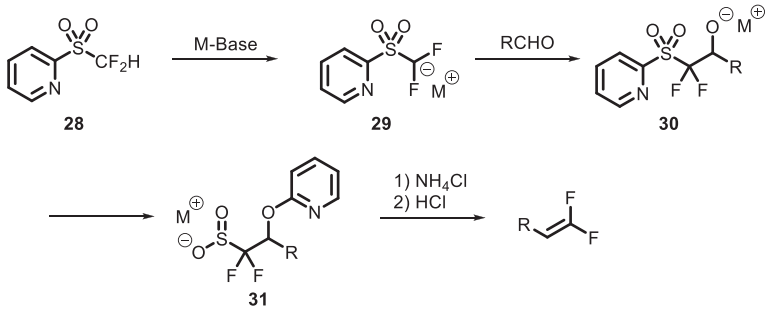
Generally, Julia-Kocienski reaction occurs in one-pot manner, while two divided steps under different conditions are required for some less reactive substrate. Considering the poor stability of **29**, the first step often needs low temperatures, unless **29** is formed in situ gradually and slowly. But for the 2-pyridyl sulfone, relatively higher temperature is required to accelerate the sluggish Smiles rearrangement. If quenched at low temperature, the addition products (**30**) are obtained instead of the expected alkenes. Many reactions adopt the gradually warming process to meet different demands of the two steps. The addition step occurs at low temperature with high efficiency and the Smiles rearrangement proceeds smoothly at high temperature. The Smiles rearrangement gives the difluorinated sulfinate salts (**31**), which is stable at the reaction temperature. The final fragmentation step will be triggered by the quenching with acids, so the Julia-Kocienski reaction always needs a work-up with hydrochloric acid except a special case in which the reaction can proceed at a rather high temperature.

To synthesize the monofluoroalkenes via Julia-Kocienski olefination, monofluoromethyl heteroaryl sulfones are needed. A wide range of substituted monofluoromethyl sulfones were prepared. The non-substituted monofluoromethyl heteroaryl sulfones (**34**) could be obtained by oxidation of the monofluoromethyl heteroaryl sulfides (**33**) which are generated from the reaction between the heteroaryl thiol (**32**) and chlorofluoromethane. The substituted monofluoromethyl heteroaryl sulfones are usually prepared through the electrophilic fluorination of the non-fluorinated sulfones (**35**) or through the modification of the non-substituted monofluoromethyl heteroaryl sulfones (Scheme 18). The specific routes to fluorinated heteroaryl sulfones will be introduced in the following part.

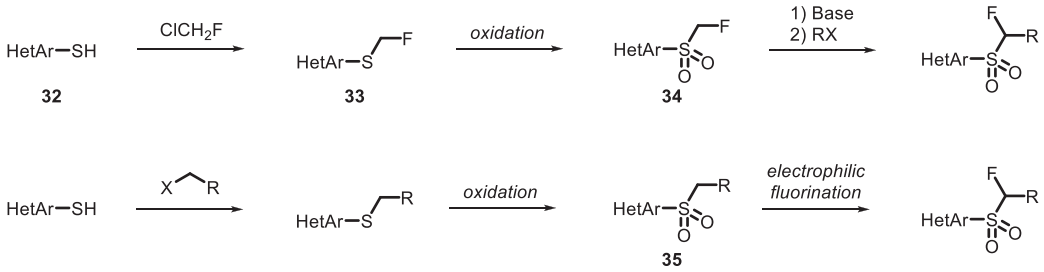
Four kinds of difluoromethyl heteroaryl sulfones were prepared on gram-scale in the original report about the gem-difluoroolefination, which was shown in Scheme 19.



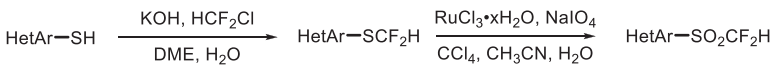
Scheme 16. Different elimination pathways.



Scheme 17. Proposed mechanism of Julia-Kocienski reaction of difluoromethyl 2-pyridylsulfone.



Scheme 18. General protocols for preparation of monofluoromethyl heteroaryl sulfones.



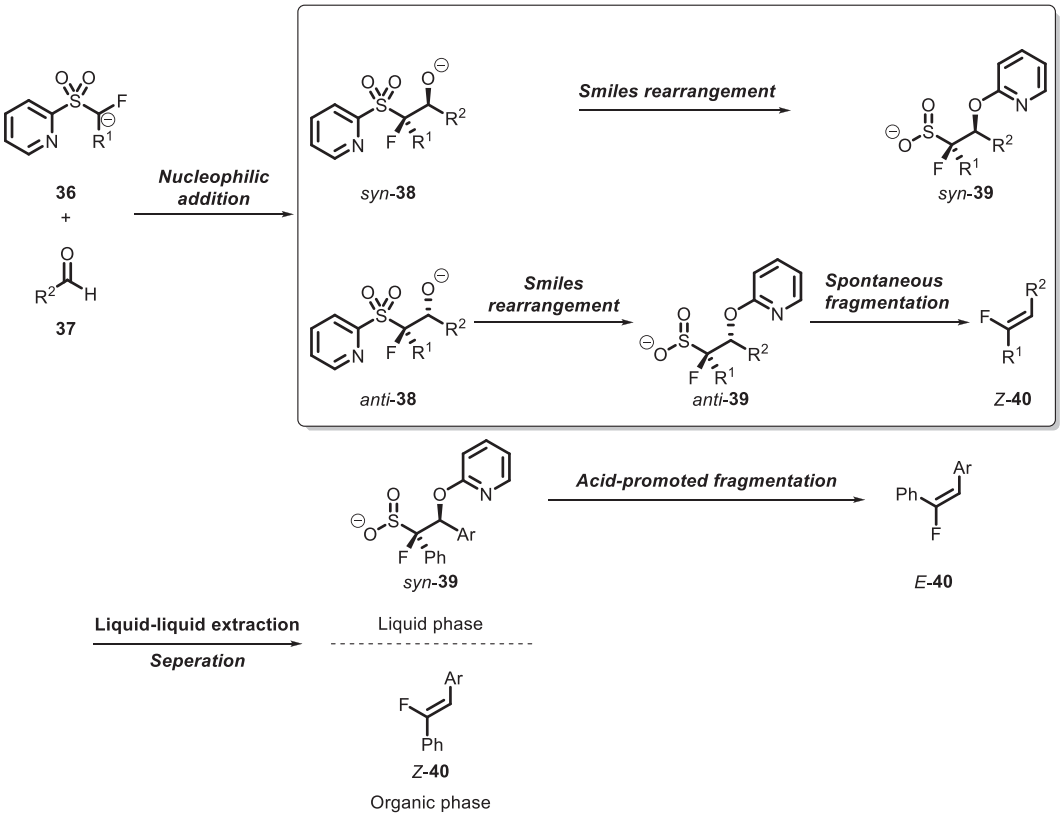
Scheme 19. General protocols for preparation of difluoromethyl heteroaryl sulfones.

3.2. Synthesis of monofluoroalkenes via Julia-Kocienski Reaction

3.2.1. Reactions with 2-pyridyl sulfones and their derivatives

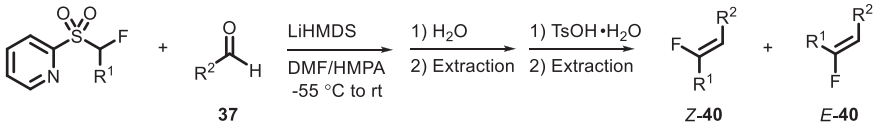
3.2.1.1. Reactions with substituted monofluoromethyl 2-pyridyl sulfones. In 2015, the Hu group reported a Julia-Kocienski reaction of aryl substituted monofluoromethyl 2-pyridyl sulfone and carbonyl compounds [60] (Scheme 20). Through the kinetic resolution in the fragmentation step of the Julia-Kocienski reaction, *Z*- and *E*-monofluoroalkene could be separated by liquid-liquid extraction. Deprotonation of aryl substituted monofluoromethyl 2-pyridyl sulfone by LiHMDS at −55 °C generated the corresponding anion **36** which adds to the aldehyde **37** to afford alcoholate **38** as a mixture of stereoisomer. With the increasing of the temperature, Smiles rearrangement occurred and gave the sulfinate salt *syn*-**39** and *anti*-**39**. *Anti*-**39** was unstable and collapsed to the final product *Z*-**40** while the *syn*-**39** remained in the reaction. *Z*-**40** was separated by extraction of the organic phase and acidification of the aqueous phase transferred *syn*-**39** into the monofluoroalkene *E*-**40**. The total yields of **40** are moderate to good (Table 4).

3.2.1.2. Reactions with monofluoromethyl 2-pyridyl sulfoximine. The Julia-Kocienski reactions between monofluoromethyl 2-pyridyl sulfoximine and aromatic ketones give highly *E*-selective monofluoroalkenes [61]. Various aromatic ketones are successfully converted into trisubstituted monofluoroalkenes (Table 5). For the aromatic aldehyde, the reaction should be quenched at lower temperature than standard procedure and the product is obtained in lower yield. The high *E*-selectivity is proposed to result from the



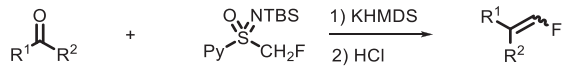
Scheme 20. Mechanism of the kinetic resolution.

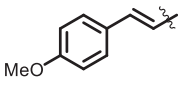
Table 4
Reactions with substituted monofluoromethyl 2-pyridyl sulfones.



Entry	R^1	R^2	*Z*-40 (%)	Ratio of *Z*-40 (*Z*:*E*)	*E*-40 (%)	Ratio of *E*-40 (*Z*:*E*)	Ref
1	Ph	2-naphthyl	46	>99:1	37	1:99	[60]
2	Ph	*o*-MeC_6H_4	47	99:1	27	3:97	[60]
3	Ph	*p*-$CF_3C_6H_4$	26	99:1	42	<1:99	[60]
4	Ph	Cy	53	>99:1	25	1:99	[60]
5	Ph	cinnamyl	17	93:7	45	3:97	[60]
6	Cy	2-naphthyl	45	97:3	18	3:97	[60]
7	*i*-Pr	2-naphthyl	48	97:3	24	4:96	[60]

Table 5
E-selective monofluoroalkene formation employing fluoromethyl 2-pyridyl sulfoximine.



Entry	R^1	R^2	Yield (%)	Ratio (*E*:*Z*)	Ref
1	*p*-$MeOC_6H_4$	Me	84	96:4	[61]
2	*p*-$NO_2C_6H_4$	Me	81	93:7	[61]
3	*o*-$MeOC_6H_4$	Me	83	>99:1	[61]
4	2-naphthyl	Me	86	97:3	[61]
5	Ph	*n*-Pr	86	97:3	[61]
6	Ph	*i*-Pr	78	97:3	[61]
7		Me	85	90:10	[61]
8	*t*-Bu	Me	74	93:7	[61]
9	2-Naphthyl	H	65	94:6	[61]

highly enantioselective addition step, which is supported by trapping the addition product with high diastereoselectivity at low temperature by HCl. TBS group at the nitrogen atom is conceived to exhibit excellent ability of 1,2- and 1,3-diastereocontrol.

3.2.1.3. Reactions with difluoromethyl 2-pyridyl sulfoxide. When difluoromethyl 2-pyridyl sulfoxide is used in the Julia-Kocienski reaction, monofluoroalkenes or *gem*-difluoroalkenes could be obtained under different conditions [62]. The Smiles rearrangement of α,α-difluoro-β-hydroxy sulfoxides under basic conditions leads to monofluoroalkenes via intramolecular substitution (Scheme 21).

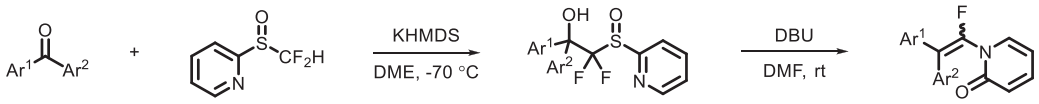
3.2.2. Reaction of pyrimidin-2-yl sulfone

The Julia-Kocienski fluoroolefination reaction with fluorinated pyrimidinyl sulfones was reported in 2014 [63]. Pyrimidin-2-yl sulfone **41** could be synthesized (as shown in Scheme 22). The condensation between this pyrimidinyl sulfone reagent **41** and aldehyde **42** could afford α-fluorine-α,β-unsaturated esters **43** with good *Z*-selectivity (Table 6).

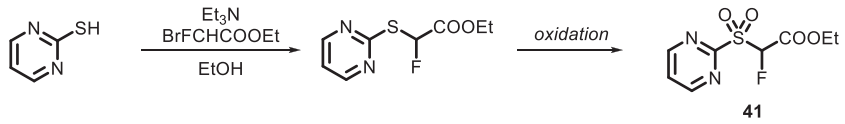
3.2.3. Reactions with 1,3-benzothiazol-2-yl monofluoromethyl sulfone and its derivatives

3.2.3.1. Reaction of 1,3-benzothiazol-2-yl monofluoromethyl sulfone. 1,3-Benzothiazol-2-yl monofluoromethyl sulfone (**44**) could be applied to the olefination of lactones through the Julia-Kocienski reaction [64]. In the presence of LiHMDS as a Brønsted base and sometimes BF_3 as a Lewis acid, the reaction between sugar-derived lactone (**45**) and **44** affords the fluorinated *exo*-glycals **46**(Table 7).

3.2.3.2. Reactions with alkyl substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfone. The reactions between a carbonyl compound and methyl substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones (**47**) are the pioneering work in the fluoro Julia-Kocienski reaction [65]. Sulfone **47** could be synthesized through a Halex reaction followed by oxidation of the resulting fluorinated sulfide. Some 1,3-benzothiazol-2-yl monofluoromethyl sulfones bearing an amino group (**48**) could be prepared by the Michael addition of amine onto vinyl sulfones (**49**) [66,67] (Scheme 23). The reaction between alkyl substituted monofluoromethyl benzothiazolyl sulfones and carbonyl compounds proceeds smoothly in the presence of strong base such as NaHMDS or *t*-BuOK. Aromatic and aliphatic



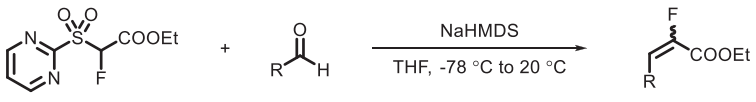
Scheme 21. Formation of monofluoroalkenes from difluoromethyl 2-pyridyl sulfoxide.



41

Scheme 22. Preparation of ethyl 2-fluoro-2-(pyrimidin-2-ylsulfonyl)acetate **41**.

Table 6
Julia-Kocienski reaction employing pyrimidine sulfone **41**.



41 **42** **43**

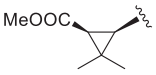
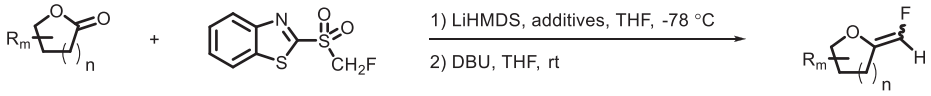
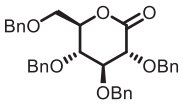
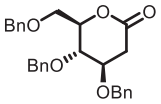
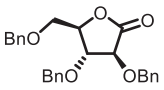
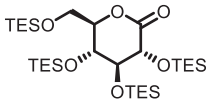
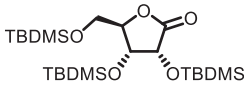
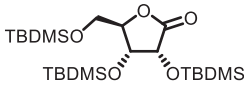
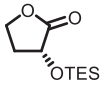
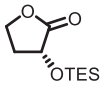
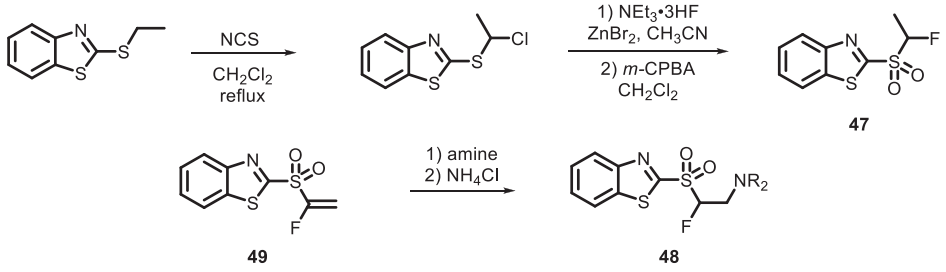
Entry	R	Yield (%)	Ratio (*Z*:*E*)	Ref
1	*p*-BrC_6H_4	72	100:0	[63]
2	2-thienyl	69	100:0	[63]
3	2-furyl	87	99:1	[63]
4	*n*-C_6H_{13}	84	100:0	[63]
5	Cy	60	99:1	[63]
6		72	95:5	[63]

Table 7
Reaction of sugar-derived lactone and fluoromethyl 1,3-benzothiazol-2-yl sulfone.



45 44 46

Entry	Lactone 45	Additives	Yield (%)	Ratio (*E*:*Z*)	Ref
1		$BF_3{\cdot}Et_2O$	85	6:4	[64]
2		$BF_3{\cdot}Et_2O$	82	3:7	[64]
3		$BF_3{\cdot}Et_2O$	77	7:3	[64]
4		$BF_3{\cdot}Et_2O$	60	6:4	[64]
5			94	8:2	[64]
6		$BF_3{\cdot}Et_2O$	46	7:3	[64]
7			43	7:3	[64]
8		$BF_3{\cdot}Et_2O$	20	4:6	[64]
9			68	5:5	[64]



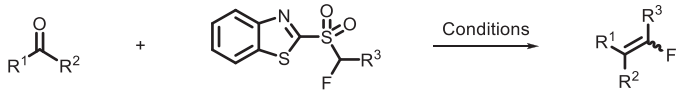
Scheme 23. Preparation of various alkyl substituted fluoromethyl 1,3-benzothiazol-2-yl monofluoromethyl sulfones.

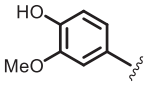
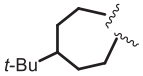
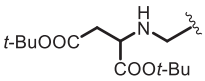
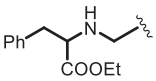
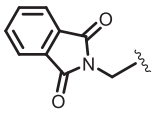
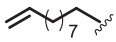
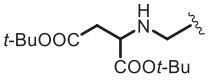
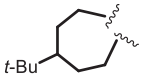
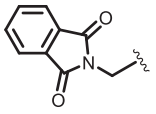
aldehydes as well as cyclohexanone are suitable partners in this reaction with moderate to good yields (Table 8).

Some derivatives of nuclei base-bearing 2-fluoroallyl group could be prepared through this method. The choice of base is influenced by specific structure of nuclei base [67]. The olefination reaction with sulfones bearing a uracil prefers NaHMDS as the base. When the nuclei base part in the sulfone is the more sensitive purine, *t*-BuOK is applied as a base for a clean reaction (Table 9).

Alkyl-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones could react with sugar-derived lactones to give fluorinated *exo*-glycals (**50**) bearing an alkyl group [64] (Table 10).

Table 8
The Julia-Kocienski reaction employing alkyl substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones.



Entry	R^1	R^2	R^3	Conditions	Yield (%)	Ratio (*Z*:*E*)	Ref
1	*p*-$O_2NC_6H_4$	H	Me	*t*-BuOK, THF, −15 °C	88	39:61	[65]
2		H	Me	*t*-BuOK, THF, −15 °C	48	51:49	[65]
3	cinnamyl	H	Me	*t*-BuOK, THF, −15 °C	55	38:62	[65]
4		H	Me	*t*-BuOK, THF, −15 °C	80	55:45	[65]
5	Ph	Ph	Me	NaHMDS, THF, −78 to −20 °C	49	–	[65]
6			Me	NaHMDS, THF, −78 to −20 °C	69	–	[65]
7	*p*-BrC_6H_4	H		NaHMDS, THF, −78 to 0 °C	72	60:40	[66]
8	*p*-BrC_6H_4	H		NaHMDS, THF, −78 to 0 °C	58	52:48	[66]
9	*p*-BrC_6H_4	H		NaHMDS, THF, −78 to 0 °C	56	90:10	[66]
10		H		NaHMDS, THF, −78 to 0 °C	75	75:25	[66]
11				NaHMDS, THF, −78 to 0 °C	63	–	[66]

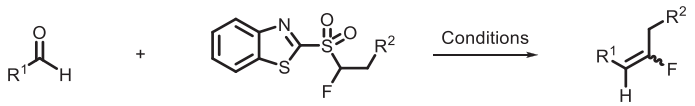
3.2.3.3. Reactions with (het)aryl-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfone. The Julia-Kocienski fluoroolefination reaction with aryl-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfone leads to the formation of aryl-substituted monofluoroalkenes [68–71]. Aryl-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfone (**51**) could be prepared by the electrophilic fluorination (Scheme 24). Generally, strong base such as LiHMDS at 0 °C is proved to be optimal reaction conditions for the aldehydes and ketones (Table 11). The fluoroolefination of paraformaldehyde could smoothly proceed in the presence of DBU or Cs_2CO_3 at room temperature [70]. The reaction between aromatic aldehydes and aryl-substituted monofluoromethyl benzothiozolyl sulfones afford monofluoroalkenes bearing two aryl groups, and these products may give the fluorinated polycyclic aromatics via oxidative photocyclization [71].

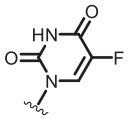
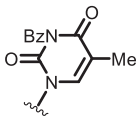
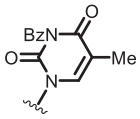
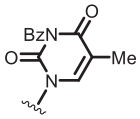
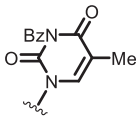
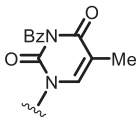
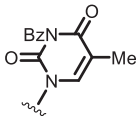
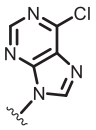
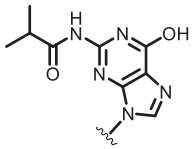
The Julia-Kocienski fluoroolefination reactions of triazolyl-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones introduce a triazolyl group into the target fluoroalkenes [72,73]. The alkyne moiety could be converted into triazole moiety with an azide via a Cu-catalyzed azide-alkyne cycloaddition (Scheme 25). The olefination process of triazolyl-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones (**52**) could be performed in the presence of DBU at room temperature or in the presence of LiHMDS at −78 °C or 0 °C (Table 12).

3.2.3.4. Reactions with alkynyl-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfone. The alkynyl-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfone (**53**) could be prepared by electrophilic fluorination. The Julia-Kocienski reaction between **53** and aldehydes leads to alkynyl-substituted monofluoroalkenes [74] (Table 13). Further conversion of the target products via Sonogashira reaction or hydrogenation, could give internal fluorinated enynes or isomeric dienes.

3.2.3.5. Reactions with 1,3-benzothiazol-2-yl monofluoromethyl sulfone bearing an electron-withdrawing group. The Julia-Kocienski fluoroolefination reactions with ester-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones are well documented [75–77] (Table 14). Other electron-withdrawing groups, such as cyano, acyl, amide and sulfonyl groups, have also been introduced to the sulfone reagents and applied to the fluoroolefination process [78–81] (Table 15). There is no standard procedure

Table 9
The reaction of nuclei base-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones.



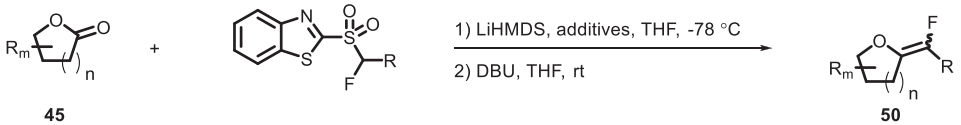
Entry	R^1	R^2	Conditions	Yield (%)	Ratio (*E*:*Z*)	Ref
1	Ph		NaHMDS, THF, −78 to −20 °C	69	47:53	[67]
2	Ph		NaHMDS, THF, −78 to −20 °C	87	5:95	[67]
3	*p*-$MeOC_6H_4$		NaHMDS, THF, −78 to −20 °C	79	4:96	[67]
4	*p*-$O_2NC_6H_4$		NaHMDS, THF, −78 to −20 °C	63	32:68	[67]
5	Cy		NaHMDS, THF, −78 to −20 °C	83	28:72	[67]
6	Me		NaHMDS, THF, −78 to −20 °C	88	41:59	[67]
7	*n*-C_6H_{13}		NaHMDS, THF, −78 to −20 °C	61	29:71	[67]
8	Ph		*t*-BuOK, THF, −17 °C to rt	61	55:45	[67]
9	Ph		*t*-BuOK, THF, −17 °C to rt	55	2:3	[67]

to achieve good *Z*/*E* selectivity for most substrates and sulfone reagents; however, for some specific reactants [80], high *Z*/*E* selectivities are accomplished (Table 16). At different reaction temperatures and with different reaction times, either strong base or weak base could promote the reaction.

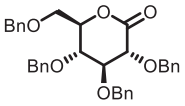
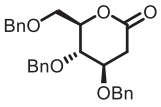
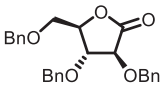
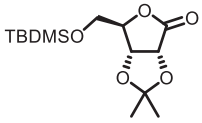
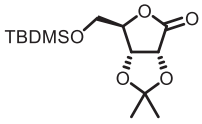
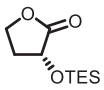
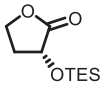
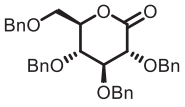
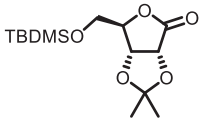
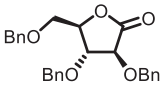
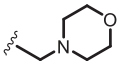
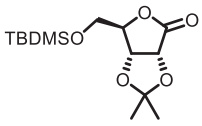
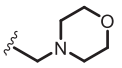
3.2.3.6. Special cases. The classical Julia-Kocienski reaction occurs via a β-hydroxy sulfone, which is resulted from the addition of α-carbanion of sulfone to carbonyl compound. Besides this process, β-hydroxy sulfone could be generated through an addition of nucleophile to the β-keto sulfone. In 2011, Jørgenson reported a process for the synthesis of optically active monofluoroalkenes with α-stereocenter [82] (Scheme 26). The Michael addition, catalyzed by an organic catalyst (**57**), of α-fluoro-β-keto 1,3-benzothiazol-2-yl sulfone (**54**) to α,β-unsaturated ketone (**55**) could lead to a new α-fluoro-β-keto-1,3-benzothiazol-2-yl sulfone (**56**). This new α-fluoro-β-keto-1,3-benzothiazol-2-yl sulfone **56** could be reduced under different conditions to yield *E*-selective or *Z*-selective monofluoroalkenes (**58**).

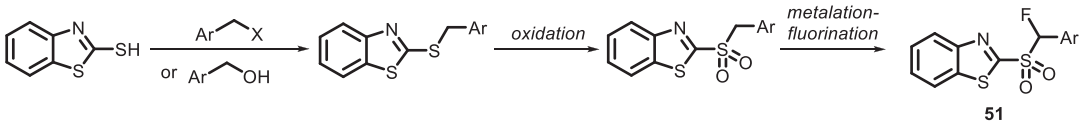
When this new α-fluoro-β-keto 1,3-benzothiazol-2-yl sulfone

Table 10
The reaction between alkyl-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones and sugar-derived lactones.



45 50

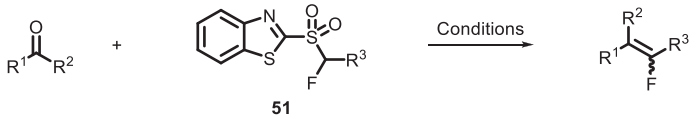
Entry	Lactone 45	Additives	R	Yield (%)	Ratio (*E*:*Z*)	Ref
1		$BF_3{\cdot}Et_2O$	Me	85	4:6	[64]
2		$BF_3{\cdot}Et_2O$	Me	58	7:3	[64]
3		$BF_3{\cdot}Et_2O$	Me	70	3:7	[64]
4		$BF_3{\cdot}Et_2O$	Me	83	3:7	[64]
5			Me	40	3:7	[64]
6		$BF_3{\cdot}Et_2O$	Me	29	2:8	[64]
7			Me	68	3:7	[64]
8		$BF_3{\cdot}Et_2O$	n-$C_{12}H_{25}$	53	3:7	[64]
9		$BF_3{\cdot}Et_2O$	n-$C_{12}H_{25}$	83	2:8	[64]
10		$BF_3{\cdot}Et_2O$		61	2:8	[64]
11		$BF_3{\cdot}Et_2O$		91	2:8	[64]



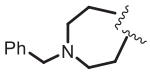
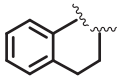
51

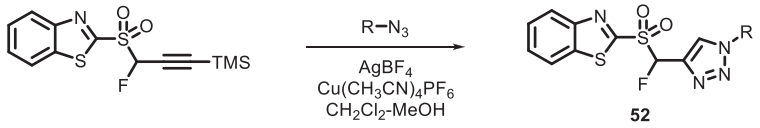
Scheme 24. Preparation of aryl-substituted fluoromethyl 1,3-benzothiazol-2-yl monofluoromethyl sulfones.

Table 11
Olefination employing aryl substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones.



51

Entry	R^1	R^2	R^3	Conditions	Yield (%)	Ratio (*E*:*Z*)	Ref
1		H	*o*-BrC_6H_4	LiHMDS, THF, 0 °C	57	100:0	[68]
2	*o*-$CF_3C_6H_4$	H	*p*-ClC_6H_4	LiHMDS, THF, 0 °C	65	0.4:1	[68]
3	2-naphthyl	H	Ph	LiHMDS, THF, 0 °C	quant	2.3:1	[69]
4	2-naphthyl	H	2-naphthyl	LiHMDS, THF, 0 °C	98	3.6:1	[69]
5	2-naphthyl	H	2-thienyl	LiHMDS, THF, 0 °C	quant	2.7:1	[69]
6	cinnamyl	H	Ph	LiHMDS, THF, 0 °C	90	1:1	[69]
7	*n*-C_7H_{15}	H	Ph	LiHMDS, THF, 0 °C	quant	1.9:1	[69]
8			Ph	LiHMDS, THF, 0 °C	quant	–	[69]
9			Ph	LiHMDS, THF, 0 °C	91	15.7:1	[69]
10	paraformaldehyde		Ph	DBU, CH_2Cl_2, rt	71	–	[70]
11	paraformaldehyde		Ph	Cs_2CO_3, CH_2Cl_2, rt	86	–	[70]
12	1-naphthyl	H	Ph	LiHMDS, THF, 0 °C to rt	99	2.8:1	[71]



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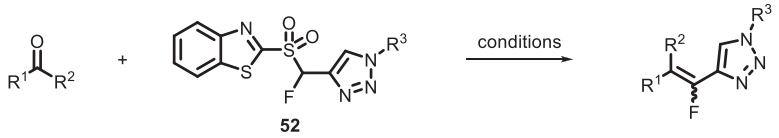
Scheme 25. Preparation of triazolyl-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones.

Table 12
Julia-Kocienski fluoroolefination reaction with triazolyl-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones.



52

Entry	R^1	R^2	R^3	Conditions	Yield (%)	Ratio (*E*:*Z*)	Ref
1	*p*-$MeOC_6H_4$	H	*p*-$MeOC_6H_4$	DBU, THF, reflux	80	81:19	[73]
2	*p*-$MeOC_6H_4$	H	*p*-$MeOC_6H_4$	LiHMDS, DMF, DMPU, −78 °C	72	14:86	[72]
3	*p*-$CF_3C_6H_4$	H	*p*-$O_2NC_6H_4$	DBU, THF, reflux	87	60:40	[73]
4	*p*-$CF_3C_6H_4$	H	*p*-$O_2NC_6H_4$	LiHMDS, DMF, DMPU, −78 °C	73	15:85	[72]
5	*n*-C_7H_{15}	H	$PhCH_2CH_2CH_2$	DBU, THF, reflux	56	61:39	[73]
6	*n*-C_7H_{15}	H	$PhCH_2CH_2CH_2$	LiHMDS, DMF, DMPU, −78 °C	63	36:64	[72]
7	3-pentyl	H	*p*-$MeOC_6H_4$	DBU, THF, reflux	47	54:46	[73]
8	3-pentyl	H	*p*-$MeOC_6H_4$	LiHMDS, DMF, DMPU, −78 °C	60	15:85	[72]
9	Ph	Me	*p*-$MeOC_6H_4$	LiHMDS, THF, 0 °C	64	28:72	[73]
10	Ph	Me	$PhCH_2CH_2CH_2$	LiHMDS, THF, 0 °C	77	20:80	[73]

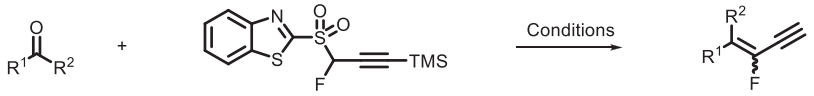
56 is treated with base, the generated enolate could be converted to a bicyclic monofluoroalkene (**59**) (Scheme 27). When the α-fluoro-β-keto 1,3-benzothiazol-2-yl sulfone **54** adds to proper imine, followed by reduction, 2-fluoroallyl amine (**60**) is afforded (Scheme 28). When chiral phase-transfer catalyst is used, optically active 2-fluoroallyl amine could also be prepared.

Various kinds of nucleophiles could add to the α-fluoro-β-keto 1,3-benzothiazol-2-yl sulfone (**61**) and the spontaneous Smiles rearrangement take place to give the expected monofluoroalkenes [83] (**62**). When enolate is used as nucleophile, only *E*-monofluoroalkene is generated (Table 17).

3.2.4. Reactions with 1-phenyl-1*H*-tetrazol-5-yl sulfones

The Julia-Kocienski reaction with fluorinated 1*H*-tetrazol-5-yl sulfone is rare comparing to the wide application of 1-phenyl-1*H*-tetrazol-5-yl and 1-*tert*-butyl-1*H*-tetrazol-5-yl sulfones in the non-

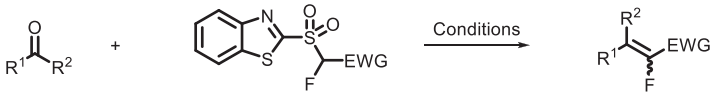
Table 13
Olefination employing alkynyl substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones.



53

Entry	R^1	R^2	Conditions	Yield (%)	Ratio (*E*:*Z*)	Ref
1	*p*-$MeOC_6H_4$	H	DBU, CH_2Cl_2, -55 °C	92	81:19	[74]
2	*p*-$MeOC_6H_4$	H	LiHMDS, THF, −78 °C	97	95:5	[74]
3	*o*-$MeOC_6H_4$	H	DBU, CH_2Cl_2, -55 °C	92	78:22	[74]
4	*o*-$MeOC_6H_4$	H	LiHMDS, THF, −78 °C	87	90:10	[74]
5	*o*-$O_2NC_6H_4$	H	DBU, CH_2Cl_2, -55 °C	59	51:49	[74]
6	*o*-$O_2NC_6H_4$	H	LiHMDS, THF, −78 °C	81	72:28	[74]
7	cinnamyl	H	DBU, CH_2Cl_2, -55 °C	95	72:28	[74]
8	cinnamyl	H	LiHMDS, THF, −78 °C	96	80:20	[74]
9	$PhCH_2CH_2$	H	DBU, CH_2Cl_2, -55 °C	54	80:20	[74]
10	$PhCH_2CH_2$	H	LiHMDS, THF, −78 °C	63	70:30	[74]
11	Ph	Me	LiHMDS, THF, −78 °C	88	100:0	[74]

Table 14
The fluorolefination employing ester-substituted 1,3-benzothiazol-2-yl monofluoromethyl sulfones.



Entry	R^1	R^2	EWG	Conditions	Yield (%)	Ratio (*Z*:*E*)	Ref
1	*p*-$O_2NC_6H_4$	H	COOEt	NaHMDS, THF, 20 °C	85	84:16	[75]
2	*p*-$O_2NC_6H_4$	H	COOEt	DBU, THF, −78 °C to −20 °C	72	12:88	[75]
3	*p*-$O_2NC_6H_4$	H	COOEt	DBU, $MgBr_2$, THF, 20 °C	66	94:6	[75]
4	*m*-$MeOC_6H_4$	H	COOEt	NaHMDS, THF, 20 °C	75	85:15	[75]
5	Cy	H	COOEt	NaHMDS, THF, 20 °C	56	65:35	[75]
6	Cy	H	COOEt	DBU, THF, −78 °C to −20 °C	86	28:72	[75]
7	Cy	H	COOEt	DBU, $MgBr_2$, THF, 20 °C	77	90:10	[75]
8			COOEt	DBU, THF, rt	57	–	[76]
9	2-naphthyl	H	COO*t*-Bu	DBU, CH_2Cl_2, rt	93	23:77	[77]
10	*p*-$O_2NC_6H_4$	H	COO*t*-Bu	DBU, CH_2Cl_2, rt	84	28:72	[77]
11	*m*-$MeOC_6H_4$	H	COO*t*-Bu	DBU, CH_2Cl_2, rt	87	17:83	[77]
12	cinnamyl	H	COO*t*-Bu	DBU, CH_2Cl_2, rt	93	24:76	[77]
13	3-pentyl	H	COO*t*-Bu	DBU, CH_2Cl_2, rt	77	36:64	[77]
14	*n*-C_7H_{15}	H	COO*t*-Bu	DBU, CH_2Cl_2, rt	82	29:71	[77]

fluorinated Julia-Kocienski reaction. Some monofluoromethyl 1-phenyl-1*H*-tetrazol-5-yl sulfone substituted by primary alkyl, cyclopropyl and alkenyl could be synthesized via electrophilic fluorination (Scheme 29). The reaction between sulfone reagents and aldehydes proceeds smoothly under the basic conditions [84] (Table 18). The reaction also works well for ketones (Table 19). Good *Z* selectivities for electron-rich aromatic aldehydes are observed when LiHMDS employed as the base and $MgBr_2$ as the additive. The reaction of ketones need slightly lower reaction temperature.

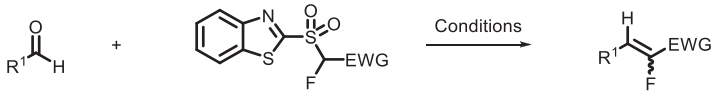
3.2.5. Reactions with substituted 1-tert-butyl-1H-tetrazol-5-yl sulfones

1-*tert*-Butyl-1*H*-tetrazol-5-yl monofluoromethyl sulfones could be prepared according to the following procedure (Scheme 30). Reaction of 1-*tert*-Butyl-1*H*-tetrazol-5-yl monofluoromethyl sulfone (**63**) and aromatic aldehydes or ketones are carried out in the presence of LiHMDS in THF at 0 °C, affording the resulting fluoroalkene in good yields [85]. For aliphatic aldehydes and ketones, the yields of desired products decreased (Table 20). Derivatization of the 1-*tert*-butyl-1*H*-tetrazol-5-yl monofluoromethyl sulfone could form the resulting new sulfone reagent substituted by alkyl, ester and sulfonyl group (Scheme 30). The reactions of alkyl sulfone reagents and carbonyl compounds take place under the previous conditions. The 1-*tert*-Butyl-1*H*-tetrazol-5-yl monofluoromethyl sulfones substituted by ester and sulfonyl groups could react with the 2-naphthaldehyde employing DBU as the base (Table 21).

3.2.6. Reactions with monofluoromethyl 3,5-bis(trifluoromethyl) phenyl sulfones

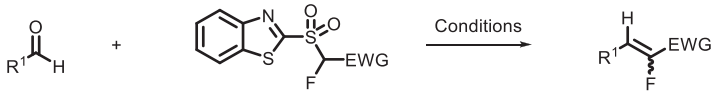
3,5- Bis(trifluoromethyl)phenyl sulfonyl group is a good leaving group. The monofluoromethyl 3,5-bis(trifluoromethyl)phenyl sulfone (**64**) could be synthesized as other monofluoromethyl sulfones. And the synthesis of some substituted 3,5-bis(trifluoromethyl)phenyl sulfones (**65**) could be achieved by the method shown in Scheme 31. The Julia-Kocienski monofluoroolefination reaction employing monofluoromethyl 3,5-

Table 15
The fluoroolefination with other 1,3-benzothiazol-2-yl monofluoromethyl sulfones bearing electron-withdrawing group.

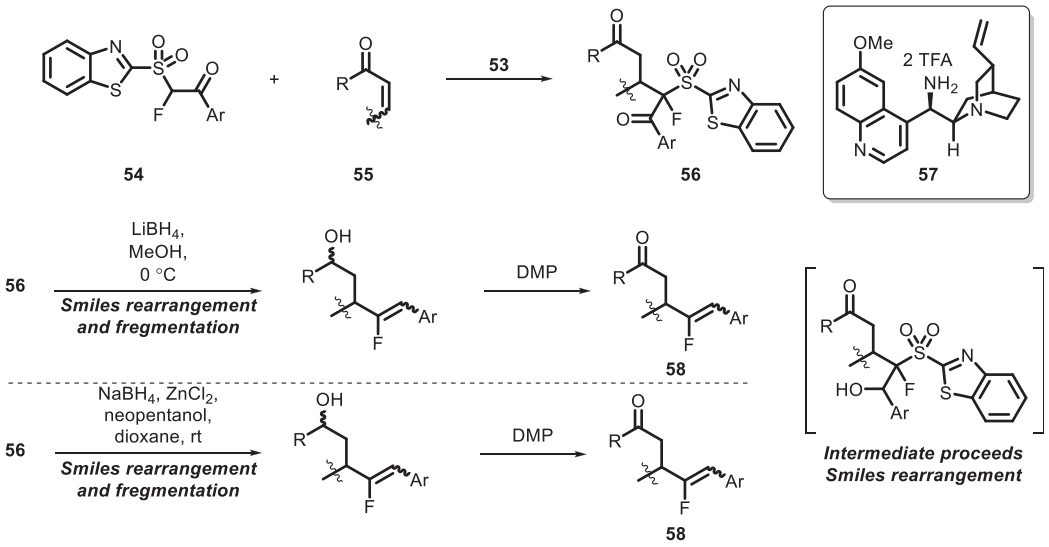


Entry	R^1	EWG	Conditions	Yield (%)	Ratio (*E*:*Z*)	Ref
1	2-naphthyl	CN	DBU, CH_2Cl_2, rt	98	15:85	[78]
2	2-naphthyl	CN	DBU, CH_2Cl_2, -78 °C	97	8:92	[78]
3	*p*-$MeOC_6H_4$	CN	DBU, CH_2Cl_2, rt	95	16:84	[78]
4	*p*-$O_2NC_6H_4$	CN	DBU, CH_2Cl_2, rt	72	17:83	[78]
5	*n*-C_7H_{15}	CN	DBU, CH_2Cl_2, rt	97	23:77	[78]
6	*p*-ClC_6H_4	SO_2Ph	DBU, CH_2Cl_2, rt	89	17:83	[79]
7	*p*-$O_2NC_6H_4$	SO_2Ph	DBU, CH_2Cl_2, rt	85	22:78	[79]
8	*p*-$MeOC_6H_4$	SO_2Ph	DBU, CH_2Cl_2, rt	90	12:88	[79]
9	cinnamyl	SO_2Ph	DBU, CH_2Cl_2, rt	87	13:87	[79]
10	*n*-C_7H_{15}	SO_2Ph	DBU, CH_2Cl_2, rt	85	22:78	[79]
11	2-naphthyl	CON(OMe)Me	DBU, THF, −78 °C	86	6:94	[80]
12	2-naphthyl	CON(OMe)Me	DBU, DMPU, rt	93	78:22	[80]
13	cinnamyl	CON(OMe)Me	DBU, THF, −78 °C	74	54:46	[80]
14	cinnamyl	CON(OMe)Me	DBU, DMPU, rt	69	67:33	[80]

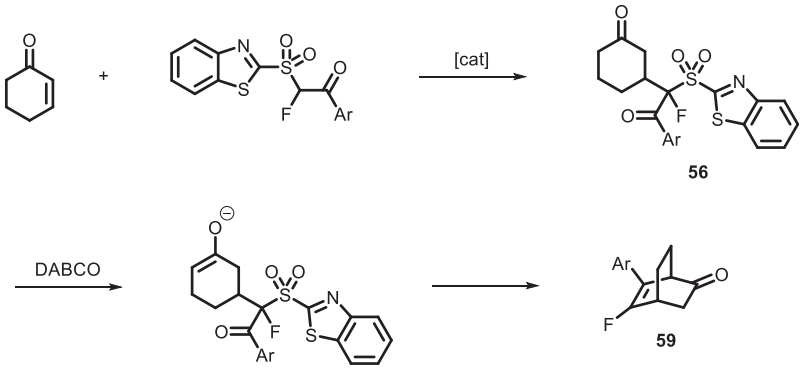
Table 16
Highly stereoselective fluoroolefinations using other 1,3-benzothiazol-2-yl monofluoromethyl sulfones bearing electron-withdrawing group.



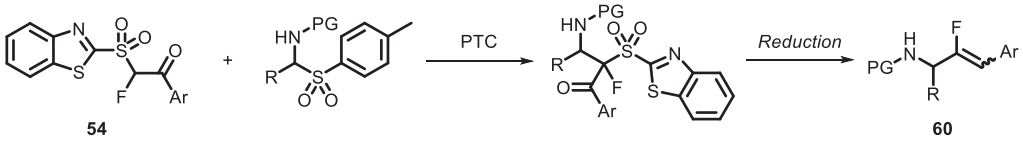
Entry	R^1	EWG	Conditions	Yield (%)	Ratio (*E*:*Z*)	Ref
1	2-naphthyl	CON(OMe)Me	NaH, THF, rt	90	Z-isomer only	[80]
2	*p*-$MeOC_6H_4$	CON(OMe)Me	NaH, THF, rt	89	1:99	[80]
3	*p*-$O_2NC_6H_4$	CON(OMe)Me	NaH, THF, rt	85	<1:99	[80]
4	*o*-MeC_6H_4	CON(OMe)Me	NaH, THF, rt	85	<1:99	[80]
5	*n*-C_7H_{15}	CON(OMe)Me	NaH, THF, rt	83	<1:99	[80]
6	3-pentyl	CON(OMe)Me	NaH, THF, rt	71	Z-isomer only	[80]
7	*p*-$MeOC_6H_4$	COPh	DBU, THF, reflux	61	Z-isomer only	[80]
8	*p*-$MeOC_6H_4$	$COCH_2CH_2CH_3$	DBU, THF, CH_2Cl_2, 0–5 °C	89	Z-isomer only	[80]
9	*o*-$MeOC_6H_4$	COPh	DBU, THF, reflux	64	Z-isomer only	[80]
10	*p*-$O_2NC_6H_4$	COPh	DBU, THF, reflux	81	Z-isomer only	[80]
11	*p*-$O_2NC_6H_4$	$COCH_2CH_2CH_3$	DBU, THF, CH_2Cl_2, 0 °C to rt	86	Z-isomer only	[80]
12	$PhCH_2CH_2$	$COCH_2CH_2CH_3$	DBU, THF, CH_2Cl_2, 0 °C–5 °C	73	Z-isomer only	[80]



Scheme 26. The monofluorovinylation with α,β-unsaturated ketone.

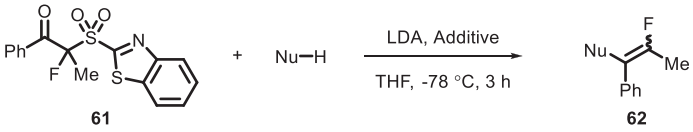


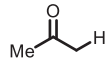
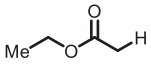
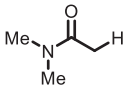
Scheme 27. The formation of monofluorinated bicyclo [2,2,2]oct-5-en-2-ones.



Scheme 28. The monofluorovinylation of imines.

Table 17
The monofluoroolefination with α-fluoro-β-carbonyl 1,3-benzothiazol-2-yl sulfones.



Entry	Nu-H	Additive	Yield (%)	Ratio (*Z*/*E*)	Ref
1	EtOOC—≡—H	2,2′-bipyridine	78	93:7	[83]
2		HMPA	74	0:100	[83]
3		HMPA	57	0:100	[83]
4		HMPA	69	0:100	[83]
5		HMPA	62	0:100	[83]
6	O_2N	HMPA	46	0:100	[83]

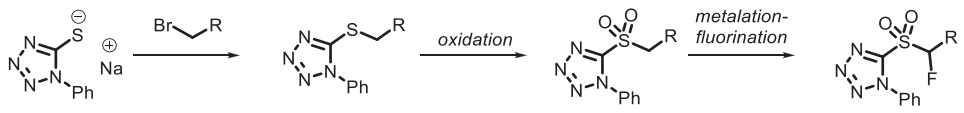
bis(trifluoromethyl)phenyl sulfone **64** could be realized by using KOH or CsF as the base [86] (Table 22). When KOH is used as the base, the reactions are fast but the yields are poor for the electron-poor aromatic aldehydes. When CsF is used as the base, moderate to good yields are obtained for various aromatic aldehydes and aromatic ketones, despite the enolizable carbonyl compounds suffer from lower yields. For the cases when ester or amide groups are substituted at the fluoromethyl, a combination of K_2CO_3 and TBAB could promote the condensation smoothly at room temperature [87] (Table 23). The sulfone reagents substituted by ester groups could react with aromatic aldehydes to give monofluoroalkene products with good *Z* selectivity, while *E*-monofluoroalkenes are dominated with aliphatic aldehyde. Notably, the amide group substitution results the *Z*-monofluoroalkenes.

3.3. Synthesis of gem-difluoroalkenes via Julia-Kocienski difluoroolefination

3.3.1. Reactions with difluoromethyl 2-pyridyl sulfone

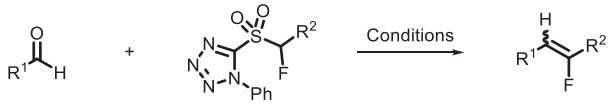
3.3.1.1. Reactions with difluoromethyl 2-pyridyl sulfone with aldehydes. Difluoromethyl pyridinyl sulfone **28** is the first sulfone reagent used to accomplish the Julia-Kocienski reaction for the synthesis of difluoroalkenes [59]. The synthetic method of **28** is practical and scalable, which is now commercially available. Hu reported the first transformation of **28** with carbonyl compounds to difluoroalkenes (Table 24). The yields of olefination products employed 1,3-benzothiazol-2-yl difluoromethyl sulfone drop to 42%, and two kinds of difluoromethyl tetrazol-5-yl sulfones show no reactivity with carbonyl compounds.

To achieve the *gem*-difluoroalkenation of enolizable aldehydes, a strategy of generating trace amount of base in situ was used to avoid the deprotonation of the aldehydes [88] (Table 25). CsF reacts with N $(TMS)_3$ leading to the slow formation of $^{-}$N $(TMS)_2$ in DMF



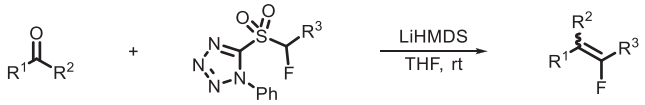
Scheme 29. Preparation of substituted monofluoromethyl 1-phenyl-1*H*-tetrazol-5-yl sulfones.

Table 18
Fluoroolefination reaction between substituted monofluoromethyl 1-phenyl-1*H*-tetrazol-5-yl sulfones and aldehydes.



Entry	R^1	R^2	Conditions	Yield (%)	Ratio (*E*:*Z*)	Ref
1	2-naphthyl	Et	LiHMDS, $MgBr_2 \cdot Et_2O$, THF, rt	94	14:86	[84]
2	2-naphthyl	Cyclopropyl	LiHMDS, $MgBr_2 \cdot Et_2O$, THF, rt	70	38:62	[84]
3	2-thiophenyl	2-propenyl	LiHMDS, $MgBr_2 \cdot Et_2O$, THF, rt	78	*Z* only	[84]
4	*p*-$MeOC_6H_4$	Et	LiHMDS, $MgBr_2 \cdot Et_2O$, THF, rt	87	3:97	[84]
5	*o*-MeC_6H_4	Et	LiHMDS, $MgBr_2 \cdot Et_2O$, THF, rt	77	18:82	[84]
6	*p*-$O_2NC_6H_4$	Et	LiHMDS, $MgBr_2 \cdot Et_2O$, THF, rt	66	50:50	[84]
7	cinnamyl	Et	LiHMDS, $MgBr_2 \cdot Et_2O$, THF, rt	72	19:81	[84]
8	*n*-C_7H_{15}	Et	LiHMDS, $MgBr_2 \cdot Et_2O$, THF, rt	71	44:56	[84]
9	*n*-C_7H_{15}	Cyclopropyl	LiHMDS, $MgBr_2 \cdot Et_2O$, THF, rt	63	42:58	[84]
10	*n*-C_7H_{15}	2-propenyl	LiHMDS, $MgBr_2 \cdot Et_2O$, THF, rt	63	80:20	[84]
11	2-naphthyl	Et	KHMDS, THF, −78 to −60 °C	64	73:27	[84]
12	2-naphthyl	Cyclopropyl	KHMDS, THF, −78 to −60 °C	83	50:50	[84]
13	2-naphthyl	2-propenyl	KHMDS, THF, −78 to −60 °C	73	46:54	[84]
14	*n*-C_7H_{15}	Et	KHMDS, THF, −78 to −60 °C	74	27:73	[84]
15	*n*-C_7H_{15}	Cyclopropyl	KHMDS, THF, −78 to −60 °C	72	36:64	[84]
16	*n*-C_7H_{15}	2-propenyl	KHMDS, THF, −78 to −60 °C	83	50:50	[84]

Table 19
Fluoroolefination reaction between substituted monofluoromethyl 1-phenyl-1*H*-tetrazol-5-yl sulfones and ketones.



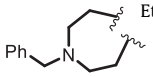
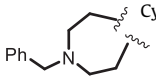
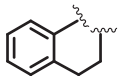
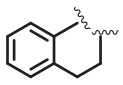
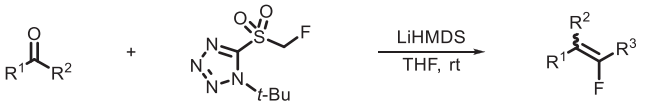
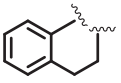
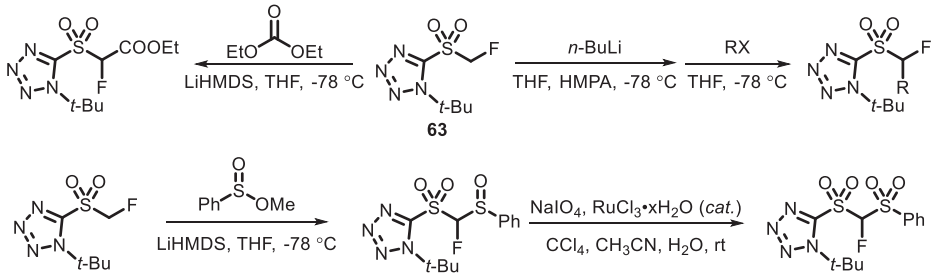
Entry	R^1	R^2	R^3	Yield (%)	Ratio (*E*:*Z*)	Ref
1			Et	77	–	[84]
2			Cyclopropyl	71	–	[84]
3	Ph	Ph	Et	99	–	[84]
4	Ph	Ph	Cyclopropyl	91	–	[84]
5	Ph	Me	Et	88	74:26	[84]
6	Ph	Me	Cyclopropyl	96	75:25	[84]
7			Et	77	78:22	[84]
8			Cyclopropyl	88	78:22	[84]

Table 20
Fluoroolefination with 1-*tert*-butyl-1*H*-tetrazol-5-yl fluoromethyl sulfones.



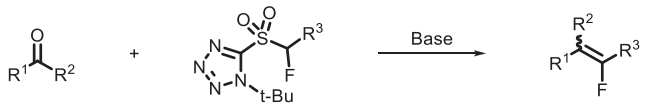
Entry	R^1	R^2	Yield (%)	Ratio (*E*:*Z*)	Ref
1	2-naphthyl	H	87	42:58	[85]
2	*p*-$BnOC_6H_4$	H	87	34:66	[85]
3	*p*-BrC_6H_4	H	73	47:53	[85]
4	$PhCH_2CH_2$	H	51	48:52	[85]
5	Ph	Me	75	30:70	[85]
6	*p*-$MeOC_6H_4$	Me	69	30:70	[85]
7	*p*-BrC_6H_4	Me	84	28:72	[85]
8			67	76:24	[85]
9	Ph	Ph	89	–	[85]
10	$PhCH_2CH_2$	Me	52	49:51	[85]

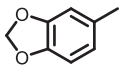
solution at room temperature. Trace amount of $^{-}N(TMS)_2$ could circumvent the waste of base in reacting with aldehydes, and the reaction between difluoromethyl pyridinyl sulfone and enolizable aldehydes proceeds smoothly.

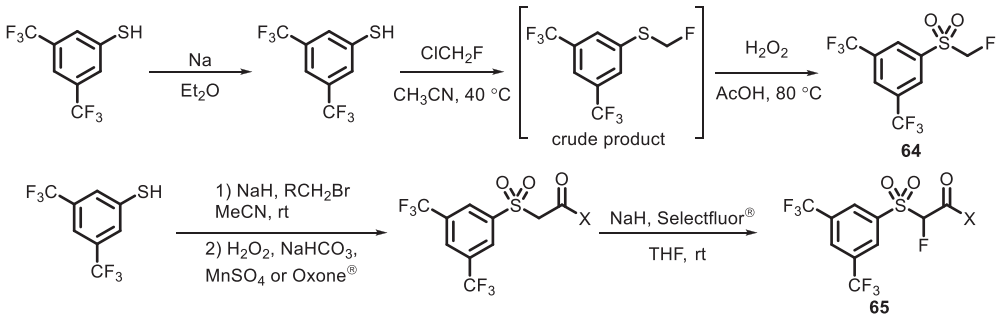


Scheme 30. Preparation of substituted 1-*tert*-butyl-1*H*-tetrazol-5-yl fluoromethyl sulfones.

Table 21
Fluoroolefination with substitiuted 1-*tert*-butyl-1*H*-tetrazol-5-yl fluoromethyl sulfones.

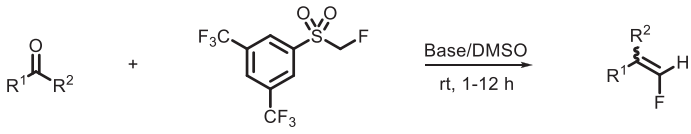


Entry	R^1	R^2	R^3	Conditions	Yield (%)	Ratio (*E*:*Z*)	Ref
1	2-naphthyl	H	Et	LiHMDS, THF, rt	64	33:67	[85]
2	*p*-BrC_6H_4	Me	Et	LiHMDS, THF, rt	52	36:64	[85]
3	*p*-BrC_6H_4	H	*n*-C_6H_{13}	LiHMDS, THF, rt	70	27:73	[85]
4	*o*-BrC_6H_4	H	*i*-Bu	LiHMDS, THF, rt	66	51:49	[85]
5	*p*-$MeOC_6H_4$	H	*i*-Bu	LiHMDS, THF, rt	53	100:0	[85]
6	*p*-$MeOC_6H_4$	Me	*i*-Bu	LiHMDS, THF, rt	53	100:0	[85]
7		H	Allyl	LiHMDS, THF, rt	54	46:54	[85]
8	2-naphthyl	H	COOEt	DBU, CH_2Cl_2, -78 °C to rt	80	64:36	[85]
9	2-naphthyl	H	SO_2Ph	DBU, CH_2Cl_2, rt	70	27:73	[85]



Scheme 31. Preparation of monofluoromethyl 3,5-bis(trifluoromethyl)phenyl sulfones.

Table 22
Fluoroolefination with monofluoromethyl 3,5-bis(trifluoromethyl)phenyl sulfone.



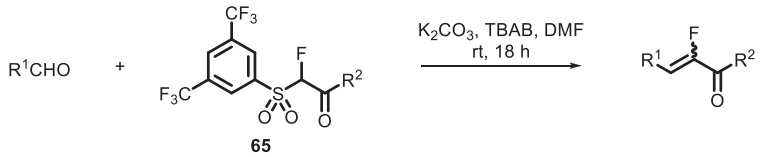
Entry	R^1	R^2	Base	Yield (%)	Ratio (*E*:*Z*)	Ref
1	Ph	H	KOH	35	1.8:1	[86]
2	Ph	H	CsF	78	1.7:1	[86]
3	*p*-$MeOC_6H_4$	H	KOH	82	2.0:1	[86]
4	*p*-$MeOC_6H_4$	H	CsF	73	1.6:1	[86]
5	*p*-FC_6H_4	H	KOH	8	10.0:1	[86]
6	*p*-FC_6H_4	H	CsF	92	1.3:1	[86]
7	Ph	Ph	KOH	75	–	[86]
8	*p*-$MeOC_6H_4$	Ph	KOH	70	1:1	[86]
9	*p*-NCC_6H_4	Ph	CsF	58	1:1	[86]
10	*n*-C_9H_{19}	H	CsF	17	2.9:1	[86]

3.3.1.2. Reactions between difluoromethyl 2-pyridyl sulfone and ketones. The standard procedure for the reaction between **28** is suitable for some simple and less-steric ketones such as methyl phenyl ketone and 9*H*-fluoren-9-one. For the *gem*-difluoroalkenation of these ketones, the reaction may need to be heated to a higher temperature before quenching with NH_4Cl solution [59] (Table 26, Entry 1–5). For Julia-Kocienski difluoroolefination of pregnenone [59] (Table 26, Entry 6), LiHMDS and lower temperature are employed. For another two ketones with more complex structures (Table 25, Entry 7 and 8), *t*-BuOK-DMF system were chose and the reaction conditions were carefully optimized and quite different with the origin one [89,90]. These two ketones were converted to the expected *gem*-difluoroalkenes with moderate to low yields in much longer reaction time. This shows the difficulties in the *gem*-difluoroalkenation of complex ketones.

But this standard condition is much less efficient for the diphenyl ketone. In mechanism study, it is shown that the retro-addition dominates the reaction, which occurs faster than the Smiles rearrangement under the standard condition. After the condition screening, the addition products could give the expected difluoroalkene products through Smiles rearrangements at higher temperature with Lewis acid additives [88]. The condition for the Smiles rearrangement is completely different with the former basic condition at low temperature. Thus the difluoroolfination of diphenyl ketone needs two steps, the addition step mediated by base at low temperature and the rearrangement step mediated by Lewis acid at high temperature (Table 27).

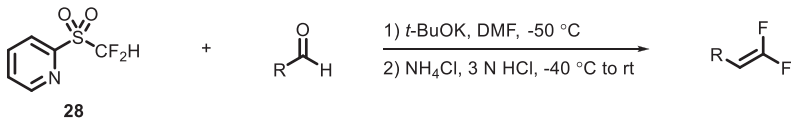
3.3.1.3. Reactions between difluoromethyl 2-pyridyl sulfone and lactones. To the less reactive sugar-derived lactones, the Julia-Kocienski difluoroolefination proceeds in two steps (Table 28). The first addition step should be carried out at −78 °C to ensure the generation of the addition products. Smiles rearrangement of addition products occur at room temperature or higher temperature, giving the difluoro-*exo*-glycals in good yields [91]. The work-up with acid can be omitted; this may result from the fragmentation of **31** (for its structure, see Scheme 17) under the conditions of

Table 23
Fluoroolefination with substituted monofluoromethyl 3,5-bis(trifluoromethyl)phenyl sulfone.



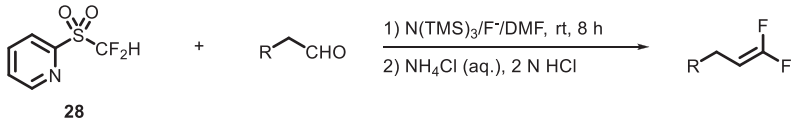
Entry	R^1	R^2	Yield (%)	Ratio (*Z*:*E*)	Ref
1	Ph	OMe	>95	93:7	[87]
2	Ph	O*t*-Bu	75	82:18	[87]
3	*p*-$CF_3C_6H_4$	OMe	50	94:6	[87]
4	*p*-$CF_3C_6H_4$	O*t*-Bu	42	88:12	[87]
5	*p*-$MeOC_6H_4$	O*t*-Bu	94	61:39	[87]
6	*o*-ClC_6H_4	OMe	68	90:10	[87]
7	$PhCH_2CH_2$	OMe	66	48:52	[87]
8	$PhCH_2CH_2$	O*t*-Bu	92	23:77	[87]
9	Cy	OMe	71	93:7	[87]
10	Cy	O*t*-Bu	91	85:15	[87]
11	Ph	N(OMe)Me	83	only Z	[87]
12	*p*-$CF_3C_6H_4$	N(OMe)Me	63	only Z	[87]
13	*p*-ClC_6H_4	N(OMe)Me	62	only Z	[87]
14	*p*-$MeOC_6H_4$	N(OMe)Me	45	only Z	[87]
15	*o*-ClC_6H_4	N(OMe)Me	99	only Z	[87]
16	*n*-C_9H_{19}	N(OMe)Me	56	only Z	[87]
17	Cy	N(OMe)Me	65	only Z	[87]

Table 24
gem-Difluoroalkenation of aldehydes.



Entry	R	Yield (%)	Ref
1	*p*-$MeOC_6H_4$	86	[59]
2	*m*-$O_2NC_6H_4$	72	[59]
3	*p*-BrC_6H_4	72	[59]
4	2-naphthyl	92	[59]
5	cinnamyl	62	[59]
6	$PhCH_2CH_2$	40	[59]

Table 25
Modified *gem*-difluoroolefination of enolizable aldehydes.



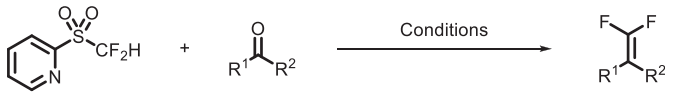
Entry	R	Yield (%)	Ref
1	$PhCH_2$	60	[88]
2	*p*-$BrC_6H_4CH_2$	85	[88]
3	*p*-$MeOC_6H_4CH_2$	71	[88]
4	*n*-$C_{10}H_{21}$	80	[88]
5	*n*-$C_{14}H_{29}$	66	[88]
6	*n*-$C_{16}H_{33}$	64	[88]

the second step. Furthermore, a similar reaction with only one example [92] was reported in 2014.

3.3.2. Reactions with potassium 2-pyridylsulfonyldifluoroacetate

In addition to the deprotonation of the difluoromethyl pyridinyl sulfone, the decarboxylation of potassium 2-pyridylsulfonyldifluoroacetate (**66**) can also generate the anion of

Table 26
gem-Difluoroolefination of ketones.



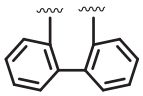
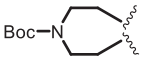
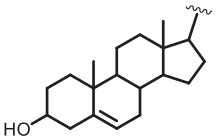
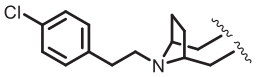
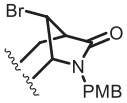
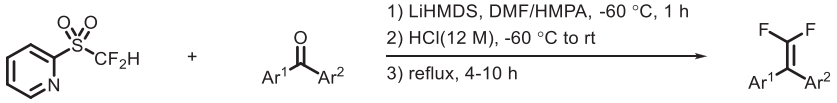
Entry	R^1	R^2	Conditions	Yield (%)	Ref
1	*p*-BrC_6H_4	Me	1) *t*-BuOK, DMF, −50 °C to −20 °C 2) NH_4Cl, HCl	77	[59]
2	$PhCH_2CH_2$	Me	1) *t*-BuOK, DMF, −50 °C to rt 2) NH_4Cl, HCl	72	[59]
3	cinnamyl	Me	1) *t*-BuOK, DMF, −50 °C to −40 °C 2) NH_4Cl, HCl	80	[59]
4			1) *t*-BuOK, DMF, −50 °C to −40 °C 2) NH_4Cl, HCl	87	[59]
5			1) *t*-BuOK, DMF, −50 °C to −40 °C 2) NH_4Cl, HCl	84	[59]
6		Me	1) LiHMDS, THF-HMPA, −78 °C to rt 2) NH_4Cl, HCl	57	[59]
7			1) *t*-BuOK, DMF, −25 °C 2) HCl	30	[59]
8			1) *t*-BuOK, DMF, −60 °C 2) NH_4Cl, HCl 3) warm to 23 °C, 60 °C	58	[59]

Table 27
gem-Difluoroolefination of diaryl ketones.



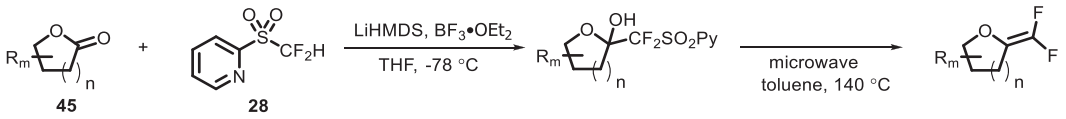
Entry	Ar^1	Ar^2	Yield (%)	Ref
1	Ph	Ph	75	[88]
2	Ph	*p*-FC_6H_4	67	[88]
3	Ph	*p*-$MeOC_6H_4$	69	[88]
4	Ph	*o*-$MeOC_6H_4$	72	[88]
5	Ph	*p*-$CF_3C_6H_4$	67	[88]
6	Ph	2-thienyl	63	[88]

difluoromehtyl 2-pyridyl sulfone. **66** in pure state is stable below 100 °C; however, it shows slow decomposition in polar solvents such as DMF even at room temperature. Expected difluoroalkenes could be obtained by slightly warming the solution of **66** and aldehydes followed by quenching with HCl [93] (Table 29). This procedure could convert aromatic aldehydes with good yields, whereas lower efficiencies are observed with aliphatic aldehydes and conjugated aldehydes. Few success has been achieved with ketones. This reaction could be carried out under mild conditions without strong base and low temperature. Intermediate **31** was detected by ^{19}F NMR, which confirms the similar mechanism with former report [59].

3.3.3. *Reactions with difluoromethyl 2-pyridyl sulfoxide*

The non-fluorinated heteroaryl sulfoxides can react with carbonyl compounds to afford disulfides, while the reaction between difluoromethyl pyridyl sulfoxide and carbonyl compounds could give monofluoroalkenes or difluoroalkenes in stepwise manner (Scheme 32): difluoromethyl pyridinyl sulfoxide reacts with carbonyl compounds to form β-hydroxy sulfoxides in the presence of a base at low temperature, and the rearrangement of β-hydroxy sulfoxides yield fluorinated alkenes under different conditions. Difluoroalkenes are generated in the presence of Lewis acid at high temperature [62], and the rearrangement conditions are similar to the reaction with sulfones.

Table 28
Stepwise *gem*-difluoroolefination of sugar-derived lactone.



45 28

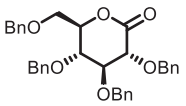
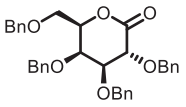
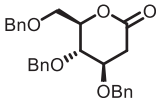
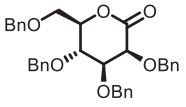
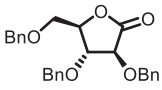
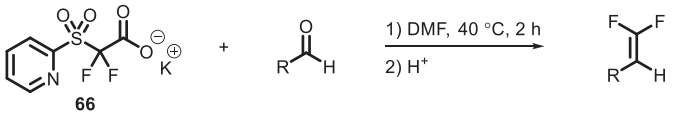
Entry	Lactone	Yield (%)	Ref
1		64	[91]
2		69	[91]
3		58	[91]
4		63	[91]
5		59	[91]

Table 29
gem-Difluoroolefination with potassium 2-pyridylsulfonyldifluoroacetate.



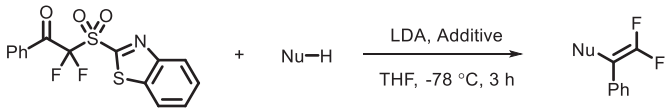
66

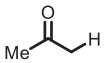
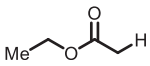
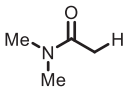
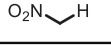
Entry	R	Yield (%)	Ref
1	*p*-BrC_6H_4	90	[93]
2	*m*-$O_2NC_6H_4$	99	[93]
3	*p*-$MeOC_6H_4$	65	[93]
4	2-naphthyl	87	[93]
5	cinnamyl	51	[93]
6	$PhCH_2CH_2$	48	[93]

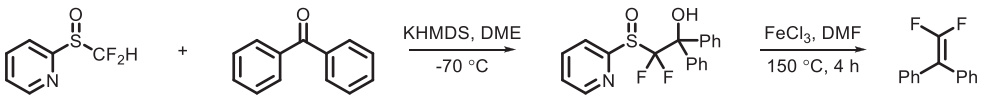
3.3.4. Special cases

Similar to its monofluorinated counterpart, α,α-difluoro-β-hydroxy 1,3-benzothiazol-2-yl sulfone could be generated by the nucleophilic attack to α,α-difluoro-β-keto 1,3-benzothiazol-2-yl sulfone. Under basic conditions, α,α-difluoro-β-hydroxy 1,3-benzothiazol-2-yl sulfones give *gem*-difluoroalkenes via spontaneous Smile rearrangement (Table 30) [94].

Table 30
gem-Difluoroolefination triggered by nucleophilic addition.



Entry	Nu-H	Additive	Yield (%)	Ref
1		2,2′-bipyridine	82	[94]
2		2,2′-bipyridine	74	[94]
3		HMPA	75	[94]
4		HMPA	37	[94]
5		HMPA	43	[94]
6		HMPA	51	[94]
7		HMPA	69	[94]



Scheme 32. *gem*-Difluoroolefination with difluoromethyl 2-pyridyl sulfoxide.

4. Conclusions

In summary, Julia and Julia-Kocienski fluoroolefination reactions have been developed since 2003, and various mono- and difluorinated sulfone reagents were used in these reactions. In general, phenyl sulfones are employed in Julia fluoroolefination, and heteroaryl fluoroolefination sulfones are used in Julia-Kocienski fluoroolefination. Two or three steps are required in Julia fluoroolefination, while Julia-Kocienski fluoroolefination usually proceeds in one-step. Currently, Julia-Kocienski fluoroolefination is much more widely applied in organic synthesis compared to the Julia fluoroolefination.

Among different methods for the synthesis of fluoroalkenes, Julia and Julia-Kocienski fluoroolefination possesses the following advantages. Firstly, since most sulfone reagents can be easily prepared and carbonyl compounds are readily available, these olefination protocols can be used as convenient synthetic methods for fluorinated alkenes. Secondly, the side products in Julia reaction are water-soluble, which enables the convenient purification of products. Thirdly, these methods work well with some difficult substrates and perform better than other olefination methods.

Despite the advantages mentioned above, several challenges need to be addressed for Julia and Julia-Kocienski fluoroolefination reactions. First of all, yields decrease in different extent for the enolizable carbonyl compounds and special conditions are required. Second, reactions with bulky ketone substrates are less efficient. Finally, Z/E selectivity is low in most cases. In the future, we expect that new fluoroolefination reactions will be developed for the bulky ketones and enolizable carbonyl compounds, and new methods for highly Z/E selective monofluoroolefination will emerge.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Financial support of this work by the National Key Research and Development Program (2021YFF0701700), National Natural Science Foundation of China (21632009), the Key Programs of the Chinese Academy of Sciences (KGZD-EW-T08), the Key Research Program of Frontier Sciences of CAS (QYZDJ-SSW-SLH049), is acknowledged.

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