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Synthesis of Fluoroolefins via Julia-Kocienski Olefination

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Abstract

The Julia-Kocienski olefination provides a versatile platform for the synthesis of fluorovinyl compounds. This review describes our efforts as well as those of others in the synthesis of various fluorinated aryl and heteroaryl sulfones and their utility as olefination reagents for the modular assembly of fluoroalkenes. Where data is available, the influence of the fluorine atom on the reactivity of the olefination reagents and the stereochemical outcome of the olefination are described.

1 Introduction

The change in physical, chemical and biological properties1 of organic compounds as a consequence of substituting hydrogen atoms by fluorine is well recognized and fuels significant interest in the synthesis of fluoroorganics.2 There is an increased demand for selectively fluorinated organic molecules in various fields, such as agrochemicals3a and pharmaceuticals.3b,c Despite the development of an impressive number of fluorinating reagents,2 there is a dearth of selective and broadly applicable methods for the preparation of fluoroorganics. One attractive synthetic approach to fluoroorganics involves modular assembly using fluorinated building blocks.4 In this context, fluorovinyl compounds are either important end products5 or can serve as potential synthetic intermediates.6 Among the various approaches to fluorovinyl compounds, Wittig and Wittig-like olefination reactions are the most commonly encountered.7

The Julia-Kocienski olefination, also called modified or one-pot olefination, is a convenient method for introduction of unsaturation and has been described in several excellent reviews.8 The modified Julia-Kocienski olefination hinges on the use of heteroaryl sulfones,9–12 or electron-deficient aryl sulfones13–15 (Scheme 1). Among these, benzothiazol-2-yl (BT) and 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfones, are the most widely used in synthesis. Briefly, addition of the carbanion formed by deprotonation of the sulfone to the carbonyl compound furnishes a β-alkoxy sulfone, which closes to a spirocyclic intermediate. The spirocyclic intermediate then opens via cleavage of a C–S bond, and subsequent elimination of heteroaryl (or aryl) alkoxide and sulfur dioxide yields the olefin (Scheme 1). For more detailed discussion of proposed mechanistic pathways and consequently the stereochemical outcome of the olefination, the reader is referred to the original Julia publications9,12 and subsequent reviews.8

Despite its popularity, use of the modified Julia-Kocienski olefination for the preparation of fluorovinyl compounds has been scarce until recently. Lequeux et al. first reported the synthesis of fluoroalkylidenes via base-mediated condensation reactions of benzothiazol-2-yl 1-fluoroethyl sulfone (**6**) with aldehydes and ketones.16 Direct fluorination of

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benzothiazol-2-yl ethyl sulfide (**1**) using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) gave the fluorinated derivative **2** in only 30–35% yield, whereas the reaction of *N*-fluorodibenzenesulfonimide (NFSI) with benzothiazol-2-yl ethyl sulfone was reported to give multiple fluorinated products. The required fluoro-Julia reagent **6** was therefore synthesized using either a commercial fluorinated precursor or via chlorination of benzothiazol-2-yl ethyl sulfide (**1**), followed by Cl–F exchange, and oxidation (Scheme 2). In the latter case, partial chlorination of the benzothiazol-2-yl moiety occurred as well, but this did not influence the olefination.16 In a related patent application, fluorination of benzothiazol-2-yl ethyl sulfone (obtained via *m*CPBA oxidation of **1**) with Selectfluor, in the absence of base, was reported to yield **6** in 65% yield.17

Since there was no broadly applicable approach for accessing fluoroolefins via the Julia-Kocienski reaction, we became interested in development of a general methodology. This review describes subsequent developments by us and by others leading to the synthesis of various classes of fluorovinyl compounds, using the Julia-Kocienski olefination as a key step.

2 Synthesis of Fluorostilbene-like and Fluorostyrene-like Derivatives

Synthesis of α-fluorobenzyl BT sulfones, the requisite reagents for the preparation of fluorostilbene-like and fluorostyrene-like derivatives, was initially attempted using various methods. These included fluorination of benzyl BT sulfide and BT sulfoxide with several fluorinating reagents, as well as chlorination of benzyl BT sulfide for subsequent Cl–F exchange.18 However, no desired halobenzyl derivative was isolated. Successful synthesis, resulting in high and reproducible yields of desired α-fluorobenzyl BT sulfones **10a**–**d** (Scheme 3), was achieved by metalation–electrophilic fluorination of sulfones **9** (Scheme 3). *Critical to the synthesis was fluorination under heterogeneous conditions, by the use of toluene as solvent and addition of solid NFSI.*18 When metalation–fluorination was performed under homogeneous conditions using tetrahydrofuran as the solvent, no fluorinated products **10** were formed and the starting sulfones were recovered. Single electron transfer (SET) has been suggested as a competing process in the fluorination reactions.19 It is plausible that in the current case, SET predominates under homogeneous conditions, whereas under heterogeneous conditions either the formation or diffusion of radicals is minimized, resulting in fluorinated products. In this context, several years ago we reported that the choice of toluene as solvent was critical for the fluorination of a lithiated electron-rich pyrene derivative.20 Subsequently, we have demonstrated that heterogeneous fluorination of lithio derivatives of nontrivial nucleoside and deoxynucleoside substrates resulted in fluorinated products. This further confirmed our hypothesis that electrophilic fluorination of metalated, electron-rich systems can be accomplished using heterogeneous conditions.21 In this context, Beller et al22 have recently reported the high-yield fluorination of simple electron-rich magnesiated aromatics with *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate23 under apparently heterogeneous conditions,23c although it was not explicitly stated to be such, but was ascribed to ‘solvent effect’.22 A similar simultaneous independent study by Knochel et al. involves fluorination of magnesiated aromatics with NFSI in a mixed dichloromethane–perfluorodecalin solvent.24 A yield increase observed in the presence of the fluorinated solvent was ascribed to possible fluorine atom abstraction from the solvent by radical intermediates that could be formed via competing SET.

Fluoro sulfones **10a**–**d** were reacted with aldehydes and ketones under Barbier-type8 conditions. This involved addition of base to sulfone and aldehyde, to afford fluoroalkenes in yields ranging from 62%-quantitative.18 Selectivity under these LHMDS/THF conditions

at 0 °C depended on the sulfone and the aldehyde (Scheme 4). All condensations with **10d**, reactions of ferrocenecarbaldehyde with **10a**–**d**, and reactions of cinnamaldehyde with **10b**–**d** were *Z*-selective. Condensations of other aldehydes with **10a**–**c** were *E*-selective. A reversal from moderate *E*-selectivity to high *Z*-selectivity was obtained in the reaction of 2-naphthaldehyde and **10a** using conditions reported by Jacobsen25a and Williams25b (low temperature and a coordinating solvent mixture DMF–DMPU). The effect of fluorine on the stereoselectivity was demonstrated by reactions of *n*-octanal with sulfone **9c** and the fluoro analogue **10c**. Whereas a similar stereoselectivity trend was observed in both reactions, it was highly *Z*-selective with **9c**, and moderately *E*-selective with **10c**, indicating that fluorine decreased the selectivity (Scheme 5).

Finally, we showed that fluorination and the subsequent condensation step could be performed as *a one-pot* procedure.18

3 Synthesis of Fluoroalkylidenes

3.1 Benzothiazole-Based Reagents

α-Fluoroethyl BT sulfone **6** (for synthesis, please see Scheme 2) has been used in condensation reactions under Barbier conditions.16 The choice of base was critical in these reactions. Whereas aldehydes reacted in the presence of either potassium *tert*-butoxide or sodium hexamethyldisilazide, the latter was required for reactions with ketones. Fluoroalkylidenes were isolated in 45–88% yields, with olefination selectivity ranging from moderate to unselective (Scheme 6). The more complex cyclopropanal **13** gave a high yield of an *E*/*Z* (~1:1) mixture of fluoroalkene **14**,16 a compound with reported insecticidal activity.26

De-ethoxycarbonylation of fluorinated BT sulfones **15**–**18** (Scheme 7) has recently been reported to give fluoromethyl **21**, 1-fluoroethyl **6**, 1-fluoropropyl **22**, and difluoromethyl BT sulfone **23**.27 The yield of the reaction was solvent dependent, and the presence of a catalytic amount of water was critical. Reactions appear to be highly substrate dependent, since BT sulfones **19** and **20** did not undergo de-ethoxycarbonylation, but produced fluoroalkenes **24** and **25** instead via desulfonylative elimination.27

We have screened conditions for metalation–fluorination of alkyl BT sulfones, using various bases, solvents, and fluorinating agents. However, no efficient method for the preparation of fluoroalkyl BT sulfones emerged.28 Only starting material was recovered with NaH/Selectfluor, whereas use of stronger bases in combination with NFSI resulted in either complex reaction mixtures or mixtures containing a BT sulfone selfcondensation product (Scheme 8).28

3.2 Phenyltetrazole-Based Reagents

Tetrazole-based sulfones, i.e. 1-phenyl-1*H*-tetrazol-5-yl (PT)10 and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT)11 sulfones have been reported to be more stable under basic conditions compared to the BT analogues, which tend to undergo self-condensation. 11,12 We were indeed able to successfully synthesize a series of fluoroalkyl PT sulfones via direct metalation–fluorination (Scheme 9).28 Interestingly, in this case reactions proceeded well under homogeneous conditions. Notably, no cyclized or olefin migration products were detected when reactions were performed with hex-5-enyl PT sulfone **30d**, indicating that SET was either not a competing process, or that cyclization/migration was substantially slower than recombination of fluorine atom with alkyl radical. An exception was fluorination of 2-methylprop-2-enyl PT sulfone **30c**, where use of heterogeneous metalation–fluorination conditions was required for reproducibility in larger scale synthesis.

Dimerization products were generally not observed. The only exception was (cyclopropyl)methyl PT sulfone **30b**, where dimerization was a competing process under heterogeneous, but was very minimal under homogeneous conditions.

Effect of reaction conditions on olefination stereoselectivity was screened in reactions of 2-naphthaldehyde with 1-fluoropropyl PT sulfone **31a**. Whereas the use of LHMDS/THF gave low *E*-selectivity and a high yield of isolated product, use of polar solvents and additives resulted in *Z*-selectivity (DMPU solvent, *E*/*Z* 25/75; DMF/DMPU or DMF/HMPA, *E*/*Z* 37/63). This selectivity increased to *E*/*Z* 14/86 when LHMDS/$MgBr_2$·OEt_2/THF was used. Complementary stereoselection, i.e. moderate *E*-selectivity (*E*/*Z* 73/27), could be achieved with KHMDS/THF at low temperature. The stereoselectivity trend was tested for different types of aldehydes and for sulfones **31a**–**c** (Scheme 10). All electron-rich aromatic aldehydes tested gave the *Z*-isomer as the major or exclusive product with **31a**–**c** using LHMDS/$MgBr_2$·OEt_2/THF (Method A, Scheme 10). However this was not the case with other types of aldehydes and sulfones where the outcome depended strongly on the sulfone and aldehyde. Yields were in the range of 45–94%. No generality in stereoselection was observed under the KHMDS/THF/low temperature conditions (Method B), but yields were in the range of 64–90%. It is noteworthy that the reaction of *n*-octanal with 1-fluoropropyl PT sulfone **31a** using Method B was *Z*-selective, with *trans* disposition of the two alkyl chains, and this is consistent with report by Blakemore et al. for unfluorinated PT sulfones.11

Ketones reacted with fluoroalkyl PT sulfones **31a**,**b** as well and the yields depended strongly on stoichiometry of reagents. Higher excesses of PT sulfone and base gave products in yields ranging from 71–99% (Scheme 11).

4 Synthesis of Functionalized Fluoroolefins

4.1 α-Fluoroacrylates

4.1.1 Benzothiazole- and Phenyltetrazole-Based Reagents—The use of the Julia-Kocienski olefination for the synthesis of functionalized olefins was first reported by Blakemore et al. for the synthesis of acrylates.29 In independent work, we have prepared a series of benzothiazole-based reagents for the synthesis of α-fluoroacrylates, as well as one that is phenyltetrazole derived. This was accomplished via simple metalation–fluorination of precursor sulfones **32**–**35** (Scheme 12) using NaH/Selectfluor.30 In this manner *tert*-butyl (BT: **36** and PT: **38**), ethyl (**15**), and 8-phenylmenthyl (**37**) fluoro(heteroarylsulfonyl)acetates were obtained in yields ranging from 59–73% (Scheme 12).30

Reactions of *tert*-butyl (BT-sulfonyl)fluoroacetate **36** with aldehydes were conducted under mild, DBU-mediated conditions at room temperature to give α-fluoroacrylates with predominant *E*-selectivity and in yields ranging from 75–99%. Lowering the reaction temperature to −78 °C resulted in increased *E*-selectivity (Scheme 13). Sterically hindered ferrocenecarbaldehyde and 2-ethylbutanal gave low *E*-selectivity. Only marginal variation of yield and *E*/*Z*-selectivity was observed upon the change of ester moiety to ethyl **15** and 8-phenylmenthyl **37** (Scheme 13). Notably, 8-phenylmenthyl-derived α-fluoroacrylates are important in asymmetric Diels–Alder reactions.31 In the single example tested, BT and PT sulfones gave comparable yields and selectivity.30

In a comparison of the reactivities under DBU-mediated conditions, BT sulfone **36** showed much higher reactivity with 2-naphthaldehyde compared to the Horner-Wadsworth-Emmons analogue [$EtO_2CCHFP(O)(OEt)_2$]. Also, the stereochemical outcome of the olefination with **36** was opposite to that with the Horner-Wadsworth-Emmons reagent.30 The effect of

fluorine on the reactivity of the Julia-Kocienski reagent was demonstrated in a competitive experiment between **15** and unfluorinated sulfone **33**, which resulted in the α-fluoroacrylate as the only product. This indicates that substitution of hydrogen by fluorine substantially increases the reactivity of the reagent.

Olefination stereoselectivity was also *significantly influenced* by the fluorine atom. A reversed trend in stereoselectivity was observed in DBU-mediated condensations of aromatic aldehydes with BT sulfones **36** and **15**,30 compared to the unfluorinated analogue **33**.29 On the other hand, a similar trend in stereoselectivity was observed in the condensations of *n*-alkyl aldehydes with **33** and its fluoro analogues **36** and **15** (Scheme 14).

In an extension of our work, Lequeux et al. studied stereoselectivity of olefinations involving **15** using either NaHMDS/THF, or DBU/$MgBr_2$/THF. In both cases, *Z*-stereoselectivity was obtained, which is complementary to our results (Scheme 15).32a

Reactivity with ketones was highly dependent on the ketone structure. *n*-Alkanones and α-substituted cyclic ketones gave traces or no fluoroolefin, respectively. De-ethoxycarbonylation of **15** was observed in reactions with α-substituted cyclic ketones (see Scheme 7).27 Unsubstituted, β- and δ-substituted cyclic ketones, on the other hand, afforded fluoroalkenes with **15** in 40–82% yields (Scheme 16).27,32 Other heteroaryl analogues of **15**, PT and 2-pyrimidyl sulfones, gave lower yields of products.

4.1.2 Bis(trifluoromethyl)phenyl-Based Reagents—Alonso and Nájera et al. have shown that [3,5-bis(trifluoromethyl) phenylsulfonyl]fluoroacetates (α-(BTFP-sulfonyl)-α-fluoroacetates) react with aldehydes under mild conditions to give α-fluoroacrylates.33 The requisite reagents were synthesized via metalation–electrophilic fluorination of sulfones **39** and **40** (Scheme 17). A better yield was obtained for *tert*-butyl ester **42**, presumably due to higher stability.33

Condensation reactions of **41** and **42** with aldehydes gave best yields when anhydrous conditions, a twofold excess of sulfone, and non-Barbier-type addition were used. Under these conditions, a competing decarboxylation leading to BTFP fluoromethyl sulfone was suppressed.33

Yields were in the range of 42–95% (Scheme 17). Reactions of aromatic aldehydes were *Z*-selective, and selectivities were lower in the case of electron-rich systems, but were unaffected by steric hindrance. *Z*-Selectivity was lower with *tert*-butyl derivative **42** than that with the methyl analogue **41**. Olefination with α-branched aliphatic aldehyde was also *Z*-selective, but reversal of selectivity occurred with 3-phenylpropanal and citronellal; **41** reacted with marginal *E*-selectivity that increased to 4:1 in reaction with *tert*-butyl ester derivative **42** (Scheme 17). It is noteworthy that olefinations with the unfluorinated BTFP sulfone **40** showed a similar trend of *trans*-selectivity, which was good to excellent for all types of aromatic aldehydes.34 Unlike reactions of BT sulfone **33**,29 the use of **40** is limited to aromatic aldehydes due to the competing aldol reactions of aliphatic aldehydes under the reaction conditions.34 Not surprisingly, here again the reactivity of **40** was much lower than that of fluorinated BTFP sulfone **42**, as can be judged by the much higher temperatures required for reactions of **40**. This influence of fluorine substitution on reactivity has previously been demonstrated by us in competitive experiments of several fluorinated and unfluorinated BT sulfones.30,35

4.2 α-Fluoro Acrylonitriles

Known methods for the synthesis of α-fluoroacrylonitriles involve use of diethyl (cyano)(fluoro)methanephosphonate36 or (diphenylphosphinoyl)fluoroacetonitrile,37 both derived

from fluoroacetonitrile. In each case it was necessary to prepare the reagent in situ in order to obtain good condensation yields. Therefore, our focus was the preparation of a stable, isolable building block from which α-fluoroacrylonitriles could be synthesized via the Julia olefination. Initial attempts at the synthesis of a suitable building block via metalation–fluorination of a variety of precursors proved unsuccessful.38 Benzothiazole-based reagent **45** (Scheme 18) was, therefore, prepared via functional group interconversions from ethyl (benzothiazol-2-ylsulfanyl)fluoroacetate (**43**). The requisite sulfide **43** was synthesized either via metalation–fluorination of ethyl (benzothiazol-2-ylsulfanyl)acetate,38 or from commercially available ethyl bromofluoroacetate.32a,38 Conversion of the ester moiety to the amide, followed by dehydration using cyanuric chloride,39 and subsequent oxidation furnished (benzothiazol-2-ylsulfonyl)fluoroacetonitrile (**45**). In reactions of **45** with aldehydes a *slow, dropwise addition* of **45** to a solution of DBU and aldehyde was required in order to obtain high yields of the acrylonitriles (Scheme 18).38 At room temperature or at −78 °C, condensations proceeded with good to excellent *Z*-selectivity. Increase in *Z*-selectivity was observed at the lower temperature. Stereoselectivity was practically independent of the aldehyde structure (Scheme 18).

4.3 α-Fluorovinyl Phenyl Sulfones

Synthesis of the benzothiazole-based reagent for preparation of α-fluorovinyl phenyl sulfones is shown in Scheme 19.35 Introduction of fluorine into a bis-sulfone, (benzothiazol-2-ylsulfonyl)methyl phenyl sulfone, using sodium hydride or potassium *tert*-butoxide and Selectfluor resulted in recovered starting material (35–40%) and various amounts of the difluoro byproduct. Better conversion was achieved when fluorine was introduced into BT sulfide **46**, which was subsequently oxidized to bissulfone reagent **47** (Scheme 19).35

Condensation reactions of **47** with aldehydes gave high yields of products. Except for sterically hindered aromatic aldehydes, good to high *Z*-selectivity was observed with all other aromatic and aliphatic aldehydes, including the hindered 2-ethylbutanal.35 Addition of $MgBr_2$ increased the *Z*-selectivity for *n*-octanal and *o*-anisaldehyde, but had little effect on the reactions with thiophene-2-carbaldehyde and 4-nitrobenzaldehyde. It is noteworthy that known methods yield α-fluorovinyl sulfones with predominant40 or exclusive41 *E*-stereoselectivity. Thus, the Julia olefination method is complementary to existing ones. Reactivity of 1-benzylpiperidin-4-one with **47** depended on the conditions; with DBU/CH_2Cl_2 only 47% conversion was observed in 24 hours. Upon changing the solvent to tetrahydrofuran, the reaction was complete in 3.5 hours (65% yield), a result comparable to that obtained with LHMDS/THF/0 °C (70% yield).

Reactivity of **47** was higher compared to Horner-Wadsworth-Emmons analogue [$PhSO_2CHFP(O)(OEt)_2$].35 Under identical olefination conditions, the Horner-Wadsworth-Emmons reagent showed moderate *Z*-selectivity with 2-naphthaldehyde and no selectivity with *n*-octanal.

We have previously demonstrated the higher reactivity of the fluoro-Julia-Kocienski reagent **15**,30 compared to the unfluorinated reagent **33**.30 Similarly, the reactivity of fluorinated and unfluorinated bis-sulfone reagents **47** and **48** was also compared (Scheme 20). A competitive reaction of fluorinated reagent **47** and unfluorinated (benzothiazol-2-ylsulfonyl)methyl phenyl sulfone (**48**) with 2-naphthaldehyde afforded the α-fluorovinyl sulfone as *the sole product*. This again demonstrates the influence of fluorine substitution on the reactivity of the Julia reagent.35

One possible structure-based explanation for these results can be derived from a thorough study of a series of substituted bis(phenylsulfonyl)methide anions that have recently been

reported by Prakash and Olah et al.42 Comparison of the structural and electronic properties of the anions derived from the protio- as well as chloro-, bromo-, fluoro-, and methoxy-substituted compounds by X-ray, computational, and NMR analyses showed very interesting differences. Whereas the protio-, chloro-, and bromosubstituted methide anions are planar, the fluoro and methoxy derivatives show pyramidalization. This study also showed that introduction of chloro and bromo into the bis(phenylsulfonyl)methide anion causes stabilization, whereas fluoro and methoxy substituents result in destabilization by coulombic repulsion between the carbanionic charge and substituent.42 This could be the basis for the higher reactivity of the analogous fluoro-Julia-Kocienski reagent **47** in comparison to the protio derivative **48**, by the 'α-effect' of fluorine on nucleophilicity.

4.4 α-Fluorovinyl Weinreb Amides

Synthesis of a benzothiazole-based Julia reagent for vinyl Weinreb amide synthesis was originally published by Aidhen et al.43 Sodium hydride mediated condensation reactions of *N*-methoxy-*N*-methyl-(benzothiazol-2-ylsulfonyl)acetamide with aldehydes proceeded with exclusive *E*-selectivity.43 Subsequently, Nájera et al. reported synthesis of vinyl34 and α - fluorovinyl33 Weinreb amides using 3,5-bis(trifluoromethyl)phenyl-derived (BTFP) reagents, whereas our group pursued the synthesis of α-fluorovinyl Weinreb amides using a benzothiazole-based Julia reagent.44

4.4.1 Bis(trifluoromethyl)phenyl-Based Reagent—Fluorine was introduced into BTFP sulfone **49** using NaH/Selectfluor to yield **50** in 74% yield (Scheme 21).33 Condensation reactions were performed using K_2CO_3/TBAB/DMF at room temperature. Reactions were highly (>99%) *Z*-selective for all types of aldehydes, whereas product yields depended on the structure of the aldehyde. Among aryl aldehydes, yields were lowest for methoxy-substituted ones (Scheme 21). Interestingly, the highest yield (99%) was obtained with the sterically hindered 2 - chlorobenzaldehyde.33

4.4.2 Benzothiazole-Based Reagent—The fluoro-Julia-Weinreb amide reagent was synthesized via two routes (Scheme 22). Fluorine could be either introduced into sulfone **52** using LDA/NFSI to yield **53** (Route 1, 76% from **51**, Scheme 22) or, sulfide **51** could be fluorinated using LDA/NFSI to furnish **54**, which was then oxidized to **53** (Route 2, 68% from **51**, Scheme 22).44

Using **53**, we have shown that choice of reaction conditions can be used to tune olefination reactions with aldehydes towards either *E* or *Z*-selectivity (Scheme 23). Condensations mediated by DBU in less polar solvents (CH_2Cl_2 or THF) were *Z*-selective, and *Z*-selectivity increased when temperature was lowered from room temperature to −78 °C. Condensations with DBU in polar solvents (DMF or DMPU) at room temperature favored the *E*-isomers. High *Z*-selectivity was obtained under DBU/$MgBr_2$/THF conditions, whereas NaH/THF gave ≥98% of the *Z*-isomer.

Reaction of acetophenone with **53** using NaH/THF gave complex reaction mixture, whereas 1-benzylpiperidin-4-one yielded the alkene (57%). Cyclohexanone and 1-benzylpiperidin-4-one could be reacted with **53** using Cs_2CO_3/DMF as well (42% and 59%, respectively). We have also demonstrated the use of fluoro-Julia-Weinreb methodology for synthesis of a α-fluoroallylamine44 which is dipeptidyl peptidase II inhibitor.45

4.5 α-Fluoroenones

Fluorinated BT sulfide **54**, an intermediate in the synthesis of Julia-Weinreb reagent **53**, was reacted with Grignard reagents and then oxidized to yield Julia reagents for the synthesis of

α-fluoroenones **57** and **58** (Scheme 24).44 This demonstrates that two sets of Julia reagents can be synthesized from a common fluorinated precursor.

Condensations proceeded with aldehydes under mild DBU mediated conditions to yield α-fluoroenones with high *Z*-stereoselectivity, in yields ranging from 61–90% (Scheme 24).44

5 Synthesis of 1,1-Difluoroalkenes

While this manuscript was under preparation, the synthesis of 1,1-difluoroalkenes was reported via difluoromethyl 2-pyridyl sulfone (**61**) (Scheme 25).46 Aldehydes and ketones reacted with **61** to give *gem*-difluoroalkenes in 40–93% yields (some yields could be affected due to product volatility). In test reactions using 2-naphthaldehyde, difluoromethyl BT sulfone **23** gave a lower product yield compared to **61**, whereas the PT- and TBT-analogues gave a trace and no product, respectively. The requisite heteroaryl sulfone reagents were prepared by reactions of heteroarenethiolates with chlorodifluoromethane (*vide infra*, Scheme 33) followed by oxidation (Scheme 25).46

Due to a slow elimination of sulfur dioxide and 2-pyridyl alkoxide after Smiles rearrangement, it was possible to trap the intermediate sulfinate salt with iodomethane, providing additional mechanistic proof for the olefination reaction.46

6 Mechanism of Julia-Kocienski Olefination

Various stereochemical outcomes of Julia-Kocienski olefination, which are not always predictable, have been discussed in several excellent reviews.8 The mechanism originally proposed by Julia for benzothiazole, 2-pyridyl and 2-pyrimidyl derivatives, is shown in Scheme 26.8,9,12 Addition of the carbanion to a carbonyl compound can proceed in either a *syn* or *anti* fashion. The resulting β-alkoxy sulfones undergo Smiles rearrangement via spirocyclic intermediates SI and SII. Among the two, SII derived from the *syn*-adduct A_s, forms faster due to less steric strain. Opening of the spirocyclic intermediates and concerted *anti*-elimination of sulfur dioxide and heteroaryl alkoxide then yields *E*/*Z* alkenes.

Besides E2 elimination, an alternate route was proposed by Julia in the case of aromatic aldehydes or those stabilized by conjugation.8,12b In such cases, zwitterionic intermediates ZI_s and ZI_a were suggested to form by BT-alkoxide elimination (Scheme 27). Here, the *trans*-alkenes would be formed predominantly, due to equilibration of zwitterionic intermediates to more stable ZI_s.

Interesting differences were observed when we compared the stereochemical outcome in the DBU-mediated synthesis of α-fluoroacrylates30 to that of the unfluorinated analogues reported by Blakemore et al.29 That is, aromatic and α-branched alkyl aldehydes gave *trans*-alkenes as major products in reactions with unfluorinated **33**, whereas the *cis*-isomers predominated when *n*- or β-branched alkanals were used. The major isomer in synthesis of α-fluoroacrylates had *cis*-disposition of substituents for all aldehydes tested (Schemes 13 and 14). These comparisons led us to suggest the following. Assuming that the first step leading to A_a and A_s (Scheme 26) is reversible, this would result in predominant formation of kinetic SII in both cases, which could then collapse to alkenes via different elimination processes. Due to the destabilizing effect of fluorine on a β-fluorocarbocation, formation of zwitterionic intermediates would not be favored, unlike in reactions of the unfluorinated analogue, where an E1 mechanism could occur. This could explain opposing stereochemical outcomes in condensations of **33** with aromatic aldehydes, compared to reactions of **36** and **15** (Scheme 28).30

Recently, Alonso and Nájera suggested an alternate pathway in the synthesis of fluorinated and unfluorinated acrylates and vinyl Weinreb amides using BTFP sulfones.33,34 An exclusive or predominant formation of *trans*-alkenes (*trans* disposition of alkyl/aryl substituent and ester/amide moiety, Schemes 17 and 21) was supported by computational analysis.33,34 As described in their work, upon reversible addition of the sulfone carbanion to the aldehyde formation of spirocyclic intermediate SII resulting from the *syn*-adduct is kinetically favored. Collapse of spirocyclic intermediates via an E1cB-like mechanism was suggested, with sulfur dioxide elimination preceding that of BTFP-alkoxide. Kinetically formed SII is therefore responsible for the *trans*-alkenes. Further, as shown in Scheme 29, rotation around the single C–C bond in CB_a to energetically favored CB_s would also lead to *trans*-alkenes, and explain the high stereoselectivity observed.

Various aspects, discussed in previous original work9¯12 and subsequent reviews,8 need to be considered when evaluating the stereochemical outcome of the Julia olefination: (i) Does the initial addition step proceed via an open or closed transition state, or both? This would affect the ratio of *anti*/*syn* adducts. (ii) Is the first step reversible or not? (iii) What are the relative rates of addition/retroaddition and spirocyclization steps? Finally, (iv) What elimination path is operative leading to final alkene formation?8 Since additional mechanistic studies are needed for better understanding of alkene stereochemistry produced, some pattern seems to be emerging in the synthesis of functionalized fluoroolefins.

The stereochemical outcome under DBU-mediated conditions, in the absence of a metal counterion, is compared for differently functionalized BT sulfones in Table 1. As can be seen, predominant *cis* selectivity was observed with fluoro(phenylsulfonyl)methyl BT sulfone **47** whereas exclusive *trans* selectivity was obtained with (BT-sulfonyl) fluoromethyl *n*-propyl ketone **58**. Recent reports on the X-ray structures of anions from bis(phenylsulfonyl)fluoromethane42 and 2-fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide47 show them to be pyramidal. Using ab initio computation, Wiberg et al. have reported that the anion of fluoroacetonitrile shows pyramidalization, whereas anions of acetaldehyde and fluoroacetaldehyde are planar.48 If one assumes comparable trends among the BT-sulfonyl derivatives, on the net basis of the previous observations, it is tempting to postulate that the shape of the anion (hybridization) could plausibly influence the stereochemical outcome. Thus, the anions from bis-sulfone **47** and keto sulfone **58** may represent the two boundaries of the anionic hybridization, although clear and convincing evidence is yet to emerge. In the presence of magnesium bromide, an increase in *trans* selectivity was observed with **15**32a, 49 and **53**44 but not with **47**.35 Thus, if metal–enolate complex formation leads to greater planarization of the anion in **15** and **53**, the observed increase in *trans* selectivity would be consistent with the discussion above.

In this context, pyramidal α-fluorocarbanions are reported to be more stable compared to planar ones, due to minimized lone-pair repulsions.1 With more stable anions, reversibility of initial addition could partition the pathway via SII. If E1 elimination is minimal due to fluorine substitution (as described for α-fluoroacrylates), this could account for the predominant *cis* selectivity observed with the more stable anions. The bases for the high *trans* selectivity in DBU-mediated olefination of **58** are less clear at the present time and could be due to a variety of reasons. For example, irreversible predominant *anti* addition of a more planar carbanion, followed by E2 elimination after Smiles rearrangement, or a nonstereoselective addition, with E1cB mechanism subsequent to Smiles rearrangement (Scheme 29). It should be noted however that in the case of the cyano group other effects could also be operative, due to its small size relative to other substituents.

7 Miscellaneous Syntheses of Heteroaryl-Derived Fluorinated Sulfides and Sulfones

Described in this section are some miscellaneous methods for the preparation of α-fluorinated derivatives of BT, PT, 2-pyridyl and 2-pyrimidyl sulfides and sulfones. Some of these could plausibly be intermediates in the synthesis of fluoroolefins.

Synthesis of benzothiazole-derived reagents for preparation of α-fluoroallylamines via Julia-Kocienski olefination has recently been reported.50 The key fluorinated building block α-fluorovinyl BT sulfone **63** was synthesized either from ethyl (benzothiazol-2-ylsulfanyl)fluoroacetate (**43**) (Route 1), or by Horner-Wadsworth-Emmons olefination with formaldehyde and **64** (Route 2, Scheme 30).

Michael addition of alkyl- and arylamines, and esters of L-amino acids to **63** yielded 2-amino-1-fluoroethyl BT sulfones **65**, which are potential reagents for allylamine synthesis. In the case of L-amino acids, a mixture of diastereomers in ~1:1 ratio was obtained (Scheme 31).50

Among the heteroaromatic nucleophiles, imidazole gave a high yield of product, whereas pyrrole, pyrazole and benzimidazole did not react under these conditions. The use of a reagent **65** (NR_1R_2 = pyrrolidin-1-yl) in olefination was demonstrated by its reaction with 4-bromobenzaldehyde (alkene: 70% yield, ratio *E*/*Z* 1/1).50

α-Fluorovinyl BT sulfone **63** can also serve as the precursor in the synthesis of α-fluoroalkyl BT sulfones, via conjugate addition of organometallics formed from alkyl iodides and Zn/CuI (Scheme 32). On the other hand, organocuprate, lithium, magnesium and indium carbanions gave predominantly *ipso* substitution. The choice of solvent was also important, since in formamide alone a competing conjugate addition of solvent to **63** was observed at 100 °C. Better yields of products were obtained using DMSO/formamide 2:1 (53–66%, Scheme 32).50

S-Difluoromethylated tetrazole-5-thiols **68** were prepared from tetrazole-5-thiols **67** under mild alkaline conditions using chlorodifluoromethane (Scheme 33, equation 1). On the other hand, use of potassium hydroxide in *N*,*N*-dimethylformamide at 100–120 °C yielded a regioisomeric mixture of major *N*-difluoromethyl and minor *S*-difluoromethyl products.51 Reaction of benzothiazole-2-thiol (**3**) gave a 3:1 mixture of *S*- and *N*-difluoromethylated derivatives **69**/**70** (Scheme 33, equation 2).52a Synthesis of the 5-methoxy analogue of **69** using CHF_2Cl chlorodifluoromethane and sodium hydroxide has previously been described, but no yields were reported.52b

Difluoromethylation of thiolates using difluoromethyl sulfoximine, which is a new *S*-, *N*- and *C*-difluoromethylating agent, has recently been reported.53 Benzothiazolethiolate gave a mixture of *S*- and *N*-difluoromethyl regioisomers (Scheme 34), comparable to that obtained with CHF_2Cl/KOH.52a Phenyltetrazole and 4,6-dimethylpyrimidine-2-thiolate yielded *S*-difluoromethyl derivatives **68** and **71** in 57% and 71% yields, respectively.53 The intermediacy of a difluorocarbene was proposed.

Monofluoromethylation of heteroarenethiols using chlorofluoromethane yielded *S*-monofluoromethyl derivatives.54 An S_N2 mechanism was proposed, since radical scavengers had no effect on reaction progress (Scheme 35).54

A series of variously functionalized heteroaryl methyl sulfides was subjected to anodic fluorination using $Et_4NF{\cdot}3HF$ or $Et_4NF{\cdot}4HF$ as a supporting electrolyte and fluoride source,

to yield benzothiazolyl,55,56 5-chloro-benzothiazol-2-yl (5-Cl-BT),55,56 phenyltetrazolyl, 57 2-pyridyl56,58–60 and 2-pyrimidyl56,58,60 fluoromethyl sulfide derivatives (Scheme 36).

Recently, Fuchigami et al. have reported indirect anodic fluorination of pyrimidyl sulfides, in an ionic liquid $Et_3N{\cdot}3HF$ using a 'task-specific' iodoarene mediator (Scheme 37).61

Mixed fluoroolefination reagents containing a phosphonate and either a pyridyl or pyrimidyl sulfone moiety have also been synthesized (Scheme 38).62,63 Olefination reactions with these reagents occurred at the phosphorus center leading to pyridyl or pyrimidyl α-fluorovinyl sulfones, which are handles for additional functionalization.63 The synthesis of α-fluorovinyl BT sulfone **63** shown in Scheme 30 parallels such an approach.

8 Conclusions

The Julia-Kocienski olefination is emerging as a versatile tool for the synthesis of fluoroolefins, ranging from fluoroalkylidenes to functionalized fluoroalkenes and *gem*-difluorides. Metalation–electrophilic fluorination provides a general access to the requisite fluorinated heteroaryl sulfones, which can then be used in synthetic modular assembly. Wherever tested, introduction of fluorine substantially increases the reactivity of the Julia-Kocienski reagents, compared to their unfluorinated analogues. Also, Horner-Wadsworth-Emmons reagents showed lower reactivity than the corresponding Julia reagents, in the cases where they were comparatively evaluated. As has been shown in the synthesis of fluoroacrylates, certain fluoroalkylidenes and fluorovinyl Weinreb amides, olefination reactions can be tuned towards *E* or *Z*-selectivity. In many cases fluorine also influences the olefination stereochemistry and future studies will hopefully provide greater insight into the underlying reasons. Further work is clearly needed to understand the intricacies of the fluoro-Julia-Kocienski olefination as well as a continued evaluation of this approach for the construction of hitherto unknown fluoroorganics.

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49. For the purpose of comparison, 2-naphthaldehyde was reacted with **15** in the presence of $MgBr_2$, using the same conditions as those reported for **47** (ref 35). Fluoroalkene was obtained in *E*/*Z* ratio 14/86, consistent with reported results (ref 32a).
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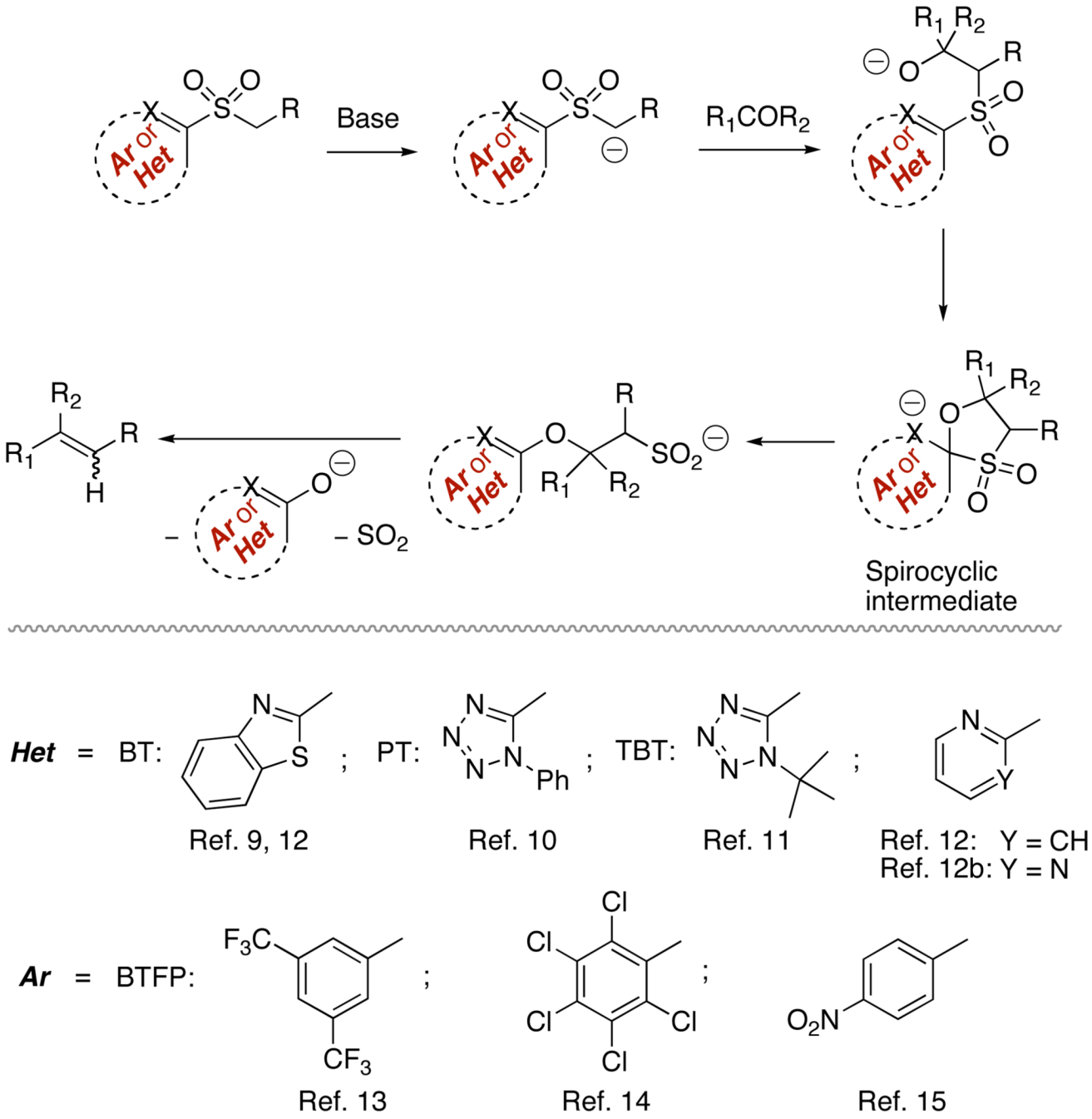
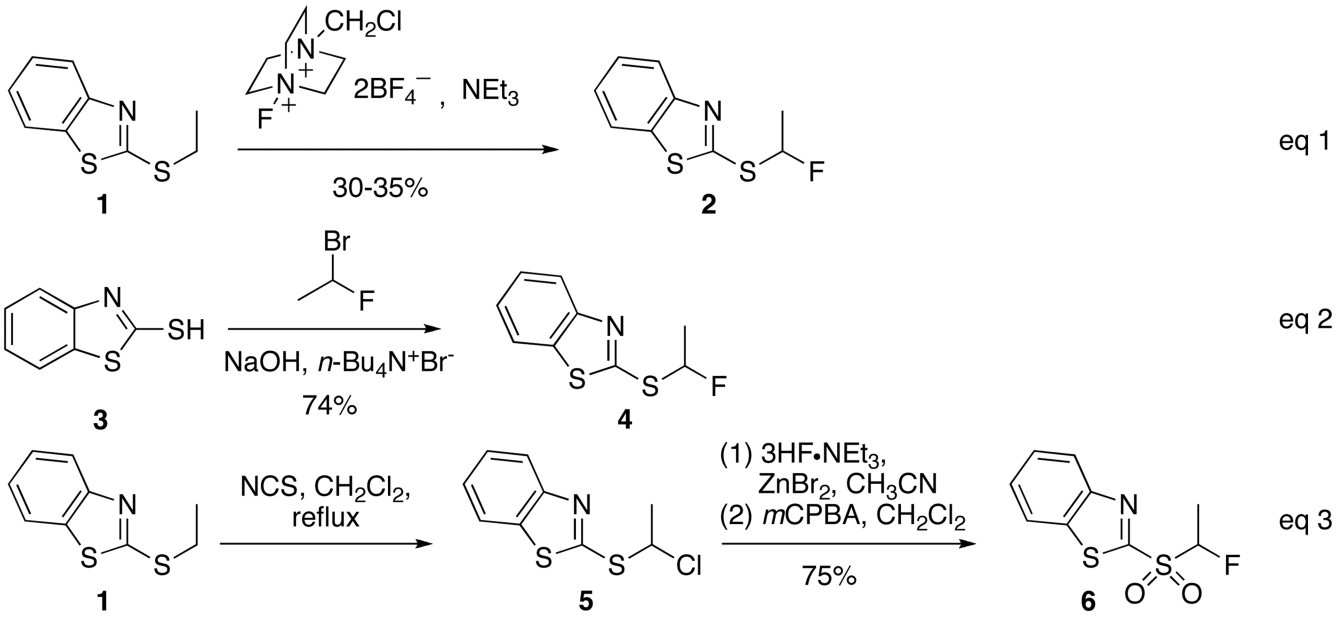
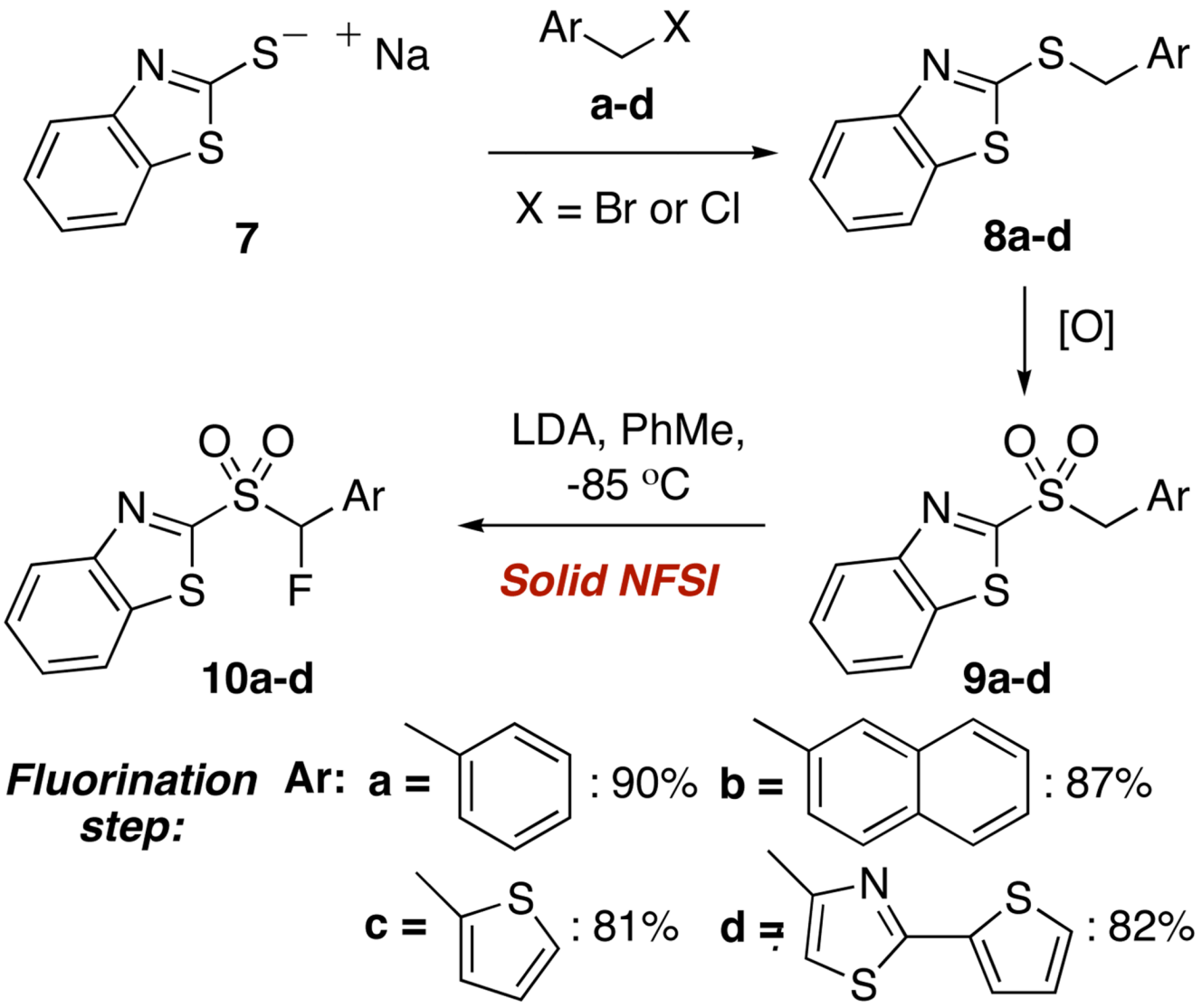


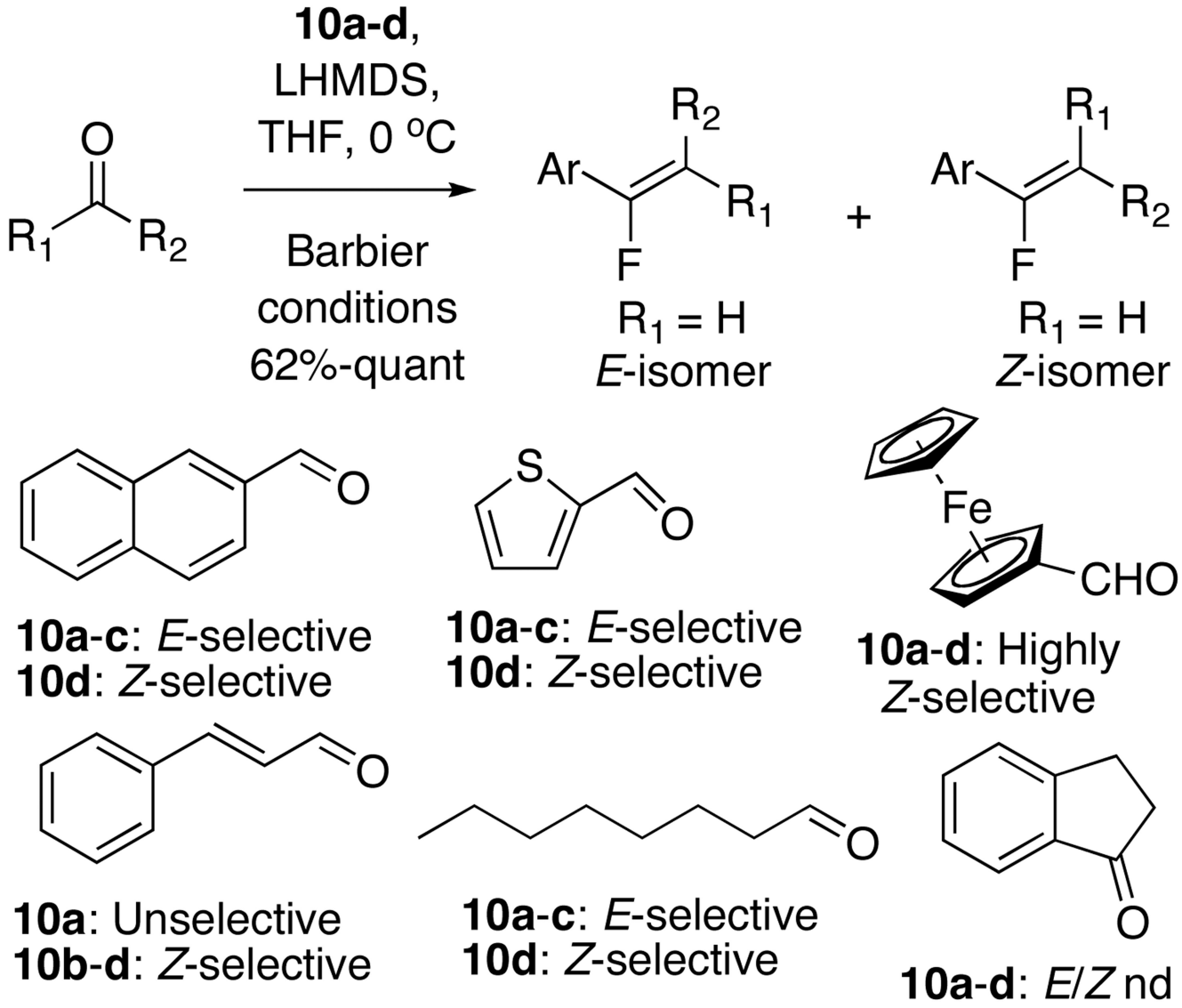
Scheme 1.
Modified or One-Pot Julia-Kocienski Olefination



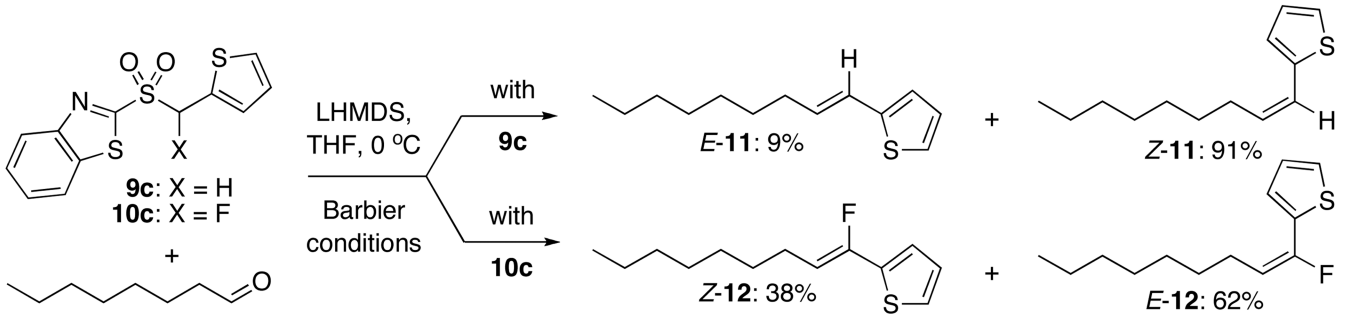
Scheme 2.
First Report of a Fluoro-Julia Reagent for the Preparation of Fluoroalkylidenes



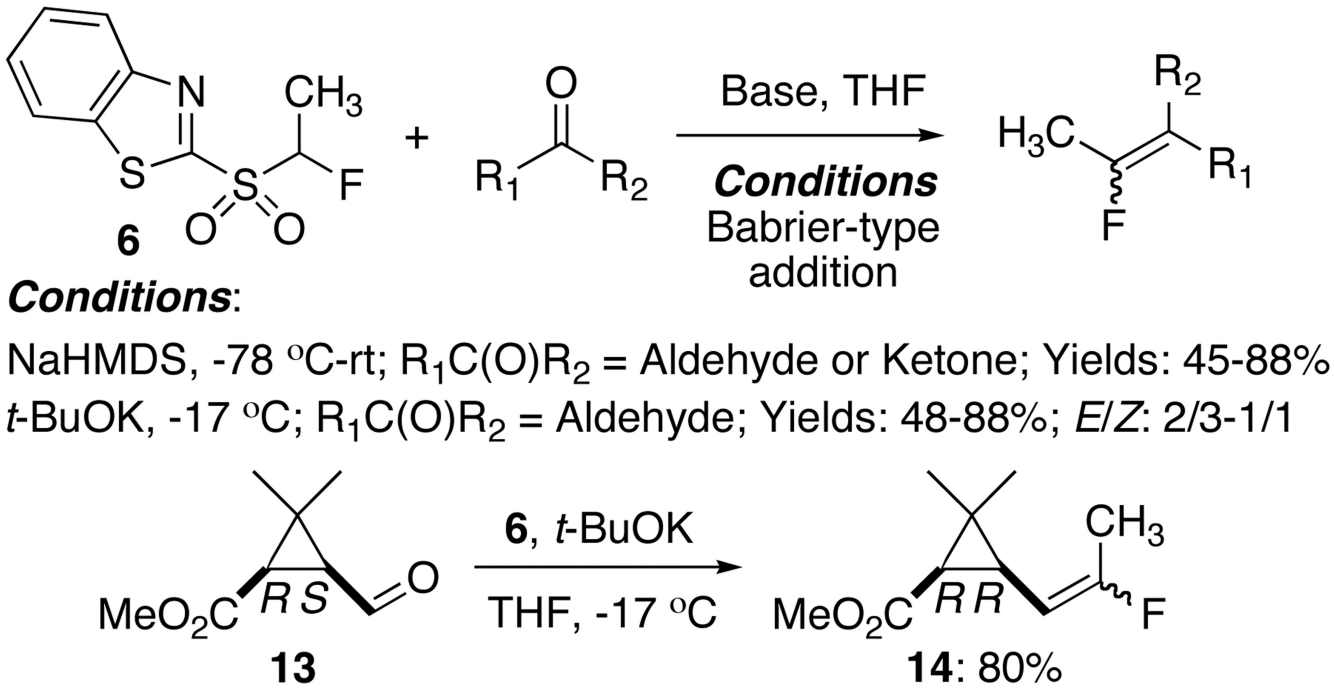
Scheme 3.
Synthesis of α-Fluorobenzyl BT Sulfones



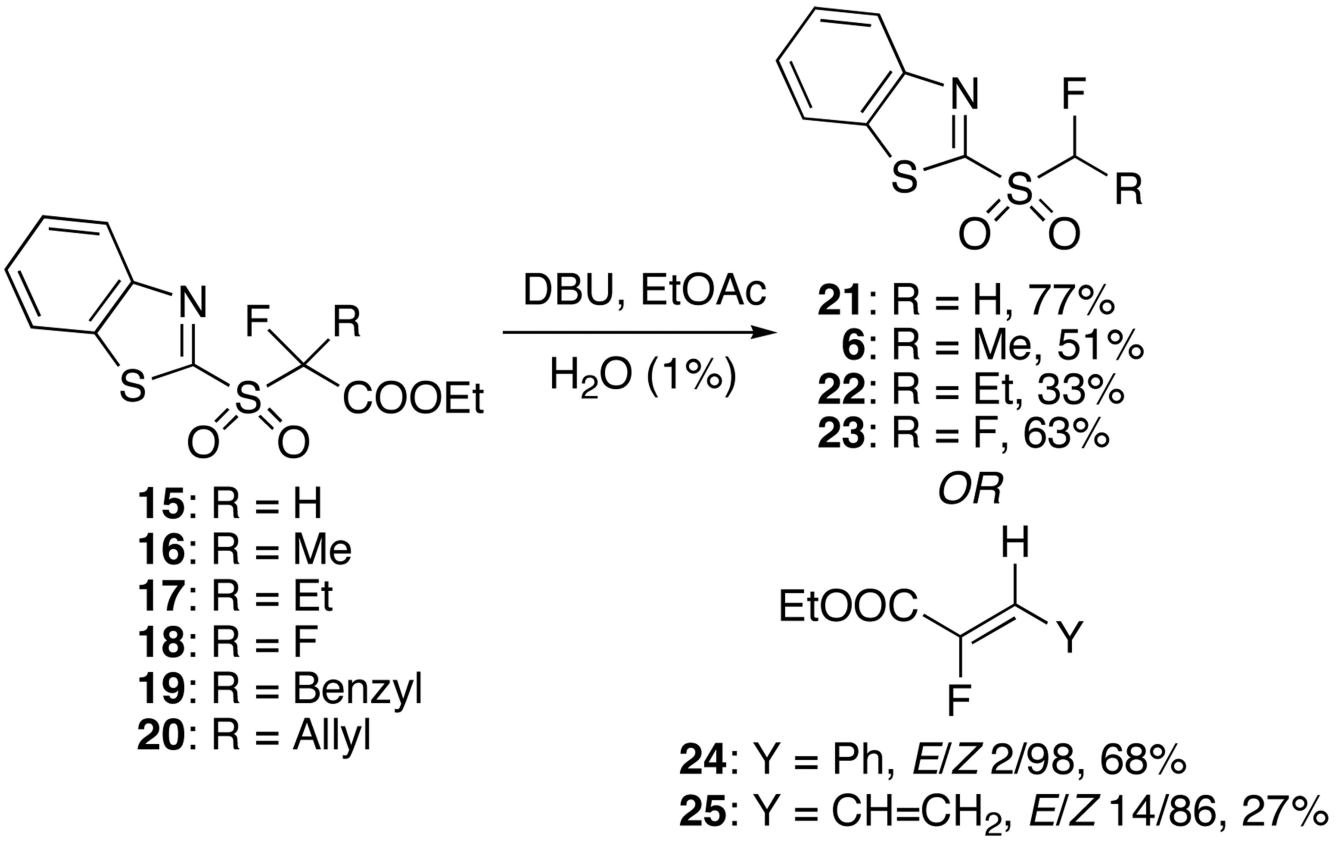
Scheme 4.
Condensations of α-Fluorobenzyl BT Sulfones



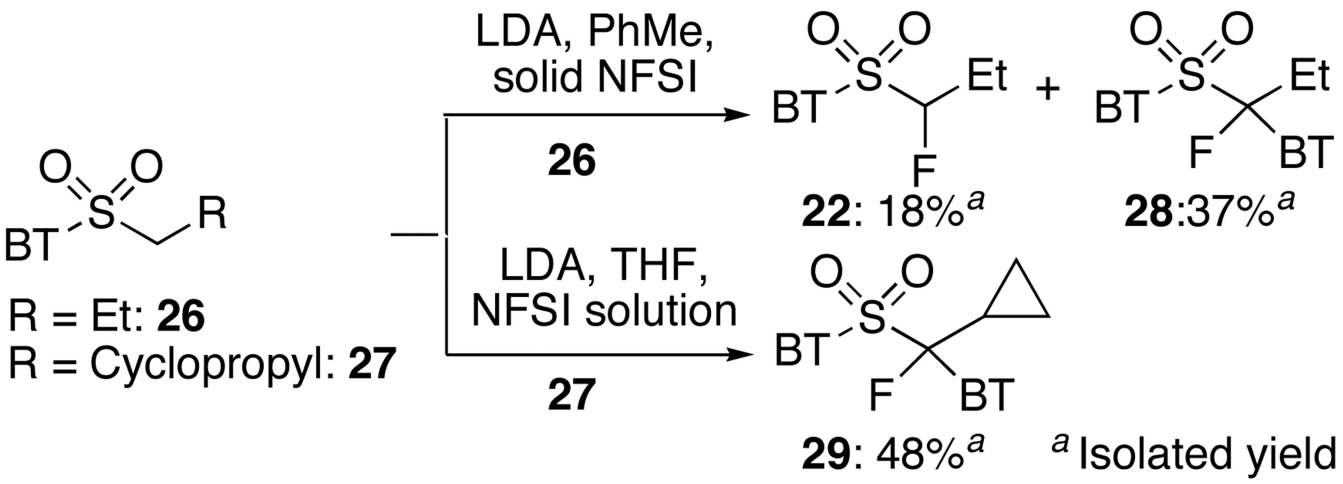
Scheme 5.
Effect of Fluorine on the Olefination Selectivity



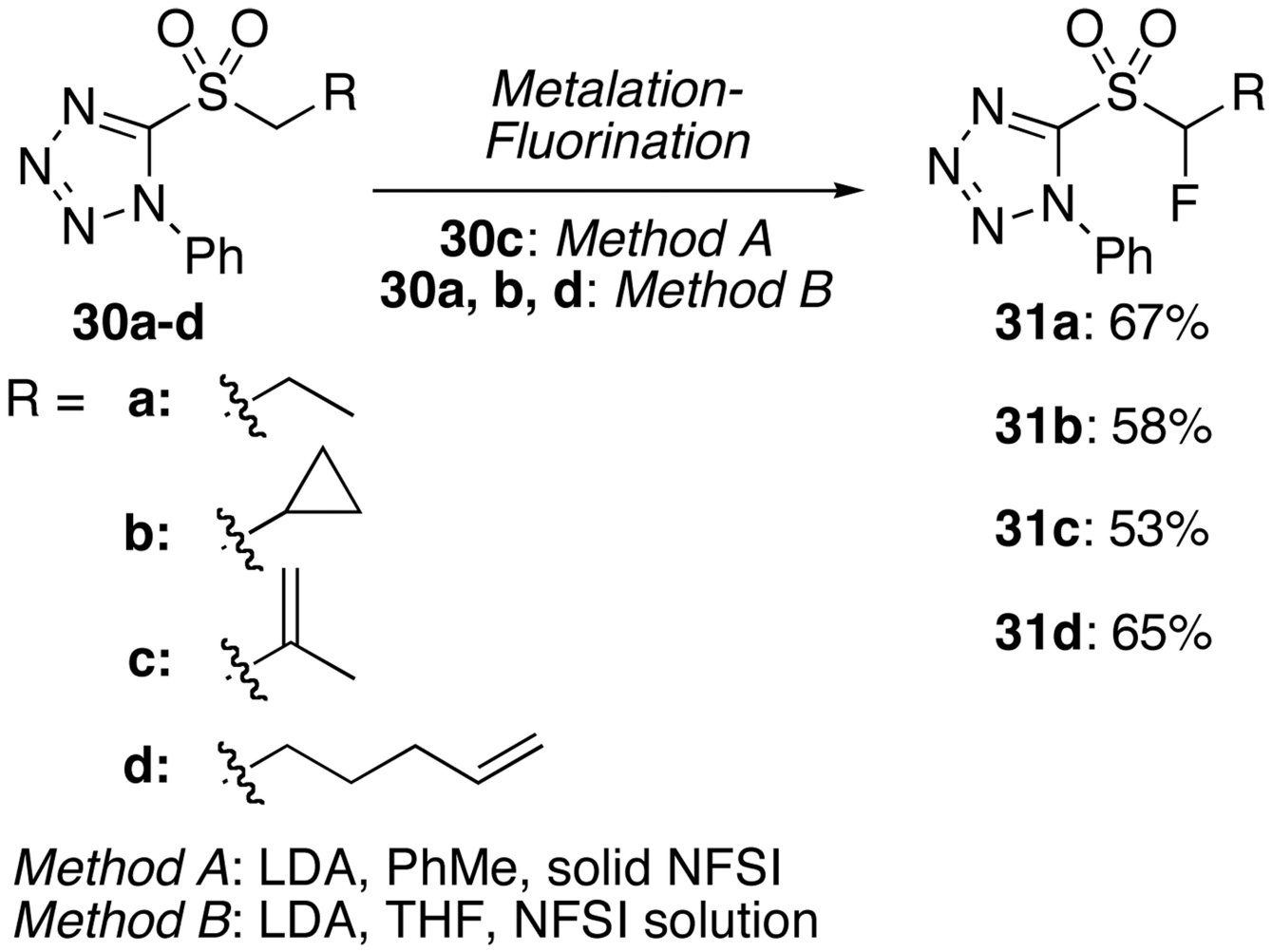
Scheme 6.
Condensation Reactions of α-Fluoroethyl BT Sulfone **6**



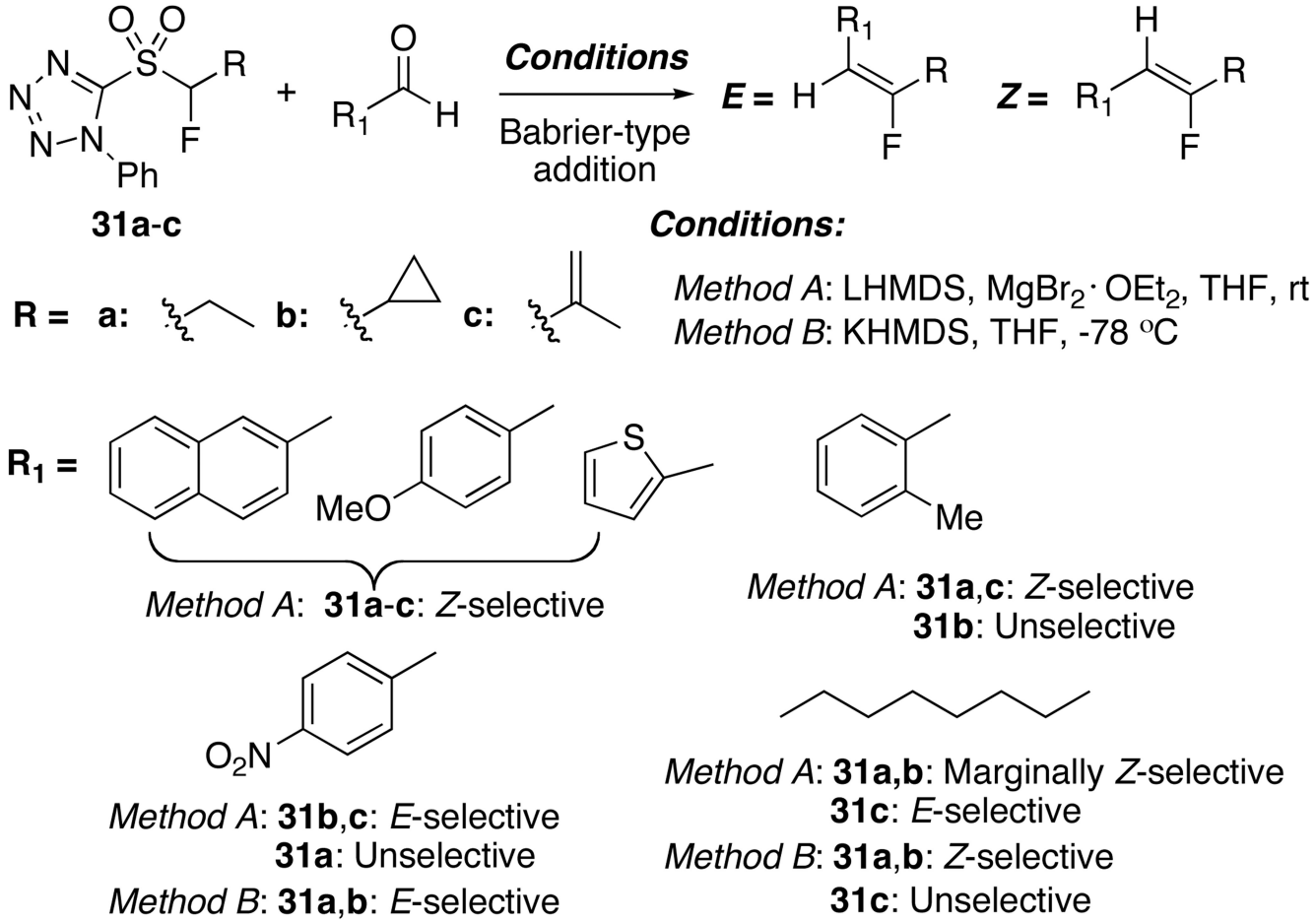
Scheme 7.
Synthesis of Fluoroalkyl BT Sulfones via De-ethoxycarbonylation



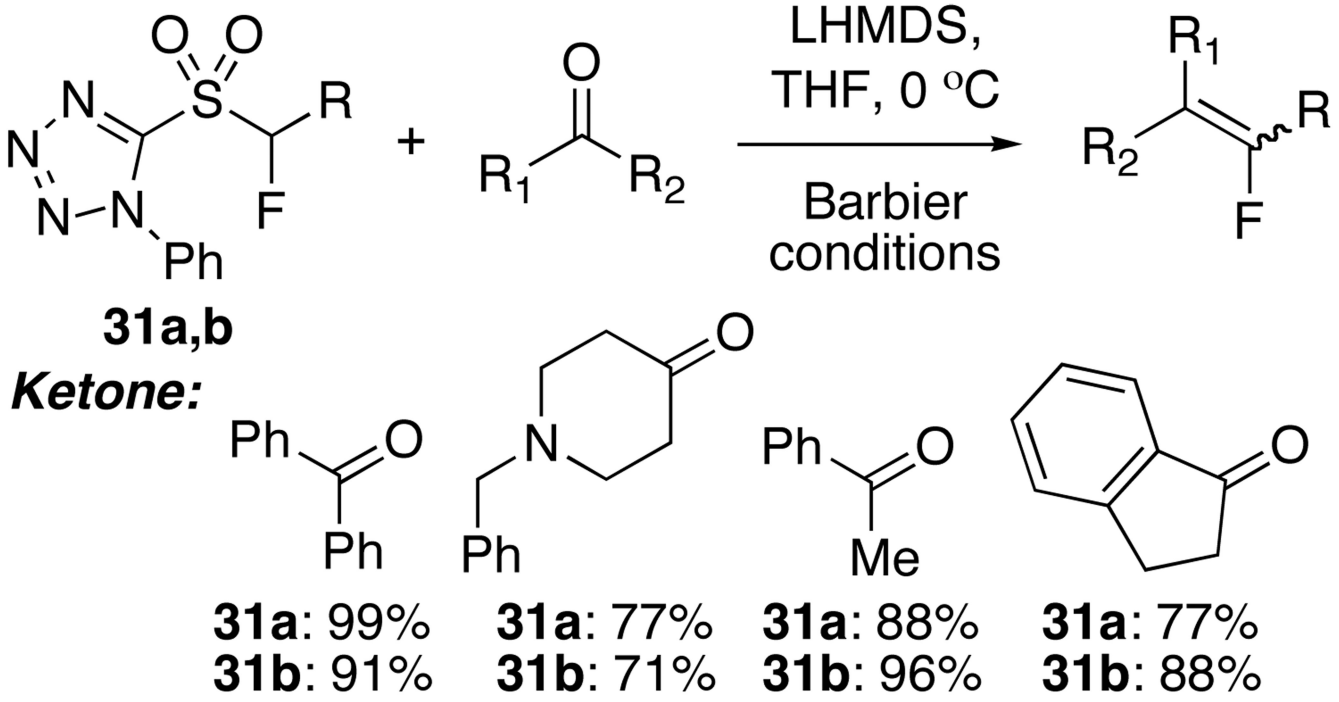
Scheme 8.
Metalation–Fluorination of Alkyl BT Sulfones



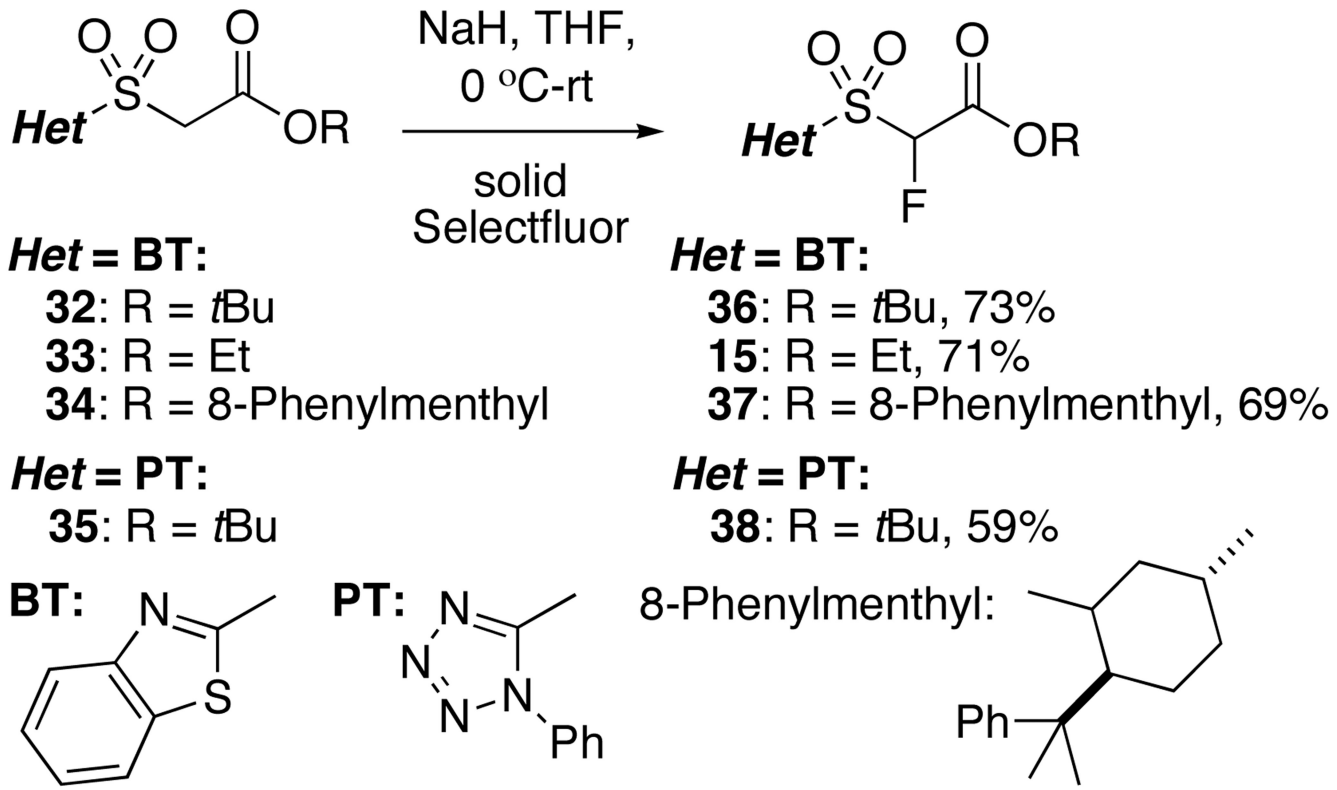
Scheme 9.
Metalation–Fluorination of Alkyl PT Sulfones



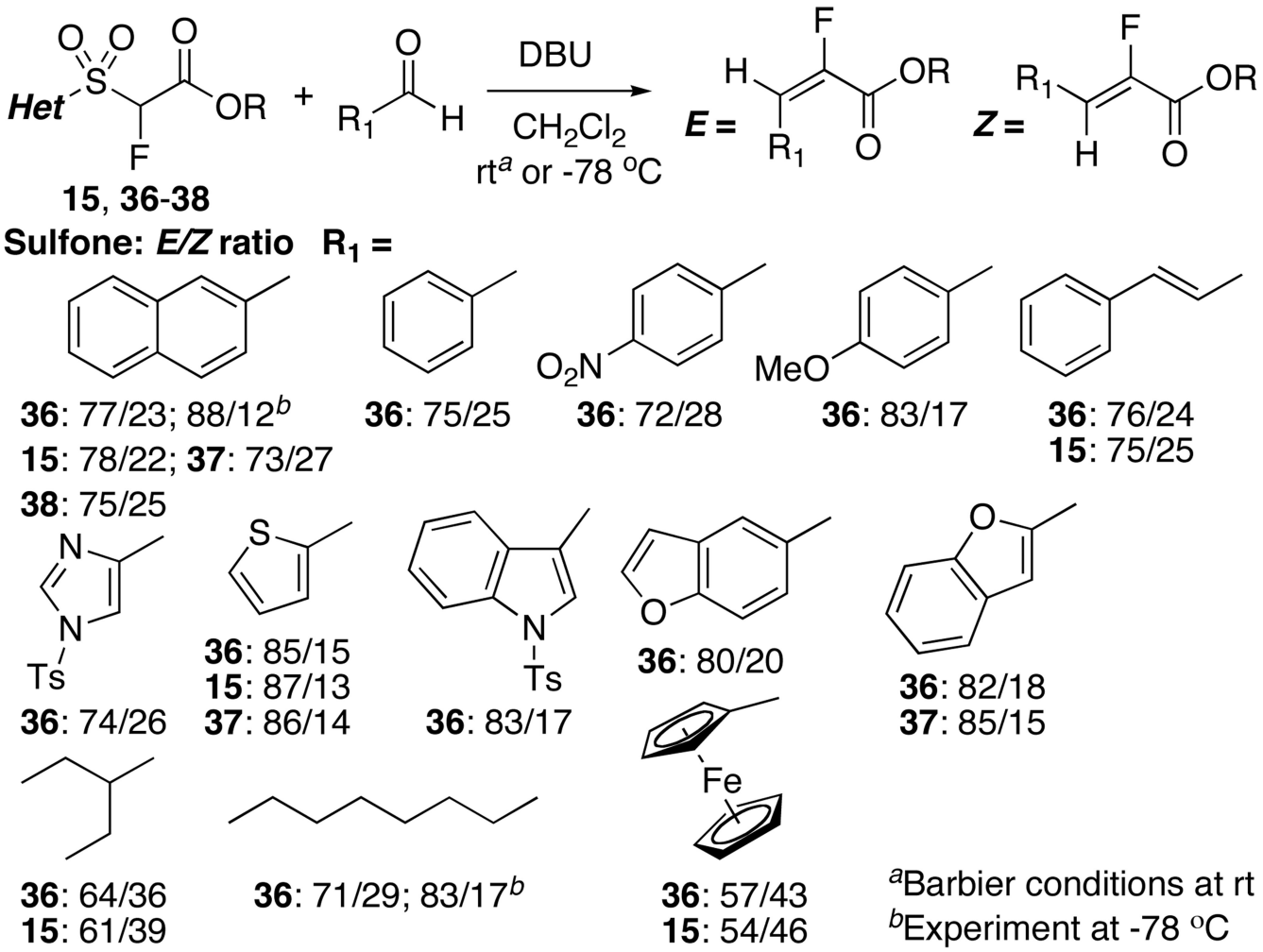
Scheme 10.
Effect of Reaction Conditions on Stereoselection



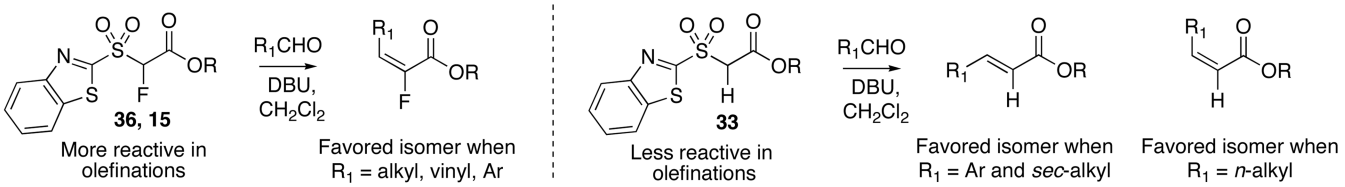
Scheme 11.
Reactivity of Ketones with Fluoroalkyl PT Sulfones



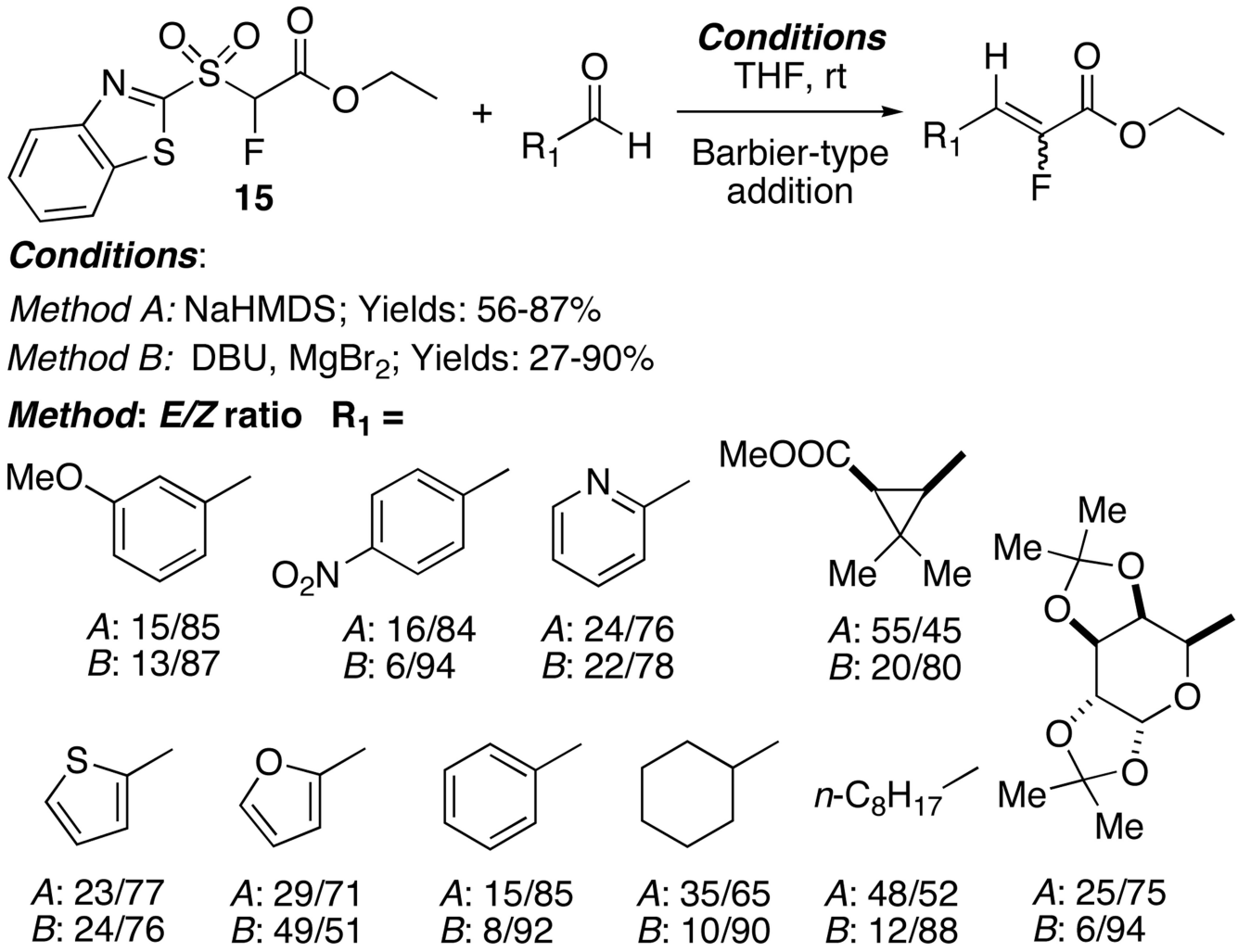
Scheme 12.
Fluorination of (Heteroarylsulfonyl)acetates



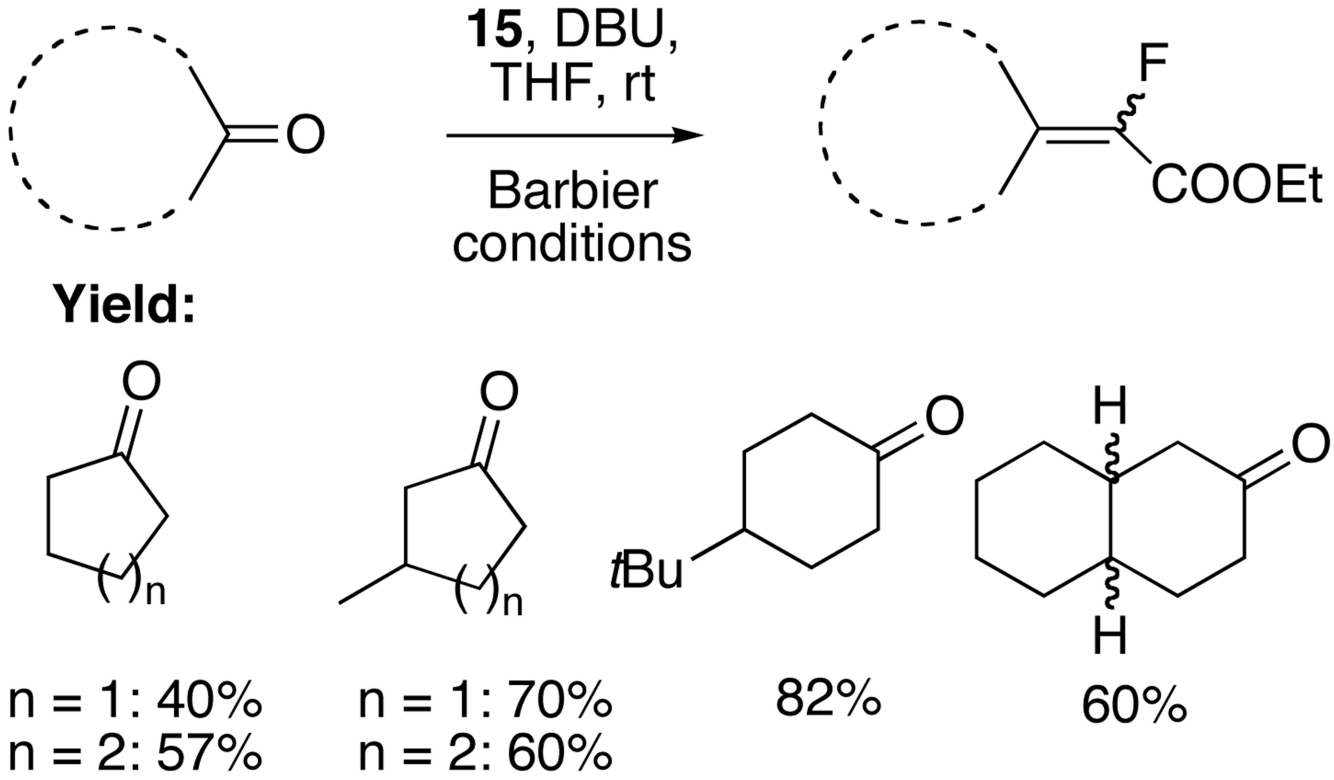
Scheme 13.
Selectivity of Olefinations in the Synthesis of α-Fluoroacrylates



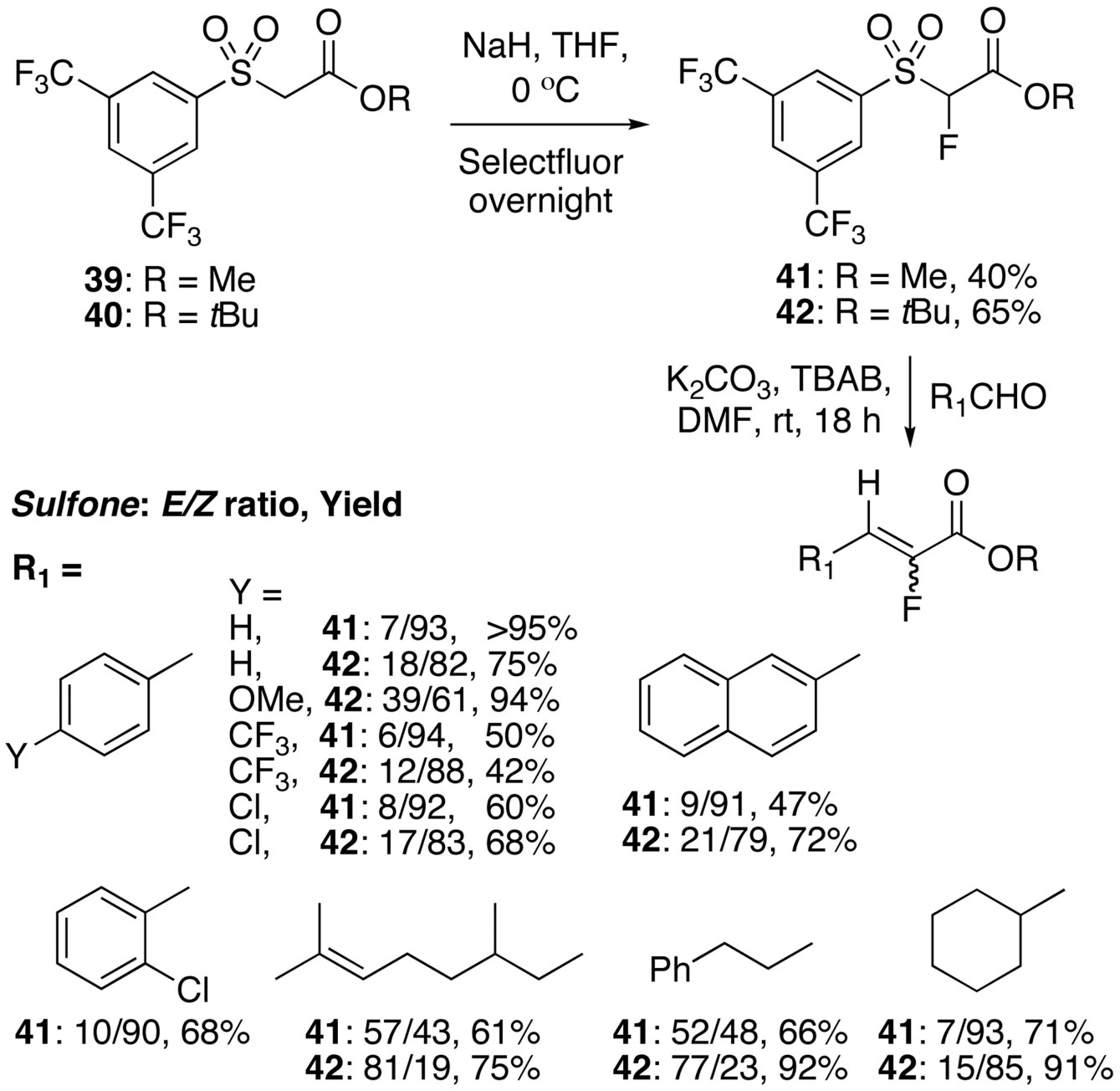
Scheme 14.
Effect of Fluorine on Reactivity and Olefination Stereoselectivity



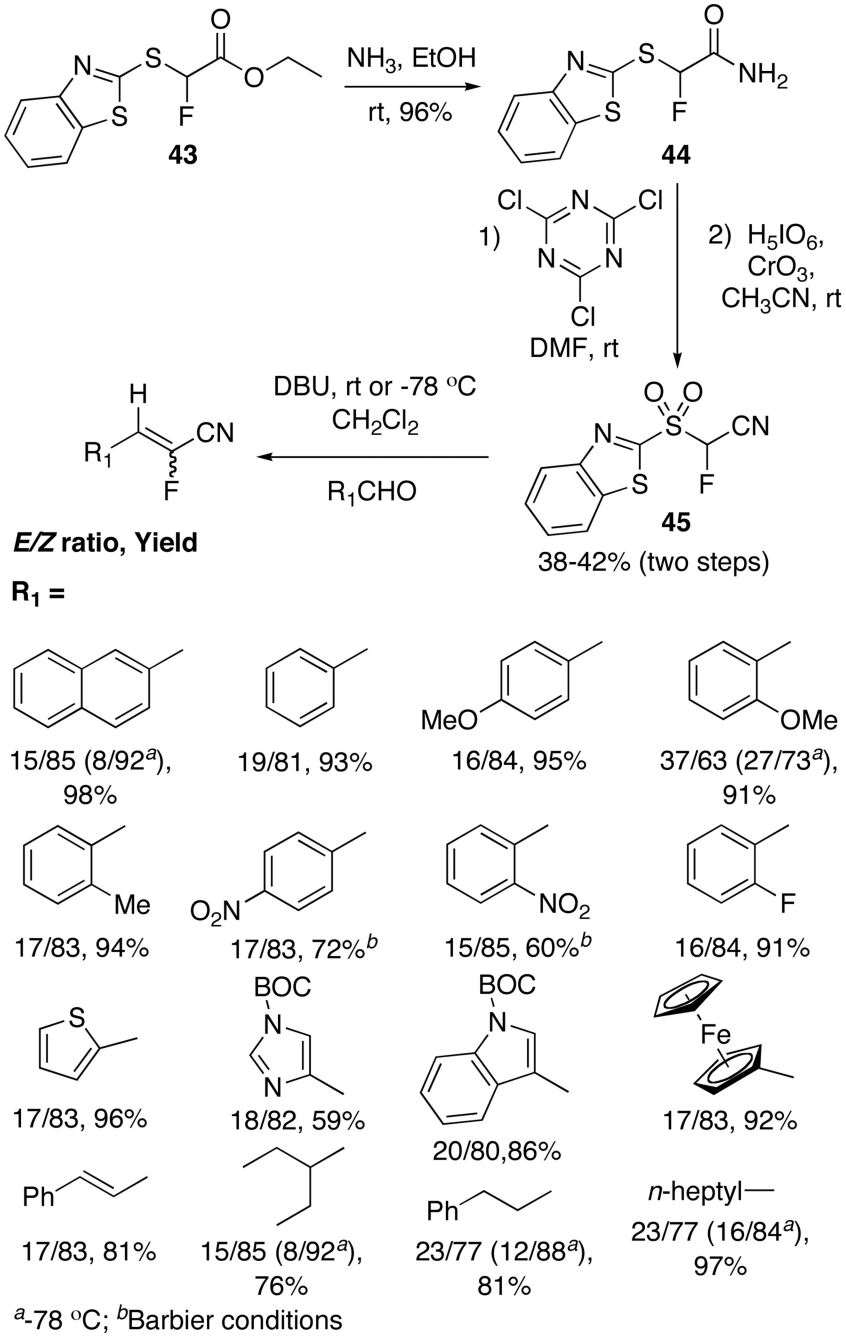
Scheme 15.
Effect of Reaction Conditions on Stereoselectivity



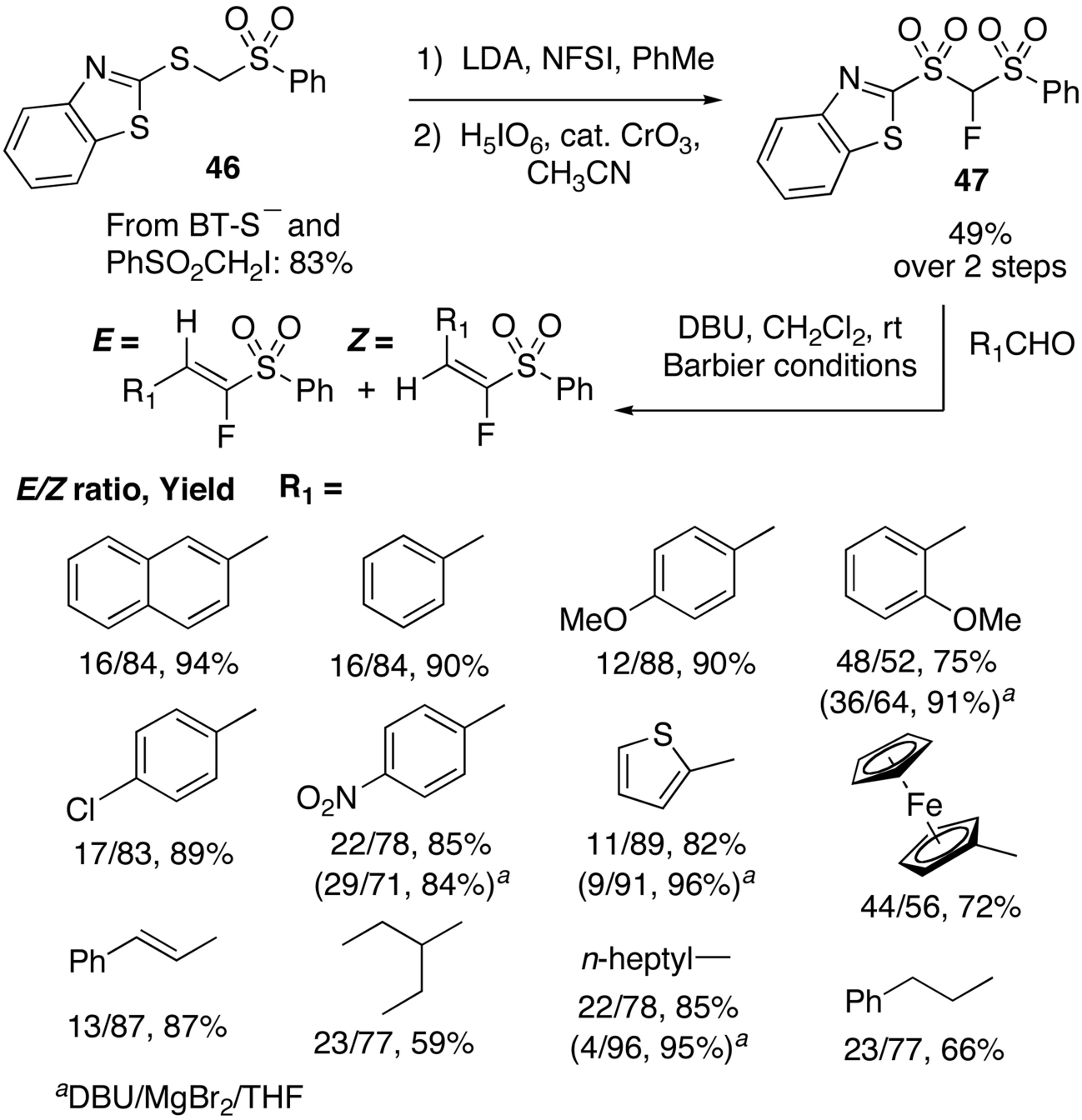
Scheme 16.
Condensations of Cyclic Ketones



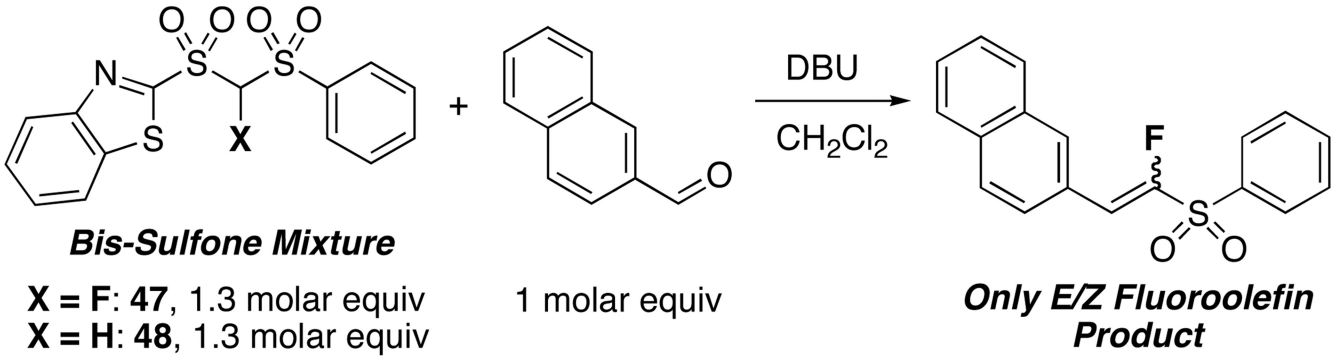
Scheme 17.
Synthesis and Reactivity of (BTFP-sulfonyl)fluoroacetates



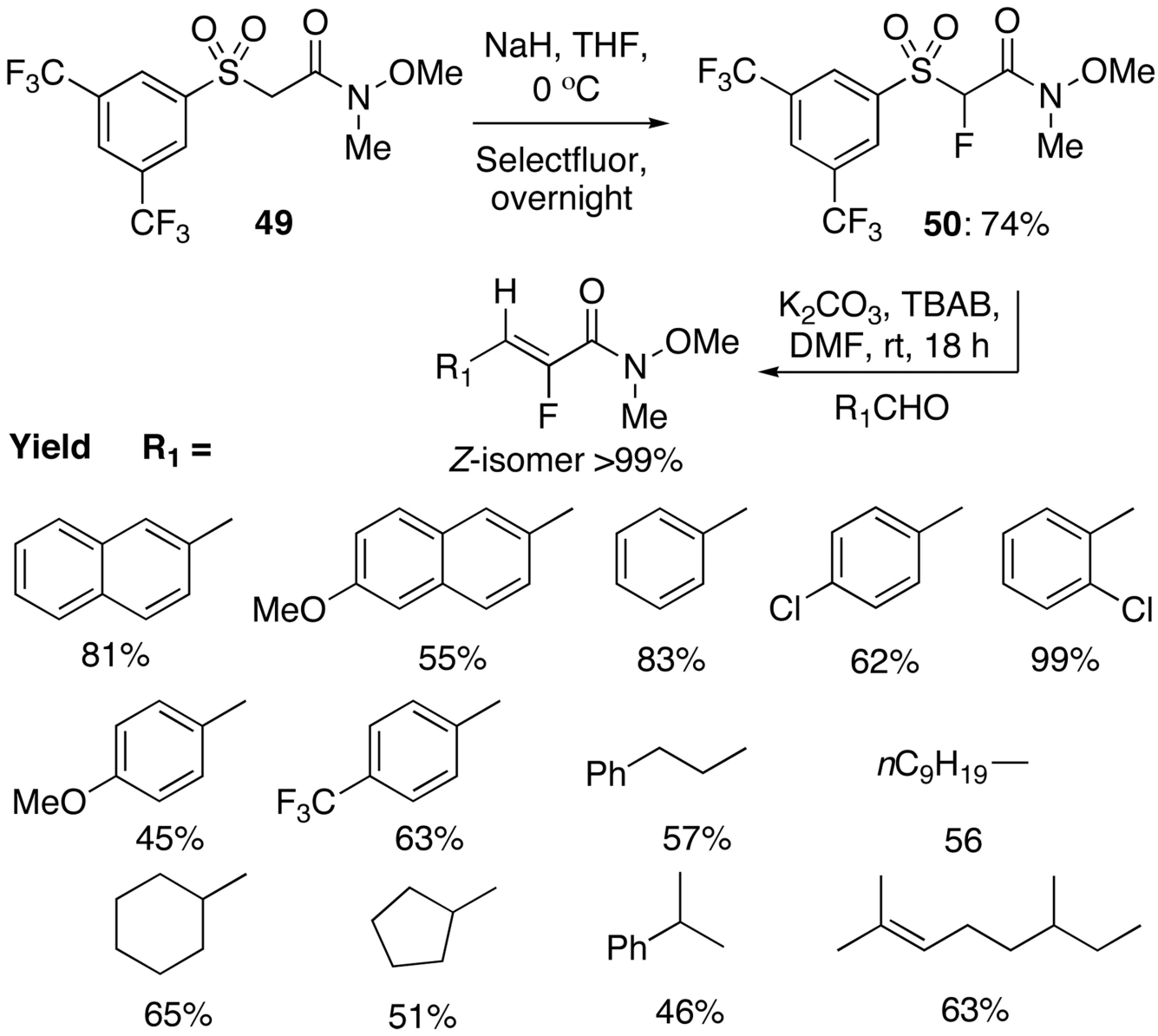
Scheme 18.
Synthesis and Reactivity of (Benzothiazol-2ylsulfonyl)fluoroacetonitrile (**45**)



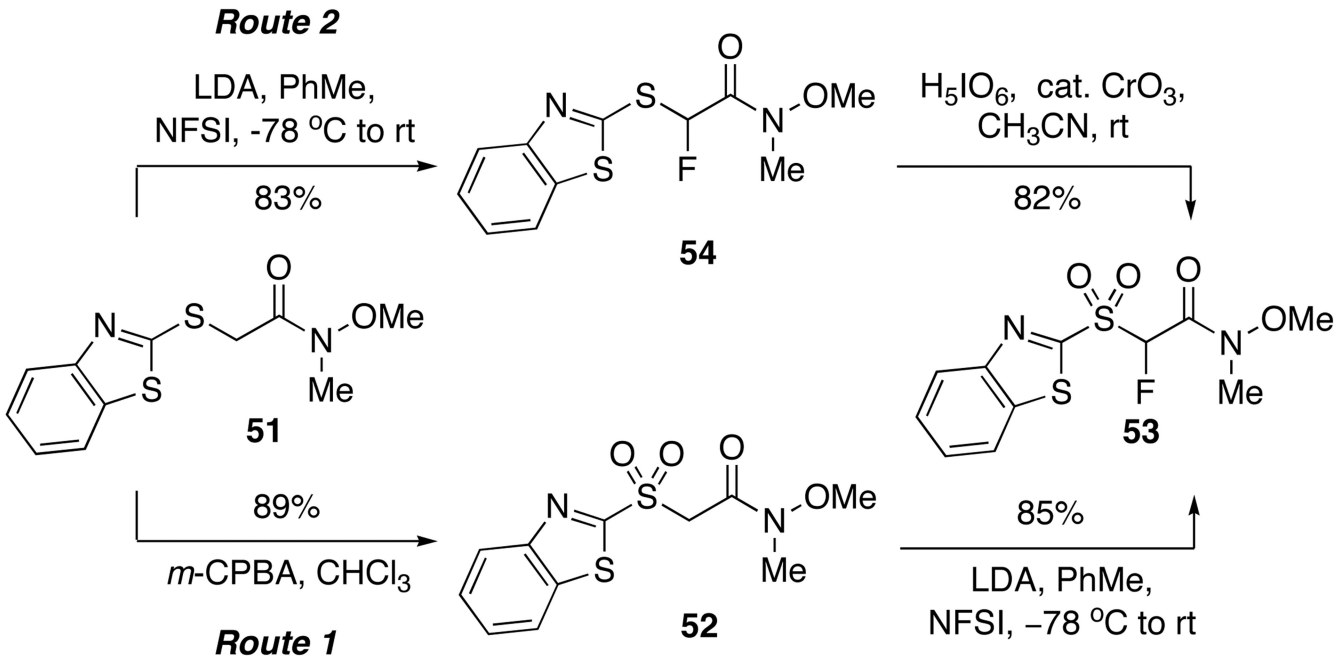
Scheme 19.
Julia Reagent for the Synthesis of α-Fluorovinyl Phenyl Sulfones



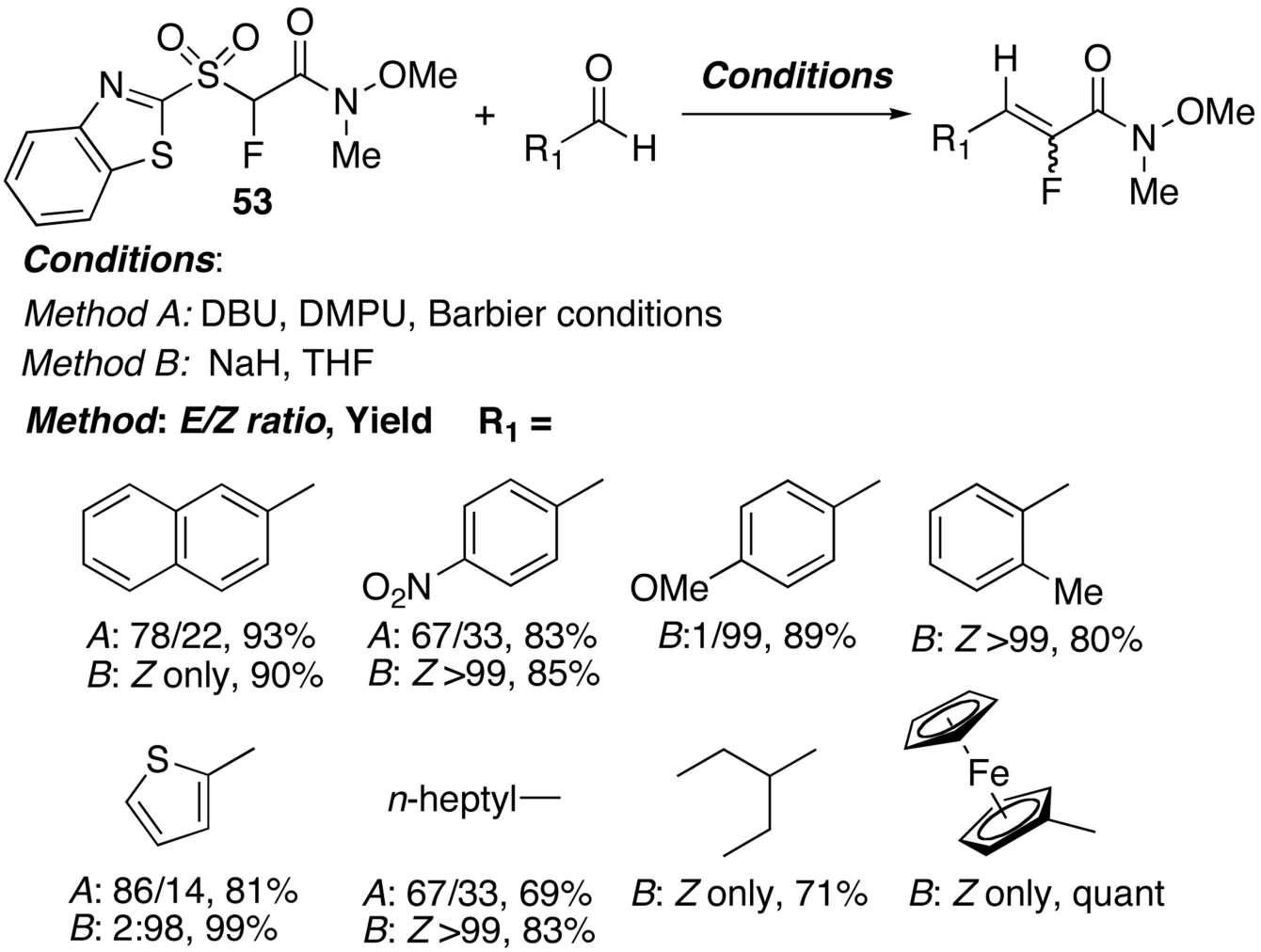
Scheme 20.
Competitive Reaction of Bis-Sulfone Reagents **47** and **48**



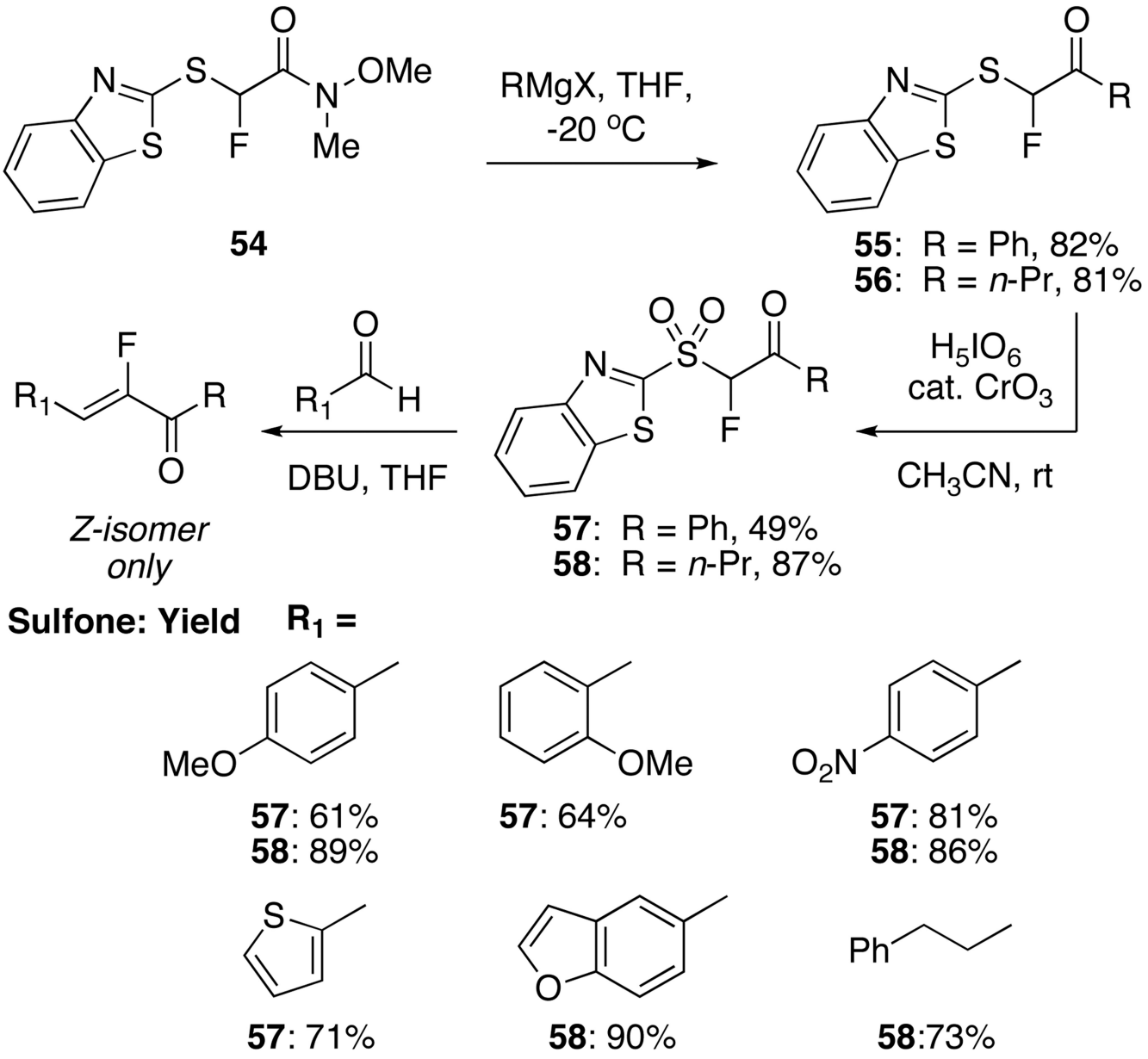
Scheme 21.
Synthesis of α-Fluorovinyl Weinreb Amides Using BTFP-Derived Sulfone



Scheme 22.
Two Routes to Fluoro-Julia-Weinreb Amide Reagent **53**

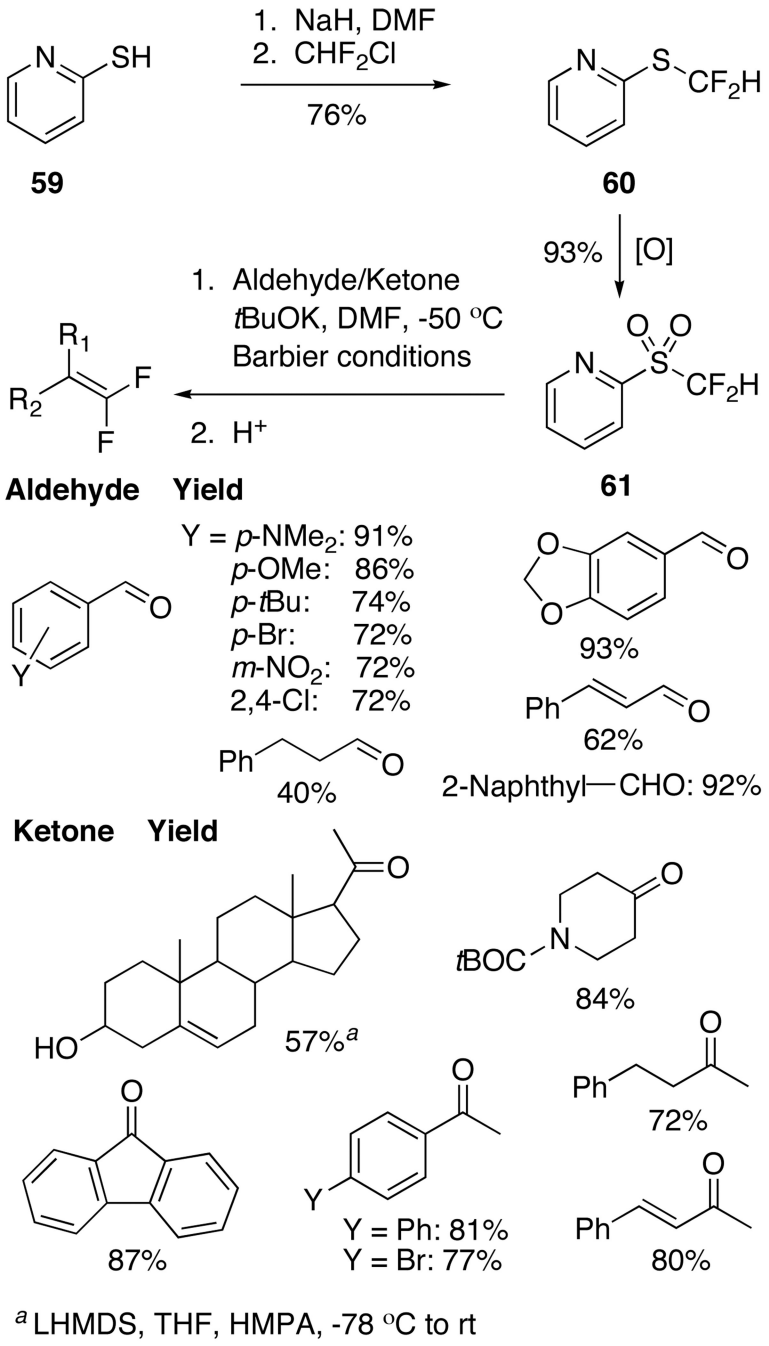


Scheme 23.
Tunability of Olefinations in α-Fluorovinyl Weinreb Amide Synthesis

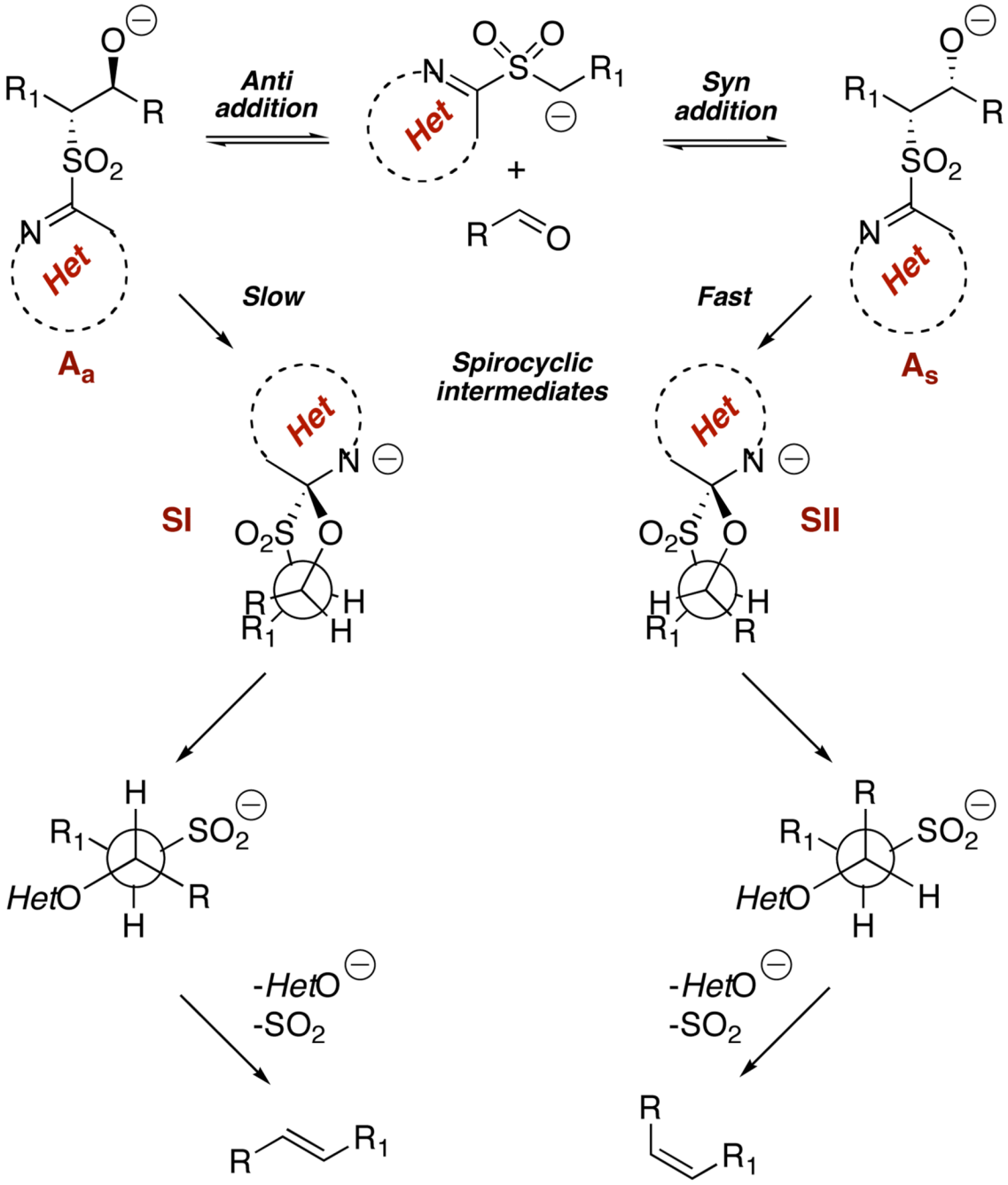


Sulfone: Yield R_1 =

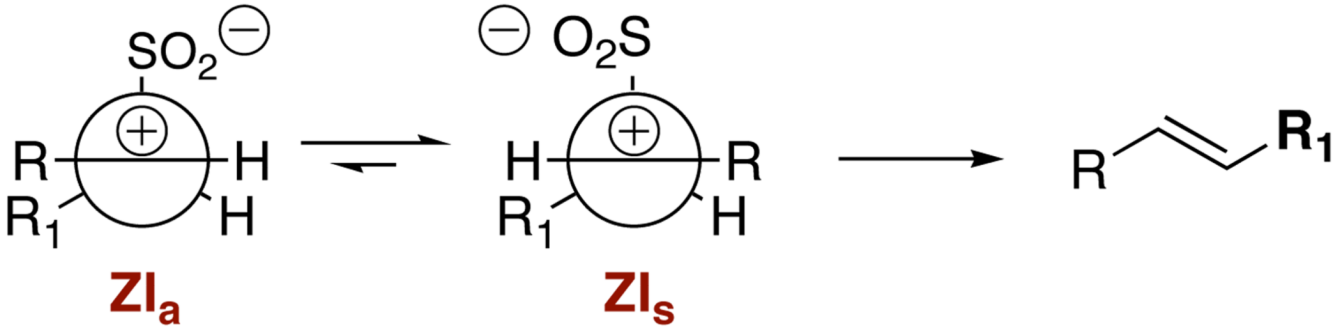
Scheme 24.
Highly Stereoselective Synthesis of a-Fluoroenones



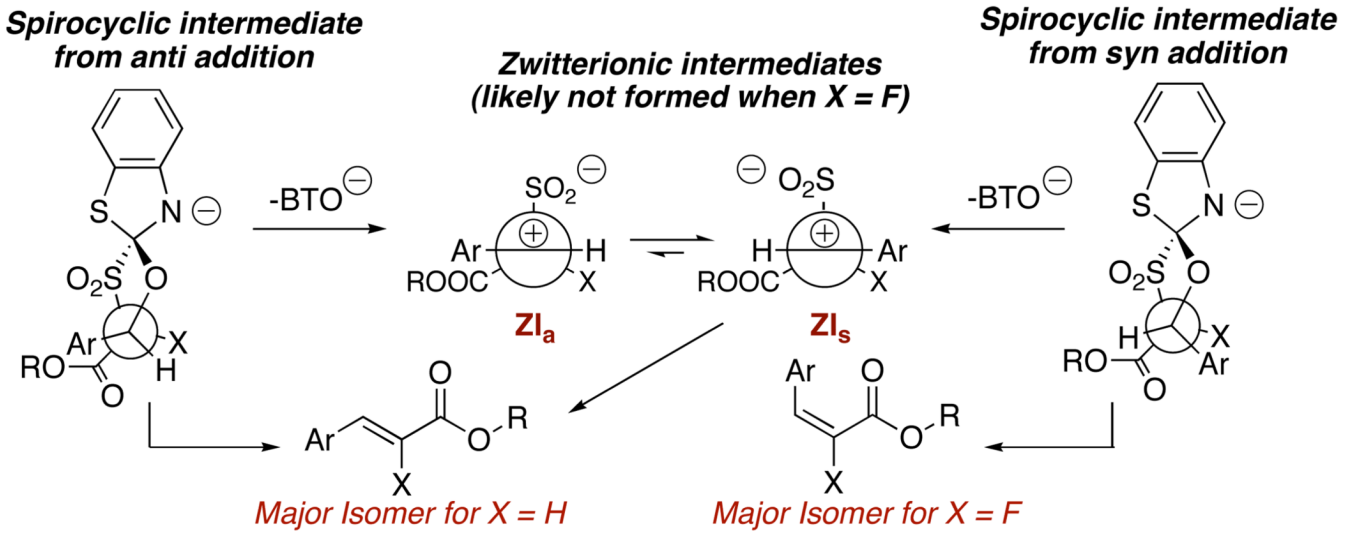
Scheme 25.
Synthesis of 1,1-Difluoroalkenes



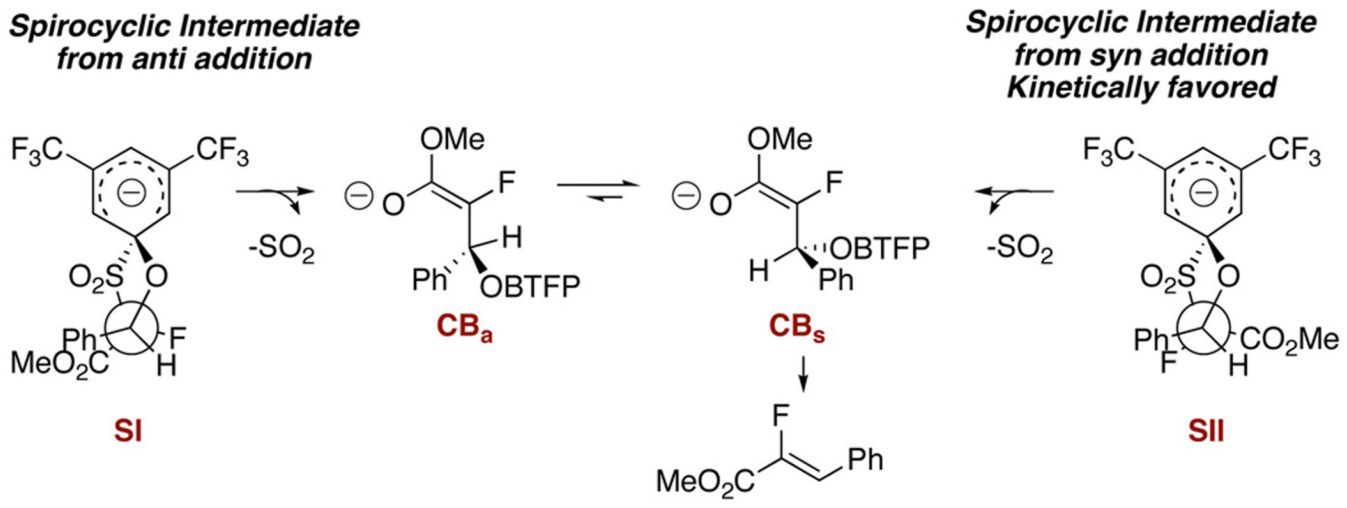
Scheme 26.
Mechanism of the Julia-Kocienski Olefination



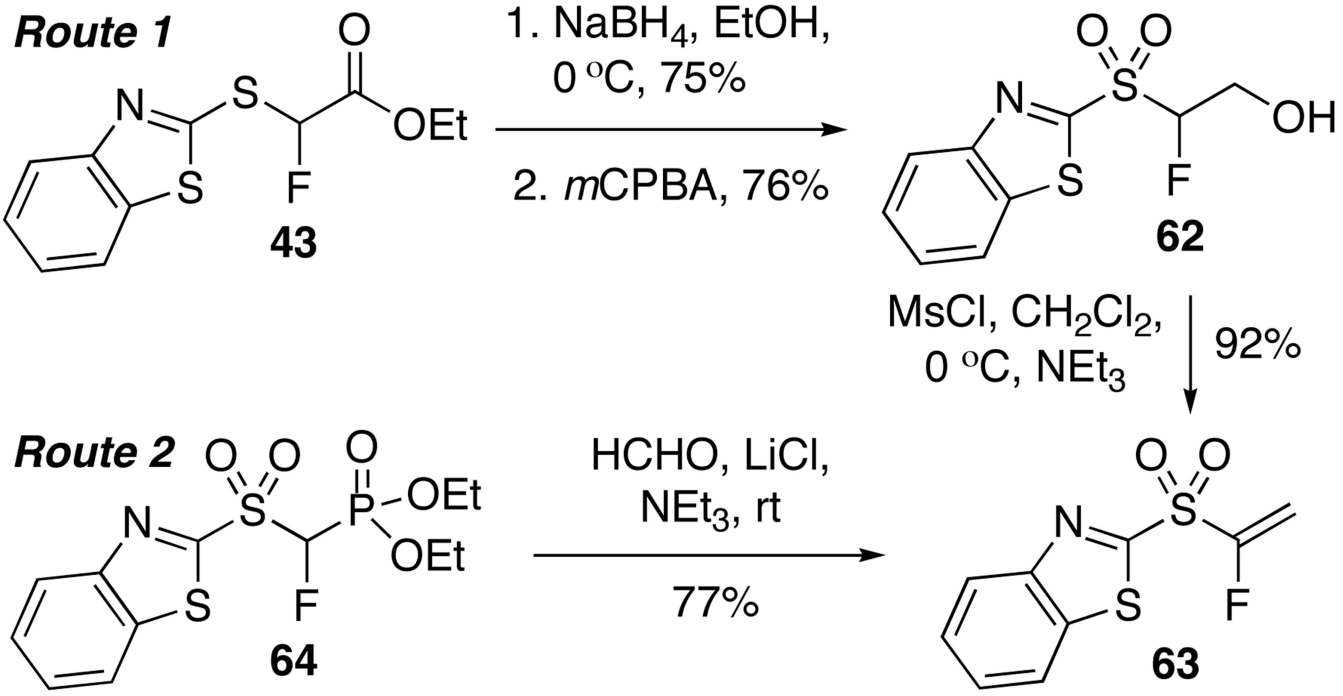
Scheme 27.
Zwitterionic Intermediates en Route to the Alkenes



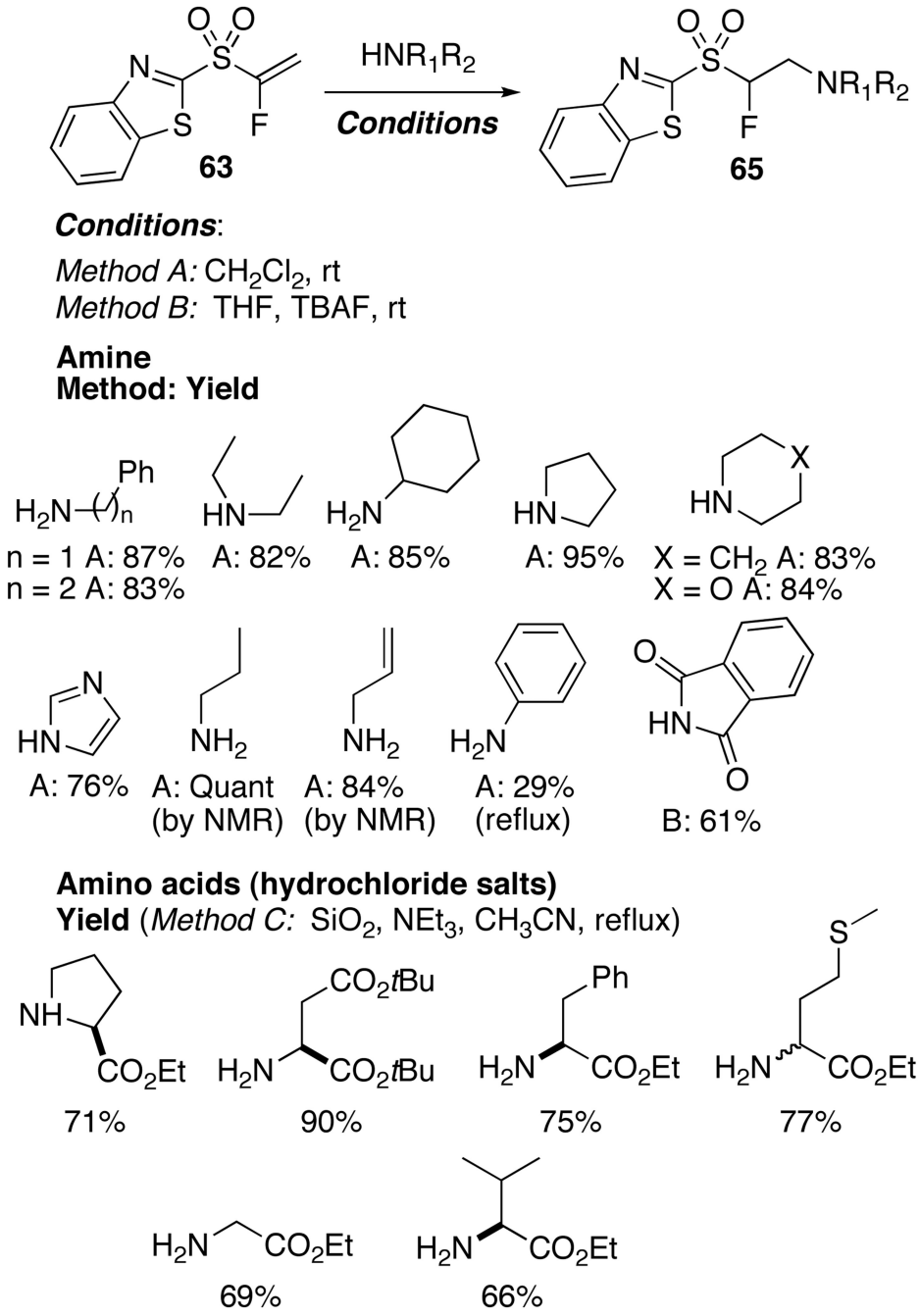
Scheme 28.
Rationale for Different Stereochemical Outcomes in Acrylate and α-Fluoroacrylate Synthesis



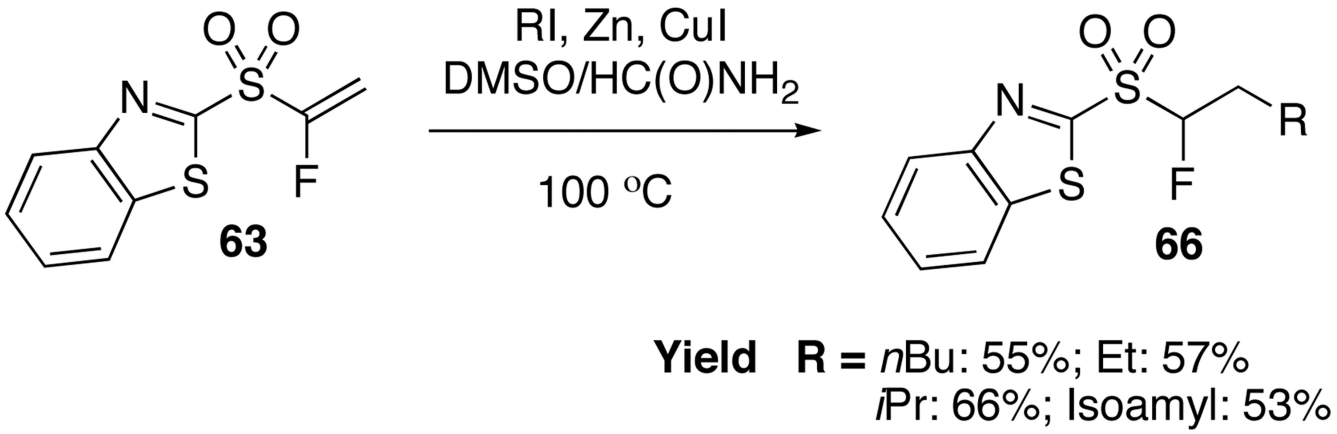
Scheme 29.
An Alternate Elimination Process



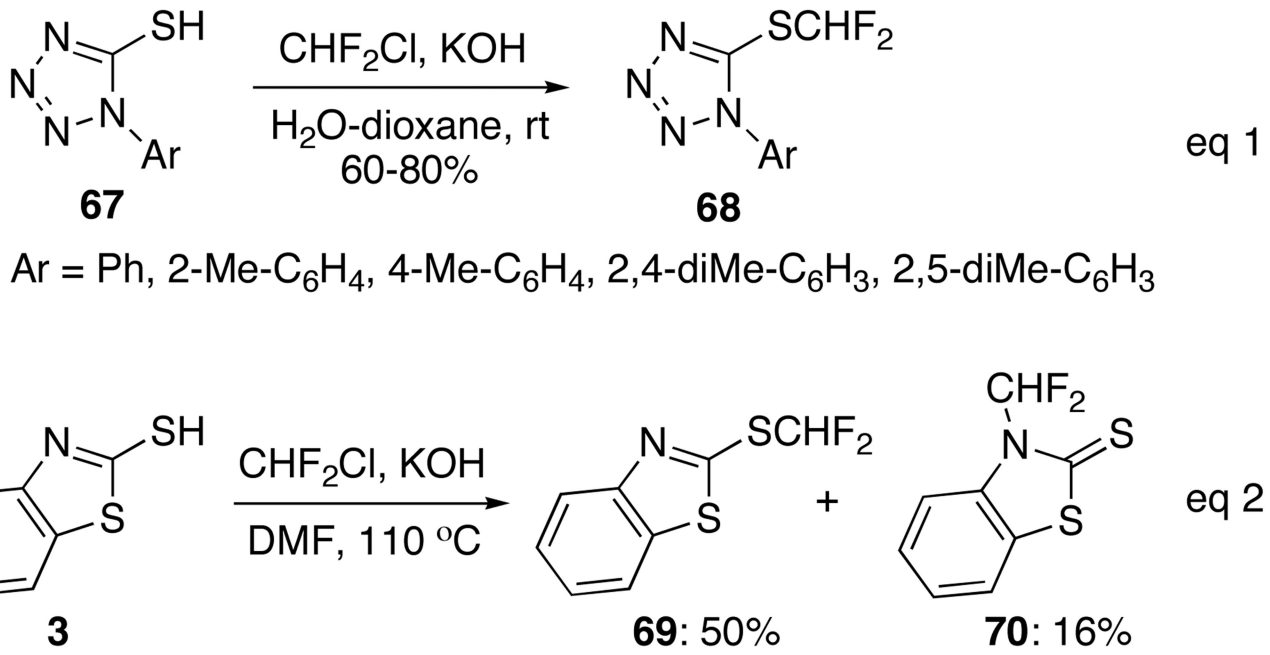
Scheme 30.
Synthesis of α-Fluorovinyl BT sulfone **63**



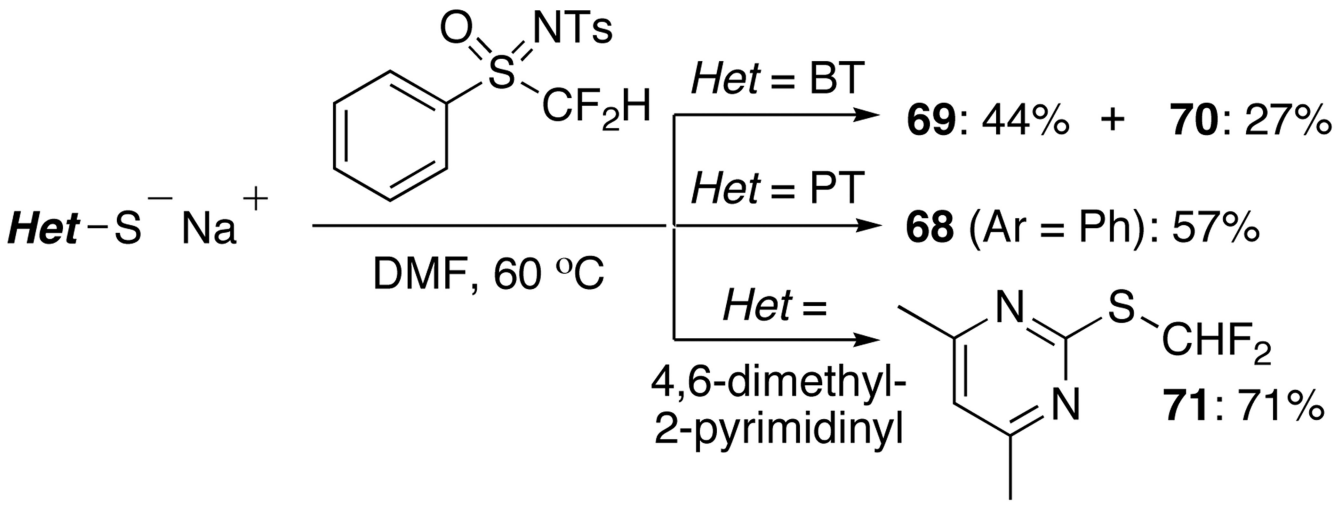
Scheme 31.
Michael Addition of Amines to α-Fluorovinyl BT Sulfone **63**



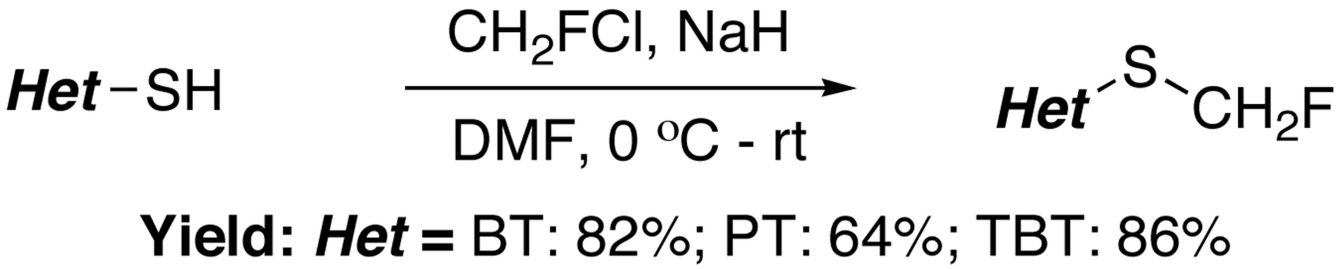
Scheme 32.
Michael Addition of Organometallics to α-Fluorovinyl BT Sulfone **63**



Scheme 33.
Difluoromethyl PT and BT Sulfides

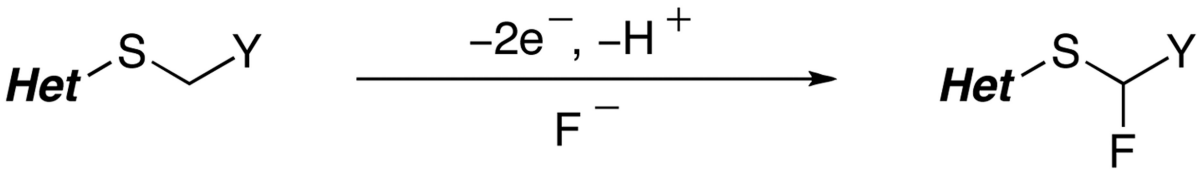


Scheme 34.
S-Difluoromethylation Using Difluoromethyl Sulfoximine



Yield: *Het* = BT: 82%; PT: 64%; TBT: 86%

Scheme 35.
Monofluoromethyl PT and BT Sulfides



Het = BT, Y = CN (48%), CO_2Me (62%), COMe (46%), ethynyl (20%, 22%[a])

Het = 5-Cl-BT, Y = CN (51%), CO_2Me (82%), COMe (58%), ethynyl (30%, 35%[a])

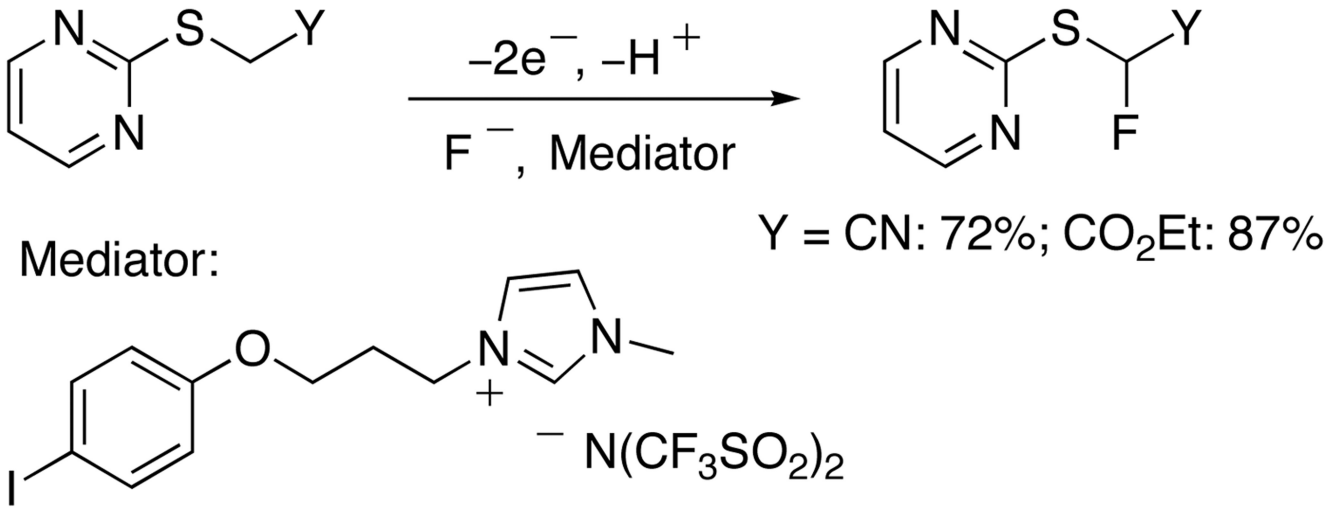
Het = PT, Y = Ph (38%, 45%[a]), CO_2Et (46%, 54%[a]), CN (20%, 26%[a])

Het = 2-Pyridyl, Y = H (22%, 42%[a]), $P(O)(OEt)_2$ (82%, 91%[a]), ethynyl (50%, 55%[a]), SO_2Ph (55%)

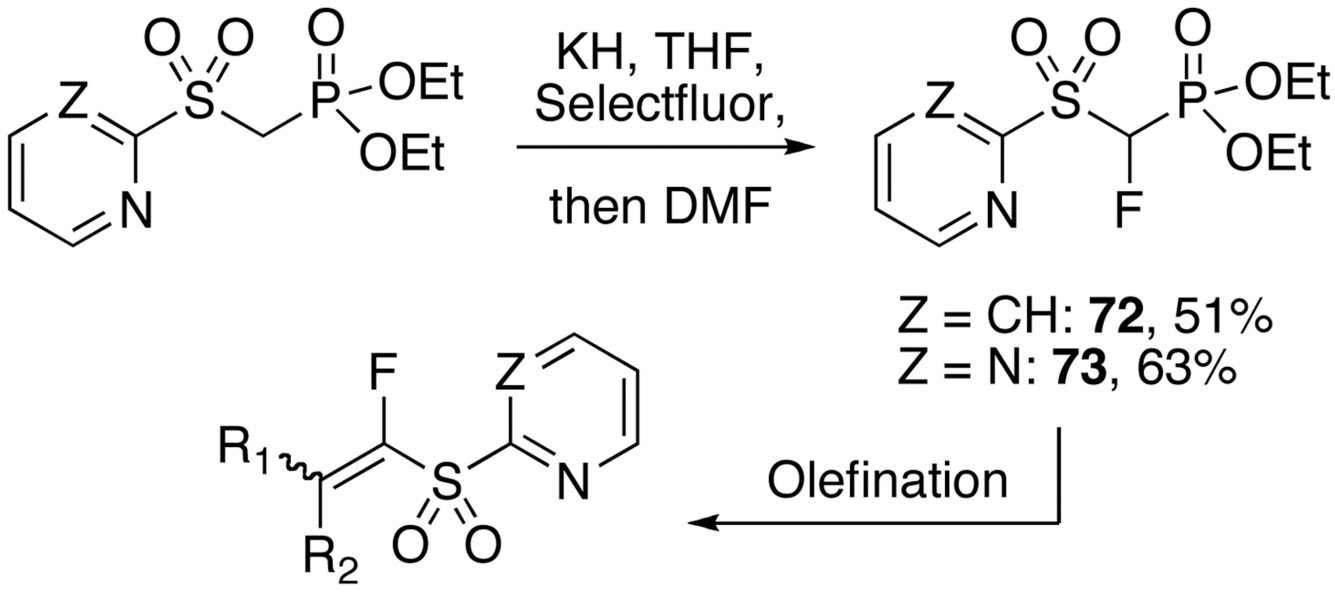
Het = 2-Pyrimidyl, Y = H (46%, 63%[a]), $P(O)(OEt)_2$ (72%, 80%[a]), COMe (78%, 92%[a]), CO_2Et (78%, 98%[a]), CN (35%, 39%[a]), ethynyl (55%, 60%[a])

[a]Yield determined by ^{19}F NMR

Scheme 36.
Anodic Fluorination of Heteroaryl Sulfides



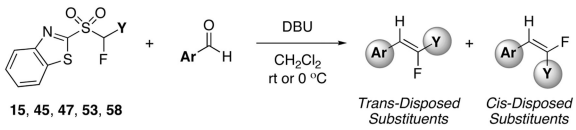
Scheme 37.
Indirect Anodic Fluorination in an Ionic Liquid



Scheme 38.
Synthesis of α-Fluorovinyl Heteroaryl Sulfones

Table 1

Comparison of Stereoselectivities in DBU-Mediated Condensations



15, **45**, **47**, **53**, **58**

Sulfone[a]	Y	Ar	Ratio	
			Trans[b]	*Cis*[b]
47	$PhSO_2$	2-naphthyl	16	84
15	CO_2Et	2-naphthyl	22	78
53	C(O)N(OMe)Me	2-naphthyl	67	33
45	CN	2-naphthyl	85	15
58	C(O)Pr[c]	4-$MeOC_6H_4$	>99	–

[a] Sulfone: **47**, 35 **15**, 30 **53**, 44 **45**, 38 **58**. 44

[b] Relationship between Y and Ar.

[c] Solvent THF–CH_2Cl_2.