Cyclopropanation

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Enantioselective Synthesis of Cyclopropanes That Contain Fluorinated Tertiary Stereogenic Carbon Centers: A Chiral α-Fluoro Carbanion Strategy**

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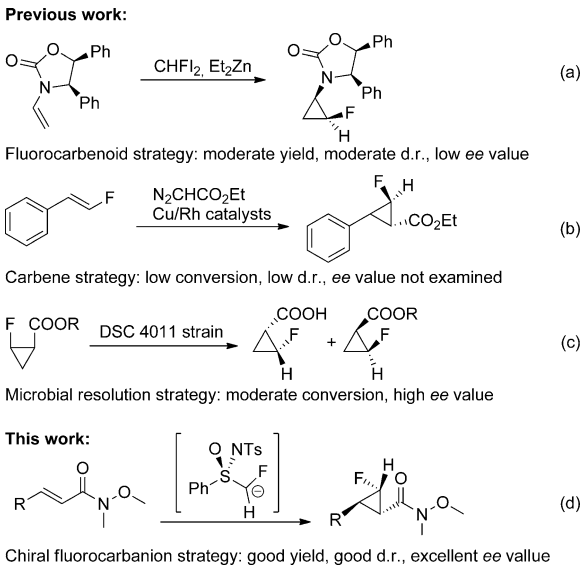
Dedicated to Professor George A. Olah on the occasion of his 85th birthday

The unique bonding in the cyclopropyl group causes it to be an important structural motif that can be essential for biological activity, and hence, it is found in a large number of naturally occurring compounds.[1] Many well-established drugs in diverse therapeutic areas contain this prominent pharmacophore. Among them, Odanacatib (a cathepsin K inhibitor), Singulair (an antiasthmatic agent), and Ciprofloxacin (a broad-spectrum antibiotic) are a few examples.[1] Fluorine, which has a small atomic radius similar to that of hydrogen, is the most electronegative element. Therefore, the incorporation of fluorine into a bioactive molecule, a change, which causes minimal steric alterations, often causes an increase in metabolic stability and an improvement in membrane permeation.[2] In many cases, the replacement of a hydrogen atom with a fluorine atom in a drug molecule can result in a tenfold enhancement of its biological potency.[3] In this context, monofluorinated cyclopropanes have become the subject of special interest because they combine the advantages of two known chemical leads, namely the strained ring and the fluorine substituent.

Several methods have been reported for the synthesis of racemic monofluorinated cyclopropanes.[4] However, there have been very few successful syntheses of chiral monofluorinated cyclopropanes with high enantiopurity.[4f,5] The enantioselective construction of a fluorinated tertiary stereogenic carbon center, which bears both fluorine and hydrogen atoms, in cyclopropanes is generally a challenging task because it is often difficult to sterically distinguish fluorine from hydrogen.[6] In 1992, Terashima and co-workers reported the asymmetric Simmons–Smith reaction between $CHFI_2$ and an enantiomerically enriched alkene, a reaction, which afforded a monofluorinated cyclopropane in 38% *de* (for the fluorine-substituted stereogenic carbon center; see Scheme 1a).[7] Haufe and co-workers reported an asymmetric cyclopropanation of β-fluorostyrene, which bears a fluorine substituent in the terminal position; this reaction afforded the fluorinated cyclopropane products in low yields, although the enantioselectivity of the reaction was not examined (see Scheme 1b).[4f] Imura and co-workers also reported the resolution of *cis*-2-fluorocyclopropanecarboxylic acid by a microbial enantioselective hydrolysis of the corresponding ester with moderate conversions albeit with high enantioselectivity (see Scheme 1c).[8] Therefore, the development of a new and efficient protocol for the highly stereoselective synthesis of cyclopropanes bearing a fluorinated tertiary stereogenic carbon center is highly desired. Herein, we report our recent success in tackling this interesting problem by using a chiral α-fluoro carbanion strategy (see Scheme 1d).

Nucleophilic fluoroalkylation, which typically involves the transfer of a fluorinated carbanion or carbanion equivalent to an electrophile, is one of the most important and frequently used methods to synthesize fluorinated organic



Scheme 1. Strategies for the preparation of cyclopropanes that contain fluorinated tertiary stereogenic carbon centers. Ts = *p*-toluenesulfonyl.

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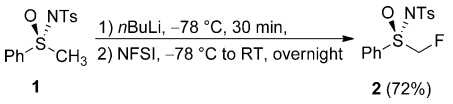
molecules. In the past several years, our research group and those of others have developed many nucleophilic fluoroalkylation reactions using α-fluoro carbanions generated from α-fluorinated sulfones.[9] The phenylsulfonyl functionality was found to be a highly useful modulating group to tackle the "negative fluorine effect" (NFE) of α-fluoro carbanions.[9,10] However, an additional step was needed to remove the phenylsulfonyl group after the desired fluoroalkylation step.[9] Therefore, we have been interested in seeking new removable modulating groups for designing efficient nucleophilic fluoroalkylation reactions in one pot, that is, the modulating group can be removed spontaneously during the one-pot reaction process.

Owing to their physiological and diverse chemical properties, sulfoximines, which contain a stereogenic sulfur center, have been widely used in organic synthesis.[11] Recently, the use of fluorinated sulfoximines as fluoroalkylation reagents has also attracted much attention.[12,13] However, there have been no reports on stereoselective fluoroalkylations using enantiopure fluorinated sulfoximines as the reagents. We envisioned that, because of the good leaving-group ability of the sulfoximine functionality, a Michael-type addition–elimination reaction could be achieved between the chiral anion of (*R*)-*N*-tosyl-*S*-fluoromethyl-*S*-phenylsulfoximine (**2**) and α,β-unsaturated carbonyl compounds (see Scheme 1 d). Importantly, the sulfoximine group could be removed during the subsequent one-pot cyclopropanation process. Therefore, the unique properties of the sulfoximine group offer excellent opportunities to design new fluoroalkylation reactions.

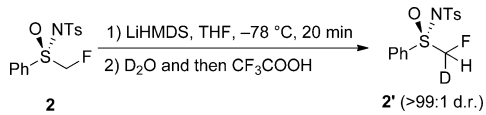
(*S*)-*N*-Tosyl-*S*-methyl-*S*-phenylsulfoximine (**1**) was readily prepared according to the literature procedures.[14] The fluorination of **1** by using *N*-fluorodibenzenesulfonamide (NFSI) as the fluorinating reagent gave (*R*)-*N*-tosyl-*S*-fluoromethyl-*S*-phenylsulfoximine (**2**) in 72% yield (Scheme 2).



Scheme 2. Preparation of (*R*)-*N*-tosyl-*S*-fluoromethyl-*S*-phenylsulfoximine (**2**).

With compound **2** in hand, we first tested the reaction between the anion, which was formed in situ from the reaction of **2** and lithium hexamethyldisilazide (LiHMDS), and D_2O. Thus, under N_2 atmosphere, LiHMDS (1 M in THF, 0.375 mL, 0.375 mmol) was added to a solution of **2** (98 mg, 0.3 mmol) in THF (3 mL), at −78 °C. After stirring the reaction mixture for 20 minutes at −78 °C, the reaction was quenched by adding D_2O (0.5 mL); the resulting mixture was then acidified by adding CF_3COOH (0.3 mL). High diastereoselectivity (> 99:1) was observed for monodeuterated product **2′** (Scheme 3).

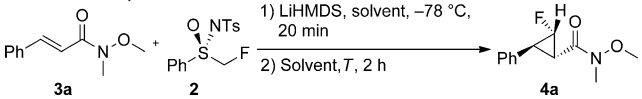
Encouraged by this result, we started to investigate the chiral fluorocarbanion strategy for the stereoselective synthesis of cyclopropanes that bear a fluorinated tertiary stereogenic carbon center. α,β-Unsaturated Weinreb amides



Scheme 3. Reaction of (*R*)-*N*-tosyl-*S*-fluoromethyl-*S*-phenylsulfoximine (**2**) with D_2O.

were chosen as the Michael acceptor, because of their wide synthetic applications.[15] *N*-Methoxy-*N*-methylcinnamamide **3a** was used as a model compound to study the addition–elimination reaction under the carefully optimized reaction conditions, which are listed in Table 1. When we used LiHMDS as the base, the reaction took place smoothly in

Table 1: Survey of reaction conditions.[a]



Entry	**3a**/**2**/Base	Solvent	*T* [°C]	Yield [%][b]	d.r.[c]	*ee*[d] [%]
1	1:1.2:1.5	THF	RT	80	91:9	92
2	1:1.5:1.5	THF	RT	96	99:1	93
3	1:1.5:1.3	THF	RT	90	99:1	94
4	1:1.5:1.3	THF	−30	92	99:1	94
5	1:1.5:1.3	$PhCH_3$	RT	94	95:5	97
6[e]	1:1.5:1.3	$PhCH_3$	−15	90	95:5	97
7[f]	1:1.5:1.3	THF/$PhCH_3$ (v/v = 3:1)	RT	70	98:2	94
8[f]	1:1.5:1.3	THF/$PhCH_3$ (v/v = 1:3)	RT	75	96:4	96

[a] Typical procedure: LiHMDS (1 M in THF or $PhCH_3$) was added to a mixture of **3a** and **2** (0.2 mmol) in solvent at −78 °C. After 20 min, the dry-ice bath was removed and the reaction mixture was stirred at the corresponding temperature (*T*) for 3 h. [b] Yield of isolated product. [c] Determined by ^{19}F NMR spectroscopy. [d] Determined by HPLC on chiral stationary phase column. [e] Stirred at −15 °C for 4 h. [f] Yield was determined by ^{19}F NMR spectroscopy with $PhCF_3$ as internal standard.

THF or $PhCH_3$. More importantly, we found that the relative amounts of **3a**, **2**, and base was crucial to the diastereoselectivity and enantioselectivity of the reaction (Table 1, entries 1–3). When the ratio of **3a**/**2**/base was 1:1.2:1.5, the product was obtained with a d.r. of 91:9 and an *ee* value of 92% (Table 1, entry 1). When the ratio was changed to 1:1.5:1.5, the d.r. increased to 99:1 and the *ee* value was slightly increased (Table 1, entry 2). However, when the amount of LiHMDS was decreased to 1.3 equivalents, the *ee* value increased to 94% (Table 1, entry 3). When toluene was used as a solvent, the *ee* value was increased to 97%, albeit the d.r. was decreased to 95:5 (Table 1, entry 5). Lowering the reaction temperature did not improve the diastereoselectivity or the enantioselectivity (Table 1, entries 4 and 6) and the use of a mixed solvent system did not result in any improvement either (Table 1, entries 7 and 8). It is noteworthy that only one pair of diastereoisomers was detected amongst the products of the reaction, as determined by ^{19}F NMR spectroscopy.

Eventually, we chose entry 3 (conditions A) and entry 5 (conditions B) shown in Table 1 as the standard conditions to study the scope of the reaction between α,β-unsaturated

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Weinreb amides **3** and the sulfoximine **2**. The results are summarized in Table 2. The reaction proved to be general and a variety of structurally diverse α,β-unsaturated Weinreb amides were successfully monofluoromethylenated by **2** to give the corresponding enantiomerically enriched monofluorinated cyclopropanes **4**. For aryl-substituted substrates, the products were obtained in good to excellent yields (73–97%), excellent diastereoselectivity (96:4–99:1 d.r.), and high enantioselectivity (92–98% *ee*) under conditions A. The reaction tolerates many substituents such as methyl, *tert*-butyl, methoxy, fluoro, chloro, and bromo groups (Table 2, entries 2–10). The heteroaryl-substituted Weinreb amide also reacted with the monofluoromethylenating reagent **2**, thus affording the monofluorinated cyclopropane **4k** in good yield (81%) and with excellent d.r. (99:1) and high *ee* value (93%; Table 2, entry 11). In addition, monofluoromethylenation of a naphthyl-substituted unsaturated Weinreb amide was also successful, giving the product **4l** in 93% yield, 97:3 d.r., and 92% *ee* (Table 2, entry 12). It is remarkable that the current fluoromethylenation reaction is also amenable to alkyl-substituted unsaturated Weinreb amide **3m**, thus giving the major diastereoisomer **4m** in 62% yield with 94% *ee*, albeit in a relatively lower d.r. (three diastereoisomers could be observed by ^{19}F NMR spectroscopy; Table 2, entry 13). Under conditions B, the reaction generally gave improved enantioselectivity (Table 2, entries 1, 2, 7, 8, 11, and 12), although the diastereoselectivity was lower (89:11–98:2 d.r.). The absolute configuration of product **4e** was confirmed by single-crystal X-ray structure analysis (see Figure 1a), and that of the other products were assigned by analogy.[16]

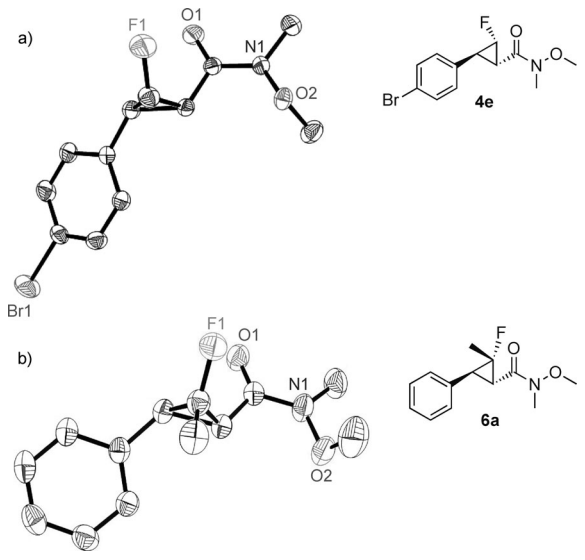
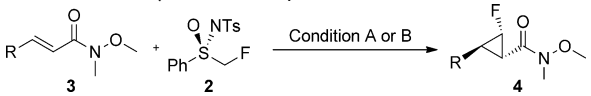
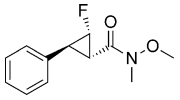
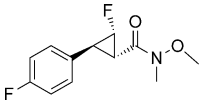
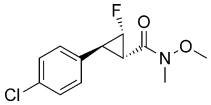
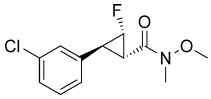
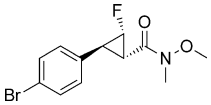
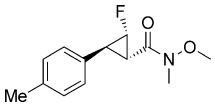
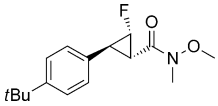
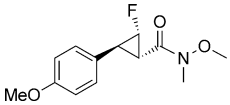
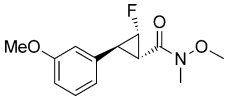
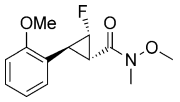
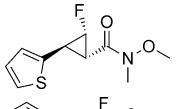
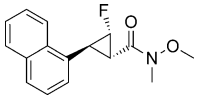
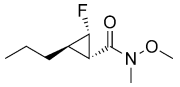


Figure 1. Single-crystal X-ray structures of product **4e** and **6a**. Hydrogen atoms have been omitted for clarity and thermal ellipsoids are shown at 30% probability.

By using conditions A, we also attempted the present cyclopropanation reaction of α-methyl-α-fluoro-substituted sulfoximine **5**[17] with **3a** and **3e** (Scheme 4). Despite the fluorinated carbon atom of reagent **5** being tertiary, both reactions were successful, affording the product **6a** in 75%

Table 2: Fluoromethylenation of α,β-unsaturated Weinreb amides.



Entry	Product[a]	Conditions[b]	Yield [%][c,d]	d.r.[e]	*ee* [%][f]
1		A	90	99:1	94
		B	85 (90)	99:5	97
2		A	95	98:2	94
		B	88 (90)	94:6	97
3		A	97	98:2	96
		B	80 (90)	96:4	96
4		A	95	98:2	93
5		A	95	99:1	98
		B	89 (93)	96:4	98
6		A	91	99:1	98
		B	80 (90)	96:4	98
7		A	73 (83)	98:2	93
		B	77 (93)	96:4	97
8		A	79	98:2	95
		B	73 (85)	98:2	97
9		A	74 (90)	99:1	97
		B	75 (84)	96:4	97
10		A	75 (88)	96:4	93
11		A	81	99:1	93
		B	89 (90)	93:7	96
12		A	93	97:3	92
		B	73 (75)	89:11	93
13[g]		A	62	75:19:6	94

[a] For **4e**, the absolute configuration was determined by single-crystal X-ray structure analysis (see Figure 1a), and the others were assigned by analogy. [b] Conditions A: see entry 3 in Table 1; conditions B: see entry 5 in Table 1. [c] Yield of the isolated major diastereoisomer. [d] The data in the parentheses refers to the yield determined by ^{19}F NMR spectroscopy with $PhCF_3$ as internal standard. [e] Unless otherwise noted, only one pair of diastereoisomers were observed and the d.r. was determined by ^{19}F NMR spectroscopy. [f] The *ee* value was determined by HPLC on a chiral stationary phase column. [g] Three diastereoisomers were observed by ^{19}F NMR spectroscopy.

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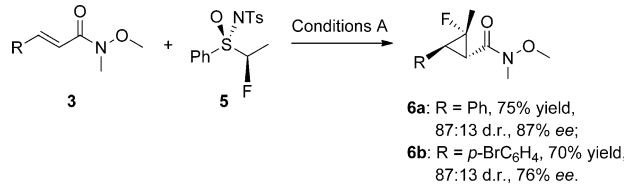
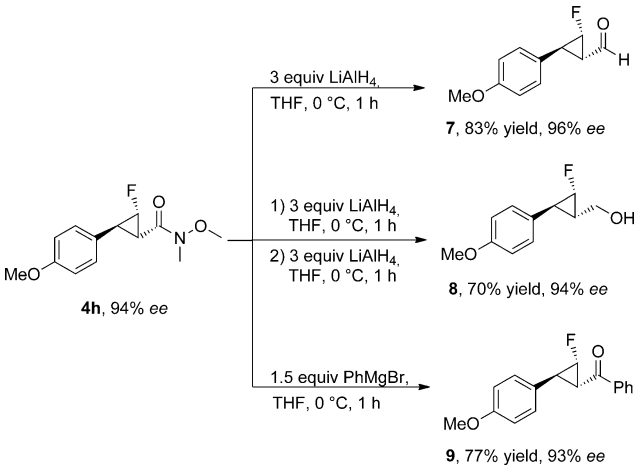


Scheme 4. Preparation of cyclopropanes **6a** and **6b**, which contain fluorinated quaternary stereogenic carbon centers.

yield, 87:13 d.r., and 87% *ee* and **6b** in 70% yield, 87:13 d.r., and 76% *ee*, respectively. The absolute configuration of **6a** was determined by single-crystal X-ray structure analysis (see Figure 1b), and that of **6b** was assigned by analogy.

To show the high value of our present cyclopropanation (or fluoromethylenation) reaction in synthesis, the monofluorinated cyclopropane **4h** was transformed into several other useful products (Scheme 5). Upon treatment with three equivalents of $LiAlH_4$ in THF at 0°C for 1 hour, compound **4h** was reduced to the aldehyde **7**, which was obtained in 83% yield and with 96% *ee* after purification with column chromatography on silica gel. Reduction of **4h** with $LiAlH_4$ in THF at 0°C in two separate steps led to the alcohol **8** in 70% yield without loss of optical purity. The optically pure monofluorinated cyclopropyl ketone **9** was also prepared in 77% yield and with 93% *ee* by treating **4h** with 1.5 equivalents of PhMgBr in THF at 0°C for 1.5 hours.



Scheme 5. Synthetic applications of product **4h**.

In conclusion, with a chiral α-fluoro carbanion strategy, an unprecedented highly enantioselective reaction for the preparation of cyclopropanes containing fluorinated tertiary stereogenic carbon centers has been accomplished. To our knowledge, this is the first example of highly enantio- and diastereoselective monofluoromethylenation of α,β-unsaturated carbonyl compounds.[18] The reaction was shown to be general and a variety of structurally diverse α,β-unsaturated Weinreb amides were successfully monofluoromethylenated to give the corresponding monofluorinated cyclopropanes in good yield, with good diastereoselectivity, and with excellent enantioselectivity. The strategy was also amenable to prepare cyclopropanes containing fluorinated quaternary stereogenic carbon centers. The diverse applications of the reaction and its products illustrate the wide synthetic utility of the new procedure. It should be pointed out that, to our knowledge, (*R*)-*N*-tosyl-*S*-monofluoromethyl-*S*-phenylsulfoximine is the first homochiral monofluoromethylenation reagent. This type of novel chiral fluoroalkylation reagent is expected to find many applications in designing various other asymmetric fluoroalkylation reactions.

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Keywords: asymmetric synthesis · chiral fluoroalkylation reagent · cyclopropanation · fluorine · sulfoximine

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[17] Compound **5** was prepared in 75% yield from **2** by using *n*BuLi as a base, MeI as a methylation reagent and THF as a solvent (see the Supporting Information).

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