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Modified Julia Fluoroolefination: Selective Preparation of Fluoroalkenoates

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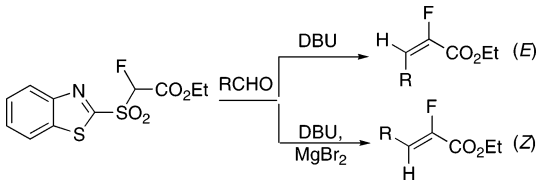

The modified Julia olefination reaction has been applied to develop a stereoselective synthesis of fluoroalkenoate derivatives from a fluorobenzothiazolyl sulfone and aldehydes or a ketone. The olefination reaction can be achieved by using a variety of bases. DBU and DBU in the presence of $MgBr_2$ were found to be the most efficient systems to prepare either (*Z*)- or (*E*)-alkenoates in moderate to excellent stereoselectivity.

Introduction

Fluoroolefins are well-known as precursors of biologically active compounds and have been successfully used to prepare a new generation of modified pheromones, herbicides, and medicines.[1] The major approach for their preparation is based on the Wittig or related reactions.[2] However, these methods are often limited to the synthesis of terminal fluoroalkenes, α-fluoro-α,*β*-unsaturated esters, or 1-fluoro-1-arylmethylidene derivatives. Some efforts have been made during the past decade to prepare a variety of fluoroalkenes bearing an alkyl or functionalized alkyl chain, to obtain enzyme inhibitors or peptide mimics.[3] The most efficient strategies install the carbon−carbon double bond through a concerted elimination pathway from fluorosulfoxides, fluorosilylacetates, fluorocarboxylates, or a chemical modification of fluorovinylsulfones, *gem*-bromofluoroalkenes, or fluoroalkenoates.[4] Due to the number of steps

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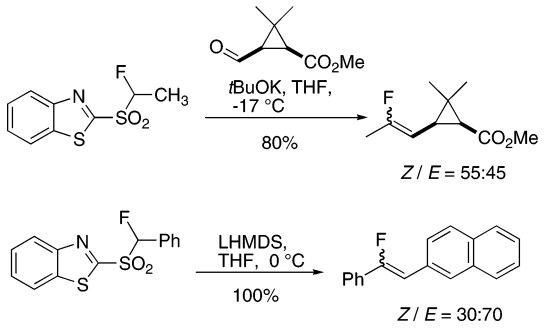
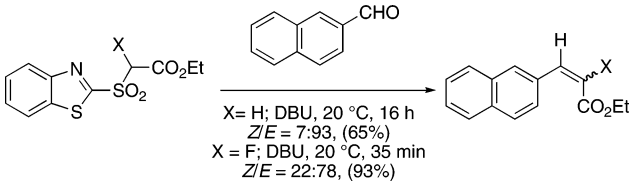
SCHEME 1. Fluoroalkylidene Synthesis and Recent Application



involved in the synthesis of fluoroalkenes by using these strategies, the modified Julia (or Julia−Kocienski) olefination reaction appeared attractive as an elegant alternative one-step procedure.[5] Indeed, in a preliminary work we have already described a modified Julia fluoroolefination of carbonyl compounds to prepare fluoroalkylidene derivatives in one step, from a fluoroalkylbenzothiazolylsulfone and aldehydes or ketones in the presence of *t*BuOK or NaHMDS, respectively (Scheme 1).[6] This method was applied to the synthesis of an important intermediate to an insecticide and represents the most direct route to build fluoroalkylidene derivatives. Other groups have supported this approach and extended this reaction to the synthesis of *gem*-fluoroaryl derivatives from the in situ prepared fluoroarylbenzothiazolylsulfones.[7] Nevertheless, the major limitation of this methodology is the poor control of the double bond configuration. A mixture of fluoroalkenes was generally obtained, depending on the nature of the electrophile and the aromatic sulfone.[8] The use of 1-phenyltetrazolylsulfone or bis-trifluoromethylphenylsulfone instead of benzothiazolylsulfone to control the formation of the double bond has allowed progress for the synthesis of natural products,[9] but moderate selectivity was observed with fluorinated derivatives.[6]

The synthesis of α,β-unsaturated esters from heteroaromatic sulfones and carbonyl compounds has been recently reported as an alternative route to the Horner−Wadworth−Emmons reaction.[10] It has been shown that the influence of the nature of the base and the solvent are important to control the geometry of the double bond. The use of DBU in DCM at room temperature appeared to be the most efficient method to prepare the (*E*)-alkenoates selectively from ethyl benzothiazolylsulfonyl acetate and aromatic aldehydes. When extended to the fluorobenzothiazolylsulfonyl acetate derivatives this approach showed a great influence of the fluorine atom on the reactivity of the sulfone, and on the geometry of the alkenoates.[11] Due to the presence of the fluorine atom the alkenes were formed faster (20 min vs 16 h) with selectivity opposite to those observed from nonfluorinated sulfones (Scheme 2).

SCHEME 2. Contrasted Reactivity of a Fluorosulfone



These observations in connection with our present work prompted us to report our additional results in this field. Selective syntheses of both (*Z*)- and (*E*)-fluoroalkenoates from a fluorobenzothiazolylsulfone and aldehydes or ketones are described in this paper.

Results and Discussion

Previously we reported the synthesis of fluoroalkylbenzothiazolylsulfones by alkylation of the 2-mercaptobenzothiazole with *gem*-bromofluoroalkane or by halogen-exchange reaction from the 2-chloroalkyl-2-mercaptobenzothiazole derivatives. The electrophilic fluorination of a 2-substituted-2-benzothiazolylsulfone with F-TEDA or NFSI can be used as an alternative route.[6,11] For the synthesis of fluoroalkenoate derivatives, the preparation of the benzothiazolylsulfone **2** was carried out from the commercially available ethyl 2-bromo-2-fluoroacetate and 2-mercaptobenzothiazole (Scheme 3).

The alkylation proceeded smoothly at room temperature to afford the corresponding sulfide **1** in excellent yield (up to 85%). The slow oxidation of this fluorosulfide with *m*CPBA (3 equiv molar) resulted in a mixture of sulfoxides and sulfone even after stirring the mixture for over 60 h at room temperature. Better results were obtained when the oxidation was performed with a stronger oxidant (H_2O_2, 5% $(NH_4)_6Mo_7O_{24}$).[12] The corresponding fluorosulfone **2** was isolated in 72−75% yield as a white crystalline compound.[11] This procedure was reproducibly and efficiently scaled-up to 5 g. With a large amount of fluorobenzothiazolylsulfone in hand, the study was then focused on the selective synthesis of either (*Z*)- or (*E*)-fluoroalkenoates from the sulfone **2** (Scheme 4, Table 1). To control the geometry of the carbon−carbon double bond, a variety of experimental conditions were screened. THF was selected as a suitable solvent, and the reactions were performed from benzaldehyde and nonanal as model electrophiles. The Barbier-type conditions as originally reported by Julia and co-workers[5a] were applied: the base (1.4 equiv neat or in solution in THF) was added to a mixture of sulfone (1 equiv) and electrophile (1.2 equiv) in THF. The reaction was performed at −78, −17, or 20 °C with or without additive. Results are reported in Table 1.

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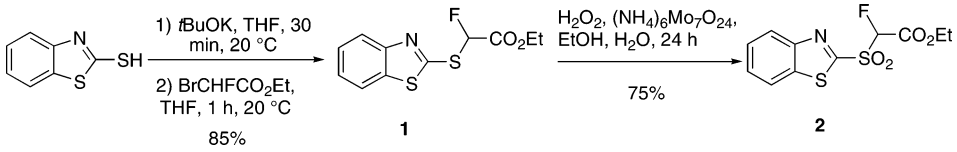
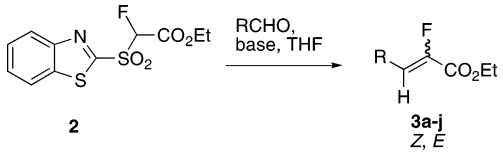
SCHEME 3. Synthesis of a Fluorobenzothiazolysulfone



SCHEME 4. Synthesis of Fluoroalkenoates



From NaHMDS and benzaldehyde the (*Z*)-fluoroalkenoate **3a** was formed as the major product in a *Z*/*E* ratio up to 85:15 (entries 1−3) when the reaction was performed at −78, −17 °C, or room temperature. After flash chromatography, the alkenes were isolated in 53−69% yield. Changing the nature of the metalated base slightly modified the observed selectivity as exemplified by the experiment realized with KHMDS (entries 4 and 5). In contrast, the replacement of a metal amide by a milder base such as DBU[10,11] resulted in reverse selectivity. When the reaction was performed from −78 to 20 °C, the (*E*)-fluoroalkenoate **3a** was formed as the major product in a 24:76 *Z*/*E* ratio (entry 6), and isolated in good yield (70%). The polarity of the solvent and the temperature of the medium appeared crucial to control the formation of alkenes. High *E*-selectivity was observed when the reaction was run in the presence of DBU in THF from −78 to 20 °C (entry 6), while similar results were obtained in DCM at 20 °C.[11] This ratio decreased with the reaction temperature and an equimolar mixture of isomers was obtained at reflux (entries 7−9). The trans olefin (*Z*-alkene) appeared as the thermodynamic product. Indeed, a reverse selectivity in favor of the *Z*-alkene was observed by stirring the mixture over 48 h at 20 °C. Similar observations were made when the reaction was carried out with quinuclidine. In this case, the reaction was slower and needed at least 47 h at room temperature to reach completion affording the (*Z*)-alkenoate as the major product (entry 10). This reaction can be performed under phase-transfer conditions in the presence of KOH and the alkenes were isolated in 75% yield after 27 h at room temperature (entry 11) though with modest stereoselectivity. It is still difficult to rationalize the selectivity observed in the modified Julia reaction; however, the presence of the metal is highly important,[13] as shown by the reverse selectivity obtained when the reaction was performed in the presence of DBU or NaHMDS. To confirm these observations an alternative method was attempted by using DBU in the presence of a chelating metal such as magnesium(II). A THF solution of benzaldehyde and the fluorosulfone **2** containing $MgBr_2$ (1.4 equiv) was exposed to DBU (1.4 equiv) at room temperature or at reflux. At these two temperatures the (*Z*)-alkenoate **3a** was formed in an excellent selectivity (*Z*/*E* = 92:8) and 72% isolated yield (entries 12 and 13). During these experiments, we noticed that the most reproducible results were obtained when $MgBr_2$ was prepared in situ from Mg^0 and 1,2-dibromoethane, instead of using the commercially available $MgBr_2$−Et_2O.

Low selectivity in favor of the *E*-alkene **3b** was observed from nonanal and NaHMDS at either −78 or 20 °C (entries 14 and 15). From DBU the best results were obtained when the reaction was conducted from −78 to 20 °C (entries 16 and 17), and *E*-alkene was formed as the major product in a 24:76 *Z*/*E* ratio. After purification a mixture of alkenes **3b** was isolated in moderate yield. Quinuclidine afforded the expected alkene in 59% yield as a *Z*/*E* mixture after 48 h at 20 °C (entry 18). In contrast, the addition of $MgBr_2$ allowed control of the formation of the *Z*-alkene. After 2 h at 20 °C, the alkenes **3b** were formed in a 88:12 *Z*/*E* ratio and isolated in good yield (87%, entry 19). The scope and the limitation of this reaction were explored by using other aldehydes and NaHMDS, DBU, or DBU/$MgBr_2$ as bases (Table 2).

With all aromatic aldehydes tested, DBU was the most efficient base affording the (*E*)-alkenoates **3c**−**g** preferentially, while NaHMDS was the most effective for the preparation of the (*Z*)-alkenoates. The observed yields ranged from 71% to 91%. The selectivity depended on the nature of the base. The (*E*)-alkenoates can be obtained in a 85:15 to 98:2 *E*/*Z* ratio when the reaction was performed in the presence of DBU, while (*Z*)-alkenoates were obtained in a 71:29 to 85:15 *Z*/*E* ratio in the presence of NaHMDS. The reaction performed with 4-nitrobenzaldehyde and DBU (1.4 equiv) in the presence of $MgBr_2$ (1.4 equiv) afforded the expected alkenes **3c** accompanied by at least 24% of other products (^{19}F NMR δ: −171.5 (d, J = 26 Hz) and −160.5 (d, J = 16 Hz)) suspected to be the two intermediate β-hydroxysulfones. Indeed, the addition of an excess of DBU to the crude mixture allowed their complete conversion and the alkenes were obtained as the sole products. By working in the presence of an excess of DBU (3 equiv instead of 1.4 equiv) no traces of the intermediate β-hydroxysulfones were observed, and the alkenes were isolated in 66% yield and excellent *Z* selectivity. From the other aromatic aldehydes a good *Z* selectivity was still observed except for the reaction with furfuraldehyde. However, the yields were lower than those obtained when the experiment was conducted in the presence of NaHMDS.

From aliphatic aldehydes a reverse of stereoselectivity was also observed when the reaction was performed in the presence of NaHMDS or DBU. However, a modest selectivity was observed, especially from sterically hindered aliphatic aldehydes (Table 2). From these aldehydes, the alkenes **3h**−**j** were isolated in good yield (up to 81%) but in a low *E* or *Z* selectivity depending on the base used to perform the reaction. The best results were obtained in the presence of $MgBr_2$. In this case, the (*Z*)-alkenoates **3h**−**j** were obtained in excellent *Z*/*E* ratios (up to 94:6) even from a D-galacto-dialdopyranose derivative. It is worthy of note that during the preparation of alkenes **3i** and **3j** no epimerization of the stereogenic center was observed, even under refluxed solvent. In contrast, the same reaction performed with Garner's aldehyde afforded an equimolar mixture of epimeric *Z*/*E* alkenes in 87% yield.

As mentioned in a recent review on the modified Julia olefination, it is difficult to predict the selectivity in the alkene formation.[5b] However, some points of the mechanism have been clarified: (a) in major cases the *E*/*Z* ratio of the product olefins

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TABLE 1. Influence of the Nature of the Base and the Temperature on the *Z*/*E* Ratio

entry	aldehyde	base (additive)	temp (°C)	time	*Z*/*E*[a] (%)	product, yield[b] (%)
1	PhCHO	NaHMDS	−78 to 20	2 h	85:15	**3a**, 53
2			−17 to 20	2 h	83:17	**3a**, 61
3			20	2 h	85:15	**3a**, 69
4		KHMDS	−78 to 20	2 h	70:30	**3a**, 64
5			−17 to 20	2 h	78:22	**3a**, 59
6		DBU	−78 to 20	2 h	24:76	**3a**, 70
7			−17 to 20	2 h	36:64	**3a**, 78
8			20	2 h	44:56[c]	**3a**, 72
9			reflux	10 min	50:50	**3a**, 75
10		quinuclidine	20	47 h	86:14	**3a**, 58
11		KOH (Bu_4NBr)	20	27 h	63:37	**3a**, 75
12		DBU ($MgBr_2$)[d]	20	2 h	92:8	**3a**, 71
13		DBU ($MgBr_2$)[d]	reflux	10 min	93:7	**3a**, 72
14	*n*-$C_8H_{17}CHO$	NaHMDS	20	2 h	52:48	**3b**, 76
15			−78 to 20	2 h	34:66	**3b**, 74
16		DBU	−78 to 20	2 h	24:76	**3b**, 66
17			20	2 h	31:69	**3b**, 57
18		quinuclidine	20	48 h	48:52	**3b**, 59
19		DBU ($MgBr_2$)[d]	20	2 h	88:12	**3b**, 87

[a] Relative ratio of the crude determined by ^{19}F NMR. [b] Isolated yield. [c] Stirring over 48 h at 20 °C, leading to alkenes in a 66:34 *Z*/*E* ratio. [d] In situ prepared in THF from Mg^0 and 1,2-dibromoethane.

reflects the *anti*/*syn* ratio of the intermediate β-alkoxysulfones; (b) retroaddition in the reaction of metalated sulfones with aldehydes could occur; (c) the energy barrier to Smiles rearrangement is higher for the *anti* β-alkoxysulfone; and (d) in some cases aromatic aldehydes undergo formation of zwitterionic betaine more easily providing the *trans* alkene as the major product. In the present case, assuming a nonchelated transition state by using DBU (Figure 1), two different pathways were proposed going through the formation of the *syn* (I) and *anti* (II) β-alkoxysulfones. After a Smiles rearrangement followed by an antiperiplanar elimination, these sulfones afforded the *cis* and *trans* alkenes, respectively. The presence of the fluorine atom destabilizes the carbanion issued from the sulfone,[14] and no retroaddition could occur. In the presence of DBU at −78 °C, kinetic control was expected and the *syn* β-alkoxysulfone (I) was formed as the major intermediate, the *cis* olefin (*E*-alkene) was then obtained selectively (entry 6, Table 1). However, as mentioned recently,[11] the *E*-selectivity decreased with bulky aldehydes as exemplified for the preparation of the alkenes **3h**−**j** (Table 2). Raising the temperature favored the equilibration between the β-alkoxysulfones (I) and (II), and the proportion of the thermodynamic *trans* olefin (*Z*-alkene) rose concomitantly (entries 7−9, Table 1).

The transition state differed when the olefination was performed in the presence of metal as exemplified by the experiments carried out with NaHMDS, or DBU/$MgBr_2$. In these cases, we assume that the reaction goes through a metalated or closed chairlike transition state. The two pathways leading to the *cis* and the *trans* olefins go through the formation of the β-alkoxysulfones (III) and (IV), respectively (Figure 2). From aryl aldehydes, the *anti* β-alkoxysulfone (IV), where the alkyl chain opposes the benzothiazolyl group, appeared as the most stable intermediate. This preferred pathway was observed when the reaction was performed from −78 to 20 °C or at 20 °C from aromatic aldehydes only, and was exclusive at 20 °C by using DBU in the presence of $MgBr_2$ either from aromatic or aliphatic aldehydes. This mechanism led to the *trans* olefin (*Z*-alkene) preferentially (Tables 1 and 2).

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It is noteworthy that in both cases the formation of the *trans* olefins could result from a zwitterionic intermediate, as postulated originally by Julia and co-workers.[5a,b]

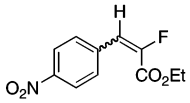
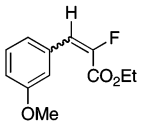
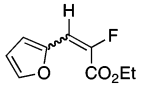
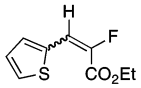
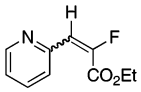
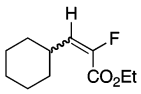
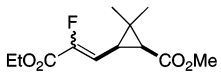
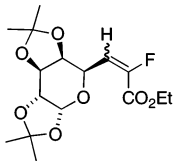
The olefination of ketones was more difficult under these experimental conditions and only preliminary results are reported here. From aromatic ketones such as benzophenone and acetophenone no reaction occurred even at reflux over 24 h (the starting material was recovered). From aliphatic ketone such as the 4-*tert*-butylcyclohexanone the reaction was slower and needed at least 6 h at room temperature to reach completion. In the presence of DBU at 20 °C the expected alkenoate **4** was obtained in 83% isolated yield (Scheme 5).

These preliminary results showed that it might be possible to extend this reaction to other aliphatic ketones after optimization of the experimental conditions. The fact that the reaction failed from aromatic ketones is not clearly understood but was probably due to a retroreaction. Current work seeks to understand this limitation and to generalize this reaction to other aliphatic and aromatic functionalized ketones.

Conclusion

In summary, we have shown that the modified Julia olefination is an efficient strategy for the selective preparation of the (*E*)- or (*Z*)-α-fluoro-α,β-unsaturated esters from a benzothiazolyl fluorosulfone. Depending on the base and the additive used to perform the reaction, it is possible to prepare selectively both the (*Z*)- and the (*E*)-alkenoates in good yields, from aromatic and aliphatic aldehydes. Several bases can be used with or without a metal and it has been observed that the role of the metal is crucial in controlling the double bond geometry. In most cases the chelation with $MgBr_2$ allowed the (*Z*)-alkenoates to be obtained from either aromatic or aliphatic aldehydes. The (*Z*)-alkenoates appeared as the thermodynamic product of the reaction, and its formation can be exclusive under refluxed solvent. In the absence of metal, the reaction was selective from aromatic aldehydes to afford the (*E*)-alkenoates. This method has been extended to a ketone, and appeared to be limited to aliphatic ketones under the present experimental conditions. Efforts are underway to extend the scope of the modified Julia fluoroolefination to ketones and to apply this

TABLE 2. Preparation of Fluoroalkenoates from Aromatic and Aliphatic Aldehydes

Electrophile		Product	NaHMDS, 20 °C, 2 h, THF		DBU, -78 °C to 20 °C, 2 h, THF		DBU, $MgBr_2$,[c] 2 h, THF, 20 °C,	
			Z/*E* [a]	Yield[b] (%)	*Z*/*E*[a]	Yield[b] (%)	*Z*/*E*[a]	Yield[b] (%)
4-NO_2PhCHO	**3c**		84:16	85	12:88	72	94:6	66[d]
3-MeOPhCHO	**3d**		85:15	75	15:85	74	87:13	49[d]
Furfural	**3e**		71:29	71	2:98	77	51:49	37[d]
Thiophene-carboxaldehyde	**3f**		77:23	75	2:98	83	76:24	45[d]
Pyridine 1-carboxaldehyde	**3g**		76:24	78	39:61	90	78:22	27[d]
Cyclohexane carboxaldehyde	**3h**		65:35	56	28:72	86	90:10	77[e]
Biocartol methyl ester	**3i**		45:55	87	35:65	83	80:20	90[e]
galactosaldehyde	**3j**		75:25	81	51:49	82	94:6	72[e]

[a] Relative ratio of the crude determined by ^{19}F NMR. [b] Isolated yield. [c] Prepared in situ in THF from Mg^0 and 1,2-dibromoethane. [d] Experiment run in the presence of DBU (3 equiv) and $MgBr_2$ (1.4 equiv). [e] Experiment run in the presence of DBU (1.4 equiv) and $MgBr_2$ (1.4 equiv).

approach to the preparation of fluoroalkenes such as peptidyl peptidase (IV) inhibitors.

Experimental Section

2-(1-Ethylfluoroacetate)sulfanyl-1,3-benzothiazole (1). A solution of *t*BuOK (3.15 g, 0.0281 mol) in THF (20 mL) was added dropwise via a canula to a solution of 2-mercaptobenzothiazole (3.98 g, 0.0237 mol) in THF (30 mL) at −17 °C under N_2. After 30 min ethyl bromofluoroacetate (4 g, 0.0216 mol) was added dropwise. The mixture was stirred for 1 h 30 at 20 °C, then quenched with a saturated solution of NH_4Cl (20 mL) and extracted with Et_2O/CH_2Cl_2 (1:1, 100 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica, pentane/EtOAc, 9:1) to afford 2-(1-ethylfluoroacetate)sulfanyl-1,3-benzothiazole (**1**) (4.77 g, 0.0176 mol, 81%). ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 4.24 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 6.82 (d, $^2J_{HF}$ = 51.2 Hz, 1H), 7.19−7.44 (m, 2H), 7.71 (d, $^3J_{HH}$ = 6.5 Hz, 1H), 7.85 (d, $^3J_{HH}$ = 7.8 Hz, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −161.10 (d, $^2J_{HF}$ = 49.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 63.5, 92.4 (d, $^1J_{CF}$ = 237.4 Hz), 121.6, 123.0, 125.8, 126.9, 136.6, 153.0, 159.9, 165.3 (d, $^2J_{CF}$ = 27.2 Hz); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{11}FNO_2S_2$ 272.0215, found 272.0215.

2-(1-Ethylfluoroacetate)sulfonyl-1,3-benzothiazole (2). A solution of **1** (4 g, 0.0147 mol) in ethanol (24 mL) was added dropwise to a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (3.64 g, 0.00295 mol) in 30% H_2O_2 (46 mL, 0.441 mol) at 0 °C under N_2. The mixture was stirred for 48 h at room temperature, then quenched with H_2SO_4 (10%, 10 mL). The ethanol was removed by evaporation under reduced pressure and NaCl (5 g) was added. The resulting solution was extracted twice with CH_2Cl_2/Et_2O (1:1, 100 mL). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (silica, CH_2Cl_2/pentane 8:2) to afford 3.22 g of **2** as a white solid (3.22 g, 0.0106 mol, 72%). Mp 76 °C; registry number 910803-66-6; ^1H NMR (250 MHz, $CDCl_3$) δ 1.23 (t, $^3J_{HH}$

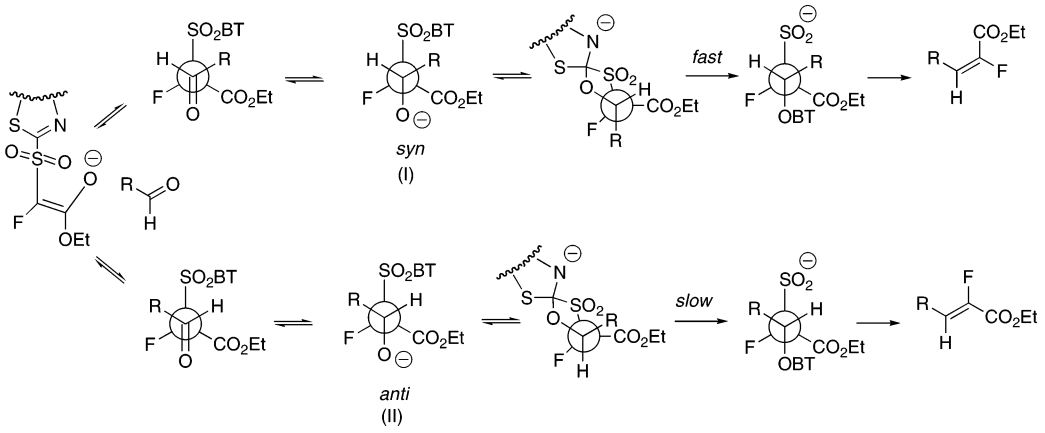


FIGURE 1. Plausible mechanism for a nonchelated transition state (opened transition state).

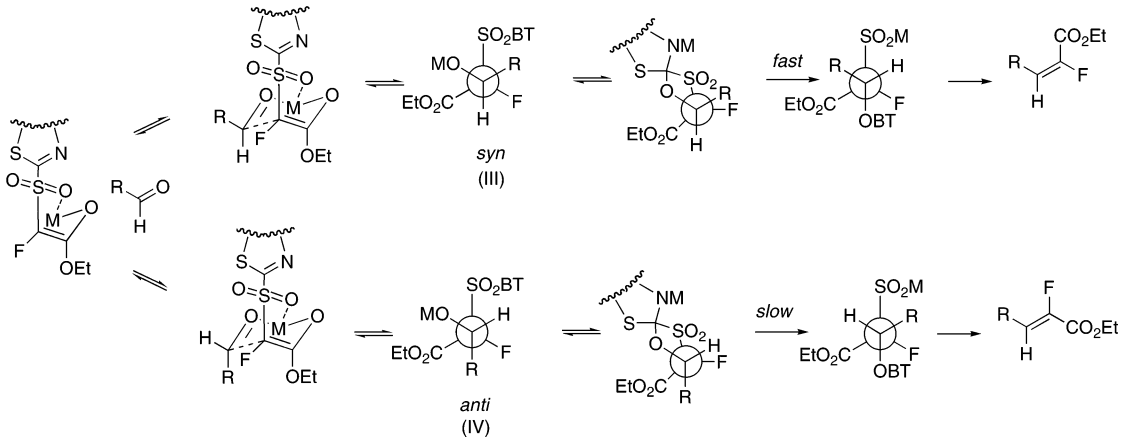
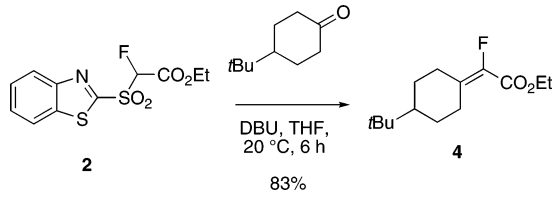


FIGURE 2. Plausible mechanism for a metalated chairlike transition state (closed transition state).

SCHEME 5. Fluoroolefination of a Ketone



2 **4**

= 7.2 Hz, 3H), 4.32 (m, 2H), 5.98 (d, $^2J_{HF}$ = 47.5 Hz, 1H), 7.53−7.58 (m, 2H), 7.95 (m, 1H), 8.16 (m, 1H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −180.90 (d, $^2J_{HF}$ = 47.3 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.1, 64.3, 96.7 (d, $^1J_{CF}$ = 234.9 Hz), 122.6, 126.1, 128.3, 129.1, 137.8, 152.8, 160.2 (d, $^2J_{CF}$ = 23.3 Hz), 161.2; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{11}FNO_4S_2$ 304.0114, found 304.0100.

Representative Procedure for Olefination with NaHMDS: Ethyl 2-Fluoro-3-phenylacrylate (3a) (Table 1, Entry 3). NaHMDS (1.7 mL, 1.38 mmol, 1.4 equiv, 0.8 M) was added dropwise to a solution of sulfone **2** (300 mg, 0.989 mmol, 1 equiv) and benzaldehyde (126 mg, 1.18 mmol, 1.2 equiv) in THF (5 mL) at room temperature under N_2. The mixture was stirred for 2 h at 20 °C, then was quenched with a saturated solution of NH_4Cl (1 mL) and brine (2 mL) and extracted with CH_2Cl_2/Et_2O (1:1, 20 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give 200 mg of crude product. The crude product was purified by chromatography (silica, pentane/AcOEt 95:5) to afford ethyl 2-fluoro-3-phenylacrylate (132 mg, 0.68 mmol, 69%) (*Z*:*E* = 85:15). Registry number 350-99-2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, $^3J_{HH}$ = 7.1 Hz, 3H, *E*), 1.30 (t, $^3J_{HH}$ = 7.2 Hz, 3H, *Z*), 4.16 (q, $^3J_{HH}$ = 7.1 Hz, 2H, *E*), 4.27 (q, $^3J_{HH}$ = 7.2 Hz, 2H, *Z*), 6.85 (d, $^3J_{HF}$ = 22.3 Hz, 1H, *E*), 7.25−7.55 (m, 5H), 7.57 (d, $^3J_{HH}$ = 1.6 Hz, 2H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −125.75 (d, $^3J_{HF}$ = 37.7 Hz, *Z*), −117.66 (d, $^3J_{HF}$ = 22.6 Hz, *E*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (*E*), 14.5 (*Z*), 61.9 (*E*), 62.2 (*Z*), 117.8 (d, $^3J_{CF}$ = 4.6 Hz), 121.8 (d, $^3J_{CF}$ = 25.7 Hz), 128.3, 129.0 (*E*), 129.1 (*Z*), 129.9 (d, $^3J_{CF}$ = 3.0 Hz), 130.0 (d, $^3J_{CF}$ = 2.8 Hz), 130.6 (d, $^2J_{CF}$ = 8.3 Hz), 131.3, 131.4 (d, $^2J_{CF}$ = 4.5 Hz), 147.3 (d, $^1J_{CF}$ = 267.6 Hz, *Z*), 161.7 (d, $^3J_{CF}$ = 34.4 Hz); HRMS (ESI) *m*/*z* [M + H] calcd for $C_{11}H_{12}FO_2$ 195.0821, found 195.0815.

Representative Procedure for Olefination with DBU: Ethyl 3-Cyclohexyl-2-fluoroacrylate (3h, Table 2). DBU (0.21 mL, 1.38 mmol, 1.4 equiv) was added dropwise to a solution of sulfone **2** (300 mg, 0.989 mmol, 1 equiv) and cyclohexylcarboxaldehyde (132 mg, 1.18 mmol) in THF (5 mL) at −78 °C under N_2. After addition the mixture was stirred for 30 min at −78 °C and then 1 h and 30 min at 20 °C. The reaction was quenched with a saturated solution of NH_4Cl (1 mL) and brine (2 mL), then extracted with CH_2Cl_2/Et_2O (1:1, 20 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by chromatography (silica, pentane/AcOEt, 95:5) to afford **3h** (170 mg, 0.85 mmol, 86%) (*Z*:*E* = 29:71). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01−1.29 (m, 9H), 1.57−1.65 (m, 4H), 2.49 (m, 1H, *Z*), 2.95 (m, 1H, *E*), 4.16−4.27 (m, 2H), 5.73 (dd, $^3J_{HF}$ = 22.00 Hz, $^3J_{HH}$ = 10.4 Hz, 1H, *E*), 5.90 (dd, $^3J_{HF}$ = 33.6 Hz, $^3J_{HH}$ = 9.6 Hz, 1H, *Z*); ^{19}F NMR (235 MHz, $CDCl_3$) δ −125.03 (d, $^3J_{HF}$ = 22.4 Hz, *E*), −131.82 (d, $^3J_{HF}$ = 33.9 Hz, *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (*E*), 14.3 (*Z*), 25.6, 25.7, 25.9, 26.0, 32.2 (*Z*), 33.0 (*E*), 34.1 (*Z*), 34.8 (d, $^3J_{CF}$ = 4.6 Hz, *E*), 61.4 (*E*), 61.6 (*Z*), 125.8 (d, $^2J_{CF}$ = 11.2 Hz, *E*), 129.0 (d, $^2J_{CF}$ = 15.3 Hz, *Z*), 146.3 (d, $^1J_{CF}$ = 251.7 Hz, *E*), 147.1 (d, $^1J_{CF}$ = 255.2 Hz, *Z*), 161,1 (d, $^2J_{CF}$ = 36.2 Hz, *E*), 161.4 (d, $^2J_{CF}$

= 36.1 Hz, *Z*); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{18}FO_2$ 201.1291, found 201.1275.

Representative Procedure for Olefination with DBU (1.4 equiv) and $MgBr_2$ in Situ: Ethyl 2-Fluoro-3-(2,2,7,7-tetramethyltetrahydrobis[1,3]dioxolo[4,5-*b*;4′,5′-*d*]pyran-5-yl)-acrylate (3j). Dibromoethane (0.128 mL, 1.48 mmol, 1.5 equiv) was added dropwise to a suspension of Mg^0 (34 mg, 1.38 mmol, 1.4 equiv) in THF (5 mL) at 20 °C under N_2. After disappearance of all magnesium (1 h of stirring), a solution containing galactosaldehyde (305 mg, 1.18 mmol, 1.2 equiv) and sulfone **2** (300 mg, 0.989 mmol, 1 equiv) in THF (1 mL) was added. After 10 min, DBU (0.21 mL, 1.38 mmol, 1.4 equiv) was added dropwise, and the solution was stirred for 2 h at 20 °C. The reaction was quenched with a saturated solution of NH_4Cl (1 mL) and brine (2 mL), then extracted with CH_2Cl_2/Et_2O (1:1, 20 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by chromatography (silica, pentane/AcOEt 92:8) to afford **3j** (246 mg, 0.71 mmol, 72%) (*Z*:*E* = 94:6). ^1H NMR (250 MHz, $CDCl_3$) δ 1.31 (m, 15 H), 1.46 (m, 4H), 1.55 (m, 4H), 4.29 (m, 5H), 4.64 (dd, $^3J_{HH}$ = 3.1 Hz, $^2J_{HH}$ = 8.5 Hz, 1H), 4.83 (dt, $^3J_{HH}$ = 4.1 Hz, $^2J_{HH}$ = 16.2 Hz, 1H, *Z*), 5.33 (m, 1H), 5.52 (d, $^3J_{HH}$ = 5.3 Hz, 1H), 5.98 (dd, $^3J_{HH}$ = 11.2 Hz, $^3J_{HF}$ = 20.4 Hz, 1H, *E*), 6.23 (dd, $^3J_{HH}$ = 8.5 Hz, $^3J_{HF}$ = 34.2 Hz, 1H, *Z*); ^{19}F NMR (235 MHz, $CDCl_3$) δ −123.78 (dd, $^3J_{HF}$ = 34.5 Hz, $^4J_{HF}$ = 2.0 Hz, *Z*), −120.13 (d, $^3J_{HF}$ = 20.2 Hz, *E*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4 (*E*), 23.0 (*E*), 24.6 (*Z*), 24.7 (*E*), 25.2 (*Z*), 25.3 (m), 26.3, 29.7 (*Z*), 30.0 (*E*), 30.1, 32.2, 62.1, 63.9 (d, $^3J_{HH}$ = 1.9 Hz), 64.0 (d, $^3J_{HH}$ = 9 Hz), 70.4 (*Z*), 70.6 (*E*), 71.0 (*Z*), 71.3 (*E*), 72.9 (d, $^3J_{CF}$ = 1.2 Hz), 73.4 (d, $^3J_{CF}$ = 2.5 Hz), 96.6 (*Z*), 96.7 (*E*), 109.3 (*E*), 109.4 (*Z*), 109.8, 110.0 (m), 116.5 (d, $^3J_{CF}$ = 8.0 Hz, *E*), 120.6 (d, $^2J_{CF}$ = 21.5 Hz, *Z*), 147.1 (d, $^1J_{CF}$ = 262.3 Hz, *Z*), 148.2 (d, $^1J_{CF}$ = 259.9 Hz, *E*), 160.4 (d, $^2J_{CF}$ = 36.2 Hz, *E*), 160.8 (d, $^2J_{CF}$ = 35.3 Hz, *Z*); HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{23}FNaO_7$ 369.1326, found 369.1330.

Representative Procedure for Olefination with DBU (3 equiv) and $MgBr_2$ in Situ: Ethyl 2-Fluoro-3-(4-nitrophenyl)acrylate (3c). Dibromoethane (0.128 mL, 1.48 mmol, 1.5 equiv) was added dropwise to a suspension of Mg^0 (35 mg, 1.38 mmol, 1.4 equiv) in THF (5 mL) at 20 °C under N_2. After disappearance of the magnesium (1 h of stirring), a solution of 4-nitrobenzaldehyde (180 mg, 1.18 mmol, 1.2 equiv) and sulfone **2** (300 mg, 0.989 mmoles, 1 equiv) in THF (1 mL) was added. After 10 min DBU (0.44 mL, 2.96 mmol, 3 equiv) was added dropwise. The reaction mixture was stirred for 2 h at 20 °C, then quenched with a saturated solution of NH_4Cl (1 mL) and brine (2 mL) and extracted with CH_2Cl_2/Et_2O (1:1, 20 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by chromatography (silica, pentane/AcOEt 95:5) to afford **3c** (156 mg, 0.65 mmol, 66%) (*Z*:*E* = 94:6). Registry number 18238-98-7; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, $^3J_{HH}$ = 7.2 Hz, 3H, *E*), 1.31 (t, $^3J_{HH}$ = 7.2 Hz, 3H, *Z*), 4.17 (q, $^3J_{HH}$ = 8.0 Hz, 2H, *E*), 4.30 (q, $^3J_{HH}$ = 8.0 Hz, 2H, *Z*), 6.86 (d, $^3J_{HF}$ = 20.3 Hz, 1H, *E*), 7.52 (d, $^3J_{HH}$ = 12.0 Hz, 2H, *E*), 7.71 (d, $^3J_{HH}$ = 8.0 Hz 2H, *Z*), 8.11 (d, $^3J_{HH}$ = 12.0 Hz, 2H, *E*), 8.15 (d, $^3J_{HH}$ = 8.0 Hz, 2H, *Z*); ^{19}F NMR (235 MHz, $CDCl_3$) δ −120.15 (d, $^3J_{HF}$ = 34.5 Hz, *Z*), −112.98 (d, $^3J_{HF}$ = 23.1 Hz, *E*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (*E*), 14.3 (*Z*), 62.3 (*E*), 62.6 (*Z*), 115.1 (d, $^3J_{CF}$ = 4.5 Hz, *E*), 119.3 (d, $^2J_{CF}$ = 27.3 Hz), 123.4, 124.1, 130.7 (d, $^3J_{CF}$ = 3.2 Hz, *E*), 131.0 (d, $^3J_{CF}$ = 9.1 Hz, *Z*), 137.5 (d, $^3J_{CF}$ = 8.7 Hz), 138.1 (d, $^3J_{CF}$ = 10.2 Hz), 147.3, 149.0 (d, $^1J_{CF}$ = 222.8 Hz, *E*), 149.4 (d, $^1J_{CF}$ = 251.0 Hz, *Z*), 160.0 (d, $^2J_{CF}$ = 35.7 Hz, *E*), 160.7 (d, $^2J_{CF}$ = 34.2 Hz, *Z*); HRMS *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{11}FNO_4$ 240.0672, found 240.0677.

Representative Procedure for Olefination with DBU and Ketone: (4-*tert*-Butylcyclohexylidene)fluoroacetic Acid Ethyl Ester (4). DBU (0.21 mL, 1.38 mmol, 1.4 equiv) was added dropwise to a solution of sulfone **2** (300 mg, 0.989 mmol, 1 equiv) and 4-*tert*-butylcyclohexanone (182 mg, 1.18 mmol, 1.2 equiv) in THF (5 mL) at 20 °C under N_2. After 6 h of stirring at 20 °C, the reaction mixture was quenched with a saturated solution of NH_4Cl (1 mL) and brine (2 mL), then extracted with CH_2Cl_2/Et_2O (1:1, 20 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by chromatography (silica, pentane/AcOEt 98:2) to afford **4** (198 mg, 0.82 mmol, 83%). Registry number 425407-78-9; ^1H NMR (250 MHz, $CDCl_3$) δ 0.83 (s, 9H), 1.03−1.21 (m, 3H), 1.26 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.58−1.88 (m, 4H), 2.92 (m, 1H), 3.55 (m, 1H), 4.19 (q, $^3J_{HH}$ = 7.2 Hz, 2H); ^{19}F NMR (235 MHz, $CDCl_3$) δ −131.78; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 26.4, 26.6, 26.7 (d, $^3J_{CF}$ = 1.9 Hz), 27.1 (d, $^3J_{CF}$ = 2.4 Hz), 28.3, 28.6, 28.7, 30.9, 31.4, 46.5, 61.2, 135.3 (d, $^2J_{CF}$ = 12.3 Hz), 139.7 (d, $^1J_{CF}$ = 246.6 Hz), 161.8 (d, $^2J_{CF}$ = 36.4 Hz); HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{24}FO_2$ 243.1760, found 243.1770.

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Supporting Information Available: Additional experimental procedures for the preparation of **3b**, **3d**−**g**, and **3i** and ^{19}F, ^1H, ^{13}C NMR spectra of the compounds **1**, **2**, and **3a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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