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Stereoselective Synthesis of Fluoroalkenoates and Fluorinated Isoxazolidinones: N-Substituents Governing the Dual Reactivity of Nitrones

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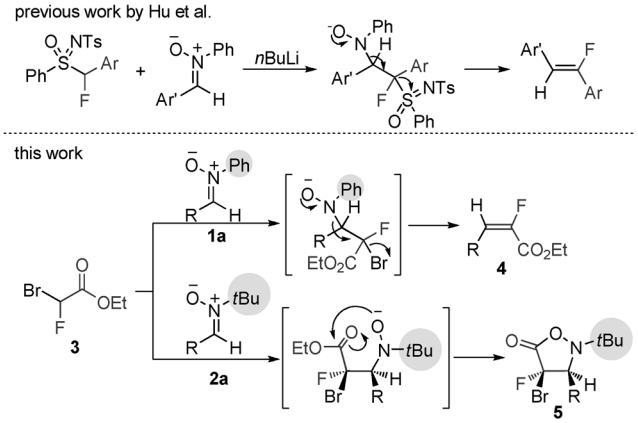
Abstract: α-Fluoroalkenoates and 4-fluoro-5-isoxazolidinones are of vast interest due to their potential biological applications. We now demonstrate the syntheses of (*E*)-α-fluoroalkenoates and 4-fluoro-5-isoxazolidinones by the reactions between nitrones and α-fluoro-α-bromoacetate. By altering N-substituents in nitrones, (*E*)-α-fluoroalkenoates and 4-fluoro-5-isoxazolidinones can be achieved, respectively, with high chemo- and stereoselectivities. Experimental and computational studies have been conducted to elucidate the reaction mechanisms. Linear free energy relationship studies further revealed that the N-substituent effects are primarily of electronic origin.

Introduction

Fluorine substitution[1] has been a viable tool for modifying biological and physicochemical properties of organic compounds.[2] Among various fluorinated functionalities, monofluoroalkenoates have been of immense interest due to their potential medicinal applications.[3] While many methods have been developed to prepare monofluoroalkenoates,[4,5] stereoselective syntheses of monofluoroalkenoates are limited to a handful of reactions, such as the Horner–Wadsworth–Emmons (HWE) reaction[4,6] and the Julia–Kocienski olefination.[7] Recently, Hu et al. demonstrated a one-step synthesis of (*Z*)-monofluoroolefin by the reaction between nitrones and α-fluoro-α-sulfoximines aryl methides,[5j,8] in which the sulfoximine moiety served as both an activating and a leaving group (Scheme 1). Considering the high nucleofugality of bromide,[9] we envisioned that monofluoroalkenoates can be synthesized by a similar reaction with α-fluoro-α-bromoacetate as a pronucleophile.

On the other hand, isoxazolidinone derivatives have been recognized as key heterocyclic skeletons in numerous bioactive compounds,[10] which can be constituted through the reaction of esters with nitrones.[11,12] In principle, with a precise modulation of reaction pathways, the preparation of monofluoroalkenoates and fluorinated isoxazolidinones can be achieved, respectively, by the reactions between α-fluoro-α-bromoacetate and nitrones. Herein, we report the stereoselective synthesis of α-fluoroalkenoates by using ethyl α-fluoro-α-bromoacetate (**3**) and nitrones. By altering the N-substituent in nitrones, (*E*)-α-fluoroalkenoates (**4**), 4-fluoro-5-isoxazolidinones (**5**), and 4-fluoro-5-isoxazolones (**6**) could be obtained under respective reaction conditions.



Scheme 1. Synthesis of monofluorinated olefins using nitrones.

Results and Discussion

Our studies were initiated by adding **1a** to a mixture of **3** and KHMDS in THF at −78 °C, which resulted in the complete decomposition of **3** probably through α-fluoride[13,1d,i] and/or α-bromide eliminations. Further investigation was conducted by treating a mixture of **1a** and **3** with KHMDS, expecting the in situ capture of **3**-enolate. As desired, product **4a** was obtained

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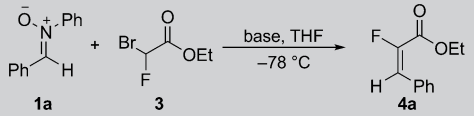
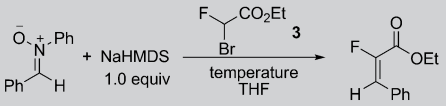
Table 1. Effects of bases on reaction yield and stereoselectivity.



Entry[a]	Base	Yield [%][c]	*E/Z*
1	KHMDS	36	94:6
2	NaHMDS	38	90:10
3	LiHMDS	11	94:6
4		9	99:1
5		–[d]	–[d]
6		–[d]	–[d]
7[b]	NaH	–[e]	–[d]
8[f]	KHMDS	22	97:3
9[f]	NaHMDS	30	97:3

[a] The base in THF (0.1 M, 2.0 equiv) was added dropwise to a mixture of **1a** (0.05 M, 1 equiv) and **3** (0.075 M, 1.5 equiv) in THF at −78 °C within 5 min (ca. 1.2 M h^{-1}). [b] The reaction was performed with **1a**, **3**, and NaH in a molar ratio of 1.0:3.0:3.0, respectively. [c] ^{19}F NMR yields were determined using $PhCF_3$ as an the internal standard. [d] Complete decomposition of **3**. [e] Compound **3** was recovered. [f] 2.0 equiv HMPA was added.

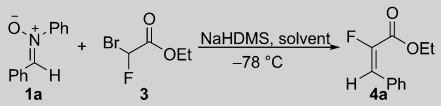
Table 2. Effects of temperatures, additives, and concentrations on reaction yield and stereoselectivity.



Entry[a]	*T* [°C]	**1a** [equiv]	Yield [%][b]	*E/Z*
1[c]	−78	2.0	53	94:6
2	−78	2.0	63	93:7
3	−50	2.0	47	91:9
4	−30	2.0	46	90:10
5	0	2.0	15	85:15
6	−78	1.5	62	92:8
7	−78	1.2	47	93:7
8	−78	1.0	45	90:10
9[d]	−78	1.0	28	96:4
10	−78	3.0	58	89:11

[a] A solution of $BrFCHCO_2Et$ (**3**, 1.0 equiv) in THF was added to a solution of **1a** and NaHMDS in THF within 5 min. The concentration of reaction solution is 0.2 M, i.e., **1a** (0.2 mmol) in THF (1.0 mL). [b] ^{19}F NMR yields were determined using $PhCF_3$ as the internal standard. [c] The concentration of reaction solution is 0.05 M, i.e., **1a** (0.2 mmol) in THF (4.0 mL). [d] 2.0 equiv of **3** was used.

Table 3. Reaction condition screening on solvent effects and substrate proportions.



Entry[a]	Solvent	**3** [equiv]	Base [equiv]	Yield [%][b]	*E/Z*
1[d]	THF	1.0	1.0	50	92:8
2	THF	1.0	1.5	62	97.3
3	THF	2.0	2.0	71	91:9
4	toluene	2.0	2.0	10	49:51
5	1,2-dimethoxy-ethane	2.0	2.0	–[c]	–[c]
6	Et_2O	2.0	2.0	–[c]	–[c]

[a] A solution of $BrFCHCO_2Et$ (**3**, 0.4 mmol) in THF (1.0 mL) was added to a solution of **1a** (1.0 equiv) and base in THF at −78 °C using syringe pump over 3 h (ca. 0.13 M h^{-1}). [b] ^{19}F NMR yields were determined using $PhCF_3$ as the internal standard. [c] Severe decomposition of **3**. [d] 1.5 equiv of **1a** was used.

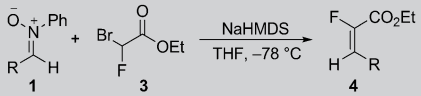
with satisfactory *E/Z* selectivity (Table 1, entry 1); however, the reaction yields did not significantly improve even after an extensive screening of bases (entries 2–7). Hexamethylphosphoric triamide (HMPA) was utilized as a cation-coordinating additive in the hope of enhancing both the yields and the stereoselectivities.[14] While this modification led to slight increase in the *E/Z* ratio of the product, detrimental effects on the reaction yield were observed (entries 1–2 and 8–9). Other solvents, such as DMF, were found to be unsuitable for the present reaction (see the Supporting Information).

Since **3** and the corresponding enolate co-existed under the above-mentioned reaction conditions, the observed low yields could be partially ascribed to the self-Claisen condensation of **3**. To eliminate this competing reaction, an alternative addition sequence was adopted by adding **3** to a solution of **1a** and NaHMDS, which increased the yield to 53% with slightly improved stereoselectivity (Table 2, entry 1). Despite the fact that the addition of HMPA did not show any positive effects (see the Supporting Information), the reaction yield was enhanced by increasing the reaction concentration (entries 1 with 2). This was presumably due to the higher reaction order of the aldol-like addition relative to the above-mentioned enolate decomposition (possibly a second-order reaction versus a first-order reaction, respectively). Further reaction condition screening was focused on alternating reaction temperatures and proportions of reagents; however, the yields did not improve (entries 3–10).

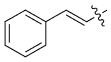
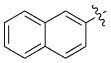
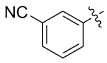
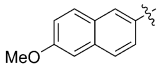
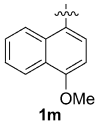
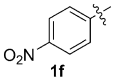
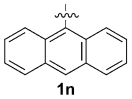
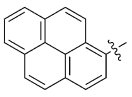
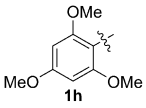
It was recognized that a quick addition of **3** (ca. 2.4 M h^{-1}) could lead to high local concentration of **3**-enolate, thereby favoring the decomposition reaction over the desired addition reaction. A syringe pump was therefore utilized to enable a significantly lower addition rate of **3** (ca. 0.13 M h^{-1}, Table 3, entries 1–2). The product was obtained in 71% yield by employing **1a**, **3**, and NaHMDS in a molar ratio of 1.0:2.0:2.0, respectively (entry 3). Further attempts to enhance the efficacy of the reaction by varying solvents and bases were not successful (entries 4-6).

Table 4 outlines the substrate scope of the present protocol. A variety of aromatic nitrones readily reacted with **3** to afford α-fluoroalkenoates **4** with high *E/Z* selectivity. Compound **4c** was obtained in poor yield probably because of the lability of the cyano group under basic conditions,[15] whereas the low yield of **4f** was likely due to the *ipso* substitution of the nitro group with strong nucleophiles.[16] As indicated by entries 1, 4,

Table 4. Preparation of *E*-monofluoroalkenoates by using *N*-phenyl nitrones **1** and α-bromo-α-fluoroacetate **3**.



1 **3** **4**

Entry[a]	R	Yield [%][b]	*E*/*Z*	Entry[a]	R	Yield [%][b]	*E*/*Z*
1	 **1a**	71 (56)	90:10	9		30 (24)	67:33
2	 **1b**	15 (10)	90:10	10	 **1j**	81 (80)	93:7
3	 **1c**	39 (28)	94:6	11	 **1k**	68 (61)	97:3
4	 **1d**	54 (43)	92:8	12	 **1l**	72 (63)	94:6
5	 **1e**	60 (44)	99:1	13	 **1m**	60 (52)	90:10
6	 **1f**	22 (21)	90:10	14	 **1n**	–[c]	–[e]
7	 **1g**	–[c]	–[e]	15	 **1o**	–[c]	–[e]
8	 **1h**	–[d]	–[e]				

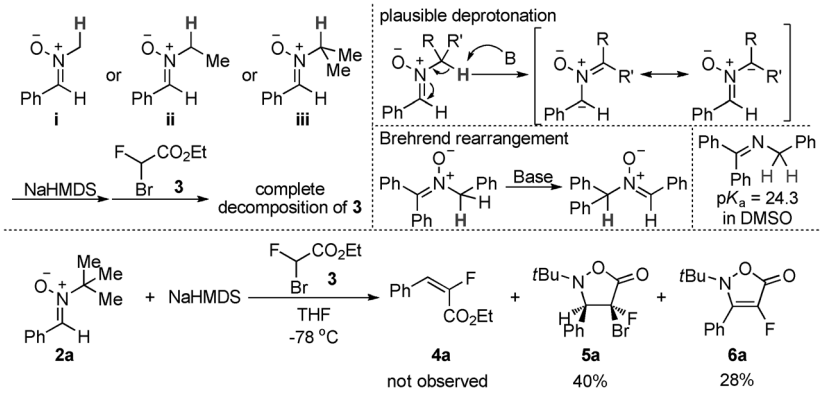
[a] The reaction was carried out as follows: A solution of **3** (2.0 mmol) was added into a solution of **1** (1.0 mmol) and NaHMDS (2.0 mmol) in THF (5.0 mL) at −78 °C using syringe pump over 3 h (ca. 0.13 M h^{-1}). [b] The yields are illustrated in the form of ^{19}F NMR yield% (isolated yield%). [c] No product was observed in ^{19}F NMR spectrum. [d] Complex mixture. [e] Not isolated.

5 and 10–13 in Table 4, the electron-withdrawing ability of substituents was found to exert little influence on reaction yields. Nevertheless, the low reactivity of nitrones bearing *ortho*-substituents and bulky aryl groups indeed revealed the pivotal role of steric effects (entries 2, 7, 8, 14 and 15). Noticeably, nitrones **1i** also participated in the present transformation to render an *E* isomer as the major product; however, with low yield and reduced stereoselectivity (entry 9).

To modulate the reactivity of nitrones, we explored the N-substituent effects in the present reaction. By using *N*-methyl, ethyl, and isopropyl nitrones under the above-mentioned reaction conditions, our initial investigation led to the complete decomposition of **3** (Scheme 2). These unsuccessful reactions with **i–iii** could be probably ascribed to the acidity of α-protons on the *N*-alkyl groups, which not only consumed the base but also diminished the reactivity of the nitrones.[17] *N*-*tert*-butyl nitrones (**2a**) was thus chosen to react with **3**. Instead of α-fluoroalkenoate **4a**, isoxazolidinone (**5a**) and the corresponding dehydrobrominated product isoxazolone (**6a**) were isolated and their structures were confirmed by X-ray diffraction (Scheme 2 and Figure 1).[18]

After a careful screening, the optimal reaction conditions were achieved with **2a**, NaHMDS, and **3** in a molar ratio of 1.0:2.0:2.0, respectively (Table 5, entry 1). Similar to the fluoroalkenoates-forming reaction described above, the present reaction also required the slow addition of **3** into reaction mixture using a syringe pump. It is worth mentioning that **5a** could also be formed exclusively in 54% yield when NaHMDS and **3** were simultaneously added to **2a** via a syringe pump (entry 5).

With the optimal reaction conditions in hand, we examined the substrate scope of this reaction. As shown in Table 6, a variety of *N*-*tert*-butyl-substituted nitrones reacted with **3** to afford **5** and **6** with moderate over-



Scheme 2. Investigation of N-substituent effects in the reaction between nitrones and α-bromo-α-fluoroacetate **3**. The indicated relative configuration of **5a** was confirmed by X-ray diffraction. Other diastereoisomers were not observed.

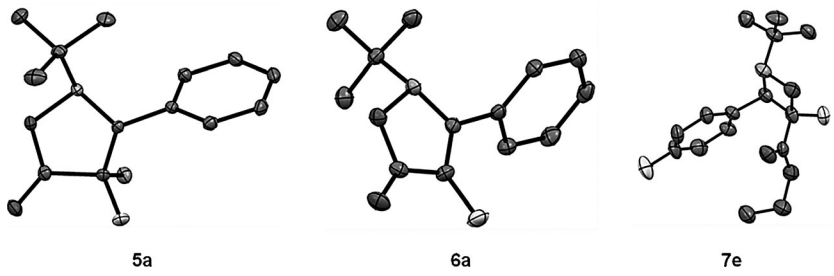
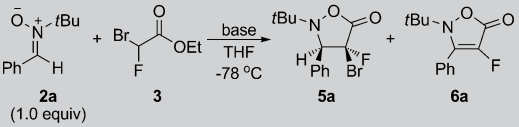


Figure 1. X-ray crystal structures of **5a**, **6a**, and **7e**.[27]

Table 5. Reaction-condition optimization for the isoxazolidinone forming reaction.



Entry[a]	Base (equiv)	Yield **5a** [%][b]	Yield **6a** [%][b]
1	NaHMDS (2.0)	45	22
2	NaHMDS (1.0)	10	0
3	NaHMDS (1.5)	20	0
4	NaHMDS (3.0)	0	37
5[c]	NaHMDS (4.0)	54	0
6[d]	KHMDS (3.0)	0	0
7	LiHMDS (3.0)	0	39

[a] $BrFCHCO_2Et$ (**3**, 0.4 mmol, 2.0 equiv) in THF (1.0 mL) at −78 °C was added using a syringe pump over 3 h (ca. 0.13 M h^{-1}) to a solution of **2a** and base in THF (0.5 mL). [b] ^{19}F NMR yields were determined using $PhCF_3$ as an internal standard. [c] A solution of base (0.8 M) and another solution of **3** (0.4 M, 4.0 equiv) were added simultaneously using a syringe pump over 3 h. [d] Complete decomposition of **3**.

all yields (Table 6, entries 1–5). Nevertheless, sterically hindered substrates demonstrated rather low reactivity (entries 6 and 7). Differing from the fluoroalkenoation reaction, naphthyl-substituted nitrones (**2i** and **2j**) were found to be inactive (entries 9 and 10). Nitrone **2h** was found to be incompatible with the present reaction (entry 8), although its counterpart **1i** could participate in the fluoroalkenoate-forming reaction.[19]

To gain in-depth insight into these two reactions, we have performed detailed experimental and computational mechanistic studies. As depicted in Scheme 3a, these reactions have been proposed to initially undergo an addition reaction to generate an aldol-type key reaction intermediate, which leads to the formation of alkenoate product **4** and isoxazolidinone product **5**. The GCMS analysis of the reaction mixture of **3**-enolate with *N*-phenyl nitrone **1a** revealed the existence of imine **9a** aside from nitrobenzene **8a**[20] and fluoroalkenoate **4a** (Scheme 3b, left). Although a four-membered ring intermediate **7** (R = Ph) can provide a rationale for this observation, we found that the observed imine **9a** can in fact be formed by the reaction between *N*-phenyl nitrone **1** and NaHMDS (Scheme 3d). In addition, 1,2-oxazetidine **7e** was isolated as a side product from the reaction of *N*-*tert*-butyl nitrone **2e** with **3**-enolate in 15% yield. Considering the essential stability of **7e** at 50 °C and the inertness of many other 1,2-oxazetidines,[21,22] phenyl-substituted **7** can be presumably ruled out as key reaction intermediates (Scheme 3c, TS1). Similarly, isoxazolidinone **5a** was also shown to be fairly stable at elevated temperature (−50 °C), therefore, excluding the intermediacy of isoxazolidinone in the olefination reaction.

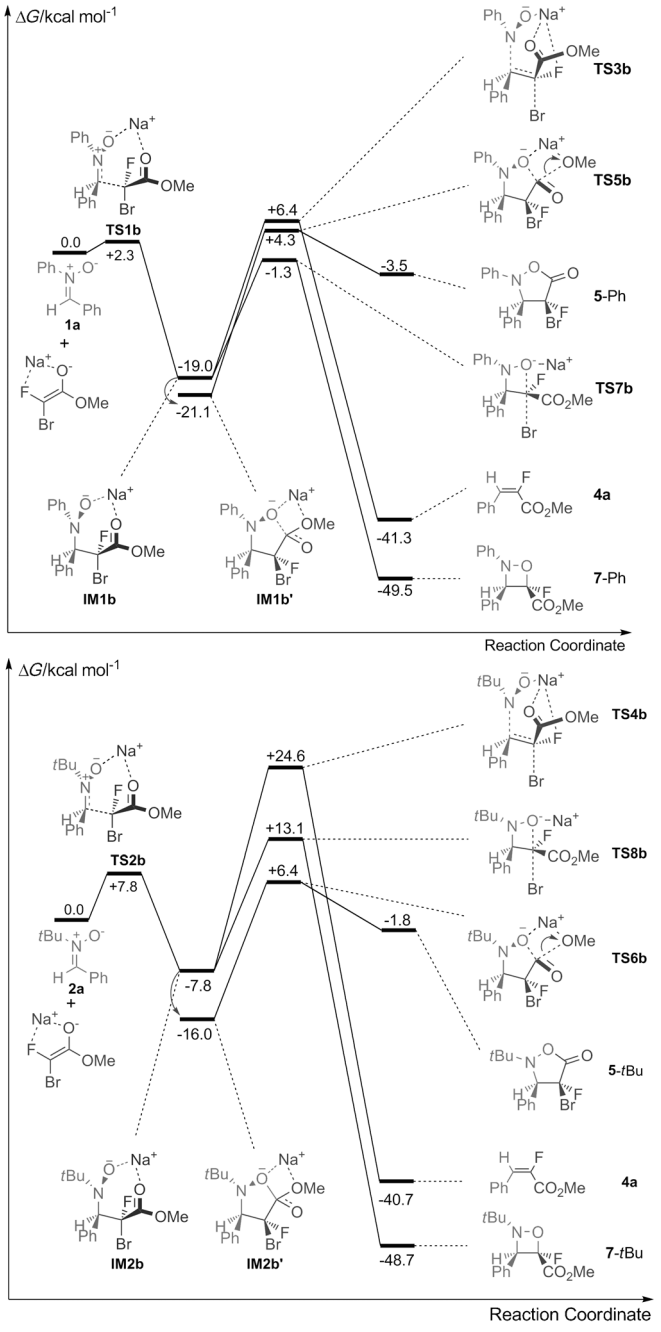
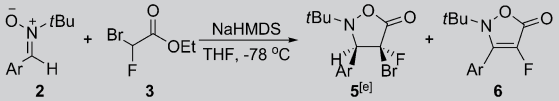


Figure 2. Calculated reaction pathways of *N*-phenyl-substituted nitrones (top) and *N*-*tert*-butyl-substituted nitrones (bottom).

Table 6. Preparation of isoxazolidinones using *N*-*tert*-butyl nitrones **2** and α-bromo-α-fluoroacetate **3**.



Entry[a]	Ar	^{19}F NMR yield [%][b] **5/6**	Isolated yield [%] **5/6**	Entry[a]	Ar	^{19}F NMR yield [%][b] **5/6**	Isolated yield [%] **5/6**
1	**2a**	45/35	40/28	6	**2f**	–[c]	–[d]
2	**2b**	64/0	48/0	7	**2g**	–[c]	–[d]
3	**2c**	30/14	25/11	8	**2h**	–[c]	–[d]
4	**2d**	51/15	43/13	9	**2i**	2/0	–[d]
5	**2e**	39/15	30/14	10	**2j**	26/0	21/0

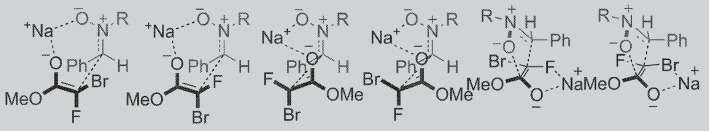
[a] The reaction was carried out by syringe pumping with **3** (2.0 mmol in 5.0 mL of THF) into a mixture of **2** (1.0 mmol) and NaHMDS in 5.0 mL of THF at −78 °C over 3 h (ca. 0.13 M h^{-1}). [b] ^{19}F NMR spectroscopic yield was determined using $PhCF_3$ as the internal standard. [c] Complete decomposition of **3**. [d] Not isolated. [e] The indicated relative configuration of **5** was deduced by ^{19}F NMR spectroscopy. Other diastereoisomers were not observed.

To decipher the detailed mechanistic profiles of the present reactions, we have performed DFT calculations at the M06-2X/6-311+G(d,p)//B3LYP/6-31+G(d,p) level of theory in Gaussian 09.[23,24] Solvent effects of THF were included implicitly through the self-consistent reaction field approach, as implemented in the default PCM model.[25] Thermal and entropic corrections were obtained by frequency analysis at the B3LYP/6-31+G(d,p) level in THF. The frequency analysis confirmed that all considered ground structures were true minima on the PES. The transition-state structures were indicated by a single imaginary frequency.

As depicted in Table 7, the barriers ($\Delta G^{\neq}_{TS1e}$ and $\Delta G^{\neq}_{TS1f}$) to the nitrone–enolate [3+2]cycloaddition[12f,26] were calculated to be +13.5 ~ +16.0 kcal mol^{-1}. In comparison, the aldol-type addition of **3**-enolate to *N*-phenyl nitrone **1a** is kinetically more favorable with the corresponding activation energies ranging from +2.3 to +4.7 kcal mol^{-1} (Table 7). Among the four possible aldol-type transition states, TS1b is the most preferential structure, which also leads to a thermodynamically favorable aldol-type adduct with a corresponding ΔG_{IM1b} of −19.0 kcal mol^{-1}. Similarly, the reaction between **3**-enolate and *N*-*tert*-butyl nitrone **2a** also preferentially adopts the aldol-type addition pathway by the TS2b transition-state structure. However, this reaction is kinetically and thermodynamically less feasible than the corresponding reaction with *N*-phenyl nitrone **1a**.

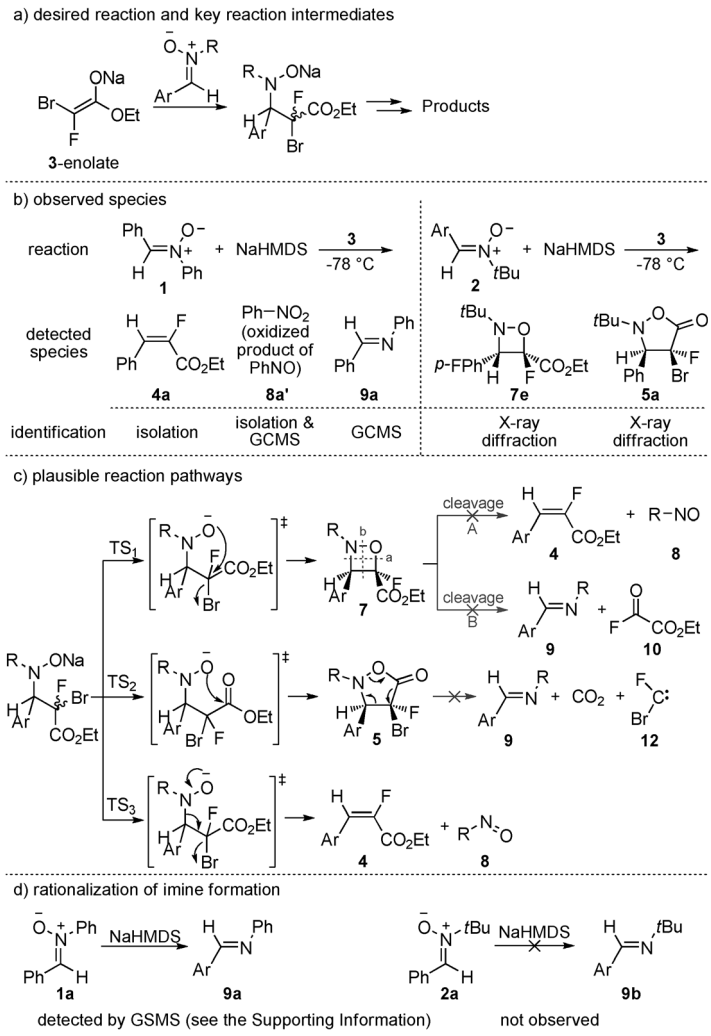
Following the above-mentioned results, further calculations focused on elucidating different reaction pathways toward the observed products. As shown in Figure 2, through the transition-state **TS1b**, an aldol-type adduct can be formed as **IM1b**, which can rearrange to **IM1b′** with similar thermostability. The former can undergo an elimination reaction with a barrier of +25.4 kcal mol^{-1} to generate the *E*-fluoroalkenoate **4a**. Although the isoxazolidinone formation reaction toward **5**-Ph was also found to be kinetically feasible, such a reaction is thermodynamically unfavorable. Similarly, the aldol-type addition of **2a** also leads to the formation of **IM2b** and **IM2b′**. Despite that *E*-fluoroalkenoate **4a** and 1,2-oxazetidine **7**-*t*Bu are thermodynamically preferred products, the corresponding reactions are kinetically impeded by high activation barriers of +40.6 and +29.1 kcal mol^{-1}, respectively. In comparison, the formation of isoxazolidinone **5**-*t*Bu, although thermodynamically unfavorable, was calculated to be kinetically feasible with a barrier of +22.4 kcal mol^{-1}.

Table 7. Calculated thermodynamics and kinetics of the aldol and [3+2] reactions between nitrones and α-bromo-α-fluoroacetate enolate.



R = Ph						
ΔG_{TS1}	+4.3 (**TS1a**)	+2.3 (**TS1b**)	+4.6 (**TS1c**)	+4.7 (**TS1d**)	+13.5 (**TS1e**)	+16.0 (**TS1f**)
ΔG_{IM1}	−16.5 (**IM1a**)	−19.0 (**IM1b**)	−18.0 (**IM1c**)	−16.1 (**IM1d**)	NC (**IM1e**)[a]	NC (**IM1f**)[a]
R = *t*Bu						
ΔG_{TS2}	+10.3 (**TS2a**)	+7.8 (**TS2b**)	+11.8 (**TS2c**)	+13.2 (**TS2d**)	+19.7 (**TS2e**)	+21.7 (**TS2f**)
ΔG_{IM2}	−5.4 (**IM2a**)	−7.8 (**IM2b**)	−8.2 (**IM2c**)	−4.9 (**IM2d**)	NC (**IM2e**)[a]	NC (**IM2f**)[a]

[a] NC = not calculated.



Scheme 3. Elucidation of possible reaction pathways based on the detection of byproducts and side products.

In other words, the reaction between **2a** and **3** leads to equilibrium between **IM2b′** and isoxazolidinone **5**-*t*Bu, which can shift to the latter by acidic workup of the NaOMe side product. Overall, with N-phenyl-substituted **1a**, the generation of fluoroalkenoates is favored by its low kinetic barrier. However, due to the relatively high barrier to the olefination reaction, **IM2b′** can only undergo the five-membered ring-forming reaction to generate isoxazolidinone **5**-*t*Bu. It is worth mentioning that the ring-opening reactions of **7**-Ph and **7**-*t*Bu were calculated to possess barriers of approximately $+40$ kcal mol^{-1} (see the Supporting Information for details). This is in good agreement with our experimental results, which excludes the four-membered ring-opening reaction as a plausible pathway toward fluoroalkenoates.

Noticeably, the formation of 1,2-oxazetidine **7**-Ph was calculated to be kinetically and thermodynamically favorable, which is inconsistent with our experimental observation. Moreover, the calculation of *Z*-olefination demonstrated a low barrier ($\Delta G_{TS}^{\neq} = +1.9$ kcal mol^{-1}) relative to the observed *E*-olefination pathway (see the Supporting Information for details). It is likely that this is due to specific THF–Na^+ interactions, which have not been considered in our implicit solvation calculations. More detailed investigations of these reaction pathways are still needed in future work.

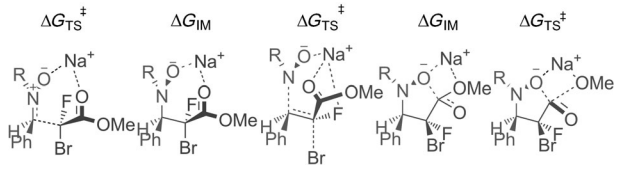
We have further calculated the reaction of **3**-enolate with *N*-methyl and *N*-vinyl (Table 8a and c). Given the N-substituent's electronegativities χ_P[28] Hammett's σ_{para} parameters,[29] Taft's steric parameters E_s[30] and Charton's steric parameters υ (Table 8b),[31] various correlations can be established with our computational results. As shown in Table 8d, the substituent effects in the aldol reaction step can be primarily attributed to electronic effects, as reflected by the high correlation coefficients of ΔG_{IM} and $\Delta G_{TS}^{\neq}$ with σ_{para}. Despite the fact that ΔG_{IM} also correlates with E_s and υ to some extent ($R^2 \approx 0.4$), the relatively weaker dependence suggests the diminished role of steric effects. On the other hand, the transition-state energies of the olefination reaction correlate with both electronic and steric parameters of the N-substituents with moderate correlation coefficients, respectively. Although the electronic effects are predominant, the sterics of the N-substituents also has a noticeable contribution to the overall substituent effects. According to the strong σ_{para}–ΔG_{IM} and σ_{para}–$\Delta G_{TS}^{\neq}$ correlations, the electronic effects also operate as the major contributor to the overall substituent effects in the five-membered ring-forming reaction. On this basis, we can conclude that the observed different reactivities of **1a** and **2a** are mainly due to the electronic effects of the N-substituents. In other words, the phenyl ring in **1a** can facilitate the formation of nitrosobenzene as a byproduct through π-conjugation, which can stabilize the transition-state during the olefination reaction. However, the *t*Bu group would increase the charge density and the nucleophilicity of the N–O^- moiety, therefore enabling the five-membered ring-forming reaction. This hypothesis is supported by the significant stabilization of **IM2b′** and **TS6b** relative to **IM2b′** and **TS4b**, respectively (Figure 2).

Conclusion

We report a one-step reaction between ethyl fluorobromoacetate and nitrones. By altering the N-substituents of nitrones, both fluorinated alkenoates and isoxazolidinones can be obtained with high stereoselectivity. Experimental mechanistic studies have provided convincing evidence for possible reaction pathways. The computational study has further revealed the mechanistic aspects of the reactions. By correlating steric and electronic parameters with DFT calculation results, the observed N-substituent effects have been found to be primarily of electronic origin as reflected by the good correlation of ΔG and Hammett σ_{para} parameters.

Table 8. Correlations of steric and electronic parameters with calculated Gibbs free energies of reaction key intermediates and transition states.[a]

a) Calculated transition states and reaction key intermediates



b) Steric and electronic parameters of N-substituents

R	Electronegativity χ_P (Pauling scale)	σ_{para}	E_s	Charton's parameter (ν)
Ph	2.49	−0.01	−2.55	0.57
CH=CH$_2$	2.41	−0.04	−1.60	1.31
Me	2.25	−0.17	0.00	0.52
*t*Bu	2.29	−0.20	−1.54	1.24

c) Calculated Gibbs free energies [kcal mol^{-1}]

R	Aldol reaction		Olefination		5-Membered ring formation
	$\Delta G_{TS}^{\neq}$	ΔG_{IM}	$\Delta G_{TS}^{\neq}$	ΔG_{IM}	$\Delta G_{TS}^{\neq}$
Ph	2.3	−19.1	6.4	−21.1	4.3
CH=CH$_2$	1.2	−16.8	13.5	−20.5	4.3
Me	5.9	−10.1	14.9	−16.8	5.6
*t*Bu	7.8	−7.8	16.7	−16.0	6.4

d) ΔG steric /electronic parameters correlation coefficients (R^2)

Parameters	Aldol reaction		Olefination		5-Membered ring formation
	$\Delta G_{TS}^{\neq}$	ΔG_{IM}	$\Delta G_{TS}^{\neq}$	ΔG_{IM}	$\Delta G_{TS}^{\neq}$
χ_P	0.676	0.884	0.762	0.885	0.720
σ_{para}	0.910	0.996	0.707	0.999	0.948
E_s	0.230	0.425	0.454	0.441	0.240
ν	0.250	0.425	0.408	0.451	0.249

Experimental Section

General experimental section

Unless otherwise mentioned, all the chemicals were purchased from commercial sources. Preparative thin-layer chromatography was performed to isolate products using 1500 microns preparative thin-layer chromatography plates and using suitable solvent systems as the eluent. ^{1}H, ^{13}C, and ^{19}F spectra were recorded on 400 or 500 MHz Varian NMR spectrometers. ^{1}H NMR chemical shifts were determined relative to $CDCl_3$ as the internal standard ($\delta =$ 7.26 ppm). ^{13}C NMR shifts were determined relative to $CDCl_3$ at $\delta =$ 77.16 ppm. ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ at $\delta = 0.00$ ppm. Mass spectra were recorded on a high-resolution mass spectrometer, in the EI, FAB, or ESI modes.

General procedure for reaction between ethyl monofluorobromoacetate 3 and (*Z*)-aryl-*N*-phenylnitrones 1 and (*Z*)-aryl-*N*-*tert*-butylnitrones 2

Nitrones **1** or **2** and NaHMDS were massed under a nitrogen atmosphere (nitrogen filled glovebox) in a 20 mL sealed tube. BrFCHCOOEt **3** (2.0 mmol in 3.0 mL) was added with syringe pump over 3 h to a solution of nitrones **1** or **2** (1.0 mmol) and NaHMDS (2.0 mmol) in THF (2.0 mL) at −78 °C. The reaction mixture was then warmed to room temperature. $PhCF_3$ (0.5 mL 0.1 M solution in THF) was added and the ^{19}F NMR spectrum was obtained. HCl (1 M, 2.0 mL, in the case of nitrones **1**) or saturated NH_4Cl (aq, 2.0 mL, in the case of nitrones **2**) was added and the solution was extracted with EtOAc (3×2 mL). The combined organic phase was dried over $MgSO_4$, evaporated under vacuum, and purified with preparative thin layer chromatography (hexanes/CH_2Cl_2 10:1).

Theoretical calculations

DFT calculations were performed at the M06-2X/6-311+G(d,p)//B3LYP/6-31+G(d,p) level of theory in Gaussian 09.[23,24] Solvent effects of THF were included implicitly through the self-consistent reaction field approach, as implemented in the default PCM model.[25] Thermal and entropic corrections were obtained by frequency analysis at the B3LYP/6-31+G(d,p) level in THF. The frequency analysis confirmed that all considered ground structures were true minima on the PES. The transition-state structures were indicated by a single imaginary frequency.

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Keywords: fluoroalkenoates · linear free energy relationship · nitrone · olefination · substituent effects

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