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α-Fluoroallenoate Synthesis via N-Heterocyclic Carbene-Catalyzed Fluorination Reaction of Alkynals

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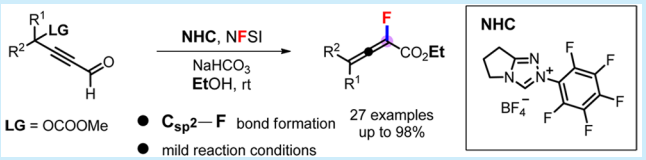
Supporting Information

ABSTRACT: The first catalytic α-fluoroallenoate synthesis is described. With a suitable combination of N-heterocyclic carbene precatalyst, base, and fluorine reagent, the reaction proceeded smoothly to yield a wide range of α-fluoroallenoates with excellent chemoselectivity. These substituted α-fluorinated allenoates have been synthesized for the first time, and they are versatile synthetic intermediates toward other useful fluorine-containing building blocks.



It has become increasingly evident that fluorine has a significant impact on drug discovery.[1] The incorporation of fluorine in a potential drug can lead to a dramatic change in the molecule's properties. For example, fluorine can increase the efficacy of the drug and can make the administration process convenient.[1] Consequently, the insertion of fluorine into organic molecules has drawn long-standing attention from medicinal chemists. In addition, allenes have also been proven to be highly valuable synthons in preparative organic chemistry due to their ability to undergo a variety of transformations.[2] We speculated that, if the fluorine atom can be installed into the allene scaffold, a variety of fluorinated functional molecules could be feasibly accessed through a late-stage transformation (Figure 1b).

Although significant progress has been made toward the production of C−F bonds, there remains a great need for further development of novel methodology for the construction of diversified functional molecules.[3] For example, the efficient incorporation of fluorine into the allenoate backbone remains unknown. In the process of proving the hypothesis, several challenges may be encountered: (1) both α and γ positions of the N-heterocyclic carbene (NHC)−trienolate are nucleophilic; (2) instead of C−F bond formation, the NHC−trienolate can undergo protonation at the α position to afford a nonfluorinated product.

NHCs are well-known for their unique capability to reverse the polarity of aldehydes.[4,5] On this basis, the Rovis group developed an elegant example of NHC-catalyzed directed hydration of α,β-unsaturated aldehydes, leading to a variety of α-fluoro carboxylic acids.[6] In 2012, Sun and co-workers reported a catalytic efficient synthesis of β,γ-unsaturated α-fluoroesters catalyzed by NHCs.[7] More recently, the Wang[8a] and the Sun groups[8b] independently disclosed a progress regarding the NHC-catalyzed α-fluorination of aliphatic aldehydes for the synthesis of α-fluoroesters, amides and thioesters (Figure 1). In brief, the above reactions afforded α-fluoro carbonyls through an NHC-catalyzed C_{sp^3}−F bond forming process. To the best of our knowledge, the example of NHC-catalyzed C_{sp^2}−F bond forming process has not yet been reported by far. With this goal, we set out to efficiently construct α-fluoroallenoates[9] by using a catalytic umpolung strategy.[9]

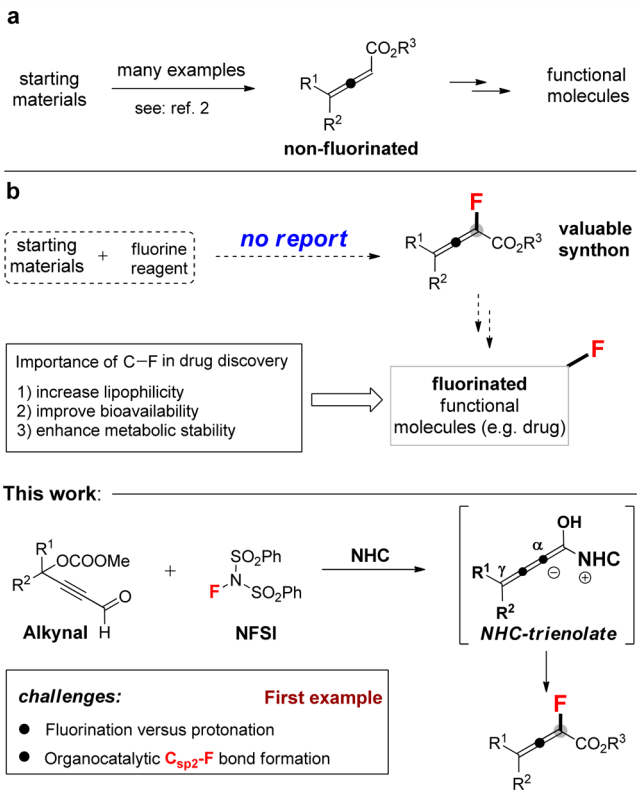


Figure 1. (a) Methods for allenoate synthesis. (b) Our strategy for α-fluorinated allenonate synthesis.

We first undertook the screening of achiral carbene precursors, including thiazoliums, imidazoliums, and triazoliums. Results from our catalyst evaluation are shown in Table 1. Although cat. **III** and **IV**[10] indicated moderate to good reactivity, low levels of chemoselectivity were obtained (entries 3 and 4). However, cat.

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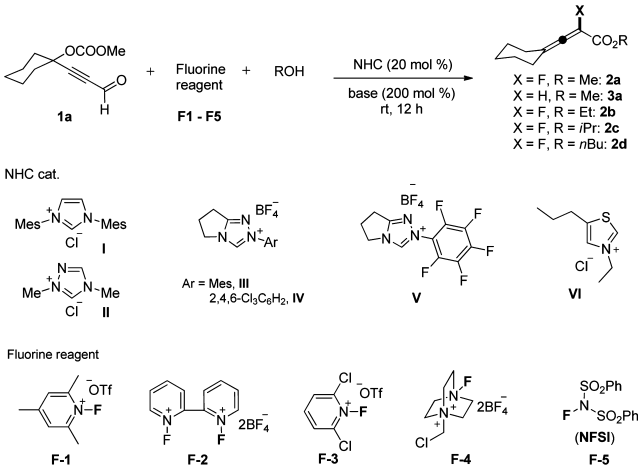
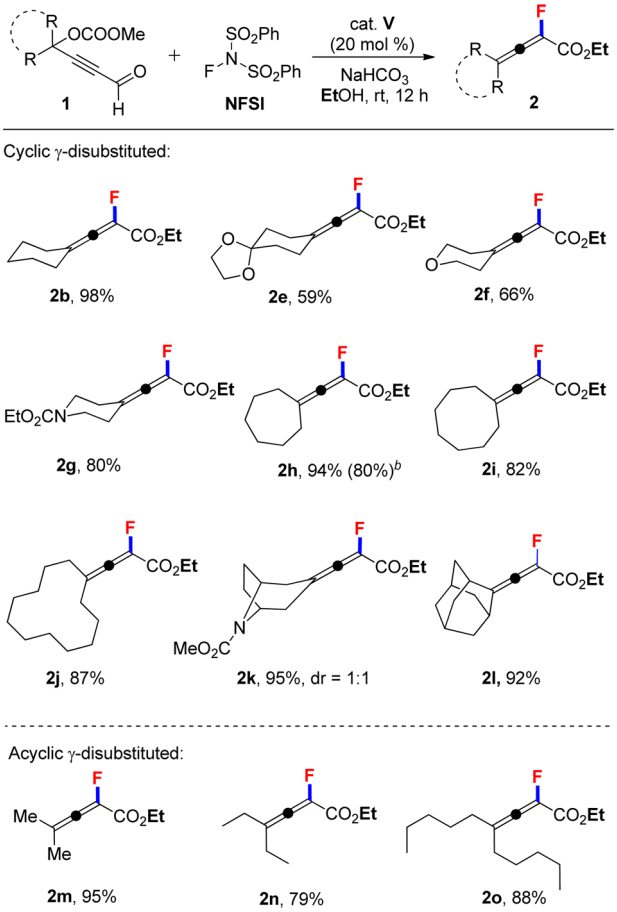
Table 1. Optimization of the Reaction Conditions[a,c]



entry	NHC	ROH	base	"F"	F/H	2 (%)[b]
1	**I**	MeOH	K_2CO_3	F-5	N.D.	<5 (**2a**)
2	**II**	MeOH	K_2CO_3	F-5	N.D.	<5 (**2a**)
3	**III**	MeOH	K_2CO_3	F-5	1:1	40 (**2a**)
4	**IV**	MeOH	K_2CO_3	F-5	3:1	74 (**2a**)
5	**V**	MeOH	K_2CO_3	F-5	8:1	71 (**2a**)
6	**VI**	MeOH	K_2CO_3	F-5	N.D.	<5 (**2a**)
7	**V**	MeOH	Cs_2CO_3	F-5	2:5	23 (**2a**)
8	**V**	MeOH	$NaHCO_3$	F-5	>19:1	60 (**2a**)
9	**V**	MeOH	NaOMe	F-5	1:1	43 (**2a**)
10	**V**	MeOH	$PhCO_2Na$	F-5	1:1	32 (**2a**)
11	**V**	EtOH	$NaHCO_3$	F-5	>19:1	91 (**2b**)
12[d]	**V**	EtOH	$NaHCO_3$	F-5	>19:1	98 (**2b**)
13	**V**	*i*PrOH	$NaHCO_3$	F-5	>19:1	61 (**2c**)
14	**V**	*n*BuOH	$NaHCO_3$	F-5	N.D.	<5 (**2d**)

[a]Reaction conditions: A mixture of **1a** (0.10 mmol), catalyst (20 mmol %), fluorine reagent (0.15 mmol), base (0.2 mmol) in MeOH (1.0 mL) was stirred at room temperature for 12 h. [b]Isolated yield after flash chromatography. [c]Under standard conditions, other F-reagents (**F-1** to **F-4**) gave no desired product **2a** or **2b**. [d]F-5 (0.2 mmol %).

Table 2. Scope of Symmetric Germinal Disubstituted Alkynals[a]



[a]Reaction conditions: alkynal **1**(0.5 mmol), cat. **V** (0.1 mmol), NFSI (1.0 mmol), $NaHCO_3$ (1.0 mmol), EtOH (5.0 mL), rt, 12 h. [b]Yield in parentheses was obtained at a scale of 5.0 mmol.

V[11] provided **2a** in a 71% yield and also with a ratio of **2a**/**3a** = 8:1 (entry 5). Based on these findings, we further investigated other reaction parameters, such as base and fluorination reagent, in order to achieve a better chemoselectivity and a higher chemical yield. Pleasingly, $NaHCO_3$ was found to be an ideal base for this α-fluorination study (entry 8, ratio of **2a**/**3a** > 19:1). Examination of a range of fluorination reagents revealed that *N*-fluorobenzenesulfonimide (NFSI) was superior with respect to reaction efficiency. The use of other fluorine reagents, such as *N*-fluoropyridine salts (**F−1**, **F−2**, and **F−3**) and Selectfluor (**F−4**), resulted in poor yield or no reaction. Further improvement was achieved via the use of EtOH (a replacement of MeOH) and 2 equiv of NFSI (product **2b**, 98% yield, >19:1 chemoselectivity). The critical effect of the size of alcohols was demonstrated by comparison to various dimensional alcohols (**2c** and **2d**, 61% and <5%, respectively). Moreover, a brief survey of different leaving groups at the alkynal γ-position, e.g., OMe, OAc, and OTs, reveals that the methyl carbonate group (OCO_2Me) is the most suitable one.

We then investigated the scope of this method. In general, symmetric cyclic γ-disubstituted alkynals were efficiently converted to desired products (Tables 2 and 3). Notably, a wide array of carbocyclic and heterocyclic γ-disubstitutedalkynals (six-, seven-, eight-, and 12-membered) is amenable to this approach (**2b**, **2e−2j**). In addition, two specific α-fluoroalleno ates, built on scaffolds of azabicyclooctane and adamantine, had been successfully constructed (Table 2, **2k** and **2l**, 95% and 92%, respectively). Moreover, introduction of symmetric acyclic γ-disubstituted alkynals could be tolerated without loss in yield or chemoselectivity (**2m−2o**). A large scale synthesis of **2h** was also examined and provided a good chemical yield (Table 2, 80%, data in parentheses).

Lastly, we turned our attention to unsymmetric γ-disubstituted alkynal. It should be noted that this new protocol has yet to be successfully implemented with this type of alkynals, bearing unsymmetric disubstitution at the alkynal γ-position. Using alkyl−alkyl γ-disubstituted alkynals, high conversions were observed (**4a−4f**, 85−95%). With respect to functional group tolerance, protected alcohols and aldehydes are readily tolerated using these mild reaction conditions (**4g** and **4h**, 61% and 78%, respectively). Importantly, we have found that this new protocol can be readily applied to alkyl−aryl γ-disubstituted alkynals (**4i**, 65%). Moreover, γ-monosubstituted alkynals were also found to be suitable partners and afforded the corresponding products in good chemical yields (**4j** and **4k**, 60% and 62%, respectively). Having successfully examined a series of commonly used alkynals, we next directed our standard fluorination conditions to more complex substrates. Remarkably, an array of cyclic γ-disubstituted alkynals was successfully fluorinated, affording the

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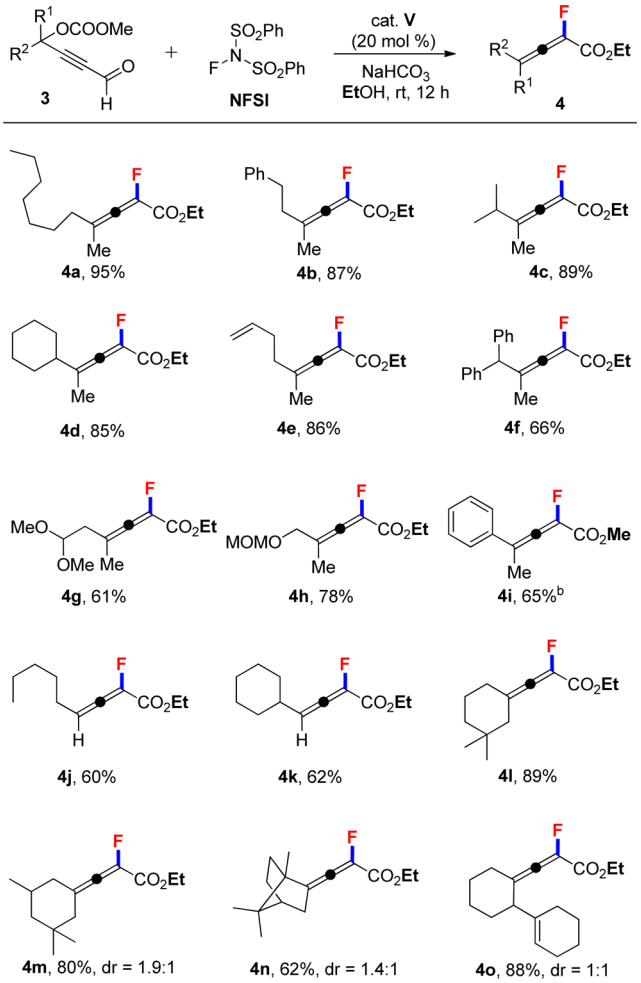
Table 3. Scope of Unsymmetrical γ-Substituted Alkynals[a]



[a]Reaction conditions: alkynal **3** (0.5 mmol), cat. **V** (0.1 mmol), NFSI (1.0 mmol), $NaHCO_3$ (1.0 mmol), EtOH (5.0 mL), rt, 12 h. [b]MeOH (5.0 mL) as solvent.

corresponding α-fluoroallenoates **4l**–**4o** in good to high yields and moderate dr. Additionally, the α-fluoroallenoates can be smoothly transformed into other useful fluorinated molecules (Figure 2).

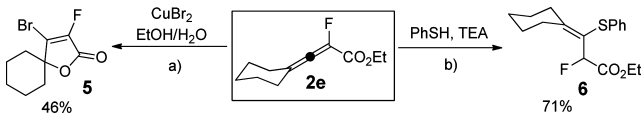


Figure 2. Synthetic transformations.

A postulated mechanism is depicted in Figure 3. The catalytic cycle begins with the addition of NHC catalyst **V** to alkynal **2a** in the presence of $NaHCO_3$. The resulting Breslow intermediate **A** then undergoes elimination to afford a cumulative allenol **B**.[12,13] Nucleophilic addition of intermediate **B** to NFSI generates a NHC-bound α-fluorinated intermediate **C**.[14] Further acyl substitution by ethanol proceeds via intermediate **C** to form the desired product **2b** and regenerate the NHC catalyst. In addition, a plausible competition reaction could take place in the conversion of intermediate **B** to **C**. As highlighted in Figure 3, the nucleophilic addition of intermediate **B** to proton, generated from the NHC catalyst in the presence of base, could lead to the

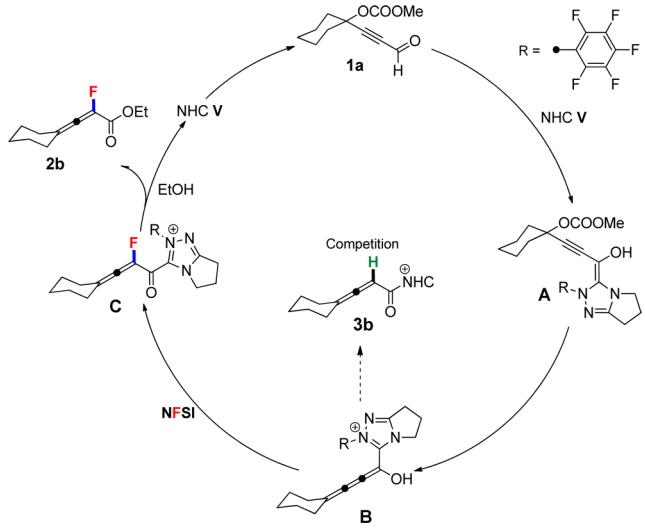


Figure 3. Postulated mechanism.

formation of by product **3b**. The observed excellent chemoselectivity (>19:1) was attributed to below two plausible reasons. First, NFSI exhibits a high electrophilicity,[15] thus facilitating the nucleophilic substitution reaction and resulting in the desired C–F bond; Second, the potential π–π stacking between NFSI (phenyl ring) and intermediate **B** (perfluorophenyl group) allows the C–F bond generation to be an intramolecular-like reaction.

In summary, we have developed an efficient α-fluorination of azolium allenols that were generated from various γ-substituted alkynals. With a suitable combination of NHC precatalyst, base, and fluorine reagent, the reaction proceeded smoothly to yield a wide range of α-fluoroallenoates with excellent chemoselectivity. NFSI serves as the fluorine source in the reactions. These substituted α-fluorinated allenoates have been synthesized for the first time, and they are useful synthetic intermediates toward other fluorine-containing building blocks

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03615.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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