N-Heterocyclic Carbene (NHC) Catalyzed Synthesis of α,α-Difluoro Esters

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Abstract: A process for the synthesis of α,α-difluoro esters by NHC-catalyzed fluorination is described. The internal redox process exhibits good efficiency, selectivity, and functional-group compatibility. It provides an alternative strategy for the formation of the useful *gem*-difluoromethylene unit in organic molecules.

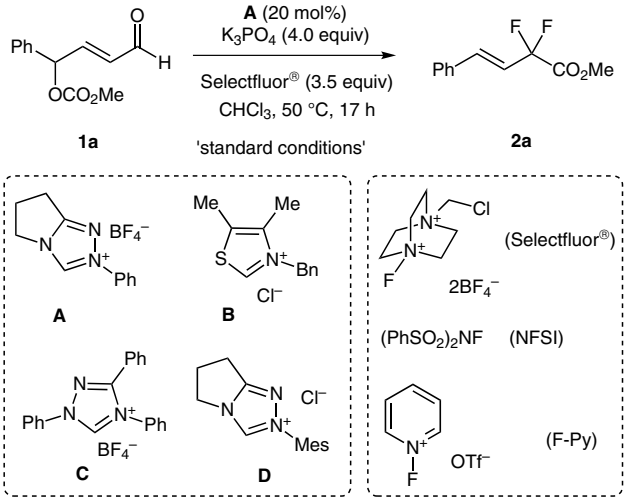
Key words: carbenes, fluorine, umpolung, aldehydes, esterification

Organofluorine compounds have found wide applications in the areas of agrochemical, pharmaceutical, and materials sciences.[1] Incorporation of fluorine can result in dramatic influence in the physical and chemical properties of organic compounds. Consequently, there has been significantly increasing attention to the development of new methods for monofluorination and trifluoromethylation.[2] In contrast, strategies for the introduction of *gem*-difluoromethylene (CF_2) unit into organic molecules are much less explored.[3] Nevertheless, *gem*-difluoromethylene unit exhibits unique and useful properties.[4] For example, it has been demonstrated to be a useful isopolar and isosteric replacement for oxygen as well as a surrogate for a carbonyl group.[4] In particular, α,α-difluoro carbonyl compounds are a family of useful compounds in medicinal chemistry.[5] Typical strategies for the synthesis of this class of compounds include the Reformatsky reaction and coupling reactions from small halodifluoro compounds.[3] Here we report an alternative synthesis of α,α-difluoro esters with a double fluorination strategy enabled by N-heterocyclic carbene (NHC) redox catalysis.[6–8]

Recently, we have reported an NHC-catalyzed enantioselective fluorination process for the synthesis of α-fluoro esters.[8] During the optimization of the reaction conditions for the monofluorination process, we were able to observe an α,α-difluoro ester generated as byproduct. We reasoned that the formation of the α,α-difluoro product may result from the readily enolizable monofluorinated product or intermediate. We hypothesized that the α,α-difluorination can be a major pathway upon careful choice of the reaction parameters, thereby representing a useful strategy for the α,α-difluoro ester synthesis.

We began the study with racemic enal **1a**, which is known to generate the corresponding NHC enolate for subsequent C–F bond formation with an electrophilic fluorination reagent. After rigorous evaluation of the reaction parameters (Table 1), we were pleased to identify that the reaction between **1a** and Selectfluor (3.5 equiv), in the presence of 20 mol% of triazolium salt **A** as the precatalyst and K_3PO_4 (4.0 equiv) as the base, proceeds at 50 °C to give the desired α,α-difluoro ester **2a** in good yield (77%, Table 1, entry 1). Other achiral precatalysts, such as thiazolium salt **B** as well as triazolium salts **C** and **D**, give

Table 1 Optimization of Reaction Parameters



Entry	Variation from the 'standard conditions'	Yield (%)[a]
1	none	77
2	precatalyst **B** instead of **A**	12
3	precatalyst **C** instead of **A**	14
4	precatalyst **D** instead of **A**	32
5	NFSI instead of Selectfluor	71
6	F-Py instead of Selectfluor	<10
7	NaOAc instead of K_3PO_4	61
8	K_2CO_3 instead of K_3PO_4	24
9	NaOMe instead of K_3PO_4	<10
10	KHMDS instead of K_3PO_4	<10
11	CH_2Cl_2 instead of $CHCl_3$	42
12	EtOAc instead of $CHCl_3$	36
13	THF instead of $CHCl_3$	<10
14	with MeOH (5 equiv) additive	<10

[a] Determined by ^1H NMR spectroscopy with CH_2Br_2 as an internal standard.

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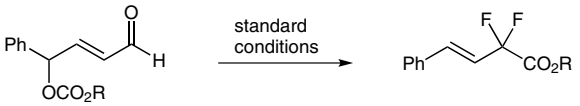
significantly lower yields (Table 1, entries 2–4). The use of NFSI as the fluorination reagent results in slightly decreased yield, but the fluoropyridium reagent (F-Py) is essentially ineffective (Table 1, entries 5 and 6). The reaction is quite sensitive to base and solvent (Table 1, entries 7–13). For example, the use of relative strong bases, such as K_2CO_3, NaOMe, and KHMDS, is detrimental to the formation of the desired product. Other commonly used solvents, for example, dichloromethane, ethyl acetate, and tetrahydrofuran, slow down the reaction and give inferior results. The use of methanol (5 equiv) as additive leads to exclusive formation of the monofluoro ester product (Table 1, entry 14), which is consistent with our previous study.[8] Finally, it is worth noting that the use of 10 mol% of the precatalyst **A** could cause yield decrease, but the Selectfluor loading can be reduced to 2.2 equivalents with comparable efficiency.

With the standard conditions, we next evaluated the reaction scope. As depicted in Table 2, a range of β,γ-unsaturated α,α-difluoro esters can be synthesized in moderate to good yields.[9] The process is compatible with a diverse set of functional groups, such as esters, ethers, silyl ethers, alkenes, aryl halides, and even aryl aldehydes. The alkene configuration in the products is exclusively *E*. In most cases, a small amount of monofluoro ester could be observed, but the major mass balance is an unknown mixture. While γ-aryl-substituted enals (R = aryl) participate smoothly in the difluorination reaction, γ-alkyl-substituted enals (R = alkyl) give the corresponding monofluoro esters as the major products.

With ethyl carbonate and *tert*-butyl carbonate as the γ leaving group, the corresponding ethyl and *tert*-butyl ester products can also be obtained, respectively (Equation 1). However, since the nucleophile is generated in situ from the γ leaving group, and the addition of an external alcohol nucleophile is not effective to enhance the reaction efficiency or outcompete the in situ generated nucleophile, the reaction exhibits a limitation of nucleophiles.



1j (R = Et)
1k (R = *t*-Bu)

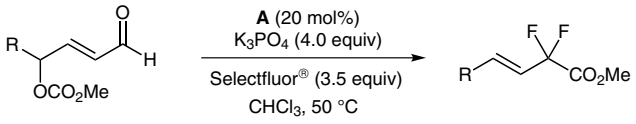
2j 64% (41 h)
2k 40% (65 h)

Equation 1

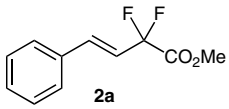
In order to gain insight into the reaction mechanism, we have done control experiments. As shown in Equation 2, subjection of nonfluoro ester **3a** or monofluoro ester **3b** to our standard reaction protocol does not give a trace of the desired difluoro ester **2a**. Thus, this observation rules out the possibility of initial redox ester formation followed by fluorination of the corresponding ester enolate or the monofluoro ester enolate.

We have proposed a mechanism (Scheme 1). The reaction begins with the formation of free NHC from the precatalyst and base. Addition of the free NHC to aldehyde **1** followed by elimination of the carbonate leaving group

Table 2 Reaction Scope[a]

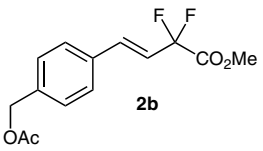


1 **2**



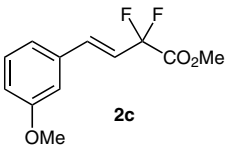
2a

68% (17 h)



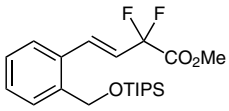
2b

57% (41 h)



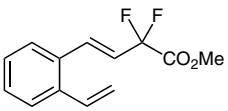
2c

66% (17 h)



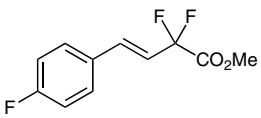
2d

56% (17 h)[b]



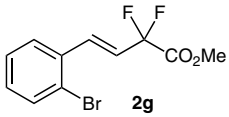
2e

63% (17 h)



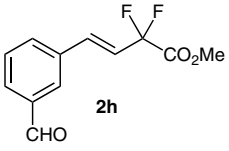
2f

57% (17 h)



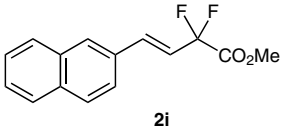
2g

71% (41 h)



2h

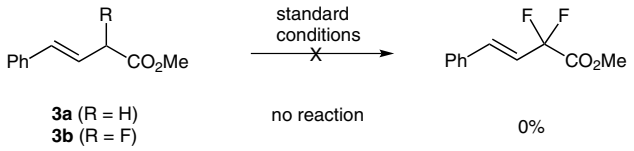
42% (17 h)



2i

63% (41 h)

[a] Yield of purified product.
[b] TIPS = triisopropylsilyl.



Equation 2

forms NHC enolate **F**. Subsequent C–F bond formation with Selectfluor gives **G**. With a relatively low concentration of nucleophile (methoxide ion), the monofluoro acyl NHC species **G** is readily enolized to give NHC enolate **H**. A second fluorination step to form **I** followed by acyl substitution with methoxide furnishes the desired product **2** and regenerates the NHC catalyst. The mechanism is consistent with our control experiments in Equation 2 as well as the observation of exclusive formation of monofluoro ester with five equivalents of methanol additive. The added methanol can facilitate the monofluoro ester formation by trapping of the monofluoro acyl NHC species **G** and thus outcompete the desired enolization towards **H**.

In summary, we have developed a new strategy for the synthesis of α,α-difluoro esters by NHC catalysis. With proper choice of the precatalyst, base, solvent, and fluorination reagent, the internal redox fluorination process exhibits good efficiency, selectivity, and functional-group compatibility. It represents a new addition to the strategies for efficient formation of the useful *gem*-difluoromethylene unit in organic molecules. Control experiments provided insight into the reaction mechanism.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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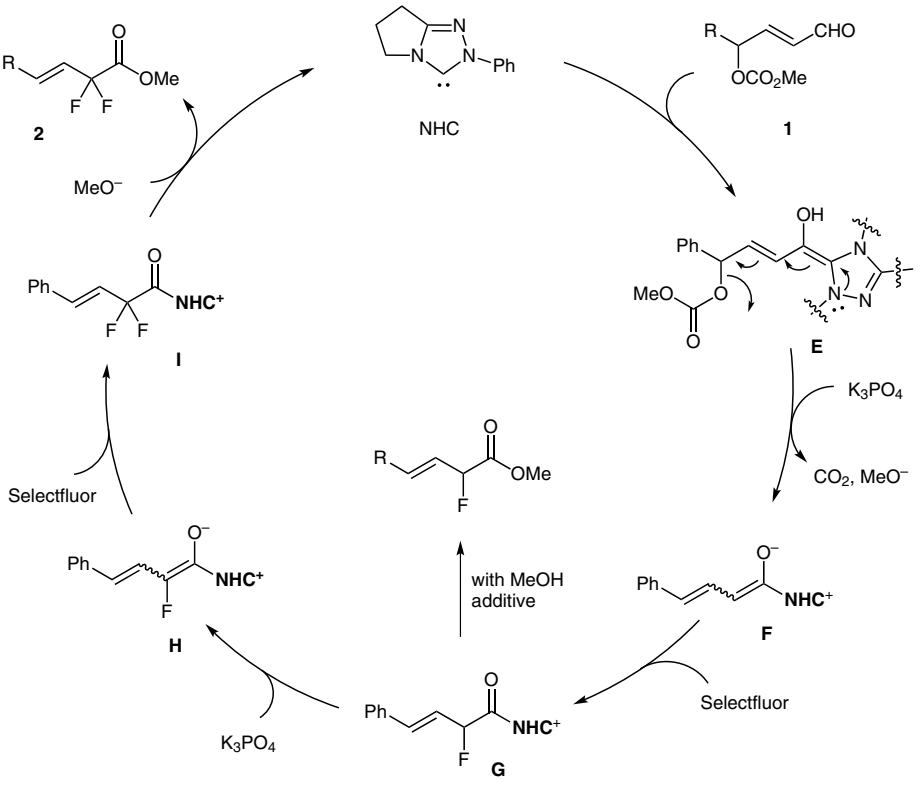

Scheme 1 Plausible mechanism

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(9) **Typical Procedure**

In a glove box, an oven-dried 4 mL vial was charged with triazolium salt **A** (10.9 mg, 0.04 mmol), anhyd $CHCl_3$ (2 mL), K_3PO_4 (169.8 mg, 0.8 mmol), and enal **1a** (0.2 mmol). Selectfluor (248 mg, 0.7 mmol) was then added, and the vial was capped and removed from the glove box. The reaction mixture was stirred at 50 °C for 17 h. The solvent was removed in vacuo, and the product **2a** was purified by silica gel chromatography (10% EtOAc in hexanes) as colorless oil (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.40 (m, 2 H), 7.39–7.35 (m, 3 H), 7.11–7.06 (dt, J_1 = 16.0 Hz, J_2 = 2.4 Hz, 1 H), 6.35–6.26 (dt, J_1 = 16.4 Hz, J_2 = 11.6 Hz, 1 H), 3.91 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4 (t, J = 35.0 Hz), 136.9 (t, J = 9.0 Hz), 134.0, 129.7, 128.8, 127.4, 118.7 (t, J = 25.0 Hz), 112.8 (t, J = 244.0 Hz), 53.5.

