Asymmetric Fluorination

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Enantioselective Synthesis of β,γ-Unsaturated α-Fluoroesters Catalyzed by N-Heterocyclic Carbenes (NHCs)**

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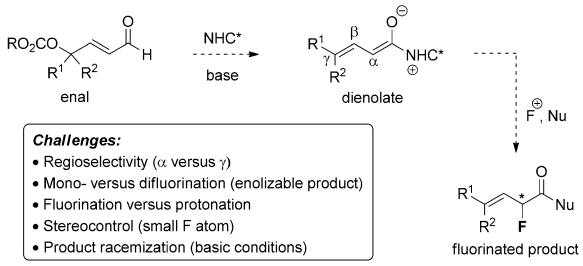
Chiral organofluorine compounds have attracted increasing attention because of their valuable applications in pharmaceutical, agrochemical, and materials industries.[1] Thus, the development of catalytic enantioselective C–F bond-formation processes has become an important area in organic synthesis.[2] In particular, the stereocontrolled fluorination at the α position of a carbonyl group has been intensively explored.[3,4] Since the first report by Hintermann and Togni in 2000,[3a] a range of catalytic enantioselective α fluorination of carbonyl compounds have been developed.[3,4] Despite the significant progress, there remains a great need for further development of useful enantioselective fluorination processes. For example, organocatalyzed asymmetric fluorination for the synthesis of simple α-fluoroesters remains unknown. Herein, we report the first enantioselective fluorination reaction catalyzed by N-heterocyclic carbenes (NHCs).

NHCs are well-known for their unique capability in reversing the polarity of aldehydes.[5] For example, in the presence of an NHC catalyst, the carbonyl carbon atoms of simple aldehydes (acyl anion equivalents), the α position of aldehydes with a leaving group at this position (enolates), and the β position of enals (homoenolates) can be rendered nucleophilic.[5] Very recently, Chi and co-workers have also demonstrated the generation of dienolates in which the γ position is nucleophilic.[6] Thus, a range of new NHC-catalyzed bond-forming processes for functionalization at the α, β, and γ positions of carbonyl carbon atoms of aldehydes have been developed with different electrophiles. However, NHC-catalyzed enantioselective carbon–halogen bond formation, a family of important processes with paramount utility, has not been realized.[7] In this work, we targeted the challenging fluorination.

Previously, we have reported an NHC-catalyzed redox reaction of alkynals that bear a leaving group in γ position for the synthesis of allenoates through a key cumulative allenolate intermediate.[8] In continuation of our effort, we hypothesized that enals that bear a leaving group in γ position would provide access to an NHC-bound dienolate (Scheme 1), which is expected to subsequently react with an electrophilic fluorinating reagent and a nucleophile to afford a fluorinated product. We also expected that a chiral NHC would induce enantioselective C–F bond formation. However, during executing the hypothesized reaction, several challenges may be encountered: 1) There might be a regioselectivity issue, because both the α and γ positions are nucleophilic. 2) The mono-fluorinated product is quite easily deprotonated for a second fluorination, thereby invoking competing difluorination. 3) Instead of C–F bond formation, the dienolate can undergo protonation at the α or γ position to afford a non-fluorinated product. 4) It is not trivial to control the facial selectivity, given the extremely high reactivity of electrophilic fluorine and the small size of the fluorine atom. 5) The typical basic conditions for NHC catalysis would potentially cause product racemization. Additional complications include the possible incompatibility of the NHC catalyst with the electrophilic fluorinating reagent, thereby affecting catalyst turnover.



Scheme 1. Formation of NHC-bound dienolate and further fluorination.

We started the evaluation of our hypothesis with racemic enal **1**, which bears a γ-methyl-carbonate leaving group (Table 1). In view of the above-mentioned challenges, we initially employed a weak base (NaOAc) and a mild fluorine source (F–TEDA). Screening of chiral precatalysts (**A**–**E**) identified **B**, first developed by Bode,[9] as a promising catalyst precursor, and the desired product **2** was obtained with reasonably good enantioselectivity, albeit in low yield (entry 2). As expected, the difluorinated product **3** and the simple redox product **4** account for the mass balance. We next examined other fluorinating reagents and found that the use of NFSI can immediately improve the enantioselectivity (94% *ee*, entry 7). Further solvent screening (entries 8–11) reveals that the reaction in chloroform gives an improved yield (55%, entry 10). The use of other bases, such as DBU, HCO_2Na, and K_3PO_4, results in either no reaction or no formation of the desired product (entries 12–14). In the absence of a base, no reaction was observed, suggesting that free NHC is the active catalyst (entry 15). Decreased loading

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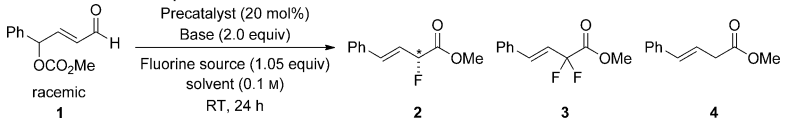
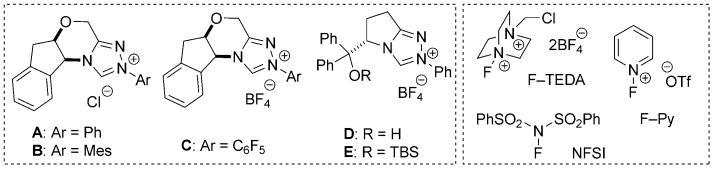
Table 1: Effect of reaction parameters.[a]



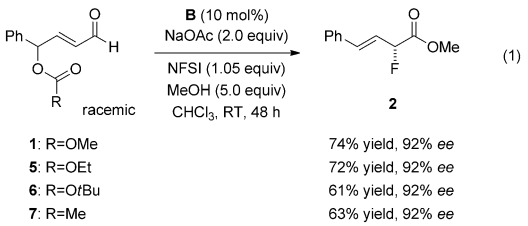
Entry	Precat.	Base	Fluorine source	Solvent	Additive	Yield of **2** [%]	*ee* of **2** [%]	**2**:**3**:**4**
1	**A**	NaOAc	F–TEDA	CH_2Cl_2	–	22	5	53:36:11
2	**B**	NaOAc	F–TEDA	CH_2Cl_2	–	32	75	66:27:7
3	**C**	NaOAc	F–TEDA	CH_2Cl_2	–	48	12	87:10:3
4	**D**	NaOAc	F–TEDA	CH_2Cl_2	–	n.r.	–	–
5	**E**	NaOAc	F–TEDA	CH_2Cl_2	–	n.r.	–	–
6	**B**	NaOAc	F–Py	CH_2Cl_2	–	0[c]	–	–
7	**B**	NaOAc	NFSI	CH_2Cl_2	–	20	94	67:33:0
8	**B**	NaOAc	NFSI	THF	–	<10	–	21:76:3
9	**B**	NaOAc	NFSI	CH_3CN	–	0[d]	–	0:100:0
10	**B**	NaOAc	NFSI	$CHCl_3$	–	55	92	82:18:0
11	**B**	NaOAc	NFSI	benzene	–	26	91	61:39:0
12	**B**	DBU	NFSI	$CHCl_3$	–	0[d]	–	0:100:0
13	**B**	HCO_2Na	NFSI	$CHCl_3$	–	n.r.	–	–
14	**B**	K_3PO_4	NFSI	$CHCl_3$	–	0[d]	–	0:100:0
15	**B**	–	NFSI	$CHCl_3$	–	n.r.	–	–
16	**B**	NaOAc[b]	NFSI	$CHCl_3$	–	<10[e]	–	–
17	**B**	NaOAc	NFSI	$CHCl_3$	MeOH[f]	82	92	>98:1:1
18[g]	**B**[h]	NaOAc	NFSI	$CHCl_3$	MeOH[f]	91	92	>98:1:1
19[g]	**B**[i]	NaOAc	NFSI	$CHCl_3$	MeOH[f]	82	92	>98:1:1

[a] Order of substrate/reagent addition: precatalyst, aldehyde, fluorination reagent, additive, and base. The yield was determined by GC analysis with *n*-decane as an internal standard. The *ee* value was determined by HPLC analysis. [b] 0.2 equiv. [c] Decomposition of starting material. [d] Product **3** was formed exclusively. [e] Conversion was <10%. [f] 5.0 equiv. [g] The concentration was 0.05 M. [h] 10 mol%. [i] 5 mol%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Mes = 2,4,6-trimethylphenyl, n.r. = no reaction, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.



of NaOAc gives a lower conversion (entry 16). After considerable efforts, we were pleased to find that the addition of methanol significantly improves the yield of **2** (entry 17). Finally, the use of 10 mol% of **B** and a concentration of 0.05 M leads to exclusive formation of the desired product **2** in both excellent yield and enantioselectivity (entry 18). It is noteworthy that no product of γ fluorination was observed and product **2** was obtained as a single *E* alkene.

We also prepared enals with different leaving groups in γ position, such as ethyl and *tert*-butyl carbonates as well as acetate [Eq. (1)]. Under our standard conditions (entry 18, Table 1), the reactions of these substrates all proceed to form the same methyl ester product (**2**) with essentially the same enantioselectivity and slightly different yields, with methyl carbonate being the best starting material. The results also suggest that the added methanol, which is used in excess, outcompetes the alkoxide that results from the carbonate leaving group, and serves as the nucleophile in the last acyl substitution step.[10]



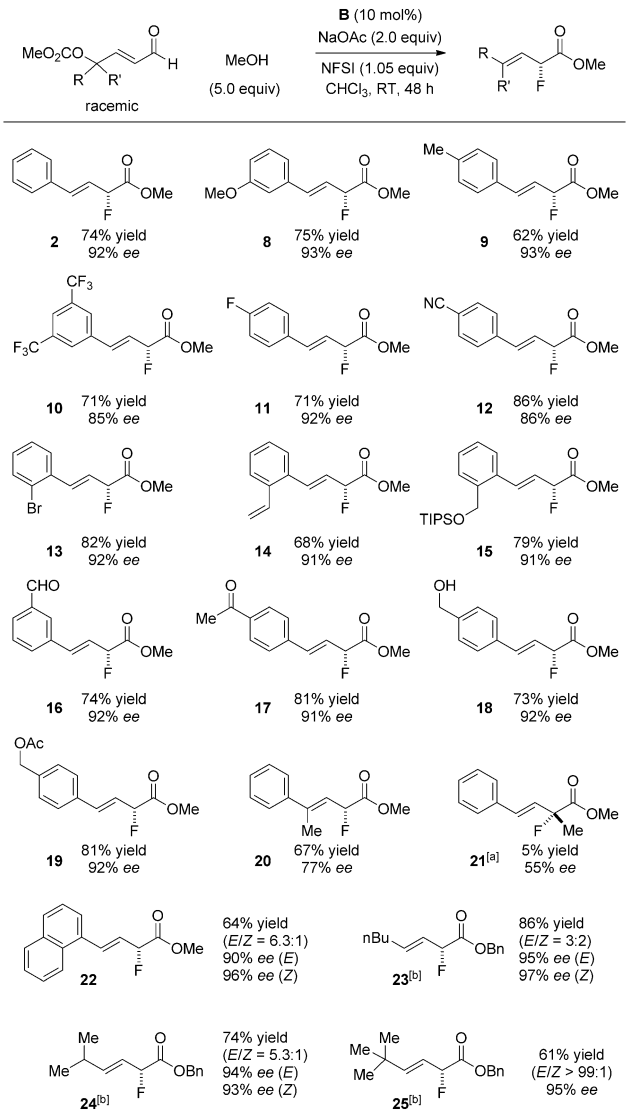
(1)

The NHC-catalyzed asymmetric α fluorination proceeds in good yield for a range of enals (Scheme 2). Thus, the C–F bond formation occurs exclusively in the α position with high *ee* values in the presence of a variety of functional groups, including ethers, halides, cyanides, alkenes, aryl aldehydes, ketones, free alcohols, esters, and silyl-protected alcohols. Moreover, the presence of a quaternary carbon atom in γ position does not significantly affect the reaction efficiency and trisubstituted alkene **20** was obtained as a single *E* isomer. In contrast, a substituent in the α position significantly slows down the reaction (<10% conversion after 48 h), although the desired product **21** with a chiral quaternary carbon center in α position was obtained with a moderate ee value. Enals with an alkyl substituent at the γ position also participate smoothly in the α fluorination. For example, desired product **23** with an *n*Bu substituent was obtained in excellent yield and enantioselectivity, albeit with a low *E*/*Z* ratio. With bulkier alkyl groups, such as *i*Pr and *t*Bu, the desired products were obtained with excellent enantioselectivity and good *E*/*Z* ratio.

The efficient fluorination reaction is not limited to the synthesis of methyl esters. It can also be applied to the synthesis of a range of alkyl esters in the presence of different alcohol additives, such as ethanol, isopropanol, benzyl alcohol, allylic alcohol, propargyl alcohol, as well as CD_3OD (Table 2), in good yield and excellent enantioselectivity.

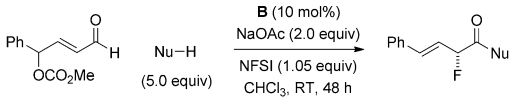
The β,γ-unsaturated α-fluoroesters can be transformed into other useful compounds. For example, saturated α-fluoroesters or acids can be obtained after a simple hydrogenation step, with the chiral center staying untouched [Eqs. (2) and (3)]. The optical rotation of **33** is comparable to the literature value.[11] These α-fluoroesters and acids have practical utility as optical materials themselves[12a] or as synthetic intermediates for bioactive compounds.[12b–d]

With the aid of DFT calculations (see the Supporting Information), we have proposed a reaction mechanism



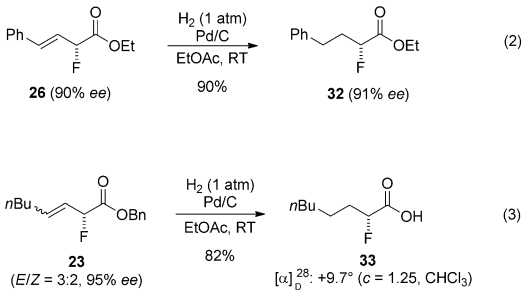
Scheme 2. Scope of the fluorination reaction in α position. Yields of purified products are given. [a] The starting material (>90%) was recovered. [b] 5.0 equiv of BnOH was used instead of MeOH, because of the low boiling point of the methyl ester product. Bn = benzyl, TIPS = triisopropylsilyl.

Table 2: Synthesis of different esters with alternative alcohols.

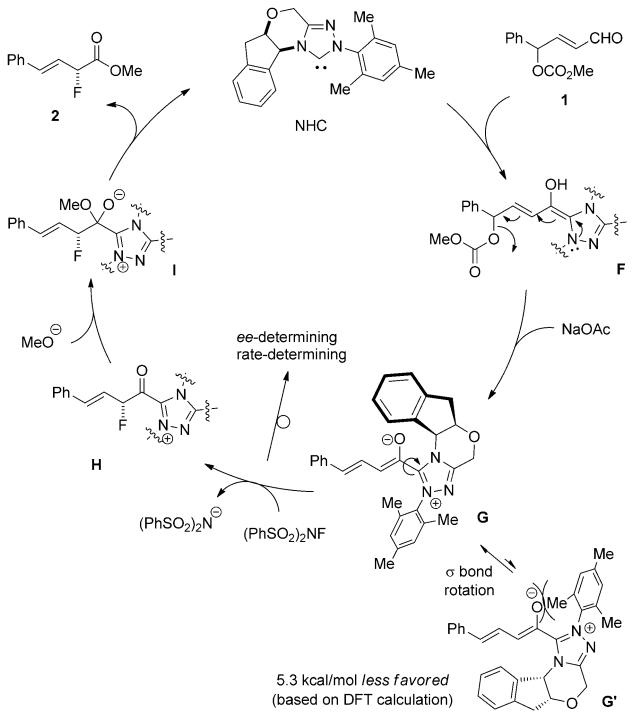


Entry	Nu–H	Product	Yield [%][a]	*ee* [%]
1	EtOH[b]	**26**	72	90
2	*i*PrOH[b]	**27**	51	96
3	BnOH	**28**	64	94
4		**29**	73	93
5		**30**	72	92
6	CD_3OD	**31**	69	93

[a] Yield of purified product. [b] A mixed solvent was used (Nu–H/$CHCl_3$ = 1:1).



(Scheme 3). The catalytic cycle begins with the addition of NHC to the enal carbonyl group. The resulting Breslow intermediate **F** then undergoes elimination and deprotonation to afford dienolate **G**, in which the chiral backbone of the NHC blocks the *Si* face. The results of the calculation suggest

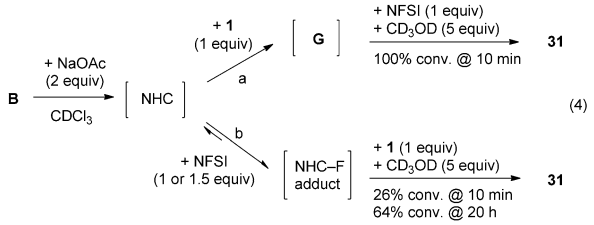


Scheme 3. Possible reaction mechanism.

that its rotamer **G′**, in which the *Re* face is blocked, is about 5.3 kcal mol^{-1} (in free energy) less favored than **G** because of the unfavored interaction between the enolate oxygen atom and the methyl group when fully conjugated. This result is consistent with our observed stereochemical outcome as well as other reports.[13] Thus, subsequent C–F bond formation takes place selectively on the *Re* face. The observed excellent α (vs. γ) regioselectivity is also consistent with DFT calculations. The barrier for C–F bond formation at the γ position is higher than that at the α position by 7.1 kcal mol^{-1}. This preference is related to the relatively high electron density at α-C (vs. γ-C) of the dienolate **G**, likely because of the proximate positive charge of the triazolium moiety. Further acyl substitution by methoxide proceeds via intermediate **I** to form the desired product and regenerate the NHC catalyst.

DFT calculations also suggest that the C–F bond formation step is both enantioselectivity- and rate-determining ($\Delta G^{\ddagger} = 18.3$ kcal mol^{-1}). The tetrahedral intermediate **I** was also located in our calculations.[14]

To gain further insight into the reaction mechanism, we also carried out a series of NMR experiments [see Eq. (4) and the Supporting Information]. Firstly, the formation of free



NHC was observed when a solution of **B** was treated with NaOAc, which was evidenced by the disappearance of the proton signal at approximately 12 ppm. Subsequent addition of enal **1** to the NHC resulted in immediate disappearance of the signals of **1** with concomitant formation of a new set of signals, presumably corresponding to dienolate **G** [Eq. (4a)]. Next, NFSI followed by CD_3OD was added and the formation of product **31** was observed with full conversion within ten minutes. Furthermore, we were also interested in probing the nature of the potential interaction between the NHC and NFSI. Thus, instead of adding enal **1** to NHC, we added NFSI (1 or 1.5 equiv) to the free NHC, which quickly established an equilibrium that favored the formation of the NHC–F adduct [Eq. (4b)]. The following addition of substrate **1** and CD_3OD led to the formation of the desired product, but in a significantly slow rate. Indeed, the decreased reaction rate was also observed under our catalytic conditions when the order of substrate/reagent addition was changed to **B**→NaOAc→NFSI→**1**. These results suggest that the free NHC reacts faster with the aldehyde substrate than with NFSI, which explains the observed smooth catalyst turnover.

In conclusion, we have developed the first NHC-catalyzed asymmetric fluorination reaction. It represents a new reaction of NHC-bound enolates and the first general enantioselective synthesis of β,γ-unsaturated α-fluoroesters, complementary to existing strategies for the enantioselective synthesis of α-fluoro carbonyl compounds. In the presence of an appropriate combination of a precatalyst, a base, and an additive, the C–F bond formation occurs efficiently at the α position of enals, thus overcoming nontrivial challenges, such as competitive γ fluorination, difluorination, nonfluorination, and NHC/NFSI interaction, and proceeds with very good enantioselectivity. The enantioenriched β,γ-unsaturated α-fluoroester products and their derivatives have broad practical utility. DFT calculations and NMR studies on the reaction progress both provided important insights into the reaction mechanism. These results are helpful for further development of new processes.

Experimental Section

General procedure: In a glovebox, an oven-dried 20 mL vial was charged with triazolium salt **B** (0.05 mmol), the enal (0.5 mmol), NFSI (0.525 mmol, 171 mg), anhydrous $CHCl_3$ (10 mL), and the nucleophile (2.5 mmol). NaOAc (1.0 mmol, 82 mg) was then added and the vial was capped and removed from the glovebox. The reaction mixture was stirred at room temperature for 48 h. Next, diethyl ether (60 mL) and H_2O (10 mL) were added. The organic layer was separated and washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the desired α-fluoroester.

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Communications

Asymmetric Fluorination

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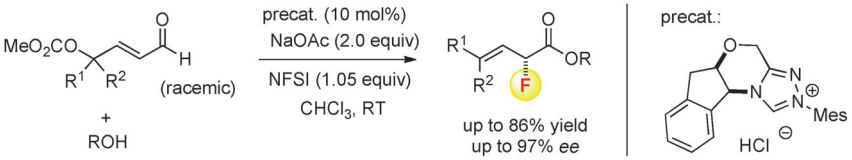
Enantioselective Synthesis of β,γ-Unsaturated α-Fluoroesters Catalyzed by N-Heterocyclic Carbenes (NHCs)



NHC meets F: NHC-bound enolates undergo a catalytic asymmetric fluorination reaction to β,γ-unsaturated α-fluoroesters, which are obtained with good efficiency and stereoselectivity (see scheme, *N*-fluorobenzenesulfonimide). The strategy overcomes possible challenges, such as fluorination in γ position and difluorination. Experimental evidence combined with DFT calculations provides insight into the reaction mechanism.