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Recent advances in N-heterocyclic carbene (NHC)-catalyzed fluorination and fluoroalkylation

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Fluorine and fluoroalkyl groups widely exist in organic molecules that are useful in numerous fields such as biological chemistry, medicinal science, agrochemistry, materials science and synthetic chemistry. The efficient modification of organic molecules with fluorine or fluoroalkyl groups is a very important topic in organic synthesis. In addition, N-heterocyclic carbenes (NHCs) are a class of robust and versatile organocatalysts that have been intensely utilized for the assembly of many functionalized organic compounds. NHC-catalyzed fluorination and fluoroalkylation reactions serve as robust and versatile strategies for accessing various fluorine-containing molecules efficiently and conveniently. Herein, we provide an overview of the important advances in this field with an intriguing focus from 2005 to 2023. This review summarizes the recent developments in NHC-catalyzed transformations where the fluorine-containing groups are introduced using fluorinating and fluoroalkylating reagents. These fluorination and fluoroalkylation transformations are illustrated from three major aspects based on the different properties of the reagents.

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1. Introduction

During the last two decades, fluorination and fluoroalkylation have drawn considerable attention since the chemical, physical and biological properties of organic molecules can be significantly improved after they are modified with fluorine or fluoroalkyl groups.[1] About one third of the outstanding commercial drugs contain at least one fluorine atom, indicating that C–F containing motifs play very important roles in medicinal science.[2] Fluorine and fluoroalkyl groups are also present in numerous natural products[3] and agrochemicals.[4] A number of important functional materials are organofluorine derivatives.[5] Fluorine-containing compounds are also of high value in organic synthesis since they exhibit unique reactivity and can be easily converted to diverse functionalized molecules.[6] It is reasonable to conclude that more fluorinated and fluoroalkylated organic molecules will be created and studied in the near future.

In addition, great progress has been achieved in the studies on N-heterocyclic carbine (NHC) catalysis over the past few decades.[7] To date, NHCs have emerged as a class of versatile and useful organocatalysts that could be applied to activate not only aldehydes but also ketones, esters, imines, and alkenes. For instance, NHCs are especially useful for the umpolung of aldehydes. The addition of carbenes to aldehydes generates nucleophilic enaminol intermediates known as the Breslow intermediates or homoenolate equivalents. NHC-bound intermediates have also been extensively researched. The development of NHC catalysis as a useful tool to assemble various functionalized molecules has become increasingly important in modern organic synthesis, biological chemistry, medicinal science, agrochemistry, materials science and related fields.

Since the past two decades, the research in NHC-catalyzed fluorination and fluoroalkylation reactions has attracted great interest, and great progress has been achieved in this area.[8] These studies show that NHCs play a powerful and versatile role in the relevant transformations.

This review provides a brief overview of the recent developments in NHC-catalyzed fluorination and fluoroalkylation reactions since 2005 (Fig. 1). In this article, we focus on the NHC-catalyzed transformations where the fluorine atom(s) and fluoroalkyl groups are introduced using fluorinating and fluoroalkylating reagents, and the utilization of fluorine-containing substrates themselves as substrates or building blocks for NHC-catalyzed transformations (such as NHC-catalyzed benzoin reactions of fluoroalkyl aldehydes/ketones[9]) is not covered in

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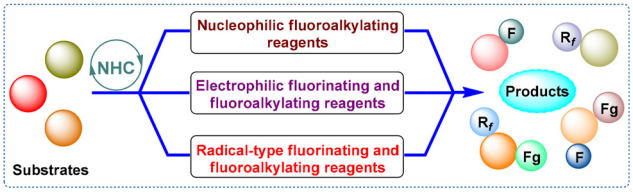


Fig. 1 The NHC-catalyzed fluorination and fluoroalkylation reactions.

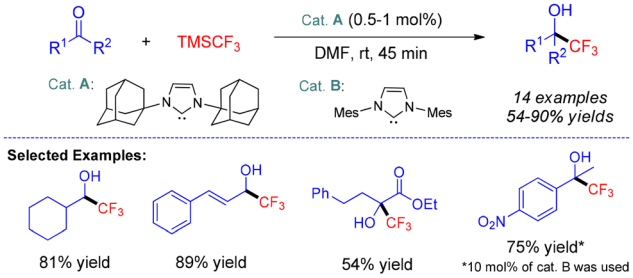
this paper. Special emphasis is given to the discussion of the fluorination and fluoroalkylation reactions through different activation modes, which form the basis of our classification. According to the properties of the fluorinating and fluoroalkylating reagents and the types of activation modes, the main content of the article is divided into three parts: (1) reactions with nucleophilic fluoroalkylating reagents; (2) reactions with electrophilic fluorinating and fluoroalkylating reagents; and (3) reactions with radical-type fluoroalkylating reagents; the 2nd and 3rd parts are further subdivided by the reaction types. The general equations and the selected examples of these reactions, the features of the methods, and the reaction mechanisms are outlined in this review. We hope that this summary will benefit readers from relevant areas of chemistry and beyond.

2. Reactions with nucleophilic fluoroalkylating reagents

Compounds containing fluoroalkyl groups (such as trifluoromethyl and difluoroalkyl) are significant in medicinal science, polymer chemistry, and agrochemistry.[2–5] The NHC-catalyzed direct fluoroalkylation of carbonyl/imine compounds is a facile and straightforward strategy to incorporate a fluoroalkyl group into organic molecules.

Some NHC-catalyzed fluoroalkylation reactions of electrophilic substrates with nucleophilic fluoroalkylating reagents (such as $TMSR_f$) have been explored. To date, very limited examples of nucleophilic fluoroalkylation through NHC catalysis have been exploited,[10,11,13] and greater efforts are required to develop novel types of nucleophilic fluoroalkylating reagents and relevant new transformations including the asymmetric catalytic versions.

The Song group demonstrated the first NHC-catalyzed nucleophilic trifluoromethylation of carbonyl compounds in 2005 (Scheme 1). In the presence of a catalytic amount of the NHC diadamantylimidazol-2-ylidene (cat. **A**) (0.5–1 mol%), nucleophilic trifluoromethyltrimethylsilane ($TMSCF_3$) reacted with a variety of aldehydes and active ketones at room temperature to afford the corresponding α-CF_3-substituted alcohols in moderate to excellent yields (54–90%).[10] A wide range of aryl aldehydes bearing either electron-withdrawing or electron-donating substituents exhibited good reactivities. The reactions of many vinyl and alkyl aldehydes afforded the anticipated products in good to excellent yields. Two α-keto esters also smoothly participated in the transformation. The reaction

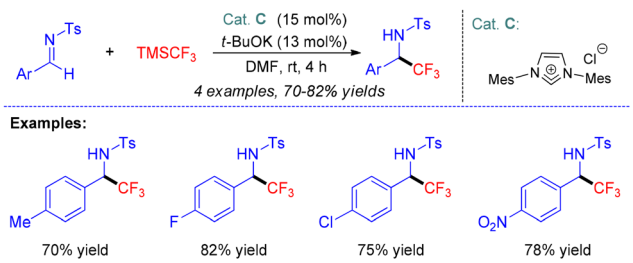


Scheme 1 The NHC-catalyzed trifluoromethylation of aldehydes/active ketones reported by Song *et al.*

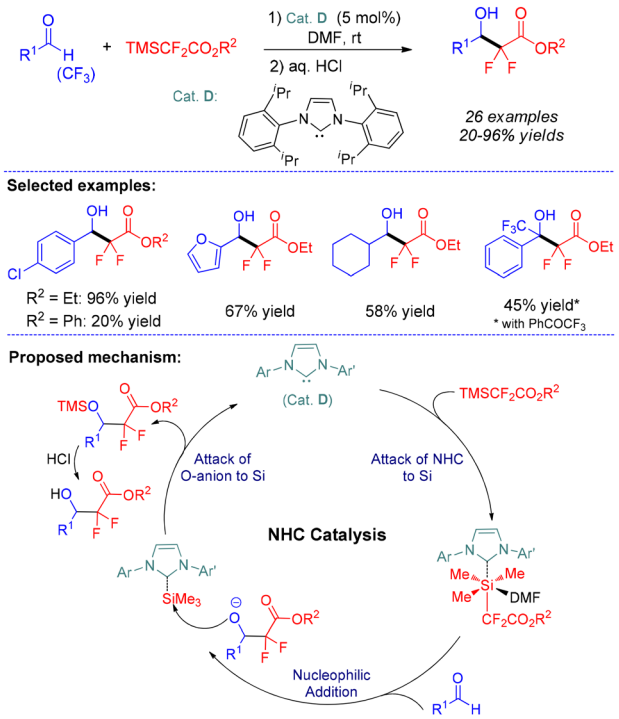
of acetophenone afforded very low conversion (<1%) under NHC catalysis. However, the 1,2-addition of an active acetophenone bearing a *p*-NO_2 group at the phenyl group could be effectively achieved when another NHC (dimesitylimidazol-2-ylidene, cat. **B**) was utilized. The protocol possesses many advantages such as mild conditions, simple procedures and good functional group tolerance. Notably, this method avoids the use of strong bases (such as fluoride or alkoxides) to facilitate the trifluoromethyl transfer from $TMSCF_3$ and is more compatible to base-sensitive substrates.

In 2018, Reddy *et al.* disclosed an NHC-catalyzed nucleophilic trifluoromethylation of aromatic *N*-tosylaldimines (Scheme 2).[11] Facilitated by the *in situ* formed NHC from an imidazolium salt (cat. **C**), the reactions of $TMSCF_3$ with aromatic *N*-tosylaldimines furnished the desired trifluoromethylated sulfonamides in moderate to good yields under mild conditions. Both the *N*-tosylaldimines bearing electron-rich phenyl and electron-poor phenyl are well compatible with the catalytic system. However, aliphatic *N*-tosylaldimine is unsuitable for this transformation.

β-Hydroxy *gem*-difluoroesters are useful in the assembly of biologically active molecules.[6c,d] Although the incorporation of *gem*-difluoromethylene into aldehydes/ketones has been achieved by Mukaiyama aldol reactions and Reformatsky reactions,[12] these protocols are restricted by the harsh conditions, the use of stoichiometric amounts of transition-metal reagents, and the unstable fluorinated silicon enolates. Therefore, there is still a demand for exploiting mild and effective methods for the synthesis of these molecules. In order to cater to this demand, the Li and Du group developed



Scheme 2 The NHC-catalyzed trifluoromethylation of aldehydes reported by Reddy *et al.*



Scheme 3 The NHC-catalyzed silyl-Reformatsky reaction of aldehydes reported by Li and Du *et al.*

the fluorinated *silyl*-Reformatsky reaction of aldehydes with 2,2-difluoro-2-trimethylsilylacetate under NHC catalysis (Scheme 3) in 2017.[13] Employing 1,3-bis(2,6-diisopropylphenyl)-imidazolium-derived NHC (cat. **D**) as the catalyst, the reactions of various aromatic/aliphatic aldehydes or 2,2,2-trifluoroacephenone with 2,2-difluoro-2-trimethylsilylacetate delivered the corresponding β-hydroxy *gem*-difluoroesters in 20–96% yields. A broad range of (hetero)aryl aldehydes with various substitutions and alkyl aldehydes underwent the reaction efficiently. The difluoroalkylation of an active trifluoromethyl ketone also proceeded well. As shown in Scheme 3, the authors proposed that this transformation was initiated by the attack of NHC towards the Si-atom of 2,2-difluoro-2-trimethylsilylacetate to generate a reactive hexavalent Si species in DMF, followed by a nucleophilic addition towards the aldehyde to form the oxy-anion intermediate; the latter attacked the TMS group of NHC–TMS to generate the trimethyl ether intermediate, which was converted to the final product after acidic work-up. This method might be beneficial due to the merits such as good efficiency, simple procedures, and mild reaction conditions.

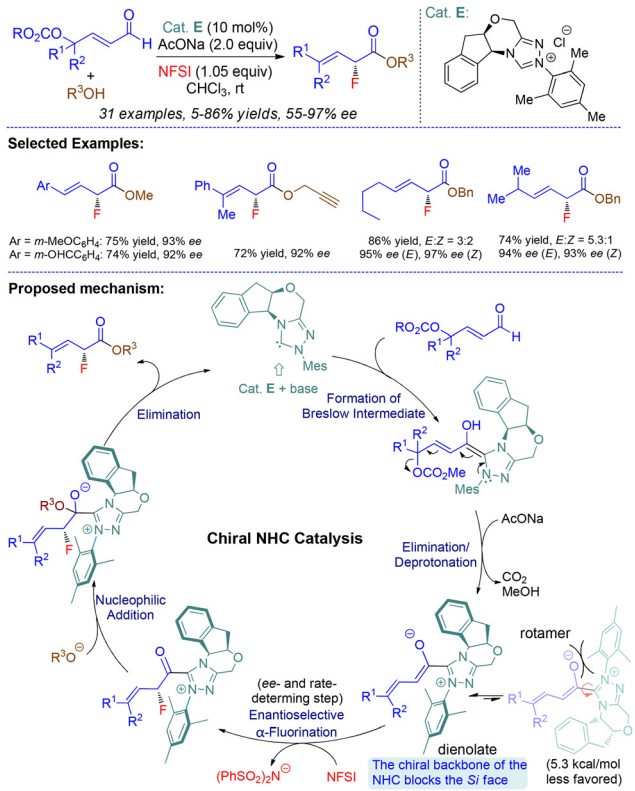
3. Reactions with electrophilic fluorinating and fluoroalkylating reagents

In recent years, several types of electrophilic fluorinating [such as *N*-fluorobenzenesulfonimide (NFSI) and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor)][15,17–19,24,26–28] and fluoroalkylating (such as R_fX and Togni's reagents)[27,30] reagents have been applied in NHC-catalyzed fluorination and fluoroalkylation transformations. Some enantioselective electrophilic fluorination reactions under chiral NHC catalysis have also been realized.[15,18,19,26–28] However, enantioselective fluoroalkylation with electrophilic fluoroalkylating reagents is yet to be developed.

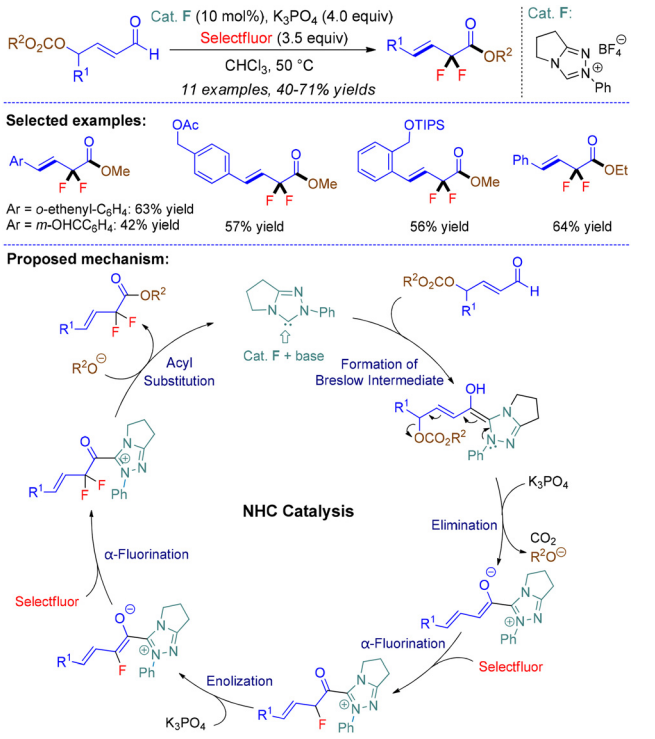
3.1. Electrophilic fluorination

Enantioenriched organofluorine molecules are significant in medicinal science, agrochemistry and the materials industry.[2–5] Therefore, the exploration of enantioselective C–F bond forming strategies has attracted great interest in organic synthesis. A number of catalytic enantiocontrolled α-fluorination reactions of carbonyl compounds have been disclosed.[14] Despite these tremendous developments, the exploration of efficient asymmetric α-fluorination of carbonyl compounds is still highly desirable. Moreover, although NHCs had evolved as efficient catalysts for the functionalization of aldehydes and ketones, NHC-catalyzed enantioselective α-fluorination of enals had not been documented until Sun *et al.*'s pioneering work in 2012. The group firstly studied the chiral NHC-catalyzed enantioselective synthesis of β,γ-unsaturated α-fluoroesters from α-fluorination of enals with a carbonate leaving group at the γ-position (Scheme 4).[15] The C–F bond formation proceeded highly stereoselectively and efficiently at the α-position of enals in the presence of a chiral NHC precatalyst (cat. **E**), NaOAc, and NFSI. A broad spectrum of γ-modified enals reacted with NFSI to generate the optically active β,γ-unsaturated α-fluoroesters in moderate to good yields with moderate to excellent enantioselectivities. The transformation is well tolerated with a number of functional groups such as ethers, alkenes, aryl aldehydes, ketones, halides, free/silyl-protected alcohols and esters. No significant influence was observed when there was a quaternary carbon atom at the γ-position. Moreover, the method is also applicable to substrates with other alkyl ester groups. The α-fluorination proceeded efficiently at the α-position of enals, overcoming the challenges including competitive nonfluorination, γ-fluorination, difluorination, and NHC/NFSI interaction. As shown in Scheme 4, their mechanistic study indicated that this type of enantioselective α-fluorination might involve Breslow intermediate formation, an elimination and a deprotonation to generate the dienolate intermediate, an enantioselective α-fluorination, and a nucleophilic acyl substitution. It is also noteworthy that in the dienolate intermediate, the chiral backbone of the NHC blocks the *Si* face, and the rotamer of this dienolate is less favoured. Therefore, the subsequent C–F bond formation occurred selectively on the *Re* face. Furthermore, their DFT calculations proved that the C–F bond forming process was the enantioselectivity- and rate-determining step. The protocol would be a powerful tool for the effective and selective assembly of various enantioenriched β,γ-unsaturated α-fluoroesters.

Many α,α-difluoro carbonyl compounds are valuable in pharmaceutical chemistry. Common routes to these molecules



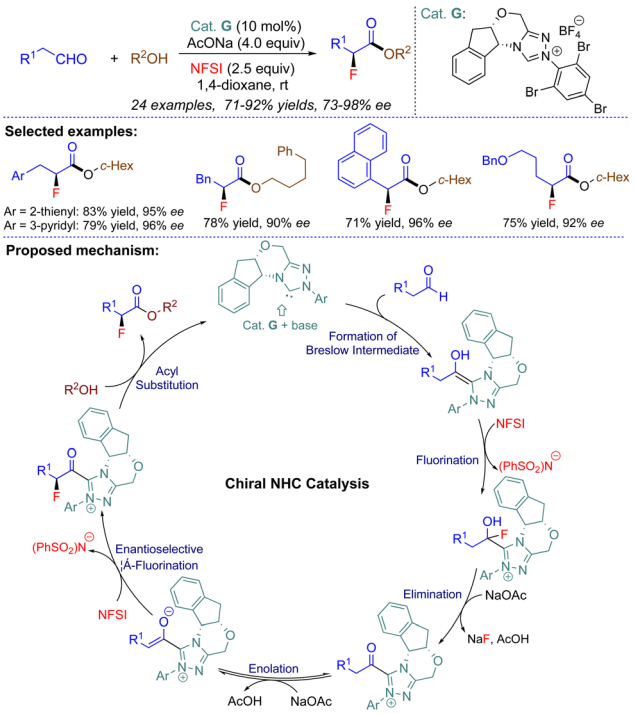
Scheme 4 The NHC-catalyzed enantioselective α-fluorination of enals reported by Sun *et al.*



Scheme 5 The NHC-catalyzed α,α-difluorination of enals reported by Sun *et al.*

include the Reformatsky reaction[12] and the coupling reaction with small halodifluoro compounds as difluoromethylene sources.[16] In 2013, an NHC-catalyzed synthesis of α,α-difluoroesters from difluorination of enals was developed by the same group (Scheme 5).[17] With 1,2,4-triazolium salt (cat. **F**) as the NHC precatalyst, Selectfluor (3.5 equiv.) as the electrophilic fluorine source, and K_3PO_4 as the base, a series of racemic enals with a carbonate leaving group at the γ-position were transformed into the corresponding α,α-difluoroesters. Since an alkoxide ion was generated *in situ* when the carbonate leaving group was eliminated, it was unnecessary to add an extra alcohol to react with the acylazolium in this transformation. A wide range of enal substrates reacted efficiently. A diverse set of functional groups including (silyl) ethers, esters, aryl aldehydes, alkenes, and aryl halides are well compatible. As depicted in the scheme, the proposed pathway might involve Breslow intermediate formation/elimination/1st α-fluorination/enolization under basic conditions/2nd α-fluorination/acyl substitution processes. The advantages of the method include good selectivity, high efficiency and good functional group tolerance. This strategy has become an alternative way for the efficient assembly of *gem*-difluoromethylene-containing carbonyl compounds.

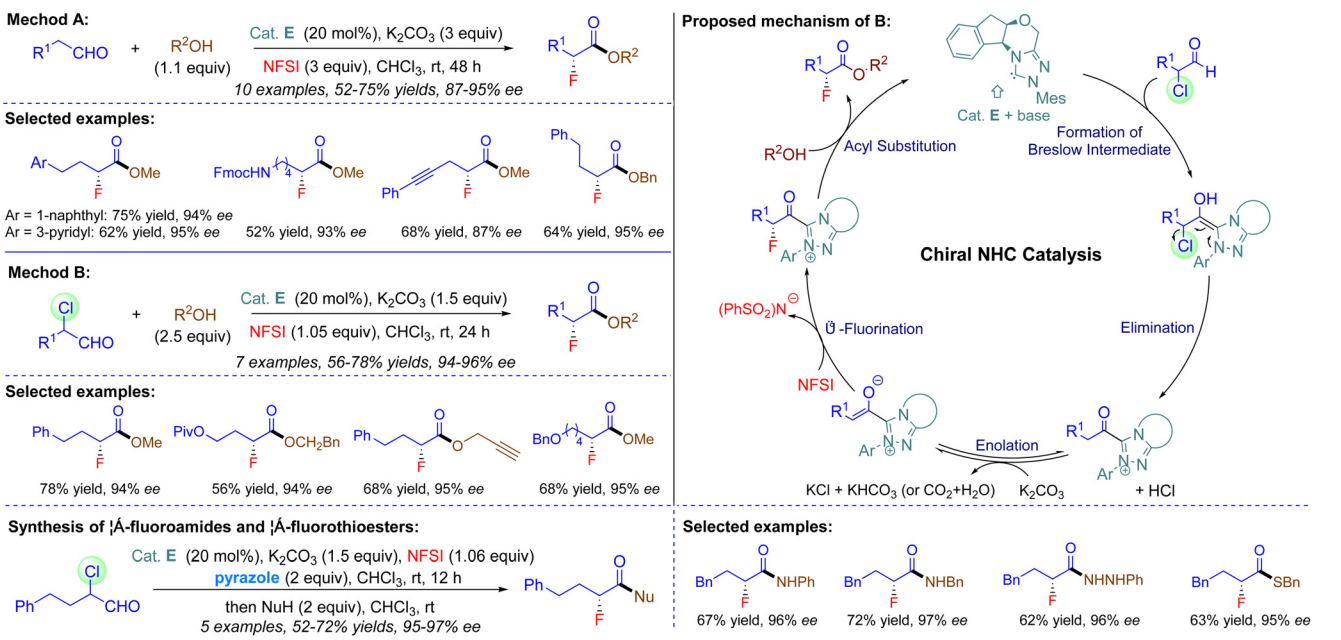
In spite of the great progress in enantioselective α-fluorination of aldehydes/ketones,[14,15] the use of simple aldehydes in enantiocontrolled α-fluorination under NHC catalysis had not been unveiled until the Wang group firstly realized the chiral NHC-catalyzed enantioselective oxidative α-fluorination of nonmodified aliphatic aldehydes in 2015 (Scheme 6).[18] A novel 2,4,6-tribromophenyl-substituted chiral triazolium (cat. **G**) was utilized as the suitable precatalyst in the work. A broad spectrum of α- or β-aryl aldehydes with various substitution patterns reacted efficiently. Both electron-donating and electron-withdrawing groups at the β-phenyl were well tolerated. The transformations of β-heteroaryl aldehydes (with a thienyl, furyl or pyridyl group) also afforded satisfactory results. Notably, the substrates bearing F-sensitive atoms (such as N and S) were also compatible under the reaction conditions. Good yields and high enantioselectivities were still achieved when several aliphatic aldehydes with a long alkyl chain or a functionalized alkyl group (alkoxyl/phthalimidyl/Cbz-containing alkyl) were used. A longer reaction time was required when more bulky α-substituted alkyl aldehydes were tested. A wide range of alcohols such as primary alcohols bearing a phenyl or a phthalimidyl group, cyclic secondary alcohols, allyl alcohol and propargylic alcohol are good partners in the reaction. However, the reaction with methanol or ethanol only afforded the anticipated product in a trace amount, possibly because the less sterically hindered alcohols prefer to interact with the non-fluorinated acyl azolium intermediate rather than the α-fluorinated acyl azolium. The pathway possibly includes the generation of a Breslow intermediate, the formation of non-fluorinated acyl azolium *via* oxidation by NFSI (through fluorination/elimination), enolation under basic conditions, the generation of α-fluorinated acyl



Scheme 6 The NHC-catalyzed enantioselective oxidative α-fluorination of aldehydes reported by Wang *et al.*

azolium *via* enantioselective α-fluorination, and acyl substitution. It is noteworthy that NFSI served as both an oxidant and a fluorine source in this reaction. This work represents the first example of chiral NHC-catalyzed enantioselective α-fluorination of simple aliphatic aldehydes.

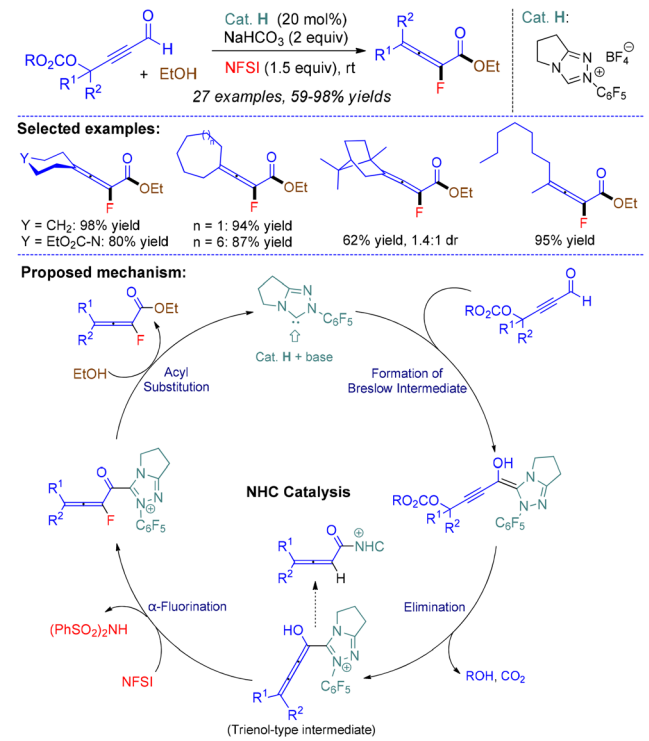
Almost concurrently, Sun and coworkers disclosed a chiral NHC-catalyzed asymmetric α-fluorination of aliphatic aldehydes or α-chloroaldehydes for the convenient access to α-fluoro esters, amides and thioesters with excellent enantioselectivity (Scheme 7).[19] Before this work, they had developed the mono- and bisfluorination of vinylogous azolium enolates generated from α,β-unsaturated aldehydes with a leaving group at the γ-position.[15,17,20] Those protocols might be restricted by the limited substrate scope and the requirements of multistep substrate synthesis. Inspired by the studies on the oxidative generation of azolium enolates from simple aliphatic aldehydes pioneered by Rovis[21] and Chi[22] groups, Sun *et al.* envisioned that the expansion of their asymmetric fluorination strategy to the transformation of easily accessible aliphatic aldehydes might enhance the synthetic applicability.[19] In this work, a broad range of aliphatic aldehydes or α-chloro alkyl aldehydes bearing different types of substituents and functional groups are shown to react efficiently and enantioselectively. A wide range of α-fluoro esters, amides and thioesters were conveniently assembled in moderate to good yields with excellent ee values. Moreover, pyrazole was used as an excellent acyl transfer reagent for catalytic amide/thioester formation. In the α-fluorination reaction of non-halogenated aliphatic aldehydes, NFSI performed as both the fluorine source and the oxidant. The α-fluorination of α-chloroaldehydes might proceed through a reaction involving the formation of a Breslow intermediate, an elimination to form the enolate of acyl azolium, an enantioselective α-fluorination, and a nucleophilic acyl substitution (Scheme 7). The method provides a powerful and versatile tool for the assembly of various chiral α-fluoro carboxylic acid derivatives with high enantioselectivity from easily accessible aldehydes in a single vessel.



Scheme 7 The NHC-catalyzed enantioselective α-fluorination of aliphatic or α-chloro aldehydes reported by Sun *et al.*

The detailed pathway, stereoselectivity and chemoselectivity of the chiral NHC-catalyzed α-fluorination of aliphatic aldehydes were further investigated by Wei and coworkers.[23] They applied a density functional theory (DFT) method to reveal the processes involved in the transformation. The fluorination process was the stereoselectivity-determining step according to the computational outcomes. Non-covalent interaction (NCI) analysis showed that relatively more efficient non-covalent interactions (such as C–H···O, C–H···π, and π–π stacking) were favorable for the formation of S-configuration. Moreover, the global reactivity index (GRI) revealed that the NHC served as a Lewis base catalyst that increased the nucleophilicity of the enolate intermediate and the electrophilicity of the fluorinated intermediate.

The NHC-catalyzed fluorination to efficiently and selectively incorporate a fluorine atom into an allenoate motif is challenging since both α- and γ-positions of NHC–trienolate are nucleophilic and NHC–trienolate may be protonated at the α-position to form a nonfluorinated product. In 2016, the Wang group found that by utilizing a combination of a suitable NHC precatalyst (cat. **H**), $NaHCO_3$, and NFSI, a series of γ-substituted alkynals were effectively converted into the corresponding α-fluoroallenoates (Scheme 8).[24] Generally, both symmetric and unsymmetric γ-disubstituted alkynals including various cyclic and bridged γ-disubsitituted substrates reacted well under the optimized conditions. The products were delivered in 59–98% yields with excellent chemoselectivity. The obtained α-fluoroallenoates could be successfully modified to produce the relevant useful F-containing functionalized organic molecules. They postulated that the reaction might proceed through a cascade reaction initiated by the formation of an alkynyl Breslow intermediate, followed by the generation of an allenol-tethered azolium intermediate *via* elimination, α-fluorination, and nucleophilic acyl substitution. To explain the excellent chemoselectivity (>19 : 1), the authors postulated that the highly electrophilic NFSI facilitated the nucleophilic substitution to form the C–F bond, and the potent π–π stacking between the phenyl ring of NFSI and the perfluorophenyl group of the trienol-type intermediate led to the formation of C–F bonds like an intramolecular process. The case is the first example of NHC-catalyzed fluorination for the synthesis of α-fluoroallenoates.

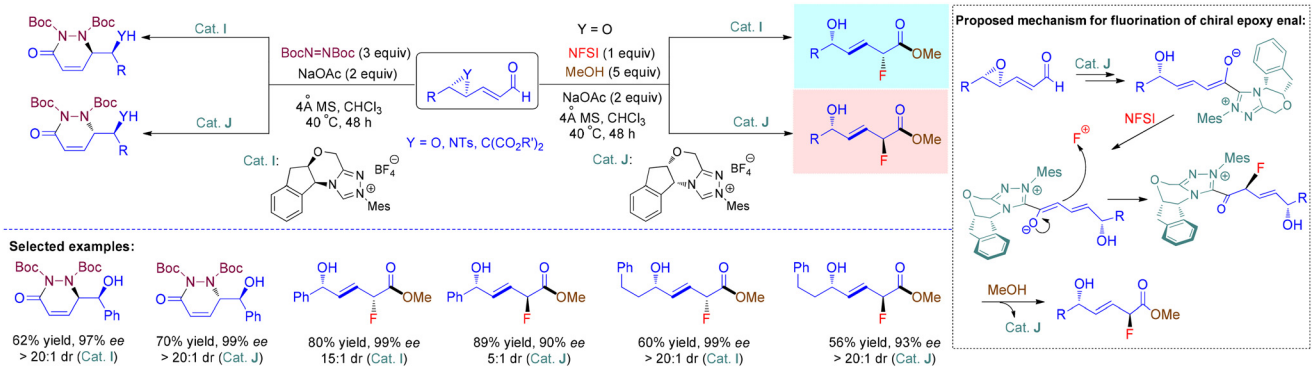


Scheme 8 The NHC-catalyzed enantioselective α-fluorination of alkynals reported by Wang *et al.*

Lately, Wei and colleagues further systematically studied the mechanism and the chemoselectivity of the NHC-catalyzed α-fluorination of alkynals.[25] Their DFT calculations showed that the transformation involved a nucleophilic attack of NHC on the carbonyl group, the formation of a Breslow intermediate, elimination, C–F bond formation, esterification, and the dissociation of NHC from the product. The study also found that the proton transfer processes were drastically facilitated by explicit inclusion of ethanol since it decreased the free energy barriers for these steps. Moreover, they also disclosed that the *in situ* generated Brønsted base (BB) $(SO_2Ph)_2N^-$ anion played an important role in the esterification step, and the transformation proceeded via an NHC–BB cooperatively catalytic pathway.

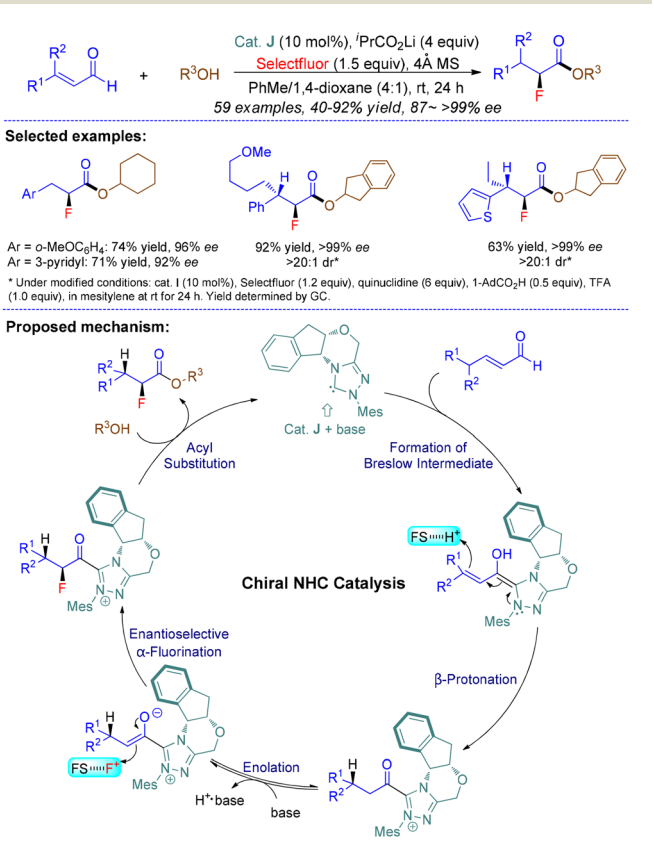
In 2018, Zhao and coworkers disclosed novel chiral NHC-catalyzed stereodivergent cascade ring-opening reactions of chiral γ,δ-epoxy, cyclopropyl and aziridinyl enals (Scheme 9).[26] Various cyclic and linear products with multiple stereocenters were highly diastereo- and enantioselectively delivered under the catalysis of two chiral NHCs (cat. **I** and cat. **J**). In the presence of NFSI (1 equiv.) and MeOH (5 equiv.), the chiral γ,δ-epoxy enals were effectively transformed into the corresponding ring-opening α-fluorination β,γ-unsaturated esters bearing two continuous stereogenic centers in moderate to good yields with excellent enantioselectivities (90%–>99% ee) and high diastereoselectivities (5 : 1–>20 : 1 dr). The transformation might proceed through the formation of a key dienolate intermediate, enantioselective α-fluorination, and final nucleophilic acyl substitution.

Although the Sun,[15,19] Wang,[18] and Zhao[26] groups realized the enantioselective α-fluorination of acyl azolium species using aliphatic aldehydes, their strategies could not be extended to β-protonation because of the absence of a proton source in the reaction. The combination of β-protonation and α-fluorination is challenging as (1) there are two reactive electrophiles (H^+ and F^+) and α-protonation might also occur; (2) the premature esterification of the acyl azolium arises prior to α-fluorination; and (3) increasing the concentration of enolate would accelerate the α-protonation, and the β-protonation may be suppressed due to the low concentration of H^+. Thus the competitive β-fluorination or direct oxidation of homoenolate might also lead to the complications.



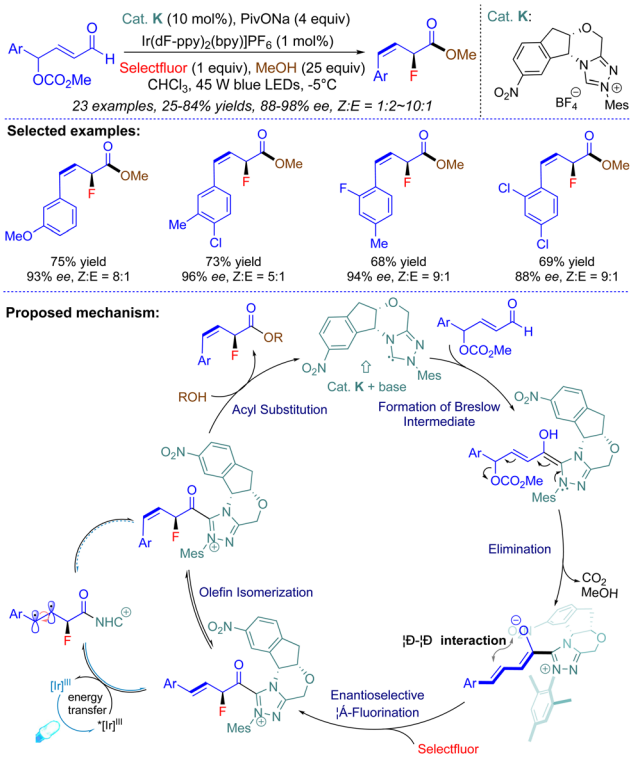
Scheme 9 The NHC-catalyzed stereodivergent ring-opening reactions of γ,δ-cyclized enals reported by Zhao *et al.*

In order to overcome the abovementioned challenges, Huang and coworkers in 2019 proposed that the use of suitable fluorine- and proton-transfer agents and NHC turnover agents could facilitate achieving a delicate kinetic balance for the β-protonation–α-fluorination cascade reaction. A broad spectrum of β-(hetero)aryl/alkyl α,β-unsaturated aldehydes underwent enantioselective hydrofluorination cascades in the presence of a chiral precatalyst (cat. **J**) (Scheme 10).[27] Moderate to excellent yields of the desired α-fluoroesters were obtained in one step with high dr and ee values. The cascade reaction might involve the formation of a homoenolate catalyzed by NHC, the generation of an acyl azolium through β-protonation, enolation, enantioselective α-fluorination, and nucleophilic acyl substitution. The method would be a universal protocol for the preparation of chiral α-fluoroesters from easily accessible enals. A dual promoter strategy was applied in the transformation to control the diastereo- and enantioselectivity. A wide range of β-(hetero)aryl enals with various substituents including electron-enriched and electron-poor aromatic rings reacted effectively and highly enantioselectively. The reactions of *o*-substituted cinnamaldehydes that usually exhibit poor reactivity in homoenolate chemistry also proceeded smoothly with excellent enantioselectivity. However, the chemoselectivity of hydrofluorination *vs.* hydrogenation deteriorated when the protocol was applied in the reaction with β-alkyl enals. Therefore, the authors re-optimized the conditions. Under the modified conditions, numerous β-alkyl enals efficiently participated in the reaction with excellent enantioselectivities. The reaction also performed well when cyclohexyloxy was replaced by other bulky secondary alkoxy groups. They also found that many side-reactions could be suppressed by suitable selection of modifiers, and carboxylate ($^{i}PrCO_2Li$ or $PivONa{\cdot}H_2O$) acted as a dual promotor for efficient enantioselective reactions. Moreover, quinuclidine, TFA and $1\text{-}AdCO_2H$ were proved to be competent additives to facilitate these reactions.



Scheme 10 The NHC-catalyzed enantioselective hydrofluorination cascade reactions reported by Huang *et al.*

Combining NHC catalysis and photoredox catalysis within the same reaction system provides a powerful and attractive methodology for novel transformations of carbonyl compounds. In 2021, the Chen and Huang group reported a photoinduced energy transfer relay of NHC catalysis for the asymmetric α-fluorination/isomerization cascade that led to the synthesis of optical active (*Z*)-allylic α-fluoroesters (Scheme 11).[28] Using enals with a γ-leaving group as the substrates and Selectfluor as the fluorinating reagent, a broad spectrum of corresponding allylic fluorides with *cis*-olefin geometry were effectively and selectively assembled under the catalysis of a chiral NHC and the irradiation of blue LEDs. They postulated that the pathway of the reaction might involve the formation of a Breslow intermediate, elimination to generate a dienolate



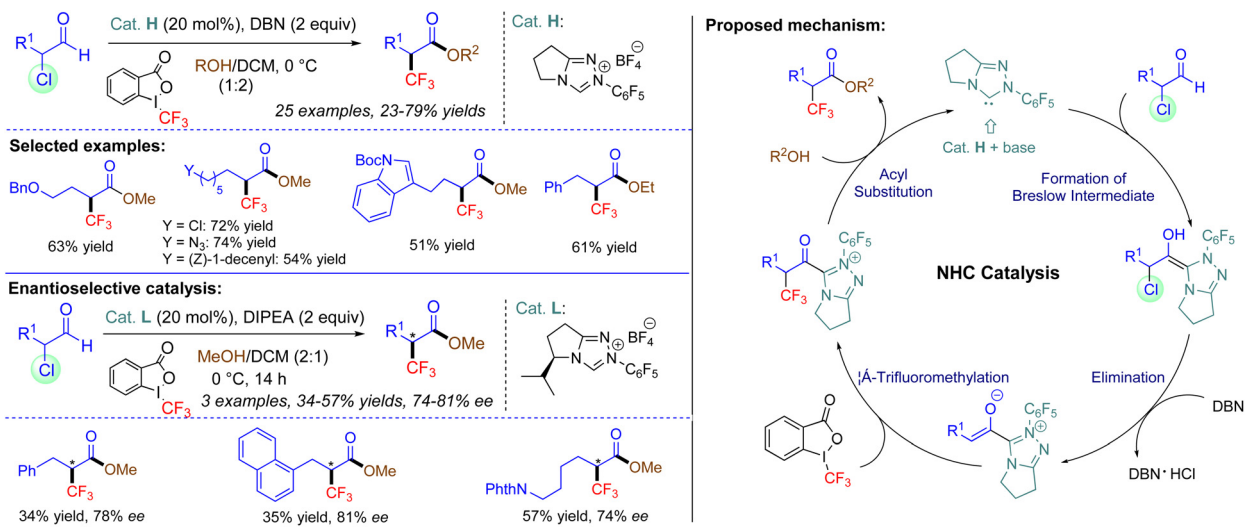
Scheme 11 The photo-induced chiral NHC-catalyzed asymmetric reactions of enal, Selectfluor and alcohol by Chen and Huang *et al.*

intermediate, enantioselective electrophilic α-fluorination, photo-induced olefin isomerization, and nucleophilic acyl substitution. They suspected that the asymmetric control of this transformation was probably enhanced by the π–π interactions between NHC and olefin, and it was important to choose a suitable photocatalyst to control the rate and stage of isomerization.

3.2. The electrophilic fluoroalkylation

3.2.1. α-Fluoroalkylation of α-chloroaldehydes. Many protocols of α-trifluoromethylation of esters are limited by the use of highly activated ester derivatives (such as β-keto esters), prefunctionalized esters (such as α-diazo esters) or sensitive ketene silyl acetals.[29] Therefore, the α-trifluoromethylation of esters from simple and stable substrates remains a challenge. In order to explore a straightforward method for the assembly of α-trifluoromethylated esters under mild conditions from easily accessible and bench-stable starting materials, Poisson and Besset *et al.* developed a one-step synthesis of α-trifluoromethyl esters from the reactions of α-chloroaldehydes, the Togni reagent and alcohols under NHC catalysis (using cat. **F**) (Scheme 12).[30] Generally, moderate to good yields of the desired α-trifluoromethylated esters were delivered (23–79% yield). A wide range of aliphatic α-chloroaldehydes with various substituents and functional groups (such as vinyl, alkynyl, CF_3, CN, N_3, Cl, BzO, alkoxy, silyloxy, and indolyl) at the aliphatic chain performed well in this transformation. Several cases of enantioselective assembly of α-trifluoromethyl esters could be achieved when a chiral NHC precursor (cat. **L**) was employed (34–57% yields, 74–81% ee). This type of reaction probably proceeded through a pathway including the formation of an α-chloro Breslow intermediate, dehydrohalogenation under basic conditions, α-trifluoromethylation with Togni's reagent, and nucleophilic acyl substitution. The research showed that the combination of an electrophilic trifluoromethylation reagent with NHC catalysis was the key for this transformation. This protocol represents a novel synthetic tool for synthesizing α-trifluoromethylesters under mild reaction conditions from easily accessible materials.

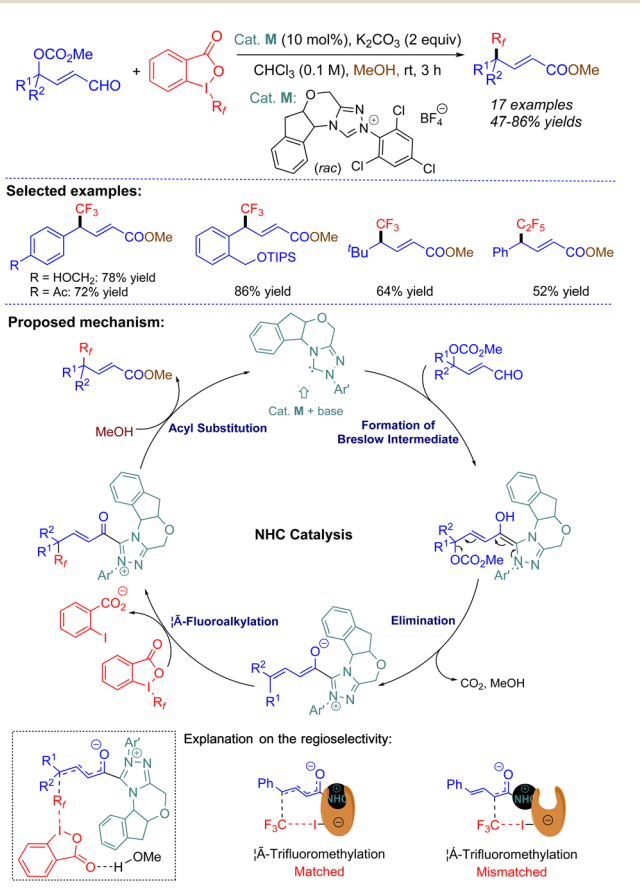
3.2.2. γ-Fluoroalkylation of enals. Although tremendous efforts have been made in the α-trifluoromethylation of carbonyl compounds, fluoroalkylation at remote positions rela-



Scheme 12 The reactions of α-chloroaldehydes, Togni reagent and alcohols reported by Poission and Besset *et al.*

tive to a carbonyl group has been rarely explored.[31] The selective installation of a trifluoromethyl group at the γ-position of carbonyl compounds remained unknown until Sun and coworkers developed the first electrophilic γ-trifluoromethylation of vinylogous enolates catalyzed by NHC in 2018 (Scheme 13).[32] With a proper selection of the precatalyst (such as **L**) and the electrophilic CF_3 source (such as Togni's reagent), the γ-trifluoromethylation reactions of enals bearing a γ-leaving group feature good efficiency and regioselectivity. A broad range of β-aryl enals bearing versatile substituents (such as Me, MeO, X, $TIPSOCH_2$, $HOCH_2$, Ac and CHO) at the aryl ring reacted smoothly to afford moderate to good yields of the γ-trifluoromethylated α,β-unsaturated esters.

The reactions of some bulky β-alkyl and β-disubstituted enals also proceeded well. The γ-difluoroethylation was also viable when a modified Togni reagent was utilized. This reaction probably proceeded *via* a pathway including the formation of the Breslow intermediate, the generation of a dienolate intermediate through an elimination, regioselective γ-fluoroalkylation, and nucleophilic acyl substitution. The key NHC-bound vinylogous enolate intermediate might act as the nucleophile. Their mechanistic study also revealed that the hypervalent iodine motif of the trifluoromethylating reagent was located at a suitable position for its electrostatic interaction with the NHC motif in the γ-pathway, and the trifluoromethylation at the γ-position had a lower barrier comparing with that at the α-position. This strategy may be beneficial due to the merits such as a broad substrate scope, good functional group tolerance and excellent regioselectivity. It is noteworthy that this reaction is different from the previous α-fluorination of the same vinylogous enolates.



Scheme 13 The electrophilic γ-trifluoromethylation of vinylogous enolates reported by Sun *et al.*

4. Reactions with radical-type fluoroalkylating reagents

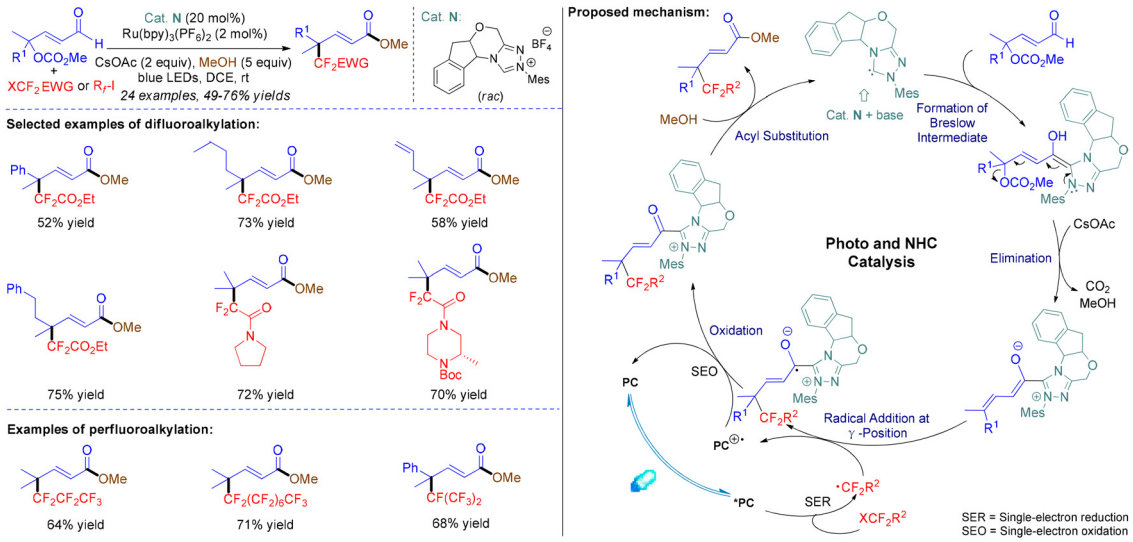
Based on the previous mechanistic understandings and to further explore the translational potential of Breslow-centered radical cations, a series of promising NHC-catalyzed free radical reactions have been developed by Studer, Chi, Rovis, Ohmiya, Huang, Ye, and other research teams.[33–45,47–50,53,55] Ohmiya and coworkers presented an elegant overview of the NHC-based radical catalysis in 2020.[33]

Generally, these NHC-catalyzed radical transformations proceed effectively with good functional group tolerance under mild reaction conditions. However, only two reports have demonstrated asymmetric fluoroalkylation with moderate enantioselectivities in the presence of a chiral NHC catalyst. Therefore, asymmetric versions of NHC-catalyzed radical fluorination and fluoroalkylation reactions still need to be explored.

In this section, the plausible pathways of most examples involving complex processes are depicted in more detail to further illustrate the processes and features of these novel transformations that might be promising in the near future.

4.1. γ-Fluoroalkylation of enals

In 2020, Ye *et al.* developed the photoredox NHC-catalyzed γ-difluoroalkylation of enals with a γ-leaving group under the irradiation of blue LEDs (Scheme 14).[35] A variety of γ-difluoroalkyl-α,β-unsaturated esters containing an all-carbon quaternary center at the γ-position were smoothly delivered. Both γ-methylarylenals with electron-donating groups and those with electron-withdrawing groups (Ar = Ph, *p*-tol, *m*-tol, 4-ClC_6H_4, and 3-BrC_6H_4) participated in the reaction smoothly. A wide range of γ-diarylenals efficiently reacted to yield the anticipated products in moderate to good yields (49–76% yields). The reactions with iodoperfluoroalkanes were also successfully achieved (61–68% yields) under these conditions. The transformation might proceed through the formation of a homoenolate-type Breslow intermediate, an elimination to produce a dienolate-type intermediate, a single-electron reduction of the difluoroalkyl reagent R_f-X to generate a difluoroalkyl radical, a γ-addition of a difluoroalkyl radical to the homoenolate, single-electron oxidation, and acyl substitution. The authors also attempted to realize an asymmetric catalytic version of the γ-difluoroalkylation reaction. When a chiral NHC was utilized in the reaction, a moderate yield of the desired product with 48% ee was obtained. The method

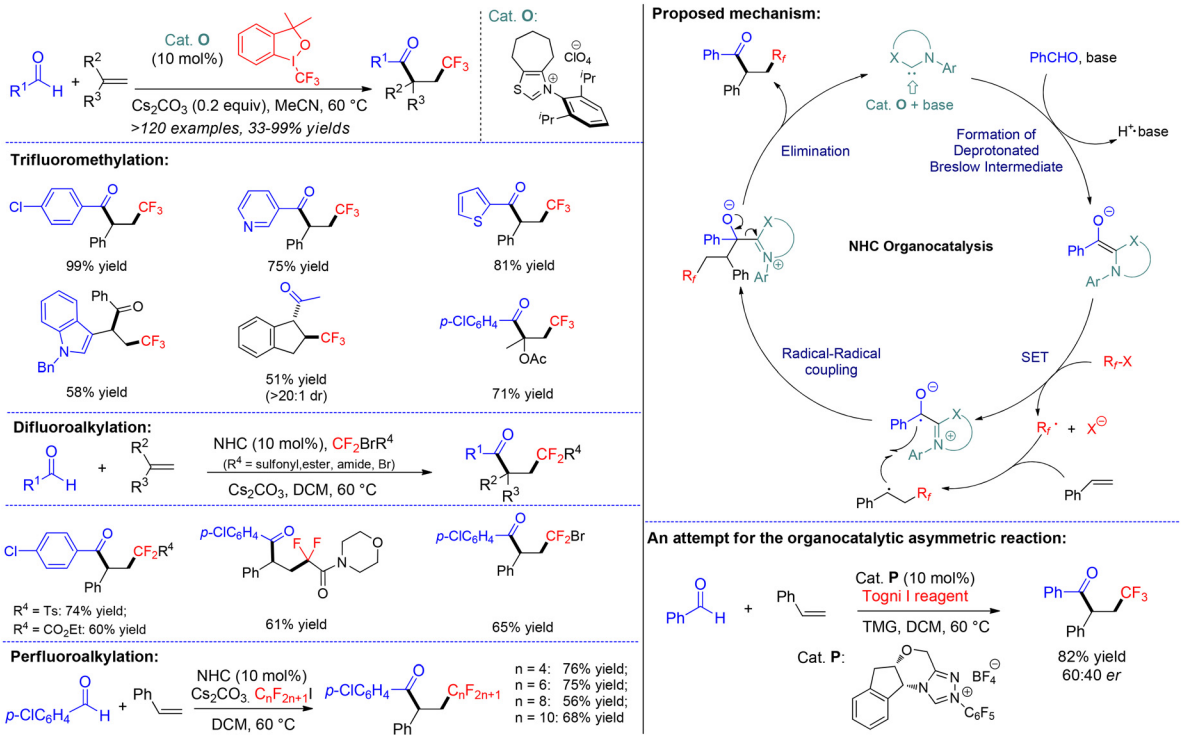


Scheme 14 The photoredox NHC-catalyzed γ-difluoroalkylation of enals reported by Ye *et al.*

pioneered the first γ-difluoroalkylation of carbonyl compounds.

4.2. Difunctionalization of alkenes

In 2019, the Nagao and Ohmiya group disclosed the first NHC-catalyzed radical relay for the vicinal alkylacylation of styrenes, acrylates and acrylonitrile by using aldehydes and tertiary alkyl carboxylic acid-derived redox-active esters.[36] Their mechanistic study revealed that the pathway of this transformation might involve a SET from the enolate form of the Breslow intermediate and a radical addition of the corresponding alkyl radical to the olefin followed by a radical–radical coupling process. Inspired by these pioneering reports, several other groups also engaged in the exploration of NHC-catalyzed radical relay reactions for the difunctionalization of alkenes involving fluoroalkylation. In 2020, Li and coworkers reported the first NHC-catalyzed radical acylfluoroalkylation of olefins (Scheme 15).[37] Using various (hetero)aryl aldehydes, alkenes and fluoroalkyla-

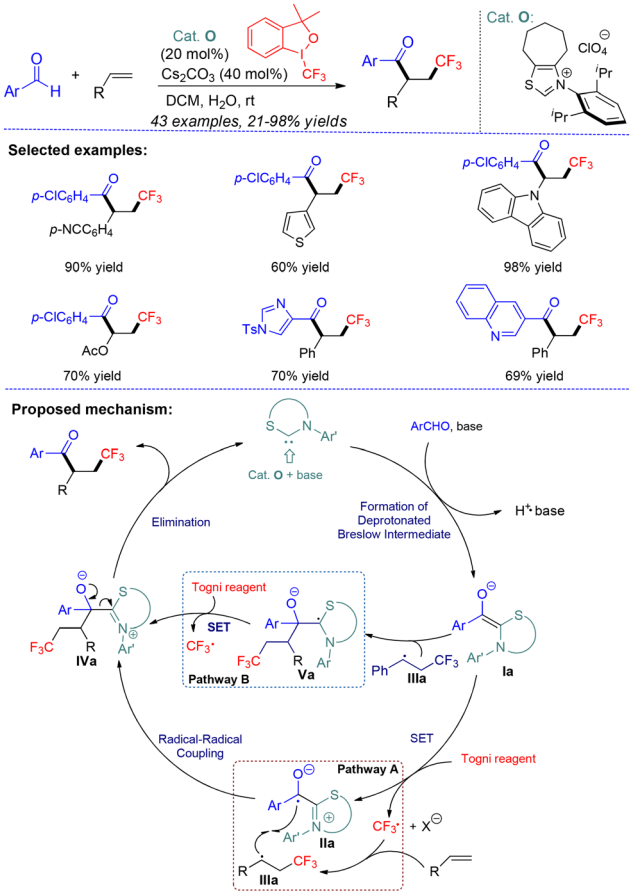


Scheme 15 The NHC-catalyzed radical acylfluoroalkylation of olefins reported by Li *et al.*

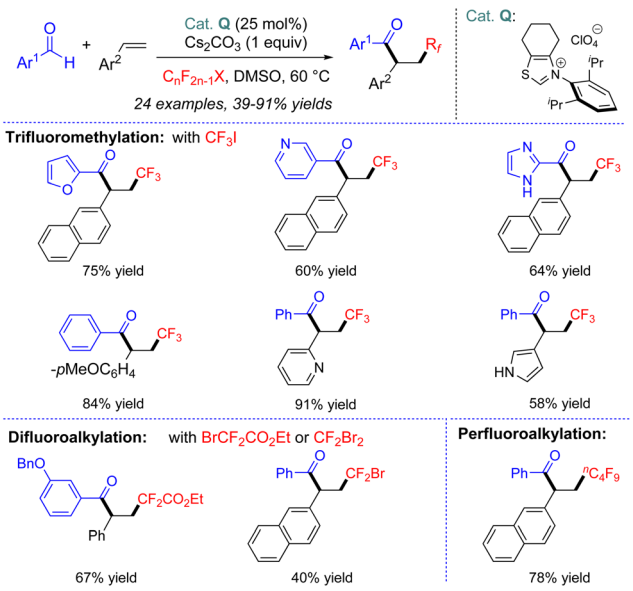
tion sources (Togni I reagent, difluoroalkyl bromides or perfluoroalkyl iodides) as the starting materials in the presence of a thiazolium-type precatalyst (cat. **O**), over 120 examples of functionalized ketones were furnished regiospecifically in up to 99% yields. A great number of aryl aldehydes bearing different functional groups (such as MeO, X and HO) at the aryl ring reacted well. Several heteroaryl (including 2-furyl, 2-thienyl, 3-N-benzylindolyl and 3-pyridyl) aldehydes also exhibited high reactivities. A broad range of substituted styrenes with both electron-rich and electron-poor (hetero)aryl rings were suitable reaction partners. The performance of many alkyl alkenes and functionalized alkenes was also good. By using different types of fluoroalkyl bromides, diverse fluoroalkyl substituents (*e.g.* CF_3, CF_2Br, CF_2Ts, CF_2Cs, CF_2CO_2R, and CF_2CONR_2) were effectively installed at the β-position of the ketone products. An organocatalytic asymmetric acyltrifluoromethylation was also tried with a chiral triazolium-type precatalyst (cat. **P**), and the desired product was obtained in good yield with a 60 : 40 er. After several mechanistic experiments were carried out, the authors found that this type of reaction might proceed through a radical pathway involving the formation of an electron-enriched deprotonated Breslow intermediate, a single-electron reduction of the fluoroalkyl reagent R_f-X to generate a fluoroalkyl radical and a ketyl radical, benzylic radical formation *via* the addition of a fluoroalkyl radical towards the vinyl substrate, a radical–radical cross-coupling of the ketyl radical with the benzylic radical, and elimination.

Almost concurrently, Wang and coworkers also developed an NHC-catalyzed radical trifluoromethylation enabled by a three-component reaction of aldehydes, olefins, and Togni's reagent.[38] A broad spectrum of (hetero)aryl aldehydes and a variety of mono-substituted alkenes were well tolerated under these conditions (Scheme 16). Both of the aryl aldehydes with electron-donating groups (such as Me and RO) and those with electron-withdrawing substituents (such as F, CF_3, NO_2, and CN) at the phenyl ring were well compatible. Many heteroaryl aldehydes could also react smoothly. Notably, several functionalized olefins such as the alkenes bearing azolyl, amido, alkoxy, acetoxy, and phenylthio groups also successfully participated in this reaction. A proposed mechanism for this type of radical transformation is similar to Li's work (pathway A).[37] An alternative pathway is also postulated in this report. The CF_3-containing alkyl radical addition to the alkene resulted in the formation of alkyl radical **IIIa**, which interacted with another molecule of Breslow intermediate **Ia** to generate an NHC-bound radical intermediate, **Va**, followed by a SET process to furnish intermediate **IVa** (pathway B).

In the next year, Wu and coworkers reported the acylfluoroalkylation of olefins through NHC catalysis (Scheme 17).[39] In the presence of a thiazolium-type carbene precursor (cat. **Q**, 25 mol%) and Cs_2CO_3 (1 equiv.), a variety of α-aryl-β-perfluoroalkyl ketones were synthesized from the three-component reactions of (hetero)aryl aldehydes, styrenes, and perfluoroalkyl halides. In this work, various perfluoroalkylating reagents (CF_3I, CF_2Br_2, $BrCF_2CO_2Et$, and $^nC_4F_9I$) were found to



Scheme 16 The NHC-catalyzed radical acylfluoroalkylation of olefins reported by Wang *et al.*



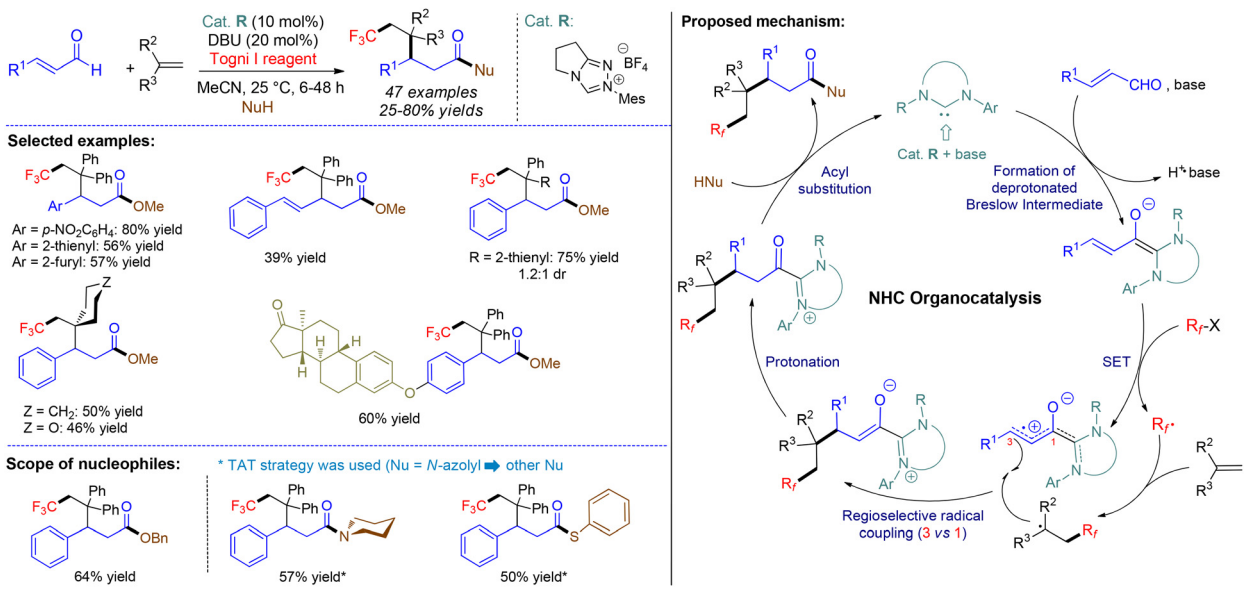
Scheme 17 The NHC-catalyzed radical acylfluoroalkylation of olefins reported by Wu *et al.*

be applicable. A wide range of benzaldehydes bearing electron-donating or electron-withdrawing groups at the *p*- or *m*-position of the phenyl ring reacted well. Some heteroaryl aldehydes also participated in the cascade reaction effectively. Various substituted phenyl, 2-naphthyl, and heteroaryl alkenes were good reaction partners. The plausible mechanism of this transformation is similar to that documented by Li's group, and the generation of the deprotonated Breslow intermediate and radical–radical coupling are also the key steps of the reaction.[37] Many functional groups were well compatible under these conditions, though the use of relatively high catalyst loading is the major limitation.

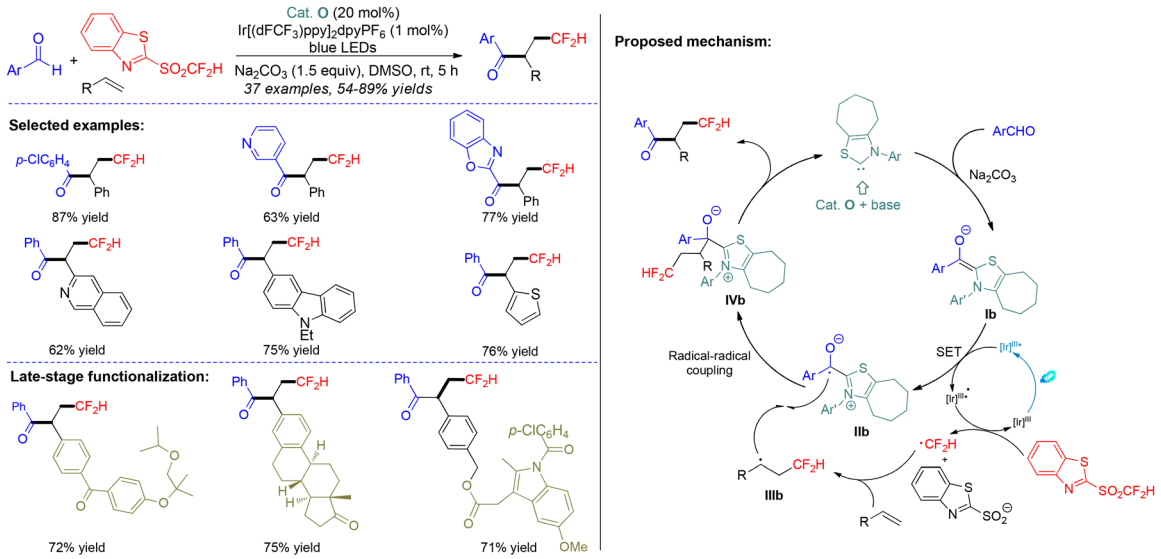
In 2021, Chen, Huang and colleagues disclosed an NHC-catalyzed four-component reaction through radical relay coupling *via* a homoenolate intermediate (Scheme 18).[40] A variety of β-tertiary–γ-quaternary carboxylic acid derivatives were efficiently and regioselectively assembled through the reaction of an enal, an alkene, Togni's reagent and a nucleophile with thiazolium (cat. **R**) as the precatalyst. Various γ-(hetero)aryl enals underwent the reaction effectively. They found a slight difference in reactivity between electron-poor and electron-rich (hetero)aryl rings. Numerous olefins including styrene, substituted 1,1-diphenylethylenes, 1,1-unsymmetric ethylenes, and 1,1-dialkylethylenes also participated in the reaction smoothly. In this study, they describe high site control using a triazolium NHC catalyst and a transient acyl trapping protocol for accessing diverse carboxylic acid derivatives in one pot. When steric alcohols or other types of nucleophiles were utilized, pyrazole and imidazole were excellent additives for promoting catalyst turnover and *in situ* derivatization. Their mechanism investigation supported that one of the key steps of the pathway was the radical-radical coupling process.

In 2022, the Wang group developed an acyldifluoromethylation of inert alkenes through a synergistic NHC–photoredox catalysis (Scheme 19).[41] With 2-((difluoromethyl)sulfonyl) benzo[*d*]thiazole as the difluoromethylating reagent, a wide range of aryl and heteroaryl aldehydes and a broad spectrum of (hetero)aromatic alkenes reacted effectively under the mild conditions. Several bioactive compounds were also modified efficiently using this protocol. The method is beneficial due to the advantages such as a wide substrate scope and good functional group compatibility. A plausible pathway for this radical alkene acyldifluoromethylation is also shown in the scheme. The deprotonated Breslow intermediate **Ib** was generated from the reaction of the NHC and the aldehyde. Next, a single-electron oxidation of **Ib** led to the generation of intermediate **IIb** through SET between **Ib** and the activated photocatalyst $[Ir]^{III*}$. Meanwhile, a single-electron reduction of 2-((difluoromethyl) sulfonyl)benzo[*d*]thiazole by the photocatalyst $[Ir]^{III*\bullet}$ resulted in the formation of a CF_2H radical and the regeneration of ground state $[Ir]^{III}$. Then, the short-lived CF_2H radical addition to the olefin gave a relatively stable alkyl radical, **IIIb**. Subsequently, a radical–radical cross-coupling of alkyl radical **IIIb** with radical **IIb** afforded the NHC-bound intermediate **IVb**, followed by the release of NHC to furnish the product and reproduce the NHC catalyst.

In the same year, an NHC-catalyzed three-component acyldifluoromethylation of vinylarenes, aldehydes and CF_2HSO_2Na was reported by Wang, Tsui and coworkers (Scheme 20).[42] A variety of aldehydes including various substituted aromatic aldehydes and an aliphatic aldehyde smoothly participated in the reaction. Many vinyl (hetero)arenes were good reaction partners. Their method was also successfully applied in the late-state modification of some pharmaceutical or bioactive molecules. A probable mechanism was proposed by the authors (Scheme 20). The reaction of the NHC with the aldehyde delivered Breslow intermediate **Ic**, which was transformed into the deprotonated intermediate **IIc**. Then, the

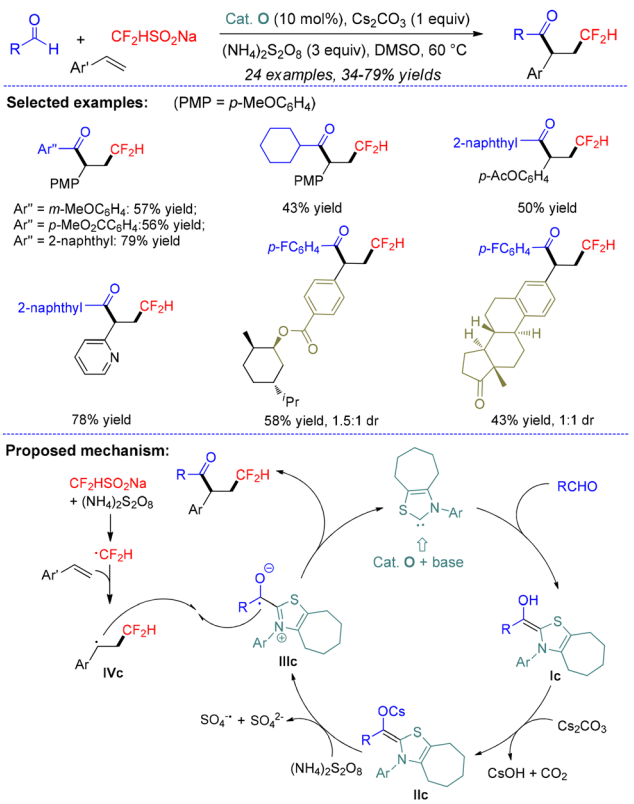


Scheme 18 The NHC-catalyzed acyltrifluoroalkylation reported by Chen and Huang *et al.*



Scheme 19 The NHC-photo co-catalyzed acyldifluoromethylation reported by Wang *et al.*

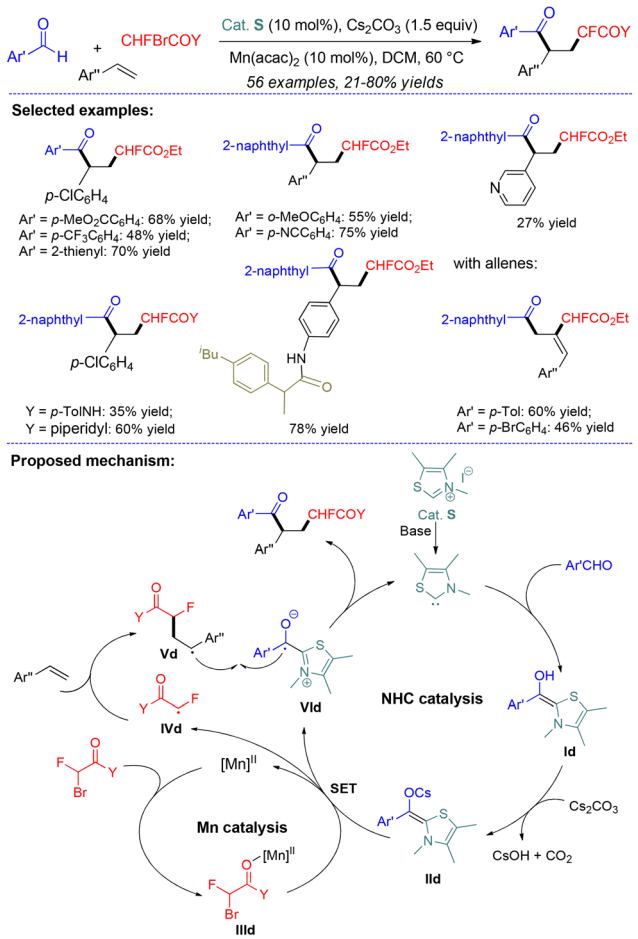
single-electron oxidation of **IIc** by $(NH_4)_2S_2O_8$ gave the radical intermediate **IIIc**. On the other hand, the addition of vinylarene to the CF_2H radical, which was *in situ* formed from the reaction between CF_2HSO_2Na and $(NH_4)_2S_2O_8$, afforded the alkyl radical **IVc**. The final product was generated after the radical–radical coupling of **IIIc** and **IVc** followed by the release of the NHC.



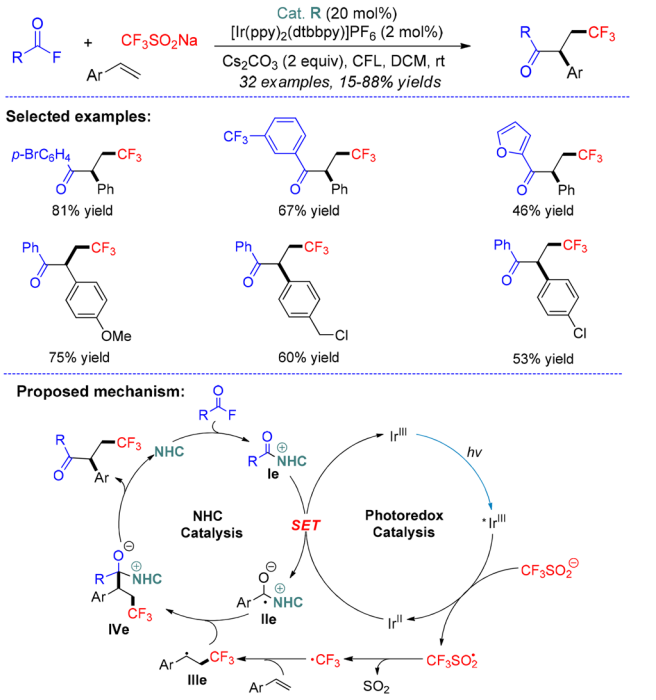
Scheme 20 The acyldifluoromethylation of vinylarenes reported by Wang and Tsui *et al.*

Very recently, the Cheng and Wang group disclosed a three-component radical acylmonofluoroalkylation of alkenes under NHC and Mn synergistic catalysis (Scheme 21).[43] A broad spectrum of aryl/heteroaryl aldehydes and substituted alkenes/allenes/1,3-enynes reacted well in the presence of an NHC pre-catalyst (cat. **S**) and a manganese(II) catalyst $[Mn(acac)_2]$ with α-bromo-α-fluoro acetic acid derivative (CHFBrCOY) as the monofluoroalkyl reagent. The merits of the method involve broad substrate scope and good functional group compatibility. The possible mechanism for this transformation was also postulated by the authors (Scheme 21). Breslow intermediate **Id** was generated *via* the reaction between the NHC catalyst and the aldehyde. Subsequently, **Id** was deprotonated by the base to furnish intermediate **IId**. Next, the Mn^{II}-catalyzed SET from **IId** to CHFBrCOY gave rise to the formation of alkyl radical **IVd** and NHC-bound ketyl radical **VId** (*via* Lewis acid Mn^{II}-complex **IIId**). Then, the **IVd** radical addition towards the C–C double bond of the alkene delivered transposed radical species **Vd**, which underwent a radical–radical coupling with ketyl radical **VId** and released the NHC catalyst to provide the final product.

The oxidation of Breslow intermediates to provide the ketyl-type intermediates has been rather well investigated. However, the SET-reduction of easily generated acylazolium to afford ketyl-type radicals has been rarely investigated. In 2020, the Studer group developed a "reductive" strategy for the radical acyltrifluoromethylation of styrenes. The three-component coupling of aroyl fluorides, styrenes and the Langlois reagent (CF_3SO_2Na) afforded various β-trifluoromethylated alkyl aryl ketones in moderate to high yields by cooperative photoredox/NHC catalysis (Scheme 22).[44] A wide range of phenyl aldehydes with various substituents (such as Me, ^{t}Bu, MeO, X, CN, CF_3,



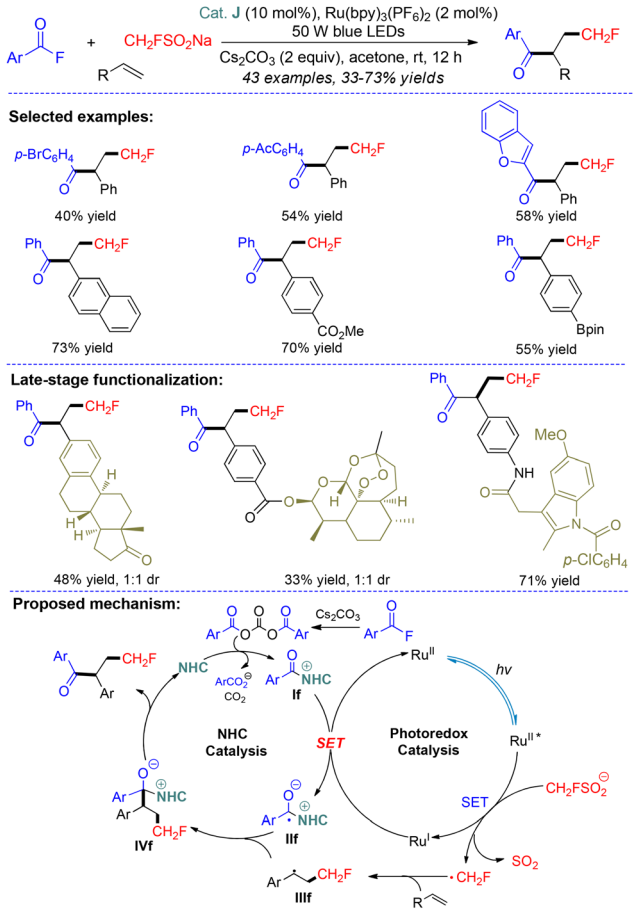
Scheme 21 The acyldifluoromethylation of alkenes reported by Cheng and Wang *et al.*



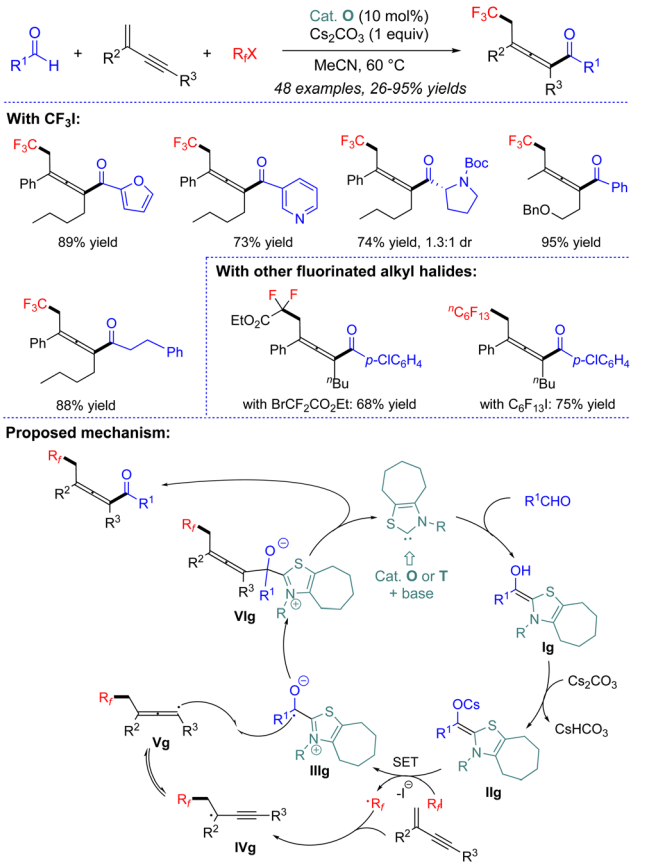
Scheme 22 The reactions of acyl fluoride, alkene, and Langlois reagent reported by Studer *et al.*

and CF_3O) at the benzene ring expressed good reactivity. β-Naphthyl, 2-furyl and 2-thienyl aldehydes reacted to deliver moderate yields of the products. Numerous substituted styrenes and some alkyl alkenes were good partners. The reaction with 2-vinylnaphthalene or 2-vinylpyridine also proceeded smoothly. The method features a wide substrate scope, mild reaction conditions, and good functional group tolerance. In this transformation, the reduction of the acylazolium intermediate *via* SET might provide a neutral persistent ketyl-type radical that probably exhibits similar radical reactivity to its protonated congener generated by the SET-oxidation of the corresponding Breslow intermediate. A possible mechanism involving cooperative NHC and photoredox catalysis for the radical alkene acyltrifluoromethylation is depicted in Scheme 18. Upon visible light irradiation, the excited state of $[Ir(ppy)_2(dtbbpy)]PF_6$ was reductively quenched by TfO^- to afford the Ir^{II} complex and the TfO radical that released SO_2 to furnish the CF_3 radical. Then, the persistent ketyl radical **IIe** along with the starting Ir^{III} species was generated through the SET between the Ir^{II} complex and the acylazolium intermediate **Ie** that was generated *in situ* from the reaction of benzoyl fluoride and the NHC. Meanwhile, the CF_3 radical addition towards the double bond of styrene resulted in the formation of the transient benzylic radical **IIIe**. Subsequently, a radical–radical cross-coupling of ketyl radical **IIe** with transient C-radical **IIIe** resulted in the generation of the NHC-bound intermediate **IVe**, followed by the release of NHC to deliver the product.

Very recently, the Cheng and Wang group disclosed the monofluoromethylation of alkenes with aroyl fluorides and CH_2FSO_2Na using cooperative NHC/photoredox catalysis.[45] A variety of monofluorinated alkyl aryl ketones were synthesized in moderate to good yields (Scheme 23). The strategy might be beneficial due to the merits such as mild conditions, broad substrate scope, and excellent functional group tolerance. A broad spectrum of vinylarenes with diverse electronic and steric properties were compatible. Many functionalities (such as Bpin, pyridyl, thienyl, and amino groups) were well tolerated, though hydroxyl and formyl groups were incompatible. Numerous aroyl fluorides bearing electron-rich and electron-deficient groups participated in the reaction smoothly. Some pharmaceutical or biologically active molecules could also be successfully modified using this protocol. The probable pathway of the reaction was also proposed by the authors based on their experimental studies and literature reports. The acyl fluoride was converted to the bisacyl carbonate in the presence of Cs_2CO_3, followed by the acylation of the *in situ* generated NHC catalyst to furnish the acylated NHC **If**. Meanwhile, the Ru^{II} catalyst was photoexcited under the irradiation of blue LEDs to form the excited Ru^{II}* catalyst, which was reduced by CH_2FSO_2Na to generate the corresponding CH_2F radical and Ru^{I} species. Subsequently, the CH_2F radical addition towards the C–C double bond of the alkene delivered alkyl radical



Scheme 23 The reactions of acyl fluoride, alkene, and Langlois reagent reported by Cheng and Wang *et al.*



Scheme 24 The 1,4-alkylacylation of 1,3-enynes reported by Feng and Du *et al.*

intermediate **IIIf**. The SET between the acyl NHC **If** and Ru^{I} led to the generation of the Ru^{II} catalyst and the persistent ketyl radical **IIf**. The latter underwent a radical–radical cross-coupling with alkyl radical **IIIf** to deliver an NHC-bound intermediate **IVf**. Finally, an NHC fragmentation resulted in the formation of the product and the regeneration the NHC catalyst.

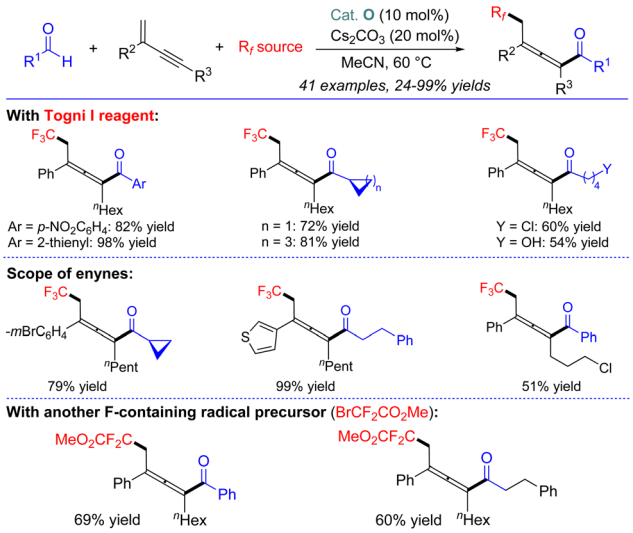
4.3. 1,4-Difunctionalization of 1,3-enynes

Recently, 1,3-enynes have been employed as useful building blocks for the assembly of polysubstituted allenes *via* 1,4-addition.[46] In spite of these great developments, the 1,4-difunctionalization of conjugated enynes through allenyl radical intermediates is still challenging and the relevant reports are rare, probably because the highly reactive allenyl radical intermediates easily oxidize or reduce to form corresponding allenyl cations or anions.

In 2021, an NHC-catalyzed radical relay 1,4-alkylcarbonylation reaction of 1,3-enynes for installing tetra-substituted allenyl ketones was explored by Feng, Du and coworkers (Scheme 24).[47] A variety of aldehydes, 1,3-enynes, and fluoroalkyl halides successfully participated in this NHC-catalyzed domino radical reaction under transition metal- and photocatalyst-free conditions. High efficiency, high regioselectivity and good functional group compatibility were featured in this method. The proposed pathway is also shown in Scheme 24. This transformation might be initiated by the formation of Breslow intermediate **Ig**, which was converted to its enolate form **IIg** in the presence of Cs_2CO_3. Subsequently, the thermally controlled SET between the intermediate **IIg** and the fluoroalkyl halide afforded an NHC-bound radical intermediate **IIIg** and a fluoroalkyl radical. The fluorinated alkyl radical addition to 1,3-enyne generated a propargyl radical, **IVg**, which was reversibly isomerized to the allenyl radical **Vg**. Then, a radical–radical coupling of **IIIg** with **Vg** delivered intermediate **VIg**. Finally, the release of NHC from **VIg** delivered the product.

In the same year, the Huang group disclosed a radical transformation for the 1,4-difunctionalization of alkenes under similar conditions (Scheme 25).[48] In the presence of the NHC precursor (cat. **O**), the 1,4-alkylacylation of 1,3-enynes with an aldehyde and a radical precursor proceeded effectively to synthesize the tetrasubstituted allenes. After the examination of the scope of this radical coupling reaction, the authors found that various aromatic/aliphatic aldehydes and disubstituted 1,3-enynes were well tolerated, and generally, good to excellent yields of the desired products were obtained.

Later, Li and coworkers also reported similar methods of NHC-catalyzed radical trifluoromethylation enabled by three-

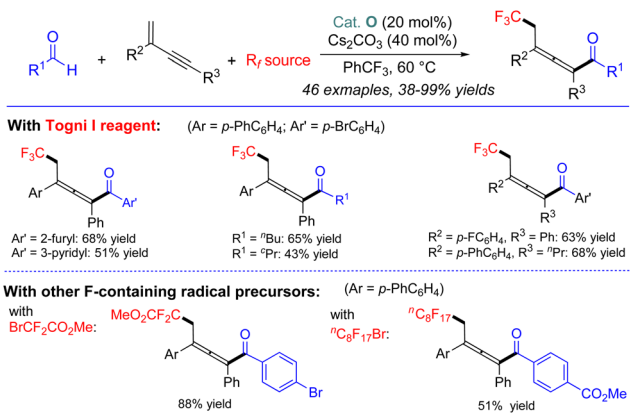


Scheme 25 The 1,4-alkylacylation of 1,3-enynes reported by Huang *et al.*

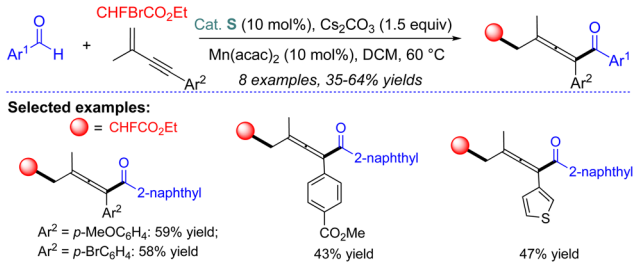
component reactions of aldehydes, 1,3-enynes, and fluoroalkyl halides in $PhCF_3$ (Scheme 26).[49] The reaction proceeded effectively to assemble a broad spectrum of polysubstituted fluoroalkylated allenic ketones. Other difluoroalkyl- and perfluoroalkyl-acylation reactions of 1,3-enynes could also be successfully achieved.

In 2023, the Cheng and Wang group found that their NHC/Mn-cocatalyzed three-component radical acylmonofluoroalkylation method could also be successfully applied in the 1,4-difunctionalization of an array of 1,3-enynes (Scheme 27).[43]

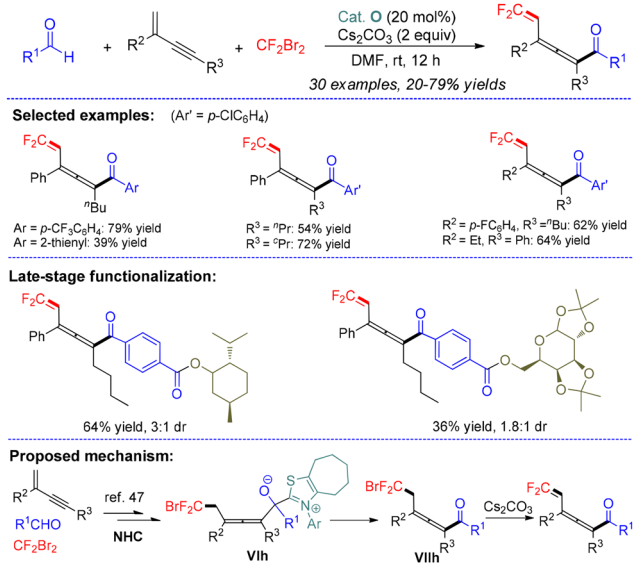
In 2022, Zhu, Du and coworkers explored the NHC-catalyzed difluoroolefination of 1,3-enynes using CF_2Br_2 as a source for the incorporation of the *gem*-difluorovinyl motif into an allene framework (Scheme 28).[50] The method possesses many merits such as the readily available starting materials, transition metal-free mild conditions, broad substrate scope and ease of late-stage modification. Different from the traditional *gem*-difluoroolefination methods, CF_2Br_2 was



Scheme 26 The 1,4-alkylacylation of 1,3-enynes reported by Li *et al.*



Scheme 27 The 1,4-alkylacylation of 1,3-enynes reported by Wang and Cheng *et al.*

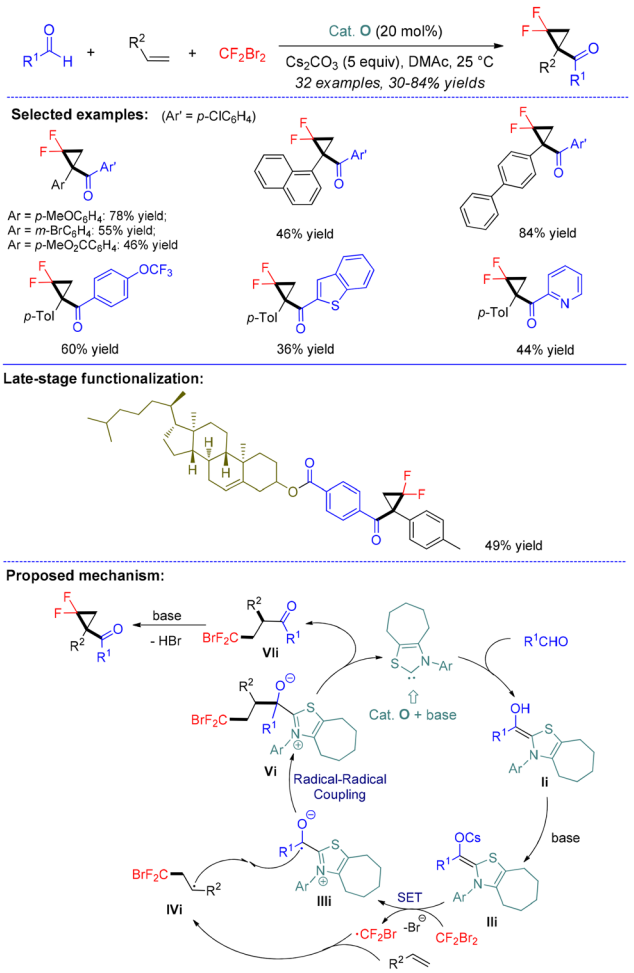


Scheme 28 The difluoroolefination of 1,3-enynes reported by Zhu and Du *et al.*

employed as a new and easily accessible source for *gem*-difluoroolefination reactions. In this transformation, the brominated *gem*-difluorovinyl-containing difunctionalized product **VIIh** was generated probably through the mechanism similar to the pathway depicted in Scheme 24.[47] After that, **VIIh** underwent a base-assisted elimination of HBr to furnish the final *gem*-difluorovinyl-containing difunctionalized product.

4.4. Other radical-involved reactions

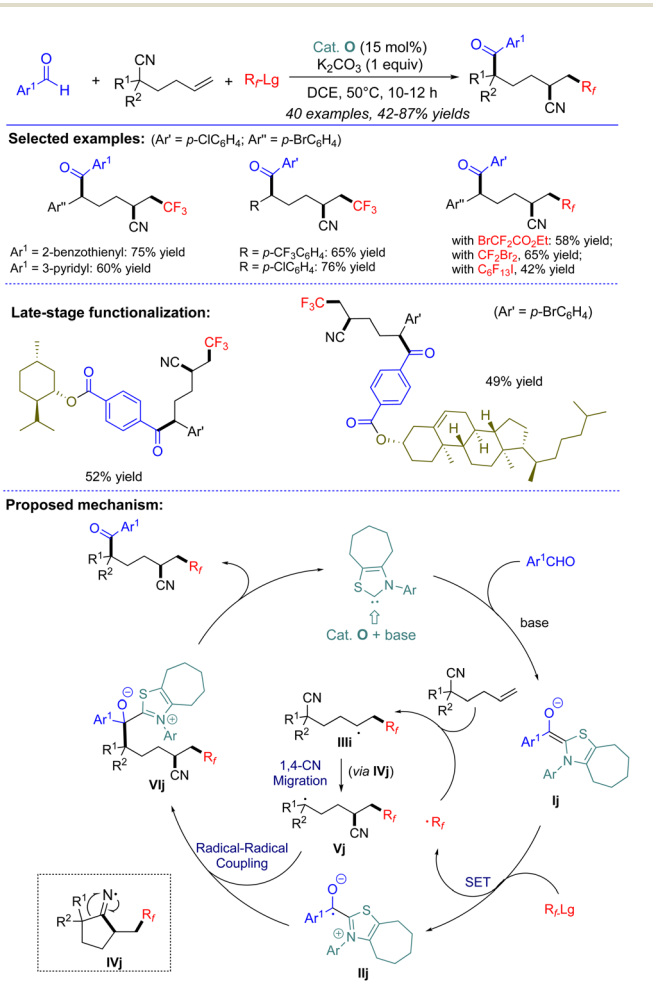
4.4.1. *gem*-Difluorocyclopropanation of alkenes. *gem*-Difluorocyclopropanes are potentially useful in biological chemistry, medicinal science,[51] and organic synthesis.[52] Recently, the Gao and Du group developed a facile synthesis of *gem*-difluorocyclopropanes using an NHC-catalyzed radical relay/cyclization method (Scheme 29).[53] A broad spectrum structurally diverse styrenes and (hetero)aryl aldehydes underwent the reactions to generate the desired products in moderate to good yields. However, the reactions of sterically hindered *o*-substituted aldehydes and aliphatic aldehydes failed to afford the desired products. The method has the merits such



Scheme 29 The *gem*-difluorocyclopropanation of styrenes reported by Gao and Du *et al.*

as good functional group tolerance, mild conditions, easy scalability, and ease to be converted to bioactive molecules through late-stage derivatization. The pathway of the relay radical/annulation reaction is also depicted in Scheme 29. The NHC reacted with aldehyde to furnish Breslow intermediate **Ii**, which was deprotonated into its enolate form **IIi** in the presence of Cs_2CO_3. Then, a SET of **IIi** with CF_2Br_2 led to the formation of the NHC-bound ketyl radical **IIIi** and the CF_2Br radical. Subsequently, the CF_2Br radical was captured by alkene with the generation of alkyl radical **IVi**. Next, a radical–radical coupling between **IIIi** and **IVi** resulted in the formation of intermediate **Vi**, which delivered intermediate **VIi** *via* the release of the NHC catalyst. The final product was obtained through an intramolecular nucleophilic cyclization under the basic conditions.

4.4.2. Radical relay trifunctionalization of alkenes. In recent years, radical functionalization of unactivated alkenes *via* remote functional group migration has been utilized as a useful protocol for the preparation of functionalized compounds that might be difficult to obtain by other methods.[54] Very recently, Feng, Du and coworkers realized the organocatalytic radical relay trifunctionalization of unactivated alkenes bearing a γ-cyano group by a combination of cyano migration and alkylacylation (Scheme 30).[55] A variety of hexenenitriles with diverse substituents at different positions of the aryl rings were well tolerated under the conditions. The aryl ring could be replaced by an electron-poor group (an ester or a cyano group) and moderate yields were obtained. The alkene with α-cyano and α-alkyl groups was a good substrate for cyano migration, while the hexenenitriles bearing α-phenyl and any other α-groups or α,α-biaryls were unsuitable for this reaction. Some fluorinated reagents with a good leaving group also showed good compatibility. Their DFT calculation results indicated that the pathway involving the 1,4-cyano migration process was much more energetically favourable than the pathway without cyano migration. The reaction was started with the generation of the deprotonated Breslow intermediate **I**. Then, a SET event between **Ij** and the fluoroalkylating reagent furnished the fluoroalkyl radical and the NHC-bound ketyl radical intermediate **IIj**. Meanwhile, the cyano-containing alkene substrate captured the fluoroalkyl radical to afford alkyl radical **IIIj**, which underwent a 1,4-cyano migration to deliver



Scheme 30 The trifunctionalization of γ-cyanoalkenes reported by Feng and Du *et al.*

another alkyl radical **Vj** (*via* cyclized intermediate **IVj**). Next, the radical–radical cross-coupling between intermediates **IIIj** and **Vj** afforded intermediate **VIj**. The final product was generated after the release of NHC.

5. Summary and perspectives

In summary, we have presented an overview on the recent advances in N-heterocyclic carbene catalyzed fluorination and fluoroalkylation reactions. Generally, these NHC-catalyzed transformations feature high efficiency, good functional group tolerance, and relatively mild conditions. By the use of suitable chiral NHC catalytic conditions, several enantioselective fluorination transformations have also been successfully achieved with excellent enantioselectivities. We hope that this review will be useful for synthetic chemists to understand the reactivity of these promising methodologies and the further potential in synthetic applications.

Although remarkable progress has been made in this field, there are still some limitations and challenges for this strategy. For example, the method might be restricted by the limitations of substrates/reagents, more types of transformations need to be explored, only two cases of NHC-catalyzed enantioselective fluoroalkylation have been achieved (without very satisfactory results) to date,[30,37] and there are very limited examples for the assembly of more complex linear moieties and cyclic systems. Therefore, in the next stage, more attention needs to be paid in the expansion of the substrate scope, the development of new reagents, the exploration of novel types of transformations (especially for the development of NHC-catalyzed asymmetric fluoroalkylation), and ingenious design of starting materials and reaction processes for the construction of complex and cyclic frameworks.

Conflicts of interest

There are no conflicts to declare.

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