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Radical Acylfluoroalkylation of Olefins through *N*-Heterocyclic Carbene Organocatalysis

Jun-Long Li, Yan-Qing Liu, Wen-Lin Zou, Rong Zeng, Xiang Zhang, Yue Liu, Bo Han,* Yu He, Hai-Jun Leng, and Qing-Zhu Li*

Abstract: Fluorinated ketones are widely prevalent in numerous biologically interesting molecules, and the development of novel transformations to access these structures is an important task in organic synthesis. As an emerging powerful strategy, the concurrent installation of fluorine and ketone moieties into target molecules from simple, variable, and abundant feedstocks remains synthetically challenging and underdeveloped. Here, we report a multicomponent radical acylfluoroalkylation of olefins in the presence of various commercially available aromatic aldehydes and fluoroalkyl reagents through *N*-heterocyclic carbene organocatalysis. Notably, a broad spectrum of olefin substrates, including styrenes, cyclic internal alkenes, indoles, vinyl ethers, vinyl esters, and the unactivated simple alkenes, could be compatible in this organocatalytic system. With this protocol, over 120 examples of functionalized ketones with diverse fluorine substituents have been facilely synthesized in up to 99% yield with complete regioselectivity. The generality of this catalytic strategy was further highlighted by its successful application in the late-stage functionalization of pharmaceutical skeletons. Interestingly, excellent diastereoselectivity could be achieved in the reactions forging multiple stereocenters. In addition, preliminary results have been achieved on the catalytic asymmetric variant of the olefin difunctionalization process. The reaction mechanism involves a single-electron reduction of fluoroalkyl reagents by deprotonated Breslow intermediates, radical addition to alkenes, and the radical–radical recombination.

Introduction

Fluorine represents one of the most privileged elements in pharmaceutical chemistry, crop protection, and material science. The introduction of fluorine atoms into organic compounds usually results in a profound and positive effect on molecular properties, including permeability, lipophilicity, and metabolic stability.[1] Consequently, the creation of various fluorinated substances with diverse functionalities has attracted considerable attention from academia and industry.[2] Fluorine-containing ketones are among the most popular structures in the discovery of drug candidates and functional materials. For example, the β-trifluoromethylated ketones (Figure 1, **I**–**IV**) could be used for the treatment of colon and lung cancers,[3a,3b] and for the discovery of anticonvulsant[3c] and antidiabetic agents.[3d] The γ-difluorinated ketone **V** was utilized as liquid crystalline material,[3e] and **VI** shows outstanding insecticidal activity[3f] (Figure 1). As a result, the development of efficient and practical methods to access fluoroketones is of high significance.[2h] Conventional strategies were mainly concentrated on exploring the ionic carbonyl chemistry of ketones to furnish fluorination decorations, or performing a tedious step-by-step functional group conversion from a specific prefunctionalized material.[1a,1b] As the demand for synthetic efficiency and versatility is constantly increasing,[4] bringing new technologies to refresh the synthesis strategy is highly desirable.

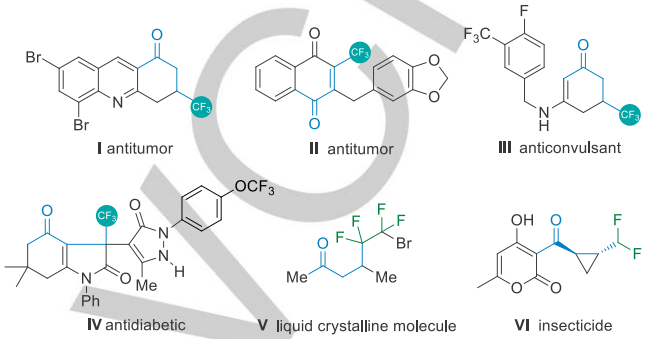

Figure 1. Selected examples of functional molecules containing fluorinated ketone moiety.

The radical fluoroalkylation of simple olefins, which allows the concomitant introduction of fluorine and additional functional groups across an alkene double bond, has recently emerged as a powerful tool for rapid generation of complex fluorinated molecules.[5] Significant progress has been achieved in a plethora of olefinic difunctionalizations, including carbo-, oxy-, halo-, thio-, cyano-, azido-, and amino-fluoroalkylation.[6] By contrast, the radical acylfluoroalkylation of generally available and simple alkenes, which would directly deliver various fluoroketones, remains challenging and underdeveloped (Figure 2a). Previous efforts along this line typically focused on exploring the chemistry of radical-mediated functional group migration or intramolecular radical cascade.[7] Despite being successful, these methods were typically prompted by transition metals and often required the multi-step preparation of rationally designed, carbonyl-

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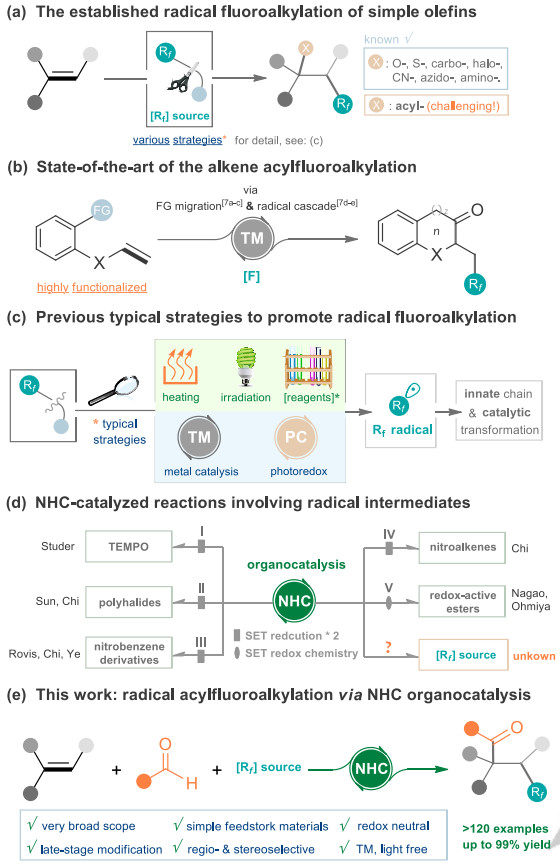


Figure 2. Research motivation for olefinic acylfluoroalkylation *via* NHC catalysis. [Reagents]*: refers to radical initiators or oxidants.

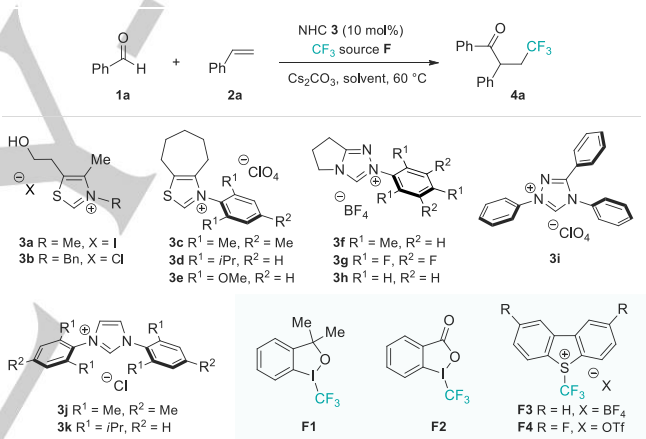
functionalized alkene substrates (Figure 2b). In addition, the established radical initiation strategies, such as heating, ultraviolet-light irradiation, addition of chemical initiators or oxidants, transition-metal catalysis, and the emerging photoredox catalysis (Figure 2c),[8] still feature limitations in integrating the challenging intermolecular acylation step into the fluoroalkylation process. Therefore, the development of a new radical catalytic system that inherently favors acylation chemistry might be a feasible solution to achieve the direct acylfluoroalkylation of simple olefins.

The *N*-heterocyclic carbene (NHC) organocatalysis is featured for its unique umpolung reactivity that enables various interesting acylations in ionic chemistry.[9] In parallel, the NHC-mediated radical reactions have also been disclosed by many research groups, in which a sequential two-times single-electron reduction scenario was typically involved (for details, see: Figure 2d, **I**–**IV**).[10-12] Recently, Nagao, Ohmiya, and co-workers reported an elegant NHC-catalyzed radical decarboxylative coupling of aldehydes with redox-active esters. In this reaction, the deprotonated Breslow intermediate (BI) can serve as a single-electron reductant to reduce the redox-active esters, and the resulting alkyl radical could be recombined with the BI-evolved ketyl radical to deliver the cross-coupling products (Figure 2d, **V**).[13a] Considering this scenario, we speculated that the NHC-mediated single-electron transfer (SET) might also be applicable to various fluoroalkyl sources, such as Togni reagents, and the produced radical R_f could trigger the cascade radical addition to alkenes, followed by radical–radical recombination, to achieve the unprecedented radical acylfluoroalkylation of simple olefins (Figure 2e).[13b] This protocol features several advantages, including broad substrate scope, easily available feedstock materials, excellent regio- and diastereoselectivity, metal-free radical catalysis, and diversity-oriented multicomponent synthesis. The generality and synthetic potential of this method is further highlighted by the late-stage modification of pharmaceutical skeletons.[14]

Results and Discussion

We started the investigation by selecting the commercially available benzaldehyde **1a**, styrene **2a**, and Togni **I** reagent **F1** as the model substrates to test the feasibility of this organocatalytic approach. First, we screened a variety of NHC catalysts in the presence of Cs_2CO_3 in MeCN at 60 °C. As shown in Table 1, the

Table 1: Optimization for the acyltrifluoromethylation of alkene.[a]



entry	catalyst **3**	CF_3 source	solvent	yield (%)[b]
1	**3a**	**F1**	MeCN	65
2	**3b**	**F1**	MeCN	28
3	**3c**	**F1**	MeCN	92
4	**3d**	**F1**	MeCN	97
5	**3e**	**F1**	MeCN	54
6	**3f**	**F1**	MeCN	32
7	**3g**	**F1**	MeCN	30
8	**3h**–**3k**	**F1**	MeCN	<5
9[c]	**3d**	**F2**	MeCN	21
10[c]	**3d**	**F3**–**F4**	MeCN	<5
11	**3d**	**F1**	DCM	80
12	**3d**	**F1**	THF	<5
13	**3d**	**F1**	DMSO	78

[a] The reactions were carried out with **1a** (0.12 mmol), **2a** (0.1 mmol), CF_3 source **F** (0.20 mmol), NHC catalyst **3** (10 mol %) and Cs_2CO_3 (0.02 mmol) in 1 mL of solvent at 60 °C for 12 h. [b] Isolated yield of **4a**. [c] With 0.15 mmol of Cs_2CO_3. DCM = dichloromethane; THF = tetrahydrofuran; DMSO = dimethyl sulfoxide.

10.1002/anie.201912450

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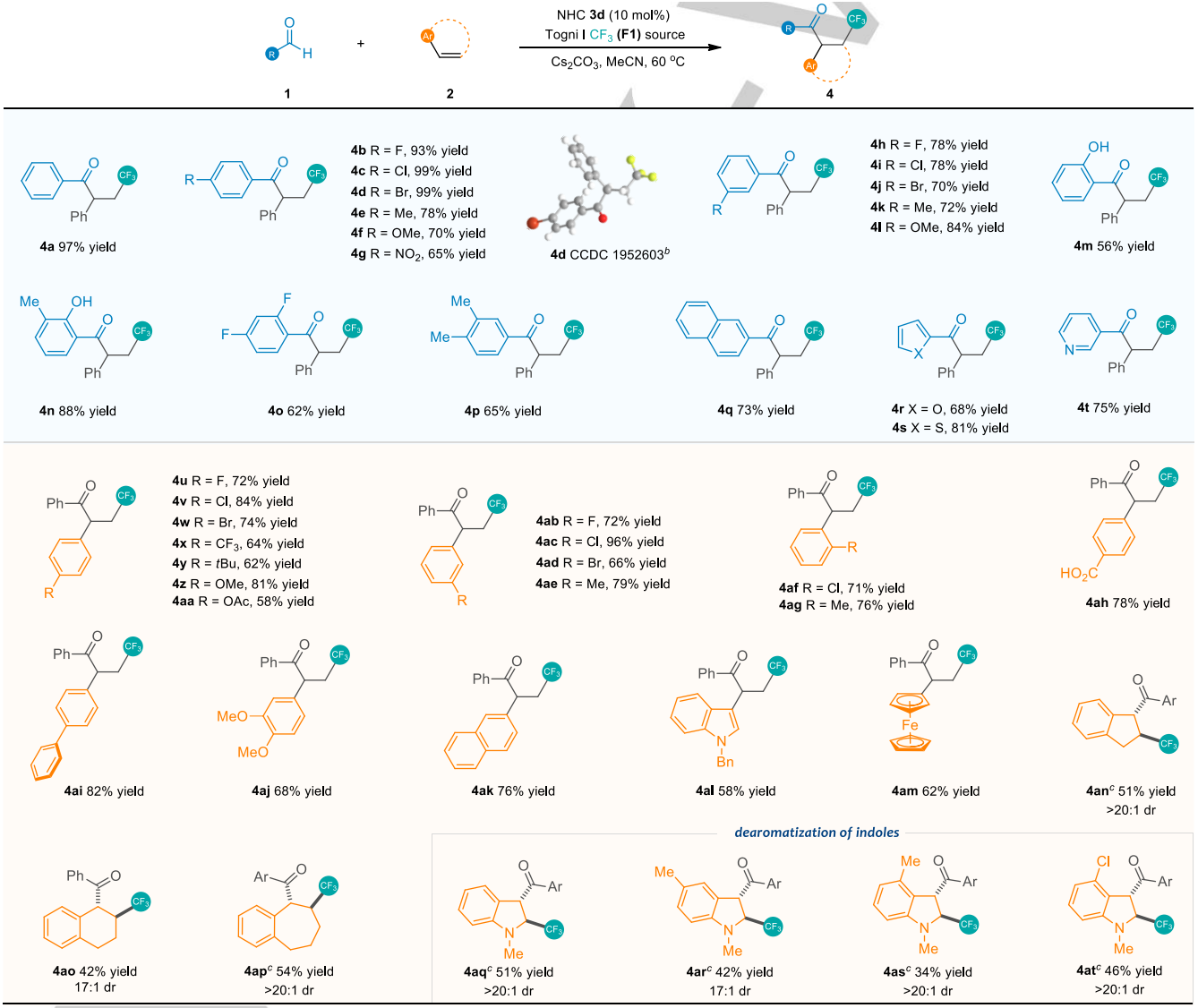
commercially available, inexpensive *N*-methyl thiazolium salts **3a** could smoothly afford the desired product **4a** in good yield, whereas the *N*-benzyl analogue **3b** showed a lower catalytic reactivity (entries 1–2). To our satisfaction, the reaction efficiency increased significantly upon the catalysis of the Glorius' cycloheptane-fused thiazolium salt **3c**,[15] and the modified *N*-2,6-diisopropylphenyl substituted catalyst **3d** provided the best result among **3c**–**3e** (entries 3–5). The catalytic efficiencies of triazolium salts **3f**–**3g** were unsatisfactory, and delivered **4a** in poor yield (entries 6–7). Unfortunately, the other catalysts **3h**–**3k** cannot promote the target radical transformation (entry 8). Next, we evaluated the reactivity of other electrophilic CF_3 sources, including the Togni **II** reagent (**F2**) and Umemoto's reagents (**F3**–**F4**). However, a significant reduction in conversion was observed (entries 9–10). Further solvent screening also led to inferior results (entries 11–13).[16]

With the optimal condition in hand, the generality of this method was subsequently evaluated by testing various substituted aromatic aldehydes **1** and styrenes **2**. As illustrated in Table 2, a broad range of aldehydes with diverse electronic and steric properties was well tolerated, offering the fluoroketones **4a**–**4p** in satisfying yields. The reactions were also suitable for naphthyl and various heteroaryl aldehydes to afford products **4q**–**4t**. On the other hand, the styrenes bearing both electron-withdrawing and electron-donating substituents on the phenyl ring at *para*-, *meta*-, and *ortho*-positions could all participate in this reaction and give products **4u**–**4aj** in generally high yields. Notably, a free carboxylic group was also compatible in the reaction, and the corresponding **4ah** was obtained in 78% yield. The reactions proceeded smoothly with naphthyl, indolyl or ferrocenyl substituted styrenes, delivering the fluoroketones **4ak**–**4am** in reasonable yields. In addition, the cyclic internal alkenes were

Table 2: Scope of the acyltrifluoromethylation of styrenes and indoles.[a]



[a] See Table 1 and SI for detailed experimental procedure; isolated yield. [b] The structure of **4d** was determined by X-ray analysis, and other products were assigned by analogy.[17] [c] With 20 mol % of NHC catalyst. Ar = 4-Cl-C_6H_4.

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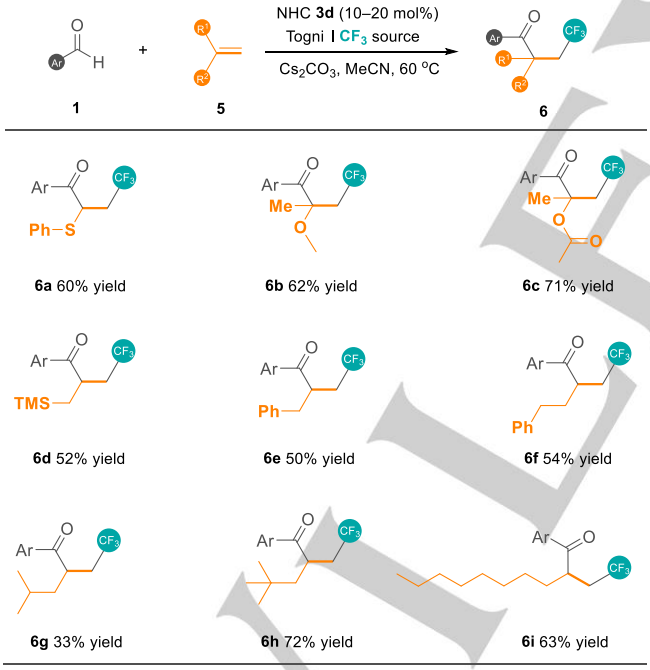
also tested. To our delight, the *trans* functionalized product **4an**–**4ap** were smoothly obtained with outstanding diastereoselectivities. Moreover, it is worth mentioning that the organocatalytic radical strategy could be successfully applied in the dearomatizative difunctionalization of indoles. Under the established optimal conditions, several representative examples of *N*-methyl indoles were facilely dearomatized to afford the trifluoromethylated indolinyl ketones **4aq**–**4at** in a highly diastereoselective manner.

To further demonstrate the robustness and generality of this method, an array of non-conjugated alkenes was tested. As shown in Table 3, the radical acyltrifluoromethylation of phenyl vinyl sulfide proceeded smoothly to give **6a** in outstanding yield. The 1,1-disubstituted vinyl ether and vinyl ester could also well participate in the reaction, and the corresponding functionalized ketones **6b**–**6c** with a quaternary stereocenter were obtained. Gratifyingly, a collection of the challenging unactivated alkenes also proved to be compatible with this catalytic system. For instance, the allyltrimethylsilane, allylbenzene, and phenylbutene could deliver the products **6d**–**6f** smoothly, albeit with moderate yields. Importantly, the simple, unfunctionalized terminal olefins, including isobutylethylene, 2,2-dimethyl-4-pentene and 1-decene, also performed well in target transformations (**6g**–**6i**).

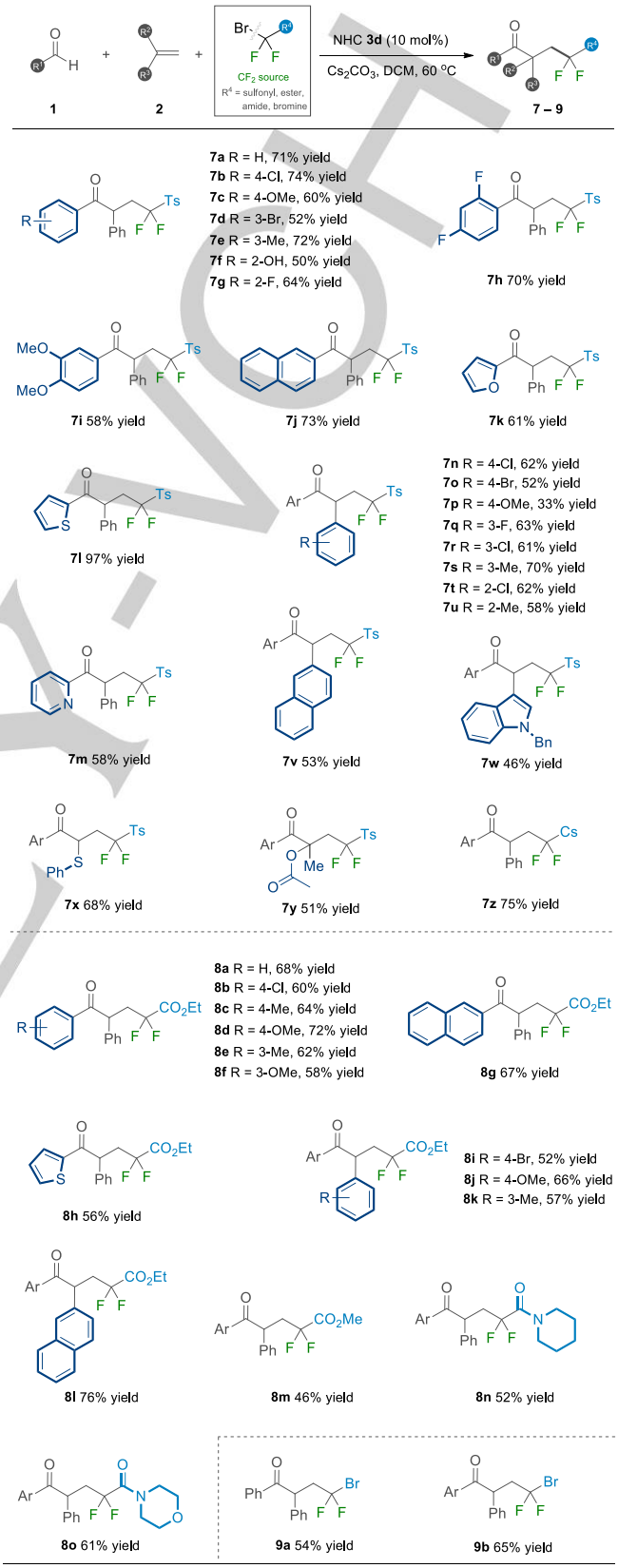
Table 3: Acyltrifluoromethylation of non-conjugated alkenes.[a]



[a] See SI for detailed experimental procedure; isolated yield. Ar = 4-Cl-C_6H_4.

As difluorinated substances also play a significant role in modern organofluorine chemistry,[18] we desired to expand the NHC organocatalytic strategy to include the radical acyldifluoroalkylation of various olefins. To our delight, a variety of the readily available difluoromethyl bromides could successfully participate in the reactions with a broad scope of

Table 4: Substrate scope for the acyldifluoromethylation.[a]



[a] See SI for detailed experimental procedure; isolated yield. Ar = 4-Cl-C_6H_4.

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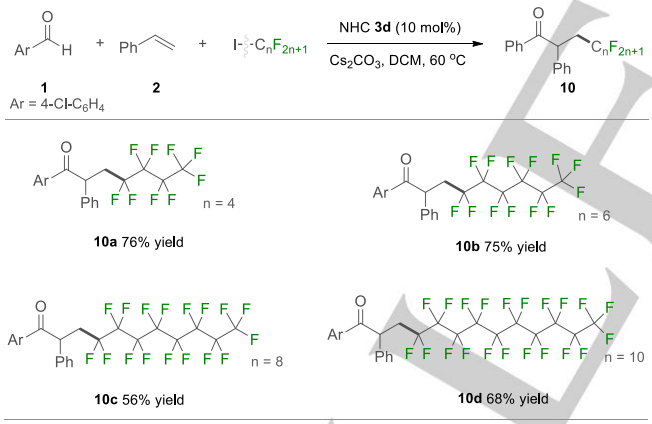
aromatic aldehydes and alkenes under the previously established catalytic conditions. As summarized in Table 4, the *p*-toluenesulfonyl (Ts)-substituted difluoromethyl radical could be readily generated and trigger a wide range of acyldifluoroalkylation with diversely substituted styrenes and aldehydes, affording the corresponding γ,γ-difluorinated ketones **7a**–**7w** in moderate to good yields. The non-conjugated phenyl vinyl sulfide and vinyl ester also proved to be compatible with the reaction, delivering **7x**–**7y** in satisfying yields. The tosyl substituent on the difluoroalkyl reagent could also be replaced with a *p*-chlorobenzenesulfonyl (Cs) moiety, and the related ketone **7z** was obtained in 75% yield. Similarly, general suitability and high functional group tolerance were also observed in the difunctionalization process by using the carboxylic ester- and amide-containing difluoromethyl reagents (**8a**–**8o**). Moreover, the commercially available, inexpensive dibromodifluoromethane could be directly used as the fluoroalkyl source in this NHC organocatalytic system to rapidly access the γ-trihalogented ketone derivatives from simple materials (**9a**–**9b**).

Encouraged by the success of difluoromethylation of olefins, the NHC-catalyzed radical perfluoroalkylation was immediately investigated. As illustrated in Table 5, various readily available perfluoroalkyl iodides featuring different lengths of the fluoroalkyl chain have proven to be suitable substrates, and the desired perfluorinated ketones **10a**–**10d** were facilely synthesized in 56%–76% yields.

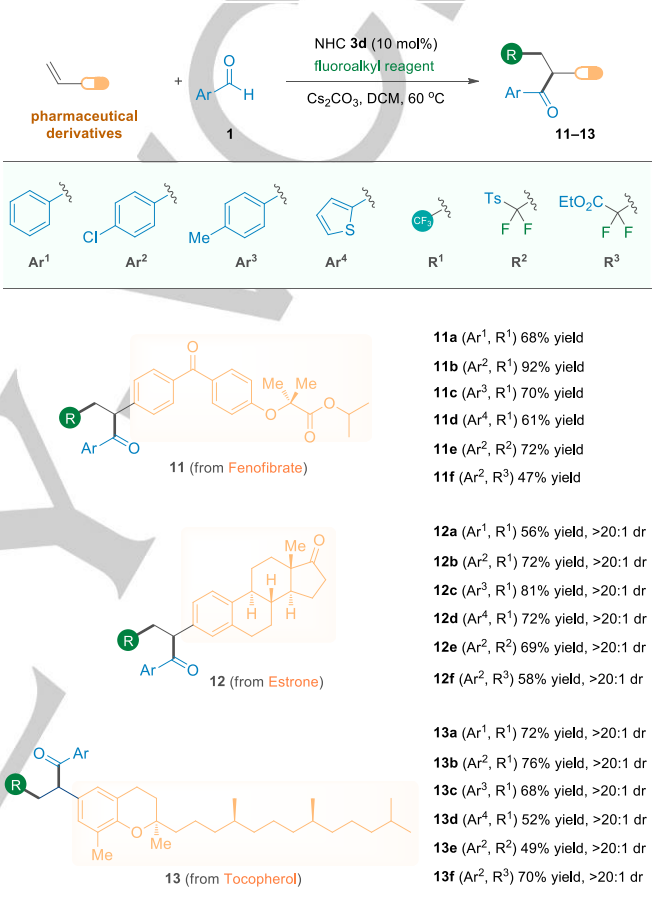
Table 5: NHC-catalyzed perfluoroalkylation of styrenes.[a]



[a] See SI for detailed experimental procedure; isolated yield.

To further highlight the practicability of this protocol, we applied the established metal-free catalytic system into the late-stage acylfluoroalkylation of pharmaceutical skeletons, and the results are summarized in Table 6.[19] First, the olefinic derivatives of fenofibrate, which is used clinically in treatment of hyperlipemia, was modified to simultaneously install a ketone and fluoroalkyl moiety under optimal conditions. Various aromatic aldehydes and fluoroalkyl sources were tested to afford the drug-like molecules **11a**–**11f** in moderate to excellent yields. Aside from the modification of achiral drugs, this method could be used to post-functionalize the enantioenriched pharmaceutical molecules in a highly diastereospecific manner. For example, the acylfluoroalkylation of estrone and tocopherol derivatives, both of which contain chiral stereocenters several chemical bonds away from the styrene moiety on the skeletons, exhibited excellent stereoselectivity without affecting the reaction efficiency. Either trifluoromethylation or difluoromethylation reaction would respectively afford the target molecules **12a**–**12f** and **13a**–**13f** in satisfying yields with uniformly >20:1 diastereoselective ratio.

Table 6: Stereoselective late-stage modification of drug derivatives.[a]



11a (Ar^1, R^1) 68% yield
11b (Ar^2, R^1) 92% yield
11c (Ar^3, R^1) 70% yield
11d (Ar^4, R^1) 61% yield
11e (Ar^2, R^2) 72% yield
11f (Ar^2, R^3) 47% yield

12a (Ar^1, R^1) 56% yield, >20:1 dr
12b (Ar^2, R^1) 72% yield, >20:1 dr
12c (Ar^3, R^1) 81% yield, >20:1 dr
12d (Ar^4, R^1) 72% yield, >20:1 dr
12e (Ar^2, R^2) 69% yield, >20:1 dr
12f (Ar^2, R^3) 58% yield, >20:1 dr

13a (Ar^1, R^1) 72% yield, >20:1 dr
13b (Ar^2, R^1) 76% yield, >20:1 dr
13c (Ar^3, R^1) 68% yield, >20:1 dr
13d (Ar^4, R^1) 52% yield, >20:1 dr
13e (Ar^2, R^2) 49% yield, >20:1 dr
13f (Ar^2, R^3) 70% yield, >20:1 dr

[a] See SI for detailed experimental procedure; isolated yield.

The rational of the observed remarkable stereoselectivity is probably because the sterically demanding NHC catalyst is actively involved in the C–C bond-forming event of the radical-radical recombination (see the proposed mechanism in Figure 3), which might govern the final stereoselective acylation process. It is worth noting that the diastereoselective control of a radical-mediated late-stage modification of chiral complex molecules remains a challenging issue in most previously reported reaction systems. The present NHC-catalyzed difunctionalization protocol exhibits a unique superiority in stereoselective radical transformations.

The practical synthetic utility of this method was demonstrated by a large-scale reaction, which proceeded smoothly to afford 1.11 g of the desired product **4a** in 80% yield (Scheme 1a). As another attractive direction, the chiral NHC-catalyzed asymmetric acyltrifluoromethylation was enthusiastically investigated.

10.1002/anie.201912450
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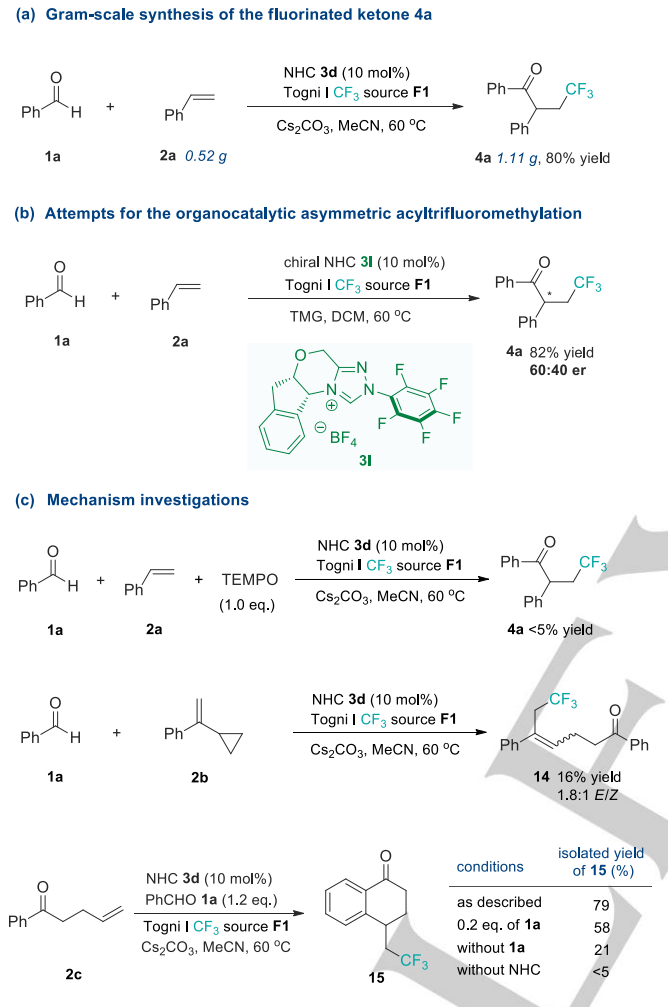
However, after extensive screening studies (for detailed optimizations, see Supporting Information), the use of Rovis' chiral NHC **3l** proved to be the best choice at the current stage,[20] and the enantioenriched product **4a** was obtained in 79% yield with 60:40 enantioselective ratio (Scheme 1b). Despite the observed poor level of enantiochemical outcomes, the great potential of the NHC-catalyzed asymmetric radical reactions was unambiguously demonstrated.[21]



Scheme 1. Further synthetic and mechanistic investigations.

To explore the mechanism of this transformation, several related experiments were performed. As shown in Scheme 1c, 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) could effectively inhibit the acyltrifluoromethylation process. In addition, a radical clock reaction was also investigated, and the cyclopropane moiety on the styrene could be opened to deliver a linear α-allylic ketone **14** as the sole product under standard catalytic reaction conditions. The results strongly suggest a radical mechanism for the present NHC-catalyzed acyltrifluoromethylations. As another specific evidence (Scheme 1c, bottom), an unacylated tetralone **15** was obtained with high isolated yield when 4-pentenophenone **2c** was used as the alkene substrate under standard conditions. In order to gain more insights into this specific transformation, several control experiments were performed. Reducing the loading of aldehyde **1a** to 0.2 equivalents led to a slightly decreased yield. The reaction could also occur in the absence of aldehyde **1a**, and the yield significantly reduced to 21%. No reaction was observed without the NHC catalyst. These experimental results indicate that the NHC species itself, as an electron-rich organic base, can trigger the single-electron reduction of Togni **I** reagent to initiate the radical chain reaction. If aldehydes were added into the reaction system, more electron-rich Breslow intermediate would be generated *in-situ* and induce the SET reduction process in a more efficient manner. Thus, the Breslow intermediate is probably able to serve as a versatile radical initiator, because its electronic and steric properties could be easily regulated through different combinations of various aldehydes and the NHC precursors.

On the basis of the above experimental evidence, a plausible reaction mechanism was suggested. As illustrated in Figure 3, the catalytic acylfluoroalkylation was started by the *in-situ* generation of deprotonated Breslow intermediate **I** from the NHC catalyst and aldehyde in the presence of base. Then, single-electron reduction of the fluoroalkyl reagent R*f*-X by the electron-rich **I** occurred, and two radical intemediates, a fluoroalkyl radical A and a persistent ketyl radical B, were generated. The addition of radical A to the styrene substrate produced a benzylic radical C. Subsequently, radical C was recombined with radical B through a radical–radical cross-coupling pathway to form intermediate **II**, and the fluoroketone product was delivered by releasing NHC to close the catalytic cycle.

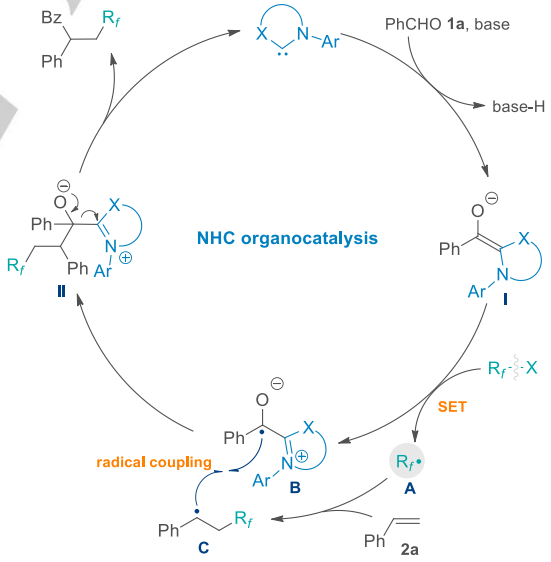


Figure 3. Proposed mechanism of the radical acylfluoroalkylation.

Conclusion

In summary, we have developed a NHC-catalyzed multicomponent acylfluoromethylation of alkenes in the presence of aldehydes and electrophilic fluoroalkyl reagents through a single-electron transfer process. As an emerging radical catalytic strategy, the NHC organocatalysis is compatible with a broad

spectrum of simple alkene substrates, including styrenes, cyclic internal alkenes, vinyl ethers, vinyl esters, and unactivated olefins, to achieve direct acyltrifluoromethylation. Notably, a dearomative difunctionalization of indoles could be readily achieved in a highly diastereoselective manner. This protocol was also compatible with various difluoroalkyl bromides bearing diverse functionalities, such as sulfonyl, ester, amide, and bromide moieties. Moreover, perfluoroalkylation could also be realized. With this strategy, over 120 examples of fluoroketones were facilely accessed from simple feedstock materials. The generality and practicality were highlighted by the late-stage modification of drug skeletons. In addition, preliminary results of the catalytic asymmetric version were achieved, indicating the great potential of NHC catalysis in radical-mediated enantioselective synthesis. Further investigations on the diversity oriented radical transformations through NHC organocatalysis are currently underway in our laboratory, and the results will be reported in due cause.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: NHC organocatalysis • radical acylfluoroalkylation • olefin difunctionalization • multicomponent reaction • fluoroketone

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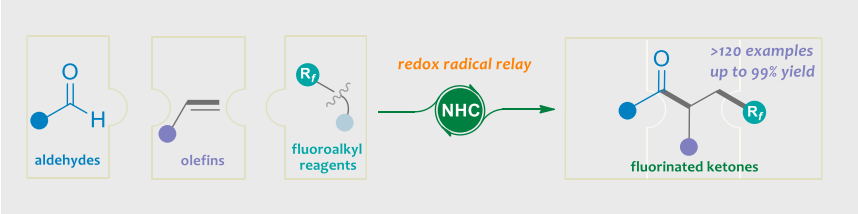

Organocatalytic Acylfluoroalkylation: A multicomponent radical acylfluoroalkylation of olefins through NHC organocatalysis was developed, and over 120 examples of fluoroketones were facilely accessed from simple materials. Moreover, a dearomative difunctionalization of indoles could be readily achieved in a highly diastereoselective manner. The generality and practicality were highlighted by the late-stage modification of drug skeletons.

Jun-Long Li, Yan-Qing Liu, Wen-Lin Zou, Rong Zeng, Xiang Zhang, Yue Liu, Bo Han, Yu He, Hai-Jun Leng, and Qing-Zhu Li**

Page No. – Page No.

Radical Acylfluoroalkylation of Olefins through *N*-Heterocyclic Carbene Organocatalysis