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FULL PAPER

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Selective C(sp^3)-H Functionalization of Alkyl Esters with *N*-/*S*-/*O*-Nucleophiles Using Perfluoroalkyl Iodide as Oxidant

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Abstract. An efficient transition metal-free approach to achieve the selective cleavage of the α-carbonyl C(sp^3)-H bond in alkyl esters by using inexpensive, low-toxic, and insensitive perfluoroalkyl iodide as the radical initiator has been developed. A variety of enamides, *N*-heterocycles, amides, thiophenols, and phenols could be successfully incorporated into functionalized alkyl groups by intermolecular amination, thioetherification, and etherification. The distinguishing features of this CDC reaction are its broad substrate scope, synthetic simplicity and mild reaction conditions.

Keywords: alkyl esters; C(sp^3)-H functionalization; perfluoroalkyl iodide; CDC reaction; transition metal-free

Introduction

The direct transformation of C-H bonds to C-X (X = C, O, N, S) bonds has advanced significantly by developing efficient and practical strategies for the synthesis of complex compounds with high atom-/step-economy, such as materials, pharmaceuticals, and natural products, starting from readily available molecules.[1] Among them, oxidative cross-dehydrogenative-coupling (CDC) reactions involving the activation of less reactive C(sp^3)-H bonds *via* radical pathway have been recognized as ideal and environmentally attractive tools because these methods usually does not require prefunctionalization of coupling partners and defunctionalization of directing groups.[2] In this context, an impressive range of synthetic strategies *via* free radical-initiated C(sp^3)-H bond functionalization of ethers,[3] alkyl nitriles,[4] alcohols,[5] amines,[6] ketones,[7] alkanes,[8] and active methylene compounds[9] have been developed in the past few decades (Scheme 1, 1). Nevertheless, there are still many issues associated with the generation of α-carbonyl radicals from simple alkyl esters under classical conditions, such as transition metal catalysis, an excess amount of strong oxidants, UV light irradiation, and high temperature.[10]

In 2014, Ji and coworkers reported a radical addition/1,2-aryl migration cascade of α,α-diaryl allylic alcohol with carbonyl compound in the presence of *tert*-butylperoxybenzoate (TBPB, 2 equiv.) at 120 °C (Scheme 1, 2a).[10a] However, the regioselectivity of hydrogen abstraction in the alkyl esters was problematic due to the similar bond dissociation energies (BDEs) of substrates' multiple C(sp^3)-H bonds. Instead, the cleavage of the C-H bond could also occur competitively at the α-position of the ethoxy group.[10b-c] In 2019, Tang group developed a site-selective α-alkoxy alkynylation of alkyl sulfones with alkynyl esters which was mediated by stoichiometric pyridine-ligated boryl radicals (Scheme 1, 2b).[10d] Compared with the complicated boryl reaction system, soon after, a visible-light-promoted alkylheteroarylation of unactivated olefins with esters was discovered by Xu and co-workers (Scheme 1, 2c).[10e] In their case, expensive photocatalyst and explosive peroxides should be

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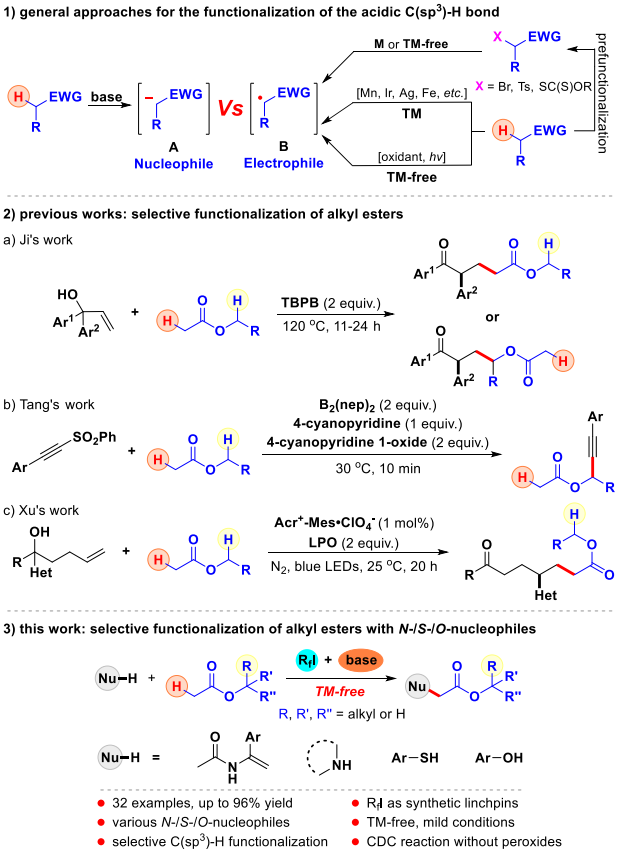
employed. Therefore, the development of new synthetic approach to achieve the selective functionalization of alkyl esters are still urgently demanded.

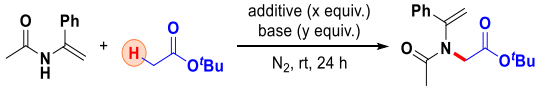


Scheme 1. General strategies for the functionalization of the acidic C(sp^3)-H bond.

Perfluoroalkyl halide, as a low-toxic and environmentally friendly perfluoroalkyl radical precursor,[11] has been extensively utilized as a unique promoter in the C(sp^3)-H bonds conversions through abstracting hydrogen atoms to afford hydrodehalogenated products over the direct perfluoroalkylated products.[12] Herein, we report a radical-type transformation[13] which involves site-selective oxidative C(sp^3)-H functionalization of alkyl esters with various *N*-, *S*-, and *O*-nucleophiles (Scheme 1, 3). The synthetic linchpin for realizing the incorporation of the alkyl ester moieties on *N*-/*S*-/*O*-atom centres[14] largely relies on the use of perfluorobutyl iodide (^{n}C$_4$F$_9$I) as an efficient oxidant. Moreover, this transition-metal-free approach involved new C(sp^3)–X (X = N, S, O) bond formations through a single electron transfer (SET) pathway, which overcomes the difficulty of the previously reported methods[10] and features broad substrate scope, good functional group compatibility, and synthetic simplicity in a green manner.

Results and Discussion

Table 1. Oxidative C(sp^3)-H functionalization of ^{t}BuOAc with enamide **1a**: optimization of reaction conditions[a]



Entry	Additive (x equiv.)	Base (y equiv.)	Yield (%)[b]
1	^{n}C$_4$F$_9$I (2.0)	NaOH (2.5)	31
2	^{n}C$_4$F$_9$I (2.0)	Et$_3$N (2.5)	0
3	^{n}C$_4$F$_9$I (2.0)	DABCO (2.5)	0
4	^{n}C$_4$F$_9$I (2.0)	Cs$_2$CO$_3$ (2.5)	0
5	^{n}C$_4$F$_9$I (2.0)	NaOAc (2.5)	0
6	^{n}C$_4$F$_9$I (2.0)	K$_3$PO$_4$ (2.5)	0
7	^{n}C$_4$F$_9$I (2.0)	^{t}BuONa (2.5)	99 (93)[c]
8	^{n}C$_4$F$_9$I (2.0)	^{t}BuOK (2.5)	21
9	^{n}C$_4$F$_9$I (2.0)	^{t}BuOLi (2.5)	trace
10	^{n}C$_4$F$_9$I (2.0)	LDA (2.5)	0
11	**^{n}C$_4$F$_9$I (2.0)**	**^{t}BuONa (2.0)**	**99 (93)[c]**
12	^{n}C$_4$F$_9$I (2.0)	^{t}BuONa (1.5)	70
13	^{n}C$_4$F$_9$I (1.5)	^{t}BuONa (2.0)	48
14	^{n}C$_4$F$_9$I (2.0)	^{t}BuONa (2.0)	52[d]
15	^{n}C$_6$F$_{13}$I (2.0)	^{t}BuONa (2.0)	58
16	^{n}C$_8$F$_{17}$I (2.0)	^{t}BuONa (2.0)	47
17	^{n}C$_4$H$_9$I (2.0)	^{t}BuONa (2.0)	12
18	C$_6$F$_5$I (2.0)	^{t}BuONa (2.0)	trace
19	I$_2$ (2.0)	^{t}BuONa (2.0)	29[e]
20	^{n}C$_4$F$_9$I (2.0)	^{t}BuONa (2.0)	10[e]
21	^{n}C$_4$F$_9$I (2.0)	^{t}BuONa (2.0)	16[f]

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (2 mL), additive (0.45-0.6 mmol), and base (0.45-0.75 mmol) at room temperature for 24 h under N$_2$. [b] Yields were determined by NMR analysis with 1,4-dimethoxybenzene as an internal standard. [c] Isolated yield. [d] For 12 h. [e] ^{t}BuOAc (20 equiv.) was used in DCE (2 mL). [f] ^{t}BuOAc (20 equiv.) was used in PhCF$_3$ (2 mL).

Initially, we started our investigation by using *N*-(1-phenylvinyl)acetamide (**1a**) as a nitrogen nucleophile,[15] along with *tert*-butyl acetate (**2a**, 2 mL) as both the reactant and solvent, in the presence of 2.0 equiv. of ^{n}C$_4$F$_9$I and 2.5 equiv. of NaOH at room temperature for 24 h under N$_2$ (Table 1, entry 1). Gratifyingly, it was found that the desired CDC reaction proceeded smoothly to afford the C–N bond-forming product **3aa** in 31% NMR yield (entry 1). Evaluation of various organic and inorganic bases (entries 2-10) led to the discovery of ^{t}BuONa as the best base for the oxidative coupling, whose loading could be further decreased to 2 equiv. (entries 11-12) affording the product **3aa** in 99% NMR yield and 93% isolated yield (entry 11). In addition, attempts to reduce either the amount of ^{n}C$_4$F$_9$I (1.5 equiv., entry 13) or the reaction time (12 h, entry 14) only gave rise to the corresponding product **3aa** in 48% and 52% NMR yields, respectively. Furthermore, low reaction efficiency was observed when other perfluoroalkyl iodides such as ^{n}C$_6$F$_{13}$I and ^{n}C$_8$F$_{17}$I were introduced into the reaction (entries 15-16). Interestingly, non-fluorinated ^{n}C$_4$H$_9$I[16] and perfluoroaryl iodide were found to be inferior to perfluoroalkyl iodide as the reaction promoters (entries 17-18). It might be due to

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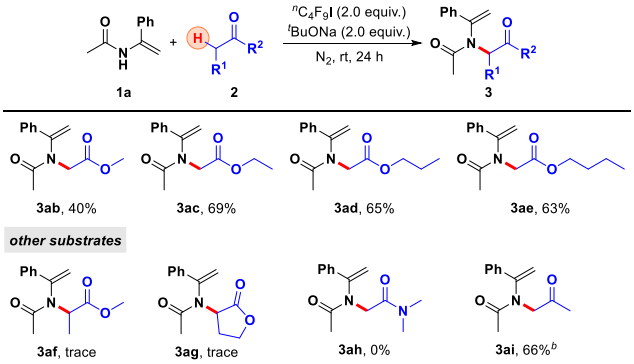
the formed reactive and strongly electrophilic R_f radicals[12] that perfluoroalkyl iodides (R_fI) could facilitate the activation of the C(sp^3)–H bond in *tert*-butyl acetate (**2a**). However, only 29% yield of product **3aa** was obtained by using I_2 as a promoter (entry 19). It should be noted that no competitive reaction occurred at the terminal C-C double bond of the *N*-acyl enamides under the optimized reaction conditions.[15] Moreover, performing the reaction with stoichiometric amounts of ^{t}BuOAc (20 equiv.) in 1,2-dichloroethane (DCE) or trifluorotoluene ($PhCF_3$) has been proven to be fruitless (entries 20-21).

Table 2. Oxidative C(sp^3)-H functionalization of various aliphatic C-H components **2** with enamide **1a**[a]

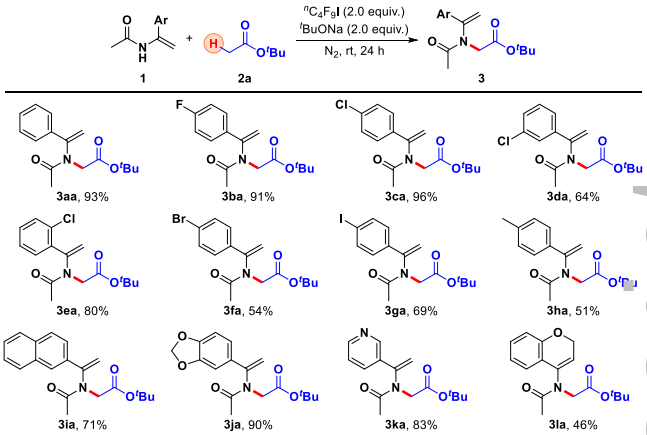


[a] Standard reaction conditions (0.3 mmol scale); isolated yield. [b] Cs_2CO_3 (3.3 equiv.) instead of ^{t}BuOK was used.

With the optimal reaction conditions in hand, we continued our task to explore the substrate scope of the present α-C(sp^3)-H amination, which delivered functionalized alkyl groups by intermolecular C-N bond formation. As summarized in Table 2, several commercially available alkyl acetates **2b**-**2e** were first applied to the reactions with enamide **1a**. Notably, in these cases, the methyl group adjacent to carbonyl group was the sole reactive site without affecting the existing ester functionality, and exclusive products **3ab**-**3ae** were produced in moderate to good yields. However, other variants such as methyl propionate (**2f**), lactone **2g**, and acetamide **2h** were proven to be inappropriate candidates for the present reaction system. Nevertheless, acetone was found to be suitable for this oxidative C-N coupling reaction, furnishing the product **3ai** in 66% yield by using Cs_2CO_3 as the base.

Next, the substrate generality with respect to various enamides **1** was examined in the perfluorobutyl iodide-mediated oxidative coupling (Table 3). To our delight, a variety of *N*-vinylacetamides **1** containing different substituents with varying electronic characteristics (electron-donating or electron-withdrawing) or steric demands (*para*-, *meta*-, and *ortho*-) on the aryl moieties smoothly coupled with ^{t}BuOAc (**2a**) to furnish the corresponding products **3aa**–**3ha** in 51-96% yields. Impressively, functional moieties of synthetic potential such as F, Cl, Br, and I were well-tolerated, which could be retained for late-stage manipulation. In addition, the use of naphthalenyl, benzo[*d*][1,3]dioxoly, and pyridinyl substituted enamides could also deliver the products **3ia**-**3ka** in 71-90% yields. Furthermore, the presence of α-substituent in *N*-vinylacetamide did not interfere with the intermolecular reaction, as cyclic substrate **1l** efficiently underwent the present organic transformation to provide the product **3la** in 46% yield.

Table 3. Oxidative C(sp^3)-H functionalization of ^{t}BuOAc with various enamides **1**[a]



[a] Standard reaction conditions (0.3 mmol scale); isolated yield.

Subsequently, the present protocol was successfully extended to the use of a wide range of structurally varied *N*-, *S*-, and *O*-nucleophiles (Table 4). Heterocyclic compounds bearing free N-H motifs such as benzimidazoles and 1,5,6,7-tetrahydro-4*H*-indol-4-one, were transformed into the *N*-alkylated products **5a**-**5d** in 34-51% yields after a prolonged reaction time. In addition, by switching to acetyl-substituted sulfonamide, moderate conversion to the amination product **5e** was still achieved. Based on diverse structural library design for pharmaceutical chemistry, important *S*-nucleophiles were selected as coupling partners to accomplish thioetherification of *tert*-butyl acetate. For instance, thiophenols containing different substituents (halides, methyl, and methoxy group) well participated in this reaction, leading to thioethers **6a**–**6g** in 56-95% yields. Additionally, heteroaryl *S*-nucleophiles including 2-methylfuran-3-thiol and benzo[*d*]thiazole-2-thiol were compatible with the mild reaction conditions to give the corresponding heterocyclic variants **6h** and **6i** in 43% and 51% yields, respectively. In a same manner, the reaction of 4-methoxyphenol worked equally well with ^{t}BuOAc to afford the etherification product **7a** in 41% yield.

We also performed the large-scale synthesis of *tert*-butyl *N*-acetyl-*N*-(1-phenylvinyl)glycinate (**3aa**), which could serve as versatile building block to prepare various multi-substituted amines and olefin derivatives **8**,[15] leading to 61% yield of the corresponding product **3aa** (Scheme 2, 1). In order to clarify the putative mechanism of the selective C(sp^3)-H functionalization process, several control experiments were performed. Firstly, when radical scavenger of 2,2,6,6-tetramethylpiperidin-1-oxyl

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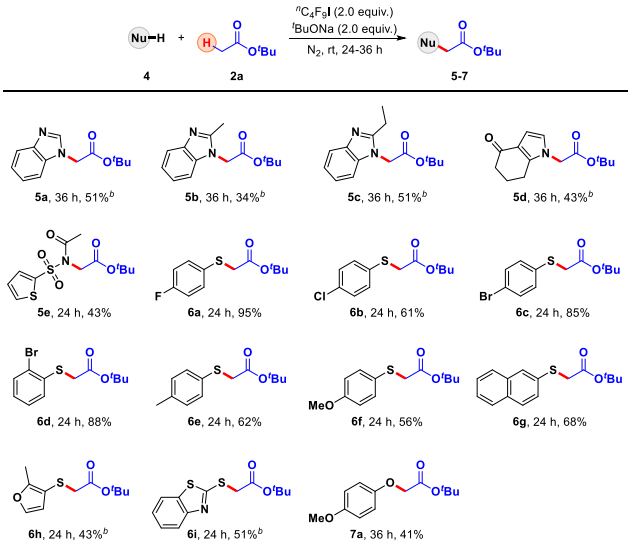
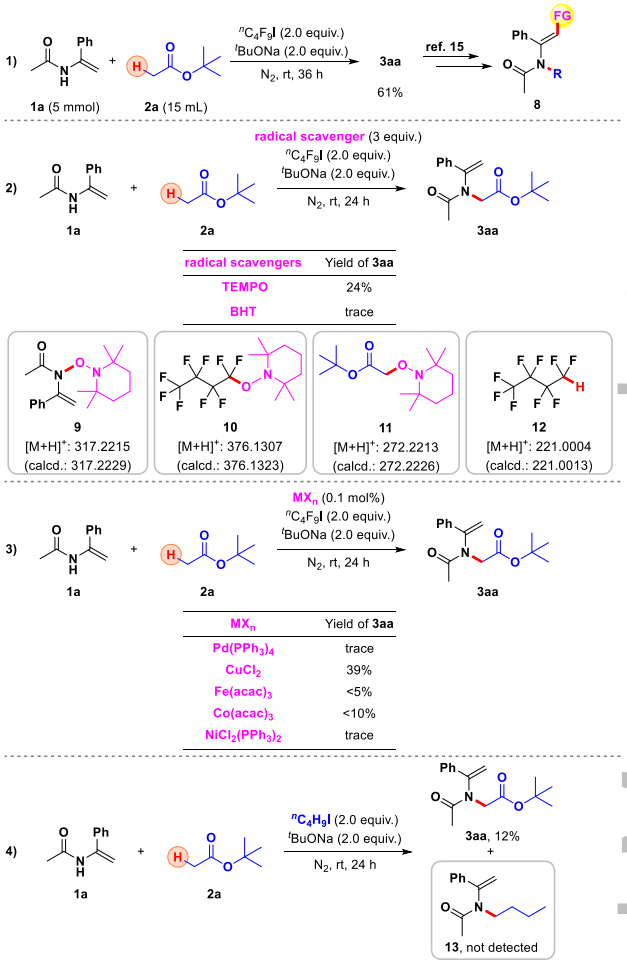
(TEMPO, 3 equiv) was added to the model reaction under standard reaction conditions, the yield of product **3aa** was dramatically decreased to 24%, indicative of the involvement of a radical-type mechanism in the reaction (Scheme 2, 2). Meanwhile, the formation of TEMPO-adduct **9-11** were detected by LC-MS which suggested that *N*-centered radical,[17] $^{n}C_4F_9$ radical, and α-C-centered radical of alkyl ester[10] might be involved in this process (see the Supporting Information for more details). Secondly, the addition of 3.0 equiv. of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as radical scavenger completely suppressed the formation of **3aa**. Moreover, 1,1,1,2,2,3,3,4,4-nonafluorobutane (**12**, R_f-H) was detected in these reactions by LC-MS, implying that $^{n}C_4F_9I$ might work as the H-abstraction reagent (see Supporting Information for more details). Thirdly, we found that the addition of 0.1 mol% of $Pd(PPh_3)_4$, $CuCl_2$, $Fe(acac)_3$, $Co(acac)_3$, or $NiCl_2(PPh_3)_2$ to the reaction system did not obviously enhance the reaction performance, and in some cases the reaction efficacy was even reduced, which indicated that the transformation was not catalyzed by trace metal impurities possibly brought from the added reagents and solvent (Scheme 2, 3). Finally, the aminated product **3aa** was obtained in a relatively low yield when 1-iodobutane, instead of $^{n}C_4F_9I$, was used (Scheme 2, 4). In contrast, the direct alkylated product **13** was not formed in the reaction, indicating that *N*-nucleophilic substitution of enamides might not be the main reaction pathway.

Table 4. Oxidative C(sp^3)-H functionalization of ^{t}BuOAc with various *N*-/*S*-/*O*-nucleophiles[a]

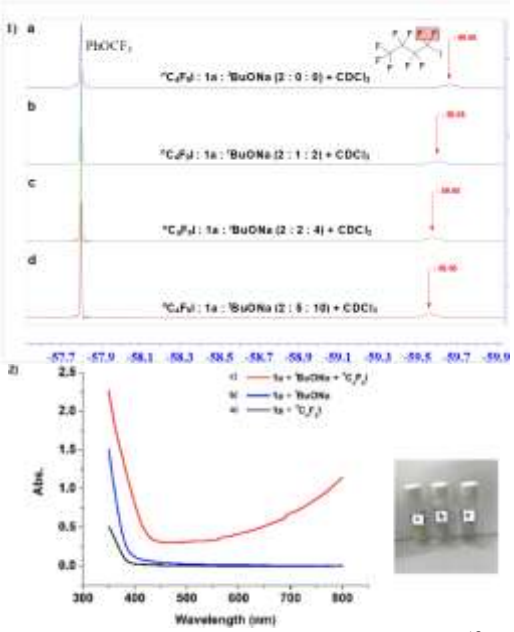


[a] Standard reaction conditions (0.3 mmol scale); isolated yield. [b] ^{t}BuOK (3.3 equiv.) was used.

The ^{19}F NMR titration experiment and UV-Vis spectroscopic measurement were performed on various combinations of *N*-(1-phenylvinyl)acetamide (**1a**), $^{n}C_4F_9I$, and ^{t}BuONa, which proved the formation of electron donor-acceptor (EDA) complex in the reaction (Scheme 3). First, the ^{19}F NMR signal of CF_2I moiety shifted upfield when the amount of **1a** and ^{t}BuONa increased (Scheme 3, 1). Second, we also observed a red shift of absorption and color change when enamide **1a**, $^{n}C_4F_9I$, and ^{t}BuONa were combined in ^{t}BuOAc (Scheme 3, 2). These results indicated the formation of EDA complex between **1a** and $^{n}C_4F_9I$.



Scheme 2. A large-scale synthesis and control experiments



Scheme 3. Studies of the EDA complex. 1) ^{19}F NMR

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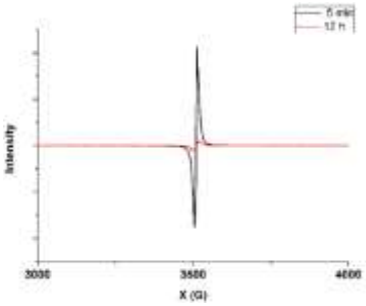
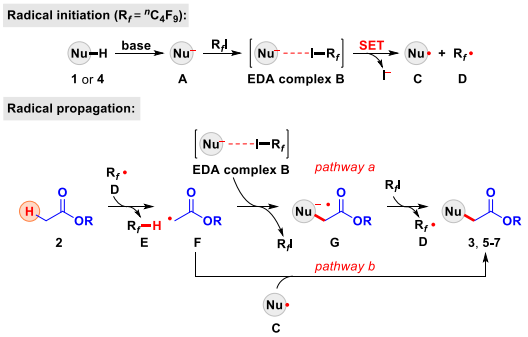
titration by using $PhOCF_3$ as an internal standard in $CDCl_3$. 2) Optical absorption spectra recorded and the color change of different combinations of **1a**, C_4F_9I, and ^{t}BuONa in ^{t}BuOAc.

The radical nature of this reaction was further confirmed by electron paramagnetic resonance (EPR) experiment (Scheme 4). A strong single EPR signal (g = 2.00) was observed in ^{t}BuOAc solution of *N*-(1-phenylvinyl)acetamide (**1a**), ^{n}C_4F_9I, and ^{t}BuONa at room temperature (black line). We also found that the EPR signal was attenuated after 12 h (red line).



Scheme 4. Electron paramagnetic resonance (EPR) experiment

On the basis of above control experiments and literature survey,[11-14] a plausible mechanism of radical chain process was depicted in Scheme 5. The initiation of the reaction begins with the deprotonation of nucleophiles **1** or **4** under basic conditions. Next, the interaction of transiently formed anion **A** with perfluorobutyl iodide leads to the generation of EDA complex **B**, which subsequently affords strongly reactive ^{n}C_4F_9 radical **D** and *N*-/*S*-/*O*-centered radical **C** after an intramolecular single electron transfer from anion **A** to ^{n}C_4F_9I.[12] Due to its high electrophilicity and pyramidal geometry, the perfluoroalkyl radical **D** could then selectively abstract the α-C(sp^3)-H of alkyl ester **2** adjacent to the carbonyl site to produce the hydrofluorocarbon **E** (R_f-H) and alkyl radical **F**.[11] The latter could be trapped by another molecule of nucleophilic anion from EDA complex **B** to generate the unstable radical anion **G**, which could be easily oxidized by the ^{n}C_4F_9I oxidant to give the CDC product and regenerate the radical species **D** (pathway a). Alternatively, the direct cross-coupling of the radicals **C** and **F** could also lead to the formation of final product (pathway b). However, the low concentration of these open-shell radical species made it difficult for the intermolecular coupling to take place.[18]



Scheme 5. Proposed mechanism.

Conclusion

In summary, we have developed an oxidative strategy for C(sp^3)-H functionalization of alkyl esters with various *N*-/*S*-/*O*-nucleophiles under transition metal-free conditions. A distinguishing feature of this method is that the inexpensive, low-toxic, and insensitive perfluoroalkyl iodide could be used as efficient oxidant to selectively abstract the less reactive α-C(sp^3)-H of carbonyl group rather than the α-C(sp^3)-H of alkoxy group in alkyl esters, leading to regioselective C-X (X = N, S, O) bond formation. Moreover, the broad substrate scope, mild reaction conditions, and synthetic simplicity inarguably provides chemists an alternative entry for site-selective alkylation by using simple alkyl esters. In addition, mechanistic studies revealed that the reaction presumably proceeded *via* a radical chain propagation process.

Experimental Section

General procedures for the oxidative C(sp^3)-H functionalization of aliphatic C-H components with *N*-/*S*-/*O*-nucleophiles

A solution of *N*-/*S*-/*O*-nucleophile (0.3 mmol), aliphatic C-H component (2 mL), perfluorobutyl iodide (208 mg, 0.6 mmol), and ^{t}BuONa (58 mg, 0.6 mmol) was stirred under nitrogen atmosphere at room temperature for 24-36 h. The reaction was then quenched by saturated NH_4Cl solution (20 mL) and diluted with EtOAc (20 mL). The organic layer was washed with saturated brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (300-400 mesh) using petroleum ether/ethyl acetate or dichloromethane/methanol as eluent to afford the pure products **3** or **5**-**7**.

Acknowledgements

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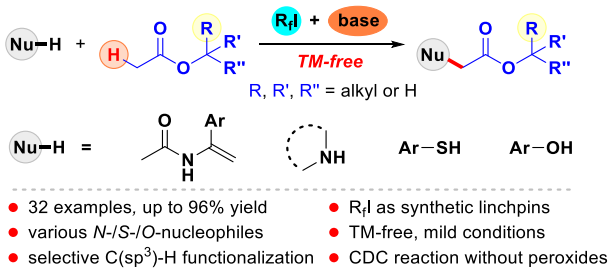

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