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Authors: Weigang Zhang, Zhenlei Zou, Yuanheng Wang, Yi Wang, Yong Liang, Zhengguang Wu, Youxuan Zheng, and Yi Pan

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A General Leaving Group-Assisted Strategy for Photoinduced Fluoroalkylations using *N*-Hydroxybenzimidoyl Chloride Esters

Weigang Zhang,[#] Zhenlei Zou,[#] Yuanheng Wang, Yi Wang,* Yong Liang,* Zhengguang Wu,* Youxuan Zheng and Yi Pan

Abstract: Redox-active esters (RAEs) as alkyl radical precursors have been extensively developed for C-C bond formations. However, the analogous transformations of fluoroalkyl radicals from the corresponding acid or ester precursors remain challenging due to the high oxidation potential of the fluoroalkyl carboxylate anions. The newly developed N-hydroxybenzimidoylchloride (NHBC) ester provides a general leaving group-assisted strategy to generate a portfolio of fluoroalkyl radicals, which can be successfully applied in decarboxylative hydrofluoroalkylation photoinduced and heteroarylation of unactivated olefins. In addition, DFT calculations revealed that the NHBC ester was in favor of fluorocarbon radical pathway while other well-known RAEs were in preference of the nitrogen radical pathway.

The wide application of fluorinated compounds in agrochemicals, pharmaceuticals and materials science has triggered every endeavor to develop efficient methods for selective incorporation of a fluoroalkyl group into organic molecules.¹ Despite progress in the past decade, the existing trifluoromethylation reagents require multistep syntheses and costly starting materials.²⁻⁵ The well-documented redox-active esters (RAEs) as alkyl radical precursors appear to be feasible strategy for C-C bond formation, some of which taking the advantage of the weak N-O bond cleavage and decarboxylative fragmentation. However, the analogous transformations of fluoroalkyl radicals (•CF₃, •CF₂H, •C₂F₅, etc.) generating from the corresponding acids or esters have confronted inevitable difficulties⁶⁻¹⁰ due to the high oxidation potential of the fluoroalkyl carboxylate anions (e.g. CF_3CO_2 $E_{1/2}^{ox}$ > +2.4V vs SCE) (Figure 1A).⁶ For the mere reason, the versatile N-hydroxyphthalimide (NHPI) esters found unable to engage in decarboxylative radical trifluoromethylation in a photocatalytic manner.¹¹ As Sanford demonstrated, increasing the electron withdrawing character of the alkyl substituent on NHPI ester (CF3 in particular) resulted in the formation of PhthN• and the release of CF₃CO₂⁻¹² Recently, Stephenson and co-workers have taken an in-situ activation strategy using pyridine N-oxide to activate volatile TFAA for radical trifluoromethylations of arenes (Figure 1B).13 The development of practical and air-stable redox-active fluoroalkylating agents using inexpensive fluorine sources still represents unmet challenge and urgent demand.

Drawing inspiration from the work of Leonori and Studer on photoredox single-electron reductions of oximes to provide iminyl radicals¹⁴, we envisioned that the cleavage of weak N-O bond (BDE = $54 \text{ kcal} \cdot \text{mol}^{-1}$) could also generate an oxygenated

Weigang Zhang, Zhenglei Zou, Yuanheng Wang, Dr. Zhengguang Wu, Prof. Yi Wang*, Prof. Yong Liang* and Prof. Yi Pan State Key Laboratory of Coordination Chemistry, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210023, China *E-mail: yiwang@nju.edu.cn; yongliang@nju.edu.cn *These authors contribute equally to this work.

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Figure 1. Origin of the Reaction Design.

radical by manipulating the nature of the electron affinity of the oxime.¹⁵ Indeed, by simply installing a chlorine to oxime, the stabilized electron-rich imine in harness, for surpassing the strong electron-withdrawing effect of CF₃ group in the redoxactive ester, in favor of generating TFA radical and iminyl anion. Thus, the CF₃-bearing *N*-hydroxybenzimidoyl chloride (NHBC) ester **1a** (E_{1/2}^{red} -1.09V *vs* SCE) should be activated by photocatalyst Ir(III)* to release benzonitrile, chloride, CO₂ and generate **•**CF₃ *via* N-O bond breaking followed by decarboxylative fragmentation (Figure 1B). Herein, we report a general strategy for photoinduced fluoroalkylation of unactivated olefins using bench-stable redox-active NHBC esters.¹⁶

ns.

R Ph	+ CI N-0 CF3	BF _{3.} Et ₂ p-Me-C ₆ H Ir[{dF(CF ₃)ppy} ₂ (MeCN (2.0 m	O (2.5 equiv) ₄ SH (2.5 equ dtbbpy)]PF ₆ (nL), rt, Ar, blu	v) 10 mol%) e LED Ph	
2a (0.2 mmol)	1a (R=H, 2 equiv)				3a
Entry	Variati	on from the react	ion conditio	ons Yield (%	5) ^[a]
1		none		79	
2	Ir(ppy) ₃ instead			54	
3	Ir[(dtbbpy)(ppy) ₂]PF ₆ insted			18	
4		78			
5	1c (R = CI) instead			73	
6	1d ($R = NO_2$) instead				
7	6 mol% Ir loading 81 ^{[t}				1
8	Without photocatalyst				
9	Without BF ₃ .Et ₂ O			56	
[a] Crude	yields determi	ned by ¹⁹ F	NMR	spectroscopy	using
hexafluorobe	enzene as an inter	nal standard. [b	ol 74% iso	lated vield.	

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Scheme 1. Substrate Scope of the Hydrotrifluoromethylation Reaction with Condition A: 0.2 mmol of **2**, 2.0 equiv of **1** (**1a** isolated, **1j** and **1k** in situ), 2.5 equiv. of BF₃·Et₂O, 2.5 equiv. of *p*-toluenethiol, 6 mmol% of Ir[{dF(CF₃)ppy}₂(dtbbpy)]PF₆, 2 mL of CH₃CN at room temperature. [a] The reaction was conducted for 36 h. [b] The ratios of diastereomers were determined by ¹H and ¹⁹F NMR.

To determine the suitable conditions for NHBC-initiated radical fluoroalkylation, we first studied the hydrotrifluoromethylation^{3,4} of butenylbenzene (2a) in the presence of trifluoroacetoxyarylimidoyl chloride (1a-1d, 2 equiv), 2.5 equivalents each of BF3·OEt2 and p-toluenethiol with a survey of iridium catalysts in acetonitrile at room temperature (Table 1). $Ir[{dF(CF_3)ppy}_2(dtbbpy)]PF_6$ (PC1) was able to promote the radical fragmentation to afford the desired trifluoromethylated product 3a in 79% yield. When using $Ir(ppy)_3$ (PC2) and Ir[(dtbbpy)(ppy)₂]PF₆ (PC3), low to moderate yields were obtained (entries 2-3). When switching 1a to electron-donating group substituted NHBC esters 1b and 1c, similar yields were achieved (entries 4-5), while electron-withdrawing substitution showed very poor result (entry 6). Decreasing the catalyst loading to 6 mol% did not affect the reaction (entry 7). In the absence of BF3•Et2O, the yield decreased to 56%, and a small amount of chlorinated byproduct was observed (entry 8).¹⁷ Thus, the optimized conditions were selected for further investigation of the reaction scope.

Using 6 mol% of the iridium catalyst, trifluoroacetoxybenzimidoyl chloride (2.0 equiv), and thiol (2.5 equiv) at ambient temperature, a range of unactivated terminal and internal alkenes underwent hydrotrifluoromethylation with good regioselectivity (Scheme1). Terminal alkenes bearing amide (3b-3g) and ester (3h-3g) functionalities were tolerated in this NHBC-initiated radical process. Sulfonamide (3r), sulfonate (3s), and oxygenated alkyl (3u-3y) substituted alkenes also furnished the corresponding CF3 adducts. Notably, the unsaturated carboxylic acid (3t) which was susceptible to decomposition in other RAE conditions could be well-adopted in this catalytic system. In addition, alanine and boldenone-derived terminal alkenes were compatible to afford the trifluoromethylated products in high yields (3z and 3aa). Internal alkenes also transformed into the desired products 3bb (diastereomeric ratio of 3:1) and 3cc. Moreover. perfluoroalkylated NHBC esters 1j and 1k were prepared and reacted with unactivated olefins in the same manner to afford the corresponding products 3dd and 3ee in high yields.

With slight variation of the optimized conditions, we expanded the scope of this NHBC strategy to difunctionalization of unactivated olefins.¹⁸ Using heteroaryl-substituted unsaturated tertiary alcohol, the distal migration induced by radical fluoroalkylation could go smoothly in chemoselective fashion. Various fluoroalkyl radicals including $\cdot CF_2H$, $\cdot CF_3$, $\cdot C_2F_5$ and $\cdot C_3F_7$ were susceptible to the reaction conditions to acheive corresponding ketones in good to excellent yields (Scheme 2). The migration of substituted benzothiazoles (**5y**) and thiazoles also took place (**5n**, **5o**, **5u** and **5w**). The aryl group with different electronic and steric characters were tolerated (**5a**-**5j** and **5p**-**5r**). Linear or cyclic alkyl substituted alcohols could also furnish the diffunctionalized products (**5k**-**5m**, **5s** and **5x**). Increasing the steric hindrance around the olefin led to slightly decreased yield (**5t**).



Scheme 2. Substrate Scope of the Aryl Migration Reaction with Condition B

Furthermore, this fluorine-bearing RAE protocol was applied to the fluoroalkylation of diallylic and alkynyl substrates (Scheme 3). NHBC ester-derived $\cdot R_F$ precursors were employed in intramolecular cyclization processes with diallyl sulphonamides, and diesters to afford the corresponding fluorinated products (**7a**-**7f**) in good diastereomeric ratios (1.5:1 to 13:1). Phenylpropiolate **8** was also submitted to the standard conditions to furnish chromenones **9a** and **9b**.¹⁹

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Scheme 3. Further Elaborations.

To gain insight into this fluoroalkyl radical formation, we conducted computational studies using DFT calculations (M06-2X with solvation).²⁰⁻²² We compared the thermodynamics for the generation of nitrogen radical or oxygen radical. As shown in Figure 2A, when Sanford's CF₃-NHPI reagent gets an electron, the formation of PhthN radical and TFA anion is favored by 14.0 kcal mol⁻¹ as compared to the formation of TFA radical and PhthN anion. This is consistent with their experiments.¹² In the case of our CF3-bearing NHBC ester, the radical formation selectivity is reversed (Figure 2B). Calculations indicate that the chloro-imine anion is not a minimum in the potential energy surface, which decomposes into benzonitrile and chloride spontaneously. Since chloride is a good leaving group, this process is highly exergonic, making the formation of TFA radical 1.2 kcal mol⁻¹ lower in Gibbs free energy than that for TFA anion. Therefore, CF₃ radical would be generated predominantly from the decarboxylation of TFA radical, while a small amount of chlorine radical would be formed from the decomposition of chloro-imine radical. This accounts for our experimental results and confirms our hypothesis on the leaving group assisting effect. Similar trends are observed for perfluoroalkyl radicals $C_2F_5^{\bullet}$ and $C_3F_7^{\bullet}$, which are favored by 0.3 and 1.0 kcal mol⁻¹ in Gibbs free energy respectively. In the case of difluoromethyl radical, a 7.3 kcal mol⁻¹ Gibbs free energy difference was expected, indicating that the generation of •CF₂H is extremely favorable for its NHBC ester.



Figure 2. DFT Study on the selectivity of radical formation.

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In summary, we have developed a leaving group assisted strategy for generating a portfolio of fluoroalkyl radicals from redox-active N-hydroxybenzimidoyl chloride esters, which has been successfully employed in the photoinduced hydrofluorination and arylation of unactivated alkenes. Compared with the commonly used fluorinating reagents, the fluorine-bearing NHBC esters are air-stable non-volatile crystalline solid, readily achievable in large quantities from their fluorocarboxylic acid, and easy to initiate under mild photocatalytic conditions. Further study of NHBC-derived RAEs is underway in our laboratory.

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Keywords: Fluoroalkylation • photoredox • olefins • imidoyl chloride

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	+ R L Fluorination	PC ewis Acid, hv, rt	FG RF
$\begin{array}{c} CI^{F} & AF \\ \hline -ArCN \\ -CO_{2} \\ -CI^{+} \\ \hline R_{F} & \overline{LG} \\ R_{F} = CF_{3}, \end{array}$	CF ₃ -bearing RAEs Chap precursors Air and moisture-sta rminal & Internal Alkenes -assisted RAE Strategy CF ₂ H, C ₂ F ₅ , C ₃ F ₇	Mild reaction conditions Broad substrate scope ble trifluoromethylating agent R_RF <u>H donor or Aryl</u> HAT	65 examples up to 94% yields t Migrate

The newly developed N-hydroxybenzimidoyl chloride (NHBC) ester provides a general leaving group-assisted strategy to generate a portfolio of fluoroalkyl radicals, which can be successfully applied in photoinduced decarboxylative hydrofluoroalkylation and heteroarylation of unactivated olefins.

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