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Authors: Ji-Chang Xiao

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Photocatalyzed Cyanodifluoromethylation of Alkenes

Min Zhang, Jin-Hong Lin, and Ji-Chang Xiao*

Dedicated to Professor Qing-Yun Chen on the occasion of his 90th birthday

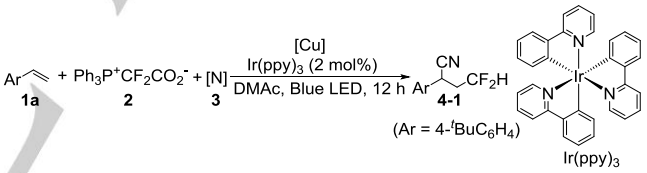
Abstract: Photocatalyzed cyanodifluoromethylation of alkenes with a $Ph_3P^+CF_2CO_2^-$/$NaNH_2$ (or NH_3) system is described. $Ph_3P^+CF_2CO_2^-$ acted as both the HCF_2 source and CN carbon source, and the cyanide anion was generated in situ under mild conditions, avoiding the use of toxic cyanation reagents.

The difluoromethyl group (HCF_2) can act as a lipophilic hydrogen bond donor and a bioisostere of hydroxyl or thiol groups,[1] and it has found widespread application in pharmaceutical chemistry and agrochemistry.[2] During the past decades, a number of HCF_2-based pharmaceuticals and agrochemicals, such as Eflornithine, Deracoxib, Sedaxane, Isopyrazam, Bixafen, and Thiazopir, have been developed.[2] The incorporation of a HCF_2 group into organic molecules has garnered significant attention.[2-3] Because difluoromethylation is the most straightforward strategy for incorporation of HCF_2 in organic molecules, many difluoromethylation reagents have been developed,[4] such as $TMSCF_2H$[5] and XCF_2H (X=F, Cl, or Br)[6]. Simultaneous incorporation of a second functional group into molecules would allow further transformation; the second functional group could also have excellent potentials for the design of pharmaceuticals and agrochemicals. Therefore, much effort has been devoted to the development of efficient methods for difluoromethylative difunctionalization of alkenes, including hydrodifluoromethylation,[7] carbodifluoromethylation,[8] oxydifluoromethylation,[9] and halodifluoromethylation[10].

The nitrile group (CN) is a versatile functionality in synthetic chemistry and life sciences, and thus cyanation has received increasing attention.[11] Various cyanation reagents have been developed, such as NaCN, KCN, and TMSCN.[11] However, many of these reagents are volatile or highly toxic, or harsh reaction conditions such as a high reaction temperature (130 – 150 °C) are required for the cyanation reaction. Considering the importance of HCF_2 and the potential derivatization of CN, the incorporation of both of these groups into organic molecules would be worthwhile. However, efficient cyanodifluoromethylation of alkenes under mild conditions remains a challenging task. On the basis of our recent observation that $Ph_3P^+CF_2CO_2^-$ reacts with elemental sulfur (S_8) to generate thiocarbonyl fluoride (CF_2=S),[12] we envisioned that $Ph_3P^+CF_2CO_2^-$ could be trapped by a suitable nitrogen source to produce a cyanide anion (CN^-). Inspired by the discovery of cyanotrifluoromethylation of alkenes,[13] we investigated the cyanodifluoromethylation of alkenes with $Ph_3P^+CF_2CO_2^-$ in the presence of a nitrogen source and without external addition of any CN^- source.

Photoredox catalysis has proven to be a valuable synthetic tool and $Ir(ppy)_3$ has become one of the most commonly used photocatalysts.[14] Therefore, we screened the cyanodifluoromethylation of alkene **1a** with the $Ph_3P^+CF_2CO_2^-$/$NaNH_2$ system under photocatalytic conditions by using $Ir(ppy)_3$ as the photocatalyst. Because a copper source is usually required in cyanotrifluoromethylation of alkenes,[13] various Cu complexes were examined (entries 1–4) and CuI was found to be a superior choice (entry 1). Increasing the loading of $Ph_3P^+CF_2CO_2^-$ led to an increase in the yield (entries 6–8). A 78% yield was obtained when 3 equiv. of $NaNH_2$ (entry 9) was used. The use of 10 mol % of CuI afforded an 83% yield of the corresponding product (entry 10), whereas almost no desired product was detected without the addition of CuI (entry 11). Both a photocatalyst [$Ir(ppy)_3$] and light source (blue LED) were essential for this reaction, and the expected conversion was completely suppressed when one of them was not used (entries 12–13). The use of TMSCN as the cyanide source only gave a low yield under these conditions (entry 14). Other nitrogen sources of the nitrile group were also screened (entries 15–19), and ammonia (NH_3) was also an efficient source (entry 15). In the case of ammonium carbamate ($NH_2CO_2NH_4$) as a nitrogen source, the yield was decreased dramatically (entry 16).

Table 1. Optimization of reaction conditions[a]



Entry	**3**	[Cu]	**1a**:**2**:**3**:[Cu]	Yield (%)[b]
1	$NaNH_2$	CuI	1:2:2:0.2	28
2	$NaNH_2$	CuCN	1:2:2:0.2	13
3	$NaNH_2$	$CuBr_2$	1:2:2:0.2	21
4	$NaNH_2$	$Cu(OAc)_2$	1:2:2:0.2	21
5	$NaNH_2$	CuI	1:1.5:2:0.2	16
6	$NaNH_2$	CuI	1:3:2:0.2	57
7	$NaNH_2$	CuI	1:4:2:0.2	64
8	$NaNH_2$	CuI	1:4.5:2:0.2	66
9	$NaNH_2$	CuI	1:4.5:3:0.2	78
10[c]	$NaNH_2$	CuI	1:4.5:3:0.1	83
11[c]	$NaNH_2$	-	1:4.5:3:0	trace
12[c][d]	$NaNH_2$	CuI	1:4.5:3:0.1	ND
13[c][e]	$NaNH_2$	CuI	1:4.5:3:0.1	ND
14[c]	TMSCN	CuI	1:4.5:3:0.1	38
15[f]	NH_3	CuI	1:4.5:4.9:0.1	83
16[c]	$NH_2CO_2NH_4$	CuI	1:4.5:3:0.1	42
17[c]	NH_4BF_4	CuI	1:4.5:3:0.1	trace
18[c]	NH_4Br	CuI	1:4.5:3:0.1	trace
19[c]	$NH_4H_2PO_4$	CuI	1:4.5:3:0.1	trace

[a] Reaction conditions: Substrate **1a** (0.2 mmol), $Ph_3P^+CF_2CO_2^-$, [N] source, $Ir(ppy)_3$ (2 mol%) and Cu complex in DMAc (2 mL) irradiated with blue LED at room temperature under a N_2 atmosphere for 12 h; [b] The yields were determined by ^{19}F NMR spectroscopy; [c] 3 mL of DMAc was used instead of

[*] Min Zhang, Dr. Jin-Hong Lin, Prof. Dr. Ji-Chang Xiao
Key laboratory of organofluorine chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Science, 345 Lingling Road, Shanghai 200032, China, E-mail: jchxiao@sioc.ac.cn

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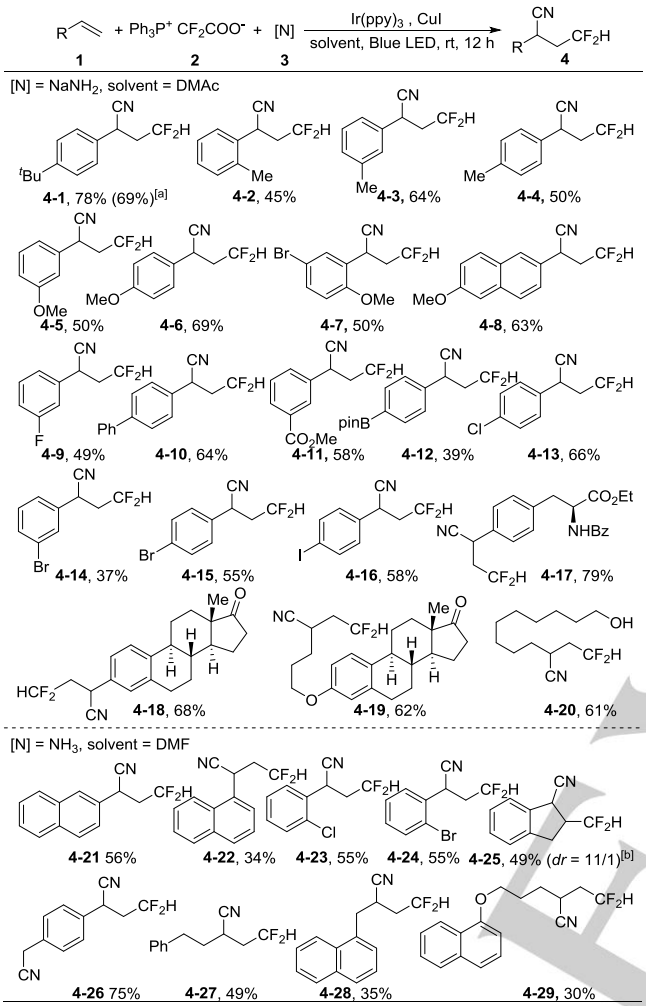
2 mL; [d] $Ir(ppy)_3$ was not used; [e]The light source (blue LED) was not used; [f] DMF (3 mL) was used instead of DMAc.

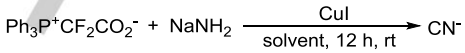


Scheme 1. Substrate scope of the photocatalyzed cyanodifluoromethylation of alkenes. Isolated yields. Reaction conditions: substrate **1** (0.4 mmol), $Ph_3P^+CF_2CO_2^-$ (4.5 equiv.), $NaNH_2$ (3 equiv.) or NH_3 (5 ~ 7.5 equiv.), $Ir(ppy)_3$ (2 mol %), CuI (10 mol %), in DMAc (6 mL) or DMF (6 mL) irradiated with blue LED at room temperature under a N_2 atmosphere for 12 h. [a] A gram-scale reaction (1.12 g of **1a**) gave **4-1** in 69% isolated yield. [b] The *dr* value was determined by ^{19}F NMR spectroscopy.

With the optimal reaction conditions in hand (Table 1, entry 10 or entry 15), we investigated the substrate scope of the photocatalyzed cyanodifluoromethylation of alkenes. As shown in Scheme 1, various aryl alkenes could be converted into the desired products in moderate to good yields. A gram-scale conversion was performed and a 69% isolated yield of **4-1** was obtained, revealing the potential application of this reaction. An examination of the substituent effects in aryl alkenes showed that neither electron-withdrawing nor -donating groups had an obvious impact on the yields. A variety of functional groups were tolerated, such as ether, ester, ketone, chloride, bromide, iodide, boronic acid ester and amide groups. The compatibility of this reaction with the reactive functional groups, including bromide (**4-14**, **4-15**, **4-24**), iodide (**4-16**), and boronic acid ester (**4-12**), allowed further C–C coupling transformations. The HCF_2/CN-containing estrone derivatives were synthesized by this cyanodifluoromethylation conversion, further demonstrating the synthetic utility of this protocol (**4-18**, **4-19**). Internal alkenes showed low reactivity, which resulted in a lower yield (**4-25**). Besides aryl alkenes, alkyl alkenes were also reactive and smoothly converted into the expected products (**4-19**, **4-20**, **4-27** ~ **4-29**).

It has been reported that the generation of cyanide anion (CN^-) can be detected by a CN^- indicator, sodium picrate,[15] and therefore this method was adopted to identify the sources of the CN^- anion [Please see Supporting Information (SI) for experimental details]. No CN^- anion was detected in the absence of $Ph_3P^+CF_2CO_2^-$ (Table 2, entries 1-2) or $NaNH_2$ (entry 3), but the anion was formed when both $Ph_3P^+CF_2CO_2^-$ and $NaNH_2$ were present (entry 4), indicating that $Ph_3P^+CF_2CO_2^-$ and $NaNH_2$ are the carbon source and the nitrogen source of the CN^- anion, respectively. Furthermore, the CN^- anion can also be produced in THF or CH_3CN, suggesting that DMAc is not a source of the CN^- anion (entries 5-6).

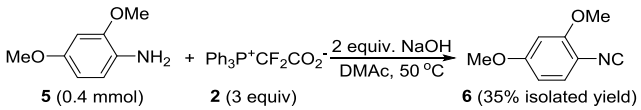
Table 2. Detection of CN^- by indicator paper[a]



Entry	$NaNH_2$ (0.6 mmol)	$Ph_3P^+CF_2CO_2^-$ (0.9 mmol)	CuI (10 mol%)	Solvent (3 mL)	CN^- produced
1	√	×	×	DMAc	–
2	√	×	√	DMAc	–
3	×	√	×	DMAc	–
4	√	√	×	DMAc	+
5	√	√	×	THF	+
6	√	√	×	CH_3CN	+

[a] "√" means the reagent was used; "×" means the reagent was not used; "+" means positive result; "–" means negative result.

Besides the cyanide detection test, other experimental evidence was collected. The reaction of phenyl amine **5** with $Ph_3P^+CF_2CO_2^-$ gave isocyanobenzene **6** (Scheme 2). The formation of the isocyano (NC) moiety also indicated that both $Ph_3P^+CF_2CO_2^-$ and $NaNH_2$ were sources of the nitrile group.



Scheme 2. Formation of an isocyano moiety

$Ph_3P^+CF_2CO_2^-$ was not only the carbon source of the nitrile group, but also the source of the HCF_2 group. The proton in the HCF_2 group should be from the $NaNH_2$ reagent, or a trace amount of water present in the reaction system, as evidenced by the observation that the presence of D_2O generated a deuterated product (Scheme 3, eq 1). A radical scavenger such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), dibutylhydroxytoluene (BHT), or hydroquinone could dramatically suppress the formation of the desired product. A TEMPO-CF_2H byproduct was produced in 32% yield (by ^{19}F

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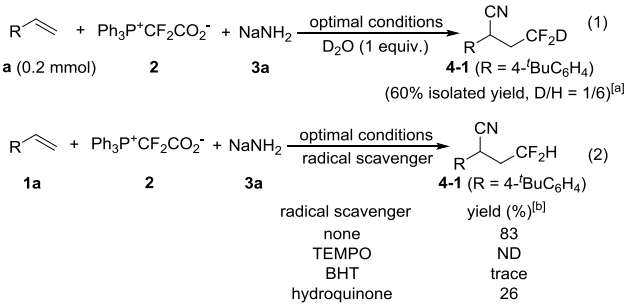
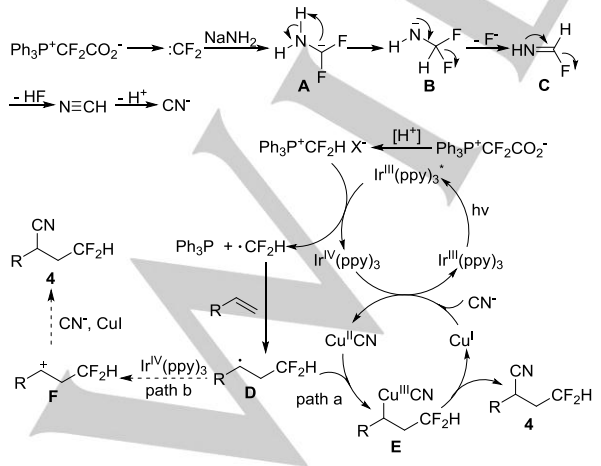
NMR) when TEMPO was used, suggesting that a radical reaction mechanism was operative (Scheme 3, eq 2).



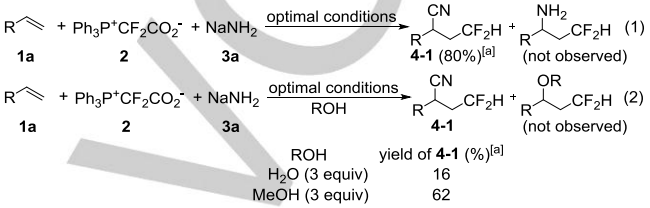
Scheme 3. Experimental evidence. [a] The D/H ratio was determined by ^{19}F NMR spectroscopy. [b] Determined by ^{19}F NMR spectroscopy.

On the basis of the above results, we proposed a plausible reaction mechanism, as shown in Scheme 4. Difluorocarbene generated from $Ph_3P^+CF_2CO_2^-$ is readily trapped by $NaNH_2$ to produce carbon anion **A**. Hydrogen migration from the N-H moiety to the carbon anion provides intermediate **B**, which undergoes β-fluorine elimination to afford formimidoyl fluoride **C**. Further F-elimination generates a proton and furnishes hydrogen cyanide, and the deprotonation of hydrogen cyanide gives a cyanide anion. $Ph_3P^+CF_2CO_2^-$ could also abstract a proton to form the phosphonium salt $[Ph_3P^+CF_2H\ X^-]$.[16] The cyclic voltammetry studies and Stern–Volmer measurements (Please see SI for experimental details) reveals that the phosphonium salt $[Ph_3P^+CF_2H\ X^-]$ (Ep^{red} = -0.959 V vs. SCE, See SI) could be easily reduced by the photoexcited complex $[Ir(ppy)_3^*]$ ($E_{1/2}^{red}[Ir^{IV}/Ir^{*III}]$ = −1.73 V vs. SCE)[14a] to generate an Ir^{IV} complex and the $HCF_2\cdot$ radical.[4f, 10a, 17] The capture of this radical by an alkene substrate gives radical intermediate **D**. The Ir^{IV} complex is an oxidant ($E_{1/2}^{ox}[Ir^{IV}/Ir^{III}]$ = +0.77 V vs. SCE),[14a] and would therefore oxidize Cu^I into Cu^{II} ($E_{1/2}^{ox}[Cu^{II}/Cu^I]$ = +0.71 V vs. SCE, See SI). Rapid ligand exchange affords $Cu^{II}CN$ complex, the combination of which with radical intermediate **D** produces Cu^{III} complex **E** (path a).[13d, 13e, 18] Reductive elimination of complex **E** furnishes the final product **4** and re-generates the Cu^I catalyst.



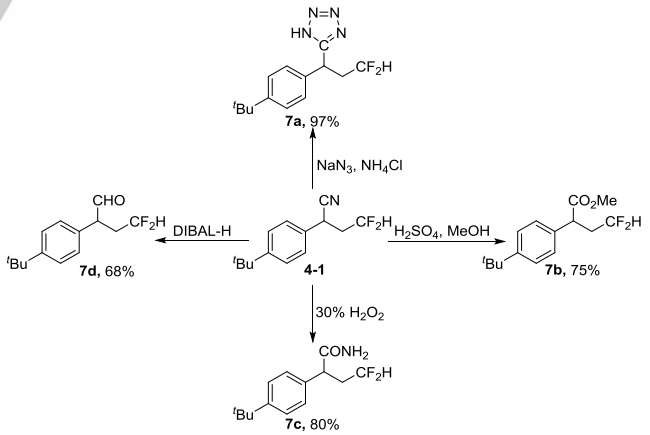
Scheme 4. The proposed reaction mechanism.

The possibility of generating cation intermediate **F** (path b in Scheme 4) was excluded based on the following evidence. If this cation was generated, it might be trapped by the ambient nucleophiles. $NaNH_2$ is a good nucleophile, but no aminodifluoromethylation product was detected (Scheme 5, eq 1). Besides, the in situ generated CN^- was also a nucleophile. However, almost no cyanodifluoromethylation product was formed if CuI was not used (see Table 1, entry 11), suggesting that the cyanodifluoromethylation was not from a direct nucleophilic attack of CN^- on the cation **F**. Furthermore, the external addition of a nucleophile, H_2O or MeOH, did not afford hydroxylation or methoxylation byproduct (eq 2).



Scheme 5. The capture of a possible cation **F**. R = 4-^{t}BuC$_6$H$_4$. [a] The yield was determined by ^{19}F NMR spectroscopy.

We developed an efficient protocol for cyanodifluoromethylation of alkenes. This approach is highly attractive as the simultaneous incorporation of both HCF_2 and CN groups could be achieved under mild conditions and the use of highly toxic or volatile cyanation reagents was avoided. To demonstrate the synthetic versatility of the HCF_2/CN-containing products, diversifications of product **4-1** were performed (Scheme 6). HCF_2-tetraazole (**7a**) was obtained in a high yield through cyclization of **4-1** with sodium azide. Some other typical transformations into an ester (**7b**), amide (**7c**), and aldehyde (**7d**) were also illustrated.



Scheme 6. Representative transformations of product **4-1**.

In summary, we have described the photocatalyzed cyanodifluoromethylation of alkenes with a $Ph_3P^+CF_2CO_2^-$ /$NaNH_2$ (or NH_3) reagent system. $Ph_3P^+CF_2CO_2^-$ acted as a difluoromethylation reagent and carbon source of the nitrile group in the reaction. This work represents the first example of efficient cyanodifluoromethylation using easy-to-handle reagents

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to generate a cyanide anion in situ under mild conditions. The convenient cyanodifluoromethylation protocol may find utility in the synthesis of HCF_2/CN-containing biologically active molecules.

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Keywords: Difluorocarbene • Cyanodifluoromethylation • Alkenes • Photocatalysis • Fluorine

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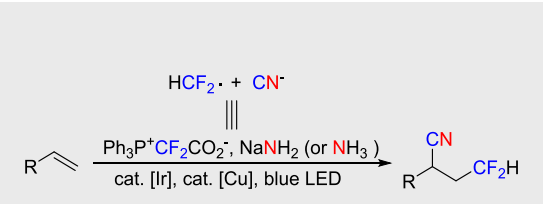

*Min Zhang, Jin-Hong Lin, and Ji-Chang Xiao**

Page No. – Page No.
Photocatalyzed Cyanodifluoromethylation of Alkene

Photocatalyzed cyanodifluoromethylation of alkenes with a $Ph_3P^+CF_2CO_2^-/NaNH_2$ (or NH_3) system is described. The use of toxic cyanation reagents were avoided because $Ph_3P^+CF_2CO_2^-$ acted as both the HCF_2 source and CN carbon source.

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