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Difluorocarbene-based cyanodifluoromethylation of alkenes induced by a dual-functional Cu-catalyst†

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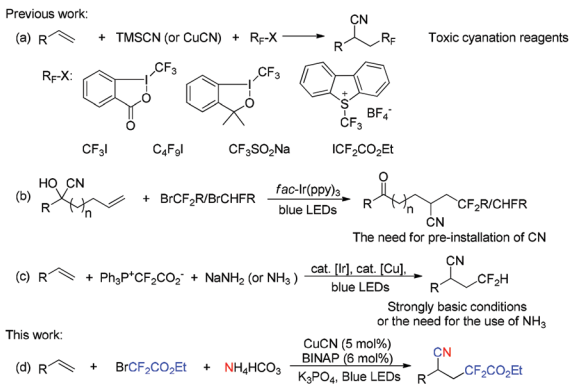
Although cyanofluoroalkylation has received increasing attention, a toxic cyanation reagent is usually required. Herein, a Cu-catalyzed difluorocarbene-based cyanodifluoromethylation of alkenes with $BrCF_2CO_2Et/NH_4HCO_3$ under photocatalytic conditions is described. $BrCF_2CO_2Et$ and NH_4HCO_3 serve as a carbon source and a nitrogen source of the nitrile group, respectively, avoiding the use of a stoichiometric toxic cyanation reagent. The Cu-complex plays a dual role. It is not only a photocatalyst, but also a coupling catalyst for the formation of a C–CN bond.

Owing to the unique properties of the fluorine element, such as high electronegativity and small atomic radius, the incorporation of a fluorinated group into organic molecules would usually lead to profound changes in their physicochemical properties.[1] Fluoroalkyl groups, which usually show high lipophilicity and strong electron-withdrawing nature,[2] are commonly found in pharmaceuticals, such as Gemcitabine, Tafluprost and Lubiprostone. Therefore, significant efforts have been directed towards the development of efficient methods for the installation of fluoroalkyl groups.[3] Among them, fluoroalkylative difunctionalization of alkenes has received increasing attention because this type of reaction has been proved to be a powerful tool for constructing two vicinal chemical bonds in a single step from simple precursors.[4]

As the nitrile group (CN) has served as an important moiety in a large number of pharmaceuticals, such as Verapamil and Anastrozole, and can be further transformed into many other functional groups, many cyanation reagents and cyanation methods have been developed.[5] Since the incorporation of both fluoroalkyl and nitrile groups may provide more opportunities for drug/agrochemical development, it is highly desirable to develop cyanofluoroalkylation approaches. Cyanotrifluoromethylation of alkenes has been independently reported by the groups of Szabó,[6] Liang,[7] Liu,[8] and others[9] (Scheme 1a). All of these reactions are very efficient for the incorporation of both CF_3 and CN groups, and some processes have been extended to other fluoroalkyl groups,[9b–d] such as C_4F_9 and CF_2CO_2Et. However, these approaches suffer from the stoichiometric use of a toxic cyanation reagent (mostly TMSCN), and the fluoroalkyl groups are mainly limited to the CF_3 group. Recently, Zhu and co-workers developed an effective cyanofluoroalkylation of alkyl alkenes *via* an intramolecular CN migration (Scheme 1b).[10] A wide substrate scope was demonstrated and high yields were obtained, but the pre-installation of a CN group into substrates by using a toxic cyanation reagent (TMSCN) is required.

Difluorocarbene has served as a valuable intermediate in organic synthesis.[11] This reactive species can be used to enable many reactions, such as [2+1] cyclization of alkenes,[12] difluoromethylation of X–H bonds (X = carbon or heteroatom),[13] and difluorocarbene transfer by transition metal catalysis.[14] Recently, we disclosed that difluorocarbene can be trapped by $NaNH_2$ or NH_3 to generate a cyanide anion, a process which was developed into a synthetic tool to achieve cyanodifluoromethylation of



Scheme 1 Cyanofluoroalkylation of alkenes.

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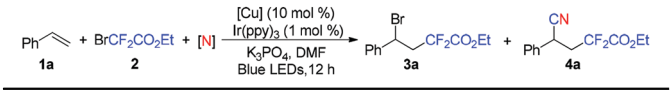
alkenes (Scheme 1c).[15] Although no toxic cyanation reagent was used, the protocol may suffer from strongly basic conditions ($NaNH_2$) or the use of NH_3, which is a gas with a characteristic pungent smell. Furthermore, the difluorocarbene source, $Ph_3P^+CF_2CO_2^-$ (PDFA), has to be used in a large excess (4.5 equiv.), and an expensive Ir complex has to be used as a photocatalyst. Due to these deficiencies, we further develop a mild cyanodifluoromethylation reaction of alkenes with $BrCF_2CO_2Et$/NH_4HCO_3 under visible-light induced photocatalytic conditions (Scheme 1d). NH_4HCO_3 can act the nitrogen source of the CN group, and $BrCF_2CO_2Et$ is not only the carbon source of the CN group, but also the difluoromethyl source. In this process, the Cu-catalyst plays a dual role, as both a photoredox catalyst for single electron transfer and a cross-coupling catalyst for C–CN bond formation.

For our previous cyanodifluoromethylation of alkenes with PDFA/$NaNH_2$, $Ir(ppy)_3$ was used as a photocatalyst and CuI was used as a cross coupling catalyst (Scheme 1c).[15] In the initial attempts by using $BrCF_2CO_2Et$ instead of PDFA as a difluorocarbene source, the expected product **4a** was obtained in a very low yield under similar conditions (Table 1, entry 1). An undesired bromination compound, **3a**, was produced as a major product. A brief survey of the nitrogen sources revealed that the yield of **4a** could not be significantly increased (entries 2–4). A 13% yield was obtained with the use of NH_4HCO_3 as the nitrogen source (entry 2). To our delight, the presence of a base, K_3PO_4, gave product **4a** in 43% yield (entry 5). The formation of a cyanide anion from CF_2/NH_4HCO_3 involves sequential deprotonation processes. A base could obviously accelerate deprotonation, and is thus favorable for the final cyanation. Other bases led to a slight decrease in the yield (entries 6 and 7). Cu sources were also screened (entries 8–10), and CuCN was found to be a better choice (entry 8). The yield was further increased by adding a ligand, 1,1′-binaphthalene-2,2′-diylbis-diphenylphosphine (BINAP) (entry 11). Other ligands were also examined (please see the ESI†) but BINAP was found to be a superior choice. Surprisingly, the absence of $Ir(ppy)_3$ did not dramatically decrease the yield, probably because the (BINAP)Cu complex can act as a photocatalyst (entry 12).[16] A high yield (85%) was obtained when H_2O and diglyme (DG) were used as additives (entry 13). These two additives may easily dissolve the inorganic salts, such as M^+ CN^- and K_3PO_4, and therefore favor the participation of these inorganic salts in the reaction. Under these conditions, the side bromination product (**3a**) was almost completely suppressed. No desired product was observed without the irradiation of blue LEDs, indicating that this is a photocatalyzed process.

With the optimal conditions in hand (Table 1, entry 13), we then investigated the substrate scope of the Cu-catalyzed difluorocarbene-based cyanodifluoromethylation of alkenes. As shown in Table 2, the process could be extended to a wide variety of alkenes, including aryl and alkyl alkenes. Various

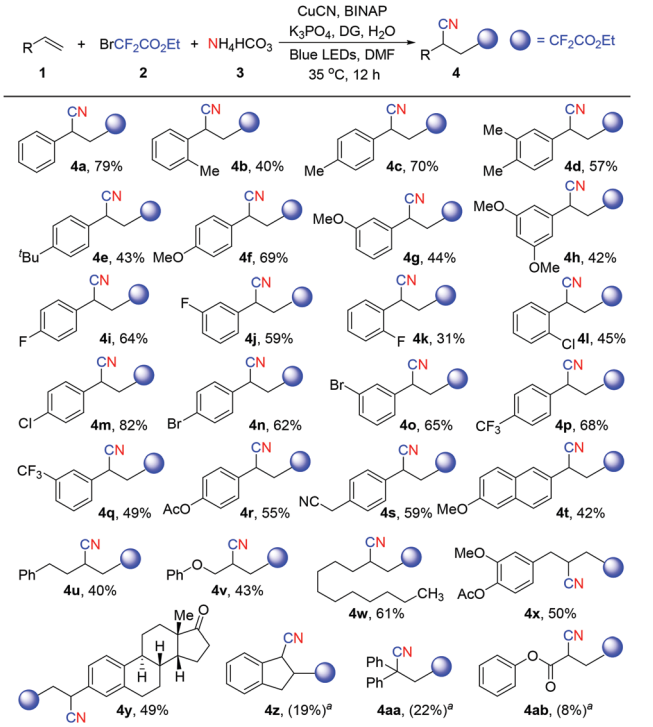
Table 1 The optimization of reaction conditions[a]



Entry	[N]	[Cu]	Yield[b] (%) 3a	4a
1[c]	$NaNH_2$	CuI	60	6
2[c]	NH_4HCO_3	CuI	55	13
3[c]	$(NH_4)_2CO_3$	CuI	16	3
4[c]	$NH_2CO_2NH_4$	CuI	38	6
5	NH_4HCO_3	CuI	26	43
6[d]	NH_4HCO_3	CuI	30	42
7[e]	NH_4HCO_3	CuI	44	27
8	NH_4HCO_3	CuCN	13	57
9	NH_4HCO_3	$CuBr_2$	21	43
10	NH_4HCO_3	$Cu(OTf)_2$	23	49
11[f]	NH_4HCO_3	CuCN	10	68
12[fg]	NH_4HCO_3	CuCN	12	50
13[fgh]	NH_4HCO_3	CuCN	Trace	85
14[fghi]	NH_4HCO_3	CuCN	ND	ND

[a] Reaction conditions: substrate **1a** (0.2 mmol), $BrCF_2COOEt$ (5.0 equiv.), a nitrogen source (2 equiv.), $Ir(ppy)_3$ (1 mol%), Cu complex (10 mol%) and K_3PO_4 (2 equiv.) in DMF (2 mL) irradiated with blue LEDs at 35 °C under a N_2 atmosphere for 12 h. [b] The yields were determined by ^{19}F NMR spectroscopy with 1-fluoronaphthalene as the internal standard. [c] Without K_3PO_4. [d] $KHCO_3$ was used instead of K_3PO_4. [e] K_2HPO_4 was used instead of K_3PO_4. [f] 5 mol% CuCN and 6 mol% BINAP were used. [g] $Ir(ppy)_3$ was not used and the loading of $BrCF_2CO_2Et$ was decreased to 2.5 equiv. [h] H_2O (3 equiv.) and DG (2.5 equiv.) were added. [i] No blue LED was used. ND = not detected.

Table 2 Difluorocarbene-based cyanodifluoromethylation of alkenes



Reaction conditions: substrate **1** (0.4 mmol), $BrCF_2CO_2Et$ (1.0 mmol), NH_4HCO_3 (0.8 mmol), CuCN (5 mmol%), BINAP (6 mmol%), DG (1.0 mmol) and H_2O (1.2 mmol) in DMF (4 mL) irradiated with blue LEDs at 35 °C under a N_2 atmosphere for 12 h. Isolated yields are shown. [a] The yields in parentheses are determined by ^{19}F NMR spectroscopy.

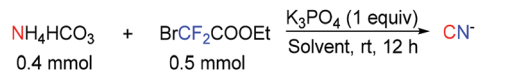
functional groups could be tolerated under these conditions, such as ether, ester and halide groups. Electron-rich, -neutral and -deficient aryl alkenes could all be converted into the desired products in moderate to good yields. Alkyl alkenes show similar reactivity to aryl alkenes, and moderate yields were obtained (**4u–4x**). An estrone derivative was synthesized, which may show biological activity. The reaction is sensitive to steric effects, and thus a low yield was obtained in the case of internal alkenes (**4z**). α,β-Unsaturated alkenes also show low reactivity (**4ab**).

The reaction should involve the generation of a cyanide anion from the difluorocarbene source, $BrCF_2CO_2Et$, and the nitrogen source, NH_4HCO_3, like our previous difluorocarbene-based cyanodifluoromethylation process.[15] Indeed, CN^- was not detected using an indicator paper in the absence of either $BrCF_2CO_2Et$ or NH_4HCO_3 (Table 3, entries 1 and 2), and the anion could be clearly detected only when both of them were present (entry 3) (please see the ESI† for experimental details). In addition, CN^- was produced not only in DMF, but also in DMAc, MeCN, and DG (entries 4–6), reflecting that the reaction solvent DMF is neither a carbon source nor a nitrogen source of the CN^-.

During the optimization of reaction conditions, we found that bromination compound **3a** was produced as a side product under some conditions (Table 1). A question arises whether this compound is an intermediate of the final product **4a**. Compound **3a** was then subjected to the optimized conditions shown in Table 1, entry 13, and it was found that no product **4a** was formed (Scheme 2). Instead, a dehydrobromination compound **5a** was obtained, indicating that **3a** is not a necessary intermediate.

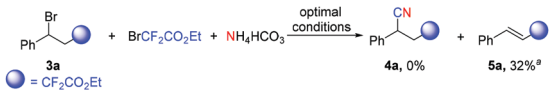
The analysis of UV-VIS absorption spectra of BINAP, CuCN and (BINAP)CuCN showed that only (BINAP)CuCN has

Table 3 Detection of CN^- using indicator paper[a]

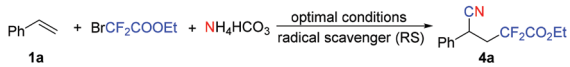


Entry	NH_4HCO_3	$BrCF_2CO_2Et$	Solvent	CN^- produced
1	√	×	DMF	−
2	×	√	DMF	−
3	√	√	DMF	+
4	√	√	DMAc	+
5	√	√	MeCN	+
6	√	√	DG	+

[a] "√" means the reagent was used; "×" means the reagent was not used; "+" means CN^- was produced; "−" means CN^- was not produced.



Scheme 2 The exclusion of the possible reaction path. [a] The yield was determined by ^{19}F NMR spectroscopy with 1-fluoronaphthalene as the internal standard.

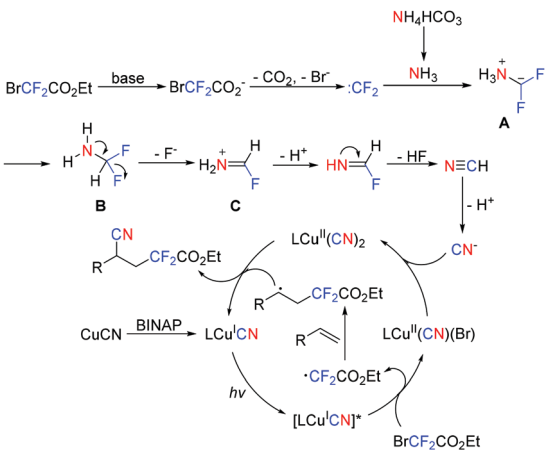


RS	yield(%)[a]
without RS	85
TEMPO	0
hydroquinone	trace
HOBT	22

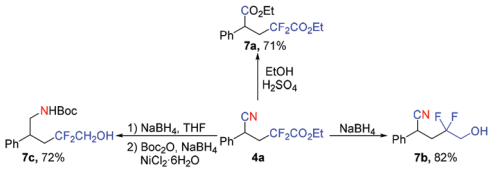
Scheme 3 The evidence for a radical mechanism. [a] The yields were determined by ^{19}F NMR spectroscopy with 1-fluoronaphthalene as the internal standard.

absorptions in the visible light range (please see the ESI†). Since the cyanodifluoromethylation proceeded under visible light irradiation and it has been reported that a Cu complex could act as a photocatalyst,[16,17] we propose that the (BINAP)-CuCN complex should be the photocatalyst for this difluorocarbene-based cyanodifluoromethylation. Stern–Volmer measurements (please see the ESI†) revealed that $BrCF_2CO_2Et$ could effectively quench the excited state of the (BINAP)CuCN complex generated *in situ*, reflecting that a single electron transfer between $BrCF_2CO_2Et$ and the (BINAP)CuCN complex would occur to generate a $^{\bullet}CF_2CO_2Et$ radical under visible light irradiation. A radical scavenger, including 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), hydroquinone or 1-hydroxybenzotriazole (HOBt), could dramatically suppress the desired cyanodifluoromethylation process, indicating that a radical process is indeed operative (Scheme 3).

On the basis of the above results and our previous studies on cyanodifluoromethylation,[15] we propose the plausible reaction mechanism as shown in Scheme 4. $BrCF_2CO_2Et$ is not only the carbon source of the nitrile group, but also the source of the terminal CF_2CO_2Et group in the final products. First, $BrCF_2CO_2Et$ hydrolyzes to give $BrCF_2CO_2^-$, which could readily undergo decarboxylation to release difluorocarbene. Difluorocarbene is an electrophilic species, and would be easily trapped by NH_3 produced from NH_4HCO_3 to form intermediate **A**. A proton transfer from the NH_3^+ moiety to the CF_2^- group provides intermediate **B**, and the subsequent defluorination delivers intermediate **C**, which would further undergo deprotonation and defluorination to afford HCN. Neutralization of HCN



Scheme 4 The plausible reaction mechanism.



Scheme 5 Diversification of cyanodifluoromethylation product **4a**.

delivers the CN^- anion. On the other hand, the coordination of BINAP to CuCN produces the (BINAP)–CuCN complex. The photoexcitation of this complex could easily reduce $BrCF_2CO_2Et$ to give the $^\bullet CF_2CO_2Et$ radical and Cu^{II} complex. The ligand exchange between CN^- and the Br ligand generates the $LCu^{II}(CN)_2$ complex. The addition of the $^\bullet CF_2CO_2Et$ radical to a double bond provides an alkyl radical. The interaction of the alkyl radical with the $Cu^{II}(CN)_2$ complex furnishes the final product and releases the catalyst. As we have described before,[15] a Cu complex is essential for the transfer of a CN group to the alkyl radical. Therefore, the Cu catalyst plays a bifunctional role in this transformation. It is not only a photocatalyst, but also a coupling catalyst for C–CN bond formation.

Since CN and CF_2^- groups are both incorporated under mild conditions, this cyanodifluoromethylation protocol may find potential applications in the synthesis of unique molecules. To further demonstrate the synthetic utility of the protocol, diversification of product **4a** was performed (Scheme 5). Both CN and CF_2CO_2Et could be easily transformed, and various fluorinated compounds were obtained, such as amino alcohols (**7c**) and cyano alcohols (**7c**).

In summary, we have described a difluorocarbene-based cyanodifluoromethylation of alkenes catalyzed by a dual-functional Cu-catalyst. $BrCF_2CO_2Et$ is not only the $^\bullet CF_2CO_2Et$ radical source, but also a difluorocarbene reagent, which releases difluorocarbene to serve as the carbon source of the nitrile group. No stoichiometric toxic cyanation reagent was used, and a cheap Cu complex, playing a dual role, could effectively promote this transformation. The Cu complex is not only a photocatalyst, but also a catalyst for C–CN bond formation. The cyanodifluoromethylation protocol may find great utility in the synthesis of biologically active molecules.

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Conflicts of interest

The authors declare no competing financial interest.

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