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$BrCF_2CN$ for photocatalytic cyanodifluoromethylation

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Considering the unique electronic properties of the CF_2 and the CN groups, the CF_2CN group has significant potential in drug and agrochemical development, as well as material sciences. However, incorporating a CF_2CN group remains a considerable challenge. In this work, we disclose a use of bromodifluoroacetonitrile ($BrCF_2CN$), a cost-effective and readily available reagent, as a radical source for cyanodifluoromethylation of alkyl alkenes, aryl alkenes, alkynes, and (hetero)arenes under photocatalytic conditions. This protocol demonstrates an exceptionally broad substrate scope and remarkable tolerance to various functional groups. Notably, the cyanodifluoromethylation of alkynes predominantly provides sterically hindered alkenes, a thermodynamically unfavorable outcome, and (hetero)arene C-H bonds are directly amenable to cyanodifluoromethylation without pre-functionalization.

The unique electronic characteristics of fluorine, such as its high electronegativity and small atomic radius, typically cause substantial alterations in the physicochemical properties of organic molecules when a fluorinated group is incorporated[1,2]. For example, in pharmaceutical chemistry, numerous fluorinated groups, such as F, HCF_2, and CF_3, have been identified for enhancing the properties of biologically active molecules, particularly their lipophilicity and metabolic stability[3,4]. Despite these advances, it is crucial to focus efforts on developing more fluorinated groups to meet the growing demand for structural and functional diversity in drug discovery. The cyanodifluoromethyl group (CF_2CN) represents a distinctive fluorinated functional group that could be useful in drug chemistry. Given that both the CF_2H ($\sigma_m = 0.29$, $\sigma_p = 0.32$) and CN ($\sigma_m = 0.56$, $\sigma_p = 0.66$) groups are electron-withdrawing[5], it is plausible to expect that CF_2CN would similarly act as an electron-withdrawing group. This property could be advantageous in deactivating neighboring groups, making them less susceptible to oxidative metabolism. In addition, the CF_2 moiety can serve as a bioisostere for an oxygen atom[6] or an isopropyl group[7], and the cyano group can potentially act as a hydrogen bond acceptor and function as a bioisostere for many different groups, such as hydroxyl, halogen, and carbonyl groups[8]. Despite its distinctive properties, CF_2CN has been rarely studied in biological contexts[9], primarily due to the lack of efficient methods for the installation of this functionality. The potential utility of CF_2CN in biological chemistry and its role as intermediates for synthesizing unique fluorinated compounds[10–13] may stimulate research endeavors aimed at facilitating CF_2CN group installation.

Typically, installing the CF_2CN group involves a multi-step synthetic process. One traditional method is to construct R-CF_2CO_2Et molecules and then convert CF_2CO_2Et into CF_2CN through amination followed by dehydration (Fig. 1A, Eqs. (a) and (b))[14–16]. Acyl cyanide, generated by cyanation of acyl chloride, can be fluorinated with DAST to form the CF_2CN group (Fig. 1A, Eq. (c))[17]. In studies of C–F bond functionalization of CF_3-arenes by Bandar, one selected functionalization product was further converted for the synthesis of an R-CF_2CN molecule (Fig. 1A, Eq. (d))[18]. Alternative methods involving the fluorination of CN-containing substrates require the use of hazardous or highly reactive reagents, including ^{t}BuLi[19], IF_5[20], or SbF_3[21] (Fig. 1A, Eqs. (e)–(g)). Despite the seemingly straightforward CF_2CN installation by direct cyanodifluoromethylation, only two reports have investigated this process (Fig. 1B)[22,23], utilizing $TMSCF_2CN$ as the CF_2CN source, a reagent developed by the Dilman group through difluorocarbene insertion into TMSCN[22]. Dilman found that $TMSCF_2CN$ can serve as a $[CF_2CN]^-$ equivalent, enabling the pioneering nucleophilic cyanodifluoromethylation of aldehydes and imines (Fig. 1B, Eq. (h))[22]. Very recently, while this manuscript was being prepared, Hartwig disclosed a groundbreaking copper-mediated coupling reaction for cyanodifluoromethylation of aryl and heteroaryl iodides and activated aryl and heteroaryl bromides with $TMSCF_2CN$ (Fig. 1B, Eq. (i))[23].

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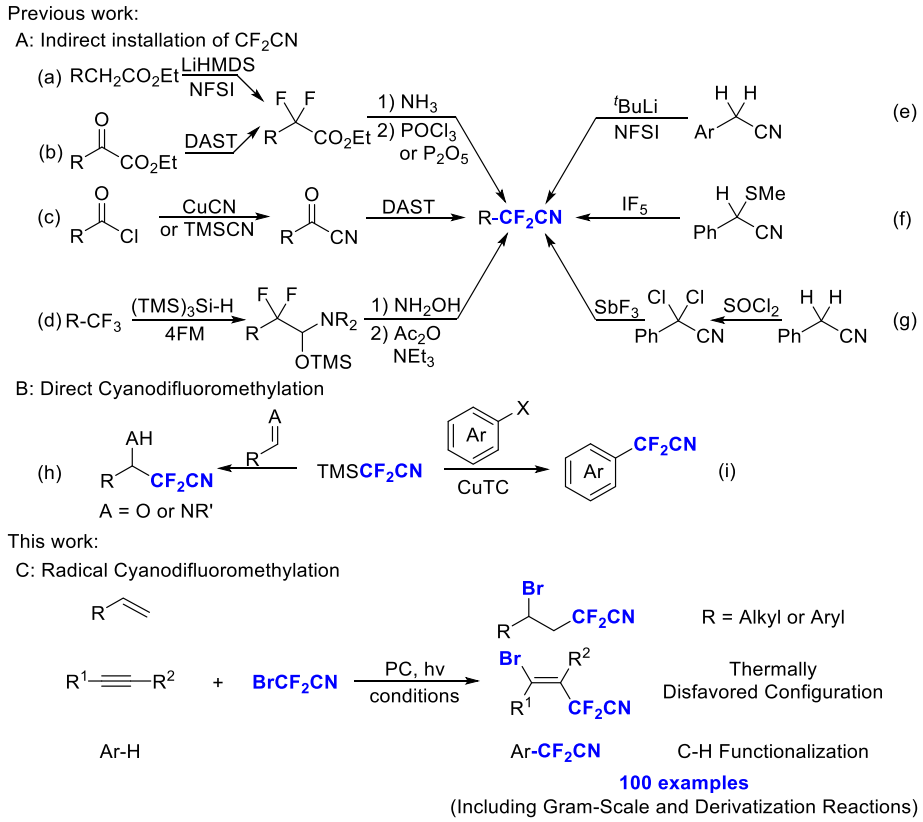

Fig. 1 | The installation of the CF_2CN group. A Indirect installation of the CF_2CN group via multi-step procedures. **B** Direct installation of the CF_2CN group by cyanodifluoromethylation. **C** our work on photocatalytic cyanodifluoromethylation.

$BrCF_2CN$, initially synthesized by Grindahl and colleagues[24], has scarcely been explored for its reactivity[25]; particularly, cyanodifluoromethylation using this reagent has never been studied. Given its ease of availability, as evidenced by the fact that its synthesis can be easily scaled up to hundreds of grams[24], it would be advantageous to develop $BrCF_2CN$ as an efficient cyanodifluoromethylation reagent. As photoredox catalysis has emerged as a valuable platform for the construction of C–C bonds[26–33], it is reasonable to speculate that $BrCF_2CN$ could be reduced to active intermediates for cyanodifluoromethylation under photocatalytic conditions. Herein we describe the use of $BrCF_2CN$ in cyanodifluoromethylation of alkyl alkenes, aryl alkenes, alkynes, and (hetero)arenes under photocatalytic conditions, observing a remarkably broad range of substrates and exceptional tolerance towards various functional groups (Fig. 1C). For alkenes and alkynes, difunctionalization reactions occurred, a research area which has received significant attention[34–37]. The potential features of the CF_2CN group make this difunctionalization particularly attractive. Notably, cyanodifluoromethylation of alkynes predominantly formed sterically hindered alkenes, a thermodynamically disfavored outcome, and (hetero)arene C–H bonds were directly amenable to cyanodifluoromethylation without pre-functionalization. Although $BrCF_2CN$ can be efficiently reduced under photocatalytic conditions, different photocatalytic strategies need to be used for different types of reactions, revealing the varied reactivity of $BrCF_2CN$ towards diverse substrates.

Results

We used **1a** as a template substrate to screen reaction conditions for the bromo-cyanodifluoromethylation of alkyl alkenes with $BrCF_2CN$ under photocatalytic conditions. Following extensive condition screening, the target product **2a** was obtained in a 79% isolated yield using DMF as the solvent, $Ru(phen)_3(PF_6)_2$ as a photocatalyst, and blue light irradiation at room temperature (Supplementary Table 1). After determining the optimal conditions, the substrate scope was explored. As shown in Fig. 2, a wide variety of alkyl alkenes delivered the desired products with moderate to excellent yields. Many synthetically useful functional groups, such as halide (**2b**), hydroxyl (**2c**, **2g**), ester (**2d**) and cyano (**2j**) groups, were well tolerant. Notably, the tolerance for the hydroxyl group deserves attention, as seen in products **2c** and **2g**. As discussed in the proposed mechanism[38–40], a cationic intermediate is generated, which is then attacked by a bromide to give the final product. Surprisingly, the cation is not attacked by the hydroxyl group. In addition to monosubstituted alkenes, 1,1-disubstituted alkenes were also smoothly converted, achieving moderate yields of the target products (**2f** and **2g**). Beyond alkenes with a benzene ring framework (**2h**–**2l**), heterocyclic alkenes with various structures (**2m**–**2t**), such as chromone (**2m**), phthalimide (**2n**), benzotriazole (**2o**), pyridine (**2p**), isoxazole (**2q**), furan (**2r**), thiophen (**2s**) and pyrimidine (**2t**), were well compatible and produced the corresponding products with moderate to good yields.

The success with alkyl alkenes inspired us to further investigate the bromo-cyanodifluoromethylation of aryl alkenes under photocatalysis. Unfortunately, aryl alkenes cannot undergo smooth transformation under the previous conditions, likely due to side oligomerization, as they are more reactive than alkyl alkenes, leading to immediate capture of the benzyl radical generated in situ by another molecule of aryl alkene for oligomerization[41]. To overcome this limitation, we hypothesized that metal bromides could serve as halogen atom transfer (XAT) mediators, effectively promoting the XAT step and suppressing side oligomerization, thereby providing the desired product[42–44]. Therefore, we examined the ability of various metal bromides to promote the bromo-cyanodifluoromethylation of 4-vinylbiphenyl under photocatalysis and found that copper bromide was the best choice (Supplementary Table 2). After establishing the

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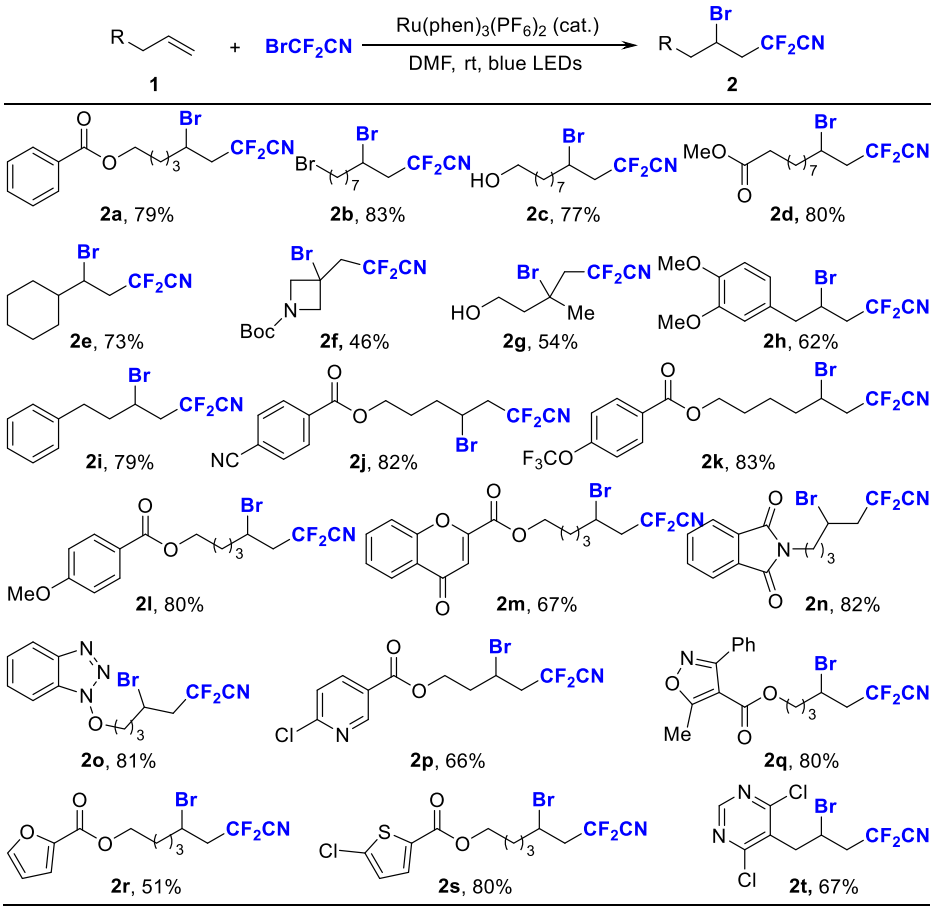

Fig. 2 | Bromo-cyanodifluoromethylation of alkyl alkenes. Isolated yields are shown. Reaction conditions: **1** (0.5 mmol, 1.0 equiv), $BrCF_2CN$ (1.25 mmol, 2.5 equiv), $Ru(phen)_3(PF_6)_2$ (2.3 mg, 0.5 mol%), DMF (2.5 mL), N_2, rt, 36 h, blue LEDs.

optimal conditions, the substrate scope was investigated. As shown in Fig. 3, various aryl alkenes smoothly underwent bromo-cyanodifluoromethylation, yielding the target products in moderate to good yields. Aryl alkenes with either electron-donating or electron-withdrawing groups at the *para* or *meta* position of the benzene ring participated well in the reaction (**4a**–**4o**). These experimental results indicate that the electronic effects of substituents on the aromatic ring do not significantly impact the transformation of the target reaction. The *ortho*-methyl substrate afforded the target product at a 68% yield (**4p**), suggesting that the reaction is minimally influenced by steric effects. Many functional groups were tolerated, including hydroxyl (**4d**), triazole (**4e**), boronic ester (**4f**), trimethylsilyl (**4g**), bromide (**4i**), cyano (**4j**), ester (**4k**), and aldehyde (**4l**). Notably, the boronic ester (**4f**) and the TMS-product (**4g**) provide a useful synthetic handle for further transformations. Heteroaryl alkynes can also be transformed into the expected products, albeit in moderate yields (**4r** and **4s**). Besides terminal alkenes, internal alkenes are also reactive towards this process. Surprisingly, a high dr value was obtained (**4t**).

To further broaden the substrate scope and achieve a high degree of universality in the bromo-cyanodifluoromethylation protocol, we turned our attention to the reaction of alkynes. Using phenylacetylene as a model substrate, its conversion under conditions optimized for the reaction of aryl alkenes resulted in a low product yield (27%) and low *E*/*Z* selectivity (*E*/*Z* = 59:41). Consequently, we carried out an extensive evaluation of reaction parameters. [Ir(dF(CF_3)ppy)$_2$(dtbbpy)][PF_6] was identified as the optimal photocatalyst (Supplementary Table 3). With the optimal conditions established, we explored the substrate scope. As shown in Fig. 4, the bromo-cyanodifluoromethylation process was successfully extended to a wide range of alkynes, demonstrating excellent stereoselectivity and yielding moderate to good yields. Surprisingly, the thermally disfavored *E*-alkenes were obtained as the major products, the reasoning for which is discussed in the mechanism section. In this reaction, the substituent electronic effects had little impact on the stereoselectivity but significantly influenced the yield for the conversion of aryl alkynes (**6a**–**6n**). Alkynes with electron-donating substituents on the aryl ring yielded higher than those with electron-withdrawing substituents, likely due to the electrophilic nature of the cyanodifluoromethyl radical. Various functional groups, such as amide (**6c**), hydroxyl (**6d**), and aldehyde (**6k**), were well-tolerated, offering potential reactive sites for further product transformations. Alkynes with methoxy group at the *para*, *meta*, or *ortho* position of the benzene ring participated well in the reaction (**6o**–**6q**). Heteroaryl alkenes were also reactive under these conditions, but lower yields were obtained (**6r**–**6t**). Despite the strong steric effects compared with terminal alkynes, internal alkynes could also be smoothly converted (**6u**–**6x**). However, electronic effects played an important role. Electron-deficient internal alkynes resulted in significantly lower yields. For example, a substrate containing a carbonyl group gave a lower yield than one containing an ester group (**6x** vs. **6w**). This protocol is also applicable to terminal alkyl alkynes (**6y**–**6aa**). Surprisingly, a *Z*-isomer was obtained from an ordinary alkyl alkyne (**6aa**). The *E*/*Z* selectivity will be addressed in the discussion of the proposed mechanism. Additionally, alkyl alkynes that contain a propargyl hydroxyl group were primarily converted into *E*-isomers, likely due to the coordinating ability of the hydroxyl group (**6y** and **6z**). The structure of **6a** was confirmed by X-ray diffraction analysis (CCDC 2360341 contains the supplementary crystallographic data of compound **6a**).

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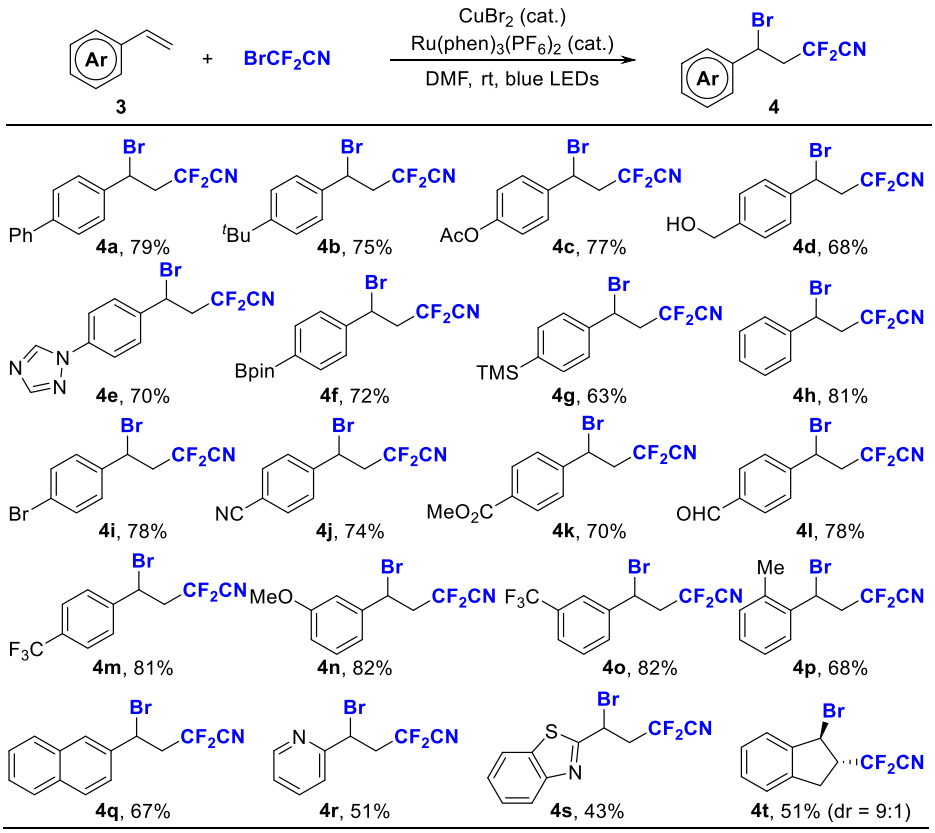

Fig. 3 | Bromo-cyanodifluoromethylation of aryl alkenes. Isolated yields are shown. Reaction conditions: **3** (0.5 mmol, 1.0 equiv), $BrCF_2CN$ (1.25 mmol, 2.5 equiv), $CuBr_2$ (0.05 mmol, 0.1 equiv), $Ru(phen)_3(PF_6)_2$ (2.3 mg, 0.5 mol%), DMF (2.5 mL), N_2, r.t., 24 h, blue LEDs.

We believe the above bromo-cyanodifluoromethylation processes occur via a $\cdot CF_2CN$ radical[45]. We then hypothesized that this radical might attack arenes, enabling the construction of Ar–CF_2CN molecules through C–H cyanodifluoromethylation[46]. After screening various conditions (Supplementary Table 4), $[Ir(dtbbpy)(ppy)_2][PF_6]$ can facilitate this process. The substrate scope for the C–H cyanodifluoromethylation of (hetero)arenes is illustrated in Fig. 5. Under these reaction conditions, synthetically useful functional groups, including boronic ester (**8b**), tosyl (**8d**), and hydroxyl (**8k**) groups, exhibited good tolerance. Various arenes and heteroarenes could be functionalized with a CF_2CN group. For phenyl rings, electron-rich substituents were necessary for successful conversion. Benzene, an electron-neutral arene, was converted into the desired product only in a very low ^{19}F NMR yield (19%). In the case of heteroarenes, the presence of electron-withdrawing groups, such as carbonyl and ester did not decrease the yield (**8e**–**8g**). For very electron-rich substrates, the reaction time must be carefully controlled to prevent the incorporation of two CF_2CN groups (**8c** and **8d**). Methyl 2,2-dithienylglycolate could yield both mono- and di-cyanodifluoromethylated products due to the presence of two thiophene rings available for reaction (**8m** and **8m'**). For heterocycles, in addition to pyrroles, thiophenes, and furans, other heterocycles could also undergo the desired cyanodifluoromethylation (**8o**–**8r**). The structure of **8e** was confirmed by X-ray diffraction analysis (CCDC 2360342 contains the supplementary crystallographic data of compound **8e**).

To further showcase the synthetic utility of this protocol, we subsequently employed these processes for the synthesis of derivatives of biologically active molecules containing the CF_2CN moiety. This included pharmaceuticals such as Probenecid, Fenofibrate, Gemfibrozil, Oxaprozin, Loxoprofen, and Clofibrate, natural products like Estrone, 4-Methylumbelliferone, and Pentoxifylline, as well as the herbicide Propyzamide. As shown in Fig. 6, all products were obtained in moderate to good yields, demonstrating both high efficiency and a high level of functional group tolerance.

Successful gram-scale reactions are essential to ensure that CF_2CN can serve as a valuable fluorine-containing group for research and screening purposes. It can be observed that these reactions can be smoothly scaled up to gram scales, yielding the corresponding products (Fig. 7A). There is no significant difference in efficiency between gram-scale reactions and small-scale reactions, as demonstrated in the above figures, highlighting the overall practicality and robustness of these strategies.

To illustrate the inherent synthetic utility of these products, various transformations of the $[CF_2CN]$-containing product were carried out. Both the C–Br bond and the CN group in the products can be further functionalized. First, the potential applications of the bromine atom were demonstrated (Fig. 7, B1). A C–S bond was constructed through nucleophilic substitution with NaSCN (**9**). Treatment of **2a** with DBU obtained the elimination product with an 88% yield (**10**). Additionally, the CN group offers multiple possibilities for subsequent transformations (Fig. 7, B2 and B3). The CF_2CO_2Me group could be generated easily and in a high yield in the presence of H_2SO_4 and MeOH (**11**). It is noteworthy that $NaBH_4$ can effectively reduce the CN group without the need for a Lewis acid (**12**). The strong electronegativity of the fluorine atoms decreases the nucleophilicity of the cyano group. As a result, converting **6a** into the corresponding amide (**13**) via the Ritter reaction under acidic conditions takes over 36 h. Compound **8a** can be converted to a difluorobenzothiazole with a moderate yield (**14**). Tetrazole, a common structural unit in pharmaceuticals[47], can be obtained under mild conditions by reacting **8e** with NaN_3 followed by an alkylation (**15**).

We believe the cyanodifluoromethylation process involves a photoredox radical mechanism based on the following results. Firstly, control experiments involving photocatalysts and visible light

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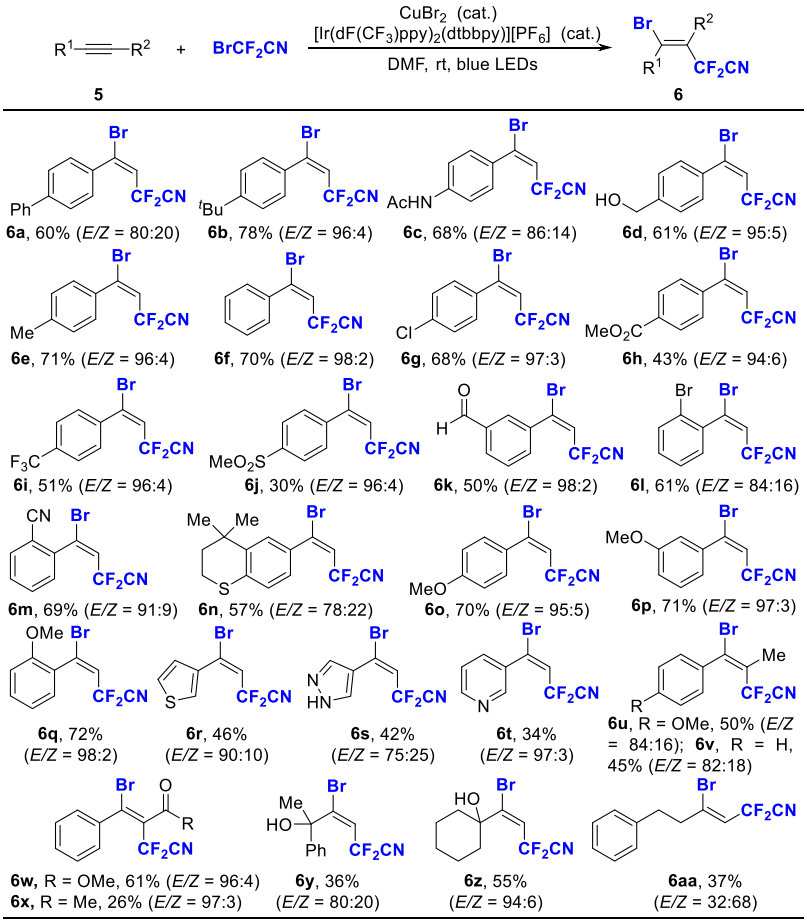

Fig. 4 | Bromo-cyanodifluoromethylation of alkynes. Isolated yields of the major isomers are shown. *E/Z* ratio in parentheses was determined by analysis of the crude ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. Reaction conditions: **5** (0.5 mmol, 1.0 equiv), $BrCF_2CN$ (1.25 mmol, 2.5 equiv), $CuBr_2$ (8.4 mg, 7.5 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)][PF_6]$ (5.6 mg, 1 mol%), DMF (2.5 mL), N_2, rt, 36 h, blue LEDs.

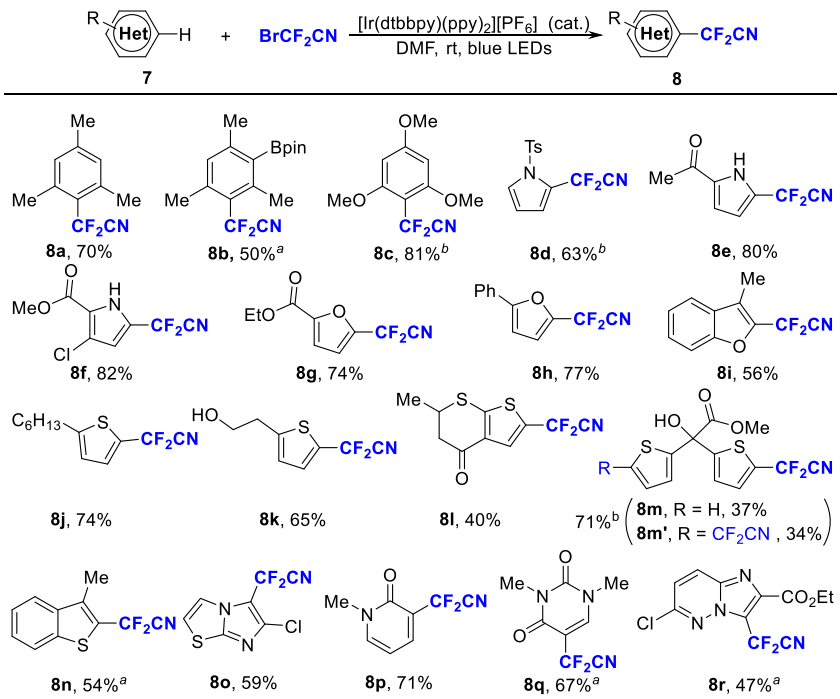

Fig. 5 | C–H cyanodifluoromethylation of (hetero)arenes. Isolated yields are shown. Reaction conditions: **7** (0.5 mmol, 1,0 equiv), $BrCF_2CN$ (1.25 mmol, 2.5 equiv), $[Ir(dtbbpy)(ppy)_2][PF_6]$ (2.3 mg, 0.5 mol%), DMF (2.5 mL), N_2, rt, 24 h, blue LEDs. [a]The reaction time was 36 h; [b]The reaction time was 12 h.

demonstrated the necessity of these components for product formation, as the absence of either one led to the complete suppression of the desired reaction (Supplementary Tables 5–8). Secondly, the radical inhibitor (TEMPO) significantly suppressed the formation of the target products (Supplementary Tables 5–8). Thirdly, ring-opening products **16** and **17** were obtained from cyclobutylmethyl[48,49] and cyclopropylmethyl[50,51] radical clocks[52], respectively, indicating the $\cdot CF_2CN$ radical as the key species in the reaction system (Fig. 8, A1). Additionally, the addition of $(TMS)_3SiH$ or Hantzsch ester as a hydrogen source to the reaction systems fortunately allowed the detection of HCF_2CN via ^{19}F NMR and GC–MS, further supporting the involvement of the key $\cdot CF_2CN$ radical (Fig. 8, A2). These findings suggest a radical pathway. However, for the reactions of alkyl and aryl alkenes, the radical evidence cannot rule out the possibility of a carbocation pathway (Supplementary Figs. 14, 15).

For the bromo-cyanodifluoromethylation of alkynes, the thermally disfavored *E*-products were obtained as major products. Interestingly, the X-ray analysis shows that the aryl ring is not conjugated with the double bond at all, meaning that both steric and conjugation effects disfavor the *E*-configuration (Fig. 8, B1). To elucidate the reason behind the preferential formation of these disfavored products, further experimental evidence was gathered. Regardless of whether ***E***- or ***Z***-**6a** was stirred under blue light irradiation in the presence of the Ir photocatalyst, isomerization was observed. Partial isomerization occurred for ***E***-**6a**, resulting in an *E/Z* ratio of 82:18. ***Z***-**6a** experienced significant isomerization under the same conditions, yielding the same *E/Z* ratio of 82:18, which closely matched the ratio obtained from the bromo-cyanodifluoromethylation reaction (Fig. 8, B2). Similarly, for compounds ***E***- and ***Z***-**6f**, stirring each one under blue light irradiation with the Ir photocatalyst also produced an *E/Z* mixture with an *E/Z* ratio identical to that from the bromo-cyanodifluoromethylation reaction. These findings suggest that energy transfer induced by the photocatalyst facilitated the predominant formation of *E*-configuration, a research area that has been extensively studied[53,54].

Based on the above results, we propose mechanisms for each cyanodifluoromethylation process, bromo-cyanodifluoromethylation of alkyl alkenes, aryl alkenes and alkynes, and cyanodifluoromethylation of (hetero)arenes. Here, we only discuss the mechanism for the transformation of alkynes (Fig. 9), with other mechanisms provided in the Supplementary Information to maintain brevity in the article.

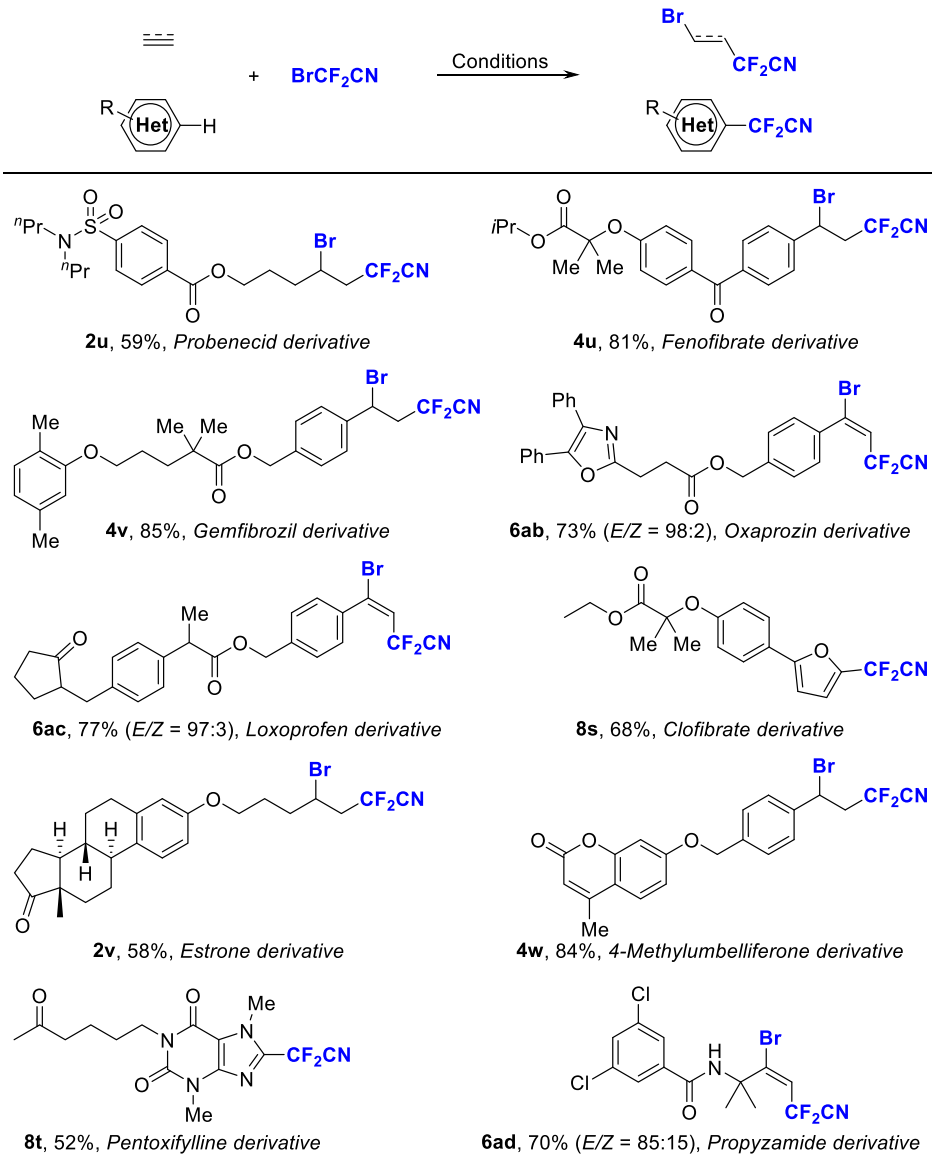

Fig. 6 | The synthesis of CF_2CN-containing derivatives of biologically active molecules. Isolated yields are shown. The reaction conditions are the same as those of the corresponding types of substrates mentioned above.

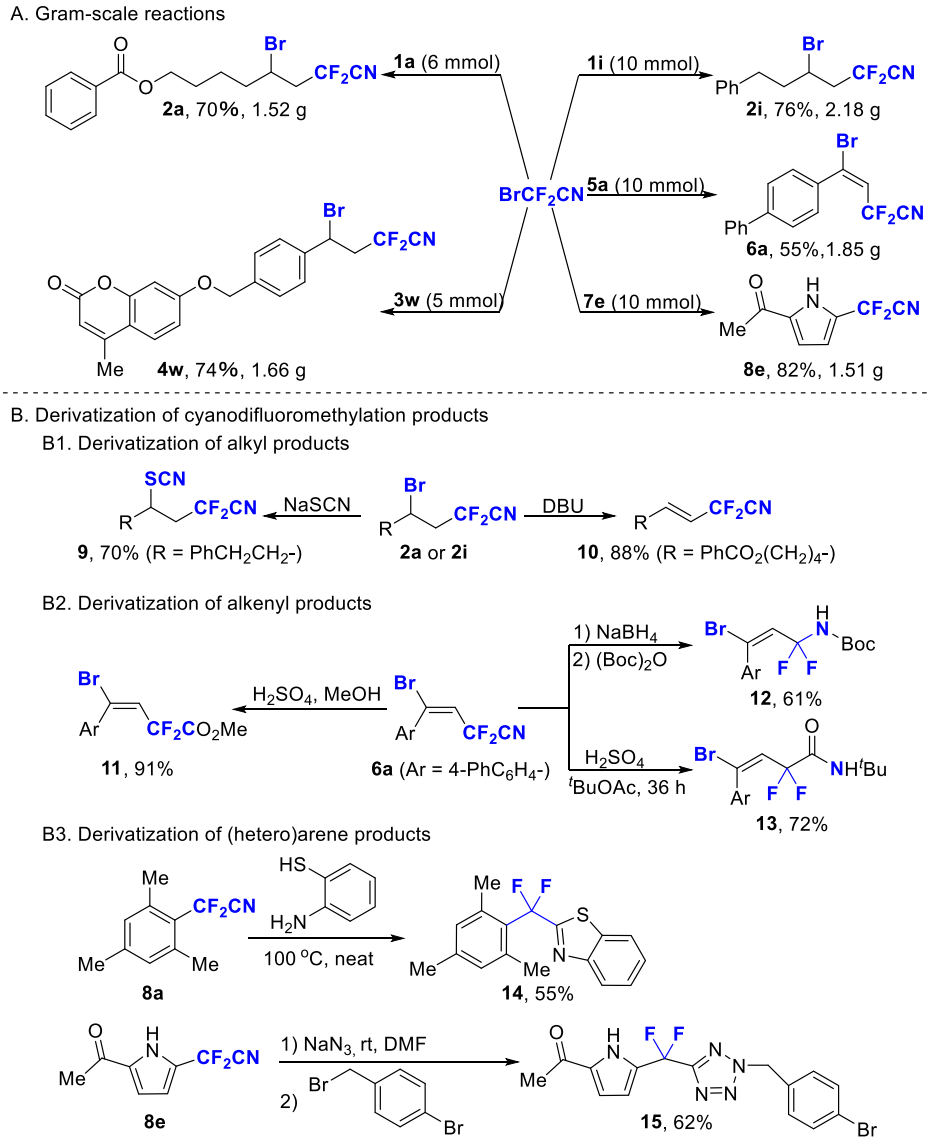

Fig. 7 | Demonstrative reactions highlighting the synthetic utility of the cyanodifluoromethylation protocol. Isolated yields are shown. **A** Gram-scale reaction for demonstrating the scalability and practical application of the cyanodifluoromethylation protocol. **B** Derivatization of cyanodifluoromethylation products to demonstrate their versatility.

Initially, the photocatalyst Ir(III) absorbs visible light to generate the excited states $(Ir^{III})^*$, which can reduce $BrCF_2CN$ to produce a $\cdot CF_2CN$ radical and a bromide anion, oxidizing $(Ir^{III})^*$ into Ir^{IV} in this process. Next, the $\cdot CF_2CN$ radical is captured by an alkyne to yield an alkenyl radical intermediate (**Int 1**). The alkenyl radical intermediate abstracts a bromine atom from $Cu^{II}Br_2$ to form the ***Z*-6** product and $Cu^{I}Br$. Subsequently, Ir^{IV} is reduced by $Cu^{I}Br$, completing the regeneration of the catalyst. The transformation of ***Z*-6** into ***E*-6** is facilitated by an energy transfer sensitization (E_nT)[53,54]. After the photocatalyst is excited, intersystem crossing (ISC) occurs from the singlet to the triplet state. The photocatalyst in its triplet state then transfers energy to the ***Z*-6** aryl product, resulting in the formation of an aryl biradical intermediate (**Int 2**) and the return of the photocatalyst to its ground state. The final step involves the formation of a π bond, yielding the ***E*-6** aryl product. Due to allylic strain disrupting conjugation in the *E*-isomer, which prevents electronic delocalization and increases the triplet state energy of the *E*-product, energy transfer sensitization would not easily take place for *E*-products. The last formation of the π bond may also give the ***Z*-6** product; however, this ***Z*-6** product would undergo another E_nT process, ultimately leading to an accumulation of the *E*-isomer. For ordinary alkyl alkynes, the formation of *Z*-isomers as major products can be attributed to the absence of conjugation, which increases the triplet state energy and prevents energy transfer sensitization.

Since CF_2CN is a group with unknown electronic properties, we decided to determine its Hammett constants σ_m and σ_p (Fig. 10). After measuring the pK_a values of *meta*-substituted and *para*-substituted benzoic acids to be 3.77 and 3.80, respectively, we calculated the Hammett constants using the Hammett equation, resulting in $\sigma_m = 0.43$ and $\sigma_p = 0.40$[5]. The constants reflect that its electron-withdrawing effect is slightly higher than that of the OCF_3 group ($\sigma_m = 0.38$, $\sigma_p = 0.35$) and is comparable to that of CO_2Et ($\sigma_m = 0.37$, $\sigma_p = 0.45$) and $SeCF_3$ ($\sigma_m = 0.44$, $\sigma_p = 0.45$)[5]. The electron-withdrawing effects are highly valuable in pharmaceutical chemistry.

Discussion

In summary, we have described the use of $BrCF_2CN$ as an efficient CF_2CN source for cyanodifluoromethylation of alkyl alkenes, aryl alkenes, alkynes, and (hetero)arenes. These mild and highly atom-economical methods feature a broad substrate scope, good functional group

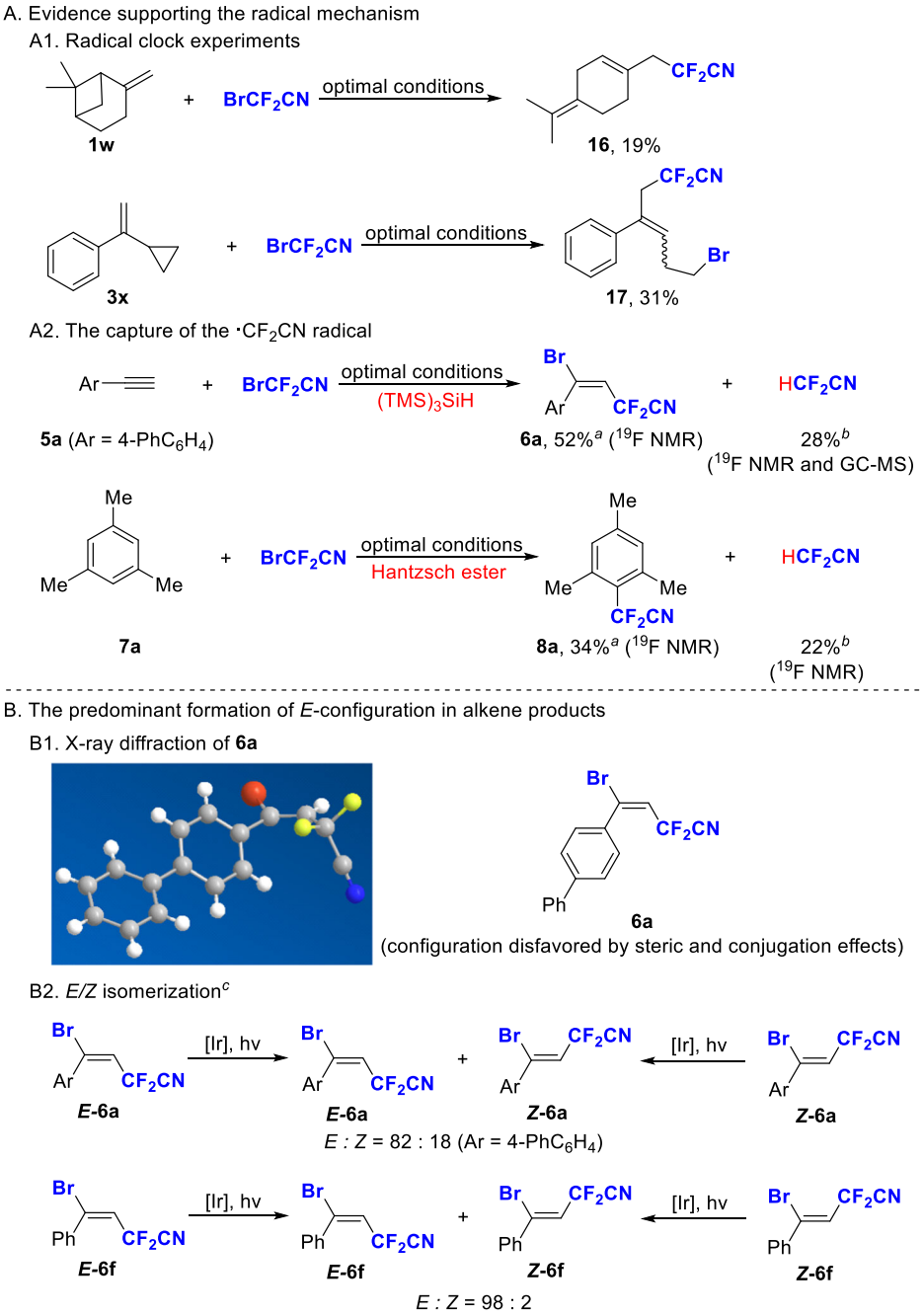

Fig. 8 | Mechanistic investigations. A Evidence supporting the photoredox radical mechanism. [a]The yield was determined with respect to the corresponding substrate. [b]The yield was determined with respect to $BrCF_2CN$. **B** The predominant formation of *E*-configuration in alkene products. [c]The *E*/*Z* ratios were determined by ^{19}F NMR spectroscopy.

compatibility, high regioselectivity, and stereoselectivity, providing the corresponding products in moderate to good yields. The successful application in the late-stage modification of bioactive molecules renders these methods highly valuable, and gram-scale preparations have demonstrated their practicality. Furthermore, the synthetic utility of the CF_2CN-containing products is illustrated by diverse transformations. For the bromo-cyanodifluoromethylation of aryl alkenes, copper bromide serves as an excellent XAT mediator, overcoming the challenge of oligomerization. The combination of Ir/Cu-cooperative catalysis and E_nT catalysis provides a highly valuable strategy for achieving the stereoselective bromo-cyanodifluoromethylation of alkynes with a thermally disfavored configuration. The cyanodifluoromethylation of (hetero) arenes can also proceed under photo-redox catalysis without the need for pre-activation of the substrates. Cyanodifluoromethyl functional group (CF_2CN) possesses strong electron-withdrawing properties, suggesting its broad applicability in the life and material sciences upon incorporation into organic compounds.

Methods

General produce for the bromo-cyanodifluoromethylation of alkyl alkenes

A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with an alkyl alkene substrate (0.5 mmol, 1.0 equiv, if it is a solid) and $Ru(phen)_3(PF_6)_2$ (2.3 mg, 0.5 mol%) under an air atmosphere. The tube was evacuated and refilled with N_2 (three times). The solution of $BrCF_2CN$ in DMF (0.5 mmol/mL, 2.5 mL) and an alkyl

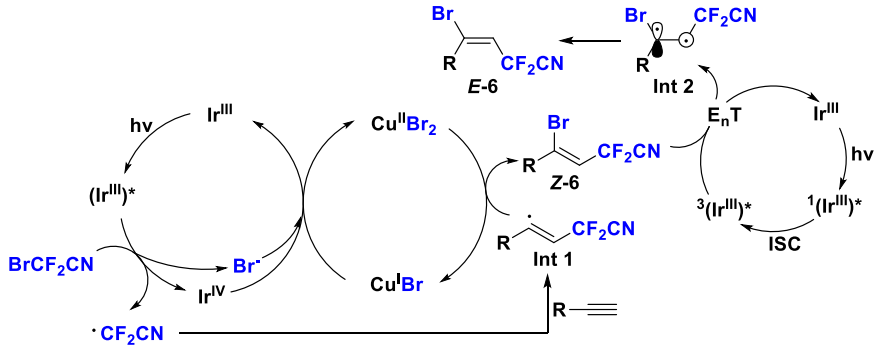

Fig. 9 | The plausible reaction mechanism for the bromo-cyanodifluoromethylation of alkynes. The reaction may firstly generate thermodynamically favorable *Z*-alkenes, which are then converted to sterically *E*-products via energy transfer sensitization (E_nT).

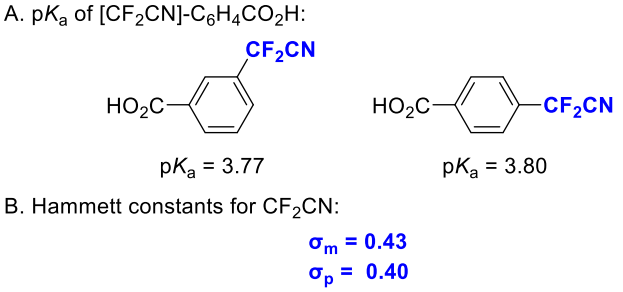

Fig. 10 | The determination of Hammett constants for CF_2CN. A pK_a of [CF_2CN]-substituted benzoic acids. **B** Hammett constants of the CF_2CN group.

alkene substrate (0.5 mmol, 1.0 equiv, if it is a liquid) were added. (Note: If the alkene is solid, it was first added to the Schlenk tube along with the photocatalyst, followed by nitrogen purging, and then bromodifluoroacetonitrile was added. And if the alkene is a liquid, the photocatalyst was first added to the Schlenk tube, followed by nitrogen purging, and then bromodifluoroacetonitrile and the alkene were added. For the following alkyne and aromatics substrates, similar procedures were adopted.) The mixture was stirred at room temperature for 36 h under blue LEDs irradiation (For the reaction setup, please see Supplementary Figs. 1 and 2.) with a fan serving as a cooler. The final mixture was diluted with EtOAc or DCM. The organic phases were washed with brine and then concentrated. The residue was subjected to flash column chromatography to afford the desired product.

General produce for the bromo-cyanodifluoromethylation of aryl alkenes

A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with an aryl alkene substrate (0.5 mmol, 1.0 equiv, if it is a solid), $CuBr_2$ (11.2 mg, 0.05 mmol, 0.1 equiv), and $Ru(phen)_3(PF_6)_2$ (2.3 mg, 0.5 mol%) under an air atmosphere. The tube was evacuated and refilled with N_2 (three times). The solution of $BrCF_2CN$ in DMF (0.5 mmol/mL, 2.5 mL) and an aryl alkene substrate (0.5 mmol, 1.0 equiv, if it is a liquid) were added. The mixture was stirred at room temperature for 24 h under blue LEDs irradiation with a fan serving as a cooler. The final mixture was diluted with EtOAc or DCM. The organic phases were washed with brine and then concentrated. The residue was subjected to flash column chromatography to afford the desired product.

General produce for the bromo-cyanodifluoromethylation of alkynes

A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with an alkyne substrate (0.5 mmol, 1.0 equiv, if it is a solid), $CuBr_2$ (8.4 mg, 7.5 mol%) and [$Ir(dF(CF_3)ppy)_2(dtbbpy)$][$PF_6$] (5.6 mg, 1 mol%) under an air atmosphere. The tube was evacuated and refilled with N_2 (three times). The solution of $BrCF_2CN$ in DMF (0.5 mmol/mL, 2.5 mL) and an alkyne substrate (0.5 mmol, 1.0 equiv, if it is a liquid) were added. The mixture was stirred at room temperature for 36 h under blue LED irradiation with a fan serving as a cooler. The final mixture was diluted with EtOAc or DCM. The organic phases were washed with brine and then concentrated. The residue was subjected to flash column chromatography to afford the desired product.

General produce for the C–H cyanodifluoromethylation of (hetero)arenes

A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with a (hetero)arene substrate (0.5 mmol, 1.0 equiv, if it is a solid), and [$Ir(dtbbpy)(ppy)_2$][PF_6] (2.3 mg, 0.5 mol%) under an air atmosphere. The tube was evacuated and refilled with N_2 (three times). A solution of $BrCF_2CN$ in DMF (0.5 mmol/mL, 2.5 mL) and a (hetero) arene substrate (0.5 mmol, 1.0 equiv, if it is a liquid) were added. The mixture was stirred at room temperature for 24 h under blue LEDs irradiation with a fan serving as a cooler. The final mixture was diluted with EtOAc or DCM. The organic phases were washed with brine and then concentrated. The residue was subjected to flash column chromatography to afford the desired product.

Data availability

The X-ray crystal structure data generated in this study have been deposited in the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC 2360341 and 2360342 for compounds **6a** and **8e**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/. The data supporting the findings of this study are available within the article and its Supplementary Information. Data supporting the findings of this manuscript are also available from the corresponding author upon request.

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Author contributions

X.-J. Yang performed the experiments and analyzed the data. J.-H. Lin wrote the manuscript and analyzed the data. J.-C. Xiao directed the project and wrote the manuscript. All authors reviewed and edited the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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