Organic &
Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c8ob02486c

Received 6th October 2018,
Accepted 6th November 2018

DOI: 10.1039/c8ob02486c

rsc.li/obc

Synthesis of fluoroalkylated alkynes *via* visible-light photocatalysis†

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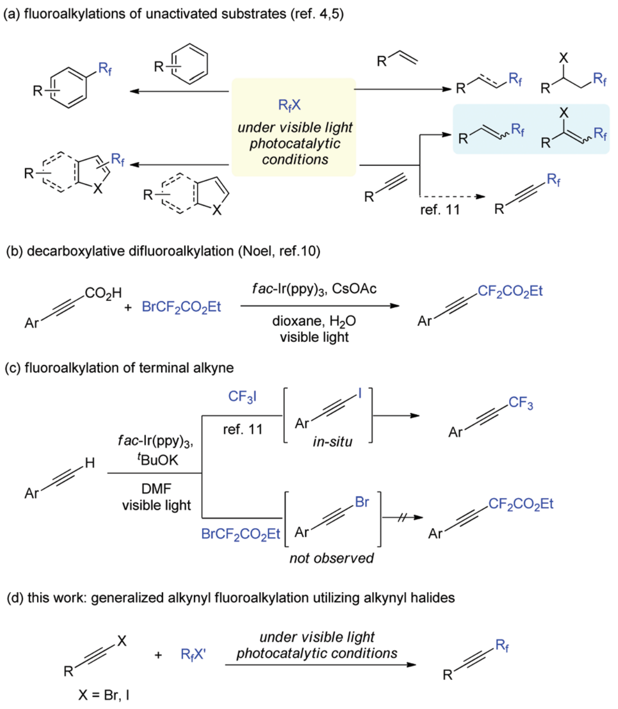
Fluoroalkylated alkynes, which are versatile building blocks for the synthesis of various biologically active organofluorine compounds, were synthesized from easily available alkynyl halides and fluoroalkyl halides by visible-light photocatalysis. Addition of fluoroalkyl radicals to alkynes and subsequent dehalogenation selectively yielded fluoroalkylated alkynes.

Incorporation of fluorinated moieties into organic molecules has gained tremendous importance among synthetic/medicinal chemists mainly because of the unique properties that fluorine imparts to the organic molecules.[1] Fluoroalkylation can change the properties of organic molecules, such as metabolic stability, lipophilicity, and bioavailability, with minimum structural alterations.[2] The significant medicinal importance and natural scarcity of fluorinated organic molecules have urged synthetic chemists to develop new methods for the incorporation of fluoroalkyl moieties into organic compounds.[3]

Radical fluoroalkylation has long been employed for the installation of fluoroalkyl groups and the recent research interest in visible-light photocatalysis has provided this protocol significant augmentation.[4,5] However, most of the previous research efforts were dedicated towards aryl and alkenyl fluoroalkylation (Scheme 1a), while alkynyl fluoroalkylation has been less explored.[6] Terminal alkynes have not been suitable substrates for the selective synthesis of fluoroalkylated alkynes in photocatalysis,[7] because most reactions with terminal alkynes yielded di- or tri-substituted fluoroalkylated alkene products instead (Scheme 1a).[8] Considering that fluoroalkylated alkynes are important organofluorine compounds, in that they are versatile building-blocks for the synthesis of complex biologically active organofluorine target molecules through further reactions of the alkyne moiety,[9] development of methods for selective synthesis of fluoroalkylated alkynes is in high demand.

Recently, Noël and co-workers have reported the synthesis of difluoroalkylated alkynes from phenyl propionic acid derivatives by visible-light photocatalysis (Scheme 1b).[10] We have previously reported that trifluoromethylated alkynes could be obtained from terminal alkynes *via* alkynyl iodide intermediates (Scheme 1c).[11] We have tried to extend these results for the preparation of a diverse range of synthetically important alkynyl fluoroalkylated compounds. However, replacing CF_3I with other fluoroalkyl halides such as ethyl bromodifluoroacetate ($BrCF_2CO_2Et$) did not yield the expected difluoroalkylated



Scheme 1 Visible light-mediated radical fluoroalkylations.

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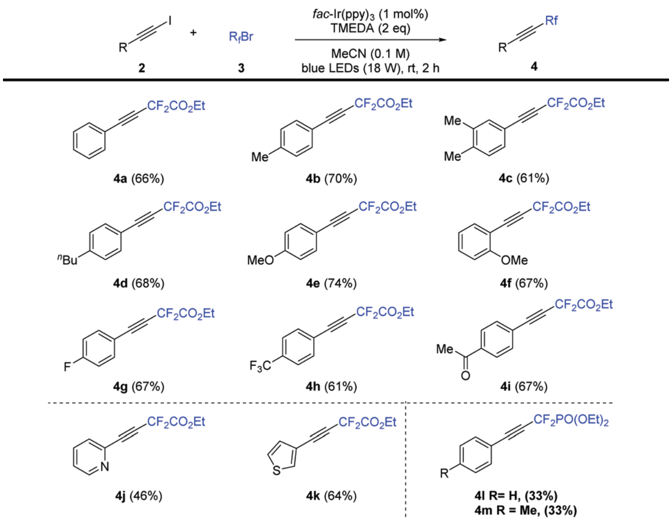
† Electronic supplementary information (ESI) available: Characterization data and ^1H and ^{13}C NMR spectra of the synthesized compounds. See DOI: 10.1039/c8ob02486c

alkyne because the necessary bromide intermediate could not be formed under the photocatalytic conditions (Scheme 1c). Probably, *in situ* generation of the required halide intermediate is limited to CF_3I. The inability of terminal alkynes to undergo selective alkynyl fluoroalkylations forced us to use prefunctionalized alkynyl halides with various fluoroalkyl halides under mild photocatalytic conditions (Scheme 1d).

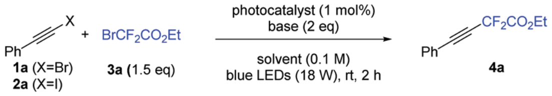
The investigation was initiated by reacting an alkynyl bromide **1a** with $BrCF_2CO_2Et$ (**3a**) as the fluoroalkylating source (Table 1). The reaction with *fac*-Ir(ppy)$_3$ and TMEDA at 0.1 M concentration in MeCN (entry 1) produced the desired product **4a** in 48% yield under visible light irradiation. As expected, the use of terminal alkynes did not yield any difluoroalkylated product under the same conditions (entry 2). The different cyclometalated Ru catalysts showed slightly better reactivities (entries 3 and 4). Replacement of bromide with iodide (**2a**) in the alkynyl substrate gave improved results (entries 5 and 6), and *fac*-Ir(ppy)$_3$ emerged as the better photocatalyst. Solvent screening did not improve the reaction yield (entries 7 and 8). Surprisingly, no reaction occurred when DBU was used as a base (entry 9). Fluctuation in the stoichiometric ratio of the reactants showed that the use of **3a** as the limiting reactant with 1.5 equivalents of the alkynyl substrate provided a better reaction yield (Table 1, entries 10–12). The absence of the photocatalyst, light source, or base almost completely suppressed the reaction (Table 1, entries 13–15).

Table 2 Substrate scope of alkynyl difluoroalkylation[a,b]



[a] Reaction scale: **2** (1.5 mmol), **3** (1 mmol). [b] Isolated yields.

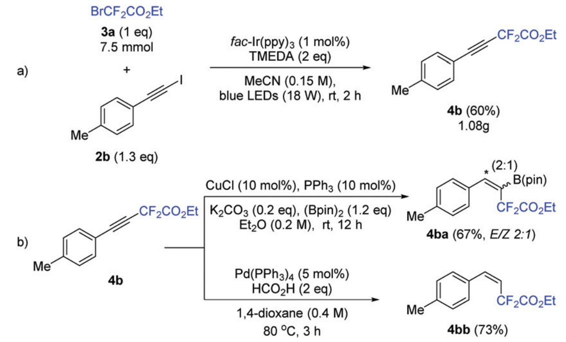
Table 1 Optimization of alkynyl difluoroalkylation[a]



Entry	X	Photocatalyst	Base	Solvent	Variation	Yield[b] (%)
1	Br	*fac*-Ir(ppy)$_3$	TMEDA	MeCN	—	48
2	H	*fac*-Ir(ppy)$_3$	TMEDA	MeCN	—	0
3	Br	[Ru(phen)$_3$]Cl$_2$	TMEDA	MeCN	—	52
4	Br	[Ru(bpy)$_3$]Cl$_2$	TMEDA	MeCN	—	51
5	I	*fac*-Ir(ppy)$_3$	TMEDA	MeCN	—	60
6	I	[Ru(phen)$_3$]Cl$_2$	TMEDA	MeCN	—	56
7	I	*fac*-Ir(ppy)$_3$	TMEDA	DMF	—	58
8	I	*fac*-Ir(ppy)$_3$	TMEDA	DMSO	—	49
9	I	*fac*-Ir(ppy)$_3$	DBU	MeCN	—	0
10	I	*fac*-Ir(ppy)$_3$	TMEDA	MeCN	**3a** (1.2 eq.)	38
11[c]	**I**	***fac*-Ir(ppy)$_3$**	**TMEDA**	**MeCN**	**3a (1 eq.)**	**70**
12	I	*fac*-Ir(ppy)$_3$	TMEDA	MeCN	**3a** (3 eq.)	66
13	I	—	TMEDA	MeCN	—	0
14	I	*fac*-Ir(ppy)$_3$	—	MeCN	—	6
15	I	*fac*-Ir(ppy)$_3$	TMEDA	MeCN	No light	4

[a] All reactions were carried out at the 0.1 mmol scale. [b] GC yields are reported by using 2,2,2-trifluoroacetophenone as the internal standard. [c] (Iodoethynyl)benzene **2a** (1.5 eq.).

Next, to investigate the generality of this alkynyl-difluoroalkylation, various substrates were examined under the optimal catalytic conditions (Table 2). Reactions of phenylacetylene derivatives, containing both electron-donating (**4b**, **4c**, **4d**, **4e**, **4f**) and electron-withdrawing substituents (**4g**, **4h**, **4i**), gave good results. Various functional groups including phenolic ether (**4e**, **4f**) and ketone **4i** were tolerated under the mild reaction conditions. Heteroaryl-substituted compounds were also found to be suitable substrates to obtain the corresponding difluoroalkylated products **4j** and **4k**. α,α-Difluoropropargylphosphonates **4l** and **4m** were synthesized under the given conditions, where the phosphonate moiety can be utilized as a versatile intermediate in the synthesis of biologically important molecules. It is also notable that aromatic and heteroaromatic rings remained unreactive under the reaction conditions. However, aliphatic alkynylhalides did not undergo selective fluoroalkylation, producing multiple unidentified side products. The optimized conditions were also amenable for gram-scale reaction, proving the practicality of the process



Scheme 2 Gram-scale reaction and synthetic applications.

(Scheme 2a). Furthermore, the synthetic utility of fluoroalkylated alkynes was investigated. Product **4b** was borylated to give **4ba** despite the formation of a mixture of isomers. In addition, **4b** was selectively reduced to give difluoroalkylated *Z*-alkene **4bb** (Scheme 2b).[12,13]

To extend the scope of fluoroalkylation, we next tried alkynyl perfluoroalkylations using other perfluoroalkyl iodides as the fluoroalkylating reagents. The use of iodide **2a** with nanofluoro-1-iodo butane **5a** provided the alkynyl-perfluoroalkylated product **6a** in 48% yield (Table 3, entry 1). The use of the bromide substrate **1a** instead of **2a** as the model substrate resulted in an improved yield (60%) of **6a** (Table 3, entry 2). Ru catalysts were found to be better photocatalysts for this perfluoroalkylation reaction (Table 3, entries 2–4). Unlike the aforementioned difluoroalkylation reaction, DBU proved to be the best base for perfluoroalkylation (Table 3, entries 5–7). Replacement of the solvents has a detrimental effect on the reaction yields (Table 3, entries 7–9), and increasing the reaction concentration to 0.2 M resulted in slightly better reactivity (Table 3, entries 10 and 11). These conditions were not very effective on a larger scale, which forced us to increase the amounts of catalyst and base to obtain full conversion and higher yield in large-scale reactions (Table 3, entry 12). Controlled reactions showed that the light source, catalyst, and base were compulsory components for the reaction (Table 3, entries 13–15).

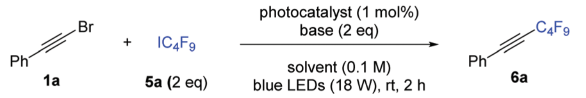
The optimized reaction conditions were applied for the perfluoroalkylation of different alkynyl bromides **1** (Table 4). Substrates having electron-donating groups on the aromatic rings (**6a**, **6b** and **6d**) gave a slightly higher yield than those having an electron-withdrawing substituent (**6e**). Perfluoroalkylating sources with longer and shorter carbon chain lengths (C_8F_{17} (**6f**), C_3F_7 (**6g**), and CF_3 (**6h**)) were also suitable for obtaining the corresponding fluoroalkylated alkynyl products. Unfortunately, alkynyl fluoroalkylation was not successful with an aliphatic side chain.

Subjecting terminal alkynes to the optimized conditions with C_4F_9I resulted in the formation of the desired product in only 31% yield, along with the generation of alkenyl fluoroalkylated products. This also supports the fact that the use of prefunctionalized alkynyl halides is required for selective alkynyl fluoroalkylation (Scheme 3).

Controlled experiments were conducted to gain insight into the reaction mechanism. Complete suppression of the reaction in the presence of radical scavengers like 1,4-dinitrobenzene supports the hypothesis that the reaction proceeds *via* a radical mechanism (Scheme 4a).[14] Furthermore, coupling of the CF_2CO_2Et radical with TEMPO resulted in the formation of compound **8**, which confirms that the reaction follows a radical pathway (Scheme 4b).

Based on these observations we proposed a reaction mechanism for the synthesis of alkynyl fluoroalkylations (Scheme 5).

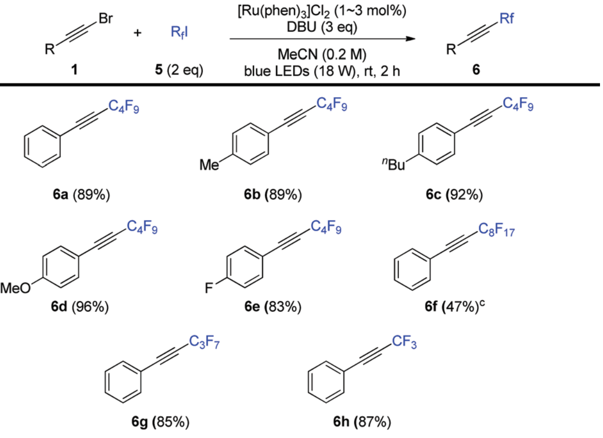
Table 3 Optimization of alkynyl-fluoroalkylation conditions[a]



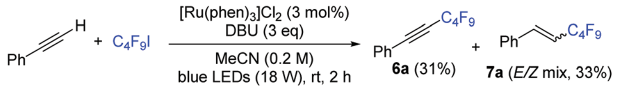
Entry	Photocatalyst	Base	Solvent	Variation	Yield[b] (%)
1	*fac*-Ir(ppy)$_3$	TMEDA	MeCN	**2a** instead of **1a**	48
2	*fac*-Ir(ppy)$_3$	TMEDA	MeCN	—	60
3	[Ru(bpy)$_3$]Cl$_2$	TMEDA	MeCN	—	65
4	[Ru(phen)$_3$]Cl$_2$	TMEDA	MeCN	—	65
5	[Ru(phen)$_3$]Cl$_2$	TEA	MeCN	—	13
6	[Ru(phen)$_3$]Cl$_2$	DIPEA	MeCN	—	7
7	[Ru(phen)$_3$]Cl$_2$	DBU	MeCN	—	80
8	[Ru(phen)$_3$]Cl$_2$	DBU	DMF	—	66
9	[Ru(phen)$_3$]Cl$_2$	DBU	DMSO	—	56
10	[Ru(phen)$_3$]Cl$_2$	DBU	MeCN	0.2 M	82
11	[Ru(phen)$_3$]Cl$_2$	DBU	MeCN	0.5 M	64
12[c]	[Ru(phen)$_3$]Cl$_2$	DBU	MeCN	DBU (3 eq.), (0.2 M)	89
13	—	TMEDA	MeCN	—	0
14	[Ru(phen)$_3$]Cl$_2$	—	MeCN	—	12
15	[Ru(phen)$_3$]Cl$_2$	TMEDA	MeCN	No light	0

[a] All reactions were carried out at the 0.1 mmol scale. [b] GC yields by using 2,2,2-trifluoroacetophenone as the internal standard. [c] [Ru(phen)$_3$]Cl$_2$ (3 mol%).

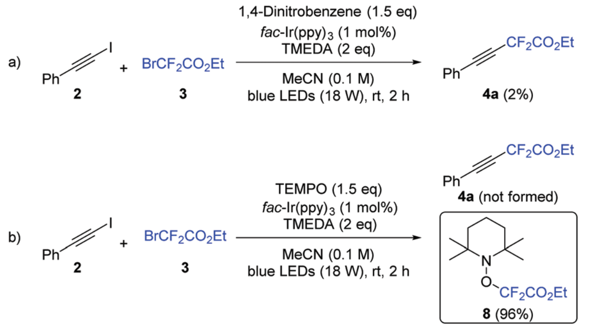
Table 4 Substrate scope of alkynyl-perfluoroalkylations[a,b]



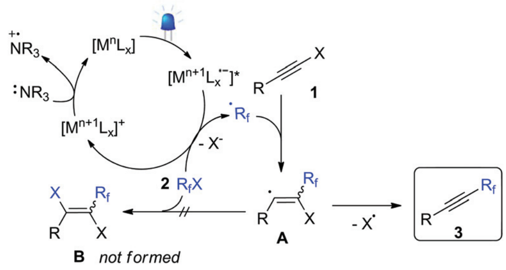
[a] Reaction scale: **1** (1.0 mmol). [b] GC yields by using 2,2,2-trifluoroacetophenone as the internal standard. [c] Isolated yield.



Scheme 3 Alkynyl perfluoroalkylation of terminal alkynes.



Scheme 4 Reactions with radical scavengers.



Scheme 5 Proposed mechanism.

Photoexcitation of cyclometalated Ru or Ir complexes $[M^nL_x]$ under visible-light irradiation by using blue LEDs will produce $[M^{n+1}L_x^{\bullet -}]^*$ *via* metal-to-ligand charge-transfer (MLCT). Single-electron donation to fluoroalkylhalide **2** will generate the oxidized photocatalyst $[M^{n+1}L_x]^+$ and the fluoroalkyl radical $^{\bullet}R_f$. The $[M^nL_x]$ complex is then regenerated by electron transfer from the sacrificial electron donor (TMEDA or DBU), and $^{\bullet}R_f$ adds to the alkynyl halide in a regioselective manner to produce a fluoroalkylated alkenyl radical **A**. This intermediate can undergo dehalogenation to yield the alkynyl fluoroalkylated product **3**. Based on our previous observations,[11] we proposed that the fluoroalkenyl radical intermediate may also abstract a halogen from the fluorinating source to produce the fluoroalkylated dihalogenated tetrasubstituted alkene **B**. However, this dihalogenated alkene **B** was not observed during the reaction.

Conclusions

In conclusion, we have developed alkynyl-difluoroalkylation and alkynyl-perfluoroalkylation reactions of alkynyl halides by visible-light photocatalysis to access a diverse range of fluoroalkyl alkynes. The mild reaction conditions tolerated a wide range of functional groups. The synthesized molecules can be used as versatile building blocks for the synthesis of fluorinated target molecules because alkynes can undergo a diverse range of organic transformations.[9]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the National Research Foundation of Korea [NRF-2012M3A7B4049657, NRF-2014-011165, NRF-2016K1A3A1A19945930, and NRF-2017R1A2B2004082].

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