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Distal Functional Group Migration for Visible-light Induced Carbo-difluoroalkylation/monofluoroalkylation of Unactivated Alkenes

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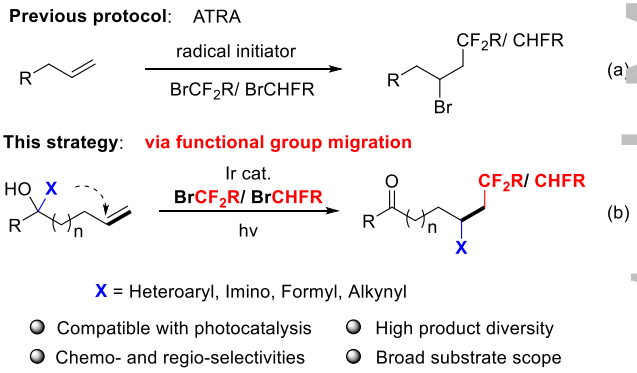
Abstract. A general and practical protocol for elusive carbo-difluoroalkylation/ monofluoroalkylation of unactivated alkenes based on the distal functional group migration is described. A portfolio of functional groups including heteroaryl, imino, formyl, and alkynyl groups showcase the migratory aptitude. In combination with visible-light photocatalysis, a broad range of di- and mono-fluorinated alkyl ketones are readily obtained in synthetically useful yields under mild reaction conditions.

Keywords: difluoroalkylation; monofluoroalkylation; photocatalysis; alkene difunctionalization; functional group migration

Introduction

Given that the fluorine atom usually results in a remarkable change of lipophilicity, chemical stability, and bioactivity,[1] fluorine-containing compounds have gained wide attention in the past decades in many research areas across synthetic chemistry, agrochemicals, pharmaceuticals, and material sciences. Consequently, the development of practical methods to incorporate the fluorine atom into organic molecules is of high importance.[2] Recently, a considerable progress has been made with radical fluoroalkylation of alkenes to provide powerful and divergent approaches for the installation of fluoroalkyl groups. In these efforts, di- and mono-fluoroalkylation of alkenes are relatively less investigated than trifluoromethylation of alkenes,[3,4] regardless of the special use of CF_2 and CF units in medicinal chemistry.[5] Moreover, the present studies regarding di- and mono-fluoroalkylation of alkenes are generally employing the activated alkenes as substrates.[6] The reactions with unactivated alkenes are mostly dependent upon the process of atom transfer radical addition (ATRA) (Scheme 1a).[7] Therefore, the development of a general protocol for di- and mono-fluoroalkylation of unactivated alkenes with simultaneous introduction of an additional valuable functional group is still highly desirable.



Scheme 1. Di- and mono-fluoroalkylation of unactivated olefins

Despite the great progress made in the field of radical-mediated difunctionalization of alkenes,[8] the manipulation of unactivated alkenes still remains challenging. In this scenario, the strategy of intramolecular functional group migration provides an efficient solution for difunctionalization of unactivated olefins.[9] A common protocol is the radical-mediated 1,2-aryl migration.[10] In addition, a few examples of distal aryl migration have also been reported.[11] Recently, we achieved the first example of application of distal cyano migration to the radical azidocyanation of unactivated alkenes, affording the azido-substituted alkyl nitriles.[12] Afterward, we disclosed the distal heteroaryl and alkynyl migration

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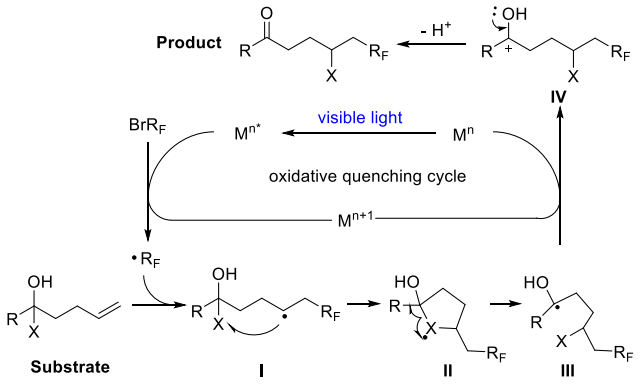
for the trifluoromethylative heteroarylation and alkynylation of unactivated alkenes for the first time, furnishing the trifluoroalkylated alkyl ketones.[13] Prompted by these results, we considered to apply the strategy of intramolecular functional group migration to di- and mono-fluoroalkylation of unactivated alkenes.

Visible-light photoredox catalysis provides a robust and eco-friendly tool for production of free radicals.[14] Based on the analysis of catalytic pathways, we hypothesize that the combination of photocatalysis and functional group migration might serve for our purpose. As depicted in Scheme 2, the transient excited state of photocatalyst M^{n}* triggered by the visible-light irradiation can be oxidatively quenched by the bromoalkane to form a fluoroalkyl radical and M^{n+1}.[15] Addition of the fluoroalkyl radical to alkene gives rise to the intermediate **I** that subsequently cyclizes with the radical acceptor X group to generate the intermediate **II**. Ring-opening homolysis of **II** results in a hydroxyl-stabilized radical **III** which is then oxidized by M^{n+1} to produce the intermediate **IV** and regenerates M^{n}. The final product is obtained after the deprotonation of **IV**.



Scheme 2. Combined strategies of functional group migration and photocatalysis.

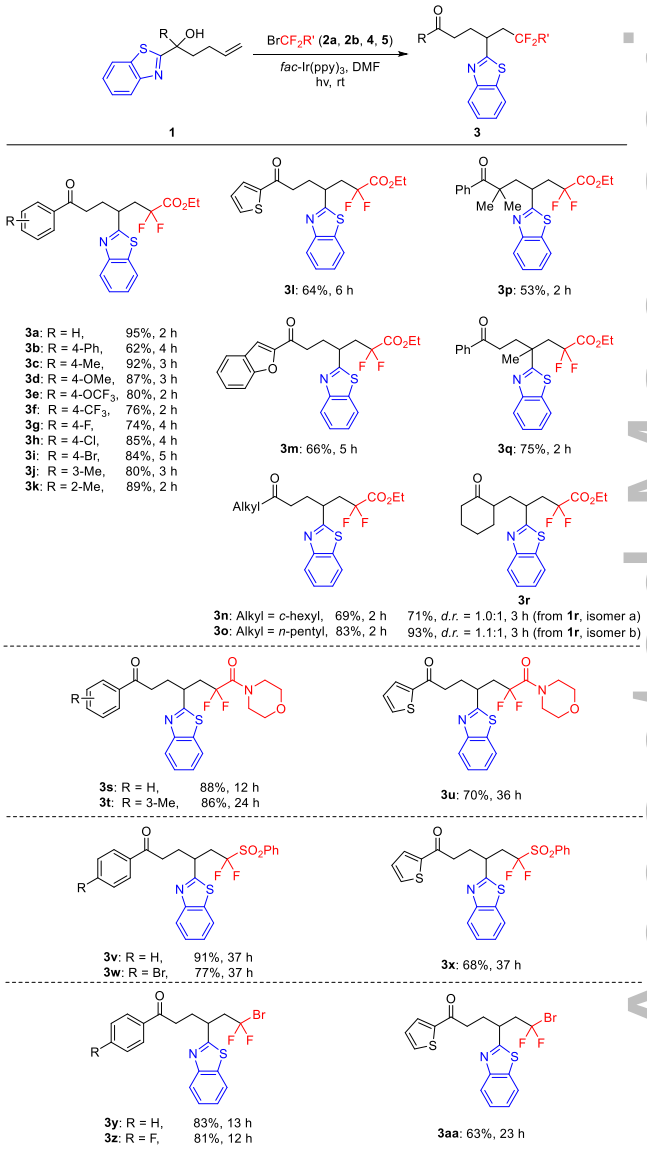
Herein, we provide concrete support for the hypothesis. A general protocol for the carbo-difluoroalkylation/ monofluoroalkylation of unactivated alkenes by merging the intramolecular migration of functional group and photocatalysis is described (Scheme 1b). The migratory aptitude of a portfolio of functional groups such as heteroaryl, imino, formyl, and alkynyl is investigated. A broad range of synthetically useful di- and mono-fluorinated alkyl ketones are readily furnished under mild reaction conditions.

Results and Discussion

Heteroaryl-fluoroalkylation of unactivated alkenes

Heteroarenes are of high importance in both organic and medicinal chemistry. For example, they are present in almost half of the top 200 on-sale pharmaceuticals.[16] The radical-mediated heteroarylfluoroalkylation of alkenes provides an efficient tool for the preparation of fluoroalkyl-substituted heteroarenes.

With the benzothiazole-substituted tertiary alcohol **1** and bromodifluoroacetate **2a** as substrates, the reaction was performed under the irradiation of visible light (Scheme 3). The substrates bearing either electron-rich or deficient aryl substituent consistently provided satisfactory chemical yields (**3a**-**3k**). The yield was not appreciably affected by changing the position (*p*-, *m*-, *o*-) of substituents (**3c**, **3j**, and **3k**). The migration reaction demonstrated a unique chemoselectivity that only the migration of



Scheme 3. Heteroaryldifluoroalkylation of unactivated olefins. Reaction conditions: **1** (0.2 mmol, 1 equiv), **2a** (or **2b**, **4**, **5**) (0.4 mmol, 2.0 equiv), *fac*-Ir(ppy)$_3$ (0.008 mmol, 4 mol %) in DMF (2 mL) at rt, 10 W blue LEDs irradiation.

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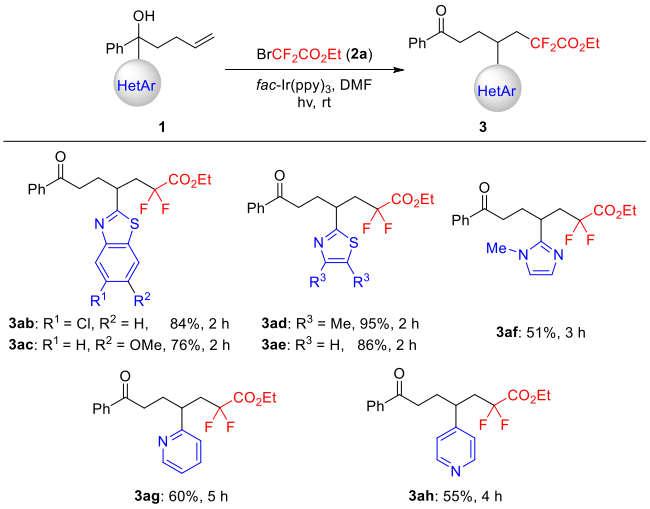
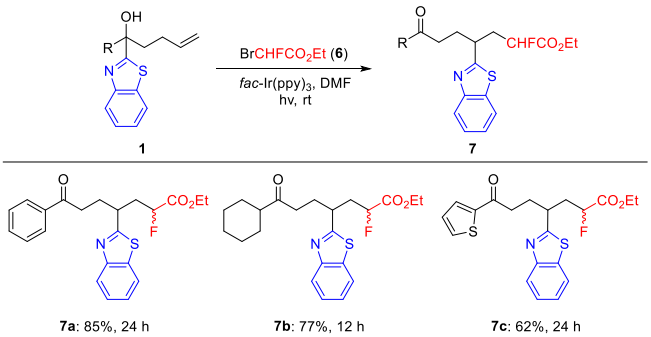
benzothiazolyl group took place while the presence of other sulfur or oxygen-containing heteroarenes (**3l** and **3m**). The alkyl-substituted tertiary alcohols also proved to be apt substrates (**3n** and **3o**). Notably, the stereoselective migration of heteroaryl group remains difficult as both two isomers of **1r** generated the corresponding products **3r** with the similar diastereomeric ratios. Other difluoroalkylation reactions were examined with **2b** (bromodifluoroacetamide), **4** (bromodifluoromethanesulfonylbenzene), and **5** (dibromodifluoromethane). A variety of synthetically useful difluorinated alkyl ketones were readily obtained (**3s-3aa**).

We then assessed the migratory aptitude of various heteroaryl groups. Under the visible-light irradiation, a set of nitrogen-containing heteroarenes proved to be suitable migratory functional group (Scheme 4). The functionalized benzothiazolyls as well as thiazolyls migrated smoothly to give the corresponding products in good yields (**3ab-3ae**). The migration of imidazolyl led to a lower yield (**3af**). In addition to five-membered heteroaryl, the migration of six-membered heteroaryl such as 2-pyridyl and 4-pyridyl could also proceed efficiently (**3ag** and **3ah**). Obviously, extension of this protocol to the migration of other functionalized five- and six-membered nitrogen-containing heteroaryls can also be anticipated.

This protocol was also applied to the heteroarylmonofluoroalkylation of alkenes (Scheme 5). A variety of aryl, alkyl, and heteroaryl substituted tertiary alcohols were readily converted into the monofluorinated alkyl ketones in practical yields (**7a-7c**).



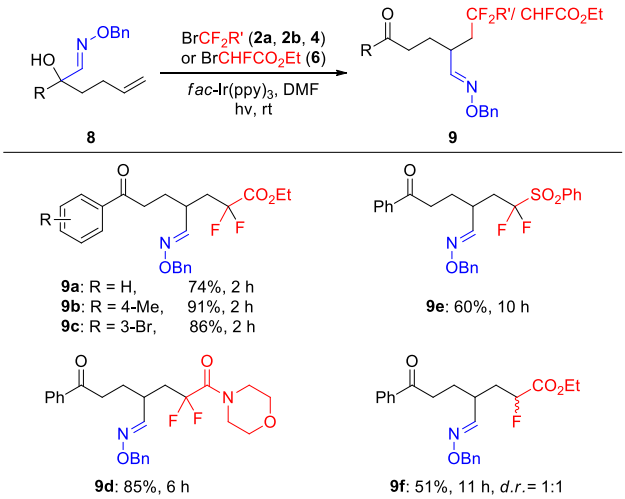
Scheme 4. Scope of migratory N-containing heteroarenes. Reaction conditions: **1** (0.2 mmol, 1 equiv), **2a** (0.4 mmol, 2.0 equiv), *fac*-Ir(ppy)$_3$ (0.008 mmol, 4 mol %) in DMF (2 mL) at rt, 10 W blue LEDs irradiation.



Scheme 5. Heteroarylmonofluoroalkylation of unactivated olefins. Reaction conditions: **1** (0.2 mmol, 1 equiv), **6** (0.4 mmol, 2.0 equiv), *fac*-Ir(ppy)$_3$ (0.008 mmol, 4 mol %) in DMF (2 mL) at rt, 10 W blue LEDs irradiation. Yields of isolated products are given, *d.r.* = 1 : 1.

Imino-fluoroalkylation of unactivated alkenes

Upon completion of the migration of heteroaryl group, we were prompted to explore the migration of other unsaturated C-N bonds such as imine. With the imino-substituted tertiary alcohol **8** as substrate, as expected, the reaction with either difluoroalkyl or monofluoroalkyl reagent (**2a**, **2b**, **4**, and **6**) readily proceeded under the visible-light irradiation to afford the corresponding imino-migrated product **9** (Scheme 6). Both electron-rich and deficient substrates were well tolerated, furnishing a set of di- and mono-fluorinated alkyl ketones (**9a-9f**). Notably, the imino moiety of products could be conveniently transformed into many other useful functionalities, e.g., amine, aldehyde, and alcohol. This is the first report of a difunctionalization of unactivated olefins with concomitant introduction of a versatile imino group.



Scheme 6. Iminofluoroalkylation of unactivated olefins. Reaction conditions: **8** (0.2 mmol, 1 equiv), **2a** (**2b**, **4**, or **6**) (0.4 mmol, 2.0 equiv), *fac*-Ir(ppy)$_3$ (0.008 mmol, 4 mol %) in DMF (4 mL) at rt, 10 W blue LEDs irradiation. Yields of isolated products are given.

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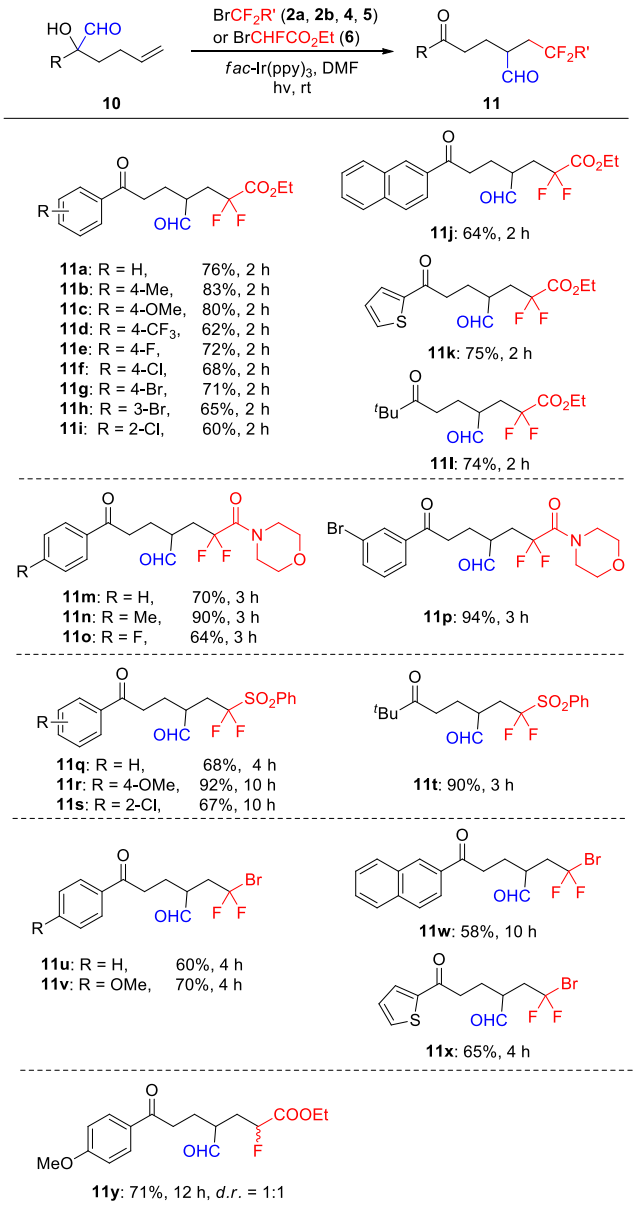
Formyl-fluoroalkylation of unactivated alkenes

We envisioned that the migration of unsaturated C-O bond such as formyl group could also be realized under the photocatalytic reaction conditions. When we were carrying out this project, Liu and coworkers disclosed the radical-mediate formylation of alkenes by means of intramolecular formyl group migration.[17] However, only a single example of formyldifluoroalkylation of alkene by using bromodifluoroacetate **2a** under visible-light irradiation was reported in 43% yield. From the practical point of view, the systematic studies for the photocatalytic formyldifluoroalkylation of alkenes is still in demand.



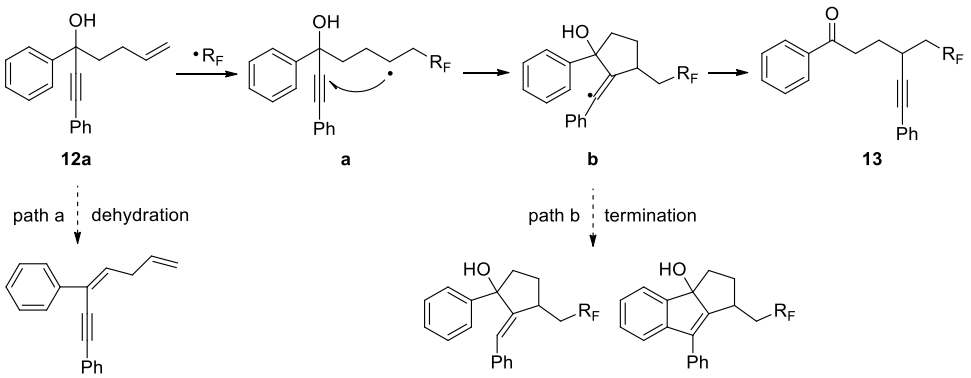
Scheme 7. Formylfluoroalkylation of unactivated olefins. Reaction conditions: **10** (0.2 mmol, 1 equiv), **2a** (**2b**, **4**, **5**, or **6**) (0.4 mmol, 2.0 equiv), *fac*-Ir(ppy)$_3$ (0.008 mmol, 4 mol %) in DMF (4 mL) at rt, 10 W blue LEDs irradiation. Yields of isolated products are given.

With the α-formyl substituted tertiary alcohol **10** as substrate, the migration of formyl group was induced by addition of a fluoroalkyl radical to the olefin part, furnishing the resultant fluorinated aliphatic aldehyde **11** (for detailed reaction conditions survey, see SI; Scheme 7). The reaction demonstrated a broad functional group tolerance that both electron-rich and deficient substrates smoothly led to the desired products. In addition to the phenyl and naphthyl substituted tertiary alcohols (**11a-11j**), the thienyl and *t*-butyl substrates were also compatible with the reaction conditions to deliver good yields (**11k** and **11l**). Other difluoroalkylating reagents including **2b**, **4**, and **5** were also suitable coupling partners to give the difluoroalkylated products in synthetically useful yields (**11m-11x**). Moreover, the efficient formylmonofluoroalkylation of unactivated alkene was exemplified as well (**11y**).

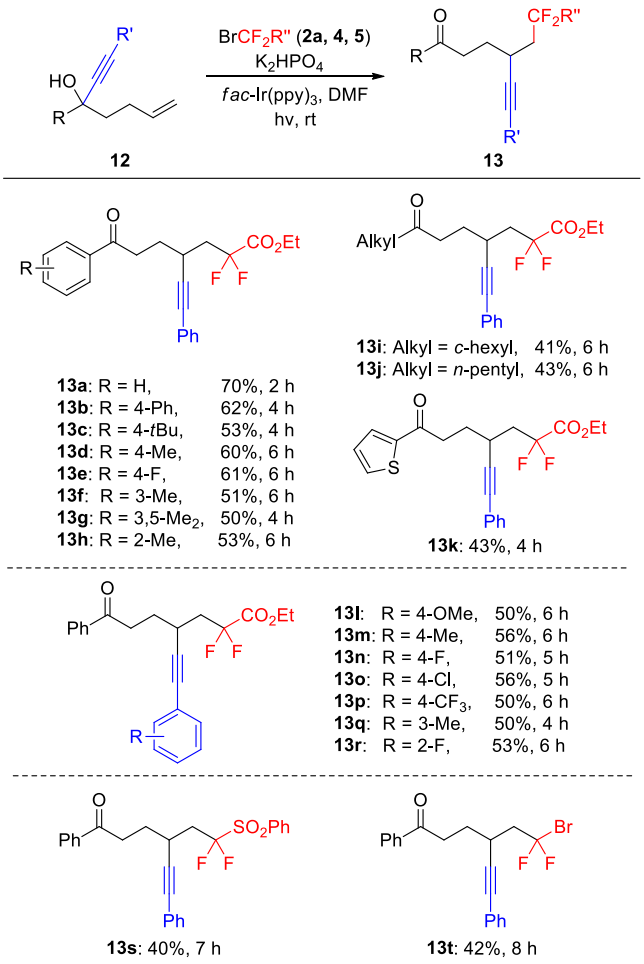
Alkynyl-fluoroalkylation of unactivated alkenes

As a prominent example of unsaturated C-C bonds, alkynyl group was also studied for the migratory aptitude. Mechanistically, there are several challenges present in the migration of alkynyl group (Scheme 8): (1) the addition of an extrinsic fluoroalkyl radical should be chemoselective to the alkenyl rather than the alkynyl part of **12a**; (2) the alkynyl-substituted tertiary alcohol **12a** is prone to dehydration (path a); and (3) the highly reactive olefinic radical **b** could be terminated by other competitive pathways, e.g., hydrogen abstraction, intramolecular cyclization (path b). When subjecting compound **12a** to the previous reaction conditions, indeed, the reaction was severely suffered from the dehydration. However, the dehydration was efficiently inhibited by the addition of K_2HPO_4, affording the expected alkynyl-migrated product **13a** in 70% yield (for detailed reaction conditions survey, see SI). Of note, the synthesis of such distally alkynyl-substituted alkyl ketones is useful but usually difficult.[18]

With the optimized reaction conditions in hand, we evaluated the generality of the protocol (Scheme 9). Both electron-rich and deficient aryl substrates furnished the corresponding products in synthetically useful yields (**13a-13e**). Substitution at different positions (*p*-, *m*-, *o*-) did not significantly change the reaction yields (**13d**, **13f-13h**). The reaction with aliphatic and heteroaryl substrates readily proceeded, albeit in modest yields (**13i-13k**). The migratory alkynyl group could also be variated. A set of functionalized aryl alkynes were smoothly migrated regardless of the electronic and steric effects (**13l-13r**). However, the migration of aliphatic alkyne was failed with the current reaction conditions. Moreover, bromodifluoromethanesulfonylbenzene **4** and dibromodifluoromethane **5** were also competent coupling partners to generate the difluoroalkylated products (**13s** and **13t**).



Scheme 8. Competitive pathways in the alkynyl migration process



Scheme 9. Alkynyldifluoroalkylation of unactivated olefins. Reaction conditions: **12** (0.2 mmol, 1 equiv), **2a** (**4**, or **5**) (0.4 mmol, 2 equiv), *fac*-Ir(ppy)$_3$ (0.008 mmol, 4 mol %), and K_2HPO_4 (0.16 mmol, 0.8 equiv) in DMF (3 mL) at rt, 10 W blue LEDs irradiation. Yields of isolated products are given.

Conclusion

In summary, we have described a general and practical protocol for elusive carbo-difluoroalkylation/ monofluoroalkylation of unactivated alkenes based on the combinational strategy of intramolecular functional group migration and visible-light photocatalysis. A series of functional groups including heteroaryl, imino, formyl, and alkynyl groups have showcased the migratory aptitude. The reaction demonstrates a good tolerance for various functionalities that a wide range of di- and mono-fluorinated alkyl ketones are readily obtained in synthetically useful yields under mild reaction conditions. The combination of functional group migration and photoredox catalysis paves a new avenue for the radical-mediated difunctionalization of unactivated alkenes.

Experimental Section

General Procedure for the Heteroaryl Migration Reaction

Heteroaryl-substituted tertiary alcohol (**1**) (0.2 mmol, 1.0 equiv), *fac*-Ir(ppy)$_3$ (0.008 mmol, 4 mol%), and $BrCF_2R$ (**2a**, **2b**, **4**, **5**)/ BrCHFR (**6**) (0.4 mmol, 2.0 equiv.) were loaded in a flask which was subjected to evacuation/flushing with nitrogen for three times. DMF (2.0 mL) was added to the mixture via syringe and the mixture was then irradiated by 10 W blue LEDs. The reaction was allowed for stirring at rt until the starting material had been consumed as determined by TLC. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed by brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography on silica gel (eluent: ethyl acetate/ petroleum ether) to give the corresponding product **3** or **7**.

General Procedure for the Imino Migration Reaction

Imino-substituted tertiary alcohol (**8**) (0.2 mmol, 1.0 equiv), *fac*-Ir(ppy)$_3$ (0.008 mmol, 4 mol%), and $BrCF_2R$ (**2a**, **2b**, **4**)/ BrCHFR (**6**) (0.4 mmol, 2.0 equiv) were loaded in a flask which was subjected to evacuation/flushing with nitrogen for three times. DMF (4.0 mL) was added to the mixture via syringe and the mixture was then irradiated by 10 W blue

LEDs. The reaction was allowed for stirring at rt until the starting material had been consumed as determined by TLC. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed by brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography on silica gel (eluent: ethyl acetate/ petroleum ether) to give the corresponding product **9**.

General Procedure for the Formyl Migration Reaction

Formyl-substituted tertiary alcohol (**10**) (0.2 mmol, 1.0 equiv), *fac*-Ir(ppy)$_3$ (0.008 mmol, 4 mol%), and $BrCF_2R$ (**2a**, **2b**, **4**, **5**)/ BrCHFR (**6**) (0.4 mmol, 2.0 equiv) were loaded in a flask which was subjected to evacuation/flushing with nitrogen for three times. DMF (4.0 mL) was added to the mixture via syringe and the mixture was then irradiated by 10 W blue LEDs. The reaction was allowed for stirring at rt until the starting material had been consumed as determined by TLC. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed by brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography on silica gel (eluent: ethyl acetate/ petroleum ether) to give the corresponding product **11**.

General Procedure for the Alkynyl Migration Reaction

Alkynyl-substituted tertiary alcohol (**12**) (0.2 mmol, 1.0 equiv), *fac*-Ir(ppy)$_3$ (0.008 mmol, 4 mol%), and $BrCF_2R$ (**2a**, **4**, **5**) (0.4 mmol, 2.0 equiv) were loaded in a flask which was subjected to evacuation/flushing with nitrogen for three times. DMF (3.0 mL) was added to the mixture via syringe and the mixture was then irradiated by 10 W blue LEDs. The reaction was allowed for stirring at rt until the starting material had been consumed as determined by TLC. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed by brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography on silica gel (eluent: ethyl acetate/ petroleum ether) to give the corresponding product **13**.

Acknowledgements

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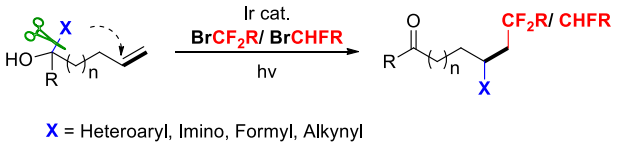
FULL PAPER

Distal Functional Group Migration for Visible-light Induced Carbo-difluoroalkylation/ monofluoroalkylation of Unactivated Alkenes



X = Heteroaryl, Imino, Formyl, Alkynyl

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