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Concise Report

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Unusual Single Electron Transfer Reactions between Alkenes and Iodine Electrophiles†

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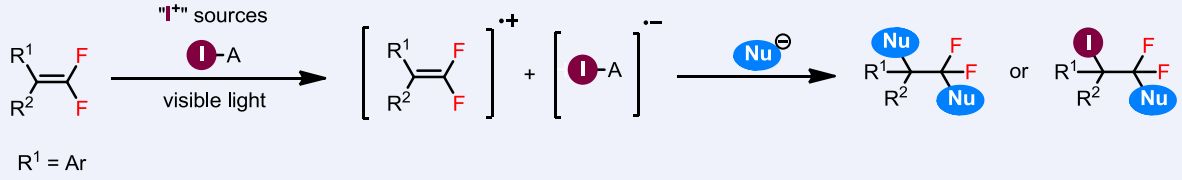
Keywords

Electrophilic addition | Radical ions | Reaction mechanisms | Alkenes | Fluorine

Comprehensive Summary



The electrophilic addition to an alkene with an electrophile has been widely studied and applied in organic synthesis. The organic chemistry textbook describes the classical reaction between an alkene and an iodine electrophile (such as elemental iodine and *N*-iodosuccinimide (NIS)) as a typical ionic reaction, in which an iodonium ion is formed and then attacked by a nucleophile. However, in this article, we report a new and unusual reaction mode between an alkene and NIS; that is, a single electron transfer (SET) process occurs between these two reactants by forming an electron-donor acceptor complex. Not only does this unusual single electron transfer reaction between an alkene and NIS add fundamentally important knowledge to organic chemistry, it also provides a valuable synthetic method as the new SET reaction mode with opposite regioselectivity as compared with the traditional ionic mode.

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‡ These authors contributed equally to this work.
† Dedicated to the Memory of Professor Xiyan Lu.

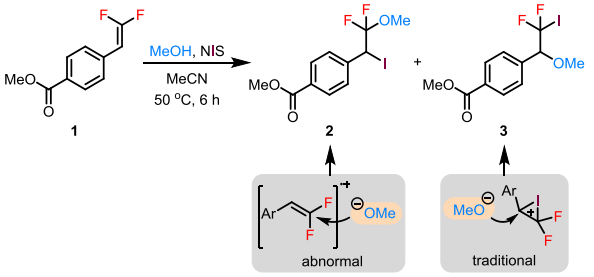
Background and Originality Content

The electrophilic addition to alkenes is a traditional method for the difunctionalization of alkenes. Particularly, the halofunctionalization of alkenes with halogenated electrophiles is well documented in organic chemistry textbooks.[1] The electrophilic addition mechanism is mainly presented as the Ad_E2 (bimolecular electrophilic addition) ionic mechanism (Scheme 1a).[1a] Additionally, Jackson and co-workers proposed a new coherent Ad_E3-type path of nucleophile-assisted alkene activation (NAAA), in which the alkene is activated by the nucleophilic partner's simultaneous electron donation for the electrophilic attack.[2] Up to now, the electrophilic addition of alkenes and halogen electrophiles mainly involves a typical halonium ion intermediate.[2b,3] The bridged halonium ion intermediate was first suggested to account for the *trans* stereochemistry observed in electrophilic halogenations of alkenes by Roberts and co-workers in 1937.[4] Although many studies have demonstrated that an electron donor-acceptor (EDA) complex formed between an alkene and a halogen electrophile, this EDA complex was proposed to be very reactive and was quickly transformed to cyclic halonium ion.[1b,5] In 1995, Herges and co-workers obtained stable EDA complexes of (*E*)-2,2,5,5-tetramethyl-3,4-diphenylhex-3-ene and halogen molecules for the first time.[5d] However, theoretical calculations indicate that these complexes are Mulliken-outer-type with no or little charge transfer.[5c-e] Olah and co-workers also suggested no difference between the EDA complex and the cyclic species of carbon-carbon double bonds with I^+ in terms of experimentally measurable physical and chemical properties.[5a] Herein, we report a new and unusual reaction mode between an alkene and NIS; that is, a single electron transfer process occurs between these two reactants instead of a traditional ionic process described in textbooks (Scheme 1b). It also provides a valuable synthetic method as the new SET reaction mode offers the opposite regioselectivity as compared with the traditional ionic mode.

Results and Discussion

Our group has a long-standing interest in the synthesis of halodifluoromethylated compounds due to their widespread applications in organic synthesis and medicinal chemistry.[6] Conventional method for the construction of RCF_2I compounds is Lewis acid-promoted difunctionalization of *gem*-difluoroalkenes with NIS via the iodonium ion intermediate (Ad_E2 mechanism).[3e,g,k] Surprisingly, during our reaction of *gem*-difluoroalkenes with NIS and methanol in the absence of Lewis acid, an unexpected addition product **2** with opposite regioselectivity was detected instead of traditional iododifluoromethylated product **3** (Table 1). We tried to perform this reaction under the darkness, only 5% yield of **2** was observed (entry 1). Notably, the product **2** could be afforded in 69% and 96% yields in the presence of fluorescent lamp and blue LEDs, respectively (entries 2—3). These results showed that visible light played a decisive role in the reaction. Since this reaction undergoing intermediate iodonium ion to deliver traditional product **3** usually is not affected by light, product **2** was probably generated via blue light-irradiated electron-transfer process.[9] This abnormal regioselectivity aroused our interest to explore the new chemistry in the addition reaction of *gem*-difluoroalkenes with NIS and different nucleophiles.

Table 1 Abnormal regioselectivity of the addition reaction of *gem*-difluoroalkenes with NIS and methanol[a]



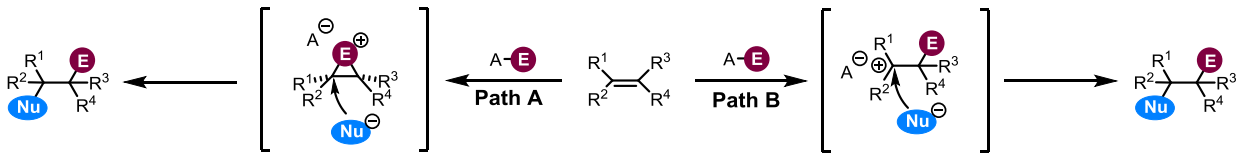
Entry	Visible light	Yield/%	
		2[b]	**3**[b]
1	Dark	5	N.D.
2	Fluorescent lamp	69	N.D.
3[c]	Blue LEDs	96	N.D.

[a] **1** (0.1 mmol), NIS (0.45 mmol), MeOH (0.6 mmol), MeCN (1.0 mL), Ar, 50 °C, 6 h. [b] Yields were determined by ^{19}F NMR with $PhOCF_3$ as an internal standard. [c] Irradiated under blue LEDs at rt for 2 h. "Not detected" is abbreviated as N.D.

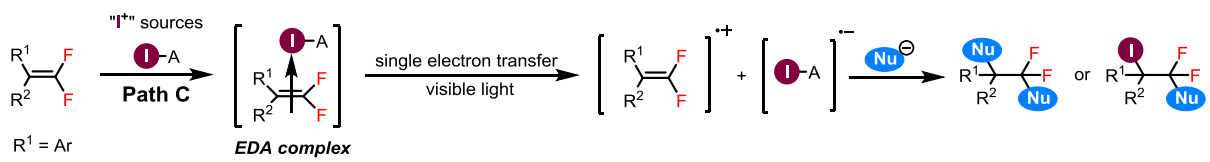
Oxazolines are commonly found in biologically active natural products and pharmaceuticals, such as Trehazolin (an insecticide),[7] Rilmendine (an antihypertensive drug),[7b] and A289099 (a tubulin polymerization inhibitor).[8] However, the synthetic methods of fluorine-containing oxazoline are rare. To prove the generality of this unprecedented electron transfer process between NIS and *gem*-difluoroalkenes, different nucleophiles such as amides to construct the fluorine-containing oxazolines were investigated (Table 2). Product **5** was obtained in 91% yield from the cyclization reaction of 1.0 equivalent of **1**, 2.5 equivalents of amide and NIS in MeCN at room temperature for 4 h with white fluorescent light (Table 2, entry 1). The nuclear magnetic

Scheme 1 Mechanisms of electrophilic addition to alkenes.

a. Conventional ionic mechanisms of electrophilic addition to alkenes with halogenated electrophiles.

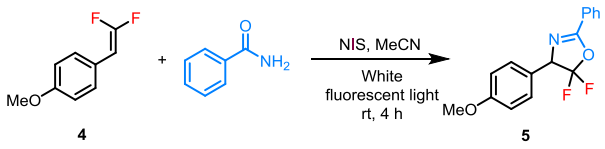


b. This work: Unusual single electron transfer mechanism of electrophilic addition to alkenes with halogenated electrophiles.



resonance (NMR) analysis demonstrated that *gem*-difluoro substituent is directly connected to the oxygen atom of **5**. Diametrically opposite regioselectivity was exhibited comparing the previously reported oxazoline cyclization of alkenes via halonium ion.[3n]

Table 2 Optimization of the reaction conditions for cyclization of *gem*-difluoroalkenes with amides[a]



Entry	Difference from the standard conditions	Yield[b]/%
1	None	91
2	No NIS added	N.D.
3	H_2O (2.5 equiv.) added	87
4	I_2 (2.5 equiv.) instead of NIS	7
5	In the air	54
6	50 °C, in the dark	N.D.
7	In the dark	N.D.

[a] **4** (0.1 mmol), NIS (2.5 equiv.), amide (2.5 equiv.), MeCN (1.5 mL), rt, 4 h, white fluorescent light. [b] Yields determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

To gain more insights into the reaction mechanism, control experiments under the optimized reaction conditions without NIS were conducted. Full recovery of starting materials indicated that benzamide and *gem*-difluoroalkenes cannot react (Table 2, entry 2). The addition of water does not affect the efficiency of this transformation, and iodine is likely to be generated by observing the color of the mixture gradually changing from colorless to purple-black (entry 3). NIS was further replaced by iodine to exclude the possibility of iodine as a catalyst, however, only a 7% yield of product was observed (entry 4). In addition, the yield of the target product decreased when the reaction was carried out in the air, which indicated that oxygen has a relatively large impact on the reaction (entry 5). Finally, the reaction failed no matter performing at 50 °C or room temperature in the dark, which proved the vital role of white fluorescent light in facilitating this reaction (entries 6—7).

The scopes of amides and *gem*-difluoroalkenes in this reaction were examined, respectively (Scheme 2). First, alkyl- (**6**—**9**) and aryl amides (**5**, **10**—**35**) can afford the corresponding *gem*-difluoro-substituted oxazolines in good to excellent yields. Among them, products **6**—**8** were delivered in 80%—97% NMR yields from 1° or 2° alkyl amides, while hydrolysis occurred during purification via column. Notably, the stability of the corresponding product **9** from 3° alkyl amides was enhanced with a 92% isolated yield. In the cases of aryl amides, neutral aryl amides (**5**, **10**), aryl amides with electron-deficient groups such as halogens (**11**—**17**), tosyl (**20**), trifluoromethoxy (**21**), trifluoromethyl (**22**), cyano (**23**), nitro (**24**—**25**), with electron-donating groups such as methoxy (**18**) and polymethoxy (**19**) in different positions were all compatible. Furthermore, heteroaryl amides (**26**—**28**) all participated well under the identified reaction conditions. On the other hand, the utility of this protocol was further verified by the participation of a series of *gem*-difluoroalkenes, affording products **29**—**35** in 60%—81% yields.

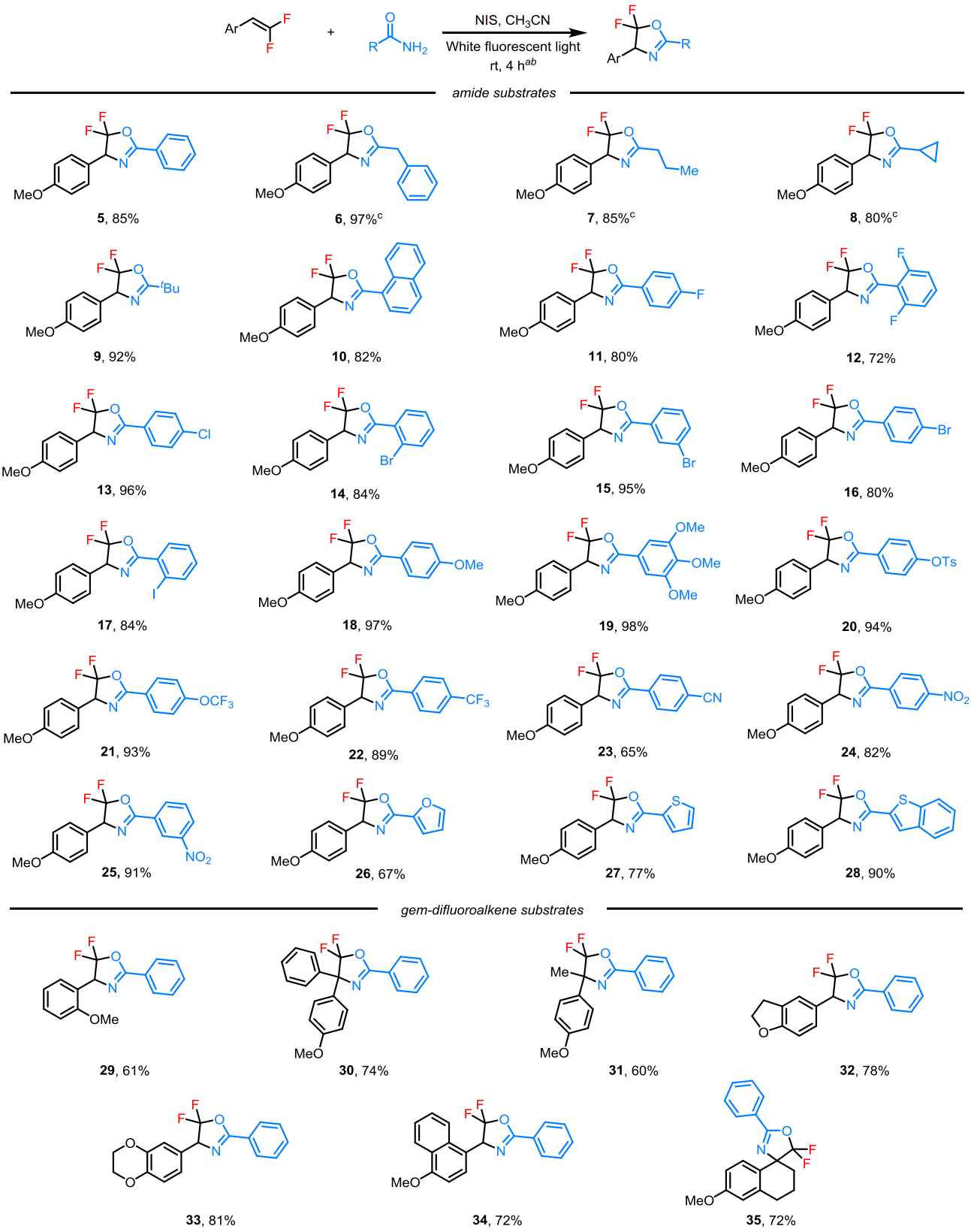
Besides amides, other nucleophiles including alcohols and triethylamine trihydrofluoride were also tested (Scheme 3). Both primary alcohols such as methanol, β-phenethyl alcohols, ethylene glycol, cyclopropylmethanol, 1,3-propanediol, propanol, 2-phenoxyethanol, as well as phenylmethanol, and secondary alcohols such as cyclohexanol and isopropyl alcohol reacted smoothly in difunctionlization of electron-rich *gem*-difluoroalkenes. However, tertiary alcohol such as *tert*-butanol only afforded the corresponding product in 43% yield. Surprisingly, **42** with the six-membered ring was readily constructed using 3.0 equivalents of ethylene glycol as the nucleophile, while 1,3-propanediol as its derivatives converted into product **44** instead of the seven-membered ring. Except for the mono-substituted electron-rich *gem*-difluoroalkenes, di-substituted electron-rich *gem*-difluoroalkenes also showed good reactivity in this transformation. In addition, the difunctionalizaztion of electron-rich *gem*-difluoroalkenes with triethylamine tri(hydrogen fluoride) complex as the nucleophile was also tried. A series of tetrafluoroethyl compounds (**62**—**66**) were obtained successfully, which can easily be converted into α,β,β-trifluoroalkanes.[10] For the electron-deficient *gem*-difluoroalkenes, highly efficient methoxylation-iodination occurred due to the specific stability of the electron-deficient benzylic iodine compound. The *gem*-difluoroalkenes with cyano, bromo, tosyl, and ester groups at the *para* positions are well compatible, delivering products (**69**, **70**, **73**—**75**) in 78%—80% yields. Notably, these benzyl iodides are found to be decomposed slowly in the air.

To gain further insights into the mechanism and origins of regioselectivity, a series of control experiments were investigated. Firstly, visible light absorption experiments were conducted by mixing different starting materials reagents (Scheme 4a). A pronounced absorption peak near the blue absorption frequency (450—480 nm) was observed from the mixture of *gem*-difluoroalkenes and NIS via the generation of a donor-acceptor complex. Next, we studied the vital role of NIS in this electron-transfer process (Scheme 4b). No product was observed using *N*-methylsuccinimide instead of NIS, while 1,3-diiodo-5,5-dimethylhydantoin (DIH) gave product **36** in 85% yield, which indirectly ruled out the influence of the succinimide moiety in NIS on this reaction. In addition, a 4% yield of the dialkoxylated product **36** and a 31% yield of **84** were obtained by the reaction of iodide and *gem*-difluoroalkenes under blue light irradiation, which suggested iodonium ion mechanism prior to single electron transfer using iodine instead of NIS under blue light irradiation (Scheme 4b). Moreover, the reaction of **84** instead of *gem*-difluoroalkenes was examined under the identified reaction conditions, however, no dialkoxylated product **36** was observed. This result demonstrated that the dimethoxylation product was not generated by the nucleophilic substitution of **84**. Then, we investigated the reactivity of alkenes containing different numbers of fluorine atoms under blue light irradiation or darkness (Scheme 4c). Under blue light irradiation, dialkoxylated product **80** was obtained in 98%, 8%, and 16% yields (by GC-MS) using *gem*-difluoroalkenes, mono-fluoroalkenes, and non-fluorinated alkenes as the substrates, along with the addition product **79** in 0%, 86% and 84% GC-MS yields (entries 1—3). The more electron-deficient nature of *gem*-difluoroalkenes than mono- or non-fluorinated alkenes was preferred for the electron transfer process rather than the formation of iodonium ion intermediate under blue light irradiation. When in the darkness, none of the addition products **79** or **80** was detected with *gem*-difluoroalkenes (entry 4). And only traditional addition product **79** was generated from mono- or non-fluorinated alkenes with decreased yields (entries 5—6). These results further suggest that product **80** is unlikely to be formed from iodonium ion intermediate. In addition, we attempted to carry out the reaction under air atmosphere (Scheme 4d). However, the desired product **71** was not observed in the NMR spectra. This suggests that the reaction may undergo a radical pathway.

Finally, we propose the plausible reaction mechanism as shown in Scheme 4e. The *gem*-difluoroalkene initially forms an EDA complex **B** with NIS. Subsequently, under light conditions, EDA complex **B** undergoes electron transfer to generate intermediate **C**. When alcohols are used as nucleophiles, they attack **C** to form intermediate **D**. In the presence of electron-donating groups

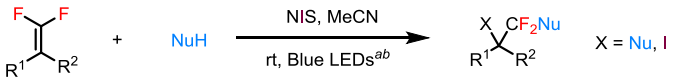
on the aromatic ring, **D** is easily oxidized by NIS to form intermediate **E**. **E** is further attacked by alcohols, resulting in the formation of product **F**. It is worth noting that when amides are employed as nucleophiles, the nucleophilic attack primarily occurs at the oxygen atom rather than the nitrogen atom of amides, leading to the formation of intermediate **G**. **G** is subsequently oxidized by NIS and undergoes intramolecular cyclization, resulting in the formation of the product **H**.

Scheme 2 Scope of cyclization of *gem*-difluoroalkenes with amides

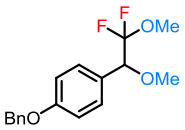


[a] Reaction conditions (unless otherwise noted): *gem*-difluoroalkenes (0.4 mmol), amides (2.5 equiv.), NIS (2.5 equiv.), MeCN (5.0 mL), white fluorescent light, rt, 4 h. [b] Isolated yields. [c] ^{19}F NMR yields using $PhOCF_3$ as an internal standard.

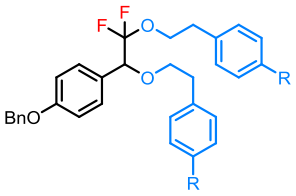
Scheme 3 Scope of difunctionalization of *gem*-difluoroalkenes with different nucleophiles



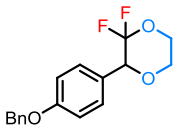
Electron-rich gem-difluoroalkene substrates



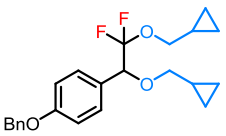
36, 95%



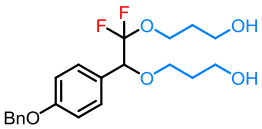
37, R = OCF_3, 67%[c]
38, R = NO_2, 69%[c]
39, R = F, 80%[c]
40, R = Br, 97%[c,d]
41, R = I, 82%[c,d]



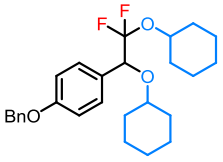
42, 77%[c]



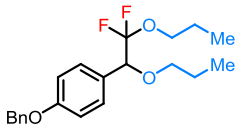
43, 90%[c,d]



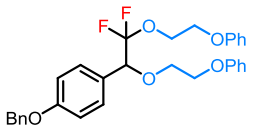
44, 73%[c]



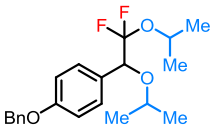
45, 90%[c,d]



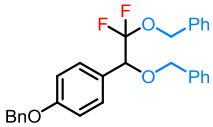
46, 98%[c,d]



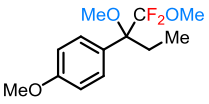
47, 63%[c,d]



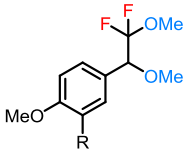
48, 90%[c,d]



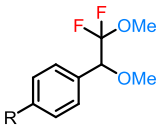
49, 95%[c,d]



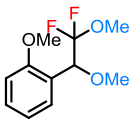
50, 97%



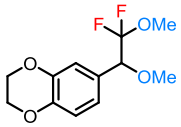
51, R = F, 91%
52, R = Br, 65%



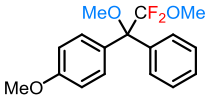
53, R = OMe, 91%
54, R = OPh, 80%
55, R = O^{n}Pr, 88%



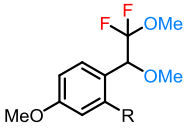
56, 68%



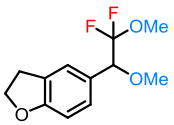
57, 87%[c,d]



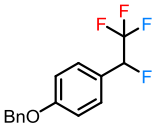
58, 96%[c,d]



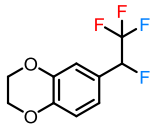
59, R = Me, 86%
60, R = Br, 70%



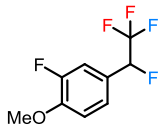
61, 70%[c,d]



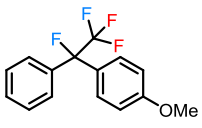
62, 75%[c,d,e]



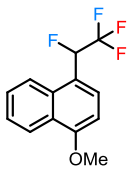
63, 76%[c,d]



64, 75%[c,d,e,g]

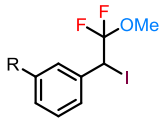


65, 70%[c,d,e,g]

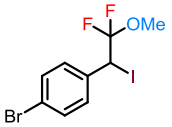


66, 68%[c,d,e]

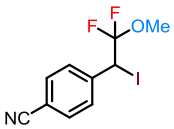
Electron-deficient gem-difluoroalkene substrates



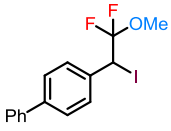
67, R = Br, 75%[c]
68, R = OMe, 64%[c]



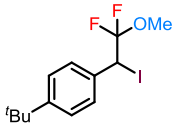
69, 80%[c,d]



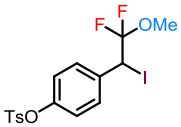
70, 79%[c]



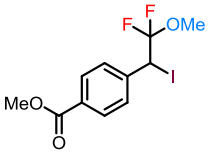
71, 71%[c]



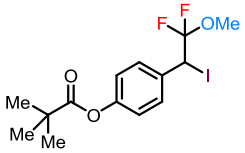
72, 83%[c]



73, 86%[c]



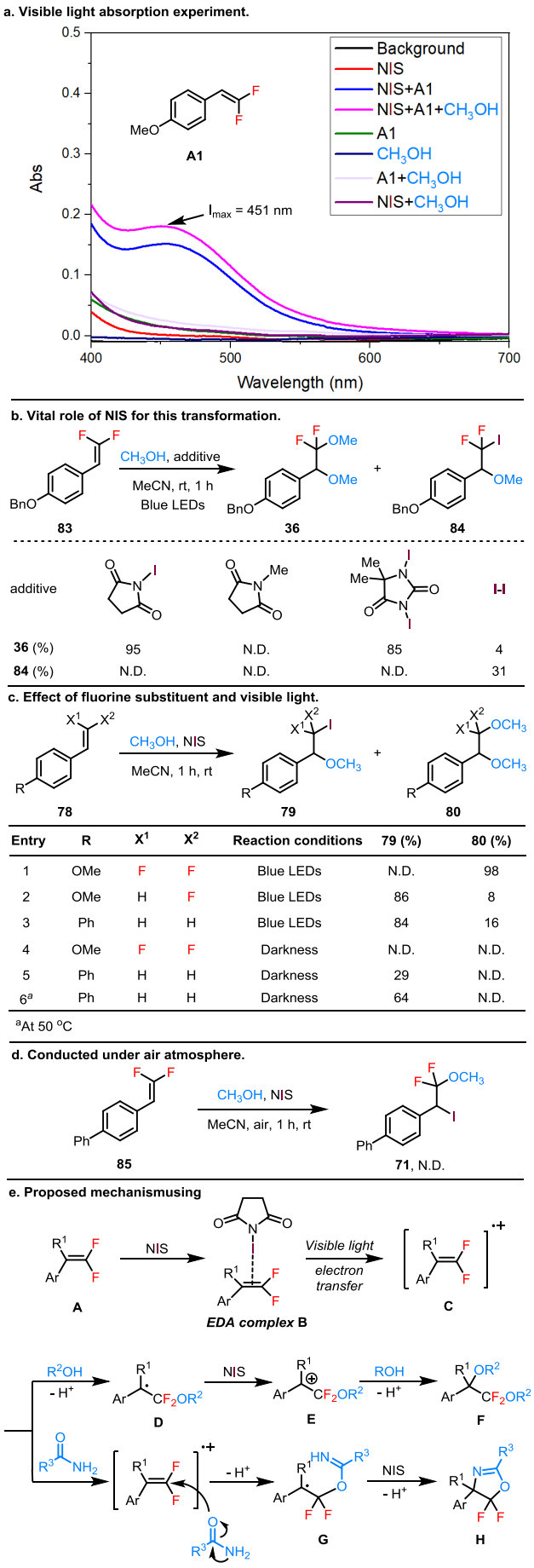
2, 78%[c]



75, 78%[c]

[a] Reaction conditions (unless otherwise noted): *gem*-difluoroalkenes (0.3 mmol), NuH (3.0 equiv.), NIS (2.0 equiv.), MeCN (3.0 mL), blue LEDs, rt, 2.0 h. [b] Isolated yields. [c] 4.5 equivalents of NIS were used. [d] 6.0 equivalents of NuH were used. [e] MeCN (0.5 mL) was used. [f] 5.0 h. [g] ^{19}F NMR yields using $PhOCF_3$ as an internal standard.

Scheme 4 Mechanistic studies on the difunctionalization of *gem*-difluoroalkenes with NIS



Entry	R	X^1	X^2	Reaction conditions	79 (%)	80 (%)
1	OMe	F	F	Blue LEDs	N.D.	98
2	OMe	H	F	Blue LEDs	86	8
3	Ph	H	H	Blue LEDs	84	16
4	OMe	F	F	Darkness	N.D.	N.D.
5	Ph	H	H	Darkness	29	N.D.
6[a]	Ph	H	H	Darkness	64	N.D.

[a]At 50 °C

Conclusions

In summary, we have developed the visible light-promoted difunctionalization of *gem*-difluoroalkenes with NIS and different nucleophiles, such as amides, alcohols, and triethylamine trihydrofluoride. The formation of donor-acceptor complex from iodine electrophiles and *gem*-difluoroalkenes enabled single electron transfer (SET) process instead of the traditional formation of iodonium ion, which enables its unusual and opposite regioselectivity compared with the traditional iodonium ion involved reactions. The synthetic application of this new type of visible light-promoted difunctionalization of *gem*-difluoroalkenes provides a reliable and efficient access to fluorinated oxazolines and 1,2-dialkoxylated compounds.

Experimental

The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information files. For the experimental procedures, and spectroscopic and physical data of compounds, see Supplementary Methods.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.202300611.

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