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Difluoroalkylation/Lactonization of Alkenes with $BrCF_2CO_2K$ via Photoredox Catalysis: Access to α,α-Difluoro-γ-lactones†

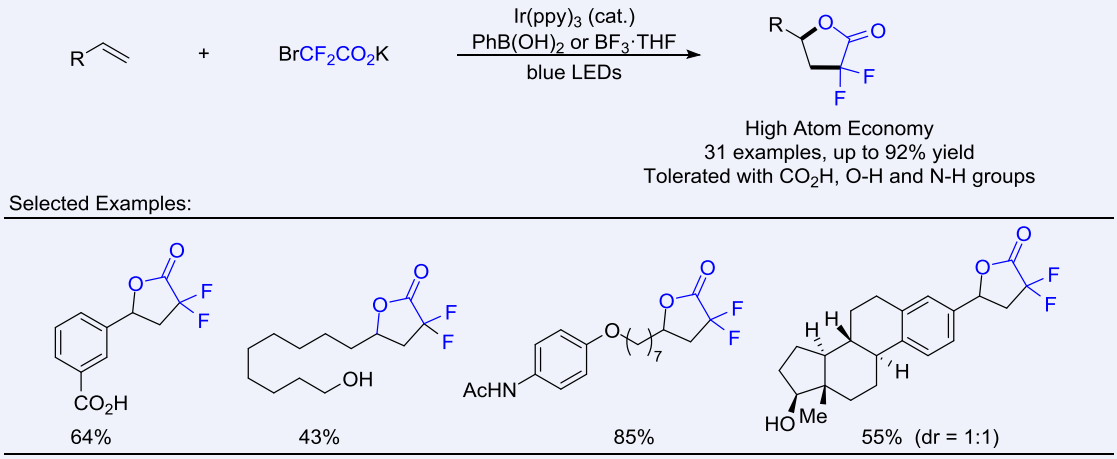
Min Zhang,[‡,a] Qiang Li,[‡,a] Jin-Hong Lin,[a,b] and Ji-Chang Xiao*[,a]

[a] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China*
[b] *Department of Chemistry, Innovative Drug Research Center, Shanghai University, Shanghai 200444, China*

Keywords

Photoredox | Catalysis | Fluorine | Lactones | Alkenes

Comprehensive Summary



Due to its unique electronic properties, the difluoromethylene group (CF_2) has served as a valuable unity in the design of biologically active molecules. Since γ-lactones display a broad range of biological properties, α,α-difluoro-γ-lactones may exhibit unexpected biological activities, and thus their synthesis has received increasing attention. Traditional synthetic methods suffer from tedious multi-step processes, and very few effective methods have been reported recently. Herein, we describe the difunctionalization of alkenes with $BrCF_2CO_2K$ under photoredox catalysis with the use of a boron-Lewis acid for the access to α,α-difluoro-γ-lactones. In this transformation, the alkene substrates and the used reagents, including $BrCF_2CO_2K$ and the boron-Lewis acid, $PhB(OH)_2$ or BF_3·THF, are cheap and widely available. High efficiency and atom economy may make this protocol attractive.

*E-mail: jchxiao@sioc.ac.cn
‡ These authors contributed equally to this work.
† Dedicated to the Memory of Professor Xiyan Lu.

Background and Originality Content

Fluorine has been considered as a magic element owing to its unique electronic properties, such as strong electronegativity, a small atomic radius and low polarizability. The incorporation of a fluorinated group into organic molecules can usually lead to profound changes of their physicochemical properties.[1] For example, the CF_2 moiety, which can act as a bioisostere of an oxygen atom[2] or an isopropyl group,[3] may improve various biological properties of drug molecules, such as lipophilicity, metabolic stability, and bioavailability.[4] A large number of CF_2-containing pharmaceuticals have been developed, including Eflornithine,[5] Roflumilast,[6] Gemcitabine,[7] and Voxilaprevir (Figure 1).[8] Therefore, significant efforts have been directed towards the development of efficient methods for the incorporation of a CF_2 moiety into organic molecules.[9] Difunctionalization of alkenes has proven to be an attractive strategy for the installation of a CF_2 group, such as amino-difluoroalkylation,[10] oxy-difluoroalkylation,[11] and halo-difluoroalkylation reactions.[12]

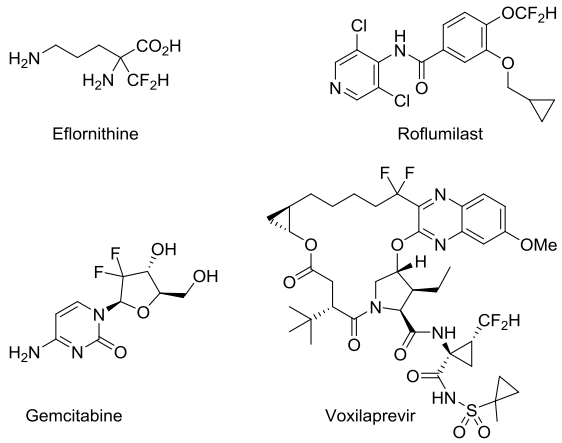
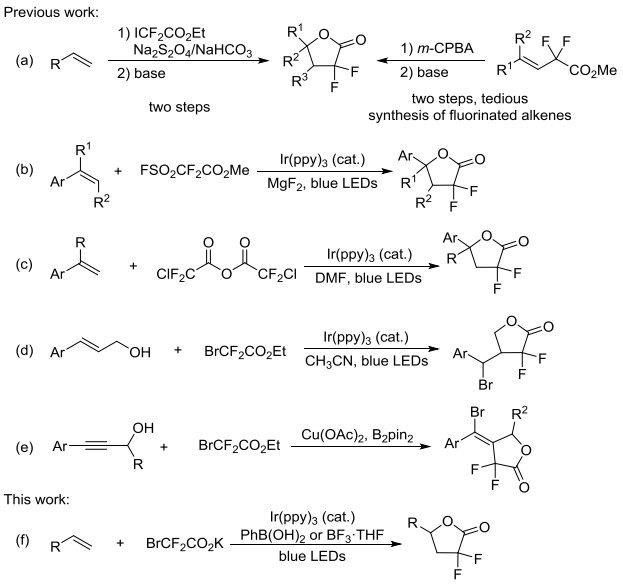


Figure 1 CF_2-containing pharmaceuticals.

γ-Lactones, displaying a broad range of biological properties, can be found in many natural sources and used as building blocks in organic synthesis.[13] Given the unique effects of the CF_2 moiety, α,α-difluoro-γ-lactones may exhibit superior biological activities over nonfluorinated counterparts.[14] In addition, α,α-difluoro-γ-lactones can also be used as intermediates for the synthesis of biologically active molecules.[15] Therefore, the synthesis of α,α-difluoro-γ-lactones has received increasing attention. Traditional methods usually require a tedious multi-step process for the construction of the lactone rings and the incorporation of fluorine atoms.[16] Some recent studies involved the formation of α,α-difluoro-γ-lactones, but only one example was shown and thus the substrate scope and functional group tolerance are both unknown.[17] The lactones can be synthesized by difunctionalization of alkenes followed by cyclization (Scheme 1a, left side),[18] or by epoxidation of fluorinated alkenes followed by cyclization (Scheme 1a, right side).[19] The two-step process and/or the tedious synthesis of fluorinated alkenes may limit the wide applicability of these approaches. Chen's reagent, $FSO_2CF_2CO_2Me$, which has served as a versatile fluoroalkylation reagent,[20] can also enable difluoroalkylation/cyclization of alkenes for the access to lactones (Scheme 1b).[21] Recently, the Katayev group found that chlorodifluoroacetic anhydride was able to act as a radical source for a solvent-controlled switchable synthesis of *gem*-difluoro-compounds, including fluorinated lactones with the use of DMF as the solvent (Scheme 1c).[22] Molander and co-workers described a trifunctionalization of allylic alcohols with $BrCF_2CO_2Et$ via one-pot Giese addition/lactonization/halogen-atom transfer processes (Scheme 1d).[23] The addition to alkynols can provide alkenyl-substituted α,α-difluoro-γ-lactones (Scheme 1e).[24] In the last two cases (Schemes 1d and 1e), the allylic or propargyl hydroxyl groups are necessary for the lactonization.

Scheme 1 The synthesis of α,α-difluoro-γ-lactones

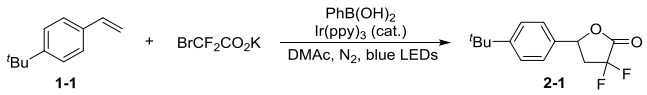


Our group has been interested in the chemistry of fluoroalkylation.[25] We have previously found that $BrCF_2CO_2Et$ can be used as a radical source and a difluorocarbene reagent for cyanodifluoromethylation of alkenes via photoredox catalysis.[26] On the basis of this work, we originally speculated that phenyl-difluoromethylation of alkenes may occur if $PhB(OH)_2$ was used as a phenyl source. However, difluoroalkylation/lactonization was observed, and $PhB(OH)_2$ was found to play an important role in this conversion. Herein, we describe the difunctionalization of alkenes under photoredox catalysis for the access to α,α-difluoro-γ-lactones (Scheme 1f). In this transformation, the alkene substrates and the used reagents, including $BrCF_2CO_2K$ and $PhB(OH)_2$ (or BF_3·THF), are cheap and widely available. High efficiency and atom economy may make this protocol attractive.

Results and Discussion

After an extensive screening of reaction conditions (see Supporting Information), a 98% yield was obtained by using $Ir(ppy)_3$ as a photocatalyst and $PhB(OH)_2$ as a Lewis acid in DMAc under the blue-light irradiation for the difluoroalkylation/lactonization of alkenes (Table 1, entry 1). $PhB(OH)_2$ played an important role for this conversion. No desired product was detected without its presence (entry 2). It may act as a Lewis acid, as evidenced by the good yield (76%) with the use of BF_3 instead of $PhB(OH)_2$ (entry 3). Photocatalyst $Ir(ppy)_3$ and the blue light irradiation are both essential for this conversion (entries 4—5), indicating this is a photo-induced process. The air atmosphere would completely suppress the transformation, probably O_2 would quench the key radical intermediates generated *in situ* (entry 6). The reaction is not very sensitive towards water, and a moderate yield still could be obtained in the presence of water (entry 7). $ClCF_2CO_2Na$ cannot undergo this transformation under these conditions, probably due to the stronger C—Cl bond compared with C—Br bond (entry 8). Surprisingly, the use of $Ph_3P^+CF_2CO_2^-$ (PDFA), a reagent which was developed by us recently,[25] gave the desired product in a 69% yield (entry 9). We have shown that PDFA would readily undergo decarboxylation to generate ylide $Ph_3P^+CF_2^-$, which can release difluorocarbene by the direct cleavage of P—CF_2 bond.[27] However, in this photo-induced process, PDFA may not undergo decarboxylation, but first be reduced to cleave the P—CF_2CO_2 bond. Other reaction solvents were examined (entries 10—12), and DMAc was found to be a superior choice.

Table 1 Optimization of the reaction condition



Entry	Variations from the optimal conditions	Yield[a]/%
1	None	98
2	No $PhB(OH)_2$	ND
3	BF_3·THF instead of $PhB(OH)_2$	76
4	No $Ir(ppy)_3$	ND
5	No light	ND
6	Under an atmosphere of air instead of N_2	ND
7	100 μL H_2O added	53
8	$ClCF_2CO_2Na$ instead of $BrCF_2CO_2K$	ND
9	$Ph_3P^+CF_2CO_2^-$ instead of $BrCF_2CO_2K$	69
10	MeOH instead of DMAc	ND
11	MeCN instead of DMAc	18
12	DMF instead of DMAc	72

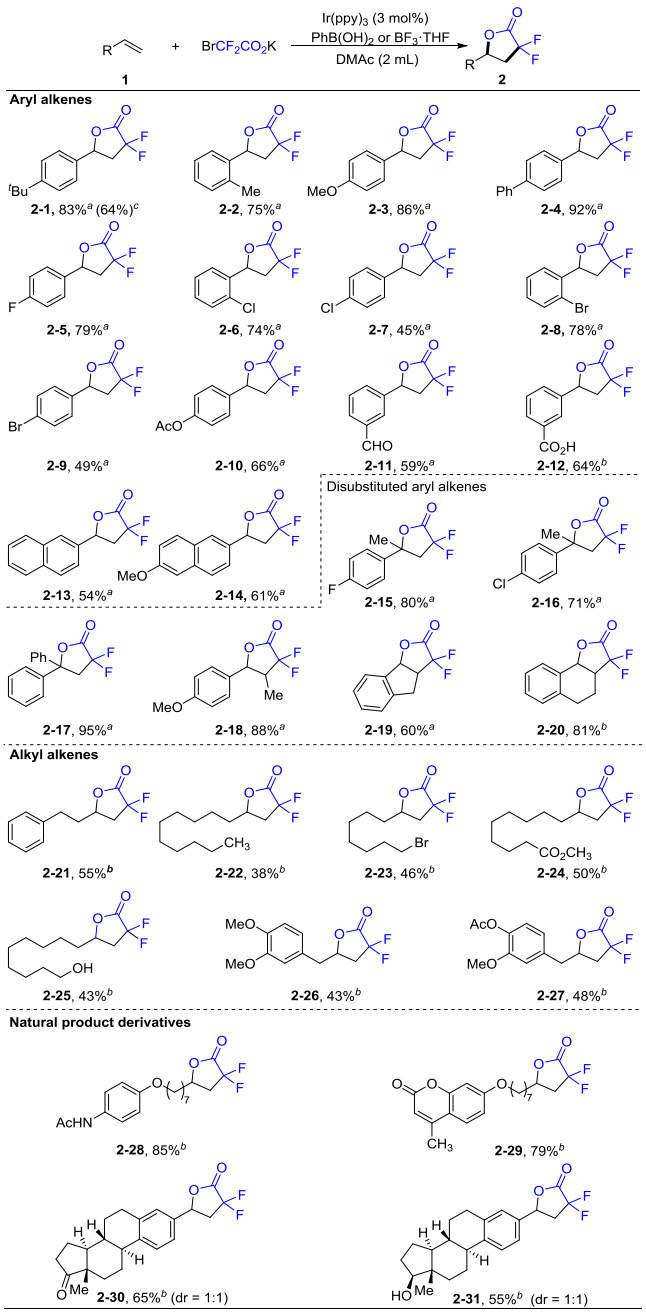
Optimal reaction conditions: Substrate **1-1** (0.2 mmol), $BrCF_2CO_2K$ (1.5 equiv.), $Ir(ppy)_3$ (3 mmol%) and $PhB(OH)_2$ (3.0 equiv.) in DMAc (2 mL) irradiated with blue LED under a N_2 atmosphere for 10 h. ND = not detected. [a] The yields were determined by ^{19}F NMR spectroscopy by using $PhCF_3$ as an internal standard.

With the optimal reaction conditions in hand (Table 1, entry 1), we then investigated the substrate scope of the difluoroalkylation/lactonization of alkenes with $BrCF_2CO_2K$ for the access to α,α-difluoro-γ-lactones. As shown in Scheme 2, the process could be extended to a wide range of alkenes, including aryl alkenes and alkyl alkenes. Especially, a high level of functional group tolerance was observed. The CO_2H (**2-12**), OH (**2-25**, **2-31**), and AcNH (**2-28**) groups could remain intact under these conditions, in spite of their high reactivity. As discussed in the proposed mechanism, the reaction may occur via a nucleophilic attack at a carbocation intermediate. The reactive CO_2H, OH and AcNH groups are nucleophilic species, but they did not suppress the desired conversions. Various aryl alkenes can be converted smoothly. Electron-donating groups are favorable for this transformation, but electron-withdrawing groups would result in lower yields. High yields were obtained for the reactions of disubstituted aryl alkenes (**2-15**—**2-20**), suggesting that the process is not very sensitive towards steric effects. Compared with aryl alkenes, alkyl alkenes showed lower reactivity and the desired products were produced only in moderate yields (**2-21**—**2-27**). In the case of alkyl alkenes, BF_3·THF is a superior Lewis acid. In order to further demonstrate the synthetic utility, some natural product derivatives were synthesized by this process (**2-28**—**2-31**), including Estrone (**2-30**) and Estradiol (**2-31**). Terminal alkynes, such as 4-Ph-C_6H_4-≡, are inert towards this process under these conditions.

As mentioned in Table 1, photocatalyst $Ir(ppy)_3$ and the blue light irradiation are both essential for this conversion, reflecting that this is a photoredox process.[28] The presence of a radical scavenger, TEMPO, completely suppressed the desired conversion. Although no TEMPO-CF_2 species was detected, no observation of the desired product suggests that single-electron-transfer (SET) mechanism is operative (Scheme 3).

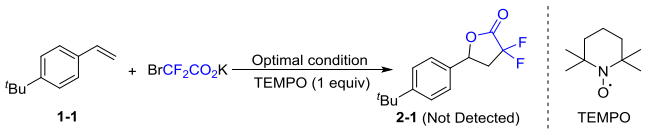
On the basis of the above results, the plausible reaction mechanism is proposed as shown in Scheme 4. The coordination of $BrCF_2CO_2^-$ to the boron center leads to the decreasing electron density in the $BrCF_2CO_2$ moiety. This moiety would thus be readily reduced by the excited $Ir(ppy)_3^*$ complex to generate $^{\bullet}CF_2CO_2^-$ radical intermediate. The attack of the radical at alkene produces intermediate **A**, the oxidation of which by Ir^{IV} provides cation **B**. The intramolecular attack of the CO_2^- anion at the cation center delivers the final product (path c). Intermediate **A** may also

Scheme 2 The substrate scope



[a] Reaction conditions: Substrate **1** (0.2 mmol), $BrCF_2CO_2K$ (0.3 mmol), $Ir(ppy)_3$ (3 mol%), and $PhB(OH)_2$ (0.6 mmol) in DMAc (2 mL) were irradiated with blue LEDs under a N_2 atmosphere for 10 h. [b] Reaction conditions: Substrate **1** (0.2 mmol), $BrCF_2CO_2K$ (0.3 mmol), $Ir(ppy)_3$ (3 mol%), and BF_3·THF (0.6 mmol) in DMAc (2 mL) were irradiated with blue LEDs under a N_2 atmosphere for 10 h. [c] For the 1-mmol-scale reaction of **1-1**, a 64% isolated yield was obtained.

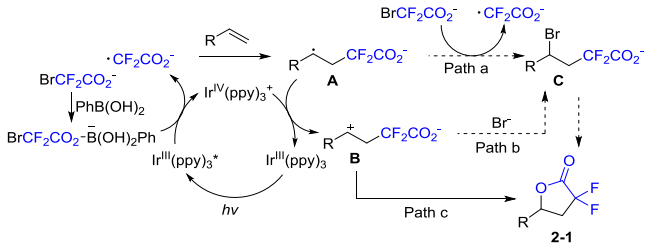
Scheme 3 Experimental evidence for a SET mechanism



abstract Br from $BrCF_2CO_2^-$ to give compound **C** (path a), and the subsequent nucleophilic substitution affords the final product. Intermediate **B** may be captured by Br^- anion to give compound **C**

(path b). We believe path c is the dominant path, because compound **C** was not detected in the reaction system, and path b can also be excluded on the basis of on-off light evidence (see Supporting Information) which reveals that light cannot be turned off until the reaction is completed.

Scheme 4 The plausible reaction mechanism



Conclusions

In summary, we have described the photoredox catalyzed difluoroalkylation/lactonization of alkenes with $BrCF_2CO_2K$ for the access to α,α-difluoro-γ-lactones. The used reagents, including $BrCF_2CO_2K$ and $PhB(OH)_2$ (or BF_3·THF), are cheap and widely available. A high level of functional group tolerance was observed. CO_2H, OH and AcNH groups remain intact under these conditions in spite of their high nucleophilic reactivity. High efficiency and atom economy may make this protocol attractive for the synthesis of biologically active α,α-difluoro-γ-lactones.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.202300295.

Acknowledgement

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The Authors

Left to Right: Min Zhang, Qiang Li, Jin-Hong Lin, and Ji-Chang Xiao