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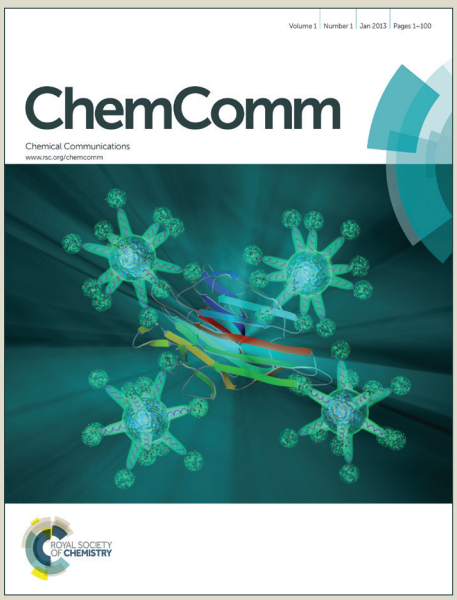





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# A Novel Visible Light Mediated Radical Cyclization of Enol Lactone: A Concise Method for Fluorinated Polycyclic Lactone Scaffold

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**A novel visible light mediated radical cyclization of enol lactone with difluoroacylarenes is presented. The reaction experienced a tandem radical cyclization and tolerated a wide range of substrates, resulting in fluorinated γ-butyrolactone with good chemical yields and excellent diastereoselectivity.**

Fluorinated compounds are greatly important in pharmaceuticals, agrochemicals and materials science, and thus, which has triggered an explosion of research efforts in developing efficient and novel methods to introduce fluorinated functional groups into organic molecules.[1] In particular, the incorporation of difluoromethyl group($CF_2$) into organic compounds is of great concern in medicinal chemistry owing to its isosteric with the hydroxy group, which leads to increased acidity of its neighboring group, enhanced dipole moments, and conformational changes.[2] Sesquiterpene lactones (SLs), a large group of structurally diverse natural products, are prevalently found in plants from the Asteraceae family.[3] Notably, the presence of an α-methylene-γ-butyrolactone moiety in most SLs, which plays a pivotal role as Michael acceptor for biological nucleophiles such as cysteine sulfhydryl groups, has been profiled as a structural prerequisite for their anti-cancer, anti-inflammatory, anti-malarial, anti-bacterial, allergenic agents and growth inhibitors properties (Fig 1).[3][4]

As a safe, cheap and renewable source of chemical energy to facilitate the construction of complex organic molecules, visible light catalysis has emerged recently as a powerful theme in organic chemistry.[5] In particular, free radical fluorination is emerging as a powerful tool for C($sp^3$)−F bond formation, especially under the catalysis of visible light. Building on pioneering work of Stephenson who demonstrated activated haloalkane ($BrCF_2CO_2Et$) could serve as a

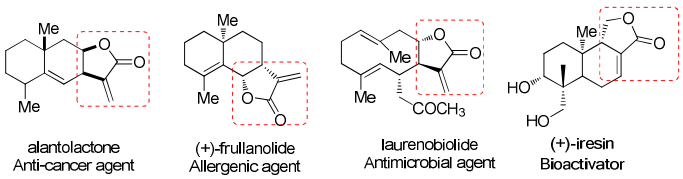
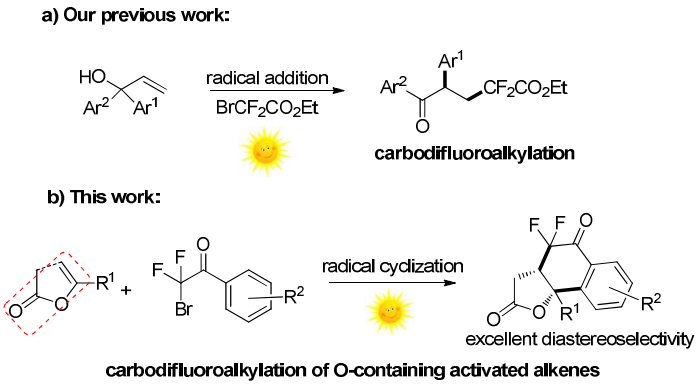


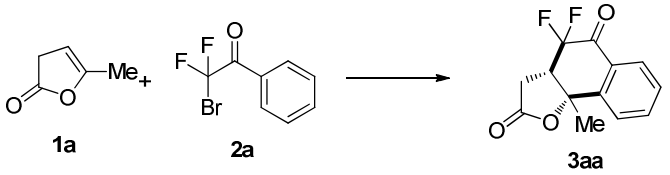

**Fig.1** Example of natural sesquiterpene lactones.




**Scheme 1** Tandem $Csp^3$ – $CF_2$ and carbon – carbon bond formation of alkenes.

$CF_2$ radical precursor under visible light catalysis in 2011.[6] A series of important studies involved $CF_2$ radical generated by activated haloalkane ($BrCF_2CO_2Et$) were reported.[7] In previous work, we developed a photoredox mediated carbodifluoroalkylation of allylic alcohols protocol through 1,2-aryl migration (Scheme 1a).[8f] Consistent with our interest in the development of methods for the preparation of fluoroorganic compounds.[8] Herein, we speculated a method in view of tandem difluoroalkylaion and C-C coupling of butenolides (Scheme 1b). This strategy provides a facilely approach to potential biological fluorinated polycyclic lactone, which can be easily modified into α-methylene-γ-butyrolactone unit of the sesquiterpene lactones.[9]

Table 1 Optimization of reaction conditions [a]

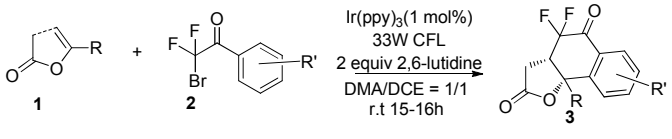


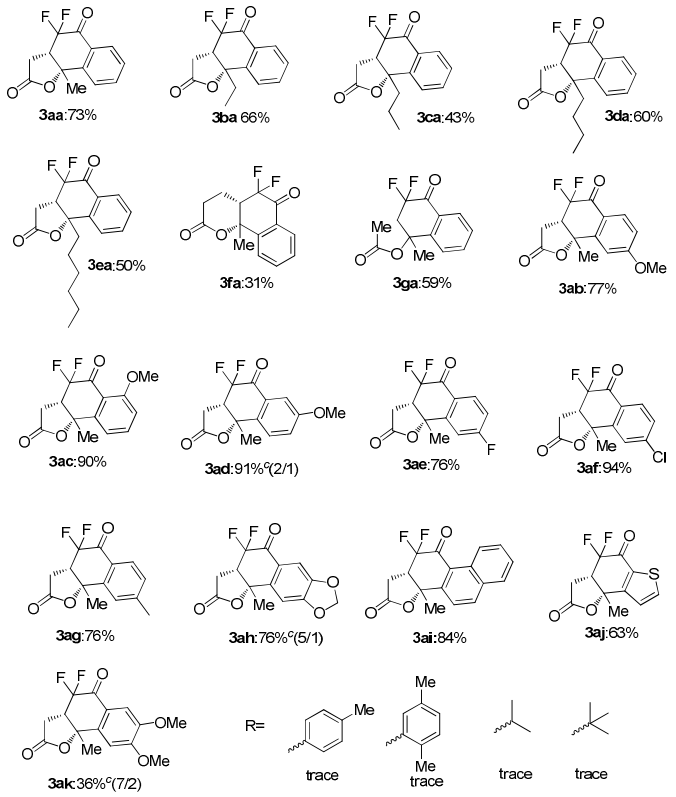
| Entry | Photocatalyst | Solvent | Additive | Yield(%) [b] |
|---|---|---|---|---|
| 1 | *fac*-Ir(ppy)$_3$ | $CH_2Cl_2$ | / | 9[c] |
| 2 | Ir(ppy)(dtbpy)$PF_6$ | $CH_2Cl_2$ | / | N.R |
| 3 | [IrdF($CF_3$)(ppy)$_2$(dtbbpy)]$PF_6$ | $CH_2Cl_2$ | / | N.R |
| 4 | [Ru(bpy)$_3$]$PF_6$ | $CH_2Cl_2$ | / | N.R |
| 5 | *fac*-Ir(ppy)$_3$ | $CHCl_3$ | / | N.R |
| 6 | *fac*-Ir(ppy)$_3$ | DCE | / | 24 |
| 7 | *fac*-Ir(ppy)$_3$ | DMSO | / | trace |
| 8 | *fac*-Ir(ppy)$_3$ | MeOH | / | trace |
| 9 | *fac*-Ir(ppy)$_3$ | DMA | / | 40 |
| 10 | *fac*-Ir(ppy)$_3$ | DMA | PhCOOH | 20 |
| 11 | *fac*-Ir(ppy)$_3$ | DMA | $Et_3N$ | 36 |
| 12 | *fac*-Ir(ppy)$_3$ | DMA | $Na_2HPO_4$ | trace |
| 13 | *fac*-Ir(ppy)$_3$ | DMA | NaOAc | trace |
| 14 | *fac*-Ir(ppy)$_3$ | DMA | 2,6-lutidine | 68 |
| 15 | *fac*-Ir(ppy)$_3$ | DMA/DCE =1/1 | 2,6-lutidine | 73 |
| 16 | | DMA/DCE =1/1 | 2,6-lutidine | N.R |
| 17[d] | *fac*-Ir(ppy)$_3$ | DMA/DCE =1/1 | 2,6-lutidine | N.R |

. [a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), additive (0.4 mmol), photocatalyst (1 mol%), solvent (1 mL), 33W fluorescent light bulb, 15 h, rt. [b] Isolated yield. [c] Determined by 1H-NMR analysis 1,1,2,2-tetrachloroethane as an internal standard. [d] In the dark.

Initial investigations focused on the Ir(ppy)$_3$ catalyzed photoredox reaction of α-angelica lactone **1a** and α-bromo-α,α-difluoroacetophenones **2a** (Table 1). When the reaction was operated in $CH_2Cl_2$ irradiated by 33W fluorescent light bulb in the presence of Ir(ppy)$_3$ (1 mol%), only 9 % **3aa** was formed in the Table 1 (entry 1). Various catalysts have been employed instead of Ir(ppy)$_3$. However, no other photocatalysts was found to give the desired product (Table 1, entries 2-4). The reaction was also found very sensitive to the solvents and only occured smoothly in dichloroethane (DCE) and *N*, *N*-dimethylacetamide (DMA) with yield 24% and 40%, respectively (Table 1, entries 6, 9). Other solvents such as $CHCl_3$, MeOH and DMSO substantially decreased the reaction efficiency (Table 1, entries 5, 7, 8). To maximize the yield of this radical annulative reaction, some additives were added in the reaction system (entries 10-14). However, when PhCOOH or $Et_3N$ was used, the yield somewhat decreased (entries 10-11). Remarkably, additives like $Na_2HPO_4$ and NaOAc absolutely prevented the reaction (entries 12 and 13). To our delight, when 2, 6-lutidine was examined, a dramatically improved yield of **3aa** (68%) was obtained (Table 1, entry 14). Finally, the optimal reaction condition was identified by use of component solvents of DCE and DMA in ratio of 1:1, thus providing **3aa** in 73% yield (Table 1, entry 15). (The target molecule can be easily modified into α-methylene-γ-butyrolactone unit of the sesquiterpene lactones.[9]) **delete** The control experiment disclosed that no reaction occurred in the absence of a photoredox catalyst or visible light (Table 1, entries 16 and 17). Especially, it is worth noting that this reaction shows excellent diastereoselectivity (only *cis* products were obtained).

Table 2 Scope of radical cyclization of enol lactone[a,b]



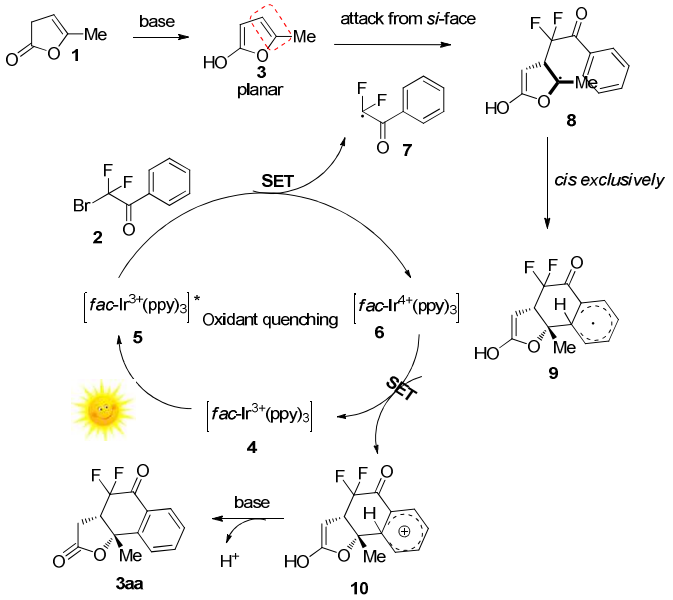

[a] Reaction conditions unless otherwise specified: **1** (0.2 mmol), **2** (0.3 mmol), Ir(ppy)$_3$ (1 mol%), 2, 6-lutidine (0.4 mmol), DCE (0.5 mL), DMA (0.5 mL) r.t, under Ar atmosphere for 15-16 h. [b] Yields are reported for the isolated products. [c] Major isomers are shown.

With optimized reaction conditions in hand, various butenolides **1** were studied for visible light catalyzed radical annulation with α-bromo-α,α-difluoroacetophenones **2a**, and the results are summarized in Table 2. The length of γ-alkyl groups effect was first examined (Table 2). For a series of different chain length of β,γ-butenolides **1a-1e** with α-bromo-α, α-difluoroacetophenones **2a** in the reaction can be attained in fair to good yields (43-73%) (**3aa-3ea**), which indicated that the longer chain (**3ca-3ea**) has a more negative influence on reactivity. Next, six-membered-ring enol lactone and acyclic ester have been employed instead of α-angelica lactone, however, only 31% and 59% yields were obtained, respectively (**3fa** and **3ga**). The results demonstrate that the generation of electron-rich enol is necessary for this reaction (see the proposed mechanism). Morever, more bulky enol lactones bearing aryl groups, *t*-Bu and *i*-Pr were explored in standard conditions, however, only tiny products were achieved (Table 2).

Next, we applied this protocol to a variety of difluoroacyl arenes with various substitution patterns (Table 2). The reaction of *para*-substituted aryl substrate **2b** gave the annulative products **3ab** in 77% yield. Comparatively, *ortho*-substituted aryl substrate **2c** afforded **3ac** in 90% yield, whereas a mixture of regioisomers was obtained from the *meta*-methoxy substrate **2d** in 91% yield. In contrast, difluoroacyl arene bearing either electron-donating or -withdrawing substituents at the *para*-position of the aryl ring gave the annulative products **3ae-3ag** in moderate to excellent yields (76-94%).

Difluoroacyl arene **2h** showed moderate regioselectivity and the corresponding polycyclic lactone **3ah** was obtained in 76% yield, probably owing to both the steric and electronic effects. Additionally, the difluoro-substituted ketone **2i**, which contains α-naphthalene was also tolerated in this reaction. Especially, difluoroketone with heteroaromatic ring **2j** was also effective to undergo the radical annulative to deliver **3aj**. In contrast, when **2k** with 3,4- dimethoxy benzene was tried, the annulative product **3ak** was detected in a low yield and moderate regioselectivity.

The specific mechanistic details of our proposed visible light-mediated radical annulation of vinyl ester are outlined in Scheme 2. Initially, irradiation of heteroleptic iridium (III) photocatalyst *fac*-$Ir^{3+}(ppy)_3$ **4** with visible light leads to the formation of a excited state *fac*-*$Ir(ppy)_3$ **5**, which can undergo oxidative quenching in the presence of α-bromo-α,α-difluoroacetophenones as an appropriate electron acceptor via a single electron transfer (SET) process with the generation of the strongly oxidizing *fac*-$Ir^{4+}(ppy)_3$ **6** and $CF_2$ radical precursor **7**. Subsequently, active radical **7** will attack the carbon-carbon double bond of the α-angelica lactone **1**, which can proceed tautomerism by base in situ generated electron-rich enol **3**. At this stage, both the *re*-face and *si*-face of the carbon-carbon double bond in planar **3** could be attacked by planar $CF_2$ radical **7** in identical way (attack from *si* face is shown in Scheme 2), which is proposed to




**Scheme 2** Proposed mechanism.

forge the oxy-alkyl radical **8** with concomitant formation of the corresponding *cis* intermediate radical **9**, exclusively. Ultimately the generated intermediate **9** is oxidized to the corresponding key carbocation **10** through single-electron oxidation. Further deprotonation and keto-enol tautomerism of **10** will give product **3aa**.

## Conclusions

In summary, we have developed an efficient and convenient tandem protocol for the synthesis of difluoroalkylated heterocyclic skeleton in excellent diastereoselectivity by visible light photoredox catalysis. The structural motifs are important in pharmaceutical and agrochemical products. In addition, the synthetic utility of the products provides a potential application by their modification into various $CF_2$-containing α-methylene-γ-butyrolactone unit through conventional organic reactions. We are working to develop this useful reaction further.

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## Notes and references

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