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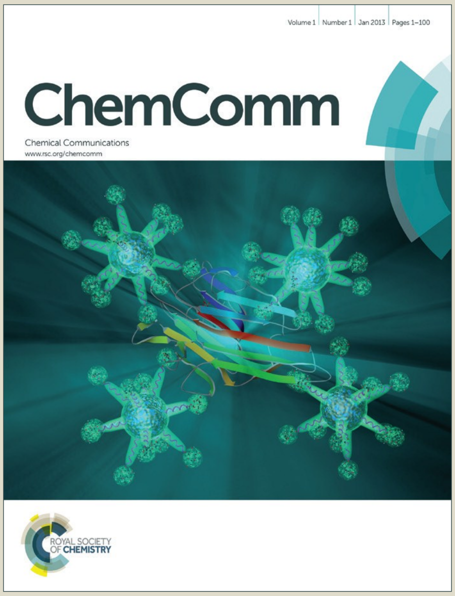

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Visible-light-initiated Difluoromethylation of Arene Diazonium Tetrafluoroborates †

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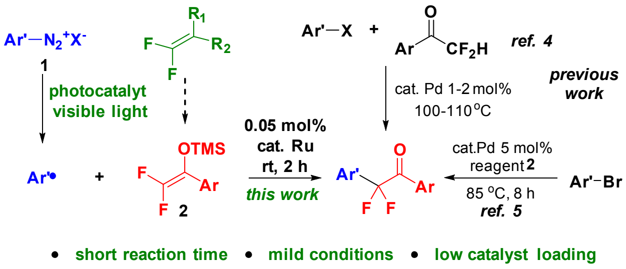
Ye-bin Wu [a], Guo-ping Lu* [a], Bao-jing Zhou [a], Mei-jie Bu [a], Li Wan [c], and Chun Cai* [a,b]

A mild and efficient method for the radical addition of α-aryl-β,β-difluoroenol silyl with arene diazonium tetrafluoroborates at room temperature has been disclosed, which contains an innate long chain cycle so only small amount (0.05 mol%) of photocatalyst and short timescale light are required as an radical initiator. A proposed mechanism of the transformation is also illustrated based on the results of control experiments and quantum calculations. A variety of α-aryl-α,α-difluoroketones were formed in moderate to high yields, which can be easily further transformed into various difluoromethylarenes under basic conditions.

The incorporation of fluoroalkyl groups into organic molecules is widespread utilized in synthetic chemistry due to the apparent impact on the physical and biological properties of the material, such as enhanced lipophilicity and membrane permeability, elevated electronegativity and oxidation resistance.[1] Meanwhile, difluoroalkylation compared with perfluoroalkylation can not only introduce fluorine atoms into a molecule, but also install a nonfluorinated moiety simultaneously which can be further modified into various CF_2 containing functional groups.[2] Thus, compounds containing-CF_2R groups are widely applied in the preparation of pharmaceuticals, agrochemicals, and enzyme inhibitors.[3]

The carbonyl functionality is an important cornerstone of organic chemistry, since it can be smoothly transformed into a range of functional groups including hydroxyl, amino, alkyl and ester. The typical approaches for the introduction of a difluorocarbonyl group onto an aromatic ring rely on the conversion of halogen substituents through Pd-catalyzed reactions (Scheme 1).[4,5] Although remarkable progresses have been made, the problems still exist, such as elevated temperatures, long reaction time and high catalyst loadings. Therefore, it is still urgent to develop a milder and more environment friendly transformation for this.



Scheme 1. The strategies for the preparation of α-aryl-α,α-difluoroketones

Diazonium salts especially arenediazonium salts, are important intermediates and have been commonly used in organic synthesis.[6] Recently, several intriguing researching studies have been reported on introducing the per- and difluoroalkylation of diazonium salts or aromatic amines via Sandmeyer-type reactions. Goossen and coworkers achieved trifluoro-methylation and difluoromethylation of diazonium salts,[7] and copper-promoted trifluoromethylation of aromatic amines was described by Fu's groups.[8] In the same year, Wang's groups explored the reaction of anilines with $[AgCF_3]$, which can be considered as variation of the classic Sandmeyer reaction.[9] However, unstable tri- or difluoromethyl metal complexes (such as $[AgCF_3]$ and $[CuCF_2H]$), which should be prepared in situ and handled carefully, are employed in these strategies. Moreover, these methods require excess transition metal salts and harsh conditions, reducing their versatility and simplicity.

On the one hand, visible-light photoredox catalysis has been widely applied in modern catalysis and synthesis, due to its low cost, easy availability and environmental friendliness.[10] On theother hand, aryl diazonium salts are an excellent precursor of aryl radicals through photoelectron transfer (PET) process,[11]

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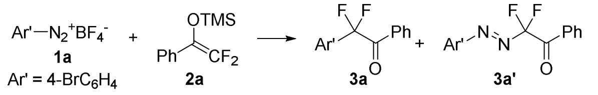
which can be easily trapped by vinyl group. Inspired by these results, we propose that aryl radicals generated in situ from diazonium salts induced by visible light can react with difluoroalkylation reagents containing vinyl groups. To the best of our knowledge, no report has mentioned the photo catalytic difluoromethylation with aryl diazonium salts. Along this line, we have introduced a visible-light-initiated difluoromethylation of arenediazonium salts for the synthesis of α-aryl-α,α-difluoroketones using α-aryl-β,β-difluoroenol silyl as the difluoroalkylation reagent, which can be easily prepared from trifluoroacetophenone (Scheme 1).[12]

Table 1. Optimization of reaction conditions[a]



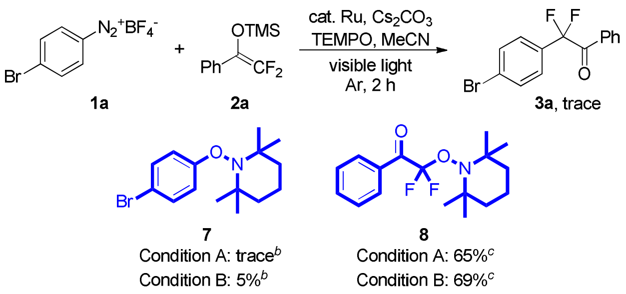
Entry	Catalyst	Additive	**3a/3a'** (%)[b]
1[c]	$Ru(bpy)_3Cl_2·6H_2O$	None	64/24
2[c]	EosinY	None	25/58
3[c]	Rhodamine B	None	16/65
4	$Ru(bpy)_3Cl_2·6H_2O$	None	48/33
5[d]	$Ru(bpy)_3Cl_2·6H_2O$	None	43/42
6	None	None	0/94
7	$Ru(bpy)_3Cl_2·6H_2O$	Cs_2CO_3	83/Trace
8	$Ru(bpy)_3Cl_2·6H_2O$	Na_2CO_3	58/Trace
9	$Ru(bpy)_3Cl_2·6H_2O$	KOH	65/Trace
10	$Ru(bpy)_3Cl_2·6H_2O$	K_3PO_4	20/Trace
11[e]	$Ru(bpy)_3Cl_2·6H_2O$	Cs_2CO_3	73/Trace
12	None	Cs_2CO_3	15/Trace
13[f]	$Ru(bpy)_3Cl_2·6H_2O$	Cs_2CO_3	11/Trace
14[g]	$Ru(bpy)_3Cl_2·6H_2O$	Cs_2CO_3	84/Trace
15[h]	$Ru(bpy)_3Cl_2·6H_2O$	Cs_2CO_3	87 (80)[i]/Trace
16[h,j]	$Ru(bpy)_3Cl_2·6H_2O$	Cs_2CO_3	88/Trace
17[k]	$Ru(bpy)_3Cl_2·6H_2O$	Cs_2CO_3	82/Trace

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (1.5 equiv.), catalyst (2 mol%), additive (3 equiv.), MeCN (2 mL), irradiation with visible light under an Ar atmosphere at room temperature, 2 h. [b]Yield based on GC. [c]10 h. [d]**2a** (2 equiv.). [e]Additive (1 equiv.). [f]The experiment was carried out without light. [g]Catalyst (0.5 mol%). [h]Catalyst (0.05 mol%). [i]Value in parentheses refers to isolated yield. [j]Sunlight instead of LED lamps irradiation. [k]Catalyst (0.01 mol%).

Initially, we treated 4-bromobenzenediazonium tetrafluoroborate (**1a**) with **2a** in the presence of 2 mol% $Ru(bpy)_3Cl_2·6H_2O$ in MeCN at room temperature under LED lamps irradiation. To our delight, the reaction provided a 64% yield of the desired product **3a**. After screening different photocatalysts, the ruthenium complex gave the best result (Table 1, entries 1-3). To eliminate the undesired product **3a'**, various bases were applied in the process. The results indicated that excess base was required to suppress the side reaction completely (entries 6-12). Not surprisingly, little product was generated either in the dark or in the absence of a photocatalyst (entries 12-13). The reaction also proceeded smoothly using sunlight instead of LED lamps irradiation (entry 16). Remarkably, a satisfactory yield can be afforded in the reaction even using 0.01 mol% photocatalyst (entry 17), indicating a plausible radical natural chain cycle may be contained in the reaction. Therefore, further investigations were made to testify the proposed assumption.

The reaction is inhibited in the presence of TEMPO (4 equiv.), and compounds **7**, **8** are detected by GC-MS, suggesting a radical process is existed in this transformation (Table 2). "Light/dark" experiments were also used to prove the occurrence of chain processes in this photoredox reaction (Figure 1).[13] The reaction was irradiated with a LED at first half minute, then carried out in dark. Because the formation of product **3a** still occurs, a radical long chain process is confirmed. Further control experiments (Scheme S1, ESI) were carried out to investigate the role of Cs_2CO_3. It was found the desired product **3a** was generated in 25% yield when the by-product **3a'** was treated with **2a** and Cs_2CO_3. Thus, **3a** can be produced through another pathway in the presence of Cs_2CO_3, which was also confirmed by the results of ^{19}F NMR (Figure S1, ESI).

Table 2. Mechanistic studies experiments[a]



[a]Condition A: $Ru(bpy)_3Cl_2•6H_2O$ (0.05 mol%), TEMPO (4 equiv.). Condition B: $Ru(bpy)_3Cl_2•6H_2O$ (2 mol%), TEMPO (4 equiv.). [b]Yield based on GC. [c]Isolated yields.

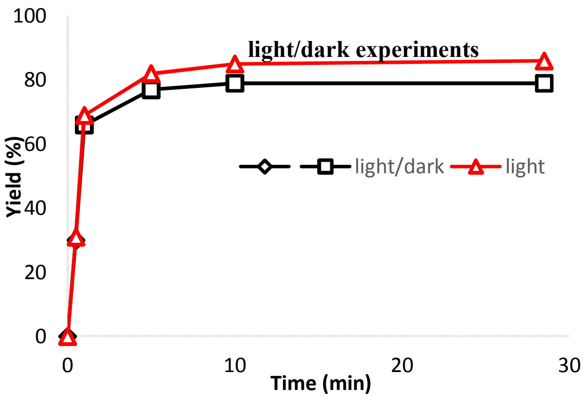


Figure 1. "light/dark" experiments

Based on these preliminary results, a purposed mechanism was iullstrated in Figure 2. Initially, aryl radical **4** is formed by SET from the excited state of $Ru(bpy)_3^{2+}$ initiated by visible light to diazoniym salt **1**. Subsequent addition of aryl radical **4** to the double bond of **2** gives radical intermediate **5**, which is further oxidized to carbocation intermediate **6** via SET from another aryl diazonium salt **1**. Finally, **6** is transformed to the desired product **3** by losing the trimethylsilyl group (***path I***).

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Meanwhile, part of the by-product **3a'** is transformed to **3a** via the electrophilic addition process (***path II***), which can explain why only 15% yield of product **3a** is obtained without the photocatalyst (Table 1, entry 12). It should be noted that the conversion of path **II** is poor, so the path **I** may contain an innate cycle, and be the major route for the reaction.

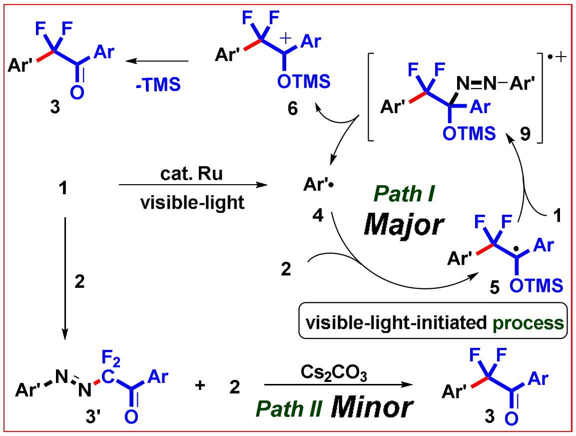
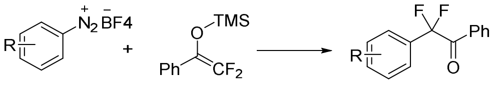
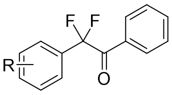


Figure 2. A proposed mechanism for the difluoro-methlylation of diazonium salts

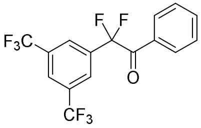
Table 3. Visible-light-initiated difluoromethylation of diazonium salts[a,b]



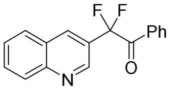
1 **2a** **3**



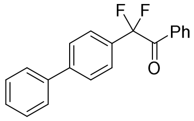
R = 4-Br **3a**, 80%, 81%[c]
R = 4-Cl **3b**, 76%
R = 4-I **3c**, 70%
R = 4-F **3d**, 82%
R = 4-NO_2 **3e**, 90%, 88%[c]
R = 3-NO_2 **3f**, 87%
R = 4-COOEt **3g**, 87%
R = 4-$COCH_3$ **3h**, 85%
R = 4-CN **3i**, 83%
R = 4-CF_3 **3j**, 89%
R = 3-CF_3 **3k**, 86%
R = 3-Cl **3l**, 65%
R = H **3n**, 67%
R = 4-OMe **3o**, 50%
R = 2-Cl **3p**, 40%
R = 2-NO_2 **3q**, 20%[d]



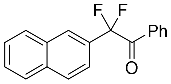
3m, 90%, 87%[c]



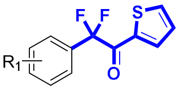
3r, 45%



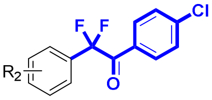
3s, 55%



3t, 50%



R$_1$ = 4-NO_2 **3u**, 89%
R$_1$ = 4-CF_3 **3v**, 85%
R$_1$ = 4-COOEt **3w**, 88%



R$_2$ = 4-$COCH_3$ **3x**, 86%
R$_2$ = 4-NO2 **3y**, 90%

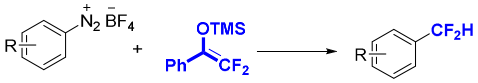
[a]Reaction conditions: **1** (0.25 mmol), **2a** (1.5 equiv.), Cs_2CO_3 (3 equiv.), $Ru(bpy)_3Cl_2$•$6H_2O$ (0.05 mol%), MeCN (2 mL), irradiation with visible light under an Ar atmosphere at room temperature, 2 h. [b]Isolated yields. [c]Sunlight instead of LED lamps irradiation. [d]yield based on GC-MS.

To investigate further the innate cycle of path **I**, we employed quantum mechanical (QM) density functional theory (DFT) calculations to explore the process from **1**, **5** to **4**, **6** (ESI).[14] It is found an intermediate **9** is afforded from **1** and **5**, which can provide **4** and **6**, following by a two-step cleavage of **9**'s C-N bonds (Figure 2). The energy barrier of the process is around 42.1 kJ/mol (the calculated value in vacuum), which may be lower owing to the promotion of Cs_2CO_3 in the cleavage of **9**'s C-N bonds and the solvation effects[15]. Therefore, the process from **1**, **5** to **4**, **6** may take place under optimized conditions, and the innate cycle of path **I** is probable based on the results of quantum calculation.

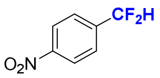
With the optimized conditions in hand, the substrate scope of the protocol was surveyed (Table 3). A range of aryl diazonium salts which bear electron-withdrawing and neutral groups could reacted with **2a** to give the corresponding adducts in moderate to excellent yields (**3a-3m**). Not surprisingly, sunlight can also initiate the reactions successfully (**3a, 3e, 3m**). 3-Quinoline diazonium salt was also applied in the reaction successfully with a moderate yield (**3r**). However, ortho-subsituted products (**3p-3q**) were formed in lower yields than their para-substituted analogues due to strong electron repulsion between two fluorine atoms and ortho-subsituted groups. It was worth noting that diazonium salts bearing carbonyl groups were selectively dilfluoromethylated at the arene ring without nucleophilic addition of the difluoromethyl group to the carbonyl group. This difluoromethylation procedure was also applied to two other silyl enol ethers (**3u-3y**).

Of particular interest, the C-C bond adjacent to the carbonyl group in these ketones can be readily cleaved to afford difluoromethyarenes. Aromatic compounds containing a difluoromethyl (CF_2H) group are valuable for medicinal chemistry because the CF_2H group is considered isosteric and isopolar with the hydroxyl group.[7] As reported by Hartwig et al.,[4a] a one-pot procedure for the synthesis of difluoromethylarenes was developed (Table 4, **4a-4c**).

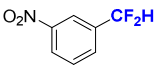
Table 4. The synthesis of difluoromethyarenes from α-aryl-α,α-difluoroacetophenones[a,b]



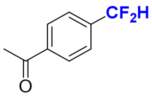
1 **2a** **4**



4a
84%



4b
80%



4c
75%

[a]Reaction conditions: [step 1] **1** (0.25 mmol), **2a** (1.5 equiv.), Cs_2CO_3 (3 equiv.), $Ru(bpy)_3Cl_2$·$6H_2O$ (0.05 mol%), MeCN (2 mL), irradiation with visible light under an Ar atmosphere at room temperature, 2 h; [step 2] KOH (8 equiv.), H_2O (0.1 mL), 100 °C, 2 h. [b]Isolated yields.

Conclusions

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In summary, we have developed a convenient and environment friendly protocol for the visible-light-initiated difluoromethylation of diazonium salts at room temperature. Both LED lamps irradiation and sunlight can initiate the transformation efficiently. Only small amount of $Ru(bpy)_3Cl_2·6H_2O$ and short timescale light are essential, which certifies that a radical natural cycle is existed in the chemistry. The reaction mechanism is also investigated by performing the control experiments and quantum chemical calculations. These results indicate that two pathways are existed in the reaction, and the radical process containing an innate cycle is the major route. The use of bases can completely suppress the side reaction. Moreover, mild conditions and the simplicity of this method underline the great potential for the preparation of more complicated molecules.

Acknowledgements

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