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# Copper-Catalyzed Coupling Cyclization of *gem*-Difluoroalkenes with Activated Methylene Carbonyl Compounds: Facile Domino Access to Polysubstituted Furans

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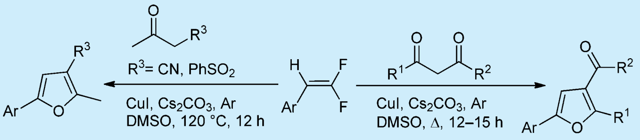
Supporting Information



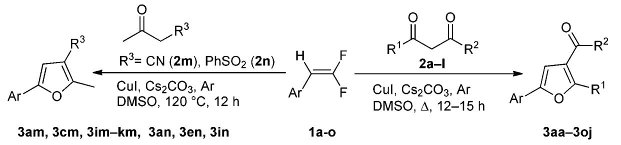
**ABSTRACT:** A novel and efficient CuI-catalyzed synthesis of 2,3,5-trisubstituted furans was developed via coupling cyclization of *gem*-difluoroalkenes with active methylene carbonyl compounds such as 1,3-dicarbonyl compounds, acetoacetonitrile, and phenylsulfonylacetone with the assistance of a base. Commercial availability of substrates or reagents, good to high isolated yields, and excellent functional group compatibility make this transformation a powerful tool for the synthesis of various furans. A plausible mechanism involving the allenyl ketone is suggested.

Highly functionalized furan rings are very important fundamental heterocyclic motifs widely found in biologically active natural products, pharmaceuticals, and materials.[1] They have also frequently been used as basic building blocks in synthetic chemistry.[2] Consequently, the development of efficient methods for the preparation of multiply substituted furans has attracted substantial interest from synthetic chemists.[3] To date, therefore, numerous methods have been developed for the synthesis of various multisubstituted furans.[4] The two traditional methods used for the synthesis of furans are Feist–Bénary cyclocondensation of 1,3-dicarbonyl compounds with haloketones and Paal–Knorr cyclocondensation of 1,4-dicarbonyl compounds.[5] Other alternative approaches to substituted furans include the functionalization of existing furans such as Pd-catalyzed direct arylation of furans via C–H activation,[6] the transition-metal-catalyzed cycloisomerizations of alkynyl or allenyl ketones and (*Z*)-2-en-4-yn-1-ols,[7] the CuBr-catalyzed cyclization reaction of 2-(1-alkynyl)-2-alken-1-ones,[8] and the transition-metal-catalyzed cycloaddition of *α*-diazocarbonyl compounds with alkynes.[9]

Although the present methods are very efficient and versatile and can be applied to the synthesis of a variety of substituted furans, these methodologies generally suffer from the use of expensive or highly air-sensitive transition-metal catalysts, poor accessibility of the starting materials, limited substrate scopes, and harsh reaction conditions. Therefore, it is highly desirable to further develop a general and practical strategy for the synthesis of various substituted furans.

*gem*-Difluoroalkenes have received much attention within the chemical community in the past few years due to their much higher reactivity toward nucleophiles compared to normal alkenes.[10] They can also usually serve as versatile fluorine-containing synthons for a variety of fluorinated molecules such as monofluoroalkenes,[11] ring-fluorinated isoquinoline and quinoline,[12] 5-fluoro-3*H*-pyrroles,[13] and 3-fluoropyrazoles.[14] In continuation of our efforts on the functionalization of carbon–fluorine bonds of *gem*-difluoroalkenes,[15] we herein report a novel and versatile approach to valuable trisubstituted furans through the base-assisted CuI-catalyzed cyclization of *gem*-difluoroalkenes with various activated methylene carbonyl compounds (Scheme 1).

**Scheme 1. CuI-Catalyzed Cyclization of *gem*-Difluoroalkenes with Activated Methylene Carbonyl Compounds**



We began our investigation using the cyclization of 1-(2,2-difluorovinyl)-4-methoxybenzene (**1a**) with acetylacetone (**2a**) as the model reaction to optimize the reaction conditions (Table 1). Initially, different metal catalysts were tested (entries 2–9). It was found that copper catalyst was essential to the reaction efficiency. Further screening of Cu salts revealed that CuI was the most effective copper catalyst and dramatically increased the yield of **3aa** to 93% (entry 9). However, no conversion was observed in the absence of metal catalyst (entry 1). Among the bases evaluated, $Cs_2CO_3$ proved to be the most efficient (entries 9, 11–15). The reaction did not proceed at all in the absence of base, with the starting materials being recovered nearly quantitatively (entry 10). Furthermore, decreasing or increasing the amount of $Cs_2CO_3$ led to lower yields (entries 16 and 17).

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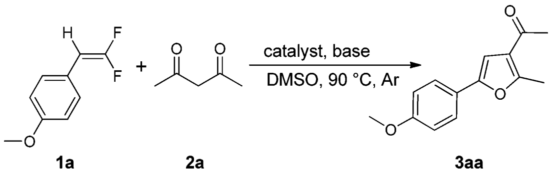
**Table 1. Optimization of the Reaction Conditions**[a]

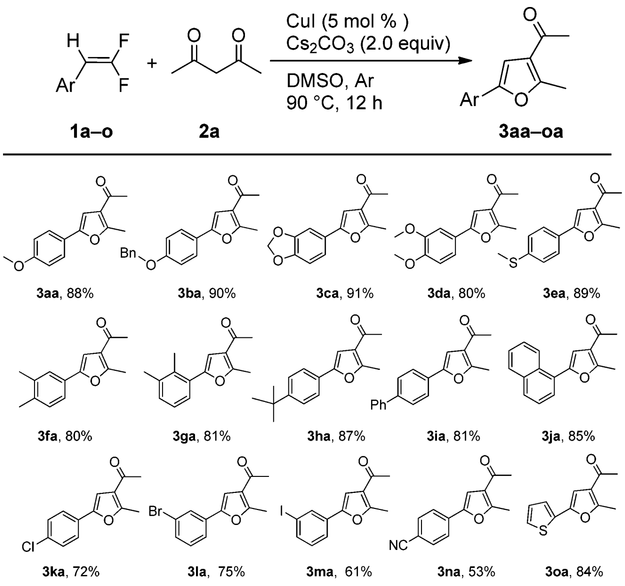


| entry | catalyst (mol %) | base (equiv) | yield (%)[b] |
|---|---|---|---|
| 1 | none | $Cs_2CO_3$ (2.0) | 0 |
| 2 | $NiCl_2(PCy)_3$ (5) | $Cs_2CO_3$ (2.0) | 2 |
| 3 | $RuCl_3$ (5) | $Cs_2CO_3$ (2.0) | 2 |
| 4 | $Pd(PPh_3)_4$ (5) | $Cs_2CO_3$ (2.0) | 13 |
| 5 | CuOAc (5) | $Cs_2CO_3$ (2.0) | 62 |
| 6 | $Cu(OAc)_2$ (5) | $Cs_2CO_3$ (2.0) | 76 |
| 7 | CuCl (5) | $Cs_2CO_3$ (2.0) | 43 |
| 8 | CuBr (5) | $Cs_2CO_3$ (2.0) | 72 |
| 9 | CuI (5) | $Cs_2CO_3$ (2.0) | 93 |
| 10 | CuI (5) | none | 0 |
| 11 | CuI (5) | *t*BuOLi (2.0) | 5 |
| 12 | CuI (5) | NaH (2.0) | 11 |
| 13 | CuI (5) | $K_3PO_4$ (2.0) | 21 |
| 14 | CuI (5) | KHMDS (2.0) | 38 |
| 15 | CuI (5) | $K_2CO_3$ (2.0) | 80 |
| 16 | CuI (5) | $Cs_2CO_3$ (1.5) | 68 |
| 17 | CuI (5) | $Cs_2CO_3$ (2.5) | 71 |

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), DMSO (5 mL), 90 °C, 12 h. [b] Yield determined by GC analysis and based on **1a**.

To gain insight into the tolerance of this reaction, we investigated the reaction scope with various *gem*-difluoroalkenes and activated methylene carbonyl compounds under the optimized reaction conditions (Table 1, entry 9). We first explored the scope with respect to the *gem*-difluoroalkenes (Scheme 2). As shown in Scheme 2, either an electron-donating group or an electron-withdrawing group on the benzene ring of the *gem*-difluoroalkenes was well-tolerated, affording the corresponding furans in moderate to excellent yields. Generally, *gem*-difluoroalkenes with electron-donating substituents gave yields higher than those with electron-withdrawing ones. However, a substrate bearing a strong electron-withdrawing group on the aromatic ring, such as cyano, gave relatively lower yield (**3na**). The position of the substituents on the benzene ring has no significant influence on the reactivity of *gem*-difluoroalkene substrates (**1f** and **1g**). When the benzene ring of the substrates was changed to naphthalene or thiophene, the reactions could also provide the cyclization products in good yields (**3ja** and **3oa**).

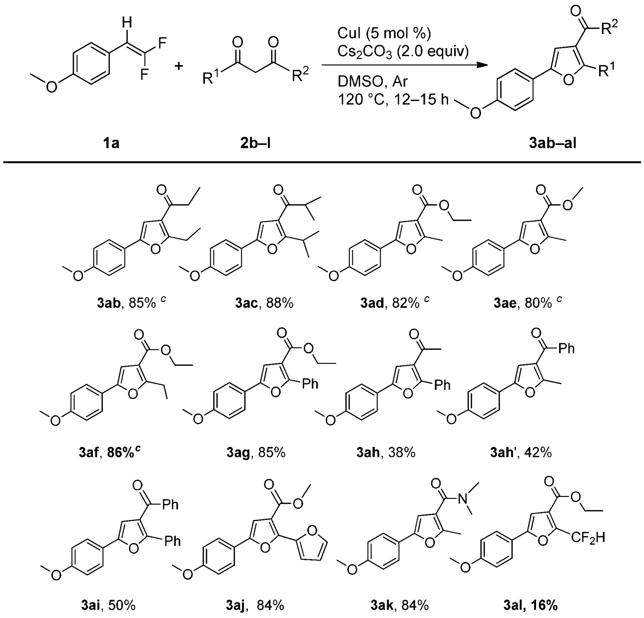
**Scheme 2. Scope of *gem*-Difluoroalkenes**[a,b]



[a] Reaction conditions: *gem*-difluoroalkenes **1a**–**o** (1.0 mmol), **2a** (2.0 mmol), DMSO (5 mL). [b] Isolated yield.

Subsequently, the scope of 1,3-dicarbonyl compounds was investigated (Scheme 3). A variety of 1,3-dicarbonyl substrates were subjected to the cyclization reaction with **1a** under the optimized reaction conditions. In most cases, the reaction also worked smoothly, giving the corresponding polysubstituted furans in good to high yields. To get satisfactory yields, the reaction was carried out at a higher temperature (120 °C), except where noted in Scheme 3.

**Scheme 3. Scope of 1,3-Dicarbonyl Compounds**[a,b]



[a] Reaction conditions: **1a** (1.0 mmol), **2b**–**l** (2.0 mmol), DMSO (5 mL). [b] Isolated yield. [c] Reaction temperature: 90 °C.

It was found that there was no significant difference in reactivity between *β*-diketones and *β*-keto esters or amide (e.g., **3aa**, **3ae**, and **3ak**). Ethyl benzoylacetate (**2g**) was also a good substrate, giving the corresponding polysubstituted furans in good yield (**3ag**). The reaction of unsymmetrical *β*-diketone with **1a** proceeded smoothly; however, two isomers were obtained (**3ah** and **3ah′**). In the case of 1,3-diphenylpropane-1,3-dione (**2i**), the desired product (**3ai**) was obtained only in 50% yield. The low reactivity of **2i** may be due to the steric effect of two phenyl groups in *β*-diketone. We were pleased to observe that the reaction was also effective for ethyl 3-(furan-2-yl)-3-oxopropanoate (**2j**), and 2-furyl-substituted furan was obtained in high yield (**3aj**). When ethyl 4,4-difluoro-3-oxobutanoate (**2l**) was used as substrate, only a small amount of **3al** was formed, whereas ethyl 4,4,4-trifluoro-3-oxobutanoate failed to give the desired product. The structure of compound **3ad** was confirmed by X-ray crystallographic analysis (Figure 1).

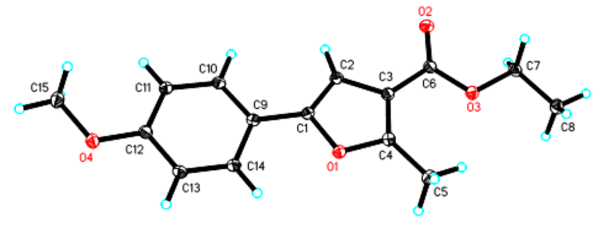
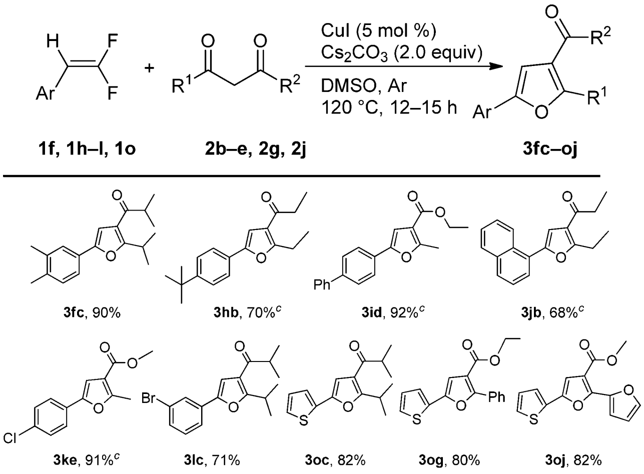


**Figure 1.** Crystal structure of compound **3ad**.

To further verify the generality of this transformation, various *gem*-difluoroalkenes were applied to the reaction with different 1,3-dicarbonyl compounds, and the results are summarized in Scheme 4. All reactions proceeded in generally moderate to excellent yields. The synthesis of **3oj** is particularly interesting. It provides an alternative approach to polyheterocyclic compounds. However, when a symmetrical *gem*-difluoroalkene, such as (2,2-difluoroethene-1,1-diyl)dibenzene, or an aliphatic difluoroalkene, such as 1,1-difluoro-2-benzyl ethylene, was used as substrate, no desired product was observed. It implied that the aryl group and hydrogen atom attached at the C—C double bond of *gem*-difluoroalkenes are necessary for the cyclization reaction.

**Scheme 4. Cyclization of Different *gem*-Difluoroalkenes with Various 1,3-Dicarbonyl Compounds**[a,b]

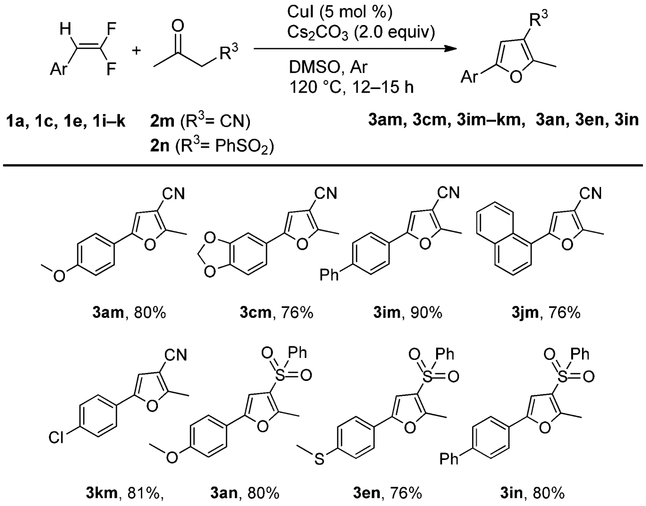


[a]Reaction conditions: *gem*-difluoroalkenes **1f**, **1h–l**, **1o** (1.0 mmol), **2b–e**, **2g**, **2j** (2.0 mmol), DMSO (5 mL). [b]Isolated yield. [c]Reaction temperature: 90 °C.

Encouraged by the above success, we then turned our attention to apply this methodology to the cyclization of *gem*-difluoroalkenes with acetoacetonitrile and phenylsulfonylacetone (Scheme 5). To our delight, these substrates were smoothly converted into the corresponding furans in high yields. These studies further demonstrate the excellent substrate generality and remarkable functional group tolerance of this Cu(I)-catalyzed cyclization reaction.

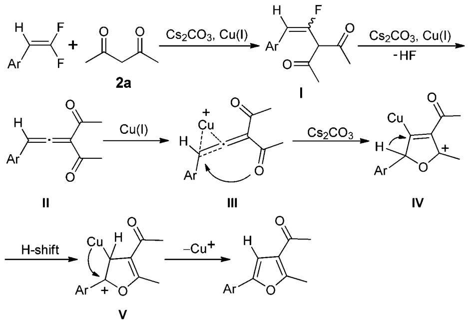
Based on the above results and related literature,[4a,16] a plausible reaction mechanism is depicted in Scheme 6 (with **2a** as the example). Initially, *gem*-difluoroalkene reacts with **2a** to give intermediate **I** with the assistance of copper salt and $Cs_2CO_3$.[17] It should be noted that the starting material **2a** was almost quantitatively recovered in the absence of CuI (Table 1, entry 1), and no intermediate **I** was observed. Elimination of HF from **I** leads to the formation of allenyl ketone **II**. The coordination of the allenyl $\pi$-system to CuI enhances the electrophilicity of allenyl ketone **III**, and subsequent intramolecular nucleophilic attack of the carbonyl oxygen on a Cu(I)—allene complex would form the oxocation **IV**.[16a] Complex **IV** could be transformed into **V** by a 1,2-hydride migration.[16b] Finally, elimination of Cu(I) from the intermediate **V** would afford the expected furan and regenerate the active Cu(I) catalyst.

**Scheme 5. Cyclization of *gem*-Difluoroalkenes with Acetoacetonitrile (2m) and Phenylsulfonylacetone (2n)**[a,b]



[a]Reaction conditions: *gem*-difluoroalkenes **1a**, **1c**, **1e**, **1i–k** (1.0 mmol), acetoacetonitrile **2m**, and phenylsulfonylacetone **2n** (2.0 mmol), DMSO (5 mL). [b]Isolated yield.

**Scheme 6. Proposed Mechanism**



In summary, we have developed the first general route for the efficient synthesis of trisubstituted furans through the copper-catalyzed cyclization of *gem*-difluoroalkenes with various activated methylene carbonyl compounds. The methodology displays broad substrate scope and excellent functional group compatibility and affords the corresponding products in moderate to excellent yields. Because the activated methylene carbonyl compounds are easily accessible, and furthermore a diverse range of *gem*-difluoroalkenes can also be easily prepared from a less expensive commercially available reagent such as methyl fluorosulfonyldifluoroacetate and difluoromethyl 2-pyridyl sulfone (Hu reagent),[18] we anticipate that this method opens up a new avenue for the synthesis of various valuable furans.

## ■ ASSOCIATED CONTENT

### S Supporting Information

Experimental details, spectroscopic data for all new compounds **3**, and crystallographic data of **3ad**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01123.

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) (a) Rao, A. U.; Xiao, D.; Huang, X.; Zhou, W.; Fossetta, J.; Lundell, D.; Tian, F.; Trivedi, P.; Aslanian, R.; Palani, A. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1068. (b) Kumari, N.; Mishra, C. B.; Prakash, A.; Kumar, N.; Mongre, R.; Luthra, P. M. *Neurosci. Lett.* **2014**, *558*, 203. (c) Hasegawa, F.; Niidome, K.; Migihashi, C.; Murata, M.; Negoro, T.; Matsumoto, T.; Kato, K.; Fujii, A. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4266. (d) Abd-Elzaher, M. M.; Labib, A. A.; Mousa, H. A.; Moustafa, S. A.; Abdallah, M. M. *Res. Chem. Intermed.* **2014**, *40*, 1923. (e) Zeng, C.; Seino, H.; Ren, J.; Hatanaka, K.; Yoshie, N. *Macromolecules* **2013**, *46*, 1794. (f) Zeng, C.; Seino, H.; Ren, J.; Hatanaka, K.; Yoshie, N. *Polymer* **2013**, *54*, 5351.

(2) (a) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076. (b) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (c) Wang, Z.-L.; Li, H.-L.; Ge, L.-S.; An, X.-L.; Zhang, Z.-G.; Luo, X.; Fossey, J. S.; Deng, W.-P. *J. Org. Chem.* **2014**, *79*, 1156. (d) Kalaitzakis, D.; Triantafyllakis, M.; Alexopoulou, I.; Sofiadis, M.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 13201.

(3) (a) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955. (b) Keay, B. A. *Chem. Soc. Rev.* **1999**, *28*, 209. (c) Yang, Y.; Ni, F.; Shu, W.-M.; Wu, A.-X. *Tetrahedron* **2014**, *70*, 6733. (d) Zheng, Q.; Hua, R.; Jiang, J.; Zhang, L. *Tetrahedron* **2014**, *70*, 8252. (e) Miao, M.; Xu, X.; Xu, L.; Ren, H. *Eur. J. Org. Chem.* **2014**, 5896. (f) Daru, J.; Benda, Z.; Póti, Á.; Novák, Z.; Stirling, A. *Chem.—Eur. J.* **2014**, *20*, 15395.

(4) (a) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 850. (b) Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. (c) Frey, H. *Synlett* **1993**, 905. (d) Han, X.; Widenhoefer, R. A. *J. Org. Chem.* **2004**, *69*, 1738.

(5) (a) Mross, G.; Holtz, E.; Langer, P. *J. Org. Chem.* **2006**, *71*, 8045. (b) Holtz, E.; Langer, P. *Synlett* **2004**, 1805. (c) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277.

(6) Battace, A.; Lemhadri, M.; Zair, T.; Doucet, H.; Santelli, M. *Organometallics* **2007**, *26*, 472.

(7) (a) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280. (b) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450. (c) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409.

(8) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531.

(9) Hossain, M. L.; Ye, F.; Zhang, Y.; Wang, J. *Tetrahedron* **2014**, *70*, 6957.

(10) (a) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119. (b) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, 1917. (c) Li, Q.; Lin, J.-H.; Deng, Z.-Y.; Zheng, J.; Cai, J.; Xiao, J.-C. *J. Fluorine Chem.* **2014**, *163*, 38. (d) Yamada, S.; Shimoji, K.; Takahashi, T.; Konno, T.; Ishihara, T. *Chem.—Asian J.* **2010**, *5*, 1846. (e) Huang, X.; He, P.; Shi, G. *J. Org. Chem.* **2000**, *65*, 627. (f) Ichikawa, J.; Yokota, N.; Kobayashi, M.; Amano, K.; Minami, T. *Synlett* **1996**, 243.

(11) (a) Zhang, H.; Zhou, C.-B.; Chen, Q.-Y.; Xiao, J.-C.; Hong, R. *Org. Lett.* **2011**, *13*, 560. (b) Landelle, G.; Turcotte-Savard, M.-O.; Angers, L.; Paquin, J.-F. *Org. Lett.* **2011**, *13*, 1568.

(12) Ichikawa, J.; Wada, Y.; Miyazaki, H.; Mori, T.; Kuroki, H. *Org. Lett.* **2003**, *5*, 1455.

(13) Sakoda, K.; Mihara, J.; Ichikawa, J. *Chem. Commun.* **2005**, 4684.

(14) Fuchibe, K.; Takahashi, M.; Ichikawa, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 12059.

(15) (a) Xiong, Y.; Zhang, X.; Huang, T.; Cao, S. *J. Org. Chem.* **2014**, *79*, 6395. (b) Dai, W.; Xiao, J.; Jin, G.; Wu, J.; Cao, S. *J. Org. Chem.* **2014**, *79*, 10537. (c) Jin, G.; Zhang, J.; Wu, W.; Cao, S. *J. Fluorine Chem.* **2014**, *168*, 240. (d) Zhang, X.; Lin, Y.; Zhang, J.; Cao, S. *RSC Adv.* **2015**, *5*, 7905. (e) Wang, M.; Liang, F.; Xiong, Y.; Cao, S. *RSC Adv.* **2015**, *5*, 11996.

(16) (a) Kel'in, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95. (b) Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169.

(17) (a) Mae, M.; Hong, J. A.; Xu, B.; Hammond, G. B. *Org. Lett.* **2006**, *8*, 479. (b) Nomada, E.; Watanabe, H.; Yamamoto, M.; Udagawa, T.; Zhou, B.; Kobayashi, A.; Minakawa, M.; Kawatsura, M. *Synlett* **2014**, *25*, 1725. (c) Yamamoto, M.; Hayashi, S.; Isa, K.; Kawatsure, M. *Org. Lett.* **2014**, *16*, 700.

(18) (a) Thomoson, C. S.; Martinez, H.; Dolbier, W. R., Jr. *J. Fluorine Chem.* **2013**, *150*, 53. (b) Zhao, Y.; Huang, W.; Zhu, L.; Hu, J. *Org. Lett.* **2010**, *12*, 1444. (c) Gao, B.; Zhao, Y.; Hu, J.; Hu, J. *Org. Chem. Front.* **2015**, *2*, 163.