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Direct Approach to *N*-Substituted-2-Fluoroindoles by Sequential Construction of C–N Bonds from *gem*-Difluorostyrenes

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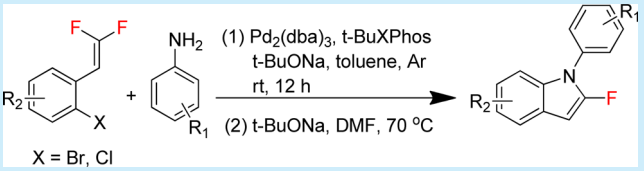
Supporting Information

ABSTRACT: A mild and efficient synthesis of *N*-substituted-2-fluoroindole derivatives was achieved via Buchwald–Hartwig couplings and a sequential, base-promoted intramolecular nucleophilic reaction–β-fluorine elimination. By employing easily obtained *gem*-difluorostyrenes and primary arylamines, the scope, advantages, and limitations of this reaction were well investigated. Furthermore, this strategy distinguishes itself by high modularity, operational simplicity, and a wide substrate scope, giving rise to a broad array of 2-fluoroindole derivatives in moderate to excellent yields.



Indoles, as one kind of very important heterocyclic scaffold, are widespread in natural products, bioactive compounds, and other functional molecules.[1] Indole derivatives display various and unique properties, such as the drug for depression and anxiety (**1**, Naratriptan),[2] potential plant growth hormone regulated transcription factor 2-fluoroindole-3-acetic acid (**2**),[3] inhibitor of sortase A, and isocitratelyase (**3**)[4] (Figure 1). Furthermore, the inhibitors targeting Gp41 (**4**)[5] and the cytosolic phospholipase A2α (**5**)[6] can also be found to have an indole scaffold.

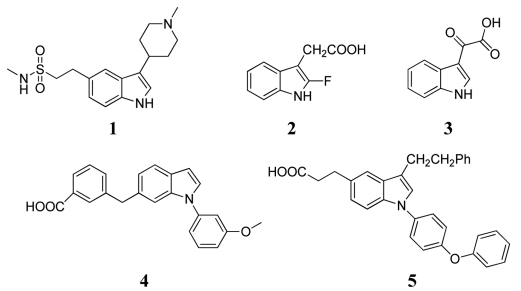


Figure 1. Representative examples of bioactive indole derivatives.

The unique physical and chemical properties of fluorine atom or fluorine-containing groups, such as acidity and basicity, lipid solubility and metabolism stability, are known by organic and medicinal chemists. Additionally, fluorine can also control the reactivity and stereochemistry in asymmetric reactions.[7] During the past decade, the introduction of fluorine atoms to bioactive scaffolds has gained more and more attention in organic and medicinal chemistry.[8,9]

Based on the importance of indole and fluorine in medicinal chemistry, constructing fluorine-containing indole derivatives has attracted great interest. In recent years, some related research has been reported for the synthesis of 2-fluoroindole derivatives. Among several typical examples (Scheme 1), Widdowson's group synthesized 2-fluoroindole derivatives for the first time from stannylated indoles reacting with cesium fluoroxysulfate in 1997 (a).[10a] Later, the same group obtained 2-fluoroindole derivatives by the fluorination of arylheteroaryliodonium salts(a).[10b] In 2013, Daugulis's group obtained 2-fluoroindole derivatives by directing group-assisted, copper-catalyzed fluorination (b).[10c] Then, Huang's group developed a $RuCl_3$ catalyzed fluorination of indoles from *N*-fluorobenzenesulfonimide in 2015 (c).[10d] In the protocols mentioned above, poisonous reagents or directing groups are employed. Minami's group synthesized 2-fluoroindole derivatives by a cyclization reaction after incorporation of fluorine atoms (d).[10e] In addition, Ichikawa's group developed some new methods to synthesize desired products from β,β-difluoro-*o*-sulfonamidostyrenes or gem-difluoroalkenes via base (*t*-BuONa, KH etc.)[10f,g] or $AgSbF_6$ (e).[10h] Furthermore, the synthesis of 2-fluoroindole derivatives was achieved via the palladium-catalyzed 1,1-difluoroallylation of heteronucleophiles followed by an intramolecular Heck reaction (f).[10i] It was noted that the requirement of specific substrates for these reactions limited their applications to some extent. Therefore, development of a convenient approach to synthesize 2-fluoroindole derivatives from simple and readily available starting materials is still in high demand.

Due to the high polarization of the C=C bond caused by the two fluorine atoms, *gem*-difluorostyrenes possess specific reactivity and have become useful building blocks for fluorine-containing compounds.[11] Some pioneering and important works constructing fluorine-containing molecules were re-

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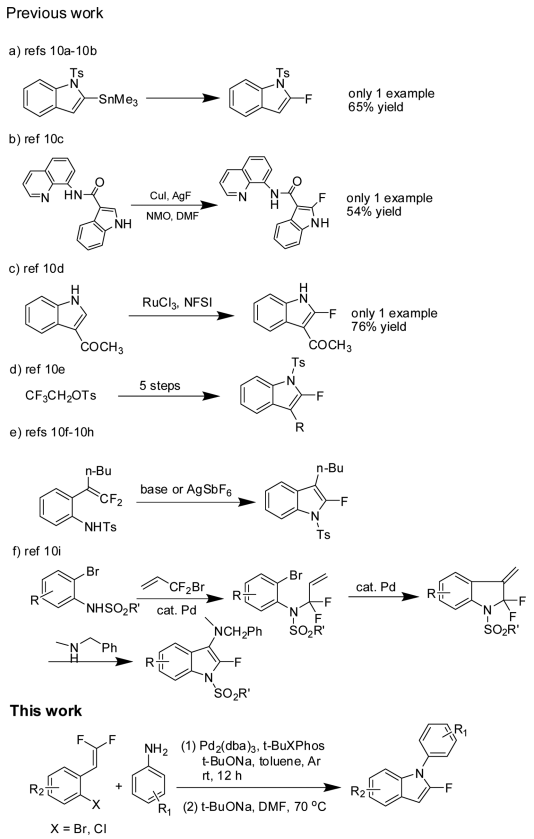
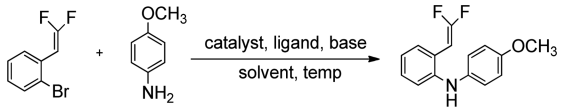
Scheme 1. Synthesis of 2-Fluoroindole Derivatives



ported by Cao and co-workers.[12] Also, the introduction of the trifluoromethyl group from *gem*-difluorostyrenes has particularly gained some attention.[13a,b] Based on the previous work of our group in fluorine chemistry,[14] we continued to pursue new synthetic strategies to construct novel, interesting, fluorine-containing compounds with potential bioactivities such as *N*-substituted-2-fluoroindoles from *gem*-difluorostyrenes. We predicted that *N*-substituted-2-fluoroindoles could be obtained by Buchwald–Hartwig type couplings and a sequential intramolecular nucleophilic aromatic reaction, and two C–N bonds would be formed to complete the reaction from accessible *gem*-difluorostyrenes.[15]

At first, we tried to synthesize 2-fluoroindole derivatives directly using 1-bromo-2-(2,2-difluoroethenyl)benzene and 4-methoxy-aniline as the substrates via a Pd-catalyzed one-pot reaction but failed. We did not detect any desired product and only obtained the Buchwald–Hartwig coupling product. Afterward, we initiated our investigation by screening the coupling reaction conditions of **1a** with **2a** and different Pd catalysts were examined (Table 1). $Pd_2(dba)_3$ was found to give a coupling product in 65% yield with *t*-BuXPhos and Cs_2CO_3 in toluene under an argon atmosphere at room temperature (entries 1–3). After the reaction mixture was slightly warmed to 40 °C, the reaction was found to be complete with a yield of 67% (entry 4 vs 2). The ligands were also screened, and *t*-BuXPhos was found to be better than other ligands (entries 2, 5, 6, 7, 8). Encouraged by this promising result, we further screened different bases and solvents. Finally, *t*-BuONa and toluene were found to be the most effective with an 84% yield (entries 9–15). In addition, reducing the amount of the Pd catalyst and ligand decreased the yield of **3a** to 42% (entry 16). Therefore, the optimal coupling reaction conditions were

Table 1. Optimization of Reaction Conditions[a]



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

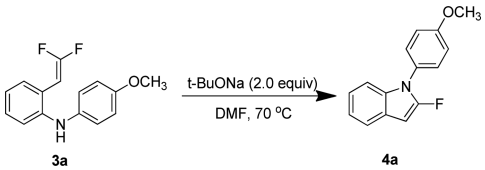
entry	catalyst	ligand	base	solvent	yield (%)[b]
1	$Pd(PPh_3)_4$	*t*-BuXPhos	Cs_2CO_3	toluene	0
2	$Pd_2(dba)_3$	*t*-BuXPhos	Cs_2CO_3	toluene	65
3	$Pd(dppf)Cl_2$	*t*-BuXPhos	Cs_2CO_3	toluene	0
4[c]	$Pd_2(dba)_3$	*t*-BuXPhos	Cs_2CO_3	toluene	67
5	$Pd_2(dba)_3$	XPhos	Cs_2CO_3	toluene	27
6	$Pd_2(dba)_3$	BrettPhos	Cs_2CO_3	toluene	30
7	$Pd_2(dba)_3$	JohnPhos	Cs_2CO_3	toluene	41
8	$Pd_2(dba)_3$	BINAP	Cs_2CO_3	toluene	30
9	**$Pd_2(dba)_3$**	***t*-BuXPhos**	***t*-BuONa**	**toluene**	**84**
10	$Pd_2(dba)_3$	*t*-BuXPhos	*t*-BuOK	toluene	50
11	$Pd_2(dba)_3$	*t*-BuXPhos	K_3PO_4	toluene	48
12	$Pd_2(dba)_3$	*t*-BuXPhos	*t*-BuOLi	toluene	34
13	$Pd_2(dba)_3$	*t*-BuXPhos	*t*-BuONa	dioxane	50
14	$Pd_2(dba)_3$	*t*-BuXPhos	*t*-BuONa	THF	58
15	$Pd_2(dba)_3$	*t*-BuXPhos	*t*-BuONa	DMF	25
16[d]	$Pd_2(dba)_3$	*t*-BuXPhos	*t*-BuONa	toluene	42

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.6 mmol), catalyst (10 mol %), ligand (20 mol %), base (0.8 mmol) in solvent (2.0 mL) at 25 °C for 12 h under Ar. [b]Isolated yields. [c]At 40 °C. [d]Catalyst (5 mol %), ligand (10 mol %).

determined, including the catalyst $Pd_2(dba)_3$ (10 mol %), the ligand *t*-BuXPhos (20 mol %), *t*-BuONa as a base, and the solvent toluene (2.0 mL) at room temperature under an argon atmosphere.

Subsequently, we turned our attention to the rapid cyclization of **3a** to produce a *N*-substituted-2-fluoroindole. However, because of the high bond energy of C–F, the fluorine atom of the vinylic C–F bond was not easily substituted by other atoms. By screening bases, solvents, and temperature (Supporting Information p S2), we determined that *t*-BuONa promoted **3a** to **4a** with a 73% yield in DMF at 70 °C (Scheme 2). Based on these optimizations, we developed a mild and effective method to synthesize *N*-substitued 2-fluoroindole derivatives.

Scheme 2. 5-*endo-trig* Cyclization of 2-(2,2-Difluorovinyl)-*N*-aryl-anilines[a]



3a **4a**

[a]Conditions: **3a** (0.4 mmol), *t*-BuONa (0.8 mmol), DMF (1.5 mL).

With the optimized reaction conditions in hand, we explored the substrate scope of this method (Scheme 3). First, the reaction between 1-bromo-2-(2,2-difluoroethenyl)benzene (**1a**) and various anilines and analogues were investigated (**4a**–**4p**). The steric effect of the substituents affected the yield of the coupling reaction slightly. For example, the coupling reaction of **1a** with *para*-, *meta*-, and *ortho*-methoxyaniline gave similar yields (84%, 75%, and 79%), while the cyclization gave quite

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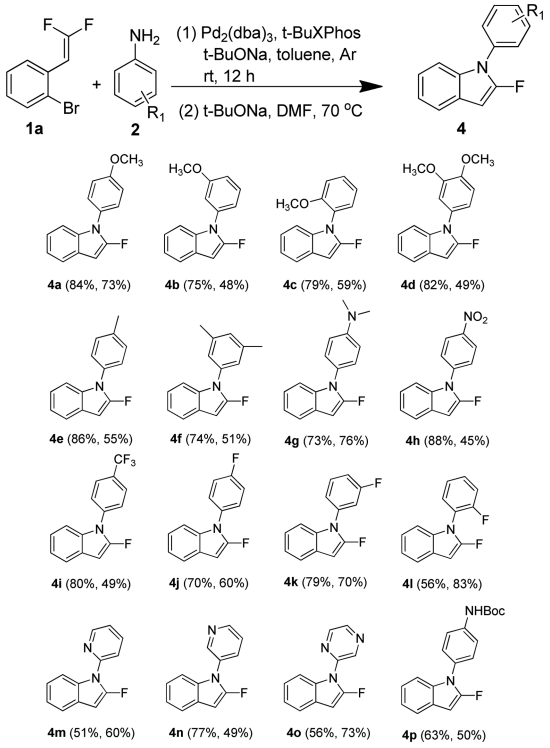
Scheme 3. Synthesis of *N*-Substituted-2-fluoroindole Derivatives of 1a with Various Aromatic Amines[a]



[a]Conditions: (1) **1a** (0.4 mmol), **2** (0.6 mmol), $Pd_2(dba)_3$ (10 mol %), *t*-BuXPhos (20 mol %), *t*-BuONa (0.8 mmol), toluene (2 mL), 25 °C, 12 h, Ar. (2) **3** (0.4 mmol), *t*-BuONa (0.8 mmol), DMF (1.5 mL). Isolated yields were presented as (yield of the coupling reaction, yield of the cyclization reaction).

different yields of 73%, 48%, and 59%, respectively (**4a**, **4b**, **4c**). Notably, treatment of 3,4-dimethoxyaniline with **1a** also proceeded smoothly and gave the desired product **4d** with a coupling yield of 82% and a cyclization yield of 49%, respectively.

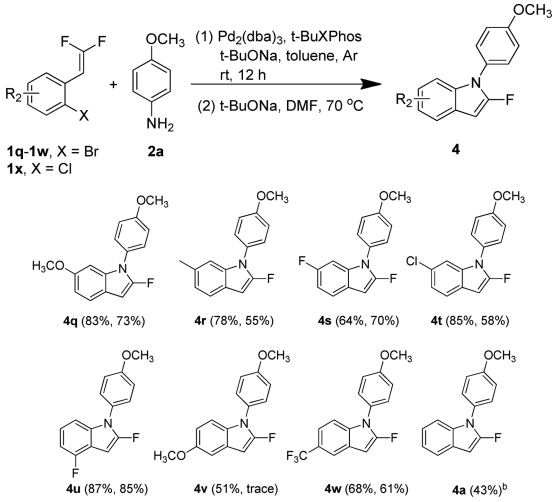
According to the yield of **4d** and **4f**, polysubstituted aromatic amines are well tolerated in this reaction. After the introduction of the electron-withdrawing F group on different positions of aniline, both the coupling reaction and cyclization gave acceptable yields (**4j**, **4k**, **4l**).

The electronic properties of the substituents on the phenyl ring had some effect on the cyclization yield of this reaction. In general, the aromatic amine bearing electron-donating substituents [$-OCH_3$, $-CH_3$, $-N(CH_3)_2$] produced a similar yield of products to those analogues bearing electron-withdrawing substituents ($-NO_2$, $-CF_3$, $-F$) in the coupling reaction. However, the cyclization yields of electron-donating substituents are usually higher (**4a**, **4g** vs **4h**, **4i**, **4j**, **4m**, **4n**).

In addition, 2-pyridinamine, 3-pyridinamine, and 2-pyrazinamine also generated the desired products in moderate yield from the coupling reaction (51%, 77%, and 56%, respectively) and in moderate yield from the cyclization reaction (60%, 49%, and 73%, respectively) for **4m**, **4n**, and **4o**. A substrate with base-sensitive group was also tolerated in the coupling reaction and the cyclization step (**4p**). To demonstrate the synthetic utility of the reaction, the procedure was successfully scaled up to 2.0 mmol of **1a** with **2l**, and the yield of **3l**/**4l** was 64% and 90%, respectively. In brief, various aromatic primary amines were tolerated under the optimized reaction conditions.

We next examined the scope of the *gem*-difluorostyrenes, and they showed very good reactivity (Scheme 4, **4q**–**4w**). For example, substrates with either electron-donating ($-CH_3$ and $-OCH_3$) or electron-withdrawing substituents ($-F$ and $-Cl$) were all effectively converted into the target products (**4q**–**4t**). A similar yield was observed with $-CH_3$ (55%) or $-Cl$ (58%) in the cyclization step. Notably, we also obtained **4u** in good yield (87% and 85%) from the coupling reaction and cyclization. In addition, 5-trifluoromethyl-2-fluoroindole was obtained in good yield from cyclization, while 5-methoxy-2-fluoroindole was not obtained (**4w** vs **4v**). This implies that the electronic properties of substituents on the 5-position have a great impact on the reaction. Furthermore, when Br was replaced by Cl on the phenyl ring of *gem*-difluorostyrene, the yield of the coupling reaction was reduced to 43% from 84%.

Scheme 4. Synthesis of *N*-Substituted-2-fluoroindole Derivatives of 2a with Various *gem*-Difluorostyrenes[a]



[a]Conditions: (1) **1q**–**1x** (0.4 mmol), **2a** (0.6 mmol), $Pd_2(dba)_3$ (10 mol %), *t*-BuXPhos (20 mol %), *t*-BuONa (0.8 mmol), toluene (2.0 mL), 25 °C, 12 h, Ar. Isolated yield. (2) **3** (0.4 mmol), *t*-BuONa (0.8 mmol), DMF (1.5 mL). Isolated yield were presented as (yield of the coupling reaction, yield of the cyclization reaction). [b]The coupling yield of 1-chloro-2-(2,2-difluorovinyl)benzene.

Based on all these observations and Ichikawa's work,[10f−h] we propose a possible mechanism for synthesizing *N*-aryl-2-fluoroindoles from *gem*-difluorostyrenes. The reaction was achieved via Buchwald−Hartwig couplings and a sequential, base-promoted nucleophilic 5-*endo*-*trig* cyclization.

In conclusion, here we report a new and mild method for the synthesis of diverse *N*-substituted-2-fluoroindoles via a Pd-catalyzed coupling reaction and a base-promoted intramolecular nucleophilic addition−*β*-fluorine elimination in moderate to good yields. This protocol is easy to carry out and has a wide scope of substrates. Furthermore, as important building blocks or bioactive scaffolds, studies of *N*-aryl-2-fluoroindoles in medicinal chemistry are still in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00549.

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Experimental procedure and characterization of new compounds (^{1}H and ^{13}C NMR spectra) (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected recent articles and reviews on the application of the indole scaffold, see: (a) Melander, R. J.; Minvielle, M. J.; Melander, C. *Tetrahedron* **2014**, *70*, 6363−6372. (b) Hanif, N.; Yamada, K.; Kitamura, M.; Kawazoe, Y.; de Voogd, N. J.; Uemura, D. *Chem. Nat. Compd.* **2015**, *51*, 1130−1133. (c) Biswas, N. N.; Kutty, S. K.; Barraud, N.; Iskander, G. M.; Griffith, R.; Rice, S. A.; Willcox, M.; Black, D. S.; Kumar, N. *Org. Biomol. Chem.* **2015**, *13*, 925−937. (d) Quirante, J.; Dubar, F.; González, A.; Lopez, C.; Cascante, M.; Cortés, R.; Forfar, I.; Pradines, B.; Biot, C. *J. Organomet. Chem.* **2011**, *696*, 1011−1017. (e) Mesaik, M. A.; Khan, K. M.; Rahim, F.; Taha, M.; Haider, S. M.; Perveen, S.; Khalid, A. S.; Abdalla, O. M.; Soomro, S.; Voelter, W. *Bioorg. Chem.* **2015**, *60*, 118−122. (f) Greig, I. R.; Baillie, G. L.; Abdelrahman, M.; Trembleau, L.; Ross, R. A. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4403−4407. (g) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508−3549. (h) Chen, T.; Foo, T. J. Y.; Yeung, Y. Y. *ACS Catal.* **2015**, *5*, 4751−4755. (i) Chang, G.; Shang, Z. F.; Yu, T.; Yang, L. *J. Mater. Chem. A* **2016**, *4*, 2517−2523.

(2) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489−4497.

(3) Schachtman, D. P.; Shin, R. Y. Plant growth hormone regulated transcription factors and promoters thereof. WO2007127923A2, November 8, 2007.

(4) Lee, Y. J.; Han, Y. R.; Park, W.; Nam, S. H.; Oh, K. B.; Lee, H. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6882−6885.

(5) Zhou, G. Y.; Wu, D.; Hermel, E.; Balogh, E.; Gochin, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1500−1503.

(6) Tomoo, T.; Nakatsuka, T.; Katayama, T.; Hayashi, Y.; Fujieda, Y.; Terakawa, M.; Nagahira, K. *J. Med. Chem.* **2014**, *57*, 7244−7462.

(7) Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014**, *43*, 135−147. Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11860−11871.

(8) Champagne, P.; Desroches, J.; Paquin, J. F. *Synthesis* **2015**, *47*, 306−322.

(9) (a) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496−3508. (b) Nakajima, T. *J. Fluorine Chem.* **2013**, *149*, 104−111. (c) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303−319. (d) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013−1029. (e) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432−2506.

(10) (a) Hodson, H. F.; Madge, D. J.; Widdowson, D. A. *Synlett* **1992**, *1992*, 831−832. (b) Martín-Santamaría, S.; Carroll, M. A.; Carroll, C. M.; Carter, C. D.; Pike, V. W.; Rzepa, H. S.; Widdowson, D. A. *Chem. Commun.* **2000**, *8*, 649−650. (c) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342−9345. (d) Shao, Q.; Huang, Y. *Chem. Commun.* **2015**, *51*, 6584−6586. (e) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **1997**, *51*, 1537−1538. (f) Fujita, T.; Sakoda, K.; Ikeda, M.; Hattori, M.; Ichikawa, J. *Synlett* **2013**, *24*, 57−60. (g) Fujita, T.; Ikeda, M.; Hattori, M.; Sakoda, K.; Ichikawa, J. *Synthesis* **2014**, *46*, 1493−1505. (h) Fujita, T.; Watabe, Y.; Yamashita, S.; Tanabe, H.; Nojima, T.; Ichikawa, J. *Chem. Lett.* **2016**, *45*, 964−966. (i) Fujita, T.; Sugiyama, K.; Sanada, S.; Ichitsuka, T.; Ichikawa, J. *Org. Lett.* **2016**, *18*, 248−251.

(11) (a) Tian, P.; Feng, C.; Loh, T. P. *Nat. Commun.* **2015**, *6*, 7472−7478. (b) Xie, J.; Yu, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 9416−9421. (c) Gao, B.; Zhao, Y. C.; Ni, C. F.; Hu, J. B. *Org. Lett.* **2014**, *16*, 102−105. (d) Riss, P. J.; Aigbirhio, F. I. *Chem. Commun.* **2011**, *47*, 11873−11875. (e) Kong, L. H.; Zhou, X. K.; Li, X. W. *Org. Lett.* **2016**, *18*, 6320−6323. (f) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119−2183. (g) Zhang, X. X.; Cao, S. *Tetrahedron Lett.* **2017**, *58*, 375−392.

(12) (a) Jin, G. Y.; Zhang, J.; Wu, W.; Cao, S. *J. Fluorine Chem.* **2014**, *168*, 240−246. (b) Dai, W. P.; Shi, H. Y.; Zhao, X. H.; Cao, S. *Org. Lett.* **2016**, *18*, 4284−4287. (c) Zhang, X. X.; Lin, Y. Y.; Zhang, J.; Cao, S. *RSC Adv.* **2015**, *5*, 7905−7908. (d) Wang, M. J.; Liang, F.; Xiong, Y.; Cao, S. *RSC Adv.* **2015**, *5*, 11996−11999. (e) Xiong, Y.; Huang, T.; Ji, X. F.; Wu, J. J.; Cao, S. *Org. Biomol. Chem.* **2015**, *13*, 7389−7392.

(13) (a) Gao, B.; Zhao, Y. C.; Hu, J. B. *Angew. Chem., Int. Ed.* **2015**, *54*, 638−642. (b) Tian, P. P.; Wang, C. Q.; Cai, S. H.; Song, S. J.; Ye, L.; Feng, C.; Loh, T. P. *J. Am. Chem. Soc.* **2016**, *138*, 15869−15872.

(14) (a) Han, X. D.; Yue, Z. Z.; Zhang, X. F.; He, Q.; Yang, C. H. *J. Org. Chem.* **2013**, *78*, 4850−4856. (b) Xiang, H. Y.; Yang, C. H. *Org. Lett.* **2014**, *16*, 5686−5689. (c) Jiang, M.; Zhu, F. X.; Xiang, H. Y.; Xu, X.; Deng, L. F.; Yang, C. H. *Org. Biomol. Chem.* **2015**, *13*, 6935−6939. (d) Zhang, X. F.; Yang, C. H. *Adv. Synth. Catal.* **2015**, *357*, 2721−2727.

(15) (a) Thomoson, C. S.; Martinez, H.; Dolbier, W. R. *J. Fluorine Chem.* **2013**, *150*, 53−59. (b) Zheng, J.; Lin, J. H.; Cai, J.; Xiao, J. C. *Chem. - Eur. J.* **2013**, *19*, 15261−15266.

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