

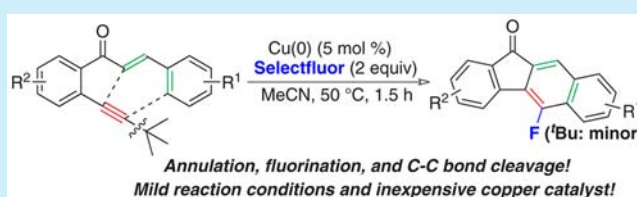
Cu(0)/Selectfluor System-Mediated Mild Synthesis of Fluorinated Fluorenones from Nonaromatic Precursors (1,6-Enynes) Involving C–C Single Bond Cleavage

Jian Zhang, Heng Wang, Shaobo Ren, Wei Zhang, and Yunkui Liu*

State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou 310014, P. R. China

S Supporting Information

ABSTRACT: A novel and facile method for the mild construction of fluorinated fluorenones from nonaromatic precursors (1,6-enynes) mediated by a Cu(0)/Selectfluor system has been successfully achieved. Preliminary mechanistic investigations indicate that the reaction may proceed via an unprecedented annulation/C–C single bond cleavage/fluorination sequence.



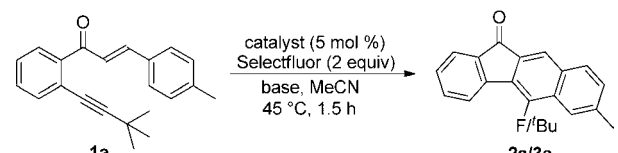
Thanks to the unique properties of the fluorine atom, the introduction of the fluorine atom to organic molecules may significantly affect their original properties such as solubility, biological activity, metabolic stability, and physical properties.¹ For example, fluorinated arenes are widely used as pharmaceuticals, agrochemicals, and PET imaging reagents owing to their desirable biological properties and unique electronic characteristics.² Thus, the development of efficient and mild methods for the construction of aryl fluoride containing compounds is of increasing interest for both academic and industrial communities.³ The traditional synthetic routes to fluorinated arenes, the Balz–Schiemann reaction,⁴ and Halex process,⁵ generally suffer from harsh reaction conditions and substrate limitations. Recently, a variety of new protocols have been developed for the synthesis of fluoroarenes based on the aromatic C–F bond formation.² In particular, the coupling of an Ar–X (X = halo,⁶ OSO₂CF₃,⁷ I⁺Ar,⁸ BR₂ (or BF₃K),⁹ SiR₃,¹⁰ SnR₃,¹¹ MgBr·LiCl,¹² Ni,¹³ Li,¹⁴ etc.) with a nucleophilic or an electrophilic fluorinating agent in the presence or absence of a transition metal has proven to be a promising approach to the construction of aromatic C–F bonds and synthesis of fluoroarenes. In addition, several methods for the construction of aromatic C–F bonds to access fluorinated arenes based on the transition-metal-catalyzed direct aromatic C–H bond fluorination has also been explored in recent years.^{15,21c} Other approaches include the direct transformation of phenols to aryl fluorides with a proper fluorinating agent.¹⁶ All these reactions have attractive features for the synthesis of fluorinated arenes. However, this research on the formation of aromatic C–F bonds mainly focuses on the cleavage of a C–X (X ≠ C, X = halo, O, N, B, Si, I, M(metal), and H) bond. In contrast, to the best of our knowledge, only very limited studies for the construction of aromatic C–F bonds from C–C single bond cleavage have been reported.^{17,18} Besides, the dominant pathways for the construction of

aromatic C–F bonds generally require aromatic precursors to react with fluorinating agents.² In contrast, the construction of aromatic C–F bonds for the synthesis of fluoroarenes from nonaromatic precursors and fluorinating agents has rarely been documented.^{19,20} As our continued interest in developing efficient approaches for the synthesis of fluoro-containing molecules,²¹ we herein describe a novel and facile method for the construction of aromatic C–F bonds to access fluorinated fluorenones from nonaromatic precursors (1,6-enynes) and Selectfluor involving a C–C single bond cleavage.

Regarding research interest in the annulation of 1,*n*-enynes,²² we recently reported a Cu(0)/Selectfluor system-mediated oxidative cyclization of 1,5-enynes to afford 3-formyl-1-indenone derivatives via an annulation/C–C bond cleavage process.²³ Interestingly, when a 1,6-enyne **1a** was subjected to the reaction conditions (5 mol % Cu(0), 2 equiv of Selectfluor, 2 equiv of NaHCO₃ in acetonitrile at 80 °C), an unexpected fluorinated fluorenone **2a** was obtained in 62% yield along with a small amount of an annulated product **3a** (Table 1, entry 1). This unique construction of fluorinated arenes from nonaromatic precursors based on C–C single bond cleavage encouraged us to further optimize the reaction conditions (Table 1; also see Table S1 in the Supporting Information). It was found that the reaction performed better at 45 °C even without a base (92% yield of **2a**, entry 9 vs 4). However, attempts to conduct the reaction at 25 °C gave a low yield of **2a** (entry 5). Among several copper species tested, the use of Cu(0) powder gave the highest yield of **2a** and selectivity (entry 9, Table 1; also see Table S1). The reaction failed to give the fluorinated product **2a** if the amount of Selectfluor was less than 1 equiv (entries 6, 7). Control experiments showed that the copper species was indispensable for the reaction (entry 8).

Received: April 16, 2015

Published: May 29, 2015

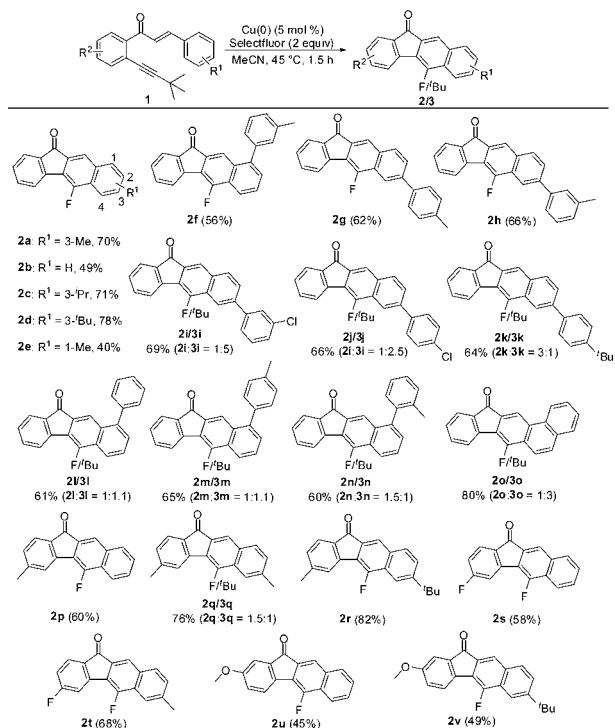
Table 1. Optimization of Reaction Conditions^a


entry	catalyst	base	solvent	yield (%) ^b	
				2a	3a
1 ^c	Cu(0)	NaHCO ₃	MeCN	62	5
2 ^c	Cu(0)	Na ₂ CO ₃	MeCN	33	6
3 ^c	Cu(0)	K ₂ CO ₃	MeCN	65	28
4	Cu(0)	K ₂ CO ₃	MeCN	90	2
5 ^d	Cu(0)	K ₂ CO ₃	MeCN	13	14
6 ^e	Cu(0)	K ₂ CO ₃	MeCN	0	26
7 ^f	Cu(0)	K ₂ CO ₃	MeCN	0	0
8	—	—	MeCN	0	0
9	Cu(0)	—	MeCN	92 (70 ^g)	3
10 ^h	Cu(0)	—	MeCN	91	2
11	Cu(0)	—	solvent ⁱ	0	0
12 ^j	Cu(0)	—	MeCN	0	0
13 ^k	Cu(0)	—	MeCN	42	26

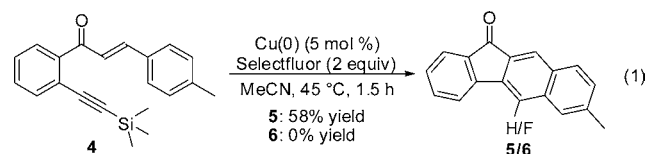
^aAll reactions were carried out with **1a** (0.2 mmol), catalyst (5 mol % based on **1a**), Selectfluor (2 equiv), base (2 equiv), in solvent (2 mL) at 45 °C for 1.5 h unless otherwise noted. ^bDetermined by GC using dodecane as an internal standard. ^cThe temperature is 80 °C. ^dThe temperature is 25 °C. ^eUsing 1 equiv of Selectfluor. ^fIn the absence of Selectfluor. ^gIsolated yield. ^hUsing 3 equiv of Selectfluor. ⁱDMSO, DMF, DCE, toluene, and 1,4-dioxane were used as the solvent, respectively. ^jSelectfluor was replaced by 1-fluoropyridinium tetrafluoroborate and *N*-fluorobenzenesulfonimide (NFSI), respectively. ^kSelectfluor was replaced by 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis(hexafluorophosphate) (F-TEDA-PF₆).

A series of solvents were investigated, and MeCN was identified as the best choice of solvent (entry 11 vs 9). Among several fluorinating agents screened, Selectfluor showed the most effectiveness for the formation of **2a** (entries 12, 13 vs 9).

With the optimized reaction conditions in hand, a variety of 1,6-enynes **1** with different substitution patterns were synthesized and examined for the annulation/fluorination reaction (Scheme 1). It was found that the electronic properties of the R¹ group had a significant effect on the outcome of the reaction. When the R¹ group included aryl rings (**1f–1o**) or electron-donating groups (**1a**, **1c–1e**, and **1p–1v**), the reaction proceeded smoothly and the desired fluorinated products were obtained in modest to good yields. However, substrates **1** were reluctant to be annulated when R¹ was an electron-deficient group (e.g., Cl, F, and CF₃, not listed in Scheme 1). On the other hand, the electronic natures of R² groups had little influence on the annulations/fluorination process, and the corresponding fluorinated fluorenones could be obtained in moderate to good yields (45%–82%, **2p–2v**). Generally, the reaction showed high chemoselectivity to afford **2** rather than **3** as the predominant products (**2:3** ≥ 1.5:1–95:5; **2a–2h**, **2k**, **2n**, **2p**, **2q**, and **2r–2v**). However, in several cases, non-fluorinated products **3** accounted for a large proportion of the total yield (**2i/3i**, **2j/3j**, **2l/3l**, **2m/3m**, and **2o/3o**). Fortunately, in these cases, **2** and **3** could be separated by high performance liquid chromatography (HPLC). Several substituents including halo, alkyl, aryl, and methoxy groups were compatible with the optimized reaction conditions.

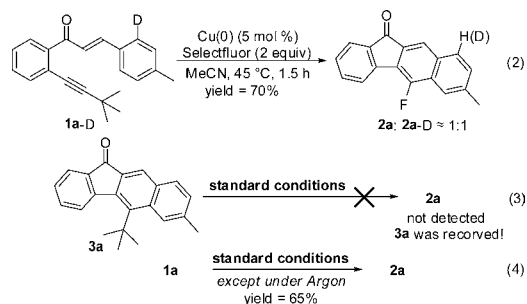
Scheme 1. Scope of the Annulation/Fluorination of **1**

Encouraged by the successful construction of fluoroarenes from 1,6-enynes **1** based on C–C single bond cleavage, we envisioned that 1,6-enyne **4** bearing a C–Si bond should be more easily cleaved and fluorinated than **1** (eq 1). When **4** was



subjected to the standard conditions, the process of annulation and C–Si bond cleavage did occur, but the reaction gave a nonfluorinated product **5** as the exclusive product in 58% yield while the desired **6** was not detected.

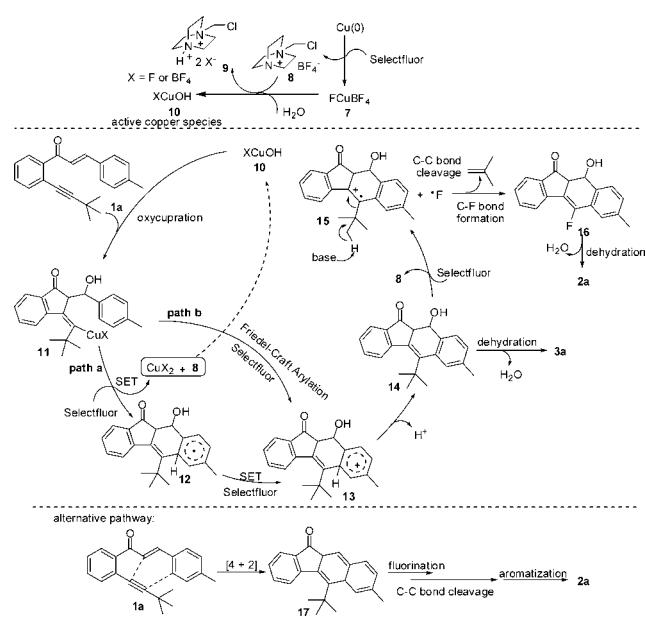
In order to gain some insight into the reaction pathways, several preliminary mechanistic studies on the annulation/fluorination reaction of **1a** were conducted (Scheme 2; see the Supporting Information). First, the intramolecular kinetic isotope effects (KIE) were investigated by using **1a-D** as the substrate under the standard reaction conditions (eq 2, Scheme 2). An intramolecular competitive KIE of 1.0 was obtained,

Scheme 2. Preliminary Mechanistic Studies Based on **1a**

suggesting that the cleavage of the C–H bond is not the rate-determining step. Second, the direct conversion of the preparative **3a** to **2a** was carried out under the standard conditions, but no formation of **2a** was detected while the starting substrate was recovered (eq 3, Scheme 2), demonstrating that **3a** was not likely an intermediate for the formation of **2a**. In addition, when **1a** was subjected to the standard reaction conditions except under an argon atmosphere, the reaction also gave the target product in 65% yield, indicating that dioxygen was not involved in the reaction (eq 4, Scheme 2).

At the present stage, the exact mechanism for the formation of **2a** has not yet been clearly understood. On the basis of the above-mentioned results and the previous literature,^{23–29} a possible mechanism is proposed in Scheme 3. According to our

Scheme 3. Proposed Mechanism



previous work,^{23,24} the reaction of copper powder with Selectfluor may generate a copper species XCuOH ($X = \text{F}$ or BF_4) which could easily undergo oxycupration toward multiple bonds. Thus, an oxycupration of **1a** by **10** may generate an intermediate **11**. Under the oxidative conditions, a radical intermediate **12** may be produced through a single electron transfer (SET) process followed by a cyclization step (path a).²⁵ A further oxidation of **12** by the SET process followed by an abstraction of a proton from the resulting **13** delivered an intermediate **14**.²⁵ The direct dehydration of **14** furnished the product **3a**. Alternatively, **14** may be oxidized by Selectfluor through an SET pathway to generate a radical cationic intermediate **15** and the fluorine radical.^{26,27} With the aid of a base, **15** may undergo a C–C single bond cleavage followed by a C–F bond formation to afford an intermediate **16**.^{17a,b,26,27} A dehydration of **16** may finally give the fluorinated product **2a**. Attempts to detect the intermediates **14** and **16** by ESI-mass spectrometry were not successful, possibly because they were too active to be detected. In addition, an annulation of **11** to **13** through a Friedel–Craft arylation pathway under the oxidative conditions may also be possible (path b).²⁸ Furthermore, an alternative pathway for the formation **2a** via [4 + 2] cyclization of 1,6-eneyne **1a** followed by a fluorination/C–C single bond cleavage/aromatization process is not likely

because most of such [4 + 2] cyclizations require high temperatures;²⁹ yet it could not be completely excluded.

In summary, we have achieved the construction of aromatic C–F bonds based on a C–C single bond cleavage in the tandem annulation–fluorination of 1,6-enynes. The present method for the synthesis of fluoroarenes features (1) the use of nonaromatic precursors, (2) mild reaction conditions, and (3) the use of inexpensive copper species as the catalyst. Furthermore, the resulting fluorinated arenes containing both fluorenone³⁰ and fluorinated aryl moieties² potentially may have biological and pharmaceutical activities as well as optical and electronic properties. Further studies to gain a better understanding of the mechanism of the present reaction are currently undertaken in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental details, full characterization data, charts of the mechanistic studies, and copies of NMR spectra for compounds **2** and **3**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01110.

AUTHOR INFORMATION

Corresponding Author

*E-mail: ykuiliu@zjut.edu.cn.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the Natural Science Foundation of China (Nos. 21172197 and 21372201) and the Opening Foundation of Zhejiang Key Course of Chemical Engineering and Technology, Zhejiang University of Technology for financial support.

REFERENCES

- (a) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214.
- (b) Tredwell, M.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 26.
- (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
- (2) (a) Campbell, M.; Ritter, T. *Chem. Rev.* **2015**, *115*, 612.
- (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
- (c) Jeschke, P. *Pest Manage. Sci.* **2010**, *66*, 10.
- (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.
- (e) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15.
- (f) Jeschke, P. *ChemBioChem* **2004**, *5*, 570.
- (3) (a) Chambers, R. D. *Fluorine in Organic Chemistry*; Oxford: New York, 2004.
- (b) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug. Discovery Dev.* **2008**, *11*, 803.
- (4) Balz, G.; Schiemann, G. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1186.
- (5) Finger, G. C.; Kruse, C. W. *J. Am. Chem. Soc.* **1956**, *78*, 6034.
- (6) (a) Maimone, T. G.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 18106.
- (b) Casitas, A.; Canta, M.; Solà, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* **2011**, *133*, 19386.
- (c) Samant, B. S.; Bhagwat, S. S. *Appl. Catal. A: General* **2011**, *394*, 191.
- (d) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 10795.
- (e) Mu, X.; Zhang, H.; Chen, P.; Liu, G. *Chem. Sci.* **2014**, *5*, 275.
- (f) H. G. Lee, H. G.; Milner, P. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 3792.
- (7) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661.
- (8) Ichishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 5134.

- (9) (a) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993. (b) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860. (c) Fier, P. S.; Luo, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 2552. (d) Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 16292. (e) Mazzotti, A. R.; Campbell, M. G.; Tang, P.; Murphy, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 14012. (f) Tredwell, M.; Preshiock, S. M.; Taylor, N. J.; Gruber, S.; Huiban, M.; Passchier, J.; Mercier, J.; Génicot, C.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2014**, *53*, 7751. (g) Dubbaka, S. R.; Narreddula, V. R.; Gadde, S.; Mathew, T. *Tetrahedron* **2014**, *70*, 9676.
- (10) (a) Gouverneur, V.; Greedy, B. *Chem.—Eur. J.* **2002**, *8*, 766. (b) Tang, P.; Ritter, R. *Tetrahedron* **2011**, *67*, 4449.
- (11) (a) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662. (b) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150.
- (12) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2219.
- (13) Lee, E.; Hooker, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 17456.
- (14) Nagaki, A.; Uesugi, Y.; Kim, H.; Yoshida, J.-I. *Chem.—Asian J.* **2013**, *8*, 705.
- (15) (a) Lin, A.; Huehls, C. B.; Yang, J. *Org. Chem. Front.* **2014**, *1*, 434. (b) Li, Y.; Wu, Y.; Li, G.-S.; Wang, X.-S. *Adv. Synth. Catal.* **2014**, *356*, 1412. (c) Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 10330 and references cited therein.
- (16) (a) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482. (b) Wannberg, J.; Wallinder, C.; Unlusoy, M.; Skoeld, C.; Larhed, M. *J. Org. Chem.* **2013**, *78*, 4184.
- (17) Limited examples for the construction of aromatic C–F bonds from C–C single bond cleavage: (a) Bienvenu, A.; Barthelemy, A.; Boichut, S.; Marquet, B.; Billard, T.; Langlois, B. R. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1467. (b) Gao, Z.; Lim, Y. H.; Tredwell, M.; Li, L.; Verhoog, S.; Hopkinson, M.; Kaluza, W.; Collier, T. L.; Passchier, J.; Huiban, M.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 6733. For other examples of the formation of alkyl C–F bonds based on C–C single bond cleavage, see: (c) Zhao, H.; Fan, X.; Yu, J.; Zhu, C. *J. Am. Chem. Soc.* **2015**, *137*, 3490.
- (18) For select review articles for C–C single bond cleavage, see: (a) Ruhland, K. *Eur. J. Org. Chem.* **2012**, 2683. (b) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (c) Bonesi, S. M.; Fagnoni, M. *Chem.—Eur. J.* **2010**, *16*, 13572. (d) Winter, C.; Krause, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 2460.
- (19) For several examples of fluoroarenes from nonaromatic nonfluoro-containing precursors, see: (a) Wang, K.-P.; Yun, S. Y.; Manidipalli, P.; Lee, D. *Chem. Sci.* **2013**, *4*, 3205. For several examples for the construction of fluoroarenes from fluoro-containing nonaromatic precursors, see: (b) Peter, L. *Synlett* **2009**, 1205 and references cited therein. (c) Patrick, T. B.; Rogers, J.; Gorrell, K. *Org. Lett.* **2002**, *4*, 3155.
- (20) For several examples for the construction of heteroarylfluorides from nonaromatic precursors, see: (a) Xu, T.; Liu, G. *Org. Lett.* **2012**, *14*, 5416. (b) Liu, Q.; Wu, Y.; Chen, P.; Liu, G. *Org. Lett.* **2013**, *15*, 6210. (c) Xu, T.; Mu, X.; Peng, H.; Liu, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 8176.
- (21) (a) Qian, J.; Liu, Y.; Zhu, J.; Jiang, B.; Xu, Z. *Org. Lett.* **2011**, *13*, 4220. (b) Liu, Y.; Zhu, J.; Qian, J.; Xu, Z. *J. Org. Chem.* **2012**, *77*, 5411. (c) Lou, S.-J.; Xu, D.-Q.; Xia, A.-B.; Wang, Y.-F.; Liu, Y.-K.; Du, X.-H.; Xu, Z.-Y. *Chem. Commun.* **2013**, *49*, 6218.
- (22) For review articles, see: (a) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (b) Anorbe, L.; Dominguez, G.; Perez Castells, J. *Chem.—Eur. J.* **2004**, *10*, 4938.
- (23) Zhang, J.; Wu, D.; Chen, X.; Liu, Y.; Xu, Z. *J. Org. Chem.* **2014**, *79*, 4799.
- (24) (a) Zhang, W.; Zhang, J.; Liu, Y.; Xu, Z. *Synlett* **2013**, *24*, 2709.
- (25) (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Jin, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Kochi, J. K.; Tang, R. T.; Bernath, T. *J. Am. Chem. Soc.* **1973**, *95*, 7114.
- (26) (a) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192. (b) Stavber, S. *Molecules* **2011**, *16*, 6432.
- (27) Zhang, X.; Wang, H.; Guo, Y. *Rapid Commun. Mass Spectrom.* **2006**, *20*, 1877 and references cited therein.
- (28) Hopkinson, M. N.; Tessier, A.; Salisburg, A.; Giuffredi, G. T.; Combettes, L. E.; Gee, A. D.; Gouverneur, V. *Chem.—Eur. J.* **2010**, *16*, 4739.
- (29) (a) Rodríguez, D.; Navarro, A.; Castedo, L.; Domínguez, D.; Saá, C. *Org. Lett.* **2000**, *2*, 1497. (b) Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **2002**, *43*, 2712. (c) Rodríguez, D.; Martínez-Esperón, M. F.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Org. Chem.* **2004**, *69*, 3842.
- (30) (a) Perry, P. J.; Read, M. A.; Davies, R. T.; Gowan, S. M.; Reszka, A. P.; Wood, A. A.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **1999**, *42*, 2679. (b) Greenlee, M. L.; Laub, J. B.; Rouen, G. P.; DiNinno, F.; Hammond, M. L.; Huber, J. L.; Sundelof, J. G.; Hammond, G. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3225. (c) Shultz, D. A.; Sloop, J. C.; Washington, G. J. *Org. Chem.* **2006**, *71*, 9104. (d) Tierney, M. T.; Grinstaff, M. W. *J. Org. Chem.* **2000**, *65*, 5355. (e) Itami, K.; Tonogaki, K.; Nokami, T.; Ogashi, Y.; Yoshida, J.-I. *Angew. Chem., Int. Ed.* **2006**, *45*, 2404. (f) Usta, H.; Facchetti, A.; Marks, T. J. *Org. Lett.* **2008**, *10*, 1385. (g) Zhao, Q.; Hu, Q.; Wen, L.; Wu, M.; Hu, Y. *Adv. Synth. Catal.* **2012**, *354*, 2113.