Organic LETTERS

Letter

pubs.acs.org/OrgLett

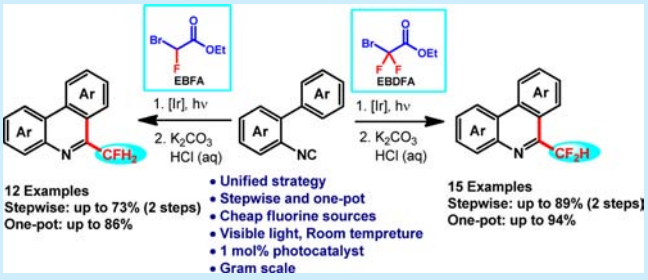
Visible-Light-Mediated Fluoroalkylation of Isocyanides with Ethyl Bromofluoroacetates: Unified Synthesis of Mono- and Difluoromethylated Phenanthridine Derivatives

Xiaoyang Sun and Shouyun Yu*

State Key Laboratory of Analytical Chemistry for Life Science and Institute of Chemical Biology and Drug Innovation, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, 210093, China

Supporting Information

ABSTRACT: A practical and unified strategy has been described for the preparation of mono- and difluoromethylated phenanthridine derivatives using a visible-light-promoted alkylation and decarboxylation sequence from biphenyl isocyanides with ethyl bromofluoroacetate (EBFA) or ethyl bromodifluoroacetate (EBDFA). These reactions could be carried out at room temperature in good to excellent chemical yields. Both stepwise and one-pot procedures have been developed, which makes this strategy more attractive.



Over the past two decades, fluorine-containing organic molecules have received increasing attention because of the elevated reactivity, lipophilicity, and bioactivity compared to their nonfluorinated counterparts.[1] Promoted by a wide range of applications, organofluorine chemistry is booming and offers fruitful results to chemists across many disciplines.[2] In this field, the great development of new methodologies for highly efficient and selective incorporation of a trifluoromethyl group (CF_3) into diverse skeletons has been achieved by numerous synthetic chemists.[3] Yet, compared to trifluoromethylation chemistry, the analogous mono- or difluoromethylation (selective introduction of a CF_2H or CH_2F group into organic molecules) is much less studied.[4] Incorporation of partially fluoromethyl groups into organic molecules is a challenging task and remains mainly unexplored.

Recently, significant progress has been achieved on mono- and difluoromethylation of aromatic compounds based on two major strategies.[5−7] One is the direct transfer of a "CF_2H" or "CH_2F" group into arenes (Figure 1A).[5] For example, Baran and co-workers reported elegant direct oxidative fluoromethylations of heterocycles using zinc fluoromethanesulfinates as fluorine sources.[5a,b] Hartwig's group described stoichiometric copper-mediated difluoromethylation of aryl iodides with trimethylsilyl diflormethane ($TMSCF_2H$) at 120 °C.[5c] Prakash and co-workers also reported an alternative stoichiometric copper-mediated difluoromethylation of aryl iodides with tributyl(difluoromethyl) stannane (n-Bu_3SnCF_2H) at more than 100 °C.[5d] The other is the transfer of a functionalized fluoromethyl group (such as "CF_2R" or "CFHR"), followed by removal of the functional groups, to give a CF_2H or CH_2F group (Figure 1B).[6] Based on this strategy, Amii and co-workers reported a stoichiometric CuI-mediated three-step approach (C−C coupling of aryl iodides with $TMSCF_2CO_2Et$, hydrolysis, and decarboxylation) for the synthesis of difluoromethyl aromatic and heteroaromatic compounds.[6a,b] Both coupling and decarboxylation reactions were carried out at an elevated temperature. Hu's group developed a new monofluoromethylation of aryl iodides with α-fluorinated arylsulfonyl-substituted active methylene compounds. However, the subsequent desulfonylation is plagued by strong reductive conditions (Bu_3SnH at 110 °C).[6c,d] Thus, a catalytic method to form mono- and difluoromethylated aromatic compounds under mild conditions with simple and cheap fluorine sources is very valuable and provides an important tool for synthetic and medicinal chemistry.

Ethyl bromodifluoroacetate (EBDFA, **2a**) and ethyl bromofluoroacetate (EBFA, **2b**) are two commercially available liquids and can be purchased in bulk quantities, which are ideal materials for fluoromethylations.[8] However, partial fluoromethylation with these two readily available fluorine reagents is less studied.[9] Very recently, we succeeded in incorporating these two building blocks into heteroarenes using visible-light-promoted somophilic isocyanide insertion (Figure 1C).[10,11] We contemplate whether the ester moieties can be removed under mild conditions. If so, mono- and difluoromethylated phenanthridine derivatives can be accessed rapidly with an alkylation and decarboxylation sequence.

In order to examine this design, phenanthridine derivative **3a**, which could be prepared from biphenyl isocyanide **1a** with EBDFA (**2a**) according to our previous work,[10] was treated with a mixture of 1 M K_2CO_3 (aq) in methanol. An acidic workup at room temperature was followed after hydrolysis was completed as indicated by TLC monitoring. To our delight, the desired 6-difluoromethylated phenanthridine derivative **5a** was

Received: April 14, 2014
Published: May 21, 2014

dx.doi.org/10.1021/ol501081h | Org. Lett. 2014, 16, 2938−2941

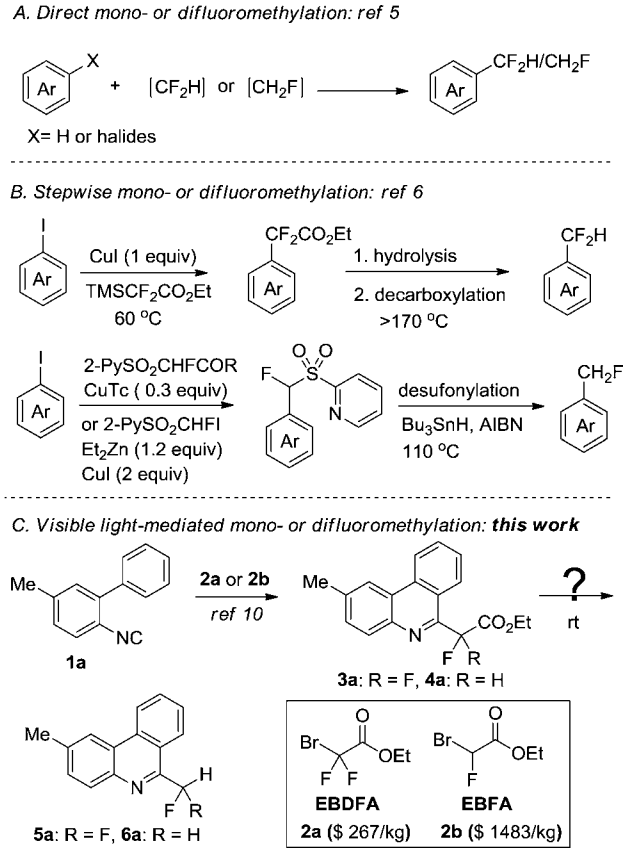
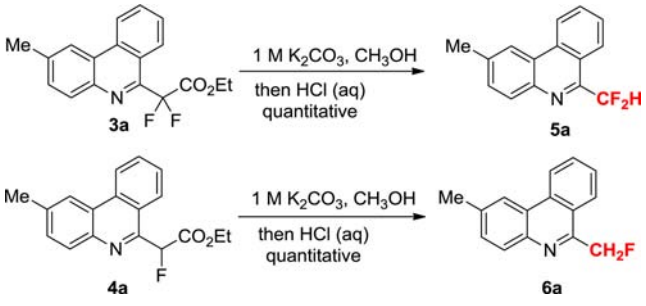


Figure 1. Major strategies of mono- and difluoromethylation of arenes.

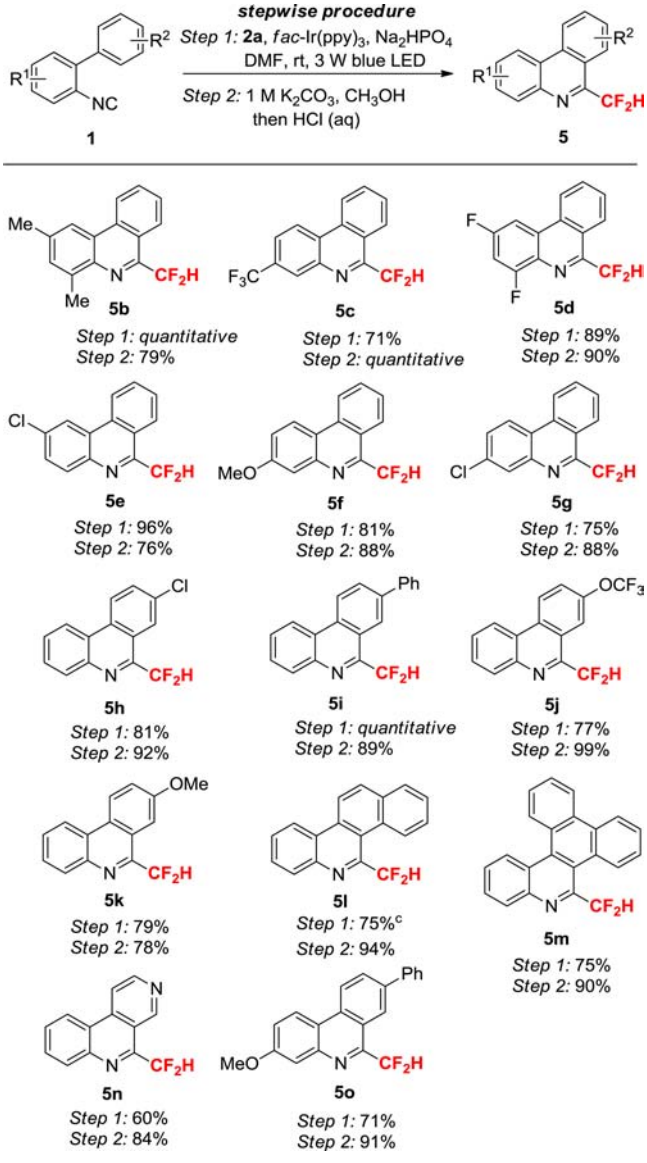
generated directly without further operations in quantitative yield. Similarly, 6-monofluoromethylated phenanthridine derivative **6a** could also be produced quantitatively with the same procedure (Scheme 1).

Scheme 1. Room Temperature Decarboxylation



The great success prompted us to investigate the generalities of this stepwise fluoromethylation. First, a series of 6-difluoromethylated phenanthridine derivatives were prepared enabled by the alkylation and decarboxylation sequence from biphenyl isocyanides and EBDFA (**2a**) as shown in Scheme 2. A variety of biphenyl isocyanides were employed to react with **2a** under the established alkylation conditions. The corresponding 6-alkylated phenanthridine derivatives were prepared in good to perfect yields (60−100%). The substituents on both benzene rings did not affect this transformation significantly. The subsequent decarboxylation also worked quite well. All the isolated 6-alkylated phenanthridine derivatives could go through hydrolysis and decarboxylation smoothly to afford 6-

Scheme 2. Scope of Isocyanides of Difluoromethylation[a,b]



[a]Reaction conditions: Step 1: **1** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv), Na_2HPO_4 (0.24 mmol, 1.2 equiv), and $Ir(ppy)_3$ (0.002 mmol, 1.0 mol %) in dry DMF (2.0 mL) were irradiated by 3 W blue LED; Step 2: **3** (0.1 mmol) in 1 M K_2CO_3 (1 mL) and CH_3OH (1 mL), then diluted HCl (aq). [b] Isolated yield. [c] 3.0 equiv of **2a** were used.

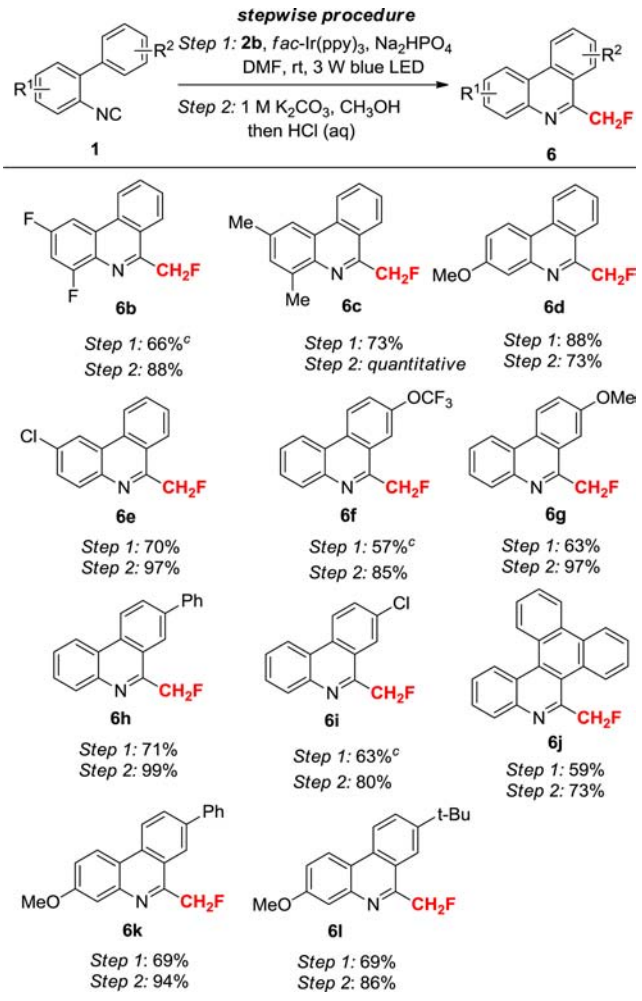
difluoromethylated phenanthridine derivatives in high yields (76−100%).

We then turned our attention to prepare 6-monofluoromethylated phenanthridine derivatives as shown in Scheme 3. A broad range of 2-isocyanobiphenyl compounds reacted smoothly with EBFA (**2b**) to give the corresponding 6-alkylated phenanthridine derivatives in satisfactory yields (59−88%). After alkylation, the subsequent decarboxylation also worked smoothly. All the 6-alkylated phenanthridine derivatives afforded 6-monofluoromethylated phenanthridine derivatives in good to excellent yields (73−100%) after hydrolysis and acidic workup.

The miscibility of DMF with MeOH and H_2O prompted us to investigate the possibility of a one-pot procedure for the synthesis of di- and monofluoromethylated phenanthridine

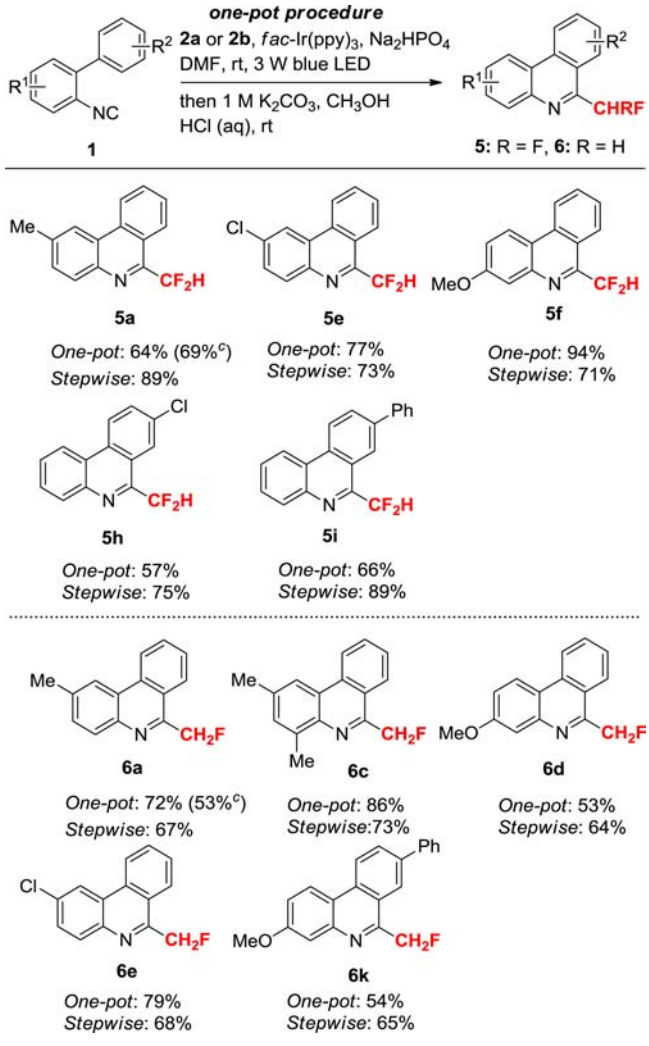
dx.doi.org/10.1021/ol501081h | Org. Lett. 2014, 16, 2938−2941

Scheme 3. Scope of Isocyanides of Monofluoromethylation[a,b]



[a]Reaction conditions: Step 1: **1** (0.2 mmol, 1.0 equiv), **2b** (0.4 mmol, 2.0 equiv), Na_2HPO_4 (0.24 mmol, 1.2 equiv), and $Ir(ppy)_3$ (0.002 mmol, 1.0 mol %) in dry DMF (2.0 mL) were irradiated by 3 W blue LED; Step 2: **4a** (0.1 mmol) in 1 M K_2CO_3 (1 mL) and CH_3OH (1 mL), then diluted HCl (aq). [b] Isolated yield. [c] 3.0 equiv of **2b** were used.

Scheme 4. A One-Pot Procedure[a,b]



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2a** or **2b** (0.4 mmol, 2.0 equiv), Na_2HPO_4 (0.24 mmol, 1.2 equiv), and $Ir(ppy)_3$ (0.002 mmol, 1.0 mol %) in dry DMF (2.0 mL) were irradiated by 3 W blue LED; After the alkylation was complete, to the solution were added 1 M K_2CO_3 (1 mL) and MeOH (1 mL), and then diluted HCl (aq) was added. [b] Isolated yield. [c] 10 mmol scale.

derivatives, which can improve the overall efficiency of this transformation significantly. After the alkylation step was complete, the solution was treated with 1 M K_2CO_3 (aq, 1 mL) and MeOH (1 mL) at room temperature directly. And then the reaction mixture was acidified to about pH 3 with diluted HCl (aq). Fortunately, we found the sequential one-pot protocol worked quite well for a number of substrates without significantly affecting the yield compared to the stepwise procedure for both di- and monofluoromethylations (Scheme 4). More importantly, the one-pot procedure could be scaled up easily with comparable yields. **5a** (1.68 g) and **6a** (1.20 g) were prepared when the reaction was run in 10 mmol scale. This greatly improved the practicability of this synthetic procedure and provided a convenient route to the preparation of 6-mono- and difluoromethylated phenanthridine derivatives.

In summary, we have described a practical and unified strategy for the preparation of 6-mono- and difluoromethylated phenanthridine derivatives using alkylation and decarboxylation sequences. Both alkylation and decarboxylation reactions proceeded at room temperature in good to excellent chemical yields with a broad substrate scope. Furthermore, the fluoromethylation reagents (EBDFA, **2a** and EBFA, **2b**) are inexpensive and readily available, which serve as ideal fluorine sources. Both stepwise and one-pot procedures worked quite well, which makes these protocols ideal choices for the synthesis of mono- and difluoromethylated heteroarenes. Further work on the mono- and difluoromethylation of various substrates using these reagents is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yushouyun@nju.edu.cn.

dx.doi.org/10.1021/ol501081h | Org. Lett. 2014, 16, 2938−2941

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the 863 program (2013AA092903), the National Natural Science Foundation of China (21272113), and the Natural Science Foundation of Jiangsu Province (BK20131266).

■ REFERENCES

(1) (a) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 2000. (d) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: New York, 1993. (e) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000.

(2) (a) Wen, L.; Shen, Q.; Lu, L. *Org. Lett.* **2010**, *12*, 4655. (b) Liu, C.; So, L.; Lo, J. C. Y.; Chan, M. C. W.; Kaneyoshi, H.; Makio, H. *Organometallics* **2012**, *31*, 5274. (c) Rudnitskaya, A.; Huynh, K.; Török, B.; Stieglitz, K. *J. Med. Chem.* **2009**, *52*, 878. (d) Watson, W. J. *Org. Process Res. Dev.* **2006**, *10*, 1314. (e) O'Hagan, D. *J. Org. Chem.* **2012**, *77*, 3689. (f) Török, M.; Abid, M.; Mhadgut, S. C.; Török, B. *Biochemistry* **2006**, *45*, 5377. (g) Amii, H.; Kageyama, K.; Kishikawa, Y.; Hosokawa, T.; Morioka, R.; Katagiri, T.; Uneyama, K. *Organometallics* **2012**, *31*, 1281. (h) Jin, G.; Zhang, X.; Cao, S. *Org. Lett.* **2013**, *15*, 3114.

(3) (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (b) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832. (c) Yamazaki, T.; Tagauchi, T.; Ojima, I. In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, 2009; pp 3−46. (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (e) Schlosser, M. *Angew. Chem.* **2006**, *118*, 5558; *Angew. Chem., Int. Ed.* **2006**, *45*, 5432. (f) Shimizu, M.; Hiyama, T. *Angew. Chem.* **2005**, *117*, 218; *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (g) Kirsch, P. In *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004. (h) Jeschke, P. *ChemBioChem.* **2004**, *5*, 570.

(4) For recent reviews, see: (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (b) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465. (c) Macé, Y.; Magnier, E. *Eur. J. Org. Chem.* **2012**, 2479.

(5) (a) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95. (b) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494. (c) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524. (d) Prakash, G. K. S.; Ganesh, S. K.; Jones, J.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090.

(6) (a) Fujikawa, K.; Kobayashi, A.; Amii, H. *Synthesis* **2012**, *44*, 3015. (b) Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, *13*, 5560. (c) Zhao, Y.; Ni, C.; Jiang, F.; Gao, B.; Shen, X.; Hu, J. *ACS Catal.* **2013**, *3*, 631. (d) Zhao, Y.; Gao, B.; Ni, C.; Hu, J. *Org. Lett.* **2012**, *14*, 6080.

(7) For other related works on mono- and difluoromethylations, see: (a) Liu, G.; Wang, X.; Lu, X.; Xu, X.; Tokunaga, E.; Shibata, N. *Chemistry Open* **2012**, *1*, 227. (b) Nomura, Y.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 1885. (c) Liu, J.; Hu, J. *Chem.—Eur. J.* **2010**, *16*, 11443. (d) Shen, X.; Zhou, M.; Ni, C.; Zhang, W.; Hu, J. *Chem. Sci.* **2013**, *5*, 117. (e) Zhu, J.; Zhang, W.; Zhang, L.; Liu, J.; Zheng, J.; Hu, J. *J. Org. Chem.* **2010**, *75*, 5505. (f) Wang, X.; Liu, G.; Xu, X.; Shibata, N.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 1827. (g) Prakash, G. K. S.; Krishnamoorthy, S.; Ganesh, S. K.; Kulkarni, A.; Haiges, R.; Olah, G. A. *Org. Lett.* **2014**, *16*, 54. (h) Wang, F.; Luo, T.; Hu, J.; Wang, Y.; Krishnan, H. S.; Jog, P. V.; Ganesh, S. K.; Prakash, G. K. S.; Olah, G. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 7153. (i) Iida, T.; Hashimoto, R.; Aikawa, K.; Ito, S.; Mikami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 9535. (j) Hu, M.; He, Z.; Gao, B.; Li, L.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 17302. (k) Min, Q.; Yin, Z.; Feng, Z.; Guo, W.; Zhang, X. *J. Am. Chem. Soc.* **2014**, *136*, 1230. (l) Kosobokov, M. D.; Dilman, A. D.; Struchkova, M. I.; Belyakov, P. A.; Hu, J. *J. Org. Chem.* **2012**, *77*, 2080. (m) Prakash, G. K. S.; Paknia, F.; Mathew, T.; Mlostoń, G.; Joschek, J. P.; Olah, G. A. *Org. Lett.* **2011**, *13*, 4128. (n) Mizuta, S.; Stenhagen, I. S. R.; O'Duill, M.; Wolstenhulme, J.; Kirjavainen, A. K.; Forsback, S. J.; Tredwell, M.; Sandford, G.; Moore, P. R.; Huiban, M.; Luthra, S. K.; Passchier, J.; Solin, O.; Gouverneur, V. *Org. Lett.* **2013**, *15*, 2648. (o) Zhou, Q.; Ruffoni, A.; Gianatassio, R.; Fujiwara, Y.; Sella, E.; Shabat, D.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3949. (p) Matsuzak, K.; Furukawa, T.; Tokunaga, E.; Matsumoto, T.; Shiro, M.; Shibata, N. *Org. Lett.* **2013**, *15*, 3282.

(8) The price of **2a** and **2b** from TCI, China: CNY 460/25g (US $77/25 g) for **2a**, CNY 1450/25g (US $242/25 g) for **2b**. They can also be purchased in bulk quantities from a local company with much lower prices: CNY 1600/kg (US $267/kg) for **2a** and CNY 8900/ kg (US $1483/kg) for **2b**.

(9) For selected reactions employing **2a** or **2b**, see: (a) Kaneda, T.; Komura, S.; Kitazume, T. *J. Fluorine Chem.* **2005**, *126*, 17. (b) Ashwood, M. S.; Cottrell, I. F.; Cowden, C. J.; Wallace, D. J.; Davies, A. J.; Kennedy, D. J.; Dolling, U. H. *Tetrahedron Lett.* **2002**, *43*, 9271. (c) Cheguillaume, A.; Lacroix, S.; Marchand-Brynaert, J. *Tetrahedron Lett.* **2003**, *44*, 2375. (d) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160. (e) Wallentin, C.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875.

(10) Jiang, H.; Cheng, Y.; Wang, R.; Zheng, M.; Zhang, Y.; Yu, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 13289.

(11) For other related works on biphenyl isocyanides, see: (a) Liu, J.; Fan, C.; Yin, H.; Qin, C.; Zhang, G.; Zhang, X.; Yi, H.; Lei, A. *Chem. Commun.* **2014**, *50*, 2145. (b) Zhang, B.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2014**, *16*, 250. (c) Leifert, D.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2013**, *15*, 6286. (d) Cheng, Y.; Jiang, H.; Zhang, Y.; Yu, S. *Org. Lett.* **2013**, *15*, 5520. (e) Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792. (f) Wang, Q.; Dong, X.; Xiao, T.; Zhou, L. *Org. Lett.* **2013**, *15*, 4846. (g) Tobisu, M.; Koh, K.; Furukawa, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11363.