ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: D. Li, T. Mao, J. Huang and Q. Zhu, *Chem. Commun.*, 2017, DOI: 10.1039/C6CC08543A.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the author guidelines.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the ethical guidelines, outlined in our author and reviewer resource centre, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C6CC08543A

Journal Name

COMMUNICATION

A one-pot synthesis of [1,2,3]triazolo[1,5-a]quinoxalines from 1-azido-2-isocyanoarenes with high bond-forming efficiency

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

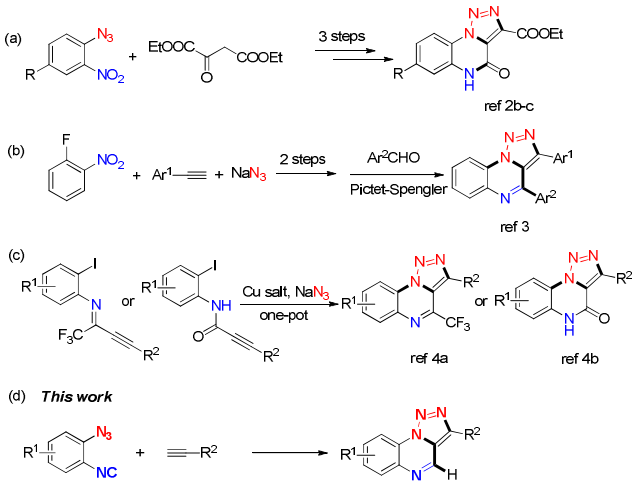
www.rsc.org/

Dengke Li, Tingting Mao, Jinbo Huang,* and Qiang Zhu*

An efficient approach to prepare the 1,2,3-triazolo[1,5-a]quinoxaline scaffold, starting from 1-azido-2-isocyanoarenes and terminal acetylenes or substituted acetaldehydes, has been developed. In the case of the trifluoromethylation triggered cyclization, four chemical bonds, including two C-C and two C-N bonds were formed consecutively without isolating the triazole intermediate. In addition, these triazo-fused products were readily transformed into diversified quinoxaline derivatives via rhodium-catalyzed carbenoid insertion reactions.

The 1,2,3-triazole-containing heterocycles have been widely applied in medicinal chemistry due to their diverse pharmacological properties, including anticancer, antituberculosis, and antibacterial.[1] For example, the scaffold of [1,2,3]triazolo[1,5-*a*]-quinoxaline exists in G-protein-coupled Niacin receptor 109A[2a] as well as inhibitors binding to benzodiazepine and adenosine receptors.[2b-c] Classical methods for the construction of this tricyclic system require multiple steps through triazole intermediates followed by cycloamidation[2] or Pictet–Spengler cyclization[3] starting from 2-nitrophenylazide or 1-fluoro-2-nitrobenzene, respectively (a and b, Scheme 1). In 2010, Gong and Yu developed a one-step cascade cycloaddition of substituted 1,1,1-trifluoro-*N*-(2-iodophenyl)but-3-yn-2-imines with sodium azide followed by copper-catalyzed Ullmann coupling to construct two heterocyclic rings.[4a] Later on, Cai and Ding also applied the strategy for the synthesis of [1,2,3]-triazolo[1,5-*a*]quinoxalin-4(5*H*)-ones from *N*-(2-iodophenyl) propiolamides (c, Scheme 1).[4b] However, these linear approaches are not convenient for product diversification.

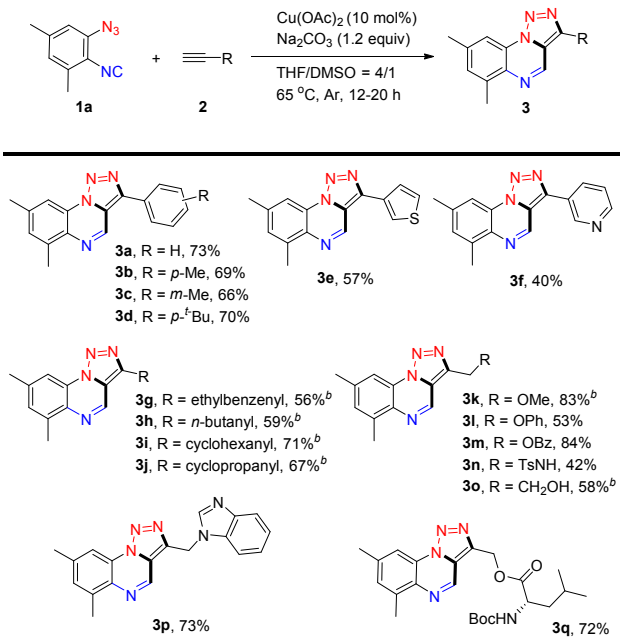
Isocyanide has been recognized as a powerful C1 synthon in the synthesis of heterocycles. Besides acting as a C1 synthon, the inbuilt functional group in isocyanide can also participate in the ring construction together with the isocyano moiety (NC).[5] For example, biaryl isocyanides have been extensively studied in the synthesis of various C6 substituted phenanthridines.[5-6] Continuing our interest on heterocycle synthesis using functionalized isocyanide,[7] we anticipated that the title compounds could be accessed convergently from 1-azido-2-isocyanoarenes and terminal alkynes through copper-catalyzed azide-alkyne [3+2] cycloaddition (CuAAC) followed by isocyanide insertion (d, Scheme 1). The 1-azido-2-isocyanoarenes could be easily prepared by Jiao's method from anilines.[8] However, their synthetic application is underdeveloped.[9]



Scheme 1. Approaches to 1,2,3-triazolo[1,5-a]quinoxalines.

We designed this study with 1-azido-2-isocyano-3,5-dimethylbenzene **1a** and ethynylbenzene **2a** through CuAAC.[10] Under the optimized reaction conditions involving $Cu(OAc)_2$ as a catalyst in THF/DMSO (see table S1, ESI), [1,2,3]triazolo[1,5-*a*]quinoxaline **3a** was obtained in 73% yield (Scheme 2). It was notable that no triazole intermediate was detected during the reaction, probably due to the expeditiousness of intramolecular isocyanide insertion into the cuprate intermediate after CuAAC. Various aromatic, heteroaromatic as well as aliphatic substituted terminal alkynes underwent the tandem cyclization smoothly to generate the corresponding products **3a**–**3j** in moderate to good yields. Derivatives of propargyl alcohol and propargyl amine and even unprotected but-3-yn-1-ol could be served as coupling partners (**3k**-**3o**). Benzimidazole and amino acid derivatives bearing a terminal alkyne moiety were also compatible with the reaction and produced **3p** and **3q** in 73% and 72% yield, respectively.

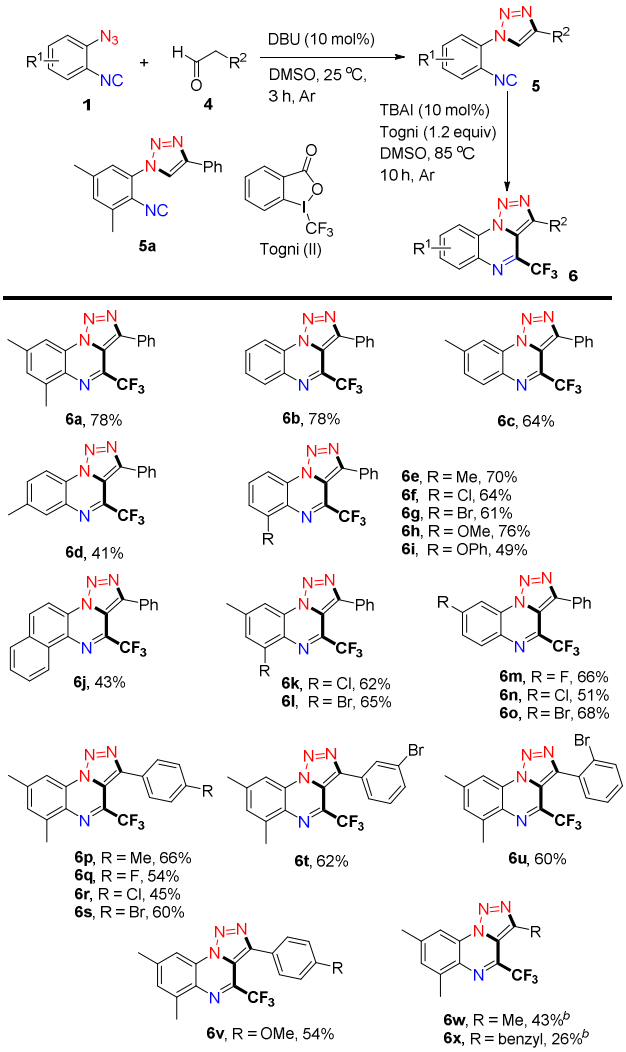
View Article Online
DOI: 10.1039/C6CC08543A



Scheme 2. Synthesis of [1,2,3]triazolo[1,5-*a*]quinoxalines[a]
[a Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2** (1.5 equiv), $Cu(OAc)_2$ (10 mol%), Na_2CO_3 (1.2 equiv) in THF/DMSO (v/v = 4/1, 1.5 mL), 65 °C, 12 h, in Ar. b **2** (3.0 equiv), 20 h.]

Considering the versatility of bi(hetero)aryl isocyanide in heterocycle synthesis,[11] we hope that the isocyano group could survive the triazole-forming step, so that the introduction of different substituents at the C4 position of the cyclized product would be easier. Then, an alternative triazole synthesis without using transition metal catalyst was tested.[12] As expected, the isocyano group remained unchanged after cycloaddition of **1a** with 2-phenylacetaldehyde **4a** in the presence of DBU (10 mol%) in DMSO at room temperature (25 °C), furnishing 1-(2-isocyano-3,5-dimethylphenyl)-4-phenyl-1*H*-1,2,3-triazole **5a** in excellent isolating yield (92%) (see table S2, ESI). Next, trifluoromethylation of **5a** was investigated preferentially due to the great importance of CF_3-containing molecules in agrochemicals, pharmaceuticals, and specialty materials.[13-14] Satisfyingly, treating **5a** with Togni reagent (II) (1.2 equiv) in the presence of TBAI (10 mol%) in DMSO gave C4 trifluoromethylated [1,2,3]triazolo[1,5-*a*]quinoxaline **6a** in good yield (85%).[15] Next, direct trifluoromethylation of **5a** without its purification was investigated, because both the triazole-forming and cyclotrifluoromethylation steps were high-yield and clean in the same solvent (DMSO). After stirring a mixture of **1a**, **4a**, and DBU (10 mol%) in DMSO at 25 °C for 3 h, Togni reagent (II) (1.2 equiv) and TBAI (10 mol%) were added to the reaction mixture which was further stirred at elevated temperature (85 °C) for 10 h. The desired product **6a** was isolated in 78% total yield for this one-pot two-step protocol in which four chemical bonds, including two C-C and two C-N bonds, were formed consecutively (Scheme 3). It was noteworthy that **6a** could not be accessed by reacting **3a** with Togni reagent (II).

Then, the feasibility of the current one-pot tandem reaction was studied with a range of 1-azido-2-isocyanoarenes **1** and 2-phenylacetaldehyde **4a** (Scheme 3). The 1-azido-2-isocyanoarenes bearing various substituents such as Me, OMe, OPh, F, Cl, and Br at different positions of the benzene ring underwent the tandem annulation smoothly to generate the corresponding trifluoromethylated products (**6a-6c**, **6e-6i**, and **6k-6o**) in 49-78% yields. The 1-azido-2-isocyano-4-methylbenzene and 2-azido-1-isocyanonaphthalene were less compatible with the reaction, giving **6d** and **6j** in 41% and 43% yield, respectively.



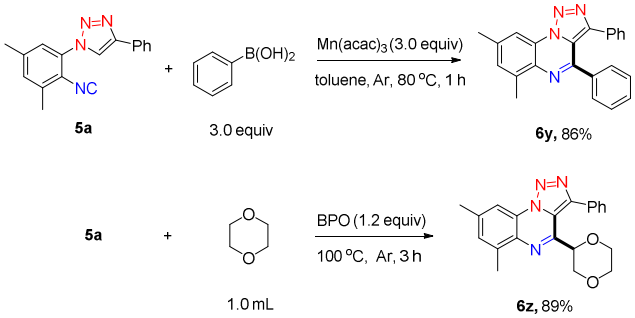
Scheme 3 One-pot synthesis of 4-(trifluoromethyl)-[1,2,3]triazolo[1,5-*a*]quinoxalines[a]
[a Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **4** (0.15 mmol 1.5 equiv), DBU (10 mol%), DMSO (2.0 mL), 25 °C, 3 h, in Ar; then TBAI (10 mol%) and Togni (II) (1.2 equiv) were added, 85 °C, 10 h, in Ar. b **1a** (0.15 mmol) and **4** (2.0 equiv), pyrrolidine (2.0 equiv), toluene (2.0 mL), 50 °C, 20 h; then *m*-CPBA (1.5 equiv for **6w**, 3.0 equiv for **6x**), 0 to 25 °C, 5 h; then, TBAI (10 mol%), Togni (II) (1.2 equiv), in DMSO (2.0 mL), 85 °C, 10 h.]

Next, a variety of substituted acetaldehydes were tested in reactions with **1a**. Phenylacetaldehydes substituted with electron-withdrawing 4-F, 4-Cl, 4-Br, 3-Br, and 2-Br or electron-donating 4-Me and 4-OCH_3 had little influence on product formation, delivering the corresponding products **6p-6v** in 45-66% yields.

View Article Online
DOI: 10.1039/C6CC08543A

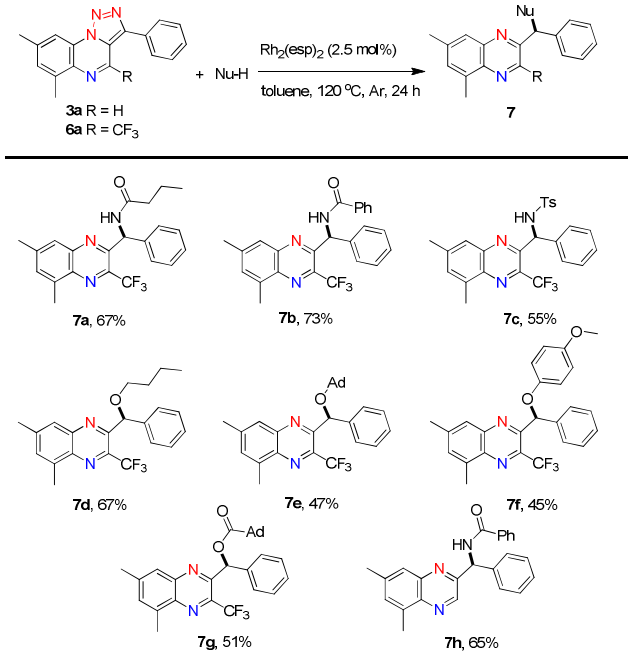
Unfortunately, aliphatic aldehydes such as *n*-propaldehyde and 3-phenylpropionaldehyde were not successful in producing the desired products under the standard conditions. To our delight, by following a modified condition for triazole synthesis,[12i] C3 methyl and benzyl substituted 4-(trifluoromethyl)-[1,2,3]triazolo[1,5-*a*]quinoxalines **6w** and **6x** were also generated, albeit in 43% and 26% yields.

Besides cascade trifluoromethylation-annulation, arylation- and alkylation-annulation of **5a** also took place smoothly by following literature methods, resulting arylated and alkylated **6y** and **6z** in excellent yields (Scheme 4).[11a, 11e] It is reasonable to anticipate that triazolo arylisocyanide like **5a** can serve as valuable intermediate for the synthesis of C4 diversified [1,2,3]triazolo[1,5-*a*]quinoxalines.



Scheme 4 Synthesis of aryl and alkyl substituted [1,2,3]triazolo[1,5-*a*]quinoxalines from **5a**

As we know, C-H and X-H insertion into carbenoid intermediate has been well established as a powerful method for C-C and C-X bond formation starting from diazo compounds.[16a] Recently, electron-deficient 1,2,3-triazoles, such as *N*-sulfonyl-1,2,3-triazoles and pyridotriazoles, were used as alternative progenitors of carbene in organic synthesis.[16b-c] To test the possibility of using the aforementioned triazole-containing products as carbene precursors, **6a** was studied using $Rh_2(esp)_2$ as a catalyst in the presence of various N-H nucleophiles. Satisfyingly, denitrogenative ring-opening of the triazole moiety and subsequent carbene insertion into N-H bond of *N*-butyl amide indeed happened, offering trifluoromethylated quinoxaline derivative **7a** in 67% yield.[17a] Other amides, such as benzamide and 4-methylbenzenesulfonamide were also suitable substrates in this reaction (**7b-7c**). In addition to amides, alcohols and carboxylic acids could also be used as coupling partners via O-H insertion,[17b] giving the corresponding ether or ester derivatives **7d-7g** in moderate yields (Scheme 5). Importantly, less electron-deficient **3a** could also be transformed to **7h** in 65% yield.



Scheme 5 Diversification through Rh(II) catalysis[a]
[[a] Reaction conditions: **3a** or **6a** (0.1 mmol, 1.0 equiv), NuH (2.0 equiv), [Rh] (2.5 mol%), toluene (2.0 mL), 120 °C, 24 h, in Ar.]

In summary, we have developed a cascade annulation approach to diversely substituted 1,2,3-triazolo[1,5-*a*]quinoxalines convergently from 1-azido-2-isocyanoarenes and terminal alkynes or substituted acetaldehydes. The reaction occurred in one pot under mild conditions with high bond-forming efficiency and good functional group tolerance. Furthermore, densely functionalized quinoxalines were also obtained from the triazole-containing products through rhodium-catalyzed N-H or O-H insertion to the carbenoid intermediates. These reactions demonstrate that 1-azido-2-isocyanoarenes are a valuable class of functionalized isocyanides in the synthesis of N-heterocycles.

Acknowledgement

We are grateful to the National Science Foundation of China (NSFC) (21272233, 21472190 and 21532009) and the Science Foundation of Guangdong Province, China (2014A030313796) for financial support.

Notes and references

State Key Laboratory of Respiratory Disease, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, 190 Kaiyuan Avenue, Guangzhou 510530 (China), Fax: (+86) 20-3201-5299.
E-mail: zhu_qiang@gibh.ac.cn; huang_jinbo@gibh.ac.cn.
Electronic Supplementary Information (ESI) available: See DOI: 10.1039/c000000x/

View Article Online
DOI: 10.1039/C6CC08543A

1 (a) R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* 1994, **37**, 4185; (b) C. Sheng, W. Zhang, *Curr. Med. Chem.* 2011, **18**, 733; (c) A. H. El-Sagheer, T. Brown, *Acc. Chem. Res*. 2012, **45**, 1258; (d) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* 2013, **113**, 4905.

2 (a) H. C. Shen, F.-X. Ding, Q. Deng, L. C. Wilsie, M. L. Krsmanovic, A. K. Taggart, E. Carballo-Jane, N. Ren, T.-Q. Cai, T.-J. Wu, K. K. Wu, K. Cheng, Q. Chen, M. S. Wolff, X. Tong, T. G. Holt, M. G. Waters, M. L. Hammond, J. R. Tata, S. L. Colletti, *J. Med. Chem.* 2009, **52**, 2587; (b) L. Bertelli, G. Biagi, I. Giorgi, C. Manera, O. Livi, V. Scartoni, L. Betti, G. Giannaccini, L. Trincavelli, P. L. Barili, *Eur. J. Med. Chem.* 1998, **33**, 113; (c) G. Biagi, I. Giorgi, O. Livi, V. Scartoni, L. Betti, G. Giannaccini, M. L. Trincavelli, *Eur. J. Med. Chem.* 2002, **37**, 565.

3 B. Saha, S. Sharma, D. Sawant, B. Kundu, *Tetrahedron* 2008, **64**, 8676.

4 (a) Z. Chen, J. Zhu, H. Xie, S. Li, Y. Wu, Y. Gong, *Adv. Synth. Catal.* 2010, **352**, 1296; (b) J. Yan, F. Zhou, D. Qin, T. Cai, K. Ding, Q. Cai, *Org. Lett.* 2012, **14**, 1262.

5 For selected reviews, see: (a) S. Lang, *Chem. Soc. Rev.* 2013, **42**, 4867; (b) G. Qiu, Q. Ding, J. Wu, *Chem. Soc. Rev.* 2013, **42**, 5257; (c) S. Chakrabarty, S. Choudhary, A. Doshi, F.-Q. Liu, R. Mohan, M. P. Ravindra, D. Shah, X. Yang, F. F. Fleming, *Adv. Synth. Catal.* 2014, **356**, 2135; (d) V. P. Boyarskiy, N. A. Bokach, K. V. Luzyanin, V. Y. Kukushkin, *Chem. Rev.* 2015, **115**, 2698; (e) T. Vlaar, E. Ruijter, B. U. W. Maes, R. V. A. Orru, *Angew. Chem., Int. Ed.* **2013**, *52*, 7084.

6 For selected reviews, see: (a) B. Zhang, A. Studer, *Chem. Soc. Rev.* 2015, **44**, 3505; (b) J. Lei, J. Huang, Q. Zhu, *Org. Biomol. Chem.* 2016, **14**, 2593.

7 (a) J. Wang, S. Luo, J. Huang, T. Mao, Q. Zhu, *Chem. Eur. J.* 2014, **20**, 11220; (b) J. Wang, S. Luo, J. Li, Q. Zhu, *Org. Chem. Front.* 2014, **1**, 1285; (c) J. Wang, J. Li, Q. Zhu, *Org. Lett.* 2015, **17**, 5336; (d) J. Wang, S. Tang, Q. Zhu, *Org. Lett.* 2016, **18**, 3074; (e) Z. Xia, J. Huang, Y. He, J. Zhao, J. Lei, Q. Zhu, *Org. Lett.* 2014, **16**, 2546; (f) J. Li, Y. He, S. Luo, J. Lei, J. Wang, Z. Xie, Q. Zhu, *J. Org. Chem.* 2015, **80**, 2223.

8 (a) C. Tang, N. Jiao, *J. Am. Chem. Soc.* 2012, **134**, 18924; (b) Y. Fan, W. Wan, G. Ma, W. Gao, H. Jiang, S. Zhu, J. Hao, *Chem. Commun.* 2014, **50**, 5733.

9 (a) F. E. Hahn, V. Langenhahn, N. Meier, T. Lüger, W. P. Fehlhammer, *Chem. Eur. J.* 2003, **9**, 704; (b) F. E. Hahn, V. Langenhahn, T. Lügger, T. Pape, D. Le Van, *Angew. Chem., Int. Ed.* 2005, **44**, 3759; (c) O. Kaufhold, A. Flores-Figueroa, T. Pape, F. E. Hahn, *Organometallics* 2009, **28**, 896; (d) A. C. Dumke, T. Pape, J. Kösters, K.-O. Feldmann, C. Schulte to Brinke, F. E. Hahn, *Organometallics* **2013**, *32*, 289.

10 For selected examples, see: (a) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem*. 2002, **67**, 3057; (b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem., Int. Ed.* 2002, **41**, 2596; (c) M. Meldal, C. W. Tornøe, *Chem. Rev.* 2008, **108**, 2952.

11 Selected examples: (a) M. Tobisu, K. Koh, T. Furukawa, N. Chatani, *Angew. Chem., Int. Ed.* 2012, **51**, 11363; (b) T. Xiao, L. Li, G. Lin, Q. Wang, P. Zhang, Z.-W. Mao, L. Zhou, *Green Chem.* 2014, **16**, 2418; (c) H. Jiang, Y. Cheng, R. Wang, M. Zheng, Y. Zhang, S. Yu, *Angew. Chem., Int. Ed.* 2013, **52**, 13289; (d) J.-J. Cao, T.-H. Zhu, S.-Y. Wang, Z.-Y. Gu, X. Wang, S.-J. Ji, *Chem. Commun.* 2014, **50**, 6439; (e) L. Wang, W. Sha, Q. Dai, X. Feng, W. Wu, H. Peng, B. Chen, J. Cheng, *Org. Lett.* 2014, **16**, 2088; (f) W. Sha, J.-T. Yu, Y. Jiang, H. Yang, J. Cheng, *Chem. Commun.* 2014, **50**, 9179; (g) D. Leifert, C. G. Daniliuc, A. Studer, *Org. Lett.* 2013, **15**, 6286; (h) J. Liu, C. Fan, H. Yin, C. Qin, G. Zhang, X. Zhang, H. Yi, A. Lei, *Chem. Commun.* 2014, **50**, 2145; (i) Z. Li, F. Fan, J. Yang, Z.-Q. Liu, *Org. Lett.* 2014, **16**, 3396.

12 For selected examples, see: (a) D. B. Ramachary, K. Ramakumar, V. V. Narayana, *Chem. Eur. J.* 2008, **14**, 9143; (b) D. B. Ramachary, A. B. Shashank, S. Karthik, *Angew. Chem., Int. Ed.* 2014, **53**, 10420; (c) A. B. S. Shashank, K. R. Madhavachary, D. B. Ramachary, *Chem. Eur. J.* 2014, **20**, 16877; (d) M. Belkheira, D. E. Abed, J.-M. Pons, C. Bressy, *Chem. Eur. J.* 2011, **17**, 12917; (e) J. Thomas, J. John, N. Parekh, W. Dehaen, *Angew. Chem., Int. Ed.* 2014, **53**, 10155; (f) L. J. T. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, *Chem. Eur. J.* 2011, **17**, 3584; (g) L. Wang, S. Peng, L. J. T. Danence, Y. Gao, Wang, J. *Chem. Eur. J.* 2012, **18**, 6088; (h) W. Li, Q. Jia, Z. Du, J. Wang, *Chem. Commun.* 2013, **49**, 10187; (i) Q. Jia, G. Yang, L. Chen, Z. Du, J. Wei, Y. Zhong, J. Wang, *Eur. J. Org. Chem.* 2015, **16**, 3435; (j) W. Li, J. Wang, *Angew. Chem., Int. Ed.* 2014, **53**, 14186; and selected reviews, see: (k) S. S. V. Ramasastry, *Angew. Chem., Int. Ed.* 2014, **53**, 14310; (l) J. John, J. Thomas, W. Dehaen, *Chem. Commun.* 2015, **51**, 10797.

13 (a) P. Kirsch, Modern Fluoroorganic Chemistry; Wiley-VCH, Weinheim, Germany, 2004; (b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* 2014, **114**, 2432.

14 (a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* 2008, **37**, 320; (b) L. Chu, F.-L. Qing, *Acc. Chem. Res*. 2014, **47**, 1513; (c) X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* 2015, **115**, 731.

15 (a) B. Zhang, C. Mück-Lichtenfeld, C. G. Daniliuc, A. Studer, *Angew. Chem., Int. Ed.* 2013, **52**, 10792; (b) Q. Wang, X. Dong, T. Xiao, L. Zhou, *Org. Lett.* 2013, **15**, 4846; (c) Y. Cheng, H. Jiang, Y. Zhang, S. Yu, *Org. Lett.* 2013, **15**, 5520; (d) X. Sun, S. Yu, *Org. Lett.* 2014, **16**, 2938; (e) B. Zhang, A. Studer, *Org. Lett.* 2014, **16**, 3990; (f) J.-W. Gu, X. Zhang, *Org. Lett.* 2015, **17**, 5384; (g) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu, J. Hu, *Angew. Chem., Int. Ed.* 2016, **55**, 2743; (h) J. Lei, X. Wu, Q. Zhu, *Org. Lett.* 2015, **17**, 2322; (i) Y.-C. Yuan, H.-L. Liu, X.-B. Hu, Y. Wei, M. Shi, *Chem. Eur. J.* 2016, **22**, 13059; (j) D. Leifert, A. Studer, *Angew. Chem., Int. Ed*. 2016, **55**, 11660; (k) M. G. Mackay, A. Studer, *Chem. Eur. J*. 2016, **22**, 13455.

16 For reviews, see: (a) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* 2003, **103**, 2861; (b) B. Chattopadhyay, V. Gevorgyan, *Angew. Chem., Int. Ed*. 2012, **51**, 862; (c) H. M. L. Davies, J. S. Alford, *Chem. Soc. Rev.* 2014, **43**, 5151.

17 (a) Y. Shi, A. V. Gulevich, V. Gevorgyan, *Angew. Chem., Int. Ed.* 2014, **53**, 14191; (b) S. Chuprakov, B. T. Worrell, N. Selander, R. K. Sit, V. V. Fokin, *J. Am. Chem. Soc.* 2014, **136**, 195.