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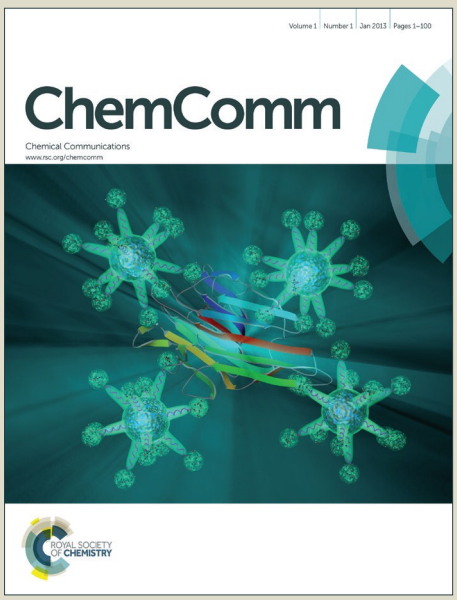

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Cu-Catalyzed Selective Cascade sp^3 C-H Bonds Oxidative Functionalization towards Isoxazoline Derivatives

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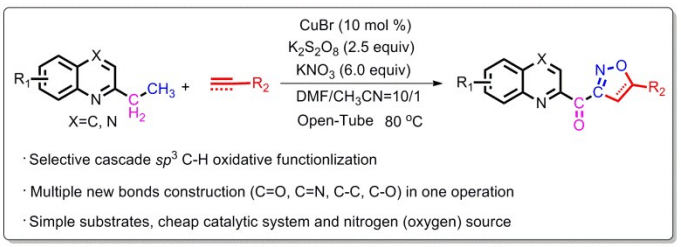
The first Cu-catalyzed cascade sp^3 C–H bonds oxidative functionalization of the 2-ethylazaarenes has been developed. The two different sp^3 C–H bonds in 2-ethylazaarenes are selectively oxidized and four new types of bonds (C=O, C=N, C–C, C–O) are constructed in one operation. Starting from the simple substrates and cheap nitro source, this reaction provides an efficient approach to new kinds of isoxazolines.

Transition-metal-catalyzed sp^3 C–H bond functionalization has unimpeachably emerged as an atom- and step-economical synthetic method for the construction of new C–X bonds (X=C, N, O, etc).[1] In particular, multiple C–H bonds functionalizations which involve cascade reaction procedures to achieve complex structures with non-prefunctionalized substrates in a single operation represents an advanced methodology in organic synthesis,[2] because potentially difficult work-up and isolation steps can be avoided and the generation of chemical waste is minimized. Although some groundbreaking results have been made,[3] the reaction types of transition-metal-catalyzed cascade C–H functionalization are still very limited, especially in the field of sp^3 C–H bonds.

Isoxazolines constitute an important class of heterocycles in organic chemistry and pharmaceutical science, which are frequently found in a wide range of natural products and biologically active compounds as well as chiral ligands[4,5] Moreover, isoxazoline derivatives as excellent precursors have been widely used in the synthetic chemistry.[6] As a consequence, the development of synthetic methods for these compounds has lasted for more than one hundred years.[7] Among them, the most classic and long-studied method is the 1,3-dipolar cycloaddition of dipolarophiles with nitrile oxides which is in situ generated from specific substrates such as hydroximinoyl chlorides, aldoximes and primary nitro compounds.[6c,8] Besides that, oximation and cyclization of α, β-unsaturated compounds (or 1,3-dicarbonyl compounds) with hydroxylamine, and condensation of oxime dianions are also common approaches to isoxazolines derivatives.[9] Recently, several new strategies have been developed[10] such as, palladium-catalyzed cyclization of β, γ-unsaturated oximes,[10e-10i] gold-catalyzed cyclization and rearrangement of alkynyl oxime,[10d] and base-mediated rearrangement of oxetanes[10f] as well as by using acetone (or acetophenone) as solvent to access isoxazolines derivatives under iron salts or ammonium cerium nitrate (CAN),[10a-10c] these achievements represent important advances in this field. However, the direct production of new isoxazoline derivatives from brief steps, simple substrates and cheap reagents is highly attractive alternative. Recently, transition-metal-catalyzed benzylic sp^3 C–H bond oxidative functionlization of alkylazaarenes has been a hot topic.[11] We speculate that, the application of transition-metal-catalyzed sp^3 C–H bonds oxidation in a cascade manner will provide not only a cutting-edge method for C–H bond functionalizations, but also a more straightforward and simple access to isoxazoline derivatives. Under our persistent endeavors, we have developed the first Cu-catalyzed selective cascade sp^3 C–H bonds oxidative functionalization reaction of the alkylazaarenes to produce a series of new kinds of isoxazoline derivatives which may be

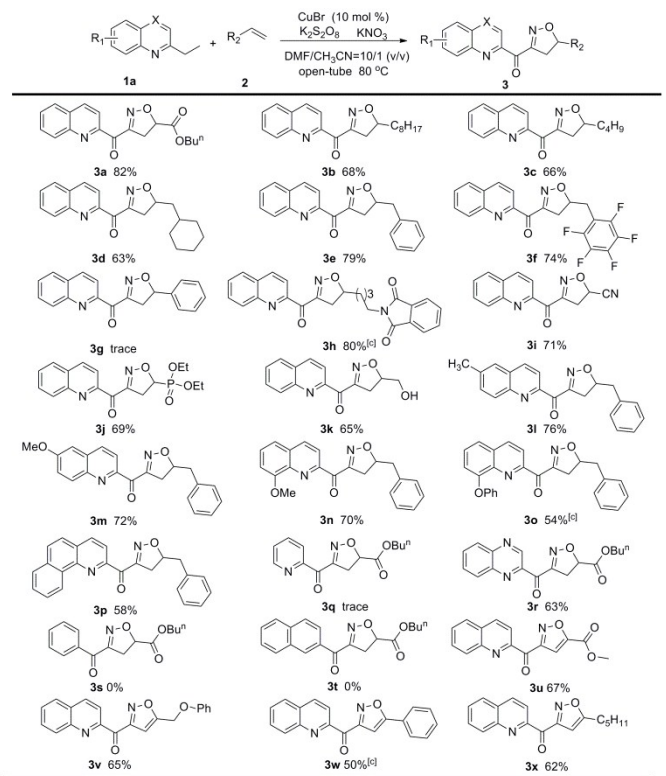


Scheme 1. Cu-catalyzed selective cascade sp^3 C–H bond oxidative functionalization towards new kinds of isoxazoline derivatives

used as ligands or biologically active molecules. Two groups of different sp^3 C–H bonds of 2-ethylquinoline (and quinoxaline) are selectively functionalized resulting in construction of four new types of bonds (C=O, C=N, C–C, C–O) in one operation. This ability to achieve the isoxazoline derivatives in one pot via sp^3 C–H bonds cascade functionalizations has never been demonstrated (Scheme 1).

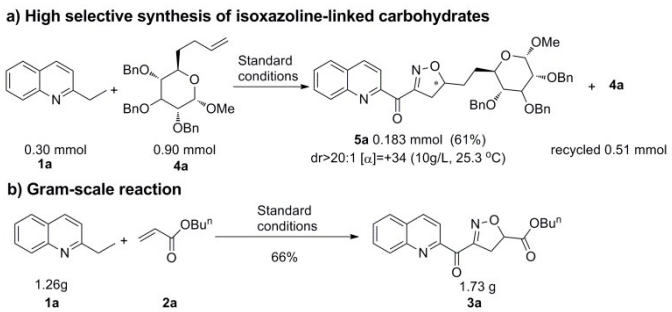
2-Ethylquinoline **1a** was initially used as the substrate to react with butyl acrylate **2a** in order to identify the suitable reaction conditions. After a series of screens on different catalysts, oxidants, solvents, and nitro sources, we settled on the following reaction conditions: 10 mol % of CuBr as catalysts, 2.5 equiv of $K_2S_2O_8$ as oxidant, 6 equiv of KNO_3 as nitro source, and DMF/CH_3CN = 10/1 (v/v) as a solvent at 80 ^oC for 24 hr in an open tube. (Details see SI). Upon optimization of the reaction conditions, different alkenes were first applied to test the generality of this reaction system. By using 2-ethylquinoline **1a** as the standard substrate, a variety of terminal alkenes were successfully converted into desired products in moderate to good yields (Table 1). Aliphatic alkenes were the good reaction partners under reaction conditions. (**3b**, **3c**, **3d**). Allylbenzene and allylpentafluoro benzene provided products in a yield of 79% and 74%, respectively (**3e**, **3f**). However, styrene only produced desired product in a trace amount (**3f**). Synthetically important functional group such as cyan, hydroxyl, isoindoline-1,3-dione and phosphate were well tolerated under catalytic system (**3i**, **3k**, **3h**, **3j**). Disubstituted alkene, such as cyclohexene and 1,2-diphenylethene failed to provide any desired product. Next, different alkylazaarenes were applied into the reaction to expand the substrate scope. 2-ethylquinoline bearing different substituent groups (Me, OMe, OPh) at different positions exhibited moderate to good reactivity (**3l**, **3m**, **3n**, **3o**), and 2-ethylquinoxaline and 2-ethylbenzo[*h*]quinoline also could be successfully oxidized to afford the products in moderate yields (**3p**, **3r**). When 2-ethylpyridine used as substrate, desired product was only obtained in a trace amount (**3q**). When we used alkylarylketones as substrates, ethylbenzene and 2-ethylnaphthalene for example, no desired products were detected (**3s**, **3t**). Other 2-substituted quinolines, such as 2-propylquinoline could not provide any oxidized product, and different oxidized product was obtained when 2-methylquinoline was used as substrate (Details see SI). Besides alkenes, terminal alkynes were also suitable substrates for this reaction, alkyl-substituted acetylene converted into the desired products in moderate yields (**3v**, **3x**). Methyl propiolate furnished the product in a yield of 67% (**3u**). Unlike the styrene, ethynylbenzene reacted smoothly with 2-ethylquinoline **1a** and gave the product in 50% yield (**3w**).

Table 1. Reaction substrates scope.[a,b]



[a]Reaction was carried out with CuBr (10 mol %), $K_2S_2O_8$ (2.5 equiv), KNO_3 (6.0 equiv), 2-ethylazaarenes (0.30 mmol), alkenes or alkynes (0.9 mmol) in DMF/CH_3CN = 3 mL/0.3 mL at 80 ℃ for 24 h in an open tube.; [b]Yield of isolated product. [c]Mixed with trace amount of impurities.

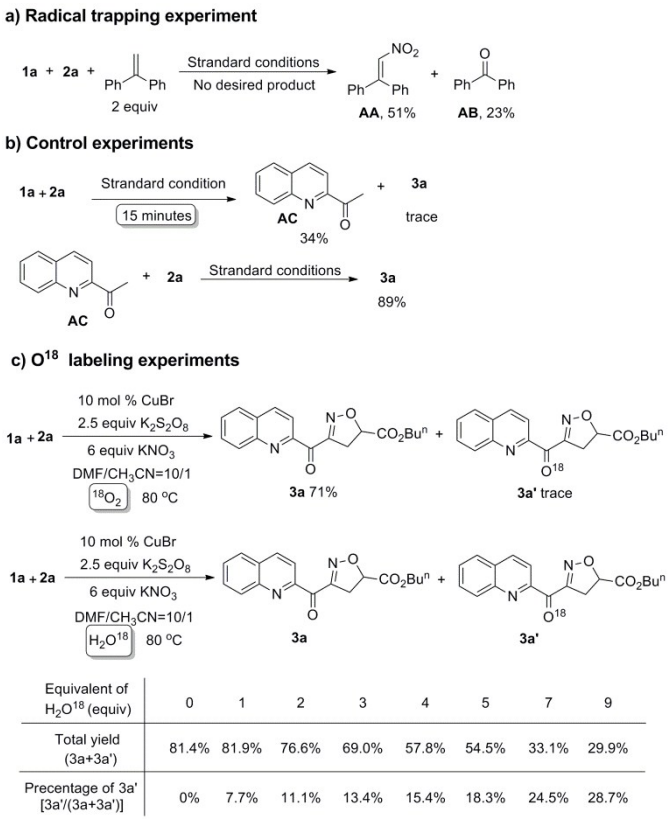
In order to expand the synthetic efficiency of this reaction, a chiral carbohydrate-derivative **4a** was applied in the reaction system to our delight, desired product **5a** which may possess interesting biologically actives[12] was obtained in a yield of 61% with an excellent diastereoselectivity (dr > 20:1), and 0.51 mmol of **4a** was recycled. Furthermore, the success of gram-scale reaction between **1a** with **2a** under standard conditions showed the robustness and potential industrial application of our transformation (Scheme 2).



Scheme 2. Synthetic application

Next, several control experiments were carried out to probe the mechanism of this cascade oxidation reaction (Scheme 3). When the standard reaction was conducted in the presence of 1, 1-diphenylethylene (2 equiv), a radical scavenger, the desired product was not detected at all, but (2-nitroethene-1, 1-diyl) dibenzene **AA** and benzophenone **AB** were produced (Scheme 3a). These results indicated that this reaction might involve the generation of nitro radical, (under the open-tube condition, **AB** could be generated by the reaction of 1,1-diphenylethylene with

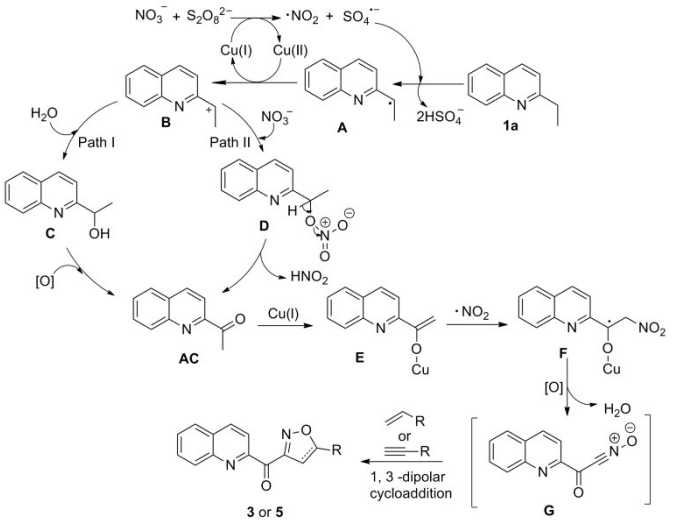
oxygen).[13] When the standard reaction was stopped at 15 minutes, 1-(quinolin-2-yl)ethan one **AC** was obtained in 34% yield with trace amount of **3a**, and when we used **AC** instead of **1a** as the substrate to run this reaction, **3a** was isolated in an excellent yield of 89%, which implied that **AC** might served as the key intermediate for this reaction. Then, O^{18}–labeled experiments were preformed to find out the oxygen source for the construction of the carbonyl group. When $^{18}O_2$ was applied into the reaction under the degassed condition, **3a** was obtained in 71% yield with a trace amount of O^{18}–labeled product **3a'**. This result indicated that molecular oxygen was not the oxygen source of the carbonyl group. Then different equivalents of H_2O^{18} were added to the reaction, with the increase of the H_2O^{18}, the total yield of product (**3a**+**3a'**) was decreased and the percentage of **3a'** [**3a'**/ (**3a**+**3a'**)] was increased accordingly (Scheme 3c). This experiment showed that H_2O might only serve as a small part of the oxygen source for the carbonyl group at most. (We could not rule out the possibility of the oxygen exchanging of carbonyl group under high H_2O^{18} concentration).



Equivalent of H_2O^{18} (equiv)	0	1	2	3	4	5	7	9
Total yield (3a+3a')	81.4%	81.9%	76.6%	69.0%	57.8%	54.5%	33.1%	29.9%
Precentage of 3a' [3a'/(3a+3a')]	0%	7.7%	11.1%	13.4%	15.4%	18.3%	24.5%	28.7%

Scheme 3. Mechanism experiments

Based on the above experiments and previous literatures,[13-15] a possible mechanism was proposed in Scheme 4. Initially, in the presence of Cu(I) catalyst, KNO_3 reacted with $K_2S_2O_8$ to generate the nitro radical, sulfate anion radical and Cu(II)[14a,14b], then intermediate **A** was obtained by a single electron transfer (SET) process from **1a** with the assistance of sulfate anion radical.[14b,14c] Subsequently, **A** was oxidized by Cu (II) to produce the benzylic cation **B,** which might go through two pathways to generate the intermediate **AC**. In path I, H_2O (or OH anion) attacked at intermediate **A** to give **AC**, and in path II, intermediate **A** was attacked by the NO_3 anion, then after the elimination of HNO_2, **AC** was formed.[15] The experiments of H_2O^{18} proved that the path I might only served as a minor way at most to produce **AC**. Next, **AC** reacted with copper catalyst to provide the active metal enol species **E**, and **E** was subsequently attacked by NO_2 radical and the intermediate **F** was achieved.[13b,14b] The oxidation and dehydration of **F** led to the formation of nitrile oxides **G** which would convert into the desired isoxazolines through 1, 3 -dipolar cycloaddition.[8]



Scheme 4. Proposed reaction mechanism

In conclusion, we have developed the first Cu-catalyzed cascade sp^3 C–H bonds oxidative functionalization of the ethylazaarenes, and applied it to produce a series of new kinds of isoxazoline derivatives. The two different sp^3 C–H bonds in ethylazaarenes are selectively oxidized and four new types of bonds (C=O, C=N, C–C, C–O) are constructed in one operation. Preliminary mechanistic studies show that this transformation may go through a radical process, H_2O and NO_3 anion provide the oxygen source for the carbonyl group jointly, and KNO_3 served as the nitrogen source for isoxazoline unit. The combination of simple substrates and cheap catalytic system, as well as the potential application of the final products further increase the practicality of this methodology.

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Notes and references

1 For selected reviews on sp^3 C−H functionalization, see: (a) F. Collet, R. H. Dodd and P. Dauban, *Chem. Commun*. 2009, **45**, 5061; (b) C.-J. Li, *Acc. Chem. Res.* 2009, **42**, 335; (c) P. S. Baran and Y. Ishihara, *Synlett* 2010, 1733; (d) T. W. Lyons and M. S. Sanford, *Chem. Rev.* 2010, **110**, 1147; (e) O. Baudoin, *Chem. Soc. Rev.* 2011, **40**, 4902; (f) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.* 2011, **50**, 3362; (g) H. M. L. Davies, J. D. Bois and J.-Q. Yu, *Chem. Soc. Rev*. 2011, **40**, 1855; (h) M. C. White, *Science* 2012, **335**, 807; (i) G. Rouquet and N. Chatani, *Angew. Chem. In. Ed.* 2013, **52**, 11726.

2 (a) A. J. McCarroll and J. C. Walton, *Angew. Chem. Int. Ed*. 2001, **40**, 2224; (b) M. Catellani, E. Motti and N. D. Ca, *Acc. Chem. Res*. 2008, **41**, 1512; (c) X. Zeng, *Chem. Rev.* 2013, **113**, 6864.

3 (a) Y. Yamamoto, H. Hayashi, T. Saigoku and H. Nishiyama, *J. Am. Chem. Soc*. 2005, **127**, 10804; (b) D. J. Gorin, P. Dubé and F. D. Toste, *J. Am. Chem. Soc.* 2006, **128**, 14480; (c) J.-P. Leclerc, M. Andéand K. Fagnou, *J. Org. Chem*. 2006, **71**, 1711; (d) B.-J. Li, S.-L. Tian, Z. Fang and Z.-J. Shi, *Angew. Chem. Int. Ed*. 2008, **47**, 1115; (e) J.-R. Chen, C.-F. Li, X.-L. An, J.-J. Zhang, X.-Y. Zhu and W.-J. Xiao, *Angew. Chem. Int. Ed.* 2008, **47**, 2489; (f) K. M. Gericke, D. I. Chai, N. Bieler and M. Lautens, *Angew. Chem. Int. Ed*. 2009, **48**, 1447; (g) S. Suárez-Pantiga, D. Palomas, E. Rubio and J. M. González, *Angew. Chem. Int. Ed*. 2009, **48**, 7857; (h) Y. Lu, X. Du, X. Jia and Y. Liu, *Adv. Synth. Catal*. 2009, **351**, 1517; (i) V. S. Thirunavukkarasu, K. Parthasarathy and C.-H. Cheng, *Chem. Eur. J.* 2010, **16**, 1436; (j) J. Mo, D. Eom, E. Lee and P. H. Lee, *Org. Lett.* 2012, **14**, 3684; (k) C. Kourra, F. Klotter, F. Sladojevich and D. J. Dixon, *Org. Lett*. 2012, **14**, 1016; (l) J. Xie, H. L. Jiang, Y. X. Chen and C. J. Zhu, *Chem. Commun*. 2012, **48**, 979; (m) X. Tan, B. X. Liu, Y. Y. Li, B. Li, S. S. Xu, H. B. Song and B. Q. Wang, *J. Am. Chem. Soc*. 2012, **134**, 16163; (n) H. Chen, Z. F. Wang, Y. G. Zhang and Y. Huang, *J. Org. Chem*. 2013, **78**, 3503; (o) P. M. Vaibhav, J.-A. García-López and F. G. Michael, *Angew. Chem. Int. Ed.* 2014, **53**, 1529. (p) Y. Liu, J.-L. Zhang, R.-J. Song, P.-C. Qian and J.-H. Li, *Angew. Chem. Int. Ed.* 2014, **53**, 9017.

4 (a) Y. Xiang, J. Chen, R. F. Schinazi and K. Zhao, *Bioorg. Med. Chem*. 1996, **6**, 1051; (b) C. Antczak, B. Bauvois, C. Monneret and J.-C. Florent, *Bioorg. Med. Chem.* 2001, **9**, 2843; (c) M. P. Giovannoni, C. Vergelli, C. Ghelardini, N. Galeotti, A. Bartolini and V. DalPiaz, *J. Med. Chem*. 2003, **46**, 1055; (e) B. Heasley, *Angew. Chem. Int. Ed*. 2011, **50**, 8474.

5 (a) M. A. Arai, M. Kuraishi, T. Arai and H. Sasai, *J. Am. Chem. Soc.* 2001, **123**, 2907; (b) M. A. Arai, T. Arai, H. Sasai, *Org. Lett*. 1999, **1**, 1795.

6 (a) A. P. Kozikowski, *Acc. Chem. Res.* 1984, **17**, 410; (b) K. C. Nicolaou, W. M. Dai and R. K. Guy, *Angew. Chem. Int. Ed.* 1994, **33**, 15; (c) J. W. Bode, N. Fraefel, D. Muri and E. M. Carreira, *Angew. Chem. Int. Ed.* 2001, **40**, 2082; (d) N. Sewald, *Angew. Chem. Int. Ed.* 2003, **42**, 5794; (e) A. A. Fuller, B. Chen, A. R. Minter and A. K. Mapp, *J. Am. Chem. Soc*. 2005, **127**, 5376; (f) F. Kleinbeck and E. M. Carreira, *Angew. Chem. Int. Ed.* 2009, **48**, 578; (g) H. Jiang, P. Elsner, K. L. Jensen, A. Falcicchio, V. Marcos and K. A. Jørgensen, *Angew. Chem. Int. Ed.* 2009, **48**, 6844.

7 A. Werner, H. Buss, *Chem. Ber*. 1894, **27**, 2193.

8 (a) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* 1963, **2**, 565; (b) K.-I. Itoh, T. Aoyama, H. Satoh, Y. Fujii, H. Sakamaki, T. Takido and M. Kodomari, *Tetrahedron Lett*. 2011, **52**, 6892; (c) R. G. Chary, G. R. Reddy, Y. S. S. Ganesh, K. V. Prasad, A. Raghunadh, T. L. Cecchi, F. D. Sarlo and F. Machetti, *Chem. Eur. J*. 2008, **14**, 7903; (d) S. Grecian and V. V. Fokin, *Angew. Chem. Int. Ed*. 2008, **47**, 8285; (e) A. Yoshimura, K. R. Middleton, A. D. Todora, B. J. Kastern, S. R. Koski, A. V. Maskaev and V. V. Zhdankin, *Org. Lett*. 2013, **15**, 4010; (f) R. G. Chary, G. R. Reddy, Y. S. S. Ganesh, K. V. Prasad, A. Raghunadh, T. Krishna, S. Mukherjee and M. Pal, *Adv. Synth. Catal*. 2014, **356**, 160.

9 (a) G. N. Barber and R. A. Olofson, *J. Org. Chem.* 1978, **43**, 3015; (b) T. Bandiera, P. Grünanger and F. M. Albini, *J. Heterocycl. Chem.* 1992, **29**, 1423; (c) Y. He and N.-H. Lin, *Synthesis* 1994, **9**, 989; (d) T. J. Nitz, D. L. Volkots, D. J. Aldous and R. C. Oglesby, *J. Org. Chem.* 1994, **59**, 5828; (e) P. Cuadrado, A. M. Gonzalez-Nogal and R. Valero, *Tetrahedron* 2002, **58**, 4975; (f) T. Jen, B. A. Mendelsohn and M. A. Ciufolini, *J. Org. Chem*. 2011, **76**, 728.

10 (a) K.-I. Itoh and C. A. Horiuchi, *Tetrahedron* 2004, **60**, 1671; (b) K.-I. Itoh, H. Sakamak, N. Nakazato, A. Horiuchi, E. Horn and C. A. Horiuchi, *Synthesis* 2005, **20**, 3541; (c) S. Bóna, D. Giguére, R. Patnam and R. Roy, *Synlett* 2006, **11**, 1739; (d) M. Ueda, A. Sato, Y. Ikeda, T. Miyoshi, T. Naito and O. Miyata, *Org. Lett.* 2010, **12**, 2594; (e) D. H, Jiang, J. S. Peng and Y. W. Chen, *Org. Lett.* 2008, **10**, 1695; (f) J. A. Burkhard, B. H. Tchitchanov and E. M. Carreira, *Angew. Chem. Int. Ed*. 2011, **50**, 5379; (g) K.-Y. Dong, H.-T. Qin, X.-X. Bao, F. Liu and C. Zhu, *Org. Lett.* 2014, **16**, 5266. (h)Y. Xie, Y. Yang, L. Huang, X. Zhang and Y. Zhang, *Org. Lett.* 2012, **14**, 1238; (i) T. Nanjo, C. Tsukano and Y. Takemoto, *Org. Lett*. 2012, **14**, 4270.

11 (a) Examples on metal-catalyzed benyzlic C-H oxidation, (a) A. J. Catino, J. M. Nichols, H. Choi, S. Gottipamula and M. P. Doyle, *Org. Lett*. 2005, **7**, 5167; (b) Y. Bonvin, E. Callens, I. Larrosa, D. A. Henderson, J. Oldham, A. J. Burton and A. G. M. Barrett, *Org. Lett*. 2005, **7**, 4549; (c) C. S. Yi, K.-H. Kwon and D. W. Lee, *Org. Lett*. 2009, **11**, 1567; (d) B. Qian, P. Xie, Y. Xie and H. Huang, *Org. Lett.* 2011, **13**, 2580; (e) Y. Yan, K. Xu, Y. Fang and Z. Wang, *J. Org. Chem.* 2011, **76**, 6849; (f) J. D. Houwer, K. A. Tehrani and B. U. W. Maes, *Angew. Chem. Int. Ed*. 2012, **51**, 2745; (g) S.-J. Lou, D.-Q. Xu, D.-F. Shen, Y.-F. Wang, Y.-K. Liu and Z.-Y. Xu, *Chem. Commun*. 2012, **48**, 11993; (h) X. Gao, F. Zhang, G. Den and L. Yang, *Org. Lett*. 2014, **16**, 3664; (i) M. Itoh, K. Hirano, T. Satoh and M. Miura, *Org. Lett*. 2014, **16**, 2050.

12 C. P. Zhang, C. Wei, E. Wang, W, Wang,M. Liu, Q. Yin, H. Chen, K. Wang, X. Li and J. Zhang, *Carbohydrate Research* 2012, **351**, 7.

13 (a) S. Hirashima, Y. Kudo, T. Nobuta, N. Tada and A. Itoh, *Tetrahedron Lett*. 2009, **50**, 4328. (b) S, Maity, S. Manna, S. Rana, A. Mallick and D. Maiti, *J. Am. Chem. Soc.* 2013, **135**, 3355.

14 (a) S. Manna, S. Maity, S. Rana, S. Agasti and D. Maiti, *Org. Lett*. 2012, **14**, 1736; (b) Y.-M. Li, X.-H. Wei, X.-A. Li and S.-D. Yang, *Chem. Commun*. 2013, **49**, 11701; (c) D. G. Wu, J. Zhang, J. H. Cui, W. Zhang and Y. K. Liu, *Chem. Commun*. 2014, **50**, 10857.

15 (a) P. Strazzolimi and A. Runcio, *Eur. J. Org. Chem*. **2003**, 526; (b) S. Kamijo, Y. Amaoka and M. Inoue, *Tetrahedron Lett*. **2011**, *52*, 4654.

