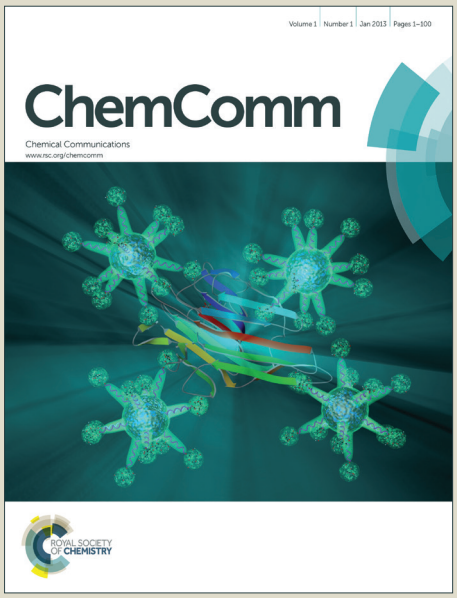
CrossMark
click for updates

View Article Online
View Journal

ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: H. Jiang, W. guo, K. Huang, F. Ji and W. Wu, *Chem. Commun.*, 2015, DOI: 10.1039/C5CC02110C.



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 Information for Authors.

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 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

www.rsc.org/chemcomm

Dynamic Article Links ►
View Article Online
DOI: 10.1039/C5CC02110C

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

A Facile Approach to 3,5-Disubstituted-1,2,4-Oxadiazoles via Copper-Catalyzed-Cascade Annulation of Amidines and Methylarenes

Wei Guo,[a,b] Kunbo Huang,[a] Fanghua Ji,[a] Wanqing Wu,[a] and Huanfeng Jiang*[a]

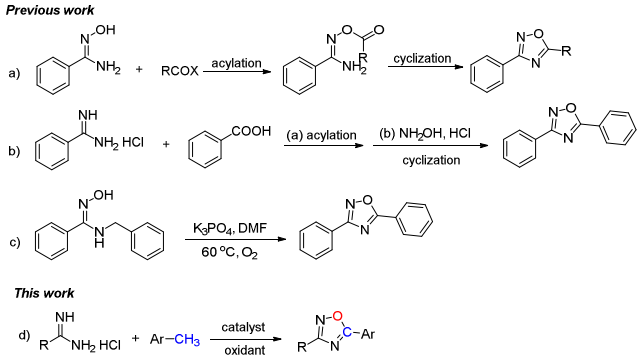
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Various 3,5-disubstituted-1,2,4-oxadiazoles are smoothly formed via copper-catalyzed cascade annulation of amidines and methylarenes. This tandem oxidation-amination-cyclization transformation represents a straightforward protocol to prepare 1,2,4-oxadiazoles from easily available starting materials, with inexpensive copper catalyst and green oxidants. It is of atom- and step-economy, good functional group tolerance, as well as operational simplicity.

N-Heterocycles are undoubtedly one of the most important substructures present in many natural products, synthetic drugs and advanced functional materials.[1] For example, 3,5-disubstituted-1,2,4-oxadiazoles have been used as anti-asthmatics,[2] anti-inflammatory agents,[3] anti-diabetics,[4] anti-microbial agents and anti-cancer agents etc.[5,6] Therefore, a diversity of methods have been explored for the synthesis of such heterocycles.[7] Traditional methods for their synthesis typically involve the first *O*-acylation step of amidoximes or their precursors by activated carboxylic acid derivatives such as esters,[8a] aldehydes,[8b] acid chlorides,[8c] anhydrides[8d] and orthoesters,[8e] followed by intramolecular cyclodehydration (Scheme 1a). Recently, *N*-acylamidine was used as the intermediate to form 1,2,4-oxadiazoles by tandem nucleophilic addition-deamination intramolecular cyclization process, which possessed a highly valuable advantage (Scheme 1b).[9] The oxidative free radical transformation of *N*-benzyl amidoximes to 3,5-disubstituted-1,2,4-oxadiazoles was also successfully developed in an atom- and step-economical manner (Scheme 1c).[10] However, most of the mentioned methods suffered from harsh reaction conditions (microwave radiation, high reaction temperature or some special catalysts) and the use of relatively unavailable starting materials. Hence, the development of a simple and efficient procedure for acquisition of 3,5-disubstituted-1,2,4-oxadiazoles from easily available starting materials under mild conditions continues to attract the interest of organic chemists due to their remarkable application value.

Transition metal-catalyzed reactions have been attracted as a powerful tool for the formation of C-C, C-hetero and N-N bonds.[11] Despite the prevalence of synthetic and medicinal utility of oxa-aza heterocycles with N-O bonds, methods that directly form a bond between nitrogen and oxygen atoms remain rare.[12] Transition metals including Fe[12d] and Cu[12e] have been investigated for the N-O bond formations. Consequently, construction of the N-O bond provides an atom economic approach to 3,5-disubstituted-1,2,4-oxadiazoles. It is well-known that methylarenes are cheap, low toxic, stable, commercially available, and easy to handle, thus making it advantageously to be used as ideal starting materials.[13] Examples for the transformation of primary benzylic C-H bonds in toluene derivatives (including C-H amination and oxidation) are relatively scarce, in which a large excess of toluene is usually necessary.[14] Herein, we report a facile one-step synthesis of 3,5-disubstituted-1,2,4-oxadiazoles from amidines and methylarenes by copper-catalyzed cascade annulation, followed by Csp^3-H oxidation of methylarenes under mild conditions. The reaction possesses an efficient oxidation-amination-cyclization tandem process and involves copper-catalyzed oxidative C-H bond acylation and C-N/C-O/N-O bond formations (Scheme 1d).

Scheme 1. Selected synthetic methods for 3,5-disubstituted-1,2,4-oxadiazoles



With the optimal reaction conditions in hand (see ESI† for details), we then explored the scope and generality of this transformation. As summarized in Table 1, a number of methylarenes were employed as simple synthetic blocks to react with benzamidine hydrochloride (**1a**) to generate the desired 3,5-disubstituted-1,2,4-oxadiazoles. In general, the reactions of benzamidine hydrochloride with the toluene derivatives with electron-donating groups (CH_3, OCH_3) or electron-withdrawing groups (F, Cl, Br and CF_3) on the aromatic ring gave moderate to good yields (**3aa-3an**). It is worth noting that to the toluene derivatives with more than one methyl group, the reaction only took place on one methyl group and others remained (**3ab**, **3ah**, **3al** and **3ao**). This result might be attributed to that one of the

Published on 14 April 2015. Downloaded by Karolinska Institutet University Library on 15/04/2015 01:30:26.

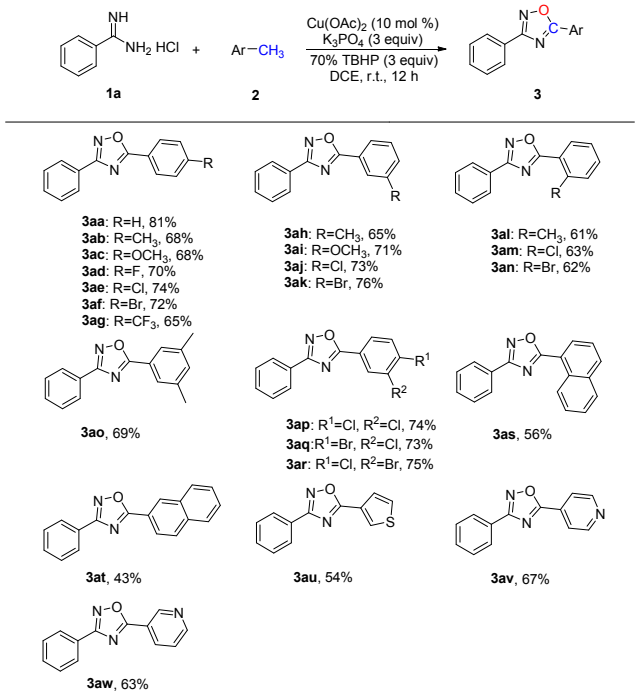
ChemComm Accepted Manuscript

View Article Online
DOI: 10.1039/C5CC02110C

Published on 14 April 2015. Downloaded by Karolinska Institutet University Library on 15/04/2015 01:30:26.

methyl groups on the aromatic ring was involved in the reaction and its electron-withdrawing property was unfavourable to the subsequent oxidation. For example, toluene derivatives bearing a ketone (1-(*p*-tolyl)ethan-1-one) or ester group (ethyl 4-methylbenzoate) were not suitable substrates for the reaction under current conditions. It seemed that this method was also not favourable to the toluene derivatives with strong electron-withdrawing groups. When a nitro or cynano substituent existed, just trace amount of the oxadiazole product could be obtained. Interestingly, the reaction tolerated the presence of one or two halogen atoms at the aromatic ring of the toluene derivatives (**3ap-3ar**). α-Methylnaphthalene and β-methylnaphthalene could also be employed to react with benzamidine hydrochloride and gave the corresponding products **3as-3at** in moderate yields. To our delight, the heterocyclic methylthiophene and methylpyridine were compatible in this transformation (**3au-3aw**). To 2-methylthiophene, only trace desired product was detected, which could be attributed to the electronic effects. However, 2-methylfuran and 3-methylfuran failed to give the desired product, which might be due to the instabilities of the furan structure under the standard reaction conditions. The tolerance of the reaction to these functional groups in substrates provided the possibility for the further useful transformation of the products.

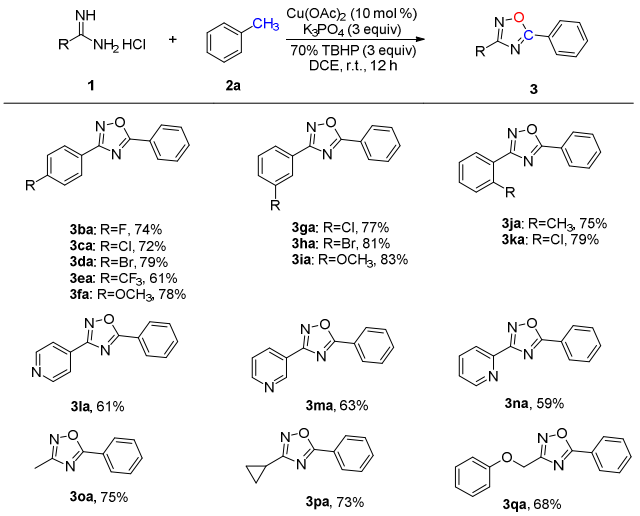
Table 1. Scope of aryl methyl substrates[a]



[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.5 mmol), $Cu(OAc)_2$ (10 mol %), 70% TBHP (3 equiv) and K_3PO_4 (3 equiv) in a 1.0 mL DCE for 12 h. Isolated yield based on **1a**.

Various substituted amidine hydrochloride salts under the optimized reaction conditions were also examined as well, and the results are shown in Table 2. Benzamidine salts bearing either an electron-donating or electron-withdrawing group on the benzene ring were able to undergo this transformation to afford an array of 3,5-disubstituted 1,2,4-oxadiazoles in moderate to good yields (**3ba-3ka**). However, to nitro-substituted benzamidine, only trace amount of the desired product was obtained. Gratifyingly, isonicotinamidine, nicotinamidine and picolinamidine could also be transformed in combination with toluene into the desired products in moderate yields upon isolation (**3la-3na**). Surprisingly, acetamidine, cyclopropanecarboxamidine and 2-phenoxyacetamidine were successfully subjected to this reaction system and provided **3oa-3qa** in good yields.

Table 2. Substrate scope of various amidines[a]



[a] Reaction conditions: **1** (0.25 mmol), **2a** (0.5 mmol), $Cu(OAc)_2$ (10 mol %), 70% TBHP (3 equiv) and K_3PO_4 (3 equiv) in a 1.0 mL DCE for 12 h. Isolated yield based on **1**.

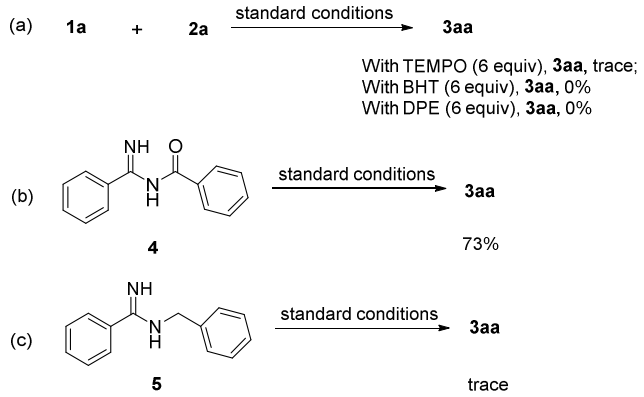
To gain more insight into the mechanism of this unique reaction, several controlled experiments were conducted. Without benzamidine hydrochloride, the toluene was oxidized to benzaldehyde by TBHP with a low yield. The reactions failed to give the desired product **3aa** when benzamidine hydrochloride was reacted with benzylic alcohol or benzoic acid under the standard conditions. To benzaldehyde, 32% yield of the desired product was obtained (see ESI for details). Trace or no **3aa** was detected in the presence of the radical scavengers (2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), or 1,1-diphenylethylene (DPE), which indicated that a radical pathway should be involved (Scheme 2a). We next investigated whether *N*-(imino(phenyl)methyl)benzamide **4** or *N*-benzylbenzamidinewas **5** was the reaction intermediate, and the results indicated that **4** might be an intermediate (Scheme 2b, c).

ChemComm Accepted Manuscript

This journal is © The Royal Society of Chemistry [year]

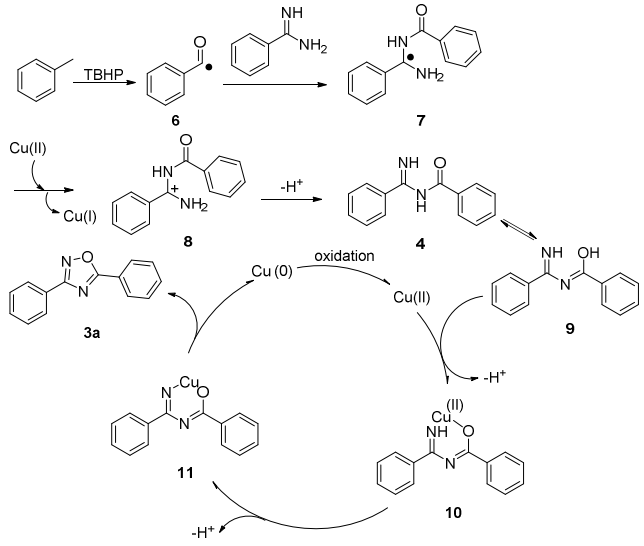
View Article Online
DOI: 10.1039/C5CC02110C

Published on 14 April 2015. Downloaded by Karolinska Institutet University Library on 15/04/2015 01:30:26.



Scheme 2. Investigation into the reaction mechanism

According to the above experimental results and previous reports,[15] a plausible mechanism is illustrated in Scheme 3. Firstly, benzamidine **1a** was reacted with the acyl radical **6** which was formed from the oxidation of toluene to generate the intermediate **7** by a radical addition process. Subsequently, a single-electron-oxidation process occurred to give intermediate **8**. Then, intermediate **4** was formed by losing a proton. Further, the intermediate **4** was transformed to intermediate **9** by an enol isomerization. Intermediate **9** was coordinated with copper catalyst to give intermediate **10**. Finally, with the release of H^+, intermediate **10** was converted to intermediate **11**, which underwent reductive elimination and afforded the desired product **3aa**.



Scheme 3. Possible reaction mechanism

In conclusion, we have developed a novel straightforward synthesis of 3,5-disubstituted-1,2,4-oxadiazoles via copper-catalyzed amidines with methylarenes. This process involved acyl radical formation and N-O/C-N/N-O bondsformation. The reaction occupied good functional group methylarenes. In addition, easily available amidines [16] and low toxic, stable and commercially available methylarenes were used as important synthetic blocks. Moreover, inexpensive, safe, and environmentally benign TBHP was also employed to be an effective oxidant in these transformations. This mild synthetic method provides a highly attractive practical strategy in organic synthesis, medicinal and material chemistry. Ongoing research involves detail mechanism and further broadening the synthetic scope of the methodology is currently underway in our laboratory, and the results will be reported in due course.

We are grateful for the financial support from the National natural Science Foundation of China (2117276 and 21420102003), the National Basic Research Program of China (973 Program) (2011CB808600), the China Postdoctoral Science Foundation Funded Project (2014M562165), and Guangdong Natural Science Foundation (10351064101000000).

Notes and references

[a] *School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China. Fax: +86 20-87112906; Tel: +86 20-87112906; E-mail: jianghf@scut.edu.cn*
b Key laboratory of organo-pharmaceutical chemistry of Jiangxi province, Gannan Normal University, Ganzhou, 341000, China

† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^1H and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

1 (*a*) D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435; (*b*) A. Seed, *Chem. Soc. Rev.*, 2007, **36**, 2046; (c) J. Boström, A. Hogner, A. Llinàs, E. Wellner and A. T. Plowright, *J. Med. Chem.*, 2012, **55**, 1817. (*d*) C.-G. Zhen, Z.-K. Chen, Q.-E. Liu, Y.-F. Dai, R. Y. C. Shin, S.-Y. Chang and J. Kieffer, *Adv. Mater.*, 2009, **21**, 2425; (*e*) A. Pace and P. Pierro, *Org. Biomol. Chem.*, 2009, **7**, 4337.
2 (*a*) J. T. Palmer, R. M. Rydzewski, R. V. Mendonca, D. Sperandio, J. R. Spencer, B. L. Hirschbein, J. Lohman, J. Beltman, M. Nguyen and L. Liu, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3434; (*b*) J. Garfunkle, C. Ezzili, T. J. Rayl, D. G. Hochstatter, I. Hwang and D. L. Boger, *J. Med. Chem.*, 2008, **51**, 4392.
3 (*a*) M. Farooqui, R. Bora and C.R. Patil, *Eur. J. Med. Chem.*, 2009, **44**, 794; (*b*) N. M. M. Bezerra, S. P. De Oliveira, R. M. Srivastava and J. R. Da Silva, *Il Farmaco*, 2005, **60**, 955; (*c*) M. A. Weidner-Wells, T. C. Henninger, S. A. Fraga-Spano, C. M. Boggs, M. Matheis, D. M. Ritchie, D. C. Argentieri, M. P. Wachter and D. J. Hlasta, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4307.
4 R. M. Jones, J. N. Leonard, D. J. Buzard and J. Lehmann, *Expert Opin. Ther. Pat.*, 2009, **19**, 1339.
5 M. H. Gezginci, A. R. Martin and S. G. Franzblau, *J. Med. Chem.*, 2001, **44**, 1560.
6 (*a*) D. Kumar, G. Patel, E. O. Johnson and K. Shah, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2739; (*b*) H.-Z. Zhang, S. Kasibhatla, J. Kuemmerle, W. Kemnitzer, K. Ollis-Mason, L. Qiu, C. Crogan-Grundy, B. Tseng, J. Drewe and S. X. Cai, *J. Med. Chem.*, 2005, **48**, 5215; (*c*) G. L. Khatik, J. Kaur, V. Kumar, K. Tikoo and V. A. Nair, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 1912.
7 For selected examples, see: (*a*) K. Itoh, H. Sakamaki and C. A. Horiuchi, *Synthesis*, 2005, **12**, 1935; (*b*) Y. Wang, R. L. Miller, D. R. Sauer and S. W. Djuric, *Org. Lett.*, 2005, **7**, 925; (*c*) D. Grant, R. Dahl and N. D. P. Cosford, *J. Org. Chem.*, 2008, **73**, 7219; (*d*) J. K. Augustine, V. Akabote, S. G. Hegde and P. Alagarsamy, *J. Org. Chem.*, 2009, **74**, 5640.
8 For selected examples, see: (*a*) K. K. D. Amarasinghe, M. B. Maier, A. Srivastava and J. L. Gray, *Tetrahedron Lett.*, 2006, **47**, 3629; (*b*) M. Adib, A. H. Jahromi, N. Tavoosi, M. Mahdavi and H. R. Bijanzadeh, *Tetrahedron Lett.*, 2006, **47**, 2965; (*c*) B. Kaboudin and F. Saadati, *Tetrahedron Lett.*, 2007, **48**, 2829; (*d*) B. Kaboudin and L. Malekzadeh, *Tetrahedron Lett.*, 2011, **52**, 6424; (*e*) D. Suresh, K. Kanagaraj and K. Pitchumani, *Tetrahedron Lett.*, 2014, **55**, 3678.
9 P. K. Gupta, M. K. Hussain, M. Asad, R. Kant, R. Mahar, S. K. Shukla and K. Hajela, *New J. Chem.*, 2014, **38**, 3062.

ChemComm Accepted Manuscript

View Article Online
DOI: 10.1039/C5CC02110C

Published on 14 April 2015. Downloaded by Karolinska Institutet University Library on 15/04/2015 01:30:26.

10 F.-L. Zhang, Y.-F. Wang and S. Chiba, *Org. Biomol. Chem.*, 2013, **11**, 6003.

11 (*a*) X. Chen, K. M. Engle, D. Wang and J. Yu, *Angew. Chem. Int. Ed*., 2009, **48**, 5094; (*b*) C. Li, *Acc. Chem. Res*., 2009, **42**, 355; (*c*) A. A. O. Sarhanw and C. Bolm, *Chem. Soc. Rev*., 2009, **38**, 2730; (*d*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*e*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*f*) S. Zhang, F. Zhang and Y. Tu, *Chem. Soc. Rev*., 2011, **40**, 1937; (*g*) X. Li, L. He, H. Chen, W. Wu and H. Jiang, *J. Org. Chem.*, 2013, **78**, 3636; (*h*) A. S. Girard, T. Knauber and C. Li, *Angew. Chem. Int. Ed.*, 2014, **53**, 74; (*i*) X. Li, L. Huang, H. Chen, W. Wu, H. Huang and H. Jiang, *Chem. Sci.*, 2012, **3**, 3463.

12 For selected recent examples, see: (*a*) P. Supsana, P. G. Tsoungas, A. Aubry, S. Skoulika and G. Varvounis, *Tetrahedron*, 2001, **57**, 3445; (*b*) O. Prakash, R. K. Saini, S. P. Singh and R. S. Varma, *Tetrahedron Lett.*, 1997, **38**, 3147; (*c*) G. Rai, C. J. Thomas, W. Leister and D. J. Maloney, *Tetrahedron Lett.*, 2009, **50**, 1710; (*d*) B. J. Stokes, C. V. Vogel, L. K. Urnezis, M. Pan and T. G. Driver, *Org. Lett.*, 2010, **12**, 2884; (*e*) O. Das, S. Paria and T. K. Paine, *Tetrahedron Lett.*, 2008, **49**, 5924; (*f*) M. J. Raihan, V. Kavala, P. M. Habib, Q.-Z. Guan, C.-W. Kuo and C.-F. Yao, *J. Org. Chem.*, 2011, **76**, 424.

13 For selected examples, see: (*a*) T. Wang and N. Jiao, *Acc. Chem. Res.*, 2014, **47**, 1137; (*b*) Q. Li, Y. Huang, T. Chen, Y. Zhou, Q. Xu and S.-F. Yin, *Org. Lett.*, 2014, **16**, 3672; (*c*) Q. Xue, J. Xie, H. Li, Y. Cheng and C. Zhu, *Chem. Commun.*, 2013, **49**, 3700; (*d*) R. Samanta, J. Lategahn and A. P. Antonchick, *Chem. Commun.*, 2012, **48**, 3194; (*e*) M. R. Fructos, S. Trofimenko, M. M. Díaz-Requejo and P. J. Pérez, *J. Am. Chem. Soc.*, 2006, **128**, 11784; (*f*) R. T. Gephart, D. L. Huang, M. J. B. Aguila, G. Schmidt, A. Shahu and T. H. Warren, *Angew. Chem., Int. Ed.*, 2012, **51**, 6488; (*g*) S. Wiese, Y. M. Badiei, R. T. Gephart, S. Mossin, M. S. Varonka, M. M. Melzer, K. Meyer, T. R. Cundari and T. H. Warren, *Angew. Chem., Int. Ed.*, 2010, **49**, 8850; (*h*) Z. Ni, Q. Zhang, T. Xiong, Y. Zheng, Y. Li, H. Zhang, J. Zhang and Q. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 1244; (*i*) Y. M. Badiei, A. Dinescu, X. Dai, R. M. Palomino, F. W. Heinemann, T. R. Cundari and T. H. Warren, *Angew. Chem., Int. Ed.*, 2008, **47**, 9961; (*j*) W. Xiao, J. Wei, C.-Y. Zhou and C.-M. Che, *Chem. Commun.*, 2013, **49**, 4619; (*k*) Y. Amaoka, S. Kamijo, T. Hoshikawa and M. Inoue, *J. Org. Chem.*, 2012, **77**, 9959.

14 For selected examples, see: (*a*) D. Zhao, T. Wang and J.-X. Li, *Chem. Commun.*, 2014, **50**, 6471; (*b*) H. J. Kim, J. Kim, S. H. Cho and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 16382; (*c*) Q. Xia, W. Chen and H. Qiu, *J. Org. Chem.*, 2011, **76**, 7577; (*d*) D. A. Powell and H. Fan, *J. Org. Chem.*, 2010, **75**, 2726; (*e*) L. J. Gu, C. Jin, J. M. Guo, L. Z. Zhang and W. Wang, *Chem. Commun.*, 2013, **49**, 10968; (*f*) T. B. Nguyen, L. Ermolenko and A. Al-Mourabit, *Org. Lett.*, 2013, **15**, 4218.

15 (*a*) X. Tang, L. Huang, J. Yang, Y. Xu, W. Wu and H. Jiang, *Chem. Commun.*, 2014, **50**, 14793; (*b*) Y.-F. Wang, H. Chen, X. Zhu and S. Chiba, *J. Am. Chem. Soc.*, 2012, **134**, 11980; (*c*) Z. Yin and P. Sun, *J. Org. Chem.*, 2012, **77**, 11339; (*d*) Y. Wu, P. Y. Choy, F. Mao and F. Y. Kwong, *Chem. Commun.*, 2013, **49**, 689.

16 Y. Bai, W. Chen, Y. Chen, H. Huang, F. Xiao and G.-J. Deng. *RSC Adv.*, 2015, **5**, 8002.

ChemComm Accepted Manuscript

This journal is © The Royal Society of Chemistry [year]