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DOI: 10.1039/C6CC08788D

Journal Name

COMMUNICATION

Synthesis of Oxindole from Acetanilide via Ir(III)-Catalyzed C–H Carbenoid Functionalization

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

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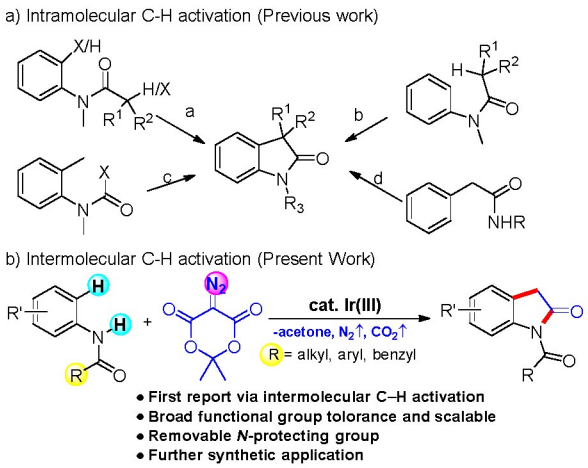
Herein we disclose the first report on synthesis of oxindole derivatives from acetanilide via Ir(III)-catalyzed intermolecular C–H functionalization with diazotized Meldrum's acid. A broad range of substituted anilides were found to react smoothly under the Ir(III)-catalyst system to afford corresponding *N*-protected oxindoles. The *N*-protecting groups, such as Ac, Bz or Piv can be easily removed to furnish the oxindole. Various synthetic applications of the synthesized oxindole were also demonstrated.

Oxindoles are important structural units widely present in many natural products[1] and biologically active compounds. In fact, molecules derived from oxindole exhibit excellent pharmacological properties such as anticancer,[2] anti-angiogenic,[3] and calcium channel blockers.[4] As a consequence, numerous efficient methods have been developed for their synthesis,[5] which include derivatization of isatin and indoles,[6] radical cyclizations,[7] Friedel–Crafts-type cyclizations,[8] and metal mediated reactions.[9-10] Recently, intramolecular C–H activation has become a powerful and atom economic strategy for oxindole synthesis (Scheme 1).[11–15] In particular, Hartwig and Buchwald independently reported the Pd-catalyzed intramolecular C–H annulations of *ortho*-halo acetanilides and α-halo acetanilides respectively (path a, Scheme 1).[12] After this various strategy for oxindole synthesis via C-H activation has been documented by several groups (path b-d).[13–15] However, all these methods involve intramolecular C–H functionalization and required the fully functionalized starting precursor. Additionally, a majority of these methods lead to either 3-substituted or 3,3-disubstituted oxindoles, whereas syntheses of the parent oxindole have very rarely been reported. Therefore, development of an efficient and straightforward method for the synthesis of oxindole from simple and readily available starting materials is of foremost research interest.



Scheme 1 Synthesis of oxindole via C–H activation

Very recently, transition metal catalyzed intermolecular C–H carbenoid functionalization has emerged as a powerful and straightforward approach to the synthesis of various *N*-heterocyclic compounds.[16] In this context, Yu and co-workers reported the first Rh(III)-catalyzed C–H carbenoid functionalization.[17a] Following this report, several group have made significant progress for the synthesis of various heterocycles using different metal catalysts such as Rh,[17] Ir,[18] Ru,[19] Co[20]. Despite these advancements, to the best of our knowledge, there is no literature precedent on intermolecular C–H functionalization leading to oxyindoles. Continuing our study on Ir(III)-catalyzed C–H carbenoid functionalization,[21] we envisioned the feasibility of Ir(III)-catalyzed C–H alkylation of acetanilide with diazotized Meldrum's acid followed by intramolecular annulations leading to oxindole. Herein we disclose the first report of oxindole synthesis from acetanilides via Ir(III)-catalyzed C–H annulations with diazotized Meldrum's acid (Scheme 1b). A brief synthetic application of oxindole has also been demonstrated to illustrate the generality of the present reaction.

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Electronic Supplementary Information (ESI) available: Full experimental details, characterization, NMR spectra and crystallographic data of the synthesized products. See DOI: 10.1039/x0xx00000x

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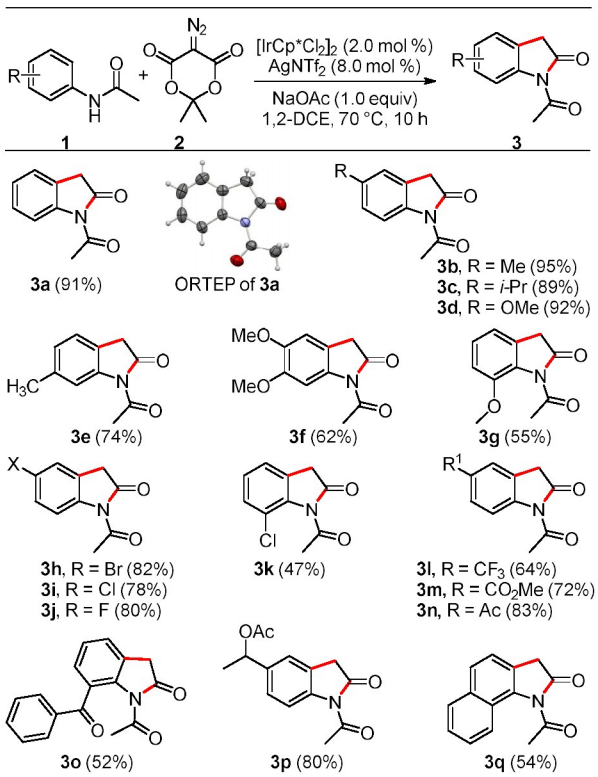
DOI: 10.1039/C6CC08788D

To authenticate our postulation, readily available acetanilide **1a** was chosen as a model substrate to react with diazotized Meldrum's acid **2** under Ir(III)-catalytic system. After screening various reaction parameters, we were pleased to observed 91% isolated yield of desired oxindole product **3a**, using 2.0 mol % of the $[IrCp^*Cl_2]_2$, 8.0 mol % of $AgNTf_2$ and 1.0 equiv of NaOAc in 1,2-dichloroethane (DCE) at 70 °C [See the electronic supplementary information (ESI) for details of the optimization study]. The structure of **3a** was unambiguously confirmed by single crystal X-ray analysis (Table 1). It is noteworthy that previously applied catalytic systems such as $[RhCp^*Cl_2]_2$, $[Ru(p\text{-cymene})Cl_2]_2$, and $[CoCp^*(CO)I_2]$ were found to be totally ineffective under identical reaction condition.

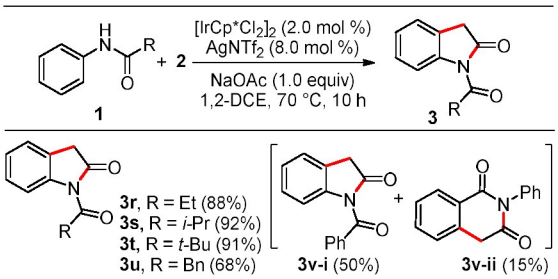
Table 1 Scope of various substituted acetanilides[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (1.2 equiv), in 1,2-DCE (1 mL); yields of isolated products are given.

With the optimized reaction conditions available, the substrate scope for the oxindole synthesis was investigated (Table 1). First, various *N*-acetyl anilines having different aryl substituents were reacted with **2** under standard reaction conditions. Substrates bearing both electron-donating (**3b–3g**) as well as electron-withdrawing (**3h–3o**) substituents on the aryl ring were smoothly converted to the corresponding oxindole derivatives in good to excellent yields irrespective of the substituent position. For *meta*-substituted acetanilides such as 3-methylacetanilide (**3e**) and 3,4-dimethoxyacetanilide (**3f**), the reaction took place exclusively at the sterically less hindered site. However, reactions of sterically hindered *ortho*-substituted acetanilides such as 2-methoxyacetanilide (**3g**) and 2-chloroacetanilide (**3k**) furnished the desired products in modest yields. The tolerance of halide groups under these conditions demonstrated the additional synthetic utility of the present method (**3h–3k**). Notably, the reaction efficiency is not affected by the presence of other carbonyl chelating groups such as ester and acetyl (**3m–3o**) and gave exclusively the desired oxindole derivatives in modest to high yields. Furthermore, substrate bearing an –OAc group was well tolerated and readily furnished the corresponding oxindole derivative **3p** in good yields. Bicyclic substrate such as *N*-(naphthalen-1-yl)acetamide also furnished the desired product **3q** in 54% yield.

Table 2 Scope of various *N*-substitutions[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (1.2 equiv), in 1,2-DCE (1 mL); yields of isolated products are given.

After successful exploration of various substituted acetanilides, the scope of different *N*-substitutions was investigated (Table 2). Anilines bearing *N*-protecting groups such as propionyl, isobutyryl, pivaloyl and 2-phenylacetyl were found to be facile for the present annulations with high yields (**3r–3u**). However, reaction of *N*-benzoyl aniline furnished the required indolin-2-one derivative (**3v-i**) as the major product, along with a minor product, the isoquinolinedione derivative (**3v-ii**). Surprisingly, the starting compounds remained intact when other commonly *N*- protected anilines such as *N*-Ts, *N*-Boc and *N*-Cbz were employed. However, the reason for this selective reactivity is unknown and further studies are required to understand properly.

To shed light on the broad synthetic utility of the present reaction, further functionalization of oxindole was carried out (Scheme 2).[22] The reaction can be easily scaled up using lower catalyst loading with a slight decrease in yield (see the ESI). As anticipated, the *N*-acetyl group was readily removed using K_2CO_3 in methanol to afford oxindole **4** (Scheme 2a). Furthermore compound **3a** was selectively amidated at the C-7 position under Ir(III)-catalytic conditions to furnish the amidated product **5** in 80% yield (Scheme 2a). Treatment of oxindole **4**, with pyrrole-2-carbaldehyde in the presence of catalytic piperidine gave compound **6** (Scheme 2b), which is an important structural unit present in many pharmacologically active compounds.[2, 23] Similarly, isoindigo **7** was synthesized

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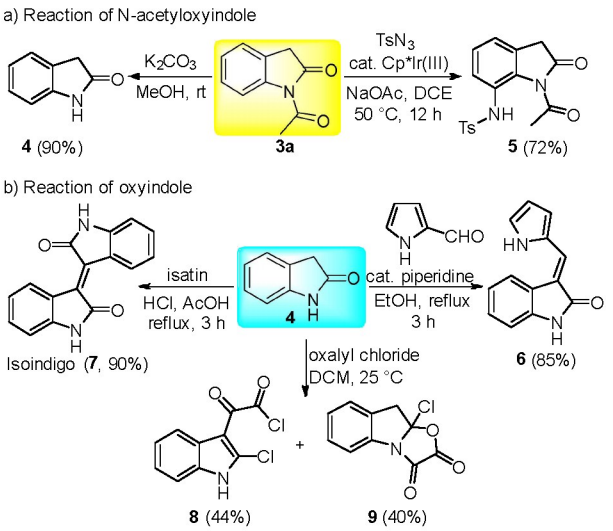
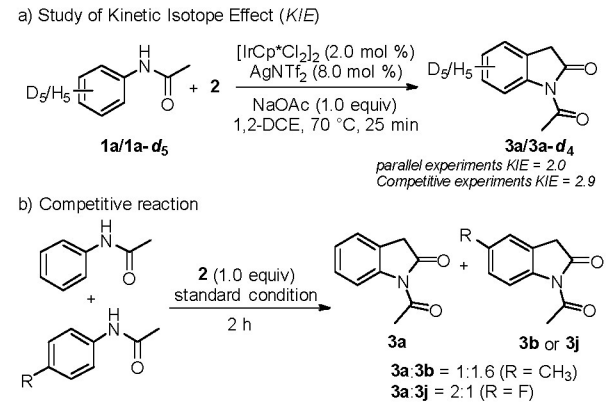
when oxindole **4** was reacted with isatin under acidic conditions.[24] Further, treatment of oxindole **4** with oxalyl chloride gave a mixture of compound **8** and **9**.[25]

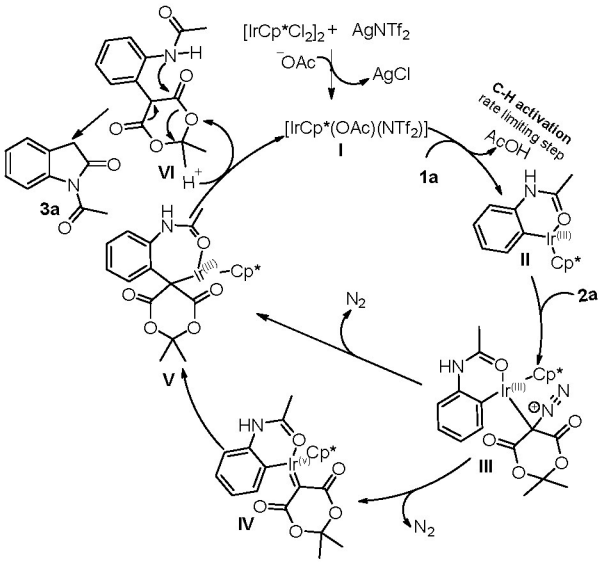


Scheme 2 Synthetic application of oxindole



Scheme 3 Preliminary mechanistic studies

To gain some mechanistic insight into the present Ir(III)-catalyzed intermolecular C–H carbenoid functionalization, a series of preliminary experiments were carried out. First, replacing the catalytic system with $[IrCp^*(OAc)_2]\cdot H_2O$ (4 mol %) in the absence of any additive, the reaction was found to be sluggish, whereas addition of $AgNTf_2$ (4 mol %) furnished the desired product in good yield (See the ESI). These results indicate the putative formation of the active cationic iridium species bound to acetate with a vacant site filled by -NTf_2, and is believed to be the active catalytic species responsible for the C–H activation. In fact, formation of such reactive catalytic species is already well documented by Chang et al.[26] The reversibility of the C–H activation step was investigated by performing the reaction with D_2O in the absence of the diazo compound, which shows <10% of H/D scrambling, indicating the C–H activation is largely irreversible (See the ESI). A significant primary kinetic isotope effect was observed both in parallel experiments (*KIE* = 2.0) and in an intermolecular competition reaction (*KIE* = 2.9) signifying that the C–H bond cleavage is likely the rate-determining step (Scheme 3a). Furthermore, the intermolecular competitive reactions between the acetanilide (**1a**) with electron rich 4-methylacetanilide (**1b**) or electron deficient 4-fluoroacetanilde (**1j**) revealed the beneficial effect of electron-donating groups on the intermolecular oxindole synthesis and also the possible involvement of aromatic electrophilic mechanism (Scheme 3b).



Scheme 4 Plausible catalytic cycle

On the basis of the above experimental results and precedented literature reports,[17-19, 26-27] a plausible catalytic cycle is depicted in Scheme 4. First, treatment of the $[IrCp^*Cl_2]_2$ with four excess of $AgNTf_2$ and NaOAc generates the active cationic Ir(III) species **I**.[26] Next, species **I** induces the key C–H bond cleavage of substrates to generate a cyclometalated Ir(III) complex **II**, possibly via a base-assisted concerted metalation-deprotonation (CMD) process.[26] The diazo carbon would then coordinate to a vacant site of **II** to form **III**, which subsequently transfers its carbene group into the Ir–C bond with simultaneous release of N_2 to afford complex **V**. Alternately, intermediate **V** can be formed via concerted pathway from **III**. Protodemetalation of complex **V** will liberate the alkylated product **VI**, with the regeneration of the active iridium species (**I**). Finally, intermediate **VI** undergoes intramolecular annulations to give the desired product **3a** with the release of acetone and carbon dioxide.[27]

In summary, we have successfully developed the first Ir(III)-catalyzed intermolecular oxindole synthesis from acetanilide. The reaction was found to proceed in amicable conditions with high functional group tolerance and is easily scalable. Oxindole with various *N*-substitutions such as acetyl, propenoyl, pivaloyl, and benzoyl can be synthesized easily using the present protocol. Further chemistry of the oxindole was explored to show its synthetic significance. We firmly believe that the synthetic strategy depicted herein will have its

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usefulness given the fact that a multitude of highly bio-active compounds are synthesized starting from oxindole, as attested by numerous reports.

We thank DST-INSPIRE Faculty program for fellowship and funding (GAP-0738). We also thank Director, CSIR-NEIST, Jorhat, for his support and providing all the facility.

Notes and references

1 (a) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (b) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209.

2 (a) A. Andreani, A. Cavalli, M. Granaiola, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, M. Recanatini, M. Garnier and L. Meijer, *Anticancer Drug Des.*, 2000, **15**, 447; (b) M. Sassatelli, É. Debiton, B. Aboab, M. Prudhomme and P. Moreau, *Eur. J. Med. Chem.*, 2006, **41**, 709.

3 J.L. Whatmore, E. Swann, P. Barraja, J. J. Newsome, M. Bunderson, H. D. Beall, J. E. Tooke and C. J. Moody, *Angiogenesis*, 2002, **5**, 45.

4 A. M. Swensen, J. Herrington, R. M. Bugianesi, G. Dai, R. J. Haedo, K. S. Ratliff, M. M. Smith, V. A. Warren, S. P. Arneric, C. Eduljee, D. Parker, T. P. Snutch, S. B. Hoyt, C. London, J. L. Duffy, G. J. Kaczorowski and O. B. McManus, *Mol. Pharmacol.*, 2012, **81**, 488.

5 For reviews on oxyindole synthesis, see: (a) R. Dalpozzo, G. Bartoli and G. Bencivenni, *Chem. Soc. Rev.*, 2012, **41**, 7247; (b) N. R. Ball-Jones, J. J. Badillo and A. K. Franz, *Org. Biomol. Chem.*, 2012, **10**, 5165.

6 For selected example see: (a) S. A. Shaw, P. Aleman and E. Vedejs, *J. Am. Chem. Soc.*, 2003, ***125***, 13368; (b) R. Shintani, M. Inoue and T. Hayashi, *Angew. Chem., Int. Ed.*, 2006, ***45***, 3353; (c) D. Tomita, K. Yamatsugu, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, ***131***, 6946.

7 Selected recent example on radical cyclization, see: (a) K. Matcha, R. Narayan and A. P. Antonchick, *Angew. Chem., Int. Ed.*, 2013, **52**, 7985; (b) W. Wei, M. Zhou, J. Fan, W. Liu, R. Song, Y. Liu, M. Hu, P.Xie and Li, J. *Angew. Chem., Int., Ed.*, 2013, **52**, 3638; (c) W. Ji, H. Tan, M. Wang, P. Li and L. Wang, *Chem. Commun.*, 2016, **52**, 1462.

8 For recent examples of Friedel–Crafts-type cyclization, see: (a) I. Gorokhovik, L. Neuville and J. Zhu, *Org. Lett.*, 2011, **13**, 5536; (b) D. C. Fabry, M. Stodulski, S. Hoerner and T. Gulder, *Chem. Eur. J.*, 2012, **18**, 10834; (c) M. Zhang, W. Sheng, Q. Jiang, M. Tian, Y. Yin and C. Guo, *J. Org. Chem.*, 2014, **79**, 10829.

9 (a) A. Ashimori, B. Bachand, L. E. Overman and D. J. Poon, *J. Am. Chem. Soc.*, 1998, **120**, 6477; (b) X. Mu, T. Wu, H. Wang, Y. Guo and G. Liu, *J. Am. Chem. Soc.*, 2012, **134**, 878; (c) B. Zhou, W. Hou, Y. Yang, H. Feng and Y. Li, *Org. Lett.*, 2014, **16**, 1322; (d) C. Li and S. Yang, *Org. Lett.*, 2015, **17**, 2142.

10 For selected metal free approach, see: (a) C. Ma, D. Xing and W. Hu, *Org. Lett.*,2016, **18**, 3134; (b) W. Ji, Y. A. Liu and X. Liao, *Angew. Chem., Int. Ed.*, 2016, **55**, 13286 (c) D. Xu, W.-W. Sun, Y. Xie, J.-K. Liu, B. Liu, Y. Zhou and B. Wu, *J. Org. Chem.*, 2016, **81**, 11081.

11 For selected reviews on C–H bond activation, see: (a) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (b) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (c) L. McMurray, F. O'Hara and M. Gaunt, J. *Chem. Soc. Rev.*, 2011, **40**, 1885; (d) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (e) C. S. Yeung and V. M. Dong, *Chem. Rev.* ,2011, **111**, 1215; (f) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068; (g) N. Kuhl, N. Schroder and F. Glorius, *Adv. Synth. Catal.*, 2014, **356**, 1443; (h) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107; (i) P. Gandeepan and C. H. Cheng, *Chem. Asian J.*, 2015, **10**, 824.

12 For selected example see: (a) K. H. Shaughnessy, B. C. Hamann and J. F. Hartwig, *J. Org. Chem.*, 1998, **63**, 6546; (b) E. J. Hennessy and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 12084; (c) S. P. Marsden, E. L. Watson and S. A. Raw, *Org. Lett.*, 2008, **10**, 2905; (d) F. Glorius, G. Altenhoff, R. Goddard and C. Lehmann, *Chem. Commun.*, 2002, 2704; (e) E. P. Kündig, T. M. Seidel, Y. X. Jia and G. Bernardinelli, *Angew. Chem., Int. Ed.*, 2007, **46**, 8484; (f) L. Liu, N.Ishida, S. Ashida and M. Murakami, *Org. Lett.*, 2011, **13**, 1666.

13 (a) Y. Jia and E. P. Kündig, *Angew. Chem., Int. Ed.*, 2009, **48**, 1636; (b) A. Perry and R. J. K. Taylor, *Chem. Commun.*, 2009, **45**, 3249; (c) J. E. M. N. Klein, A. Perry, D. S. Pugh and R. J. K. Taylor, *Org. Lett.*, 2010, **12**, 3446.

14 C. Tsukano, M. Okuno and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2012, **51**, 2763.

15 M. Wasa and J. Q. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 14058.

16 For review see: F. Hu, Y. Xia, C. Ma, Y. Zhang and J. Wang, *Chem. Commun.*, 2015, **51**, 7986.

17 For selected examples in Rh(III)-catalyzed metal carbene migratory insertion, see: (a) W.W. Chan, S.F. Lo, Z. Zhou and W.Y. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 13565; (b) Z. Shi, D. C. Koester, M. Boultadakis-Arapinis and F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 12204; (c) F. Hu, Y. Xia, F. Ye, Z. Liu, C. Ma, Y. Zhang, and J. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 1364; (d) H.W. Lam, K.Y. Man, W.W. Chan, Z. Zhou and W.Y. Yu, *Org. Biomol. Chem.*, 2014, **12**, 4112; (e) Y.Liang, K. Yu, B. Li, S. Xu, H. Song and B. Wang, *Chem. Commun.*, 2014, **50**, 6130; (f) B. Ye and N.Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 7896; (g) J. Y. Son, S. Kim, W. H. Jeon and P. H. Lee, *Org. Lett.*, 2015, **17**, 2518; (h) S. Yu, S. Liu, Y. Lan, B. Wan and X. Li, *J. Am. Chem. Soc.*, 2015, **137**, 1623; (i) B. Zhou, Z. Chen, Y. Yang, W. Ai, H.Tang, Y. Wu, W. Zhu and Y. Li, *Angew. Chem., Int. Ed.*, 2015, **54**, 12121; (j) Y. Yang, X. Wang, Y. Li and B. Zhou, *Angew. Chem., Int. Ed.*, 2015, **54**, 15400; (k) N. K. Mishra, M. Choi, H. Jo, Y. Oh, S. Sharma, S. H. Han, T. Jeong, S. Han, S.Y. Lee and I. S. Kim, *Chem. Commun.,* 2015, **51**, 17229; (l) J. Shi, J. Zhou, Y. Yan, J. Jia, X. Liu, H. Song, H. E. Xu and W. Yi, *Chem. Commun.*, 2015, ***51***, 668; (m) X. Chen, X. Hu, S. Bai, Y. Deng, H. Jiang and W. Zeng, *Org. Lett.*, 2016, **18**, 192; (n) H. Jiang, S. Gao, J. Xu, X. Wu, A. Lin and H. Yao, *Adv. Synth. Catal.,* 2016, **358**, 188.

18 (a) W. Ai, X. Yang, Y. Wu, X. Wang, Y. Li, Y. Yang and B. Zhou, *Chem. Eur. J.*, 2014, **20**, 17653; (b) Y. Xia, Z. Liu, S. Feng, Y. Zhang and J. Wang, *J. Org. Chem.*, 2015, **80**, 223; (c) S.S. Zhang, C. Y. Jiang, J. Q. Wu, X. G. Liu, Q. Ll, Z. S. Huang, D. Li and H. Wang, *Chem. Commun.*, 2015, **51**, 10240.

19 Y. Li, Z. Qi, H. Wang, X. Yang and X. Li, *Angew. Chem., Int. Ed.*, 2016, DOI: 10.1002/anie.201606316.

20 (a) D. Zhou, J. H. Kim, L. Stegemann, C. A. Strassert and F. Glorius, *Angew. Chem., Int. Ed.*, 2015, **54**, 4508; (b) J. H. Kim, S. Greβies and F. Glorius, *Angew. Chem., Int. Ed.*, 2016, **55**, 5577.

21 (a) R. S. Phatake, P. Patel and C. V. Ramana, *Org. Lett.*, 2016, **18**, 292; b) R. S. Phatake, P. Patel and C. V. Ramana, *Org. Lett.*, 2016, **18**, 2822.

22 B. Alcaide, P. Almendros, T. M. Campo and M. T. Quirós, *Chem. Eur. J.*, 2009, **15**, 3344.

23 M. H. Ngai, C. L. So, M. B. Sullivan, H. K. Ho and C. L. L. Chai, *ChemMedChem*, 2016, **11**, 72.

24 W. Zhang and M.L. Go, *Bioorg. Med. Chem.*, 2009, **17**, 2077.

25 J. Bergman, R. Carlsson and B. *J.* Sjöberg, *Heterocyclic Chem.*, 1977, **14**, 1123.

26 (a) J. Kim and S. Chang, *Angew. Chem., Int. Ed.*, 2014, **53**, 2203; (b) H. Kim, G. Park, J. Park and S. Chang, *ACS Catal.*, 2016, **6**, 5922.

27 Meldrum, A. N. J. *Chem . Soc*., 1908, **93**, 598.