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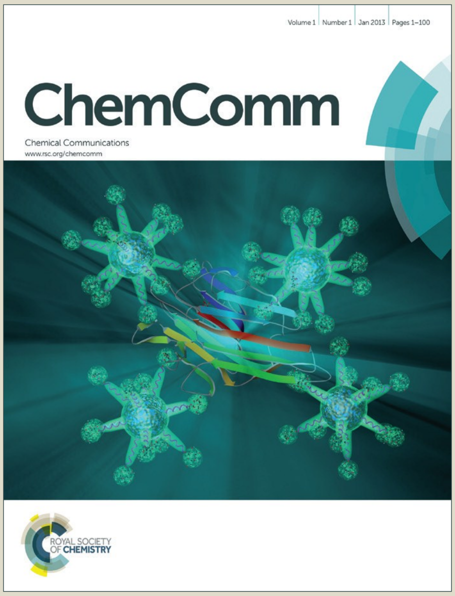

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Copper-catalyzed, hypervalent iodine mediated C=C bond activation of enaminones for the synthesis of α-keto amides

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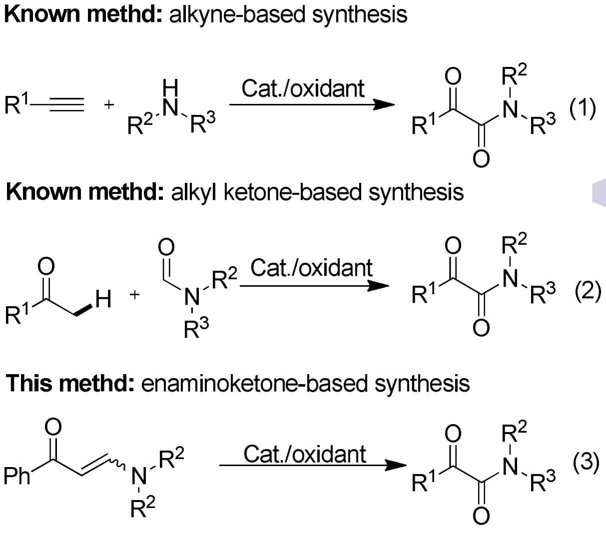
An unprecedented C=C bond cleavage of enaminones has been realized by means of copper catalysis in the presence of hypervalent iodine ($PhI(OAc)_2$). The cascade transformation based on this bond cleavage leads to the synthesis of various α-keto amides. Isotope labeling experiments suggest that water has acted as the source of oxygen atom during the generation of the new carbonyl group.

α-Keto amides are a class of special amides possessing invaluable biological and chemical functions. The α-keto amide structure presents prevalently in natural products, pharmaceuticals and biologically relevant lead compounds as key fragment.[1] The unique structural feature of these compounds makes them privileged candidates in the design of enzyme inhibitors.[2] More over, the α-keto amides are also highly useful precursors in synthetic organic chemistry because of their distinct and versatile reactivity.[3] Correspondingly, the synthesis of α-keto amides has been an issue of extensive research interest. A number of synthetic approaches such as double carbonylation,[4] oxoaldehyde amidation,[5] α-keto acid amidation,[6] carbonylation coupling of acyl chlorides/esters,[7] and the isocyanide-based coupling carbonylation,[8] among others[9] have been developed during the past decades.

Owing to the ubiquitous reactant availability, the synthesis of α-keto amides using alkynes and alkanes via direct carbonylation of the raw carbon-carbon bonds and alkyl C-H bonds has been dominantly employed in recent years. The alkyne-based synthesis (eq 1, Scheme 1) usually takes place in the presence of the catalyst/oxidant and an additive.[10] On the other hand, the alkyl C-H bond-based synthesis could be achieved based on the carbonylation mediated by strong peroxide oxidant or transition metal catalyst (eq 2, Scheme 1).[11] Surprisingly, as another class of most universal chemical bond, the alkene C=C double bond have been rarely employed in the synthesis of α-keto amides with success in despite of their application in carbonylation-based amide synthesis.[12] Enaminones are a class of stable alkene derivatives with highly versatile application in the synthesis of tremendous organic products.[13] As our successive efforts in exploring the application of enaminones in the synthesis of diverse small organic molecules via C=C bond functionalization,[14] we report herein the first example of generally applicable α-keto amide synthesis by using enaminones via the cleavage of the C=C double bond (Eq 3, Scheme 1).



Scheme 1 Different routes to α-keto amides

The investigation started from the model reaction of enaminone **1a**. The tentative operation of the reaction in the presence of CuI and different oxidants disclosed that the combination of CuI with oxidant such as air, pure molecular oxygen, $PhI(OAc)_2$ enabled the production of α-keto amide **2** , and $PhI(OAc)_2$ exhibited the best oxidative effect (entries 1-3, Table 1). On the other hand, TBHP and $K_2S_2O_8$ were found unpractical for this reaction (entries 4-5, Table 1). Subsequ

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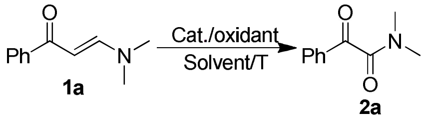
Electronic Supplementary Information (ESI) available: [Experimental information, characterization data, ^1H and ^{13}C NMR spectra of all products]. See DOI: 10.1039/x0xx00000x examination on different catalysts, including copper species, molecular iodine and the blank entries suggested that CuI was the best catalyst (entries 6-10, Table 1). In further experiments, entries with different CuI loading showed that increasing the amount of CuI from 0.4 to 0.6 equiv mol provided evidently improved yield of **2a** (entries 11-13, Table 1). On the other hand, no enhancement in product yield was observed by increasing the loading of $PhI(OAc)_2$ (entries 14, Table 1). A brief screening on the reaction medium proved that DMSO was most favoured in the reaction (entries 15-17, Table 1). Finally, variation on the reaction temperature was not able to further improve the efficiency of the reaction, either (entries 18-19, Table 1).

Table 1 Optimization on the conditions for α-keto amide synthesis[a]

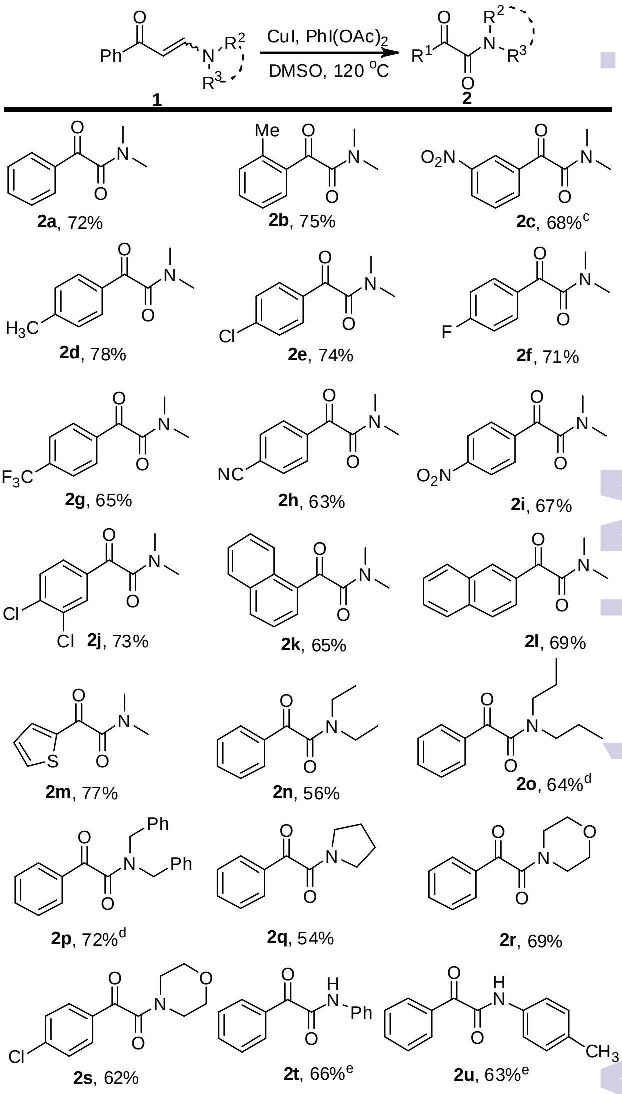


Entry	Catalyst	Oxidant	Solvent	Yield (%)[b]
1	CuI	air	DMSO	13
2	CuI	O_2	DMSO	27
3	CuI	$PhI(AcO)_2$	DMSO	53
4	CuI	TBHP	DMSO	nr
5	CuI	$K_2S_2O_8$	DMSO	nr
6	CuBr	$PhI(AcO)_2$	DMSO	23
7	CuCl	$PhI(AcO)_2$	DMSO	27
8	$Cu(AcO)_2$	$PhI(AcO)_2$	DMSO	25
9	I_2	$PhI(AcO)_2$	DMSO	nr
10	—	$PhI(AcO)_2$	DMSO	nr
11[c]	CuI	$PhI(AcO)_2$	DMSO	31
12[d]	**CuI**	**$PhI(AcO)_2$**	**DMSO**	**72**
13[e]	CuI	$PhI(AcO)_2$	DMSO	51
14[d,f]	CuI	$PhI(AcO)_2$	DMSO	69
15[d]	CuI	$PhI(AcO)_2$	DMF	25
16[d]	CuI	$PhI(AcO)_2$	NMP	16
17[d,g]	CuI	$PhI(AcO)_2$	CH_3CN	trace
18[d,h]	CuI	$PhI(AcO)_2$	DMSO	53
19[d,i]	CuI	$PhI(AcO)_2$	DMSO	70

[a] Unless specified, the general conditions: **1a** (0.3 mmol), copper catalyst (0.12 mmol) and oxidant (0.3 mmol, except in the entries 1-2) in 2 mL solvent, stirred at 120 °C for 12 h, nr = no reaction. [b] Isolated yield. [c] 0.06 mmol CuI. [d] 0.18 mmol CuI. [e] 0.24 mmol CuI. [f] 0.45 mmol $PhI(OAc)_2$. [g] Reaction at reflux. [h] Reaction at 110 °C. [i] Reaction at 130 °C.

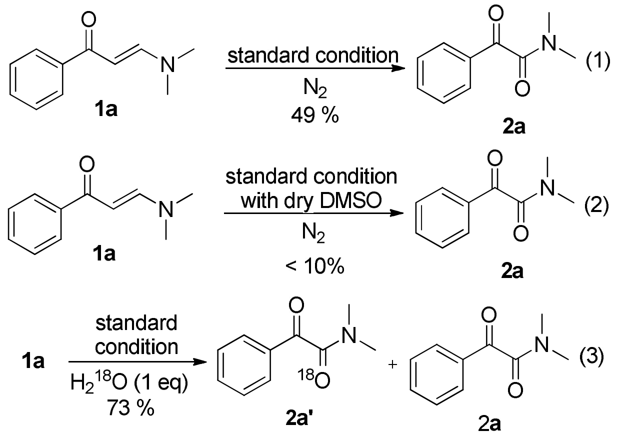
On the basis of the above optimization experiment, the application scope of the present method in synthesizing different α-keto amides was investigated by employing different enaminones. According to the results acquired in this section (Table 2), the present method was generally applicable in the synthesis of α-keto amides containing different substructures. Functional groups of distinct properties such as alkyl, halogen, nitro, cyano and trifluoromethyl etc all exhibited tolerance to the transformation. Notably, the heteroaryl-based enaminone was also successfully employed to provide corresponding product (**2m**, Table 2). Based on the results acquired from the entries using enaminones with different aryl substructure, no evident impact of the aryl ring was observed on the yield of products. As for the amine component, both acylic and (hetero)cyclic secondary amines were smoothly utilized in the synthesis. Compared with *N,N*-dimethylamino functionalized enaminones, the more bulky acyclic *N,N*-substituted amino group in the enaminones displayed negative effect to the formation of α-keto amides (**2n**, **2o**, Table 2). Notably, besides secondary amines, primary amines were also found applicable to the catalytic reaction to enable the synthesis of secondary α-keto amides (**2t** and **2u**, Table 2) by simply employing morpholine as additional additive.

Table 2 Scope of α-keto amide synthesis[a,b]



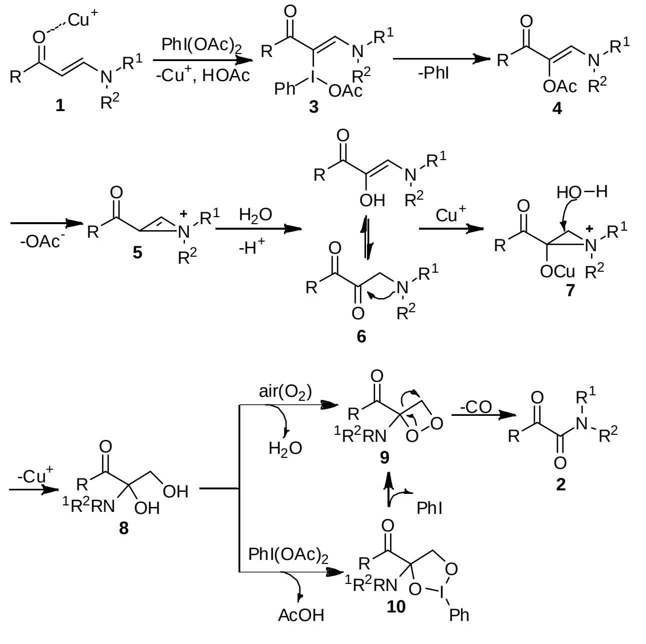
[a] General conditions: enaminone **1** (0.3 mmol), CuI (0.18 mmol) and $PhI(AcO)_2$ (0.3 mmol) in 2 mL DMSO under open air, stirred at 120 °C for 12 h. [b] Isolated yield. [c] The reaction time was 16 h. [d] Instead of $PhI(OAc)_2$, molecular oxygen (1 atm balloon) was used as the oxidant. [e] Additional 0.09 mmol of morpholine was employed.

In order to probe the source of oxygen in the newly generated carbonyl, some control experiments were then designed and conducted. Firstly, the model reaction of **1a** was performed under nitrogen atmosphere, and it was found that the product **2a** could be acquired with fair yield (eq 1, Scheme 2). The result excluded the possibility that air (molecular oxygen) was the source of carbonyl oxygen. On the other hand, a parallel experiment in dry DMSO gave only trace amount of product **2a** (eq 2, Scheme 2), which implied that presence of water was indispensable in the reaction and might act as the source of oxygen in the newly formed carbonyl. In addition, when this reaction was run under standard condition in the presence of additional $H_2{}^{18}O$, the simultaneous formation of products **2a** and ^{18}O labeled **2a'** were observed by HRMS analysis, and the relative peak intensity are **2a** : **2a'** ≈ 1 : 1.27 (eq 3, Scheme 2). What's more, considerably higher ratio of ^{18}O labeled product was given by an additional entry performed with dry DMSO under N_2 in the presence of identical $H_2{}^{18}O$ (the relative peak intensity are **2a** : **2a'** ≈ 1 : 1.82, see ESI for ESI-HRMS spectra from both entries). Once again, the result demonstrated the reliance of the reaction on water.



Scheme 2 Some control experiments

Based on the in hand results from the control experiments, a possible mechanism of the reaction is proposed as out-lined in Scheme 3. Originally, the activation effect of copper salt to the enaminones **1** facilitates the incorporation of $PhI(OAc)_2$ to enaminone,[15] which gives intermediate **3**. The reduction elimination of **3** by releasing PhI leads to the formation of intermediate **4** which undergoes intramolecular nucleophilic substitution to afford **5**. The subsequent hydrolysis of **5** yields amino ketone **6** which cyclizes to aonther key interme diate **7** via the promotion of copper salt. Further hydrolysis of **7** then gives diol species **8**. The oxidation of **8** with either molecular oxygen or $PhI(OAc)_2$ could provide 1,2-dioxetane intermediate **9**. The ring opening of **9** by releasing CO finally produces α-keto amide **2**.



Scheme 3 The proposed reaction mechanism

In conclusion, under the catalyst system consisting of copper/$PhI(OAc)_2$, we have achieved the synthesis of α-keto amides via the cleavage of the C=C double bond in enaminones. The synthetic method has exhibited broad application scope for the synthesis of both secondary and tertiary α-keto amides. The easy availability of reactants as well as the employment of simple catalyst/oxidant ensures the present method as a useful new option for α-keto amide synthesis.

Acknowledgements

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Notes and references

1 (a) H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto and T. Taga, *J. Am. Chem. Soc.,* 1987, **109**, 5031; (b) N. Fusetani, S. Matsunaga, H. Matsumoto and Y. Takebayashi, *J. Am. Chem. Soc.*, 1990, **112**, 7053; (c) H. Deng, J. K. Jung, T. Liu, K. W. Kuntz, M. L. Snapper and A. H. Hoveyda, *J. Am. Chem. Soc.,* 2003, **125**, 9032.

2 (a) H.-H. Otto and T. Schirmeister, *Chem. Rev.*, 1997, **97**, 133; (b) B. E. Maryanoff, H. C. Zhang, M. N. Greco, K. A. Glover, J. A. Kauffman and P. Andrade-Gordon, *Bioorg. Med. Chem.*, 1995, **3**, 1025; (c) Z. Li, A. C. Ortega-Vilain, G. S. Patil, D. L. Chu, J. E. Foreman, D. D. Eveleth and J. C. Powers, *J. Med. Chem.*, 1996, **39**, 4089; (d) A. Papanikos, J. Rademann and M. Meldal, *J. Am. Chem. Soc.*, 2001, **123**, 2176.

3 (a) Y.-X. Jia, D. Katayev and E. P. Kündig, *Chem. Commun.*, 2010, **46**, 130; (b) L. Yang, D.-X. Wang, Z.-T. Huang and M.-Wang, *J. Am. Chem. Soc.*, 2009, **131**, 10390; (c) K. K. S. Sai, P. M. Esteves, E. T. da Penha and D. A. Klumpp, *J. Org. Chem.*, 2008, **73**, 6506; (d) J. W. Bode, R. M. Fox and K. D. Baucom, *Angew. Chem. Int. Ed.*, 2006, **45**, 1248; (e) E. R. Koft and M. D. Williams, *Tetrahedron Lett.*, 1986, **27**, 2227.

4 (a) J. Liu, R. Zhang, S. Wang, W. Sun and C. Xia, *Org. Lett.*, 2009, **11**, 1321; (b) M. Iizuka and Y. Kondo, *Chem. Commun.*, 2006, 1739; (c) Q. Xing, L. Shi, R. Lang, C. Xia and F. Li, *Chem. Commun.*, 2012, **48**, 11023.

5 (a) C. Zhang, X. Zong, L. Zhang and N. Jiao, *Org. Lett.*, 2012, **14**, 3280; (b) N. Mupparapu, S. Khan, S. Battula, M. Kushwaha, A. P. Gupta, Q. N. Ahmed and R. A. Vishwakarma, *Org. Lett.*, 2014, **16**, 1152; (c) A. Y. Shaw, C. R. Denning and C. Hulme, *Tetrahedron Lett.*, 2012, **53**, 4151.

6 (a) X. Zhang, W. Yang and L. Wang, *Org. Biomol. Chem.*, 201, **11**, 3649; (b) H. Wang, L.-N. Guo and X.-H. Duan, *Org. Biomol. Chem.*, 2013, **11**, 4573.

7 (a) H. H. Wasserman and W.-B. Ho, *J. Org. Chem.*, 1994, **5**, 4364; (b) Z. Yang, Z. Zhang, N. A. Meanwell, J. F. Kadow and T.

Wang, *Org. Lett.*, 2002, **4**, 1103; (c) J. Chen and R. F. Cunico, *J. Org. Chem.*, 2004, **69**, 5509.

8 (a) I. Ugi and U. Fetzer, *Chem. Ber.*, 1961, **94**, 1116; (b) J.-M. Grassot, G. Masson and J. Zhu, *Angew. Chem. Int. Ed.*, 2008, **47**, 947; (c) M. Bouma, G. Masson and J. Zhu, *J. Org. Chem.*, 2010, **75**, 2748; (d) J. J. Chen and S. V. Deshpande, *Tetrahedron Lett.*, 2003, **44**, 8873.

9 (a) D. Li, M. Wang, J. Liu, Q. Zhao and L. Wang, *Chem. Commun.*, 2013, **49**, 3640; (b) D. Shanmugapriya, R. Shankar, G. Satyanarayana, V. H. Dahanukar, U. K. S. Kumar and N. Vembu, *Synlett*, 2008, 2945.

10 (a) C. Zhang and N. Jiao, *J. Am. Chem. Soc.*, 2010, **132**, 28; (b) A. Sagadevan, A. Ragupathi, C.-C. Lin, J. R. Hwu and K. C. Hwang, *Green Chem.*, 2015, **17**, 1113; (c) R. Deshidi, M. Kumar, S. Devari and B. A. Shah, *Chem. Commun.*, 2014, **50**, 9533.

11 (a) W.-P. Mai, H.-H. Wang, Z.-C. Li, J.-W. Yuan, Y.-M. Xiao, L.-R. Yang, P. Mao and L.-B. Qu, *Chem. Commun.*, 2012, **48**, 10117; (b) W. Wei, Y. Shao, H. Hu, F. Zhang, C. Zhang, Y. Xu and X. Wan, *J. Org. Chem.*, 2012, **77**, 7157; (c) F.-T. Du and J.-X. Ji, *Chem. Sci.*, 2012, **3**, 460; (d) C. Zhang, Z. Xu, L. Zhang and N. Jiao, *Angew. Chem. Int. Ed.*, 2011, **50**, 11088; (e) J. Zhang, Y. Wei, S. Lin, F. Liang and P. Liu, *Org. Biomol. Chem.*, 2012, **10**, 9237; (f) X. Zhang, M. Wang, Y. Zhang and L. Wang, *RSC Adv.*, 2013, **3**, 1311; (g) M. Zhou and Q. Song, *Synthesis*, 2014, **46**, 1853; (h) N. Mupparapu, R. A. Vishwakarma and Q. N. Ahmed, *Tetrahedron*, 2015, **71**, 3417; (i) X. Wu, Q. Gao, S. Liu and A. Wu, *Org. Lett.*, 2014, **16**, 2888; (j) J.-L. Gong, X. Qi, D. Wei, J.-B. Feng and X.-F. Wu, *Org. Biomol. Chem.*, 2014, **12**, 7486.

12 (a) L. Liu, L. Du, D. Zhang-Negrerie, Y. Du and K. Zhao, *Org. Lett.*, 2014, **16**, 5772; (b) R. Deshidi, S. Devari and B. A. Shah, *Eur. J. Org. Chem.*, 2015, 1428; (c) S. Dutta, S. S. Kotha and G. Sekar, *RSC Adv.*, 2015, **5**, 47265; (d) M. Sharif, J.-L. Gong, P. Langer, M. Beller and X.-F. Wu, *Chem. Commun.*, 2015, **50**, 4747.

13 (a) Z.-Y. Gu, T.-H. Zhu, J.-J. Cao, X.-P. Xu, S.-Y. Wang, and S.-J. Ji, *ACS Catal.,* 2014, **4**, 49; (b) Z.-H. Guan, L. Li, Z.-H. Ren, J. Li and M.-N. Zhao, *Green Chem.,* 2011, **13**, 1664; (c) J.-P. Wan, Y. Lin, Q. Huang and Y. Liu. *J. Org. Chem.,* 2014, **79**, 7232; (c) P. A. Suryavanshi, V. Sridharan and J. C. Menéndez, *Chem. Eur.—J.* 2013, **19**, 13207; (d) D. Xiang, X. Xin, X. Liu, R. Zhang, J. Yang and D. Dong, *Org. Lett.,* 2012, **14**, 644; (e) Z. Yang, B. Jiang, W.-J. Hao, P. Zhou, S.-J. Tu and G. Li, *Chem. Commun.,* 2015, **51**, 1267; (f) H. Ge, M. J. Niphakis and G. I. Georg, *J. Am. Chem. Soc.,* 2008, **130**, 3708; (g) R. V. Edwankar, C. R. Edwankar, O. A. Namjoshi, J. R. Deschamps and J. M. Cook, *J. Nat. Prod.,* 2012, **75**, 181; (h) J.-P. Wan, Y. Zhou, K. Jiang and H, Ye, *Synthesis,* 2014, **46**, 3256.

14 (a) J.-P. Wan, Y. Zhou, Y. Liu and S. Sheng, *Green Chem.*, 2015, in press, DOI: 10.1039/C5GC01821H; (b) J.-P. Wan, S. Cao and Y. Liu, *J. Org. Chem.*, 2015, **80**, 9028; (c) J.-P. Wan, Y. Zhou and S. Cao, *J. Org. Chem.*, 2014, **79**, 9872; (d) S. Cao, S. Zhong, L. Xin, J.-P. Wan and C. Wen, *ChemCatChem*, 2015, **7**, 1478.

15 T. Wirth, *Angew. Chem. Int. Ed.*, 2005, **44**, 3656; (b) V. V. Zhdankin, *Arkivoc*, 2009, **i**, 1; (c) S. Shang, D. Zhang-Negrerie, Y. Du and K. Zhao, *Angew. Chem. Int. Ed.*, 2014, **53**, 6216; (d) Y. Yuan, W. Hou, D. Zhang-Negrerie, K. Zhao and Y. Du, *Org. Lett.*, 2014, **16**, 5410; (e) Z. Zheng, L. Dian, Y. Yuan, D. Zhang-Negrerie, Y. Du and K. Zhao, *J. Org. Chem.*, 2014, **79**, 7451; (f) E. Mejía and A. Togni, *ACS Catal.*, 2012, **2**, 521; (g) S. Okumura, Y. Takeda, K. Kiyokawa and S. Minakata, *Chem. Commun.*, 2013, **49**, 9266; (h) A. G. Santana, N. R. Paz, C. G. Francisco, E. Suárez and C. C. Conzález, *J. Org. Chem.*, 2013, **78**, 7527.