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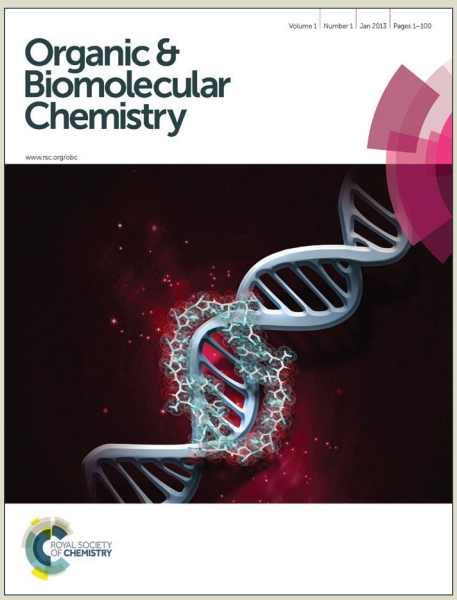

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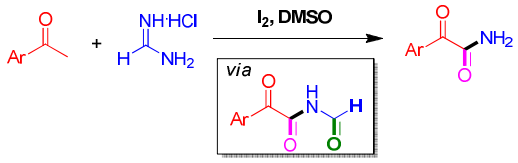
Graphical Abstract for

Formamidine hydrochloride as an amino surrogate: I_2-catalyzed oxidative amidation of aryl methyl ketones leading to free (N-H) α-ketoamides

*Shan Liu, Qinghe Gao, Xia Wu, Jingjing Zhang, Kerong Ding and Anxin Wu**



A highly efficient molecular iodine catalyzed oxidative amidation of aryl methyl ketones has been developed. This reaction represents a novel strategy for the synthesis of free (N-H) α-ketoamides. Based on the experimental results, a self-sequenced iodination/Kornblum oxidation/amidation/oxidation/decarbonylation mechanism was proposed.

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ARTICLE TYPE

Formamidine hydrochloride as an amino surrogate: I_2-catalyzed oxidative amidation of aryl methyl ketones leading to free (N-H) α-ketoamides

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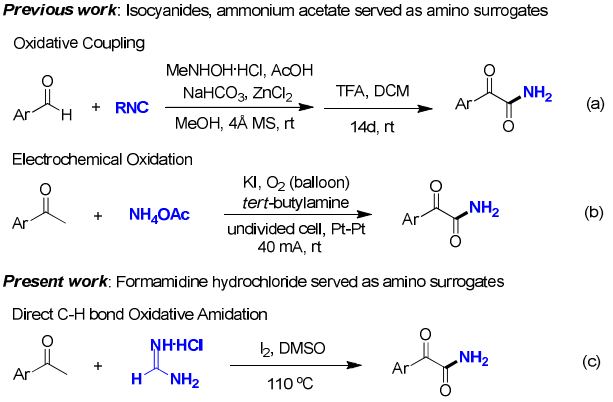
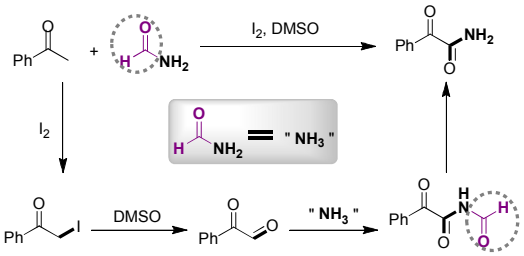
A highly efficient molecular iodine catalyzed oxidative amidation of aryl methyl ketones with formamidine hydrochloride has been developed. This reaction represents a novel strategy for the synthesis of free (N-H) α-ketoamides. Based on the experimental results, a self-sequenced iodination/Kornblum oxidation/amidation/oxidation/ decarbonylation mechanism was proposed.

α-Ketoamides are known to be embedded in a wide range of biologically active natural products and pharmaceuticals.[1] In particular, primary α-ketoamides are valuable precursors in a variety of functional group transformations with remarkable biological activity.[2] Consequently, the development of rapid and efficient routes to α-ketoamides has attracted considerable attention. Recent advances have focused on the construction of *N*-substituted α-ketoamides,[3] however, the attainment of free (N-H) α-ketoamides has rarely been reported.[4] Zhu and co-workers first developed a $ZnCl_2$ promoted formal oxidative coupling of 4-methoxybenzaldehyde and 1,1,3,3-tetramethylbutyl-isocyanide, which was then treated with TFA in DCM to form aryl primary α-ketoamides (Scheme 1a).[5a] More recently, an electrochemical oxidation synthesis of α-oxophenylacetamide derivatives from acetophenones and ammonium acetate was reported by Wang et al. (Scheme 1b).[5b] Nevertheless, an oxidative cross-coupling with amidines as nucleophiles to provide free (N-H) α-ketoamides has not yet been reported. In this work, the first known example of an I_2-catalyzed oxidative cross-coupling of formamidine hydrochloride with aryl methyl ketones is reported (Scheme 1c).



Scheme 1 The methods of synthesis of free (N-H) α-ketoamides.

In the light of our previous work on in situ iodination-based oxidative coupling of aryl methyl ketones,[6] it was supposed that an oxidative amidation approach could be adapted for the construction of free (N-H) α-ketoamides from aryl methyl ketones and a free ammonia equivalent (NH_4OAc or $NH_3{\cdot}H_2O$). However, 2-aryloxazoles have been predominantly formed by an oxidative cyclization approach.[7] As formamide can be a free ammonia surrogate via $C(sp^2)$–N bond cleavage,[8] it was utilized in our work as a potential amino source for the construction of free (N-H) α-ketoamides under acidic conditions (Scheme 2). To our delight, α-oxophenylacetamide was obtained in 31% yield. Subsequently, formamidine hydrochloride was served as an alternative substrate leading to a considerable increase in the yield. The results suggested that the suitable concentration of acid could promote the yield of free (N-H) α-ketoamides. To the best of our knowledge, formamidine hydrochloride has not yet been utilized as a free ammonia surrogate; herein, a novel I_2-catalyzed oxidative amidation of aryl methyl ketones with formamidine hydrochloride is presented for the construction of free (N-H) α-ketoamides.



Scheme 2 Design strategy.

Initially, an optimized I_2-catalyzed oxidative cross-coupling of acetophenone (**1a**) with formamidine hydrochloride (**2**) was inspected in DMSO. When acetophenone (**1a**) was reacted with formamidine hydrochloride (**2**) in the presence of I_2 at 100 °C, an oxidative coupling reaction and a decarbonylation process occurred to afford the desired product in 83% yield (Table 1, entry 1). Subsequent studies indicated that increases in the amount of **2** did not result in higher yields (Table 1, entries 2-3). The influence of temperature on the reaction was also investigated, and 110 °C was determined as optimum for the formation of α-oxophenylacetamide (Table 1, entries 4-8). To our surprise, a reduction in the equivalent of I_2 to 0.8 equiv. provided

3a in 88% yield (Table 1, entry 12). Further increasing or decreasing the amount of I_2 led to no improvement in the yields (Table 1, entries 9-11 and 13-15). Furthermore, it was established that the reaction could not proceed in the absence of I_2, suggesting that I_2 played a crucial role in the reaction (Table 1, entry 16). After screening on different parameters, the optimal reaction conditions were determined as **1a** (1.0 mmol) with **2** (1.0 mmol) in the presence of I_2 (0.8 mmol) in DMSO at 110 °C for 11 h.

Table 1 Optimization of the reaction conditions[a]

1a **2** **3a**

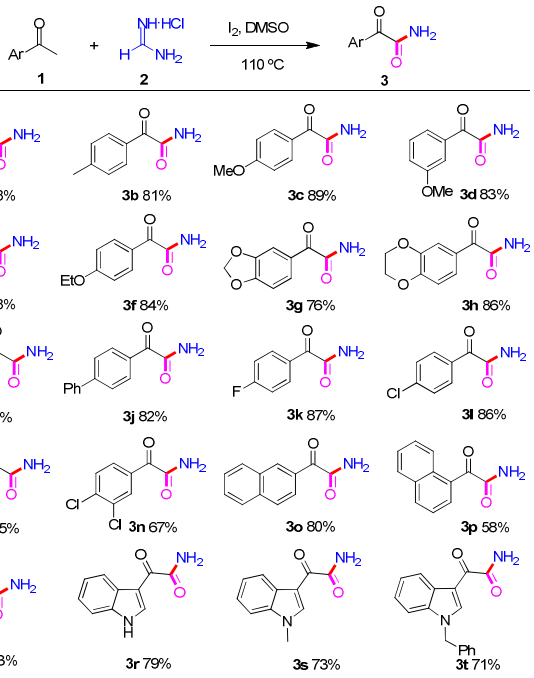
Entry	I_2 (equiv.)	Temp. (°C)	Time (h)	Yield[b] (%)
1	1.6	100	8	83
2[c]	1.6	100	8	80
3[d]	1.6	100	8	78
4	1.6	60	8	0
5	1.6	80	8	64
6	1.6	90	8	78
7	1.6	110	8	86
8	1.6	130	2	81
9	2.0	110	8	67
10	1.2	110	8	87
11	1.0	110	11	88
12	**0.8**	**110**	**11**	**88**
13	0.5	110	23	79
14	0.3	110	23	78
15	0.1	110	23	71
16	–	110	23	0

[a] Reaction Conditions: **1a** (1.0 mmol), **2** (1.0 mmol), and I_2, heated in DMSO (2 mL). [b] Isolated yields. [c] **2** (1.5 mmol). [d] **2** (2.0 mmol).

Under these optimized conditions, the substrate generality of the I_2-catalyzed oxidative coupling reaction was next evaluated with a range of different methyl ketones (Table 2). The results demonstrated that aryl methyl ketones bearing electronically neutral (4-H, 4-Me), electron-donating (4-OMe, 3-OMe, 2-OMe, 4-OEt, 3,4-OCH_2O, 3,4-OCH_2CH_2O), and electron-withdrawing (4-NO_2, 4-Ph) substituents all reacted smoothly to afford the corresponding aryl primary α-ketoamides in moderate to excellent yields (69-89%; **3a-j**). In general, aryl methyl ketones with electron-donating groups proceeded more efficiently than those containing electron-withdrawing groups. It was noteworthy that the halo-substituted aromatic ketones survived well, leading to halo-substituted α-ketoamides (67-87%; **3k-n**), which could be used for further transformations. Meanwhile, sterically hindered 2-naphthyl methyl ketone and 1-naphthyl methyl ketone furnished the desired products **3o** and **3p** in 80% and 58% yields, respectively. Moreover, the desired free (N-H) α-ketoamide could also be obtained in moderate yield from heteroaryl methyl ketone (43%; **3q**). Gratifyingly, the optimized conditions were successfully applied to both *N*-free and *N*-protective indolyl methyl ketones, giving the corresponding products in good yields (71-79%; **3r-t**). In addition, aliphatic methyl ketones such as acetone, cyclohexanone, and methylethylketone, were also investigated. However, none of the desired products were observed under the standard conditions.

To gain some insight into the reaction mechanism, a series of control experiments were performed (Scheme 3). The reaction

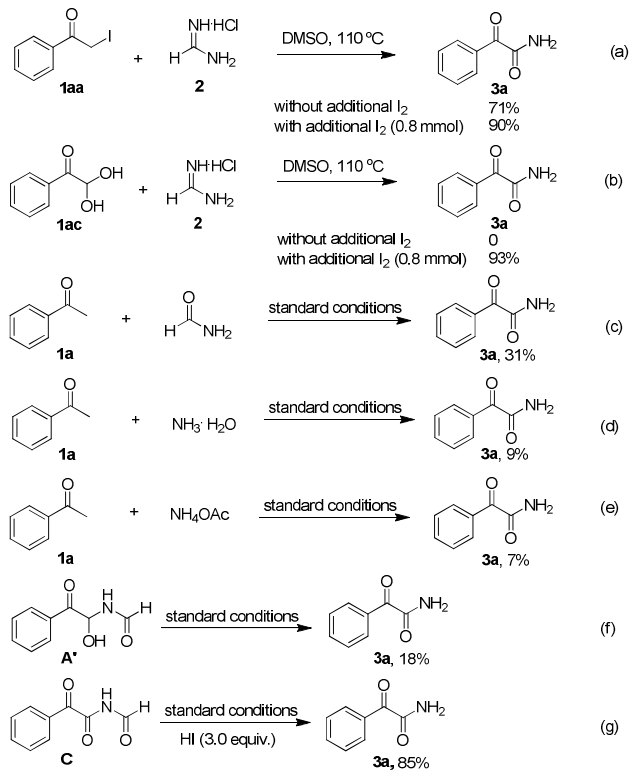
Table 2 Oxidative amidation of aryl methyl ketones with formamidine hydrochloride[a, b]



[a] Reaction Conditions: **1** (1.0 mmol), **2** (1.0 mmol), and I_2(0.8 mmol) in DMSO (2 mL) at 110 °C for 11 h. [b] Isolated yields.

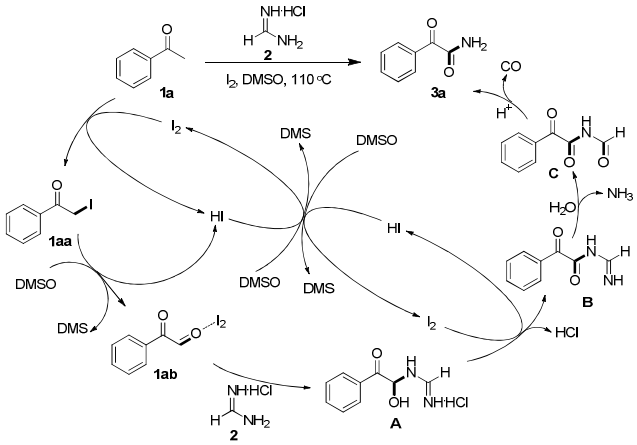
of α-iodo acetophenone (**1aa**) with formamidine hydrochloride (**2**) was found successful, and the desired product **3a** was obtained both with I_2 (0.8 mmol) and without I_2 (Scheme 3a). In the presence of additional I_2, hydrated hemiacetal (**1ac**) could react with **2** and afford the product **3a** in 93% yield (Scheme 3b). These results clearly confirmed that phenacyl iodine (**1aa**) and phenylglyoxal (**1ab**) were the key intermediates in the transformation. However, the reaction was unable to proceed when hydrated hemiacetal (**1ac**) was tested in the absence of I_2 (Scheme 3b), which indicated that I_2 played an important role in the subsequent domino process. The target product **3a** was generated in 31% yield when formamide was used as the substrate instead of formamidine hydrochloride under the standard conditions (Scheme 3c). This suggested that formamidine hydrochloride may first react with acetophenone and then undergo hydrolysis. Furthermore, reactions performed with ammonium acetate or ammonium hydroxide under the standard conditions led to sharp decreases in yields of **3a** (Scheme 3d, 3e). These results demonstrated that the direct release of ammonia could not be involved in this process. Additionally, when *N*-(1-hydroxy-2-oxo-2-phenylethyl)formamide (**A'**) was employed as the reaction substrate, only 18% product yield of **3a** was obtained and no corresponding oxidative product **C** was detected(Scheme 3f). The treatment of *N*-formyl-2-oxo-2-phenylacetamide (**C**) under the standard conditions afforded the desired product **3a** in 46% yield, which increased to 85% when 3 equiv. HI was added to the reaction system (Scheme 3g). These results suggested that **C** was an important intermediate in this transformation, which could not be formed through the direct oxidation of **A'**, and the acid could promote the decarbonylation of **C** to yield **3a**.

On the basis of the aforementioned information and previous work,[9] a possible mechanism was illustrated using acetophenone (**1a**) and formamidine hydrochloride (**2**) as an example (Scheme



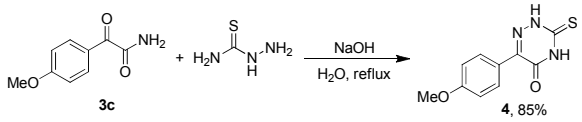
Scheme 3 Control experiments.

4). Initially, the reaction of **1a** with molecular iodine resulted in the formation of α-iodo acetophenone (**1aa**), which subsequently converted into phenylglyoxal (**1ab**) and released HI via Kornblum oxidation in the presence of DMSO. The aldehyde of **1ab** was activated by regenerated Lewis acid I_2; it was then attacked by formamidine hydrochloride (**2**) to afford the intermediate **A**, which was further oxidized to intermediate **B** by I_2.[6, 10] Intermediate **B** underwent hydrolysis to afford intermediate **C**, which could subsequently transform to the desired product **3a** through an acid-catalyzed decarbonylation process.



Scheme 4 A possible mechanisim.

Considering that primary α-ketoamides are important intermediates in organic synthesis, we treated **3c** with thiosemicarbazide in refluxing sodium hydroxide and the resulting thio-1,2,4-triazinone (**4**) could be isolated in 85% yield.[11]



In conclusion, a highly efficient molecular iodine catalyzed sp^3 C-H bond oxidative amidation of aryl methyl ketones has been developed with the use of formamidine hydrochloride as an amino surrogate for the construction of free (N-H) α-ketoamides. Preliminary studies of the mechanism suggested that this reaction occurred through a self-sequenced iodination/Kornblum oxidation/amidation/oxidation/decarbonylation cascade reaction. Further studies to elucidate a detailed mechanism and identify applications of this protocol are currently underway in our laboratory.

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Notes and references

Key Laboratory of Pesticide & Chemical Biology, Ministry of Education; College of Chemistry, Central China Normal University, 152 Luoyu Road,
Wuhan, Hubei 430079, China. E-mail: chwuax@mail.ccnu.edu.cn; Fax: +86 027-67867773; Tel: +86 027-67867773;

† Electronic Supplementary Information (ESI) available: Experimental procedures and compound characterisation data. For ESI or other electronic format See DOI: 10.1039/b000000x/

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*) 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*) S. Álvarez, R. Álvarez, H. Khanwalkar, P. Germain, G. Lemaire, F. Rodríguez-Barrios, H. Gronemeyer and Á. R. de Lera, *Bioorg. Med. Chem.*, 2009, **17**, 4345; (*e*) A. Ovat, Z. Li, C. Y. Hampton, S. A. Asress, F. M. Fernández, J. D. Glass and J. C. Powers, *J. Med. Chem.*, 2010, **53**, 6326.

2 (*a*) L. I. Kruse, C. Kaiser, W. E. DeWolf, J. S. Frazee, E. Garvey, E. L. Hilbert, W. A. Faulkner, K. E. Flaim, J. L. Sawyer and B. A. Berkowitz, *J. Med. Chem.*, 1986, **29**, 2465; (*b*) F. Y. Miyake, K. Yakushijin and D. A. Horne, *Org. Lett.*, 2002, **4**, 941; (*c*) W. Lubisch, E. Beckenbach, S. Bopp, H.-P. Hofmann, A. Kartal, C. Kästel, T. Lindner, M. Metz-Garrecht, J. Reeb, F. Regner, M. Vierling and A. Möller, *J. Med. Chem.*, 2003, **46**, 2404; (*d*) B. P. Smart, Y. H. Pan, A. K. Weeks, J. G. Bollinger, B. J. Bahnson and M. H. Gelb, *Bioorg. Med. Chem.*, 2004, **12**, 1737; (*e*) Y. K. Lee, D. J. Parks, T. Lu, T. V. Thieu, T. Markotan, W. Pan, D. F. McComsey, K. L. Milkiewicz, C. S. Crysler, N. Ninan, M. C. Abad, E. C. Giardino, B. E. Maryanoff, B. P. Damiano and M. R. Player, *J. Med. Chem.*, 2007, **51**, 282; (*f*) A. Veerareddy, G. Surendrareddy and P. K. Dubey, *Synthetic Commun.*, 2013, **43**, 2236.

3 (*a*) C. Zhang and N. Jiao, *J. Am. Chem. Soc.*, 2010, **132**, 28. (*b*) C. Zhang, Z. Xu, L. Zhang and N. Jiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 11088; (*c*) F. Du and J. Ji, *Chem. Sci.*, 2012, **3**, 460; (*d*) X. Zhang and L. Wang, *Green. Chem.*, 2012, **14**, 2141; (*e*) W. Mai, H. Wang, Z. Li, J. Yuan, Y. Xiao, L. Yang, P. Mao and L. Qu, *Chem. Commun.*, 2012, **48**, 10117; (*f*) M. Lamani and K. R. Prabhu, *Chem.-Eur. J.*, 2012, **18**, 14638; (*g*) J. Zhang, Y. Wei, S. Lin, F. Liang and P. Liu, *Org. Biomol. Chem.*, 2012, **10**, 9237; (*h*) D. Li, M. Wang, J. Liu, Q. Zhao and L. Wang, *Chem. Commun.*, 2013, **49**, 3640; (*i*) J. Zhang, Y. Liu, S. Chiba and T.-P. Loh, *Chem. Commun.*, 2013, **49**, 11439; (*j*) B. Du, B. Jin and P. Sun, *Org. Biomol. Chem.*, 2014, **12**, 4586; (*k*) N. Mupparapu, S. Khan, S. Battula, M. Kushwaha, A. P. Gupta, Q. N. Ahmed and R. A. Vishwakarma, *Org. Lett.*, 2014, **16**, 1152; (*l*) S. Guin, S. K. Rout, A. Gogoi, W. Ali and B. K. Patel, *Adv. Synth. Catal.*, 2014, **356**, 2559; (*m*) H. Huang, G. He, X. Zhu, X. Jin, S. Qiu and H. Zhu, *Eur. J. Org. Chem.*, 2014,

7174; (*n*) V. Rajeshkumar, S. Chandrasekar and G. Sekar, *Org. Biomol. Chem.*, 2014, **12**, 8512.

4 G. Wang, Q. Yu, S. Chen and X. Yu, *Org. Biomol. Chem.*, 2014, **12**, 414.

5 (*a*) M. Bouma, G. Masson and J. Zhu, *J. Org. Chem.*, 2010, **75**, 2748; (*b*) Z. Zhang, J. Su, Z. Zha and Z. Wang, *Chem. Commun.*, 2013, **49**, 8982.

6 Q. Gao, X. Wu, S. Liu and A. Wu, *Org. Lett.*, 2014, **16**, 1732.

7 (*a*) W. Xue, W. Zhang, K. Zheng, Y. Dai, Y. Guo, H. Li, F. Gao and A. Wu, *Asian J. Org. Chem.*, 2013, **2**, 638; (*b*) W. Xue, Q. Li, Y. Zhu, J. Wang and A. Wu, *Chem. Commun.*, 2012, **48**, 3485.

8 (*a*) S. H. Cho, J. Y. Kim, S. Y. Lee and S. Chang, *Angew. Chem., Int. Ed.*, 2009, **48**, 9127; (*b*) Y. Li, Y. Xie, R. Zhang, K. Jin, X. Wang and C. Duan, *J. Org. Chem.*, 2011, **76**, 5444; (*c*) J. Wang, J. Hou, J. Wen, J. Zhang and X. Yu, *Chem. Commun.*, 2011, **47**, 3652; (*d*) S. Ding and N. Jiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 9226; (*e*) Q. Zhao, T. Miao, X. Zhang, W. Zhou and L. Wang, *Org. Biomol. Chem.*, 2013, **11**, 1867; (*f*) M. Zhou and Q. Song, *Synthesis*, 2014, **46**, 1853.

9 (*a*) W. Wei, Y. Shao, H. Hu, F. Zhang, C. Zhang, Y. Xu and X. Wan, *J. Org. Chem.*, 2012, **77**, 7157; (*b*) R. Samanta, K. Matcha and A. P. Antonchick, *Eur. J. Org. Chem.*, 2013, 5769; (*c*) P. Finkbeiner and B. J. Nachtsheim, *Synthesis*, 2013, **45**, 979; (*d*) Y. Zhu, M. Lian, F. Jia, M. Liu, J. Yuan, Q. Gao and A. Wu, *Chem. Commun.*, 2012, **48**, 9086; (*e*) Y. Yang, M. Gao, W. Shu, L. Wu, D. Zhang and A. Wu, *Org. Biomol. Chem.*, 2013, **11**, 1226; (*f*) Q. Gao, Z. Fei, Y. Zhu, M. Lian, F. Jia, M. Liu, N. She and A. Wu, *Tetrahedron*, 2013, **69**, 22; (*g*) Q. Gao, X. Wu, Y. Li, S. Liu, X. Meng and A. Wu, *Adv. Synth. Catal.*, 2014, **356**, 2924; (*h*) Q. Gao, S. Liu, X. Wu and A. Wu, *Org. Lett.*, 2014, **16**, 4582; (*i*) Q. Gao, S. Liu, X. Wu and A. Wu, *Tetrahedron Lett.*, 2014, **55**, 6403; (*j*) Q. Gao, J. Zhang, X. Wu, S. Liu and A. Wu, *Org. Lett.*, 2014, **16**, DOI: 10.1021/ol503366r.

10 (*a*) C. Zhang, X. Zong, L. Zhang and N. Jiao, *Org. Lett.*, 2012, **14**, 3280; (*b*) H. Togo and S. Iida, *Synlett*, 2006, 2159; (*c*) X. Wu, Q. Gao, S. Liu and A. Wu, *Org. Lett.*, 2014, **16**, 2888.

11 (*a*) F. M. Adam, A. J. Burton, K. S. Cardwell, R. A. Cox, R. A. Henson, K. Mills, J. C. Prodger, M. B. Schilling and D. T. Tape, *Tetrahedron Lett.*, 2003, **44**, 5657.