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ARTICLE TYPE

Ammonium iodide-promoted cyclization of ketones with DMSO and ammonium acetate for synthesis of substituted pyridines

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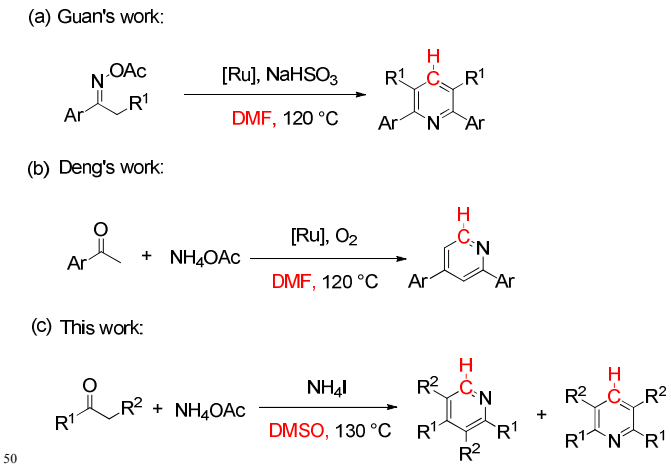
A simple and efficient method has been developed for the synthesis of symmetrical and unsymmetrical pyridines via NH_4I-promoted cyclization of ketones with DMSO and NH_4OAc. It was found that methyl ketones always gave selective formation of the unsymmetrical pyridine, while non-methyl ketones gave unpredictable results (symmetrical or non-symmetrical product only, or a mixture of the two). In addition, the deuterium-labeling experiments indicated that the C4 or C6 of the target product pyridine rings resulted from DMSO.

As an important class of nitrogen-containing heterocyclic compounds, substituted pyridines are found in numerous natural products and extensively used in functional materials, synthetic pharmaceuticals and various valuable ligands.[1] Consequently, diverse synthetic approaches toward substituted pyridines have been developed in the past few decades.[2] Among them, condensation of carbonyl compounds with amines is a traditional method for the synthesis of pyridine rings.[3] As modern synthetic methodologies, transition-metal-catalyzed cycloaddition, cycloisomerization and C−H functionalization reactions promote the construction of pyridine rings greatly.[4] Although a number of synthetic methods have been established, simple and flexible strategies for the synthesis of symmetrical and unsymmetrical pyridines are still highly needed. Exploring new carbon sources to construct pyridine ring is a critical issue.

Recently, Guan and co-workers reported a ruthenium-catalyzed cyclization of ketoxime acetates with DMF for the synthesis of symmetrical pyridine, in which DMF acts as both C4 source and reaction medium (Scheme 1a).[5] Different from Guan's work, Deng and co-workers developed a method for construction of unsymmetrical pyridines by employing DMF as C6 source (Scheme 1b).[6] DMSO, a cheap and low-toxic solvent, has been widely used in organic synthesis. In addition, DMSO can be used as a multipurpose precursor for the formation of −Me,[7] −SMe,[8] $-SO_2Me$,[9] −CHO,[10] −CN,[11] and



Scheme 1 Various methods for the synthesis of pyridines.

–OH.[12] Based on DMSO playing multiple roles in the organic synthesis, we have reported an efficient ammonium iodide-induced sulfonylation of alkenes for the synthesis of vinyl methyl sulfones by using DMSO and H_2O as the source of $-SO_2Me$, [13] and the coupling of alkenes with DMSO and alcohols for the synthesis of β−alkoxy methyl sulfides by employing DMSO as the source of −SMe.[14] In the experimental process, we found that DMSO was easily subjected to decomposition to produce MeSH and HCHO. The formation of formaldehyde makes the utilization of DMSO as a new carbon source for the synthesis of substituted pyridines become possible. Herein, we report an efficient ammonium iodide-promoted cyclization of ketones with DMSO and ammonium acetate for synthesis of unsymmetrical and symmetrical pyridines by employing DMSO as C4 or C6 source, respectively (Scheme 1c).

We initially employed acetophenone (**1a**) as model substrate to optimize the reaction conditions. In the presence of NH_4I, acetophenone **1a** was converted to 2,4-diarylpyridines (**2a**) in 22% yield without ammonium acetate in DMSO at 130 °C for 14 h (Table 1, entry 1). Instead of NH_4I, 33% yield of **2a** was obtained when equal amount of ammonium acetate was added into this reaction system (Table

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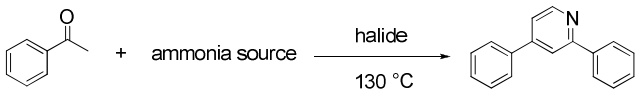
Table 1 Optimization of reaction conditions.[a]



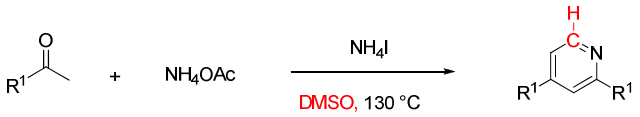
1a **2a**

Entry	Halide (equiv.)	Ammonia source	Solvent	Yield (%) [b]
1	NH_4I (1)	—	DMSO	22
2	—	NH_4OAc	DMSO	33
3	**NH_4I (0.5)**	**NH_4OAc**	**DMSO**	**87**
4[c]	NH_4I (0.5)	NH_4OAc	DMSO	23
5	NH_4I (0.5)	NH_4OAc	DMF	6
6	NH_4I (0.5)	NH_4OAc	DMA	5
7	NH_4I (0.5)	NH_4OAc	CH_3CN	trace
8	NH_4I (0.5)	$(NH_4)_2CO_3$	DMSO	16
9	NH_4I (0.5)	NH_4HCO_3	DMSO	6
10	NH_4I (0.5)	NH_4Cl	DMSO	5
11	NH_4Br (0.5)	NH_4OAc	DMSO	53
12	NH_4Cl (0.5)	NH_4OAc	DMSO	60
13	NaI (0.5)	NH_4OAc	DMSO	38
14	n-Bu_4NI (0.5)	NH_4OAc	DMSO	36
15	I_2 (0.25)	NH_4OAc	DMSO	25
16	HI (0.5)	NH_4OAc	DMSO	50
17[d]	HI/I_2 = 2:1	NH_4OAc	DMSO	61
18	HI/I_2 = 1:1	NH_4OAc	DMSO	42
19	HI/I_2 = 1:1.5	NH_4OAc	DMSO	30
20[e]	NH_4I (0.5)	NH_4OAc	DMSO	75

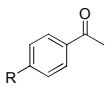
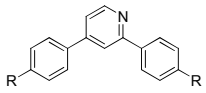
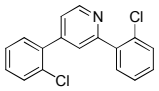
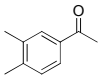
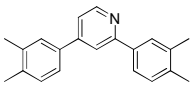
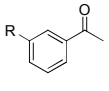
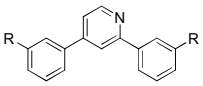
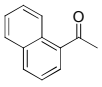
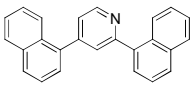
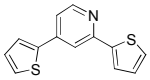
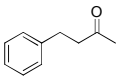
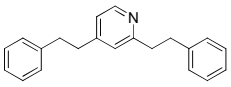
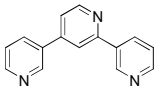
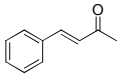
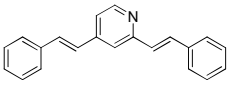
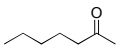
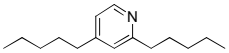
[a] Reaction conditions: **1a** (1 mmol), solvent (2.0 mL), ammonia source (1 equiv.), 130 °C, 14 h under air in a sealed tube. [b] Determined by GC based on **1a**. [c] Reaction temperature 120 °C. [d] I_2 (0.125 equiv.), HI (0.25 equiv.). [e] Under N_2 in a sealed tube.

1, entry 2). To our delight, the yield of **2a** could be increased from 33% to 87% when the reaction was performed in the presence of 0.5 equiv. of NH_4I and 1.0 equiv. of NH_4OAc (Table 1, entry 3). However, the efficiency of this transformation decreased significantly when the reaction was carried out at 120 °C (Table 1, entry 4). Subsequently, the effect of solvents on the reaction was also investigated. Unfortunately, only a little or even trace amount of **2a** was detected in DMF, DMA and acetonitrile (Table 1, entries 5–7). These results indicated that the solvent was probably involved in this transformation. In addition, the source of ammonia was also varied and it was observed that ammonium acetate was the most suitable ammonia source for this reaction (Table 1, entries 8–10). Compared to NH_4I, a similar ammonium salt NH_4Br or NH_4Cl resulted in a lower yield (Table 1, entries 11 and 12). Neither NaI nor tetrabutylammonium iodide (*n*-Bu_4NI) could be used to facilitate this reaction (Table 1, entries 13 and 14). When employing 0.25 equiv. of I_2 instead of 0.5 equiv. of NH_4I, only 25% yield of **2a** was obtained (Table 1, entry 15). Compared to I_2, HI could afford a higher yield of **2a** (Table 1, entry 16). In addition, different ratios of HI and I_2 have a great effect on this reaction (Table 1, entries 17–19). Obviously, a high initial concentration of I_2 is unfavorable to this reaction (Table 1, entry 15). Based on these results, it was proposed that in-situ generated I_2 from NH_4I was an active promoter in this reaction.

Table 2 Synthesis of unsymmetrical pyridines from methyl ketones.[a,b]



1 **2**

Entry	Substrate	Product	Yield
1			R =H **2a**, 81%
2			R =F **2b**, 78%
3			R =Cl **2c**, 72%
4			R =Br **2d**, 77%
5			R =I **2e**, 80%
6			R =CH_3 **2f**, 83%
7			R =OCH_3 **2g**, 76%
8			R =n-butyl **2h**, 60%
9			R =isopropyl **2i**, 75%
10			**2j**, 40%
11			**2k**, 65%
12			R =F **2l**, 85%
13			R =Cl **2m**, 80%
14			R =Br **2n**, 70%
15			R =OCH_3 **2o**, 75%
16			**2p**, 45%
17			**2q**, 45%
18			**2r**, 52%
19			**2s**, 0%
20			**2t**, 0%
21			**2u**, 21%[c]

[a] Reaction conditions: **1** (1 mmol), NH_4I (0.5 equiv.), NH_4OAc (1 equiv.), DMSO (2.0 mL), 130 °C, 14 h. [b] Isolated yield. [c] GC yield.

With the optimal reaction conditions established, a number of ketones (1) were investigated to evaluate the generality and scope of this reaction. Very interestingly, methyl ketones always afforded unsymmetrical pyridines, as shown in Table 2. Using various methyl aryl ketones with electron-withdrawing and electron-donating groups as the substrates, the reaction could give the corresponding unsymmetrical products in moderate to good yields (Table 2, entries 1–9). In addition, functional group at the meta positions of the aromatic ring was also applicable for this transformation (Table 2, entries 12–15). However, when ortho-substituted of acetophenone was involved in this reaction, only 40% yield of the desired product was obtained (Table 2, entry 10). The

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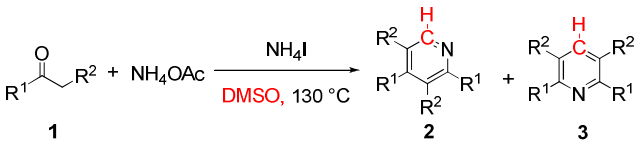
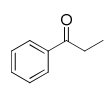
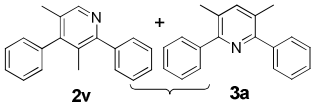
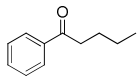
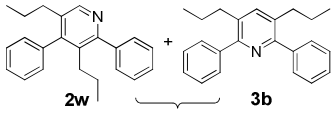
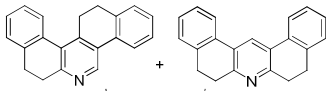
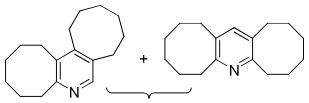
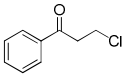
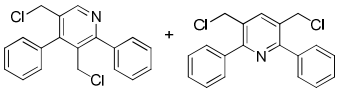
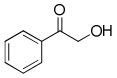
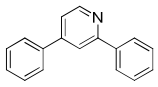
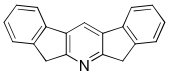
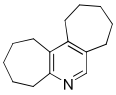
similar results

Table 3 Synthesis of symmetrical and unsymmetrical pyridines from non-methyl ketones.[a,b]



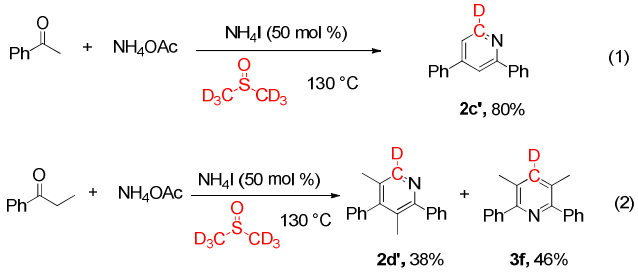
Entry	Substrate	Product	Yield
1		 **2v** : **3a** (**2v** : **3a** = 1:1.3)	70%
2		 **2w** : **3b** (**2w** : **3b** = 2.3:1)	75%[c]
3		 **2x** : **3c** (**2x** : **3c** = 1:2.2)	69%
4		 **2y** : **3d** (**2y** : **3d**= 1:1.8)	86%
5		 **2z** : **3e**	0%
6		 **2a**	0%
7		 **2a'**	76%
8		 **2b'**	85%[d]

[a] Reaction conditions: **1** (1 mmol), NH_4I (0.5 equiv.), NH_4OAc (1 equiv.), DMSO (2.0 mL), 130 °C, 14 h. [b] Isolated yield. [c] 1.5 equiv. of NH_4OAc was used. [d] A small amount of the corresponding regioisomer was detected by GC.

were observed when employing 1-(naphthalen-1-yl)ethanone and 1-(thiophen-2-yl)ethanone as the substrates (Table 2, entries 16 and 17). Besides, 3,4-dimethylacetophenone and 4-phenylbutan-2-one could smoothly perform in this process (Table 2, entries 11 and 18). However, only 21% yield of desired product was detected by GC when employing heptan-2-one as the substrate (Table 2, entry 21). Also, the product was difficult to be separated. No desired products could be obtained when 1-(pyridin-3- yl)ethanone or (*E*)-4-phenylbut-3-en-2-one was employed as the substrate (Table 2, entries 19 and 20).

For non-methyl ketone substrates, the reaction gave unpredictable results (symmetrical or non-symmetrical pyridine only, or a mixture of the two), as shown in Table 3. For example, the reactions utilizing propiophenone and valerophenone as the substrates gave a mixture of two regioisomers in a ratio of 1:1.3 and 2.3:1, respectively (Table 3, entries 1 and 2). The same phenomenon occurred when 3,4-dihydronaphthalen-1(2H)-one and cyclooctanone were used as the substrates (Table 3, entries 3 and 4). Surprisingly, only one desired product was obtained when the substrate above was replaced by 2,3-dihydro-1H-inden-1-one or cycloheptanone (Table 3, entries 7 and 8). It was worth noting that the corresponding product was symmetrical pyridine for 2,3-dihydro-1H-inden-1-one and unsymmetrical pyridine for cycloheptanone. No desired products could be observed if 3-chloro-1-phenylpropan-1-one and 2-hydroxy-1-phenylethanone were employed as the substrates (Table 3, entries 5 and 6).

Several deuterium-labeling experiments were carried out to gain a preliminary insight into the reaction mechanism (Scheme 2). The reaction was carried out successfully under N_2 to afford the corresponding product in 75% yield, which indicated that oxygen was not an important factor in this reaction system (Table 1, entry 20). Instead of DMSO, when DMSO-D_6 was subjected to the procedure under the standard conditions, 6-deuterated pyridine **2c'** was obtained in 80% yield (Scheme 2, eqn (1)). This result confirmed that the C6 in the pyridine ring was provided by DMSO. In addition, the reaction occurred as well to give 6-deuterated unsymmetrical pyridine **2d'** and 4-deuterated symmetrical pyridine **3f** when propiophenone was used, which could also provide the evidence of the source of C6 or C4 (Scheme 2, eqn (2)).



Scheme 2 Deuterium-labeling experiments.

Based on the above experimental results and literature reports,[6,15] two possible reaction pathways are proposed in Scheme 3. Initially, the intermediate **2** is formed by the condensation of ketone **1** itself, which can react with ammonium acetate to give imine intermediate **3**. Then, intermediate **3** easily undergoes tautomerization leading to an intermediate **4**. Meanwhile, the formaldehyde is generated via decomposition of DMSO (eqn (5)), followed by the reaction with **4** to afford intermediate **5**. Subsequently, **5** is oxidized to intermediate **6** by I_2 resulting from the reaction of DMSO with HI (eqn (4)). The final product **7** is formed by the intramolecular condensation of intermediate **6** (**path a**). According to the experimental results (Table 2), methyl ketones seem to exclusively follow **path a**. It is also possible

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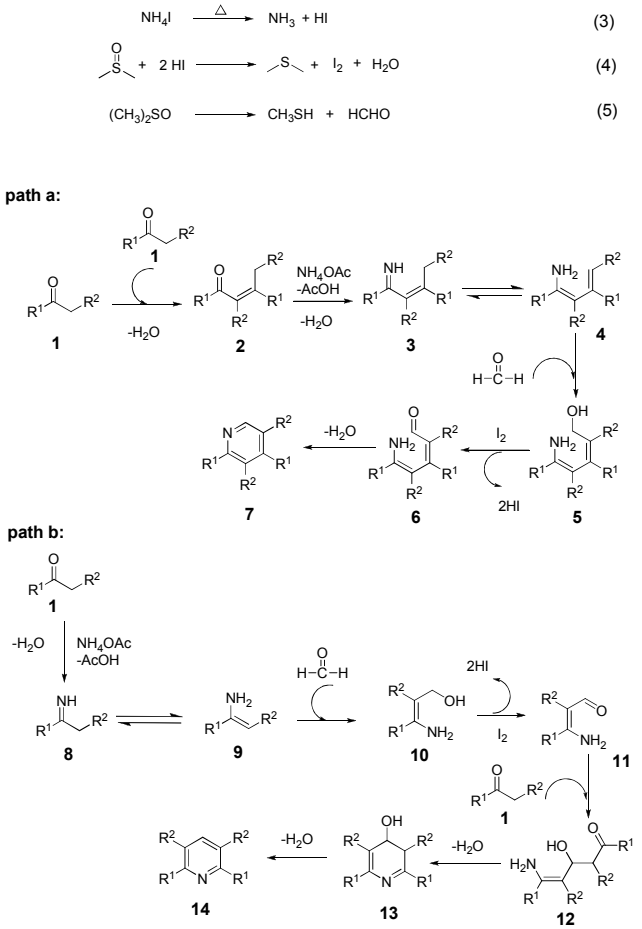
that ketone **1** has priority to react with ammonium acetate to afford imine intermediate **8**, which is easily converted to intermediate **9** via tautomerization. Subsequently, the intermediate **9** combines with formaldehyde provided by DMSO to give intermediate **10**. With the help of I_2, intermediate **10** is oxidized into intermediate **11**. Addition of **1** to **11** generates intermediate **12**, which gives intermediate **13** via a intramolecular condensation. Finally, losing a molecule of water, intermediate **13** is transformed into the desired product **14** (**path b**). For non-methyl ketones, the reaction may undergo **path a** and/or **path b.** In addition, it should be pointed out that if the imine intermediate **8** was formed from a methyl ketone it would be less likely to tautomerize to enamine **9** due to the lower stability of less-alkyl substituted C=C bonds. So methyl ketones do not follow **path b**.



Scheme 3 Proposed reaction mechanism.

In conclusion, a convenient and efficient method has been developed for the preparation of symmetrical and unsymmetrical pyridines via ammonium iodide-promoted cyclization of ketones with DMSO and ammonium acetate. In this reaction system, DMSO is used not only as an effective reaction medium, but also as the source of C4 or C6 for the formation of pyridines. It is worth mentioning that a mixture of two regioisomers, or only symmetrical or unsymmetrical product is obtained when non-methyl ketones are used as substrates, while methyl ketones alwalys gives unsymmetrical pyridines. The present work provides a new strategy for the synthesis of symmetrical and unsymmetrical pyridines.

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Notes and references

1 (*a*) G. D. Henry, *Tetrahedron,* 2004, **60**, 6043; (*b*) A. Gueiffier, S. Mavel, M. Lhassani, A. Elhakmaoui, R. Snoeck, G. Andrei, O. Chavignon, J. C. Teulade, M. Witvrouw, J. Balzarini, E. D. Clercq and J. P. Chapat, *J. Med. Chem.,* 1998, **41**, 5108; (*c*) F. Sha and X. Huang, *Angew. Chem*., *Int. Ed.,* 2009, **48**, 3458; (*d*) Z. He, D. Dobrovolsky, P. Trinchera and A. K. Yudin, *Org. Lett.,* 2013, **15**, 334; (*e*) F. Durola, J. P. Sauvage and O. S. Wenger, *Chem. Commun.,* 2006, 171.

2 (*a*) W. Gati, M. M. Rammah, M. B. Rammah, F. Couty and G. Evano, *J. Am. Chem. Soc.,* 2012, **134**, 9078; (*b*) S. B. Liu and L. S. Liebeskind, *J. Am. Chem. Soc.,* 2008, **130**, 6918; (*c*) J. A. Varela and C. Saá, *Chem. Rev.,* 2003, **103**, 3787; (*d*) J. P. Wan, Y. Y. Zhou and S. Cao, *J. Org. Chem.,* 2014, **79**, 9872; (*e*) N. D. Rycke, G. Berionni, F. Couty, H. Mayr, R. Goumont and O. R. P. David, *Org. Lett.,* 2011, **13**, 530; (*f*) D. Srimani, Y. B. David and D. Milstein, *Chem. Commun.,* 2013, **49**, 6632.

3 (*a*) R. L. Frank and R. P. Seven, *J. Am. Chem. Soc.,* 1949, **71**, 2629; (*b*) F. L. Muller, C. Allais, T. Constantieux and J. Rodriguez, *Chem. Commun.,* 2008, 4207; (*c*) H. T. Abdel-Mohsen, J. Conrad and U. Beifuss, *Green Chem.,* 2012, **14**, 2686; (*d*) T. J. Donohoe, J. A. Basutto, J. F. Bower and A. Rathi, *Org. Lett.,* 2011, **13**, 1036.

4 (*a*) Y. Wei and N. Yoshikai, *J. Am. Chem. Soc.,* 2013, **135**, 3756; (*b*) D. Srimani, Y. Ben-David and D. Milstein, *Chem. Commun.,* 2013, **49**, 6632; (*c*) Y. F. Wang, K. K. Toh, E. P. J. Ng and S. Chiba, *J. Am. Chem. Soc.,* 2011, **133**, 6411; (*d*) C. X. Wang, X. C. Li, F. Wu and B. S. Wan, *Angew. Chem*., *Int. Ed.,* 2011, **50**, 7162; (*e*) I. Nakamura, D. Zhang and M. Terada, *J. Am. Chem. Soc.,* 2010, **132**, 7884.

5 M. N. Zhao, R. R. Hui, Z. H. Ren, Y. Y. Wang and Z. H. Guan, *Org. Lett.,* 2014, **16**, 3082.

6 Y. Bai, L. C. Tang, H. W. Huang and G. J. Deng, *Org. Biomol. Chem.,* 2015, **13**, 4404.

7 D. J. Keddie, T. E. Johnson, D. P. Arnold and S. E. Bottle, *Org. Biomol. Chem.,* 2005, **3**, 2593.

8 (*a*) F. Luo, C. D. Pan, L. P. Li, F. Chen and J. Cheng, *Chem. Commun.,* 2011, **47**, 5304; (*b*) C. Dai, Z. Q. Xu, F. Huang, Z. K. Yu and Y. F. Gao, *J. Org. Chem.,* 2012, **77**, 4414; (*c*) G. D. Yin, B. H. Zhou, X. G. Meng, A. X. Wu and Y. J. Pan, *Org. Lett.,* 2006, **8**, 2245.

9 (*a*) Y. J. Jiang and T. P. Loh, *Chem. Sci.,* 2014, **5**, 4939; (*b*) G. Q. Yuan, J. H. Zheng, X. F. Gao, X. W. Li, L. B. Huang, H. J. Chen and H. F. Jiang, *Chem. Commun.,* 2012, **48**, 7513.

10 (*a*) J. J. Qian, Z. G. Zhang, Q. F. Liu, T. X. Liu and G. S. Zhang, *Adv. Synth. Catal.,* 2014, **356**, 3119; (*b*) H. Cao, S. Lei, N. Y. Li, L. B. Chen, J. Y. Liu, H. Y. Cai, S. X. Qiu and J. W. Tan, *Chem. Commun.,* 2015, **51**, 1823; (*c*) H. Y. Fei, J. T. Yu, Y. Jiang, H. Guo and J. Cheng, *Org. Biomol. Chem.,* 2013, **11**, 7092; (*d*) Z. G. Zhang, Q. Tian, J. J. Qian, Q. F. Liu, T. X. Liu, L. Shi and G. S. Zhang, *J. Org. Chem.,* 2014, **79**, 8182.

11 X. Y. Ren, J. B. Chen, F. Chen and J. Cheng, *Chem. Commun.,* 2011, **47**, 6725;

12 (*a*) R. S. Xu, J. P. Wan, H. Mao and Y. J. Pan, *J. Am. Chem. Soc.,* 2010, **132**, 15531; (*b*) Y. Ashikari, T. Nokami and J. I. Yoshida, *Org. Lett.,* 2012, **14**, 938; (*c*) Y. F. Liang, K. Wu, S. Song, X. Y. Li, X. Q. Huang and N. Jiao, *Org. Lett.,* 2015, **17**, 876.

13 X. F. Gao, X. J. Pan, J. Gao, H. W. Huang, G. Q. Yuan and Y. W. Li, *Chem. Commun.,* 2015, **51**, 210.

14 X. F. Gao, X. J. Pan, J. Gao, H. F. Jiang, G. Q. Yuan and Y. W. Li, *Org. Lett.,* 2015, **17**, 1038.

View Article Online
DOI: 10.1039/C5RA07584J

15 (*a*) A. Smith and R. P. Calvert, *J. Am. Chem. Soc.,* 1914, **36**, 1363; (*b*) V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.,* 1964, **29**, 221; (*c*) P. T. Parvatkar, P. S. Parameswaran and S. G. Tilve, *Chem. Eur. J.,* 2012, **18**, 5460; (*d*) K. Wu, Z. L. Huang, C. Liu, H. Zhang and A. W. Lei, *Chem. Commun.,* 2015, **51**, 2286; (*e*) W. L. Ge, X. Zhu and Y. Y. Wei, *RSC Adv.,* 2013, **3**, 10817.