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Metal-free oxidative esterification of acetophenones with alcohols: a facile one-pot approach to α-ketoesters†

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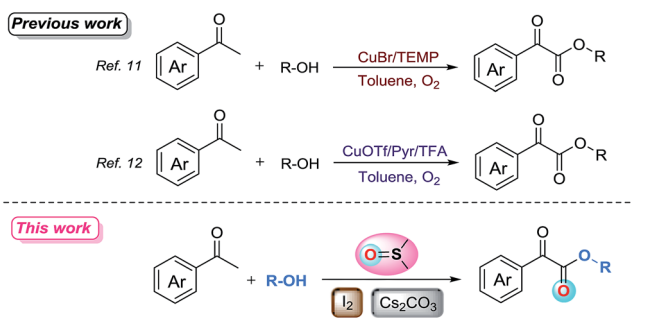
A novel and efficient oxidative esterification method for the synthesis of α-ketoesters has been developed under mild and environmentally benign conditions, which is a facile one-pot approach to α-ketoesters from commercially available acetophenones with alcohols, especially under metal-free conditions, with broad substrate scope. A possible mechanism is proposed on the basis of a series of control experiments and DMSO[18] isotopic labelling experiments.

Introduction

α-Ketoesters as an important and prevalent structural element of numerous biologically active molecules have attracted the considerable interest of chemists all over the world.[1] In addition to this biological application, α-ketoesters could also act as versatile synthetic precursors for further transformations in organic synthesis.[2]

Owing to these useful characters of α-ketoesters, the synthesis of α-ketoesters is a significant process and more and more novel synthetic methodologies have been developed. Traditionally, α-ketoesters could be generated from the esterification of α-ketoacyl halides and α-ketoacids,[3] oxidation of α-hydroxy esters,[4] double carbopalladative esterification[5] or some other methods.[6] Moreover, Jiao and co-workers reported two novel methodologies to α-ketoesters: (1) Cu-catalyzed aerobic oxidative dehydrogenative coupling of α-carbonyl aldehydes with alcohols;[7] (2) Cu-catalyzed aerobic oxidative C–C bond cleavage of ketones.[8] Sharada and co-workers developed an I_2-promoted cross-dehydrogenative coupling of α-carbonyl aldehydes with alcohols for the synthesis of α-ketoesters.[9] However, these methods mentioned above suffer from some drawbacks, such as (1) the usage of expensive or impractical starting materials; (2) harsh reaction conditions; (3) low atom economy, which restrict the utility of these methods. Relatively, acetophenones as commercially available and cheaper starting materials were applied universally to further transformations.[10] Transition-metal-catalyzed especially Cu-catalyzed aerobic oxidative esterification for the construction of α-ketoesters from acetophenones has been reported effectively in the last few years. For example, Jiao's group reported a TEMP and CuBr co-catalyzed oxygenation of acetophenones with O_2 to construct α-ketoesters.[11] Besides, Song's group reported a CuOTf catalyzed esterification of acetophenones with alcohols to α-ketoesters.[12] In the past decades, reactions under metal-free conditions are very popular and attract much attention in organic synthesis, such as I_2/TBHP (*tert*-butyl peroxybenzoate) system,[13] NIS (*N*-iodosuccinimide)/TBHP system[14] and I_2/IBX (2-iodoxybenzoic acid) system,[15] avoiding the usage of expensive, poisonous and air-sensitive metals or organometallics. Iodine, a popular available mild Lewis acid with less toxicity and low cost, is often chosen as an alternative of toxic rare metals and transition-metal catalysts in organic synthesis.[16] Previously, our group has reported an I_2-promoted aerobic oxidative coupling of acetophenes with amines to α-ketoamides under metal-free conditions.[17] Referring to relative literatures, there has no



Scheme 1 Facile one-pot approach to α-ketoesters from acetophenes under metal-free conditions.

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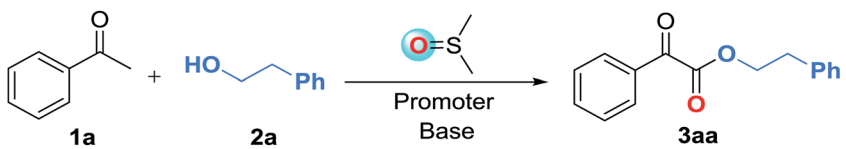
reported work on the synthesis of α-ketoesters under metal-free conditions from acetophenones so far. Herein, we wish to develop a feasible, effective and mild method to α-ketoesters from acetophenes, which is a novel methodology to α-ketoesters from acetophenones with alcohols under metal-free conditions with broad substrate scope, employing DMSO as both important oxidant and solvent (Scheme 1).

Results and discussion

Initially, this investigation focused on the optimization of the reaction conditions and a model reaction of acetophenone **1a** (0.5 mmol) and 2-phenylethanol **2a** (1.5 mmol) was carried out in the present of iodine as the promoter to screen a series of parameters. As listed in Table 1, effects of different oxidants on this reaction, such as *tert*-butyl hydroperoxide (TBHP), *tert*-butyl perbenzoate (TBPB), H_2O_2, dimethylsulfoxide (DMSO), $PhI(OAc)_2$ and molecular oxygen were examined under the model reaction in toluene at 50 °C, results showed that DMSO exhibited the highest reactivity to the reaction with 30% yield of the desired product **3aa** obtained (Table 1, entry 4). On this base, DMSO was examined to serve as both oxidant and solvent in the model reaction. Interestingly, a better yield of product **3aa** was obtained, demonstrating that it was actually feasible (Table 1, entry 7). Subsequently, when the model reaction was treated with a variety of bases, including inorganic and organic bases, Cs_2CO_3 exhibited the most positive effect with 68% yield of desired product isolated, while organic bases performed a little bit worse (Table 1, entry 8–12). To further improve the yield of product **3aa**, temperature of the reaction was raised to higher gradients, the best yield of 80% **3aa** was obtained at 110 °C (Table 1, entry 15). Next, different concentrations of iodine and Cs_2CO_3 were screened (Table 1, entry 17–22), the optimized reaction conditions were finally confirmed: **1a** (0.5 mmol), **2a** (1.5 mmol), 2.5 equivalents of iodine and 2.5 equivalents of Cs_2CO_3 were dissolved in 3 mL DMSO and stirred at 110 °C for 24 h, affording 89% yield of product **3aa** (Table 1, entry 21).

With the optimized reaction conditions in hands, we next probed the scope of synthesizing a series of α-ketoesters **3** applying optimized conditions and the results were summarized in Table 2. Firstly, acetophenones bearing both electron-deficient (–F, –Cl, $–NO_2$) or electron-rich substituents (–Me, –OMe) reacted well with 2-phenylethanol to produce corresponding α-ketoesters in moderate to excellent yields (Table 2, **3aa–3ia**). In addition to this feature, the results indicated that the position of these substituents on the aromatic groups had no obvious differences on the yields of corresponding products (Table 2, **3aa–3ia**). Some other aromatic rings and heterocyclic ring, such as 1-acetonaphthone, 2-acetonaphthone and 2-acetylthiophene, could also undergo the reaction with 2-

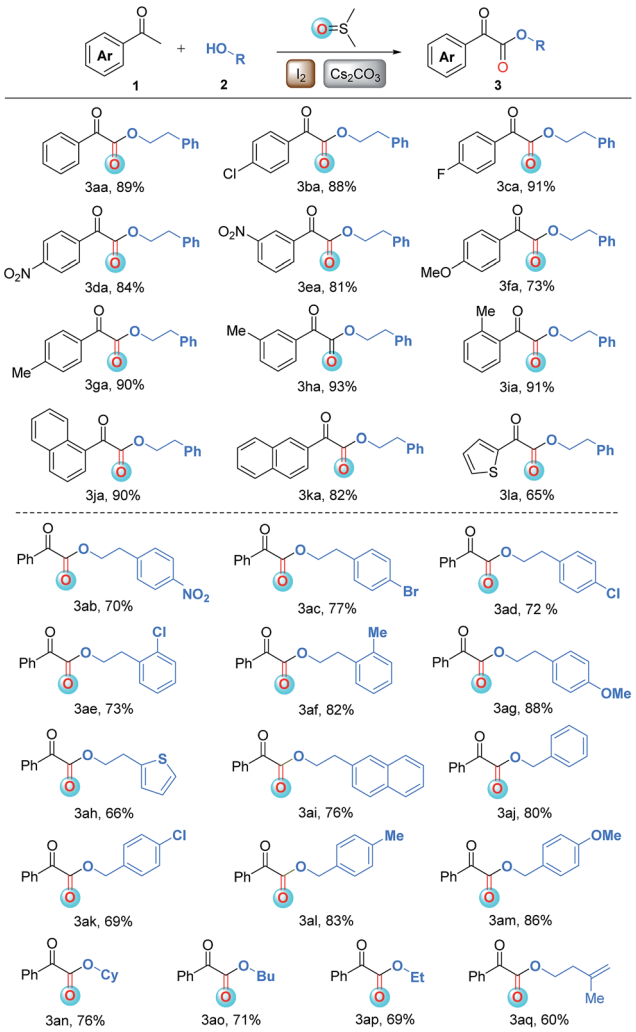
Table 1 Optimization studies of the model reaction conditions[a]



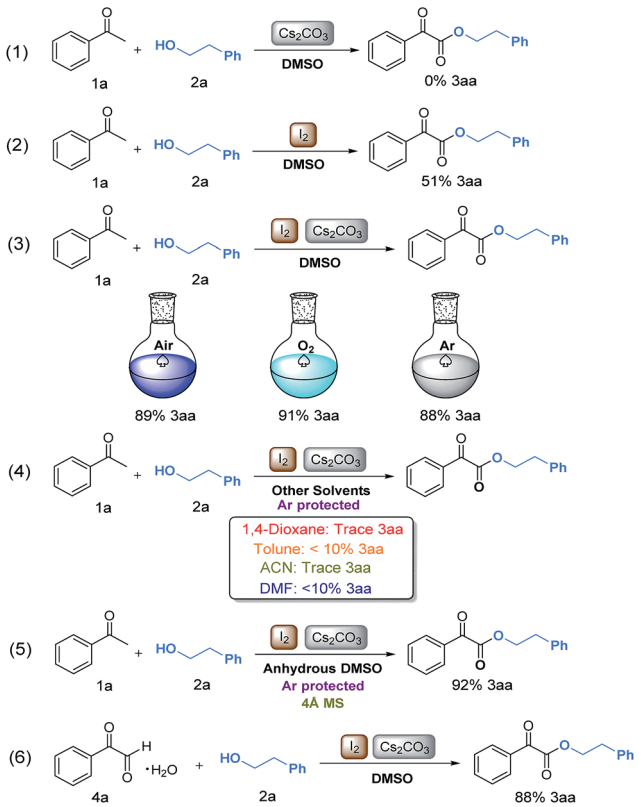
Entry	Promoter (equiv.)	Base (equiv.)	Oxidant	Solvent	Temp (°C)	Yield[b] (%)
1	I_2 (2.0)	—	TBHP	Toluene	50	13
2	I_2 (2.0)	—	TBPB	Toluene	50	15
3	I_2 (2.0)	—	H_2O_2	Toluene	50	<10
4	I_2 (2.0)	—	DMSO	Toluene	50	30
5	I_2 (2.0)	—	$PhI(OAc)_2$	Toluene	50	Trace
6	I_2 (2.0)	—	O_2	Toluene	50	<10
7	I_2 (2.0)	—	DMSO	—	50	44
8	I_2 (2.0)	K_2CO_3 (2.0)	DMSO	—	50	58
9	I_2 (2.0)	Cs_2CO_3 (2.0)	DMSO	—	50	68
10	I_2 (2.0)	Et_3N (2.0)	DMSO	—	50	Trace
11	I_2 (2.0)	DBU (2.0)	DMSO	—	50	49
12	I_2 (2.0)	Pyridine (2.0)	DMSO	—	50	52
13	I_2 (2.0)	Cs_2CO_3 (2.0)	DMSO	—	70	70
14	I_2 (2.0)	Cs_2CO_3 (2.0)	DMSO	—	90	74
15	I_2 (2.0)	Cs_2CO_3 (2.0)	DMSO	—	110	80
16	I_2 (2.0)	Cs_2CO_3 (2.0)	DMSO	—	130	75
17	I_2 (1.5)	Cs_2CO_3 (2.0)	DMSO	—	110	Trace
18	I_2 (2.5)	Cs_2CO_3 (2.0)	DMSO	—	110	84
19	I_2 (2.7)	Cs_2CO_3 (2.0)	DMSO	—	110	82
20	I_2 (2.5)	Cs_2CO_3 (1.5)	DMSO	—	110	57
21	I_2 (2.5)	Cs_2CO_3 (2.5)	DMSO	—	110	89
22	I_2 (2.5)	Cs_2CO_3 (3.0)	DMSO	—	110	33

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), promoter (2.0 equiv.), base (2.0 equiv.), oxidant (2.0 mmol) in 3 mL solvent, stirred at 50 °C for 24 h in the sealed tube. [b] Yields of the isolated product.

Table 2 Substrate scope of acetophenes with alcohols[a]



[a] Reaction conditions: acetophenes **1** (0.5 mmol), alcohols **2** (1.5 mmol), I_2 (1.25 mmol) and Cs_2CO_3 (1.25 mmol) solved in DMSO (3 mL) were stirred at 110 °C for 24 h in the sealed tube. Yields given for isolated products after chromatography.



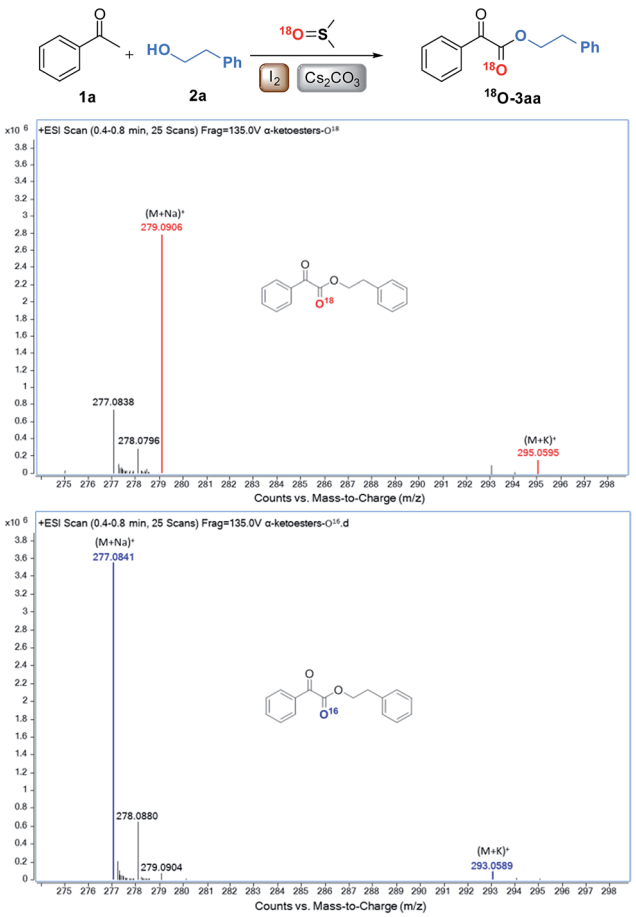
Scheme 2 Control experiments under optimized conditions.

phenylethanol to afford desired α-ketoesters **3ja**, **3ka** and **3la** in 92%, 82% and 65% yields, respectively. Aliphatic methyl ketones, such as acetone, cyclohexanone, and methylethylketone have been tested in our optimized reaction conditions. However, none of the desired products were observed. In order to further expand the universality under the optimized reaction conditions, the substrate scope of alcohols was explored, including aromatic and aliphatic alcohols. To our satisfaction, a range of 2-phenylethanols and phenylmethanols bearing different electronic variation substituents or substitution pattern were all suitable to optimized reaction conditions and produced the desired products in 69–88% yields (Table 2, **3ab**–**3am**). Notably, 2-thiopheneethanol as heteroaromatic ethanol could also be transformed to corresponding products **3ah** in 66% yield (Table 2, **3ah**). Besides, a variety of aliphatic alcohols were carried out under our optimized conditions. The results suggest that both primary and second aliphatic alcohols, such as cyclohexanol, *n*-butyl alcohol, ethanol and 3-methyl-3-butenol were all feasible and tolerated under this oxidative coupling reaction conditions with 60–76% yields of corresponding products obtained (Table 2, **3an**–**3aq**). According to the results of Table 2, this novel methodology to α-ketoesters has a board substrate scope with good yields, which implies its potential application in the last-stage functionalization of natural alcohols or some ketones with alcoholic hydroxyl group, such as cholesterol, androsterone, testosterone and the like.[18]

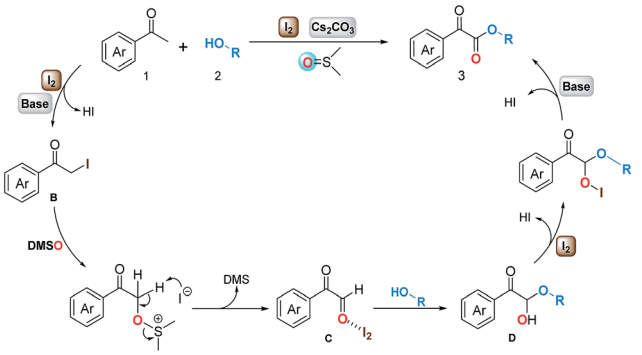
To gain deeper insight into the reaction mechanism and investigate the special role of DMSO, a series of control experiments were carried out between acetophenes **1a** and 2-phenylethanol **2a** under optimized reaction conditions (Scheme 2, experiments (1–6)). In the experiment (1), no desired product **3aa** was obtained when iodine was removed from optimized conditions. Meanwhile, the yield reduced greatly to 51% in the absence of Cs_2CO_3 (Scheme 2, experiment (2)). In the experiment (3), the parallel reactions were performed under air, O_2 and argon environment, affording similar yields of products respectively, demonstrating that aerobic conditions are not essential in this reaction process. Moreover, when the model reaction was performed in other solvents instead of DMSO, such as 1,4-dioxane, toluene, ACN and DMF, we failed to isolated the products **3aa** in an acceptable yield (Scheme 2, experiment (4)). For the purpose of ruling out the possible effect of water in the process, the same reaction was carried out in relatively dry and inert conditions with anhydrous DMSO and 4 Å MS added into the reaction conditions (experiment (5)). In

this case also, comparable yields of desired product **3aa** were observed. Next, the reaction between phenylglyoxal monohydrate **4a** and 2-phenylethanol **2a** were performed under optimized conditions as shown in experiment (6), the results showed that it could also be transformed smoothly to α-ketoesters **3aa** in 88% yield under optimized reaction conditions, indicating that phenylglyoxal monohydrate **4a** might act as the intermediate in this esterification process. Meanwhile, the results above obviously imply the significant role of DMSO in this reaction. Therefore, ^{18}O-labeled isotope experiment and ESI-MS analysis were conducted between acetophenone **1a** and 2-phenylethanol **2a** under optimized reaction conditions to further validate our conjecture (Scheme 3). When this reaction were carried out in ^{18}O-labeled DMSO replacing the general one, the ESI-MS analysis of this corresponding **^{18}O-3aa** product clearly assigned the presence of the signal $[M + Na]^+$ and $[M + K]^+$ at 279.0906 and 295.0595 in noticeable detection, proving that DMSO served as the important oxidant in this transformation.

Based on the results above and the previous literatures reported, a plausible mechanism is proposed as shown in Scheme 4. To begin with, compound **B** is generated from the iodination of arylmethylketone and then undergoes Kornblum oxidation in the presence of DMSO, affording the key intermediate arylglyoxal (compound **C**) with the release of DMS. Next, alcoholic



Scheme 3 ^{18}O-Labeled isotope experiment and ESI-MS analysis.



Scheme 4 Possible reaction mechanism.

hydroxyl group attacks the aldehyde group of α-carbonyl aldehyde that is activated by iodine to generate the alcohol (compound **D**), which is finally oxidized by the system of I_2 and base to give desired product α-ketoesters in good yields.

Conclusion

In conclusion, we have developed a novel one-pot strategy for the synthesis of functional and valuable α-ketoesters from acetophenones with alcohols in moderate to excellent yields. What's more, this facile methodology takes advantage of cheap and abundant starting materials under mildly metal-free conditions and has wide functional group universality, implying its potential value in industrialization and the last-stage functionalization of natural alcohols. Plausible mechanism was proposed based on a series of control experiments and DMSO^{18} isotopic labelling experiments. Further studies on the applications of this strategy are ongoing in our group.

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Notes and references

1 (*a*) M. Wessels, G. M. Konig and A. D. Wright, *J. Nat. Prod.*, 2001, **64**, 1556–1558; (*b*) G. Blay, I. Fernandez, M. C. Munoz, J. R. Pedro, A. Recuenco and C. Vila, *J. Org. Chem.*, 2011, **76**, 6286–6294; (*c*) Y. Nie, R. Xiao, Y. Xu and G. T. Montelione, *Org. Biomol. Chem.*, 2011, **9**, 4070–4078; (*d*) E. Sanchez-Larios, K. Thai, F. Bilodeau and M. Gravel, *Org. Lett.*, 2011, **13**, 4942–4945; (*e*) B. A. Boughton, L. Hor, J. A. Gerrard and C. A. Hutton, *Bioorg. Med. Chem.*, 2012, **20**, 2419–2426; (*f*) Y. Aoki, S. Tanimoto, D. Takahashi and K. Toshima, *Chem. Commun.*, 2013, **49**, 1169–1171.

2 (*a*) G. Blay, I. Fernandez, M. C. Munoz, J. R. Pedro, A. Recuenco and C. Vila, *J. Org. Chem.*, 2011, **76**, 6286–

6294; (*b*) M. Hayashi and S. Nakamura, *Angew. Chem., Int. Ed.*, 2011, **50**, 2249–2252; (*c*) E. Sanchez-Larios, K. Thai, F. Bilodeau and M. Gravel, *Org. Lett.*, 2011, **13**, 4942–4945; (*d*) B. A. Boughton, L. Hor, J. A. Gerrard and C. A. Hutton, *Bioorg. Med. Chem.*, 2012, **20**, 2419–2426; (*e*) B. Eftekhari-Sis and M. Zirak, *Chem. Rev.*, 2015, **115**, 151–264; (*f*) W. Zhao, P. K. Yan and A. T. Radosevich, *J. Am. Chem. Soc.*, 2015, **137**, 616–619.

3 (*a*) M. V. Dealmeida, D. H. R. Barton, I. Bytheway, J. A. Ferreira, M. B. Hall, W. S. Liu, D. K. Taylor and L. Thomson, *J. Am. Chem. Soc.*, 1995, **117**, 4870–4874; (*b*) P. Wipf and C. R. J. Stephenson, *Org. Lett.*, 2003, **5**, 2449–2452; (*c*) A. Bacchi, M. Costa, N. D. Ca, B. Gabriele, G. Salerno and S. Cassoni, *J. Am. Chem. Soc.*, 2005, **70**, 4971–4979.

4 (*a*) M. Tanaka, T. Kobayashi and T. Sakakura, *Angew. Chem., Int. Ed.*, 1984, **23**, 518–518; (*b*) F. Ozawa, N. Kawasaki, T. Yamamoto and A. Yamamoto, *Chem. Lett.*, 1985, **5**, 567–570; (*c*) T. Sakakura, H. Yamashita, T. Kobayashi, T. Hayashi and M. Tanaka, *J. Org. Chem.*, 1987, **52**, 5733–5740; (*d*) E. V. Johnston, E. A. Karlsson, L.-H. Tran, B. Akermark and J.-E. Backvall, *Eur. J. Org. Chem.*, 2010, **10**, 1971–1976.

5 (*a*) R. Hosseinzadeh, M. Mohadjerani, M. Tajbakhsh and M. Nouzarian, *Synth. Commun.*, 2011, **41**, 1725–1732; (*b*) S. R. Reddy, S. Stella and A. Chadha, *Synth. Commun.*, 2012, **42**, 3493.

6 (*a*) K. C. Nicolaou, Q. Kang, T. R. Wu, C. S. Lim and D. Y. K. Chen, *J. Am. Chem. Soc.*, 2010, **132**, 7540–7548; (*b*) M. Hayashi and S. Nakamura, *Angew. Chem., Int. Ed.*, 2011, **50**, 2249–2252; (*c*) C. G. Screttas, B. R. Steele, M. Micha-Screttas and G. A. Heropoulos, *Org. Lett.*, 2012, **14**, 5680–5683.

7 C. Zhang and N. Jiao, *Org. Chem. Front.*, 2014, **1**, 109–112.

8 C. Zhang, P. Feng and N. Jiao, *J. Am. Chem. Soc.*, 2013, **135**, 15257–15262.

9 A. Sagar, S. Vidyacharan and D. S. Sharada, *RSC Adv.*, 2014, **4**, 37047–37050.

10 (*a*) F.-T. Du and J.-X. Ji, *Chem. Sci.*, 2012, **3**, 460–465; (*b*) W. Wei, Y. Shao, H. Hu, F. Zhang, C. Zhang, Y. Xu and X. Wan, *J. Org. Chem.*, 2012, **77**, 7157–7165; (*c*) X. Wu, Q. Gao, S. Liu and A. Wu, *Org. Lett.*, 2014, **16**, 2888–2891; (*d*) Q. Gao, J. Zhang, X. Wu, S. Liu and A. Wu, *Org. Lett.*, 2015, **17**, 134–137.

11 X. Q. Huang, X. W. Li, M. C. Zou, J. Pan and N. Jiao, *Org. Chem. Front.*, 2015, **2**, 354–359.

12 X. Xu, W. Ding, Y. Lin and Q. Song, *Org. Lett.*, 2015, **17**, 516–519.

13 (*a*) M. Lamani and K. R. Prabhu, *J. Org. Chem.*, 2011, **76**, 7938–7944; (*b*) Y. Yan and Z. Wang, *Chem. Commun.*, 2011, **47**, 9513–9515; (*c*) X. Zhang and L. Wang, *Green Chem.*, 2012, **14**, 2141–2145.

14 M. Lamani and K. R. Prabhu, *Chem.–Eur. J.*, 2012, **18**, 14638–14642.

15 S. Dutta, S. S. Kotha and G. Sekar, *RSC Adv.*, 2015, **5**, 47265–47269.

16 (*a*) M. Uyanik and K. Ishihara, *Chem. Commun.*, 2009, 2086–2099; (*b*) P. T. Parvatkar, P. S. Parameswaran and S. G. Tilve, *Chem.–Eur. J.*, 2012, **18**, 5460–5489; (*c*) P. Finkbeiner and B. J. Nachtsheim, *Synthesis*, 2013, **45**, 979–999; (*d*) S. Pal, M. N. Khan, S. Karamthulla and L. H. Choudhury, *RSC Adv.*, 2013, **3**, 15705–15711.

17 S. Guo, Z. Fang, Z. Yang, C. Liu, Z. Dai, L. Zhao and K. Guo, *RSC Adv.*, 2016, **6**, 1503–1507.

18 (*a*) E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker and T. Ritter, *Science*, 2011, **334**, 639–642; (*b*) T. Kang, Y. Kim, D. Lee, Z. Wang and S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 4141–4144; (*c*) S. H. Oh, Y. R. Malpani, N. Ha, Y.-S. Jung and S. B. Han, *Org. Lett.*, 2014, **16**, 1310–1313.

