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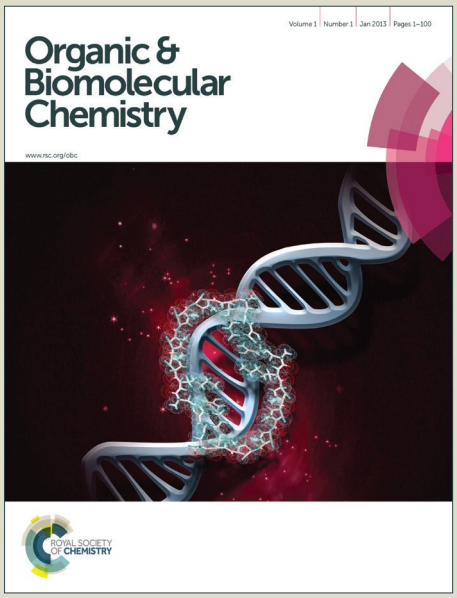

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Synthesis of 1,3,5-Triazines via $Cu(OAc)_2$-Catalyzed Aerobic Oxidative Coupling of Alcohols and Amidine hydrochlorides

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Abstract: $Cu(OAc)_2$ was found to be an efficient catalyst for dehydrogenative synthesis of 1,3,5-triazine derivatives via oxidative coupling reaction of amidine hydrochlorides and alcohols in air. Both aromatic and aliphatic alcohols can be involved in and thirty-three products were obtained with good to excellent yields. Moreover, the use of ligand, strong base and organic oxidant is unnecessary.

Introduction

1,3,5-triazines are very important skeletons of many biologically active compounds, such as herbicides, insecticides, fungicides, anticarcinogens and antivirals (Figure 1).[1] In addition, they are also widely used as organic dyestuff, liquid crystal, flourescent brightener, electroluminescent materials, gas generating agent, solid propellant and pyrotechnics.[2–3] In the past decades, a few approaches, including transition metal-catalyzed coupling reaction of halogenated 1,3,5-triazines,[4] the cycotrimerizations of nitriles[5] and multicomponent reaction of cyanamid, 1,2,4-triazole and triethyl orthoformate have been developed for the synthesis of 1,3,5-triazine derivatives.[6] Alternatively, these compounds were also obtained through the pathways based on the use of available amidines as substrates, for example, domino heterocyclization of isothiocyanates with aryl amidines,[7] cesium carbonate-promoted cyclodehydrogenation of amidine hydrochloride with aromatic aldehyde.[8] However, these methods suffer from limitations of operating difficulties or tough reaction conditions involving strong base, microwave, noble metal catalyst and organic oxidant. Recently, Zhang et al. reported new strategies for the synthesis of 2,4,6-triaryl-1,3,5-triazines based on ruthenium-catalyzed reaction of aryl methanols and amidines.[9] The disadvantages of the strategy lies in noble metal ruthenium-based catalysts and limitation of substrate suitability. As a result, more robust and efficient method for the synthesis of 1,3,5-triazine is still extremely in demand, especially involving the synthesis carried out under gentle conditions with inexpensive catalysts.

Copper catalysts with features of low cost and environmental friendliness were frequently utilized to synthesize novel heterocyclic compounds.[10–12] For example, Nagasawa et al. have reported that $Cu(OTf)_2$ exhibited impressive catalytic ability in intramolecular oxidative C–N coupling reaction and

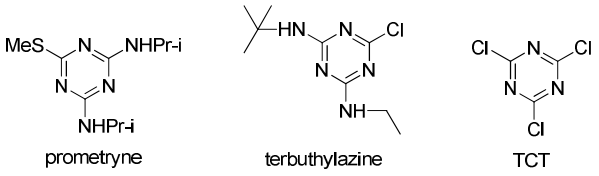
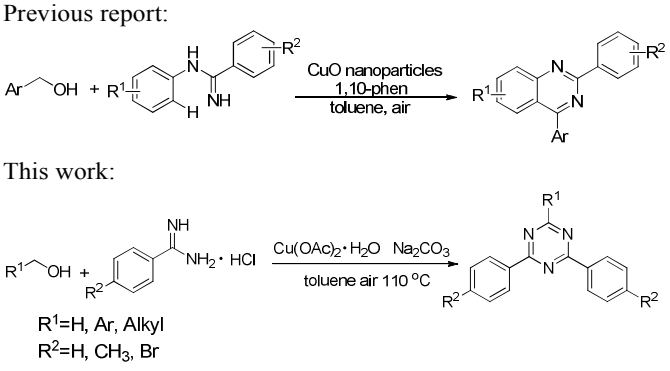


Figure 1. Parts of Products of 1,3,5-Triazines



Scheme 1. Synthesis of 1,3,5-Triazines

intermolecular amino cyclization.[13] Our previous findings also showed that copper-based catalysts are attractive in the catalytic formation of carbon–heteroatom bonds (Scheme 1).[14] Herein, we report the synthesis of 1,3,5-triazine derivatives directly by oxidative coupling of amidine hydrochlorides and alcohols in air with $Cu(OAc)_2$ as a catalyst. Compared with the relevant reported reactions for the synthesis of 1,3,5-triazine derivative,[8,9] our method is more efficient as evidenced by the fact that both aryl methanols and alkyl alcohols are utilizable as starting reactants in the oxidative coupling reaction.

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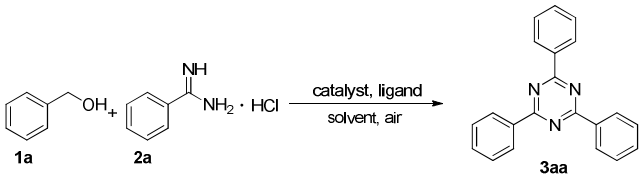
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol%)	ligand	solvent	base	yield (%)[b]
1	nanoCuO (5)	Phen	toluene	K_2CO_3	85
2	$CuCl_2$ (10)	Phen	toluene	K_2CO_3	75
3	$Cu(NO_3)_2$ (10)	Phen	toluene	K_2CO_3	70
4	$Cu(OAc)_2$ (10)	Phen	toluene	K_2CO_3	88
5	$Cu(acac)_2$ (10)	Phen	toluene	K_2CO_3	80
6	$Cu(OTf)_2$ (10)	Phen	toluene	K_2CO_3	85
7	$Cu(OAc)_2$ (5)	Phen	toluene	K_2CO_3	60
8	$Cu(OAc)_2$ (15)	Phen	toluene	K_2CO_3	89
9	$Cu(OAc)_2$ (10)	–	toluene	K_2CO_3	88
10	$Cu(OAc)_2$ (10)	–	toluene	$NaHCO_3$	87
11	$Cu(OAc)_2$ (10)	_	toluene	Na_2CO_3	88
12	$Cu(OAc)_2$ (10)	_	toluene	_	_
13	$Cu(OAc)_2$ (10)	_	DMF	Na_2CO_3	45
14	$Cu(OAc)_2$ (10)	_	DMSO	Na_2CO_3	55
15[c]	$Cu(OAc)_2$ (10)	_	toluene	Na_2CO_3	30
16[d]	$Cu(OAc)_2$ (10)	_	toluene	Na_2CO_3	60
17[e]	$Cu(OAc)_2$ (10)	_	toluene	Na_2CO_3	55
18[f]	$Cu(OAc)_2$ (10)	_	toluene	Na_2CO_3	70
19[g]	$Cu(OAc)_2$ (10)	_	toluene	Na_2CO_3	80

[a]Reaction conditions: benzamidine hydrochloride (1 mmol), benzyl alcohol (0.6 mmol), $Cu(OAc)_2$ (10 mol %), Na_2CO_3 (1 mmol), toluene (2.5 mL) under reflux in air for 24 h. [b]Isolated yield. Reaction temperature: [c]80 °C, [d]100 °C. Reaction time: [e]6 h, [f]12 h, [g]18 h.

Results and discussion

We started with the optimization of the oxidative coupling conditions exploiting benzyl alcohol (**1a**) and benzamidine hydrochloride (**2a**) as the model substrates. The results obtained from screening of the copper catalysts, ligands and solvents are summarized in Table 1. Given efficient catalytic activity and good recyclability of CuO nanoparticles,[15] they were evaluated in the first place and the result indicates that the reaction of **1a** with **2a** in the presence of 5 mol% of CuO nanoparticles at 110 °C for 24 h in toluene affords the production of 2,4,6-triphenyl-1,3,5-triazine (**3aa**) in 85% yield (Table 1, entry 1). However, the transformation of CuO nanoparticles into Cu(II) in the reaction limits their further uses. Therefore, different copper catalysts such as $CuCl_2$, $Cu(NO_3)_2$, $Cu(OAc)_2$, $Cu(OTf)_2$ and $Cu(acac)_2$ were detected, and $Cu(OAc)_2$ stood out from the rest with 88% yield (Table 1, entries 2–6). Decreasing the amount of catalyst to 5% resulted in much lower yield (Table 1, entry 7). Increasing the amount of catalyst to 15% resulted in slightly higher yield (Table 1, entry 8). To our delight, we discovered that none of ligand wasnecessary (Table 1, entry 9). The yields of reactions performed in the presence of different bases such as $NaHCO_3$, K_2CO_3 and Na_2CO_3 are essentially the same (Table 1, entries 9–11). Notably, base plays a vital role in the oxidative coupling reaction as the reaction cannot proceed without it (Table 1, entry 12). Na_2CO_3 was selected as base in the following due to its moderate basic strength and low-cost. Unfortunately, yields decreased remarkablly when DMF and DMSO were used as solvents, and a new product was detected (Table 1, entries 13 and 14). Lowering temperature to 80 °C, the yield reduced rapidly (Table 1, entries 15 and 16). With the reduction of reaction time to 18, 12 and 6 h, reduced yields of 80%, 70% and 55% were obtained, respectively (Table 1, entries 17–19).

With the optimized reaction conditions presented in entry 11 of Table 1 in hand, a variety of primary alcohols and amidine hydrochlorides with different substituents were exploited as starting reactants to the synthesis of 1,3,5-triazine derivatives, and representative results are listed in Figure 2. Several functional groups, such as methoxy, chloro, fluoro and nitro were well-tolerated. No significant substitute effect was observed on aromatic alcohols, excellent yields were obtained for alcohols with both electron-donating and electron-withdrawing substituents on the para-position of aryl ring (Figure 2, **3ba, 3ea, 3ha, 3ia, 3la** and **3ma**). Relatively, low yields were obtained when alcohols were substituted with electron-withdrawing substituents such as Br and NO_2, for example, the presence of a nitro group reduced yield to 46% (Figure 2, **3ja** and **3ka**). Besides, the steric hindrance has obvious effect on the reaction. For example, when methyl substituted benzyl alcohols were used, *para* and *meta* substituted substances gave higher yields than those with *ortho* substituents (Figure 2, **3ea, 3fa** and **3ga**). Apparent substitute effect was observed on amidine hydrochlorides. The reaction favored **1** with both 4-methylbenzamidine hydrochloride **2b** and 4-(trifluoromethyl)benzamidine hydrochloride **2d,** afforded 1,3,5-triazines in excellent yields (Figure 2, **3ab**–**3mb**, **3ad**, **3bd** and **3id**), while **2c** with 4-Br on the phenyl ring led to 1,3,5-triazines in moderate yields (Figure 2, **3ic** and **3lc**). To our delight, good results were obtained as primary aliphatic alcohols such as methanol, ethanol, n-butyl alcohol and

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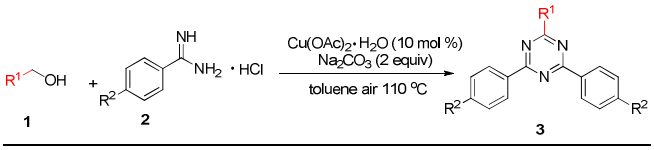
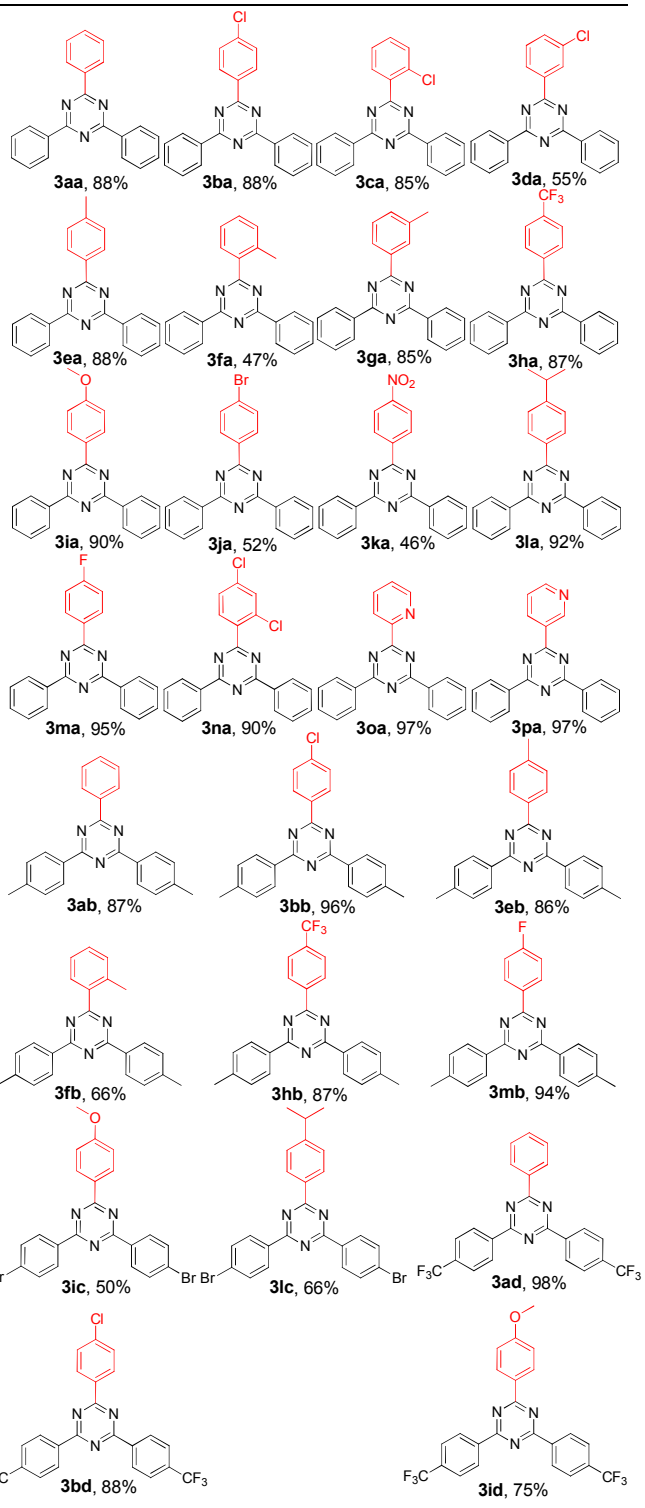
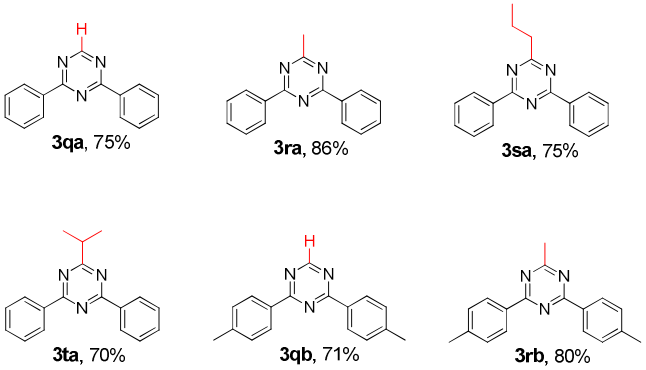




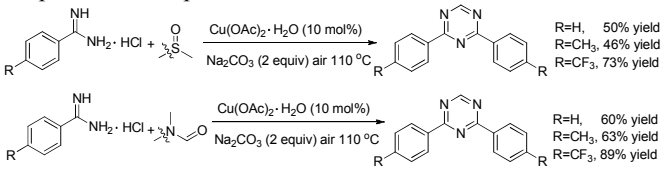


[a]Reaction conditions: benzamidine hydrochloride (1 mmol), benzyl alcohol (0.6 mmol), $Cu(OAc)_2$ (10 mol %), Na_2CO_3 (1 mmol), toluene (2.5 mL) under reflux in air for 24 h.

Figure 2. Scope of the Synthesis of 1,3,5-Triazines[a]

isobutanol were tested (Figure 2, **3qa–3ta, 3qb** and **3rb**). In addition, isopropyl alcohol and sec-butyl alcohol were tested successively and the results showed that **3ra** are the majorproduct, in accordance with the product from ethanol. However, the reaction of alkyl amidines such as acetamidine with benzylic alcohol failed to yield the desired product may be due to its boiling point was lower than our reaction temperature[16].

Furthermore, the reaction between benzamidine hydrochlorides (**2a** and **2b**) and DMF (or DMSO) was investigated respectively (Scheme 2). The results showed that **3qa**, **3qb** and 2,4-bis(4-(trifluoromethyl)phenyl)-1,3,5-triazine were obtained in good to excellent yields via aerobic copper-catalyzed cyclization of amidines with DMF or DMSO, a one-carbon supplier. Comparing with Zhang's report about CuI-catalyzed reaction of amidine with DMF in oxygen,[17] more straight and simple route was presented.



Scheme 2. Formation of 1,3,5-Triazines from DMSO/DMF and Benzamidine hydrochlorides

On the basis of great progress about metal catalyzed dehydrogenation formation of aldehyde from alcohol,[18] a possible pathway for the formation of 2,4,6-trisubstituted-1,3,5-triazines was proposed (Scheme 3). Initially, aldehyde was formed by $Cu(OAc)_2$ catalyzed alcohol oxidation in air.[18a] Then, the reaction of aldehyde and amidine was initiated and promoted by $Cu(OAc)_2$ and air oxidation, giving rise to 1,3,5-triazines. The role of base is to neutralize hydrochloride of the amidine. The mechanism of the reaction is similar to that reported in the literature.[8,9]

Conclusions

In summary, an efficient and simple method for the preparation

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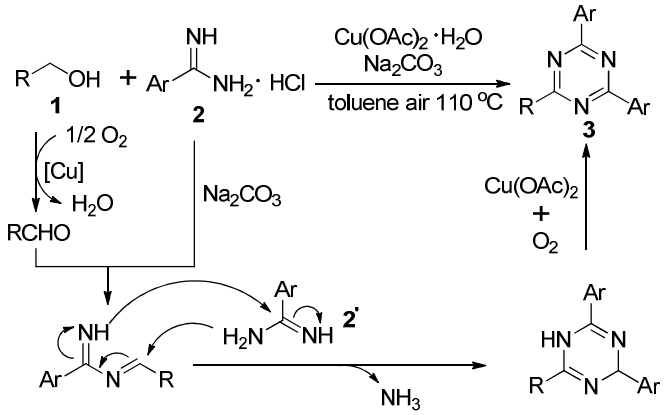

Scheme 3. Plausible Mechanism for synthesis of 1,3,5-Triazine

of 1,3,5-triazine derivatives has been successfully developed based on direct oxidizing coupling reaction between benzamidine hydrochlorides and alcohols exploiting $Cu(OAc)_2$ as catalyst. The obvious benefit of this approach is its tolerance to a broad range of both aromatic and fatty alcohols. In addition, the facile reaction atmosphere of air and no need of ligands make this approach highly practical for industrial manufacture. Further studies for the construction of diverse heterocyclic compounds relying on present strategy are ongoing in our lab.

Acknowledgements

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Experimental

General information

All starting materials and reagents were commercially available and used directly without further purification. All known products gave satisfactory analytical data by NMR spectra, which corresponding to the reported literature values. Unknown compounds were confirmed by HRMS additionally. NMR spectra were determined at room temperature on Bruker Avance-300 or Bruker Avance-500 at 300 MHz or 500 MHz with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ relative to TMS, the coupling constants J are given in Hz. High-resolution mass spectral (HRMS) were obtained using APCI, ESI or EI in positive mode.

Typical experimental procedure for the synthesis of 3

A mixture of alcohol **1** (0.6 mmol), amidine hydrochloride **2** (1.0 mmol), $NaCO_3$ (1.0 mmol, 1.0 equiv) and $Cu(OAc)_2$ (10 mol %) was stirred in toluene (2.5 mL) under reflux in air for 24 h. The resulting mixture was cooled to room temperature and then extracted it for several times with EtOAc (10 mL) and brine (5 mL). The organic phases were combined and dried with anhydrous Na_2SO_4 and evaporated under vacuum. The crude product was purified by column chromatography on silica gel using petroleum ether/EtOAc (100:1) as an eluent to give the corresponding products **3aa**–**3rb**.

Notes and references

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† Electronic Supplementary Information (ESI) available: Catalyst characterization, analytic data, images of ^1H and ^{13}C NMR of all products and other electronic format. See DOI: 10.1039/b000000x/

1 (a) Z. Brzozowski, F. Saczewski and M. Gdaniec, *Eur. J. Med. Chem*, 2000, **35**, 1053-1064; (b) F. Saczewski, A. Bulakowska and P. Bednarski, *Eur. J. Med. Chem*, 2006, **41**, 219-225; (c) R. Menicagli, S. Samaritani and G. Signore, *J. Med. Chem*, 2004, **47**, 4649-4652; (d) A. Kumar, K. Srivastava and P. M. S. Chauhan, *Bioorg. Med. Chem. Lett*, 2008, **18**, 6530-6533; (e) K. Srinivas, U. Srinivas and K. Bhanuprakash, *Eur. J. Med. Chem*, 2006, **41**, 1240-1246; (f) V. Garaj, L. Puccetti and G. Fasolis, *Bioorg. Med. Chem. Lett*, 2005, **15**, 3102-3108.

2 (a) T. Konstantinova and P. Petrova, *Dyes and Pigments*, 2002, **52**, 115-120; (b) S. Um, Y.H. Kang and J. K. Lee, *Dyes and Pigments*, 2007, **75**, 681-686; (c) A. Garcia, B. Insuasty and N. Martin, *Org. Lett*, 2009, **13**, 5398-5401; (d) A. P. Melissaris and J. A. Mikroyannidis, *Polymer bulletin (Burlin)*, 1987, **18**, 1-8.

3 (a) C. F. Ye, H. X. Gao, J. A. Boatz and J. M. Shreeve, *Angew. Chem. Int. Ed*, 2006, **45**, 7262-7265; (b) A. Hammerl, T. M. Klapotke and R. Rocha, *Eur. J. Inor. Chem*, 2006, **16**, 2210-2228; (c) K. Banerk, Y. Joo and T. Ruffer, *Angew. Chem. Int. Ed*, 2007, **46**, 1168-1171; (d) A. Fischer, M. Antonietti and A. Thomas, *Adv. Mater*, 2007, **19**, 264-267.

4 (a) D. Janietz and M. Bauer, *Synthesis*, 1993, **1**, 33-34; (b) A. L. Isfahani, M. B. Iraj, V. Mirkhani, M. Moghadam, S. Tangestaninejad and R. Kia, *Adv. Synth. Catal*, 2013, **355**, 957-972.

5 F. Xu, J. H. Sun, H. B. Yan and Q. Shen, *Synthetic Communications*, 2000, **30**, 1017-1022.

6 A. V. Dolzhenko, S. A. Kalinina and D. V. Kalinin, *RSC Adv*, 2013, **3**, 15850-15855.

7 N. Li, M. S. Tu, B. Jiang, X. Wang and S. J. Tu, *Tetrahedron Letters*, 2013, **54**, 1743-1746.

8 S. Biswas and S. Batra, *Eur. J. Org. Chem*, 2012, **18**, 3492-3499.

9 F. Xie, M. M. Chen, X. T. Wang, H. F. Jiang and M. Zhang, *Org. Biomol. Chem*, 2014, **12**, 2761-2768.

10 (a) Y. X. Jia and E. P. Kündig, *Angew. Chem. Int. Ed*, 2009, **48**, 1636-1639; (b) G. Brasche and S. L. Buchwald, *Angew. Chem. Int. Ed*, 2008, **47**, 1932-1934; (c) H. G. Wang, Y. Wang, D. D. Liang, L. Y. Liu, J. C. Zhang and Q. Zhu, *Angew. Chem. Int. Ed*, 2011, **50**, 5678-5681; (d) A. Perry and R. J. K. Taylor, *Chem. Commun*, 2009, **22**, 3249-3251.

11 (a) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev*, 2013, **113**, 6234-6458; (b) S. R. Chemler, *Science*, 2013, **341**, 624-626; (c) L. Zhang, G. Y. Ang and S. Chiba, *Org. Lett*, 2010, **12**, 3682-3685; (d) J. E. M. N. Klein, A. Perry, D. S. Pugh and R. J. K. Taylor, *Org. Lett*, 2010, **12**, 3446-3449; (e) G.

View Article Online
DOI: 10.1039/C5OB00724K

Gangadhararao, A. Uruvakilli and K. C. K. Swamy, *Org. Lett*, 2014, **16**, 6060-6063; (f) X. L. Pang, C. Chen, X. Su, M. Li and L. R. Wen, *Org. Lett*, 2014, **16**, 6228-6231.

12 (a) B. X. Tang, R. J. Song, C. Y. Wu, Y. Liu and J. H. Li, *J. Am. Chem. Soc*, 2010, **132**, 8900-8902; (b) Y. M. Li, Y. H. Xie, R. Zhang, K. Jin, X. N. Wang and C. Y. Duan, *J. Org. Chem*, 2011, **76**, 5444-5449; (c) M. Y. Li, Y. Xie, Y. Ye, Y. Zou, H. H. Jiang and W. Zeng, *Org.Lett*, 2014, **16**, 6232-6235; (d) Y. H. Lv, Y. Li, T. Xiong, W. Y. Pu, H. W. Zhang and Q. Zhang, *Chem. Commun*, 2013, **49**, 6439-6441.

13 (a) S. Ueda and H. Nagasawa, *Angew. Chem. Int. Ed*, 2008, **47**, 6411-6413; (b) S. Ueda and H. Nagasawa, *J. Am. Chem. Soc*, 2009, **131**, 15080-15081.

14 (a) W. Zhang, F. Guo, F. Wang, N. Zhao, L. Liu, J. Li and Z. H. Wang, *Org. Biomol. Chem*, 2014, **12**, 5752-5756; (b) N. Zhao, L. Liu, F. Wang, J. Li and W. Zhang, *Adv. Synth. Catal*, 2014, **356**, 2575-2579.

15 (a) S. Jammi, S. Sakthivel, L. Rout, T. Mukherjee, S. Mandal and T. Punniyamurthy, *J. Org. Chem*, 2009, **74**, 1971-1976; (b) S. G. Babu and R. Karvembu, *Ind. Eng. Chem. Res*, 2011, **50**, 9594-9600; (c) L. Rout, S. Jammi and T. Punniyamurthy, *Org. Lett*, 2007, **9**, 3397-3399.

16 F. C. Schaefer, *J. Org. Chem*. **1962**, *27*, 3608-3613.

17 X. W. Xu, M. Zhang, H. F. Jiang, J. Zheng and Y. Q. Li, *Org. Lett*, 2014, **16**, 3540-3543.

18 (a) S. H. Liao, K. K. Yu, Q. Li, H. W. Tian, Z. P. Zhang, X. C. Yu, Q. Xu, *Org. Biomol. Chem*, 2012, **10**, 2973-2978; (b) S. S. Shen, V. Kartika, Y. S. Tan, R. D. Webster and K. Narasaka, *Tetrahedron Letters*, 2012, **53**, 986-990; (c) I. A. Ansari and R. Gree, *Org. Lett*, 2002, **4**, 1507-1509; (d) A. Martinez-Asencio, D. J. Ramon and M. Yus, *Tetrahedron*, 2011, **67**, 3140-3149; (e) S. Velusamy, A. Srinivasan and T. Punniyamurthy, *Tetrahedron Letters*, 2006, **47**, 923-926; (f) M. Herbert, F. Montilla and A. Galindo, *Dalton Trans*, 2010, **39**, 900-907; (g) L. Liang, G. D. Rao, H. L. Sun and J. L. Zhang, *Adv.Synth. Catal*, 2010, **352**, 2371-2377.