Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

ARTICLE

Copper-catalysed intramolecular *O*-arylation: a simple and efficient method for benzoxazoles synthesis

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Fengtian Wu, Jie Zhang, Qianbing Wei, Ping Liu, Jianwei Xie*, Haojie Jiang and Bin Dai

A wide range of 2-substituted benzoxazoles could be efficiently synthesized from the *N*-(2-iodo-/bromo-phenyl)benzamides, even less reactive *N*-(2-chlorophenyl)benzamides *via* Cu-catalysed intramolecular coupling cyclization using methyl 2-methoxybenzoate as the ligand under mild reaction conditions. In addition, the benzoxazoles are well prepared from the primary amides coupling with the *o*-dihalobenzene in a single step.

Introduction

Benzoxazole motifs not only exist in several important natural products[1] but also are important subunits of many compounds due to their efficient biological and pharmaceutical activities (Fig. 1),[2] some of which with the recent application include antitumor agents,[2a-2d] HIV reverse transcriptase inhibitors,[2e,f] cathepsin S inhibitors,[2g] 5-HT_3 receptor partial agonists,[2h] DNA topoisomerase inhibitors,[2i] peroxisome proliferator-activated receptor γ (PPARγ) antagonists,[2j] estrogen receptor-β agonists[2k] and epifluorescence excitation ratio imaging agents.[2l] Consequently, their preparation has attracted considerable attention. Classical methods for the construction of benzoxazole ring system involve the condensation of *ortho*-aminophenol with either carboxylic acid or aldehydes,[3] which unfortunately often suffered from harsh reaction conditions such as strong acids in combination with high temperature. Recently, some of these drawbacks have been overcome by the development of transition-metal-catalysed intramolecular *O*-arylation of *ortho*-haloanilides under comparatively milder reaction conditions. For example, several copper-based catalytic systems have been used for intramolecular *O*-arylation of *N*-(2-halophenyl)-benzamides, which provided a straight forward route for the synthesis of functionalized benzoxazoles frameworks.[4] At the same time, iron[5] and cobalt[6] were employed as the catalyst for the cyclization of *N*-(2-bromo- or iodo-phenyl)benzamides to provide 2-arylbenzoxazoles. Transition-metal-catalyst free direct base-mediated intramolecular C-O couplings have also been demonstrated, but with relatively high reaction temperature.[7] Although significant improvements have been achieved for the synthesis of benzoxazoles from *N*-(2-halophenyl)benzamides through intramolecular C-O bond formation, there is still a need to develop a generally efficient catalytic system for this class of reaction.

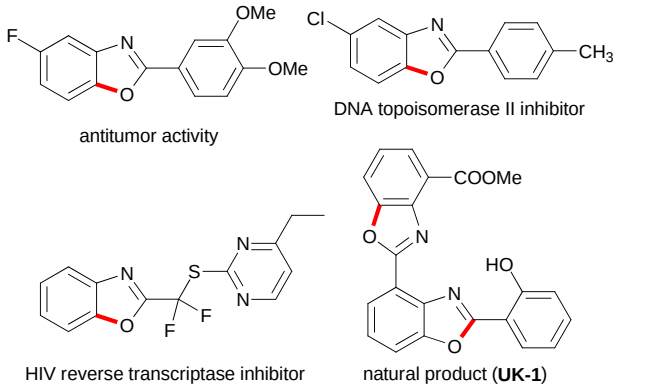


Fig. 1 Examples of biologically and pharmaceutically active compounds.

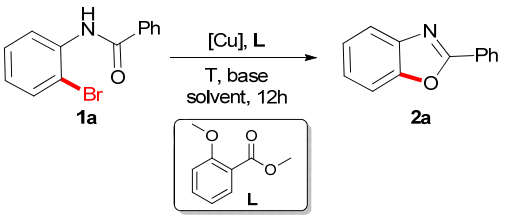
Previously, we have reported a typical Ullmann-type C-N coupling reaction in water using $CuSO_4$ as the catalyst and 2-hydroxybenzohydrazides as the ligands.[8] In order to explore the scope of the catalytic system to other types of coupling reactions, we have carried out a set of experiments to test all the ligands activities for copper-based intramolecular *O*-arylation of *N*-(2-bromophenyl)benzamides. In surprise, methyl 2-methoxybenzoate, an intermediate for 2-hydroxybenzohydrazides synthesis, showed the highest activity (ESI†). To further check the catalytic activity, we undertook studies to evaluate copper-based cyclization of *N*-(2-halophenyl)-benzamides using methyl 2-methoxybenzoate as the ligand. Herein, we wish to report our results.

Results and discussion

In preliminary studies, the optimized reaction conditions were carried out with *N*-(2-bromophenyl)benzamide as a model substrate using different copper sources, bases and solvents at

varied temperature, and the results were summarised in Table 1. Several copper catalysts containing CuI, CuBr, CuCl, Cu_2O, CuO and $CuSO_4$ were tested by using methyl 2-methoxybenzoate as the ligand, KOH as the base in DMF at 90°C for 12 h, and CuI was found to be the best one (entries 1-6). Carrying out the reaction in the absent of copper catalyst resulted in no product, whereas only 15% yield of the product obtained without ligand (entries 7 and 8). Screening the bases of K_2CO_3, K_3PO_4 and Cs_2CO_3, potassium phosphate was turned out to be the best choice in terms of isolated yield (entries 9-11). Also the use of DMF is superior to other solvents, such as DMSO, 1,4-dioxane and toluene (entries 12-14). Lowering reaction temperature from 90 °C to 80 °C led to a dramatically decrease of the yield, whereas raising the reaction temperature from 90 °C to 110 °C only led to a slight increase of the yield (entries 15 and 16). In addition, decreasing the catalyst loading from 10 mol% to 5 mol%, only 55% yield was obtained (entry 17). In summary, the optimal conditions for the intramolecular coupling cyclization of *N*-(2-bromophenyl)benzamide consist of the combination of CuI (10 mol%), ligand (20 mol%), K_3PO_4 (2 equiv) in DMF (1 mL) at 90°C for 12 h.

Table 1 Screening reaction conditions for the synthesis of 2-phenyl-benzoxazole[a]



Entry	[Cu]	Base	Solvent	T (°C)	Yield[b] (%)
1	CuI	KOH	DMF	90	40
2	CuBr	KOH	DMF	90	29
3	CuCl	KOH	DMF	90	28
4	Cu_2O	KOH	DMF	90	19
5	CuO	KOH	DMF	90	0
6	$CuSO_4$	KOH	DMF	90	36
7	-	KOH	DMF	90	0
8	CuI	KOH	DMF	90	15[c]
9	CuI	K_2CO_3	DMF	90	41
10	CuI	K_3PO_4	DMF	90	78
11	CuI	Cs_2CO_3	DMF	90	10
12	CuI	K_3PO_4	DMSO	90	66
13	CuI	K_3PO_4	Dioxane	90	12
14	CuI	K_3PO_4	Toluene	90	0
15	CuI	K_3PO_4	DMF	110	79
16	CuI	K_3PO_4	DMF	80	46
17	CuI	K_3PO_4	DMF	90	55[d]

[a] Reaction conditions: *N*-(2-bromophenyl)benzamide (0.5 mmol), [Cu] (10 mol%), L (20 mol%), base (1.0 mmol), solvent (1.0 mL), 90 °C, 12 h. [b] Isolated yield. [c] Ligand-free. [d] CuI (5 mol%), **L** (10 mol%).

With the optimal conditions in hand, the scope of this transformation was initially extended toward the synthesis of various 2-substituted benzoxazoles from *N*-(2-iodophenyl)-benzamide and *N*-(2-bromophenyl)benzamide, and the results were showed in Table 2. Most of the substrates **1** worked well to afford the corresponding products in good to excellent yields under the standard reaction conditions. In general, *ortho*-iodoanilides gave preferable results to their bromo analogues. For 2-iodoanilides, we found that both of the electron-releasing and electron-withdrawing group of the aromatic motifs linked to the carbonyl moiety could smoothly be converted to the desired products in good to excellent yields (entries 1-7). Interestingly, o*rtho*-substituted substrate seemed not to hamper the reaction and afforded 75% yield (entry 4). *N*-(2-iodophenyl)cinnamamide and aliphatic *N*-(2-iodophenyl)-dodecanamide were successfully cyclised in 82% and 65% yields, respectively (entries 8 and 9). Conversely, the intra-molecular *O*-arylation of bromo derivatives was also efficiently carried out by using CuI/methyl 2-methoxybenzoate catalyst system, and substitutions on the aromatic moiety of both the aryl halide as well as the amide were tolerated. In addition, we carried out the reaction in a large scale by taking 10 mmol of *N*-(2-iodophenyl)benzamide in 15 mL DMF at 90 °C for 12 h. The reaction proceeded without any difficulty to obtain 80% yield (1.56g) of the desired product (Fig. 2).

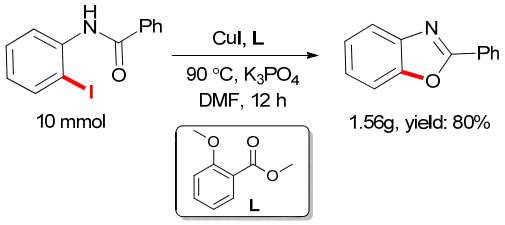


Fig. 2 Large-scale reaction of N-(2-iodophenyl)benzamide.

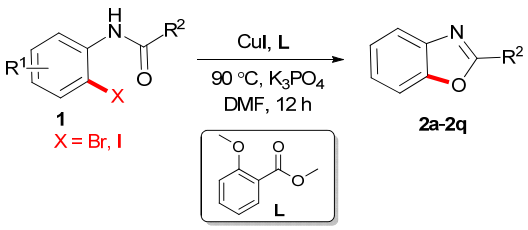
We are pleased to find that various less reactive *ortho*-chloroanilides could be reacted well under the optimal conditions to give the respective benzoxazoles in good to excellent yields only by increasing the reaction temperature to 135 °C. Furthermore, the substrates with electron-releasing group, electron-neutral and electron-withdrawing were all well tolerated (Table 3).

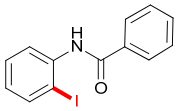
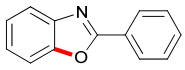
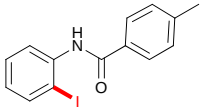
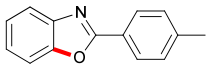
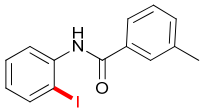
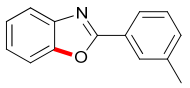
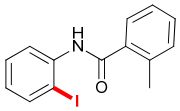
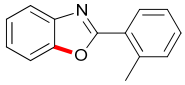
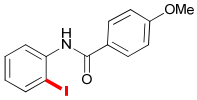
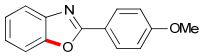
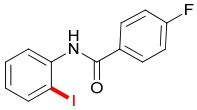
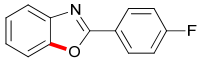
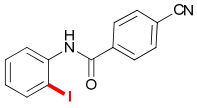
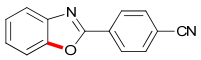
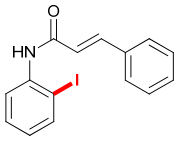
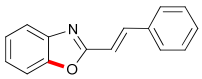
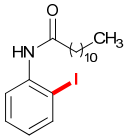
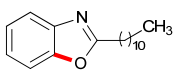
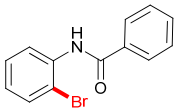
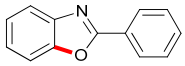
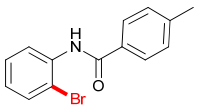
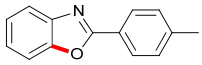
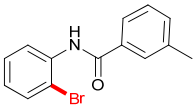
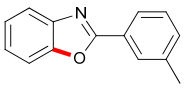
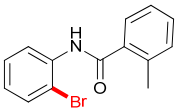
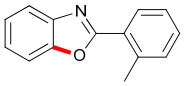
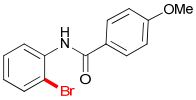
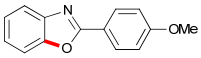
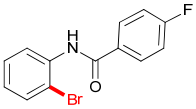
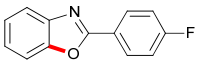
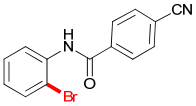
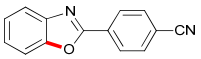
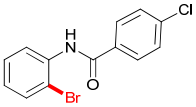
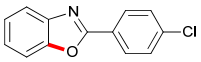
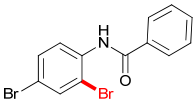
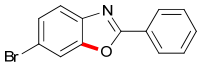
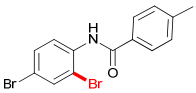
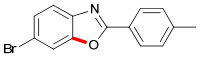
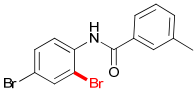
As reported, benzoxazoles could be prepared in a single step from primary amides and *o*-dihalobenzenes using copper catalyst.[9] Therefore, we reasonably explored a domino intermolecular C-N / intramolecular C-O cross-coupling protocol to afford benzoxazoles (Table 4). Utilizing the reaction conditions described for cyclization of *ortho*-chloroanilides, 1,2-diiodobenzene (entries 1-3), 1-bromo-2-iodobenzene (entries 4-6) and 1,2-dibromobenzene (entry 7) could react with benzamides to yield promising results, which will increase the popularity of the synthetic methodology. But it was still a challenge for *ortho*-chlorohalobenzene (entry 8).

Conclusion

In summary, we have established an efficient CuI/methyl 2-methoxybenzoate catalytic systems for intramolecular *O*-arylation for the synthesis of benzoxazoles from *N*-(2-iodo or bromo-phenyl)benzamides with high yields, broad functional group tolerance and ambient reaction conditions. Less reactive chloro precursors were also worked well under the similar reaction conditions. In addition, the benzoxazoles can be gained

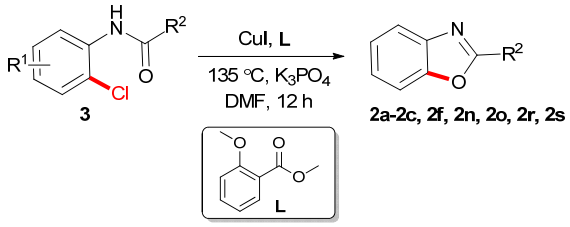
Table 2 CuI-catalysed synthesis of benzoxazoles from *N*-(2-iodo/bromo-phenyl)benzamides using methyl-2-methoxybenzoate as the ligand[a]

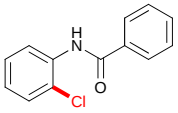
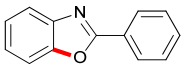
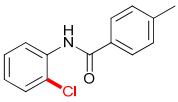
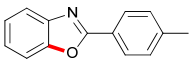
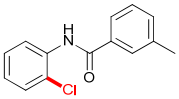
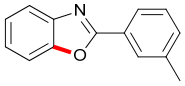
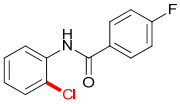
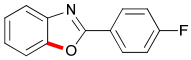
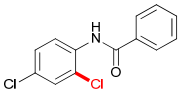
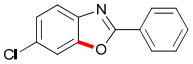
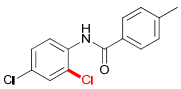
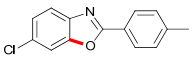
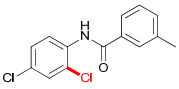
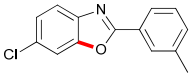
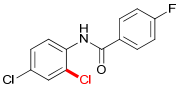
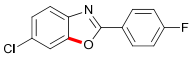


Entry	1	2		Yield[b] (%)
1			**2a**	87
2			**2b**	98
3			**2c**	90
4			**2d**	75
5			**2e**	99
6			**2f**	91
7			**2g**	78
8			**2h**	82
9			**2i**	65
10			**2a**	78
11			**2b**	75
12			**2c**	72
13			**2d**	53
14			**2e**	70
15			**2f**	80
16			**2g**	65
17			**2j**	71
18			**2k**	65
19			**2l**	75
20			**2m**	70
21			**2n**	75
22			**2o**	70
23			**2p**	63
24			**2q**	82

[a] Reaction conditions: *N*-(2-iodo/bromo-phenyl)benzamides (0.5 mmol), CuI (10 mol%), **L** (20 mol%), K_3PO_4 (1.0 mmol), DMF (1.0 mL), 90 °C, 12 h. [b] Isolated yield.

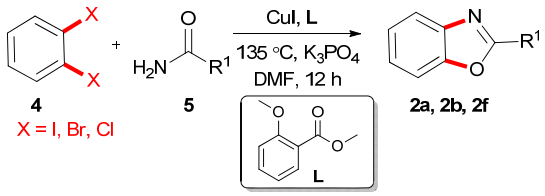
Table 3 CuI-catalysed synthesis of benzoxazoles from *N*-(2-chlorophenyl) benzamides using methyl-2-methoxybenzoate as the ligand[a]

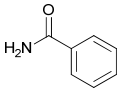
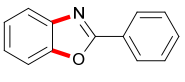
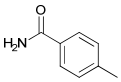
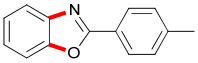
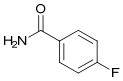
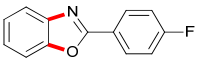
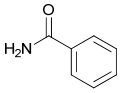
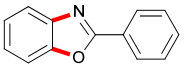
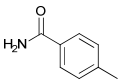
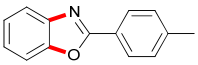
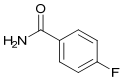
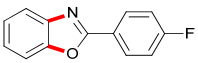
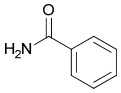
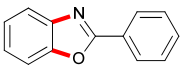


Entry	3	2		Yield[b] (%)
1			**2a**	80
2			**2b**	78
3			**2c**	73
4			**2f**	85
5			**2r**	70
6			**2n**	85
7			**2o**	80
8			**2s**	86

[a] Reaction conditions: *N*-(2-chlorophenyl)benzamides (0.5 mmol), CuI (10 mol%), **L** (20 mol%), K_3PO_4 (1.0 mmol), DMF (1.0 mL), 90 °C, 12 h. [b] Isolated yield.

Table 4 One-step synthesis of benzoxazoles from *orth*-dihalobenzene and primary amides using methyl-2-methoxybenzoate as the ligand[a]



Entry	4	5	2		Yield[b] (%)
1				**2a**	30
2				**2b**	28
3				**2f**	57
4				**2a**	45
5				**2b**	25
6				**2f**	50
7				**2a**	25
8				**2a**	0

[a] Reaction conditions: *orth*-dihalobenzene (0.5 mmol), amide (0.75 mmol), CuI (10 mol%), L (20 mol%), K_3PO_4 (1.5 mmol), DMF (1.0 mL), 135 °C, 12 h. [b] Isolated yield.

through domino intermolecular C-N bond formation followed by intramolecular C-O bond formation from coupling of primary amides with *ortho*-dihalobenzene. The convenient operation, stable and simple catalytic system, in combination with the efficient process for large scale preparation, made the operation much more practical.

Experimental

General information

All reagents were purchased from commercial suppliers and used without further purification. Column chromatography was performed with silica gel (200-300 mesh) purchased from Qingdao Haiyang Chemical Co. Ltd. Thin-layer chromatography was carried out with Merck silica gel GF254 plates. All 2-substituted benzoxazoles were characterized by ^{1}H NMR, ^{13}C NMR and MS, which were compared with the previously reported data. NMR spectra were recorded at room temperature on a Bruker Avance III HD 400 instrument at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Mass spectra were recorded on GC-MS (Agilent 7890A/5975C) instrument under EI model.

General procedure for benzoxazoles synthesis *via* intra-molecular *O*-arylation

To a 10 mL of tube was added CuI (0.05 mmol), L (0.1 mmol), *N*-(2-halophenyl)benzamide (0.5 mmol), K_3PO_4 (1.0 mmol) and anhydrous DMF (1 mL). The tube was then sealed with a rubber septum without inert atmosphere and heated at 90 °C (for 2-iodoanilides and 2-bromoanilides) or 135 °C (for 2-chloroanilides) in a preheated oil bath for 12 h. The reaction mixture was cooled to room temperature, diluted with 10 mL water and extracted with ethyl acetate (3×20 mL). The combined organic phase was washed with water and brine,

dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel (ethyl acetate/petroleum ether as the eluent) to afford the target products.

General procedure for benzoxazoles synthesis *via* domino C-N/C-O coupling reaction

To a 10 mL of tube was added CuI (0.05 mmol), L (0.1 mmol), benzamides (0.75 mmol), 1,2-dihalobenzene (0.5 mmol), K_3PO_4 (1.0 mmol) and anhydrous DMF (1 mL). The tube was then sealed with a rubber septum without inert atmosphere and heated at 135 °C in a preheated oil bath for 12 h. The reaction mixture was cooled to room temperature, diluted with 10 mL water and extracted with ethyl acetate (3×20 mL). The combined organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatograph on silica gel (ethyl acetate/petroleum ether as the eluent) to afford the target products.

Acknowledgements

We are grateful to the National Basic Research Program of China (973 Program, No. 2012CB722603), the NSFC (No. 21103114), and the Ministry of Education Innovation Team (No. IRT1161) for financial support of this work.

Notes and references

[a] *School of Chemistry and Chemical Engineering/Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, Shihezi University, Shihezi 832003, China. E-mail: cesxjw@gmail.com; Fax: +86-0993-2057270; Tel: +86-0993-2057213*

† Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data for all products. See DOI: 10.1039/ b000000x/

1 (a) M. Ukei, K. Ueno, S. Miyadoh, K. Abe, K. Shibata, M. Taniguchi and S. Oi, *J. Antibiot.*, 1993, **46**, 1089; (b) S. Sato, T. Kajiura, M. Noguchi, K. Takehana, T. Kobayashi and T. Tsuji, *J. Antibiot.*, 2001, **54**, 102; (c) P. S. M. Sommer, R. C. Almeida, K. Schneider, W. Beil, R. D. Süssmuth and H.-P. Fiedler, *J. Antibiot.*, 2008, **61**, 683; (d) G. Daletos, N. J. de Voogd, W. E. G. Muller, V. Wray, W. Lin, D. Feger, M. Kubbutat, A. H. Aly and P. Proksch, *J. Nat. Prod.*, 2014, **77**, 218; (e) S. P. B. Ovenden, J. L. Nielson, C. H. Liptrot, R. H. Willis, D. M. Tapiolas, A. D. Wright and C. A. Motti, *J. Nat. Prod.*, 2011, **74**, 65.

2 For some selected examples, see: (a) J. Easmon, G. Pürstinger, K.-S. Thies, G. Heinisch and J. Hofmann, *J. Med. Chem.*, 2006, **49**, 6343; (b) D. Kumar, M. R. Jacob, M. B. Reynolds and S. M. Kerwin, *Bioorg. Med. Chem.*, 2002, **10**, 3997; (c) M. L. Mckee and S. M. Kerwin. *Bioorg. Med. Chem.*, 2008, **16**, 1775; (d) S. Aiello, G. Wells, E. L. Stone, H. Kadri, R. Bazzi, D. R. Bell, M. F. G. Stevens, C. S. Matthews, T. D. Bradshaw and A. D. Westwell, *J. Med. Chem.*, 2008, **51**, 5135; (e) J. Boyer, E. Arnoult, M. Médebielle, J. Guillemont and J. Unge, *J. Med. Chem.*, 2011, **54**, 7974; (f) J. A. Grobler, G. Dornadula, M. R. Rice, A. L. Simcoe, D. J. Hazuda and M. D. Miller, *J. Biol. Chem.*, 2007, **282**, 8005; (g) D. C. Tully, H. Liu, P. B. Alper, A. K. Chatterjee, R. Epple, M. J. Roberts, J. A. Williams, K. T. Nguyen, D. H. Woodmansee, C. Tumanut, J. Li, G. Spraggon, J. Chang, T. Tuntland, J. L. Harris and D. S. Karanewsky, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1975; (h) Y. Sato, M. Yamada, S. Yoshida, T. Soneda, M. Ishikawa, T. Nizato, K. Suzuki and F. Konno, *J. Med. Chem.*, 1998, **41**, 3015; (i) E. Oksuzoglu, B. Tekiner-Gulbas, S. Alper, O. Temiz-Arpaci, T. Ertan, I. Yildiz, N. Diril, E. Sener-Aki and I. Yalcin, *J. Enzyme Inhib. Med. Chem.*, 2008, **23**, 37; (j) J. Nishiu, M. Ito, Y. Ishida, M. Kakutani, T. Shibata, M. Matsushita and M. Shindo, *Diabetes Obes. Metab.*, 2006, **8**, 508; (k) L. Leventhal, M. R. Brandt, T. A. Cummons, M. J. Piesla, K. E. Rogers and H. A. Harris, *Eur. J. Pharmacol.*, 2006, **553**, 146; (l) M. Taki, J. L. Wolford and T. V. O'Halloran, *J. Am. Chem. Soc.*, 2004, **126**, 712.

3 (a) R. S. Varma and D. Kumar, *J. Heterocycl. Chem.*, 1998, **35**, 1539; (b) J. Chang, K. Zhao and S. Pan, *Tetrahedron Lett.*, 2002, **43**, 951; (c) K. Bougrin, A. Loupy and M. Soufiaoui. *Tetrahedron*, 1998, **54**, 8055; (d) S. M. Inamdar, V. K. More and S. K. Mandal, *Tetrahedron Lett.*, 2013, **54**, 579.

4 (a) G. Evindar and R. A. Batey, *J. Org. Chem.*, 2006, **71**, 1802; (b) N. Barbero, M. Carril, R. SanMartin and E. Domínguez, *Tetrahedron*, 2007, **63**, 10425; (c) A. B. Naidu and G. Sekar, *Synthesis*, 2010, **4**, 579; (d) P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul and T. Punniyamurthy, *J. Org. Chem.*, 2009, **74**, 8719; (e) S. Ueda and H. Nagasawa, *Angew. Chem. Int. Ed.*, 2008, **47**, 6411; (f) N. Khatun, S. Guin, S. K. Rout and B. K. Patel, *RSC Adv.*, 2014, **4**, 10770.

5 J. Bonnamour and C. Bolm, *Org. Lett.*, 2008, **10**, 2665.

6 P. Saha, M. A. Ali, P. Ghosh and T. Punniyamurthy, *Org. Biomol. Chem.*, 2010, **8**, 5692.

7 (a) J. Peng, C. Zong, M. Ye, T. Chen, D. Gao, Y. Wang and C. Chen, *Org. Biomol. Chem.*, 2011, **9**, 1225; (b) Y. Yuan, I. Thomé, S. H. Kim, D. Chen, A. Beyer, J. Bonnamour, E. Zuidema, S. Chang and C. Bolm, *Adv. Synth. Catal.*, 2010, **352**, 2892.

8 N.-N. Yan, F.-T. Wu, J. Zhang, Q.-B. Wei, P. Liu, J.-W. Xie and B. Dai, *Asian J. Org. Chem.*, doi: 10.1002/ajoc.201402136.

9 (a) G. Altenhoff and F. Glorius, *Adv. Synth. Catal.*, 2004, **346**, 1661; (b) M. A. Ali, M. Suri and T. Punniyamurthy, *Synthesis*, 2013, **45**, 501; (c) R. D. Viirre, G. Evindar and R. A. Batey, *J. Org. Chem.*, 2008, **73**, 3452.