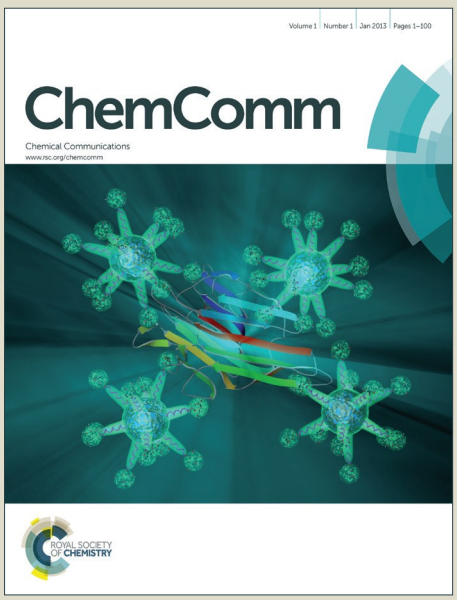
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

Communication

Metal-free oxidative cyclization of acetophenones with diamines: A facile access to phenylpyridines†‡

Rohit Sharma,[ab] Neha Patel,[c] Ram A. Vishwakarma,[ab] Prasad V. Bharatam,[c] Sandip B. Bharate[ab]*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

An efficient metal-free access to 2- and 3-phenylpyridines via oxidative coupling of acetophenones or phenylacetones with 1,3-diaminopropane has been described. Reaction involves shorter reaction time, excellent yields and a broad substrate scope. Reaction proceeds via formation of imine, which further undergoes oxidative C-N bond cleavage, C-C bond formation and oxidation to give pyridine skeleton. The quantum chemical calculations identified the transition state for the reaction and helped in tracing reaction mechanism.

Pyridine is one of the most widely investigated biologically important heterocycle[1] and is prevalent among natural products, pharmaceuticals, functional materials[2] and organometallic catalysts.[3] Due to large spectrum of fascinating applications, the synthesis of pyridine derivatives has long been an area of intense interest, and the development of methodologies for direct access to pyridine skeleton is a challenging task for modern synthetic organic chemists. Thus, the development of a new method for synthesis of pyridine nucleus from easily accessible starting materials is highly desirable. Nevertheless, methods for synthesis of pyridine derivatives have been reported in literature which involves transition-metal-catalyzed cross-coupling, ring-closing metathesis, cycloadditions, radical reactions and microwave-assisted procedures.[4]

The coupling of acetophenones with 1,3-diaminopropane is one of the elegant strategy for direct access to 2-phenylpyridines, for which, only two reports[5] are available, both involving the use of metal catalysts. Furthermore, these protocols produce lower yields, require high reaction temperature, and longer reaction times. In continuation to our interest in the synthesis of *N*-heterocycles,[6] herein we disclose a metal-free iodine-catalyzed protocol to construct 2- and 3-phenylpyridines via iodine-mediated aerobic oxidative cyclization of readily available aryl ketones with 1,3-diaminopropane (Figure 1). The reaction process involves cleavage of C-N bond and the formation of C-C bond under metal-free conditions. Furthermore, it is noteworthy to mention that the synthesis of 3-phenylpyridines from diamines has been reported for the first time.

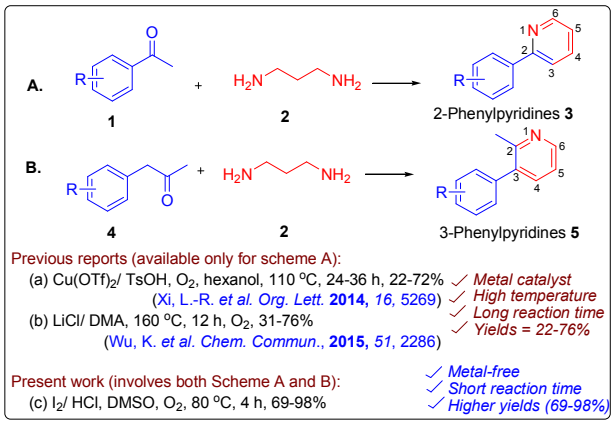


Figure 1 Literature reports and present work on synthesis of 2- and 3-phenylpyridines

Our efforts started with the preliminary reaction of acetophenone (**1a**) with 1,3-diaminopropane (**2**) in the presence of 10 mol% I_2 at 80 °C for 2 h; however, the desired product was not formed (Table 1, entry 1). Among other catalysts investigated, TBAI produced desired product **3a** in 25% yield (entry 2). Although iodine was ineffective (entry 1), we thought to investigate iodine in the presence of acid additive. As the coupling of these two precursors possibly occurs *via* imine formation; we thought to investigate the effect of different acids in this reaction. Among various acids (*viz*. HCl, acetic acid, formic acid, TFA) investigated (entries 5-8), the use of 10 µl HCl as an additive led to drastic increase in the yield of desired product **3a** (entry 5). Further optimization of the I_2/ acid loading, reaction temperature and reaction time (entries 9-11, 13-16) indicated that 8 mol% iodine with 10 µl HCl at 80 °C for 4 h is an optimal reaction condition producing 98% yield of product **3a** (entry 9). Higher loading of HCl (20-30 µl) resulted is decreased product yield. The effect of HCl quantity on the product yield is depicted in Figure S1 of ESI. The control experiments without iodine indicated that the desired product **3a** is formed; however in lesser yields (entries 14-16). Reaction in DCE as a solvent produced

[a]*Medicinal Chemistry Division, CSIR - Indian Institute of Integrative Medicine, Canal Road, Jammu-180001, India. Fax: +91-191-2586333; Tel: +91-191-2585006; *E-mail: sbharate@iiim.ac.in (SBB).*

[b]*Academy of Scientific & Innovative Research (AcSIR), CSIR - Indian Institute of Integrative Medicine, Canal Road, Jammu-180001, India*

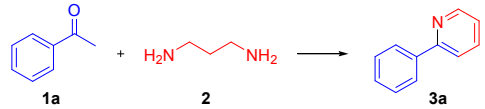
[c]*Departments of Pharmacoinformatics and Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), SAS Nagar, Punjab-160062.*

IIIM Communication number. IIIM/ 1836/2015.

[#]*Electronic supplementary information (ESI) available: Experimental and computational details, NMR spectra scans. See DOI: 10.1039/xxxx*

20% product (entry 17). Thus, entry 9 is considered as an optimal reaction condition and was used for further studies.

Table 1 Optimization of reaction conditions[a,b]



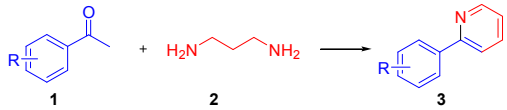
1a 2 3a

Entry	Catalyst (mol%)	Temp.(°C)	Acid (µl)	Time (h)	% yield[c]
1	I_2 (10)	80	none	2	traces
2	TBAI (10)	80	none	12	25
3	CuBr (10)	60	none	12	traces
4	CuI (10)	80	none	12	20
5	I_2 (10)	80	HCl (10)	2	70
6	I_2 (10)	80	AcOH (10)	2	50
7	I_2 (10)	80	HCOOH (10)	2	40
8	I_2 (10)	80	TFA (10)	2	50
9[d]	I_2 **(8)**	**80**	HCl (10)	**4**	**98**
10	I_2 (8)	rt	HCl (10)	4	5
11	I_2 (8)	80	HCl (10)	12	98
12	I_2 (8)	80	Silica-$HClO_4$	4	traces
13	I_2 (8)	80	HCl (5)	24	30
14	none	80	HCl (5)	4	45
15	none	80	HCl (5)	10	48
16	none	80	HCl (10)	10	48
17[e]	I_2 (8)	80	none	8	20

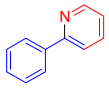
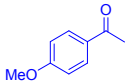
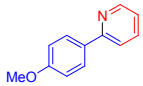
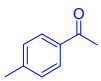
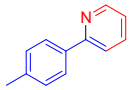
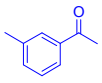
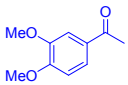
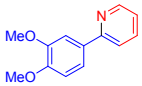
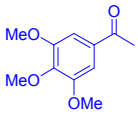
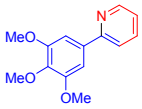
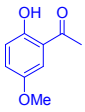
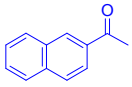
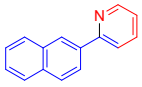
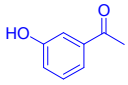
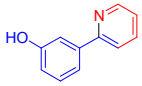
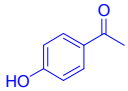
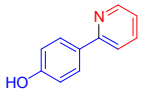
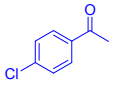
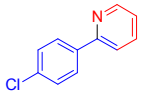
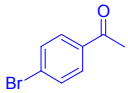
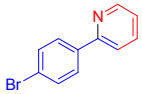
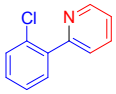
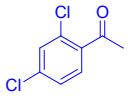
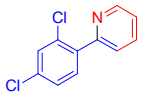
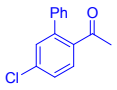
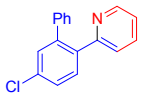
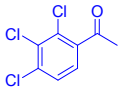
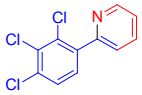
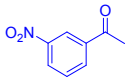
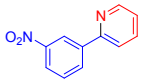
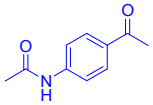
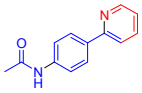
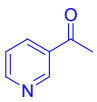
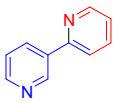
[a] For 100 mg (1.2 mmol) reaction, 1 mL of DMSO solvent was used. [b] all reactions were carried out under oxygen atmosphere. [c] isolated yield. [d] optimized reaction condition, wherein for a 100 mg reaction, 10 µl HCl was added. [e] reaction was carried out using dichloroethane as a solvent without addition of acid additive or DMSO.

With the optimized reaction condition in our hand, we started to explore the substrate scope of the reaction (Table 2). The reaction proceeds well with various substituted aryl ketones. Aryl ketones substituted with electron-donating (examples **3b-g**) as well as electron-withdrawing groups (examples **3k-q**) produced desired products in good yields. It is noteworthy to mention that phenolic –OH group containing acetophenones also participated well in this reaction (examples **3g, 3i** and **3j**). In the case of acetamido-substituted acetophenone (entry 18 of Table 2), reaction proceeded selectively on ketone moiety and not on acetamido group, and produced desired product **3r** in good yield. Fused aryls e.g. 1-(naphthalen-6-yl)ethanone also produced corresponding pyridine product **3h** in good yield (entry 8). Heterocyclic ketones 1-(pyridin-3-yl)ethanone and 1-(pyridin-2-yl)ethanone produced desired products **3s** and **3t** in 85 and 82% yields (entries 19 and 20). It is noteworthy to mention that bis-pyridyl product **3t** was obtained only in 27% yield by Yu and coworkers,[5b] and the other group[5a] have not prepared it.

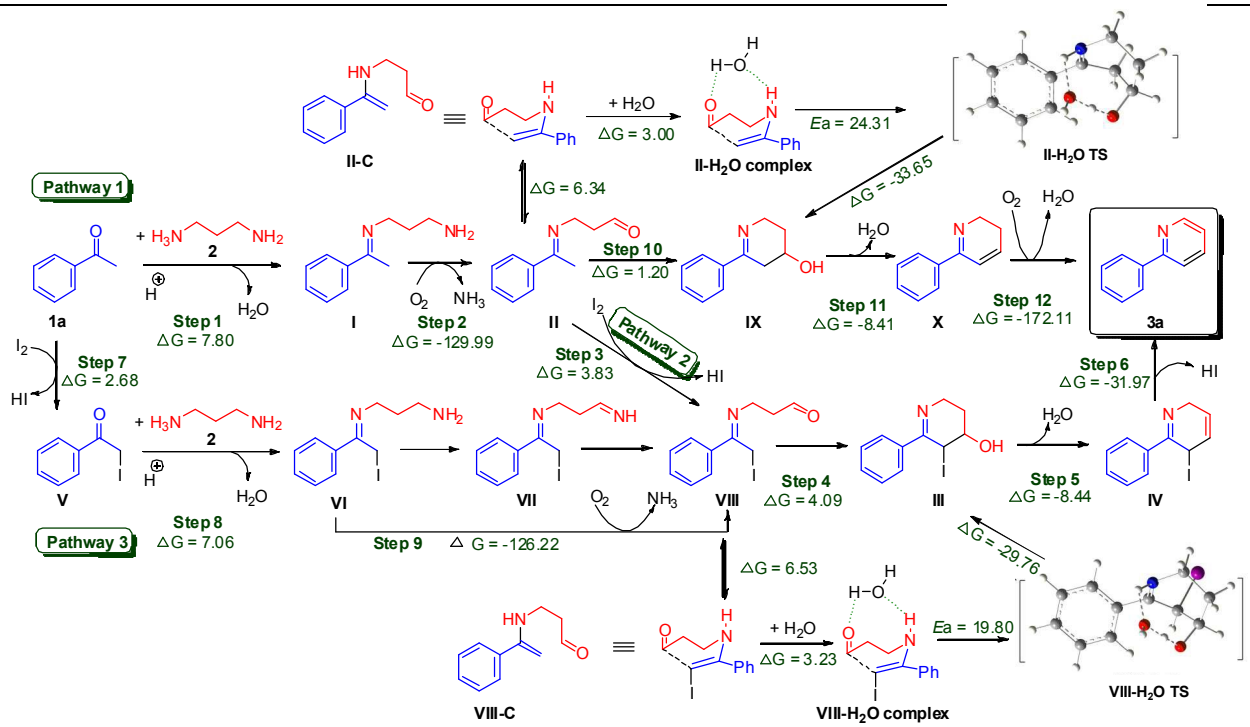
Table 2 Substrate scope of the reaction[a]



1 2 3

Entry	acetophenone	product	product code	% yield[b]
1			**3a**	98
2			**3b**	98
3			**3c**	85
4			**3d**	79
5			**3e**	88
6			**3f**	80
7			**3g**	75
8			**3h**	79
9			**3i**	82
10			**3j**	88
11			**3k**	90
12			**3l**	89
13			**3m**	75
14			**3n**	75
15			**3o**	78
16			**3p**	69
17			**3q**	70
18			**3r**	80
19			**3s**	85
20			**3t**	82

[a] Reagents and conditions: acetophenone (1 equiv.), 1,3-diaminopropane (3 equiv.), I_2 (8 mol%), HCl (10 µl), DMSO (2 mL), O_2, 80 °C, 4 h.



Scheme 1 Reaction mechanism showing energy calculations at each step. All the energy values are in kcal/mol, positive values indicate endergonic processes, negative values indicate exergonic processes.

For mechanistic insights, various control experiments were performed. Reaction when performed under nitrogen atmosphere, gave ~10% yield of the product **3a**, however in the presence of oxygen, yield was 98%, which indicated that oxygen is required for the reaction. Secondly, reaction in the absence of iodine gave only 48% yield of the product, indicating that iodine also plays a key role in the reaction mechanism. Further, we performed quantum chemical studies on the reactants, intermediates, products and transition states of the reaction path regarding various proposed pathways, using B3LYP/6-311+G(d,p) level to elucidate the complete mechanism. Free energy changes associated with each step are given in Scheme 1. Pathway 1 proceeds via step 1→step 2→step 10→step 11→step 12. Pathway 2 involves step 1→step 2→step 3→step 4→step 5→step 6. Pathway 3 includes step 7→step 8→step 9→step 4→step 5→step 6. Comparison of step 1 (common for pathway 1 and 2) and step 8 (pathway 3) indicates that initial iodination at alpha carbon to the carbonyl group, marginally favours formation of corresponding Schiff base *i.e.* imine derivative **VI**. Steps 2 (common for pathway 1 and 2) and step 9 (pathway 3) are quite similar and are very favourable reactions with large free energy changes. On a relative scale, step 2 gives better free energy. Iodination is possible on the starting material **1a** or on the intermediate **II**. Free energy change associated with the iodination reaction (step 7) is 2.68 kcal/mol, whereas the free energy change in step 3 is 3.82 kcal/mol.

Thus, the most favourable mechanism (pathway 3) involves first iodination of **1a** to form **V**, followed by Schiff base formation. Next, the oxidative C-N bond cleavage of **VI** leads to the formation of intermediate **VIII** via imine intermediate **VII**, which is an exothermic reaction by 126.22 kcal/mol. The intermediates **II** and **VIII** can adopt several tautomeric and conformational states. However, only the conformation **II-C** and **VIII-C** are suitable for cyclization. Also, it was found that during cyclization, 1,5-hydrogen shift needs to take place. The 1,5-hydrogen shift can only take place via participation of a water molecule. The energy barriers for the cyclization of **II-C** and **VIII-C** with the help of one water molecule (each) were estimated via transition states. The energy barriers involving **II-H_2O-Ts** and **VIII-H_2O-Ts**, shown in the potential energy diagram (Figure 2) were found to be 33.65 kcal/mol and 29.76 kcal/mol for the conversion of **II** to **IX** and **VIII** to **III**, respectively. This clearly indicates that the cyclization is relatively easier under the iodinized state. The cyclic intermediate **III** then undergoes elimination of water to produce **IV**, a process which is exothermic by 8.44 kcal/mol. Finally, intermediate **IV** quickly releases HI molecule to produce product **3a**, which is again an exothermic reaction releasing 31.97 kcal/mol.

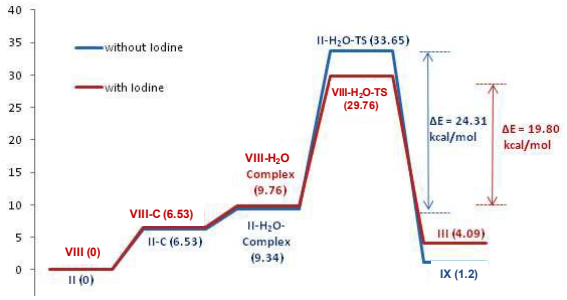


Figure 2 Potential energy surface diagrams of pathway 1 (without I_2) and pathway 3 (with I_2). y axis is showing relative energy values in kcal/mol. All energy differences are taken from the most stable tautomer **VIII**

To experimentally support the most plausible pathway 3, LCMS study of the reaction mixture was performed to trap possible reaction intermediates using the model reaction of 4-methoxyacetophenone (**1b**) with diamine **2** (Figure 3A and Figure S3). LCMS analysis of a reaction mixture after 2 hrs, was able to trap three important iodo-intermediates of pathway 3. This includes α-iodo acetophenone **Vb** (*m/z* 276 at t_R 3.1 min), imine **VIIb** (*m/z* 330 at t_R 15.9 min) and **VIIIb-H_2O complex** (*m/z* 349 at t_R 9.1 min). A control experiment of acetophenone **1a** without addition of diamine **2** does not produced α-iodoacetophenone **V**,

however solely a phenylglyoxal was formed, possibly because of the immediate *in-situ* oxidation of **V**. Therefore, α-iodo acetophenone (**V**) was prepared via reported method (CuO/I_2)[7] and was reacted with diamine **2** under optimized conditions, which resulted in formation of product **3a** in excellent yield (Figure 3B). These results further supported pathway 3 as the most favourable reaction pathway.

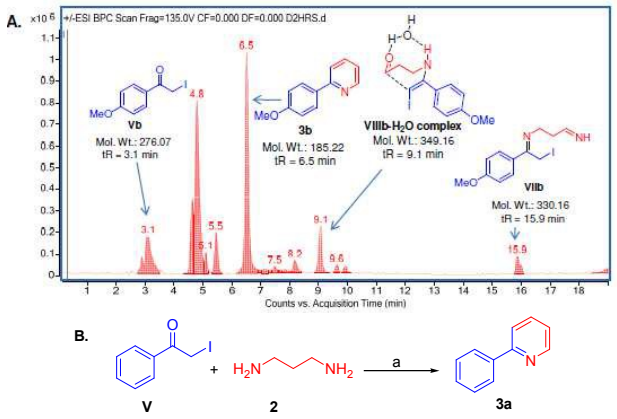
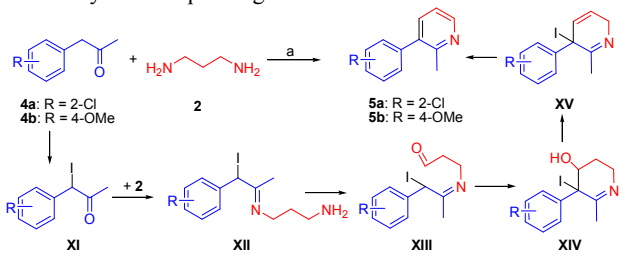


Figure 3 Experimental evidences to support reaction mechanism pathway 3. (A). LCMS chromatogram of reaction mixture showing presence of three key iodo-intermediates of pathway 3. (B). Reaction of α-iodoacetophenone **V** with diamine **2** produces product **3a**. Reagents and conditions: (a) α-iodoacetophenone **V** (1 equiv.), 1,3-diaminopropane (3 equiv.), I_2 (8 mol%), HCl (10 µl), DMSO (2 mL), 80 °C, O_2, 4 h, 95%.

Next, we conducted reaction of phenylacetones **4a-b** with 1,3-diaminopropane (**2**) under optimized reaction conditions. To our surprise, we observed formation of 3-phenylpyridines **5a-b** and not the 2-benzylpyridine products. The formation of **5a-b** clearly indicated that this reaction must be occurring via C-C bond formation at active methylene group. The plausible mechanism for formation of 3-phenylpyridine **5a-b** from **4a-b** is depicted in Scheme 2. Next, when we performed the reaction of phenyl acetaldehyde with diamine **2**, no product was formed. Finally, the utility of this reaction for large scale synthesis of 2-phenylpyridines was investigated (Figure S2). Reaction of 1 g of **1a** (8.33 mmol) with diamine **2** (24.99 mmol) afforded 1.1 g of product **3a** (85% yield). This indicated that this reaction could be efficiently scaled-up on a gram scale.



Scheme 2 Reaction of phenylacetones **4a-b** with 1,3-diaminopropane (**2**). Reagents and conditions: (a) **4a-b** (1 equiv.), **2** (3 equiv.), I_2 (8 mol%), HCl (10 µl), DMSO (2 mL), 80 °C, O_2, 4 h, 75-80%.

In conclusion, we have reported a new scalable metal-free approach for oxidative cyclization of aryl ketones with 1,3-diaminopropanes for synthesis of 2 and 3-arylpyridines in good yields. The distinct features of this method are metal-free nature, high reaction yields, excellent yields, particularly for heteroaryl ketones, and feasibility at gram scale. Using quantum chemical calculations and LCMS analysis, mechanism of the reaction has been established.

Acknowledgements

RS is thankful to DST for the award of research fellowship. SBB thanks DST-SERB for financial support under Fast-Track Scheme (grant no. SR/FT/CS-168/2011).

Notes and references

1. For biological activities of pyridines, see: (a) M. Horiuch, C. Murakami, N. Fukamiya, D. Yu, T.-H. Chen, K. F. Bastow, D.-C. Zhang, Y. Takaishi, Y. Imakura and K.-H. Lee, *J. Nat. Prod.*, 2006, **69**, 1271-1274; (b) S. Follot, J.-C. Debouzy, D. Crouzier, C. Enguehard-Gueiffier, A. Gueiffier, F. Nachon, B. Lefebvre and F. Fauvelle, *Eur. J. Med. Chem.*, 2009, **44**, 3509-3518; (c) V. Onnis, M. T. Cocco, R. Fadda and C. Congiu, *Bioorg. Med. Chem.*, 2009, **17**, 6158-6165; (d) C. D. Duffy, P. Maderna, C. McCarthy, C. E. Loscher, C. Godson and P. J. Guiry, *ChemMedChem*, **5**, 517-522; (e) G. M. Buckley, N. Cooper, R. J. Davenport, H. J. Dyke, F. P. Galleway, L. Gowers, A. F. Haughan, H. J. Kendall, C. Lowe, J. G. Montana, J. Oxford, J. C. Peake, C. L. Picken, M. D. Richard, V. Sabin, A. Sharpe and J. B. H. Warneck, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 509-512; (f) B. Vacher, B. Bonnaud, P. Funes, N. Jubault, W. Koek, M. B. Assie, C. Cosi and M. Kleven, *J. Med. Chem.*, 1999, **42**, 1648-1660; (g) D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435-446; (h) Y. Abe, H. Kayakiri, S. Satoh, T. Inoue, Y. Sawada, N. Inamura, M. Asano, I. Aramori, C. Hatori, H. Sawai, T. Oku and H. Tanaka, *J. Med. Chem.*, 1998, **41**, 4062-4079; (i) S. Zheng, Q. Zhong, M. Mottamal, Q. Zhang, C. Zhang, E. LeMelle, H. McFerrin and G. Wang, *J. Med. Chem.*, **57**, 3369-3381; (j) W. M. Eldehna, A. Altoukhy, H. Mahrous and H. A. Abdel-Aziz, *Eur. J. Med. Chem.*, **90**, 684-694.
2. J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, *Chem. Rev.*, **112**, 2642-2713.
3. (a) D. Bora, B. Deb, A. L. Fuller, A. M. Z. Slawin, J. Derek Woollins and D. K. Dutta, *Inorg. Chim. Acta*, **363**, 1539-1546; (b) M.-D. Zhou, K. R. Jain, A. Günyar, P. N. W. Baxter, E. Herdtweck and F. E. Kühn, *Eur. J. Med. Chem.*, 2009, **2009**, 2907-2914; (c) Y.-T. Chan, C. N. Moorefield, M. Soler and G. R. Newkome, *Chem. Eur. J.*, **16**, 1768-1771; (d) S. Lin and X. Lu, *Org. Lett.*, **12**, 2536-2539.
4. (a) C. Liu and W. Yang, *Chem. Commun.*, 2009, 6267-6269; (b) A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, **113**, 3084-3213; (c) O. M. Kuzmina, A. K. Steib, J. T. Markiewicz, D. Flubacher and P. Knochel, *Angew. Chem. Int. Ed.*, **52**, 4945-4949; (d) R. S. Senaiar, D. D. Young and A. Deiters, *Chem. Commun.*, 2006, 1313-1315; (e) I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127-2198.
5. (a) K. Wu, Z. Huang, C. Liu, H. Zhang and A. Lei, *Chem. Commun.*, 2015, **51**, 2286-2289; (b) L.-Y. Xi, R.-Y. Zhang, S. Liang, S.-Y. Chen and X.-Q. Yu, *Org. Lett.*, 2014, **16**, 5269-5271.
6. (a) S. Mohammed, R. A. Vishwakarma and S. B. Bharate, *J. Org. Chem.*, 2015, **80**, 6915-6921; (b) S. Mohammed, R. A. Vishwakarma and S. B. Bharate, *RSC Adv.*, 2015, **5**, 3470-3473; (c) J. B. Bharate, S. Abbat, P. V. Bharatam, R. A. Vishwakarma and S. B. Bharate, *Org. Biomol. Chem.*, 2015, **13**, 7790-7794; (d) R. Mudududdla, R. Sharma, S. Abbat, P. V. Bharatam, R. A. Vishwakarma and S. B. Bharate, *Chem. Commun.*, 2014, **50**, 12076-12079; (e) J. B. Bharate, S. B. Bharate and R. A. Vishwakarma, *ACS Comb. Sci.*, 2014, **16**, 624–630; (f) J. B. Bharate, A. Wani, S. Sharma, S. I. Reja, M. Kumar, R. A. Vishwakarma, A. Kumar and S. B. Bharate, *Org. Biomol. Chem.*, 2014, **12**, 6267-6277; (g) J. B. Bharate, R. Sharma, B. Singh, S. Aravinda, V. K. Gupta, S. B. Bharate and R. A. Vishwakarma, *RSC Adv.*, 2013, **3**, 21736–21742; (h) J. B. Bharate, S. K. Guru, S. K. Jain, S. Meena, P. P. Singh, S. Bhushan, B. Singh, S. B. Bharate and R. A. Vishwakarma, *RSC Adv.*, 2013, **3**, 20869–20876; (i) S. B. Bharate, A. Padala, B. A. Dar, R. R. Yadav, B. Singh and R. A. Vishwakarma, *Tetrahedron Lett.*, 2013, **54**, 3558-3561; (j) R. Mudududdla, S. K. Jain, J. B. Bharate, A. P. Gupta, B. Singh, R. A. Vishwakarma and S. B. Bharate, *J. Org. Chem.*, 2012, **77**, 8821-8827; (k) S. B. Bharate, R. Mudududdla, J. B. Bharate, N. Battini, S. Battula, R. R. Yadav, B. Singh and R. A. Vishwakarma, *Org. Biomol. Chem.*, 2012, **10**, 5143-5150.
7. M. Gao, Y. Yang, Y.-D. Wu, C. Deng, L.-P. Cao, X.-G. Meng and A.-X. Wu, *Org. Lett.*, 2010, **12**, 1856-1859.