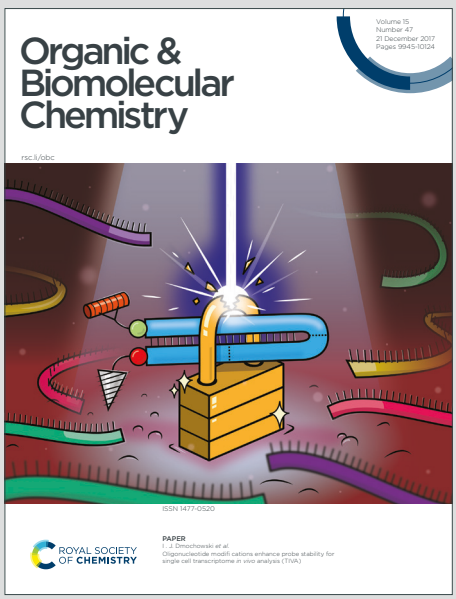
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: R. Gorre, D. Enagandhula, S. Balasubramanian and S. M. Akondi, *Org. Biomol. Chem.*, 2020, DOI: 10.1039/C9OB02730K.



ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C9OB02730K

COMMUNICATION

Visible-Light-Driven Metal-Free Aerobic Synthesis of Highly Diastereoselective Phosphinoylpyrroloindoles

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Ramesh Gorre, [+,a,b] Damodar Enagandhula, [+,a] Sridhar Balasubramanian [b,c] and Srirama Murthy Akondi *[a,b]

A visible-light-driven metal-free phosphorus radical mediated construction of 2-phosphinoyl-3*H*-pyrrolo[1,2,*a*]indoles is described. This mild tandem phosphinoylation/cyclization protocol utilizes air as a green oxidant and proceeds in a short span of time at room temperature with high functional group tolerance, excellent chemo- and diastereoselectivity.

Pyrrolo[1,2-*a*]indoles are an important class of indole derivatives owing to their presence in drug molecules and natural products. For instance, flinderoles and isoborreverine have shown significant antimalarial activity and JTT-010 is a protein kinase C (PKC) inhibitor (Figure 1).[1] Additionally, indole derivatives containing phosphorus functionality have attracted attention in the synthetic community due to their occurrence in the fields of pharmaceuticals, organic synthesis and material science.[2]

Considering the importance of the pyrrolo[1,2-*a*]indole scaffold and indolyl-based organophosphorus compounds, the development of highly efficient methodologies to synthesize phosphorus containing pyrrolo[1,2-*a*]indole frameworks that combine both characteristics together is desirable and has attracted attention in recent years. For instance, Tang and co-workers[3] developed a silver-mediated phosphinoylation-cyclization-isomerization cascade for the preparation of various 2-phosphinoyl-9*H*-pyrrolo[1,2-*a*]-indoles (Scheme 1a). The Song[4] and Yue[5] groups independently reported a silver-catalysed carbon-phosphorus functionalization for the preparation of 2-phosphinoyl-3*H*-pyrrolo[1,2-*a*]indoles with excellent diastereoselectivity (Scheme 1b). And, a copper-catalyzed tandem radical cyclization of 1-(3-phenylprop-2-yn-1-yl)-1*H*- indoles leading to 2-phosphinoyl-9*H*-pyrrolo[1,2-*a*]indoles was developed by Zhu and co-workers in 2017 (Scheme 1a).[6] Despite these achievements, each of these methods requires an external oxidant (either metal oxidant or peroxide), elevated temperatures, long reaction times and more importantly, a transition metal reagent, which limit their widespread application. From the stand point of sustainable chemistry, the realization of a transition-metal-free and toxic oxidant-free procedure to construct phosphorus containing pyrrolo[1,2-*a*]indole derivatives at room temperature is an important challenge to meet.

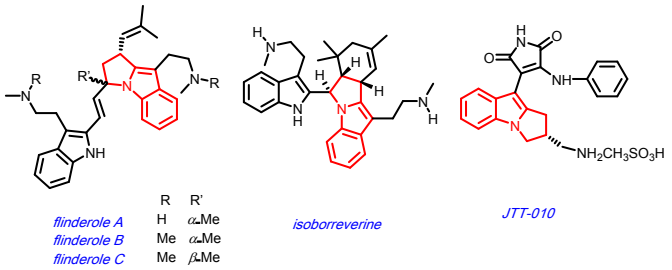
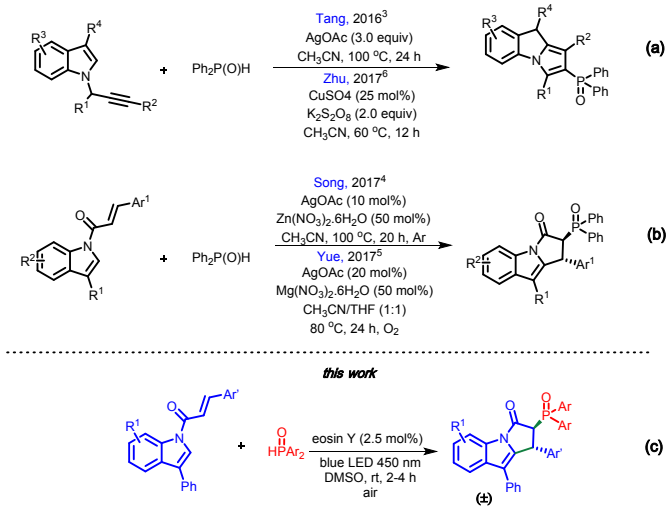


Figure 1 Some biologically active compounds featuring pyrrolo[1,2-a]indole framework.

Visible light driven organo-photoredox catalysis provides an environmentally benign way of generating various reactive radicals for the construction of complex carbocyclic and polyheterocyclic skeletons. This technology has been utilized by several research groups in recent years to construct useful phosphorylated compounds by generating P-centered radicals under mild conditions without using toxic reagents.[7,8] However, the construction of highly diastereoselective P-containing pyrrolo[1,2-*a*]indole derivatives *via* mild and cost-effective photoredox catalysis is still unexplored. Herein, we report a visible light driven organic dye catalysed simultaneous C-P and C-C bond formation for the synthesis of 2-phosphinoyl-3*H*-pyrrolo[1,2-*a*]indoles through exclusive 5-endo-trig cyclization (Scheme 1c). This reaction utilizes air as a green oxidant and proceeds at room temperature with just 2.5 mol% of eosin Y as a single catalyst with no use of toxic oxidants and additives. These milder conditions offer excellent functional group compatibility and diastereoselectvity.

[a] *Department of Organic Synthesis and Process Chemistry, CSIR-Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad 500007, India Email : sriramakondi@iict.res.in; sriramiict@gmail.com*
[b] *Academy of scientific and innovative research (AcSIR), Ghaziabad 201002, India*
[c] *Department of Analytical Chemistry, CSIR-IICT, Hyderabad 500007, India*
† These authors contributed equally
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x



Scheme 1 Previous and present works for the synthesis of phosphorus containing pyrrolo[1,2-*a*]indole.

Motivated by the desire to develop an environmentally benign protocol for the construction of 2-phosphinoyl-3*H*-pyrrolo[1,2-*a*]indoles, we evaluated reaction conditions employing **1a** and **2a** as model substrates using air as an oxidant and a suitable organic dye as a photocatalyst. To our delight, the anticipated product **3aa** was obtained in 42% yield when a solution of **1a** (0.1 mmol), **2a** (0.25 mmol) with 4 mol% rose bengal in 0.1 M DMSO was irradiated with 14 W white LED for 12 h in an open pot exposed to ambient air at room temperature (Table 1, entry 1). We also examined the use of the Sigma-Aldrich® SynLED parallel photoreactor (blue LED, 465-470 nm) instead of a white LED, though a slight reduction in yield was observed (Table 1, entry 2). A remarkable improvement in the yield as well as the rate was observed when the same transformation was conducted using the Penn *PhD* photoreactor m2 (blue LED, 450 nm).[10] There was a 6-fold rate enhancement, generating the desired product **3aa** in 68% yield after only 2 h (Table 1, entry 3). Encouraged by this result, we further optimized the reaction conditions by exploring a range of organophotocatalysts such as rhodamine B, 9,10-dicyanoanthracene, eosin Y and [Acr-Mes] ClO_4 under the same conditions (Table 1, entries 4-7). These results indicated that eosin Y is the most effective photocatalyst for this transformation, affording **3aa** in 74% yield. The structure of **3aa** was unambiguously confirmed by X-ray crystallographic analysis (Figure 2), and exclusive trans diastereoselectivity was observed.[11]

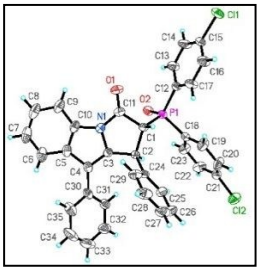
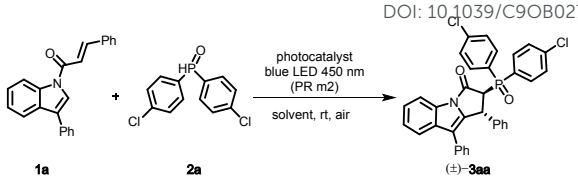
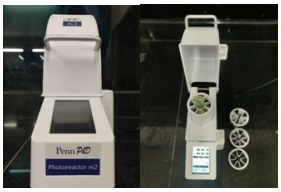


Figure 2 X-ray crystal structure (ORTEP) of **3aa**.

Table 1 Optimization of reaction conditions[a]

View Article Online
DOI: 10.1039/C9OB02730K





Penn *PhD* photoreactor m2 (PR m2)

Entry	Photocatalyst (mol%)	Solvent	Yield %[b]
1	rose bengal (4)[c]	DMSO	42
2	rose bengal (4)[d]	DMSO	39
3	rose bengal (4)	DMSO	68
4	rhodamine B (4)	DMSO	n.r.
5	9,10-dicyanoanthracene (4)	DMSO	n.r.
6	eosin Y (4)	DMSO	74
7	[Acr-Mes]ClO_4 (4)	DMSO	trace
8	eosin Y (4)	MeCN	23
9	eosin Y (4)	toluene	n.r.
10	eosin Y (4)	*i*-PrOH	n.r.
11	eosin Y (4)	H2O	n.r.
12	**eosin Y (2.5)**	**DMSO**	**72**
13	eosin Y (1)	DMSO	39
14	none	DMSO	n.r.
15	eosin Y (2.5)[e]	DMSO	trace
16	eosin Y (2.5)[f]	DMSO	42
17	eosin Y (2.5)[g]	DMSO	12

[a] The reaction was carried out with **1a** (0.1 mmol), **2a** (0.25 mmol) and eosin Y (2.5 mol%) in DMSO (1.0 mL) at room temperature under ambient air using PR m2 (blue LED 450 nm) for 2 h. [b] Isolated yields. [c] Irradiated with 14 W white LED for 12 h. [d] Irradiated in synLED photoreactor for 12 h. [e] No irradiation. [f] Under O_2 (1atm). [g] Under N_2

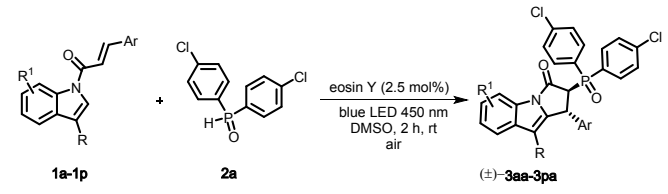
A screening of solvents of varying polarities revealed that DMSO is the best solvent for this reaction system (Table 1, entries 8-11). The optimum catalyst loading was found to be 2.5 mol% since a further decrease to 1 mol% had a negative effect on the yield of the reaction (Table 1, entries 12 and 13). No desired product was detected in the absence of either photocatalyst or light irradiation, indicating that the transformation proceeds through a photoredox mechanism (Table 1, entries 14 and 15). When the reaction was conducted under 1 atm of O_2, the yield of **3aa** was reduced to 42% because of the faster decomposition of **2a** into its oxidative byproduct (Table 1, entry 16).[8b,8d] Finally, the yield of the reaction was attenuated under an N_2 atmosphere, giving the desired product **3aa** in only 12% yield (Table 1, entry 17). These optimization studies imply that eosin Y, ambient air and visible light are all crucial for the progress of this transformation.

Using the optimized reaction conditions described in entry 12 of Table 1, we then explored the scope and generality of this protocol using various cinnamides and indoles **1a-1p**. As shown

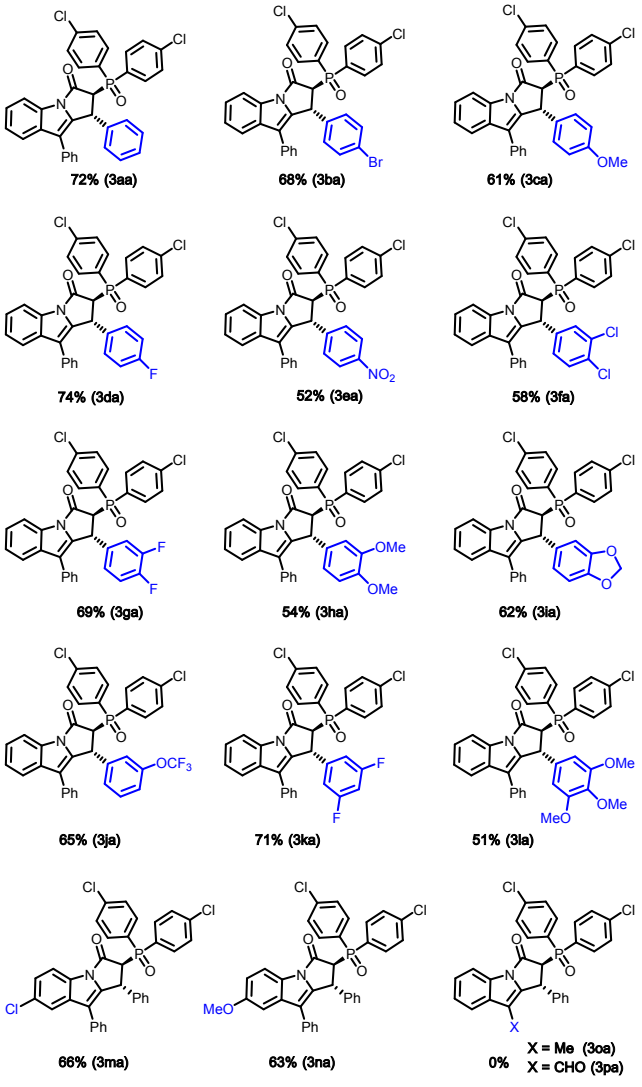
View Article Online
DOI: 10.1039/C9OB02730H

in Table 2, cinnamides bearing either electron-rich or electron-deficient substituents at para, meta or on both positions of the phenyl rings were well tolerated in this protocol, providing the desired products (**3aa–3la**) in 51-74% yields with high diastereoselectivity.

Table 2 Scope of cinnamides and indoles[a]



1a-1p 2a (±)-3aa-3pa

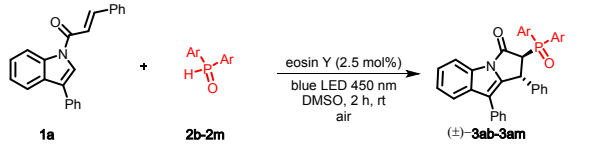


[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.25 mmol) and eosin Y (2.5 mol%) in DMSO (0.1 M) irradiated in Penn *PhD* PR m2 (blue LED 450 nm) at room temperature under ambient air. Isolated yields are reported.

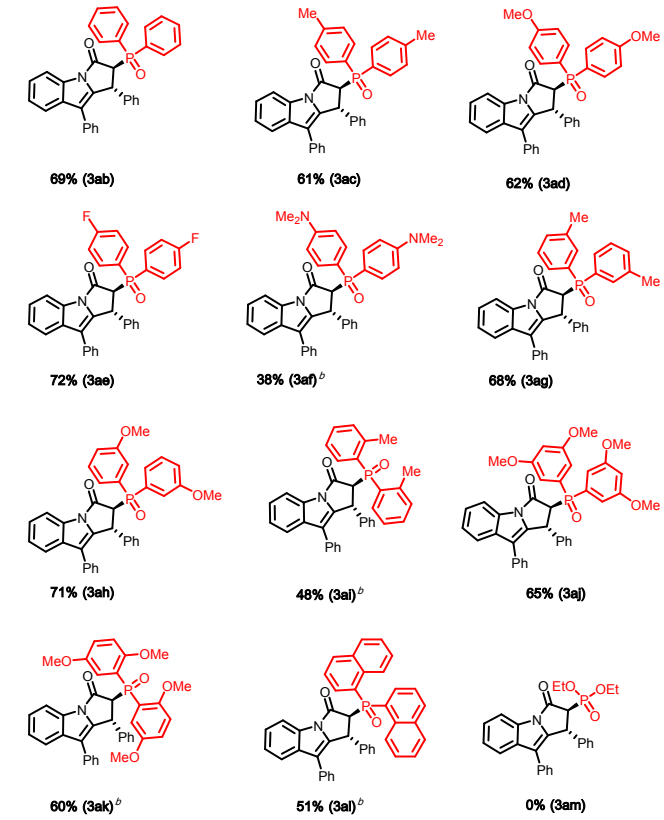
A range of functional groups, such as methoxy (**3ca**, **3ha** and **3la**), methylenedioxy (**3ia**), trifluoromethoxy (**3ja**), halogens (**3ba**, **3da**, **3fa**, **3ga** and **3ka**) and nitro substituents (**3ea**) were well tolerated in this transformation. Compatibility with the functional groups was further demonstrated by substituting the electron-donating group methoxy (**3na**) and electron-withdrawing group chloro (**3ma**) on the aromatic ring of the indole, wherein the desired products were obtained in good yields. Notably, this transformation happened only when there was an aryl substituent at the 3-position of the indole ring and no desired product was obtained when there was alkyl (**3oa**) or electron-withdrawing (**3pa**) group. These observations might be attributed to the poor stabilization of the radical, carbocation intermediates by alkyl and electron withdrawing substituents when compared to an aryl substituent.

Next, the scope of different H-phosphine oxides was examined (Table 3). Simple diphenylphosphine oxide (DPPO) (**3ab**), 4-Me-DPPO (**3ac**), 4-OMe-DPPO (**3ad**) and 4-F-DPPO (**3ae**) furnished the corresponding products in good yields. Diphenylphosphine oxide with an $-NMe_2$ group in the *para* position (**3af**) furnished lower yield due to the incomplete conversion of **1a** and formation of byproducts.

Table 3 Scope of phosphine oxides[a]



1a 2b-2m (±)-3ab-3am



[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.25 mmol) and eosin Y (2.5 mol%) in DMSO (0.1 M) irradiated in Penn *PhD* PR m2 (blue LED 450 nm) at room temperature under ambient air. Isolated yields are reported. [b] Reaction continued for 4 h.

Diphenylphosphine oxides bearing meta substituents (**3ag, 3a h** and **3aj**) reacted smoothly to furnish the anticipated products

in moderate to good yields. Notably, dihenylphosphine oxides having *ortho* substituents (**3ai** and **3ak**) were also well tolerated under these reaction conditions despite the longer reaction times (4 h). 1-Naphthyl-DPPO was also a suitable substrate for this transformation, giving the product **3al** in 51% yield. Diethyl phosphite did not participate in the reaction, perhaps because of its high oxidation potential and poor ability to undergo tautomerization.[8b,12]

To demonstrate the practicability of this methodology, a one mmol-scale experiment was then performed, employing **1a** and **2a** as substrates under optimized conditions (Figure 3). The reaction took 6 hours for the completion to give the desired product **3aa** in a good yield of 65%.

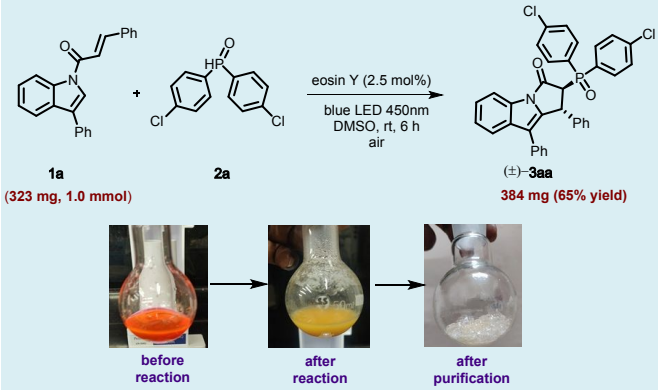
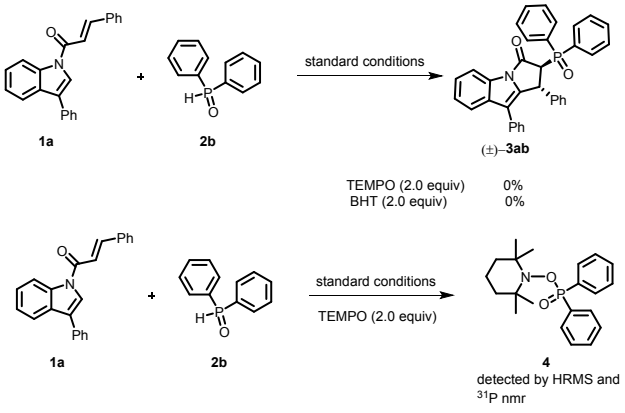


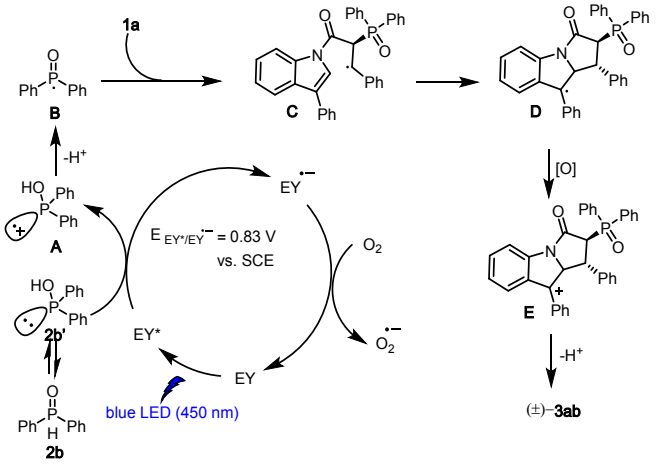
Figure 3 One mmol scale reaction for the synthesis of **3aa.**

Some control experiments have been conducted to gain more insights into this reaction mechanism (Scheme 4). When the reaction was conducted in the presence of radical scavengers such as butylated hydroxytoluene (BHT) and 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO), the reaction was completely shut down. Also, we identified the TEMPO-trapped product **4** by high-resolution mass spectrometry and ^{31}P nmr spectroscopy. These control experiments clearly support the phosphorus-centered radical reaction pathway. We also conducted fluorescence quenching experiments and found that the photoexcited eosin Y (EY*) was quenched by the phosphine oxide **2a** (see the Supporting Information).



Scheme 4 Control experiments for mechanistic studies

A plausible catalytic cycle has been proposed based on the above control experiments and preceding literature (Scheme 5).[8b,8f,9]



Scheme 5 Plausible mechanism.

Firstly, single electron oxidation of the diphenylphosphine oxide **2b** by photoexcited eosin Y (EY*) generates radical cation **A** and reduced eosin Y (EY$^{\bullet-}$). Radical cation A upon deprotonation generates the phosphinoyl radical **B** which adds on to the highly electron dense α-position of the carbonyl group followed by 5-endo-trig cyclization, leading to the radical intermediates **C** and **D** respectively. Oxidation of intermediate **D** gives the carbocation intermediate **E**, which upon deprotonation produces the final product **3ab**. The reduced photocatalyst (EY$^{\bullet-}$) will be oxidized by O_2 to complete the photocatalytic cycle.

Conclusions

In conclusion, we have developed an environmentally benign and practical method for the synthesis of 2-phosphinoyl-3*H*-pyrrolo[1,2-*a*]indoles under visible light conditions using only 2.5 mol% of organophotocatalyst eosin Y. This transformation proceeded through a tandem C-P and C-C bond formation with excellent chemo (only 5-endo-trig instead of 6-endo-trig) and diastereoselectivity. The efficiency of this protocol was further enhanced by using air as green oxidant.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

RG thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, for a research fellowship. The authors thank Dr. S. Chandrasekhar and Dr. Prathama S. Mainkar for their support and valuable discussions (IICT/pubs./2019/383). ASR thanks prof. Lanny S. Liebeskind for his constructive criticism.

Notes and references

View Article Online
DOI: 10.1039/C9OB02730K

1 a) R. Vallakati and J. A. May, *J. Am. Chem. Soc.*, 2012, **134**, 6936–6939; b) M. Tanaka, M. Ubukata, T. Matsuo, K. Yasue, K. Matsumoto, Y. Kajimoto, T. Ogo and T. Inaba, *Org. Lett.*, 2007, **9**, 3331–3334.

2 a) P. Gong, K. Ye, J. Sun, P. Chen, P. Xue, H. Yang and R. Lu, *RSC Adv.*, 2015, **5**, 94990–94996; b) T. Jia, A. Bellomo, K. El Baina, S. D. Dreher and P. J. Walsh, *J. Am. Chem. Soc.*, 2013, **135**, 3740–3743; c) X.-J. Zhou, R. C. Garner, S. Nicholson, C. J. Kissling and D. Mayers, *J. Clin. Pharmacol.*, 2009, **49**, 1408–1416; d) F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, U. Dingerdissen and M. Beller, *Chem. - A Eur. J.*, 2004, **10**, 2983–2990; e) F. R. Alexandre, A. Amador, S. Bot, C. Caillet, T. Convard, J. Jakubik, C. Musiu, B. Poddesu, L. Vargiu, M. Liuzzi, A. Roland, M. Seifer, D. Standring, R. Storer and C. B. Dousson, *J. Med. Chem.*, 2011, **54**, 392–395; f) L. Chen and Y. X. Zou, *Org. Biomol. Chem.*, 2018, **16**, 7544–7556.

3 S. Chen, P. Zhang, W. Shu, Y. Gao, G. Tang and Y. Zhao, *Org. Lett.*, 2016, **18**, 5712–5715.

4 J. Xu, X. Yu and Q. Song, *Org. Lett.*, 2017, **19**, 980–983.

5 J. Liu, S. Zhao, W. Song, R. Li, X. Guo, K. Zhuo and Y. Yue, *Adv. Synth. Catal.*, 2017, **359**, 609–615.

6 H. Zhang, W. Li and C. Zhu, *J. Org. Chem.*, 2017, **82**, 2199–2204.

7 For selected reviews see; a) K. Luo, W. C. Yang and L. Wu, *Asian J. Org. Chem.*, 2017, **6**, 350–367; b) B. G. Cai, J. Xuan and W. J. Xiao, *Sci. Bull.*, 2019, **64**, 337–350.

8 For selected metal-free photoinduced phosphorylation reactions, see; a) W. J. Yoo and S. Kobayashi, *Green Chem.*, 2013, **15**, 1844–1848; b) P. Peng, L. Peng, G. Wang, F. Wang, Y. Luo and A. Lei, *Org. Chem. Front.*, 2016, **3**, 749–752; c) J. G. Sun, H. Yang, P. Li and B. Zhang, *Org. Lett.*, 2016, **18**, 5114–5117; d) I. Kim, M. Min, D. Kang, K. Kim and S. Hong, *Org. Lett.*, 2017, **19**, 1394–1397; e) D. Liu, J. Q. Chen, X. Z. Wang and P. F. Xu, *Adv. Synth. Catal.*, 2017, **359**, 2773–2777; f) Y. Yin, W. Z. Weng, J. G. Sun and B. Zhang, *Org. Biomol. Chem.*, 2018, **16**, 2356–2361; g) H. Wang, Y. Li, Z. Tang, S. Wang, H. Zhang, H. Cong and A. Lei, *ACS Catal.*, 2018, **8**, 10599–10605; h) H. F. Qian, C. K. Li, Z. H. Zhou, Z. K. Tao, A. Shoberu and J. P. Zou, *Org. Lett.*, 2018, **20**, 5947–5951; i) M. Singsardar, A. Dey, R. Sarkar and A. Hajra, *J. Org. Chem.*, 2018, **83**, 12694–12701; j) Q. Fu, Z.-Y. Bo, J.-H. Ye, T. Ju, H. Huang, L.-L. Liao and D.-G. Yu, *Nat. Commun.*, 2019, **10**, 3592.

9 S. Mitra, M. Ghosh, S. Mishra and A. Hajra, *J. Org. Chem.*, 2015, **80**, 8275–8281.

10 C. C. Le, M. K. Wismer, Z. C. Shi, R. Zhang, D. V. Conway, G. Li, P. Vachal, I. W. Davies and D. W. C. MacMillan, *ACS Cent. Sci.*, 2017, **3**, 647–653.

11 CCDC 1960675 contains supplementary Crystallographic data for the structure **3aa**. This data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html.

12 B. G. Janesko, H. C. Fisher, M. J. Bridle and J. L. Montchamp, *J. Org. Chem.*, 2015, **80**, 10025–10032.