ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2021, **57**, 8437

Received 13th July 2021,
Accepted 26th July 2021

DOI: 10.1039/d1cc03777c

rsc.li/chemcomm

$K_2S_2O_8$ activation by glucose at room temperature for the synthesis and functionalization of heterocycles in water†

Joydev K. Laha * and Mandeep Kaur Hunjan

While persulfate activation at room temperature using glucose has primarily been focused on kinetic studies of the sulfate radical anion, the utilization of this protocol in organic synthesis is rarely demonstrated. We reinvestigated selected $K_2S_2O_8$-mediated known organic reactions that invariably require higher temperatures and an organic solvent. A diverse, mild functionalization and synthesis of heterocycles using the inexpensive oxidant $K_2S_2O_8$ in water at room temperature is reported, demonstrating the sustainability and broad scope of the method. Unlike traditional methods used for persulfate activation, the current method uses naturally abundant glucose as a $K_2S_2O_8$ activator, avoiding the use of higher temperature, UV light, transition metals or bases.

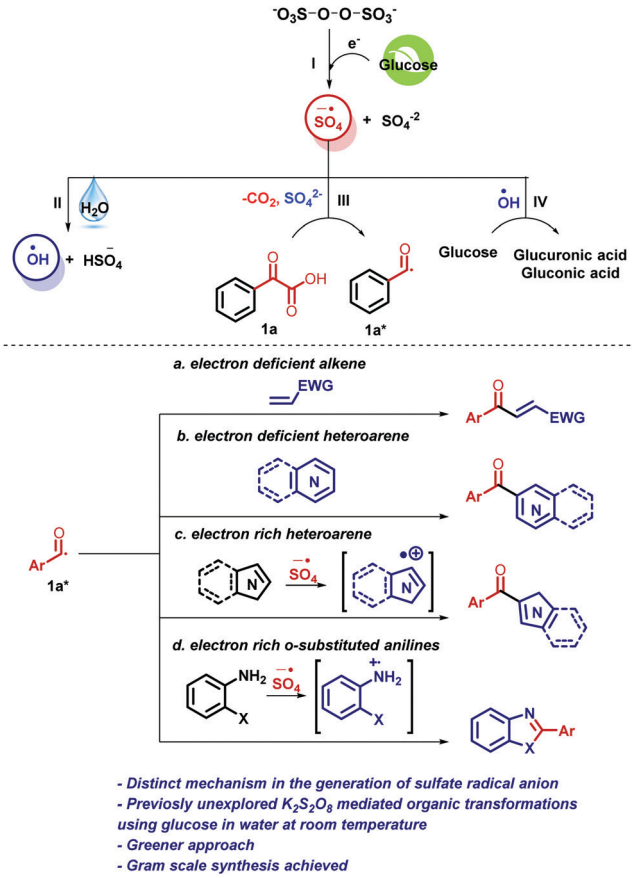
C–C (and C–X) bond formation occurring in the functionalization[1] and synthesis of heterocycles[2] *via* oxidative C–H functionalization in the presence of an oxidant has been the central focus in current organic synthesis obviating the use of prefunctionalized substrates.[3] Among the various oxidants, both inorganic and organic, used in these transformations, potassium persulfate ($K_2S_2O_8$, an inorganic oxidant which is inexpensive and readily available at a price of $130 per 500 g (Sigma) and a bulk price of $50 per 25 Kg) has been shown to be extremely compatible with a wide array of oxidative transformations practiced from academic laboratories to industrial processes.[4] The activation of $K_2S_2O_8$ by high temperature, ultraviolet light, a base, activated carbon, ultrasound or a transition metal is known to produce the key oxidant, the sulfate radical anion ($SO_4^{\bullet -}$, a strong one electron oxidant (2.5–3.1 V)) from $S_2O_8^{2-}$.[5] More specifically, $K_2S_2O_8$ activation at room temperature requires the presence of an electron donating species, *e.g.* a transition metal-catalyst or even an organic compound.[6] Considering the obvious use (also often the associated toxicity) of transition metals[7] and organic solvents, we questioned ourselves whether activation could be performed at room temperature in the presence of an environmentally benign organic electron donor, especially in water. Nevertheless, the poor solubility of organic compounds in water, especially at room temperature, could present a significant challenge in these transformations.

It has been shown that sugars, which are regarded as electron donors which are naturally abundant and inexpensive, can activate persulfate and generate $SO_4^{\bullet -}$ at room temperature.[8] $K_2S_2O_8$ activation, especially using glucose, could have advantages over traditional activation: (a) avoiding the use of higher temperatures, UV light, transition metals or bases, (b) reactions can be performed in water,[9] and (c) it is convenient to adopt in scale up synthesis. Unlike the homolytic cleavage of peroxy linkages which occurs under thermal conditions at an elevated temperature, the mechanism of $K_2S_2O_8$ activation[10] using glucose at room temperature is substantially different, involving the heterolytic cleavage of the peroxy linkage by the transfer of one electron from glucose to $S_2O_8^{2-}$ (Scheme 1).[11] In addition, $SO_4^{\bullet -}$ can react with water at room temperature, forming the hydroxyl ($HO^{\bullet}$) radical which also could participate in the reaction.[8a] While persulfate activation at room temperature using glucose has primarily focused on kinetic studies of the sulfate radical anion,[12] waste water treatment,[13] degradation studies,[14] the utilization of this protocol in mild C–H functionalization[15] and the synthesis of heterocycles,[16] to the best of our knowledge remain unexplored. To demonstrate the compatibility of $K_2S_2O_8$ activation using glucose at room temperature in water, we revisited $K_2S_2O_8$-mediated organic reactions[4,7,17] that invariably require higher temperature and an organic solvent.

We describe herein the $K_2S_2O_8$ mediated mild and diverse functionalization and synthesis of heterocycles in water at room temperature. The diverse functionalization reported herein includes the aroylation of nitrogen heterocycles, the decarboxylative cross-coupling of two carboxylic acids and the amidation of arylglyoxylic acids using a tertiary amine *via* C–N bond cleavage. The tandem synthesis of various N-heterocycles

Department of Pharmaceutical Technology (Process Chemistry), National Institute of Pharmaceutical Education and Research, S. A. S. Nagar, Punjab, 160062, India. E-mail: jlaha@niper.ac.in

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1cc03777c

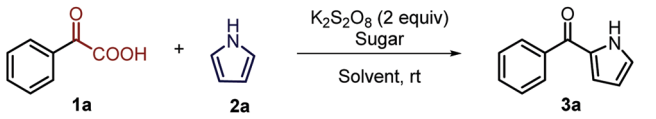


Scheme 1 $K_2S_2O_8$ activation and various organic transformations.

from arylglyoxylates and *ortho*-substituted anilines, the synthesis of phenazines from dibenzodiazepines *via* benzylic methylene group extrusion and the preparation of fluorenones and dipyrromethanes have been reported. The aroyl radical is generated *in situ* from arylglyoxylic acid and $SO_4^{\bullet-}$ *via* decarboxylation. While the nucleophilic aroyl radical could directly react with the electron-deficient alkenes or heteroarenes, the aroyl radical could react with electron-rich heteroarenes or anilines through their corresponding radical cations. Although the mechanisms of the reactions of the aroyl radical and various substrates postulated herein are similar to those of the original literature, any other possibility is not ruled out (see the ESI†). Unlike previous methods that used higher temperatures and an organic solvent in these transformations, the current method uses naturally abundant glucose as the persulfate activator, enabling the reaction to occur at room temperature, especially in water, demonstrating the sustainability of the chemistry reported herein. A gram scale synthesis of the aroylation of isoquinoline in water is also achieved, demonstrating the potential scalability of this method.

We commenced our studies by investigating the compatibility of $K_2S_2O_8$ activation using various naturally abundant sugars in aroylation reactions using the model substrates phenylglyoxylic acid **1a** and pyrrole **2a**. Thus, **1a** (1 equiv.) was reacted with **2a** (1 equiv.) in the presence of $K_2S_2O_8$ (2 equiv.) in MeCN at room temperature for 12 h, which did not result in the formation of 2-acylpyrrole **3a**, suggesting that the activation of

Table 1 Optimization of the compatibility of $K_2S_2O_8$ activation in aroylation reactions using sugar[a]

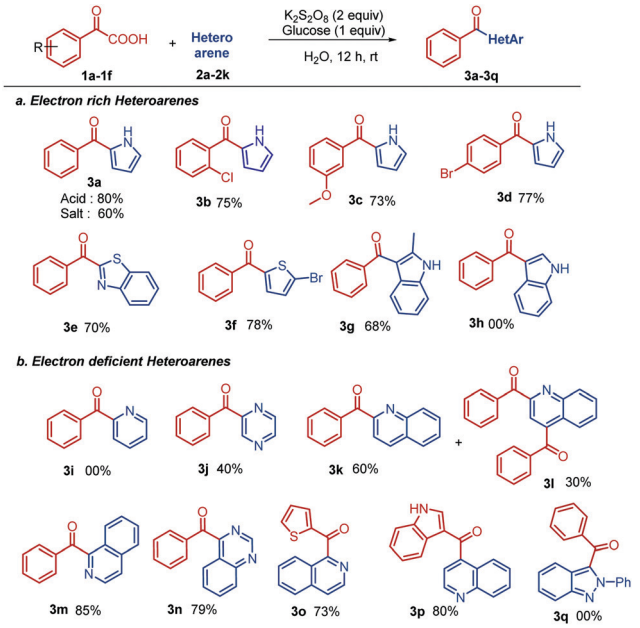


Entry	Sugar	Additive	Solvent	Time (h)	Yield[b] (%)
1	—	—	MeCN	12	00
2	Glucose (1 equiv.)	—	MeCN	12	30
3	Glucose (1 equiv.)	—	MeCN : H_2O (1 : 1)	12	75
4	Glucose (1 equiv.)	—	H_2O	12	80
5	Glucose (1 equiv.)	0.1 N NaOH	H_2O	12	85
6	Chitosan	—	H_2O	12	40
7	Galactose	—	H_2O	12	70
8	Raffinose	—	H_2O	12	40
9	Lactose	—	H_2O	12	50
10	Starch	—	H_2O	12	30
11	Glucose (0.5 equiv.)	—	H_2O	12	74
12	Glucose (1 equiv.)	TEMPO	H_2O	12	00

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $K_2S_2O_8$ (2 equiv.), additive (1 equiv.), solvent (2 mL), room temp (nearly 40 °C). [b] Isolated yield (%).

persulfate was not supported at room temperature (Table 1, entry 1). However, the addition of glucose (1 equiv.) under the same conditions yielded **3a** in 30% yield (entry 2). Solvent screening indicated that the solubility of glucose was optimal in water, yielding an 80% yield of **3a** (entries 2–4). Employing a base as an additive (0.1 N NaOH) could lead to a slightly better yield (entry 5). Changing the sugar from glucose to chitosan, galactose, raffinose, lactose or starch gave **3a** with variable yields (30–70%, entries 6–10). Lowering the equivalent of glucose to half also gave **3a**, however in a somewhat reduced yield (74%, entry 11). The addition of the radical scavenger TEMPO ceased the reaction completely, revealing the involvement of a radical in the reaction (entry 12). As the reaction mixture appears turbid throughout the reaction, the reaction may be regarded as an "on water" reaction. Unlike other $K_2S_2O_8$ mediated organic transformations, the distinct features of this reaction include (a) the presence of both radicals ($SO_4^{\bullet-}$ and $HO^{\bullet}$, see the ESI†) and (b) persulfate chemistry in water.

We next explored the scope and generality of the aroylation reaction (Scheme 2). The reaction of electron-rich pyrrole **2a** with the acid or salt of **1a** proceeded smoothly, affording **3a** in 80% and 60% yields, respectively. The presence of halide and methoxy groups at different positions on the arylglyoxylic acid is tolerated, delivering the corresponding products in good yields (73–77%, **3b–3d**). The acylation was successfully extended to benzothiazole **2b**, 2-bromothiophene **2c**, and 2-methylindole **2e** in good yields (**3e–3g**, 68–78%). Further, switching to other electron deficient heteroarenes like pyrazine **2g**, quinoline **2h**, isoquinoline **2i** and quinazoline **2j**, the corresponding benzolyated products **3i–3n** were obtained in 40%, 60% (also 2,4-diacylated quinoline in 30% yield), 75% and 79% yields, respectively. The addition of 0.1 N NaOH (0.5 equiv.) improved the yields with pyrazine **2g** and



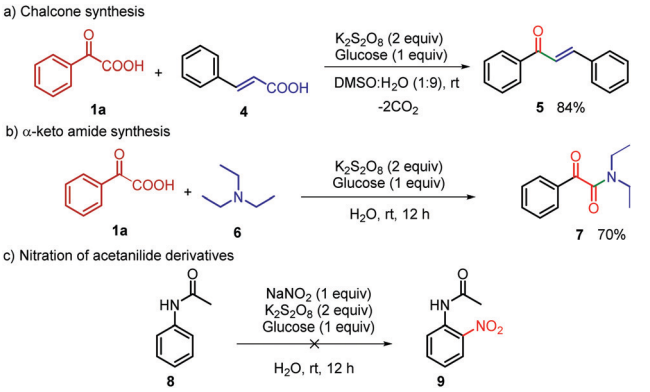
Scheme 2 Aroylation of N-heterocycles.

quinazoline **2j**. The reaction also proceeded well when different heteroarylglyoxylic acids were used, affording **3o–3p** in 73–80% yields. However, the unsubstituted indole **2d**, pyridine **2f** and 2-phenylindazole **2k** failed to undergo acylation. Advantages of this protocol over the reported literature include the elimination of the Lewis acid or transition metal catalyst, organic solvents and higher temperature, delivering products with comparable yields. To demonstrate the scalability of our protocol, the reaction of isoquinoline **2i** (6 mmol) and **1a** (6 mmol) under the optimized condition gave 1.11 g of **3m** in 80% yield at room temperature in water.

Subsequent to the manifestation of the aroylation of various N-heterocycles, we revisited some other functionalization reactions to demonstrate the diverse applications of the protocol.

The reaction of **1a** and cinnamic acid **4** under the optimized conditions gave chalcone **5** in 84% yield (Scheme 3a).[17c] Likewise, the reaction of **1a** and the tertiary amine **6** under the optimized conditions afforded arylglyoxylic amide **7** in 70% yield (Scheme 3b).[17a] The rates of both reactions were improved by the addition of 0.1 equiv. of 0.1 N NaOH. Unlike the obvious use of silver or a transition metal at higher temperatures in previously reported reactions,[17a,c] these reactions proved successful under our optimized conditions. However, the regioselective *ortho* C–H nitration of the anilide **8** was unsuccessful using our protocol (Scheme 3c).[17f]

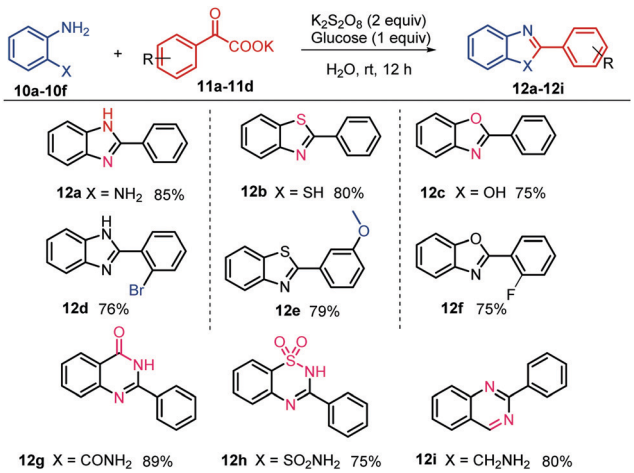
To demonstrate the synthetic applicability of this protocol in the synthesis of N-heterocycles, we reinvestigated the tandem reactions of various *ortho*-substituted anilines (**10a–10f**) and aryl glyoxylates (**11a–11d**) under the optimized conditions (Scheme 4).[17d,h] *o*-Phenylenediamine **10a** reacted with **11a** under our optimized conditions to give the mono-acylated product, which upon subsequent intramolecular cyclization gave (NH)-benzimidazole **12a** in 85% yield. To our delight, 2-aminothiophenol **10b** and 2-aminophenol **10c**



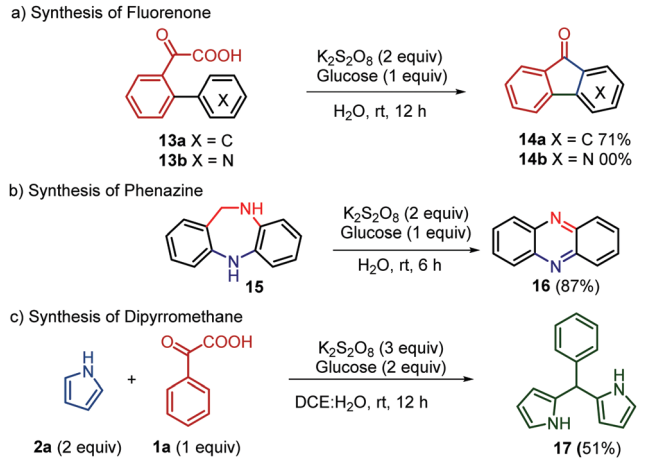
Scheme 3 Demonstration of other functionalization reactions.

gave 2-phenyl benzothiazole **12b** and benzoxazole **12c** in 80% and 75% yields, respectively. The other derivatives **12d–12f** were also synthesized under the optimized conditions. The reactions of 2-aminobenzamide **10d**, 2-aminobenzenesulfonamide **10e** and 2-aminobenzylamine **10f** occurred, although in the presence of 0.1 N NaOH, affording quinazolinone **12g**, 1,2,4-benzothiadiazine-1,1-dioxide **12h** and quinazoline **12i** in 75–89% yield. The yields of the products formed using this protocol are either comparable or higher than those reported in the literature.[17d,h]

When the intramolecular aroylation of 2-([1,1′-biphenyl]-2-yl)-2-oxoacetic acid **13a** under our optimized conditions was performed, the reaction successfully gave fluorenone **14a** in 71% yield.[17e] Similar to our unsuccessful attempt at the intermolecular aroylation of pyridines, the intramolecular aroylation of **13b** did not yield azafluorenone **14b**, revealing that our reaction conditions were not compatible with pyridine derivatives (Scheme 5a). The tandem oxidative conversion of 10, 11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepine **15** to phenazine **16** was successfully achieved at room temperature, giving 87% yield (Scheme 5b).[17b] The synthesis of dipyrromethane **17** from the pyrrole **2a** and **1a** under slightly modified conditions afforded **17** in 51% yield (Scheme 5c).[17i] While the yields are slightly lower than previously reported yields, the advantages in



Scheme 4 Synthesis of N-heterocycles.



Scheme 5 Scope for the synthesis of other heterocycles.

our protocol include the use of room temperature and water.[17b,e,i]

By reinvestigating $K_2S_2O_8$-mediated organic reactions that invariably require higher temperature and an organic solvent, we have developed a mild, green strategy for the diverse synthesis and functionalization of N-heterocycles at room temperature in water using inexpensive $K_2S_2O_8$ as the primary reagent. Unlike traditional methods used for persulfate activation, the current method uses glucose as the persulfate activator at room temperature to generate $SO_4^{\bullet-}$. Although the involvement of $SO_4^{\bullet-}$ in these organic transformation is likely, whether the mechanisms of all of these transformations mirror those reported in the original literature remains a question. Further applications of this protocol and the underlying mechanism are currently under investigation.

M. K. H. performed all experimentation and manuscript preparation. J. K. L. was involved in the inception of the concept, manuscript preparation and editing.

The generous funding of the project by SERB, New Delhi is greatly appreciated (award no. CRG/2020/000462). M. K. H. thanks the NIPER S.A.S. Nagar for a research fellowship.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 See review on oxidative C–H functionalization: (*a*) C. Zheng and S. L. You, *RSC Adv.*, 2014, **4**, 6173; (*b*) G. Qiu, K. Zhou and J. Wu, *Chem. Commun.*, 2018, **54**, 12561; (*c*) P. J. Borpatra, B. Deka, M. L. Deb and P. K. Baruah, *Org. Chem. Front.*, 2019, **6**, 3445; (*d*) S. Ye, M. Yang and J. Wu, *Chem. Commun.*, 2020, **56**, 4145.

2 See review on synthesis of heterocycles *via* oxidative C–H functionalization: (*a*) D. J. Abrams, P. A. Provencher and E. J. Sorensen, *Chem. Soc. Rev.*, 2018, **47**, 8925; (*b*) B. Nie, W. Wu, Y. Zhang, H. Jiang and J. Zhang, *Org. Chem. Front.*, 2020, **7**, 3067.

3 See review on oxidative C–C and C–X bond formation: (*a*) H. M. Davies, J. D. Bois and J. Q. Yu, *Chem. Soc. Rev.*, 1855, **2011**, 40; (*b*) G. B. Shul'pin, *Catalysts*, 2016, **6**, 50; (*c*) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, *Chem. Rev.*, 2017, **117**, 9016.

4 (*a*) F. Minisci and A. Citterio, *Acc. Chem. Res.*, 1983, **16**, 27; (*b*) S. Sathyamoorthi and S. Banerjee, *ChemistrySelect*, 2017, **2**, 10678; (*c*) S. Mandal, T. Bera, G. Dubey, J. Saha and J. K. Laha, *ACS Catal.*, 2018, **8**, 5085; (*d*) S. Kumar and K. Padala, *Chem. Commun.*, 2020, **56**, 15101.

5 J. Wang and S. Wang, *Chem. Eng. J.*, 2018, **334**, 1502.

6 (*a*) G. Fang, J. Gao, D. D. Dionysiou, C. Liu and D. Zhou, *Environ. Sci. Technol.*, 2013, **47**, 4605; (*b*) Y. Fenga, D. Wub, Y. Zhoua and K. Shih, *Chem. Eng. J.*, 2017, **330**, 906.

7 G. Fang, X. Cong, G. Zanoni, Q. Liu and X. Bi, *Adv. Synth. Catal.*, 2017, **359**, 1422.

8 (*a*) R. J. Watts, M. Ahmad, A. K. Hohner and A. L. Teel, *Water Res.*, 2018, **133**, 247; (*b*) W. C. Vasudeva, M. I. Taha and S. Wasif, *J. Inorg. Nucl. Chem.*, 1972, **34**, 3159.

9 S. Wacławeka, H. V. Lutzeb, K. Grübele, V. V. T. Padila, M. Černíka and D. D. Dionysiou, *Chem. Eng. J.*, 2017, **330**, 44.

10 (*a*) I. M. Kolthoff and I. K. Miller, *J. Org. Chem.*, 1951, **73**, 3055; (*b*) D. A. House, *Chem. Rev.*, 1962, **62**, 185.

11 M. Brienza and I. A. Katsoyiannis, *Sustainability*, 2017, **9**, 1604.

12 C. Lee, H. H. Kim and N. B. Park, *Membr. Water Treat.*, 2018, **9**, 405.

13 J. Lee, U.-v. Gunten and J.-H. Kim, *Environ. Sci. Technol.*, 2020, **54**, 3064.

14 L. W. Matzek and K. E. Carter, *Chemosphere*, 2016, **151**, 178.

15 Review on functionalization in water: (*a*) C.-J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68; (*b*) B. H. Lipshutz, F. Gallou and S. Handa, *ACS Sustainable Chem. Eng.*, 2016, **4**, 5838–5849; (*c*) T. Kitanosono, K. Masuda, P. Xu and S. Kobayashi, *Chem. Rev.*, 2018, **118**, 679.

16 Review on synthesis of heterocycles in water: (*a*) N. R. Candeias, L. C. Branco, P. M. P. Gois, C. A. M. Afonso and A. F. Trindade, *Chem. Rev.*, 2009, **109**, 2703; (*b*) A. Chanda and V. V. Fokin, *Chem. Rev.*, 2009, **109**, 725; (*c*) M. B. Gawande, V. D. B. Bonifácio, R. Luque, P. S. Branco and R. S. Varma, *Chem. Soc. Rev.*, 2013, **42**, 5522; (*d*) N. A. Harry, S. Radhika, M. Neetha and G. Anilkumar, *ChemistrySelect*, 2019, **4**, 12337.

17 (*a*) X. Zhang, W. Yanga and L. Wang, *Org. Biomol. Chem.*, 2013, **11**, 3649; (*b*) J. K. Laha, K. S. S. Tummalapalli and A. Gupta, *Org. Lett.*, 2014, **16**, 4392; (*c*) Q. Jiang, J. Jia, B. Xu, A. Zhao and C. Guo, *J. Org. Chem.*, 2015, **80**, 3586; (*d*) J. K. Laha, K. V. Patel, K. S. S. Tummalapalli and N. Dayal, *Chem. Commun.*, 2016, **52**, 10245; (*e*) J. K. Laha, K. V. Patel, G. Dubey and K. P. Jethava, *Org. Biomol. Chem.*, 2017, **15**, 2199; (*f*) E. Kianmehr and S. B. Nasab, *Eur. J. Org. Chem.*, 2018, 6447; (*g*) J. K. Laha, M. K. Hunjan, S. Hegde and A. Gupta, *Org. Lett.*, 2020, **22**, 1442; (*h*) J. K. Laha, S. Panday, M. Tomar and K. V. Patel, *Org. Biomol. Chem.*, 2021, **19**, 845; (*i*) J. K. Laha and M. K. Hunjan, *J. Porphyrins Phthalocyanines*, 2021, DOI: 10.1142/S1088424621500619.

