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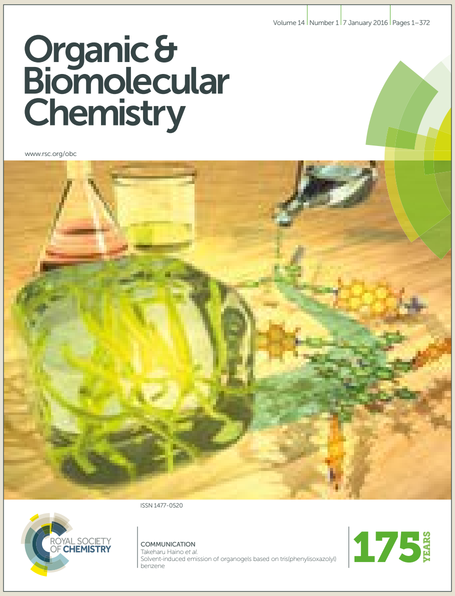

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COMMUNICATION

Photocatalytical aerobic α-thiolation/annulation of carbonyls with mercaptobenzimidazoles

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A concise aerobic photocatalysis by blue LED combined with Lewis acid has been developed to enable α-thiolation/annulation of carbonyls. Inexpensive, nontoxic Rose Bengal was demonstrated as the best catalyst. Hence, this transition-metal-free protocol allows mild Csp^3-S couplings with both ketones and aliphatic aldehydes with a range of useful functionalities compatible.

Organosulfur compounds widely exist in pharmaceuticals, naturally occurring products, and advanced functional materials.[1] Hence, the development of C–S bond formation reactions has been receiving much interest in molecule synthesis.[2] Beyond the well-established nucleophilic substitution of organohalides with mercaptans and thiophenols, recently disclosed oxidative C–H/S–H couplings represent a straightforward strategy to construct C–S bonds, which therein shows advantages with respect to reaction convergence and productivity. Furthermore, electrocatalysis[3] and photocatalysis[4] found effective to this event, featuring easy manipulation, mild reaction conditions, and environmental benign byproducts. For example, Lei[5] and Guo[6] have independently revealed dehydrogenative C–H/S–H cross-coupling of electron-rich arenes with aryl/heteroaryl thiols through catalyst- and oxidant-free electrochemistry and metal-free aerobic photocatalysis, respectively. Regarding oxidative Csp^3–S bond formation, in 2015, Lei *et al.* reported a iodine-catalyzed oxidative coupling between 1,3-diketones and thiophenols to form β-dicarbonyl thioethers (Figure 1a).[7] Soon later, the same group developed an oxidative *β*-Csp^3–H thiolation of ^{t}BuOH (Figure 1b).[8] In both cases, di-*t*-butyl peroxide (DTBP) was used as the oxidant. In 2016, Wang and co-workers described a protocol to access α-arylthioethers via visible-light-induced direct α-Csp^3–H thiolation of ethers with diaryl disulfides with acridine red as the efficient photocatalyst (Figure 1c).[9] In reaction complementary to these works, radical addition-involved difunctionalization of alkenes also provides viable access to Csp^3–S bond formation, in which sulfur radicals were generally in-situ formed by the initiation of single electron oxidation or pyrolysis of X–S bonds (Figure 1d).[10] Very recently, Wang and co-workers described a one-pot, two-step synthesis of pharmacologically important pyridine-2-ylmethyl thioethers using 2-picoline N-oxides as an internal oxidant.[11]

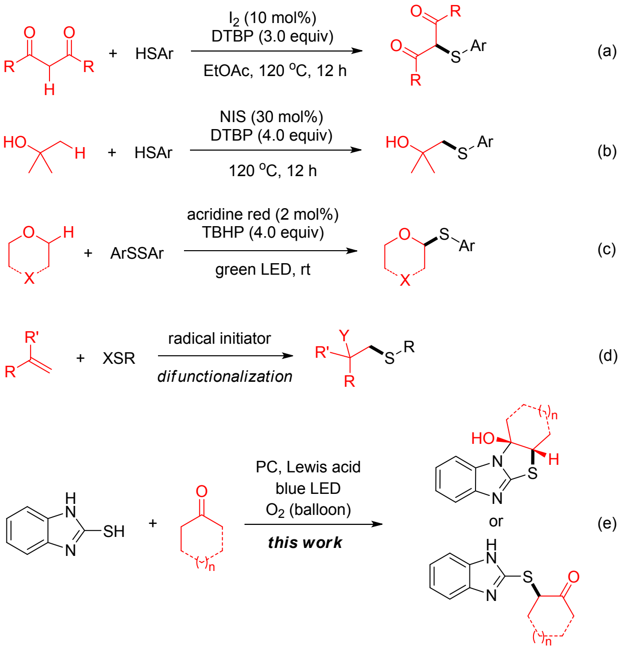

Figure 1 Oxidative Csp^3–S bond formation.

In spite of these utilities, the mild and sustainable Csp^3–S bond formation and related applications are still highly desirable. Within our own program on green chemistry with molecular oxygen,[12] herein, we have revealed a photocatalytic aerobic Csp^3–H/S–H coupling of mercaptobenzimidazole with carbonyls triggered by visible light (Figure 1e). Thus, salient features of this protocol include (a) inexpensive, nontoxic Rose Bengal as the catalyst, (b) easily available dioxygen as the green oxidant, (c) Csp^3–S couplings with both ketones and challenging aliphatic aldehydes, and (d) cyclic

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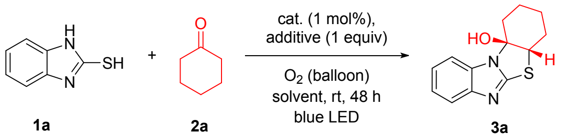
products via a formal oxidative [3+2] cycloaddition accessed in most cases.

To commence our studies, 1*H*-benzo[*d*]imidazole-2-thiol (**1a**) and cyclohexanone (**2a**) were utilized as the model substrates (Table 1). While stoichiometric amounts of $AlCl_3$ were used as a Lewis acid to activate ketone **2a**, photocatalysts such as $Ru(bpy)_3Cl_2{\cdot}6H_2O$, *fac*-$Ir(ppy)_3$, Eosin Y, and Rose Bengal (RB) combined with O_2 found all effective to trigger the oxidative $Csp^3{-}S$ bond formation (entries 1–4). Therein, cyclic product **3a** via formal oxidative [3+2] cycloaddition was generated in moderate yields, and the diastereoselectivity of **3a** was determined by comparison with literature and nOe spectrum (See ESI for details). Among those photocatalysts tested, Rose Bengal showed the most active for this reaction (entry 4). Then, other Lewis acids such as $Sc(OTf)_3$ and $Y(OTf)_3$ and Brønsted acid CF_3COOH (TFA) instead of $AlCl_3$ decreased the yield to some extent (entries 5–7). Solvent screening revealed that 1,4-dioxane (entry 8) and THF (entry 9) slightly lowered the yield to 48% and 42%, respectively, while DMF completely quenched the transformation (entry 10). We also tested some other oxidants including previously established peroxides and found that among them only $Na_2S_2O_8$ featured the same efficiency (entries 11–13). Control experiments showed that photocatalyst, light, Lewis acid, and O_2 were all essential to this reaction (entries 14–18).

Table 1 Optimization of the reaction conditions[a]

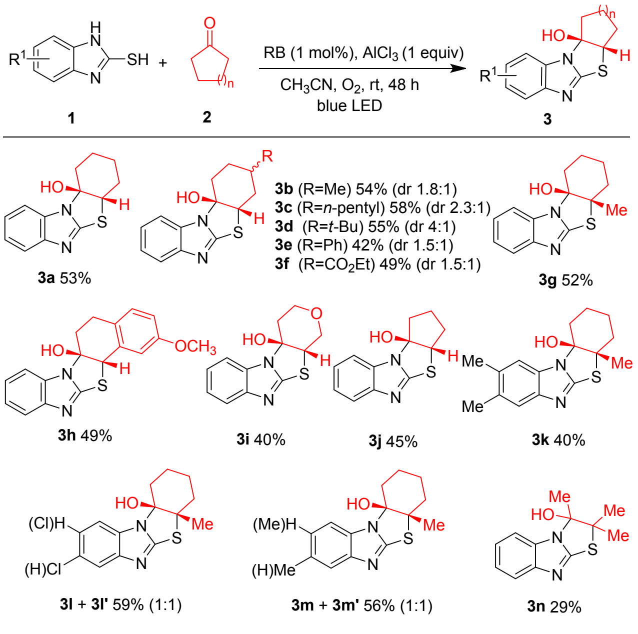


entry	catalyst	Lewis acid	solvent	yield (%)[b]
1	[Ru]	$AlCl_3$	CH_3CN	42
2	[Ir]	$AlCl_3$	CH_3CN	45
3	Eosin Y	$AlCl_3$	CH_3CN	41
4	RB	$AlCl_3$	CH_3CN	58 (53)
5	RB	TFA	CH_3CN	19
6	RB	$Sc(OTf)_3$	CH_3CN	40
7	RB	$Y(OTf)_3$	CH_3CN	25
8	RB	$AlCl_3$	1,4-dioxane	48
9	RB	$AlCl_3$	THF	42
10	RB	$AlCl_3$	DMF	0
11[c]	RB	$AlCl_3$	CH_3CN	22
12[d]	RB	$AlCl_3$	CH_3CN	55
13[e]	RB	$AlCl_3$	CH_3CN	33
14[f]	RB	$AlCl_3$	CH_3CN	0
15[g]	RB	$AlCl_3$	CH_3CN	0
16	RB	-	CH_3CN	0
17[h]	RB	$AlCl_3$	CH_3CN	trace
18	-	$AlCl_3$	CH_3CN	trace

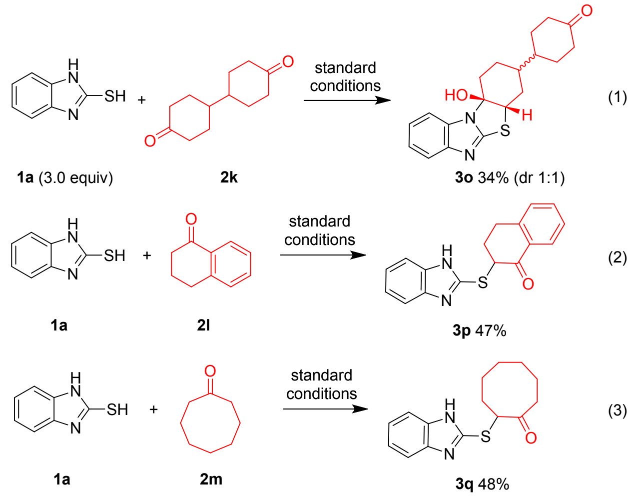
[a] Reaction condition: **1a** (0.3 mmol), **2a** (0.3 mmol), cat. (1 mol%), Lewis acid (1 equiv), solvent (3 mL), 7 W blue LED, O_2 balloon, 48 h. [Ru] = $Ru(bpy)_3Cl_2{\cdot}6H_2O$; [Ir] = *fac*-$Ir(ppy)_3$. [b] Yields were determined from the crude ^1H NMR spectra using CH_2Br_2 as an internal standard. Isolated yield in parentheses. [c] TBHP (1 equiv) was used under N_2 atmosphere. [d] $Na_2S_2O_8$ (1 equiv) was used under N_2 atmosphere. [e] BPO (1 equiv) was used under N_2 atmosphere. [f] In dark. [g] Performed at 60 °C in dark. [h] Under N_2 atmosphere.

With the optimized reaction conditions in hand, the substrate scope was explored (Table 2). Regarding 4-substituted cyclohexanones, the corresponding cyclic products **3b-3f** were furnished in modest yields with a mixture of two diastereomers (dr = 1.5:1 to 4:1). Notably, most of those products with poor diastereoselectivity could not be separated by column chromatography. We only got pure diastereomers of **3b** and the structure of *cis*-**3b** was determined by nOe spectrum. Synthetically useful ester group was well tolerated in this acidic system. To our delight, the reaction with 2-methylcyclohexanone featured good reactivity and excellent regioselectivity, in which **3g** was exclusively formed in 52% yield. For this formal oxidative [3+2] cycloaddition, β-tetralone also gave cyclic product (**3h**) with exclusive regioselectivity. Other effective ketones included tetrahydropyranone and cyclopentanone, both of which afforded moderate yields of products. The reaction of 5,6-dimethyl-1*H*-benzo[*d*]imidazole-2-thiol and 2-methylcyclohexanone formed **3k** in 40% yield. Both of 5-methyl- and 5-chloro-1*H*-benzo[*d*]imidazole-2-thiol delivered a 1:1 mixture of two regio-isomers. For acyclic aliphatic ketones, the corresponding products were generally formed in lower yields. For example, 3-methylbutan-2-one afforded **3n** as the major product in only 29% yield.

Table 2 Aerobic α-thiolation of ketones.

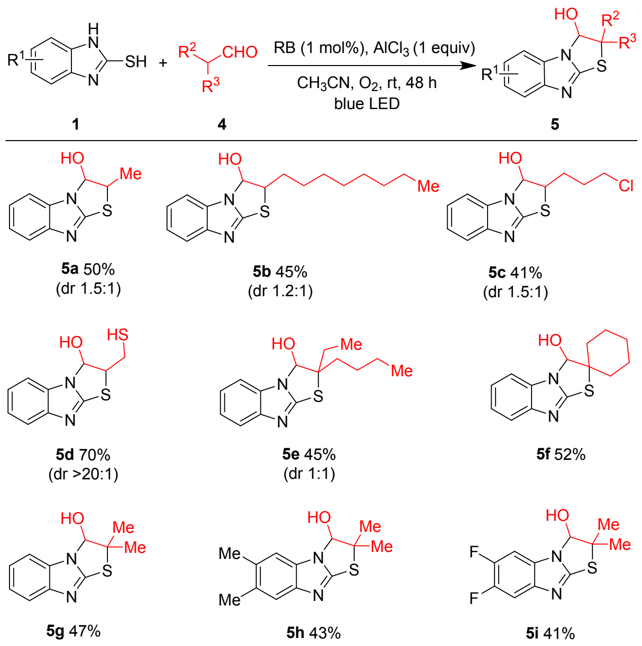


Unexpectedly, two-fold cycloaddition was not happened when [1,1'-bi(cyclohexane)]-4,4'-dione (**2k**) was subjected to present aerobic photocatalysis even with excessive **1a**. In this case, product **3o** was furnished in 34% yield [Eq. (1)]. Furthermore, α-tetralone [Eq. (2)] and cyclooctanone [Eq. (3)] gave only α-C-H thiolation products **3p** and **3q**, respectively, while propiophenone and cycloheptanone generated a mixture of cyclic and acyclic products and acetophenone did not work in present system.



Besides cyclic ketones, aliphatic aldehydes found also effective to this aerobically photocatalytic Csp^3-S coupling/cycloaddition (Table 3). For example, propionaldehyde generated **5a** in 50% yield with 1.5:1 dr value, while decanal afforded **5b** with similar reactivity and selectivity. Alkylchloride was well accommodated with this system when 5-chloropentanal was employed. Excellent stereoselectivity was observed when 3-mercaptopropanal was used, in which only cis isomer was detected probably due to the hydrogen bonding effect. Finally, the α-branched aldehydes worked all well, giving the corresponding products **5e**–**5i** in moderate yields.

Table 3 Aerobic α-thiolation of aldehydes.



As shown above, the oxidative annulation products **3** and **5** were generally obtained in moderate yields. Actually, mercaptobenzimidazole was not stable in present photocatalytic system, and decomposition of it was observed. Minor amounts of acyclic products were also observed in some cases. However, the robust nature of the present aerobically photocatalytic system was further reflected by the effective gram-scale preparation, which gave an acceptable productivity (46%, Figure 2a). Notably, the resultant fused hydroxyl thiazoline **3a** could be easily transformed to tetrahydrobenzo[d]benzo[4,5] imidazo[2,1-b]thiazole **6a** in an almost quantitative yield in acidic systems (Figure 2b). Moreover, hydroxyl thiazoline **5g** was readily oxidized to amide product **6b** by pyridinium chlorochromate (PCC) (Figure 2c).

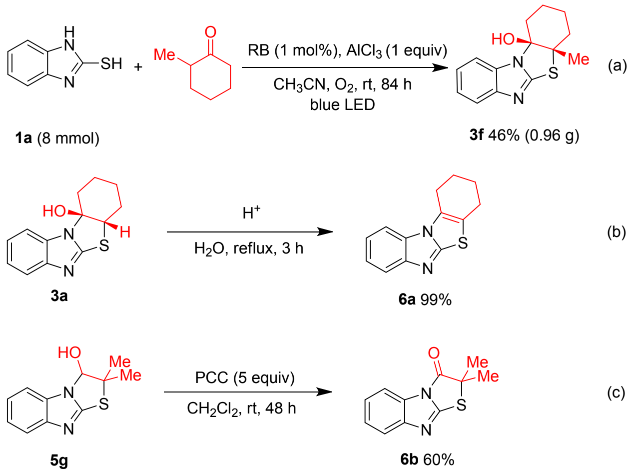


Figure 2. Applications of the aerobic α-thiolation.

To determine the reaction mechanism for the visible-light triggered aerobic C-S bond formation, some control experiments were performed (Figure 3a). The addition of radical scavengers such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT), and 1,1-diphenylethene dramatically reduced the product yields, which suggests a radical pathway is taking place. Furthermore, when the singlet oxygen quencher 1,4-diazabicyclo[2.2.2]octane (DABCO) was added to the reaction mixture, the yield of **3a** decreased to 23%. In addition, fluorescence quenching experiments were also investigated to prove an energy transfer process between mercaptobenzimidazole (**1a**) and Rose Bengal (Stern–Volmer studies) (Figure 3b). Indeed, it was found that the emission intensity of excited Rose Bengal (RB*) was dramatically diminished along with the increasing of the amount of **1a**. In contrast, no such effect was observed when cyclohexanone **2a** was added separately. Thus, the interaction of **1a** and photocatalyst should be the initial step.

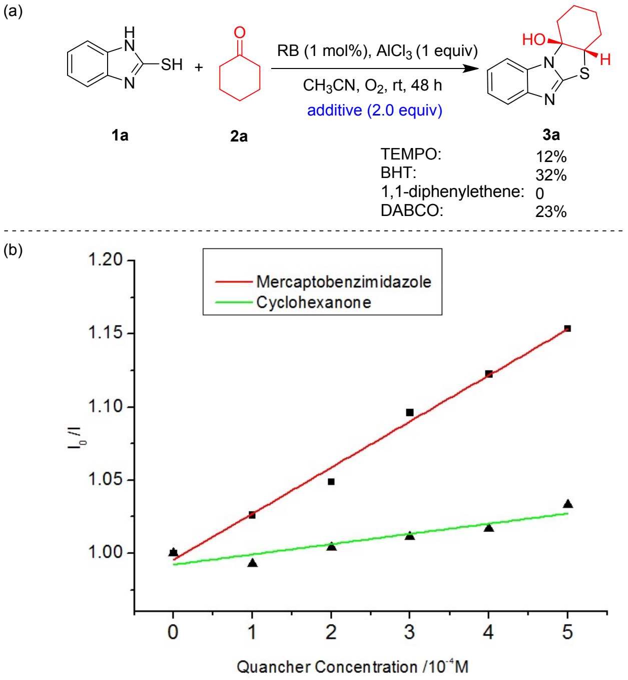


Figure 3. Key mechanistic findings. (a) Radical trapping reactions; (b) Fluorescence quenching experiments (Stern–Volmer studies).

On the basis of the experimental results and previous reports,[4g, 10b, 10d] a plausible reaction mechanism was proposed (Figure 4). Initially, Rose Bengal (RB) was converted into the excited RB* under visible-light irradiation. Then, a single electron transfer (SET) from thiol **1a** to RB* afforded the thiyl radical ion **A**, which underwent a deprotonation to form radical **B**. Subsequently, the addition of thiyl radical **B** to enol **C**, in situ activated by Lewis acid, led to the formation of alkyl radical **D**. Furthermore, a SET process and deprotonation occurred again to give sulfide intermediate **E**, which underwent nucleophilic annulations and workup to afford the final product **3a**. The reductive photocatalyst RB• would transfer to catalytically active catalyst via SET with O_2 and light stimulation.

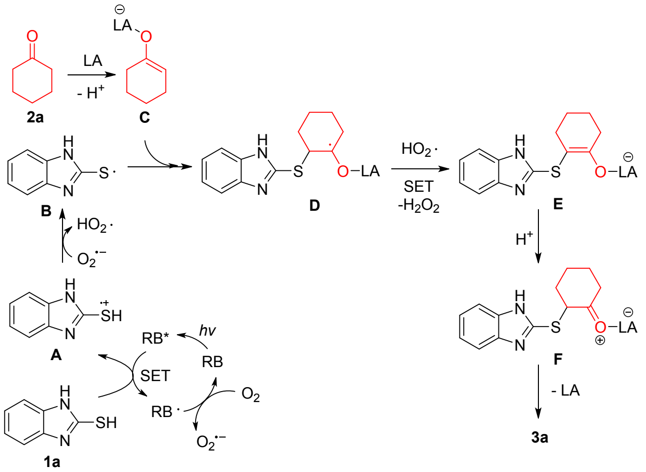


Figure 4 Possible reaction mechanism.

In summary, a photocatalytically aerobic reaction system with visible light has been developed for the efficient dehydrogenative couplings of Csp^3–S bonds. This protocol provides a novel entry to oxidative formal [3+2] annulation, which allows smooth participation of a broad range of carbonyls including cycloketones and aliphatic aldehydes. The application of this method was further demonstrated by the effective gram-scale reaction and readily viable late-stage modification of the resultant adducts.

ACKNOWLEDGMENT

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Notes and references

1 (a) A. Dondoni, *Angew. Chem. Int. Ed.*, 2008, **47**, 8995-8997; (b) D. A. Boyd, *Angew. Chem. Int. Ed.*, 2016, **55**, 15486-15502.

2 (a) T. B. Nguyen, *Adv. Synth. Catal.* , 2017, **359**, 1066–1130; (b) T. Chivers and P. J. Elder, *Chem. Soc. Rev.*, 2013, **42**, 5996-6005; (c) H. Liu and X. Jiang, *Chem. Asian. J.*, 2013, **8**, 2546-2563.

3 (a) M. Yan, Y. Kawamata and P. S. Baran, *Angew. Chem. Int. Ed.*, 2018, **57**, 4149-4155; (b) S. Mohle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe and S. R. Waldvogel, *Angew. Chem. Int. Ed.*, 2018, **57**, 6018-6041; (c) S. Tang, Y. Liu and A. Lei, *Chem*, 2018, **4**, 27-45; (d) S. R. Waldvogel, S. Lips, M. Selt, B. Riehl and C. J. Kampf, *Chem. Rev.*, 2018, **118**, 6706-6765; (e) G. Zhang, C. Liu, H. Yi, Q. Meng, C. Bian, H. Chen, J. X. Jian, L. Z. Wu and A. Lei, *J. Am. Chem. Soc.*, 2015, **137**, 9273-9280.

4 (a) T. P. Yoon, M. A. Ischay and J. Du, *Nat. Chem.*, 2010, **2**, 527-532; (b) J. Xuan and W. J. Xiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 6828-6838; (c) C. K. Prier, D. A. Rankic and D. W. MacMillan, *Chem. Rev.*, 2013, **113**, 5322-5363; (d) N. Corrigan, S. Shanmugam, J. Xu and C. Boyer, *Chem. Soc. Rev.*, 2016, **45**, 6165-6212; (e) D. C. Fabry and M. Rueping, *Acc. Chem. Res.*, 2016, **49**, 1969-1979; (f) C. Bian, A. K. Singh, L. Niu, H. Yi and A. Lei, *Asian J. Org. Chem.*, 2017, **6**, 386-396; (g) W. Guo, K. Tao, W. Tan, M. Zhao, L. Zheng and X. Fan, *Org. Chem. Front.*, 2019, 10.1039/c8qo01353e.

5 P. Wang, S. Tang, P. Huang and A. Lei, *Angew. Chem. Int. Ed.*, 2017, **56**, 3009-3013.

6 W. Guo, W. Tan, M. Zhao, K. Tao, L.-Y. Zheng, Y. Wu, D. Chen and X.-L. Fan, *RSC Adv.*, 2017, **7**, 37739-37742.

7 H. Cao, J. Yuan, C. Liu, X. Hu and A. Lei, *RSC Adv.*, 2015, **5**, 41493-41496.

8 Y. Li, D. Liu, C. Liu and A. Lei, *Chem. Asian J.*, 2016, **11**, 2246-2249.

9 X. Zhu, X. Xie, P. Li, J. Guo and L. Wang, *Org. Lett.*, 2016, **18**, 1546-1549.

10 (a) Q. Lu, H. Wang, P. Peng, C. Liu, Z. Huang, Y. Luo and A. Lei, *Org. Chem. Front.*, 2015, **2**, 908-912; (b) S. Tang, K. Liu, C. Liu and A. Lei, *Chem. Soc. Rev.*, 2015, **44**, 1070-1082; (c) Y. Yuan, Y. Chen, S. Tang, Z. Huang and A. Lei, *Sci. Adv.* , 2018, **4**, eaat5312; (d) H. Cui, W. Wei, D. Yang, Y. Zhang, H. Zhao, L. Wang and H. Wang, *Green Chem.*, 2017, **19**, 3520-3524.

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DOI: 10.1039/C9OB00625G

11 D. Wang, Z. Liu, Z. Wang, X. Ma and P. Yu, *Green Chem.*, 2019, **21**, 157-163.

12 (a) H. Huang, J. Cai, X. Ji, F. Xiao, Y. Chen and G. J. Deng, *Angew. Chem. Int. Ed.*, 2016, **55**, 307-311; (b) X. Ji, D. Li, X. Zhou, H. Huang and G.-J. Deng, *Green Chem.*, 2017, **19**, 619-622; (c) X. Ji, DongdongLi, Z. Wang, MuyunTan, H. Huang and G.-J. Deng, *Asian J. Org. Chem.*, 2018, **7**, 711–714; (d) Z. Wang, X. Chen, H. Xie, D. Wang, H. Huang and G. J. Deng, *Org. Lett.*, 2018, **20**, 5470-5473.

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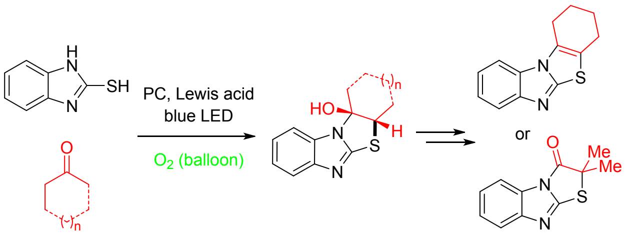

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