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View Article Online
DOI: 10.1039/D0CC02416C

Journal Name

COMMUNICATION

Visible-Light Driven Synthesis of Polycyclic Benzo[*d*][1,3]oxazocine From 2-Aminochalcone

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Herein, we report a tandem cycloisomerization/nucleophilic addition/cyclization of 2-amino chalcone with bifunctional nucleophiles driven by visible light. This cascade process is realized by the irradiation of blue LED at room temperature, which provides a concise access to structurally diverse benzo[*d*][1,3]oxazocine scaffold. Mechanistic studies show that the reaction is initiated with the *E* to *Z* isomerization of C-C double bond upon the irradiation of visible light, followed by cyclization/rearomatization to generate a transient quinolinium intermediate, which is trapped by the nucleophile and cyclized to produce the polycyclic benzo[*d*][1,3]oxazocine.

Dearomatization is a promising strategy for creating complex architecture from easily available aromatic molecules.[1] Particularly, it enables building up sp^3-rich carbocyclic molecules with unique three-dimensional structure from planar molecules via cycloaddition or cascade process, which offer a competent tool for increasing structural complexity. However, this strategy largely relies on the innate reactivity of aromatic compounds and those with higher resonance energy often show inert reactivity, which needs force reaction conditions (e.g. Birch reduction, using organolithium reagent) to break up the aromaticity.[2] Therefore, generation of reactive species by combining hetereoaromatic molecules with activating reagents constitutes an alternative strategy for the dearomatization reaction.[3] However, this protocol needs the pre-activation of the hetereoaromatic compounds, which complicates the operation.

Harnessing visible light in the presence of photoredox catalyst for chemical synthesis has experienced incredible progresses due to the increasing demand for developing green and sustainable chemistry.[4] In most cases, photoredox catalyst plays an important role in transferring light energy to reaction partners via redox neutral pathway. Depending on the unique activating mode of photoredox catalyst, molecules could be activated via energy transfer or single electron transfer (SET) pathways and involved in the subsequent transformations. In this context, the directly utilizing visible light for dearomatization reaction in the absence of any photoredox catalyst or sensitizer has remained scarcely developed.[5]

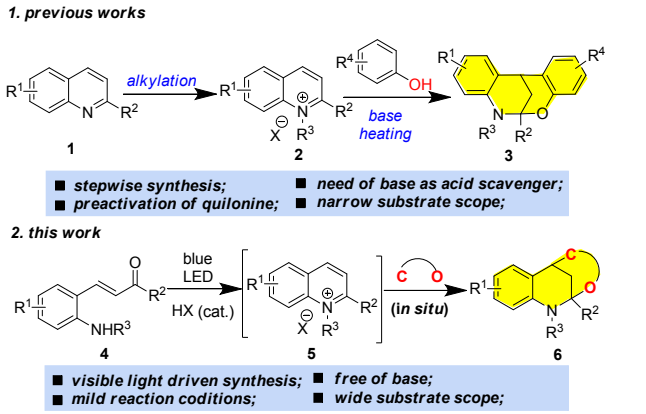

Figure 1. Previous protocols for the synthesis polycyclic benzo[*d*][1,3]oxazocine and a light-driven synthesis of such scaffold.

Benzoxazocine is a family of molecules embedding both oxygen and nitrogen in the eight-membered ring system, which exhibits important pharmaceutical properties including analgesic, antithrombotic, anticancer and antioxidant activities.[6] In this regard, benzo[*d*][1,3]oxazocine is far less studied despite of its tetrahydruquinoline[7] and *N,O*-acetal[8] moieties which are commonly existed in natural products and pharmaceutical molecules. In previous reports,[9] quinolinium salts **2** have been employed for the synthesis of such skeleton via nucleophilic dearomatization with bifunctional nucleophiles (Figure 1). However, base is needed to

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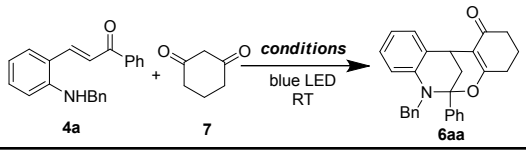
Electronic Supplementary Information (ESI) available: General experimental procedures, and spectroscopic date for the all new compounds. See DOI: 10.1039/x0xx00000x

functionalize as the acid scavenger and a preformation of quinolinium from quinoline is necessitated. Furthermore, those precedents showed narrow substrate scope and only phenol or naphthol have been surveyed as the bifunctional nucleophile.

Recently, we disclosed a bio-inspired synthesis of hybrid flavonoids from 2-hydroxychalconet.[10] This reaction relies on the generation of a reactive transient flavylium from 2-hydroxychalcone under the irradiation of 24W CFL followed by dehydrated cyclization, which *in situ* engaged in the subsequent cascade transformations to deliver hybrid flavonoids. In continuation of our work on this bio-inspired strategy, we surmised that under the irradiation of visible light, 2-amiochalcone **4** would undergo tandem *E-Z* isomerization/cyclization/dehydration process to yield a transient quinolinium **5**. Subsequently, this intermediate would involve in cascade nucleophilic addition/cyclization process, delivering polycyclic benzo[*d*][1,3]oxazocine **6**. Herein, we would like to report our preliminary results on this visible-light driven synthesis, which eliminates the pre-activation of quinoline and the use of strong base.

Table 1. Survey of the reaction conditions.[a]

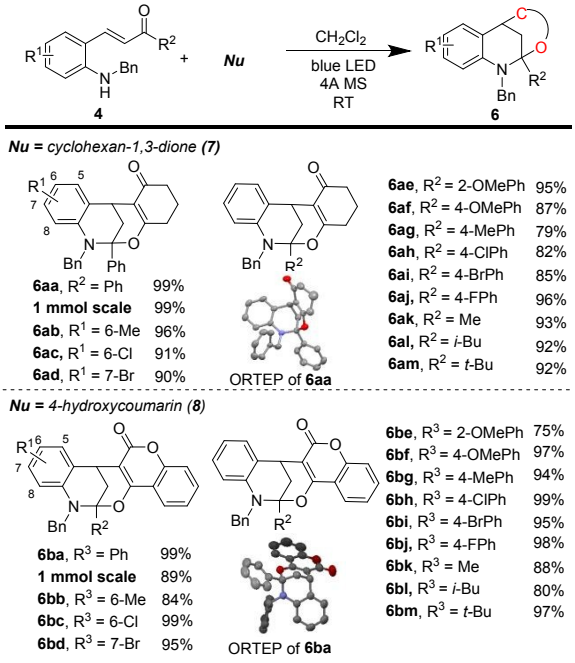


entry	catalyst	solvent	time (min)	yield[b] (%)
1	HCl	CH_2Cl_2	20	97
2	TsOH	CH_2Cl_2	10	95
3	CSA	CH_2Cl_2	10	96
4	$(PhO)_2O$=POH	CH_2Cl_2	20	95
5	Benzoic acid	CH_2Cl_2	15	98
6	Benzoic acid	THF	25	97
7	Benzoic acid	Et_2O	65	90
8	Benzoic acid	$PhCH_3$	25	96
9	Benzoic acid	CCl_4	90	70
10	Benzoic acid	CH_2ClCH_2Cl	15	97
11	Benzoic acid	$CHCl_3$	10	98
12	--	CH_2Cl_2	10	99
13[c]	--	CH_2Cl_2	13	ND

[a] Reaction conditions: To a mixture of 2-aminochalcone **4a** (0.1 mmol) and cyclohexan-1,3-dione **7** (0.12 mmol) was added solvent (3 mL) and 4Å MS (100 mg). The reaction mixture was stirred with the irradiation of blue LED. [b] isolated yields. [c] The reaction was carried out in dark.

On the outset, reaction of 2-aminochalcone **4a** with cyclohexan-1,3-dione **7** was evaluated to validate our hypothesis. To our delight, the desired benzoxazocine **6aa** could be isolated in 97% yield under the irradiation of household blue LED in the presence of catalytic amount of hydrochloride (Table 1, entry 1). It should be pointed out that the reaction proceeded very fast, reaching full conversion of **4a** only in 10 min. Subsequently, screening of different Brønsted acids revealed that benzoic acid was the most optimal promoter, which provided the desired product in 98% yield (Table 1, entries 2 to 5). Survey of solvent was then performed (Table 1, entries 6 to 11). Ethereal solvents (Et_2O and THF) as well as toluene were all suitable for this reaction, while longer time was needed to secure the full consumption of **4a** (Table 1, entries 6 to 8). Non-polar solvents such as CCl_4, gave much lower yields, while other halogenated solvents (eg. $CHCl_3$ and CH_2ClCH_2Cl) gave comparable yields (Table 1, entries 9 to 12). To our surprise, almost quantitative yield was obtained in control reaction with the absence of any promoter (Table 1, entry 12). This result indicated a different reaction pathway may be involved compared with our previous report. In contrast, no product could be detected when the reaction was performed in dark, which was consisted with our previous observation (Table 1, entry 13).

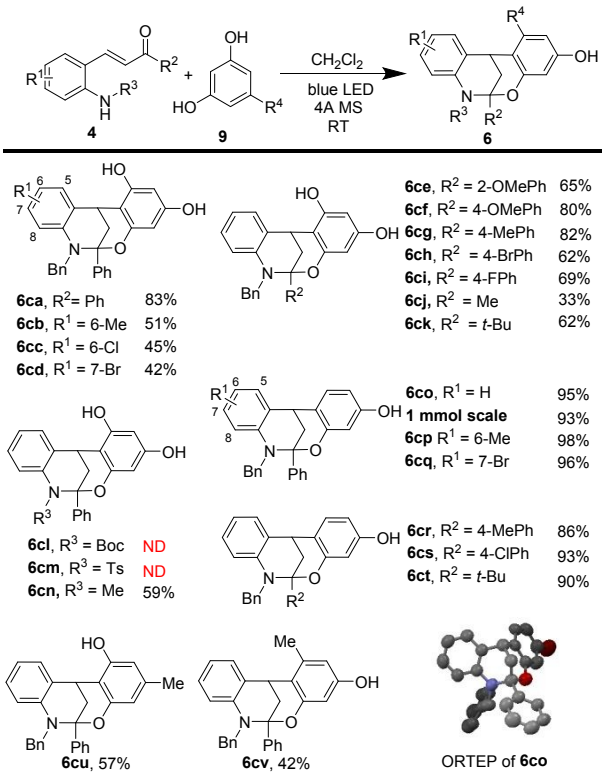
View Article Online DOI: 10.1039/D0CC02456E



Scheme 1. Substrate scope with respect to cyclohexan-1,3-dione and 4-hydroxycoumarin as nucleophile.

With the optimal reaction conditions being on hand, we turned our attention to examine the substrate scope of this reaction (Scheme 1). Electron-donating and electron-withdrawing groups (R^1) presented on the aniline ring were all tolerated, delivering benzo[*d*][1,3]oxazocine **6aa**[11] to **6ad** in 90%-96% yields. On the other hand, 2-aminochalcone with both electron-rich and electron-deficient phenyl (R^2) could also be smoothly transferred to benzo[*d*][1,3]oxazocine **6** in good excellent yields (Scheme 1, **6ae** to **6aj**). It was noteworthy that the alkyl substituted enone (R^2 = Me, *i*-Bu and *t*-Bu) could also be employed, affording benzo[*d*][1,3]oxazocine **6ak** to **6am** in excellent yields. Furthermore, tetrahydroquinoline hybrid coumarin could be facilely established by using 4-hydroxycoumarin as the reaction partner under the irradiation of blue LEDs. Slight decrease in isolated yield was observed when electron-donating group was attached on the aniline ring (R^1 = 6-Me), while electron-withdrawing groups (R^1 = 6-Cl or 7-Br) were compatible (Scheme 1, **6ba** to **6bd**). Excellent yields

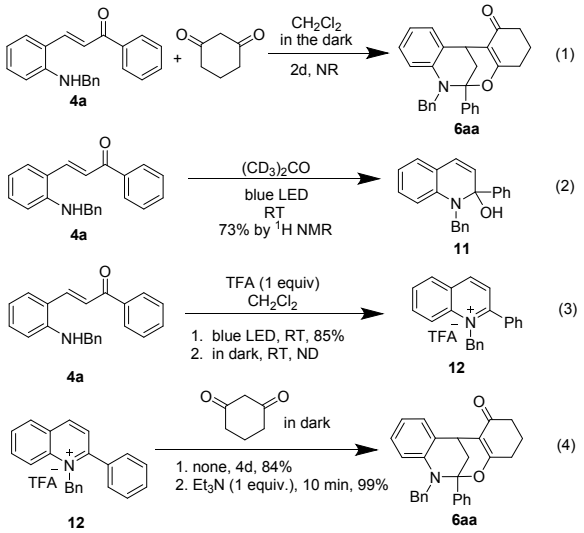
were detected for hybrid coumarin **6bf** to **6bj** excepting **6be**, indicating the reaction was insensitive to the electronic property of R^2. The low yield for **6be** may be originated from steric hindrance of 2-OMe. Eventually, when R^2 was alkyl such as Me, *i*-Bu and *t*-Bu, corresponding hybrid coumarins **6bk** to **6bm** could be isolated in high yields.



Scheme 2. Substrate scope using other bifunctional nucleophiles.

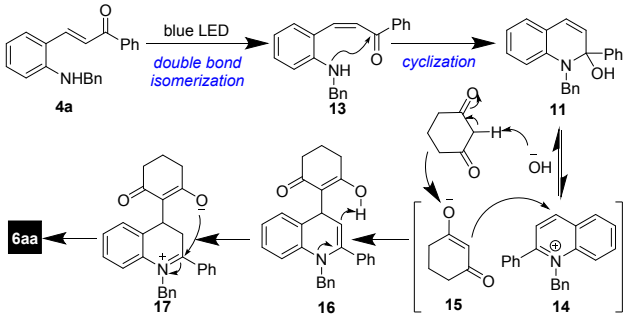
Next, we also evaluated pholoroglucinol as bifunctional nucleophile (Scheme 2). The reaction was sensitive to the substituents on the aniline ring and much lower yields (42% to 52%) were obtained for both electron-withdrawing and electron-donating groups (Scheme 2, **6ca** to **6cd**). With respect to R^2, phenyl with electron-donating group (Scheme 2, **6cf** and **6cg**) gave higher yields than those with electron-withdrawing group (Scheme 2, **6ch** and **6ci**). To our delight, even alkyl group could be tolerated, albeit resulting in lower isolated yield (Scheme 2, **6cj** and **6ck**). Alkyl protected-amino was indispensable for the success of this reaction as Boc protected substrate only delivered 2-phenylquinoline in 86% yield (Scheme 2, **6cl**) and Ts protected 2-aminochalcone only led to recovery of starting material. Less bulky methyl on amino was detrimental for the outcome (Scheme 2, **6cn**). In sharp contrast, resorcinol was a more suitable nucleophile for this reaction, delivering **6co**[11] to **6ct** in excellent isolated yields irrespective to the electronic property of R^1 and R^2. When orcinol was employed as nucleophile, two regioisomers **6cu** and **6cv**[12] were isolated in 57% and 42% yield respectively.

To shed light on the reaction mechanism of this reaction, a series of control reactions were carried out. When the reaction was run in the dark, no conversion of 2-aminochalcone **4a** or cyclohexan-1,3-dione was observed (Scheme 3, eqn (1)). Irradiation of **4a** in $(CD_3)_2CO$ with blue LEDs led to the identification of the putative *N,O*-acetal **11** by ^{1}H NMR, which was too unstable to be isolated (Scheme 3, eqn (2)). Fortunately, the quinolinium salt **12** could be obtained from **4a** in quantitative yield in the presence of stoichiometric TFA under the irradiation of blue LEDs, while no product were detected when the reaction was run in the dark (Scheme 3, eqn (3)). Furthermore, nucleophilic attack of cyclohexan-1,3-dione to quinolinium salt **12** proceeded very slowly (Scheme 3, eqn (4)), which needed four days to reach full conversion. However, this reaction was significantly accelerated when stoichiometric Et_3N was employed as acid scavenger.



Scheme 3. Mechanistic studies.

Based on the mechanistic studies together with previous reports,[13] we proposed the reaction pathway for this reaction. The initial step was the light-driven *E* to *Z* isomerization of 2-aminochalcone, which was followed by cyclization to afford *N,O*-acetal **11**. In following step, the rearomatization of *N,O*-acetal **11** might act as the drive force for the generation of a quinolinium **14** and hydroxide, which deprotonated the cyclcohexa-1,3-dione to form an enolate **15**. Nucleophilic attack of enolate **15** to the C4 of quinolinium **14** gave coupled product **16**. The intramolecular proton transfer from the enol to the enamine moiety of **16** would produce iminium **17**, which eventually underwent intramolecular cyclization to deliver the benzo[*d*][1,3]oxazocine **6aa**.



Scheme 4. Proposed reaction pathway.

In summary, a visible-light driven synthesis of polycyclic benzo[*d*][1,3]oxazocine from 2-aminochalcone with bifunctional nucleophile was described. This protocol enabled facile construction of diverse benzo[*d*][1,3]oxazocine from an array of substituted 2-aminochalcone with different bifunctional nucleophiles. Mechanistic studies supported the generation of quinolinium from 2-amonchalcene via tandem *E* to *Z* isomerization/cyclization/rearomatization driven by visible light, which was *in situ* captured by bifunctional nucleophiles. Subsequent cyclization of the coupled product enabled establishing the bridged ring system.

Conflicts of interest

There are no conflicts to declare

Acknowledgement

We are grateful for financial support from the National Natural Science Foundation of China (grants. 21722206, 21672171 to WX and 21978124 to YH) and Shaanxi government. Financial support from Chinese Universities Scientific Fund and the Scientific Fund of Northwest A&F University are also acknowledged. Innovative Talent Project of Educational Department of Liaoning Provincial, (No. LR2018019 to YH).

Notes and references

1 (a) A. R. Pape, K. P. Kaliappan and E. P. Kundig, *Chem. Rev.*, 2000, **100**, 2917-2940; (b) S. P. Roche and J. A. Porco Jr., *Angew. Chem., Int. Ed.*, 2011, **50**, 4068-4093; (c) C. X. Zhuo, W. Zhang and S. L. You, *Angew. Chem., Int. Ed*, 2012, **51**, 12662-12686; (d) C. Zheng and S. L. You, *Chem*, 2016, **1**, 830-857; (e) J. Wu, J. W. Li, H. Li and C. Y. Zhu, *Chinese J. Org. Chem.*, 2017, **37**, 2203-2210; (f) Z. L. Wu Wen-Ting, You Shu-Li, *Acta Chim. Sinica*, 2017, **75**, 419-438; (g) W. C. Wertjes, E. H. Southgate and D. Sarlah, *Chem. Soc. Rev.*, 2018, **47**, 7996-8017.

2 (a) A. J. Birch, *J. Agric. Food Chem.*, 1974, **22**, 162-167; (b) J. M. Hook and L. N. Mander, *Nat. Prod. Rep.*, 1986, **3**, 35-85; (c) T. J. Donohoe, R. Garg and C. A. Stevenson, *Tetrahedron: Asymmetry*, 1996, **7**, 317-344; (d) A. G. Schultz, *Chem. Commun.*, 1999, 14, 1263-1271; (e) F. López Ortiz, M. J. Iglesias, I. Fernández, C. M. Andújar Sánchez and G. Ruiz Gómez, *Chem. Rev.*, 2007, **107**, 1580-1691

3 (a) M. Ahamed and M. H. Todd, *Eur. J. Org. Chem.*, 2010, **2010**, 5935-5942; (b) J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, *Chem. Rev.*, 2012, **112**, 2642-2713; (c) D. L. Comins, K. Higuchi and D. W. Young, in *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky, Academic Press, 2013, vol. 110, pp. 175-235; (d) Q. Ding, X. Zhou and R. Fan, *Org. Biomol. Chem.*, 2014, **12**, 4807-4815; (e) S. Sowmiah, J. M. S. S. Esperança, L. P. N. Rebelo and C. A. M. Afonso, *Org. Chem. Front.*, 2018, **5**, 453-493.

4 (a) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102-113; (b) J. Xuan and W. J. Xiao, *Angew. Chem., Int. Ed,* 2012, **51**, 6828-6838; (c) X. J. Dai, X. L. Xu and X. N. Li, *Chinese J. Org. Chem.*, 2013, **33**, 2046-2062; (d) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322-5363; (e) T. P. Nicholls, D. Leonori and A. C. Bissember, *Nat. Prod. Rep.*, 2016, **33**, 1248-1254; (f) Q. Q. Zhou, Y. Q. Zou, L. Q. Lu and W. J. Xiao, *Angew. Chem., Int. Ed*, 2019, **58**, 1586-1604.

5 (a) (g) Y. Z. Cheng, X. Zhang and S. L. You, *Sci. Bull.*, 2018, **63**, 809-811; (b) H. E. Ho, A. Pagano, J. A. Rossi-Ashton, J. R. Donald, R. G. Epton, J. C. Churchill, M. J. James, P. O'Brien, R. J. K. Taylor and W. P. Unsworth, *Chem. Sci.*, 2020, DOI: 10.1039/C9SC05311E.

6 (a) R. Glaser, S. Cohen, D. Donnell and I. Agranat, *J. Pharm. Sci.*, 1986, **75**, 772-774; (b) M. Díaz-Gavilán, F. Rodríguez-Serrano, J. A. Gómez-Vidal, J. A. Marchal, A. Aránega, M. Á. Gallo, A. Espinosa and J. M. Campos, *Tetrahedron*, 2004, **60**, 11547-11557; (b) C. J. Ohnmacht, J. S. Albert, P. R. Bernstein, W. L. Rumsey, B. B. Masek, B. T. Dembofsky, G. M. Koether, D. W. Andisik and D. Aharony, *Bioorg. Med. Chem.*, 2004, **12**, 2653-2669; (c) J. K. Mishra, K. Samanta, M. Jain, M. Dikshit and G. Panda, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 244-247; (d) W. Prapalert, D. Santiarworn, S. Liawruangrath, B. Liawruangrath and S. G. Pyne, *Nat. Prod. Commun.*, 2014, **9**, 1433-1435.

7 (a) A. R. Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron*, 1996, **52**, 15031-15070; (b) V. Sridharan, P. A. Suryavanshi and J. C. Menéndez, *Chem. Rev.*, 2011, **111**, 7157-7259.

8 (a) K. Fujimoto, T. Oka and M. Morimoto, *Cancer Res.*, 1987, **47**, 1516-1522; (b) M. E. Flanagan and R. M. Williams, *J. Org. Chem.*, 1995, **60**, 6791-6797; (c) . H. Lim, T. Etoh, M. Hayashi, K. Komiyama and T. S. Kam, *Tetrahedron Lett.*, 2009, **50**, 752-754.

9 (a) F. M. Moghaddam, H. Saeidian, M. Kiamehr, Z. Mirjafary and S. Taheri, *ARKIVOC*, 2010, **11**, 91-100; (b) . Matloubi Moghaddam, S. Taheri, Z. Mirjafary, H. Saeidian, M. Kiamehr and M. Tafazzoli, *Helv. Chim. Acta*, 2011, **94**, 142-147; (c) S. Mondal, R. Paira, A. Maity, S. Naskar, K. B. Sahu, A. Hazra, P. Saha, S. Banerjee and N. B. Mondal, *Tetrahedron Lett.*, 2011, **52**, 4697-4700.

10 Y.-Q. Gao, Y. Hou, L. M. Zhu, G. Z. Chen, D. Y. Xu, S. Y. Zhang, Y. P. He and W. Q. Xie, *Rsc Adv.*, 2019, **9**, 29005-29009.

11 CCDC 1993548 and 1993549 contain the supplementary crystallographic data for compound **6ba** and **6co**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

12 The structure of **6cu** and **6cv** was established by 2D NMR studies (see supporting information for details).

13 (a) T. Horaguchi, N. Hosokawa, K. Tanemura and T. Suzuki, *J. Heterocyclic Chem.*, 2002, **39**, 61-67 (b) X. Z. Chen, S. X. Qiu, S. S. Wang, H. F. Wang and H. B. Zhai, *Org. Biomol. Chem.*, 2017, **15**, 6349-6352.

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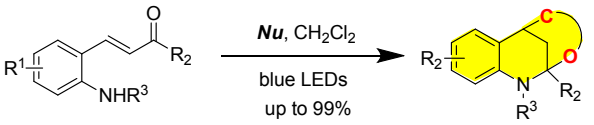

- *visible light driven synthesis;*
- *mild reaction coditions;*
- *free of base;*
- *wide substrate scope;*