Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2019, **17**, 8958

Received 5th September 2019,
Accepted 27th September 2019

DOI: 10.1039/c9ob01946d

rsc.li/obc

Cercosporin-photocatalyzed sp^3 (C–H) activation for the synthesis of pyrrolo[3,4-*c*]quinolones†

Jia Li,[a] Wenhao Bao,[a] Yan Zhang *[b] and Yijian Rao *[a]

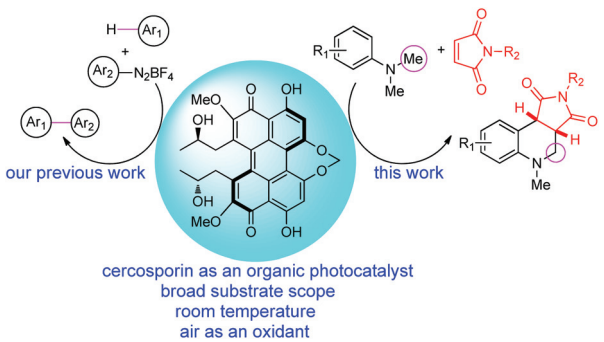
We reported a new method that visible light along with cercosporin, one of the naturally occurring perylenequinonoid pigments with excellent properties of photosensitization, photocatalyzed sp^3 (C–H) activation for the synthesis of pyrrolo[3,4-*c*]quinolones through the annulation of anilines and maleimides under mild conditions.

C–H bond activation or functionalization offers an efficient and straightforward way for the synthesis of useful organic compounds.[1] Photocatalysis, which makes use of clean, abundant and endlessly renewable light,[2] has been widely used for the activation of C–H bonds. However, the least reactive sp^3 (C–H) bond is difficult to be directly activated under mild reactions. One of the alternative ways is to activate sp^3 (C–H) bonds adjacent to N atoms, since amine is the most electron-rich species and can be easily converted to a reactive α-aminoalkyl radical through a photo-induced electron transfer (PET) process,[3] and then facilitates chemical reactions that are otherwise difficult to proceed.[3,4]

Cercosporin (Scheme 1), one of the perylenequinonoid pigments (PQP), is well known as a photodynamic therapy reagent, owing to its ability of strong light absorption in the UV-vis region and the ability of generating active oxygen species through a single electron transfer (SET) process or energy transfer process (ET) with high efficiency upon irradiation.[5,6] Although these properties make cercosporin a potential photocatalyst, there is rarely a report of cercosporin utilized in photocatalysis reactions, which has aroused our great interest to probe its catalytic activity. Recently, our group obtained cercosporin through low-cost liquid fermentation and successfully applied cercosporin in the photocatalytic reaction for the sp^2 (C–H) activation of arenes and heteroarenes (Scheme 1).[7] Based on this successful activation of sp^2 (C–H) bonds and our continuous interest in photocatalytic C–H bond activation, we next attempt to investigate the reactivity of cercosporin in the least reactive sp^3 (C–H) activation.

sp^3 (C–H) activated annulation of electron rich anilines and maleimides has offered a powerful strategy for the synthesis of an important organic intermediate [3,4-*c*]quinolone, which is the core structural unit of a lot of bioactive molecules, including caspase-3 inhibitors,[8] 5-HT4R antagonists,[9] and ADAMTS inhibitors.[10] Apart from traditional annulation reactions achieved with high-cost or toxic metal catalysts, or quantitative strong oxidants such as ^{t}Bu-OOH, $K_2S_2O_8$ and high temperature,[11–16] photocatalytic systems using toxic or expensive metal complexes, such as Ir, Ru, *etc.*, have been applied for the synthesis of pyrrolo[3,4-*c*]quinolones.[17–23] However, metal-free photocatalytic protocols for the synthesis of pyrrolo [3,4-*c*]quinolones have been less reported,[24–29] most of which utilized organic dyes[24–26,28] or expensive chlorophy II as photocatalysts.[29] So it is still highly desired to develop a cost-effective and metal-free method for the effective synthesis of pyrrolo[3,4-*c*]quinolones under mild conditions.

Herein we report a cercosporin-photocatalyzed sp^3 (C–H) bond activation for the synthesis of pyrrolo[3,4-*c*]quinolones



Scheme 1 Cercosporin photo-catalyzed C–H activation.

[a]*Key Laboratory of Carbohydrate Chemistry and Biotechnology, Ministry of Education, School of Biotechnology, Jiangnan University, Wuxi 214122, P. R. China.*
E-mail: raoyijian@jiangnan.edu.cn
[b]*School of Pharmaceutical Science, Jiangnan University, Wuxi 214122, P. R. China.*
E-mail: zhangyan@jiangnan.edu.cn

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c9ob01946d

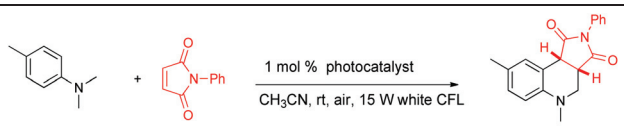
through the annulation of anilines and maleimides (Scheme 1). In this process, tertiary anilines and maleimides were readily converted into pyrrolo[3,4-*c*]quinolones through a PET pathway with the formation of a reactive α-aminoalkyl radical. This method provides a great example for exploring green, economical and mild reaction conditions for the synthesis of pyrrolo[3,4-*c*]quinolones.

Results and discussion

The investigation was started by subjecting 1.0 equiv. of *N*,*N*,4-trimethylbenzenamine (**1a**) to 1.0 equiv. of *N*-phenylmaleimide (**2a**) with 1 mol% cercosporin as the photocatalyst. The reaction was conducted with irradiation of a 15 W white CFL in various solvents under an air atmosphere to test the reactivity (Table 1). The results were unsatisfactory with trace to low yields when the reactions were performed in CH_3OH, $CHCl_3$, CH_2Cl_2 and THF (Table 1, entries 1–4). However, DMF and DMSO gave much better yields of products (Table 1, entries 5 and 6). To our delight, the highest yield of the pyrrolo[3,4-*c*]quinolone product **3a** was obtained in 90% yield after 20 h when the reaction was performed in CH_3CN (Table 1, entry 7). The control experiment showed that the existence of air was prerequisite, as the yield of the reaction was low if we changed the air atmosphere to nitrogen (Table 1, entry 8). When the reaction was conducted under an oxygen atmosphere, we did not observe the increase of the yield for the desired product (Table 1, entry 9).

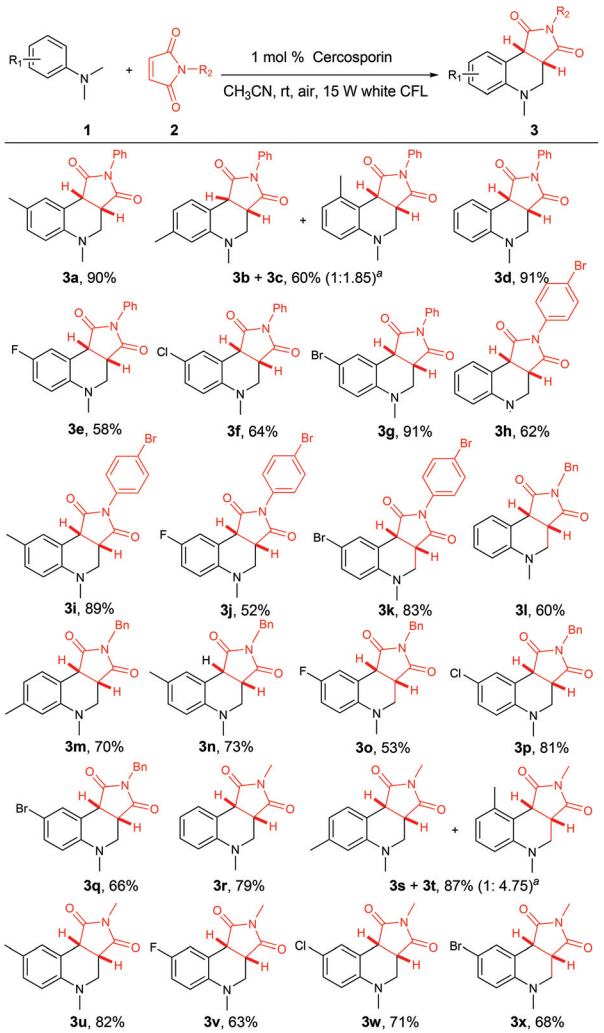
Additionally, control experiments showed that the presence of light was necessary for the reaction (Table 1, entry 10). Although the reaction can proceed slowly in air upon photoirradiation without cercosporin (Table 1, entry 11), the addition of a catalytic amount of cercosporin largely improved the yield of the reaction.

Table 1 Screening of the conditions for the reaction of **1a** and **2a**[a]



Entry	Conditions	Yield[b]
1	CH_3OH	No reaction
2	$CHCl_3$	10%
3	CH_2Cl_2	30%
4	THF	45%
5	DMF	75%
6	DMSO	80%
7	CH_3CN	90%
8	CH_3CN, N_2	10%
9	CH_3CN, O_2	82%
10	CH_3CN, no light	No reaction
11	CH_3CN, no catalyst	30%

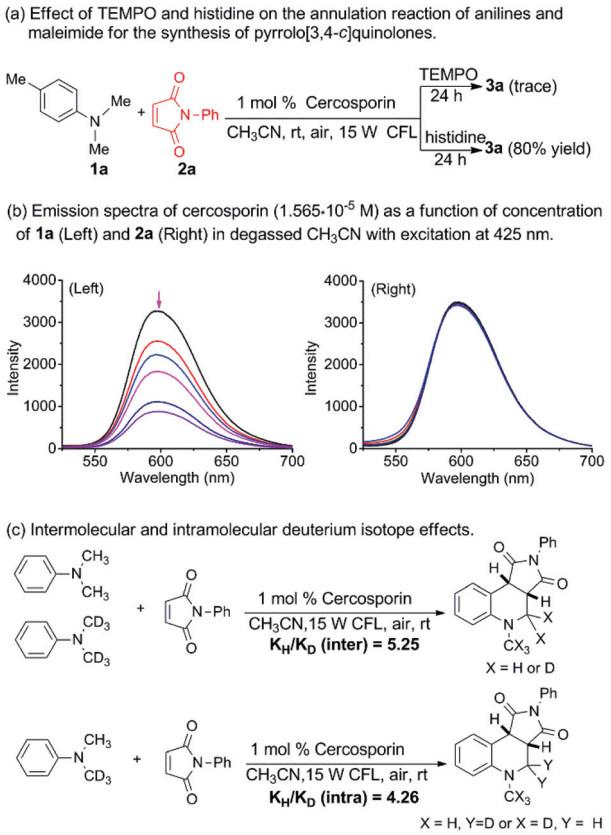
[a] All reactions were carried out on a scale of 0.25 mmol of **1a** and 0.25 mmol of **2a** in 2 mL of solvent at room temperature in air, with the irradiation of a 15 W white CFL for 20 h. [b] Isolated yields.



Scheme 2 Scope of pyrrolo[3,4-*c*]quinolones. Standard conditions: tertiary amine (0.25 mmol), *N*-phenylmaleimide (0.25 mmol), cercosporin (1 mol%), CH_3CN (2 mL), at room temperature in air, with the irradiation of a 15 W white CFL for 20 h. [a] Determined by ^{1}H-NMR.

Having established optimal reaction conditions, we next started to probe the scope of substrates (Scheme 2). With the optimized conditions, the desired products were obtained in 52–91% yields. *N*,*N*-Dimethylanilines can tolerate substitution of *meta*- and *para*-methyl groups. They also tolerated halogen atoms (F, Cl, and Br) on the phenyl ring, which facilitated further functionalization. Meanwhile, maleimides were tolerated well with methyl-, phenyl- and benzyl-groups on the nitrogen atoms.

To unveil the mechanism of the photocatalytic reaction, we next conducted the radical inhibition experiment. When the radical inhibitor 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (Scheme 3a) was added to the reaction mixture under standard conditions, the reaction was obviously quenched, which showed that the photocatalytic process may proceed through a PET process. Since cercosporin had strong ability to produce singlet oxygen, then we designed the singlet oxygen inhibition experiment to check whether singlet oxygen was involved in

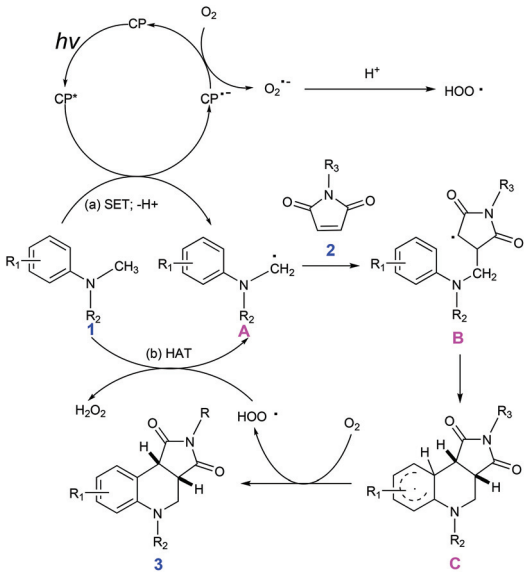


Scheme 3 Mechanistic experiments.

the reaction. When the singlet oxygen scavenger histidine was added to the reaction mixture under optimized reaction conditions (Scheme 3a), the reaction can proceed smoothly without obvious depression, which implied that the singlet oxygen pathway could be ruled out from the reaction.

We next attempted to verify the PET process using spectroscopy. As shown in Fig. S1,† cercosporin exhibits maximum absorption at 470 nm. With excitation, cercosporin shows maximum emission at 597 nm. Then titration experiments were conducted to monitor the PET process. When **1a** was gradually added to the solution of cercosporin with irradiation, both the characteristic absorption and emission of cercosporin were gradually quenched due to the PET process (Scheme 3b and see the ESI†). We concluded that the electron transferred from **1a** to cercosporin according to the redox potential ($CP^*/CP^{\bullet-}$) = +1.87 V *vs.* SCE,[7] ($\mathbf{1a}^{\bullet+}/\mathbf{1a}$) = +0.79 V *vs.* SCE.[2b,20] The same titration experiment was conducted for cercosporin and **2a**, but **2a** could not quench the absorption and emission of cercosporin (Scheme 3b and see the ESI†). The Stern–Volmer plots also clearly showed that *N*,*N*-dimethylaniline (**1a**) can obviously quench the emission of cercosporin in degassed CH_3CN due to the PET process from **1a** to cercosporin (see the ESI†).

Finally, we designed experiments for both inter- and intramolecular deuterium isotope effects, and the results were shown in Scheme 3c. The (k_H/k_D) inter and (k_H/k_D) intra values



Scheme 4 Proposed reaction mechanism.

were determined by the reaction of **2a** with the mixture of *N*,*N*-di(trideuteriomethyl) aniline and *N*,*N*-dimethyl aniline as well as the reaction of **2a** and *N*-methyl-*N*-trideuteriomethyl aniline to be 5.25 and 4.26, respectively, and were larger than the values for the electron/proton transfer process.[30] So, we conclude that both the electron/proton transfer (ET/–H^+) and the hydrogen atom transfer (HAT) were involved in the formation process of α-aminoalkyl radicals **A**.

Based on the results of our control experiments and previous reports,[18,20,29] we proposed the mechanism for the reaction (Scheme 4). First, cercosporin **CP** was excited to excited state CP* upon irradiation. Then one electron transferred from aniline **1** to CP*, which produced an amine cation radical and cercosporin radical anion $CP^{\bullet-}$ at the same time. In the next step, the amine cation radical was converted to α-aminoalkyl radical **A** through a deprotonation process.[18,20,29] Upon addition of maleimide **2**, **A** attacked the double bond of **2** to generate the intermediate **B**, which subsequently underwent intra-cyclization to form radical **C**. Then **C** was rapidly oxidized by O_2 to produce aromatic pyrrolo[3,4-*c*]quinolone **3** after losing an electron and proton.[18,20,29] O_2 was reduced to superoxide radical anion $HOO^{\bullet}$ at the same time. $HOO^{\bullet}$ could abstract one hydrogen atom from **1**, which opened another route for the formation of α-aminoalkyl radical **A**.[18,20,29] The catalyst cercosporin could be recovered from CP^- through the oxidation of oxygen, with the formation of superoxide radical anion $HOO^{\bullet}$.

Conclusions

In conclusion, we have developed a metal-free cercosporin-photocatalyzed sp^3 (C–H) activation system for the synthesis of pyrrolo[3,4-*c*]quinolones. The reaction proceeded effectively upon 15 W white CFL irradiation under an air atmosphere at

room temperature without the addition of extra oxidants. The reaction mechanism was deeply investigated by conducting control experiments, showing that both the electron/proton transfer (ET/–H^+) and the hydrogen atom transfer (HAT) may involve in the reaction.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Key R&D Program of China (2018YFA0901700), the Natural Science Foundation of Jiangsu Province (Grant No. BK20160167), the Thousand Talents Plan (Young Professionals), the Fundamental Research Funds for the Central Universities (JUSRP51712B), the National First-class Discipline Program of Light Industry Technology and Engineering (LITE2018-14) and Postdoctoral Foundation in Jiangsu Province (2018K153C) for the funding support.

Notes and references

1 (*a*) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, **417**, 507–514; (*b*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2009, **110**, 624–655; (*c*) I. Hussain and T. Singh, *Adv. Synth. Catal.*, 2014, **356**, 1661–1696; (*d*) P. L. Arnold, M. W. McMullon, J. Rieb and F. E. Kühn, *Angew. Chem., Int. Ed.*, 2015, **54**, 82–100; (*e*) G. B. Shul'pin, *Org. Biomol. Chem.*, 2010, **8**, 4217–4228.

2 (*a*) G. Ciamician, *Science*, 1912, **36**, 385–394; (*b*) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363; (*c*) D. M. Schultz and T. P. Yoon, *Science*, 2014, **343**, 985–993; (*d*) J. Xuan and W. J. Xiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 6828–6838; (*e*) Z. J. Shen, S. C. Wang, W. J. Hao, S. Z. Yang, S. J. Tu and B. Jiang, *Adv. Synth. Catal.*, 2019, **361**, 3837–3851; (*f*) Z. J. Shen, H. N. Shi, W. J. Hao, S. J. Tu and B. Jiang, *Chem. Commun.*, 2018, **54**, 11542–11545; (*g*) L. Y. Xie, T. G. Fang, J. X. Tan, B. Zhang, Z. Cao, L. H. Yang and W. M. He, *Green Chem.*, 2019, **21**, 3858–3863; (*h*) Q. S. Liu, L. L. Wang, H. L. Yue, J. S. Li, Z. D. Luo and W. Wei, *Green Chem.*, 2019, **21**, 1609–1613.

3 (*a*) K. Nakajima, Y. Miyake and Y. Nishibayashi, *Acc. Chem. Res.*, 2016, **49**, 1946–1956; (*b*) A. K. Yadav and L. D. S. Yadav, *Tetrahedron Lett.*, 2015, **56**, 6696–6699; (*c*) M. L. Deb, S. S. Dey, I. Bento, M. T. Barros and C. D. Maycock, *Angew. Chem., Int. Ed.*, 2013, **52**, 9791–9795.

4 T. P. Yoon, *ACS Catal.*, 2013, **3**, 895–902.

5 (*a*) S. Yamazaki, A. Okubo, Y. Akiyama and K. Fuwa, *Agric. Biol. Chem.*, 1975, **39**, 287–288; (*b*) P. E. Hartman, W. J. Dixon, T. A. Dahl and M. E. Daub, *Photochem. Photobiol.*, 1988, **47**, 699–703; (*c*) F. Macri and A. Vianello, *Plant, Cell Environ.*, 1979, **2**, 267–271; (*d*) M. E. Daub and M. Ehrenshaft, *Annu. Rev. Phytopathol.*, 2000, **38**, 461–490.

6 (*a*) S. Kuyama and T. Tamura, *J. Am. Chem. Soc.*, 1957, **79**, 5725–5726; (*b*) S. Kuyama and T. Tamura, *J. Am. Chem. Soc.*, 1957, **79**, 5726–5729.

7 (*a*) S. W. Zhang, Z. C. Tang, W. H. Bao, J. Li, B. D. Guo, S. P. Huang, Y. Zhang and Y. J. Rao, *Org. Biomol. Chem.*, 2019, **17**, 4364–4369; (*b*) Y. Zhang, Y. Cao, L. Lu, S. Zhang, W. Bao, S. Huang and Y. Rao, *J. Org. Chem.*, 2019, **84**, 7711–7721.

8 D. V. Kravchenko, V. M. Kysil, S. E. Tkachenk, S. Maliarchouk, I. M. Okun and A. V. Ivachtchenko, *Eur. J. Med. Chem.*, 2005, **40**, 1377–1383.

9 X. M. Lu, J. Li, Z. J. Cai, R. Wang, S. Y. Wang and S. J. Ji, *Org. Biomol. Chem.*, 2014, **12**, 9471–9477.

10 A. Cappelli, C. Nannicini, S. Valenti, G. Giuliani, M. Anzini, L. Mennuni and G. Giorgi, *ChemMedChem*, 2010, **5**, 739–748.

11 Z. Song and A. P. Antonchick, *Tetrahedron*, 2016, **72**, 7715–7721.

12 A. K. Yadav and L. D. S. Yadav, *Tetrahedron Lett.*, 2016, **57**, 1489–1491.

13 C. Huo, F. Chen, Z. Quan, J. Dong and Y. Wang, *Tetrahedron Lett.*, 2016, **57**, 5127–5131.

14 N. Sakai, S. Matsumoto and Y. Ogiwara, *Tetrahedron Lett.*, 2016, **57**, 5449–5452.

15 R. Kawade, K. D. B. Huple, R. J. Lin and R. S. Liu, *Chem. Commun.*, 2015, **51**, 6625–6628.

16 M. Nishino, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2011, **76**, 6447–6451.

17 F. Peng, P. Zhi, H. Ji, H. Zhao, F. Y. Kong, X. Z. Liang and Y. M. Shen, *RSC Adv.*, 2017, **7**, 19948–19953.

18 X. Ju, D. Li, W. Li, W. Yu and F. Bian, *Adv. Synth. Catal.*, 2012, **354**, 3561–3567.

19 J. Tang, G. Grampp, Y. Liu, B. X. Wang, F. F. Tao, L. J. Wang, X. Z. Liang, H. Q. Xiao and Y. M. Shen, *J. Org. Chem.*, 2015, **80**, 2724–2732.

20 X. L. Yang, J. D. Guo, T. Lei, B. Chen, C. H. Tung and L. Z. Wu, *Org. Lett.*, 2018, **20**, 2916–2920.

21 T. P. Nicholls, G. E. Constable, J. C. Robertson, M. G. Gardiner and A. C. Bissember, *ACS Catal.*, 2015, **6**, 451–457.

22 S. Firoozi, M. Hosseini-Sarvari and M. Koohgard, *Green Chem.*, 2018, **20**, 5540–5549.

23 (*a*) M. Hosseini-Sarvari, M. Koohgard, M. Firoozi, S. Mohajeri, A. Tavakolian and H. Alizarin, *New J. Chem.*, 2018, **42**, 6880–6888; (*b*) K. Sharma, B. Das and P. Gogoi, *New J. Chem.*, 2018, **42**, 18894–18905.

24 L. Chen, C. S. Chao, Y. Pan, S. Dong, Y. C. Teo, J. Wang and C. H. Tan, *Org. Biomol. Chem.*, 2013, **11**, 5922–5925.

25 G. Wei, C. Basheer, C. H. Tan and Z. Jiang, *Tetrahedron Lett.*, 2016, **57**, 3801–3809.

26 Z. Liang, S. Xu, W. Tian and R. Zhang, *Beilstein J. Org. Chem.*, 2015, **11**, 425–430.

27 A. K. Yadav and L. D. S. Yadav, *Tetrahedron Lett.*, 2017, **58**, 552–555.

28 J. R. Xin, J. T. Guo, D. Vigliaturo, Y. H. He and Z. Guan, *Tetrahedron*, 2017, **73**, 4627–4633.
29 J. T. Guo, D. C. Yang, Z. Guan and Y. H. He, *J. Org. Chem.*, 2017, **82**, 1888–1894.
30 (*a*) E. Baciocchi, O. Lanzalunga, A. Lapi and L. Manduchi, *J. Am. Chem. Soc.*, 1998, **120**, 5783–5787; (*b*) S. Murahashi, T. Nakae, H. Terai and N. Komiya, *J. Am. Chem. Soc.*, 2008, **130**, 11005–11012.