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Visible-light-promoted aerobic metal-free aminothiocyanation of activated ketones†

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A direct, redox-neutral, highly atom-economical and metal-free aerobic method for the synthesis of multi-substituted olefins *via* simply coupling ammonium thiocyanate with activated ketones is described. A series of multi-substituted olefins could be easily and efficiently obtained in excellent yields by using low-toxicity and inexpensive ammonium thiocyanate as an amine and thiocyanate source, and water is the only by-product.

Organic thiocyanate synthesis by means of C–SCN bond formation is a widely used strategy in medicinal chemistry and organic synthesis.[1] Key structural motifs within this important class of compounds are C(sp^2)–SCN and C(sp^3)–SCN thiocyanates, which are represented in a significant portion of bioactive natural products.[2] Additionally, thiocyanates stand out as a core structural scaffold for the assembly of functionalized heterocycles and sulfur-based compounds.[3] In particular, α-ketothiocyanates are useful intermediates in the synthesis of thymidine, triazole, thiazolidine, *etc.*[4] Hence, tremendous effort has been devoted to developing the formation of α-ketothiocyanates. Significant advancements have been made in the development of general, catalytic protocols that help generate α-ketothiocyanates, and conventional approaches include: (i) nucleophilic substitution reactions of Nu-X (X = halogen, OTs, N_2^+ *etc.*);[5] (ii) transition metal catalysis: $PhICl_2$/$Pb(SCN)_2$ and $Pd(OAc)_2$/NaSCN;[6] (iii) oxidative dehydrogenative coupling;[7] and (iv) using electrophilic thiocyanating reagents: thiocyanogen $(SCN)_2$, thiocyanogen chloride (ClSCN), *N*-thiocyanatosuccinimide, *N*-thiocyanatophthalimide, and *N*-thiocyanatosaccharin.[8] Despite the fact that several achievements have been made using these methods, there are still some issues to be addressed, such as the necessity of pre-activation of the partners, the requirement of excess oxidants, and the generation of equivalents of toxic byproducts (*e.g.*, succinimide, saccharin, and benziodoxole).

The (*E*)-3-amino-2-thiocyanato-α,β-unsaturated compounds are a new significant class of multi-substituted olefins in synthetic chemistry.[9] They were widely used in the preparation of multifunctional compounds by asymmetric hydrogenation, and could easily convert to ubiquitous structural motifs, such as 2-aminothiazoles and pyridones. Recently, Zeng and coworkers have developed a facile electro-catalyzed aminothiocyanation of β-keto esters by using ammonium carbamodithioate or XSCN (X = K, NH_4) as the thiocyano source.[9c] In particular, the employment of NH_4SCN as the source of SCN and NH_2 for the aminothiocyanation is highly atom-economical although *in situ* pre-activation of β-keto esters is still necessary and only moderate yields were obtained (Scheme 1).

Using molecular oxygen in air to realize efficient chemical transformations has attracted much attention because dioxygen is an ideal, green and most abundant oxidant.[10] In continuation of our interest in visible-light-driven aerobic oxidation,[11] we propose that, if dioxygen can serve as a terminal hydrogen acceptor to form water in aminothiocyanation, the overall waste of the reaction will be only water. We herein disclose a simple but efficient aerobic aminothiocyanation of ketones with NH_4SCN that is catalyzed by fluorescein under visible-light irradiation. Further synthetic applications of the products and mechanism investigation are also achieved in this work.

Initial investigations revealed the feasibility of a thiocyanate oxidation step *via* Stern–Volmer experiments (see Fig. S2†). With these results in hand, we examined the proposed visible light-mediated C–H thiocyanation of ethyl acetoacetate **1a** and NH_4SCN using photocatalysts and blue light-emitting diodes (LEDs). Extensive optimization studies established that a combination of CH_3CN and 3 equivalents of NH_4SCN resulted in a clean reaction under irradiation with blue LEDs in the presence of fluorescein, giving **2a** in 95% yield (see ESI Tables S1–S3† for

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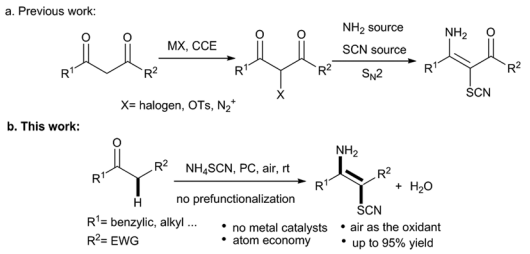


Scheme 1 Methods of the synthesis of (*E*)-3-amino-2-thiocyanato-*α*,*β*-unsaturated compounds.

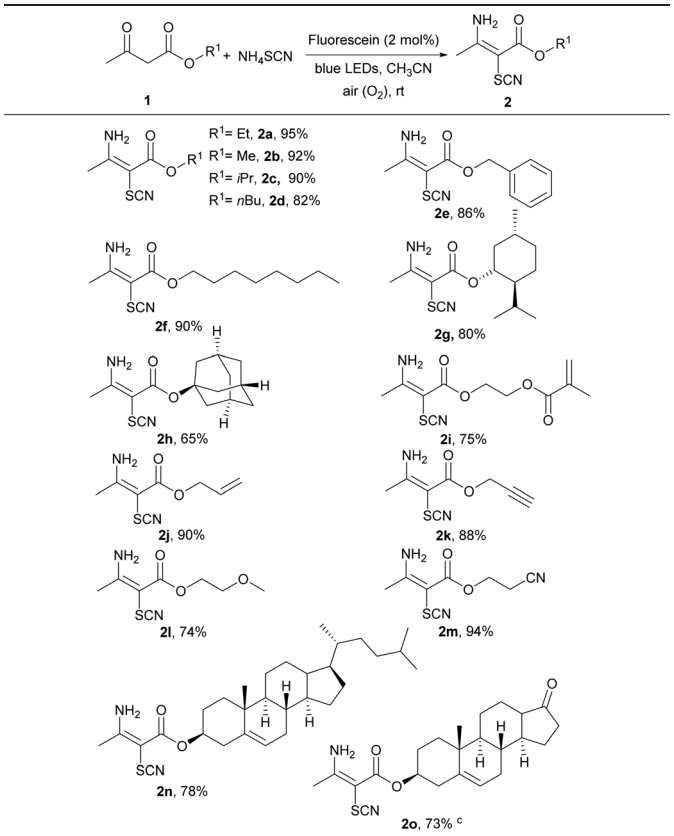
details). Control experiments established that fluorescein, air (O_2) and visible-light irradiation were required for an efficient reaction. Gratifyingly, the reaction still proceeded smoothly with comparable results, even when using sunlight as the light source.

With optimized conditions in hand, we sought to evaluate the scope of the C_{sp^3}–SCN bond-forming reaction. As shown in Table 2, only an *E*-selective process was observed. A myriad of β-keto esters, including ethyl, methyl, isopropyl, *tert*-butyl, benzyl, *n*-octyl, and DL-menthyl esters, are successful substrates, providing the corresponding SCN and NH_2 analogues in good to excellent yields (80–95%, Table 1, **2a–2g**). Notably, when the steroid-derived adamantyl derivative **1h** was subjected to the optimal conditions, adduct **2h** was not significantly diminished. The reaction is also amenable for a range of substituents, such as Michael acceptor (**1i**), allyl (**1j**) or propargyl (**1k**), methoxyethyl (**1l**), and cyanoethyl (**1m**) groups, affording the desired adducts in good yields. Pharmaceutical intermediates cholesterol and dehydroepiandrosterone derivatives can also be functionalized, affording 78% and 73% yields, respectively (**2n** and **2o**).

Further investigation of the substrate scope of this transformation is illustrated (Table 2). To our delight, β-keto esters containing ethyl, isopropyl, long alkyl chain, (hetero)benzyl, phenoxy, and chloro moieties, worked efficiently in this transformation giving products **4a–4j**, while the substrate with a cyclopropyl moiety produced adduct **4k** in comparable isolated yield (40%). In addition, ethyl benzoylacetate could be directly transformed into 2-aminothiazole **4l** *via* intramolecular cyclization of the aminothiocyanated product under the standard conditions.

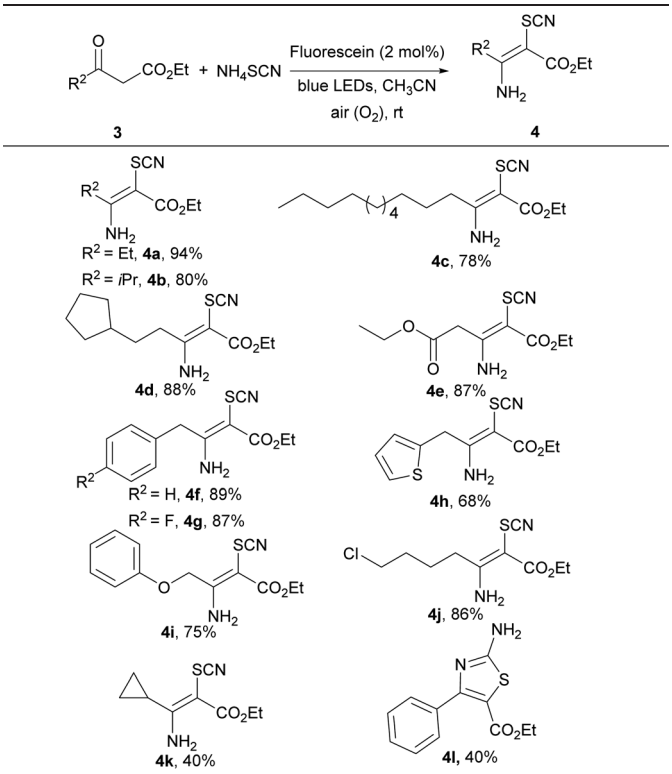
Finally, on the basis of investigations we found that not only β-keto esters but also a diverse range of electron-withdrawing ketones were good reaction partners in this transformation. Aliphatic 1,3-diketones were examined in the reaction, showing good reactivity (Table 3, **6a–6b**). To our delight,

Table 1 Reaction scope[a,b]



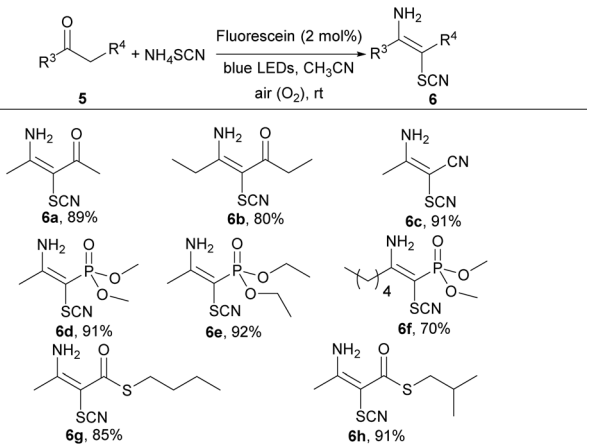
[a] Reaction conditions: **1** (0.5 mmol, 1.0 equiv.), NH_4SCN (1.5 mmol, 3 equiv.), and fluorescein (2.0 mol%) in CH_3CN (2.0 mL) were irradiated with blue LEDs in air at rt. The reaction was monitored by TLC. [b] Isolated yield. [c] 3 mL THF was used instead of CH_3CN.

Table 2 Reaction scope[a,b]



[a] Reaction conditions: **3** (0.5 mmol, 1.0 equiv.), NH_4SCN (1.5 mmol, 3 equiv.), and fluorescein (2.0 mol%) in CH_3CN (2.0 mL) were irradiated with blue LEDs in air at rt. The reaction was monitored by TLC. [b] Isolated yield.

Table 3 Reaction scope[a,b]

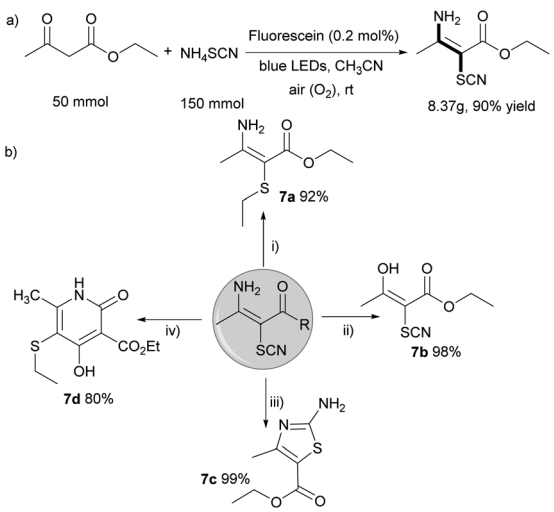


[a] Reaction conditions: **5** (0.5 mmol, 1.0 equiv.), NH_4SCN (1.5 mmol, 3 equiv.), and fluorescein (2.0 mol%) in CH_3CN (2.0 mL) were irradiated with blue LEDs in air at rt. The reaction was monitored by TLC. [b] Isolated yield.

β-electron withdrawing groups such as cyano, phosphonate, and thioate groups could also be applied with good to excellent yields (**6c–6h**).

To further demonstrate the utility of this C–H thiocyanation protocol, a gram-scale reaction of β-ketoester **1a** (50 mmol, 6.5 g) was performed with NH_4SCN (150 mmol, 11.4 g) in CH_3CN for 18 h delivering the desired product **2a** in excellent yield (8.37 g, 90% yield, Scheme 2). The obtained products were then further transformed into useful building blocks for organic synthesis. The thiocyano group could be readily transformed using tributylphosphine, thus affording the sulfoether **7a** in 92% yield. Hydroxy-thiocyanatobut-2-enoate **7b** could also be easily obtained by hydrolysis in the presence an acid. Furthermore, we choose β-keto esters as the raw material to synthesize the aminothiazole backbone **7c** in two steps in excellent yield. Thiazole carboxanilides are also well known as members of the carboxamide family of fungicides. Examples include Metsulfovax, Scedlavax, Ethaboxam and Thifluzamide, which can be constructed from **7c**.[12] Pyridones are privileged scaffolds, and they play key roles in many medicinally related molecules.[13] However, the functionalization on the pyridone ring is a great challenge due to the low reactivity and is usually accessed *via* longer multi-step procedures. Remarkably, 5-(ethylthio)pyridone **7d** can be easily obtained from **2a** in two steps in our method.

To gain some insight into the mechanism, investigations were conducted as shown (see the ESI†). First, Stern–Volmer experiments (see Fig. S2†) illustrated that the luminescence emission of fluorescein was quenched by NH_4SCN more efficiently than **1a**, which indicated a reduction quenching mechanism. Furthermore, when radical inhibitor BHT was introduced into the photocatalytic system, the adduct of the radical inhibitor with $^{\bullet}SCN$ was detected by ESI-HRMS (see Fig. S3†), thus providing straightforward evidence of $^{\bullet}SCN$ radical formation. To confirm the proposed reaction mechanism, quantum mechanical calculations were performed (Fig. 1). The energy profiles reveal that the initiation of an electron-deficient α-carbonyl carbon radical (INT1) is the rate-determining step; the free energy of activation of the enolate attacking the dimer is 47.9 kcal mol^{-1} (through TS1′), whereas it is reduced to 23.1 kcal mol^{-1} by the hydrogen extraction process, with the corresponding transition state being TS1. Then **INT1** is immediately trapped by $(SCN)_2$ to yield INT2 through TS2,[14] using an activation energy of 15.72 kcal mol^{-1}



Scheme 2 (a) Larger scale reaction and (b) further transformations of products: (i) **2a**, ethanol, tri-*n*-butylphosphine, THF, room temperature, 3 h; (ii) **2a**, HCl, H_2O, room temperature, 15 minutes; (iii) **2a**, TBAF, THF, room temperature, 2 h; and (iv) **7a** diethyl malonate, C_2H_5ONa, toluene reflux, 48 h. TBAF = tetrabutylammonium fluoride.

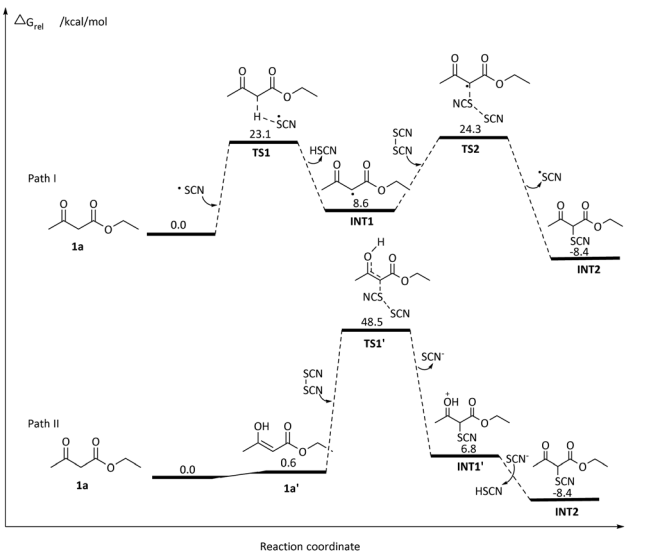
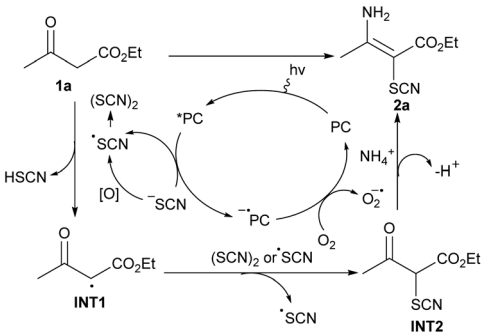


Fig. 1 Analysis of the reaction pathway. Quantum mechanical calculations were performed using Gaussian 09. All geometries and single point energies were calculated with M06-2x/6-31+G(d,p) and the SMD model for acetonitrile.



Scheme 3 Proposed mechanism.

(see Fig. S4†). Gratifyingly, the adduct of intermediate INT1 with TEMPO was confirmed by ESI-HRMS.

We postulated a plausible mechanism for this aminothiocyanation process. The reaction begins with the visible light-induced SET oxidation of NH_4SCN[15] (E_{ox} = 0.61 V *vs.* SCE in CH_3CN) by the excited state photocatalyst *fluorescein[16] (E^*_{red} = 0.78 V *vs.* SCE) generating the thiocyanate radical and the reduced species fluorescein$^{\bullet-}$. The fluorescein$^{\bullet-}$ could be oxidized with dioxygen to provide a superoxide and regenerate the photocatalyst. Then, the $^{\bullet}$SCN radical abstracts a hydrogen from **1a** to produce a carbon-centered radical and thiocyanic acid (HSCN).[13] The obtained α-carbonyl radical INT1 was subsequently trapped by other $^{\bullet}$SCN or $(SCN)_2$ to form coupling intermediate INT2, which has a more electron-deficient carbonyl group and can be easily attacked by nucleophilic NH_3. Finally, the elimination of water from the adduct of INT2 and NH_3 affords the desired product (Scheme 3).

Conclusions

In summary, we have developed a highly efficient metal-free visible-light promoted aminothiocyanation of activated ketones using air as the terminal oxidant to afford (*E*)-3-amino-2-thiocyanato-α,β-unsaturated compounds. The net reaction is very clean and water is the only byproduct when NH_4SCN is used as the source of SCN and NH_2. The resulting multi-substituted olefins can be used as direct precursors to construct an array of important molecules.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) I. P. Beletskaya and V. P. Ananikov, *Chem. Rev.*, 2011, **111**, 1596; (*b*) H. Yang, X. H. Duan, J. F. Zhao and L. N. Guo, *Org. Lett.*, 2015, **17**, 1998; (*c*) S. P. Brown and A. B. Smith III, *J. Am. Chem. Soc.*, 2015, **137**, 4034; (*d*) C. C. Palsuledesai, S. Murru, S. K. Sahoo and B. K. Patel, *Org. Lett.*, 2009, **11**, 3382.

2 (*a*) T. Castanheiro, J. Suffert, M. Donnard and M. Gulea, *Chem. Soc. Rev.*, 2016, **45**, 494; (*b*) S. Dutta, H. Abe, S. Aoyagi, C. Kibayashi and K. S. Gates, *J. Am. Chem. Soc.*, 2005, **127**, 15004; (*c*) R. J. Capon, C. Skene, E. H. T. Liu, E. Lacey, J. H. Gill, K. Heiland and T. Friedel, *J. Org. Chem.*, 2001, **66**, 7765; (*d*) E. Elhalem, B. N. Bailey, R. Docampo, I. Ujváry, S. H. Szajnman and J. B. Rodriguez, *J. Med. Chem.*, 2002, **45**, 3984; (*e*) Y. Yasman, R. A. Edrada, V. Wray and P. Proksch, *J. Nat. Prod.*, 2003, **66**, 1512.

3 (*a*) L. Li, M. Ganesh and D. Seidel, *J. Am. Chem. Soc.*, 2009, **131**, 11648; (*b*) M. D'hooghe, A. Waterinckx and N. De Kimpe, *J. Org. Chem.*, 2005, **70**, 227; (*c*) B. Bayarmagnai, C. Matheis, K. Jouvin and L. J. Goossen, *Angew. Chem., Int. Ed.*, 2015, **54**, 5753; (*d*) Z. P. Demko and K. B. Sharpless, *J. Org. Chem.*, 2001, **66**, 7945.

4 (*a*) R. B. Fabricio, C. Aníbal, L. Ivan and V. Gotor, *Green Chem.*, 2009, **11**, 452; (*b*) J. S. Qiu, D. Wu, P. G. Karmaker, H. Q. Yin and F. X. Chen, *Org. Lett.*, 2018, **20**, 1600; (*c*) S. Liang, H. Y. Tian, X. G. Luo, F. Z. Ren, B.-G. Sun and C. C. Zeng, *Adv. Synth. Catal.*, 2018, **360**, 1444; (*d*) F. Pan, X. L. Li, X. M. Chen, C. Shu, P. P. Ruan, C. H. Shen, X. Lu and L. W. Ye, *ACS Catal.*, 2016, **6**, 6055.

5 (*a*) P. B. Thakur, B. M. Babu, V. M. Bangade and H. M. Meshram, *Tetrahedron Lett.*, 2012, **53**, 5265; (*b*) J. S. Yadav, B. V. Subba Reddy, Y. G. Rao and A. V. Narsaiah, *Tetrahedron Lett.*, 2008, **49**, 2381.

6 (*a*) O. Prakash, H. Kaur, H. Batra, N. Rani, S. P. Singh and R. M. Moriarty, *J. Org. Chem.*, 2001, **66**, 2019; (*b*) Y. T. Chen, S. F. Wang, Q. W. Jiang, C. G. Cheng, X. H. Xiao and G. G. Zhu, *J. Org. Chem.*, 2018, **83**, 716.

7 (*a*) S. Mitra, M. Ghosh, S. Mishra and A. Hajra, *J. Org. Chem.*, 2015, **80**, 8275; (*b*) A. K. Yadav and L. D. S. Yadav, *Tetrahedron Lett.*, 2015, **56**, 6696.

8 (*a*) B. Exner, B. Bayarmagnai, F. Jia and L. J. Goossen, *Chem. – Eur. J.*, 2015, **21**, 17220; (*b*) F. D. Tosté and I. W. J. Stil, *J. Am. Chem. Soc.*, 1995, **117**, 7261; (*c*) D. Wu, J. S. Qiu, P. G. Karmaker, H. Q. Yin and F. X. Chen, *J. Org. Chem.*, 2018, **83**, 1576; (*d*) H. Egami, T. Yoneda, M. Uku, T. Ide, Y. Kawato and Y. Hamashima, *J. Org. Chem.*, 2016, **81**, 4020.

9 (*a*) Y. S. Park and K. Kim, *Tetrahedron Lett.*, 1999, **40**, 6439; (*b*) J. M. Chen and X. Huang, *Synlett*, 2004, 552; (*c*) L. S. Kang, M. H. Luo, C. M. Lam, L. M. Hu, R. D. Little and C. C. Zeng, *Green Chem.*, 2016, **18**, 3767; (*d*) J. P. Wan, S. S. Zhong, L. L. Xie, X. J. Cao, Y. Y. Liu and L. Wei, *Org. Lett.*, 2016, **18**, 584; (*e*) S. S. Zhong, Y. Y. Liu, X. J. Cao and J. P. Wan, *ChemCatChem*, 2017, **9**, 465; (*f*) Y. H. Guo, Y. F. Xiang, L. Wei and J. P. Wan, *Org. Lett.*, 2018, **20**, 3971;

(*g*) J. P. Wan, S. Cao, C. F. Hu and C. P. Wen, *Asian J. Org. Chem.*, 2018, **7**, 328.

10 (*a*) A. Y. Nosaka and Y. Nosaka, *Chem. Rev.*, 2017, **117**, 11302; (*b*) Y. F. Liang and N. Jiao, *Acc. Chem. Res.*, 2017, **50**, 1640; (*c*) Q. Liu and L.-Z. Wu, *Natl. Sci. Rev.*, 2017, **4**, 359.

11 (*a*) T. Song, B. Zhou, G.-W. Peng, Q.-B. Zhang, L.-Z. Wu, Q. Liu and Y. Wang, *Chem. – Eur. J.*, 2014, **20**, 678; (*b*) L. Wang, Z.-G. Ma, X.-J. Wei, Q.-Y. Meng, D.-T. Yang, S.-F. Du, Z.-F. Chen, L.-Z. Wu and Q. Liu, *Green Chem.*, 2014, **16**, 3752; (*c*) X. J. Wei, L. Wang, W. L. Jia, S. F. Du, L. Z. Wu and Q. Liu, *Chin. J. Chem.*, 2014, **32**, 1245; (*d*) Q.-B. Zhang, Y.-L. Ban, D.-G. Zhou, P.-P. Zhou, L.-Z. Wu and Q. Liu, *Org. Lett.*, 2016, **18**, 5256; (*e*) Q. B. Zhang, Y. L. Ban, P. F. Yuan, S. J. Peng, J. G. Fang, L. Z. Wu and Q. Liu, *Green Chem.*, 2017, **19**, 5559.

12 (*a*) A. P. Liu, X. G. Wang, X. P. Liu, J. M. Li, H. B. Chen, L. Hu, W. Q. Yu, L. He, W. D. Liu and M. Z. Huang, *J. Heterocycl. Chem.*, 2017, **54**, 1625; (*b*) S. Annadurai, R. Martinez, D. J. Canney, T. Eidem, P. M. Dunman and M. Abou-Gharbia, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 7719; (*c*) B. H. Chen, S. S. Guo, X. Guo, G. L. Zhang and Y. P. Yu, *Org. Lett.*, 2015, **17**, 4698.

13 (*a*) G. Claassen, E. Brin, C. Crogan-Grundy, M. T. Vaillancourt, H. Z. Zhang, S. X. Cai, J. Drewe, B. Tseng and S. Kasibhatla, *Cancer Lett.*, 2009, **274**, 243; (*b*) W. T. McElroy and P. DeShong, *Org. Lett.*, 2003, **5**, 4779; (*c*) L. M. Halo, M. N. Heneghan, A. A. Yakasai, Z. S. Song, K. Williams, A. M. Bailey, R. J. Cox, C. M. Lazarus and T. J. Simpson, *J. Am. Chem. Soc.*, 2008, **130**, 17988.

14 (*a*) Sk. S. Shah and N. D. P. Singh, *Tetrahedron Lett.*, 2018, **59**, 247; (*b*) G. Wojciechowski, L. S. Huang and P. R. Ortiz de Montellano, *J. Am. Chem. Soc.*, 2005, **127**, 15871; (*c*) M. T. Ashby and H. Aneetha, *J. Am. Chem. Soc.*, 2004, **126**, 10216.

15 W. G. Fan, Q. Yang, F. S. Xu and P. X. Li, *J. Org. Chem.*, 2014, **79**, 10588.

16 S. P. Pitre, C. D. McTiernan and J. C. Scaiano, *Acc. Chem. Res.*, 2016, **49**, 1320.

