

PAPER

 View Article Online
 View Journal | View Issue
Cite this: *RSC Adv.*, 2019, 9, 3403
 Received 28th November 2018
 Accepted 20th January 2019

DOI: 10.1039/c8ra09784d

rsc.li/rsc-advances

DMSO-mediated palladium-catalyzed cyclization of two isothiocyanates *via* C–H sulfurization: a new route to 2-aminobenzothiazoles†

 Guangkai Yao,^{ac} Bing-Feng Wang,^{ab} Shuai Yang,^{ac} Zhi-Xiang Zhang,^{ac}
 Han-Hong Xu^{id}*^{ac} and Ri-Yuan Tang^{id}*^{ab}

DMSO was found to activate arylisothiocyanates for self-nucleophilic addition. A subsequent intramolecular C–H sulfurization catalyzed by PdBr₂ enables access to a wide range of 2-aminobenzothiazole derivatives in moderate to good yields. This is the first example of a DMSO-mediated Pd-catalyzed synthesis of 2-aminobenzothiazoles through cyclization/C–H sulfurization of two isothiocyanates.

2-Aminobenzothiazole derivatives are privileged scaffolds which have been widely used in medicine and agricultural chemicals (Scheme 1a).¹ Significant effort has been devoted to the development of synthetic methodologies for the preparation of such species.² Thioureas,^{3,4} isothiocyanates,^{5,6} and benzothiazoles⁷ are effective reaction partners for the synthesis of 2-aminobenzothiazole derivatives *via* cross-coupling reactions or C–H functionalization. Intramolecular C–H sulfurization of *N*-arylthioureas is an effective strategy for the synthesis of 2-aminobenzothiazoles. Such a transformation can be achieved through metal-catalyzed C–H activation³ or *via* radical reactions.⁶ For example, Doi and coworkers reported a Pd-catalyzed intramolecular C–H sulfurization of arylthiourea using O₂ as an oxidant.^{3c} Metal-free iodine-catalyzed intramolecular C–H sulfurization also provides an effective pathway to 2-aminobenzothiazoles.^{6c} Zhu *et al.* developed an efficient oxidative radical strategy for the synthesis of 2-aminobenzothiazoles *via* an aminyl radical addition to aryl isothiocyanates followed by C–H sulfurization in the presence of *n*-Bu₄NI and TBHP.^{6c} Interestingly, Lei *et al.* reported a “green” synthesis of 2-aminobenzothiazoles by employing electro-catalysis technology for an external oxidant-free intramolecular C–H sulfurization.^{6d} In terms of metal-catalyzed C–H sulfurization,⁸ palladium-catalyzed C–H sulfurization has not been widely reported because thioureas are often strong metal-chelating species that may lead to poisoning of palladium catalysts. Thus, only a few

examples of Pd-catalyzed protocols have been reported (Scheme 1b).^{3b,c,e} Therefore, the development of novel palladium-catalyzed C–H sulfurization reaction is of great interest. As a continuation of our interest in sulfur chemistry and C–H sulfurization,⁹ we attempted to transform isothiocyanates into sulfur-containing compounds.¹⁰ Unexpectedly, a newly formed 2-aminobenzothiazole was observed for the reaction of a phenylisothiocyanate. Encouraged by this discovery, we developed a new, facile and efficient DMSO-mediated palladium-catalyzed C–H sulfurization/cyclization of two isothiocyanates for the synthesis of 2-aminobenzothiazoles (Scheme 1c).

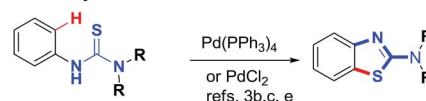
Our study began with the reaction of phenyl isothiocyanate (**1a**) with PdCl₂ in different solvents (Table 1). Solvents including toluene, chlorobenzene, DCE, CH₃CN, DMF, NMP (*N*-methyl-2-pyrrolidinone), and DMSO, were examined (Table 1, entries 1–7). Only highly polar solvents, such as DMF, NMP, and DMSO were suitable for this reaction; however, DMF and NMP

a. Examples of 2-Aminobenzothiazoles drug



b. Previous work

Pd-catalyzed C–H sulfurization



c. This work



Scheme 1 Biological application and synthetic methods for the preparation of 2-aminobenzothiazoles.

^aKey Laboratory of Natural Pesticide and Chemical Biology, Ministry of Education, South China Agricultural University, Guangzhou 510642, China. E-mail: hhxu@scau.edu.cn; rytang@scau.edu.cn

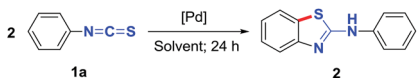
^bDepartment of Applied Chemistry, College of Materials and Energy, South China Agricultural University, Guangzhou 510642, China

^cState Key Laboratory for Conservation and Utilization of Subtropical Agro-Bioresources, South China Agricultural University, Guangzhou 510642, China

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ra09784d



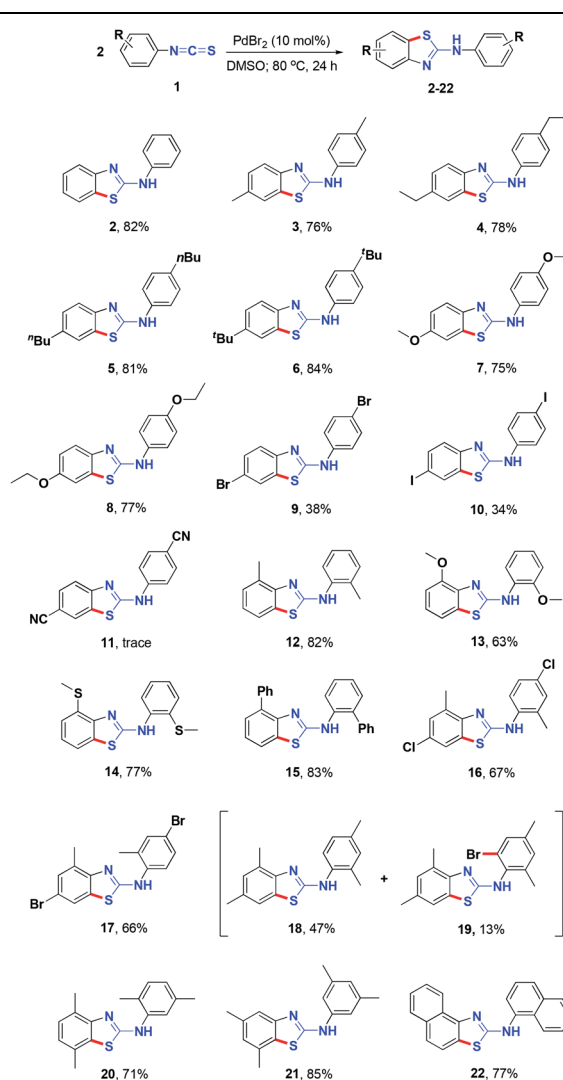
Table 1 Screening of reaction conditions^a

			
Entry	Catalyst	Solvent	Yield ^b (%)
1	PdCl ₂	Toluene	0
2	PdCl ₂	Chlorobenzene	0
3	PdCl ₂	DCE	0
4	PdCl ₂	CH ₃ CN	0
5	PdCl ₂	DMF	12
6	PdCl ₂	NMP	16
7	PdCl ₂	DMSO	72
8 ^c	PdCl ₂	DMSO	32
9 ^d	PdCl ₂	DMSO	58
10	PdBr ₂	DMSO	82
11	Pd(OAc) ₂	DMSO	Trace
12	Pd(PPh ₃) ₂ Cl ₂	DMSO	Trace
13 ^e	PdBr ₂	DMSO	70
14	—	DMSO	0
15 ^f	PdBr ₂	DMSO/CH ₃ CN	55
16 ^g	PdBr ₂	DMSO/CH ₃ CN	23
17 ^h	PdBr ₂	DMSO/H ₂ O	61
18 ⁱ	PdBr ₂	DMSO/H ₂ O	75

^a Reaction conditions: **1a** (0.4 mmol), [Pd] (10 mol%), stirred at 80 °C in solvent (2 mL) for 24 h. ^b Isolated yield. ^c At 100 °C. ^d At 60 °C. ^e PdBr₂ (5 mol%). ^f DMSO/CH₃CN = 1 : 1. ^g DMSO/CH₃CN = 1 : 4. ^h DMSO/H₂O = 10 : 1. ⁱ DMSO/H₂O = 20 : 1.

gave low yields of the desired product (entries 5 and 6). DMSO was found to be the preferable solvent for the reaction giving the desired product **2** in 72% yield in the presence of 10 mol% PdCl₂ at 80 °C over 24 hours (entry 7). Increasing or decreasing the reaction temperature led to lower yields (e.g. 32% at 100 °C and 58% at 60 °C) (entries 8 and 9). Next, other palladium catalysts, such as PdBr₂, Pd(OAc)₂, and Pd(PPh₃)₂Cl₂, were evaluated (entries 10–12). Compared with PdCl₂, PdBr₂ was more effective affording product **2** in 82% yield (entry 10). However, Pd(OAc)₂ and Pd(PPh₃)₂Cl₂ were not suitable catalysts for this reaction (entries 11 and 12). The yield of the desired product decreased to 70% when the reaction was conducted in the presence of 5 mol% PdBr₂ (entry 13). The reaction did not proceed in the absence of PdBr₂ (entry 14). When the reaction was carried out in a mixed DMSO/CH₃CN solvent system, lower yields of product were obtained (entries 15 and 16). The influence of water was also examined. The addition of water facilitated the formation of thiourea, but reduced the yield of target product (entries 17 and 18).

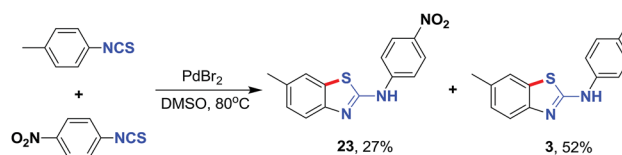
With the optimized reaction conditions in hand, the reaction scope was investigated (Table 2). Initially, 4-substituted arylisothiocyanates were subjected to the reaction conditions. Substituents, including methyl, ethyl, butyl, *t*-butyl, methoxy, ethoxyl, bromo, and iodo groups, were all tolerated. Electron-donating substituents promoted the reaction, affording their corresponding products **2–8** in moderate to good yields. Although both the C–Br and C–I bonds are reactive units for cross-coupling reactions, the C–H sulfurization was selectively carried out to afford products **9** and **10** in 38% and 34% yields,

Table 2 The scope of 2-aminobenzothiazoles^a

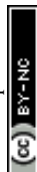
^a Reaction conditions: **1** (0.4 mmol), PdBr₂ (10 mol%), stirred at 80 °C in DMSO (2 mL) for 24 h.

respectively. However, the electron-withdrawing cyano group was not amenable to the reaction conditions (products **11**). This suggests that the reaction may involve an electrophilic cyclo-palladation process and the electron-withdrawing group would thus decrease the reactivity.

Ortho-substituents, such as methyl, methoxy, methylthio, and phenyl, which increase steric hindrance, still performed well to give their corresponding products in moderate to good yields (products **12–20**). For reactions involving *ortho*-



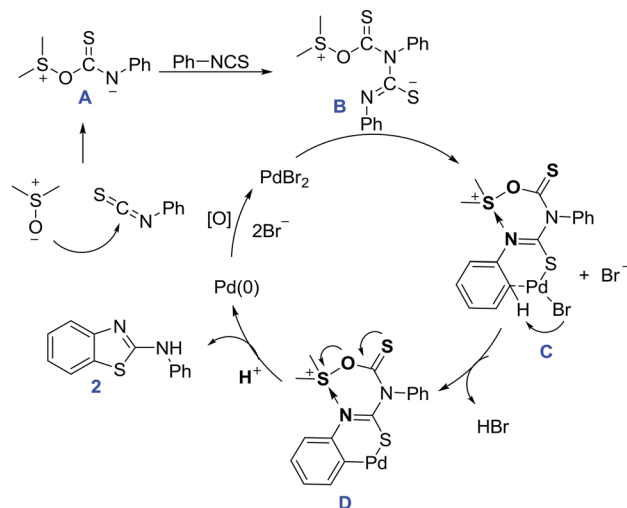
Scheme 2 PdBr₂-catalyzed cross-reaction of two different isothiocyanates.



substituted substrates, a small amount of brominated by-product similar to compound **19** was observed; however, the majority of these by-products were obtained in far lower yield than **19**. To our delight, a naphthyl isothiocyanate also underwent reaction smoothly to give product **22** in 77% yield. 3-Isothiocyanatopyridine was also subjected to the reaction conditions. However, no cyclization/C–H sulfurization occurred; the electron-deficient pyridine ring is not reactive enough for C–H sulfurization. The reaction of *meta*-substituted methyl phenylisothiocyanates provided two isomers which could not be easily purified.

To prove the feasibility of the cyclization of two different aryl isothiocyanates, a cross-reaction between 4-methylphenylisothiocyanate and 4-nitro-phenylisothiocyanate was conducted. The cross-reaction product **23**, was obtained in 27% yield with compound **3** being formed as the main product in 52% yield (Scheme 2). The strong electron-withdrawing nitro group greatly reduces the electron density of the benzene ring, thus C–H sulfurization is disfavored; C–H sulfurization only occurred on the methyl-substituted benzene ring.

To gain insight into the reaction mechanism, control experiments were conducted, as shown in Scheme 3. In the absence of PdBr_2 , thiourea **24** was obtained in 35% yield for the reaction of 4-methyl phenylisothiocyanate in DMSO at 80 °C over 24 hours (Scheme 3, eqn (1)). This suggested that the thiourea may be the reaction intermediate; however, when thiourea **24** was subjected to reaction with PdBr_2 , product **3** was obtained in only 16% yield (Scheme 3, eqn (2)). Aryl isothiocyanate may decompose to aniline, and react with isothiocyanate for C–H sulfurization. However, only a trace amount of product **25** was observed in the reaction between 4-methylphenyl isothiocyanate and aniline (Scheme 3, eqn (3)). None of the target product **26** was observed for the reaction of benzothiazole with 4-methyl phenylisothiocyanate, suggesting



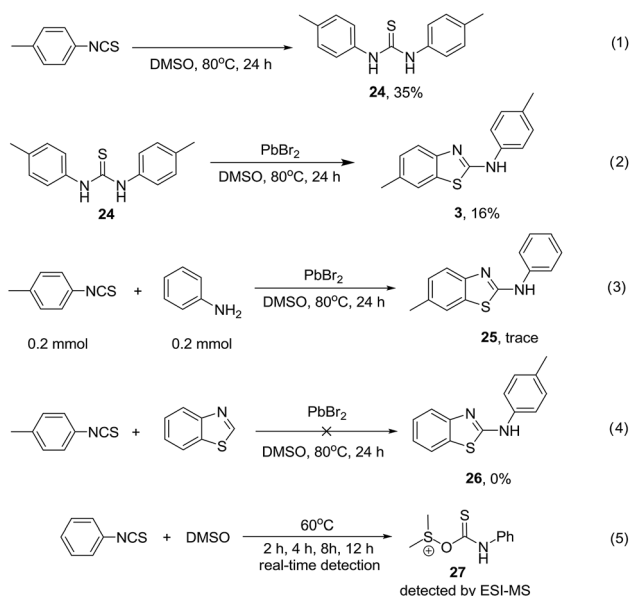
Scheme 4 A possible mechanism.

that benzothiazole is not a reaction intermediate (Scheme 3, eqn (4)). To our delight, a mass peak corresponding to intermediate **27** was observed with real-time ESI-MS when phenylisothiocyanate was stirred in DMSO at 60 °C (Scheme 3, eqn (5)) (see the ESI, Fig. S1†). Based on theoretical calculations,¹¹ the dipole moment of the DMSO molecule is 3.9274 debye (gas) or 5.1281 debye in solvent form. Natural bond orbital analysis shows the differences in the charge distribution on the O and S atoms. Obviously, the polarity of the S–O bond increases and a greater distribution of the negative charge on the O atom leads to an improvement in its nucleophilic character. The oxygen atom attacks the carbon atom with the most positive NBO charge in PhNCS (see the ESI, Fig. S2 and S3†). These results indicate that DMSO acts as a nucleophilic agent for the activation of arylisothiocyanates for C–H sulfurization.

Based on the above results and previous work,³ a possible reaction mechanism has been proposed and is shown in Scheme 4. Firstly, the polarized DMSO undergoes a nucleophilic addition with phenylisothiocyanate to afford the active intermediate **A**, which then reacts with another equivalent of phenylisothiocyanate to produce an intermediate **B**. Intermediate **B** chelates with PdBr_2 to form an intermediate **C**. Subsequent elimination of HBr leads to the formation of intermediate **D**, which undergoes reductive elimination to afford the desired product **2**. The $\text{Pd}(0)$ is oxidized by DMSO to PdBr_2 for the next catalytic cycle.

Conclusions

In summary, a DMSO-mediated PdBr_2 -catalyzed synthesis of 2-aminobenzothiozoles *via* the cyclization/C–H sulfurization of two aryl isothiocyanates has been developed for the first time. In the presence of DMSO and PdBr_2 , a variety of aryl isothiocyanates underwent reaction to afford the corresponding 2-aminobenzothiozoles in moderate to good yields. In this tandem reaction, DMSO acts as a key initiator for the activation of aryl isothiocyanates, although the exact role of DMSO is unclear.



Scheme 3 Control experiments.



Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for financial support from the Science Technology Program Project of Guangdong Province (No. 2016B020204005), Natural Science Foundation of Guangdong Province (Grant 2016A030313387), and China Postdoctoral Science Foundation (Grant 2018M643105).

Notes and references

- (a) P. C. Sharma, K. K. Bansal, A. Deep and M. Pathak, *Curr. Top. Med. Chem.*, 2017, **17**, 208–237; (b) J. B. Sweeney, M. Rattray, V. Pugh and L. A. Powell, *ACS Med. Chem. Lett.*, 2018, **9**, 552–556; (c) L. Hroch, P. Guest, O. Benek, O. Soukup, J. Janockova, R. Dolezal, K. Kuca, L. Aitken, T. K. Smith, F. Gunn-Moore, D. Zala, R. R. Ramsay and K. Musilek, *Bioorg. Med. Chem.*, 2017, **25**, 1143–1152; (d) Z. Ji, F. Zhou and S. Wei, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 4065–4068.
- For reviews, see: (a) T. L. Dadmal, S. D. Katre, M. C. Mandewale and R. M. Kumbhare, *New J. Chem.*, 2018, **42**, 776–797; (b) N. P. Prajapati, R. H. Vekariya, M. A. Borad and H. D. Patel, *RSC Adv.*, 2014, **4**, 60176–60208.
- Synthesis of benzothiazoles via C–H sulfurization, see: (a) A. D. Jordan, C. Luo and A. B. Reitz, *J. Org. Chem.*, 2003, **68**, 8693–8696; (b) L. L. Joyce and R. A. Batey, *Org. Lett.*, 2009, **11**, 2792–2795; (c) K. Inamoto, C. Hasegawa, J. Kawasaki, K. Hiroya and T. Doi, *Adv. Synth. Catal.*, 2010, **352**, 2643–2655; (d) H. Wang, L. Wang, J. Shang, X. Li, H. Wang, J. Gui and A. Lei, *Chem. Commun.*, 2012, **48**, 76–78; (e) S. K. Sahoo, A. Banerjee, S. Chakraborty and B. K. Patel, *ACS Catal.*, 2012, **2**, 544–551; (f) J. Wang, Y. Zong, X. Zhang, Y. Gao, Z. Li, G. Yue, Z. Quan and X. Wang, *Synlett*, 2014, **25**, 2143–2148; (g) S. Sharma, R. S. Pathare, A. K. Maurya, K. Gopal, T. K. Roy, D. M. Sawant and R. T. Pardasani, *Org. Lett.*, 2016, **18**, 356–359.
- Synthesis of benzothiazoles via cross-coupling reaction of *ortho*-halothioureia, see: (a) C. Benedi, F. Bravo, P. Uriz, E. Fernández, C. Claver and S. Castillón, *Tetrahedron Lett.*, 2003, **44**, 6073–6077; (b) L. L. Joyce, G. Evindar and R. A. Batey, *Chem. Commun.*, 2004, 446–447; (c) R. Wang, W.-J. Yang, L. Yue, W. Pan and H.-Y. Zeng, *Synlett*, 2012, **23**, 1643–1648; (d) S. K. Rout, S. Guin, J. Nath and B. K. Patel, *Green Chem.*, 2012, **14**, 2491–2498; (e) H. Min, G. Xiao, W. Liu and Y. Liang, *Org. Biomol. Chem.*, 2016, **14**, 11088–11091; (f) W. Zeng, P. Dang, X. Zhang, Y. Liang and C. Peng, *RSC Adv.*, 2014, **4**, 31003–31006.
- Metal-catalyzed tandem reaction of isothiocyanates with amines, see: (a) Q. Ding, X. He and J. Wu, *J. Comb. Chem.*, 2009, **11**, 587–591; (b) Y.-J. Guo, R.-Y. Tang, P. Zhong and J.-H. Li, *Tetrahedron Lett.*, 2010, **51**, 649–652; (c) N. Khatun, L. Jamir, M. Ganesh and B. K. Patel, *RSC Adv.*, 2012, **2**, 11557–11565; (d) L. Chen, B. Huang, Q. Nie and M. Cai, *Appl. Organomet. Chem.*, 2016, **30**, 446–450; (e) N. Zhao, L. Liu, F. Wang, J. Li and W. Zhang, *Adv. Synth. Catal.*, 2014, **356**, 2575–2579; (f) Q. Ding, B. Cao, X. Liu, Z. Zong and Y.-Y. Peng, *Green Chem.*, 2010, **12**, 1607–1610.
- Metal-free conditions: (a) Z.-G. Le, J.-P. Xu, H.-Y. Rao and M. Ying, *J. Heterocycl. Chem.*, 2006, **43**, 1123–1124; (b) W. Zhang, Y. Yue, D. Yu, L. Song, Y.-Y. Xu, Y.-J. Tian and Y.-J. Guo, *Adv. Synth. Catal.*, 2012, **354**, 2283–2287; (c) Y. He, J. Li, S. Luo, J. Huang and Q. Zhu, *Chem. Commun.*, 2016, **52**, 8444–8447; (d) P. Wang, S. Tang and A. Lei, *Green Chem.*, 2017, **19**, 2092–2095; (e) Y. Xu, B. Li, X. Zhang and X. Fan, *J. Org. Chem.*, 2017, **82**, 9637–9646.
- (a) S. Toulot, T. Heinrich and F. R. Leroux, *Adv. Synth. Catal.*, 2013, **355**, 3263–3272; (b) A. Armstrong and J. C. Collins, *Angew. Chem., Int. Ed.*, 2010, **49**, 2282–2285; (c) S. Mitsuda, T. Fujiwara, K. Kimigafukuro, D. Monguchi and A. Mori, *Tetrahedron*, 2012, **68**, 3585–3590; (d) D. Monguchi, T. Fujiwara, H. Furukawa and A. Mori, *Org. Lett.*, 2009, **11**, 1607–1610.
- (a) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. A. Hor and X. Liu, *Chem. Soc. Rev.*, 2015, **44**, 291–314; (b) F.-J. Chen, G. Liao, X. Li, J. Wu and B.-F. Shi, *Org. Lett.*, 2014, **16**, 5644–5647.
- (a) J.-R. Zhang, L.-Z. Zhan, L. Wei, Y.-Y. Ning, X.-L. Zhong, J.-X. Lai, L. Xu and R.-Y. Tang, *Adv. Synth. Catal.*, 2018, **360**, 533–543; (b) J.-C. Deng, J.-H. Chen, J.-R. Zhang, T.-T. Lu and R.-Y. Tang, *Adv. Synth. Catal.*, 2018, **360**, 4795–4806; (c) J.-R. Zhang, Y.-Y. Liao, J.-C. Deng, K.-Y. Feng, M. Zhang, Y.-Y. Ning, Z.-W. Lin and R.-Y. Tang, *Chem. Commun.*, 2017, **53**, 7784–7787; (d) J.-C. Deng, S.-B. Zhuang, Q.-Z. Liu, Z.-W. Lin, Y.-L. Su, J.-H. Chen and R.-Y. Tang, *RSC Adv.*, 2017, **7**, 54013–54016; (e) J. Jiao, L. Wei, X.-M. Ji, M.-L. Hu and R.-Y. Tang, *Adv. Synth. Catal.*, 2016, **358**, 268–275; (f) X.-M. Ji, S.-J. Zhou, F. Chen, X.-G. Zhang and R.-Y. Tang, *Synthesis*, 2015, **47**, 659–671.
- Y.-Y. Liao, J.-C. Deng, Y.-P. Ke, X.-L. Zhong, L. Xu, R.-Y. Tang and W. Zheng, *Chem. Commun.*, 2017, **53**, 6073–6076.
- M. J. Frisch, G. W. Trucks and H. B. Schlegel, *et al.*, *Gaussian 09, rev. D. 01*, Gaussian, Inc., Wallingford, CT2009.

