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TBAI–HBr system mediated generation of various thioethers with benzenesulfonyl chlorides in PEG_{400}†

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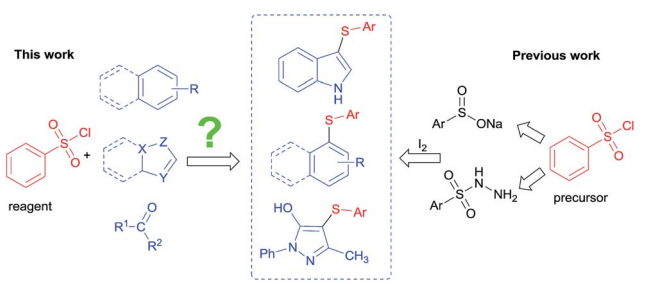
An efficient procedure for the formation of C–S bonds *via* C–H functionalization was developed for the synthesis of aryl sulfides in good to excellent yields using TBAI–HBr system promoted direct sulfenylation of various compounds, such as phenols, pyrazolones, indoles and related heteroarenes. Low cost and widely available arylsulfonyl chlorides were used as the sulfur source to provide various sulfur-containing compounds. The characteristic of the present protocol is convenient, green, highly efficient with a wide-application and short reaction time.

Introduction

Aryl sulfides as important building blocks for creating molecules often appear in total synthesis, in functional materials science, and in medicinal chemistry.[1] In the last few decades, many scientists have reported transition metal (*e.g.*, Pd,[2] Cu,[3] Ni,[4] In,[5] Fe,[6] Co (ref. 7) *etc.*) catalyzed cross-coupling reactions of aryl halides, boronic acids and triflates with S-containing nucleophiles. For the preparation of aryl thioethers, the above mentioned methods are the main techniques of traditional synthesis. Aryl thiols and disulfides are often used as the choice of sulfur sources. Nevertheless, many of these sulfur sources are often limited because of their expensiveness, instability and high-toxicity. Therefore, a new, direct, flexible and green sulfenylation of (hetero)arenes to synthesize aryl sulfides under metal-free conditions is always a hot issue for chemists.

In the past few years, many efficient methods to synthesize sulphur compounds have been reported by groups of Yi,[8] Tian,[9] Hiebel,[10] Bolm[11] and others.[12] Recently, we reported the I_2-mediated thiolation of phenol/phenylamine derivatives and sodium arylsulfinates in water.[13] Obviously, the synthesis of sulfur-containing compounds have made great progress. From the perspective of green chemistry, scientists have found the other new sulfur sources (*e.g.*, sodium benzenesulfinates, benzenesulfonyl hydrazides, diphenyl disulfides *etc.*) to replace thiophenols. Although these sulfur sources are environmentally friendly, we are hard to get their derivatives from the market directly. For example, the derivatives of sodium benzenesulfinate and benzenesulfonyl hydrazide need to be synthesized. It is noteworthy that inexpensive and easily available benzenesulfonyl chlorides are their precursor. Apparently, several issues of these strategies should be addressed: (1) use benzenesulfonyl chlorides to replace some sulfur sources that they are green but unavailable, such as sodium benzenesulfinates, benzenesulfonyl hydrazides and so on; (2) find an efficient and green reaction system to synthesize sulfur-containing compounds by directly using benzenesulfonyl chlorides as a sulfur source in the absence of a transition metal catalyst; (3) look for a reaction system is suitable for several compound to synthesize sulfocompounds using benzenesulfonyl chlorides (Scheme 1).

In order to solve these problems, PPh_3-mediated sulfenylation of indolizines and related heteroarenes by directly using aryl-sulfonyl chlorides as a sulfur source has been reported by You.[14] The protocol proves to be an efficient and convenient way to synthesize di(hetero)aryl sulfides using benzenesulfonyl chlorides directly. But in the view of green chemistry, it also encounters disadvantages, such as a mass of PPh_3 as reducing agent was used. The reaction was finished in toluene under the conditions of high temperature and longer reaction time. Previous relevant literature indicates that benzenesulfonyl chlorides can be readily reduced to reactive aryl sulfide species,[15] which reacts with electron donor compounds to



Scheme 1 Methods for the construction of thioethers.

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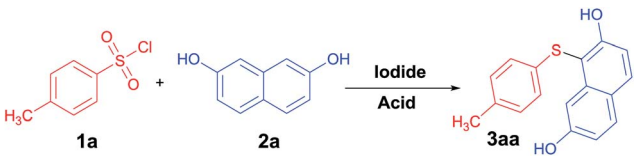
produce various thioethers. To explore a convenient, green and high efficient reaction system which has a wider substrate scope by directly using arylsulfonyl chlorides as a sulfur source thus interested us.

Results and discussion

To prove the feasibility of our proposed assumption, we started the investigation by selecting the reaction of tosyl chloride **1a** with 2,7-naphthalenediol **2a** as the model reaction (Table 1). From the perspective of green chemistry, poly(ethylene glycol) is an ideal solvent for chemical transformation because of its non-toxic, odorless, neutral, nonvolatile, and non-irritating and is used in a variety of pharmaceuticals and medications. Tosyl chloride was treated with 2,7-naphthalenediol (**2a**, 1.2 equiv.), tetrabutyl-ammonium iodide (TBAI, 2.0 equiv.) and HCOOH (2.0 equiv.) in 2 mL of PEG_{400} at 100 °C for 5 h in the opening system (Table 1, entry 7). Not surprisingly, the reaction provided a 52% yield of the desired product **3aa**. First, several iodide-containing were initially investigated, and among them TBAI showed the best efficiency to give the corresponding product **3aa** in 86% (Table 1, entries 1–4). Then, we screened different solvents, PEG_{400} proved to be the best choice in the transformation (entries 4, 12–15). The reaction was less efficient when other acid were used (Table 1, entries 4–11). The reactions were investigated using different amounts of TBAI/HBr. The results are shown in Table 1 (entries 16–20). Under the standard conditions, different amounts of TBAI ranging from 1.5 to 2.5 equivalents were applied in the reactions. The obtained yields increased as the TBAI amounts increased up to 2 equivalents to reach the maximum (Table 1, entry 5). Decreasing or increasing the amount of HBr both slightly decreased the reaction yields (Table 1, entries 18–20). Finally, when the reaction was carried out at 50 °C with prolonged reaction time, the yield of **3aa** was significantly lower (Table 1, entry 21). On the basis of the results shown in Table 1, the TBAI–HBr system at 100 °C in PEG_{400} for 5 h emerged as the optimized reaction conditions for follow-up studies.

With optimized conditions now in hand, a series of phenols and benzenesulfonyl chlorides were applied in the reaction to investigate the scope and generality of this protocol (Table 2). A range of benzenesulfonyl chlorides which have electron-donating and electron-withdrawing groups reacted with **2** to get the target products **3aa–3dc** and **3af–3df** in moderate to excellent yields. It's worth mentioning that we have not found C–halogen bond cleavage during the reaction. Besides, apart from phenols, methoxy-benzenes (**3d** and **3e**) were able to react with benzenesulfonyl chlorides to provide the corresponding products **3ad–3de** in a few hours in 85–92% yields as well. In general, benzenesulfonyl chlorides with electron-donating groups on the yield of target products were higher than those with electron-withdrawing groups.

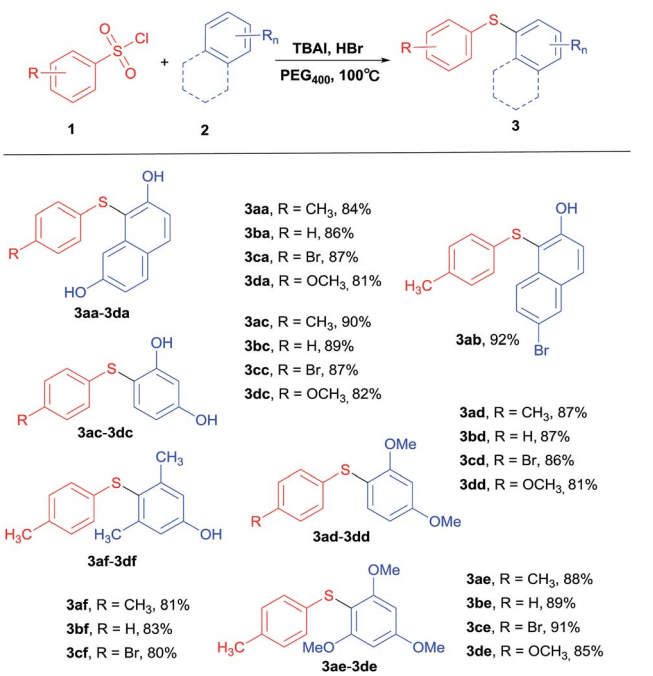
Table 1 Optimization of the reaction condition[a]



Entry	Iodide (equiv.)	Acid (equiv.)	Solvent	Yield[b] (%)
1	NaI (2.0)	HBr (2.0)	PEG_{400}	23
2	NH_4I (2.0)	HBr (2.0)	PEG_{400}	40
3	HI (2.0)	—	PEG_{400}	27
4	TBAI (2.0)	HBr (2.0)	PEG_{400}	86
5	TBAI (2.0)	HF (2.0)	PEG_{400}	25
6	TBAI (2.0)	HCl (2.0)	PEG_{400}	45
7	TBAI (2.0)	HCOOH (2.0)	PEG_{400}	52
8	TBAI (2.0)	AcOH (2.0)	PEG_{400}	47
9	TBAI (2.0)	TFA (2.0)	PEG_{400}	32
10	TBAI (2.0)	PvOH (2.0)	PEG_{400}	27
11	TBAI (2.0)	TsOH (2.0)	PEG_{400}	57
12	TBAI (2.0)	HBr (2.0)	Dioxane	82
13	TBAI (2.0)	HBr (2.0)	Toluene	75
14	TBAI (2.0)	HBr (2.0)	EtOH	55
15	TBAI (2.0)	HBr (2.0)	H_2O	42
16	TBAI (1.5)	HBr (2.0)	PEG_{400}	69
17	TBAI (2.5)	HBr (2.0)	PEG_{400}	85
18	TBAI (2.0)	HBr (1.5)	PEG_{400}	71
19	TBAI (2.0)	HBr (2.5)	PEG_{400}	84
20	TBAI (2.0)	HBr (4.0)	PEG_{400}	76
21[c]	TBAI (2.0)	HBr (2.0)	PEG_{400}	51
22[d]	TBAI (2.0)	HBr (2.0)	PEG_{400}	80

[a] Conditions: **1a** (0.30 mmol), **2a** (0.36 mmol), solvent (2 mL), iodide (2.0 equiv.), acid (2.0 equiv.), 5 h, 100 °C, under air. [b] Yield of isolated product. [c] 50 °C. [d] Under N_2.

Table 2 Substrate scope[a]



[a] Conditions: 1 (0.30 mmol), 2 (0.36 mmol), TBAI (0.60 mmol), HBr (0.60 mmol, 40% aqueous), PEG_{400} (2 mL), 100 °C, 5 h.

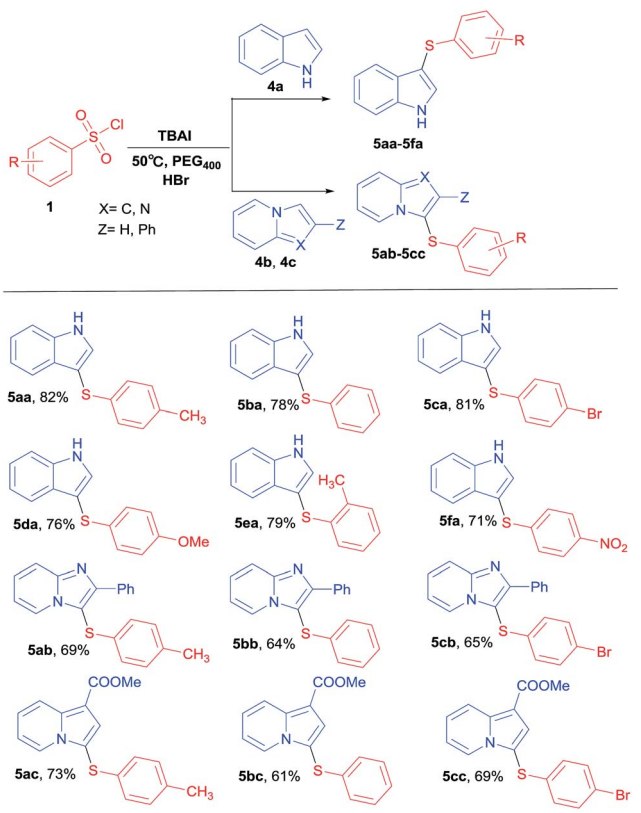
On the basis of satisfied results obtained under TBAI–HBr system, we further apply this system to show the functional group tolerance. For this purpose, we carried out the reactions of various benzenesulfonyl chlorides with different benzoheterocycles under the aforementioned conditions (Table 3). It was exhilarating to find that different benzenesulfonyl chlorides having electron-withdrawing and electron-donating halo groups at the 4-position were able to react with indoles (**4a**) to afford the desired products (**5aa–5fa**) in good yields under the optimized conditions. Fortunately, indolizines and related heteroarenes were also suitable for this kind of transformation in the presence of HBr. It's worth mentioning that we found benzenesulfonyl chlorides could react with benzoheterocycles under mild conditions. The reaction temperature could go down to 50 °C. Under the optimized conditions, a series of *para*-substituted benzenesulfonyl chlorides smoothly reacted with **4b** and **4c** to give desired products in moderate yields (Table 3). According to the results analysis, much lower yields were obtained when indolizines (**4c**) and related heteroarenes (**4b**) instead of indoles (**4a**) were employed in this kind of transformation.

To further examine whether our reaction conditions are also suitable for ketone compounds, we sought to expand the scope of sulphenylation of pyrazolones with benzenesulfonyl chlorides under TBAI–HBr system. It was found that the reactions proceeded well, and the results are showed in Table 4. The result showed that pyrazolones reacted well with benzenesulfonyl chlorides bearing electron-donating substituents and electron-withdrawing groups at the *para*-position giving good and regioselective thioethers **7aa–7fa** in good to excellent yields under an air atmosphere. At the same time, we are pleased to find that the reaction was completed in minutes. Moreover, benzenesulfonyl chlorides do not react with phenyl from pyrazolones under the same reaction conditions.

In order to gain further insight into the plausible reaction pathway of TBAI–HBr system mediated generation of various thioethers, some control experiments were conducted under various reaction conditions, as showed in Scheme 2. In the presence of 1.0 equivalents of iodine, tosyl chloride **1a** reacted with 2,7-naphthalenediol **2a** led to the desired product **3aa** in 23% yield (Scheme 2a). In the absence of TBAI, treatment of tosyl chloride (**1a**) with 2,7-naphthalenediol (**2a**) and HBr (2.0 equiv.) under standard reaction conditions in a closed tube to yield the target product (**3aa**, 46%), and bromine was detected after the end of reaction. On the other hand, the reaction was carried out in the presence of HI led to **3aa** in 27% (Scheme 2c).

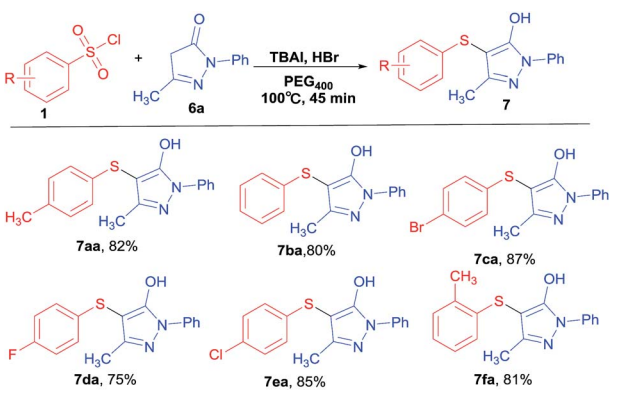
On the basis of the experimental results described above and together with previous relevant mechanistic studies,[14,16] a plausible reaction mechanism for aryl sulfides formation from phenols/benzoheterocycles and benzenesulfonyl chlorides is proposed below (Scheme 3). HI is formed by the reaction of TBAI with acid, then HI and HBr started to reduce benzenesulfonyl chlorides, electrophilic ArSCl (**8**) was generated, which continued to react with phenols, indole, indolizine and related heteroarene to give intermediates **A**, **B**, **C** and **D** and then the loss of protons from intermediates **A**, **B**, **C** and **D** to Cl^- regioselectively afforded target products. In another minor pathway (Scheme 3), ArSCl (**8**) also be formed *via* reduction of benzenesulfonyl chlorides (**1**) with iodine.

Table 3 Reaction of benzenesulfonyl chlorides with indoles, indolizines and related heteroarenes[a]

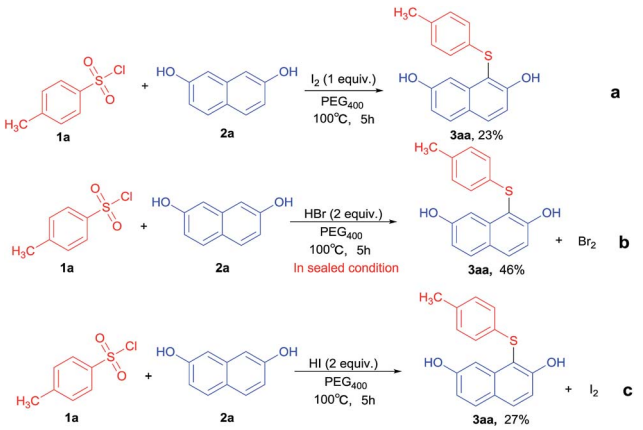


[a] Conditions: **1** (0.30 mmol), **4** (0.36 mmol), TBAI (0.60 mmol), HBr (0.60 mmol, 40% aqueous), PEG_{400} (2 mL), 50 °C, 2–4 h.

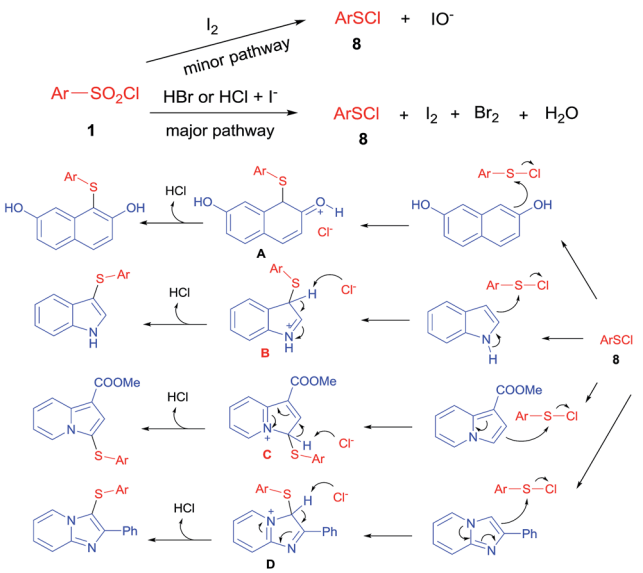
Table 4 Cross-coupling of pyrazolones and benzenesulfonyl chlorides[a]



[a] Conditions: **1** (0.30 mmol), **6a** (0.36 mmol), TBAI (0.60 mmol), HBr (0.60 mmol, 40% aqueous), PEG_{400} (2 mL), 100 °C, 45 min.



Scheme 2 Control experiments.



Scheme 3 Proposed mechanisms for aryl sulfides formation from phenols/benzoheterocycles and benzenesulfonyl chlorides.

Conclusions

In summary, a classical TBAI–HBr system induced thioether-generating method is reported. By using this system, phenols, ketones, indoles and related heteroarenes thioether derivatives were easily made *via* using extensive source arylsulfonyl chlorides as sulfur sources, generating highly regioselective ArS-substituted products in moderate to good yields in shorter time. The method has enriched current thioether-producing methods, providing an alternative method to generate thioethers and instead of iodine-induced methods. An investigation on other types of reaction using TBAI–acid system is currently underway.

Experimental section

General methods

4b and **4c** were prepared according to the literature procedure.[17] The rest of chemicals were purchased from the Sinopharm Chemical Reagent Co., Adamas, Aladdin and TCI used as received.

General procedure: (3)

HBr (40% aqueous, 88 μL, 0.6 mmol) was added to a solution of **2** (0.36 mmol), aryl sulfonyl chlorides **1** (0.30 mmol) and TBAI (221 mg, 0.60 mmol) in PEG_{400} (2 mL), and the reaction mixture was stirred at 100 °C for 5 h. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, and quenched with saturated sodium thiosulfate solution (10 mL) and extracted twice with ethyl acetate (2 × 15 mL). The organic layer was washed with water and dried over anhyd. sodium sulfate. The solvent was evaporated *in vacuo*, and the residue was subjected to column chromatography using ethyl acetate in petroleum ether as the eluent to afford the pure target compound **3**.

General procedure: (5)

HBr (40% aqueous, 88 μL, 0.6 mmol) was added to a solution of **4** (0.36 mmol), aryl sulfonyl chlorides **1** (0.30 mmol) and TBAI (221 mg, 0.60 mmol) in PEG_{400} (2 mL), and the reaction mixture was stirred at 50 °C for 2 h. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, and quenched with saturated sodium thiosulfate solution (10 mL) and extracted twice with ethyl acetate (2 × 15 mL). The organic layer was washed with water and dried over anhyd. sodium sulfate. The solvent was evaporated *in vacuo*, and the residue was subjected to column chromatography using ethyl acetate in petroleum ether as the eluent to afford the pure target product.

General procedure: (7)

HBr (40% aqueous, 88 μL, 0.6 mmol) was added to a solution of **6a** (0.36 mmol), aryl sulfonyl chlorides **1** (0.30 mmol) and TBAI (221 mg, 0.60 mmol) in PEG_{400} (2 mL), and the reaction mixture was stirred at 100 °C for 45 min. After completion of the reaction, the reaction mixture was diluted with ethyl acetate, and quenched with saturated sodium thiosulfate solution (10 mL) and extracted twice with ethyl acetate (2 × 15 mL). The organic layer was washed with water and dried over anhyd. sodium sulfate. The solvent was evaporated *in vacuo*, and the residue was subjected to column chromatography using ethyl acetate in petroleum ether as the eluent to afford the pure target product.

Acknowledgements

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Notes and references

1 (*a*) T. Nakazawa, J. Xu, T. Nishikawa, T. Oda, A. Fujita, K. Ukai, R. E. P. Mangindaan, H. Rotinsulu, H. Kobayashi and M. Namikoshi, *J. Nat. Prod.*, 2007, **70**, 439; (*b*) M. Gingras, Y. M. Chabre, M. Roy and R. Roy, *Chem. Soc. Rev.*, 2013, **42**, 4823; (*c*) K. Takimiya, S. Shinamura, I. Osaka and E. Miyazaki, *Adv. Mater.*, 2011, **23**, 4347–4370;

(*d*) A. Y. Sizov, A. N. Kovergin and A. F. Ermolov, *Russ. Chem. Rev.*, 2003, **72**, 357; (*e*) T. Mori, T. Nishimura, T. Yamamoto, I. Doi, E. Miyazaki, I. Osaka and K. Takimiya, *J. Am. Chem. Soc.*, 2013, **135**, 13900–13913; (*f*) T. Oda, T. Fujiwara, H. Liu, K. Ukai, R. E. P. Mangindaan, M. Mochizuki and M. Namikoshi, *Mar. Drugs*, 2006, **4**, 15.

2 M. A. Fernández-Rodríguez, Q. Shen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 2180–2181.

3 E. Sperotto, G. P. van Klink, J. G. de Vries and G. van Koten, *J. Org. Chem.*, 2008, **73**, 5625–5628.

4 Y. Zhang, K. C. Ngeow and J. Y. Ying, *Org. Lett.*, 2007, **9**, 3495–3498.

5 V. P. Reddy, K. Swapna, A. V. Kumar and K. R. Rao, *J. Org. Chem.*, 2009, **74**, 3189–3191.

6 A. Correa, M. Carril and C. Bolm, *Angew. Chem.*, 2008, **47**, 2880–2883.

7 Y.-C. Wong, T. T. Jayanth and C.-H. Cheng, *Org. Lett.*, 2006, **8**, 5613–5616.

8 Y.-m. Lin, G.-p. Lu, C. Cai and W.-b. Yi, *Org. Lett.*, 2015, **17**, 3310–3313.

9 F. L. Yang and S. K. Tian, *Angew. Chem., Int. Ed.*, 2013, **125**, 5029–5032.

10 M.-A. Hiebel and S. Berteina-Raboin, *Green Chem.*, 2015, **17**, 937–944.

11 L.-H. Zou, J. Reball, J. Mottweiler and C. Bolm, *Chem. Commun.*, 2012, **48**, 11307–11309.

12 (*a*) X. Zhao, L. Zhang, X. Lu, T. Li and K. Lu, *J. Org. Chem.*, 2015, **80**, 2918–2924; (*b*) S. K. R. Parumala and R. K. Peddinti, *Green Chem.*, 2015, **17**, 4068–4072; (*c*) P. Katrun, S. Hongthong, S. Hlekhlai, M. Pohmakotr, V. Reutrakul, D. Soorukram, T. Jaipetch and C. Kuhakarn, *RSC Adv.*, 2014, **4**, 18933–18938; (*d*) X. Kang, R. Yan, G. Yu, X. Pang, X. Liu, X. Li, L. Xiang and G. Huang, *J. Org. Chem.*, 2014, **79**, 10605–10610; (*e*) K. Yan, D. Yang, P. Sun, W. Wei, Y. Liu, G. Li, S. Lu and H. Wang, *Tetrahedron Lett.*, 2015, **56**, 4792–4795; (*f*) J. Sun, J.-K. Qiu, Y.-L. Zhu, C. Guo, W.-J. Hao, B. Jiang and S.-J. Tu, *J. Org. Chem.*, 2015, **80**, 8217–8224; (*g*) D. Yang, K. Yan, W. Wei, J. Zhao, M. Zhang, X. Sheng, G. Li, S. Lu and H. Wang, *J. Org. Chem.*, 2015, **80**, 6083–6092.

13 D. Wang, R. Zhang, S. Lin, Z. Yan and S. Guo, *RSC Adv.*, 2015, **5**, 108030–108033.

14 Q. Wu, D. Zhao, X. Qin, J. Lan and J. You, *Chem. Commun.*, 2011, **47**, 9188–9190.

15 (*a*) S. R. Dubbaka and P. Vogel, *J. Am. Chem. Soc.*, 2003, **125**, 15292–15293; (*b*) G. A. Olah, S. C. Narang, L. D. Field and R. Karpeles, *J. Org. Chem.*, 1981, **46**, 2408; (*c*) G. A. Olah, S. C. Narang, L. D. Field and G. F. Salem, *J. Org. Chem.*, 1980, **45**, 4792; (*d*) G. W. Kabalka, M. S. Reddy and M.-L. Yao, *Tetrahedron Lett.*, 2009, **50**, 7340.

16 (*a*) M.-A. Hiebel and S. Berteina-Raboin, *Green Chem.*, 2015, **17**, 937–944; (*b*) C.-R. Liu and L.-H. Ding, *Org. Biomol. Chem.*, 2015, **13**, 2251–2254.

17 (*a*) Y. Yang, K. Cheng and Y. Zhang, *Org. Lett.*, 2009, **11**, 5606–5609; (*b*) S.-Y. Takizawa, J.-I. Nishida, T. Tsuzuki, S. Tokito and Y. Yamashita, *Inorg. Chem.*, 2007, **46**, 4308–4319.