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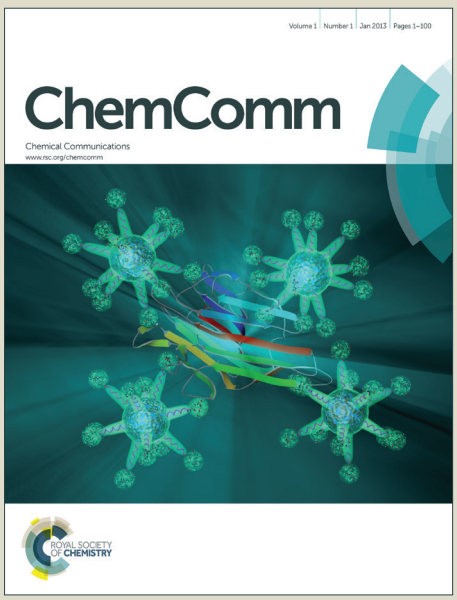

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ARTICLE TYPE

Copper-catalyzed Reductive Coupling of Aryl Sulfonyl Chlorides with H-Phosphonates Leading to S-Aryl Phosphorothioates

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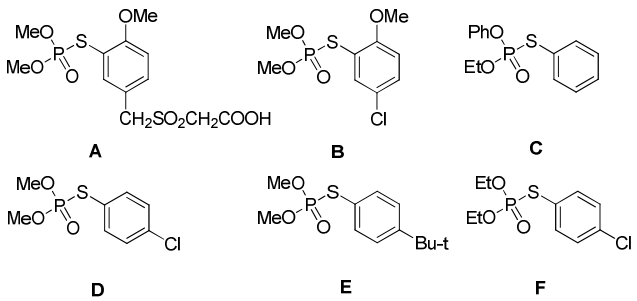
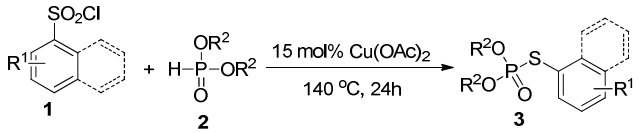
An efficient protocol for copper-catalyzed reductive cross-coupling of aryl sulfonyl chlorides with H-phosphonates has been developed. The various S-aryl phosphorothioates were afforded in up to 86% yield for 20 examples. This protocol features high efficiency, wide functional groups tolerance, commercially aryl sulfonyl chlorides as starting materials and base-free conditions.

Phosphorothioate has proven to be a useful skeleton in organic synthesis as a valuable building block, in pharmaceuticals and pesticides due to its biological and physical properties.[1-4] In particularly, S-aryl phosphorothioate represents an important structural element in antiproliferative agent (**A**),[5] pesticide (**B**),[6] antibacterial (**C**),[7] curing accelerators (**D**),[8] antistatic agent (**E**),[9] and anticholinesterase (**F**)[10] (Scheme 1). However, the investigation on building such a structure is lagged behind. Hence, a rapid, efficient and practical access to S-aryl phosphorothioates is highly desired.



Scheme 1 Several examples illustrating the importance of S-aryl phosphorothioate.

Traditional procedures to S-aryl phosphorothioates involved the reaction of trialkyl phosphites with sulfenyl chlorides by chlorinating the mercaptan or disulfide with sulfuryl chloride,[11] and the coupling of H-phosphonates with disulfides by complicated electrosynthesis process.[12] Witt's group obtained phosphorothioates by the treatment of (5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorin-2-yl) disulfanyl derivatives with trimethyl phosphate, in which the substrate was limited to trimethyl phosphate.[13] Until very recently, Liu and co-workers reported a two-steps process to synthesize phosphorothioates from thiols and phosphonates promoted by N-chlorosuccinimide.[14] Transition-metal-catalyzed direct coupling reactions of dialkyl phosphonates with organic disulfides (or benzenethiols) have provided an alternative protocol to S-aryl phosphorothioates, and a base was required.[15, 16] In summary, some problems exit with these procedures, such as: 1) requirement of the complicated or foul odor starting material, which are not commercially available; 2) narrow scope of substrates. The remaining challenge is to develop a general and applicable strategy for a variety of S-aryl phosphorothioates. Therefore, we focus our current research interests on building such a structure. Herein, we disclose a simple and practical procedure to various S-aryl phosphorothioates via copper-catalyzed direct cross-coupling reaction of commercially available aryl sulfonyl chlorides with dialkyl phosphonates under air atmosphere and base-free conditions (Scheme 2).

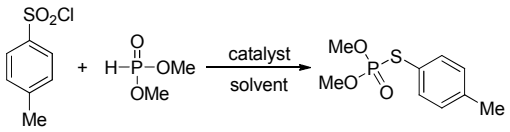


Scheme 2 Synthesis of S-aryl phosphorothioates

We initiated our investigation with the reaction of tosyl chloride (**1a**) with dimethyl phosphonate (**2a**) as a model reaction to identify the optimal reaction conditions. Several parameters, such as catalyst sources, solvents and reaction temperature were screened. The results were listed in Table 1. The absence of any metal and the presence of $Pd(OAc)_2$ (15 mol%) led to disappointing results at 100 °C under air atmosphere (Table 1, entries 1 and 2). Among the copper salts investigated (Table 1, entries 3-7), $Cu(OAc)_2$ was proved to be an ideal choice, and gave the desired product in a promising yield of 60% (Table 1, entry 7). A variety of solvents (e.g. DCE, dioxane, toluene, DMSO) were tested (Table 1, entries 7–11). CH_3CN was clearly the best choice for this catalytic system (Table 1, entry 7). To our delight, the yield was improved to 70% when the ratio of **1a** and **2a** was changed to 1:7, which indicated that the ratio of substrates played an important role in this reaction (Table 1, entries 12–15). The yield was improved to 76% when the temperature was increased to 140 °C (Table1, entry 17). The optimized reaction conditions were eventually identified as: the ratio of **1a** and **2a** was 1:7 in the presence of $Cu(OAc)_2$ (15 mol%) in CH_3CN at 140 °C for 24 h in the absence of base, oxidant, ligand and under air atmosphere (Table1, entry 17). With the optimal reaction conditions, remaining tosyl chloride was not detected after the model reaction was complete. **4a** and **4b** as byproducts were

generated in 7% and 4% isolated yield, respectively (Scheme 3).

Table 1. Screening the reaction parameters for the copper-catalyzed the coupling reaction of tosyl chloride (**1a**) with dimethyl phosphonate (**2a**). [a]



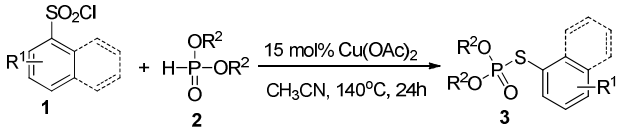
1a **2a** **3a**

Entry	Catalyst	Solvent	T (^oC)	Yield(%)[g]
1	--	CH_3CN	100	0
2	$Pd(OAc)_2$	CH_3CN	100	0
3	CuI	CH_3CN	100	37
4	CuBr	CH_3CN	100	45
5	$CuBr_2$	CH_3CN	100	35
6	$Cu(OTf)_2$	CH_3CN	100	trace
7	$Cu(OAc)_2$	CH_3CN	100	60
8	$Cu(OAc)_2$	DCE	100	58
9	$Cu(OAc)_2$	dioxane	100	33
10	$Cu(OAc)_2$	toluene	100	33
11	$Cu(OAc)_2$	DMSO	100	0
12[b]	$Cu(OAc)_2$	CH_3CN	100	63
13[c]	$Cu(OAc)_2$	CH_3CN	100	65
14[d]	$Cu(OAc)_2$	CH_3CN	100	66
15[e]	$Cu(OAc)_2$	CH_3CN	100	70
16[f]	$Cu(OAc)_2$	CH_3CN	100	67
17[e]	$Cu(OAc)_2$	CH_3CN	120	72
18[e]	**$Cu(OAc)_2$**	**CH_3CN**	**140**	**76**
19[e]	$Cu(OAc)_2$	CH_3CN	150	74

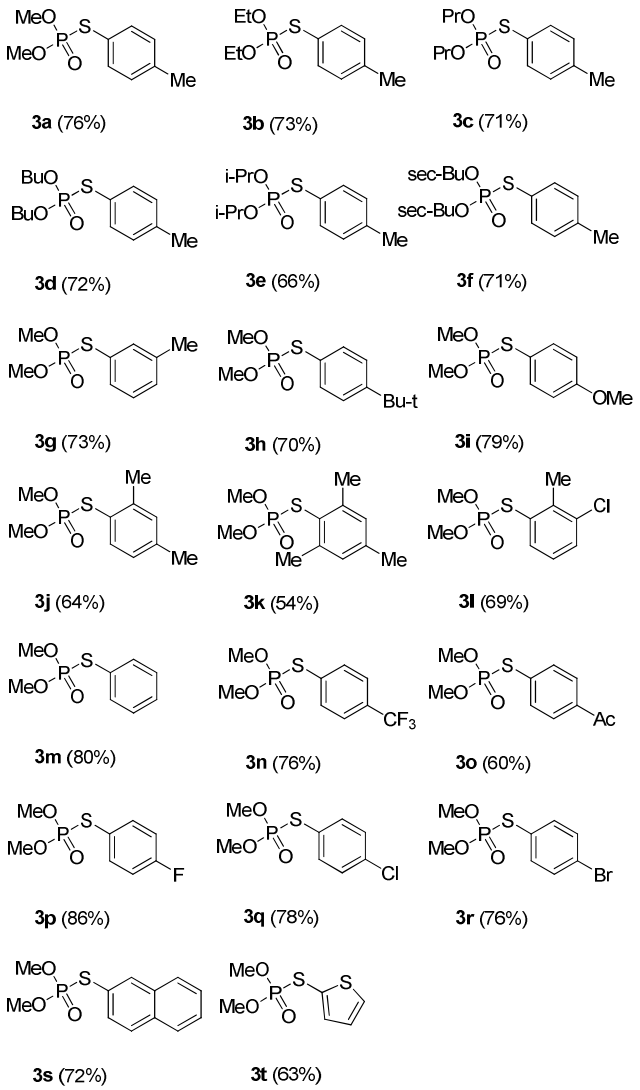
Reaction conditions: [a] **1a** (0.4 mmol), **2a** (0.8 mmol), catalyst (15 mol%), solvent (2.5 mL), under air, 24h. [b] **2a** (3 equiv.). [c] **2a** (5 equiv.). [d] **2a** (6 equiv.). [e] **2a** (7 equiv.). [f] **2a** (8 equiv.). [g] Isolated yields based on **1a**.

With the optimal reaction conditions in hand, the scope of the substrates was examined. It was gratifying to find that a variety of H-phosphonates could couple with diverse sulfonyl chlorides in satisfactory yields. The results were shown in Table 2. Firstly, various H-phosphonates were tested. Dimethyl phosphonate, diethyl phosphonate, dipropyl phosphonate, dibutyl phosphonate, diisopropyl phosphonate and di-sec-butyl phosphonate could be coupled well with tosyl chloride (**1a**), affording the corresponding products in 66-76% yields (Table 2, **3a**–**3f**). The steric hindrance of H-phosphonates did not significantly affect this transformation. Diisopropyl phosphonate and di-sec-butyl phosphonate gave similar result as dipropyl phosphonate and dibutyl phosphonate (Table 2, **3c** vs **3e**, **3d** vs **3f**). Then aryl sulfonyl chlorides substituted by electron-withdrawing and electron-donating groups were tested (Table 2, **3a**, **3g**-**3s**). The significant influence of the electron density in aryl sulfonyl chloride on this transformation was not observed. All of electron-rich (**3a**, **3g**-**3i**), electron-neutral (**3m**) and electron-deficient (**3n**-**3r**) aryl sulfonyl chloride could give the corresponding products in good yields. Moreover, the halo groups remained intact in the products, which would provide the possibility for the further useful transformation. 4-Fluoro, 4-chloro, and 4-bromo benzenesulfonyl chloride were suitable and reacted smoothly with dimethyl H-phosphoante (**2a**), leading to the S-aryl phosphorothioates in 86%, 78%, 76% yields, respectively (Table 2, **3p**–**3r**). Worthy of note was that this standard reaction condition were applied to 2-naphthalenesulfonyl chloride and 2-thiophenesulfonyl chloride, affording the corresponding products **3s** and **3t** in 72% and 63% yields, respectively. Sterically hindered aryl sulfonyl chlorides, such as 2,4-dimethylphenyl sulfonyl chloride, 2,4,6-trimethylphenyl sulfonyl chloride, and 2-methyl-3-chloro-phenyl sulfonyl chloride, were also suitable substrates and successfully afforded the desired products in 65%, 54% and 69% yields, respectively (Table 2, **3j**, **3k** and **3l**). In summary, donating, withdrawing and large bulk groups in aryl sulfonyl chlorides could be compatible in this catalytic system.

Table 2. Synthesis of S-aryl phosphorothioates from sulfonyl chlorides and H-phosphonates.

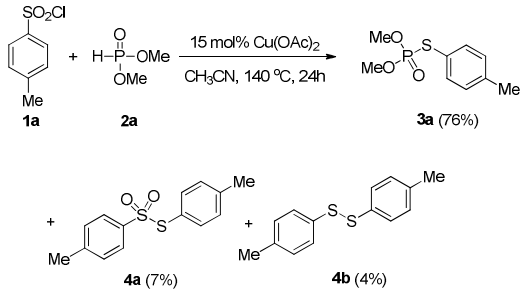


1 **2** **3**

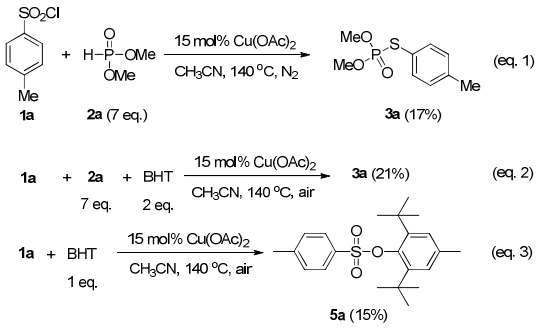


Reaction conditions: 0.4 mmol aryl sulfonyl chlorides, 2.8 mmol phosphite esters, 15 mol% $Cu(OAc)_2$, 140 ^oC, air, 24h. Isolated yields in parentheses.

To clarify the role of air and the reaction mechanism，some controlled experiments were performed (Scheme 4). When the reaction of tosyl chloride (**1a**) with dimethyl phosphonate (**2a**) was carried out under nitrogen atmosphere, the desired product **3a** was provided in 17% yield (Scheme 4, eq. 1). While air atmosphere could afford 76% yield. These results indicate that the oxygen molecule in air was necessary. When 2 equivalent of BHT was added to the reaction mixture of **1a** and **2a**, the yield of desired product was reduced dramatically (Scheme 4, eq. 2). The reaction of BHT with **1a** gave product **5a** in 15% yield (Scheme 4, eq. 3). These results indicated that the reaction might proceed via a radical pathway.



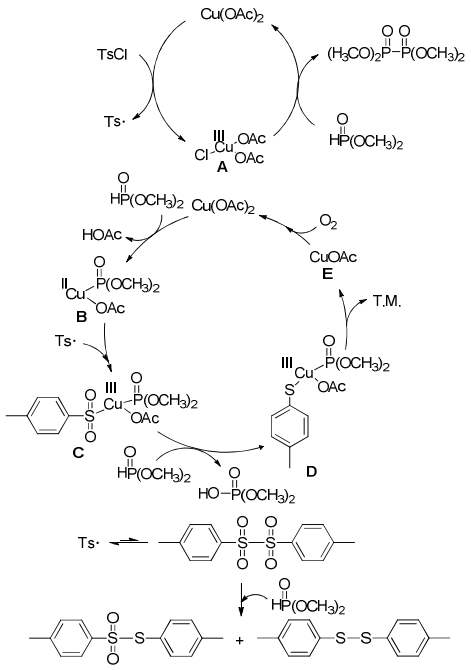
Scheme 3 The corresponding product and byproducts under the optimal reaction conditions



Scheme 4 Controlled experiments

A proposed reaction mechanism was outlined in Scheme 5 according to the results obtained and literature reported.[17-18] Tosyl chloride (**1a**) underwent single-electron-transfer (SET) with $Cu(OAc)_2$ to produce tosyl radical and Cu(III) intermediate **A**. The homo-coupling phosphorus compound P(O)-P(O) in reaction system was detected by Q-TOF LC/MS. The ligand-exchange reaction between $Cu(OAc)_2$ and **2a** could occur to afford intermediate **B** and released HOAc. The intermediate **B** was attacked by tosyl radical to obtain the Cu(III) intermediate **C**. Then, the intermediate **C** was reduced by H-phosphonate, affording the intermediate Cu(III) **D**. Finally, reductive elimination of the intermediate **D** provided S-aryl phosphorothioates and generated Cu(I). The Cu(I) **E** was oxidized by oxygen to the Cu(II) for the next cycle.

In conclusion, a novel, simple and efficient protocol for synthesis of S-aryl phosphorothioates via copper-catalyzed direct coupling of commercially available aryl sulfonyl chlorides with H-phosphonates under air atmosphere and base-free conditions has been developed. Various S-aryl phosphorothioates were obtained in moderate to good yields for 20 examples. Both electronic and steric effect from both of sulfonyl chloride and H-phosphonate had not significant influence on this reaction.



Scheme 5. Proposed reaction mechanism.

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Notes and references

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1 (a) S. W. Rhee, R. P. Iyer, J. E. Coughlin, S. Padmanabhan and J. P. Malerich, *J. Label Compd. Radiopharm*, 2012, **55**, 197; (b) A. Leisvuoria, Z. Ahmeda, M. Ora, L. Beigelmanb, L. Blattb and L. Harri, *Helvetica Chimica Acta*, 2012, **95**, 1512; (c) M. Noro, S. Fujita and T. Wada, *Org. Lett.*, 2013, **15**, 5948; (d) R. Xie, Q. Zhao, T. Zhang, J. Fang, X. Mei, J. Ning and Y. Tang, *Bioorg. Med. Chem.*, 2013, **21**, 278; (e) T. S. Kumar, T. Yang, S. Mishra, C. Cronin, S. Chakraborty, J. B. Shen, B. T. Liang and K. A. Jacobson, *J. Med. Chem.*, 2013, **56**, 902.

2 (a) M. Fukuoka, S. Shuto, N. Minakawa, Y. Ueno and A. Matsuda, *J. Org. Chem.*, 2000, **65**, 5238; (b) P. Jhajharia, M. K. Samota and G. Seth, *Heteroat. Chem.*, 2010, **21**, 84; (c) A. M. Lauer, F. Mahmud and J. Wu, *J. Am. Chem. Soc.*, 2011, **133**, 9119; (d) F. Robertson and J. Wu, *Org. Lett.*, 2010, **12**, 2668; (e) A. M. Lauer and J. Wu, *Org. Lett.*, 2012, **14**, 5138; (f) K. A. Mazzio, K. Okamoto, Z. Li, S. Gutmann, E. Strein, D. S. Ginger, R.. Schlaf and C. K. Luscombe, *Chem. Commun.*, 2013, **49**, 1321.

3 S. T. Crooke and C. F. Bennett, *Annu. Rev. Pharmacol. Toxicol.*, 1996, **36**, 107.

4 (a) P. Guga, M. Boczkowska, M. Janicka, A. Maciaszek, B. Nawrot, S. Antoszczyk and W. J. Stec, *Pure Appl. Chem.*, 2006, **78**, 993; (b)

H. Yan, X. Wanga, R. KuoLee and W. Chen, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5631.
5 E. P. Reddy, M. V. R. Reddy and S. C. Bell, *PCT Int. Appl.*, 2005, WO 2005089269 A2 20050929.
6 S. Tadao, K. Hiroshi, S. Tadashi and T. Akira, *Jpn. Kokai Tokkyo Koho.*, 1974, JP 49069836 A 19740705.
7 H. Kazuo, S. Katsuki, H. Mitsuo, N. Masaru, T. Kenji and Y. Masaaki, *Jpn. Tokkyo Koho.*, 1973, JP 48018461 B 19730606.
8 M. Yasuhiko, K. Yasuyuki, T. Harumi and Y. Takashi, *Jpn. Kokai Tokkyo Koho.*, 1976, JP 51033200 A 19760322.
9 K. Hiroshi, *Jpn. Tokkyo Koho.*, 1970, JP 45026974 B4 19700904.
10 L. L. Murdock and T. L. Hopkins, *J. Agr. Food Chem.*, 1968, **16**, 954.
11 D. C. Morrison, *J. Am. Chem. Soc.*, 1955, **77**, 181.
12 S. Torii, H. Tanaka and N. Sayo, *J. Org. Chem.*, 1979, **44**, 2938.
13 S. Lach and D. Witt, *Synthesis*, 2011, **24**, 3975.
14 Y. C. Liu and C. F. Lee, *Green Chem.*, 2014, **16**, 357.
15 (a) Y. X. Gao, G. Tang, Y. Cao and Y. F. Zhao, *Synthesis*, 2009, 1081. (b) B. Kaboubin, Y. Abedi, J. Kato and T. Yokomatsu, *Synthesis*, 2013, **45**, 2323.
16 Y. J. Ouyang, Y. Y. Li, N. B. Li and X. H. Xu, *Chin. Chem. Lett.*, 2013, **24**, 1103.
17 (a) W. Zhou, L. Zhang and N. Jiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 7094; (b) J. E. M. N. Klein, A. Perry, D. S. Pugh and R. J. K. Taylor, *Org. Lett.*, 2010, **12**, 3446; (c) C. Gou, J. Song, S. W. Luo and L. Z. Gong, *Angew. Chem., Int. Ed.*, 2010, **49**, 5558; (d) S. Chiba, L. Zhang and J. Y. Lee, *J. Am. Chem. Soc.*, 2010, **132**, 7266; (e) L. Zhang, G. Y. Ang and S. Chiba, *Org. Lett.*, 2011, **13**, 1622; (f) K. K. Toh, Y. F. Wang, E. P. J. Ng and S. Chiba, *J. Am. Chem. Soc.*, 2011, **133**, 13942; (g) C. Yu, Y. Zhang, S. Zhang, H. Li and W. Wang, *Chem. Commun.*, 2011, **47**, 1036; (h) G. S. Kumar, C. U. Maheswari, R. A. Kumar, M. L. Kantam and K. R. Reddy, *Angew. Chem., Int. Ed.*, 2011, **50**, 11748; (i) S. P. Simonovich, J. F. V. Humbeck and D. W. C. MacMillan, *Chem. Sci.*, 2012, **3**, 58.
18 (a) A. Amine, Z. Atmani, A. E. Hallaoui, M. Giorgi, M. Pierrot and M. Réglier, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 57; (b) S. H. Bertz, S. Cope, D. Dorton, M. Murphy and C. A. Ogle, *Angew. Chem. Int. Ed.,* 2007, **46**, 7082; (c) S. H. Bertz, S. Cope, M. Murphy, C. A. Ogle and B. J. Taylor, *J. Am. Chem. Soc.*, 2007, **129**, 7208; (d) H. P. Hu and J. P. Snyder, *J. Am. Chem. Soc.*, 2007, **129**, 7210; (e) T. Gärtner, W. Henze and R. M. Gschwind, *J. Am. Chem. Soc.*, 2007, **129**, 11362; (f) R. J. Phipps, N. P. Grimster and Matthew J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 8172; (g) A. E. King, T. C. Brunold and S. S. Stahl, *J. Am. Chem. Soc.*, 2009, **131**, 5044; (h) A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas and S. S. Stahl, *J. Am. Chem. Soc.*, 2010, **132**, 12068; (i) X. M. Zeng, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2011, **133**, 17638; (j) S. H. Bertz, R. A. Hardin, M. D. Murphy, C. A. Ogle, J. D. Richter and A. A. Thomas, *J. Am. Chem. Soc.*, 2012, **134**, 9557; (k) L. Zhang, C. Peng, D. Zhao, Y. Wang, H. J. Fu, Q. Shen and J. X. Li, *Chem. Commun.*, 2012, **48**, 5928; (l) D. K. Li, M. Wang, J. Liu, Q. Zhao and L. Wang, *Chem. Commun.*, 2013, **49**, 3640.