Green Chemistry

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c4gc00944d

TBPB-promoted metal-free synthesis of thiophosphinate/phosphonothioate by direct P–S bond coupling†

Jichao Wang, Xin Huang, Zhangqin Ni, Sichang Wang, Jun Wu and Yuanjiang Pan*

Received 22nd May 2014,
Accepted 28th August 2014

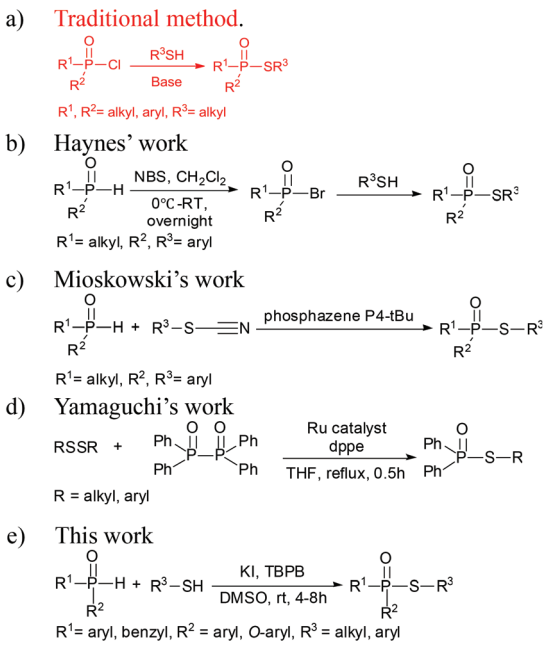
DOI: 10.1039/c4gc00944d

www.rsc.org/greenchem

An efficient method for the direct coupling of thiol/thiophenol with H-phosphine oxides or H-phosphinate esters is reported. Without using any metallic catalyst, the direct sulfur–phosphorus bond coupling reaction was promoted using *tert*-butyl peroxybenzoate in the presence of KI at room temperature. Consequently, thiophosphinate/phosphonothioate was produced in moderate to excellent yields.

Introduction

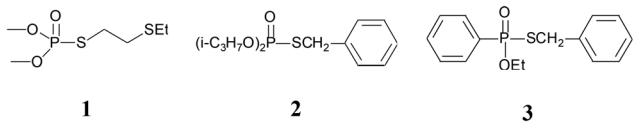
Sulfur-containing organophosphorus compounds have received considerable attention for more than 60 years because of their promising bioactivities[1] and pest-control application.[2] Accordingly, research on the synthesis of these compounds is extensive, especially for the thioesters of dialkyl (or diaryl) phosphites,[3] which could be found in organophosphorus pesticides (Fig. 1), such as demeton-*S*-methyl (**1**) and iprobenfos (**2**). Yokomatsu *et al.* recently reported a CuI-catalyzed synthesis method of thiophosphates through the coupling of diethyl phosphites and benzenethiols.[3j] Lee *et al.* developed an NCS promoted thiophosphation reaction between thiols and phosphites.[3k] The synthesis of thiophosphates based on dialkyl (or diaryl) phosphites is extensively studied, but less attention is paid to the thioester of H-phosphine oxides or H-phosphinate esters,[4] which are core structures of certain pesticides, such as inezin (**3**). These compounds could also be used as phosphoryl transfer reagents in organic syntheses.[5] Traditional synthesis work of thiophosphinate often proceeds *via* the reaction between phosphinic chlorides and thiols [Scheme 1(a)].[5a,b,6] Haynes *et al.* [Scheme 1(b)] reported a synthesis strategy through the coupling of the H-phosphine oxides with thiophenols in the presence of NBS and a base.[4c] Mioskowski *et al.* [Scheme 1(c)] developed phosphazene P4-*t*Bu-promoted phosphonothioate formation using alkyl thiocyanates as the thiol source.[4d] In their work, both H-phosphine oxides and H-phosphinate esters smoothly afford the products in good yields. Yamaguchi *et al.* [Scheme 1(d)] reported a thiophosphinate synthesis protocol by a rhodium-catalyzed coupling between tetraphenyldiphosphine dioxides and disulfides.[4e] However, extensive application of this protocol is limited by the use of toxic phosphinic chlorides, strong bases or Lewis acids, complex multiple steps, and expensive transition metals.



Scheme 1 Synthesis of thiophosphates.

From the perspective of atom economy, direct coupling between H-phosphine oxides/H-phosphinate esters and thiols is the best option to form thiophosphinates or phosphonothioates. A similar strategy involves C–S bond construction for thioester synthesis.[7] Based on our previous work on C–S and S–N bond coupling,[8] we present in this work a thiophosphinate/phosphonothioate synthesis method through direct

Department of Chemistry, Zhejiang University, Hangzhou, Zhejiang, China.
E-mail: cheyjpan@zju.edu.cn
† Electronic supplementary information (ESI) available: See DOI: 10.1039/c4gc00944d



1 2 3

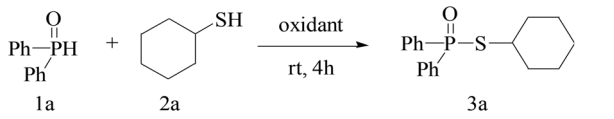
Fig. 1 Thiophosphate structures in pesticides.

P–S bond coupling using peroxide (TBPB). As a green synthetic method, our work exhibited several advantages, including good atom economy (more than 99%), easy one-step work-up, without any acid or base, avoids the use of any transition metal, relative mild reaction conditions, and most substrates could react at room temperature while with good to excellent yields (up to 99%). Besides, the method has a wide range of functional group compatibilities for H-phosphine oxides/H-phosphinate esters and thiols.

Results and discussion

In our initial work, diphenylphosphine oxide and cyclohexanethiol were used as model reactants to optimize the reaction conditions. First, several oxidants (*e.g.* peroxides and potassium persulfate) were introduced to the reaction (Table 1, entries 1–5); however, no relative product was detected. Based on Prabhu's work,[9] we then added iodine to the reaction and elevated the temperature to 50 °C (Table 1, entries 6–10), and the desired product **3a** was thus formed. Screening of the oxidants showed that TBPB had the best reactivity (Table 1, entry 10), although the yield was still unsatisfactory. The poor yield might be attributed to iodine catalyzed disulfide formation.[10] We replaced iodine with a less reactive potassium salt (KI) and finally obtained thiophosphinate **3a** in nearly quantitative yield at room temperature (Table 1, entry 11). Notably, the decrease in KI loading and oxidant did not affect this result (Table 1, entries 12 and 13). But an increase of the additive amount and temperature results in a reduced yield, which is due to the oxidation of **1a** into diphenylphosphinic acid (Table 1, entries 14 and 15). Other iodine sources such as NaI and TBAI were tested, both gave acceptable yields (Table 1, entries 16 and 17). We also studied the effect of solvents, including toluene, CH_3CN and water (Table 1, entries 18–20). However, both showed poor yields, and this reaction was ceased when reacted in water.

Table 1 Optimization of reaction conditions[a]



1a 2a 3a

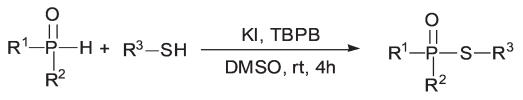
Entry	Oxidant	Additive	Solvent	Yield[b] (%)
1	H_2O_2	None	DMSO	N.R.
2	TPHP	None	DMSO	N.R.
3	DTBP	None	DMSO	N.R.
4	$K_2S_2O_8$	None	DMSO	N.R.
5	TBPB	None	DMSO	N.R.
6[c]	H_2O_2	I_2 (0.2 eq.)	DMSO	Trace
7[c]	TPHP	I_2 (0.2 eq.)	DMSO	Trace
8[c]	$K_2S_2O_8$	I_2 (0.2 eq.)	DMSO	13
9[c]	DTBP	I_2 (0.2 eq.)	DMSO	10
10[c]	TBPB	I_2 (0.2 eq.)	DMSO	21
11	TBPB	KI (0.2 eq.)	DMSO	97
12	TBPB	KI (0.1 eq.)	DMSO	89
13[d]	TBPB	KI (0.2 eq.)	DMSO	85
14	TBPB	KI (0.4 eq.)	DMSO	77
15[c]	TBPB	KI (0.2 eq.)	DMSO	63
16	TBPB	NaI (0.2 eq.)	DMSO	79
17	TBPB	TBAI (0.2 eq.)	DMSO	62
18	TBPB	KI (0.2 eq.)	Toluene	28
19	TBPB	KI (0.2 eq.)	CH_3CN	21
20	TBPB	KI (0.2 eq.)	H_2O	N.R.

[a] Reaction conditions: diphenylphosphine oxide (0.75 mmol), cyclohexanethiol (0.5 mmol), and oxidant (1.0 mmol) were reacted at room temperature for 4 h. [b] Isolated yield. [c] Reacted at 50 °C. [d] 0.5 mmol TBPB was added. (TPHP = *tert*-Butyl hydroperoxide, DTBP = *tert*-butyl peroxide, TBPB = *tert*-butylperoxybenzoate, TBAI = tetrabutylammonium iodide).

Under the optimized reaction conditions, we then investigated the scope and limitations of the substrate for application to our novel P–S bond coupling method. As summarized in Table 2, a variety of thiols with different chain lengths were readily reacted with H-phosphine oxides or H-phosphinate esters, giving the relative products in moderate to excellent yields. The long-chain thiols such as 1-hexylthiol (Table 2, entry 5), 1-octanethiol (Table 2, entry 6) and 1-dodecanethiol (Table 2, entry 7) were successfully coupled with H-phosphine oxides. Our method exhibited great functionality tolerance, with carboxy (Table 2, entry 8), thiyl (Table 2, entry 9) and benzyl groups (Table 2, entry 10) being well tolerated under our conditions and smoothly forming the products. Other H-phosphine oxides (Table 2, entries 11–13) also efficiently produced P–S coupling products. However, unsymmetric phosphine oxides bearing an alkyl group (Table 2, entry 13) needed more reaction time and still had a decreased yield. According to our method, phosphonothioates (Table 2, entries 14–16) were easily generated in a good yield using simple H-phosphinate esters. Among them, product **3o** was named "inezin", a low toxic pesticide used against rice blast (a serious rice disease).

A series of thiophenol substrates was further examined to expand the synthesis utility of our proposed protocol. The coupling reaction between thiophenol and H-phosphine oxide/H-phosphinate ester generally took more time than its thiol counterpart, *i.e.*, at least 8 hours was needed to complete reactant transformation. However, a reduced peroxide amount (1.2 equiv.) was found to be beneficial for this process. A nearly quantitative conversion was obtained for the reaction between substituted thiophenols and diphenylphosphine oxides (Table 3, entries 1–10). Steric hindrance showed little influence on this reaction, and *ortho*-substituted thiophenols (Table 3, entries 5 and 7) afforded similar yields as their *meta*- or *para*- analogs. However, thiophenols bearing strong electron-withdrawing groups (*e.g.*, trifluoromethyl and nitro) yielded no relative

Table 2 TBPB promoted P–S coupling reaction between H-phosphine oxides/H-phosphinate esters and thiols[a]



1 2 3

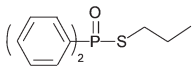
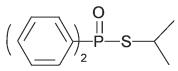
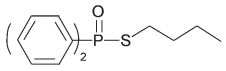
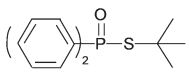
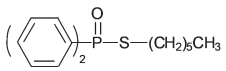
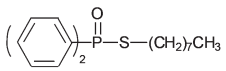
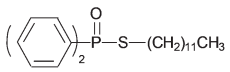
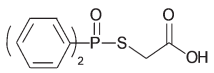
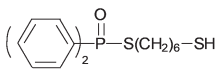
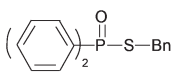
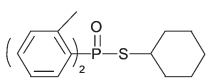
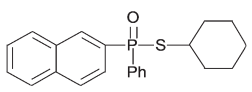
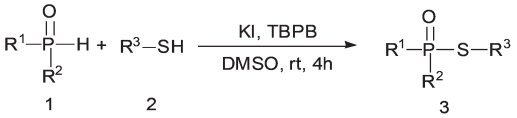
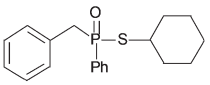
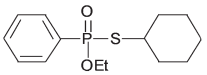
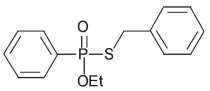
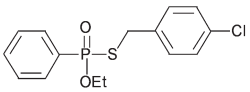
Entry	3	Yield[b] (%)
1	 3b	97
2	 3c	99
3	 3d	97
4	 3e	88
5	 3f	90
6	 3g	98
7	 3h	96
8	 3i	66
9	 3j	82
10	 3k	95
11	 3l	81
12	 3m	76

Table 2 *(Contd.)*



1 2 3

Entry	3	Yield[b] (%)
13[c]	 3n	65
14[d]	 3o	73
15[d]	 3p	81
16[d]	 3q	84

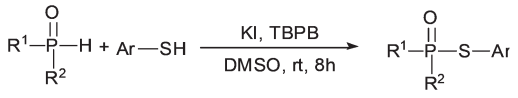
[a] Reaction conditions: H-phosphine oxides/H-phosphinate esters (0.75 mmol), thiols (0.5 mmol), TBPB (1.0 mmol) and KI (0.1 mmol) in 1.5 ml DMSO, reacted at room temperature. [b] Isolated yield. [c] Reacted for 18 h. [d] Reacted in 2 mL EtOAc at 50 °C, 0.6 mmol TBPB was added as an oxidant.

products probably because of their higher S–H bond dissociation energies.[11] Other functional groups including methoxyl (Table 3, entries 3–5), chloro (Table 3, entries 6 and 7), bromo (Table 3, entry 8), fluoro (Table 3, entry 9) and amide (Table 3, entry 10) were tolerated under our reaction conditions. We also investigated the reactivity of other H-phosphine oxides and H-phosphinate esters (Table 3, entries 11–17), and both were found to provide the target compounds in good to excellent yields.

The mechanism of the TBPB promoted P–S coupling reaction was investigated by radical trapping experiments. As shown in Scheme 2, when 2.0 equiv. of TEMPO (a radical scavenger) was added in our reaction system, only a traceable product was detected, which implied that a radical process might be involved. Further experiments suggested that KI may play an important role in catalyzing the oxidation of thiol into the thiyl radical (see ESI†).

Based on the TEMPO trapping experiment results and previous reports,[12] a plausible reaction pathway is depicted in Scheme 3. The *in situ* formed iodine radical (initiated by TBPB) generated thiyl radical **A** whereas the alkoxyl radical abstracted a hydrogen and produced phosphoryl radical **B**. Radical **B** then quickly coupled with the thiyl radical **A** to yield the thiophosphinate **3a**.

Table 3 TBPB promoted P–S coupling reaction between H-phosphine oxides/H-phosphinate esters and thiophenols[a]



1 4 5

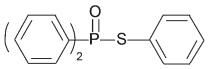
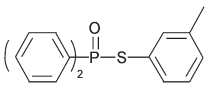
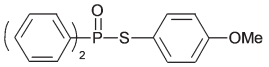
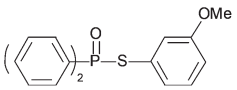
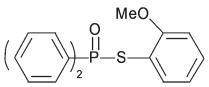
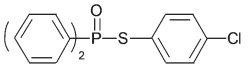
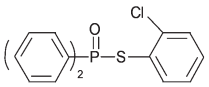
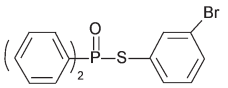
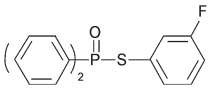
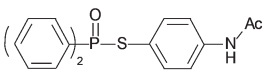
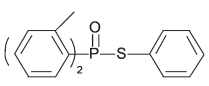
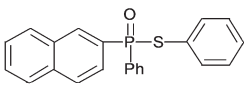
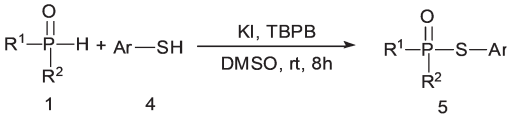
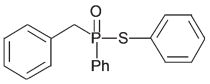
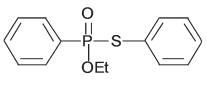
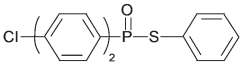
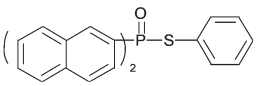
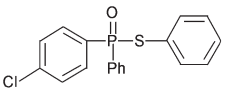
Entry	5	Yield[b] (%)
1	 5a	96
2	 5b	99
3	 5c	98
4	 5d	99
5	 5e	99
6	 5f	99
7	 5g	95
8	 5h	96
9	 5i	97
10	 5j	51
11	 5k	87
12	 5l	97

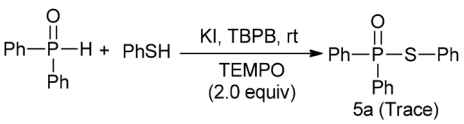
Table 3 *(Contd.)*



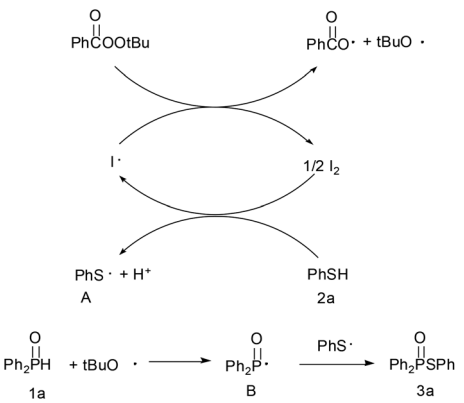
1 4 5

Entry	5	Yield[b] (%)
13[c]	 5m	71
14	 5n	99
15	 5o	90
16	 5p	99
17	 5q	95

[a] Reaction conditions: H-phosphine oxides/H-phosphinate esters (0.75 mmol), thiophenols (0.5 mmol), TBPB (0.6 mmol) and KI (0.1 mmol) in 1.5 ml DMSO, reacted at room temperature. [b] Isolated yield. [c] Reacted for 18 h.



Scheme 2 Radical trapping experiments using TEMPO.



Scheme 3 Plausible reaction pathway.

Conclusions

We developed an easy and efficient TBPB-promoted P–S coupling reaction for synthesizing thiophosphinates/phosphonothioates. The reaction was conducted without the presence of metallic catalysts at room temperatures (for H-phosphinate ester 50 °C) and afforded the products in good to excellent yields. The method also exhibited a great functionality tolerance for the substrates and a plausible mechanism was proposed.

Experimental

General

All chemicals were obtained from commercial suppliers or prepared according to the former reference (see ESI†). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker ARX-400. Mass spectra were performed on a Bruker Esquire 3000 plus mass spectrometer equipped with ESI interface and ion trap analyzer.

General procedure A: for the preparation of products 3a–3q (for thiol substrates)

Thiol (0.5 mmol), H-phosphine oxides/H-phosphinate esters (0.75 mmol) and TBPB (1.0 mmol) were dissolved in 1.5 ml DMSO in a round-bottom flask, then KI (0.1 mmol) was added and reacted at room temperature for 4 h. After reaction completion, the mixture was quenched with 15 ml of $Na_2S_2O_4$ solution (5%) and extracted with ethyl acetate (3 × 15 ml). The combined organic layer was then dried with anhydrous Na_2SO_4 and evaporated under vacuum. The crude product was purified by silica gel column chromatography, using PE–EtOAc (3 : 1) as the eluent.

General procedure B: for the preparation of products 5a–5q (for thiophenol substrates)

Thiophenol (0.5 mmol), H-phosphine oxides/H-phosphinate esters (0.75 mmol) and TBPB (0.6 mmol) were dissolved in 1.5 ml DMSO in a round bottomed flask, then KI (0.1 mmol) was added and reacted at room temperature for 8 h. After reaction completion, the mixture was quenched with 15 ml of $Na_2S_2O_4$ solution (5%) and extracted with ethyl acetate (3 × 15 ml). The combined organic layer was then dried with anhydrous Na_2SO_4 and evaporated in a vacuum. The crude product was purified by silica gel column chromatography using PE–EtOAc (3 : 1) as the eluent.

Acknowledgements

The authors gratefully acknowledge financial support from the National Science Foundation of China (21025207).

Notes and references

1 (*a*) J. F. Milligan and O. C. Uhlenbeck, *Biochemistry*, 1989, **28**, 2849–2855; (*b*) S. H. Vollmer, M. B. Walner, K. V. Tarbell and R. F. Colman, *J. Biol. Chem.*, 1994, **269**, 8082–8090; (*c*) G. G. Durgam, T. Virag, M. D. Walker, S. Y. Ryoko Tsukahara, K. Liliom, L. A. v. Meeteren, W. H. Moolenaar, X. W. S. Nicole Wilke, G. Tigyi and D. D. Miller, *J. Med. Chem.*, 2005, **48**, 4919–4930; (*d*) V K. Pandey, A. Dwivedi, O. P. Pandey and S. K. Sengupta, *J. Agric. Food Chem.*, 2008, **56**, 10779–10784; (*e*) T. Ruman, K. Długopolska, A. Jurkiewicz, D. Rut, T. Frączyk, J. Cieśla, A. Leś, Z. Szewczuk and W. Rode, *Bioorg. Chem.*, 2010, **38**, 74–80; (*f*) M. W. Loranger, S. A. Beaton, K. L. Lines and D. L. Jakeman, *Carbohydr. Res.*, 2013, **379**, 43–50.

2 N. N. Melnilkov, *Chemistry of Pesitcides*, Springer-Verlag, New York, 1971.

3 For selected reports on thiophosphate synthesis, see: (*a*) R. G. Harvey, H. I. Jacobson and E. V. Jensen, *J. Am. Chem. Soc.*, 1963, **85**, 1623–1626; (*b*) S. Torii, H. Tanak and N. Sayo, *J. Org. Chem.*, 1979, **44**, 2938–2941; (*c*) B. Kaboudin, *Tetrahedron Lett.*, 2002, **43**, 8713–8714; (*d*) C. M. Timperley, S. A. Saunders, J. Szpalek and M. J. Waters, *J. Fluorine Chem.*, 2003, **119**, 161–171; (*e*) Q. Xu, C. G. Liang and X. Huang, *Synth. Commun.*, 2003, **33**, 2777–2785; (*f*) Y. X. Gao, G. Tang, Y. Cao and Y. F. Zhao, *Synthesis*, 2009, 1081–1086; (*g*) X. Han and J. Wu, *Org. Lett.*, 2010, **12**, 5780–5782; (*h*) X. Han, Y. Zhang and J. Wu, *J. Am. Chem. Soc.*, 2010, **132**, 4104–4106; (*i*) Z. J. Quan, R. G. Ren, Y. X. Da, Z. Zhang and X. C. Wang, *Heteroat. Chem.*, 2011, **22**, 653–658; (*j*) B. Kaboudin, Y. Abedi, J. Kato and T. Yokomatsu, *Synthesis*, 2013, **45**, 2323–2327; (*k*) Y. C. Liu and C. F. Lee, *Green Chem.*, 2014, **16**, 357–364.

4 (*a*) W. A. Mosher and R. R. Irino, *J. Am. Chem. Soc.*, 1969, **91**, 756–757; (*b*) C. Yuan, H. Feng and Q. Lin, *Synthesis*, 1990, **2**, 140–141; (*c*) T. A. Yeung, K. Y. Chan, W. K. Chan, R. K. Haynes, I. D. Williams and L. L. Yeung, *Tetrahedron Lett.*, 2001, **42**, 453–456; (*d*) P. Y. Renard, H. Schwebe, P. Vayron, L. Josien, A. Valleix and C. Mioskowski, *Chem. – Eur. J.*, 2002, **8**, 2910–2916; (*e*) M. Arisawa, T. Ono and M. Yamaguchi, *Tetrahedron Lett.*, 2005, **46**, 5669–5671; (*f*) Y. Zhou, G. Wang, Y. Saga, R. Shen, M. Goto, Y. Zhao and L. B. Han, *J. Org. Chem.*, 2010, **75**, 7924–7927; (*g*) M. Arisawa, T. Watanabe and M. Yamaguchi, *Tetrahedron Lett.*, 2011, **52**, 2410–2412.

5 (*a*) P. Carta, N. Puljic, C. Robert, A. L. Dhimane, L. Fensterbank, E. Lacoate and M. Malacria, *Org. Lett.*, 2007, **9**, 1061–1063; (*b*) P. Carta, N. Puljic, C. Robert, A. L. Dhimane, C. Ollivier, L. Fensterbank, E. Lacote and M. Malacria, *Tetrahedron*, 2008, **64**, 11865–11875; (*c*) A. Sato, H. Yorimitsu and K. Oshima, *Tetrahedron*, 2009, **65**, 1553–1558; (*d*) N. Hoshi, T. Kashiwabara and M. Tanaka, *Tetrahedron Lett.*, 2012, **53**, 2078–2081.

6 (*a*) L. Hornera and H. W. Flemming, *Phosphorus, Sulfur Relat. Elem.*, 1983, **14**, 245–251; (*b*) R. A. Moss, H. M. Rojas, H. Zhang and B. D. Park, *Langmuir*, 1999, **15**, 2738–2744.

7 Selected examples of direct C–S coupling in thioester preparation: (*a*) S. B. Bandgar, B. P. Bandgar, B. L. Korbad and S. S. Sawant, *Tetrahedron Lett.*, 2007, **48**, 1287–1290; (*b*) T. Uno, T. Inokuma and Y. Takemoto, *Chem. Commun.*,

2012, **48**, 1901–1903; (*c*) C. L. Yi, Y. T. Huang and C. F. Lee, *Green Chem.*, 2013, **15**, 2476–2484; (*d*) Y. Q. Yuan, S. R. Guo and J. N. Xiang, *Synlett*, 2013, **24**, 443–448; (*e*) Y. T. Huang, S. Y. Lu, C. L. Yi and C. F. Lee, *J. Org. Chem.*, 2014, **79**, 4561–4568; (*f*) J. W. Zeng, Y. Liu, P. A. Hsieh, Y. T. Huang, C. L. Yi, S. S. Badsara and C. F. Lee, *Green Chem.*, 2014, **16**, 2644–2652.

8 (*a*) R. S. Xu, J. P. Wan, H. Mao and Y. J. Pan, *J. Am. Chem. Soc.*, 2010, **132**, 15531–15533; (*b*) Z. Q. Ni, S. C. Wang, H. Mao and Y. J. Pan, *Tetrahedron Lett.*, 2012, **53**, 3907–3910; (*c*) R. S. Xu, L. Yue and Y. J. Pan, *Tetrahedron*, 2012, **68**, 5046–5052; (*d*) X. Huang, J. C. Wang, Z. Q. Ni, S. C. Wang and Y. J. Pan, *Chem. Commun.*, 2014, **50**, 4582–4584.

9 J. Dhineshkumar and K. R. Prabhu, *Org. Lett.*, 2013, **15**, 6062–6065.

10 (*a*) C. C. Silveira and S. R. Mendes, *Tetrahedron Lett.*, 2007, 7469–7471; (*b*) T. Waag, C. Gelhaus, J. Rath, A. Stich, M. Leippe and T. Schirmeister, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5541–5543.

11 (*a*) F. G. Bordwell, X. M. Zhang, A. V. Satish and J. P. Cheng, *J. Am. Chem. Soc.*, 1994, **116**, 6605–6610; (*b*) W. M. Nau, *J. Org. Chem.*, 1996, **61**, 8312–8314; (*c*) F. Dénès, M. Pichowicz, G. Povie and P. Renaud, *Chem. Rev.*, 2014, **114**, 2587–2693.

12 For selected reports on mechanism study, see: (*a*) Z. J. Liu, J. Zhang, S. L. Chen, E. B. Shi, Y. Xu and X. B. Wan, *Angew. Chem., Int. Ed.*, 2012, **51**, 3231–3235; (*b*) W. P. Mai, H. H. Wang, Z. C. Li, J. W. Yuan, Y. M. Xiao, L. R. Yang, P. Mao and L. B. Qu, *Chem. Commun.*, 2012, **48**, 10117–10119; (*c*) W. P. Mai, G. Song, J. W. Yuan, L. R. Yang, G. C. Sun, Y. M. Xiao, P. Mao and L. B. Qu, *RSC Adv.*, 2013, **3**, 3869–3872; (*d*) Q. C. Xue, J. Xie, P. Xu, K. D. Hu, Y. X. Cheng and C. J. Zhu, *ACS Catal.*, 2013, **3**, 1365–1368; (*e*) Y. H. Lv, Y. Li, T. Xiong, Y. Lu, Q. Liu and Q. Zhang, *Chem. Commun.*, 2014, **50**, 2367–2369; (*f*) Y. Gao, Q. Song, G. Cheng and X. L. Cui, *Org. Biomol. Chem.*, 2014, **12**, 1044–1047.

