Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Organic & Biomolecular Chemistry

Dynamic Article Links ►

Cite this: DOI: 10.1039/coxxoooooox
www.rsc.org/xxxxxx

COMMUNICATION

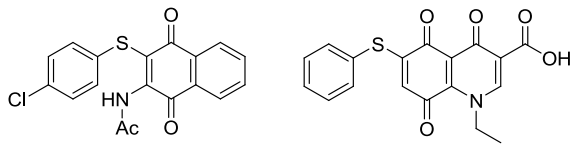
Silver–Mediated Oxidative Vinylic C-H Bond Sulfenylation of Enamides with Disulfides

Luo Yang,* Qing Wen, Fuhong Xiao and Guo-Jun Deng*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A silver-mediated oxidative vinylic C-H bond sulfenylation of enamides was developed. This method is compatible with diaryl and dialkyl disulfides to deliver biological precious chalcogenated olefins efficiently. A plausible non-chain radical mechanism was proposed to understand this novel sulfenylation based on the mechanistic studies.

Arylvinyl sulfides are potential scaffolds found in biologically important natural product and natural product inspired pharmaceutical molecules, for example, the following two arylvinyl sulfides are efficient inhibitor for Cdc25B dual specifity protein phosphatase[1a-1b] and HIV-1 integrase[1c] respectively.

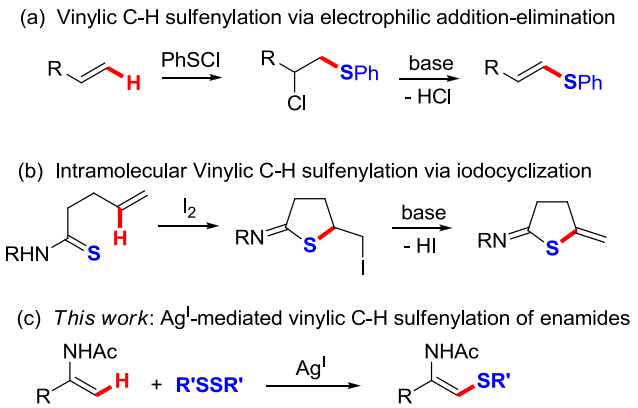


Cdc25B dual specifity protein phosphatase inhibitors

HIV-1 integrase inhibitor

Figure 1 Representative examples of biologically important arylvinyl sulfides

Therefore, the preparation of these arylvinyl sulfides has gained much attention. Traditionally, vinylic C-H bond sulfenylation of olefins has been realized by tandem addition of phenylsufenyl chloride (PhSCl) to olefins and subsequent elimination of HCl under basic conditions [Scheme 1 (a)].[2] The intramolecular vision via iodocyclization and dehydroiodination of unsaturated thioamides,[3a] thioesters [3b] and ketene dithioacetals [3c] has also been developed [Scheme 1 (b)]. In recent years, the thiol-based transformations such as thiol/vinyl halides cross-coupling[4] and thiol/alkynes hydrothiolation[4a, 5] have been widely used for the C(sp^2)-S bond construction. Due to the rapid progress of direct C-H functionalization, numerous transition-metal catalyzed/mediated C-H sulfenylations have been reported for the synthesis of diaryl sulfides,[6] but seldom of them can be applied to the vinylic C-H bond. To the best of our knowledge, there is no silver promoted vinylic C-H bond sulfenylation has been reported so far. Due to our recent interest in the development of various C-S bond formation methods,[7] herein, we are pleased to report a silver mediated oxidative vinylic C-H bonds sulfenylation of enamides with disulfides [Scheme 1 (c)].



Scheme 1 Different pathways for vinylic C-H sulfenylation

Enamides are stable enamine surrogates and provide key intermediates for the synthesis of small but complex nitrogen-containing compounds. Therefore, the direct and selective functionalization of enamides remains an attractive challenge.[7] The vinylic C_β-H bond activation of enamides was pioneered by Loh and coworkers in 2009 on Pd^{II}-catalyzed arylation with organoboron,[8a] organosilane reagents[8b] or arenes,[8c] which was further developed by Park[8d], Duan[8e] and Backvall *et al*..[8f] Besides arylation, the vinylic C_β-H bond activation and subsequent nucleophilic addition to isocyanates was reported by Bergman and Ellman using Rh^{III} catalyst instead. [9]

Based on our previous work on sulfenylation and sulfonylation of indoles using sodium sulfinates as sulfur source,[10a] we first examined the reaction of enamide **1a** and sodium benzenesulfinate under the same conditions. But the desired sulfenylation product was not detected by GC-MS after several

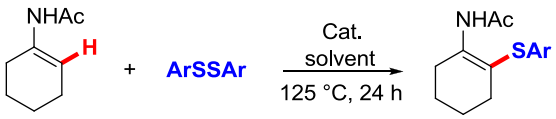
Key Laboratory for Environmentally Friendly Chemistry and Application of the Ministry of Education, College of Chemistry, Xiangtan University, Hunan, 411105, China
E-mail: yangluo@xtu.edu.cn; Tel: +86-731-5829-8351

E-mail: gjdeng@xtu.edu.cn; Tel: +86-731-5829-8601

† Electronic Supplementary Information (ESI) available: experimental details, synthesis and characterisation of products. See DOI: 10.1039/b000000x/

trials. Next, diaryl disulfide (**2a**) was tried as the sulfur source, which indeed can afford the anticipated C-H sulfenylation product catalyzed by I_2, albeit in low yields (<5%). During the subsequent optimization, common transition-metal catalysts such as $Cu(OTf)_2$, $Pd(OAc)_2$ and AgOAc were screened (Table 1, entries 1-3, for detailed screening of other copper or silver catalyst, see ESI). The silver-mirror phenomenon observed on the reaction tube indicated the metal catalysts were been reduced so stoichiometric amounts of metal catalyst were used and 1.2 equiv of AgOAc afforded the highest yield (entry 5). Examination of other silver salts such as Ag_2O and Ag_2CO_3 resulted in much lower yields (entries 6 and 7). The attempt to combine substoichiometric amounts of AgOAc and other cheaper organic/metallic oxidant was failed. Next, the effect of solvents on this reaction was investigated. The reaction can proceed in organic solvents such as chlorobenzene, toluene, THF, *tert*-butanol and DMF (entries10-14), but DCE is optimal.

Table 1 Optimization of the silver mediated oxidative vinylic C-H sulfenylation [a]



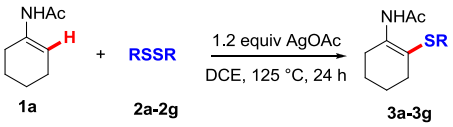
1a **2a** Ar = *p*-Cl-C_6H_4

entry	Cat. (equiv)	solvent	yield [%][b]
1	$Cu(OTf)_2$ (0.1)	DCE	15
2	$Pd(OAc)_2$ (0.1)	DCE	32
3	AgOAc (0.1)	DCE	21
4	AgOAc (1.0)	DCE	76
5	**AgOAc (1.2)**	**DCE**	**82**
6	Ag_2O (1.2)	DCE	17
7	Ag_2CO_3 (1.2)	DCE	36
8[c]	AgOAc (1.2)	DCE	68
9[d]	AgOAc (1.2)	DCE	47
10	AgOAc (1.2)	PhCl	38
11	AgOAc (1.2)	Toluene	44
12	AgOAc (1.2)	THF	26
13	AgOAc (1.2)	*t*-BuOH	14
14	AgOAc (1.2)	DMF	60

[a] Conditions: **1a** (0.2 mmol), **2a** (2 equiv, 0.4 mmol), solvent (0.6 mL), reacted for 24 h at 125°C under argon atmosphere unless otherwise noted. [b] Isolated yields. [c] 1.5 equiv. of disulfide (**2a**) was used. [d] Reacted at 110 °C.

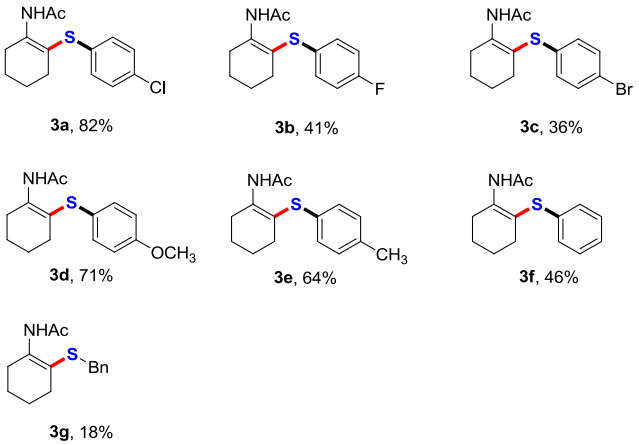
Under the optimized conditions (Table 1, entry 5), the substrate scope and limitation of this vinylic C-H bond sulfenylation was explored. The effect of substituents on the disulfide moiety is listed in Table 2. Diaryls disulfide bearing electron donating or withdrawing substituents were successfully transformed into the desired sulfenylation products in medium yields, such as halo (**2a-2c**), methoxyl (**2d**), methyl (**2e**). Besides diaryls disulfide, the optimized reaction condition can also be applied to dibenzyl disulfide (**2g**) and diaryl diselenide (Scheme 2, **2h**), the anticipated sulfenylation and selenation products (**3g** and **3h**) was isolated successively, albeit in low yields, leaving most part of the both starting materials unreacted.

Table 2 The influence of diaryl disulfides for the vinylic C-H sulfenylation [a]



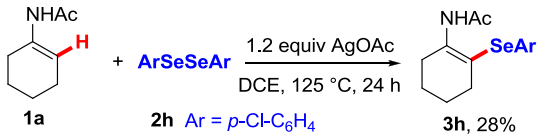
1a **2a-2g** **3a-3g**

2a R = *p*-Cl-C_6H_4 **2b** R = *p*-F-C_6H_4
2c R = *p*-Br-C_6H_4 **2d** R = *p*-CH_3O-C_6H_4
2e R = *p*-CH_3-C_6H_4 **2f** R = C_6H_5
2g R = Bn



3a, 82% **3b**, 41% **3c**, 36%
3d, 71% **3e**, 64% **3f**, 46%
3g, 18%

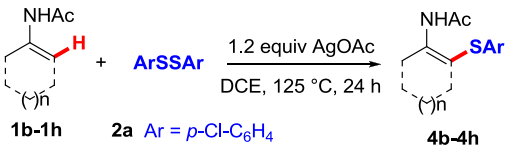
[a] Conditions: **1a** (0.2 mmol), **2a-2h** (0.4 mmol), AgOAc (1.2 equiv, 0.24 mmol), DCE (0.6 mL), reacted for 24 h at 125°C under argon. Isolated yields.



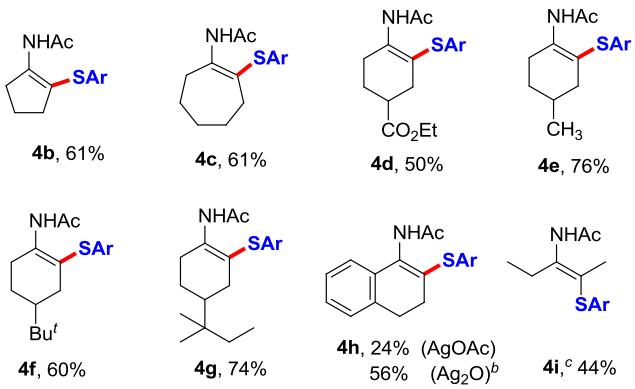
1a **2h** Ar = *p*-Cl-C_6H_4 **3h**, 28%

Scheme 2 AgOAc mediated oxidative vinylic C-H selenation

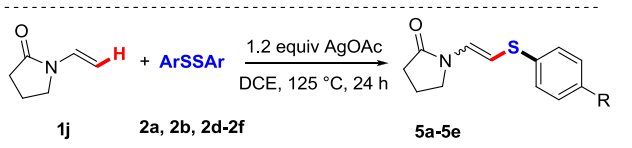
Table 3 The influence of enamides for the vinylic C-H sulfenylation[a]



1b-1h **2a** Ar = *p*-Cl-C_6H_4 **4b-4h**



4b, 61% **4c**, 61% **4d**, 50% **4e**, 76%
4f, 60% **4g**, 74% **4h**, 24% (AgOAc) 56% (Ag_2O)[b] **4i**,[c] 44%

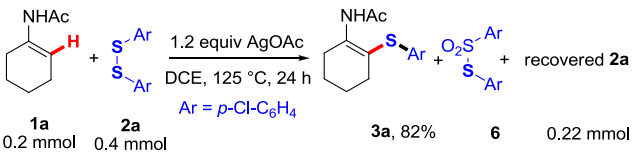


5a, R = Cl, 88% yield, *E*:*Z* = 92:8[d]
5b, R = F, 62% yield, *E*:*Z* > 99:1[e]
5c, R = OCH_3, 82% yield, *E*:*Z* = 94:6
5d, R = CH_3, 68% yield, *E*:*Z* = 94:6
5e, R = H, 55% yield, *E*:*Z* > 99:1[e]

[a] Conditions: **1** (0.2 mmol), **2** (0.4 mmol), AgOAc (1.2 equiv, 0.24 mmol), DCE (0.6 mL), reacted for 24 h at 125°C under argon. Isolated yields. [b] Ag_2O (1.2 equiv, 0.24 mmol) was used. [c] E configuration was determined by NOE. [e] Determined by ^{1}H NMR. [e] The *cis* isomer was not detected by GC.

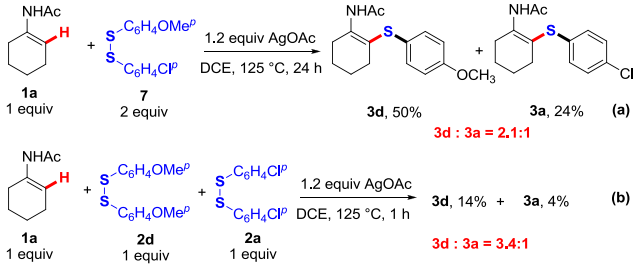
On the other hand, different enamide substrates were investigated (Table 3) and we are pleased to observe that all of the cyclic (**1b-1h**) and liner (**1i**) secondary enamides participated in this vinylic C-H bond sulfenylation successively. The sulfenylation of enamide **1h** with disulfide **2a** afforded **4h** in only 24 % yield due to the further oxidative aromatization of **4h** to α-naphthalenylacetamide. By using 1.2 equiv of Ag_2O instead, the overoxidation was depressed and the yield increased up to 56%. For the tertiary enamide, *N*-vinyl-2-pyrrolidone (**1j**) was chosen as the model, which reacted with diaryl disulfides (**2a, 2b, 2d-2f**) smoothly.

To obtain more insights about the mechanism of the current reaction, a series of experiments were carried out. First, as we have mentioned, 2 equiv of diaryl disulfide was required for the complete conversion of enamide **1a** (Table 1, entries 5 and 8), so carefully examination of the reaction mixture was conducted after the reaction, which revealed that most part of the excessed disulfide was recovered and small part of it was oxidized to *p*-chlorobenzenesulfonothioate ($ArSO_2SAr$, **6**), but no aryl thiol can be detected (Scheme 3).



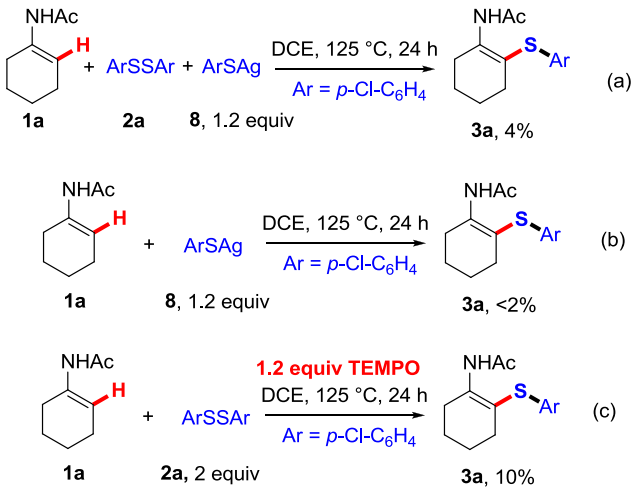
Scheme 3 Recovery of diaryl disulfides

Next, unsymmetrical diaryl disulfide **7** was synthesized according literature[11] and reacted with enamide **1a** under the optimized conditions, and after 1 hour, C-H sulfenylation products **3d** and **3a** were isolated in ratio 2.1:1 (Scheme 4a). This finding indicated that the enamide **1a** prefers reacting with the sulfur connected with an electron-rich aryl group. The similar results can also be obtained from competition reactions between diaryl disulfide **2d** and **2a** with enamide **1a** (Scheme 4b), which afforded a larger ratio of **3d** to **3a** (3.4:1). These results ruled out the possibility that the S-S bond cleavage of the diaryl disulfide was realized by nucleophilic attack, since in this pathway the reaction should prefer the electron-deficient reaction sites.



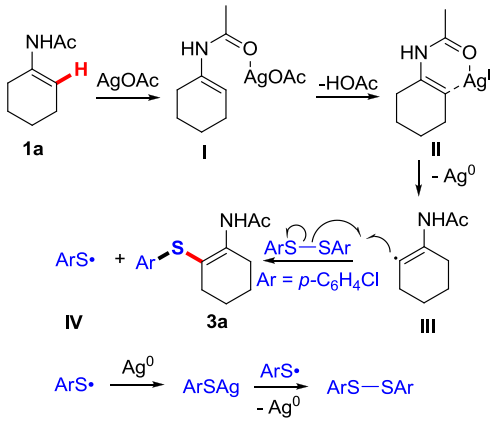
Scheme 4. Competition experiments of enamide **1a** with diaryl disulfides

Then, silver thiophenolate (ArSAg, **8**) was synthesized[12] and used as the silver catalyst (Scheme 5a) or sulfur source (Scheme 5b) for this C-H sulfenylation. Both reactions afforded product **3a** in very low yields, which may imply that ArSAg **8** was not an active intermediate in this reaction. Furthermore, TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl, 1.2 equiv) as radical inhibitor was subjected to the standard procedure, which still led to 10% yield of product **3a** (Scheme 5c). Thus, a chain radical mechanism should be excluded.



Scheme 5 Silver thiophenolate as silver catalyst or sulfur source

Upon the basis of these experimental results, a plausible pathway for this vinylic C-H sulfenylation was outlined in Scheme 6. First, the coordination of silver catalyst to enamide **1a** and subsequent cyclometalation (via electrophilic substitution or concerted metalation-deprotonation) affords the vinylsilver complex **II**,[13] which further generates the vinylradical **III** and the reduced Ag^0.[14] Next, the vinylradical **III** promotes the homolytic cleavage of the diaryl disulfide to provide the sulfenylation product **3a** and arylthiol radical **IV**. The arylthiol radical **IV** might be temporally stabilized by reacting with Ag^0 to yield the inactive silver thiophenolate (ArSAg, **8**) and eventually terminated by coupling with each other to regenerate the diaryl disulfide **2a**.



Scheme 6 Plausible mechanism

In summary, we have described a Ag-mediated oxidative vinylic C-H sulfenylation of enamides with diaryl disulfides, furnishing biologically important arylvinyl sulfides in a simple, efficient way. This method can also be applied to vinylic C-H selenation of enamides with diaryl diselenide. A plausible non-chain radical mechanism was proposed based on the preliminary mechanistic study. Further extension and application of the current method will be pursued.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21202138), Xiangtan University "Academic Leader Program" (11QDZ20), New Teachers' Fund for Doctor Stations, Ministry of Education (20124301120007), and Hunan Provincial Natural Science Foundation (13JJ4047, 12JJ7002), Hunan Provincial Excellent Young Scientist Foundation (13B114).

The authors declare no competing financial interest.

Notes and references

1 (a) J.S. Lazo, K. Nemoto, K. E. Pestell, K. Cooley, E. C. Southwick, D. A. Mitchell, W. Furey, R. Gussio, D. W. Zaharevitz, B. Joo and P. Wipf, *Mol. Pharmacol.*, **2002**, *61*, 720; (b) A. Lavecchia, S. Cosconati, V. Limongelli and E. Novellino, *ChemMedChem*, **2006**, *1*, 540; (c) S. Pasquini, C. Mugnaini, C. Tintori, M. Botta, A. Trejos, R. K. Arvela, M. Larhed, M. Witvrouw, M. Michiels, F. Christ, Z. Debyser and F. Corelli, *J. Med. Chem.*, **2008**, *51*, 5125.

2 (a) P. Bakuzis and M. L. F. Bakuzis, *J. Org. Chem.*, **1985**, *50*, 2569; (b) Y. Masaki, K. Sakuma and K. Kaji, *Chem. Lett.* **1979**, 1235.

3 (a) H. Takahata, K. Moriyama, M. Maruyama and T. Yamazaki, *J. Chem. Soc., Chem. Commun.*, **1986**, 1671; (b) N. F. Haley and M. W. Fichtner, *J. Org. Chem.*, **1980**, *45*, 2959; (c) G. Zheng, X. Ma, B. Liu, Y. Dong and M. Wang, *Adv. Synth. Catal.*, **2014**, 356, 743.

4 For recently selected examples on the cross-coupling reactions of thiols and aryl/vinyl halides, see: (a) I. P. Beletskaya and V. P. Ananikov, *Chem. Rev.*, **2011**, *111*, 1596; (b) S. V. Ley and A. W. Thomas, *Angew. Chem. Int. Ed.*, **2003**, *42*, 5400; (c) C. C. Eichman and J. P. Stambuli, *Molecules*, **2011**, *16*, 590; (d) Y.-Y. Lin, Y.-J. Wang, C.-H. Lin, J.-H. Cheng, C.-F. Lee, *J. Org. Chem.* **2012**, *77*, 6100; (e) Q. Liao, C. Xi, *Chin. J. Org. Chem.* **2012**, *32*, 986; (f) H.-L. Kao and C.-F. Lee, *Org. Lett.*, **2011**, *13*, 5204; (g) W. You, X. Yan, Q. Liao and C. Xi, *Org. Lett.*, **2010**, *12*, 3930; (h) M. S. Kabir, M. Lorenz, M. L. Van Linn, O. A. Namjoshi, S. Ara and J. M. Cook, *J. Org. Chem.*, **2010**, *75*, 3626; (i) C.-K. Chen, Y.-W. Chen, C.-H. Lin, H.-P. Lin and C.-F. Lee, *Chem. Commun.*, **2010**, *46*, 282.

5 For recently selected examples on the hydrothiolation of alkynes, see: (a) R. Castarlenas, A. D. Giuseppe, J. J. Perez-Torrente and L. A. Oro, *Angew. Chem. Int. Ed.*, **2013**, *52*, 211; (b) T. Kondo and T.-A. Mitsudo, *Chem. Rev.*, **2000**, *100*, 3205; (c) I. P. Beletskaya and V. P. Ananikov, *Eur. J. Org. Chem.*, **2007**, 3431; (d) A. D. Giuseppe, R. Castarlenas, J. J. Pérez-Torrente, M. Crucianelli, V. Polo, R. Sancho, F. J. Lahoz and L. A. Oro, *J. Am. Chem. Soc.*, **2012**, *134*, 8171; (e) K. Liu, F. Jia, H. Xi, Y. Li, X. Zheng, Q. Guo, B. Shen and Z. Li, *Org. Lett.*, **2013**, *15*, 2026; (f) S. Ranjit, Z. Duan, P. Zhang and X. Liu, *Org. Lett.*, **2010**, *12*, 4134; (g) C. J. Weiss and T. J. Marks, *J. Am. Chem. Soc.*, **2010**, *132*, 10533.

6 For recently selected examples on the transition-metal catalyzed C-H sulfenylation, see: (a) Y. Yang, W. Hou, L. Qin, J. Du, H. Feng, B. Zhou and Y. Li, *Chem. Eur. J.*, **2014**, *20*, 416; (b) M. Iwasaki, M. Iyanaga, Y. Tsuchiya, Y. Nishimura, W. Li, Z. Li and Y. Nishihara, *Chem. Eur. J.*, **2014**, *20*, 2459; (c) C. Shen, H. Xia, H. Yan, X. Chen, S. Ranjit, X. Xie, D. Tan, R. Lee, Y. Yang, B. Xing, K. Huang, P. Zhang and X. Liu, *Chem. Sci.*, **2012**, *3*, 2388; (d) C. Yu, C. Zhang and X. Shi, *Eur. J. Org. Chem.*, **2012**, 1953; (e) M. L. Zhang,S. H. Zhang, C. D. Pan and F. Chen, *Synth. Commun.*, **2012**, *42*, 2844; (f) S. Ranjit, R. Lee, D. Heryadi, C. Shen, J. Wu, P. Zhang, K. Huang and X. Liu, *J. Org. Chem.*, **2011**, *76*,8999; (g) X. L. Fang, R. Y. Tang, X. G. Zhang and J. H. Li, *Synthesis*, **2011**, 1099; (h) S. Zhang, P. Qian, M. Zhang, M. Hu and J. Cheng, *J. Org. Chem.*, **2010**, *75*, 6732; (i) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, **2006**, *128*, 6790.

7 For a recently review on direct metal-catalyzed regioselective functionalization of enamides, see: N. Gigant, L. Chausset-Boissarie, and I. Gillaizeau, *Chem. Eur. J.*, **2014**, *20*, 7548.

8 (a) H. Zhou, W.-J. Chung, Y.-H. Xu and T.-P. Loh, *Chem. Comm.*, **2009**, *48*, 3472; (b) H. Zhou, Y.-H. Xu, W.-J. Chung and T.-P. Loh, *Angew. Chem. Int. Ed.*, **2009**, *48*, 5355; (c) S. Pankajakshan, Y.-H. Xu, J. K. Cheng, M. T. Low and T.-P. Loh, *Angew. Chem. Int. Ed.*, **2012**, *51*, 5701; (d) Y. Liu, D. Li and C.-M. Park, *Angew. Chem. Int. Ed.*, **2011**, *50*, 7333; (e) H. Wang, L.-N. Guo and X.-H. Duan, *Org. Lett.*, **2012**, *14*, 4358; (f) S. K. Alamsetti, A. K. A. Persson, T. Jiang and J.-E Backvall, *Angew. Chem. Int. Ed.* **2013**, *52*, 13745.

9 K. H. Hesp, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, **2011**, *133*, 11430.

10 (a) F. Xiao, H. Xie, S. Liu and G.-J. Deng, *Adv. Synth. Catal.*, **2014**, *356*, 364; (b) Y. Liao, P. Jiang, S. Chen, H. Qi and G.-J. Deng, *Green Chem.*, **2013**, *15*, 3302; (c) S. Liu, L. Tang, H. Chen, F. Zhao and G.-J. Deng, *Org. Biomol. Chem.*, **2014**, *12*, 6076.

11 H. Kutuk, N. Turkoz, *Phosphorus, Sulfur Silicon Relat. Elem.* **2011,** 186, 1515.

12 I. G. Dance, K. J. Fisher, R. M. H. Banda and M. L. Scudder, *Inorg. Chem.*, **1991**, *30*, 183.

13 (a) X. Zhang, B. Liu, X. Shu, Y. Gao, H. Lv and J. Zhu, *J. Org. Chem.*, **2012**, *77*, 501; (b) J. Dupont, C. S. Consorti, J. Spencer and *Chem. Rev.*, **2005**, *105*, 2527.

14 (a) Y.-R. Chen and W.-L. Duan, *J. Am. Chem. Soc.*, **2013**, *135*, 16754; (b) Y. R. Lee and B. S. Kim, *Tetrahedron Lett.*, **1997**, *38*, 2095; (c) M. Alvarez-Corral, M. Munoz-Dorado and I. Rodriguez-Garcia, *Chem. Rev.*, **2008**, *108*, 3174; (d) J.-M. Weibel, A. Blanc and P. Pale, *Chem. Rev.*, **2008**, *108*, 3149.