



Cite this: *Chem. Commun.*, 2014, 50, 12923

Received 30th August 2014,
Accepted 9th September 2014

DOI: 10.1039/c4cc06851c

www.rsc.org/chemcomm

Room temperature alkynylation of H-phosphi(na)tes and secondary phosphine oxides with ethynyl-benziodoxolone (EBX) reagents†

C. Chun Chen and Jerome Waser*

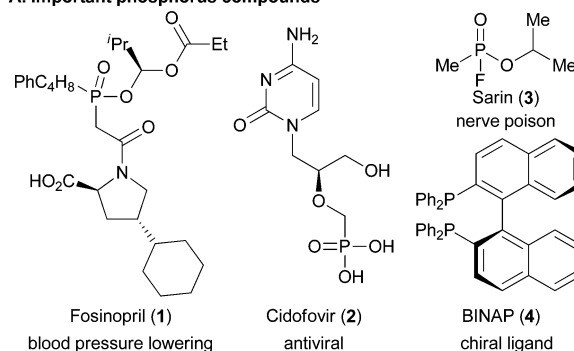
Highly efficient protocols for the alkynylation of H-phosphi(na)tes and secondary phosphine oxides with silyl, aryl and alkyl ethynyl-benziodoxolone (EBX) reagents are reported. Alkynyl phosphorus compounds were obtained in 69–93% yield without the need for a transition metal catalyst at room temperature under open flask conditions.

Phosphorus-based functional groups are important in biology, medicine and synthetic chemistry.¹ Synthetic phosphorus derivatives display a broad range of bioactivities, including drugs like the blood-pressure lowering fosinopril **1**^{2a} and the antiviral cidofovir **2**^{2b} and the nerve poison sarin **3** (Fig. 1, A). Furthermore, ligands such as BINAP **4** based on phosphorus play a privileged role in modern organic and organometallic chemistry. Phosphonium salts and phosphonic esters are also important building blocks to access alkenes *via* Wittig or Horner–Wadsworth–Emmons (HWE) reactions. The development of general methods for the synthesis of organophosphorus compounds is consequently an important goal in organic chemistry.

In this context, alkynyl phosphorus derivatives constitute an important class of building blocks because of the versatile reactivity of the triple bond (Fig. 1, B).³ Hydration of the alkyne leads to β -ketophosphonates, which are used in the HWE reaction.⁴ The addition of other nucleophiles has been also intensively investigated.^{3b} The use of alkynyl phosphorus in [3+2], [4+2] and [2+2+2] cycloadditions⁵ gives access to important phosphorus cyclic compounds, including versatile chiral ligands for metal catalysis^{3b,5f–h} or amino acids analogues for studies in chemical biology.^{5a}

To date, four different approaches have been developed for the synthesis of alkynyl phosphorus compounds, including: (1) reaction of electrophilic alkynes or their precursors with nucleophilic phosphorus(III) reagents involving Michaelis–Arbuzov and Michaelis–Becker reactions,^{4a,6} (2) reaction of nucleophilic alkynes

A. Important phosphorus compounds



B. Alkynyl phosphorus compounds as building blocks

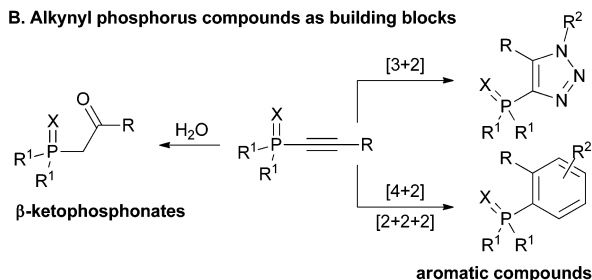


Fig. 1 Important phosphorus-containing bioactive molecules (A) and alkynyl phosphorus derivatives as important building blocks (B).

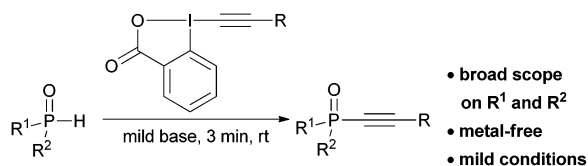
with electrophilic phosphorus,⁷ (3) β -elimination of heteroatom-substituted vinylphosphonates,⁸ and (4) metal-mediated reaction of H-phosphites with 1,1-dibromo alkenes, terminal acetylenes, propionic acid derivatives, copper acetylides or bromo alkynes.⁹

In addition, metal-catalyzed method to access alkynyl phosphines have also been reported.¹⁰ Despite these different alternatives, there are currently no general access to alkynyl phosphorus compounds under mild conditions in absence of transition metals. Most works focus on only one class of phosphorus compounds, especially phosphonates.

In this context, alkynyl iodonium salts have been long known as electrophilic alkynylation reagents,¹¹ but their use for the synthesis of alkynyl phosphorus compounds has been

Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne (CH), Switzerland.
E-mail: jerome.waser@epfl.ch; Web: <http://lcsa.epfl.ch>; Fax: +41 21 693 97 00

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc06851c



Scheme 1 Our approach towards phosphorus alkynylation.

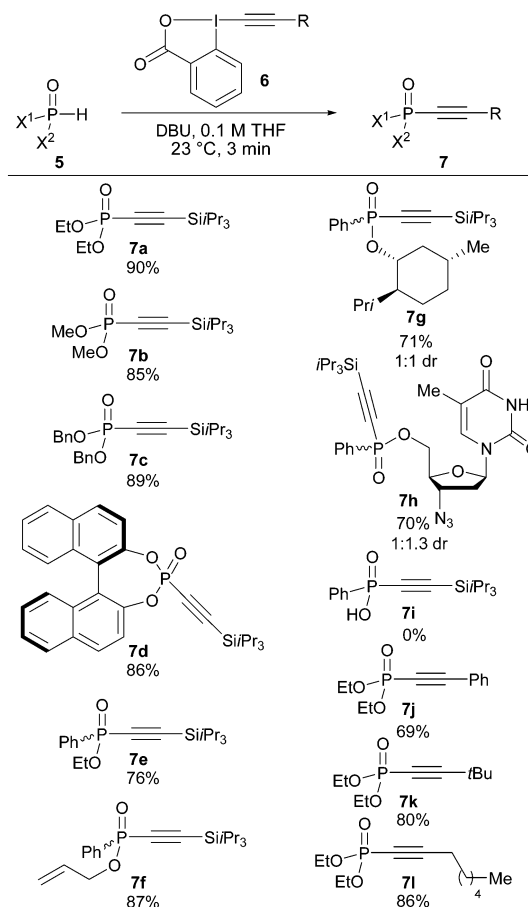
limited to phosphites^{6b} and phosphonates salts.¹² Our group has discovered and exploited the properties of cyclic alkynyl benziodoxolone reagents, such as TIPS-ethynyl-benziodoxolone (TIPS-EBX, **6a**) for the alkynylation of nucleophiles.¹³ This class of reagents, first synthesized by Ochiai and Zhdankin,¹⁴ has then later also been exploited by others.¹⁵ Herein, we would like to report the successful alkynylation of H-phosphites, H-phosphinates and secondary phosphine oxides at room temperature in open flask and a short reaction time (<5 minutes) using EBX reagents (Scheme 1).

To start our studies, we selected 1,1,3,3-tetramethyl guanidine (TMG) for the preparation of alkyne **7a** from diethyl phosphinate **5a** with TIPS-EBX **6a**, as it has been the base of choice in the case of thiol nucleophiles.^{13h} To our delight, 53% isolated yield of **7a** was obtained (Table 1, entry 1). Other amine bases such as 4-dimethylaminopyridine (4-DMAP), 1,4-diazabicyclo[2,2,2]octane (DABCO) and triazabicyclodecene (TBD) led to lower yields (entries 2–4). In contrast, the use of 1,8-diazabicycloundec-7-ene (DBU) gave product **7a** in 82% isolated yield (entry 5). A fast examination of base and reagent loading showed that 1.5 equivalents of DBU and 1.1 equivalents of TIPS-EBX **6a** were optimal (entries 6–8). Other solvents gave lower yields when compared to THF (entries 9–13). Alkynyl phosphite **7a** was already formed within 3 min in 90% isolated yield (entry 14). The formation of **7a** was not observed in the absence of DBU (entry 15).

Table 1 Optimization of the alkynylation of phosphite **8a**

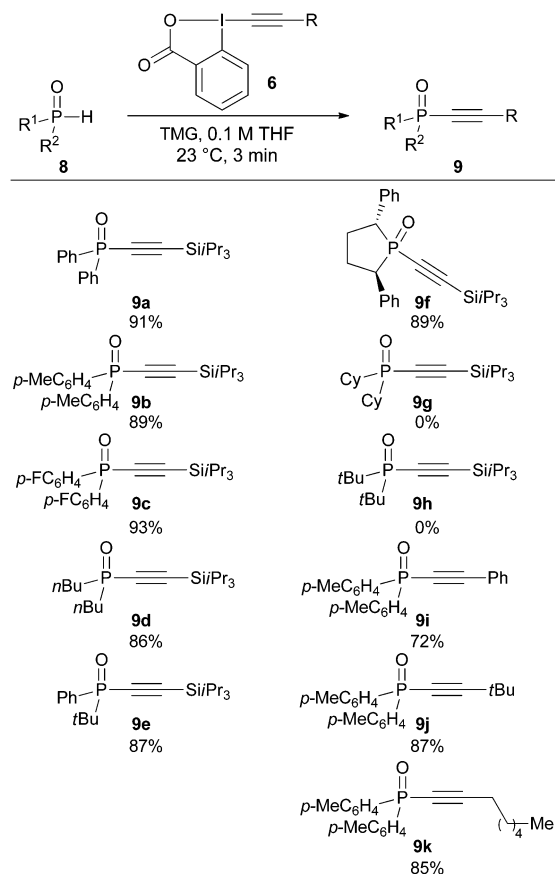
Entry	Equiv. 6a	Base (equiv.)	Solvent	Time (min)	Yield ^a (%)
1	1.2	TMG (2.0)	THF	90	55 (53) ^b
2	1.2	4-DMAP (2.0)	THF	90	0
3	1.2	DABCO (2.0)	THF	90	30
4	1.2	TBD (2.0)	THF	90	0
5	1.2	DBU (2.0)	THF	90	85 (82) ^b
6	1.2	DBU (1.5)	THF	90	84
7	1.2	DBU (1.2)	THF	90	50
8	1.1	DBU (1.5)	THF	90	89 (88) ^b
9	1.1	DBU (1.1)	THF	90	45
10	1.1	DBU (1.5)	i-PrOH	90	5
11	1.1	DBU (1.5)	TBME	90	22
12	1.1	DBU (1.5)	MeCN	90	61
13	1.1	DBU (1.5)	CH ₂ Cl ₂	90	23
14	1.1	DBU (1.5)	THF	3	92 (90) ^b
15	1.1	DBU (0)	THF	3 or 90	0

^a 0.05 mmol **5a** was used. The yield is obtained from ¹H-NMR with 1,3,5-trimethoxybenzene as internal reference. ^b Isolated yield after purification on column chromatography.

Scheme 2 Scope of the alkynylation of phosphites and phosphinates. Reaction conditions: 0.15–0.29 mmol of H-phosphite or H-phosphinate **5** (1.0 equiv.), 1.5 equiv. of DBU and 1.2 equiv. of R-EBX **6**, 0.1 M in THF at 23 °C. Isolated yield after purification on column chromatography is given. 2.5 equiv. of DBU was used in the case of **7i**.

With optimum conditions in hand the scope of H-phosphites and H-phosphinates was examined (Scheme 2).¹⁶ Dimethyl and dibenzyl phosphites **6b** and **6c** gave the desired product **7b** and **7c** in 85% and 89% yield respectively. H-(R)-BINOL phosphite derivative **7d** was obtained in 86% yield. In addition, alkynes **7e** and **7f** were obtained from the corresponding phosphinates in 76% and 87% yield respectively. More complex (R)-phenyl menthoxy and phenyl AZT H-phosphinates were also suitable substrates to deliver the products **7g** (71%) and **7h** (70%) as a mixture of diastereoisomers. However, phenylphosphinic acid **6i** could not be converted into alkyne **7i**. Substituted ethynyl-benziodoxolones (R-EBXs), such as Ph-EBX **6b**,^{13f} *t*Bu-EBX **6c**,^{13f} and *n*Hex-EBX **6d**^{15g} could also be used in this direct alkynylation successfully to give products **7j–l**. Notably, an 1,5-C–H insertion product resulting from a carbene intermediate was not observed in the alkynylation of **5a** with ketoesters were used as nucleophiles with alkynylodonium salts.¹⁷

We then turned our attention to the alkynylation of secondary phosphine oxides (SPO) (Scheme 3).¹⁶ The alkynylation of this class of substrates has been much less studied in the past. Indeed, to the best of our knowledge, only the alkynylation of diphenyl



Scheme 3 Scope of the H-phosphine oxides. Reaction conditions: 0.15–0.29 mmol of H-phosphine oxide **8** (1.0 equiv.), 1.5 equiv. of TMG and 1.5 equiv. of R-EBX **6**, 0.1 M in THF at 23 °C. Isolated yield after purification on column chromatography is given.

phosphine oxide **8a** has been reported.^{6d,9e,f} Initially, the conditions used in alkynylation of H-phosphites and H-phosphinates using DBU as a base (Table 1, entry 14) were tested for the alkynylation of diphenyl phosphine oxide **8a**, but only 60% isolated yield of **9a** was obtained. TMG, which had been the second best base in the case of phosphites, gave better results and the alkynylation product **9a** was isolated in 91% yield. This protocol could also be used in the synthesis of di-(4-tolyl) phosphinite **9b** (89%), di-(4-fluorophenyl) phosphinite **9c** (93%), di-(*n*-butyl) phosphinite **9d** (86%), and phenyl-*t*-butyl phosphinite **9e** (87%). Significantly, cyclic phosphinite **9f** can be made in 89% yield. However, bulky substituted phosphinite, such as **9g** and **9h** could not be synthesized. We further investigated the synthesis of ethynyl phosphinite bearing aryl or alkyl groups on the alkyne. Phenylethynyl phosphine **9i** and *t*-butylethynyl phosphine **9j** were obtained in 72% and 87% yield respectively. *n*-Hexyl ethynyl phosphine **9k** could also be obtained in 85% yield.

Several plausible mechanisms could be envisaged for the direct alkynylation reaction. For the reaction of alkynylodonium salts with carbon nucleophiles, conjugate addition onto the β -carbon of ethynyl-benziodoxolone, followed by an α -elimination of the arylidide and 1,2-shift rearrangement to deliver the alkyne has been most often proposed.¹⁷ The fact that no products resulting from C–H insertion

had been observed in the case of aliphatic alkynes could be rationalized by a fast 1,2-shift of the phosphorus atom. Nevertheless, an alternative mechanism involving nucleophilic attack of phosphi(na)te/phosphine oxide onto the iodine atom of benziodoxolone, followed by C–P bond formation to give the alkyne product cannot be excluded at this stage. A single electron transfer (SET) from phosphi(na)te/phosphine oxide to the ethynyl-benziodoxolone, could also be proposed as a first step in the reaction. Recombination on the iodine to give an I–P bond followed by reductive elimination or direct alkynylation of the phosphorus atom would then lead to the observed product. However, when TEMPO was added to the reaction mixture under the standard reaction conditions (Table 1, entry 14), alkyne **7a** was still obtained in 85% yield. This result suggests that long-living radical intermediates are probably not involved. It is also important to notice that SET pathways often require further activation of the hypervalent iodine reagent by a Lewis or Brønsted acid to facilitate electron transfer, and the developed method proceeded under basic conditions.¹⁸

In conclusion, we have described very simple and general protocols for the alkynylation of H-phosphites, -phosphinates, and secondary phosphine oxides using ethynyl-benziodoxolone reagents in good to excellent yield. The developed alkynylation method proceeded at room temperature in a few minutes and did not require the use of transition metals. It could be applied to the synthesis of silyl, alkyl and aryl substituted alkynes and was efficient for a broad range of different substituents on phosphorus. Further extension of the scope, application of the obtained building blocks in synthesis, and more detailed investigation of the reaction mechanism are currently ongoing in our laboratory and the results will be reported in due course.

EPFL, F. Hoffmann-La Roche Ltd and ERC (Starting Grant iTools4MC, number 334840) are acknowledged for financial support. We also thank Dr P. A. Donets and Prof. N. Cramer from the Laboratory of Asymmetric Catalysis and Synthesis at EPFL for donation of starting materials **5d**, **8e**, **8f** and **8g**. Dr C. C. Chen dedicates this article to Prof. V. K. Aggarwal FRS at University of Bristol.

Notes and references

- (a) F. H. Westheimer, *Science*, 1987, **235**, 1173; (b) C. S. Demmer, N. Krogsgaard-Larsen and L. Bunch, *Chem. Rev.*, 2011, **111**, 7981; (c) J. L. Montchamp, *Acc. Chem. Res.*, 2013, **47**, 77; (d) D. E. C. Corbridge, *Phosphorus: Chemistry, Biochemistry and Technology*, CRC Press, 6th edn, 2013.
- (a) P. Tatti, M. Pahor, R. P. Byington, P. Di Mauro, R. Guarisco, G. Strollo and F. Strollo, *Diabetes Care*, 1998, **21**, 597; (b) U. Eriksson, L. W. Peterson, B. A. Kashemirov, J. M. Hilfinger, J. C. Drach, K. Z. Borysko, J. M. Breitenbach, J. S. Kim, S. Mitchell, P. Kijek and C. E. McKenna, *Mol. Pharmaceutics*, 2008, **5**, 598.
- For reviews, see: (a) B. Iorga, F. Eymery, D. Carmichael and P. Savignac, *Eur. J. Org. Chem.*, 2000, 3103; (b) A. Kondoh, H. Yorimitsu and K. Oshima, *Chem. – Asian J.*, 2010, **5**, 398.
- (a) G. Sturz, C. Charrier and H. Normant, *Bull. Soc. Chim. Fr.*, 1966, 1707; (b) E. J. Corey and S. C. Virgil, *J. Am. Chem. Soc.*, 1990, **112**, 6429; (c) X. Li, G. Hu, P. Luo, G. Tang, Y. Gao, P. Xu and Y. Zhao, *Adv. Synth. Catal.*, 2012, **354**, 2427; (d) L. Y. Xie, R. Yuan, R. J. Wang, Z. H. Peng, J. N. Xiang and W. M. He, *Eur. J. Org. Chem.*, 2014, 2668.
- Selected examples: [3+2]: (a) J. M. Kee, B. Villani, L. R. Carpenter and T. W. Muir, *J. Am. Chem. Soc.*, 2010, **132**, 14327; [4+2]: (b) D. Seyferth and J. Paetsch, *J. Org. Chem.*, 1969, **34**, 1483; (c) B. O. Ashburn and

- R. G. Carter, *Angew. Chem., Int. Ed.*, 2006, **45**, 6737; (d) B. O. Ashburn, R. G. Carter and L. N. Zakharov, *J. Am. Chem. Soc.*, 2007, **129**, 9109; [2+2+2]: (e) M. Schelper, O. Buisine, S. Kozhushkov, C. Aubert, A. de Meijere and M. Malacria, *Eur. J. Org. Chem.*, 2005, 3000; (f) G. Nishida, K. Noguchi, M. Hirano and K. Tanaka, *Angew. Chem., Int. Ed.*, 2007, **46**, 3951; (g) G. Nishida, S. Ogaki, Y. Yusa, T. Yokozawa, K. Noguchi and K. Tanaka, *Org. Lett.*, 2008, **10**, 2849; (h) N. Sakiyama, D. Hojo, K. Noguchi and K. Tanaka, *Chem. – Eur. J.*, 2011, **17**, 1428.
- 6 (a) B. I. Ionin and A. A. Petrov, *J. Gen. Chem. USSR (Engl. Transl.)*, 1962, **32**, 2355; (b) J. S. Lodaya and G. F. Koser, *J. Org. Chem.*, 1990, **55**, 1513; (c) Y. Yatsumonji, A. Ogata, A. Tsubouchi and T. Takeda, *Tetrahedron Lett.*, 2008, **49**, 2265; (d) Y. Wang, J. Gan, L. Liu, H. Yuan, Y. Gao, Y. Liu and Y. Zhao, *J. Org. Chem.*, 2014, **79**, 3678. For a review on electrophilic alkynylation, see: (e) J. P. Brand and J. Waser, *Chem. Soc. Rev.*, 2012, **41**, 4165.
- 7 (a) A. M. Aguiar and M. S. Chattha, *J. Org. Chem.*, 1971, **36**, 2719; (b) A. J. Rudinskas and T. L. Hullar, *J. Med. Chem.*, 1976, **19**, 1367.
- 8 (a) H. I. Jacobson, M. J. Griffin, S. Preis and E. V. Jensen, *J. Am. Chem. Soc.*, 1957, **79**, 2608; (b) J. E. Hong, C. W. Lee, Y. Kwon and D. Y. Oh, *Synth. Commun.*, 1996, **26**, 1563.
- 9 From 1,1-dibromo alkenes: (a) M. Lera and C. J. Hayes, *Org. Lett.*, 2000, **2**, 3873. From terminal alkynes: (b) Y. Gao, G. Wang, L. Chen, P. Xu, Y. Zhao, Y. Zhou and L. B. Han, *J. Am. Chem. Soc.*, 2009, **131**, 7956; (c) Z. B. Qu, X. L. Chen, J. W. Yuan, L. B. Qu, X. Li, F. J. Wang, X. L. Ding and Y. F. Zhao, *Can. J. Chem.*, 2012, **90**, 747. From propiolic acid derivatives: (d) J. Hu, N. Zhao, B. Yang, G. Wang, L. N. Guo, Y. M. Liang and S. D. Yang, *Chem. – Eur. J.*, 2011, **17**, 5516; (e) X. Li, F. Yang, Y. Wu and Y. Wu, *Org. Lett.*, 2014, **16**, 992. From copper acetylides: (f) K. Jouvin, J. Heimbürger and G. Evano, *Chem. Sci.*, 2012, **3**, 756; (g) C. Theunissen, M. Lecomte, K. Jouvin, A. Laouiti, C. Guissart, J. Heimbürger, E. Loire and G. Evano, *Synthesis*, 2014, 1157. From bromoalkynes: O. Berger, C. Petit, E. L. Deal and J. L. Montchamp, *Adv. Synth. Catal.*, 2013, **355**, 1361.
- 10 Selected examples: (a) I. P. Beletskaya, V. V. Afanasiev, M. A. Kazankova and I. V. Efimova, *Org. Lett.*, 2003, **5**, 4309; (b) E. Bernoud, C. Alayrac, O. Delacroix and A. C. Gaumont, *Chem. Commun.*, 2011, **47**, 3239; (c) K. Jouvin, R. Veillard, C. Theunissen, C. Alayrac, A. C. Gaumont and G. Evano, *Org. Lett.*, 2013, **15**, 4592. For a review, see: (d) E. Bernoud, R. Veillard, C. Alayrac and A. C. Gaumont, *Molecules*, 2012, **17**, 14573.
- 11 V. V. Zhdankin and P. J. Stang, *Tetrahedron*, 1998, **54**, 10927.
- 12 J. L. Zhang and Z. C. Chen, *Synth. Commun.*, 1998, **28**, 175.
- 13 Selected examples: (a) J. P. Brand, J. Charpentier and J. Waser, *Angew. Chem., Int. Ed.*, 2009, **48**, 9346; (b) J. P. Brand and J. Waser, *Angew. Chem., Int. Ed.*, 2010, **49**, 7304; (c) D. Fernandez Gonzalez, J. P. Brand and J. Waser, *Chem. – Eur. J.*, 2010, **16**, 9457; (d) S. Nicolai, S. Erard, D. Fernandez Gonzalez and J. Waser, *Org. Lett.*, 2010, **12**, 384; (e) S. Nicolai, C. Piemontesi and J. Waser, *Angew. Chem., Int. Ed.*, 2011, **50**, 4680; (f) J. P. Brand, C. Chevalley, R. Scopelliti and J. Waser, *Chem. – Eur. J.*, 2012, **18**, 5655; (g) D. Fernández González, J. P. Brand, R. Mondière and J. Waser, *Adv. Synth. Catal.*, 2013, **355**, 1631; (h) R. Frei and J. Waser, *J. Am. Chem. Soc.*, 2013, **135**, 9620; (i) Y. Li, J. P. Brand and J. Waser, *Angew. Chem., Int. Ed.*, 2013, **52**, 6743. For a review see: (j) J. P. Brand, D. Fernandez Gonzalez, S. Nicolai and J. Waser, *Chem. Commun.*, 2011, **47**, 102.
- 14 (a) M. Ochiai, Y. Masaki and M. Shiro, *J. Org. Chem.*, 1991, **56**, 5511; (b) V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz and A. J. Simonsen, *J. Org. Chem.*, 1996, **61**, 6547.
- 15 (a) Y. Ohta, Y. Tokimizu, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2010, **12**, 3963; (b) X. Liu, Z. Wang, X. Cheng and C. Li, *J. Am. Chem. Soc.*, 2012, **134**, 14330; (c) Z. Wang, X. Li and Y. Huang, *Angew. Chem., Int. Ed.*, 2013, **52**, 14219; (d) T. Aubineau and J. Cossy, *Chem. Commun.*, 2013, **49**, 3303; (e) M. Kamlar, P. Putaj and J. Vesely, *Tetrahedron Lett.*, 2013, **54**, 2097; (f) A. Nierth and M. A. Marletta, *Angew. Chem., Int. Ed.*, 2014, **53**, 2611; (g) H. Huang, G. Zhang, L. Gong, S. Zhang and Y. Chen, *J. Am. Chem. Soc.*, 2014, **136**, 2280; (h) C. Feng and T. P. Loh, *Angew. Chem., Int. Ed.*, 2014, **53**, 2722; (i) F. Xie, Z. Qi, S. Yu and X. Li, *J. Am. Chem. Soc.*, 2014, **136**, 4780; (j) K. D. Collins, F. Lied and F. Glorius, *Chem. Commun.*, 2014, **50**, 4459; (k) L. F. Silva Jr, A. Utaka and L. Calvalcanti, *Chem. Commun.*, 2014, **50**, 3810; (l) P. Finkbeiner, N. M. Weckenmann and B. J. Nachtsheim, *Org. Lett.*, 2014, **16**, 1326.
- 16 Preparation of non-commercially available H-phosphi(na)tes and secondary phosphine oxides: (a) X. B. Sun, J. X. Kang and Y. F. Zhao, *Chem. Commun.*, 2002, 2414; (b) K. Afarinkia and H. W. Yu, *Tetrahedron Lett.*, 2003, **44**, 781; (c) C. A. Busacca, J. C. Lorenz, N. Grinberg, N. Haddad, M. Hrapchak, B. Latli, H. Lee, P. Sabila, A. Saha, M. Sarvestani, S. Shen, R. Varsolona, X. Wei and C. H. Senanayake, *Org. Lett.*, 2005, **7**, 4277; (d) P. Fourgeaud, C. Midrier, J. P. Vors, J. N. Volle, J. L. Pirat and D. Virieux, *Tetrahedron*, 2010, **66**, 758. For detail, see the ESI†.
- 17 (a) M. Ochiai, M. Kunishima, Y. Nagao, K. Fuji, M. Shiro and E. Fujita, *J. Am. Chem. Soc.*, 1986, **108**, 8281; (b) M. Ochiai, T. Ito, Y. Takaoka, Y. Masaki, M. Kunishima, S. Tani and Y. Nagao, *J. Chem. Soc., Chem. Commun.*, 1990, 118.
- 18 T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka and Y. Kita, *Tetrahedron*, 2009, **65**, 10797.