Green Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c8gc02026d

Received 30th June 2018,
Accepted 18th July 2018

DOI: 10.1039/c8gc02026d

rsc.li/greenchem

Oxidant-free oxidation of C–H bonds by cathodic hydrogen evolution: a phosphonic Kolbe oxidation/cyclization process†

Lei Zhang,‡§ Zhenxing Zhang,‡§ Jianning Zhang, Kangle Li and Fanyang Mo *

An anodic oxidation/cyclization of 2-(aryl)aryl phosphonic acid monoesters for ethoxy dibenzooxaphosphorin oxide synthesis has been developed. This unprecedented electrochemical oxidation reaction proceeds at room temperature with no oxidant or electrolyte required, and exhibits high atom-economy with H_2 being the only byproduct. A series of ethoxy dibenzooxaphosphorin oxides were obtained in good yields.

The development of green and sustainable methods for chemical manufacturing represents a vital aspect in modern organic synthesis.[1,2] Oxidation reactions are fundamentally important and frequently applied in both academic and industrial settings every day.[3] However, the use of such highly reactive reagents often causes safety issues and generates much waste, leading to poor atom economy. In addition, chemical oxidants can also lead to oxidative side reactions. It is quite reasonable that an oxidation reaction requires a stoichiometric amount of an oxidant, but this is not always the case. If the fate of hydrogen atoms can be properly handled, for example, in hydrogen gas formation, the oxidant would not be indispensable. In this context, cathodic hydrogen evolution represents one such ideal oxidant-free oxidation reaction. In this case, protons can be considered as a sacrificial oxidant, since they are forced by electric potential to combine with electrons to form hydrogen gas (Scheme 1A).

The past decade has witnessed resurging interest in organic electrochemistry that dramatically improved organic chemists' toolbox for green and sustainable synthesis.[4–15] In terms of C–H activation/functionalization, Ackermann's,[16–18] Xu's,[19–21] Zeng's,[22–24] Lei's,[25–27] Mei's,[28,29] Sanford's[30] and Muñiz's[31] groups have developed ingenious electrochemical methods for C–X construction, C–C cross-coupling and dehydrogenative annulation recently.

Department of Energy and Resources Engineering, College of Engineering, Peking University, Beijing 100871, China. E-mail: fmo@pku.edu.cn

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c8gc02026d

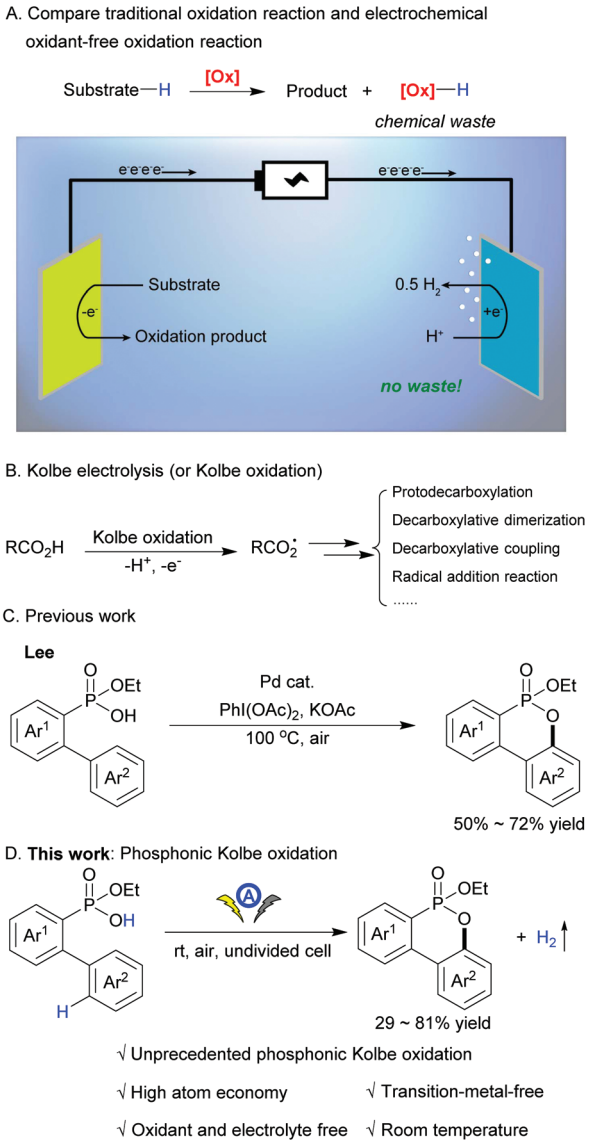
‡These authors contributed equally.

§Co-first authors.

We have recently been interested in Kolbe electrolysis. As one of the most well-known organic electrochemical reactions, Kolbe electrolysis can be categorized as an oxidant-free oxidation reaction. It was first discovered by Faraday in 1834,[32] and then elaborated in detail and utilized in organic synthesis by Kolbe in 1849.[33] Though the Kolbe reaction is a century-old transformation, it is still alive as an important synthetic tool in organic chemistry, and a vast number of studies have been carried out to unveil its synthetic potential (Scheme 1B).[34–37] In a recent study, we have developed a practical intramolecular Kolbe oxidative cyclization method for the synthesis of dibenzopyranones starting from 2-arylbenzoic acids.[38] In this reaction, the key step is a Kolbe oxidation of aryl benzoic acid affording an aroyloxy radical. Then this radical is trapped intramolecularly by an aromatic ring. Further anodic oxidation of this trapped radical leads to the final cyclized product. In this context, we envision that an analogue of the phosphonic Kolbe oxidative cyclization process might be feasible towards the synthesis of ethoxy dibenzooxaphosphorin oxides starting from 2-(aryl)aryl phosphonic acid monoesters.

Organophosphorus compounds have been proved to be valuable and effective in pharmaceuticals,[39] pesticides,[40] materials,[41] catalysis,[42] *etc*. In this context, it's essential to develop efficient and practical methods to synthesize these crucial compounds. Previously, facilitated by transition metal catalysis, Lee's,[43–46] Miura's[47] and Glorius's[48] groups have developed robust methods to realize oxidative cyclization of phosphonic acids or their derivatives. In 2014, Lee's group developed a palladium-catalyzed oxidative cyclization starting from 2-(aryl)aryl phosphonic acid monoesters. A series of ethoxy dibenzooxaphosphorin oxides could be obtained effectively in the presence of Pd catalyst, $PhI(OAc)_2$ and KOAc under heat conditions (Scheme 1C).[49] Herein we develop a simple electrochemical method to realize this cyclization under transition metal catalyst- and oxidant-free conditions (Scheme 1D). To the best of our knowledge, the anodic oxidation of phosphonic acids has not been disclosed yet.

The starting materials were synthesized according to Lee's report.[49] A range of 2-(aryl)aryl phosphonic acid monoethyl

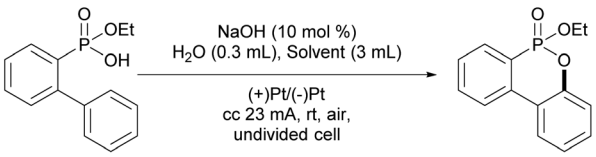


Scheme 1 Kolbe oxidation and phosphonic Kolbe oxidation.

esters were efficiently accessed by sequentially conducting a Suzuki coupling of 2-bromoiodoarenes with arylboronic acids, a Pd-catalyzed phosphorylation of 2-bromobiaryls, and hydrolysis of diethyl 2-(aryl)arylphosphonates using L-selectride or under basic conditions (see the ESI†).

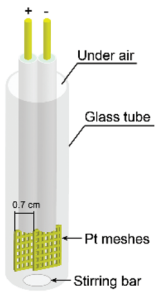
With the starting materials available, we initially studied the anodic oxidation of 2-phenyl phosphonic acid **1a** (Table 1). Platinum materials were chosen as the electrodes due to their chemical inertness and low overpotential for hydrogen evolution. Thus, electrolysis of **1a** with a constant current of 23 mA for 2.5 h afforded the desired cyclized product **2a** in 74% NMR yield and 62% isolated yield in the presence of 10% NaOH in a MeOH/H_2O solvent mixture (entry 1). The reaction gave slightly less product when the temperature was kept at 0 °C (entry 2). We next screened a series of solvents, and found that except DMF, other solvents such as 1,1,1,3,3,3-hexafluoropropanol

Table 1 Optimization of the reaction conditions[a]



1a **2a**

Entry	Reaction conditions	Yield[b] (%)
1	MeOH, 2.5 h	74 (62)
2	MeOH, 2.5 h, 0 °C	69
3	HFIP, 24 h	Trace
4	DMF, 12 h	76
5	MeCN, 4.6 h	16
6	Acetone, 12 h	15
7	i-PrOH, 18 h	23
8	EtOH, 5 h	36
9	**MeOH/DMF (9 : 1), 3 h**	**84 (71)**



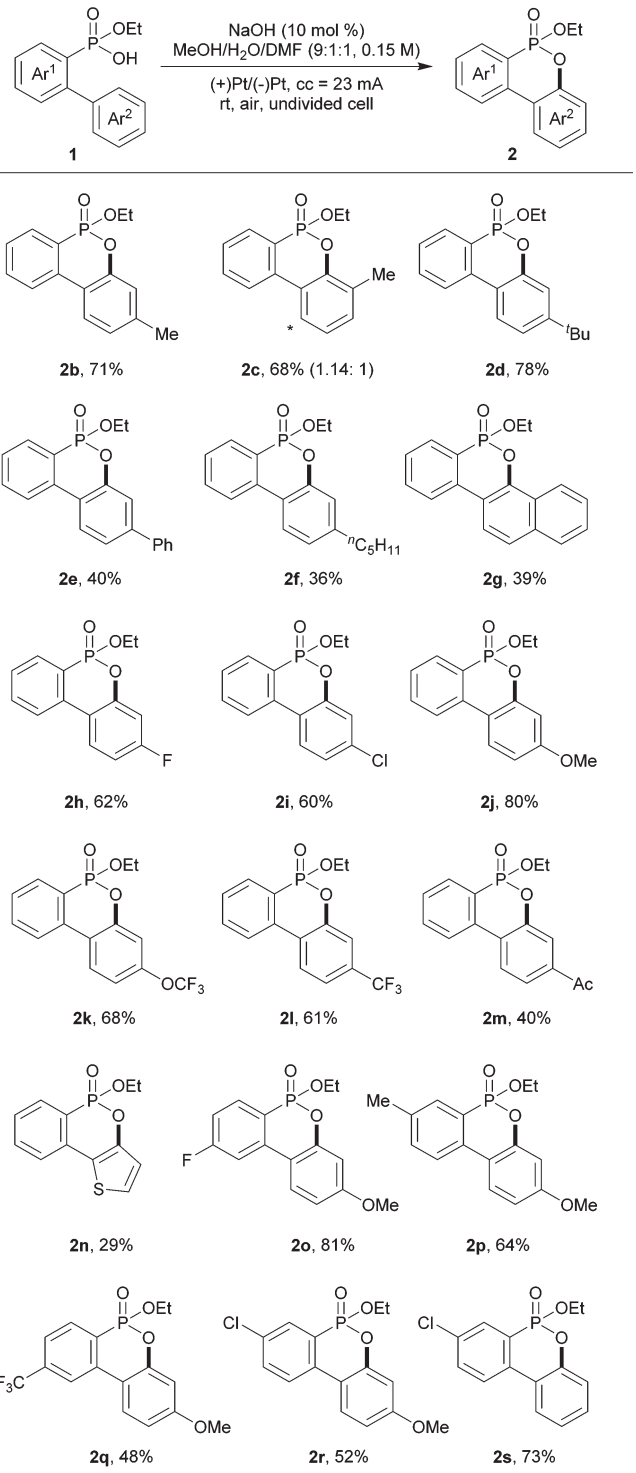
[a] Reaction conditions: **1a** 0.5 mmol, 3 mL solvent, 0.3 mL H_2O, Pt mesh electrodes, 1 cm × 1 cm, 52 mesh. cc constant current. HFIP 1,1,1,3,3,3-hexafluoro-2-propanol. [b] Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yield in parentheses.

(HFIP), MeCN, acetone, isopropanol and EtOH proved to be less efficient with a longer reaction time being required (entries 3–8). Gratifyingly, the use of a solvent mixture MeOH/DMF further increased the yield to 84% (71% isolated yield, entry 9).

With the optimized reaction conditions in hand, the substrate scope was then studied with the results depicted in Table 2. A variety of substituents on both the Ar^1 and Ar^2 rings were examined, and the desired products were obtained readily in moderate to good yields. This electrochemical approach tolerates diverse functional groups, such as halides, ether, trifluoromethyl, trifluoromethoxyl, ketone *etc*. When the substituent on the Ar^2 ring was at the *meta* position, a mixture of isomers was obtained (**2c**). Due to the solubility issue of **1e–1g** substrates, the yields of products **2e–2g** were relatively low. This electrochemical oxidation reaction favoured the substrates bearing electron-donating groups on the Ar^2 ring, and the corresponding products were obtained in better yields (**2b**, **2d**, **2j**, and **2o**). In regard to the substituents on the Ar^1 ring (**2o–2s**), the electronic effect does not operate prominently. The desired cyclized products were obtained in a range of 48–81% yields. Although the yield of product **2n** was not satisfactory, ethoxy dibenzooxaphosphorin oxides containing a heterocycle could be synthesized by this anodic oxidation method conveniently.

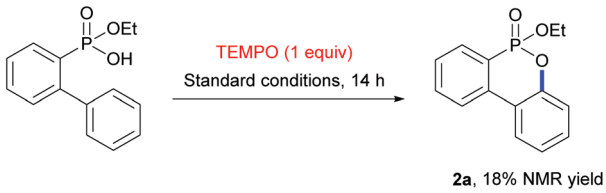
To explore the mechanism of this electrochemical reaction, a free radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), was introduced as an additive under the standard conditions. The starting material 2-(aryl)aryl phosphonic acid largely remained even after 14 h (Scheme 2), indicating a hindrance of cyclization in the presence of TEMPO and a probable

Table 2 Substrate scope[a]



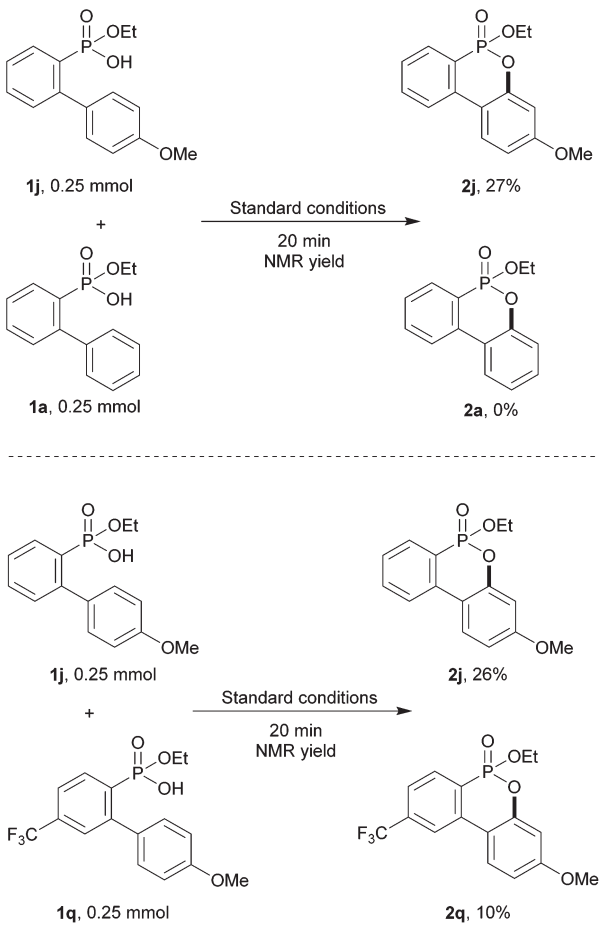
[a] Reaction conditions: **1** 0.5 mmol, 2 mg NaOH, 2.7 mL MeOH, 0.3 mL H_2O, 0.3 mL DMF, Pt net electrodes, 1 cm × 1 cm, 52 mesh. cc constant current. Isolated yields were reported.

electrically generating radical process. To gain deeper insight into the reaction mechanism, as well as a better understanding of the electronic effect of substituents on both Ar^1 and Ar^2

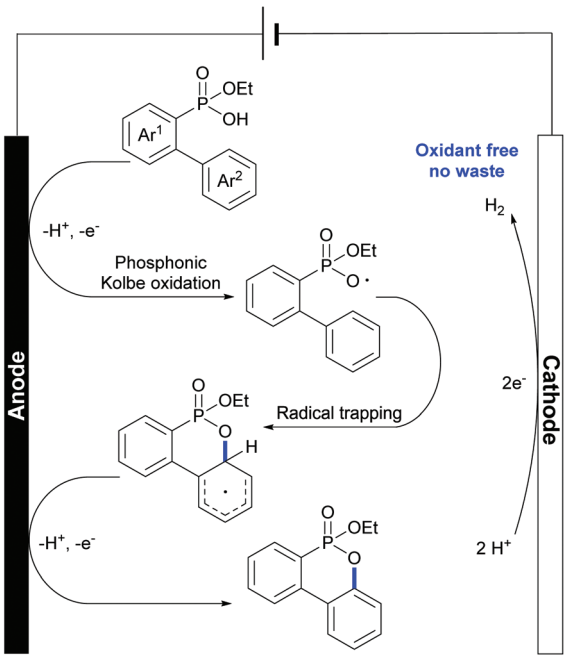


Scheme 2 Reaction with TEMPO.

rings, two competitive reactions were designed and performed between **1a** and **1j**, **1j** and **1q**, respectively (Scheme 3). We found that substrate **1j** is predominantly oxidized when competing with **1a**, while **1j** and **1q** are oxidized to give **2j** and **2q** in a *ca.* 2.6 : 1 ratio. This result indicated that the substituents on the Ar^2 ring have a greater influence on the reaction rate. Moreover, this influence is smaller with the substituents on the Ar^1 ring. These competitive experiments demonstrated that the anodic oxidation of phosphonic acids is not likely a rate-determining step in this cyclization reaction, and the rate-determining step probably involves the trapping of phosphonic acid radicals by the Ar^2 ring.



Scheme 3 Competitive reactions between **1a** and **1j**, **1j** and **1q**, respectively.



Scheme 4 Proposed mechanism.

Based on the information above, a plausible reaction mechanism was proposed as shown in Scheme 4. A phosphonic anion resulting from deprotonation by a catalytic amount of NaOH is anodically oxidized to afford the phosphonic acid radical intermediate. Then this radical is trapped by the aryl ring intramolecularly, generating an aryl radical. Finally, this aryl radical is oxidized again at the anode to deliver the final cyclized product. The two consecutive electron transfers between the electrode and the substrate taking place on the same electrode (double anodic oxidation) favour implementation of the reaction. Meanwhile, cathodic proton reduction to hydrogen gas accurately balanced the redox of the overall reaction.

In summary, we have developed a general, practical intramolecular phosphonic Kolbe oxidative cyclization method for the synthesis of ethoxy dibenzooxaphosphorin oxides. This method is transition metal- and oxidant-free, does not involve electrolytes, and proceeds at ambient temperature. We expect this electrochemical reaction to find wide applications in the synthesis of phosphorus-containing compounds in future synthetic endeavours.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The project was supported by the Natural Science Foundation of China (Grants 21502003 and 21772003). We also thank the "1000-Youth Talents Plan", Peking University, for start-up funds.

Notes and references

1 P. T. Anastas and J. C. Warner, *Green chemistry: theory and practice*, Oxford University Press, 2000.
2 C.-J. Li and B. M. Trost, *Proc. Natl. Acad. Sci. U. S. A.*, 2008, **105**, 13197–13202.
3 J.-E. Bäckvall, *Modern oxidation methods*, John Wiley & Sons, 2011.
4 K. D. Moeller, *Tetrahedron*, 2000, **56**, 9527–9554.
5 J. B. Sperry and D. L. Wright, *Chem. Soc. Rev.*, 2006, **35**, 605–621.
6 A. Jutand, *Chem. Rev.*, 2008, **108**, 2300–2347.
7 J.-i. Yoshida, K. Kataoka, R. Horcajada and A. Nagaki, *Chem. Rev.*, 2008, **108**, 2265–2299.
8 B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma and R. Vasquez-Medrano, *Green Chem.*, 2010, **12**, 2099–2119.
9 H. J. Schäfer, *C. R. Chim.*, 2011, **14**, 745–765.
10 R. Francke and R. D. Little, *Chem. Soc. Rev.*, 2014, **43**, 2492–2521.
11 E. J. Horn, B. R. Rosen and P. S. Baran, *ACS Cent. Sci.*, 2016, **2**, 302–308.
12 M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230–13319.
13 Y. Jiang, K. Xu and C. Zeng, *Chem. Rev.*, 2018, **118**, 4485–4540.
14 S. Tang, Y. Liu and A. Lei, *Chem.*, 2018, **4**, 27–45.
15 Q.-L. Yang, P. Fang and T.-S. Mei, *Chin. J. Chem.*, 2018, **36**, 338–352.
16 N. Sauermann, R. Mei and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 5090–5094.
17 C. Tian, L. Massignan, T. H. Meyer and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 2383–2387.
18 N. Sauermann, T. H. Meyer, C. Tian and L. Ackermann, *J. Am. Chem. Soc.*, 2017, **139**, 18452–18455.
19 Z.-J. Wu, S.-R. Li, H. Long and H.-C. Xu, *Chem. Commun.*, 2018, **54**, 4601–4604.
20 H. B. Zhao, Z. J. Liu, J. Song and H. C. Xu, *Angew. Chem., Int. Ed.*, 2017, **56**, 12732–12735.
21 Z.-W. Hou, Z.-Y. Mao and H.-C. Xu, *Synlett*, 2017, **28**, 1867–1872.
22 M. Y. Lin, K. Xu, Y. Y. Jiang, Y. G. Liu, B. G. Sun and C. C. Zeng, *Adv. Synth. Catal.*, 2018, **360**, 1665–1672.
23 S. Zhang, L. Li, H. Wang, Q. Li, W. Liu, K. Xu and C. Zeng, *Org. Lett.*, 2018, **20**, 252–255.
24 Q.-Q. Wang, K. Xu, Y.-Y. Jiang, Y.-G. Liu, B.-G. Sun and C.-C. Zeng, *Org. Lett.*, 2017, **19**, 5517–5520.
25 L. Zeng, H. Li, S. Tang, X. Gao, Y. Deng, G. Zhang, C.-W. Pao, J.-L. Chen, J.-F. Lee and A. Lei, *ACS Catal.*, 2018, **8**, 5448–5453.
26 K. Liu, S. Tang, P. Huang and A. Lei, *Nat. Commun.*, 2017, **8**, 775.

27 X. Gao, P. Wang, L. Zeng, S. Tang and A. Lei, *J. Am. Chem. Soc.*, 2018, **140**, 4195–4199.
28 Y.-Q. Li, Q.-L. Yang, P. Fang, T.-S. Mei and D. Zhang, *Org. Lett.*, 2017, **19**, 2905–2908.
29 Q.-L. Yang, Y.-Q. Li, C. Ma, P. Fang, X.-J. Zhang and T.-S. Mei, *J. Am. Chem. Soc.*, 2017, **139**, 3293–3298.
30 A. Shrestha, M. Lee, A. L. Dunn and M. S. Sanford, *Org. Lett.*, 2018, **20**, 204–207.
31 S. Herold, D. Bafaluy and K. Muñiz, *Green Chem.*, 2018, **20**, 3191–3196.
32 M. Faraday, *Ann. Phys.*, 1834, **108**, 401–453.
33 H. Kolbe, *Justus Liebigs Ann. Chem.*, 1849, **69**, 257–294.
34 A. K. Vijh and B. E. Conway, *Chem. Rev.*, 1967, **67**, 623–664.
35 H.-J. Schäfer, in *Electrochemistry IV*, ed. E. Steckhan, Springer Berlin Heidelberg, Berlin, Heidelberg, 1990, pp. 91–151, DOI: 10.1007/BFb0034365.
36 Z. Wang, in *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, Inc., 2010, DOI: 10.1002/9780470638859.conrr369.
37 H. Tanaka, M. Kuroboshi and S. Torii, in *Organic Electrochemistry, Fifth Edition Revised and Expanded*, ed. O. Hammerich and B. Speiser, CRC Press, Boca Raton, 2015, pp. 1267–1307.
38 L. Zhang, Z. Zhang, J. Hong, J. Yu, J. Zhang and F. Mo, *J. Org. Chem.*, 2018, **83**, 3200–3207.
39 D. E. Corbridge, *Phosphorus: chemistry, biochemistry and technology*, CRC Press, 2016.
40 M. A. Sogorb and E. Vilanova, *Toxicol. Lett.*, 2002, **128**, 215–228.
41 T. Baumgartner and R. Réau, *Chem. Rev.*, 2006, **106**, 4681–4727.
42 J.-H. Xie and Q.-L. Zhou, *Acc. Chem. Res.*, 2008, **41**, 581–593.
43 Y. Park, J. Seo, S. Park, E. J. Yoo and P. H. Lee, *Chem. – Eur. J.*, 2013, **19**, 16461–16468.
44 T. Ryu, J. Kim, Y. Park, S. Kim and P. H. Lee, *Org. Lett.*, 2013, **15**, 3986–3989.
45 J. Seo, Y. Park, I. Jeon, T. Ryu, S. Park and P. H. Lee, *Org. Lett.*, 2013, **15**, 3358–3361.
46 P. Youngchul, S. Jungmin, P. Sangjune, Y. E. Jeong and L. P. Ho, *Chem. – Eur. J.*, 2013, **19**, 16461–16468.
47 Y. Unoh, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2013, **52**, 12975–12979.
48 D. Zhao, C. Nimphius, M. Lindale and F. Glorius, *Org. Lett.*, 2013, **15**, 4504–4507.
49 S. Shin, D. Kang, W. H. Jeon and P. H. Lee, *Beilstein J. Org. Chem.*, 2014, **10**, 1220–1227.