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We herein report a versatile and environmentally friendly electrochemical oxidative C–H phosphonylation protocol. This protocol features a broad substrate scope; not only C(sp²)–H phosphonylation, but also C(sp³)–H phosphonylation is tolerated well under exogenous-oxidant-free and metal catalyst-free electrochemical oxidation conditions.

Phosphorus containing compounds are of much importance because they are widely found in a vast number of natural products, biological compounds, and agricultural chemicals,¹ as well as represent outstanding synthetic intermediates for the preparation of complex organic molecules.² As such, methods for the preparation of these valuable molecules are very important synthetic technologies. Over the past decades, considerable works have been conducted on the synthesis of significant phosphorus containing compounds.³ Compared with conventional synthetic methods that employed pre-functionalized aryl halides or arylboronic acids as the starting materials,⁴ direct C–H phosphonylation represents a much more attractive strategy for C–P bond formation.⁵ Although this strategy avoided the use of pre-functionalized starting materials and has achieved considerable development, most of the reported reactions still suffer from some drawbacks, such as the need for metal catalysts or stoichiometric oxidants. Therefore, developing a much more elegant method for producing phosphorus containing compounds under metal catalyst-free and exogenous-oxidant-free reaction conditions is urgently needed.

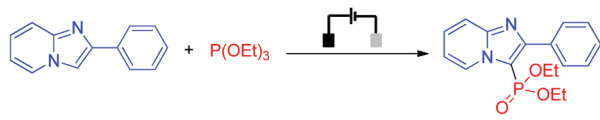
As an ideal alternative to chemical oxidants, electrochemical anodic oxidation provides an efficient and environmentally benign synthetic method for C–H functionalization.⁶ In this context, considerable progress has been made, such as in electrochemical

Exogenous-oxidant-free electrochemical oxidative C–H phosphonylation with hydrogen evolution†

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oxidative C–H amination,⁷ oxygenation,⁸ thiolation,⁹ alkylation,¹⁰ etc.¹¹ Nevertheless, electrochemical oxidative C–H phosphonylation is still underexplored.¹² As part of our recent research interest in the area of electrochemical oxidative C–H functionalization, we herein report an elegant and versatile electrochemical oxidative C–H phosphonylation protocol. Overall, the notable features of this reaction include the following: (1) neither a metal catalyst nor an exogenous-oxidant/additive is required; and (2) this protocol features a broad substrate scope – not only C(sp²)–H phosphonylation, but also C(sp³)–H phosphonylation is tolerated well under electrochemical conditions.

We initiated our studies by investigating the reaction of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) with triethyl phosphite (**2a**) because the imidazopyridine unit is a widely existing substructure in many commercially available drugs and the resultant C–H phosphonylation products may also have a potential utility in pharmaceutical chemistry (Table 1).¹³ To our delight, when the reaction was performed in an undivided cell employing a carbon rod as the anode and a platinum plate as the cathode as well as using ⁿBu₄NBF₄ as electrolyte, the reaction worked smoothly in

Table 1 Optimization of the reaction conditions^a


Entry	Electrolysis conditions	Yield ^b (%)
1	Carbon rod anode, platinum plate cathode, ⁿ Bu ₄ NBF ₄	70
2	Entry 1 but ⁿ Bu ₄ NClO ₄ as electrolyte	54
3	Entry 1 but ⁿ Bu ₄ NPF ₆ as electrolyte	77, 70 ^c
4	Entry 3 but nickel plate cathode	61
5	Entry 3 but carbon cloth anode	49
6	Entry 3 but no electric current	0

^a Reaction conditions: carbon rod anode, platinum plate cathode, undivided cell, **1a** (0.3 mmol), **2a** (0.6 mmol), ⁿBu₄NBF₄ (0.1 mmol), MeCN (10 mL), 50 °C, 4 mA, 6 h (3 F mol⁻¹). ^b Yields were determined by ³¹P NMR using PPh₃ as an internal standard. ^c Isolated yield.

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acetonitrile under a constant current of 4 mA, providing the desired C–H phosphonylation product **3a** in 70% NMR yield (Table 1, entry 1). At the same time, H₂ was also detected by GC-TCD. Further explorations showed that ⁿBu₄NPF₆ was a better choice for electrolyte, affording **3a** in 77% NMR yield and 70% isolated yield (Table 1, entries 2 and 3). In comparison, conducting the reaction with a nickel plate cathode or a carbon cloth anode showed decreased reaction efficiency (Table 1, entries 4 and 5). In addition, a control experiment showed that the constant current was crucial for the reaction (Table 1, entry 6) (for more details about optimization of reaction conditions, see the ESI[†]). Note that for some conditions with low yields, **1a** and its homo-coupling product were often observed.

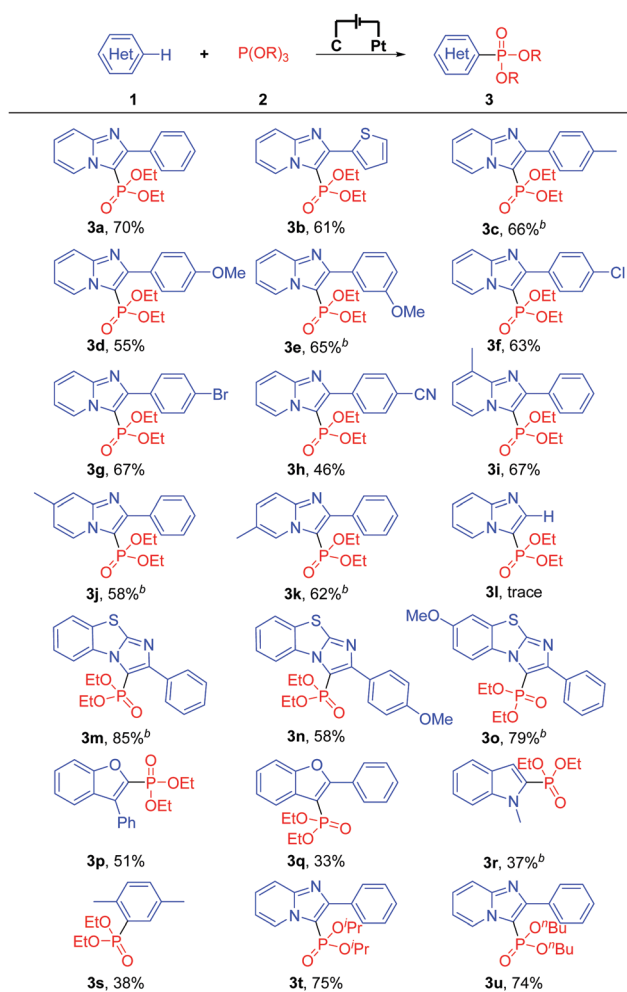
With the optimized reaction conditions in hand, the scope of the exogenous-oxidant-free electrochemical oxidative C(sp²)-H phosphonylation was subsequently explored. Initially, different heteroarenes were investigated. As shown in Table 2, 2-phenylimidazo[1,2-*a*]pyridine and 2-thiophenylimidazo[1,2-*a*]pyridine

could be transformed into the C–H phosphonylation products in 70% and 61% yields, respectively (Table 2, **3a** and **3b**). 2-Phenylimidazo[1,2-*a*]pyridines bearing both electron-donating groups and weak electron-withdrawing groups at the 2-phenyl moiety afforded the products in moderate to good yields (Table 2, **3c–3g**). In comparison, 2-phenylimidazo[1,2-*a*]pyridine with a strong electron-withdrawing group at the 2-phenyl moiety delivered the C(sp²)-H phosphonylation product in moderate yield (Table 2, **3h**). When 8-methyl, 7-methyl, and 6-methyl substituted imidazopyridines were treated with triethyl phosphite (**2a**), the corresponding products could still be obtained in moderate to good yields (Table 2, **3i–3k**). However, when using imidazo[1,2-*a*]pyridine as the substrate, only a trace amount of the C(sp²)-H phosphonylation product (Table 2, **3l**) was obtained; the reason for this may be that imidazo[1,2-*a*]pyridine has a relatively high oxidation potential and is not easily oxidized. It is worth noting that other heteroarenes such as important benzo[*d*]-imidazo[2,1-*b*]thiazole derivatives, 3-phenylbenzofuran, 2-phenylbenzofuran, *N*-methylindole, and *p*-xylene were also suitable for this reaction, affording the respective products in 33% to 85% yields (Table 2, **3m–3s**). Other phosphonylation reagents for this electrochemical oxidative C(sp²)-H phosphonylation protocol were investigated as well. Delightfully, despite the bulky steric hindrance or a long alkyl chain, P(OⁱPr)₃ and P(OⁿBu)₃ were well suitable for the reaction and afforded the C(sp²)-H phosphonylation products in 75% and 74% yields, respectively (Table 2, **3t** and **3u**). Note that for some examples with longer durations of electrolysis (Table 2, **3c**, **3e**, **3j**, **3k**, **3m**, **3o**, and **3r**), the reason for prolonging the duration of electrolysis is mainly to increase the conversion rates, thereby further improving the yields.

Subsequently, we turned our attention to the more challenging C(sp³)-H phosphonylation because no examples have been reported in which C(sp²)-H phosphonylation and C(sp³)-H phosphonylation were accomplished concurrently under similar or the same reaction conditions. Gratefully, under the electrochemical conditions, C(sp³)-H phosphonylation was also accomplished. As shown in Table 3, when xanthene and *N*-methyl-9,10-dihydroacridine were employed as substrates, the reaction worked smoothly and afforded the corresponding C(sp³)-H phosphonylation products in 87% and 74% yields, respectively (Table 3, **5a** and **5b**). Besides, an *N,N*-dimethylaniline derivative and *N*-phenyl tetrahydroisoquinoline were also compatible with the reaction conditions (Table 3, **5c** and **5d**). Notably, other phosphonylation reagents such as P(OMe)₃, P(OⁿBu)₃, P(OC₂H₄Cl)₃, and even diphenylphosphine oxide all were suitable substrates and afforded the C(sp³)-H phosphonylation products in good to high yields (Table 3, **5e–5h**). Unfortunately, only a trace amount of the product was detected when P(OⁱPr)₃ was applied as a substrate, possibly because of its bulky steric hindrance.

To demonstrate the practicality of this electrochemical oxidative C–H phosphonylation, reactions of P(OEt)₃ with **1a** and **4a** on a 6.0 mmol scale were performed. The reactions worked smoothly and afforded the corresponding C–H phosphonylation products in 55% and 50% yields (for more details about gram scale synthesis, see the ESI[†]), respectively.

Table 2 Substrate scope for electrochemical oxidative C(sp²)-H phosphonylation^a



^a Reaction conditions: carbon rod anode, platinum plate cathode, undivided cell, **1** (0.3 mmol), **2** (0.6 mmol), ⁿBu₄NPF₆ (0.1 mmol), MeCN (10 mL), 50 °C, 4 mA, 6 h (3 F mol⁻¹), isolated yield. ^b 8 h (4 F mol⁻¹).

Notes and references

- 1 (a) M. Pramanik, N. Chatterjee, S. Das, K. D. Saha and A. Bhaumik, *Chem. Commun.*, 2013, **49**, 9461–9463; (b) X. Chen, D. J. Kopecky, J. Mihalic, S. Jeffries, X. Min, J. Heath, J. Deignan, S. Lai, Z. Fu, C. Guimaraes, S. Shen, S. Li, S. Johnstone, S. Thibault, H. Xu, M. Cardozo, W. Shen, N. Walker, F. Kayser and Z. Wang, *J. Med. Chem.*, 2012, **55**, 3837–3851; (c) E. A. Wydysh, S. M. Medghalchi, A. Vadlamudi and C. A. Townsend, *J. Med. Chem.*, 2009, **52**, 3317–3327; (d) K. Moonen, I. Laureyn and C. V. Stevens, *Chem. Rev.*, 2004, **104**, 6177–6216.
- 2 (a) R. M. Yebeutchou, F. Tancini, N. Demitri, S. Geremia, R. Mendichi and E. Dalcanale, *Angew. Chem., Int. Ed.*, 2008, **47**, 4504–4508; (b) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029–3070; (c) M. R. Hamden, A. Parkin, M. J. Parratt and R. M. Perkins, *J. Med. Chem.*, 1993, **36**, 1343–1355; (d) T. Minami and J. Motoyoshiya, *Synthesis*, 1992, 333–349.
- 3 (a) X. Ma, Q. Xu, H. Li, C. Su, L. Yu, X. Zhang, H. Cao and L.-B. Han, *Green Chem.*, 2018, **20**, 3408–3413; (b) L. Niu, J. Liu, H. Yi, S. Wang, X.-A. Liang, A. K. Singh, C.-W. Chiang and A. Lei, *ACS Catal.*, 2017, **7**, 7412–7416; (c) R. E. Islas and J. J. Garcia, *ChemCatChem*, 2017, **9**, 4125–4131; (d) S. Wang, D. Qiu, F. Mo, Y. Zhang and J. Wang, *J. Org. Chem.*, 2016, **81**, 11603–11611; (e) S.-Y. Chen, R.-S. Zeng, J.-P. Zou and O. T. Asekun, *J. Org. Chem.*, 2014, **79**, 1449–1453.
- 4 (a) I. Ghosh, R. S. Shaikh and B. König, *Angew. Chem., Int. Ed.*, 2017, **56**, 8544–8549; (b) R. S. Shaikh, S. J. S. Düsel and B. König, *ACS Catal.*, 2016, **6**, 8410–8414; (c) R. A. Dhokale and S. B. Mhaske, *Org. Lett.*, 2013, **15**, 2218–2221; (d) G. Yang, C. Shen, L. Zhang and W. Zhang, *Tetrahedron Lett.*, 2011, **52**, 5032–5035; (e) C. S. Demmer, N. Krogsgaard-Larsen and L. Bunch, *Chem. Rev.*, 2011, **111**, 7981–8006; (f) Y.-L. Zhao, Y. Li, S.-M. Li, Y.-G. Zhou, F.-Y. Sun, L.-X. Gao and F.-S. Han, *Adv. Synth. Catal.*, 2011, **353**, 1543–1550; (g) R. Zhuang, J. Xu, Z. Cai, G. Tang, M. Fang and Y. Zhao, *Org. Lett.*, 2011, **13**, 2110–2113.
- 5 (a) J. Wang, J. Li, Y. Wei, J. Yang and C. Huo, *Org. Chem. Front.*, 2018, **5**, 3534–3537; (b) Q. Chen, X. Wang, G. Yu, C. Wen and Y. Huo, *Org. Chem. Front.*, 2018, **5**, 2652–2656; (c) R. S. Shaikh, I. Ghosh and B. König, *Chem. – Eur. J.*, 2017, **23**, 12120–12124; (d) Q. Gui, L. Hu, X. Chen, J. Liu and Z. Tan, *Chem. Commun.*, 2015, **51**, 13922–13924; (e) M. Yadav, S. Dara, V. Saikam, M. Kumar, S. K. Aithagani, S. Paul, R. A. Vishwakarma and P. P. Singh, *Eur. J. Org. Chem.*, 2015, 6526–6533; (f) D. Zhao, C. Nimphius, M. Lindale and F. Glorius, *Org. Lett.*, 2013, **15**, 4504–4507.
- 6 (a) N. Saueremann, T. H. Meyer, Y. Qiu and L. Ackermann, *ACS Catal.*, 2018, **8**, 7086–7103; (b) M. D. Kärkäs, *Chem. Soc. Rev.*, 2018, **47**, 5786–5865; (c) Y. Zhao and W. Xia, *Chem. Soc. Rev.*, 2018, **47**, 2591–2608; (d) C. Ma, P. Fang and T.-S. Mei, *ACS Catal.*, 2018, **8**, 7179–7189; (e) S. Tang, Y. Liu and A. Lei, *Chem.*, 2018, **4**, 27–45; (f) A. Jutand, *Chem. Rev.*, 2008, **108**, 2300–2347.
- 7 (a) P. Qian, Z. Yan, Z. Zhou, K. Hu, J. Wang, Z. Li, Z. Zha and Z. Wang, *Org. Lett.*, 2018, **20**, 6359–6363; (b) Y. Qiu, J. Struwe, T. H. Meyer, J. C. A. Oliveira and L. Ackermann, *Chem. – Eur. J.*, 2018, **24**, 12784–12789; (c) X. Gao, P. Wang, L. Zeng, S. Tang and A. Lei, *J. Am. Chem. Soc.*, 2018, **140**, 4195–4199; (d) X. Hu, G. Zhang, F. Bu, L. Nie and A. Lei, *ACS Catal.*, 2018, **8**, 9370–9375; (e) S. Tang, S. Wang, Y. Liu, H. Cong and A. Lei, *Angew. Chem., Int. Ed.*, 2018, **57**, 4737–4741; (f) Q.-L. Yang, X.-Y. Wang, J.-Y. Lu, L.-P. Zhang, P. Fang and T.-S. Mei, *J. Am. Chem. Soc.*, 2018, **140**, 11487–11494; (g) N. Saueremann, R. Mei and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 5090–5094; (h) 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;
- (i) J. Wu, Y. Zhou, Y. Zhou, C.-W. Chiang and A. Lei, *ACS Catal.*, 2017, **7**, 8320–8323; (j) W.-J. Gao, W.-C. Li, C.-C. Zeng, H.-Y. Tian, L.-M. Hu and R. D. Little, *J. Org. Chem.*, 2014, **79**, 9613–9618;
- (k) T. Morofuji, A. Shimizu and J.-I. Yoshida, *J. Am. Chem. Soc.*, 2014, **136**, 4496–4499; (l) S.-K. Zhang, R. C. Samanta, N. Saueremann and L. Ackermann, *Chem. – Eur. J.*, 2018, **24**, 19166–19170; (m) Y. Yu, Y. Yuan, H. Liu, M. He, M. Yang, P. Liu, B. Yu, X. Dong and A. Lei, *Chem. Commun.*, 2019, **55**, 1809–1812.
- 8 (a) A. Shao, N. Li, Y. Gao, J. Zhan, C.-W. Chiang and A. Lei, *Chin. J. Chem.*, 2018, **36**, 619–624; (b) X.-Z. Tao, J.-J. Dai, J. Zhou, J. Xu and H.-J. Xu, *Chem. – Eur. J.*, 2018, **24**, 6932–6935; (c) S. Zhang, L. Li, H. Wang, Q. Li, W. Liu, K. Xu and C. Zeng, *Org. Lett.*, 2018, **20**, 252–255; (d) L. Li, Q. Yang, Z. Jia and S. Luo, *Synthesis*, 2018, 2924–2929; (e) F. Wang, M. Rafiee and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2018, **57**, 6686–6690; (f) 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; (g) F. Xu, X.-Y. Qian, Y.-J. Li and H.-C. Xu, *Org. Lett.*, 2017, **19**, 6332–6335; (h) Y.-Q. Li, Q.-L. Yang, P. Fang, T.-S. Mei and D. Zhang, *Org. Lett.*, 2017, **19**, 2905–2908; (i) N. Saueremann, T. H. Meyer, C. Tian and L. Ackermann, *J. Am. Chem. Soc.*, 2017, **139**, 18452–18455; (j) L. Meng, J. Su, Z. Zha, L. Zhang, Z. Zhang and Z. Wang, *Chem. – Eur. J.*, 2013, **19**, 5542–5545.
- 9 (a) Y. Yuan, Y. Cao, J. Qiao, Y. Lin, X. Jiang, Y. Yeng, S. Tang and A. Lei, *Chin. J. Chem.*, 2019, **37**, 49–52; (b) Y. Yuan, Y. Yu, J. Qiao, P. Liu, B. Yu, W. Zhang, H. Liu, M. He, Z. Huang and A. Lei, *Chem. Commun.*, 2018, **54**, 11471–11474; (c) A. A. Folgueiras-Amador, X.-Y. Qian, H.-C. Xu and T. Wirth, *Chem. – Eur. J.*, 2018, **24**, 487–491; (d) X.-Y. Qian, S.-Q. Li, J. Song and H.-C. Xu, *ACS Catal.*, 2017, **7**, 2730–2734; (e) P. Wang, S. Tang, P. Huang and A. Lei, *Angew. Chem., Int. Ed.*, 2017, **56**, 3009–3013; (f) P. Wang, S. Tang and A. Lei, *Green Chem.*, 2017, **19**, 2092–2095; (g) M.-L. Feng, L.-Y. Xi, S.-Y. Chen and X.-Q. Yu, *Eur. J. Org. Chem.*, 2017, 2746–2750; (h) S. H. Kim, K. H. Kim, J. W. Lim and J. N. Kim, *Tetrahedron Lett.*, 2014, **55**, 531–534; (i) V. A. Kokorekin, V. L. Sigacheva and V. A. Petrosyan, *Tetrahedron Lett.*, 2014, **55**, 4306–4309.
- 10 (a) Z.-J. Wu, S.-R. Li, H. Long and H.-C. Xu, *Chem. Commun.*, 2018, **54**, 4601–4604; (b) Q.-L. Yang, C.-Z. Li, L.-W. Zhang, Y.-Y. Li, X. Tong, X.-Y. Wu and T.-S. Mei, *Organometallics*, 2019, DOI: 10.1021/acs.organomet.8b00550; (c) C. Ma, C.-Q. Zhao, Y.-Q. Li, L.-P. Zhang, X.-T. Xu, K. Zhang and T.-S. Mei, *Chem. Commun.*, 2017, **53**, 12189–12192; (d) Z.-J. Wu and H.-C. Xu, *Angew. Chem., Int. Ed.*, 2017, **56**, 4734–4738; (e) N. Fu, L. Li, Q. Yang and S. Luo, *Org. Lett.*, 2017, **19**, 2122–2125; (f) H. Gao, Z. Zha, Z. Zhang, H. Ma and Z. Wang, *Chem. Commun.*, 2014, **50**, 5034–5036; (g) Y. B. Dudkina, D. Y. Mikhaylov, T. V. Gryaznova, O. G. Sinyashin, D. A. Vivic and Y. H. Budnikova, *Eur. J. Org. Chem.*, 2012, 2114–2117.
- 11 (a) A. Wiebe, S. Lips, D. Schollmeyer, R. Franke and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2017, **56**, 14727–14731; (b) X. Zhang, C. Wang, H. Jiang and L. Sun, *Chem. Commun.*, 2018, **54**, 8781–8784.
- 12 (a) F. Effenberger and H. Kottmann, *Tetrahedron*, 1985, **41**, 4171–4182; (b) T. V. Grayaznova, Y. B. Dudkina, D. R. Islamov, O. N. Kataeva, O. G. Sinyashin, D. A. Vivic and Y. H. Budnikova, *J. Organomet. Chem.*, 2015, **785**, 68–71.
- 13 (a) C. Hamdouchi, J. de Blas, M. del Prado, J. Gruber, B. A. Heinz and L. Vance, *J. Med. Chem.*, 1999, **42**, 50–59; (b) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba and W. Murmann, *J. Med. Chem.*, 1965, **8**, 305–312; (c) S. Boggs, V. I. Elitzin, K. Gudmundsson, M. T. Martin and M. J. Sharp, *Org. Process Res. Dev.*, 2009, **13**, 781–785.