Energy-, time-, and labor-saving synthesis of α-ketiminophosphonates: Machine-learning-assisted simultaneous multiparameter screening for electrochemical oxidation

Journal:	*Green Chemistry*
Manuscript ID	GC-ART-05-2021-001583.R1
Article Type:	Paper
Date Submitted by the Author:	26-Jun-2021
Complete List of Authors:	Kondo, Masaru; Osaka University ISIR; Ibaraki University College of Engineering, Department of Materials Science and Engineering Sugizaki, Akimasa; Osaka University ISIR Khalid, Md. Imrul; Osaka University ISIR Wathsala, H. D. P.; Osaka University, The Institute of Scientific and Industrial Research Ishikawa, Kazunori; Osaka University, The Institute of Scientific and Industrial Research Hara, Satoshi; Osaka Daigaku, The Institute of Scientific and Industrial Research Takaai, Takayuki; Osaka University Washio, Takashi; Osaka University Takizawa, Shinobu; Osaka University, ISIR Sasai, Hiroaki; The Institute of Scientific and Industrial Research, Osaka University, Department of Synthetic Organic Chemistry

Journal Name

ARTICLE

Energy-, time-, and labor-saving synthesis of α-ketiminophosphonates: Machine-learning-assisted simultaneous multiparameter screening for electrochemical oxidation

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Masaru Kondo[a,d], Akimasa Sugizaki[a], Md. Imrul Khalid[a], H. D. P. Wathsala[a], Kazunori Ishikawa[b], Satoshi Hara[b], Takayuki Takaai [b], Takashi Washio*[b,c], Shinobu Takizawa*[a,c], Hiroaki Sasai*[a,c]

A highly efficient synthesis of α-ketiminophosphonates has been established for the electrochemical oxidation of α-amino phosphonates with the utilization of machine-learning-assisted simultaneous multiparameter screening. After brief experimental screening, the Bayesian optimization with the experimental data (up to 12 entries) could rapidly predict the optimal conditions for the synthesis of α-ketiminophosphonates and sulfonyl ketimines with aryl and alkyl groups. The obtained α-ketiminophosphonates could be converted into highly functionalized α-amino acid analogues with a tetrasubstituted carbon center.

Introduction

Imines are attractive synthetic intermediates because an addition of various nucleophiles to the imines produces highly functionalized amines.[1] Among them, α-iminophosphonates[2] are important precursors for the synthesis of α-amino phosphoric acid motifs that can function as isosteric or bioisosteric analogues of the corresponding amino acids, exhibiting biological properties such as antimicrobial,[3] antioxidant,[4] and anticancer activities.[5] The condensation reaction of α-ketophosphonates with amines, and chemical oxidation of α-amino phosphonates are well-known approaches for the synthesis of α-ketiminophosphonates.[6] Arbuzov reaction[7] and aza-Wittig reaction[8] has also provided α-ketiminophosphonates (Fig. 1a). However, these reactions have some potential drawbacks such as the requirement for excess amount of reagents (e.g., oxidants such as trichloroisocyanuric acid (TCCA), MnO_2, and nucleophiles such as phosphites) and reflux conditions. In contrast, the electrochemical oxidative dehydrogenation processes have many advantages. They can decrease the amount of an external oxidant, resulting in lower or no chemical waste derived from the oxidant. In addition, their oxidative transformation can be conducted under mild reaction conditions.[9] Recently, Zeng and Ruan independently presented the electrochemical oxidative C-H phosphorylation of aldimine derivatives such as quinoxalin-2(1H)-ones[10] and hydrazones[11] for the first time.[12] However, the selective oxidation of amine derivatives to the corresponding ketimines is still a challenging task because of their ready over-oxidation.[13] Several methodologies for the optimization of an electrochemical reaction have been developed to accelerate the optimization[14] (e.g. design of experiments,[14a-e] statistical methods,[14f,g] and multivariate linear regression analysis[14h-k]). Herein, we report a facile electrochemical synthesis of α-ketiminophosphonates with machine-learning (ML)-assisted reaction conditions screening based on Bayesian optimization (BO) strategy (Fig. 1b). Notable advantages of our approach Notable advantages of our approach include (i) external oxidant free synthesis of α-ketiminophosphonates under air and mild conditions; (ii) saving energy, time, and labor for the reaction optimization; (iii) a broad substrate scope, affording various sulfonyl ketimines bearing phosphonyl, aryl, and alkyl groups.

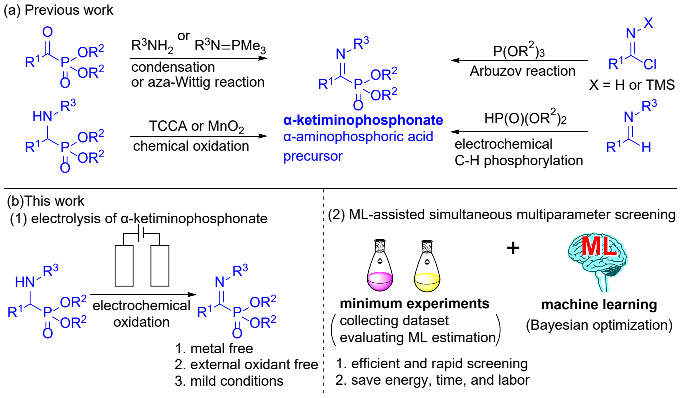


Fig. 1. Synthesis of α–ketiminophosphonate: (a) Previously reported methods; (b) electrochemical approach with machine-learning (ML)-assisted screening

To improve the efficiency of reaction optimization, automated[15] and computational[16] approaches have been attracting increasing interest in the field of organic synthesis. Recently, our group demonstrated that a Gaussian process regression (GPR) as ML accelerates the

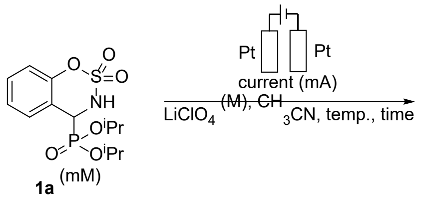
---

[a] Department of Synthetic Organic Chemistry, The Institute of Scientific and Industrial Research (SANKEN), Osaka University, Mihogaoka, Ibaraki, Osaka 567-0047, Japan
E-mail: taki@sanken.osaka-u.ac.jp, sasai@sanken.osaka-u.ac.jp
[b] Department of Reasoning for Intelligence, SANKEN, Osaka University
E-mail: washio@ar.sanken.osaka-u.ac.jp
[c] Artificial Intelligence Research Center, SANKEN, Osaka University
[d] Department of Materials Science and Engineering , Graduate School of Science and Engineering, Ibaraki University, Hitachi 316-8511, Ibaraki, Japan
Electronic Supplementary Information (ESI) available:
DOI: 10.1039/x0xx00000x

multiparameter screening of an enantioselective organocatalyzed domino reaction under flow-reaction conditions.[17] Because the established method was limited to two-parameter screening to minimize the number of experiments and visualize a regression model, our interest shifted to BO as an ML-approach to evaluate more than two-dimensional parameters. BO is a powerful probabilistic method to determine the maximum (or the minimum) of a black-box objective function based on the Bayesian approach using a dataset collected in the previous sampling and ML-modeling iteration.[18] BO can not only search around a probable maximum (*exploitation*), but also escape from a local maximum (or the minimum) by searching a value of unexplored black-box object function (*exploration*).[19] Furthermore, BO estimates the next parameters to search based on the Gaussian process modelling of a collected experimental dataset and the maximization of the acquisition function.[20] Then, the estimated parameters are evaluated by performing a practical experiment, subsequently the newly obtained dataset is reapplied to the above-mentioned ML process again. Finally, the appropriate reaction parameters affording a good result are predicted through the iteration of the ML estimation and experimental evaluation. Owing to its utility and versatility, BO has been applied to various research fields such as material sciences,[21] drug discovery,[22] and theoretical chemistry.[16c,23] To the best of our knowledge, this is the first report on BO-assisted rapid multiparameter screening for electrochemical syntheses.

Result and Discussion

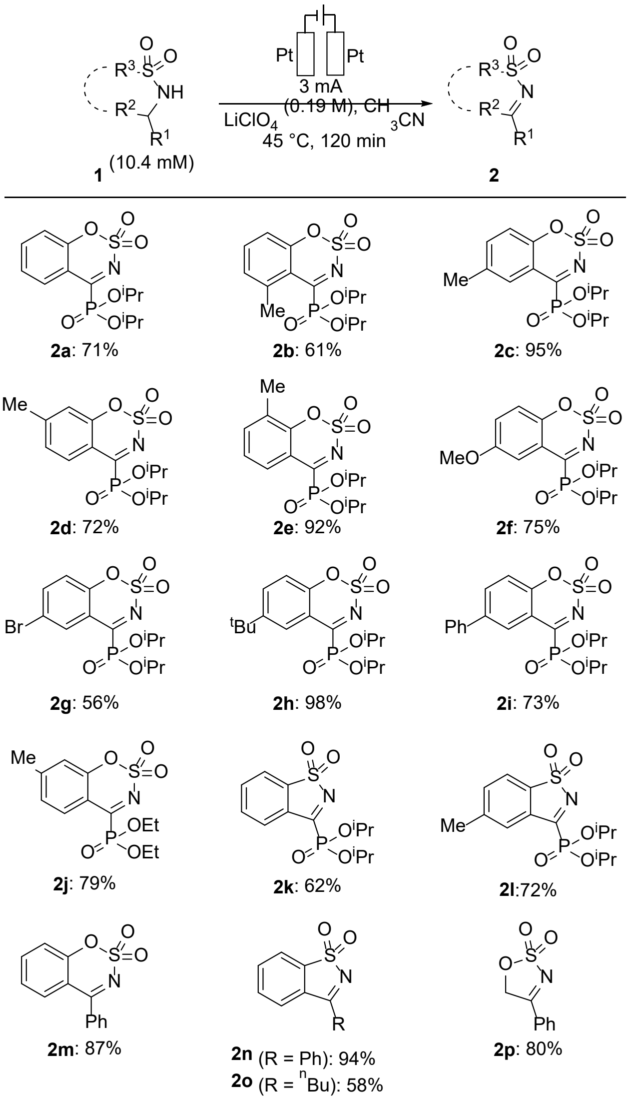
Table 1. BO-assisted multiparameter screening for suitable reaction conditions for electrochemical oxidation using **1a**[a]



entry	current (mA)	**1a** (mM)	$LiClO_4$ (M)	Temp. (°C)	Time (min)	NMR yield (%)[b]
1	1	10	0.05	60	180	8
2	2	20	0.2	25	60	16
3	3	10	0.1	40	120	65
4	4	15	0.1	40	60	38
5	5	5	0.05	25	120	26
6	4	11	0.22	50	130	60
7	3	11	0.13	45	120	66
8	1	18	0.05	45	120	3
9	3	9.7	0.12	45	120	65
10	5	10	0.21	45	120	41
11	2	10	0.06	45	120	50
12	**3**	**10.4**	**0.19**	**45**	**120**	**72** (71)[c]

[a]Reaction conditions: Undivided cell, Pt anode, Pt cathode, **1a**, $LiClO_4$, CH_3CN (6 mL), under air. [b]1,3,5-Trimethoxybenzene was used as an internal standard. [c]Isolated yield

Initially, a brief reaction conditions screening with α–amino phosphonate **1a** as a prototypical substrate was conducted for the following fundamental conditions (electrode: Pt electrode for the anode and cathode, solvent: CH_3CN, electrolyte: $LiClO_4$) (see Supplementary Table S1).[24] To accomplish multiple numeric parameter screening and optimization of the electrochemical oxidation reaction conditions, we carried out five reactions to screen five parameters: current (1–5 mA), concentrations of **1a** (5–20 mM) and $LiClO_4$ (0.05–0.2 M), temperature (25–60 °C), reaction time (60–180 min) (Table 1, entries 1–5). After estimating five different reaction conditions and the resulting yields (entries 1–5), BO was used to propose the reaction conditions (current: 4 mA, concentration of **1a**: 11 mM, and $LiClO_4$: 0.22 M, temperature: 50 °C, reaction time: 130 min) for the next investigation (entry 6).[25] Using the BO-suggested parameters, the desired product **2a** was obtained in 60% yield. On the basis of the six datasets (entries 1–6), the conditions to produce **2a** in 66% yield were proposed based on the *exploitation* (entry 7). The *exploitation* and *exploration* on BO were repeatedly conducted (entries 8–11). Finally, we performed 12 reactions to determine the appropriate reaction conditions (entry 12,



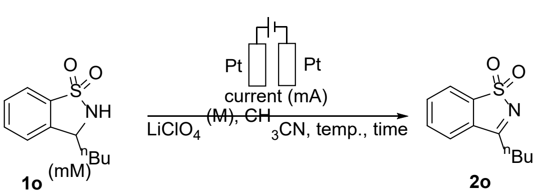
[a]Reaction conditions: Undivided cell, Pt anode, Pt cathode, **1a** (0.0702 mmol), $LiClO_4$ (1.14 mmol), CH_3CN (6 mL), 120 min, constant current = 3 mA, 45 °C, under air. Isolated yield.

Scheme 1. Substrate scope for electrochemical oxidation of sulfonamides **1**[a].

current: 3 mA, concentration of **1a**: 10.4 mM, and $LiClO_4$: 0.19 M, temperature: 45 °C, reaction time: 120 min) to increase the isolated yield of **2a** to 71% (current efficiency = 40%).[26]

After estimating the optimal conditions, we investigated the substrate scope of the electrochemical oxidation reaction of **1** (Scheme 1). The electrochemical oxidation of 5-, 6-, 7-, and 8-methylated substrates **1b–1e** afforded the corresponding products **2b–2e** in 61–95% yields (38-59% current efficiency). Both electron-rich and electron-deficient substrates **1f** and **1g**, respectively, could be used, affording the α-ketiminophosphonates (**2f**: 75% yield; **2g**: 56 % yield). α-Amino phosphonates **1h** and **1i** with sterically bulky substituents such as *tert*-butyl and phenyl groups were smoothly converted into the desired imines **2h** and **2i** in 98% and 73% yields, respectively. Substrate **1j**, derived from diethyl phosphonate, was also tolerated under these conditions (**2j**: 79% yield). When the non- and methyl-substituted 5-membered cyclic compounds **1k** and **1l** were used, the desired products **2k** and **2l** were obtained in 62% and 72% yields, respectively. To further extend the substrate generality, we evaluated sulfonamides **1m–1p** bearing aryl and alkyl groups instead of phosphonyl group.[27] 6-Membered sulfonamide **1m** was suitable for this transformation, affording the desired product **2m** in 87% yield. The electrochemical reaction with 5-memberd substrates **1n–1p**, including aliphatic substrates, provided the corresponding products **2n–2p** in 58–94% yields.

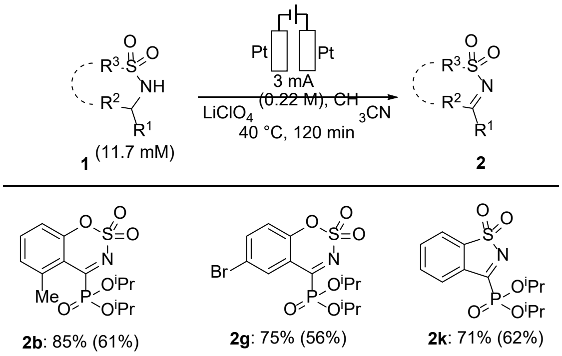
Table 2. BO-assisted multiple parameter rescreening for suitable reaction conditions for electrochemical oxidation using **1o**[a]



entry	current (mA)	**1o** (mM)	$LiClO_4$ (M)	Temp. (°C)	Time (min)	NMR yield (%)[b]
1	1	10	0.05	60	180	46
2	2	20	0.2	25	60	22
3	3	10	0.1	40	120	62
4	4	15	0.1	40	60	53
5	5	5	0.05	25	120	14
6	4	10	0.12	60	180	29
7	**3**	**11.7**	**0.22**	**40**	**120**	**67 (66)**[c]

[a]Reaction conditions: Undivided cell, Pt anode, Pt cathode, **1o**, $LiClO_4$, CH_3CN (6 mL), under air. [b]1,3,5-Trimethoxybenzene was used as an internal standard. [c]Isolated yield.

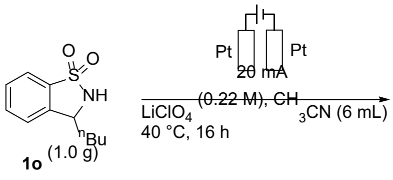
Although most of substrates **1** were successfully converted into the desired ketimines **2** (Scheme 1), the yields of some products (**2b**, **2g**, **2k**, and **2o**) still remained low (56–62%) because of the formation of a small amount of by-products.[13] Thus, to determine suitable reaction conditions to improve the chemical yields, we performed the BO-assisted multiple parameter rescreening using substrate **1o** as a model substrate (Table 2 and Supplementary Table S3). The experimental dataset (Table 2, entries 1–5) was collected under the same reaction conditions as those listed in Table 1 (entries 1–5). To our delight, when BO (*exploitation* and *exploration*) and experimental evaluation were performed twice, the isolated yield of product **2o** was improved to 66% (current efficiency = 42%) (Table 2, entry 7) from 58% (Scheme 1). The newly established reaction conditions (Table 2, entry 7) could increase yields of **2b** (from 61% to 85%), **2g** (from 56% to 75%), and **2k** (from 62% to 71 %) as shown in Scheme 2.



[a]Reaction conditions: Undivided cell, Pt anode, Pt cathode, **1a** (0.0684 mmol), $LiClO_4$ (1.32 mmol), CH_3CN (6 mL), 120 min, constant current = 3 mA, 40 °C, under air. Isolated yield. In parentheses, isolated yields are shown under the optimal conditions established in Table 1.

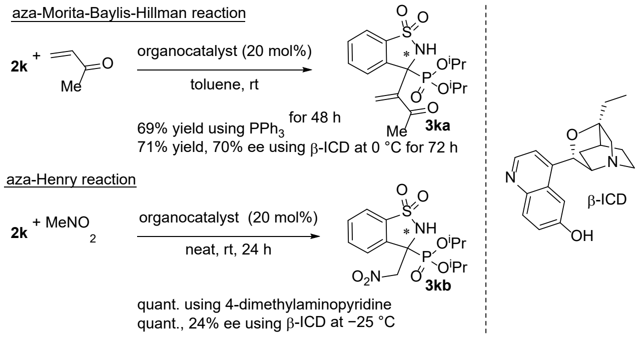
Scheme 2. Electrochemical oxidation of the substrates **1b**, **1g**, and **1k** under newly established reaction conditions listed in Table 2[a].

When the electrochemical oxidation of **1o** was carried out in one-gram scale at a higher current (20 mA) and longer reaction time (16 h), the desired product **2o** was obtained in 53% yield (current efficiency = 39%) (Scheme 3).

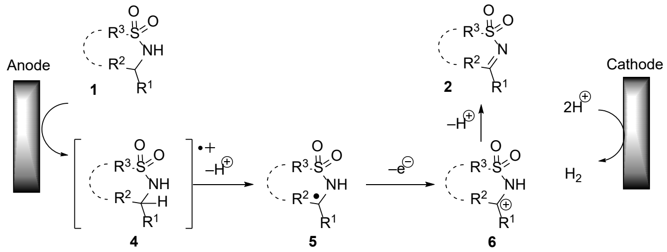


Scheme 3. Electrochemical synthesis of **2o** using one gram of **1o**

To demonstrate the utility of the obtained α-ketiminophosphonates **2**, a no-metal-catalyzed synthesis of highly functionalized α-amino phosphonates was performed (Scheme 4, Supplementary Table S4).[2b,28] Among the carbon–carbon bond-forming reactions studied, we found that the aza-Morita-Baylis-Hillman reaction[29] and aza-Henry reaction[30] of **2k** afforded the corresponding α-amino acid analogues **3ka** and **3kb** with a tetrasubstituted carbon center in 69% and quantitative yields, respectively. Enantioenriched products **3** (**3ka**: 70% ee, **3kb**: 24% ee) were also obtained when β-ICD was utilized as a chiral organocatalyst.[31]



Scheme 4. No-metal-catalyzed synthesis of highly functionalized α-amino phosphonates **3**



Scheme 5. A plausible reaction mechanism of electrochemical oxidation of sulfonamide **1**

A plausible reaction mechanism is proposed as illustrated in Scheme 5. Initially, the radical cation intermediate **4** was generated through the anodic oxidation of **1**. Subsequently, deprotonation of **4** provides the radical intermediate **5**, which can be oxidized to the cation intermediate **6**. Finally, the desired product **2** is obtained by the deprotonation of **6**. At the cathode, the proton is reduced to molecular hydrogen. Cyclic voltammetry (CV) analysis of **1n** was carried out to gain further insights into the proposed reaction mechanism (see Supplementary Fig. S2).[32] Two oxidation peaks (2.1 V and 2.4 V would indicate the first anodic oxidation from **1n** to **4n** and the second reaction from **5n** to **6n**, respectively (electrolyte: $LiClO_4$, vs. $Ag/AgNO_3$) (see Supplementary Fig. S2A).[33]

Conclusions

We demonstrated a highly efficient, metal- and chemical oxidant-free electrolytic dehydrogenative synthesis of cyclic sulfonyl ketimines bearing phosphonyl, aryl, or alkyl groups. The BO and experimental assessment using positive and negative results were successfully combined to accomplish the simultaneous multiparameter screening. In addition to the minimized chemical waste, the present approach saves time and energy, and also simplifies many practical aspects. Further practical applications of BO in organic synthesis and the application of **2** in fine chemical synthesis are underway in our laboratory and the results will be reported in due course. After preparation of this manuscript, a paper by Doyle and co-workers was published, in which the first BO-assisted reaction optimization for the transformation of alcohols such as Mitsunobu reaction and deoxyfluorination.[34]

Conflicts of interest

There are no conflicts of interest to declare.

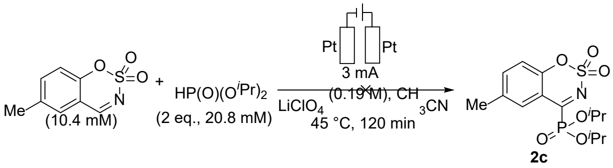
Acknowledgements

This work was supported by JSPS KAKENHI Grant Numbers JP18K14221 in Early-Career Scientists, JP18KK0154 in Promotion of Joint International Research (Fostering Joint International Research (B)), JST CREST Grant Number JPMJCR1666, JPMJCR20R1, Iketani Science and Technology Foundation, Research Foundation for Opto-Science and Technology, Daiichi Sankyo Foundation of Life, Hoansha Foundation, the Iwatani Naoji Foundation, the NOVARTIS Foundation (Japan) for the Promotion of Science, Kansai Research Foundation for Technology Promotion, and AIRC-Grant 2019. We acknowledge the technical staff of the Comprehensive Analysis Center of SANKEN, Osaka University (Japan).

Notes and references

1. For selected reviews, see: (*a*) A. Ting and S. E. Schaus, *Eur. J. Org. Chem.*, 2007, **2007**, 5797–5815; (*b*) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg and F. P. J. T. Rutjes, *Chem. Soc. Rev.*, 2008, **37**, 29–41; (*c*) B. Karimi, D. Enders and E. Jafari, *Synthesis*, 2013, **45**, 2769–2812; (*d*) J. Iwanejko and E. Wojaczyńska, *Org. Biomol. Chem.*, 2018, **16**, 7296–7314; (*e*) D.-J. Cheng and Y.-D. Shao, *ChemCatChem*, 2019, **11**, 2575–2589.
2. For selected reviews, see: (*a*) J. Vicario, D. Aparicio and F. Palacios, *Phosphorus Sulfur Silicon Relat. Elem.*, 2011, **186**, 638–643; (*b*) A. Maestro, E. M. de Marigorta, F. Palacios and J. Vicario, *Asian J. Org. Chem.*, 2020, **9**, 538–548.
3. (*a*) J.-Y. Che, X.-Y. Xu, Z.-L. Tang, Y.-C. Gu and D.-Q. Shi, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 1310–1313; (*b*) M. V. N. Reddy, A. Balakrishna, M. A. Kumar, G. C. S. Reddy, A. U. R. Sankar, C. S. Reddy and T. M. Krishna, *Chem. Pharm. Bull.,* 2009, **57**, 1391–1395.
4. (*a*) K. U. M. Rao, S. Swapna, D. M. Manidhar, K. M. K. Reddy and C. S. Reddy, *Phosphorus Sulfur Silicon Relat. Elem.,* 2015, **190**, 232–239; (*b*) R. Damiche and S. Chafaa, *J. Mol. Struct.,* 2017, **1130**, 1009–1017.
5. (*a*) G.-Y. Yao, M.-Y. Ye, R.-Z. Huang, Y.-J. Li, Y.-M. Pan, Q. Xu, Z.-X. Liao and H.-S. Wang, *Bioorg. Med. Chem. Lett.,* 2014, **24**, 501–507; (*b*) Q. Wang, L. Yang, H. Ding, X. Chen, H. Wang and X. Tang, *Bioorg. Chem.,* 2016, **69**, 132–139.
6. (*a*) Y. V. Rassukana, P. P. Onys'ko, K. O. Davydova and A. D. Sinitsa, *Eur. J. Org. Chem.* 2004, **2004**, 3643–3649; (*b*) J. Vicario, J. M. Ezpeleta and F. Palacios, *Adv. Synth. Catal.,* 2012, **354**, 2641–2647; (*c*) Z. Yan, B. Wu, X. Gao, M.-W. Chen and Y.-G. Zhou, *Org. Lett.,* 2016, **18**, 692–695.
7. (*a*) G. A. Flynn, D. W. Beight, E. H. W. Bhome and B. W. Metcalf, *Tetrahedron Lett.,* 1985, **26**, 285–288; (*b*) W. Huang, Y. Zhang and C. Yuan, *Phosphorus Sulfur Silicon Relat. Elem.,* 1995, **107**, 21–26; (*c*) C. Yuan, Y. Zhang, W. Luo and Z. Yao, *Heteroat. Chem.,* 1998, **9**, 139–146; (*d*) Y. V. Rassukana, M. V. Kolotylo, O. A. Sinitsa, V. V. Pirozhenko and P. P. Onys'ko, *Synthesis,* 2007, 2627–2630. (*e*) N. M. Karimova, D. V. Vorobyeva, G. T. Shchetnikov and S. N. Osipov, *Russ. Chem. Bull. Int. Ed.,* 2010, **59**, 107–109.
8. F. Palacios, J. Vicario, A. Maliszewska, D. Aparicio, *J. Org. Chem.,* 2007, **72**, 2682–2685.
9. For selected reviews and recent reports on electrochemical reaction, see: (*a*) J.-i. Yoshida, K. Kataoka, R. Horcajada, and A. Nagaki, *Chem. Rev.*, 2008, **108**, 2265–2299; (*b*) E. J. Horn, B. R. Rosen and P. S. Baran, *ACS Cent. Sci.*, 2016, **2**, 302–308; (*c*) C. Sambiagio, H. Sterckx and B. U. W. Maes, *ACS Cent. Sci.*, 2017, **3**, 686–688; (*d*) N. Sauermann, T. H. Meyer, Y. Qiu, and L. Ackermann, *ACS Catal.*, 2018, **8**, 7086–7103; (*e*) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230–13319; (*f*) S. Tang, Y. Liu and A. Lei, *Chem.*, 2018, **4**, 27–45; (*g*) Y. Jiang, K. Xu and C. Zeng, *Chem. Rev.*, 2018, **118**, 4485–4540; (*h*) K. D. Moeller, *Chem. Rev.*, 2018, **118**, 4817–4833; (*i*) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, **57**, 6018–6041; (*j*) J.-i. Yoshida, A. Shimizu and R. Hayashi, *Chem. Rev.*, 2018, **118**, 4702–4730; (*k*) L. M. Reid, T. Li, Y. Cao and C. P. Berlinguette, *Sustainable Energy Fuels*, 2018, **2**, 1905–1927; (*l*) H. Wang, X. Gao, Z. Lv, T. Abdelilah, and A. Lei, *Chem. Rev.*, 2019, **119**, 6769–6787; (*m*) Y. Yuan, and A. Lei, *Acc. Chem. Res.*, 2019, **52**, 3309–3324; (*n*) K.-S. Du and J.-M. Huang, *Green Chem.*, 2019, **21**, 1680–1685; (*o*) D. Pollok and S. R. Waldvogel, *Chem. Sci.*, 2020, **11**, 12386–12400; (*p*) S. B. Beil, D. Pollok and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2021, **60**, 14750–14759.
10. K.-J. Li, Y.-Y. Jiang, K. Xu, C.-C. Zeng and B.-G. Sun, *Green Chem.*, 2019, **21**, 4412–4421.

11. Z. Xu, Y. Li, G. Mo, Y. Zheng, S. Zeng, P.-H. Sun and Z. Ruan, *Org. Lett.*, 2020, **22**, 4016–4020.
12. We found that the electrochemical oxidative C-H phosphorylation from the corresponding aldimines to give no desired products **2** at all.



13. (*a*) M. Okimoto, Y. Takahashi, K. Numata, Y. Nagata and G. Sasaki, *Synth. Commun.*, 2005, **35**, 1989–1995; (*b*) M. T. Schümperli, C. Hammond and I. Hermans, *ACS Catal.*, 2012, **2**, 1108–1117; (*c*) K. Sato, T. Ono, Y. Sasano, F. Sato, M. Kumano, K. Yoshida, T. Dairaku, Y. Iwabuchi and Y. Kashiwagi, *Catalysts*, 2018, **8**, 649.
14. Selected publications on screening and optimization strategies for electrochemical reaction: see, (*a*) R. Möckel, J. Hille, E. Winterling, S. Weidemüller, T. M. Faber and G. Hilt, *Angew. Chem., Int. Ed.*, 2018, **57**, 442–445; (*b*) M. Santi, J. Seitz, R. Cicala, T. Hardwick, N. Ahmed and T. Wirth, *Chem. Eur. J.*, 2019, **25**, 16230–16235; (*c*) B. Gleede, M. Selt, C. Gütz, A. Stenglein and S. R. Waldvogel, *Org. Process Res. Dev.*, 2020, **24**, 1916–1926; (*d*) M. Selt, R. Franke and S. R. Waldvogel, *Org. Process Res. Dev.* 2020, **24**, 2347–2355 (*e*) J. L. Röckl, M. Dörr and S. R. Waldvogel, *ChemElectroChem*, 2020, **7**, 3686–3694; (*f*) S. Arndt, D. Weis, K. Donsbach and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2020, **59**, 8036–8041; (*f*) A. R. Katritzky, D. C. Fara, M. Kuanar, E. Hur and M. Karelson, *J. Phys. Chem. A*, 2005, **109**, 10323–10341; (*g*) P. M. Murray, F. Bellany, L. Benhamou, D.-K. Bučar, A. B. Tabor and T. D. Sheppard, *Org. Biomol. Chem.* 2016, **14**, 2373–2384; (*h*) R. Möckel, E. Babaoglu and G. Hilt, *Chem. Eur. J.*, 2018, **24**, 15781–15785; (*i*) Y. Chen, B. Tian, Z. Cheng, X. Li, M. Huang, Y. Sun, S. Liu, X. Cheng, S. Li and M. Ding, *Angew. Chem., Int. Ed.*, 2021, **60**, 4199–4207; (*j*) D. E. Blanco, B. Lee and M. A. Modestino, *Proc. Natl. Acad. Sci. U. S. A.*, 2019, 17683–17689; (*k*) R. Hardian, Z. Liang, X. Zhang and G. Szekely, *Green Chem.,* 2020, **22**, 7521–7528; (*l*) M. Dörr, M. Hielscher, J. Proppe and S. R. Waldvogel, *ChemElectroChem*, 2021, **8**, DOI: 10.1002/celc.202100318.
15. (*a*) B. J. Reizman and K. F. Jensen, *Acc. Chem. Res.*, 2016, **49**, 1786–1796; (*b*) V. Sans and L. Cronin, *Chem. Soc. Rev.*, 2016, **45**, 2032–2043; (*c*) D. E. Fitzpatrick, T. Maujean, A. C. Evans and S. V. Ley, *Angew. Chem., Int. Ed.*, 2018, **57**, 15128–15132; (*d*) A.-C. Bédard, A. Adamo, K. C. Aroh, M. G. Russell, A. A. Bedermann, J. Torosian, B. Yue, K. F. Jensen and T. F. Jamison, *Science*, 2018, **361**, 1220–1225; (*e*) M. Trobe and M. D. Burke, *Angew. Chem., Int. Ed.*, 2018, **57**, 4192–4214; (*f*) C. Mateos, M. J. Nieves-Remacha and J. A. Rincón, *React. Chem. Eng.*, 2019, **4**, 1536–1544; (*g)* A. D. Clayton, A. M. Schweidtmann, G. Clemens, J. A. Manson, C. J. Taylor, C. G. Niño, T. W. Chamberlain, N. Kapur, A. J. Blacker, A. A. Lapkin and R. A. Bourne, *Chem. Eng. J.*, 2020, **384**, 123340.
16. (*a*) Z. Zhou, X. Li and R. N. Zare, *ACS Cent. Sci.*, 2017, **3**, 1337–1344; (*b*) H. Gao, T. J. Struble, C. W. Coley, Y. Wang, W. H. Green and K. F. Jensen, *ACS Cent. Sci.*, 2018, **4**, 1465–1476; (*c*) L. Häse, L. M. Roch, C. Kreisbeck and A. Aspuru-Guzik, *ACS Cent. Sci.*, 2018, **4**, 1134–1145; (*d*) A. M. Schweidtmann, A. D. Clayton, N. Holmes, E. Bradford, R. A. Bourne and A. A. Lapkin, *Chem. Eng. J.*, 2018, **352**, 277–282; (*e*) P. Vámosi, K. Matsuo, T. Masuda, K. Sato, T. Narumi, K. Takeda and N. Mase, *Chem. Rec.*, 2019, **19**, 77–84; (*f*) M. Fujinami, J. Seino, T. Nukazawa, S. Ishida, T. Iwamoto and H. Nakai, *Chem. Lett.*, 2019, **48**, 961–964; (*g*) N. S. Eyke, W. H. Green and K. F. Jensen, *React. Chem. Eng.*, 2020, **5**, 1963–1972.
17. M. Kondo, H. D. P. Wathsala, M. Sako, Y. Hanatani, K. Ishikawa, S. Hara, T. Takaai, T. Washio, S. Takizawa and H. Sasai, *Chem. Commun.*, 2020, **56**, 1259–1262.
18. (*a*) B. Shahriari, K. Swersky, Z. Wang, R. P. Adams and N. de Freitas, *Proc. IEEE,* 2016, **104,** 148–175; (*b*) S. Greenhill, S. Rana, S. Gupta, P. Vellanki and S. Venkatesh, *IEEE Access*, 2020, **8**, 13937–13948.
19. Although BO-suggested parameters based on *exploration* can escape from a local maximum, they cannot always lead to higher yield than the previously obtained results in the chemical reaction because these parameters have hardly ever been investigated.
20. EI (Expected improvement), which is one of the most general acquisition functions, was employed for BO.
21. (*a*) T. Ueno, T. D. Rhone, Z. Hou, T. Mizoguchi and K. Tsuda, *Mater. Discov.*, 2016, **4**, 18–21; (*b*) C. Li, D. R. de Celis Leal, S. Rana, S. Gupta, A. Sutti, S. Greenhill, T. Slezak, M. Height and S. Venkatesh, *Sci. Rep.*, 2017, **7**, 5683; (*c*) T. Yamashita, N. Sato, H. Kino, T. Miyake, K. Tsuda and T. Oguchi, *Phys. Rev. Mater.*, 2018, **2**, 013803; (*d*) M. Yamawaki, M. Ohnishi, S. Ju and J. Shiomi, *Sci. Adv.*, 2018, **4**, eaar4192; (*e*) Y. Zhang, D. W. Apley and W. Chen, *Sci. Rep.*, 2020, **10**, 4924; (*f*) H. C. Herbol, M. Poloczek and P. Clancy, *Mater. Horiz.*, 2020, **7**, 2113–2123.
22. (*a*) E. Pyzer-Knapp, *IBM J. Res. Dev.*, 2018, **62**, 2:1–2:7; (*b*) S. Sano, T. Kadowaki, K. Tsuda and S. Kimura, *J. Pharm. Innov.*, 2020, **15**, 333–343; (*c*) C. Réda, E. Kaufmann and A. Delahaye-Duriez, *Comput. Struct. Biotechnol. J.*, 2020, **18**, 241−252.
23. (*a*) L. Chan, G. R. Hutchison and G. M. Morris, *J. Cheminf.*, 2019, **11**, 32; (*b*) R. V. Krems, *Phys. Chem. Chem. Phys.*, 2019, **21**, 13392–13410; (*c*) L. Chan, G. R. Hutchison and G. M. Morris, *Phys. Chem. Chem. Phys.*, 2020, **22**, 5211−5219; (*d*) R. A. Vargas-Hernández, *J. Phys. Chem. A*, 2020, **124**, 4053−4061.
24. (*a*) Any preferable reaction conditions were not found during the usual screening of fundamental conditions with eleven experiments (up to 22% yield); (*b*) CH_3CN/ $LiClO_4$ system would be crucial for a good reactivity in this reaction. A high polar solvent and electrolyte would increase polarity surrounding the anode. The high polar sulfonamide **1** would easily approach the polar electrode. This possibility was reported by Moeller, see G. Xu and K. D. Moeller, *Org. Lett.* 2010, **12**, 2590−2593.
25. To carry out the BO-assisted-multiparameter screening, GPyOpt was used as a BO framework in python, see: https://github.com/SheffieldML/GPyOpt
26. We concluded the parameter values in entry 12, Table 1 were suitable for this transformation since further ML estimation and experimental evaluation exhibited the deteriorated outcomes (see Supplementary Table S2). The BO script is also shown in Table S2.
27. In 2020, Shi, Jiang, and co-workers reported visible-light photocatalytic oxidation of cyclic sulfamides to imines in good yields as an environmental friendly reaction, see: Z.-Y. Ming, K.-R. Li, F.-J. Meng, L. Shi and W.-F. Jiang, *Tetrahedron Lett.*, 2020, **61**, 152059. However, this reaction has some limitations such as use of the Ir photocatalyst and the difficult access to the aliphatic product.
28. (*a*) J. Vicario, J. M. Ezpeleta and F. Palacios, *Adv. Synth. Catal.*, 2012, **354**, 2641–2647; (*b*) Y. V. Rassukana, I. P. Yelenich, Y. G. Vlasenko and P. P. Onys'ko, *Tetrahedron:Asymmetry*, 2014, **25**, 1234–1238; (*c*) J. Vicario, P. Ortiz, J. M. Ezpeleta and F. Palacios, *J. Org. Chem.*, 2015, **80**, 156−164; (*d*) Z. Yan, B. Wu, X. Gao and Y.-G. Zhou, *Chem. Commun.,* 2016, **52**, 10882−10885; (*e*) K. Morisaki, M. Sawa, R. Yonesaki, H. Morimoto, K. Mashima and T. Ohshima, *J. Am. Chem. Soc.*, 2016, **138**, 6194−6203; (*f*) Z. Yan, X. Gao and Y.-G. Zhou, *Chin. J. Catal.*, 2017, **38**, 784−791; (*g*) Q. Shao, L. Wu, J. Chen, I. D. Gridnev, G. Yang, F. Xie and W. Zhang, *Adv. Synth. Catal.*, 2018, **360**, 4625−4633; (*h*) J. Sun, C. Mou, C. Liu, R. Huang, S. Zhang, P. Zheng and Y. R. Chi, *Org. Chem. Front.*, 2018, **5**, 2992−2996; (*i*) J. Sun, C. Mou, Z. Wang, F. He, J. Wu and Y. R. Chi, *Org. Lett.*, 2018, **20**, 5969−5972; (*j*) Z. Luo, Z.-H. Gao, C.-L. Zhang, K.-Q. Chen and S. Ye, *Asian J. Org. Chem.*, 2018, **7**, 2452−2455; (*k*) Y.-J. Liu, J.-S. Li, J. Nie and J.-A. Ma, *Org. Lett.*,

2018, **20**, 3643−3646; (*l*) A. Maestro, E. M. de Marigorta, F. Palacios and J. Vicario, *Org. Lett.*, 2019, **21**, 9473−9477.

29. Selected reviews and reports on enantioselective aza-MBH reaction: see, (*a*) K. Matsui, S. Takizawa and H. Sasai, *J. Am. Chem. Soc.,* 2005, **127**, 3680–3681; (*b*) K. Matsui, S. Takizawa and H. Sasai, *Synlett*, 2006, 761–765; (*c*) G. Masson, C. Housseman and J. Zhu, *Angew. Chem., Int. Ed.*, 2007, **46**, 4614–4628; (*d*) S. Takizawa, E. Rémond, F. A. Arteaga, Y. Yoshida, V. Sridharan, J. Bayardon, S. Jugé and H. Sasai, *Chem. Commun.*, 2013, **49**, 8392–8394; (*e*) Y. Wei and M. Shi, *Chem. Rev.*, 2013, **113**, 6659–6690; (*f*) Y. Yoshida, M. Sako, K. Kishi, H. Sasai, S. Hatakeyama and S. Takizawa, *Org. Biomol. Chem.*, 2015, **13**, 9022–9028; (*g*) H. Pellissier, *Tetrahedron*, 2017, **73**, 2831–2861.
30. Enantioselective aza-Henry reaction of acyclic α–ketiminophosphonates was reported by Palacios and co-workers, see ref 28c.
31. Y. Iwabuchi, M. Nakatani, N. Yokoyama and S. Hatakeyama, *J. Am. Chem. Soc.*, 1999, **121**, 10219–20220.
32. The CV analysis of **1n** and **1o** were performed in the presence of $LiClO_4$ and $^nBu_4NPF_6$, respectively. In the CV chart of **1n** with $LiClO_4$, the two oxidation peaks were clearly observed.
33. Under nitrogen or argon atmosphere, the electrochemical oxidation reaction of **1a** smoothly proceeded to afford the product **2a** in up to 62% yield. These outcomes support the reaction mechanism in Scheme 5.
34. B. J. Shields, J. Stevens, J. Li, M. Parasram, F. Damani, J. I. M. Alvarado, J. M. Janey, R. P. Adams and A. G. Doyle, *Nature*, 2021, **590**, 89−96.