Chinese Chemical Letters 34 (2023) 107935

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Electrochemical C–H/N–H cross-coupling of 2-phenylindolizines with phenothiazines to synthesize novel *N*-aryl phenothiazine derivatives

Chenglong Feng, Xin Liu, Yuanbin She, Zhenlu Shen*, Meichao Li*

College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310032, China

A R T I C L E I N F O

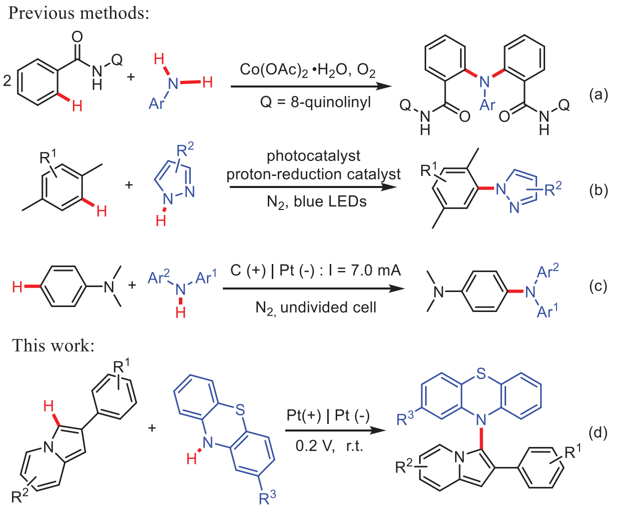
Article history:
Received 17 August 2022
Revised 11 October 2022
Accepted 13 October 2022
Available online 22 October 2022

Keywords:
N-Aryl phenothiazine derivatives
Electrochemical oxidation
2-Phenylindolizines
Phenothiazines
Cross-coupling

A B S T R A C T

A facile and elegant method for synthesis of novel *N*–aryl phenothiazine derivatives from 2-phenylindolizines and phenothiazines through direct electrochemical oxidation has been developed. This approach was performed smoothly at room temperature without external oxidant and catalyst. Cyclic voltammetry and *in situ* FTIR techniques were applied to analyze the cross-coupling process of phenothiazines and 2-phenylindolizines, which helped to select the appropriate reaction potential. Under the optimized conditions, a broad range of substrates were well tolerated, affording the desired products in moderate to excellent isolated yields (up to 91%) with high regioselectivity. Meanwhile, a plausible mechanism involving a radical pathway has been proposed.

Triarylamines were becoming increasingly important due to their hole-transporting capabilities and unusual stable radical cations [1–3]. Among them, *N*-aryl phenothiazine derivatives played an important role in organic light-emitting diodes [4–7], sensitized solar cells [8–11] and photochromic materials [12,13]. The methods for efficient synthesis of *N*-aryl phenothiazines *via* the formation of C–N bonds were fascinating. Over the past decade, strategies for constructing C–N bonds have been intensively developed [14–19]. Du *et al.* reported an efficient protocol for C–H amination of arenes with anilines to synthesize triarylamines catalyzed by $Co(OAc)_2{\cdot}4H_2O$ (Scheme 1a) [18]. A method for photo-induced C–H/N–H cross-coupling between arenes and azoles without oxidant was proposed by Niu and co-workers [19]. The C–N bonds were constructed conveniently under synergistic effect of photocatalyst and proton-reduction catalyst at room temperature (Scheme 1b). However, part of classical synthetic methods inevitably required chemical oxidants, transition metal catalysts or photosensitizers, which were not in line with the characteristics of sustainability and green chemistry.



Scheme 1. Construction of the C–N bonds.

As an environmentally friendly and efficient synthetic method, electrochemistry provided new possibilities for green organic synthesis [20–25]. In recent years, electrocatalytic C–H functionalization to construct C–N bonds has been successfully established [26–31]. In 2019, Lei and co-workers developed an elegant strategy for C–H/N–H cross-coupling with hydrogen evolution to synthesize triarylamine derivatives from electron-rich aromatic hydrocarbons and diarylamines (Scheme 1c) [32].

Encouraged by these exciting results and with our continuation of research on electrochemical synthesis [33–35], we envisioned that phenothiazines and 2-phenylindolizines might be promising to synthesize novel compounds for optoelectronic materials, due to both structural motifs of the compounds had excellent electrochemical and photochemical characteristics [36–38]. Herein, we re-

---

* Corresponding authors.
E-mail addresses: zhenlushen@zjut.edu.cn (Z. Shen), limc@zjut.edu.cn (M. Li).

https://doi.org/10.1016/j.cclet.2022.107935

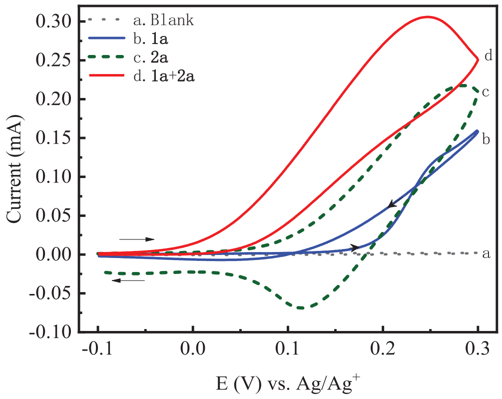
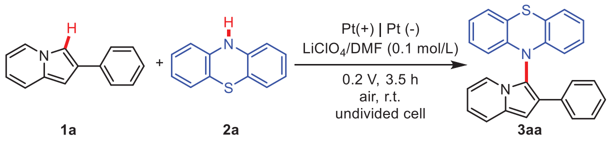


Fig. 1. Cyclic voltammograms recorded in 0.1 mol/L $LiClO_4$/DMF (15 mL) from −0.1 V to 0.3 V at 50 mV/s scan rate with (a) blank solution; (b) **1a** (0.016 mol/L); (c) **2a** (0.013 mol/L); (d) **1a** (0.016 mol/L) and **2a** (0.013 mol/L).

Table 1
Optimization of the reaction conditions.[a]



Entry	Variation from the standard conditions	Yield (%)[b]
1	none	85
2	MeCN instead of DMF	55
3	EA instead of DMF	23
4	$^{n}Bu_4NBF_4$ instead of $LiClO_4$	63
5	$^{n}Bu_4NPF_6$ instead of $LiClO_4$	67
6	$NaClO_4$ instead of $LiClO_4$	75
7	C(+)|Pt(-) instead of Pt(+)|Pt(-)	80
8	C(+)|C(-) instead of Pt(+)|Pt(-)	75
9	**1a**:**2a** =1:1 instead of **1a**:**2a** =1.2:1	79
10	**1a**:**2a** =1.5:1 instead of **1a**:**2a** =1.2:1	85
11	0.1 V instead of 0.2 V, 7.0 h	82
12	0.3 V instead of 0.2 V, 2.5 h	79
13	15 °C instead of r.t.	72
14	35 °C instead of r.t.	85
15	in N_2	85
16	without electric potential	n.r.

[a] Standard conditions: Pt anode, Pt cathode, undivided cell, 0.2 V, 3.5 h, **1a** (0.24 mmol), **2a** (0.20 mmol), 0.1 mol/L $LiClO_4$/DMF (15 mL), air, room temperature.
[b] Isolated yield.

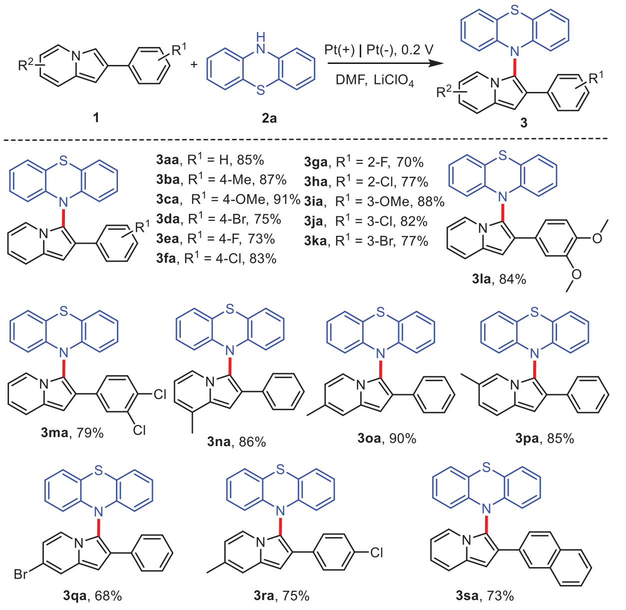
ported an efficient and convenient method for electrochemical oxidative C−H/N−H cross-coupling of 2-phenylindolines with phenothiazines to synthesize a series of novel *N*-aryl phenothiazine derivatives (Scheme 1d). Redox properties of the reactions were investigated by cyclic voltammetry and *in situ* FTIR [39–41].

Cyclic voltammetry experiments were carried out to study the redox behavior of the reactants. As shown in Fig. 1, no distinct electrochemical reaction peaks existed in the cyclic voltammogram of the $LiClO_4$/DMF solution (blank solution). With the addition of 2-phenylindolizine (**1a**) into the blank solution, the oxidation current began to increase from about 0.15 V and the oxidation peak was clearly observed at about 0.25 V. A classic nucleation loop exhibited near 0.20 V on the backward scanning and the surface of the anode was covered by a yellow thin film during the cyclic voltammetry experiment. It was related to the homogeneous formation of oligomeric products from **1a** [36,42]. When phenothiazine (**2a)** was added into the blank solution alone, **2a** began to be oxidized at about 0.03 V. An obvious oxidation peak and a reduction peak appeared at 0.29 V and 0.11 V, respectively. The oxidation of **2a** was *quasi*-reversible and just one electron was transferred in the oxidation process [43,44]. As shown in Fig. 1d, with the addition of **1a** and **2a** in the blank solution, the onset oxidation potential shifted negatively to −0.05 V and a new oxidation peak with higher current was noticed at 0.23 V. Most importantly, the loop at about 0.2 V for the oxidation of **1a** disappeared and thin film was not formed on the anode surface, which indicated that the polymerization of **1a** was inhibited. Meanwhile, the reduction peak of **2a** was not observed. The above phenomena suggested that **1a** reacted with **2a** during the process of cyclic voltammetry experiment.

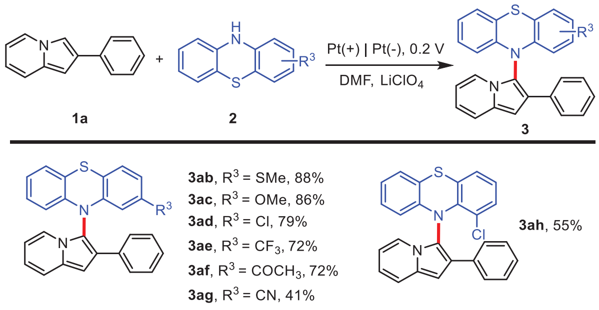
As an initial attempt, the cross-coupling of **1a** with **2a** was selected as the model reaction to screen out the optimal conditions and the results were summarized in Table 1. When **1a** (0.24 mmol) reacted with **2a** (0.20 mmol) in 0.1 mol/L $LiClO_4$/DMF solution at the potential of 0.2 V for 3.5 h, the yield of 10-(2-phenylindolizin-3-yl)−10*H*-phenothiazine (**3aa**) could reach 85% (entry 1). The X-ray crystallographic coordinates for structure of **3aa** were shown in Fig. S1 (Supporting information). Replacing DMF with acetonitrile and ethyl acetate, the yields were decreased to 55% and 23%, respectively. It might be related to the poor solubility of **1a** in acetonitrile and the weak conductivity of ethyl acetate solution (entries 2 and 3). The supporting electrolytes had a certain influence on the reaction. Three other supporting electrolytes ($^{n}Bu_4NBF_4$, $^{n}Bu_4NPF_6$, $NaClO_4$) were tested instead of $LiClO_4$ in the standard conditions, the yield of **3aa** was decreased slightly (entries 4–6). When a graphite rod was employed as the anode instead of a platinum plate, 80% yield of **3aa** could be obtained (entry 7). Using graphite rods both as the anode and cathode was less effective than platinum plates (entry 8). When the dosage of **1a** was reduced to 1.0 equiv., the yield of **3aa** was decreased to 79% (entry 9). While 1.5 equiv. of **1a** could not improve the yield of **3aa** obviously (entry 10). Though the reactions were also carried out well at 0.1 V or 0.3 V, no better yields were achieved (entries 11 and 12). When the reaction temperatures were 15 °C and 35 °C, the yields of **3aa** were 72% and 85%, respectively. Therefore, room temperature was suitable for the reaction (entries 13 and 14). In addition, nitrogen atmosphere had little effect on the reaction (entry15), and almost no reaction took place without electric potential (entry 16).

With the optimized conditions in hand, we caried out an exploration of the substrate range. A series of 2-phenylindolazines were investigated and the results were summarized in Scheme 2. C2-substituted phenyl moiety of 2-phenylindolizines bearing –Me or –OMe at para-position reacted with **1a** to generate corresponding products in excellent yields (**3ba** and **3ca**). The presence of –Cl, –Br, –F groups at para-position of C2-substituted phenyl moiety slightly reduced the synthetic efficiency, and the desired coupling products **3da-3fa** were isolated in 75%–83% yields. Meanwhile, the different position of substituent group had little effect on the reaction, which was shown in the yields of **3ga-3ka** and **3na-3qa**. The 2-phenylindolazines with disubstituent on phenyl moiety also performed well to generate the corresponding products in 84% and 79%, respectively (**3la** and **3ma**). In addition, the 2-(4-chlorophenyl)−7-methylindolizine and 2-(naphthalen-2-yl)indolizine could afford good results under optimized conditions (**3ra** and **3sa**). Either electron-withdrawing groups or electron-donating groups substituted on **1a**, the coupling reactions could be carried out smoothly.

Subsequently, the coupling of a variety of phenothiazines (**2b-2g**) with **1a** was investigated, and the results were shown in Scheme 3. 2-Methylthio-10*H*-phenothiazine (**2b**) and 2–methoxy-10*H*-phenothiazine (**2c**) were suitable for the reaction and the desired products **3ab** and **3ac** could be isolated in 86% and 88% yields, respectively. When phenothiazines bearing –Cl, $-CF_3$, $-COCH_3$ substituents at the 2-position were submitted to the cross-coupling, the yields of **3ad-3af** were higher than 72%. How-



Scheme 2. Substrate scope of 2-phenylindolizines. Reaction conditions: **1** (0.24 mmol), **2a** (0.20 mmol), Pt(+)|Pt(-), 0.1 mol/L $LiClO_4$/DMF (15 mL), an undivided cell, 0.2 V, r.t., 3.5 h.

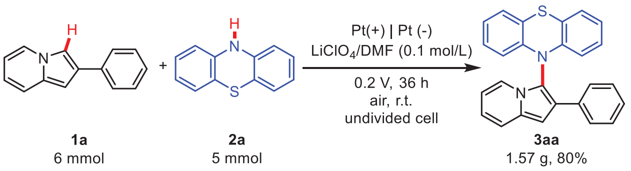


Scheme 3. Substrate scope of phenothiazines. Reaction conditions: **1a** (0.24 mmol), **2** (0.20 mmol), Pt(+)|Pt(-), 0.1 mol/L $LiClO_4$/DMF (15 mL), an undivided cell, 0.2 V, r.t., 3.5 h.

ever, 10*H*-phenothiazine-2-carbonitrile (**2g**) could not achieve a satisfactory result, the yield of **3ag** was only 41%. When –Cl was substituted at 1-position of phenothiazine, the corresponding product **3ah** was obtained in 55% yield. It indicated the steric hindrance has some influence on the reaction.

In general, 2-phenylindolazines or phenothiazines with electron-donating groups showed higher activity than that with electron-withdrawing groups. In addition, the cross-coupling of 2-phenylindolizines with phenothiazines under galvanostatic electrolysis was also investigated. However, the potential tended to increase during galvanostatic electrolysis continuously, and high potential might cause electro-polymerization of 2-phenylindolazines. Therefore, the yields of the products with galvanostatic electrolysis were lower than that with potentiostatic electrolysis. The results of galvanostatic electrolysis were described in the Supporting Information. In addition, the constant cell potential electrolysis with two electrodes was also investigated. When the cell potentials were 3.0 V, 4.0 V and 5.0 V, the yields of **3aa** were 12%, 65% and 49%, respectively.

To evaluate the scalability of this electrocatalytic system, the electrochemical cross-coupling of **1a** with **2a** was performed on 5 mmol scale. The reaction was carried out at 0.2 V for 36 h and the desired product **3aa** was obtained in 80% yield (Scheme 4). It showed that this electrochemical method was feasible in practical synthesis.



Scheme 4. Gram-scale synthesis.

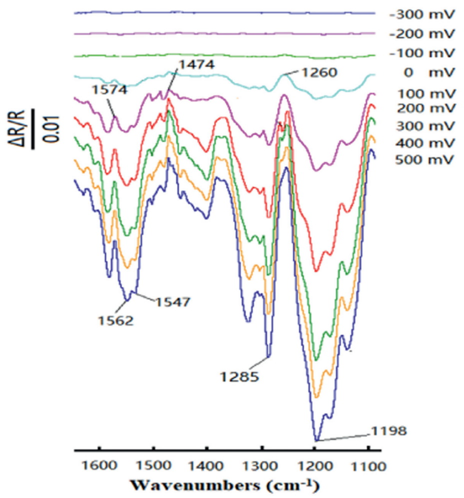
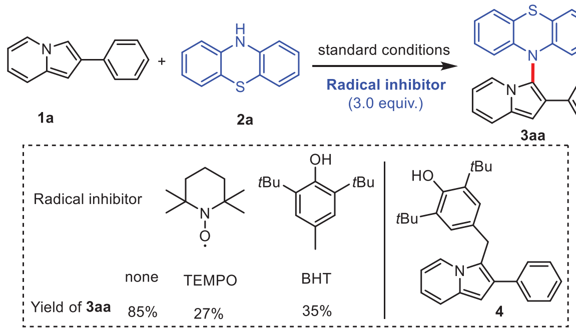


Fig. 2. *In situ* FTIR spectra collected during the reaction of **1a** (0.72 mmol) and **2a** (0.60 mmol) in 15 mL 0.1 mol/L $LiClO_4$/DMF at potentials varied from −300 mV to 500 mV.

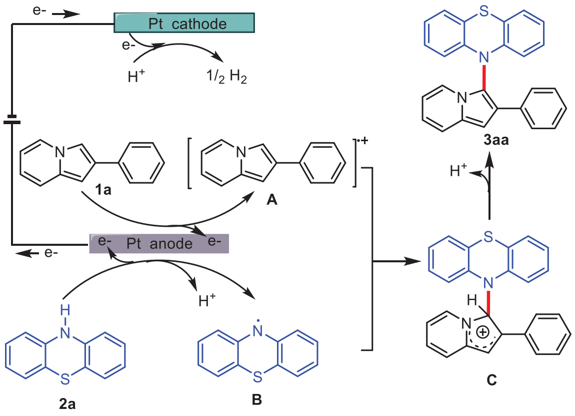
In situ FTIR spectroscopy was an important tool to study the reaction characteristics of electrode surface and helped us to analyze the consumption of reactants and the formation of products. The cross-coupling reaction of **1a** (0.72 mmol) with **2a** (0.60 mmol) was investigated by *in situ* FTIR technique, which was implemented in 0.1 mol/L $LiClO_4$/DMF solution at potentials varied from −300 mV to 500 mV. As shown in Fig. 2, three important positive bands at 1574, 1474 and 1260 cm^{-1} and four negative bands at 1562, 1547, 1285 and 1198 cm^{-1} could be observed. The positive-going band at 1574 cm^{-1} was attributed to N—H bending vibration of **2a** which was very characteristic [45], and the bond at 1260 cm^{-1} was related to C—N stretching vibration of **2a** [46]. It confirmed that **2a** was consumed during the electrochemical oxidation process. Moreover, the positive-going band located at 1474 cm^{-1} could be attributed to a characteristic of the nitrogen heterocycle skeleton vibration [47], which showed the participation of **1a** in this reaction.

It was noteworthy that due to the conjugation effect of heterocyclic aromatic hydrocarbon and lone pair electrons of nitrogen, the skeleton vibration of aromatic ring would red-shift [48]. Two negative-going bonds at 1562 and 1547 cm^{-1} were related to aromatic skeleton vibrations of **3aa**. The negative-going bond at 1285 cm^{-1} was attributed to the C—N stretching vibration of **3aa**. In addition, the band located at 1198 cm^{-1} was assigned to ClO_4^- of the supporting electrolyte [33,49]. Therefore, **3aa** could be synthesized from **1a** and **2a** successfully at low potential.

In order to gain insight into the process of dehydrogenative C–H/N–H cross-coupling between **1a** and **2a**, a few radical-trapping control experiments were conducted as shown in Scheme 5. Three equivalents of the radical scavenger 2,2,6,6-tetramethylpiperidine-oxyl (TEMPO) or 2,6-di–*tert*–butyl–4-methylphenol (BHT) was added to the standard conditions and formation of **3aa** was inhibited. It showed that a radical pathway might be involved in the coupling reaction of 2-phenylindolizines with phenothiazines



Scheme 5. Control experiments.



Scheme 6. Proposed reaction mechanism.

during the electrochemical oxidation process. Furthermore, a BHT-trapped complex **4** was detected by electrospray ionization mass spectrometry (ESI-MS) analysis (see Supporting information for details).

Based on the results of the above experiments and literatures [50–53], a plausible mechanism for this reaction was revealed in Scheme 6. Initially, the anodic oxidation of **1a** occurred to form the 2-phenylindolizine cationic radical **A**, and **2a** was oxidized at platinum plate anode to form phenothiazine radical **B**. Then, cationic radical **A** coupled with radical **B** to form intermediate **C** and C–N bond was constructed. The intermediate **C** underwent deprotonation to generate **3aa**. At the same time, the protons were reduced at the cathode to generate H_2.

In summary, we have developed a novel and atom-economical method for the synthesis of *N*-aryl phenothiazine derivatives *via* electrochemical oxidative C–H/N–H cross-coupling of 2-phenylindolizines with phenothiazines under undivided electrolytic conditions. The cross-coupling reactions were carried out smoothly without external oxidants and catalysts. The C–N bonds were constructed at a low potential which could reduce the side reactions such as electrochemical polymerization of the 2-phenylindolizines. In addition, the results of cyclic voltammetry, *in situ* FTIR and control experiments were used to further understand the oxidation process in the reactions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are grateful for the generous financial support of the National Natural Science Foundations of China (Nos. 22178321, 21773211 and 21776260).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.107935.

References

[1] J. Wang, K. Liu, L. Ma, X. Zhan, Chem. Rev. 116 (2016) 14675–14725.
[2] C.S. Wu, Y. Chen, J. Mater. Chem. 20 (2010) 7700–7709.
[3] K. Zhang, H.J. Niu, C. Wang, et al., J. Electroanal. Chem. 682 (2012) 101–109.
[4] B. Wang, Y. Zheng, T. Wang, D.G. Ma, Q. Wang, Org. Electron. 88 (2021) 106012.
[5] G. Bagdžiūnas, G. Grybauskaitė, N. Kostiv, et al., RSC Adv. 6 (2016) 61544–61554.
[6] I. Marghad, F. Bencheikh, C. Wang, et al., RSC Adv. 9 (2019) 4336–4343.
[7] B. Wang, X. Qiao, Z. Yang, et al., Org. Electron. 59 (2018) 32–38.
[8] C.J. Yang, Y.J. Chang, M. Watanabe, Y.S. Hon, T.J. Chow, J. Mater. Chem. 22 (2012) 4040–4049.
[9] A.F. Buene, D.M. Almenningen, J. Mater. Chem. 9 (2021) 11974–11994.
[10] D. Devadiga, M. Selvakumar, P. Shetty, et al., Int. J. Energy Res. 45 (2021) 6584–6643.
[11] E. Kavery, S. Muruganantham, S. Prabhu, et al., Optik 208 (2020) 164046.
[12] C. Qian, Z. Ma, J. Liu, et al., Chem. Asian. J. 16 (2021) 3713–3718.
[13] B. Ramakrishna, K. Narayanaswamy, S.P. Singh, P.R. Bangal, Asian J. Org. Chem. 7 (2018) 2254–2262.
[14] C.M. Chan, Y.C. Chow, W.Y. Yu, Synth. Stuttgart 52 (2020) 2899–2921.
[15] D.G. Ma, S. Zhai, Y. Wang, A.A. Liu, C.C. Chen, Front. Chem. 7 (2019) 635.
[16] Y. Wu, J.A. Chen, Q. Li, W.T. Wei, Chin. J. Org. Chem. 40 (2020) 589–597.
[17] N. Zheng, H.X. Zheng, T. Li, W.T. Wei, ChemSusChem 14 (2021) 5340–5358.
[18] C. Du, P.X. Li, X.J. Zhu, et al., ACS Catal. 7 (2017) 2810–2814.
[19] L.B. Niu, H. Yi, S.C. Wang, et al., Nat. Commun. 8 (2017) 14226.
[20] B. Elsler, D. Schollmeyer, K.M. Dyballa, R. Franke, S.R. Waldvogel, Angew. Chem. Int. Ed. 53 (2014) 5210–5213.
[21] T. Morofuji, A. Shimizu, J. Yoshida, J. Am. Chem. Soc. 135 (2013) 5000–5003.
[22] J. Yoshida, K. Kataoka, R. Horcajada, A. Nagaki, Chem. Rev. 108 (2008) 2265–2299.
[23] R. Francke, R.D. Little, Chem. Soc. Rev. 43 (2014) 2492–2521.
[24] Y. Yu, Y. Yuan, H. Liu, et al., Chem. Commun. 55 (2019) 1809–1812.
[25] J.W. Wu, Y. Zhou, Y.C. Zhou, C.W. Chiang, A.W. Lei, ACS Catal. 7 (2017) 8320–8323.
[26] S. Tang, S. Wang, Y. Liu, H. Cong, A.W. Lei, Angew. Chem. Int. Ed. 57 (2018) 4737–4741.
[27] Y.C. Wu, S.S. Jiang, R.J. Song, J.H. Li, Chem. Commun. 55 (2019) 4371–4374.
[28] S. Zhang, L.J. Li, M.Y. Xue, et al., Org. Lett. 20 (2018) 3443–3446.
[29] Z.M. Tan, X.R. He, K. Xu, et al., ChemSusChem 15 (2022) e202102360.
[30] P. Peng, Z.H. Zhou, K.F. Hu, et al., Org. Lett. 21 (2019) 6403–6407.
[31] K. Liu, J.R. Wu, Y.Q. Deng, et al., ChemElectroChem 6 (2019) 4173–4176.
[32] K. Liu, S. Tang, T. Wu, et al., Nat. Commun. 10 (2019) 639.
[33] Z.Q. Fan, X.J. Yang, C. Chen, Z.L. Shen, M.C. Li, J. Electrochem. Soc. 164 (2017) G54–G58.
[34] C. Chen, P.F. Niu, Z.L. Shen, M.C. Li, J. Electrochem. Soc. 165 (2018) G67–G74.
[35] Y.C. Cai, P.F. Niu, Z.L. Shen, M.C. Li, Chem. J. Chin. U. 40 (2019) 2308–2313.
[36] J.B. Henry, R.J. MacDonald, H.S. Gibbad, H. McNab, A.R. Mount, Phys. Chem. Chem. Phys. 13 (2011) 5235–5241.
[37] L. Marin, A. Bejan, S. Shova, Dyes Pigment. 175 (2020) 108164.
[38] J. Luo, Z. Wan, C. Jia, Chin. Chem. Lett. 27 (2016) 1304–1318.
[39] X. Liu, P. Niu, J. Jin, Z.L. Shen, M.C. Li, Electrochim. Acta 331 (2020) 135371.
[40] J.L. Jin, L.M. Zhao, C. Zhang, et al., J. Electrochem. Soc. 168 (2021) 025504.
[41] L.M. Zhao, X. Liu, S.X. Shi, et al., Electrochim. Acta 389 (2021) 138748.
[42] J. Heinze, A. Rasche, M. Pagels, B. Geschke, J. Phys. Chem. B 111 (2007) 989–997.
[43] M. Goswami, A. Konkel, M. Rahimi, et al., Chem. Eur. J. 24 (2018) 11936–11943.
[44] E. Madej, P. Wardman, Radiat. Phys. Chem. 75 (2006) 990–1000.
[45] Q.R. Huang, Y.C. Li, K.L. Ho, J.L. Kuo, Phys. Chem. Chem. Phys. 20 (2018) 7653–7660.
[46] S. Burman, K. Bhattacharya, D. Mukherjee, G. Chandra, BMC Complem. Altern. Altern. M. 18 (2018) 213.
[47] Q. Osmani, H. Hughes, K. Flavin, et al., Anal. Bioanal. Chem. 391 (2008) 1229–1236.
[48] M. Orief, M. Abdel-Rhman, J. Mol. Struct. 1173 (2018) 332–340.
[49] A.M. Erkabaev, T.V. Yaroslavtseva, S.E. Popov, O.V. Bushkova, Vib. Spectrosc. 75 (2014) 19–25.
[50] P.Z. Zhao, K. Wang, Y.Y. Yue, et al., ChemCatChem 12 (2020) 3207–3211.
[51] X. Pan, M. Lamson, J. Yan, K. Matyjaszewski, ACS Macro Lett. 4 (2015) 192–196.
[52] Y. Yu, Z.B. Yue, L.G. Ding, Y. Zhou, H. Cao, ChemistrySelect 4 (2019) 1117–1120.
[53] W. Kim, H.Y. Kim, K. Oh, J. Org. Chem. 86 (2021) 15973–15991.