Chinese Chemical Letters 34 (2023) 108036

Contents lists available at ScienceDirect

Chinese Chemical Letters

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

TBAI/H_2O-cooperative electrocatalytic decarboxylation coupling-annulation of quinoxalin-2(1*H*)-ones with *N*-arylglycines

Yu-Han Lu[a], Zhuo-Tao Zhang[b], Hong-Yu Wu[b], Min-Hang Zhou[b], Hai-Yang Song[b], Hong-Tao Ji[b], Jun Jiang[b], Jin-Yang Chen[b], Wei-Min He[b,*]

[a] *Hengyang Medical School, University of South China, Hengyang 421001, China*
[b] *School of Chemistry and Chemical Engineering, University of South China, Hengyang 421001, China*

ARTICLE INFO

Article history:
Received 27 September 2022
Revised 30 November 2022
Accepted 1 December 2022
Available online 5 December 2022

Keywords:
Green chemistry
Electrochemistry
Aminomethyl radical
Annulation reaction

ABSTRACT

The first example of TBAI/H_2O cooperative electrocatalytic coupling-annulation of quinoxalin-2(1*H*)-ones with *N*-arylglycines was developed. A broad range of tetrahydroimidazo[1,5-*a*]quinoxalin-4(5*H*)-ones were obtained in good to excellent yields with exclusive chemoselectivities and excellent regioselectivities. The H-hydrogen bond served as a key factor for the electrocatalytic production of aminomethyl radical at lower oxidative potential.

Electro-organic synthesis is widely recognized as a powerful and eco-friendly tool in green chemistry given its unique ability to produce radicals and radical ions through a direct single-electron-transfer manner [1–3]. Consequently, tremendous progress has been achieved in electrochemical transformations during the past years [4–12]. However, a lot of redox sensitive molecules cannot be stable at high potential, thus restricting the electrochemical transformation of such molecules. To overcome these limitations, various catalysts and/or mediators have been applied to achieve the production of reactive species at lower redox potential [13–23].

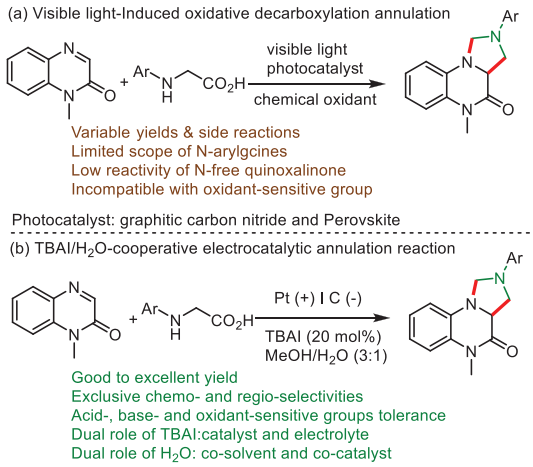
Direct utilization of naturally abundant chemical feedstocks for synthesizing high-value chemicals has become a long-standing goal in green chemistry. In this regard, α-amino acid and its derivatives have been frequently used by synthetic chemists because of its stable chemical properties [24]. Among these α-amino derivatives, *N*-arylglycines have been frequently used as the stable α-aminomethyl radical precursor for constructing carbon-carbon bonds though oxidative decarboxylation [25–32].

Quinoxalin-2(1*H*)-ones represent a valuable class of *N*-heterocycles as they are present in many synthetic drugs and biologically active compounds [33]. Therefore, various functionalized quinoxalin-2(1*H*)-ones have been synthesized through C-H functionalization of quinoxalin-2(1*H*)-ones during the past years [34–45]. Recent studies have revealed that ring-fused quinoxalinones (the combination of heterocycles and quinoxalin-2(1*H*)-one moieties) show unique biological activities and physicochemical properties, and thereby have higher applied value [46]. However, the construction of ring-fused quinoxalinones [47,48] from readily available quinoxalin-2(1*H*)-ones (particularly in a sustainable fashion) have been scarcely exploited. Imidazo[1,5-*a*]quinoxalin-4-ones represent a significant class of ring-fused quinoxalinones due to their remarkable biological and pharmacological activities [49]. Recently, Yu and Chen's group reported the synthesis of imidazo[1,5-*a*]quinoxalin-4-ones through visible light-induced oxidative coupling and annulation of quinoxalin-2(1*H*)–ones and *N*-phenylglycines with graphitic carbon nitride [50] and perovskite [51] as the photocatalyst (Scheme 1a). Although both these methods are useful, they are problematic in industrial applications due to the requirement of expensive g-C_3N_4 or toxic leaded photo-catalyst. Therefore, developing more general and more sustainable synthetic methods toward such molecules is highly desirable. As part of our continuous efforts toward green synthesis [52–58], herein we reported an elegant strategy for constructing imidazo[1,5-*a*]quinoxalin-4-ones through TBAI/H_2O cooperative electrocatalytic decarboxylation coupling-annulation of quinoxalin-2(1*H*)-ones with *N*-arylglycines in methanol aqueous solution (Scheme 1b).

The electrochemical coupling-annulation reaction of *N*-methylquinoxalin-2(1*H*)-one (**1a**) and *N*-phenylglycine (**2a**) was selected as template reaction for optimizing the reaction conditions (Table 1). After initial optimizations, the optimal results were obtained by conducting this electrolysis with 20 mol% TBAI as

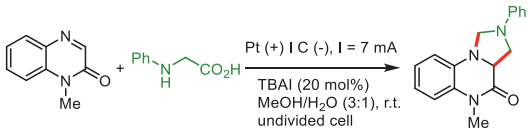
* Corresponding author.
E-mail address: weiminhe@usc.edu.cn (W.-M. He).

https://doi.org/10.1016/j.cclet.2022.108036
1001-8417/



Scheme 1. Decarboxylation coupling-annulation of quinoxalin-2(1*H*) ones with *N*-arylglycines.

Table 1
Optimization of reaction conditions.[a]



Entry	Variation from the standard reaction conditions	Yield (%)[b]
1	None	94
2	Pt(+)|RVC(-) instead of Pt(+)|C(-)	42
3	Pt(+)|Pt(-) instead of Pt(+)|C(-)	74
4	Pt(+)|Ni(-) instead of Pt(+)|C(-)	36
5	Pt(+)|Cu(-) instead of Pt(+)|C(-)	31
6	C(+)|C(-) instead of Pt(+)|C(-)	53
7	C(+)|Pt(-) instead of Pt(+)|C(-)	67
8	C(+)|Ni(-) instead of Pt(+)|C(-)	43
9	C(+)|Cu(-) instead of Pt(+)|C(-)	46
10	KI instead of TBAI	60
11	NH_4I instead of TBAI	65
12	Me_4NI instead of TBAI	47
13	nBu$_4$NBr instead of TBAI	52
14	nBu$_4$NBF$_4$ instead of TBAI	54
15	nBu$_4$NPF$_6$ instead of TBAI	61
16	nBu$_4$NClO$_4$ instead of TBAI	46
17	Anhydrous MeOH instead of MeOH/H_2O (3:1)	34
18	MeOH/H_2O (20:1) instead of MeOH/H_2O (3:1)	61
19	MeOH/H_2O (4:1) instead of MeOH/H_2O (3:1)	76
20	MeOH/H_2O (2:1) instead of MeOH/H_2O (3:1)	79
21	EtOH/H_2O (3:1) instead of MeOH/H_2O (3:1)	62
22	DCM/H_2O (3:1) instead of MeOH/H_2O (3:1)	56
23	MeCN/H_2O (3:1) instead of MeOH/H_2O (3:1)	59
24	DMF/H_2O (3:1) instead of MeOH/H_2O (3:1)	44
25	DMSO/H_2O (3:1) instead of MeOH/H_2O (3:1)	49
26	Without TBAI	N.R.
27	Without electricity	N.R.
28	Under the dark condition	94

[a] Conditions: Pt (15 mm × 10 mm × 0.1 mm) as the anode, C (15 mm × 10 mm × 2 mm) as the cathode, constant current = 7 mA, **1a** (0.2 mmol), **2a** (0.5 mmol), TBAI (20 mol%), MeOH (6 mL), H_2O (2 mL), room temperature, 5 h, undivided cell.
[b] Estimated by ^{1}H NMR using diethyl phthalate as the internal reference. TBAI: tetrabutylammonium iodide.

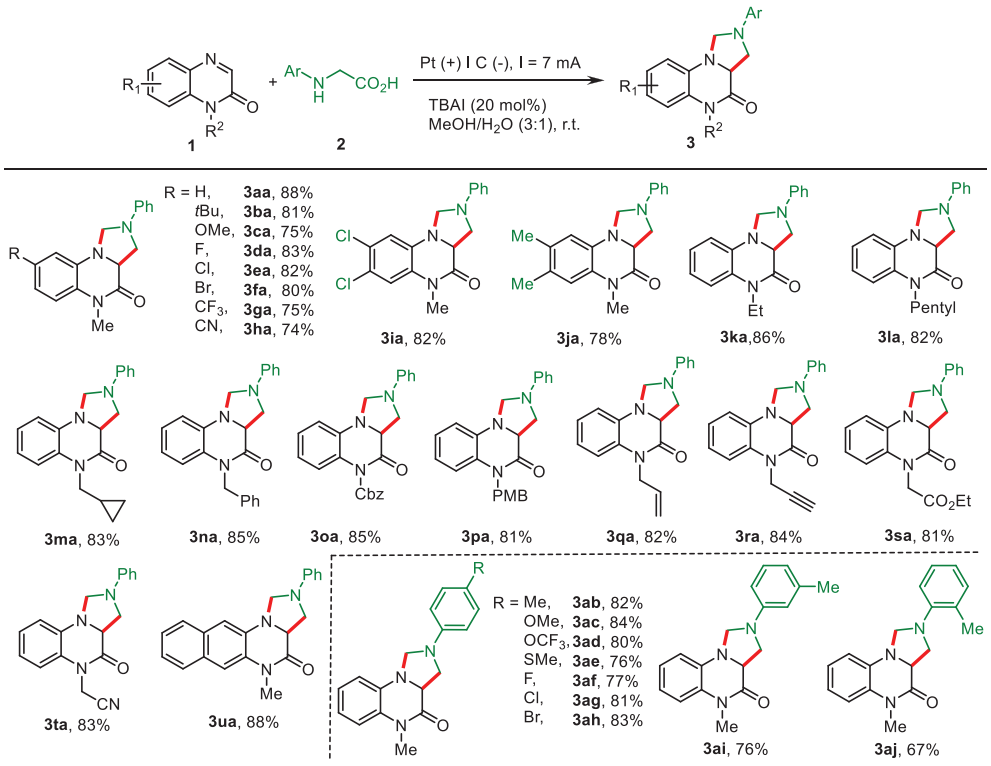
the catalyst and methanol aqueous solution (3:1) as the solvent in an undivided cell equipped with a platinum plate anode and a graphite plate cathode under 7 mA constant current, the target product **3aa** was obtained in 94% yield (Table 1, entry 1). Changing the Pt(+)/C(-) electrode pair with other electrode pairs led to reduced efficiencies (entries 2-9). Subsequently, lower yields of **3aa** was observed when TBAI was replaced by other iodide salts (entries 10-12) or tetrabutylammonium salts (entries 13-16). With anhydrous methanol as the sole solvent, only 34% yield of **3aa** was formed (entry 17). Performing the reaction in a solvent mixture of MeOH and H_2O at a 20:1 ratio could gave **3aa** in 61% yield (entry 18). Varying the water loading (entries 18-20) suggested that the optimal volume ratio of MeOH/H_2O is 3:1 for the present reaction. Next, a series of aqueous organic solvents were examined and the results revealed methanol aqueous solution was the premium reaction medium (entries 21-25). Control reactions proved that no reaction occurred in the absence of TBAI or constant current (entries 26 and 27). Performing the model reaction in the dark conditions had no effect on the yield of **3aa** (entry 28).

To evaluate the scope of this reaction, a series of quinoxalin-2(1*H*)-ones and *N*-arylglycines were screened under the optimal conditions (Scheme 2). Delightedly, both mono- and disubstituted quinoxalin-2(1*H*)-ones **1** furnished the annulated products (**3aa**–**3ja**) in good to excellent yields, suggesting that the reaction was not sensitive to the electronic effects of the substituents on the phenyl. Quinoxalin-2(1*H*)-ones **1** possessing various functional groups at N-1 position underwent the electrochemical transformation smoothly and delivered the desired products (**3ka**–**3ta**) with 81%-86% yields. Remarkably, a broad range of synthetic important functional groups including alkyl, alkoxy, halides, trifluoromethyl, cyano, alkenyl, alkynyl, ester, benzyloxycarbonyl and *p*-methoxybenzyl groups are well tolerated. *N*-Methylbenzo[*g*]quinoxalin-2(1*H*)-one was also well applicable to provide the target product (**3ua**) in good yield. Subsequently, a series of *N*-arylglycines were investigated. Pleasingly, *N*-arylglycines with diverse electron-donating or electron-withdrawing substituents on the phenyl ring successfully entered this process furnishing the target products (**3ab**-**3ah**) in good yields. It is especially noteworthy that the oxidation-sensitive methylthio group also survived under the electrochemical conditions to deliver to the corresponding product **3ae** in 76% yield. Furthermore, methyl groups at each position of the benzene ring of *N*-phenylglycine **2** were well compatible with the standard conditions, delivering the expected products (**3ab**, **3ai** and **3aj**) with good yields.

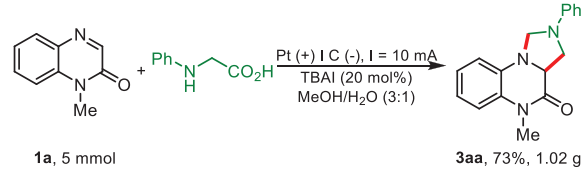
To prove the practicality of this electrocatalytic reaction, a scale-up reaction (5 mmol) was performed under the standard conditions (Scheme 3). Delightedly, the current reaction gave the desired product **3aa** in 73% isolated yield (1.02 g), showing a high potential application for industry scale-up.

To better understand the electrochemical annulation process, a series of mechanistic studies were carried out. Considering that this type of annulation reactions may involve the 3-aminomethyled quinoxalin-2(1*H*)-one (**4aa**) intermediate, generated from the coupling of the phenylaminomethyl radical and **1a** [50,51], we conducted the reaction of **1a** with different amounts of **2a**, but no **4aa** was observed (Scheme 4a). The LC-MS real-time analysis of the reaction mixture also revealed that no **4aa** was observed during the reaction. Both the experimental results highlighted the exclusive chemoselectivities and excellent regioselectivities. The annulation process was fully suppressed in the presence of radical scavenger (TEMPO, BHT and 1,1-diphenylethylene), and the TEMPO-CH_2NHPh adduct (**5aa**), BHT-CH_2NHPh adduct (**5ab**) and diphenylethylene-CH_2NHPh adduct (**5ac**) were detected (Scheme 4b). These results indicated that the phenylaminomethyl radical intermediate was involved in the present reaction. Treatment of **1a** and **2a** in the presence of molecular iodine (1 equiv.) at room temperature in MeOH aqueous solution could give the desired product **3aa** in 45% yield (Scheme 4c).

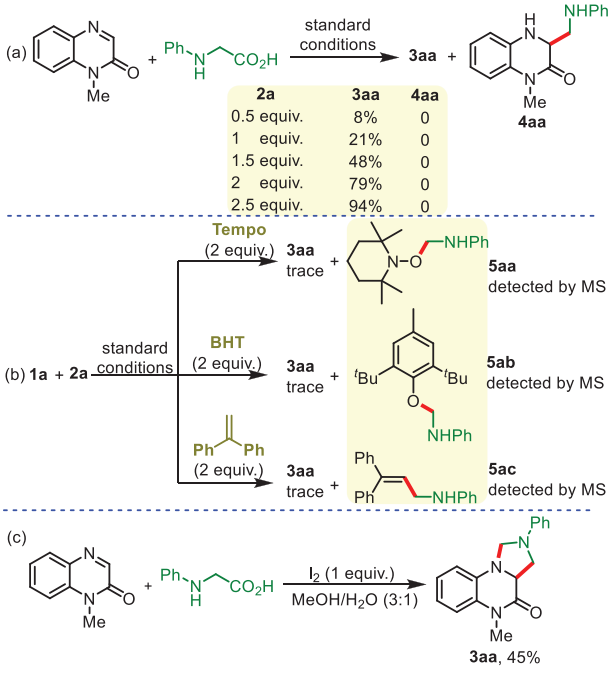
The cyclic voltammograms (CV) of related compounds were next investigated. *N*-Phenylglycine **2a** presented a higher oxidative potential (E_{onset} = 0.82 V, $E_{p/2}$ = 1.20 V, Fig. 1, curve a) with anhydrous methanol as the solvent, whereas the lowered potential of **2a** (E_{onset} = 0.42 V, $E_{p/2}$ = 0.91 V, Fig. 1, curve b) was observed



Scheme 2. Reaction scope. Conditions: Pt (15 mm × 10 mm × 0.1 mm) as the anode, C (15 mm × 10 mm × 2 mm) as the cathode, constant current = 7 mA, **1** (0.2 mmol), **2** (0.5 mmol), TBAI (20 mol%), MeOH (6 mL), H_2O (2 mL), room temperature, undivided cell. Isolated yields.



Scheme 3. Gram-scale synthesis of **3aa**.



Scheme 4. (a) LC-MS analysis of the reaction mixture; (b) Radical scavenger experiment; (c) I_2-Promoted annulation reaction.

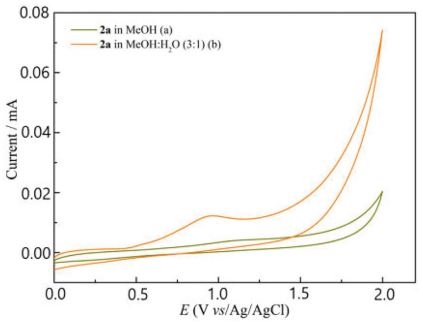


Fig. 1. Cyclic voltammograms with Pt (25 mm × 10 mm × 0.1 mm) glassy carbon as the working electrode, C (25 mm × 10 mm × 2 mm) as the counter electrode, Ag/AgCl (KCl) as the reference electrode in 0.1 mol/L $LiClO_4$ with different solvents, scan rate 50 mV/s: (a) 5 mmol/L of **2a** in MeOH, (b) 5 mmol/L of **2a** in MeOH/H_2O (3:1).

after the addition of water. These results are in accordance with the yield of **3aa** in anhydrous methanol and the mixed solvent of MeOH/H_2O (Table 1, entry 1 *vs.* 17). We believe that the reduction of oxidative potential was due to the formation of hydrogen bond association between glycine and water. TBAI displayed two obvious oxidation peaks at 0.61 V and 1.80 V (Fig. 2, curve a), which can be assigned to the oxidation of iodide ion into triiodide ion (I^- to I_3^-) and the oxidation of triiodide ion into molecular iodine (I_3^- to I_2) [59]. An un-conspicuous oxidative peak of **1a** was appeared at 1.66 V, which was much higher than that of **2a** and TBAI, indicating that the oxidation of **2a** and TBAI might occur preferentially.

Based on the above mechanistic investigations and previous related reports [50,51], a possible mechanism for the cooperative electrocatalytic decarboxylation coupling-annulation reaction was proposed, as shown in Scheme 5. Firstly, an energetically favorable six-membered ring intermediate **A** was produced due to

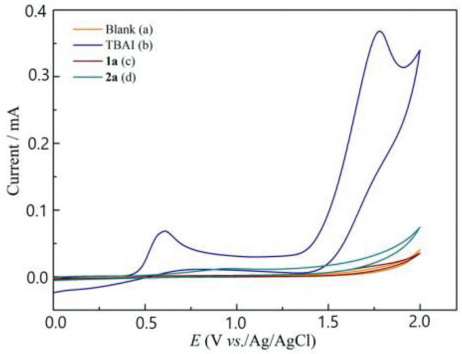
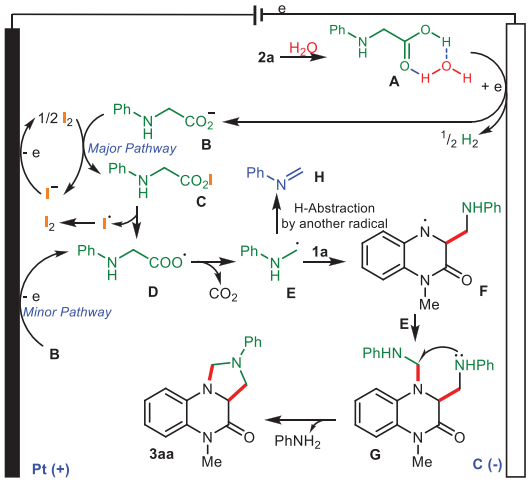


Fig. 2. Cyclic voltammograms with Pt (25 mm × 10 mm × 0.1 mm) as the working electrode, C (25 mm × 10 mm × 2 mm) as the counter electrode, and Ag/AgCl (KCl) as the reference electrode in 0.1 mol/L $LiClO_4$ with MeOH/H_2O (3:1) at 50 mV/s: (a) 5 mmol/L of TBAI, (b) 5 mmol/L of **1a** and (c) 5 mmol/L of **2a**.



Scheme 5. Plausible reaction mechanism.

the formation of intermolecular hydrogen bond between of *N*-phenylglycine **2a** and H_2O, by which the covalent O-H of **2a** was effectively activated. The cathodic reduction of intermediate **A** then gave the *N*-phenylglycine anion **B** and H_2. Meanwhile, the anodic-oxidation of an iodide ion generated the molecular iodine, which reacted with intermediated **B** to form a hypoiodite intermediated **C**, followed by the homolytic cleavage to produce the oxygen-centred radical **D** accompanied with regeneration of iodide ion. The aminomethyl radical **E**, generated from the decarboxylation of radical **D**, regioselectively attacked the C3 position of **1a** to deliver a nitrogen-centred radical **F**, followed by coupling with another molecular radical **E** to yield the intermediate **G**. Eventually, the target product **3aa** was formed through the intra-molecular nucleophilic substituent. Considering the moderate oxidative potential of *N*-phenylglycine, we can not rule out the possibility that the direct anodic oxidation of intermediate **B** to generate the carboxyl radical **D** as a minor pathway. A trace amount of iminium species **H** (generated through the oxidation of radical **E**) was detected by GC-MS. Because no compound **4aa** was detected during the model reaction process, the formation of intermediate **G** through the addition of **4aa** to intermediate **H** can be ruled out.

To summarize, we have developed a TBAI/H_2O cooperative electrocatalytic decarboxylation coupling-annulation of quinoxalin-2(1*H*) ones with *N*-arylglycines. **A** broad range of tetrahydroimidazo[1,5-*a*]quinoxalin-4(5*H*)-ones (30 examples, 67%-88%) were obtained in good to excellent yields with exclusive chemoselectivities and excellent regioselectivities. The reaction proceeds under chemical oxidant-, additive-, exogenous electrolyte-free and mild conditions with high functional-group tolerance, as demonstrated by the acid-, base- and oxidant-sensitive groups can be well tolerated. Mechanistic studies revealed that the generated H-bond between *N*-arylglycine and water served as a key factor for yielding α-aminomethyl radical at lower oxidative potential. Both the water (co-solvent and co-catalyst) and TBAI (catalyst and electrolyte) played dual functions in the electrolysis system.

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.

Acknowledgment

We are grateful for financial support from the University of South China.

References

[1] N. Chen, H.C. Xu, Chem. Rec. 21 (2021) 2306–2319.
[2] N. Chen, H.C. Xu, Green Synth. Catal. 2 (2021) 165–178.
[3] Z. Yang, Y. Yu, L. Lai, et al., Green Synth. Catal. 2 (2021) 19–26.
[4] D. Chen, X. Nie, Q. Feng, et al., Angew. Chem. Int. Ed. 60 (2021) 27271–27276.
[5] H. Shen, D. Cheng, Y. Li, et al., Green Synth. Catal. 1 (2020) 175–179.
[6] J. Jiang, Z. Wang, W.M. He, Chin. Chem. Lett. 32 (2021) 1591–1592.
[7] H. Wu, X. Yu, Z. Cao, Chin. J. Org. Chem. 41 (2021) 4712–4717.
[8] S. Guo, L. Liu, K. Hu, et al., Chin. Chem. Lett. 32 (2021) 1033–1036.
[9] S. Cheng, C. Ou, H. Lin, et al., Chin. J. Org. Chem. 41 (2021) 4718–4724.
[10] Z.L. Wu, J.Y. Chen, X.Z. Tian, et al., Chin. Chem. Lett. 33 (2022) 1501–1504.
[11] Z. Shi, Y. Li, N. Li, et al., Angew. Chem. Int. Ed. 61 (2022) e202206058.
[12] J.Y. Chen, H.X. Li, S.Y. Mu, et al., Org. Biomol. Chem. 20 (2022) 8501–8505.
[13] K. Liu, C. Song, A. Lei, Org. Biomol. Chem. 16 (2018) 2375–2387.
[14] H.T. Tang, J.S. Jia, Y.M. Pan, Org. Biomol. Chem. 18 (2020) 5315–5333.
[15] M. Saito, Y. Kawamata, M. Meanwell, et al., J. Am. Chem. Soc. 143 (2021) 7859–7867.
[16] Z.H. Wang, P.S. Gao, X. Wang, et al., J. Am. Chem. Soc. 143 (2021) 15599–15605.
[17] Z. Tan, X. He, K. Xu, C. Zeng, ChemSusChem 15 (2022) e202102360.
[18] X. Meng, H. Xu, R. Liu, Y. Zheng, S. Huang, Green Chem. 24 (2022) 4754–4760.
[19] T. Feng, S. Wang, Y. Liu, S. Liu, Y. Qiu, Angew. Chem. Int. Ed. 61 (2022) e202115178.
[20] M. Chen, Z.J. Wu, J. Song, H.C. Xu, Angew. Chem. Int. Ed. 61 (2022) e202115954.
[21] P.S. Gao, X.J. Weng, Z.H. Wang, et al., Angew. Chem. Int. Ed. 59 (2020) 15254–15259.
[22] W. Li, Y. Tang, W. Ouyang, et al., Chin. J. Org. Chem. 41 (2021) 4766–4772.
[23] H. Xu, X. Meng, Y. Zheng, J. Luo, S. Huang, Chin. J. Org. Chem. 41 (2021) 4696–4703.
[24] M. Nourisefat, F. Panahi, A. Khalafi-Nezhad, Mol. Divers. 23 (2019) 317–331.
[25] H. Yang, G. Wei, Z. Jiang, ACS Catal. 9 (2019) 9599–9605.
[26] W. Hu, Q. Zhan, H. Zhou, S. Cao, Z. Jiang, Chem. Sci. 12 (2021) 6543–6550.
[27] Y. Song, H. Zhang, J. Guo, et al., Eur. J. Org. Chem. 2021 (2021) 5914–5921.
[28] H. Xin, Z.H. Yuan, M. Yang, et al., Green Chem. 23 (2021) 9549–9553.
[29] X. Huang, Y.Q. Hu, C. Zhou, Y. Zheng, X. Zhang, Green Chem. 24 (2022) 5764–5769.
[30] W. Zeng, W. Li, H. Chen, L. Zhou, Org. Lett. 24 (2022) 3265–3269.
[31] X. Chai, X. Hu, X. Zhao, et al., Angew. Chem. Int. Ed. 61 (2022) e202115110.
[32] S. Li, X. Li, T. Wang, et al., Adv. Synth. Catal. 364 (2022) 2346–2351.
[33] M. Montana, V. Montero, O. Khoumeri, P. Vanelle, Molecules 25 (2020) 2784.
[34] J.W. Yuan, J.L. Zhu, H.L. Zhu, et al., Org. Chem. Front. 7 (2020) 273–285.
[35] K. Niu, L. Ding, P. Zhou, et al., Green Chem. 23 (2021) 3246–3249.
[36] D. Li, X. Wang, S. Li, et al., Chin. J. Org. Chem. 41 (2021) 4610–4622.
[37] M. Cao, Y.L. Fang, Y.C. Wang, et al., ACS Comb. Sci. 22 (2020) 268–273.
[38] L.Y. Xie, Y.S. Liu, H.R. Ding, et al., Chin. J. Catal. 41 (2020) 1168–1173.
[39] J. Xu, L. Huang, L. He, et al., Green Chem. 23 (2021) 6632–6638.
[40] N. Meng, Y. Lv, Q. Liu, et al., Chin. Chem. Lett. 32 (2021) 258–262.
[41] L. Yao, D. Zhu, L. Wang, et al., Chin. Chem. Lett. 32 (2021) 4033–4037.
[42] Z. Wang, Q. Liu, R. Liu, et al., Chin. Chem. Lett. 33 (2022) 1479–1482.
[43] L. Ding, K. Niu, Y. Liu, Q. Wang, Chin. Chem. Lett. 33 (2022) 4057–4060.
[44] K. Sun, F. Xiao, B. Yu, W.M. He, Chin. J. Catal. 42 (2021) 1921–1943.
[45] Q.Q. Han, D.M. Chen, Z.L. Wang, et al., Chin. Chem. Lett. 32 (2021) 2559–2561.
[46] X. Jiang, K. Wu, R. Bai, P. Zhang, Y. Zhang, Eur. J. Med. Chem. 229 (2022) 114085.
[47] Q. Yang, Y. Zhang, Q. Sun, et al., Adv. Synth. Catal. 360 (2018) 4509–4514.
[48] J. Wen, W. Zhao, X. Gao, et al., J. Org. Chem. 87 (2022) 4415–4423.
[49] A. Talukdar, D. Ganguly, S. Roy, N. Das, D. Sarkar, J. Med. Chem. 64 (2021) 8010–8041.

[50] Y.F. Si, X.L. Chen, X.Y. Fu, et al., ACS Sustain. Chem. Eng. 8 (2020) 10740–10746.
[51] Y.F. Si, K. Sun, X.L. Chen, et al., Org. Lett. 22 (2020) 6960–6965.
[52] J. Jiang, F. Xiao, W.M. He, L. Wang, Chin. Chem. Lett. 32 (2021) 1637–1644.
[53] J.Y. Chen, H.Y. Wu, Q.W. Gui, et al., Chin. J. Catal. 42 (2021) 1445–1450.
[54] J.Y. Chen, C.T. Zhong, Q.W. Gui, et al., Chin. Chem. Lett. 32 (2021) 475–479.
[55] Y. Wu, J.Y. Chen, H.R. Liao, et al., Green Synth. Catal. 2 (2021) 233–236.
[56] Y. Wu, J.Y. Chen, J. Ning, et al., Green Chem. 23 (2021) 3950–3954.
[57] W.B. He, S.J. Zhao, J.Y. Chen, et al., Chin. Chem. Lett. 34 (2023) 107640.
[58] H. Li, P. Chen, Z. Wu, et al., Chin. J. Org. Chem. 42 (2022) 3398–3404.
[59] V.A. Macagno, M.C. Giordano, A.J. Arvía, Electrochim. Acta 14 (1969) 335–357.