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通过电化学 Appel 反应合成腈

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摘要 探索了一种通过电化学 Appel 反应合成腈的方法. 该方法具有操作简单、反应条件温和、环境友好的优点, 可以合成一系列芳香腈和脂肪腈类化合物. 在循环伏安实验和控制实验基础上, 提出了电化学 Appel 反应机理用于解释反应过程.

关键词 电化学合成; Appel 反应; 肟的脱水; 腈的合成

Synthesis of Nitrile via Electrochemical Appel Reaction

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Abstract An electrochemical Appel reaction was developed for the synthesis of nitriles. This protocol features operationally simplicity, mild reaction conditions and environmental friendliness, enabling synthesis of various aromatic and aliphatic nitriles. Based on the controlled experiments and cyclic voltammetry (CV) experimental results, an electrochemical Appel reaction mechanism was proposed to explain the reaction process.

Keywords electrochemical synthesis; Appel reaction; dehydration of oximes; synthesis of nitriles

1 Introduction

Nitrile is a class of vital structural motifs widely exist in natural products, pharmaceuticals, agrochemicals, dyes and fine chemicals.[1] Moreover, nitriles serve as important synthetic intermediates which can be converted into amides, aldehydes, ketones, carboxylic acids, heterocycles and so on.[2] Because the nitrile groups can form hydrogen bonds with some certain receptors of the organisms, it is also a kind of common pharmacophore and many drugs contain nitrile groups.[3] For example, Febuxostat is reported as a non-purine xanthine oxidase inhibitor for the treatment of gout.[4] Zaleplon is a non-benzodiazepine hypnotic drug used for treating insomnia.[5] As a calcium channel antagonist, verapamil can be used as an antiarrhythmic agent to treat angina.[6] In addition, levocabastine is a selective second-generation H_1-receptor antagonist used for allergic conjunctivitis (Figure 1).[7]

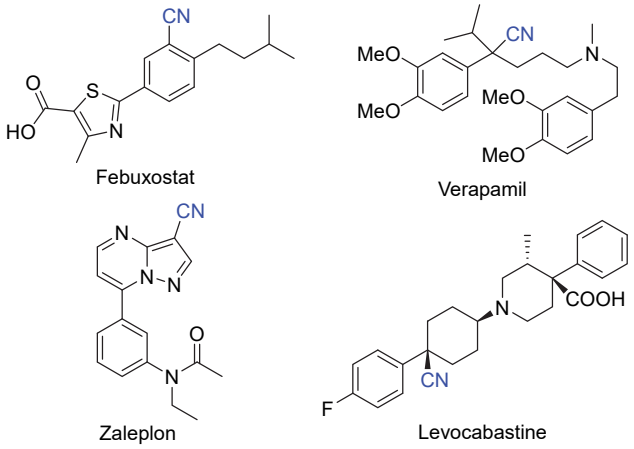

Figure 1 Representative pharmaceuticals containing nitrile groups

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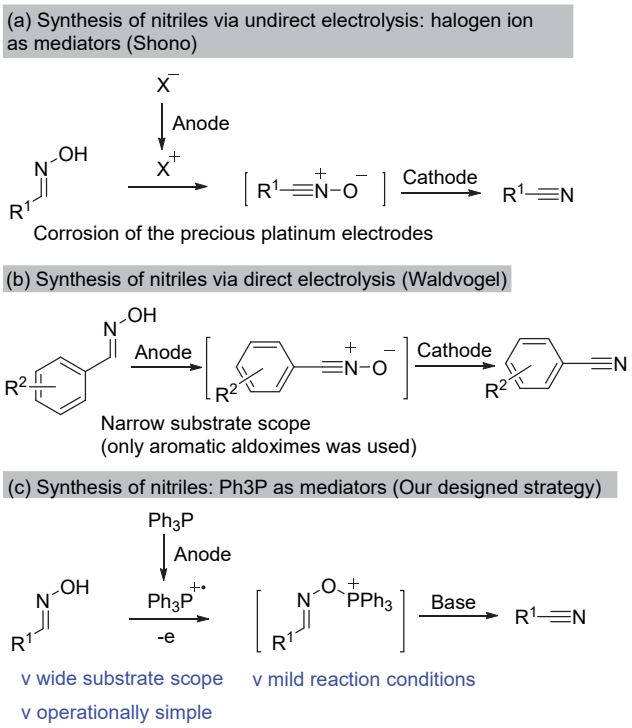
For the synthesis of nitriles, many methods have been reported in the past decades, including dehydration of aldoximes,[8] amides,[9] dehydrogenation of amines,[10] cyanation of alkyl halides,[11] aldehydes[12] and others.[13] Among the numerous synthetic methods, the dehydration of aldoximes appears to be attractive because of the ready availability of the starting materials. Simultaneously, a variety of reagents have proved to be effective for this transformation.[14] Despite these advances, there is still highly desirable to develop a safe, cheap, easy-to-operate method for the dehydration of aldoximes to nitriles.

Recently, increasing attention has been paid to organic electrosynthesis,[15-16] which is recognized as an environmentally friendly synthetic technique due to the use of electron, rather than the traditional redox reagents, as the mass-free oxidants/reductants. Because of these characteristics, the electrochemical strategy was also used for the preparation of nitriles. Onomura *et al.*[17] reported an electrochemical method for the synthesis of *α*-cyanation N-protected cyclic amines using TMSCN as a cyano source. Using the same cyanide source, Sun *et al.*[18a] described electrochemical oxidative regioselective C—H cyanation of imidazo[1,2-*a*]pyridines and cyanation imidazopyridines can be accessed through this strategy. With 2,2,6,6-tetramethyl-piperidinyl-*N*-oxyl (TEMPO) as mediators, Mei *et al.*[18b] reported *α*-cyanation of cyclic amines. This method has merits of avoiding over oxidation of some electron rich aromatic amines. A sequential electro-oxidation decarboxylation and Kolbe coupling strategy was developed by Fu *et al.*[19] in the synthesis of adiponitrile from glutamic acid 5-methyl ester. Through electrochemical oxidation process, Wang *et al.*[20] reported a preparation method of aryl nitriles from primary benzylic azides. Using NH_4I as the supporting electrolyte and nitrogen source, an electrochemical method for the conversion of aldehydes into nitriles was developed by Yuan *et al.*[21] However, to the best of our knowledge, there are only two examples of electrocatalytic synthesis of nitriles using aldoximes as starting materials. Shono *et al.*[22] reported the first example of electrochemical protocol to generate nitriles from aldoximes with halogen ions as mediators (Scheme 1, a). However, such halogen species could cause corrosion of the precious platinum electrodes. After that, Waldvogel *et al.*[23] developed a direct halogen-free strategy for the synthesis of nitriles from oximes (Scheme 1, b). This method could avoid the corrosion of platinum electrodes but only was used for the synthesis of aromatic nitriles. Despite the above-mentioned advances, methods with mild conditions and wide applicability are still urgently in demand. As far as we know, under electrocatalytic conditions, triphenylphosphine can be oxidized to phosphorus radicalcations.[24] In combination with strong binding ability of phosphorus with oxygen, we herein wish to develop a new method for the synthesis of nitriles from aldoximes with PPh_3 as mediators.

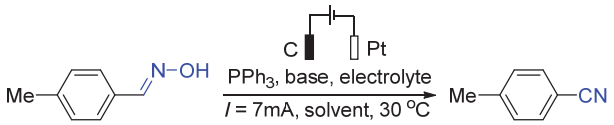


Scheme 1 Electrochemical synthesis of nitriles from aldoximes

2 Results and discussion

Our investigations were commenced with aldoxime **1a**[14g,25] as model substrate to explore the reaction conditions. Firstly, the reaction was carried out with carbon rod as anode and Pt as cathode at constant current of 7 mA in the presence of PPh_3 as catalyst, ^{n}Bu_4NPF_6 as electrolyte, $NaHCO_3$ as base at argon atmosphere. Under these conditions, the desired product nitrile **2a** was obtained in 67% NMR yield (Table 1, Entry 1). Using ^{t}Bu_3P, tri-2-furylphosphine or tripyrrolidinophosphine in place of PPh_3, lower yields were observed (Table 1, Entries 2～4). Replacement of ^{n}Bu_4NPF_6 with other electrolyte, such as ^{n}Bu_4NBF_4, Me_4NBF_4, ^{n}Bu_4NClO_4, $LiClO_4$, TBAB or TBAI, the highest yield (83%) could be obtained when TBAB was used (Table 1, Entries 5～10). Subsequently, several common organic and inorganic bases were screened. However, all of them led to inferior results (Table 1, Entries 11～14). When changing the reaction solvents, the reaction yield was not significantly improved (Table 1, Entries 15～18). Considering that the electrode has a vital influence in the electro-organic synthetic reactions, different electrode was tested. When alter the cathode materials, such as carbon rods, graphite felt, RVC were respectively used as cathode, lower yield was obtained (Table 1, Entries 19～21). In the control experiment, nitrile was not detected in the absence of triphenylphosphine which proved that triphenylphosphine is indispensable in this dehydration reaction (Table 1, Entry 22).

Table 1 Optimization of reaction conditions[a]



1a 2a

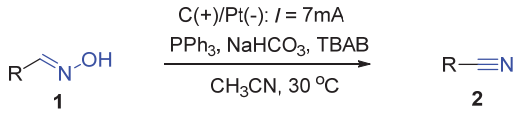
Entry	Electrolyte	Solvent	Base	Yield[b]/%
1	$^{n}Bu_4NPF_6$	CH_3CN	$NaHCO_3$	67
2[c]	$^{n}Bu_4NPF_6$	CH_3CN	$NaHCO_3$	33
3[d]	$^{n}Bu_4NPF_6$	CH_3CN	$NaHCO_3$	26
4[e]	$^{n}Bu_4NPF_6$	CH_3CN	$NaHCO_3$	48
5	$^{n}Bu_4NBF_4$	CH_3CN	$NaHCO_3$	41
6	Me_4NBF_4	CH_3CN	$NaHCO_3$	55
7	$^{n}Bu_4NClO_4$	CH_3CN	$NaHCO_3$	60
8	$LiClO_4$	CH_3CN	$NaHCO_3$	11
9	TBAB	CH_3CN	$NaHCO_3$	85 (83)[f]
10	TBAI	CH_3CN	$NaHCO_3$	60
11	TBAB	CH_3CN	Na_2CO_3	70
12	TBAB	CH_3CN	K_3PO_4	46
13	TBAB	CH_3CN	Cs_2CO_3	69
14	TBAB	CH_3CN	Et_3N	44
15	TBAB	THF	$NaHCO_3$	0
16	TBAB	DCM	$NaHCO_3$	48
17	TBAB	DMF	$NaHCO_3$	15
18	TBAB	Dioxane	$NaHCO_3$	0
19[g]	TBAB	CH_3CN	$NaHCO_3$	64
20[h]	TBAB	CH_3CN	$NaHCO_3$	57
21[i]	TBAB	CH_3CN	$NaHCO_3$	50
22[j]	TBAB	CH_3CN	$NaHCO_3$	0

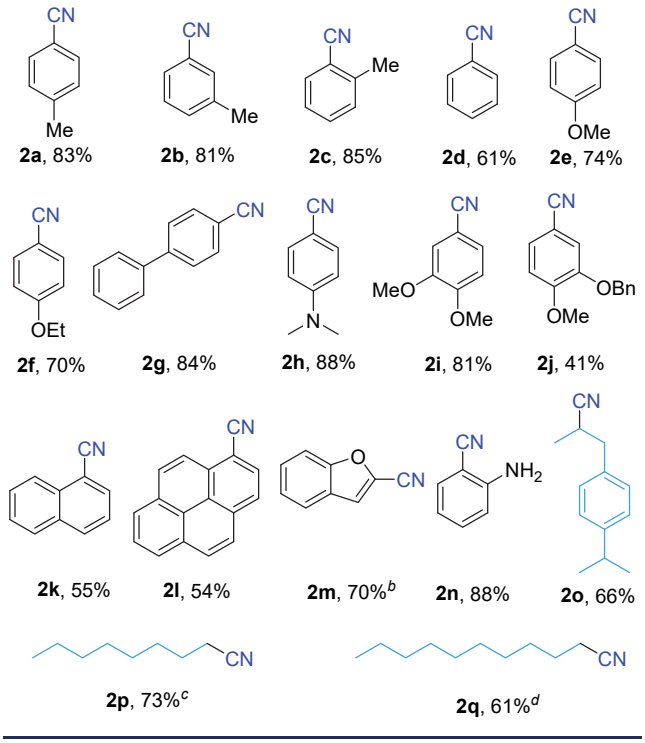
[a] Reaction conditions: carbon anode, Pt cathode, constant current=7 mA, **1a** (0.1 mmol), PPh_3 (0.15 mmol), base (0.2 mmol), electrolyte (0.08 mol/L), solvent (6 mL), under Ar; [b] Yield determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard; [c-e] $^{t}Bu_3P$, tri-2-furylphosphine, tripyrrolidinophosphine were used as catalysts respectively; [f] Isolated yield was shown in brackets; [g] Carbon anode, carbon cathode; [h] Carbon anode, graphite felt cathode; [i] Carbon anode, RVC cathode, Pt cathode; [j] No PPh_3.

With the optimized reaction conditions in hand, a series of aldoximes **1** were then screened to establish the general utility of this transformation and the results were collected in Table 2. Substrates with various groups at *ortho*, *meta* and *para* positions of benzene ring could proceed well under the optimal reaction conditions. For example, methyl, methoxyl, ethoxyl, phenyl, and dimethylaminoyl could be compatible with the reaction conditions (Table 2, **2a**～**2h**). Moreover, aldoximes with disubstituted groups or fused rings were also amenable to this reaction system, the corresponding nitriles could be acquired in moderate to excellent isolated yields (Table 2, **2i**～**2l**). When heterocyclic oxime was used as substrate, dehydrate product **2m** was also obtained in 70% isolated yield. Naked amine has no effect on this reaction and the corresponding nitrile was formed in 88% isolated yield (Table 2, **2n**). Noteworthily, aliphatic nitriles could also be obtained under optimized conditions when aliphatic oximes were used as substrates (Table 2, **2o**～**2q**).

To evaluate the synthetic potential of this protocol, a gram-scale reaction on 8.0 mmol scale was performed and

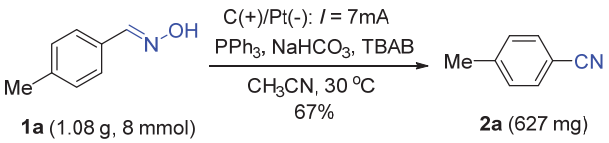
Table 2 Substrate scope of aldoximes[a]





[a] Reaction conditions: **1** (0.2 mmol), PPh_3 (0.3 mmol), $NaHCO_3$ (0.4 mmol), TBAB (0.5 mmol), CH_3CN (6 mL), under Ar, 30 ℃, 1～2 h; [b] 0.4 mmol of PPh_3 and 5 mA of constant current were used; [c] 0.4 mmol of PPh_3 was used; [d] 0.6 mmol of PPh_3 was used.

product **2a** could be easily obtained in 67% yield (Scheme 2).



1a (1.08 g, 8 mmol) **2a** (627 mg)

Scheme 2 Gram-scale synthesis

To insight the reaction mechanism, cyclic voltammetry (CV) experiments were performed using glassy carbon as working electrode, Pt wire as counter electrode and Ag/Ag^+ as reference electrode with the scan rate at 0.1 V•s^{-1} (Figure 2). The results of cyclic voltammetry experiments revealed that bromide ion is more easily oxidized than PPh_3 in CH_3CN. The control experiments (Scheme 3, a and b) demonstrated that Br_2 can be first generated on the anode.[24] Considering the presence of PPh_3, phosphonium salt PPh_3Br_2 may form in this process.[25] To further insight into the reaction process, the following control experiments were then conducted (Scheme 3). First, to verify whether phosphonium salt PPh_3Br_2 was produced during the process of this reaction, the electrolytic reaction was

conducted in the absence of substrate aldoxime (The addition of pyridine hydrobromide was to balance the electrons formed at the cathode). ^{31}P NMR analysis of the reaction mixture immediately after electrolysis at 30 ℃ revealed one major peak, which corresponds to phosphonium salt PPh_3Br_2 (Scheme 3, a). Then, treated the aldoxime **1a** with phosphonium salt PPh_3Br_2 and sodium bicarbonate, 41% nitrile **2a** was obtained and 42% aldoxime **1a** was recovered (Scheme 3, b). The experimental results show that phosphate PPh_3Br_2 may be generated in the reaction process.

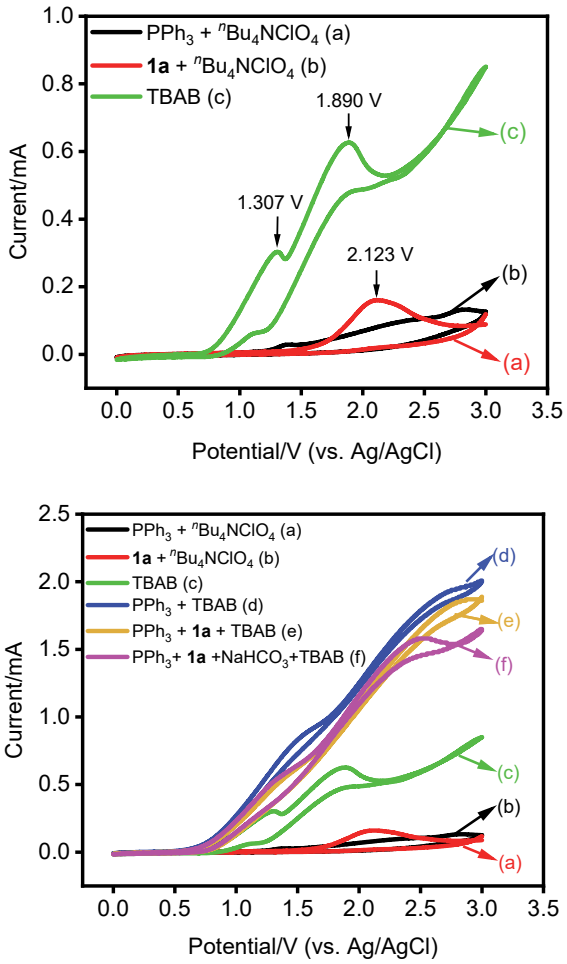
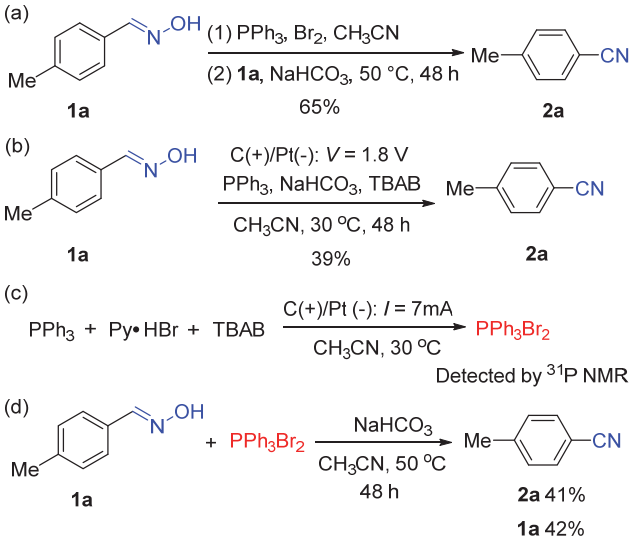


Figure 2 CV experiments

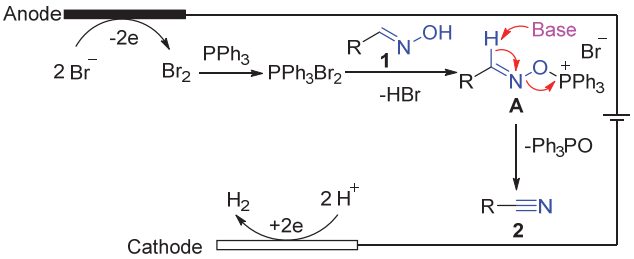
Based on the CV and controlled experimental results, a plausible Appel-style mechanism was proposed in Scheme 4. First, bromide ion was oxidized at anode to produce Br_2, and then Br_2 can coupled with PPh_3 to generate PPh_3Br_2, which was attacked by aldoxime and concomitantly eliminated an HBr to give intermediate **A**. In the presence of base, intermediate **A** eliminated Ph_3PO and HBr to afford desired product nitriles. At the cathode, H_2 was released from reduction of hydrogen ions.

3 Conclusions

In conclusion, an electrochemical Appel reaction for the synthesis of nitriles with PPh_3 and TBAB as mediators was developed. This protocol features operationally simplicity, mild reaction conditions and environmental friendliness, enabling synthesis of various aromatic and aliphatic nitriles. Ultimately, an electrochemical Appel reaction mechanism was proposed based on the controlled experiments and CV experimental results. This method will open a new avenue for the synthesis of nitriles.



Scheme 3 Controlled experiments.



Scheme 4 Proposed reaction mechanism

4 Experimental section

4.1 General information.

All the electrochemical reactions were performed in an undivided cell equipped with the carbon rod (Φ=6 mm) as anode and a platinum plate (1 cm×1 cm) as cathode unless otherwise noted. All glassware was thoroughly oven-dried before use. Commercial reagents were used as received unless otherwise stated. The purchased solvents were dried over molecular sieves and degassed by three cycles of freeze-pump-thaw before use in the reaction. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. All commercial reagents were purchased from Aladdin, Sigma-Aldrich, Adamas-beta, 9-Ding Chemistry and Energy Chemical of the highest purity grade. ^{1}H NMR and ^{13}C NMR spectra were recorded respectively at 400 and 100 MHz on a Bruker AVANCE 400 and chemical shifts are referenced to resid-

ual undeuterated solvent signal for ^{1}H NMR (δ 7.26) and ^{13}C NMR (δ 77.16). HRMS was conducted on a Thermo Scientific LTQ Orbitrap XL apparatus. All the electrochemical reactions were performed with an HY3005B DC (30 V) power supply purchased from Zhejiang Huayi Electronic Industry Co., Ltd. The electrochemical reactions were conducted in a 10 mL three-necked round-bottom flask with a magnetic stir bar and with a carbon rod (Φ=6 mm) as anode and a platinum plate (1 cm×1 cm) as cathode with a distance of about 1.0 cm between the two electrodes. Carbon rod was purchased from Beijing Jinglong special carbon technology Co., Ltd. Platinum plate was purchased from Shanghai Yueci Electronic Technology Co., Ltd.

4.2 Preparation of substrates

The substrates were prepared according to the reference method. Aldehyde (3 mmol) was dissolved in MeOH (12 mL). Hydroxylamine hydrochloride (417 mg, 6 mmol) was added to the stirred solution, followed by sodium acetate (492 mg, 6 mmol) and 12 mL of water. The reaction was stirred until aldehyde was completely consumed. Ethyl acetate (EA) (20 mL) was added and the mixture was extracted with EA (20 mL×3) drying over Na_2SO_4, filtration, concentration in vacuo and flash chromatography (petroleum ether (PE) or PE/EA) afforded the desired aldoximes.

4.3 General procedure for the synthesis of nitrile 2a～2q

Aldoxime (0.2 mmol), PPh_3 (79 mg, 0.3 mmol), TBAB (161mg, 0.5 mmol), $NaHCO_3$ (34 mg, 0.4 mmol) and anhydrous CH_3CN (6.0 mL) were added to a three-necked round bottom flask. The flask was equipped with carbon rod (Φ=6 mm) as anode and a platinum plate (1 cm×1 cm) as cathode. The reaction was electrolyzed at 30 ℃ using a constant current of 7 mA under Ar atmosphere until complete consumption of the substrate (monitored by thin layer chromatography (TLC), 1～2 h). Then the mixture was transferred to a flask and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (PE/EA) to afford corresponding nitriles.

4.4 Controlled experiments.

Br_2 (64 mg, 0.4 mmol) was added to a solution of PPh_3 (105 mg, 0.4 mmol) in CH_3CN (4 mL). After stirring for 2 h, **1a** (27 mg, 0.2 mmol) and $NaHCO_3$ (34 mg, 0.4 mmol) were added to the solution. Then the reaction was stirred at 50 ℃ for 48 h. The yield (65%) was determined by ^{1}H NMR spectra for the crude product.

Aldoxime (0.2 mmol), PPh_3 (79 mg, 0.3 mmol), TBAB (161 mg, 0.5 mmol), $NaHCO_3$ (34 mg, 0.4 mmol), anhydrous CH_3CN (6.0 mL) was added to a three-necked round bottom flask. The flask was equipped with carbon rod (Φ=6 mm) as anode and a platinum plate (1 cm×1 cm) as cathode. The reaction was electrolyzed at 30 ℃ using a constant voltage of 1.8 V under Ar atmosphere for 48 h. Then the mixture was transferred to a flask and the solvent was removed *in vacuo*. The yield (39%) was determined by ^{1}H NMR spectra for the crude product.

PPh_3 (52 mg, 0.2 mmol), TBAB (161mg, 0.5 mmol), Py•HBr (64 mg, 0.4 mmol) and anhydrous CH_3CN (6.0 mL) were added to a three-necked round bottom flask. The flask was equipped with carbon rod (Φ=6 mm) as anode and a platinum plate (1 cm×1 cm) as cathode. The reaction was electrolyzed at 30 ℃ using a constant current of 7 mA under Ar atmosphere for 2 h. Then the mixture was transferred to a flask and the solvent was removed *in vacuo*. The residues were dissolved with $CDCl_3$ and ^{31}P NMR was tested.

Aldoxime **1a** (27 mg, 0.2 mmol), PPh_3Br_2 (127 mg, 0.3 mmol), $NaHCO_3$ (34 mg, 0.4 mmol) and anhydrous CH_3CN (6.0 mL) were added to a 25 mL round bottom flask and the mixture was stirred at 50 ℃ for 48 h. Then the solvent was removed *in vacuo* and the residues was purified by flash chromatography to afford nitrile **2a** (9.6 mg, 41%) and aldoxime **1a** (11.3 mg, 42%).

For the ^{31}P NMR of PPh_3Br_2, the addition of pyridine to eliminate the effect of pyridine on the test (the copies of ^{31}P NMR spectra in page S37 of supporting information).

4.5 Characterization data for obtained products.

p-Methylbenzonitrile (**2a**): Yellow liquid (83% yield, 19.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53 (d, J=8.0 Hz, 2H), 7.26 (d, J=8.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.8, 132.1, 129.9, 119.2, 109. 5, 21.9; HRMS (ESI) calcd for C_8H_8N $[M+H]^+$ 118.0652, found 118.0652.

3-Methylbenzonitrile (**2b**): Yellow liquid (81% yield, 18.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45～7.44 (m, 2H), 7.39 (d, J=8.0 Hz, 1H), 7.34 (t, J=8.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.3, 133.7, 132.6, 129.4, 129.1, 119.1, 112.4, 21.2; HRMS (ESI) calcd for C_8H_8N $[M+H]^+$ 118.0652, found 118.0656.

2-Methylbenzonitrile (**2c**): Yellow liquid (85% yield, 19.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, J=7.6 Hz, 1H), 7.47 (t, J=7.6 Hz, 1H), 7.31～7.24 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.1, 132.7, 132.6,130.3, 126.3, 118.2, 112.9, 20.6; HRMS (ESI) calcd for C_8H_8N $[M+H]^+$ 118.0652, found 118.0655.

Benzonitrile (**2d**): Colorless liquid (61% yield, 12.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65～7.58 (m, 3H), 7.46 (t, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.8, 132.2, 129.2, 118.9, 112.5; HRMS (ESI) calcd for C_7H_6N $[M+H]^+$ 104.0495, found 104.0501.

4-Methoxybenzonitrile (**2e**): Yellow liquid (74% yield, 19.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, J=8.8 Hz, 2H), 6.95 (d, J=8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.0, 134.1, 119.3, 114.9, 104.1, 55.7; HRMS (ESI) calcd for C_8H_8NO $[M+H]^+$ 134.0600, found 134.0608.

4-Ethoxybenzonitrile (**2f**): Yellow liquid (70% yield, 20.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, J=8.8 Hz, 2H), 6.92 (d, J=8.8 Hz, 2H), 4.07 (q, J=7.2 Hz, 2H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:

162.4, 134.1, 119.4, 115.3, 103.9, 64.1, 14.7; HRMS (ESI) calcd for $C_9H_{10}NO$ $[M+H]^+$ 148.0757, found 148.0764.

[1,1'-Biphenyl]-4-carbonitrile (**2g**): Yellow solid (84% yield, 30.2 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.71 (q, J=8.4 Hz, 4H), 7.59 (d, J=8.0 Hz, 2H), 7.49 (t, J=8.0 Hz, 2H), 7.43 (t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.8, 139.3, 132.7, 129.2, 128.8, 127.9, 127.3, 119.0, 111.1; HRMS (ESI) calcd for $C_{13}H_{10}N$ $[M+H]^+$ 180.0808, found 180.0814.

4-(Dimethylamino)benzonitrile (**2h**): Yellow liquid (88% yield, 25.7 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.45 (d, J=8.8 Hz, 2H), 6.63 (d, J=8.4 Hz, 2H), 3.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.6, 133.5, 120.8, 111.5, 40.0; HRMS (ESI) calcd for $C_9H_{11}N_2$ $[M+H]^+$ 147.0917, found 147.0923.

3,4-Dimethoxybenzonitrile (**2i**): Yellow solid (81% yield, 26.5 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.47 (d, J=9.6 Hz, 1H), 7.26 (s, 1H), 7.08 (d, J=8.4 Hz, 1H), 4.11 (s, 3H), 4.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.9, 148.2, 125.5, 118.2, 113.0, 110.3, 102.9, 55.1,55.1; HRMS (ESI) calcd for $C_9H_{10}NO_2$ $[M+H]^+$ 164.0706, found 164.0710.

3-(Benzyloxy)-4-methoxybenzonitrile (**2j**): Yellow liquid (41% yield, 19.5 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.43～7.29 (m, 6H), 7.10 (s, 1H), 6.91 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.7, 148.4, 136.0, 128.9, 128.4, 127.5, 127.0, 119.3, 116.6, 111.8, 103.9, 71.3, 56.2; HRMS (ESI) calcd for $C_{15}H_{14}NO_2$ $[M+H]^+$ 240.1019, found 240.1023.

1-Naphthonitrile (**2k**): Yellow liquid (55% yield, 16.6 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.24 (d, J=8.4 Hz, 1H), 8.08 (d, J=8.4 Hz, 1H), 7.94～7.91 (m, 2H), 7.70 (t, J=7.2 Hz, 1H), 7.62 (t, J=8.0 Hz, 1H), 7.53 (t, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.4, 133.1, 132.8, 132.5, 128. 6,128.7, 127.7, 125.3, 125.1, 117.9, 110.4; HRMS (ESI) calcd for $C_{11}H_8N$ $[M+H]^+$ 154.0651, found 154.0658.

4,8-Dihydropyrene-1-carbonitrile (**2l**): Yellow solid (54% yield, 25.8 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.47 (d, J=9.2 Hz, 1H), 8.34 (d, J=8.4 Hz, 2H), 8.31 (d, J=2.4 Hz, 1H), 8.26 (t, J=7.6 Hz, 2H), 8.19 (d, J=8.0 Hz, 1H), 8.15～8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.4, 133.2, 131.1, 130.8,130.7,130.7, 129.8, 127.2, 127.2, 127.1, 127.1, 124.6, 124.3, 124.2, 123.8, 119.0, 105.8; HRMS (ESI) calcd for $C_{17}H_{10}N$ $[M+H]^+$ 228.0808, found 228.0812.

Benzofuran-2-carbonitrile (**2m**): Yellow liquid (70% yield, 20.0 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.65～7.58 (m, 3H), 7.46 (t, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.8, 128.6, 127.5, 125.6, 124.7, 122.7, 118.6, 112.2, 112.0; HRMS (ESI) calcd for C_9H_6NO $[M+H]^+$ 144.0444, found 144.0446.

2-Aminobenzonitrile (**2n**): Yellow liquid (88% yield, 20.9 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, J=8.0 Hz, 1H), 7.32 (t, J=7.6 Hz, 1H), 6.75～6.71 (m, 2H), 4.41 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.7, 134.1, 132.5, 118.1, 115.3, 96.2; HRMS (ESI) calcd for $C_7H_7N_2$ $[M+H]^+$ 119.0604, found 119.0613.

3-(4-Isopropylphenyl)-2-methylpropanenitrile (**2o**): Colorless liquid (66% yield, 24.7 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.18 (q, J=8.0 Hz, 4H), 2.94～2.77 (m, 4H), 1.33 (d, J=6.4 Hz, 3H), 1.25 (d, J=6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.0, 134.3, 129.1, 126.9, 122.8, 39.8, 33. 9, 27.7, 24.1, 17.8; HRMS (ESI) calcd for $C_{13}H_{18}N$ $[M+H]^+$ 188.1434, found 188.1438.

Nonanenitrile (**2p**): Colorless liquid (76% yield, 21.1 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.33 (t, J=7.2 Hz, 2H), 1.69～1.62 (m, 2H), 1.46～1.41 (m, 2H), 1.30～1.28 (m, 8H), 0.88 (t, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 119.9, 31.8, 29.1, 28.8,28.8, 25.5, 22.7, 17.2, 14.2; HRMS (ESI) calcd for $C_9H_{18}N$ $[M+H]^+$ 140.1434, found 140.1434.

Undecanenitrile (**2q**): Colorless liquid (61% yield, 20.4 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.32 (t, J=7.2 Hz, 2H), 1.68～1.61 (m, 2H), 1.45～1.40 (m, 2H), 1.29～1.26 (m, 12H), 0.87 (t, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 119.9, 31.9, 29.5, 29.4, 29.3, 28.9, 28.8, 25.5, 22.8, 17.2, 14.2; HRMS (ESI) calcd for $C_{11}H_{22}N$ $[M+H]^+$ 168.1747, found 168.1749.

Supporting Information Cyclic voltammograms and NMR spectra of compounds **2a**～**2q**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

References

[1] (a) Dworczak, R.; Fabian, W. M. F.; Biza, P.; Weikmann, M.; Junek, H. *Dyes Pigm.* **1995**, *28*, 297.
(b) Dworczak, R.; Fabian, W. M. F.; Pawar, B. N.; Junek, H. *Dyes Pigm.* **1995**, *29*, 65.
(c) Pearce, E. M.; Weil, E. D.; Barinov, V. Y. *Fire Smart Polymers* (*Fire and Polymers*), American Chemical Society, **2001**, pp. 37～48.
(d) Amr, M. A.; Mohamed, H. E.; Mohamed, S. E.; Hesham, R. E.-S.; Ismail, A. A. *Curr. Org. Synth.* **2018**, *15*, 487.

[2] Fatiadi, A. J. In *Preparation and Synthetic Applications of Cyano Compounds*, Eds.: Patai, S.; Rappaport, Z., Wiley, New York, **1983**.

[3] (a) Iyengar, B. S.; Dorr, R. T.; Remers, W. A. *J. Med. Chem.* **2004**, *47*, 218.
(b) Romero, M.; Renard, P.; Caignard, D.-H.; Atassi, G.; Solans, X.; Constans, P.; Bailly, C.; Pujol, M. D. *J. Med. Chem.* **2007**, *50*, 294.

[4] Pascual, E.; Sivera, F.; Yasothan, U.; Kirkpatrick, P. *Nat. Rev. Drug Discov.* **2009**, *8*, 191.

[5] Patat, A.; Paty, I.; Hindmarch, I. *Hum. Psychopharmacol.* **2001**, *16*, 369.

[6] (a) Sica, D. A.; Prisant, L. M. *J. Clin. Hypertens.* (*Shelton, CT, U. S.*) **2007**, *9*, 1.
(b) Cooper-DeHoff, R. M.; Handberg, E. M.; Mancia, G.; Zhou, Q.; Champion, A.; Legler, U. F.; Pepine, C. J. *Expert Rev. Cardiovasc. Ther.* **2009**, *7*, 1329.

[7] Noble, S.; McTavish, D. *Drugs* **1995**, *50*, 1032.

[8] (a) Shu, Z.; Ye, Y.; Deng, Y.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 10573.
(b) Liu, J.; Zheng, H.-X.; Yao, C.-Z.; Sun, B.-F.; Kang, Y.-B. *J. Am. Chem. Soc.* **2016**, *138*, 3294.
(c) Ge, J.-J.; Yao, C.-Z.; Wang, M.-M.; Zheng, H.-X.; Kang, Y.-B.; Li, Y. *Org. Lett.* **2016**, *18*, 228.
(d) Yu, L.; Li, H.; Zhang, X.; Ye, J.; Liu, J.; Xu, Q.; Lautens, M. *Org. Lett.* **2014**, *16*, 1346.

(e) Zhuang, Y.-J.; Liu, J.; Kang, Y.-B. *Tetrahedron Lett.* **2016**, *57*, 5700.
[9] (a) Zhou, S.; Addis, D.; Das, S.; Junge, K.; Beller, M. *Chem. Commun.* **2009**, 4883.
(b) Shipilovskikh, S. A.; Vaganov, V. Y.; Denisova, E. I.; Rubtsov, A. E.; Malkov, A. V. *Org. Lett.* **2018**, *20*, 728.
[10] (a) Zhou, W.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7094.
(b) Tseng, K.-N. T.; Rizzi, A. M.; Szymczak, N. K. *J. Am. Chem. Soc.* **2013**, *135*, 16352.
(c) Guo, S.; Wan, G.; Sun, S.; Jiang, Y.; Yu, J.-T.; Cheng, J. *Chem. Commun.* **2015**, *51*, 5085.
[11] (a) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224.
(b) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890.
(c) Cristau, H.-J.; Ouali, A.; Spindler, J.-F.; Taillefer, M. *Chem.-Eur. J.* **2005**, *11*, 2483.
(d) Pan, S.; Wu, F.; Yu, R.; Chen, W. *J. Org. Chem.* **2016**, *81*, 1558.
(e) Yan, G.; Zhang, Y.; Wang, J. *Adv. Synth. Catal.* **2017**, *359*, 4068.
[12] (a) Fang, C.; Li, M.; Hu, X.; Mo, W.; Hu, B.; Sun, N.; Jin, L.; Shen, Z. *RSC Adv.* **2017**, *7*, 1484.
(b) Murugesan, K.; Senthamarai, T.; Sohail, M.; Sharif, M.; Kalevaru, N. V.; Jagadeesh, R. V. *Green Chem.* **2018**, *20*, 266.
(c) Chen, H.; Sun, S.; Xi, H.; Hu, K.; Zhang, N.; Qu, J.; Zhou, Y. *Tetrahedron Lett.* **2019**, *60*, 1434.
(d) Zhan, W.; Tong, M.; Ji, L.; Zhang, H.; Ge, Z.; Wang, X.; Li, R., *Chin. Chem. Lett.* **2019**, *30*, 973.
(e) Mudshinge, S. R.; Potnis, C. S.; Xu, B.; Hammond, G. B. *Green Chem.* **2020**, *22*, 4161.
(f) Hua, M.; Song, J.; Huang, X.; Liu, H.; Fan, H.; Wang, W.; He, Z.; Liu, Z.; Han, B. *Angew. Chem., Int. Ed.* **2021**, *60*, 21479.
[13] (a) Xu, J.-H.; Jiang, Q.; Guo, C.-C. *J. Org. Chem.* **2013**, *78*, 11881.
(b) Preger, Y.; Root, T. W.; Stahl, S. S. *ACS Omega* **2018**, *3*, 6091.
(c) Vanoye, L.; Hammoud, A.; Gérard, H.; Barnes, A.; Philippe, R.; Fongarland, P.; de Bellefon, C.; Favre-Réguillon, A. *ACS Catal.* **2019**, *9*, 9705.
(d) Murata, Y.; Iwasa, H.; Matsumura, M.; Yasuike, S. *Chem. Pharm. Bull.* **2020**, *68*, 679.
(e) Takahashi, Y.; Tsuji, H.; Kawatsura, M. *J. Org. Chem.* **2020**, *85*, 2654.
(f) Lu, D.; Cui, J.; Yang, S.; Gong, Y. *ACS Catal.* **2021**, *11*, 4288.
(g) Xiao, J.; Guo, F.; Li, Y.; Li, F.; Li, Q.; Tang, Z.-L. *J. Org. Chem.* **2021**, *86*, 2028.
[14] (a) Li, Y.-T.; Liao, B.-S.; Chen, H.-P.; Liu, S.-T. *Synthesis* **2011**, 2639.
(b) Ma, X.-Y.; He, Y.; Lu, T.-T.; Lu, M. *Tetrahedron* **2013**, *69*, 2560.
(c) Ghosh, P.; Pariyar, G. C.; Saha, B.; Subba, R. *Synth. Commun.* **2016**, *46*, 685.
(d) Hyodo, K.; Kitagawa, S.; Yamazaki, M.; Uchida, K. *Chem. Asian J.* **2016**, *11*, 1348.
(e) Rapeyko, A.; Climent, M. J.; Corma, A.; Concepción, P.; Iborra, S. *ACS Catal.* **2016**, *6*, 4564.
(f) Sun, D.; Kitamura, E.; Yamada, Y.; Sato, S. *Green Chem.* **2016**, *18*, 3389.
(g) Ding, R.; Liu, Y.; Han, M.; Jiao, W.; Li, J.; Tian, H.; Sun, B. *J. Org. Chem.* **2018**, *83*, 12939.
(h) Zhang, D.; Huang, Y.; Zhang, E.; Yi, R.; Chen, C.; Yu, L.; Xu, Q. *Adv. Synth. Catal.* **2018**, *360*, 784.
(i) Ma, X.; Liu, D.; Chen, Z. *Synth. Commun.* **2021**, *51*, 3261.
[15] (a) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605.
(b) Jutand, A. *Chem. Rev.* **2008**, *108*, 2300.
(c) Yoshida, J.-I.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev.* **2008**, *108*, 2265.
(d) Francke, R.; Little, R. D. *Chem. Soc. Rev.* **2014**, *43*, 2492.
(e) Yan, M.; Kawamata, Y.; Baran, P. S. *Chem. Rev.* **2017**, *117*, 13230.
(f) Ma, C.; Fang, P.; Mei, T.-S. *ACS Catal.* **2018**, *8*, 7179.
(g) Moeller, K. D. *Chem. Rev.* **2018**, *118*, 4817.
(h) Yoshida, J.-I.; Shimizu, A.; Hayashi, R. *Chem. Rev.* **2018**, *118*, 4702.
(i) Marken, F.; Wadhawan, J. D. *Acc. Chem. Res.* **2019**, *52*, 3325.
(j) Xiong, P.; Xu, H.-C. *Acc. Chem. Res.* **2019**, *52*, 3339.
(k) Yuan, Y.; Lei, A. *Acc. Chem. Res.* **2019**, *52*, 3309.
(l) Jiao, K.-J.; Xing, Y.-K.; Yang, Q.-L.; Qiu, H.; Mei, T.-S. *Acc. Chem. Res.* **2020**, *53*, 300.
(m) Siu, J. C.; Fu, N.; Lin, S. *Acc. Chem. Res.* **2020**, *53*, 547.
[16] (a) Mo, Z.-Y.; Swaroop, T. R.; Tong, W.; Zhang, Y.-Z.; Tang, H.-T.; Pan, Y.-M.; Sun, H.-B.; Chen, Z.-F. *Green Chem.* **2018**, *20*, 4428.
(b) Zhang, Y.-Z.; Mo, Z.-Y.; Wang, H.-S.; Wen, X.-A.; Tang, H.-T.; Pan, Y.-M. *Green Chem.* **2019**, *21*, 3807.
(c) Wang, X.-Y.; Zhong, Y.-F.; Mo, Z.-Y.; Wu, S.-H.; Xu, Y.-L.; Tang, H.-T.; Pan, Y.-M. *Adv. Synth. Catal.* **2021**, *363*, 208.
(d) Wu, Y.; Chen, J.-Y.; Liao, H.-R.; Shu, X.-R.; Duan, L.-L.; Yang, X.-F.; He, W.-M. *Green Synth. Catal.* **2021**, *2*, 233.
(e) Yang, Z.; Yu, Y.; Lai, L.; Zhou, L.; Ye, K.; Chen, F.-E. *Green Synth. Catal.* **2021**, *2*, 19.
(f) Zhang, S.; Ye, X.; Wojtas, L.; Hao, W.; Shi, X. *Green Synth. Catal.* **2021**, *2*, 82.
[17] Libendi, S. S.; Demizu, Y.; Onomura, O. *Org. Biomol. Chem.* **2009**, *7*, 351.
[18] (a) Cui, T.; Zhan, Y.; Dai, C.; Lin, J.; Liu, P.; Sun, P. *J. Org. Chem.* **2021**, *86*, 15897.
(b) Gao, J.; Weng, X.; Ma, C.; Xu, X.; Fang, P.; Mei, T. *Chin. J. Org. Chem.* **2021**, *41*, 3223 (in Chinese).
(高君青，翁信军，马聪，徐学涛，方萍，梅天胜，有机化学，**2021**, *41*, 3223.)
[19] Dai, J.-J.; Huang, Y.-B.; Fang, C.; Guo, Q.-X.; Fu, Y. *ChemSusChem* **2012**, *5*, 617.
[20] Ye, J.-Q.; Zhang, Z.-L.; Zha, Z.-G.; Wang, Z.-Y. *Chin. Chem. Lett.* **2014**, *25*, 1112.
[21] Qu, Q.; Gao, X.; Gao, J.; Yuan, G. *Sci. China Chem.* **2015**, *58*, 747.
[22] Shono, T.; Matsumura, Y.; Tsubata, K.; Kamada, T.; Kishi, K., *J. Org. Chem.* **1989**, *54*, 2249.
[23] Hartmer, M. F.; Waldvogel, S. R. *Chem. Commun.* **2015**, *51*, 16346.
[24] (a) Ohmori, H.; Nakai, S.; Sekiguchi, M.; Masui, M. *Chem. Pharm. Bull.* **1980**, *28*, 910.
(b) Xu, Z.; Zheng, Y.; Wang, Z.; Shao, X.; Tian, L.; Wang, Y. *Chem. Commun.* **2019**, *55*, 15089.
[25] (a) de Andrade, V. S. C.; de Mattos, M. C. S. *Curr. Org. Synth.* **2015**, *12*, 309.
(b) Li, Z.; Sun, W.; Wang, X.; Li, L.; Zhang, Y.; Li, C. *J. Am. Chem. Soc.* **2021**, *143*, 3536.
[26] (a) Ban, Y.-L.; Dai, J.-L.; Jin, X.-L.; Zhang, Q.-B.; Liu, Q. *Chem. Commun.* **2019**, *55*, 9701.
(b) Schäfer, R. J. B.; Monaco, M. R.; Li, M.; Tirla, A.; Rivera-Fuentes, P.; Wennemers, H. *J. Am. Chem. Soc.* **2019**, *141*, 18644.

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