A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201909600
Angew. Chem. 10.1002/ange.201909600

Link to VoR: http://dx.doi.org/10.1002/anie.201909600
http://dx.doi.org/10.1002/ange.201909600

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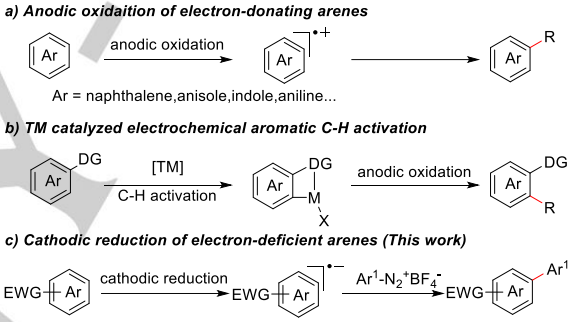
Electrochemical Arylation of Electron-Deficient Arenes through Reductive Activation

Pan Wang,[a] Zhenlin Yang,[a] Ziwei Wang,[a] Chenyang Xu,[a] Lei Huang,[a] Shengchun Wang,[a] Heng Zhang,*[a] and Aiwen Lei*[a]

Abstract: An electrochemical protocol has been developed to achieve arylation of electron-deficient arenes through reductive activation. Various electro-deficient arenes and aryl diazonium tetrafluoroborate have been examined in this transformation under the conditions of undivided cell, providing the desired products up to 92% yield. Instead of preparing diazonium reagents, these reactions could also be carried from anilines in a one-pot fashion. EPR studies supported that the cathodic reduction of quinoxaline occurred in this transformation. At the same time, cyclic voltammetry indicated that both quinoxaline and aryl diazonium salt had relatively low reduction potential, which suggested that they could be activated through reduction in the reaction.

Electron-deficient arenes are one kind of the most important components found in the structures of various functional molecules (Scheme S1).[1] For example, these kind of structures have shown pharmacologically potent in antibiotics and inhibitors. Over the past years, many efforts have been paid to develop C-H functionalization of electron-deficient arenes. C-H bond activation through transition metal catalysis is a general method to achieve functionalization of electron-deficient arenes.[2] Besides that, radical addition is an alternative way to construct new chemical bonds.[3] For example, the Minisci acylation and alkylation have been recognized as efficient pathways to realize direct C-H functionalization of electron-deficient *N*-heteroarenes.[4] Despite the significance, transition-metal catalyst and external redox reagents are necessary for most of the reported methods, which would bring about environmentally deleterious wastes. Therefore, it is desirable to develop a new strategy to achieve functionalization of electron-deficient arenes.

Utilizing traceless electrons as redox reagents, organic electrochemistry is an efficient and highly selective tool for constructing new chemical bonds.[5] Recently, many efforts have been paid to develop electrochemical C-H functionalization of arenes.[6] Anodic oxidation of arenes could furnish the corresponding radical cations, which is a widely used strategy to build C-C and C-X bonds (Scheme 1a).[5f, 6c, 7] But for this method, various electron-rich arenes including naphthalenes, anisoles, anilines, indoles, phenols, thiophenes and so on are always employed as substrates due to their lower oxidation potential. An alternative strategy to achieve C-H functionalization of arenes is to activate C-H bonds synergistically with electricity and transition metals (Scheme 1b).[8] In these transformations, directing groups are usually indispensable to achieve C-H activation. Alkylation, acylation and amination of electron-deficient arenes through radical addition process have been achieved.[9] Due to the high oxidation potential, electron-deficient arenes are hard to be oxidized at the anode. We speculate the possibility that electron-deficient arenes could be reduced at the cathode to generate the corresponding radical anion, which is undoubtedly a challenging but environmentally friendly way to achieve direct C-H functionalization of electron-deficient arenes. Herein, we would like to communicate our progress on the electrochemical arylation of electro-deficient arenes by cathodic reduction (Scheme 1c).



Scheme 1. Electrochemical functionalization of arenes.

Initially, in the presence of strong acid, we tried to electrolyze various electron-deficient *N*-heteroarenes in undivided cells. The homocoupling product of quinoxaline was detected when no other radical partner was added, which meant that the activation of quinoxaline occurred in the electrolysis. On the other hand, aryl diazonium salts are easily available arylation reagents which have been used for organic electrochemistry.[10] We commenced our study by using quinoxaline (**1a**) and 4-methylbenzenediazonium tetrafluoroborate (**2a**) as model coupling substrates to optimize the reaction conditions. Utilizing CH_3CN and trifluoroacetic acid (TFA) as the co-solvent, the arylation of quinoxaline could be obtained with 85% yield under 10 mA constant current in 3 h (Table 1, entry 1). The acid played a key role in this transformation. Only 18% desired product could be obtained when the reaction was carried out in the absence of TFA (Table 1, entry 2). Instead of TFA, other acids were examined in this transformation. Both TsOH and HCl were less efficient than TFA, while acetic acid could not promote the reaction at all (Table 1, entry 3-5). The reaction could be carried out in the absence of supporting electrolyte as well in slightly decreased yield (Table 1, entry 6). The reaction was less efficient when CH_3CN was substituted with MeOH or H_2O (Table 1, entry 7-8). Although the same yield was achieved in DMSO as in CH_3CN, quite a lot of homocoupling product of quinoxaline was detected (Table 1, entry 9). Other

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10.1002/anie.201909600

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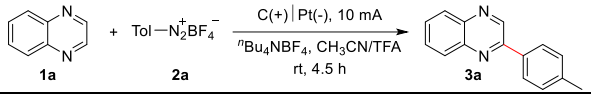
cheap cathodic materials were also evaluated. Using nickel as cathode, a good yield was delivered in the electrochemical transformation while both iron plate and carbon rod showed worse reactivity compared with platinum plate cathode (Table, 10-12). Replacing carbon rod with platinum plate as anode, a moderate yield was furnished (Table 1, 13). No desired product could be detected without electricity (Table 1, entry 14)

Table 1. Optimizing conditions.[a]



1a 2a 3a

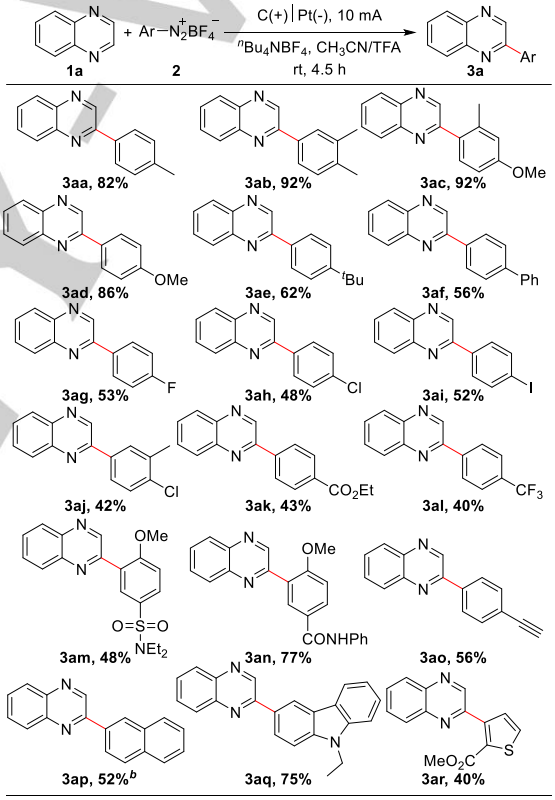
Entry	Variation from standard conditions	Yield (%)
1	none	82
2	without TFA	18
3[b]	TsOH instead of TFA	65
4	HCl instead TFA	35
5	AcOH instead of TFA	10
6	without ^{n}Bu$_4$NBF$_4$	78
7	MeOH instead of CH$_3$CN	41
8	H$_2$O instead of MeCN	30
9	DMSO instead of CH$_3$CN	82
10	carbon rod as cathode	55
11	Ni plate as cathode	79
12	Fe plate as cathode	67
13	Pt plate as anode	68
14	no electric current	n.d.

[a]Standard conditions: graphite rod anode (ϕ 6 mm), Pt plate cathode (15 mm×15 mm×0.3 mm), constant current = 10 mA, **1a** (1.5 mmol), **2a** (0.5 mmol), ^{n}Bu$_4$NBF$_4$ (0.5 mmol), CH$_3$CN/TFA (5.0/0.5 mL), rt, 4.5 h, undivided cell (3.6 F). [b] 5 equiv. TsOH was used.

With the optimized conditions in hand, many efforts have been paid to explore the applicability of this transformation (Table 2). Aryl diazonium tetrafluoroborate bearing substituents at the *meta* or *ortho* position showed good reactivity in this transformation (**3aa**-**3ac**). Electron-donating group such as methoxyl, tertiary butyl and phenyl could also be tolerated in this electrochemical reaction, providing the corresponding products in 56% to 86 yields (**3ad**-**3af**). Halide substituents including F, Cl and I could all afford the desired products in moderate yields (**3ag-3aj)**. In addition, phenyl diazonium tetrafluoroborate bearing electron-poor substituents such as ester group and trifluoromethyl group at *para* position were also suitable for this transformation in decreased yields (**3ak**-**3al**). When 4-(*N*,*N*-diethylsulfamoyl)-2-methoxybenzenediazonium tetrafluoroborate and 2-methoxy-4-(phenylcarbamoyl)benzenediazonium tetrafluoroborate were applied in this electrochemical transformation, good yields were obtained in 48% to 77% (**3am**-**3an**). Ethynyl group could also be tolerated and moderate yield was delivered (**3ao**). Moreover, other aryl diazonium tetrafluoroborates were applied as substrates to examine the reactivity. Naphthalene-2-diazonium tetrafluoroborate and 9-ethyl-9H-carbazole-3-diazonium tetrafluoroborate furnished the desired arylation products in 52% and 75% yields, respectively (**3ap-3aq**). When 2-(methoxycarbonyl)thiophene-3-diazonium tetrafluoroborate was employed as substrate, a lower yield could be obtained (**3ar**).

At the same time, various electron-deficient arenes were explored to examine the reactivity (Table 3). When quinoxaline bearing substituents at C2 position was applied in this transformation, moderate yield was obtained due to steric hindrance effect (**3ba**). Moreover, 5-methylquinoxaline and 6-bromoquinoxaline were used to test the reactivity, the corresponding desired products were delivered in a mixture of isomers (**3ca**-**3da**). A decreased yield was furnished when relatively electron-rich 6,7-dimethylquinoxaline was used (**3ea**). In view of the good solubility in DMSO, a series of quinoxalinones showed good reaction efficiency when they were applied in this electrochemical arylation of electron-deficient arenes (**3fa**-**3ha**). In addition, pyrazine derivatives were employed as substrates, providing the corresponding desired products in moderate yields (**3ia**-**3ka**). Moreover, Other *N*-heteroarenes such as naphthyridine, pyridazine and quinoline derivatives could be tolerated in this transformation (**3la**-**3oa**). 4-Isoquinolinecarbonitrile furnished the desired arylation products in 87% yield (**3pa**). It was noticeable that electron-deficient benzene ring could also be tolerated under 15 mA constant current for 3 h but with the concomitantly formed reduction side product (**3qa**).

Table 2. Substrate Scope of Diazonium Salts.[a]



[a]Standard conditions: graphite rod anode (ϕ 6 mm), Pt plate cathode (15 mm×15 mm×0.3 mm), constant current = 10 mA, **1a** (1.5 mmol), **2** (0.5 mmol), ^{n}Bu$_4$NBF$_4$ (0.5 mmol), CH$_3$CN/TFA (5.0/0.5 mL), rt, 4.5 h, undivided cell (3.6 F), isolated yield. [b]5 equiv. **1a** was used.

Compared with the aryl diazonium tetrafluoroborate, anilines were more stable and commercially available for organic synthesis. Employing anilines as starting materials directly, it is highly fulfilling to carry out *in situ* electrochemical arylation reaction (Table 4). Anilines bearing electron-neutral group on *para* or *meta* positon were well tolerated in this transformation (**3aa**, **3ab**, **3as**, **3at**). Generally, anilines with an electron-donating group gave relatively high yields than electron-deficient aniline (**3ae**, **3ak**). To our delight, quinoxaline derivatives were also

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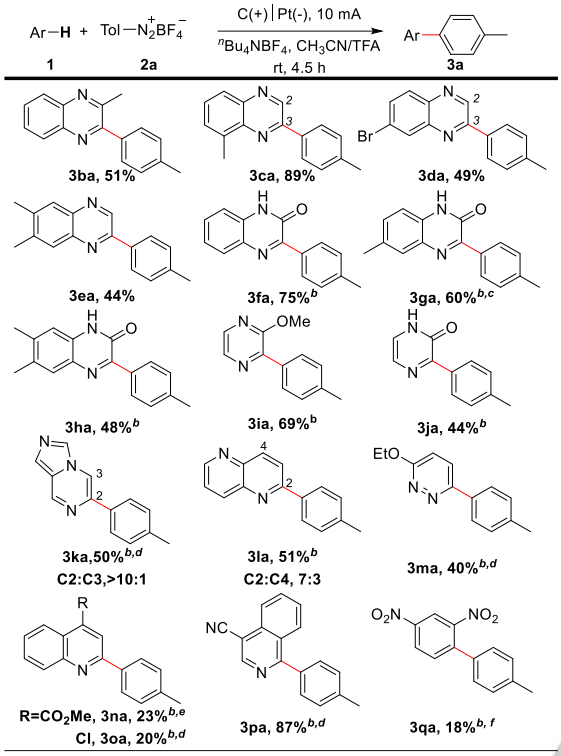
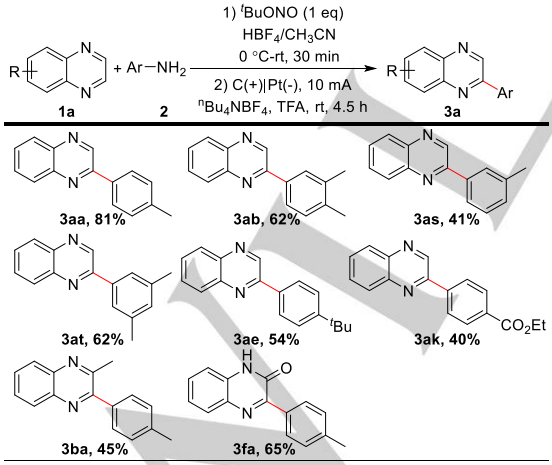
suitable for this one-pot method, providing the corresponding products in 45% and 65% yields, respectively (**3ba**, **3fa**).

Table 3. Substrate Scope of Electron Deficient Arenes.[a]



[a] Standard conditions: graphite rod anode (ϕ 6 mm), Pt plate cathode (15 mm×15 mm×0.3 mm), constant current = 10 mA, **1a** (1.5 mmol), **2** (0.5 mmol), ^{n}Bu$_4$NBF$_4$ (0.5 mmol), CH$_3$CN/TFA (5.0/0.5 mL), rt, 4.5 h, undivided cell (3.6 F), isolated yield. [b] DMSO instead of CH$_3$CN was used as solvent. [c] Product was isolated as a mixture, since the starting materials was a mixture of isomers. [d] 5 equiv. **1** was added. [e] TsOH (2.5 mmol) instead of TFA was added. [f] 15 mA, 60 °C, 3 h.

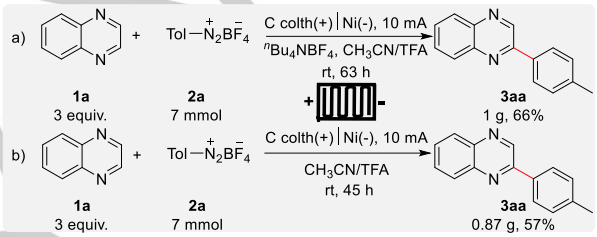
Table 4. Substrate Scope of Arylamine.[a]



[a] Standard conditions: aryl amine (0.5 mmol), ^{t}BuONO (0.5 mmol), HBF$_4$ (48 wt% in H$_2$O, 0.1 mL), CH$_3$CN (5 mL), 0 ºC-rt, 0.5 h; then **1a** (2.5 mmol), ^{n}Bu$_4$NBF$_4$ (0.5 mmol), TFA (0.5 mL), graphite rod anode (ϕ 6 mm), Pt plate cathode (15 mm×15 mm×0.3 mm), constant current = 10 mA, rt, 4.5 h, undivided cell (3.6 F), isolated yield.

To further demonstrate the utility of this electrochemical method, we carried out the scale-up reaction in 7 mmol scale. Considering the price of platinum electrode, nickel plate was employed as cathode. In the electrochemical flow cell, the reaction with quinoxaline smoothly furnished the desired product in 66% yield (Scheme 2a). At the same time, the reaction could also be carried out in the absence of supporting electrolyte with a slightly decreased yield (Scheme 2b). These results highlighted the great potential of this electrochemical cross-coupling protocol in practical synthesis.

Next, we also did several control experiments to explore the reaction mechanism. Simple quinoxalinone could resonate with 2-hydroxyquinoxaline, which could be easily reduced to furnish the corresponding radical anion. Employing the simple quinoxalinone as substrate, a good yield was obtained (Scheme S2, c). Although *N*-protected quinoxalinones were easy to undergo radical addition,[9a, 11] no desired products were detected when they were applied in this transformation. Moreover, the homocoupling product of quinoxaline was detected in 67% yield in the absence of diazonium salt, which proposed that quinoxaline could be activated in the electrochemical condition (Scheme S2, d).



Scheme 2. Gram scale synthesis.

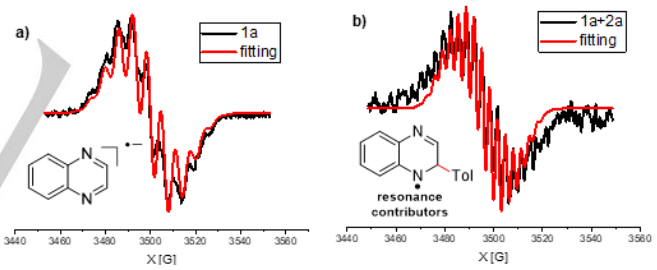


Figure 1. EPR measurements of a solution in CH$_3$CN/TFA of ^{n}Bu$_4$NBF$_4$, under constant current conditions for 30 min; a). **1a**; b). **1a** and **2a**.

Furthermore, EPR experiments have been done to probe the electrically generated radical species. Firstly, when the reaction was carried out in the absence of diazonium salt for 30 min, an EPR signal was detected (Figure 1a), which was identified as quinoxaline radical anion (g=2.0040, 2 A_N=6 G, 6 A_H=6 G).[12] To further identify the radical species of quinoxaline, we also did the experiments in the divided cell. When quinoxaline was added to the cathodic chamber, a similar EPR signal was obtained (Figure S3, c, g=2.0040, 2 A_N=6 G, 6 A_H=6 G). On the contrary, no signal could be detected when quinoxaline was added to the anodic chamber (Figure S3, d). These results indicated that quinoxaline could be reduced at cathode to generate the corresponding radical anion. However, when **1a** and **2a** were added at the same time, a different EPR signal was observed. The parameters observed for the spin adduct are g=2.0039, 2 A_N=6.3 G and 10 A_H=3.16 G (Figure 1b). We proposed that this signal could be ascribed to the aryl radical, which was generated through

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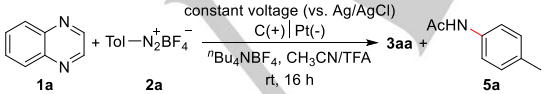
oxidation of 2-(*p*-tolyl)-1,2-dihydroquinoxaline. The same A_H also meant the existence of aryl radical resonance contributors. Previous work has reported that aryl diazonium salt was easy to deliver aryl radical through cathodic reduction.[10a]

In addition, the cyclic voltammetry of **1a** and **2a** were also carried out (see ESI, Fig. S2). An obvious reduction peak of **1a** was observed at -1.06 V (vs Ag/AgCl, the same below). A new reduction peak came out at -0.34 V in the presence of TFA. According to the computational results, the reduction potential of protonated quinoxaline was calculated to be -0.38 V (see ESI). Based on the above results, we speculated that the new reduction peak at -0.34 V might be originated from the reduction of protonated quinoxaline. Reduction peak of **2a** was obtained at -0.62 V[13] and no obvious change occurred after the addition of TFA. DFT calculations suggested that both the radical addition (between quinoxaline and 4-methylphenyl radical) and radical-radical cross coupling (between quinoxaline radical anion and 4-methylphenyl radical) were feasible pathways (see ESI, Fig. S5).

Next, the reaction was also carried out in constant voltage mode to demonstrate the reactivity of substrates. When the cathode potential was set at -0.1 V (*vs.* Ag/AgCl, the same below), no desired product was yielded (Table 2, entry 1). At the same time, we detected the formation of *p*-acetotoluidide (**5a**) which was generated by cross-coupling between aryl diazonium salt and acetonitrile.[14] Then the cathode potential was controlled to -0.3 V, both **3aa** and **5a** were detected (Table 2, entry 2). The yield of desired product increased while *p*-acetotoluidide (**5a**) was basically suppressed when the cathodic voltage was set from -0.6 V to -1.0 V (Table 2, entry 3-4). In addition, the homo-coupling of quinoxaline (**4aa**) was obtained, which meant that the reduction of quinoxaline occurred (Table 2, entry 3). These results indicated that the desired product couldn't be formed even though aryl diazonium salt had been reduced (*e.g.* the formation of *p*-acetotoluidide) at relatively positive reduction potential. With the decrease of reductive voltage, **3aa** could be detected, which meant that the quinoxaline had been involved in the cross coupling reaction through reductive activation. These series experiments proposed that the reduction of both **1a** and **2a** was indispensable for this reaction. In addition, preliminary kinetic studies were also carried out to evaluate the effect of the concentration of quinoxaline on reaction rate. The results indicated that the initial reaction rates increased with the increasing concentration of quinoxaline (see ESI, Fig. S4), which suggested that the reduction of quinoxaline was likely to be the rate-limiting step during electrolysis.

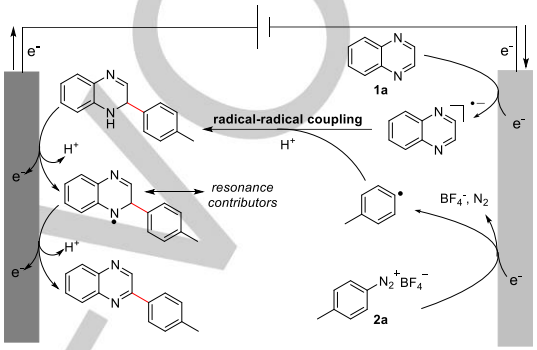
Table 2. Constant voltage reaction.[a]



Entry	Voltage (V)	Yield of **3aa** (%)	Yield of **5a** (%)
1	-0.1	n.d.	27
2	-0.3	28	42
3	-0.6	37	trace
4[b]	-1.0	53	n.d.

[a]Standard conditions: graphite rod anode (ϕ 6 mm), Pt plate cathode (15 mm×15 mm×0.3 mm), Ag/AgCl reference electrode, **1a** (1.5 mmol), **2a** (0.5 mmol), ^{n}Bu$_4$NBF$_4$ (0.5 mmol), CH$_3$CN/TFA (5.0/0.5 mL), rt, 16 h, undivided cell. [b]1 h.

Based on the above experiment results, a plausible mechanism between **1a** and **2a** was depicted in Scheme 3. Firstly, quinoxaline or protonated quinoxaline was reduced to generate the corresponding radical species. At the same time, 4-methylbenzenediazonium tetrafluoroborate could also be reduced at cathode to furnish the 4-methylphenyl radical. This radical could react with quinoxaline radical or radical anion through radical-radical coupling to deliver 2-(*p*-tolyl)-1,2-dihydroquinoxaline which could be oxidized at anode to generate the resonant aryl radical. The generated radical subsequently underwent the second single-electron-transfer (SET) oxidation and deprotonation to deliver the desired product.



Scheme 3. Proposed mechanism.

In summary, an electrochemical arylation of electron-deficient arenes through reductive activation have been developed. Various aryl diazonium tetrafluoroborate and electron-deficient arenes were compatible in this transformation. In addition, it is efficient to perform the one pot electrochemical arylation reaction with the *in situ* formed aryl diazonium salts when employing anilines as starting material. Gram-scale experiments also highlighted the synthetic practicability of this electrochemical strategy. Mechanistically, EPR experiments, control experiments, cyclic voltammetry experiments and DFT calculations indicated reduction of quinoxaline was the key step to achieve this transformation. More efforts will be paid to develop this electrochemical method in our laboratory.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21520102003) and the Hubei Province Natural Science Foundation of China (2017CFA010). The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated. The numerical calculations in this paper have been done on the supercomputing system in the Supercomputing Center of Wuhan University. We are grateful to the guidance and advice from Dr. Yi-Hung Chen in this work.

Keywords: Electrochemistry • arylation • cathodic reduction • radical anion • cross coupling

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10.1002/anie.201909600

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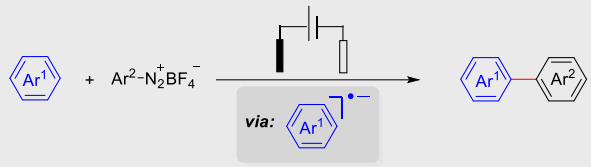

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Electrochemical Arylation of Electron-Deficient Arenes through Reductive Activation

An electrochemical protocol has been developed to achieve arylation of electron-deficient arenes through reductive activation. Various electro-deficient arenes and aryl diazonium tetrafluoroborate have been examined in this transformation under the conditions of undivided cell, providing the desired products with up to 92% yields. Mechanistically, EPR, control experiments, cyclic voltammetry experiments and DFT calculations indicated reduction of quinoxaline was the key step to achieve this transformation.