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Direct *para*-C–H heteroarylation of anilines with quinoxalinones by metal-free cross-dehydrogenative coupling under an aerobic atmosphere†

Jun Xu, Lin Huang, Lei He, Chenfeng Liang, Yani Ouyang, Jiabin Shen, Min Jiang and Wanmei Li *

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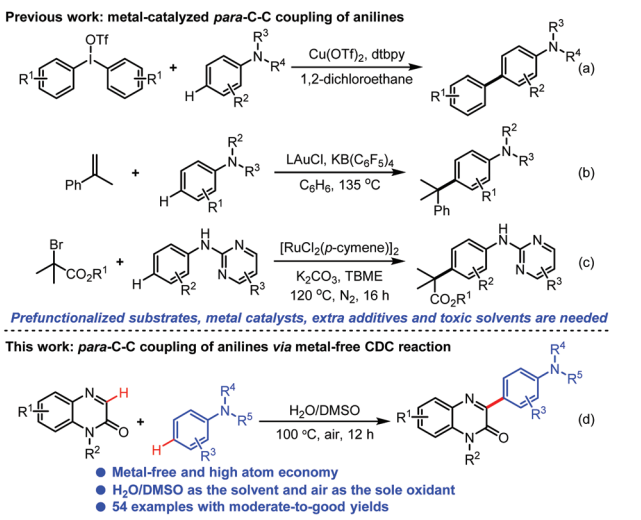
Herein, a green and efficient metal-free cross-dehydrogenative coupling (CDC) for the direct *para*-C–H heteroarylation of anilines with quinoxalinones has been described. This reaction is performed in H_2O/DMSO (v/v = 2 : 1) using air as the sole oxidant. Various anilines (primary, secondary and tertiary amines) and quinoxalinones are well compatible, affording the corresponding products in moderate-to-good yields. Such a methodology provides an environmentally friendly and efficient alternative for the late-stage modification of nitrogen-containing compounds.

Introduction

Anilines are significant structural moieties, which have a wide range of applications in pharmaceuticals, natural products and advanced materials.[1] Therefore, the development of novel methods for direct C–H functionalization of anilines has received much attention.[2] Among these transformations, considerable effort has been devoted to the *ortho*-C–C cross-coupling of anilines.[3] However, direct *para*-C–C cross-coupling of anilines through C–H functionalization has been rarely reported.[4] For example, Gaunt and coworkers reported a copper-catalyzed *para*-C–C coupling of aniline using iodine(III) compounds as the arylating reagent (Scheme 1a).[4a] Bertrand's group demonstrated a *para*-C–C coupling of *N*,*N*-dialkylanilines with alkenes by gold catalysis (Scheme 1b).[4c] In 2017, Frost *et al.* reported a directing group strategy for the *para*-C–C coupling of anilines through ruthenium catalysis (Scheme 1c).[4d] Despite their uses, the requirements of prefunctionalized substrates, metal catalysts, auxiliary group, organic ligands, additives and large amounts of toxic solvents are pushing them far away from achieving green synthesis and atom economy.

From the viewpoint of green and sustainable chemistry, cross-dehydrogenative coupling (CDC) has become an ideal tool for the construction of C–C bonds because this strategy can avoid the prefunctionalization of starting materials, shorten procedures and is more atom- and step-economical.[5] However, most of the methods still require metal catalysts, harmful oxidants and toxic solvents, causing environmental pollution and increasing the manufacturing expenses.[6] Therefore, it is more desirable to develop cross-dehydrogenative coupling (CDC) that can be conducted under green conditions.

Quinoxalinones are important bioactive skeletons, which widely exist in natural products and pharmaceuticals (Fig. 1).[7] The development of methodologies that introduce quinoxalinone skeletons into the organic molecules has received con-



Scheme 1 Direct *para*-C–C cross-coupling of anilines.

College of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China. E-mail: liwanmei@hznu.edu.cn

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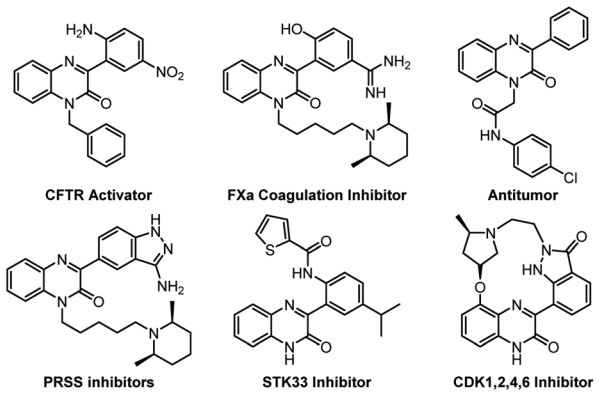
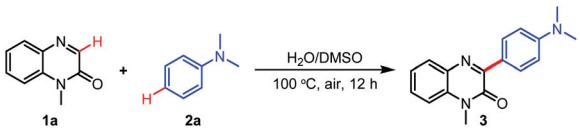


Fig. 1 Biologically active 3-arylquinoxalinones units.

Table 1 Screening of the reaction conditions[a,b]



Entry	Variation from given conditions	Yield (%)
1	None	82
2	DMSO instead of H_2O/DMSO	70
3	MeCN instead of H_2O/DMSO	23
4	1.5 equivalents of $Na_2S_2O_8$ were added	69
5	Reaction was performed at 80 °C	51
6	Reaction was performed at 120 °C	77
7	Reaction was performed for 8 h	42
8	Reaction was performed for 16 h	78

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), H_2O/DMSO (1.0 mL, v/v = 2 : 1), 100 °C, air, 12 h. [b] Isolated yields.

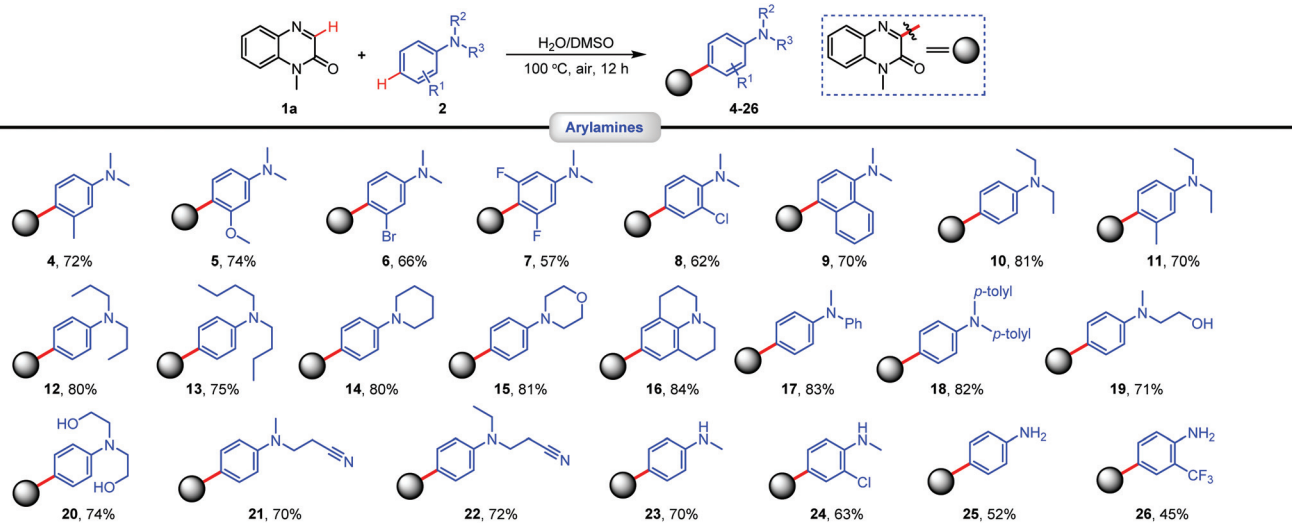
siderable attention.[8–14] Our research interest mainly focuses on developing a green catalytic system for the modification of nitrogen-containing molecules.[15] Herein, we demonstrated a metal-free cross-dehydrogenative coupling for direct *para*-C–H heteroarylation of anilines with quinoxalinones under an aerobic atmosphere (Scheme 1d). The utilization of H_2O/DMSO as the solvent and air as the sole oxidant makes the methodology meet the requirements of green chemistry.

Results and discussion

The reaction conditions were first screened by evaluating the solvent, additive, reaction temperature and time (Table 1 and the ESI†). As shown in Table 1, the arylated product **3** was isolated in 82% yield when the cross-dehydrogenative coupling of quinoxalinone (**1a**) with aniline (**2a**) was performed in H_2O/DMSO (1.0 mL, v/v = 2 : 1) at 100 °C under an air atmosphere for 12 h (Table 1, entry 1). The yield decreased when the solvent was changed (Table 1, entries 2 and 3). Addition of 1.5 equivalents of $Na_2S_2O_8$ into the reaction decreased the yield slightly (Table 1, entry 4). Further investigation on reaction temperature and time did not enhance the product yield (Table 1, entries 5–8).

With the optimized reaction conditions in hand, the substrate scope of anilines for the cross-dehydrogenative coupling was then explored under the standard reaction conditions. As demonstrated in Table 2, a wide range of different functional groups at the *ortho*- or *meta*-position of *N*,*N*-bimethylanilines were generally compatible, providing the corresponding products in moderate-to-good yields. *N*,*N*-Dimethylanilines bearing electron-donating groups could be converted into the corresponding products (**4**, **5** and **7**) with higher yields than those (**6–8**) with electron-withdrawing groups. The cross-dehy-

Table 2 Substrate scope of anilines[a,b]

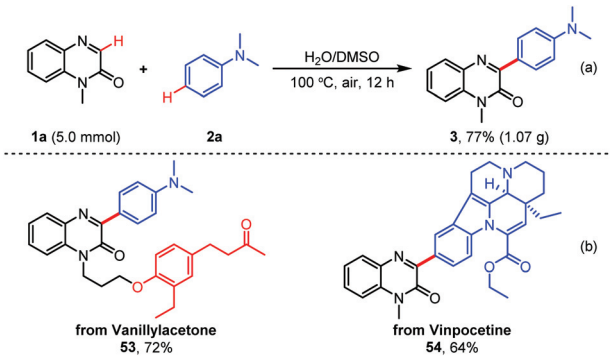


[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), H_2O/DMSO (1.0 mL, v/v = 2 : 1), 100 °C, air, 12 h. [b] Isolated yields.

drogenative coupling of quinoxalinone (**1a**) with *N*,*N*-dimethylnaphthylamine could also give the corresponding product (**9**) in 70% yield. Other tertiary amines, such as *N*,*N*-diethylanilines, *N*,*N*-dipropylanilines, *N*,*N*-butylanilines, *N*,*N*-diphenylanilines *etc*. could also undergo the reaction smoothly, affording the corresponding products (**10–18**) in 70–84% yields. It should be noted that the reactivity of substituent-free *N*,*N*-bifunctionalized anilines was higher than that of *ortho*-substituted ones probably due to the steric hindrance effect. In addition, sensitive groups such as hydroxyl and cyano, which could be further functionalized, were also well tolerated, producing the corresponding products (**19–22**) in 70–74% yields. Interestingly, primary and secondary amines could also react with quinoxalinone smoothly to give the target products (**23–26**) in 45–70% yields. However, it was obvious that their reactivity was poorer than tertiary amines probably because alkyl groups can donate electrons to the nitrogen to make it more electronegative. The greater electron density makes the amine easily to be oxidated to the key intermediate. In addition, the σ–p hyperconjugation effect of alkyl groups may also stabilize the intermediate. Regrettably, heterocyclic amines including 2-aminopyrimidine (**2aa**) and 2-aminopyridine (**2ab**) could not undergo the reaction to give the desired products. Other electron-rich arenes such as phenol (**2ac**) and thiophenol (**2ad**) were used instead of aniline, however, no corresponding products were obtained under standard conditions (see the ESI†).

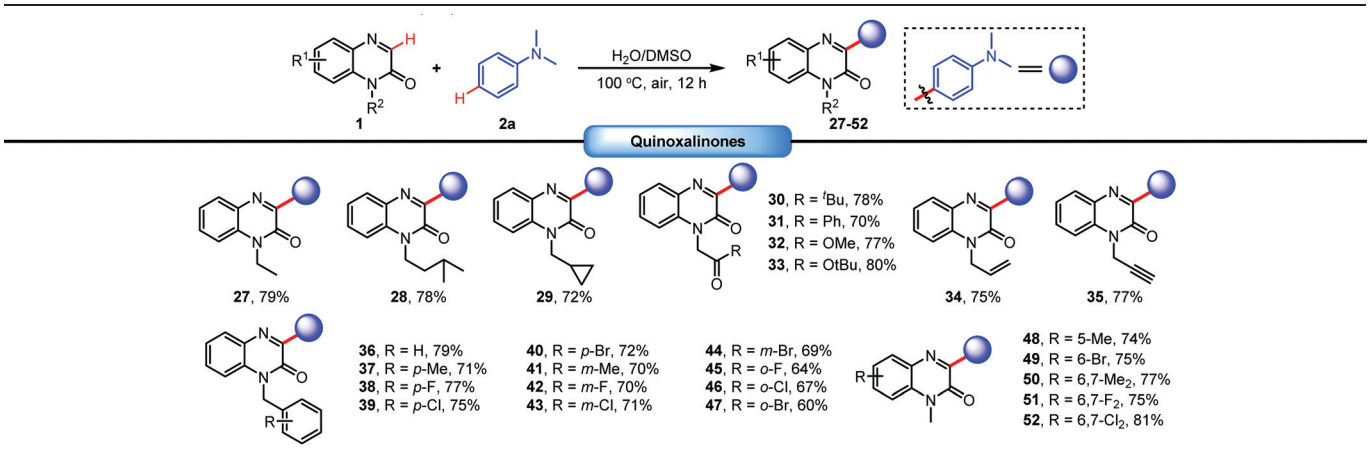
Subsequently, the substrate scope of quinoxalinones for the cross-dehydrogenative coupling was studied (Table 3). Initially, the quinoxalinones with various *N*-substituted groups such as ethyl, isoamyl, cyclopropylmethyl, keto and ester were tested under standard conditions, delivering the corresponding products (**27–33**) in 70–80% yields. It should be noted that quinoxalinones with sensitive groups, such as allyl and propargyl could be transformed into arylated products (**34** and **35**) with good yields. A wide range of quinoxalinones with different *N*-benzyl groups bearing electron-donating or electron-withdrawing substituents at the *ortho*-, *meta*-, or *para*-position of the benzyl ring provided the arylated products (**36–47**) in 60–79% yields. The cross-dehydrogenative coupling of *N*,*N*-dimethylaniline (**2a**) with quinoxalinones that bear methyl, fluoro, chloro or bromo groups at the C5-, C6-, or C7-positions gave the target products (**48–52**) in 74–81% yields. Of note, *N*-free quinoxalinone (**1aa**) could not undergo the reaction to give the desirable product. To expand the substrate scope, some other heterocycles such as quinoline (**1ab**), isoquinoline (**1ac**) and benzothiophene (**1ad**) were tested, however, such substrates could not be converted into the corresponding products (see the ESI†).

To show the efficiency and practicality of the cross-dehydrogenative coupling, the gram-scale synthesis of product **3** was performed to provide the desired product (**3**) in 77% yield (1.07 g) (Scheme 2a). Furthermore, the transformations of bioactive molecules such as vanillylacetone and vinpocetine were conducted to give the target products (**53** and **54**) in acceptable yields (Scheme 2b). The successful transformation demonstrates that the present cross-dehydrogenative coupling reaction is a green and straightforward strategy for the modification of potentially bioactive molecules.



Scheme 2 Gram-scale synthesis and application.

Table 3 Substrate scope of quinoxaline-2(1*H*)-ones[a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), H_2O/DMSO (1.0 mL, v/v = 2 : 1), 100 °C, air, 12 h. [b] Isolated yields.

To deeply understand the reaction mechanism, some control experiments were then conducted. Initially, the reaction was completely suppressed when 1.5 equivalents of 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) were added respectively (Scheme 3a, entries 1 and 2). It should be noted that the adduct of BHT with intermediate radical **D** was detected (Scheme 5). These results demonstrate that a radical mechanism may be responsible for this transformation. Secondly, addition of a singlet oxygen quencher, 9,10-dimethylanthracene, only gave a slightly decreased yield of the product (Scheme 3a, entry 3), excluding the energy transfer pathway. This conclusion was also confirmed by electron spin resonance (ESR) spectroscopy (Fig. S3†). Thirdly, addition of benzoquinone into the transformation dramatically reduced the yield (Scheme 3a, entry 4), suggesting the existence of superoxide radical species, which was further confirmed by ESR experiments (Fig. 2a). Based on the above experimental results, we further investigate the effect of reaction atmosphere on the reaction (Scheme 3b). When the reactions were carried out under an air or O_2 atmosphere, respectively, 82% and 80% yields of product (**3**) were obtained. However, there was no product generated under an N_2 atmosphere. This result clearly shows the importance of O_2 for the cross-dehydrogenative coupling. In the meantime, if the cross-dehydrogenative coupling of quinoxalinone with benzene was performed under standard conditions, the target product (**57**) could not be detected, implying that the amino moiety plays a central role in the reaction (Scheme 3c). To

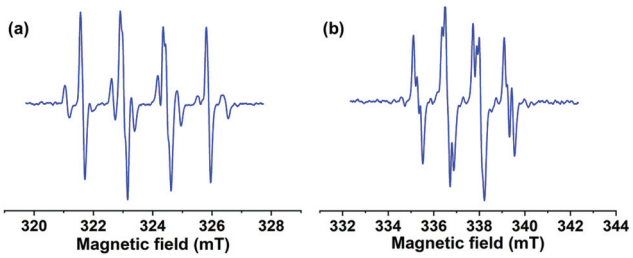
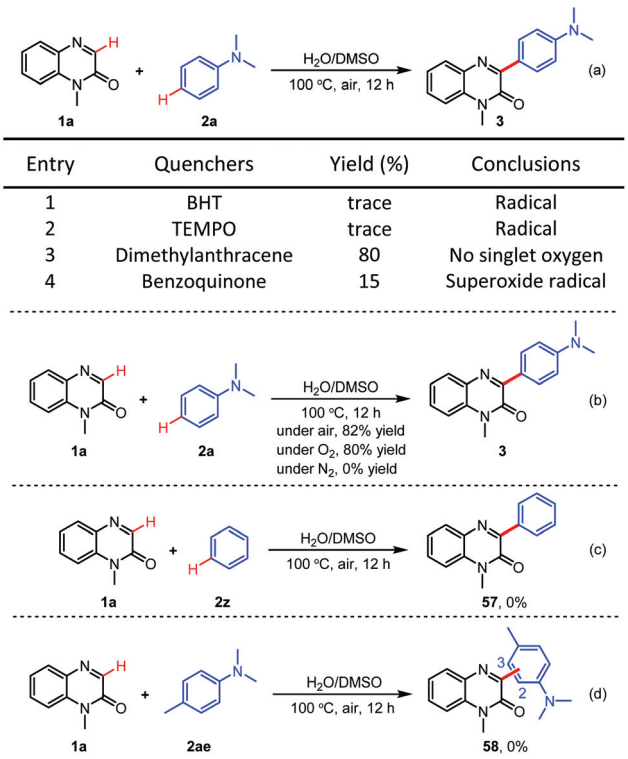


Fig. 2 Determination of reactive species by electron spin resonance (ESR) spectroscopy. (a) ESR spectra of carbon radicals and superoxide radicals captured by DMPO; (b) ESR spectra of nitrogen radicals captured by DMPO.

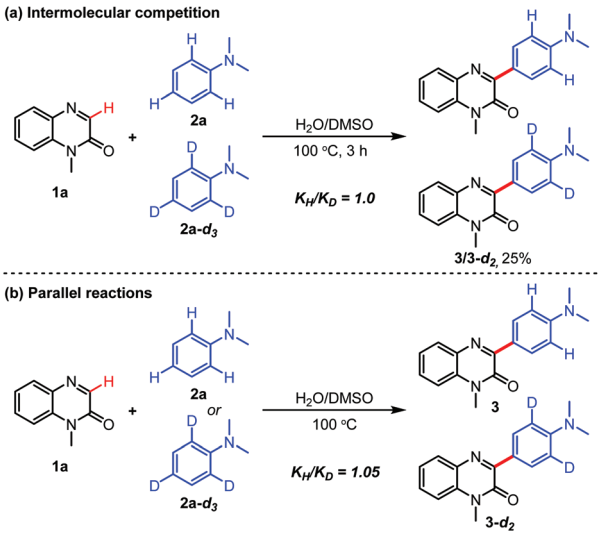
investigate the regioselectivity of this reaction, 4-methyl-*N*,*N*-dimethylaniline (**2ae**) was employed to replace *N*,*N*-dimethylaniline (**2a**) as the substrate (Scheme 3d). Regrettably, there was no new product (**58**) generated. In this context, we believe that the reaction cannot take place at the *ortho* or *meta*-position of anilines. The ESR experiments verified that both nitrogen radicals and carbon radicals were included in the reaction (Fig. 2). Further kinetic isotope analysis by employing intermolecular competition and parallel reactions demonstrated that the *para*-Csp^2–H bond cleavage process of *N*,*N*-dimethylanilines is not involved in the rate determining step (Scheme 4).[16]

From the standpoint of resource reutilization and environmental benignancy, the utilization of the reaction system would be favorable with simple separation and reusing. Therefore, the recyclability and reusability of the present system was evaluated (Fig. S4†). After the completion of the transformation, the H_2O/DMSO was recycled through vacuum distillation and was reused for the next cross-dehydrogenative coupling. As shown in Fig. 3, comparable yields (on average 74.6%) were obtained throughout all of the reaction cycles. In addition, the green chemistry metrics (atom economy,[17] E-factor[18] and eco-scale[19]) for the reaction were calculated (see the ESI†). The present reaction scored a higher atom economy (89.1%), a lower E-factor (0.6) and a higher eco-scale value (65). These results strongly show that this transformation is an environmentally friendly method for the late-stage modification of nitrogen-containing compounds.

Based on the mechanistic investigations and previous reports,[9] a plausible mechanism for the cross-dehydrogenative coupling is proposed (Scheme 5). Initially, a single electron transfer (SET) process takes place between aniline and oxygen to generate a nitrogen radical (**A**) with a superoxide radical under heating conditions.[20] Then, the tautomerism converts the nitrogen radical (**A**) into a carbon radical (**B**), which is further transformed into a carbon radical (**C**) *via* subsequent deprotonation.[21] After the generation of an intermediate (**D**) *via* the radical addition of quinoxalinone (**1a**) with the carbon radical (**C**), the target product is obtained through the successive single electron transfer (SET) and deprotonation processes.



Scheme 3 Mechanistic studies.



Scheme 4 Kinetic isotope effect investigation.

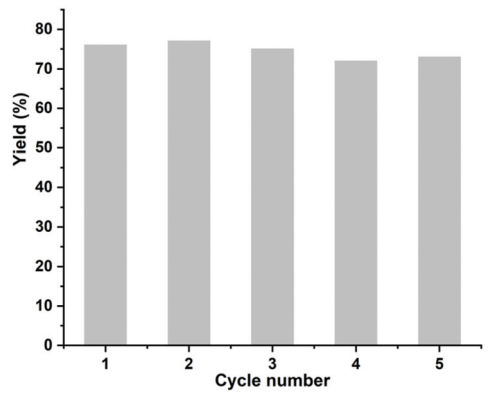
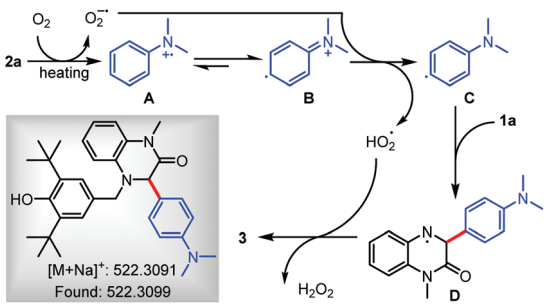


Fig. 3 Reusability of H_2O/DMSO. Reaction conditions: **1a** (10 mmol), **2a** (15 mmol), H_2O/DMSO (50 mL, v/v = 2 : 1), 100 °C, air, 12 h, isolated yields.



Scheme 5 Plausible mechanism.

Conclusions

This study describes a metal- and additive-free strategy for the cross-dehydrogenative coupling of anilines with quinoxalinones. This method features merits such as atom-economy, wide substrate scope, green oxidant and solvent. Control experiments demonstrate that a radical pathway is responsible for the reaction.

Conflicts of interest

There are no conflicts to declare.

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