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Copper-Catalyzed Aerobic Oxidative Coupling of *o*-Phenylenediamines with 2-Aryl/Heteroarylethylamines: Direct Access to Construct Quinoxalines

Kovuru Gopalaiah,*[†] Anupama Saini,[†] Sankala Naga Chandrudu,[†] Devarapalli Chenna Rao,[†] Harsh Yadav,[‡] Binay Kumar[‡]

[†] *Organic Synthesis and Catalysis Laboratory, Department of Chemistry, University of Delhi, Delhi 110007, India*

[‡] *Crystal Lab, Department of Physics & Astrophysics, University of Delhi, Delhi 110007, India*

ABSTRACT

A copper-catalyzed oxidative coupling reaction of *o*-phenylenediamines with 2-aryl/heteroarylethylamines using molecular oxygen as an oxidant has been developed. This novel approach provides a practical and direct access to construct quinoxalines in excellent yields at room temperature. The reaction has broad substrate scope and exhibits excellent functional-group tolerance. This method could be easily scaled up and applied to the synthesis of biologically active molecules bearing quinoxaline structural scaffold.

Dedicated to Professor Sosale Chandrasekhar on the occasion of his 65th birthday

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Corresponding Author: Dr. Kovuru Gopalaiah

Email: gopal@chemistry.du.ac.in

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Introduction

In recent years, oxidative cross-coupling reactions received great attention for their exemplary potential in carbon-carbon and carbon-heteroatom bond formation.[1] Conventionally, organometallic compounds can be used as one of the reaction partners in these transformations, but recent findings revealed that amines, alcohols, and hydrocarbons can directly be used as well.[2] Comparing with organometallic compounds, amines are ideal reactants to construct nitrogen-heterocycles in view of atom economy and green chemical synthesis. Until now, selection of amines and exploiting them in different oxidative C-H/N-H coupling remains a challenge.

Quinoxaline, which is one of the well-known and important classes of nitrogen heterocyclic compounds, exhibits extensive biological and pharmaceutical properties (Figure 1).[3] This scaffold is also an active core unit of several antibiotics,[4] pesticides,[5] herbicides,[6] fungicides,[7] and advanced functional materials.[8] In consequent to these important applications, a large number of synthetic methods have been developed to construct quinoxalines.[9-14]Among these methods, condensation of α-diketones with 1,2-diamines,[9] oxidative trapping of α-hydroxy ketones or vicinal diols with 1,2-diamines,[10,11] oxidative cyclisation of phenacyl bromides with 1,2-diamines,[12] and reaction of alkynes or ketones with 1,2-diamines *via* an oxidation process,[13] have widely been used. In addition, oxidative cyclization of *o*-phenylenediamines was studied to obtain quinoxalines through the metal/enzyme-catalyzed or photochemical dimerization process.[15] Despite these significant approaches toward the synthesis of quinoxalines, the development of mild, efficient and environmentally friendly methods are still desired because: 1) Precursors should be readily available or easily prepared and handled; 2)

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Instead of stoichiometric oxidants such as peroxides and toxic metal compounds, environmentally friendly molecular oxygen or air is desirable as an ideal oxidant; 3) More attention should be given to minimize the environmentally hazardous by-products.

Recently, a few elegant examples of copper-catalyzed oxidative C-N bond formations to construct quinoxalines have been disclosed. Yu and co-workers reported a copper-catalyzed tandem oxidative azidation/cyclization of enamine esters with $TMSN_3$ (Scheme 1A, a).[16] Lin, Zeng and co-workers described a copper-catalyzed cycloamination of α-Csp^3-H bond of *N*-phenyl ketimines with sodium azide (Scheme 1A, b).[17] However, these methods suffer from certain drawbacks, such as the need of large amount of nitrogen sources, usage of non-renewable oxidants/additives, narrow substrate scope, and lower yields. The groups of Chen[18] and Hwang[19] independently reported the synthesis of quinoxalines by copper-catalyzed C-N coupling between *o*-phenylenediamines and terminal alkynes using large quantity of organic and/or inorganic bases under thermal (Scheme 1B, a) and blue-LED light irradiation (Scheme 1B, b) conditions, respectively.

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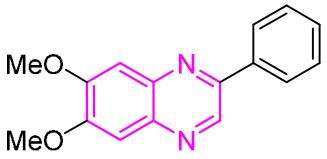

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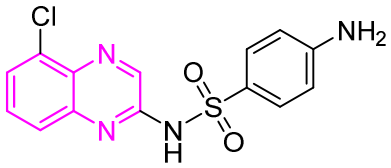

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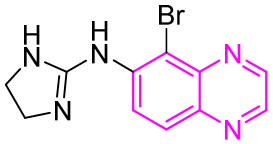

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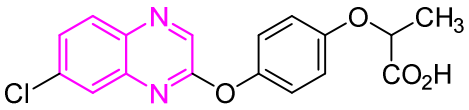

XK469
Anticancer agent

Figure 1. Representative Examples of Bioactive Quinoxaline Compounds.

In the perspective of sustainable chemistry, oxidative C(sp^3)-H bond functionalization is one of the most appealing and powerful strategies in organic synthesis.[20] For these transformations, air or molecular oxygen could be ideal oxidants. Remarkably, activation of dioxygen by copper enzymes has been explored in some biological oxygenase systems, namely dopamine β-monooxygenase and monooxygenase tyrosinase that effect hydroxylation of unactivated C-H bonds.[21] Recently, copper catalyzed reactions that implicate dioxygen activation and use rather simple models to twig biomimetic syntheses have been given much attention.[22,23] Herein, we report an efficient synthesis of 2-aryl/heteroarylquinoxalines using readily available *o*-phenylenediamines and 2-aryl/heteroarylethylamines (Scheme 1C). This transformation proceeds through Cu-catalyzed direct aerobic oxidative C-H/N-H coupling of C(sp^3)-H bonds at room temperature. Compared to the conventional methods, this procedure is

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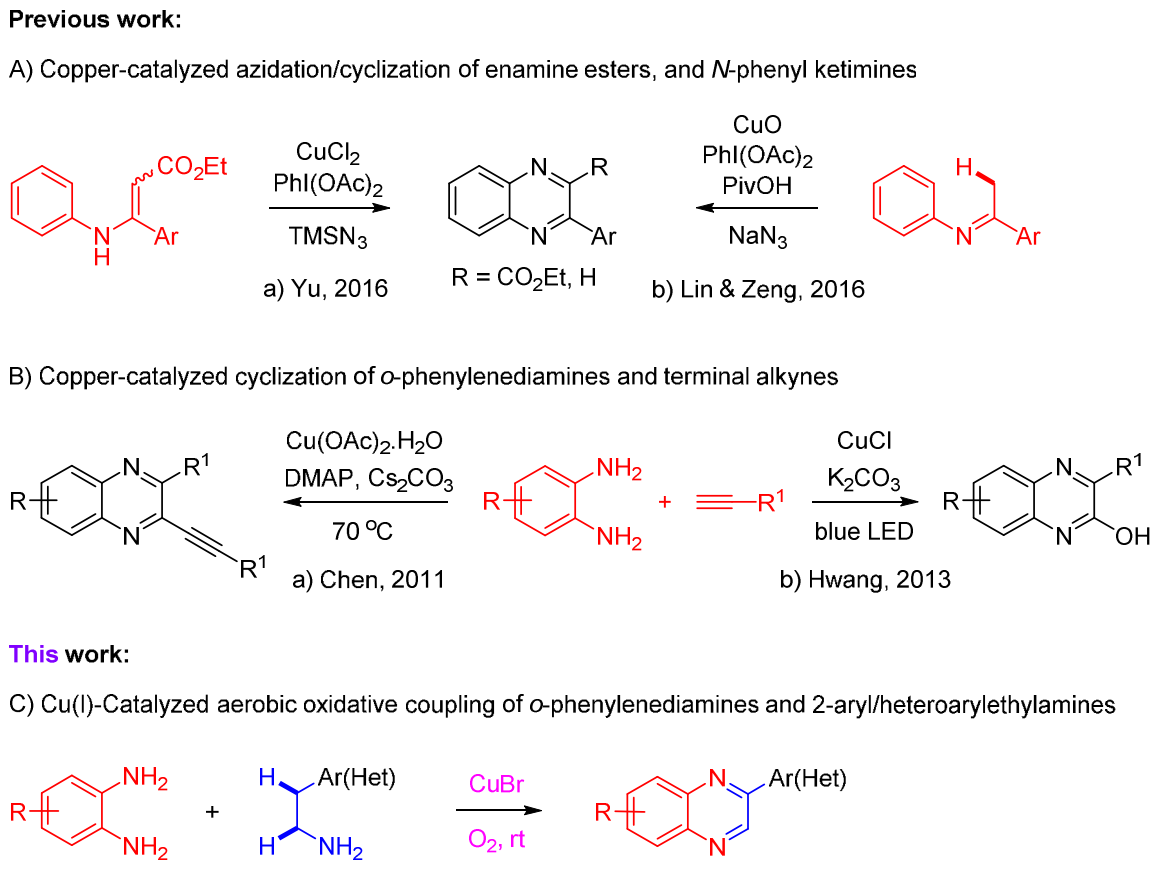
distinguished by using clean O_2 as an oxidant, avoiding the use of harmful peroxides and hypervalent iodine reagents.[16,17,24] This method provides a totally convenient and environmentally friendly direct access to construct a variety of functionalized quinoxalines under mild conditions.



Scheme 1. Copper-catalyzed C-N bond formation for synthesis of quinoxalines

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Results and discussion

Our study commenced with the reaction of *o*-phenylenediamine (**1a**) and 2-phenylethylamine (**2a**) catalyzed by copper salts (Table 1). Under the atmosphere of air, the 2-phenylquinoxaline (**3a**) was obtained in 73% isolated yield upon treatment of 1:1.2 mixture of **1a** and **2a** with 20 mol % CuBr in chlorobenzene at room temperature for 12 h (Table 1, entry 1). Other Cu salts, regardless of their oxidation state (either I or II), also showed catalytic activity, but they were found to be less effective (see, Table 1, entries 2-6 and Supporting Information). The reaction failed to give any desired product in the absence of copper catalyst (Table 1, entry 7). We then examined the effect of different solvents, and it was observed that the reactions proceeded with low yields in toluene, DMSO, and other solvents (Table 1, entries 8 and 9; also see the Supporting Information). Furthermore, various ligands were tested, but the results were unsatisfactory (see the Supporting Information). On increasing the reaction temperature from 25 ^{o}C to 50 ^{o}C or higher, the yields of desired product were not improved considerably (Table 1, entries 10 and 11). However, when we performed the reaction under the atmosphere of molecular oxygen at room temperature, to our delight, the yield of **3a** was remarkably improved to 92% (Table 1, entry 12). The yield remains the same when catalyst loading was decreased from 20 mol % to 10 mol % (Table 1, entry 13). However, a further decrease of catalyst loading resulted in relatively low yield of **3a** (Table 1, entry 14). When the reaction was conducted under argon, no desired product was observed (Table 1, entry 15). Finally, the reaction conditions described in entry 13 were chosen as the standard conditions for further exploration.

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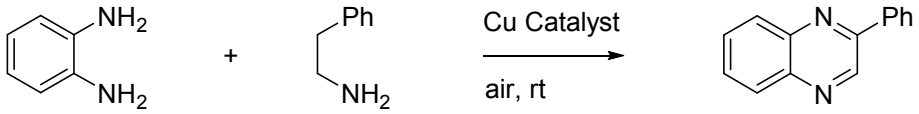
Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	CuBr	chlorobenzene	12	73
2	CuCl	chlorobenzene	12	62
3	Cu_2O	chlorobenzene	12	40
4	$CuBr_2$	chlorobenzene	12	51
5	$CuCl_2$	chlorobenzene	12	43
6	$Cu(OAc)_2$	chlorobenzene	12	35
7	none	chlorobenzene	12	0
8	CuBr	toluene	12	60
9	CuBr	DMSO	12	trace
10[c]	CuBr	chlorobenzene	12	73
11[d]	CuBr	chlorobenzene	12	75
12[e]	CuBr	chlorobenzene	6	92
13[e,f]	CuBr	chlorobenzene	6	92
14[e,g]	CuBr	chlorobenzene	12	79
15[h]	CuBr	chlorobenzene	24	0

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), catalyst (20 mol %), solvent (2 mL), air atmosphere, room temperature,12 h. [b] Yields of the isolated product. [c] The reaction was carried out at 50 °C. [d] The reaction was carried out at 90 °C. [e] The reaction was performed under molecular oxygen (O_2 balloon). [f] Using 10 mol % of CuBr. [g] Using 5 mol % of CuBr. [h] The reaction was performed under argon atmosphere.

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With the optimized experimental conditions in hand, we then investigated the generality of the synthetic approach. First, 2-arylethylamines with various substituents on the phenyl ring were subjected to the reaction with **1a** (Table 2, entries 1-11). Both electron-donating and electron-withdrawing substituents on the phenyl ring of 2-arylethylamines were well tolerated, affording the desired quinoxaline products in excellent yields. Most of the electron-withdrawing substituents have led to higher yields than electron-donating groups (**2b-2d** vs. **2f-2j**). However, a lower yield was observed for the reaction of 2-(4-nitrophenyl)ethylamine (**2e**) (Table 2, entry 5). Apparently, substitution at the *ortho* and *meta* positions were not detrimental to the reaction yield (Table 2, entries, 2, 7, and 8). Furthermore, the bulky substituent viz., 2-(1-naphthyl)ethylamine (**2k**) afforded the desired product in 85 % yield (Table 2, entry 11). In addition to the arylethylamines, a variety of 2-heteroarylethylamines could react well with **1a** to give the corresponding quinoxaline compounds in high yields (Table 2, entries 12 to 14). It is worth mentioning that the products of this transformation, namely 2-(4-bromophenyl)quinoxaline (**3c**) and 2-(4-hydroxyphenyl)quinoxaline (**3j**) (Table 2, entries 3 and 10) are used as key precursors for the synthesis of biologically active compounds as well as organic electroluminescent devices.[25]

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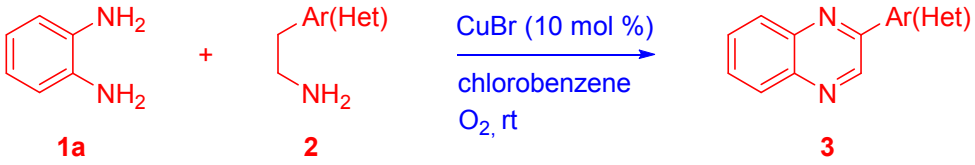
Table 2: Copper-catalyzed aerobic oxidative cross-coupling of 1a with a range of 2-aryl/heteroarylethylamines 2.[a]



1a **2** **3**

Entry	**2**	Ar(Het)	Time (h)	**3**	Yield (%)[b]
1	**2a**	C_6H_5	6	**3a**	92
2	**2b**	2-ClC_6H_4	7	**3b**	93
3	**2c**	4-BrC_6H_4	5	**3c**	97
4	**2d**	4-$CF_3C_6H_4$	7	**3d**	95
5	**2e**	4-$NO_2C_6H_4$	10	**3e**	83
6	**2f**	4-$OMeC_6H_4$	8	**3f**	88
7	**2g**	3-$OMeC_6H_4$	8	**3g**	89
8	**2h**	2-$OMeC_6H_4$	10	**3h**	85
9	**2i**	3,4-$(OMe)_2C_6H_3$	8	**3i**	86
10	**2j**	4-OHC_6H_4	9	**3j**	81
11	**2k**	1-naphthyl	10	**3k**	85
12	**2l**	2-pyridyl	16	**3l**	83
13	**2m**	3-indolyl	13	**3m**	85
14	**2n**	2-thienyl	14	**3n**	78

[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.2 mmol), CuBr (10 mol %), chlorobenzene (2 mL), room temperature, O_2 balloon. [b] Isolated yield.

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To further explore the scope of this approach, several 4-substituted and 4,5-disubstituted *o*-phenylenediamines **1** were employed to react with 2-phenylethylamine (**2a**) under the optimized conditions (Table 3). In fact, symmetrical diamines gave the corresponding products as sole compounds in high yields (Table 3, entries 1-4), whereas unsymmetrical diamines resulted in a mixture of two possible regioisomers (Table 3, entries 5-9). All these regioisomers were easily separated by column chromatography, and characterized by single crystal X-ray diffraction and/or spectroscopic methods. In addition to the 4-substituted and 4,5-disubstituted *o*-phenylenediamines, heteroaryl diamine was also examined for this transformation. For instance, 2,3-diaminopyridine (**1k**) could react well with **2a** to give the corresponding regioisomers (Table 3, entry 10). A series of functional groups such as methoxy, methyl, chloro, nitro, and benzoyl substituents on the aryl ring of diamine were well tolerated under the optimized reaction conditions.

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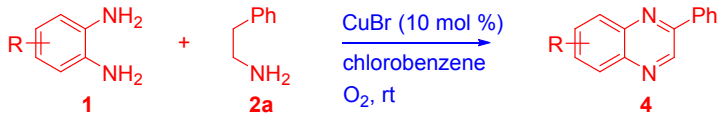
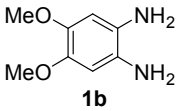
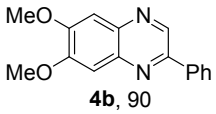
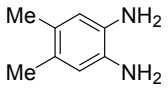
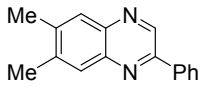
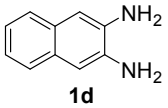
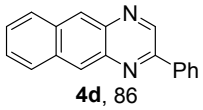
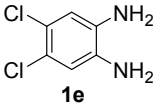
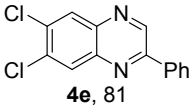
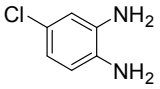
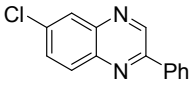
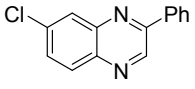
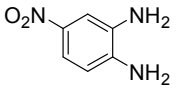
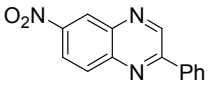
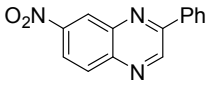
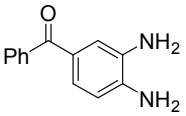
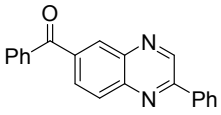
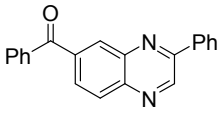
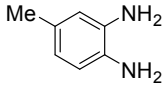
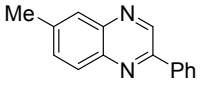
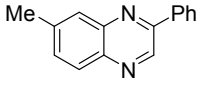
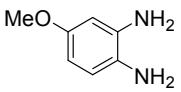
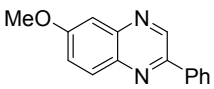
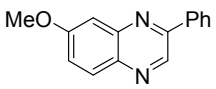
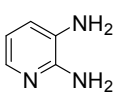
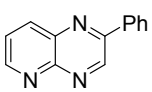
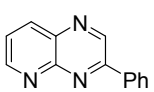
Table 3: Copper-catalyzed aerobic oxidative cross-coupling of a range of *o*-phenylenediamines 1 with 2a[a]



Entry	Substrate (**1**)	Time (h)	**4**, Yield (%)[b]	Ratio[c]
1	 **1b**	5	 **4b**, 90	
2	 **1c**	6	 **4c**, 87	
3	 **1d**	8	 **4d**, 86	
4	 **1e**	10	 **4e**, 81	
5	 **1f**	8	 **4f**, 39  **4f'**, 44	1:1.3
6	 **1g**	14	 **4g**, 35  **4g'**, 37	1:1
7	 **1h**	11	 **4h**, 37  **4h'**, 42	1:1.1
8	 **1i**	7	 **4i**, 45  **4i'**, 39	1:2:1
9	 **1j**	6	 **4j**, 53  **4j'**, 34	1:6:1
10	 **1k**	16	 **4k**, 33  **4k'**, 32	1:1

[a] Reaction conditions: **1** (1 mmol), **2a** (1.2 mmol), CuBr (10 mol %), chlorobenzene (2 mL), room temperature, O_2 balloon. [b] Isolated yield.[c] Determined by 1H NMR.

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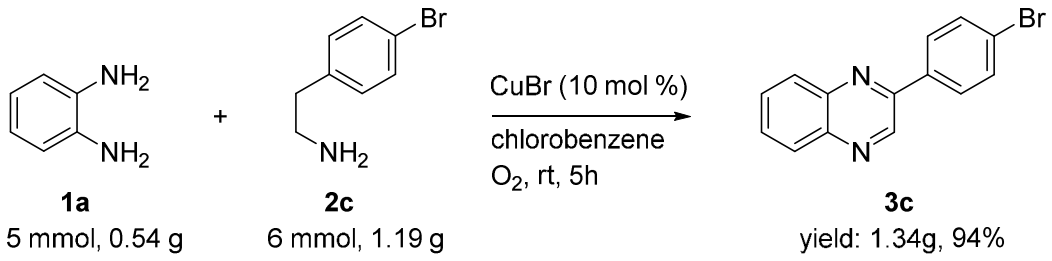
It is worth noting that the reaction could be effectively scaled up with excellent efficiency under the optimized conditions. Notably, the oxidative cross-coupling between 2-(4-bromophenyl)ethylamine (**2c**) and *o*-phenylenediamine (**1a**) is operationally simple and amenable to gram-scale synthesis with 94% yield (Scheme 2). Moreover, due to the high selectivity and efficiency, this aerobic copper-catalyzed oxidative coupling strategy offers promising synthetic routes for the construction of a library of medicinal compounds having quinoxaline structural scaffold. For instance, 2-(4-hydroxyphenyl)quinoxaline (**3j**) acts as butyrylcholinesterase inhibitor.[26] Furthermore, 6,7-dimethoxy-2-phenylquinoxaline (**4b**) and 6,7-dimethyl-2-phenylquinoxaline (**4c**) are selective inhibitors of the platelet derived growth factor (PDGF) receptor kinase and the PDGF dependent DNA synthesis in Swiss 3T3 cells,[27] and 2-phenylbenzo[g]quinoxaline (**4d**) used for treatment of platelet derived growth factor-related disorders such as cancers[28].



Scheme 2. Gram-Scale Reaction of the Synthesis of 2-Phenylquinoxaline

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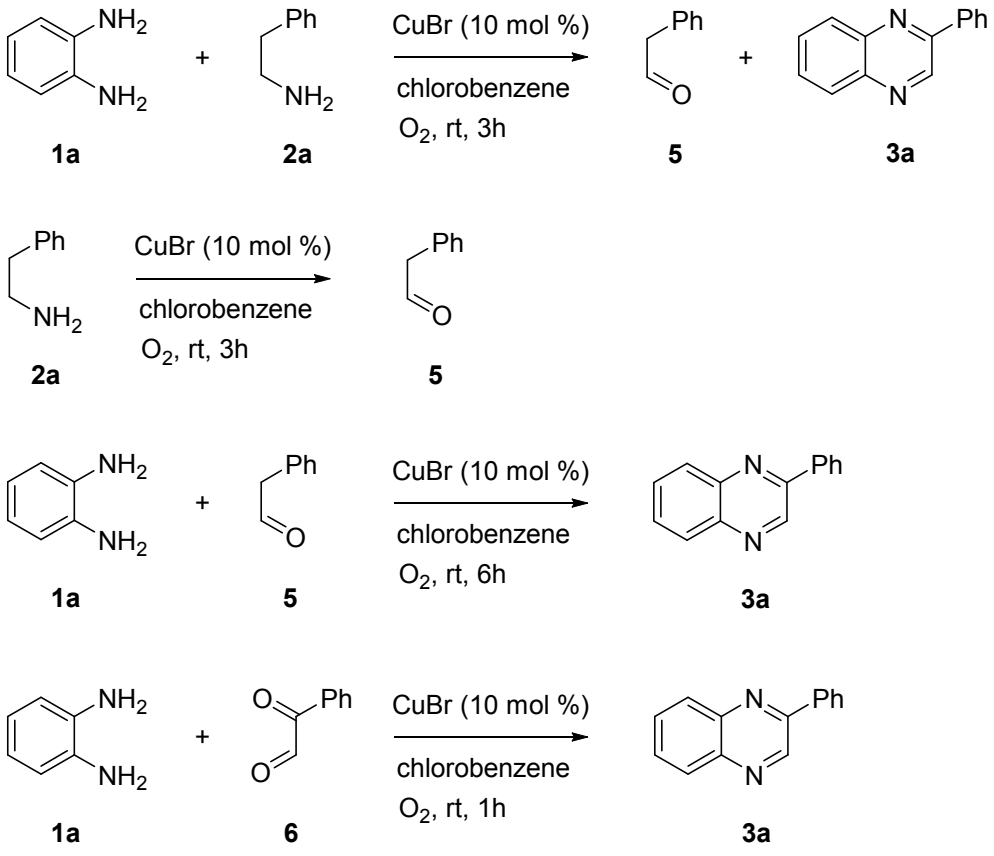
To understand the possible reaction mechanism, the following control experiments were performed under standard conditions as shown in Scheme 3. We found that phenylacetaldehyde (**5**) was formed in 26% yield along with the quinoxaline **3a** when the reaction of 2-phenylethylamine (**2a**) and *o*-phenylenediamine (**1a**) was performed under standard conditions for 3h. Moreover, the 2-phenylethylamine (**2a**) with the present catalytic system produced the corresponding aldehyde **5** in 93% yield. Gratifyingly, the desired product **3a** was obtained smoothly in 93% yield by the reaction of phenylacetaldehyde (**5**) and *o*-phenylenediamine (**1a**) under the standard conditions. In addition, the condensation reaction between phenylglyoxal (**6**) and diamine **1a** was carried out to obtain the quinoxaline compound **3a** in 96% yield.



Scheme 3. Control Experiments

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On the basis of the above experiments and relevant reports in the literature,[29]a plausible mechanism is proposed for the formation of quinoxalines (Scheme 4). The first step may involve the aerobic oxidation of 2-phenylethylamine (**2a**) leading to 2-phenylethylimine (**7**) by the use of $CuBr/O_2$ catalytic system. The Imine **7** may hydrolyze to generate the phenylacetaldehyde (**5**), which on further condensation with *o*-phenylenediamine (**1a**) form cross-imine **8**. Concomitantly, the 2-phenylethylimine (**7**) may undergo direct transimination with **1a** to produce cross-imine **8**. In the presence of copper catalyst and oxygen, the imine **8** may generate the keto-imine **11** via benzyl radical intermediate **9** and hydroperoxide **10**. Jiao et al., recently reported the formation of **11** from imine **8** using Et_3N/O_2 catalytic system.[29a] Moreover, copper-catalyzed benzylic oxidation of $C(sp^3)$-H bonds to keto-group under aerobic conditions is well documented.[30] Finally, intramolecular condensation of **11** may takes place to produce the quinoxaline **3a**.

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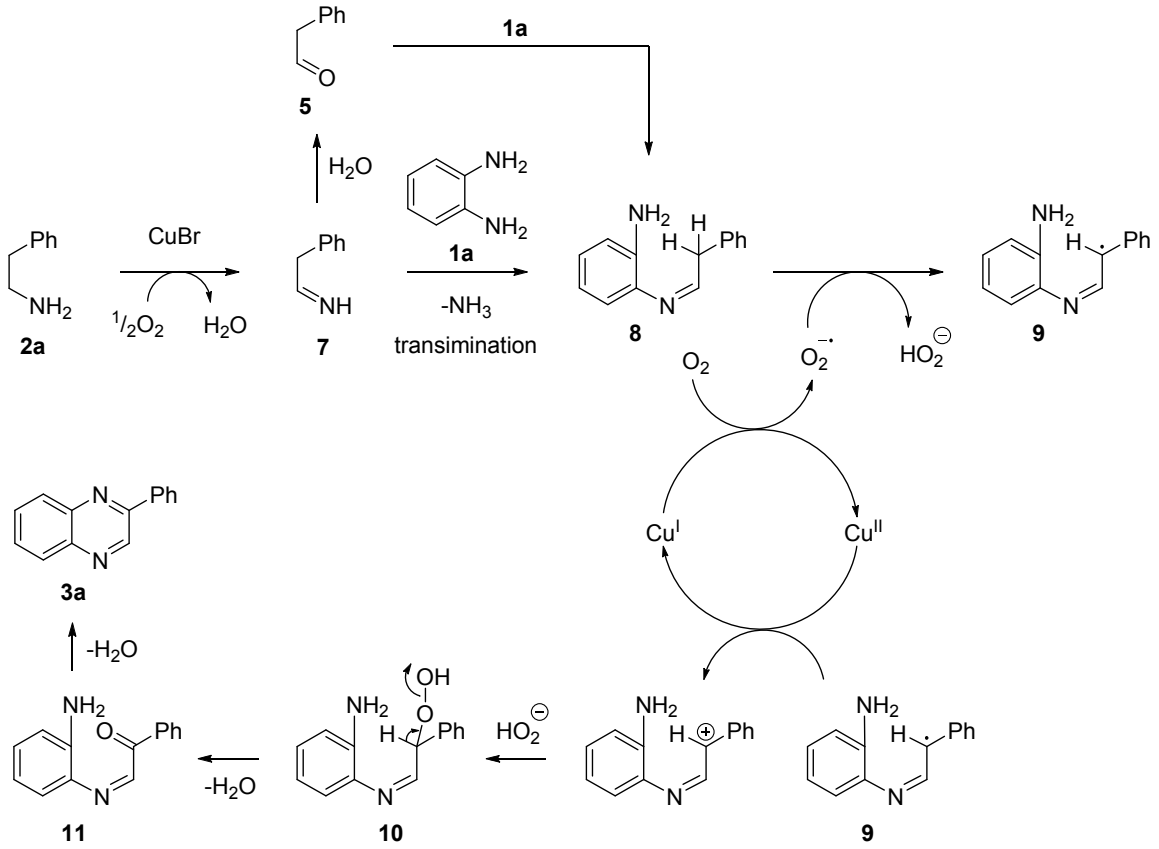

Scheme 4. A Plausible mechanism for the formation of quinoxaline

Conclusions

In summary, we have demonstrated an efficient copper-catalyzed oxidative coupling reaction of *o*-phenylenediamines with 2-aryl/heteroarylethylamines at room temperature under molecular oxygen atmosphere, which provides facile access to functionalized quinoxalines in excellent yields. This method is practical and straightforward as it can be easily scaled up by using readily available starting materials. Further studies are currently under investigation to explore the reaction mechanism and the scope of its synthetic applications.

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Experimental

General Information

All commercially obtained materials were used directly without further purification unless otherwise noted. Chlorobenzene was dried over P_2O_5 and distilled before use. Reactions were carried out in oven-dried round-bottom flask. Melting points were determined on a Büchi melting point apparatus and were uncorrected. NMR spectra were recorded on a 400 MHz spectrometer (^{1}H at 400 MHz, ^{13}C at 100 MHz). Chemical shifts are reported in ppm, relative to the internal standard of tetramethylsilane (TMS). Proton coupling patterns are described as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), multiplet (m). High-resolution mass spectra (HRMS) were obtained using an electrospray quadrupole time-of-flight (ESI-Q-TOF) mass spectrometer.

Typical experimental procedure for the copper-catalyzed synthesis of quinoxalines (3 and 4)

o-Phenylenediamine **1** (1.0 mmol), 2-aryl/heteroarylethylamine **2** (1.2 mmol), CuBr (10 mol %), and dry chlorobenzene (2.0 mL) were charged into an oven-dried round-bottom flask. The flask was equipped with oxygen balloon and stirred at room temperature, until complete consumption of *o*-phenylenediamine as monitored by TLC. After the completion of reaction, it was diluted with CH_2Cl_2 and adsorbed on silica gel. The products were purified by silica gel (100-200 mesh) column chromatography by using hexane/EtOAc as mobile phase.

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Products Characterization

2-Phenylquinoxaline (3a)[31]: White solid; yield: 92%; mp: 68-69 ^{o}C (Lit. mp: 70 ^{o}C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 8.21-8.12 (m, 4H), 7.81-7.73 (m, 2H), 7.59-7.51 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 151.8, 143.3, 142.2, 141.5, 136.7, 130.2, 130.1, 129.6, 129.5, 129.1, 129.0, 127.5; **HRMS**: m/z $[M+ H]^+$ calcd for $C_{14}H_{10}N_2$: 207.0917; found: 207.0918.

2-(2-Chlorophenyl)quinoxaline (3b)[32]: Light yellow solid; yield: 93%; mp: 135-136 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.22 (s, 1H), 8.19-8.17 (m, 2H), 7.84-7.81 (m, 2H), 7.75-7.73 (m, 1H), 7.58-7.55 (m, 1H), 7.48-7.46 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 152.4, 146.1, 142.2, 141.3, 136.5, 132.6, 131.9, 130.8, 130.3, 130.2, 130.1, 129.6, 129.2, 127.5; **HRMS**: m/z $[M + H]^+$ calcd for $C_{14}H_9ClN_2$: 241.0527; found: 241.0522.

2-(4-Bromophenyl)quinoxaline (3c)[31]: Pale yellow solid; yield: 97%; mp: 135-136 ^{o}C (Lit. mp: 134-137 ^{o}C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.29 (s, 1H), 8.15-8.10 (m, 2H), 8.08 (d, J = 8.4 Hz, 2H), 7.81-7.74 (m, 2H), 7.69 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 150.6, 142.7, 142.1, 141.6, 135.5, 132.3, 130.5, 129.8, 129.5, 129.1, 128.9, 124.9; **HRMS**: m/z $[M + H]^+$ calcd for $C_{14}H_9BrN_2$: 285.0022; found: 285.0025.

2-(4-(Trifluoromethyl)phenyl)quinoxaline (3d)[33]: Light brown solid; yield: 95%; mp: 140-141^{o}C (Lit. mp: 142 ^{o}C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.35 (s, 1H), 8.33 (d, J = 7.6 Hz, 2H), 8.19-8.14 (m, 2H), 7.84-7.78 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 150.2, 142.9, 142.2, 141.9, 140.0, 130.6, 130.2, 129.7, 129.2, 127.8, 126.1, 126.0; **HRMS**: m/z $[M + H]^+$ calcd for $C_{15}H_9F_3N_2$: 275.0791; found: 275.0799.

2-(4-Nitrophenyl)quinoxaline (3e)[34]: Light brown crystals; yield: 83%; mp: 190-191.6 ^{o}C (Lit. mp: 190-192 ^{o}C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.39 (s, 1H), 8.43-8.38 (m,

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4H), 8.20-8.16 (m, 2H), 7.86-7.83 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 149.2, 148.7, 142.6, 142.4, 142.2, 142.0, 130.9, 130.7, 129.8, 129.2, 128.3, 124.2; **HRMS**: m/z $[M + H]^+$ calcd for $C_{14}H_9N_3O_2$: 252.0768; found: 252.0784.

2-(4-Methoxyphenyl)quinoxaline (3f)[31]: Pale yellow solid; yield: 88%; mp: 97-99 ^oC (Lit. mp: 97-98 ^oC); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.29 (s, 1H), 8.18 (d, *J* = 9.2 Hz, 2H), 8.11 (t, *J* = 9.2 Hz, 2H), 7.78-7.69 (m, 2H), 7.08 (d, *J* = 9.2 Hz, 2H), 3.91 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161.4, 151.4, 143.0, 142.2, 141.1, 130.1, 129.3, 129.2, 129.0, 128.9, 114.5, 55.4; **HRMS**: m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_2O$: 237.1022; found: 237.1029.

2-(3-Methoxyphenyl)quinoxaline (3g)[35]: Pale yellow solid; yield: 89%; mp: 88-90 ^oC (Lit. mp: 87-88 ^oC); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 8.18-8.12 (m, 2H), 7.82-7.74 (m, 4H), 7.51-7.47 (m, 1H), 7.08 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.95 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 160.2, 151.6, 143.4, 142.2, 141.6, 138.1, 130.2, 130.1, 129.6, 129.5, 129.1, 119.8, 116.2, 112.6, 55.4 ; **HRMS**: m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_2O$: 237.1022; found: 237.1019.

2-(2-Methoxyphenyl)quinoxaline (3h)[36]: Yellow solid; yield: 85%; mp: 110-112 ^oC (Lit. mp: 109-110 ^oC); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 8.18-8.11 (m, 2H), 7.91-7.88 (m, 1H), 7.79-7.74 (m, 2H), 7.51-7.47 (m, 1H), 7.18-7.14 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 3.91 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.3, 152.2, 147.2, 142.6, 140.9, 131.6, 131.4, 129.8, 129.5, 129.4, 128.9, 126.4, 121.5, 111.3, 55.6; **HRMS**: m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_2O$: 237.1022; found: 237.1029.

2-(3,4-Dimethoxyphenyl)quinoxaline (3i)[34]: Brown solid; yield: 86%; mp: 116-118 ^oC (Lit. mp: 113-115 ^oC); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 8.17-8.10 (m,

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2H), 7.88-7.87 (m, 1H), 7.80-7.73 (m, 3H), 7.04 (d, *J* = 8.0 Hz, 1H), 4.06 (s, 3H), 3.99 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 151.3, 151.1, 149.7, 143.0, 142.2, 141.2, 130.2, 129.5, 129.3, 129.1, 129.0, 120.4, 111.1, 110.1, 56.0; **HRMS**: m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_2O_2$: 267.1128; found: 267.1132.

2-(4-Hydroxyphenyl)quinoxaline (3j)[31]: Orange solid; yield: 81%; mp: 206-207 ^oC (Lit. mp: 208-209 ^oC); **^{1}H NMR** (400 MHz, DMSO-d6): δ 9.89 (s, 1H, OH), 9.16 (s, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4Hz, 2H), 7.55-7.45 (m, 2H), 6.66 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO-d6): δ 159.9, 151.1, 143.4, 141.6, 140.6, 130.5, 129.2, 128.9, 128.8, 126.9, 116.1; **HRMS**: m/z $[M + H]^+$ calcd for $C_{14}H_{10}N_2O$: 223.0866; found: 223.0868.

2-(Naphthalen-1-yl)quinoxaline (3k)[31]: Light brown solid; yield: 85%; mp: 135-136 ^oC (Lit. mp: 136 ^oC); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 8.25-8.20 (m, 2H), 8.17 (d, *J* = 7.6 Hz, 1H), 8.03-7.97 (m, 2H), 7.86-7.83 (m, 2H), 7.78 (d, *J* = 6.8 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.59-7.54 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.2, 146.6, 142.2, 141.3, 135.1, 133.9, 131.1, 130.4, 130.1, 129.9, 129.6, 129.2, 128.6, 128.5, 127.2, 126.3, 125.4, 125.0; **HRMS**: m/z $[M + H]^+$ calcd for $C_{18}H_{12}N_2$: 257.1073; found: 257.1083.

2-(Pyridin-2-yl)quinoxaline (3l)[33]: Pale yellow solid; yield: 83%; mp: 117-118 ^oC (Lit. mp: 116 ^oC); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 8.80 (s, 1H), 8.61 (d, *J* = 8.0 Hz, 1H), 8.19-8.16 (m, 2H), 7.93-7.89 (m, 1H), 7.82-7.76 (m, 2H), 7.44-7.41 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.4, 150.0, 149.3, 144.1, 142.6, 141.8, 137.3, 130.2, 130.1, 129.7, 129.3, 124.7, 122.1; **HRMS**: m/z $[M + H]^+$ calcd for $C_{13}H_9N_3$: 208.0876; found: 208.0869.

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2-(1H-Indol-3-yl)quinoxaline (3m)[31]: Pale yellow solid; yield: 85%; mp: 206-207 ^{o}C (Lit. mp: 206-208 ^{o}C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.23 (s, 1H), 8.94 (br s, 1H, NH), 8.79 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 9.2 Hz, 1H), 7.94 (d, *J* = 2.8 Hz, 1H), 7.77-7.73 (m, 1H), 7.68-7.64 (m, 1H), 7.45-7.43 (m, 1H), 7.38-7.30 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 150.3, 143.8, 142.6, 140.2, 136.8, 129.9, 129.0, 128.9, 128.2, 125.7, 125.6, 123.5, 122.3, 121.8, 115.0, 111.5; **HRMS**: m/z $[M + H]^+$ calcd for $C_{16}H_{11}N_3$: 246.1011; found: 246.1030.

2-(Thiophen-2-yl)quinoxaline (3n)[31]: Pale yellow solid; yield: 78%; mp: 118-119 ^{o}C (Lit. mp: 116-117 ^{o}C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.04-8.01 (m, 2H), 7.81 (d, *J* = 3.6 Hz, 1H), 7.72-7.63 (m, 2H), 7.50 (d, *J* = 6.0 Hz, 1H), 7.16-7.14 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 147.4, 142.1, 141.9, 141.0, 130.5, 129.9, 129.3, 129.1, 128.9, 128.5, 127.1; **HRMS**: m/z $[M + H]^+$ calcd for $C_{12}H_8N_2S$: 213.0481; found: 213.0485.

6,7-Dimethoxy-2-phenylquinoxaline (4b)[37]: White solid; yield: 90%; mp: 130-132 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.13 (s, 1H), 8.15 (d, *J* = 9.2 Hz, 1H), 7.70-7.69 (m, 1H), 7.59-7.46 (m, 1H), 7.43-7.39 (m, 1H), 7.36-7.32 (m, 1H), 7.27-7.24 (m, 2H), 4.10 (s, 3H), 4.09 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 152.9, 152.6, 149.8, 140.7, 138.9, 131.4, 128.8, 128.7, 128.5, 127.1, 126.8, 126.6, 106.9, 106.5, 56.2; **HRMS**: m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_2O_2$: 267.1128; found: 267.1132.

6,7-Dimethyl-2-phenylquinoxaline (4c)[31]: Pale yellow solid; yield: 87%; mp: 130-132 ^{o}C (Lit. mp: 130-131 ^{o}C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.85 (s, 1H), 7.83 (s, 1H), 7.56-7.46 (m, 3H), 2.49 (s, 6H); **^{13}C NMR** (100 MHz,

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$CDCl_3$): δ 150.9, 142.3, 141.1, 140.7, 140.5, 140.0, 137.0, 129.8, 128.9, 128.6, 128.0, 127.3, 20.3, 20.2; **HRMS**: m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_2$: 235.1230; found: 235.1238.

2-Phenylbenzo[g]quinoxaline (4d)[38]: Orange solid; yield: 86%; mp: 145-149 ^oC (Lit. mp: 162 ^oC); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.41 (s, 1H), 8.75-8.69 (m, 2H), 8.29-8.27 (m, 2H), 8.14-8.12 (m, 1H), 8.01-7.99 (m, 1H), 7.63-7.54 (m, 4H) 7.47-7.45 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 151.7, 144.5, 138.7, 138.1, 136.7, 134.1, 133.6, 130.4, 129.2, 128.7, 128.5, 128.4, 127.9, 127.6, 127.5, 126.9, 126.7; **HRMS**: m/z $[M + H]^+$ calcd for $C_{18}H_{12}N_2$: 257.1073; found: 257.1072.

6,7-Dichloro-2-phenylquinoxaline (4e)[31]: Pale yellow solid; yield: 81%; mp: 156-158 ^oC (Lit. mp: 155-157 ^oC); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 8.28 (s, 1H), 8.24 (s, 1H), 8.20-8.18 (m, 2H), 7.61-7.56 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 152.6, 144.2, 141.1, 140.2, 135.9, 134.9, 133.9, 130.7, 130.1, 129.7, 129.2, 127.5; **HRMS**: m/z $[M + H]^+$ calcd for $C_{14}H_8Cl_2N_2$: 275.0137; found: 275.0138.

6-Chloro-2-phenylquinoxaline (4f)[39]: Less polar regioisomer; Yellow solid; yield: 39%; mp: 143-145 ^oC ; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 8.19 (d, J = 7.6 Hz, 2H), 8.12-8.09 (m, 2H), 7.73 (dd, J = 9.2, 2.4 Hz, 1H), 7.60-7.53 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 151.9, 144.1, 141.7, 140.8, 136.3, 135.2, 131.3, 130.8, 130.4, 129.2, 128.0, 127.5; **HRMS**: m/z $[M + H]^+$ calcd for $C_{14}H_9ClN_2$: 241.0523; found: 241.0523.

7-Chloro-2-phenylquinoxaline (4f')[39]: More polar regioisomer; Pale yellow solid; yield: 44%; mp: 118-119 ^oC ; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.32 (s, 1H), 8.21-8.17 (m, 3H), 8.08 (d, J = 9.2 Hz, 1H), 7.72-7.68 (m, 1H), 7.61-7.55 (m, 3H); **^{13}C NMR**

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(100 MHz, $CDCl_3$): δ 152.4, 143.3, 142.6, 140.0, 136.2, 136.0, 130.5, 130.4, 130.3, 129.2, 128.4, 127.5; **HRMS**: m/z $[M + H]^+$ calcd for $C_{14}H_9ClN_2$: 241.0507; found: 241.0507.

6-Nitro-2-phenylquinoxaline (4g)[39]: Less polar regioisomer; Pale yellow solid; yield: 35%; mp: 207-210 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.50 (s, 1H), 9.03 (m, 1H), 8.56 (dd, *J* = 9.2, 2.0 Hz, 1H), 8.30-8.26 (m, 3H), 7.65-7.61 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.9, 147.1, 145.5, 144.9, 140.3, 135.6, 131.4, 131.2, 129.4, 127.9, 125.6, 123.8; **HRMS**: m/z $[M + H]^+$ calcd for $C_{14}H_9N_3O_2$: 252.0768; found: 252.0782.

7-Nitro-2-phenylquinoxaline (4g')[39]: More polar regioisomer; Pale yellow solid; yield: 37%; mp: 175-177.2 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.49 (s, 1H), 9.07-9.06 (m, 1H), 8.51 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.29-8.24 (m, 3H), 7.63-7.56 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.7, 148.2, 146.1, 143.8, 141.3, 135.5, 131.2, 130.8, 129.4, 127.7, 125.9, 122.8; **HRMS**: m/z $[M + H]^+$ calcd for $C_{14}H_9N_3O_2$: 252.0768; found: 252.0757.

Phenyl(2-phenyl-6-quinoxalinyl)methanone (4h)[40]: Less polar regioisomer; Pale yellow solid; yield: 37%; mp: 142-143 ^oC (Lit. mp: 144-145 ^oC); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.42 (s, 1H), 8.50 (s, 1H), 8.27-8.25 (m, 4H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.68-7.53 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.6, 153.3, 144.4, 144.1, 140.6, 137.8, 137.0, 136.2, 132.9, 132.3, 130.8, 130.2, 130.1, 130.0, 129.3, 128.5, 127.7; **HRMS**: m/z $[M + H]^+$ calcd for $C_{21}H_{14}N_2O$: 311.1179; found: 311.1177.

Phenyl(3-phenyl-6-quinoxalinyl)methanone (4h')[41]: More polar regioisomer; Pale yellow solid; yield: 42%; mp: 134-136 ^oC (Lit. mp: 132-133 ^oC); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.35 (s, 1H), 8.43 (s, 1H), 8.20-8.12 (m, 4H), 7.83 (d, *J* = 7.6 Hz, 2H), 7.60-7.43 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.6, 153.3, 144.4, 144.1, 140.6, 137.8, 137.0,

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136.2, 132.9, 132.3, 130.8, 130.2, 130.1, 130.0, 129.3, 128.5, 127.7; **HRMS**: m/z $[M + H]^+$ calcd for $C_{21}H_{14}N_2O$: 311.1179; found: 311.1186.

6-Methyl-2-phenylquinoxaline (4i)[39]: More polar regioisomer; Reddish brown solid; yield: 45%; mp: 138-140 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.28 (s, 1H), 8.17 (d, *J* = 7.6 Hz, 2H), 8.05-7.99 (m, 1H), 7.93-7.89 (m, 1H), 7.62-7.51 (m, 4H), 2.61 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 151.10, 143.2, 141.6, 140.8, 140.1, 136.9, 132.6, 131.8, 130.0, 129.9, 129.1, 127.9, 127.5, 127.4, 21.8; **HRMS**: m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_2$: 221.1073; found: 221.1075.

7-Methyl-2-phenylquinoxaline (4i')[39]: Less polar regioisomer; Brown solid; yield: 39%; mp: 92-95 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.18-8.16 (m, 2H), 8.04-7.98 (m, 1H), 7.92-7.87 (m, 1H), 7.61-7.49 (m, 4H), 2.59 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 150.9, 143.1, 142.3, 141.5, 140.7, 140.0, 136.8, 132.5, 131.8, 129.9, 129.0, 128.5, 127.9, 127.3, 21.8; **HRMS**: m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_2$: 221.1073; found: 221.1072.

6-Methoxy-2-phenylquinoxaline (4j)[39]: More polar regioisomer; Yellow solid; yield: 53%; mp: 115-117 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.25 (s, 1H), 8.15 (d, *J* = 7.2 Hz, 2H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.58-7.49 (m, 3H), 7.46-7.41 (m, 2H), 3.99 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 160.7, 149.7, 142.6, 138.6, 136.8, 130.6, 129.8, 129.1, 127.2, 123.8, 106.2, 55.8; **HRMS**: m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_2O$: 237.1022; found: 237.0993.

7-Methoxy-2-phenylquinoxaline (4j')[39]: Less polar regioisomer; Yellow solid; yield: 34%; mp: 82-84 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 8.17 (dd, J = 8.4, 1.2 Hz, 2H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.59-7.52 (m, 3H), 7.47-7.46 (m, 1H), 7.41 (dd, *J* =

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9.2, 2.4 Hz, 1H), 4.00 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161.1, 151.9, 143.8, 140.5, 137.6, 136.8, 130.1, 129.9, 129.1, 127.5, 123.0, 106.7, 55.8; **HRMS**: m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_2O$: 237.1022; found: 237.1028.

2-Phenylpyrido[2,3-b]pyrazine (4k)[42]: Less polar regioisomer; Brown solid; yield: 32%; mp: 125-128 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.48 (s, 1H), 9.21 (s, 1H), 8.51 (d, *J* = 8.4 Hz, 1H), 8.36 (d, *J* = 7.6 Hz, 2H), 7.75-7.72 (m, 1H), 7.62-7.55 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.7, 154.4, 150.7, 144.5, 138.4, 136.8, 135.6, 131.1, 129.2, 128.1, 124.8; **HRMS**: m/z $[M + H]^+$ calcd for $C_{13}H_9N_3$: 208.0869; found: 28.0874.

3-Phenylpyrido[2,3-b]pyrazine (4k')[42]: More polar regioisomer; Brown solid; yield: 33%; mp: 90-92.3 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.47 (s, 1H), 9.07 (s, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 2H), 7.69-7.66 (m, 1H), 7.53-7.46 (m, 2H), 7.18-7.13 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.4, 153.0, 150.2, 146.4, 138.8, 137.6, 135.8, 130.8, 129.3, 127.7, 125.7; **HRMS**: m/z $[M + H]^+$ calcd for $C_{13}H_9N_3$: 208.0869; found: 208.0868.

2-Phenylacetaldehyde (5)[43]: Colourless liquid; yield: 26%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.75-9.7 (m, 1H), 7.41-7.21 (m, 5 H), 3.69 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 199.4, 131.7, 130.1, 129.5, 128.9, 127.9, 127.3, 50.4; **HRMS**: m/z $[M + H]^+$ calcd for C_8H_8O: 121.0648; found: 121.0646.

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