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PIDA-induced oxidative C–N bond coupling of quinoxalinones and azoles

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ABSTRACT

A metal-free promoted direct oxidative C–N bond coupling of quinoxalinones and azoles for the rapid and effective synthesis of potent pharmaceutical important 3-(azol-1-yl)quinoxalin-2-one has been developed. Employing PIDA as the easily available mediator, the desired coupling products were isolated in moderate to excellent yields with a good substrate scope under operational simplicity and mild reaction conditions. Preliminary mechanistic studies suggested that a radical process is likely to be involved in the reaction.

1. Introduction

Quinoxalin-2(1*H*)-one skeleton is one of the important structural motifs found in natural products, bioactive compounds and pharmaceuticals, known to display remarkably interesting physical and chemical properties as well as diverse biological activities [1]. A number of quinoxalinones and their derivatives have been extensively employed in drug discovery, medicinal chemistry, organic synthesis, materials chemistry as well as agrochemical research [2]. In recent years, the direct C–H functionalization of quinoxalin-2(1*H*)-ones has been served as an ideal and efficient synthetic approach to afford substituted quinoxalin-2(1*H*)-ones [3]. Particularly, a number of achievements have been reported using this strategy for the synthesis of *C-3* functionalized quinoxalin-2(1*H*)-one derivatives, including alkylation [4], arylation [5], acylation [6], cyanation [7], amination [8], alkoxylation [9], thiolation [10] and phosphonation [11].

Among these reported protocols, the direct amination (C–N bond coupling) has drawn significant research interest from synthetic and medicinal chemists as the 3-amino-quinoxalin-2(1*H*)-one derivatives have been considered as an important subfamily with broad spectrum of biological and pharmacological activities such as anticancer, antimicrobial, antiviral and anti-inflammatory properties [12]. Direct synthesis of 3-aminoquinoxalin-2(1*H*)-ones from quinoxalinone substrate with secondary or primary aliphatic amines as nitrogen sources has been reported *via* transition-metal, metal-free, or photoredox catalytic direct oxidative C–H coupling approaches (Scheme 1a) [13]. Direct C–N bond coupling of quinoxalinones with amides (amidation) was also successfully achieved through a copper-catalyzed oxidative cross-coupling reaction (Scheme 1b) [14]. In 2018, our group reported a metal-free promoted direct sulfoximination of quinoxalinones at the *C3* position using an inexpensive persulfate salt ($K_2S_2O_8$) to mediate oxidative C–N bond coupling between quinoxalinones and *NH*-sulfoximines (Scheme 1c) [15].

Despite great achievements in direct C–H/N–H bond coupling, heterocyclic amines such as azoles, which are widely recognized synthetic motif and pharmacophore in medicinal chemistry, drug discovery, material chemistry, catalysis and coordination chemistry [16], as a coupling partner for the direct oxidative C–N bond coupling with quinoxalinones have just been recently reported by Li and co-workers under a photo-driven C–N coupling (Scheme 1d) [17]. However, considering their potent applications, the alternative chemical synthetic method of connecting these two bioactive parts directly is highly desired. Herein, we report the PIDA-promoted direct C–N bond coupling of quinoxalinones at *C3* with *N*-

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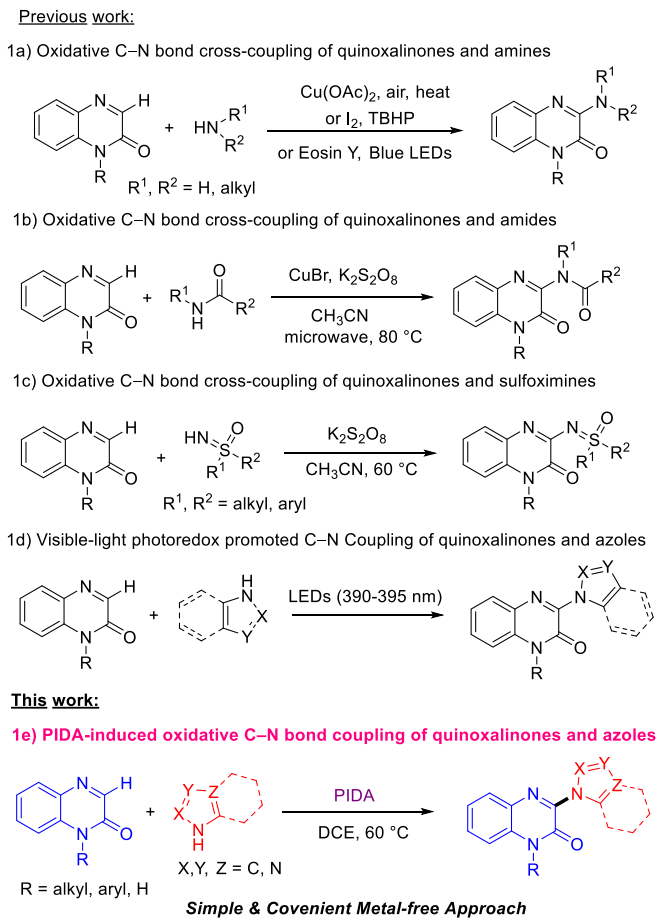


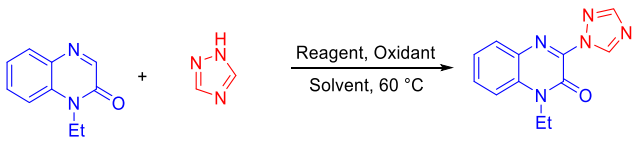
Scheme 1. Direct oxidative C–N bond cross coupling of quinoxalinone at *C-3* position.

heterocycles as nitrogen sources (Scheme 1e). This protocol features simple and mild metal-free conditions, high atom economy, employing readily available reagent, easy-to-handle experimental procedure, good to excellent product yields, together with broad substrate scope and good scalability. The present methodology provides a highly attractive and alternative approach to a preparation of a diverse range of 3-(azol-1-yl)quinoxalin-2(1*H*)-ones, which could be further employed in many applications.

2. Results and discussion

Our investigation began with testing metal-free conditions for the direct oxidative C–N bond coupling, and we used 1,2,4-triazole (**2a**) as a representative *N*-heterocyclic nitrogen source to react with quinoxalinone (**1a**). The results of reaction optimization are summarized in Table 1. As we screened various conditions, poor conversion was obtained under transition metal-mediated reactions (Pd, Ag, Cu, and Fe) [18,19]. Using a metal-free conditions such as different combination of iodine and oxidants (entries 1–6), very low to moderate amounts of the C–N coupling product (**3a**) were obtained. To our delight, upon testing various forms of iodine reagents (entries 7–11), we found that a complete conversion to the corresponding product occurred in the presence of PIFA [Bis(trifluoroacetoxy)iodo]benzene or PIDA (phenyliodine (III) diacetate) (entry 10 and 11). We chose PIDA as a mediator of this reaction for further studies as it is much less expensive and easy to handle than the PIFA. For the solvent screening, dichloroethane (DCE) was the

Table 1
Optimization of reaction conditions.[a]



1a 2a 3a

Entry	Reagent	Oxidant	Solvent	Yield [b]
1	I_2	–	DCE	0
2	I_2	TBHP	DCE	7
3	I_2	*m*-CPBA	DCE	19
4	I_2	Oxone	DCE	42
5	I_2	$K_2S_2O_8$	DCE	15
6	–	$K_2S_2O_8^c$	DCE	25
7	–	I_2O_8	DCE	0
8	–	KIO_3	DCE	0
9	–	PhIO	DCE	33
10	–	PIFA	DCE	88
11	**-**	**PIDA**	**DCE**	**89 (87)[d]**
12	–	PIDA	Toluene	69
13	–	PIDA	Et_2O	48
14	–	PIDA	THF	46
15	–	PIDA	Dioxane	37
16	–	PIDA	Acetone	55
17	–	PIDA	DMF	9

a Conditions: **1a** (0.25 mmol, 1.0 equiv), **2a** (0.38 mmol, 1.5 equiv), reagent (0.25 mmol, 1.0 equiv), oxidant (0.38 mmol, 1.5 equiv), solvent (1.0 mL), 60 °C, 16 h, b GC yield., c Using 2 equivalent of oxidant, heated at 80 °C., d Isolated yield.

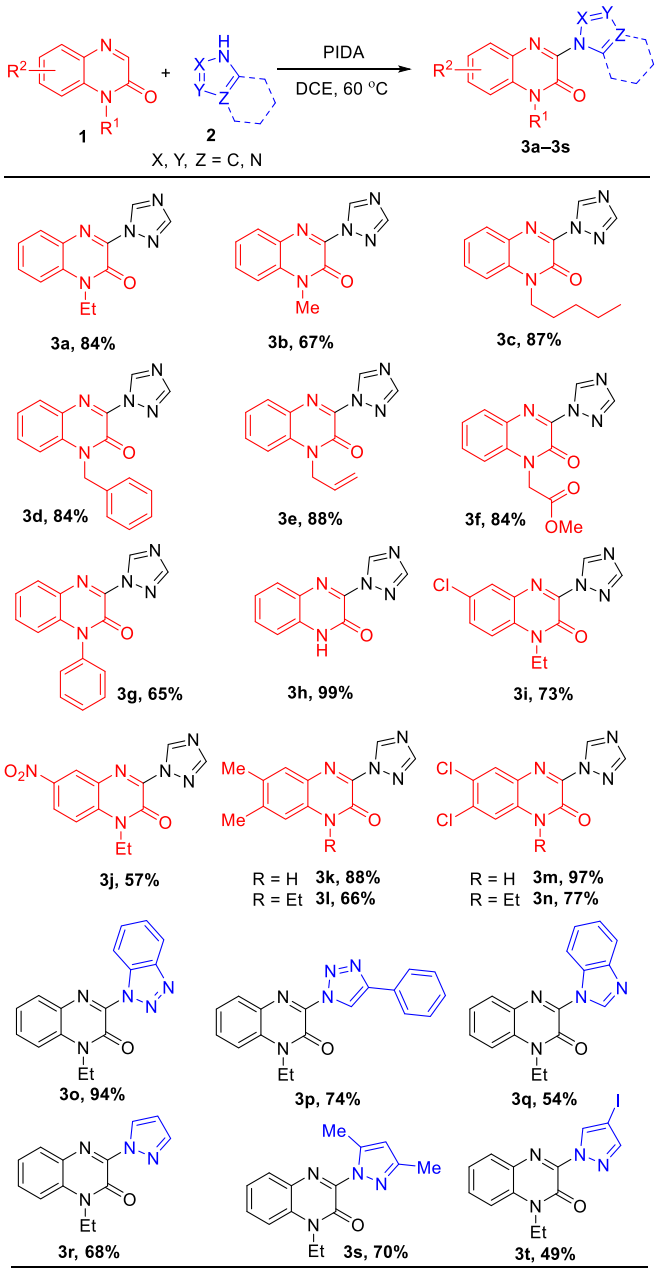
optimal solvent for this transformation (with 87% isolated yield), while other solvents gave low to moderate yields of products (entries 12–17). In addition, other temperatures or additives could not help improve the product conversion [19]. Overall, the optimal conditions for the synthesis of 3-(azol-1-yl)quinoxalin-2-one were PIDA (1.5 equiv), DCE solvent at 60 °C (see Table 2).

With the optimal conditions in hands (using PIDA to mediate the C–N bond coupling in DCE solvent), the generality and limitation of this transformation was explored with a number of.

quinoxaline-2(1*H*)-one and *N*-heterocyclic amine substrates. Firstly, the compatibility with *N*-substituted quinoxalinones was investigated. Different *N*-protected aliphatic groups such as *N*-methyl, *N*-ethyl, *N*-pentyl and *N*-benzyl groups underwent smooth transformations and gave the desired coupling products in good to decent quantities (**3a–3d**). In addition, *N*-allyl and *N*-alkyl ester protected quinoxalinones were well tolerated in this reaction, affording the desired products in very high yields (**3e** and **3f**). No side reactions were observed with the presence of allylic and ester functionality. The quinoxaline-2(1*H*)-one substrate with *N*-phenyl protected also proceeded with no difficulty under the optimal conditions, providing the product in good yield (**3g**). Notably, the unprotected *NH* quinoxalin-2(1*H*)-one substrate worked very well and furnished the corresponding product **3h** in 99% yield. Furthermore, a series of substituted quinoxalinones with halogen, nitro, and alkyl groups at the phenyl ring could react smoothly with heterocyclic amine to provide the products (**3i–3n**) in moderate to excellent yields. These could be very useful for further or late-stage functionalization of the compounds. For the *N*-heterocycle coupling partners, benzotriazole, benzimidazole, 1,2,3-triazole, and pyrazole substrates with methyl and iodo substitutions were also feasible to this transformation and the C–N coupling products were successfully obtained in moderate to excellent yields (**3o–3t**).

With the successful implementation of PIDA-promoted oxidative C–N bond protocol, we further applied this method to the direct alkoxylation of quinoxalinones using alcohols as a coupling

Table 2
Substrate scope of direct C–N coupling of quinoxalinones and *N*-heterocyclic amines.



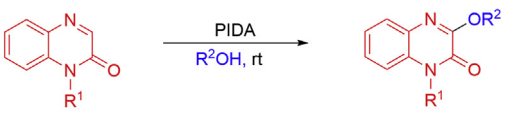
heterocyclic amines.

Conditions: **1** (0.5 mmol, 1.0 equiv), **2** (0.75 mmol, 1.5 equiv), PIDA (0.75 mmol, 1.5 equiv), solvent (2 mL), 60 °C, 16–24 h., as monitored by TLC. Isolated yields after chromatography.

partner [19]. As shown in Table 3, the present method was found to be applicable for C–H alkoxylation of many quinoxalinones with various alkyl alcohols even at room temperature. In general, this route provided the corresponding C–O bond coupling products in good to excellent yields (**5a**–**5d**, **5g** and **5h**). In addition, comparable isolated yields were obtained when carrying out the reactions in DCE solvent (using alcohol 5 equiv). Though, low yield was observed with trifluoroethanol (CF_3CH_2OH) (**5e**), which could reflect the instability of the reaction intermediate in this process. Nonetheless, upon reacting with water (H_2O), the direct oxidative hydroxylation could be obtained and gave the product in moderate yield (**5f**).

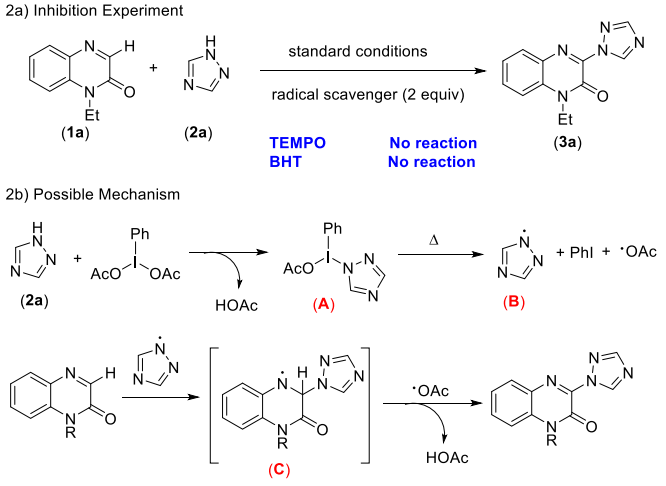
In order to understand the possible mechanism of the transformation, some control experiments were carried out. We found that the reaction was completely inhibited when adding a radical scavenger; for example, TEMPO (2,2,6,6-Tetramethylpiperidin-1-yl) oxyl) and BHT (2,6-ditert-butyl-4-methylphenol, to the standard conditions (Scheme 2a) [19]. This result indicated that a radical

Table 3
Direct alkoxylation of quinoxalinone.[a]



R^1 = H	R^2 = CH_3	**5a**, 84%
R^1 = H	R^2 = CH_2CH_3	**5b**, 90%(78%)[b]
R^1 = H	R^2 = $CH_2C_6H_5$	**5c**, 60%(76%)[b]
R^1 = H	R^2 = CH_2CHCH_2	**5d**, 83%
R^1 = CH_2CH_3	R^2 = CH_2CF_3	**5e**, 25%
R^1 = CH_2CH_3	R^2 = H	**5f**, 46%
R^1 = CH_2CHCH_2	R^2 = CH_2CH_3	**5g**, 94%
R^1 = CH_2COOCH_3	R^2 = CH_2CH_3	**5h**, 99%

[a] Conditions: **1** (0.5 mmol, 1.0 equiv), **2** (0.75 mmol, 1.5 equiv), PIDA (0.75 mmol, 1.5 equiv), solvent (2 mL), 60 °C, 16–24 h, as monitored by TLC. Isolated yields after chromatography.

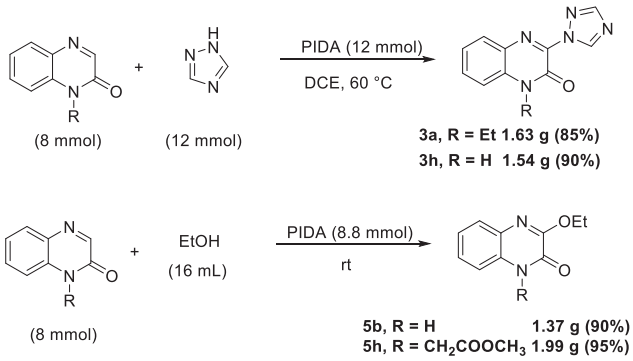


Scheme 2. Control experiments and possible mechanism.

mechanism is likely to be involved in the coupling process. On the basis of the above-mentioned result and literature reports [20,21], a *plausible* mechanism is proposed as depicted in Scheme 2b. Initially, the *N*-heterocyclic amine (**2a**) reacts with PIDA to generate the *N*-iodoamido species (**A**), which subsequently undergoes thermal homolytic cleavage to give azole radical (**B**). The resulting radical (**B**) then reacts with quinoxaline-2(1*H*)-one at C-3, which is the most electrophilic position [22], to produce the radical intermediate (**C**), in which upon a radical abstraction/oxidation could furnish the product. The mechanism of direct alkoxylation is likely to be similar to the proposed mechanism in Scheme 2b. The inhibition of reaction was observed upon subjecting the PIDA-mediated alkoxylation reactions to the radical scavengers.

[a]Conditions: **1** (0.5 mmol, 1.0 equiv), PIDA (0.55 mmol, 1.1 equiv), alcohol as solvent (2 mL), rt, 4–24 h, as monitored by TLC. Isolated yields after chromatography. [b] Using alcohol (5 equiv) in DCE solvent (2 mL), rt.

We also performed a gram-scale synthesis of the PIDA-induced C–N and C–O bonds coupling for products **3a**, **3h**, **5b** and **5h**, and both methods work well with similar efficacy to the small scale reactions (Scheme 3) [23]. These results suggested a practical utilization of this protocol.



Scheme 3. Gram-scale reaction.

3. Conclusion

In summary, the alternative, straightforward and convenient metal-free direct C–N bond coupling of quinoxalinones with azoles was developed. This protocol employed PIDA to induce the oxidative coupling process under relatively mild reaction conditions. Moreover, this method is applicable to the direct alkoxylation, can be conducted on gram-scale, and can accommodate a wide range substrate scope, providing a series of potent biologically important 3-(azol-1-yl)quinoxalin-2-one products and their related derivatives in moderate to good yields. Further expansion of the synthetic utility and study of potential biological applications of these synthesized compounds are currently in progress in our laboratory.

4. Experimental section

4.1. General methods

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. All experiments were carried out under air atmosphere, and oven-dried glasswares were used in all cases. Column chromatography was performed over silica gel (SiO_2; 60 Å silica gel, Merck Grade, 70–230 Mesh). GC experiments were carried out with an Agilent 6890 N GC-FID on chromatograph equipped with Agilent column HP-1, dimethylpolysiloxane column (30 m × 0.25 mm ID × 0.25 μm). ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in DMSO-d_6 and $CDCl_3$ solutions. NMR chemical shifts are reported in ppm and were measured relative to DMSO to DMSO (2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C) and $CHCl_3$ (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). IR spectra were recorded on Bruker FT-IR Spectrometer Model ALPHA by neat method, and only partial data are listed. Melting points were determined on Buchi Melting Point M – 565 apparatus. High-resolution mass spectroscopy (HRMS) data were analyzed by a high-resolution micrOTOF instrument with electrospray ionization (ESI). The structures of known compounds were corroborated by comparing their ^{1}H NMR, ^{13}C NMR data with those of literature [9a,17,20,24].

4.2. Preparation of the starting materials

The *N*-alkylated-quinoxalinone substrates were synthesized from the *2-hydroxyquinoxaline* and the corresponding alkyl halides *via* standard alkylation reactions according to the literature procedures [5a,25].

4.3. Typical experimental procedure for the PIDA-promoted direct C–N bond cross coupling of quinoxalinones and azoles: synthesis of compounds **3a**–**3t**

An 8 mL oven-dried scintillation vial equipped with a magnetic stir bar was charged with a mixture of 2-quinoxalinone (0.50 mmol, 1.0 equiv), triazole (0.75 mmol, 1.5 equiv), PIDA (0.75 mmol, 1.5 equiv), and DCE (CH_2ClCH_2Cl) (2 mL). The vial was capped, and the reaction mixture was stirred at 60 °C for 16–24 h. Upon completion, distilled deionized H_2O (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography to afford the desired products.

4.3.1. 1-Ethyl-3-(1H-1,2,4-triazol-1-yl)quinoxalin-2(1H)-one (**3a**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (102 mg, 84% yield); mp = 170.3–171.4 °C; IR (KBr): 3149, 3102, 1660, 1605, 1593, 1506, 1398, 1303, 1273, 1200, 1122, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.83 (s, 1H), 8.22 (s, 1H), 8.08 (d, J = 7.9 Hz, 1H), 7.69–7.65 (m, 1H), 7.48–7.44 (m, 2H), 4.48 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 149.7, 146.7, 141.1, 131.6, 131.3, 131.2.130.9, 124.9, 113.8, 38.6, 12.4 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{12}N_5O$: 242.1036; found: 242.1034.

4.3.2. 1-Methyl-3-(1H-1,2,4-triazol-1-yl)quinoxalin-2(1H)-one (**3b**) [17]

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a pale yellow solid (76 mg, 67% yield); IR (KBr): 3150, 3104, 1658, 1602, 1508, 1203, 1130, 990 952, 774, 671 cm^{-1}; ^1H NMR ($CDCl_3$/MeOD, 400 MHz): δ 9.78 (s, 1H), 8.17 (s, 1H), 8.01 (dd, J = 8.0, 1.2 Hz, 1H), 7.66–7.61 (m, 1H), 7.45–7.39 (m, 2H), 3.83 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$/MeOD, 100 MHz): δ 152.4, 150.2, 146.7, 140.9, 132.7, 131.5, 130.9, 130.6, 125.2, 114.0, 30.1 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{11}H_9N_5ONa$: 250.0699; found: 250.0698.

4.3.3. 1-Pentyl-3-(1H-1,2,4-triazol-1-yl)quinoxalin-2(1H)-one (**3c**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (123 mg, 87% yield); mp = 119.0–120.7 °C; IR (KBr): 3150, 1659, 1606, 1589, 1476, 1389, 1206, 1129, 982, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.82 (s, 1H), 8.21 (s, 1H), 8.07 (dd, J = 8.1, 1.2 Hz, 1H), 7.67–7.63 (m, 1H), 7.47–7.41 (m, 2H), 4.38 (t, J = 7.9 Hz, 2H), 1.87–1.79 (m, 2H), 1.52–1.38 (m, 4H), 0.94 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.7, 150.0, 146.8, 141.1, 131.9, 131.3, 131.2, 130.9, 124.9, 114.0, 43.5, 29.1, 27.1, 22.4, 14.0 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{17}N_5ONa$: 306.1325; found: 306.1328.

4.3.4. 1-Benzyl-3-(1H-1,2,4-triazol-1-yl)quinoxalin-2(1H)-one (**3d**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (128 mg, 84% yield); mp = 163.3–164.9 °C; IR (KBr): 3159, 3118, 1661, 1604, 1392, 1205, 1128, 986, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.84 (s, 1H), 8.22 (s, 1H), 8.07 (dd, J = 8.0, 1.2 Hz, 1H), 7.57–7.52 (m, 1H), 7.44–7.26 (m, 7H), 5.64 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.7, 150.4, 146.8, 141.2, 134.3, 132.1, 131.3, 131.2, 130.7, 129.2, 128.1, 126.8, 125.1, 114.7, 46.9 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{17}H_{13}N_5ONa$: 326.1012; found: 326.1018.

4.3.5. 1-Allyl-3-(1H-1,2,4-triazol-1-yl)quinoxalin-2(1H)-one (**3e**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a pale yellow solid (112 mg, 88% yield); mp = 151.4–152.6 °C; IR (KBr): 3168, 3107, 1164, 1605, 1476, 1393, 1195, 983, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.82 (s, 1H), 8.22 (s, 1H), 8.08 (dd, J = 8.1, 1.3 Hz, 1H), 7.66–7.61 (m, 1H), 7.48–7.39 (m, 2H), 6.04–5.94 (m, 1H), 5.27 (d, J = 10.4 Hz, 1H), 5.16 (d, J = 17.2 Hz, 1H), 5.06 (dt, J = 5.1, 1.5 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.7, 150.0, 146.8, 141.2, 132.0, 131.4, 131.2, 130.9, 129.8, 125.2, 119.0, 114.6, 45.6 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{11}N_5ONa$: 276.0856; found: 276.0854.

4.3.6. Methyl-2-(2-oxo-3-(1H-1,2,4-triazol-1-yl)quinoxalin-1(2H)-yl)acetate (**3f**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (119 mg, 84% yield); mp = 193.2–195.0 °C; IR (KBr): 3152, 3114, 1732, 1657, 1606, 1272, 1235, 1132, 980, 756 cm^{-1}; ^1H ($CDCl_3$, 400 MHz): δ 9.74 (s, 1H), 8.21 (s, 1H), 8.08 (dd, J = 8.1, 1.1 Hz, 1H), 7.65–7.61 (m, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 5.17 (s, 2H), 3.81 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.9, 152.9, 150.1, 146.8, 141.0, 131.9, 131.7, 131.1, 131.0, 125.5, 113.4, 53.3, 44.3 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{11}N_5O_3Na$, 308.0754; found: 308.0753.

4.3.7. 1-Phenyl-3-(1H-1,2,4-triazol-1-yl)quinoxalin-2(1H)-one (**3g**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a pale yellow solid (94 mg, 65% yield); mp = 250.8–251.5 °C; IR (Neat): 3165, 3098, 1672, 1604, 1386, 1202, 1122, 965, 756 cm^{-1}; ^1H ($CDCl_3$, 400 MHz): δ 9.77 (s, 1H), 8.22 (s, 1H), 8.12–8.10 (m, 1H), 7.70–7.61 (m, 3H), 7.47–7.42 (m, 2H), 7.36 (d, J = 7.3 Hz, 2H), 6.78–6.76 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.9, 150.3, 146.9, 141.6, 135.2, 133.6, 131.1, 131.0, 130.8, 130.3, 130.2, 128.0, 125.3, 115.8 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{16}H_{11}N_5ONa$, 312.0856; found: 312.0858.

4.3.8. 3-(1H-1,2,4-Triazol-1-yl)quinoxalin-2(1H)-one (**3h**)

Purification by column chromatography (pure EtOAc) as a yellow solid (105 mg, 99% yield); mp = 189.2–190.1 °C; IR (KBr): 3160, 3103, 1686, 1614, 1508, 1396, 1272, 1199, 1130, 981, 752 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 13.10 (s, 1H), 9.58 (s, 1H), 8.33 (s, 1H), 7.83 (dd, J = 8.0, 0.8 Hz, 1H), 7.63–7.59 (m, 1H), 7.42–7.38 (m, 2H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.1, 150.7, 146.5, 142.7, 131.8, 130.8, 130.1, 128.5, 124.2, 115.5 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{10}H_7N_5ONa$: 236.0543; found: 236.0544.

4.3.9. 6-Chloro-1-ethyl-3-(1H-1,2,4-triazol-1-yl)quinoxalin-2(1H)-one (**3i**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (100 mg, 73% yield); mp = 274.9–276.1 °C; IR (KBr): 3165, 3120, 1670, 1602, 1481, 1440, 1384, 1197, 1121, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.82 (s, 1H), 8.21 (s, 1H), 8.07 (d, J = 2.3 Hz, 1H), 7.61 (dd, J = 9.1, 2.2 Hz, 1H), 7.38 (d, J = 9.0 Hz, 1H), 4.45 (q, J = 7.2 Hz, 2H), 1.47 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.0, 149.6, 147.0, 142.1, 132.0, 131.5, 130.4, 130.3, 130.2, 115.0, 39.0, 12.6 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{11}ClN_5O$: 276.0647; found: 276.0648.

4.3.10. 1-Ethyl-6-nitro-3-(1H-1,2,4-triazol-1-yl)quinoxalin-2(1H)-one (**3j**)

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (82 mg, 57% yield); mp = 233.3–234.1 °C; IR (KBr): 3181, 3121, 1670, 1596, 1510, 1526, 1351, 1200, 1124 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.89 (s, 1H), 8.34–8.22 (m, 4H), 4.54 (q, J = 7.2 Hz, 2H), 1.53 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.5, 149.5, 148.5, 147.5, 143.4, 135.1, 132.0, 131.9, 119.5, 109.8, 39.4, 12.7 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{10}N_6O_3Na$: 309.0707; found: 309.0709.

*4.3.11. 6,7-Dimethyl-3-(1H-1,2,4-triazol-1-yl)quinoxalin-2(1H)-one (**3k**)*

Purification by column chromatography (pure EtOA) as a yellow solid (106 mg, 88% yield); mp = 285.4–286.8 °C; IR (KBr): 3130, 3105, 1687, 1595, 1485, 1278, 1208, 1132, 981, 966 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz):δ 13.79 (s, 1H), 9.54 (s, 1H), 8.30 (s, 1H), 7.59 (s, 1H), 7.16 (s, 1H), 2.34 (s, 3H), 2.31 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 151.9, 150.7, 146.2, 141.8, 141.2, 140.7,133.1, 130.0, 128.2, 115.5, 19.9, 19.0 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{12}H_{11}N_5ONa$: 264.0856; found: 264.0855.

*4.3.12. 1-Ethyl-6,7-dimethyl-3-(1H-1,2,4-triazol-1-yl)quinoxalin-2(1H)-one (**3l**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a pale yellow (90 mg, 66% yield); mp = 217.9–219.0 °C; IR (KBr): 3133, 3106, 1658, 1623, 1505, 1470, 1385, 1208, 1119, 977 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.78 (s, 1H), 8.19 (s, 1H), 7.81 (s, 1H), 7.18 (s, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 2.37 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.6, 149.8, 146.6, 141.8, 140.4, 134.2, 131.0, 129.8, 129.7, 114.2, 38.5, 21.0, 19.4, 12.6 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{14}H_{15}N_5ONa$: 292.1169; found: 292.1170.

*4.3.13. 6,7-Dichloro-3-(1H-1,2,4-triazol-1-yl)quinoxalin-2(1H)-one (**3m**)*

Purification by column chromatography (pure EtOAc) as a yellow solid (136 mg, 97% yield); decomposed at 298.4 °C; IR (KBr): 3150, 3099, 1681, 1610, 1511, 1408, 1278, 1130, 988, 570 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 14.00 (brs, 1H), 9.62 (s, 1H), 8.33 (s, 1H), 8.08 (s, 1H), 7.54 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.2, 150.8, 146.7, 143.6, 132.4, 132.3, 129.9, 129.2, 125.7, 116.9 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{10}H_5Cl_2N_5ONa$: 303.9763; found: 303.9766.

*4.3.14. 6,7-Dichloro-1-ethyl-3-(1H-1,2,4-triazol-1-yl)quinoxalin-2(1H)-one (**3n**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a pale yellow solid (119 mg, 77% yield); mp = 233.3–234.3 °C; IR (KBr): 3174, 1668, 1599, 1505, 1297, 1276, 1197, 977, 878, 600 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.78 (s, 1H), 8.19 (s, 1H), 8.13 (s, 1H), 7.51 (s, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.1, 149.4, 147.0, 141.9, 135.8, 131.5, 130.9, 130.4, 129.1, 115.3, 39.1, 12.5 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{10}Cl_2N_5O$: 310.0257; found: 310.0265.

*4.3.15. 3-(1H-Benzo[d] [1–3]triazol-1-yl)-1-ethylquinoxalin-2(1H)-one (**3o**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (137 mg, 94% yield); mp = 198.5–200.4 °C; IR (KBr): 1667, 1606, 1557, 1449, 1402, 1289, 1187, 1049, 987, 711, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.72–7.68 (m, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.50–7.44 (m, 3H), 4.52 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.4, 145.9, 143.7, 132.9, 132.7, 131.8, 131.4, 130.8, 129.0, 125.1, 124.7, 120.3, 114.0, 113.5, 38.8, 12.6 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{16}H_{13}N_5ONa$: 314.1012; found: 314.1016.

*4.3.16. 1-Ethyl-3-(4-phenyl-1H-1,2,3-triazol-1-yl)quinoxalin-2(1H)-one (**3p**)*

Purification by column chromatography (Hexanes/EtOAc, 4/1) as a yellow solid (117 mg, 74% yield); mp = 145.2–146.0 °C; IR (neat): 1663, 1600, 1589, 1464, 1405, 1353, 923, 752, 693, 596 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.26 (s, 1H), 8.05–8.03 (m, 1H), 7.97–7.95 (m, 2H), 7.69–7.65 (m, 1H), 7.49–7.40 (m, 5H), 4.48 (q, *J* = 7.2 Hz, 2H), 1.48 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.5, 150.1, 143.8, 134.8, 133.0, 131.7, 131.2, 129.5, 129.1, 126.9, 126.3, 125.0, 124.5, 113.9, 38.7, 12.5 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{15}N_5ONa$: 340.1169; found: 340.1170.

*4.3.17. 3-(1H-Benzo[d]imidazol-1-yl)-1-ethylquinoxalin-2(1H)-one (**3q**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (79 mg, 54% yield); mp = 157.2–158.3 °C; IR (KBr): 1660, 1603, 1592, 1560, 1492, 1447, 1262, 1211, 766, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.75 (s, 1H), 8.65–8.63 (m, 1H), 7.98 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.93–7.91 (m, 1H), 7.66–7.62 (m, 1H), 7.50–7.43 (m, 4H), 4.48 (q, *J* = 7.2 Hz, 2H), 1.48 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.8, 143.7, 143.1, 142.8, 132.8, 131.6, 131.4, 130.5, 129.9, 125.0, 124.8, 120.3, 116.2, 115.0, 114.0, 38.6, 12.6 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{17}H_{15}N_4O$: 291.1240; found: 291.1243.

*4.3.18. 1-Ethyl-3-(1H-pyrazol-1-yl)quinoxalin-2(1H)-one (**3r**) [17]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (81 mg, 68% yield); IR (KBr): 3163, 2979, 1654, 1605, 1560, 1526, 1489, 1463, 1390, 1193, 1099, 929, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.10 (d, *J* = 2.6 Hz, 1H), 8.05 (d, *J* = 7.3 Hz, 1H), 7.89 (s, 1H), 7.60–7.55 (m, 1H), 7.41–7.38 (m, 2H),6.51 (dd, *J* = 2.4, 1.6 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 150.2, 143.4, 142.6, 133.3, 131.7, 131.6, 130.5, 124.5, 113.6, 108.3, 38.4, 12.5 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{13}H_{12}N_4ONa$: 263.0903; found: 263.0904.

*4.3.19. 3-(3,5-Dimethyl-1H-pyrazol-1-yl)-1-ethylquinoxalin-2(1H)-one (**3s**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (94 mg, 70% yield); mp = 118.4–119.7 °C; IR (KBr): 2963, 1664, 1604, 1568, 1297, 1065, 1086, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, *J* = 8.3 Hz, 1H), 7.64–7.59 (m, 1H), 7.40–7.36 (m, 2H), 6.05 (s, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 2.33 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.5, 151.4, 146.1, 142.6, 132.8, 131.7, 131.1, 130.8, 124.1, 113.7, 108.5, 38.4, 14.0, 12.6, 12.5 ppm; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{17}N_4O$: 269.1397; found: 269.1396.

*4.3.20. 1-Ethyl-3-(4-iodo-1H-pyrazol-1-yl)quinoxalin-2(1H)-one (**3t**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (90 mg, 49% yield); mp = 166.3–167.6 °C; IR (KBr): 3166, 2962, 1643, 1602, 1293, 1175, 1233, 1111, 949, 817, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.21 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.88 (s, 1H), 7.63–7.59 (m, 1H), 7.44–7.40 (m, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.1, 148.0, 141.7, 137.5, 131.8, 131.5, 130.8, 130.7, 124.8, 113.7, 60.5, 38.6, 12.5 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{13}H_{11}IN_4ONa$: 388.9870; found: 388.9872.

*4.4. Typical experimental procedure for the PIDA-promoted direct C–O bond cross coupling of quinoxalinones and alcohols: synthesis of compounds **5a**–**5h***

An 8 mL oven-dried scintillation vial equipped with a magnetic stir bar was charged with a mixture of 2-quinoxalinone (0.50 mmol, 1.0 equiv), PIDA (0.55 mmol, 1.1 equiv), and alcohol (2 mL). The vial was capped, and the reaction mixture was stirred at room temperature for 4–24 h. Upon completion, distilled deionized H_2O (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated *in*

vacuo. The crude product was purified by SiO_2 column chromatography to afford the desired products.

*4.4.1. 3-Methoxyquinoxalin-2(1H)-one (**5a**) [24a]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (74 mg, 84% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.27 (s, 1H), 7.65 (dd, J = 8.0, 0.9 Hz, 1H), 7.41–7.28 (m, 3H), 4.15 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.7, 152.9, 131.4, 129.4, 127.4, 126.9, 124.7, 115.9, 55.0 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_9H_8N_2O_2Na$: 199.0478; found: 199.0480.

*4.4.2. 3-Ethoxyquinoxalin-2(1H)-one (**5b**) [24b]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (86 mg, 90% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.28 (s, 1H), 7.61 (dd, J = 8.0, 0.8 Hz, 1H), 7.41 (dd, J = 8.0, 0.8, 1H), 7.37–7.33 (m, 1H), 7.30–7.26 (m, 1H), 4.60 (q, J = 7.1 Hz, 2H), 1.53 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.3, 153.0, 131.5, 129.3, 127.1, 126.8, 124.6, 116.0, 63.8, 14.3 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{10}H_{10}N_2O_2Na$: 213.0634; found: 213.0624.

*4.4.3. 3-(Benzyloxy)quinoxalin-2(1H)-one (**5c**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (76 mg, 60% yield); mp = 195.1–196.4 °C; IR (neat): 1682, 1612, 1574, 1448, 1298, 974, 942, 758, 586 cm^{-1} ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.80 (s, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.0 Hz, 2H), 7.40–7.27 (m, 6H), 5.58 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.1, 152.5, 136.0, 131.2, 129.5, 128.9, 128.6, 128.4, 127.4, 126.9, 124.6, 115.8, 69.3 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{12}N_2O_2Na$: 275.0791; found: 275.0793.

*4.4.4. 3-(Allyloxy)quinoxalin-2(1H)-one (**5d**)*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid in (84 mg, 83% yield); mp = 190.4–191.7 °C; IR (KBr): 1682, 1611, 1308, 1237, 994, 941, 754, 588 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.64 (s, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.39–7.34 (m, 1H), 7.32–7.27 (m, 1H), 7.30–7.26 (m, 1H), 6.24–6.14 (m, 1H), 5.50 (dd, J = 17.2, 1.4 Hz, 1H), 5.35 (dd, J = 10.4, 1,2 Hz, 1H), 5.05 (d, J = 6.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.8, 152.9, 132.2, 131.3, 129.4, 127.3, 126.8, 124.6, 119.5, 116.1, 68.4 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{12}N_2O_2$: 203.0815; found: 203.0817.

*4.4.5. 1-Ethyl-3-(2,2,2-trifluoroethoxy)quinoxalin-2(1H)-one (**5e**) [9a]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a pale yellow solid (34 mg, 25% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (dd, J = 8.2, 1.5, 1H), 7.39–7.35 (m, 1H), 7.24–7.20 (m, 2H), 4.79 (q, J = 8.3, 2H), 4.26 (q, J = 7.2, 2H), 1.20 (t, J = 7.2, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.1, 149.8, 131.1, 130.4, 128.3, 128.2, 124.1, 123.3 (q, J = 275.9 Hz), 113.8, 62.9 (q, J = 36.7 Hz), 38.0, 12.5 ppm; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{12}F_3N_2O_2$: 273.0845; found: 273.0847.

*4.4.6. 1-Ethyl-3-hydroxyquinoxalin-2(1H)-one (**5f**) [24c]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a white solid (44 mg, 46% yield); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.03 (s, 1H), 7.41–7.39 (m, 1H), 7.22–7.11 (m, 3H), 4.14 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 154.8, 153.6, 125.9, 125.8, 123.5, 123.3, 115.8, 114.8, 37.3, 12.0 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{10}H_{10}N_2O_2Na$: 213.0634; found: 213.0632.

*4.4.7. 1-Allyl-3-ethoxyquinoxalin-2(1H)-one (**5g**) [24d]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a yellow solid (108 mg, 94% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (d, J = 7.9 Hz, 1H), 7.39–7.34 (m, 1H), 7.30–7.27 (m, 1H), 7.23 (d, J = 8.3 Hz, 1H), 5.98–5.88 (m, 1H), 5.26 (d, J = 10.4 Hz, 1H), 5.19 (d, J = 17.3 Hz, 1H), 4.93 (d, J = 4.2 Hz, 2H), 4.55 (q, J = 7.1 Hz, 2H), 1.51 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.0, 150.9, 131.5, 130.8, 130.7, 127.7, 126.9, 124.0, 118.2, 114.3, 63.6, 44.9, 14.3 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{14}N_2O_2Na$: 253.0947; found: 253.0946.

*4.4.8. Methyl-2-(3-ethoxy-2-oxoquinoxalin-1(2H)-yl)acetate (**5h**) [20]*

Purification by column chromatography (Hexanes/EtOAc, 1/1) as a pale orange solid (131 mg, 99% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (dd, J = 7.9, 1.4 Hz, 1H), 7.38–7.26 (m, 2H), 7.00 (dd, J = 8.2, 0.9 Hz, 1H), 5.05 (s, 2H), 4.55 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 153.7, 151.0, 131.4, 130.7, 128.0, 127.2, 124.4, 113.1, 63.8, 53.0, 43.8, 14.3 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{13}H_{14}N_2O_4Na$: 285.0846; found: 285.0846.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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