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Synthesis of 2-Methylquinoxaline Derivatives from Glycerol and Diamines Catalyzed by Iridium Complexes Bearing an *N*-Heterocyclic Carbene Ligand

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Abstract: 2-Methylquinoxaline derivatives are widely used as intermediates in the synthesis of pharmaceuticals, natural products, and dyes; however, their syntheses usually require excess reagents, making them environmentally burdensome. Meanwhile, glycerol can be sustainably obtained in large quantities as a by-product in the production of biodiesel fuel using waste oil as a raw material. Thus, it is worthwhile to develop a new catalytic system that utilizes glycerol as a C3 source. In this study, an efficient catalytic system was developed to obtain 2-methylquinoxaline derivatives from glycerol and 1,2-phenylenediamines. This system is beneficial because it is environmentally friendly and has excellent atom efficiency.

Keywords: glycerol; quinoxaline; iridium catalyst; NHC ligand

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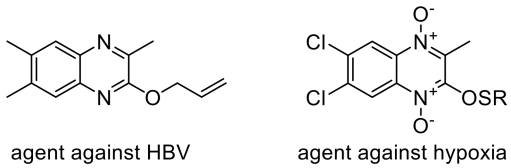
1. Introduction

N-heterocyclic compounds are an important class of organic compounds with a wide range of applications, such as pharmaceuticals [1–4], pesticides [5–7], natural products [1,4], and even functional organic materials [8,9]; therefore, it is of great significance to develop an efficient method for their synthesis. The conventional synthetic methods towards *N*-heterocyclic compounds often require excessive amounts of reagents, which imposes a large burden on the environment [10–14]. In addition, there are often difficulties in terms of selectivity and atom efficiency during such syntheses [10–14]. Therefore, studies have been actively conducted with the aim of developing new synthetic protocols for *N*-heterocyclic compounds using starting materials that are abundant, sustainable, safe, and inexpensive [10–14].

Among the various *N*-heterocyclic compounds, quinoxalines, particularly 2-methylqui noxaline derivatives, have been utilized as antiviral, anticancer, and antibacterial agents (Figure 1) [15–17]. As a specific example, an example of 2-methylquinoxaline derivatives that have been utilized as a medicaments are shown in Figure 1. Thus, it is very important to develop new catalytic reactions towards 2-methylquinoxaline derivatives.



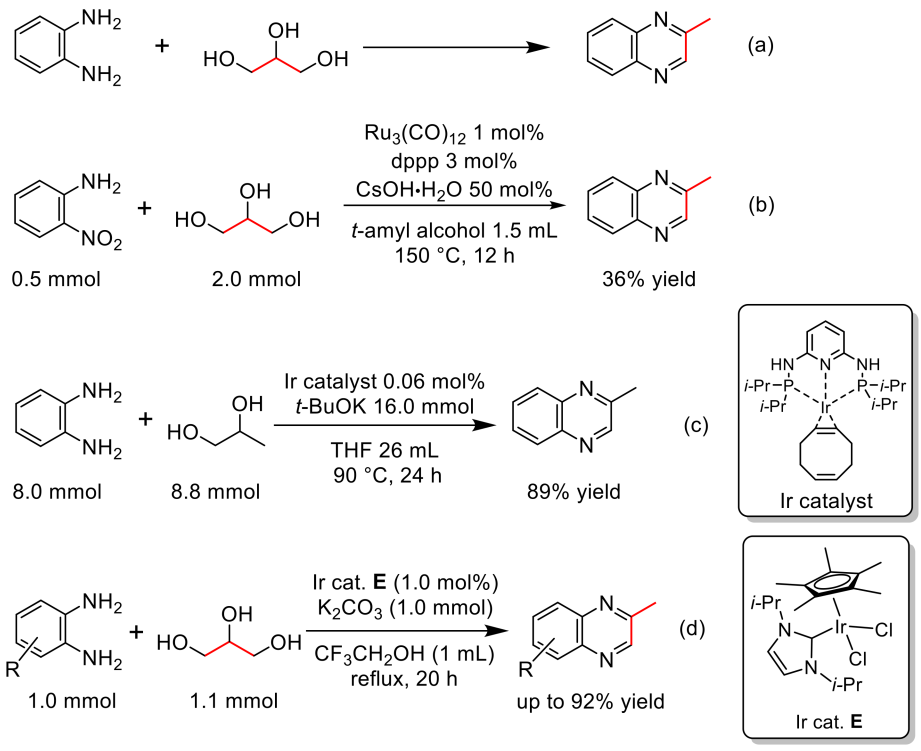
agent against HBV agent against hypoxia

Figure 1. Examples of 2-methylquinoxaline derivatives that served as medicaments.

Regarding potential reagents for the synthesis of 2-methylquinoxaline derivatives, glycerol is a harmless and safe compound composed of three carbon atoms and three

hydroxy groups, and has traditionally been obtained as a by-product of manufacturing processes producing fatty acids and soaps. Recently, glycerol has been obtained in large quantities as a by-product in the production of biodiesel fuel from waste oil [18]. Indeed, the amount of by-product glycerol produced alongside biodiesel fuel has substantially increased over the last two decades; consequently, there is an oversupply of glycerol [19]. Unfortunately, surplus glycerol is often disposed of without being effectively utilized. Therefore, it is worthwhile to develop a new catalytic synthetic method that utilizes such sustainably attained glycerol as a C3 source [20,21].

In view of these various backgrounds, it can be said that the reaction of glycerol with 1,2-phenylenediamine (which is also an inexpensive and readily available compound) to synthesize 2-methylquinoxaline derivatives is exceptionally attractive (Scheme 1a). Previously, a ruthenium-catalyzed system reported by Min Zhang et al. produced 2-methylquinoxaline from glycerol and 2-nitroaniline (Scheme 1b) [22]. This catalytic reaction was performed at a relatively high temperature of 150 °C, and four equivalents of glycerol were required. Kempe et al. also discovered an extremely efficient iridium-catalyzed method for synthesizing 2-methylquinoxaline using 1,2-phenylenediamine and 1,2-propanediol as starting materials (Scheme 1c) [23–25]. This catalytic system in particular served as the motivation for the present study. We have previously developed various catalytic systems based on hydrogen transfer processes using iridium complexes. Specifically, we have reported several carbon-nitrogen bond-forming reactions that proceed via borrowing-hydrogen [26–29].



Scheme 1. Synthesis of 2-methylquinoxaline derivatives.

In this paper, we describe the synthesis of 2-methylquinoxaline derivatives from glycerol and 1,2-phenylenediamines using iridium complexes bearing an *N*-heterocyclic carbene ligand as a catalyst (Scheme 1d). In this catalytic system, approximately equal amounts of glycerol and the 1,2-phenylenediamines were used, and the desired products were successfully obtained in good yields under reflux conditions in 2,2,2-trifluoroethanol as a solvent (boiling point: 78 °C).

2. Results and Discussion

The structures of the iridium catalysts used in this study are shown in Figure 2.

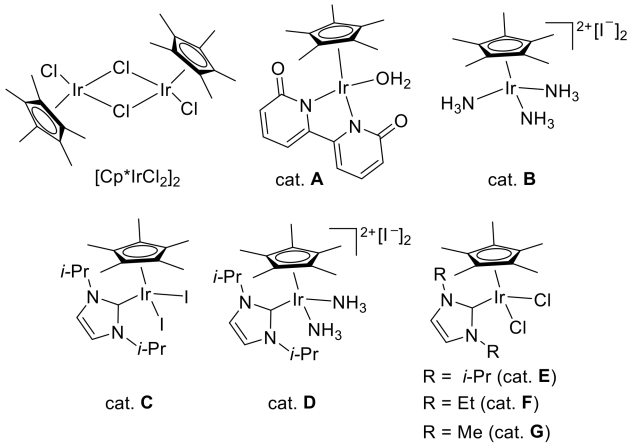
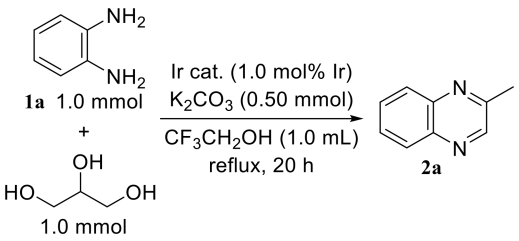


Figure 2. A series of iridium catalysts used in this study.

First, the reaction of 1,2-phenylenediamine (**1a**) with glycerol to give 2-methylquinoxaline (**2a**) was taken up as a model reaction to optimize the reaction conditions. Various catalysts were first evaluated, and the yields of **2a** obtained in the presence of these iridium catalysts are summarized in Table 1. In general, the reaction of **1a** (1.0 mmol) with glycerol (1.0 mmol) was carried out in the presence of an iridium catalyst (1.0 mol % Ir) and potassium carbonate (0.50 mmol) under reflux in 2,2,2-trifluoroethanol (1.0 mL) for 20 h. Under conditions without an iridium catalyst, **2a** was not obtained at all (entry 1). These results indicate that the use of a catalyst is essential for the synthesis of **2a** using **1a** and glycerol as the starting materials. When simple-structured $[Cp^*IrCl_2]_2$ (1.0 mol % Ir) was used, only trace amounts of **2a** were obtained (entry 2). When the reaction was conducted in the presence of bipyridonate-bearing iridium catalyst **A**, which we used in the dehydrogenative reactions of alcohols and cyclic amines, **2a** was obtained in only 13% yield (entry 3). Water-soluble triammine complex **B**, which showed high catalytic activity for a hydrogen transfer reaction in water, was also ineffective for the present reaction (entry 4). On the other hand, the yield of **2a** was greatly improved (up to 67%) in the presence of iridium complex **C**, which possesses two iodine ligands and an *N*-heterocyclic carbene (NHC) ligand having isopropyl groups on its nitrogen atoms (entry 5). A similar yield of **2a** was obtained when a dicationic iridium complex **D** similar to **C** (it bears ammine ligands instead of iodine ligands) was used as the catalyst (entry 6). The yield of **2a** was further improved to 77% using a similar iridium-NHC complex **E** bearing two chloro ligands (entry 7). However, when the *N*-isopropyl groups of the NHC ligand of **E** were replaced with ethyl (**F**, entry 8) or methyl (**G**, entry 9) groups, the yield of **2a** significantly decreased. From these results, iridium complex **E** was selected as the optimum catalyst.

Table 1. Optimization of iridium catalyst for the synthesis of 2-methylquinoxaline (**2a**).

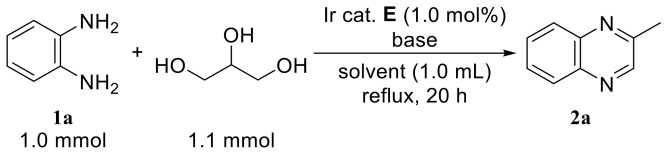


Entry	Ir Catalyst	Yield of 2a (%) [a]
1	none	0
2	$[Cp^*IrCl_2]_2$	trace
3	**A**	13
4	**B**	trace
5	**C**	67
6	**D**	68
7	**E**	77
8	**F**	41
9	**G**	10

[a] Determined by GC.

Subsequent experiments employed catalyst **E** to optimize the other conditions of the model reaction. To investigate the effects of different bases and solvents, the quantity of glycerol as a starting material was set to 1.1 mmol (Table 2). 2,2,2-Trifluoroethanol was used as the solvent for evaluating the different bases. First, in the reaction without a base, the yield of **2a** was very low (entry 1). The yield of **2a** was increased to 27% when sodium carbonate (0.50 mmol) was added as a base (entry 2). Among the alkali metal carbonates (entries 2–5), potassium carbonate was most effective as a base to give **2a** in the yield of 82% (entry 5). When the amount of potassium carbonate was increased to 1.0 mmol, the yield of **2a** reached 92% (entry 6). Potassium hydroxide was also an effective base (entry 7), but did not exceed the yield obtained when potassium carbonate was used. From these results, the optimum base was considered to be potassium carbonate.

Table 2. Optimization of the base and solvent for the synthesis of 2-methylquinoxaline (**2a**).



Entry	Base (mmol)	Solvent	Yield of 2a (%) [a]
1	none	CF_3CH_2OH	2
2	Na_2CO_3 (0.50)	CF_3CH_2OH	27
3	Li_2CO_3 (0.50)	Li_2CO_3 (0.50)	0
4	Cs_2CO_3 (0.50)	CF_3CH_2OH	75
5	K_2CO_3 (0.50)	CF_3CH_2OH	82
6	K_2CO_3 (1.0)	CF_3CH_2OH	92 (88 [b])
7	KOH (1.0)	CF_3CH_2OH	70
8	K_2CO_3 (1.0)	toluene	trace
9	K_2CO_3 (1.0)	anisole	9
10	K_2CO_3 (1.0)	H_2O	21
11	K_2CO_3 (1.0)	*t*-BuOH	1

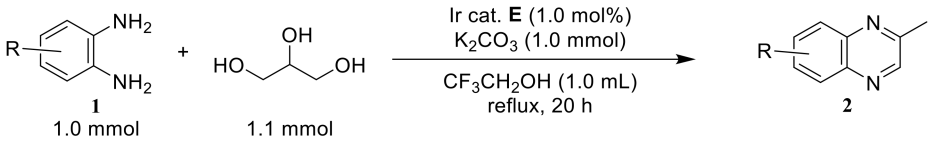
[a] Determined by GC. [b] Isolated yield.

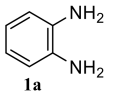
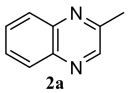
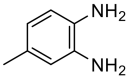
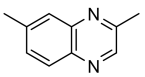
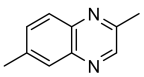
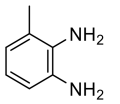
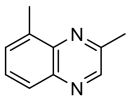
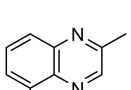
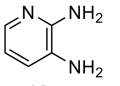
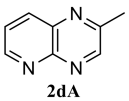
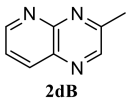
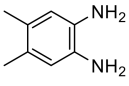
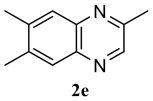
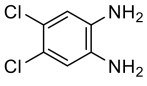
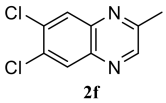
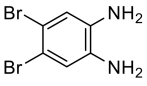
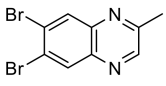
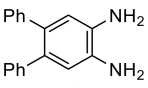
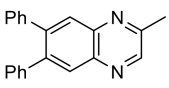
Next, the optimal solvent was explored. Reactions were carried out using toluene, anisole, water, and *t*-BuOH (entries 8–11) and compared to the reaction using 2,2,2-

trifluoroethanol (entry 6). The yield of **2a** was highest when using 2,2,2-trifluoroethanol; therefore, it was selected as the optimal solvent.

Using the optimal conditions, we then synthesized various quinoxaline derivatives from different diamines and glycerol (Table 3). When 1,2-phenylenediamines bearing methyl substituents (**1b** and **1c**) were used as starting materials, the corresponding dimethyl quinoxalines (**2b** and **2c**) were obtained in good yields (entries 2 and 3). In these reactions, the dimethylquinoxaline derivatives were obtained as a mixture of isomers (**2A** and **2B**) with different substitution positions of the methyl groups. The ratios of the respective isomers were calculated by integrating the corresponding ^{1}H NMR peaks. Reactions using a diamine with a pyridine ring skeleton (**1d**) also proceeded to afford the cyclized product in moderate yield (entry 4). In addition, the corresponding methylquinoxaline derivatives could also be obtained when 1,2-phenylenediamines (**1e**–**h**) with the same substituents at their 4- and 5-positions were used as starting materials. Thus, our protocol afforded various methylquinoxaline derivatives that are useful in the field of synthetic organic chemistry.

Table 3. Scope of substrates for the synthesis of 2-methylquinoxaline derivatives.

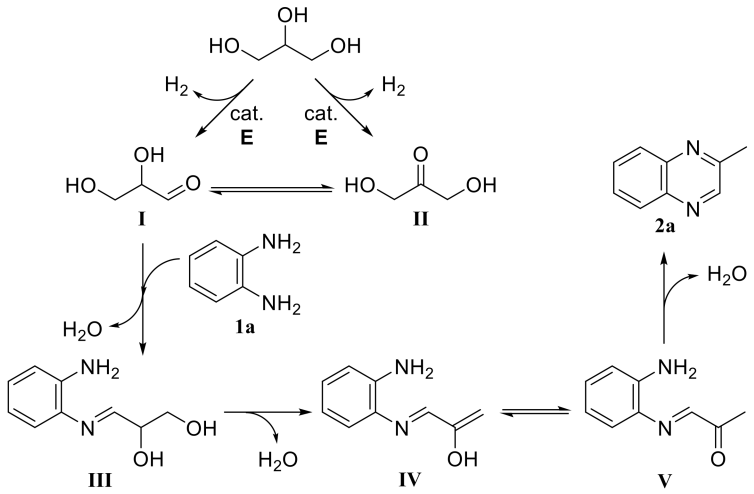


Entry	Substrate (1)	Product (2)	Ratio of 2A : 2B [a]	Yield of 2 (%) [a]
1	 **1a**	 **2a**		88
2	 **1b**	 **2bA** and  **2bB**	60 : 40	88
3 [b]	 **1c**	 **2cA** and  **2cB**	79 : 21	82
4 [c]	 **1d**	 **2dA** and  **2dB**	15 : 85	58 [d]
5	 **1e**	 **2e**		74
6 [b]	 **1f**	 **2f**		65
7 [b]	 **1g**	 **2g**		55
8 [b]	 **1h**	 **2h**		87

[a] Isolated yield. [b] Reaction time is 40 h. [c] Ir catalyst (2.0 mol%) was used. Reaction time is 60 h. [d] Determined by ^{1}H NMR.

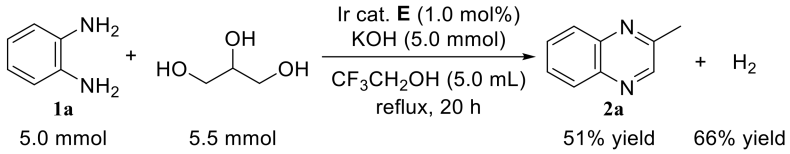
The mechanism for the conversion of 1,2-phenylenediamine (**1a**) and glycerol to 2-methylquinoxaline (**2a**) by iridium catalyst **E** is shown in Scheme 2. Initially, glycerol is dehydrogenated by **E** to give an equilibrium mixture of glyceraldehyde (**I**) and dihy-

droxyacetone (**II**) [30]. Among them, **I** is highly reactive and undergoes a dehydration reaction with **1a** to produce intermediate **III**. Subsequently, intermediate **III** is converted to species **IV** via dehydration. Finally, the species **V**, which is a tautomer of **IV**, undergoes an intramolecular dehydration between its carbonyl and amino groups to produce **2a** [31]. Since the dehydration reaction is accelerated in a solvent with a moderately acidic proton source, 2,2,2-trifluoroethanol (pKa = 12.4) is considered to be effective as a reaction solvent.



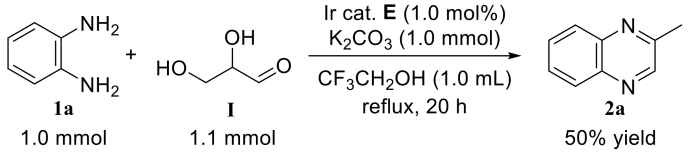
Scheme 2. A possible mechanism for the conversion of **1a** and glycerol to **2a**.

According to the mechanism illustrated in Scheme 2, the reaction producing **2a** from **1a** and glycerol involves the evolution of hydrogen gas. Therefore, to measure the generated hydrogen gas, the model reaction was carried out on a larger (five-fold) scale. The generated gas was collected in a gas burette to measure its volume. In this experiment, if potassium carbonate was used as the base, carbon dioxide gas would be generated; therefore, potassium hydroxide was used instead. As a result, **2a** was produced in 51% yield and hydrogen was obtained in 66% yield (Scheme 3) [32]. This result supports the mechanism proposed in Scheme 2.



Scheme 3. Quantitative analysis of the evolved hydrogen along with the formation of **2a**.

Furthermore, the reaction of **1a** with glyceraldehyde, which is proposed as an intermediate **I** in the possible mechanism shown in Scheme 2, was performed under the optimal catalytic conditions. As a result, **2a** was obtained in 50% yield (Scheme 4), supporting the proposed mechanism.



Scheme 4. Formation of **2a** by the catalytic reaction of **1a** with glyceraldehyde.

3. Materials and Methods

3.1. General

All reactions and manipulations were performed under argon atmosphere using standard Schlenk techniques. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on JEOL ECS-

400 (Tokyo, Japan) or ECX-500 spectrometers (Tokyo, Japan). Gas chromatograph analyses of hydrogen were per-formed on a GL-Sciences GC390 (Tokyo, Japan) gas chromatograph with packed columns (Molecular Sieve 5A and Gaskuropack 54). Gas chromatograph analysis of organic product was per-formed on a GL-Sciences GC353B (Tokyo, Japan) gas chromatograph and a GL-Sciences GC4000 gas chromatograph with a capillary column (GL-Sciences InertCap Pure-WAX or InertCap for Amines, Tokyo, Japan). Silica-gel column chromatography was performed using Wako-gel C-200 (Wako Pure Chemical Corporation, Osaka, Japan). The catalysts, $[Cp^*IrCl_2]_2$ [33] (Cp^*: η^5-pentamethylcyclopentadienyl), **A** [34], **B** [35], **C** [36], **D** [36], **E** [28], **F** [37], and **G** [38] were prepared according to the literature methods. The substrate **1i** [39] was also prepared according to the literature method. Organic solvents were dried by passage through columns (either alumina or activated molecular sieves) on a Glass Contour solvent system. Other reagents were commercially available and were used as received.

*3.2. General Procedure for Optimization of the Reaction Conditions for the Synthesis of 2-Methyquinoxaline (**2a**)*

Initially, glycerol (1.0 mmol in Table 1 and 1.1 mmol in Table 2) was placed in a two-necked test tube. After the introduction of argon, iridium catalyst (1.0 mol % Ir), 1,2-phenylenediamine (**1a**, 1.0 mmol), base, and solvent (1.0 mL) were added, and the mixture was magnetically stirred and refluxed for 20 h in an oil bath. The reaction setup is illustrated in Figure S1 in the supporting information. The yield of **2a** was determined by GC analysis using biphenyl as an internal standard.

3.3. General Procedure for the Synthesis of 2-Methylquinoxaline Derivatives

Initially, glycerol (1.1 mmol) was placed in a two-necked test tube. After the introduction of argon, the catalyst **E** (1.0 mol %), 1,2-phenylenediamine derivative (1.0 mmol), K_2CO_3 (1.0 mmol), and 2,2,2-trifluoroethanol (1.0 mL) were added, and the mixture was magnetically stirred and refluxed for 20 h in an oil bath. The reaction setup is illustrated in Figure S1 in the supporting information. In the cases of products **2b-d** (Table 3, Entries 2–4), the ratios of isomers **2A** and **2B** were determined by ^{1}H NMR analyses of the crude products. Then, the products were isolated by silica-gel column chromatography (eluent: hexane/ethyl acetate). Identification of the known products was performed based on the comparison of NMR data with their reported ones. In the case of product **2d** (Table 3, Entry 4), the total yield of **2dA** and **2dB** and the ratio of these products were determined by ^{1}H NMR analysis using triphenylmethane as an internal standard (^{1}H NMR chart of the crude mixture of this reaction is shown in the supporting information).

2-Methylquinoxaline (**2a**) [22]: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.05 (dd, *J* = 8, 1 Hz, 1H), 8.00 (d, *J* = 8, 1 Hz, 1H), 7.73–7.65 (m, 2H), 2.74 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 153.6, 145.9, 141.9, 140.8, 129.9, 129.0, 128.8, 128.5, 22.4.

2,7-Dimethylquinoxaline (**2bA**) [40]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H), 7.94 (d, *J* = 9 Hz, 1H), 7.77 (s, 1H), 7.52 (dd, *J* = 9, 2 Hz, 1H), 2.75 (s, 3H), 2.57 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.7, 145.2, 142.2, 140.6, 139.5, 131.2, 128.7, 127.6, 22.6, 21.9.

2,6-Dimethylquinoxaline (**2bB**) [40]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (s, 1H), 7.89 (d, *J* = 8 Hz, 1H), 7.82 (s, 1H), 7.56 (dd, *J* = 8, 2 Hz, 1H), 2.75 (s, 3H), 2.57 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.8, 145.9, 141.1, 140.6, 139.4, 132.3, 128.2, 128.1, 22.5, 21.8.

2,8-Dimethylquinoxaline (**2cA**) [40]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H), 7.90–7.88 (m, 1H), 7.59–7.54 (m, 2H), 2.77 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.6, 145.6, 141.4, 141.0, 137.0, 130.0, 128.6, 127.1, 22.8, 17.3.

2,5-Dimethylquinoxaline (**2cB**) [40]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H), 7.85 (d, *J* = 8 Hz, 1H), 7.62 (t, *J* = 8 Hz, 1H), 7.52 (d, *J* = 8 Hz, 1H), 2.78 (s, 3H), 2.77 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.4, 144.8, 142.3, 140.2, 137.4, 129.9, 129.1, 126.6, 22.6, 17.4.

2,6,7-Trimethylquinoxaline (**2e**) [22]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1H), 7.79 (s, 1H), 7.75 (s, 1H), 2.73 (s, 3H), 2.47 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.8, 145.1, 141.1, 140.5, 140.0, 139.3, 128.3, 127.8, 22.6,20.5, 20.3.

6,7-Dichloro-2-methylquinoxaline (**2f**) [41]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.16 (s, 1H), 8.11 (s, 1H), 2.77 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 155.2, 147.1, 140.9, 139.8, 134.6, 133.5, 129.9, 129.5, 22.8.

6,7-Dibromo-2-methylquinoxaline (**2g**): pale-pink powder, m.p. 163.9–164.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.34 (s, 1H), 8.29 (s, 1H), 2.76 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 155.3, 147.2, 141.4, 140.3, 133.3, 132.9, 126.7, 125.4, 22.9. Anal. Calcd for $C_9H_6Br_2N_2$: C, 35.70; H, 2.06; N, 9.26. Found: C, 35.80; H, 2.00; N, 9.28.

6,7-Diphenyl-2-methylquinoxaline (**2h**): pale-yellow powder, m.p. 139.7–140.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 8.12 (s, 1H), 8.08 (s, 1H), 7.27–7.22 (m, 10H), 2.79 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 154.2, 146.4, 143.4, 142.4, 141.4, 140.34, 140.30, 130.4, 130.0, 129.9, 128.1, 127.2, 127.2, 22,8. Anal. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 84.61; H, 5.45; N, 9.37.

*3.4. Procedure for Quantitative Analysis of the Evolved Hydrogen along with the Formation of **2a***

Initially, glycerol (5.5 mmol) was placed in a two-necked test tube. After the introduction of argon, the catalyst **E** (1.0 mol %), 1,2-phenylenediamine (**1a**, 5.0 mmol), KOH (5.0 mmol), and 2,2,2-trifluoroethanol (5.0 mL) were added, and the mixture was magnetically stirred and refluxed for 20 h in an oil bath. The reaction setup is illustrated in Figure S2 in the supporting information. The evolved gas was collected in a gas burette. The yield of hydrogen was calculated based on the ideal gas law. The chromatogram of the evolved gas is shown in Figure S3a in the supporting information. The chromatogram of the standard pure hydrogen gas is shown in Figure S3b in the supporting information. By the comparison of Figures S3a,b, it was confirmed that pure hydrogen was obtained by the present reaction. On the other hand, the yield of **2a** was determined by GC analysis of the reaction mixture using biphenyl as an internal standard.

*3.5. Procedure for the Synthesis of **2a** by the Catalytic Reaction of **1a** with Glyceraldehyde*

Initially, glyceraldehyde (**I**, 1.1 mmol) was placed in a two-necked test tube. After the introduction of argon, the catalyst **E** (1.0 mol %), 1,2-phenylenediamine (**1a**, 1.0 mmol), K_2CO_3 (1.0 mmol), and 2,2,2-trifluoroethanol (1.0 mL) were added, and the mixture was magnetically stirred and refluxed for 20 h in an oil bath. The reaction setup is illustrated in Figure S1 in the supporting information. The yield of **2a** was determined by GC analysis using biphenyl as an internal standard.

4. Conclusions

In summary, an efficient catalytic system was developed to synthetically obtain chemically valuable 2-methylquinoxaline derivatives using inexpensive and readily available glycerol and 1,2-phenylenediamines as starting materials. This protocol is beneficial because it is environmentally friendly and has excellent atom efficiency. Furthermore, such a catalyst system that effectively utilizes glycerol is significant because glycerol is easily obtained from natural resources and is currently a surplus C3 carbon source.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal11101200/s1, Figure S1: Illustration of the reaction setup for optimization of the reaction conditions for the synthesis of 2-methyquinoxaline (**2a**) shown in Tables 1 and 2, Figure S2: Illustration of the reaction setup for quantitative analysis of the evolved hydrogen along with the formation of **2a** shown in Scheme 3, Figure S3: GC analysis of the evolved hydrogen along with the formation of **2a** shown in Scheme 3, and NMR charts of the organic products.

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