RESEARCH ARTICLE

Successive cleavage and reconstruction of lignin β-O-4 models and polymer to access quinoxalines

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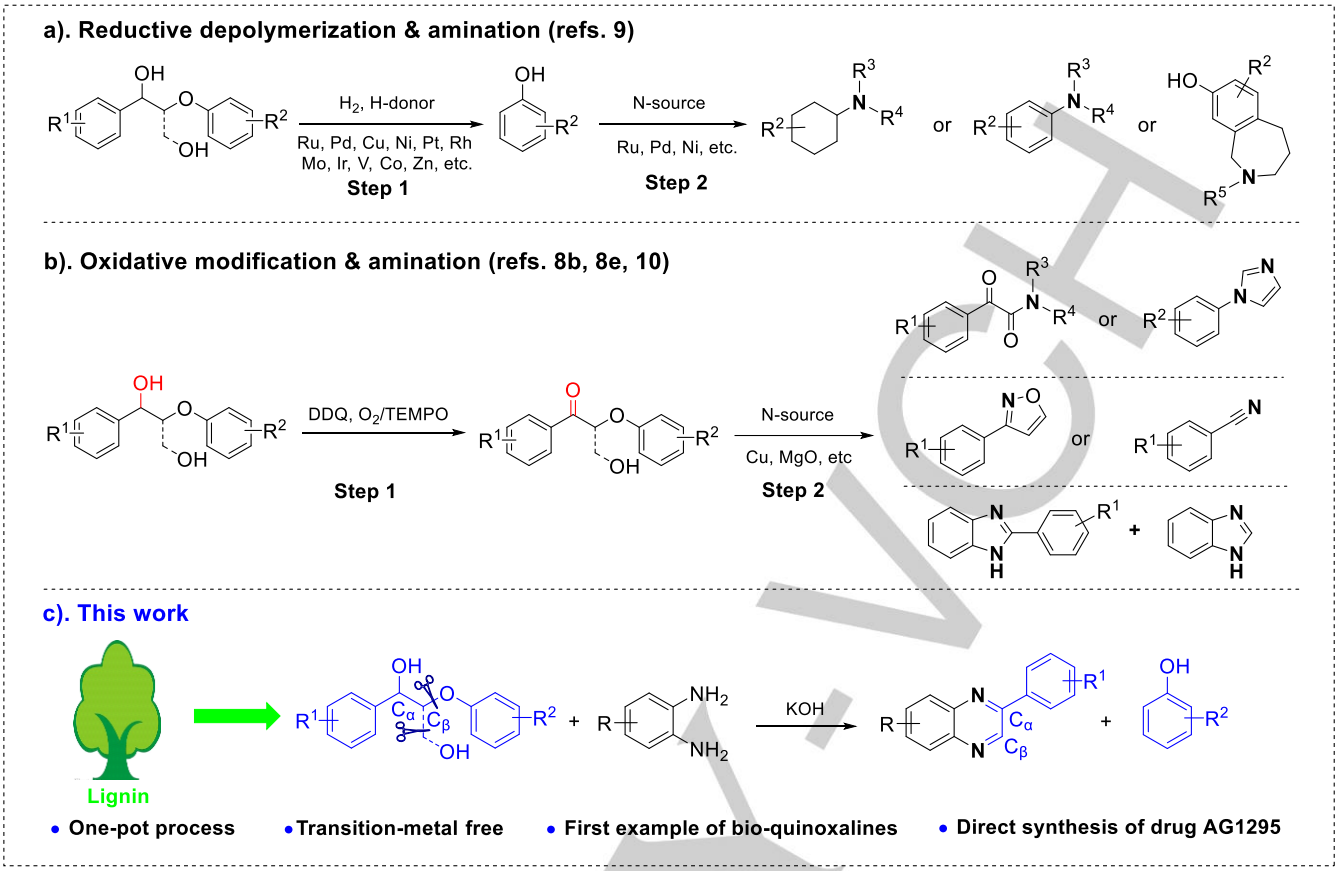
Abstract: The construction of *N*-heterocyclic compounds from lignin remains a great challenge due to the complex lignin structure and the involvement of multiple steps, including the cleavage of lignin C-O linkages and the formation of heterocyclic aromatic ring. Herein, the first example of KOH mediated sustainable synthesis of quinoxaline derivatives from lignin β-O-4 model compounds in a one-pot fashion under transition-metal-free conditions has been achieved. Mechanistic studies suggest that this transformation includes highly coupled cascade steps of cleavage of C-O bonds, dehydrative condensation, sp^3 C-H bond oxidative activation and intramolecular dehydrative coupling reaction. With this protocol, a wide range of functionalized quinoxalines, including an important drug compound AG1295, were synthesized from lignin β-O-4 model compounds and β-O-4 polymer, showcasing the application potential of lignin in pharmaceutical synthesis.

Introduction

Currently or for a long time, we are facing one of the biggest challenges of worldwide climate change and energy crisis, a situation which calls for an efficient low-carbon society and sustainable chemical industry. As the only renewable organic carbon resource, biomass plays an ever-increasing important role in the production of sustainable energy and chemicals.[1] Particularly, lignin is the most abundant natural aromatic polymer that has potential to serve as a renewable feedstock for aromatic chemicals.[1d, 1g, 2] Accordingly, extensive research efforts focus on the depolymerization of lignin into low molecular phenols[3], arenes[4], and other valueble products[5]. To increase the economics of the overall conversion process and meet value-added biorefinery demand, heteroatom-participated lignin conversion for the generation of heteroatom-containing aromatics becomes a new topic and attracts increasing interests.[6] Due to the diverse utility of *N*-containing compounds in the synthesis of pharmacological agents and fine chemicals,[7] some elegant strategies have been developed to introduce nitrogen on lignin-derived monomers or model compounds for the production of *N*-containing aromatic compounds.[8] For instance, lignin β-O-4 dimers were first reductively depolymerized to aromatic monomers over transition metals, and the monomers were further catalytic converted to *N*-containing aromatic compounds via one- or multiple steps in the presence of organic or inorganic *N*-source (Scheme 1a).[9] In another strategy, lignin β-O-4 model compounds were oxidized to active ketone derivatives, which further underwent a nitridation process to afford *N*-containing aromatic compounds (Scheme 1b).[8b, 8e, 10] On the whole, for the conversion of β-O-4 dimers, the major segments in lignin, recently developed strategies overwhelmingly require two- or more steps and in the presence of transition metal catalysts to harvest *N*-containing aromatic compounds. In the limited progresses on the direct conversion of lignin model dimers, Han et al. describe Pd-catalyzed coupling of aryl ethers and morpholines to produce 4-cyclohexylmorpholines[8c]; Jiao et al. report a site-directed C–C bond primary amination of different lignin β-O-4 and β-1 dimers for efficient preparation of anilines[8d]; Zhang et al. report $CeCl_3$ promoted photocatalytic cleavage and amination of lignin β-O-4 and produce *N*-containing products.[11] We also report the direct conversion of lignin β-O-4 dimers into benzylamines in the presence of organic amines over Pd/C.[12] Despite the above progresses, *in-situ* construction of *N*-heterocyclic compounds from lignin β-O-4 model compounds that mimicking real lignin structure is rarely reported[13] due to the challenges associating with the cleavage of C-O bonds between the aromatic units, new C-N bond formation, and further cyclization to generate heterocyclic compounds.



Scheme 1. Production of N-containing aromatics from lignin β-O-4 model compounds.

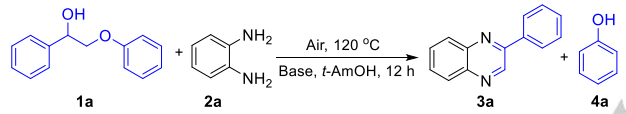
As an important class of *N*-heterocyclic compounds, quinoxaline derivatives are ubiquitous structural motifs that can be found in drugs, agrochemicals and other bioactive compounds.[14] Traditionally, quinoxalines are dominantly prepared from fossil-based resources through the coupling of 1,2-phenylenediamines with two-carbon synthons, such as 1,2-diketone[15] or vicinal diols[16], α-hydroxyketones[17], α-bromoketones[18] or ketones[19]. In addition, epoxides[20], diazenylbutenes[21], phenethylamines[22], and alkynes[23] also serve as two-carbon synthons to deliver quinoxalines. Other approaches mainly involve the coupling of 2-nitroanilines[24] with α-hydroxyketones or alcohols[25] and the reduction of 1,2-dinitrobenzenes[26] to 1,2-diamines followed by oxidative cyclization processes. The above existing methods for the synthesis of quinoxaline scaffolds prevailingly rely on non-renewable substrates and transition metal catalysts. Moreover, certain amount of these progresses require multi-step synthetic routes, complicated ligands[24, 27] and additives[28], or hazardous halogenated reagents[18], which suffer from high processing cost, low overall efficiency, and excessive carbon emission with environmental concerns. In order to adapt to a low carbon future, the development of efficient green route for the synthesis of quinoxalines from renewable feedstock such as lignin is highly desirable. Herein, a simple and sustainable protocol was developed for the one-pot synthesis of quinoxaline derivatives from lignin β-O-4 model compounds in the presence of organic N-sources and KOH under transition-metal-free conditions (Scheme 1c). Such a new strategy involves highly-coupled multi-steps of cleavage of C-O bonds, dehydrative condensation, sp^3 C-H bond oxidative activation and intramolecular dehydrative coupling reaction. Remarkably, AG1295, an important drug for inhibition of the platelet-derived growth factor receptor tyrosine kinase, can be obtained straightforwardly by this protocol. The whole transformation does not need external reducing reagent nor strong oxidant, with O_2 in air serving as an environmentally benign oxidant for the key step of sp^3 C-H bond activation, which demonstrates a good example for the production of value-added *N*-heterocyclic compounds from renewable biomass feedstock.

Results and Discussion

Phenolic β-aryl ether (β-O-4) is the most abundant linkage in all types of lignin.[1g] In previous work, alcohols[25] and ketones[19] can be used to synthesize quinoxalines. Noting that lignin β-O-4 linkages possess α-OH group in the side chain could be oxidized to generate ketone[29], we envisioned that lignin β-O-4 moiety could serve as a potential renewable precursor for quinoxaline synthesis. Specifically, the C_α and C_β atoms in the β-O-4 lignin structure could be utilized for the construction of the heterocycle of quinoxalines. Our study commenced with the model reaction between lignin β-O-4 model compound **1a** and 1,2-diaminobenzene (**2a**) in the presence of NaOH in *t*-AmOH (*tert*-Amyl alcohol) at 120 °C for 12 h under air. Pleasingly, the desired product of 2-phenylquinoxaline (**3a**) was obtained in 48% yield and the cleavage product of phenol (**4a**) was afforded in 75% yield under air (Table 1, entry 1), which verified the feasibility of

our hypothesis. Subsequently, other strong bases (KOH, and *t*-BuONa) and weak bases ($NaHCO_3$, Na_2CO_3, and K_3PO_4) were evaluated, the results indicated that KOH is the preferable choice to provide **3a** in 57% yield and **4a** in 71% yield (Table 1, entries 1-6). Then, screening of various solvents, such as DMSO (Dimethyl sulfoxide), toluene, HFIP (1,1,1,3,3,3-hexafluoro-2-propanol), *t*-BuOH (*tert*-Butanol), 2-BuOH (2-Butanol), NMP (N-Methyl-2-pyrrolidone) and PhCl (Chlorobenzene), suggested that all these solvents gave lower yields of **3a** (Table 1, entries 7-13) than that obtained in *t*-AmOH. To our delight, when a mixture of solvents consisting of PhCl/*t*-AmOH (v/v = 1:1) was used, **3a** could be obtained in a higher yield of 70%, accompany with **4a** yield of 71% (Table 1, entry 14). Further optimization of reaction parameters, including substrate ratio, base loading, temperature and reaction time (Table S1-S3), led to the optimized condition, under which **1a** (0.3 mmol) reacted with **2a** (0.1 mmol) mediated by KOH at 120 °C for 24 h under air in *t*-AmOH/PhCl, affording 76% yield (73% isolated yield) of **3a** along with 62% yield (60% isolated yield) of **4a** (Table 1, entry 16). Meanwhile, a control experiment showed that KOH is indispensable in this transformation (Table 1, entry 17).

Table 1. Optimal reaction conditions for the synthesis of quinoxaline derivatives [a]



1a 2a 3a 4a

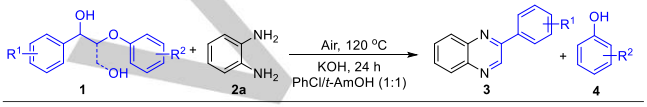
Entry	base	solvent	Yield[b] (%) 3a	4a
1	NaOH	*t*-AmOH	48	75
2	KOH	*t*-AmOH	57	71
3	*t*-BuONa	*t*-AmOH	42	47
4	$NaHCO_3$	*t*-AmOH	0	0
5	Na_2CO_3	*t*-AmOH	0	0
6	K_3PO_4	*t*-AmOH	0	0
7	KOH	DMSO	12	91
8	KOH	Toluene	53	88
9	KOH	HFIP	0	0
10	KOH	*t*-BuOH	44	31
11	KOH	2-BuOH	8	9
12	KOH	PhCl	56	81
13	KOH	NMP	34	63
14	KOH	*t*-AmOH/PhCl (1:1)	70	71
15[c]	KOH	*t*-AmOH/PhCl (1:1)	73	61
16[d]	**KOH**	***t*-AmOH/PhCl (1:1)**	**76 (73)**	**62 (60)**
17[e]	-	*t*-AmOH/PhCl (1:1)	0	0

[a] Reaction conditions: 1a (0.2 mmol), 2a (0.1 mmol), base (5 equiv), solvent (1 mL), 120 °C, 12 h, under Air. After the reaction, hydrochloric acid (1 M) was used to acidify the solution to pH = ca. 5. [b] Yields were determined by GC-FID with biphenyl as internal standard. [c] 1a (0.3 mmol), 2a (0.1 mmol). [d] 1a (0.3 mmol), 2a (0.1 mmol), 24 h, isolated yield is given in parentheses. [e] 1a (0.3 mmol), 2a (0.1 mmol), no KOH, 24 h.

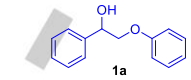
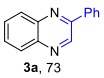
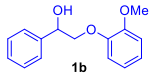
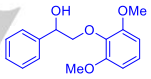
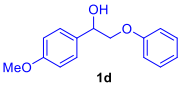
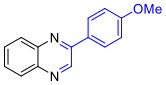
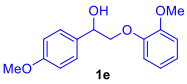
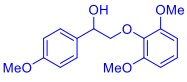
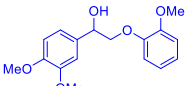
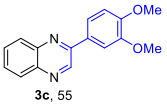
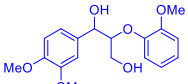
Under the optimal reaction conditions, we then investigated the scope of lignin β-O-4 model substrates. It was found that the methoxy groups on both phenyl rings are all tolerated, and the yields of targeted quinoxaline products were in the range of 48%-73% (Table 2, entries 1-7), together with phenols (**4**) in yields of 42%-60%, albeit the methoxy groups generally exhibited a negative effect on the reactivity. It is noteworthy that phenol and derivatives are also valuable precursors for the synthesis of various flavorants, pesticides and dyes.[30] This transformation also worked for the highly substituted β-O-4 model compound **1h** containing both α- and γ-OH groups, the most representative structural fragment in lignin, which provided the desired products **3c** and **4c** in yield of 15% and 45%, respectively (Table 2, entry 8). The lower yields of **3c** and **4c** are probably due to the higher steric hindrance of **1h** compared to **1a**-**1g** and side reactions induced by the γ-OH group.

Encouraged by the above results, the generality of the current protocol was further evaluated with a variety of substituted 1, 2-diaminobenzenes **2** (Table 3). It is found that all tested diaminobenzenes are tolerated and transformed into the targeted quinoxaline derivatives with moderate yields, along with the cleavage product phenol (**4a**) in yield of 32%-60% (Table 3). However, different substituents showed some diverse effects on

Table 2. The scope of lignin model compounds for the synthesis of quinoxaline derivatives [a]



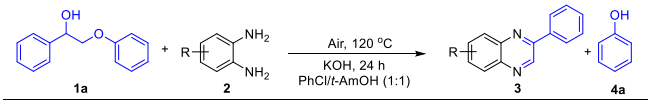
1 2a 3 4

Entry[a]	1	Yield[b] (%)	
1		 **3a**, 73	 **4a**, 60
2		**3a**, 50	 **4b**, 48
3		**3a**, 52	 **4c**, 46
4		 **3b**, 65[c]	**4a**, 55
5		**3b**, 60[d]	**4b**, 50
6		**3b**, 48	**4c**, 42
7		 **3c**, 55	**4b**, 47
8		**3c**, 15[d]	**4c**, 45

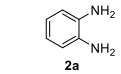
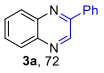
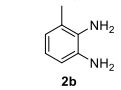
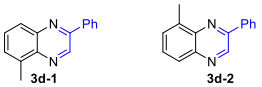
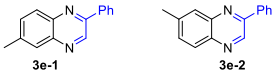
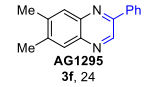
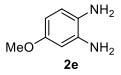
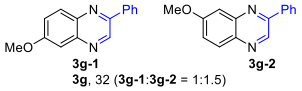
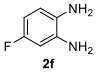
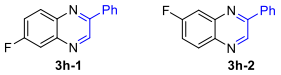
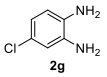
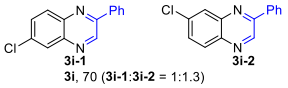
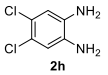
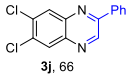
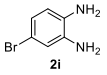
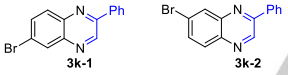
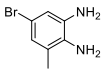
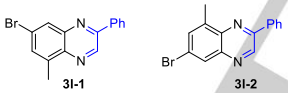
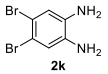
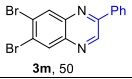
[a] Reaction conditions: 1 (0.3 mmol), 2a (0.1 mmol), KOH (5 equiv), PhCl/*t*-AmOH (v/v = 1:1, 1 mL), 120 °C, 24 h, under Air. After the reaction, hydrochloric acid (1 M) was used to acidify the solution to pH = ca. 5. [b] Yields were isolated yields. [c] 48 h. [d] *t*-AmOH (1 mL) was solvent.

the reaction performance, which does not have a clear straightforward trend. Diaminobenzenes **2** with electron-donating substituents, such as methyl and methoxy groups gave quinoxaline derivatives in yields of 24%-65% (Table 3, entries 2-5). In comparison, when diaminobenzenes containing electron-withdrawing groups (4-F, 4-Cl, 4,5-Cl, 4-Br, 5-Br-3-Me and 4,5-Br) were chosen as substrates, they reacted with **1a** and delivered the targeted products **3h**, **3i**, **3j**, **3k**, **3l** and **3m** in relatively higher

Table 3. The scope of 1,2-diaminobenzenes for the synthesis of quinoxaline derivatives [a]



1a 2 3 4a

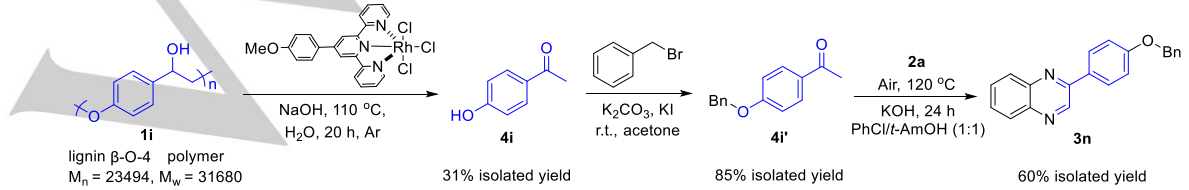
Entry[a]	2	Yield[b] (%)	
1			**4a**, 60
	2a	**3a**, 72	
2			**4a**, 41
	2b	**3d-1** **3d-2**	
		3d, 65 (**3d-1**:**3d-2** = 1:4.7)	
3			**4a**, 42
	2c	**3e-1** **3e-2**	
		3e, 30 (**3e-1**/**3e-2** could not be isolated)	
4			**4a**, 38
	2d	**AG1295**	
		3f, 24	
5			**4a**, 40
	2e	**3g-1** **3g-2**	
		3g, 32 (**3g-1**:**3g-2** = 1:1.5)	
6			**4a**, 37
	2f	**3h-1** **3h-2**	
		3h, 30[c], (**3h-1**:**3h-2** = 1:1.5)	
7			**4a**, 41
	2g	**3i-1** **3i-2**	
		3i, 70 (**3i-1**:**3i-2** = 1:1.3)	
8			**4a**, 32
	2h	**3j**, 66	
9			**4a**, 35
	2i	**3k-1** **3k-2**	
		3k, 70 (**3k-1**:**3k-2** = 1.5:1)	
10			**4a**, 34
	2j	**3l-1** **3l-2**	
		3l, 71 (**3l-1** /**3l-2** could not be isolated)	
11			**4a**, 32
	2k	**3m**, 50	

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.1 mmol), KOH (5 equiv), PhCl/*t*-AmOH (v/v = 1:1, 1 mL), 120 °C, 24 h, under Air. After the reaction, hydrochloric acid (1 M) was used to acidify the solution to pH = ca. 5. [b] Yields were isolated yields. [c] *t*-AmOH (1 mL).

yields (Table 3, entries 6-11). It is particularly noteworthy that when unsymmetrical 1,2-diaminobenzenes were employed, two regio-isomer products were observed (Table 3, entries 2-3, 5-7, 9-10). As the two pairs of regio-isomer products **3e-1/3e-2** and **3l-1/3l-2**, generated from 4-methyl-1,2-benzenediamine and 5-bromo-3-methyl-1,2-benzenediamine, have very similar physiochemical properties, the separation of **3e-1/3e-2** or **3l-1/3l-2** is challenging (Table 3, entries 3 and 10). Thus, only overall yields of **3e** and **3l** were given. Taken together, the above results demonstrated that diaminobenzenes containing both electron-donating and electron-withdrawing substituents proceeded well to afford quinoxaline derivatives in this protocol. It is interesting to note that some of these products can be directly used as valuable pharmaceutic molecules. For instance, AG1295[31] (**3f**), an excellent inhibitor of platelet-derived growth factor receptor tyrosine kinase, can be synthesized by this protocol straightforwardly (Table 3, entry 4). To the best of our knowledge, quinoxaline derivatives are also reported as privileged structures to impart in drugs, agrochemicals and other bioactive compounds.[14] These promising results demonstrate the application potential of the transformation in pharmaceutical synthesis.

Furthermore, a lignin β-O-4 polymer **1i** (M_n = 23494, M_w = 31680) was prepared to mimic the structure of lignin and was then used as a substrate in the reaction. The polymer could not be directly transformed into quinoxaline product, as the cleavage of **1i** could not occur in the presence of KOH alone. Notwithstanding, an alternative process for the transformation of **1i** was developed. As illustrated in Scheme 2, in a first step, β-O-4 polymer **1i** was converted into monomer **4i** with 31% yield by a Rh-terpyridine complex in water solvent at 110 °C according to our previous developed method.[32] Subsequently, **4i** reacted with benzyl bromide in acetone in the presence of K_2CO_3/KI at room temperature to obtain 85% yield of **4i'**. Finally, **4i'** reacted well with **2a** by this protocol and delivered the targeted product **3n** in 60% yield based on 1,2-diaminobenzene. The above results successfully converted lignin β-O-4 polymer into quinoxaline derivative **3n**, demonstrating the application possibility of this protocol for the synthesis of *N*-containing aromatic heterocyclic compounds from renewable biomass feedstock (Scheme 2).

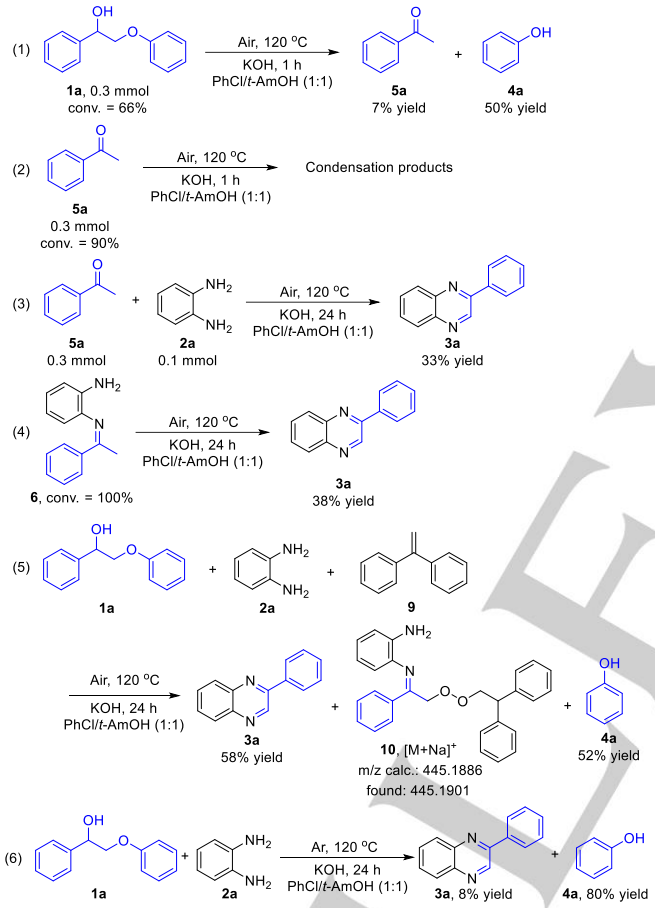
To gain insight into the pathway and mechanism of this new transformation, several control experiments were conducted. When lignin β-O-4 model compound **1a** was chosen as a sole substrate, 7% of acetophenone **5a** and 50% of phenol **4a** were obtained under the standard conditions in 1 h (Scheme 3, equation 1), indicating that the KOH-promoted C-O bond cleavage of **1a** might be the first step of the reaction. The much lower yield of **5a** than **4a** is probably attributed to side reactions of **5a** (such as aldol condensation) in the presence of KOH. The following experiment gave an evidence. When **5a** was used as a sole substrate under the reaction conditions, the conversion of **5a** reached 90%, and many products were found according to thin layer chromatography analysis. However, GC-MS showed no clearly detectable product, indicating that **5a** could have converted to high boiling-point products such as polymers via side condensation reactions under base conditions (Scheme 3, equation 2). In another comparative experiment, **5a** reacted with 1,2-diaminobenzene **2a** and provided **3a** in a yield of 33% in 24 h under the same conditions (Scheme 3, equation 3). Hence, it is assumed that KOH facilitates the cleavage of β-O-4 model compounds to release **5a** as an intermediate for subsequent reactions. We therefore proposed that the dehydrative condensation between **5a** and **2a** would occur to generate



1i lignin β-O-4 polymer M_n = 23494, M_w = 31680 → **4i** 31% isolated yield → **4i'** 85% isolated yield → **3n** 60% isolated yield

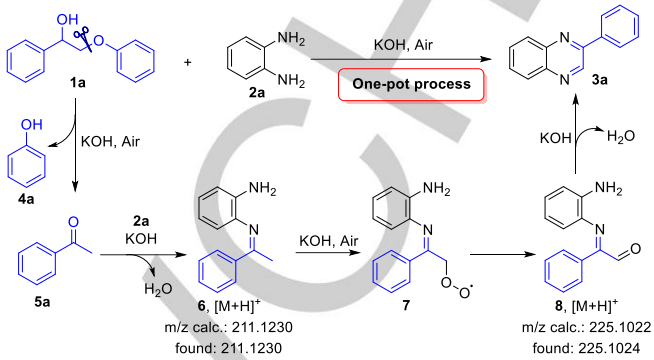
Scheme 2. Conversion of lignin β-O-4 polymer to quinoxaline derivative **3n**.

ketimine **6** (Scheme 4) as another key intermediate. The following experiment confirmed this assumption: when **6** was chosen as substrate under the standard conditions, it gave **3a** in 38% yield (Scheme 3, equation 4). Moreover, when a radical trapping experiment by using 1,1-diphenylethylene (**9**) as a radical scavenger was conducted, the yield of the desired product **3a** (Figure S1) decreased from 76% to 58% and the radical trapped product of **10** (Figure S2, section 5.3 in Supporting Information for detail) could be detected by HPLC-HRMS (Table 1, entry 16 vs Scheme 3, equation 5), suggesting that this process may undergo a radical pathway. When replacing air with Ar, the yield of the targeted product **3a** dropped sharply from 76% to 8% during the transformation, indicating that O_2 in air plays an important role (Table 1, entry 16 vs Scheme 3, equation 6) in the transformation, which will be further discussed based on Scheme 4.



Scheme 3. Control experiments to explore the mechanism.

On the basis of the above-described findings, a plausible reaction mechanism was proposed in Scheme 4. First, the C-O bond of the lignin β-O-4 model compound **1a** is cleaved by KOH to release phenol **4a** and the intermediate acetophenone **5a**. Then, **5a** and 1,2-diaminobenzene **2a** undergo a dehydrative condensation reaction to yield ketimine intermediate **6** (confirmed by HPLC-HRMS, see section 6 in Supporting Information for detail), which could be further oxidized to intermediate **8** (confirmed by HPLC-HRMS, see section 6 in Supporting Information for detail) via superoxide radical intermediate **7** in the presence of KOH under air[33]. The intermediate **7** is generated from **6** via sp^3 C-H bond oxidative activation with O_2, whilst the decomposition of **7** produces **8** and hydroxyl radical.[34] According to the literature, the role of KOH is to involve deprotonation at methyl group of intermediate **6** in this process.[33a, 33d, 35] The as-formed hydroxyl radical can react with **6** to get superoxide intermediate **7** to realize the radical chain growth under air.[33a] Finally, intramolecular condensation of **8** followed by additional dehydration reaction gives **3a** as the targeted product.



Scheme 4. Proposed mechanism for the direct transformation of lignin β-O-4 model compound to quinoxaline.

Conclusion

In conclusion, we have shown that quinoxaline derivatives could be synthesized in a one-pot fashion by the reaction of lignin β-O-4 model compounds with 1,2-diaminobenzenes in the presence of KOH under transition-metal-free conditions. The developed method shows versatility in production of various quinoxaline derivatives by varying β-O-4 model compounds and the substituted 1, 2-diaminobenzenes. The feasibility for the production of quinoxaline derivatives from lignin-related polymer has also been demonstrated. In this complicated cascade process, including cleavage of C-O bonds, dehydration condensation, sp^3 C-H bond oxidative activation and intramolecular dehydrative coupling reaction, KOH plays a crucial role and O_2 in air serves as the environmentally benign oxidant. Remarkably, the protocol can be successfully applied to access drug compounds such as AG1295. The methodology described here make it possible to build a bridge between renewable lignin and heterocyclic aromatic compounds, thus providing a petroleum-independent choice for fine chemicals and value-added pharmaceutical molecules.

Experimental Section

Procedure for KOH mediated conversion of lignin β-O-4 model compounds to quinoxaline derivatives

1a (0.3 mmol), **2a** (0.1 mmol), KOH (0.5 mmol), PhCl/*t*-AmOH (v/v = 1:1, 1 mL) were placed into a 35 mL pressure tube, then the tube was sealed under an atmosphere of air. The mixture was stirred and heated at 120 °C for 24 h. After cooling to room temperature, hydrochloric acid (1 M) was used to acidify the solution to pH = ca. 5. and biphenyl (0.1 mmol) was added to the crude products. Then, the mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, analyzed by gas chromatography to give the GC yields. Alternatively, the crude products were purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate to get the desired products.

Acknowledgements

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Keywords: lignin • *N*-heterocyclic compounds • β-O-4 model compounds • quinoxaline • transition-metal-free

[1] a) I. Delidovich, P. J. C. Hausoul, L. Deng, R. Pfützenreuter, M. Rose, R. Palkovits, *Chemical Reviews* **2016**, *116*, 1540-1599; b) P. Gallezot, *Chemical Society Reviews* **2012**, *41*, 1538-1558; c) G. W. Huber, S. Iborra, A. Corma, *Chemical Reviews* **2006**, *106*, 4044-4098; d) C. Li, X. Zhao, A. Wang, G. W. Huber, T. Zhang, *Chemical Reviews* **2015**, *115*, 11559-11624; e) J. A. Melero, J. Iglesias, A. Garcia, *Energy & Environmental Science* **2012**, *5*, 7393-7420; f) C. O. Tuck, E. Pérez, I. T. Horváth, R. A. Sheldon, M. Poliakoff, *Science* **2012**, *337*, 695-699; g) J. Zakzeski, P. C. A. Bruijnincx, A. L. Jongerius, B. M. Weckhuysen, *Chemical Reviews* **2010**, *110*, 3552-3599; h) Z. Zhang, J. Song, B. Han, *Chemical Reviews* **2017**, *117*, 6834-6880; i) X. Liu, G. Lan, Z. Li, L. Qian, J. Liu, Y. Li, *Chinese Journal of Catalysis* **2021**, *42*, 694-709.

[2] C. Yang, H. Chen, T. Peng, B. Liang, Y. Zhang, W. Zhao, *Chinese Journal of Catalysis* **2021**, *42*, 1831-1842.

[3] Z. Jiang and C. Hu, *Journal of Energy Chemistry* **2016**, *25*, 947-956.

[4] a) Y. Shao, Q. Xia, L. Dong, X. Liu, X. Han, S. F. Parker, Y. Cheng, L. L. Daemen, A. J. Ramirez-Cuesta, S. Yang, Y. Wang, *Nature Communications* **2017**, *8*, 16104; b) K. Wu, W. Wang, H. Guo, Y. Yang, Y. Huang, W. Li, C. Li, *ACS Energy Letters* **2020**, *5*, 1330-1336; c) X. Wang, R. Rinaldi, *Angewandte Chemie International Edition* **2013**, *52*, 11499-11503; d) J. Zhang, J. Sun, Y. Wang, *Green Chemistry* **2020**, *22*, 1072-1098.

[5] a) S. Gundekari, S. Kumar Karmee, *ChemistrySelect* **2021**, *6*, 1715-1733; b) K. Wu, X. Li, W. Wang, Y. Huang, Q. Jiang, W. Li, Y. Chen, Y. Yang, C. Li, *ACS Catalysis* **2022**, *12*, 8-17.

[6] a) H. Li, A. Bunrit, N. Li, F. Wang, *Chemical Society Reviews* **2020**, *49*, 3748-3763; b) M. J. Hülsey, H. Yang, N. Yan, *ACS Sustainable Chemistry & Engineering* **2018**, *6*, 5694-5707; c) M. Pelckmans, T. Renders, S. Van de Vyver, B. F. Sels, *Green Chemistry* **2017**, *19*, 5303-5331; d) Y. Rong, N. Ji, Z. Yu, X. Diao, H. Li, Y. Lei, X. Lu, A. Fukuoka, *Green Chemistry* **2021**, *23*, 6761-6788.

[7] B. Eftekhari-Sis, M. Zirak, *Chemical Reviews* **2015**, *115*, 151-264.

[8] a) H. Li, A. Bunrit, J. Lu, Z. Gao, N. Luo, H. Liu, F. Wang, *ACS Catalysis* **2019**, *9*, 8843-8851; b) N. E. S. Tay, D. A. Nicewicz, *Journal of the American Chemical Society* **2017**, *139*, 16100-16104; c) B. Zheng, J. Song, H. Wu, S. Han, J. Zhai, K. Zhang, W. Wu, C. Xu, M. He, B. Han, *Green Chemistry* **2021**, *23*, 268-273; d) J. Liu, X. Qiu, X. Huang, X. Luo, C. Zhang, J. Wei, J. Pan, Y. Liang, Y. Zhu, Q. Qin, S. Song, N. Jiao, *Nature Chemistry* **2019**, *11*, 71-77; e) X. Liu, H. Zhang, C. Wu, Z. Liu, Y. Chen, B. Yu, Z. Liu, *New Journal of Chemistry* **2018**, *42*, 1223-1227.

[9] a) Z. Qiu, J.-S. Li, C.-J. Li, *Chemical Science* **2017**, *8*, 6954-6958; b) Z. Qiu, L. Lv, J. Li, C.-C. Li, C.-J. Li, *Chemical Science* **2019**, *10*, 4775-4781; c) S. Elangovan, A. Afanasenko, J. Haupenthal, Z. Sun, Y. Liu, A. K. H. Hirsch, K. Barta, *ACS Central Science* **2019**, *5*, 1707-1716; d) B. Zheng, H. Wu, J. Song, W. Wu, X. Mei, K. Zhang, C. Xu, J. Xu, M. He, B. Han, *Green Chemistry* **2021**, *23*, 8441-8447.

[10] a) J. Zhang, Y. Liu, S. Chiba, T.-P. Loh, *Chemical Communications* **2013**, *49*, 11439-11441; b) T. Guo, T. Liu, J. He, Y. Zhang, *European Journal of Organic Chemistry* **2022**, e202101152; c) H. Li, M. Wang, H. Liu, N. Luo, J. Lu, C. Zhang, F. Wang, *ACS Sustainable Chemistry & Engineering* **2018**, *6*, 3748-3753; d) Y. Wang, Y. Du, J. He, Y. Zhang, *Green Chemistry* **2018**, *20*, 3318-3326.

[11] Y. Wang, J. He, Y. Zhang, *CCS Chemistry* **2020**, *2*, 107-117.

[12] B. Zhang, T. Guo, Y. Liu, F. E. Kühn, C. Wang, Z. K. Zhao, J. Xiao, C. Li, T. Zhang, *Angewandte Chemie International Edition* **2021**, *60*, 20666-20671.

[13] B. Zhang, T. Guo, Z. Li, F. E. Kühn, M. Lei, Z. K. Zhao, J. Xiao, J. Zhang, D. Xu, T. Zhang, C. Li, *Nature Communications* **2022**, *13*, 3365.

[14] a) M. Montana, F. Mathias, T. Terme, P. Vanelle, *European Journal of Medicinal Chemistry* **2019**, *163*, 136-147; b) J. A. Pereira, A. M. Pessoa, M. N. D. S. Cordeiro, R. Fernandes, C. Prudêncio, J. P. Noronha, M. Vieira, *European Journal of Medicinal Chemistry* **2015**, *97*, 664-672; c) S. Tariq, K. Somakala, M. Amir, *European Journal of Medicinal Chemistry* **2018**, *143*, 542-557.

[15] S. Bhargava, P. Soni, D. Rathore, *Journal of Molecular Structure* **2019**, *1198*, 126758.

[16] A. K. Bains, V. Singh, D. Adhikari, *The Journal of Organic Chemistry* **2020**, *85*, 14971-14979.

[17] Y.-B. Wang, L. Shi, X. Zhang, L.-R. Fu, W. Hu, W. Zhang, X. Zhu, X.-Q. Hao, M.-P. Song, *The Journal of Organic Chemistry* **2021**, *86*, 947-958.

[18] K. B. Harsha, K. S. Rangappa, *RSC Advances* **2016**, *6*, 57154-57162.

[19] M. Lian, Q. Li, Y. Zhu, G. Yin, A. Wu, *Tetrahedron* **2012**, *68*, 9598-9605.

[20] M. M. Ibrahim, D. Grau, F. Hampel, S. B. Tsogoeva, *European Journal of Organic Chemistry* **2014**, *2014*, 1401-1405.

[21] D. Aparicio, O. A. Attanasi, P. Filippone, R. Ignacio, S. Lillini, F. Mantellini, F. Palacios, J. M. de los Santos, *The Journal of Organic Chemistry* **2006**, *71*, 5897-5905.

[22] K. Gopalaiah, A. Saini, S. N. Chandrudu, D. C. Rao, H. Yadav, B. Kumar, *Organic & Biomolecular Chemistry* **2017**, *15*, 2259-2268.

[23] S. Okumura, Y. Takeda, K. Kiyokawa, S. Minakata, *Chemical Communications* **2013**, *49*, 9266-9268.

[24] S. Shee, D. Panja, S. Kundu, *The Journal of Organic Chemistry* **2020**, *85*, 2775-2784.

[25] W. Lv, B. Xiong, Z. Tan, H. Jiang, M. Zhang, *Asian Journal of Organic Chemistry* **2015**, *4*, 1127-1131.

[26] M. J. Climent, A. Corma, J. C. Hernández, A. B. Hungría, S. Iborra, S. Martínez-Silvestre, *Journal of Catalysis* **2012**, *292*, 118-129.

[27] A. Mondal, M. K. Sahoo, M. Subaramanian, E. Balaraman, *The Journal of Organic Chemistry* **2020**, *85*, 7181-7191.

[28] T. B. Nguyen, P. Retailleau, A. Al-Mourabit, *Organic Letters* **2013**, *15*, 5238-5241.

[29] a) A. Rahimi, A. Azarpira, H. Kim, J. Ralph, S. S. Stahl, *Journal of the American Chemical Society* **2013**, *135*, 6415-6418; b) C. S. Lancefield, O. S. Ojo, F. Tran, N. J. Westwood, *Angewandte Chemie International Edition* **2015**, *54*, 258-262.

[30] a) T. Guo, Z. Su, Q. Wang, W. Hou, J. Li, L. Zhang, J. Zhang, *Future Medicinal Chemistry* **2019**, *11*, 2081-2094; b) J. P. Kim, S. M. Burkinshaw, *Journal of Applied Polymer Science* **1993**, *49*, 1647-1652.

[31] a) S. Banai, Y. Wolf, G. Golomb, A. Pearle, J. Waltenberger, I. Fishbein, A. Schneider, A. Gazit, L. Perez, R. Huber, G. Lazarovichi, L. Rabinovich, A. Levitzki, S. D. Gertz, *Circulation* **1998**, *97*, 1960-1969; b) M. Chorny, I. Fishbein, H. D. Danenberg, G. Golomb, *Journal of Controlled Release* **2002**, *83*, 401-414.

[32] Y. Liu, C. Li, W. Miao, W. Tang, D. Xue, J. Xiao, T. Zhang, C. Wang, *Green Chemistry* **2020**, *22*, 33-38.

[33] a) C. Zhang, Z. Xu, L. Zhang, N. Jiao, *Tetrahedron* **2012**, *68*, 5258-5262; b) N. Hideshi, G. Toshio, *Bulletin of the Chemical Society of Japan* **1988**, *61*, 3776-3778; c) N. A.

Milas, *Chemical Reviews* **1932**, *10*, 295-364; d) B. Song, S. Wang, C. Sun, H. Deng, B. Xu, *Tetrahedron Letters* **2007**, *48*, 8982-8986.

[34] a) K. G. Konya, T. Paul, S. Lin, J. Lusztyk, K. U. Ingold, *Journal of the American Chemical Society* **2000**, *122*, 7518-7527; b) F. Recupero, C. Punta, *Chemical Reviews* **2007**, *107*, 3800-3842; c) J. A. Shelnutt, D. E. Trudell, *Tetrahedron Letters* **1989**, *30*, 5231-5234; d) Y. Su, L. Zhang, N. Jiao, *Organic Letters* **2011**, *13*, 2168-2171.

[35] a) K. K. Park, L. K. Tsou, A. D. Hamilton, *Synthesis* **2006**, *2006*, 3617-3620; b) C. Zhang, Z. Xu, L. Zhang, N. Jiao, *Angewandte Chemie International Edition* **2011**, *50*, 11088-11092.

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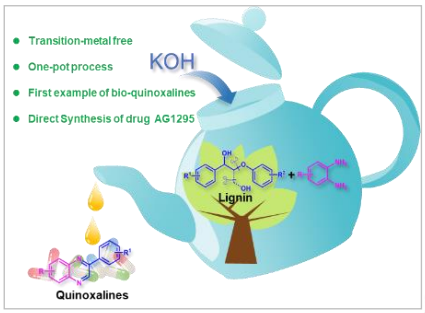

A sustainable and effecient protocol for the one-pot synthesis of quinoxaline derivatives from lignin β-O-4 models and polymer in the presence of organic N-sources and KOH is presented.