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VIP Atropisomerism Very Important Paper

Copper-Catalyzed Enantioselective Skeletal Editing through a Formal Nitrogen Insertion into Indoles to Synthesize Atropisomeric Aminoaryl Quinoxalines

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Dedicated to the memory of professor Li-Xin Dai for his 100th birthday from Shanghai Institute of Organic Chemistry.

Abstract: Skeletal editing represents an attractive strategy for adding complexity to a given molecular scaffold in chemical synthesis. Isodesmic reactions provide a complementary skeletal editing approach for the redistribution of chemical bonds in chemical synthesis. However, catalytic enantioselective isodesmic reaction is extremely scarce and enantioselective isodesmic reaction to synthesize atropisomeric compounds is unknown. Herein, we report a facile method to synthesize axially chiral aminoaryl quinoxalines through Cu(I)-catalyzed dearomatization and sequential chiral phosphoric acid (CPA) catalyzed enantioselective isodesmic C–N bond formation and cleavage from indoles and 1,2-diaminoarenes under mild reaction conditions. In this process, the five-membered ring of the indole scaffold was broken and a novel quinoxaline skeleton was constructed. This method allows the practical and atom-economical synthesis of valuable axially chiral aminoaryl quinoxalines in high yields (up to 95 %) and generally excellent enantioselectivities (up to 99 % ee). Notably, this novel type of quinoxaline atropisomers has promising applications in developing axially chiral ligand in asymmetric catalysis. This strategy represents the first example of CPA-catalyzed enantioselective isodesmic reaction to form axially chiral compounds.

Introduction

The rapid construction of molecular complexity has been a primary goal of chemical synthesis owing to the broad applications of this concept in drug discovery research.[1] In this regard, skeletal editing represents an attractive strategy for adding complexity to a given molecular scaffold because of its advantage of reaction efficiency compared with laborious de novo synthetic routes.[2] Over the past few decades, great efforts have been devoted to the development of methods for the skeletal editing to construct cyclic molecules, such as a single atom insertion,[3] deletion,[4] or transmutation.[5] Nitrogen-insertion strategy to incorporate one or more *N*-atoms into simple substrates is a green and sustainable way to prepare nitrogen-containing heterocyclic compounds.[6] Therefore, developing new methods for the skeletal editing through nitrogen-insertion to access diverse *N*-containing heterocycles is still desirable.

Isodesmic reactions, in which the type of chemical bonds broken in the reactant are the same as the type of bonds formed in the reaction product, are of high importance in the fields of chemical synthesis, materials science and chemical biology, and provide an efficient skeletal editing approach to access numerous inaccessible valuable complex molecules.[7] Classical isodesmic reactions including the industrial disproportionation of toluene to benzene and xylenes and the synthesis of amino acids through transamination in organisms.[8,9] Recently, isodesmic reactions have emerged as powerful tools for the modifications of molecules that are difficult to be obtained through tradi-

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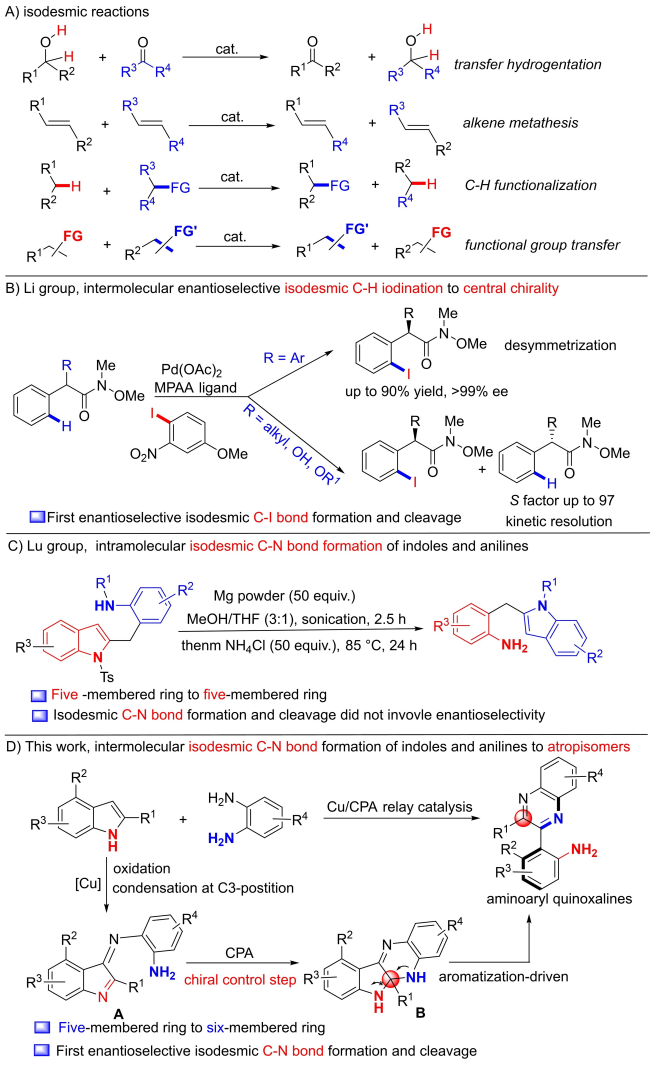
tional methods and new isodesmic transformations have been well developed including transfer hydrogenation,[10] olefin/alkyne methathesis,[11] C–H bond functionalization,[12] and functional group transfer reactions (Scheme 1-A).[13] The construction of chiral compounds has always been one of the most challenging topics in organic synthesis, and it is of great significance to use the isodesmic reaction strategy to realize the construction of chiral compounds. Although remarkable advances have been made for the isodesmic reactions, catalytic enantioselective isodesmic reactions are extremely scarce up to date. In organisms, some transaminase-catalyzed transamination reactions were efficient to synthesize chiral amino acids but the chirality-determining step did not involve isodesmic transformations.[14] The only catalytic enantioselective example of isodesmic reaction for C–I bond formation was reported by Li group in 2023 and they pioneered to develop an unprecedented highly enantioselective isodesmic C–H iodination of phenylacetic Weinreb amides by palladium-catalyzed desymmetrization or kinetic resolution (Scheme 1-B).[15] This method provided an efficiently enantioselective isodesmic reaction to construct central chirality. Consequently, the development of new catalytic enantioselective isodesmic reactions remains a great challenge and is still highly desirable in organic synthesis.



Scheme 1. Enantioselective isodesmic reactions toward the synthesis of chiral compounds.

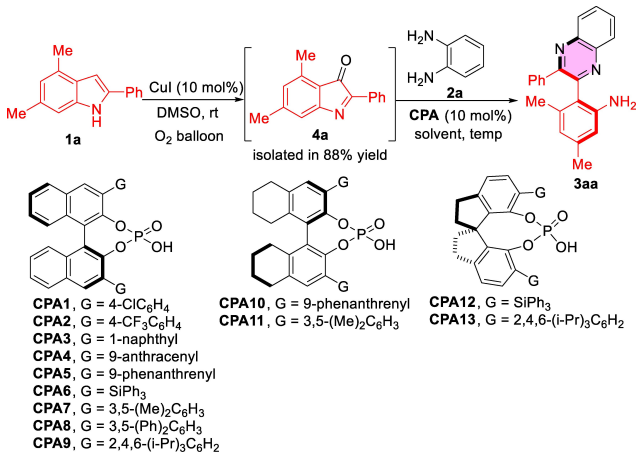
Atropisomerism is a dynamic type of axial chirality that is ubiquitous in medicinal chemistry and there are several examples of stable atropisomeric US FDA-approved drugs and experimental compounds, and in each case the atropisomers of these compounds possess drastically different biological activities.[16] Among the atropisomers, axially chiral biaryl compounds not only frequently exist in numerous natural products and biologically active molecules, but also constitute the core structures of many privileged chiral catalysts.[17] Within the broad family of axially chiral biaryl molecules, heterobiaryl atropisomers and their preparations have also received much attention from the chemistry community.[18] Many elegant methods by asymmetric catalysis toward the construction of axially chiral compounds have been well developed.[19] However, the construction of biaryl atropisomers through isodesmic reaction is still unknown. In 2024, Lu and co-workers developed an unprecedented isodesmic reaction of indoles and anilines for the facile synthesis of biologically significant new fused indole scaffolds in good yields through a hyperconjugation driving force (Scheme 1-C).[20] This method involved isodesmic C–N bond formation and cleavage but it did not involve enantioselective isodesmic reaction. Based on the isodesmic C–N bond formation and cleavage, we supposed that intermediate **A** could be easily obtained from 4-substituted indoles by oxidation and condensation with 1,2-diaminoarenes,[21] and sequential enantioselective intramolecular cyclization would give chiral intermediate **B** in the presence of chiral phosphoric acid (CPA). The key isodesmic C–N bond formation might be controlled by CPA catalyst through hydrogen bonding interaction. Aromatization of quinoxaline-driven C–N bond cleavage will provide atropisomeric aminoaryl quinoxaline scaffolds (Scheme 1-D). However, the intramolecular enantioselective C–N bond formation at the C2-position of indoles to form central chirality and aromatization-driven enantioselective C–N cleavage from central chirality to axial chirality transfer are still challenging for this type of isodesmic reaction.[22,23] On the other hand, quinoxalines, as one of the most important nitrogen heterocyclic scaffolds and privileged structures, play important roles in pharmaceuticals and medicinal chemistry due to its good biological activity.[24] Herein, we report a facile skeletal editing of indole with 1,2-diaminoarenes through copper-catalyzed oxidation and CPA-catalyzed enantioselective isodesmic C–N bond formation and cleavage to prepare novel axially chiral aminoaryl quinoxaline scaffolds under mild reaction conditions.

Results and Discussion

The 3-oxoindolenine **4a** was isolated in 88 % yield from indole **1a** in the presence of CuI and O_2 after purification by column chromatography. Then, our investigations started

with indole **1a** and 1,2-diaminoarene **2a** directly. The operational procedure was as follows: treating **1a** in the presence of Cu(I) and O_2 balloon in DMSO at room temperature for 12 h, then removal of DMSO, adding **CPA**, **2a**, solvent, and stirred at room temperature to afford aminoaryl quinoxaline product **3aa** (see Table S1–S3 for more optimization details in Supporting Information). The **CPA** catalysts screening trials revealed that **CPA4** gave better result than other **CPA1-CPA3** and **CPA5-CPA13** catalysts. It was shown that the reaction of **1a** and **2a** under the copper(I)/**CPA4** relay catalysis conditions afforded **3aa** in 67 % yield and 39 % ee (Table 1, entry 1). Molecular sieves (MS) studies showed that 5 Å MS gave product **3aa** in 66 % yield and 69 % ee (Table 1, entries 2–4). Solvent screening trials indicated that product **3aa** was obtained in good yields and good ee value in DCM and THF while lower ee value was obtained in Et_2O and hexafluoroisopropanol (HFIP) (Table 1, entries 5–8). Lowering the reaction temperature to 0 °C delivered **3aa** in 61 % yield and 91 % ee (Table 1, entry 9). Interestingly, the addition of $MgSO_4$ as an additive improved the yield and ee value of **3aa** (75 % yield, 96 % ee) and Na_2SO_4 gave **3aa** in 65 % yield and 86 % ee value (Table 1, entries 10–11). Product **3aa** cannot be observed in the absence of **CPA4** (Table 1, entry 12).

Table 1: Optimization of the Reaction Conditions.[a,b]

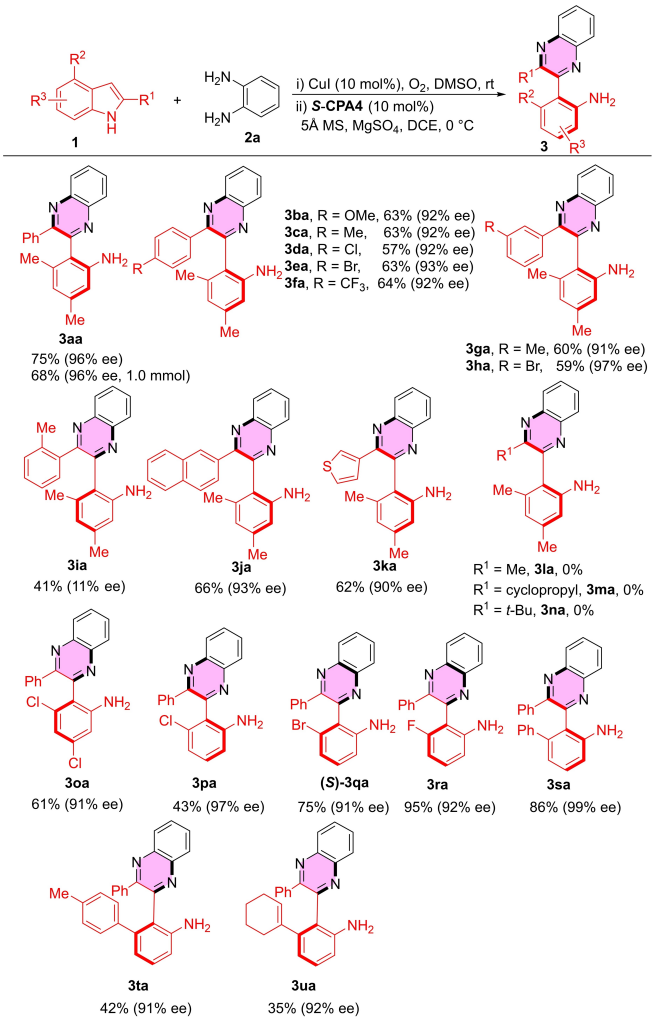


entry	**CPA**, solvent, temp	**3aa**, yield %	ee %
1	**CPA4**, DCE, rt, 48 h	67	39
2	**CPA4**, DCE, 3 Å MS, rt, 48 h	74	47
3	**CPA4**, DCE, 4 Å MS, rt, 48 h	68	52
4	**CPA4**, DCE, 5 Å MS, rt, 48 h	66	69
5	**CPA4**, DCM, 5 Å MS, rt, 120 h	58	33
6	**CPA4**, Et_2O, 5 Å MS, rt, 76 h	85	15
7	**CPA4**, THF, 5 Å MS, rt, 120 h	67	45
8	**CPA4** HFIP, 5 Å MS, rt, 48 h	41	0
9	**CPA4**, DCE, 5 Å MS, 0 °C, 72 h	61	91
10	**CPA4**, DCE, 5 Å MS, 0 °C, 84 h	75	96[c]
11	**CPA4**, DCE, 5 Å MS, 0 °C, 84 h	65	86[d]
12	No **CPA4**, DCE, 5 Å MS, 0 °C, 84 h	–	–

[a] Reaction conditions: i) **1a** (0.2 mmol), CuI (10 mol %), DMSO (2 mL), O_2 balloon for 12 h; ii) removal of DMSO, adding **2a** (0.4 mmol, 2.0 equiv), **CPA** (10 mol %), solvent (2 mL), MS (100 mg); [b] isolated yield, ee value was determined by HPLC; [c] $MgSO_4$ (100 mg); [d] Na_2SO_4 (100 mg).

Therefore, the optimal conditions for the preparation of aminoaryl quinoxaline **3aa** were indole **1a** and 10 mol % of CuI in DMSO in the presence of O_2 balloon at room temperature for 12 h; then, removal of DMSO, adding **CPA4** (10 mol %), 1,2-aminoarene **2a**, 5 Å MS, and $MgSO_4$ in DCE at 0 °C for 84 h.

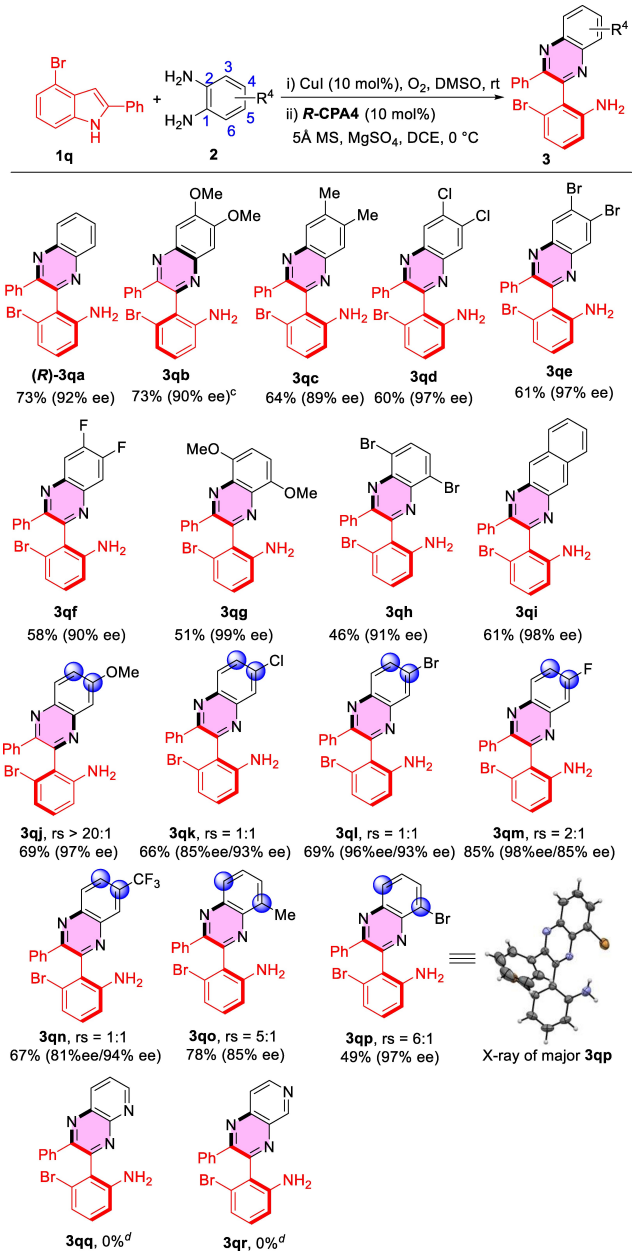
With the optimized reaction conditions in hand, the substrate scope of the cascade reaction was then evaluated. As shown in Scheme 2, the reaction of substituted indoles **1** with 1,2-diaminoarene **2a** catalyzed by *S*-**CPA4** proceeded smoothly to afford the corresponding aminoaryl quinoxalines under the standard operational procedure. To our delight, aminoaryl quinoxaline **3aa** was also obtained in 68 % yield and 96 % ee on a 1.0 mmol scale of indole **1a**. Various 2-aryl substituted indoles **1b**–**1h** bearing electron-donating groups and electron-withdrawing groups at the *para*- and *meta*-positions were well compatible, leading to the formation of the corresponding aminoaryl quinoxalines



Scheme 2. Substrate scope of indoles **1** to prepare axially chiral aminoaryl quinoxalines **3** ([a] Reaction conditions: i) **1** (0.2 mmol), CuI (10 mol %), DMSO (2 mL), in O_2 balloon, rt, 12 h; ii) then, removal of DMSO, adding **2a** (0.4 mmol, 2.0 equiv.), *S*-**CPA4** (10 mol %), 5 Å MS (100 mg), $MgSO_4$ (100 mg), DCE (2.0 mL), 0 °C, 48–96 h; [b] isolated yield, ee value was determined by HPLC).

3ba–**3ha** in 57 %–64 % yields and 91 %–97 % ee value, except for 2-methylphenyl substituted indole **1i** gave the desired product **3ia** in 41 % yield and only 11 % ee perhaps owing to the steric hindrance of *ortho*-substituent. In addition, the desired naphthyl-substituted aminoaryl quinoxaline **3ja** was obtained in 66 % yield and 93 % ee under the standard reaction conditions. To our delight, indole **1k** with a 3-thienyl at the R^1 also tolerated to give the desired product **3ka** in 62 % yield and 90 % ee. Surprisingly, when the R^1 of indole was present with alkyl groups such as methyl (**1l**), cyclopropyl (**1m**), or *tert*-butyl (**1n**), the reaction turned messy and unpurifiable mixture or did not work in this process to afford the corresponding products, presumably due to the poor structural stability of the 3-oxoindolenine intermediate. Besides the 2-aryl substituted indoles, the substituents (R^2 and R^3) at the aryl ring of indole were also studied. It was found that the R^2 group at the 4-position of indole bearing various substituents such as Cl (**1o** and **1p**), Br (**1q**), F (**1r**), Ph (**1s**), *p*-tolyl (**1t**), and cyclohexenyl (**1u**) had a great effect on the reaction yields but little effect on the enantioselectivity, furnishing the desired aminoaryl quinoxalines **3oa-3ua** in 35 %–95 % yields and 91 %–99 % ee. The absolute configuration of **3qa** was unambiguously assigned to be *(S)* by its X-ray diffraction analysis (Figure 1).[25] The good tolerance of various halides (Br, Cl) and alkenyl group (cyclohexenyl) will allow more applications by further transformations.

Next, the effect of substituents of 1,2-diaminoarenes **2** on the reaction efficiency was then studied by reacting with indole **1q**, as listed in Scheme 3. When *S*-**CPA4** was replaced by *R*-**CPA4** in the reaction, product *R*-**3qa** was obtained in 73 % yield and 92 % ee. Symmetrical disubstituted 1,2-diaminoarenes were tested. Symmetrical 4,5-disubstituted 1,2-diaminoarenes **2b-2f** bearing electron-donating groups and electron-withdrawing groups could proceed smoothly to afford the corresponding aminoaryl quinoxalines **3qb**–**3qf** in 58–73 % yields and 89 %–97 % ee. Symmetrical 3,6-disubstituted 1,2-diaminoarenes **2g** bearing -OMe and **2h** bearing -Br with steric hindrance on the aryl ring also smoothly delivered products **3qg** and **3qh** in 51 % yield with 99 % ee and 46 % yield with 91 % ee, respectively. In addition, 2,3-naphthalenediamine **1i** could give the desired product **3qi** in 61 % yield and 98 % ee. Then, the regioselectivity and enantioselectivity for unsymmetrical monosubstituted 1,2-diaminoarenes were also evaluated. Monosubstituted 1,2-diaminoarenes **2j**–**2n** at the 4-position of aryl ring bearing electron-donating groups and electron-withdrawing groups all gave the desired aminoaryl quinoxalines **3qj**–**3qn** in good yields (66 %–85 % yields) and excellent enantioselectivities (81 %–98 % ee). However, the substituents had a great effect on the regioselectivity. 1,2-Diaminoarene **2j** with OMe group gave a 20:1 regioselectivity and others gave regioselectivities of 1:1 or 2:1 ratio. The major product was confirmed by X-ray diffraction analysis of compound **3qn**.[25] Monosubstituted 1,2-diaminoarenes **2o** bearing Me at the 3-position gave the desired product **3qo**



Scheme 3. Substrate scope of 1,2-diaminoarenes **2** for the preparation of aminoaryl quinoxalines **3** ([a] Reaction conditions: i) **1q** (0.2 mmol), CuI (10 mol %), DMSO (2 mL), rt, in O_2 balloon, 12 h; ii) then, removal of DMSO, adding **2** (0.4 mmol, 2.0 equiv.), *R*-**CPA4** (10 mol %), 5 Å MS (100 mg), $MgSO_4$ (100 mg), DCE (2.0 mL), 0 °C, 48–96 h; [b] isolated yield, ee value was determined by HPLC, rs = regioselectivity of the aryl ring; [c] *S*-**CPA4** was used; [d] ran at 0 °C to 120 °C).

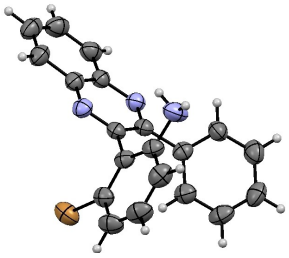
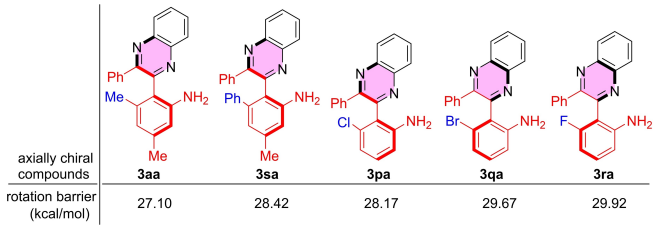


Figure 1. X-ray structure of compound **3qa**.

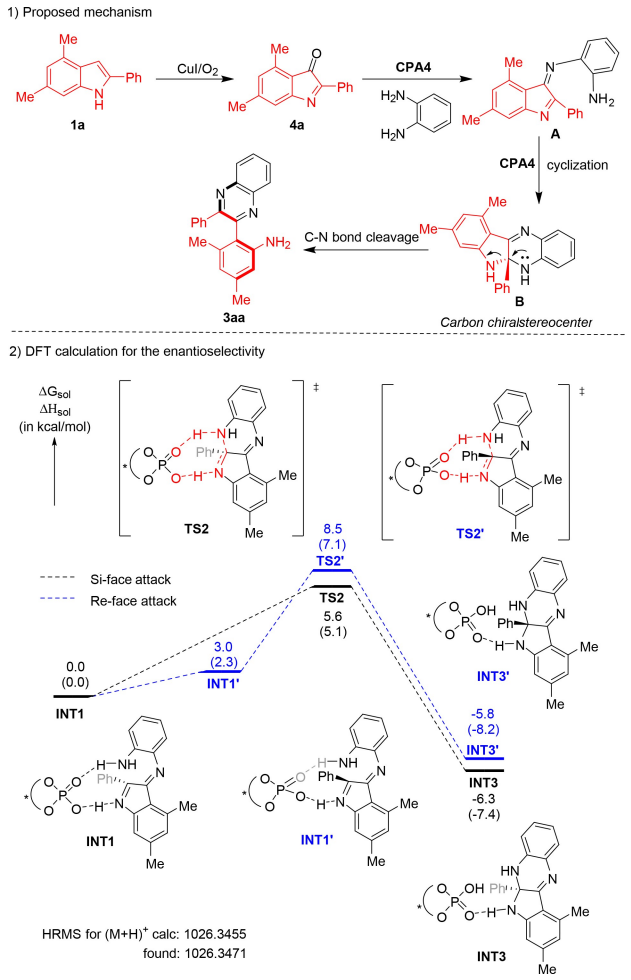
in 78% yield and 85% ee and afforded **3qo** in a regioselectivity of 5:1 ratio. Monosubstituted 1,2-diaminoarene **2p** bearing Br at the 3-position afforded the desired product **3qp** in 36% yield and 97% ee and gave **3qp** in a regioselectivity of 6:1 ratio. The structure of major product of monosubstituted aminoaryl quinoxalines was determined by X-ray diffraction analysis of compound **3qp**.[25] To our surprise, 1,2-diaminoheteroarenes such as 2,3-diaminopyridine (**2q**) and 3,4-diaminopyridine (**2r**) did not afford the desired products **3qq** and **3qr** under the standard conditions or even the reaction ran at 120 °C.

To have a better understanding on how the substituents of R^2 group in the aminoaryl quinoxalines affected the barrier of racemization, the rotation barriers were calculated based on the racemization experiments (see more details in the Supporting Information). As shown in Scheme 4, **3aa** and **3sa** with Me and Ph groups at the R^2 group gave the rotation barrier of 27.10 and 28.42 kcal/mol, respectively. These results showed that compound **3aa** easily underwent racemization. Compound **3pa** with a C–Cl bond at the R^2 group gave 28.17 kcal/mol. However, **3qa** and **3ra** bearing Br and F groups gave 29.67 and 29.92 kcal/mol. We noted that the energy barrier of **3ra** was higher than those of **3aa**, **3sa**, **3pa**, and **3qa**. Perhaps it was owing to the intermolecular π–π stack effect, which was showed by X-ray diffraction analysis of **3ra**.[25]

Then, a possible mechanism for the formation of **3aa** from indole **1a** and 1,2-diaminoarene **2a** was proposed (Scheme 5–1). Firstly, indole **1a** was converted to 3-oxoindolenine **4a** by oxidation in the presence of copper(I) and O_2. Then, condensation of **4a** with **2a** in the presence of **CPA4** afforded imine intermediate **A**, which then underwent intramolecular cyclization to furnish intermediate **B** containing chiral carbon stereocenter. Finally, C–N bond cleavage of indole in **B** would give axially chiral quinoxaline-aminoarene **3aa**. Hence, it is noted that the production of axial chirality was derived from the chiral carbon setereocenter in **B**. Then, we performed density functional theory (DFT) calculations to reveal the origins of enantioselectivity, using the **CPA4** catalyst and **1a** and **2a** as the substrates (Scheme 5-2). It was found that activating of intermediate **A** by **CPA4** through hydrogen-bonding interaction would provide **INT1**, which could be confirmed by HRMS experiment with molecular weight of 1026.3471, indicating that one molecule of **CPA4** reacted with one substrate. **INT1** would undergo intramolecular cyclization via transition state **TS2** to furnish **INT3**. Alternatively, **INT1** could isomerize to



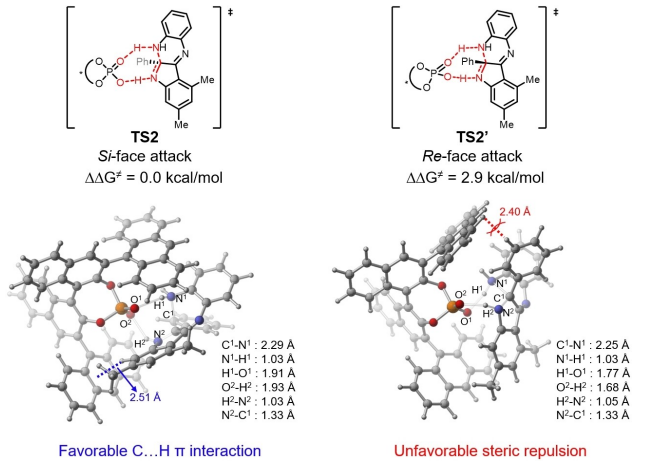
Scheme 4. Relationship between the rotation barrier and the substituents at the R^2 group.



Scheme 5. Proposed mechanism and DFT calculation.

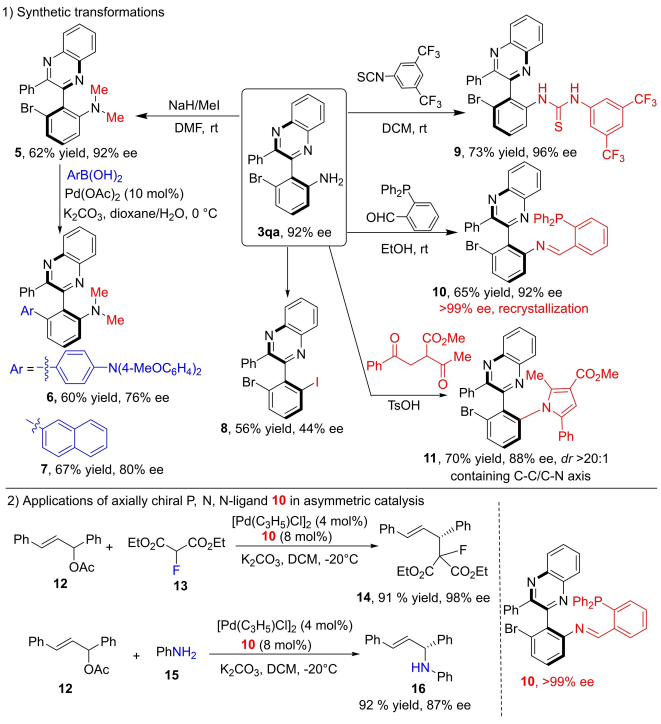
INT1', followed by cyclization via transition state **TS2'** to provide **INT-3'** (Scheme 5–2).

Based on the operative reaction mechanism, the chiral induction model in the stereoselectivity-determining intramolecular cyclization was revealed. The optimized structures and relative free energies of the enantioselectivity-determining transition states are shown in Scheme 6. Calculations showed that **TS2** (leading to major enantiomer product) was 2.9 kcal/mol more favorable than **TS2'** (leading to minor enantiomer product), which was in agreement well with the experimental enantioselectivity (96% ee, Table 2). By detailed analyses of the transition states, it is found that in **TS2**, there is a favorable C–H… π interaction between the C–H bond of the substrate and the 9-anthracenyl substituents of the **CPA4** catalyst (2.51 Å). On the contrary, in **TS2'**, there is unfavorable steric repulsion between the substrate Ph group and the 9-anthracenyl group, as manifested by the closer H–H distance (2.40 Å). Therefore, the C–H… π interaction and the steric effect are the major reasons that differentiate the competing intramolecular cyclization transition states and result in the chiral carbon stereocenters, which finally convert into C–C axial chirality.



Scheme 6. Optimized structures and relative energies of the enantioselectivity-determining nucleophilic addition transition states.

To demonstrate the synthetic utility of this methodology and this new type of axially chiral aminoaryl quinoxaline scaffold, the further synthetic transformations were then explored (Scheme 7-1). Protection of **3qa** with MeI afforded axially chiral bidentate *N*-ligand **5** in 62 % yield and 92 % ee. Suzuki cross-coupling reaction of compound **5** with 4-(4-methoxyamino)phenyl and naphthyl boronic acids furnished the desired coupling reaction products **6** and **7** in 60 % yield with 76 % ee and 67 % yield with 80 % ee, respectively. When compound **3qa** was carried out under the Sandmeyer reaction conditions with KI, an iodine-substituted product **8** was obtained in 56 % yield and 44 % ee only. Furthermore, organocatalyst and ligand based on these aminoaryl quinoxaline skeletons were successfully prepared to prove the practicability of this methodology. For example, axially chiral thiourea catalyst **9** was obtained in 73 % yield and 96 % ee by the condensation reaction of **3qa** with isothiocyanate. The condensation of **3qa** with 2-(diphenylphosphaneyl)benzaldehyde at room temperature afforded axially chiral P,N,N-ligand **10** in 65 % yield and 92 % ee and further improved to >99 % ee by recrystallization. Interestingly, the condensation of **3qa** with 1,4-diketone in the presence of TsOH catalyst delivered axially chiral compound **11** containing both C–C and C–N axis in 70 % yield and 88 % ee with high diastereoselectivity. Moreover, axially chiral compound **10** (>99 % ee) could be served as a ligand to realize the palladium-catalyzed enantioselective allylic alkylation (Scheme 7-2). Compound **12** reacted with fluoro-substituted ethyl malonate **13** leading to the desired product **14** containing a quaternary carbon in 91 % yield and 98 % ee. When benzylamine**15** was used as the nucleophile in the asymmetric allylic alkylation reaction, product **16** was obtained in 92 % yield and 87 % ee. The absolute configuration of compounds **14** and **16** were determined as *R*-configuration according to the reported literatures.[26] These results revealed that the novel synthetic ligand **10** had excellent enantioselectivities in asymmetric catalysis.



Scheme 7. Synthetic transformations and applications.

Conclusions

In summary, we have identified a formal umpolung of C3-position of indoles through oxidative dearomatization of indoles with 1,2-diaminoarenes in the presence of copper(I) and chiral phosphoric acid (CPA) relay catalysis to form axially chiral aminoaryl quinoxaline compounds in good yields and excellent enantioselectivities. This method highlights atom-economic reaction, broad substrate scope, good functional group tolerance, new type of axially chiral heterobiaryl skeletons, and enantioselective isodesmic C–N bond formation and cleavage. Moreover, the obtained axially chiral aminoaryl quinoxalines could be converted into various axially chiral building blocks and aminoaryl quinoxaline derived ligand is demonstrated to be applicable to asymmetric catalysis. Therefore, this work has not only provided a new and useful isodesmic reaction for the preparation of axially chiral aminoaryl quinoxalines, but also offered the opportunity to further study the applications of this new type of quinoxaline atropisomers in other research fields.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: isodesmic reaction · asymmetric catalysis · indole · skeletal editing · atropisomerism

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