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Visible-Light-Induced Amination of Quinoline at the C8 Position via a Postcoordinated Interligand-Coupling Strategy under Mild Conditions

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ABSTRACT: The postcoordinated interligand-coupling strategy provides a useful and complementary protocol for synthesizing polydentate ligands. Herein, diastereoselective photoreactions of Λ -[Ir(pq)₂(D-AA)] (Λ -D) and Λ -[Ir(pq)₂(L-AA)] (Λ -L, where pq is 2-phenylquinoline and AA is an amino acid) are reported in the presence of O_2 under mild conditions. Diastereomer A-D is dehydrogenatively oxidized into an imino acid complex, while diastereomer Λ -L mainly occurs via interligand C–N crossdehydrogenative coupling between quinoline at the C8 position and AA ligands at room temperature, affording Λ -[Ir(pq)(L-pq-AA)]. Furthermore, the photoreaction of diastereomer Λ -L is temperature-dependent. Mechanistic experiments reveal the ligand-radical intermediates may be involved in the reaction. Density functional theory calculations were used to eluciate the origin of diastereoselectivity and temperature dependence. This will provide a new protocol for the amination of quinoline at the C8 position via the postcoordinated interligand C-N cross-coupling strategy under mild conditions.



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INTRODUCTION

The classical metal-catalyzed cross-coupling methods play an important role in ligand synthesis but often require preactivated substrates or harsh reaction conditions.¹ Therefore, it is important to develop a facilely synthetic approach for generating new multidentate ligands. Postcoordinated interligand coupling may provide a complementary strategy for accessing this vision.² The simple and easily available organic ligands are first coordinated to a metal center via a classical protocol and then couple to each other directly, affording new polydentate ligands.³ Generally, heterocyclic ligands coordinated to a metal ion would promote the acidity of α -CH, resulting in the enhancement of the reactivity of the ligands.² Furthermore, coordination to a metal ion also preorganizes the substrates via a geometric control, facilitating their subsequent coupling in regio- and stereoselectivity.⁵ In addition, highly activated intermediates such as N and S radicals can be stabilized by coordination to a metal ion via electron delocalization.⁶ Indeed, the oxidation of metal-thiolate complexes into metal-thiyl radical intermediates, affording disulfides via S-S radical coupling, is well-documented (see Scheme 1a).^{6a,7} The most interesting instance is interligand C-C coupling, which provides a facile and straightforward method for synthesizing polydentate ligands. In 2001, a tetradentate ligand 2,2'-biphenanthroline (biphen), reported by Gao's group,⁸ was synthesized via a direct interligand coupling of the $[Co(phen)_2]^{2+}$ fragment in the presence of NH₄VO₃ and H₃BO₃ under hydrothermal conditions (see

Scheme 1b). The dehydrogenative oxidation and interligand C-C coupling reactions may be involved in these processes. Using the strategy of enhancing the acidity of α -CH in a heterocycle ligand via coordination to the $[Re(CO)_3]^+$ fragment, a series of bidentate ligands, such as bipyridine (bpy) and pyridylimidazole, have been synthesized by Riera's group from the simple imidazole and pyridine ligands via deprotonation in the presence of KN(SiMe₃)₂ as a base, followed by the oxidation reaction using Ag⁺ as an oxidant.⁵ Recently, a porphyrin analogue was synthesized in situ using a $bis(\alpha, \alpha'$ -bibromodipyrrin) Ni(II) complex and a phosphine anion in the presence of a Pd(II) catalyst (see Scheme 1b).¹⁰ Compared to C-C coupling, interligand C-N coupling is relatively scarce. A well-known instance is the interligand coupling of the pyrazole-acetonitrile complex into the pyrazolylamidino complex under mild conditions,¹¹ in which the electrophilic character of the acetonitrile ligand is significantly enhanced by the coordination to a metal ion. Moreover, a highly active metal-nitrene intermediate generated from organoazide was found to directly react with the diamide diimine complex, producing two C-N bonds (see

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Scheme 1. Selective Examples of Interligand-Coupling Reactions and Amidation of Quinoline N-Oxide at the C8 Position via C-H Functionalization

a) Intramolecular S-S coupling reaction



b) Intramolecular C-C coupling reaction



Scheme 1c).¹² More recently, an interligand C-H functionalization via a nickel-nitridyl intermediate produced by photolysis of the nickel–azide complex was also reported by Lee's group,¹³ affording a new polydentate ligand in situ. However, these protocols are still restricted to specific substrates, such as nitrile, organoazide, and azide. Therefore, a general protocol for C–N bond formation via C–H and N–H cross-coupling is still highly desirable.

Quinoline is an important structural motif in natural products and functional materials.^{14,15} In particular, 8-aminoquinolines are important motifs in biological activities,^{16–18} ligands used in coordination chemistry¹⁹ and catalysis in C-H functionalization.²⁰ However, the traditional synthesis protocol of 8-aminoquinolines is nitration of quinoline under strongly acidic conditions. In 2014, Chang's group first developed the C8 amidation of quinoline N-oxides using an Ir(III) catalyst with the sulfinyl azides as the amide source in the presence of AcOH as an additive under mild conditions (see Scheme 1d).^{21a} Following this strategy, they extended the amide source to 1,4,2-dioxazol-5-ones.^{21b} Two years later, an alternative strategy based on hypervalent iodine reagents as an amidation source was developed to directly amidate C8 of quinoline Noxides in the presence of a Rh(III) catalyst (see Scheme 1d).²² In these protocols, the specific amide sources, such as sulfinyl azides, 1,4,2-dioxazol-5-ones, and amidobenziodoxolones, are required to generate metal-nitrene intermediates in situ. Therefore, a facile and general approach to direct amination of quinoline at the C8 position using commercially available primary and secondary amines as a nitrogen source is still unexploited.

Visible-light-induced photoreaction has recently received a great deal of attention.²³ This process relies on the ability of the photosensitizer to engage in the transfer of an electron and/or energy to substrates under visible-light irradiation to produce high-energy and reactive intermediates. Polypyridyl Ru(II) and Ir(III) complexes have been widely applied in photocatalytic reactions as photosensitizers, because of their high photostability and long-lived photoexcited states as well as their tunable photophysical properties.²⁴ However, reports of self-sensitized photoreaction remain scarce.²⁵ This process may be employed in postcoordination synthesis to produce new ligands and new complexes in situ, which sometimes can work via the classical protocol,²⁶ because the reactivity of the ligand is highly enhanced by coordination to a metal ion.^{4a,27} In light of these challenges, we have observed the self-sensitized photoreaction of $[Ru(bpy)_2(TMBiimH_2)](ClO_4)_2$ (TMBiimH₂ is 4,5,4',5'-tetramethyl-2,2'-biimidazole) in the presence of O₂.²⁸ Under visible-light irradiation, the Ru(II) complex was oxidized by singlet oxygen $({}^{1}O_{2})$, producing $[Ru(bpy)_2(DMDAImH)](ClO_4)_2$ [DMDAImH is 4,5-dimethvl-2-(N,N-diacetyl) carboximidamide-1*H*-imidazole]. Moreover, a protocol of postcoordinated asymmetric oxidation of thioether complexes into sulfoxide complexes was also developed by our group using a chiral-at-metal strategy to generate enantiomeric sulfoxide ligands in situ.²⁹ As part of our ongoing study, we observe chiral Ir(III) complexes because they are highly photostable and widely used in asymmetric synthesis,^{30,31} molecular recognition,³² and chiral resolution.³³ For the α -amino acid (AA) complexes, the photophysical properties of Δ -[Ir(pq)₂(L-pro)] (Δ -L) and Δ -[Ir(pq)₂(Dpro)] (Δ -D) (where pq is 2-phenylquinoline and pro is proline) diastereomers are different.³⁴ More importantly, only the pro ligand in the Δ -L diastereomer was oxidized into an imino acid under a natural condition.³⁵ We are wondering what will happen in the Λ -L or Δ -D diastereomer under similar

conditions. This also inspires us to observe the reaction in detail. We found that the photoreactions of AA complexes are diastereoselective in the presence of O_{2j} namely, the Λ -D or Δ -L diastereomer is oxidized to the corresponding imino acid complex, while the Λ -L or Δ -D diastereomer occurs mainly via interligand C–N cross-dehydrogenative coupling between quinoline and AA ligands at room temperature (see Scheme 1e). More interestingly, the photoreaction of the Λ -L or Δ -D diastereomer is temperature-dependent. Furthermore, density functional theory (DFT) calculations were conducted to elucidate the diastereoselectivity and temperature dependence. This will provide a new protocol for amination of quinoline at the C8 position via the postcoordinated interligand C–N cross-dehydrogenative coupling reaction under mild conditions.

EXPERIMENTAL SECTION

The general information about the experiments and the instrumentation is given in the Supporting Information.

Synthesis of Λ -[Ir(pq)₂(L-AA)] and Λ -[Ir(pq)₂(D-AA)] Complexes. Λ -[Ir(pq)₂(MeCN)₂](PF₆) (1.0 mmol) was added to 25 mL of a methanol solution containing L-AA or D-AA (1.0 mmol) and MeONa (1.0 mmol). The solution was stirred for 12 h at room temperature in the dark. Upon removal of the methanol solvent, 30 mL of water was added to dissolve the residue. The resulting solution was extracted with DCM (3 × 20 mL). The extracted solution was collected and dried with Na₂SO₄. The corresponding amino acid Ir(III) complex was obtained upon removal of the solvent. The yield and characterization of the synthesized complexes are given in the Supporting Information.

Synthesis of the Λ -[Ir(pq)₂(ala-2H)] Complex by the Dehydrogenative Oxidation Reaction. The Λ -[Ir(pq)₂(D-ala)] (0.05 mmol, ala is alanine) complex was dissolved in 100 mL of ethanol. The solution was stirred at 30 °C under an O₂ atmosphere under 10 W blue light-emitting diode (LEDs) (λ = 450–470 nm) irradiation for 13 h. Upon removal of the solvent, the residue was purified by silica gel column chromatography using a DCM/MeOH mixture [from 100:0.5 to 100:4 (v/v)] as the eluent. Yield, 32 mg, 93%. The characterization data are given in the Supporting Information.

Procedure for the C–N Cross-Coupling Reaction. Λ - $[Ir(pq)_2(L-AA)]$ (0.05 mmol) was added to 100 mL of ethanol. The solution was stirred at 60 °C under an O₂ atmosphere under 10 W blue LED ($\lambda = 450-470$ nm) irradiation for an appropriate time. Upon removal of the solvent, the residue was purified by silica gel column chromatography using a DCM/MeOH mixture [from 100:0.5 to 100:4 (v/v)] as an eluent. The yield and characterization data of the synthesized complexes are given in the Supporting Information.

RESULTS AND DISCUSSION

Synthesis and Characterization of Λ -[lr(pq)₂(L-ala)] and Λ -[Ir(pq)₂(D-ala)] Complexes. Diastereomers Λ -[Ir- $(pq)_2(L-ala)$] and Λ -[Ir(pq)_2(D-ala)] were synthesized by the reaction of Λ -[Ir(pq)₂(MeCN)₂](PF₆) with L-ala and D-ala using NaOMe as a base in a MeOH solution, respectively. Their structures were determined by NMR and MS techniques (see Figures S1-S5). Their photophysical properties are similar to those of the Λ -[Ir(pq)₂(L-pro)] and Λ -[Ir(pq)₂(Dpro)] complexes.³⁴ The diastereomers can be distinguished in the resonance peaks of α -H of the pq ring at 8.81 ppm for Λ - $[Ir(pq)_2(L-ala)]$ and 8.52 ppm for Λ - $[Ir(pq)_2(D-ala)]$, as shown in Figure 1. The diastereomeric ratio was estimated to be 100:1 via integration of these peaks. CD spectra showed Λ - $[Ir(pq)_2(L-ala)]$ and Λ - $[Ir(pq)_2(D-ala)]$ diastereomers have similar profiles and identical Cotton effects at 273, 308, 354, and 467 nm (see Figure S6), suggesting the configurations at



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Figure 1. ¹H NMR spectra of Λ -[Ir(pq)₂(L-ala)], Λ -[Ir(pq)₂(D-ala)], Λ -[Ir(pq)₂(ala-2H)], and Λ -[Ir(pq)(L-pqa)] in CDCl₃.

Ir(III) centers are the main determinant. Cyclic voltammetry was used to estimate the oxidation potentials (Ir^{4+}/Ir^{3+} redox couple) of the diastereomers and revealed a single quasi-reversible oxidation wave at $E_{1/2}$ (vs FeCp₂⁺/FeCp₂) values of 0.746 and 0.787 V for Λ -[Ir(pq)₂(L-ala)] and Λ -[Ir(pq)₂(D-ala)], respectively (see Figure S7).

Absorption and emission spectra of the diastereomers in the MeOH solution were recorded at room temperature. The absorption spectra of the diastereomers are similar to those of the known Δ -[Ir(pq)₂(D-pro)] complex.³⁴ The intense absorption peak at 273 nm can be assigned to the spinallowed $\pi - \pi^*$ transitions (LC) of the pq ligand. The weaker band at 462 nm could be assigned to the metal-to-ligand (³MLCT) transitions.^{36,37} Moreover, the moderately intense peak at 344 nm is assigned to the spin-allowed metal-to-ligand charge transfer (¹MLCT).³⁸ The emission spectra of the diastereomers exhibit a band at 604 nm, which can be assigned to a mixed ³MLCT/LC state (see Figure S8).³⁴ The emission lifetimes (τ) and quantum yields (Φ_r) of Λ -[Ir(pq)₂(D-ala)] (164 ns and 4.4%, respectively) are larger than those of Λ -[Ir(pq)₂(L-ala)] (138 ns and 2.1%, respectively) (see Figure S9), indicating that the photophysical properties of the diastereomers are distinguishable.³

To gain a better understanding of the structure, the singlecrystal structure of Λ -[Ir(pq)₂(L-ala)] was determined (see Table S1). It crystallizes in space group $P4_1$. The absolute configurations at the metal center and ala ligand are Λ and L, respectively. Each Ir(III) ion is coordinated by two carbon atoms from pq ligands in cis positions and two nitrogen atoms in a trans fashion as well as an oxygen atom and a nitrogen atom from an ala ligand, resulting in a slightly distorted octahedron, as shown in Figure 2. The Ir(III) ion slightly departs from the equatorial plane that consists of two carbon atoms of pq ligands and nitrogen and oxygen atoms from the ala ligand. The Ir-N [2.084(13) and 2.082(11) Å] and Ir-C [2.003(15) and 1.991(16) Å] distances of the pq ligands are consistent with those reported for pq Ir(III) complexes (see Table S2).^{34,35} The Ir-N [2.218(12) Å] distance of the ala ligand is longer than that of the pq ligands, but consistent with the reported value [2.211(14) Å] of $[Ir(ptpy)_2(L-ala)]$ [ptpy is 2-(*p*-tolyl)pyridinato].³⁹ The oxygen atom of the carboxylate forms intramolecular hydrogen bonds with C14-H (C14-H… $O1 = 2.975 \text{ Å}, \angle C14 - H - O1 = 142.9^{\circ})$ of the pq ligand. This



Figure 2. Molecular structures of Λ -[Ir(pq)₂(L-ala)] (left) and Λ -[Ir(pq)(L-pqa)] (right) with 50% probability ellipsoids. Hydrogen atoms have been omitted for the sake of clarity.

is consistent with the observation of the resonance peak of H14 in the pq ligand shifting to low field (see Figure 1).

Photoreaction of Λ -[lr(pq)₂(D-ala)] and Λ -[lr(pq)₂(Lala)] Complexes. To the best of our knowledge, the different reactivities between the stereoisomers remain unexploited. In 1983, Keene et al. reported that Δ -[Ru(bpy)₂(*R*-Meampy)]²⁺ and Λ -[Ru(bpy)₂(S-Meampy)]²⁺ [Meampy is 2-(1aminoethy1)pyridine] diastereomers have different oxidation rates under chemo- and electro-oxidation conditions.⁴⁰ Twenty years later, Kurosaki et al. found that only the mer-[Fe(2- $DPA)(CN)_3$ [2-DPA is bis(2-pyridylmethyl)amine] isomer was oxidized into the imine complex in the presence of ammonium peroxodisulflate as an oxidant.⁴¹ Inspired by these findings, we have observed the photoreaction of Δ -[Ir(pq)₂(Dpro)] and Δ -[Ir(pq)₂(L-pro)] diastereomers and found the oxidation dehydrogenation rate of Δ -[Ir(pq)₂(L-pro)] is ~60 times faster than that of Δ -[Ir(pq)₂(D-pro)].³⁵ Therefore, only the Δ -[Ir(pq)₂(L-pro)] diastereomer was oxidized into the corresponding imino acid complex Δ -[Ir(pq)₂(pro-2H)] when it crystallized under natural conditions. When we further observed the photoreaction of the Δ -[Ir(pq)₂(D-pro)] diastereomer, we found the reaction is too slow to optimize the reaction conditions. Therefore, we turned to the primary AA complexes and selected Λ -[Ir(pq)₂(L-ala)] and Λ - $[Ir(pq)_2(D-ala)]$ as models to observe the reaction in detail (see Scheme 2). First, DFT calculation showed the Gibbs free energy of Λ -[Ir(pq)₂(D-ala)] is ~1.1 kcal/mol higher than that of Λ -[Ir(pq)₂(L-ala)] at the wB97XD/def2-TZVP, SMD (EtOH)//wB97XD/def2-SVP level of theory, indicating that the Λ -L diastereomer is thermodynamically stable (see Figure S10). NMR analysis showed the characteristic peak at 2.37 ppm assigned to the α proton of ala completely disappeared upon irradiation of the ethanol solution of Λ -[Ir(pq)₂(D-ala)] with a blue LED light under an O2 atmosphere at 30 °C for 13 h. Meanwhile, the multiple peaks of the coordinated amine group of ala at 3.29 and 2.72 ppm were found to shift to 9.89 ppm in a singlet peak, which is a characteristic peak of the imine group, as shown in Figure 1. Furthermore, the α -carbon of ala at 54.14 ppm was also found to shift to 169.62 ppm (see Figures S1 and S11). These all support the dehydrogenative oxidation of Λ -[Ir(pq)₂(D-ala)] into Λ -[Ir(pq)₂(ala-2H)]. HR-MS analysis of Λ -[Ir(pq)₂(ala-2H)] showed an intense band at m/z 688.15670 ([M + H]⁺), which is consistent with the calculated isotope pattern for the molecular formula $[C_{33}H_{24}IrN_3O_2 + H]^+$ (*m/z* 688.15705) (see Figures S5 and S12). Additionally, the photooxidation dehydrogenative products Δ -[Ir(pq)₂(pro-2H)] and Δ -[Ir(pq)₂(ala-2H)] have

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Scheme 2. Photoreaction of Λ -[Ir(pq)₂(L-ala)] and Λ -[Ir(pq)₂(D-ala)] Diastereomers in the Presence of O₂ at Various Temperatures



been confirmed by single-crystal structure analysis in our previous studies.^{35,42} We also observed the photoreaction at 60 °C to determine whether the reaction is temperature-dependent and found only product Λ -[Ir(pq)₂(ala-2H)] was obtained quantitatively but the reaction time decreased to 10 h, indicating that a higher temperature increases the rate of the photoreaction.

On the basis of our investigation of the unstable diastereomer Λ -D or Δ -L that is oxidized into the corresponding imino acid complex, we became interested in whether the stable diastereomer Λ -L or Δ -D would be able to react in the presence of O2 under visible-light irradiation. Indeed, when the Λ -[Ir(pq)₂(L-ala)] diastereomer was irradiated under identical conditions (see Scheme 2), the resonance peaks of the α -H of ala at 2.96 ppm and the coordinated amine group of ala at 3.53 and 2.12 ppm completely disappeared in 24 h (see Figure 1), suggesting that the reaction material was completely consumed. This stimulates us to isolate and identify the products. Gratifyingly, two products were isolated in a ratio of 1:2 by silica gel column chromatography. Structural analyses show one is Λ -[Ir- $(pq)_2(ala-2H)$] with a yield of 32%, the same as the dehydrogenative oxidation product from Λ -[Ir(pq)₂(D-ala)]. The other was analyzed by HR-MS spectrometry and also showed a molecular ion peak at m/z 688.15452 with a strong isotopic cluster (see Figure S15) that is consistent with the calculated isotope pattern for the molecular formula $[C_{33}H_{24}IrN_{3}O_{2} + H]^{+}$ (m/z 688.15705), indicating that it is also a dehydrogenative product of the substrate with a yield of 68%. However, their NMR spectra are different (see Figure 1). Further analysis shows the peak of the α -H of ala shifted to 3.97 ppm and the peak at 7.98 ppm assigned to H29 of the pq ring completely disappeared. Furthermore, the peak of the α carbon of ala at 51.48 ppm shifted to 67.29 ppm (see Figure S16), implying the new product may be involved in pq and ala ligands. This was further confirmed by single-crystal structural analysis, as shown in Figure 2. It is an interligand C-N coupling product between pq and L-ala ligands, namely Λ -[Ir(pq)(L-pqa)] [pqa is N-(2-phenylquinolin-8-yl)alanine]. This is a new reaction for the aromatic amination of the quinoline ring at C8 via C-H and N-H direct functionalization under mild conditions, which has never before been reported,⁴³ affording a new chiral tetradentate ligand.

 Λ -[Ir(pq)(L-pqa)] crystallizes in space group $P2_12_12_1$. The metal center and α -carbon of ala are in Λ and L configurations, respectively. These are consistent with configurations of the precursor Λ -[Ir(pq)₂(L-ala)], indicating the configurations at the Ir(III) center and carbon center of ala persist during the reaction. The N3-C29 bond is indeed formed with a length of 1.452(11) Å, comparable to the N3-C32 bond length [1.489(12) Å]. The Ir(III) ion is coordinated by pg and pga ligands in a slightly distorted octahedral geometry. The Ir-N [2.083(7), 1.965(7), and 2.245(7) Å], Ir-C [2.037(10) and 1.995(9) Å], and Ir-O [2.176(6) Å] distances are consistent with those of Λ -[Ir(pq)₂(L-ala)]. The C1-Ir1-O1 [170.1(3)°], N3-Ir1-C16 [159.4(4)°], and N2-Ir1-N3 $[81.4(3)^{\circ}]$ bond angles are significantly smaller than those of the corresponding bond angles [174.3(5)°, 165.3(6)°, and 97.2(4)°, respectively] in Λ -[Ir(pq)₂(L-ala)] because of the coupling of N3 and C29 (see Table S2).

The CD spectrum of Λ -[Ir(pq)(L-pqa)] displays the Cotton effect at 261, 290, 313, 353, and 463 nm (see Figure S13). The absorption spectrum of Λ -[Ir(pq)(L-pqa)] shows an intense band at 278 nm and a moderately intense band around 352 nm, which are slightly bathochromically shifted compared to those of Λ -[Ir(pq)₂(L-ala)]. The weaker absorption band at 438 nm is significantly blue-shifted relative to the precursor. The emission maximum slightly red shifts to 612 nm, with a longer emission lifetime (242 ns) and a larger quantum yield (5.8%) compared with those of 138 ns and 2.1% for Λ -[Ir(pq)₂(L-ala)] and 12 ns and 0.5% for Λ -[Ir(pq)₂(ala-2H)], respectively (see Figure S14).

Optimization the C-N Coupling Conditions. The finding of C-N coupling reaction encourages us to further optimize the photoreaction conditions by monitoring the characteristic resonance peaks of H14 of the pq ligand at 8.81 ppm for Λ -[Ir(pq)₂(L-ala)], 8.59 ppm for Λ -[Ir(pq)₂(ala-2H)], and 9.21 ppm for Λ -[Ir(pq)(L-pqa)] (see Figure 1). The effect of temperature on the reaction was first observed (see entries 1-4 in Table 1). When the reaction temperature was increased to 60 °C, the substrate Λ -[Ir(pq)₂(L-ala)] was completely consumed in 18 h, indicating the increase in the temperature favors the conversion rate. NMR analysis showed that the ratio of Λ -[Ir(pq)(L-pqa)] to Λ -[Ir(pq)₂(ala-2H)] increased to 96:4 from 68:32 at room temperature, meaning that the C-N coupling and dehydrogenative oxidation reactions are competitive, and the C–N coupling reaction is predominant under these conditions. When the reaction temperature is continually increased to 70 °C, the effect on the conversion rate and yield can be neglected. In contrast, the yields of Λ -[Ir(pq)(L-pqa)] and Λ -[Ir(pq)₂(ala-2H)] changed to 29% and 71%, respectively, in 36 h when the reaction temperature was decreased to 0 °C, indicating that the decreasing temperature favors conversion into the imino acid complex. Therefore, the reaction is dependent on temperature. It is well-known that the photoreaction significantly depends on the reaction solvent. Thus, the photoreaction was then estimated in various solvents (see entries 5-8 in Table 1). When polar solvents such as MeOH and MeCN were used instead of EtOH, the conversions decreased to 28% and 25%, respectively. Moreover, no product was detected when nonpolar solvents such as toluene and DCE were used, indicating that EtOH is the more efficient solvent in this reaction. In addition, the effect of the base on the coupling reaction was also observed (see entries

Table 1. Optimization of the Reaction Conditions a and Control Experiments



^{*a*}Reaction conditions: Λ -[Ir(pq)₂(L-ala)] (0.005 mmol) in 10 mL of solvent with an O₂ balloon under a 10 W blue light at 60 °C for 18 h. ^{*b*}DFSC is the deviation from standard conditions. ^{*c*}The conversion and yield were determined by ¹H NMR spectroscopy.

9–12 in Table 1). When 3 equiv of NaOMe or Na₂CO₃ was added to reaction mixture, the effects on conversion and yield could be neglected. However, when a large excess of base (50 equiv of NaOMe) was used, the yield of the imino acid product significantly increased to 76% in 12 h, indicating that the excess strong base favors the α -C–H dehydrogenation of AA (vide infra).

Scope of the C–N Coupling Reaction. With the optimal conditions in hand, the scope and limitation of the photoreaction were also investigated (see Scheme 3). First, the difference between the enantiomers was observed. When Δ - $[Ir(pq)_2(D-ala)]$ was used instead of Λ - $[Ir(pq)_2(L-ala)]$ under identical conditions, we found the photoreaction proceeded smoothly, affording Δ -[Ir(pq)(D-pqa)] with a yield of 88% in 18 h. This demonstrated no difference existed between the enantiomers in the photoreaction. Second, various AAs were used to evaluate the reactivity. When the primary AAs, such as valine (val), serine (ser), and phenylalanine (pal), were used instead of ala, the coupling reaction proceeded smoothly, affording the corresponding products Δ -[Ir(pq)(D-pqv)] [pqv is N-(2-phenylquinolin-8-yl)valine], Δ -[Ir(pq)(D-pqs)] [pqs is *N*-(2-phenylquinolin-8-yl)serine], and Δ -[Ir(pq)(D-pqpa)] [pqpa is N-(2-phenylquinolin-8-yl)phenylalanine] in yields of 83% (60 h), 53% (60 h), and 62% (72 h), respectively (see Figures S17–S34). The longer reaction time required for the

Scheme 3. Scope of the C-N Coupling Reaction^a



^{*a*}Reaction conditions: Ir(III) complexes (0.005 mmol) in 10 mL of EtOH with an O_2 balloon under a 10 W blue light at 60 °C. Reported yields are those of the isolated products. ^{*b*}The A:B ratio was determined by ¹H NMR spectroscopy. ^{*c*}In the presence of 3 equiv of NaOMe.

conversion indicates the steric effect of the α -AA is sensitive to the photoreaction. We also found the electronic effects of the substituents at α -carbon significantly impact C-N bond formation. For the ser complex, an electron-withdrawing hydroxymethyl group at the α -carbon significantly increases the acidity of the α -hydrogen of ser, leading to a decrease in the yield of the C-N coupling product to 53% relative to a yield of 83% for Δ -[Ir(pq)(D-pqv)]. In contrast, the yield of imino acid product Δ -[Ir(pq)₂(ser-2H)] increases to 33% relative to a yield of 1% for Δ -[Ir(pq)₂(val-2H)]. A similar situation was also observed in Δ -[Ir(pq)₂(D-pal)], where the yields of Δ -[Ir(pq)(D-pqpa)] and Δ -[Ir(pq)₂(pal-2H)] were 67% and 28%, respectively. This is also consistent with the observation of the large excess of a strong base that favors the formation of the imino acid complex, also indicating the dehydrogenative oxidation and C-N coupling reactions are competitive. Moreover, when the secondary AA pro was used, the corresponding C–N coupling product Δ -[Ir(pq)(D-pqp)] [pqp is *N*-(2-phenylquinolin-8-yl)proline] was also afforded in a yield of 72% (see Figures S34-S40), indicating that the primary and secondary amines are suitable nitrogen sources for the amination of quinoline at the C8 position. In addition, the achiral AA glycine (gly) was also used to examine the reaction. Indeed, the C–N coupling product Δ -[Ir(pq)(pqg)] [pqg is N-(2-phenylquinolin-8-yl)glycine] was obtained in a yield of 68% in 60 h when Δ -[Ir(pq)₂(gly)] was employed as the substrate under identical conditions (see Figures S41-S45), indicating the reaction is compatible with diverse AAs.

Then, we turned our attention to the quinoline substrate. When 7-methyl-2-phenylquinoline (Mpq), bearing an electronrich methyl group at the C7 position of pq, was used instead of the pq ligand, the reaction proceeded smoothly, affording Λ -[Ir(Mpq)(L-Mpqa)] [Mpqa is *N*-(7-methyl-2-phenylquinolin-8-yl)alanine] with a yield of 89% in 22 h (see Figures S46–

S51). When an electron-deficient group, chloro or bromo, was introduced into the pq at the C7 position, the desired product Λ -[Ir(Cpq)(L-Cpqa)] [Cpq is 7-chloro-2-phenylquinoline, and Cpqa is N-(7-chloro-2-phenylquinolin-8-yl)alanine (see Figures S52-S57 or Λ -[Ir(Bpq)(L-Bpqa)] [Bpq is 7-bromo-2phenylquinoline, and Bpqa is N-(7-bromo-2-phenylquinolin-8yl)alanine (see Figures \$58-\$63)] was obtained in a yield of 89% in 28 h or 86% in 27 h, respectively, indicating that an electron-donating or electron-withdrawing group at the quinoline ring is tolerated. The longer reaction time required for the quinoline ligands with the electron-deficient group indicates that the electronic effect of the substituents at the C7 position is sensitive to C-N bond formation and the electrondonating groups appear to be beneficial. These are consistent with the radical aromatic addition pathway.⁴⁴ Furthermore, both chloro and bromo substituents were tolerated under the reaction conditions, which enable further functionalization at this position.

Mechanistic Studies for the C–N Coupling Reaction. The previous study has demonstrated that singlet oxygen $({}^{1}O_{2})$ is the main reactive oxygen species (ROS) for the conversion of the Δ -L diastereomer into the imino acid complex under an O₂ atmosphere with light irradiation and a ligand radical may be involved in the reaction.^{35,42} To probe the photoreaction mechanism of the C-N coupling reaction, complex Λ -[Ir(pq)₂(L-ala)] was selected as a model for observation of the reaction under the optimal conditions. The control experiments showed that both blue light and O₂ are indispensable for C-N bond formation (see entries 13 and 14 in Table 1). Furthermore, no described products were observed when free L-ala was added to the solution of Λ - $[Ir(pq)_2(MeCN)_2](PF_6)$ under an O₂ atmosphere with bluelight irradiation, indicating that the reactivity of ala is significantly promoted via coordination to the Ir(III) ion.² Two main ROS, such as ${}^{1}O_{2}$ and superoxide radical $(O_{2}^{\bullet-})$, have been observed in the photoreaction under an O2 atmosphere. To demonstrate which is the main ROS, the inhibition experiments were carried out under the optimal conditions (see entries 15 and 16 in Table 1). When 5 equiv of NaN_3 , a known 1O_2 scavenger, was added to the reaction solution, the C-N coupling product was still produced in a yield of 88%. In contrast, when 5 equiv of benzoquinone (BQ), a scavenger for $O_2^{\bullet-}$, was added to the reaction solution, only a trace of the product was detected, indicating that $O_2^{\bullet-}$ is a main ROS in the reaction. This is inconsistent with the previous observation for the dehydrogenative oxidation of the unstable Δ -L diastereomer into the imino acid complex at room temperature, where ${}^{1}O_{2}$ is the predominant ROS.^{35,42} This also inspired us to further observe the inhibition experiment at room temperature (see entries 17 and 18 in Table 1). The control experiment showed $O_2^{\bullet-}$ is still the main participant in C-N bond formation at room temperature.

To probe the radical mechanism, 2 equiv of 2,2,6,6tetramethyl-1-piperidinyl-oxy (TEMPO)⁴⁵ was added to the reaction solution under the standard conditions for 18 h (see Scheme 4a). HR-MS analysis showed that a new species at m/z845.30099 was observed (see Figure S64) in addition to the peak at m/z 688.15705 assigned to the dehydrogenative products Λ -[Ir(pq)(L-pqa)] and Λ -[Ir(pq)₂(ala-2H)]. This new peak can be assigned to the trapping products Λ -[Ir(pq)(pq-TEMPO)(L-ala)] or/and Λ -[Ir(pq)₂(L-ala-TEMPO)] according to the calculated isotope pattern for the molecular formula [C₄₂H₄₃IrN₄O₃ + H]⁺ (m/z

Scheme 4. Mechanistic Experiments





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845.30372), indicating that the reaction may proceed through a radical process. We tried to separate the products to assign the exact structure. However, the major product was Λ -[Ir(pq)(L-pqa)] and the amount of the trapping species was too small to measure the NMR spectrum. This may be attributed to the intramolecular radical reaction resulting in C-N formation being faster than the intermolecular reaction. Moreover, a nitrogen-centered radical intermediate on the coordinated AA ligand, namely metal aminyl,⁴⁶ may be involved in C-N bond formation. Thus, 2 equiv of 2,6-ditert-butyl-4-methylphenol (BHT), a nitrogen radical trapping reagent,⁴⁷ was added to the reaction solution under the standard conditions for 18 h. Unfortunately, no trapping product was detected and the C-N coupling product was produced in a yield of 98% (determined by NMR). This may also be related to the quick intramolecular reaction, resulting in suppression of the intermolecular reaction between the nitrogen radical and BHT.

Furthermore, the ratios of the two products that are significantly mediated by temperature also strongly indicate that the imine product may be an intermediate in the reaction. To verify this hypothesis, the imino acid complex Λ -[Ir(pq)₂(ala-2H)] was used as a substrate instead of Λ -[Ir(pq)₂(L-ala)] under the standard reaction conditions (see Scheme 4c). However, no C–N coupling product was detected and the substrate was recovered in almost quantitative yield.⁴⁸ Therefore, imine as an intermediate can be ruled out.

To evaluate the reaction product, 3 equiv of KI was added to the resulting solution in 2 h. The ultraviolet—visible absorption showed the characteristic peaks of the I_3^- anion at 292 and 351 nm became intense (see Figure S65). This indicates the formation of the I_3^- anion, which may be generated by the oxidation of I⁻ into I₂ by H₂O₂.⁴⁹ Because H₂O₂ could be a potential oxidant for the oxidative dehydrogenative reaction, the control experiment was conducted under the optimal conditions. When 3 equiv of H₂O₂ was added to a solution of Λ -[Ir(pq)₂(L-ala)] (see entry 19 in Table 1), no desired product was detected. Thus, H₂O₂ as an oxidant in the reaction would be excluded.

On the basis of the fact that there are two competitive pathways derived from the intermediate, which is mediated by the reaction conditions, such as the effect of temperature and electron on the α -carbon of the AA ligand, and the literature evidence,⁵⁰ a possible photoreaction mechanism for the conversion of Λ -[Ir(pq)₂(L-ala)] into Λ -[Ir(pq)(L-pqa)] and Λ -[Ir(pq)₂(ala-2H)] in the presence of O₂ was proposed, as shown in Scheme 5.⁵¹ The ground state Ir(III) complex is

Scheme 5. Proposed Mechanism



excited into a high-energy excited singlet state ¹[Ir(III)]* under light irradiation, and then the singlet state undergoes intersystem crossing to a long-lived excited triplet state ³[Ir-(III)]* quickly. The excited triplet state exhibits high activity in oxidation and reduction reactions.^{23a} It undergoes a facile disproportionation to [Ir(II)] and [Ir(IV)] that have been widely accepted in the dehydrogenative oxidation of amine and AA complexes.^{27,52} Subsequent electron transfer from [Ir(II)] to O_2 regenerates [Ir(III)] and forms $O_2^{\bullet-}$ ROS.^{23a} The generated $O_2^{\bullet-}$ radical anion undergoes protonation to produce the HOO[•] radical and metal aminyl intermediate (I).^{53,54} This process may be involved in the deprotonation of an amine, followed by intramolecular single-electron transfer from the ligand to the metal center, forming a ligand radical species. Although the N-radical intermediate is highly reactive, it can be stabilized by delocalization of the electron to the coordination metal ion.47 Furthermore, the N-H bond dissociation free energy of AA is decreased by coordination to a metal.⁵⁵ This also facilitates the cleavage of the N-H bond and formation of I. The aminyl radical undergoes a radical electrophilic addition to the quinoline ring, generating a new C-N bond and carbon-centered radical (II) that was indeed trapped by TEMPO. The fact that an electron-deficient group at the C7 position of the quinoline ring is not favored for C-N coupling also supports the electrophilic addition mechanism.⁴⁴ Subsequently, the HOO[•] species abstracts a hydrogen atom from II, affording the C–N coupling product and H_2O_2 as a byproduct. On the contrary, the $O_2^{\bullet-}$ radical anion abstracts a hydrogen from the α -carbon to generate an α -amino radical (III) that was indeed trapped by TEMPO, followed by deprotonation to form the imine (C=N) product and H_2O_2 as described in the literature.⁵⁶ This is also consistent with the

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fact that the electron-withdrawing groups at the α -carbon favor the formation of imino acid products.⁵⁷

Furthermore, DFT calculations were conducted to probe the validity of the proposed mechanism. After light excitation, the reactions are exothermic (see Figure S66). On the C–N coupling pathway, intermediate I attacks the quinoline ring, generating a new C–N bond and carbon-centered radical (II; $\Delta G = -18.7 \text{ kcal/mol}$) via transition state **A**-L-**TS1** ($\Delta G = 3.5 \text{ kcal/mol}$). II reacts with HOO[•] species via transition state **A**-L-**TS2** ($\Delta G = -6.5 \text{ kcal/mol}$), affording the C–N coupling product. On the dehydrogenative oxidation pathway, intermediate III reacts with HOO[•] species to afford an imine (C=N) product. Although the C–N coupling reaction goes through the transition state with an energy barrier of 18.2 kcal/mol, the overall free energy of the C–N coupling pathway is lower than that of the C–N dehydrogenative oxidation by 5.5 kcal/mol, as shown in Scheme 6. Therefore, the C–N

Scheme 6. DFT Free Energy (in kilocalories per mole) Calculation for Two Reaction Pathways at the wB97XD/ def2-TZVP, SMD (EtOH)//wB97XD/def2-SVP Level of Theory



dehydrogenative oxidation is kinetically favored, while the C– N coupling is thermodynamically preferred. This also explains why the C–N coupling pathway is favored at high reaction temperatures.

To elucidate the origin of the diastereoselectivity in the C– N coupling reaction, the two putative transition states Λ -D-TS1 and Λ -L-TS1 that are generated from Λ -[Ir(pq)₂(D-ala)] and Λ -[Ir(pq)₂(L-ala)] diastereomers, respectively, are proposed according to the reaction mechanism in Scheme 6. DFT calculations showed that the Λ -L-TS1 configuration is favored by 2.3 kcal/mol. In Λ -D-TS1, the methyl group of ala points to the quinoline ring, which causes the repulsive interaction. On the contrary, there is no such repulsion in Λ -L-TS1. Therefore, the energy barrier to undergo an electrophilic addition, producing the C–N coupling product, should be lower. This may be the reason why no C–N coupling reaction took place in the Λ -[Ir(pq)₂(D-ala)] diastereomer (Figure 3).

CONCLUSIONS

In conclusion, we have found the photoreactions of Ir(III) AA complexes are diastereoselective in the presence of O_2 , where



Figure 3. Free energy calculation for transition state models of the C–N coupling of Λ -[Ir(pq)₂(D-ala)] (left) and Λ -[Ir(pq)₂(L-ala)] (right) at the wB97XD/def2-TZVP, SMD (EtOH)//wB97XD/def2-SVP level of theory.

the Λ -D or Δ -L diastereomer is dehydrogenatively oxidized into the imino acid complex, while the Λ -L or Δ -D diastereomer mainly participates in intramolecular C-N coupling at C8 of the quinoline ring at room temperature. It is quite remarkable that the photoreaction of the Λ -L or Δ -D diastereomer is temperature-dependent. Our results demonstrate that the reaction is compatible with various amine groups, such as chiral and achiral AAs and primary and secondary amines. This is the first example of amination of quinoline at the C8 position using commercially available primary and secondary amines as a nitrogen source. Furthermore, the configurations at metal and carbon centers remain during the C-N coupling reaction. Mechanistic studies reveal ligand-radical intermediates may be involved in the reaction. This will provide a new and complementary approach for amination of quinoline at the C8 position via the postcoordinated interligand C-N coupling reaction under mild conditions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.0c03026.

Experimental procedures, characterization of the compounds, and DFT calculations (PDF)

Accession Codes

CCDC 2019904–2019908 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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