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Visible-Light-Promoted Iminyl-Radical Formation from Acyl Oximes: A Unified Approach to Pyridines, Quinolines, and Phenanthridines**

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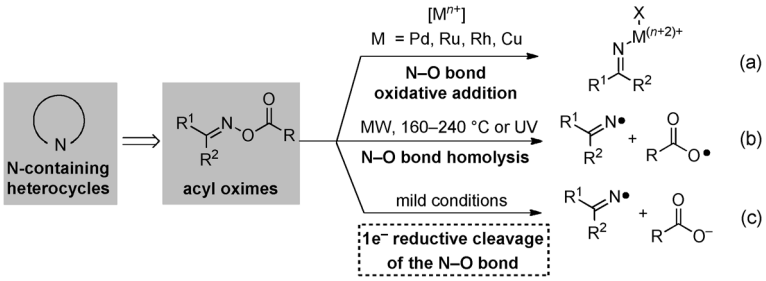
Abstract: *A unified strategy involving visible-light-induced iminyl-radical formation has been established for the construction of pyridines, quinolines, and phenanthridines from acyl oximes. With fac-[Ir(ppy)$_3$] as a photoredox catalyst, the acyl oximes were converted by 1 e$^-$ reduction into iminyl radical intermediates, which then underwent intramolecular homolytic aromatic substitution (HAS) to give the N-containing arenes. These reactions proceeded with a broad range of substrates at room temperature in high yield. This strategy of visible-light-induced iminyl-radical formation was successfully applied to a five-step concise synthesis of benzo[c]-phenanthridine alkaloids.*



Scheme 1. N–O cleavage of acyl oximes to form N-containing heterocycles. MW = microwave radiation.

Acyl oximes are versatile building blocks for the synthesis of structurally diverse and biologically active N heterocycles through N–O bond cleavage and C–N bond formation.[1] During the past few years, transition-metal catalysis has been demonstrated as a powerful tool for breaking the N–O bond of acyl oximes through oxidative addition of the metal to the N–O bond and the subsequent formation of various multisubstituted heterocycles, such as pyridines, indoles, isoquinolines, and imidazoles (Scheme 1 a).[2] Another pathway for cleavage of the N–O bond is homolysis under microwave (> 160 °C) or UV irradiation. This method has been employed to produce several heterocycles by radical cyclization of iminyl-radical intermediates (Scheme 1 b).[3] Furthermore, the N–O bond of acyl oximes can also be cleaved to give iminyl radicals, as well as acyloxy anions, through single-electron reduction with the assistance of an oxidant owing to the weak bond energy and electronic properties of the N–O bond (Scheme 1 c).[1] Although iminyl radicals were considered to be formed by a Cu^I/Cu^{II} 1 e$^-$ transfer mechanism from acyl oximes in several copper-catalyzed reactions,[2g,4] the oxidative addition of Cu^I to N–O bonds through a Cu^I/Cu^{III} cycle is an inevitable competitive pathway, especially at high temperature.[5] Therefore, efficient methods for the exclusive 1 e$^-$ reduction of acyl oximes under mild (ideally at room temperature) and catalytic conditions are still in high demand owing to the potential application of iminyl-radical intermediates in the construction of N-containing heterocycles.

The renaissance of visible-light photoredox catalysis has been witnessed since 2008.[6] By taking advantage of the 1 e$^-$ redox potential of a photoexcited catalyst, this environmentally friendly and sustainable synthetic technology can promote versatile organic transformations, including the construction of arenes and heteroarenes.[7,8] Recently, we reported a visible-light-promoted direct C–H bond amination of heteroarenes with hydroxylamine derivatives (Scheme 2 a).[9a] The key step in this transformation is the formation of amidyl radicals from hydroxylamine derivatives through 1 e$^-$ reductive cleavage of the N(sp^3)–O bond.[10] Meanwhile, the research groups of Sanford,[9b] Lee,[9c] Luo,[9d] and König[9e] also reported visible-light-induced C–H bond amination reactions of arenes and heteroarenes with different amidyl-radical precursors. This newly exploited strategy of N(sp^3)–O bond cleavage inspired us to consider the feasibility of visible-light-induced N(sp^2)–O bond cleavage and iminyl-radical formation. Accordingly, we speculated that the iminyl radical could be generated by the 1 e$^-$ reduction of acyl oximes by photoredox catalysis and could be further converted into a class of ubiquitous azaarenes, including pyridines,[11] quinolines,[12] and phenanthridines.[13]

According to the rationale outlined in Scheme 2 b, the catalytic cycle begins with the visible-light-promoted photoexcitation of a photocatalyst PC to its excited state (PC*). Reductive cleavage of an acyl oxime **I**, as assisted by PC*, produces an iminyl radical **II**, an acyl anion **V**, and the

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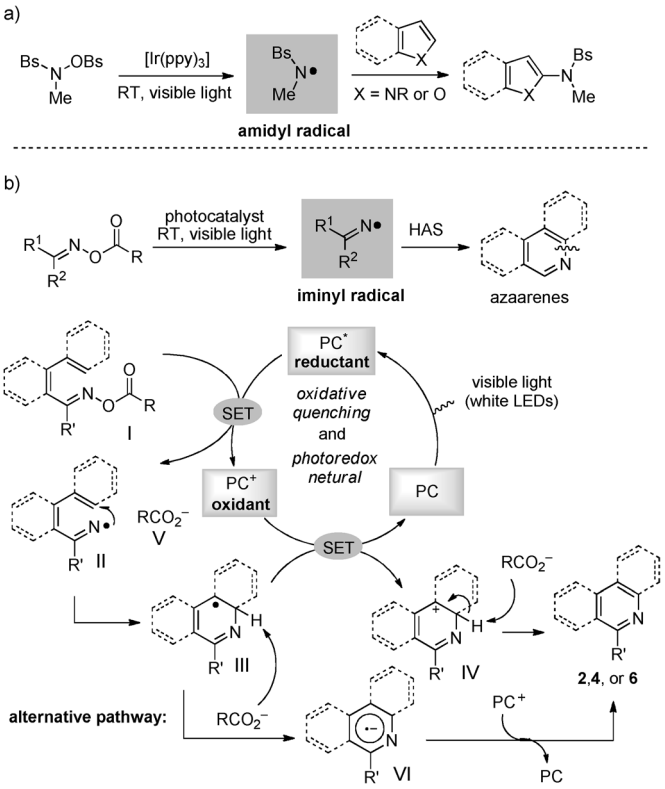
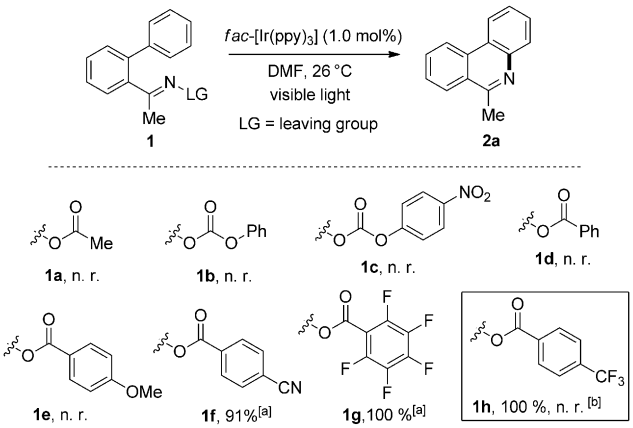


Scheme 2. Rationale for the synthesis of six-membered azaarenes. a) Previously reported visible-light-promoted C–H amination via amidyl radicals (Bs = benzenesulfonyl). b) Visible-light-promoted synthesis of azarenes via iminyl radicals (present study).



Scheme 3. Screening of acyl oxime substrates. Reaction conditions: A mixture of **1** (0.1 mmol) and *fac*-[Ir(ppy)$_3$] (0.001 mmol, 1.0 mol%) in dry DMF (2.0 mL) was irradiated by 5 W white light-emitting diodes (LEDs) for 10 h. Yields were determined by ^{1}H NMR spectroscopic analysis. [a] The reaction time was prolonged to 24 h. [b] Result observed (no reaction) without a photocatalyst or irradiation with visible light. n. r. = no reaction. DMF = *N*,*N*-dimethylformamide.

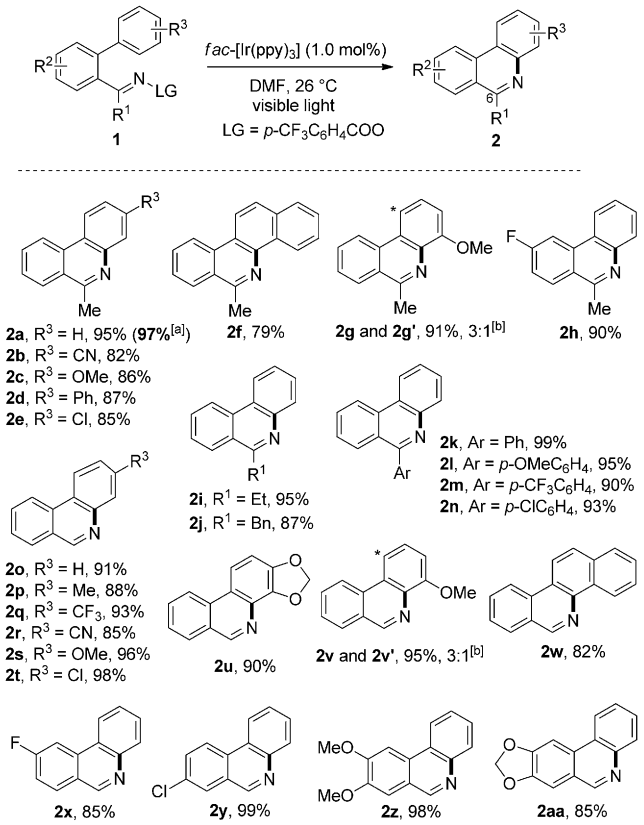
oxidized photocatalyst (PC^+). Radical **II** undergoes intramolecular homolytic aromatic substitution (HAS)[14] to form a radical intermediate **III**, which is then oxidized by PC^+ to forge a cationic intermediate **IV** and regenerate the photocatalyst. Ultimately, deprotonation of **IV** by the acyl anion **V** yields a six-membered heteroarene. Alternatively, **III** can also lose a proton to form a radical-anion intermediate **VI**,[13e,14] which is then oxidized by PC^+ to give a heteroarene and regenerate the photocatalyst.

We chose *fac*-[Ir(ppy)$_3$] (ppy = 2-phenylpyridine) as the photocatalyst owing to its superior reduction capacity in the excited state ($E_{1/2}^{IV/*III} = -1.73$ V vs. SCE).[15] A series of *O*-acyl oximes **1a–h** with different acyl groups were prepared, and their ability to form phenanthrine **2a** via an iminyl radical under visible-light catalysis was evaluated (Scheme 3). When *O*-acyl oximes **1a–e** were irradiated with visible light in the presence of *fac*-[Ir(ppy)$_3$] in DMF, the starting materials were fully recovered. To our delight, we observed the formation of phenanthridine **2a** in 91% yield (as determined by NMR spectroscopy) when the electron-deficient benzoate **1f** was employed. Further exploration showed that the perfluorobenzoate **1g** and *p*-trifluoromethylbenzoate **1h** were superior to **1f** and could be converted into **2a** quantitatively (see the Supporting Information for details of further optimization of the reaction conditions). The cyclic voltammogram recorded for **1h** contained an irreversible reduction wave at −0.79 V vs. SCE, thus indicating that **1h** is readily reduced by the excited-state photocatalyst *fac*-[Ir(ppy)$_3$]*. No conversion of **1h** was observed without the photocatalyst or visible-light irradiation, which further demonstrates the rationality of the proposed visible-light-induced single-electron-transfer (SET) mechanism.

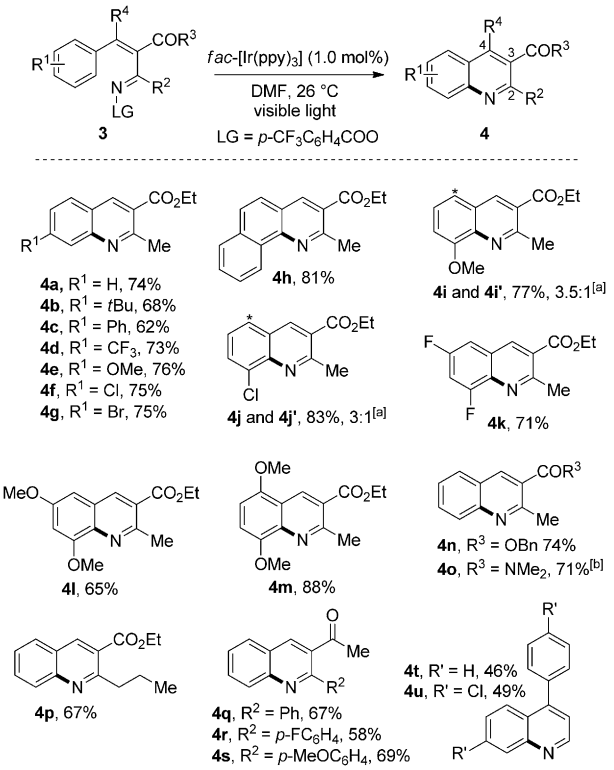
Under the optimized conditions, we first tested the transformation of a variety of biphenyl acyl oximes **1** to assess the scope of the reaction for the formation of phenanthridines **2** (Scheme 4). Generally, the desired phenanthridine derivative was isolated in high to excellent yield (79–95%) irrespective of the position and electric nature of substituents on the biphenyl moiety (products **2a–h**). The substituent at C6 could be varied to give 6-alkyl and 6-aryl phenanthridines **2i–n** in excellent yield (87–99%). Phenanthridines **2n–2aa** without a substituent at the 6-position could also be produced by means of this method with high functional-group tolerance and in high yield (82–99%). We carried out the reaction on a gram scale (3.0 mmol) to demonstrate the practicability of this methodology, and isolated **2a** in similarly high yield (97%).

We next sought to examine the applicability of this strategy to other important functionalized azaarenes. Various acyl oximes **3a–s** were prepared from benzaldehyde derivatives and 1,3-dicarbonyl compounds to evaluate the possibility of constructing quinoline derivatives **4**. As shown in Scheme 5, electron-withdrawing or electron-donating groups, as well as halides or a fused ring on the phenyl moiety, did not affect this reaction significantly (products **4a–m**, 62–88% yield). The substituent at the C3 position could be an ester (product **4n**), amide (product **4o**), or keto group (products **4q–s**). Products **4p–s** were obtained in satisfactory yield when the substituent at C2 was a propyl or phenyl group. C4-substituted quinolines **4t** and **4u** were also synthesized in moderate yield.

Polysubstituted pyridines, which are ubiquitous in pharmaceuticals and natural products, could also be accessed by



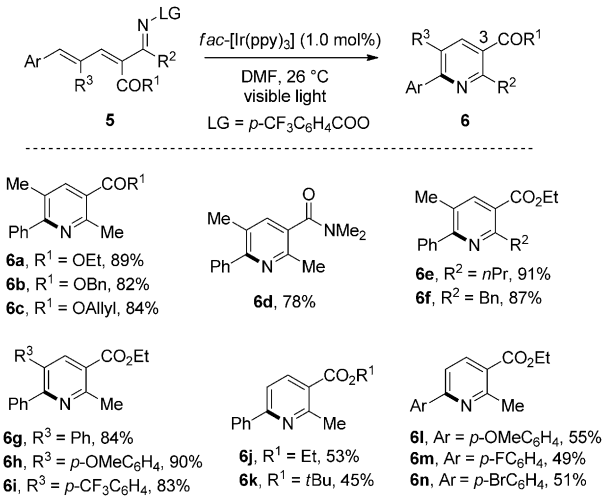
Scheme 4. Scope of the transformation of acyl oximes into phenanthridines. Reaction conditions: A mixture of **1** (0.2 mmol) and *fac*-[Ir(ppy)$_3$] (0.002 mmol, 1.0 mol%) in dry DMF (4.0 mL) was irradiated by 5 W white LEDs for 10 h. Yields are for the isolated product. [a] The reaction was carried out on a 3.0 mmol scale. [b] The major diastereoisomer is shown, and the asterisk indicates the position of the C–N bond to this ring in the minor regioisomer. Bn = benzyl.



Scheme 5. Scope of the transformation of acyl oximes into quinolines. Reaction conditions: A mixture of **3** (0.2 mmol) and *fac*-[Ir(ppy)$_3$] (0.002 mmol, 1.0 mol%) in dry DMF (4.0 mL) was irradiated by 5 W white LEDs for 10 h. Yields are for the isolated product. [a] The asterisk indicates the position of the C–N bond to this ring in the minor regioisomer. [b] The yield was obtained from the *2Z* configuration of **3**.

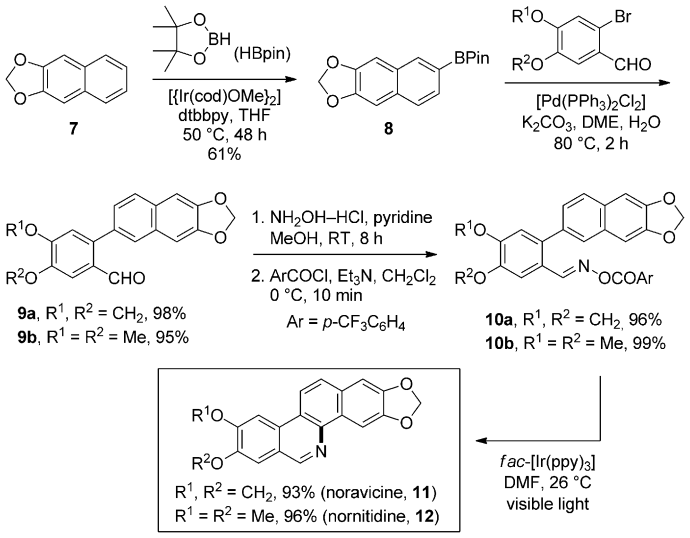
this strategy from acyl oximes **5** (Scheme 6). The substituent at the 3-position of **5** could be an ester (products **6a–c**) or an amide group (product **6d**), and the products were isolated in good yield (78–89%). Products **6e** and **6f** with R^2 as an *n*-propyl or a benzyl group were obtained in 91 and 87% yield, respectively. R^3 could also be an aryl group instead of an alkyl group. Thus, tetrasubstituted pyridines **6g–i** were obtained in 83–90% yield. Trisubstituted pyridines **6j–n** with different functionalities could also be synthesized in moderate yield (45–55%).[16]

Having established this strategy for generating phenanthridines, quinolines, and pyridines, we next sought to demonstrate the utility of this method in rapid total syntheses of the benzo[*c*]phenanthridine alkaloids noravicine (**11**) and nornitidine (**12**), which show a wide range of pharmacological properties, in particular, antitumor activity (Scheme 7).[17] Previously reported routes to **11** and **12** required 11 steps and provided the products in about 20% overall yield.[18] Our strategy began with the iridium-catalyzed C–H borylation of **7**,[19] followed by Suzuki coupling, to give biphenyl aldehydes **9a** and **9b**. The treatment of **9a** with hydroxylamine hydrochloride and then acylation with *p*-trifluoromethylbenzoyl chloride provided acyl oxime **10a** in near-quantitative



Scheme 6. Scope of the transformation of acyl oximes into pyridines. Reaction conditions: A mixture of **5** (0.2 mmol) and *fac*-[Ir(ppy)$_3$] (0.002 mmol, 1.0 mol%) in dry DMF (4.0 mL) was irradiated by 5 W white LEDs for 10 h. Yields are for the isolated product.

yield. Ultimately, the alkaloid noravicine (**11**) was completed in 93% yield by the cyclization of **10a** under our established conditions. Similarly, nornitidine (**12**) was synthesized from **9b** in 90% overall yield for three steps.



Scheme 7. Synthesis of benzo[*c*]phenanthridine alkaloids. cod = 1,5-cyclooctadiene, DME = dimethoxyethane, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

In summary, we have described the visible-light-promoted formation of iminyl radicals from acyl oximes. This transformation was utilized to construct a range of heteroarenes with N-containing six-membered rings, including pyridines, quinolines, and phenanthridines. These sophisticated N-containing heterocycles were constructed in satisfactory to excellent yields from a broad range of substrates simply by irradiation with visible light in the presence of 1.0 mol% of a photocatalyst at room temperature. Moreover, five-step rapid and highly efficient total syntheses of the biologically active alkaloids noravicine and nornitidine were accomplished by using this strategy as the key step. We expect this powerful protocol to be of broad utility in the synthesis of biologically important N-containing heterocycles, including natural products.

Keywords: acyl oximes · N heteroarenes · iminyl radicals · photochemistry · visible light

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