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Iron/Photosensitizer Hybrid System Enables the Synthesis of Polyaryl-Substituted Azafluoranthenes

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ABSTRACT: Photosensitization of organometallics is a privileged strategy that enables challenging transformations in transition metal catalysis. However, the usefulness of such photocatalyst-induced energy transfer has remained opaque in iron-catalyzed reactions despite the intriguing prospects of iron catalysis in synthetic chemistry. Herein, we demonstrate the use of iron/photosensitizer-cocatalyzed cycloaddition to synthesize polyarylpyridines and azafluoranthenes, which have been scarcely accessible using the established iron-catalyzed protocols. Mechanistic studies indicate that triplet energy transfer from the photocatalyst to a ferracyclic intermediate facilitates the thermally demanding nitrile insertion and accounts for the distinct reactivity of the hybrid system. This study thus provides the first demonstration of the role of photosensitization in overcoming the limitations of iron catalysis.

INTRODUCTION

Photochemistry plays indispensable roles in molecular sciences, as it enables reactions that are not feasible using the reactants in their ground state.¹ While direct photoexcitation is a straightforward approach to access excited states, its efficiency depends on the various absorption spectra of the compounds, which occasionally leads to limited generality in synthetic applications. On the other hand, photosensitization using photocatalysts provides a more general strategy to achieve excited state reactivities.² In this regard, the photosensitization of organometallic intermediates in a catalytic cycle has recently been recognized as a privileged strategy for the development of new reactions (**Figure 1A**, top). Nevertheless, successful merger of the transition metal catalysis and photosensitizer-induced energy transfer (EnT) has so far been limited to reactions via organonickel,³ organopalladium,⁴ or organogold⁵ intermediates, and application of the photosensitization strategy to other transition metal catalysis remains elusive.^{6,7}

In this context, the photosensitization of organoiron species deserves particular attention, considering the sustainability and unique reactivity of iron catalysts.⁸ However, few such attempts have been reported in synthetic chemistry, despite the well-known roles of organoiron compounds in catalytic bond-forming reactions (**Figure 1A**, bottom). Notably, Chakraborty and Jacobi von Wangelin reported an iron/9,10-diphenylanthracene(DPA)-cocatalyzed trimerization of alkynes in which dissociation of the iron catalyst and the product is promoted by photosensitization (**Figure 1B**).⁹ Nonetheless, the substrate scope of this reaction does not exceed the scope of thermal iron catalysis,¹⁰ and the unique synthetic advantages of combining iron catalysis and photocatalysis have yet to be elucidated.¹¹

Transition-metal-catalyzed [2+2+2] cycloaddition of diynes and nitriles, by which pyridines are constructed in one step, is

an atom-economical method to access natural products and π -extended molecules.¹² In thermal systems, iron-catalyzed [2+2+2] cycloaddition has been achieved using low-valent iron complexes¹³ or iron/additive systems in which low-valent iron species are generated *in situ*.^{10,14} However, applicable diynes have been limited to alkyl-substituted ones, and there are no reports using aryl-substituted diynes to enable the synthesis of polyarylpyridines, which are common motifs in functional molecules (**Figure 1C**). As a result of our effort to overcome the limitations of iron catalysis using photosensitization, herein we report an iron/photosensitizer-cocatalyzed [2+2+2] cycloaddition using aryl-substituted diynes and nitriles, which enables the chemoselective synthesis of polyarylpyridines (**Figure 1D**). In addition, modular synthesis of polyaryl-substituted azafluoranthenes, which are promising scaffolds for organic electro-luminescence materials, was also realized. Mechanistic experiments, DFT, and SAC-CI calculations suggest that energy transfer from the photosensitizer to an organoiron intermediate is likely to be responsible for the distinct reactivity of the developed catalytic system.

RESULTS AND DISCUSSION

Studies of reaction conditions and substrate scope. After several trials, iron-catalyzed [2+2+2] cycloaddition of aryl-substituted diyne **1a** with benzonitrile **2a** proceeded in high yield in the presence of FeI₂ (99.99% metals basis), dppp, [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ and triethylamine (an electron donor for generating a low-valent iron catalyst *in situ*) under blue LED irradiation (Table 1, entry 1). The high purity of FeI₂ indicates that the effect of the contamination of other transition metals is negligible. When FeBr₂ (entry 2) and FeCl₂ (entry 3) were used instead of FeI₂, the yields decreased in the order FeI₂ > FeBr₂ > FeCl₂. Fe(OAc)₂, Fe(acac)₂ and Fe(BF₄)_nH₂O (entries 4–6) did not afford the desired product **4aa**, suggesting that halide is crucial for this reaction to proceed.¹⁵ Evaluation of other ligands revealed that dppp is specifically suitable for

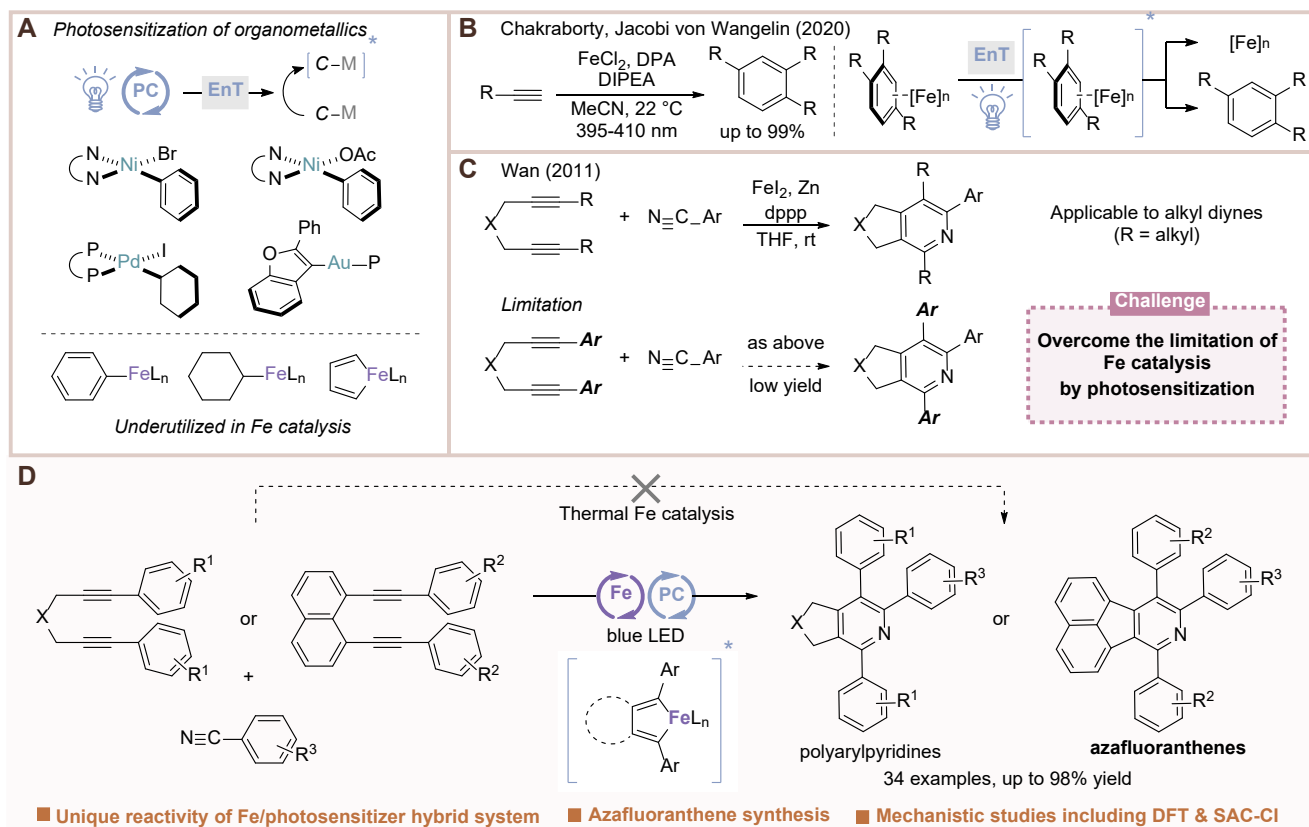
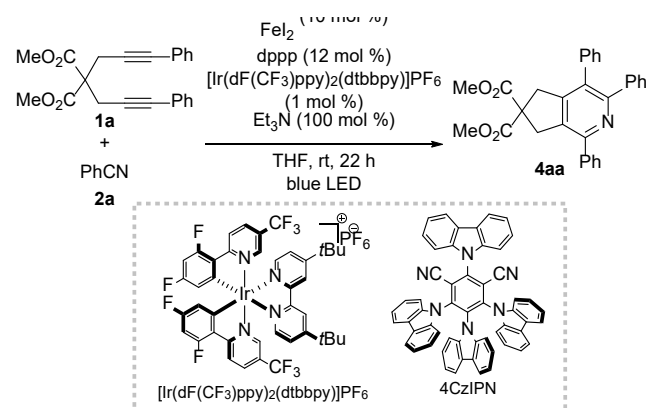


Figure 1. (A) Photosensitization as an enabling strategy in transition metal catalysis. (B) Iron/photoredox catalysis for the trimerization of alkynes. (C) Iron-catalyzed [2+2+2] cycloaddition using diynes and nitriles under thermal conditions. (D) This work: Synthesis of polyarylpiperidines and azafluoranthenes using an iron/photoredox hybrid system.

Table 1. Evaluation of reaction conditions for [2+2+2] cycloaddition under the iron/photoredox hybrid system.^a



Entry	Variation from above	Yield ^b (%)
1	none	85 ^c
2	FeBr ₂ instead of FeI ₂	57
3	FeCl ₂ instead of FeI ₂	26
4	Fe(OAc) ₂ instead of FeI ₂	0
5	Fe(acac) ₂ instead of FeI ₂	0
6	Fe(BF ₄) ₂ ·nH ₂ O instead of FeI ₂	0
7	dppe instead of dppp	16
8	dppb instead of dppp	0

9	dppbz instead of dppp	9
10	<i>cis</i> -dppen instead of dppp	60
11	PPh ₃ (12 mol%) instead of dppp	0
12	1,10-phenanthroline instead of dppp	9
13	dtbbpy instead of dppp	0
14	4CzIPN instead of [Ir(dF(CF ₃)ppy) ₂ (dtbbpy)]PF ₆	86 ^c
15	without [Ir(dF(CF ₃)ppy) ₂ (dtbbpy)]PF ₆	0

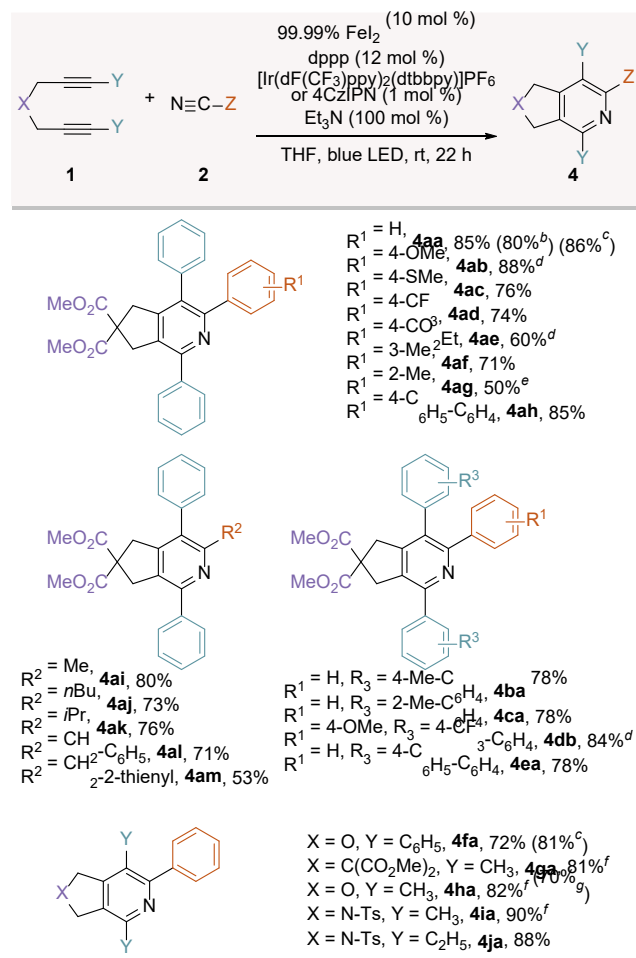
^aReaction conditions: **1a** (0.10 mmol), **2a** (0.50 mmol), FeI₂ (99.99% metals basis, 10 μmol, 10 mol%), dppp (12 μmol, 12 mol%), photocatalyst (1.0 μmol, 1 mol%), Et₃N (0.10 mmol, 100 mol%) in THF (0.5 mL) at room temperature for 22 hours under blue LED irradiation. ^b¹H NMR yield. ^cIsolated yield. For details, see Supporting Information.

this reaction, while *cis*-dppen manifested certain reactivity (entries 7–13). The origin of the beneficial effect of dppp is unclear, but it is occasionally identified to be suitable for reactions catalyzed by low-valent first-row metals.¹⁶ When 4CzIPN was used instead of [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆, the reaction proceeded smoothly (entry 14), suggesting that the iron/photoredox hybrid catalysis is also operative under noble-metal-free conditions. The desired product was not obtained in the absence of the photocatalyst (entry 15).

The scope of the iron/photoredox-catalyzed cycloaddition in terms of diynes **1** and nitriles **2** is summarized in **Scheme 1**. Nitriles possessing various aromatic rings or alkyl groups underwent the desired cycloaddition (**4aa–4am**). It is noteworthy that synthesis of **4aa** can be performed on a 1 gram

scale in 80% yield. The cycloaddition of various aryl-substituted diynes **1** also proceeded smoothly (**4ba**, **4ca**, **4db**, **4ea**). Different tethers and alkyl substituents were tolerated in the pyridine synthesis (**4fa–4ja**). The amount of the iron catalyst could be decreased to 5 mol% and the amount of nitrile to 2.5 equivalents when methyl-substituted diynes were used (**4ga–4ia**). The catalyst loading of iron could be decreased to 1 mol% and photocatalyst to 0.1 mol% by modifying the reaction conditions (**4ha**).

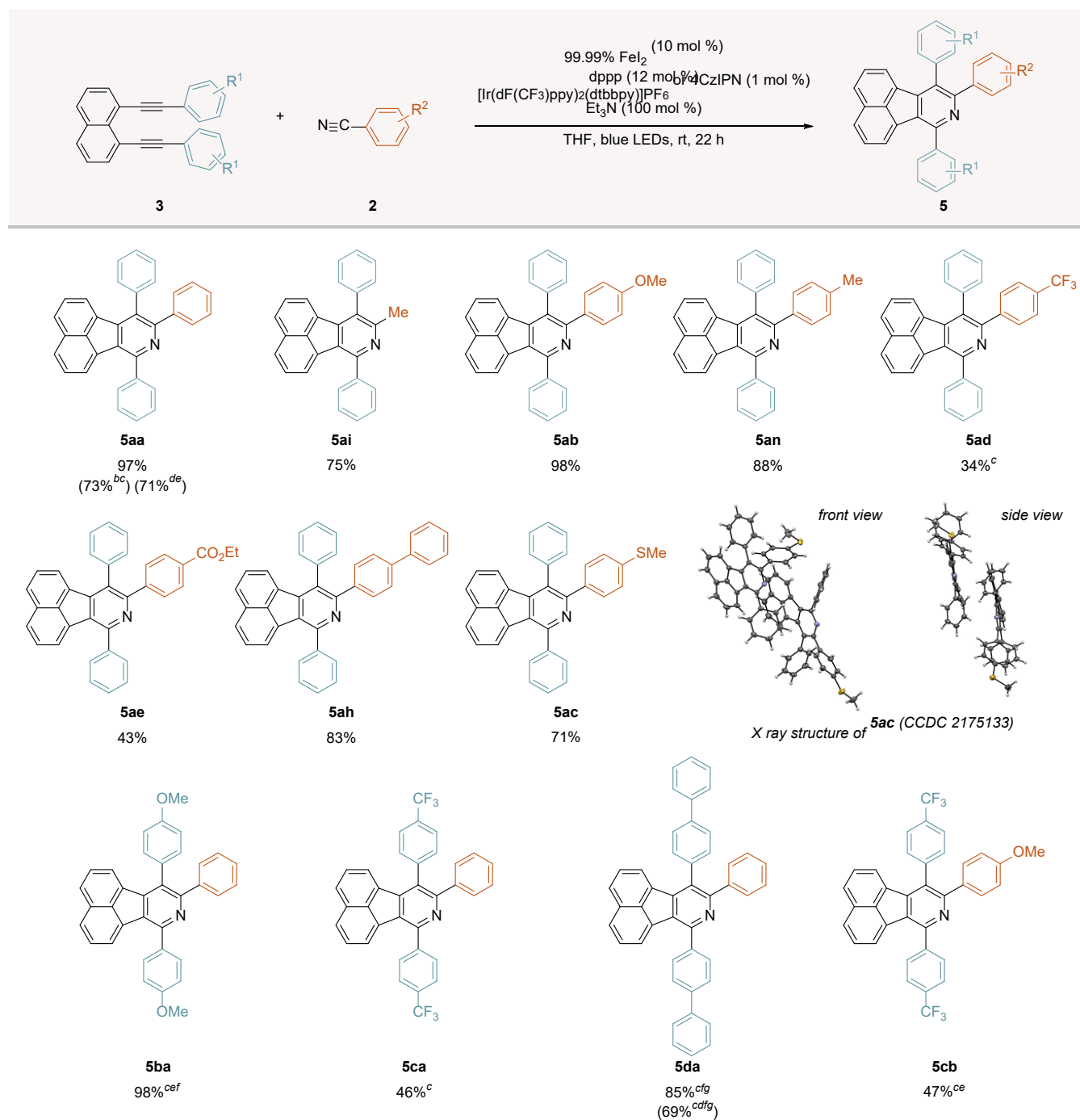
Scheme 1. Substrate scope of polyaryl-substituted pyridines^a



^aReaction conditions: **1** (0.30 mmol), **2** (1.5 mmol), FeI₂ (99.99%, trace metal basis, 30 μmol, 10 mol%), dppp (36 μmol, 12 mol%), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (3.0 μmol, 1.0 mol%), Et₃N (0.30 mmol, 100 mol%), THF (1.5 mL) at room temperature for 22 hours under blue LED irradiation. Isolated yields. ^bUsing **1a** (1.0 g, 2.8 mmol) and blue LED panel × 2 (see Supporting Information for the detailed reaction setup) under temperature control for 72 hours. ^c4CzIPN (1.0 mol%) was used instead of [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆. ^d**2** (2.4 mmol). ^e**2** (3.0 mmol). ^fFeI₂ (15 μmol, 5.0 mol%), dppp (18 μmol, 6.0 mol%), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (1.5 μmol, 0.50 mol%), **2** (0.75 mmol). ^gFeI₂ (3.0 μmol, 1.0 mol%), dppp (3.6 μmol, 1.2 mol%), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (0.30 μmol, 0.10 mol%), Et₃N (0.15 mmol, 50 mol%), **2** (0.75 mmol), THF (300 μL).

Azafluoranthenes, an azaheterocycle possessing a 6/6/5/6-fused 16π-antiaromatic system, represent an actively studied structural motif in electroluminescent materials.¹⁷ However, the known preparative methods for azafluoranthenes suffer from high temperature requirements (250–300 °C),^{17a} limited generality^{17b,17c} or the use of isonitriles.^{17d} Gratifyingly, by applying the iron/photosensitizer hybrid system to the [2+2+2] cycloaddition of diyne **3** and nitrile **2**, a variety of polyaryl-substituted azafluoranthenes were prepared in a modular manner (Scheme 2). The cycloaddition of 1,8-bis(phenylethynyl)naphthalene **3a** and **2a** afforded the corresponding azafluoranthene nearly quantitatively (**5aa**, 97%). In addition, **5aa** can be obtained in 73% yield on a 1.0 mmol scale. The cycloaddition also proceeded in synthetically useful yield under noble-metal-free conditions using 4CzIPN as the organic photosensitizer (**5aa**, 71%). Other nitriles provided the desired products in 34–98% yield (**5aa–5ae**, **5an**, **5ah**, **5ai**). The structure of azafluoranthene **5ac** was unambiguously confirmed via single-crystal X-ray diffraction analysis. Diynes with different electronic character afforded the desired products in 46–98% yield (**5ba**, **5ca**, **5cb**, **5da**).^{18,19} In addition, **5da** was also obtained using iron/4CzIPN hybrid system in 69% yield.^{20,21}

Scheme 2. Substrate scope of polyaryl-substituted azafluoranthenes^a



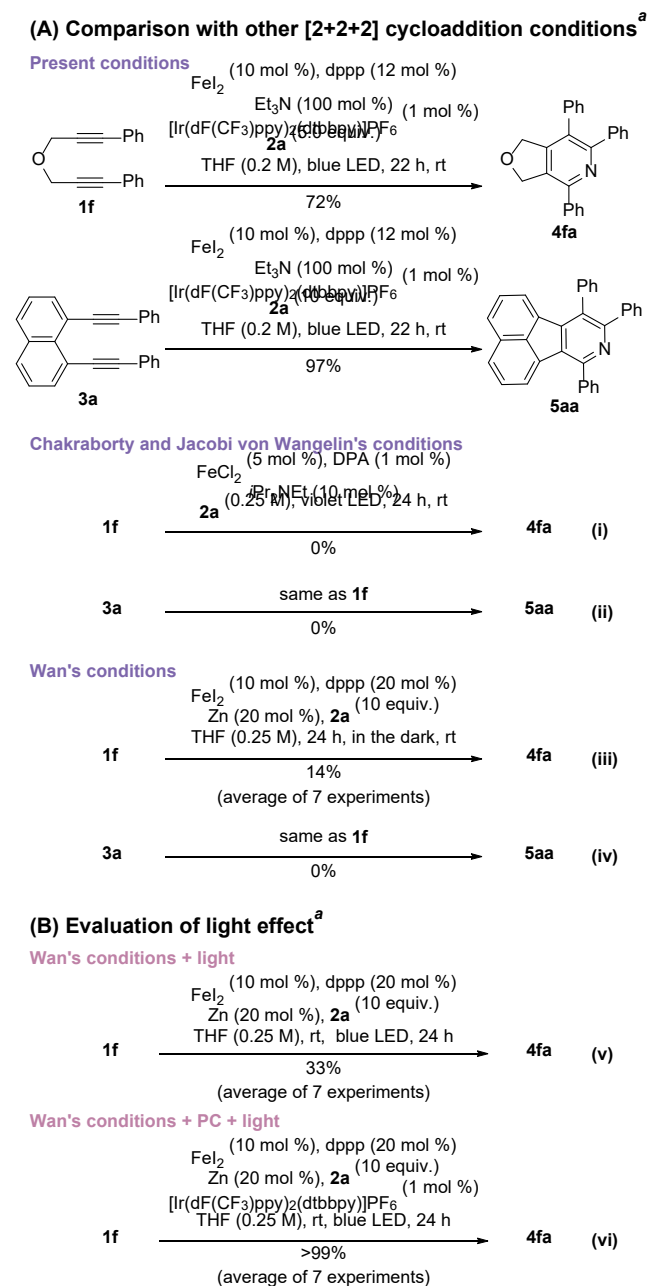
^aReaction conditions: **3** (0.30 mmol), **2** (3.0 mmol), FeI₂ (99.99%, trace metal basis, 30 μmol, 10 mol%), dppp (36 μmol, 12 mol%), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (3.0 μmol, 1.0 mol%), Et₃N (0.30 mmol, 100 mol%), THF (1.5 mL) at room temperature for 22 hours under blue LED irradiation. Isolated yields. ^bUsing **3a** (1.0 mmol) for 72 hours. ^cBlue LED panel × 2 (see Supporting Information for the detailed reaction setup) under temperature control. ^d4CzIPN was used instead of [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆. ^e0.20 mmol scale. ^f0.05 M. ^g0.10 mmol scale.

Comparison with thermal iron catalysis. The difference between the developed method and the previous iron-catalyzed [2+2+2] cycloaddition is summarized in **Scheme 3**. When **1f** and **3a** were subjected to Chakraborty and Jacobi von Wangelin's conditions,⁹ the corresponding pyridine was not observed (**Scheme 3A, (i)(ii)**). Under Wan's conditions,^{14a} the yield of pyridine was very low when **1f** or **3a** was used (**Scheme 3A, (iii)(iv)**). These results suggest that our iron/photosensitizer

hybrid catalysis is uniquely suitable for polyarylpyridine synthesis compared to known iron catalysis.

Mechanistic studies. To gain insight into the unique reactivity of this reaction system, we performed two experiments: (1) light irradiation to Wan's conditions and (2) light irradiation to Wan's conditions in the presence of the photocatalyst (**Scheme 3B**). In case (1), the yield of **4fa** increased slightly (**Scheme 3B, (v)**, 33%) compared to that

Scheme 3. Comparison experiments with other conditions and evaluation of the light effect.



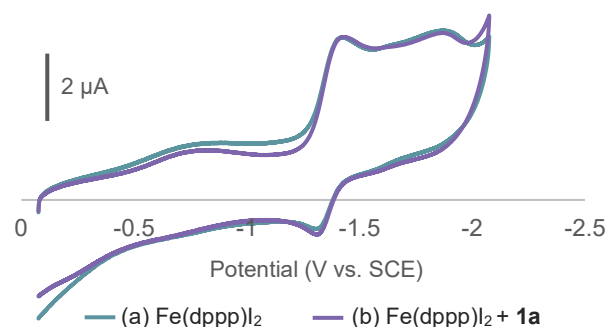
^aSee Supporting Information for details.

under the original conditions (Scheme 3A, (iii), 14%),^{22,23} suggesting an inefficient yet certain acceleration of the cycloaddition via the direct photoexcitation of an iron complex²⁴ generated *in situ*. In case (2), the reactivity increased dramatically, and 4fa was obtained in >99% yield (Scheme 3B, (vi)). These results indicate that photoinduced energy transfer to a catalytic intermediate, rather than photoredox-induced electron transfer, is more likely to be responsible for accelerating the challenging cycloaddition toward polyarylpiperidines.

To get insight of the catalytically active iron species, we conducted the cyclic voltammetry studies (Figure 2). The mixture of FeI_2 and dppp (molar ratio = 1:1.05) shows the Fe-centered reduction at -1.371 V vs. SCE ($\text{Fe}^{\text{II}}/\text{Fe}^{\text{I}}$) and at -1.869

V ($\text{Fe}^{\text{I}}/\text{Fe}^0$) (Figure 2, a). When the mixture of FeI_2 , dppp and diene 1a (molar ratio = 1:1.05:10) were subjected to analysis, the Fe-centered reduction at -1.365 V ($\text{Fe}^{\text{II}}/\text{Fe}^{\text{I}}$) and -1.877 V ($\text{Fe}^{\text{I}}/\text{Fe}^0$) were observed (Figure 2, b). These results and the reduction potential of $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ ($E_{\text{red}}(\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}) = -1.37$ V vs. SCE) suggest that the catalytically active iron species is likely to be Fe^{I} and the reduction potential of iron was not affected in the presence of the diene.

Figure 2. Cyclic voltammogram of $\text{Fe}(\text{dppp})\text{I}_2$ in the absence or presence of 1a.^a

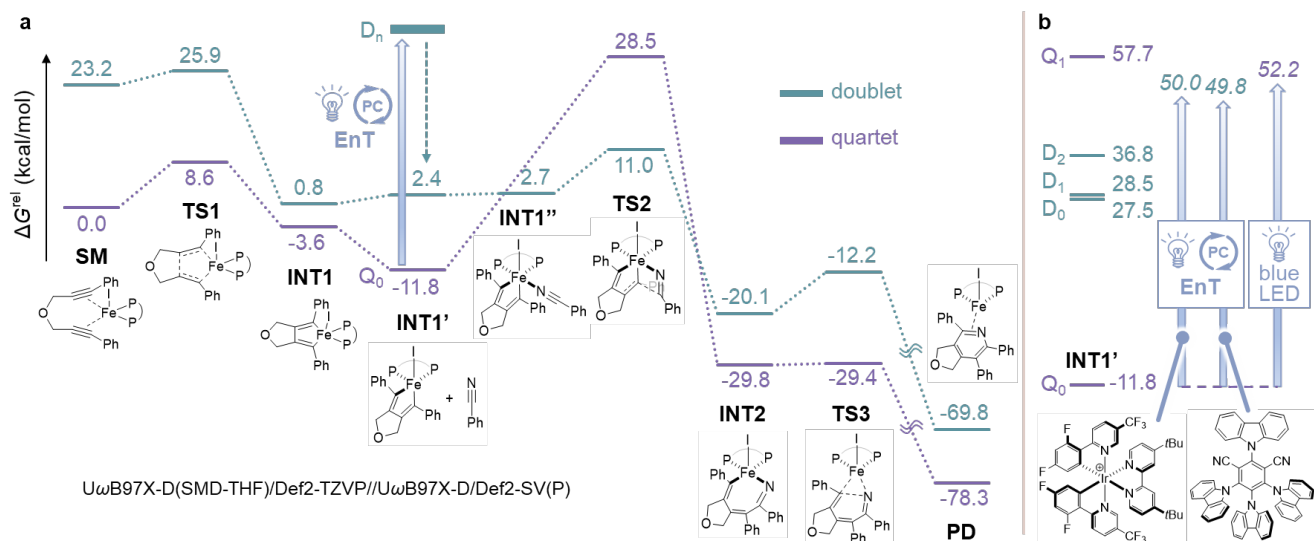


^aSee Supporting Information for details.

Next, we performed DFT calculations and obtained the energy diagrams of the iron-catalyzed [2+2+2] cycloaddition (Scheme 4a).²⁵ Based on the indispensability of halide anions (Table 1), propensity of dppp to form a 1:1 adduct with $\text{Fe}(\text{II})$ halide in the presence of THF,²⁶ and the results of the electrochemical study (Figure 2), the iodide-ligated $\text{Fe}(\text{I})$ diphenylphosphinopropane complex, which should be readily generated *in situ* by reduction of $\text{Fe}(\text{dppp})\text{I}_2$, was employed as the catalyst in the theoretical study. In both the doublet and quartet states, the insertion of nitrile into the five-membered ferracycle intermediate was identified as the turnover-limiting step. The energy barrier of the insertion in quartet state was too high (quartet $\text{INT1}'$ to quartet TS2 : 40.3 kcal/mol) for the reaction to proceed at room temperature. In case spin crossover occurs at this step, the energy barrier is still high (quartet $\text{INT1}'$ to doublet TS2 : 22.8 kcal/mol), which is consistent with the experimental result that only 14% of 4fa was obtained under thermal conditions. We surmise that the photoexcitation of the quartet $\text{INT1}'$ accounts for the distinct reactivity of the iron/photosensitizer hybrid system. In the presence of the photocatalyst, energy transfer from the excited photocatalyst to quartet $\text{INT1}'$ brings the organoiron intermediate into its doublet excited state D_n . Then, spin-allowed decay of D_n to doublet $\text{INT1}'$ allows the nitrile insertion to proceed through the doublet energy surface (doublet $\text{INT1}'$ to doublet TS2 : 8.6 kcal/mol).

The validity of this mechanistic hypothesis was more accurately elucidated by the SAC-CI method²⁷ (Scheme 4b). The excited states of the quartet $\text{INT1}'$ (Q_0) were calculated, and three doublet excited states (D_0 , D_1 , D_2) and one quartet excited state (Q_1) were identified. The three doublet excited states were respectively at 27.5, 28.5, and 36.8 kcal/mol with respect to the ground state Q_0 at -11.8 kcal/mol. The excitation energy to D_0 , D_1 , and D_2 were, therefore, 39.3, 40.3, and 48.6 kcal/mol, respectively. Thus, they are within an accessible range by photosensitization of Q_0 by $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ ($E(\text{T}_1) = 61.8$ kcal/mol:^{2a} reachable up to 50.0 kcal/mol in relative energy) or by 4CzIPN

Scheme 4. Rationale of the unique reactivity of the iron/photosensitizer-catalyzed [2+2+2] cycloaddition.



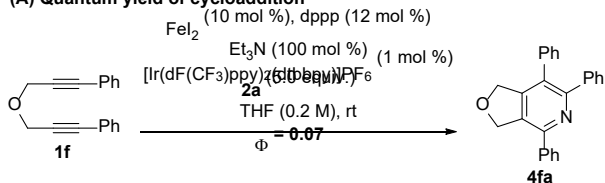
a) Computed energy diagrams of the cycloaddition using DFT. b) Relative energies of the excited states of INT1' calculated using the SAC-CI method. The energy of the quartet ground state Q_0 is equalized to that of INT1' (-11.8 kcal/mol) to facilitate interpretation.

($E(T_1) = 61.6$ kcal/mol: reachable up to 49.8 kcal/mol).²⁸ On the other hand, spin-allowed direct photoexcitation of Q_0 to Q_1 in the absence of a photosensitizer requires an energy as large as 69.5 kcal/mol. This value is larger than that available from the peak intensity of the blue LED (447 nm: 64.0 kcal/mol; reachable up to 52.2 kcal/mol), which may account for the limited efficiency of the cycloaddition under blue LED irradiation in the absence of the photocatalyst (Scheme 3B, (v)).

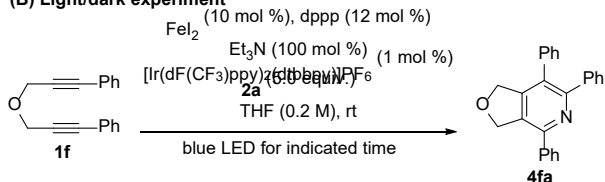
To elucidate the feasibility of the mechanism proposed in Scheme 4, in which one photon is required per each catalytic turnover, a couple of photochemical studies were conducted. First, quantum yield (Φ) of the cycloaddition toward 4fa was measured (Scheme 5A) since the theoretical limit of Φ is 1 if the mechanism in Scheme 4 is mainly responsible for the product formation. Thus, Φ of the overall transformation was determined to be 7%.²⁹ Second, light/dark experiment was conducted (Scheme 5B). In entry 1, the reaction mixture for the iron/photosensitizer-catalyzed [2+2+2] cycloaddition was irradiated for 3 hours and was worked up immediately. In entry 2, the reaction mixture was irradiated for 3 hours and then was stirred in the dark for the following 19 hours. Thus, 4fa was obtained in 47% yield in entry 1 and in 45% yield in entry 2.³⁰ The small quantum yield of the reaction ($\Phi < 1$) and the minute difference of the yield of two trials in Scheme 5 suggest that dark catalytic turnover of photochemically generated species may not play a substantial role in the iron/photosensitizer-catalyzed cycloaddition. These observations agree with the proposed mechanism in Scheme 4 which demands one photon for the photosensitization of INT1' in each catalytic cycle.

Scheme 5. Photochemical experiments toward mechanistic elucidation.^a

(A) Quantum yield of cycloaddition



(B) Light/dark experiment



Entry	Changes in light/dark conditions	Yield of 4fa
1	0 h 3 h work up	47%
2	0 h 3 h in dark 19 h work up	45%

^aSee Supporting Information for experimental details.

CONCLUSIONS

In conclusion, we have developed an iron/photosensitizer-hybrid system that enables the hitherto-challenging iron-catalyzed [2+2+2] cycloaddition of diynes and nitriles toward the synthesis of polyarylpiperidines. The unique reactivity of the developed method is highlighted by the modular syntheses of azafluoranthenes under mild and operationally benign conditions. Since the cycloaddition proceeds in only low yield under the reported iron-catalyzed protocol, our study clarified the potential of the iron/photocatalyst dual system to overcome the limitation of thermal iron catalysis. Experimental results and quantum chemical calculations suggest that

photosensitization of an organoiron intermediate is responsible for facilitating the thermally sluggish step in the catalytic cycle. The applicability of iron/photosensitizer dual catalysis in other modes of iron-catalysis is under investigation in our group.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge at <https://pubs.acs.org>.

Experimental procedures, characterization of the synthesized compounds, details of quantum chemical calculations, and NMR spectra (PDF). X-ray crystallographic data for the determination of the structure of **5ac** (CIF). These materials are available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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(19) UV-vis spectra of some new azafluoranthenes in solution and photoluminescence of **5da** at 365 nm in the solid state are provided in section 5 of Supporting Information.

(20) The cycloaddition proceeded in synthetically useful yield (**4aa**: 62%, **5aa**: 65%) when the amount of nitrile was reduced to 1.5 equivalents. For details, see section 2-3 of Supporting Information.

(21) For an attempt of fully intermolecular [2+2+2] cycloaddition, see section 2-4 of Supporting Information.

(22) The reaction in the dark under mild heating did not result in the improvement of the yield of **4fa**, indicating that the acceleration effect is more likely to be derived from light than the heat from LED. See section 4-3 of Supporting Information for details.

(23) The authors have unexpectedly discovered that, in the reaction in **Scheme 3A**, (**iii**), **4fa** was obtained in varying yield after several trials (lowest: 5%, highest: 30%). Although the exact cause of the limited repeatability is not clear at present, the reaction was repeated for 7 times with our best efforts in the purity of materials and precision in reaction setups, and the average of the thus obtained 7 results was employed for a fair comparison. The same consideration was made in the reactions in **Scheme 3B**, (**v**) and **Scheme 3B**, (**vi**). See section 4-3 of Supporting Information for details.

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