Article

Direct Dearomatization of Pyridines via an Energy-Transfer-Catalyzed Intramolecular [4+2] Cycloaddition



An energy-transfer-catalyzed dearomative [4+2] cycloaddition reaction of pyridines is presented herein. Mechanistically, a ground-state alkene is readily promoted to the corresponding triplet excited state. The resultant highly energetic intermediate then undergoes an efficient dearomative cycloaddition to a pyridine moiety, thus yielding an isoquinuclidine analog. The energy transfer process is enabled by a recyclable polymer-immobilized, iridium-based photocatalyst. This work demonstrates the contribution of visible light catalysis toward enabling thermally challenging organic transformations.



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HIGHLIGHTS

Catalytic dearomatization of pyridines through a [4+2] cycloaddition

Introduction of a recyclable polymer-supported photocatalyst

Rapid construction of isoquinuclidines

Photocatalysis enabled thermally challenging organic transformation



Article

Direct Dearomatization of Pyridines via an Energy-Transfer-Catalyzed Intramolecular [4+2] Cycloaddition

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SUMMARY

The catalytic dearomatization of pyridines, accessing medicinally relevant N-heterocycles, is of high interest. Currently direct, dearomative strategies rely generally on reduction or nucleophilic addition, thus limiting the architecture of the dearomatized products to a six-membered ring. We herein introduce a catalytic, dearomative cycloaddition reaction with pyridines using photoinduced energy transfer catalysis, thereby advancing dearomatization methodology and increasing the topology of pyridine dearomatization products. This unprecedented method features high yields, broad substrate scope (44 examples), excellent functional group tolerance, and facile scalability. Furthermore, a recyclable and sustainable polymer immobilized photocatalyst was employed. Computational and experimental investigations support a mechanism in which a cinnamyl moiety is promoted to its corresponding excited triplet state through visible-light-mediated energy transfer catalysis, followed by a regioselective and dearomative [4+2] cycloaddition to pyridines. This work demonstrates the contribution of visible light catalysis toward enabling thermally challenging organic transformations.

INTRODUCTION

Catalytic dearomatization reactions have experienced steady development owing to their unique potential to convert common aromatics into various functional molecules in a straightforward manner.^{1–3} Among the aromatics investigated in this field, pyridines have attracted considerable attention from the synthetic and medicinal chemistry communities since dearomatized partially or fully saturated *N*-heterocycles exhibit diverse inherent bioactivities or can be used as valuable feedstock for organic synthesis.⁴

Currently disclosed methods on the direct, catalytic dearomatization of pyridines generally require a sequential protocol involving initial electrophilic activation of the nitrogen center followed by nucleophilic addition.^{5–9} Products obtained from these methods are therefore limited to the architecture of six-membered rings including dihydropyridine, tetrahydropyridine, and piperidine derivatives (Figure 1A). Methodologies allowing an increase in the topology of the products in direct pyridine dearomatization have remained elusive. The rapid generation of structural complexity from readily available feedstock constitutes one of the foremost challenges in organic synthesis. Cycloaddition reactions have been recognized as a powerful protocol to achieve this goal, facilitating the construction of complex architectures with corresponding atom and step economy and stereochemical

The Bigger Picture

Driven by the demand for more sustainable chemistry and advances in synthetic methodologies, visible light photocatalysis has attracted great attention from the synthetic chemistry community over the past decade. Among the photochemical activation processes, the photoinduced energy transfer, which can promote the ground state organic molecule to its triplet excited state, is relatively underdeveloped compared to photoinduced electron transfer. Differing from the ground state molecules, the accessible excited state analog generally show unique reactivity. As a consequence, investigations of visible-light-induced energy transfer catalysis offer an exciting opportunity for the discovery of new synthetic transformations under relatively mild conditions.



Figure 1. The Concept of Pyridine Dearomatization Chemistry

(A) The state of the art of direct catalytic pyridine dearomatization.

(B) The (dehydro)isoquinuclidine core among representative natural products and drugs and as feedstocks for the synthesis of pharmaceuticals. (C) Our synthetic design of dearomative cycloaddition with pyridine. PS = photosensitizer. EnT = energy transfer.

specificity.¹⁰ To this end, merging dearomatizations of pyridines with cycloadditions is undoubtedly of high interest, which could provide medicinally important *N*-hetero bicyclic manifolds, such as isoquinuclidines, in a straightforward manner. The isoquinuclidine (2-azabicyclo[2.2.2]octane) core, identified as a semi-rigid boat form of piperidine, along with the related dehydrogenated derivatives, comprises the core of various bioactive natural products and pharmaceuticals as well as feedstock for synthesizing marketed drugs such as Tamiflu (Figure 1B).^{11,12}

Direct catalytic dearomative cycloadditions of electron-rich aromatics such as naphthalenes, pyrroles, indoles, benzothiophenes, (benzo)furans, and others have been well established; however, the pyridine manifold still presents a formidable challenge.¹³ This may be since (1) breaking the aromaticity requires harsh conditions or an extremely reactive cycloaddend and (2) the potential adducts may undergo thermally favored rearomatization. In this context, the search for non-thermal strategies might lead to a potential solution. Indeed, under UV-mediated photochemical conditions, direct dearomative cycloadditions of pyridine derivatives have been known since the 1970s.^{14,15} Unfortunately, the multistep synthesis of specific pyridine substrates, inferior yields of the dearomatization products, poor regioselectivity, and subsequently unpredictable side reactions enabled by UV light render each of these methods of very limited utility in organic syntheses. The present renaissance of visible light catalysis offers a new opportunity for dearomative cycloadditions through visible-light-induced single electron transfer (SET),¹⁶⁻²⁰ triplet-triplet energy transfer (EnT)²¹⁻²⁵ catalysis, or in special cases, direct visible light excitation.²⁶ For example, using a visible-light-excited arenophile, Sarlah and co-workers developed an elegant dearomative cyclization-fragmentation cascade strategy for benzenoid arenes, which has been incorporated into efficient syntheses of diverse natural products.^{19,20} Very recently, the groups of You²³ and Glorius²⁴ independently reported a dearomative cycloaddition strategy for indoles and naphthalenes through visible-light-induced EnT catalysis. Mechanistically, naphthalene or indole

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Figure 2. Synthesis of an Immobilized Iridium Photocatalyst

derivatives, which exhibit triplet energies of 55-60 kcal/mol after accessed by a visible-light-excited photocatalyst Ir(dF(CF₃)ppy)₂(dtbbpy)(PF₆) ([Ir-F], 60.8 kcal/ mol), are readily promoted to the corresponding excited states through EnT, subsequently undergoing highly efficient dearomative cycloadditions. Nevertheless, despite these advances, pyridine derivatives are not similarly amenable because of their inert redox activity and high triplet energy (>70 kcal/mol), which render them inaccessible to both SET and EnT. The [2+2] cycloaddition between unsaturated moieties is thermally forbidden by the Woodward-Hoffmann rules, but is commonly seen under photochemical conditions relying on the formation of a key 1,2-biradical intermediate.²⁷⁻³⁰ After consideration of these combined observations, we envisioned the 1,2-biradical intermediate could be employed to promote direct pyridine dearomatization via a cycloaddition reaction under visible-lightmediated conditions (Figure 1C). This proposal was judged to be reasonable and applicable since (1) the 1,2-biradical cycloaddend is readily accessible from activated alkenes (48-62 kcal/mol) through visible-light-mediated EnT and displays extremely high reactivity; (2) the dearomatized products were expected to be stable under the mild conditions. We hereby report the realization of this concept, thereby introducing a dearomative [4+2] cycloaddition reaction with pyridines and isoquinolines, furnishing numerous functionalized isoquinuclidine derivatives.

RESULTS AND DISCUSSION

Synthesis of an Immobilized Photocatalyst

Visible light catalysis has seen rapid development over the past decade, yet an overreliance on precious rare earth transition metal catalysts, such as iridium (Ir) and ruthenium (Ru) complexes, along with trace presences of transition metal residues in the target products, has hampered the application of visible light catalysis within the chemical industry. Employment of organic dyes³¹ or semiconductors³² may be a complementary solution, but not a fundamental substitution. A sustainable means of using transition metal photocatalysts is therefore of high relevance. Inspired by the development of heterogeneous catalysis,^{33–35} we, herein, demonstrated a polymer immobilized, Ir-based photocatalyst of high recyclability and facile separation from the reaction mixture. The synthetic route is outlined in Figure 2. Accordingly, a bis-cyclometalated iridium dimer 1 was treated with AgPF₆ in acetonitrile,³⁶ followed by the introduction of carboxylic acid based 2,2'-bipyridine ligand 2. A homogeneous iridium complex 3 was obtained in 90% yield over two steps (Figure 2). Oxalyl chloride mediated condensation of the dicarboxylic acid complex 3 with commercially available polymer (aminomethyl)polystyrene, provided the heterogeneous photocatalyst [Ir-F]@polymer as orange beads.

Dearomatization Reaction Evaluation

Inspired by the pioneering studies of UV-mediated benzenoid arenes dearomatization, as introduced by Kohmoto and co-workers,³⁷ we started our investigation by examining the reactivity of pyridine-containing cinnamyl amides under

Table 1. Evaluation of the Pyridine Dearomatization Reaction^a

Ph NPMB NPMB N N H	F]@polymer (1.5 mol%) acetone (0.1 M) De LEDs (455 nm), Ar 25 to 30 °C, 5 h trandard conditions [4+2] Physical Physical Physic	NPMB
Entry	Deviation from Standard Conditions	Yield (%) ^b
1	None	99 (95) ^c
2	CH_2CI_2 as solvent	99
3	THF as solvent	99
4	CH ₃ CN as solvent	99
5	DMF as solvent	89
6	1% H ₂ O added	99
7	0.75 mol% catalyst	99
8	No catalyst	0
9	In the dark	0
10	Under air	0

^aStandard conditions: **4a** (0.10 mmol) and [Ir-F]@polymer (1.5 mol%) in acetone (1.0 mL, 0.1 M) were stirred for 5 h under argon and irradiated with blue LEDs ($\lambda_{max} = 455$ nm, latent temperature approx. 25–30°C). ^bYield was determined by crude ¹H NMR analysis with CH₂Br₂ as internal standard.

^clsolated yield provided in parentheses. dr of products determined within a range of 1.1:1 to 2.0: 1. Ar = argon. THF = tetrahydrofuran. DMF = dimethyl formamide.

visible-light-sensitized conditions. In the presence of the heterogeneous photocatalyst [Ir-F]@polymer (1.5 mol%), after irradiation for 5 h with blue LEDs (6 W, λ_{max} = 455 nm) in acetone, an N-cinnamoyl picolinamide 4a was fully converted to the dearomative [4+2] cycloaddition product 5a in an excellent yield of 99% with 2:1 dr (Table 1, entry 1). Perfect regioselectivity was observed since no [2+2] or [3+2] cycloaddition products were detected. This reaction displayed a high reaction conditions tolerance: insensitivity to solvent polarity was observed over diverse solvents such as CH₂Cl₂ (99% yield, entry 2), tetrahydrofuran (THF) (99% yield, entry 3), CH₃CN (99% yield, entry 4), and dimethyl formamide (DMF) (89% yield, entry 5), and as well as in the presence of water (99% yield, entry 6). A decreased catalyst loading of 0.75 mol% did not lead to any decrease of the yield of 5a (99% yield, entry 7). Control experiments verified that this [4+2] dearomatization reaction relied on the photocatalyst (entry 8), visible light (entry 9), and oxygen-free conditions (entry 10).

Scope and Limitation

The reaction scope is outlined in Figure 3. A variety of substituted picolinamides were dearomatized smoothly under the photosensitized conditions. Alkylated pyridines were converted to the corresponding products (5b and 5c) in excellent yields of 93%–94% and diastereoselectivities of 1:1 to 1.3:1. Both electron-rich and electron-deficient substituents were very well tolerated, providing corresponding products (5d and 5e) in good yields (94% versus 86%) and diastereoselectivities (3.5:1 versus 7:1). A halogen substituent was also compatible, giving 5f in 84% yield and 6:1 dr. An imide-substituted pyridine was converted to the [4+2] cycload-dition product (5g) in a good yield of 82% and with good diastereoselectivity of 5:1. Nicotinamide derivatives also led to pleasing reaction outcomes (products 5h–5k, 52%–93% yield and 1.2:1 to >20:1 dr). Interestingly, by using CH_2Cl_2 instead of acetone as solvent, excellent diastereoselectivities (>20:1) were obtained for 5h



Figure 3. Scope and Limitation

Dearomatization products were obtained under standard conditions A unless otherwise noted. For details, see Supplemental Information.

and 5i. A series of polycyclic dearomatized products (5I-5p) were obtained from isoquinoline derivatives with excellent yields of 88%-97% and in high dr of 8:1 to >20:1. Both a naphthyl and a phenyl also underwent the dearomatization smoothly to afford products (5q and 5r) in 92% yield for each and 7:1 to >20:1 dr. Furthermore, substituents adjacent to the double bond displayed high tolerance with respect to the electron-donating (products 5s-5u) and withdrawing (products 5v-5y) phenyl rings, a furanyl (product 5z), and thienyl substituents (products 6a and 6b), thus providing the dearomatized products in 67%-97% yield and 1.4:1 to 5:1 dr. In contrast, when an *n*-propyl in place of the aromatics was used, no target product (6c) was detected. The reaction shows excellent functional group tolerance, including a nitrile (6g), a thioether (6h), an alkenyl substituent (6i), an acetal (6j), an N-Boc-piperidine (6k), a tetrahydropyrane (6l), a cycloheptane (6m), a cyclododecane (6n), and an additional pyridine (6o). Pyridines derived from drugs and natural products including dopamine (6p), tryptamine (6q), mexiletine (6r), and leelamine (6s), were all dearomatized efficiently under the visible-light-sensitized conditions. Following conclusion of the scope exploration, a simple and commercially available organic sensitizer benzil³⁸ (Alfa Aesar, \$19.80/100 g) was identified as being capable of catalyzing the dearomatization reaction (products 5a, 5g, 6b, 6m, 6o, and 6r) in similar efficiency. Although in the case of product 6p, the yield was dramatically decreased to 22%.

To further demonstrate the practicality of the dearomatization protocol, sequential gram scale reactions were performed using the recyclable photocatalyst [Ir-F]@polymer. As outlined in Figure 4A, [4+2] cycloaddition products 6m, 6n, 6r, and 5a were produced in 1.08 g (94% yield), 1.20 g (88% yield), 1.25 g (73% yield), and 0.94 g (76% yield), respectively. Only one portion of photocatalyst [Ir-F]@polymer was employed for these four sequential gram-scale reactions. Notably, the heterogeneous photocatalyst was separated from the reaction mixtures by simple filtration and washing and then reused directly without further purification. The heterogeneous photocatalyst could be recycled at least ten times for a standard dearomative [4+2] cycloaddition reaction without a significant drop in the yields of dearomatization products (Figure 4B, see Supplemental Information for details). The obtained pyridine dearomatization products underwent facile reduction to afford diverse (dehydro)isoquinuclidine derivatives. For example, compound 5a was converted to dehydroisoquinuclidine 7 as a single diastereomer after treatment with NaBH(OAc)₃, followed by Ts-protection (Figure 4C). Notably, the minor isomer of 5a underwent a slower reduction than the major one and could thus be separated by column chromatography. Starting from 5e, under Pd-catalyzed hydrogenation condition, isoquinuclidine 8 was afforded in 96% yield and in a completely diastereoselective fashion. A highly functionalized pyrrolidine-containing isoquinuclidine 9 was obtained in 97% yield after further treatment with LiAlH₄. The polycyclic structure of the major isomer of dehydroisoquinuclidine 11 was confirmed by X-ray crystallographic analysis (Figure 4D).

Mechanistic Investigation

To investigate mechanistic aspects of the dearomative [4+2] cycloaddition, we performed a variety of mechanistic experiments. Firstly, the kinetic profile of a standard reaction mixture shows that no detectable amounts of [2+2] or [3+2] cyclo-addition products are formed at any time, whereas the *E* to *Z* isomerization of sub-strate 4a is detected³⁹ and both isomers are ultimately converted to 5a (Figure 5A). Secondly, Stern–Volmer analysis reveals that the luminescence emission of homogeneous photocatalyst [Ir-F] is quenched efficiently by 4a, whereas no quenching was observed with compound 12 devoid of an olefin moiety (Figure 5B). The



Sequential gram-scale reactions with catalyst recycling

Figure 4. Investigation and Application of the Developed Catalytic System

(A) Sequential gram scale reactions with catalyst recycling.

(B) Evaluation of recycled catalyst performance.

(C) Synthetic transformations to (dehydro)isoquinuclidines.

(D) Structural confirmation by X-ray analysis (see also Figure S3). For detailed reaction conditions, see the Supplemental Information.

Stern–Volmer constant (K_{SV}) of 4a is determined to be 0.525 mM⁻¹. Thirdly, Z-4a could be isolated and again subjected to the standard reaction conditions to afford product 5a with the same outcome in comparison to the use of E-4a (Figure 5E). These observations indicate both E and Z-4a were converted to the common 1,2-biradical intermediate ³4a via triplet EnT. Fourthly, intermediate ³4a could be trapped by adding 2,3-dimethylbuta-1,3-diene (10 equiv.) or styrene (10 equiv.) to a standard reaction mixture, thus affording the corresponding [2+2] cycloaddition products 13 or 14 in 60% and 4:1 dr or 25% yield and 2:1 dr, respectively (Figure 5F). Finally, further evidence for triplet EnT was gained by comparing different photocatalysts. As a result, yields of the dearomatization product 5a are correlated to the intrinsic



Figure 5. Mechanistic Investigations

(A) Kinetic profile of photoinduced dearomatization reaction using E-4a as substrate with [Ir-F]@polymer.

(B) Stern-Volmer plots of homogeneous catalyst Ir(dF(CF₃)ppy)₂(dtbbpy)(PF₆) using E-4a and 12 as quenchers.

(C) Measurement of initial rates of photoinduced dearomatization reactions under different conditions.

(D) Comparison of different photocatalysts.

(E) Stereochemical information loss experiments.

(F) Biradical trapping through photoinduced [2+2] cycloadditions. For more details, see Figures S1 and S2. PC = photocatalyst. EnT = energy transfer. Conc. = concentration. Eq. = equivalent.

triplet energy of Ir-based (I, II, and III) or Ru-based (IV) photocatalysts, while unrelated to their redox properties (Figure 5D).

To rationalize the observed regio- and diastereoselectivity, DFT calculations were conducted and the result is partially outlined in Figure 6 (see Supplemental Information for details).⁴⁰ Accordingly, the triplet energy transfer from photoexcited [Ir-F]@polymer ($E_T = \sim 60.8$ kcal/mol) to substrate **E-4ad** (calculated as $E_T = 45.8$ kcal/mol), as well as its rotamer **E-4ad**' (calculated as $E_T = 46.5$ kcal/mol), is

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Computational method: (U)CAM-B3LYP / def2-TZVPP / CPCM (MeCN). For more details, see Figures S4–S9. TS = transition state. INT = intermediate.

thermodynamically feasible. From the resulting excited state, relaxation to the ground state would lead to a statistical mixture of Z- and E-configured starting material 4ad or 4ad', which is in excellent agreement with the observed $E \leftrightarrow Z$ isomerization under the photosensitized conditions (Figure 5A). Notably, ³4ad is the major intermediate in comparison to its rotamer ³4ad' because of its higher stability ($\Delta G = -1.2$ kcal/mol) and lower triplet excitation energy ($\Delta E_T = -0.7$ kcal/mol). Taking ³4ad as an example (for computations concerning ³4ad', see Supplemental Information), within this 1,2-biradical intermediate, the electrophilic α-carbonyl radical undergoes 5-exo-trig cyclization (ΔG^+ = +11.2 kcal/mol) to the pyridine moiety, giving rise to a 1,6-biradical intermediate ³INT1 ($\Delta G = -8.3$ kcal/mol). Subsequent thermoneutral intersystem crossing (ISC) into the open-shell ¹INT1 $(\Delta G = -7.9 \text{ kcal/mol})$ enables radical-radical recombination to occur and afford the [4+2] cycloaddition product 6d. The selectivity of [4+2] over [2+2] cycloaddition can be rationalized by the strong thermodynamical instability of the [2+2]-product $(\Delta G = 45.9 \text{ kcal/mol})$ and further supported by analysis of the spin population of intermediate ¹INT1, in which the spin density is preferentially located on *para*-carbon atom ($\chi s = 0.38$) over the ortho-carbon atoms ($\chi s = 0.30$).

In summary, we hereby disclose a direct dearomative [4+2] cycloaddition reaction of pyridines. This protocol allows rapid access to a variety of highly functionalized isoquinuclidine analogs in high yields, excellent functional group tolerance and facile scalability. A polymer immobilized, Ir-based photocatalyst was introduced and could be recycled by simple filtration and washing, highlighting the sustainability of this method. Mechanistic experiments, kinetic analysis and DFT calculations support the occurrence of a visible-light-mediated energy transfer event. Overall, efficient production of a highly reactive 1,2-biradical cycloaddend under mild photosensitized conditions are key to the success of this work.

EXPERIMENTAL PROCEDURES

A dried 5 mL Schlenk tube was charged with the substrate 4, the heterogeneous catalyst [Ir-F]@polymer (1.5 mol %) or the organic sensitizer benzil (20 mol %), and

acetone or CH₂Cl₂ (0.1 M). The reaction mixture was degassed via freeze-pumpthaw for two cycles. After the mixture was thoroughly degassed and filled with argon, the Schlenk tube was sealed tightly and stirred under irradiation with 6 or 30 W blue LEDs for the indicated time (monitored by TLC). The organic solution was concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (*n*-pentane/EtOAc) to afford the [4+2] cycloaddition products.

DATA AND CODE AVAILABILITY

The crystal structure data of compound 11 (CCDC 1913256) has been deposited in the Cambridge Structural Database.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr. 2019.10.016.

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AUTHOR CONTRIBUTIONS

J.M., T.D., J.L.S., and F.G. designed, performed, and analyzed experiments. F.S.-K. performed the DFT calculations. M.F. synthesized the ligand **2**. K.B. performed and analyzed the 2D NMR. C.D. performed the X-ray analysis. J.M., F.S.-K., T.D., and F.G. prepared the manuscript with contributions from all authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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