

Visible-light-induced Dearomatization *via* [2+2] Cycloaddition or 1,5-Hydrogen Atom Transfer: Regulating Reaction Pathways of Diradicals on Excited States

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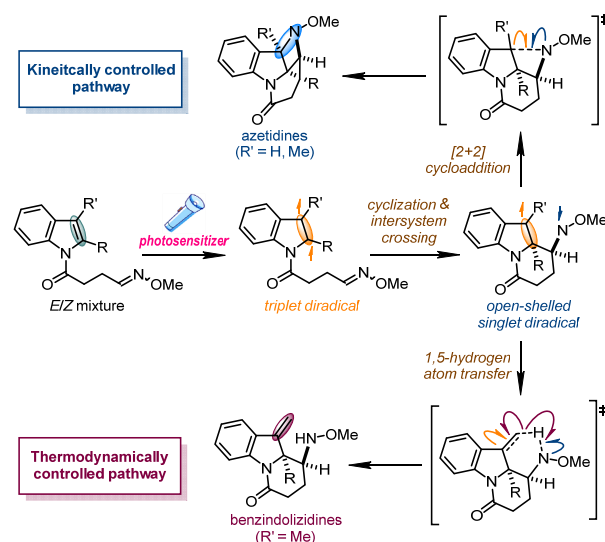
ABSTRACT: Visible-light-induced dearomatization reaction *via* energy transfer mechanism is an emerging strategy for the synthesis of highly strained polycyclic molecules. Transient, high-energy diradical species on excited states are typically involved in this type of reactions as key intermediates. Herein, we report the visible-light-induced divergent dearomatization of indole-tethered O-methyl oximes, in which the reactivity of the open-shelled singlet diradical intermediates towards competitive reaction pathways, namely [2+2] cycloaddition and 1,5-hydrogen atom transfer, can be well regulated. The mechanism has been well supported by a series of experimental and computational investigations. The dearomatization reactions allow the facile synthesis of structurally appealing indoline-fused azetidines and related polycyclic molecules with high efficiency and exclusive selectivity.

INTRODUCTION

Regulating the reactivities of key intermediates towards competitive reaction pathways is among the cutting-edge research topics in modern organic chemistry. In this regard, the kinetic *vs.* thermodynamic control of reactions is a frequently encountered situation where the distribution of products is influenced by both the relative barrier heights and the stability of each product. Although significant efforts have been devoted to manipulating the various selectivities of *ground state* reactions, yet the control of the reaction pathways of transient, high-energy species on *excited states* remains underdeveloped.¹

Recently, visible-light-induced dearomative [2+2] cycloaddition reactions *via* energy transfer mechanism have attracted broad interests due to the distinct reactivities on excited states leading to target molecules usually prohibited under thermal conditions.^{2,3,4} Mediated by properly selected photosensitizers, aromatic substrates can be excited and coupled with various unsaturated functionalities such as alkenes,⁵ alkynes,⁶ and allenes,⁷ delivering highly strained polycyclic structures that are not easily accessed otherwise. Mechanistically, these reactions proceed in a stepwise manner, involving diradical species on triplet or open-shelled singlet state.⁸ We envisioned that if multiple reaction pathways are available for such diradical intermediates, and at the meantime, their reactivities can be fully manipulated, new opportunities will emerge for convenient synthesis of diverse polycyclic products from the same starting materials under mild conditions. However, to the best of our knowledge, no precedent of such kind was known in the literature.

Scheme 1. Regulating Reaction Pathways of Open-shelled Singlet Diradicals: [2+2] Cycloaddition *vs.* 1,5-Hydrogen Atom Transfer.



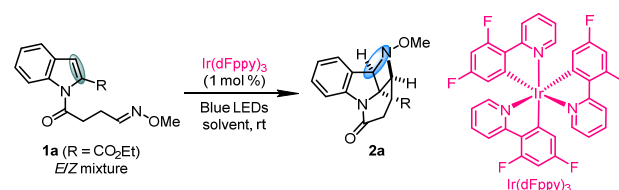
Here we report the visible-light-induced divergent dearomatization reactions of indole-tethered O-methyl oximes initiated with the energy transfer process (Scheme 1). The [2+2] cycloadditions with the C=N double bond of the oxime moiety as the diradical acceptors afford structurally appealing indoline-fused azetidine derivatives.⁹ More intriguingly, if an appropriate alkyl substituent is available at the C3 position of the indole ring, the [2+2] cycloadditions can be interrupted by 1,5-hydrogen atom transfer of the open-shelled sin-

glet diradical intermediates, delivering functionalized benzindolizidines. DFT calculations and control experiments suggested that the formations of azetidine and benzindolizidine products are under kinetic and thermodynamic controls, respectively. Guided with these mechanistic insights, the complete switch of the reaction pathways for the open-shelled singlet diradical intermediates were realized, affording each type of products with exclusive selectivity.¹⁰

RESULTS AND DISCUSSION

Reaction development. Our study commenced with the evaluation of various reaction parameters using indole-tethered O-methyl oxime **1a** (*E/Z* mixture) as the model substrate (Table 1). According to the calculated triple-singlet energy gap of **1a** [$\Delta G(T_1-S_0) = 54.4$ kcal/mol], Ir-based photosensitizer Ir(dFppy)₃ [1 mol %, $\Delta G(T_1-S_0) = 63.5$ kcal/mol] was employed under the irradiation of 24 W blue LEDs at room temperature (See the Supporting Information for the results with other photosensitizers). The dearomatic [2+2] reaction of **1a** (0.1 M) proceeded smoothly in a variety of solvents including MeOH, MeCN, DCM, acetone, DMF and DMSO (entries 1-6), with DCM as the optimal choice. When the reaction was conducted in a diluted solution of DCM (0.01 M), the desired dearomatic [2+2] cycloadduct **2a** was isolated as a single diastereoisomer in excellent yield (98%, >20:1 dr) in 3 h (entry 7). Control experiments proved that both the photosensitizer and light are essential for promoting the reaction (entries 8 and 9).

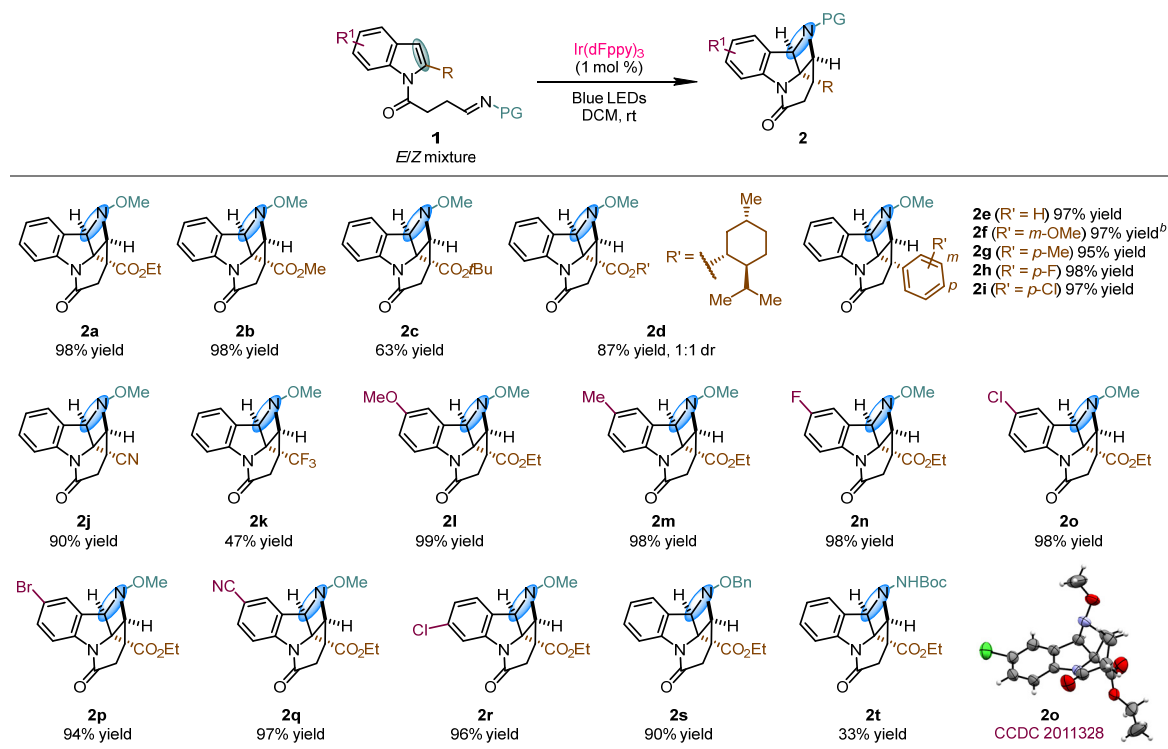
Table 1. Optimization of Reaction Conditions for Dearomatic [2+2] Cycloaddition^a



Entry	solvent	time (h)	yield of 2a (%) ^b
1	MeOH	3	9
2	MeCN	3	12
3	DCM	3	95
4	acetone	3	90
5	DMF	3	85
6	DMSO	3	92
7 ^c	DCM	3	quant. (98 ^d)
8 ^e	DCM	24	0
9 ^f	DCM	24	0

^a Reaction conditions: **1a** (0.1 mmol) and photosensitizer (1 mol %) in solvent ($c = 0.1$ M) were irradiated by 24 W blue LEDs (450 nm) at room temperature under argon. ^b NMR yield using CH₂Br₂ as the internal standard. ^c $c = 0.01$ M. ^d Isolated yield. ^e Without photosensitizer. ^f In dark.

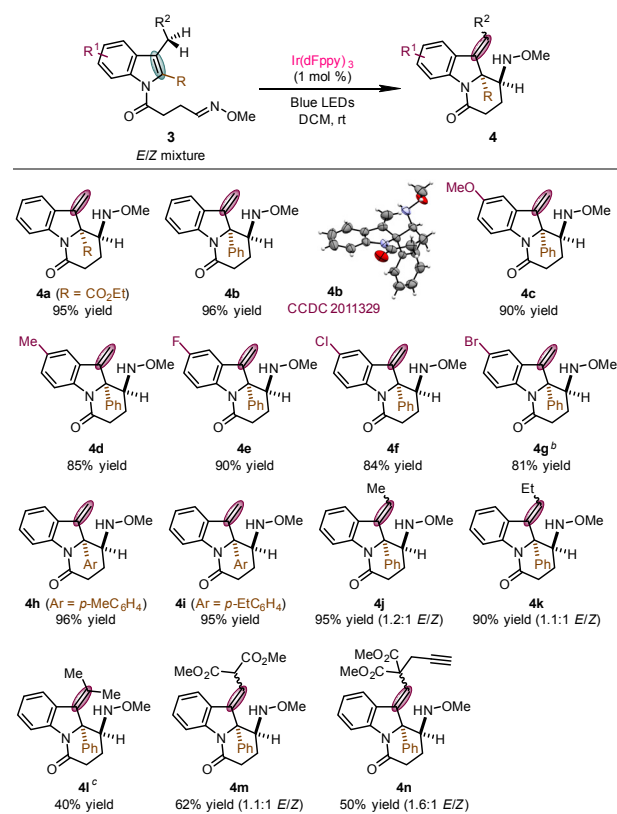
Scheme 2. Substrate Scope: Dearomatic [2+2] Cycloaddition^a



^a Reaction conditions: **1** (0.2 mmol) and Ir(dFppy)₃ (1 mol %) in DCM ($c = 0.01$ M) were irradiated by 24 W blue LEDs (450 nm) at room temperature under argon for 8 h. ^b The reaction was quenched after 48 h.

With the optimal conditions (Table 1, entry 7) in hands, the scope of the visible-light-induced dearomative [2+2] cycloaddition reaction was investigated (Scheme 2). The reaction conditions tolerate a large array of indole-tethered O-methyl oximes, leading to the corresponding polycyclic indoline-fused azetidines. In line with our previous observations,^{5a,6b} an electron-deficient substituent (esters, **2a–2d**, 63–98% yields; cyano, **2j**, 90% yield; trifluoromethyl, **2k**, 47% yield) or an aryl group (**2e–2i**, 95–98% yields) at the C2 position of the indole ring are beneficial for the reactions. In particular, compound **2d**, consisting of the ester group derived from L-menthol, was obtained as a pair of diastereoisomers (1:1 dr). Substituents of varied electronic properties like methoxy (**2l**, 99% yield), methyl (**2m**, 98% yield), halogen atoms (**2n–2p** and **2r**, 94–98% yields) and cyano (**2q**, 97% yield) at either C5 or C6 position of the indole ring are also compatible. The X-ray crystallographic analysis of **2o** confirmed that the fused tricyclic structure of the target molecules adopted the *all-cis* configuration. The switch to O-Bn oxime analog did not affect the reaction outcomes in that azetidine **2s** was delivered in 90% yield. To be noted, indole-tethered N-Boc hydrazone could also participate in the dearomative [2+2] cycloaddition reaction, albeit with moderate yield of **2t** (33%).

Scheme 3. Substrate Scope: Dearomative 1,5-Hydrogen Atom Transfer^a



^a Reaction conditions: **3** (0.2 mmol) and Ir(dFppy)₃ (1 mol %) in DCM (*c* = 0.01 M) were irradiated by 24 W blue LEDs (450 nm) at room temperature under argon for 24 h. ^b The reaction was quenched after 12 h. ^c 405 nm LEDs were used.

On the other hand, distinct reactivity was observed for substrates **3** bearing an alkyl substituent at the C3 position of the indole ring (Scheme 3). The [2+2] cycloaddition pathway was interrupted after

the first C–C bond formation at the C2 position. A formal 1,5-hydrogen atom transfer process furnished an O-methyl hydroxylamine moiety and an exocyclic C=C double bond at the benzindolizidine skeleton. For C3-methyl substituted substrates, the formation of such functionalized benzindolizidines **4a–4i** as a single diastereoisomer under the standard conditions for 12–24 h (81–96% yields, >20:1 dr). Besides the ester group or the aromatic substituent at the C2 position, the reactions further tolerated functional groups such as methoxy, methyl or halogen atoms at the C5 position of the indole ring. The X-ray crystallographic analysis of **4b** confirmed that the O-methyl hydroxylamine moiety and the C2-substituent are in the *anti* configuration. For the substrates with a longer alkyl chain at the C3 position, the corresponding products **4j**, **4k** and **4m** were isolated as a mixture of geometric isomers of olefins (62–95% combined yields, 1.1:1–1.2:1 *E/Z*). Interestingly, when a C3-tethered terminal alkyne side chain and an N-tethered O-methyl oxime moiety are available at the same time, the functionalized benzindolizidine **4n** was delivered as the only product (50% yield, 1.6:1 *E/Z*), while the corresponding dearomative [2+2] cycloaddition with the terminal alkyne towards a cyclobutene derivative was not observed. The reaction with C3-isopropyl substituted substrate was less efficient. The utilization of 405 nm LEDs was required to guarantee a moderate yield of **4l** (40%).

Mechanistic studies. To shed light on the mechanism of the visible-light induced dearomatization of indole-tethered O-methyl oximes, a series of control experiments were performed. First, cyclic voltammetry measurement and triplet quenching experiment of **1a** suggested that the reaction proceeded through the energy transfer process *via* triplet state intermediate rather than the photoredox mechanism (See the Supporting Information for details). Previously, the [2+2] photocycloaddition reactions involving imines were generally initiated with the excitation of the C=N double bond.^{9c} However, in this case, the reaction was triggered by the excitation of the indole core, as in Stern–Volmer luminescence quenching experiments **1a** readily quenched the photosensitizer Ir(dFppy)₃, but its indoline analog **1a'** did not (Figure 1).

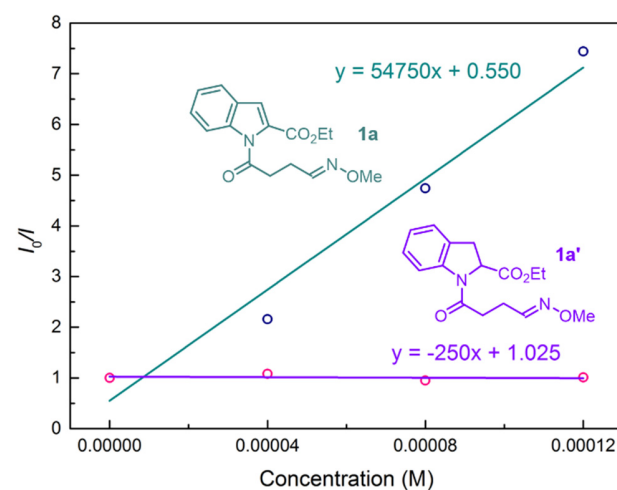


Figure 1. Stern–Volmer quenching experiments with photoexcited Ir(dFppy)₃ (0.02 mM, λ_{ex} = 335 nm, λ_{em} = 491 nm). *I*₀ and *I* are respective luminescence intensities in the absence and presence of the indicated concentration of **1a** or **1a'**.

In order to explore the energy profile of the dearomative [2+2] cycloaddition and the 1,5-hydrogen atom transfer reactions, DFT calculations were performed. A diagram of simplified energy profiles with **3a** as the model substrate is shown in Figure 2. The excitation of **3a** from the ground state to its first triplet state (**3a-T₁**) requires an energetic uphill of 53.0 kcal/mol. In line with the Stern–Volmer luminescence quenching experiments, and also what was observed in the previous dearomative [2+2] cycloaddition reactions *via* energy transfer mechanism,^{5,6b} the two spin-parallel electrons of **3a-T₁** are mainly populated at the C2 and C3 positions of the indole ring, with an elongated C2–C3 bond (1.51 Å). The oximes in both *E* and *Z* configurations are found reactive towards the cyclization with the C2 position of the indole ring (See the Supporting Information for details). The diastereoselectivity of the reaction was determined in this step. The C–C bond formation between the *Si*-face of the C2 position of the indole ring and the *Re*-face of the oxime *via* **TS1** (62.7 kcal/mol, 9.7 kcal/mol relative to **3a-T₁**) was more preferential than the *Si*-face–*Si*-face bond formation *via* **TS1'** (64.5 kcal/mol, 11.5 kcal/mol relative to **3a-T₁**), which is consistent with the *anti* configuration of the C2-substituent and the O-methyl hydroxylamine moiety in **4a**. The triplet diradical **INT1** (38.4 kcal/mol) was further transformed to the corresponding open-shelled singlet diradical species **INT1-OSS** (38.2 kcal/mol) *via* minimal energy crossing point

MECP1 (42.2 kcal/mol). Notably, there are two competitive reaction pathways available for **INT1-OSS**. One is the 1,5-hydrogen atom transfer *via* transition state **TS3** (55.5 kcal/mol, 17.3 kcal/mol relative to **INT1-OSS**), leading to the experimentally observed product **4a** (14.9 kcal/mol). The other is the energetically more feasible radical–radical combination *via* transition state **TS2** (41.6 kcal/mol, 3.4 kcal/mol relative to **INT1-OSS**), furnishing the dearomative [2+2] cycloaddition product **4a'** (19.6 kcal/mol). It should be mentioned that for substrates **1** without the C3-alkyl substituent, the [2+2] cycloaddition towards products **2** is the only reasonable reaction pathway (Scheme 2). However, for C3-alkyl substituted substrates **3**, no such [2+2] cycloaddition product was observed under the conditions reported in Scheme 3 (12–24 h). Considering that the calculated barrier height of **TS2** is much lower than that of **TS3**, and the experimentally observed benzindolizidine product **4a** is more stable than **4a'**, we envisioned that the two reaction pathways of the open-shelled singlet diradical **INT1-OSS** towards **4a'** and **4a** are under kinetic and thermodynamic controls, respectively. Therefore, our calculation results predicted that in the reactions of C3-alkyl substituted substrates **3**, the dearomative [2+2] cycloaddition products like **4a'** might also be observed at the early stage of the reaction under kinetic control, but are later transformed into thermodynamically more stable products **4**.

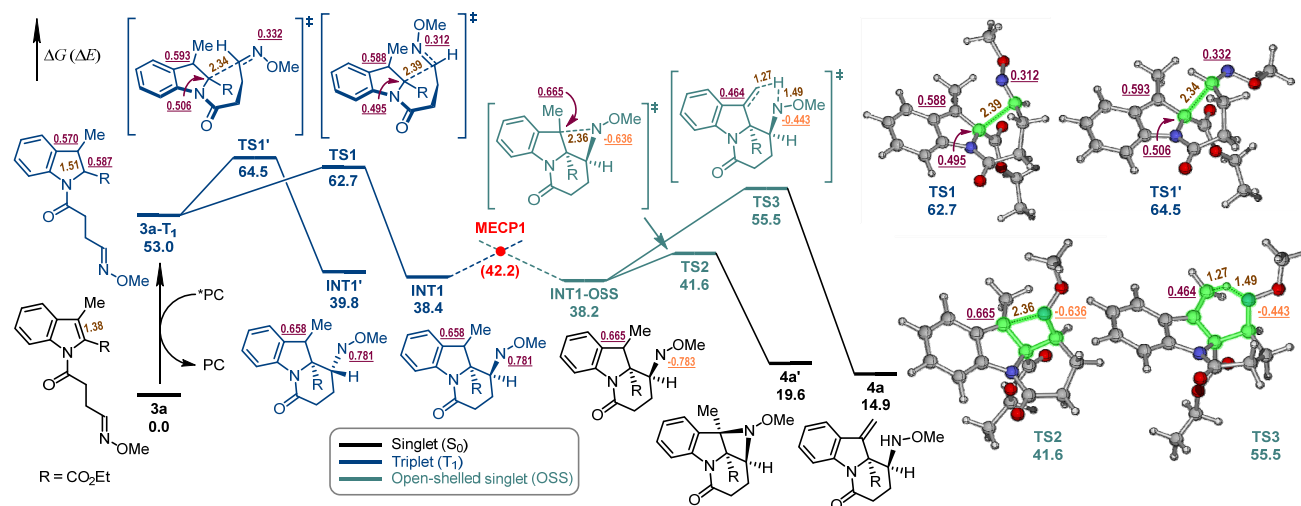
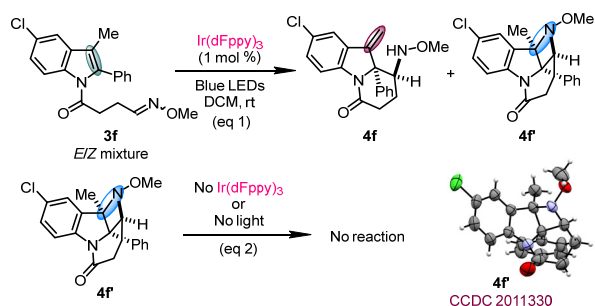


Figure 2. Energy profile of the dearomative [2+2] cycloaddition and the 1,5-hydrogen atom transfer reactions, and the optimized structures of the key transition states. Calculated at (U)B3LYP/6-31G(d,p) level of theory. The Gibbs free energies (ΔG) or electronic energies (ΔE , in parentheses) are in kcal/mol. The values in brown are bond distances in angstrom. The underlined values are Mulliken spin populations at certain atoms.

Scheme 4. Isolation and Transformation of Dearomative [2+2] Cycloaddition Product



Bearing this hypothesis in mind, we next tried to characterize the generation and the transformation of dearomative [2+2] cycloaddition product in the reaction of C3-alkyl substituted substrate **3f** by ¹H NMR spectroscopy (Scheme 4 and Figure 3). It was found that **3f** was almost fully converted to dearomative [2+2] cycloaddition product **4f'** within 1 h. **4f'** could be isolated and its structure was confirmed unambiguously by X-ray crystallographic analysis. When the reaction was allowed to further proceed, **4f'** was consumed gradually, leading to the temporary regeneration of **3f** and steady accumulation of **4f**. After 20 h, **4f** became the dominant species in the reaction mixture. Notably, **4f'** was found stable in the absence of photosensitizer or light irradiation, indicating the hemolytic C–N bond cleavage of **4f'** is a visible-light-promoted process. Collectively, these observa-

tions corroborate with the calculation results. Under the optimal reaction conditions [Blue LEDs and Ir(dFppy)₃], the formation of dearomative [2+2] cycloaddition product **4f** from **3f** is fast but reversible. Interestingly, although the ground state Gibbs free energies of the functionalized benzindolizidine products are much higher than that of the starting materials (**4a**, 14.9 kcal/mol relative to **3a**), they are still the thermodynamically favored species of the system under the reaction conditions.

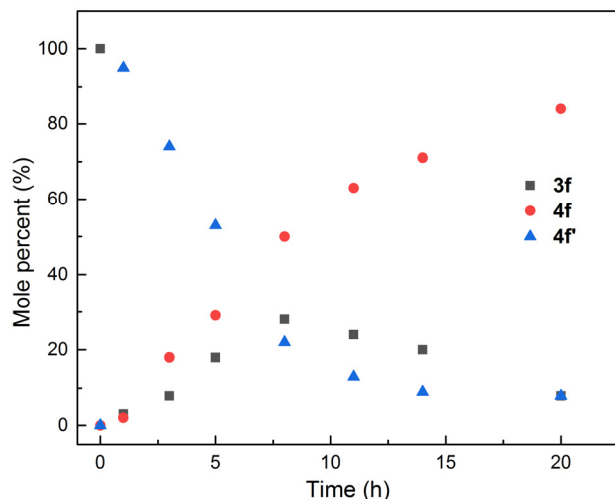
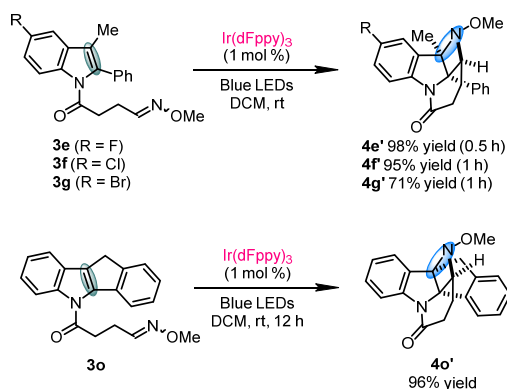


Figure 3. Time-course of the reaction of **3f** shown in eq 1 of Scheme 4 monitored by ¹H NMR spectroscopy.

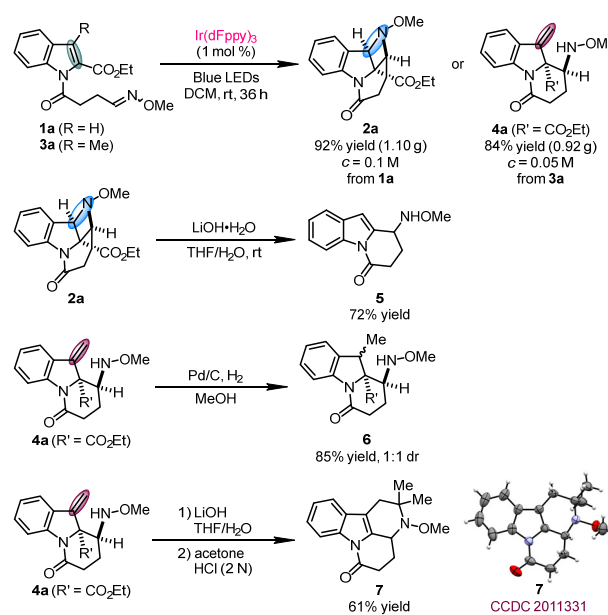
Scheme 5. Dearomative [2+2] Cycloaddition Reactions with C3-Alkyl Substituted Substrates



Guided by these mechanistic insights, the complete switch of the reaction pathway from 1,5-hydrogen atom transfer to [2+2] cycloaddition was achieved for a series of C3-alkyl substituted substrates (Scheme 5). For example, when the reactions of C3-methyl substituted substrates bearing a halogen atom the C5 position (**3e-3g**) under the standard conditions were quenched at 0.5–1 h, the corresponding [2+2] cycloaddition products **4e'-4g'** could be isolated in 71–98% yields. Besides, an indene-fused substrate **3o** could also participate in the dearomative [2+2] cycloaddition reaction, leading to **4o'** containing a unique 4,5,5,6-tetracyclic core structure in 96% yield. Notably, the 1,5-hydrogen atom transfer process was not possible here due to the conformational restriction in this bridged-ring structure. Therefore, compound **4o'** could stay intact for a longer reaction time (12 h).

Synthetic utilities. In order to demonstrate the synthetic potential of the dearomative reactions reported herein, the gram-scale synthesis of the two types of dearomative products and their derivations were demonstrated (Scheme 6). The reactions of **1a** and **3a** could be performed in more concentrated DCM solution (*c* = 0.1 or 0.05 M), affording the target molecules on gram scale (**2a**, 92% yield, 1.10 g and **4a**, 84% yield, 0.92 g). When treated with LiOH·H₂O, compound **2a** underwent cascade saponification, decarboxylation and C–N bond cleavage reactions, delivering the corresponding O-methyl hydroxylamine **5** in 72% yield. On the other hand, the exocyclic C=C double bond of **4a** could be hydrogenated with Pd/C. The indoline product **6** was obtained as a pair of diastereoisomer in 85% combined yield with 1:1 dr. In addition, the saponification of **4a** with LiOH in THF/H₂O initiated a cascade reaction towards polycyclic tetrahydro-β-carboline **7** in 61% yield, whose structure was determined by X-ray crystallographic analysis.

Scheme 6. Gram-scale Reactions and Product Derivations



CONCLUSION

In this work, we have developed visible-light-induced divergent dearomatization reactions of indole-tethered O-methyl oximes *via* energy transfer mechanism. Two reaction pathways, namely, [2+2] cycloaddition and 1,5-hydrogen atom transfer, are available for the key diradical intermediate on the open-shelled singlet state. Mechanistic studies revealed that the two reaction pathways are under kinetic and thermodynamic controls, respectively. By tuning the substitution patterns of the substrates or the reaction conditions, the two reaction pathways of the open-shelled singlet diradical species can be well regulated, allowing the facile synthesis of structurally appealing indoline-fused azetidine derivatives and functionalized benzindolizidines with high efficiency and exclusive selectivity. Currently we are working on expanding the scope of manipulating the reactivity of high-energy intermediates on excited states, towards the expedient synthesis of diverse highly strained polycyclic molecules.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at xxx.

Experimental procedures and analysis data for all new compounds and computational details (PDF)

X-ray crystallographic data for compound **2o** (CIF)

X-ray crystallographic data for compound **4b** (CIF)

X-ray crystallographic data for compound **4f** (CIF)

X-ray crystallographic data for compound **7** (CIF)

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Notes

The authors declare no competing financial interest.

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