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Letter

Dearomative Cycloadditions Utilizing an Organic Photosensitizer: An Alternative to Iridium Catalysis

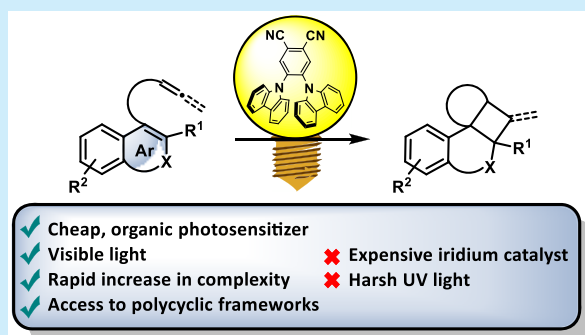Alessa B. Rolka and Burkhard Koenig*

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ABSTRACT: A highly efficient, cheap, and organic alternative to the commonly used iridium photosensitizer $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ ([**Ir−F**]) is presented for visible-light energy transfer catalysis. The organic dye **2CzPN** surpasses [**Ir−F**] in selectivity while at the same time being easily accessible in one step. The catalyst is recyclable and, due to its uncharged nature, soluble in nonpolar solvents such as toluene. Furthermore, the scope of molecular scaffolds that are compatible substrates for visible-light catalyzed dearomative cycloadditions is expanded.

✔ Cheap, organic photosensitizer
✔ Visible light
✔ Rapid increase in complexity
✔ Access to polycyclic frameworks
✖ Expensive iridium catalyst
✖ Harsh UV light

Over the past few years, energy transfer catalysis has gained significant attention and has emerged as a powerful synthetic tool.[1] The reasons for this are manifold, but of particular significance is the methodology's ability to rapidly generate high levels of molecular complexity.[1a,2] This is elegantly highlighted by the works of Glorius et al.[3] and You et al.[4] that demonstrate the generation of polycyclic cores by intramolecular dearomative cycloadditions of naphthol (Scheme 1A) and indole derivatives (Scheme 1B). The resulting molecular scaffolds often map onto natural product frameworks and are challenging to synthesize via other means.[5] One alternative to accessing these structures is the direct excitation of substrates by UV light. However, this method often leads to unwanted side reactions and poor selectivity.[6] By utilizing visible light and suitable photosensitizers to indirectly activate molecules, the need for UV light and/or other harsh reaction conditions can be avoided.

Key to the success of such a mild visible-light catalyzed process is the careful selection of a photosensitizer whose triplet energy upon excitation with visible light and intersystem crossing matches the targeted molecules. In the past, photocatalysts (PCs) with sufficiently high triplet energies for challenging dearomative processes of the type depicted in Scheme 1 have been largely limited to iridium-based systems utilizing $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ ([**Ir−F**]) (Scheme 1C) and its derivatives.[3,4,7] This catalyst, which has also been shown to be effective in other catalytic energy transfer processes, benefits from a long-lived excited triplet state and a high triplet energy.[1,8,9] Despite these desirable traits, iridium catalysis has several significant drawbacks that limit its widespread use. On the economic side, iridium has the distinction of being the rarest of the rare earth metals and has a correspondingly high price that can make the cost of the catalyst prohibitively expensive.[10] Furthermore, the presence of transition metals in pharmaceuticals is highly regulated, and use of an iridium photocatalyst in late stage steps is undesirable in regards to industrial applications of these complexity generating processes.[11] Finally, the charged nature of the expensive catalyst complicates its recyclability[8d,12] as well as limits the catalyst's solubility in many common nonpolar solvents.[10a]

This work aims to address these problems by avoiding iridium and offers a highly effective, cheap, neutral, and organic alternative for the widely utilized [**Ir−F**] photosensitizer. Based upon OLED research[13] and reports about the photochemical and photophysical properties of organic dyes, we were drawn to 1,2-bis(carbazol-9-yl)-4,5-dicyanobenzene (**2CzPN**) (Scheme 1D) as a promising candidate for this task.[14] Specifically, the high triplet energy of this system at 60.6 kcal/mol (corresponding to T_1 = 2.63 eV)[14d] as well as the prior use of this catalyst for photochromism[15] led us to explore its performance in the dearomatization reactions of aforementioned naphthol and indole derivatives.

The dearomative cycloaddition of naphthol **1a** was used as a model reaction to investigate the organic catalyst **2CzPN** (Table 1). To begin, **1a** and 5 mol % **2CzPN** were irradiated with 455 nm light in 1,4-dioxane at room temperature. Under

Scheme 1. Previously Reported Dearomatizations of Naphthol Derivatives (A)[3] and Indole Derivatives (B)[4] and Structure of the Organic Alternative 2CzPN (D) to ([Ir–F]) (C)
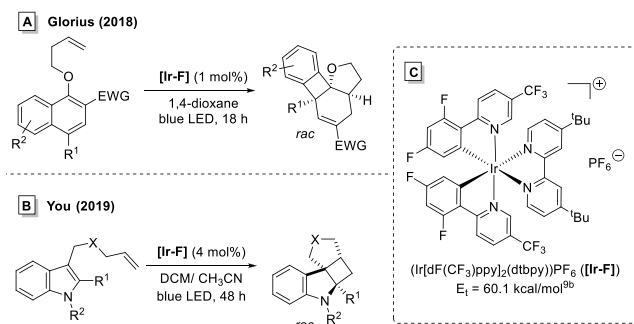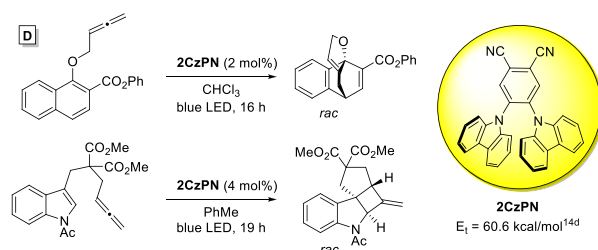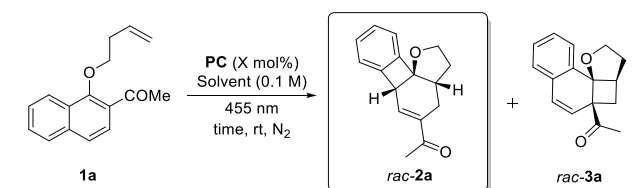

Table 1. Optimization Studies for the Organocatalytic Dearomatization of Naphthol 1a[a]

entry	PC	X	time (h)	solvent	ratio 2a:3a[b]
1[c]	2CzPN	5	17	1,4-dioxane	1.2:1
2[d]	2CzPN	5	17	1,4-dioxane	1.2:1
3	2CzPN	5	17	PhMe	1.8:1
4	2CzPN	5	17	CHCl₃	16:1
5	2CzPN	1	14	CHCl₃	16 (94%)[e]:1
6	2CzPN	0.5	14	CHCl₃	3:1
7	2CzPN	0.2	14	CHCl₃	1:1.6
8[f]	2CzPN	1	17	CHCl₃	1:20
9	TX	5	17	CHCl₃	N/A[g]
10			17	1,4-dioxane	N/A[g]

[a]Reactions were run at a 0.2 mmol scale. [b]Determined by ^{1}H-crude NMR ratio. Entries with a ratio showed no other proton signals and full conversion with isolation of a mixture of **2a** and **3a** in near quantitative yield. [c]0.04 M [d]λ_{max} = 405 nm light was used instead of λ_{max} = 455 nm. [e]94% isolated yield confirms the use of the NMR ratio is a reliable indication of yield. [f]0.1 equiv of Sc(OTf)₃. [g]Not applicable. No conversion of starting material.

these conditions, we were pleased to see full conversion of the starting material but with poor selectivity, as measured by the ratio of **2a**:**3a** (entry 1). This reaction proceeds via two sequential triplet energy excitation processes. First, excitation of **1a** results in a [2 + 2] cycloaddition to form **3a**, while subsequent excitation of **3a** followed by rearrangement

furnishes **2a**. The ultimate ratio of **2a**:**3a** is influenced by the triplet energy of the catalyst and the rate of energy transfer. For the complete mechanism, see Supporting Information 5.1.

Lowering the wavelength from 455 to 405 nm did not influence selectivity (entry 2). After a brief screening of solvents, it was found that chloroform was ideal, leading to formation of **2a** with a high selectivity of 16:1 (entry 4). We were able to lower both the reaction time to 14 h and the catalyst loading to 1 mol % without impacting the reaction (entry 5). Further lowering the catalyst loading resulted in worse selectivity (entries 6 and 7). Through the addition of a Lewis acidic additive, the reaction could be directed toward the selective formation of **3a** (entry 8). However, this observed effect proved not to be general to other substrates.

Therefore, 1 mol % **2CzPN** in chloroform irradiated at 455 nm for 14 h were chosen as the optimized conditions, giving **2a** in 94% isolated yield as a single diastereomer and with a **2a**:**3a** ratio of 16:1 (entry 5). In comparison, the optimized conditions of Glorius utilizing 1 mol % [Ir–F] (1,4-dioxane; 0.04 M; 18 h; 455 nm) achieved a ratio of 6:1 with a yield of 86%,[3] showing that **2CzPN** is able to improve the selectivity of the reaction. Control experiments utilizing the organic photosensitizer thioxanthone (TX), which absorbs at lower wavelengths[16] (entry 9), and irradiation without any catalyst (entry 10) resulted in no conversion, proving the necessity of **2CzPN**.

With optimized conditions in hand, tailored to the organic dye **2CzPN**, the substrate scope was investigated to better compare **2CzPN** with [Ir–F]. To do so, five substrates were selected with different electronic and steric properties at the activating group R[1] as well as at the naphthyl ring R[2] (Scheme 2). For ease of comparison, the already reported yields with 1 mol % of the iridium catalyst [Ir–F] are included in brackets. Based upon these yields, it is evident that **2CzPN** is able to catalyze the dearomatization of naphthols in a highly efficient fashion that is comparable or superior to [Ir–F].

Scheme 2. Substrate Scope of Naphthols[a]
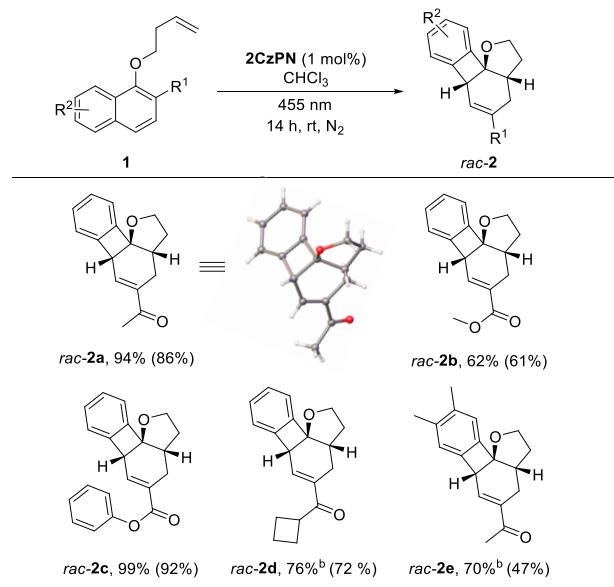
[a]Yields are isolated yields. Yields in brackets are isolated yields of the originally reported reactions with 1 mol % [Ir–F].[3] Reactions were run on a 0.2 mmol scale at 0.1 M. [b]Two mol % **2CzPN**, 42 h.

Reactions with **2CzPN** readily scale and could be performed equally effectively in multiple gram quantities with only 1 mol % catalyst (Scheme 3A). We were also able to take advantage

Scheme 3. Scale-up of the Reaction with Recycling of Catalyst (A) and Subsequent Reaction with Recycled Catalyst (B)
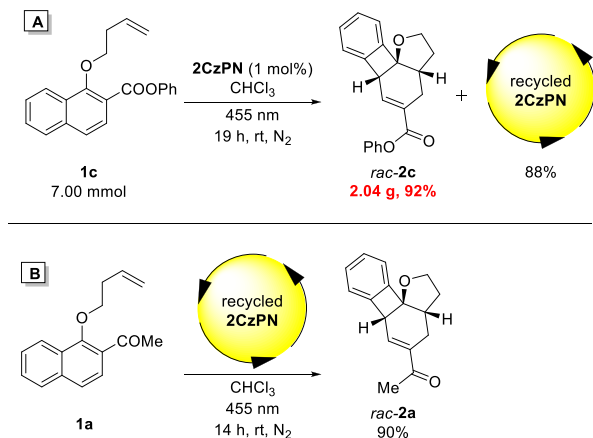
of **2CzPN**'s neutral charge to readily recycle the catalyst by means of column chromatography in 88% yield, and the recycled catalyst shows no change in activity upon reuse (Scheme 3B).

Motivated by the positive results, we explored the compatibility of **2CzPN** with the dearomatization of indole derivates. This class of compounds represents a more challenging test due to their increased triplet energy. While the optimized conditions for naphthol dearomatization resulted in very poor conversion of **4a**, it was found that utilization of toluene as solvent allowed the reaction to proceed in high yields (Supporting Information 3.1). It is thought that the use of the less polar toluene solvent inhibits electron transfer from the indole substrate to the excited photocatalyst that preferentially occurs over triplet sensitization in polar solvents.

The ability to utilize nonpolar solvents with **2CzPN** highlights another advantage of this organic photosensitizer over the [Ir−F] system, which is only minimally soluble in toluene (100−1000 ppm)[10a] and other nonpolar solvents due to its charged nature (Table 2). A comparison of the maximum solubility in a range of different solvents revealed a more than 100 times higher solubility of **2CzPN** in toluene. It is noteworthy that the organic catalyst retains high solubility in polar solvents.

Table 2. Maximum Solubilities of [Ir−F] and 2CzPN in Common Organic Solvents[a]

solvent	[Ir−F][b]	2CzPN[c]
PhMe	7.0×10^{-5}	1.3×10^{-2}
1,4-dioxane[c]	2.2×10^{-4}	1.6×10^{-2}
DCM	5.6×10^{-3}	8.3×10^{-2}
methyl *tert*-butyl ether	7.0×10^{-5}	9.2×10^{-4}
DMSO	1.6×10^{-1}	1.6×10^{-2}

[a]Maximum solubility given as concentration (Molar). [b]As reported by the group of Weaver.[10a] [c]See Supporting Information 3.4.

To demonstrate the efficiency of our conditions, a scope of indoles was investigated (Scheme 4). Just as with [Ir−F],

Scheme 4. Substrate Scope of Indoles[a]
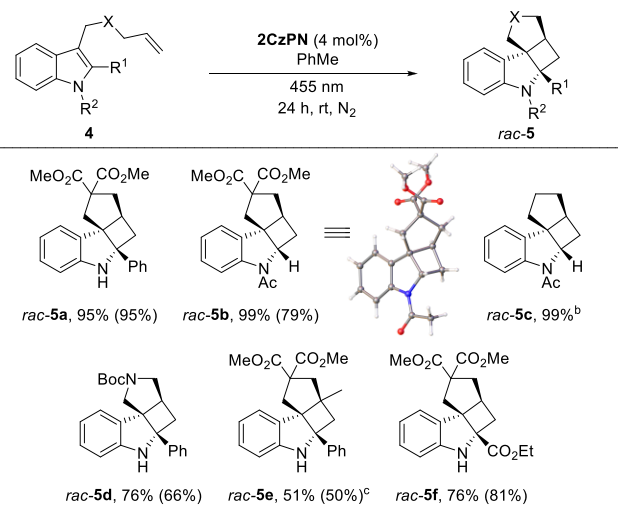
[a]Yields are isolated yields. Yields in brackets are isolated yields of the originally reported reactions with [Ir−F].[4] Reactions run on a 0.05 mmol scale at 0.0125 M. [b]Nineteen hours. [c]Originally reported reaction with 8 mol % [Ir−F].

substitution at the 2-position was well-tolerated (**5a**, **5d**, **5e**, and **5f**), as was the use of a more sterically hindered 1,1-disubstituted alkene (**5e**). The reaction proceeds utilizing substrates bearing the free indole N−H or an *N*-acetyl group, with the highest yields observed with the acetylated substrates (**5b**, **5c**). These nearly quantitative yields are thought to be attributed to the electron-withdrawing nature of the acetyl group, which lowers the triplet energy of the substrates while at the same time increasing their oxidation potential to limit redox events with the catalyst. Using an *N*-acetylated substrate, we were especially delighted to find that high levels of reactivity could be obtained without the bulky diester linker which facilitates ring closure via the Thorpe−Ingold−Effect (**5c**).[17] Once again, for all substrates tested, the organic photosensitizer proved to be comparable or superior to [Ir−F] at equivalent catalyst loadings.[4]

Having established that the organic catalyst is an effective replacement for [Ir−F], we sought to test the organic photocatalyst on more challenging cases containing allene cycloaddition partners that have the potential to form highly strained methylencyclobutane products.[18] This class of substrates is particularly intriguing due to the presence of an olefin in the product that can serve as a functional group handle for further structural elaboration.

Whereas the direct UV excitation of aromatic rings followed by their trapping with allenes has been reported, little has been done within the field of visible-light triplet-sensitized chemistry.[18] A rare example of triplet-sensitized chemistry involving allenes is the work of Arai and Ohkuma, where 50 mol % of 3′,4′-dimethoxyacetophenone sensitizer was required in the dearomative cycloaddition of indole derivatives.[18d,e] However, in addition to the high catalyst loading, a high-pressure mercury lamp was necessary (Supporting Information 5.2). Inspired by their work, we synthesized allene **6** to investigate whether **2CzPN** can overcome these significant

limitations. Applying the same optimized conditions as for **4b**, we were pleased to see full conversion of **6** to the dearomatized products **7** and **8** in high yield and with a ratio of 5.3:1 (Scheme 5).

Scheme 5. Formation of Methylencyclobutane Products from Allene Substituted Indole 6[a]
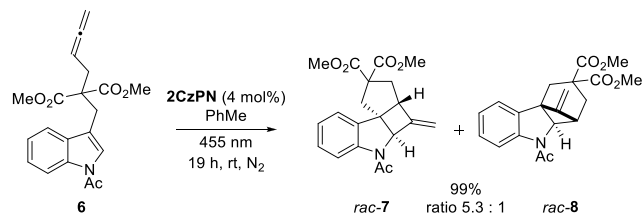
[a]Isolated yield. Reaction has previously not been reported with [Ir—F]. The reaction was run on a 0.05 mmol scale at 0.0125 M.

We next explored the previously unreported visible-light photochemistry of naphthol allene derivatives. When treating naphthol ketone **9a** with slightly modified conditions described above for the dearomatization of naphthols, we were surprised to obtain the aromatic cyclic acetal **10a** as the main product in 61% yield. The product was confirmed by a single crystal X-ray analysis (Supporting Information 7.3) and supported by the literature-known UV-photochemistry of allenyl salicylaldehydes.[18b,c] We believe that **10a** is formed via dearomatized intermediate **12** that upon 1,3-allylic transposition yields product **10a**. As a minor side product under these conditions, dihydrofuran **11a** was also obtained via a 1,4-cycloaddition. By exchanging the acetyl group (**9a**) with a phenyl ester (**9b**), only the dearomatized product **11b** was observed in 81% yield (Scheme 6).

Scheme 6. Dearomative Cycloaddition of Allene-Substituted Naphthol Derivatives[a]
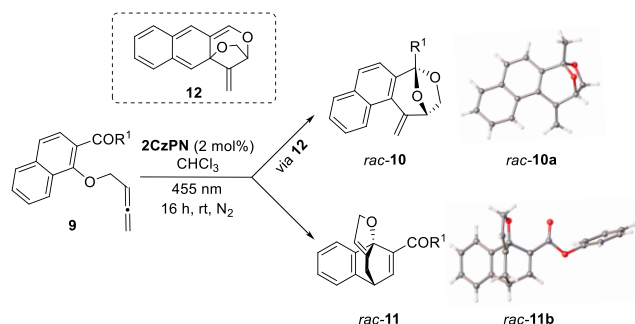
entry	R[1]	10	11
1	Me (**9a**)	61% (**10a**)	15% (**11a**)
2	OPh (**9b**)	0%	81% (**11b**)

[a]Yields are isolated yields. Reaction has previously not been reported with [Ir—F]. Reactions were run on a 0.1 mmol scale at 0.05 M.

In conclusion, we have shown **2CzPN** to be a highly effective and general triplet sensitizer that can serve as an effective replacement for the expensive [Ir—F] catalyst that has until now been the preferred sensitizer to activate substrates with high triplet energies via visible light. Through a series of direct comparisons, the organic catalyst consistently matched or outperformed the iridium catalyst in dearomative cycloadditions. The organic dye was furthermore applied in the previously not reported visible-light induced photocycloaddition of naphthol and indole allenes, giving rise to complex polycyclic frameworks. The catalyst itself is readily synthesized in gram quantities in one step from cheap and commercial starting materials and is bench-stable. Its uncharged nature allows for solubility in a broad range of polar and nonpolar solvents and for easy recovery and reuse of the catalyst via column chromatography. Finally, reactions performed with **2CzPN** have proven to be readily amenable to large, multigram scales. We believe that the presented work will facilitate a broader use of visible-light mediated triplet-sensitized reactions through the identification of a cheap organic replacement for the previously utilized iridium catalyst.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01622.

Experimental details, characterization data, and spectra (PDF)

Accession Codes

CCDC 1998653−1998654, 1998663, and 2000974 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.

■ ACKNOWLEDGMENTS

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