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James, Michael J. orcid.org/0000-0003-2591-0046, Schwarz, Jonas Luca, Strieth-Kalthoff, Felix et al. (2 more authors) (2018) Dearomative Cascade Photocatalysis:Divergent Synthesis through Catalyst Selective Energy Transfer. Journal of the American Chemical Society. pp. 8624-8628. ISSN 1520-5126

https://doi.org/10.1021/jacs.8b03302

Dearomative Cascade Photocatalysis: Divergent Synthesis through Catalyst Selective Energy Transfer

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Supporting Information Placeholder

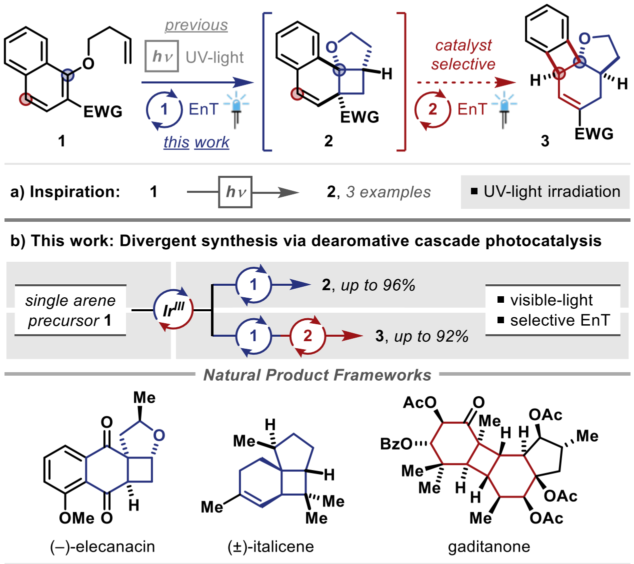
ABSTRACT: The discovery and application of dearomative cascade photocatalysis as a strategy in complex molecule synthesis is described. Visible-light-absorbing photosensitizers were used to (sequentially) activate a 1-naphthol derived arene precursor to divergently form two different polycyclic molecular scaffolds through catalyst selective energy transfer.

Cascade reactions, processes in which multiple chemical bonds are formed and cleaved in a one-pot operation via a well-understood mechanistic sequence, provide an attractive solution to minimize labor and time inputs in the synthesis of complex organic molecules.[1] The efficiency of cascade reactions is perhaps most elegantly demonstrated in nature, where multiple complex natural products are often assembled from a single intermediate in divergent enzymatic cascades.[2] Unsurprisingly, attempts to mimic nature in this regard have inspired the development of multiple methodologies and their application in total synthesis.[3,4] The power of this approach was recently illustrated by Gilmour and co-workers, who pioneered the use of (–)-riboflavin-mediated cascade photocatalysis to emulate the biosynthesis of coumarins.[3f]

In a complementary fashion to cascade reactions, dearomatization reactions offer another promising strategy to minimize synthetic costs by utilizing abundant and inexpensive two-dimensional (2D) industrial feedstocks to directly form highly complex three-dimensional (3D) molecular scaffolds.[5] Moreover, dearomatization strategies utilizing visible-light, as another abundant natural resource, offer further benefits regarding cost and environmental sustainability.[6] A prominent recent example of such an approach can be found in the elegant work of Sarlah and co-workers, who utilized visible-light absorbing arenophiles to enable the two-step dearomative functionalization of simple benzenoid arenes.[7]

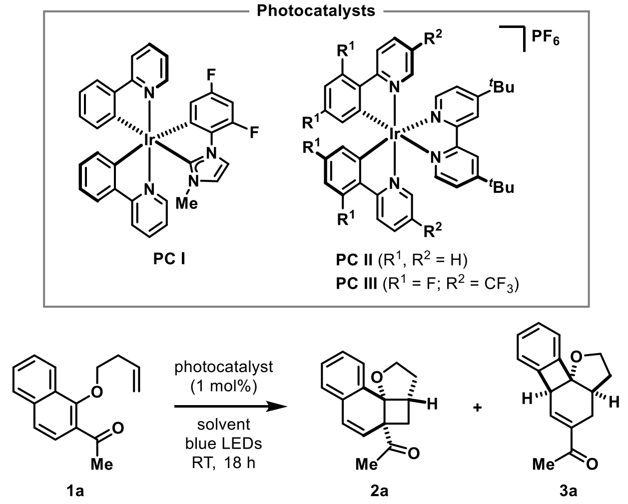
Herein, we describe a combination of the aforementioned reaction classes,[8] whereby visible-light-mediated photocatalysis was used to promote and control a dearomative cascade reaction process. This approach was inspired by the pioneering work of Wagner and co-workers, who used UV-light to induce the cycloaddition of alkenes to triplet benzenes.[9] In particular, our work focused on the underexplored photochemical reactivity of 1-naphthol arenes, which have previously been shown to undergo [2 + 2] cycloadditions under irradiation with UV-light (3 examples, Scheme 1a). In our approach, a variety of simple 2D naphthol arenes were sequentially activated with a visible-light-absorbing photosensitizer to directly prepare natural product-like 3D molecular scaffolds[10] with defined contiguous stereocenters, in a single operation (Scheme 1b). Furthermore, through careful choice of photosensitizer and conditions, we report to the best of our knowledge, the first known example of divergent synthesis using catalyst selective energy transfer (EnT).

Scheme 1. (a) Previous UV-light-promoted [2 + 2] dearomatization reactions. (b) This work: Divergent synthesis through dearomative cascade photocatalysis.



Our studies began by examining the reactivity of naphthol-derivative **1a** under visible-light photocatalytic conditions (Table 1, entries 1–3).[11] Pleasingly, a number of iridium-based photocatalysts were found to efficiently promote the expected cycloaddition to form styrene **2a**. Intriguingly, we also observed the formation of a second product **3a** with an exotic 6/4/6/5 ring system (whose structure was unambiguously confirmed by X-ray crystallographic analysis, Figure 1).[12] Further screening studies (entries 4–8) revealed that either product **2a** or **3a** could be selectively prepared in excellent yield by reaction with **PC II** (1 mol%) in MeOH (0.02 M) or **PC III** (1 mol%) in 1,4-dioxane (0.04 M) respectively. We were further intrigued by these observations when we began to suspect that benzocyclobutene **3a** was formed via a photocatalytic rearrangement of styrene **2a**, which would constitute an unusual and synthetically powerful photocatalytic dearomative cascade reaction.

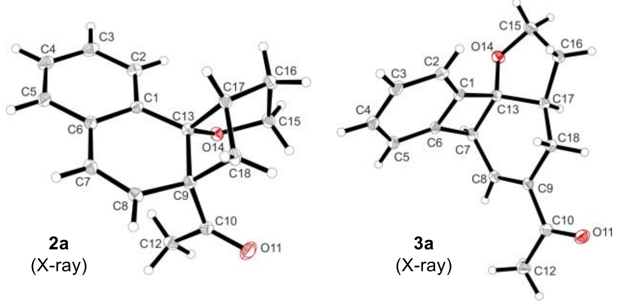
Table 1. Reaction discovery and optimization studies



Entry	Catalyst[a]	Solvent	Yield (%)[b] 2a	3a
1	**PC I**	MeCN	58	42
2	**PC II**	MeCN	67	30
3	**PC III**	MeCN	21	79
4	**PC II**	1,4-dioxane	45	53
5	**PC II**	DCE	64	36
6	**PC II**	MeOH[c]	93	7
7	**PC III**	DCE	19	81
8	**PC III**	1,4-dioxane	15	85

[a] Reactions performed with 0.1 mmol of **1a** and catalyst in the stated solvent (0.04 M) under irradiation with blue LEDs (λ_{max} = 455 nm); [b] Determined by ^{1}H NMR spectroscopy against an internal standard (1,3,5-trimethoxybenzene); [c] 0.02 M.

Figure 1. Crystal structures of 2a and 3a (thermal ellipsoids shown at 15% probability)

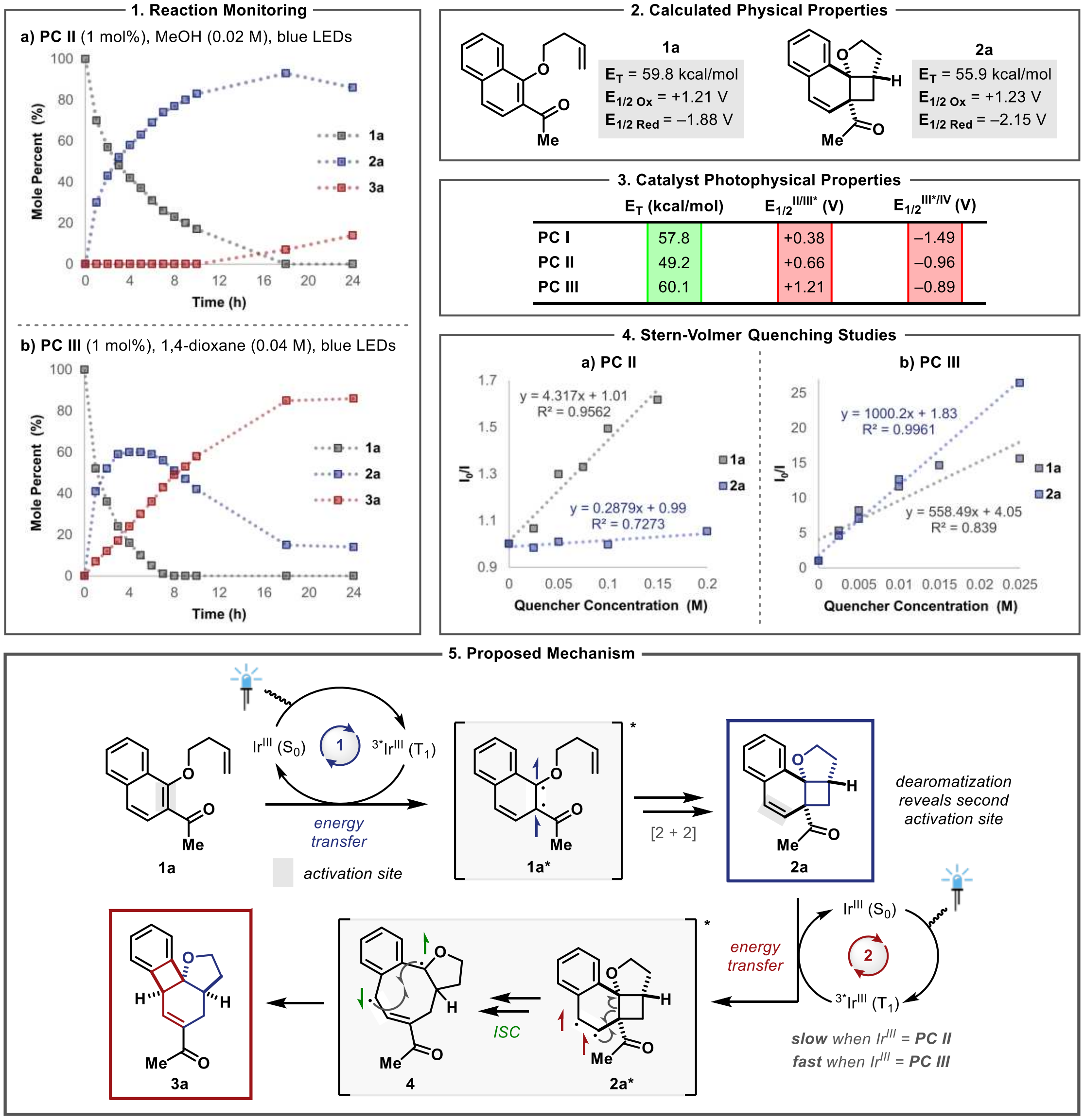


To confirm our suspicions and inspired by the analytical approach of Gilmour and co-workers,[3f] we monitored the formation of both products under the optimized conditions by ^{1}H NMR spectroscopy. Using **PC II**, only the gradual formation of styrene **2a** was observed for the first 18 h, after which the yield was diminished by low levels of conversion into benzocyclobutene **3a** (Scheme 3.1a). However, as suspected, when using **PC III** the simultaneous and rapid conversion of naphthol **1a** into styrene **2a**, and styrene **2a** into benzocyclobutene **3a**, was immediately observed (Scheme 2.1b). To decipher potential modes of photocatalyst activation (electron or energy transfer) for each step, computational studies were performed to calculate the physical properties of **1a** and **2a** (Scheme 2.2). From the comparison of these results with the known photophysical properties of **PC I–III** (Scheme 2.3),[13] it became evident that there was no feasible correlation between the oxidation or reduction potentials of the photocatalysts and the formation of **2a** and **3a**, suggesting that a photoinduced single electron transfer (SET) oxidation or reduction process was not in operation for either step. However, a clear correlation was observed between photocatalyst triplet energy and the selective formation of **2a** and **3a**.[14] Selectivity in this instance would then presumably be controlled by the relative rates of EnT. Considering this, Stern-Volmer quenching studies were then performed to illustrate the relative rates of EnT (Scheme 2.4); these studies showed that while both photocatalysts were readily quenched by naphthol **1a**, only **PC III** was effectively quenched by styrene **2a**, suggesting that there is insufficient spectral overlap for efficient EnT with **PC II** (for evidence in support of this, see the supporting information). Further control experiments also precluded the possibility that these reactions were promoted in a non-photocatalytic thermal pathway.[11] Considering these studies, we propose the following mechanistic pathway for the formation of both products (Scheme 2.5). First, irradiation of the Ir^{III} photosensitizer produces its long-lived triplet excited state, which activates naphthol **1a** via EnT (both **PC II** and **PC III**), to afford triplet intermediate **1a***. The triplet naphthalene species **1a*** then engages in an intramolecular dearomatizing [2 + 2] cycloaddition with the pendant alkene to afford styrene **2a**.[15] Following this dearomatization step, the remaining π-system of styrene **2a** is selectively activated by **PC III** via another energy transfer event to form **2a***. The triplet styrene **2a*** then undergoes a vinyl cyclobutane rearrangement,[16] whereby the C–C bond of the adjacent cyclobutane ring is fragmented to form diradical intermediate **4**, which following intersystem crossing and radical-radical recombination affords benzocyclobutene **3a**.

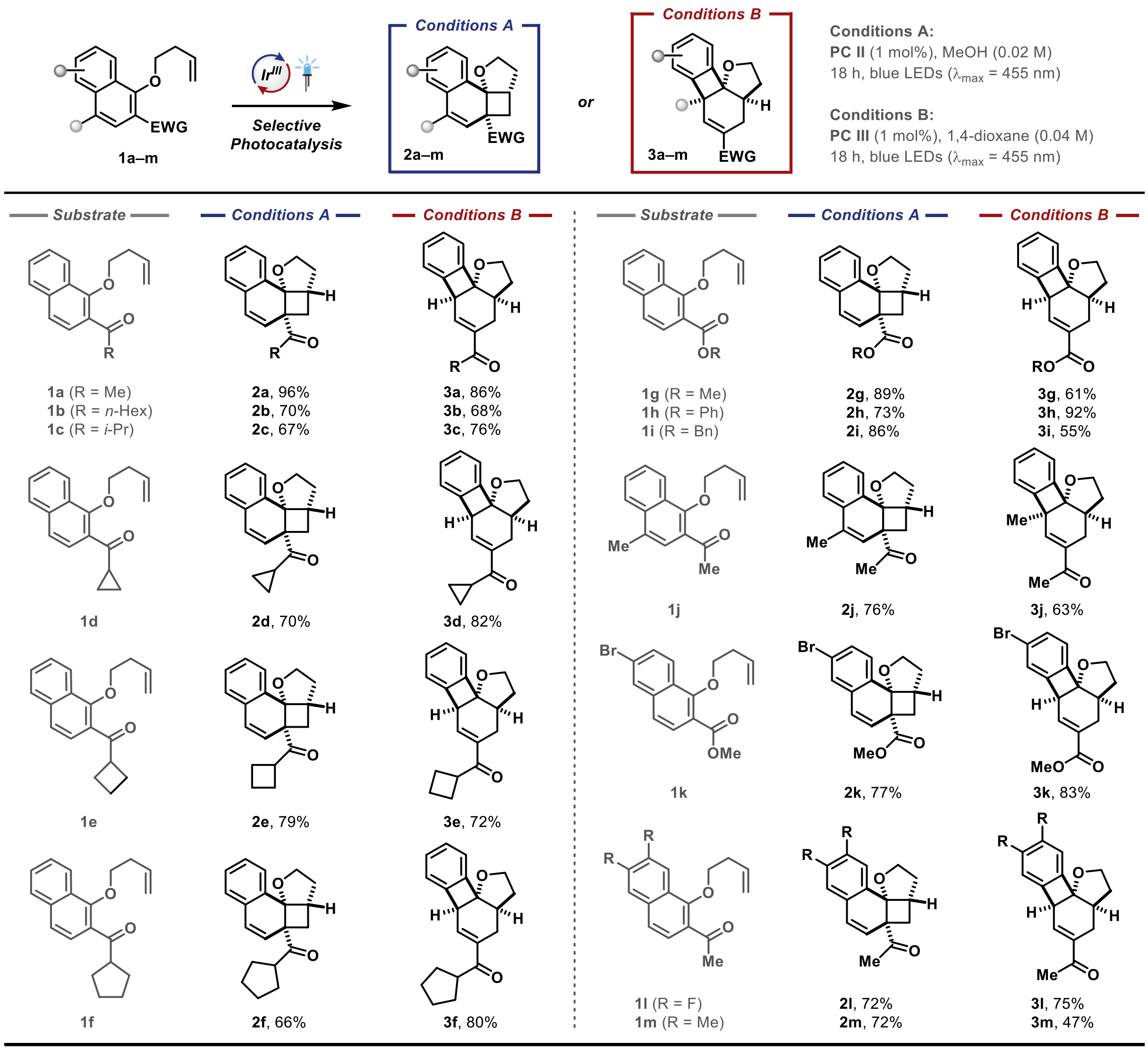
Having concluded mechanistic studies, we sought to examine and establish the generality of this photocatalytic dearomative cascade. Thus, a variety of naphthol arenes **1a**–**m** were readily prepared and reacted under both sets of the optimized reaction conditions on a larger synthetic scale (Scheme 3). First, we examined naphthols bearing primary and secondary aliphatic acyclic substituted ketones (**1a**–**c**), which were all converted into the desired products in good to excellent yield. Next, cyclic substituted ketones (**1d**–**f**) were examined, which again were all well-tolerated under both sets of conditions. Similarly, naphthols bearing alkyl (**1g**), aryl (**1h**) and benzyl esters (**1i**) also afforded the desired products in typically excellent yield, which could all be readily used to make derivatives of these complex scaffolds. However, it should be noted that no reaction was observed in the absence of a carbonyl-based electron withdrawing group, which is presumably necessary to lower the triplet energy of the aromatic system.[11] Next, naphthols with substituents and functional group handles installed on the naphthalene rings were studied to illustrate the ability of this method to access highly challenging structural motifs. For example, 4-Me substituted naphthol **1j** was readily converted into benzocyclobutene **3j**, which possess contiguous quaternary stereocenters, with perfect diastereoselectivity. The bromide substituted naphthol **1k**, which could also enable the diversification of these complex scaffolds, was converted into both of the desired products in excellent yield. Next, 6,7-disubstituted naphthols (**1l**,**m**) were then readily prepared and converted into the desired products in modest to good yield. Unfortunately, whilst substrates bearing substituted alkenes readily engaged in the [2 + 2] photocycloaddition step with **PC II**, they failed to cleanly form the corresponding benzocyclobutene products with **PC III**. This limitation is tentatively attributed to changes in radical stability, which may enable competitive ring-opening/fragmentation pathways from the triplet styrene intermediates (evidence in support of this and discussions of other limitations can be found within the supporting information).

In summary, we have reported the discovery and application of dearomative cascade photocatalysis as a strategy in complex molecule synthesis. Simple naphthol arenes were selectively and divergently converted into complex stereodefined polycyclic products using catalyst selective energy transfer.[17] We hope that the individual elements of this work will serve to inform several lines of future research, such as potential asymmetric variants[18] or the controlled photosensitized rearrangement of other styrenyl substituted ring systems. More generally, we envision the application of this synthetic strategy to other arene systems utilizing other photocatalytic activation modes and cyclization processes.[19] Overall, we believe that this work will inspire and enable the photochemical synthesis of other complex molecular frameworks with unprecedented levels of selectivity.

Scheme 2. Mechanistic studies: (1) Reaction monitoring by ^{1}H NMR with a) PC II and b) PC III. (2) DFT calculated physical properties. (3) Summary of photocatalyst photophysical properties. (4) Stern-Volmer quenching studies with 1a, 2a and a) PC II and b) PC III. (5) Proposed reaction mechanism for the divergent reaction protocols



Scheme 3. Substrate scope of the divergent reaction protocols



ASSOCIATED CONTENT

Supporting Information

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

Experimental and computational details (PDF)

Crystallographic Data for **2a** and **3a** (CIF)

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported by the Alexander von Humboldt Foundation (M.J.J.), the Alfried Krupp von Bohlen and Halbach Foundation (J.L.S., F.S-K.) and the Deutsche Forschungsgemeinschaft (Leibniz Award and SFB858). We thank Dr Z. Nairoukh, A. Tlahuext-Aca and M. Teders (all WWU) for helpful discussions.

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(12) CCDC 1831750 (**2a**) and 1831751 (**3a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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