

Polycycles

Visible-Light Promoted Intramolecular *para*-Cycloadditions on Simple Aromatics

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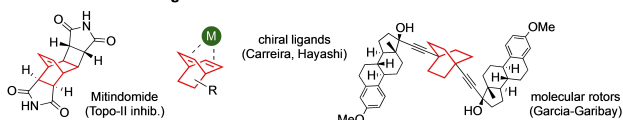
Abstract: Dearomative cycloadditions are a powerful tool to access a large chemical space exploiting simple and ubiquitous building blocks. The energetic burden due to the loss of aromaticity has however greatly limited their synthetic potential. We devised a general intramolecular method that overcomes these limitations thanks to the photosensitization of allenamides. The visible-light-promoted process gives complex [2.2.2]-(hetero)-bicyclooctadienes at room temperature, likely through the stabilization of transient (bi)radicals by naphthalene. The reaction tolerates several valuable functionalities, offering a convenient handle for a myriad of applications, including original isoindoles and metal complexes.

The minimization of time and wastes is crucial to ensure a sustainable supply of functional molecules. In this context, the conversion of aryl and alkenyl groups into bridged [2.2.2]-bicycles is an ambitious strategy because it requires lower synthetic efforts with respect to Diels–Alder cycloadditions (Scheme 1), such as those between phenol-derived cyclohexadienones and alkenes.^[1] Moreover, the bicyclooctane core is present in a myriad of bioactive species, key synthetic intermediates, molecular machines and organometallic catalysts. However, the reluctance of the aryl partner to relinquish its aromatic stabilization^[2] is the key challenge that has to be faced. Aromatic *para*-cycloadditions are still underdeveloped because of these issues. Further-

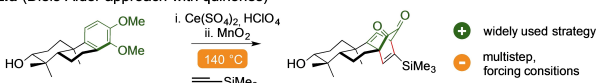
The strategy



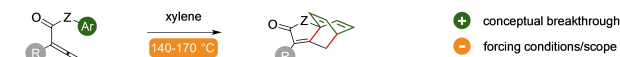
Countless diversified targets



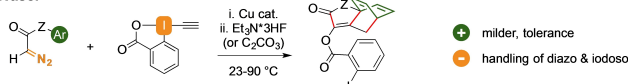
Liu (Diels–Alder approach with quinones)



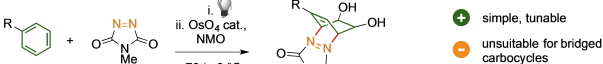
Himbert



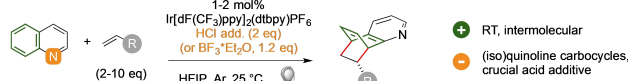
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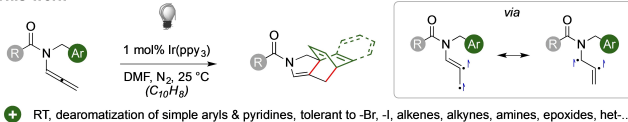
Sarlah



Brown/Houk/Glorius



This work



Scheme 1. Strategies for the assembly of [2.2.2] bicyclic cores.

more, substrates are often more thermodynamically stable than products,^[3] like in natural photosynthesis.

Himbert reported thermal approaches for the cycloaddition of cumulated double bonds on aryl rings.^[4] These elegant reactions have narrow scope because of the required heating. Similar limits are common for UV-based methods, too.^[5] Waser showed that allenates can undergo a concerted cycloaddition under gentler heating.^[6] The method is valuable, but still requires the preparation of a diazo derivative and an ethynylbenziodoxolone.

Photochemical strategies are a promising tool for dearomatizing cycloadditions because they generate highly energetic species that can evolve into endergonic products.^[7] Two complementary approaches can be used.

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Reactions involving the excitation of a conjugated double bond can be applied to different types of arenes. Sarlah reported that 1,2,4-triazolin-3,5-diones and simple arenes form adducts that can be activated by visible light.^[8] The resulting exciplex readily forms a cycloadduct that can be functionalized or fragmented. Glorius activated cinnamoyl amides^[9] via energy transfer (eT)^[10] to accomplish the intramolecular cycloaddition on conjugated pyridines and bicyclic aza-arenes.

An alternative approach involves the excitation of the aryl partner. In this case, conditions are usually specific for each type of arene, and *ortho*-cycloaddition is often favored.^[3] Recently, visible-light has been used to activate the carbocycle of quinolines^[11] by eT in the presence of an acid additive. The reaction leads to the *para*-cycloadducts, but simple arenes cannot be excited because they have triplet energies (E_T) that are beyond the energetic ceiling of visible-light photons.

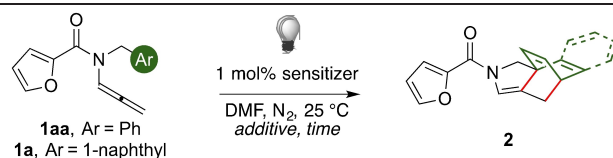
We report herein the first, general visible-light-promoted intramolecular *para*-cycloaddition on simple (hetero)aromatics. The key element is the sensitization of an acyllenamide unit, which generates an allene triplet that triggers the dearomatization. Moreover, naphthalene (NP) had a dramatic effect on rate. Its π cloud could likely stabilize transient (bi)radicals according to DFT. This concept has not been previously exploited in synthesis. It thus holds for ample future developments.

The process occurs at 25 °C and delivers complex architectures with a broad functional-group tolerance. Products are recovered in good to excellent yields and the atom-economical reaction has several applications, from synthetic purposes to the preparation of complexes.

We recently observed that it is possible to dimerize enallenamides.^[12] A minor byproduct observed in that study had a [2.2.2]-bicyclooctadiene unit, which was established through the dearomatization of a benzyl group. Reasoning on the potential of the reaction, we tried to develop it. Typically, a solution of the substrate and the photosensitizer was degassed by freeze-pump-thaw, kept at 25 °C and irradiated with a 14 W-household LED strip. Preliminary screening of substrates showed that the reaction was always very slow. Irradiation for at least two weeks was required to fully convert the starting material. This severe practical limit was coupled with partial substrate decomposition, which slowly occurred through time. We then identified **1aa** as a promising model for optimization (Table 1).^[13]

The reaction of **1aa** reached completion upon 10 days of irradiation, allowing one to isolate **2aa** in 46 % yield. Mass balance could be accounted for by substrate decomposition/deallynylation. Several different solvents, including binary mixtures, did not improve the outcome. A higher catalyst loading proved futile. Switching to different photosensitizers and photocatalyst, none proved better than Ir-complexes. These results suggested that we shelve the project. However, the model reaction was then carried out using **1a**. The rate of the reaction was ca. two orders of magnitude faster than that of **1aa** (entry 5). The product **2a** was isolated in 99 % yield upon three hours of irradiation. We thus added NP to the reaction of **1aa**. The additive proved beneficial, ensuring

Table 1: Selected optimization reactions.^[a]



Entry	Reagent	Sensitizer	Additive [equiv]	t [h]	Yield of 2 [%]
1	1aa	Ir(ppy) ₃	–	240	46
2 ^[b]	1aa	Ir(ppy) ₃	–	240	44
3 ^[c]	1aa	TXT	–	240	–
4	1aa	Ir(p-F-ppy) ₃	–	96	45
5	1a	Ir(ppy) ₃	–	3	99
6	1aa	Ir(ppy) ₃	C ₁₀ H ₈ (10)	48	60
7	1aa	Ir(ppy) ₃	C ₁₀ H ₈ (20)	38	64
8	1aa	Ir(ppy) ₃	1-Methoxy-naphthalene (10)	24	70
9	1a	–	–	96	–
10 ^[d]	1a	Ir(ppy) ₃	–	96	–

[a] Reaction condition: 0.15 mmol of **1** (0.1 M in DMF), 1 mol % sensitizer, in 5 mm NMR tube under N₂, isolated yields; [b] in toluene; [c] with 10 mol % of thioxanthone (TXT); [d] without light.

the full consumption of **1aa** in 38 hours. The use of 1-methoxynaphthalene gave a better result (entry 8). However, its higher cost and a more complicated recovery from the crude led us to prefer the conditions of entry 7. Finally, no reaction took place without either the sensitizer or light, using both **1a** and **1aa**.

Figure 1 summarizes the scope of the cycloaddition.^[14] Substrates were generally prepared by reductive amination, *N*-derivatization and alkyne isomerization. The study begun with reagents bearing a naphthyl unit (pink box). Furans, thiophene and pyridine were tolerated by the method (**2a–c**). The amido group could be replaced by a carbamate (**2d–g**). No major electronic effect was observed on the unreacted aryl ring of the substrate (**2h–m**). It is worth noting that halogens are fully compatible with the method, including bromides and iodides (**2l–m**). The R group could be further varied, allowing one to incorporate cyclopropyl, alkenes or alkynes into the final product (**2n–q**). Racemic disubstituted allenes afforded products in good yields. The naphthyl arm could be decorated without hampering the reaction (**2t–u**). Finally, a tetrahydropyridine ring could be sealed (**2v**). In all cases, the substrate was fully consumed in a few hours and overnight irradiation was required at most. The reaction could be scaled up to 1-mmol using a vial without a significant yield loss. The freeze-pump-thaw procedure is not crucial for **1a–v**, although full conversion is achieved faster by performing it (2–4 hours).

We next tested the *para*-cycloaddition onto simple aryl rings (cyan box). Several aryl amides, including perfluorinated rings and phenylacetylene ones, could be used, delivering products in moderate to good yields (**2aa–af**). The benzyl arm that underwent the dearomatization could be variously decorated at its *para*- position (**2ag–an**), affording products with an additional headbridging quaternary carbon. The series includes valuable functions such as amines, terminal vinyl groups, epoxides, pyridines and the

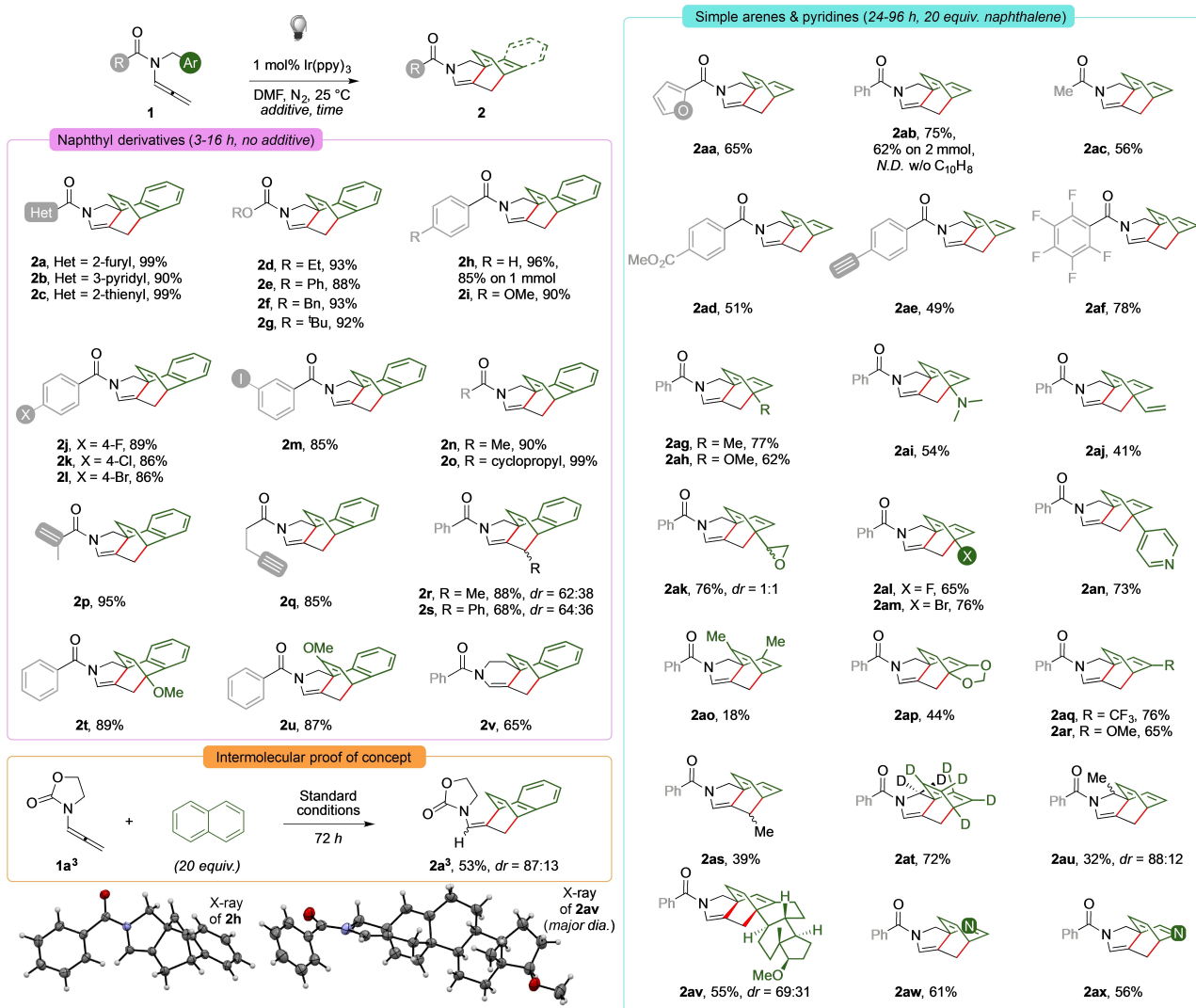


Figure 1. Reaction scope; conditions as Table 1, entry 5 for pink box, entry 7 for cyan box.

formation of allylic bromides. The dearomatization could occur on arenes functionalized in other positions, too (**2ao–ar**). The worst results were observed for 2,6-disubstituted rings, while several other functionalities, such as protected acetals or trifluoromethyl groups, were tolerated regardless of their stereoelectronic demands. Disubstituted allenes could be employed (**2as**) and the method allowed one to efficiently prepare *d*-labelled polycycles (**2at**). The yield was moderate using a reagent with a substituted benzylic position (**2au**). An estradiol-derived substrate gave congested hexacycle **2av** with good stereocontrol. Then, we attempted the cycloaddition on pyridines. 4-Pyridyl and 4-pyridinium groups were unreactive. On the contrary, both 2- and 3-pyridyl rings reacted smoothly, affording valuable imine-containing products (**2aw–ax**). The reaction can be performed on a 2 mmol-scale with a limited yield loss. Finally, an intermolecular reaction between **1a³** and NP delivered **2a³**, showing the potential of future developments.

We next performed experiments to rationalize the mechanism of the reaction (Figure 2). The crucial role of the

acyllallenamide unit was confirmed by testing substrates with either a tosylallenamide group or an allylamide one. Both failed to convert under optimized conditions (pink box). We performed Stern–Volmer quenching experiments on **1a**, **1aa** and NP (cyan box). Allenamide **1aa** is the best quencher and the efficiency of **1a** is lower than that of NP (K_{SV} are 404, 232 and 286 M⁻¹, respectively, details in Supporting Information). No meaningful differences were observed using a mixture of **1aa** and NP.

Calculations were carried out at the M06/Def2-TZVP level, using DMF as implicit solvent,^[15] to rationalize the role of NP. The redox potentials of ³Ir(ppy)₃ are unable to induce any single electron transfer on NP, **1ac** and **1n**. This is confirmed by the calculated ΔG s of these redox events. On the contrary, the E_T of ³Ir(ppy)₃, substrate **1ac**, **1n** and NP are compatible. Calculated values are very close to experimental ones,^[16] showing the reliability of the method.

The reaction of **1n**, which has a naphthyl arm, can involve two pathways. The triplet **I_n** has its spin density localized on the former allenyl arm. Its vinyl radical site

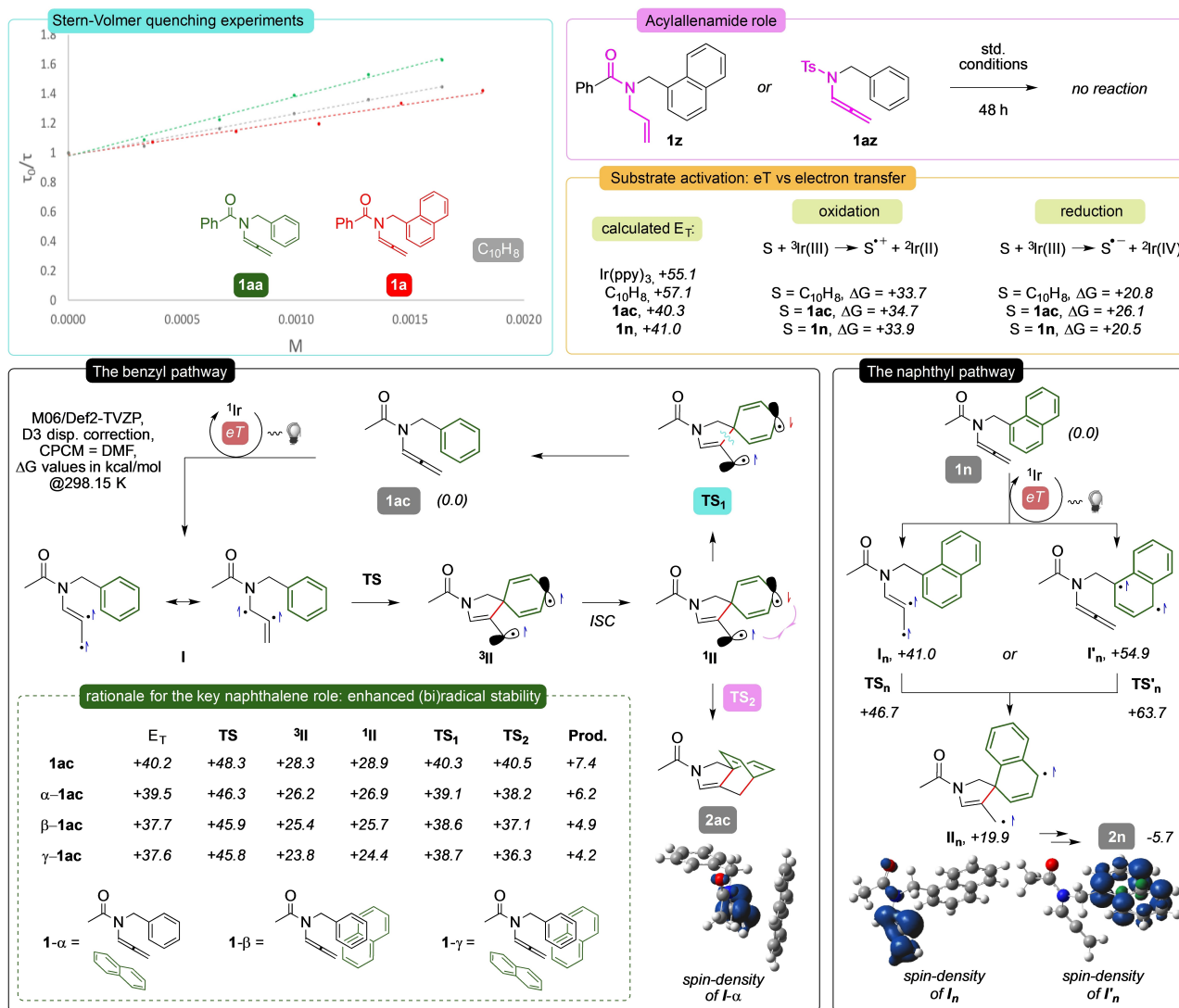


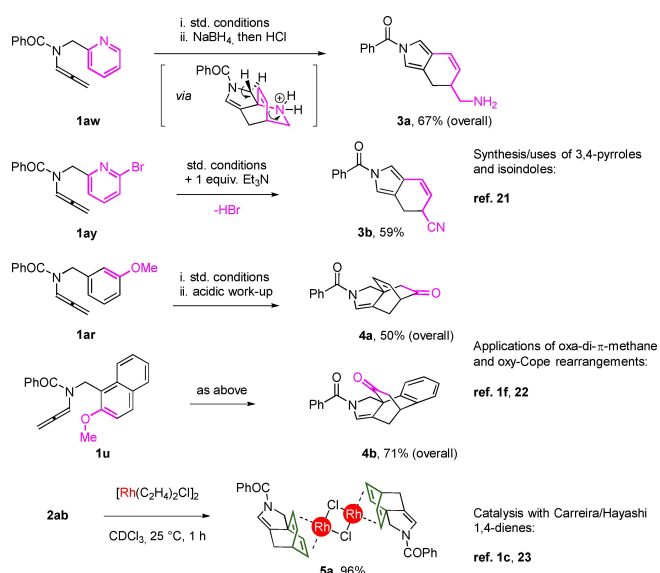
Figure 2. Mechanistic studies.

could attack the aromatic ring through a low-barrier transition state (TS) and this step generates a spiro carbon. The triplet can relax via intersystem crossing (ISC) and the resulting singlet affords **2** upon radical recombination. The less stable triplet **I_n** has the spin density spread over the naphthyl unit. This biradical might evolve into **I_n**, or it could attack the central carbon atom of the allene, delivering **II_n**. The **I'_n**-pathway involves a less stable intermediate and a higher barrier for the TS (+2.1 kcal mol⁻¹ in ΔΔG). It is thus less favorable, in agreement with the lack of reactivity showed by **1z** (pink box).

The reaction of **1ac** has a more energy-costly TS and a less stable intermediate **³II** than that of **1n** (by +2.3 and +8.3 kcal mol⁻¹ in ΔΔG). The two mono-occupied orbitals of **³II** are nearly perpendicular. This arrangement is kept in **¹II**, which forms upon ISC. A rotation of the primary radical is necessary to allow the recombination. The rotation of the primary radical causes the loss of its allylic conjugation, resulting in an additional energy barrier. Two competing

TSs were found for this rotation. The **TS₂** leads to **2ac** while the substrate **1ac** is reformed via **TS₁**, which is favored by 0.2 kcal mol⁻¹. This route prevails because **2ac** is less stable than **1ac** (while **2n** is more stable than **1n**). Overall, the **TS₁** pathway is unproductive. This can explain the large reactivity gap (Table 1) between the two types of substrates.

However, NP can likely stabilize radicals through its π cloud.^[17] Three reactions were modeled adding one NP molecule parallel to the allenyl arm of **1ac**, one stacked to its benzyl ring or two units flanking each arm of the reagent (α, β and γ, respectively). These systems were freely reoptimized taking into account dispersion interactions.^[18] In all cases, the biradicals **I**, **TS** and **II** are more stable than the corresponding entry channel α-, β- and γ-**1ac**. The stabilization is smaller for **I** and **TS** (0.7–2.6 kcal mol⁻¹), and larger for intermediates **II** (2.1–4.5 kcal mol⁻¹). Moreover, **TS₂**s are slightly favored over **TS₁**s (0.1–2.4 kcal mol⁻¹) and the NP-**2ac** adducts are less endergonic (1.2–3.2 kcal mol⁻¹).^[19] Taken together, these effects could explain the enhanced



Scheme 2. Derivatizations of **2**.

reaction rate observed in the presence of NP because the additive reduces the odds that the sensitization of **1ac** is eventually unproductive. It is worth noting that (bi)radical stabilization by π clouds is original with respect to synthetic methods.^[20]

Finally, we devised a few applications of **2** (Scheme 2) to extend the accessible chemical space of the present approach.

The reduction of the imine group of **2aw** followed by acidic work-up afforded isoindole **3a**, offering a concise route to this useful synthetic core.^[21] The dearomatization of **1ay** gave extensive decomposition. However, the addition of triethylamine led to the formation of **3b** in 59% yield via formal elimination of HBr. The dearomatization of methoxy-substituted aryls allowed one to access polycyclic 1,4-enones **4**. These cores have been used to trigger oxa-di- π -methane rearrangements and as precursors for oxy-Cope ones^[22] but their assembly require long synthetic sequences. The 1,4-diene unit of **2** could act as a tunable bidentate ligand that is reminiscent of Carreira/Hayashi dienes.^[1c,23] For instance, Rh^I dimer **5a** readily formed at room temperature.

We reported a practical method to access complex bridged polycycles from simple precursors. The reaction occurs at room temperature and has great functional group tolerance. The intramolecular dearomative cycloaddition takes place thanks to the direct sensitization of an acylallenamide. This reactivity expands the panel of functional groups that could be activated by eT. The possible stabilization of (bi)radicals by the π cloud of NP has not been exploited yet in synthesis, and could thus similarly lead to broad application. Further extension of this concept is currently underway.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Allenes · Cycloaddition · Density-Functional Calculations · Energy Transfer · π Interactions

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