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Thermoneutral synthesis of spiro-1,4-cyclohexadienes by visible-light-driven dearomatization of benzylmalonates†

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A visible-light-driven dearomatization of unactivated arenes with perfect atom economy to access spiro-1,4-cyclohexadienes is disclosed. Calculations suggest that the overall process is approximately thermoneutral, showcasing the special opportunities of light-driven processes to develop sustainable transformations that defy thermodynamic requirements.

Photocatalysis enables chemical reactions by accessing excited states or radical intermediates of appropriate precursors,[1] nevertheless, such transformations are by and large thermodynamically favored. Representative examples are photochemical ATRA reactions[2] or "uphill catalysis" [4 + 2]-cycloadditions,[3] in which the overall exchange of weak π-bonds for strong σ-bonds is the thermodynamic driving force. However, photochemical activation might also allow thermodynamically less favored processes to proceed (Scheme 1a) as demonstrated for *E*/*Z*-isomerization of alkenes[4] or [2 + 2]-cycloadditions, culminating in the synthesis of Dewar benzenes from arenes,[5] in which the products cannot absorb the light-energy offered to revert back to the starting materials.

The hydrogenation of benzene to 1,4-cyclohexadiene[6] is an endergonic process ($\Delta_R G$ = 12.9 kcal mol^{-1}, M06-2X/G-311 + G**, see ESI†) due to the thermodynamically unfavorable dearomatization of the product (Scheme 1b). Known as Birch reduction,[7] this reaction becomes thermodynamically possible ($\Delta_R G$ = −0.1 kcal mol^{-1}, M06-2X/G-311 + G**, see ESI†) by the coupling of a second, exergonic process, *i.e.* employing stoichiometric amounts of lithium metal in liquid ammonia as the terminal reducing reagent in combination with a proton source. More recently, visible light-driven photoredox catalysis has been recognized to offer new opportunities for the dearomatization of arenes under mild conditions.[8] Despite these elegant reports, the synthesis of 1,4-cyclohexadienes by dearomatization of unactivated arenes, especially without the coupling to high-energy reagents or preactivation of the substrates, is still underdeveloped, reflecting the challenge to suppress alternative reaction pathways that will result in rearomatization and thus thermodynamically more favorable products.

We report here the dearomatizative coupling of benzylmalonates and alkynes to spiroanellated 1,4-cyclohexadienes, which proceeds *via* activation with light with perfect atom economy in high yields, despite the fact that the overall process is close to being thermodynamically neutral (Scheme 1d). No preactivation of the substrates or employment of stoichiometric high-energy reagents, being the traditional approach to drive thermoneutral transformations, is necessary.

Related to our study, in 1992 Santi and co-workers described a cascade cyclization between diethyl benzylmalonate and alkynes (Scheme 1c).[9] Under high temperature conditions and using $Mn(OAc)_3$ as overstoichiometric oxidant, dihydronaphthalenes were obtained *via* generation of a malonate radical, followed by addition to an alkyne and cyclization into the benzylic arene group.[9a] When malonates bearing an activating substituent in 4-position (4-F or 4-MeO) were used, spiro[4,5]-decanones were obtained in which oxidation of the arene moiety had taken place.[9b] Zhang and co-workers achieved a visible-light driven photoredox catalytic version to obtain the same spiro[4,5]-decanones, however, in this case the preactivation of the malonate by bromination was required.[10]

Based on this precedent, we questioned if a photocatalytic dearomatization of both unactivated arenes and malonates could also be developed. Through this way, novel 1,4-cyclohexadienes should become accessible with perfect atom economy in a redox neutral and, according to our calculations (M06-2X/6-311 + G** level; see ESI†), close to thermoneutral fashion. To achieve this goal, we envisioned that an initial one-electron oxidation of the malonate to its corresponding radical and after coupling onto an alkyne and cyclization a one electron reduction of a 1,4-cyclohexadienyl radical would be the necessary key steps.

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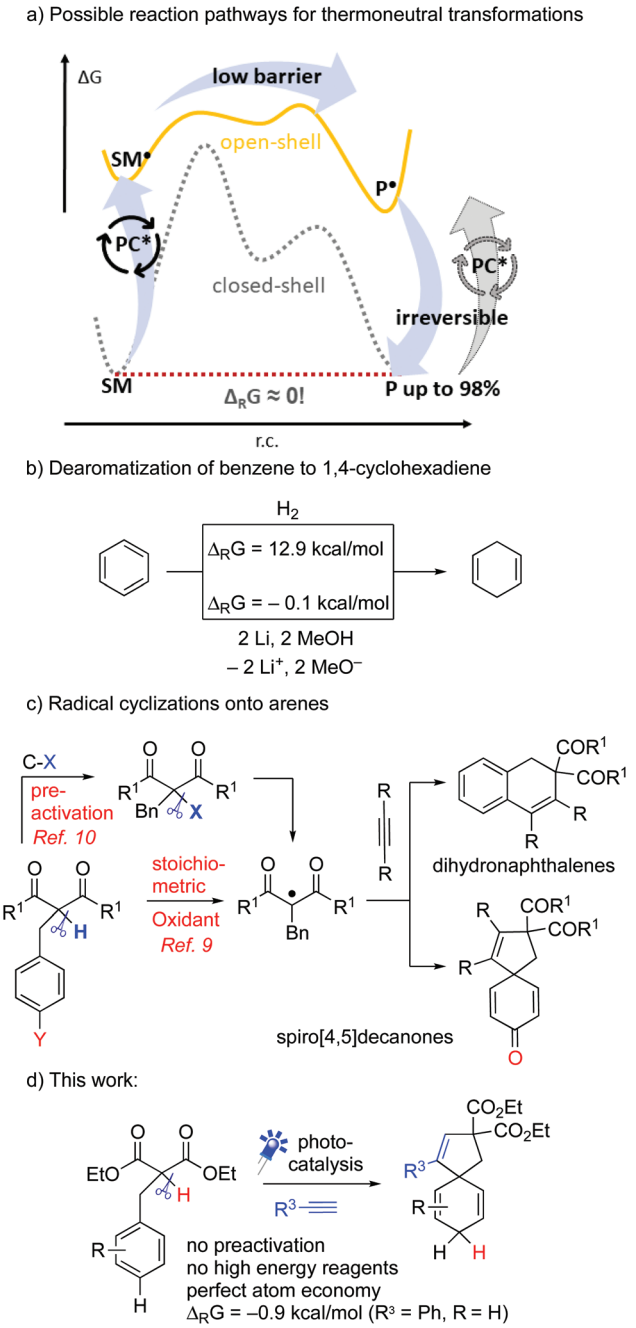
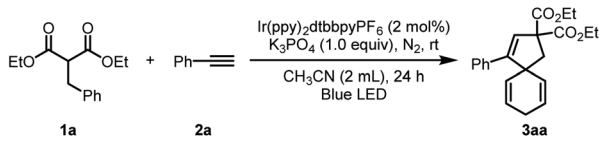


Scheme 1 Thermoneutral reactions *via* photocatalysis aiming at the dearomatization of arenes. PC = photocatalyst, SM = starting material, P = product.

We commenced our studies with readily available diethyl 2-benzylmalonate (**1a**) and phenylacetylene (**2a**) as model substrates (Table 1). After extensive screening (for details see ESI†), the desired spiro-1,4-cyclohexadiene **3aa** was obtained in 96% yield by employing $Ir(ppy)_2dtbbpyPF_6$ as photocatalyst (PC, 2 mol%) under blue LED irradiation (Table 1, entry 1).

Other photocatalysts that are known to be efficient for processes that require an initial one electron oxidation such as 4CzIPN,[11] Mes-Acr-$MeBF_4$[1f] or Cu(II)-complexes such as

Table 1 Optimization of the reaction conditions[a]



Entry	Variation from the standard conditions	Yield[b] (%)
1	None	99 (96)[c]
2	4CzIPN instead of $Ir(ppy)_2dtbbpyPF_6$	nd
3	$Cu(dmp)_2Cl_2$ instead of $Ir(ppy)_2dtbbpyPF_6$	nd
4	Mes-Acr-$MeBF_4$	nd
5	0.8 equiv. of K_3PO_4	78
6	0.5 equiv. of K_3PO_4	74
7	Without PC	nd
8	Without irradiation of visible light	nd
9	Without base	nd

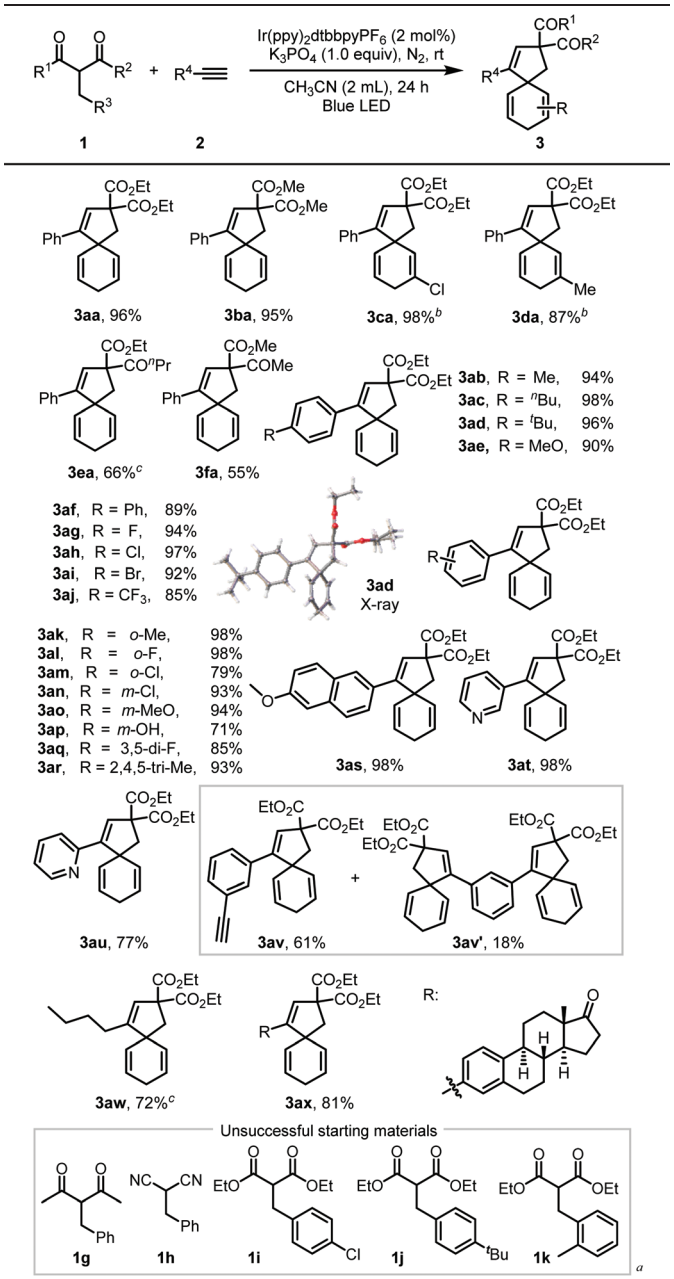
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol, 2.0 equiv.), $Ir(ppy)_2dtbbpyPF_6$ (2 mol%), K_3PO_4 (1.0 equiv.) in CH_3CN (2 mL), N_2, rt, 24 h. [b] Yields were determined by NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield in parentheses.

$Cu(dmp)_2Cl_2$,[12] did not promote the transformation (Table 1, entries 2–4). Besides acetonitrile, only DMF or DMSO as solvents were met with some success, while nonpolar solvents or THF did not result in the formation of **3aa**. The addition of a base was found to be required, and compared to other inorganic or organic bases, K_3PO_4 (1 equiv.) proved to be by far superior, which can also be employed in substoichiometric quantities, however, with somewhat reduced yields (Table 1, entries 5 and 6). Control experiments revealed that each component, *i.e.* photocatalyst, visible-light-irradiation and base is essential for the success of the reactions (Table 1, entries 7–9).

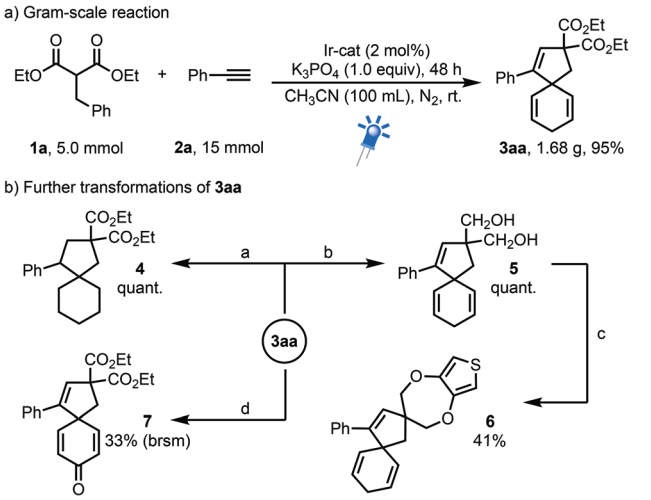
With the optimized reaction conditions in hand, we next explored the scope of the reaction (Table 2 and Scheme 2). With few exceptions, high yields with good functional group tolerance were observed for a representative selection of the two components employed. Besides the two ester groups in the malonate, exchanging one for a keto group (**3ea**, **3fa**) was possible, however, displacing both ester groups for this functionality or substitution by nitrile groups (**1h**) was unsuccessful. The benzylic group in **1** tolerated substitution in *meta*-position as demonstrated for **3ca** and **3da**, while *para* substitution (**1i**, **1j**) was not possible most likely as a consequence of steric and electronic effects to access this position for the final hydrogen transfer. Moreover, *ortho*-substitution (**1k**) was not successful, reflecting the severe steric hindrance of the resulting product.

A wide variety of substituents in the aryl ring of the alkyne component (electron donating and accepting groups in *ortho, meta, para* position) could be employed (**3ab**–**3ar**), but also substitution by naphthyl (**3as**) or pyridyl (**3at**, **3au**) was met with success (77–98% yield). Notably, phenylacetylene **2p** bearing an unprotected hydroxyl group which might be sensitive to the photocatalytic system, was amenable for the process to give rise to **3ap** in 71% yield. 1,3-Diethynylbenzene having two reactive alkyne functionalities gave the monoadduct **3av** in good yield (61%) along with the twofold adduct **3av′** (18%).

Table 2 Substrate scope[a]



[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol, 2.0 equiv.), Ir(ppy)$_2$dtbbpyPF$_6$ (2 mol%), and K_3PO_4 (1.0 equiv.) in CH_3CN (2 mL), N_2, rt, 24 h. [b] 3.0 equiv. of **2a**, 48 h. [c] 10 equiv. of **2**, 24 h.

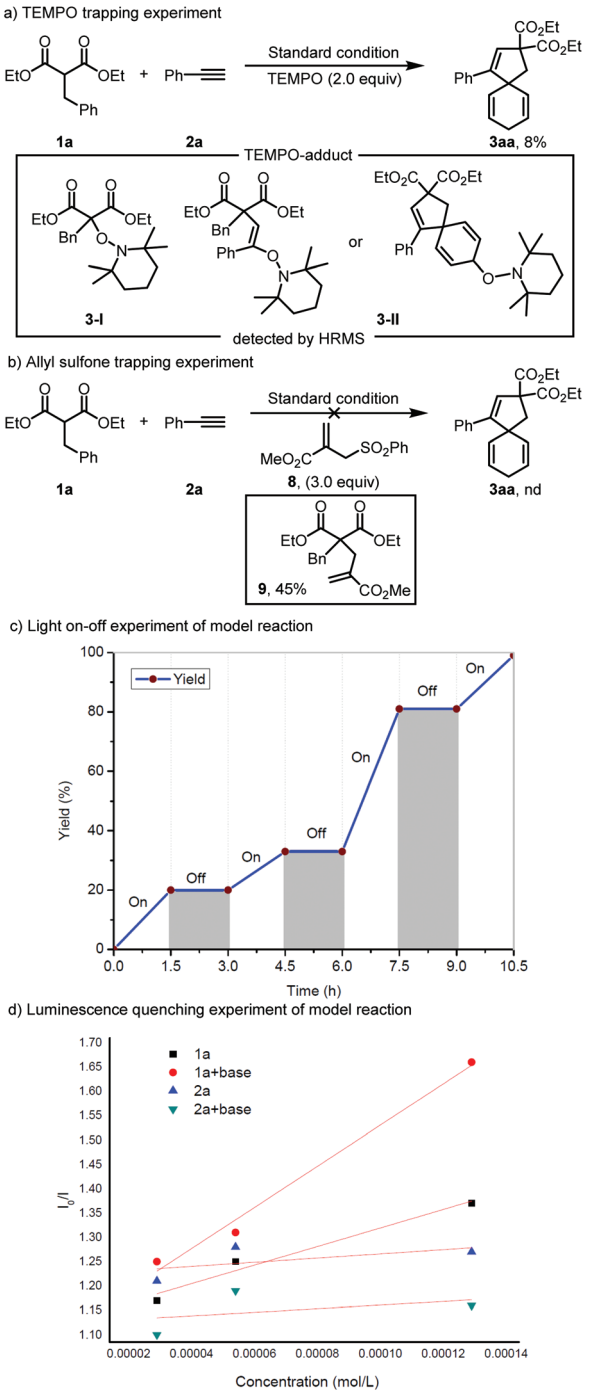


Scheme 2 Synthetic applications. (a) Reaction conditions: **1a** (5.0 mmol, 1.0 equiv.), **2a** (15 mmol, 3.0 equiv.), Ir(ppy)$_2$dtbbpyPF$_6$ (2 mol%), and K_3PO_4 (1.0 equiv.) in CH_3CN (100 mL), N_2, rt, 48 h. (b) Reaction conditions: a: Pd/C (10 mol%), NH_4HCO_2, methanol, 25 °C, N_2, 20 h, quantitative yield of **4**; b: $LiAlH_4$ (5.0 equiv.), Et_2O (4 mL), 35 °C, N_2, 20 h, quantitative yield of **5**; c: 3,4-dimethoxythiophene (1.0 equiv.), *p*-TSA (10 mol%), toluene, 24 h, reflux, 41% yield of **6**; d: Ru(bpy)$_3$Cl$_2$·6H$_2$O (2 mol%), CH_3CN (2 mL), blue LED, air, 53 h, 33% (brsm) yield of **7**.

Also, alkyl substituted alkynes can be engaged in this transformation, as demonstrated with the synthesis of **3aw**. Finally, a late-stage functionalization of a steroid derivative was achieved with the synthesis of **3ax**. X-ray structure analysis of **3ad** unambiguously confirmed the structure of all products.[13]

Preparative viability was demonstrated with the reaction of diethyl **1a** and **2a** on a 5 mmol scale, yielding **3aa** on gram scale without loss of efficiency (95% yield, Scheme 2a). Moreover, a few synthetic transformations of the products were tested: exhaustive hydrogenation of **3aa** gave rise to **4** in quantitative yield. Reduction of the ester moieties to the dialcohol **5** proceeded well with $LiAlH_4$, which was further converted to the 3,4-dihydro-2*H*-thieno[3,4-*b*][1,4]dioxepin scaffold **6**, which has gained attention in the area of material and photoelectrochemistry.[14] In an attempt to connect this methodology to the one reported by Zhang and coworkers[10] (*cf.* Scheme 1c), oxidation to cyclohexadienone **7** is possible albeit only with moderate conversion and yield.

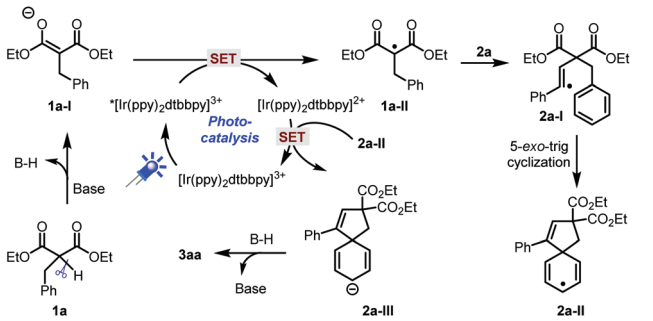
To gain insight into the mechanism, the following experiments were conducted (Scheme 3). In the presence of two equivalents of the radical scavenger TEMPO, the reaction between **1a** and **2a** was largely inhibited and only 8% yield of **3aa** was formed. In addition, the radical trapping products **3-I** and **3-II** were detected by HRMS (Scheme 3a), thus pointing to **2-I** and **2-II** (Scheme 4) as possible reaction intermediates. In the presence of allyl sulfone **8**, being an especially effective radical acceptor,[15] the product **3aa** was not formed any longer but rather the allylated product **9** was obtained (Scheme 3b, 45%), supporting the formation of the benzylmalonate radical **1a-II** (Scheme 4) as a key intermediate. Light on/off experiments in the reaction of **1a** and **2a** were conducted (Scheme 3c), which showed that the formation of **3aa** immediately is halted in the absence of irradiation. In combination with the very low quantum yield (Φ = 0.00073) that was measured[16] we suggest that a photoredox cycle (*cf.* Scheme 4) is operative, although a radical chain propagation pathway cannot be ruled out completely.[17] Stern–Volmer analysis (Scheme 3d) revealed that only benzylmalonate **1a** quenches the excited state of *[Ir(ppy)$_2$dtbbpy]$^{3+}$ to a significant extent,



Scheme 3 Mechanistic studies.

with a much higher rate constant in the presence of K_3PO_4. These data suggest that the reaction is initiated by a reductive quenching process, in which **1a** undergoes deprotonation followed by oxidation of the resulting enolate by the excited photocatalyst *[Ir(ppy)$_2$dtbbpy]$^{3+}$.

Based on the above mechanistic studies and previous reports, a plausible reaction mechanism can be postulated (Scheme 4). After deprotonation of benzylmalonate **1a** to



Scheme 4 Proposed mechanism.

generate the anionic intermediate **1a-I**, single-electron oxidation mediated by the excited state of photocatalyst *[Ir(ppy)$_2$dtbbpy]$^{3+}$ generates the benzylmalonate radical **1a-II** and the reduced state of the photocatalyst [Ir(ppy)$_2$dtbbpy]$^{2+}$. Subsequently, radical intermediate **1a-II** adds to phenylacetylene **2a**, furnishing the vinyl radical species **2a-I** that has a sufficiently high reactivity for a dearomative 5-*exo-trig* cyclization to provide the radical species **2a-II**. Finally, a single-electron reduction reaction of **2a-II** mediated by the reduced state of photocatalyst [Ir(ppy)$_2$dtbbpy]$^{2+}$ regenerates the ground state of photocatalyst [Ir(ppy)$_2$dtbbpy]$^{3+}$ and the C-anionic intermediate **2a-III** which upon protonation gives rise to **3aa**.

In conclusion, a photoredox-catalyzed transformation involving enolate oxidation, formation of vinyl radicals and dearomatization of an unactivated arene moiety has been developed with complete atom economy, requiring no preactivation of stoichiometric reagents. The title reaction is a process that is thermodynamically allowed but lacks a significant driving force. To still obtain the product in high yields the reaction design requires the inclusion of irreversible steps. In this specific case both, the reduction of the radical **2a-II** by the reduced PC and the protonation of the resulting anion **2a-III** can be in principle considered as irreversible. Confirmation of these irreversible steps is supported by no reaction of the product **3aa** under the catalysis conditions as well as by a PC*/**3aa** Stern–Volmer-plot, indicating insignificant quenching of the PC excited state by **3aa** (see ESI†).

Conflicts of interest

There are no conflicts to declare.

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