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Visible-Light Promoted Polycyclizations of Dienynes

Matteo Lanzi,^[a] Veronica Santacroce,^[a] Davide Balestri,^[a] Luciano Marchiò,^[a] Franca Bigi,^[a,b] Raimondo Maggi,^[a] Max Malacria,^[c] and Giovanni Maestri^{*[a]}

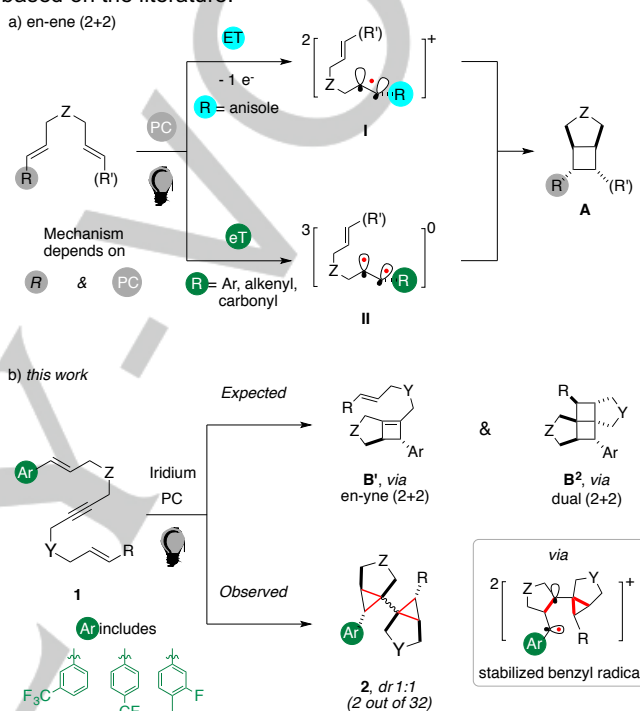
Abstract: A variety of linear dienynes can deliver complex tetracyclic frameworks in the presence of an Ir(III) complex and visible light. Products feature the assembly of four new C-C bonds and six contiguous stereocenters, which decorate two [3.1.0] bicyclic units tethered through their bridging quaternary carbons. The internal alkyne acts as a formal dicarbenoid to assemble two cyclopropanes in these radical cationic cascades. This behavior has not been previously observed among organic reactive intermediates and can be extended to intermolecular reactions and diendynes.

Tetracyclizations are fascinating reactions able to deliver a spectacular level of molecular complexity from a suitably tailored, linear reagent. Nature offers striking examples to this end, such as the assembly of lanosterol through a cationic cascade.^[1] Remarkably few complementary strategies can be retrieved in the literature.^[2] These reactions always deliver fused products, in analogy to nature, and involve diamagnetic organometallic intermediates. We report herein a complementary tetracyclization reaction that operates through organic radical cations.

The last decade saw the rise of visible light as a promoter of unique reactivities together with the development of several easily-tunable photocatalyst (PCs).^[3] PCs could induce electron-transfer (ET) mechanisms, either through initial oxidation or reduction of the substrate, and/or energy-transfer (eT) ones. The two orthogonal processes can sometimes overlap. This occurs in (2+2) reactions of dienes leading to bicycles **A** (Scheme 1, a).^[4] An anethole fragment can readily form radical cation **I** via ET.^[4a] However, the oxidation potential of electron-poor vinylarenes, yet that of β -styrene itself,^[4a,b] prevents the possibility to activate these substrates through an ET using many popular PCs and visible light. These substrates and 1,3-dienes can nonetheless undergo cyclization. They can afford **A** via eT^[4b] thanks to their conjugation, which stabilizes the corresponding biradical triplet **II** regardless of purely inductive electronic effects. Being statistically unfavorable, we are unaware of examples of cooperation between ET and eT in the same sequence.

While studying cascades on dienynes,^[5] we were surprised by the formation of two products with unusually up-fielded ¹H NMR signals upon irradiation of **1** with visible light in the presence of an Iridium PC. We initially speculated the formation of **B'** (Scheme 1,

b), formed via en-yne (2+2),^[6] and of ladderanoid tetracycle **B²**, resulting from a dual (2+2). Much to our surprise, the actual structure of the two products was different from expectations based on the literature.^[4-6]



Scheme 1. Visible-light promoted en-ene cycloadditions vs present en-yn-ene.

Furthermore, tetracycle **2** features two bicyclic [3.1.0] units^[7] tethered through their bridgehead carbons. It presents six contiguous stereocenters, including two all-carbon quaternary ones, and it is retrieved as a 1:1 mixture of just two out of its 32 potential diastereomers. The π -network of prochiral dienynone **1** is completely rearranged in this diastereoselective tetracyclization. The alkyne carbons acted as a formal dicarbenoid,^[8] which, to the best of our knowledge, has not been previously observed among organic reactive intermediates.

We thus optimized reaction conditions (Table 1, see SI for screening and limitations). Products **2a** and **3a** formed in a 50/50 ratio in DCM (entry 1, 30% combined yield). Increasing the polarity of the solvent proved beneficial (entries 2-3) and the use of DMF favored the formation of **2a** over that of **3a** (56/44 ratio). Reactivity was completely inhibited by the presence of oxygen or MeNO₂ (entries 4-5).^[9] Use of a Ruthenium PC₂ followed suit (entry 6). Replacing small vials with 4 mm NMR tubes, which have higher surface/volume ratio, pushed the combined yield to 75% (entry 7). Use of 2.5 mol% of PC₃ and of PC₄, whose excited ³Ir(III) state is the longest-living one of the series (2.3 μ sec),^[3] enabled both a better yield and a higher ratio of **2a** (entries 8-9).

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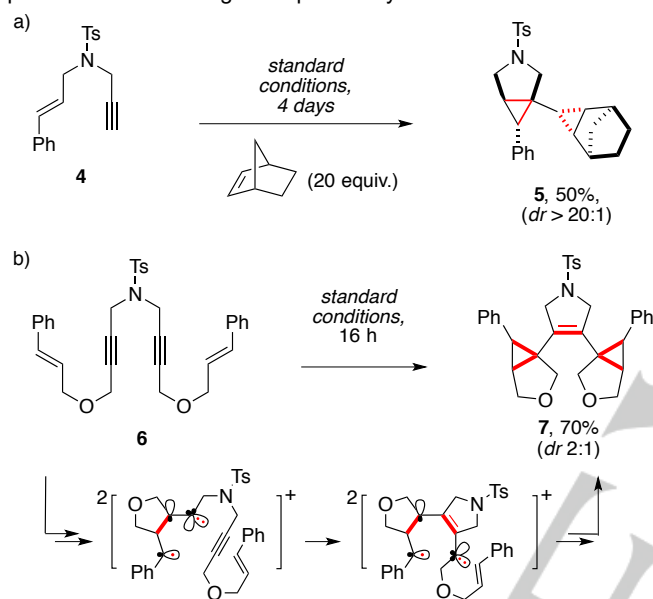
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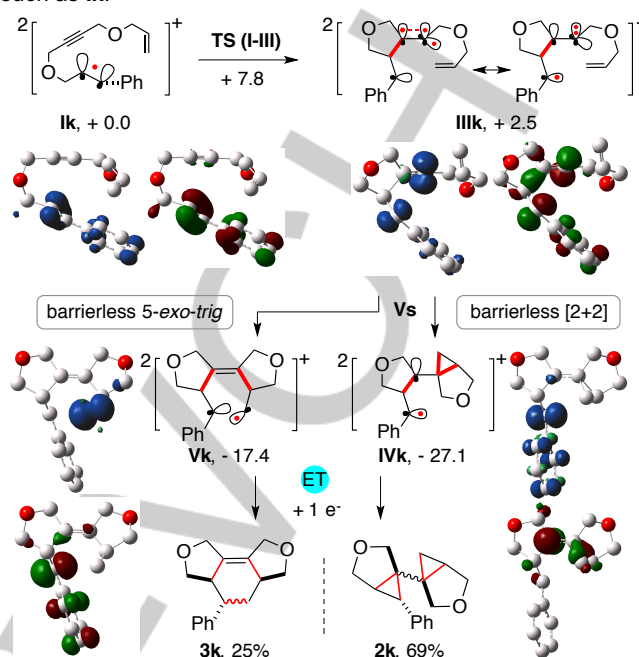
Gratifyingly, it was possible to assemble bare carbobicyclic units (**2n**, 67%)^[7c] and nitrogen containing ones (**2o**, 57%).^[7b] No **3n** formed in the former case. A trisubstituted alkene can be used, as witnessed by **2p** (61%), which presents a third contiguous all-carbon quaternary center in its structure. Cyclic alkenes can be reacted (**q-r**), leading to the corresponding penta- and tetracyclic products **2** and **3**, respectively. Just 2 out of the 64 potential diastereomers of the corresponding pentacycles **2** were observed using racemic substrates **1q** and **1r**. The same trend was observed in **3r** (20%), while **3q** did not form at all. These results indicate that each enantiomer of the reagent evenly reacted in a stereospecific way.^[11] Finally, substitution at the propargylic position was tested and led to the formation of **2s** and **3s**, which presented three contiguous quaternary carbons each.



Scheme 2. Inter- and intra-molecular carbenoid trapping.

We then tried a more challenging intermolecular reaction.^[3,4] The 1,6-enyne **4** (Scheme 2, a) was reacted under standard conditions in the presence of 20 equiv. of norbornene. Desired polycycle **5** was isolated in 50% yield as a single diastereomer upon four days of irradiation, together with (*Z*)-**4**. This result is consistent with the intermediate formation of a carbenoid on the terminal C(sp) of **4**. Encouraged by this result, we prepared diendiyne **6** aiming to seal five cycles through a single cascade by triggering an intermediate carbene dimerization (Scheme 2, b). To our delight, we isolated a 70% yield of **7** (*dr* 2:1), in which the array of 12 π -type electrons of **6** has been orderly rearranged into five new σ -bonds and a new π -one, which hold together four contiguous quaternary carbons. The mechanism of these domino sequences was studied by DFT to rationalize the formation of products (Scheme 3). Optimizations were carried out without constraints at the M06/Def2-tzvp level, which is able to accurately reproduce experimental ET potentials and eT energies,^[4d, 13] with DMF as implicit solvent (see SI for details). We modeled cationic, radical, radical cationic and anionic species, and checked multiplicities up to quintet. The most favorable series of elementary steps able to account for the

formation of **2** and **3** involved the generation of a radical cation, such as **Ik**.



Scheme 3. Formation of **2k** and **3k** from radical cation **Ik**, spin-densities (blue basins) and LUMOs (green/red lobes) of intermediates, ΔG s in kcal/mol at the M06/Def2-tzvp level, DMF as implicit solvent.

The intermediate **Ik** has a hybrid radical/cationic character, evenly spread among its styryl arm.^[14a] This intermediate can reversibly deliver **IIIk** ($\Delta G = +2.5$ kcal/mol) through the low barrier **TS(I-III)** ($\Delta G = +7.8$ kcal/mol) that is, rather surprisingly, the unique transition state of these complex polycyclizations. The dual radical/cationic nature of **IIIk**, in which the benzylic and the two former alkyne carbons share three electrons among four orbitals, is shown by its nearly identical SOMO and LUMO. This intermediate can then react through two, orthogonal, non-reversible pathways. The carbenoid character of **IIIk** emerges when this species evolves barrierless to tricyclic radical cation **IVk** ($\Delta G = -27.1$ kcal/mol), which has a marked benzyl radical character. Formal reduction (*vide infra*) of **IVk** leads directly to **2k**, establishing the fourth ring. Similarly, **3k** forms through the formal reduction of radical cation **Vk**. The latter originates from **IIIk** via radical *5-exo-trig* cyclization. This step is barrierless, too,^[14b] hence shifting the overall convenience of the sequence (*vide infra*) on the relative stability of **IV** vs **V**. The former prevails by -9.7 kcal/mol in $\Delta\Delta G$ because of the destabilizing primary C(sp²) of **Vk**. Allylated reagents **k-o** gave indeed higher **2/3** ratios compared to their *bis*-arylated peers **a-j** (Figure 1). The *dr* of products is due to the relative position of the two alkene arms that can be either on the same or on opposite faces with respect to the tether. These two conformers are nearly degenerate and they thus lead to the concomitant formation of two diastereomers, while no one else of their thirty peers forms thanks to the mechanism of the cascade.

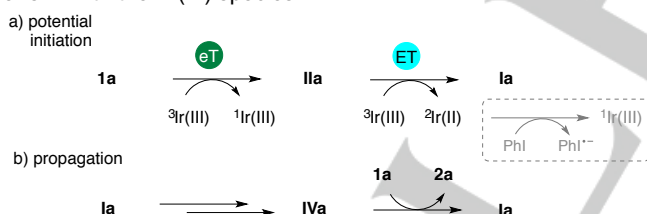
The generation of radical cation **I** puzzled us because the direct oxidation of **1a** should not be possible with any of the PCs used

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in this study,^[4b] including PC4.^[12] The oxidation of fluorinated **1d-f** is even more challenging. The ET from **1a** and **1k** to ³Ir(III) have positive calculated ΔG s (+15.3 and +14.0 kcal/mol, respectively), suggesting a reduced, if any, likelihood for these redox.

At present, we have found just one energetically feasible calculated alternative, which would involve an ET from the triplet state of the substrate. The latter could form *via* eT from a further ³Ir(III) species.^[4b] Experimentally, **2** no longer form performing experiments with traces of O₂, other eT-quenchers or the Ru complex PC2 (Table 1, entries 4-6). The (*Z*)-**1s**, which have nearly identical oxidation potentials of their (*E*)-peers but lower prowess for eT,^[9] are completely inactive, too. Taken together, these results could suggest the involvement of eT in present sequences. Even if the ET from triplet **II** to ³Ir(III) is thermodynamically favorable ($\Delta G = -31.8$ and -32.2 kcal/mol for **a** and **k**, respectively),^[15] it likely has severe limitations, too. The ³Ir(III) should more easily react with a further molecule of **1**; the ET is a second-order reaction among two species that have, each, tiny concentration and, especially for **II**, limited life-times.

Notwithstanding that a somehow direct oxidation of **1** cannot be entirely ruled out, the alternative combination of ET and eT would imply that two photons are required to activate a substrate molecule. We think that this event might have occurred thanks to the combination of two coincidences. In contrast to many PCs that are designed for either eT or ET mechanisms, Ir-based PC1, PC3 and PC4 can do both and have the longest-living excited states, too.^[3] The Ru-complex PC2 and organic photocatalysts that can trigger exclusively oxidative eT or ET, such as methylene blue, thioxanthone and acridine orange, failed to induce conversion of **1**. Then, visible light promoted reactions often use reagents and additives that are way more redox-active than electron-neutral dienyne^[3,4] and this hinder any potential dual activation. For instance, **1** does no longer react when adding 0.5 equiv. of Hünig's base or benzoquinone, which can both easily undergo eTs^[16] with the ³Ir(III) species.



Scheme 4. Radical chain propagation evidenced by a smart re-initiation.

The final ET that forms **2** (Scheme 2) can occur through the conclusion of a photoredox cycle involving a ²Ir(II) complex. The redox is highly favourable ($\Delta G = -70.7$ and -74.2 kcal/mol for **a** and **k**, respectively) but severely limited by concentration.^[17] Alternatively, a radical chain propagation can take place. The reaction involves the formation of a molecule of **2** from radical cation **IV** with the concomitant oxidation of **1** into radical cation **I** (Scheme 4). This is an energetically feasible process, although to a lower extent ($\Delta G = -6.7$ and -11.5 kcal/mol for **a** and **k**, respectively). We alternated regularly periods of irradiation and dark on the model reaction of **1a** to study which one of the two pathways prevails. No meaningful conversion occurred without light, although this result can be inconclusive.^[18] We then added

0.5 equiv. of iodobenzene to the model experiment. Consumption of **1a** occurred in a three-time shorter span (8 hours instead of 24, replicated thrice). This result shows that products formed mostly through the propagation of a radical chain reaction in the presence of PhI. The significant rate increase is likely due to a faster regeneration of a radical initiator, namely the iridium complex in his initial ground state. Iodobenzene cannot hinder a possible eT, and its redox potentials^[16] did not allow neither ET reactions with ³Ir(III). The reduction potential of PhI uniquely matches that of reduced ²Ir(II), which would result from the eT that somehow generated radical cation **I**. The rate increase suggests that in these reactions the Iridium complex acts as a smart initiator,^[19] potentially with a dual catalytic role.

We reported the original behaviour of dienyne in the presence of visible light and an iridium photoactive complex. Reagents can be converted to highly complex polycyclic frameworks by the ordered and complete rearrangement of their π -bonding network. The reaction can trigger the formation of a radical cationic carbenoid, which can be then efficiently engaged in dimerization and cyclopropanation reactions, both intra- and inter-molecularly.

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Keywords: domino reactions • carbenoids • visible light • radical cations • DFT

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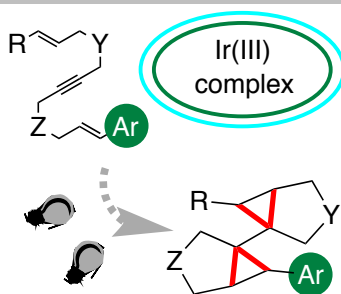
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