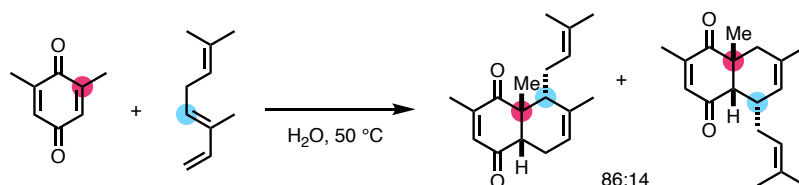
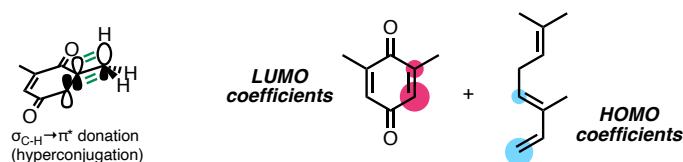


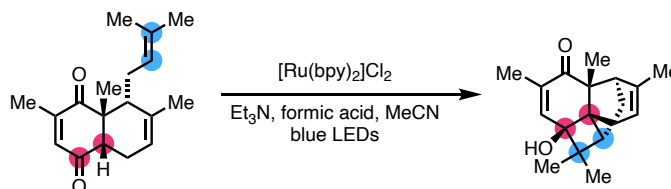
1. Explain the regioselectivity of the following Diels-Alder reaction. [★★]



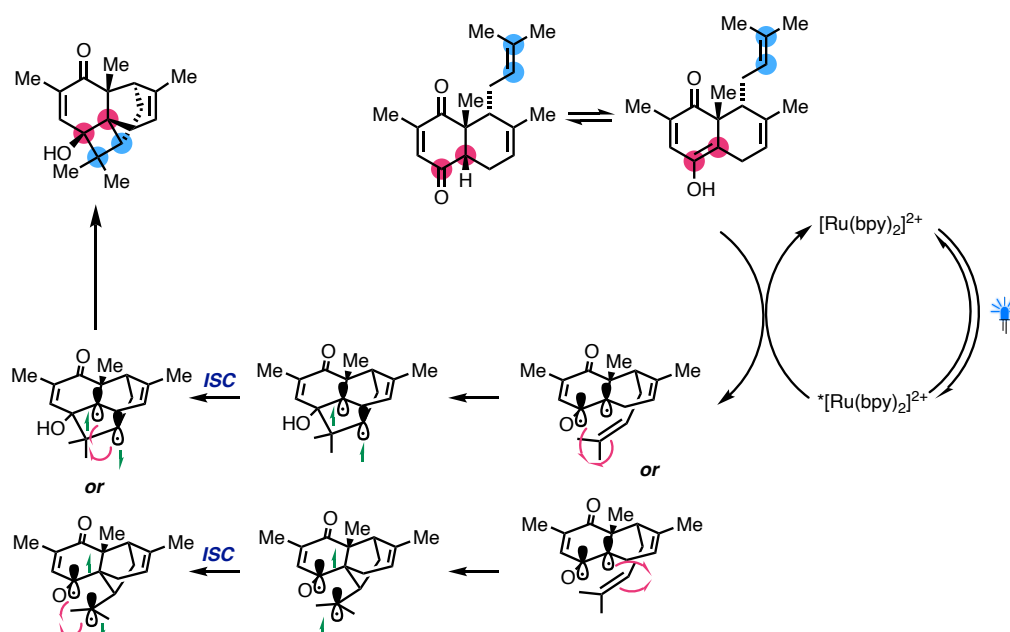
When dealing with pericyclic reactions, the regio- and stereoselective outcome of the process can usually be predicted *via* frontier orbital analysis. This is because the stronger the interaction between HOMO and LUMO, the lower the energy of the transition state will be. In the example, the reaction is a normal demand Diels-Alder reaction, and thus the diene reacts *via* its HOMO, while the quinone reacts *via* its LUMO. The carbon bearing the highest HOMO coefficient would preferentially react with the carbon with the highest LUMO coefficient (polarity match). For the dienophile, methyl hyperconjugation reduced the LUMO coefficient at the adjacent carbon, thus making the unsubstituted carbon the one with the highest coefficient. In the case of the diene, the situation is less straightforward. Empirical observations concluded that C1 substitution (in this case EDG) has a larger influence than C2 substitution, and thus the terminal carbon has the highest coefficient (I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, 2010 John Wiley & Sons, Ltd, DOI:10.1002/9780470689493).



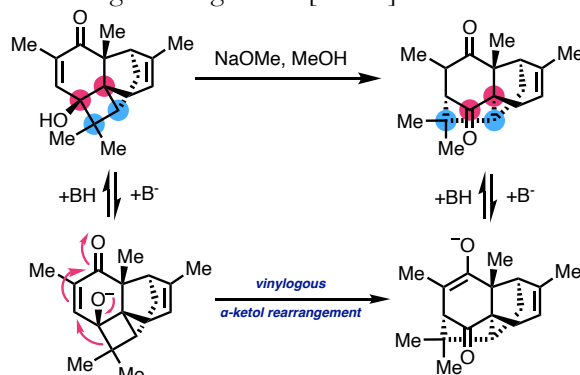
2. Hypothesize the mechanism of the following reaction. [★★]



The authors initially surmised that, in analogy with the work by Yoon and co-workers (*J. Am. Chem. Soc.* **2008**, *130*, 12886–12887; *Chem. Sci.* **2011**, *2*, 2115–2119), the substrate could undergo single-electron reduction to a radical-anion, which would trigger the [2+2] cycloaddition reaction. Upon irradiation in the absence of photocatalyst, the authors observed product formation (albeit in reduced yield and selectivity), thus suggesting that direct excitation can generate triplet-diradical species, which are possibly responsible of the formation of the product. The enol form of the quinone shows extensive delocalization and is likely to have sufficiently low triplet energy to undergo photosensitization. The triplet diradical species can add to the isoprenyl pendant chain to generate the first cyclobutane bond. Conversion of the ensuing triplet diradical to its open shell singlet (intersystem crossing, ISC) is followed by fast formation of the second bond. The Ru-photocatalyst overall facilitates the transformation, increases the photon uptake *vs.* the uncatalyzed process, and improves the reaction selectivity.

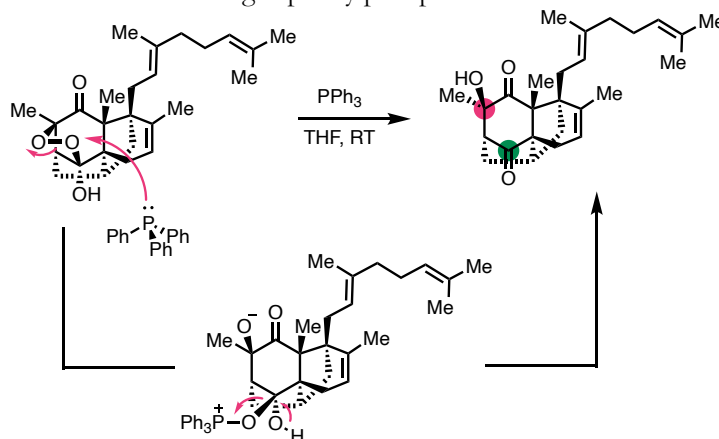


3. Propose a mechanism for the following rearrangement. [★★★]



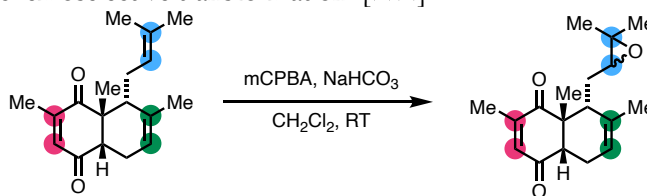
Upon base treatment, the hydroxycyclobutane system can undergo in equilibrium deprotonation, which triggers a vinyllogous α -ketol rearrangement that released the four membered ring strain. The lone pair at the oxygen forms the ketone, while the electron-rich alkyl group formally attacks the electron-poor Michael system to yield a bridged enolate with a more stable 6-membered ring. Protonation delivers the final product. Such rearrangements are generally reversible, but the increased stability due to strain relief renders the process irreversible.

4. Hypothesize the mechanism of the following triphenylphosphine-mediated reduction. [★★]



The reduction of cyclic peroxides with triphenylphosphine has found significant use in total synthesis, thanks to its mildness and selectivity. Analogously to the mechanism proposed by Pierson and Runquist (*J. Org. Chem.* **1969**, *34*, 3654–3655), nucleophilic triphenylphosphine can attack the bridged oxygen atom, which is rendered electrophilic by the inductive effect of the two contiguous oxygens. This releases the α -carbonyl alcohol and the hemiacetal moiety, which undergoes facile triphenylphosphine oxide release (strong driving force of the process) and generates the carbonyl compound.

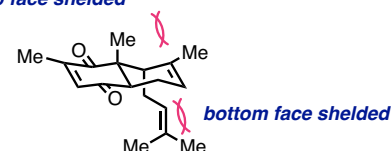
5. Rationalize the following chemoselective transformation. [★★]



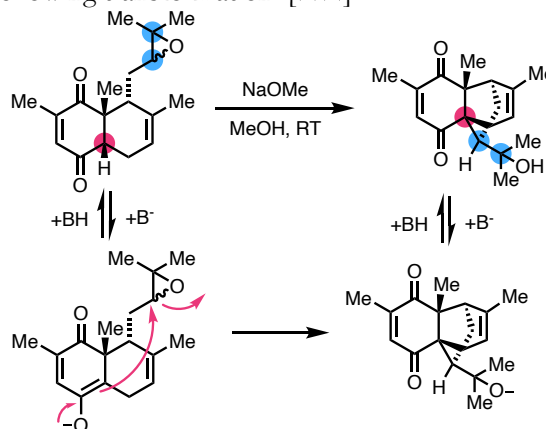
Perbenzoic acids (*i.e.* mCPBA) are electrophilic in nature, and therefore tend to react preferentially with electron-rich alkenes. In this example, the choice between the α,β -unsaturated system (pink dots) and the isoprenyl chain (blue dots) is highly biased towards the latter alkene. α,β -Unsaturated systems are electron-poor (and hence Michael acceptors) due to the mesomeric effect of the carbonyl substituents. On the other hand, alkyl substituents on alkenes render them more electron-rich, due to inductive effects.

When comparing the isoprenyl chain with the methylcyclohexene system (green dots), one should compare both the electronic of the system and steric requirements. Both alkenes are similarly electron-rich, but the accessibility of either faces of the cyclic system is prevented by the axial substituents. On the other hand, the pendant chain is easily accessible by the epoxidizing species and undergoes preferential reaction.

top face shielded



6. Detail the mechanism of the following transformation. [★★]



Upon basic treatment, the α,β -unsaturated ketone can undergo enolization. The ensuing enolate nucleophile attacks the epoxide carbon to forge a new five-membered ring. The product alcoholate is protonated to afford the final tertiary alcohol. According to the Baldwin cyclization rules, *5-exo-tet* are allowed, while *6-endo-tet* are much less favorable. This observation explains the selectivity in the epoxide attack.