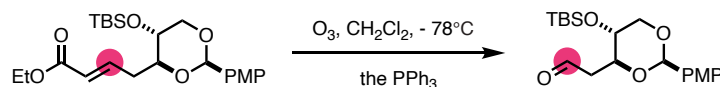
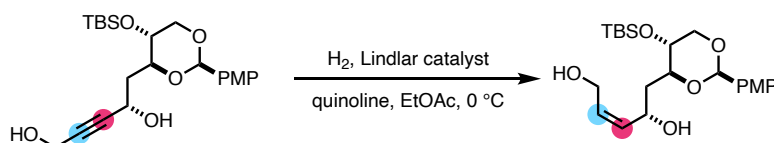


1. What is the role of triphenylphosphine in the transformation? [★]

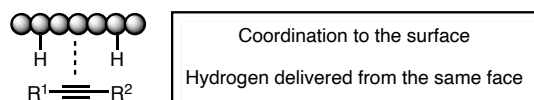


Ozonolysis is commonly followed by reductive workup, depending on the desired product—either aldehydes/ketones or alcohols. Triphenylphosphine, dimethylsulfide, thiourea or zinc commonly afford the former products, while sodium borohydride or similar hydrides can generate alcohols. It is commonly accepted that trioxolane must productively decompose during the workup process.

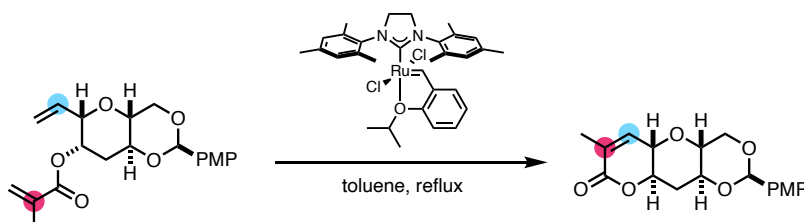
2. How can the stereoselectivity of the transformation be explained? How can the hydrogenation stop at the alkene stage? [★★]



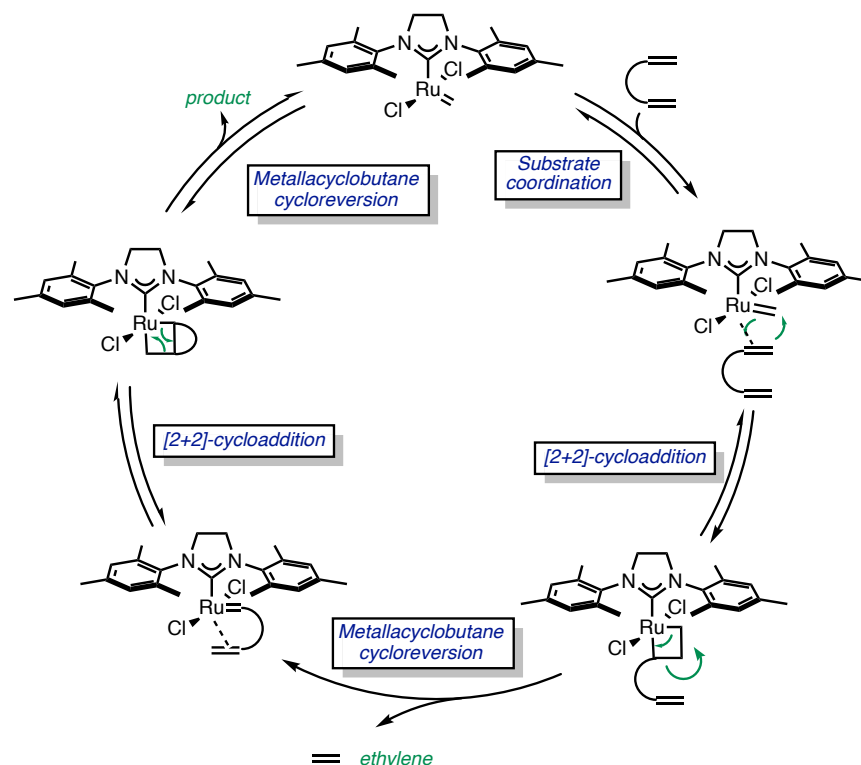
Lindlar catalyst consists in palladium(0) deposited on either calcium carbonate or barium sulfate, poisoned with lead and sulfur mixtures and can generally selectively reduced alkynes to Z-alkenes, without overreduction. This is due to the lower reactivity of the poisoned palladium species. The diastereoselectivity arises from the coordination of the unsaturated system to the catalyst surface, which causes hydrogen atom delivery from the same face of the pi-system.



3. What is the name of the following transformation? Outline the catalytic mechanism of the reaction. Can you rationalize why the reaction was performed at 18 mM concentration? [★★]

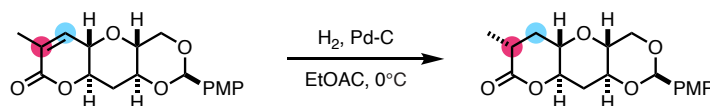


The reaction is named ring-closing metathesis (RCM) and involves the metathesis between two tethered olefins with release of a small volatile alkene (usually, but not exclusively, ethylene) as driving force for the overall process. The reaction represents a viable and widely utilized strategy to generate a plethora of ring sizes, spanning from thermodynamically favorable systems (*vide* example) to medium size and macrocycles (*Angew. Chem. Int. Ed.* **2006**, 45, 6086–6101). In the latter cases, maintaining high dilutions conditions enhances the probability of the desired intramolecular process over parasitic bimolecular reactions. The reported reaction uses a ruthenium-based Grubbs-Hoveyda catalyst (gen 1), which contains an immolative benzyldiene bidentate ligand and a strongly donating N-heterocyclic carbene. The latter ligand enhances both the stability and the reactivity of the system, enabling lower catalyst loading, manipulation under non-inert atmosphere and high catalytic turnover.

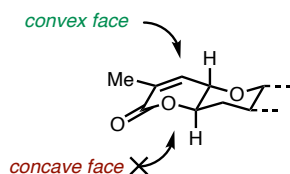


The accepted mechanism involves initial conversion of the pre-catalyst into the ethylene complex (upper center) by metathesis between the ligand and substrate. Substrate coordination and initial [2+2]-cycloaddition forms a metallacyclobutane system, which undergoes cycloreversion to irreversibly release ethylene. The metal-alkylidene and tethered olefin undergo a second [2+2]-cycloaddition which forms the ring-closed product and the catalytically active species.

4. Rationalize the diastereoselectivity of the hydrogenation reaction. Hypothesize why the reaction was conducted at reduced temperature. [★★★★]



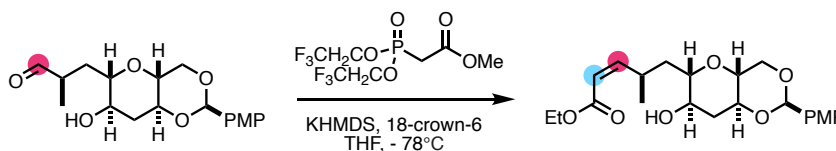
As also mentioned in problem 2, hydrogenation using heterogeneous catalysts involves the coordination of the unsaturated system to the active surface of the metal. Thus, the more accessible diastereotopic face will preferentially coordinate, and thus influence the stereoselective outcome of the transformation.



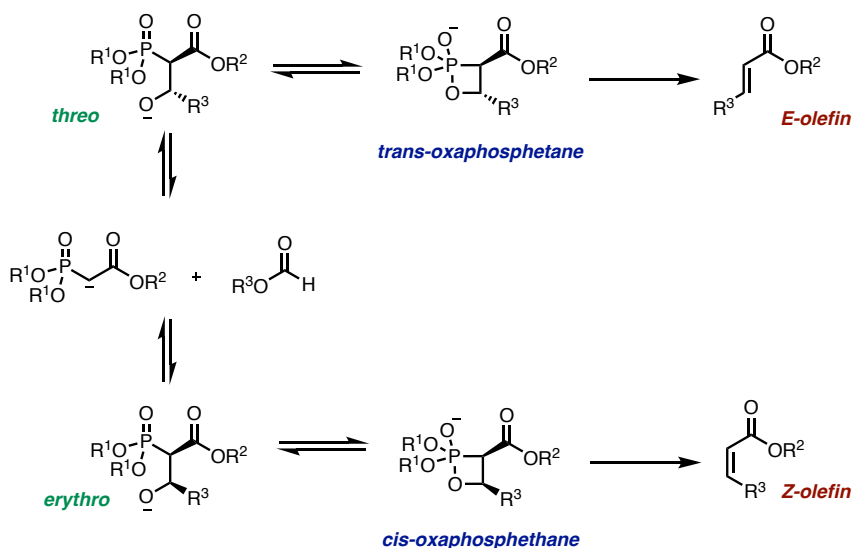
The polycyclic system possesses a convex accessible face and a more sterically encumbered concave face, which cannot be accessed by the metal surface. Hydrogen delivery will therefore occur from the former side of the rigid system.

We can hypothesize that, in order to avoid competitive hydrogenolysis of the PMP (*para*-methoxyphenyl) acetal system, lower reaction temperatures are used. In fact, cleavage of benzyl ethers is routinely performed using supported transition metals (*e.g.* Pd-C, Raney Ni) and hydrogen atmosphere.

5. Propose a set of conditions that could generate the *Z*-isomer and explain the observed selectivity. [★★★]

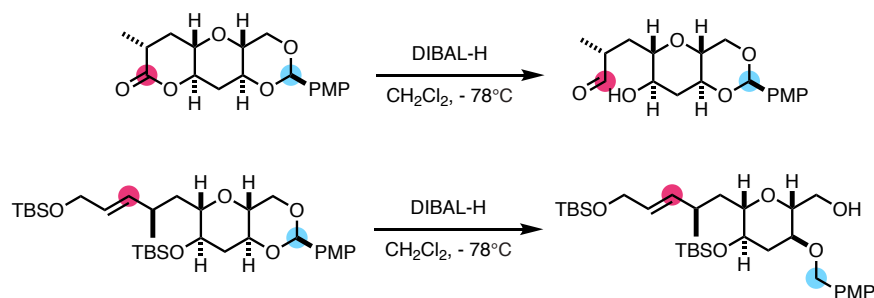


An interesting and widely employed modification of the classic Horner–Wadsworth–Emmons reaction conditions is the so-called Still–Gennari modification (*Tet. Let.* **1983**, *24*, 4405–4408; review: *Adv. Synth. Catal.* **2020**, *362*, 2552–2596). The reaction involves using phosphonates bearing fluorinated electron-withdrawing groups, strong bases like potassium hexamethyldisilazane and highly dissociating conditions (crown ethers to sequester cations).



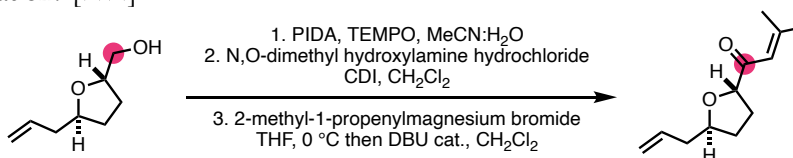
In general, equilibrium between *threo* and *erythro* betaines—generated from the addition of carbanions and carbonyls—decides the relative configuration of the corresponding intermediate oxaphosphethanes and eventually the stereochemistry of the ensuing alkenes. In the classical HWE-reaction, the reaction selectivity is believed to be thermodynamically controlled by the formation of the more stable *trans*-oxaphosphethane. In the Still–Gennari modification, the *erythro* configuration is favored, and strongly dissociating conditions, as well as electron-withdrawing substituents, allow quick breakdown of the intermediate oxaphosphethane, and therefore high selectivity.

6. What conclusion on chemoselectivity and functional group reactivity can be drawn from the following two transformations? [★★]

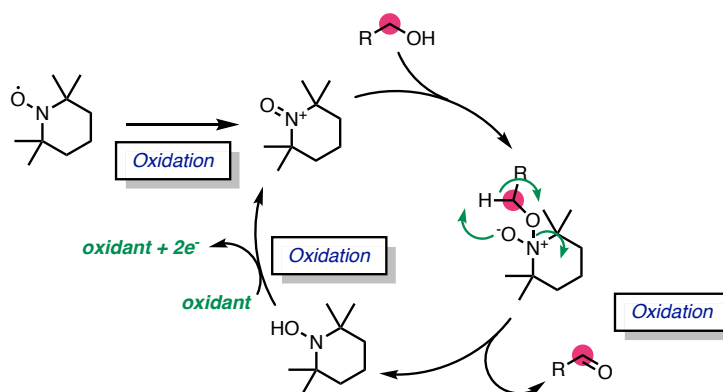


Under the same conditions, the first reaction selectively yields the corresponding hydroxyaldehyde. In the second case, the PMP-acetal group is reduced to the corresponding alcohol-ether. This suggests that the reactivity of lactones *vs.* DIBAL-H is higher than acetals, and can be selectively exploited in the chemoselective reduction of the former functional group.

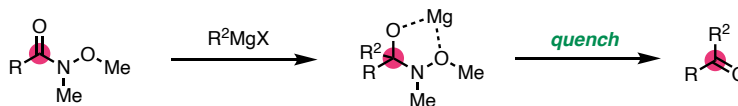
7. In the following sequence, outline the mechanism of the TEMPO-mediated oxidation. Can the oxidation be potentially stopped at the aldehyde oxidation state? Why is the installation of Weinreb amide required? What is the role of DBU in the final transformation? [★★]



Oxoammonium catalyzed oxidation are widely used for the conversion of alcohols into aldehydes/ketones or further oxidation to carboxylic acids. A method involving the hypervalent iodine-mediate oxidation of alcohols to aldehydes/ketones has been reported as early as in 1995 by scientists from the pharmaceutical company Sigma-Tau (*J. Org. Chem.* **1997**, 62, 6974–6977). In general, the following TEMPO-catalyzed mechanism for alcohol oxidation has been described (the second oxidation from aldehyde to carboxylic acid was never investigated in any detail, but probably proceeds in a manner analogous to the Pinnick oxidation):

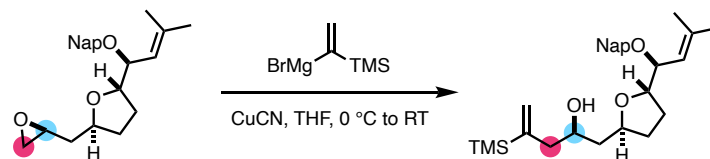


TEMPO enters the catalytic cycle by single-electron oxidation, forming the corresponding oxo-ammonium species. Such electrophilic species undergoes nucleophilic attack by the alcohol species, and the corresponding intermediate can finally complete the substrate oxidation by proton removal. Reduced TEMPO-OH can be re-oxidized by the terminal oxidant (*e.g.* hypochlorite, PIDA, *etc.*). By using one equivalent of oxidant, it is possible to stop the reaction at the aldehyde oxidation state. Weinreb amides offer a two fold advantage: (1) Carboxylic acids will undergo deprotonation rather than addition, when treated with Grignard reagents; (2) When addition happens, the ensuing ketone is more activated (electrophilic) and undergoes addition with a second equivalent of nucleophile, to yield the corresponding alcohol product. Weinreb amides can chelate the tetrahedral intermediate stemming from the first addition, thereby inhibiting further nucleophilic attack.



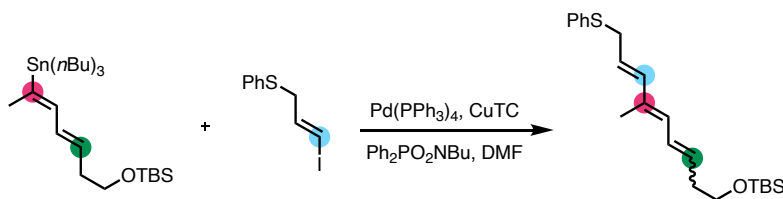
In the final transformation, the base DBU can induce isomerization of the double bond to generate the thermodynamically favorable α,β -unsaturated ketone, from the corresponding β,γ -unsaturated ketone, which was formed as side product of the transformation.

8. In the following transformation, what is the role of Cu(I) in the transformation? [★]



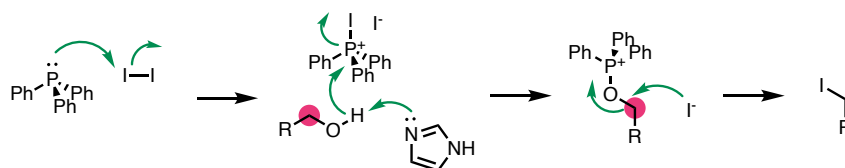
Lipshutz and co-workers observed that higher order cuprates, obtained from transmetalation of organolithiums or organomagnesium (*J. Am. Chem. Soc.* **1982**, *104*, 2305–2307), undergo nucleophilic attack onto epoxide without competitive elimination or reduction reaction. Compared to the parent lithium or magnesium reagents, their increased softness and reduced basicity is responsible for the reaction outcome. Another typical use of cuprate is the conjugate addition with α,β -unsaturated systems, which requires soft nucleophilic species.

9. Propose a mechanism for the following isomerization reaction, which occurs during the Stille coupling. [★★]



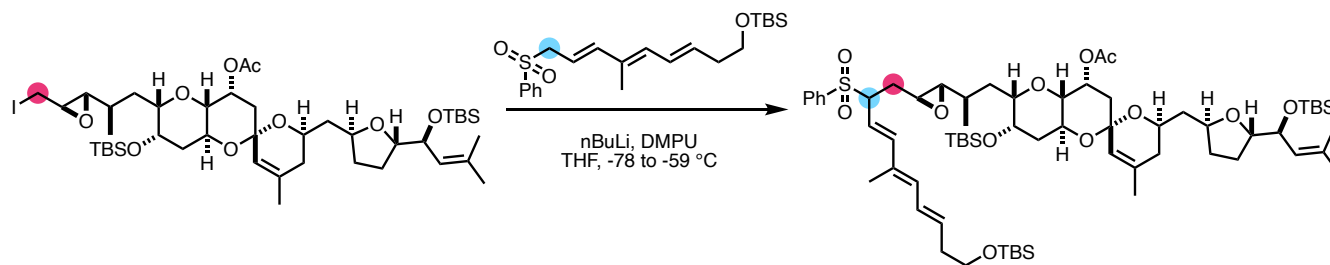
A tentative explanation could involve the C–H activation from Pd(II) of the allylic bonds, followed by generation of η^3 -allyl species, which cause possible rotation around the once-double bond and isomerization.

10. Describe the mechanism of the Appel reaction. [★]



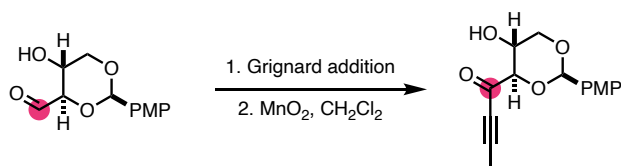
Analogously to other triphenylphosphine-mediated reactions (*e.g.* Mitsunobu reaction, Horner-Wittig reaction), the formation of the highly stable and crystalline triphenylphosphine oxide acts as driving force for the overall process. In the first step, iodine acts as electrophile and generates a cationic adduct with triphenylphosphine. The deprotonated alcohol can attack this electrophilic species, generating an activated oxyphosphonium intermediate, which undergoes facile nucleophilic displacement in S_N2 fashion by iodide.

11. This reaction represents the first step of another widely used name reaction. Which one? What is the second step? [★★]



The Julia olefination, as well as more recent variants, exploit the acidity of the α position of sulfones, which is susceptible to deprotonation. The corresponding anion can undergo nucleophilic attack onto carbonyls and generate hydroxysulfones that can undergo reductive elimination to generate olefins. The more modern Julia-Kociensky olefination features a sulfone bearing heterocycles that can undergo Smiles-type rearrangements, thus facilitating the elimination of the sulfur containing group and the liberation of the olefin, without the originally reported harsh conditions (sodium amalgam).

12. Why was manganese dioxide selected as oxidant in this transformation? [★]



Manganese dioxide is a mild oxidant that can convert activated alcohols (*i.e.* benzylic, propargylic, allylic) into the corresponding carbonyl compounds. Less activated systems are untouched. In the reported example, the authors achieved the chemoselective oxidation of the propargyl alcohol over the secondary aliphatic one. Other conditions, such as Swern-type oxidation or Dess-Martin periodinane, could have potentially touched both alcohols.

13. Outline the mechanism of the following transformation. [★★]

The Tebbe reagent is a particularly active methylene source (when for instance compared to phosphonium ylides) that can convert esters into enol ethers. Wittig reagents are not amenable to this transformation since they only react with aldehydes and ketones. In the present case, the initial step involves the conversion of the ester into the corresponding enol ether. The second step involves a titanium-catalyzed ring-closing metathesis, as reported by Nicolaou and co-workers (*J. Am. Chem. Soc.* **1996**, *118*, 1565–1566). The reaction is believed to occur *via* [2+2]-cycloaddition between the titanium-alkylidene species and one alkene, followed by cyclorevertive extrusion of a gaseous alkene. Another [2+2]-cycloaddition with the tethered alkene complete the ring-closing process.

