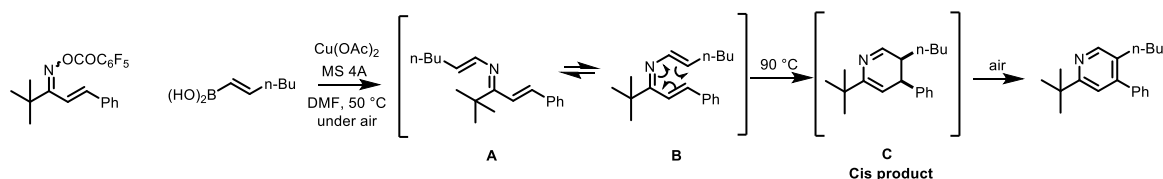
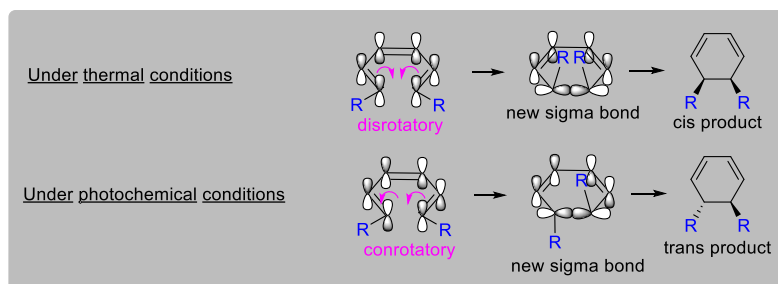


- Identify the product that S. Liu and L.S. Liebeskind obtained when treated α,β -unsaturated ketoxime with alkenylboronic acid and copper (II) acetate (*J. Am. Chem. Soc.*, **2008**, 130, 6918-6919). Identify the two intermediates **A** and **B** formed during the reactions which are in equilibrium between each other. Additionally, rationalize the stereoselectivity outcome of intermediate **C**.

Answers: The first step is a Chan-Lam type reaction to form the azatriene. The two intermediates are the E/E/E triene (intermediate A) which is in equilibrium with the intermediate B (triene E/Z/E). Only the latter undergoes a 6 π electrocycization to form intermediate C with a cis-relationship. The stereoselectivity of the reaction is explained by the frontier orbital theory which says, under thermal conditions, 6- π electrocycization occurs in a disrotatory fashion (see mechanistic insight) which leads to the cis-isomer C. This intermediate is oxidized under air to form the pyridine product.

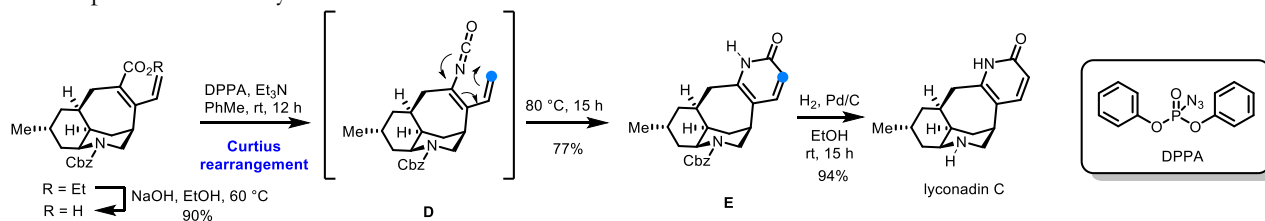


Mechanistic insight: To fully understand the mechanism, we need to look at the highest-occupied molecular orbital (HOMO) of the triene (carbon version to make things simpler) and draw it as follows. A disrotatory rotation is needed to get the two p-orbitals on the termini carbons to overlap. As a result, the cis-product is obtained. Note: the reaction is stereospecific so a Z-olefin would lead to the trans-product in the same conditions. Under photochemical conditions, the two p-orbitals on the termini carbons are now anti-symmetric due to an electron moving to the LUMO and can be drawn as follows. In this case, a conrotatory rotation of the orbitals is needed to have a constructive overlap leading to the trans-product.



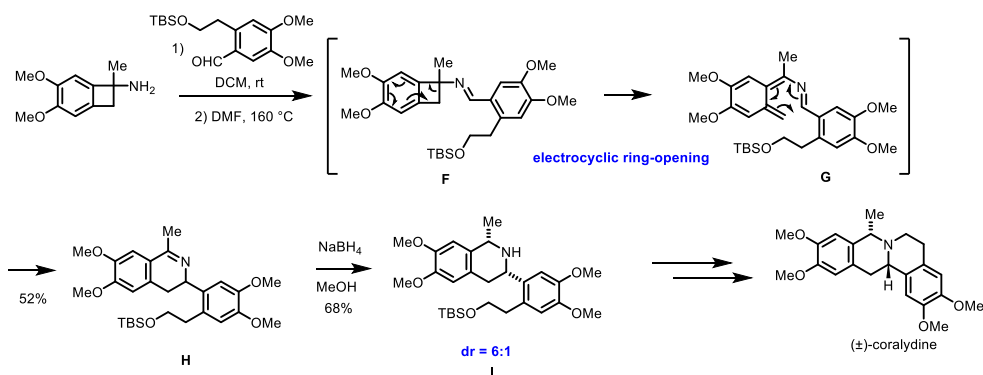
- Identify the intermediate **D** and the product **E** used in the total synthesis of lyconadin C by Cheng and Waters in 2013 (*Org. Lett.*, **2013**, 15, 4226-4229).

Answers: Authors developed a tandem Curtius rearrangement/6 π -electrocyclization to form the 2-pyridone core of the natural product in 77% yield.

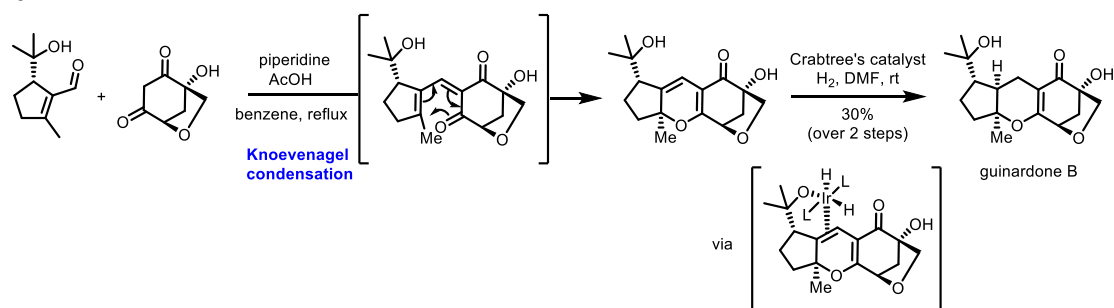


- The group of Baudoin reported the synthesis of (\pm)-coralydine in 2008 (*ACIE*, **2008**, 48, 179-182). Identify the intermediates **F**, **G** and **H**.

Answers: Once the imine **F** is formed, it undergoes an electrocyclic ring opening followed by a 6 π -electrocyclization to give the racemic dihydroisoquinoline **H**. This intermediate is then reduced with NaBH₄ to give the cis-isoquinoline **I** with d.r = 6:1.



4. Identify the intermediate **J** and the product **K** used in the synthesis of guinardone B. (*Org. Lett.*, **2020**, 22, 1644-1647)
Answers: The authors employed an intermolecular Knoevenagel condensation to combine the 1,3-diketone with the aldehyde followed by an oxa- 6π electrocyclization to give the intermediate **J**. As the oxa- 6π electrocyclization is highly reversible, Gong and Yang submitted the crude intermediate to Crabtree's reduction to afford the natural product with 30% yield over two steps. The reduction is directed by the tertiary alcohol of the left-hand side giving a single diastereomer.



5. Nitrile **K** was used in the total synthesis of phomarol in 2023 by Gui's group (*JACS*, **2023**, 145, 9354-9363). In a retrosynthesis manner, identify the two intermediates **L** and **M** which involves a 6π -electrocyclisation.
Answers: Suzuki coupling was carried out between the triflate **M** and the boronic ester **L**. The Suzuki adduct undergoes a 6π electrocyclization to give the diene in quantitative yield with $\text{dr} 3:2$. The product was then oxidized with O_2 in DMF to yield the key intermediate **K**.

