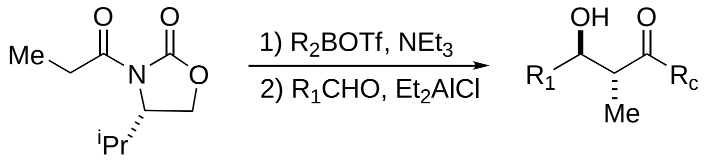
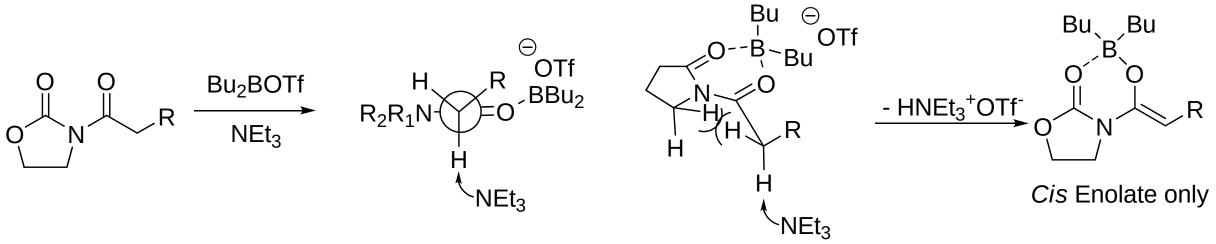
POW1



Give a mechanism for the reaction and explain the stereoselectivity observed.

POW1-Solution

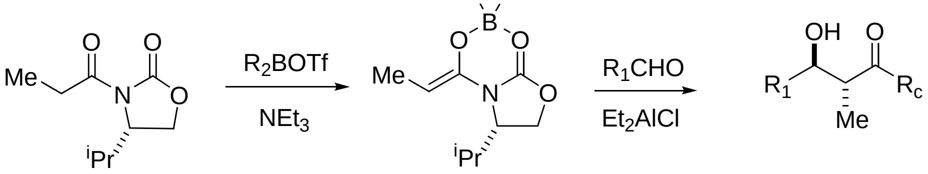
Deprotonation of Imides with Bu_2BOTf and NEt_3 (soft enolization)

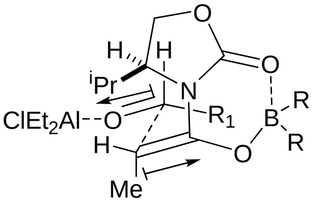


Cis Enolate only

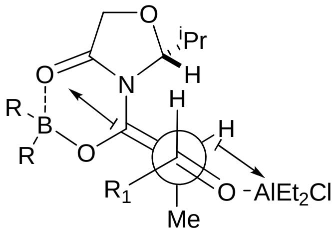
Very strong $A^{1,3}$ with Imides!

Anti aldol with external Lewis Acid



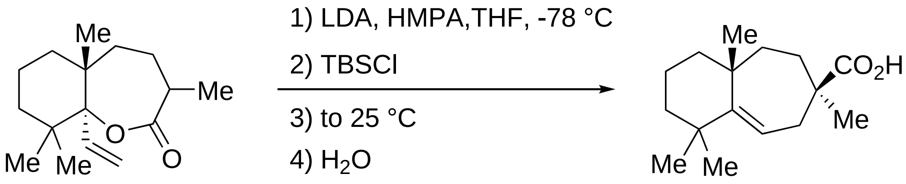


- Free transition state (no chair)
- B chelates the auxiliary
- Minimized dipoles and steric: carbonyl antiperiplanar to enolate
- Aldehyde comes opposite from ^{i}Pr
- R_1 group away from auxiliary



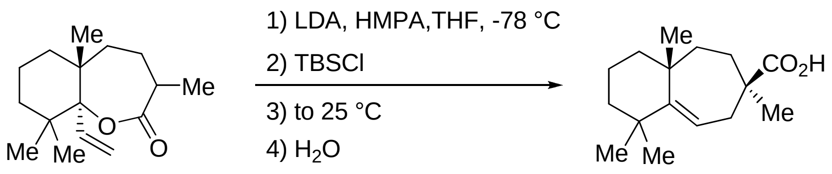
Newman view from the back

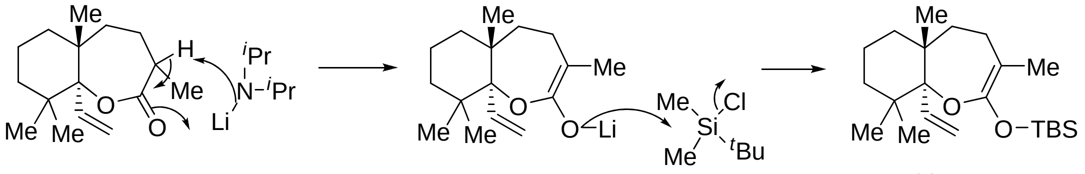
POW2



Give a mechanism for the reaction and explain the stereoselectivity observed.

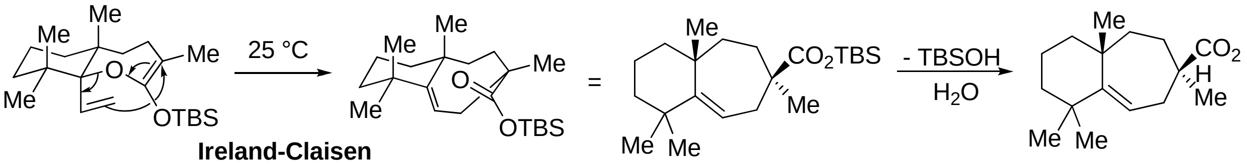
POW2-Solutions





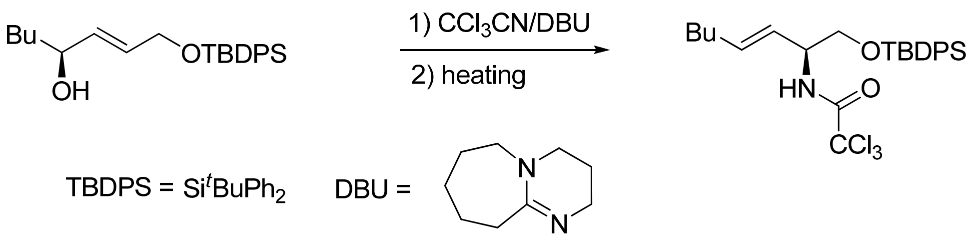
only one geometry possible
unstable T > -20 °C

stable



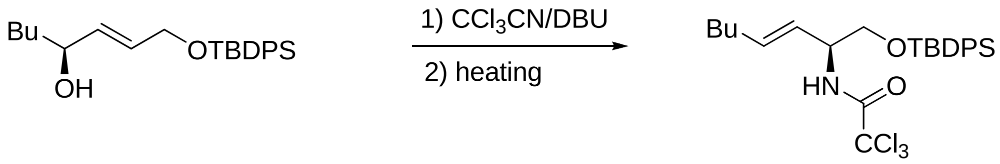
Ireland-Claisen

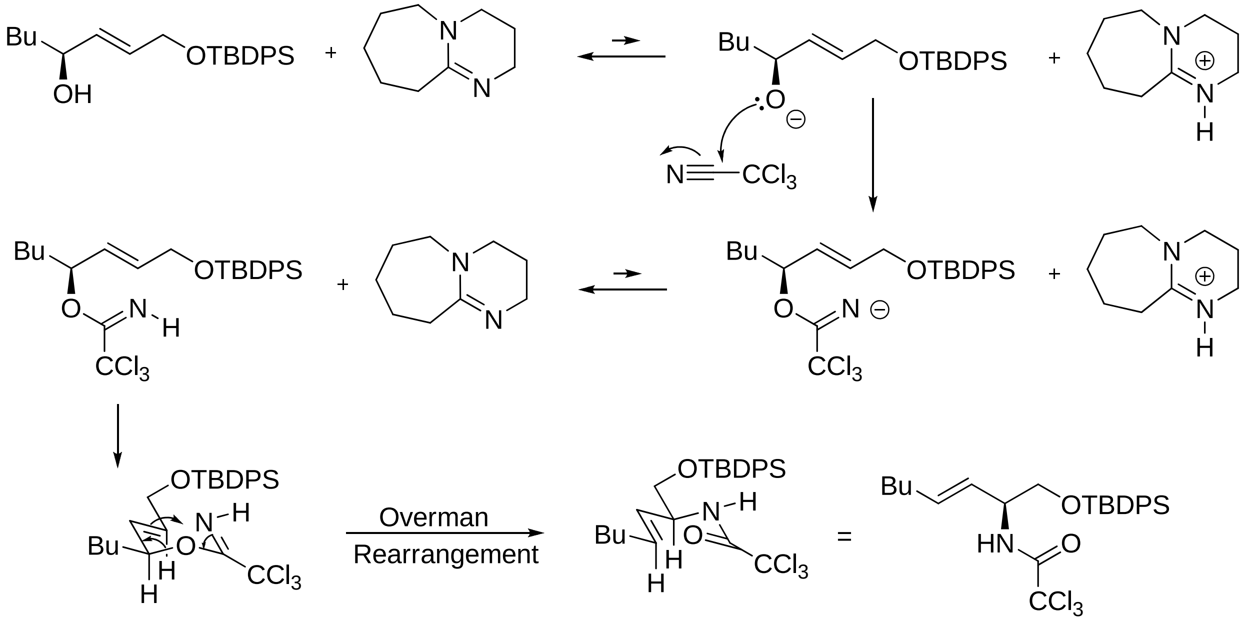
POW3



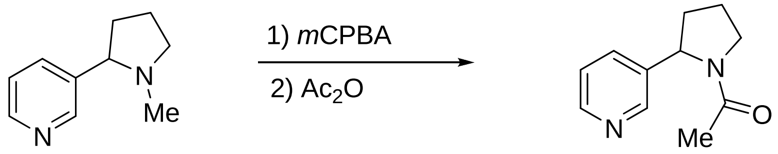
Give a mechanism for the reaction and explain the stereoselectivity observed.

POW3-Solutions



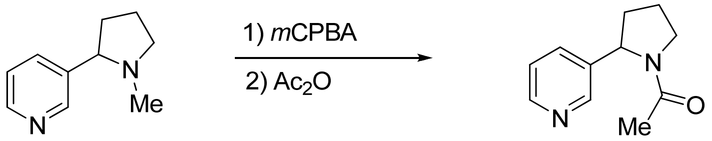


POW4

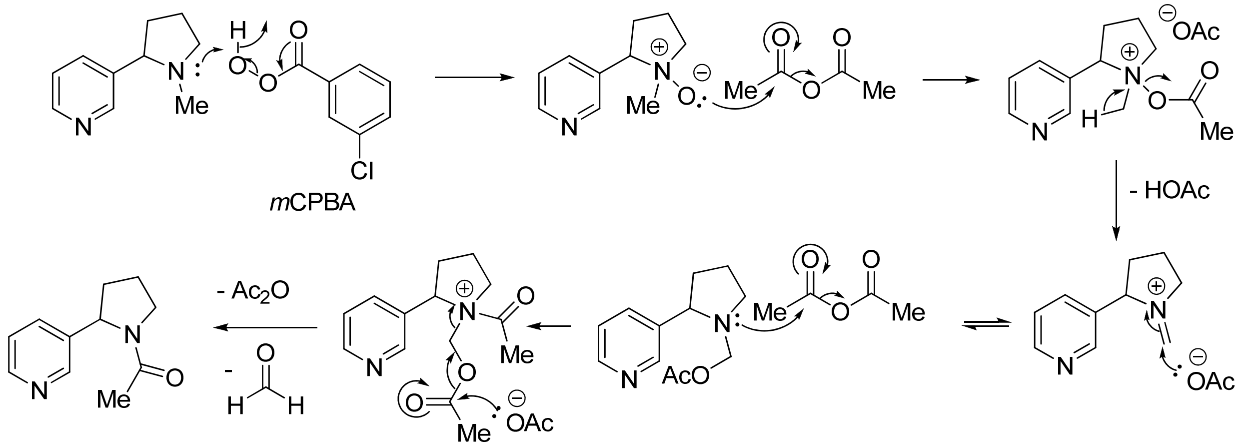


Give a mechanism for the reaction.

POW4-solution

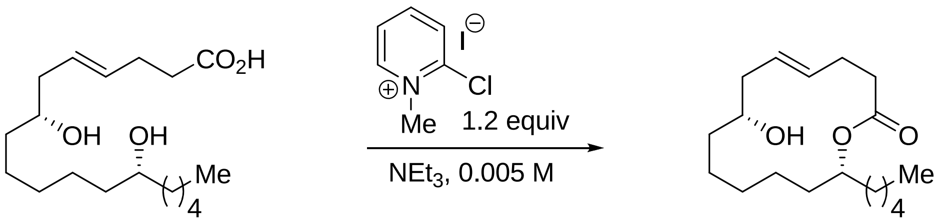


Give a mechanism for the reaction.

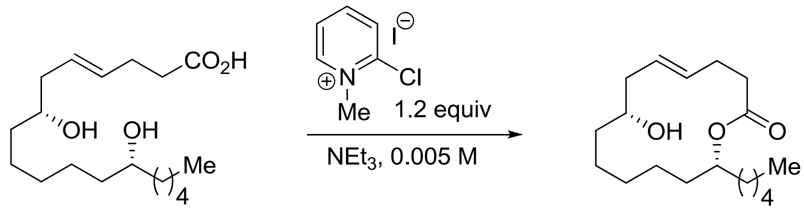


In the first step, the more nucleophilic tertiary amine is oxidized. The second step is a Polonovsky rearrangement (see lecture notes, p. 46)

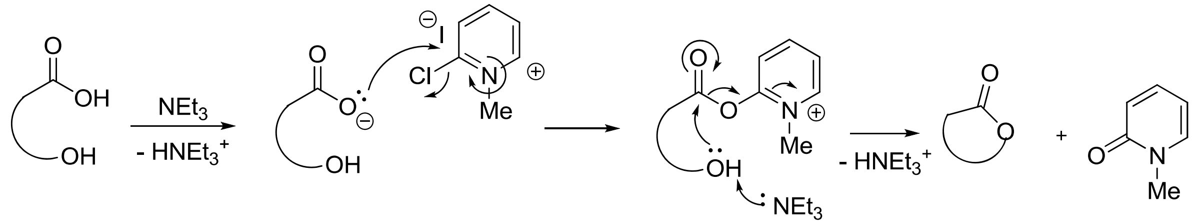
POW5



POW5-solution

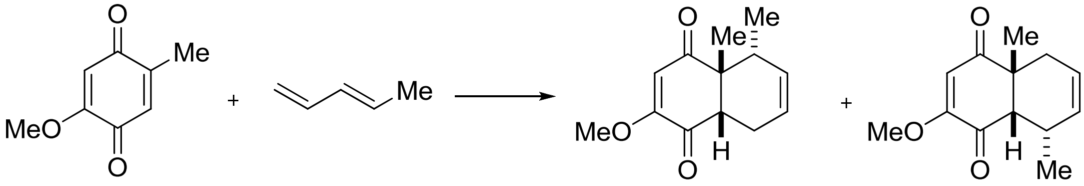


Mechanism:



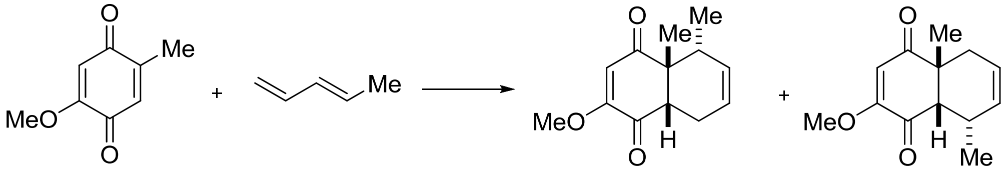
This method, developed by Mukaiyama, uses the high electrophilicity of pyridinium salts. After deprotonation with triethylamine, the carboxylate add to the pyridinium and chloride is released. The formed mixed anhydride is activated for intramolecular lactonization. Driving force for the reaction is the release of the pyridone product, which is not charged anymore. To favor the desired intramolecular reaction, it is important to run the reaction under high dilution conditions. The more strained 8-membered ring containing a trans double bond is not formed under these conditions.

POW6

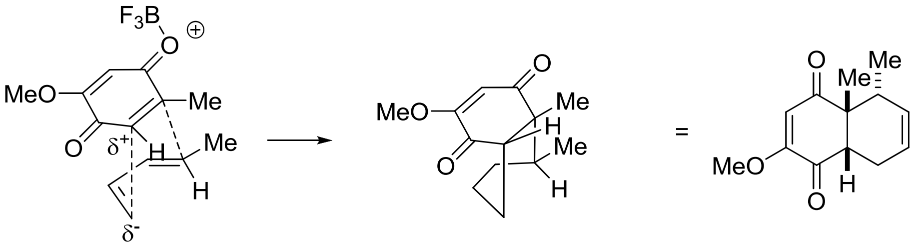


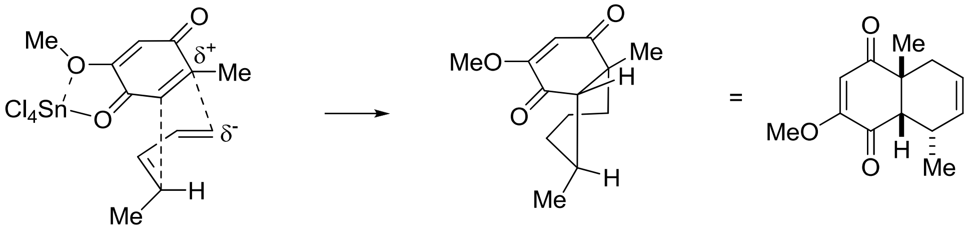
conditions:	100 °C	1:1
	BF_3•OEt_2, -20 °C	80:20
	$SnCl_4$, -20 °C	5:95

POW6-solution



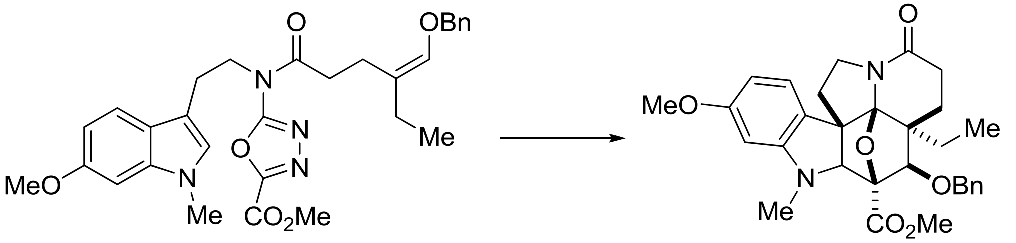
conditions:		
	100 °C	1:1
	BF_3•OEt_2, -20 °C	80:20
	$SnCl_4$, -20 °C	5:95



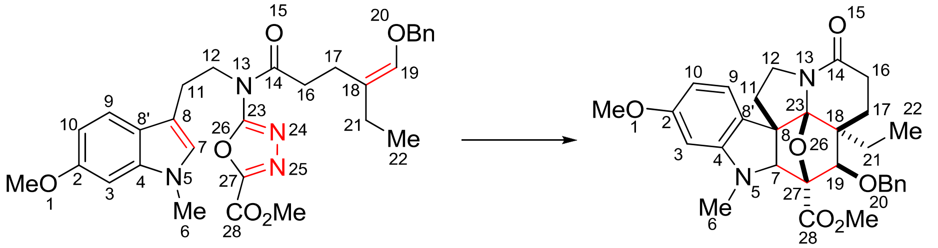


Without any catalyst, the electronic influence is in nearly symmetrical, and no selectivity is observed. BF_3 has only one free site and prefers to coordinate to the ketone without the methoxy group (space is free). $SnCl_4$ can makes a chelate with the methoxy group and favor this coordination. The presence of the Lewis acid makes the corresponding beta position much more elctrophilic and determine the regioselectivity.

POW7



POW7-solutions



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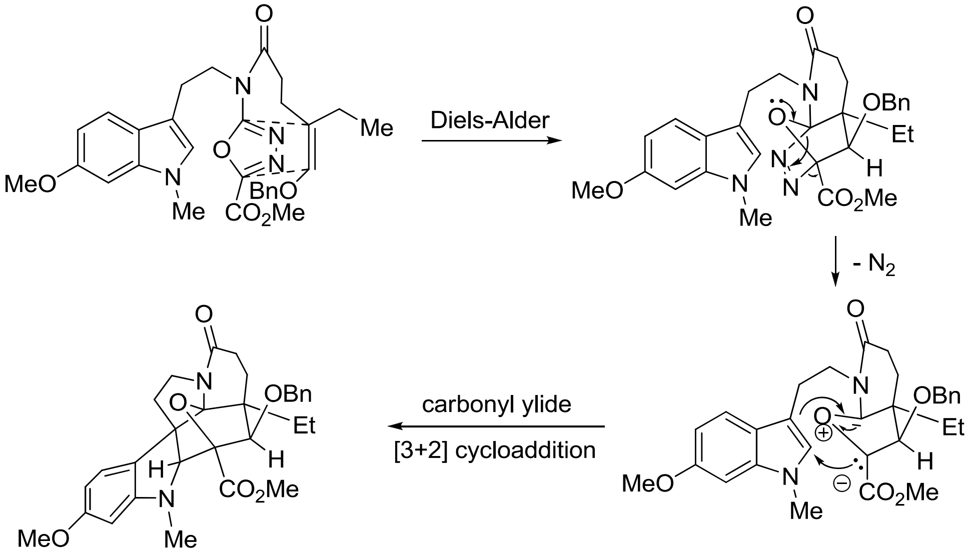
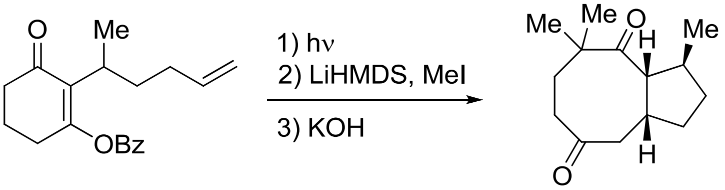
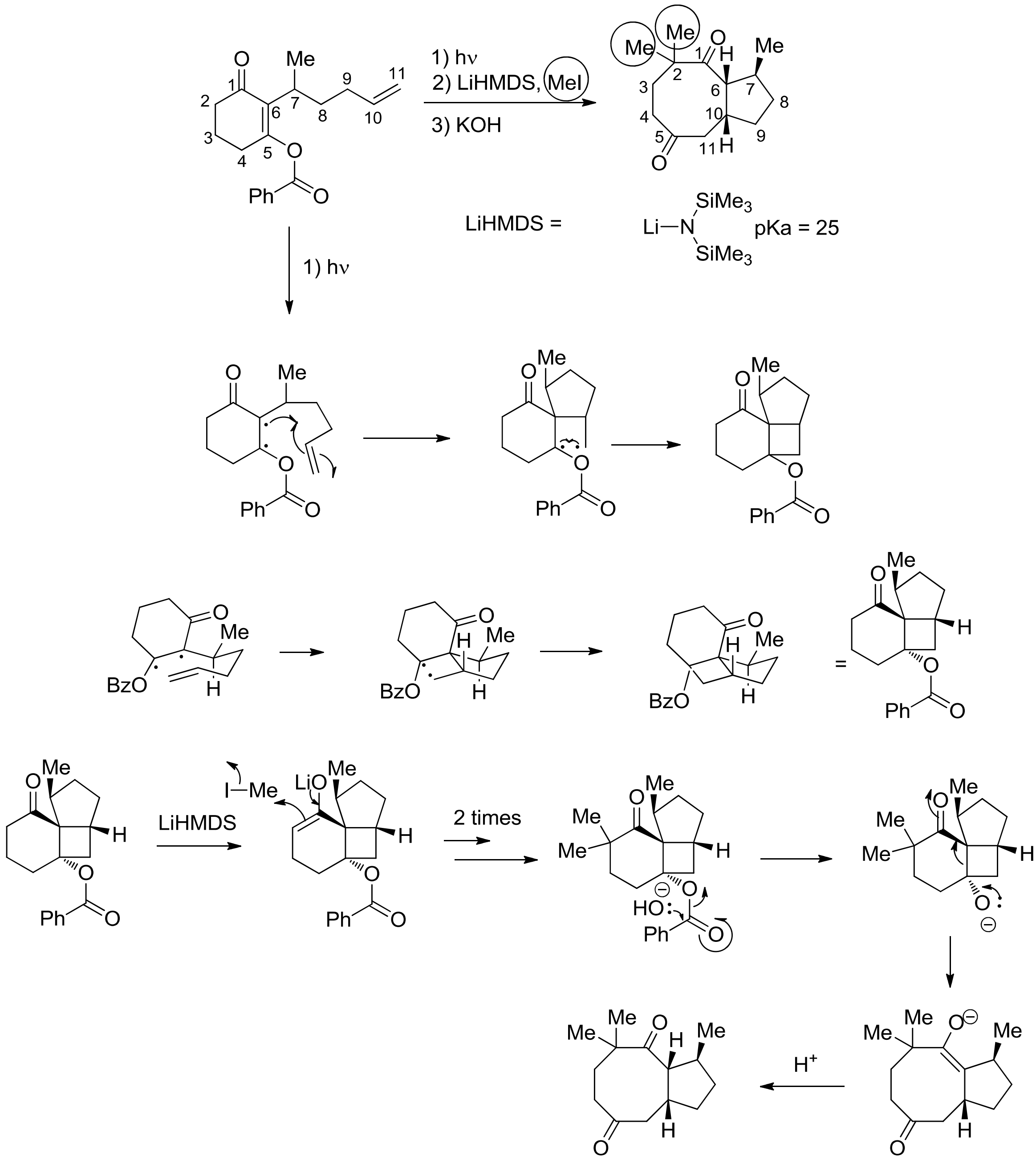


This example is the key step in the total synthesis of vindoline by Boger. In such complex exercises, it is important to begin by numbering the atoms in starting material and product to analyze what is hapening. A good start is the metoxyindole part, as it can be easily recognized in starting material and product. The other functional groups then help the numbering. One can see that 4 new bond need to be formed (8-23, 18-23, 7-27, 19-27) and two adjacent atoms of nitrogen are missing, which is a strong hint for the loss of N_2. Analysis of the starting material around the formed bond reveal 2 olefins and 1 heterodiene, which indicates a potential Diels-Alder reaction. The double-bond of indole is deactivated, as it is part of an aromatic system. Consequently, a Diels-Alder reaction between the enol ether and the diene is a logical start. As the starting material is not chiral, both top or bottom face attack can be considered: they will lead to enantiomeric products. After the Diels-Alder reaction, extrusion of nitrogen gas is easy and lead to a carbonyl ylide, which can then reacts in a [3+2] cycloaddition with the double bond of the indole. Because the reactions are intramolecular, the possible transition states are limited and high diastereoselectivity is observed. It is however difficult to predict beforehand which exact transition state will be favored.

POW8

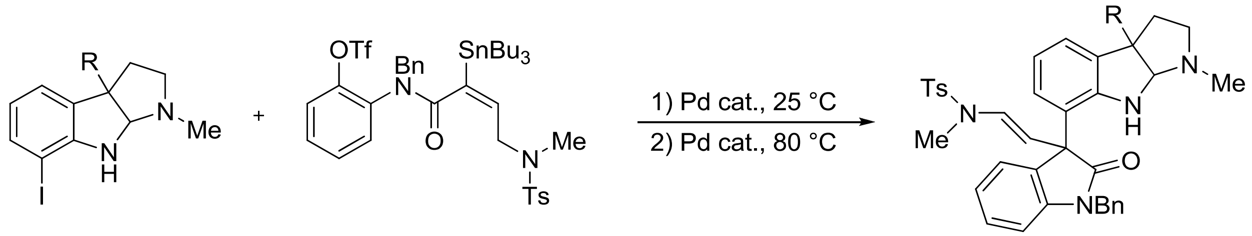


POW8-solutions

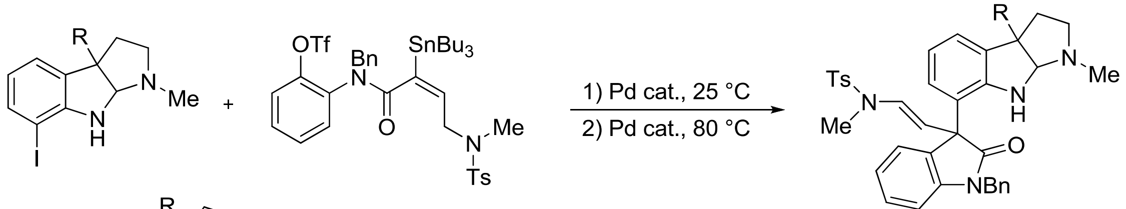


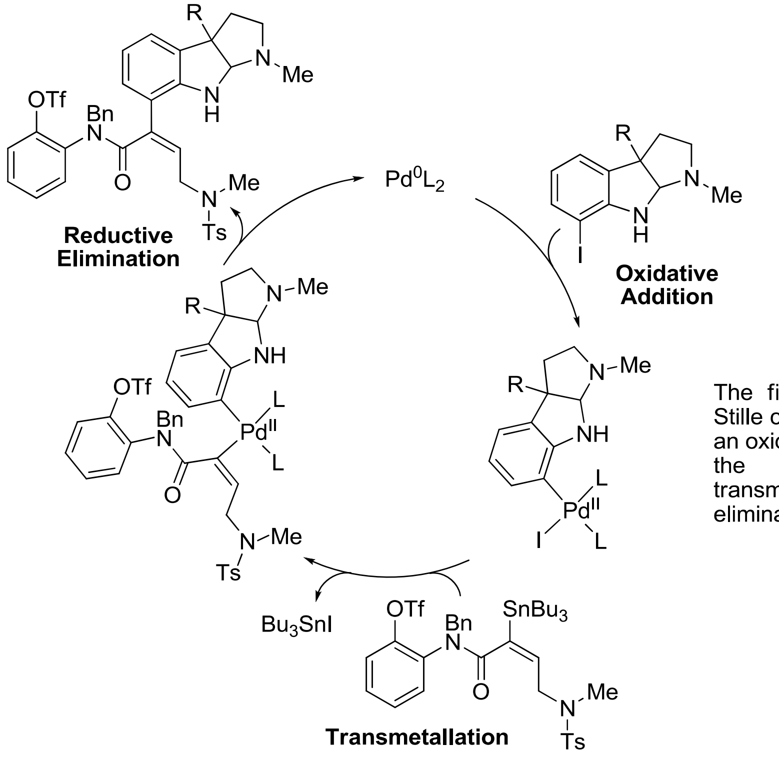
Numbering of starting material an product tell us that several bonds need to be made and broken. The only missing atoms in the starting material are the two metyl groups, which have to come from MeI. The benzyl ester has been removed in the product. In the presence of light, activation of the conjugated system is the most probable reaction. Using the simplified model of a biradical, a fast 5-exo-dig radical cyclization is now possible. The typical chair transition state with the methyl group in equatorial position explain the *cis* relationship between the proton and the methyl group. The relative stereochemistry to the OBz group is given by the geometry of the starting material and the orientation of the enone system to form a four membered ring directly. The second step is a simple methylation of the alpha position of the ketone. The last step begins with a saponification of the ester, followed by a retro-aldol reaction, driven by the release of ring strain. Finally, protonation to give the thermodynamically more stable trans 5-membered ring occurs.

POW9

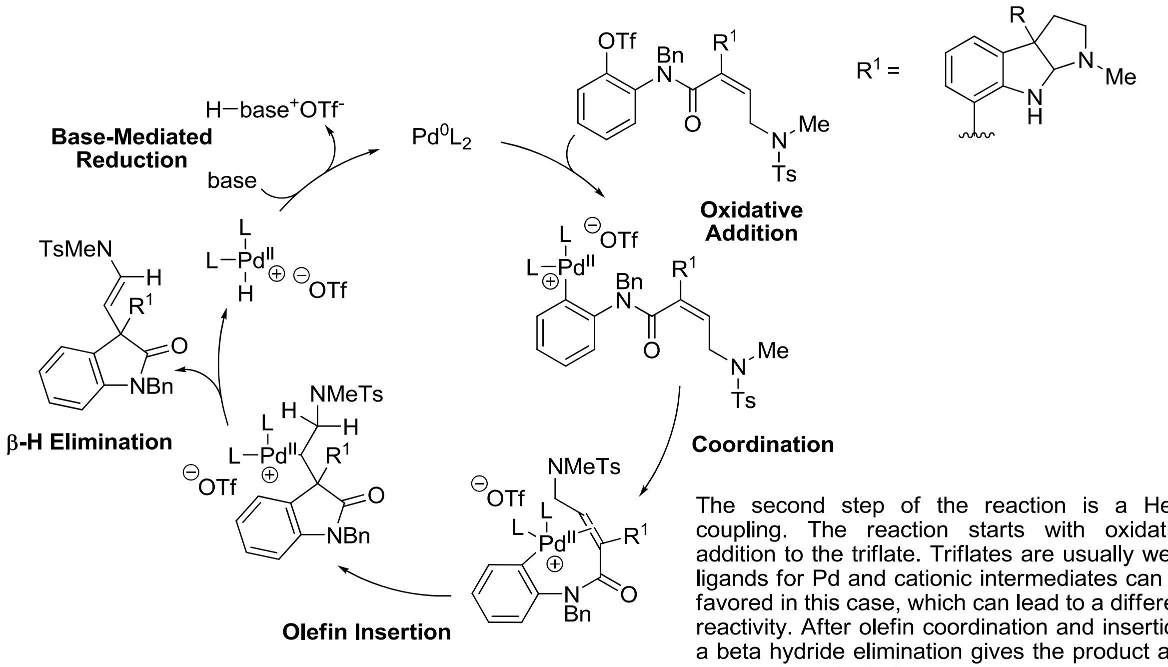

R
N
Me
NH
I
+
OTf
Bn
N
SnBu3
O
N
Me
Ts
1) Pd cat., 25 °C
2) Pd cat., 80 °C
Ts
N
Me
R
N
Me
N
H
O
NBn

POW9 -Solutions



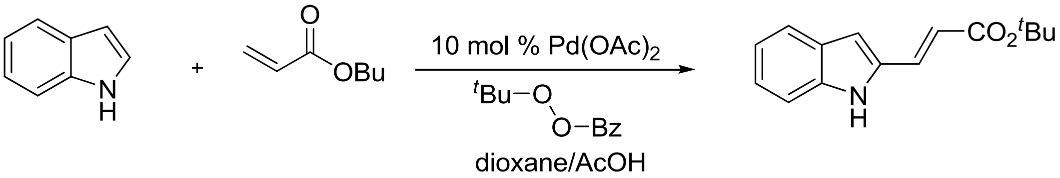


The first step is a classical intermolecular Stille cross-coupling. The reaction begins with an oxidative addition on the C-I bond, which is the weakest bond present. After transmetalation with the stannane, reductive elimination gives a first C-C coupling product.



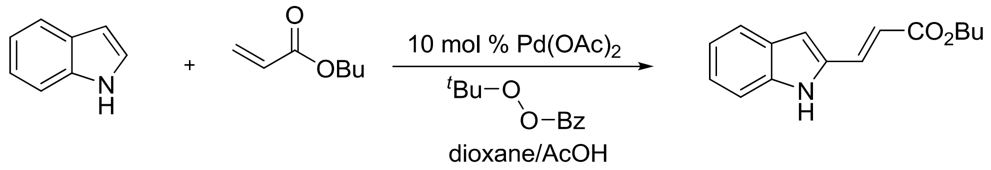
The second step of the reaction is a Heck coupling. The reaction starts with oxidative addition to the triflate. Triflates are usually weak ligands for Pd and cationic intermediates can be favored in this case, which can lead to a different reactivity. After olefin coordination and insertion, a beta hydride elimination gives the product and a palladium hydride complex. In presence of base, the palladium hydride is reduced back to Pd(0).

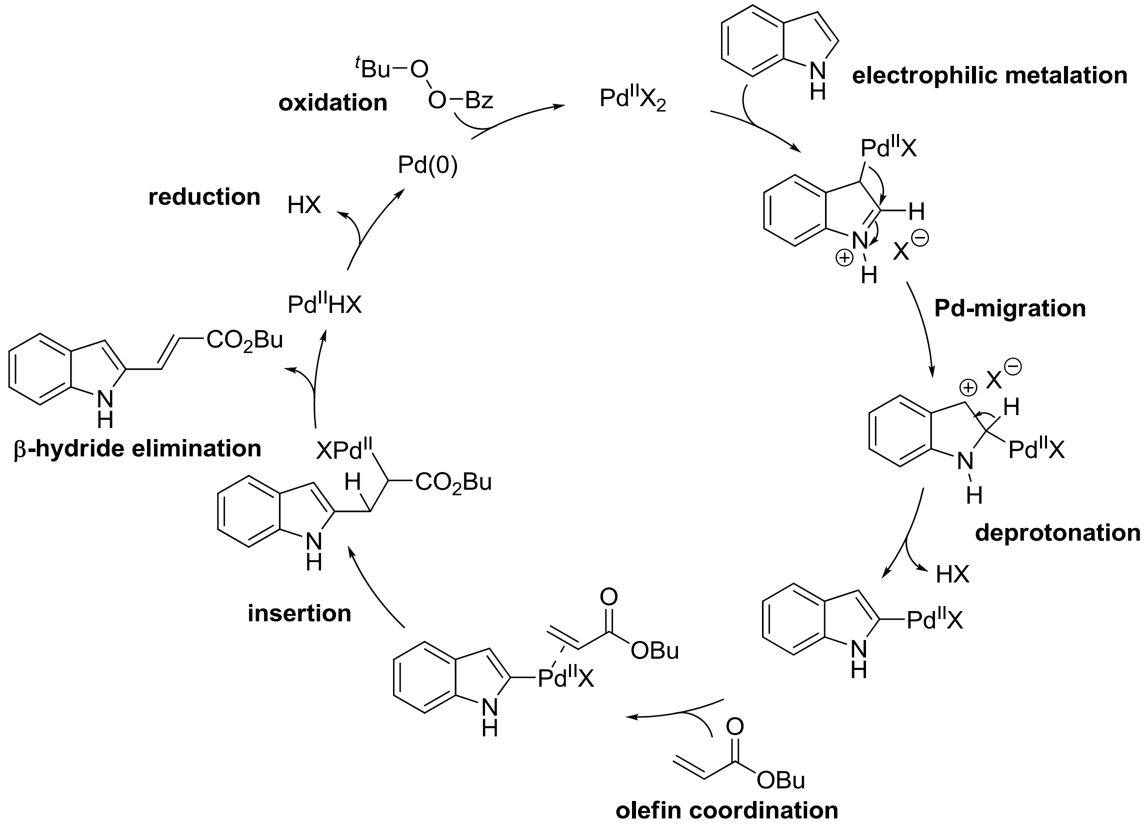
POW10



Propose a detailed reaction mechanism for this transformation.

POW10-solutions





This reaction is a combination of C-H functionalization and oxidative Heck reaction. In the first step, a metalation occurs at the more electron-rich C3 postion of indole to give a charged palladium intermediate. Depending on the reaction conditions, Pd migration is now possible to give another carbocationic intermediate. Deprotonation then occurs to give the C2-palladium indole complex. At this stage, the oxidative Heck takes place: olefin coordination, insertion, beta-hydride elimination and reduction to Pd(0). The last step is the reoxidation of Pd(0) to Pd(II) by the peroxide.