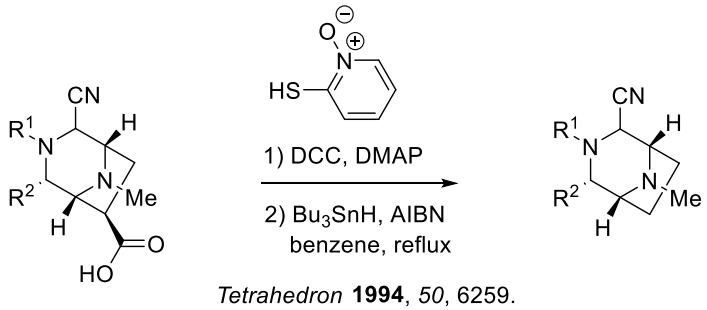
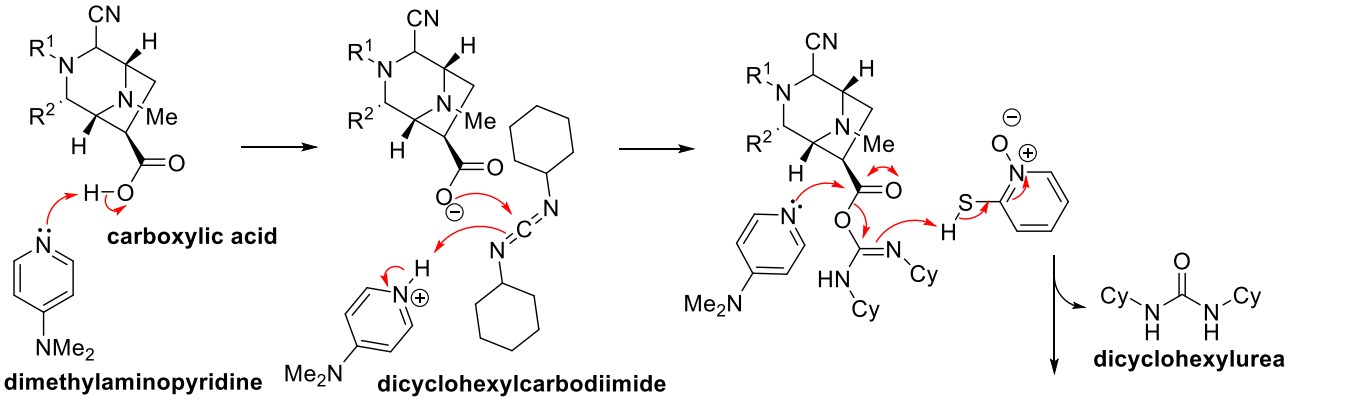
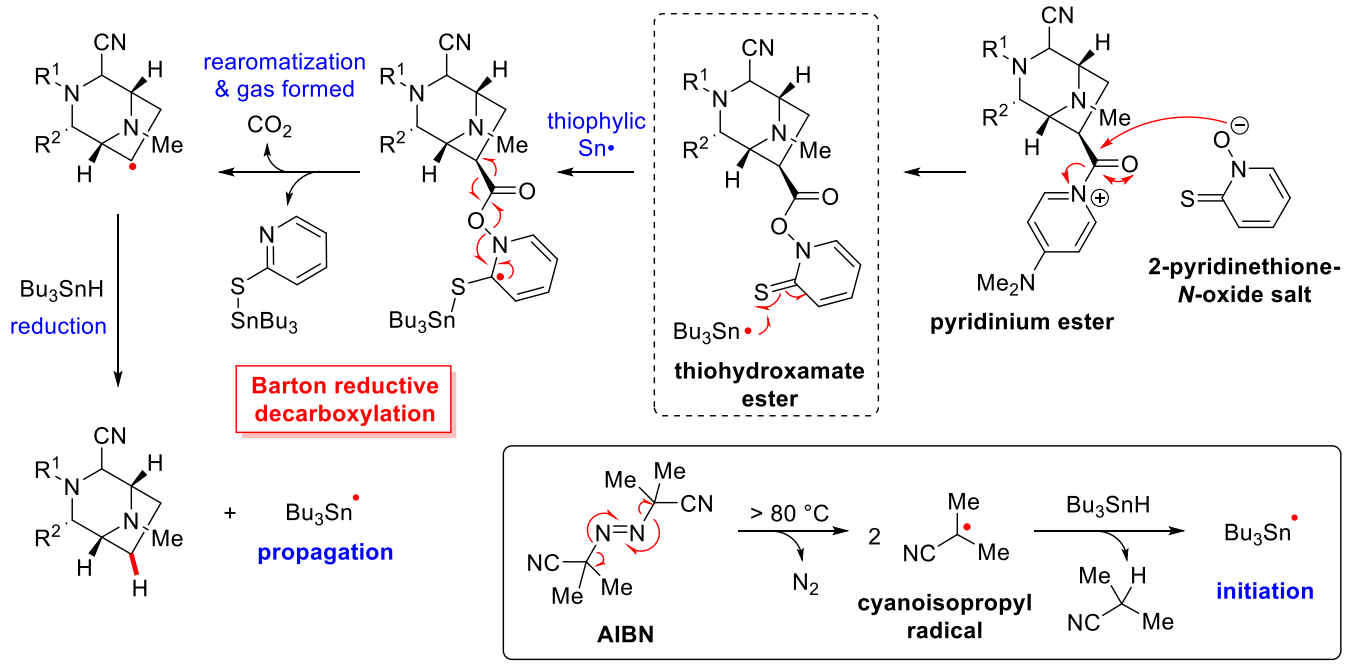
SR-2025 **Exercise series 3: Radicals, photochemistry and Umpolung - Solutions**

Exercise 1



Tetrahedron **1994**, *50*, 6259.



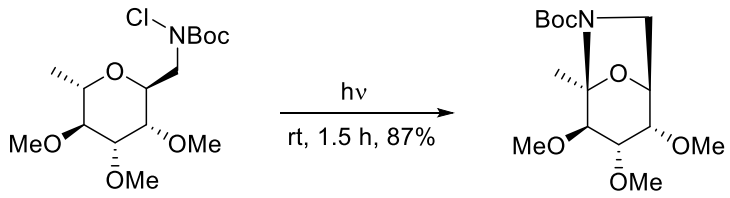


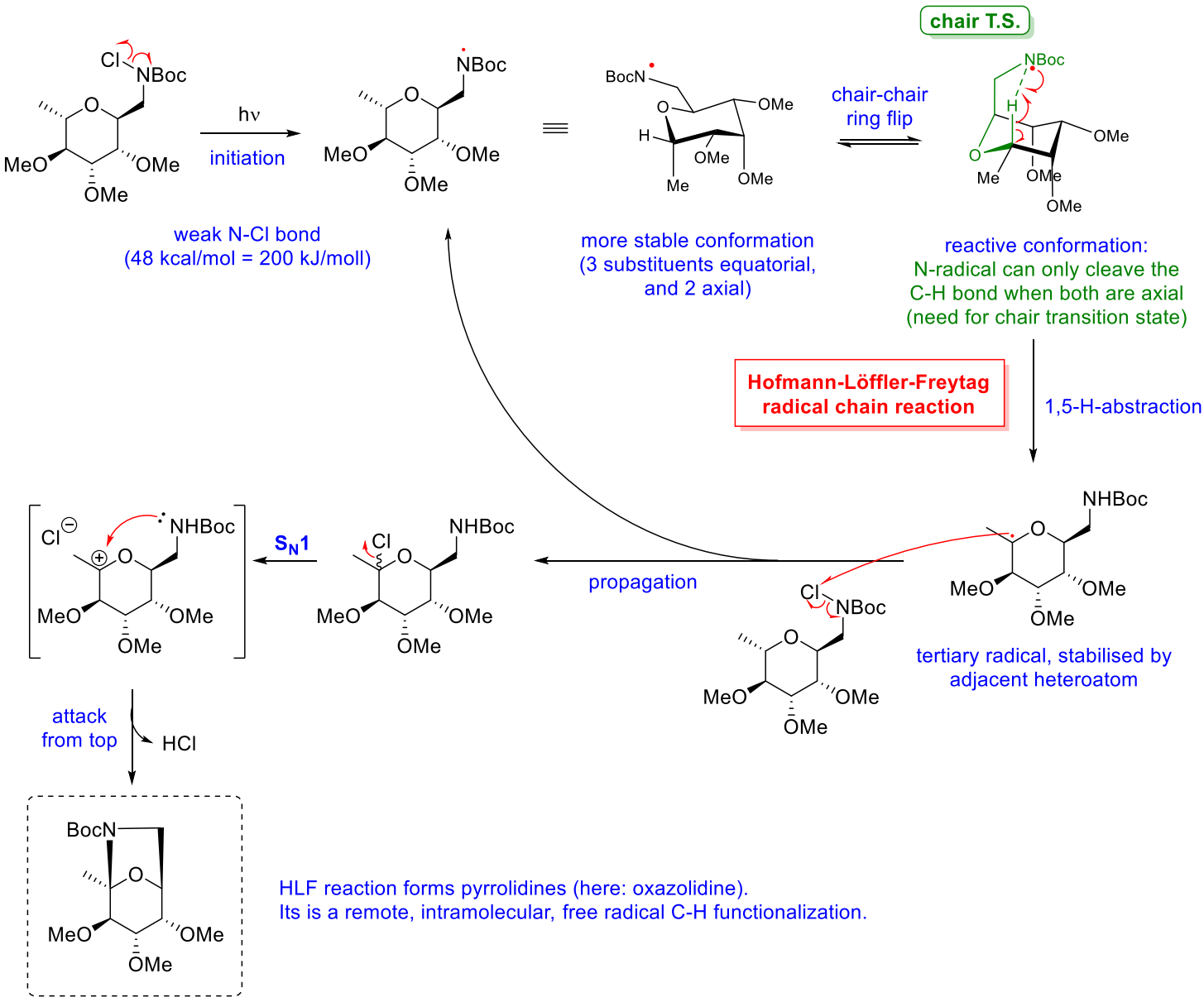
The first step of the reaction is the classical activation of a carboxylic acid with dicyclohexylcarbodiimide (DCC) as water scavanger ("coupling reagent"). The role of DMAP is first as a base to form the carboxylate, then as a nucleophilic catalyst to form a very reactive pyridinium ester. After this activation, attack of the deprotonated 2-mercaptopyridine-*N*-oxide (actually, its 2-pyridinethione-*N*-oxide tautomer) anion is easy, and gives a thiohydroxamate ester (a so-called Barton ester).

The second step begins with the thermal decomposition of AIBN to form nitrogen gas and two 2-cyanoprop-2-yl radicals, which then abstract a hydrogen radical from tributylin hydride (weak Sn-H bond, 74 kcal/mol) to form a tributyltin radical. The tributyltin radical is thiophilic and adds to the C=S double bond to form a new radical, which can fragment under rearomatization of the pyridine ring, and release of carbon dioxide to form a secondary alkyl radical.

Another classical example of such decarboxylation is fragmentation when DBPO (dibenzoylperoxide) is used as radical initiator. The secondary alkyl radical is very reactive and can abstract a hydrogen atom from the tributyltin hydride, propagating the radical chain reaction.

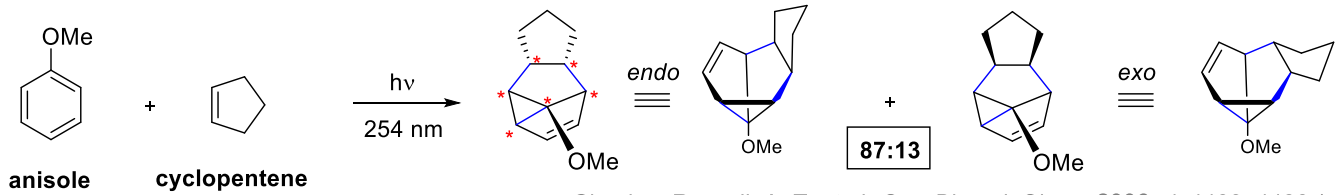
Exercise 2





HLF reaction forms pyrrolidines (here: oxazolidine).
Its is a remote, intramolecular, free radical C-H functionalization.

Exercise 3



6 new stereocenters in a single step!

Check: ♦ Russell, A. T. et al. *Org. Biomol. Chem.* **2006**, *4*, 4409–4430 (review)
♦ Cornelisse, J. *Chem. Rev.* **1993**, *93*, 615-669 (review)
♦ Houk, K. N. *Pure Appl. Chem.* **1982**, *54*, 1633–1650

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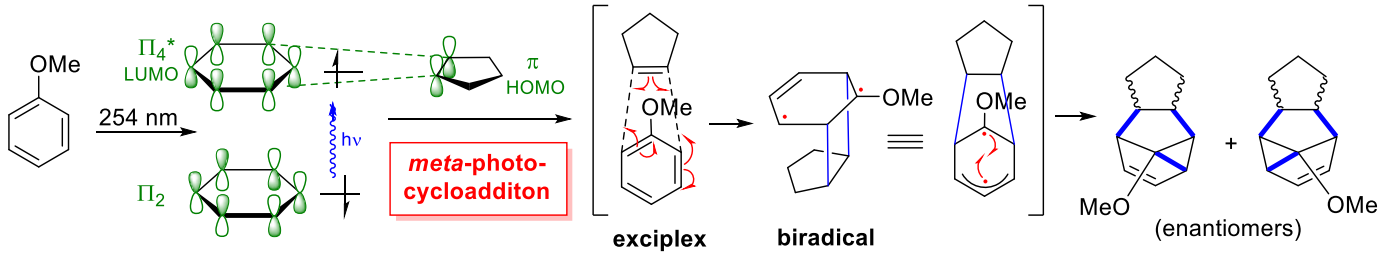
1) Overall:

The photochemical reaction between anisole and cyclopentene is initiated by the excitation of the benzene ring at 254 nm (electon goes to LUMO, the Π_4* molecular orbital), which then reacts with the HOMO of the alkene. It's an example of meta-photocycloadditions (new bonds formed in blue). A first regioselectivity issue is determined by the stability of the arising biradical intermediate.
The one next to the methoxy group is the most stabilized. Recombination forms the cyclopropane ring (two enantiomers).



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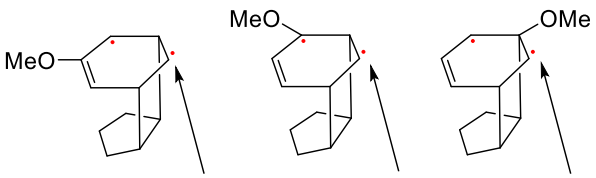
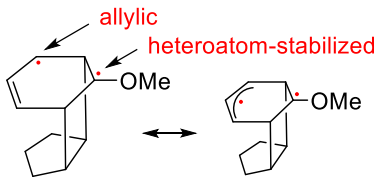
2) Regioselectivities:

All 4 principal possibilities for regioisomers, relevant for the reactivity, are shown in below.
Key factor = the stability of both radicals.
(The stability difference between the different allylic radicals is much smaller.)



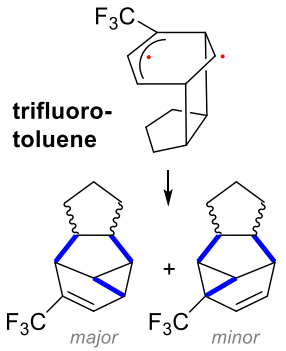
These three all have a "non-extra-stabilized" 2e radical.

EDG: 2,6-addition



best overall stabilization

EWG: 2,4-addition



(2 regiomers + endo/exo)
--> 4 products!

We see thus a "2,6-addition mode" around the electron-donating OMe-group on the benzene ring.
In fact, the bridging carbon's radical is considered slightly positively charged, and the allylic one negatively.
Note that, and in accordance with this logic, a CF_3-substituted (EWG) benzene indeed gives "2,4-addition".

There is however a second regioselectivity issue, when an unsymmetrical alkene would be used: two regiomers can be formed (racemic) because of the two possible recombinations of the π-allylic radical, furnishing the cyclopropane ring.
In this case, cyclopentene is symmetric, and therefore the other recombination mode in fact just gives the other enantiomer.
Note that the "2,4-mode" of trifluorotoluene (CF_3) on the other hand results in 2 regiomers, even with the symmetrical cyclopentene.

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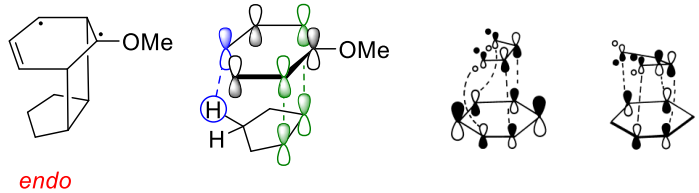
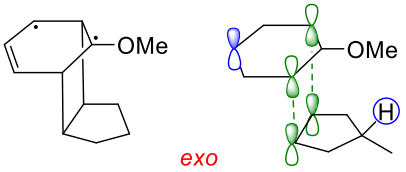
3) Stereoselectivities:



endo

secondary orbital interactions possible
--> favoured --> major diastereomer (85% yield isolated)



exo

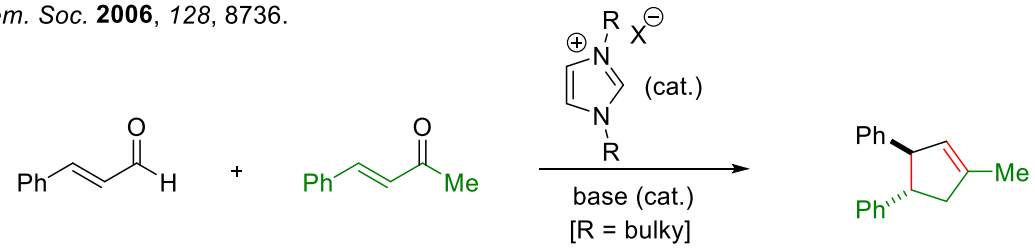
no secondary orbital interaction possible
--> minor diastereomer

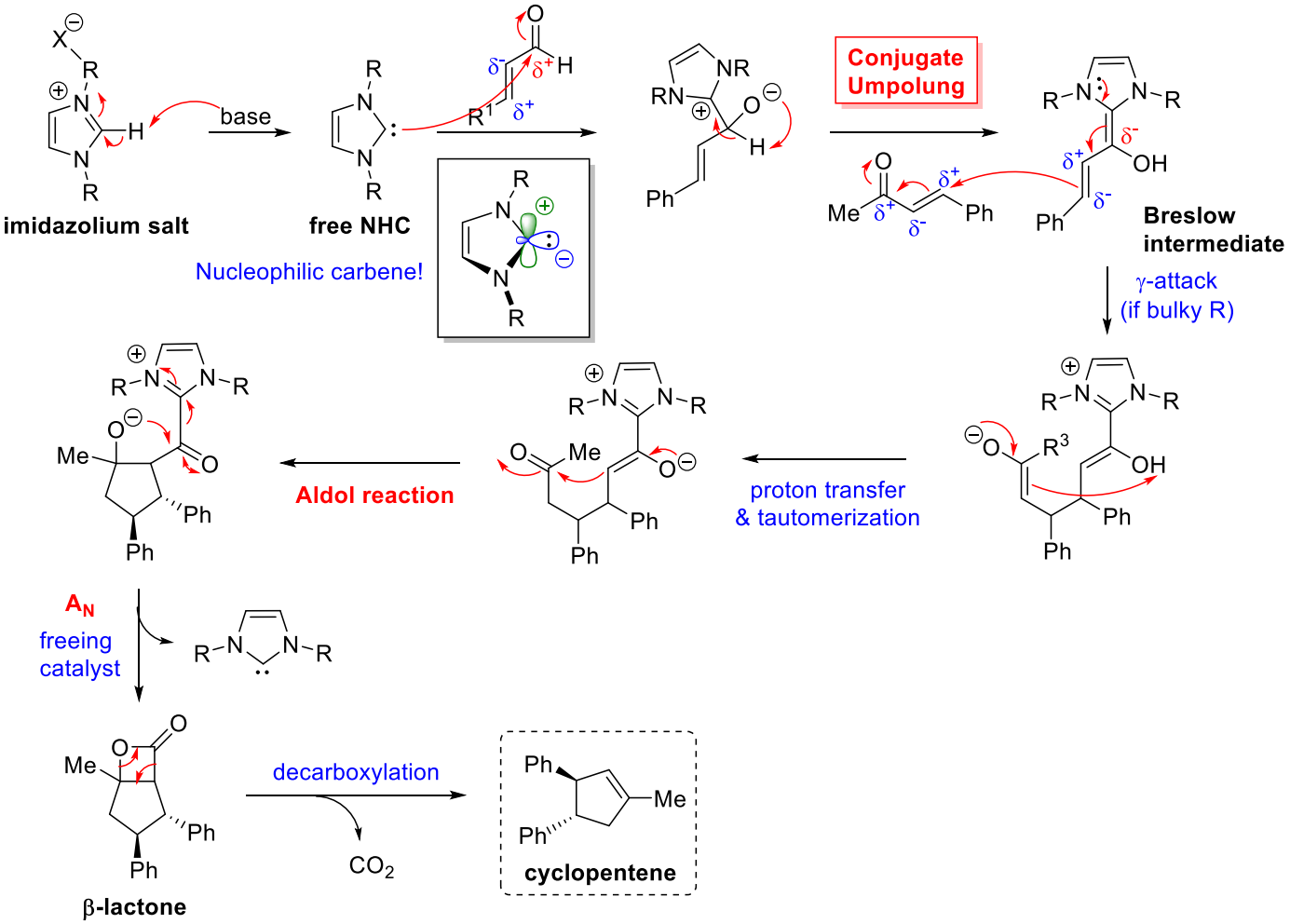
For the diastereoselectivity, secondary orbital interactions (analogue to Diels-Alder reaction) between the orbitals of the C-H bonds on the cyclopentene and the π-orbital of the benzene diradicals have been proposed to favor the *endo* product.

A second stereoselectivity issue concerns the side of attack (π-facial selectivity of the cyclopentene), which is for this transformation not relevant as the alkene had no original stereocenters attached.

Exercise 4

J. Am. Chem. Soc. **2006**, *128*, 8736.





The active catalyst is generated by deprotonation of the imidazolium salt to form the *N*-heterocyclic carbene.
This nucleophilic carbene adds then to the most electrophilic position, which is the carbonyl of the aldehyde.
The formed Breslow intermediate has now an inversed reactivity when compared with the starting material (Umpolung).

Next, the attack of the at the gamma position is favored for bulky R groups on the catalyst.
Michael type additon to the conjugated ketone is favored (softer position).

After proton transfer and tautomerization (the imidazolium keto group is more acidic than the isolated ketone), an intramolecular aldol reaction closes the cyclopentyl ring. Subsequently, a beta-lactonization occurs with release of the carbene catalyst.

Beta-lactones are not very stable and decarboxylate readily, furnishing the observed cyclopentene.