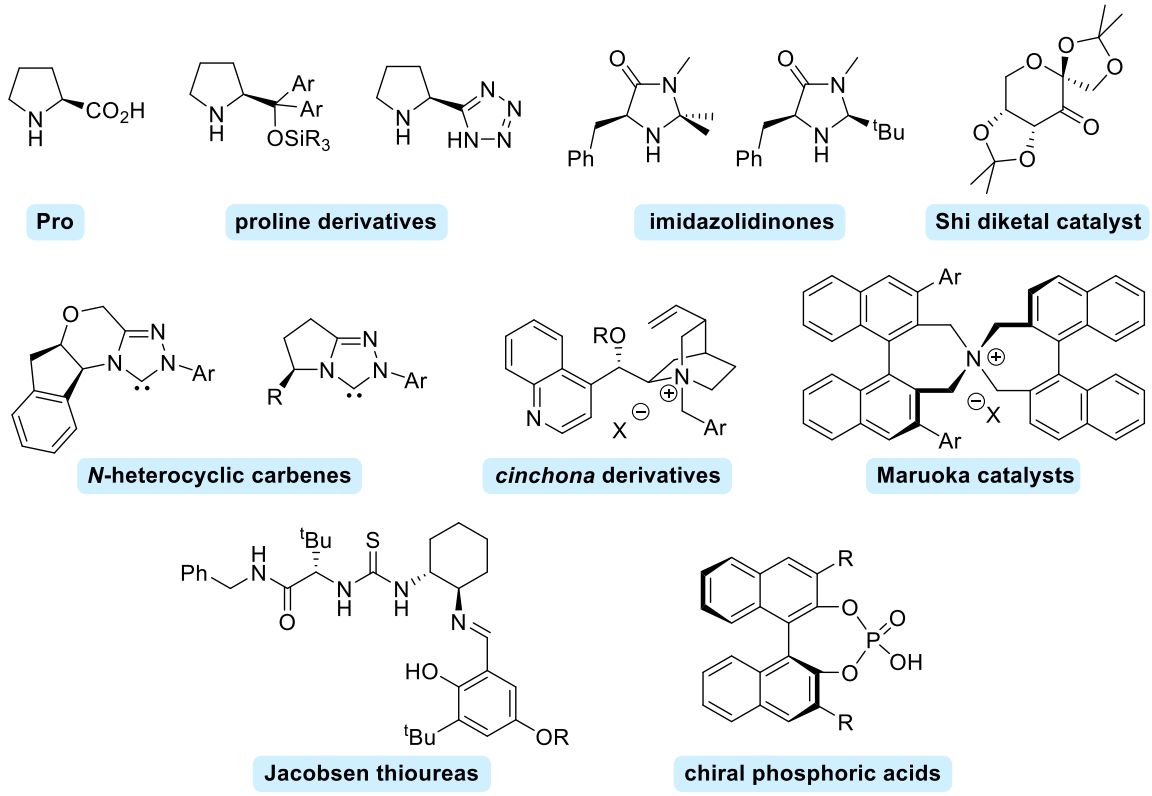
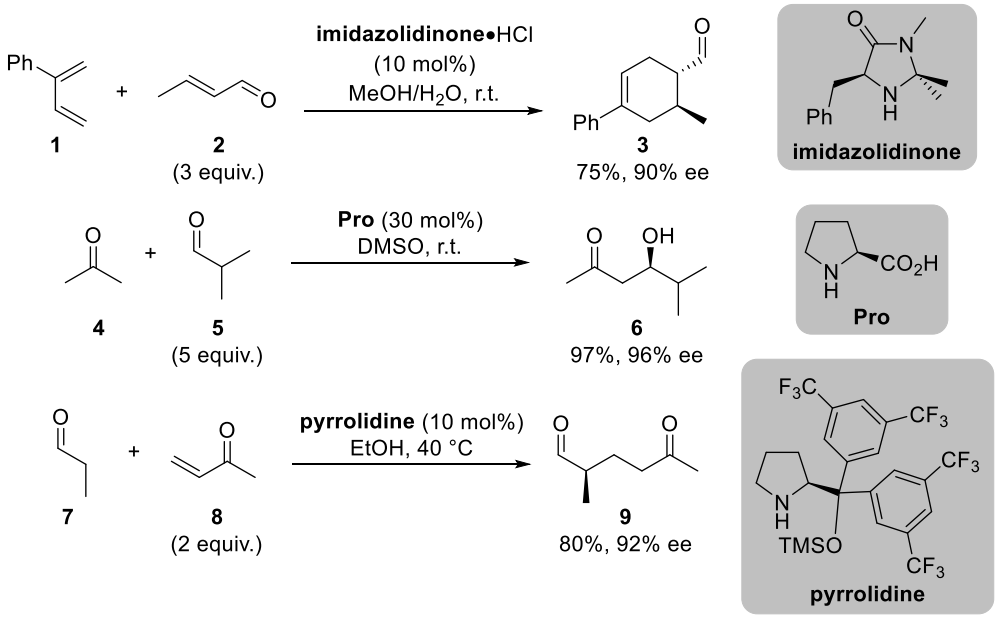
Asymmetric Organocatalysis

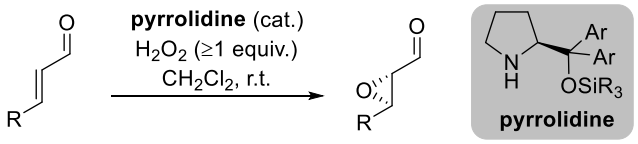


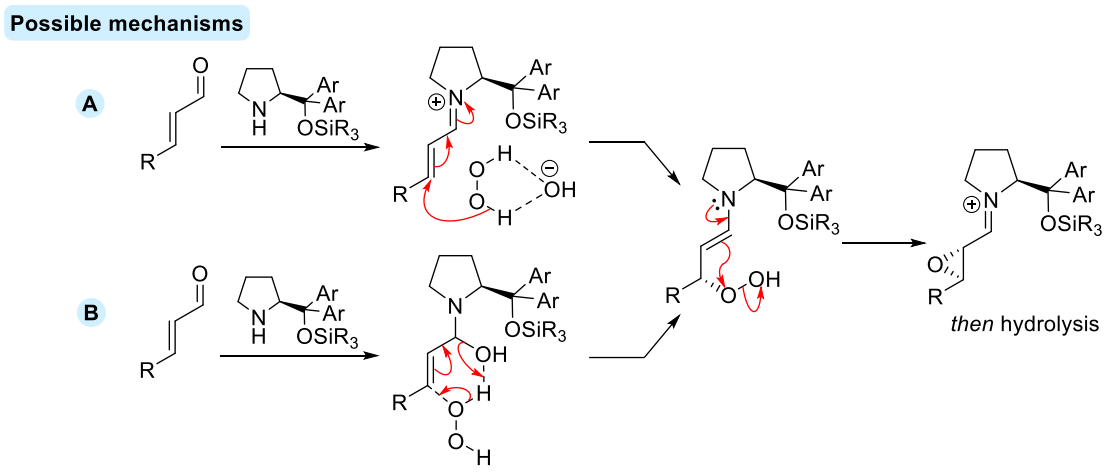
1. Modes of organocatalysis
   a. Two activation modes are typically considered for secondary amine catalysts – *enamine catalysis* and *iminium catalysis*. For the reactions shown below, suggest which of these two activation modes is operative. It is not necessary to draw full catalytic cycles for these reactions; simply explain the key step in each case.



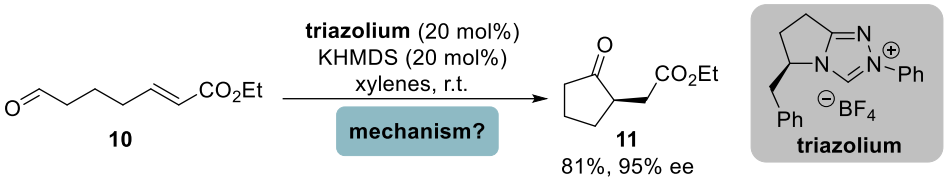
   b. Jørgensen-type pyrrolidine catalysts are well known for their use in asymmetric epoxidations of enals. Initially, it was assumed that this reaction proceeded *via*

iminium-type catalysis (pathway A, below). However, more recent work strongly supports the intermediacy of the hemiaminal instead (pathway B). Suggest a method by which the two pathways could be distinguished experimentally.

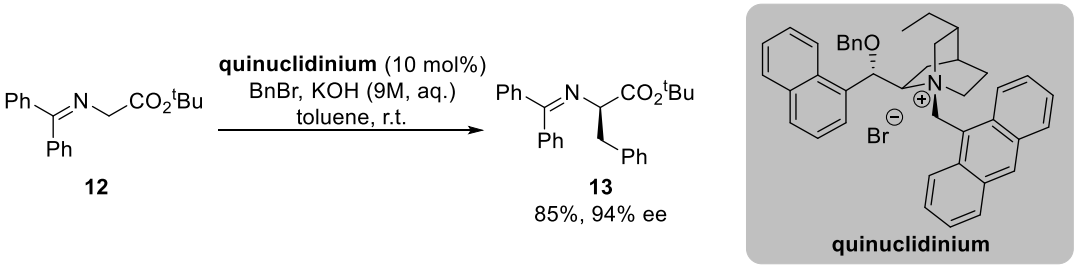




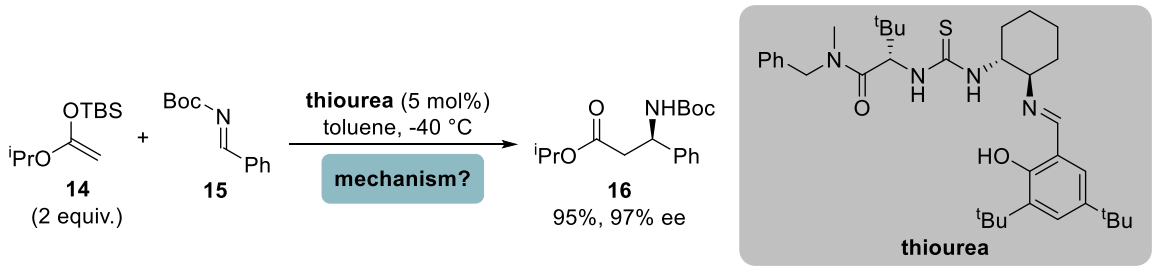
c. Organocatalysis with *N*-heterocyclic carbenes allows for *umpolung* (*i.e.*, electronically 'reversed') reactivity. With this reactivity in mind, propose a mechanism for the reaction shown below, accounting for the shown stereoselectivity.



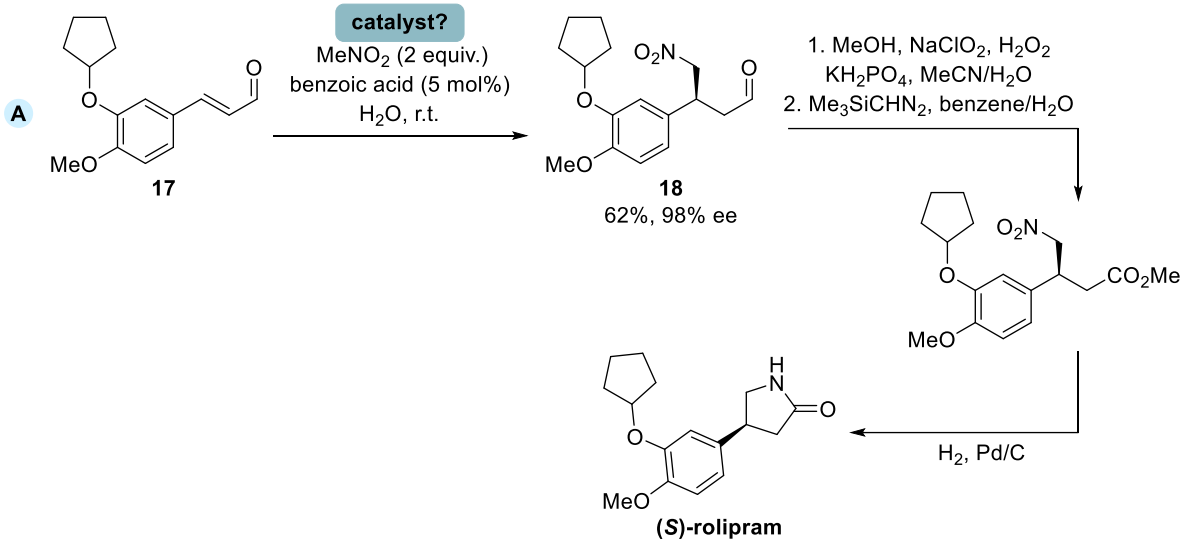
d. Explain why (and under what conditions) derivatives of *cinchona* alkaloids can be effective catalysts for the alkylation of glycine imines, an example of which is shown below.

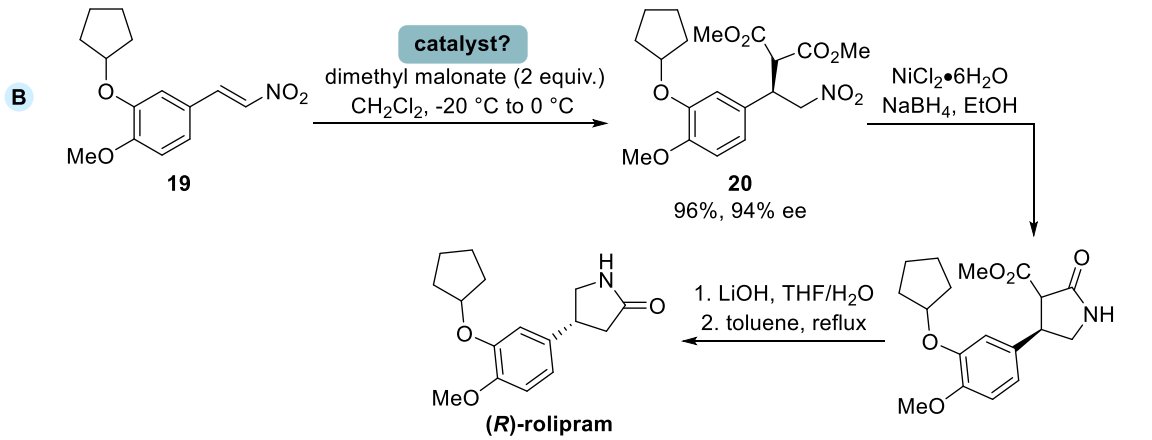


e. Thioureas can be used to catalyse additions to slow-reacting electrophiles, such as imines. Provide a mechanism for the thiourea-catalysed Mannich reaction shown overleaf. Why are thioureas - rather than ureas – typically used in catalysis?

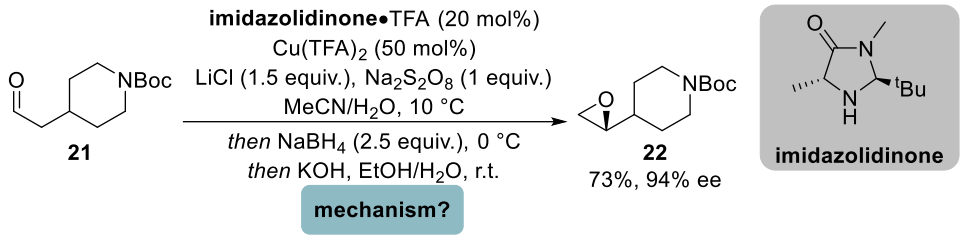


f. Consider the two synthesis routes shown below, each of which leads to a different enantiomer of rolipram – a selective PDE4 inhibitor. Suggest a general type of organocatalyst that would be appropriate for the key step in each route, as highlighted.

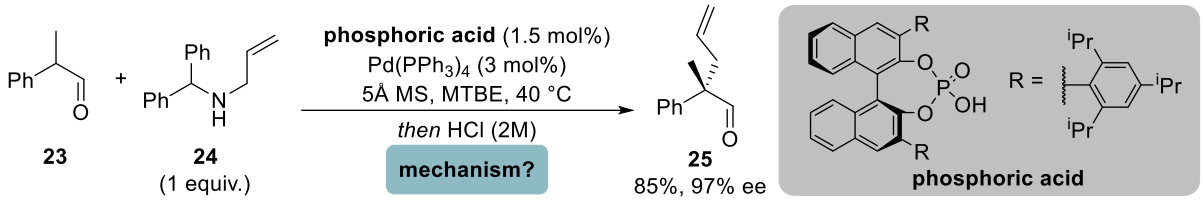




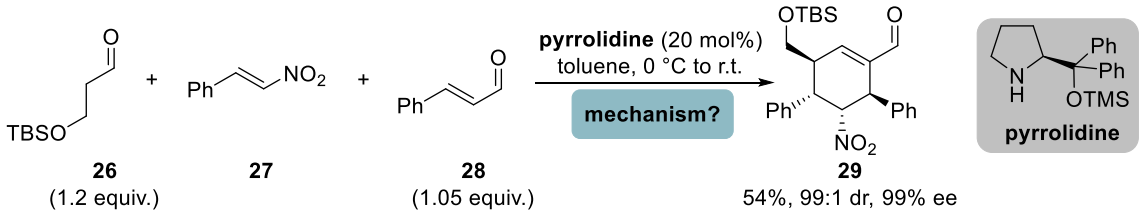
2. Merged and cascade organocatalysis
   a. Propose a mechanism for the synthesis of epoxide **22** from aldehyde **21**, as shown overleaf. What other methods exist for the asymmetric synthesis of terminal epoxides?



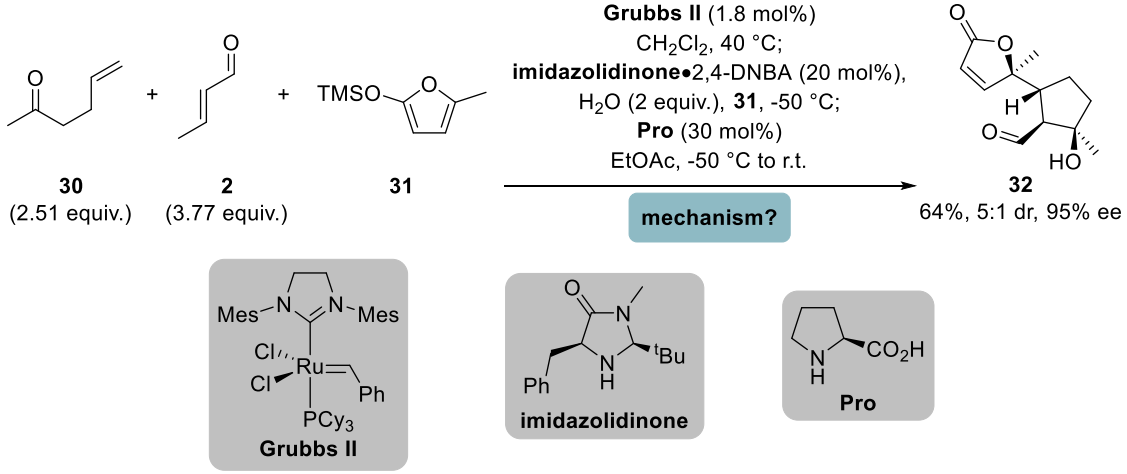
b. Propose a mechanism for the Pd/phosphoric acid co-catalysed, enantioselective allylation shown below.



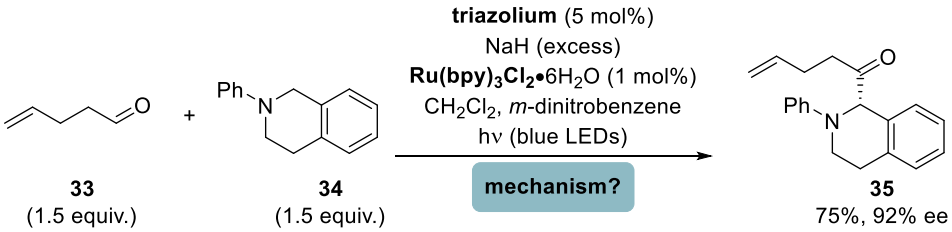
c. Consider the three-component reaction shown below. Suggest a reasonable mechanism for this process. How could the relative stereochemistry of the major product be established?

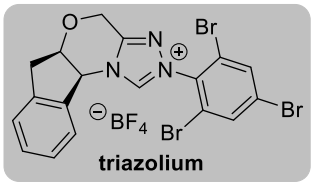


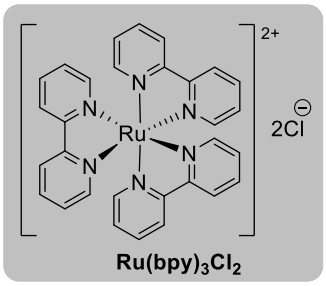
d. Consider the triple catalytic cascade process shown below. Propose a mechanism for the formation of **32** from these starting materials (note that furan **31** is added last). Explain the chemoselectivity of the Ru-catalysed step.



e. Propose a mechanism for the merged catalytic reaction – a "dehydrogenative cross coupling" – shown overleaf.


triazolium (5 mol%)
NaH (excess)
Ru(bpy)3Cl2•6H2O (1 mol%)
CH2Cl2, m-dinitrobenzene
hν (blue LEDs)
mechanism?
Ph
N
O
33
(1.5 equiv.)
34
(1.5 equiv.)
35
75%, 92% ee


O
N
N
Br
Br
Br
BF4
triazolium


2+
N
Ru
2Cl
Ru(bpy)3Cl2