CH3404 Asymmetric Synthesis of Pharmaceuticals and Natural Products LCM Lectures 1-3

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CH3404 Course Overview

Central aim of this course:
To discuss various aspects of advanced asymmetric synthesis and how these can be applied towards the production of pharmaceuticals and natural products

Course Outline:

- **Unit 1 – Organocatalysis (LCM)**
- **Unit 2 – Enabling tools for organic synthesis (DLB)**
- **Unit 3 – Alkene functionalisation (TW)**

Unit 1: Lecture Synopsis

- **Lecture 1: Introduction to Organocatalysis;** recap of fundamental concepts and definitions; definition of asymmetric catalysis and organocatalysis; historical perspective; α-functionalisation of carbonyl compounds; enamine organocatalytic activation mode (part 1).

- **Lecture 2: HOMO-Raising Organocatalysis;** enamine organocatalytic activation mode (part 2): bifunctional vs. steric control; catalyst synthesis and reactivity; dienamine organocatalytic activation mode; C(1)-, C(2)- and C(3)-enolate organocatalytic activation modes.

- **Lecture 3: LUMO-Lowering Organocatalysis;** iminium organocatalytic activation mode; iminium-enamine organocatalytic cascades; (α,β-unsaturated) acyl cation organocatalytic activation mode

- **Non-Assessed Feedback Tutorial:** Answers to be completed beforehand. Feedback provided during tutorial. Questions on lectures 1 and 2.

- **In Unit 1 we will learn how organocatalysis can be used for a variety of stereo-selective transformations and how this can be applied towards the asymmetric synthesis of pharmaceuticals and natural products.**

Unit 1: Additional Resources

- **Recommended Reading:**

1. *Organic Chemistry 2nd Ed.* (J. Clayden, N. Greeves and S. Warren, Oxford University Press, 2012, ISBN 978-0-19-927029-3). Chapter 41 is particularly relevant.
2. *Prof. MacMillan Short-Course:* www.princeton.edu/chemistry/macmillan/research/

- **Molecular Model Kits:** Invaluable for ALL organic chemistry courses. It is highly recommended that you make good use of these to visualise the molecules discussed in this course. You can also use these in your examination if you want to.

- **Learning Central:** I have set up a folder on Learning Central that will contain all information for this course including handouts and lecture capture.

- **Non-Assessed Feedback Tutorial:** In addition to the questions set, please take advantage of this opportunities to ask questions about any aspect of the course.

- **Me:** Should you not be able to find an answer to a question that specifically relates to this course, please email (MorrillLC@cardiff.ac.uk) or visit (1.47B) anytime. **In addition, I will specifically keep Monday 4-6pm free each week for office visits.**

-  **:** Indicates worked examples to be performed during lectures.

CH3404 Asymmetric Synthesis of Pharmaceuticals and Natural Products LCM Lecture 1

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Lectures 1-3 Preparation

To best prepare yourself for the contents of this course, please refresh

1st-3rd year undergraduate organic chemistry courses with particular focus on:

Carbonyl chemistry:

- Addition reactions to aldehydes and ketones
- Formation of acetals, ketals, imines and enamines
- Enols and enolates
- Aldol and Claisen condensations

Stereochemistry including:

- Assignment of stereocentres
- Enantiomers and diastereoisomers

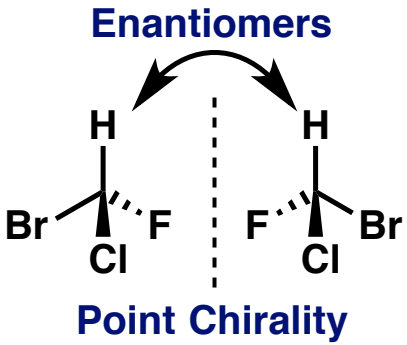
Lecture 1: Introduction to Organocatalysis

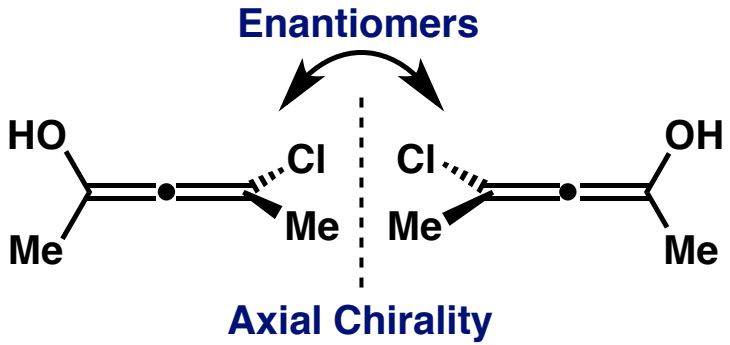
Key learning objectives:

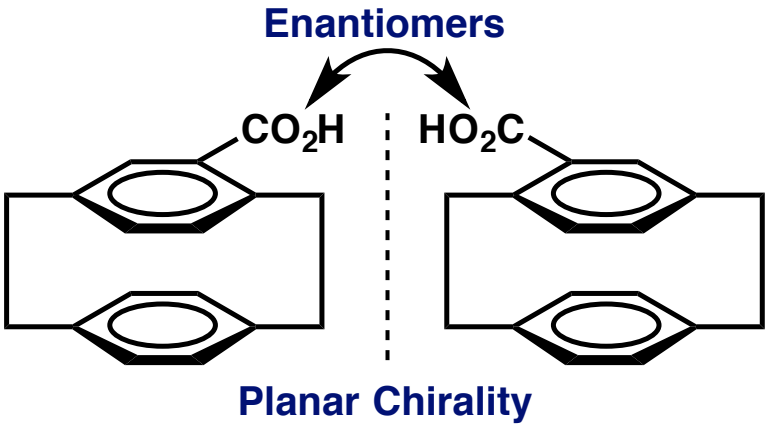
- Recap of fundamental concepts and definitions (stereochemistry)
- Definition of asymmetric catalysis and organocatalysis
- The development and introduction of organocatalysis (a historical perspective)
- Traditional α-functionalisation of carbonyl compounds (HOMO-raising)
- The enamine organocatalytic activation mode (part 1): definition; general catalytic cycle; intra- and intermolecular aldol reactions; related α-functionalisation reactions; curly arrow pushing mechanisms; stereochemical rationale.

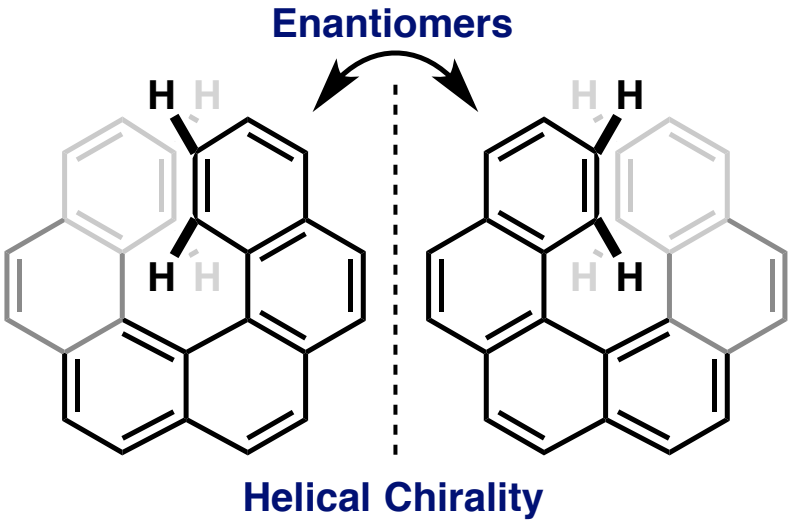
Recap of Fundamental Concepts and Definitions

- **Chirality** is a geometric property of some molecules and ions. A **chiral** molecule/ion is non-superimposable on its mirror image. This section of the course will focus on **point chirality**.





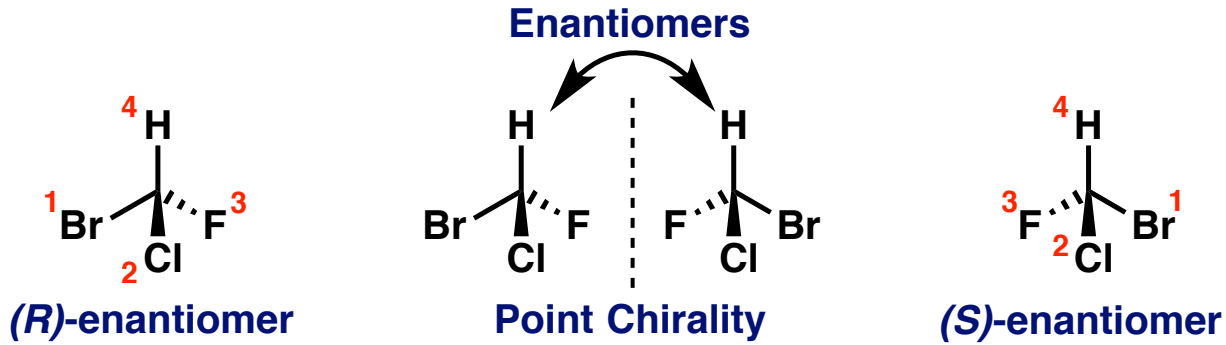




For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 14 pp 302-327.

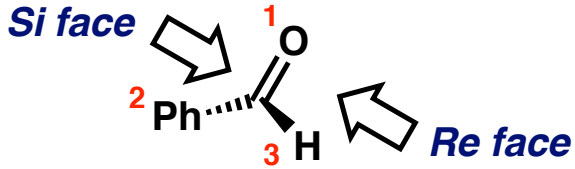
Recap of Fundamental Concepts and Definitions

- **Enantiomers** are chiral molecules that are non-superimposable mirror images.



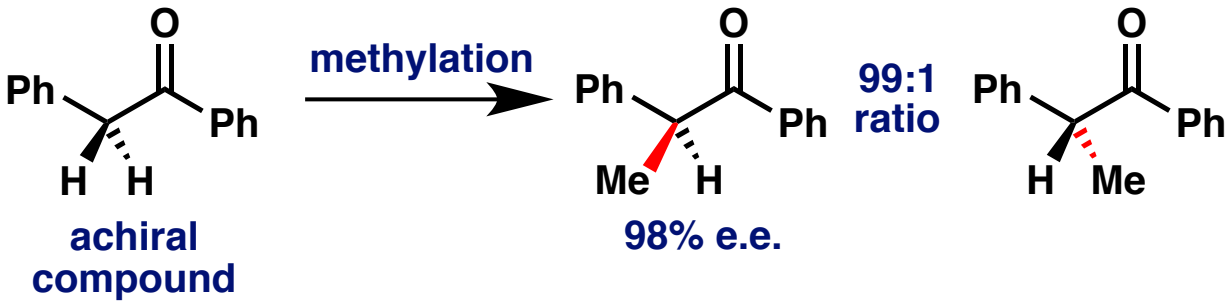
- **Diastereomers** can occur when there is more than one stereogenic center present

- **Prochiral** molecules are those that can be converted from achiral to chiral in a single step. *Re* or *Si* for sp^2 hybridised centers, labeled at the reacting atom.

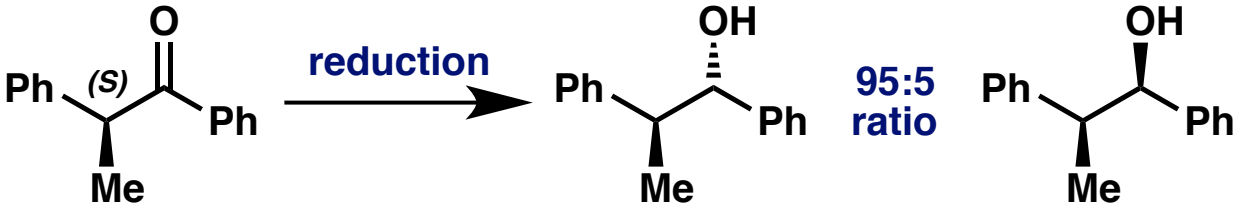


Recap of Fundamental Concepts and Definitions

- **Enantiomeric excess (e.e.)** is the excess of one enantiomeric form over another and is often quoted to describe enantio-selective reactions.



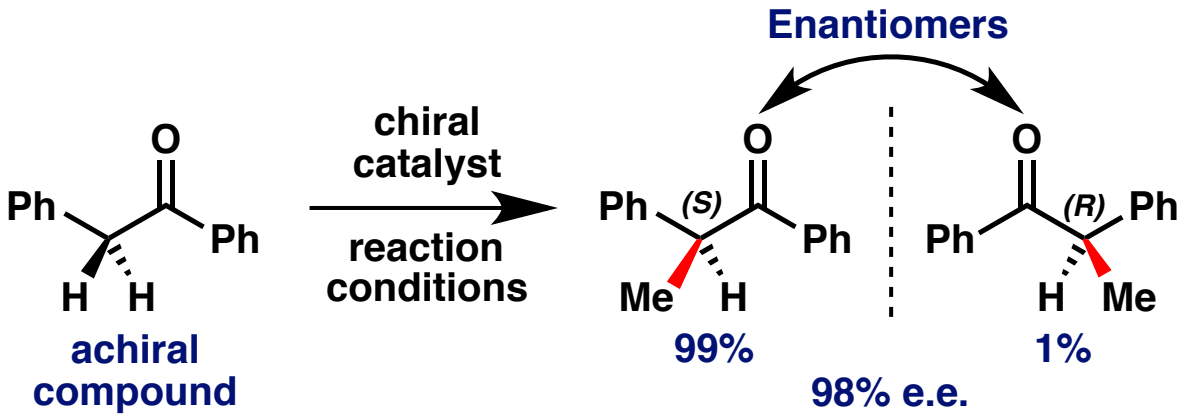
- **Diastereomeric excess (d.e.)** is the excess of one diastereomeric form over another and is often quoted to describe diastereo-selective reactions.



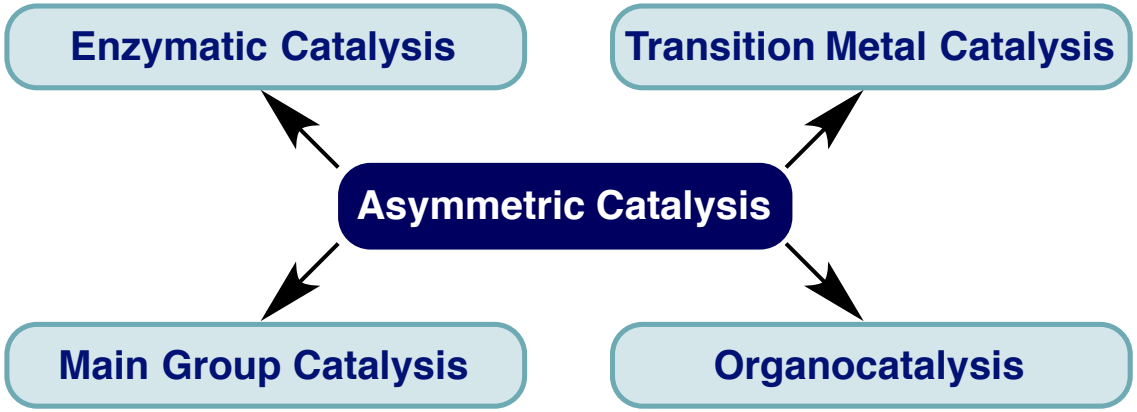
- **Stereo-selective** reactions can be both **diastereo-selective** (favours the formation of one diastereomer) AND **enantio-selective** (favours the formation of one enantiomer)

Asymmetric Catalysis

- **Asymmetric catalysis** is a type of catalysis in which a chiral catalyst directs the formation of a chiral compound such that the formation of one particular stereoisomer is favoured.

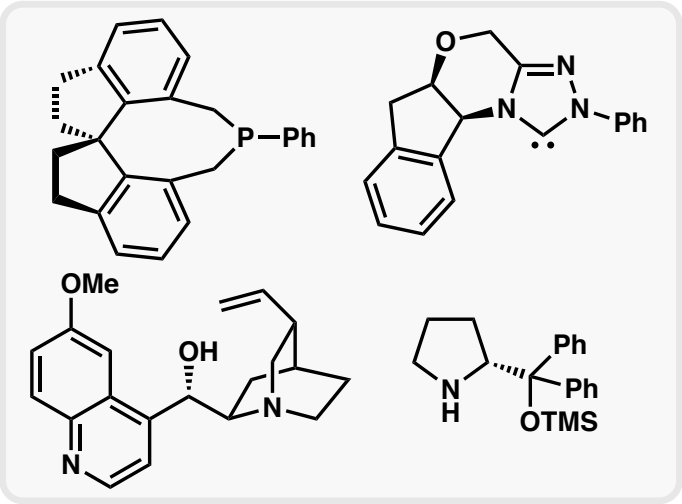


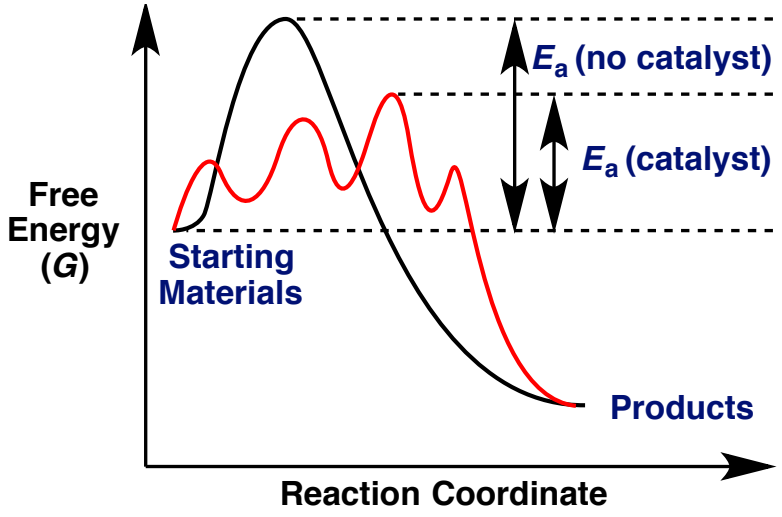
- **Asymmetric catalysis** can be sub-divided into 4 primary areas:



Organocatalysis - Definition

- **Organocatalysis** is the use of a **substoichiometric** amount of an **organic molecule** to **increase the rate** or a chemical reaction.
- **Substoichiometric** – using less than 1 equivalent of reagent = catalytic. For example, if you use 0.2 equiv of a catalyst (20 mol%), this equates to 5 turnovers.
- **Organic molecule** – there are no metal(s) present within the catalyst.
- **Increase the rate** – *via* lowering the activation barrier for productive reaction.

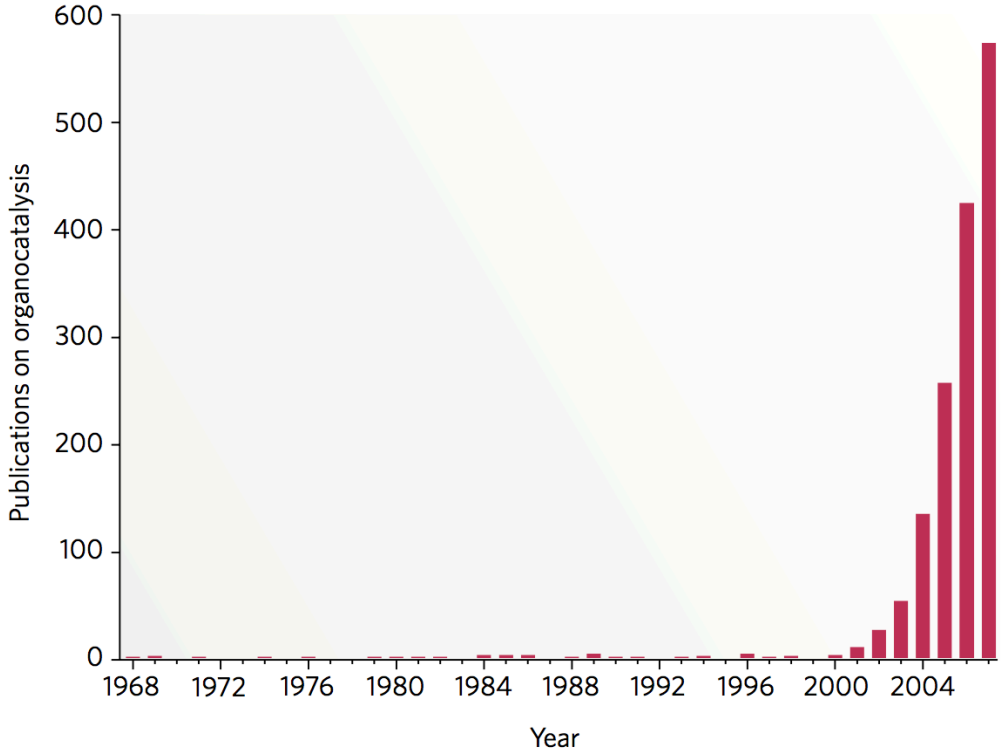




For an overview see D. W. C. MacMillan, *Nature*, 2008, **455**, 304.

Organocatalysis – A Historical Perspective

- Since the year **2000**, there has been an explosion of interest in this exciting new field.
- Between 2000 and 2008, there were more than 2000 manuscripts on >150 discrete reaction types.

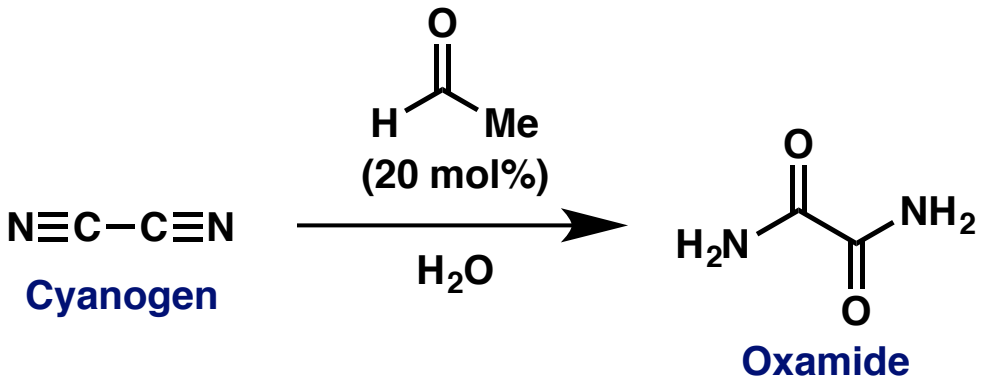


- However, there were several pioneering reports of metal-free catalysis prior to the year 2000, which laid the foundations for further development.

For an overview see D. W. C. MacMillan, *Nature*, 2008, **455**, 304.

Organocatalysis – A Historical Perspective

- The first organocatalytic transformation was reported in **1860** by Justus von Liebig in the conversion of cyanogen to oxamide in the presence of aqueous acetaldehyde.



- This reaction satisfies the definition of an organocatalytic process:

1) The reagent is substoichiometric (20 mol%), therefore it is a **catalyst**.

2) There is **no metal** present within the catalyst, therefore it is an **organocatalyst**.

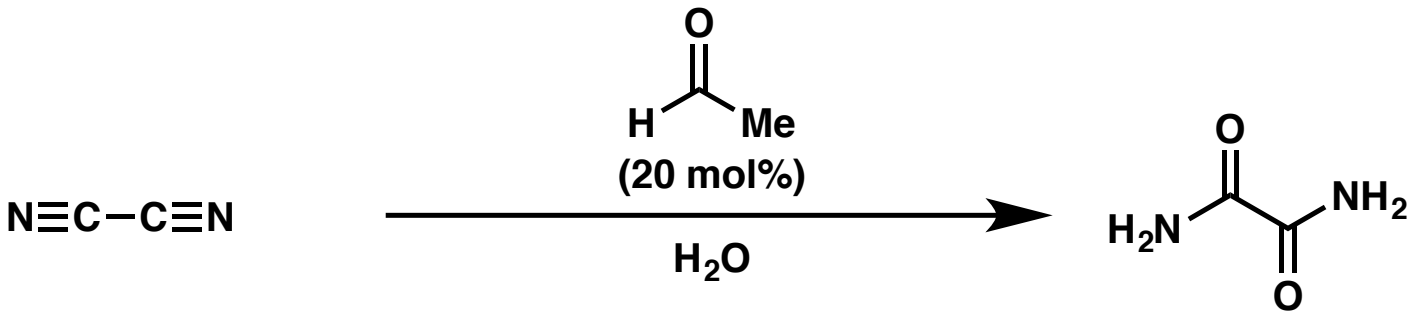
3) No reaction occurs without acetaldehyde, therefore it **increases the rate**.

- Let's consider the curly arrow pushing mechanism of this organocatalytic reaction.

J. Liebig, *Ann. Chem. Pharm.*, 1860, **13**, 246.

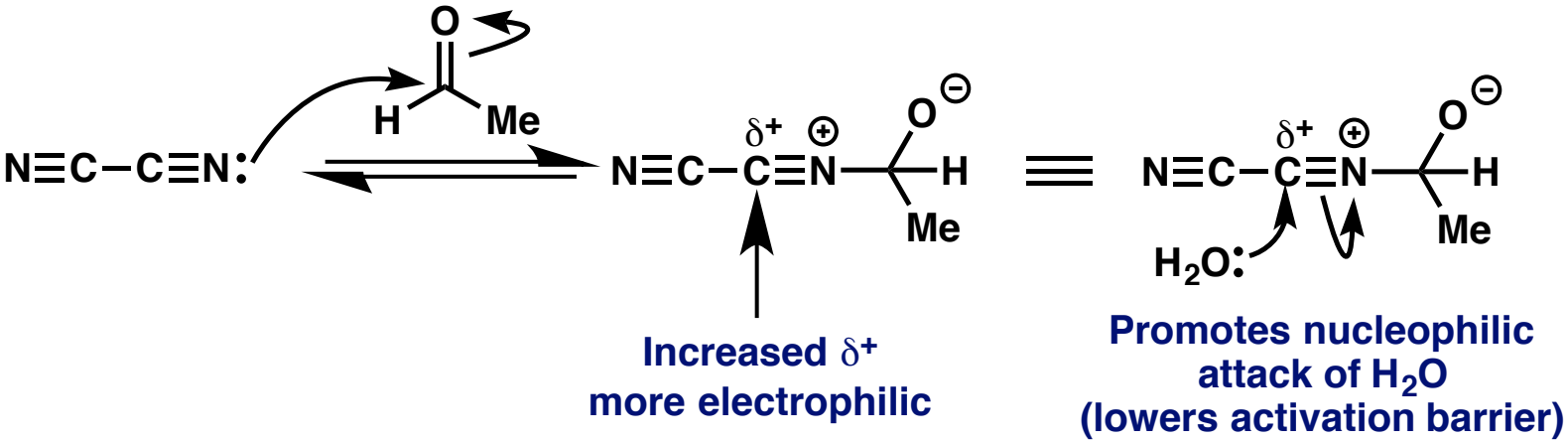
Organocatalysis – A Historical Perspective

- The conversion of cyanogen to oxamide in the presence of aqueous acetaldehyde.



Organocatalysis – A Historical Perspective

- From the curly arrow pushing mechanism we can conclude that acetaldehyde acts as an organocatalyst by **increasing the electrophilicity of the nitrile functional group towards nucleophilic attack by a water molecule**.



- When presented with any organocatalytic reaction we must consider:

1) The **curly arrow pushing mechanism**

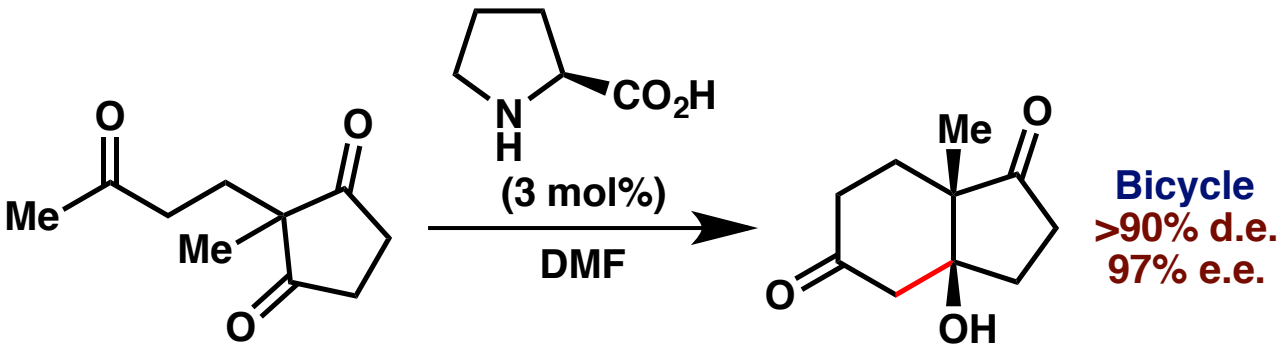
2) How the organocatalyst **activates** the substrate towards a given reaction (**activation mode**)

3) The **stereochemical outcome** of the reaction (if relevant)

J. Liebig, *Ann. Chem. Pharm.*, 1860, **13**, 246.

Organocatalysis – A Historical Perspective

- Over 100 years later, in 1974, L-proline was discovered as an organocatalyst for the **intramolecular asymmetric aldol reaction**.

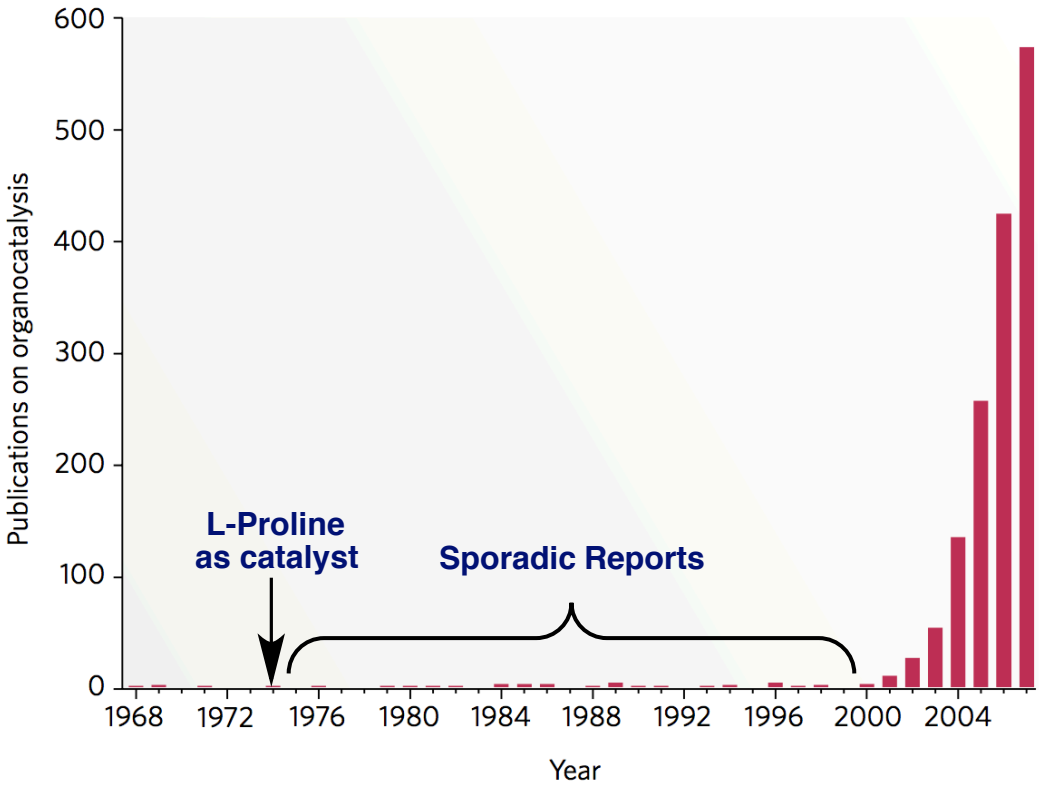


- This reaction employs a **chiral catalyst** and hence the reaction is **catalytic AND asymmetric**.
- One **stereoisomer** of the product is favoured due to the use of a chiral catalyst.
- Due to the presence of two stereogenic centres within the product, both **enantiocontrol (e.e.)** and **diastereocontrol (d.e.)** are important considerations.
- We will revisit this landmark reaction in detail later in the lecture.

Z. G. Hajos *et al.*, *J. Org. Chem.*, 1974, **39**, 1615.

Organocatalysis – A Historical Perspective

- Despite the clear precedence within the literature, the chemical synthesis community continued to largely overlook the field of organocatalysis for a further 26 years.



- Why did the field of chemical synthesis overlook the use of organic catalysts until the beginning of the 21st century?

For an overview see D. W. C. MacMillan, *Nature*, 2008, **455**, 304.

Organocatalysis – A Historical Perspective

- In 1990, **Dieter Seebach** (one of the world's leading organic chemists) wrote an essay on the future of organic synthesis and stated: *"New synthetic methods are most likely to be encountered in the fields of biological and organometallic chemistry"*

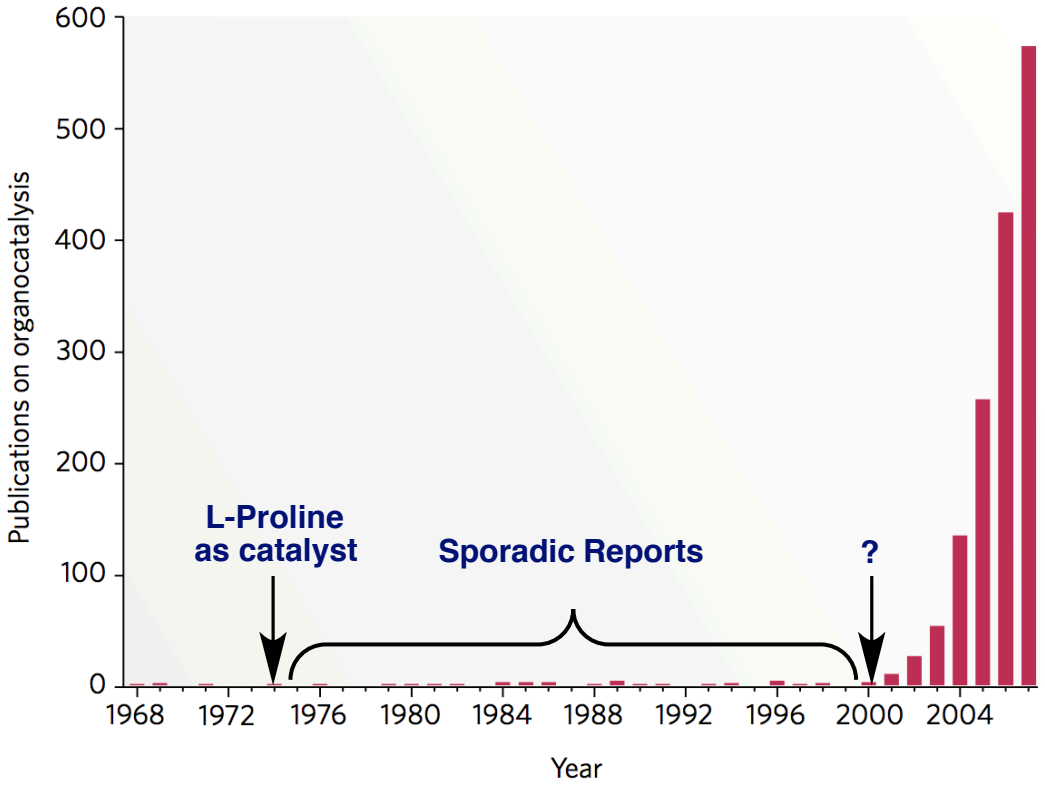
- Why did he omit organocatalysis from his vision of the future of organic synthesis?

- One interesting perspective is that it is impossible to overlook a field that **does not yet exist!** (in much the same way that you cannot work on a problem that has not yet been defined)

D. Seebach, *Angew. Chem. Int. Ed.*, 1990, **29**, 1320.

Organocatalysis – A Historical Perspective

- What happened in the year **2000** that resulted in a explosion of interest in this area of research?

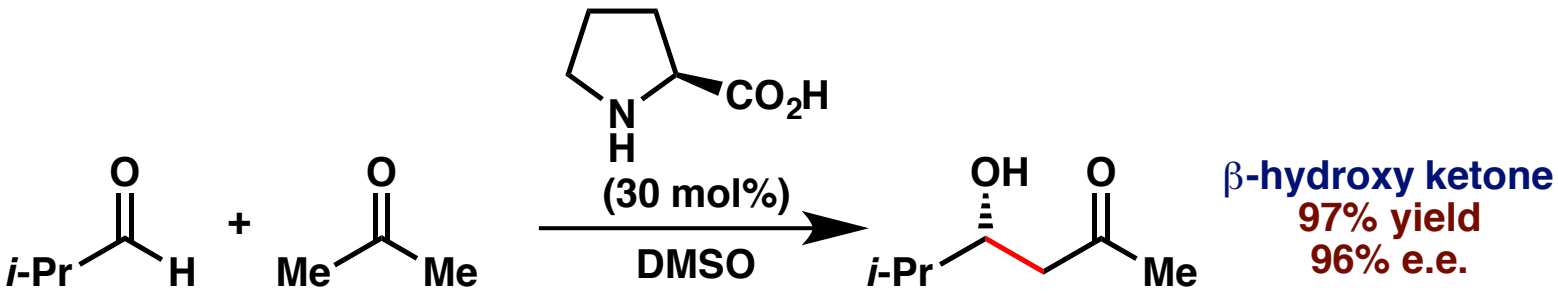


- In 2000, two landmark reports from **List** and **MacMillan** conceptualised the field, paving the way for others to contribute. Both are likely future Nobel Prize recipients!

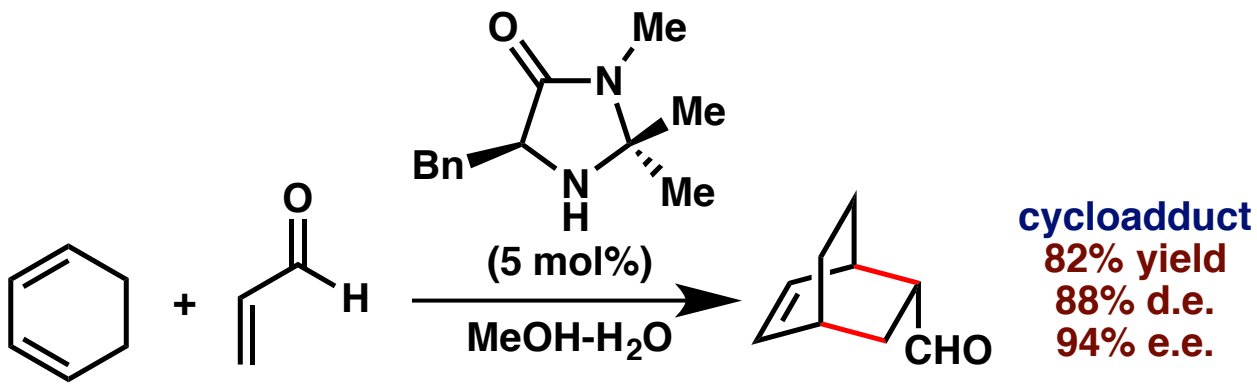
B. List *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 2395; D. W. C. MacMillan *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 4243.

Organocatalysis – A Historical Perspective

- List reported a **proline-catalysed asymmetric intermolecular aldol reaction**



- MacMillan reported a **enantioselective organocatalytic Diels-Alder reaction**



- We will revisit both of these landmark reactions in detail later in the course.

B. List *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 2395; D. W. C. MacMillan *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 4243.

Organocatalysis – A Historical Perspective

- MacMillan's manuscript conceptualised the field of organocatalysis for the first time in 3 important ways

New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels–Alder Reaction

Kateri A. Ahrendt, Christopher J. Borths, and David W. C. MacMillan*

Department of Chemistry, University of California Berkeley, California 94720

Received January 7, 2000

Over the past 30 years, enantioselective catalysis has become one of the most important frontiers in exploratory organic synthetic research. During this time, remarkable advances have been made in the development of organometallic asymmetric catalysts that in turn have provided a wealth of enantioselective oxidation, reduction, π-bond activation, and Lewis acid-catalyzed processes.[1] Surprisingly, however, relatively few asymmetric transformations have been reported which employ organic molecules as reaction catalysts,[2] despite the widespread availability of organic chemicals in enantiopure form and the accordant potential for academic, industrial, and economic benefit. Herein, we introduce a new strategy for organocatalysis that we expect will be amenable to a range of asymmetric transformations. In this context, we document the first highly enantioselective organocatalytic Diels–Alder reaction.[3]

- Introduced terms **"organocatalytic"** and **"organocatalysis"** for the first time.
- Outlined the **potential benefits** of using organic molecules as asymmetric catalysts for industry or academia.
- Introduced the concept of a **generic mode of activation** for organic catalysts that could be used of over many reaction types.

D. W. C. MacMillan *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 4243.

Organocatalysis – A Historical Perspective

- There are several **inherent benefits** of using organic molecules as catalysts:

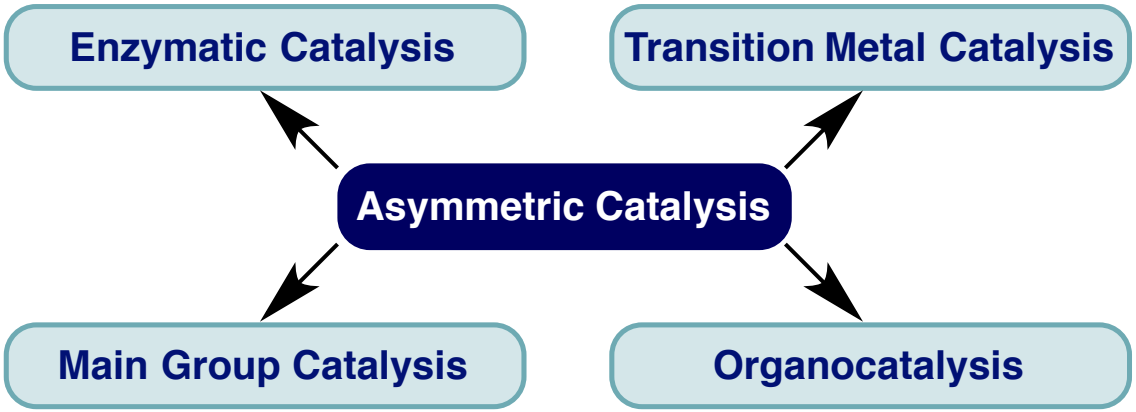
1) Low air and moisture sensitivity – operationally easy to handle.

2) Inexpensive and easy to prepare with both enantiomers commonly available.

3) Starting materials are readily available from the chiral pool, e.g. amino acids.

4) Non-toxic and easily removed from waste streams

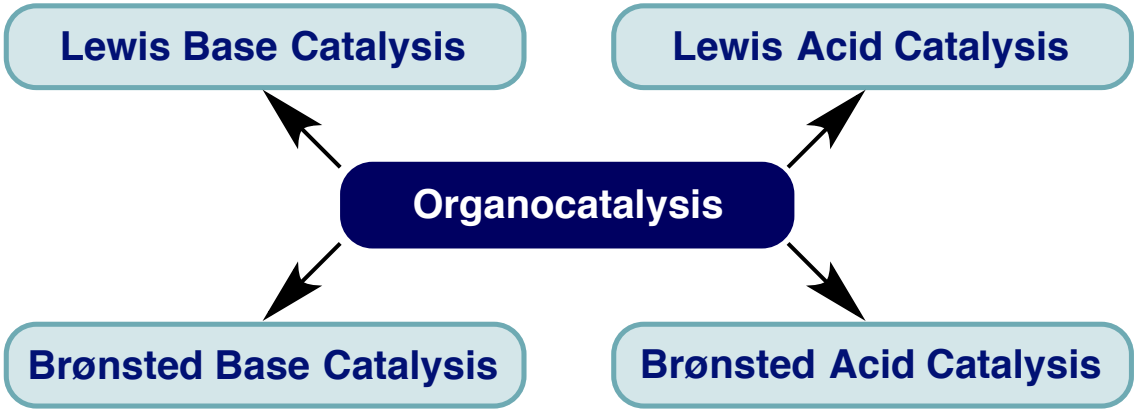
- The pioneering reports of List and Macmillan have resulted in organocatalysis being thoroughly established as the **4th main branch of asymmetric catalysis**.



B. List *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 2395; D. W. C. MacMillan *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 4243.

Organocatalysis – General Classifications

- Organocatalysts are commonly divided into 4 main sub-classes: **Lewis bases, Lewis acids, Brønsted bases and Brønsted acids**:



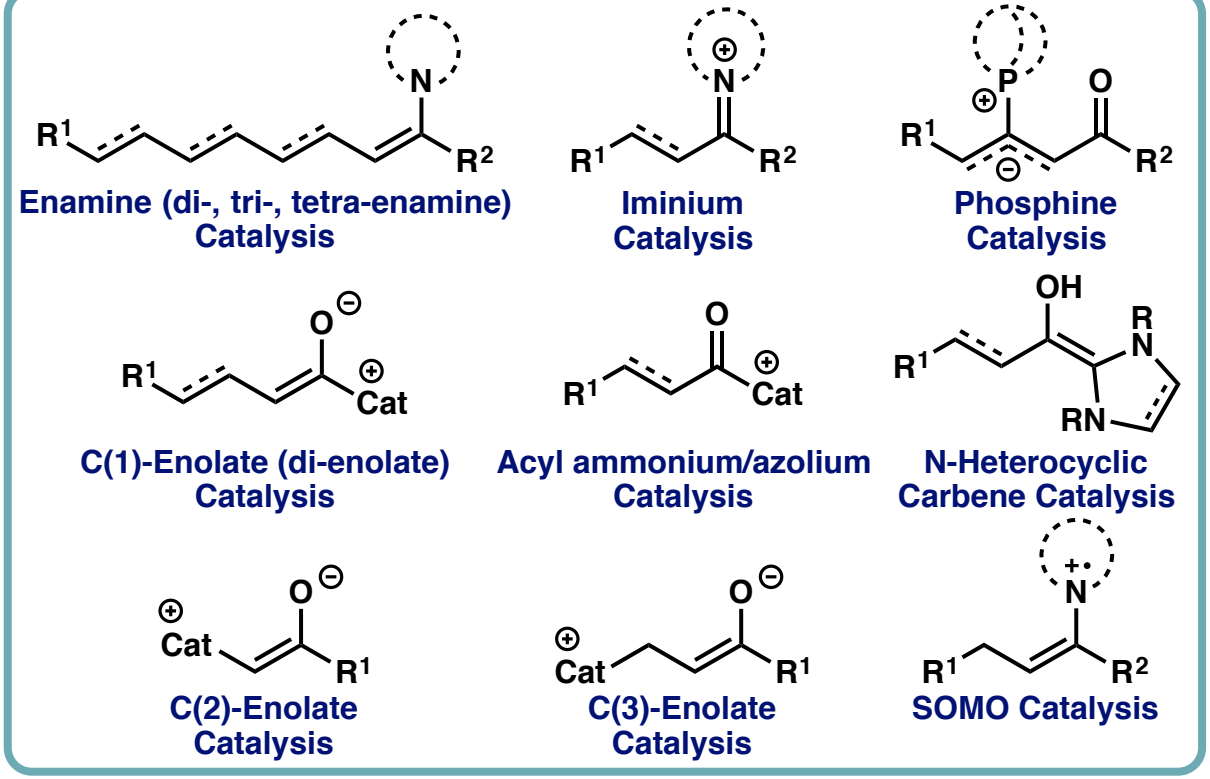
- **Lewis bases** – able to donate a lone pair of electrons
- **Lewis acids** – able to accept a lone pair of electrons
- **Brønsted bases** – able to accept a proton
- **Brønsted acids** – able to donate a proton
- This course will focus exclusively on **Lewis base organocatalysts**.

For an excellent overview see B, List *et al.*, *Org. Biomol. Chem.*, 2005, **3**, 719.

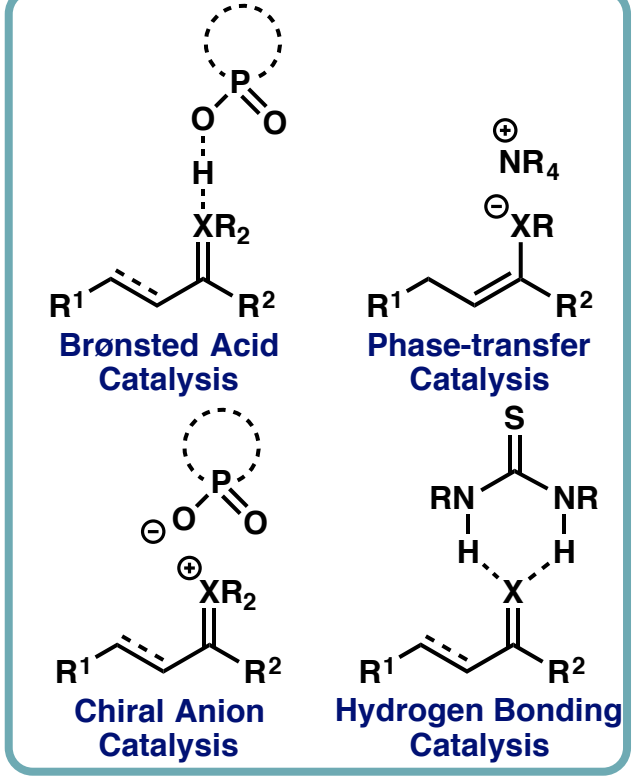
Organocatalysis – The Picture Today

- Organocatalysis is now a thoroughly established member of the synthetic toolbox, with a large number of **generic activation modes** known.

Covalent Activation Modes



Non-Covalent Activation Modes

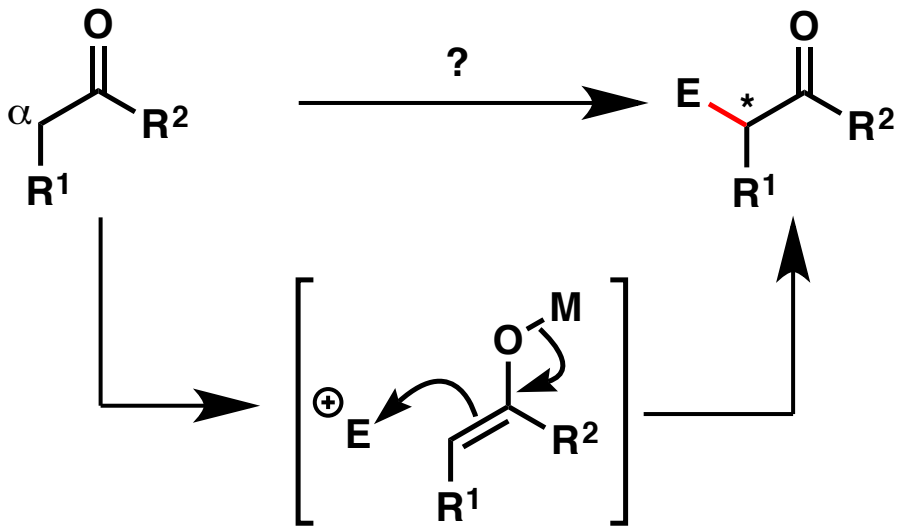


- This course will focus exclusively on **covalent activation modes**, which all employ **Lewis base organocatalysts**.

For an excellent overview see D. Romo *et al.*, *Nat. Prod. Rep.*, 2014, **31**, 1318.

Functionalisation of Carbonyl Compounds

- How can we functionalise the α-position of an aldehyde or ketone?



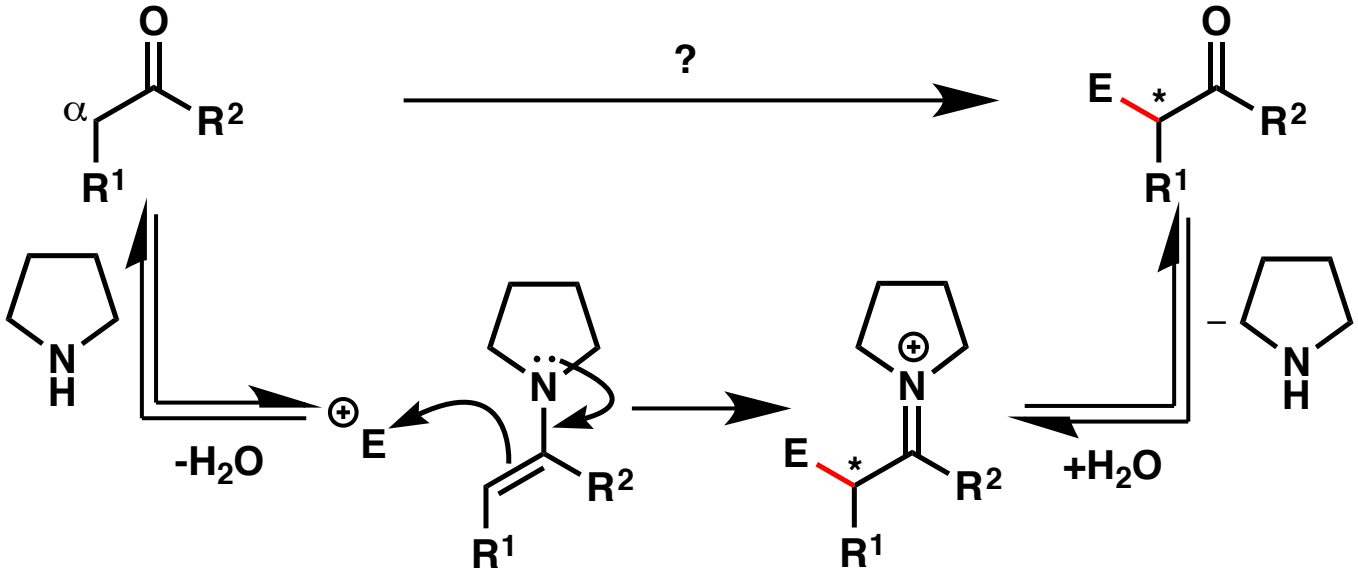
- A commonly employed method is to deprotonate at the α-position with a suitable base (e.g. lithium diisopropylamide (LDA)) to form a metal bound enolate.

- This enolate is nucleophilic and can react with an electrophile at the α-position. This is often described as raising the energy of the HOMO (increasing nucleophilicity)

- In certain cases, this can form a new stereogenic center.

Functionalisation of Carbonyl Compounds

- How can we functionalise the α-position of an aldehyde or ketone?

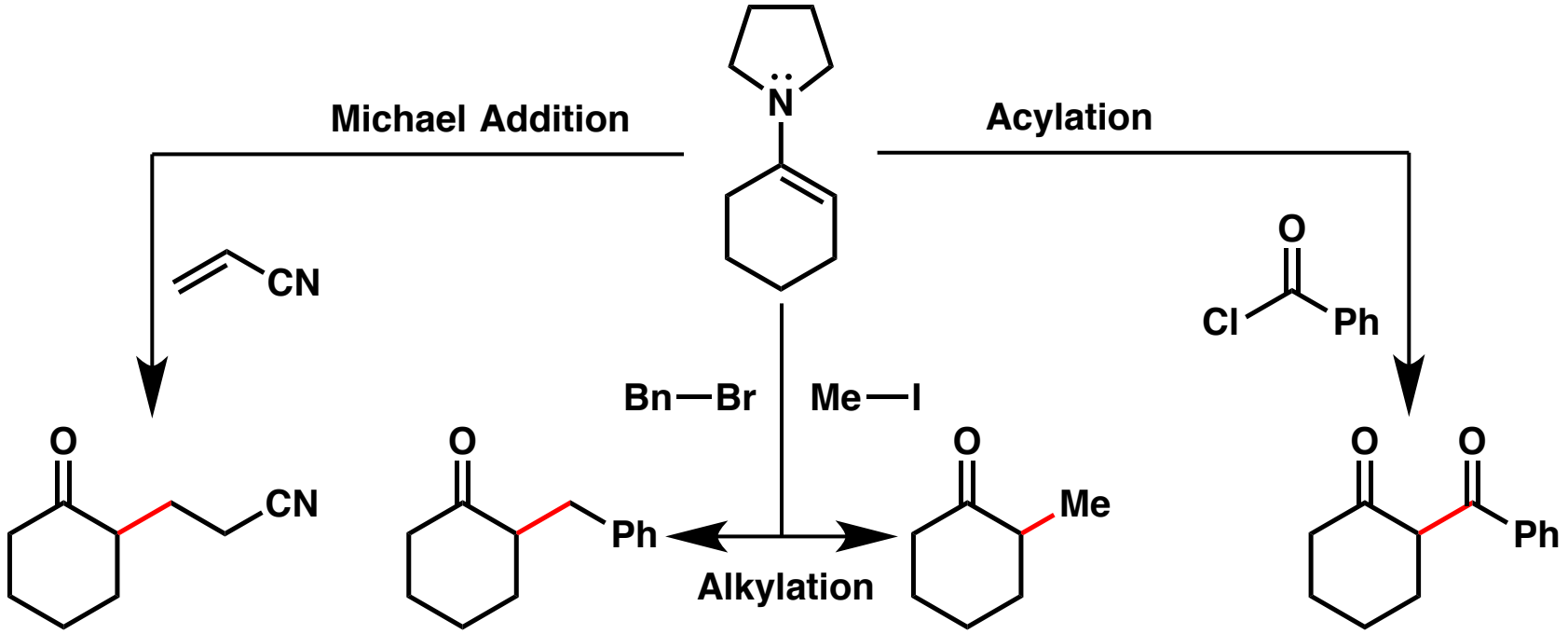


- An alternative option involves the use of a secondary amine (e.g. pyrrolidine) to generate an enamine.
- This enamine is also nucleophilic (HOMO-raised) and can react with an electrophile at the α-position.
- In certain cases, this can form a new stereogenic center.

G. Stork *et al.*, *J. Am. Chem. Soc.*, 1954, **76**, 2029.

Functionalisation of Carbonyl Compounds

- Enamines are versatile nucleophiles and can react with a broad range of electrophiles, e.g. Michael acceptors, alkyl halides, acid chlorides etc.

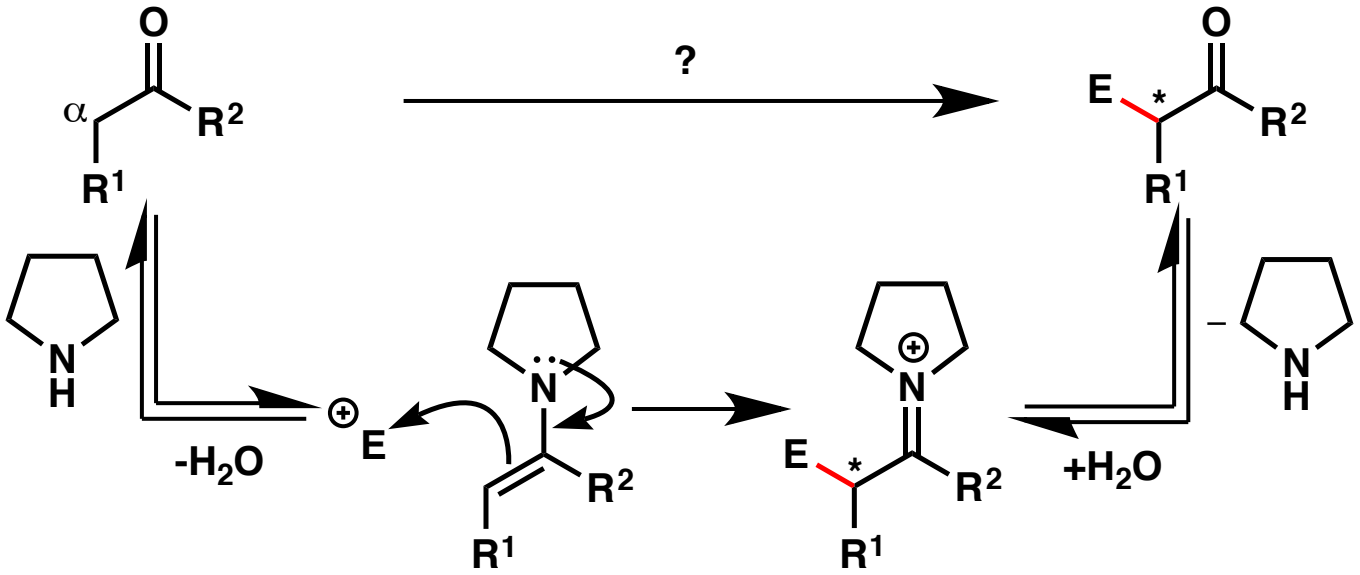


- All products shown are after hydrolysis. We must be able to draw curly arrow pushing mechanisms for all transformations.

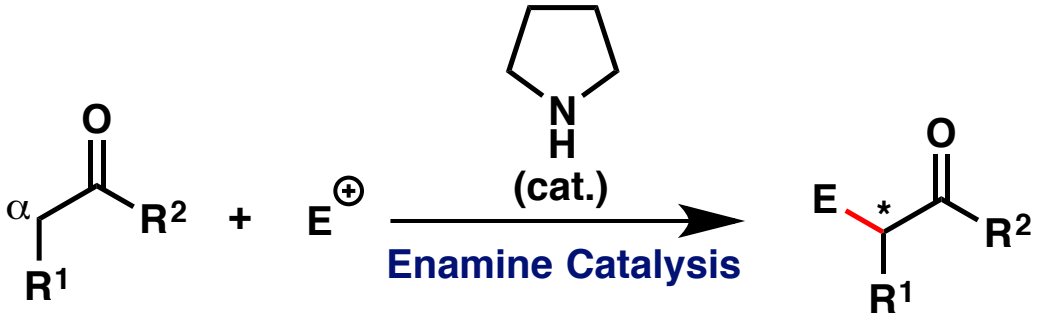
- We will go through one now in detail on the visualiser.

Functionalisation of Carbonyl Compounds

- How can we functionalise the α-position of an aldehyde or ketone?



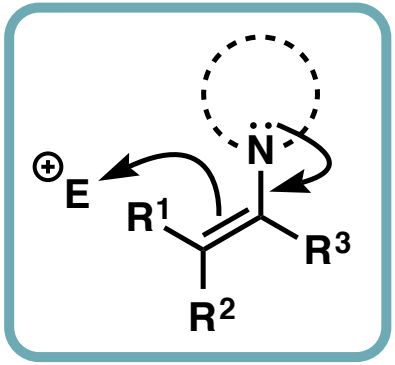
- The secondary amine is regenerated, providing the basis for a catalytic system.



Enamine Organocatalysis

- We will start by looking at the most widely explored activation mode – **enamine organocatalysis**.

Enamine Organocatalysis



- The enamine activation mode has the following key characteristics:

1) It is a **covalent** activation mode – the catalyst is covalently bound to the substrate.

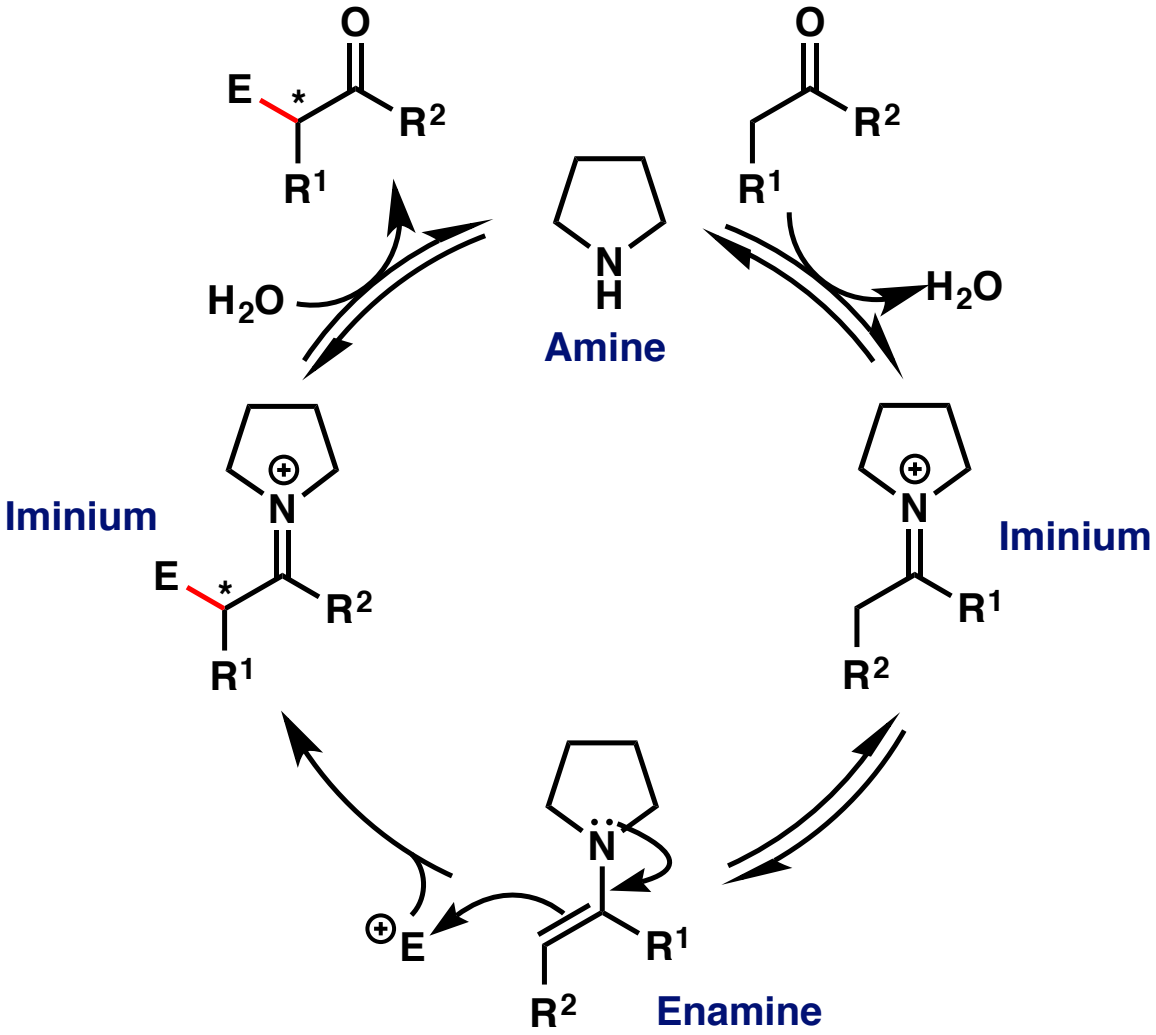
2) It is a **nucleophilic (HOMO-raised)** activation mode – it reacts with electrophiles.

3) It employs **primary and secondary amine Lewis base organocatalysts** and **enolisable aldehyde/ketone** substrates.

B. List *et al.*, *Chem. Rev.*, 2007, **107**, 5471.

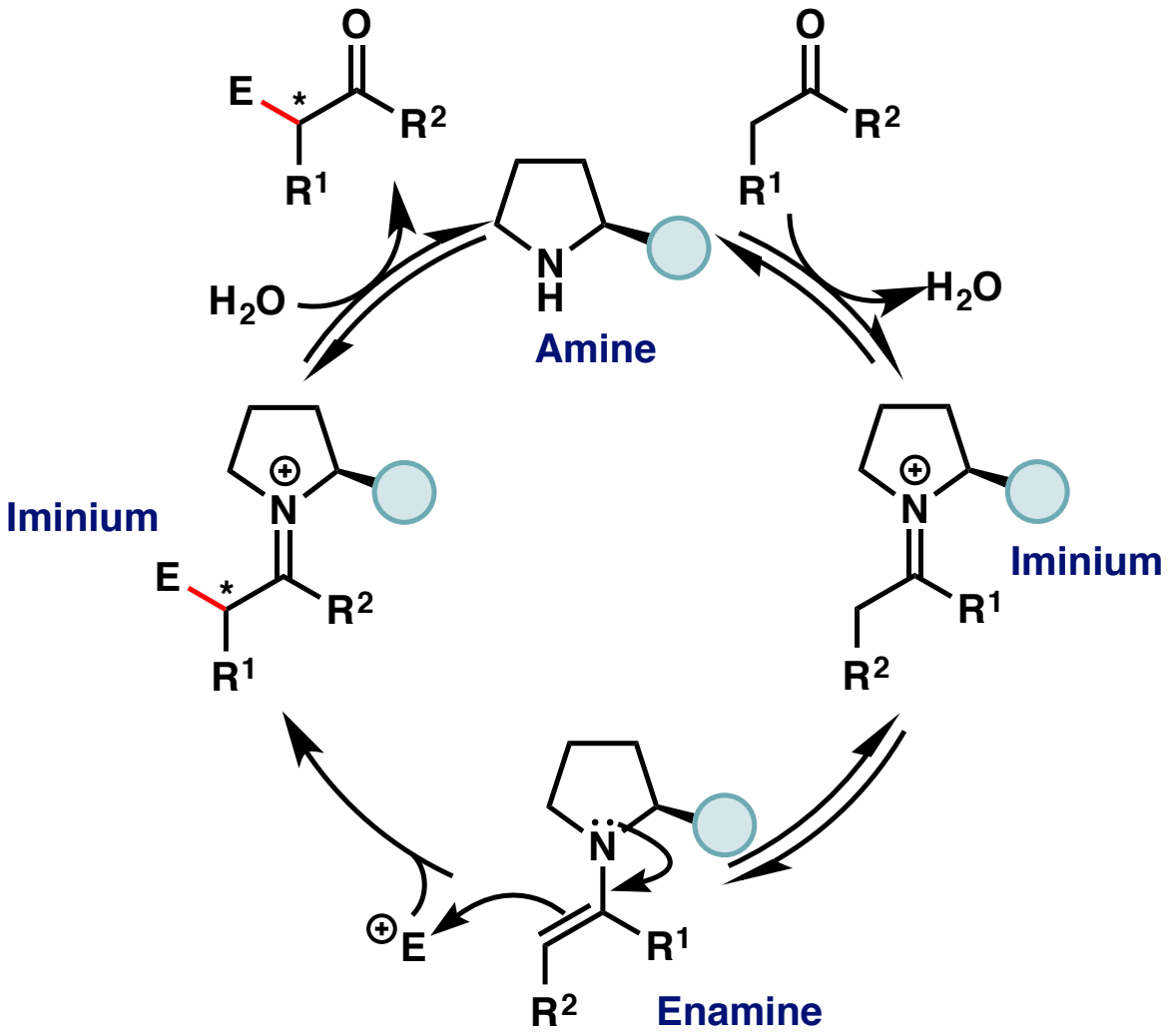
Enamine Organocatalysis – General Mechanism

- We can draw the following catalytic cycle for enamine organocatalysis:



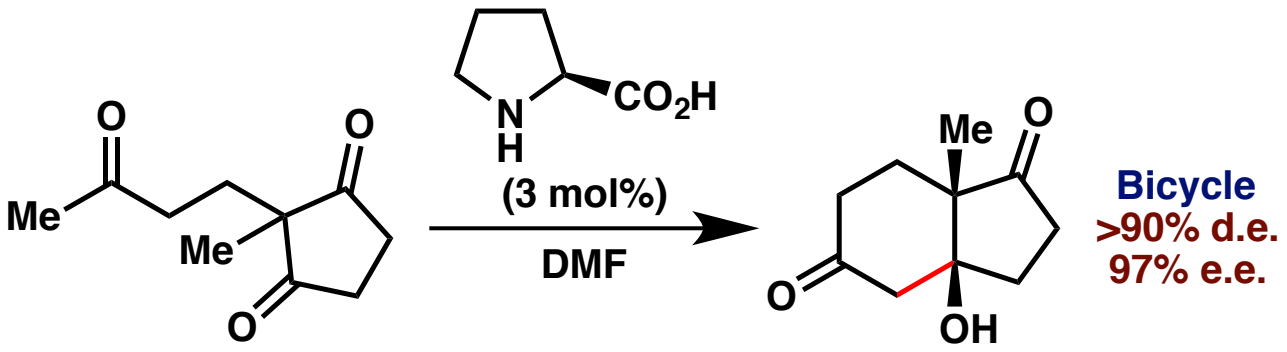
Enamine Organocatalysis – General Mechanism

- We can also imagine using a chiral secondary amine for **asymmetric** organocatalysis



Intramolecular Asymmetric Aldol Reaction

- Let's revisit the pioneering work of Z. G. Hajos *et al.*:



- For this class of organocatalytic reaction we must be able to:

1) Know how the organocatalyst **activates** the substrate (**activation mode**)

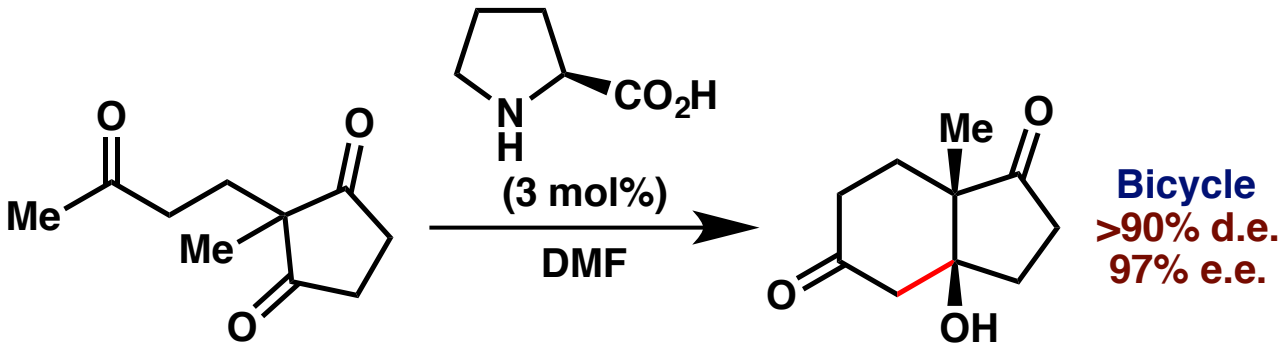
2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

3) Rationalise the **stereochemical outcome** of the reaction (both diastereo- and enantiocontrol in this case) by drawing an appropriate transition state.

Z. G. Hajos *et al.*, *J. Org. Chem.*, 1974, **39**, 1615.

Intramolecular Asymmetric Aldol Reaction

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

1) A **secondary amine Lewis base** organocatalyst is used

2) The substrate contains three **ketone** functional groups, one of which is less hindered than the other two (and hence most reactive)

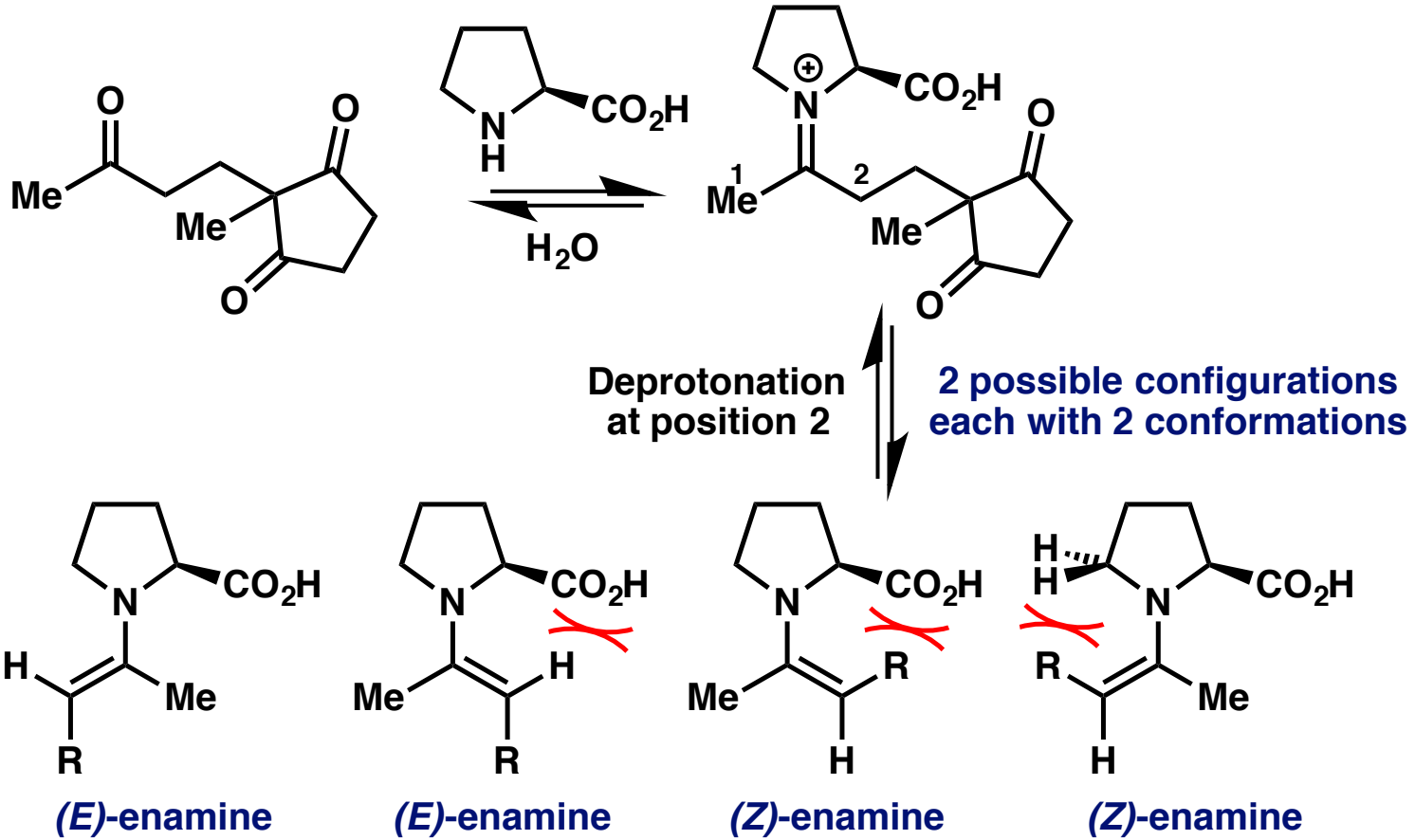
3) The least hindered ketone is **enolisable** (e.g. it has α-hydrogen atoms that can be deprotonated)

- Conclusion – this reaction proceeds *via* the **enamine** activation mode.

Z. G. Hajos *et al.*, *J. Org. Chem.*, 1974, **39**, 1615.

Intramolecular Asymmetric Aldol Reaction

- Let's think about the key nucleophilic enamine species formed in detail:

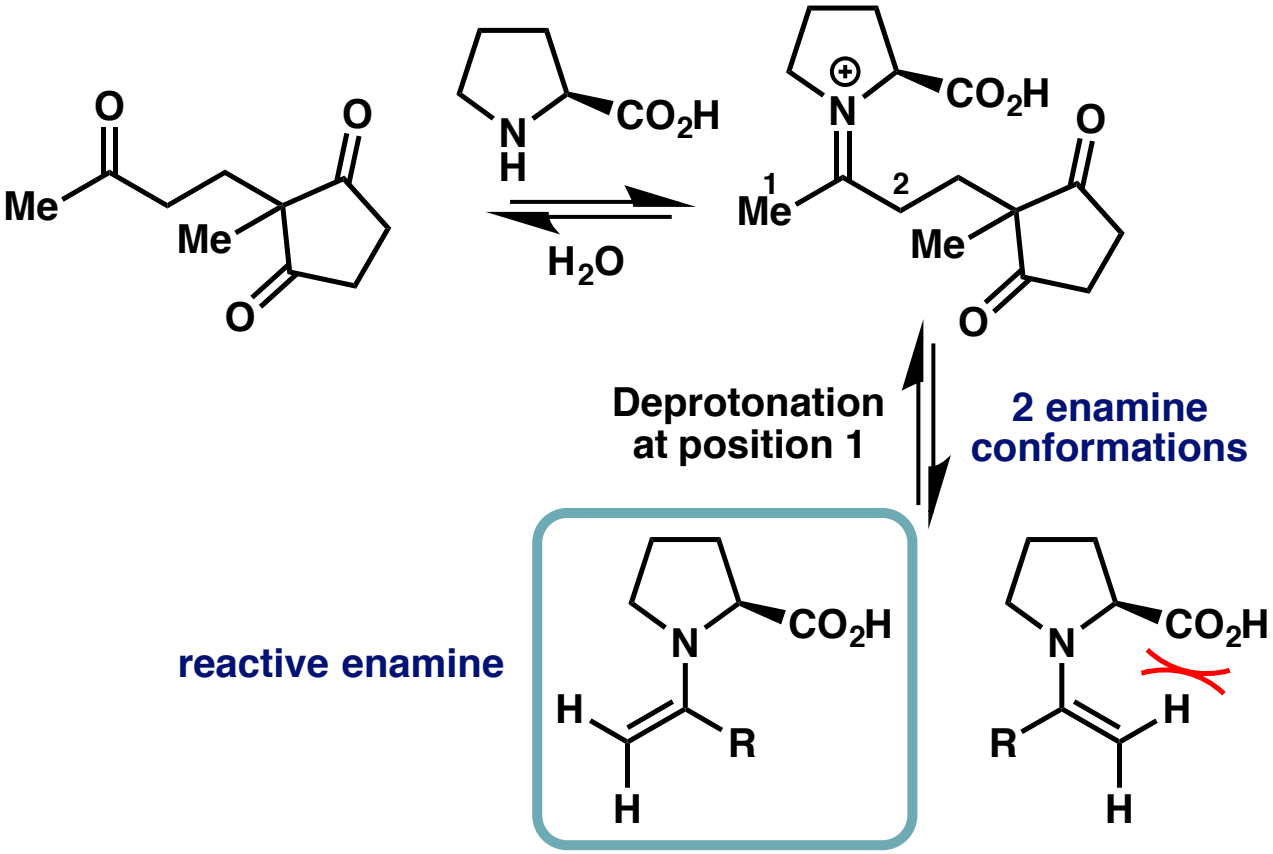


- (*E*)-configuration and conformation on the left is most stable, BUT all enamines shown above would react to give a 4-membered ring – less favoured pathway!

Z. G. Hajos *et al.*, *J. Org. Chem.*, 1974, **39**, 1615.

Intramolecular Asymmetric Aldol Reaction

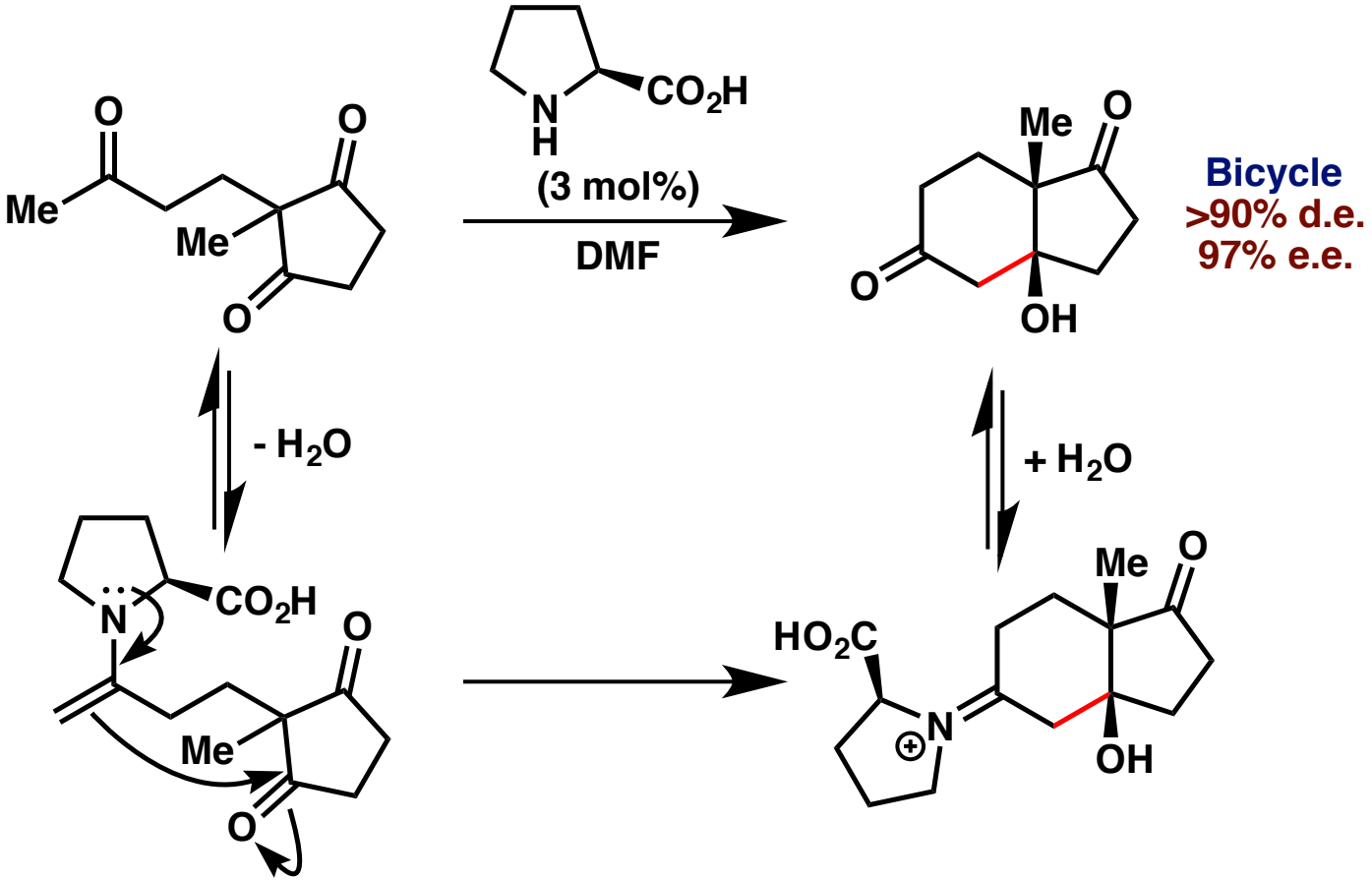
- Let's think about the key nucleophilic enamine species formed in detail:



- Enamine conformation on the left is most stable, and both enamines shown would react to give a 6-membered ring – more favoured pathway!
- Remember, all iminium and enamine formations are all **reversible**.

Intramolecular Asymmetric Aldol Reaction

- Now let's consider the **curly arrow pushing mechanism**:

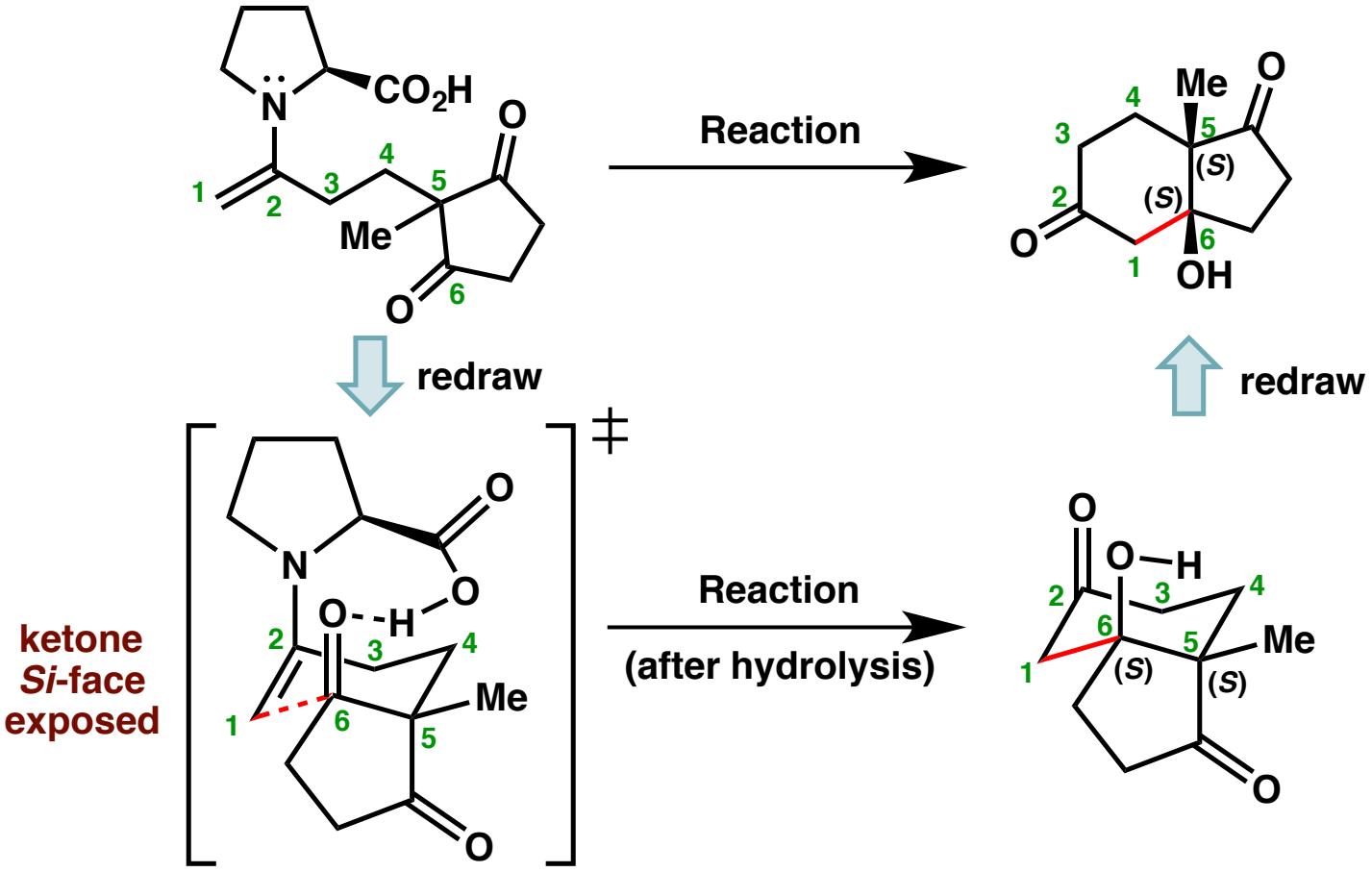


- We **must** always draw the curly arrows for **every step of the mechanisms** (including enamine formation/hydrolysis).

Z. G. Hajos *et al.*, *J. Org. Chem.*, 1974, **39**, 1615.

Intramolecular Asymmetric Aldol Reaction

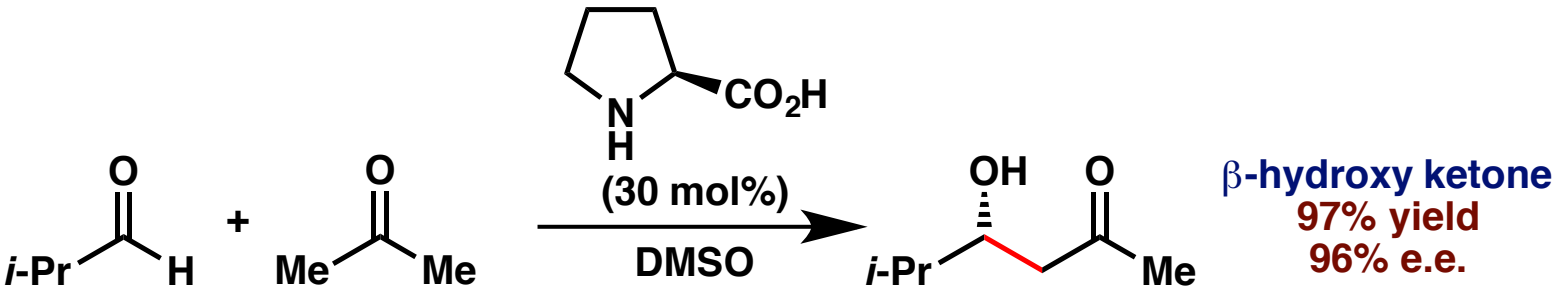
- Finally, let's rationalise the **stereochemical outcome** of the reaction:



- Conformation such that **intramolecular hydrogen bond** can occur, which stabilises the transition state. Can see that **hydroxyl** and **methyl** groups are on the **same side**.

Intermolecular Asymmetric Aldol Reaction

- Now let's consider the **intermolecular** process reported by B. List *et al.*:



- For this class of organocatalytic reaction we must be able to:

1) Know how the organocatalyst **activates** the substrate (**activation mode**)

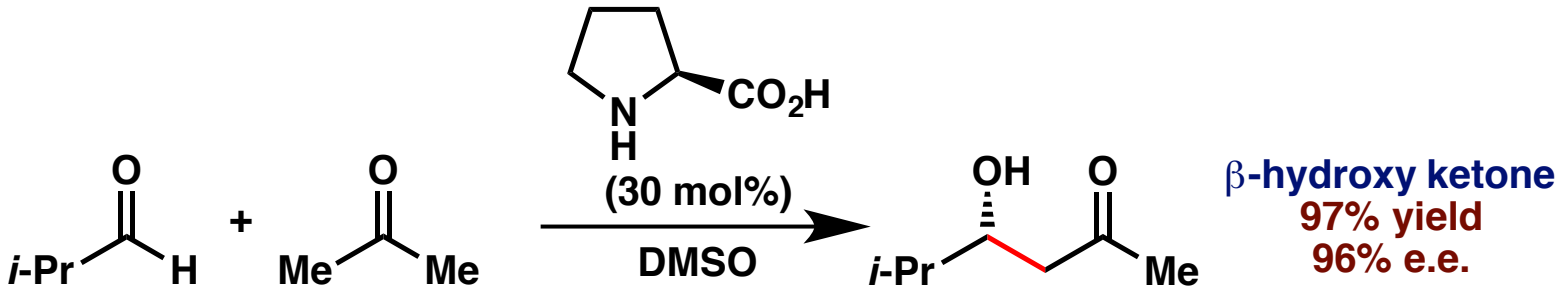
2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

3) Rationalise the **stereochemical outcome** of the reaction (only enantiocontrol is relevant in this case) by drawing an appropriate transition state.

B. List *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 2395

Intermolecular Asymmetric Aldol Reaction

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

1) A **secondary amine Lewis base** organocatalyst is used

2) One reactant contains a **ketone** functional group and the other contains an **aldehyde** functional group.

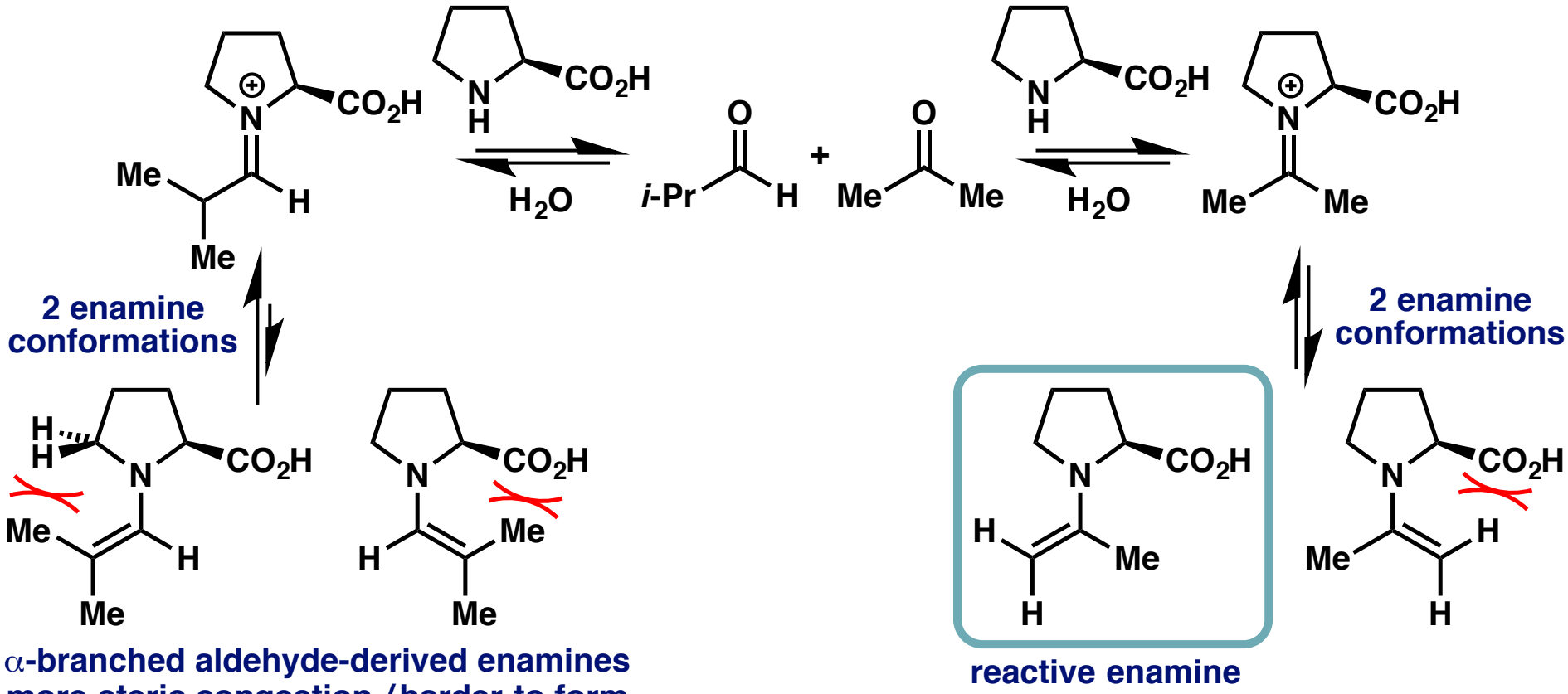
3) Both the aldehyde and ketone are **enolisable** (e.g. they have α-hydrogen atoms that can be deprotonated)

- Conclusion – this reaction proceeds *via* the **enamine** activation mode.

B. List *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 2395

Intermolecular Asymmetric Aldol Reaction

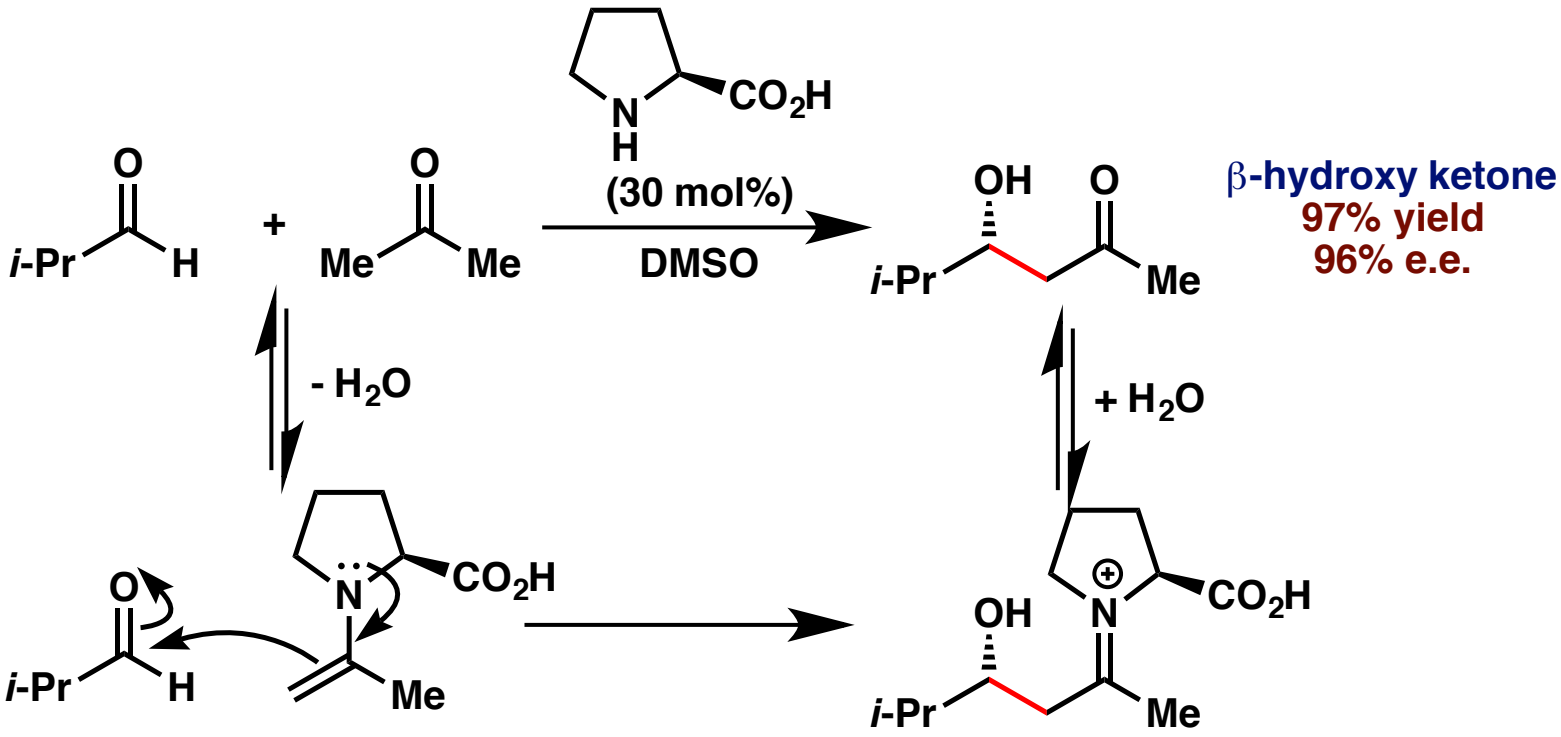
- Let's think about the key nucleophilic enamine species formed in detail:



- Ketone-derived enamine is formed in preference to the aldehyde-derived enamine.

Intermolecular Asymmetric Aldol Reaction

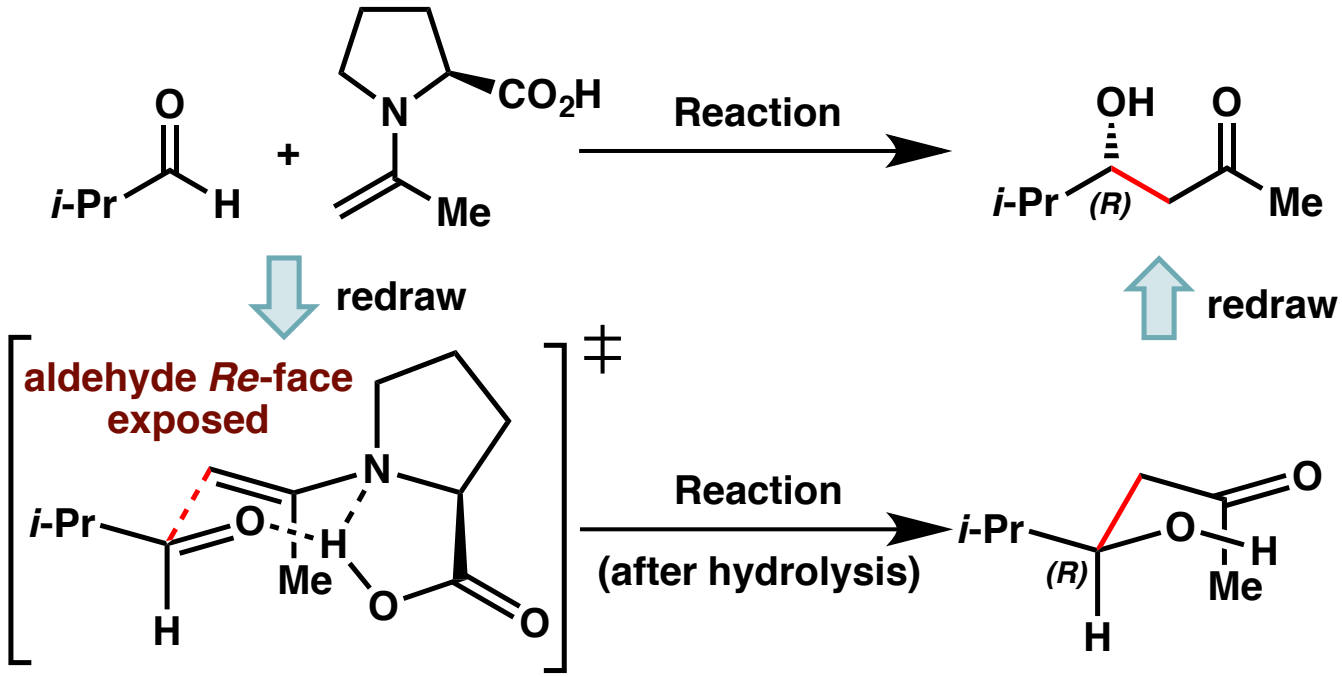
- Now let's consider the **curly arrow pushing mechanism**:



- From inspection of the product it is clear that acetone becomes the **nucleophile** and that isobutyraldehyde is the **electrophile**.

Intermolecular Asymmetric Aldol Reaction

- Finally, let's rationalise the **stereochemical outcome** of the reaction:

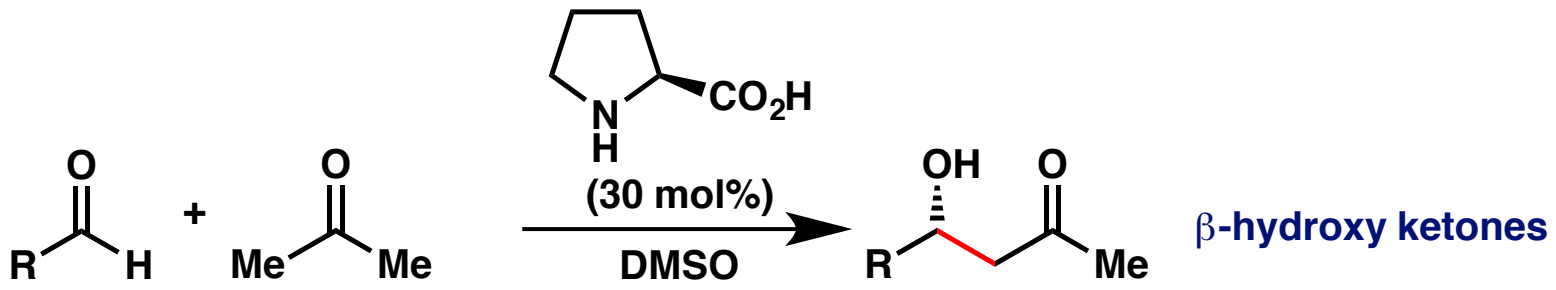


- Conformation such that **intermolecular hydrogen bond** can occur, which stabilises the transition state.

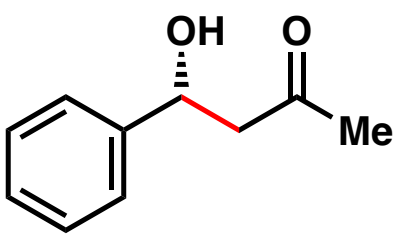
- Must place large *i*-Pr group in **pseudoequatorial** position to lower the energy. Assign the stereocentre **before and after redrawing** to convince yourself that it is correct.

Intermolecular Asymmetric Aldol Reaction

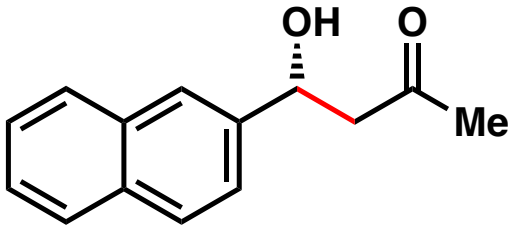
- This reaction using acetone in DMSO is limited to the use of α-branched aldehydes:



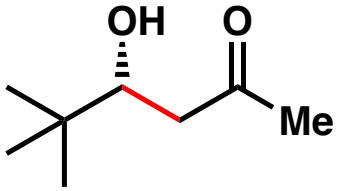
Examples



62% yield
60% e.e.



54% yield
77% e.e.



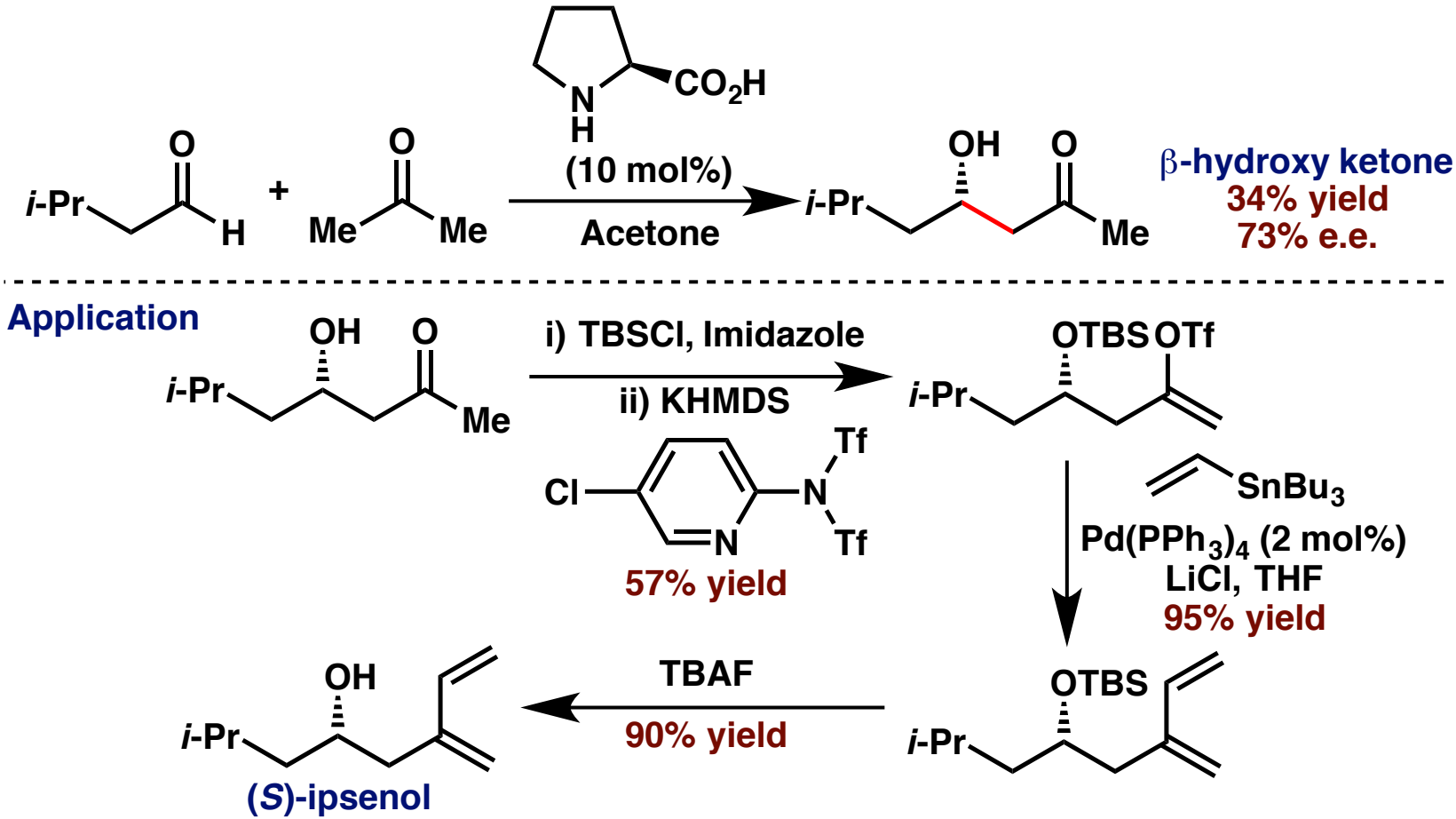
81% yield
>99% e.e.

- Which other products might form when using unbranched aldehydes in this reaction? (hint: self-aldolisation)

- In all cases, **careful consideration of the mechanism** will reveal useful information.

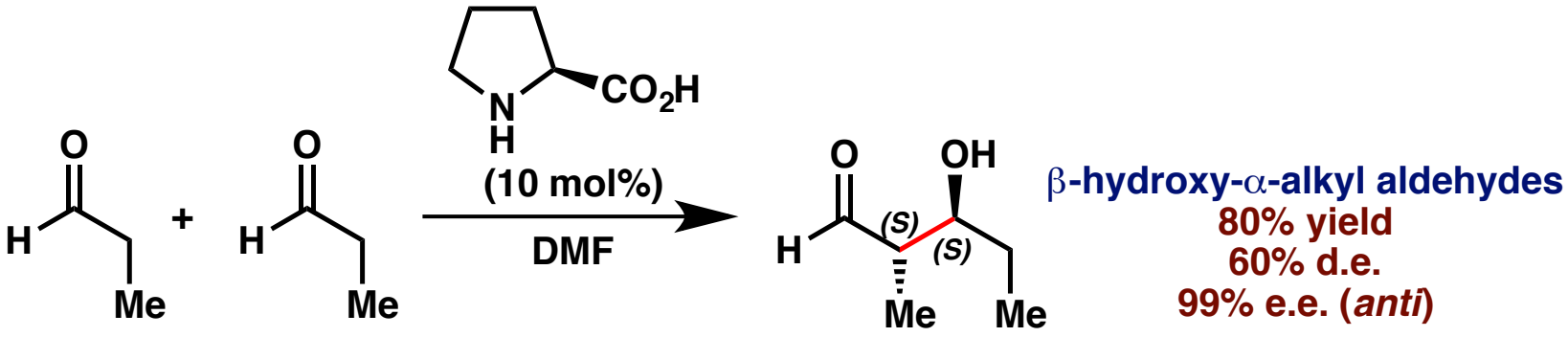
Application Towards Natural Product Synthesis

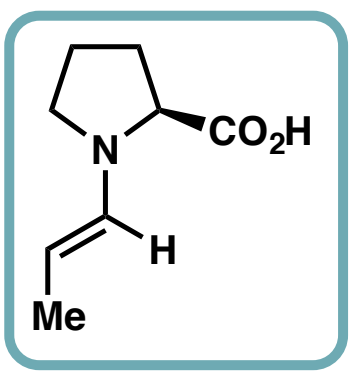
- Performing the reaction in **acetone as the solvent** allowed the cross aldol reaction with α-unbranched aldehydes in modest yields. This was applied towards the synthesis of the bark beetle pheromone (*S*)-ipsenol.



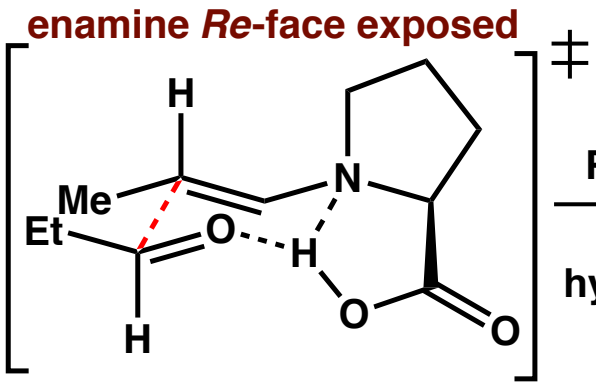
Intermolecular Asymmetric Aldol Reaction

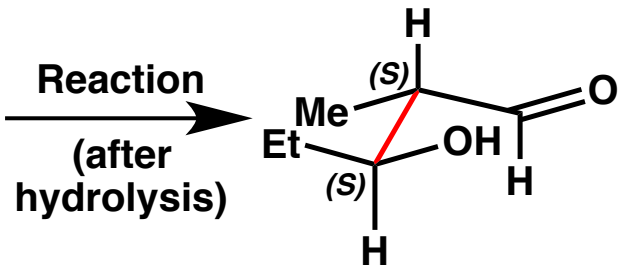
- In 2002, MacMillan developed a proline-catalysed self-aldolisation reaction:





reactive enamine

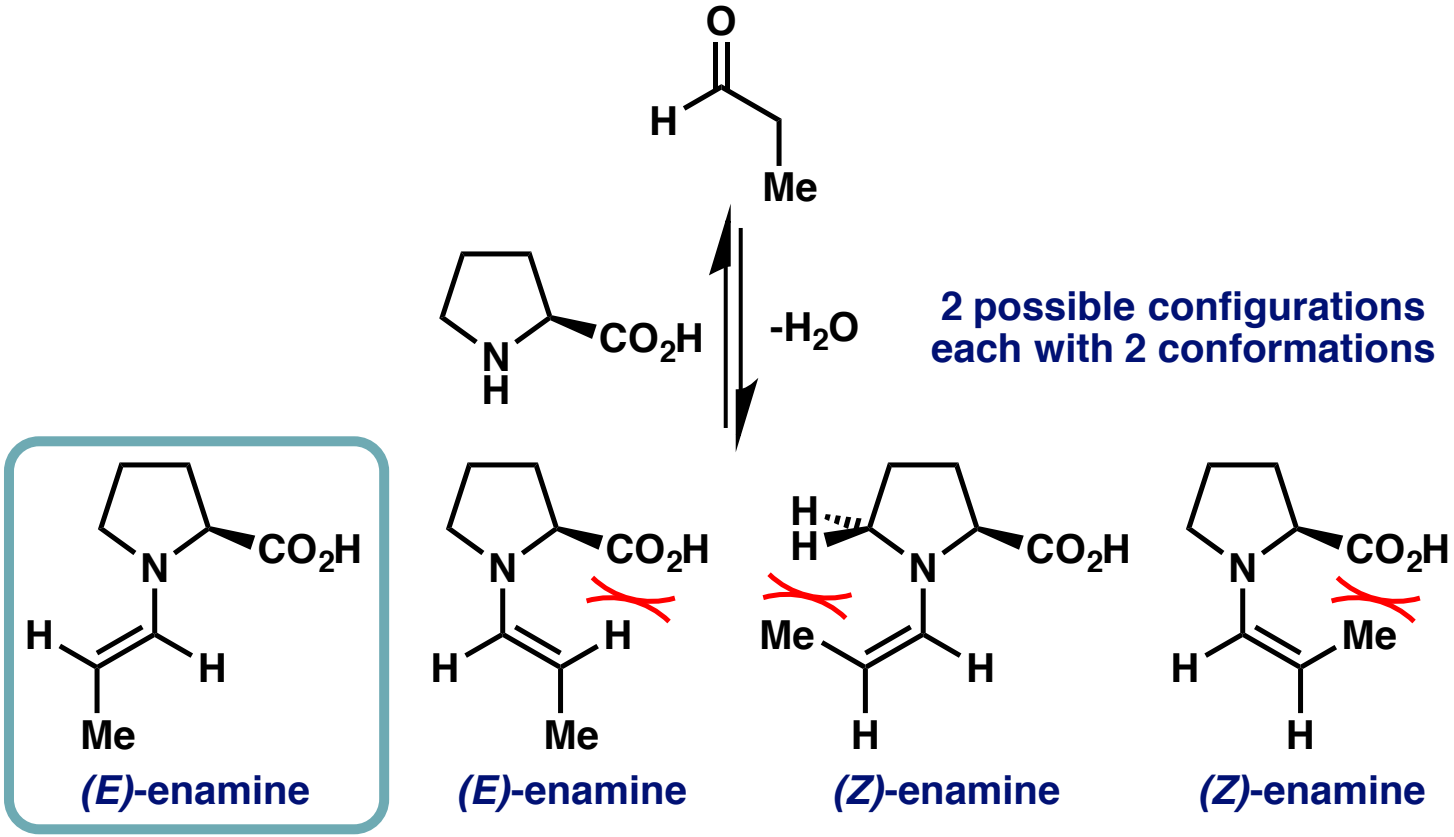




- Why does the product not **react again** with another equivalent of the aldehyde?
- The **diastereoselectivity** for this reaction is quite low. How might this be improved?

Intermolecular Asymmetric Aldol Reaction

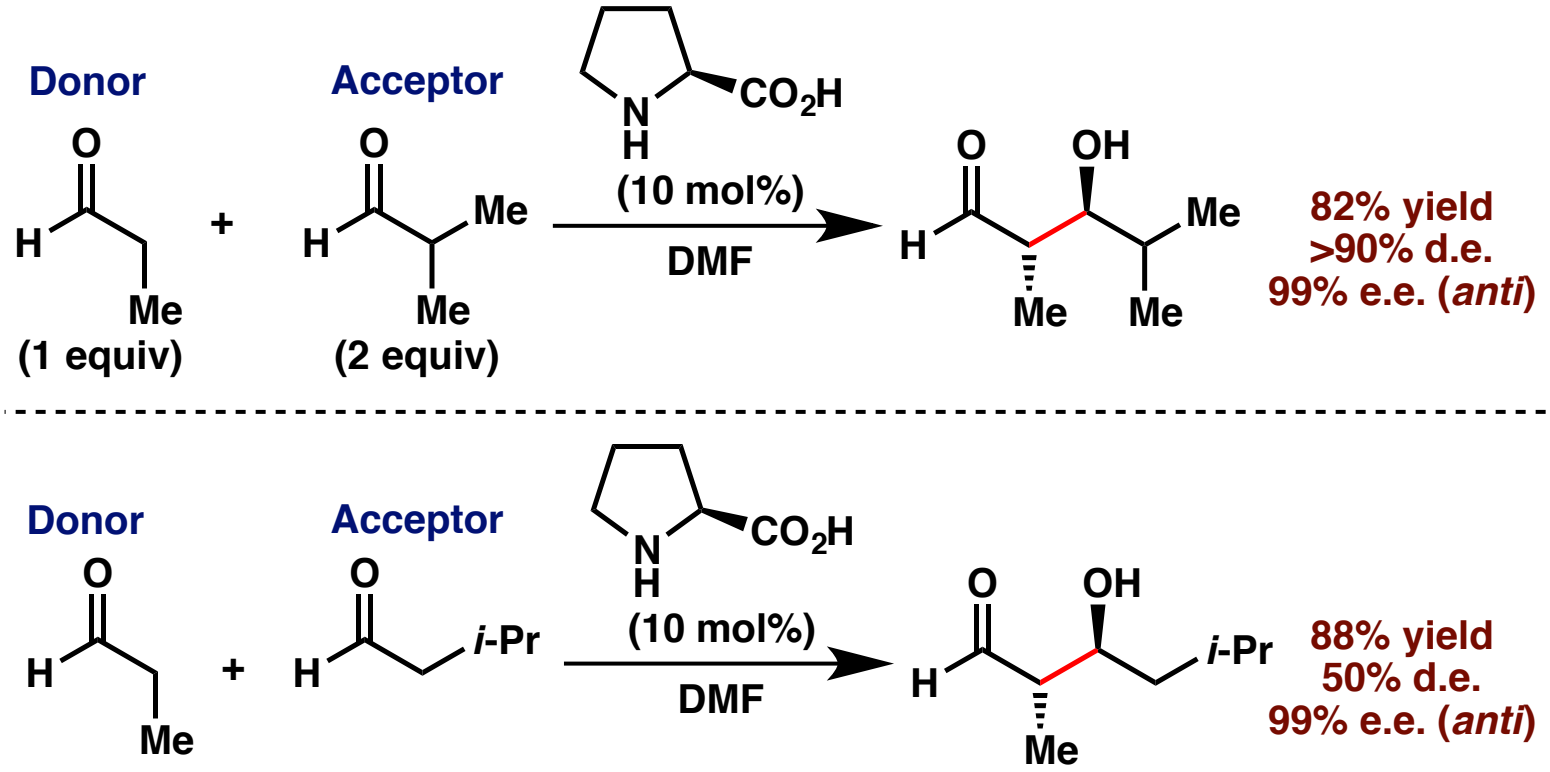
- Let's think about the key nucleophilic enamine species formed in detail:



- The (*E*)-configuration is favoured over the (*Z*)-configuration due to steric congestion involving the methyl substituent. One (*E*)-conformation is also favoured over the other

Intermolecular Asymmetric Aldol Reaction

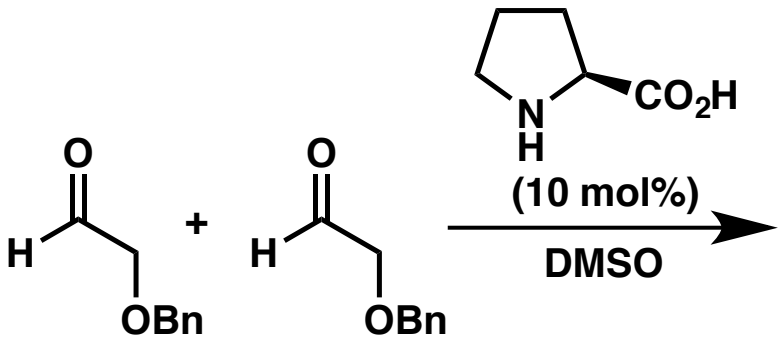
- Protocol also works for cross-aldol reactions with slow addition of donor aldehyde:



- Why do we need to keep the local concentration of the **donor aldehyde** low?
- What other products might be expected in the second reaction?

Intermolecular Asymmetric Aldol Reaction – Class Example

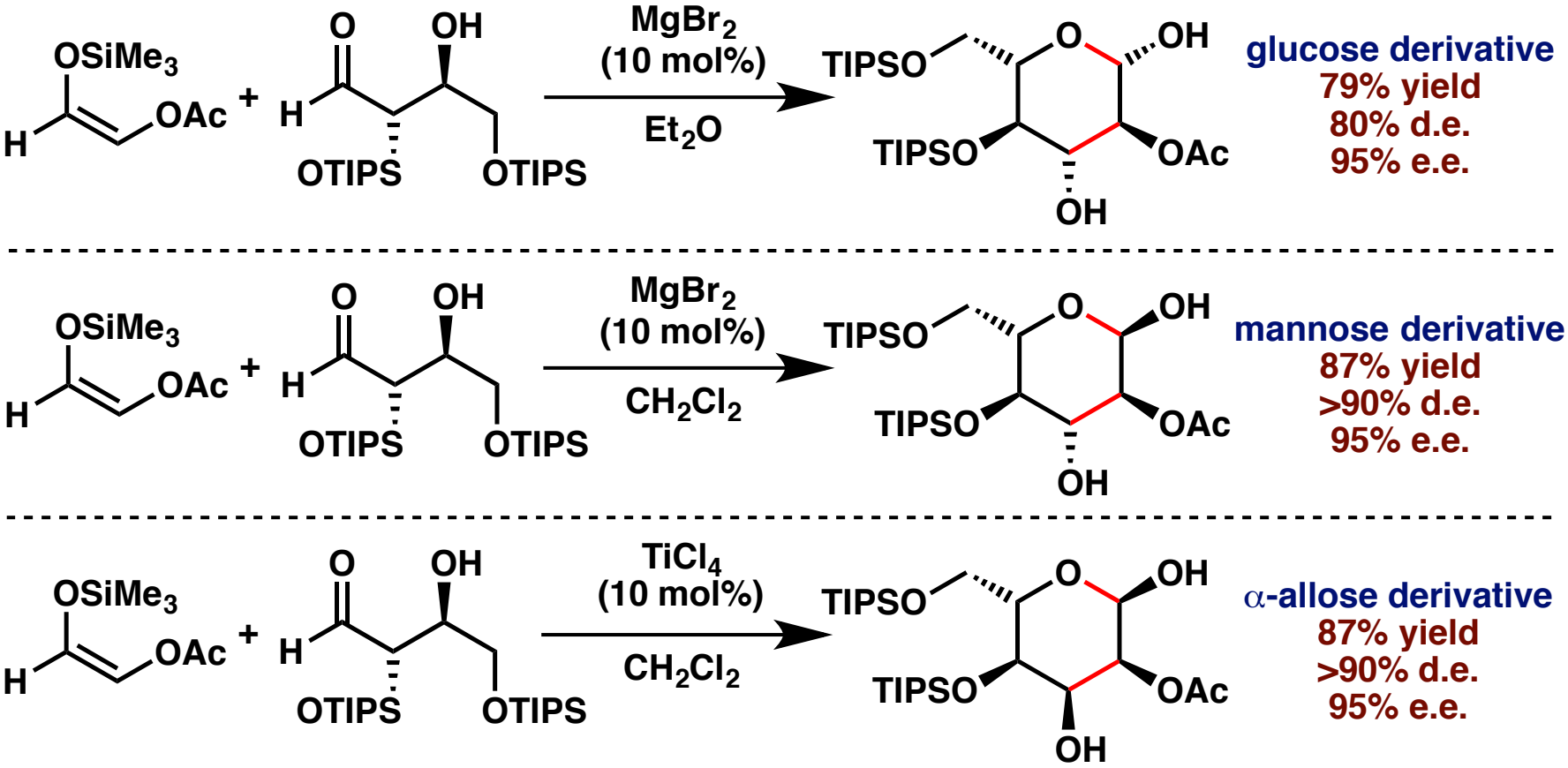
- Determine the major product for the reaction shown below:



- A number of different **protecting groups** can be incorporated (Bn, PMB, TIPS)
- These building blocks have been applied towards **enantio-selective carbohydrate synthesis**.

Enantio-Selective Carbohydrate Synthesis

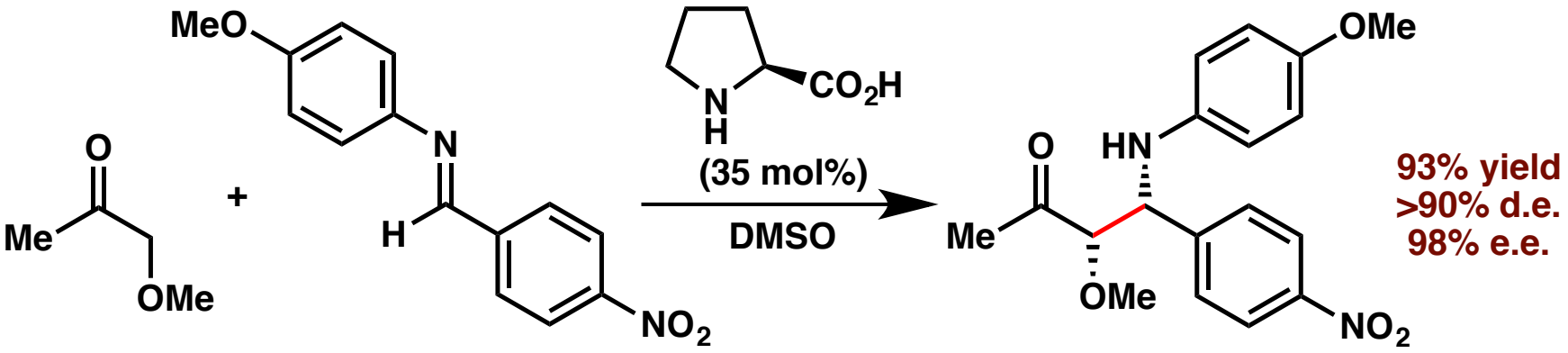
- The products formed were transformed to carbohydrates in 1 step:



- Merging catalytic technologies allows enantio- and diastereoselective access to fully differentiated carbohydrates in only two chemical steps – amazing!

Intermolecular Asymmetric Mannich Reaction

- Replacing the aldehyde with an **imine electrophile** allowed an enantio-selective Mannich reaction to be developed by B. List *et al.*:



- For this class of organocatalytic reaction we must be able to:

1) Know how the organocatalyst **activates** the substrate (**activation mode**)

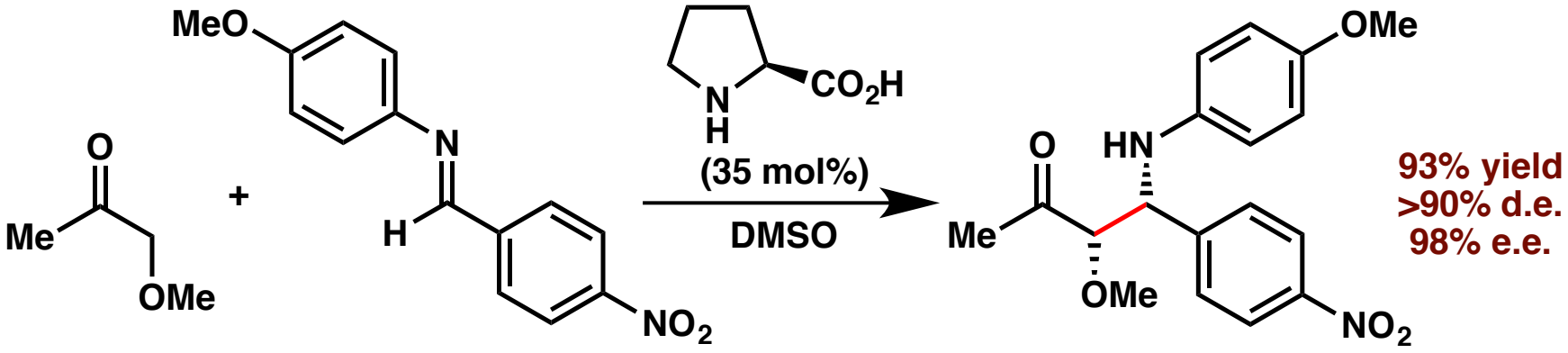
2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

3) Rationalise the **stereochemical outcome** of the reaction (diastereo- and enantiocontrol are relevant in this case) by drawing an appropriate transition state.

B. List *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 9336

Intermolecular Asymmetric Mannich Reaction

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

1) A **secondary amine Lewis base** organocatalyst is used

2) One reactant contains a **ketone** functional group and the other contains an **imine** (or more specifically an aldimine) functional group.

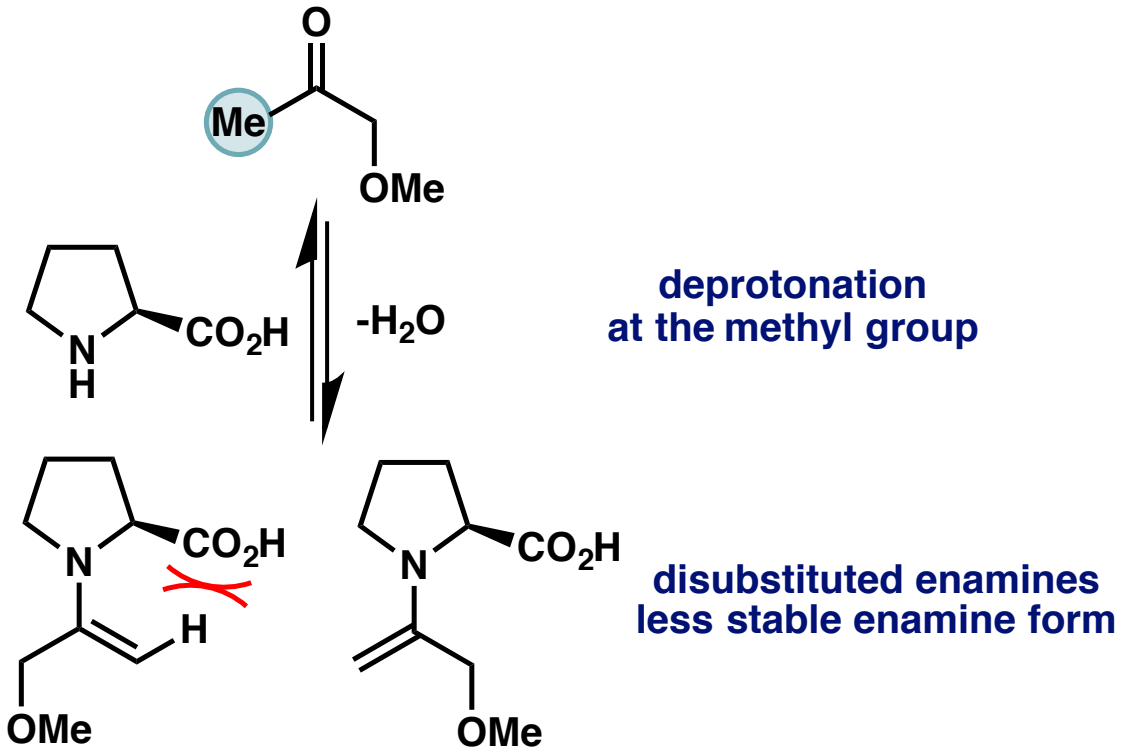
3) The ketone is **enolisable** (e.g. it has α-hydrogen atoms that can be deprotonated)

- Conclusion – this reaction proceeds *via* the **enamine** activation mode.

B. List *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 9336

Intermolecular Asymmetric Mannich Reaction

- Let's think about the key nucleophilic enamine species formed in detail:

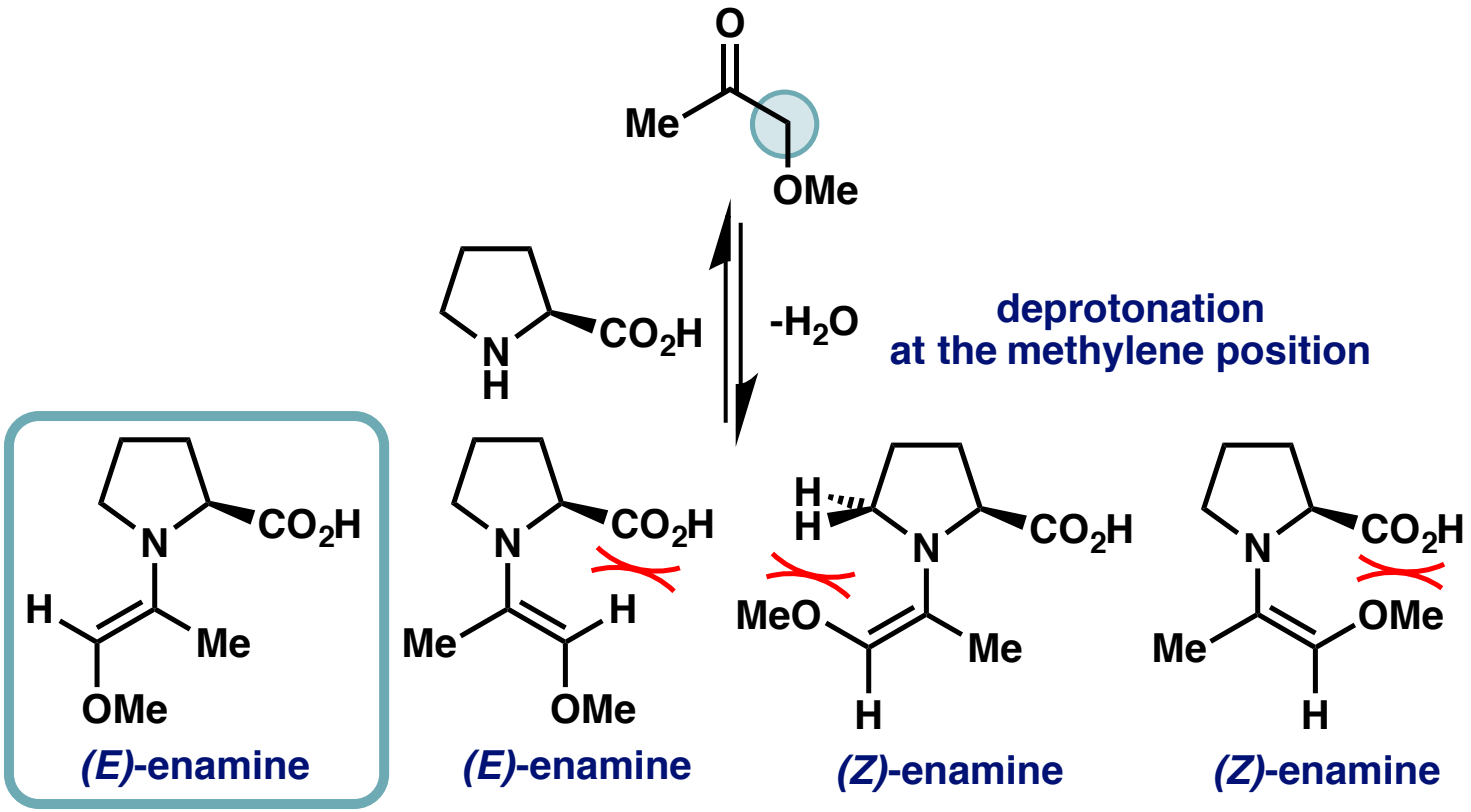


- Here, we can deprotonate at the **methyl group** or at the **methylene position**.

- Deprotonation at the methyl group gives rise to less stable **di-substituted** enamines. These will not be the major (reactive) enamine forms.

Intermolecular Asymmetric Mannich Reaction

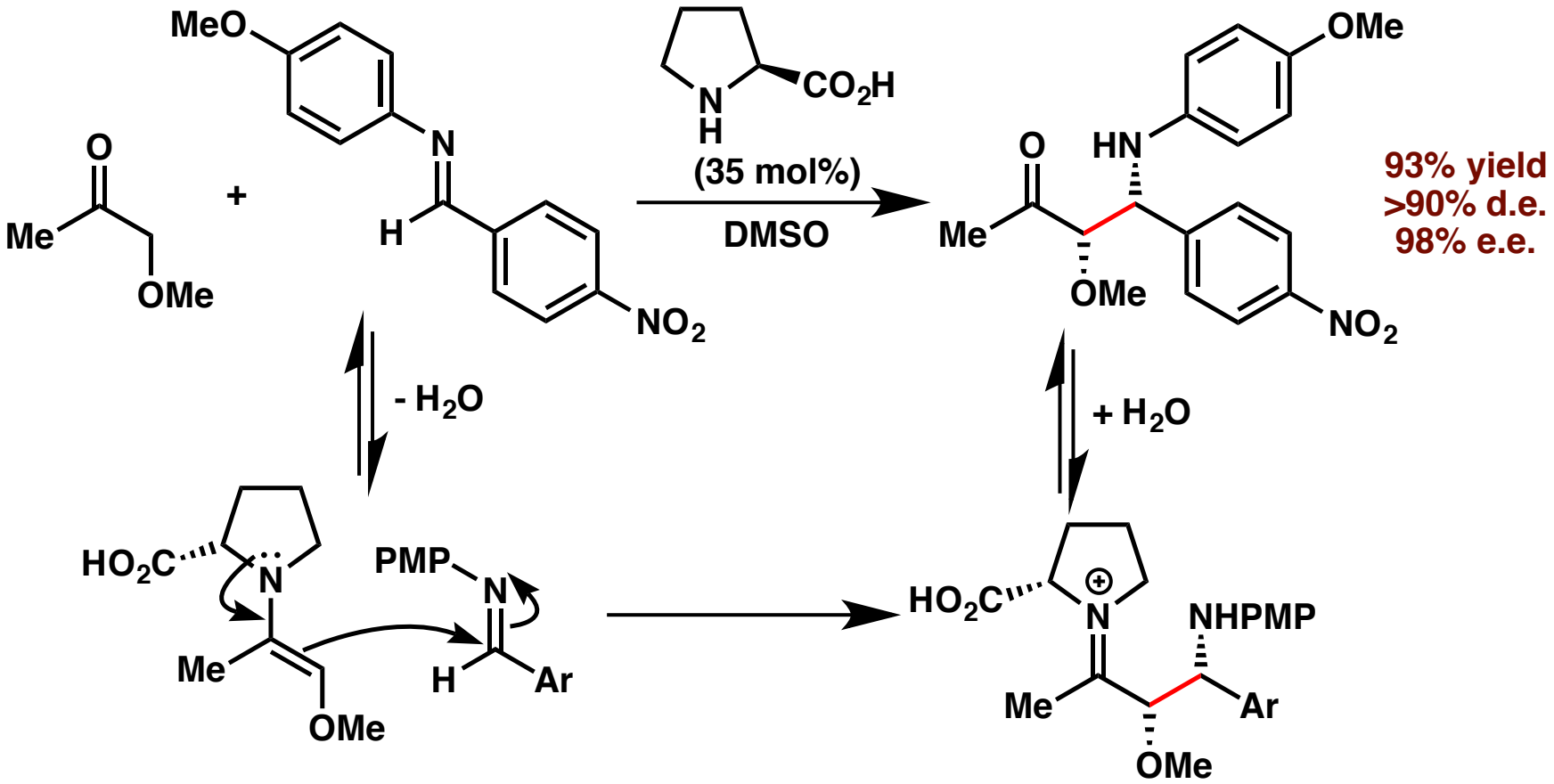
- Let's think about the key nucleophilic enamine species formed in detail:



- Deprotonation at the **methylene position** gives rise to more stable **tri-substituted** enamines. The less sterically congested **(*E*)-enamine** will be the major (reactive) enamine form.

Intermolecular Asymmetric Mannich Reaction

- Now let's consider the **curly arrow pushing mechanism**:

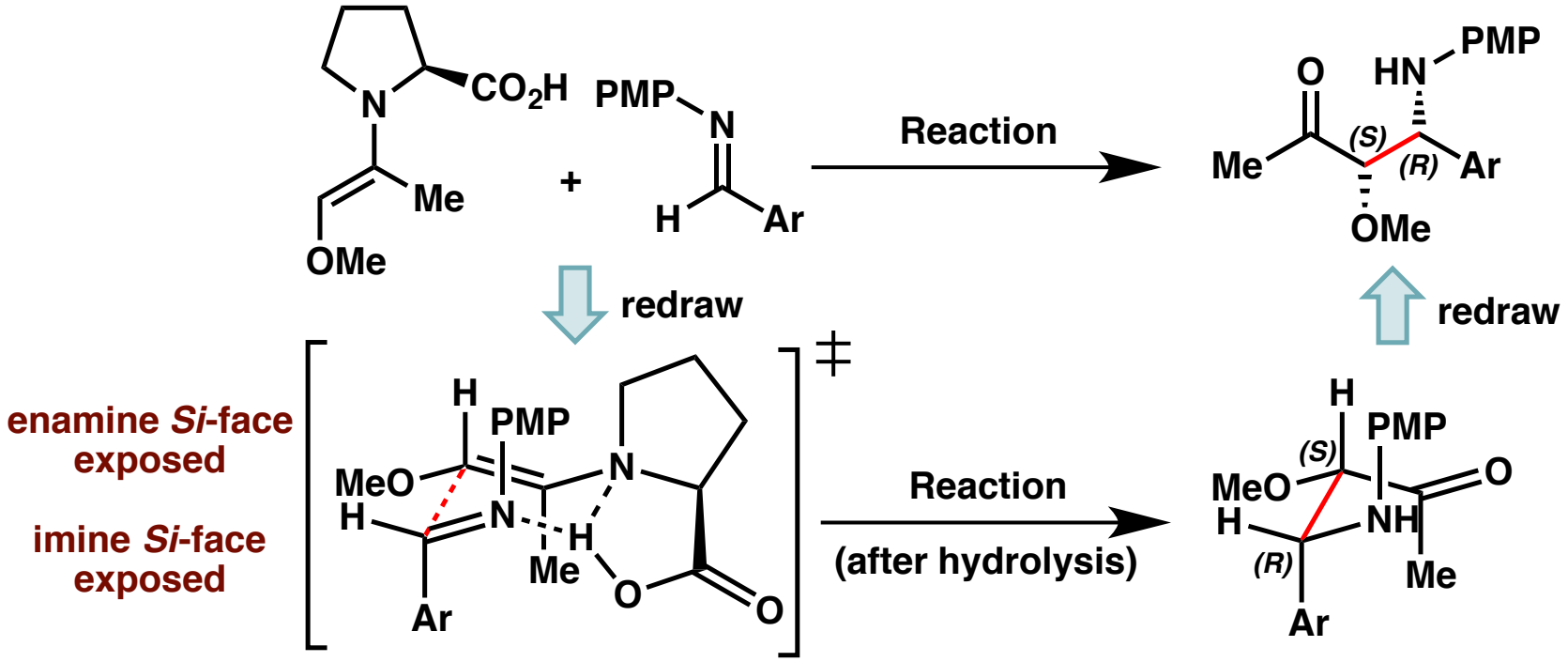


- From inspection of the product it is clear that the ketone becomes the **nucleophile** and that the imine is the **electrophile**.

B. List *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 9336

Intermolecular Asymmetric Mannich Reaction

- Finally, let's rationalise the **stereochemical outcome** of the reaction:



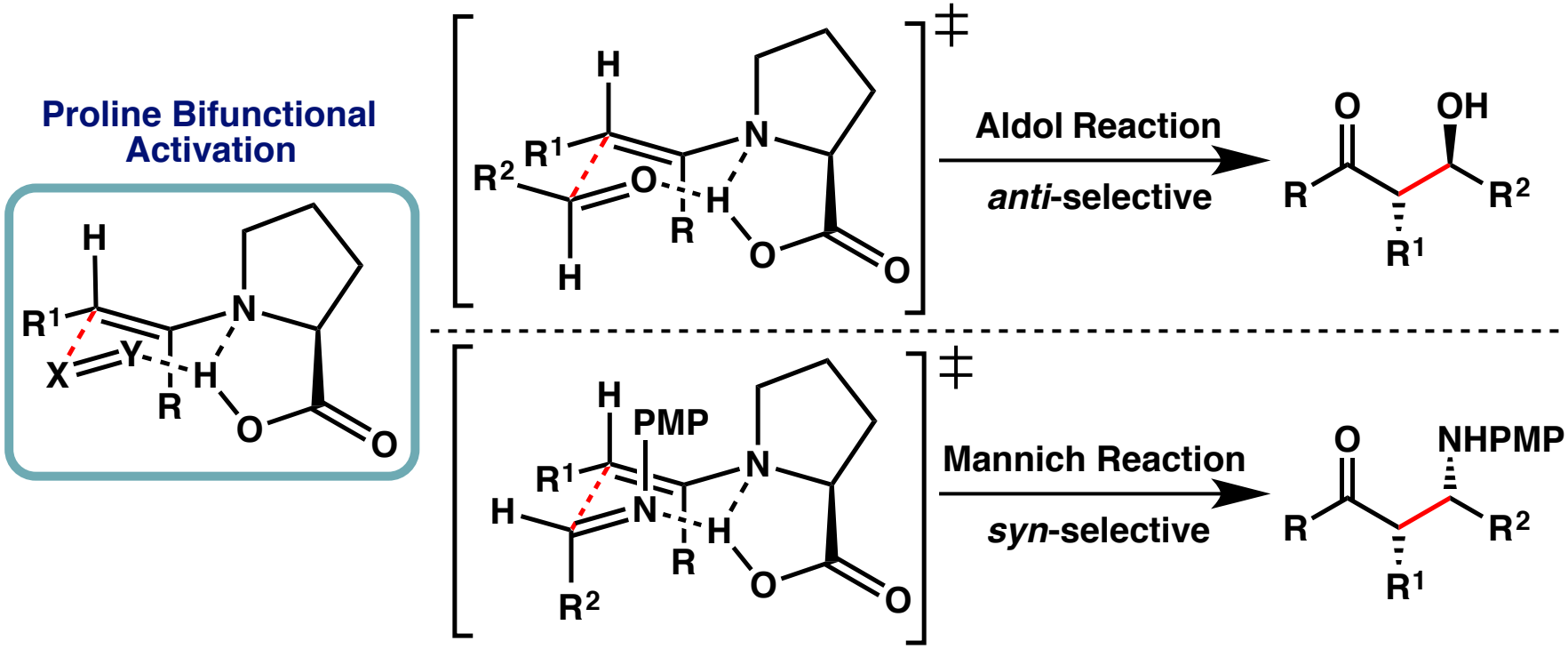
- Conformation such that **intermolecular hydrogen bond** can occur, stabilising the transition state. This forces the large Ar and PMP groups into **pseudoaxial** positions.

- Assign the two stereocentres **before and after redrawing** to convince yourself that they are both correct.

B. List *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 9336

Predictable Stereochemistry for Aldol and Mannich

- Use of proline leads to *anti*-aldol or *syn*-Mannich:

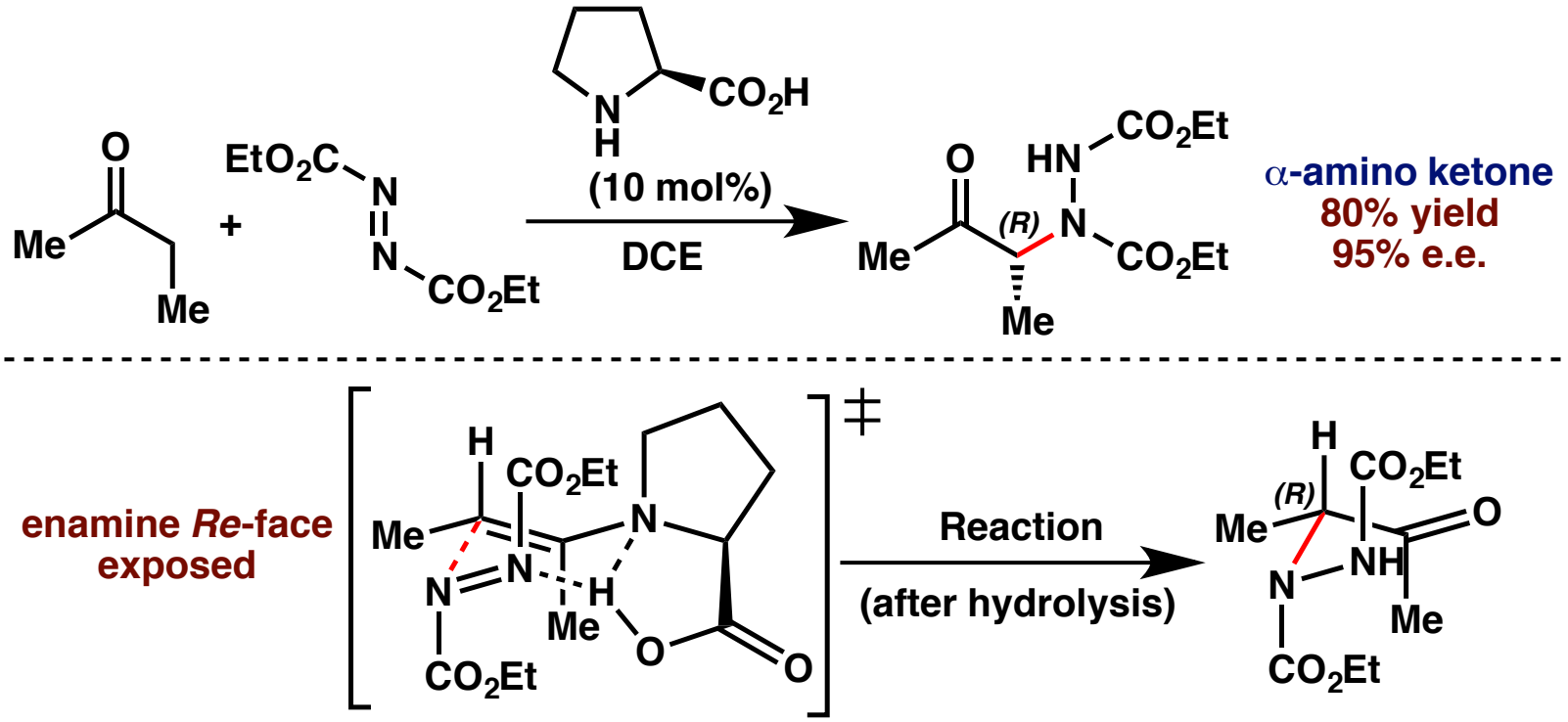


- Proline is often described as a **bifunctional catalyst** as it:

1) Activates the aldehyde/ketone substrate *via* enamine formation.
2) Activates the electrophilic component by hydrogen bonding.

Bifunctional Enamine Catalysis

- Proline has been used as a bifunctional organocatalyst for many related processes:

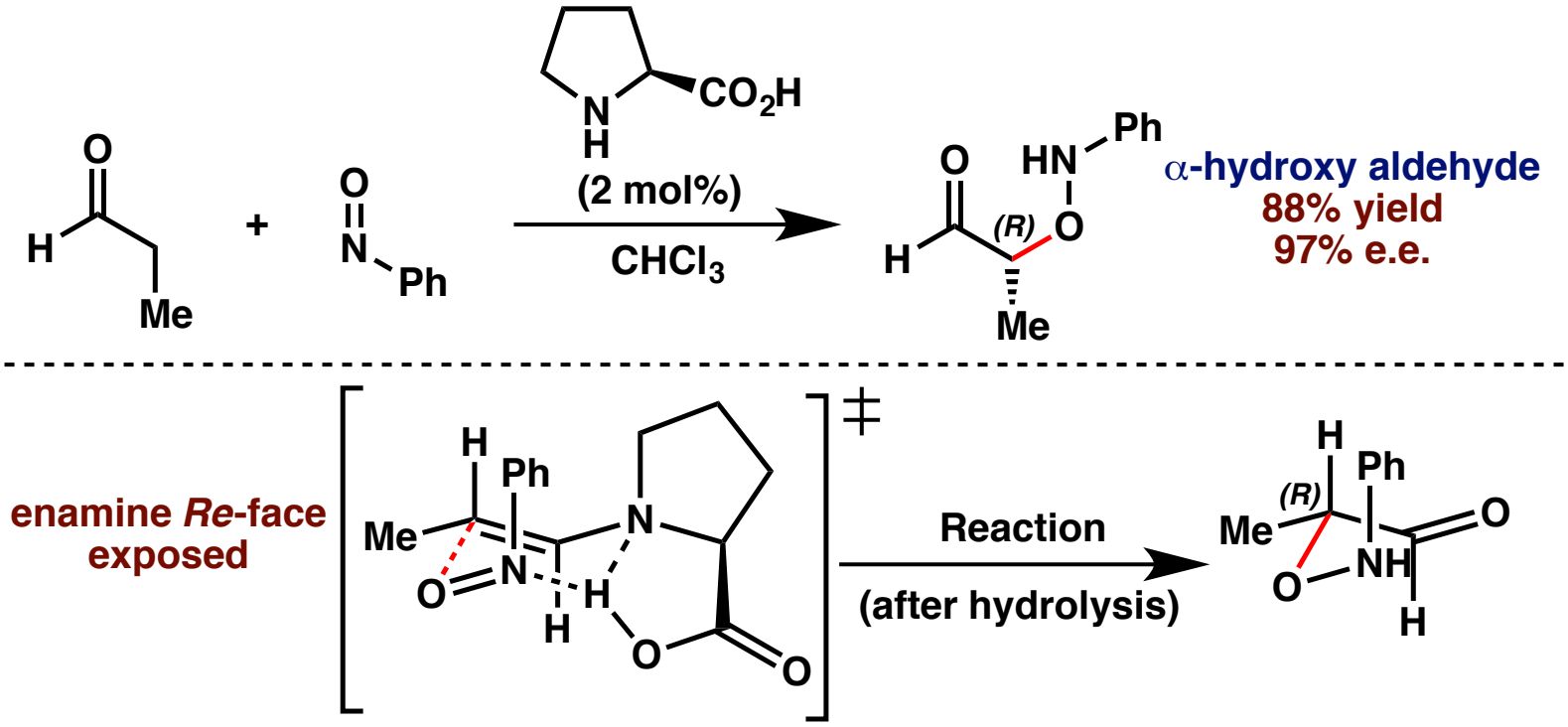


- The α-amination of ketones was reported by K. A. Jørgensen *et al.*, using diethyl azodicarboxylate (DEAD) as the electrophile.

- The proline catalyst activates the ketone substrate and the electrophile (bifunctional).

Bifunctional Enamine Catalysis

- Proline has been used as a bifunctional organocatalyst for many related processes:



- The α-oxidation of aldehydes was reported by D. W. C. MacMillan *et al.*, using nitrosobenzene as the electrophile.

- The proline catalyst activates the aldehyde and the electrophile (bifunctional).

Lecture 1: Introduction to Organocatalysis

Key learning objectives:

- Recap of fundamental concepts and definitions (stereochemistry)
- Definition of asymmetric catalysis and organocatalysis
- The development and introduction of organocatalysis (a historical perspective)
- Traditional α-functionalisation of carbonyl compounds
- The enamine organocatalytic activation mode (part 1): definition; general catalytic cycle; intra- and intermolecular aldol reactions; related α-functionalisation reactions; curly arrow pushing mechanisms; stereochemical rationale.

Lecture 1 Revision

To reinforce your understanding of the contents of this lecture, please refer to:

- *Organic Chemistry 2nd Ed.* (J. Clayden, N. Greeves and S. Warren, Oxford University Press, 2012, ISBN 978-0-19-927029-3). Chapter 41 is particularly relevant.
- *New Frontiers in Asymmetric Catalysis* (K. Mikami and M. Lautens, Wiley, 2007). Downloadable from University Network. DOI: 10.1002/0470098007
- *Catalytic Asymmetric Synthesis 3rd Ed.* (I. Okima, Wiley, 2010). Downloadable from University Network. DOI: 10.1002/9780470584248
- *Prof. MacMillan Short-Course:* www.princeton.edu/chemistry/macmillan/research/
- A leading review article on enamine organocatalysis: *Chem. Rev.*, 2007, **107**, 5471.
- CH3404 Feedback Workshop

CH3404 Asymmetric Synthesis of Pharmaceuticals and Natural Products LCM Lecture 2

Dr Louis C. Morrill
School of Chemistry, Cardiff University
Main Building, Rm 1.47B
MorrillLC@cardiff.ac.uk

Lecture 2: HOMO-Raising Organocatalysis

Key learning objectives:

- The enamine organocatalytic activation mode (part 2): Bifunctional vs. steric control; synthesis and reactivity of imidazolidinone and diarylprolinol silyl ether organocatalysts.

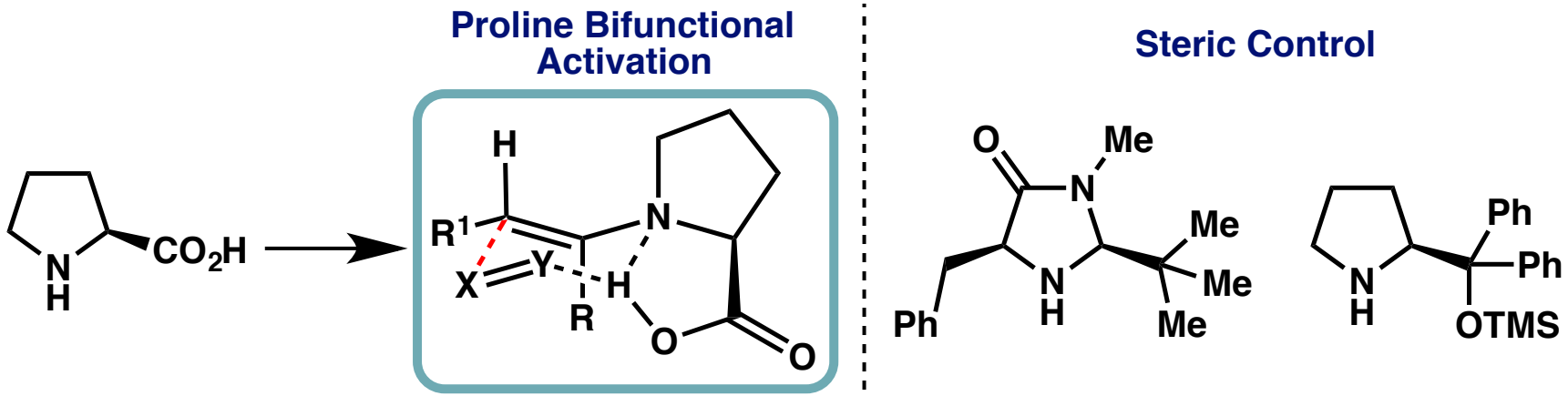
- Dienamine organocatalytic activation mode.

- Alternative HOMO-raising organocatalytic activation modes.

- C(1)-, C(2)- and C(3)-enolate activation modes: definition; general catalytic cycle; various intra- and intermolecular functionalisation reactions; curly arrow pushing mechanisms.

Bifunctional Activation vs Steric Control

- Towards the end of lecture 1 we discussed **bifunctional enamine catalysis** using naturally occurring **proline** as the organocatalyst
- However, **bifunctional activation** is not absolutely required for selective catalysis.
- Other secondary amine organocatalysts rely on **steric control**.

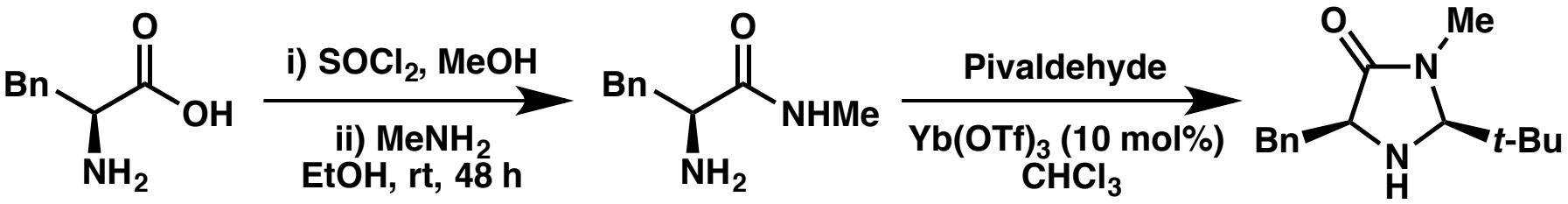


- In the following slides we will discuss the **synthesis and reactivity** of these important alternative secondary amine organocatalysts.

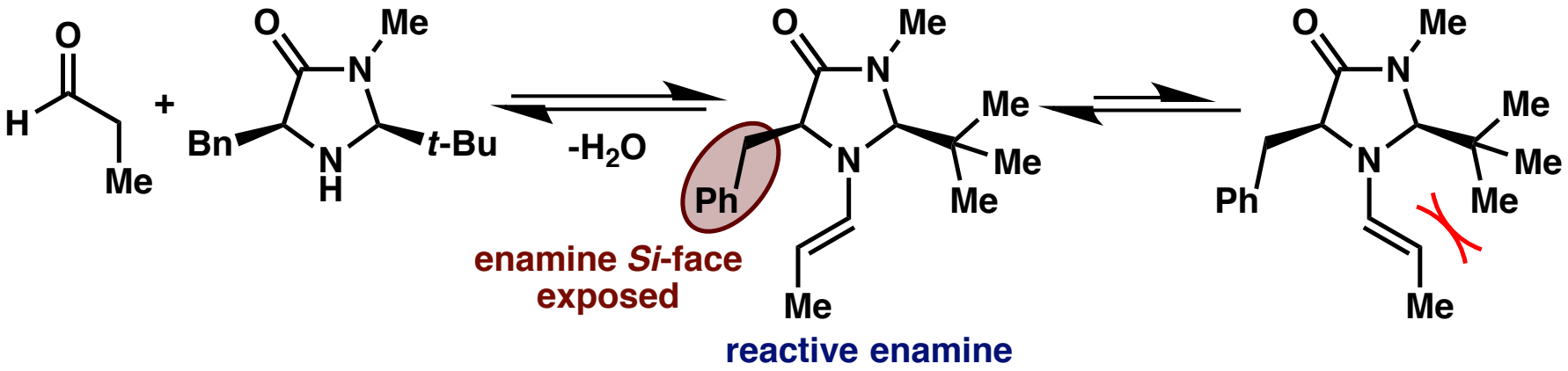
B. List *et al.*, *Chem. Rev.*, 2007, **107**, 5471.

Imidazolidinone Organocatalysts

- **Imidazolidinone organocatalysts** were introduced by MacMillan in 2000. They can be easily accessed in a short sequence from commercially available amino acids.



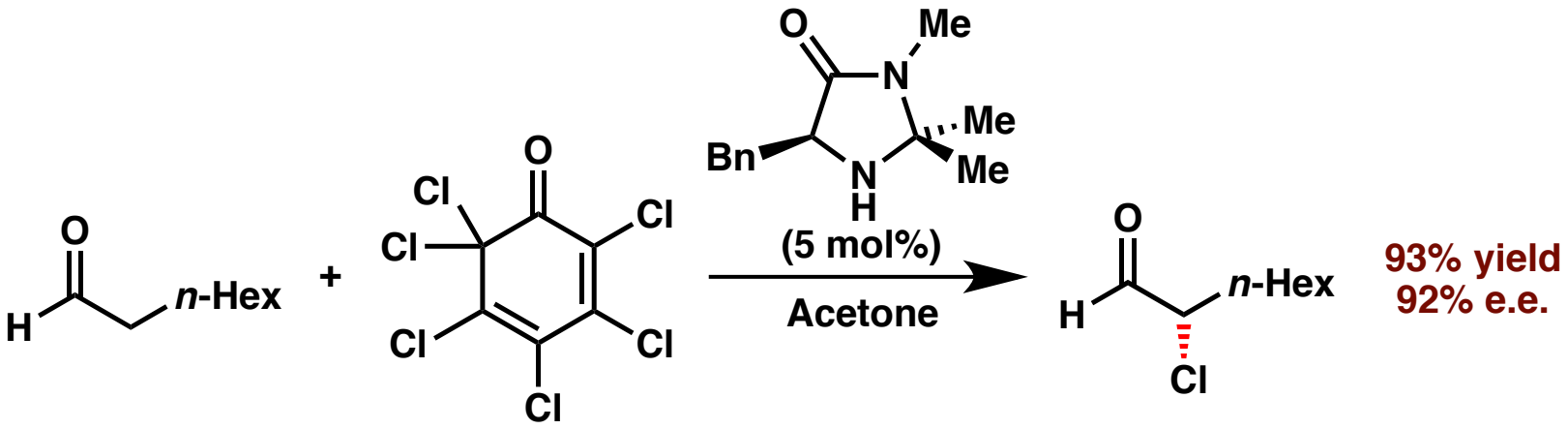
- These catalysts control **enamine geometry** and **shield one face of the enamine** in order to control the stereochemical outcome of reactions. **Control of both is crucial!**



- Let's look at some specific examples.

Enantioselective α-Chlorination of Aldehydes

- Imidazolidinone organocatalysts have been employed for the enantioselective **α-chlorination of aldehydes**.



- For this class of organocatalytic reaction we must be able to:

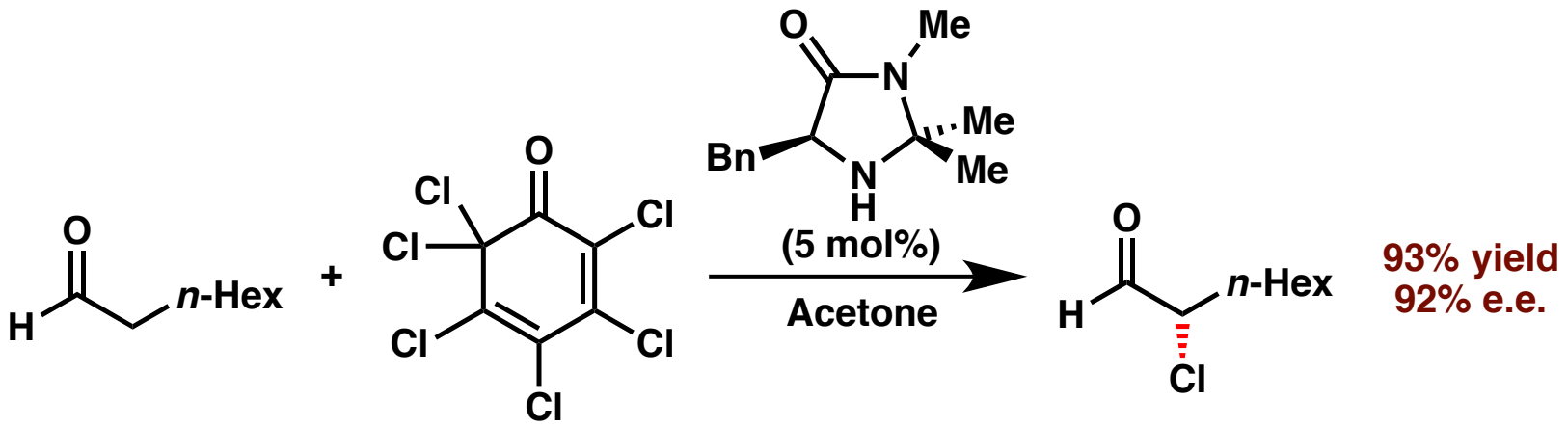
1) Identify how the organocatalyst **activates** the substrate (**activation mode**)

2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

3) Rationalise the **stereochemical outcome** of the reaction (only enantiocontrol is relevant in this case) by drawing an appropriate transition state.

Enantioselective α-Chlorination of Aldehydes

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

1) A **secondary amine Lewis base** organocatalyst is used

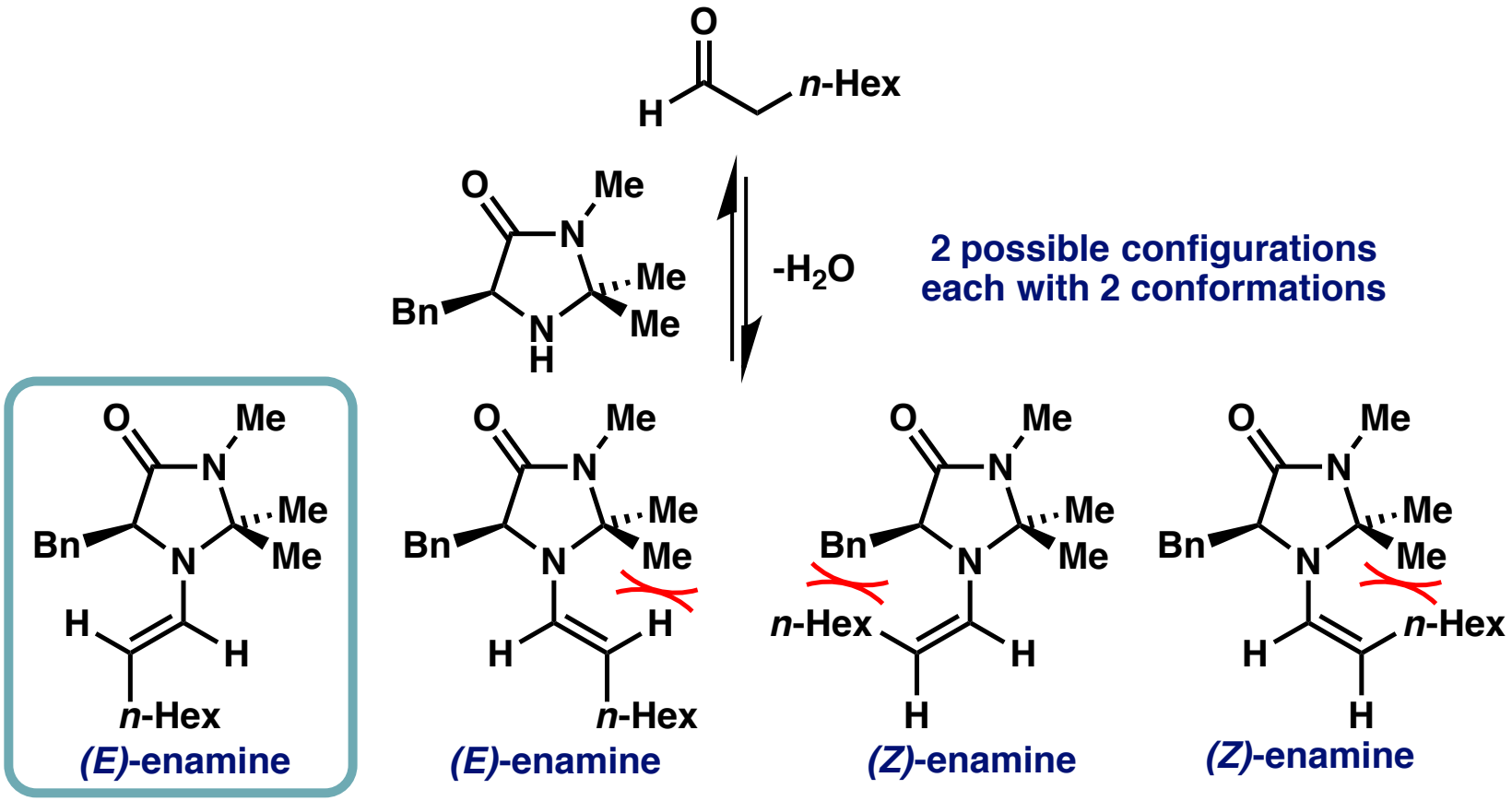
2) One reactant contains a **aldehyde** functional group and the other is a source of Cl^+.

3) The aldehyde is **enolisable** (e.g. it has α-hydrogen atoms that can be deprotonated)

- Conclusion – this reaction proceeds *via* the **enamine** activation mode.

Enantioselective α-Chlorination of Aldehydes

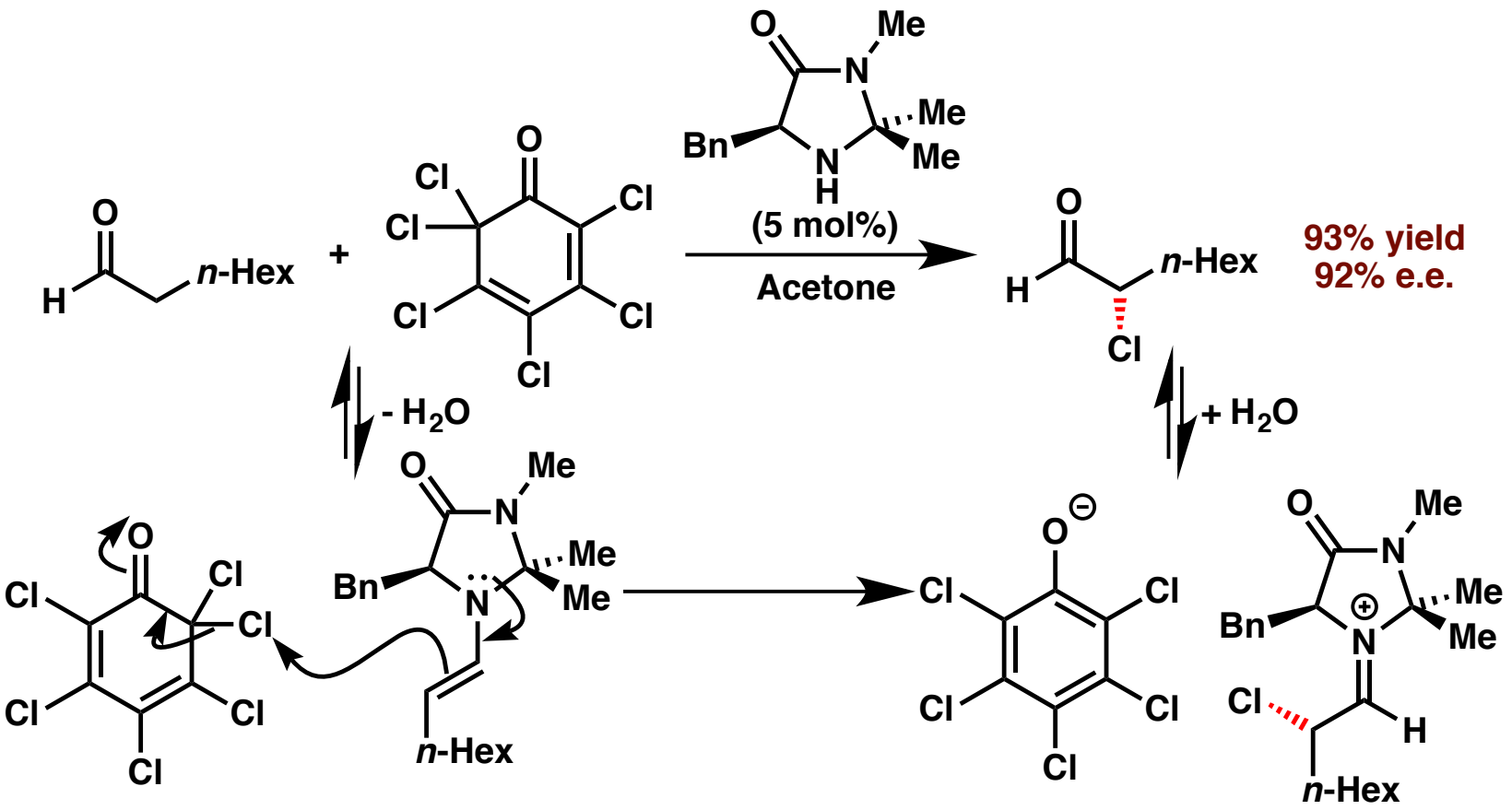
- Let's think about the key nucleophilic enamine species formed in detail:



- The (*E*)-configuration is favoured over the (*Z*)-configuration due to steric congestion involving the hexyl substituent. One (*E*)-conformation is also favoured over the other

Enantioselective α-Chlorination of Aldehydes

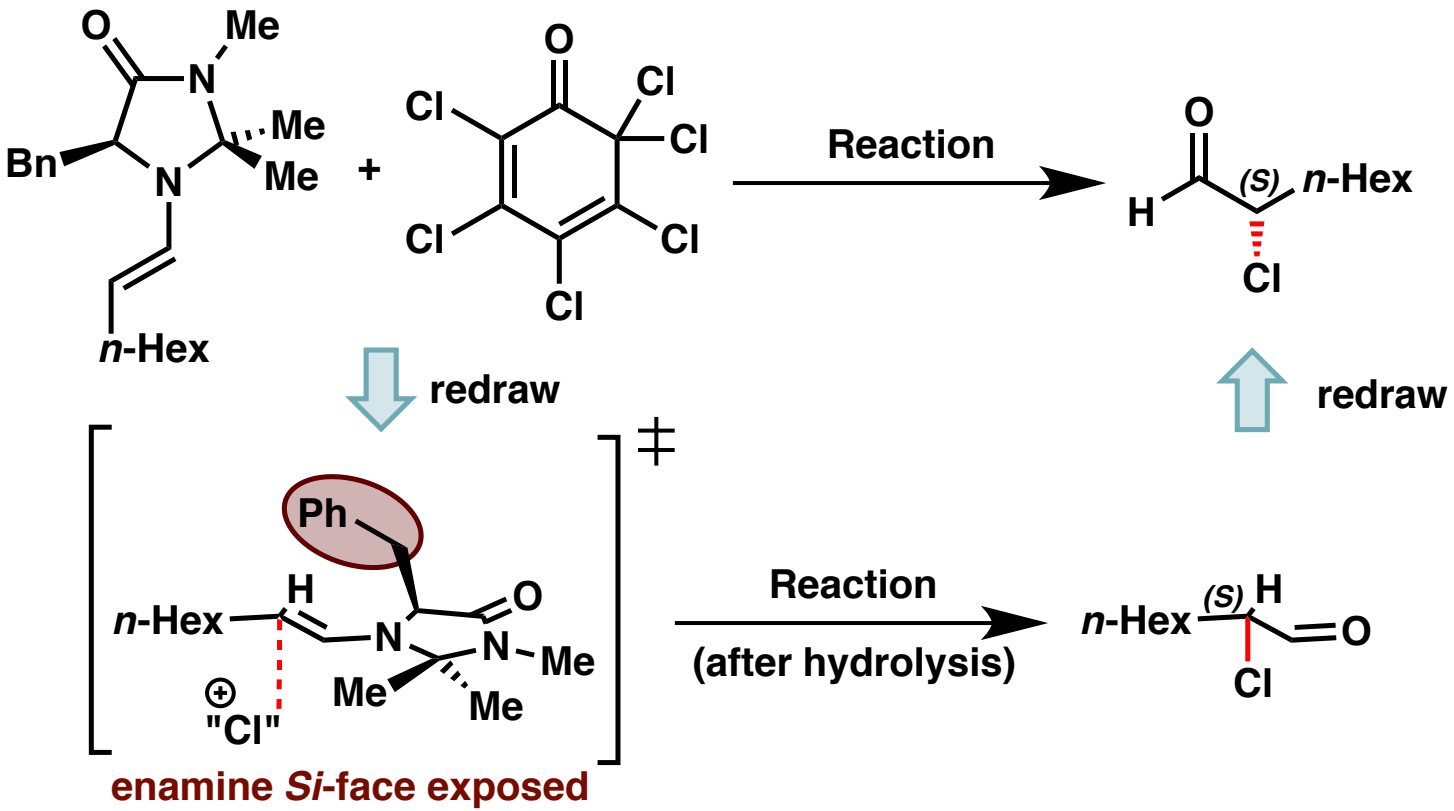
- Now let's consider the **curly arrow pushing mechanism**:



- **The thermodynamic driving force** for this reaction is the formation of an aromatic byproduct, derived from the ortho quinone chlorinating agent.

Enantioselective α-Chlorination of Aldehydes

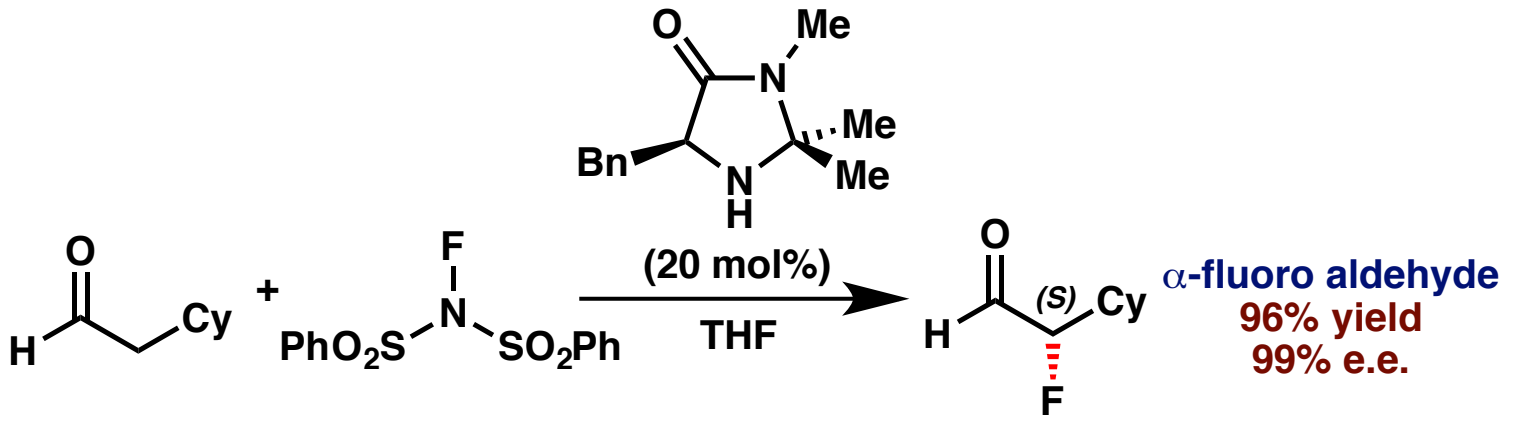
- Finally, let's rationalise the **stereochemical outcome** of the reaction:



- Conformation such that the benzyl group **blocks the *Re*-face** of the enamine. Hence the electrophile approaches the ***Si*-face** of the enamine, giving enantioselectivity.

Enantioselective α-Fluorination of Aldehydes

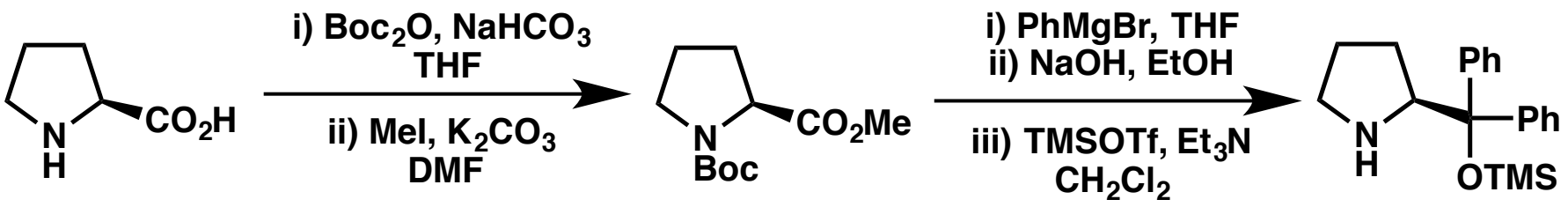
- Imidazolidinone catalysts also catalyse the **α-fluorination of aldehydes**:



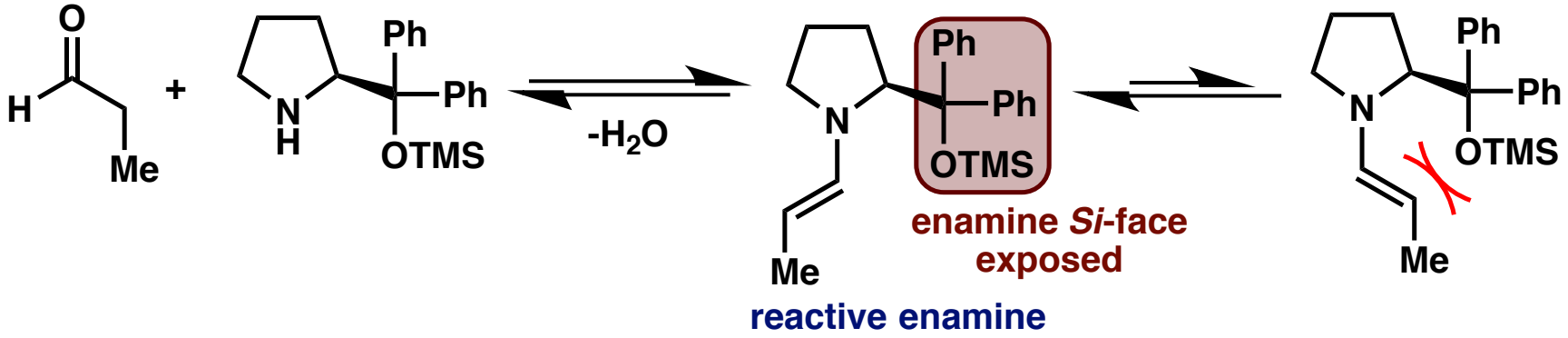
- Conformation such that the benzyl group **blocks the *Re*-face** of the enamine. In some cases, the aldehyde products are reduced to the alcohols. Why?

Diarylprolinol Silyl Ether Organocatalysts

- **Diarylprolinol silyl ether organocatalysts** were introduced by Jørgensen and Hayashi in 2005. They are readily accessed in a short sequence from proline.



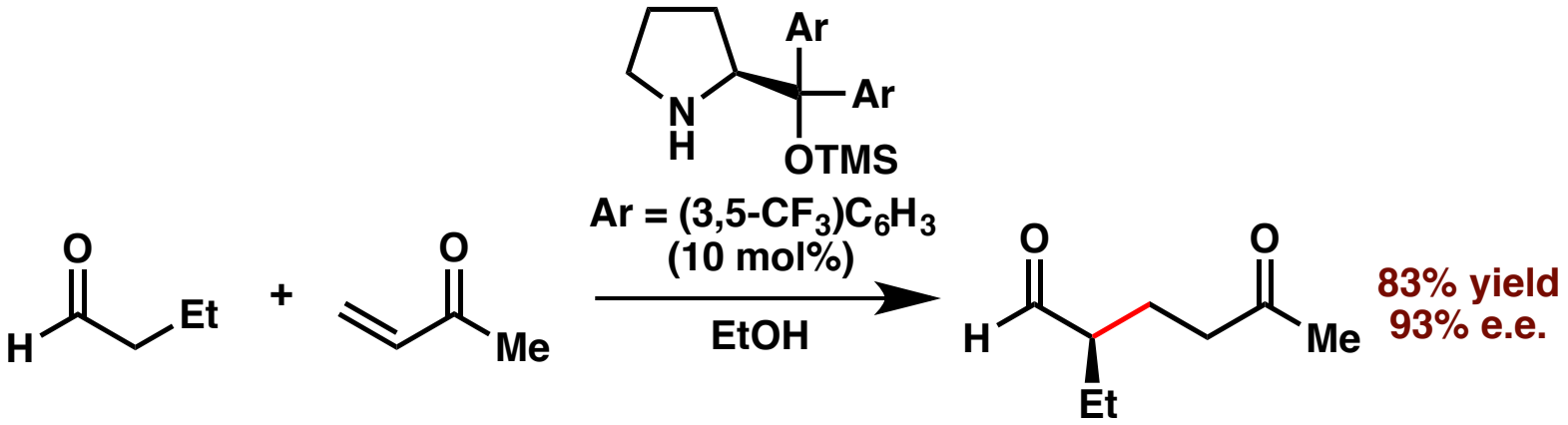
- These catalysts also control **enamine geometry** and **shield one face of the enamine** in order to control the stereochemical outcome of reactions.



- Let's look at some specific examples.

Enantioselective Michael Addition of Aldehydes

- Diarylprolinol silyl ether organocatalysts have been employed for the **enantioselective Michael addition** of aldehydes to methylvinyl ketone.



- For this class of organocatalytic reaction we must be able to:

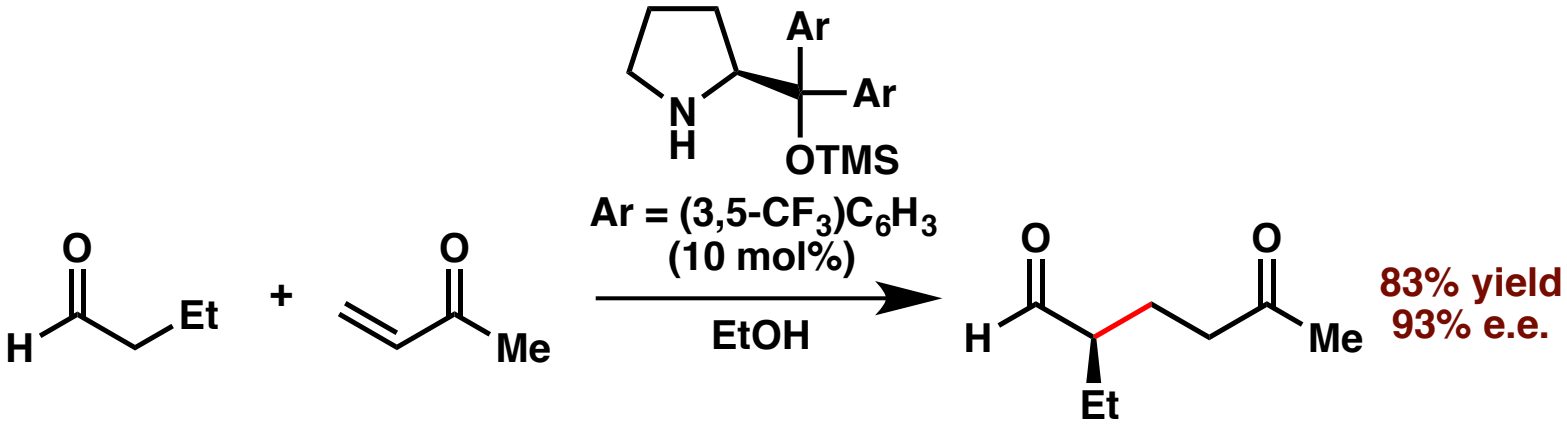
1) Identify how the organocatalyst **activates** the substrate (**activation mode**)

2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

3) Rationalise the **stereochemical outcome** of the reaction (only enantiocontrol is relevant in this case) by drawing an appropriate transition state.

Enantioselective Michael Addition of Aldehydes

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

1) A **secondary amine Lewis base** organocatalyst is used

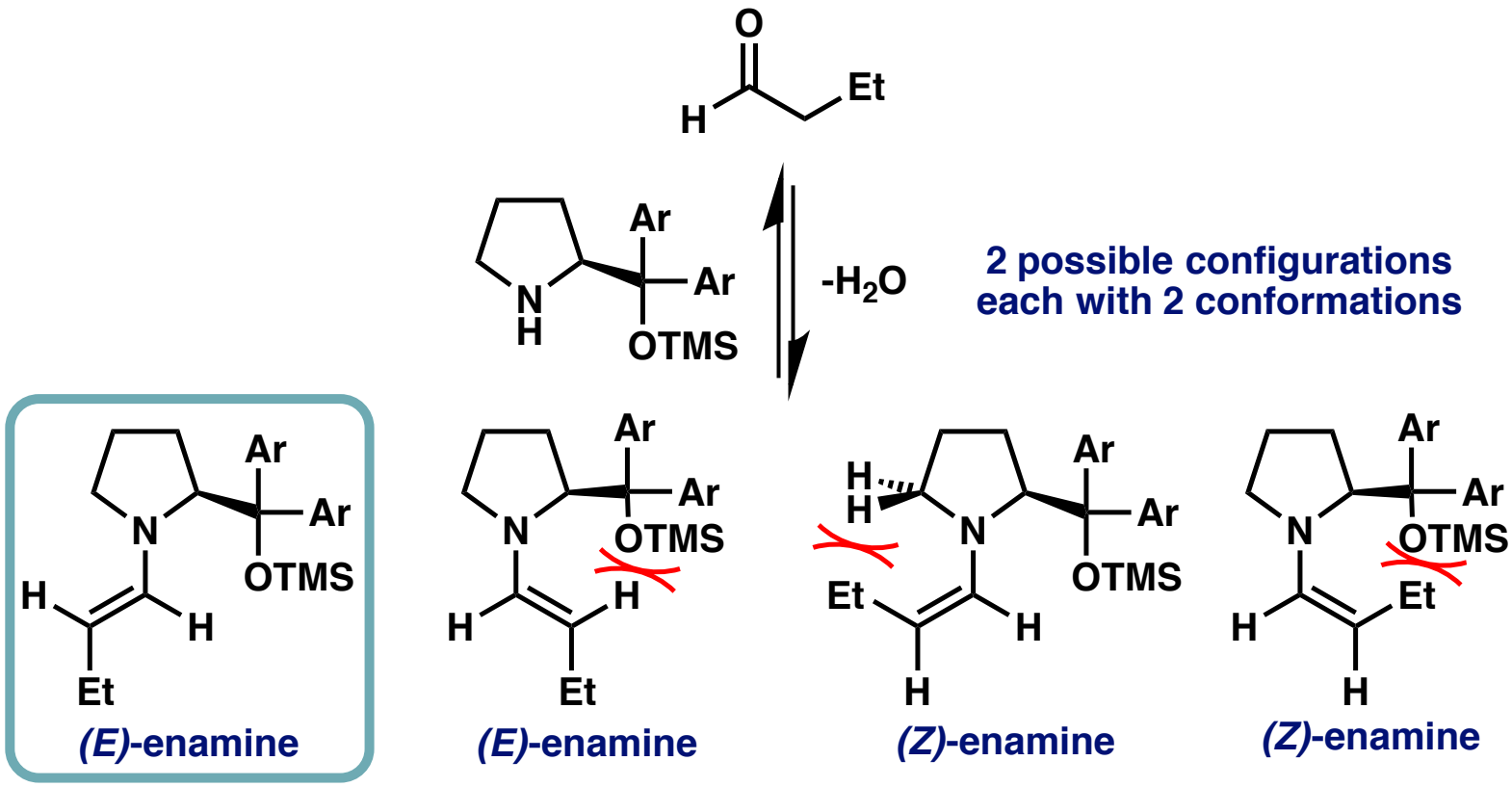
2) One reactant contains an **aldehyde** functional group and the other is an enone.

3) The aldehyde and enone are **enolisable** (e.g. they both have α-hydrogen atoms that can be deprotonated)

- Conclusion – this reaction proceeds *via* the **enamine** activation mode.

Enantioselective Michael Addition of Aldehydes

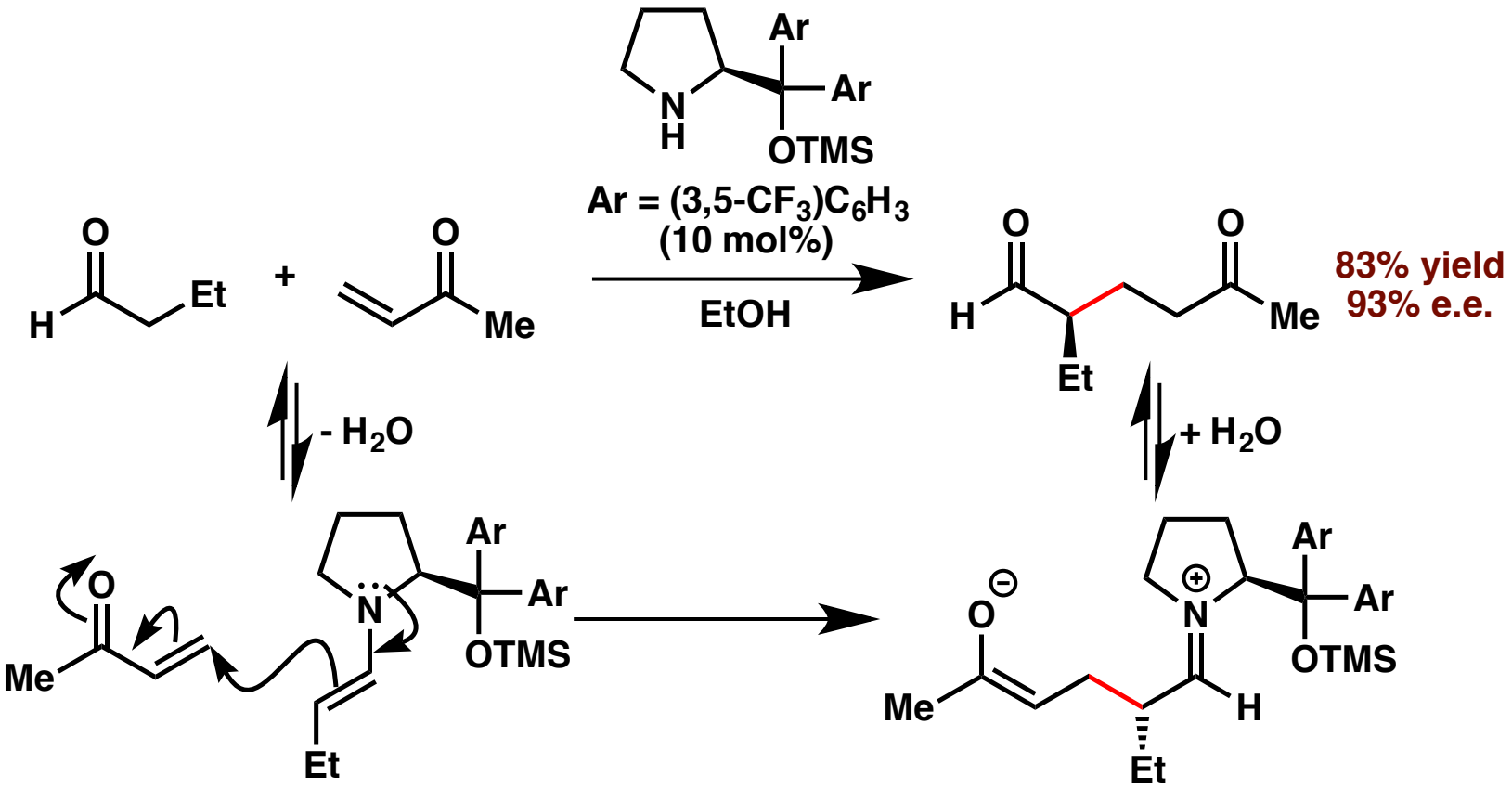
- Let's think about the key nucleophilic enamine species formed in detail:



- The (*E*)-configuration is favoured over the (*Z*)-configuration due to steric congestion involving the ethyl substituent. One (*E*)-conformation is also favoured over the other

Enantioselective Michael Addition of Aldehydes

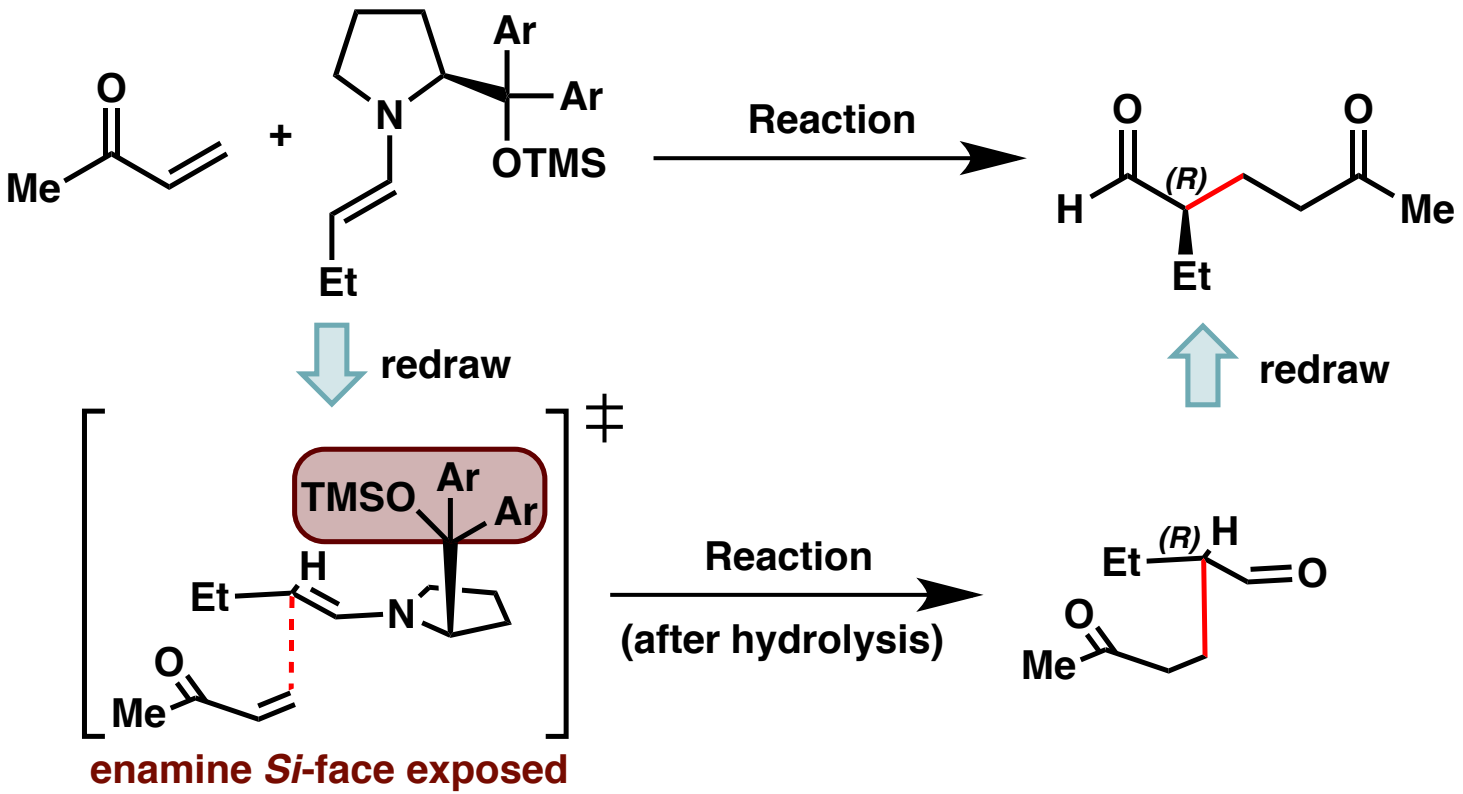
- Now let's consider the **curly arrow pushing mechanism**:



- An enamine could also be formed with the enone starting material, but the aldehyde is considerably more electrophilic that then carbonyl within the enone. Why?

Enantioselective Michael Addition of Aldehydes

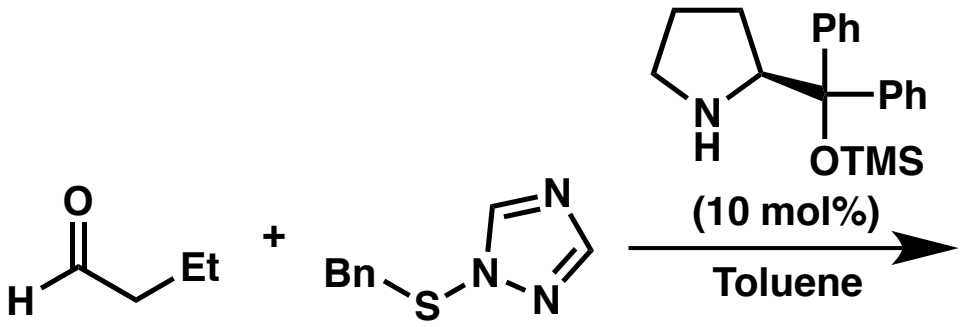
- Finally, let's rationalise the **stereochemical outcome** of the reaction:



- Conformation such that the large group **blocks the *Re*-face** of the enamine. Hence the electrophile approaches the ***Si*-face** of the enamine, giving enantioselectivity.

Enantioselective α-Sulfination of Aldehydes – Class Example

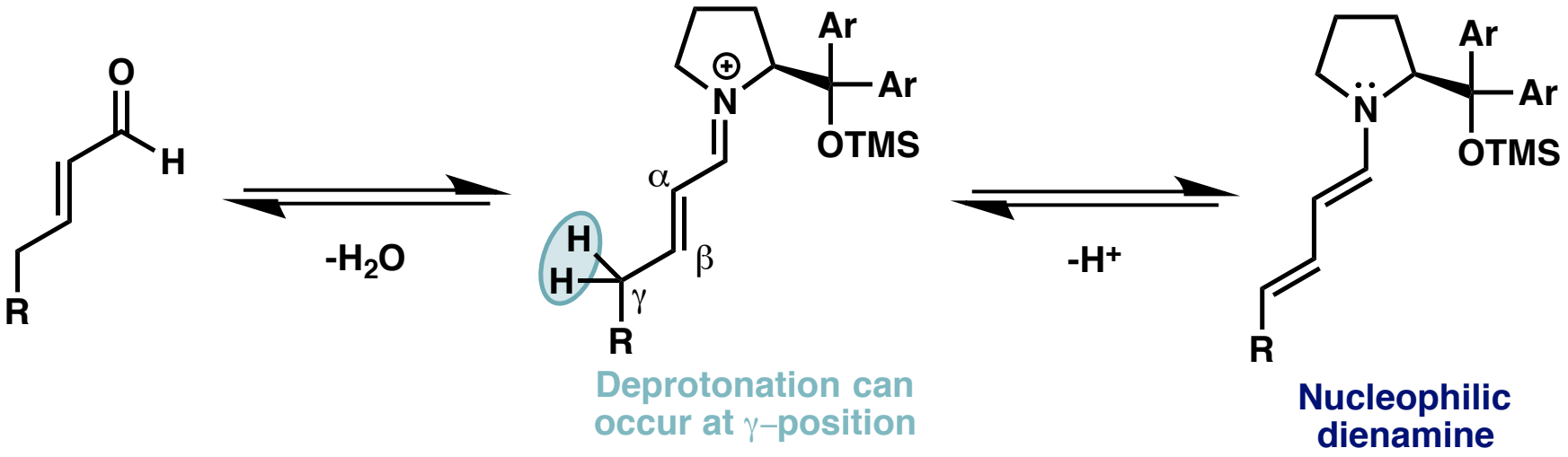
- Diarylprolinol silyl ether organocatalysts also promote the **α-sulfination of aldehydes**. Determine the major product for the reaction shown below:



- The triazole on sulfur is a good leaving group (pK_a = 10.3) which makes the sulfur compound a good electrophile, susceptible to nucleophilic attack the the enamine.

Dienamine Activation Mode

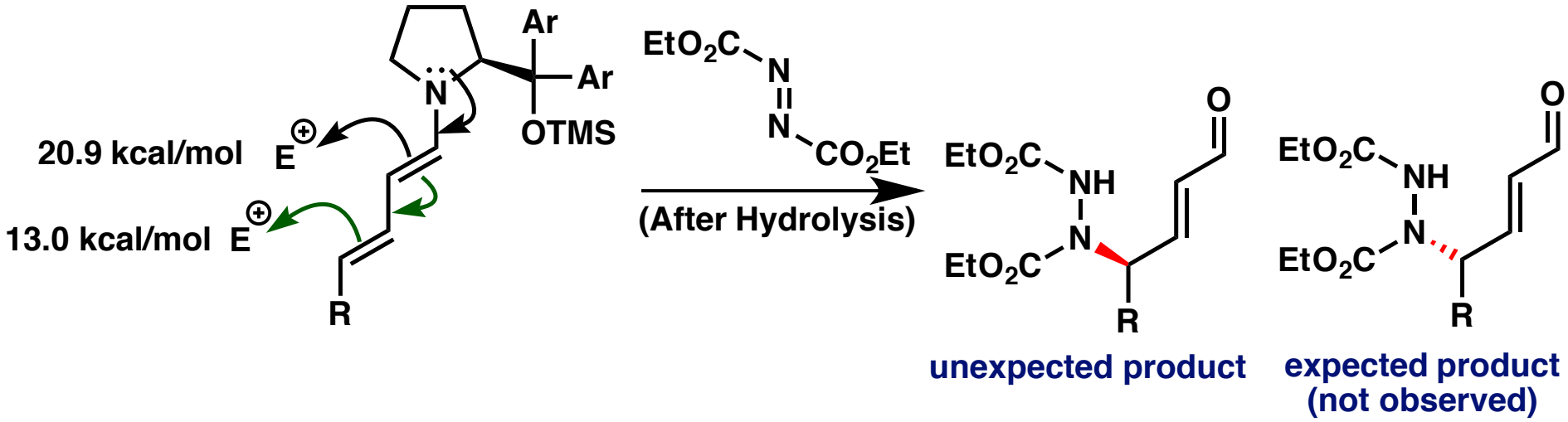
- K. A. Jørgensen has explored extending the conjugated system by employing **enolisable α,β-unsaturated aldehydes** as substrates:



- It was unknown if these dienamine species would react with electrophiles at the α-position (as with normal enamines) or at the γ-position.

γ-Amination of Enals

- Interestingly it was found the the dienamines react selectively at the at the **γ-position**, but give the **opposite enantioselectivity** to what was expected when employed in a γ-amination process.

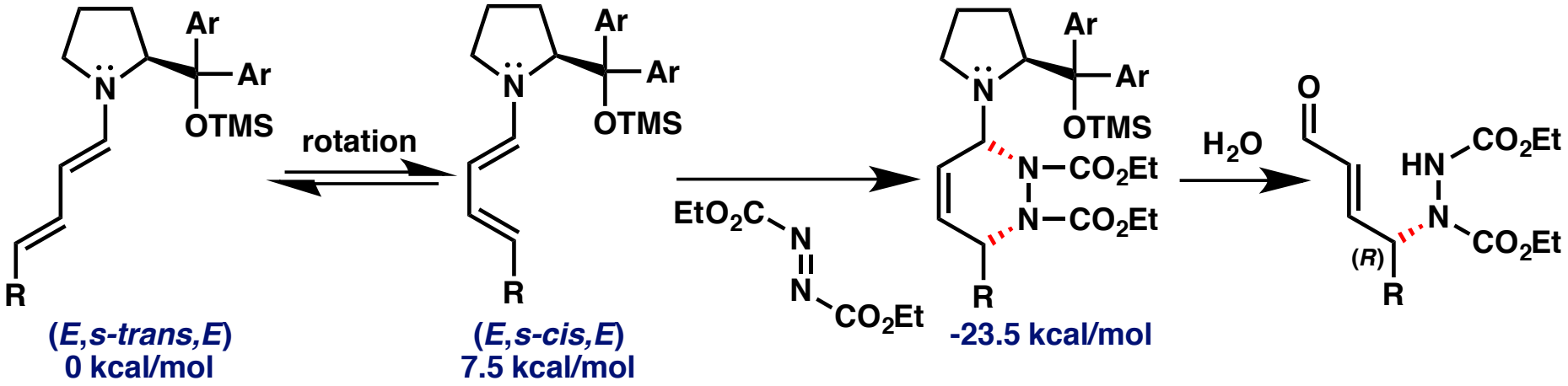


- Computation studies revealed that reaction at the γ-position was favoured (lowed in energy), explaining the observed **regiochemical outcome**.

- However, further studies were needed to rationalise the **stereochemical outcome**.

γ-Amination of Enals

- The conformation of the dienamine species is critical is this process:



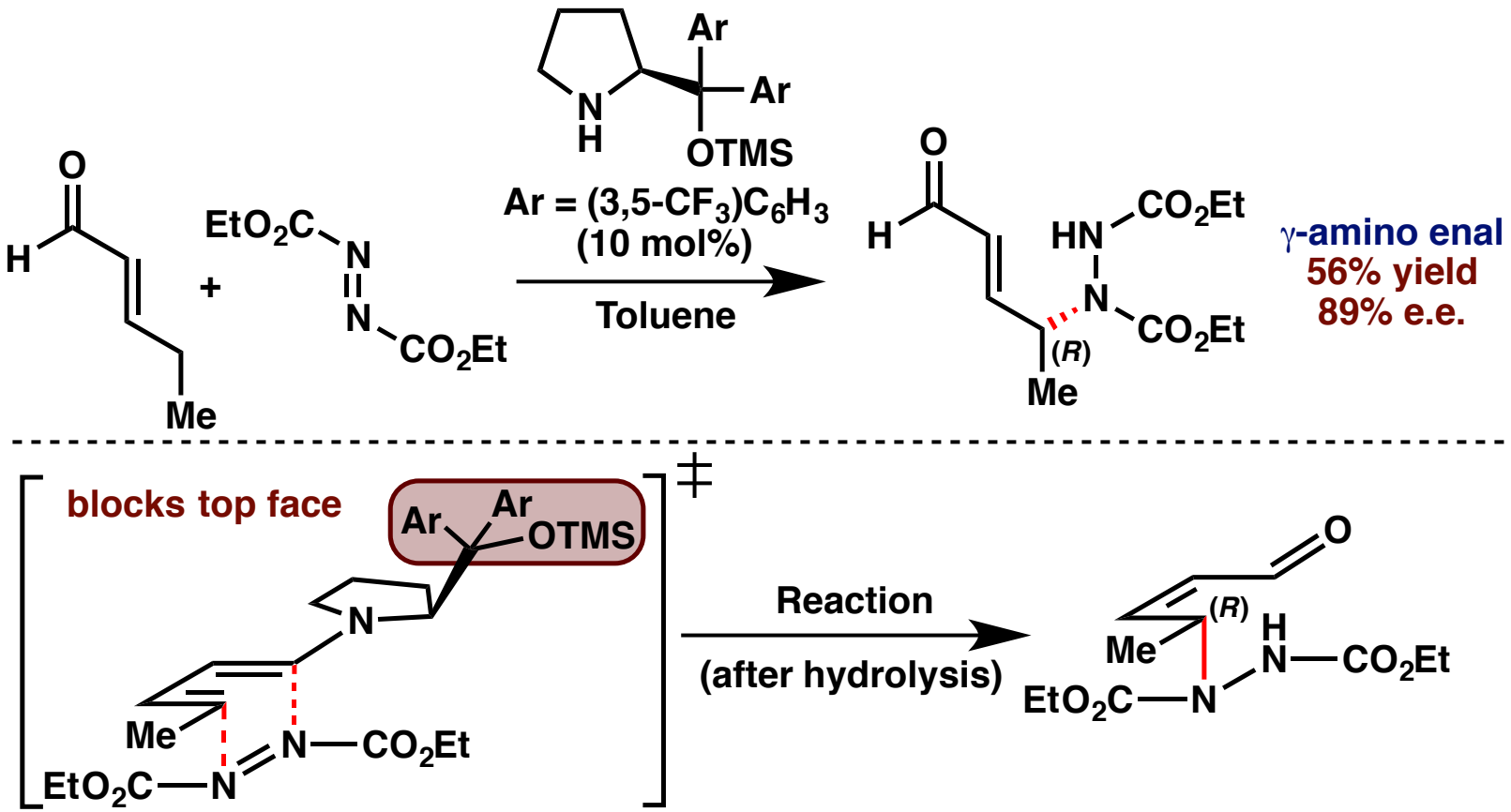
- The ***(E,s-trans,E)* conformation** is lower in energy, with rotation around the C-C bond giving rise to the higher energy ***(E,s-cis,E)* conformation**.

- The *(E,s-cis,E)* conformation can react with the diethyl azocarboxylate in a **formal [4+2] cycloaddition** process that is **very energetically favoured**.

- This is the most **energetically favoured pathway** to product formation.

γ-Amination of Enals

- Diarylprolinol silyl ether organocatalysts promote the **γ-amination of enals**:

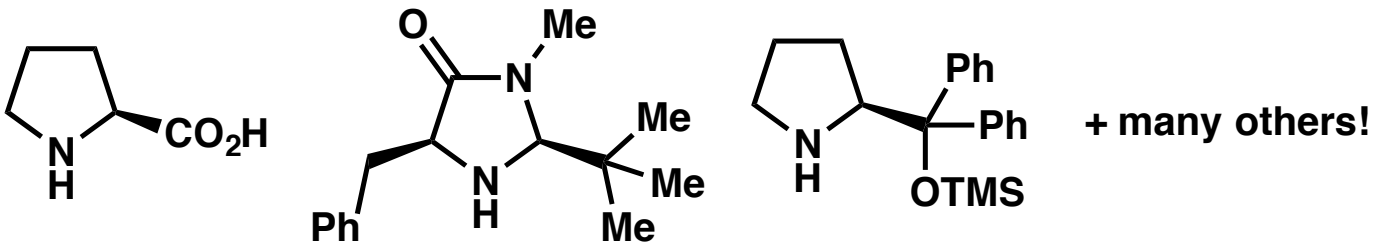


- The large group blocks the top face of the dienamine, giving rise to a highly enantio-selective process. This is another example of **steric control**.

Enamine Organocatalysis Cheat Sheet

- For enamine organocatalysis, you must remember the following key information:

- The enamine activation mode requires **primary or secondary amine organocatalysts** and **enolisable** aldehyde or ketone substrates.



- In order to rationalise the stereochemistry of reactions involving enamines you must:

1) Identifying whether the catalyst operates by **bifunctional activation** (*via* hydrogen bonding) or **steric control.**

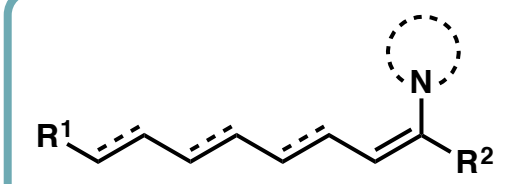
2) Carefully consider the possible **configurations** (e.g. *E* vs *Z*) and **conformations** (e.g. *s-cis* vs *s-trans*) of the key enamine intermediate.

3) Draw a suitable **3D-representation** of the transition state.

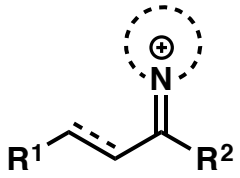
An Overview of Organocatalysis

- Organocatalysis is now a thoroughly established member of the synthetic toolbox, with a large number of **generic activation modes** known.

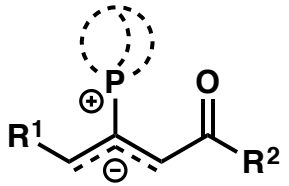
Covalent Activation Modes



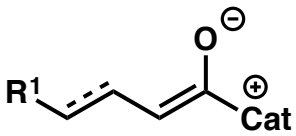
Enamine (di-, tri-, tetra-enamine) Catalysis



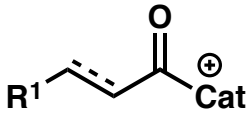
Iminium Catalysis



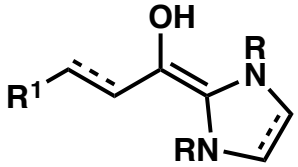
Phosphine Catalysis



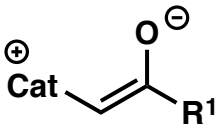
C(1)-Enolate (di-enolate) Catalysis



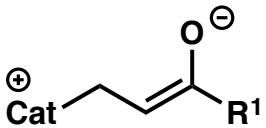
Acyl ammonium/azolium Catalysis



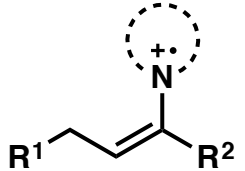
N-Heterocyclic Carbene Catalysis



C(2)-Enolate Catalysis

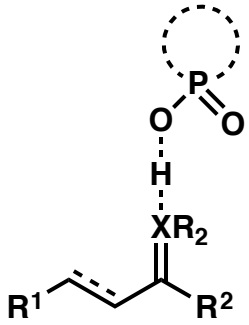


C(3)-Enolate Catalysis

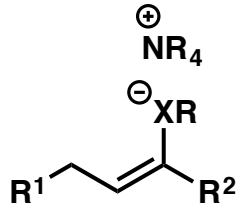


SOMO Catalysis

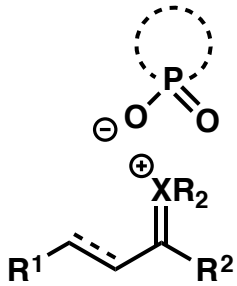
Non-Covalent Activation Modes



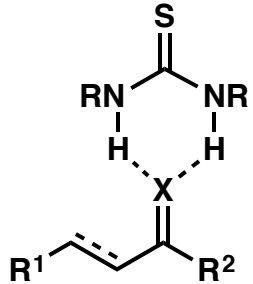
Brønsted Acid Catalysis



Phase-transfer Catalysis



Chiral Anion Catalysis



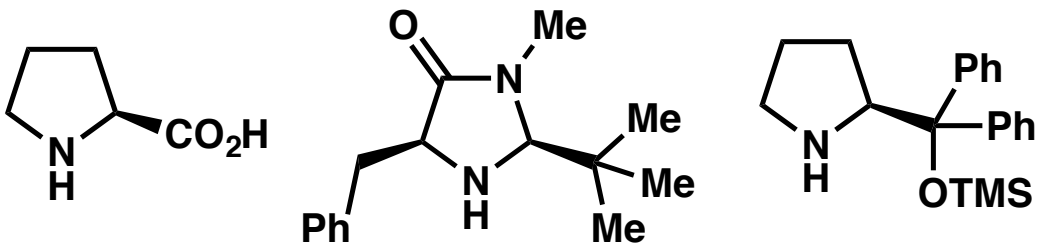
Hydrogen Bonding Catalysis

- Let's now focus on **HOMO-raising organocatalysis beyond enamine activation**.

For an excellent overview see D. Romo *et al.*, *Nat. Prod. Rep.*, 2014, **31**, 1318.

Classes of Organocatalyst

- Let's start with an overview of the **classes of organocatalyst**. We have already covered **secondary amines** in detail during lectures 1 and 2:



- There are **three** more important classes of Lewis base organocatalyst that we need to know for the remainder of this lecture:

1) Tertiary amines

2) N-heterocyclic carbenes

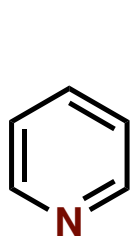
3) Phosphines

- Each is able to activate a substrate by **donating a lone pair of electrons** (Lewis base) catalysts.

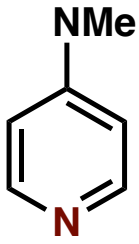
For an overview see D. W. C. MacMillan, *Nature*, 2008, **455**, 304.

Tertiary Amine Organocatalysts

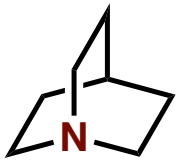
- **Tertiary amines** have found utility across a wide range of organocatalytic processes.
- Achiral examples:



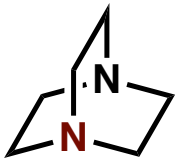
pyridine



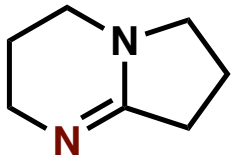
DMAP



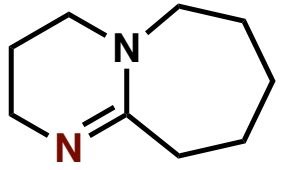
quinuclidine



DABCO

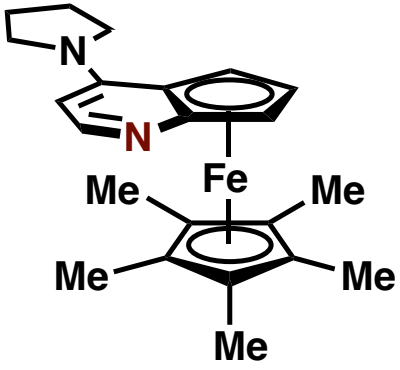


DBN

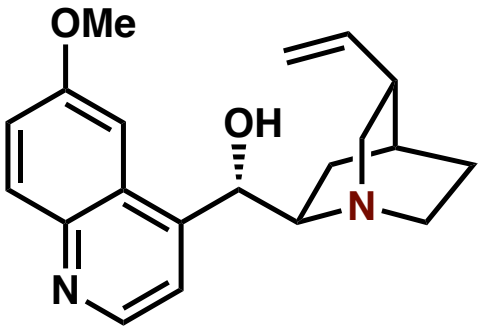


DBU

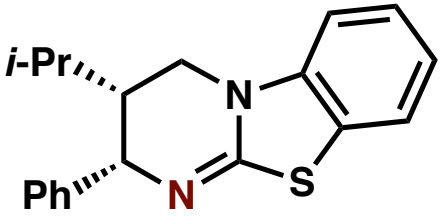
- Chiral examples:



Planar-chiral DMAP derivatives



Cinchona alkaloids (quinidine)



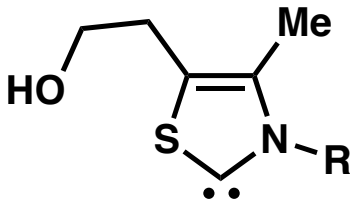
Isothioureas

M. Gaunt *et al.*, *Chem. Rev.*, 2007, **107**, 5596.

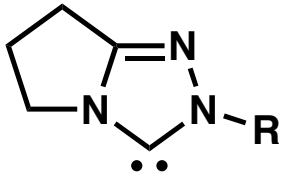
N-Heterocyclic Carbene Organocatalysts

- **N-heterocyclic carbenes (NHCs)** have become increasingly popular organocatalysts
- Achiral examples:

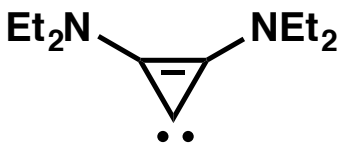
Imidazole-based



Thiazole-based

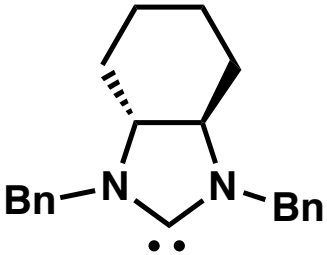


Triazole-based

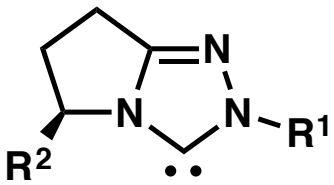


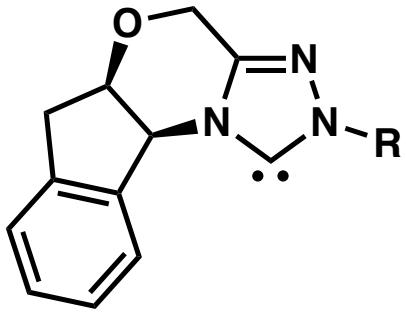
Bis(amino) cyclopropenyl-based

- Chiral examples:



C(2)-symmetric imidazole-based

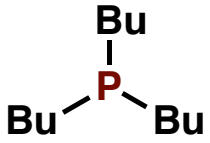




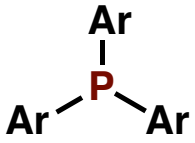
Chiral triazole-based (most common)

Phosphine Organocatalysts

- **Phosphines** demonstrate some unique organocatalytic reactivity.
- Achiral examples:

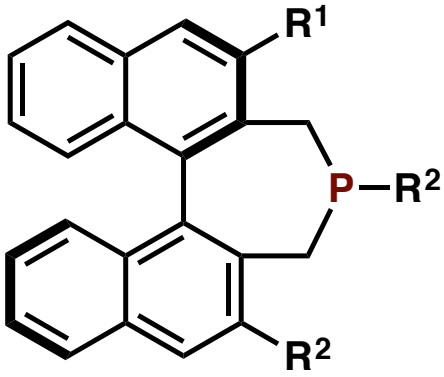


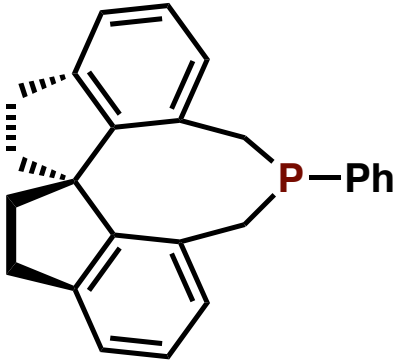
Trialkylphosphines

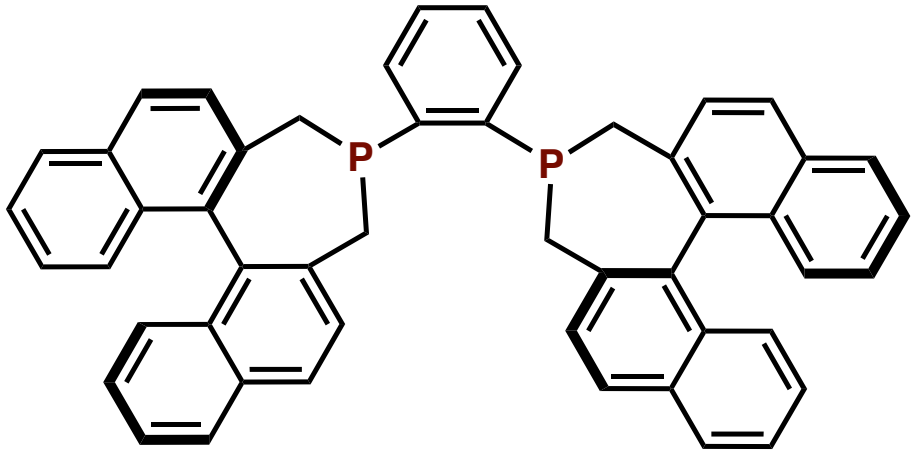


Triarylphosphines

- Chiral examples:





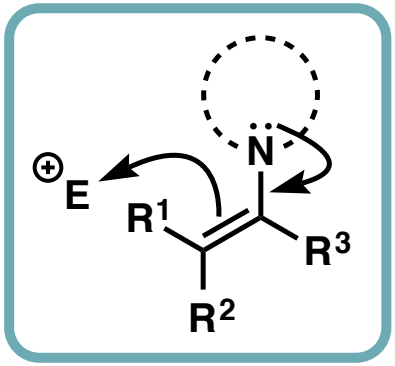


Axially chiral phosphines

HOMO-Raising Catalysis Beyond Enamine Activation

- So far we have discussed **enamine organocatalysis** as a method of **α-functionalisation** of carbonyl compounds:

Enamine Organocatalysis



- The enamine activation mode has the following key characteristics:

1) It is a **covalent** activation mode – the catalyst is covalently bound to the substrate.

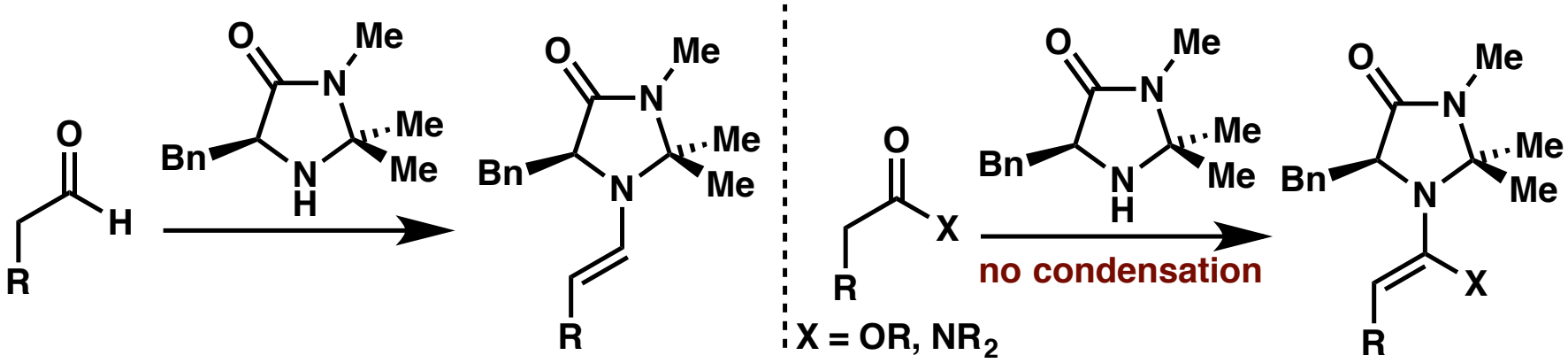
2) It is a **nucleophilic (HOMO-raised)** activation mode – it reacts with electrophiles.

3) It employs **primary and secondary amine Lewis base** organocatalysts and **enolisable aldehyde/ketone** substrates.

B. List *et al.*, *Chem. Rev.*, 2007, **107**, 5471.

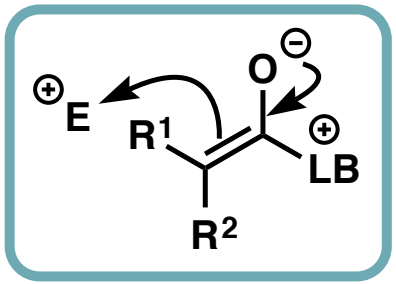
HOMO-Raising Catalysis Beyond Enamine Activation

- Enamine catalysis is extremely powerful, but it is primarily limited to **aldehyde and ketone** substrates and does not extend to esters, amides etc.



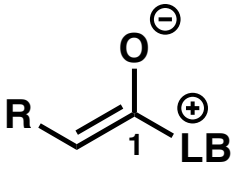
- There is an alternative way to generate chiral ester enolate equivalents, known as **enolate organocatalysis**.

Enolate Organocatalysis

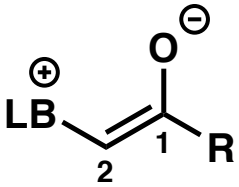


HOMO-Raising Catalysis Beyond Enamine Activation

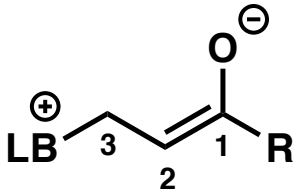
- Enolate organocatalysis is split into **three sub-classes** 3-subclasses:



C(1)-Enolate

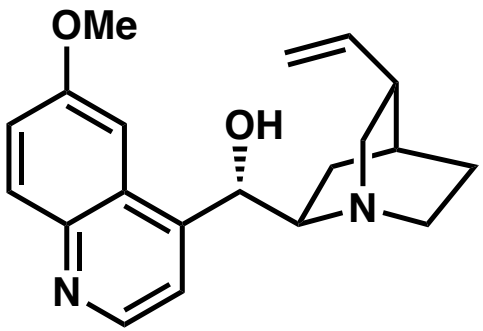


C(2)-Enolate

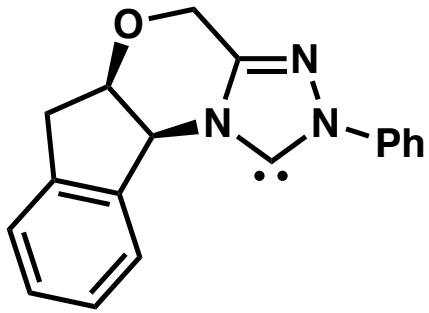


C(3)-Enolate

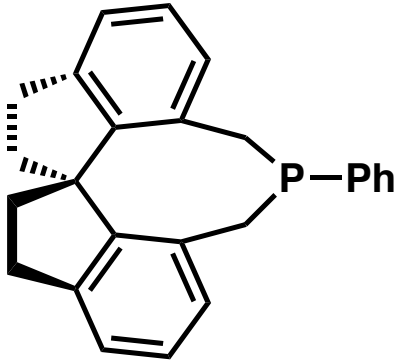
- A wide variety of **Lewis base organocatalysts** can be used to generate these species:



Tertiary Amines



N-Heterocyclic Carbenes



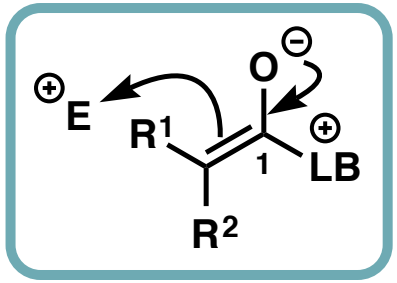
Phosphines

- We will consider the chemistry of each class of enolate in this lecture

C(1)-Enolate Organocatalytic Activation Mode

- **C(1)-enolates** are widely employed as chiral ester enolate equivalents:

C(1)-Enolate Activation Mode



- The C(1)-enolate activation mode has the following key characteristics:

1) It is a **covalent** activation mode – the catalyst is covalently bound to the substrate.

2) It is a **nucleophilic (HOMO-raised)** activation mode – it reacts with electrophiles.

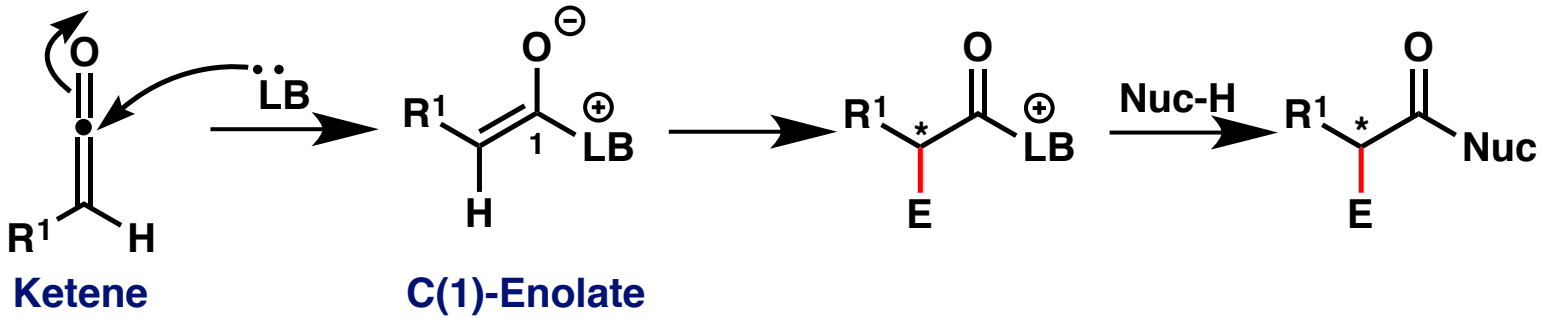
3) It employs **tertiary amine, phosphine and N-heterocyclic carbene Lewis base** organocatalysts

4) It can be accessed from a wide variety of electrophilic substrates including **ketenes, acid chlorides, carboxylic esters/acids etc.**

M. Gaunt *et al.*, *Chem. Rev.*, 2007, **107**, 5596.

Ketenes as Precursors for C(1)-Enolates

- **C(1)-enolates** can be accessed from ketene precursors:



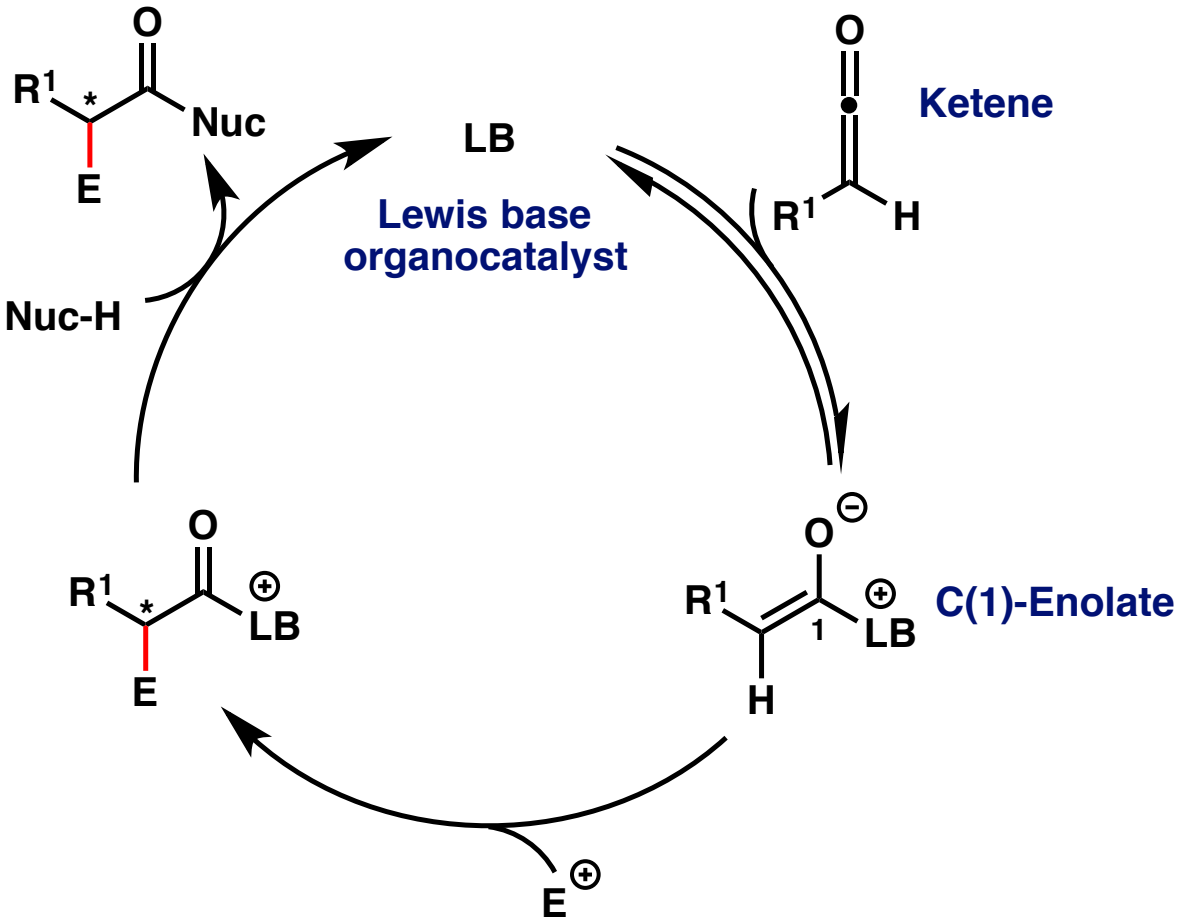
- Once generated, the C(1)-enolate can react with a variety of electrophiles at the **α-position**.

- Subsequent nucleophilic attack by an internal or external nucleophile accesses the product with regeneration of the catalyst.

- When the nucleophile is an alcohol or amine, this process amounts to a **formal α-functionalisation of esters or amides**.

C(1)-Enolate Organocatalysis – General Mechanism

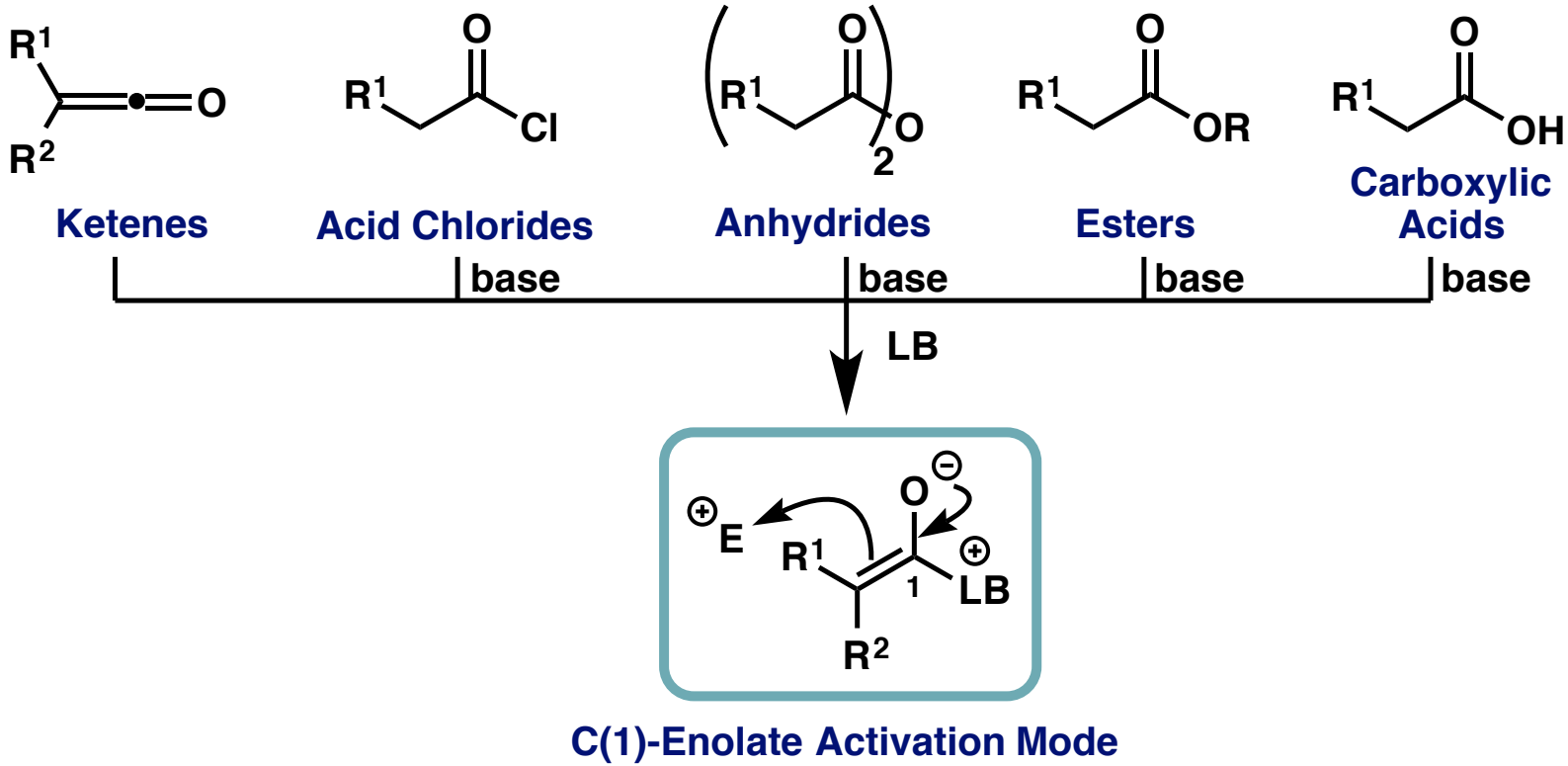
- We can draw the following catalytic cycle for C(1)-enolate organocatalysis:



- Remember that a variety of other substrates can serve as C(1)-enolate precursors.

C(1)-Enolate Organocatalysis – Precursors

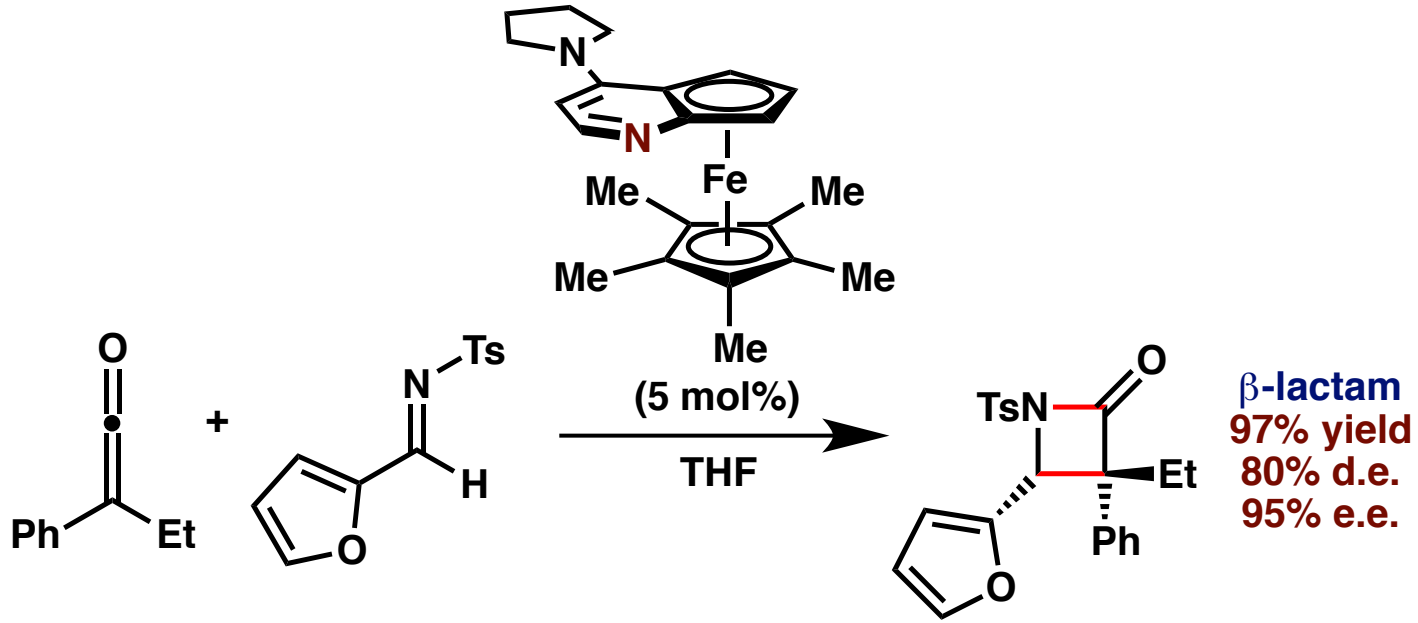
- A variety of electrophilic precursors can be used to access C(1)-enolates:



- Let's look at some specific examples.

C(1)-Ammonium Enolates

- Fu employed planar-chiral DMAP derivatives for enantioselective β-lactam synthesis:



- For this class of organocatalytic reaction we must be able to:

1) Identify how the organocatalyst **activates** the substrate (**activation mode**)

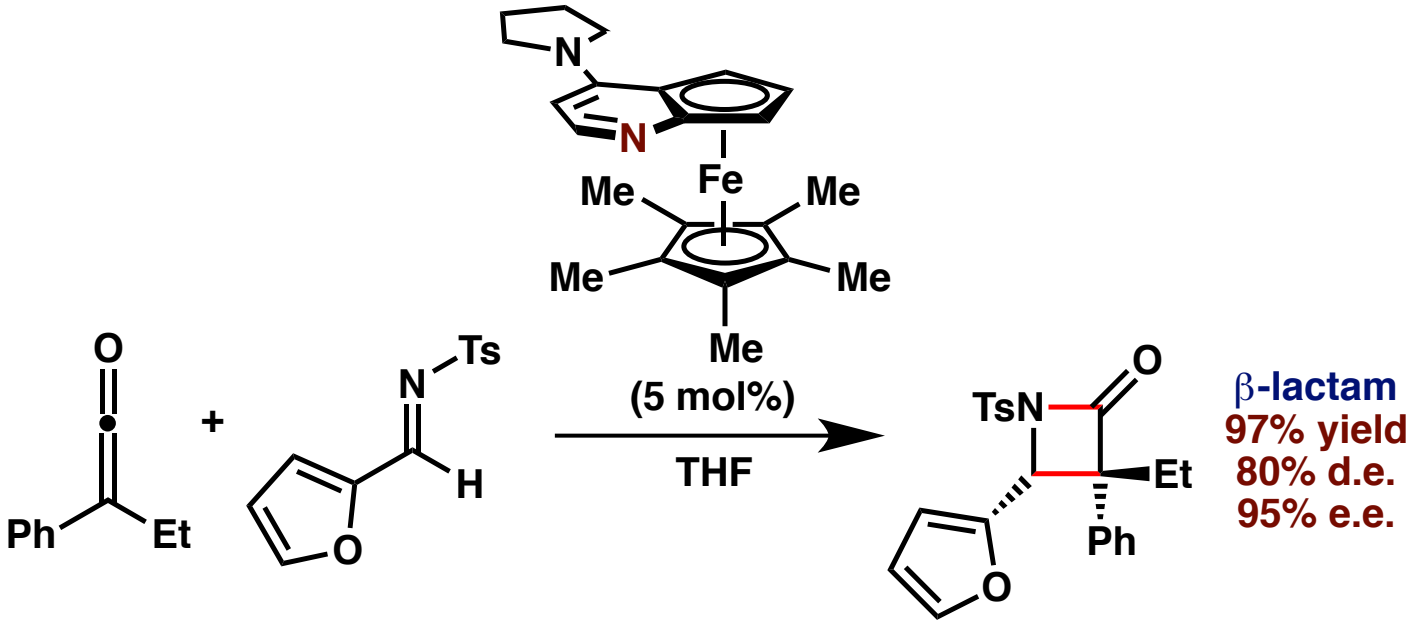
2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

3) To rationalise the **stereochemical outcome** of the reaction is beyond the scope of this course.

G. Fu *et al.*, *J. Am. Chem. Soc.*, 2002, **124**, 1578

C(1)-Ammonium Enolates

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

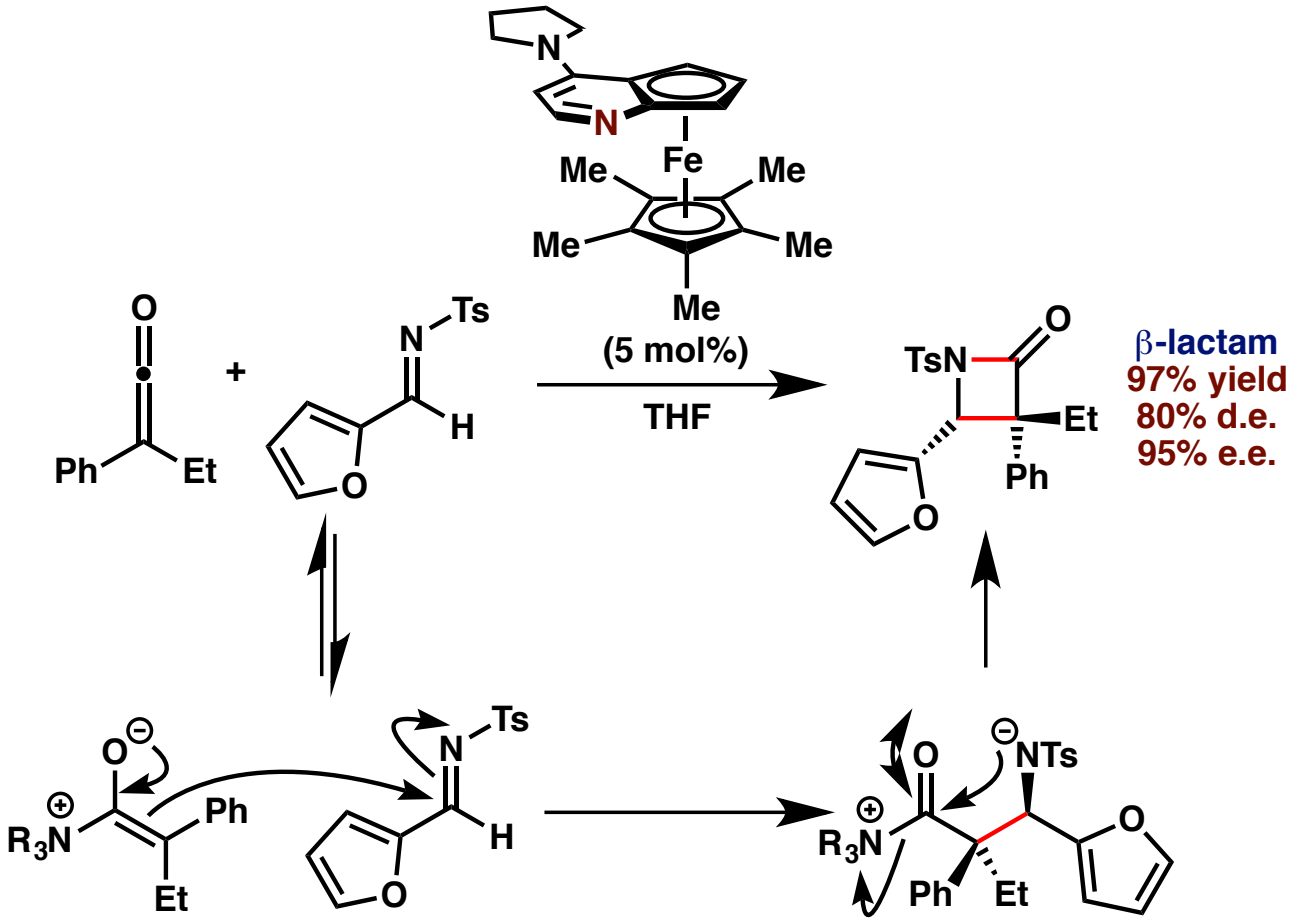
1) A **tertiary amine Lewis base** organocatalyst is used

2) One reactant is a **ketene** and the other contains an **imine** functional group.

- This reaction proceeds *via* the **C(1)-ammonium enolate** activation mode.

C(1)-Ammonium Enolates

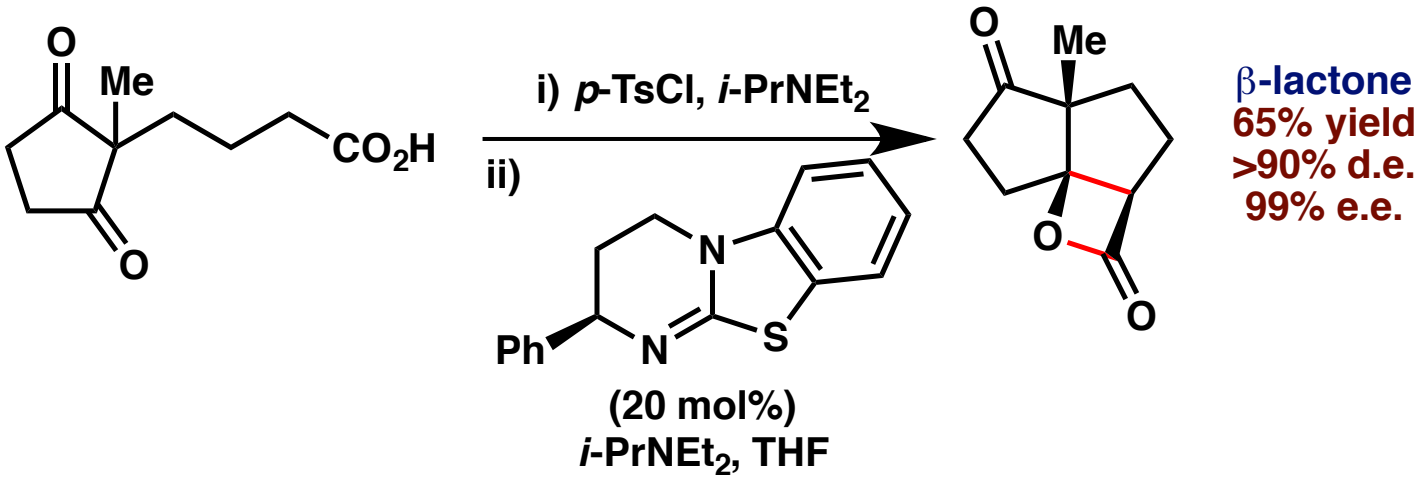
- Now let's consider the **curly arrow pushing mechanism**:



- You will not be expected to explain the diastereo- or enantioselectivity of this process.

C(1)-Ammonium Enolates

- **Carboxylic acids** are also useful **C(1)-ammonium enolate** precursors:



- For this class of organocatalytic reaction we must be able to:

1) Know how the organocatalyst **activates** the substrate (**activation mode**)

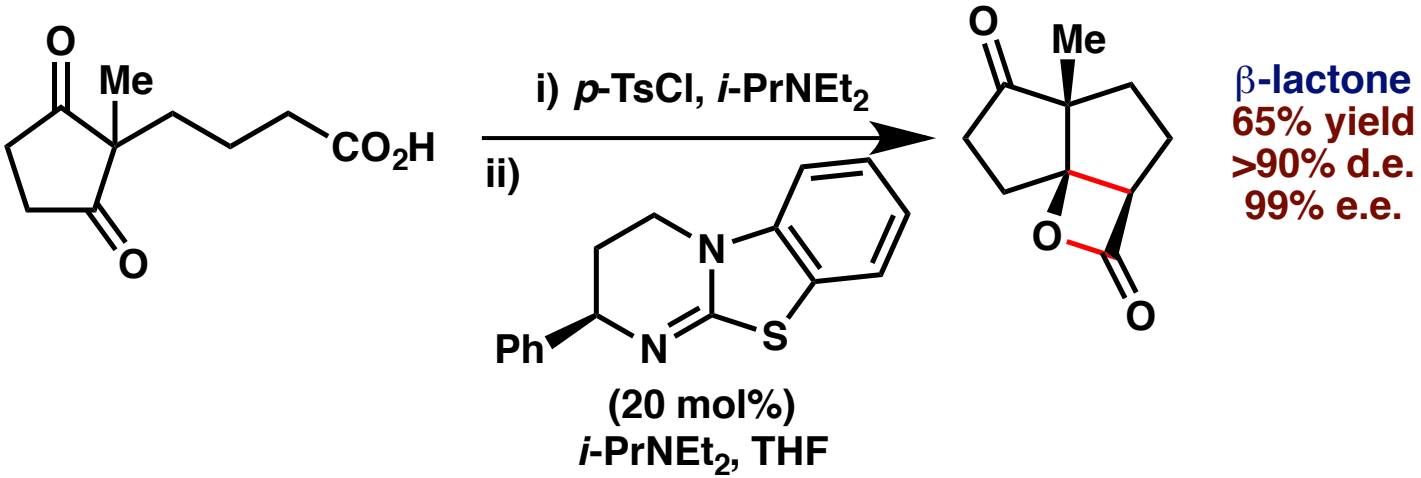
2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

3) To rationalise the **stereochemical outcome** of the reaction is beyond the scope of this course.

D. Romo *et al.*, *J. Am. Chem. Soc.*, 2012, **134**, 13348

C(1)-Ammonium Enolates

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

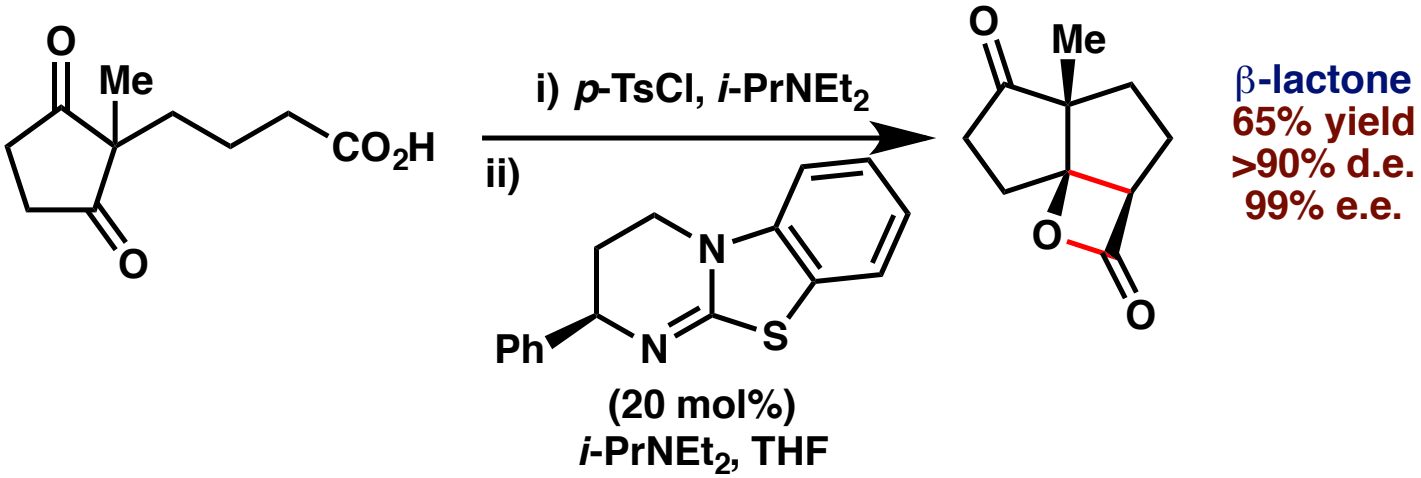
1) A **tertiary amine Lewis base** organocatalyst is used

2) The substrate contains a **carboxylic acid** and two **ketone** functional groups. The first step of the reaction is to **activate the carboxylic acid**.

- This reaction proceeds *via* the **C(1)-ammonium enolate** activation mode.

C(1)-Ammonium Enolates

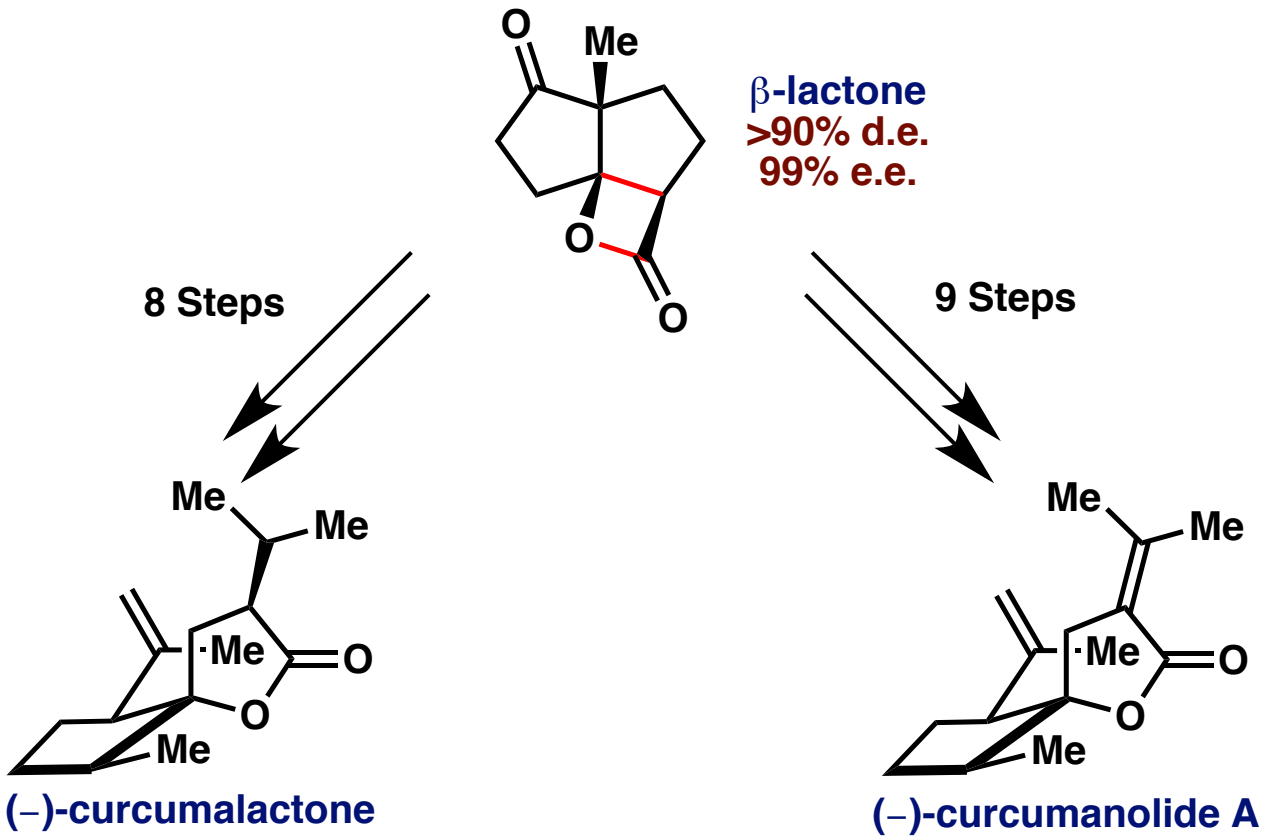
- Now let's consider the **curly arrow pushing mechanism**:



- You should be able to draw a curly arrow pushing mechanism for the activation step also but are not expected to rationalise the stereochemical outcome.

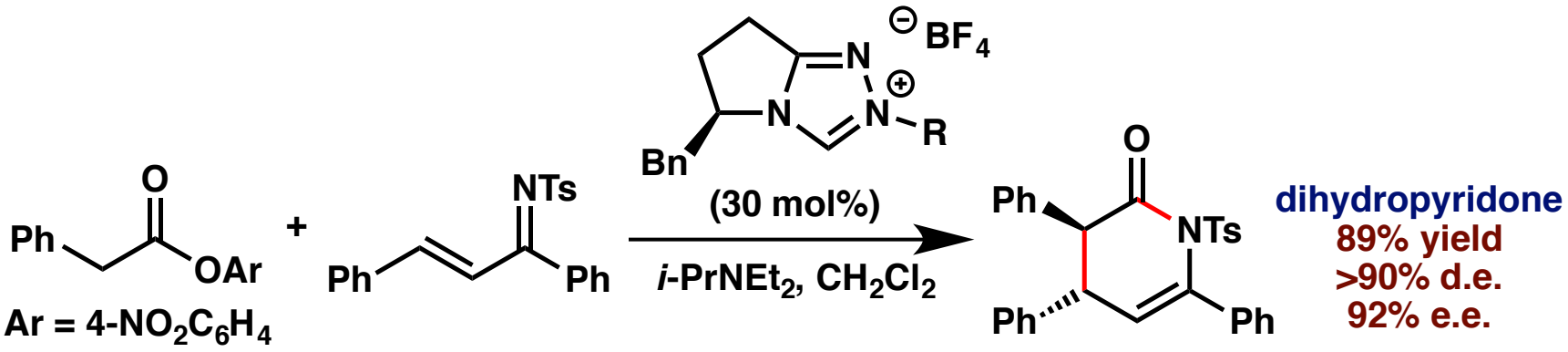
Application Towards Natural Product Synthesis

- Romo elaborated this product to (−)-cucumalacatone and (−)-curcimanolide A over 9 and 8 steps respectively:



C(1)-Azolium Enolates

- Chi has reported the use of **N-heterocyclic carbenes** for activation of **carboxylate esters**:



- For this class of organocatalytic reaction we must be able to:

1) Know how the organocatalyst **activates** the substrate (**activation mode**)

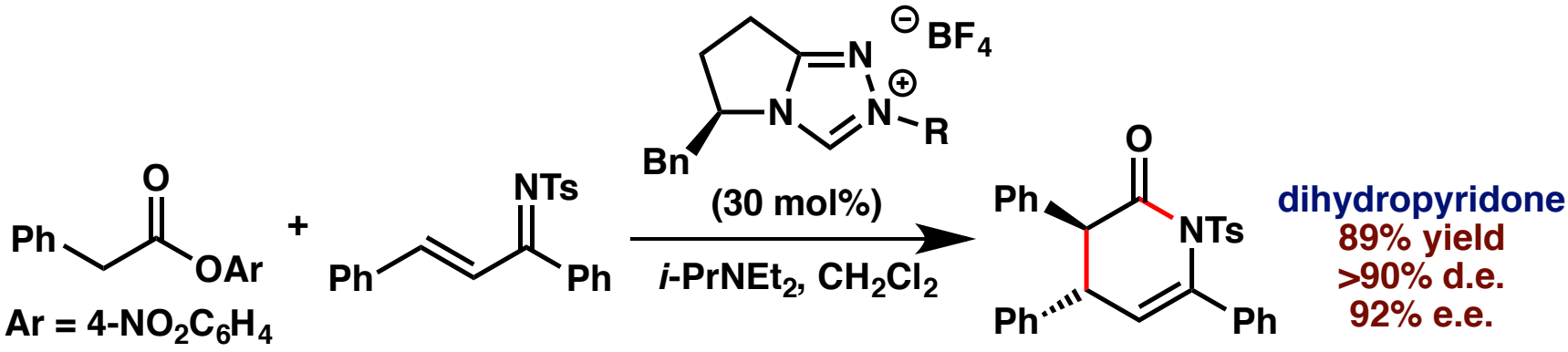
2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

3) To rationalise the **stereochemical outcome** of the reaction is beyond the scope of this course.

Y. R. Chi *et al.*, *Org. Lett.*, 2012, **14**, 2154

C(1)-Azolium Enolates

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

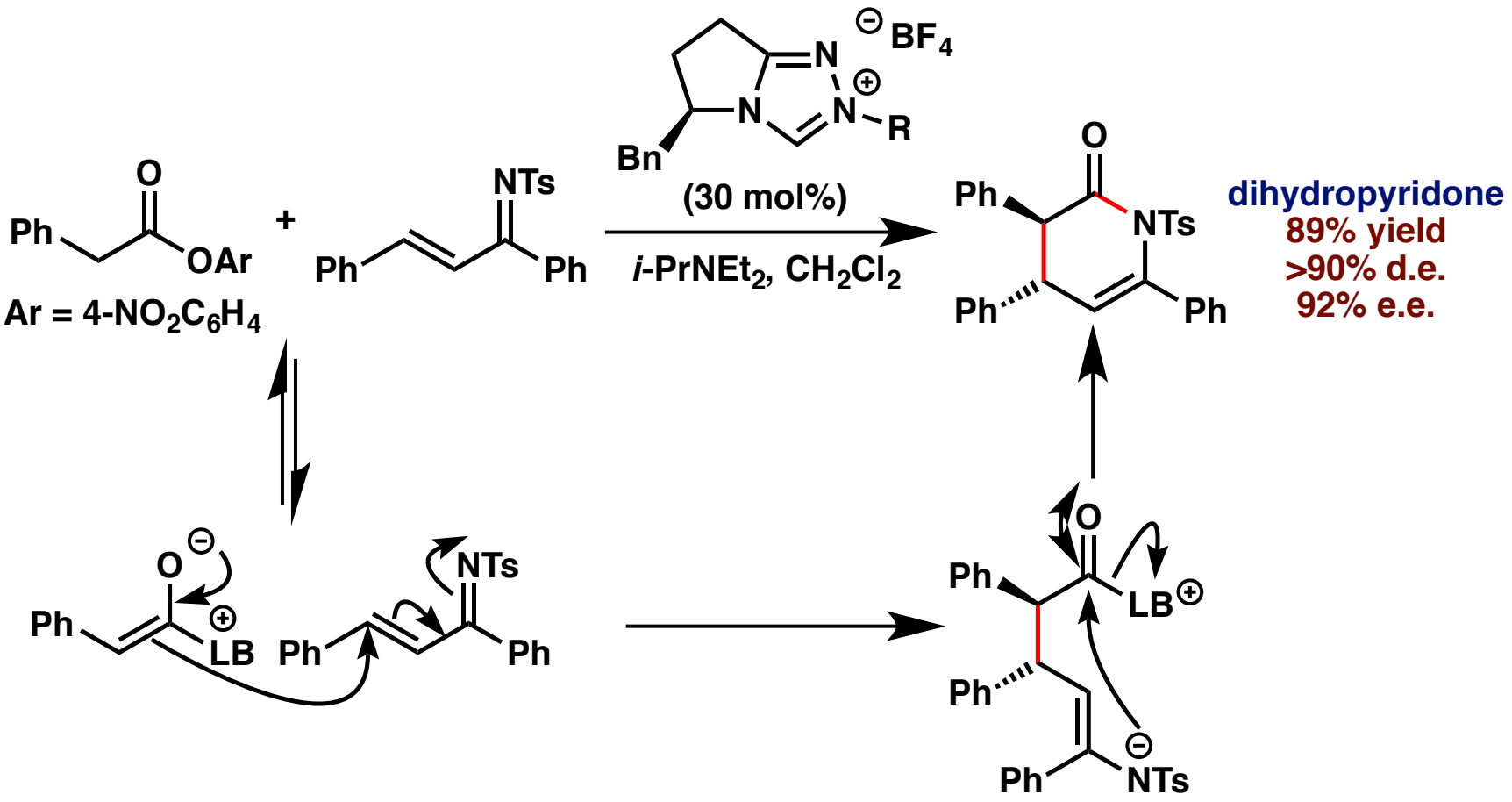
1) A **N-heterocyclic carbene Lewis base** organocatalyst is used

2) One reactant is a **carboxylic ester** and the other contains an **α,β-unsaturated imine** functional group.

- This reaction proceeds *via* the **C(1)-azolium enolate** activation mode.

C(1)-Azolium Enolates

- Now let's consider the **curly arrow pushing mechanism**:

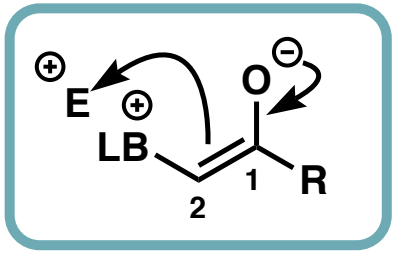


- You will not be expected to explain the diastereo- or enantioselectivity of this process.

C(2)-Enolate Organocatalytic Activation Mode

- **C(2)-enolates** are also employed as chiral nucleophilic intermediates:

C(2)-Enolate Activation Mode



- The C(2)-enolate activation mode has the following key characteristics:

1) It is a **covalent** activation mode – the catalyst is covalently bound to the substrate.

2) It is a **nucleophilic (HOMO-raised)** activation mode – it reacts with electrophiles.

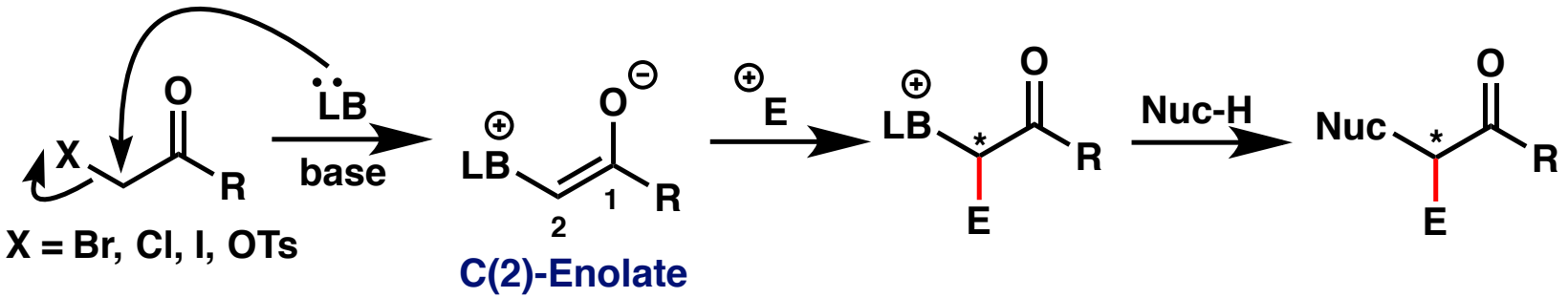
3) It employs mainly **tertiary amine Lewis base** organocatalysts

4) It is commonly accessed from **α-halo carbonyl compounds**.

M. Gaunt *et al.*, *Chem. Rev.*, 2007, **107**, 5596.

Precursors for C(2)-Enolates

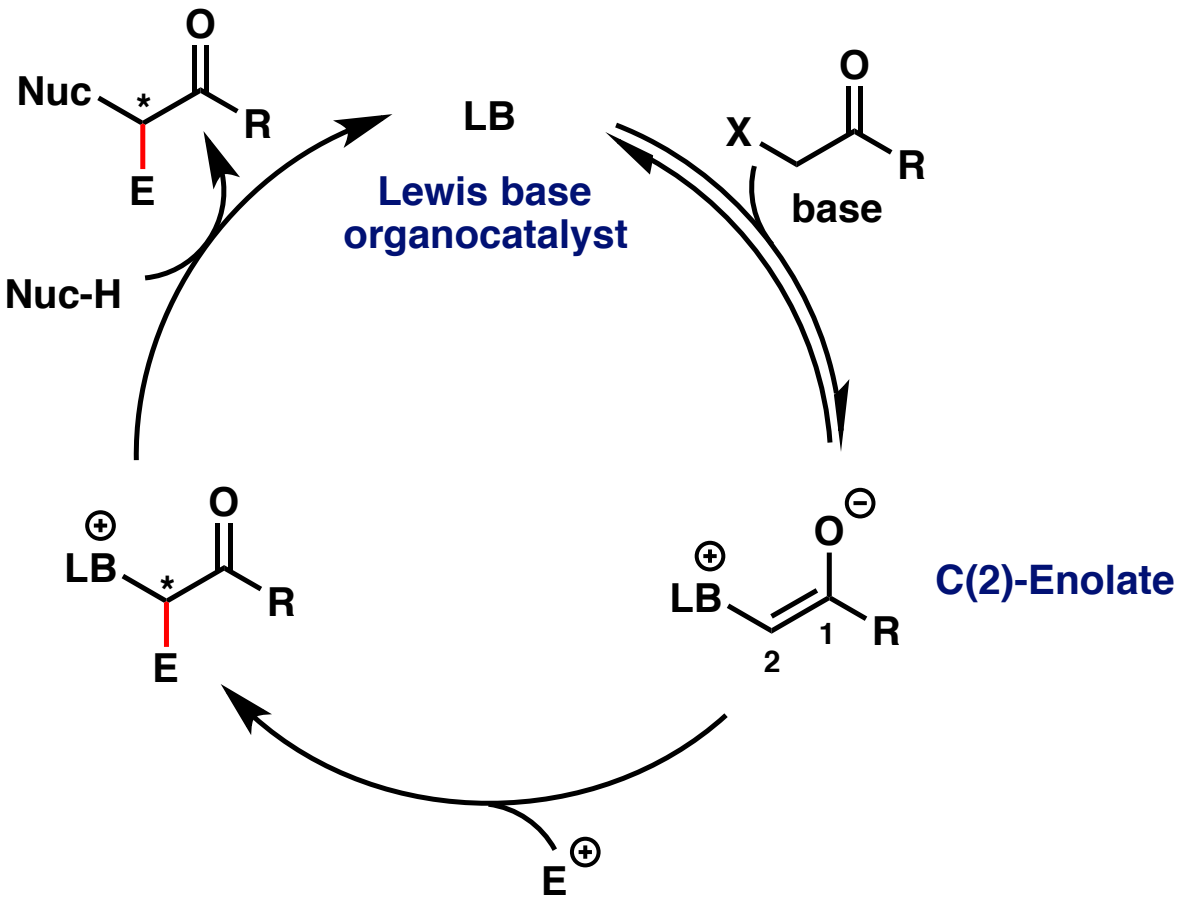
- **C(2)-enolates** are commonly accessed from **α-halo carbonyl compounds**:



- Once generated, the C(2)-enolate can react with a variety of electrophiles at the **α-position**.
- Subsequent nucleophilic attack by an internal or external nucleophile accesses the product with regeneration of the catalyst.
- When an **internal nucleophile** is used, this results in ring-forming reactions.

C(2)-Enolate Organocatalysis – General Mechanism

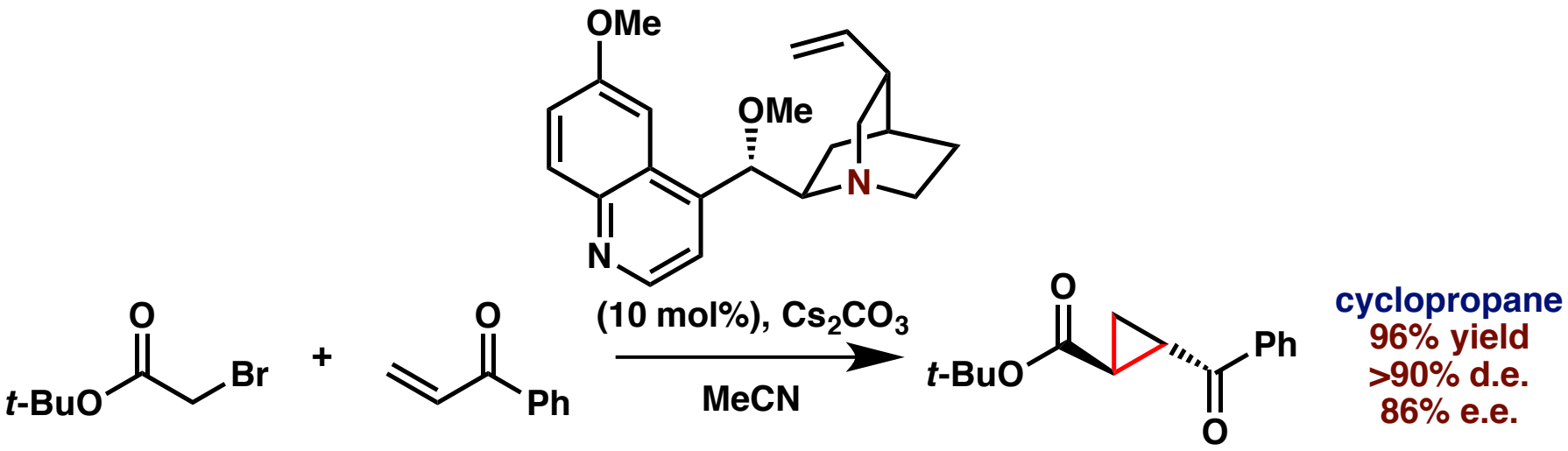
- We can draw the following catalytic cycle for C(2)-enolate organocatalysis:



- Let's consider a specific example.

C(2)-Ammonium Enolates

- Gaunt employed cinchona alkaloid-derived organocatalysts for enantioselective cyclopropanation



- For this class of organocatalytic reaction we must be able to:

1) Know how the organocatalyst **activates** the substrate (**activation mode**)

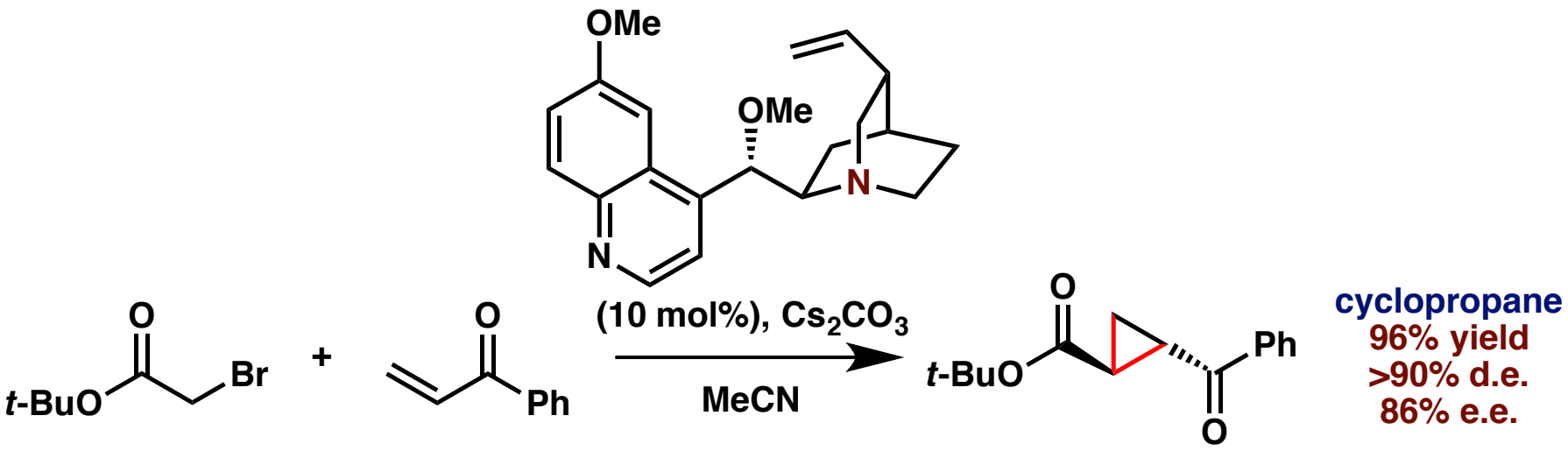
2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

3) To rationalise the **stereochemical outcome** of the reaction is beyond the scope of this course.

M. Gaunt *et al.*, *Chem. Rev.*, 2007, **107**, 5596.

C(2)-Ammonium Enolates

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

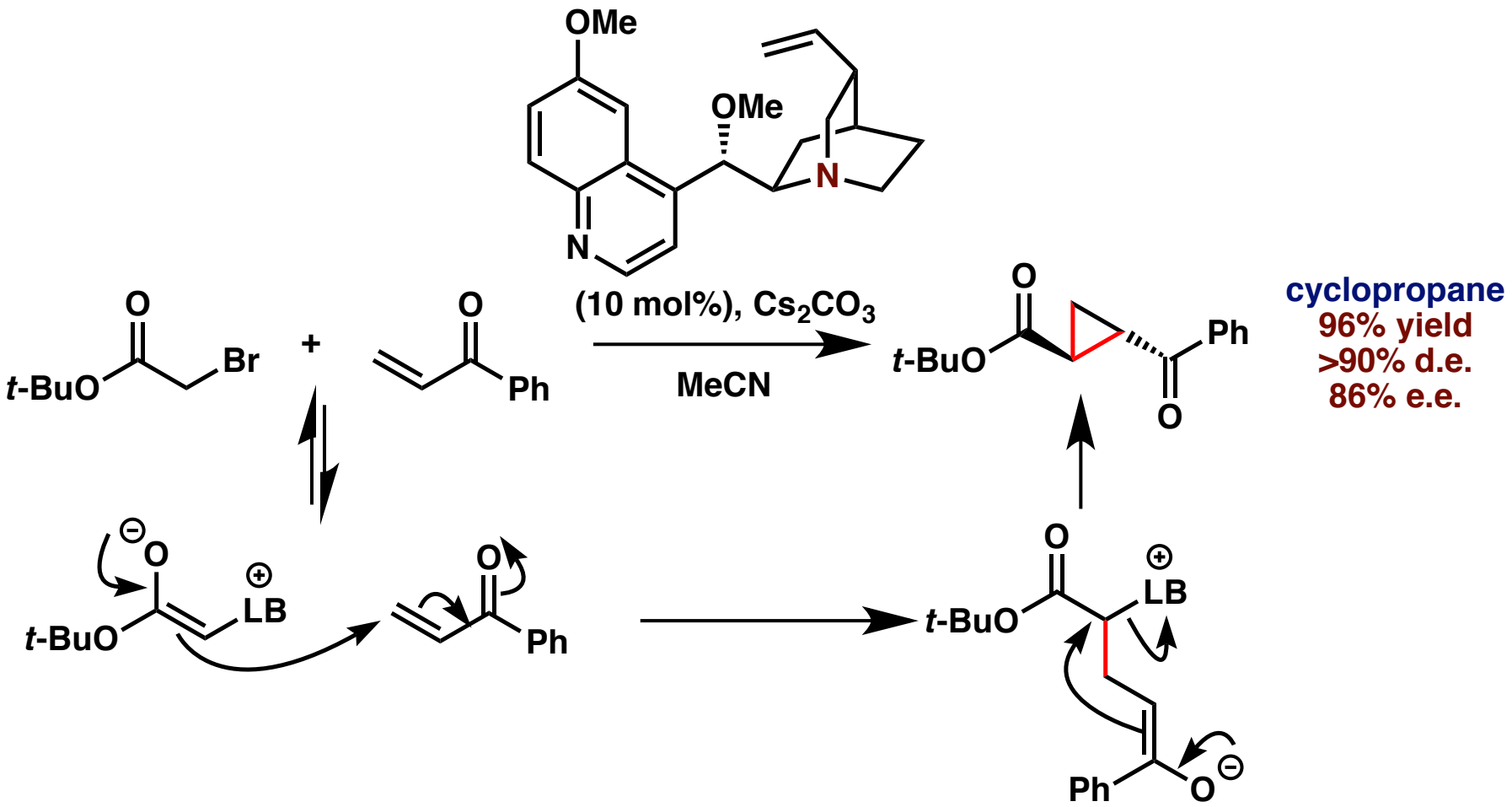
1) A **tertiary amine Lewis base** organocatalyst is used

2) One reactant is an **α-halo carbonyl compound** and the other is an **enone**.

- This reaction proceeds *via* the **C(2)-ammonium enolate** activation mode.

C(2)-Ammonium Enolates

- Now let's consider the **curly arrow pushing mechanism**:

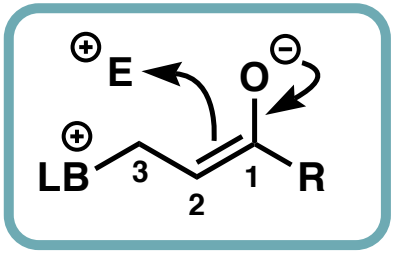


- You will not be expected to explain the diastereo- or enantioselectivity of this process.

C(3)-Enolate Organocatalytic Activation Mode

- **C(3)-enolates** are also employed as chiral nucleophilic intermediates:

C(3)-Enolate Activation Mode



- The C(3)-enolate activation mode has the following key characteristics:

1) It is a **covalent** activation mode – the catalyst is covalently bound to the substrate.

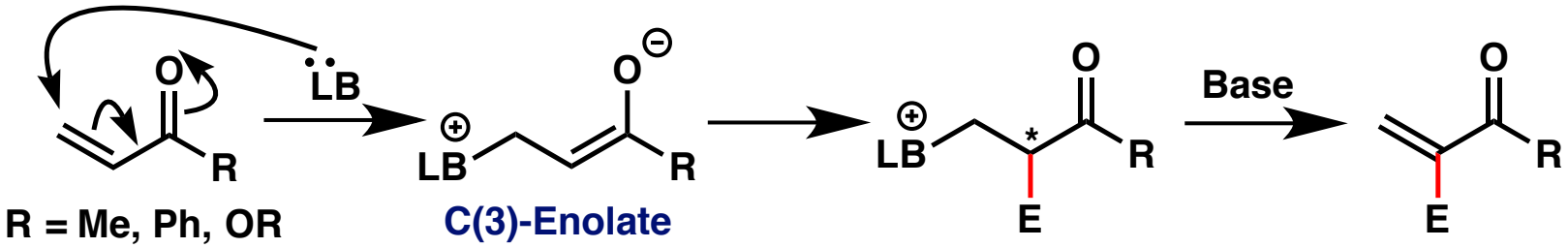
2) It is a **nucleophilic (HOMO-raised)** activation mode – it reacts with electrophiles.

3) It employs mainly **tertiary amine and phosphine Lewis base** organocatalysts

4) It is commonly accessed from **α,β-unsaturated carbonyl compounds**.

Precursors for C(3)-Enolates

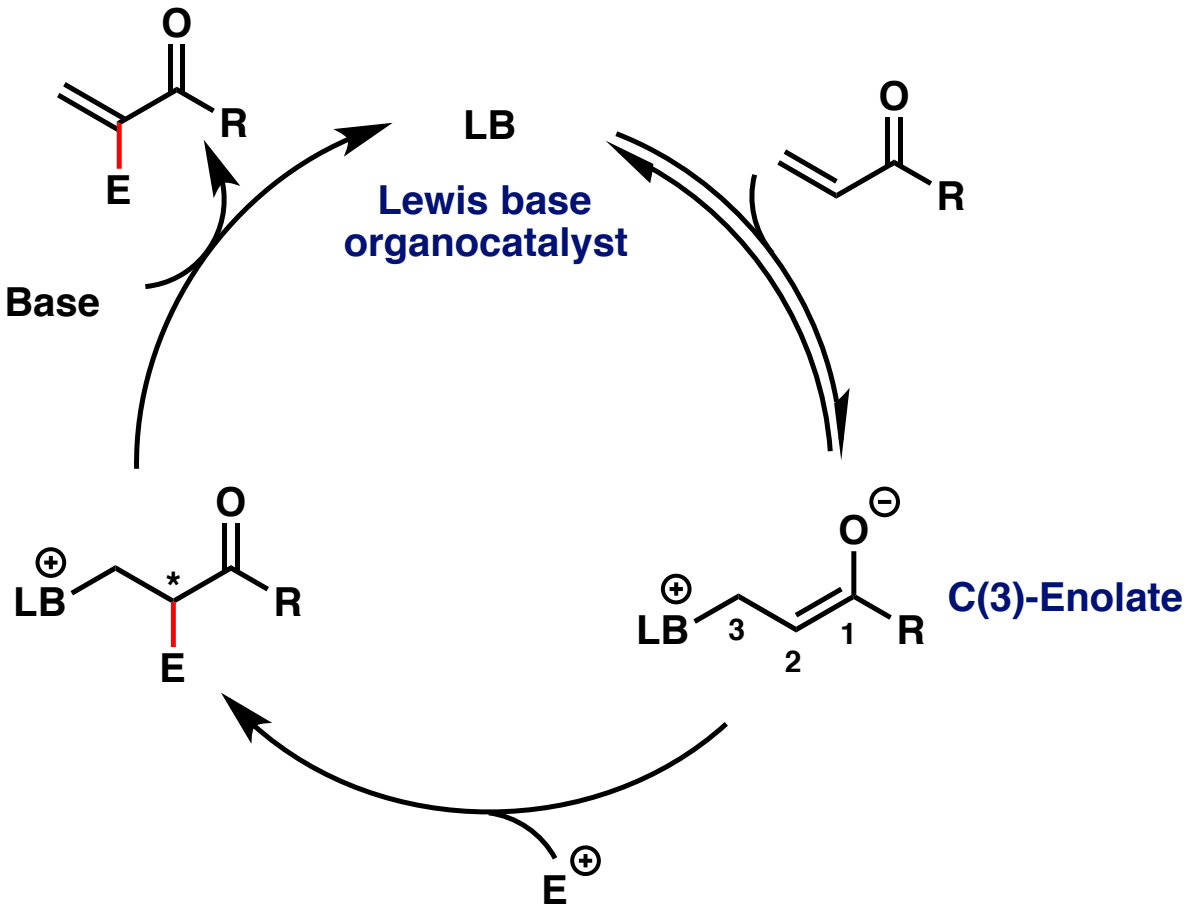
- **C(3)-enolates** are commonly accessed from **α,β-unsaturated carbonyl compounds**:



- Once generated, the C(3)-enolate can react with a variety of electrophiles at the **α-position**.
- Subsequent elimination accesses the product with regeneration of the catalyst.
- The most common reaction of C(3)-enolates is with aldehydes or imine – **the (aza)-Morita-Baylis-Hillman reaction.**

C(3)-Enolate Organocatalysis – General Mechanism

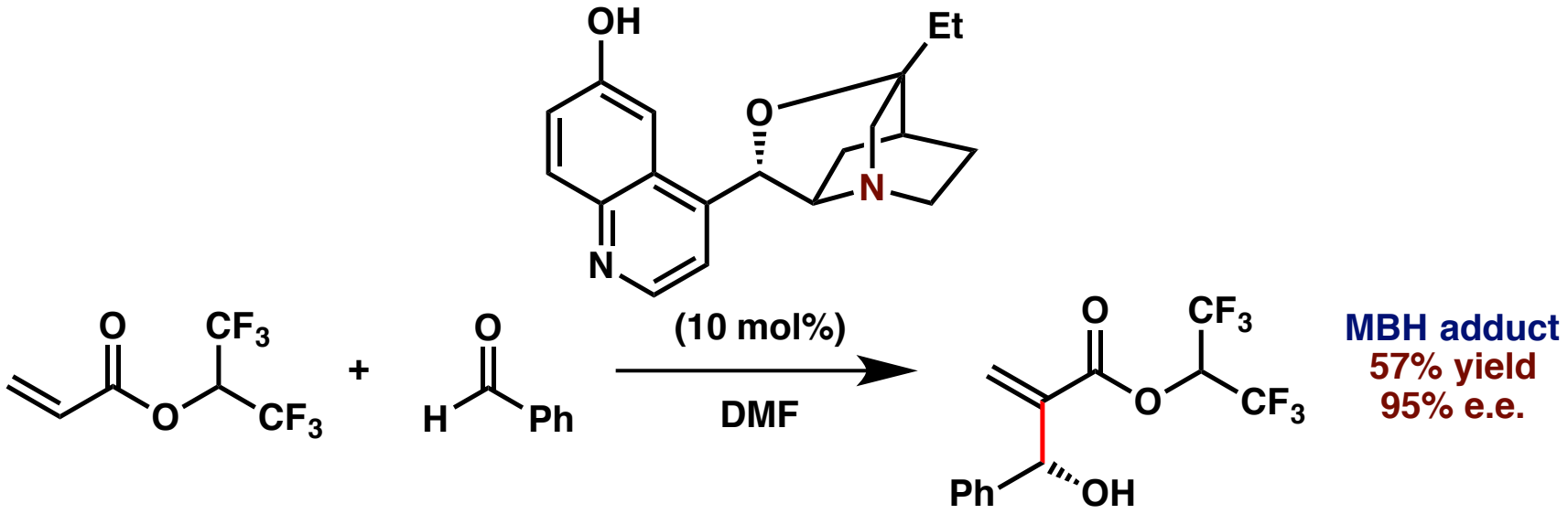
- We can draw the following catalytic cycle for C(3)-enolate organocatalysis:



- Let's consider a specific example.

C(3)-Ammonium Enolates

- Hatakeyama employed the cinchona alkaloid-derived organocatalyst, β-isocupreidine, for the enantioselective Morita-Baylis-Hillman reaction.



- For this class organocatalytic reaction we must be able to:

1) Know how the organocatalyst **activates** the substrate (**activation mode**)

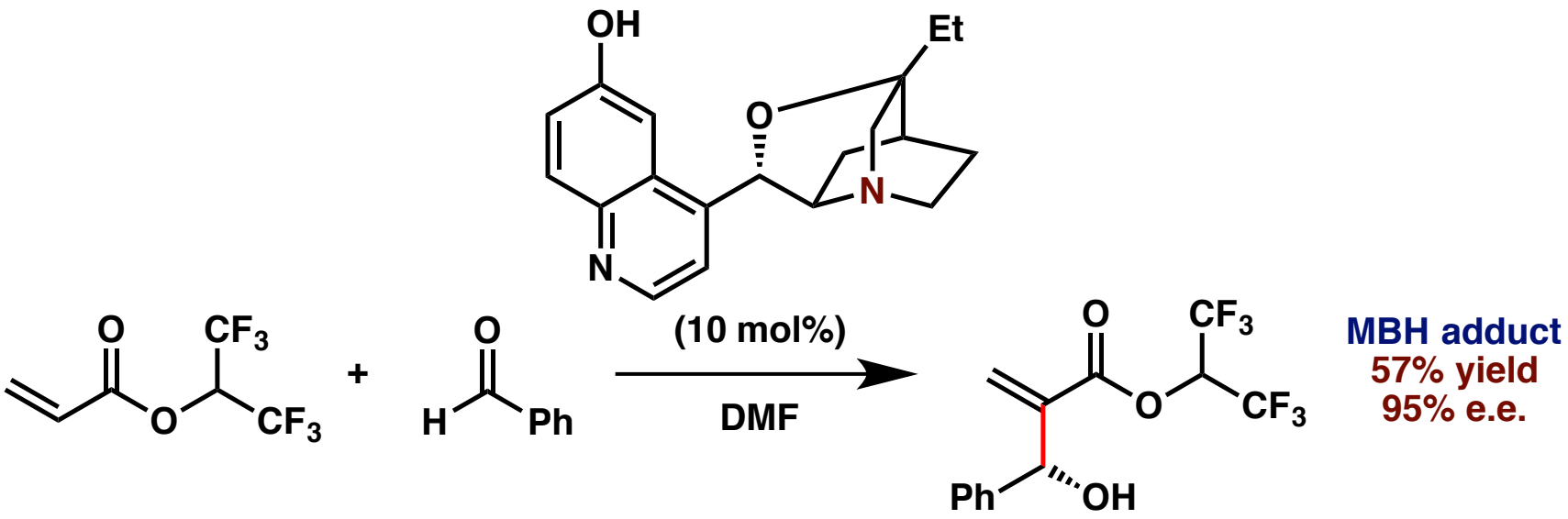
2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

3) To rationalise the **stereochemical outcome** of the reaction is beyond the scope of this course.

S. Hatakeyama *et al.*, J. Am. Chem. Soc., 1999, **121**, 10219.

C(3)-Ammonium Enolates

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

1) A **tertiary amine Lewis base** organocatalyst is used

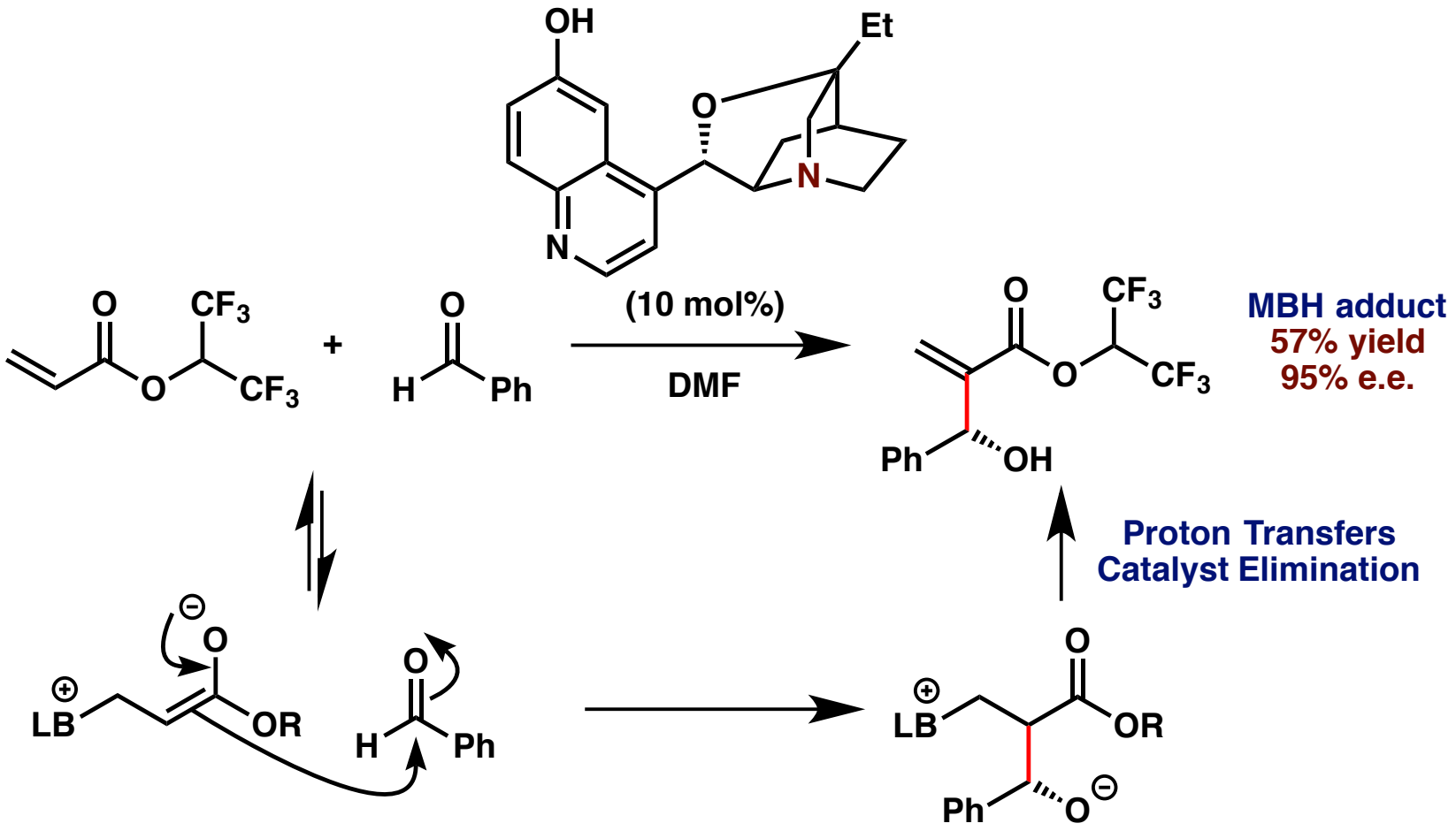
2) One reactant is an **α,β-unsaturated carbonyl compound,** the other is an **aldehyde**.

- This reaction proceeds *via* the **C(3)-ammonium enolate** activation mode.

S. Hatakeyama *et al.*, J. Am. Chem. Soc., 1999, **121**, 10219.

C(3)-Ammonium Enolates

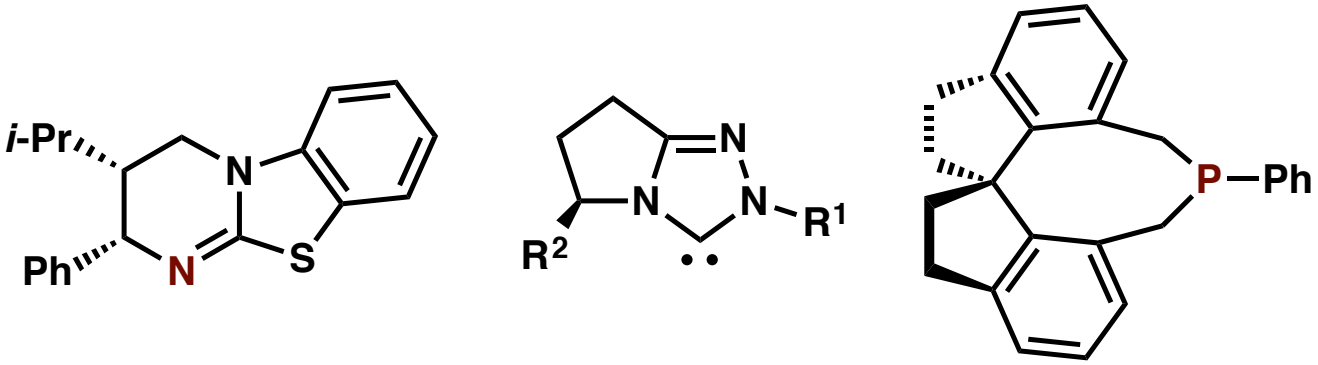
- Now let's consider the **curly arrow pushing mechanism**:



- You will not be expected to explain the enantioselectivity of this process.

Enolate Organocatalysis Cheat Sheet

- For enolate organocatalysis, you must remember the following key information:
- C(1)-, C(2)- and C(3)-enolates are typically accessed using **tertiary amines, N-heterocyclic carbenes and phosphines**.



- C(1)-, C(2)- and C(3)-enolates are generated from **ketenes (and others)**, **α-halo carbonyl** compounds and **α,β-unsaturated carbonyl** compounds respectively.
- You will be expected to be able to identify the specific **organocatalytic activation mode** involved in a given reaction and provide a **curly arrow pushing mechanism**.
- Rationalising the stereochemical outcome of reactions involving organocatalytic enolates is beyond the scope of this course.

M. Gaunt *et al.*, *Chem. Rev.*, 2007, **107**, 5596.

Lecture 2: HOMO-Raising Organocatalysis

Key learning objectives:

- The enamine organocatalytic activation mode (part 2): Bifunctional vs. steric control; synthesis and reactivity of imidazolidinone and diarylprolinol silyl ether organocatalysts.

- Dienamine organocatalytic activation mode.

- Alternative HOMO-raising organocatalytic activation modes.

- C(1)-, C(2)- and C(3)-enolate activation modes: definition; general catalytic cycle; various intra- and intermolecular functionalisation reactions; curly arrow pushing mechanisms.

Lecture 2 Revision

To reinforce your understanding of the contents of this lecture, please refer to:

- *Organic Chemistry 2nd Ed.* (J. Clayden, N. Greeves and S. Warren, Oxford University Press, 2012, ISBN 978-0-19-927029-3). Chapter 41 is particularly relevant.
- *New Frontiers in Asymmetric Catalysis* (K. Mikami and M. Lautens, Wiley, 2007). Downloadable from University Network. DOI: 10.1002/0470098007
- *Catalytic Asymmetric Synthesis 3rd Ed.* (I. Okima, Wiley, 2010). Downloadable from University Network. DOI: 10.1002/9780470584248
- *Prof. MacMillan Short-Course:* www.princeton.edu/chemistry/macmillan/research/
- Leading review articles on enamine catalysis (*Chem. Rev.*, 2007, **107**, 5471) and enolate catalysis (*Chem. Rev.*, 2007, **107**, 5596).
- CH3404 Feedback Workshop

CH3404 Asymmetric Synthesis of Pharmaceuticals and Natural Products LCM Lecture 3

Dr Louis C. Morrill
School of Chemistry, Cardiff University
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Lecture 3: LUMO-Lowering Organocatalysis

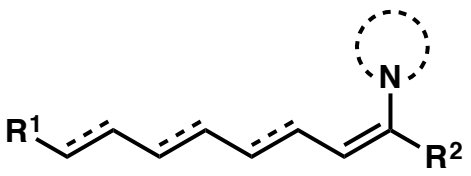
Key learning objectives:

- Traditional LUMO lowering of carbonyl compounds using Lewis acids.
- The iminium organocatalytic activation mode: definition; general catalytic cycle; various intra- and intermolecular functionalisation reactions; curly arrow pushing mechanisms; stereochemical rationale.
- Iminium-enamine organocatalytic cascades.
- Alternative LUMO-lowering organocatalytic activation modes.
- Acyl cation organocatalytic activation mode: acyl ammonium/azolium intermediates; definition; general catalytic cycle; various intra- and intermolecular functionalisation reactions; curly arrow pushing mechanisms.
- α,β-Unsaturated acyl ammonium/azolium activation modes: definition; general catalytic cycle; various intra- and intermolecular functionalisation reactions; curly arrow pushing mechanisms.

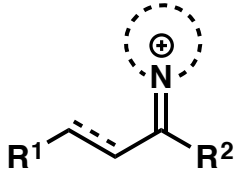
An Overview of Organocatalysis

- Organocatalysis is now a thoroughly established member of the synthetic toolbox, with a large number of **generic activation modes** known.

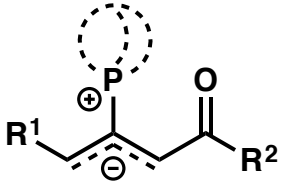
Covalent Activation Modes



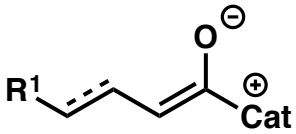
Enamine (di-, tri-, tetra-enamine) Catalysis



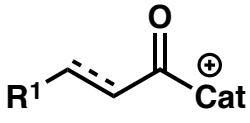
Iminium Catalysis



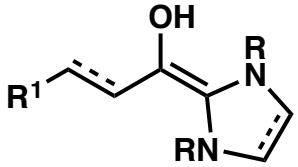
Phosphine Catalysis



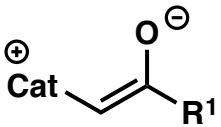
C(1)-Enolate (di-enolate) Catalysis



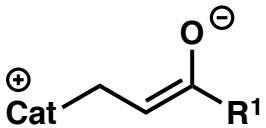
Acyl ammonium/azolium Catalysis



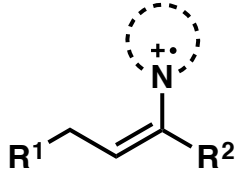
N-Heterocyclic Carbene Catalysis



C(2)-Enolate Catalysis

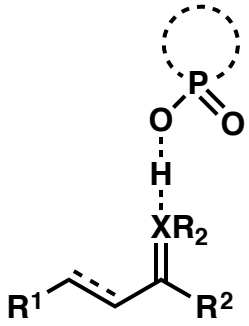


C(3)-Enolate Catalysis

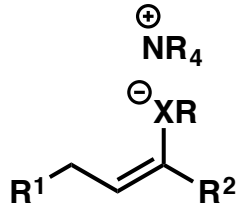


SOMO Catalysis

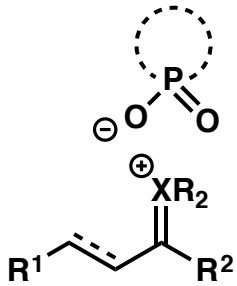
Non-Covalent Activation Modes



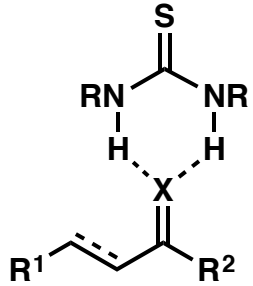
Brønsted Acid Catalysis



Phase-transfer Catalysis



Chiral Anion Catalysis



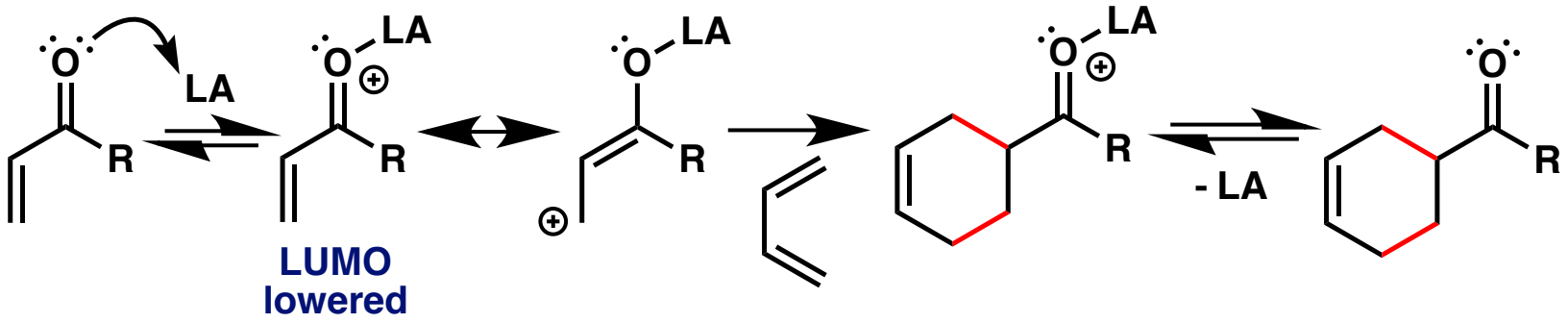
Hydrogen Bonding Catalysis

- Today we will focus on **LUMO-lowering organocatalysis**.

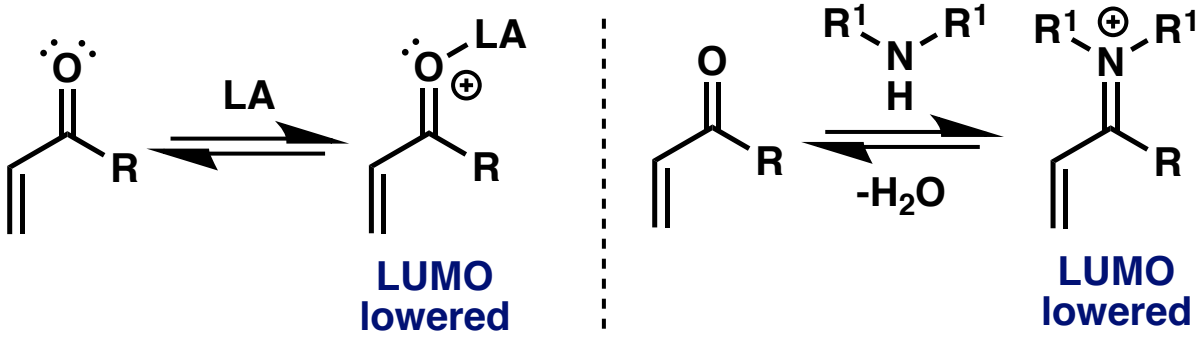
For an excellent overview see D. Romo *et al.*, *Nat. Prod. Rep.*, 2014, **31**, 1318.

LUMO-Lowering of Carbonyl Compounds

- Lewis acid catalysis typically involves the activation of a substrate towards nucleophilic attack by lowering the **LUMO** component of the electrophile with respect to the **HOMO** component of the nucleophile:



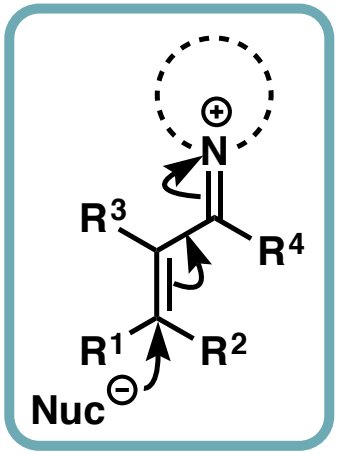
- MacMillan postulated that amines could function as catalysts that traditionally employ Lewis acids:



Iminium Organocatalysis

- Let's now focus on another important activation mode – **iminium catalysis**.

Iminium Organocatalysis



- The iminium activation mode has the following key characteristics:

1) It is a **covalent** activation mode – the catalyst is covalently bound to the substrate.

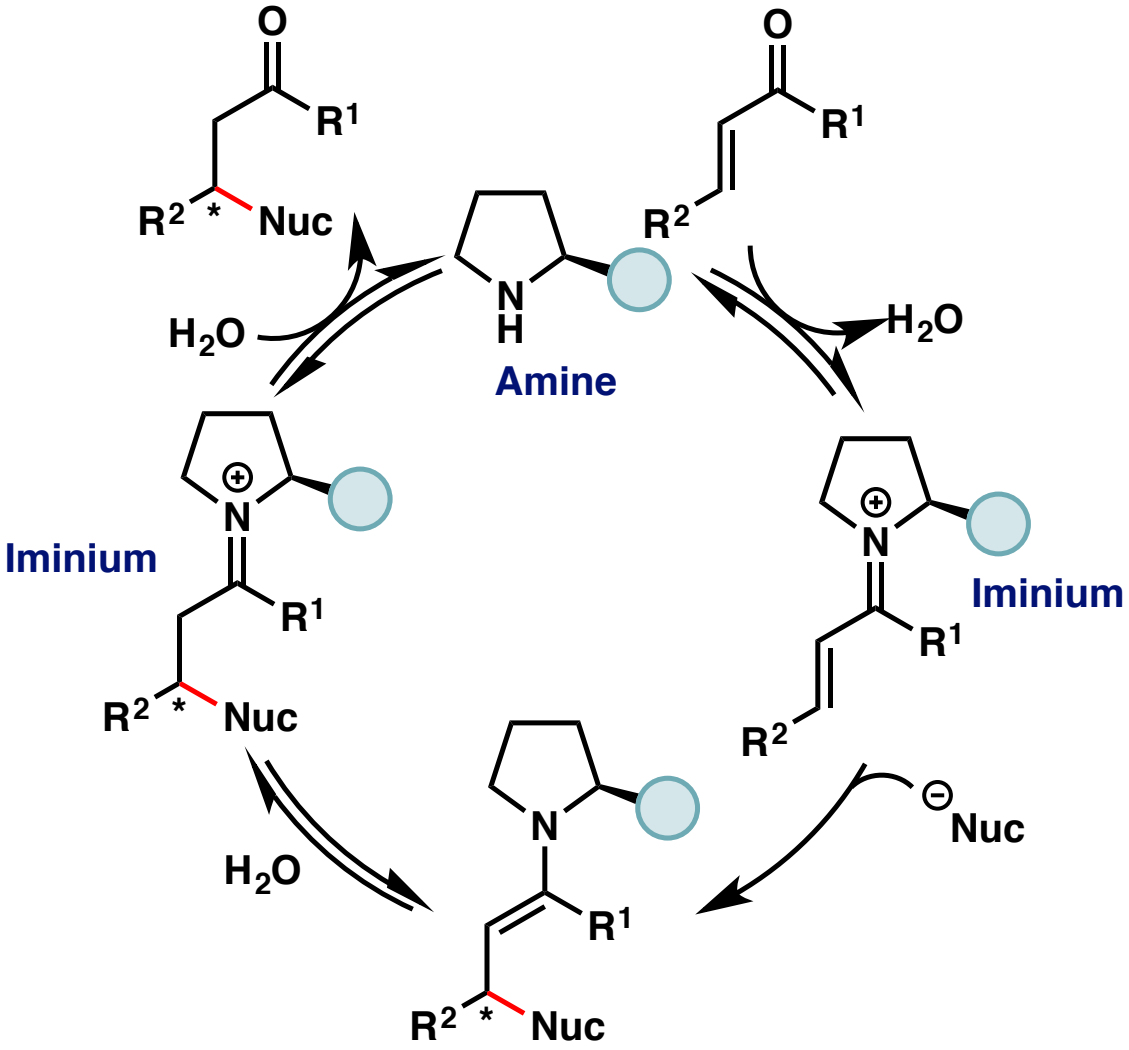
2) It is an **electrophilic (LUMO-lowered)** activation mode – it reacts with nucleophiles.

3) It employs **primary and secondary amine Lewis base** organocatalysts and **α,β-unsaturated aldehyde/ketone** substrates.

P. M. Pihko *et al.*, *Chem. Rev.*, 2007, **107**, 5416.

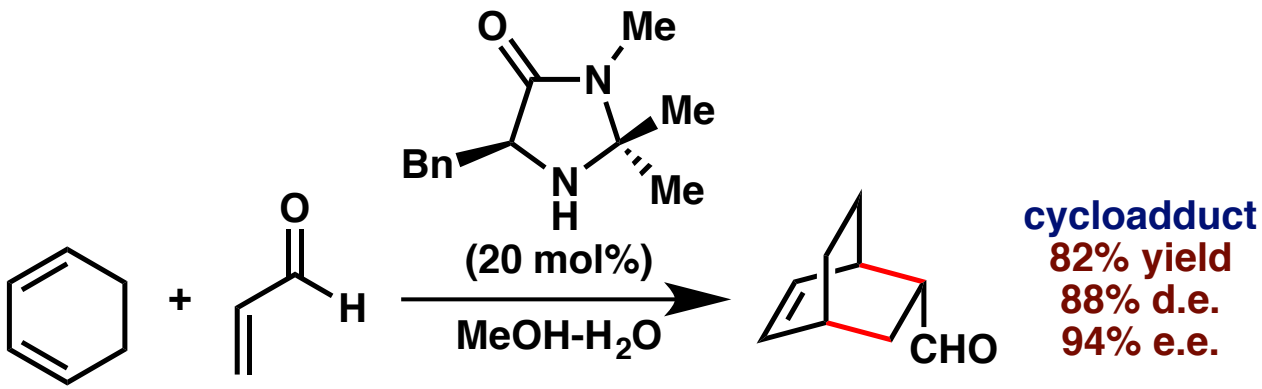
Iminium Organocatalysis – General Mechanism

- We can imagine using a chiral secondary amine for **asymmetric** organocatalysis



Iminium Organocatalysis

- Let's revisit the pioneering work of D. W. C. MacMillan who reported the first enantioselective organocatalytic Diels-Alder reaction in 2000:



- For this class of organocatalytic reaction we must be able to:

1) Know how the organocatalyst **activates** the substrate (**activation mode**)

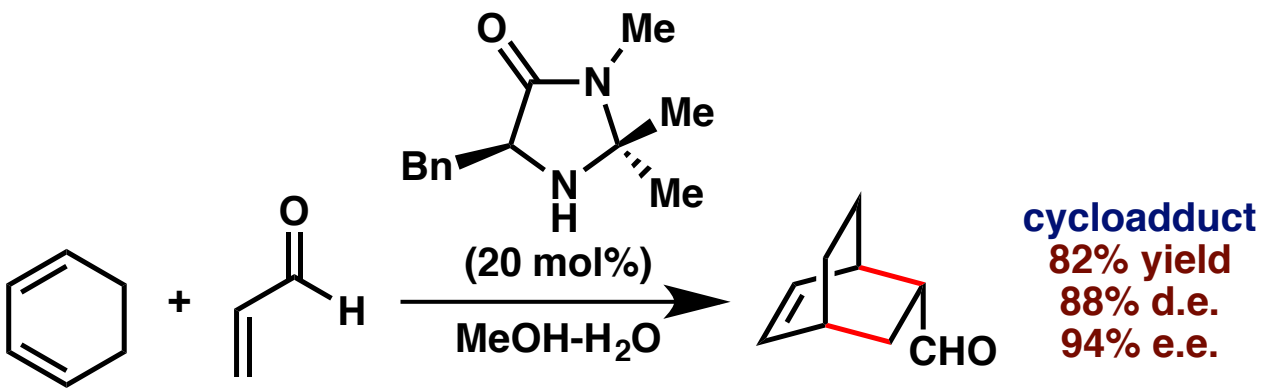
2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

3) Rationalise the **stereochemical outcome** of the reaction (both diastereo- and enantiocontrol are relevant in this case) by drawing an appropriate transition state.

D. W. C. MacMillan *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 4243.

Enantioselective Organocatalytic Diels-Alder Reaction

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

1) A **secondary amine Lewis base** organocatalyst is used

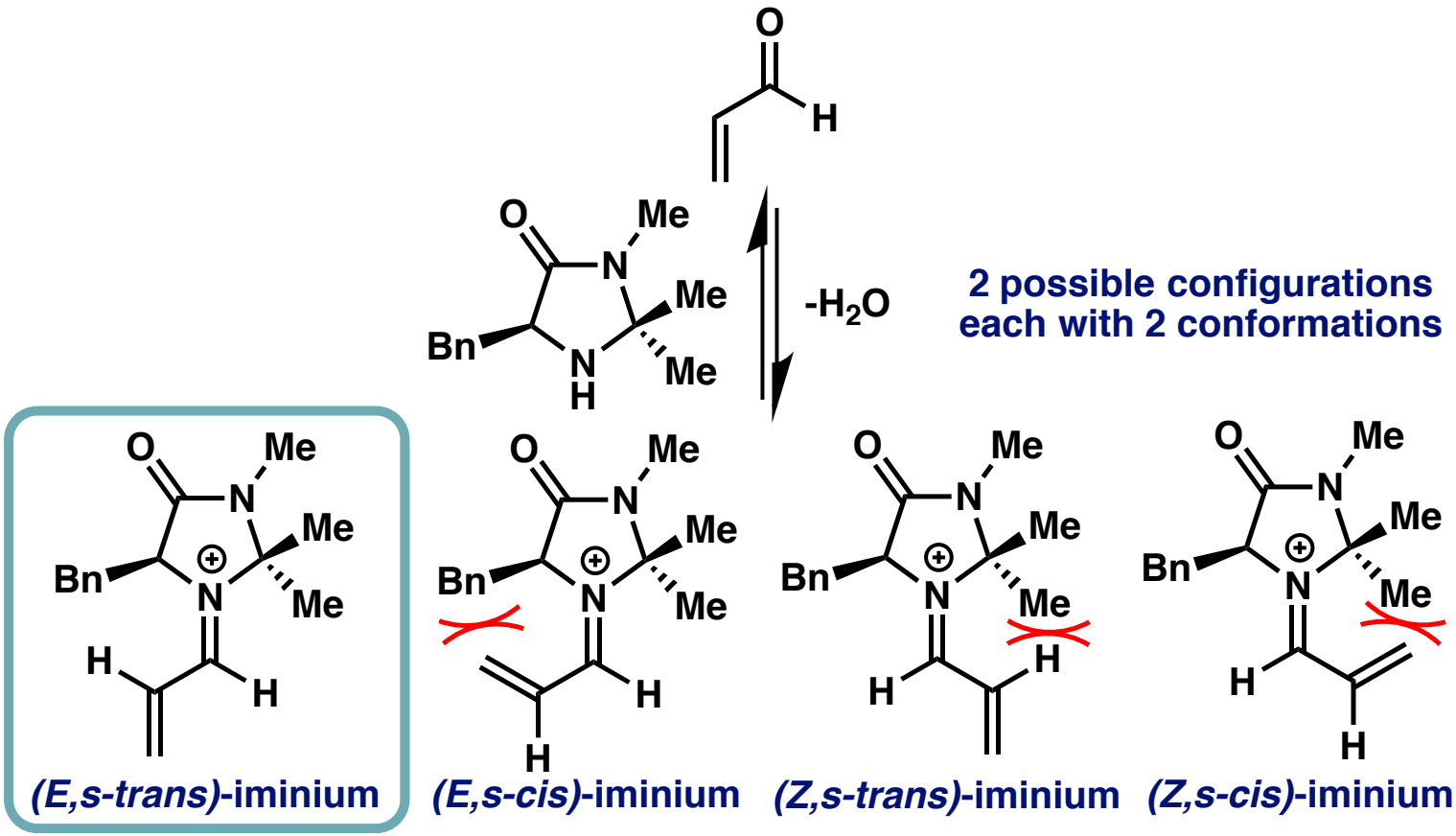
2) One substrate contains an **aldehyde** functional group, with the other being a diene

3) The aldehyde is **non-enolisable** (e.g. it has no α- or γ-hydrogen atoms that can be readily deprotonated)

- Conclusion – this reaction proceeds *via* the **iminium** activation mode.

Enantioselective Organocatalytic Diels-Alder Reaction

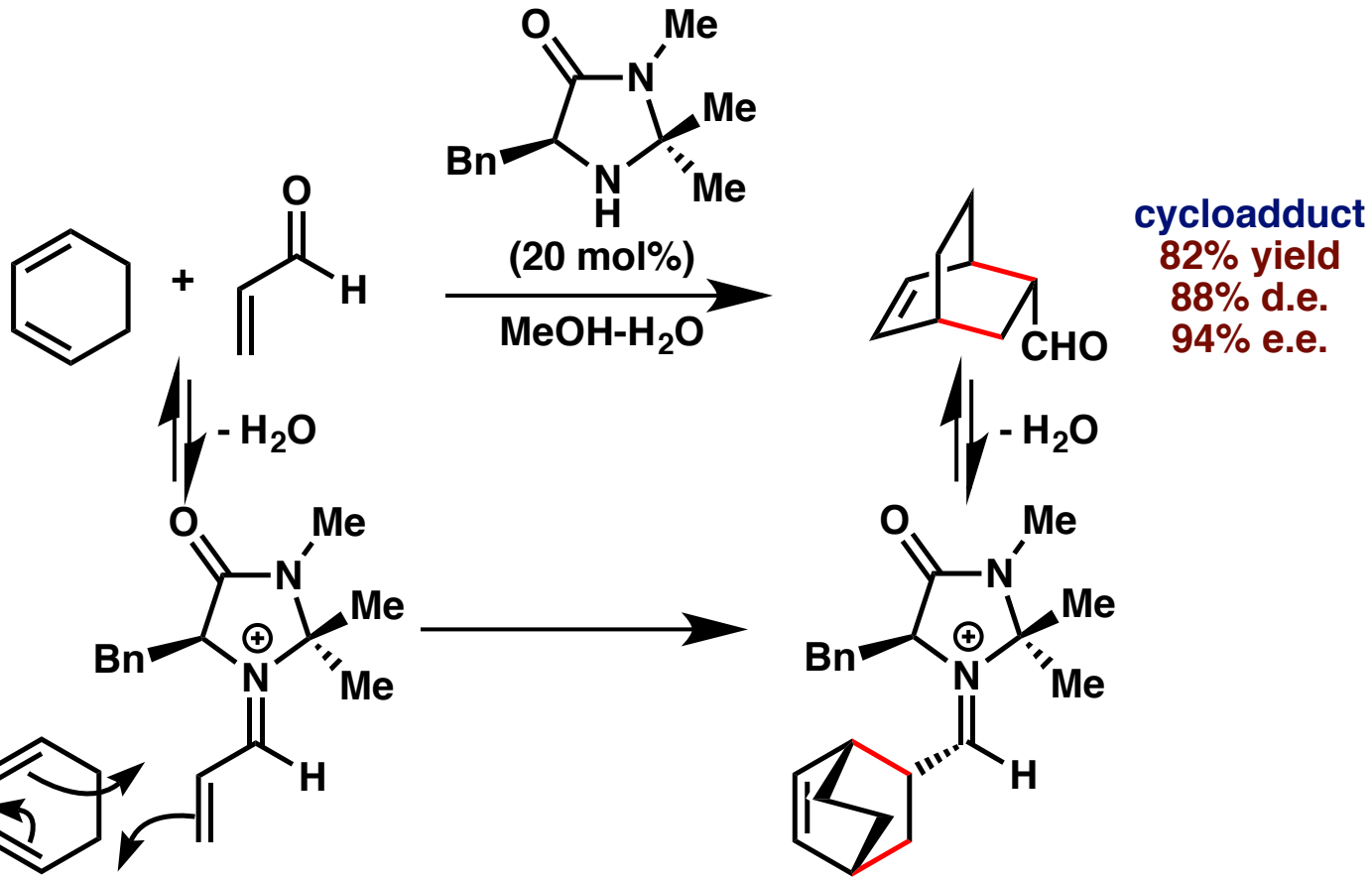
- Let's think about the key electrophilic iminium species formed in detail:



- The (*E*)-configuration is favoured over the (*Z*)-configuration due to steric congestion involving the geminal methyl substituents. The *E-s-trans* conformation is favoured.

Enantioselective Organocatalytic Diels-Alder Reaction

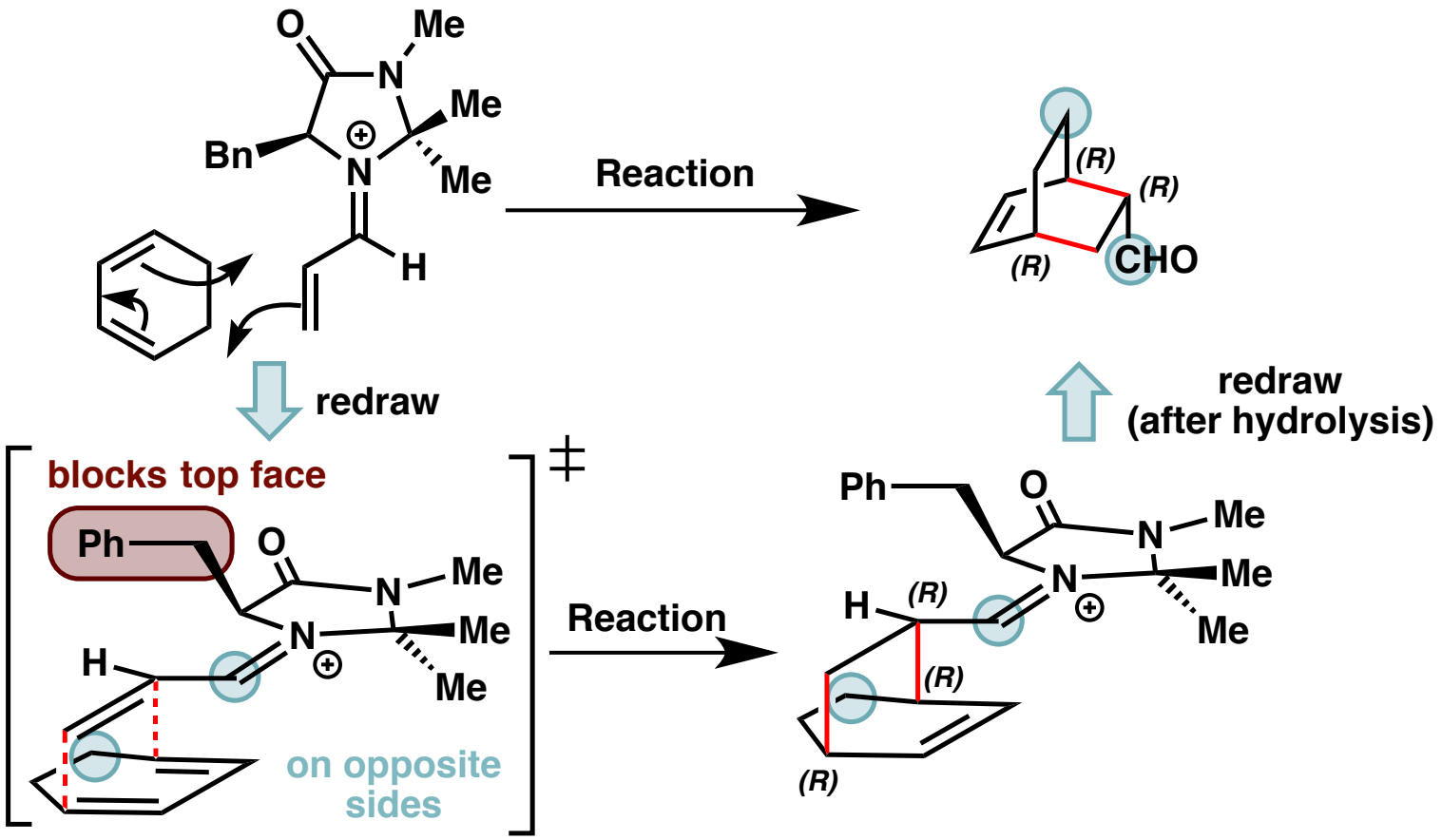
- Now let's consider the **curly arrow pushing mechanism**:



- As always, we **must** draw the curly arrows for **every step of the mechanisms** (including iminium formation/hydrolysis).

Enantioselective Organocatalytic Diels-Alder Reaction

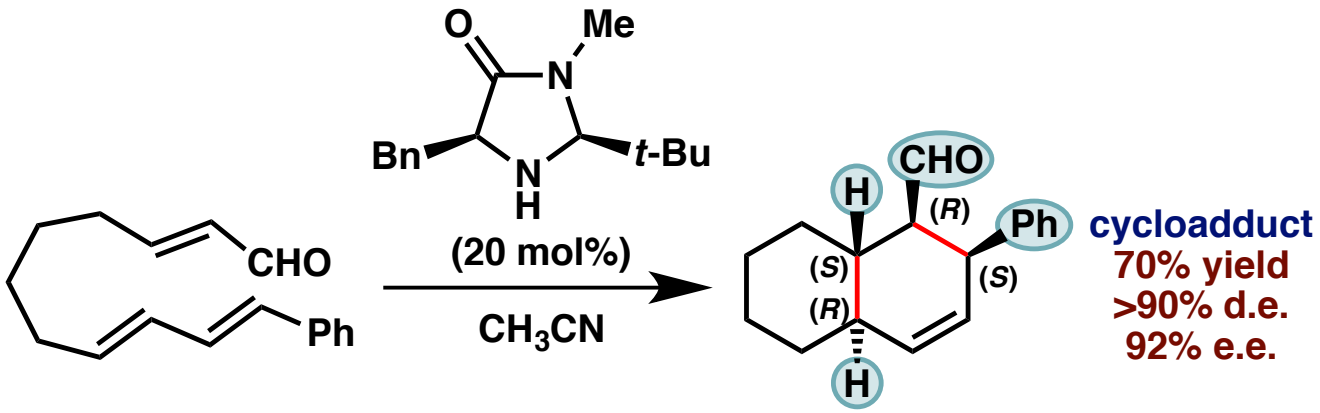
- Finally, let's rationalise the **stereochemical outcome** of the reaction:

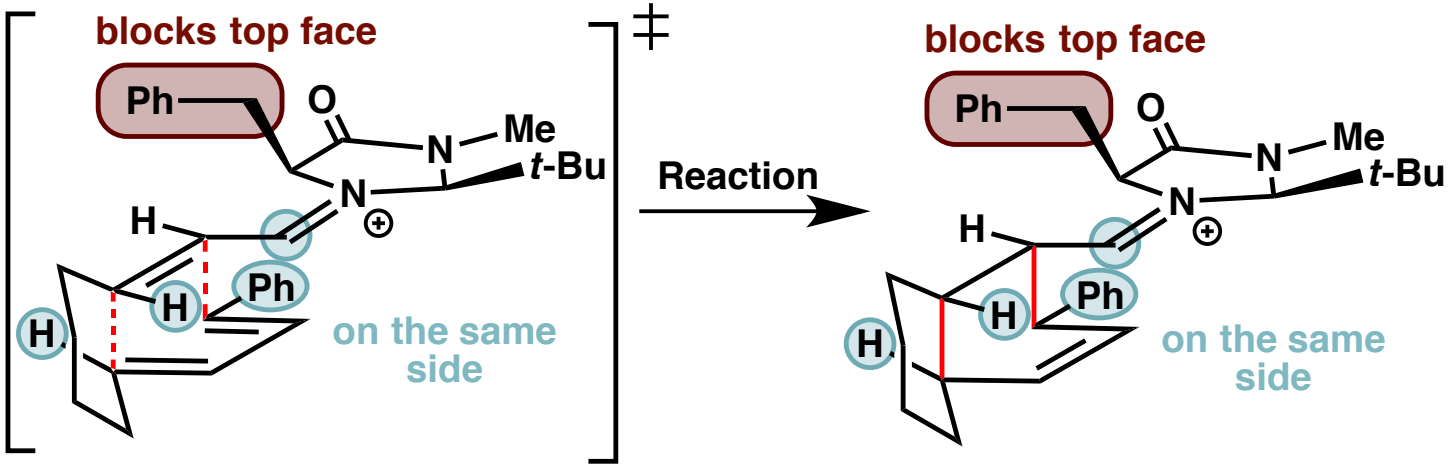


- Secondary orbital (diene filled π bonds to empty C=N π* orbital) interactions stabilise the ENDO transition state. Aldehyde and methylene bridge on **opposite sides**.

Enantioselective Organocatalytic Diels-Alder Reaction

- An *intramolecular* version of this reaction has also been reported:

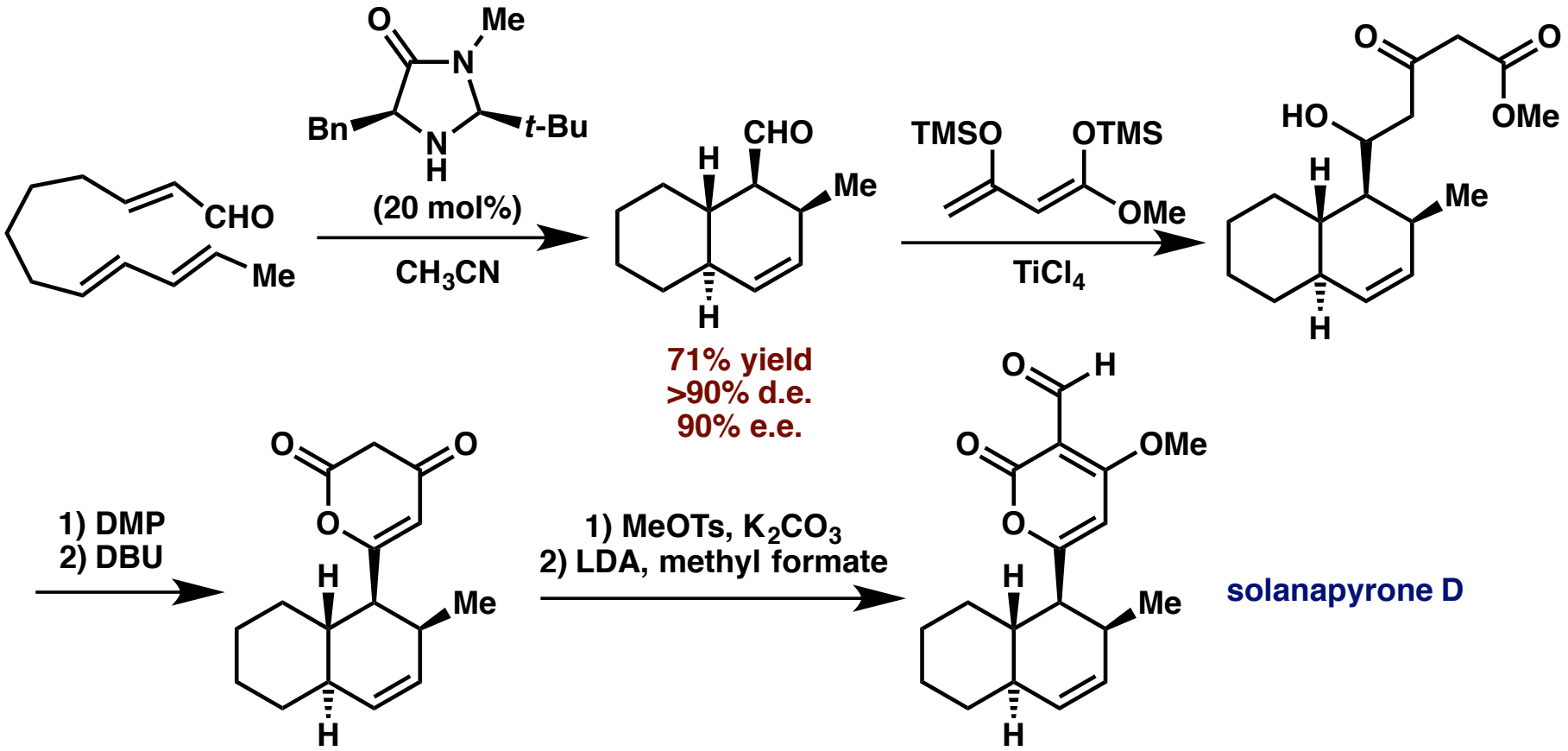




- Secondary orbital (diene filled π bonds to empty C=N π* orbital) interactions stabilise the ENDO transition state. Highlighted groups are on the **same side**.

Total Synthesis of Solanapyrone D

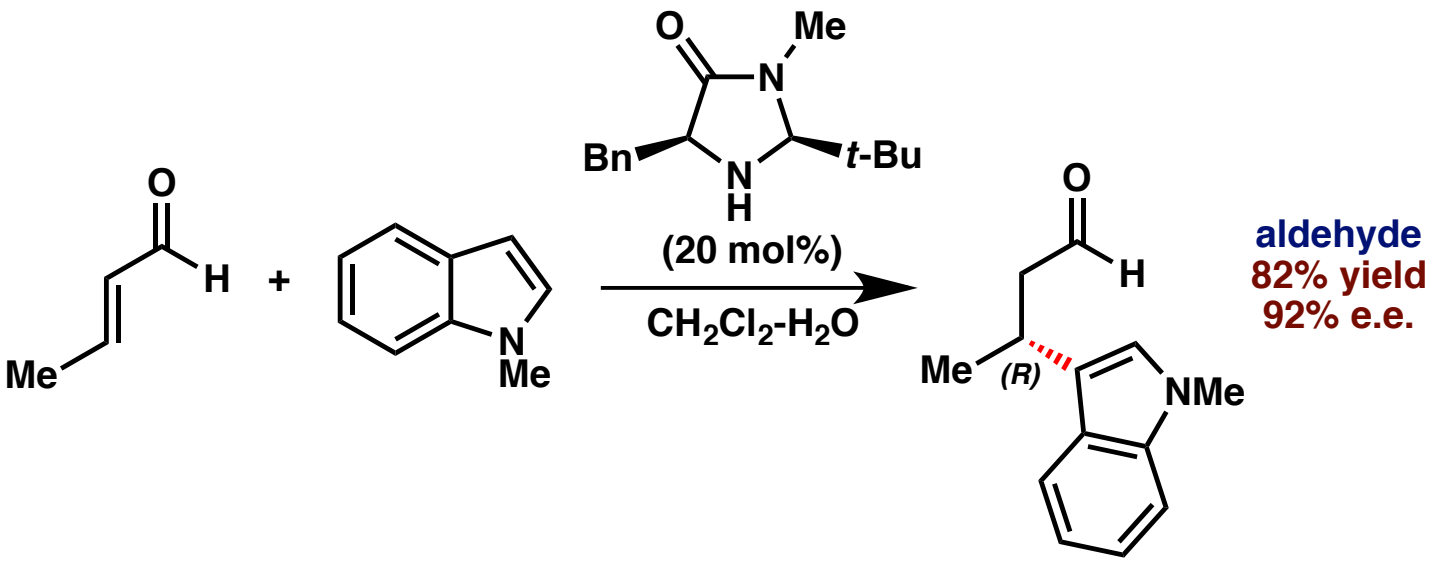
- This product was elaborated to marine metabolite solapyrone D:

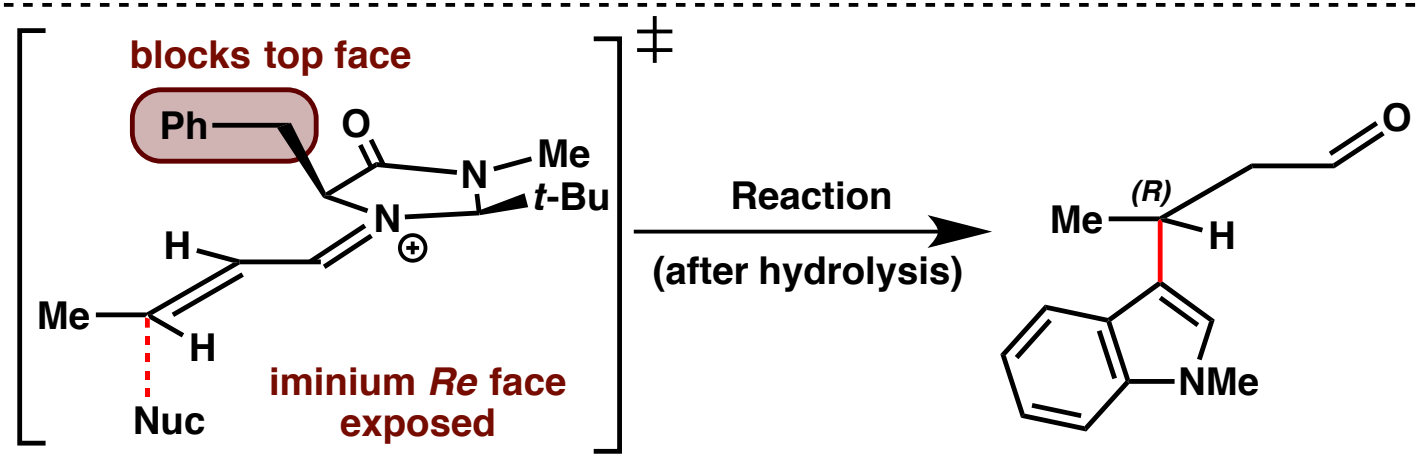


- The simple elaboration to biologically active compounds is a testament to the power of organocatalytic methodology.

Enantioselective Conjugate Addition

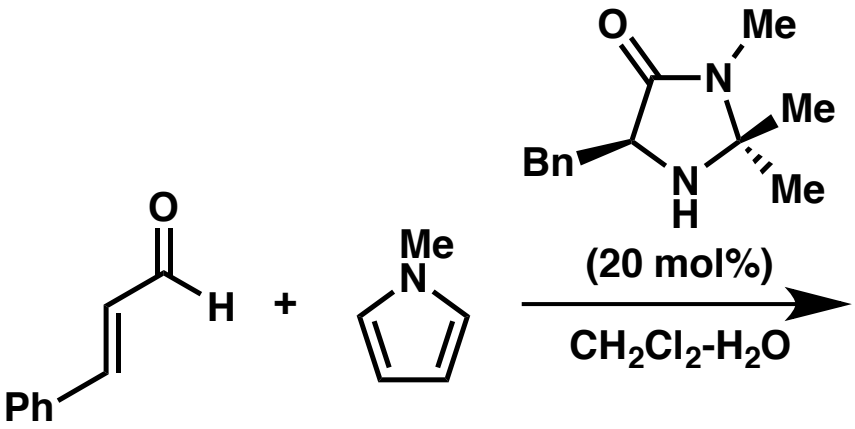
- Indoles can be employed in enantioselective conjugate addition:





Enantioselective Conjugate Addition – Class Example

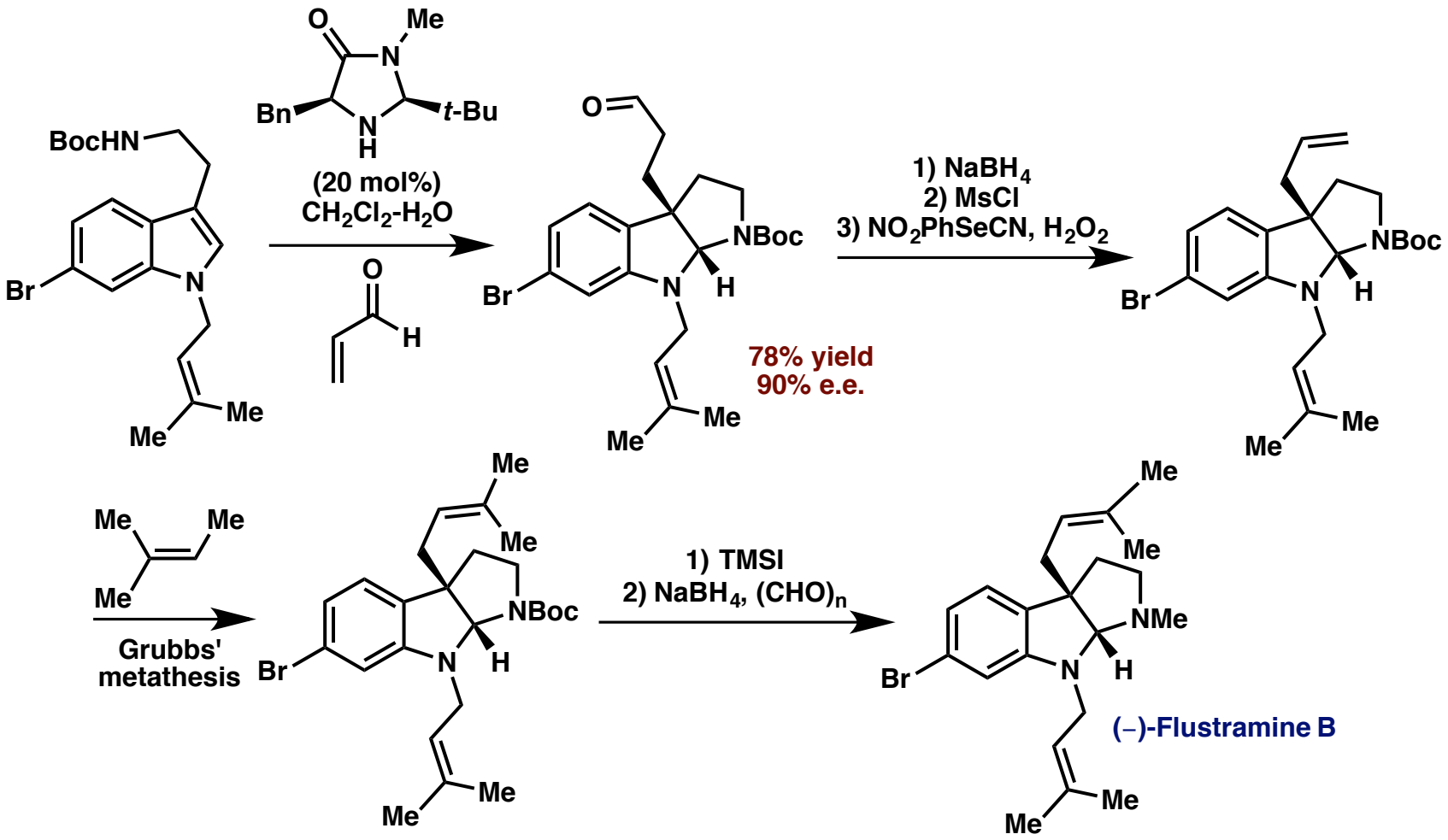
- Many alternative nucleophiles have been used in related processes. Determine the major product for the reaction shown below:



- Highly versatile approach – only one face of iminium is exposed to nucleophile.

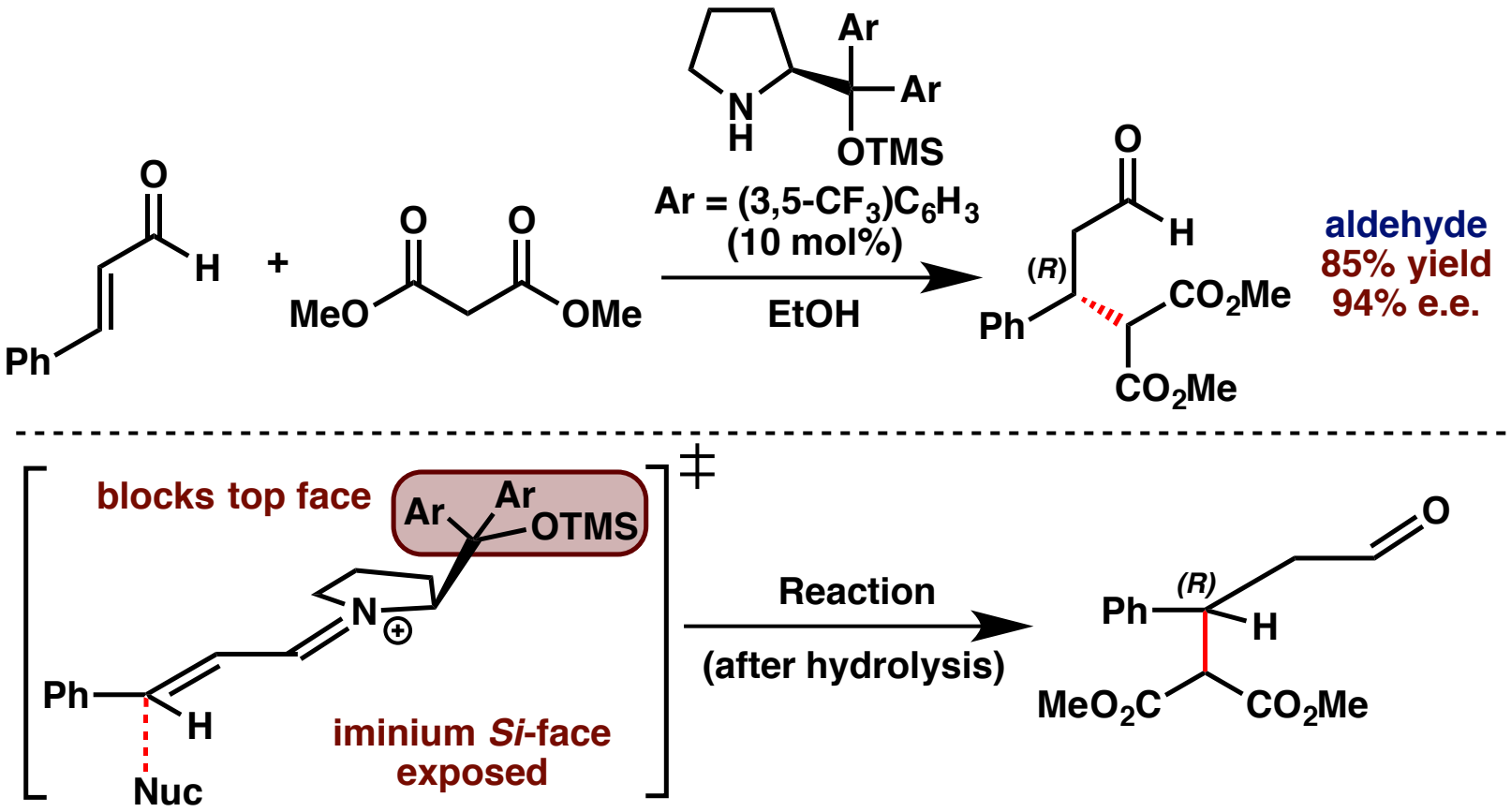
Total Synthesis of (−)-Flustramine B

- MacMillan has applied this methodology towards the total synthesis of the marine alkaloid (−)-flustramine B



Other Catalysts for Conjugate Addition

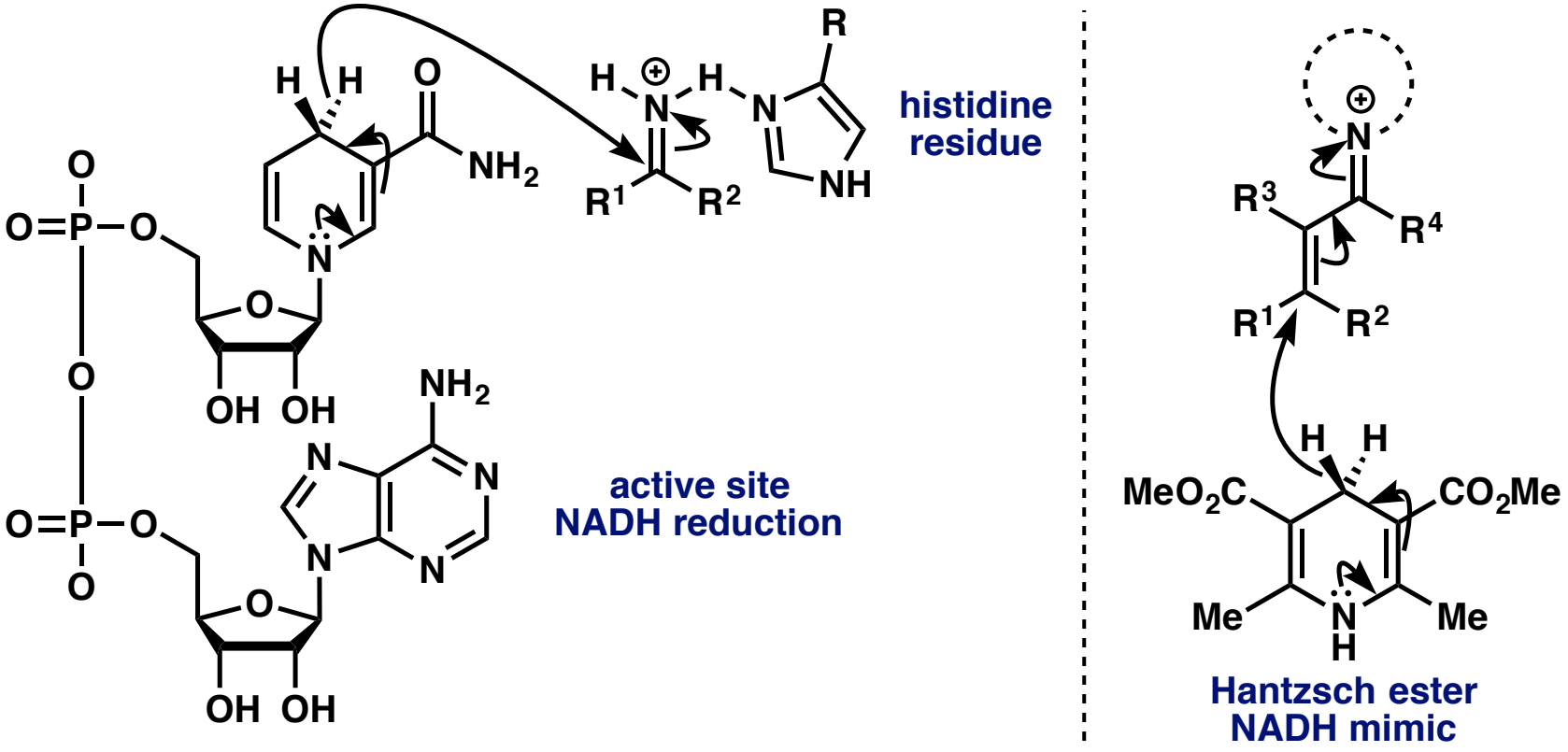
- Diarylprolinol silyl ether organocatalysts have also been used for conjugate additions:



- Large OTMS and aryl groups control iminium geometry and shield the top (*Re*) face.

Enantioselective Reduction

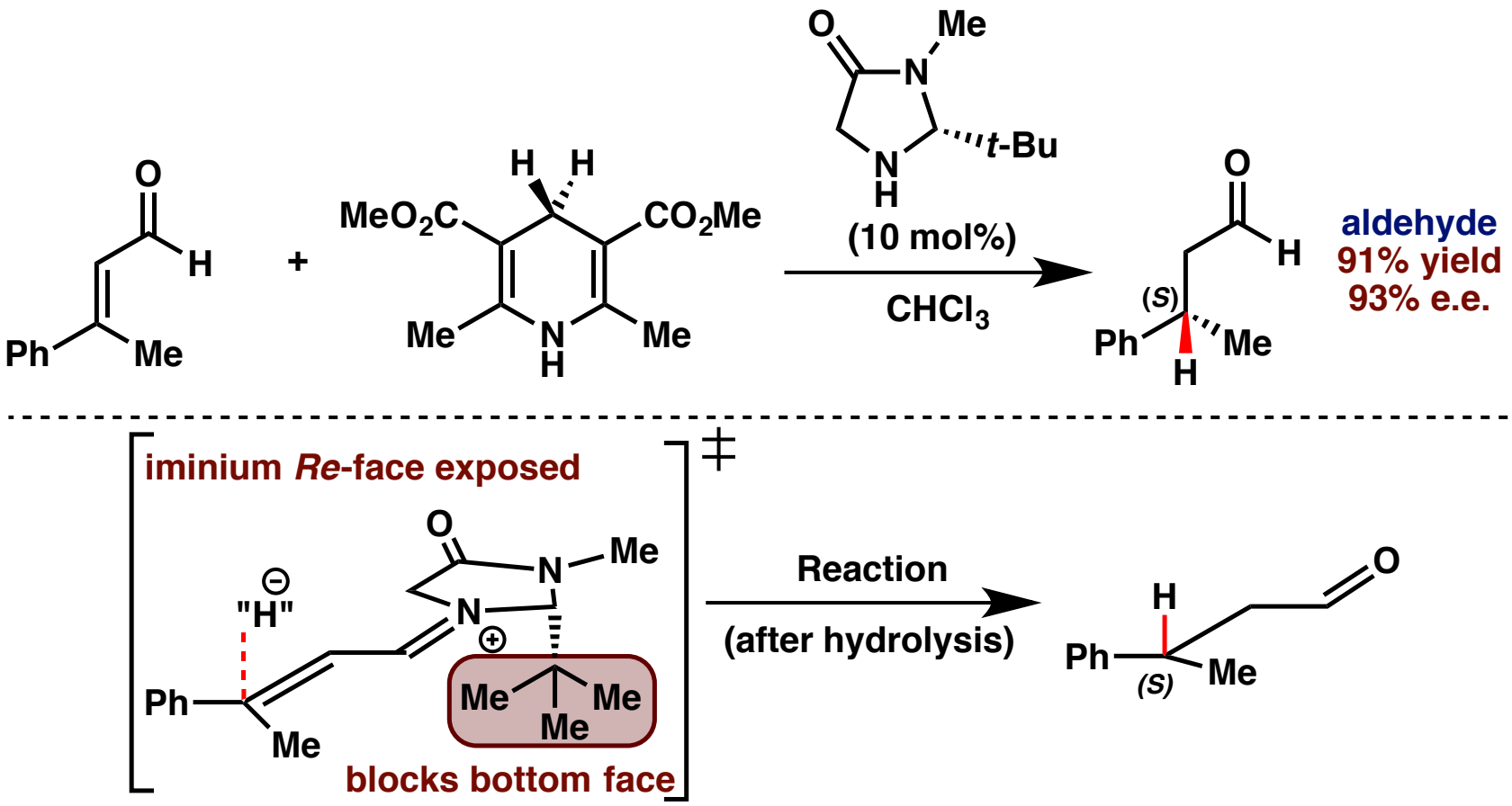
- Nature uses NADH to ezymatically reduce (hydrogenate) substrates:



- Hantzsch esters can serve as NADH mimics and are organic reductants.
- Provides the basis of an enantioselective organocatalytic reduction of enals.

Enantioselective Organocatalytic Reduction

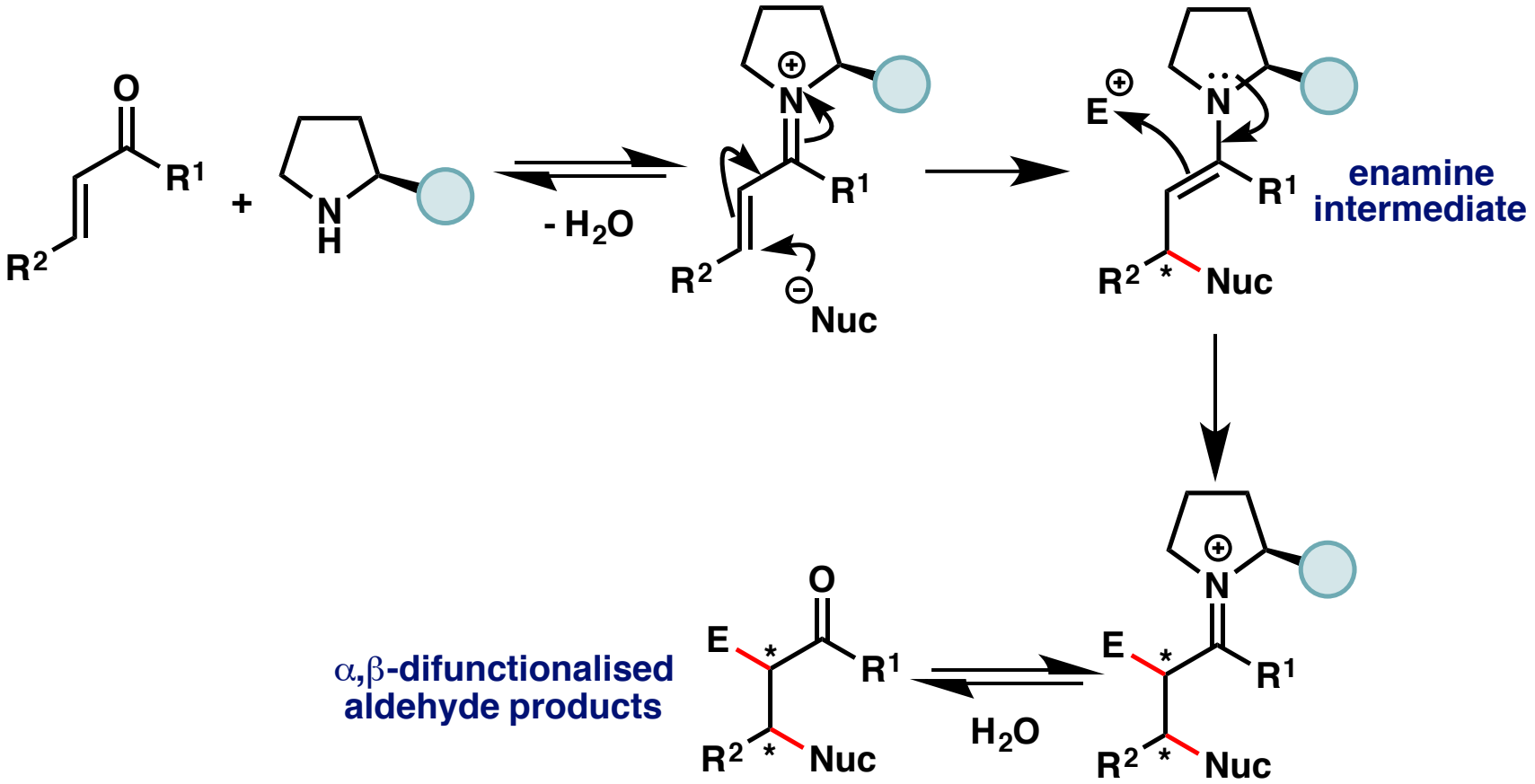
- MacMillan employed hantzsch esters as NADH mimics for enantioselective reduction:



- *Tert*-butyl group controls iminium geometry and blocks the *Si*-face.

Organocatalytic Cascade Reactions

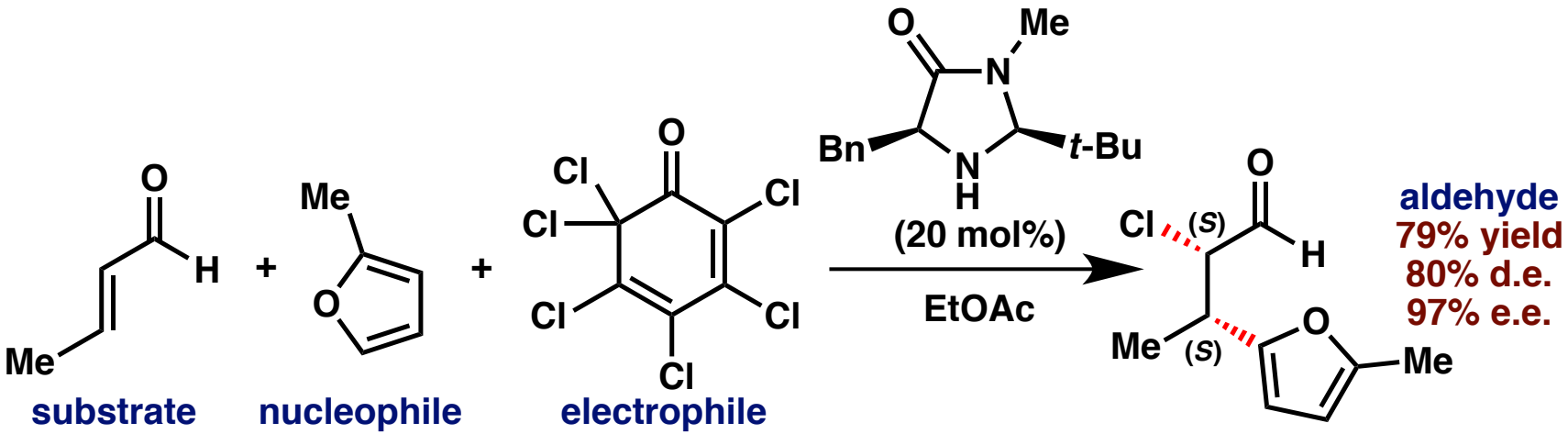
- Considering the mechanism of iminium organocatalysis reveals an opportunity:



- Can the enamine intermediate be trapped with an electrophile other than H^+ to generate difunctionalised products?

Organocatalytic Cascade Reactions

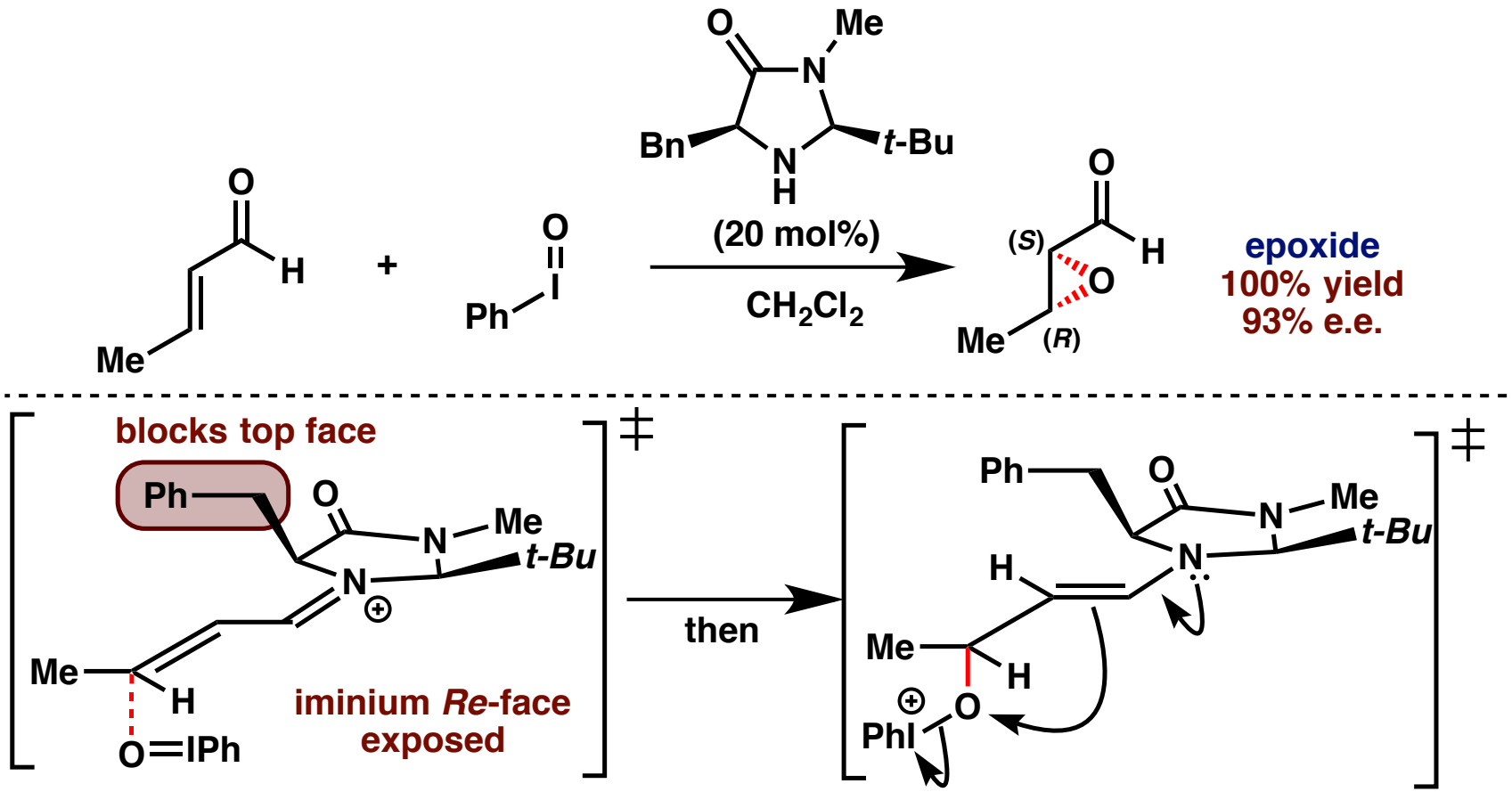
- MacMillan showed that iminium-enamine cascades can be achieved:



- The facial selectivity in both steps is controlled by the catalyst.

Organocatalytic Cascade Reactions

- Employing hypervalent iodine reagents permits access to epoxides in high ee:

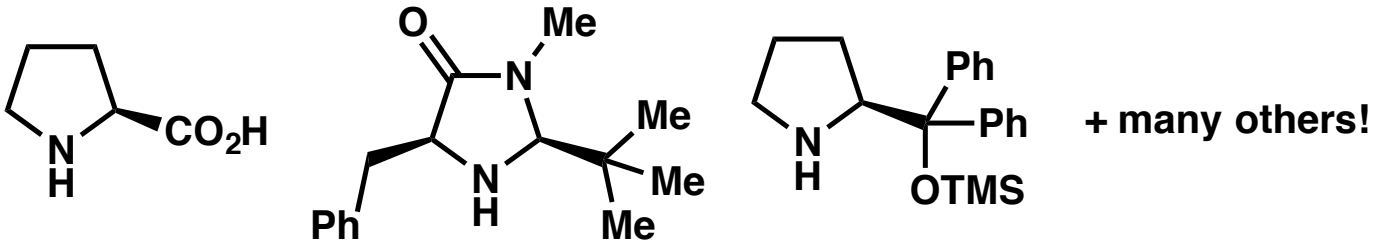


- Initial nucleophilic attack generates an electrophile for intramolecular cyclisation

Iminium Organocatalysis Cheat Sheet

- For iminium organocatalysis, you must remember the following key information:

- The iminium activation mode requires **primary or secondary amine organocatalysts** and **non-enolisable** aldehyde or ketone substrates.



- In order to rationalise the stereochemistry of reactions involving iminiums you must:

1) Identify whether the catalyst operates by **bifunctional activation** (*via* hydrogen bonding) or **steric control.**

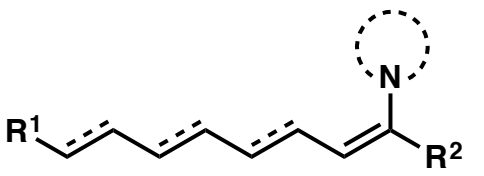
2) Carefully consider the possible **configurations** (e.g. *E* vs *Z*) and **conformations** (e.g. *s-cis* vs *s-trans*) of the key iminium intermediate.

3) Draw a suitable **3D-representation** of the transition state.

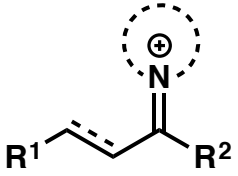
An Overview of Organocatalysis

- Organocatalysis is now a thoroughly established member of the synthetic toolbox, with a large number of **generic activation modes** known.

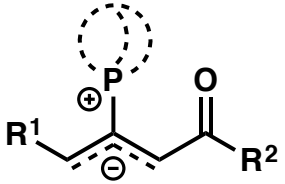
Covalent Activation Modes



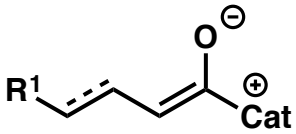
Enamine (di-, tri-, tetra-enamine) Catalysis



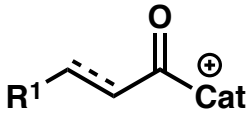
Iminium Catalysis



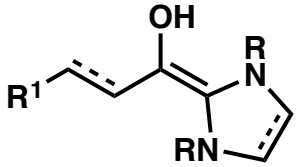
Phosphine Catalysis



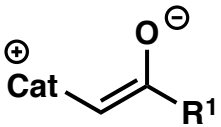
C(1)-Enolate (di-enolate) Catalysis



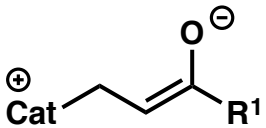
Acyl ammonium/azolium Catalysis



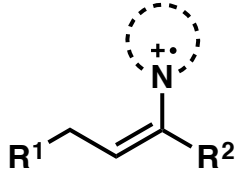
N-Heterocyclic Carbene Catalysis



C(2)-Enolate Catalysis

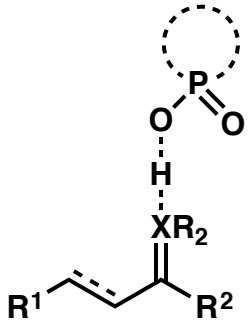


C(3)-Enolate Catalysis

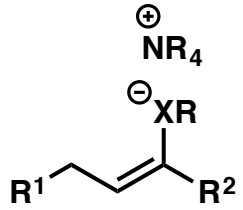


SOMO Catalysis

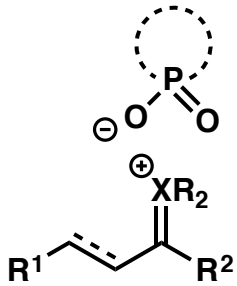
Non-Covalent Activation Modes



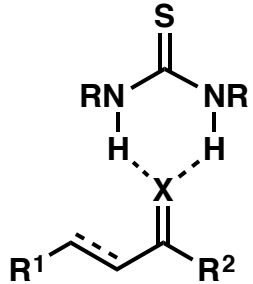
Brønsted Acid Catalysis



Phase-transfer Catalysis



Chiral Anion Catalysis



Hydrogen Bonding Catalysis

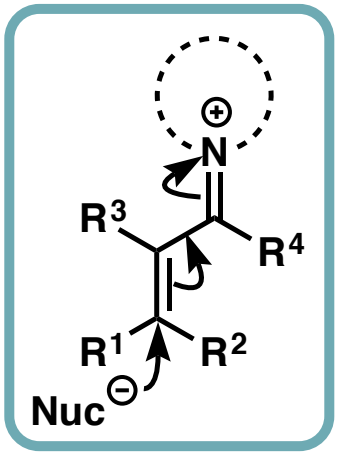
- Let's now focus on **LUMO-lowering organocatalysis beyond iminium activation**.

For an excellent overview see D. Romo *et al.*, *Nat. Prod. Rep.*, 2014, **31**, 1318.

LUMO-Lowering Catalysis Beyond Iminium Activation

- So far we have discussed **iminium organocatalysis** as a method of **β-functionalisation** of α,β-unsaturated carbonyl compounds:

Iminium Organocatalysis



- The iminium activation mode has the following key characteristics:

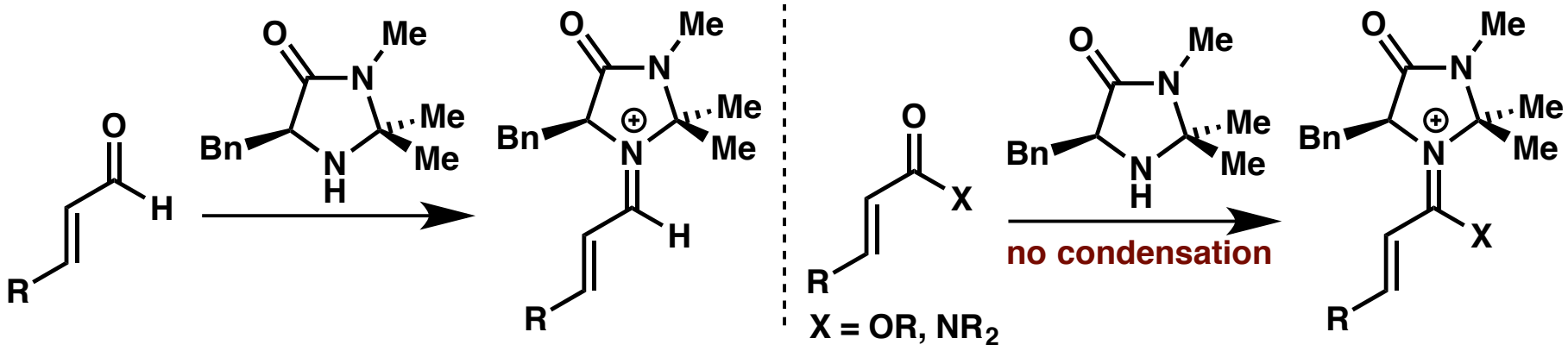
1) It is a **covalent** activation mode – the catalyst is covalently bound to the substrate.

2) It is an **electrophilic (LUMO-lowered)** activation mode – it reacts with nucleophiles.

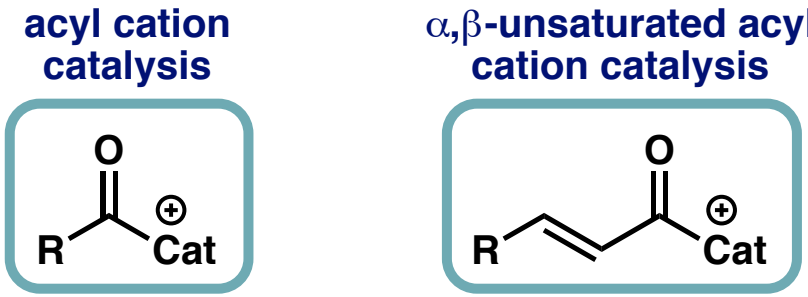
3) It employs **primary and secondary amine Lewis base** organocatalysts and α,β-**unsaturated aldehyde/ketone** substrates.

LUMO-Lowering Catalysis Beyond Iminium Activation

- Iminium catalysis is extremely powerful, but it is primarily limited to **aldehyde and ketone** substrates and does not extend to esters, amides etc.

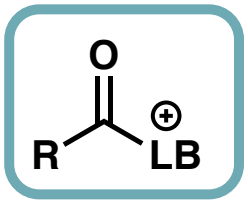


- There is an alternative way to generate chiral ester equivalents, known as (α,β-unsaturated) **acyl cation organocatalysis**.



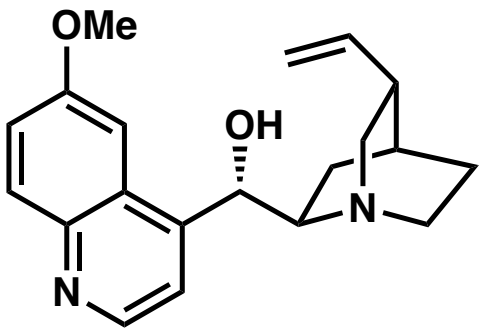
LUMO-Lowering Catalysis Beyond Iminium Activation

- Let's begin by considering **acyl cation catalysis**:

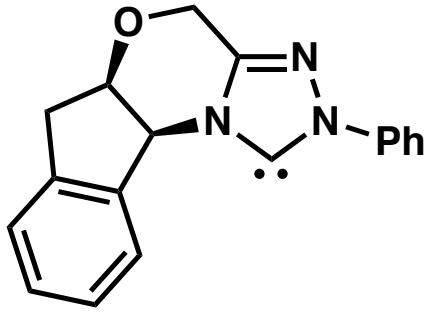


When LB = Tertiary amine, acyl ammonium
When LB = N-heterocyclic carbene, acyl azolium
When LB = Phosphine, acyl phosphonium

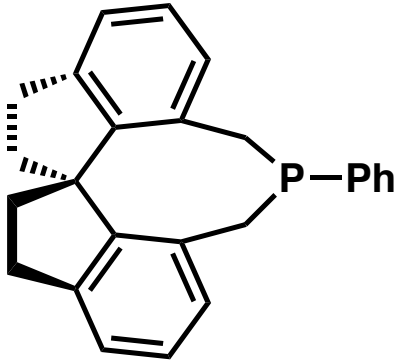
- A wide variety of **Lewis base organocatalysts** can be used to generate these species:



Tertiary Amines



N-Heterocyclic Carbenes



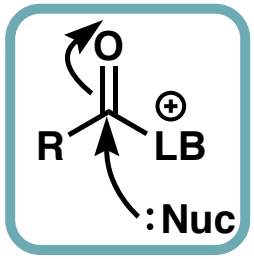
Phosphines

- Let's look at the key characteristics of this organocatalytic activation mode.

Acyl Cation Organocatalytic Activation Mode

- **Acyl cations** are widely employed as activated ester equivalents:

Acyl Cation Activation Mode



- The acyl cation activation mode has the following key characteristics:

1) It is a **covalent** activation mode – the catalyst is covalently bound to the substrate.

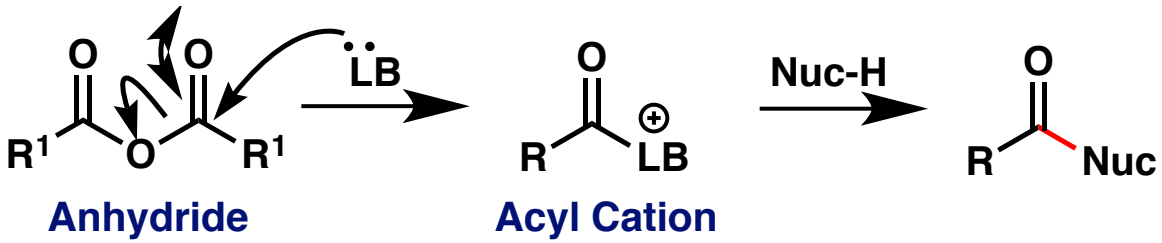
2) It is an **electrophilic (LUMO-lowered)** activation mode – it reacts with nucleophiles.

3) It employs **tertiary amine, phosphine and N-heterocyclic carbene Lewis base** organocatalysts

4) It can be accessed from a wide variety of electrophilic substrates including **acid chlorides, anhydrides, carboxylic esters/acids etc.**

Anhydrides as Precursors for Acyl Cations

- **Acyl cations** can be accessed from anhydride precursors:



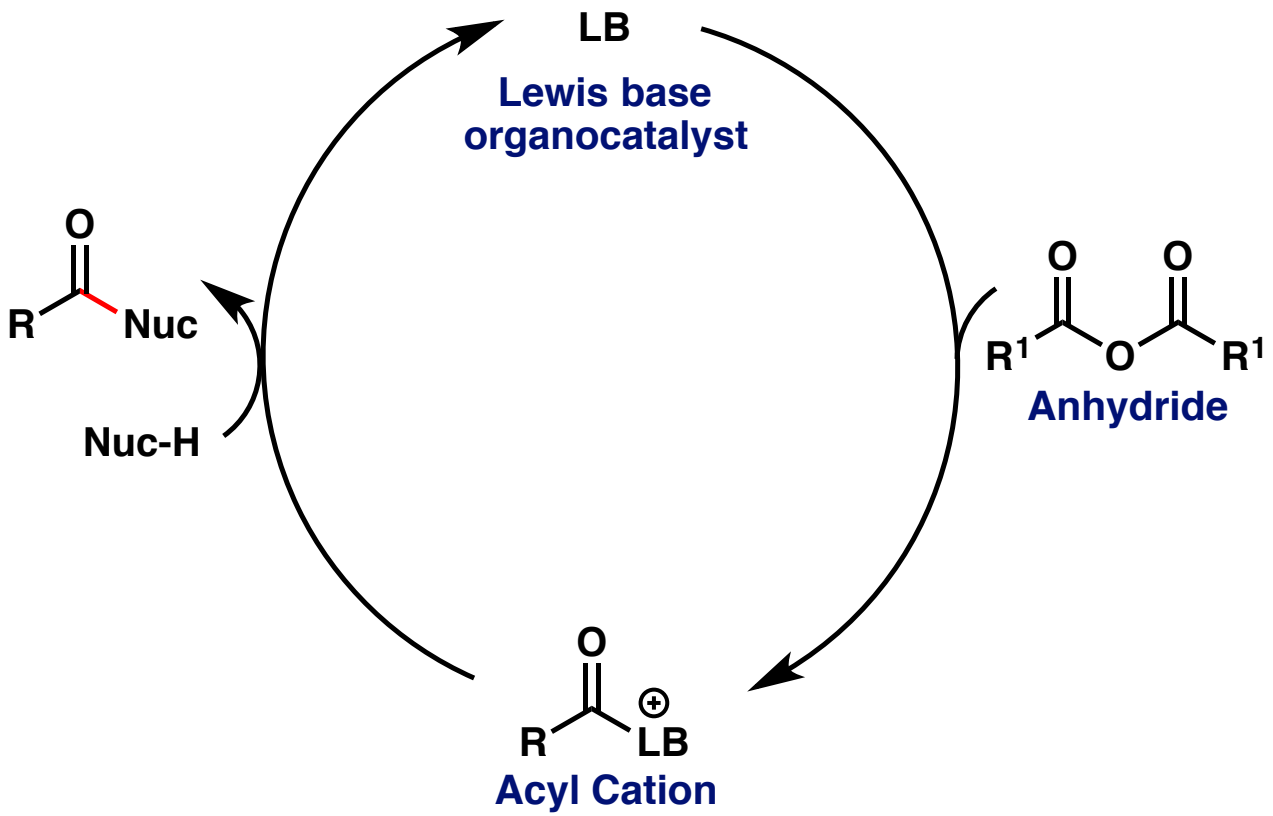
- Once generated, the acyl cation can undergo substitution with a nucleophile to access the product with regeneration of the catalyst.

- This process amounts to **an acyl transfer reaction** and has been used across a wide spectrum of substrates.

- Let's consider the general catalytic cycle for this organocatalytic activation mode.

Acyl Cation Organocatalysis – General Mechanism

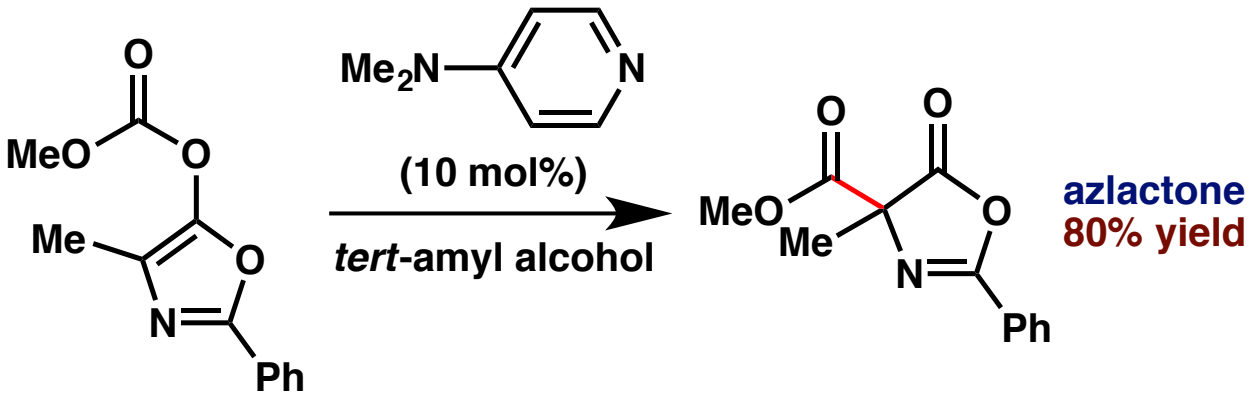
- We can draw the following catalytic cycle for acyl cation organocatalysis:



- Remember that a variety of other substrates can serve as acyl cation precursors, including acid chlorides, carboxylate esters etc. Let's look at some specific examples.

The Steglich Rearrangement

- In 1970, Steglich reported that DMAP catalysed the rearrangement of *O*-acylated azlactones to their corresponding *C*-acylated isomers:



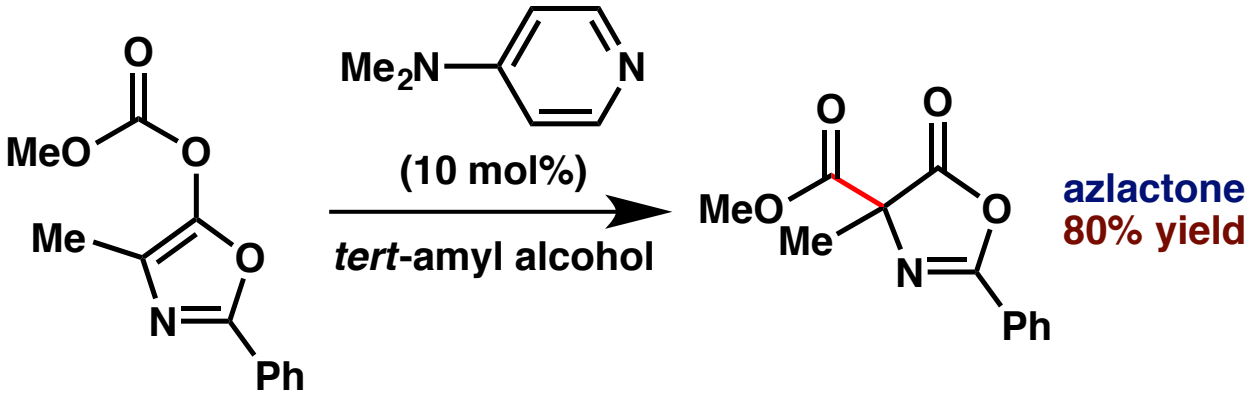
- For this class of organocatalytic reaction we must be able to:

1) Know how the organocatalyst **activates** the substrate (**activation mode**)

2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

The Steglich Rearrangement

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

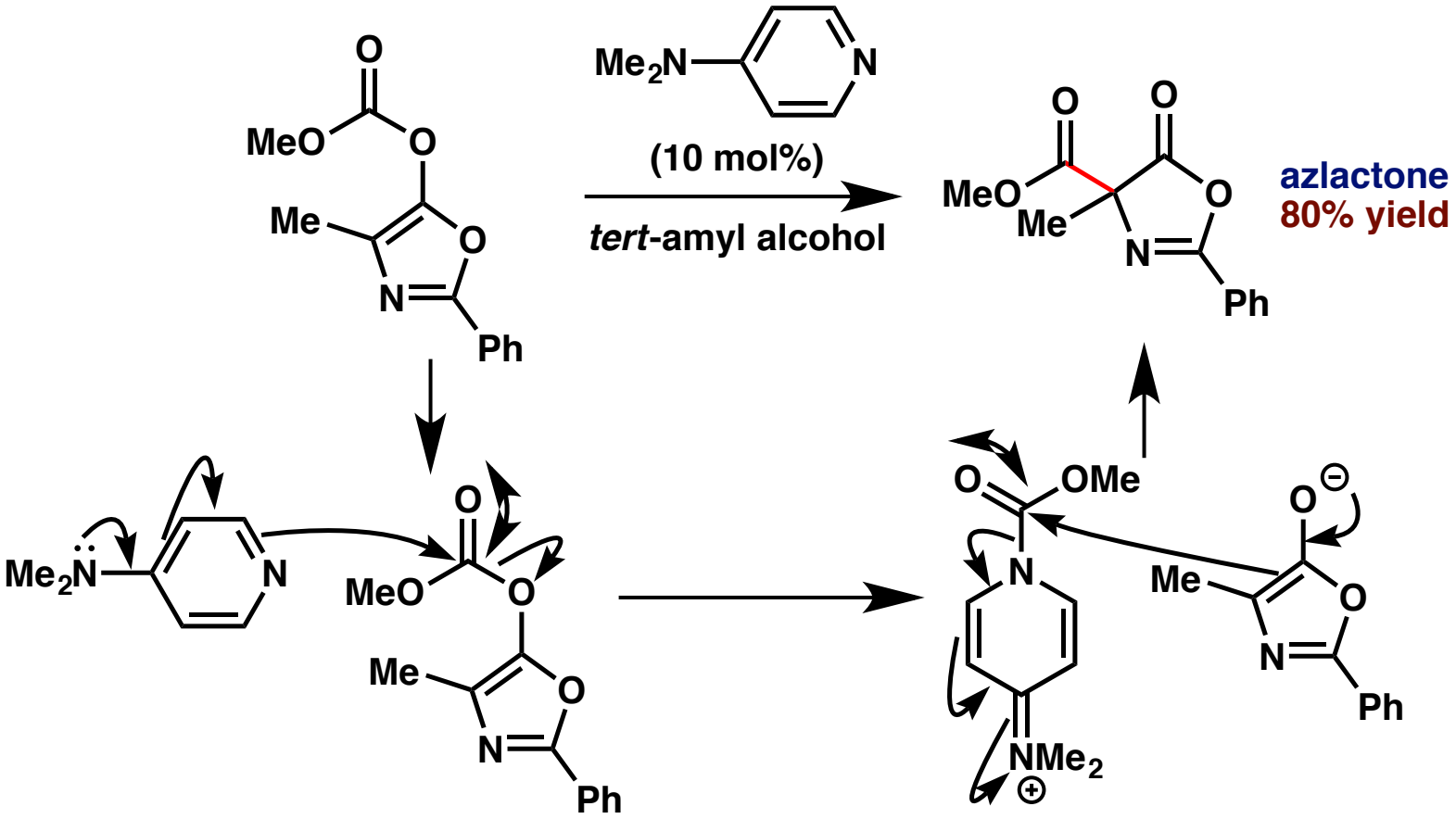
1) A **tertiary amine Lewis base** organocatalyst is used

2) The substrate has contains an electrophilic **carbonate** functional group.

- This reaction proceeds *via* the acyl ammonium activation mode.

The Steglich Rearrangement

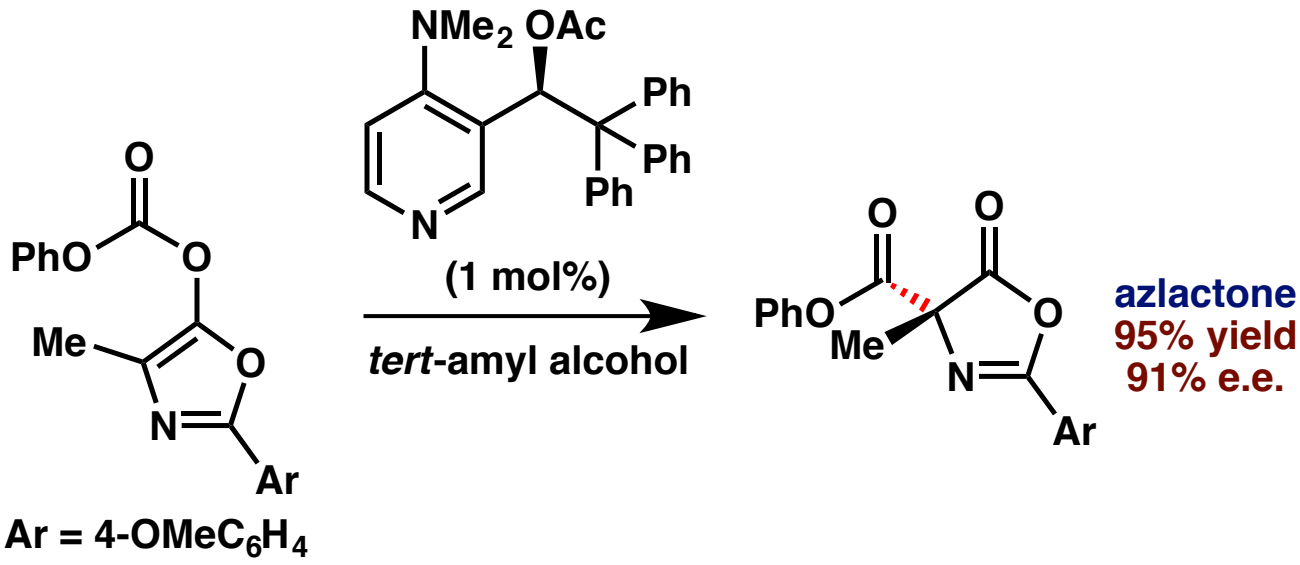
- Now let's consider the **curly arrow pushing mechanism**:



- Chiral Lewis base organocatalysts have also been employed in this reaction.

The Steglich Rearrangement

- For example, Vedejs has employed chiral DMAP derivatives to access the azlactone products in high enantioselectivity:

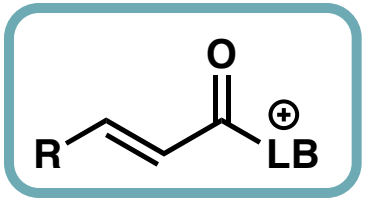


- To rationalise the **stereochemical outcome** of the reaction is beyond the scope of this course.

- Why might the products be **useful building blocks** for synthetic applications?

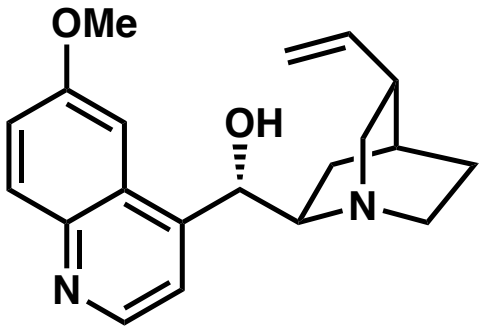
LUMO-Lowering Catalysis Beyond Iminium Activation

- Let's now think about **α,β-unsaturated acyl cation catalysis**:

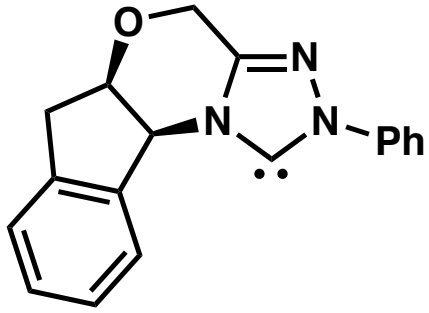


When LB = Tertiary amine, α,β-unsaturated acyl ammonium
When LB = N-heterocyclic carbene, α,β-unsaturated acyl azolium
When LB = Phosphine, α,β-unsaturated acyl phosphonium

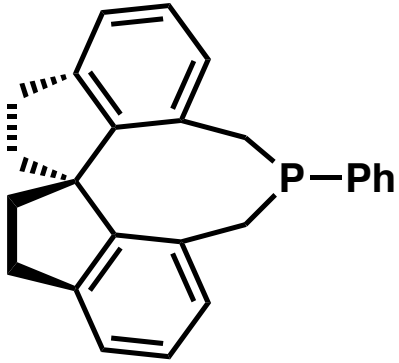
- Again, a wide variety of **Lewis base organocatalysts** can be used to generate these species:



Tertiary Amines



N-Heterocyclic Carbenes



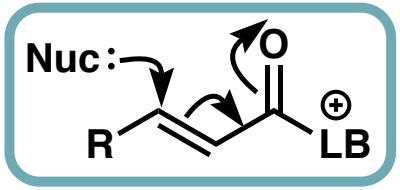
Phosphines

- Let's look at the key characteristics of this organocatalytic activation mode.

α,β-Unsaturated Acyl Cation Organocatalytic Activation Mode

- **α,β-Unsaturated acyl cations** are currently an extremely active area of research in organocatalysis:

α,β-Unsaturated Acyl Cation Activation Mode



- The α,β-unsaturated acyl cation activation mode has the following key characteristics:

1) It is a **covalent** activation mode – the catalyst is covalently bound to the substrate.

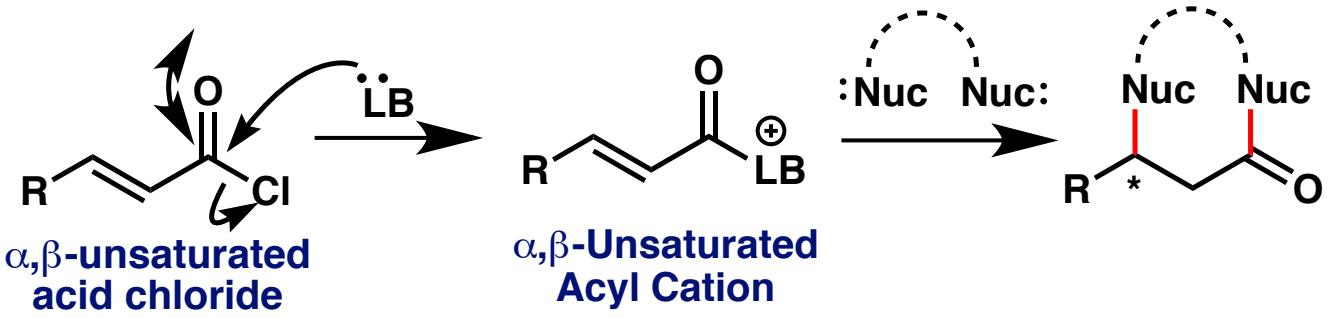
2) It is an **electrophilic (LUMO-lowered)** activation mode – it reacts with nucleophiles.

3) It employs **tertiary amine, phosphine and N-heterocyclic carbene Lewis base** organocatalysts

4) It can be accessed from a wide variety of electrophilic substrates including α,β-**unsaturated acid chlorides, fluorides, anhydrides, carboxylic esters/acids etc.**

Acid Chlorides as Precursors for α,β-Unsatured Acyl Cations

- **α,β-Unsaturated acyl cations** can be accessed from acid chloride precursors:



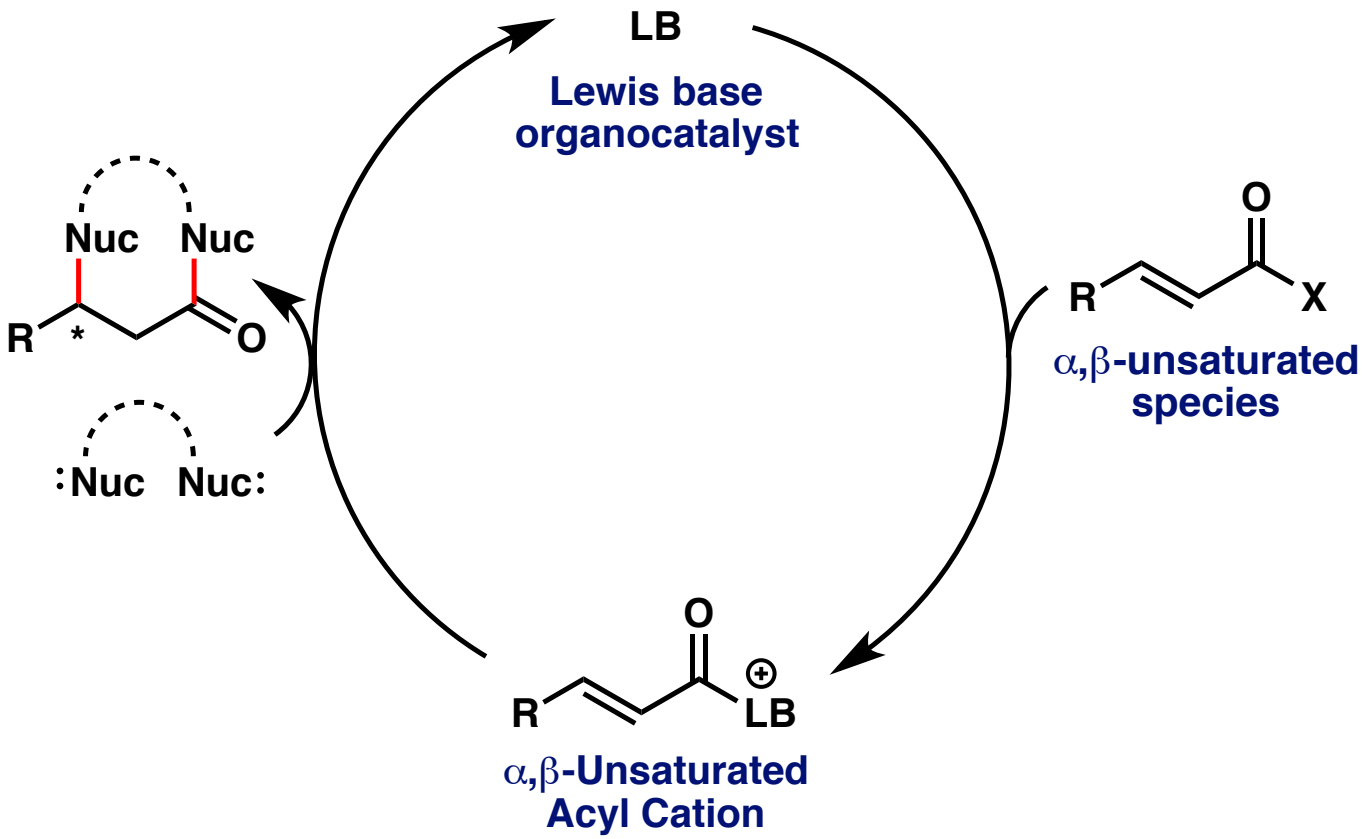
- Once generated, the α,β-unsaturated acyl cation can undergo attack with di-nucleophiles to access the product with regeneration of the catalyst.

- This process amounts to a formal **β-functionalisation,** reminiscent of iminium organocatalytic processes.

- Let's consider the general catalytic cycle for this organocatalytic activation mode.

Acyl Cation Organocatalysis – General Mechanism

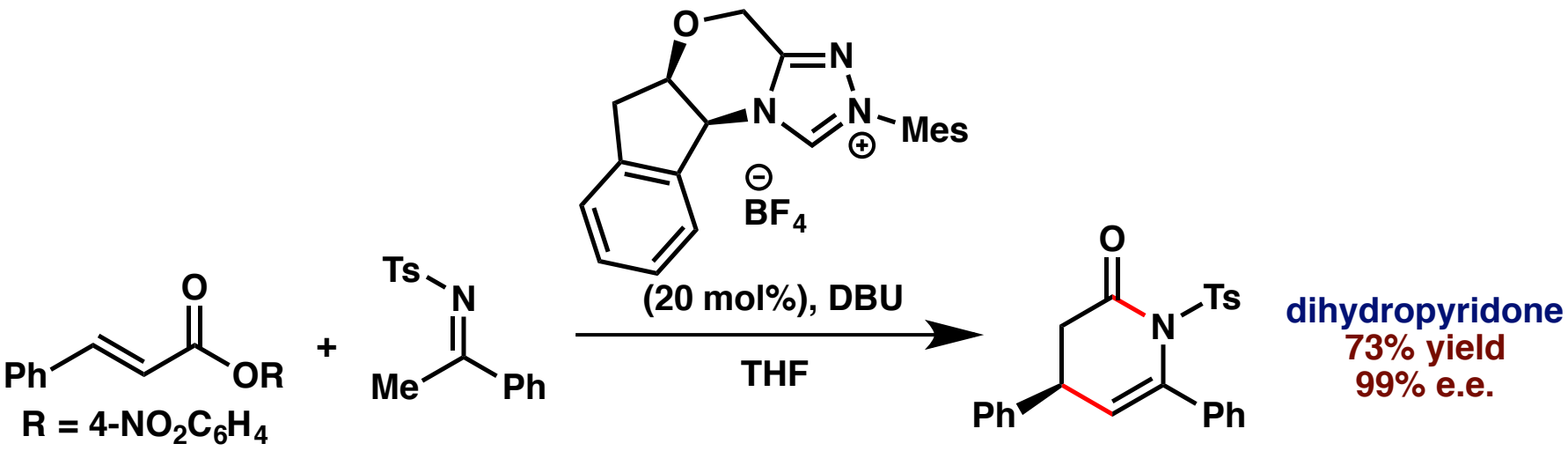
- We can draw the following catalytic cycle for acyl cation organocatalysis:



- Remember that a variety of other substrates can serve as α,β-unsaturated acyl cation precursors, including α,β-unsaturated fluorides, anhydrides etc.

Enantioselective Dihydropyridone Synthesis

- In 2013, Chi reported the NHC catalysed LUMO activation of α,β-unsaturated esters for reaction with enamides:



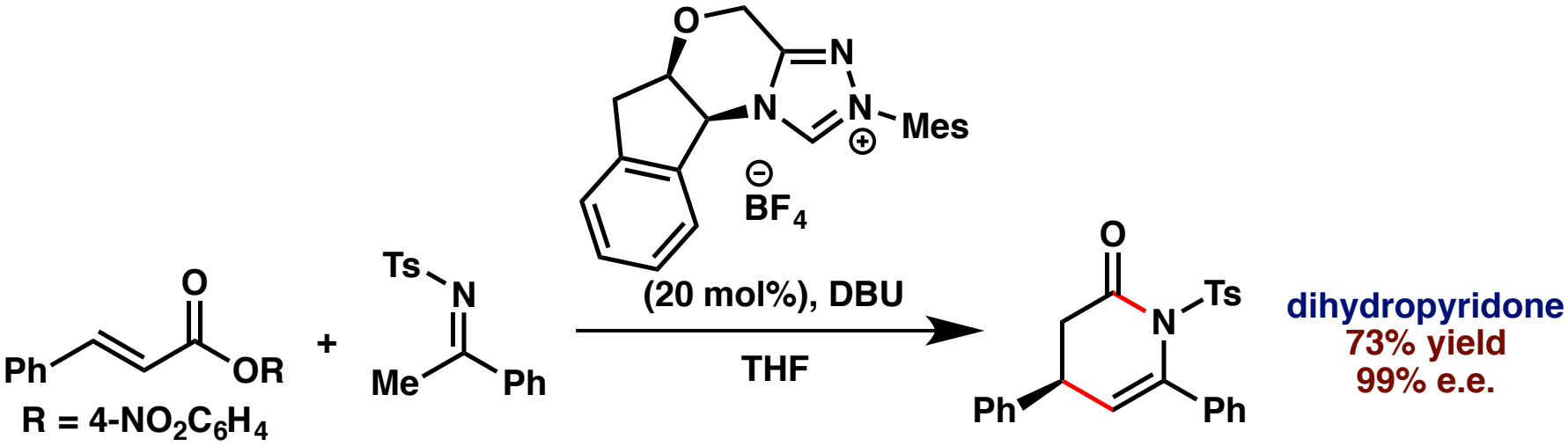
- For this class of organocatalytic reaction we must be able to:

1) Know how the organocatalyst **activates** the substrate (**activation mode**)

2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

Enantioselective Dihydropyridone Synthesis

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

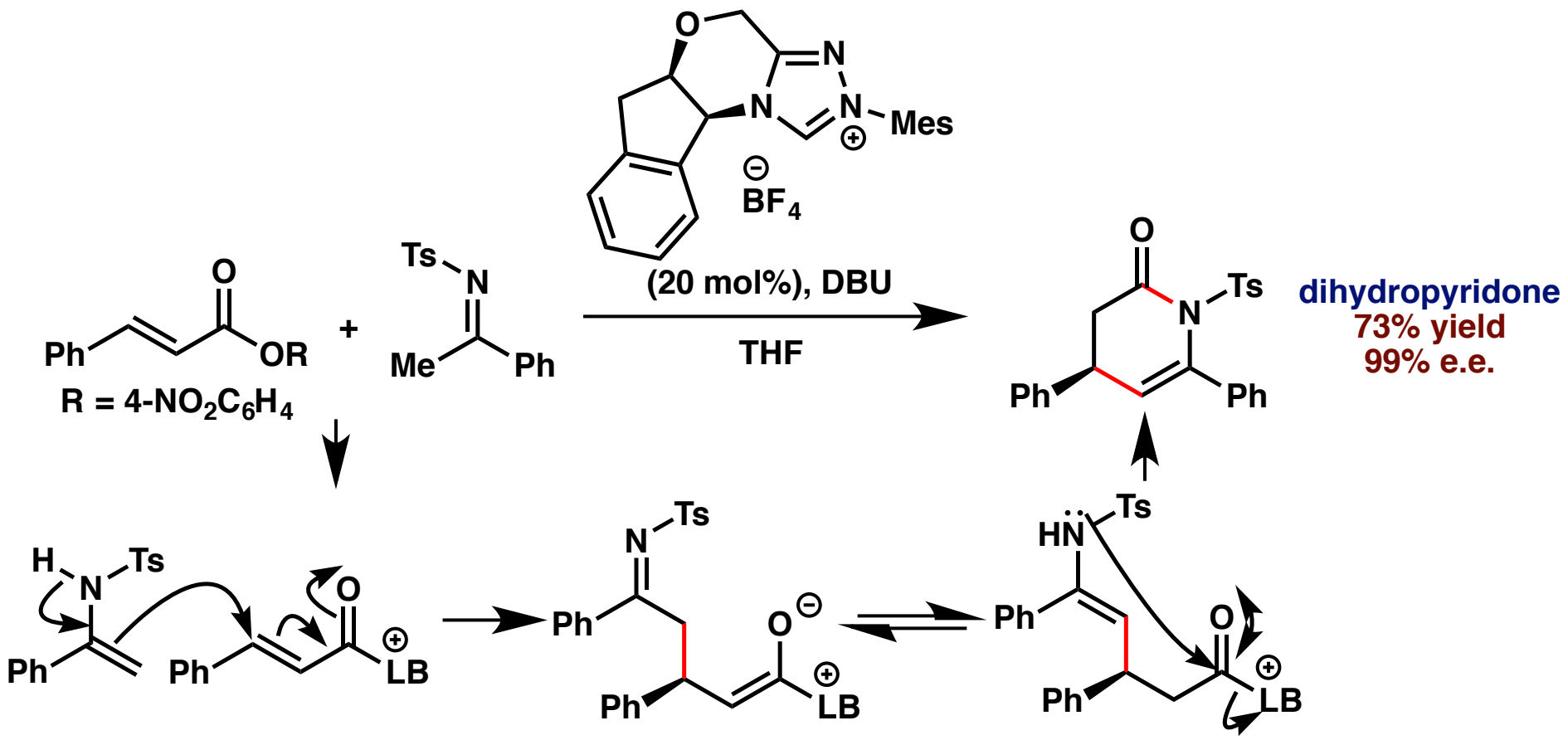
1) A **N-heterocyclic carbene Lewis base** organocatalyst is used

2) One reactant contains an electrophilic α,β-unsaturated ester. The other is a nucleophilic enamide.

- This reaction proceeds *via* the **α,β-unsaturated acyl azolium** activation mode.

Enantioselective Dihydropyridone Synthesis

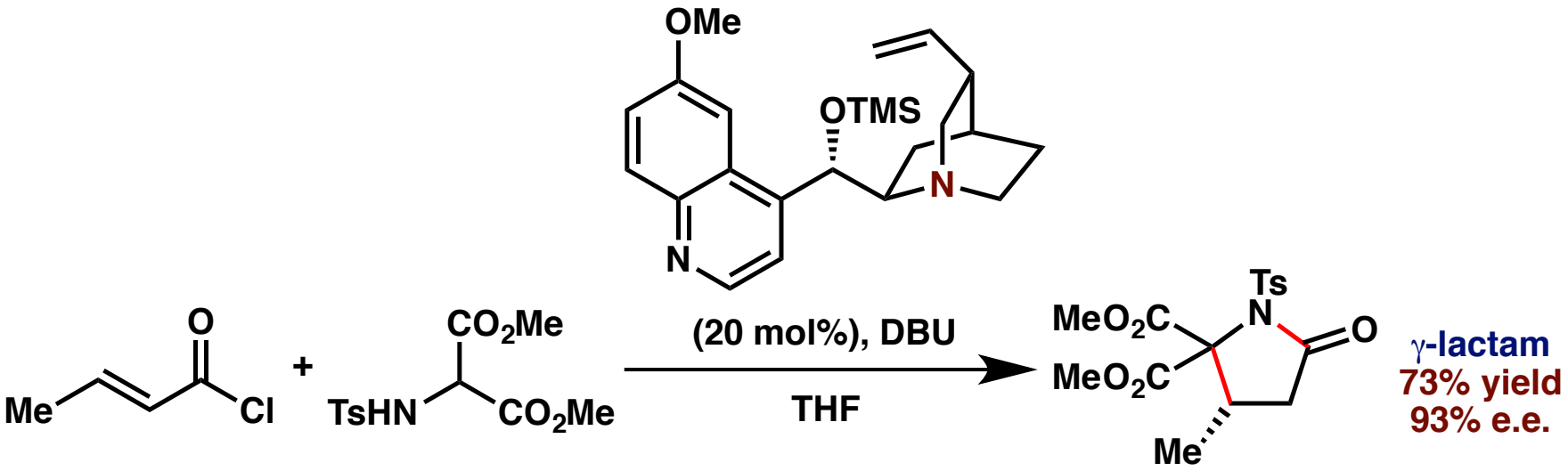
- Now let's consider the **curly arrow pushing mechanism**:



- You will not be expected to explain the enantioselectivity of this process.

Enantioselective γ-Lactam Synthesis

- In 2013, Romo reported the tertiary amine catalysed LUMO activation of α,β-unsaturated acid chlorides for reaction with aminomalonates:



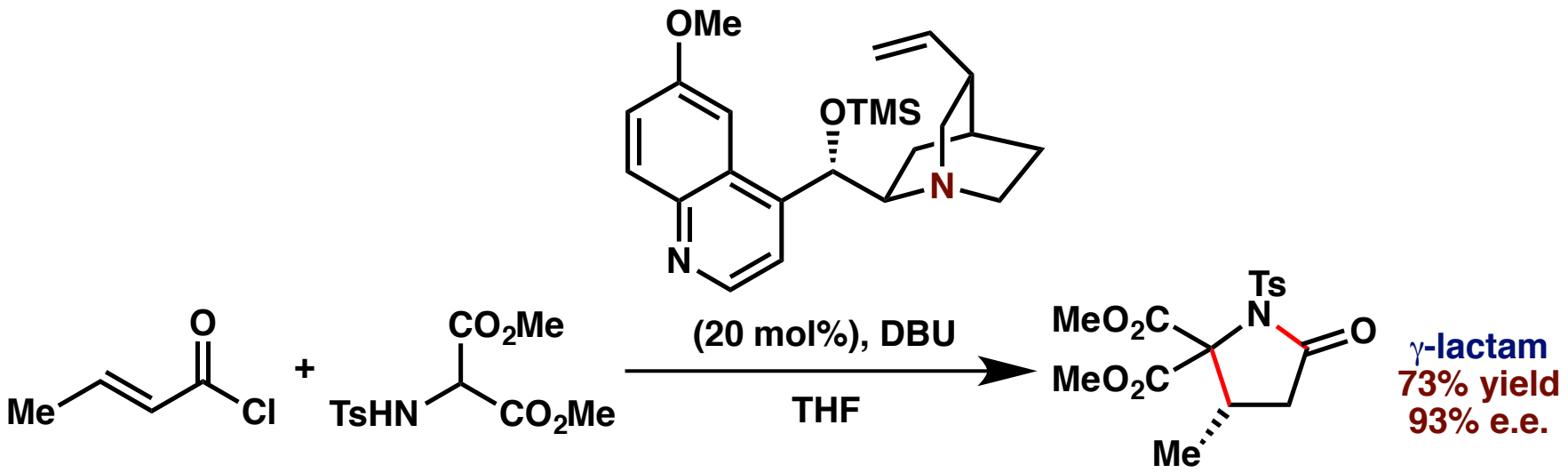
- For this class of organocatalytic reaction we must be able to:

1) Know how the organocatalyst **activates** the substrate (**activation mode**)

2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

Enantioselective γ-Lactam Synthesis

- First let's consider the **organocatalytic activation mode**:



- We have the following information:

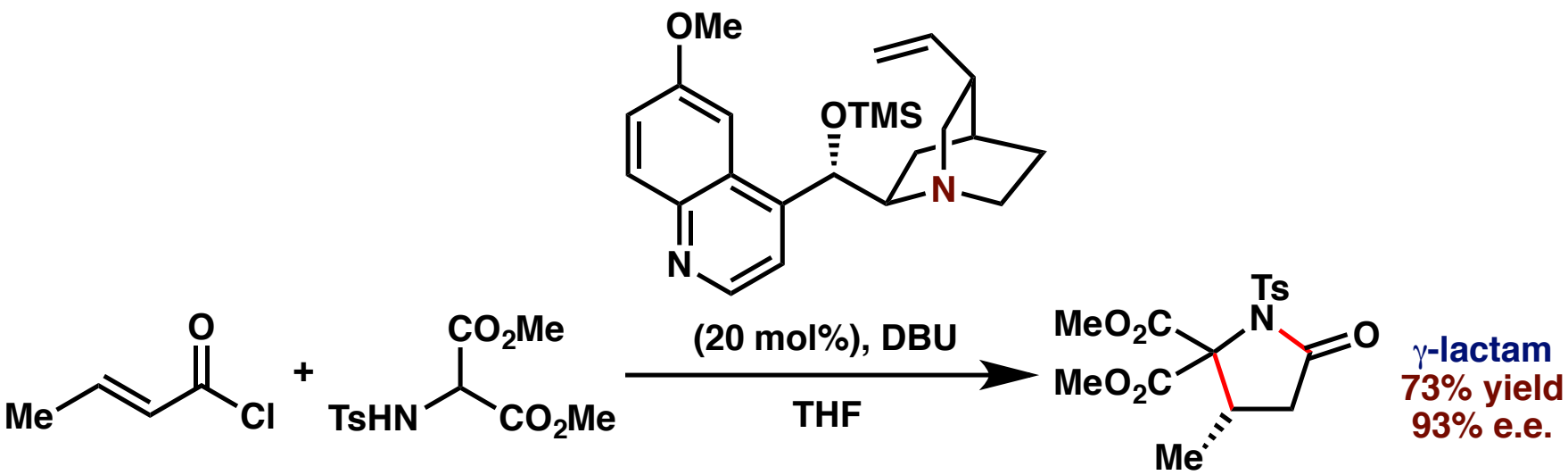
1) A **tertiary amine Lewis base** organocatalyst is used

2) One reactant contains an electrophilic α,β-unsaturated acid chloride. The other is a nucleophilic aminomalonate.

- This reaction proceeds *via* the **α,β-unsaturated acyl ammonium** activation mode.

Enantioselective γ-Lactam Synthesis

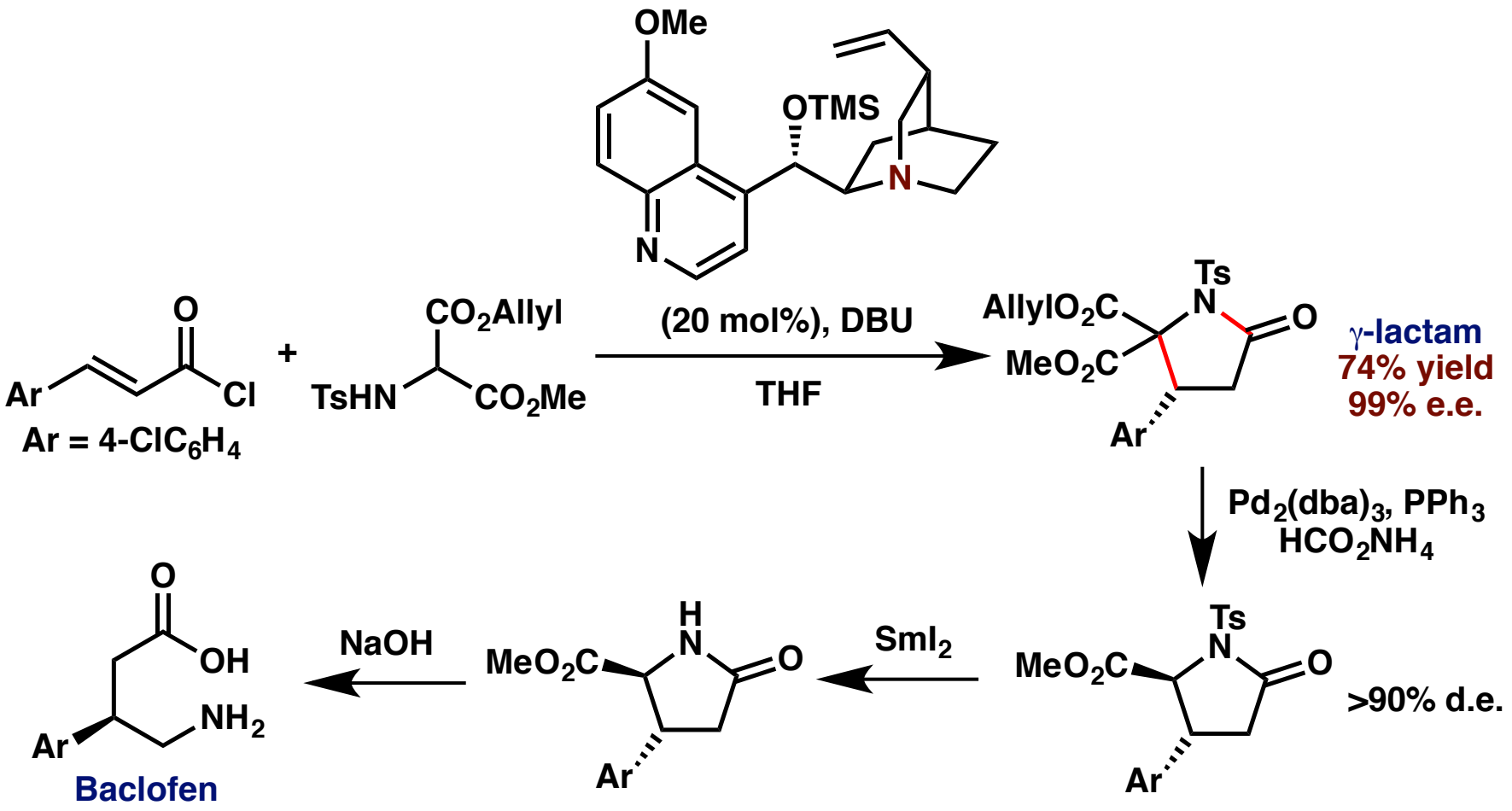
- Now let's consider the **curly arrow pushing mechanism**:



- You will not be expected to explain the enantioselectivity of this process.

Enantioselective γ-Lactam Synthesis

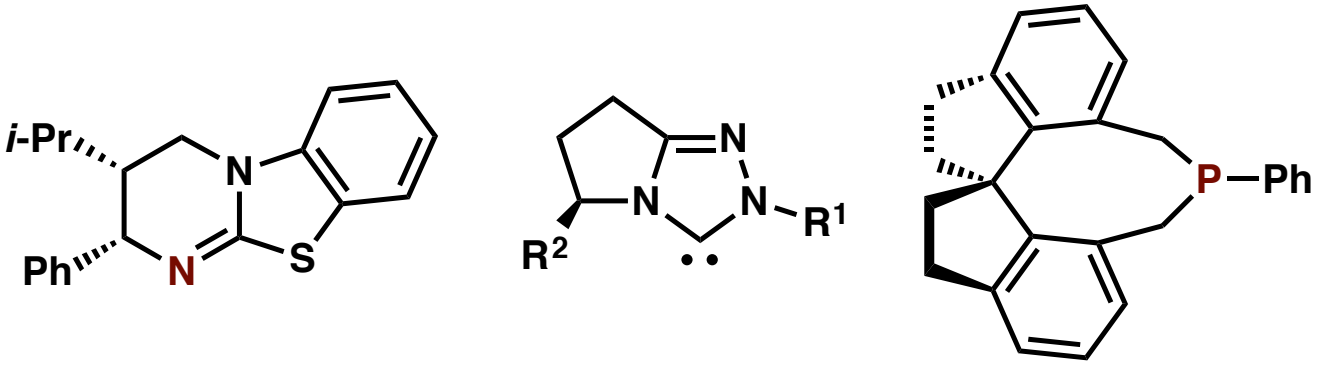
- Products were elaborated to neurotransmitter inhibitor baclofen:



Acyl Cation Organocatalysis Cheat Sheet

- For acyl cation organocatalysis, you must remember the following key information:

- Acyl cations and α,β-unsaturated acyl cations can be accessed using a variety of **tertiary amines, N-heterocyclic carbenes** and **phosphines**.



- Acyl cations and α,β-unsaturated acyl cations can be generated from a range of electrophilic substrates including acid chlorides/fluorides/esters/acids/anhydrides.

- You will be expected to be able to identify the specific **organocatalytic activation mode** involved in a given reaction and provide a **curly arrow pushing mechanism**.

- Rationalising the stereochemical outcome of reactions involving organocatalytic acyl cations is beyond the scope of this course.

Tackling Organocatalysis Questions – Strategy and Tips

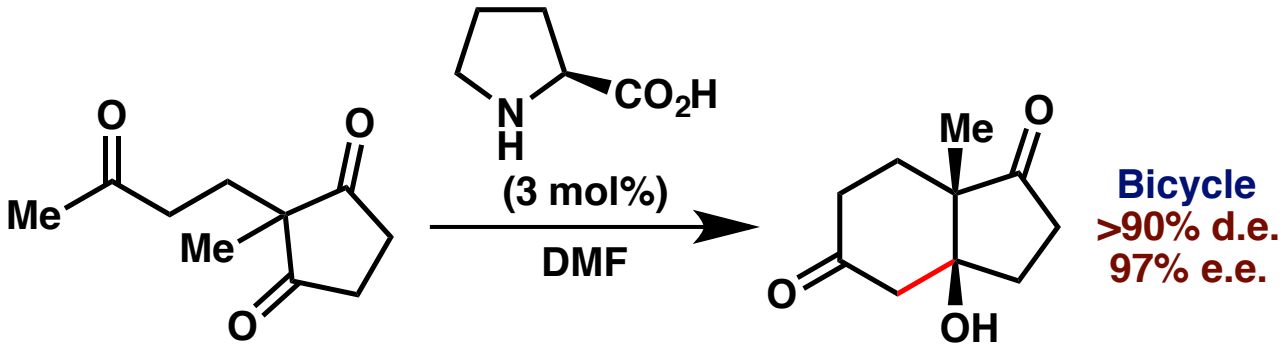
- When faced with an unseen problem you should be able to:

1) Identify how the organocatalyst **activates** the substrate (**activation mode**). This will be restricted to those described throughout in this course.

2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

3) Rationalise the **stereochemical outcome** of the reaction (enantio- and/or diastereocontrol if relevant) by drawing an appropriate 3D transition state. This is expected for organocatalytic processes involving enamine or iminium intermediates.

- Let's think of the best general strategy for solving organocatalysis problems…



Tackling Organocatalysis Questions – Strategy and Tips

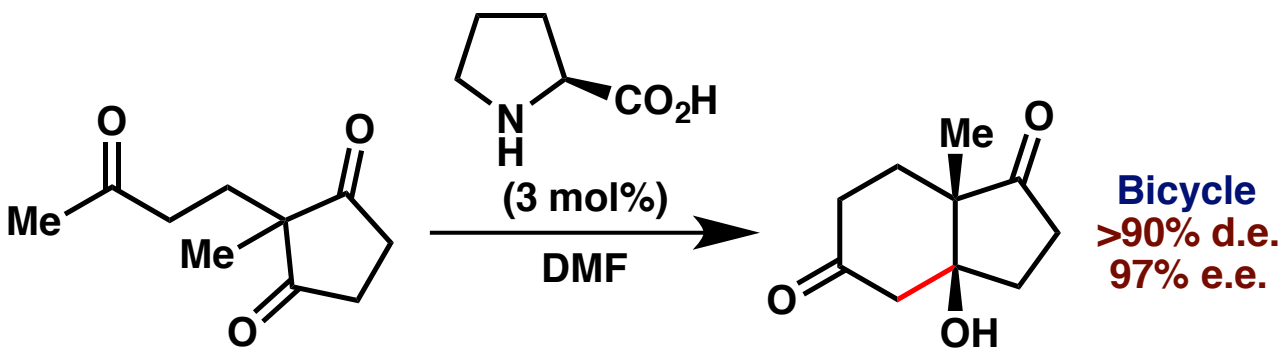
1) Identify how the organocatalyst **activates** the substrate (**activation mode**).

Step a) **Consider the organocatalyst** and classify it as either a secondary amine, tertiary amine, phosphine, N-heterocyclic carbene etc.

Step b) Next **consider the reagents** used in the reaction. What types of functional groups are present? e.g. ketones, aldehydes, acid chlorides, α,β-unsaturated species.

Step c) Finally, **look at the product** of the reaction. Identify between which atoms new bonds are formed? Consider how these new bonds are likely to be formed?

- Following this protocol should allow you to provide a reasoned justification for the organocatalytic activation mode chosen.



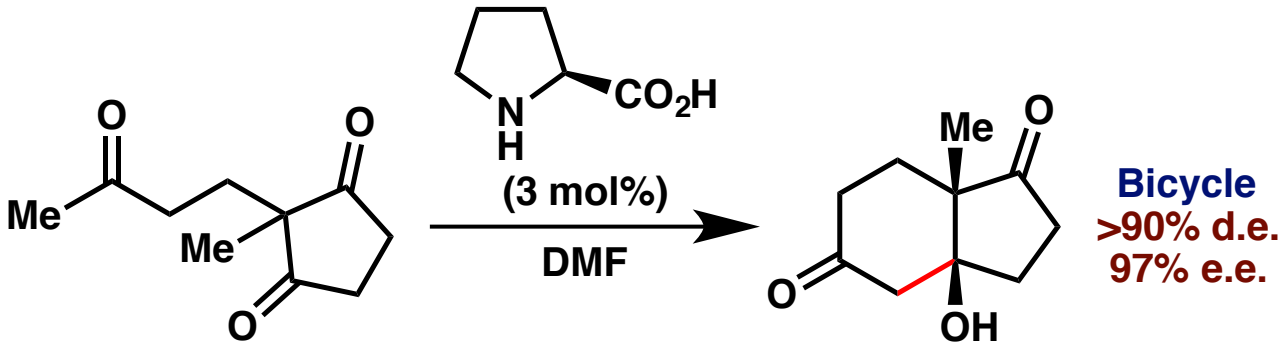
Tackling Organocatalysis Questions – Strategy and Tips

2) Draw a **curly arrow pushing mechanism** that rationalises product formation.

Step a) **Consider the activation mode**. The first step in the curly arrow pushing mechanism will be reaction of the organocatalyst with one of the reagents.

Step b) Next **look at the product** of the reaction. Identify between which atoms new bonds are formed? Consider how these new bonds are likely to be formed?

- Following this protocol should allow you to draw a suitable curly arrow pushing mechanism. **Remember to draw FULL mechanisms, with no steps left out**!



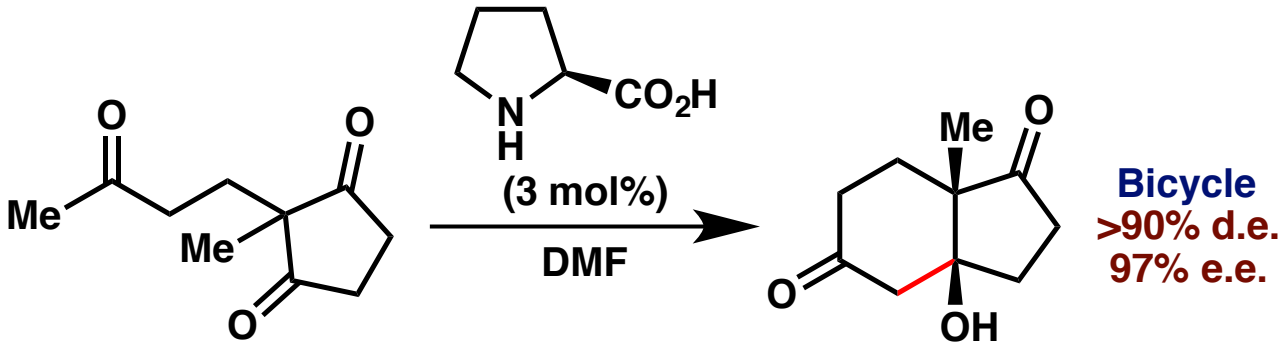
Tackling Organocatalysis Questions – Strategy and Tips

3) Rationalise the **stereochemical outcome** of the reaction (enantio- and/or diastereocontrol if relevant) by drawing an appropriate 3D transition state.

Step a) **Consider the key activated species**. What is the lowest energy form? (must consider the most stable configuration and conformation in many cases)

Step b) Next **look at the product** of the reaction. What is the stereochemistry within the product? Does it agree with the 3D transition state representation you have drawn.

- **Do not** think of every reaction as a unique case. Each activation mode has a general stereochemical model associated with it. Determine the activation mode, consider how the catalyst will function, and draw a suitable 3D transition state model.



Tackling Organocatalysis Questions – Strategy and Tips

The single best advice – practice, practice, practice!

Lecture 3: LUMO-Lowering Organocatalysis

Key learning objectives:

- Traditional LUMO lowering of carbonyl compounds using Lewis acids.
- The iminium organocatalytic activation mode: definition; general catalytic cycle; various intra- and intermolecular functionalisation reactions; curly arrow pushing mechanisms; stereochemical rationale.
- Iminium-enamine organocatalytic cascades.
- Alternative LUMO-lowering organocatalytic activation modes.
- Acyl cation organocatalytic activation mode: acyl ammonium/azolium intermediates; definition; general catalytic cycle; various intra- and intermolecular functionalisation reactions; curly arrow pushing mechanisms.
- α,β-Unsaturated acyl ammonium/azolium activation modes: definition; general catalytic cycle; various intra- and intermolecular functionalisation reactions; curly arrow pushing mechanisms.

Lecture 3 Revision

To reinforce your understanding of the contents of this lecture, please refer to:

- *Organic Chemistry 2nd Ed.* (J. Clayden, N. Greeves and S. Warren, Oxford University Press, 2012, ISBN 978-0-19-927029-3). Chapter 41 is particularly relevant.
- *New Frontiers in Asymmetric Catalysis* (K. Mikami and M. Lautens, Wiley, 2007). Downloadable from University Network. DOI: 10.1002/0470098007
- *Catalytic Asymmetric Synthesis 3rd Ed.* (I. Okima, Wiley, 2010). Downloadable from University Network. DOI: 10.1002/9780470584248
- *Prof. MacMillan Short-Course:* www.princeton.edu/chemistry/macmillan/research/
- Leading review articles on iminum catalysis (*Chem. Rev.*, 2007, **107**, 5416) and acyl cation catalysis (*Synthesis*, 2014, **46**, 1823)