CHT402
Recent Advances in Homogeneous Catalysis
Organocatalysis Workshop

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Workshop Outline

- **Unit 1: Introduction to Organocatalysis;** recap of fundamental concepts and definitions; definition of asymmetric catalysis and organocatalysis; historical perspective.

- **Unit 2: HOMO-Raising Organocatalysis;** α-functionalisation of carbonyl compounds; enamine organocatalytic activation mode; bifunctional vs. steric control; catalyst synthesis and reactivity.

- **Unit 3: LUMO-Lowering Organocatalysis;** β-functionalisation of α,β-unsaturated carbonyl compounds; iminium organocatalytic activation mode.

- **Unit 4: Research in the Morrill Group**

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

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. *Catalytic Asymmetric Synthesis 3rd Ed.* (I. Okima, Wiley, 2010). Downloadable from University Network. DOI: 10.1002/9780470584248
3. *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.

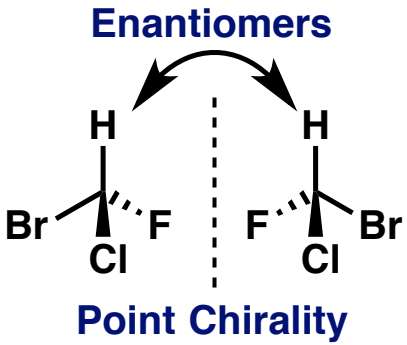
- **Learning Central:** I have set up a folder on Learning Central that will contain all information for this course.

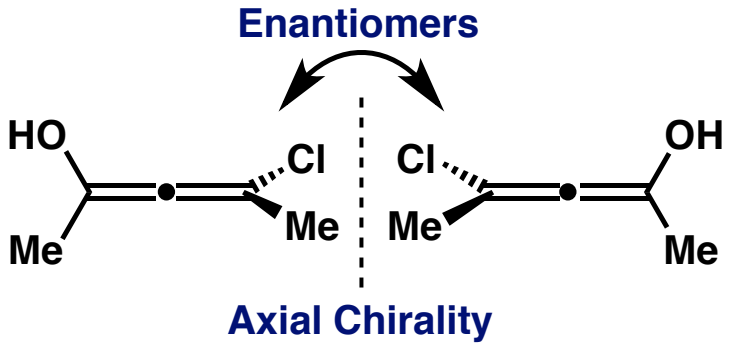
- **Me:** Should you not be able to find an answer to a question that specifically relates to this course, please email (MorrillLC@cardiff.ac.uk) or visit (1.47B) anytime. **In addition, I will specifically keep Monday 4-6pm free each week for office visits.**

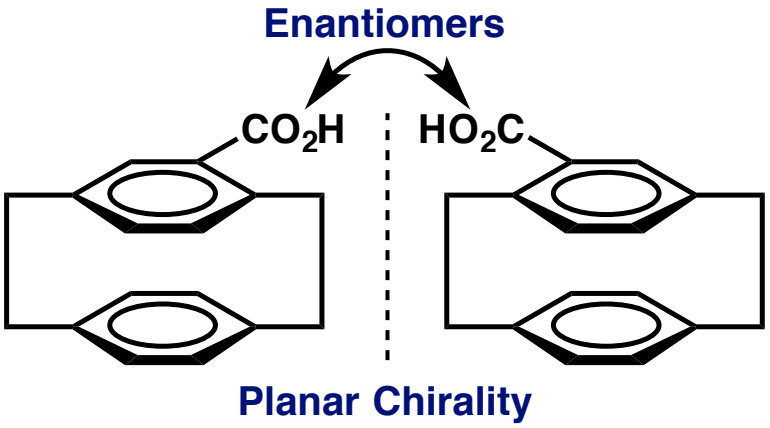
-  **:** Indicates worked examples to be performed during lectures.

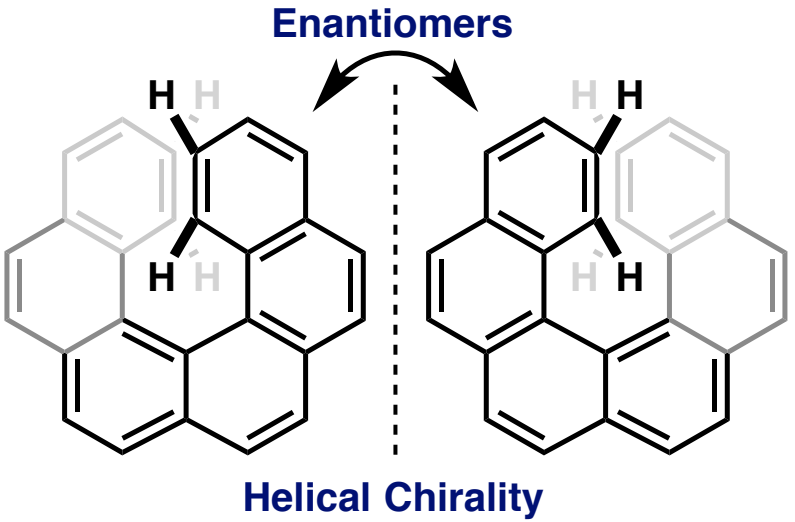
Recap of Fundamental Concepts and Definitions

- **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**.





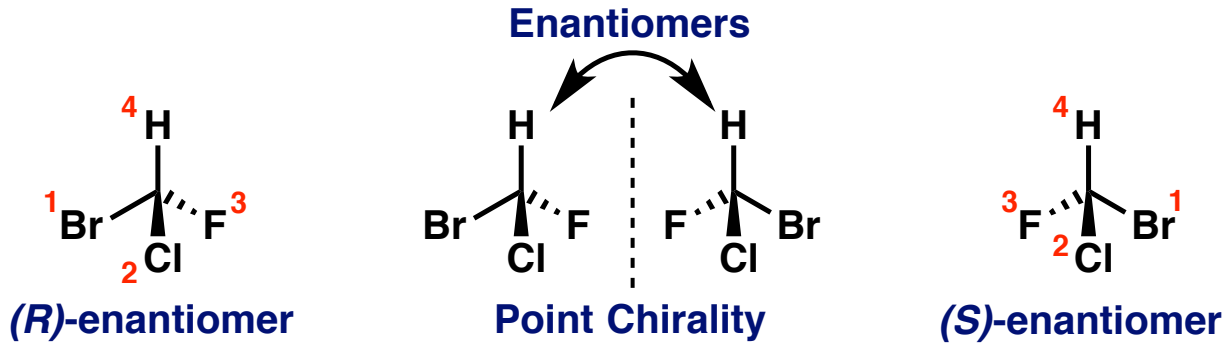




For further reading refer to *Organic Chemistry 2nd Ed.* (J. Clayden et al.) Chapter 14 pp 302-327.

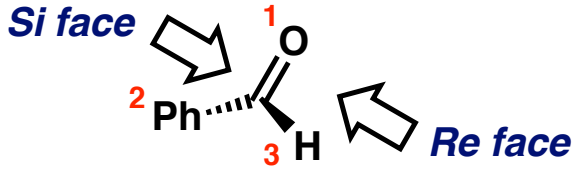
Recap of Fundamental Concepts and Definitions

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



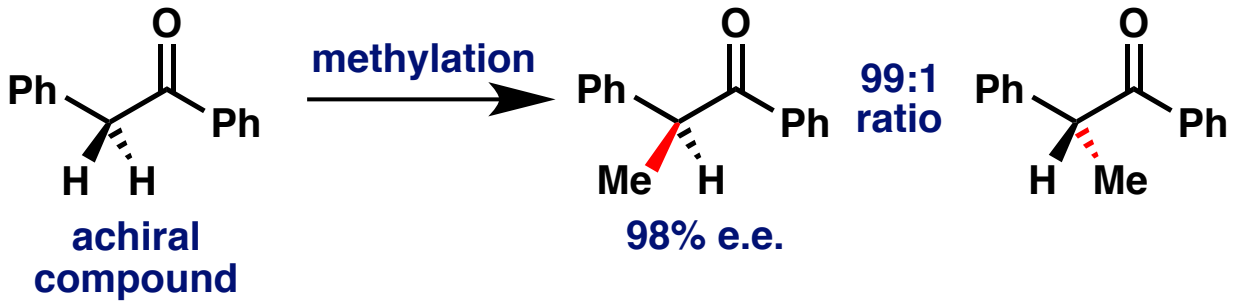
- **Diastereomers** can occur when there is more than one stereogenic center present

- **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.

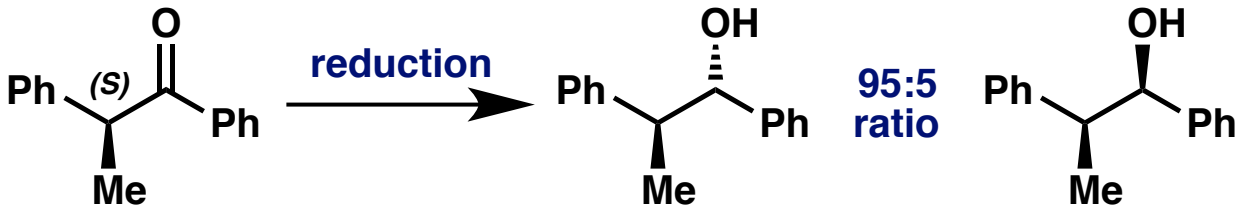


Recap of Fundamental Concepts and Definitions

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



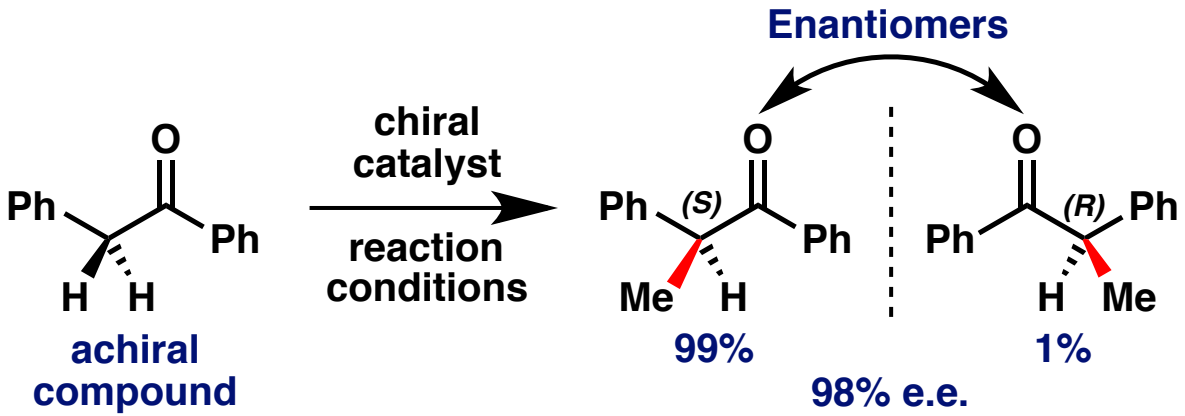
- **Diastereomeric excess (d.e.)** is the excess of one diastereomeric form over another and is often quoted to describe diastereo-selective reactions.



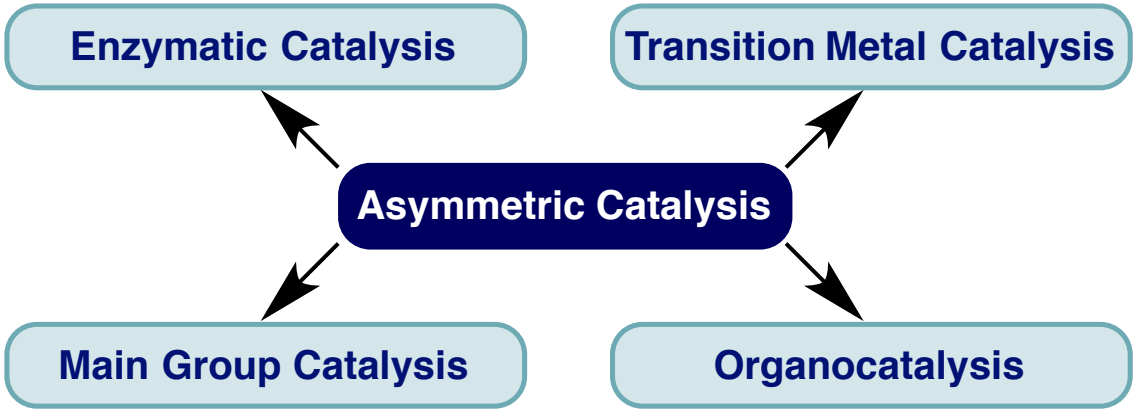
- **Stereo-selective** reactions can be both **diastereo-selective** (favours the formation of one diastereomer) AND **enantio-selective** (favours the formation of one enantiomer)

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.

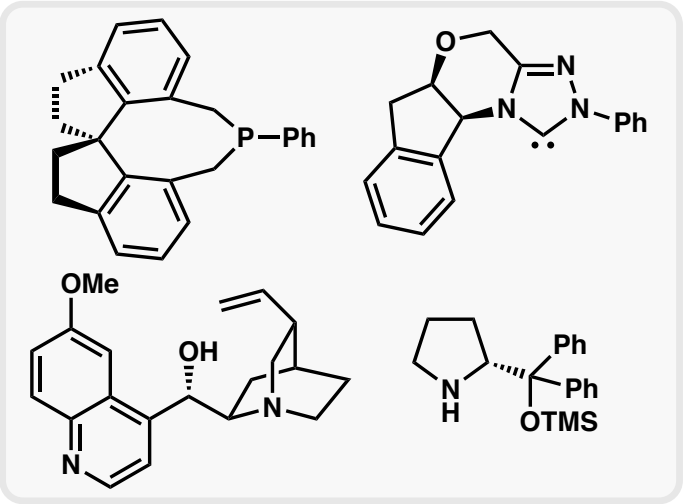


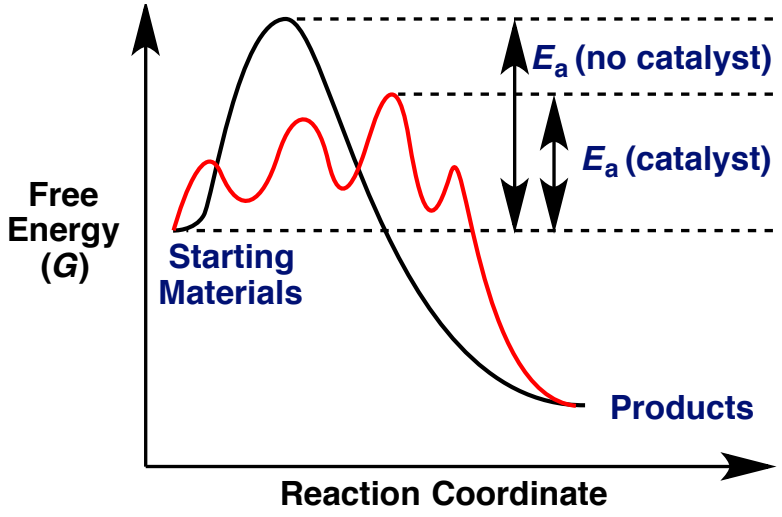
- **Asymmetric catalysis** can be sub-divided into 4 primary areas:



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.

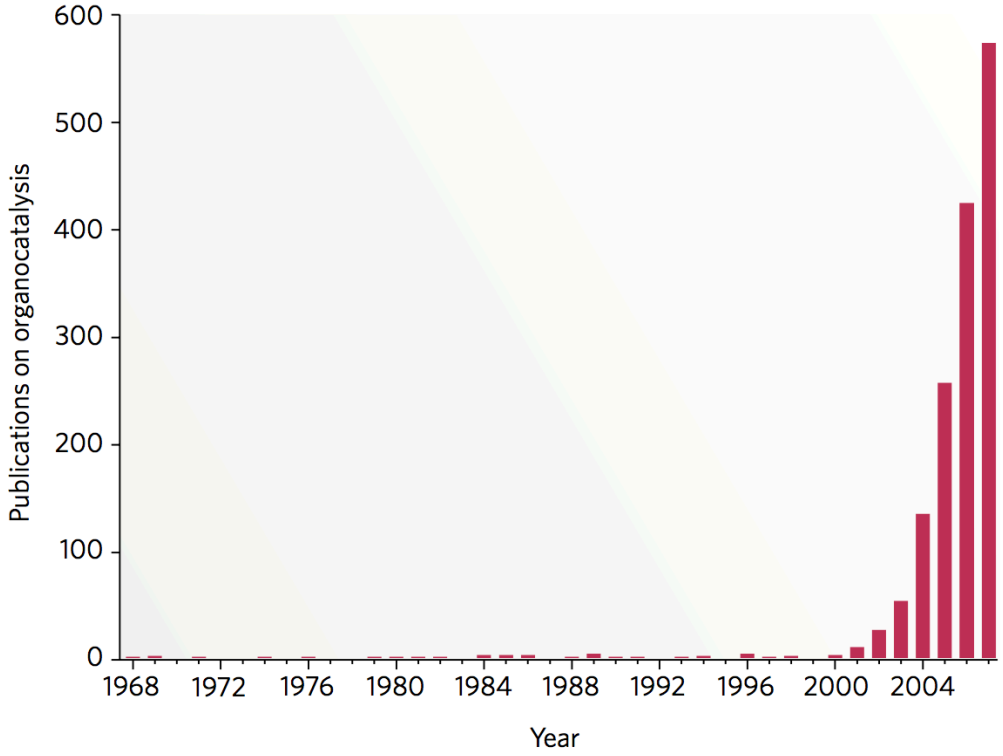




For an overview see D. W. C. MacMillan, *Nature*, 2008, **455**, 304.

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.

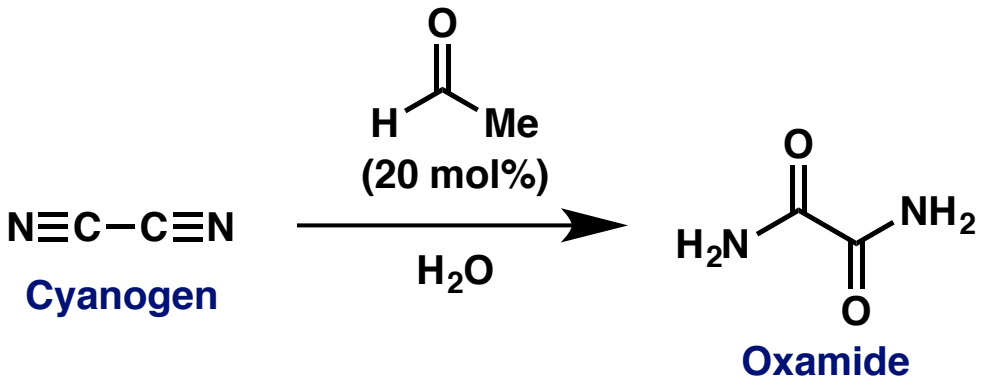


- However, there were several pioneering reports of metal-free catalysis prior to the year 2000, which laid the foundations for further development.

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**.

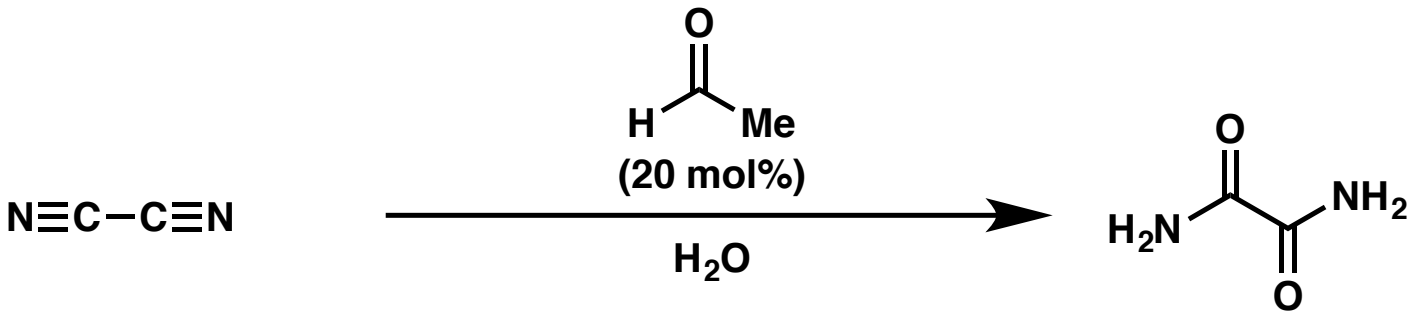
3) No reaction occurs without acetaldehyde, therefore it **increases the rate**.

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

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

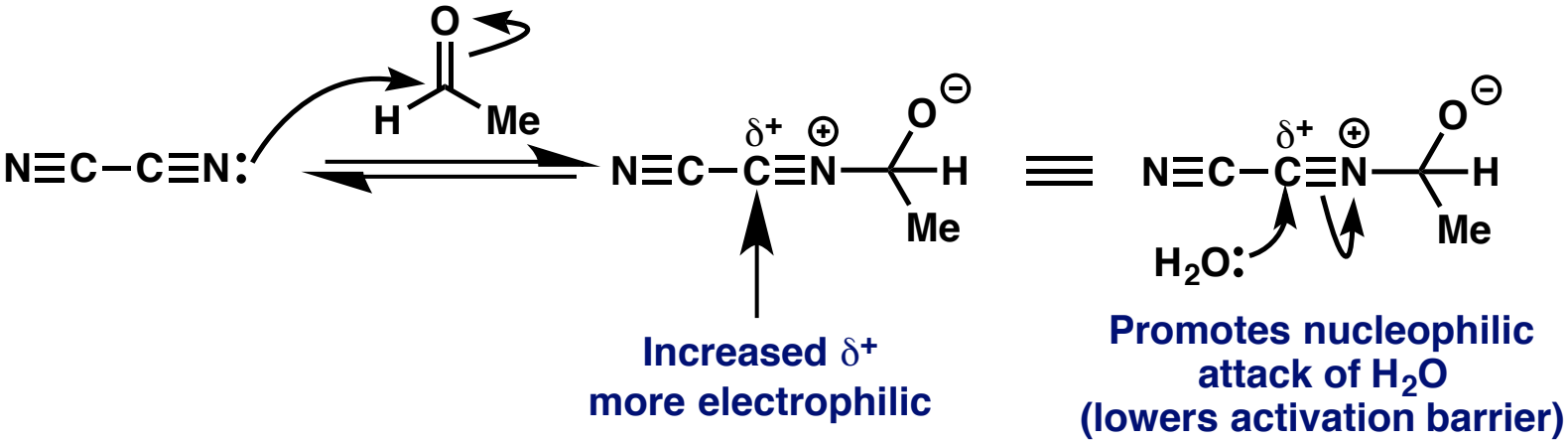
Organocatalysis – A Historical Perspective

- 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**

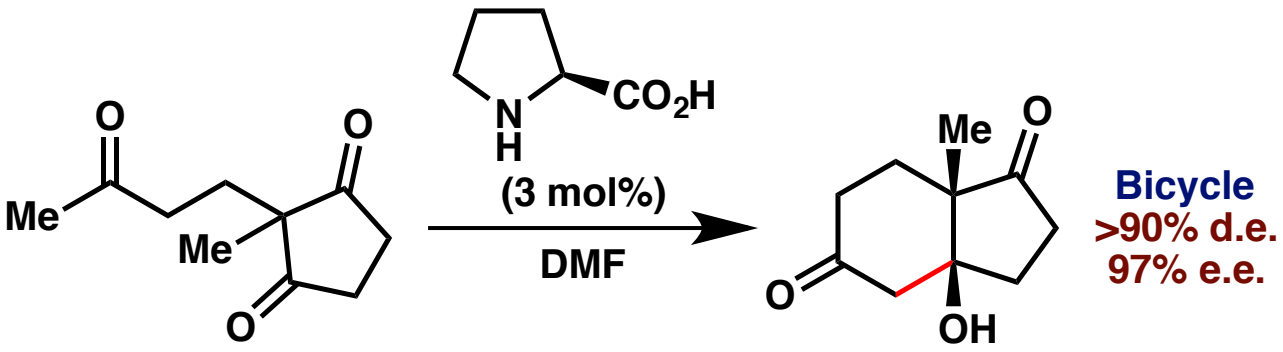
2) How the organocatalyst **activates** the substrate towards a given reaction (**activation mode**)

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**.

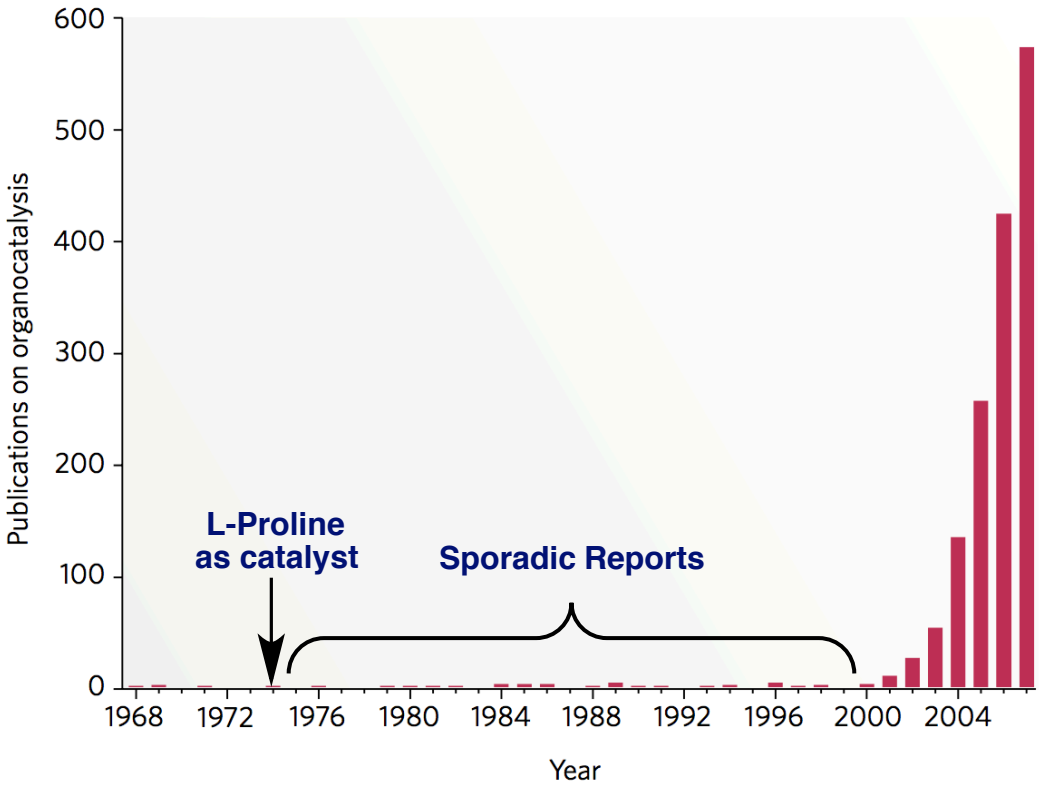


- This reaction employs a **chiral catalyst** and hence the reaction is **catalytic AND asymmetric**.
- One **stereoisomer** of the product is favoured due to the use of a chiral catalyst.
- Due to the presence of two stereogenic centres within the product, both **enantiocontrol (e.e.)** and **diastereocontrol (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"*

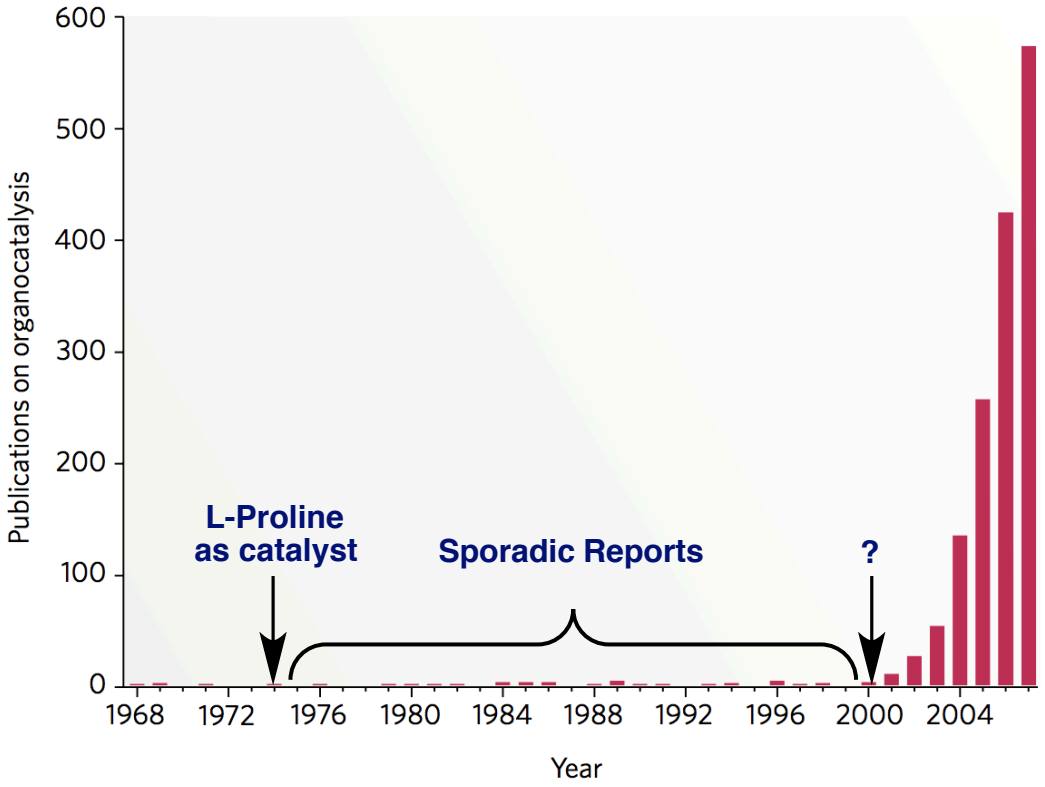
- Why did he omit organocatalysis from his vision of the future of organic synthesis?

- 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?

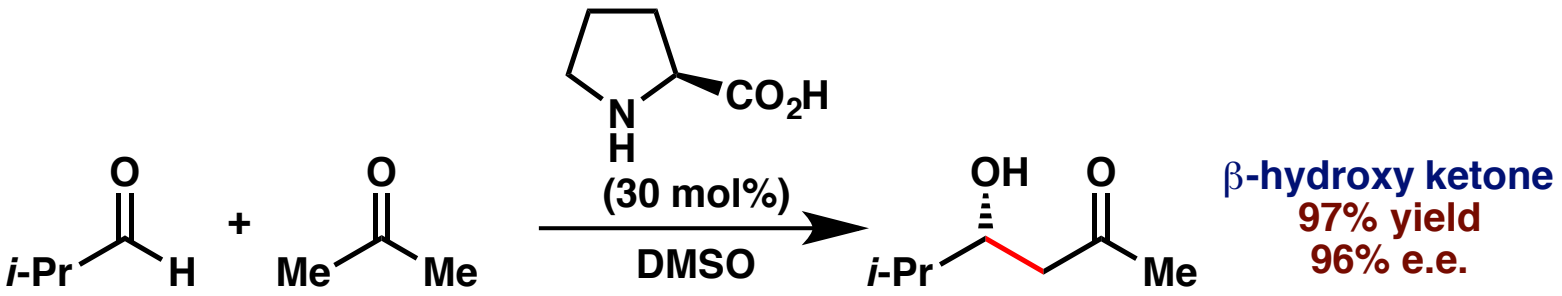


- In 2000, two landmark reports from **List** and **MacMillan** conceptualised the field, paving the way for others to contribute. Both are likely future Nobel Prize recipients!

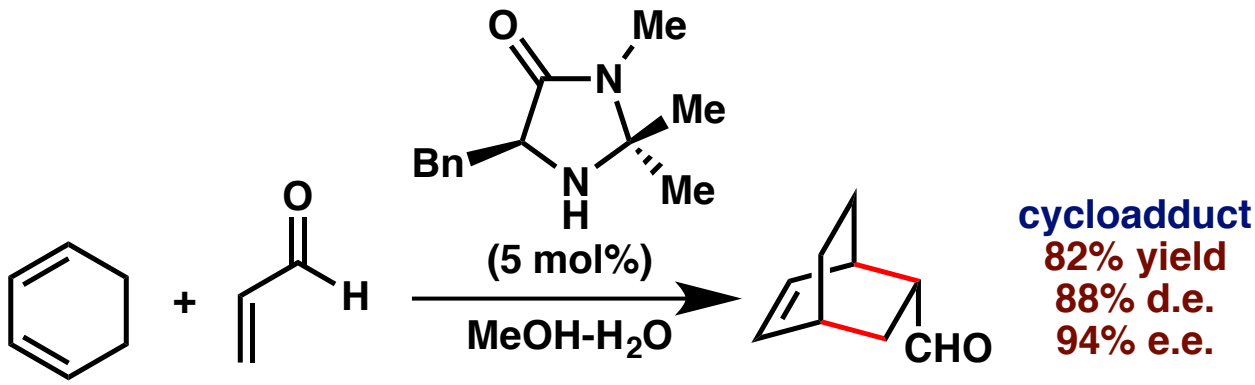
B. List *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 2395; D. W. C. MacMillan *et al.*, *J. Am. Chem. Soc.*, 2000, **122**, 4243.

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:

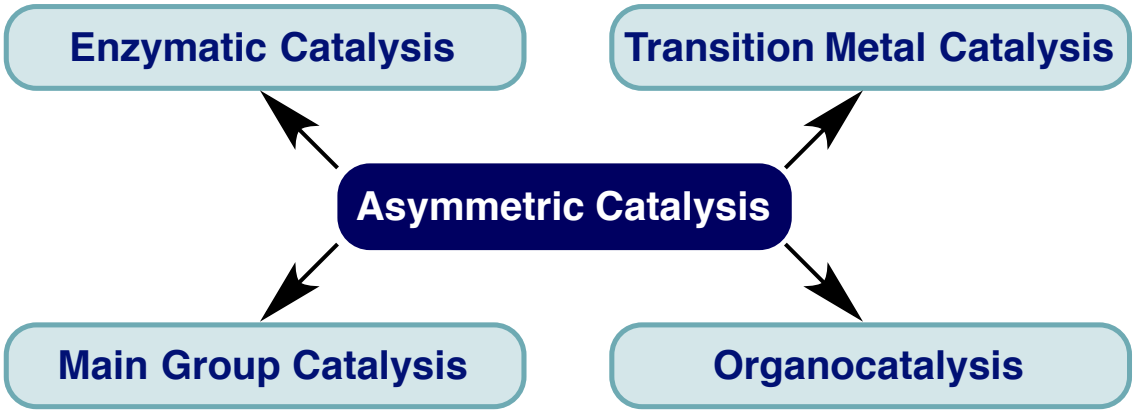
1) Low air and moisture sensitivity – operationally easy to handle.

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

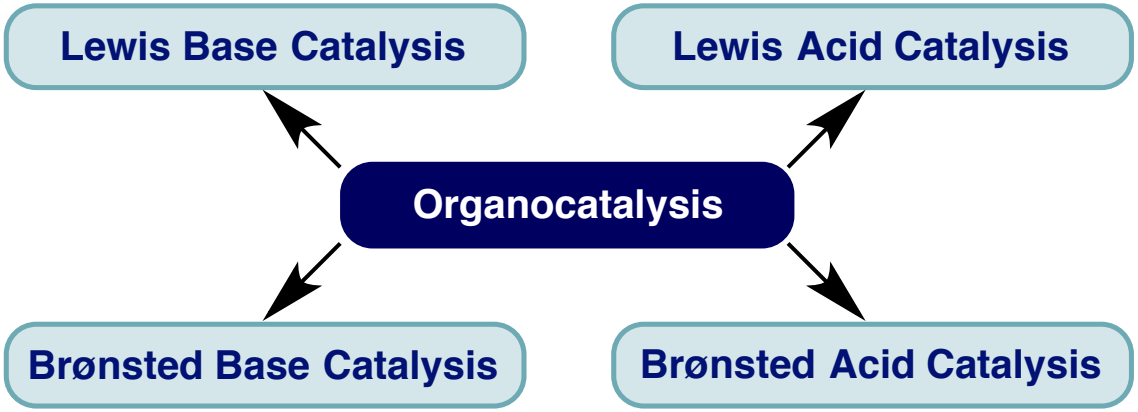
- The pioneering reports of List and Macmillan have resulted in organocatalysis being thoroughly established as the **4th main branch of asymmetric catalysis**.



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**:



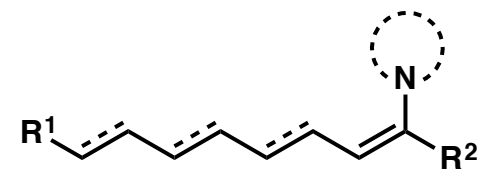
- **Lewis bases** – able to donate a lone pair of electrons
- **Lewis acids** – able to accept a lone pair of electrons
- **Brønsted bases** – able to accept a proton
- **Brønsted acids** – able to donate a proton
- This course will focus exclusively on **Lewis base organocatalysts**.

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

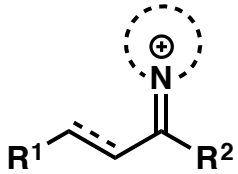
Organocatalysis – The Picture Today

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

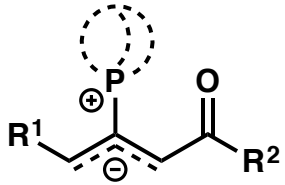
Covalent Activation Modes



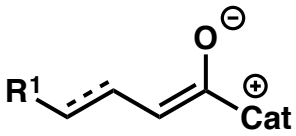
Enamine (di-, tri-, tetra-enamine) Catalysis



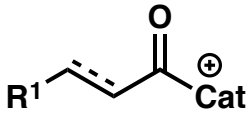
Iminium Catalysis



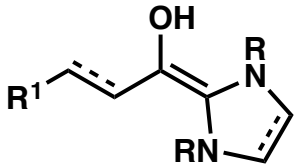
Phosphine Catalysis



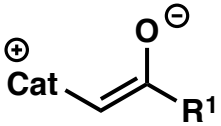
C(1)-Enolate (di-enolate) Catalysis



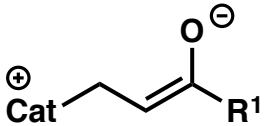
Acyl ammonium/azolium Catalysis



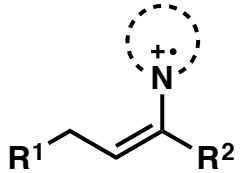
N-Heterocyclic Carbene Catalysis



C(2)-Enolate Catalysis

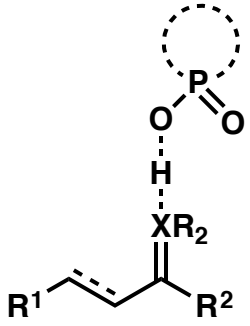


C(3)-Enolate Catalysis

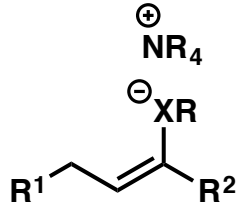


SOMO Catalysis

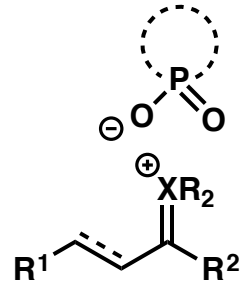
Non-Covalent Activation Modes



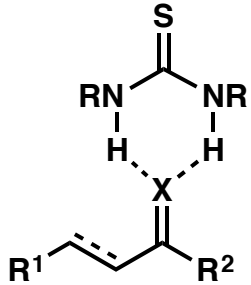
Brønsted Acid Catalysis



Phase-transfer Catalysis



Chiral Anion Catalysis



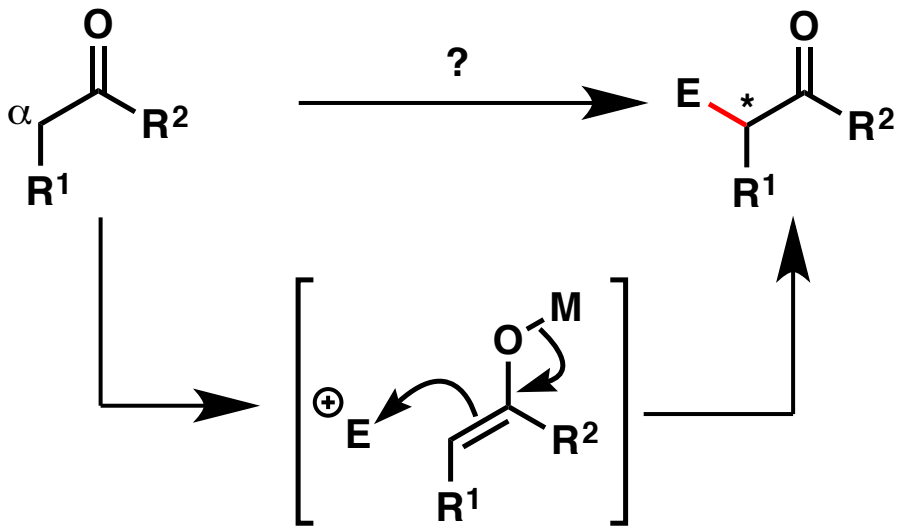
Hydrogen Bonding Catalysis

- 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?



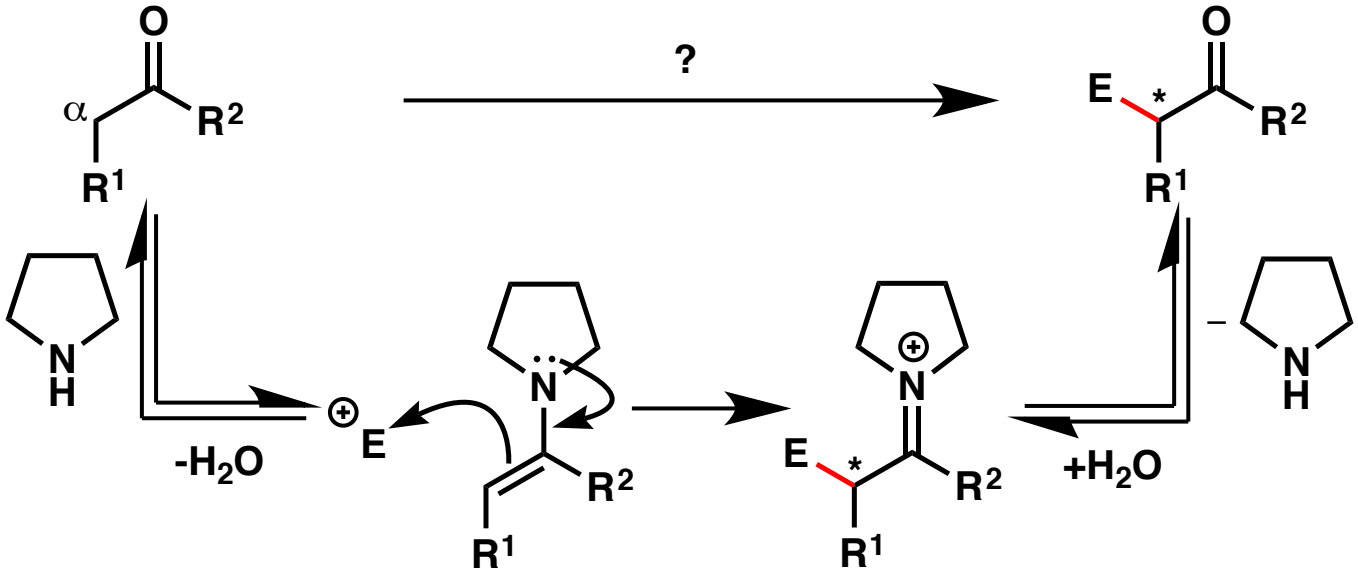
- A commonly employed method is to deprotonate at the α-position with a suitable base (e.g. lithium diisopropylamide (LDA)) to form a metal bound enolate.

- 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?

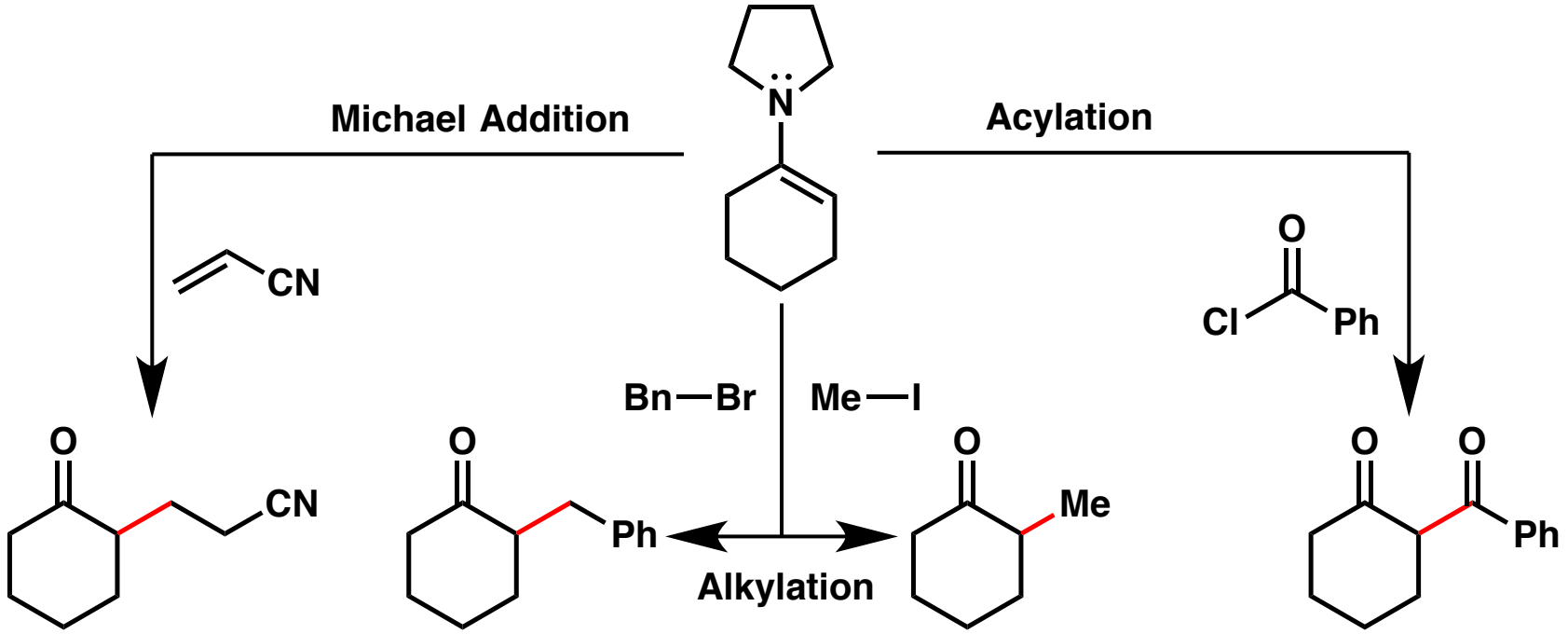


- An alternative option involves the use of a secondary amine (e.g. pyrrolidine) to generate an enamine.
- This enamine is also nucleophilic (HOMO-raised) and can react with an electrophile at the α-position.
- In certain cases, this can form a new stereogenic center.

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.

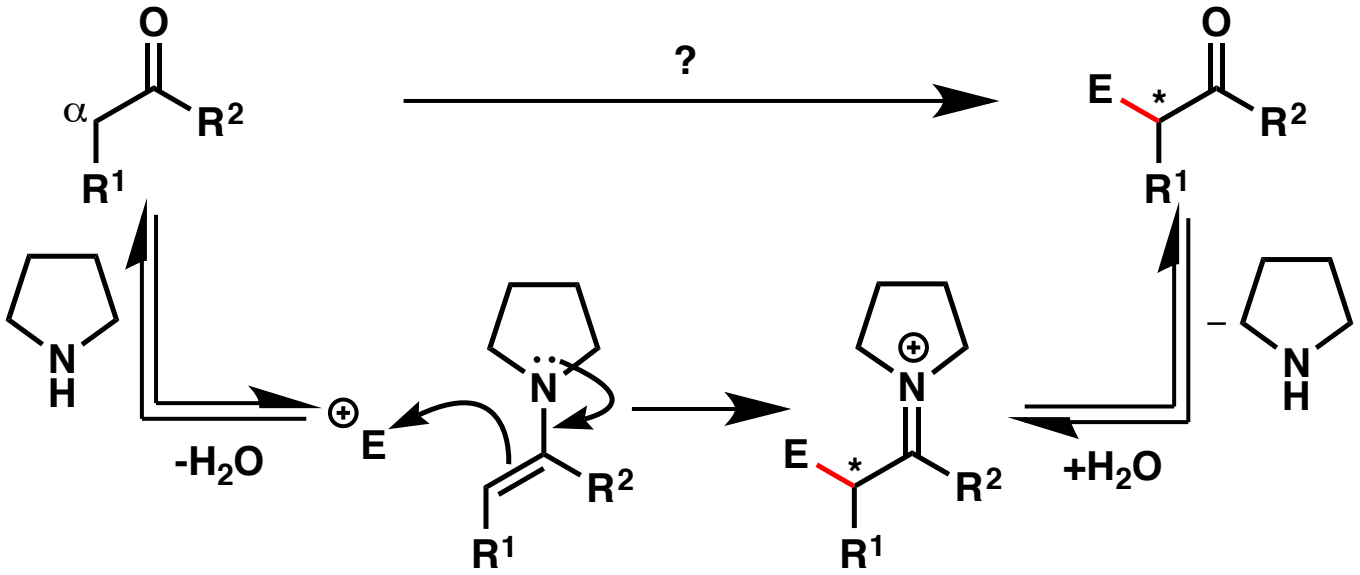


- All products shown are after hydrolysis. We must be able to draw curly arrow pushing mechanisms for all transformations.

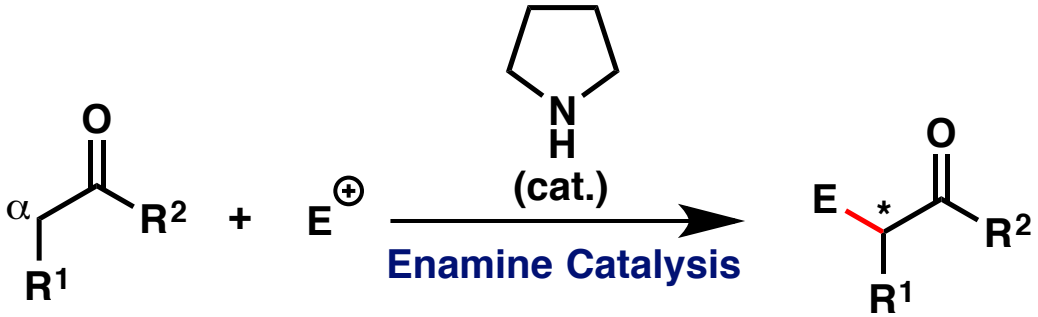
- We will go through one now in detail on the whiteboard.

Functionalisation of Carbonyl Compounds

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



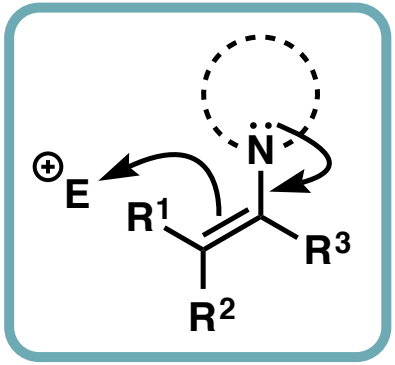
- The secondary amine is regenerated, providing the basis for a catalytic system.



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.

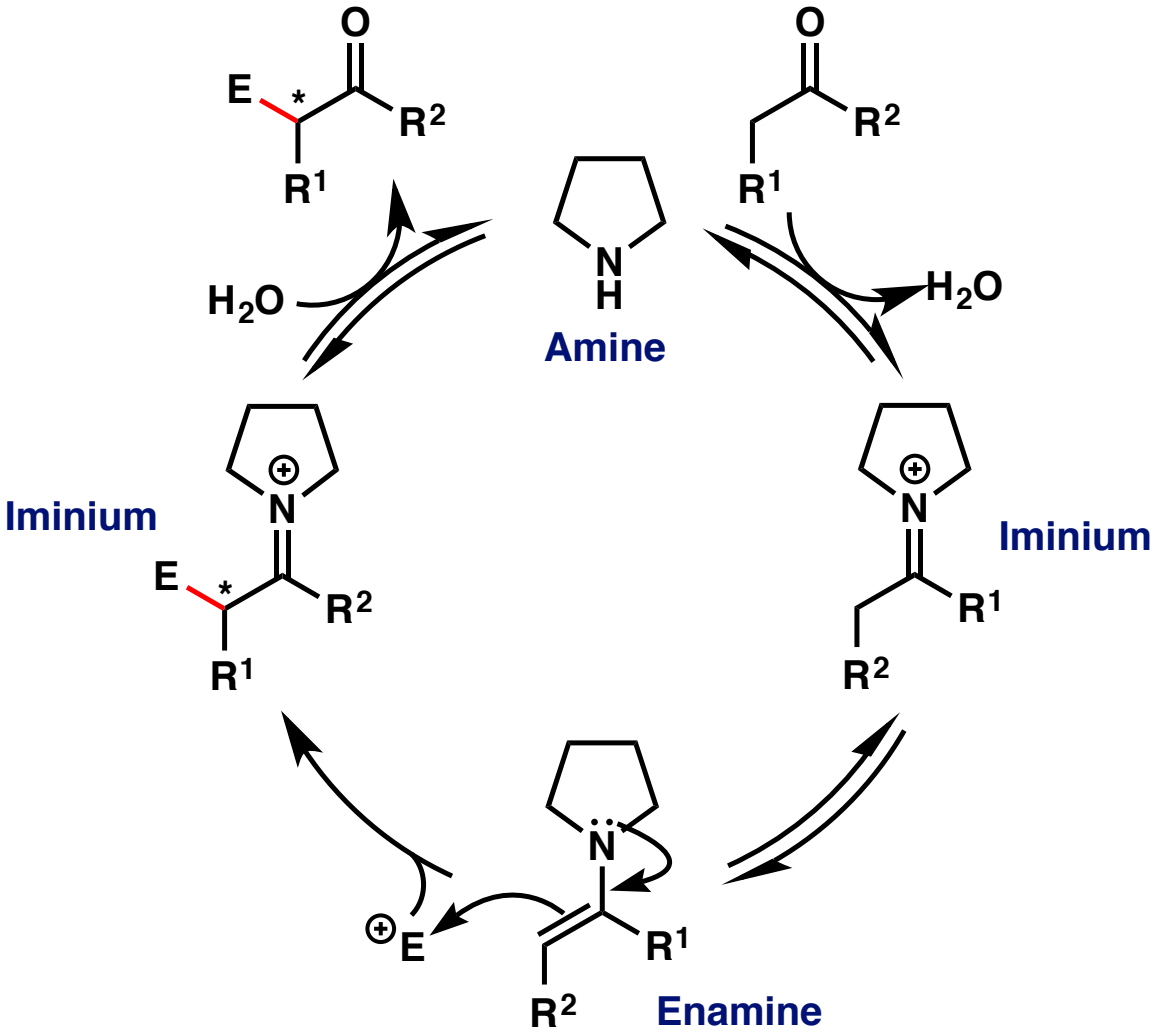
2) It is a **nucleophilic (HOMO-raised)** activation mode – it reacts with electrophiles.

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

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

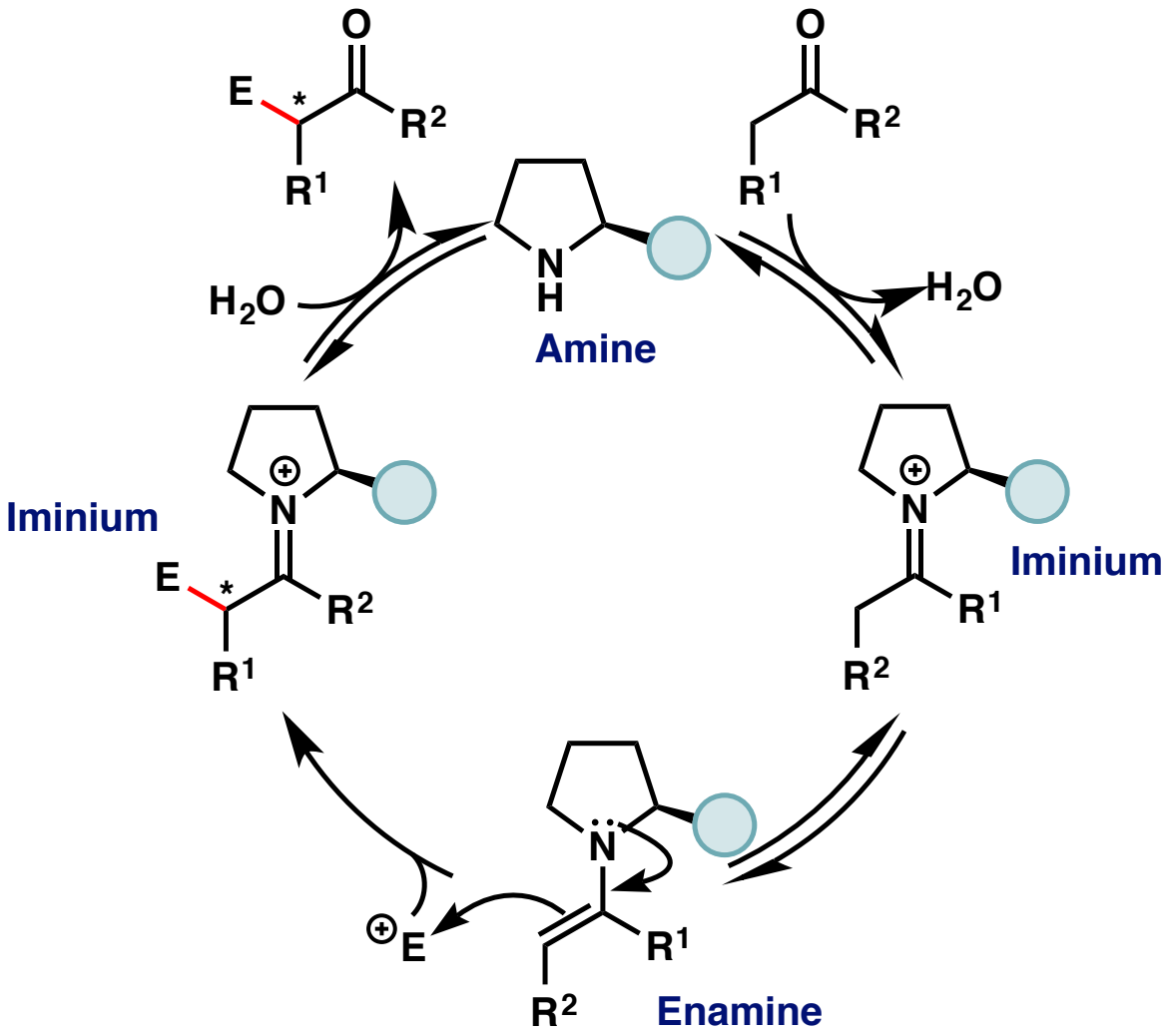
Enamine Organocatalysis – General Mechanism

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



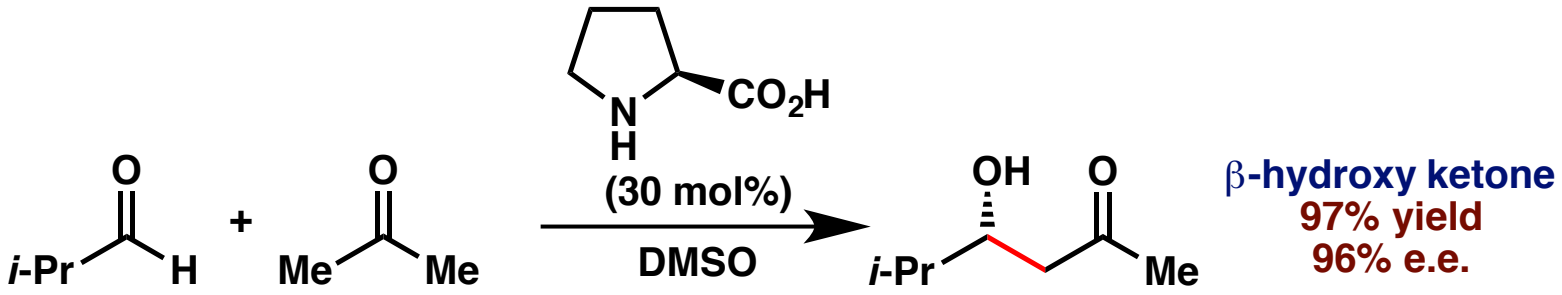
Enamine Organocatalysis – General Mechanism

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



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

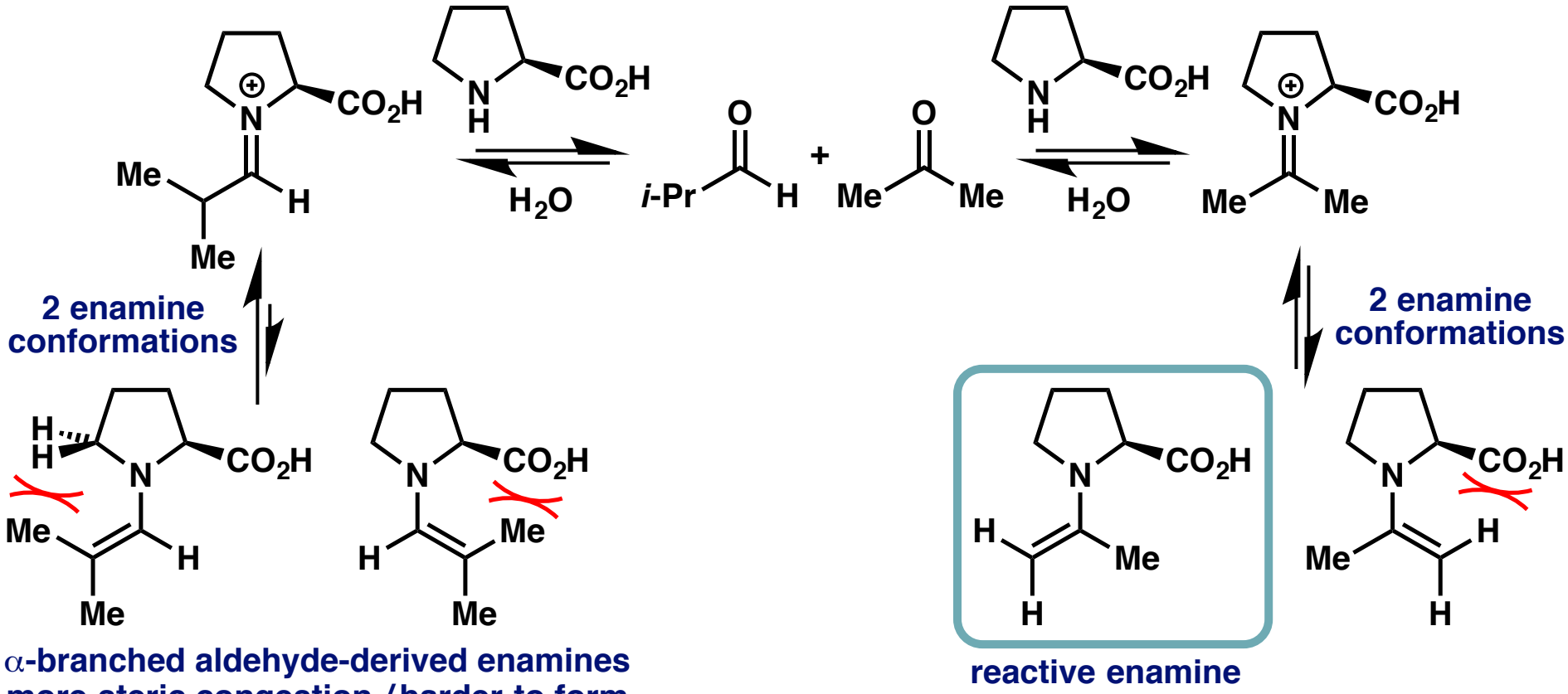
2) One reactant contains a **ketone** functional group and the other contains an **aldehyde** functional group.

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.

Intermolecular Asymmetric Aldol Reaction

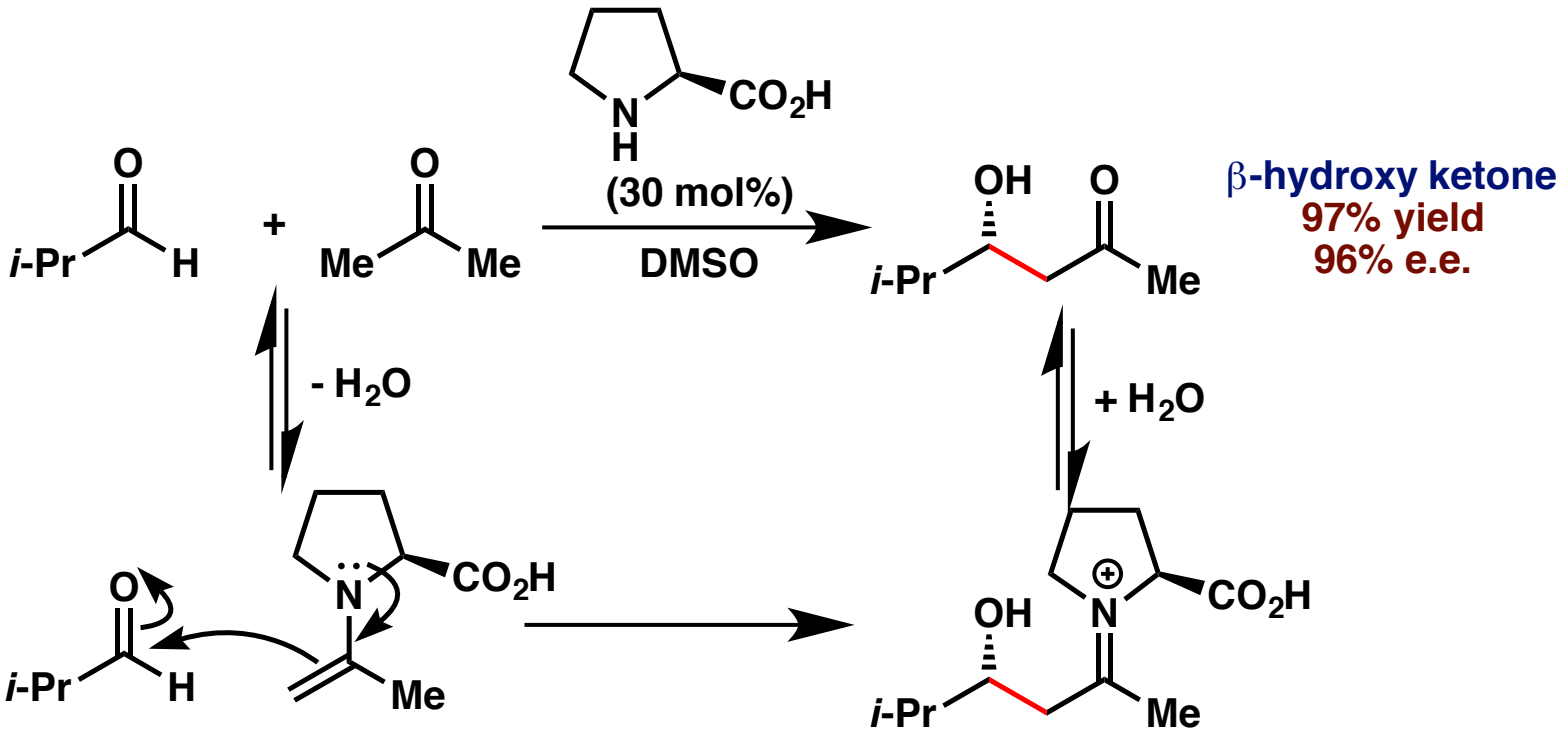
- Let's think about the key nucleophilic enamine species formed in detail:



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

Intermolecular Asymmetric Aldol Reaction

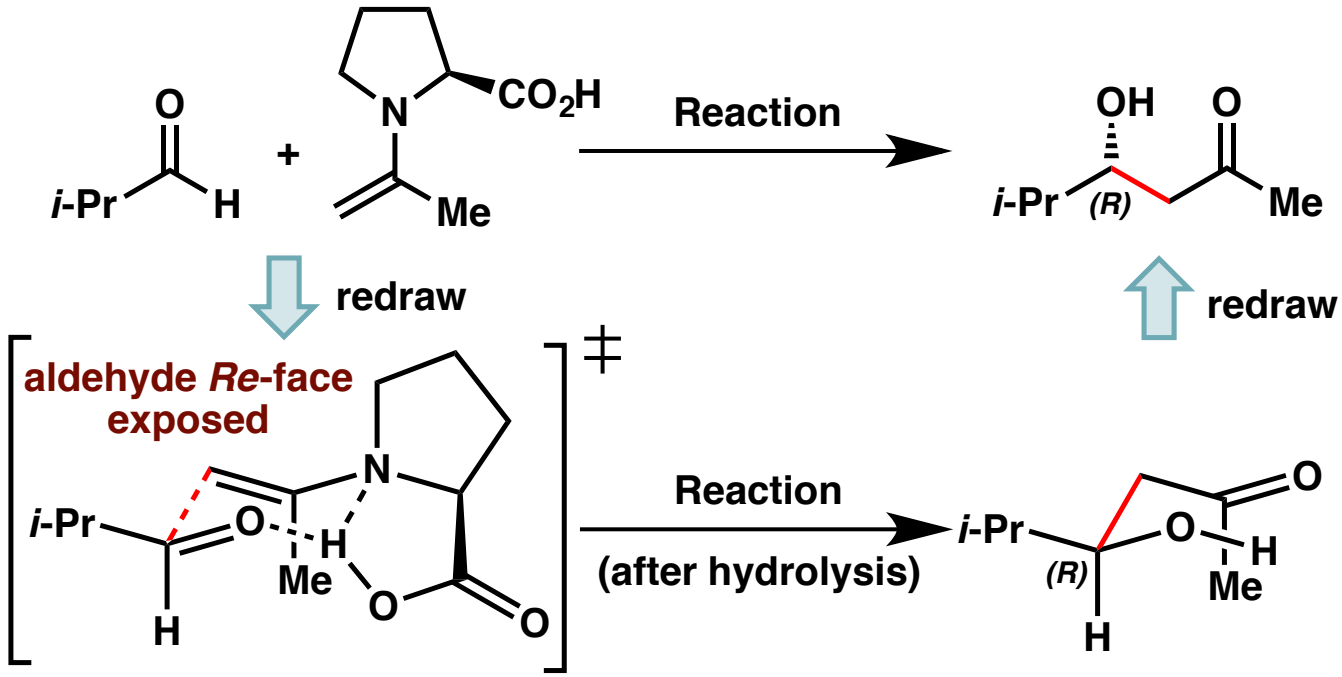
- Now let's consider the **curly arrow pushing mechanism**:



- 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:

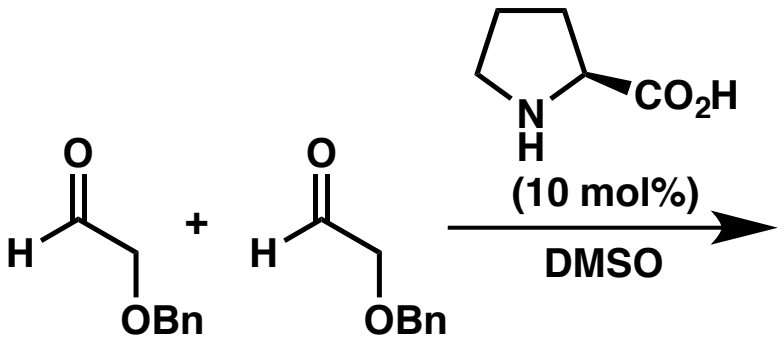


- Conformation such that **intermolecular hydrogen bond** can occur, which stabilises the transition state.

- 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 – Class Example

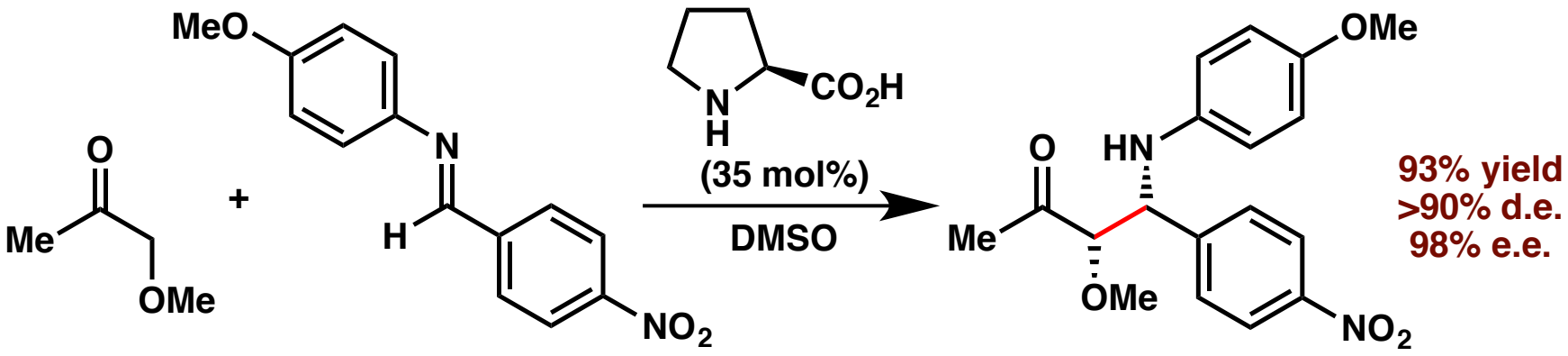
- Determine the major product for the reaction shown below:



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

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

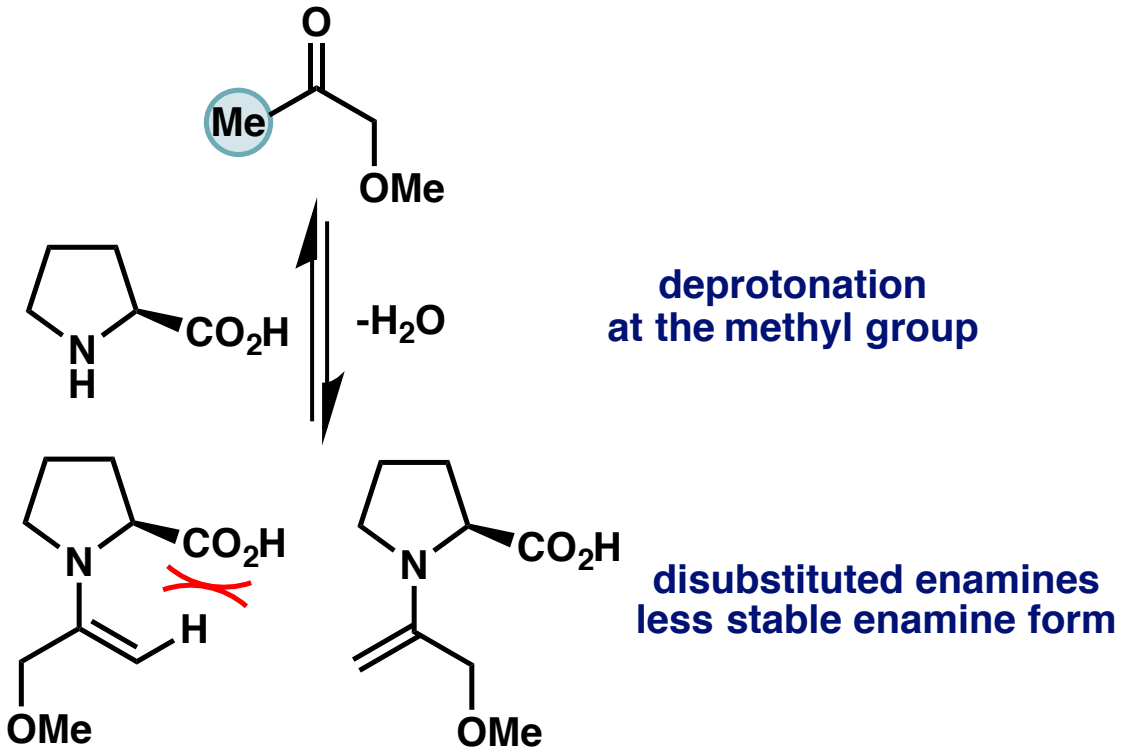
2) One reactant contains a **ketone** functional group and the other contains an **imine** (or more specifically an aldimine) functional group.

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.

Intermolecular Asymmetric Mannich Reaction

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

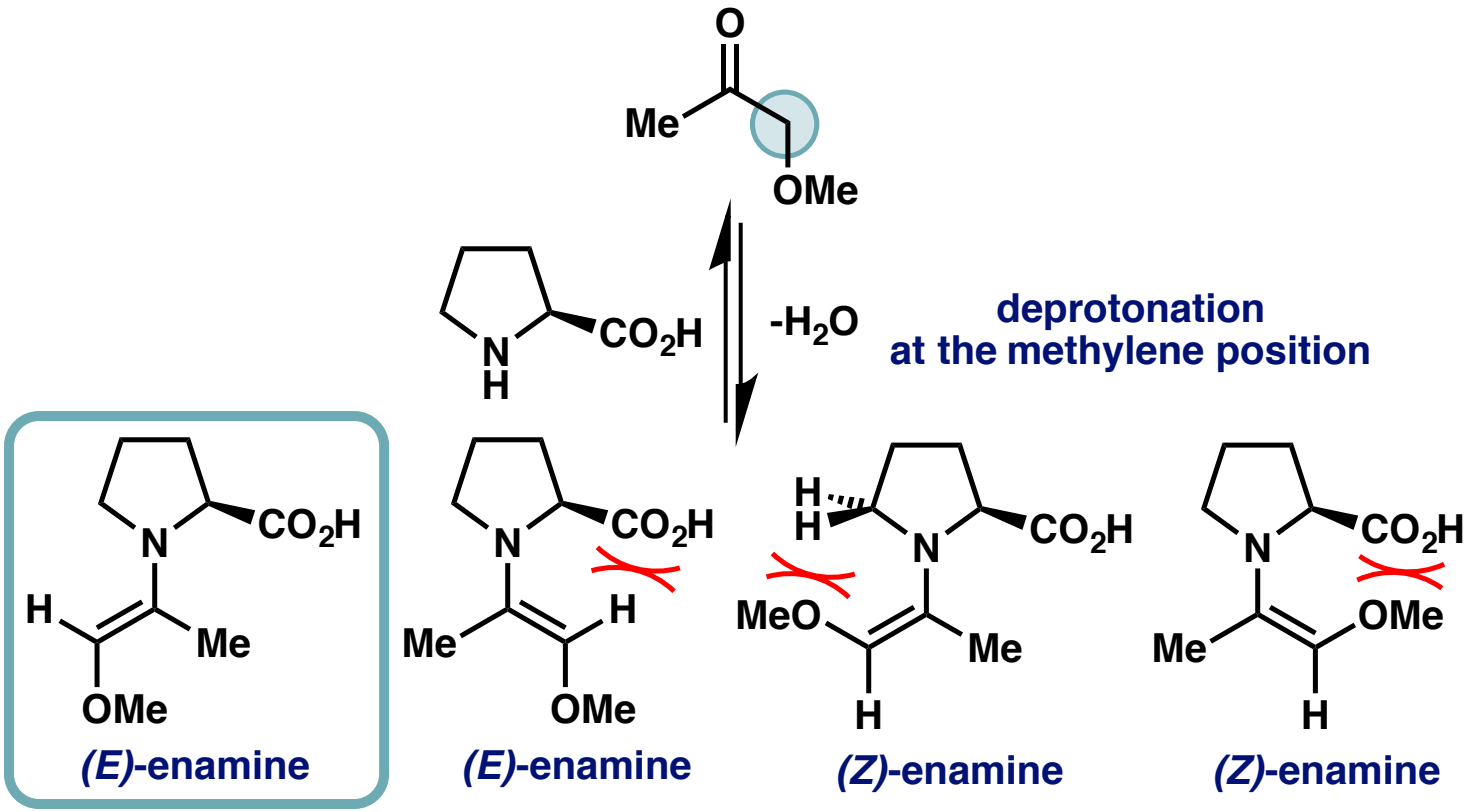


- Here, we can deprotonate at the **methyl group** or at the **methylene position**.

- 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

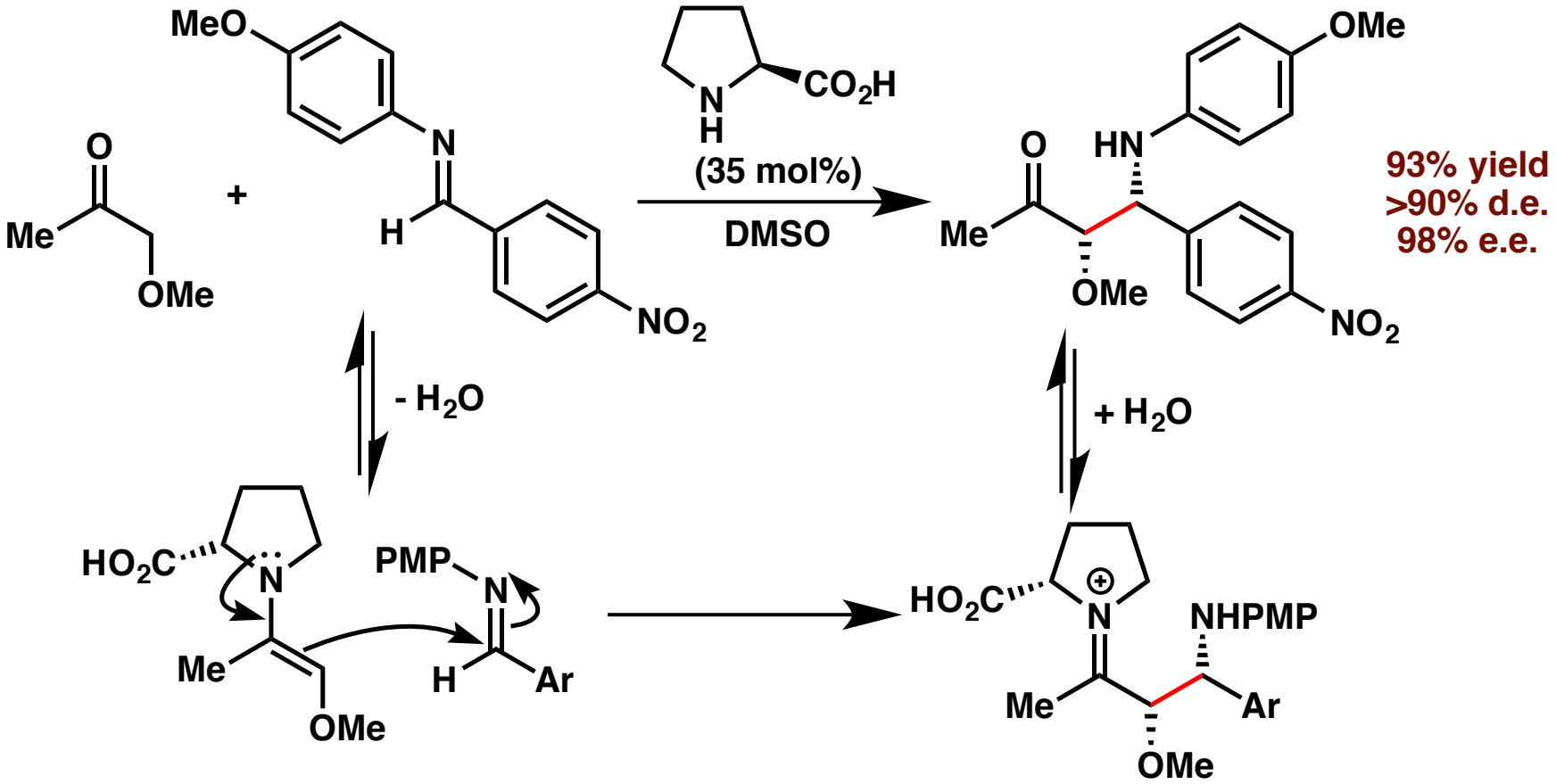
- Let's think about the key nucleophilic enamine species formed in detail:



- 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**:

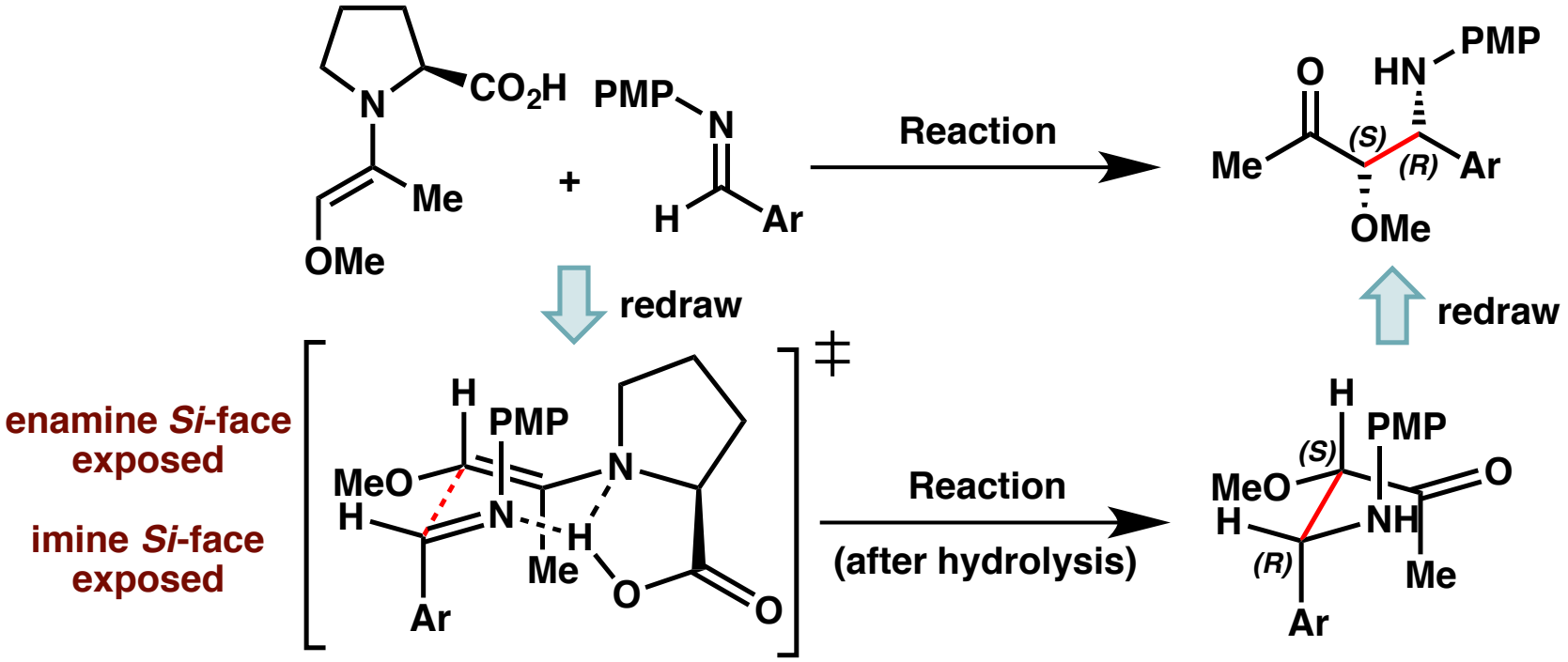


- From inspection of the product it is clear that the ketone becomes the **nucleophile** and that the imine is the **electrophile**.

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:

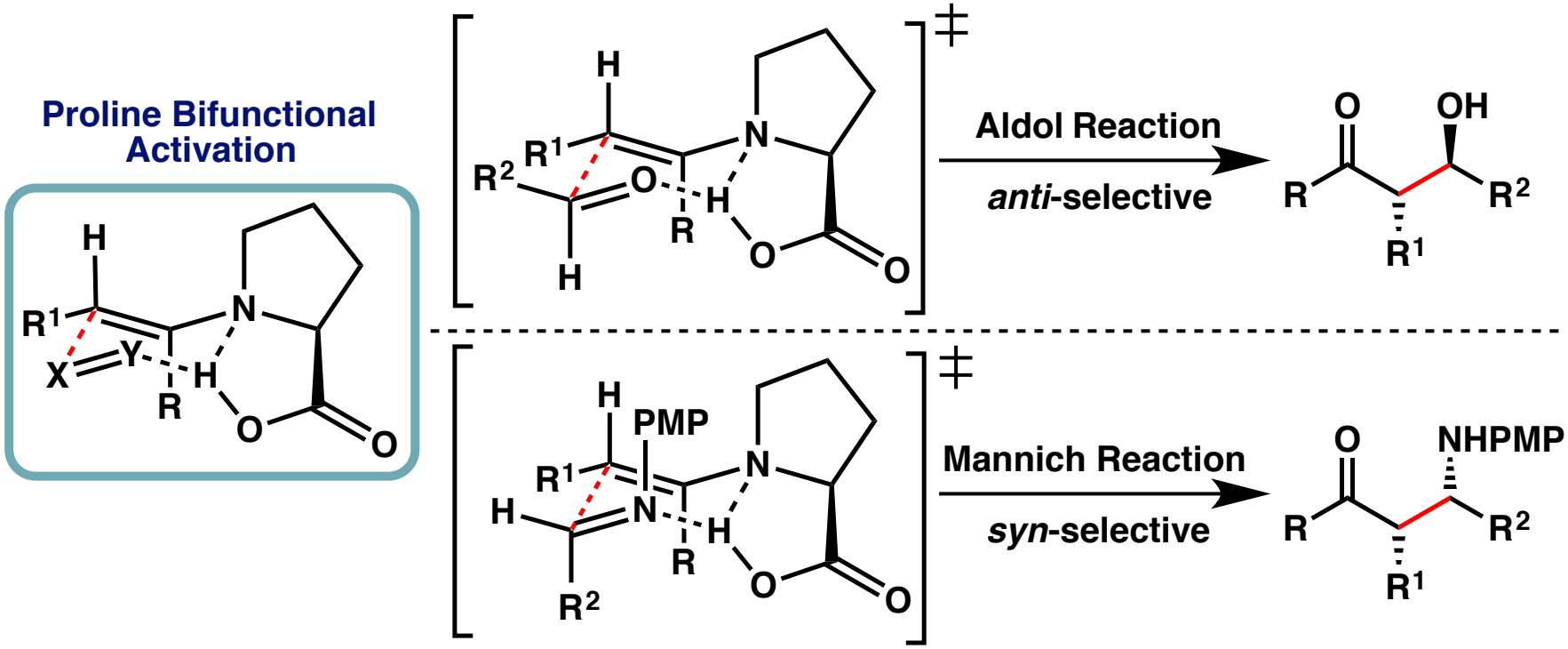


- Conformation such that **intermolecular hydrogen bond** can occur, stabilising the transition state. This forces the large Ar and PMP groups into **pseudoaxial** positions.

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

Predictable Stereochemistry for Aldol and Mannich

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

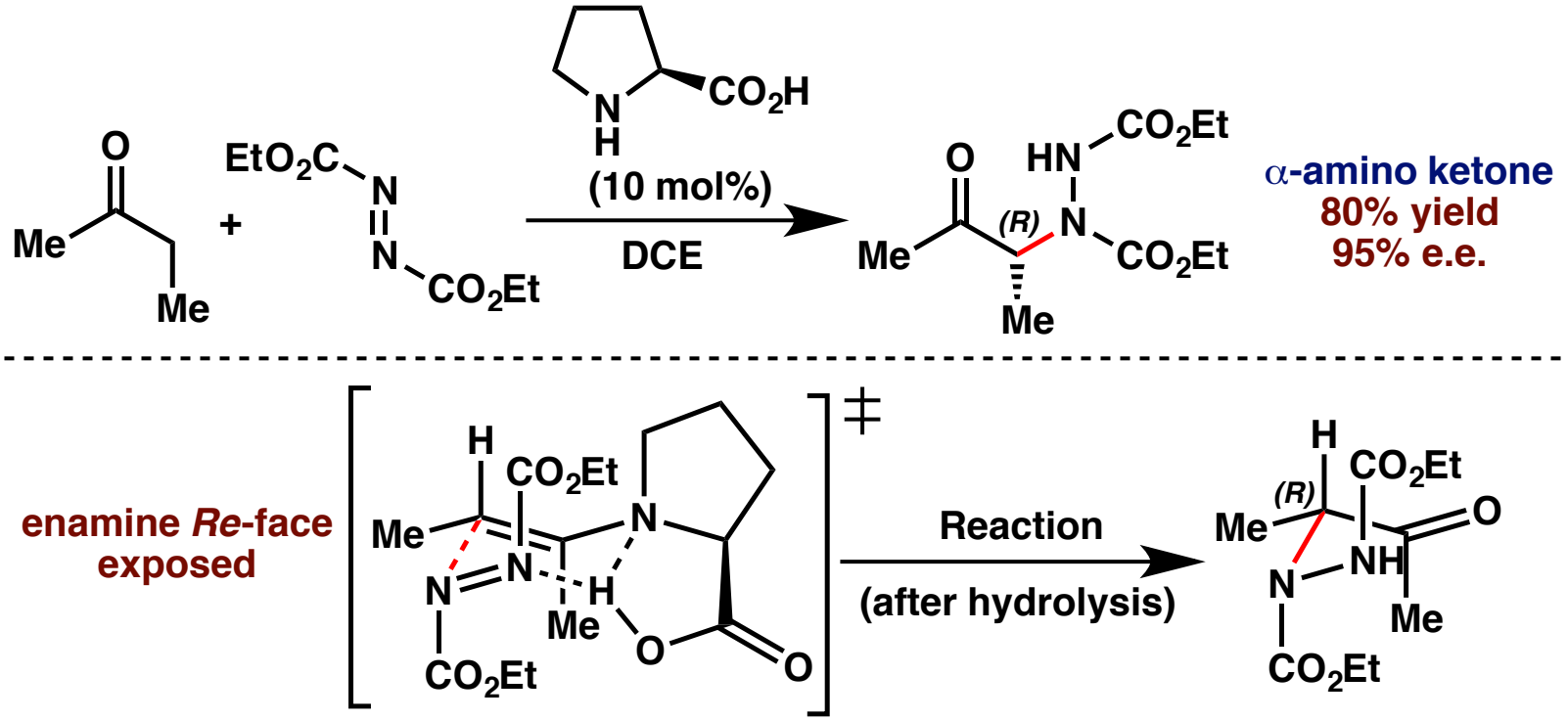


- Proline is often described as a **bifunctional catalyst** as it:

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:

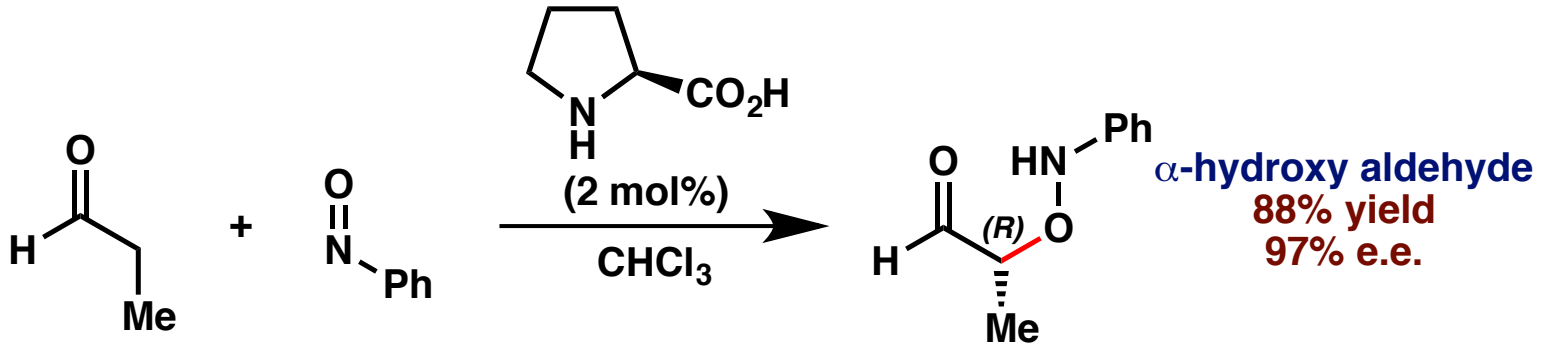


- The α-amination of ketones was reported by K. A. Jørgensen *et al.*, using diethyl azodicarboxylate (DEAD) as the electrophile.

- 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:

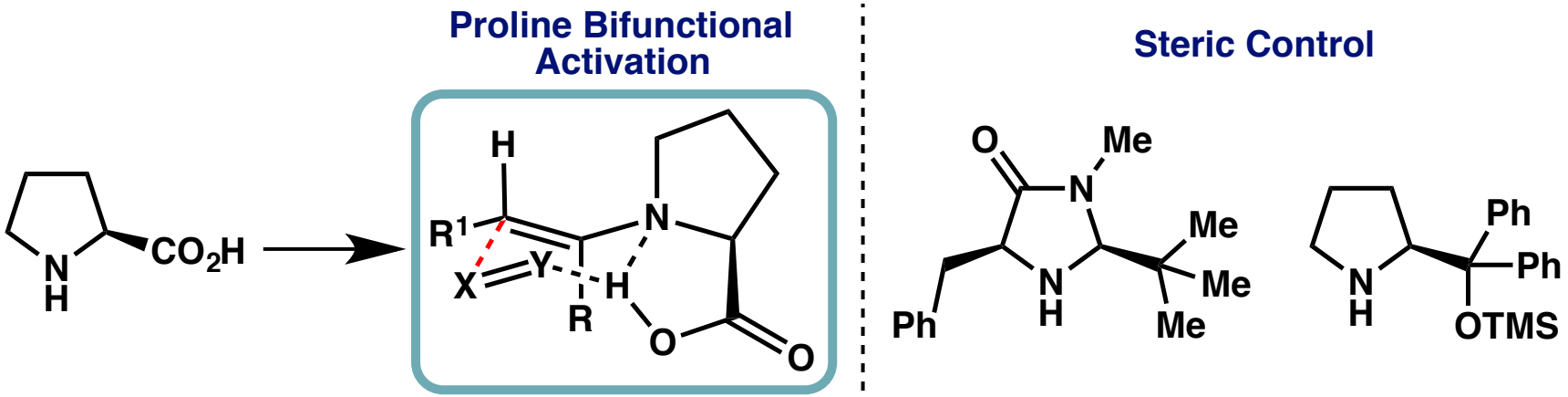


- The α-oxidation of aldehydes was reported by D. W. C. MacMillan *et al.*, using nitrosobenzene as the electrophile.

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

Bifunctional Activation vs Steric Control

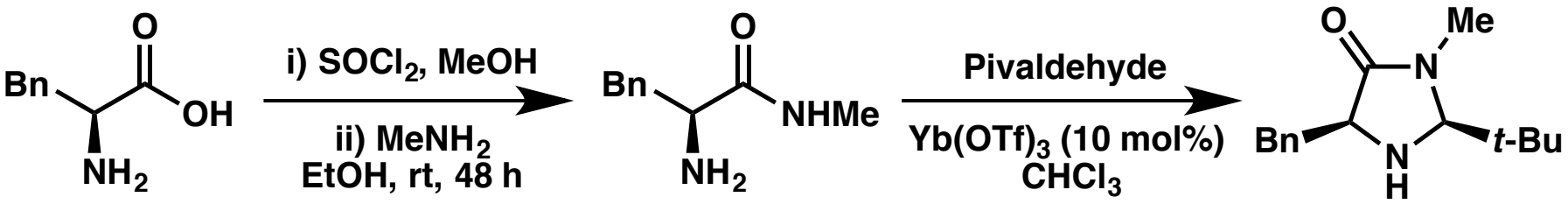
- Towards the end of lecture 1 we discussed **bifunctional enamine catalysis** using naturally occurring **proline** as the organocatalyst
- However, **bifunctional activation** is not absolutely required for selective catalysis.
- Other secondary amine organocatalysts rely on **steric control**.



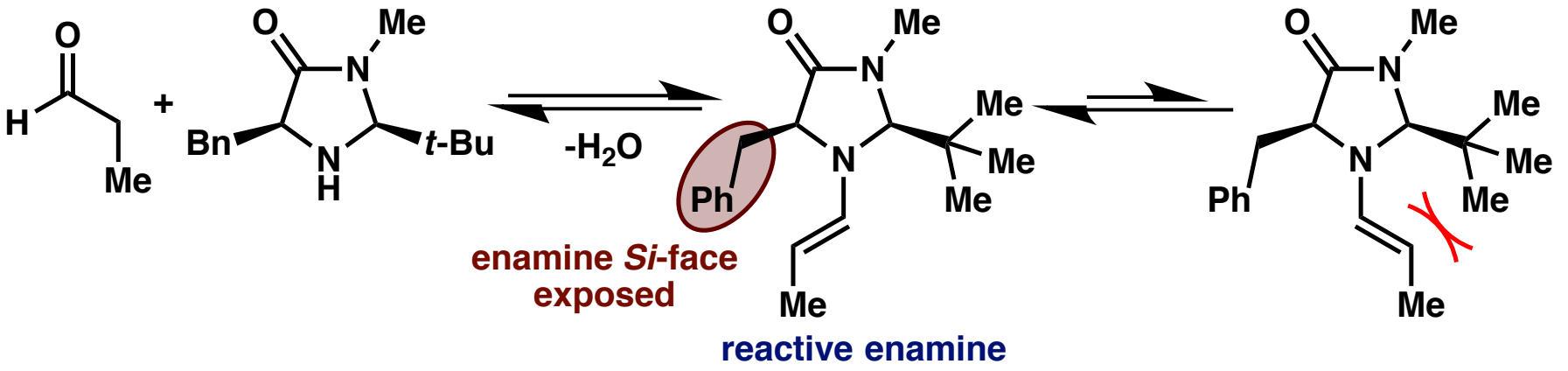
- In the following slides we will discuss the **synthesis and reactivity** of these important alternative secondary amine organocatalysts.

Imidazolidinone Organocatalysts

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



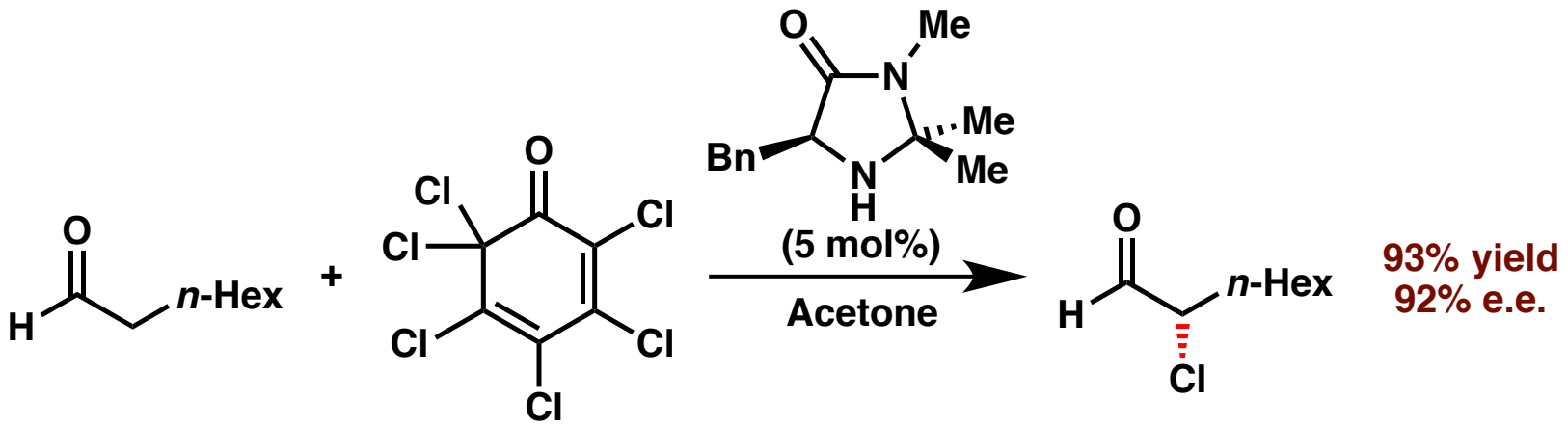
- These catalysts control **enamine geometry** and **shield one face of the enamine** in order to control the stereochemical outcome of reactions. **Control of both is crucial!**



- Let's look at some specific examples.

Enantioselective α-Chlorination of Aldehydes

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



- We have the following information:

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

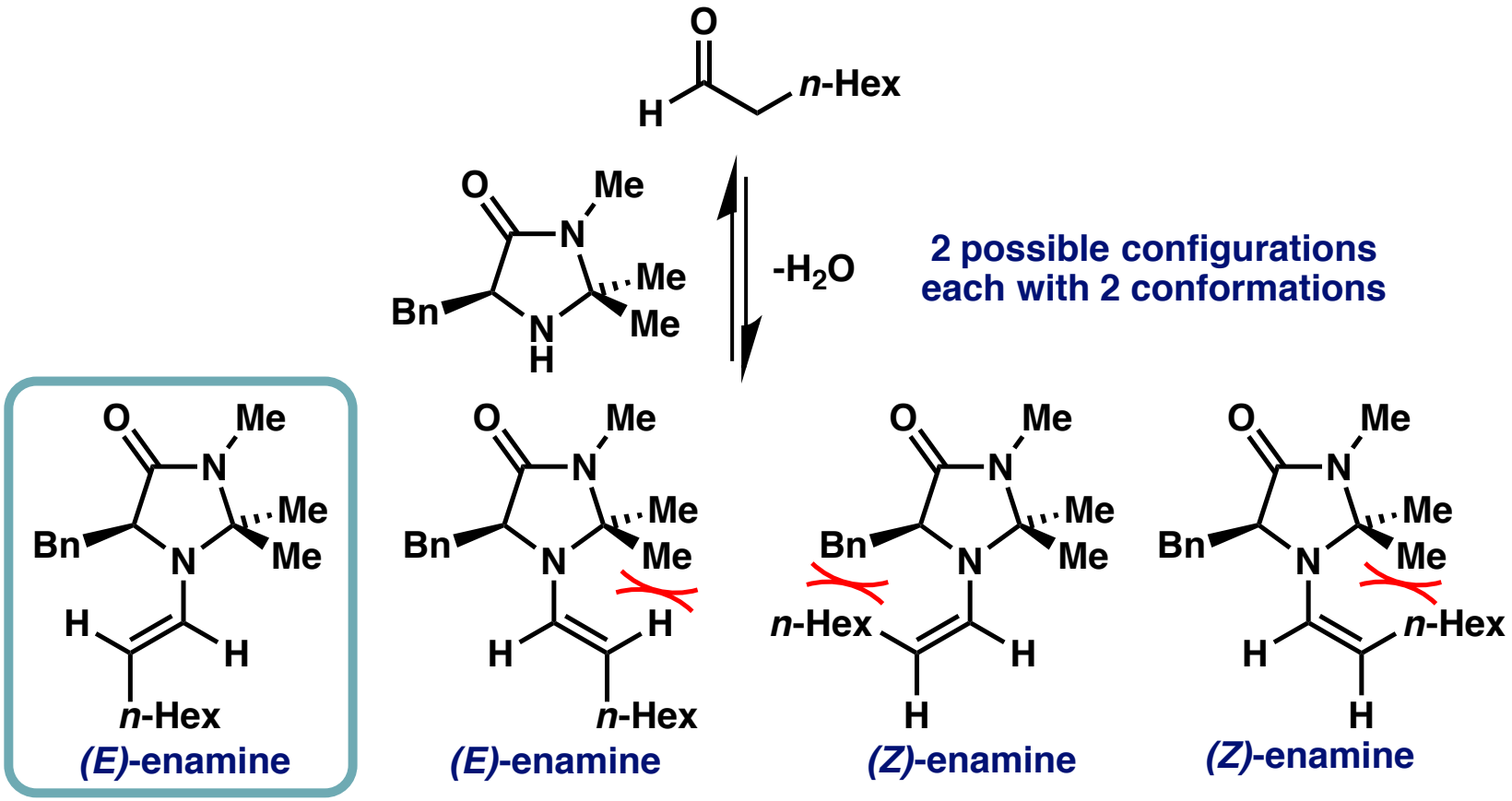
2) One reactant contains a **aldehyde** functional group and the other is a source of Cl^+.

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

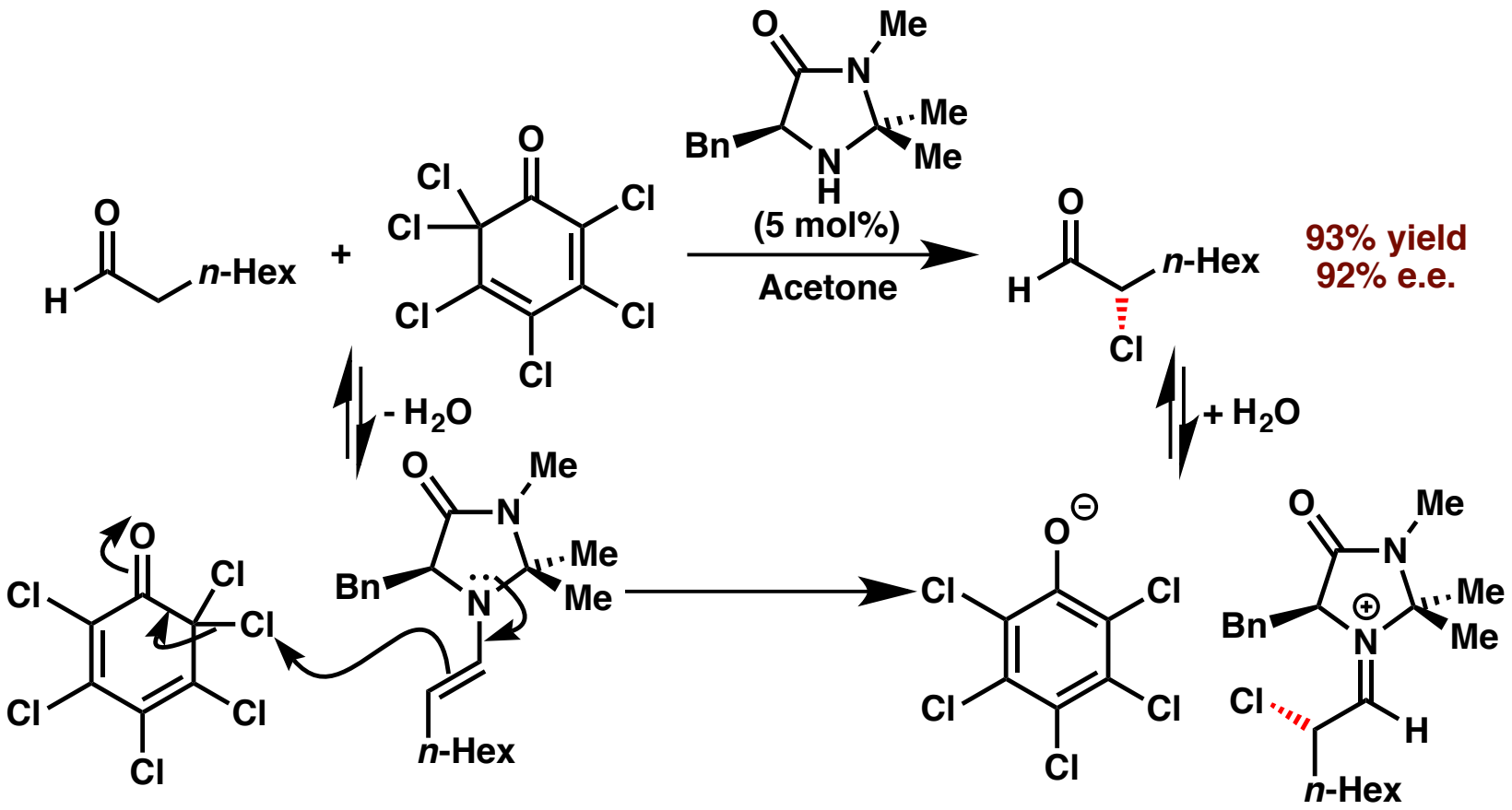
- Let's think about the key nucleophilic enamine species formed in detail:



- 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

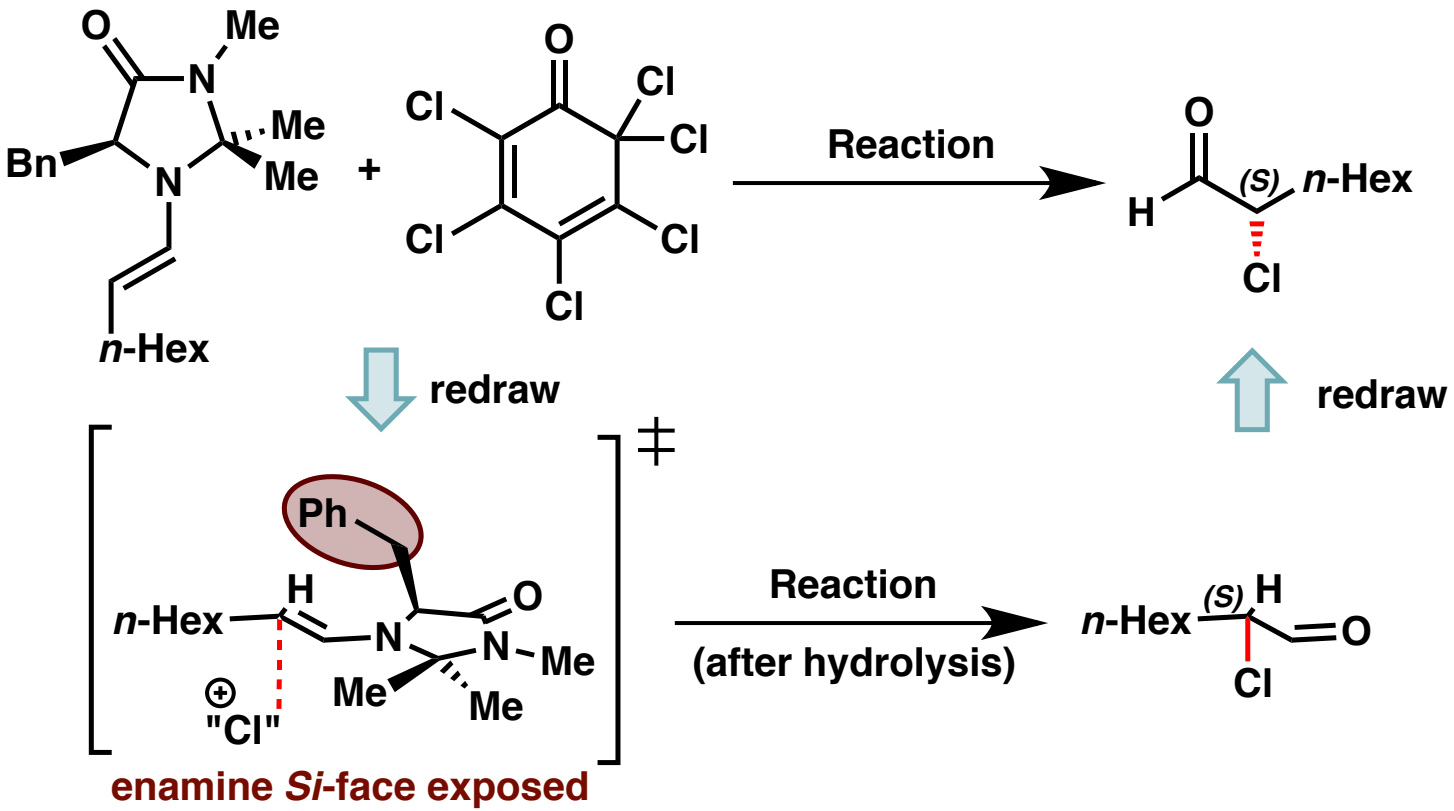
- Now let's consider the **curly arrow pushing mechanism**:



- **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

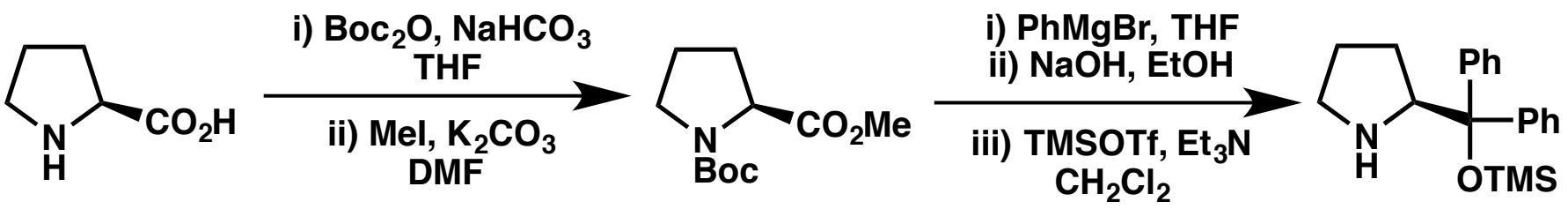
- Finally, let's rationalise the **stereochemical outcome** of the reaction:



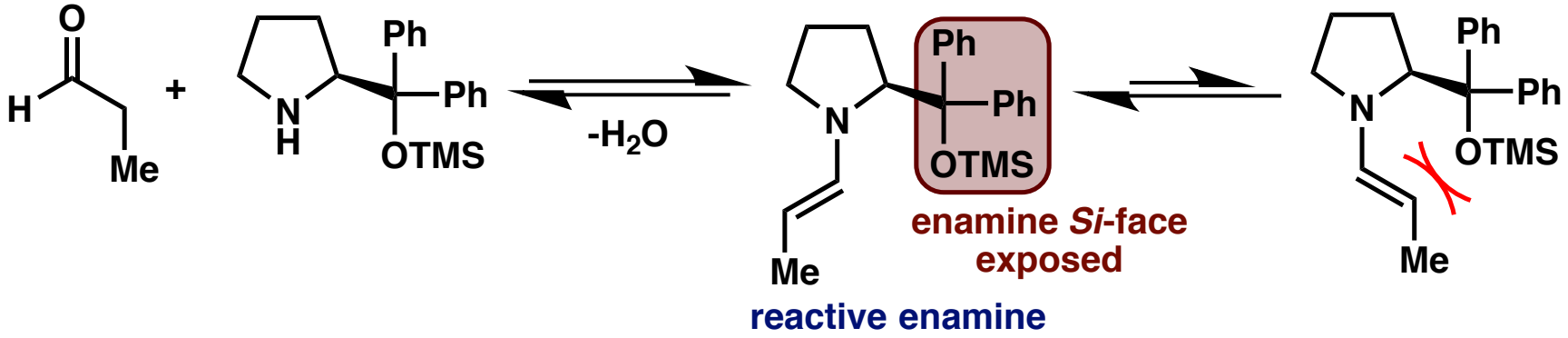
- Conformation such that the benzyl group **blocks the *Re*-face** of the enamine. Hence the electrophile approaches the ***Si*-face** of the enamine, giving enantioselectivity.

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.

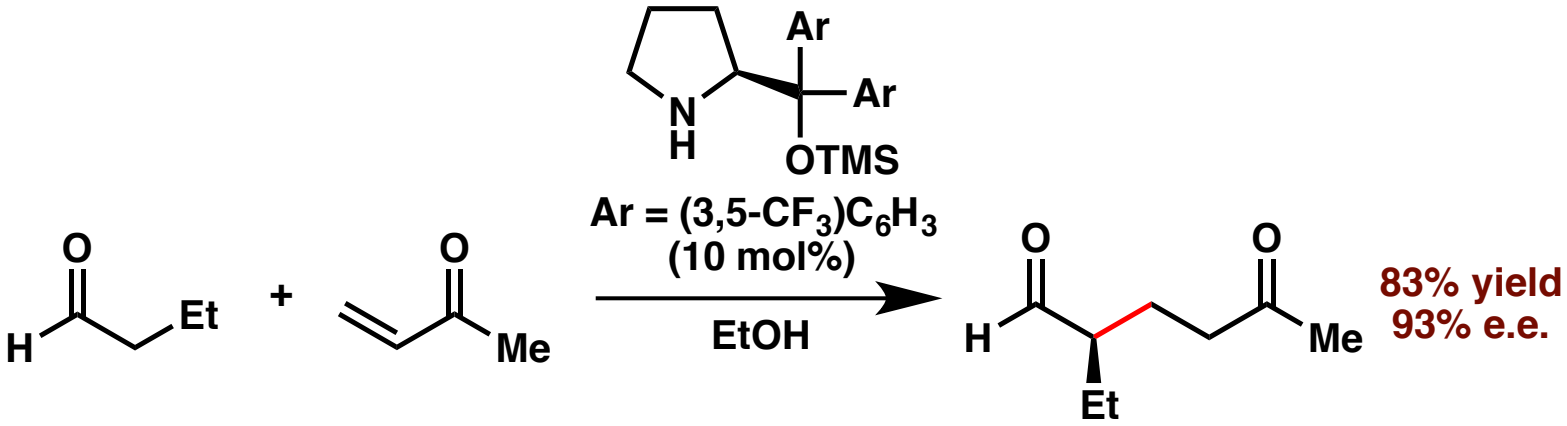


- Let's look at some specific examples.

K. A. Jørgensen *et al.*, *Angew. Chem. Int. Ed.,* 2005, **44**, 794; Y. Hayashi *et al.*, *Angew. Chem. Int. Ed.*, 2005, **44**, 4212.

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

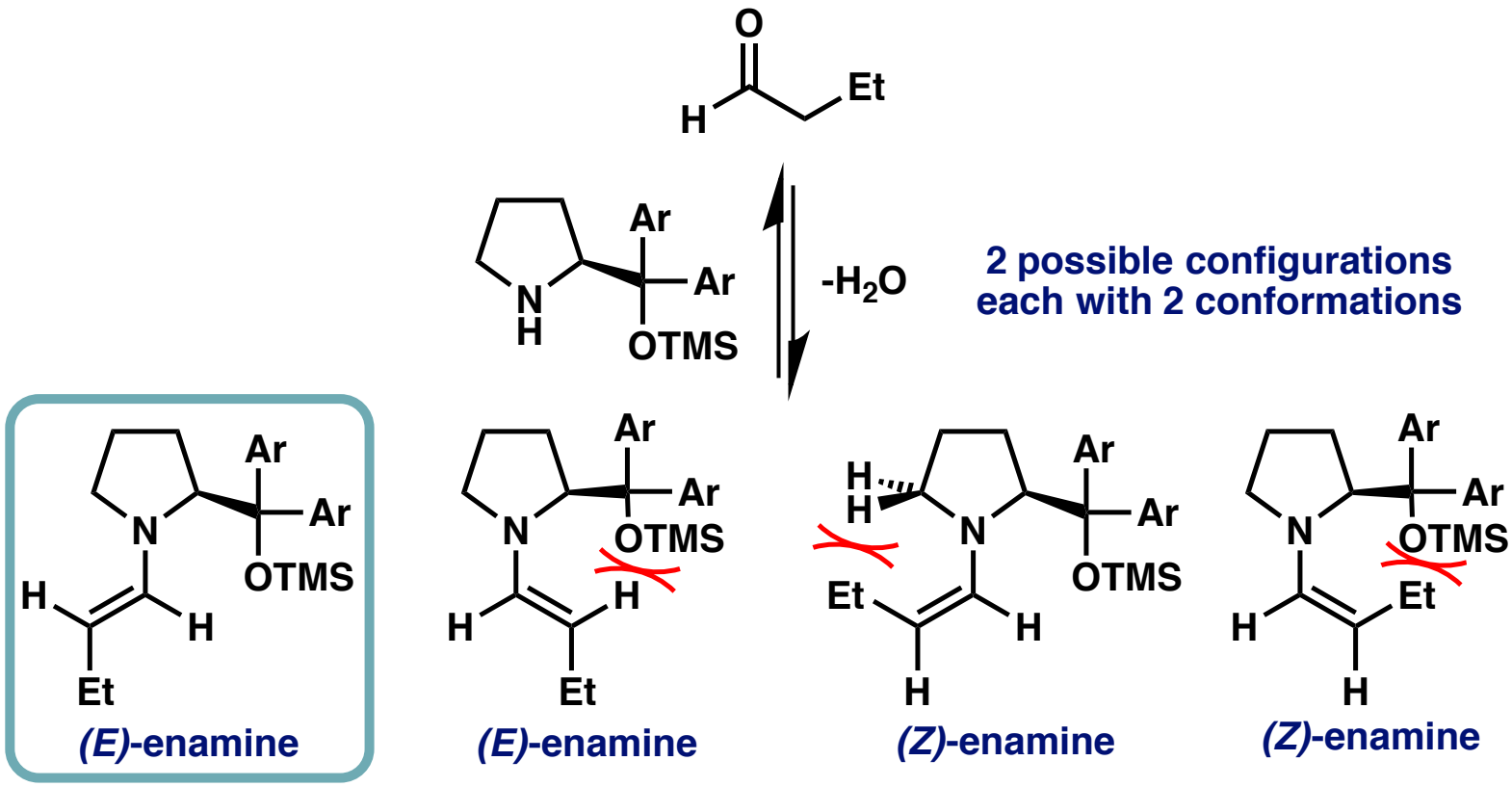
2) One reactant contains an **aldehyde** functional group and the other is an enone.

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

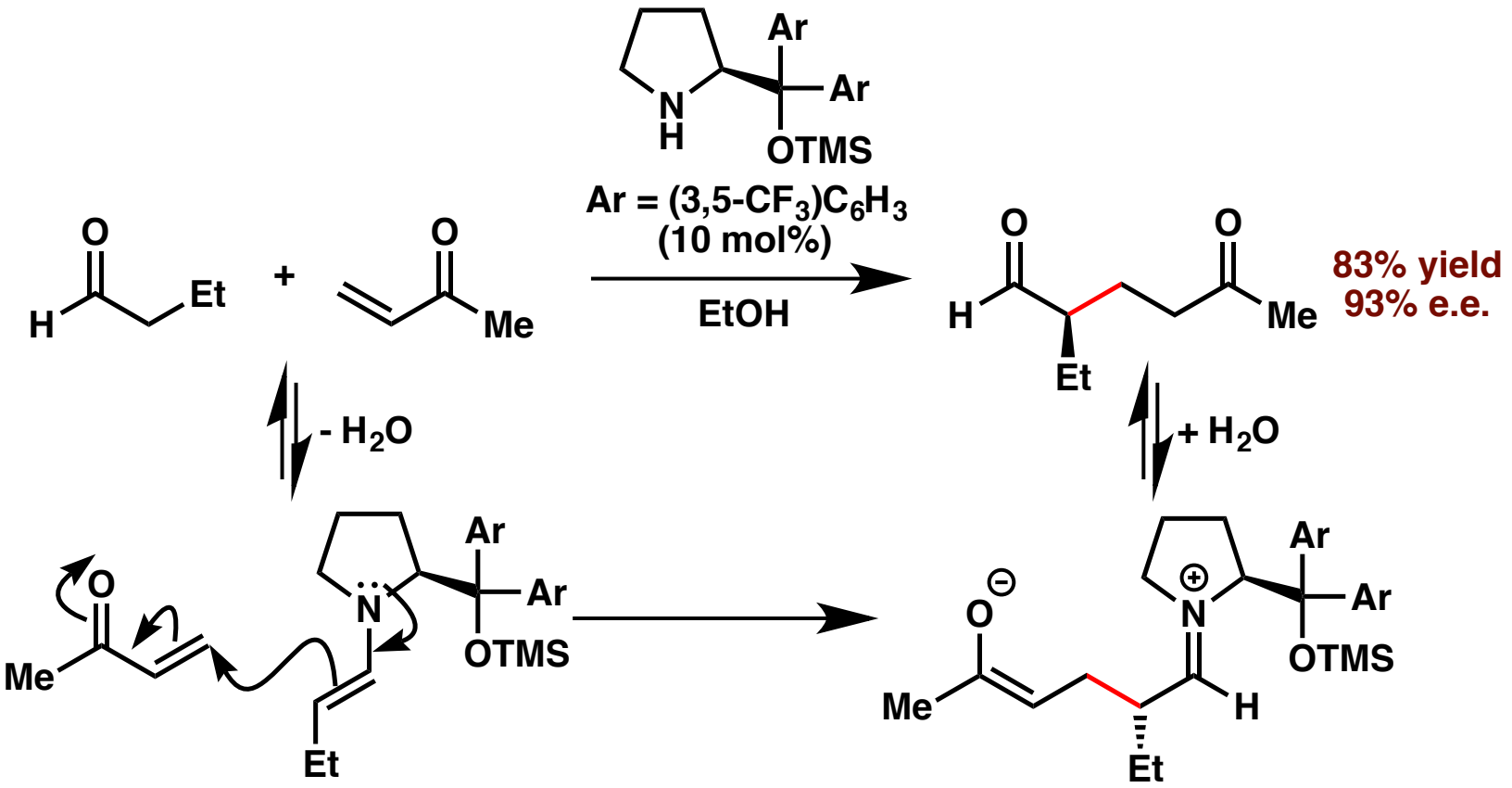
- Let's think about the key nucleophilic enamine species formed in detail:



- 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

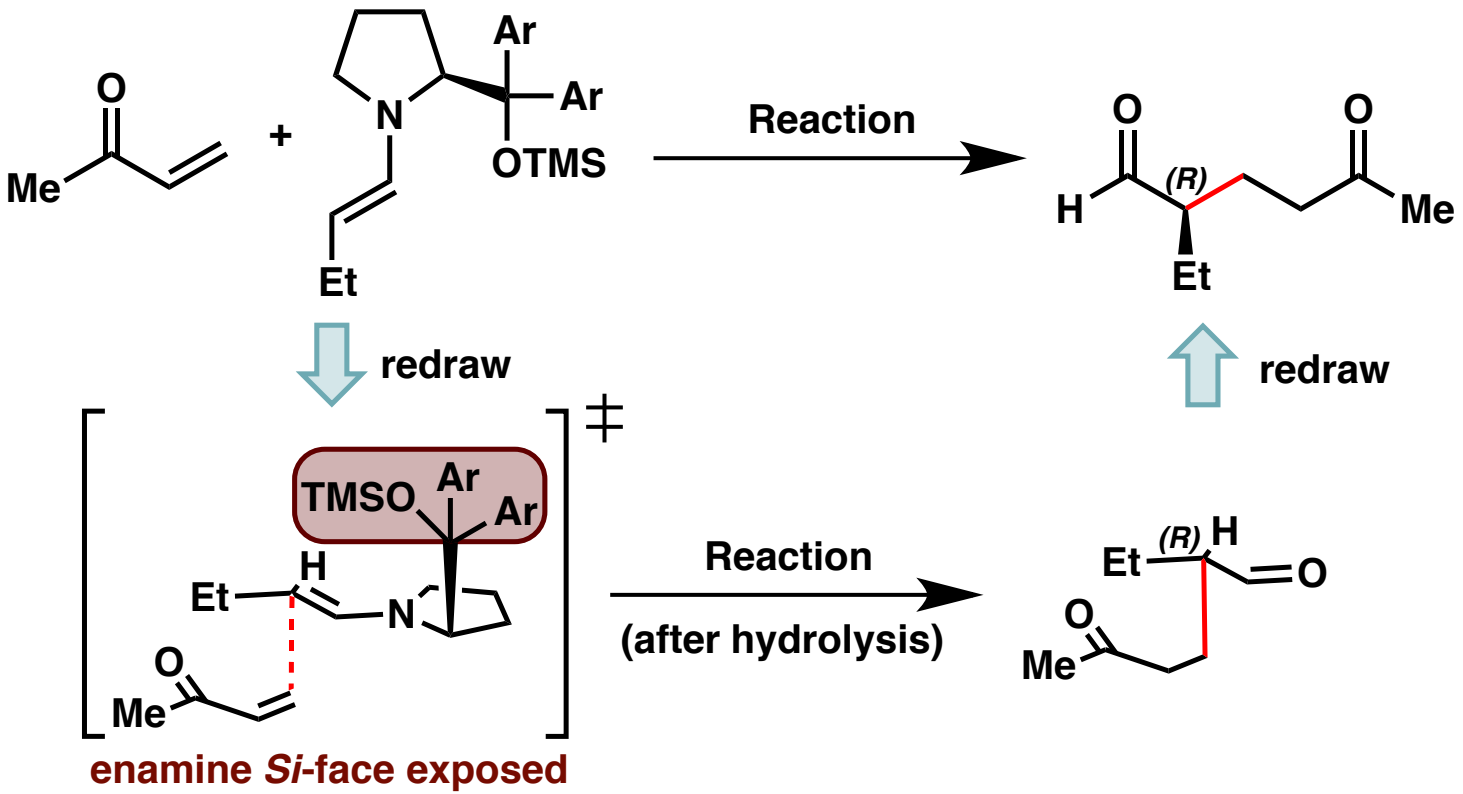
- Now let's consider the **curly arrow pushing mechanism**:



- 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

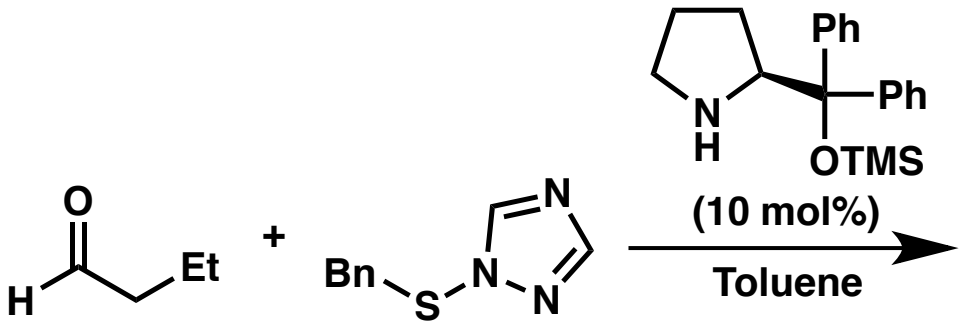
- Finally, let's rationalise the **stereochemical outcome** of the reaction:



- 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:

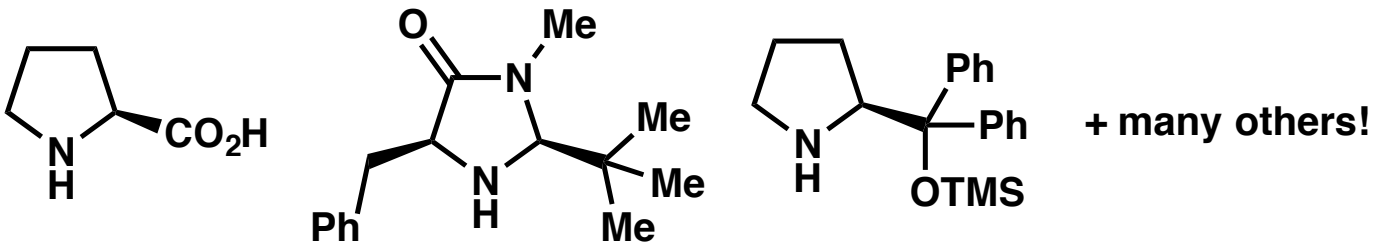


- The triazole on sulfur is a good leaving group (pK_a = 10.3) which makes the sulfur compound a good electrophile, susceptible to nucleophilic attack the the enamine.

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.**

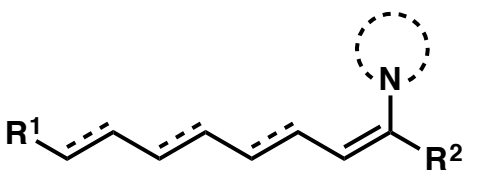
2) Carefully consider the possible **configurations** (e.g. *E* vs *Z*) and **conformations** (e.g. *s-cis* vs *s-trans*) of the key enamine intermediate.

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

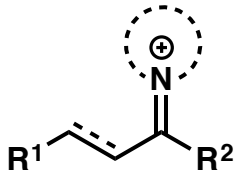
An Overview of Organocatalysis

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

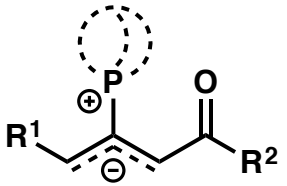
Covalent Activation Modes



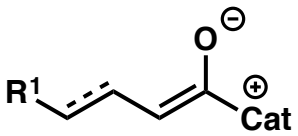
Enamine (di-, tri-, tetra-enamine) Catalysis



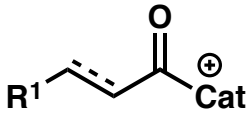
Iminium Catalysis



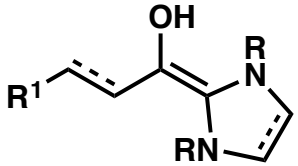
Phosphine Catalysis



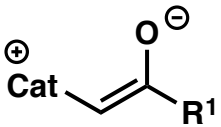
C(1)-Enolate (di-enolate) Catalysis



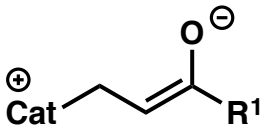
Acyl ammonium/azolium Catalysis



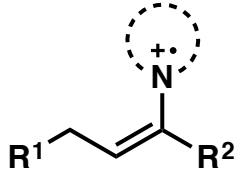
N-Heterocyclic Carbene Catalysis



C(2)-Enolate Catalysis

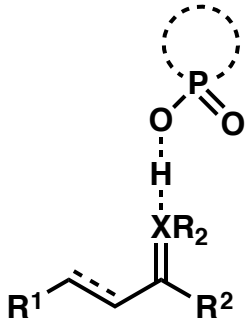


C(3)-Enolate Catalysis

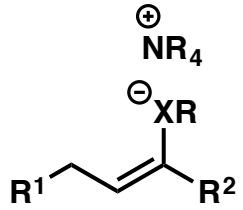


SOMO Catalysis

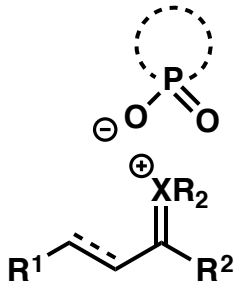
Non-Covalent Activation Modes



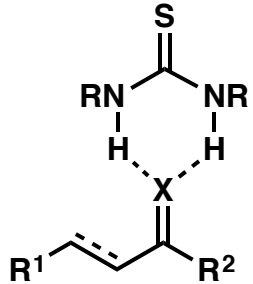
Brønsted Acid Catalysis



Phase-transfer Catalysis



Chiral Anion Catalysis



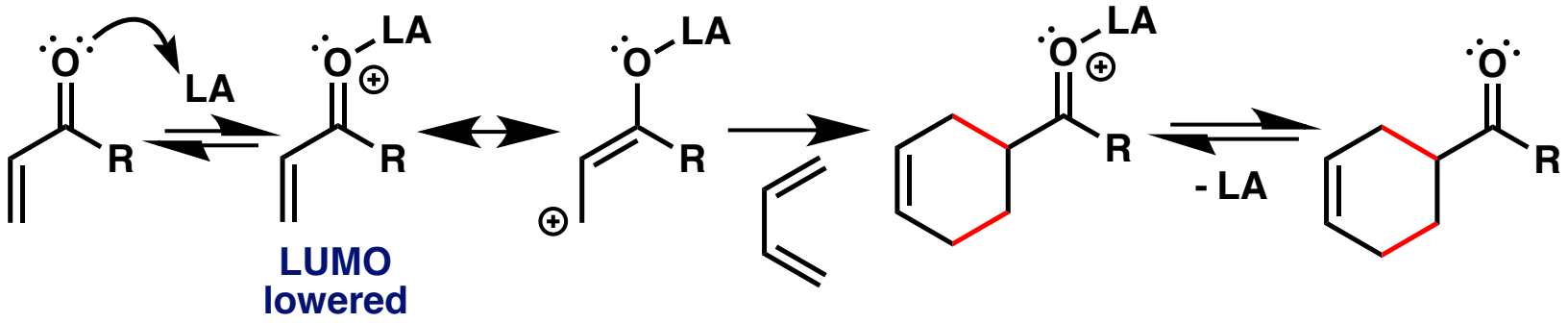
Hydrogen Bonding Catalysis

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

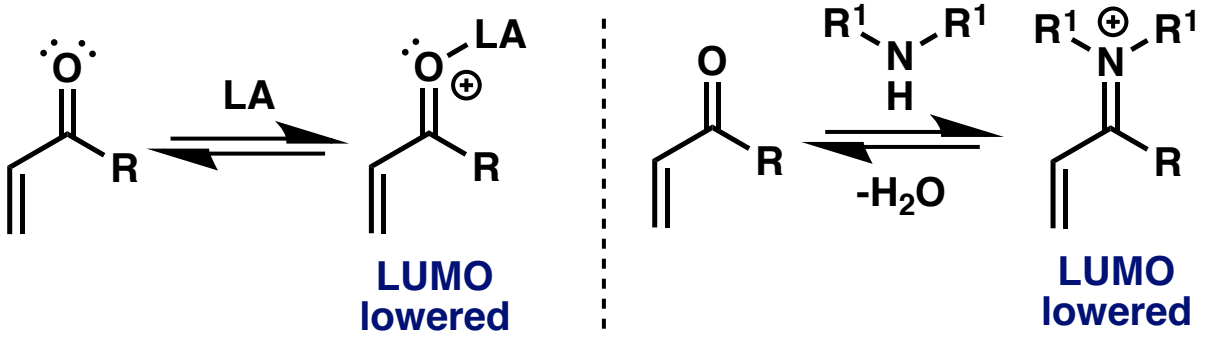
For an excellent overview see D. Romo *et al.*, *Nat. Prod. Rep.*, 2014, **31**, 1318.

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:



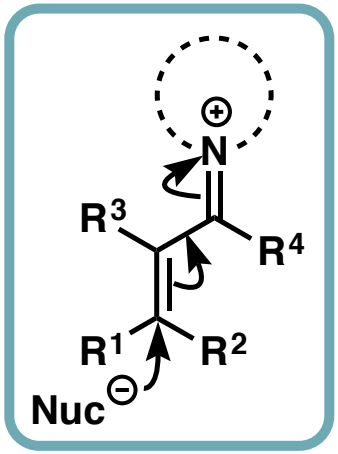
- MacMillan postulated that amines could function as catalysts that traditionally employ Lewis acids:



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.

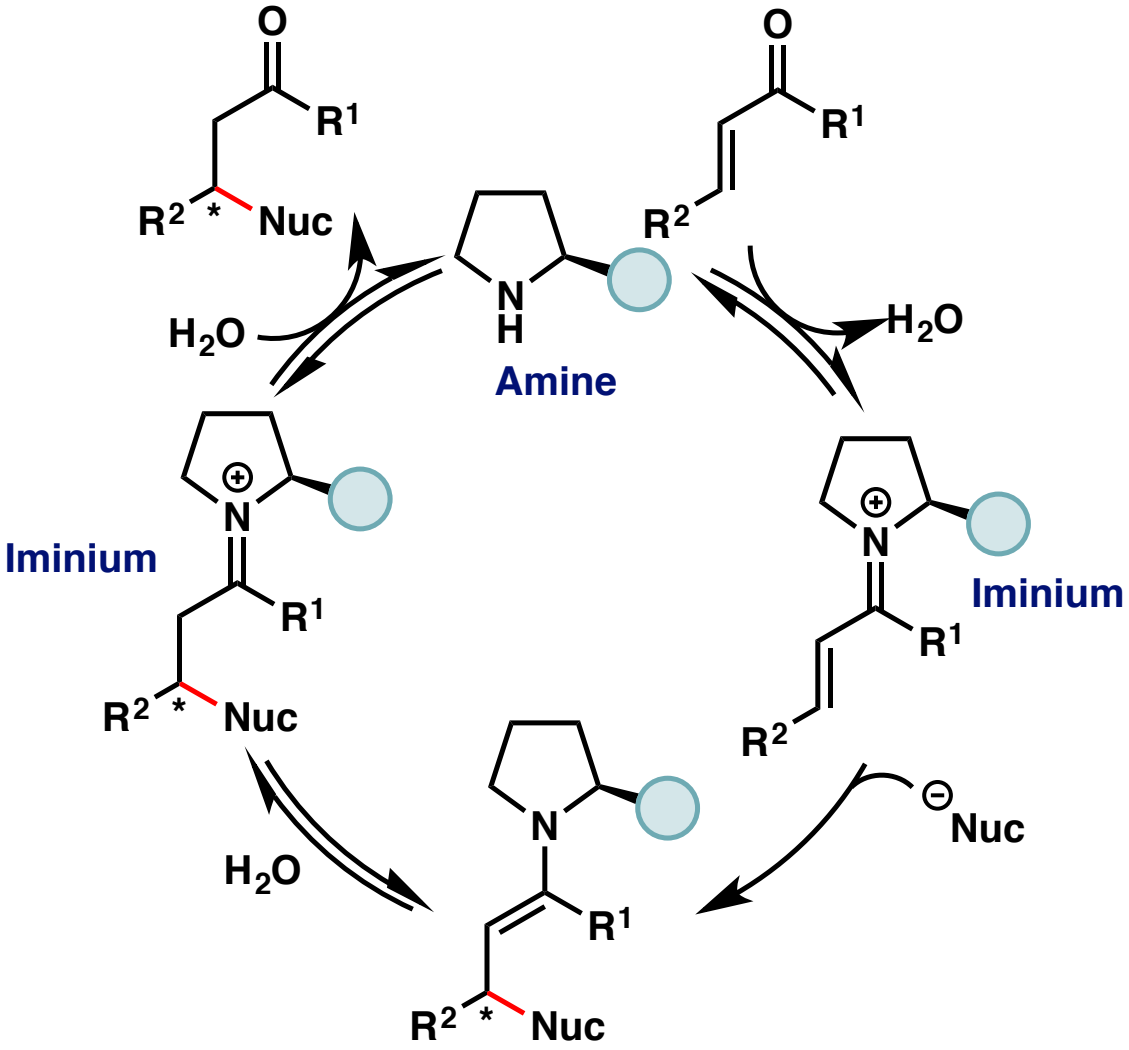
2) It is an **electrophilic (LUMO-lowered)** activation mode – it reacts with nucleophiles.

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.

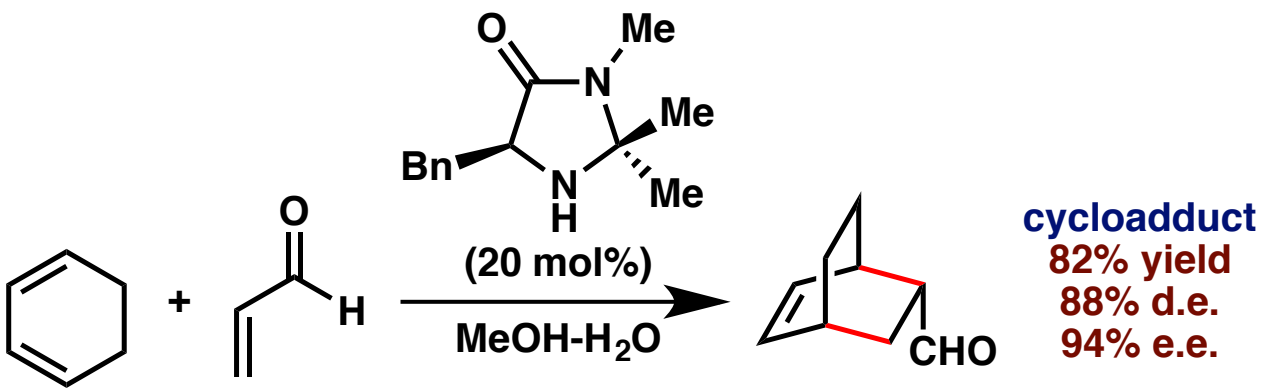
Iminium Organocatalysis – General Mechanism

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



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

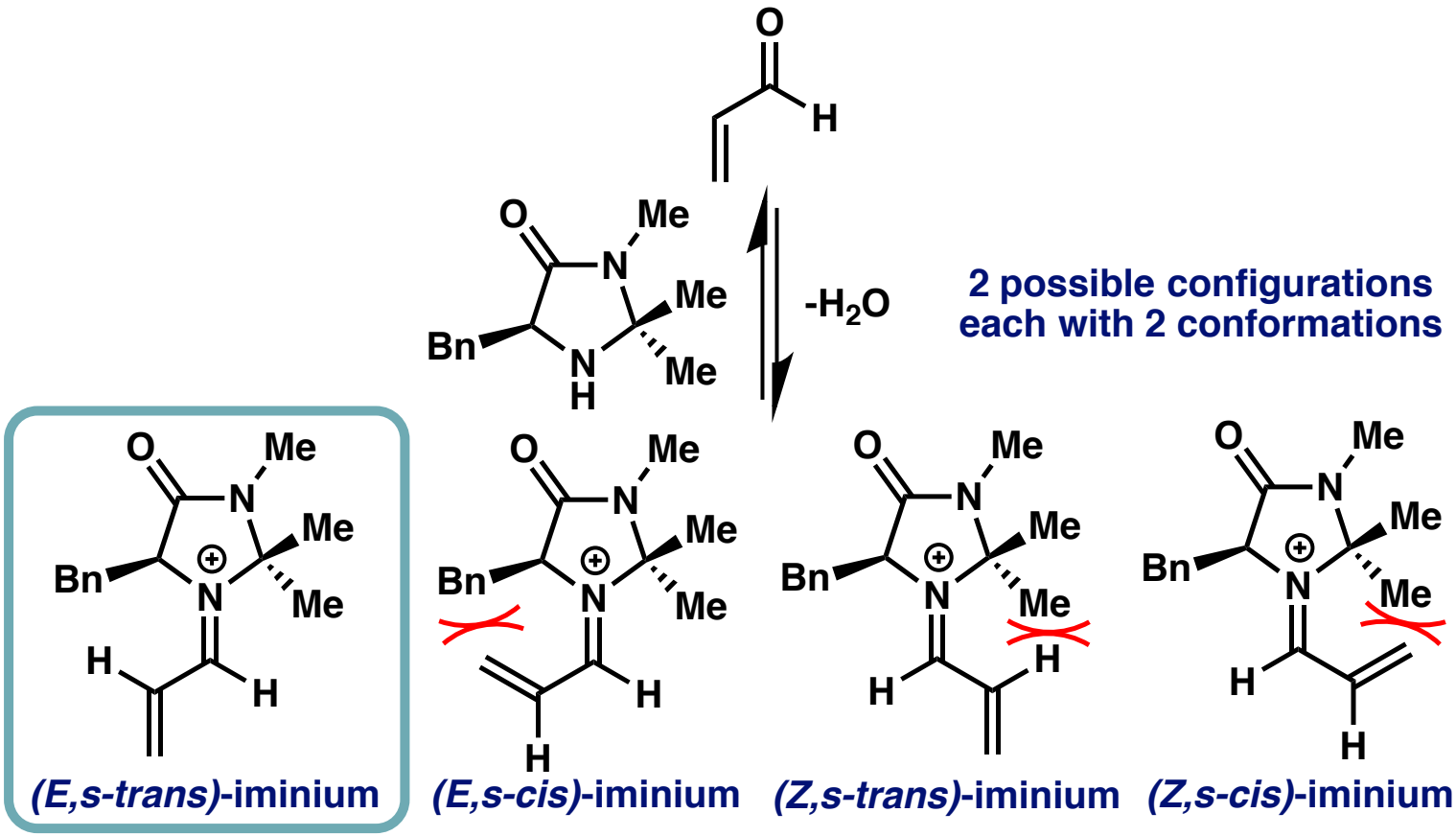
2) One substrate contains an **aldehyde** functional group, with the other being a diene

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

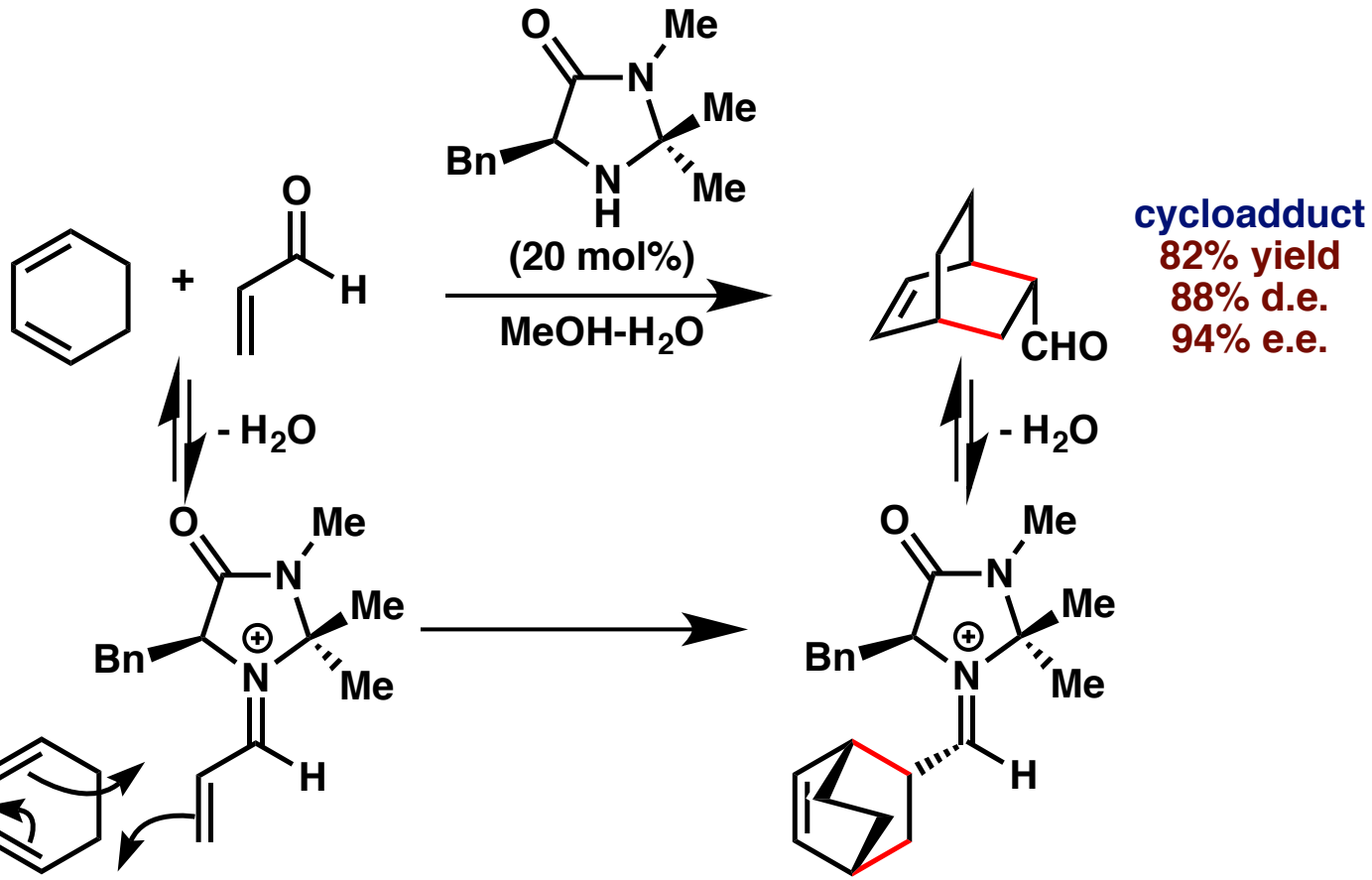
- Let's think about the key electrophilic iminium species formed in detail:



- 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

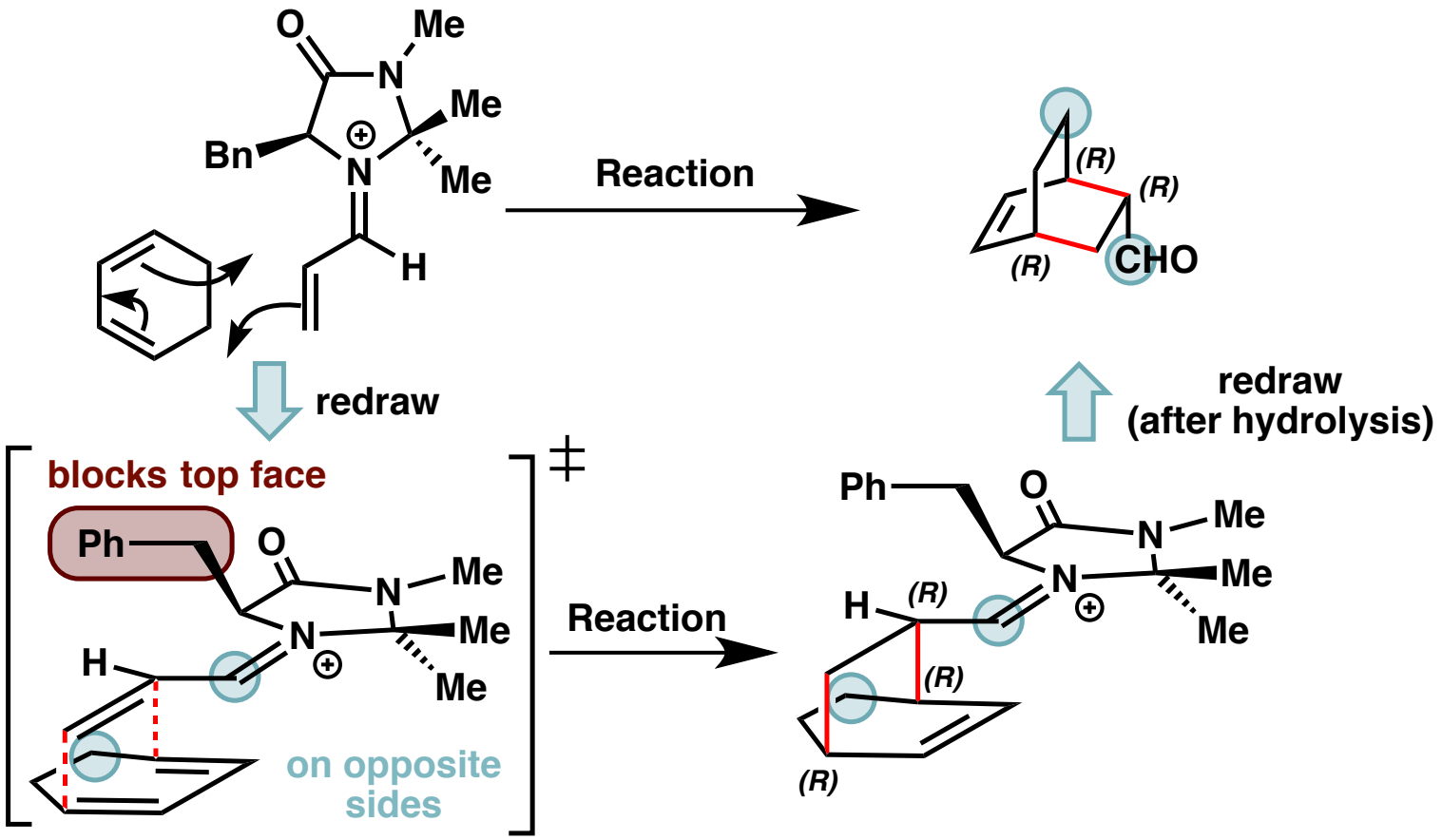
- Now let's consider the **curly arrow pushing mechanism**:



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

Enantioselective Organocatalytic Diels-Alder Reaction

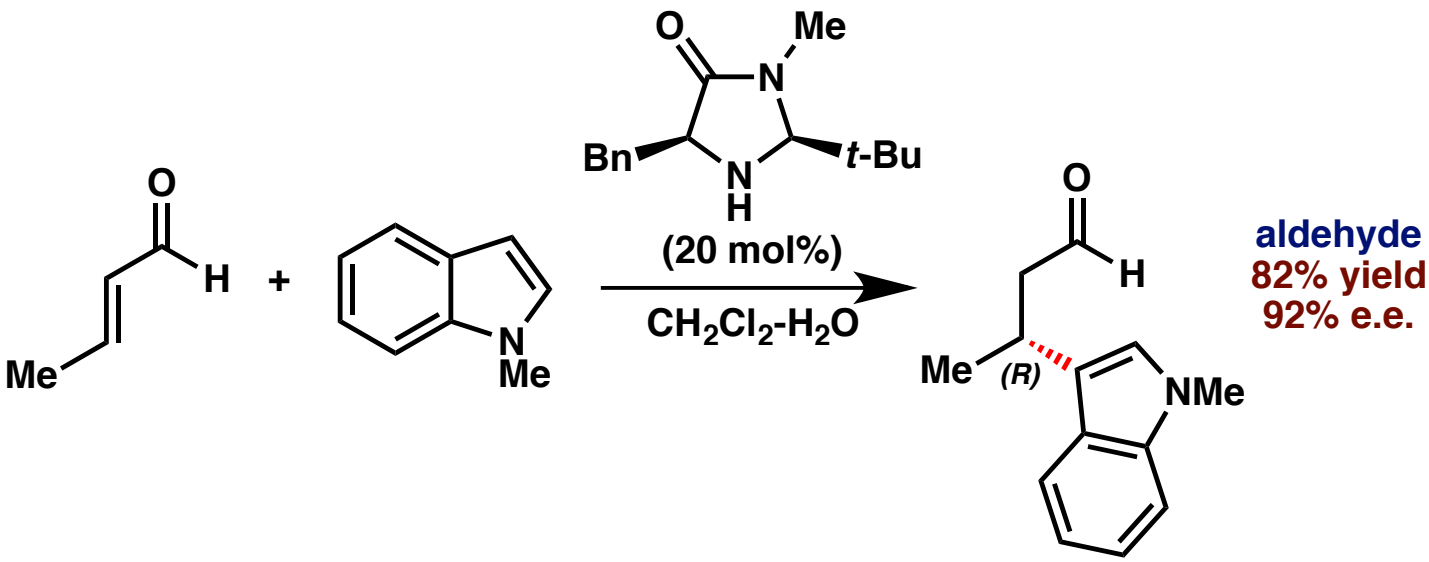
- Finally, let's rationalise the **stereochemical outcome** of the reaction:

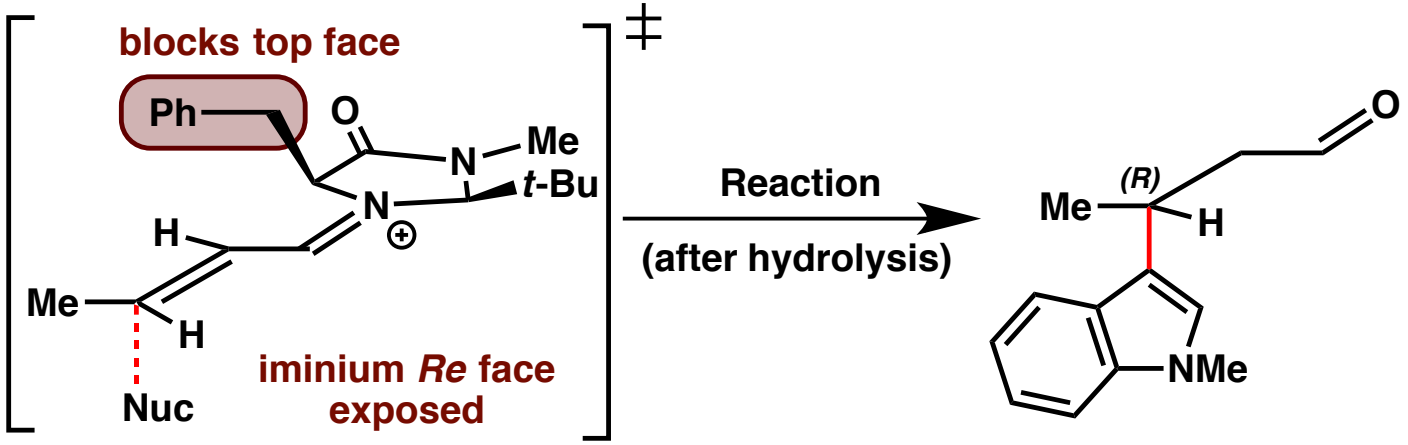


- Secondary orbital (diene filled π bonds to empty C=N π* orbital) interactions stabilise the ENDO transition state. Aldehyde and methylene bridge on **opposite sides**.

Enantioselective Conjugate Addition

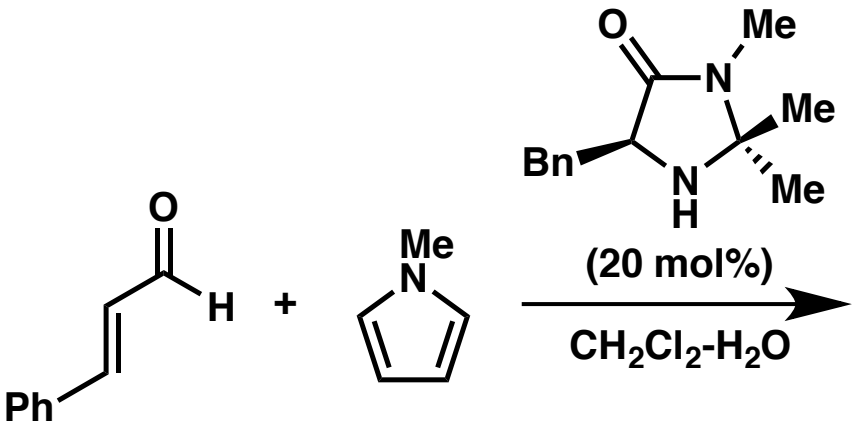
- Indoles can be employed in enantioselective conjugate addition:





Enantioselective Conjugate Addition – Class Example

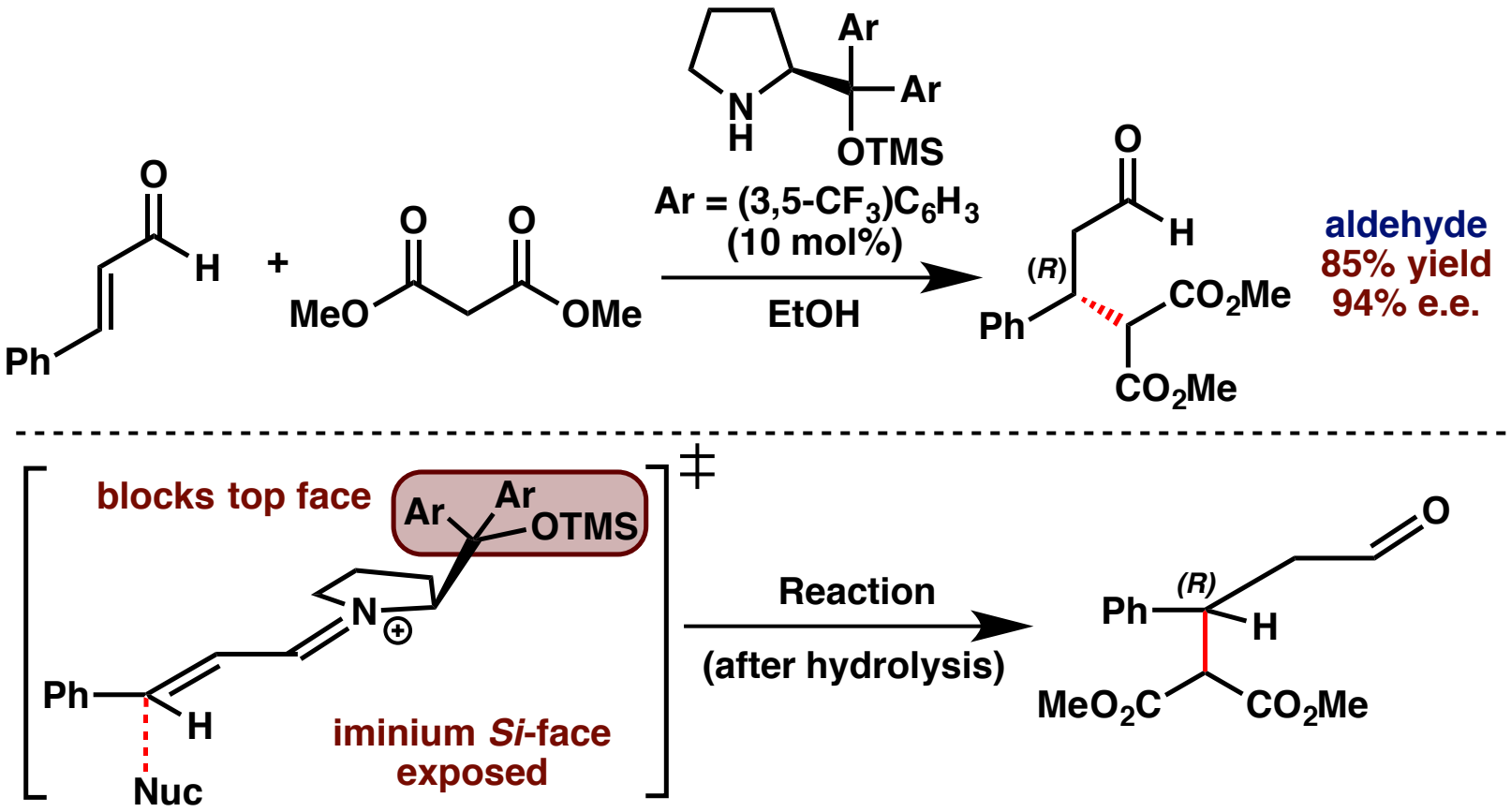
- Many alternative nucleophiles have been used in related processes. Determine the major product for the reaction shown below:



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

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.