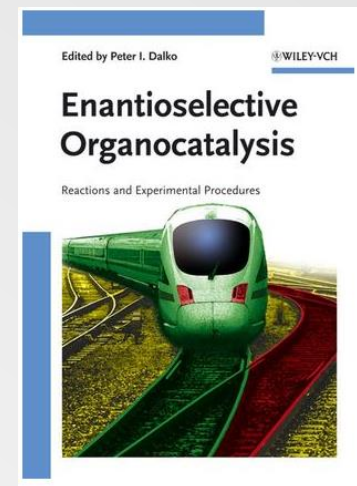
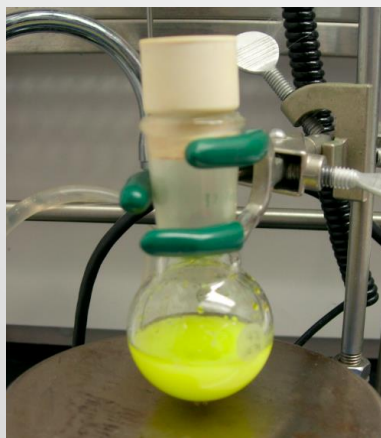
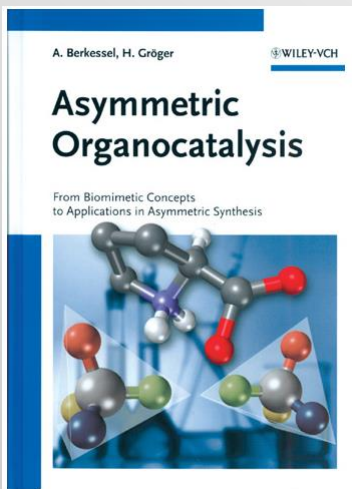


ΟΡΓΑΝΙΚΗ ΣΥΝΘΕΤΙΚΗ ΧΗΜΕΙΑ

ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

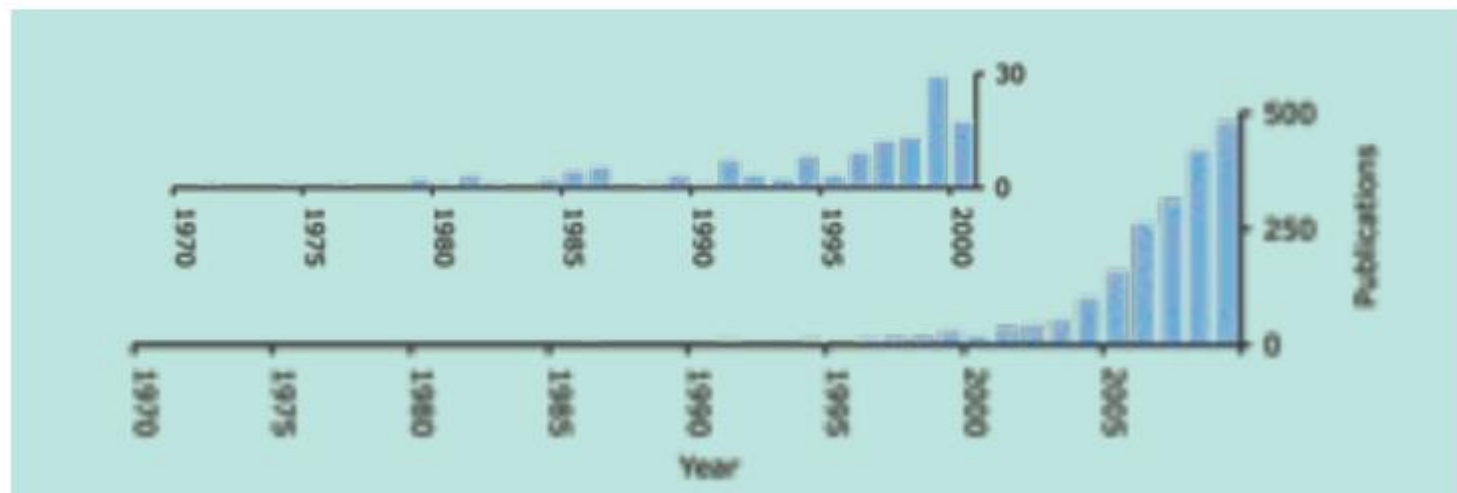


Δρ. Χριστόφορος Γ. Κόκοτος

ΟΡΙΣΜΟΣ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗΣ



Η χρήση μικρών οργανικών μορίων για την κατάλυση οργανικών αντιδράσεων.



- Between 2000 and 2008, more than 2000 manuscripts on >150 discrete reaction types
- Used for enantioselective construction of C–C, C–N, C–O, C–S, C–P, C–halogen bonds
- Now 3rd major branch of catalysis
- Transformations that employ organic catalysts sporadically documented over last 100 years
- Organocatalysis google page hits = 137,000
Olefin metathesis google page hits = 253,000
Gold catalysis google page hits = 28,600
- The field of organocatalysis was born 1998-2000

ΑΠΑΡΧΗ ΤΗΣ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗΣ

Γιατί το πεδίο της οργανικής σύνθεσης παράβλεψε τη χρήση των μικρών οργανικών μορίων ως καταλυτών μέχρι τις αρχές του 21^{ου} αιώνα;

Dieter Seebach: *Angew. Chem. Int. Ed.* **1990**, 29, 1320.

"New synthetic methods are most likely to be encountered in the fields of biological and organometallic chemistry."

Γιατί ο Seebach δεν περιλαμβάνει την οργανοκατάλυση σε αυτή την πρόβλεψη που κάνει για το μέλλον της οργανικής σύνθεσης;

Είναι πολύ δύσκολο να παραλείψεις έναν κλάδο ο οποίος ακόμα δεν υπάρχει!!!

ΑΠΑΡΧΗ ΤΗΣ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗΣ

Οργανοκατάλυση

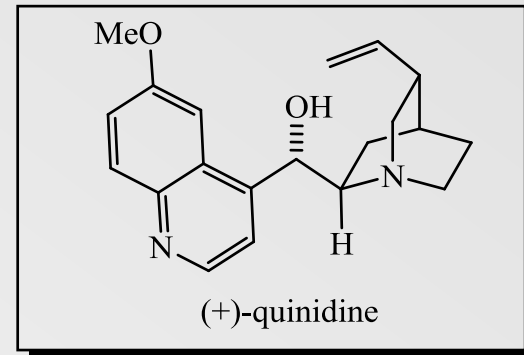
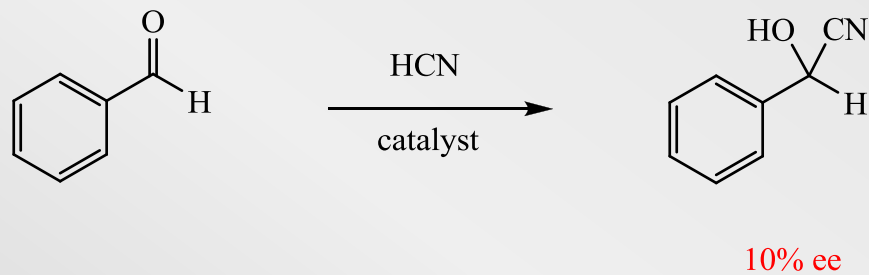


Ενζυμική κατάλυση

**Κατάλυση με
μέταλλα μεταπτώσεως**

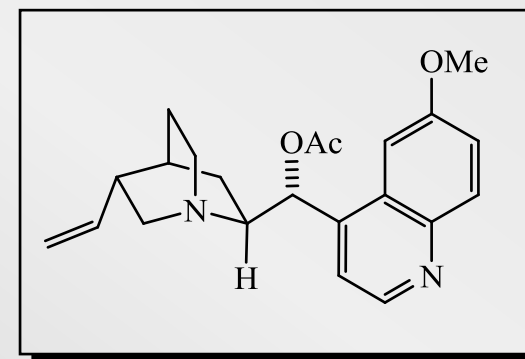
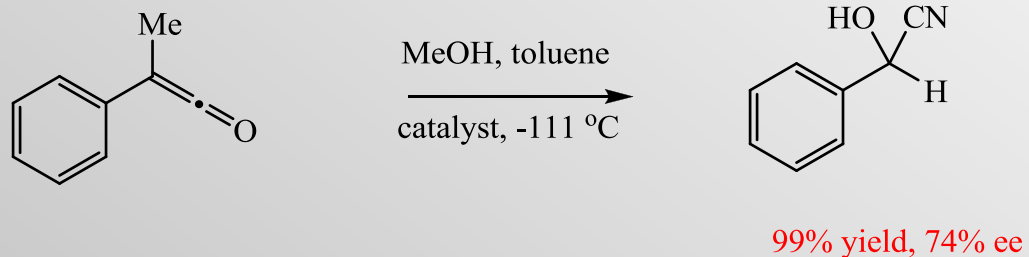
ΙΣΤΟΡΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΤΗΣ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗΣ

■ Breeding: Addition of HCN to benzaldehyde



Biochem. Z., **1912**, 46, 7

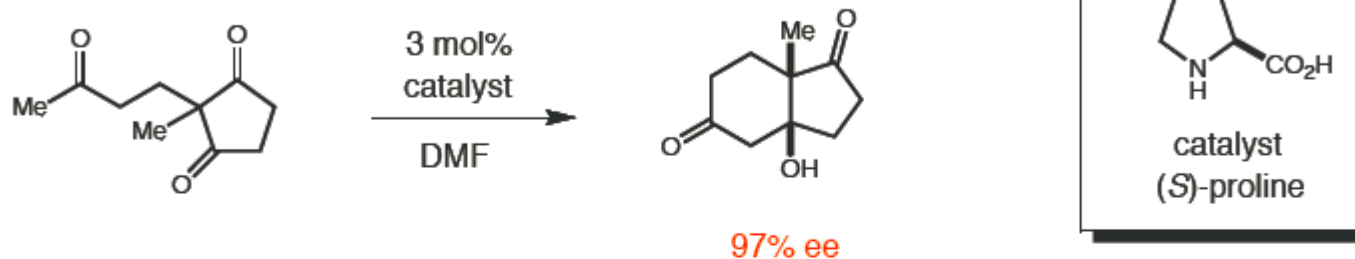
■ Pracejus: Methanolysis of ketenes



Justus Liebigs Ann. Chem., **1960**, 634, 9

ΙΣΤΟΡΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΤΗΣ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗΣ

■ Intramolecular Aldol: Hajos–Parrish *J. Org. Chem.* **1974**, *39*, 1615

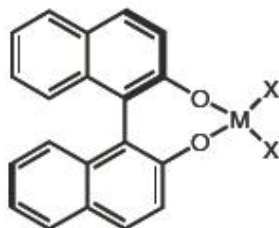


- Extraordinary result that was well received by the chemical synthesis community
- Viewed as a unique chemical reaction, not part of a larger interconnected field
- Manuscript emphasis never placed on the benefits of organocatalysts or new catalysis concepts
- General lessons were never extrapolated thereby stalling potential application over multiple reaction types (Agami mechanistic red herring) \Rightarrow
- The value of a general over-arching field that used organic catalysts was never recognized
- Between 1960 and 2001, no review articles on the collective use of organic catalysts

ΙΣΤΟΡΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΤΗΣ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗΣ

Enantioselective Metal Catalyzed Processes: State of the Art 1996

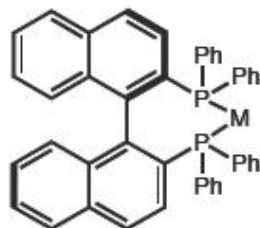
BINOL



Diels-Alder
Aldol
Ene

M = Ti, Al

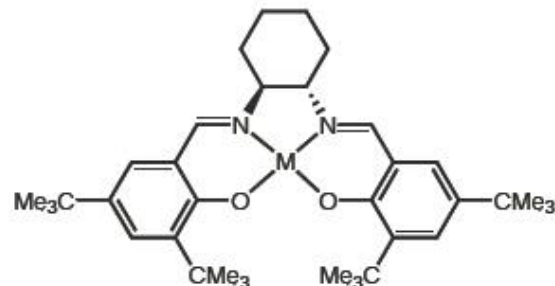
BINAP (Noyori)



Hydrogenation
Hydrosilylation
Allylation

M = Rh, Ru

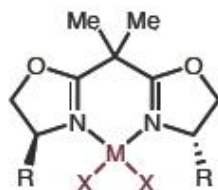
Salen (Jacobsen)



Hetero-Diels-Alder
Epoxidation, Epoxide opening

M = Mn, Cr, Co

Bisoxazoline (Evans-Pfaltz-Corey)



Cyclopropanation
Aziridination
Diels-Alder
Aldol
Michael

M = Cu, Mg, Sn



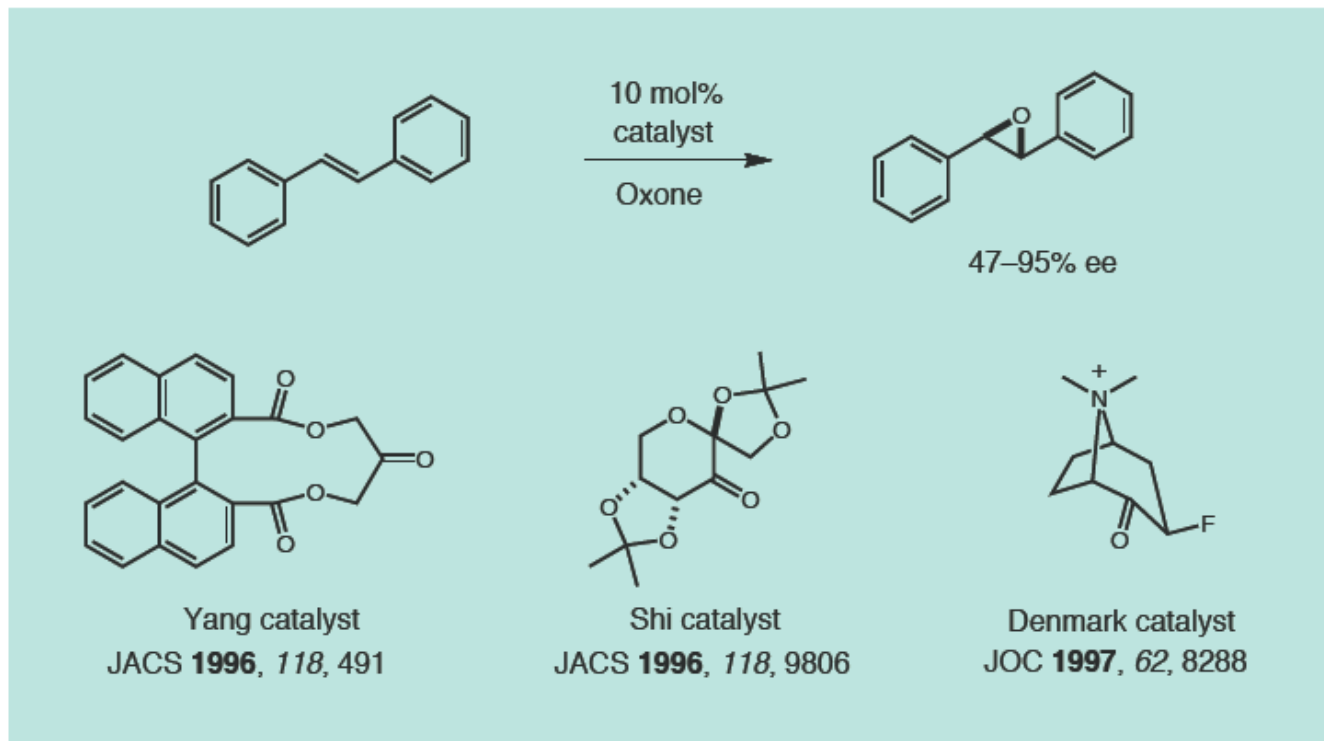
Dave Evans, Harvard

■ Chiral transition metal complexes dominate the enantioselective catalysis landscape

ΙΣΤΟΡΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΤΗΣ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗΣ

Enantioselective Catalysis using Small Organic Molecules: Epoxidation

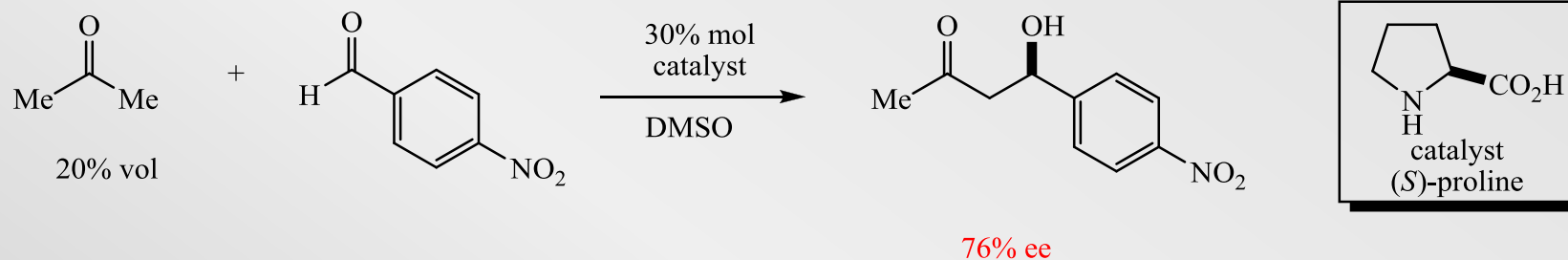
- Enantioselective Catalytic Epoxidations: Yian Shi, Scott Denmark, Dan Yang



- Employed ketones as enantioselective catalysts
- Demonstrated that organic catalysts could be employed to solve major chemical problems
 - Did not conceptualize the field or define the benefits of organocatalysis
 - Involved the invention of a single catalyst for a single reaction type

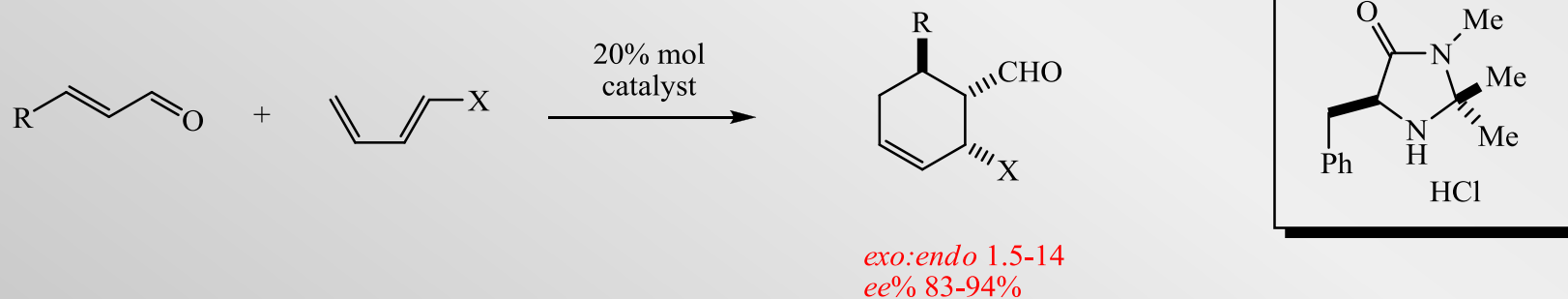
ΑΝΑΒΙΩΣΗ ΤΗΣ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗΣ

■ Intermolecular Aldol: the Enamine Activation Mode (List, Barbas, Lerner)



J. Am. Chem. Soc., **2000**, *122*, 2395

■ Diels Alder: the Iminium Activation Mode (MacMillan)



J. Am. Chem. Soc., **2000**, *122*, 4243

ΑΝΑΒΙΩΣΗ ΤΗΣ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗΣ

■ *This manuscript conceptualized 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

J. Am. Chem. Soc. **2000**, *3122*, 4243

1

Outlined the potential benefits of using organic molecules as asymmetric catalysts for industry or academia based on cost, availability, ease of use

2

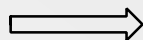
Introduced the concept of a generic mode of activation for organic catalysis that could be used over many reaction types

3

Introduced for the first time, the terminology organocatalysis, organic catalysis and organocatalytic
What's in a name?

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

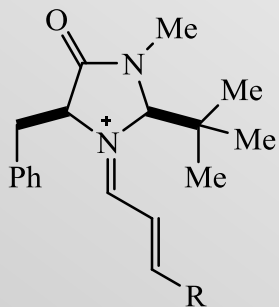
Organocatalysis



The rapid growth of organocatalysis over the last 10 years was fueled by the development of a small number of generic activation modes

Iminium catalysis

Im

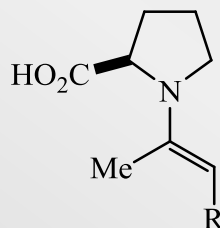


~ 50 new reactions

MacMillan, Jorgensen

Enamine catalysis

En

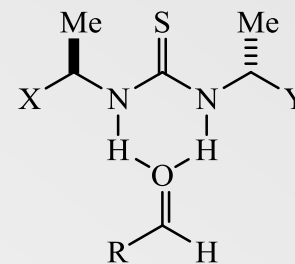


~ 20 new reactions

Hajos-Parrish, List-Barbas

H-bond catalysis

H⁺



~ 30 new reactions

Jacobsen

■ Last 10 years, organocatalysis has delivered many new asymmetric transformations

These 3 activation modes cover a large portion of the organocatalysis landscape

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

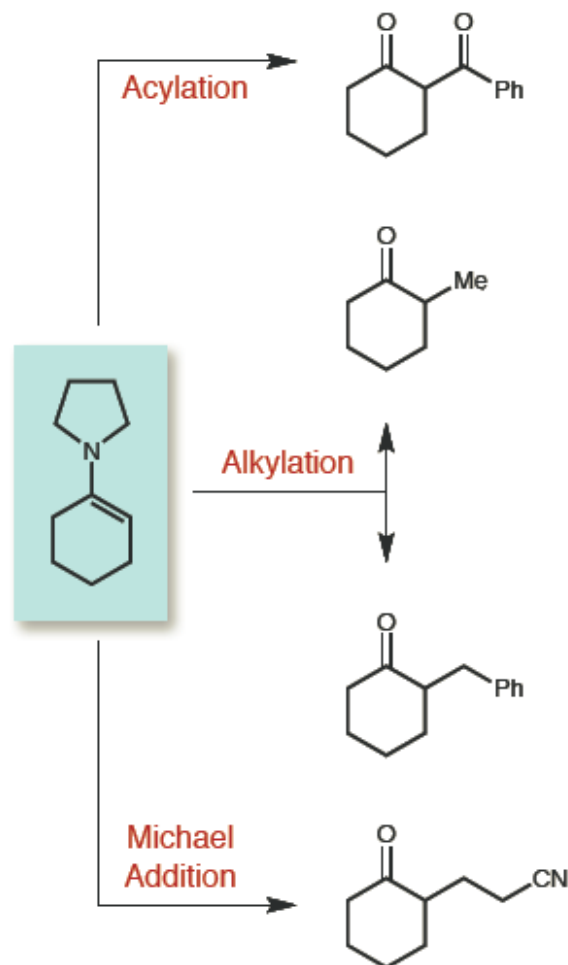
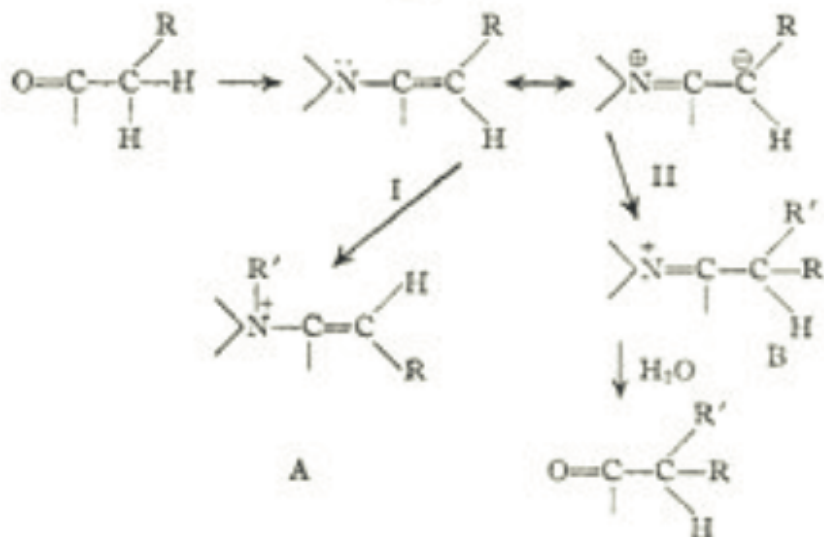
Enamine Catalysis: Fifty Years in the Making

- Stork's landmark 1954 publication outlines benefits of enamines vs enolates

A NEW SYNTHESIS OF 2-ALKYL AND 2-ACYL KETONES

Sir:

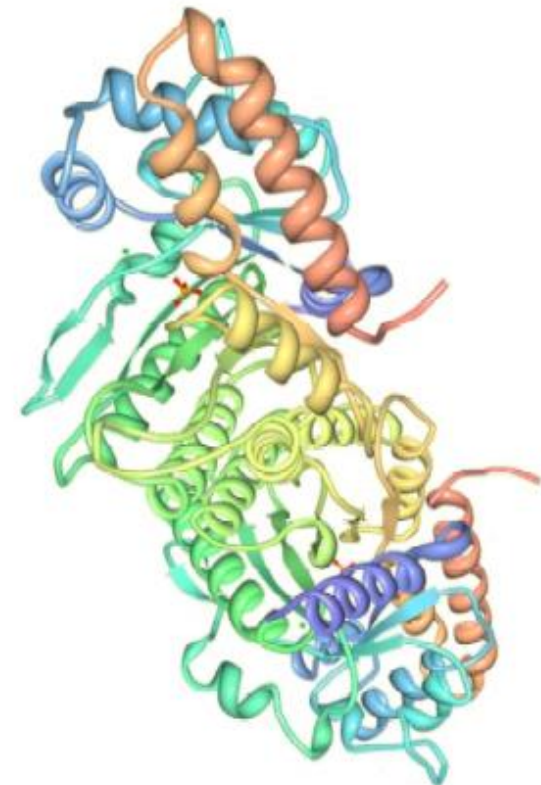
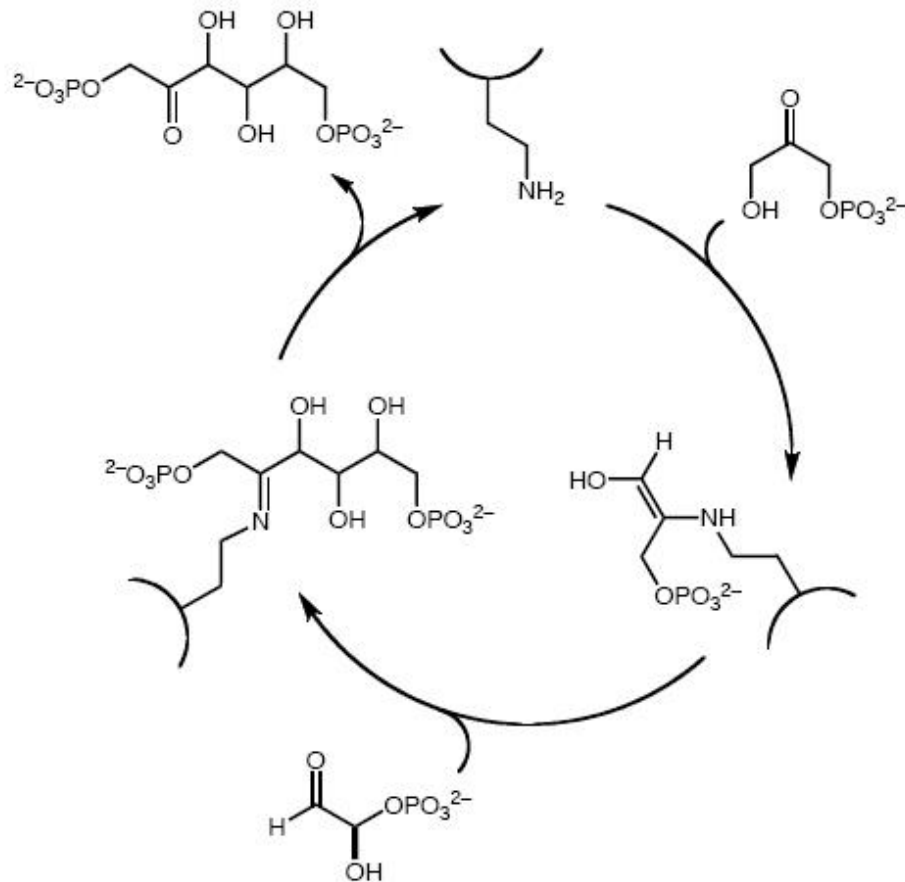
We have discovered a new method for the alkylation and acylation of ketones. The condensation products of ketones and secondary amines are well known.^{1,2} It is evident that these substances can undergo reaction with proper electron acceptors either at N or C according to path I or II:



ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

Enamine Catalysis: Inspiration from Biology

- Mechanism of class I aldolases is proposed to involve enamine intermediates



Fructose bisphosphate aldolase

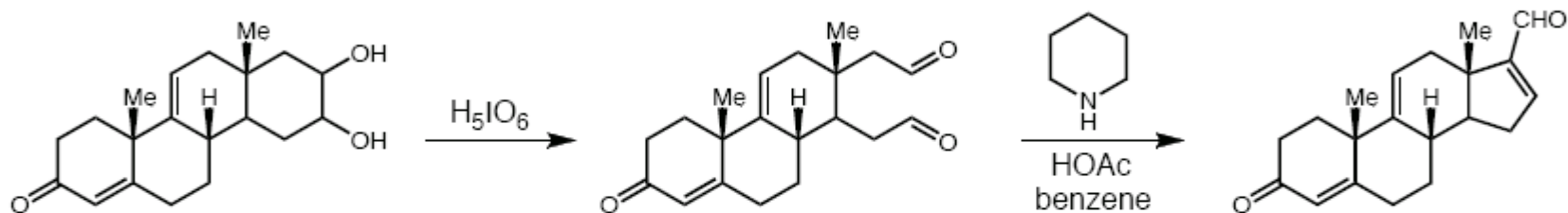
Lysine residue is required for catalytic activity

Rutter, W. J. *Fed. Proc. Am. Soc. Exp. Biol.* **1964**, 23, 1248

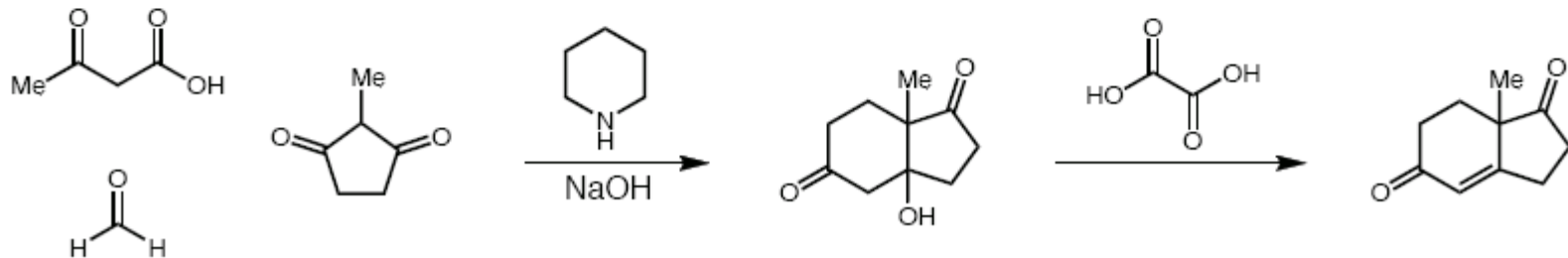
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ ΠΡΩΤΑ ΔΙΑΣΠΑΡΤΑ ΠΑΡΑΔΕΙΓΜΑΤΑ

Enamine Catalysis: Early Adoption in Total Synthesis

■ Woodward-Wieland-Miescher enamine cyclization for steroid synthesis



Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, 74, 4223

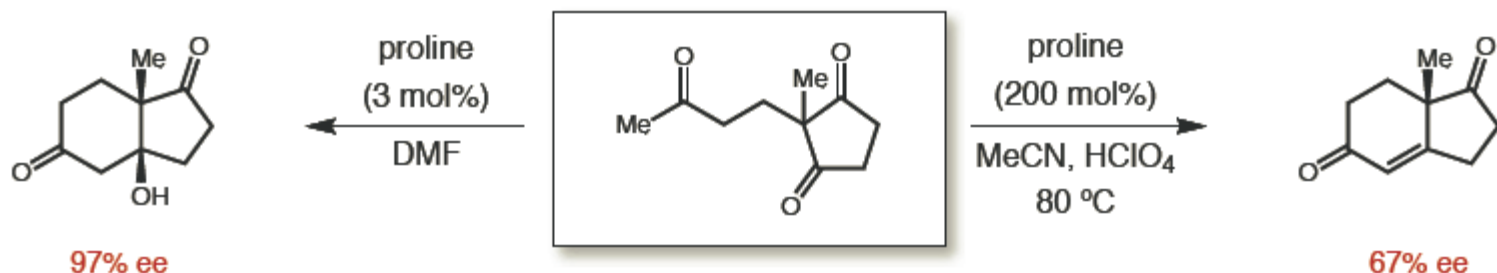


Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, 33, 2215

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ ΠΡΩΤΑ ΔΙΑΣΠΑΡΤΑ ΠΑΡΑΔΕΙΓΜΑΤΑ

Hajos-Parrish-Eder-Sauer-Wiechart: Asymmetric Breakthrough

- Use of proline to deliver the Weiland-Miescher ketone in an asymmetric fashion



J. Org. Chem. **1974**, *39*, 1615.

Angew. Chem. Int. Ed. **1971**, *10*, 496.

Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry

Zoltan G. Hajos*¹ and David R. Parrish

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received August 20, 1973

New Type of Asymmetric Cyclization to Optically Active Steroid CD Partial Structures^[**]

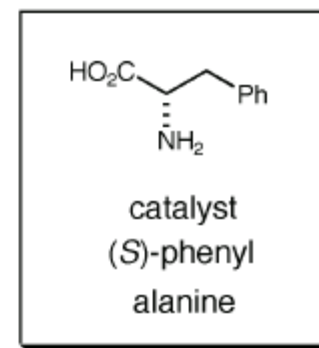
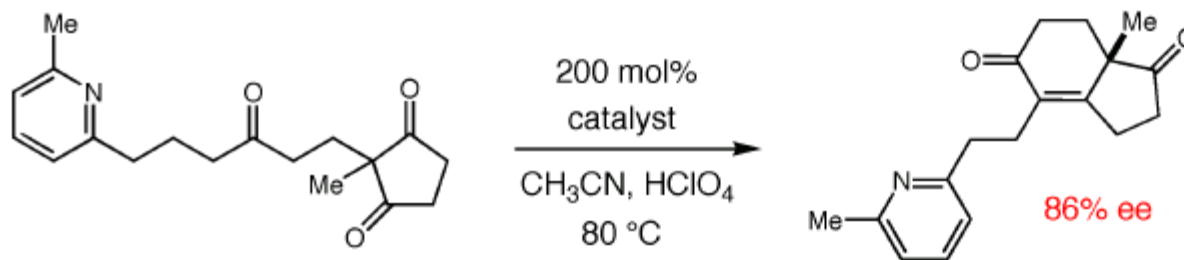
By *Ulrich Eder, Gerhard Sauer, and Rudolf Wiechert^[*]*

German Patent DE2102623 (July 29, 1971)

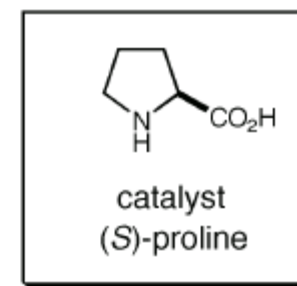
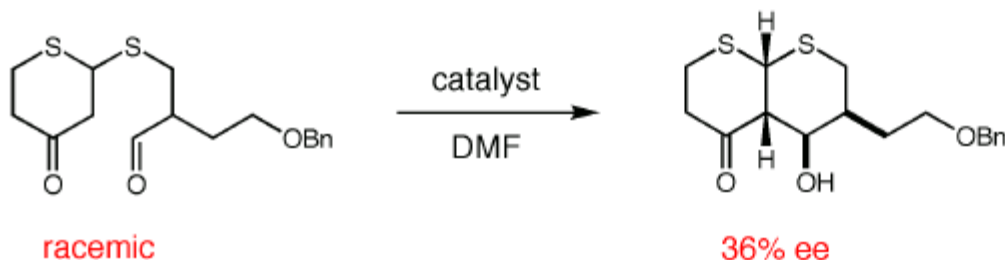
German Patent DE2014757 (Oct 7, 1971)

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ ΠΡΩΤΑ ΔΙΑΣΠΑΡΤΑ ΠΑΡΑΔΕΙΓΜΑΤΑ

- Intramolecular Aldol: Danishefsky–Cain *J. Am. Chem. Soc.* **1976**, *98*, 4975



- Erythromycin Synthesis: Woodward *J. Am. Chem. Soc.* **1981**, *103*, 3210

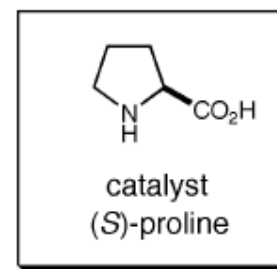
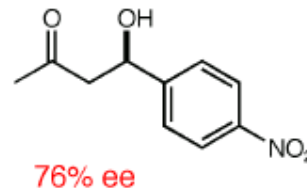
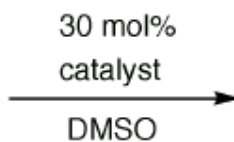
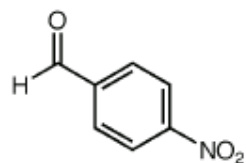
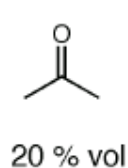


First examples of application of enamine catalysis to natural product synthesis

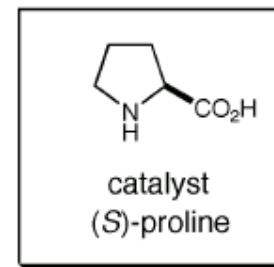
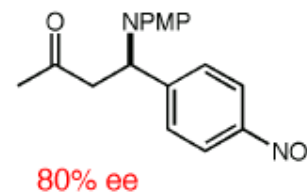
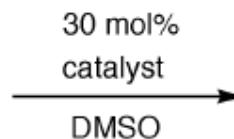
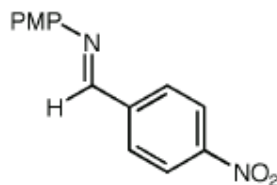
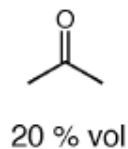
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ ΑΝΑΒΙΩΣΗ ΤΗΣ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗΣ

Enantioselective Organocatalysis, Modern Examples: Enamine Catalysis

- Intermolecular Aldol: Barbas–List–Lerner *J. Am. Chem. Soc.* **2000**, 122, 2395



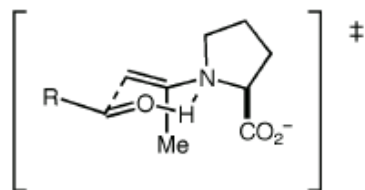
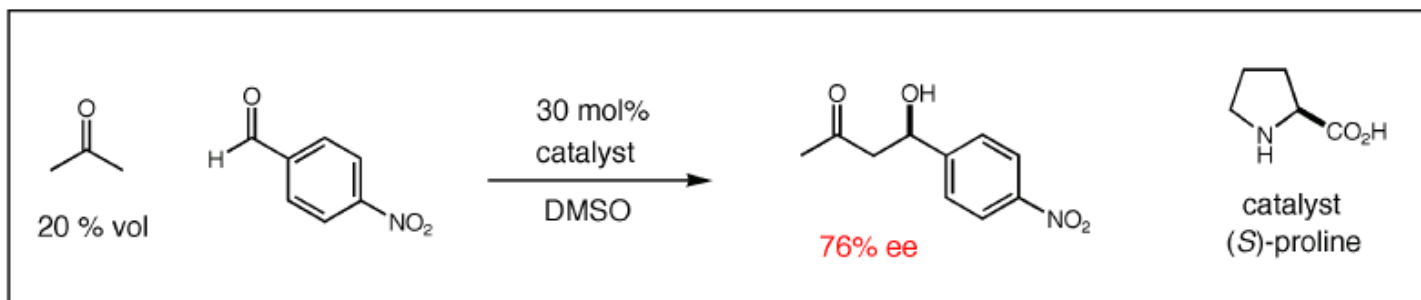
- B-Amino Carbonyls: Barbas *Tetrahedron Lett.* **2001**, 49, 199



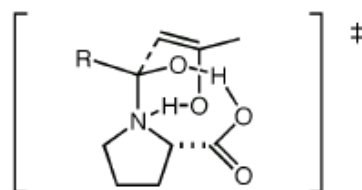
First examples of application of enamine catalysis to intermolecular reactions

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

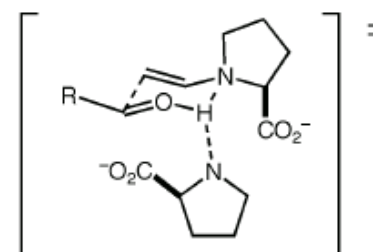
Enamine Aldol: Proposed Transition States to Date



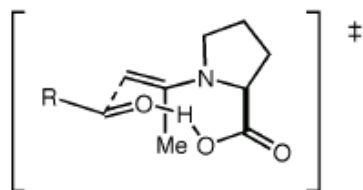
Hajos-Parrish (1971)



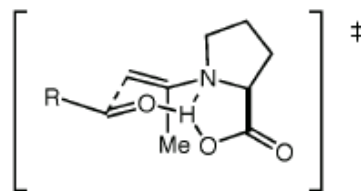
Hajos-Parrish (1971)



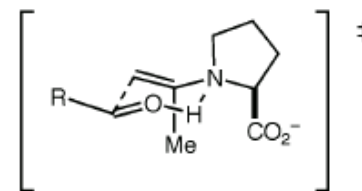
Agami (1987)



Barbas-List (2000)



Houk (2002)



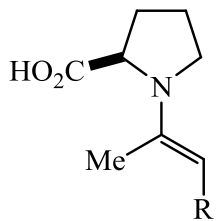
MacMillan (2003)

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

Enantioselective Organocatalysis: A Valuable Strategy for Chemical Synthesis

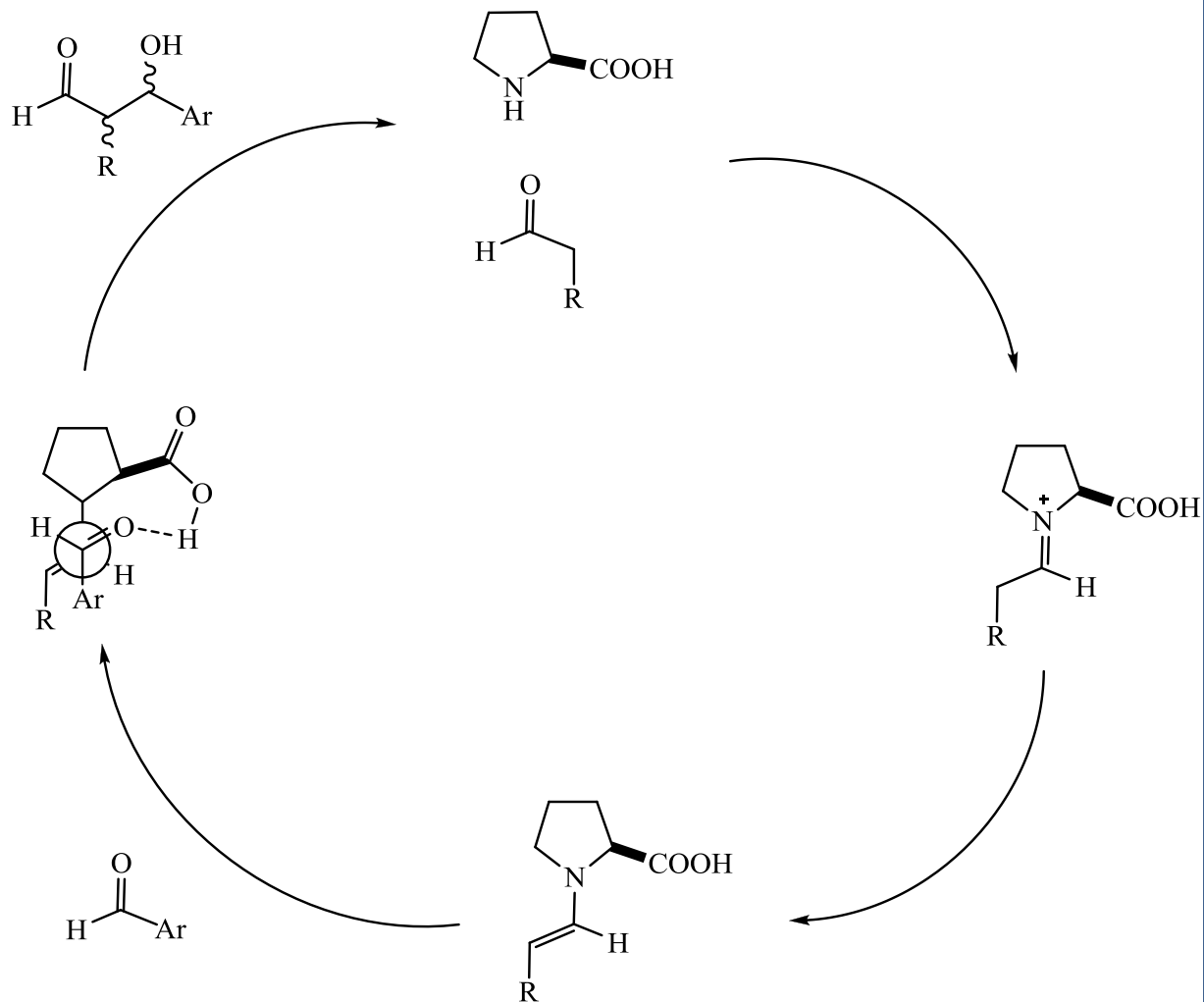
Enamine catalysis

En



~ 20 new reactions

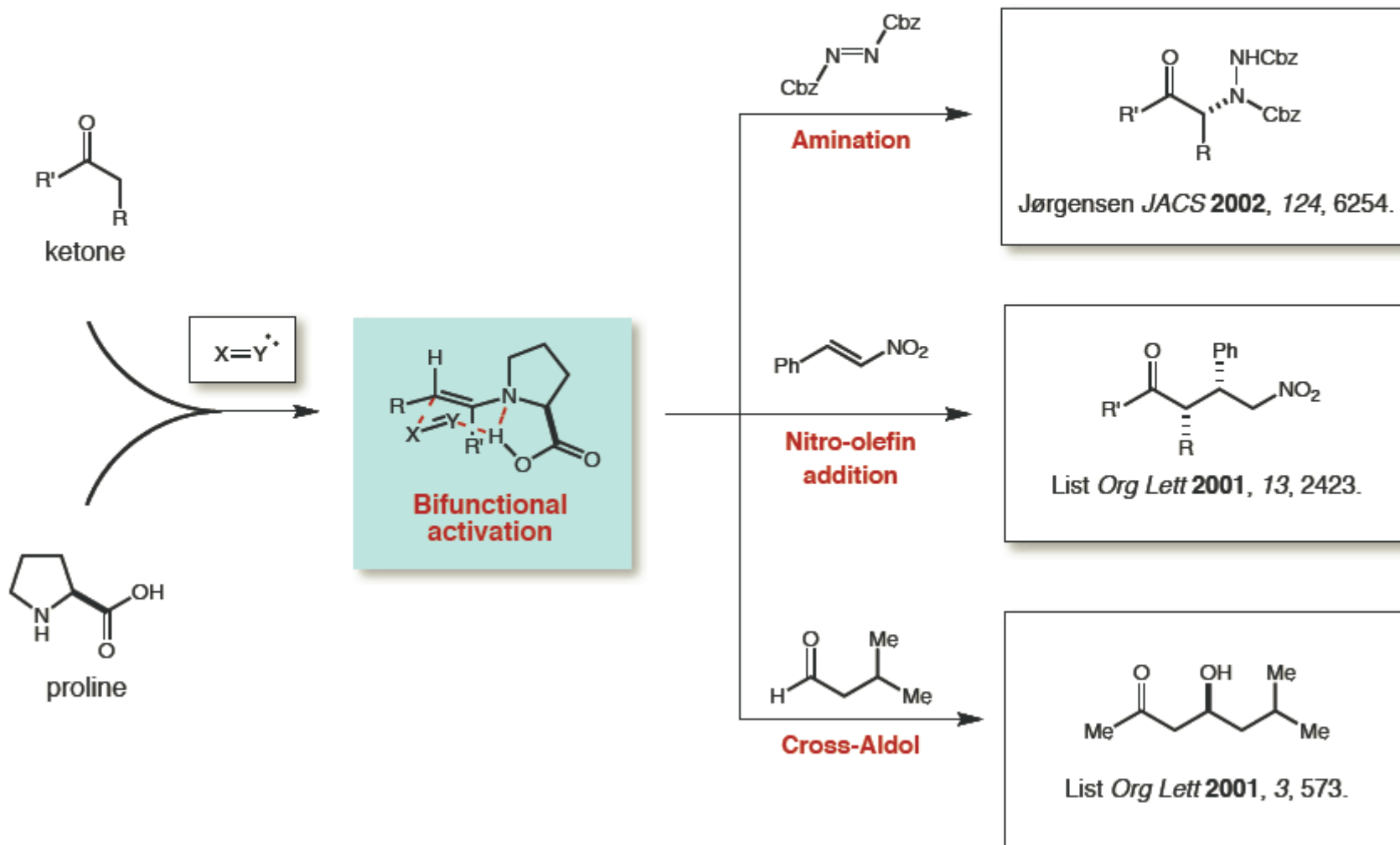
Hajos-Parrish, List-Barbas



ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

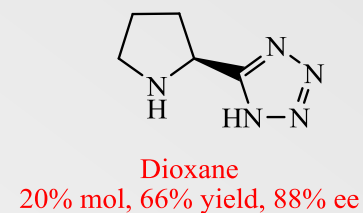
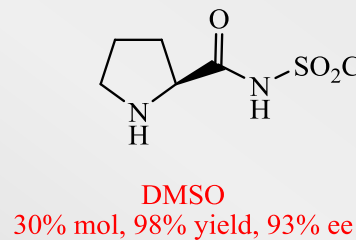
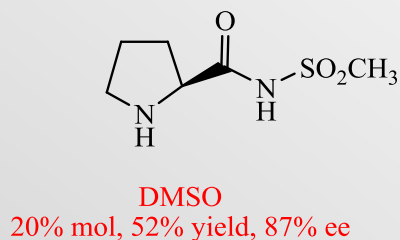
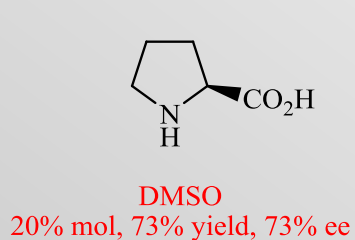
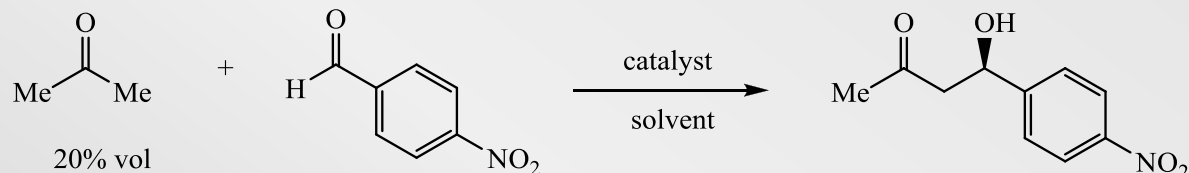
Bifunctional Enamine Catalysis: Generic Induction Platform

- Use of proline or proline-type activation a widely exploited mode of ketone activation



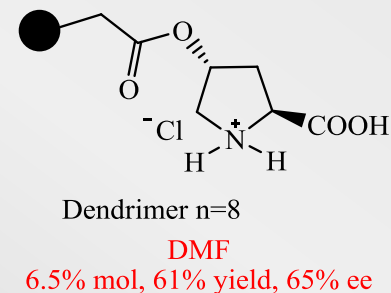
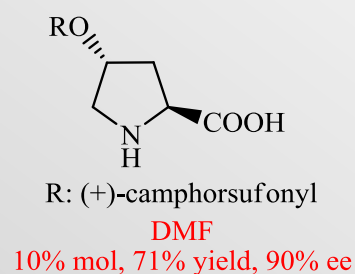
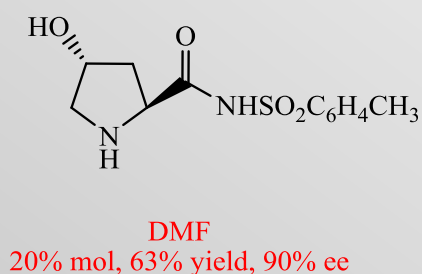
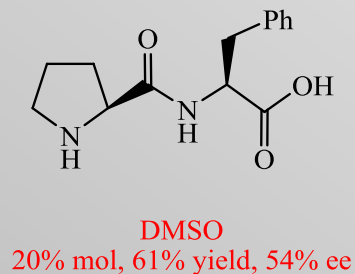
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ ΕΝΑΝΤΙΟΕΚΛΕΚΤΙΚΗ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ: ΔΙΑΜΟΡΙΑΚΗ ΑΛΔΟΛΙΚΗ ΑΝΤΙΔΡΑΣΗ

■ Προηγούμενα αποτελέσματα και οργανοκαταλύτες επιλογής



Ley et al., *Org. Biomol. Chem.*, **2005**, 3, 84

Ley et al., *Synlett*, **2004**, 558



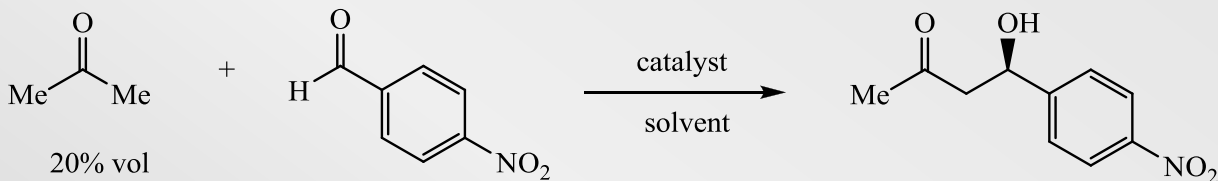
Shi et al., *Synlett*, **2004**, 2215

Kokotos et al., *Synthesis*, **2005**, 2407

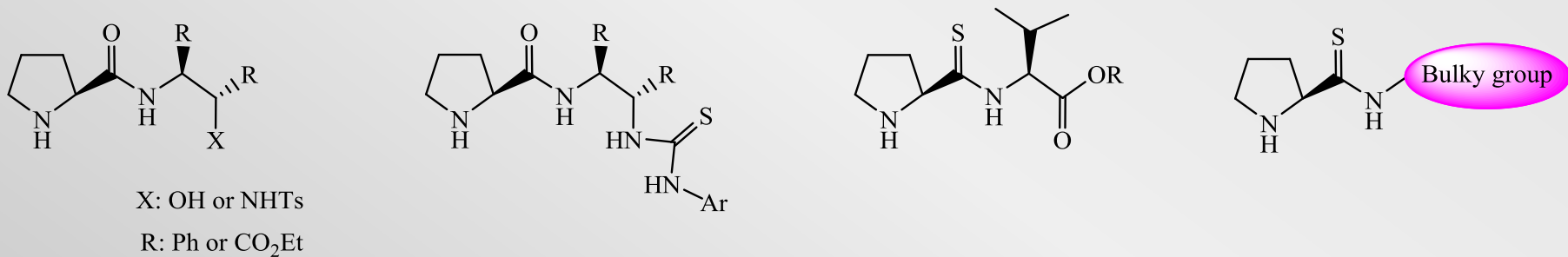
Kokotos et al., *Tetrahedron*, **2005**, 61, 8669

Kokotos et al., *J. Mol. Cat. A*, **2005**, 241, 166

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ ΕΝΑΝΤΙΟΕΚΛΕΚΤΙΚΗ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ: ΔΙΑΜΟΡΙΑΚΗ ΑΛΔΟΛΙΚΗ ΑΝΤΙΔΡΑΣΗ



Οργανοκαταλύτες διπλής ενεργοποίησης (Bifunctional organocatalysts)

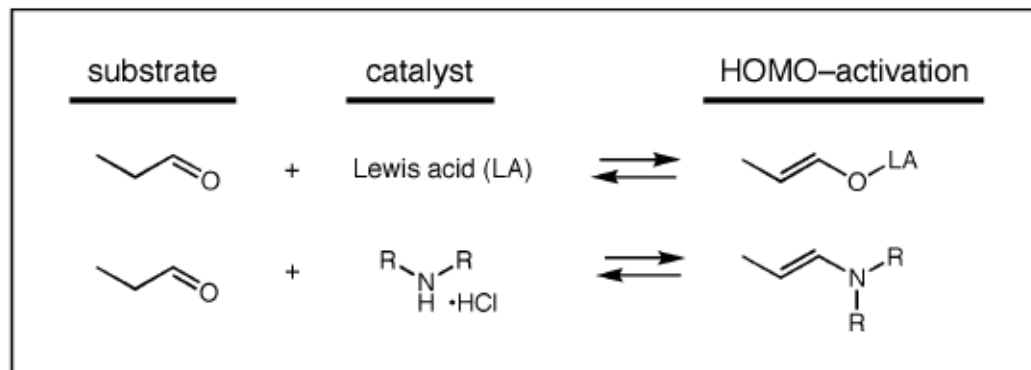


Οργανοκαταλύτες που χρησιμοποιούν στερεοχημική παρεμπόδιση

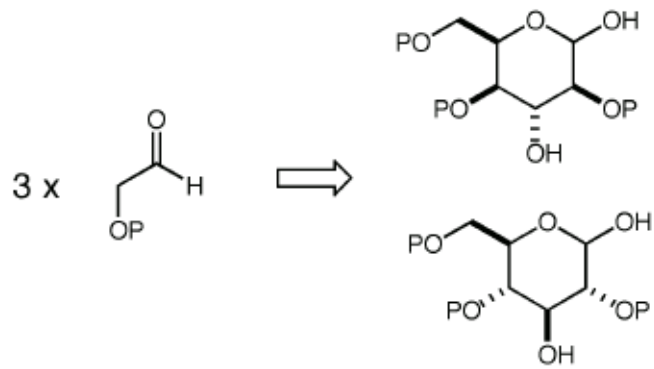
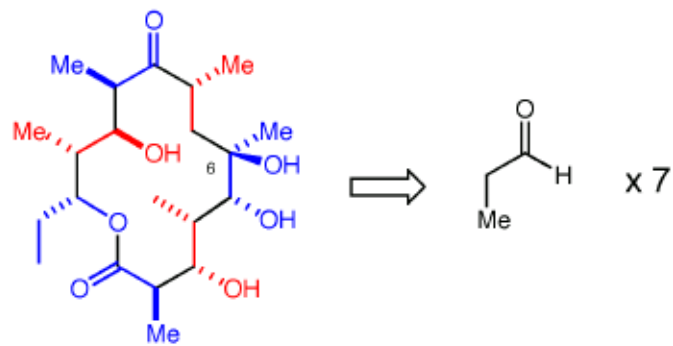


ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

Development of a New Approach to the Enantioselective Aldehyde Aldol Reaction



■ Can we conduct organocatalytic aldehyde-aldehyde direct aldol reaction

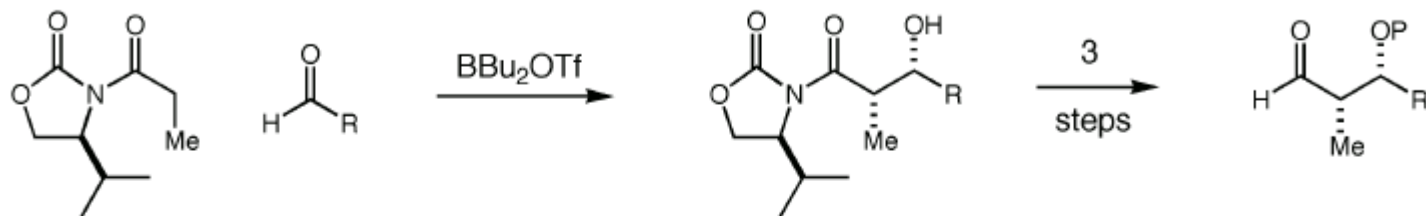


■ Control of aldehyde-aldehyde aldol reactions would allow rapid synthesis of key organic structures

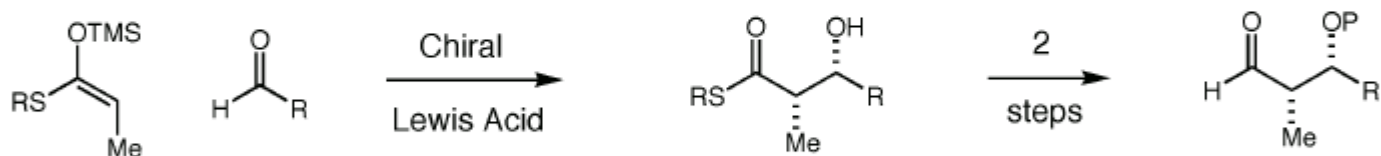
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

«ΚΛΑΣΣΙΚΟΙ» ΤΡΟΠΟΙ ΑΛΔΟΛΙΚΗΣ ΑΝΤΙΔΡΑΣΗΣ

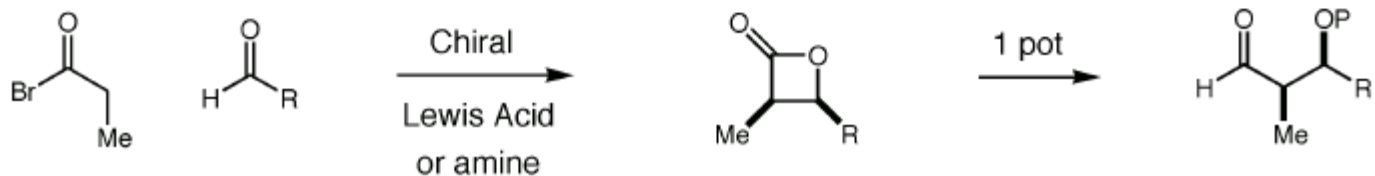
■ Auxiliary Controlled Aldol: Evans



■ Chiral Lewis Acid Controlled Aldol: Mukaiyama



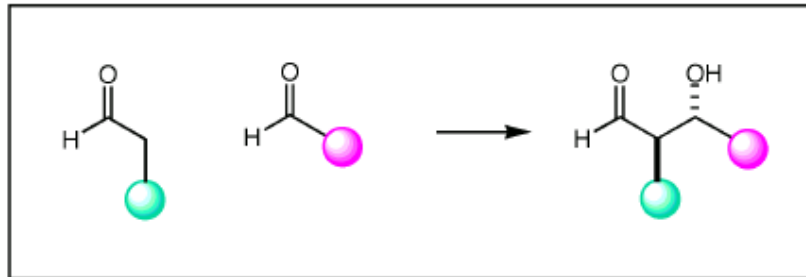
■ Chiral Lewis Acid or Amine Catalyzed Ketene [2 + 2]: Nelson



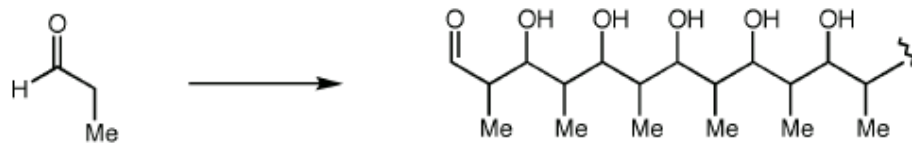
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

ΑΛΔΟΛΙΚΗ ΑΝΤΙΔΡΑΣΗ ΜΕΤΑΞΥ ΑΛΔΕΥΔΩΝ

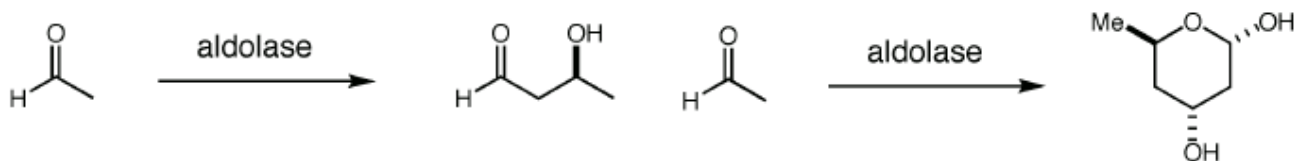
Aldehyde–Aldehyde Direct Aldol: Mechanistic Considerations



- Aldehyde–aldehyde reaction is believed to lead to polymeric materials



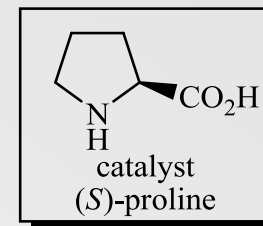
- Aldolase mechanism shows that enamine aldol reaction should not polymerise



ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

ΑΛΔΟΛΙΚΗ ΑΝΤΙΔΡΑΣΗ ΜΕΤΑΞΥ ΑΛΔΕΥΔΩΝ

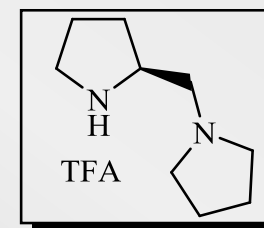
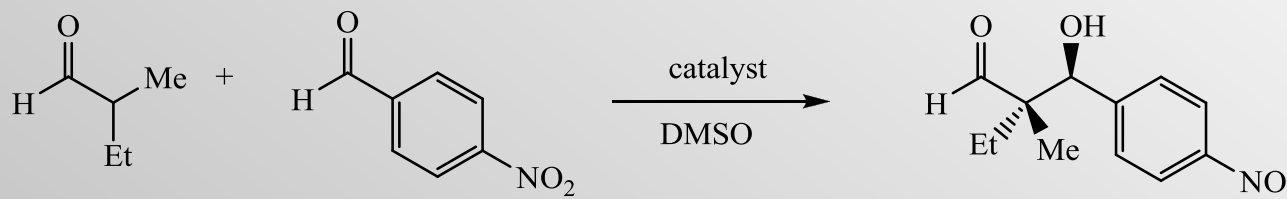
■ Διαμοριακή αλδολική αντίδραση μεταξύ αλδεϋδών



80% yield, 3:1, 97% ee

MacMillan et al, J. Am. Chem. Soc., **2002**, 124, 6798

■ Δημιουργία τεταρτοταγούς άνθρακα με αλδολική αντίδραση

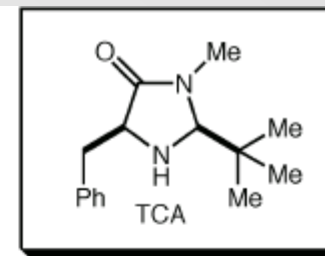


96% yield, 62:38, 91% ee

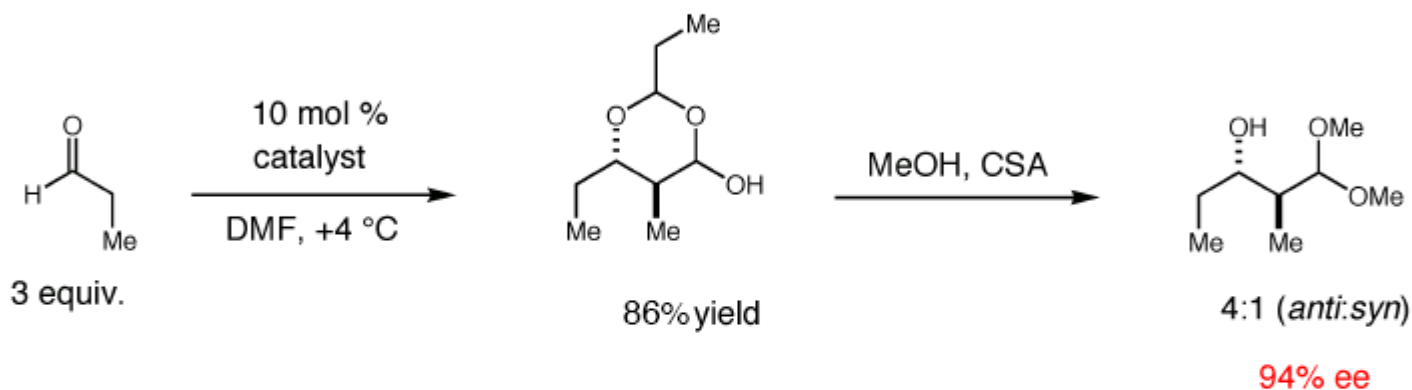
Barbas et al, Angew. Chem. Int. Ed., **2004**, 43, 2420

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

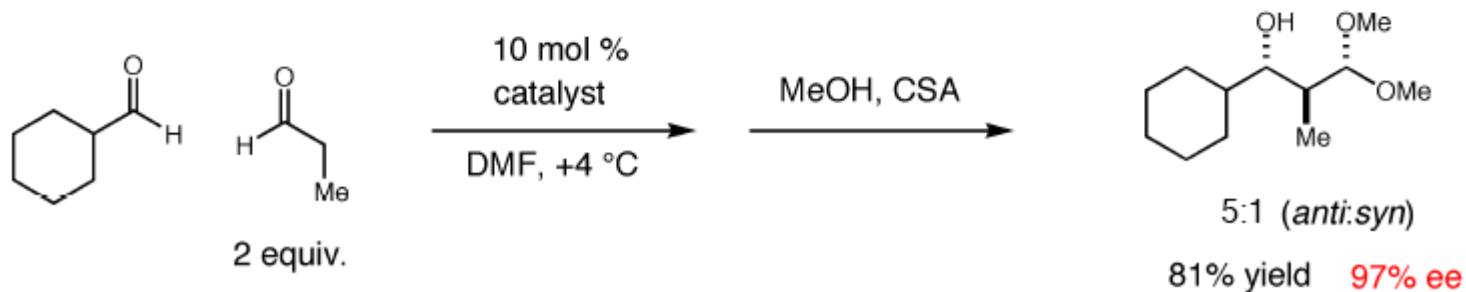
Ιμιδαζολιδινόνες ως οργανοκαταλύτες εναμίνης



■ Trimerization of propionaldehyde

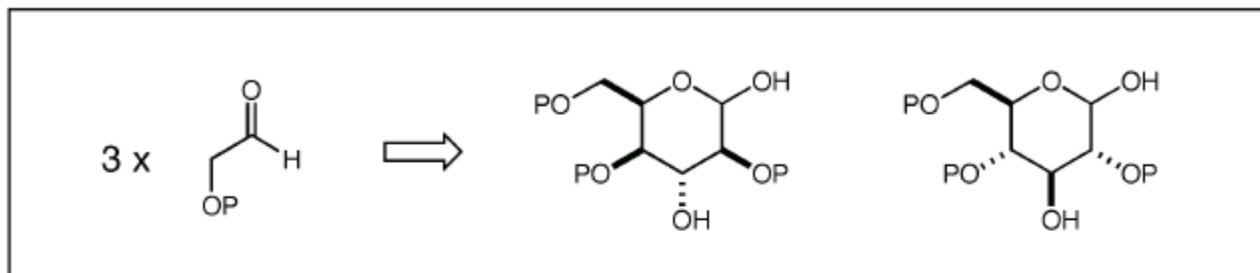


■ Cross coupling to non-enolizable aldehydes

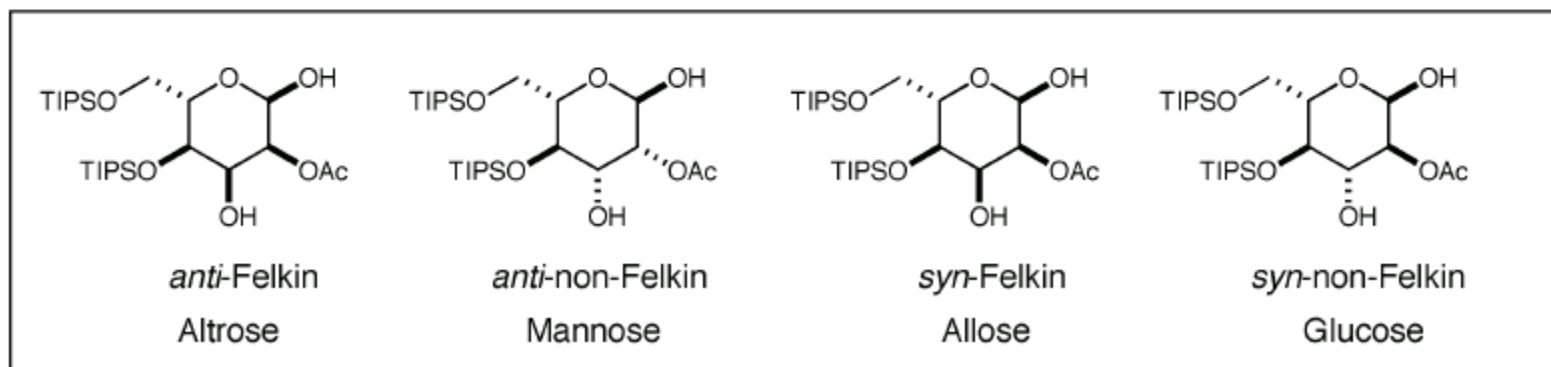
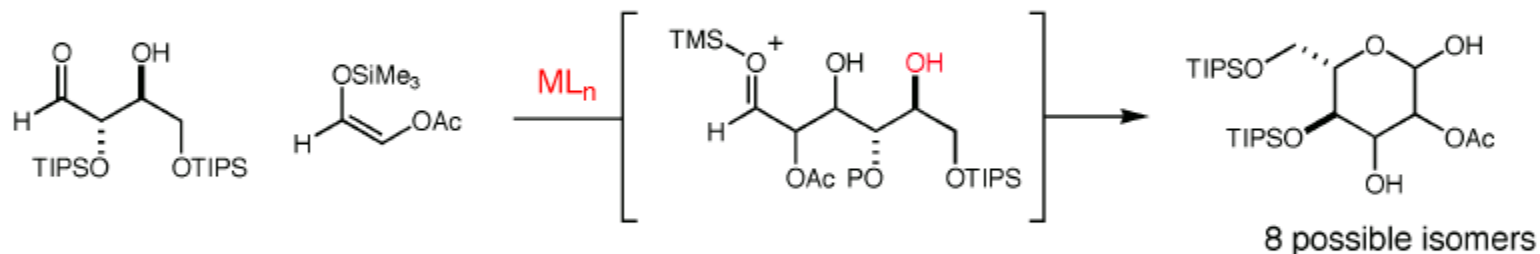


ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

- Aldehyde-aldehyde aldol reactions allows conceptually new approach to carbohydrate synthesis

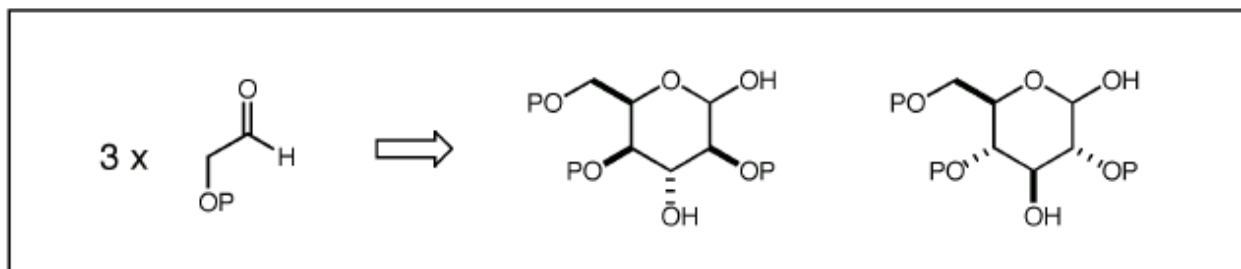


- Can we use a combination of organo and metal catalysis to rapidly generate carbohydrates

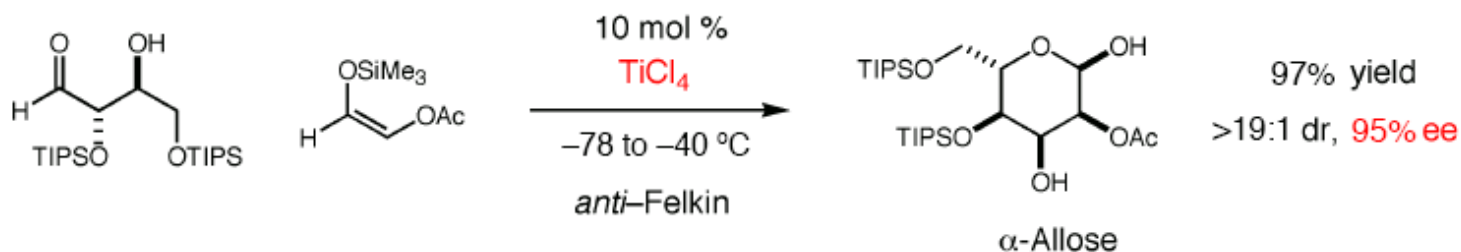


ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

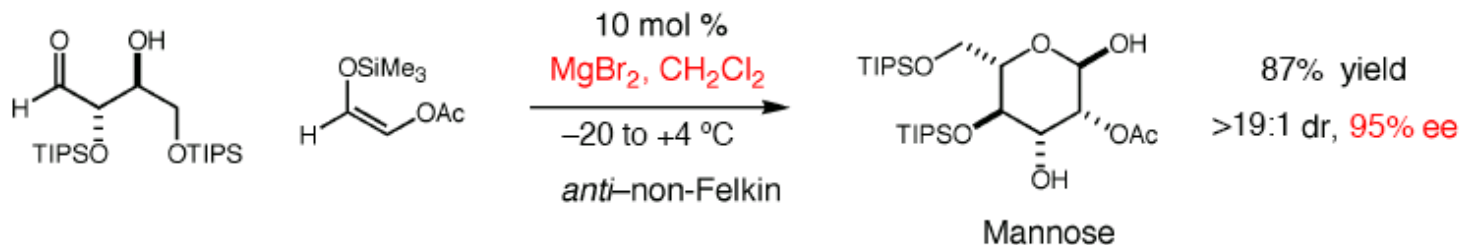
Εναντιοεκλεκτική σύνθεση υδατανθράκων συνδυάζοντας οργανοκατάλυση και κατάλυση με μέταλλα μεταπτώσεως



■ Synthesis of fully differentiated Allose in two chemical steps



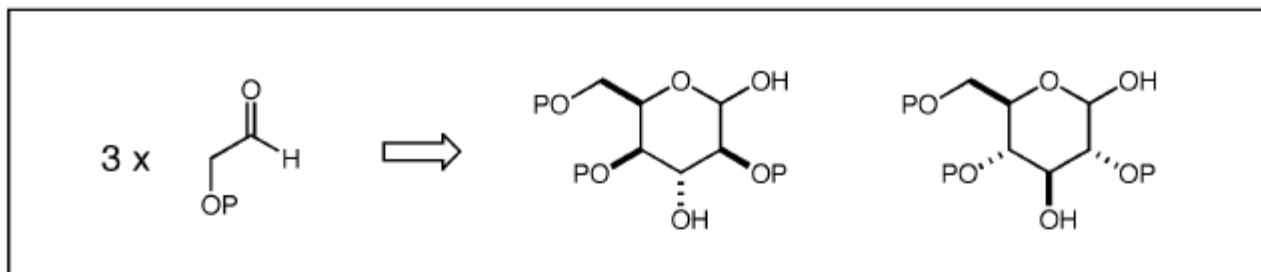
■ Synthesis of fully differentiated Mannose in two chemical steps



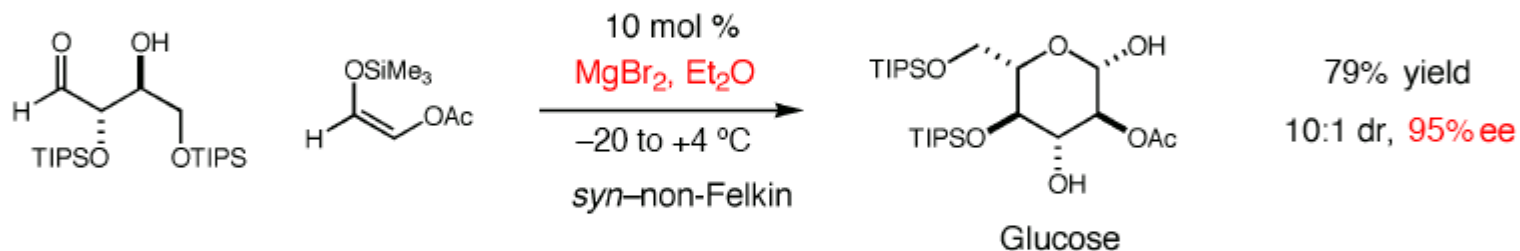
Merging catalysis technologies allows enantio- and diastereoselective access to carbohydrates

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

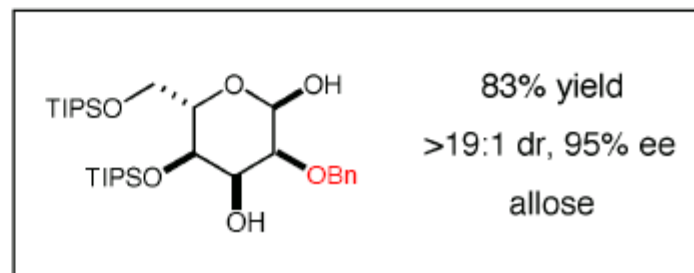
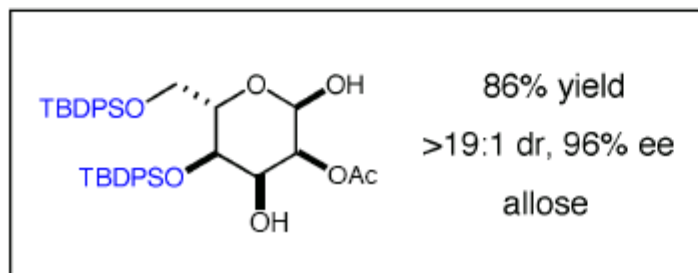
Εναντιοεκλεκτική σύνθεση υδατανθράκων συνδυάζοντας οργανοκατάλυση και κατάλυση με μέταλλα μεταπτώσεως



- Synthesis of fully differentiated Glucose in two chemical steps

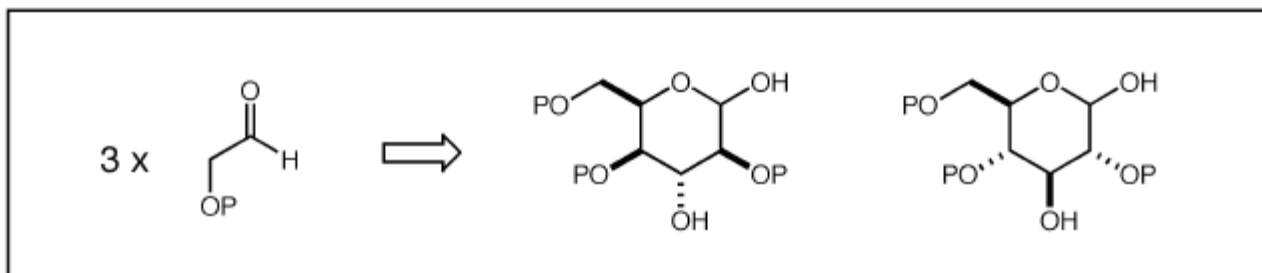


- Two-Step Strategy is Compatible with a Variety of Protecting Groups

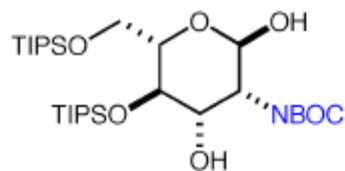


ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

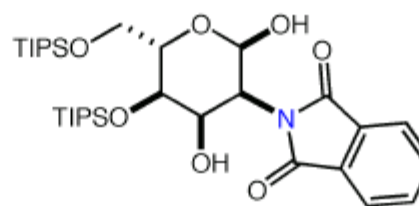
Εναντιοεκλεκτική σύνθεση υδατανθράκων συνδυάζοντας οργανοκατάλυση και κατάλυση με μέταλλα μεταπτώσεως



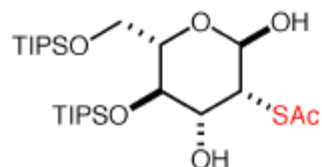
■ Synthesis of fully differentiated mannosamine in two chemical steps



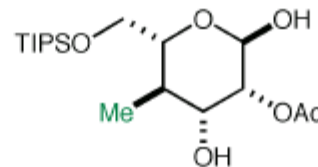
74% yield
10:1 dr, 95% ee
 α -Mannosamine



82% yield
12:1 dr, 96% ee
 α -2-Amino-Allose



71% yield
19:1 dr, 95% ee
 α -Thiomannose

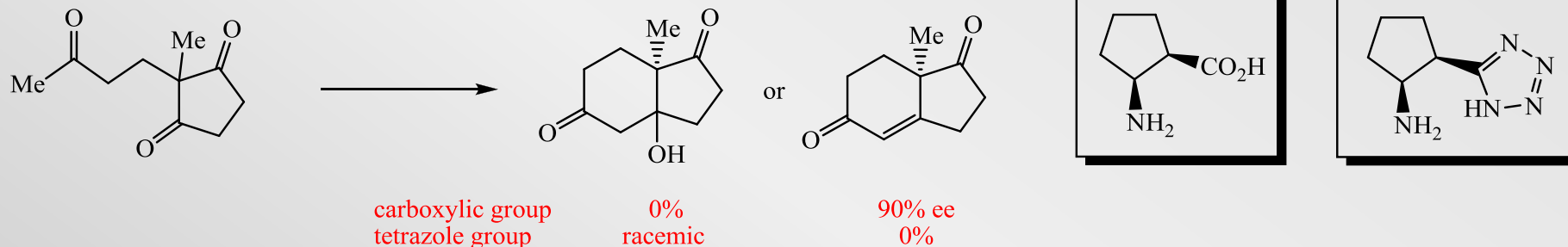


68% yield
19:1 dr, 99% ee
 α -4-carboallose

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

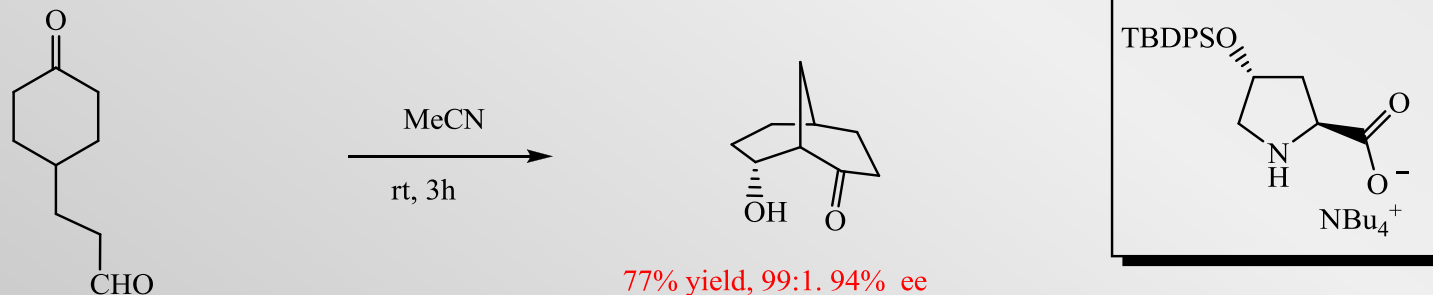
Ενδομοριακές αλδολικές αντιδράσεις

■ Αντιδράσεις τύπου Hajos-Parrish



Davies et al, Chem. Commun., **2005**, 3802

■ Σύνθεση ενδιάμεσων για τη παραγωγή βιοδραστικών ενώσεων

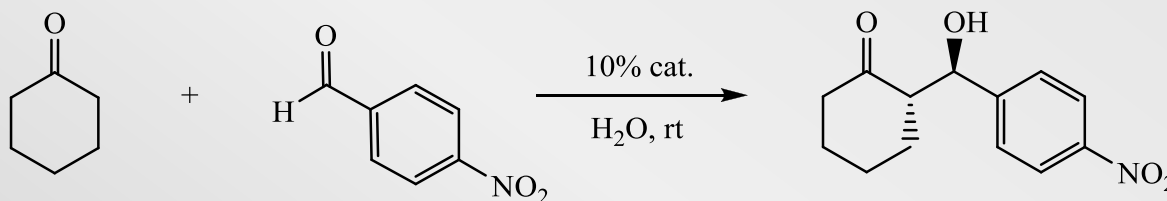


Itagaki et al, Org. Lett., **2005**, 7, 4181

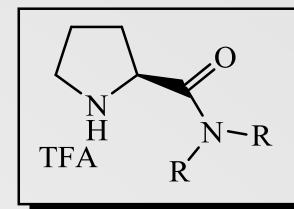
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

Οργανοκαταλυτικές αλδολικές αντιδράσεις σε ΝΕΡΟ!!!!!!!!!!!!!!!!!!!!

Αντιδράσεις τύπου Hajos-Parrish

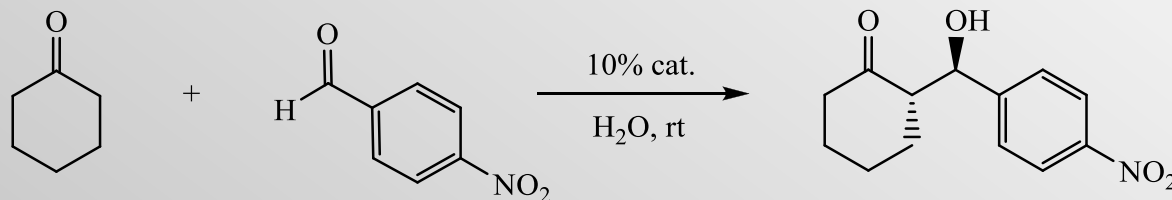


99%, 89:11, 94% ee

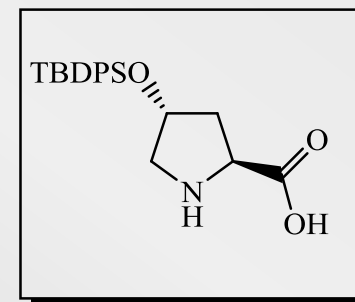


Barbas et al, J. Am. Chem. Soc., 2006, 128, 734

Σύνθεση ενδιαμέσων για τη παραγωγή βιοδραστικών ενώσεων



86%, 95:5, >99% ee



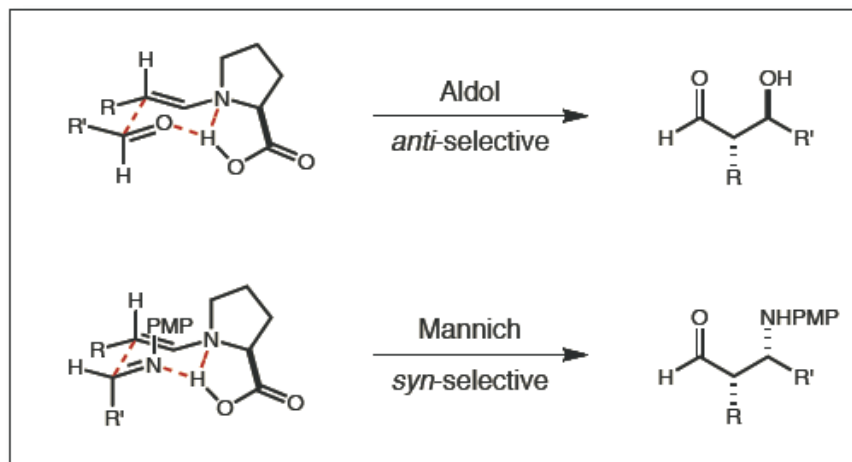
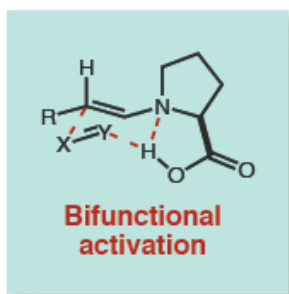
Hayashi et al, Angew. Chem. Int. Ed., 2006, 45, 958

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

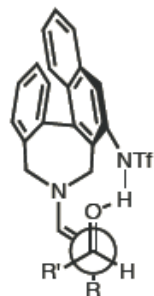
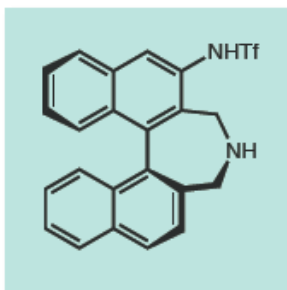
Αλλάζοντας την εκλεκτικότητα της αντίδρασης με αλλαγή των δομικών χαρακτηριστικών των οργανοκαταλυτών

Predictable Stereochemistry for Aldol and Mannich

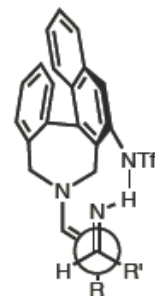
- Use of proline or proline-type catalysts leads to *anti*-aldol or *syn*-Mannich



- Maruoka's binaphthyl catalyst is a significant advance to access opposite stereoisomers



Syn-aldol: *ACIEE* **2004**, 43, 6722

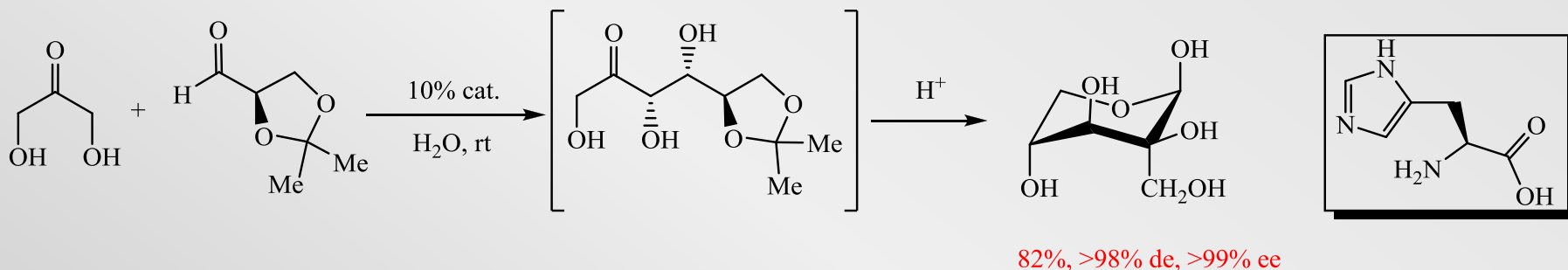


Anti-Mannich: *JACS* **2005**, 127, 16408

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

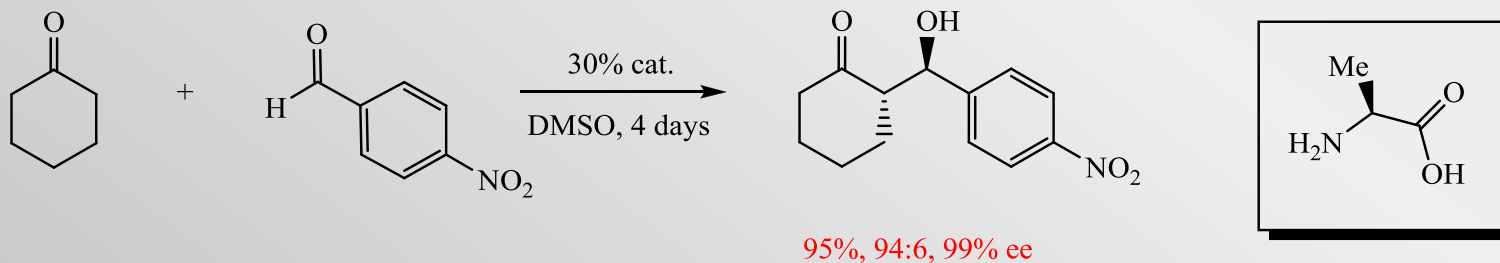
Εκτός από τις δευτεροταγείς αμινοομάδες (και ιδιαίτερα το «χαρισματικό» δακτύλιο της πυρρολιδίνης, πρωτοταγείς αμινοομάδες έχουν χρησιμοποιηθεί με επιτυχία στην οργανοκατάλυση

■ Η ιστιδίνη ως οργανοκαταλύτης για την σύνθεση σακχάρων



Mahrwald et al, J. Am. Chem. Soc., **2009**, 131, 16642

■ Η αλανίνη ως οργανοκαταλύτης για αλδολικές αντιδράσεις

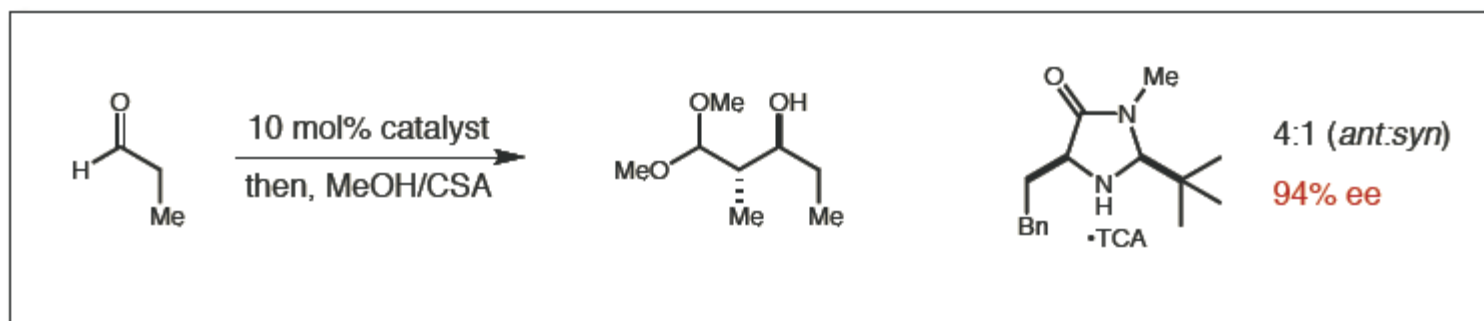


Cordova et al, Chem. Commun., **2005**, 3586

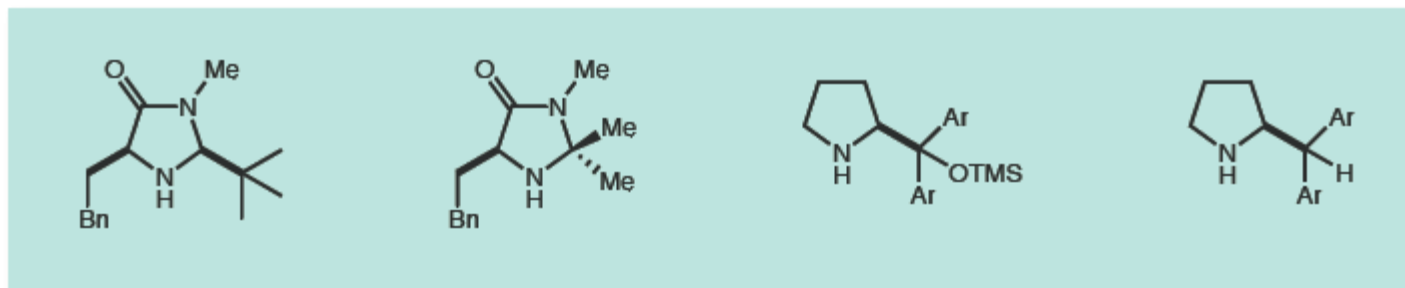
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

Monofunctional Enamine Catalysis

- Bifunctional activation is not absolutely required for selective catalysis

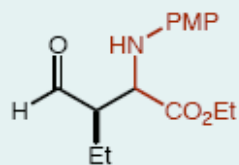
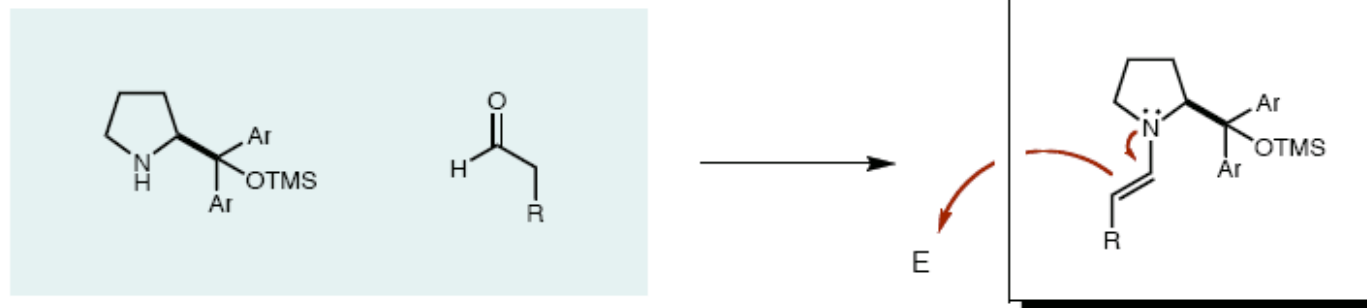


- Imidazolidinone and Jørgensen-type frameworks have been widely applied

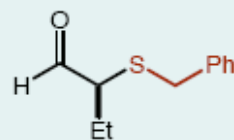


ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

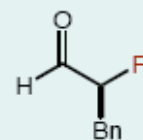
Enamine Chemistry with Jørgensen's Catalyst



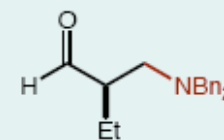
83%, 94% ee, 4:1 dr



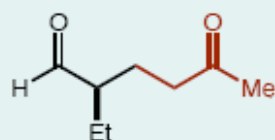
85%, 96% ee



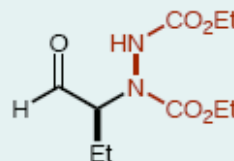
74%, 93% ee



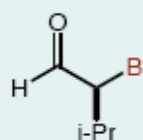
84%, 90% ee



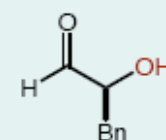
83%, 93% ee



79%, 90% ee



74%, 94% ee



70%, 87% ee

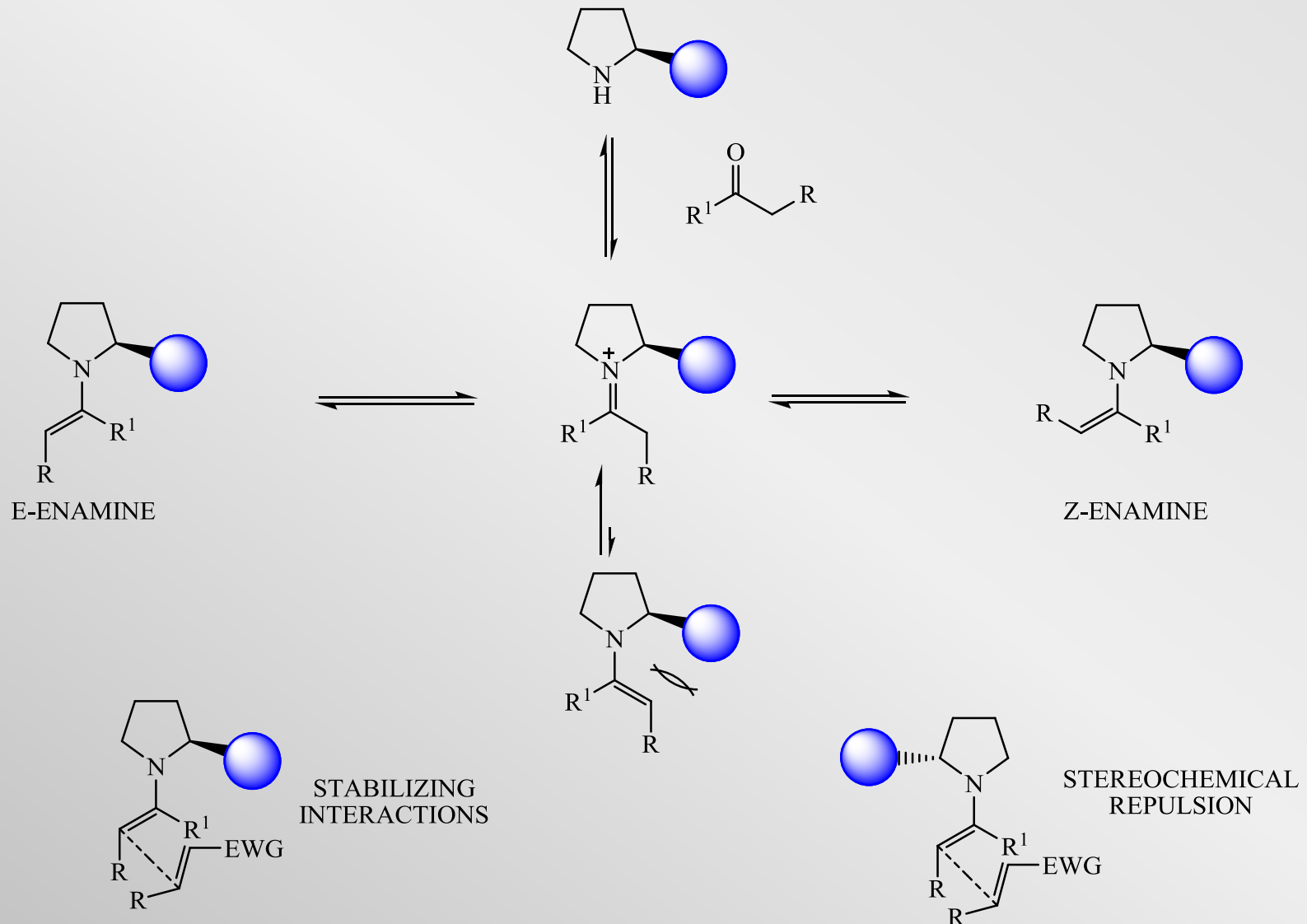
Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kaersgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.

Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804.

Ibrahem, I.; Zhao, G.-L.; Sunden, H.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 4659.

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

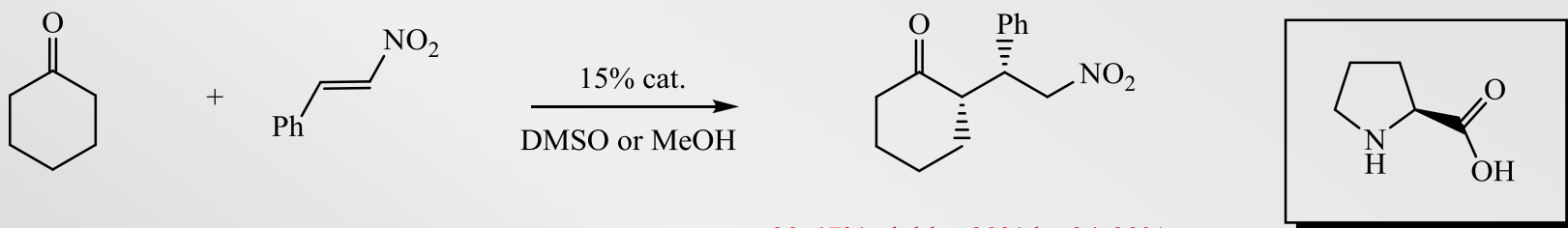
Αντιδράσεις Michael-ΜΗΧΑΝΙΣΜΟΙ ΔΡΑΣΗΣ



ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

Αντιδράσεις Michael

■ Κυκλικές κετόνες με νιτροολεφίνες χρησιμοποιώντας δευτεροταγείς αμίνες



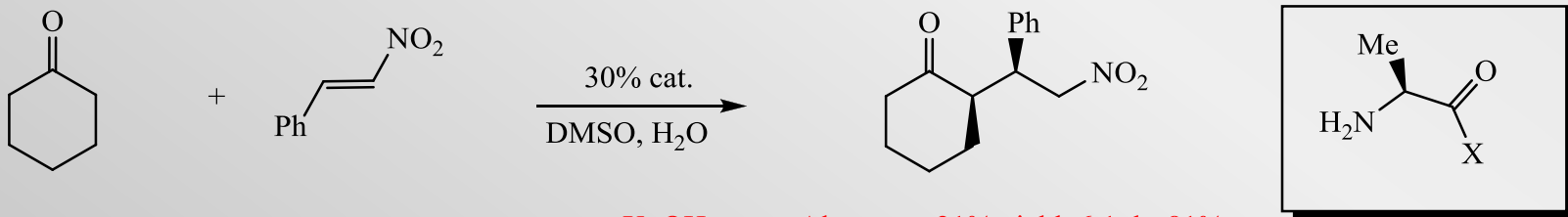
23-47% yield, >90%de, 94-99% ee

Barbas et al, Tetrahedron Lett., **2001**, 42, 4441

List et al, Org. Lett., **2001**, 3, 2423

Enders et al, Synlett, **2002**, 26

■ Κυκλικές κετόνες με νιτροολεφίνες χρησιμοποιώντας πρωτοταγείς αμίνες



X: OH, Ala 21% yield, 6:1 dr, 81% ee

X:Ala, H-Ala-Ala-OH 55% yield, 12:1dr, 84% ee

X: NHCH(Ph)₂ 92% yield, 27:1 dr, 93% ee

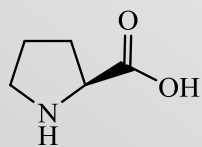
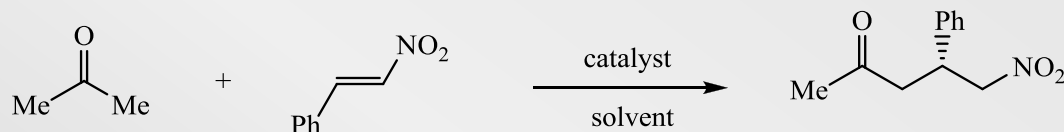
Cordova et al, Chem.Commun., **2006**, 460

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

Αντιδράσεις Michael

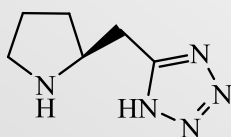
«Δύσκολη» αντίδραση Michael μεταξύ ακετόνης και νιτροστυρενίου

■ Benchmark Catalysts for the Reaction Between Acetone and Nitrostyrene



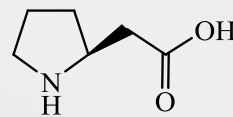
DMSO
20% mol, 63% yield, 7% ee

List et al., *Org. Lett.*, **2001**, 3, 2423



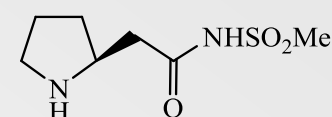
DMSO
20% mol, 68% yield, 42% ee

Ley et al., *Synlett*, **2005**, 611



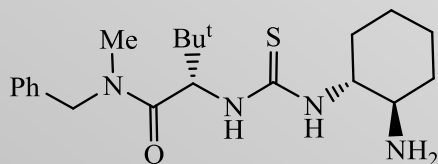
DMSO
20% mol, 67% yield, 39% ee

Terakado et al., *Chem. Lett.*, **2005**, 34, 962



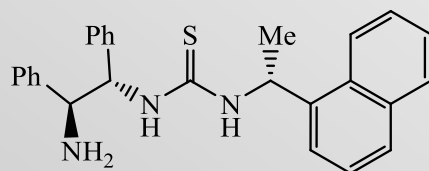
ⁱPrOH:EtOH
5% mol, 87% yield, 48% ee

Kokotos et al., *Tetrahedron*, **2009**, 65, 1444



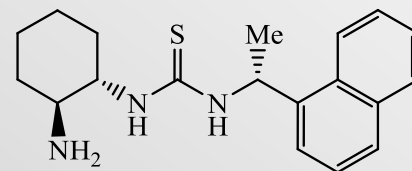
toluene, PhCOOH
10% mol, 93% yield, 99% ee

Jacobsen et al., *J. Am. Chem. Soc.*, **2006**, 128, 7170



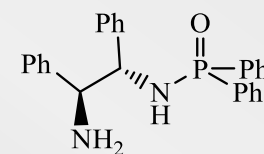
Toluene, AcOH, H₂O
15% mol, 100% yield, 91% ee

Tsogoeva et al., *Chem. Commun.*, **2006**, 1451



THF, 4-NBA
15% mol, 90% yield, 99% ee

Xu et al., *Eur. J. Org. Chem.*, **2010**, 656



neat
15% mol, 80% yield, 97% ee

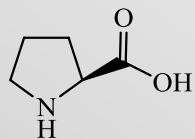
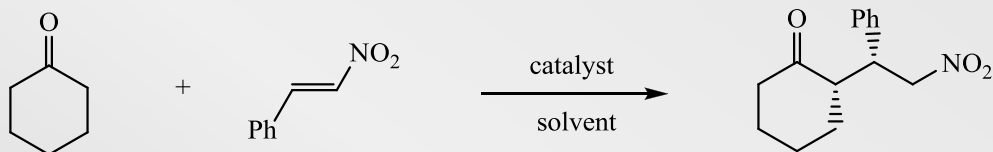
Docherty et al., *Tetrahedron Lett.*, **2010**, 51, 209

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

Αντιδράσεις Michael

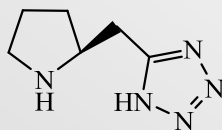
Αντίδραση Michael μεταξύ κυκλοεξανόνης και νιτροστυρενίου

■ Benchmark Catalysts for the Reaction Between Cyclohexanone and Nitrostyrene



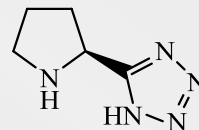
DMSO, 15% mol,
89% yield, 15:1 dr, 25% ee

List et al., *Org. Lett.*, **2001**, 3, 2423



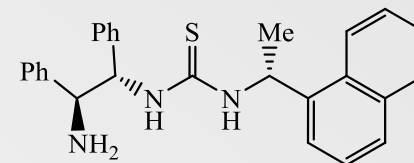
*i*PrOH:EtOH, 15% mol
88% yield, >19:1 dr, 91% ee

Ley et al., *Synlett*, **2005**, 611



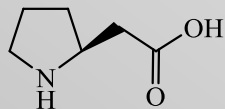
*i*PrOH:EtOH, 15% mol
80% yield, >19:1 dr, 62% ee

Ley et al., *Org. Biomol. Chem.*, **2005**, 3, 84

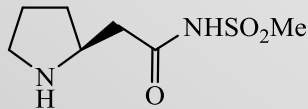


Toluene, AcOH, H₂O, 15% mol,
82% yield, 4:1 dr, 96% ee

Tsogoeva et al., *Chem. Commun.*, **2006**, 1451

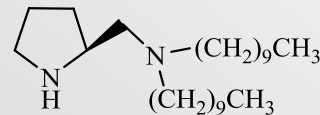


0% yield



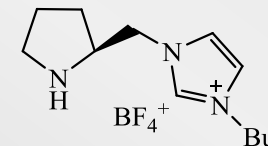
*i*PrOH:EtOH, 10% mol
64% yield, >19:1 dr, 90% ee

Kokotos et al, *Tetrahedron*, **2009**, 65, 1444



THF, 20% mol
92% yield, 98:2 dr, 90% ee

Barbas et al, *Synthesis*, **2004**, 1509



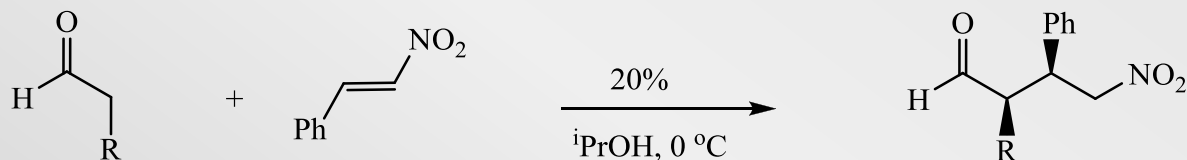
neat, 15% mol
100% yield, 99:1 dr, 99% ee

Luo et al, *Angew. Chem. Int. Ed.*, **2006**, 45, 3093

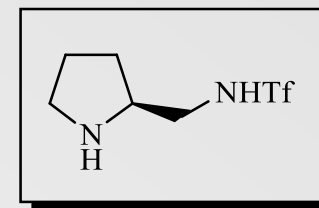
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΜΗΧΑΝΙΣΜΟΥ ΕΝΑΜΙΝΗΣ

Αντιδράσεις Michael

■ Αλδεύδες και νιτροστυρένια

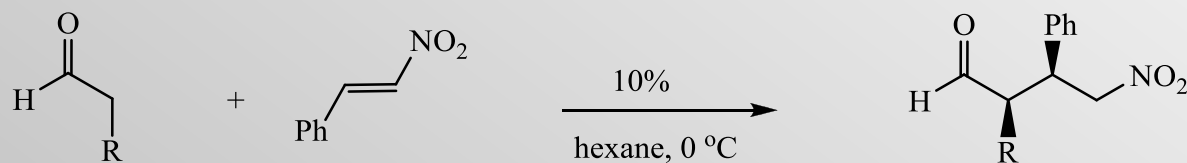


99% yield, 99:1 dr, 96% ee

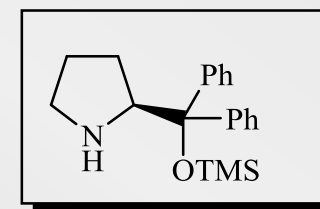


Wang et al, *Angew. Chem. Int. Ed.*, **2005**, *44*, 1369

■ Αλδεύδες και νιτροστυρένια



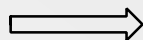
52-85% yield, 84:16 to 96:4 dr, 99% ee



Hayashi et al, *Angew. Chem. Int. Ed.*, **2005**, *44*, 4212

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

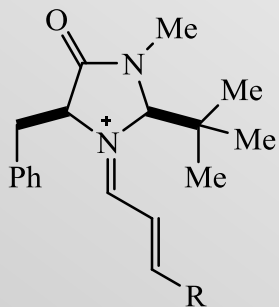
Organocatalysis



The rapid growth of organocatalysis over the last 10 years was fueled by the development of a small number of generic activation modes

Iminium catalysis

Im

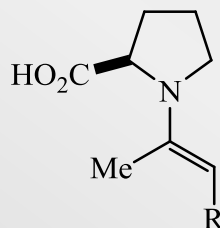


~ 50 new reactions

MacMillan, Jorgensen

Enamine catalysis

En

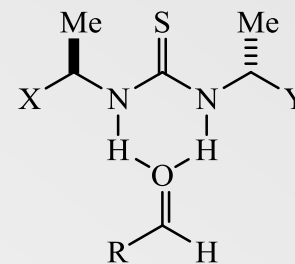


~ 20 new reactions

Hajos-Parrish, List-Barbas

H-bond catalysis

H⁺



~ 30 new reactions

Jacobsen

■ Last 10 years, organocatalysis has delivered many new asymmetric transformations

These 3 activation modes cover a large portion of the organocatalysis landscape

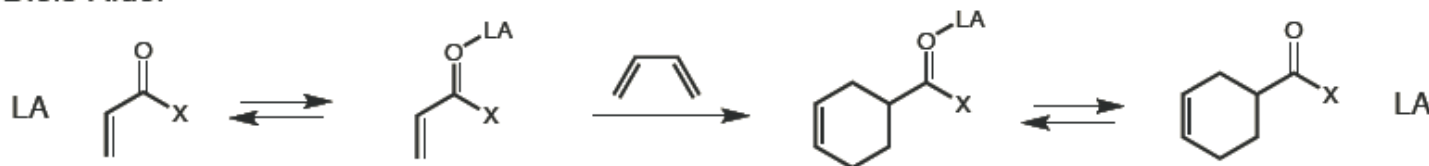
ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

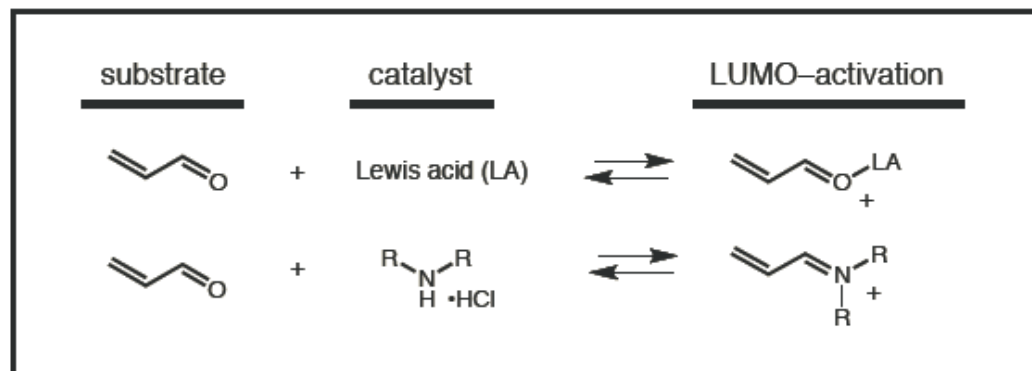
Design of General Organocatalytic Strategy: LUMO-Lowering

- Lewis acid catalysis typically involves activation of a substrate to π -facial addition by lowering the LUMO component of one reactant with respect to the HOMO of the reacting partner

- Diels-Alder



- This activation–catalyst turnover mechanism should hold for any carbogenic system that exists as an equilibrium between an electron–deficient and a relatively electron–rich state



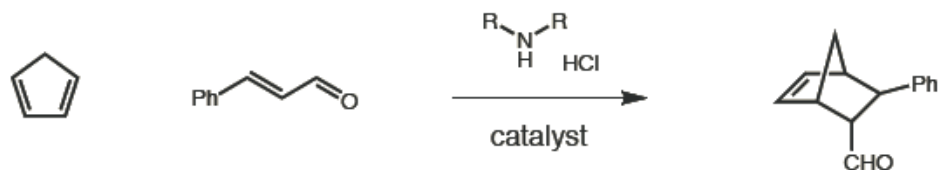
- Can amines function as catalysts for transformations that traditionally employ Lewis acids?

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

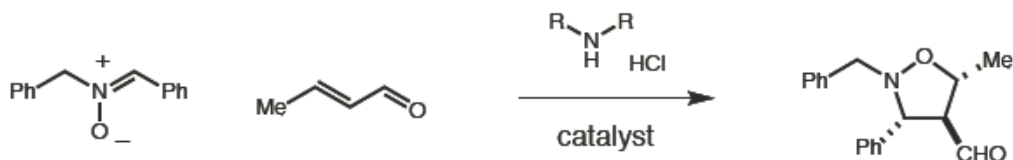
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Design of General Organocatalytic Activation Strategy: Iminium Catalysis

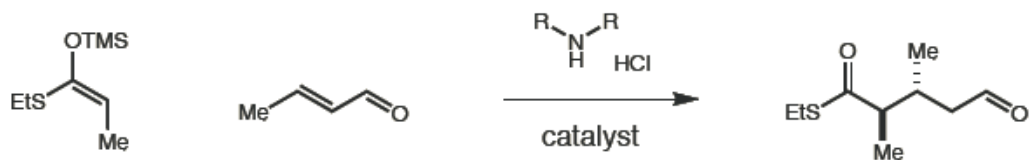
■ Amine Catalyzed Diels-Alder



■ Amine Catalyzed [3 + 2] Cycloadditions



■ Amine Catalyzed Mukaiyama Michael

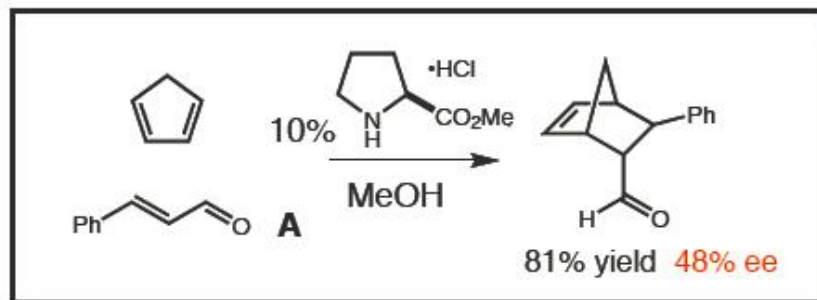
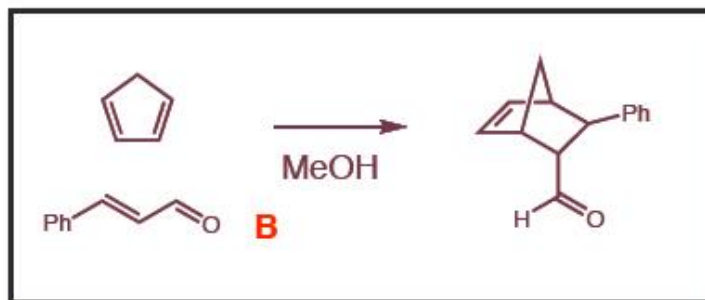
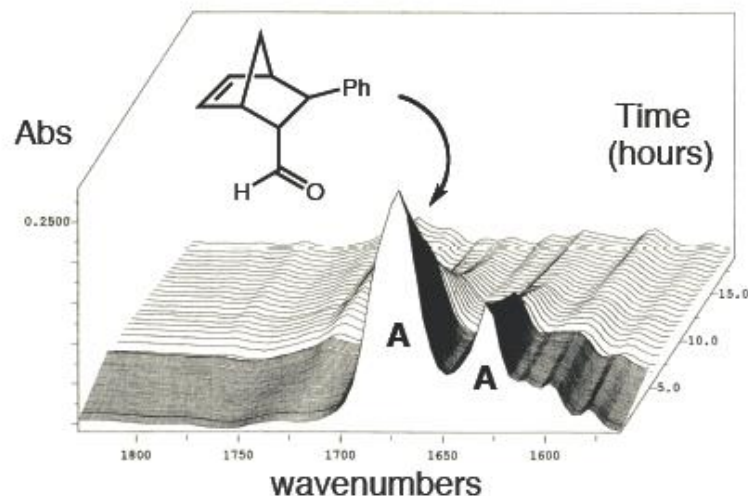
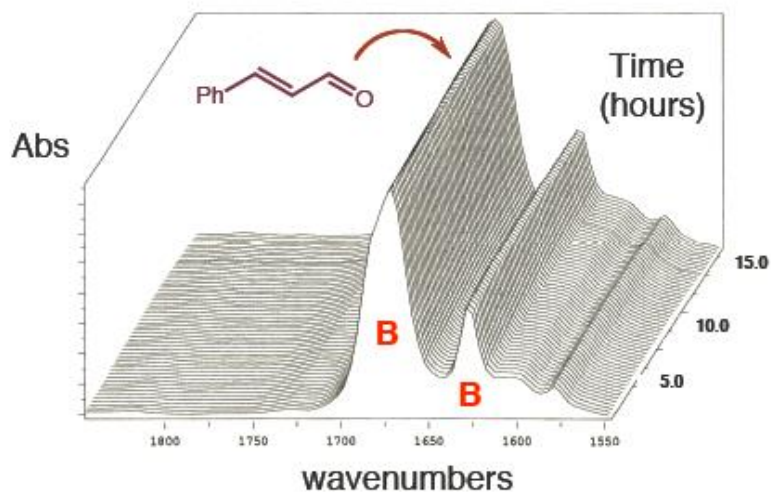


■ Many other transforms should be possible: Conjugate Additions, Epoxidations, Cyclopropanations

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Organocatalyzed Diels–Alder Reaction: ReactIR Studies



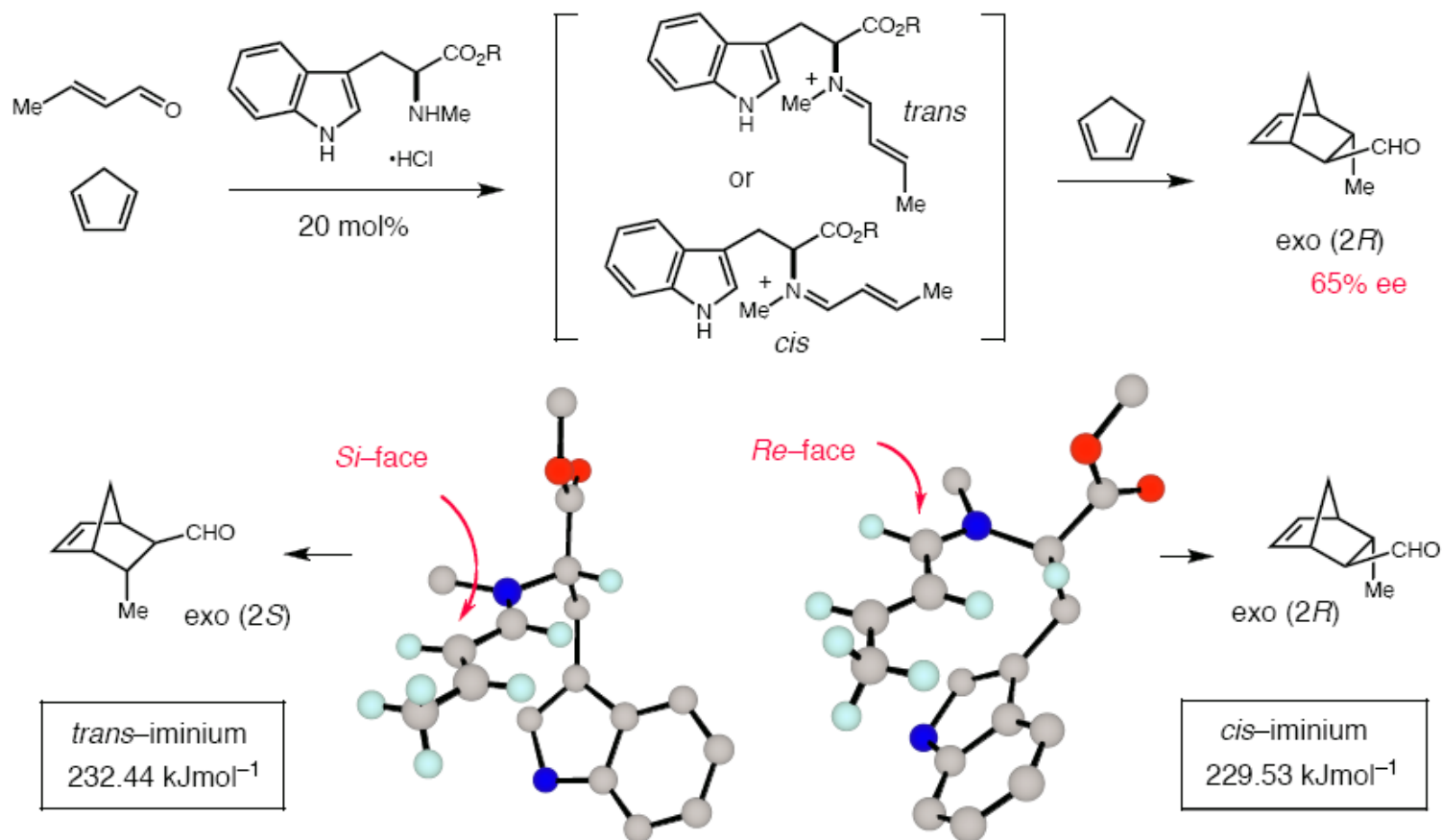
■ Amine Catalyzed Diels–Alder Reaction is facile at room temperature

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

MM3 Calculations Predict the Correct Sense of Enantioinduction

■ Two possible iminium ion intermediates



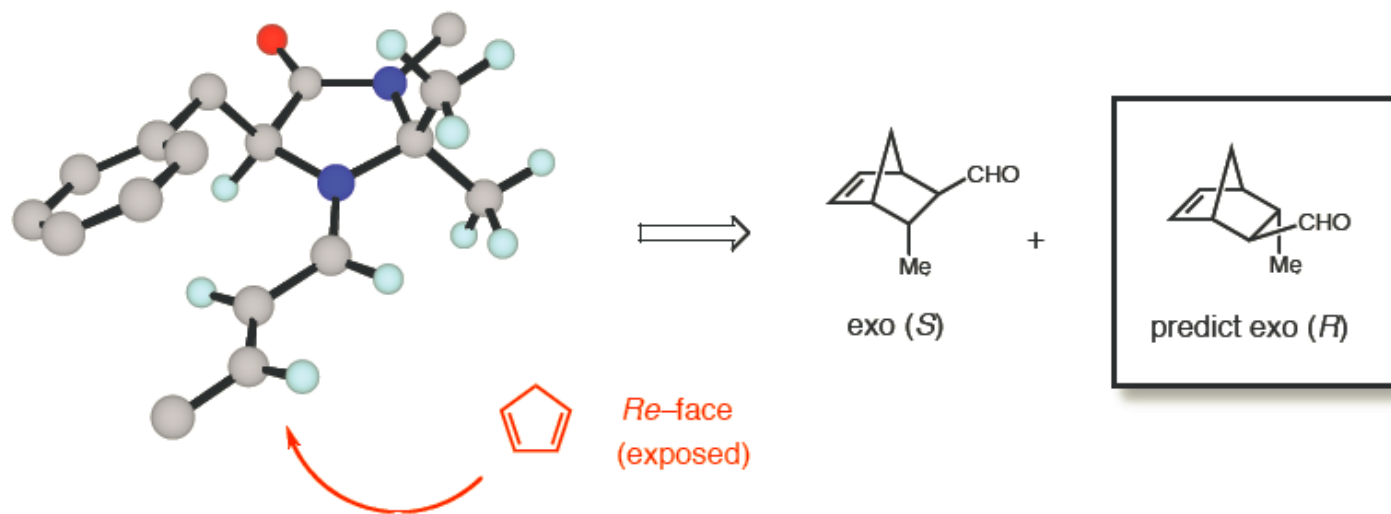
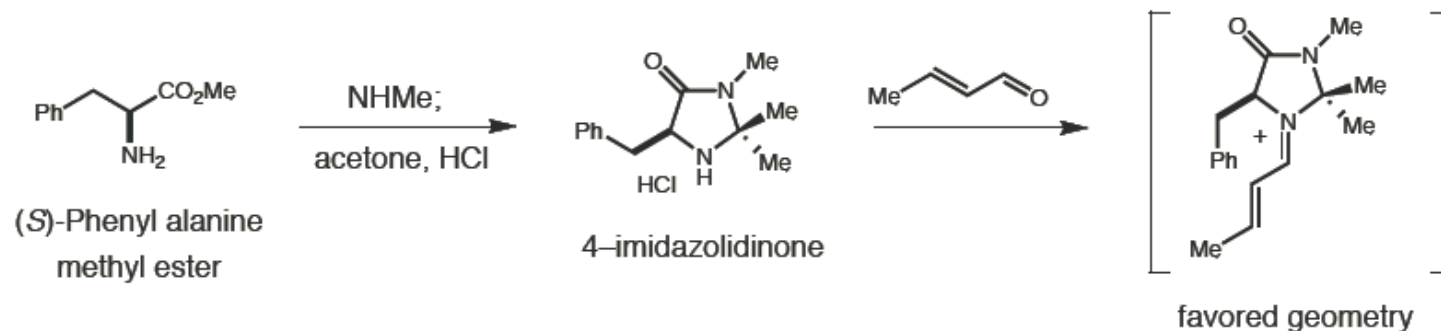
Is the reaction enantioselectivity compromised by participation of both *cis* and *trans* iminium ions

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Imidazolidinone Catalyst should also provide Iminium Ion Geometry Control

■ Readily available from chiral pool



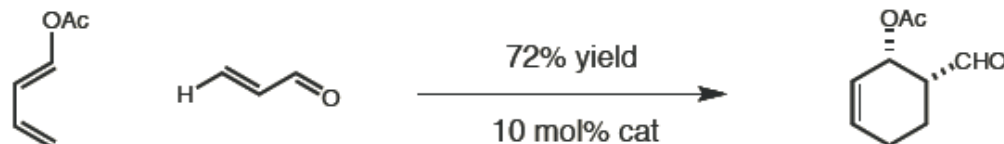
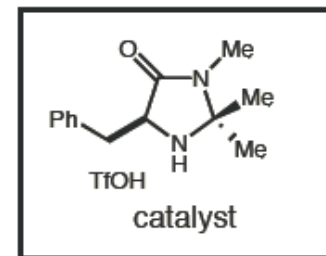
Calculations suggest strong bias for addition to exposed *Re*-face \rightleftharpoons Highly Organized TS

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

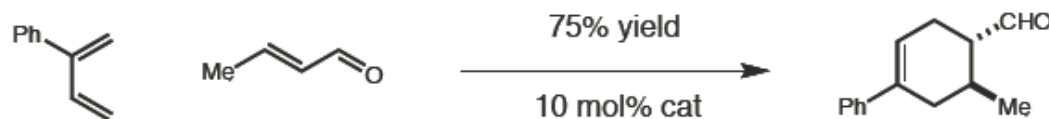
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Imidazolidinone Catalyst provides High Levels of Enantiocontrol

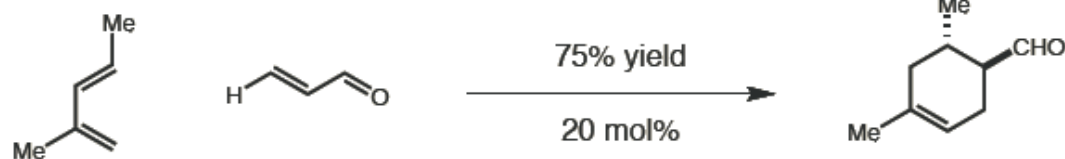
First highly enantioselective organocatalytic Diels–Alder reaction



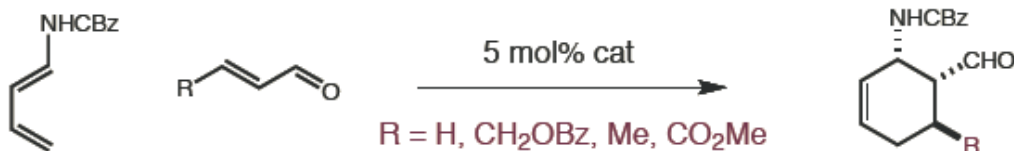
endo:exo 11:1
endo (*S*) 85% ee



90% ee



endo:exo 5:1
endo (*S*) 90% ee



endo:exo 90:10 to 96:4
endo (*S*) 93–99% ee

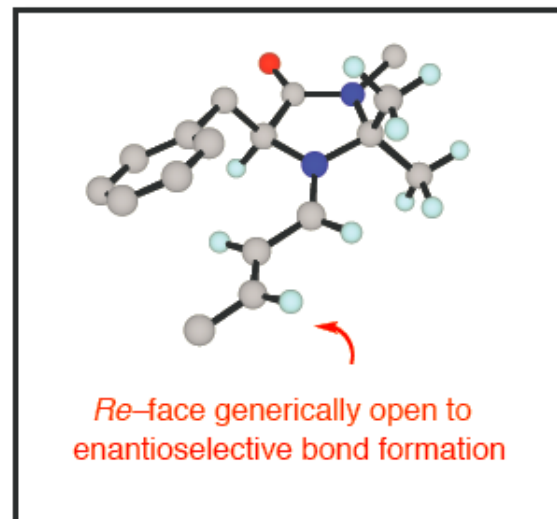
93% yield

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

A generic mode of activation and induction?

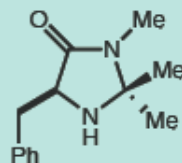
- A generic activation mode describes a reactive species that can participate in many different reaction types with generically high levels of enantioselectivity
- Would the combination of iminium catalysis and imidazolidinone catalyst provide a new generic activation mode?



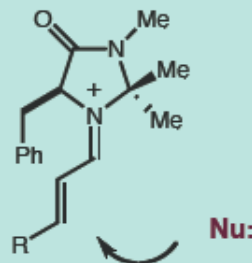
substrate



catalyst



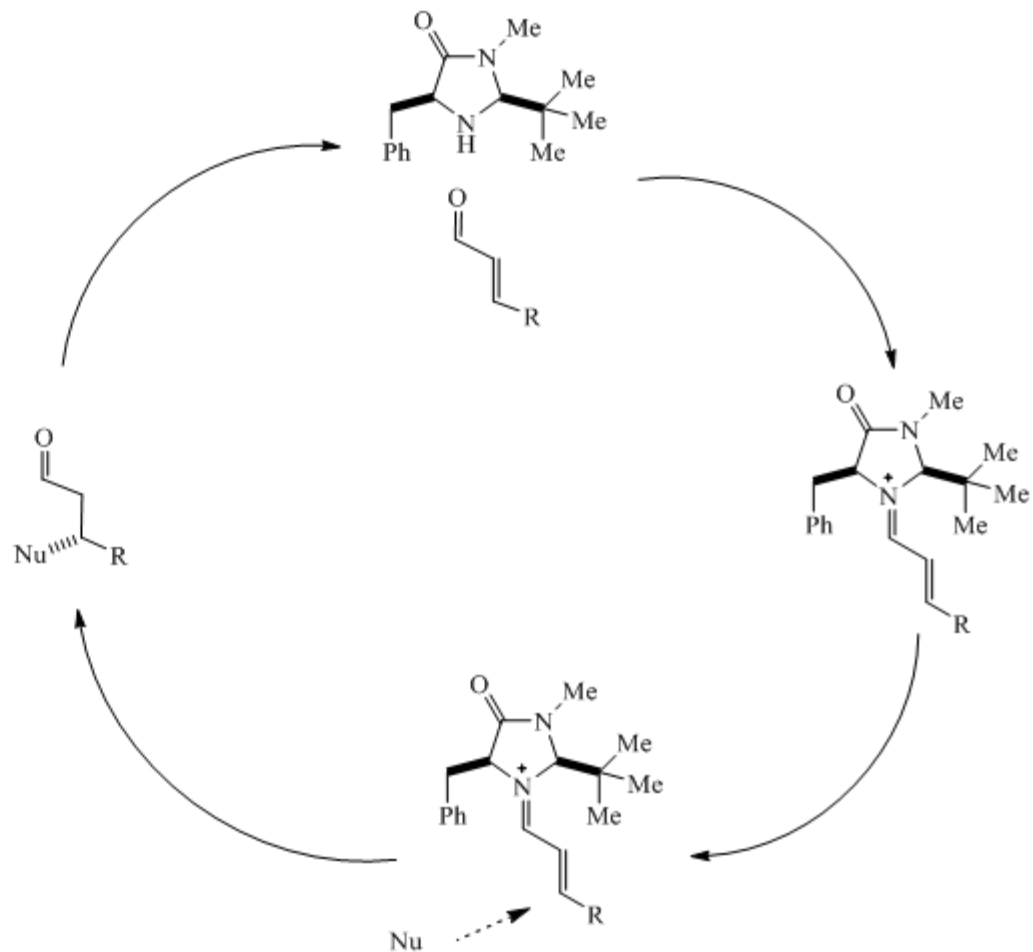
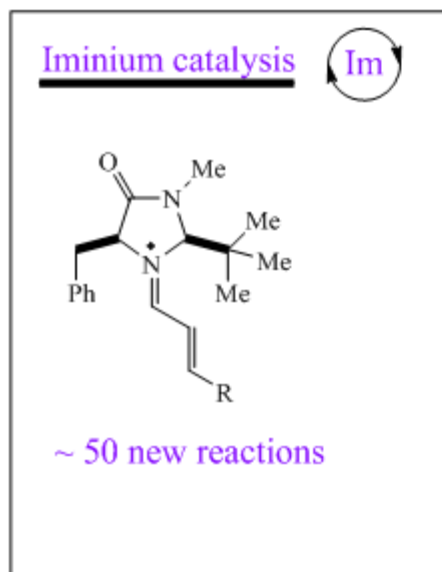
activation mode



Several enantioselective catalytic reactions?
(we hoped for 3)

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

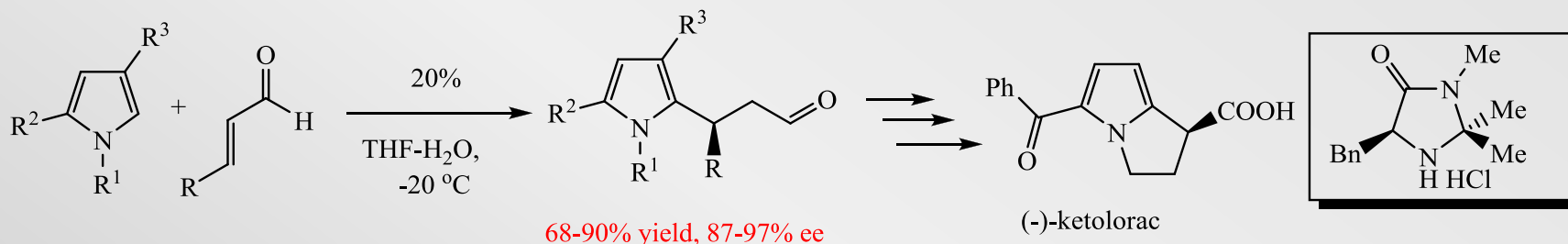
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ



ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

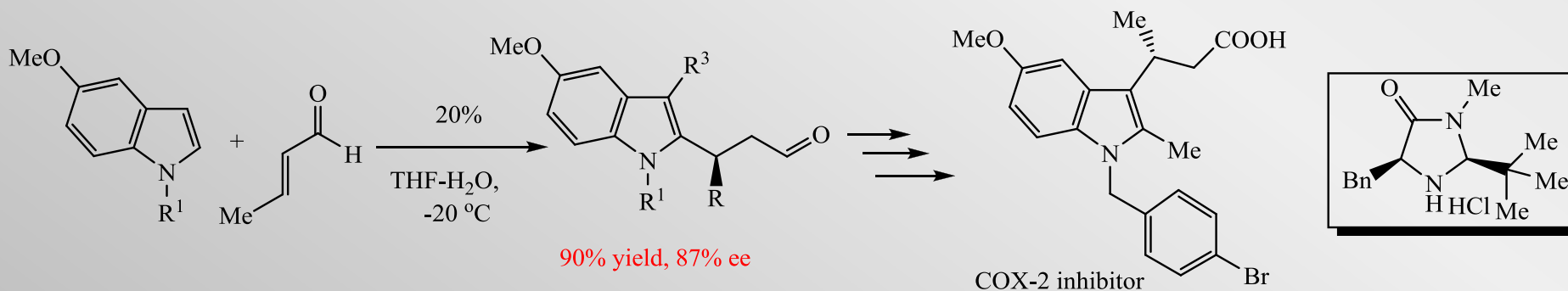
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

■ Οργανοκαταλυτική αντίδραση Friedel-Crafts με πυρρόλια



MacMillan et al, *J. Am. Chem. Soc.*, **2001**, *123*, 4370
Ishihara et al, *Adv. Synth. Catal.*, **2002**, *344*, 728

■ Οργανοκαταλυτική αντίδραση Friedel-Crafts με ινδόλια

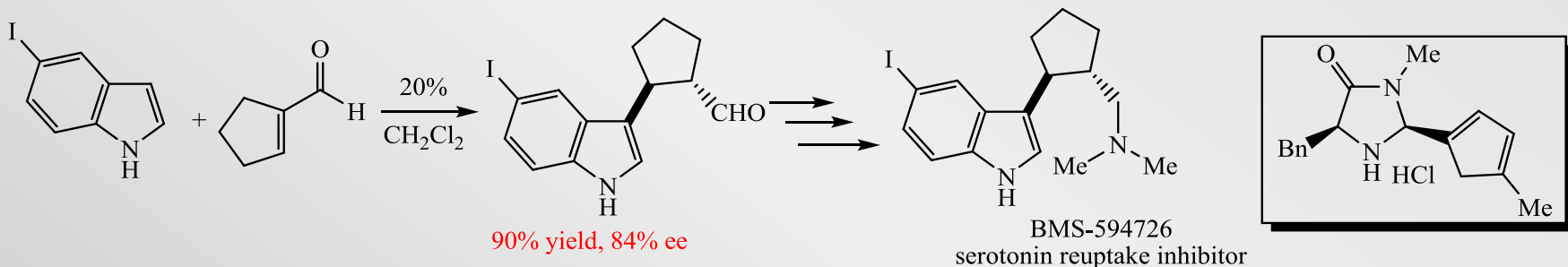


MacMillan et al, *J. Am. Chem. Soc.*, **2002**, *124*, 1172

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

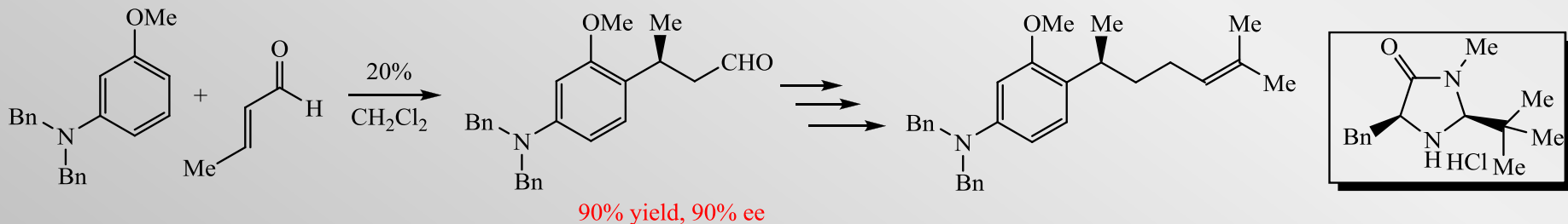
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

■ Οργανοκαταλυτική αντίδραση Friedel-Crafts με ινδόλια



King et al, Org. Lett., **2005**, 7, 3437

■ Οργανοκαταλυτική αντίδραση Friedel-Crafts με ηλεκτρονικά πλούσια αρένια



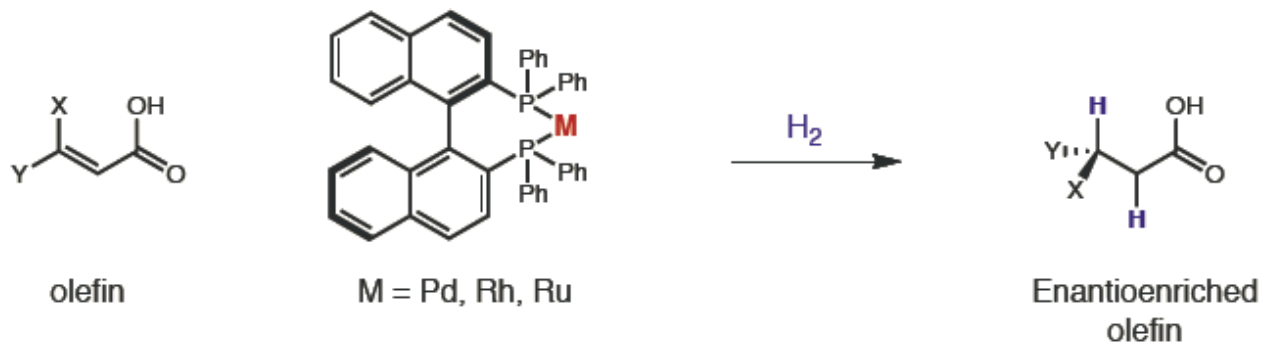
Kim et al, Tetrahedron Lett., **2005**, 46, 2437

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

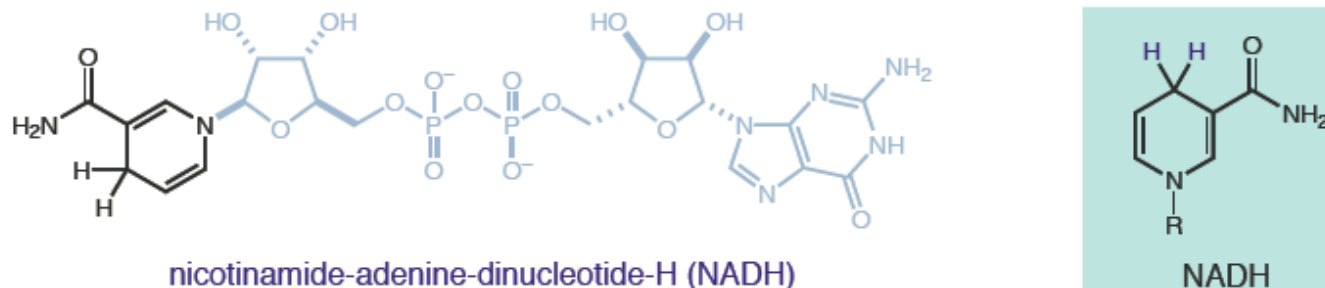
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Traditional Methods for Asymmetric Hydrogenation

■ Organometallic hydrogenation (Noyori)



■ Organic systems: Enzymatic reduction (hydrogenation) is mediated by NADH



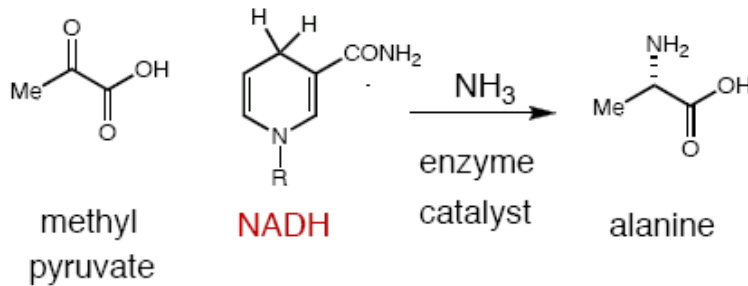
Can a coenzyme analog be utilized in the reduction of carbon-carbon bonds

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

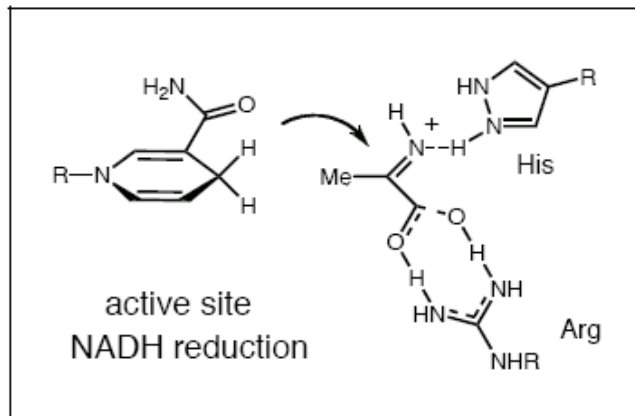
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Organic Catalyzed Reductions in Biological Systems

■ NADH: Nature's Reduction (Hydrogenation) Reagent (Coenzyme)



alanine transferase



Selective reduction of pyruvate imines to create amino acids

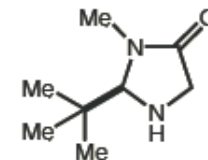
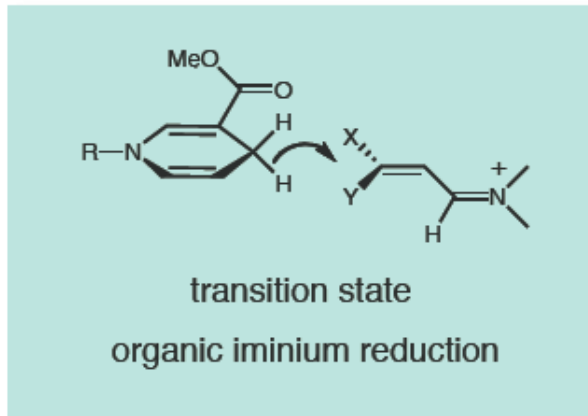
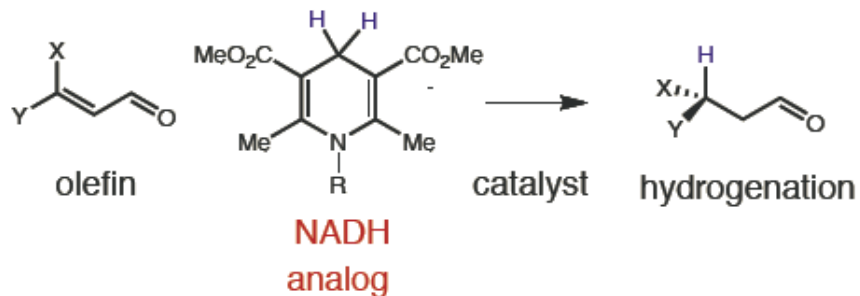
Could this organocatalytic sequence be utilized in the reduction of carbon-carbon double bonds

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Organic Catalyzed Reductions in Chemical Synthesis

■ Hansch Esters: NADH analogs for organocatalytic hydride reductions



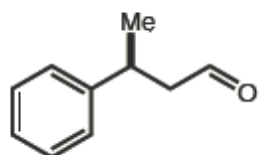
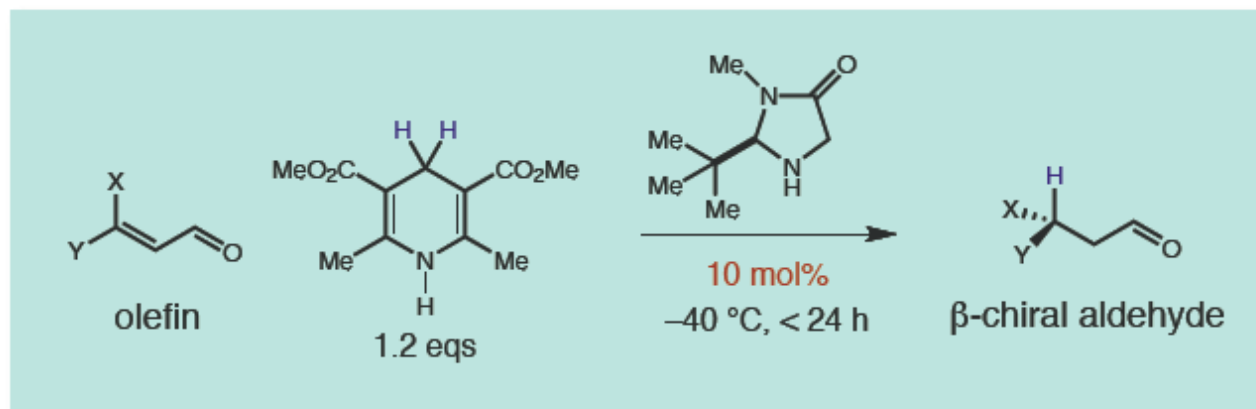
Can the Hansch ester be used to enantioselectively deliver hydride

Could this organocatalytic sequence be utilized in the reduction of carbon-carbon double bonds

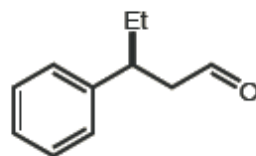
ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

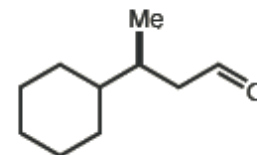
The Direct and Enantioselective Reduction of α,β -Unsaturated Aldehydes



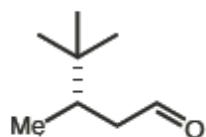
93% ee
91% yield



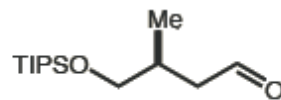
94% ee
74% yield



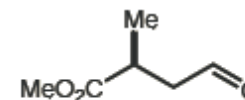
96% ee
91% yield



97% ee
95% yield



90% ee
74% yield



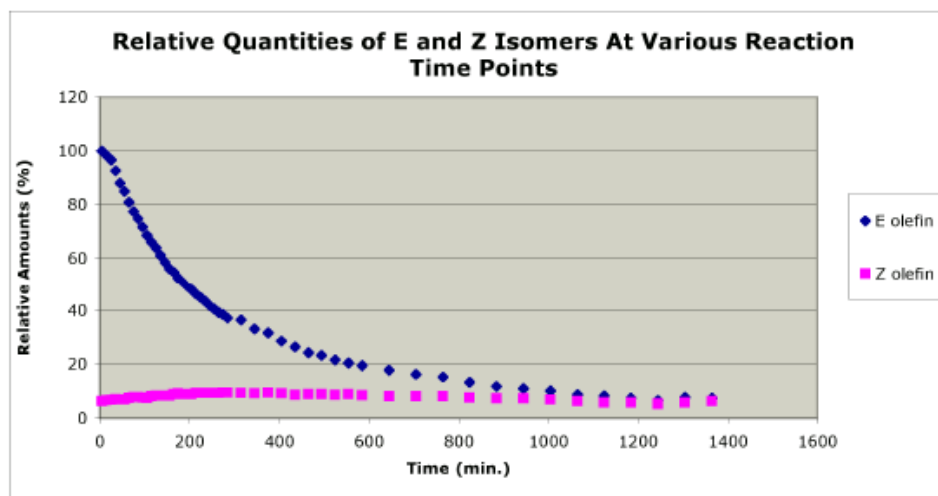
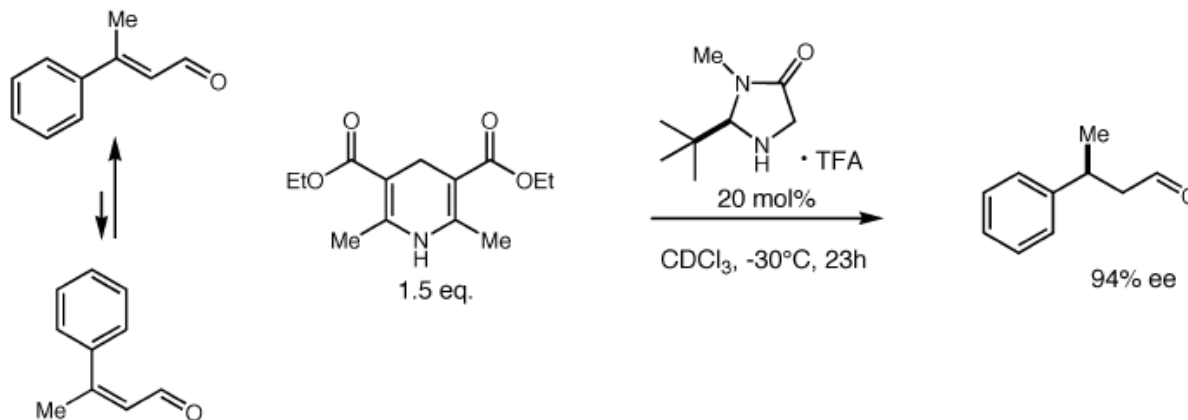
91% ee
83% yield

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Isomerization Kinetics Monitored by VT-NMR

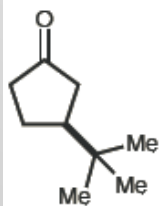
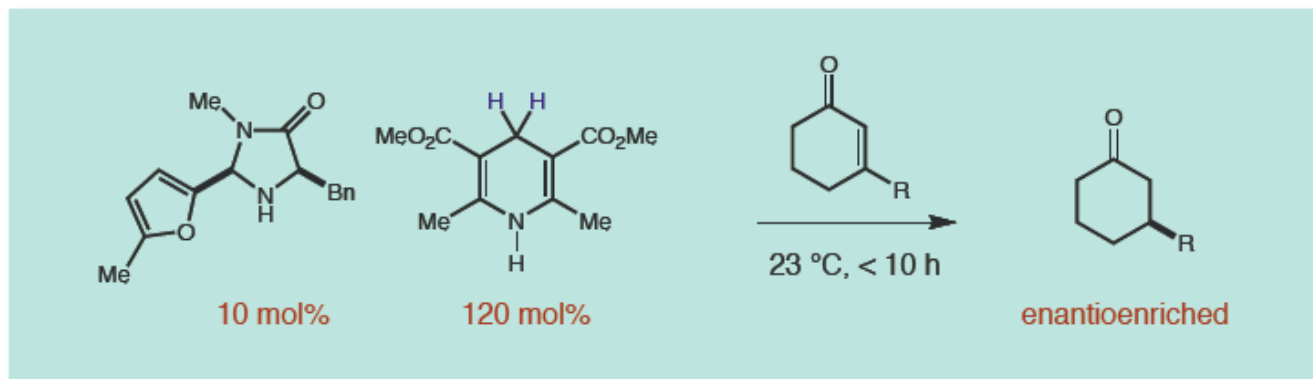
■ Interconversion of E olefin to Z olefin occurs, but high enantioselectivity is observed



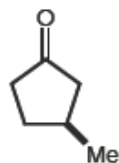
ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

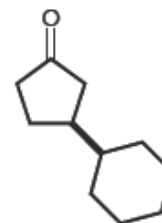
The Direct and Enantioselective Reduction of α,β -Unsaturated Enones



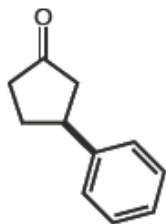
96% ee
81% yield



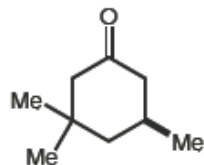
95% ee
72% yield



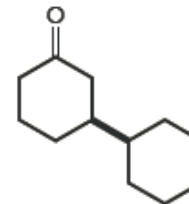
96% ee
85% yield



91% ee
73% yield



98% ee
66% yield



88% ee
71% yield

also possible with larger rings

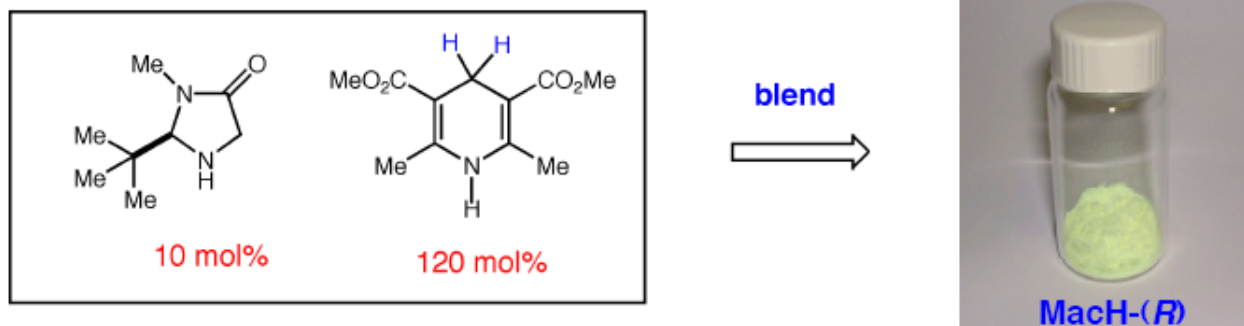
ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

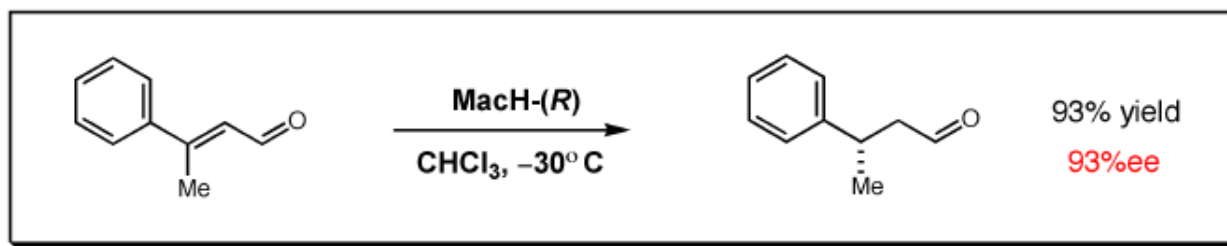
Enantioselective Hydrogenation in a Bottle: Numerous Applications

Direct Enantioselective Organocatalytic Transfer Hydrogenation of Enals, Enones

■ Mixture for Asymmetric Catalytic Hydrogenation: Mach-(R)



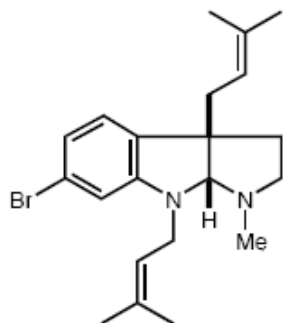
■ Asymmetric transfer hydrogenation using Mach (after 9 months shelf time)



ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

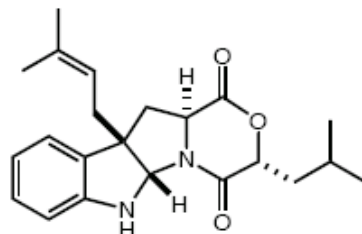
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Organocatalytic Synthesis of Pyrroloindoline Natural Products



Flustramine B

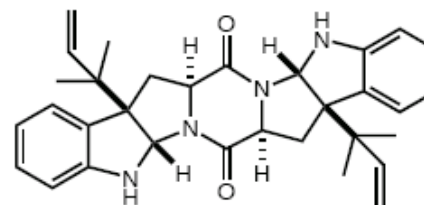
J. Org. Chem **1980**, 49, 1586



Fructigenine C

isolation

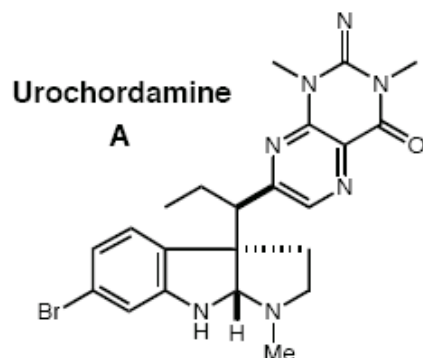
J. Nat Prod **1998**, 61, 804



Amouromine

Takase *Tetrahedron Lett.* **1985**, 847

Danishefsky *JACS* **1999**, 121, 11954

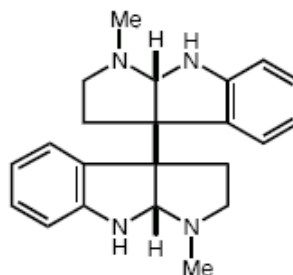


Urochordamine

A

isolation

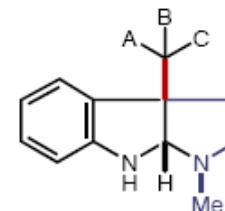
Tetrahedron Lett. **1993**, 4819



(-)-Chimonanthine

Overman

JACS **1999**, 121, 7702



- (1) Quaternary stereocenter(s)
- (2) Vicinal stereocenter control
- (3) Pyrroloindoline ring system
- (4) Enantioselective Catalysis

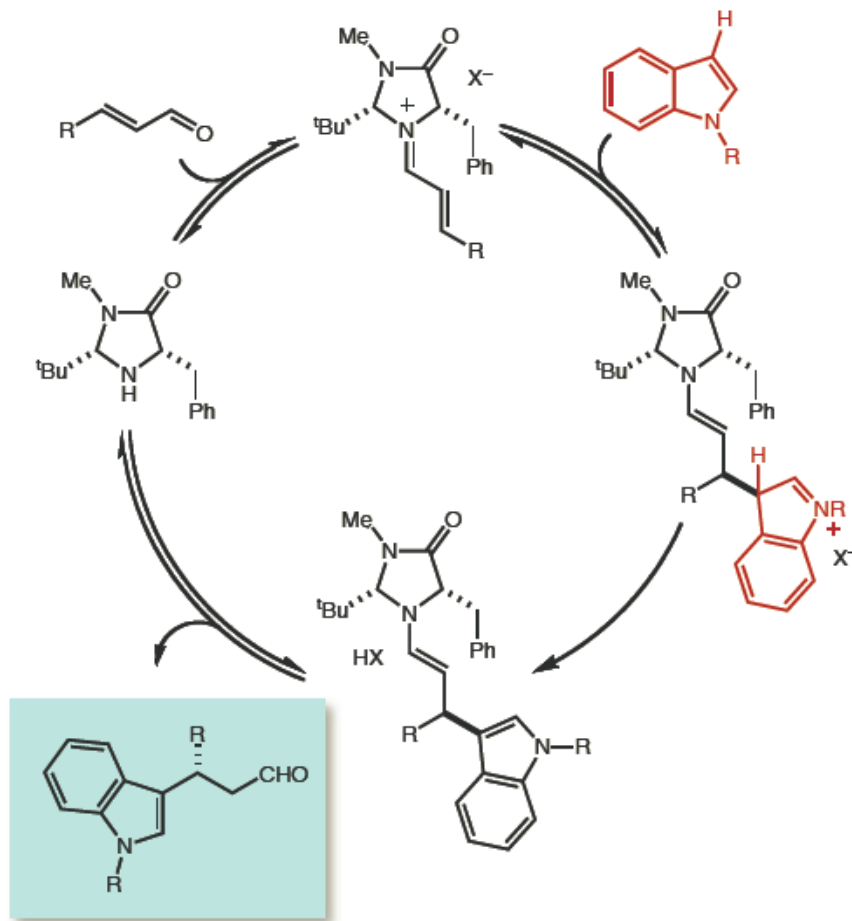
■ Can we perform enantioselective catalytic construction of pyrroloindoline core in one step?

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Organocatalyzed Pyrroloindoline Construction: Catalytic Cycle

■ Organocatalytic Indole Alkylation



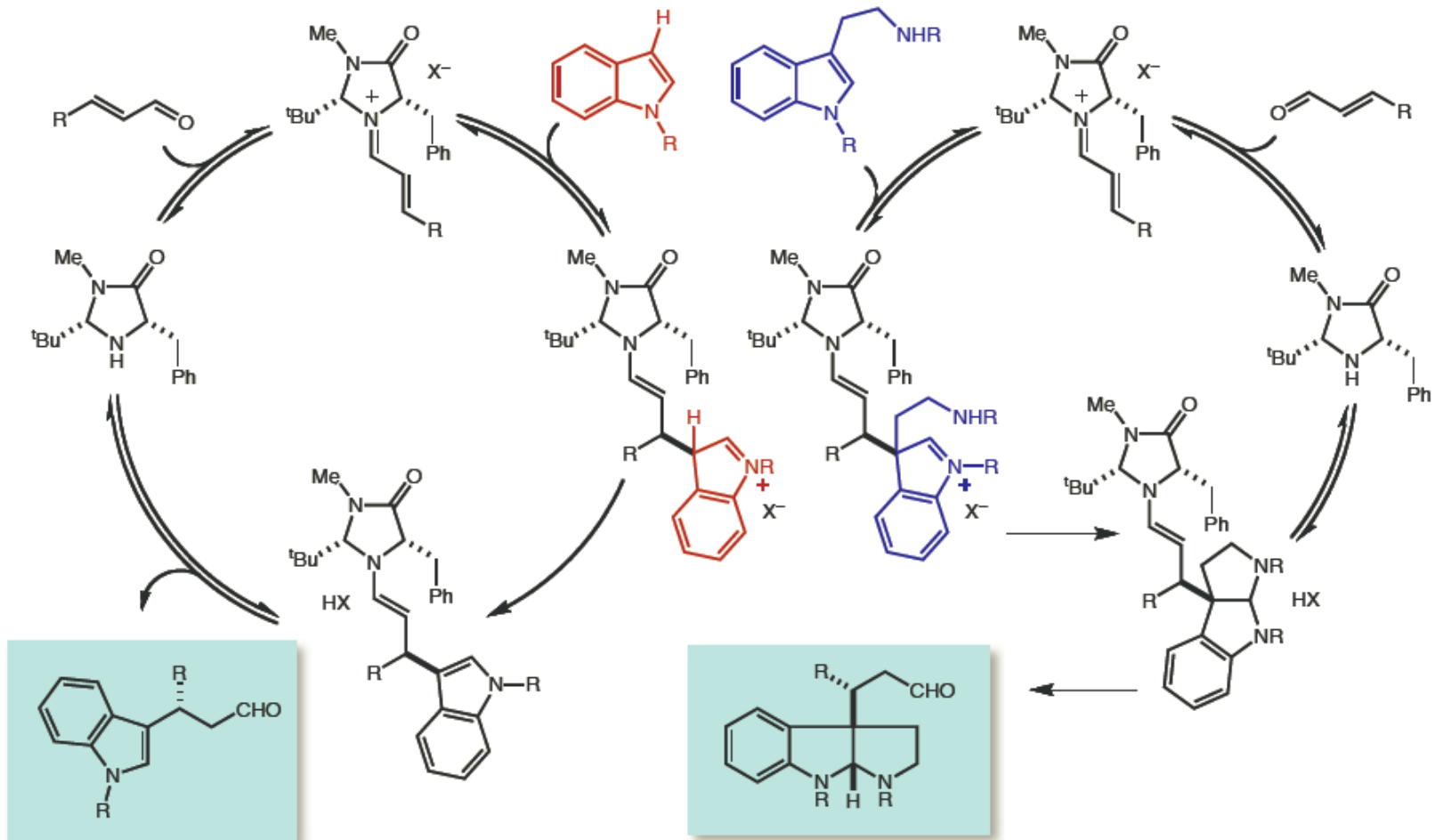
ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Organocatalyzed Pyrroloindoline Construction: Catalytic Cycle

■ Organocatalytic Indole Alkylation

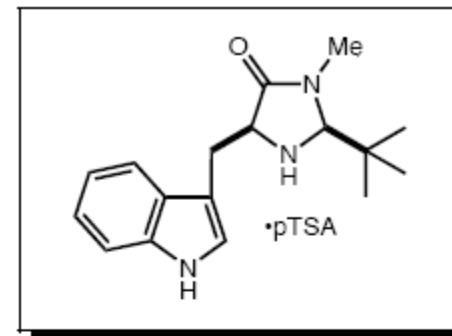
■ Organocatalytic Pyrroloindoline Construction



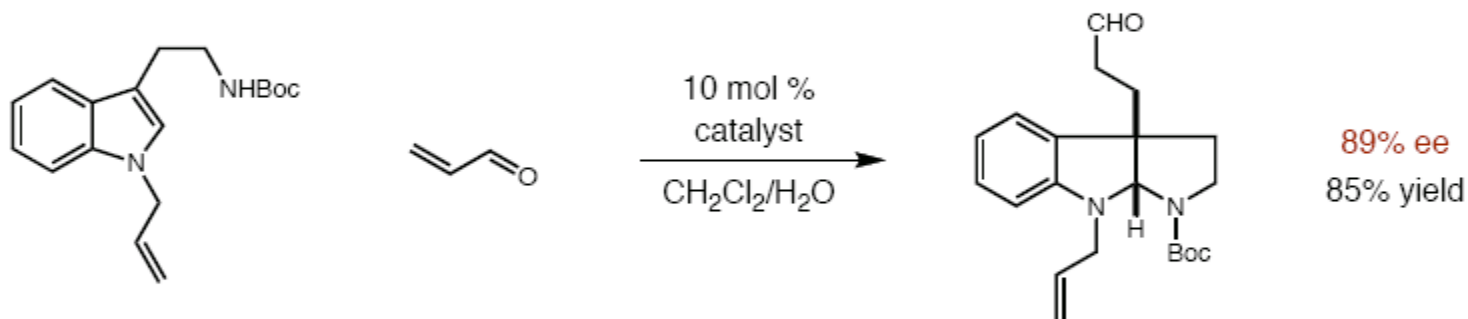
ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

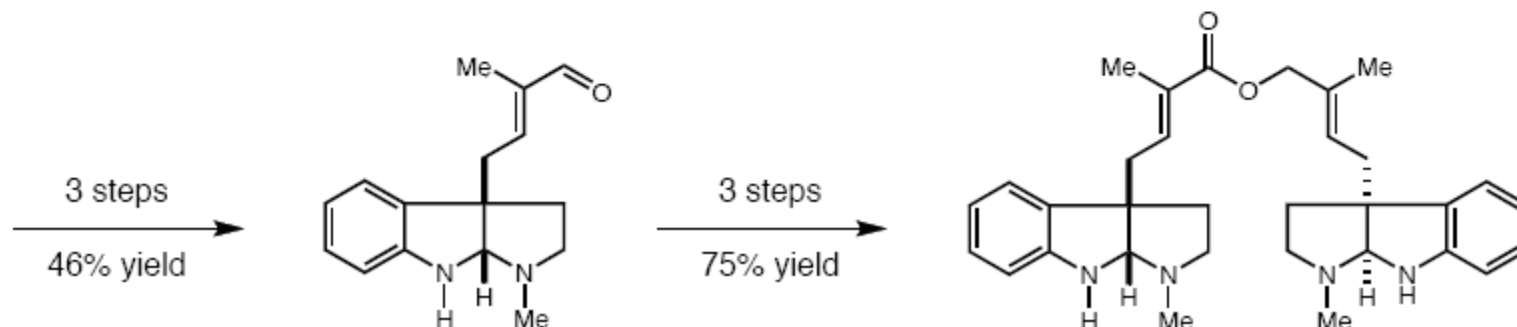
Organocatalytic pyrroloindoline strategy is amenable to the synthesis of biomedically relevant molecules



■ Enantioselective construction of pyrroloindoline core



■ Enantioselective construction of (+)-pseudophyrnamine

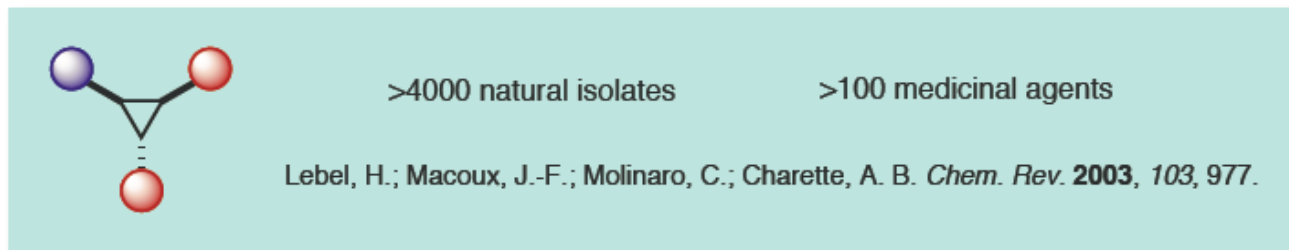


ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

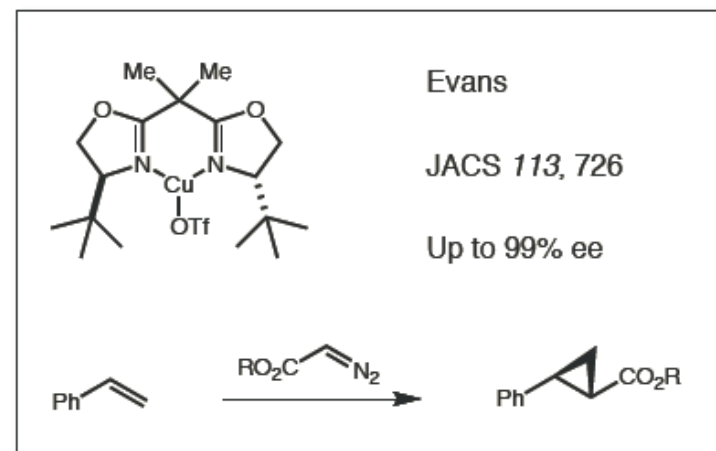
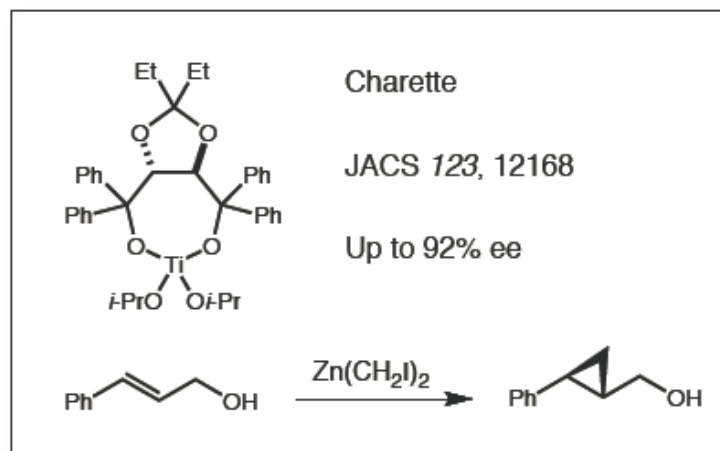
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Cyclopropanation with Ammonium and Sulfonium Ylides

- Enantioenriched cyclopropane motif widespread in nature and medicine



- A variety of metal-carbenoid methodologies exist



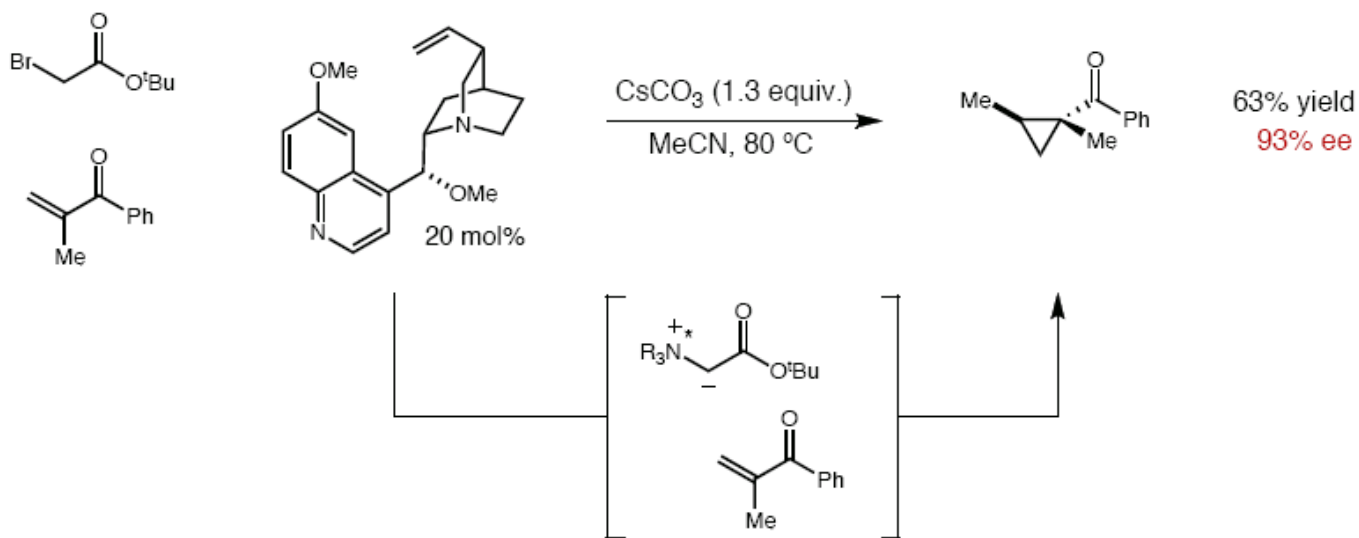
Many other important contributions (Kobayashi, Denmark, Davies, Nishiyama)

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

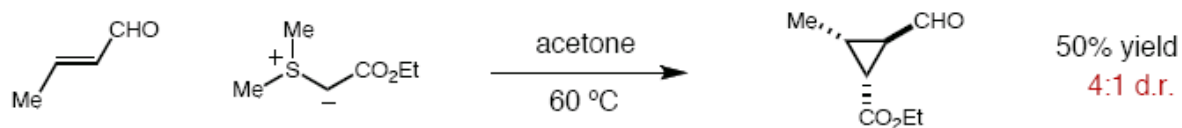
Cyclopropanation with Ammonium and Sulfonium Ylides

■ Gaunt's ammonium ylide organocatalytic cyclopropanation example



Papageorgiu, C. D.; Cubillo de Dios, M. A.; Ley, S. V.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2003**, *43*, 4641

■ Stabilized sulfonium ylides are compatible with aldehydes



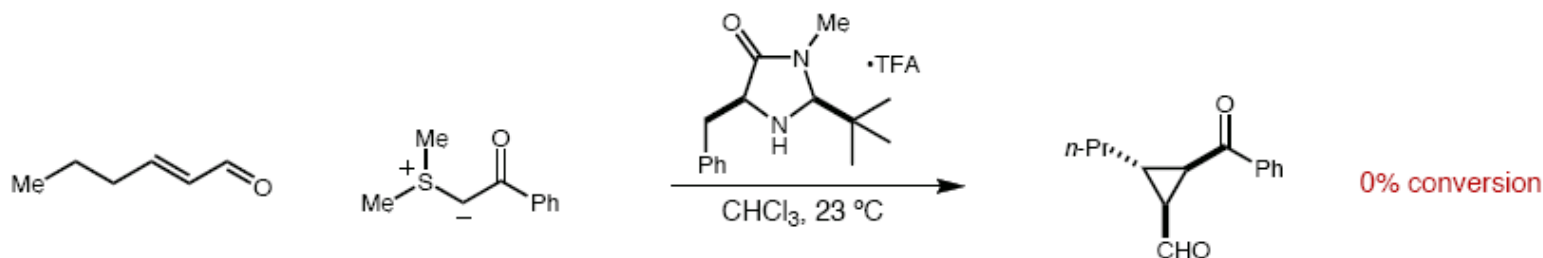
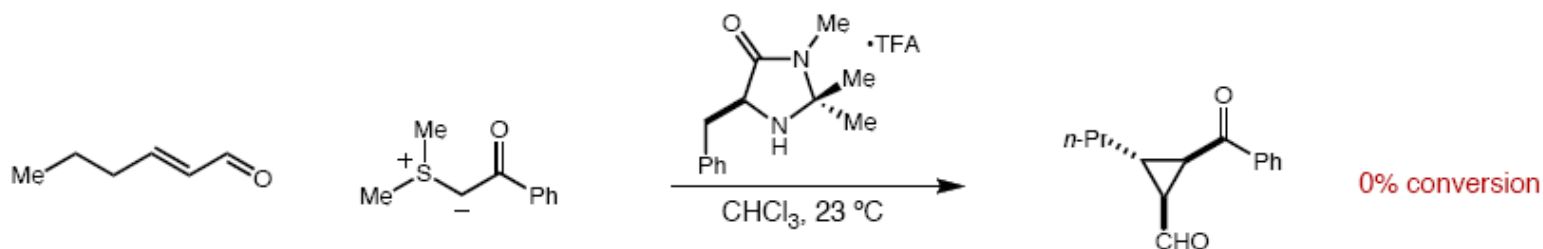
Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

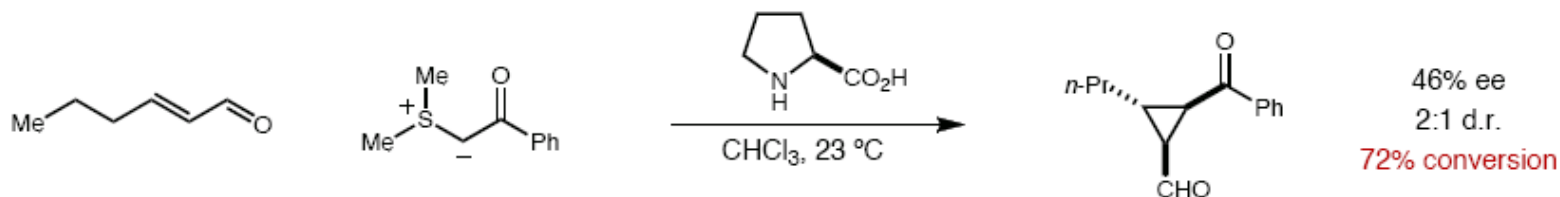
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Enantioselective Organocatalytic Cyclopropanation

- Surprisingly, imidazolidinone amine were ineffective



- An initial success using proline as a catalyst

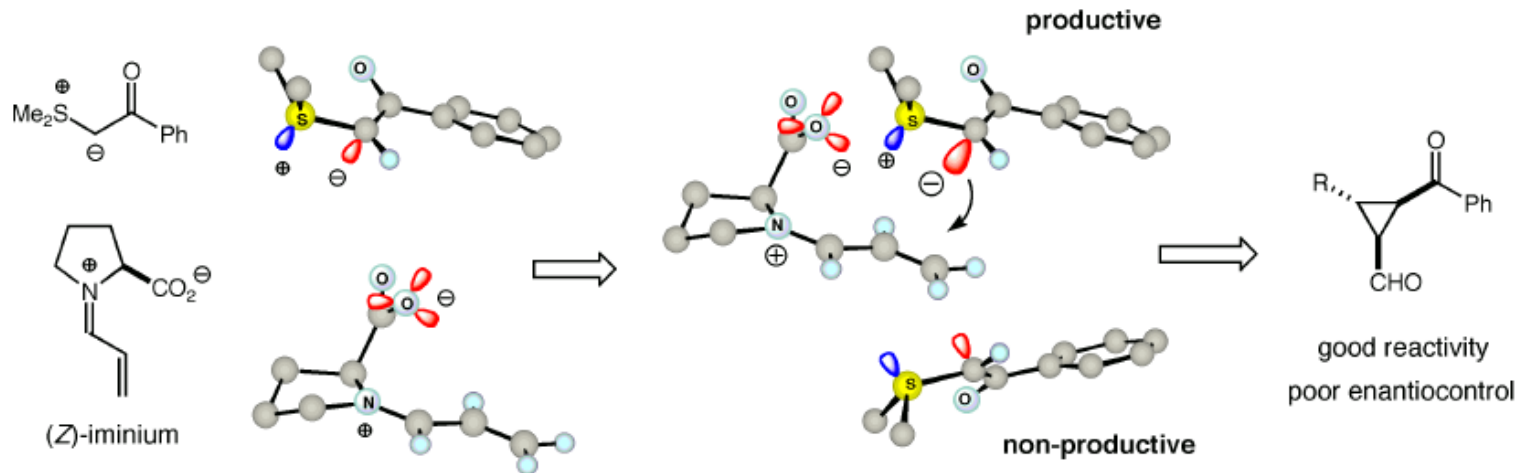


ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

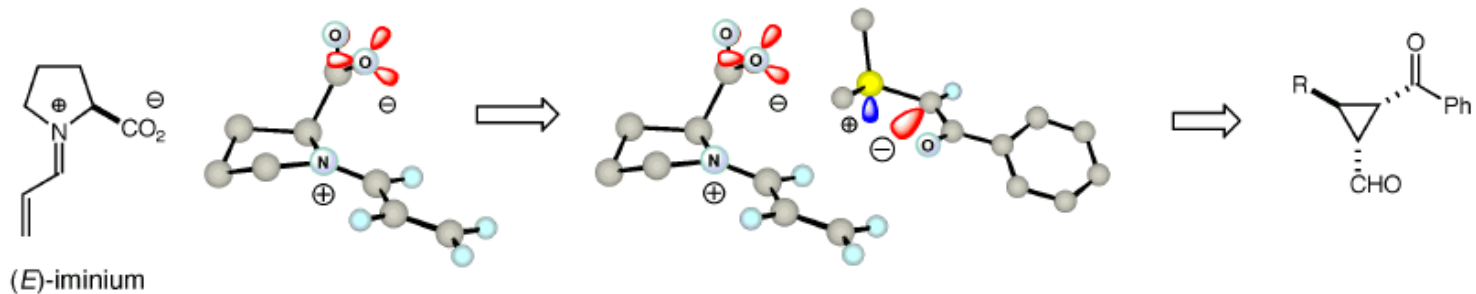
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Mechanistic Postulate for Catalytic Activation and Observed Enantioselectivity

■ Electrostatic directed enantioinduction and activation



■ Poor iminium geometry control leads to poor enantiocontrol



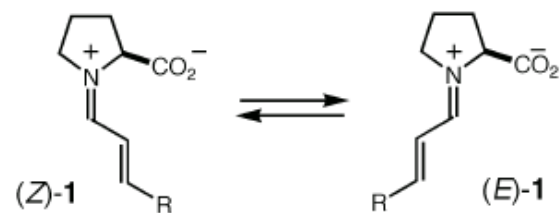
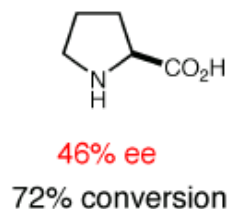
Can we retain electrostatic activation yet control iminium ion geometry?

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

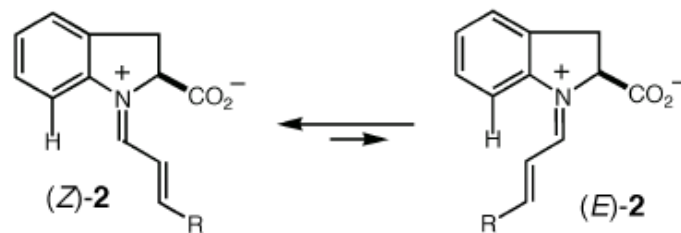
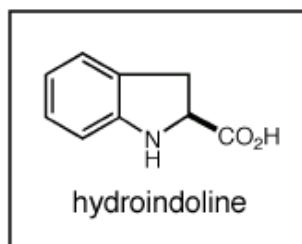
Modulation of Catalyst Architecture to Control Iminium Geometry

- Proline is an efficient but poorly selective catalyst



poor geometry control \rightarrow poor selectivity

- Introducing allylic strain to control iminium geometry



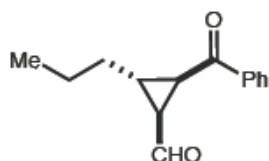
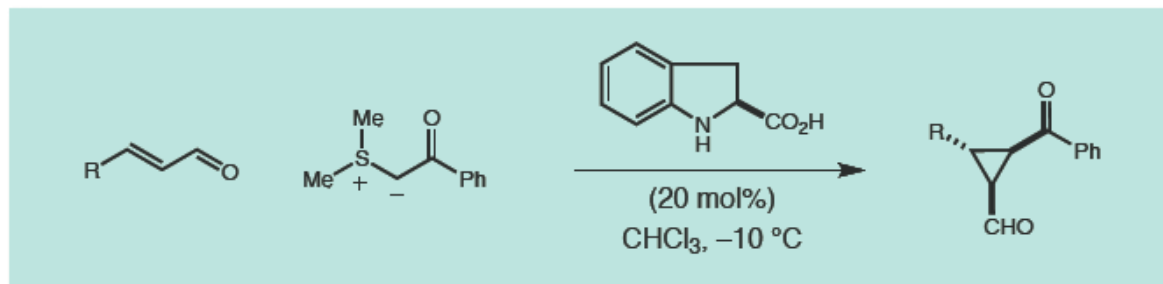
high geometry control \rightarrow high selectivity

- Can we use catalyst architecture to dictate an *E*-iminium ion geometry

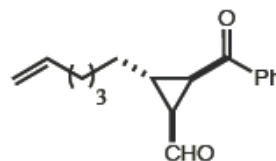
ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

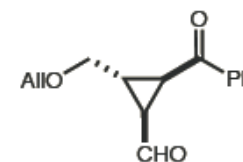
Enantioselective Organocatalytic Cyclopropanations



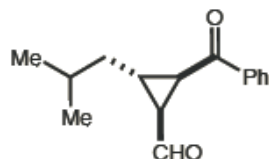
95% ee
30:1 d.r.
85% yield



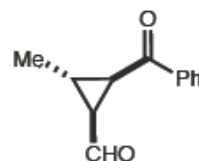
96% ee
24:1 d.r.
74% yield



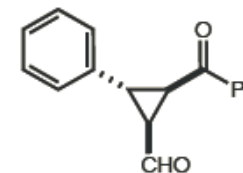
91% ee
21:1 d.r.
77% yield



96% ee
43:1 d.r.
63% yield



90% ee
>19:1 d.r.
67% yield



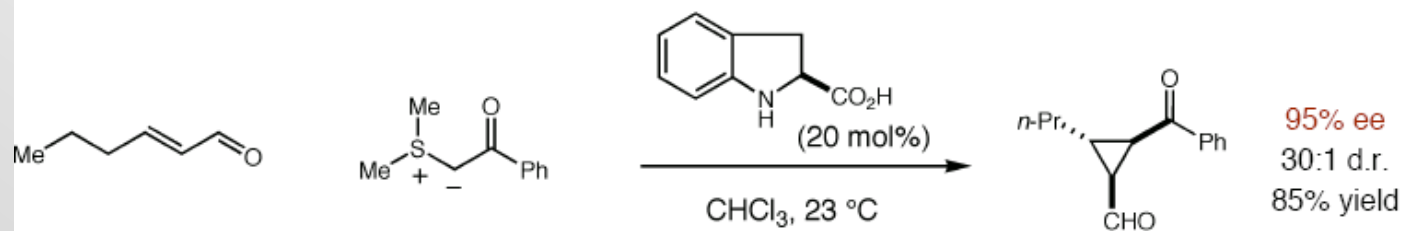
89% ee
33:1 d.r.
73% yield

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

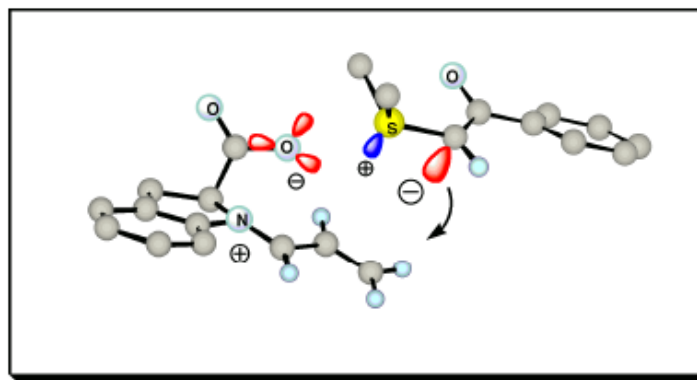
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Testing the Mechanistic Postulate for Cyclopropanation

- A highly selective organocatalytic cyclopropanation method has been developed



However is the Reactive Intermediate Truly An Activated Iminium Ion?



- Test premise of iminium ion activation

- Test the premise of electrostatic activation

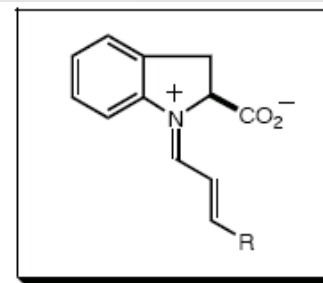
ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

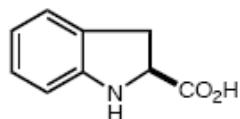
Studies To Investigate the Mechanistic Postulate

Determining the essential features for catalytic activity

- Both a secondary aniline amine and carboxylic acid are essential

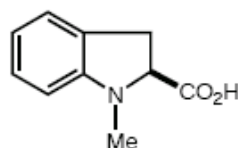


iminium ion & electrostatic activation



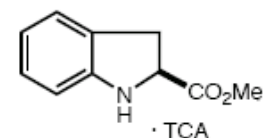
78% conversion

cannot form iminium ion



0% conversion

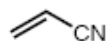
no electrostatic activation



0% conversion

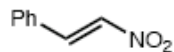
- Michael electrophiles are unsuccessful cyclopropanation substrates

cannot form iminium ion



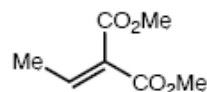
0% conversion

cannot form iminium ion



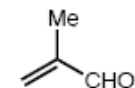
0% conversion

cannot form iminium ion



0% conversion

poor iminium substrate



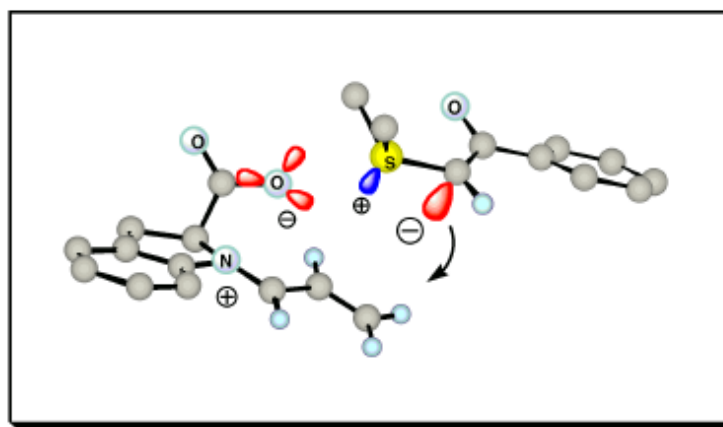
low %ee

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Studies To Investigate the Mechanistic Postulate

Probing the electrostatic association and activation



solvent	ϵ	% ee	% conv.
CHCl_3	4.7	95	85
THF	7.3	77	25
acetone	20.7	28	16
DMF	36.7	-30	20



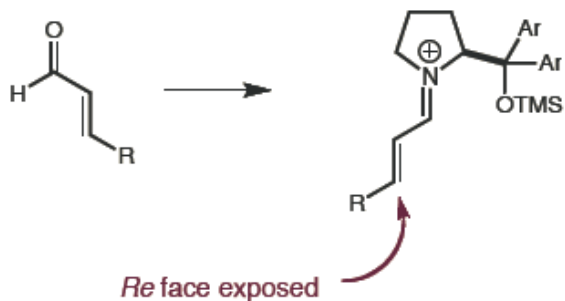
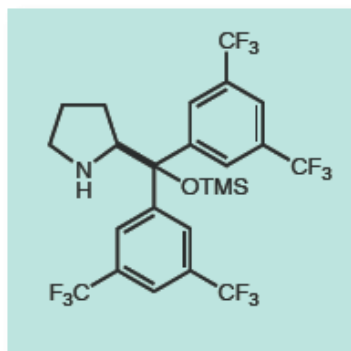
[M]	% ee
0.25	79
0.1	84
0.05	89
0.01	92
0.006	94

■ Solvent and concentration effects reinforce mechanistic model

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

The Jørgensen Diarylprolinoether Class Catalysts



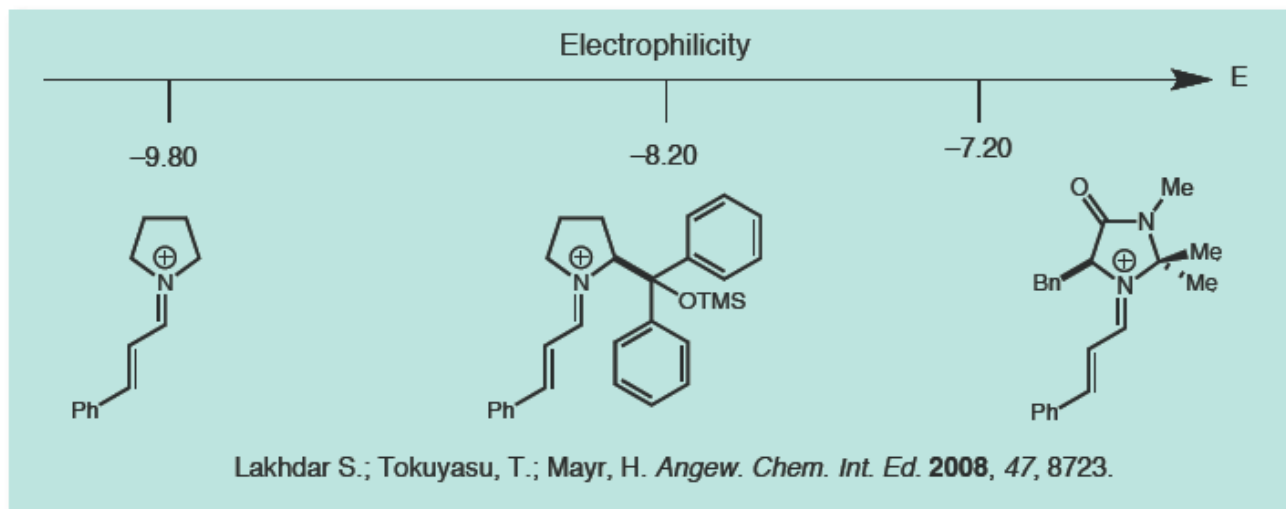
Large aryl and Si Group

■ control iminium geometry

■ shield the top face

■ In 2002 the Jørgensen group disclosed their very useful catalyst for enamine and iminium catalysis

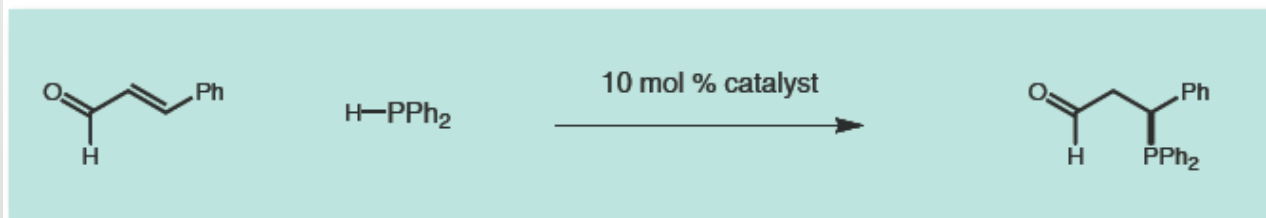
■ Reactivity is typically orthogonal to the imidizolidinone class of catalysts



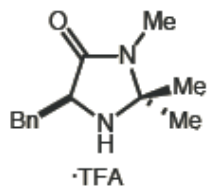
ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

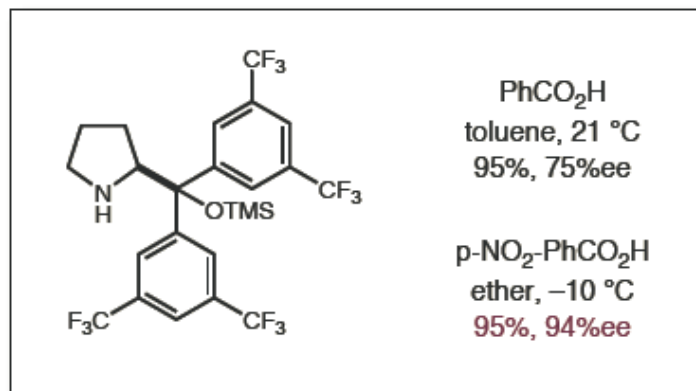
Hydrophosphination of Enals with the Jørgensen Catalyst



- Reactivity is typically orthogonal to the imidazolidinone class of catalysts



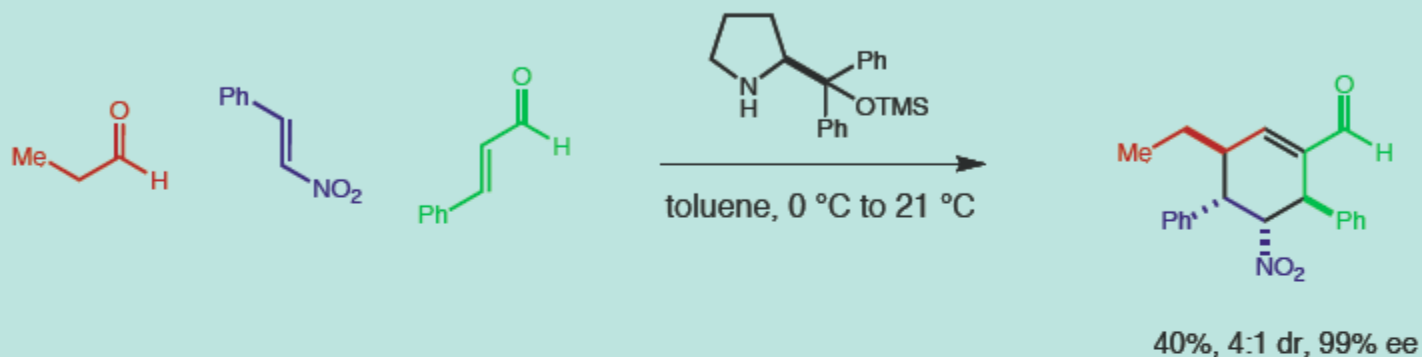
toluene, 21 °C
76%, 0%ee



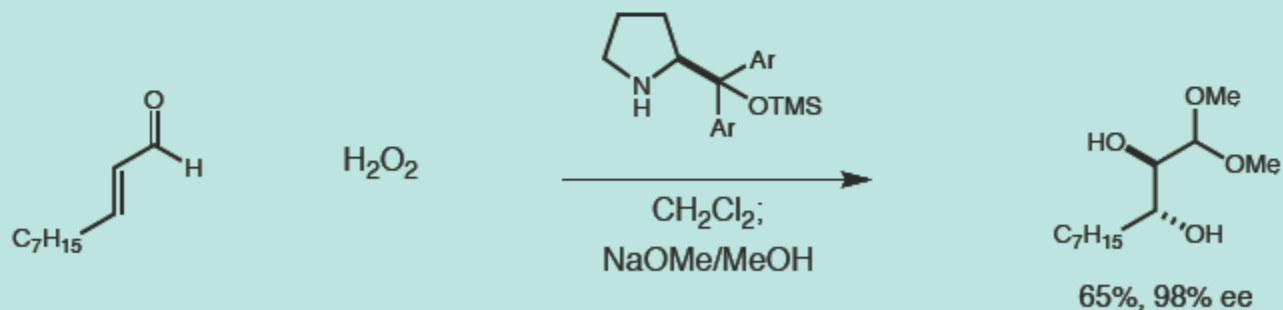
ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Scope of the Jørgensen Catalyst



Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861



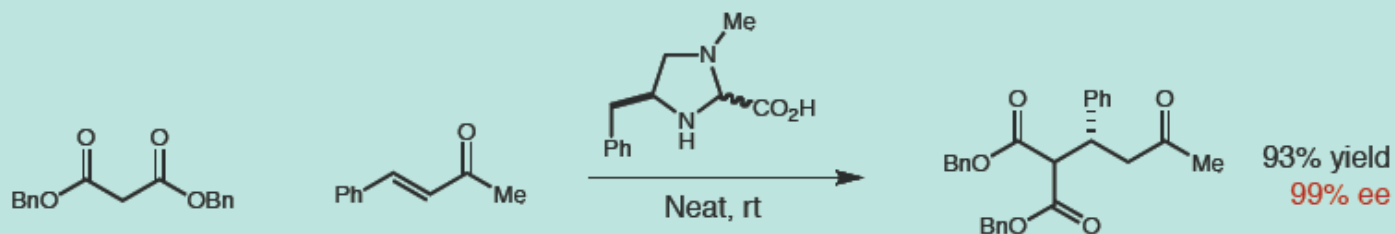
Albrecht, L.; Jiang, H.; Dickmeiss, G.; Gschwend, B.; Hansen, S. G.; Jørgensen, K. A. *J. Am. Chem. Soc.*

ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

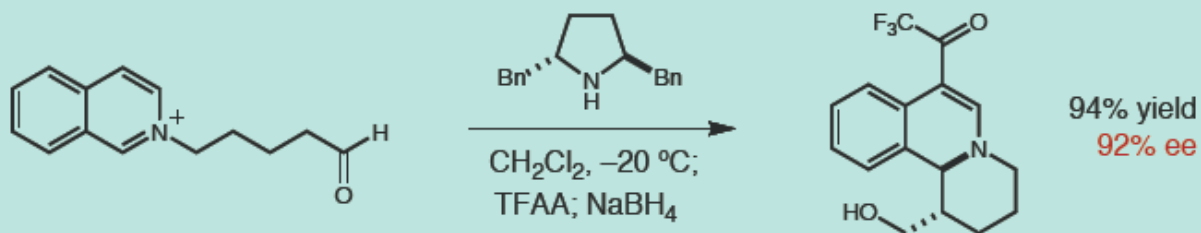
ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Scope of the Jørgensen Catalyst

- Involved in the development of other highly useful, though less well-known organocatalysts



Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 661.



Frisch, K.; Landa, A.; Saaby, S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6058.

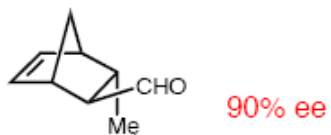
ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Iminium activation strategy is useful for a variety of organocatalytic reactions

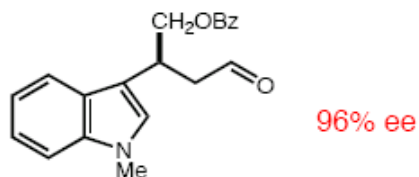
Diels–Alder

JACS **2000**, 122, 4243



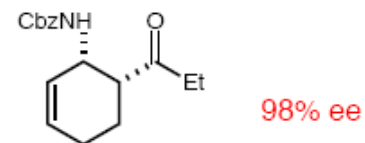
Indole Addition

JACS **2002**, 124, 1172



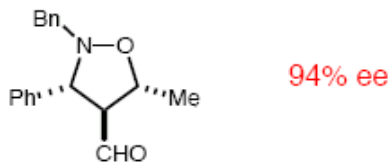
Ketone Diels–Alder

JACS **2002**, 124, 2458



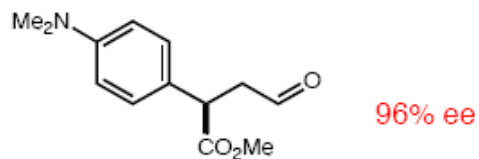
Nitrone Cycloaddition

JACS **2000**, 122, 9874



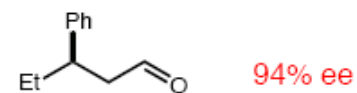
Aniline Addition

JACS **2001**, 124, 7894



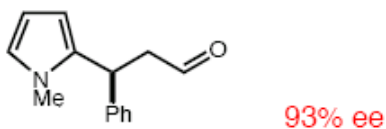
Enal hydrogenation

JACS **2005**, 127, 32



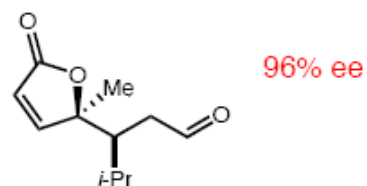
Pyrrole Friedel–Crafts

JACS **2001**, 123, 4370



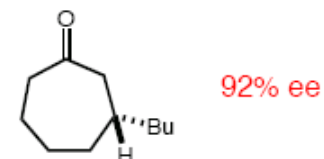
Vinylogous Michael

JACS **2003**, 125, 1192



Enone hydrogenation

JACS **2006**, 128, 12662



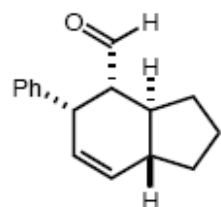
ΤΡΟΠΟΙ ΕΝΕΡΓΟΠΟΙΗΣΗΣ ΣΤΗΝ ΟΡΓΑΝΟΚΑΤΑΛΥΣΗ

ΕΝΕΡΓΟΠΟΙΗΣΗ ΜΕΣΩ ΙΟΝΤΟΣ ΙΜΙΝΙΟΥ

Iminium activation is useful for a variety of transformations

Intramolecular Diels–Alder

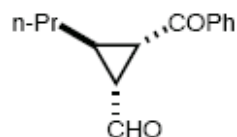
JACS **2001**, *124*, 7894



93% ee

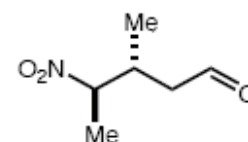
Cyclopropanation

JACS **2005**, *127*, 3240



95% ee

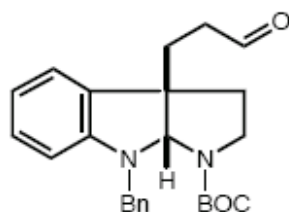
Nitroalkane Addition



95% ee

Addition–Cyclization

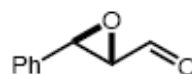
PNAS **2004**, *101*, 5482



90% ee

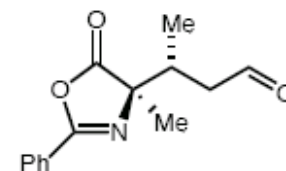
Epoxidation

Tetrahedron Yi Award
2006, 1472



92% ee

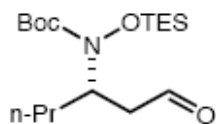
Tertiary Amino Acid



99% ee

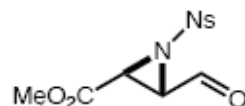
Amine Conjugate Addition

JACS **2006**, *128*, 9328



95% ee

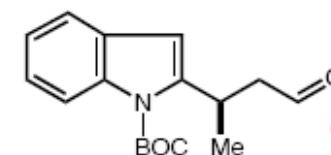
Aziridination



93% ee

Aryl or Vinyl BF₃K Addition

JACS **2007**, *127*, 15438



91% ee