Recent Investigations of Enamine Catalysis with Prolinol Silyl Ethers

Mechanism and Origin of Stereoselectivity in the α-Functionalization of Aldehydes

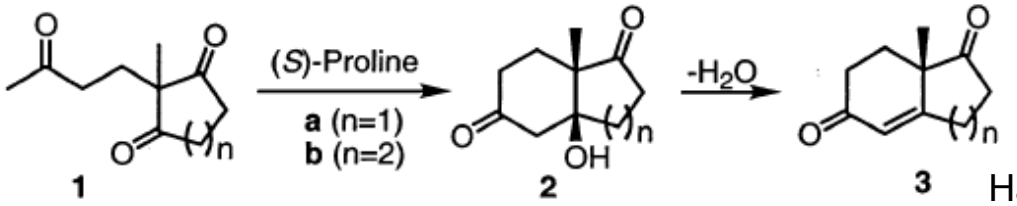
Jeremy Henle 7/17/2012

Outline

- Brief overview of the history of development of asymmetric enamine organocatalysis
- General paradigms of stereoselectivity in enamine catalyzed reactions
- Mechanistic Investigations
  - Part I: Conjugate additions of aldehydes and nitroalkenes
  - Part II: α-chlorination of aldehydes

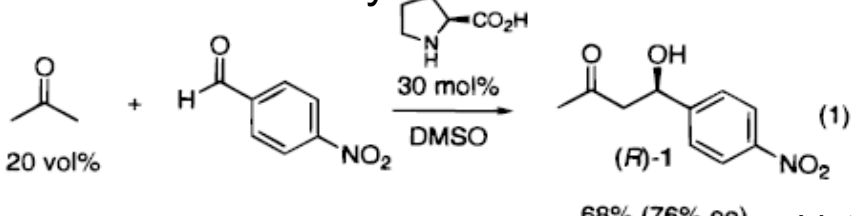
A Brief History of Asymmetric Enamine Catalysis

- 1970s (Hajos-Parrish-Eder-Sauer-Wiechert)



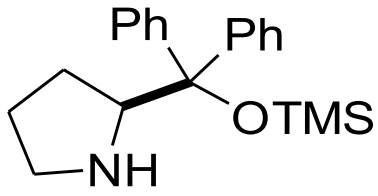
Hajos, G. et. al. *J. Org. Chem.* **1974**, *39,* 1615

- 2000: Proline used in direct asymmetric aldol reaction



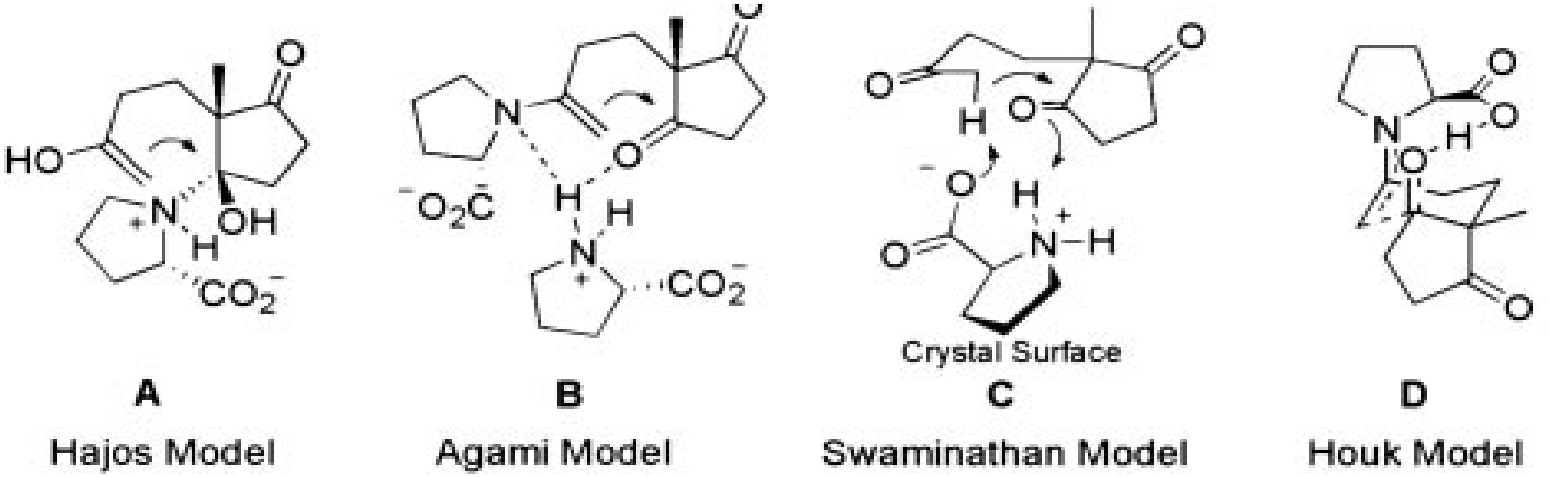
List, B., et. al.*J. Am. Chem. Soc.* **2000,** *122,* 2395.

- 2000-2004: Controversy in mechanisms utilizing proline
- 2005-present
  - Exploration of new class of proline derived catalysts, and their application to asymmetric Michael-type reactions, as well as asymmetric α-additions to aldehydes



Jorgensen, *Acct. Chem. Res.* **2011**, 45, 248.

Controversy of Enamine Mechanism



A Hajos Model

B Agami Model

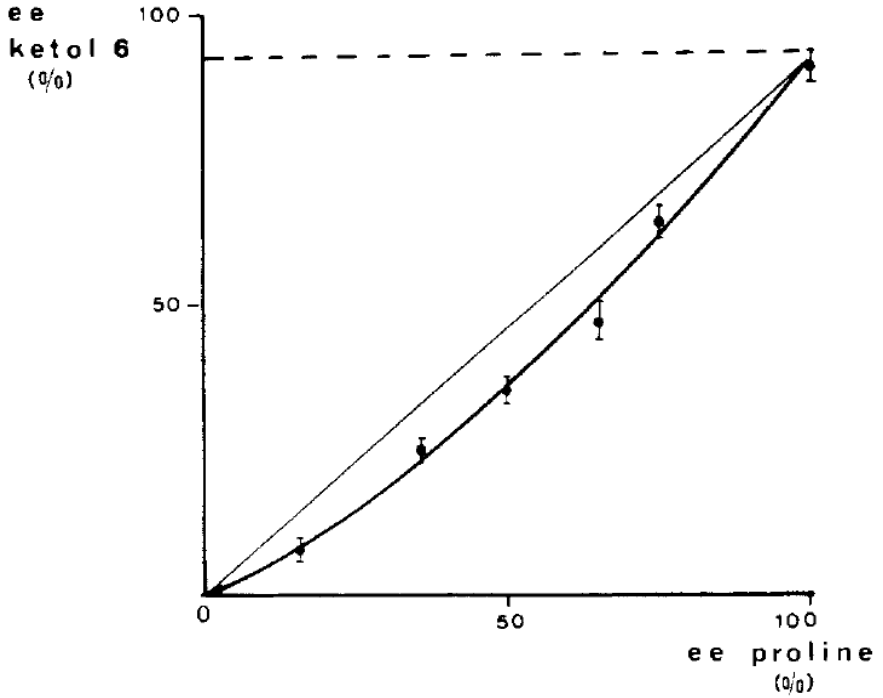
C Swaminathan Model

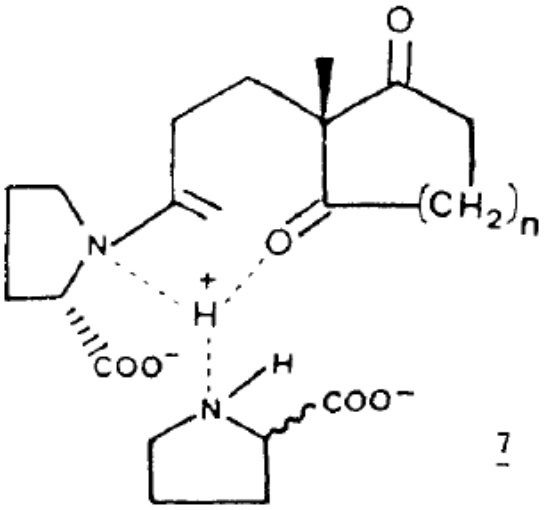
D Houk Model

Houk. *JACS,* **2001,** *123,* 11273
Houk, List. *JACS,* **2003** *125,* 16.
Houk, List. *JACS,* **2003** *125, 2475*.
List. *PNAS,* **2004** *101, 5839*.
Houk. *ACIE,* **2004 43**, *5766*.

One Proline, or Two?

- Agami





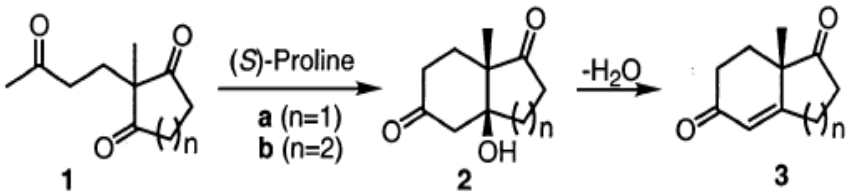
7

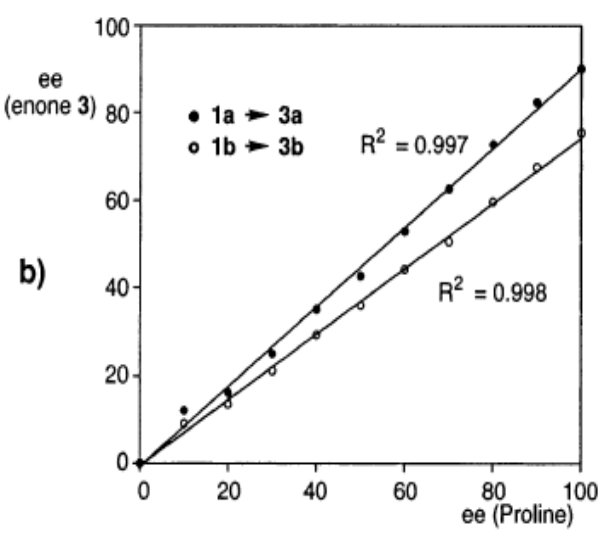
ine moiety resulting from the reaction between (

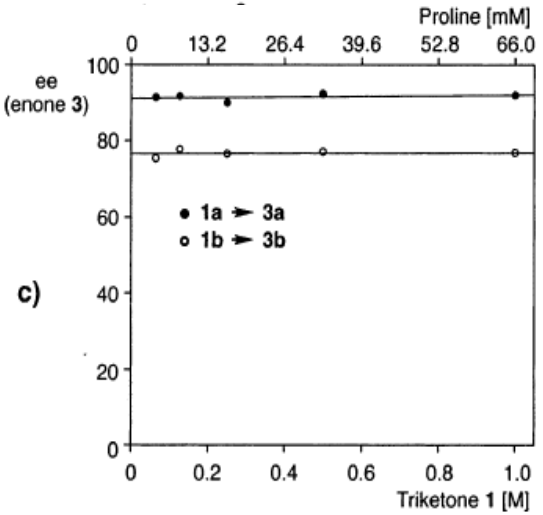
Agami, C, Kagan, H. B. *JACS,***1986,***108,* 2353.

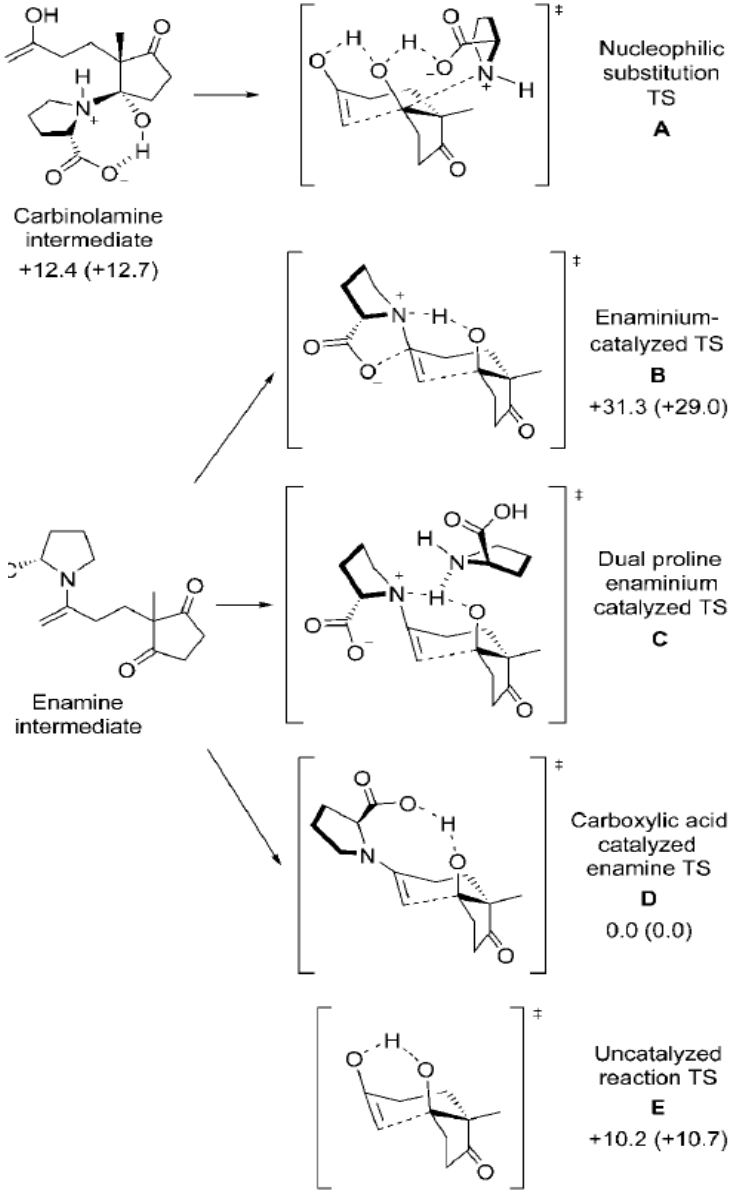
One Proline, or Two?

- 2002-2004



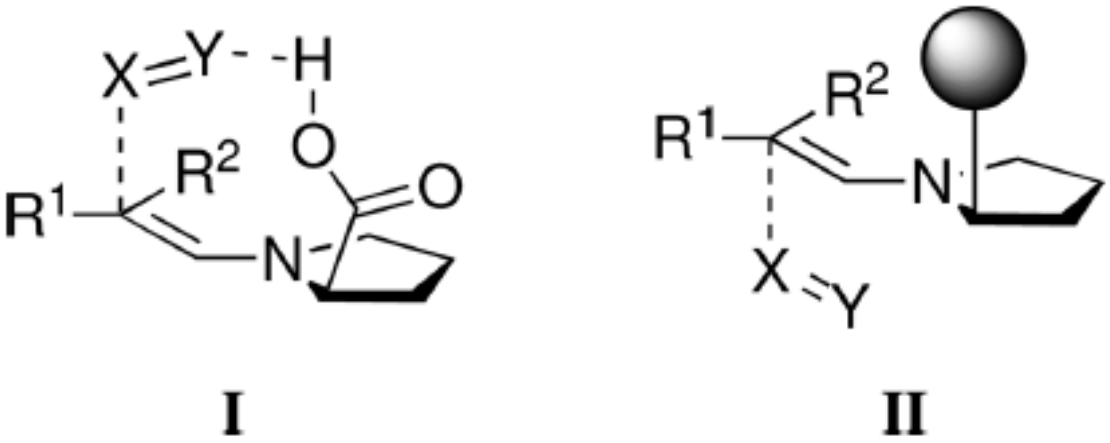






Houk, List. *JACS,* **2003** *125,* 16.
Houk, List. *JACS,* **2003** *125, 2475*.
List. *PNAS,* **2004** *101, 5839*.
Houk. *ACIE,* **2004 43**, *5766*

General Paradigms of Stereoselectivity in Enamine Catalysis

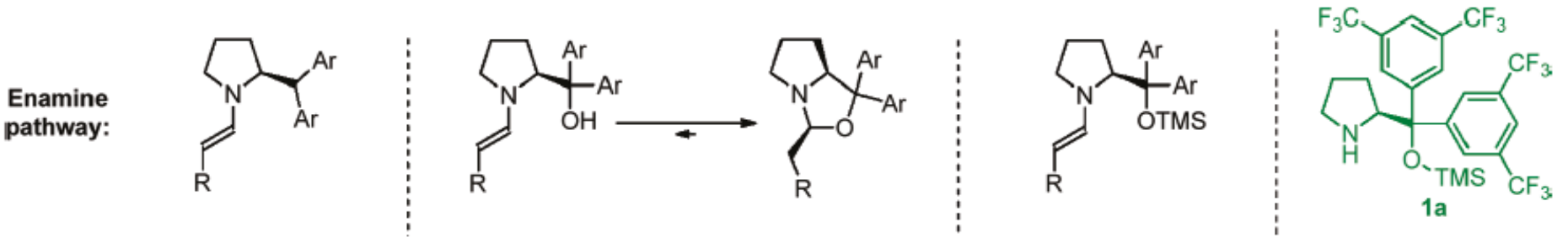


I II

Bures, J, Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

Model II:Development of Diarylprolinol Silyl Ethers

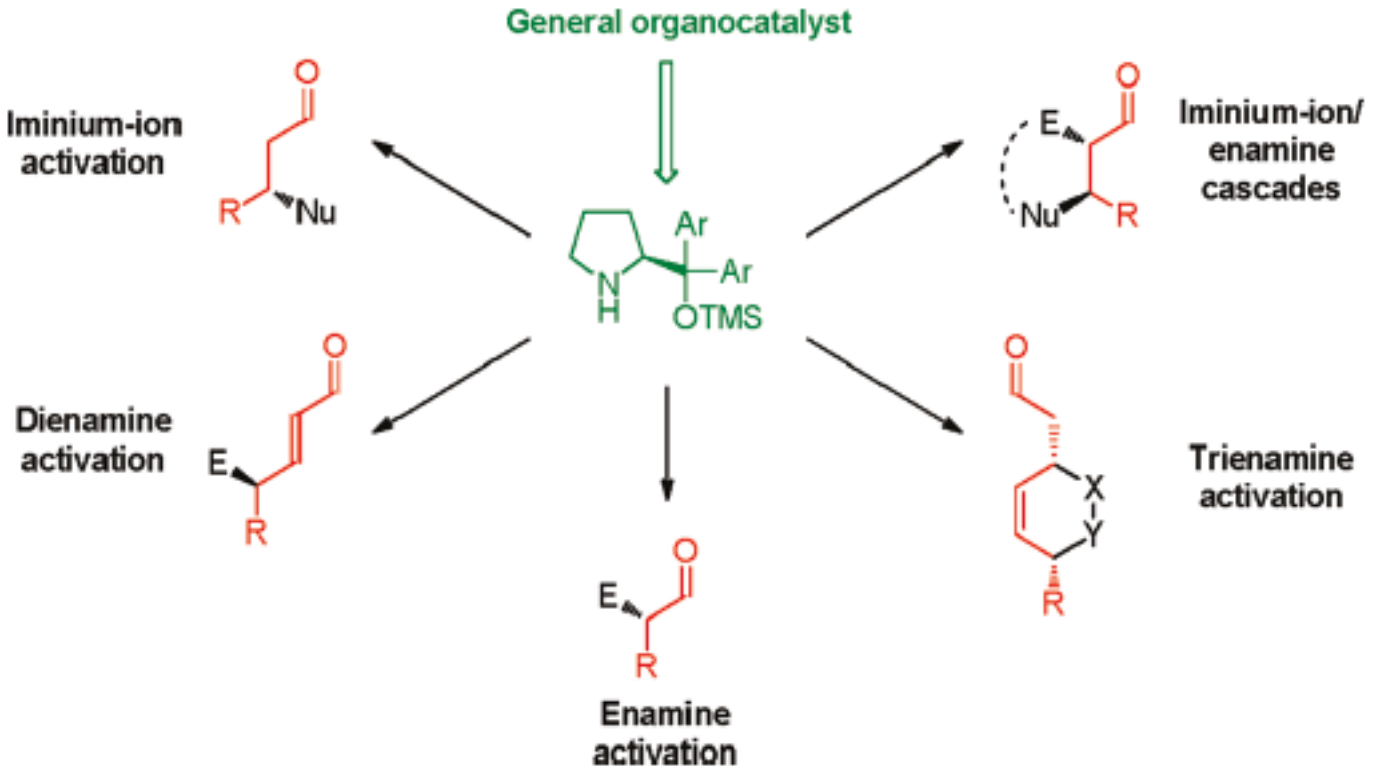
- With proline, it is known that asymmetric induction primarily arises from hydrogen bonding between electrophile and the proline carboxylic acid
- A new series of catalysts based on proline, were investigated by Hayashi and Jorgenson as general catalysts for the α-functionalization of aldehydes



Hiyashi, *ACIE,* **2005,** *44,* 4212
Jorgensen, *JACS,* **2005,** *127,* 18296.
Jorgensen, *Acct. Chem. Res.* **2011**, 45, 248.

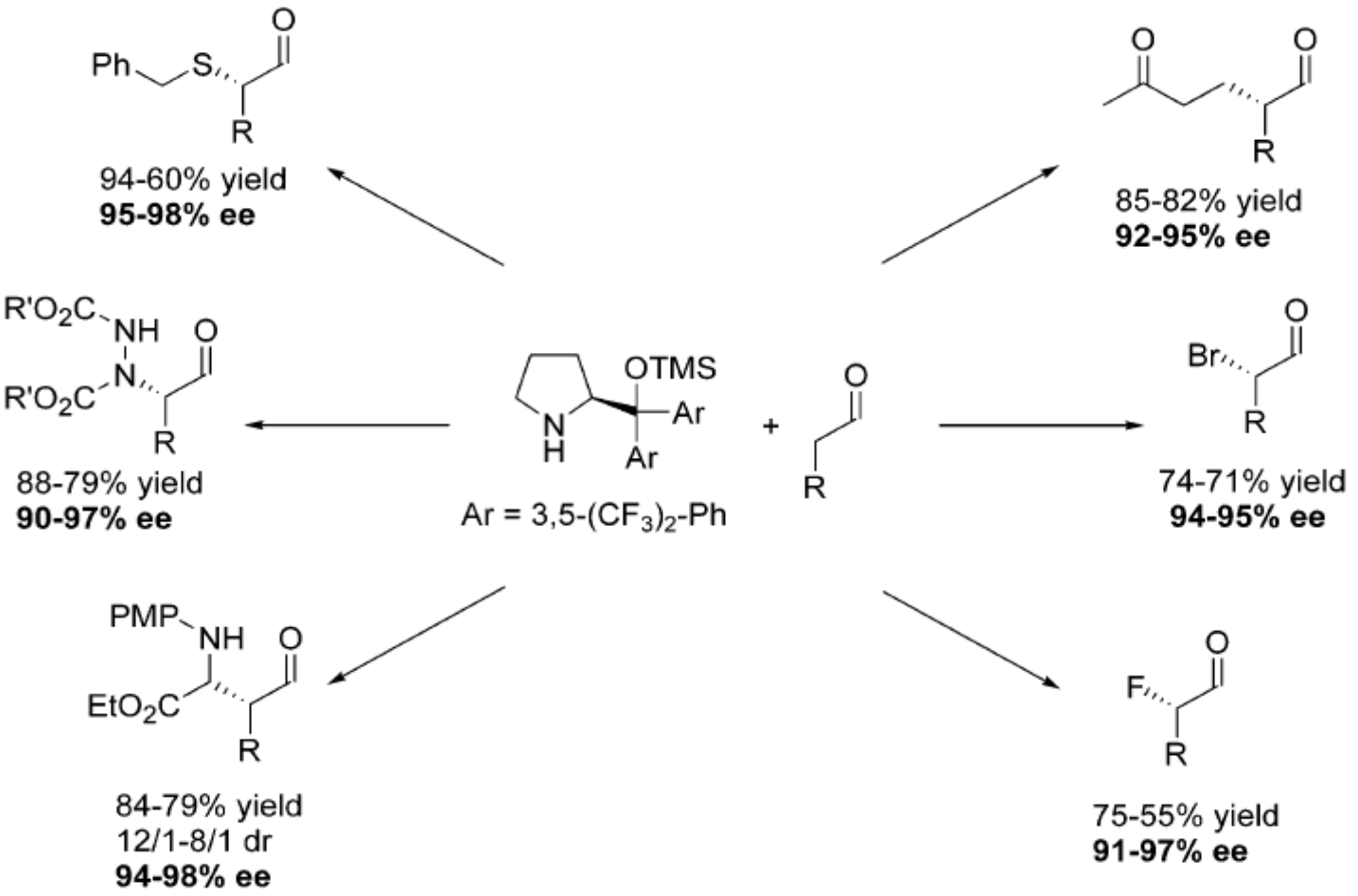
α,α-Diarylprolinol Silyl Ethers

Scope and Utility



Jorgensen, *Acct. Chem. Res.* **2011**, 45, 248.

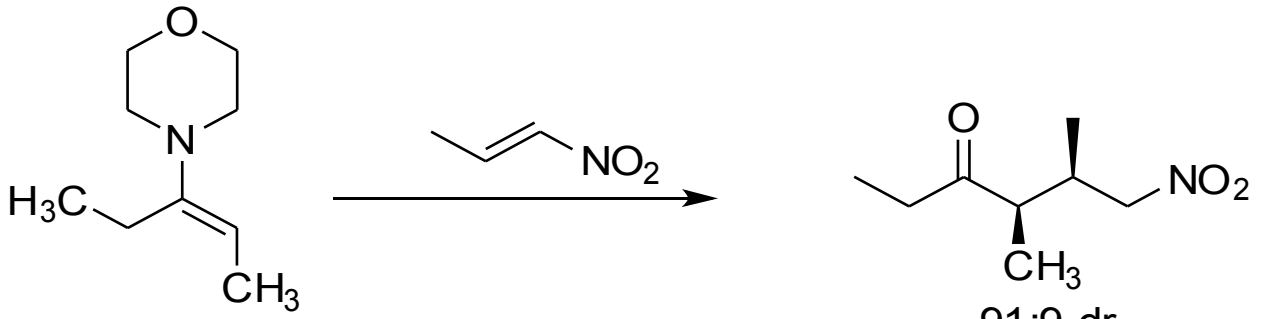
Utility of Diarylprolinol Silyl Ethers as Enamine Catalysts



Jorgensen, *JACS,* **2005,** *127,* 18296.
Jorgensen, *Acct. Chem. Res.* **2011**, 45, 248.

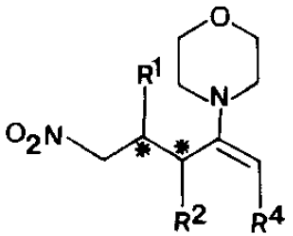
Model II: Part I
Conjugate Addition to Nitroalkenes

- 1980s: Seebach utilized open chain enamines and nitroalkenes to forge C-C bonds diastereoselectively

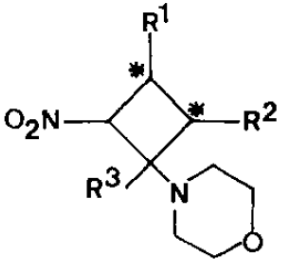


91:9 dr

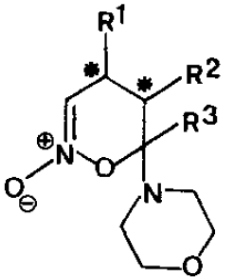
- Seebach proposes possible intermediates:



5



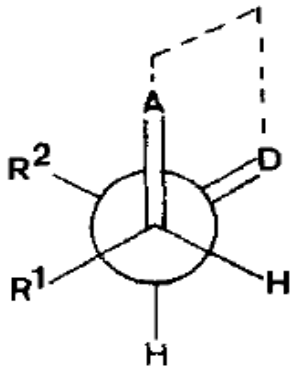
6



7

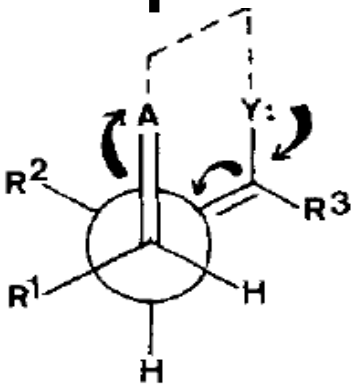
Seebach. *Helv. Chim. Acta,* **1981,** *64,* 1413

Seebach's Topological Rule



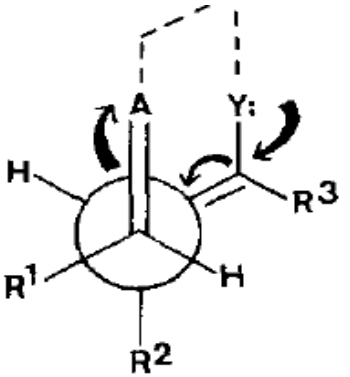
9

[*Re*Si**-approach][8])



10

(syn-donor)



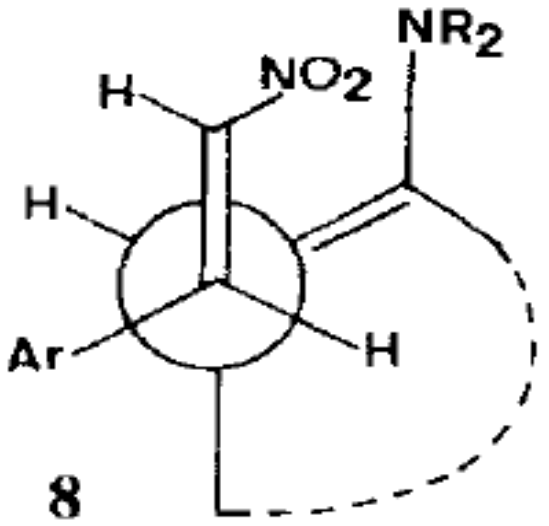
11

(anti-donor)

- General rule applicable to many donor-acceptor π-systems
- In aprotic media, under kinetic control, the preferred approach of two prochiral centers RCH=X can be predicted:
  - With *staggering* of all bonds around the newly formed bond
  - In a *gauche* (synclinal) arrangement of the donor (C=D) bond between the C-A and C-H bonds of the acceptor
  - With the *H-atom*, the smaller component of the donor component, in an *antiperiplanar* position with respect to the C=A bond
  - If the components can exist as E/Z (anti/syn) isomers, the *actual donor and acceptor* atoms are situated *close* to each other.

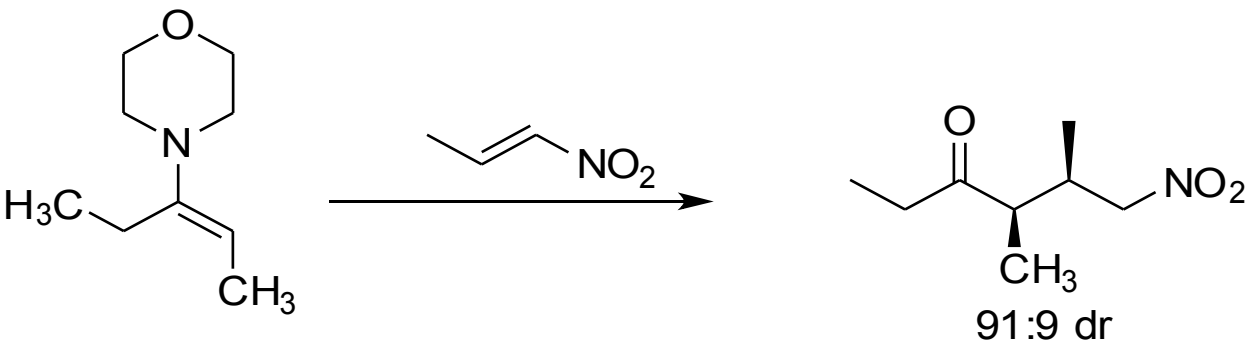
Seebach. *Helv. Chim. Acta,***1981,** *64,* 1413

Seebach's Topological Rule



8

(*anti*-donor/*anti*-acceptor)
[*Re*Re**-approach][8])

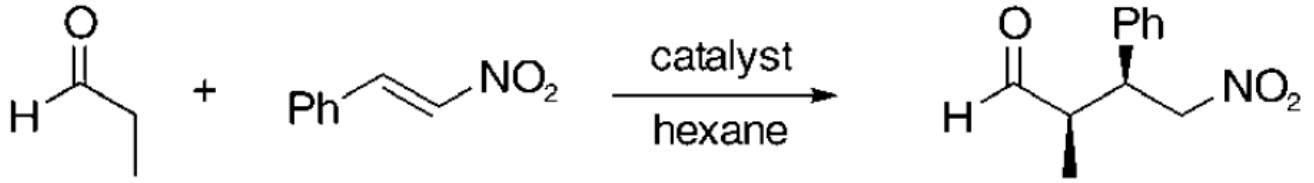


91:9 dr

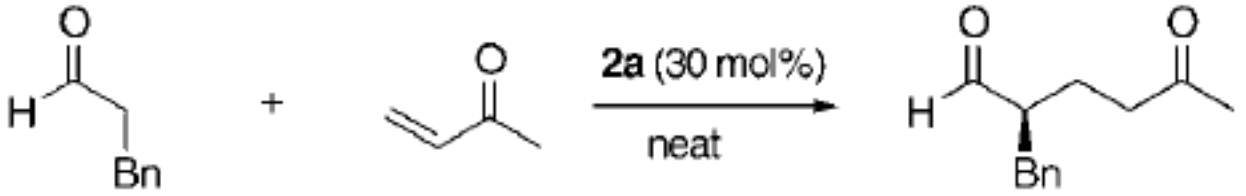
Seebach. *Helv. Chim. Acta,***1981,** *64,* 1413

Development of Asymmetric Conjugate Additions

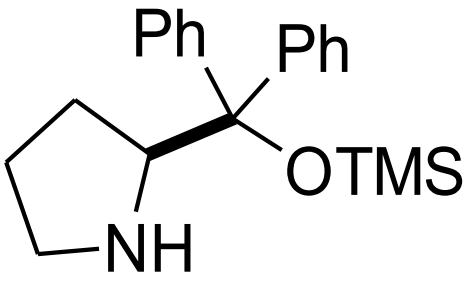
- Hiyashi, 2005



85%, 96:4 d.r., 99% ee



52%, 97% *ee*

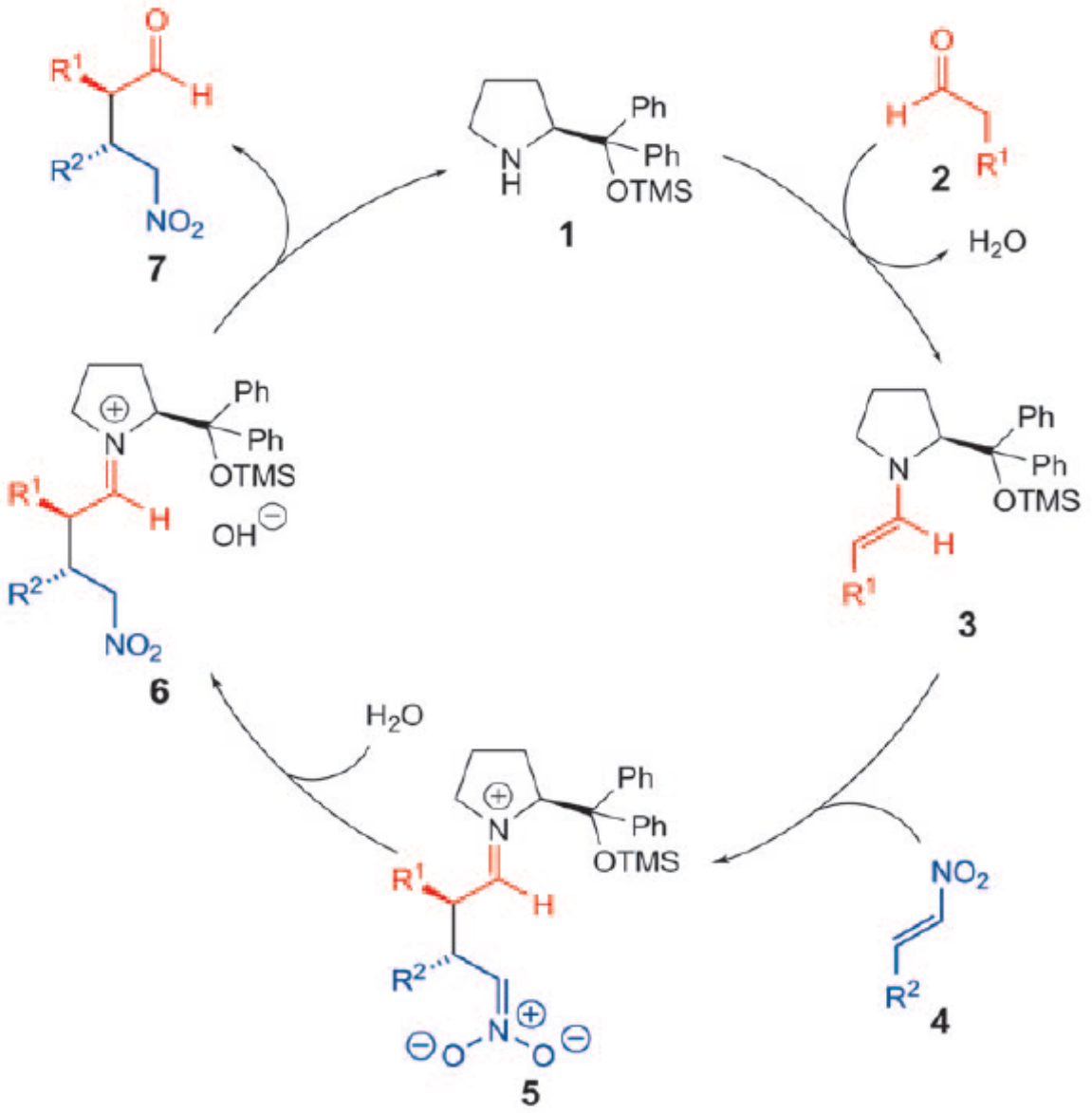


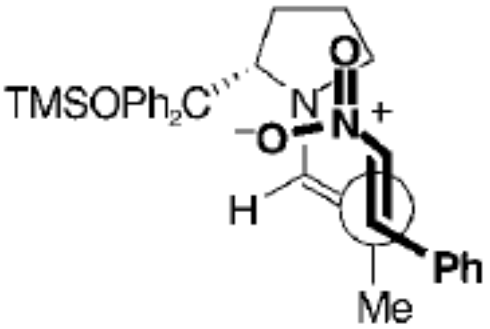
Catalyst

Hiyashi, *ACIE,* **2005,** *44,* 4212

Conjugate Addition

Accepted Catalytic Cycle

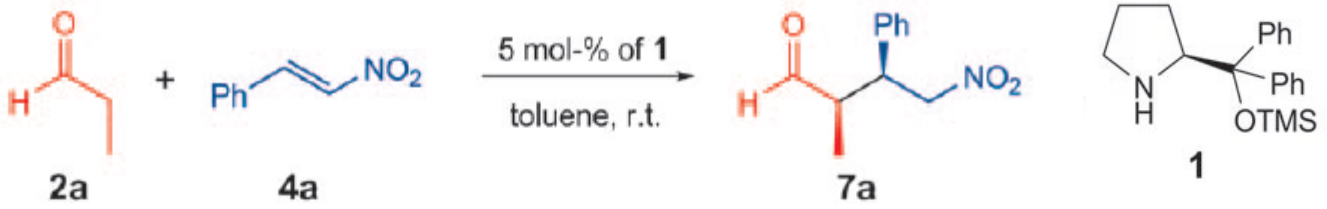




Hiyashi, *ACIE,* **2005,** *44,* 4212
Seebach, *Helv. Chim. Acta.* **2011,** *94,* 719.

Mechanistic Questions

- Experimentally, different acids resulted in varied diastereoselectivities, as well as as rates



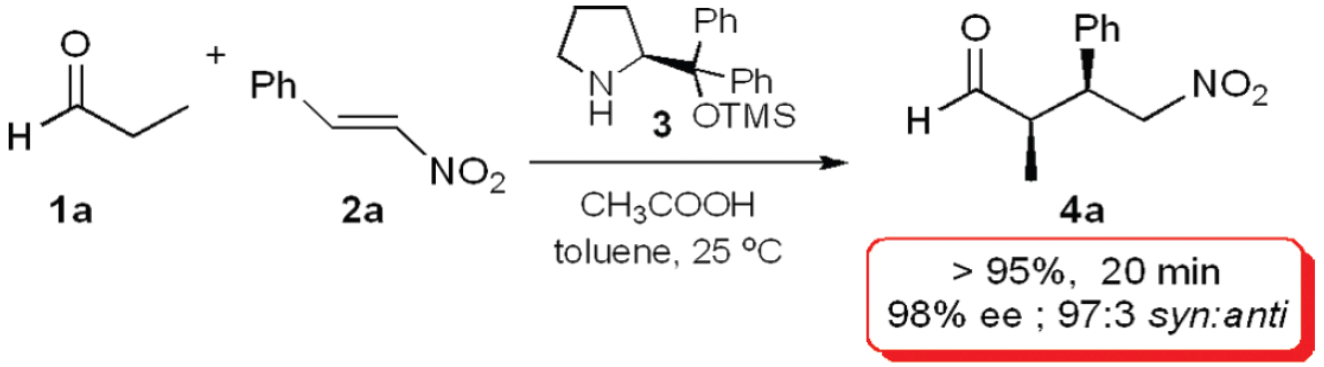
2a 4a 7a 1

Entry	Acid	pK_a in H_2O[b])	Reaction time	Yield[c]) [%]	*u*/*l*[d])	ee *u*[e]) [%]
1	Cl_3CCO_2H	0.7	10 d	25	2.5	nd[f])
2	Cl_2CHCO_2H	1.29	11 d	70	2.5	nd
3	$ClCH_2CO_2H$	2.85	18 h	85	3	nd
4	HCO_2H	3.75	120 min	88	20	99
5	$CH_2ClCH_2CO_2H$	3.98	80 min	90	6	99
6	$PhCO_2H$	4.19	75 min	90	7	99
7	$EtCO_2H$	4.87	60 min	95	17	98
8	2,4,6-Br_3–C_6H_2OH	5.97	30 min	92	10	98
9	2,4,6-Cl_3–C_6H_2OH	6.21	15 min	88	18	99
10	4-NO_2–C_6H_4OH	7.15	15 min	98	15	99
11	4-Cl–C_6H_4OH	9.18	25 min	90	20	99
12	PhOH	9.89	90 min	89	16	99
13	4-Me–C_6H_4OH	10.2	105 min	90	18	99
14	–	–	6 h	98	14	99

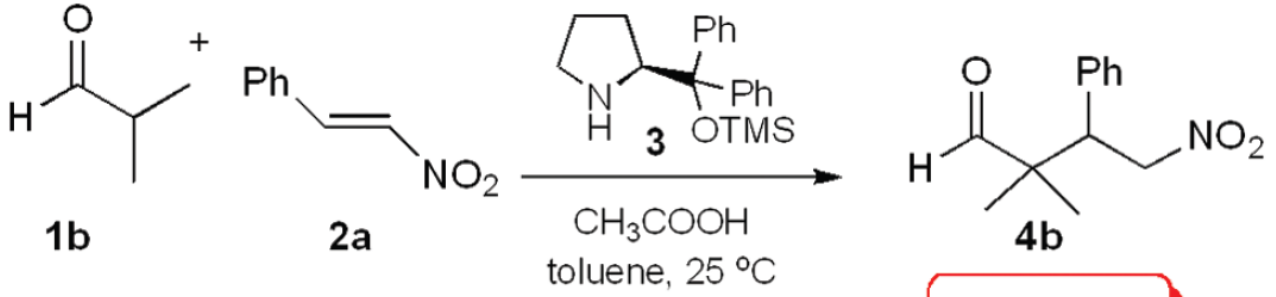
Seebach, *Helv. Chim. Acta.* **2011,** *94,* 719.

Mechanistic Questions

- Blackmond: Steric transition state model doesn't explicitly explain facial selectivity (diastereoselectivity) with respect to conjugate addition to nitroalkenes, nor the erosion of d.r. observed



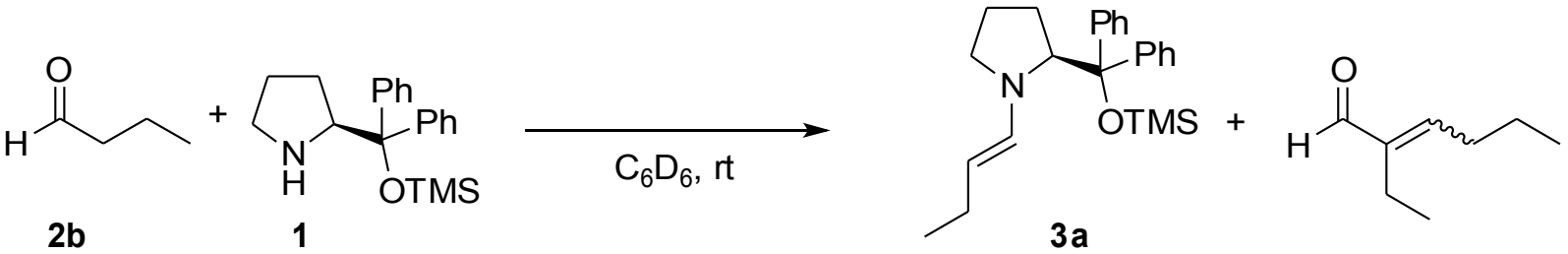
- It also doesn't explain why α,α-disubstituted aldehydes have a marked rate decrease



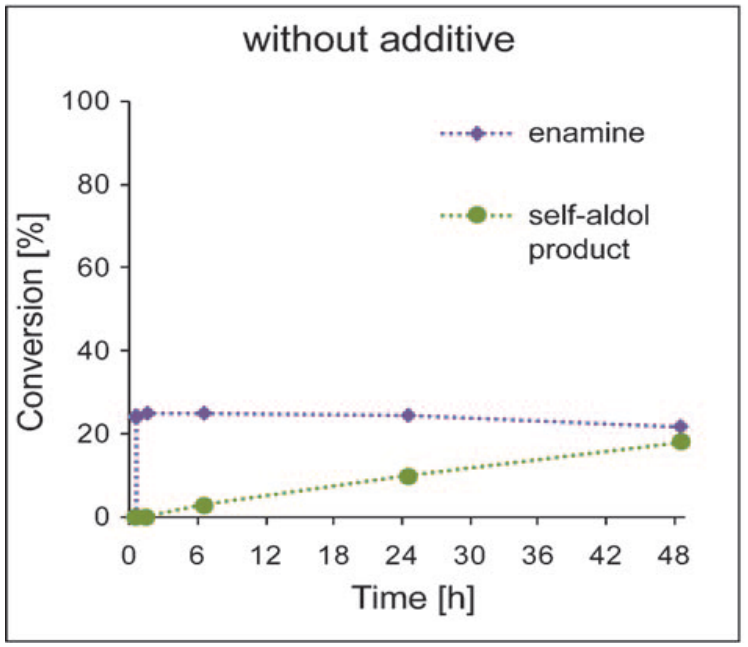
Bures, J, Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

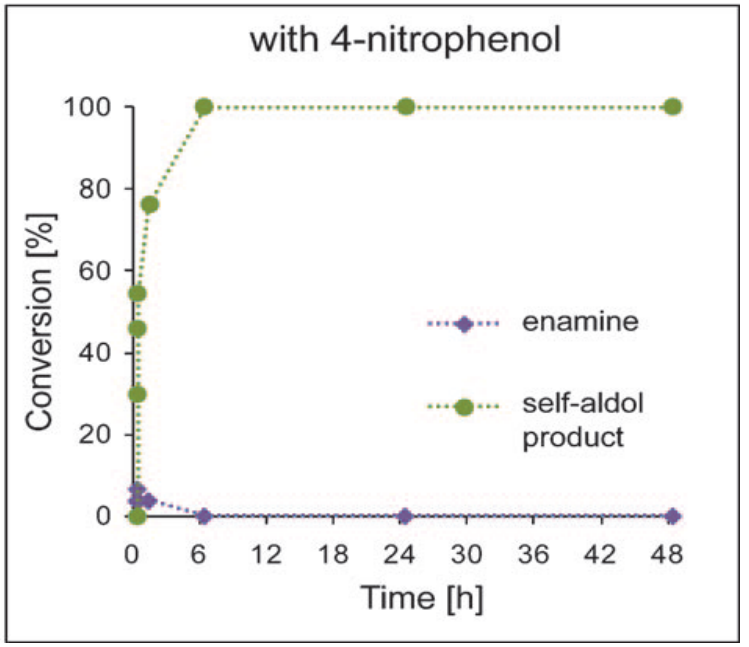
Role of the Acid

Formation of Enamine



2b **1** **3a**



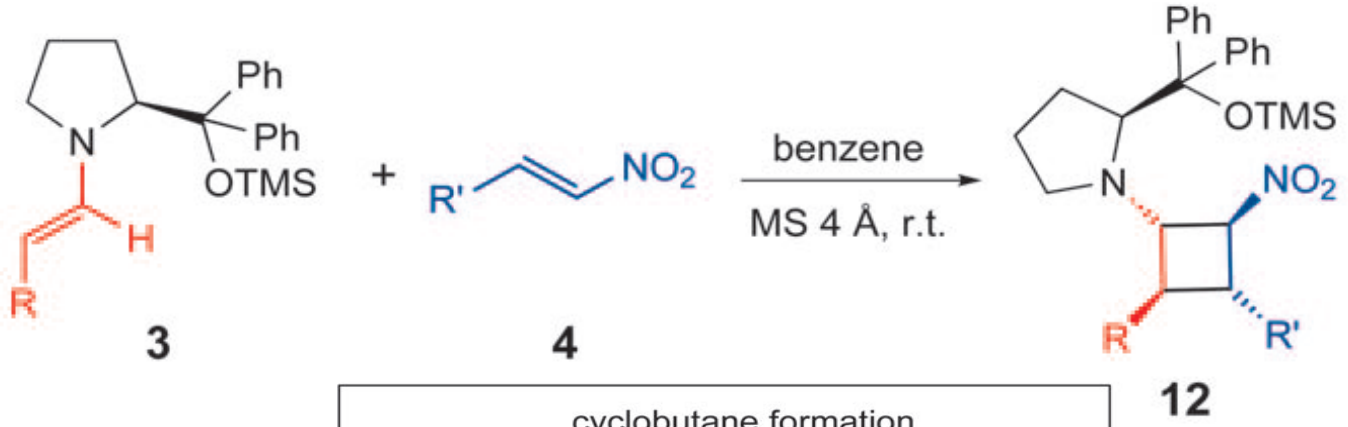


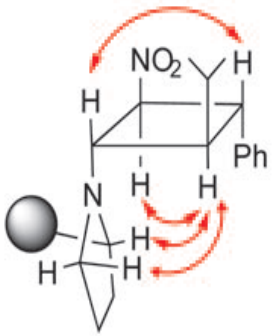
Seebach, *Helv. Chim. Acta.* **2011,** *94,* 719.

Addition of Enamine to Nitroalkene

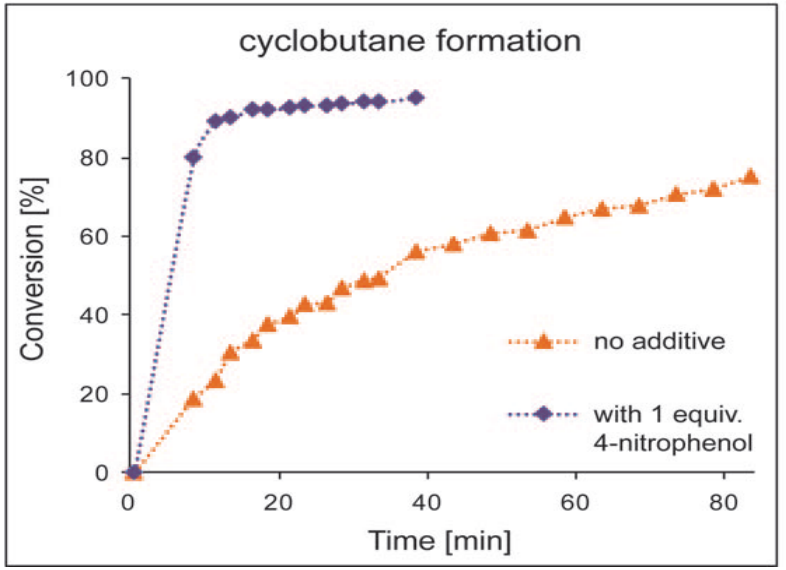
Revealing a New Intermediate

- Stoichiometric reaction of enamine with nitroalkene in anhydrous conditions yields new cyclobutane intermediate



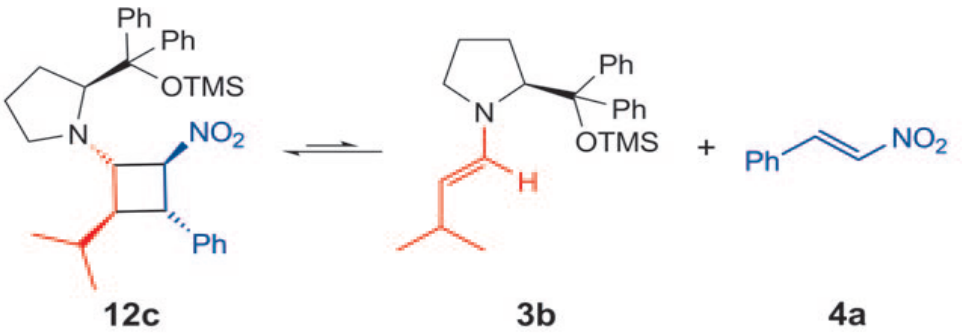


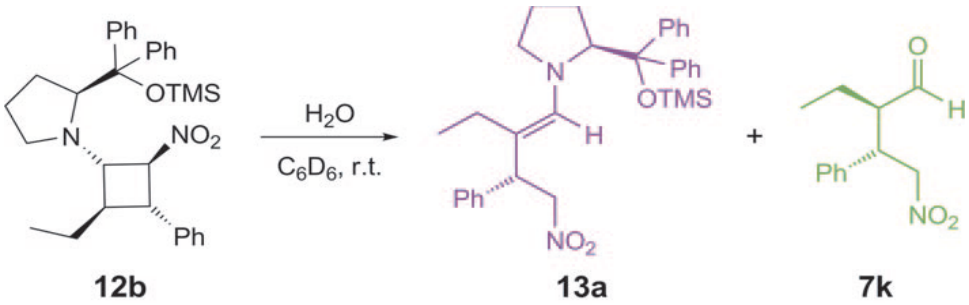
Nuclear *Overhauser* effects in the NMR spectrum of **12c**

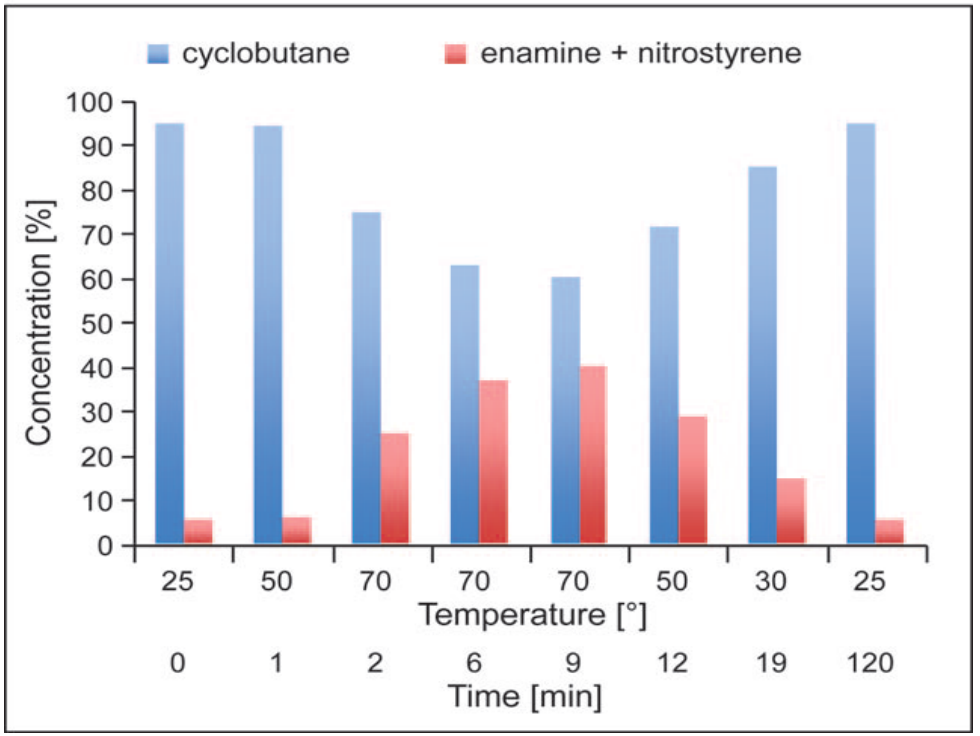


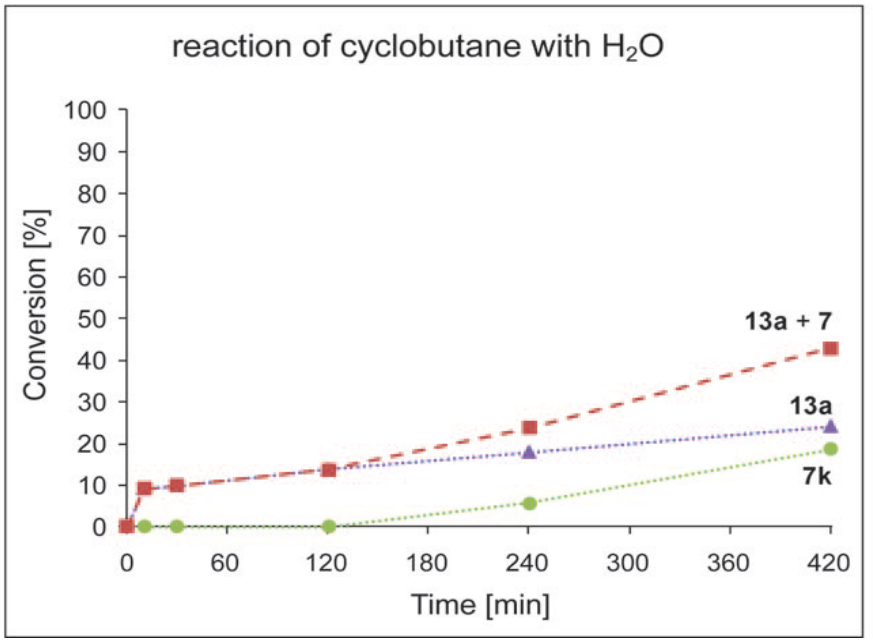
Seebach, *Helv. Chim. Acta.* **2011,** *94,* 719.

From Cyclobutane to Michael Adduct



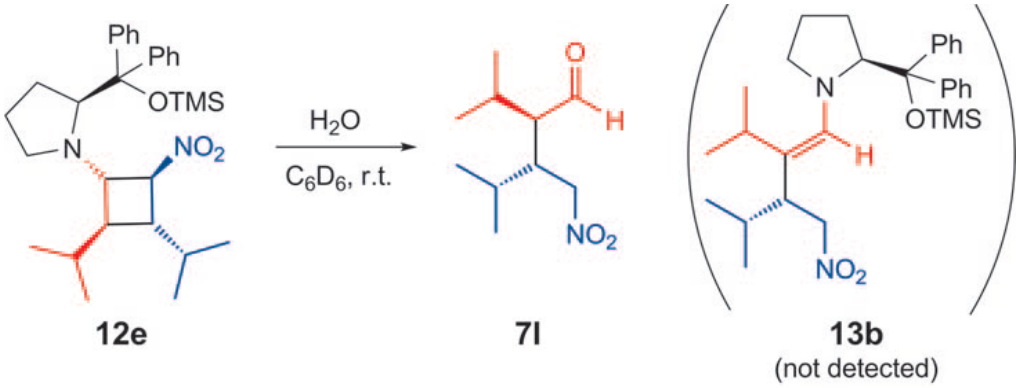


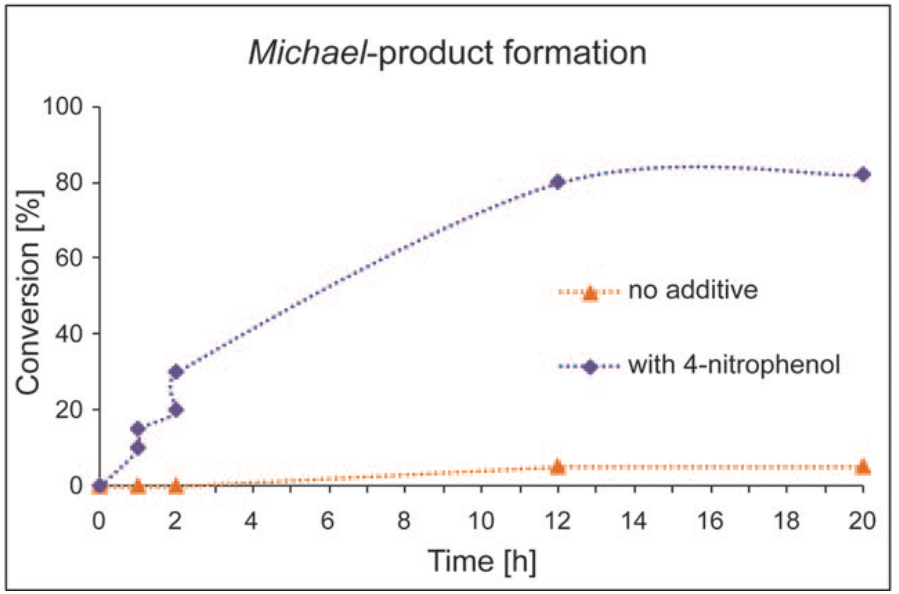




Seebach, *Helv. Chim. Acta.* **2011,** *94,* 719.

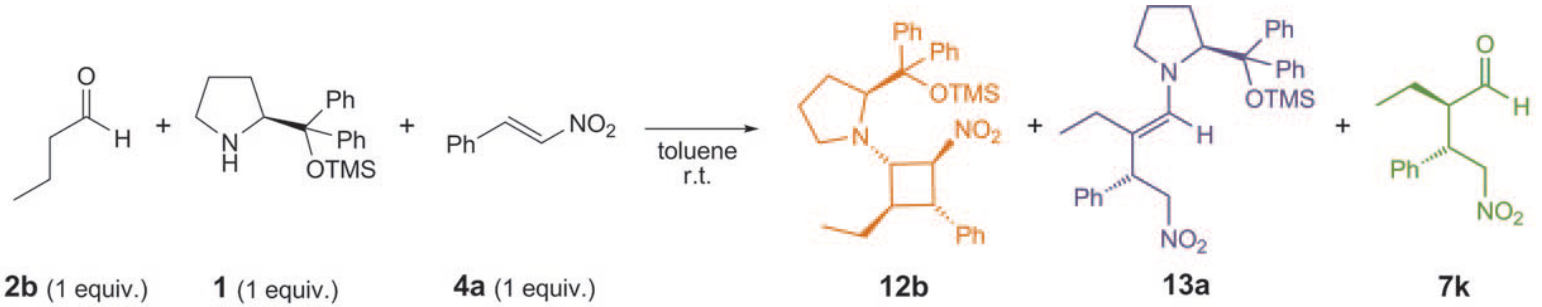
Additive Effects on Cyclic Intermediate

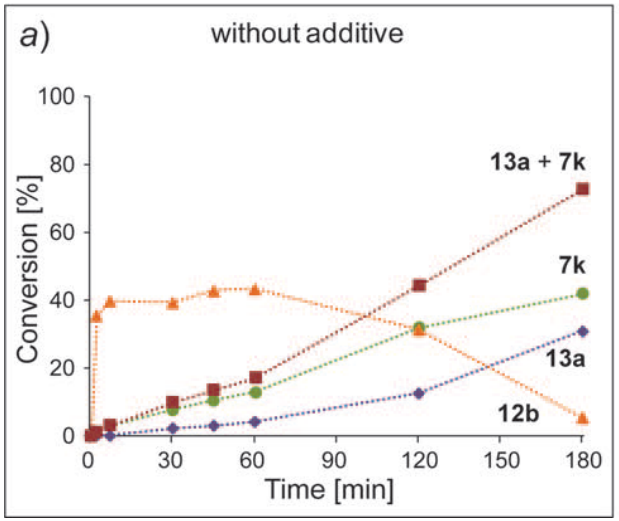


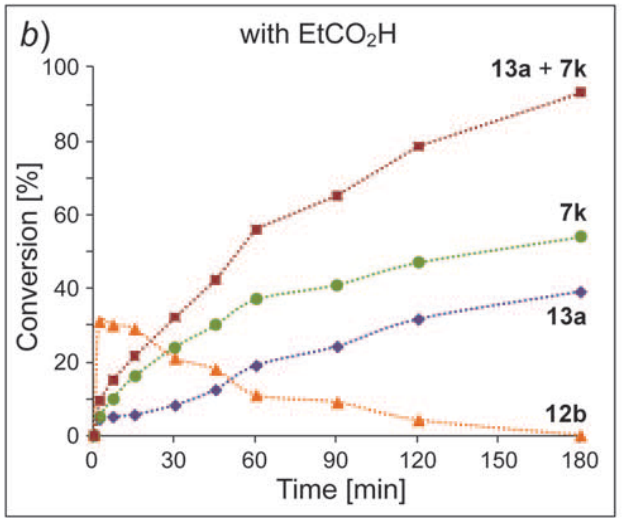


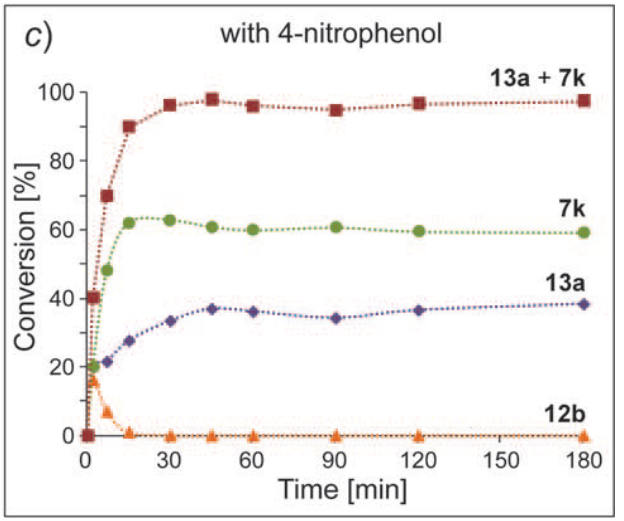
Seebach, *Helv. Chim. Acta.* **2011,** *94,* 719.

Additive Effects on Cyclic Intermediate



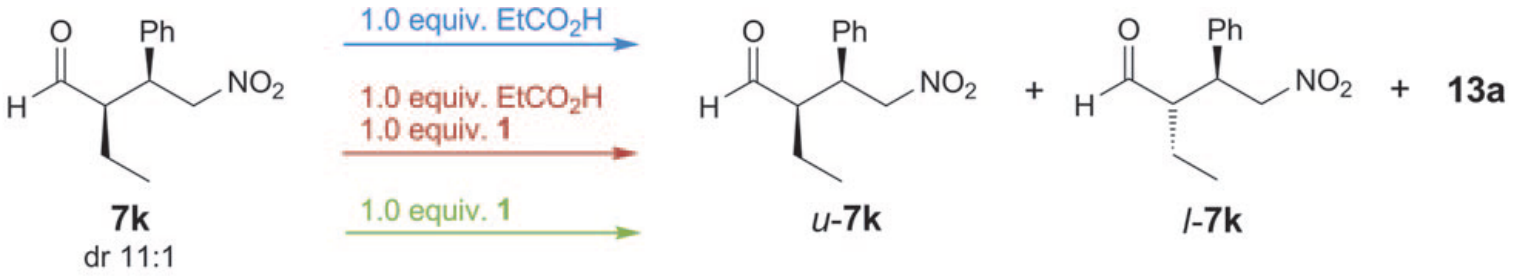


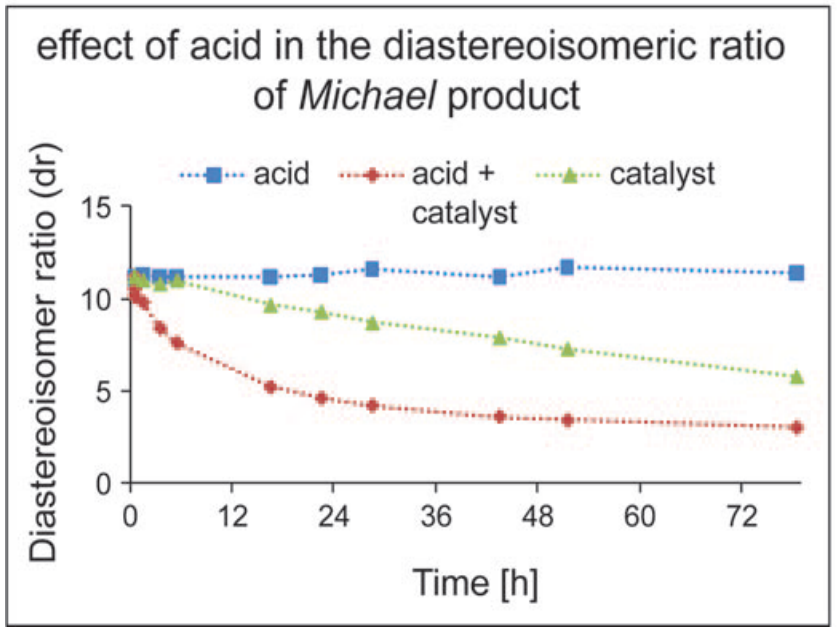


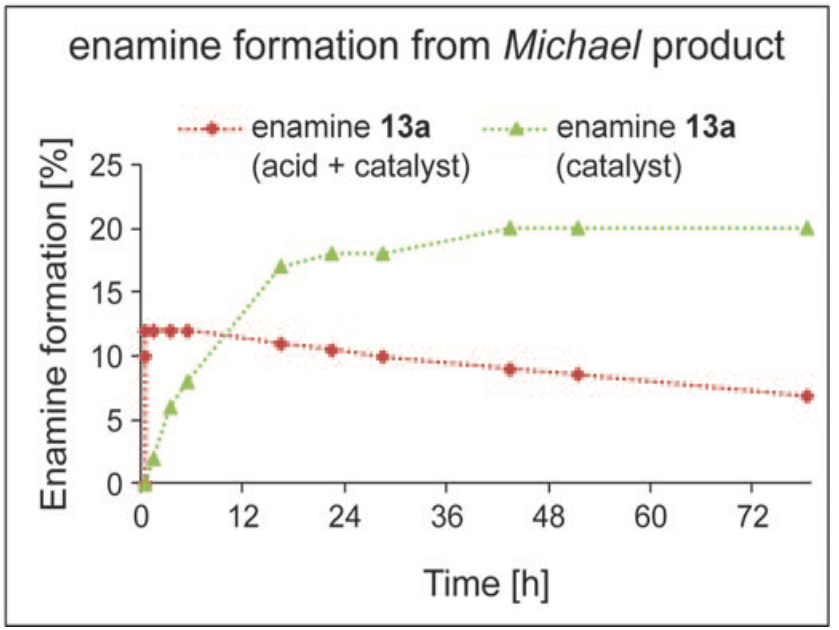


Seebach, *Helv. Chim. Acta.* **2011,** *94,* 719.

Erosion of Diastereoselectivity

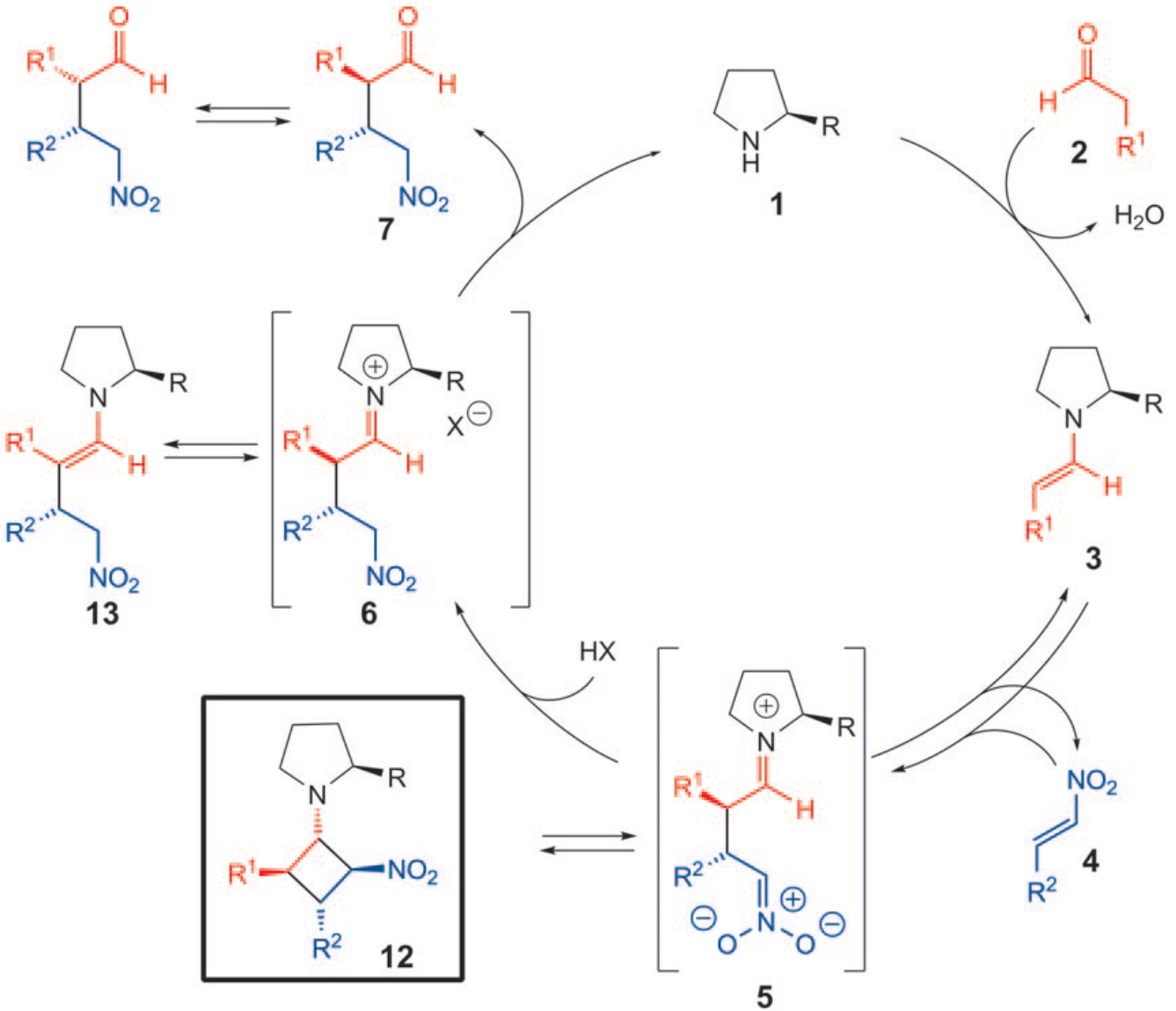






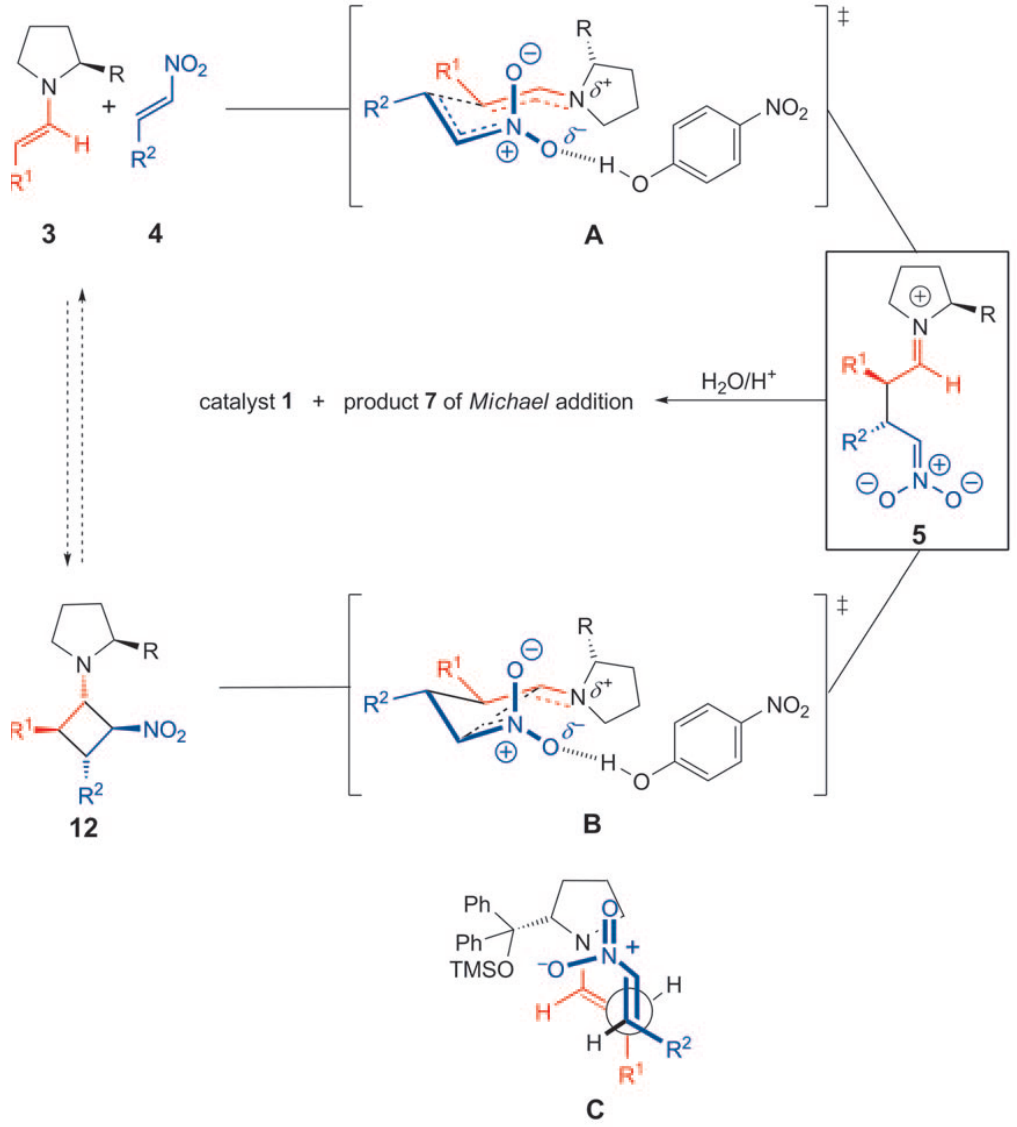
Seebach, *Helv. Chim. Acta.* **2011,** *94,* 719.

Revised Catalytic Cycle



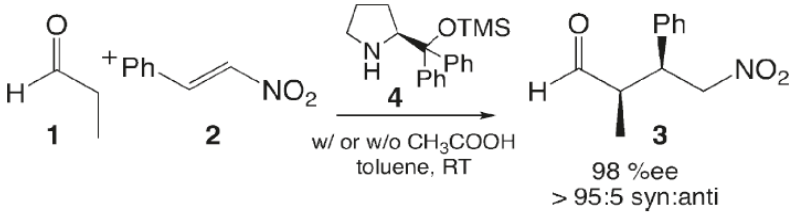
Seebach, *Helv. Chim. Acta.* **2011,** *94,* 719.

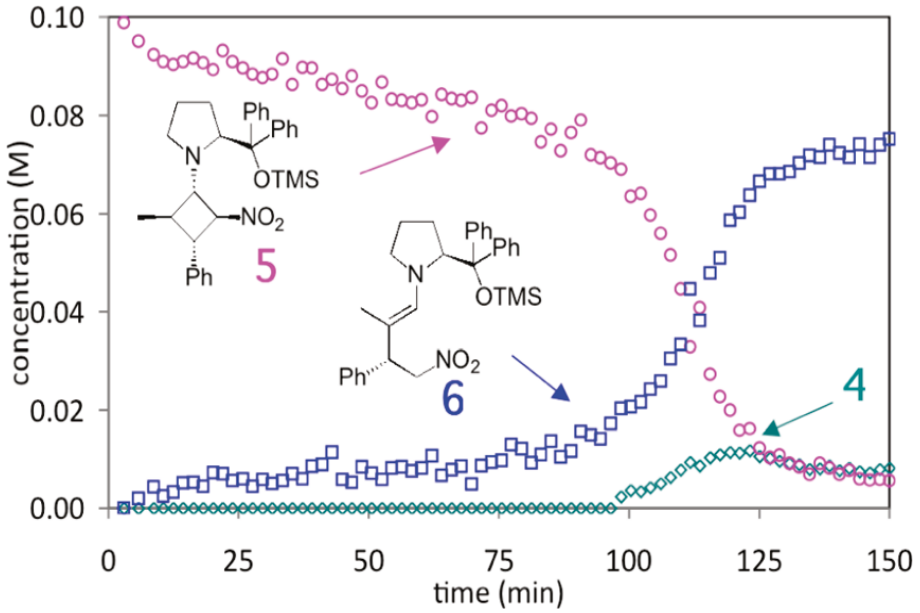
Origin of Stereoselectivity

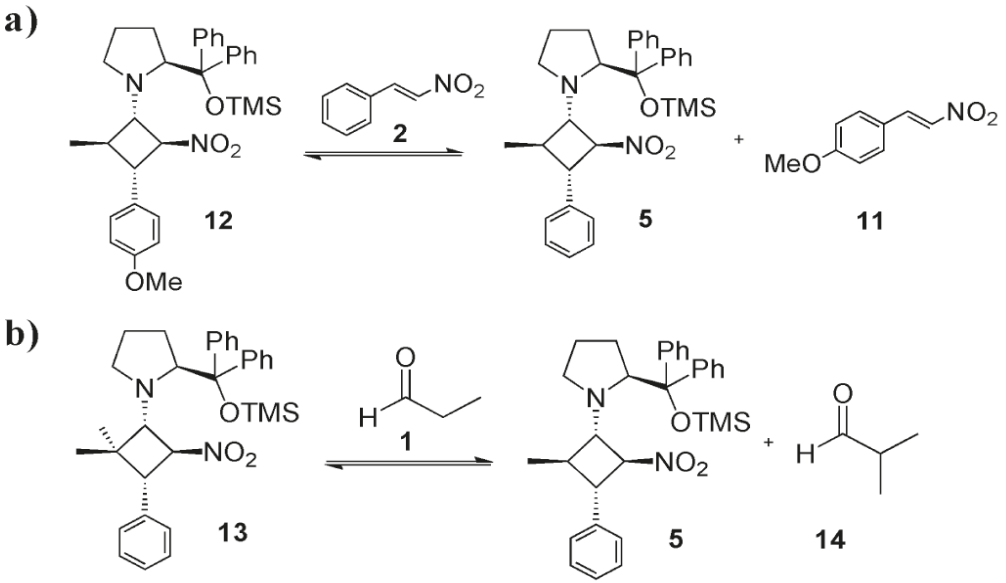


Seebach, *Helv. Chim. Acta.* **2011,** *94,* 719.

Is the Cyclobutane Intermediate “parasitic”?



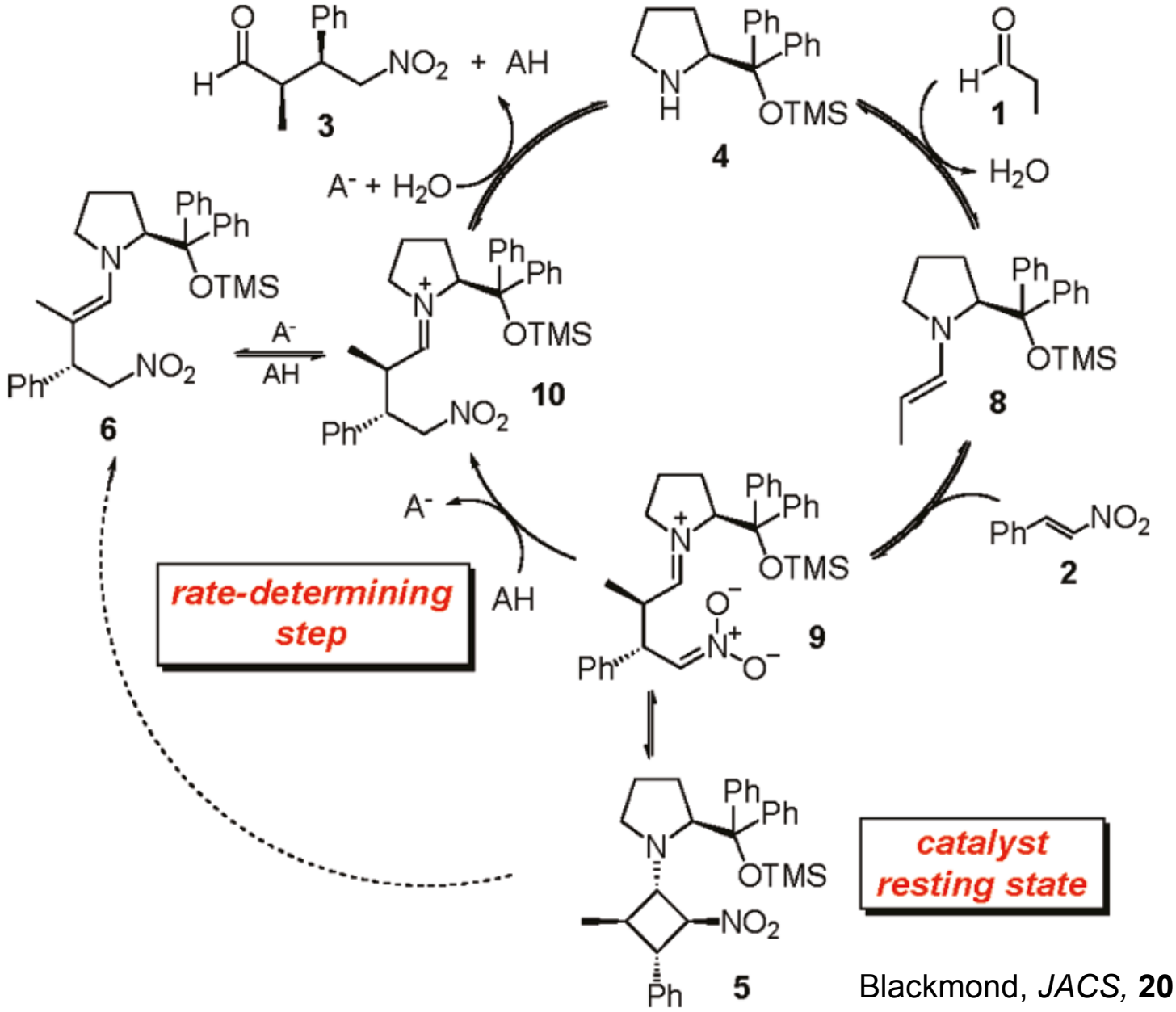




Sequestering the catalyst at cyclobutane 5 has important stereochemical consequences!

Blackmond, *JACS,* **2012,** *133,* 8822.

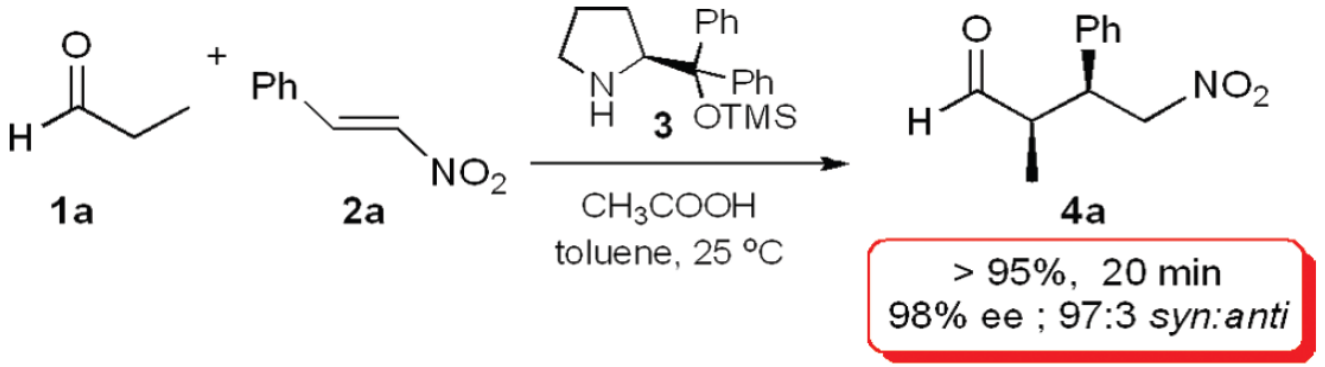
Revised Catalytic Cycle
Blackmond

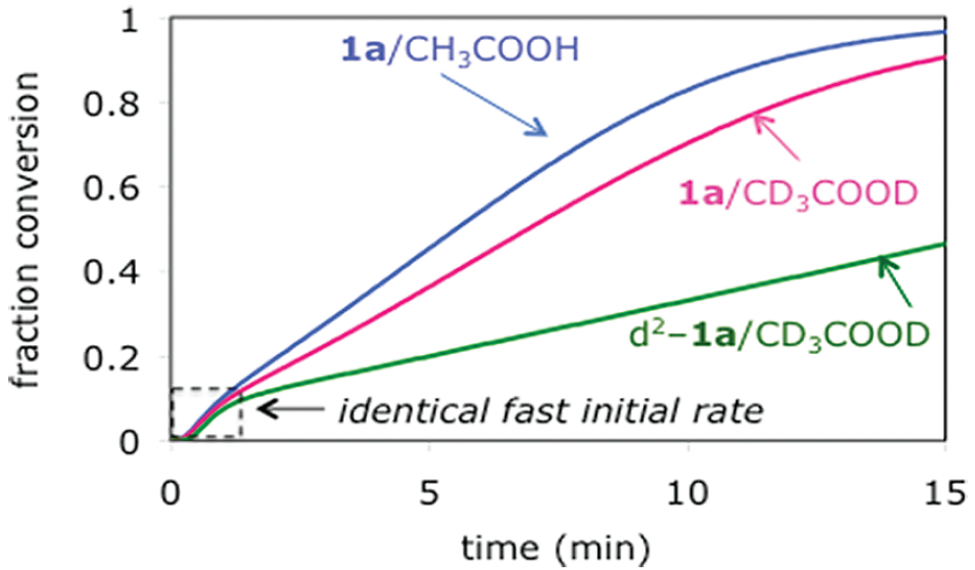


Blackmond, *JACS,* **2012,** *133,* 8822.

Kinetic Isotope Effects Reveal Another Puzzle

- A mechanism known to be accelerated by acid undergoes deprotonation at/before the RDS.

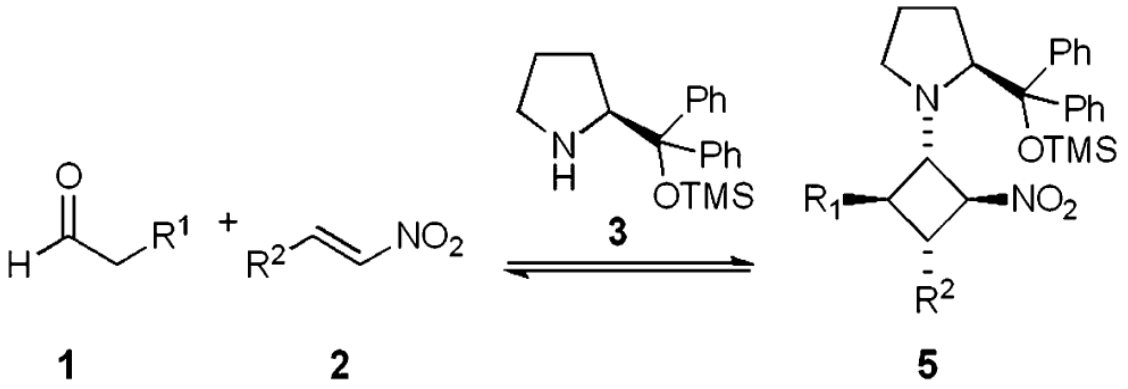




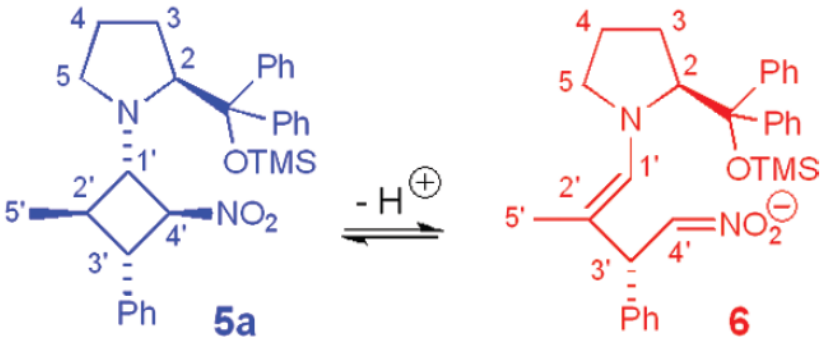
Bures, J. Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134*, 6741

New Intermediate Identified

- Recall

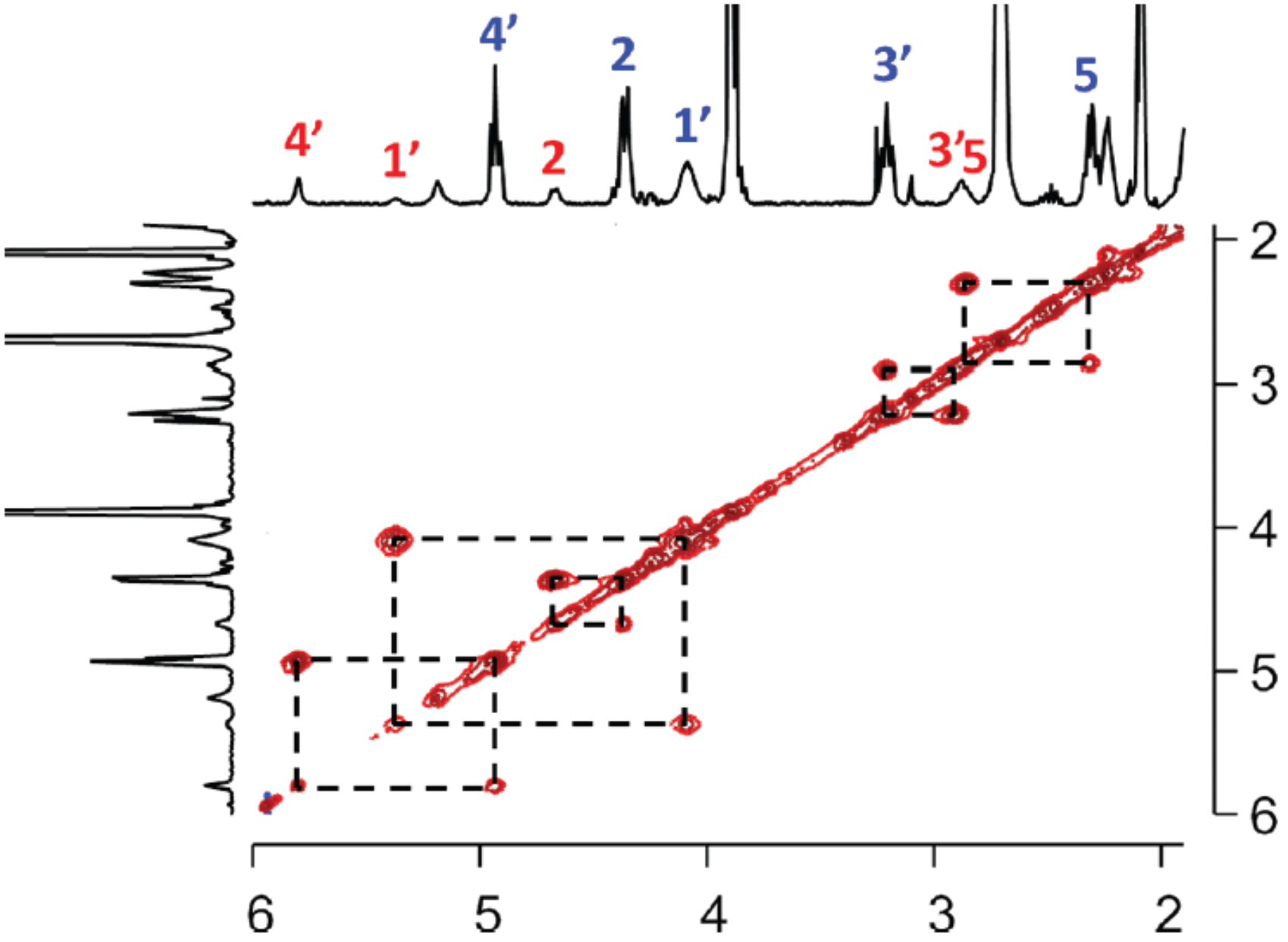


- NMR studies (EXSY) show new species 6

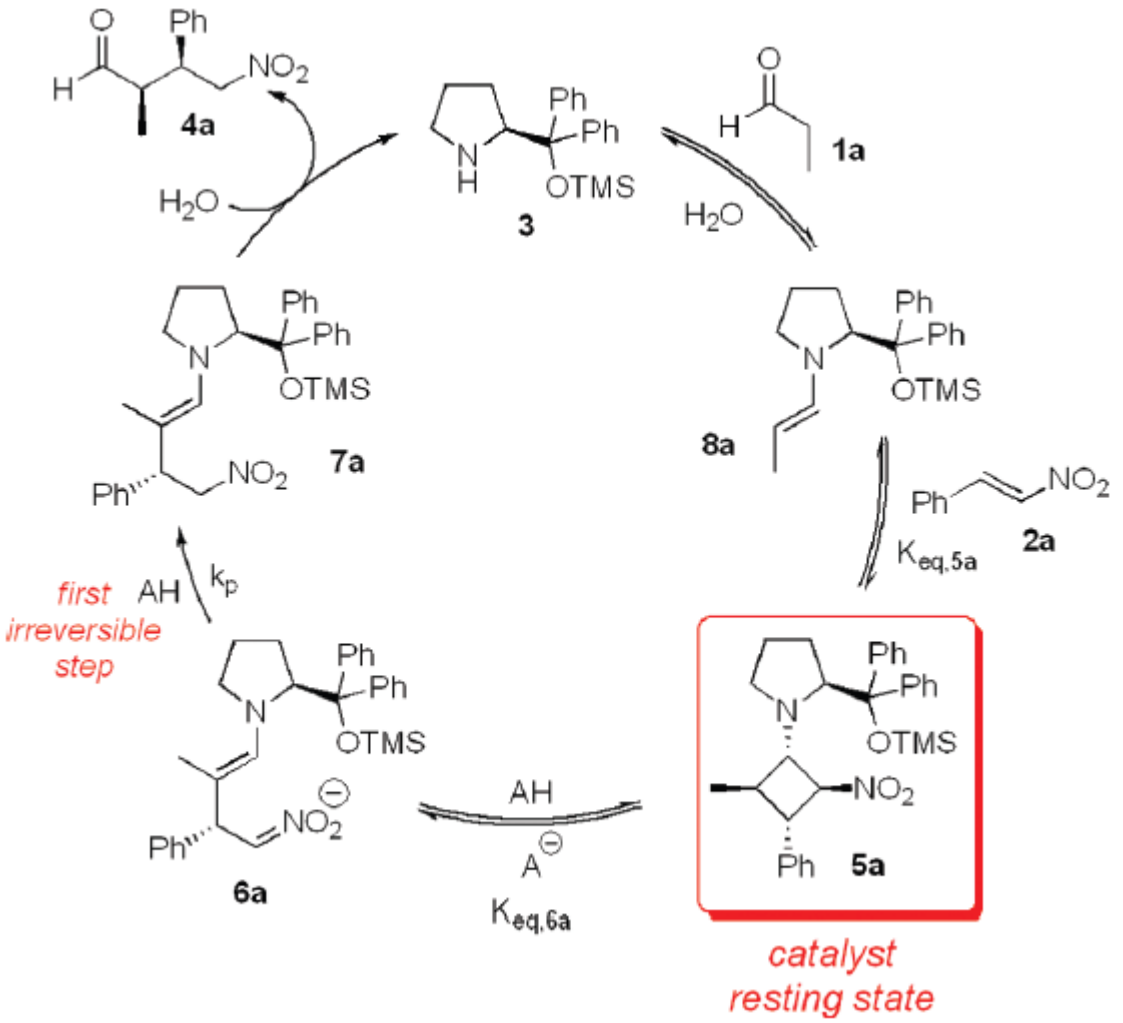


Blackmond, D. *JACS*, **2012**, *134,* 6741

NOESY Spectrum of 5 and 6



New Catalytic Cycle



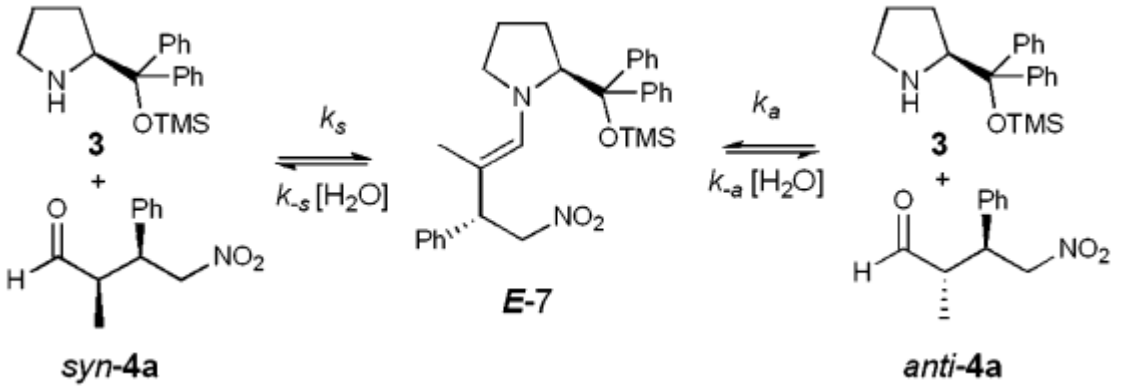
Bures, J. Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

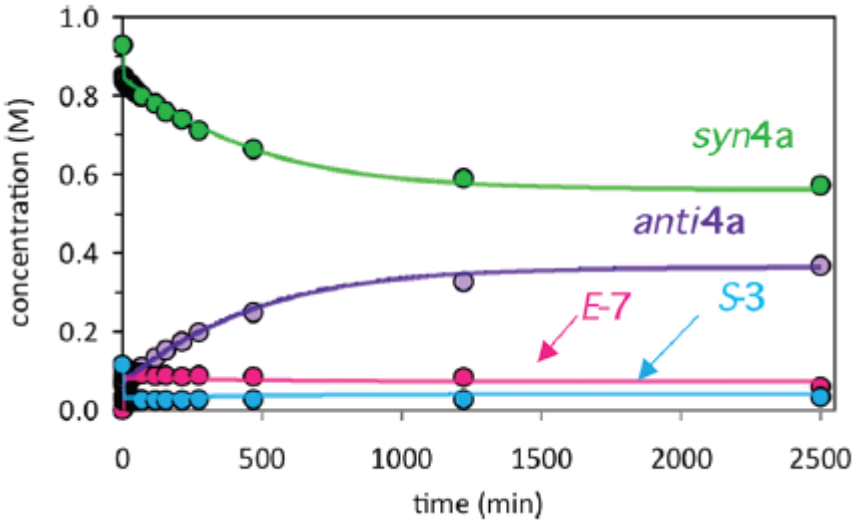
Questions Answered

- Blackmond proposes using this as an on-cycle intermediate based on the discovery of intermediate 6.
- The formation of intermediate 6 rationalizes the KIE observed experimentally, as well as rate decrease for disubstituted aldehydes.
- The slow movement from 5 to 7 yields the same equilibrium and saturation kinetic effects noted by Seebach and Blackmond previously
- Facial selectivity?

Importance of Cyclobutane 5

- The syn/anti product ratio decreases when the product remains in contact with the catalyst after turnover is complete



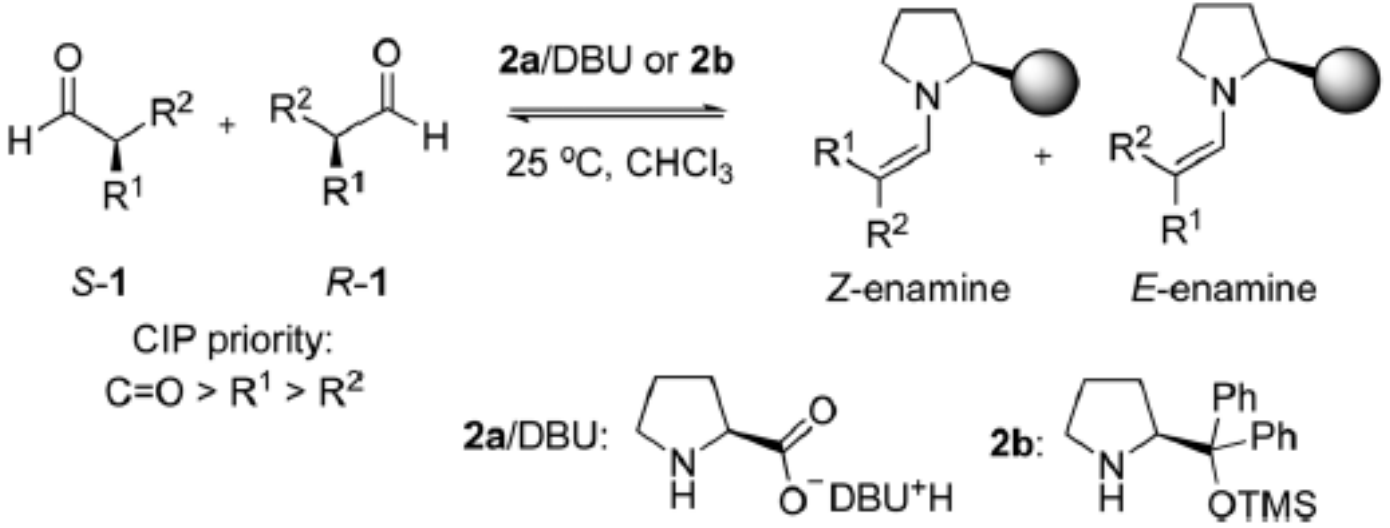


- Cyclobutane 5, instead of being parasitic, acts *on the cycle* to maintain low levels of the catalyst, and thus low levels of E-7 allowing kinetic protonation to override the erosion in d.r.

Bures, J, Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

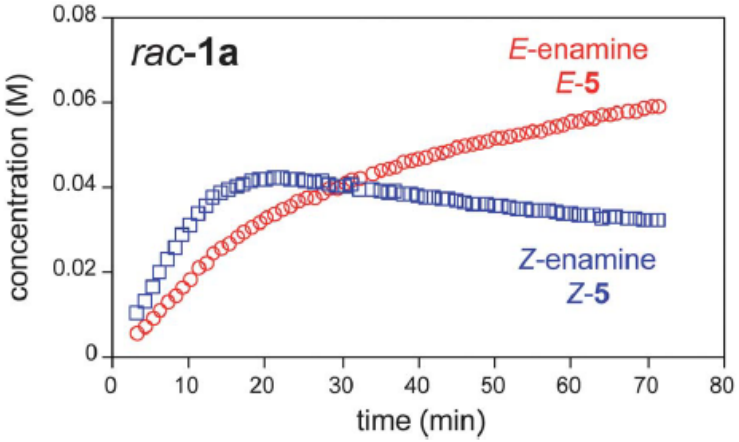
Kinetic Stereospecificity of Enamines

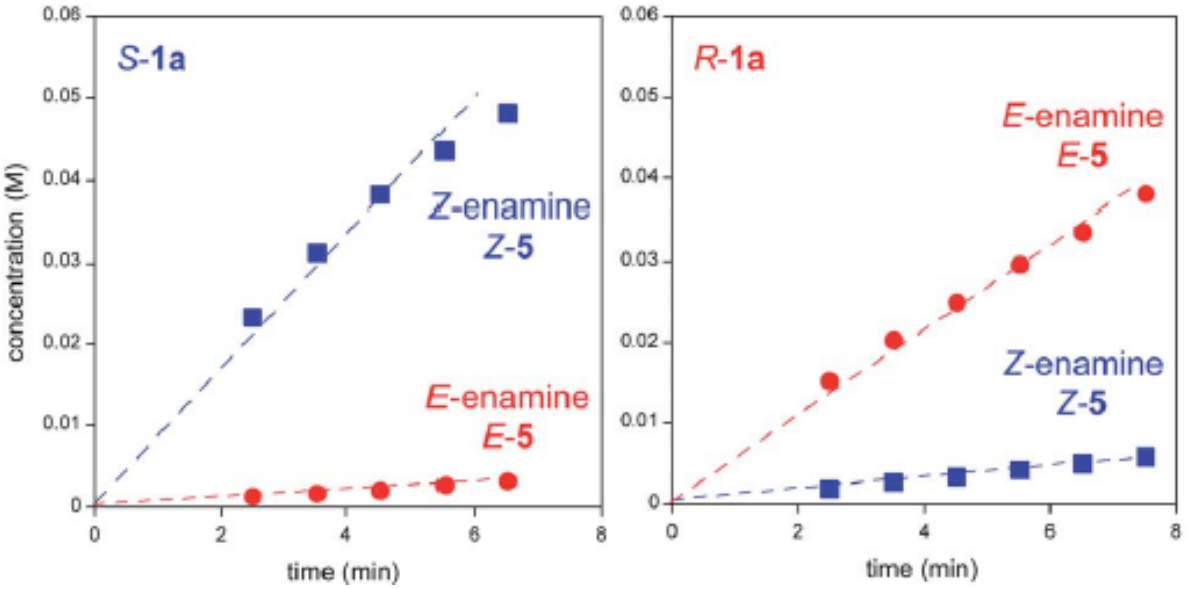
- Blackmond proposes a catalytic cycle that destroys the α-stereocenter of the intermediate.
- How stereospecific are reactions of enamines?

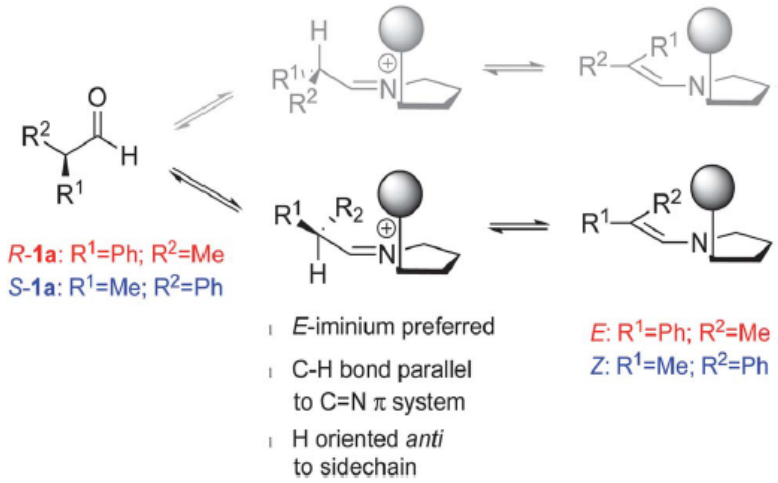


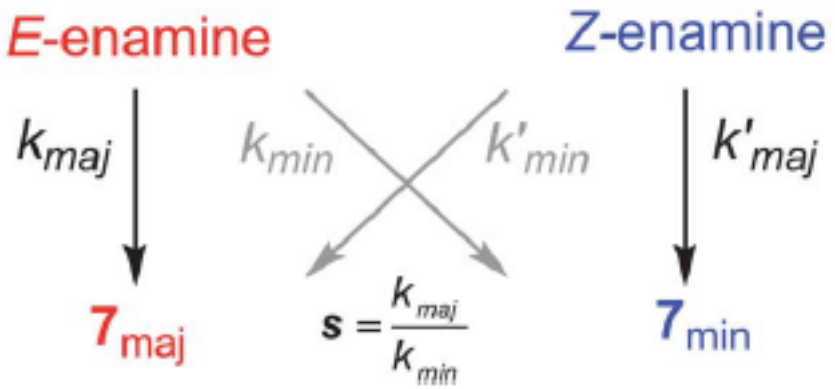
Blackmond, *Chem. Sci.,* **2012,** *3,* 1273.

Kinetic Stereospecificity of Enamines



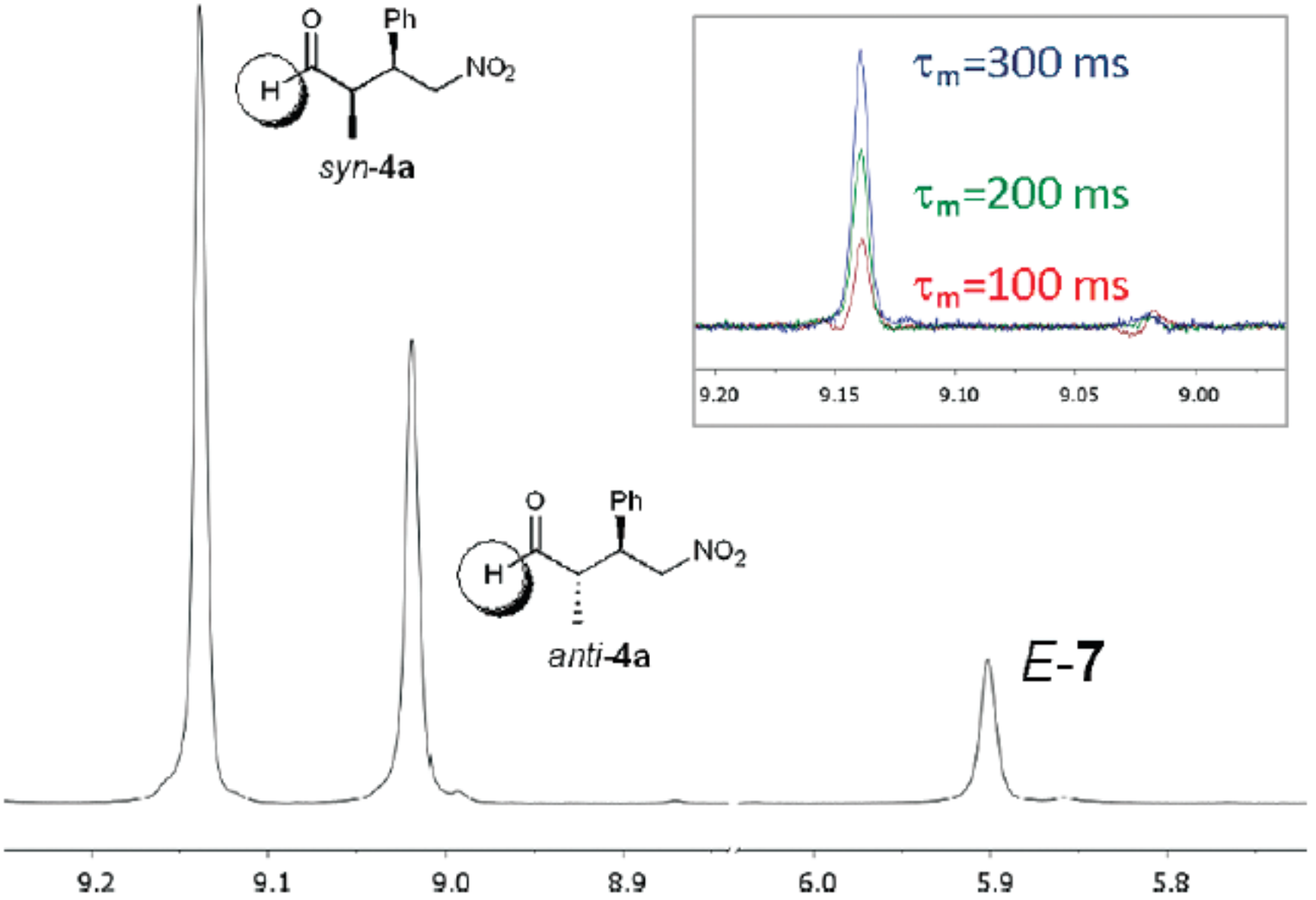






Blackmond, *Chem. Sci.*, **2012,** *3,* 1273.

Stereospecificity of Protonation of Enamine 7

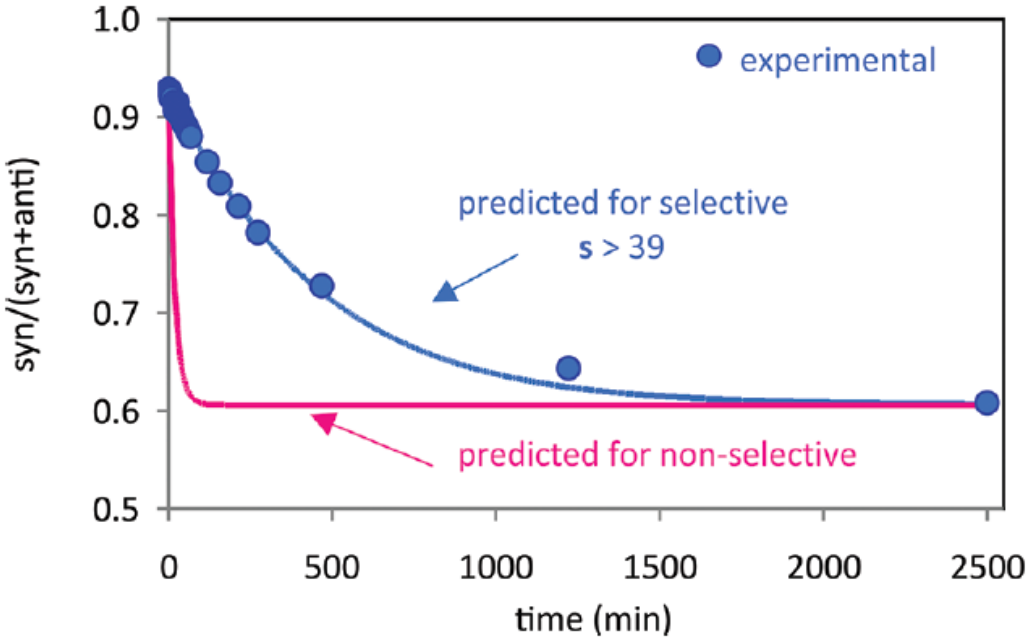


Bures, J. Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

Stereospecificity of Protonation of Enamine 7

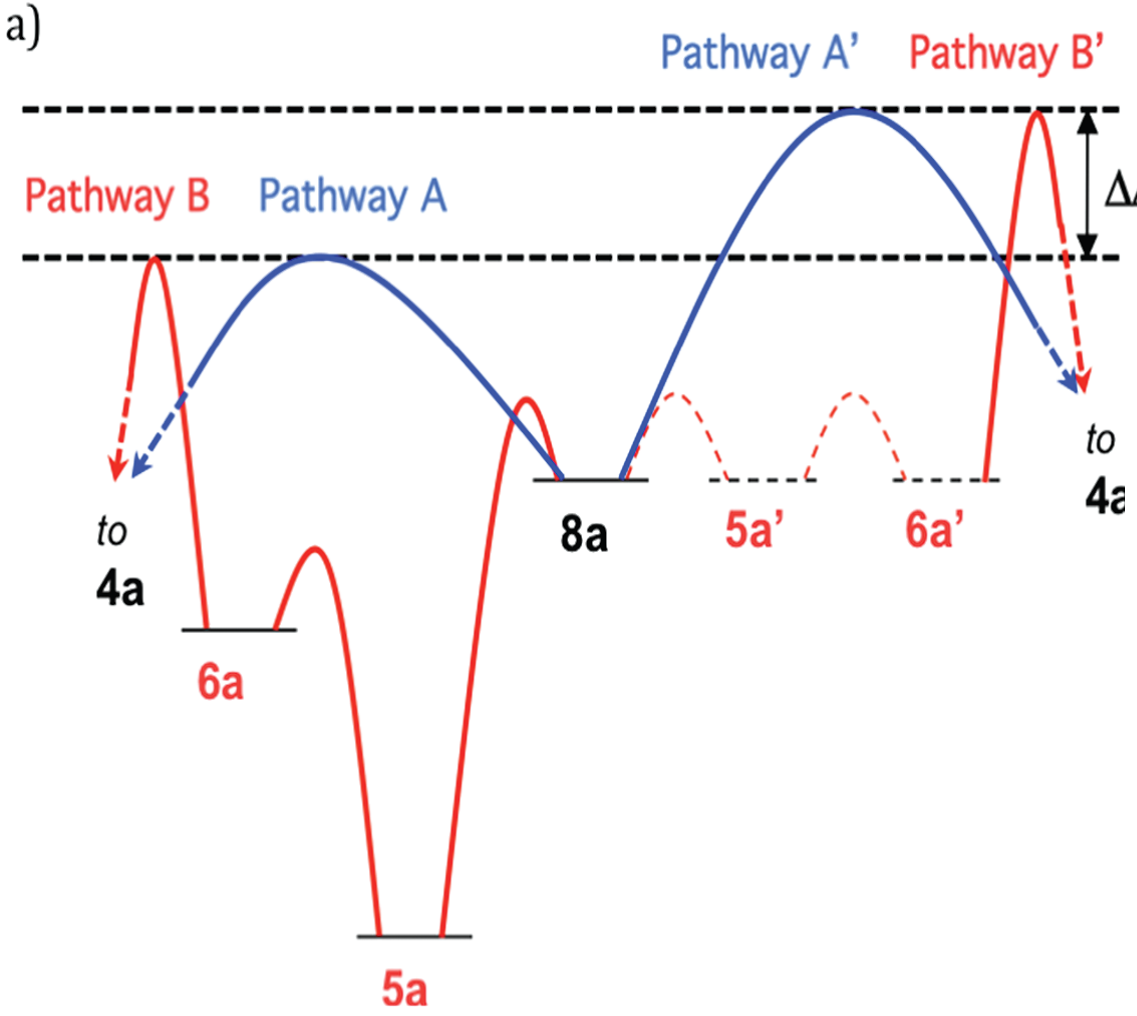
$$K_{eq,S} = \frac{k_s}{k_{-s}[H_2O]} = \frac{[E\text{-}\mathbf{7}]_{eq}}{[syn\text{-}\mathbf{4a}]_{eq}[\mathbf{3}]_{eq}} = 3.2$$

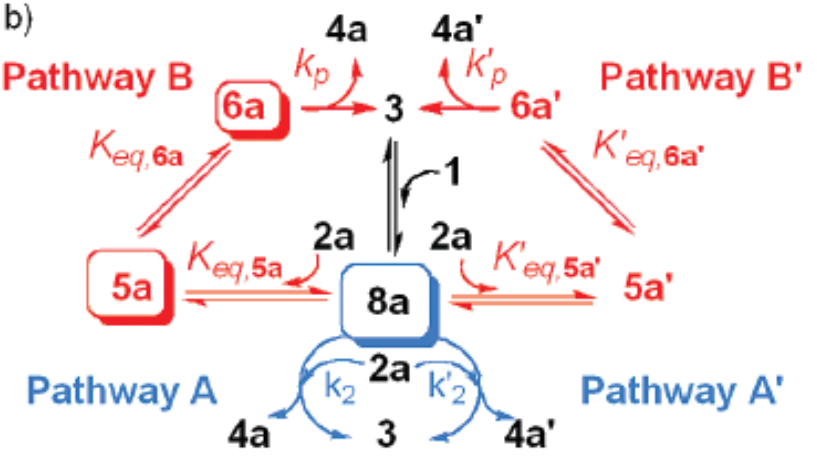
$$K_{eq,A} = \frac{k_a}{k_{-a}[H_2O]} = \frac{[E\text{-}\mathbf{7}]_{eq}}{[anti\text{-}\mathbf{4a}]_{eq}[\mathbf{3}]_{eq}} = 4.9$$



Bures, J. Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

Proposed Curtin-Hammett Scenario





Bures, J. Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

Is This Really Curtin-Hammett?

- “Cases in which the product ratio is controlled *only* by the difference in standard free-energies derived from the respective transition states, and cannot be determined *a priori* solely from knowledge of relative concentrations of intermediate species”
- Yet, Blackmond proposes that the selectivity can be gleaned from the equilibrium constants (which are based on concentration) along with the rate constants.

c) Pathway A :

$$er = \frac{[\mathbf{4a}]}{[\mathbf{4a'}]} = \exp\left(\frac{-\Delta\Delta G^{\mp}}{RT}\right) = \left(\frac{k_2}{k_2'}\right)$$

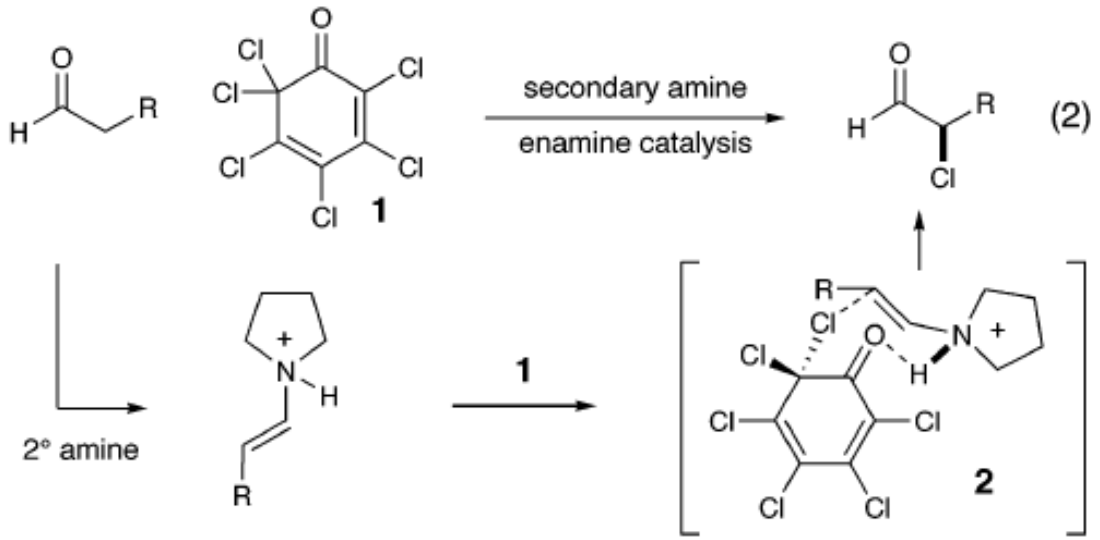
Pathway B :

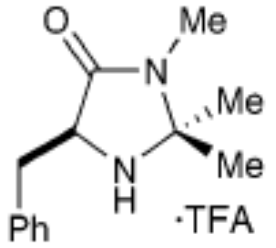
$$er = \frac{[\mathbf{4a}]}{[\mathbf{4a'}]} = \exp\left(\frac{-\Delta\Delta G^{\mp}}{RT}\right) = \left(\frac{k_p}{k_p'}\right) \cdot \left(\frac{K_{eq,\mathbf{5a}}}{K'_{eq,\mathbf{5a'}}}\right) \cdot \left(\frac{K_{eq,\mathbf{6a}}}{K'_{eq,\mathbf{6a'}}}\right)$$

Bures, J. Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

Model II: Part II
α-Chlorination of Aldehydes

- Initially reported by MacMillan, 2004

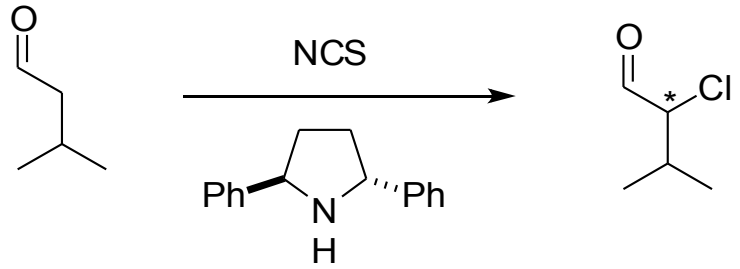




catalyst **3**

9 examples, 80-98% ee
2 examples with 7:1, 24:1 d.r.

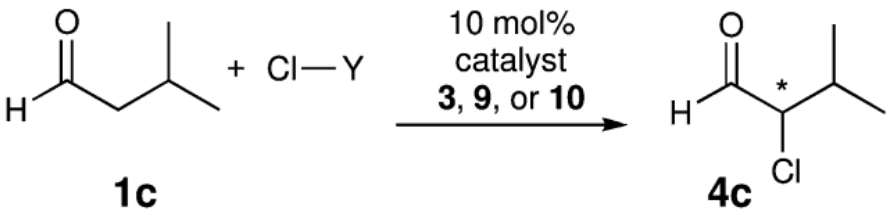
- Jorgensen reports similar system, 2004



MacMillian, *JACS,* **2004,** *126,* 4108.
Jorgensen, *JACS,* **2004,** *126,* 4790.

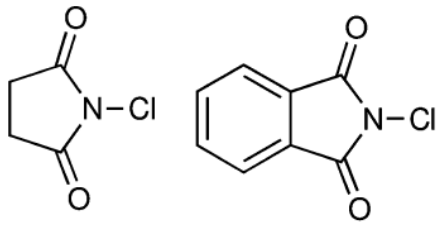
Kinetics of α-Chlorination of Aldehydes

- Blackmond determines existance of a resting state, similar to conjugate addition



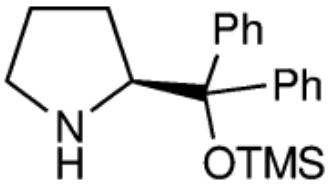
1c **4c**

Cl—Y =

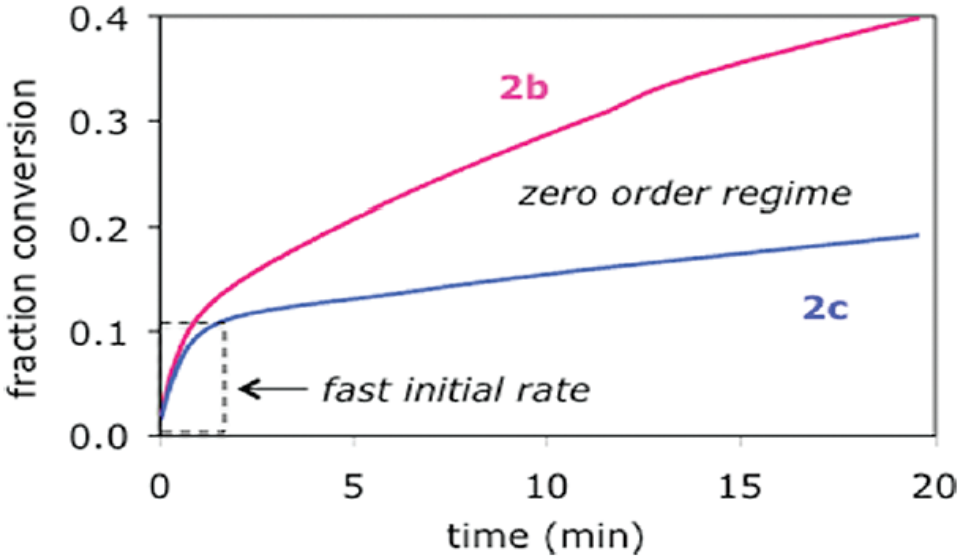


2b **2c**

catalyst =



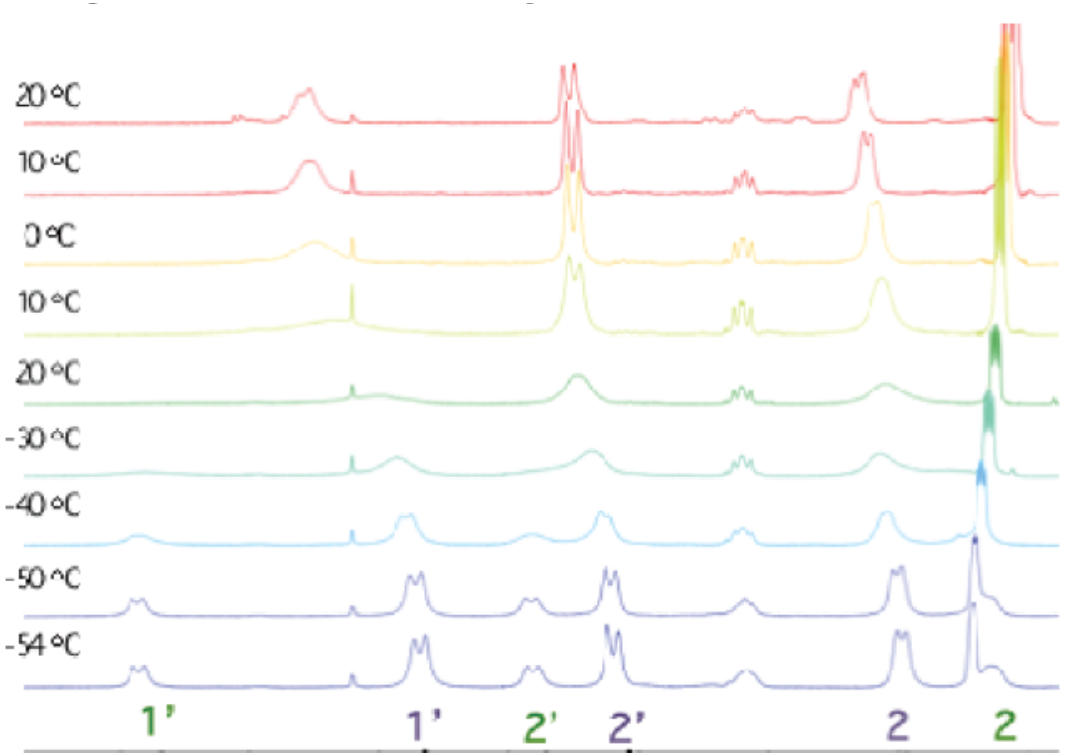
3



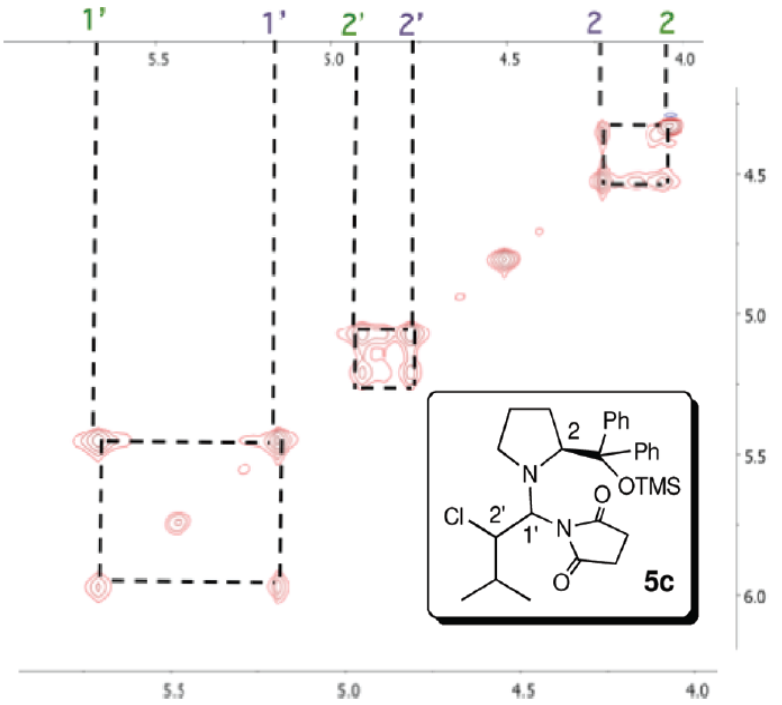
Bures, J, Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

NMR Studies Identify Resting State

- VT-NMR + EXSY allow for connectivity to be determined
- Species that exists as interconverting diastereomers in the resting state of the catalyst!

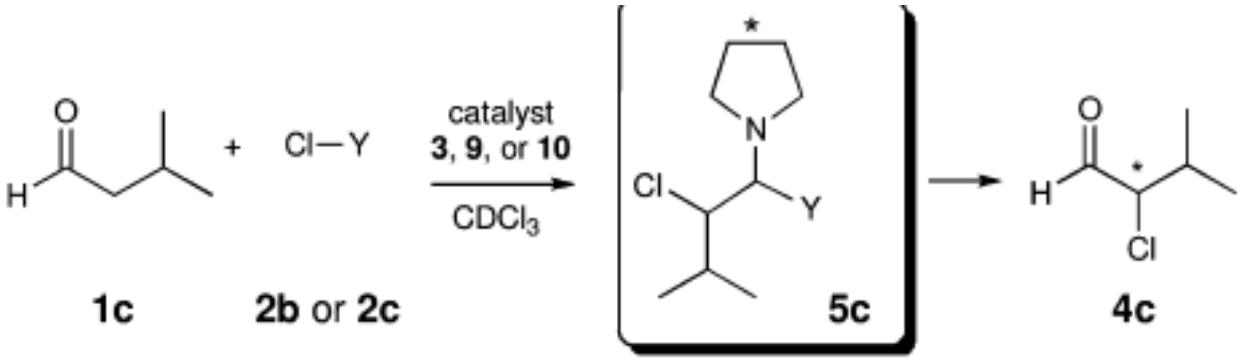


rved.



Bures, J, Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

An Interesting Correlation

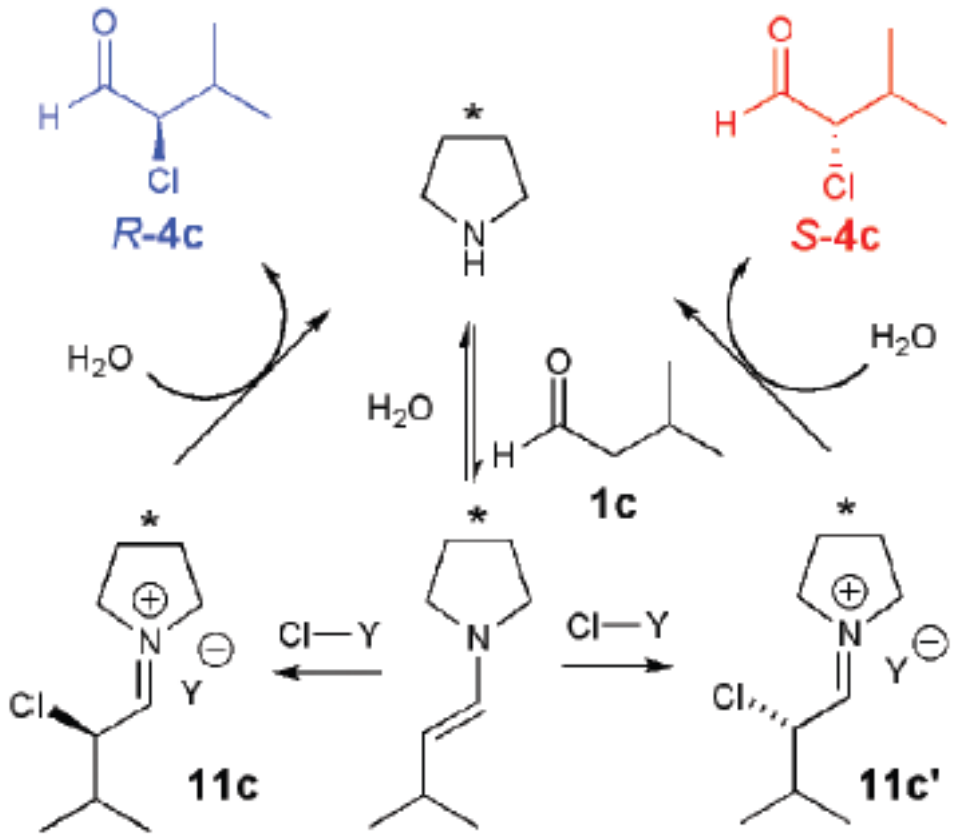


1c **2b** or **2c** **5c** **4c**

entry	catalyst	Cl—Y	dr[a] 5c:5c′ (K_{eq}^{dias})	er[b] *R*-4c:*S*-4c
1	**3**	**2b**	30:70	29:71
2	**9**	**2b**	16:84	16:84
3	**10**	**2b**	<5:95[c]	3:97[d]
4	**3**	**2c**	26:74	23:77
5	**9**	**2c**	21:79	21:79[e]
6	**10**	**2c**	<5:95[c]	3:97[d]

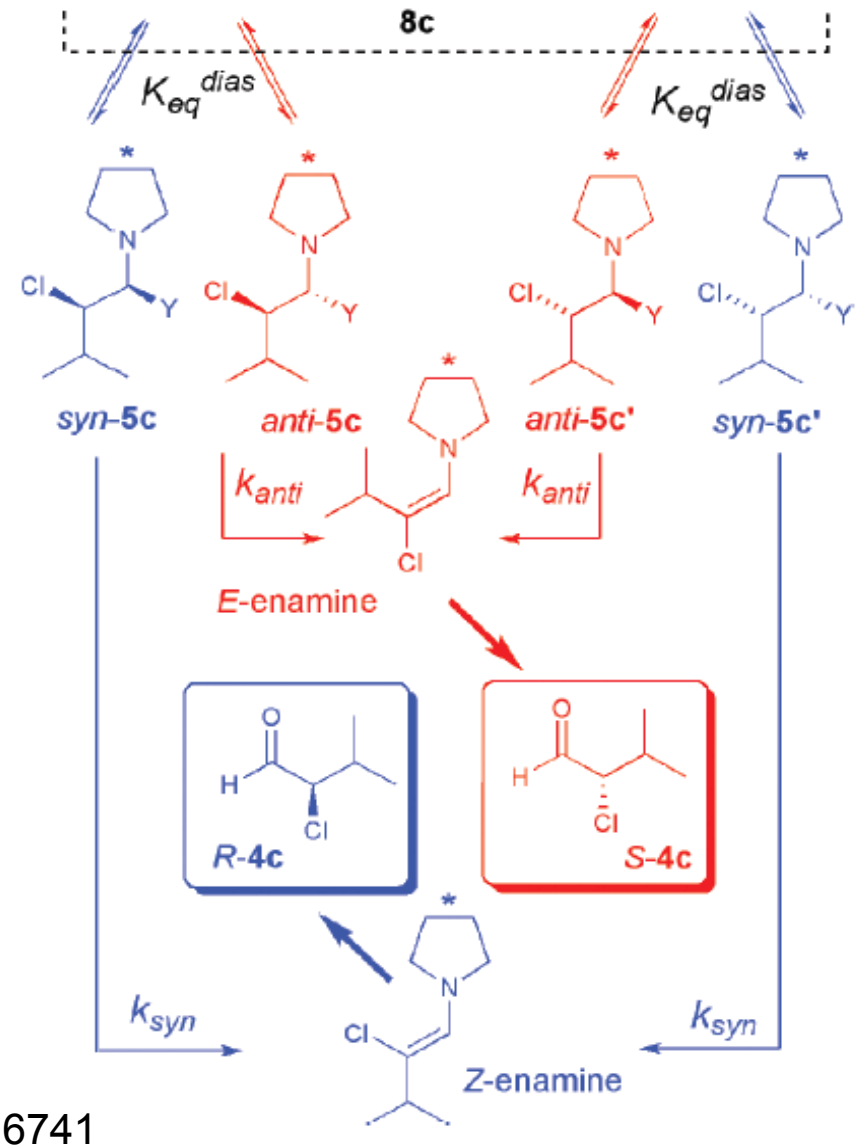
Bures, J, Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

Conventional Catalytic Cycle



Bures, J, Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

Proposed Addition to the Cycle



Blackmond, D. *JACS*, **2012**, *134,* 6741

Further Evidence Supporting the Proposed Cycle

- NMR observations only show two out of four possible diastereomers, indicating near-perfect facial selectivity in the addition of chlorine to the enamine
- Observation of non-perfect er in a reaction following the conventional route should show all four diastereomers, which is not observed.
- Thus, as non-perfect er is observed, there must be equilibration between diastereomeric species of a single type of facial addition

Bures, J, Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

Kinetic Consequences

- Enantioselectivity can be calculated if certain kinetic values can be determined.

$$er = \frac{[R-\mathbf{4c}]}{[S-\mathbf{4c}]} = \frac{k_{syn}}{k_{anti}} \cdot \frac{[syn-\mathbf{5c}]}{[anti-\mathbf{5c}]} = \frac{k_{syn}}{k_{anti}} \cdot K_{eq}^{dias}$$

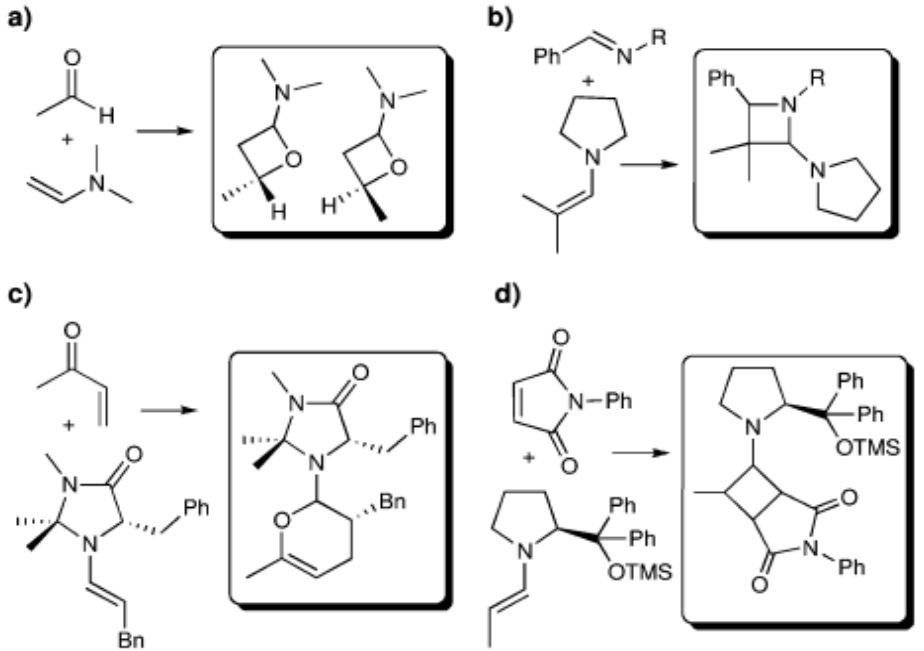
or

$$er = \frac{[R-\mathbf{4c}]}{[S-\mathbf{4c}]} = \frac{k_{syn}}{k_{anti}} \cdot \frac{[syn-\mathbf{5c'}]}{[anti-\mathbf{5c'}]} = \frac{k_{syn}}{k_{anti}} \cdot K_{eq}^{dias}$$

Bures, J, Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

Generality of Curtin-Hammett Paradigm in Organocatalysis of Enamines

- Many organocatalytic cycles may contain equilibrating intermediate species downstream from the original stereodetermining step
- Intermediates have already been calculated/observed in many systems



Bures, J, Armstrong, A., and Blackmond, D. *JACS*, **2012**, *134,* 6741

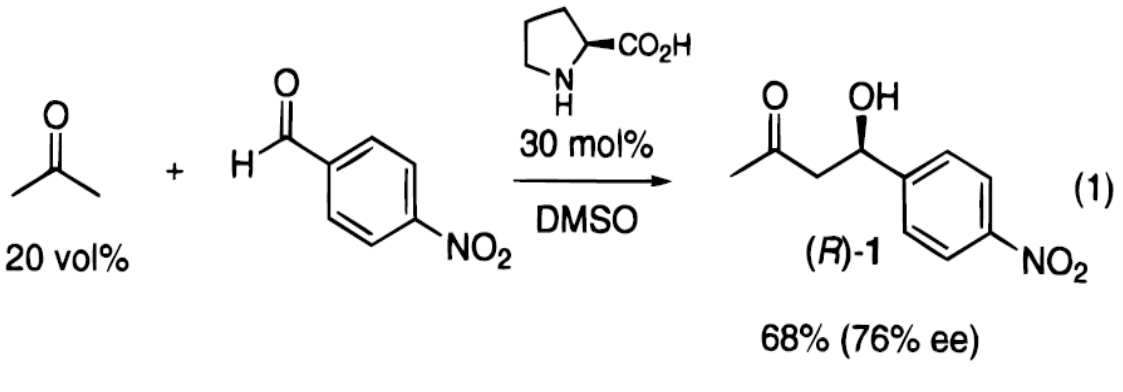
Conclusions

- While simple mechanisms may seem decent on paper, much work must be done to elucidate what's actually going on.
- Conjugate addition of aldehydes to nitroalkenes may involve stereodeterming steps subsequent to the initial stereodetermining steps, resulting in a possible Curtin-Hammett situation.
- Similarly, α-chlorination of aldehydes, the stereoselectivity arises from a set of equilibrating diastereomers subsequent to the initial stereodetermining step.
- Can this really be labeled as a Curtin-Hammett paradigm? It doesn't seem clear yet.

Thanks!

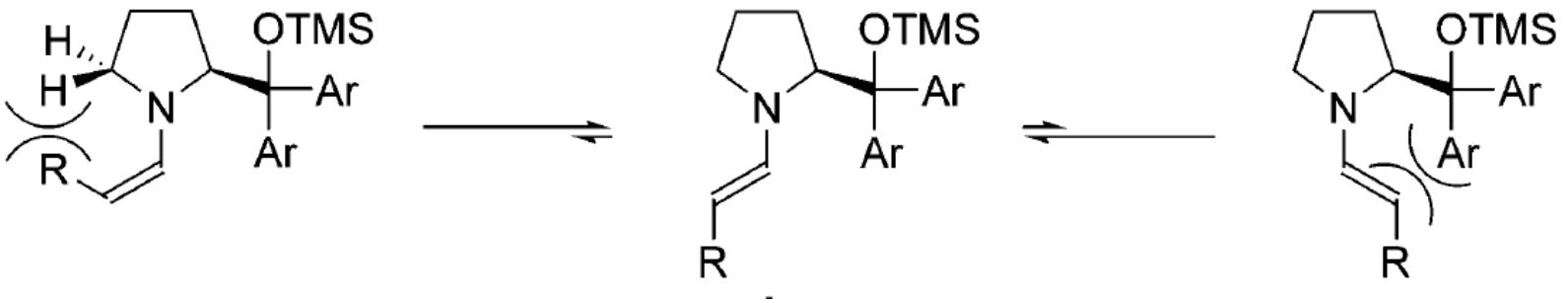
Proline Makes a Comeback

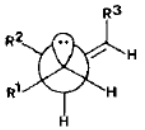
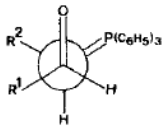
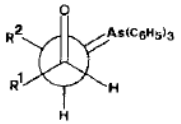
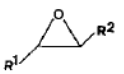
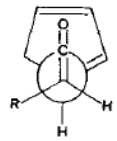
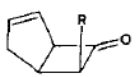
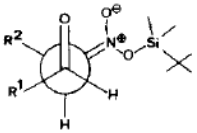
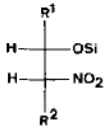
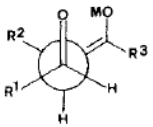
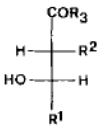
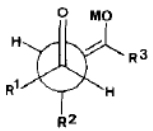
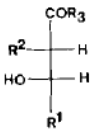
- In 2000, List, Lerner and Barbas generalize proline to the intermolecular direct asymmetric aldol reaction

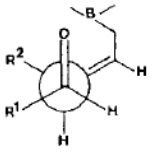
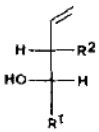
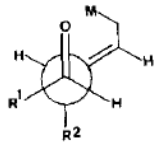
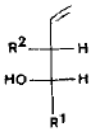
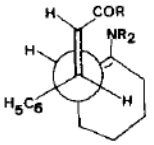
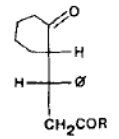
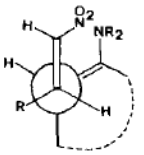
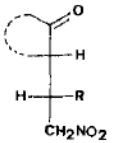
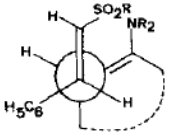
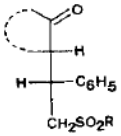


- Variety of aryl aldehydes, 54-94% yield, 60-77% ee
- Best example: isopropyl aldehyde, 97% yield, 96% ee

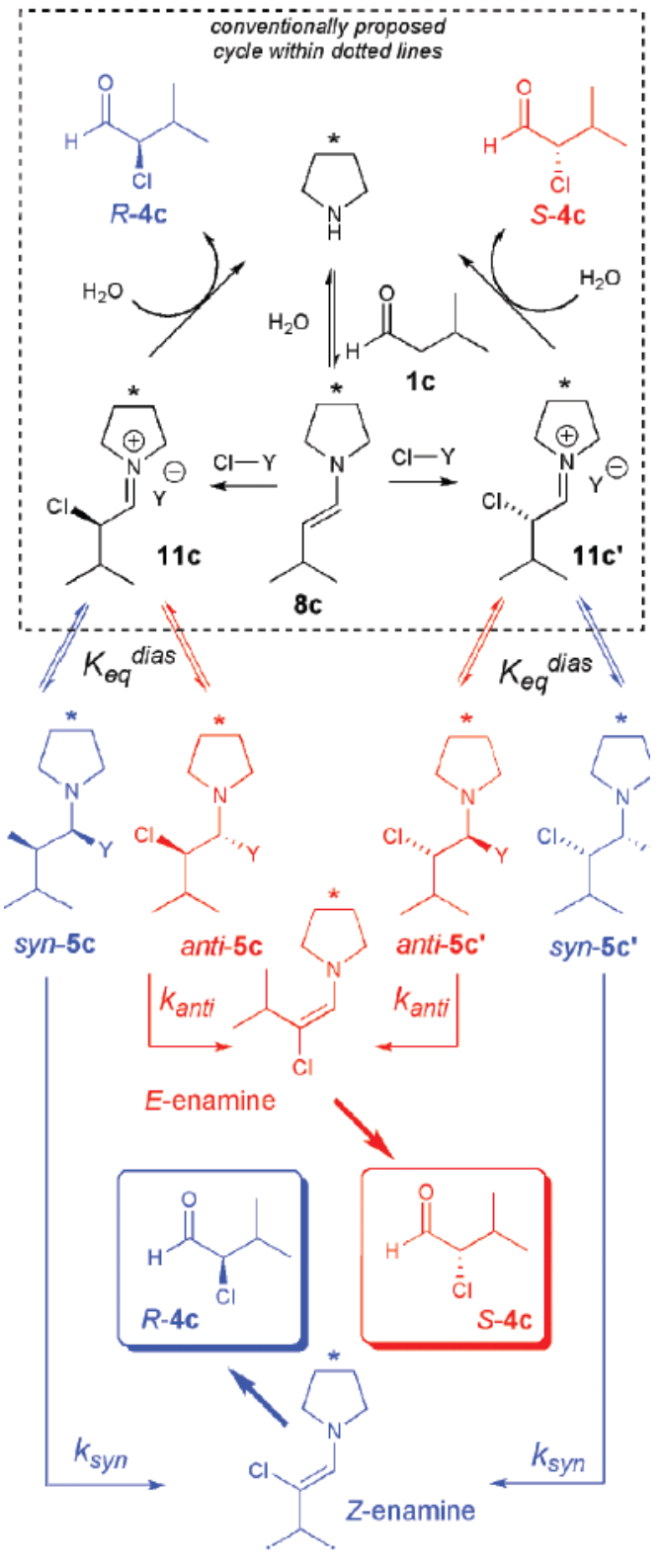
Geometry Of Enamine



Entry	Starting materials	Topology	Products	Selectivity up to
1	Mono- or (Z)-disubstituted olefin + carbene precursor[b])		 *cis*-Substituted cyclopropanes	> 95%
2	Alkylidentriphenyl-phosphane[c]) + aldehyde		 (Z)-Olefins	> 98%
3	Alkylidentriphenyl-arsane[c]) + aldehyde		 *trans*-Dialkyl-oxiranes	> 98%
4	Ketenes + cyclo-pentadiene		 *endo*-Substituted bicyclo-[3.2.0]-heptenones	98%
5	(*E*)-Silylnitronates + aldehydes		 *O*-Silylated *erythro*-nitroaldols	> 97%
6	*syn*-Li- and -B-enolates of ketones, esters, and amides[d])[e]) + aldehydes		 *threo*-Aldol adducts	> 98%
7	*anti*-Li- and -B-enolates of ketones, and esters[d])[e]) + aldehydes		 *erythro*-Aldol adducts	> 95%

Entry	Starting materials	Topology	Products	Selectivity up to
3	(Z)-Allyboranes[d])[f]) + aldehydes		 *threo*-Homo-allylic alcohols	> 95%
)	(*E*)-Alkylborane- or (*E*)-allylchromium derivatives[d]) + aldehydes		 *erythro*-Homo-allylic alcohols	99%
)	Enamine from cyclo-hexanone + cinnamic aldehyde or chalcone		 (*RS; SR*)-Dicarbonyl derivative	> 90%
)	(*E*)-Enamines + (*E*)-nitroolefins		 (*RS; SR*)- or (*RR; SS*)-Nitroketones[a])	99%
)	Enamines from cyclo-alkanones + styryl sulfone		 (*RS; SR*)-Ketosulfone	> 90%

- Proposed Catalytic Cycle
- Blackmond proposes that this leads to another Curtin-Hammett situation



Blackmond, D. *JACS*, **2012**, *134,* 6741