Double And Triple Organocatalytic Cascades Towards Complex Organic Scaffolds

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Outline

- Introduction

  - ✓ Brief History of Organocatalysis
  - ✓ Different Kinds of Organocatalysts
  - ✓ Industrial Application of Organocatalysis
  - ✓ Advantages of Organocatalysis

- Different Scaffolds

  - ✓ Mechanism
  - ✓ Stereochemical Rationale
  - ✓ Substrate Scope
  - ✓ Application

Asymmetric Catalysis

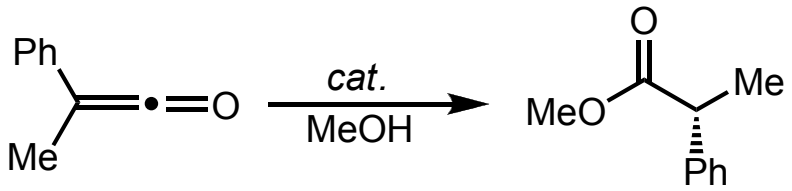
Biocatalysis

Metal Catalysis

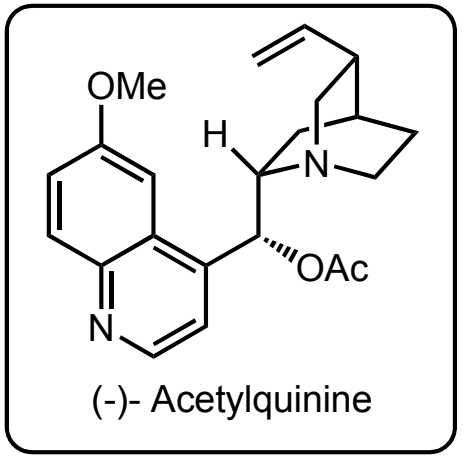
Organocatalysis

History of Organocatalysis

Ostwald introduced
"Organic catalysts"



90%, 74% *ee*

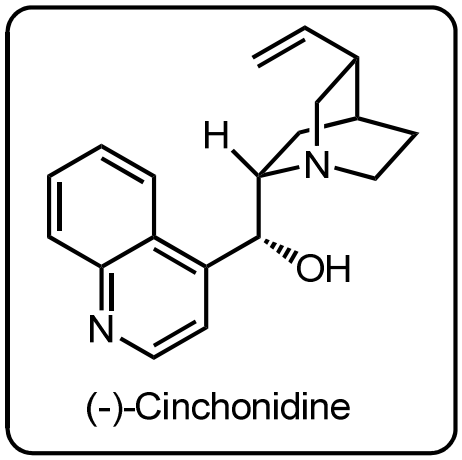


(-)- Acetylquinine

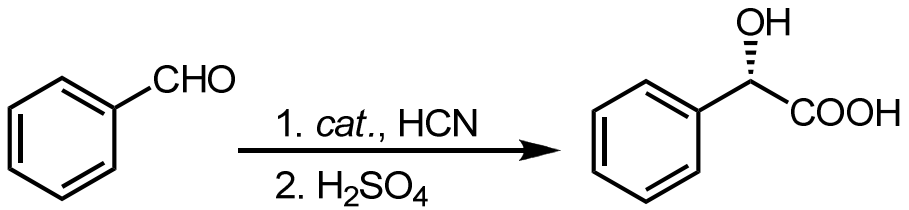
1900

1912

1960



(-)-Cinchonidine



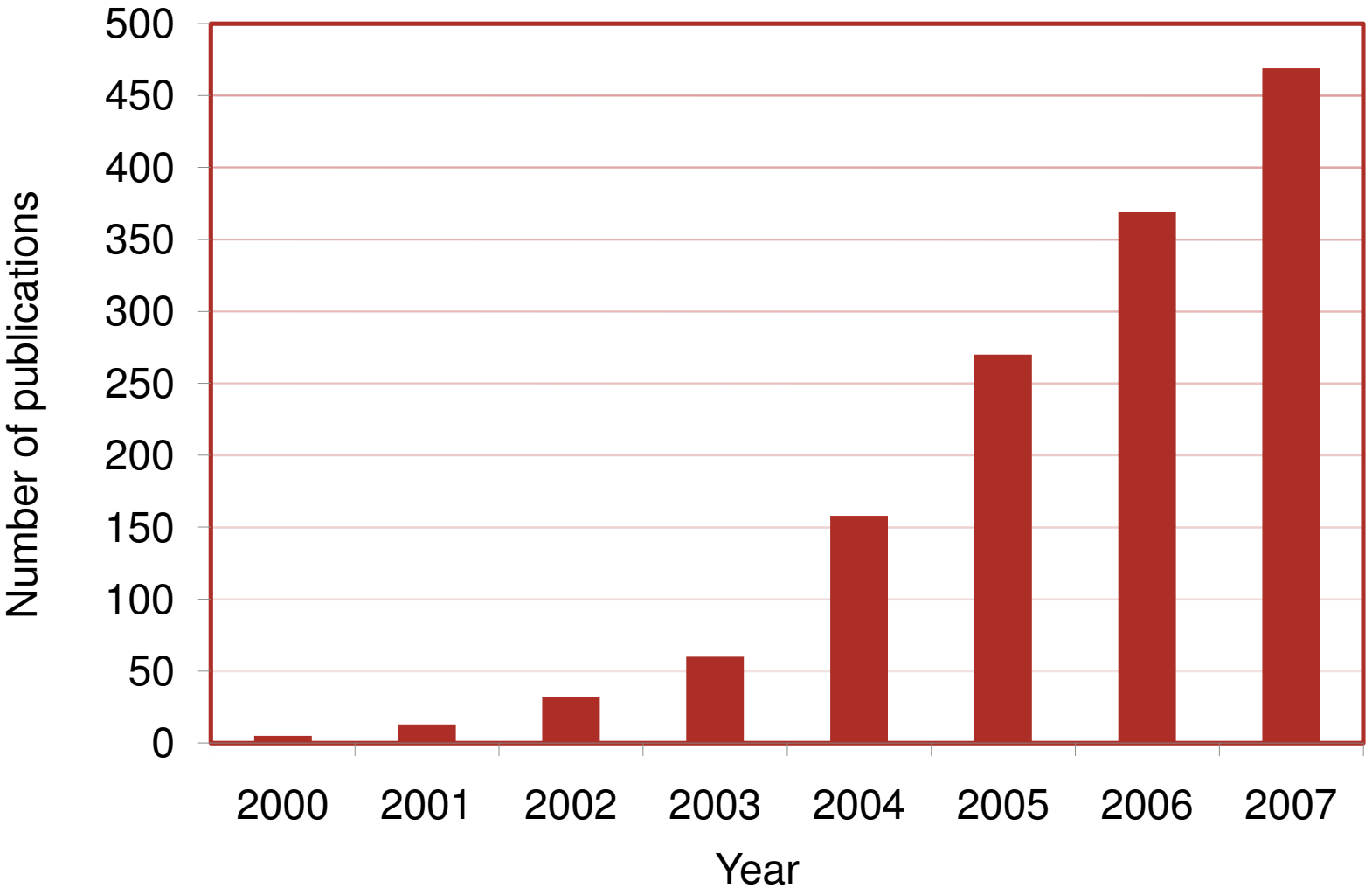
8.7%, 8.9 % *ee*

Ostwald, W. *Z. Phys. Chem.* **1900**, *32* , 509

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

Bredig, G.; Fiske, P. S. *Biochem. Z.* **1912**, *46*, 7

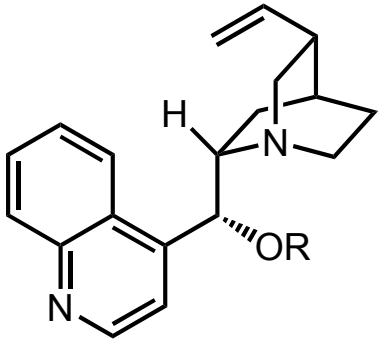
Number of Publications in Organocatalysis



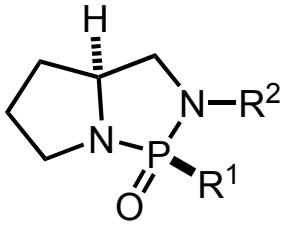
Key words: Organocatalyst, Organocatalysis, Organocatalytic

Sci-Finder

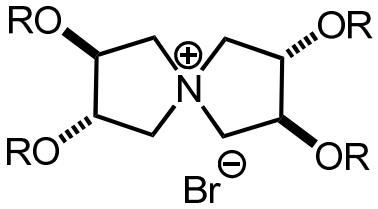
Different Kinds of Organocatalysts



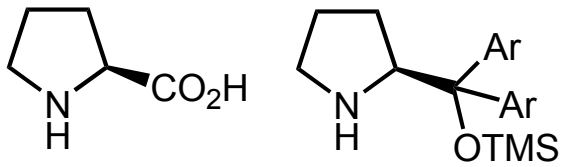
Cinchona Alkaloids

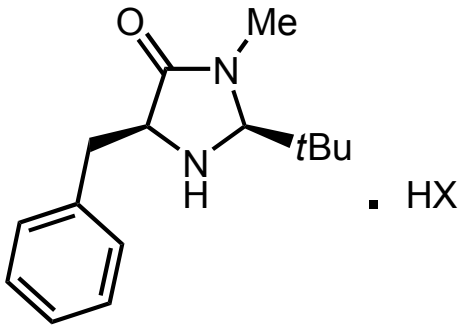


Phosphoramides

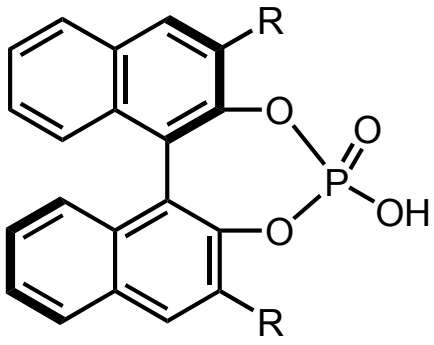


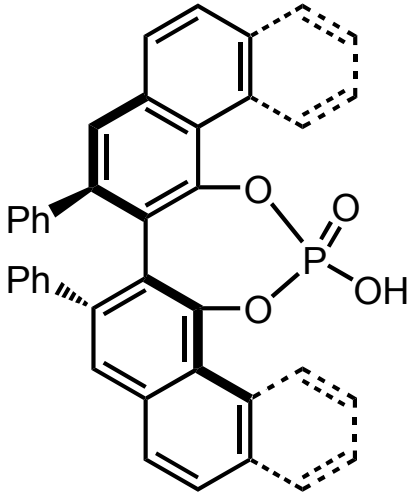
Phase transter catalysts



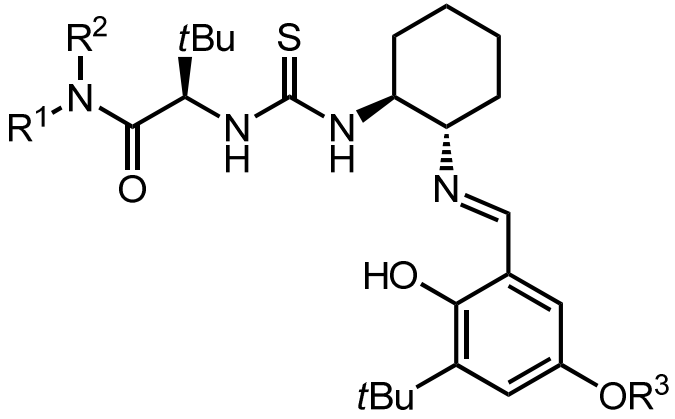


Amines



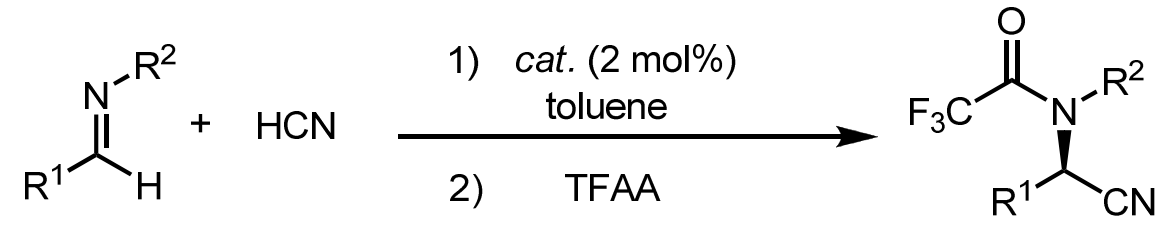


Chiral Bronsted Acids

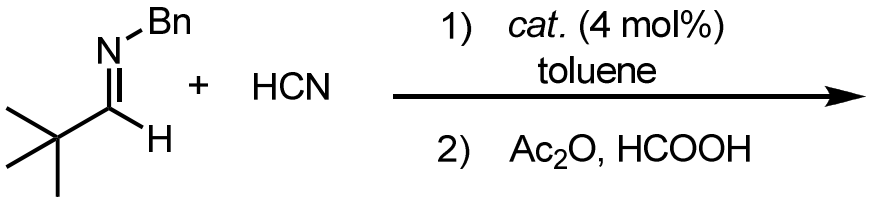


Thioureas

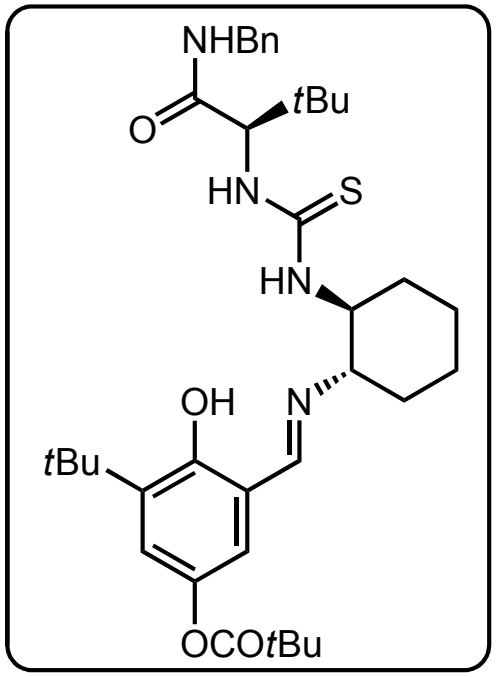
Industrial Appplication of Organocatalysis



85-99% yield
70-99% *ee*

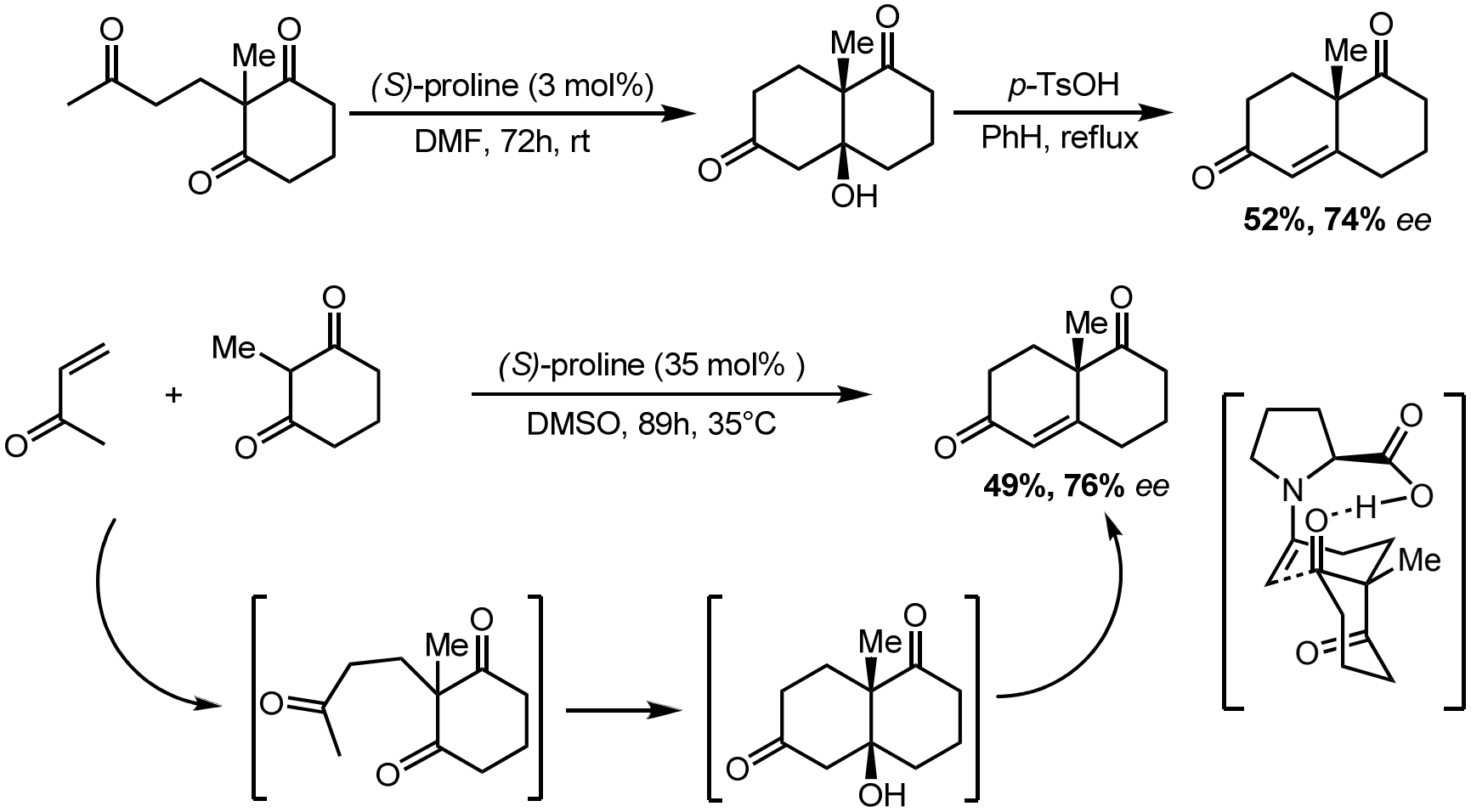


10 cycles of the catalyst
97-98% yield/cycle
92-93% ee/cycle



Jacobsen, E. N.; Vachal, P. *J. Am. Chem. Soc.* **2002**, *124*,10012
http://www.rhodiachirex.com/techpages/amino_acid_technology.htm

Asymmetric Organocatalytic Domino Reactions: Beginning of A New Era

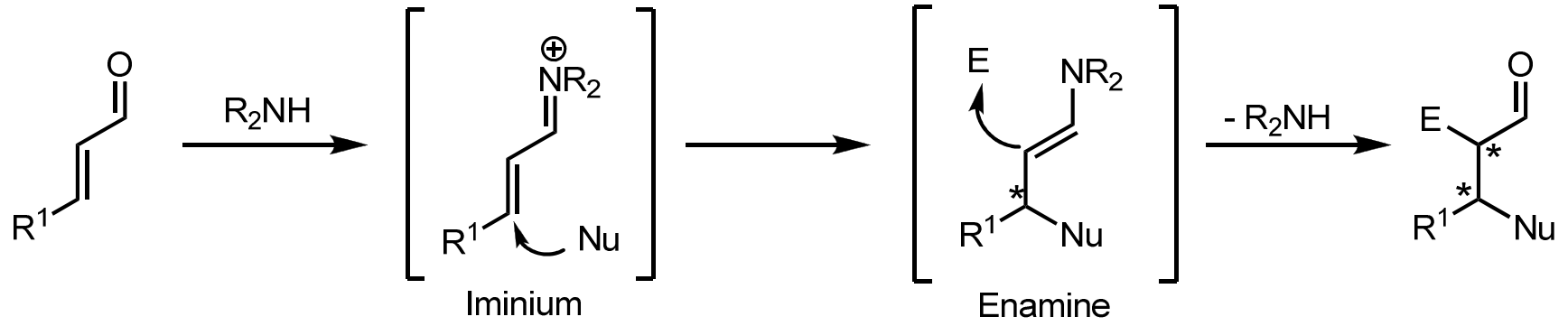


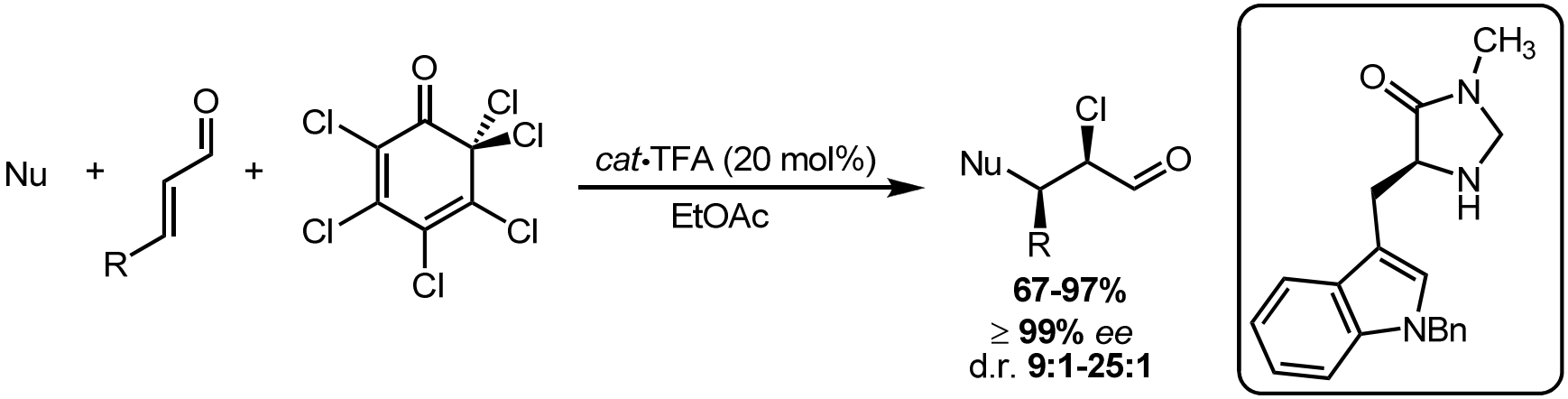
Weichert, R.; Sauer, G.; Eder, U. *Angew. Chem. Int. Ed.* **1971**,*10*, 496

Weichert, R.; Sauer, G.; Eder, U. German Patent DE 2014757

Barbas, C. F.; Bui, T. *Tetrahedron Lett.* **2000**, *41,* 6951

Enantioselective Organo-Cascade Catalysis



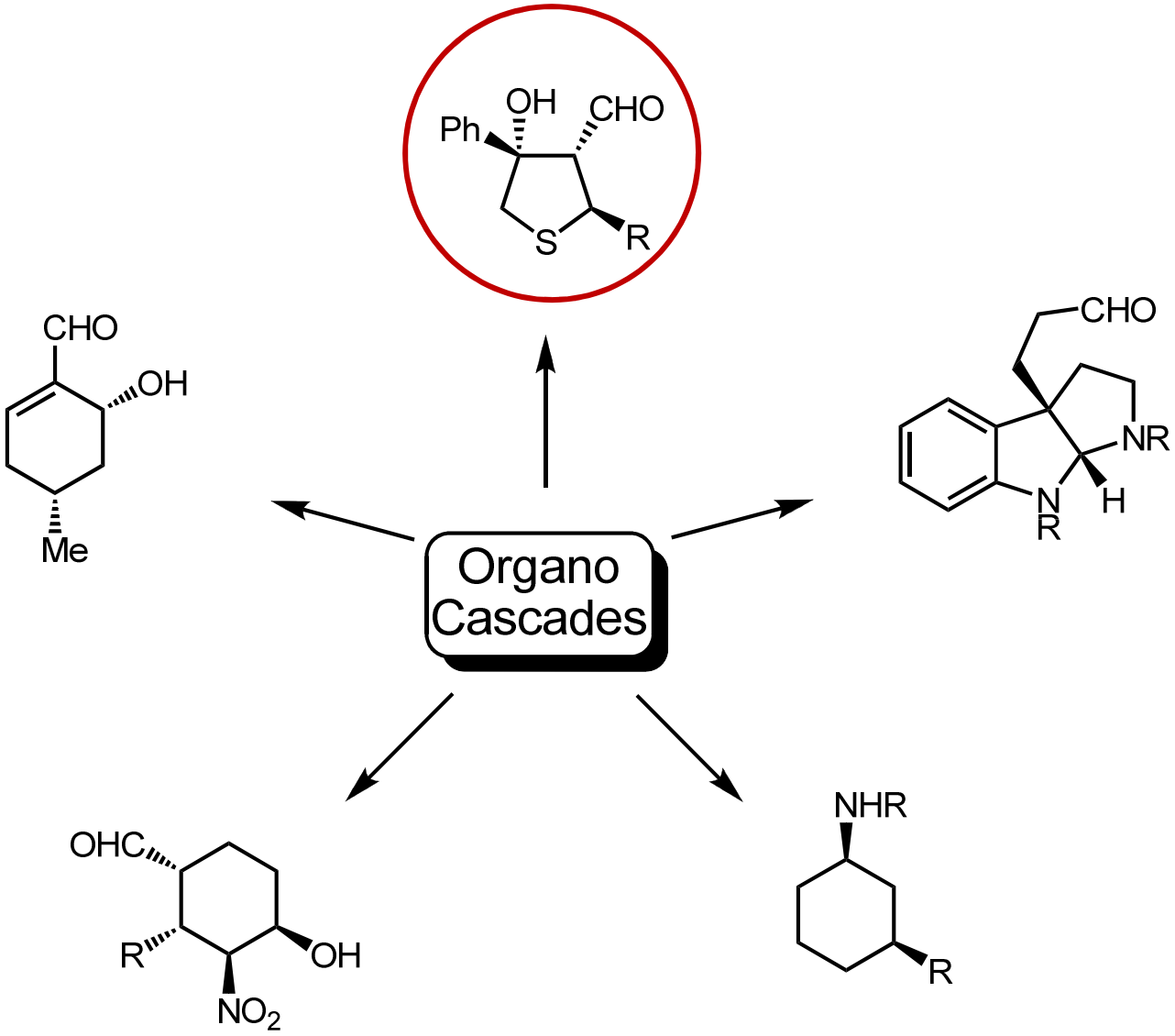


MacMillan, D. W. C.; Huang, Y.; Walji, A. M.; Larsen, C. H. *J. Am. Chem. Soc.* **2005**, *127*, 15051

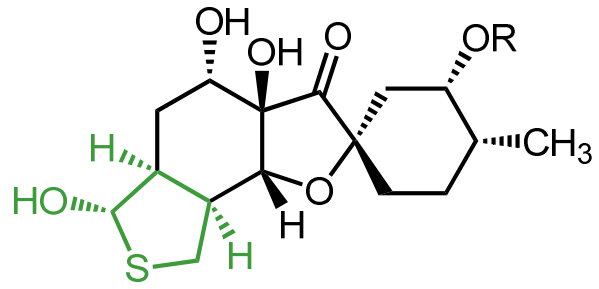
Advantages of Organocatalytic Domino Reactions

- Small chiral organic molecules act as catalytic species.
- Metal-free, relatively nontoxic, air stable and readily available.
- Capability of promoting several types of reactions through different activation modes.
- Avoids
  - time-consuming and costly protection/ deprotection processes.
  - purification of intermediates.
- Excellent stereoselectivities.
- High catalyst loading e.g. 10-20 mol%.

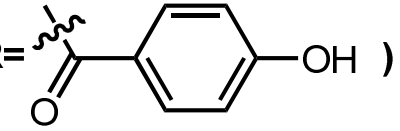
Different Scaffolds

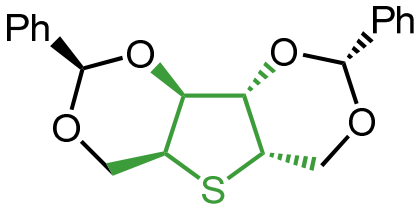


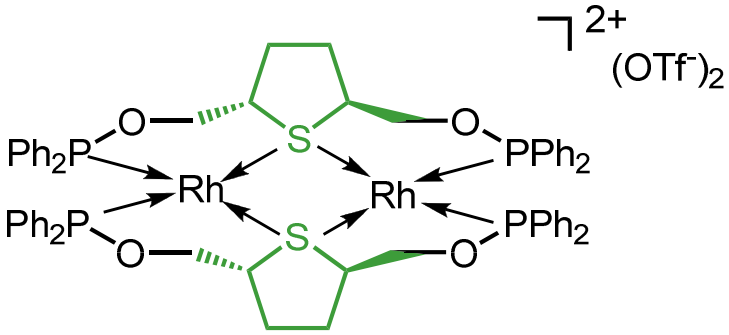
Tetrahydrothiophenes



Breynolide (R=H)

Breynogenin (R=  **)**





Copper amine oxidases Inhibitors

Plant growth regulators

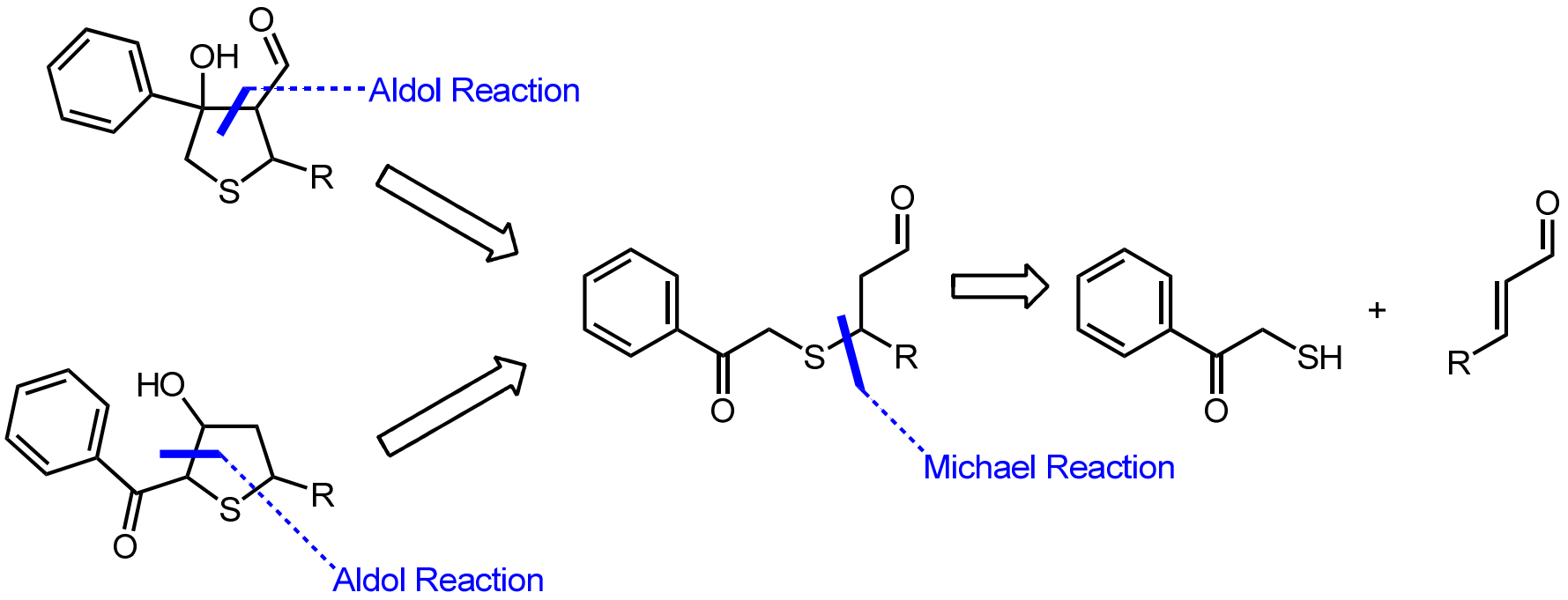
Antioxidant activities

Williams, D. R.; Jass, P. A.; Tse, H. L. A.; Gaston, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 4552

Hauptman, E.; Shapiro, R.; Marshall, W. *Organometallics* **1998**, *17*, 4976

Winn, C. L.; Bellenie, B. R.; Goodman, J. M. *Tetrahedron. Lett.* **2002**, *43*, 5427

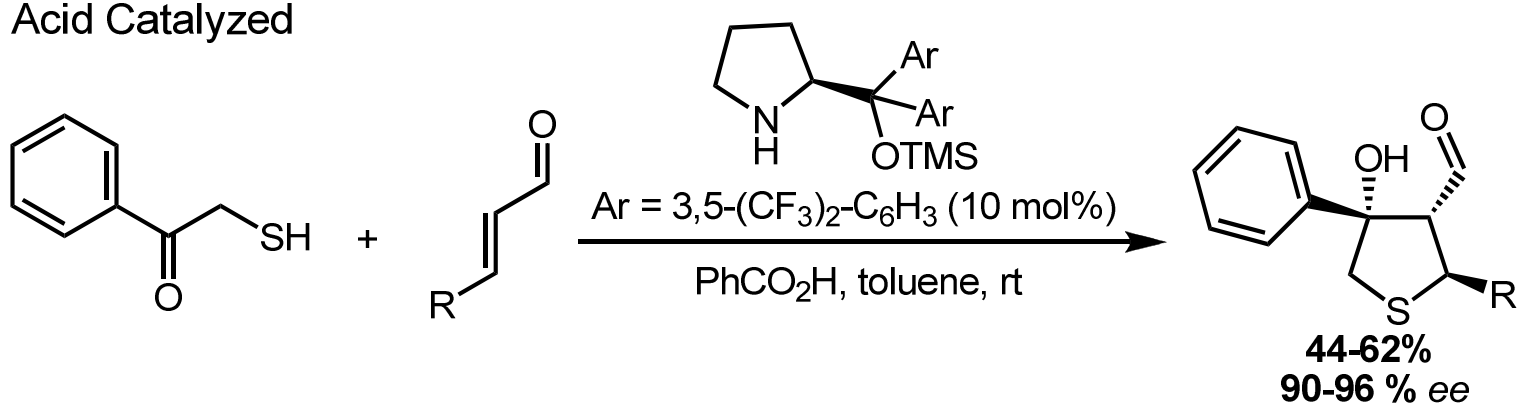
Tetrahydrothiophenes



Jørgensen, K. A.; Brandau, S.; Maerten, E. *J. Am. Chem. Soc.* **2006**, *128*, 14986

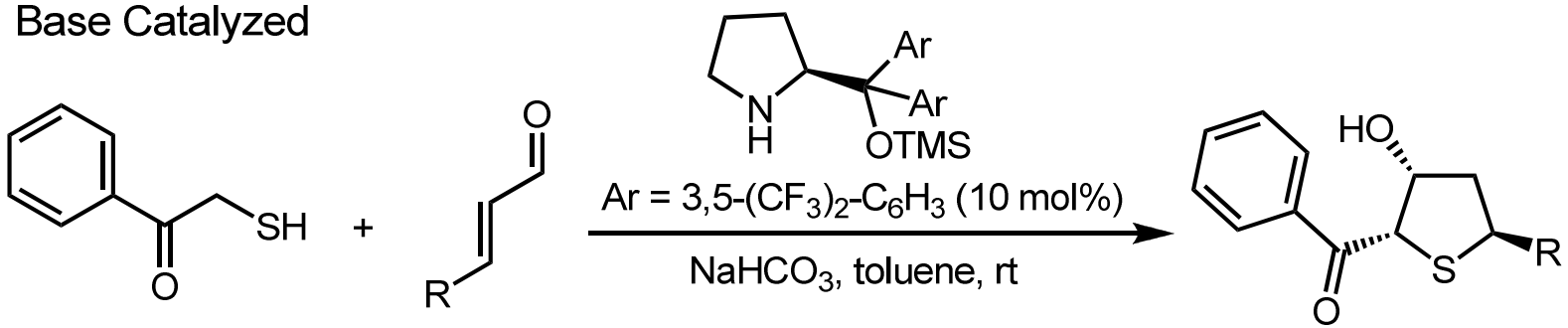
Tetrahydrothiophenes

Acid Catalyzed



44-62%
90-96 % *ee*

Base Catalyzed



43-66%
64-80 % *ee*

Catalytic Mode : Iminium-Enamine

Reactions : Michael / Aldol

Efficiency : 3 new stereocenters
2 new bonds

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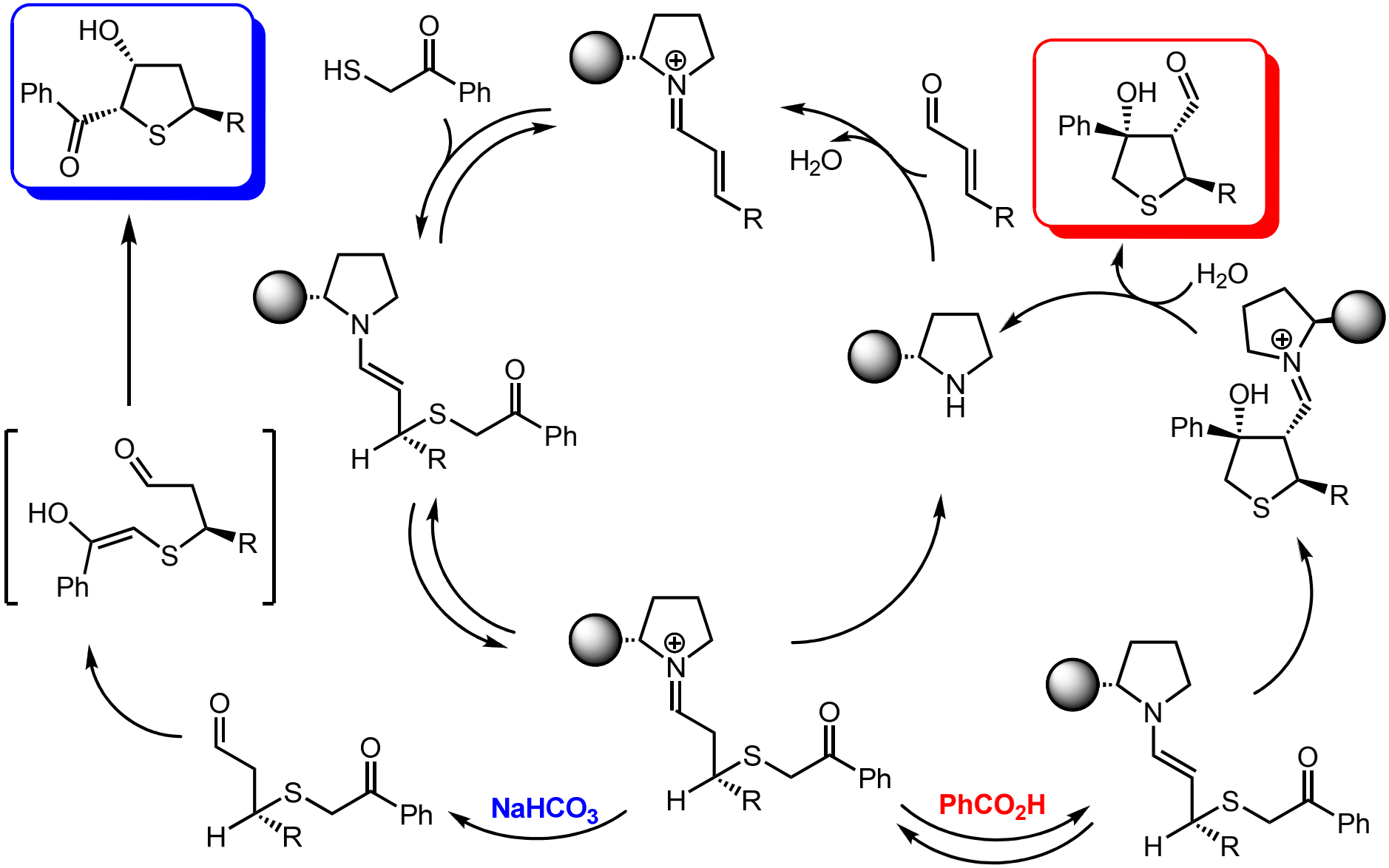
Proposed Catalytic Cycle



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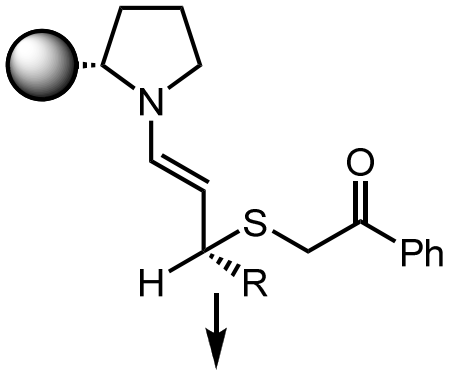
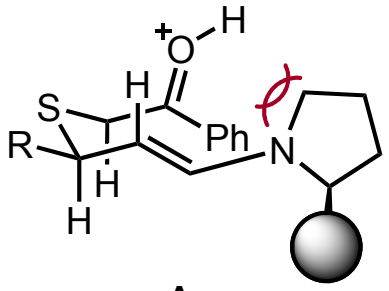
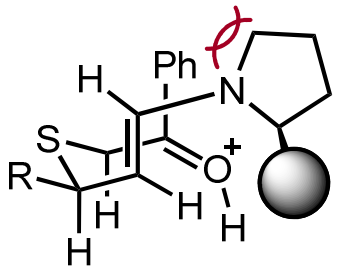
Possible Rationale for Stereochemical Outcome (Acid Catalyzed)

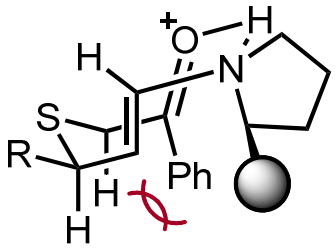




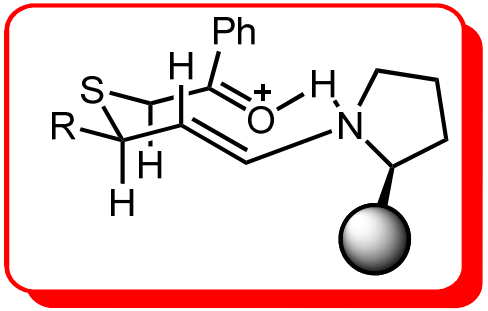
A



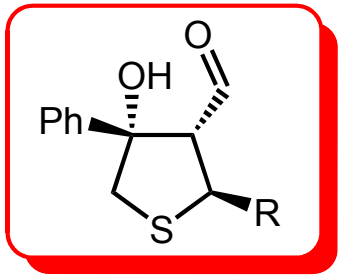
B



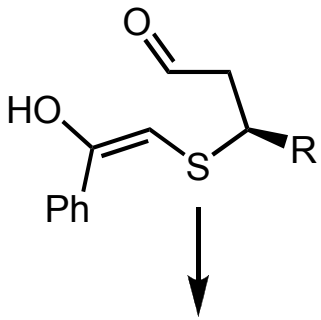
C

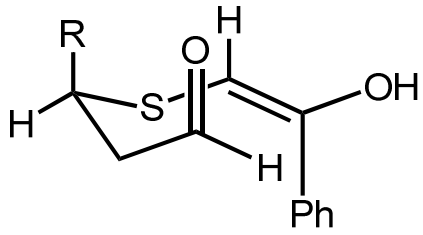


D



Possible Rationale for Stereochemical Outcome (Base Catalyzed)





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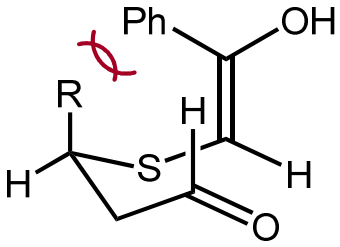

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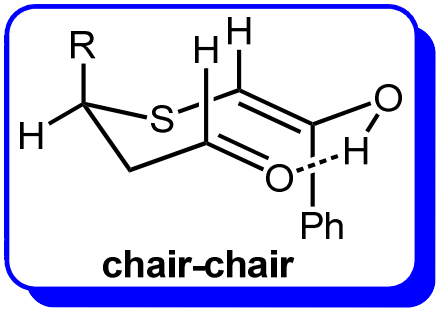

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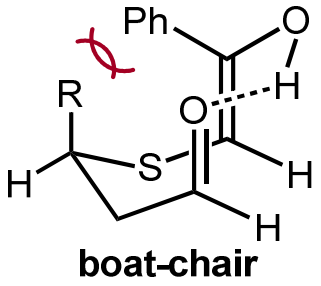
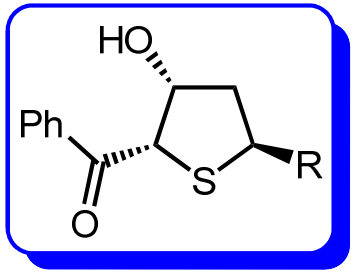
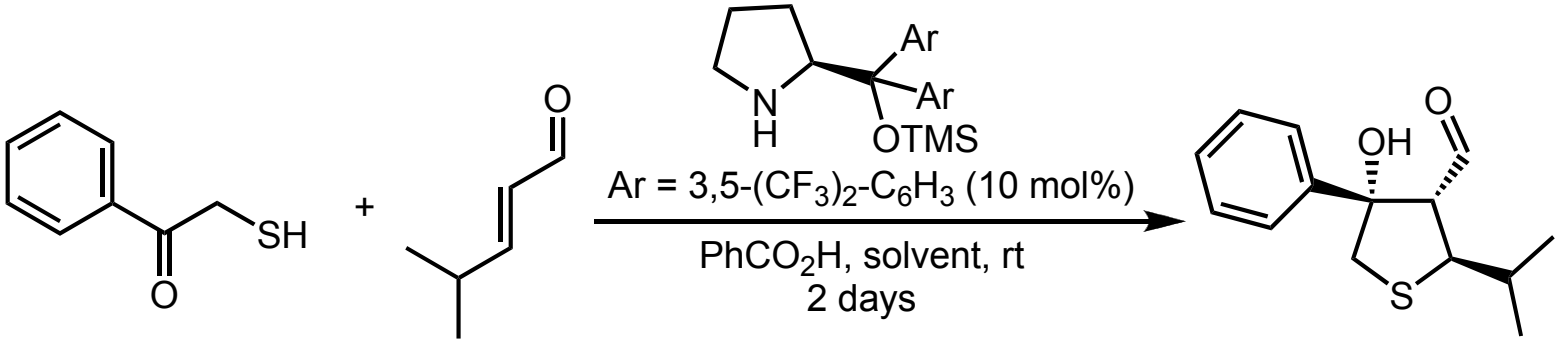


D



Solvent Screening



Entry	Solvent	Yield(%)	*ee*(%)
1	toluene	56	94
2	*o*-xylene	54	93
3	benzene	57	95
4	DCM	9	76
5	THF	30	10
6	DCE	17	80
7	Et_2O	24	60
8	DME	20	37

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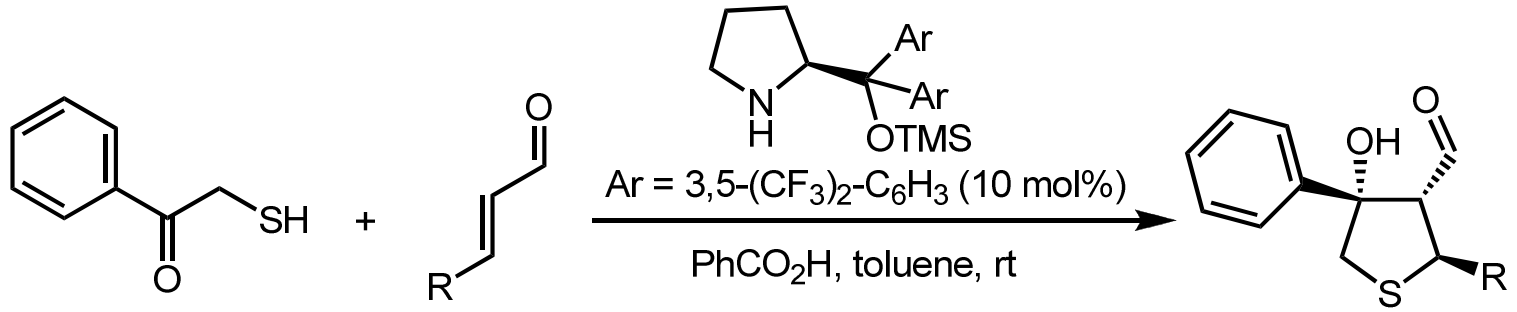
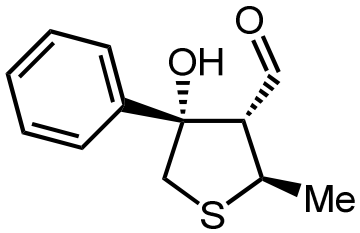
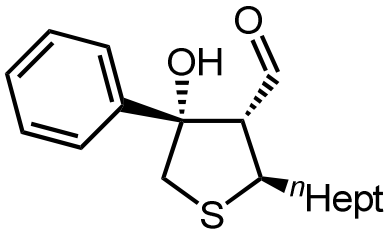
Substrate Scope (Acid Catalyzed)

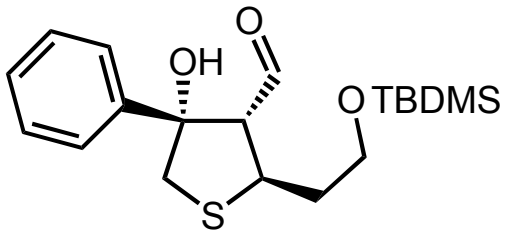




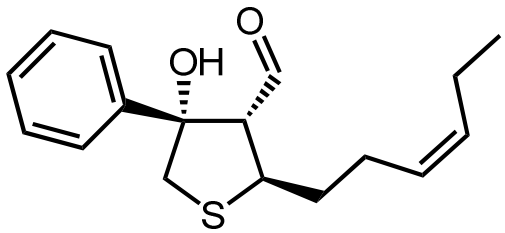
59% yield, **90%** *ee*



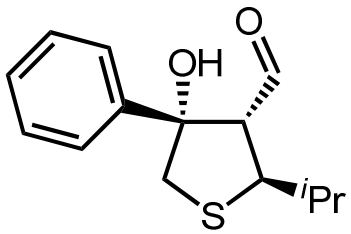
44% yield, **90%** *ee*



44% yield, **96%** *ee*

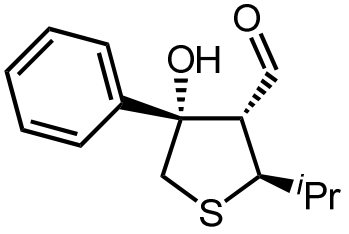


61% yield, **93%** *ee*



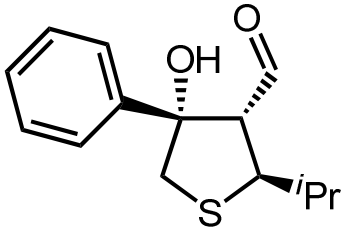
56% yield, **94%** *ee*

(S)-cat.



51% yield, **-89%** *ee*

(R)-cat.



52% yield, **-2%** *ee*

***(S)*-Proline**

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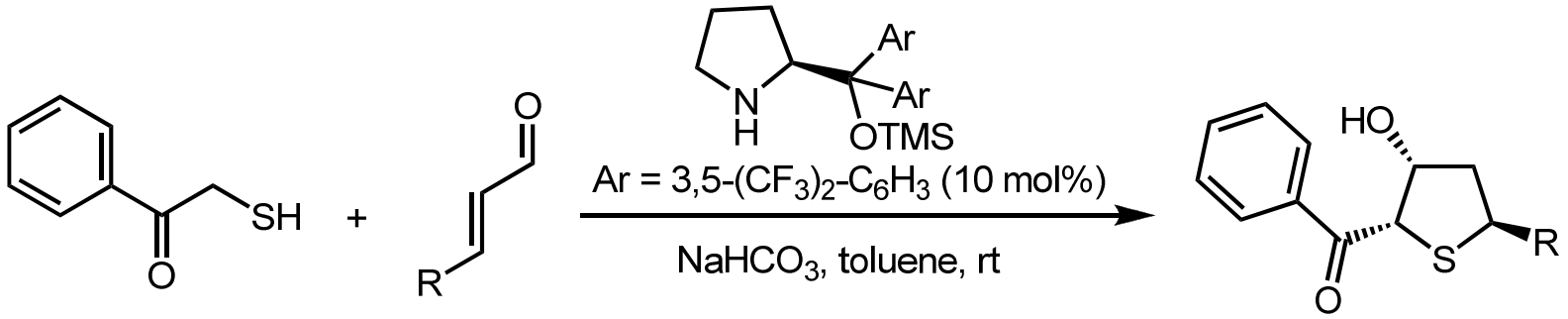
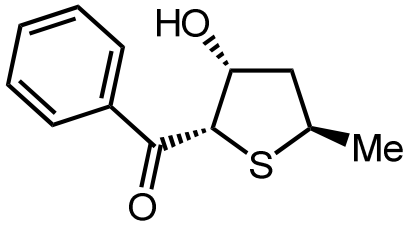
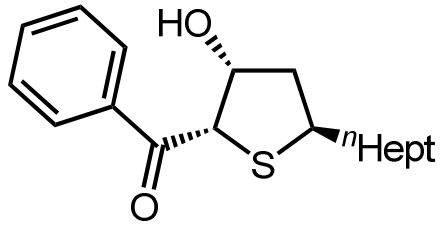
Substrate Scope (Base Catalyzed)

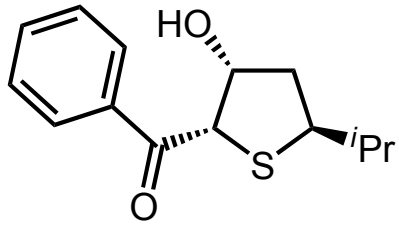




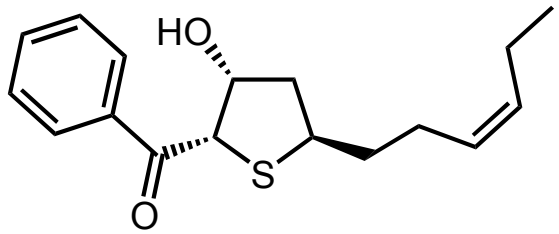
59% yield, **74%** *ee*



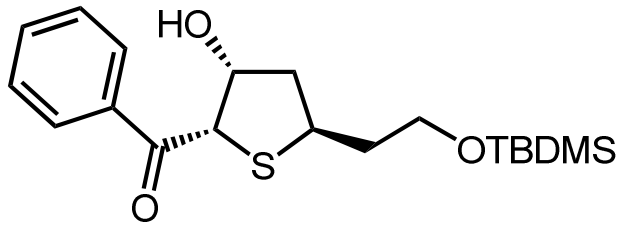
66% yield, **64%** *ee*



61% yield, **80%** *ee*



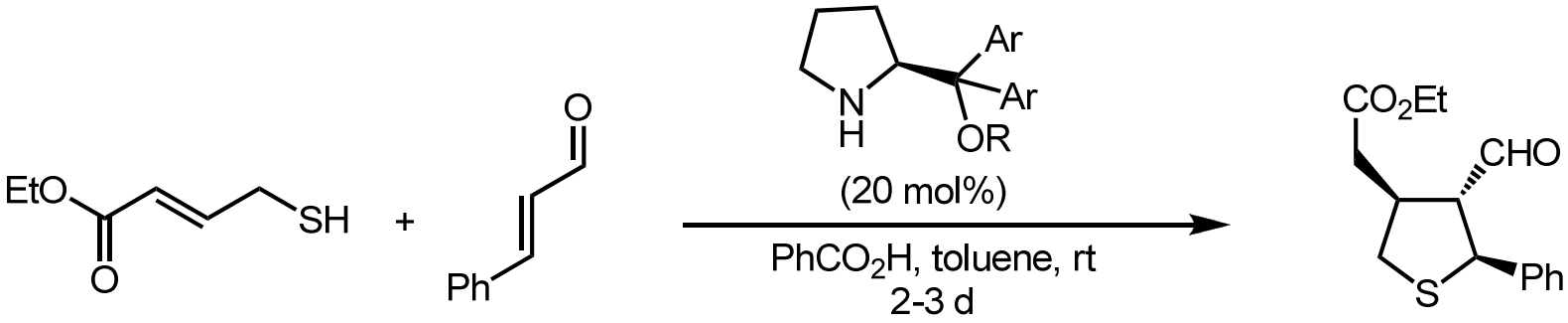
57% yield, **76%** *ee*

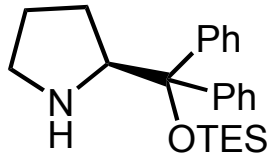


61% yield, **70%** *ee*

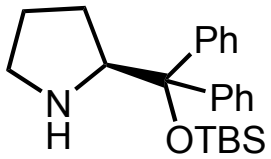
Jørgensen, K. A.; Brandau, S.; Maerten, E. *J. Am. Chem. Soc.* **2006**, *128*, 14986

Tetrahydrothiophenes

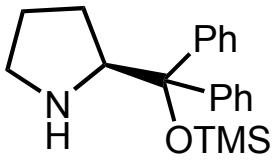




73% yield, **99%** *ee,***15:1** *dr*

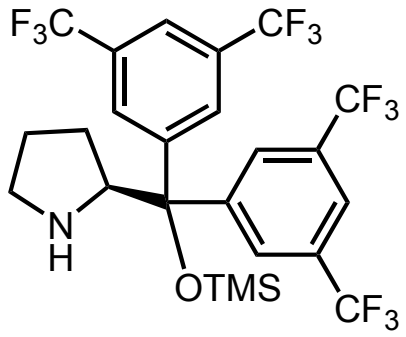


84% yield, **98%** *ee,***15:1** *dr*



75% yield, >**99%** *ee,***15:1** *dr*

76% yield, >**99%** *ee,***15:1** *dr*
Catalyst Loading: 10 mol%



0% yield, **nd %** *ee,* **nd** *dr*

Catalytic Mode : Iminium-Enamine

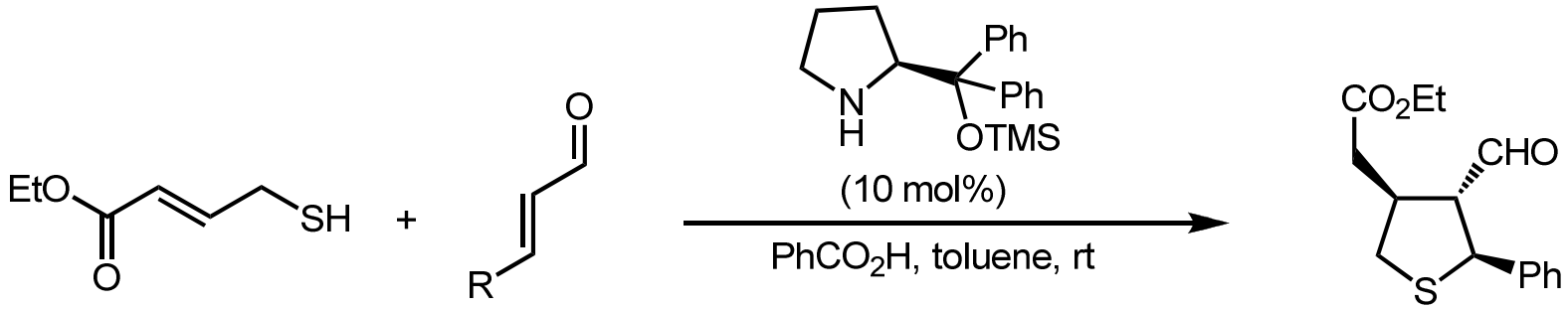
Reactions : Michael / Michael

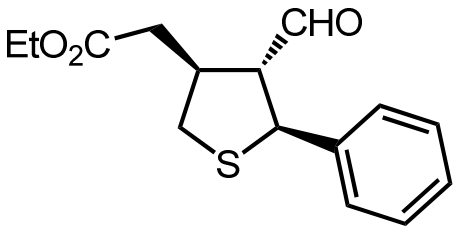
Efficiency : 3 new stereocenters

2 new bonds

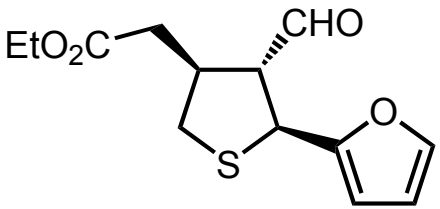
Wang, W.; Li, H.; Zu, L.; Wang, J.; Jiang, W. *Org. Lett.* **2007**, *9*,1833

Substrate Scope

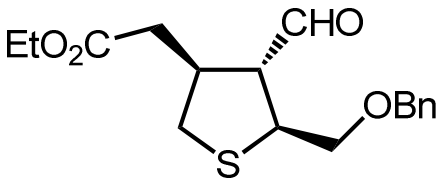




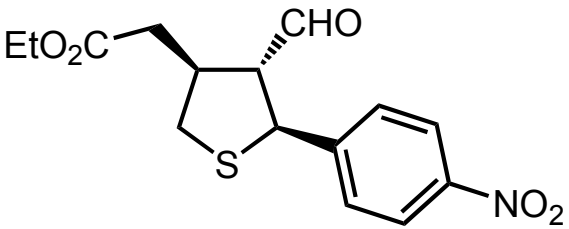
76% yield, >**99%** *ee,***15:1** *dr*



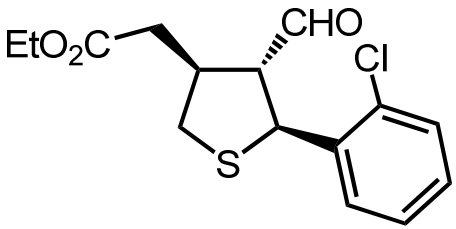
88% yield, **98%** *ee,***6:1** *dr*



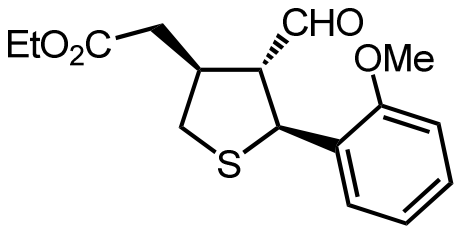
62% yield, **94%** *ee,***7:1** *dr*



84% yield, **99%** *ee,***7:1** *dr*



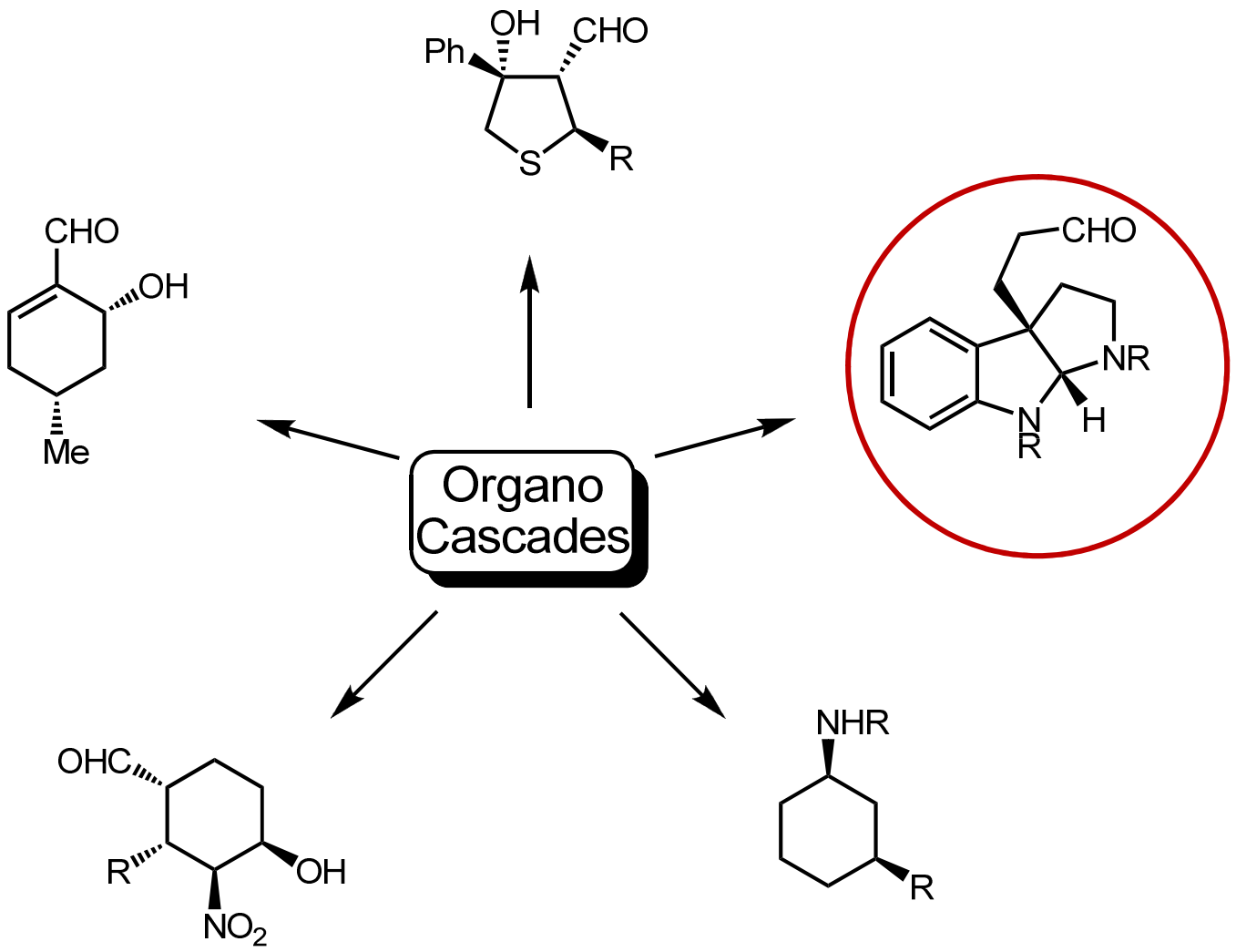
85% yield, **99%** *ee,***10:1** *dr*



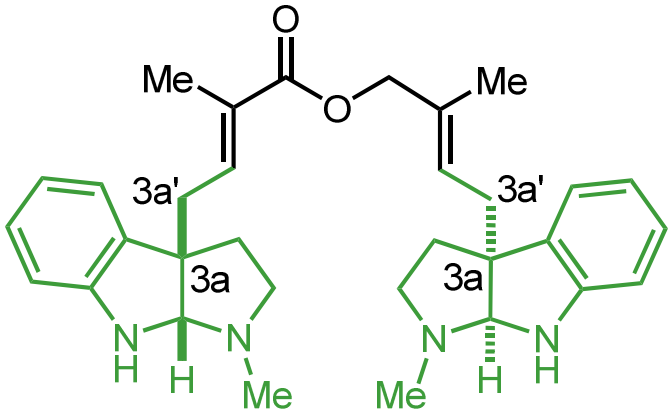
96% yield, **98%** *ee,***18:1** *dr*

Wang, W.; Li, H.; Zu, L.; Wang, J.; Jiang, W. *Org. Lett.* **2007**, *9*,1833

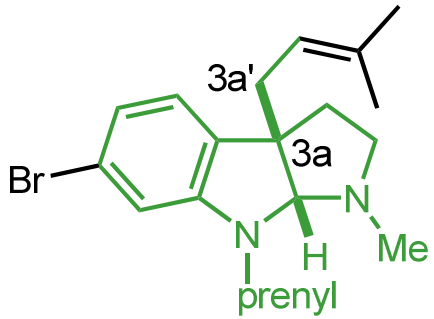
Different Scaffolds



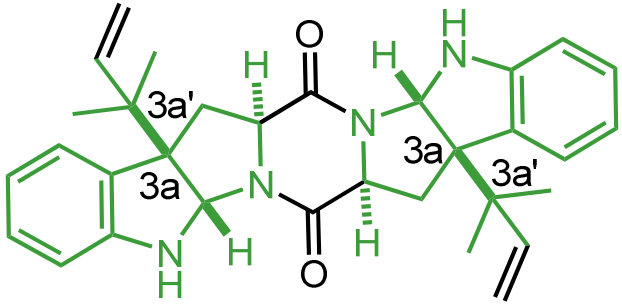
Pyrroloindoline



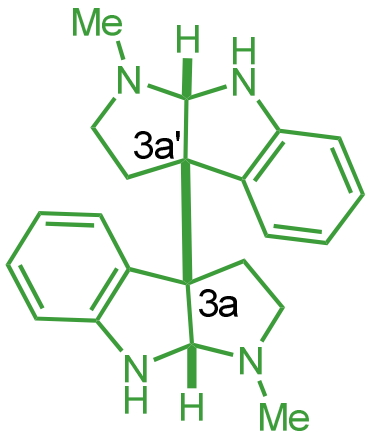
Pseudophrynamine A



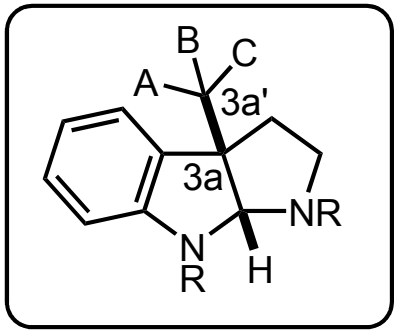
(-)-Flustramine B



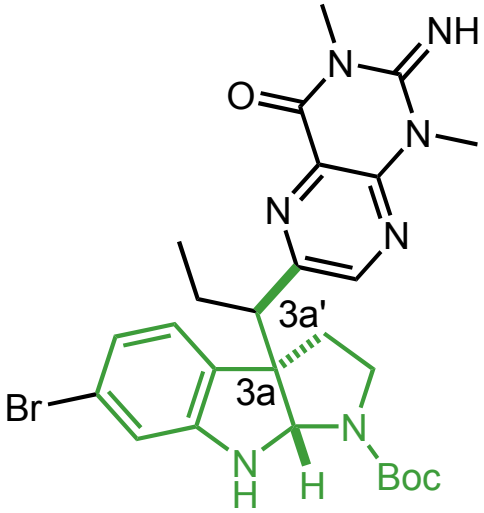
Amauromine



(-) Chimonanthine



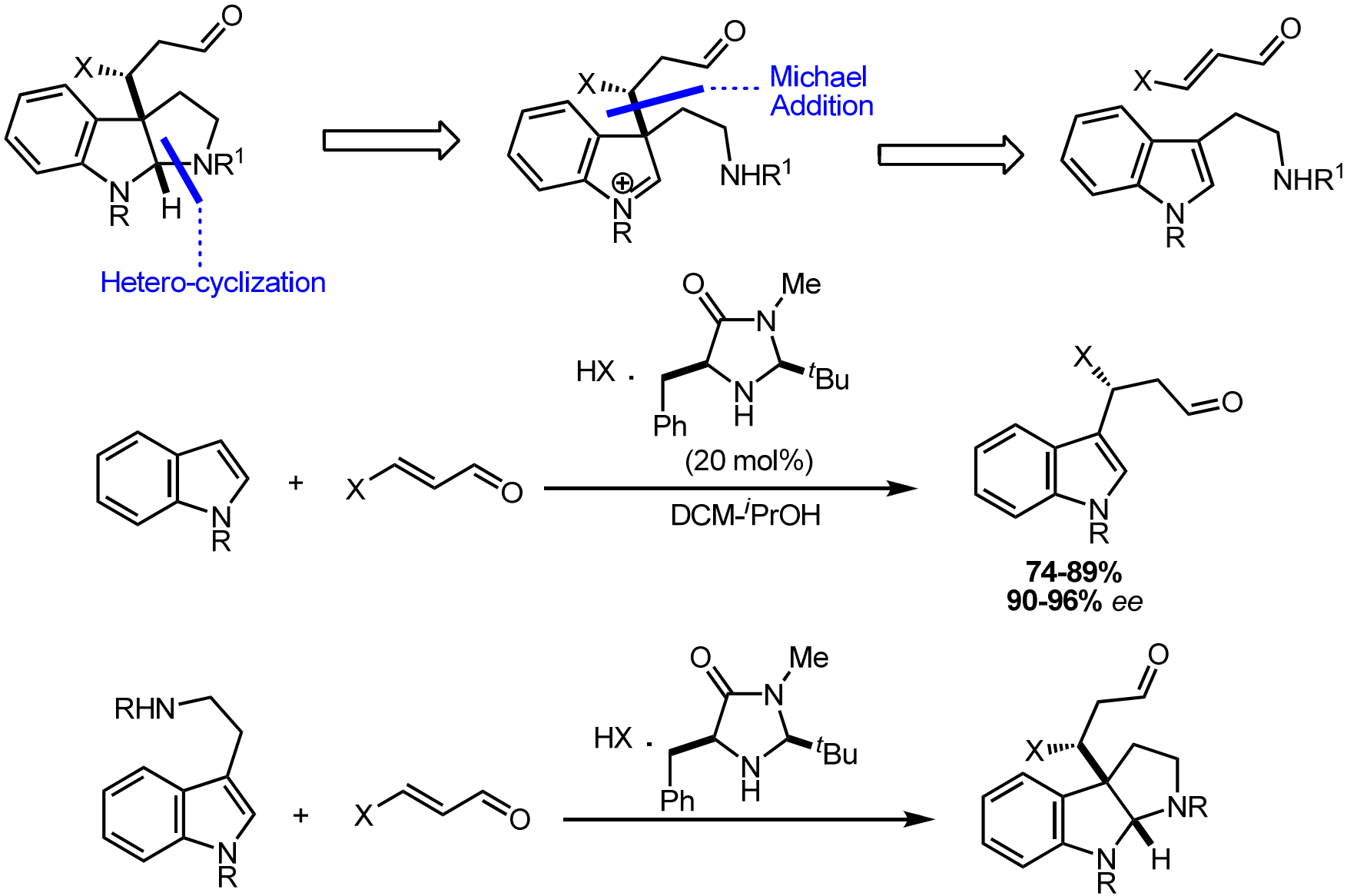
- Quaternary Center C3a
- Diastereocontrol C3a-C3a´
- Enantioselective Catalysis



Urochordamine

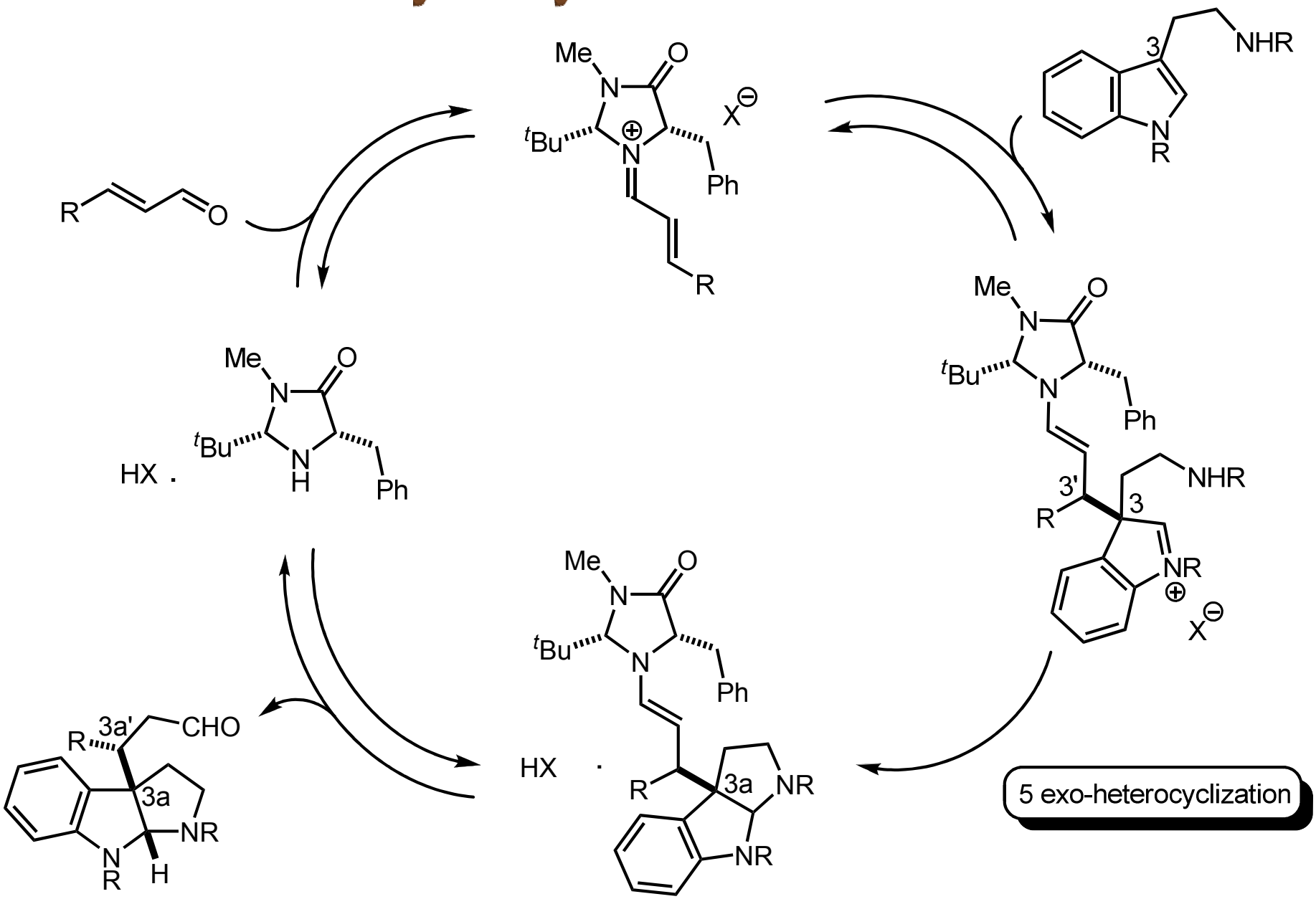
MacMillan, D. W. C.; Austin, J. F.; Kim, S.; Sinz, C. J.; Xiao, W. *PNAS.* **2004**, *101*, 5482

Organocatalytic Pyrroloindoline Construction



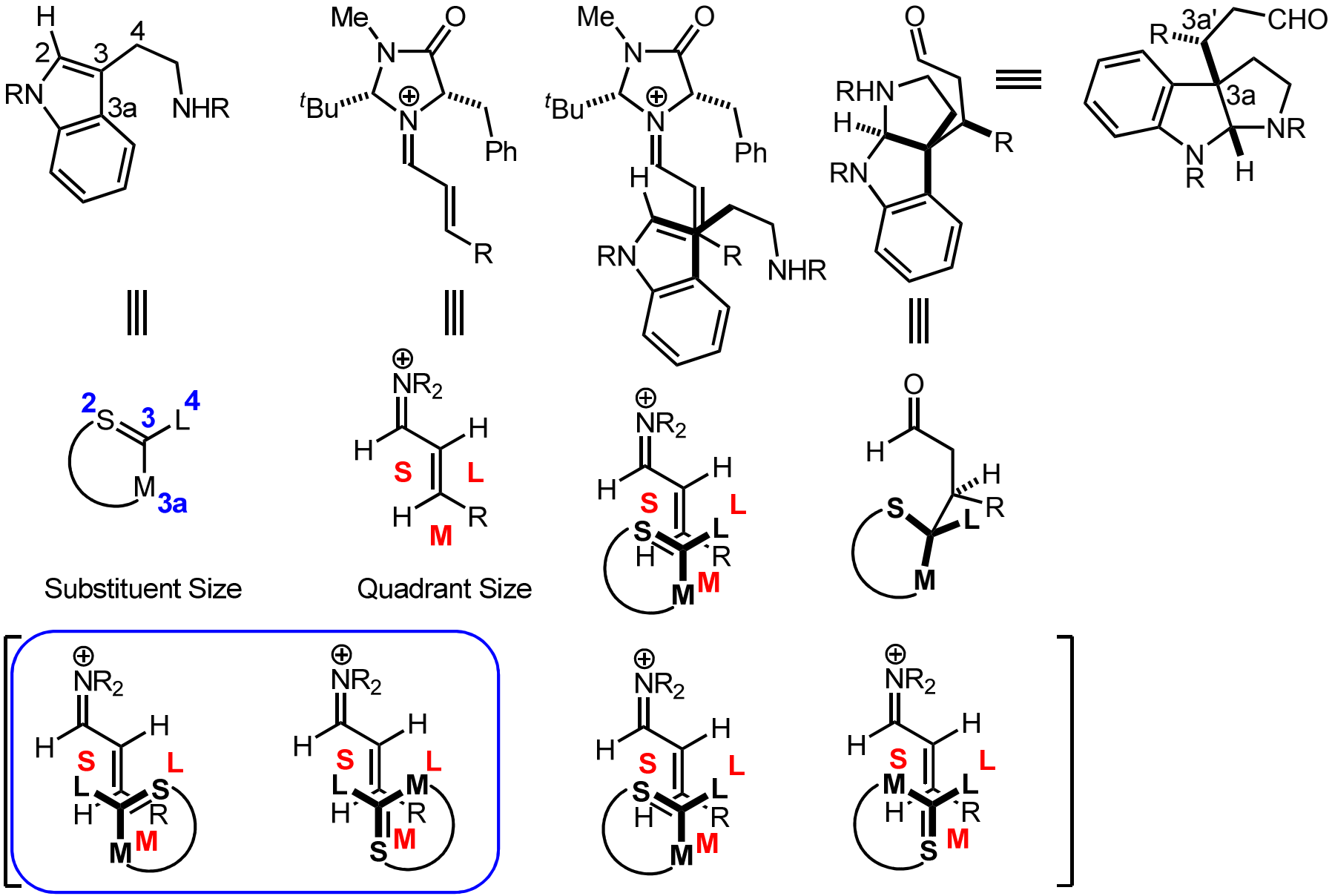
MacMillan, D. W. C.; Austin, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1172
MacMillan, D. W. C.; Austin, J. F.; Kim, S.; Sinz, C. J.; Xiao, W. *PNAS* **2004**, *101*, 5482

Catalytic Cycle: Plan of Action



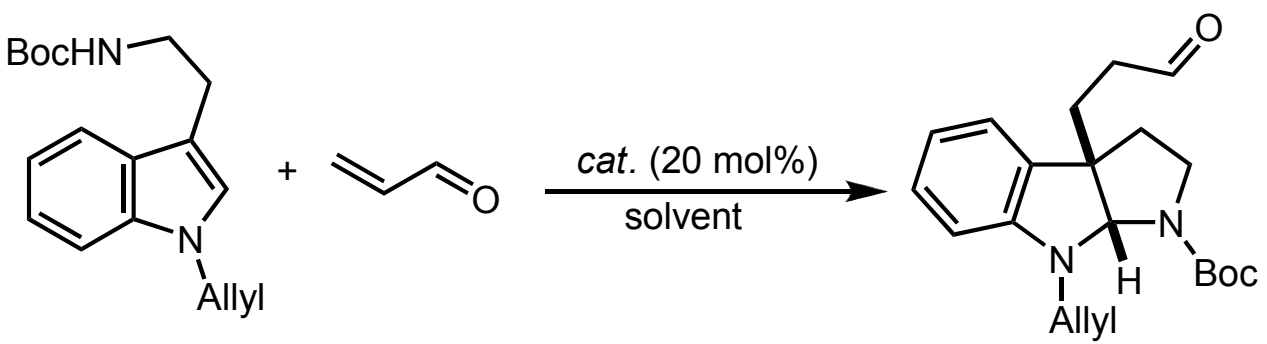
MacMillan, D. W. C.; Austin, J. F.; Kim, S.; Sinz, C. J.; Xiao, W. *PNAS.* **2004**, *101*, 5482

Stereochemical Rationale

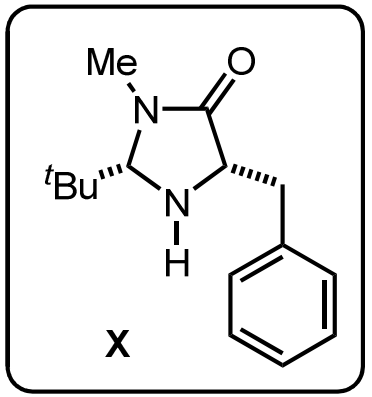


Austin. J. F., PhD Thesis, 2005, California Institute of Technology

Catalyst and Solvent Screening



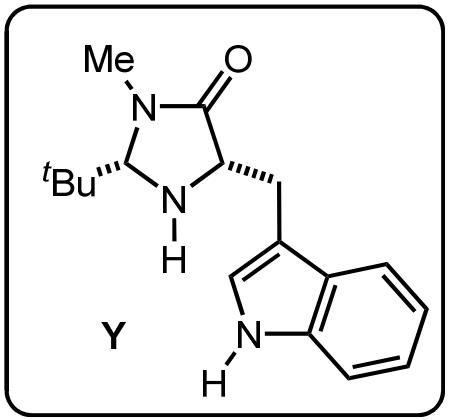
Entry	Solvent	Dielectric	Catalyst	Yield(%)	*ee*(%)
1	MeOH	32.6	Xb	64	69
2	Acetone	20.2	Xb	58	60
3	DME	7.2	Xb	18	21
4	$CHCl_3$	4.8	Xb	66	-45
5	Toluene	2.4	Xb	60	-59
6	DCM	9.1	Xa	79	70
7	DCM	9.1	Ya	85	89



X

Cocatalyst (HA)

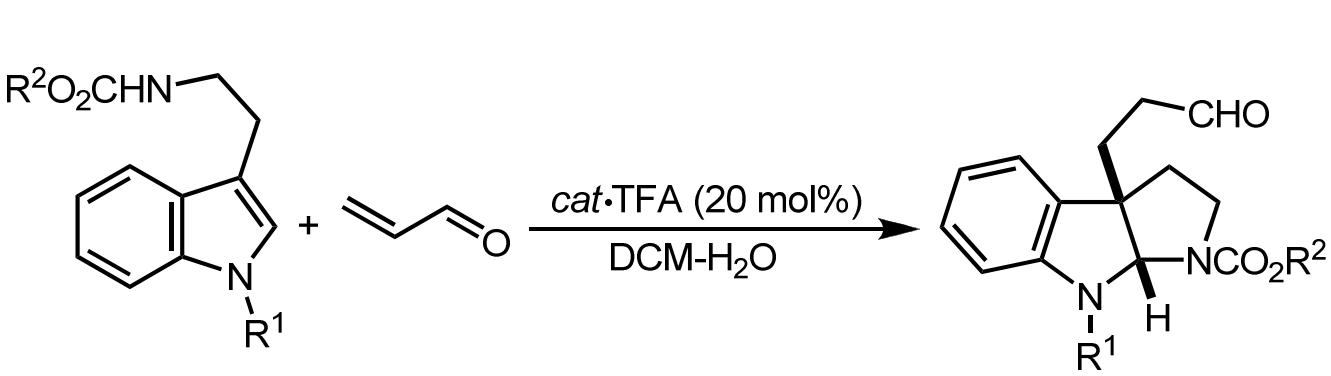
a= TFA
b= *p*-TSA

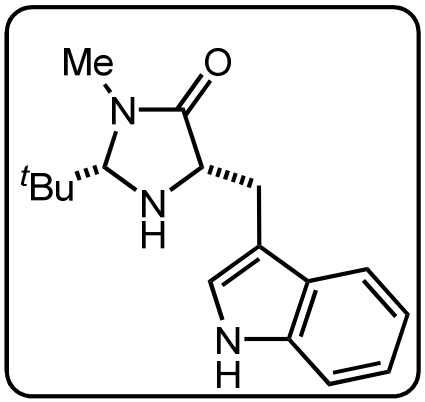


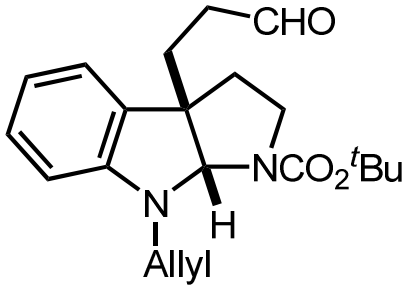
Y

MacMillan, D. W. C.; Austin, J. F.; Kim, S.; Sinz, C. J.; Xiao, W. *PNAS.* **2004**, *101*, 5482

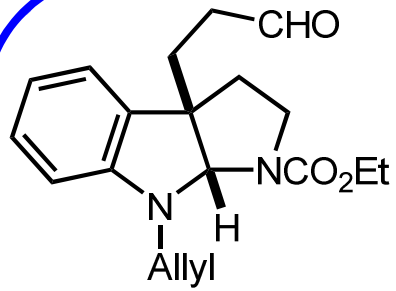
Protecting Group Screening with Acrolein



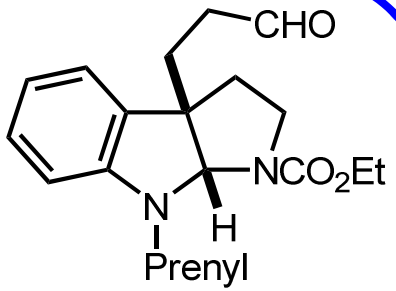




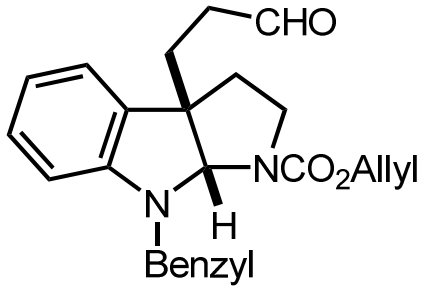
85% yield, **89%** *ee*, **25** h



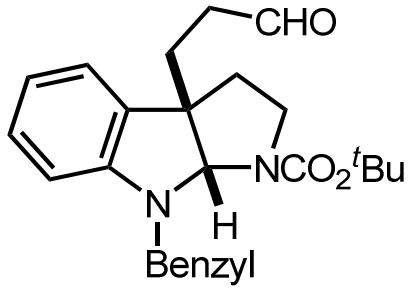
89% yield, **89%** *ee*, **26** h



89% yield, **89%** *ee*, **24** h

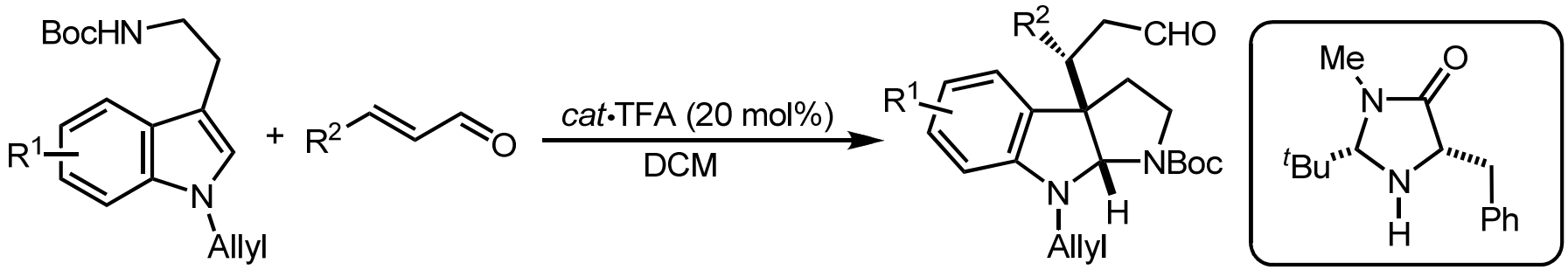


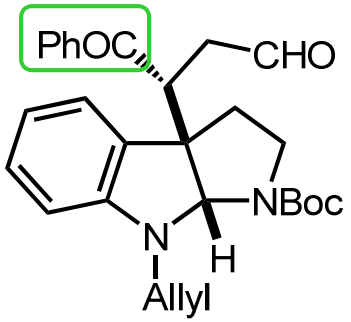
83% yield, **89%** *ee*, **48** h



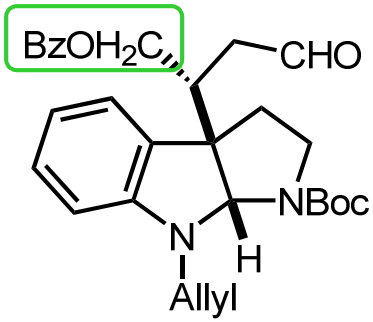
82% yield, **90%** *ee*, **30** h

Substrate Scope with β-sustituted Acrolein

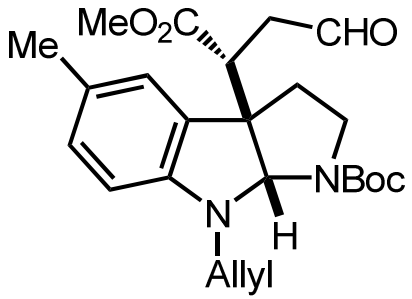




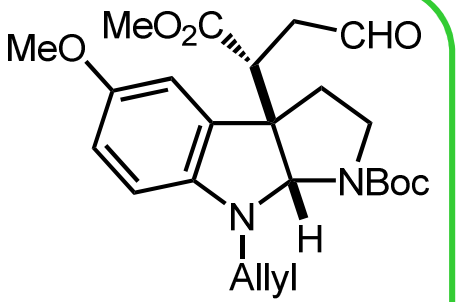
92% yield,**94%** *ee*,**13:1** dr



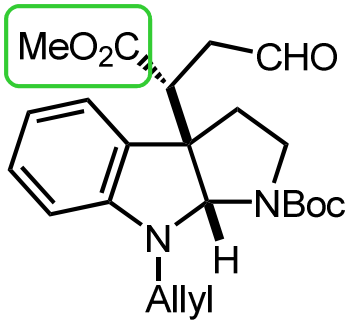
66% yield,**91%** *ee*, **22:1** dr



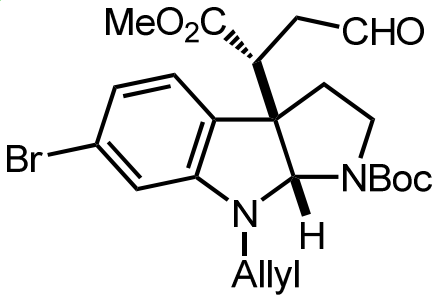
94% yield,**92%** *ee*, **50:1** dr



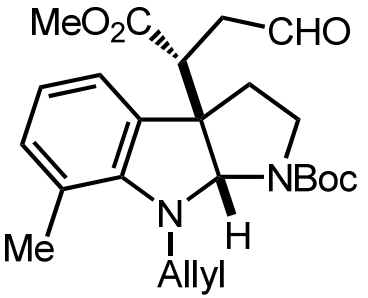
99% yield,**90%** *ee*,**10:1** dr



93% yield,**91%** *ee*, **44:1** dr

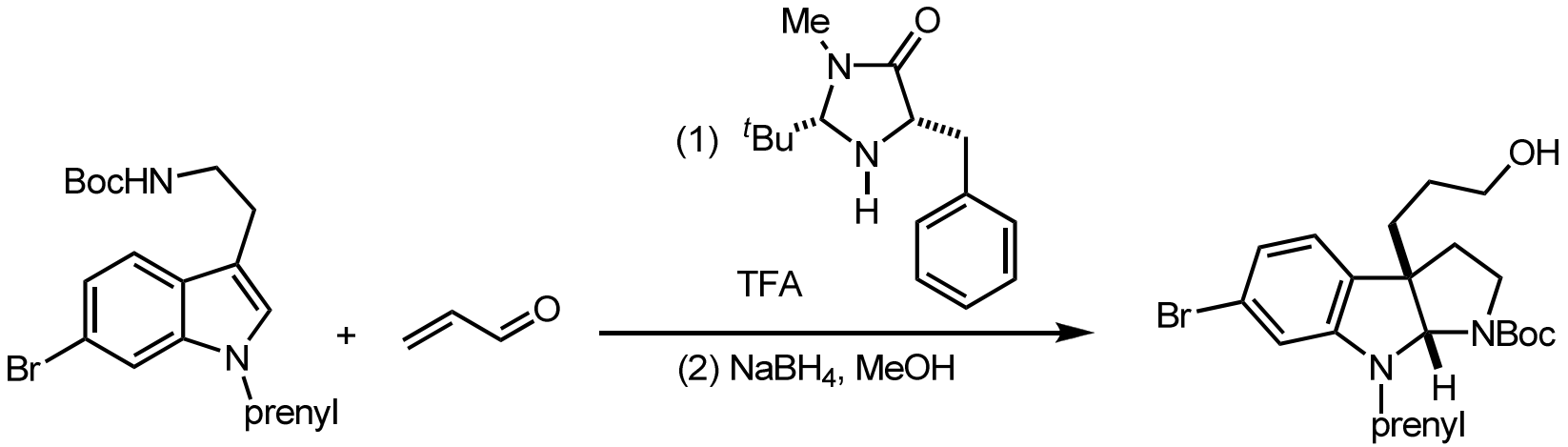


86% yield,**97%** *ee*, **31:1** dr

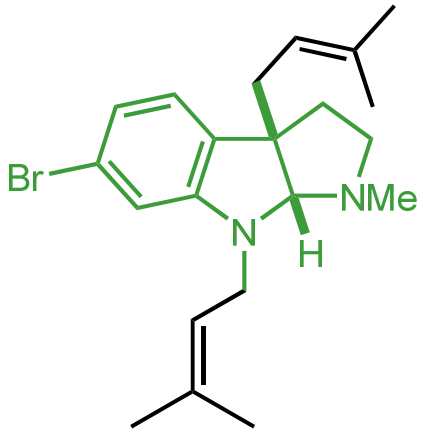


97% yield,**99%** *ee*, **17:1** dr

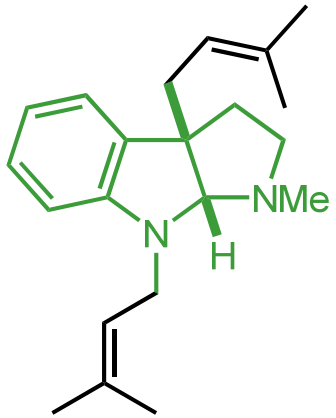
Application to Total Synthesis



78% yield, **90%** *ee*



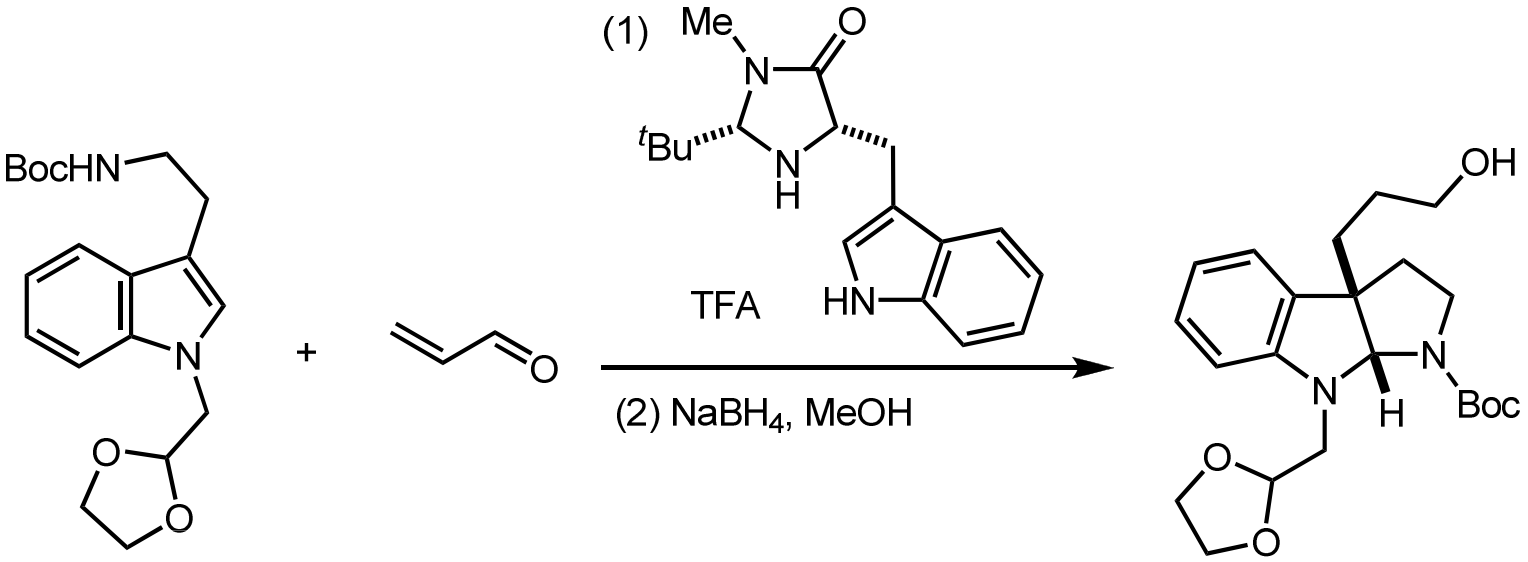
(-)-Flustramine B
(5 steps)



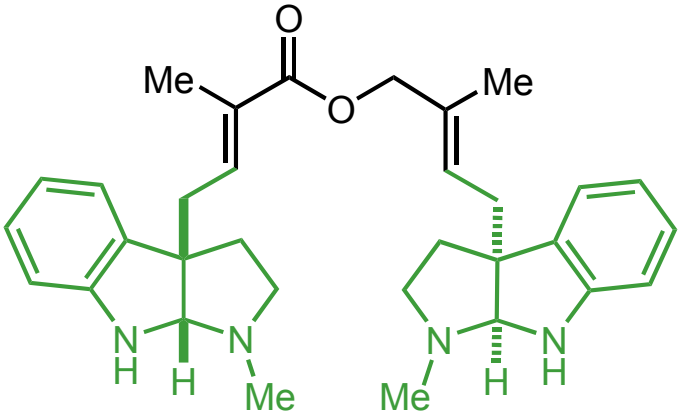
(-)-Debromoflustramine B
(4 steps)

MacMillan, D. W. C.; Austin, J. F.; Kim, S.; Sinz, C. J.; Xiao, W. *PNAS.* **2004**, *101*, 5482

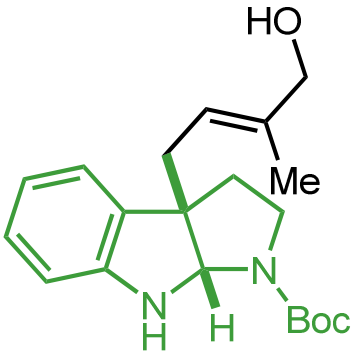
Application to Total Synthesis



70% yield, **90%** *ee*

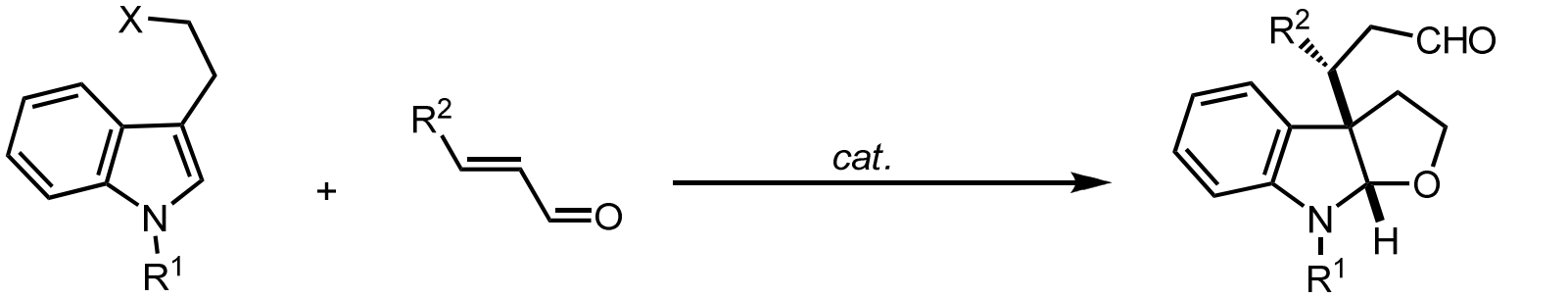


Pseudophrynamine A
(8 steps)



(-)-Pseudophrynaminol
(7 steps)

Furanoindoline

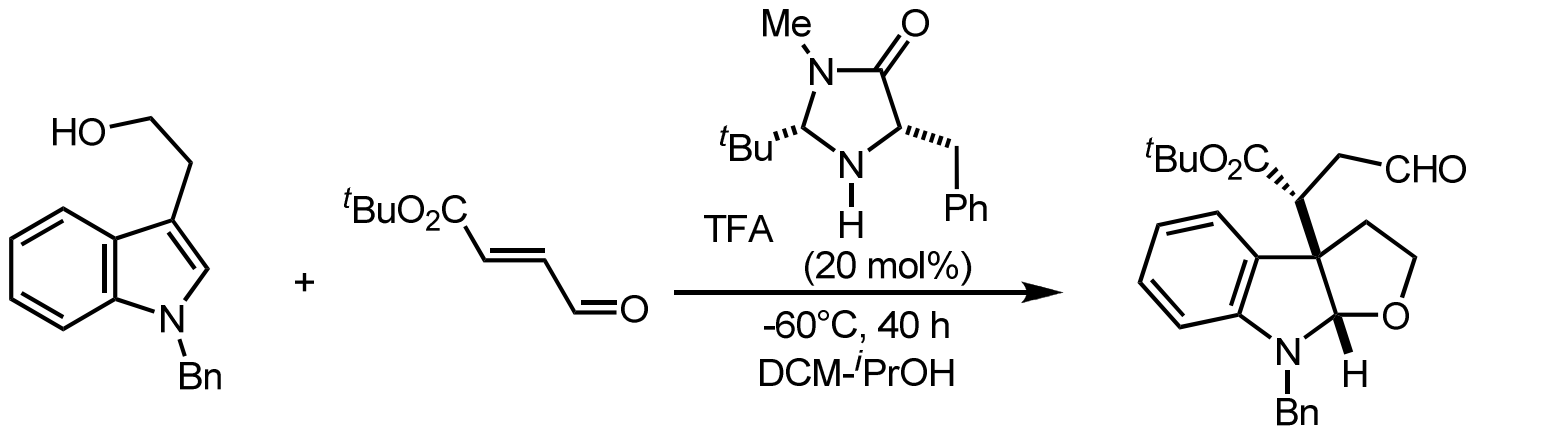


X = NH_2 = tryptamine

X = OH = tryptophol

X = NH_2 = pyrroloindoline

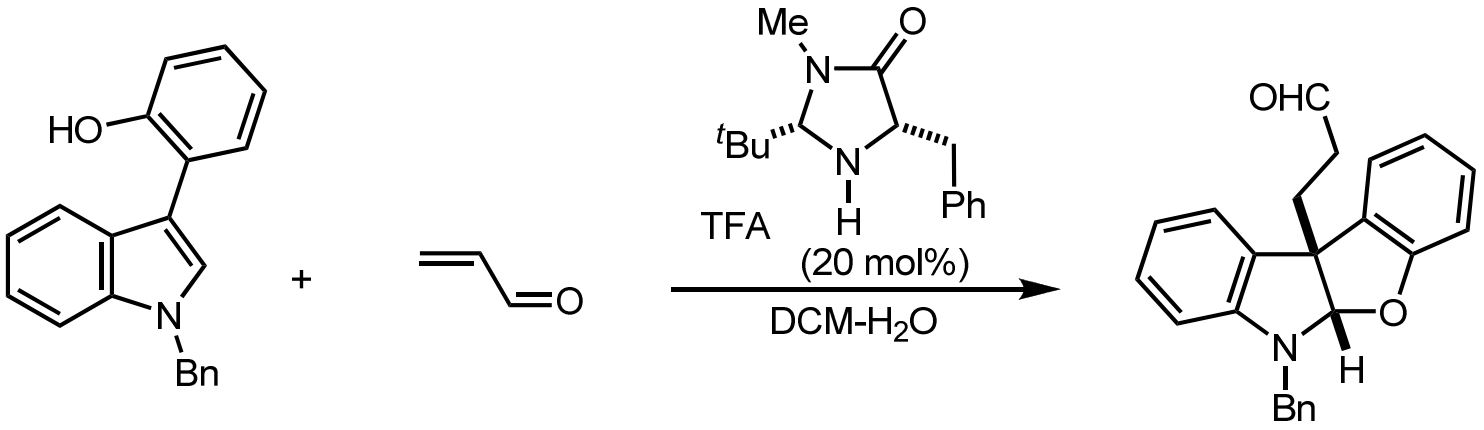
X = OH = furanoindoline



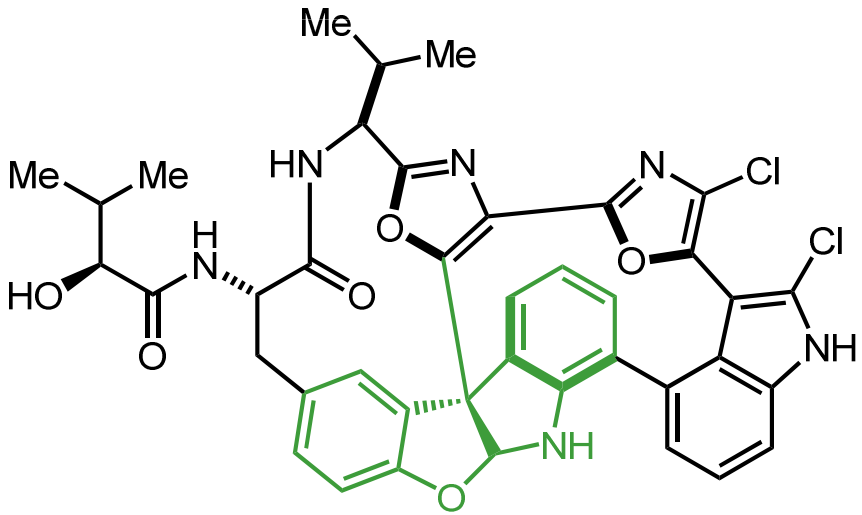
80% yield,**93%** *ee*,**12:1** dr

MacMillan, D. W. C.; Austin, J. F.; Kim, S.; Sinz, C. J.; Xiao, W. *PNAS.* **2004**, *101*, 5482

Application to Total Synthesis



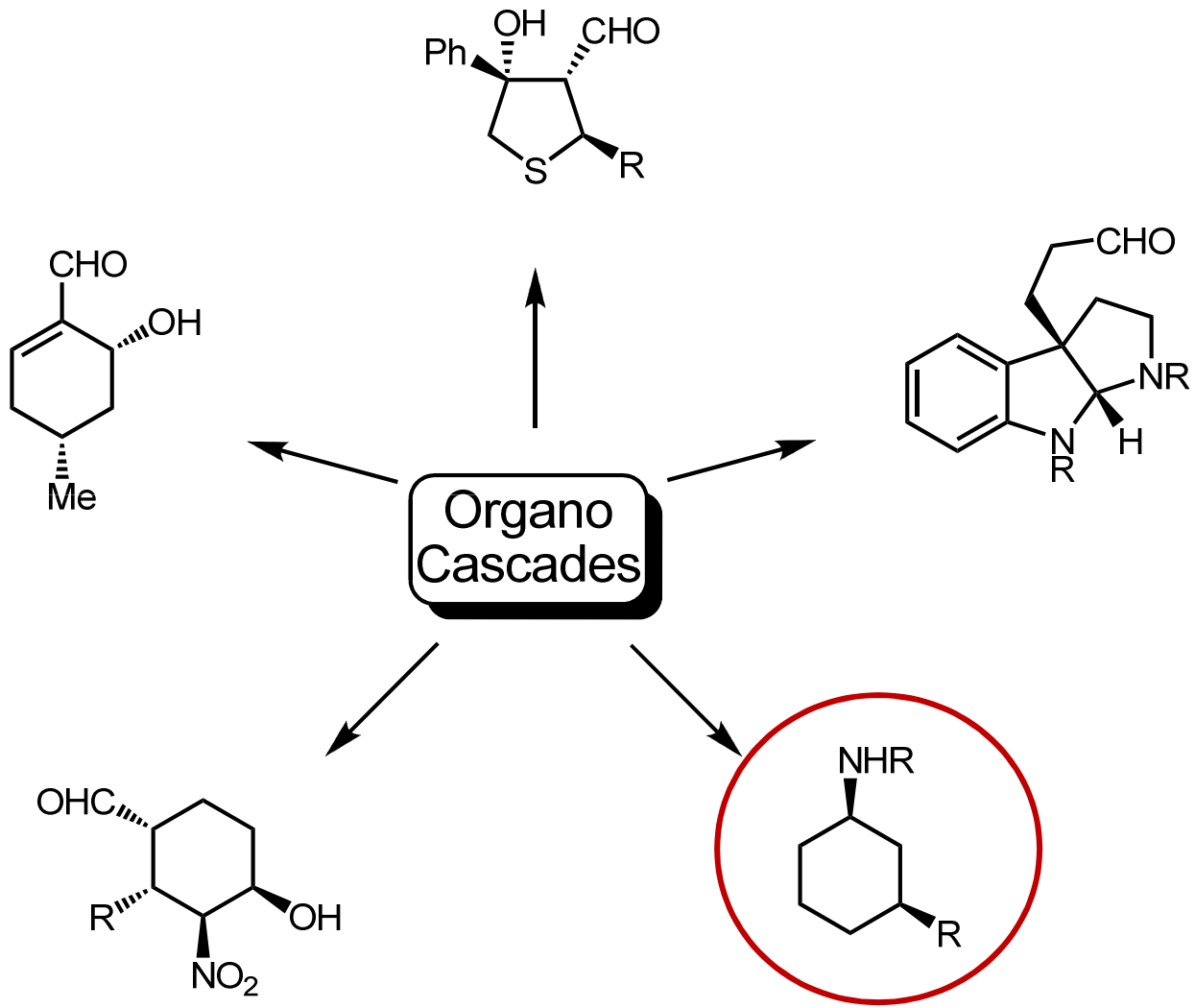
90% yield, **82%** *ee*



Diazonamide A
(19 steps)

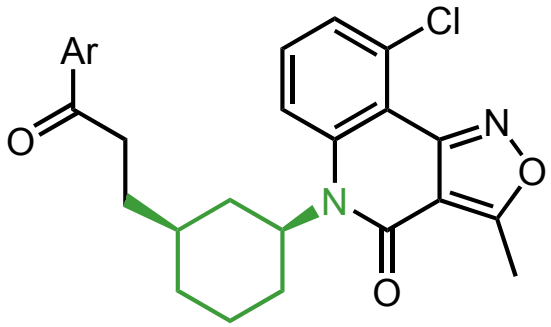
MacMillan, Unpublised results

Different Scaffolds



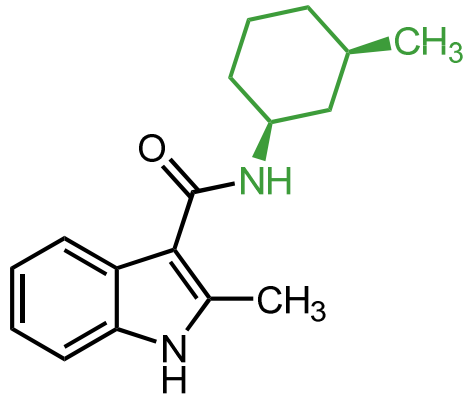
3-subsituted Cyclohexyl Amines

More than 300 patented structures containing a 3-methyl cyclohexylamine moiety



Ar = 3,4,5-$(OMe)_3$Ph, Ph

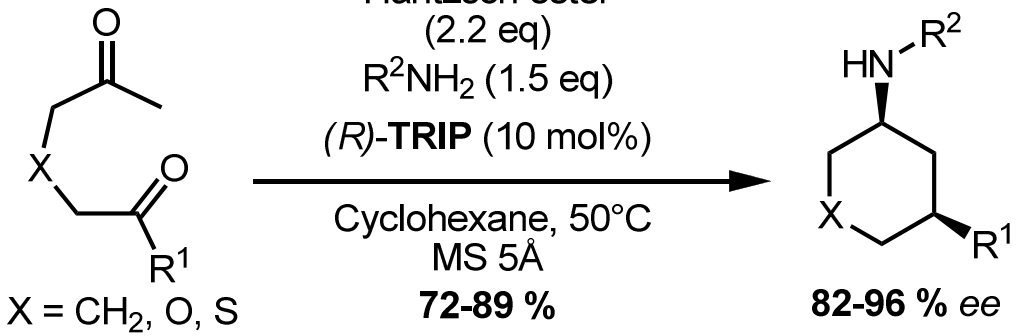
A promising scaffold for selective MRP1 modulation

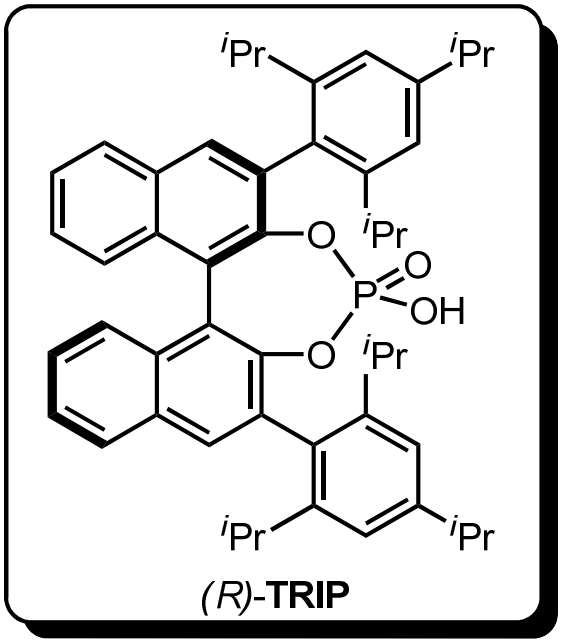


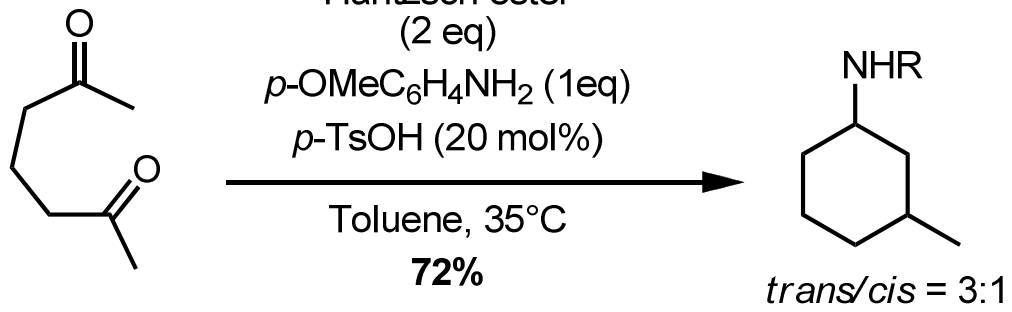
Anti-inflammatory, analgesic and ulcerogenic activities

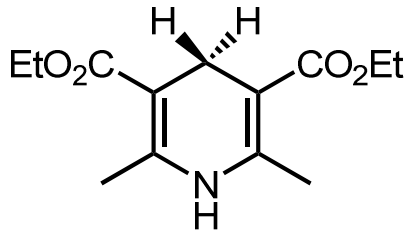
Sci-Finder

3-subsituted Cyclohexyl Amines



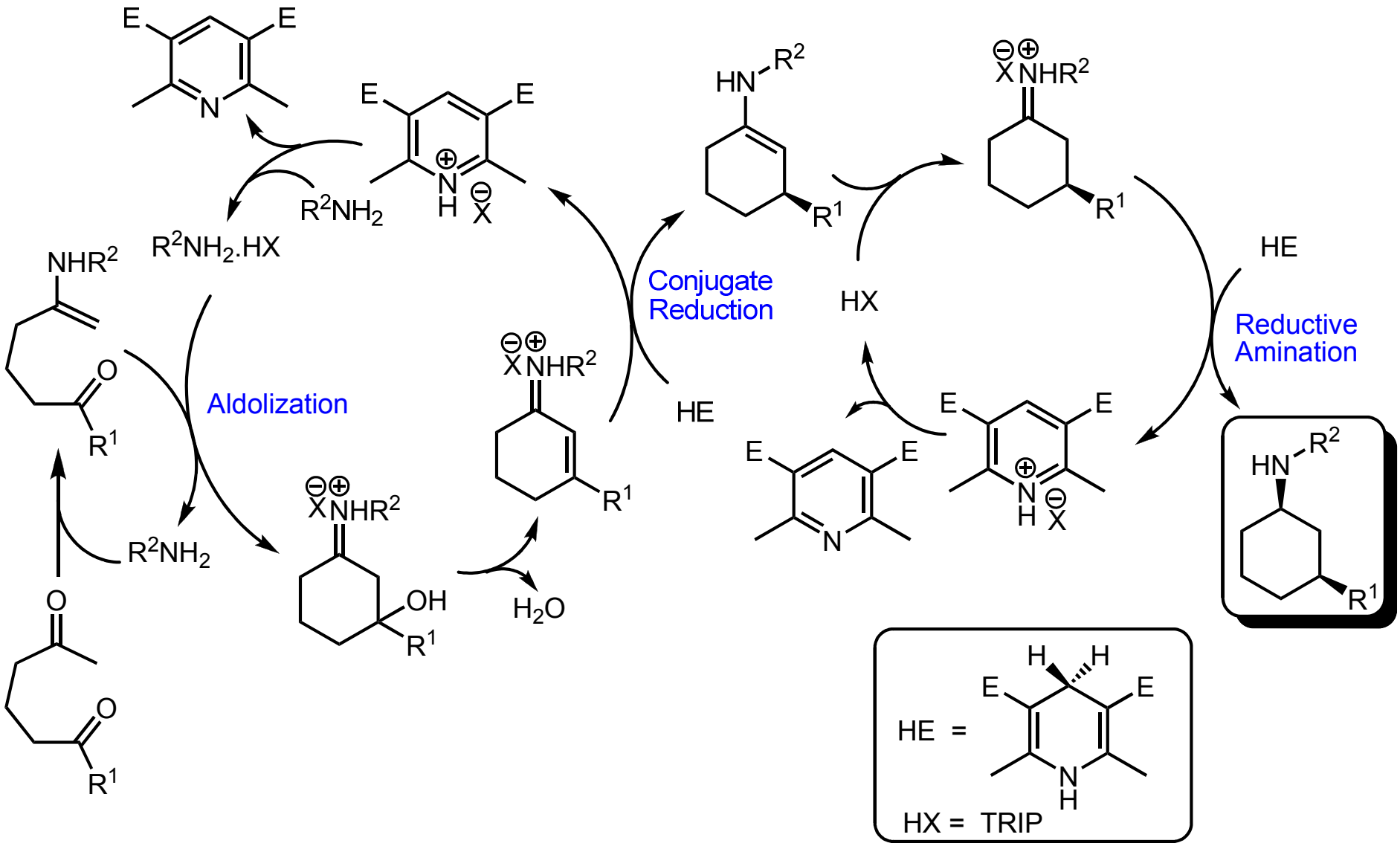




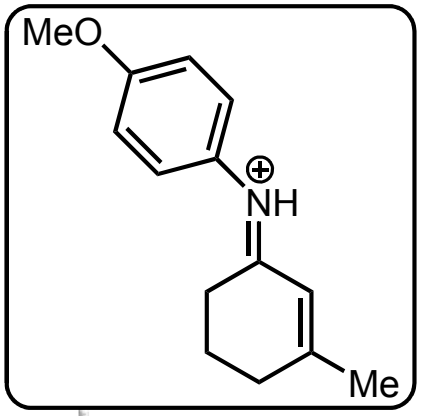


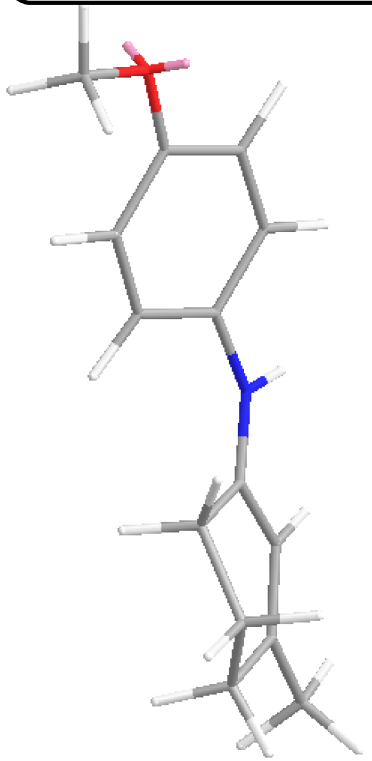
List, B.; Zhou, J. *J. Am. Chem. Soc.* **2007**, *129*, 7498

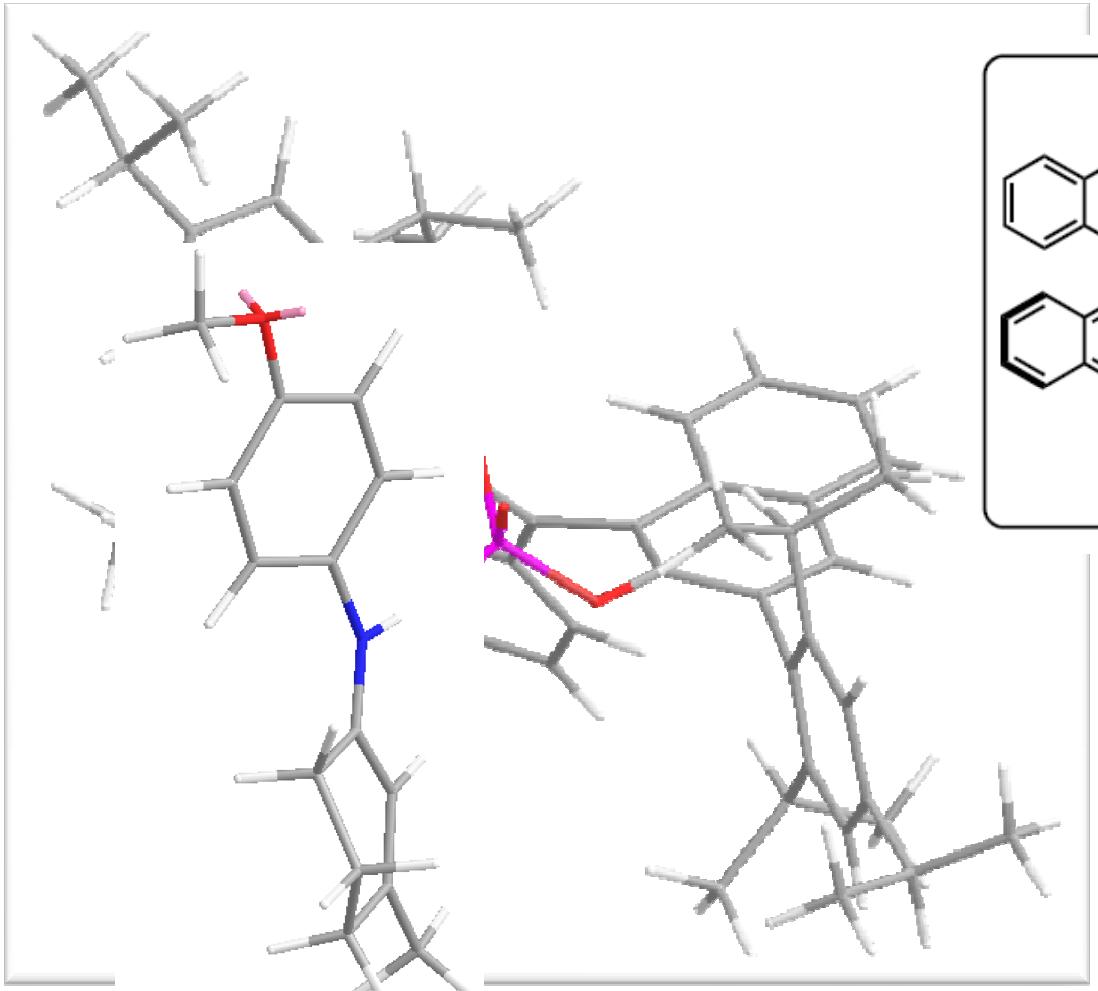
Mechanism: Catalytic Cycle

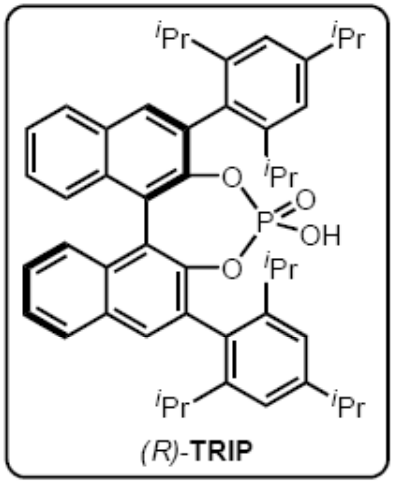


Possible Rationale for Stereochemical Outcome

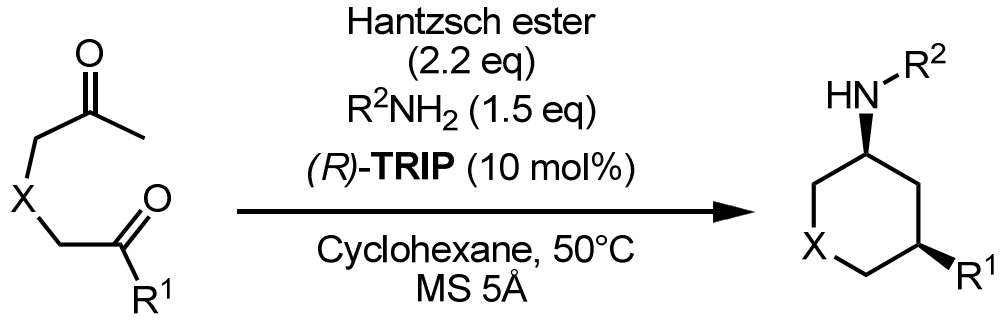


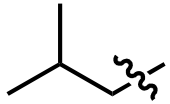
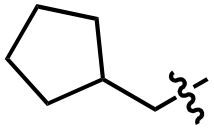
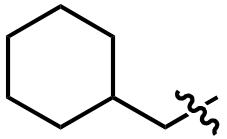






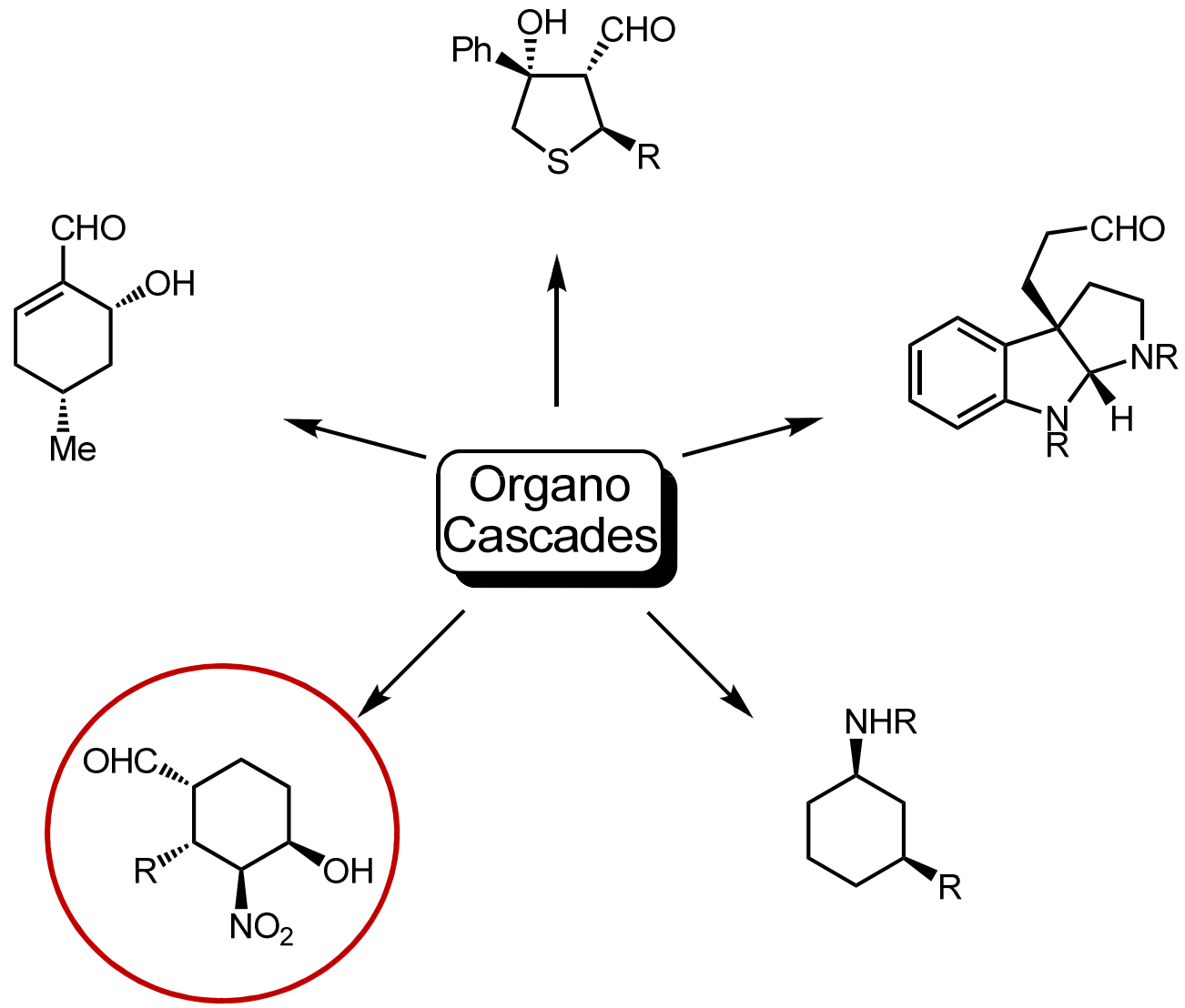
Substrate Scope



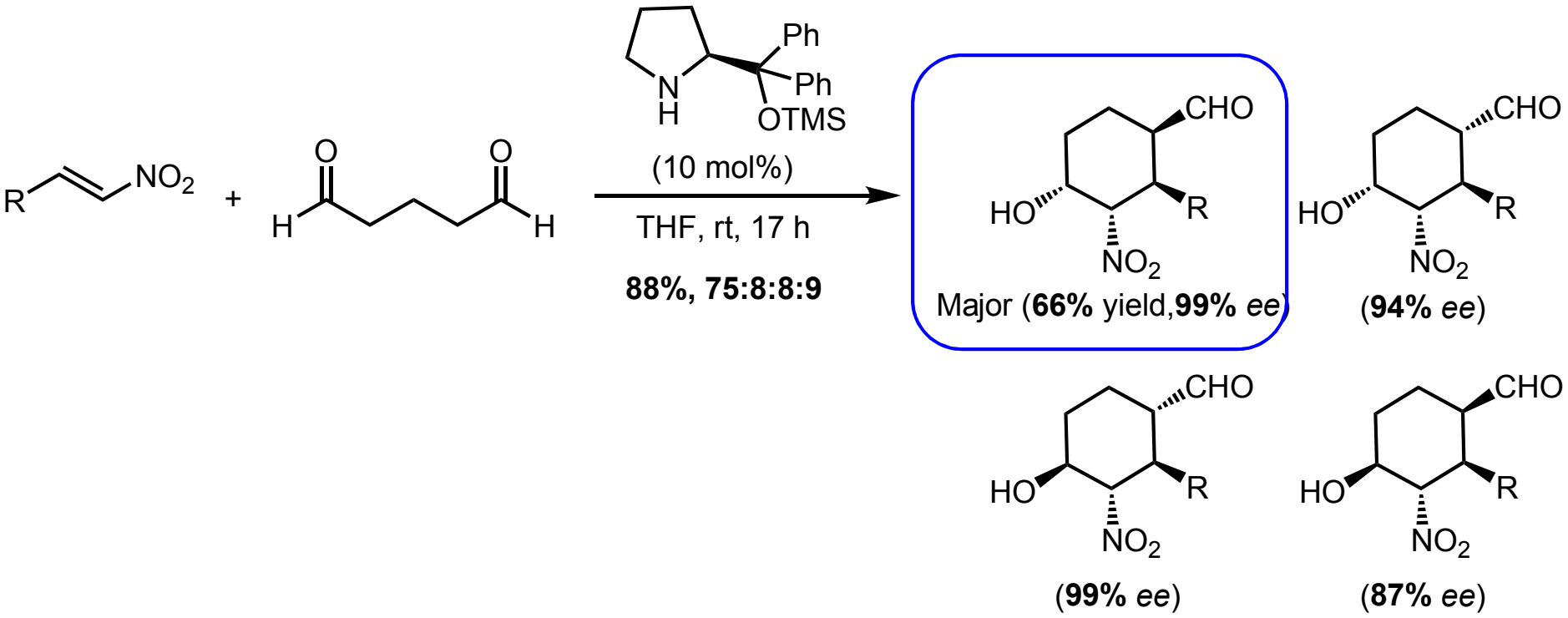
Entry	R^1	R^2	X	Yield (%)	*dr*	*er*
1		PEP	CH_2	75	10:1	95:5
2		PEP	CH_2	79	12:1	98:2
3		PEP	CH_2	72	24:1	98:2
4		PMP	CH_2	89	19:1	98:2
5	Me	PEP	CH_2	88	6:1	92:8
6	Me	PEP	O	72	99:1	96:4
7	Me	PEP	S	35	2:1	95:5

List, B.; Zhou, J. *J. Am. Chem. Soc.* **2007**, *129*, 7498

Different Scaffolds



Cyclohexane Carbaldehydes

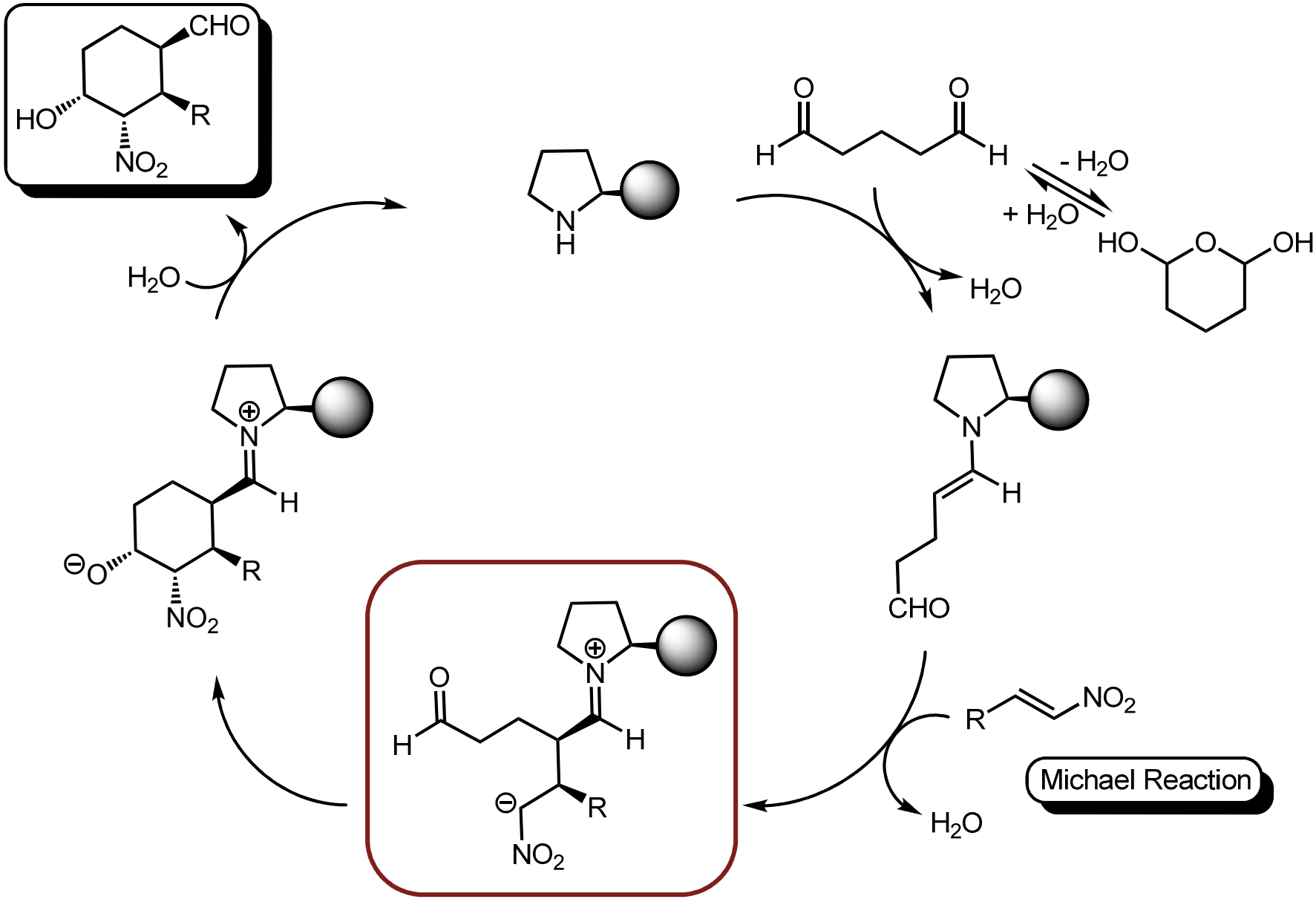


Reactions : Michael/ Henry

Efficiency : 4 new stereocenters
2 new bonds

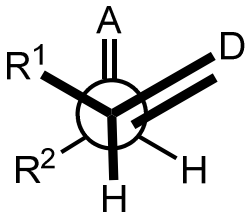
Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 4922

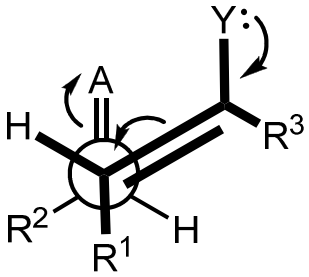
Mechanism: Catalytic Cycle



Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 4922

Diastereoselectivity in Michael addition: Seebach Model : A Topological Rule





A = Acceptor
D = Donor

The preferred approach of two prochiral centers:

1. with *staggering* of all bonds around the newly formed bond;

2. in a *gauche* arrangement of the *donor* (C=D)-bond between the (C-A)- and the (C-H)-bonds of the *acceptor*;

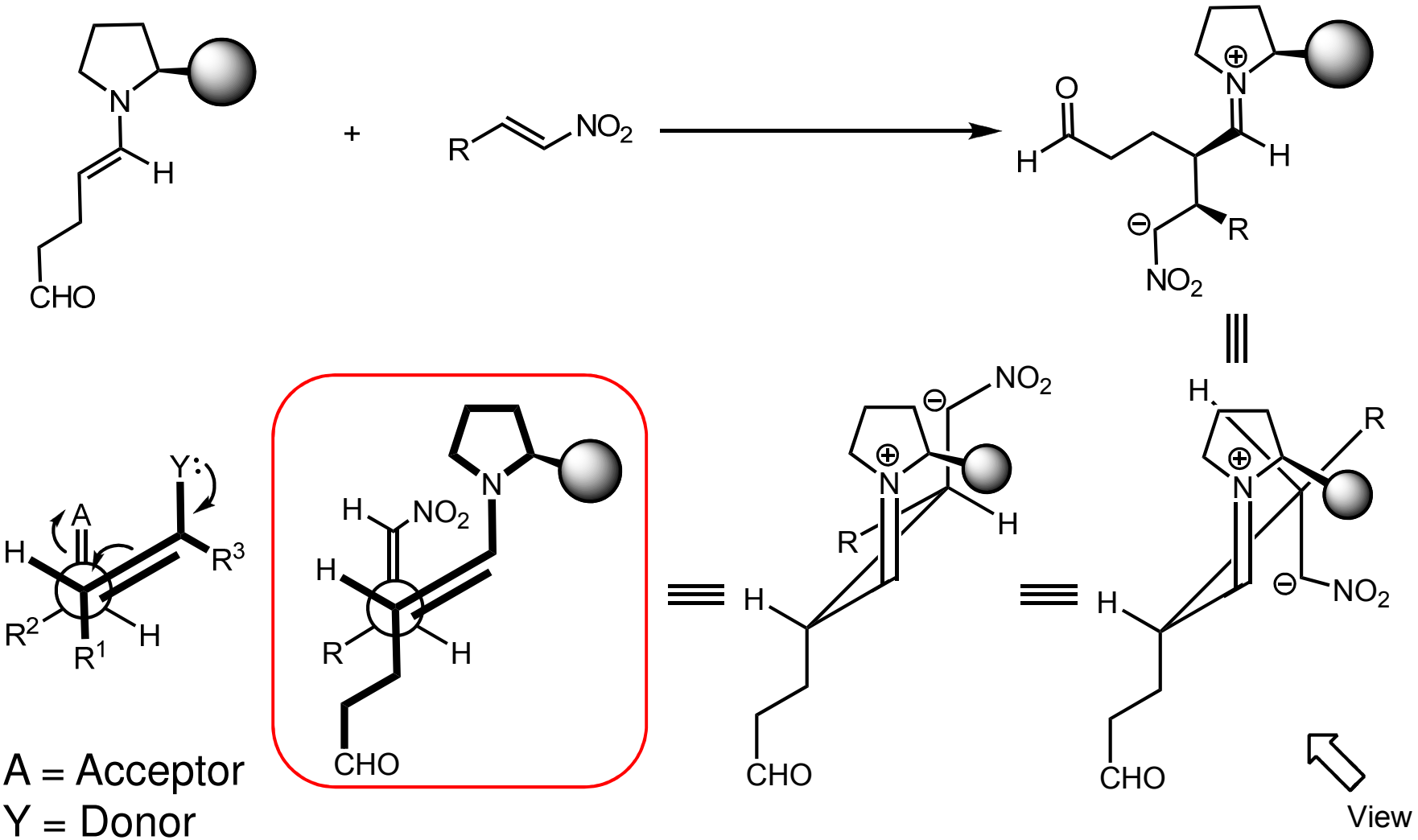
3. *with the H-atom*, the smaller substituent on the donor atom component, in an *anti* position with respect to the (C=A)-bond

4. if the components exists in *(E/Z) (anti/syn)*-isomeric forms,the *actual donor* and *acceptor* atoms are situated *close* to each other. (Coulomb attraction i.e. minimalization of the charge separation holding A and D or Y together)

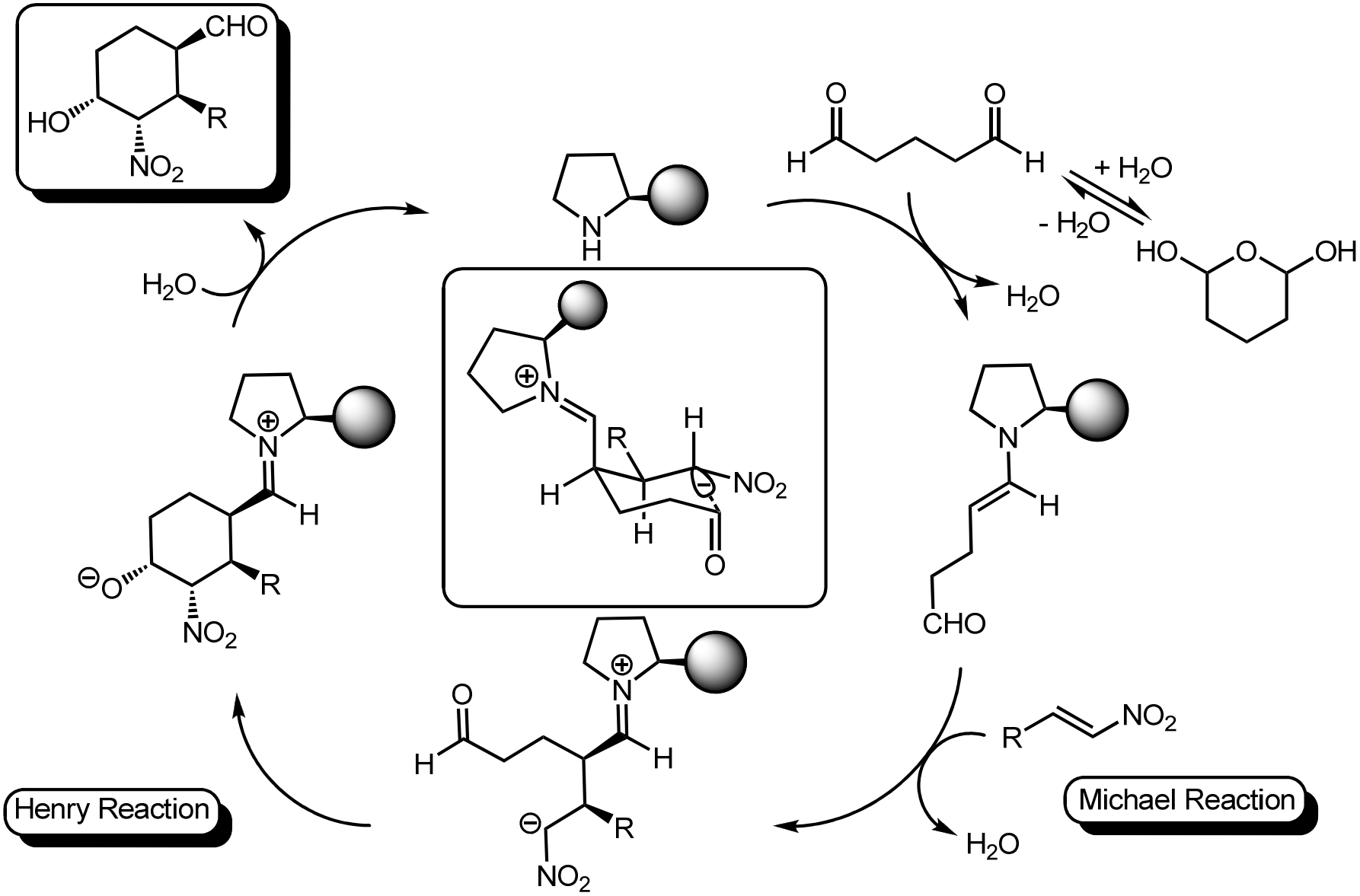
* Steric Repulsion between D/Y and R^2 push R^2 in anti position

Seebach, D.; Golinski, J. *Helv. Chim. Acta*, **1981**, *64*,1413

Diastereoselectivity in Michael Addition

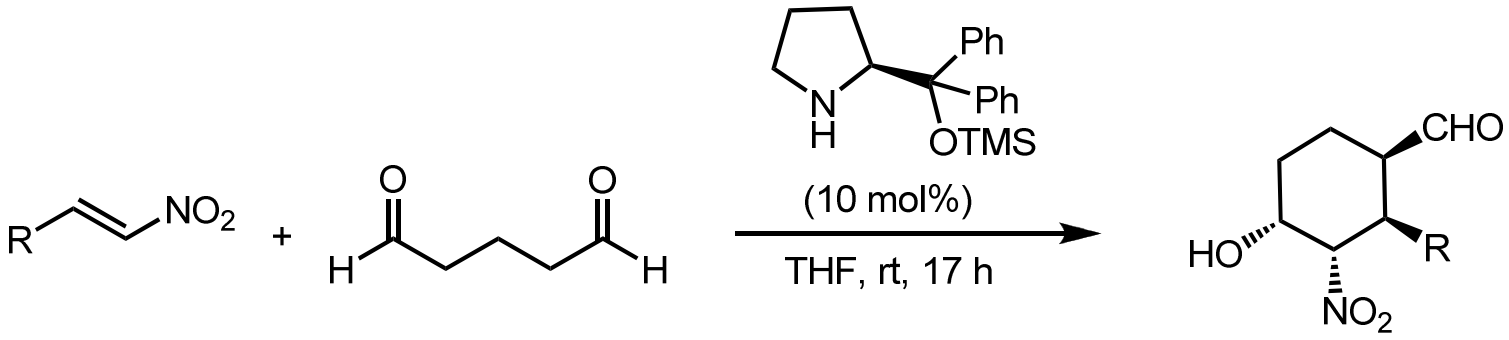


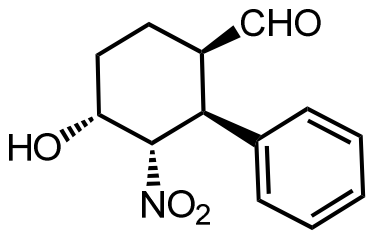
Mechanism: Catalytic Cycle



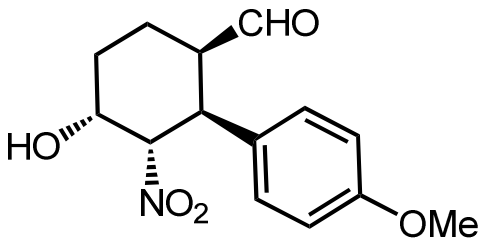
Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 4922

Substrate Scope

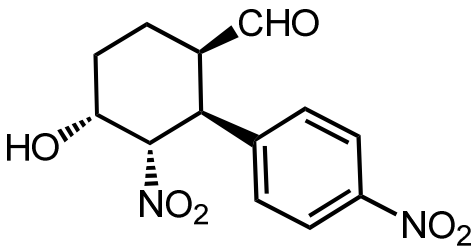




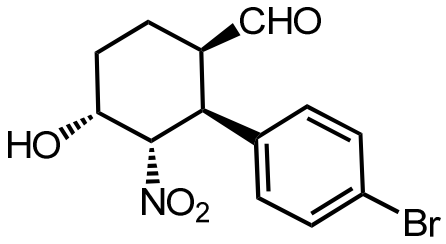
66% yield, **99%** *ee,* **17** h



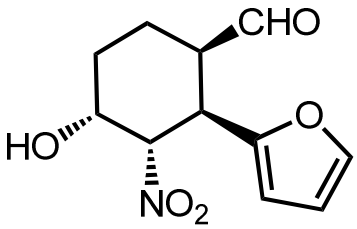
60% yield, **98%** *ee,* **20** h



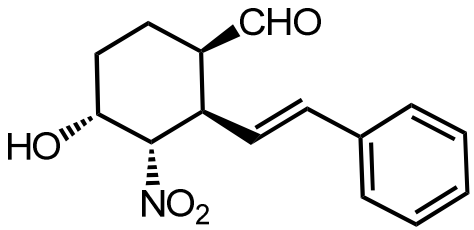
71% yield, **97%** *ee,* **3.5** h



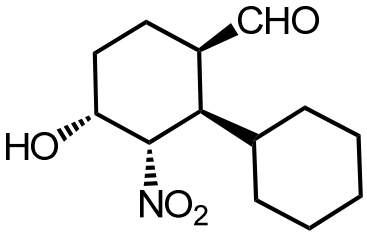
64% yield, **99%** *ee,* **4** h



68% yield, **99%** *ee,* **20** h



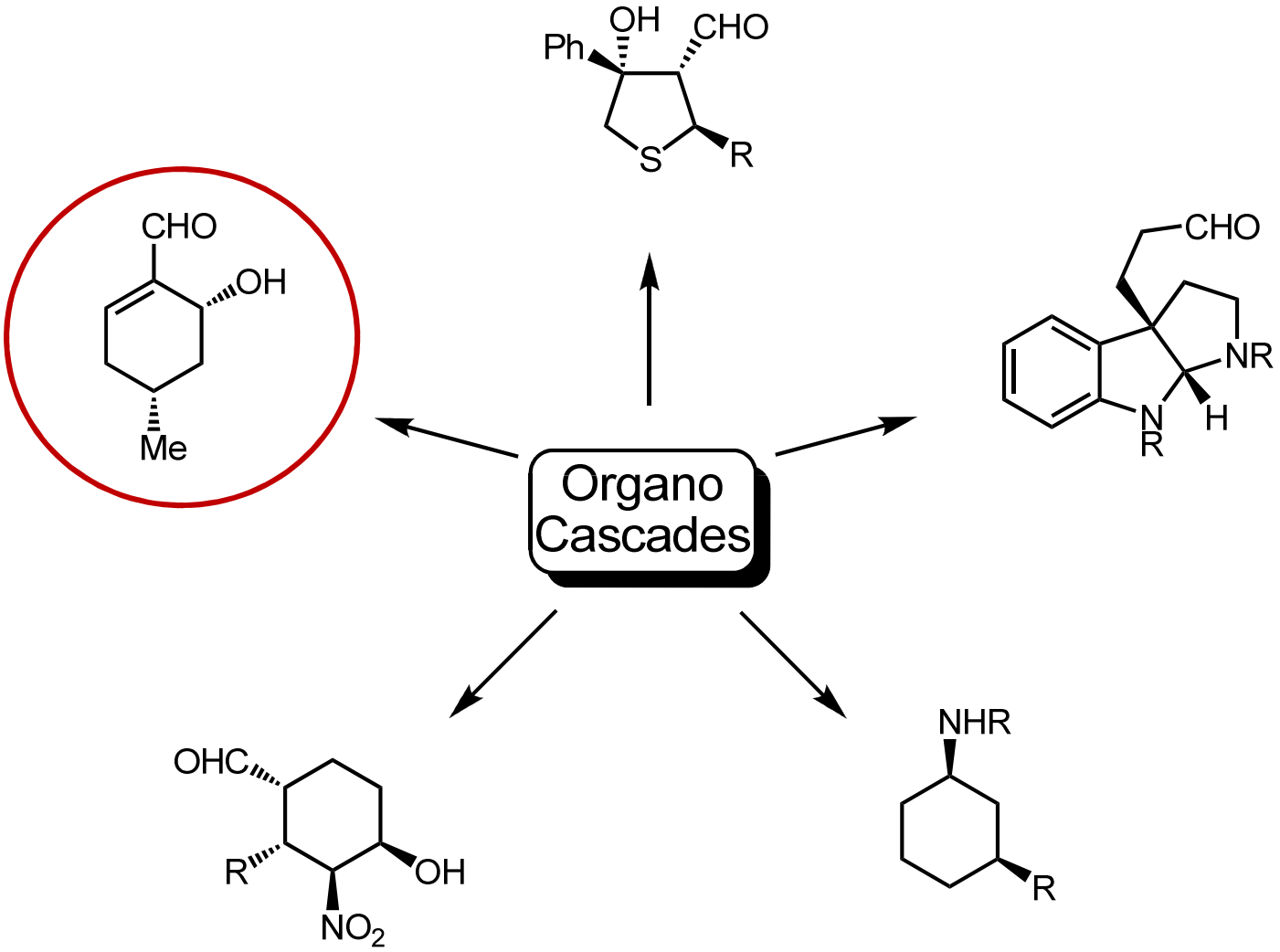
55% yield, **98%** *ee,* **10** h



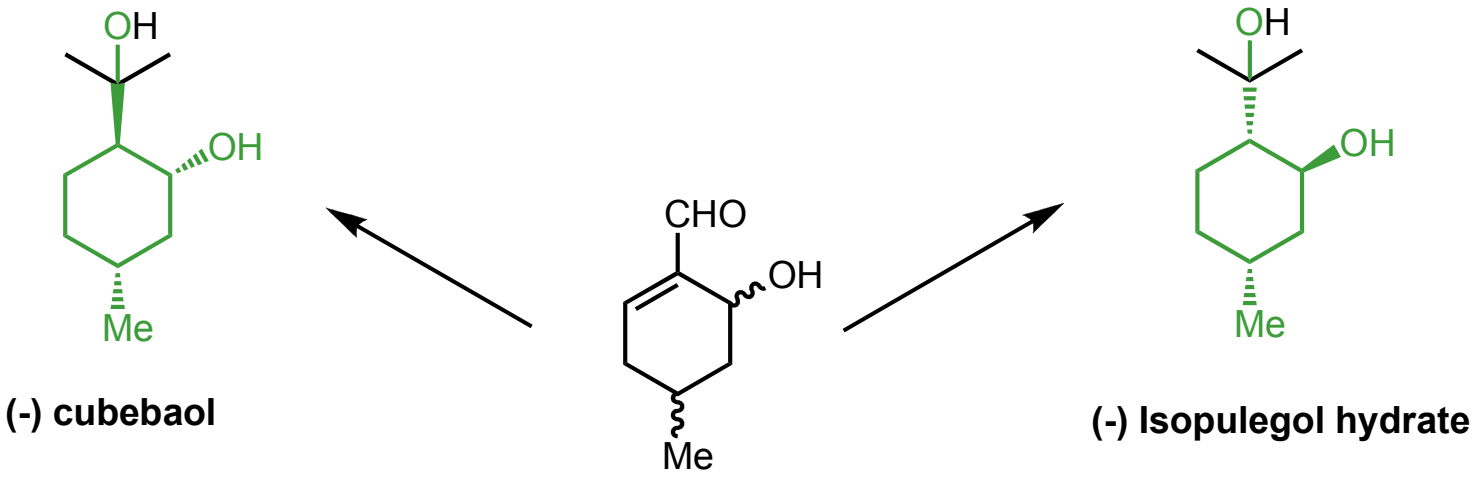
45% yield, **99%** *ee,* **24** h

Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 4922

Different Scaffolds

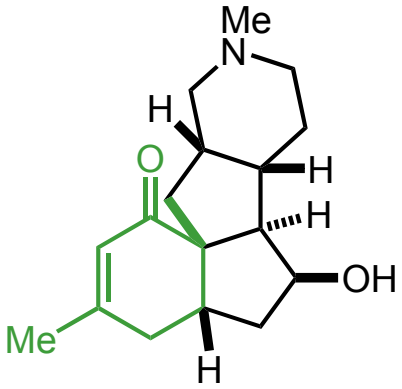


Cyclohexene Carbaldehydes



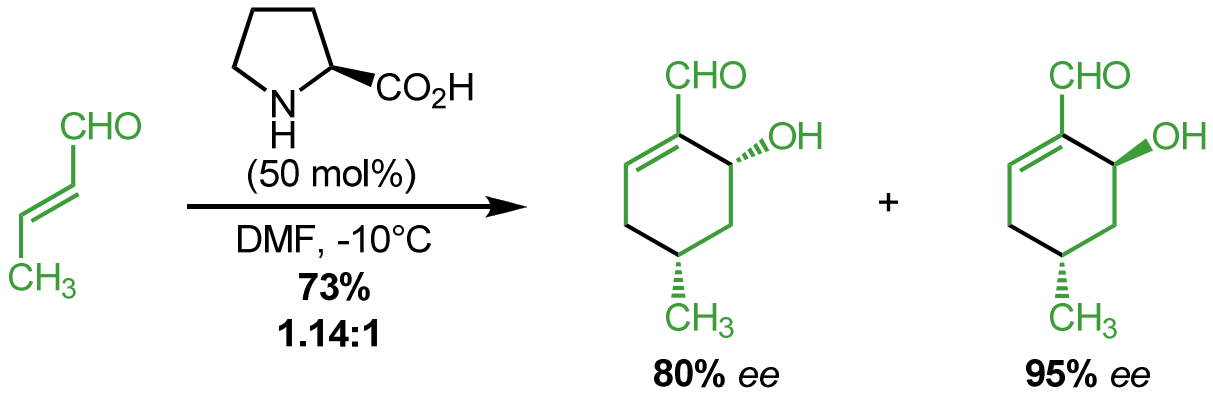
(-) cubebaol

(-) Isopulegol hydrate



magellanine

[3+3] Cycloaddition of α,β-Unsaturated Aldehydes



Catalytic Mode : Iminium-Enamine

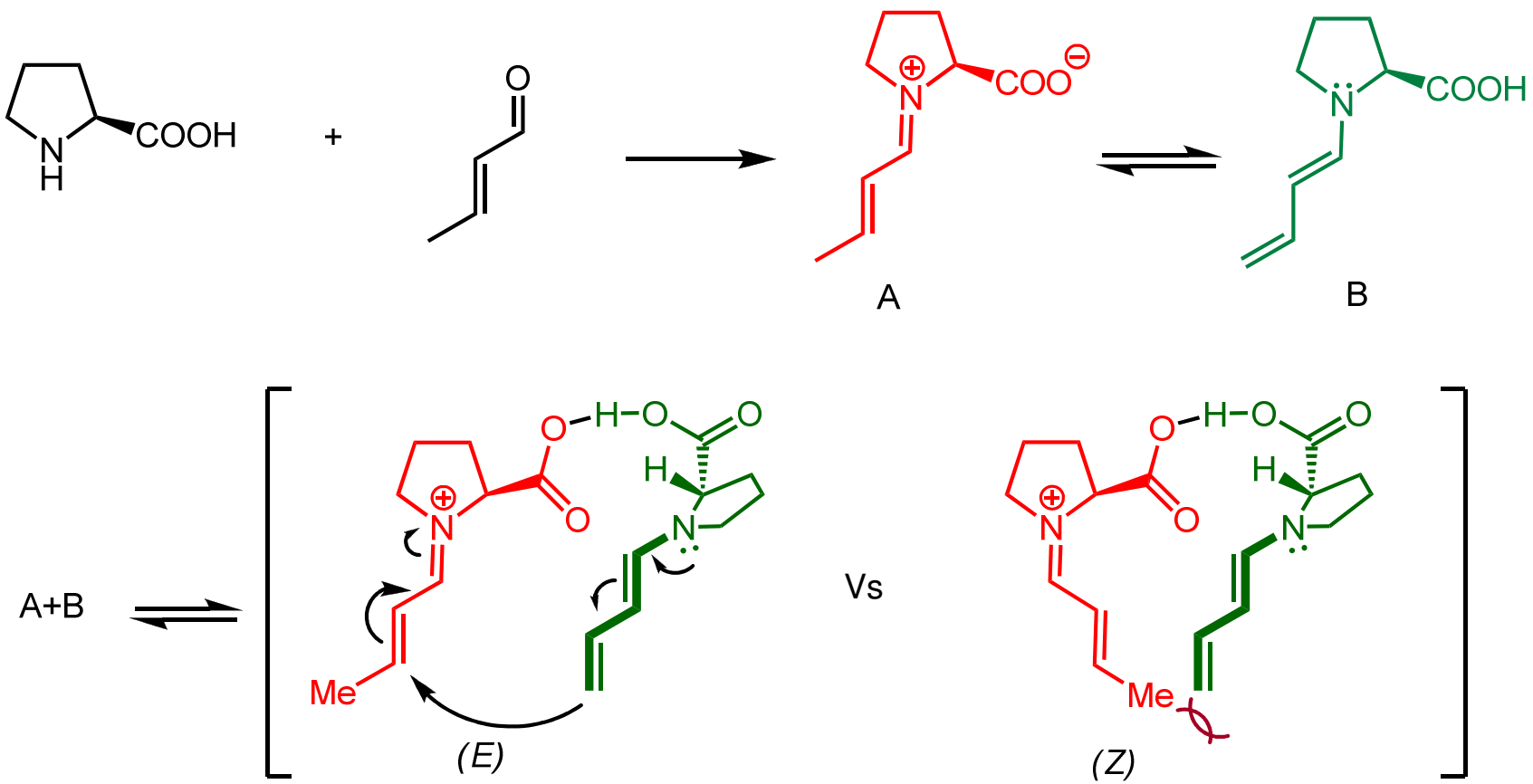
Reactions : Michael / Aldol

Efficiency : 2 new stereocenters

2 new bonds

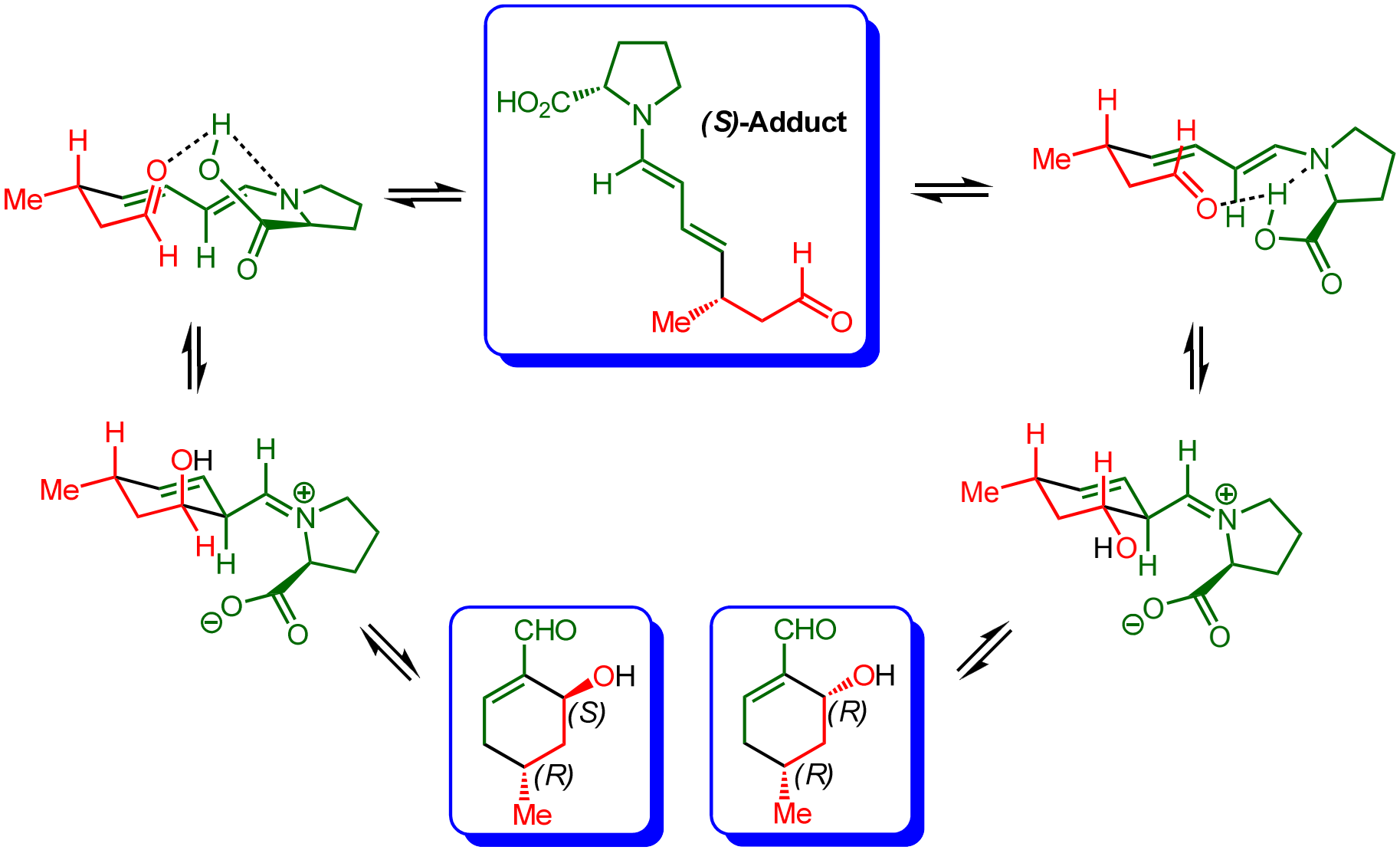
Hong, B.; Wu, M.; Tseng, H.; Liao, J. *Org. Lett.*, **2006**, *8*, 2217

Mechanism



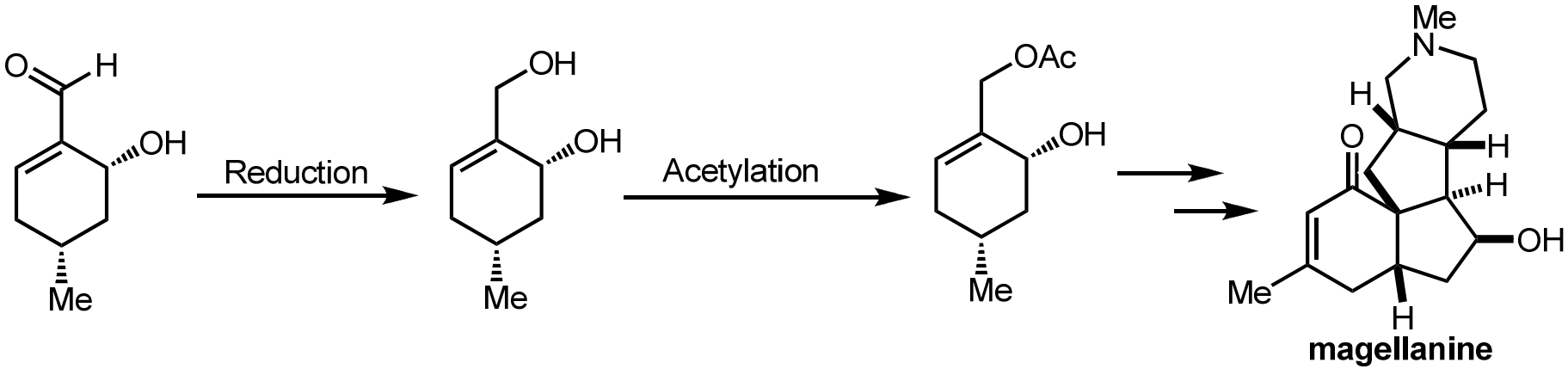
Hong, B.; Wu, M.; Tseng, H.; Liao, J. *Org. Lett.*, **2006**, *8*, 2217

Mechanism

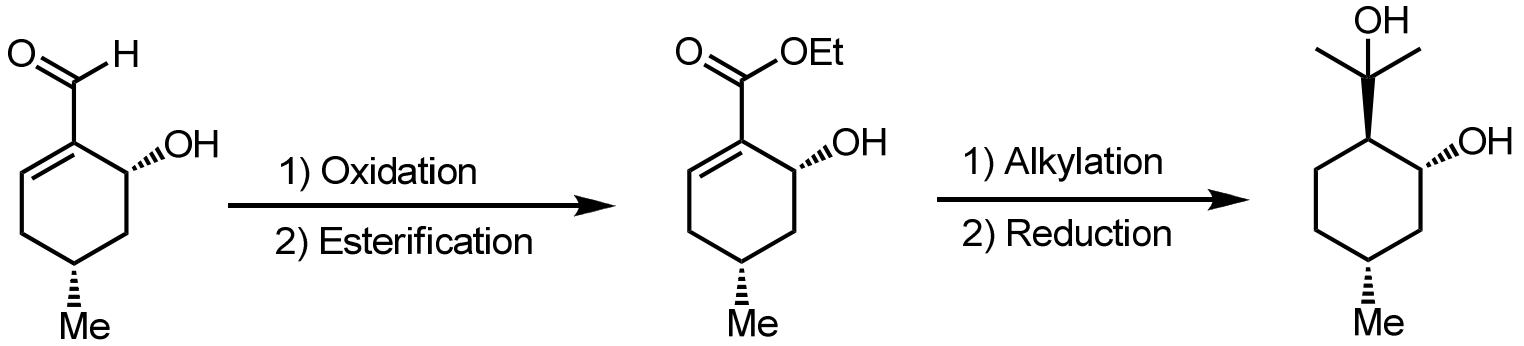


Hong, B.; Wu, M.; Tseng, H.; Liao, J. *Org. Lett.*, **2006**, *8*, 2217

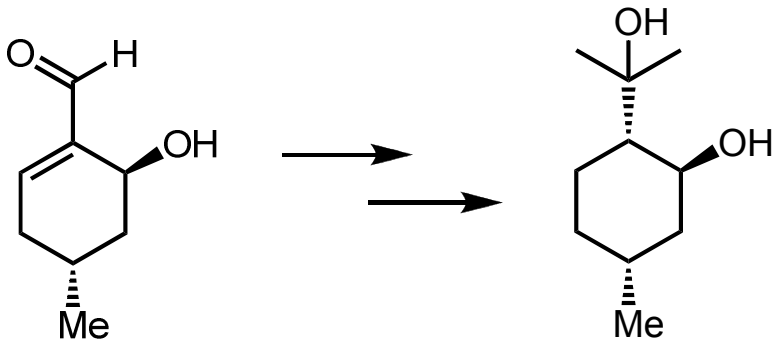
Application to Total Synthesis



magellanine



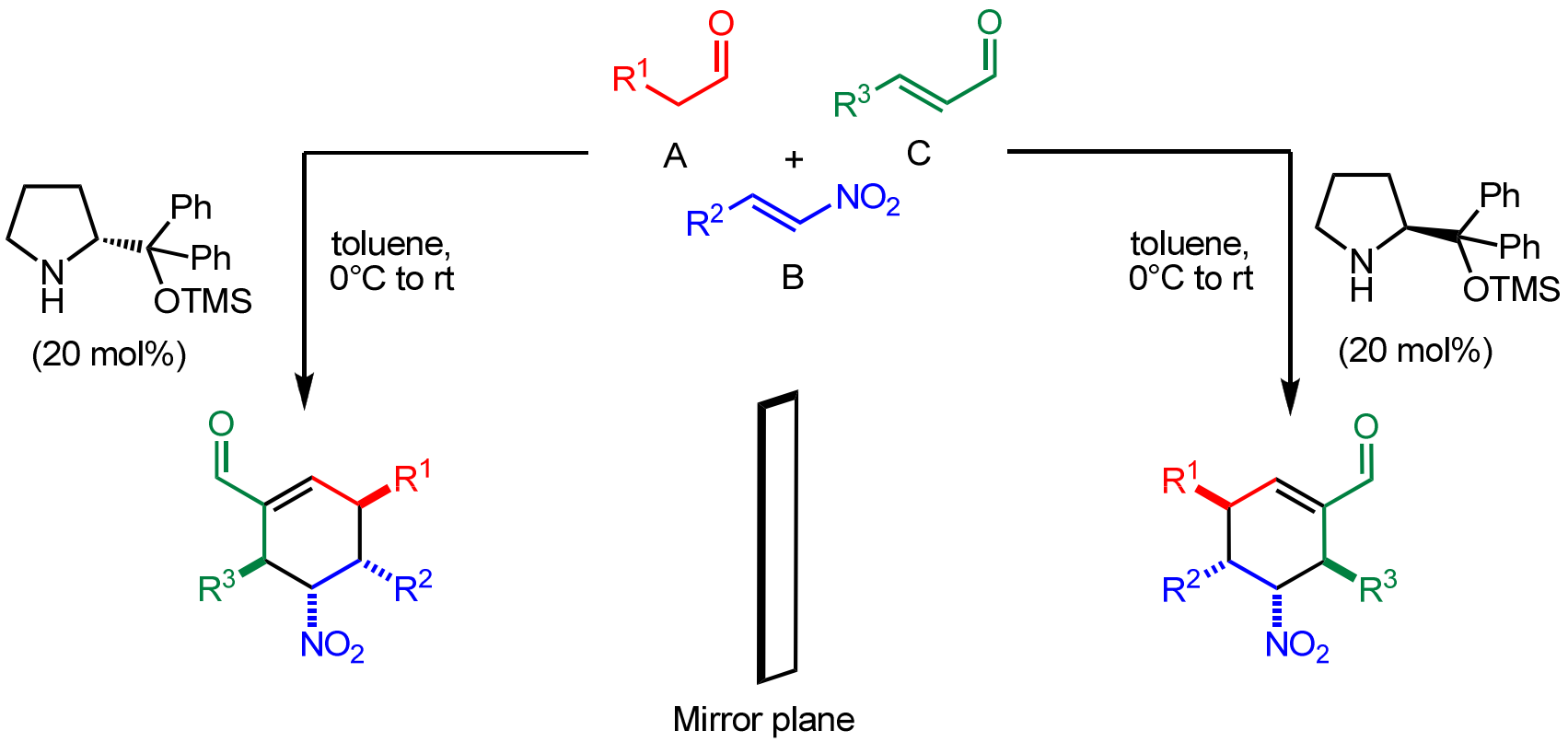
***(-)*-isopulegol hydrate**



***(-)*-cubebaol**

Hong, B.; Wu, M.; Tseng, H.; Liao, J. *Org. Lett.*, **2006**, *8*, 2217

A Triple Cascade Organocatalytic Reaction



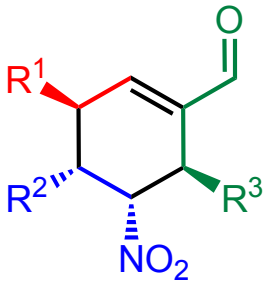
Catalytic Mode : Enamine-Iminium-Enamine

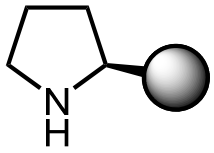
Reactions : Michael/ Michael/ Aldol

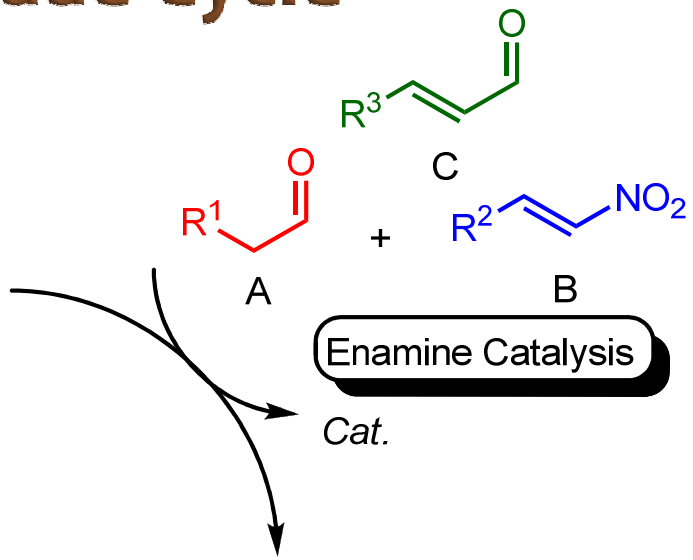
Efficiency : 4 new stereocenters , 3 new bonds

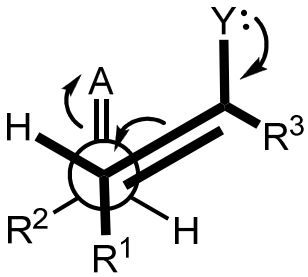
Enders, D.; Huttl, M. R. M.; Raabe, G.; Grondal, C. *Nature* **2006**, *441*, 861

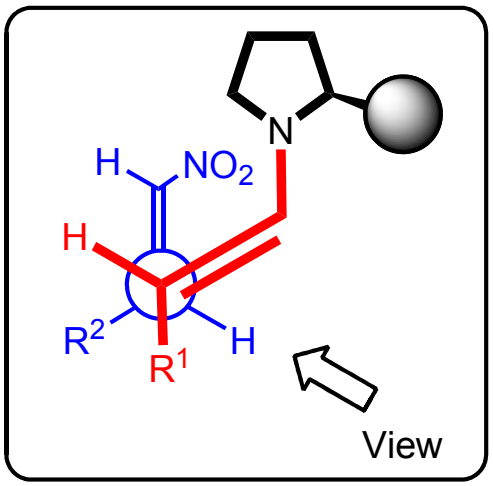
Proposed Catalytic Cascade Cycle











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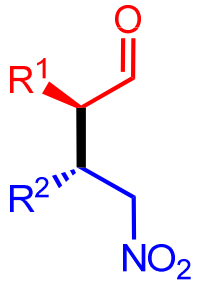
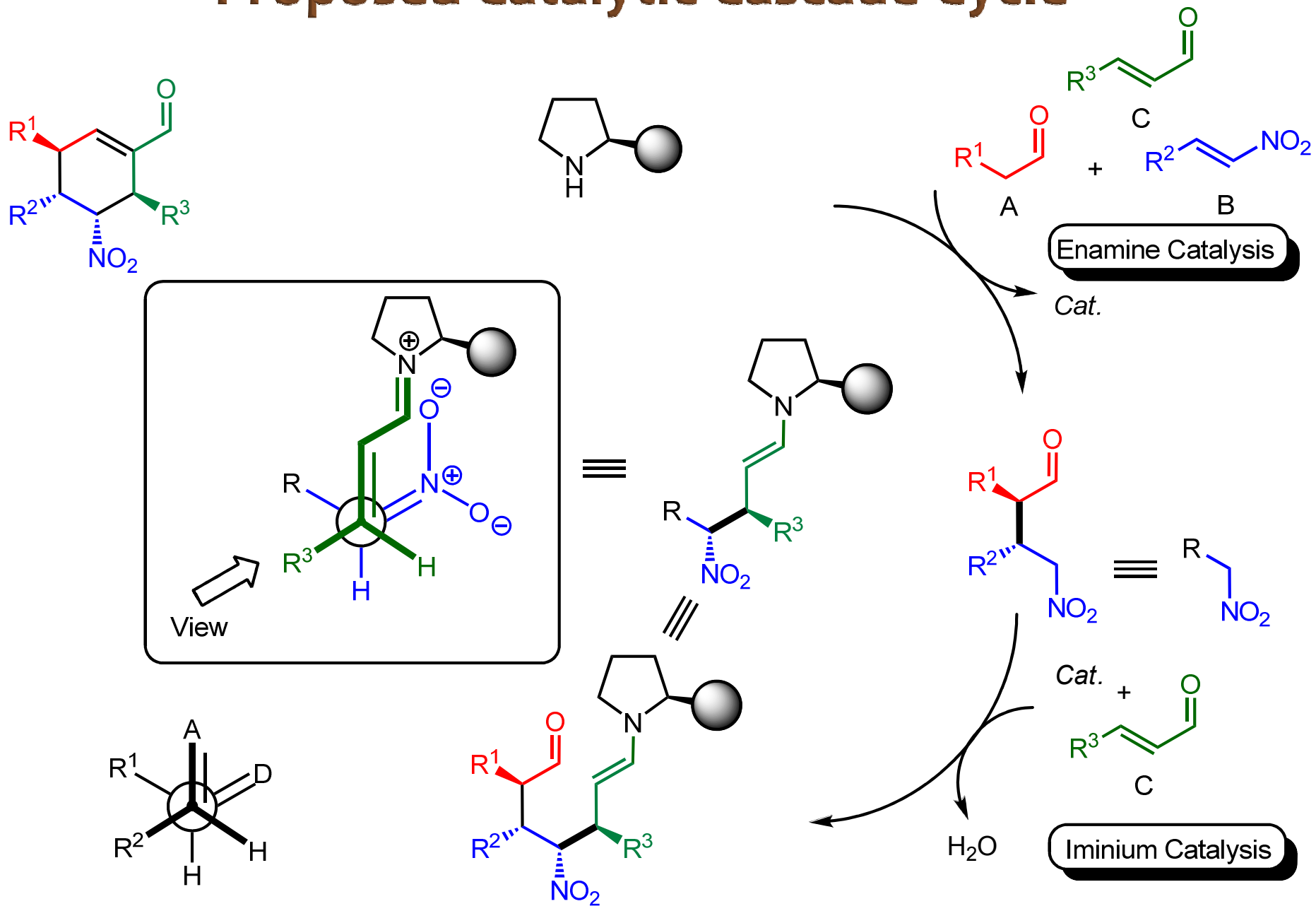


A = Acceptor
Y = Donor

Seebach, D.; Golinski, J. *Helv. Chim. Acta*, **1981**, *64*,1413

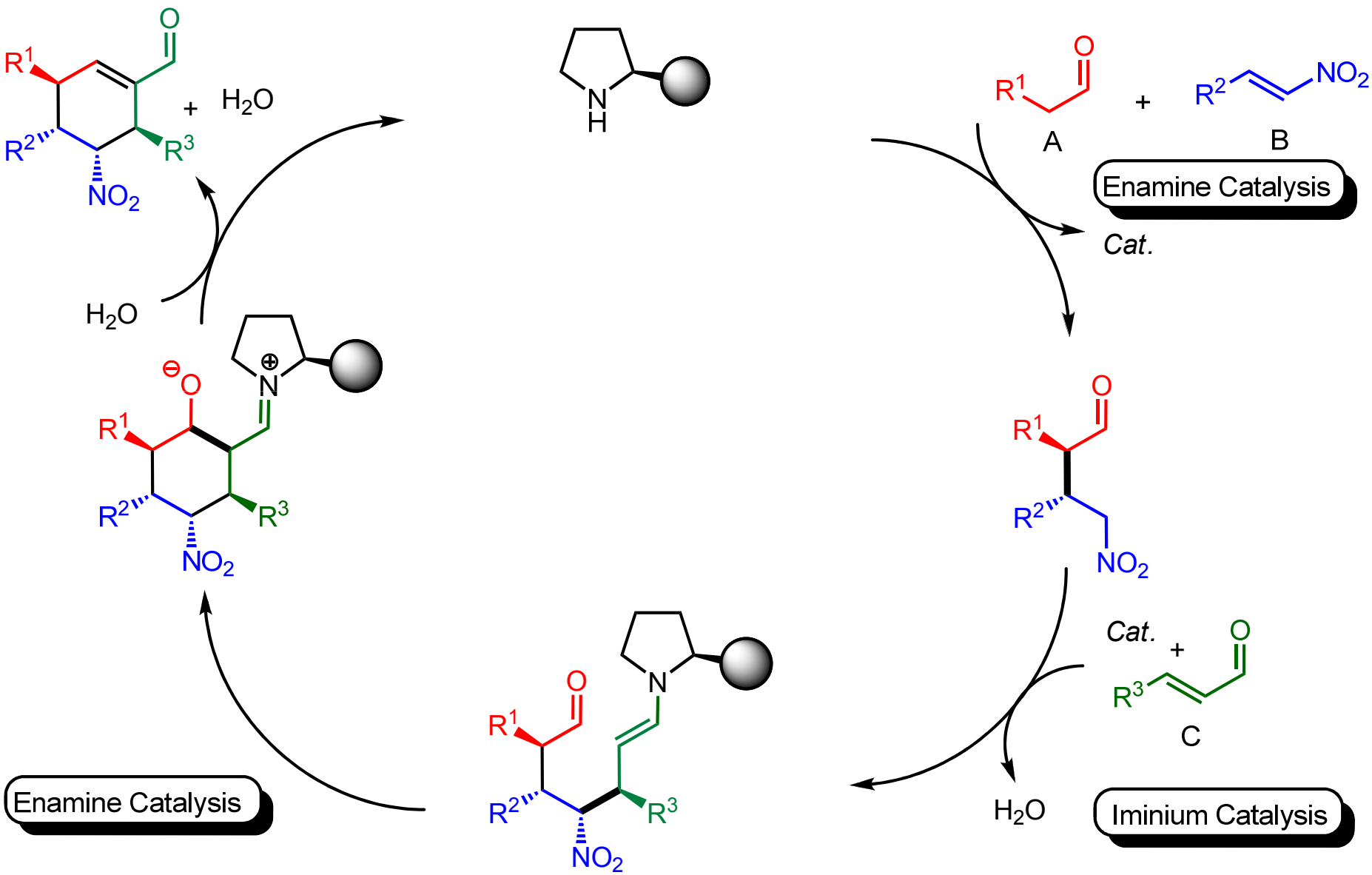
Enders, D.; Huttl, M. R. M.; Raabe, G.; Grondal, C. *Nature* **2006**, *441*, 861

Proposed Catalytic Cascade Cycle



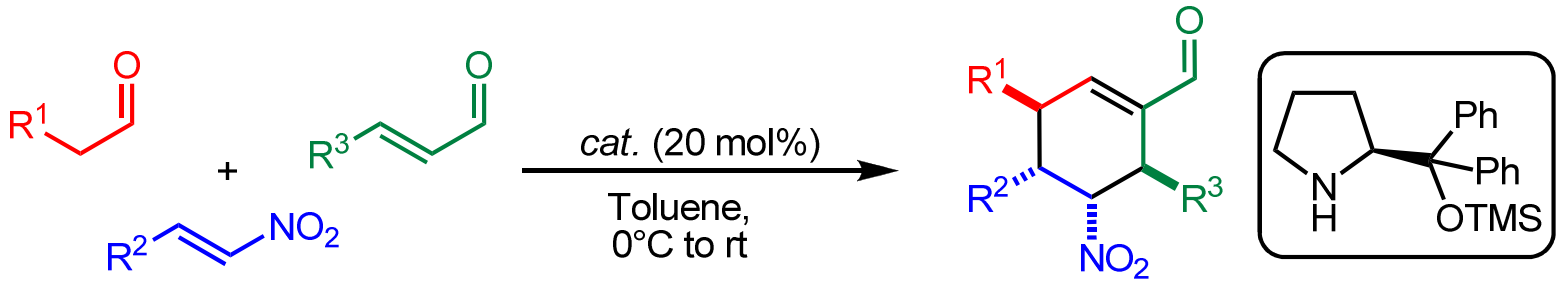
Enders, D.; Huttl, M. R. M.; Raabe, G.; Grondal, C. *Nature* **2006**, *441*, 861

Proposed Catalytic Cascade Cycle



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

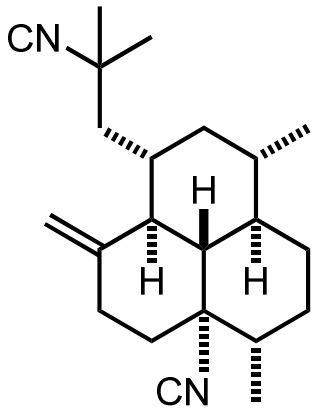
Substrate Scope



Entry	R^1	R^2	R^3	Yield(%)	*ee*(%)
1	Me	*o*-ClPh	Ph	51	>99
2	Me	*p*-MeOPh	Ph	38	>99
3	Et	Ph	Ph	58	>99
4	*i*-Pr	Ph	Ph	56	>99
5	Bn	Ph	Ph	38	>99
6	CH_2OTBS	Ph	Ph	54	99
7	Me	Ph	H	50	>99
8	Me	Ph	Me	25	>99
9	Me	Ph	*n*-Bu	29	>99
10	Me	5-Methyl-furan-2-yl	Ph	37	99

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

Potential Application to Total Synthesis

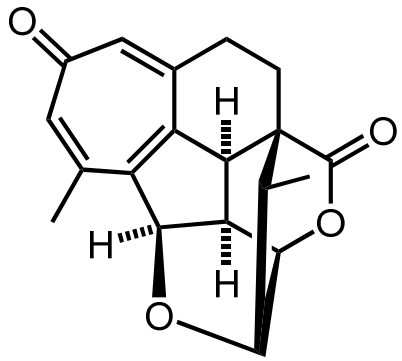


(-)-8,15-diisocyano-11, 20-amphilectene

Isolation:
Wratten *et.al. Tet. Lett*. **1978**, 4345

Biological Activity:
Antimicrobial properties

Previous Sythesis:
Edward *et.al. JOC*, **1989**, 1483

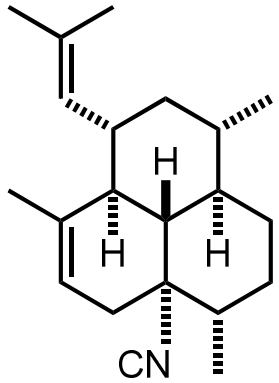


Hainanolide

Isolation:
Buta *et.al. JOC*. **1978**,1002

Biological Activity:
Antiviral properties
Antitumor properties

Previous Sythesis:
Mander *et.al. JACS* **1998**, 1914



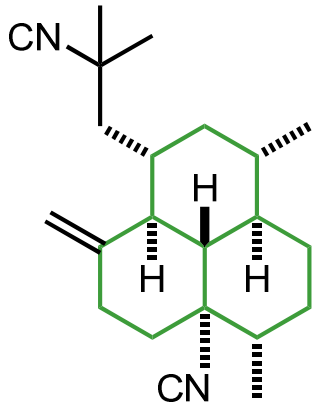
(-)-8-isocyano-10,14-amphilectadiene

Isolation:
Wratten *et.al. Tet. Lett*. **1978**, 4345

Biological Activity:
Antimicrobial properties

Previous Sythesis:
Edward *et.al. Tet. Lett.* **1993**, 5791

Potential Application to Total Synthesis



(-)-8,15-diisocyano-11, 20-amphilectene

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Wratten *et.al. Tet. Lett*. **1978**, 4345

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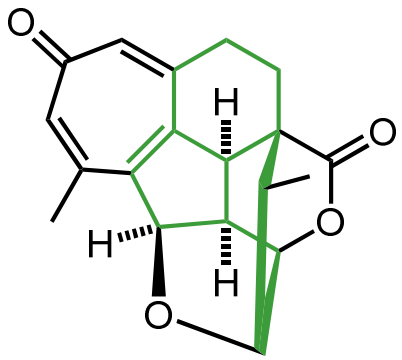

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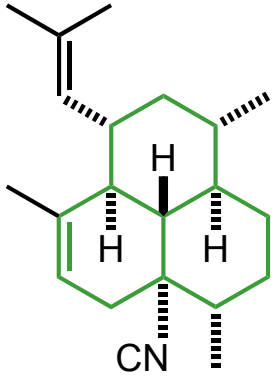


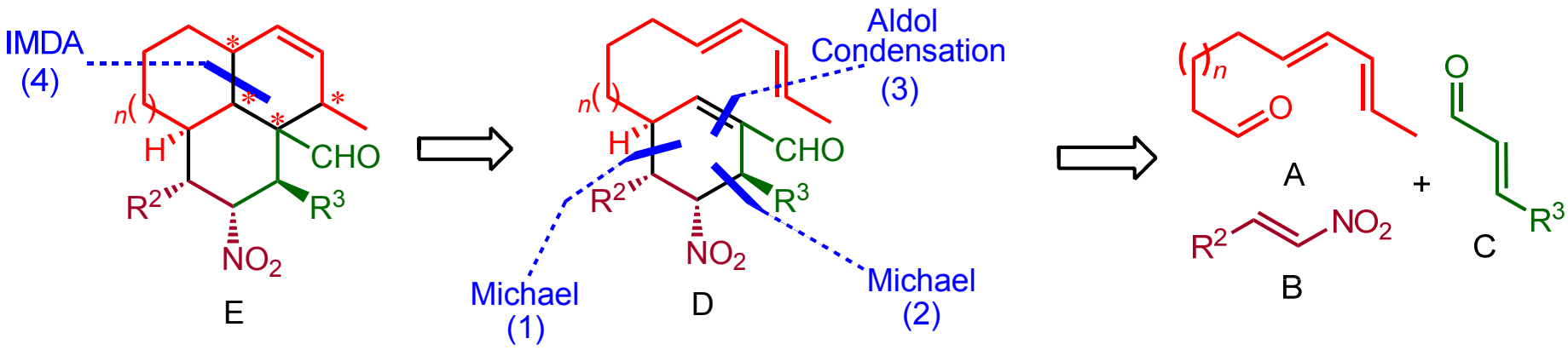
(-)-8-isocyano-10,14-amphilectadiene

Isolation:
Wratten *et.al. Tet. Lett*. **1978**, 4345

Biological Activity:
Antimicrobial properties

Previous Sythesis:
Edward *et.al. Tet. Lett.* **1993**, 5791

One-Pot Organocatalytic Triple-Cascade/Diels–Alder approach to Tricyclic Frameworks E



Catalytic Mode: Enamine-Iminium-Enamine

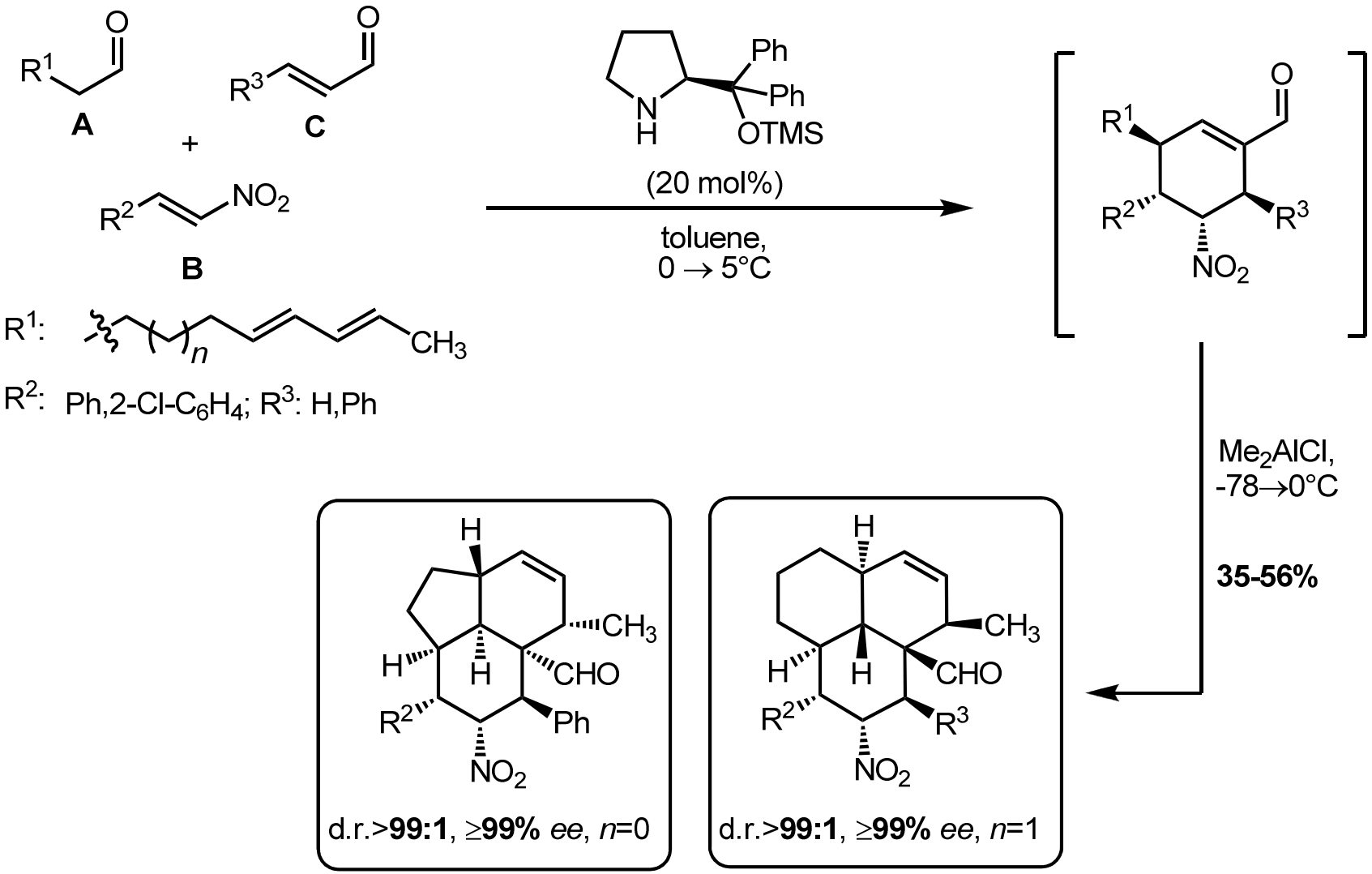
Reactions : Michael/ Michael/ Aldol/ IMDA

Efficiency : 8 new stereocenters, 5 new bonds

Others : High enantioselectivities (>99%)

Enders, D.; Huttl, M. R. M.; Raabe, G.; Wendt, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 467

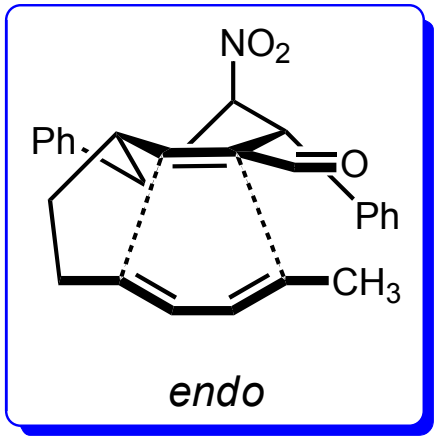
Michael/Michael/Aldol Condensation/IMDA



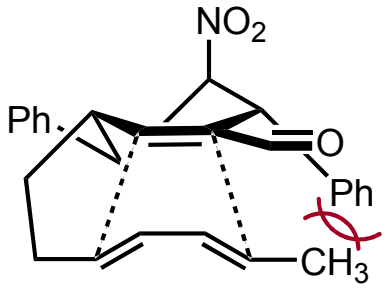
Enders, D.; Huttl, M. R. M.; Raabe, G.; Wendt, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 467

Transition States for IMDA

TS for n = 0

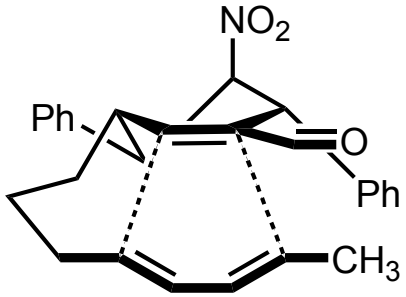


endo

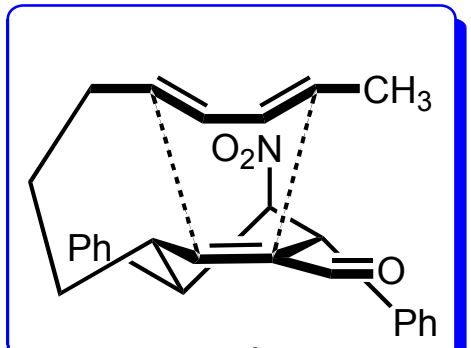


exo

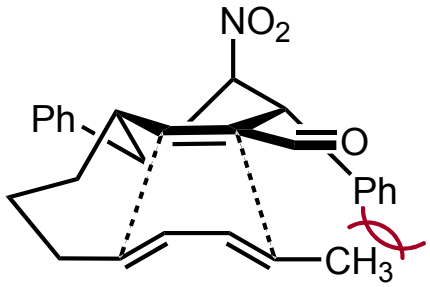
TS for n = 1



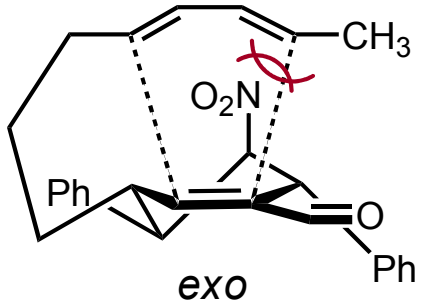
endo



endo



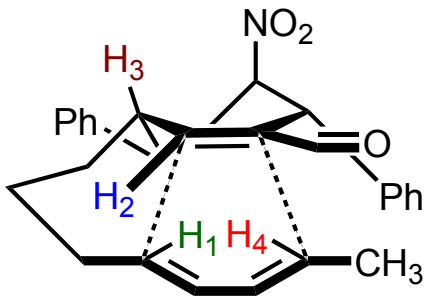
exo



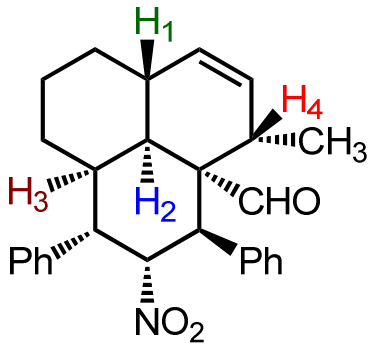
exo

Enders, D.; Huttl, M. R. M.; Raabe, G.; Wendt, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 467

Transition States for IMDA (NOE effect)



endo



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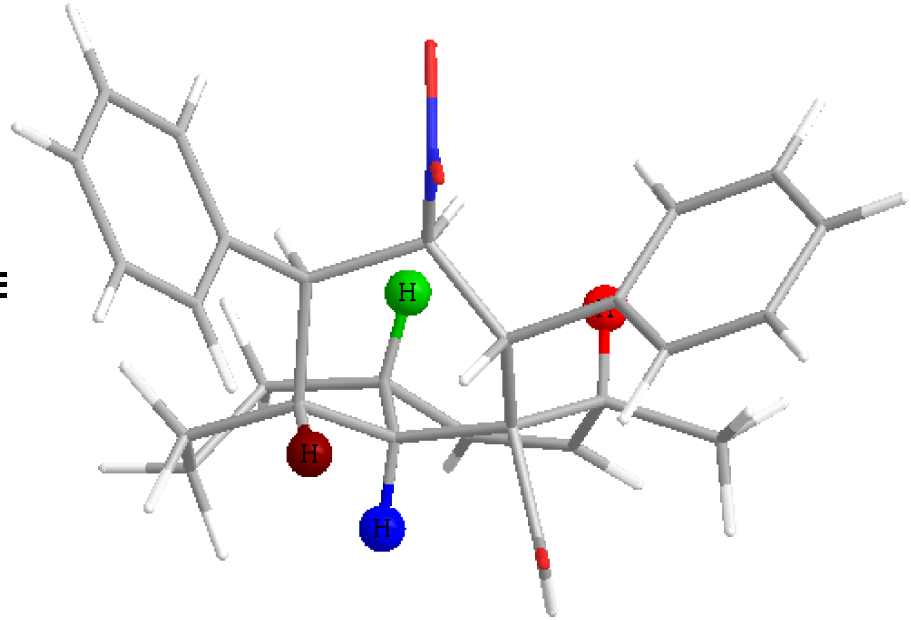
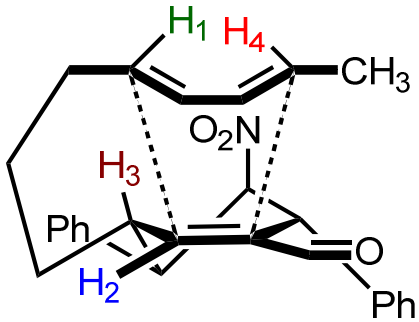
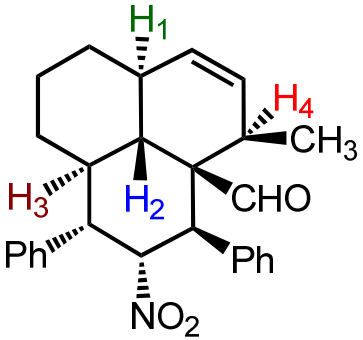
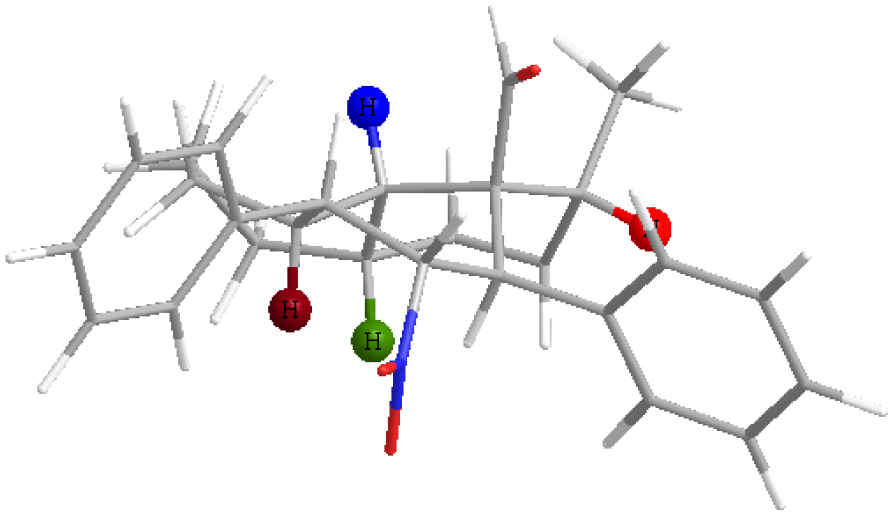




endo

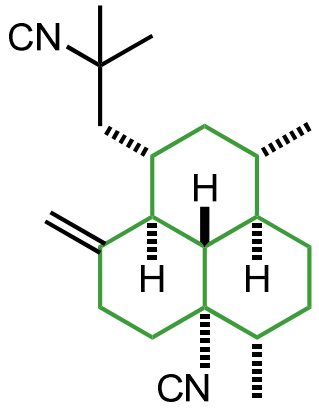


≡



Enders, D.; Huttl, M. R. M.; Raabe, G.; Wendt, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 467

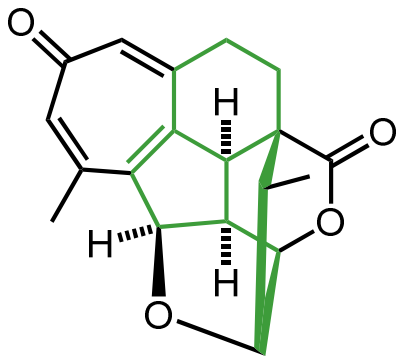
Potential Application to Total Synthesis



(-)-8,15-diisocyano-11, 20-amphilectene

Previous Sythesis:
Edward *et.al. JOC*, **1989**, 1483

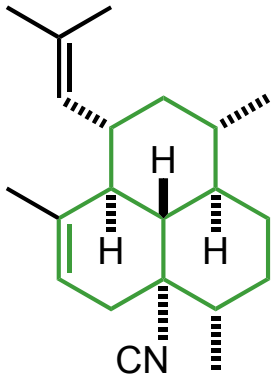
More than18 steps



Hainanolide

Previous Sythesis:
Mander *et.al. JACS* **1998**, 1914

More than16 steps

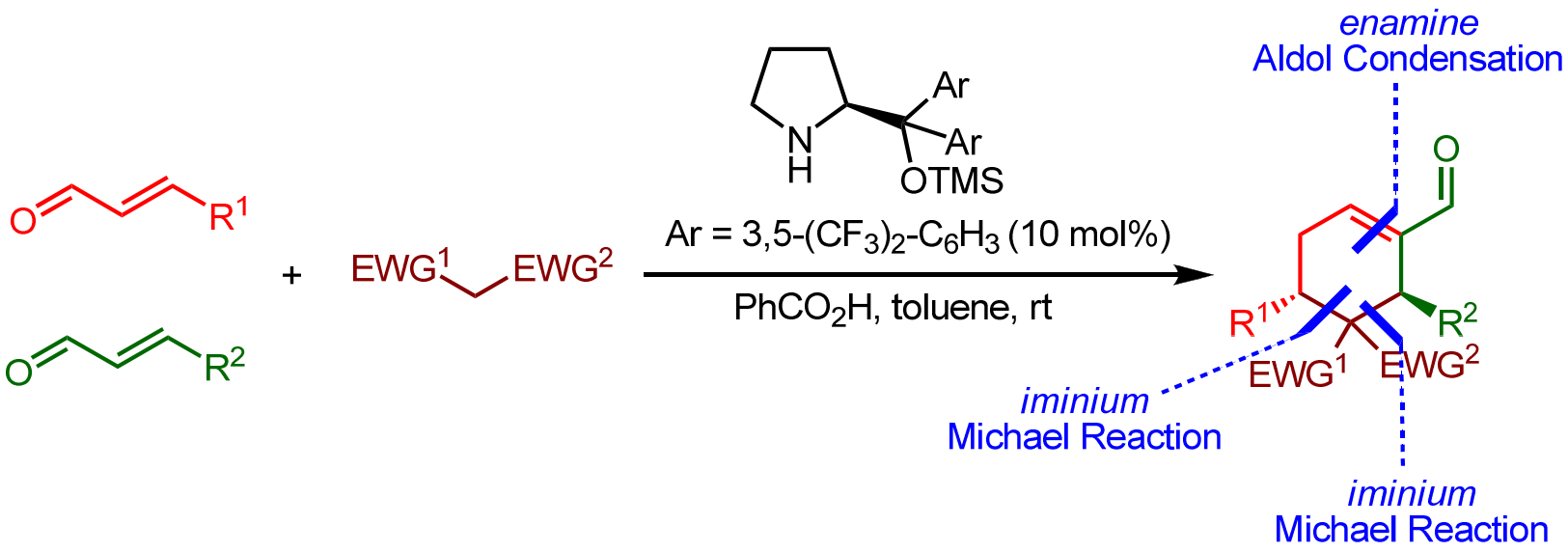


(-)-8-isocyano-10,14-amphilectadiene

Previous Sythesis:
Edward *et.al. Tet. Lett.* **1993**, 5791

More than12 steps

Organocatalytic Multicomponent Domino Asymmetric Reaction



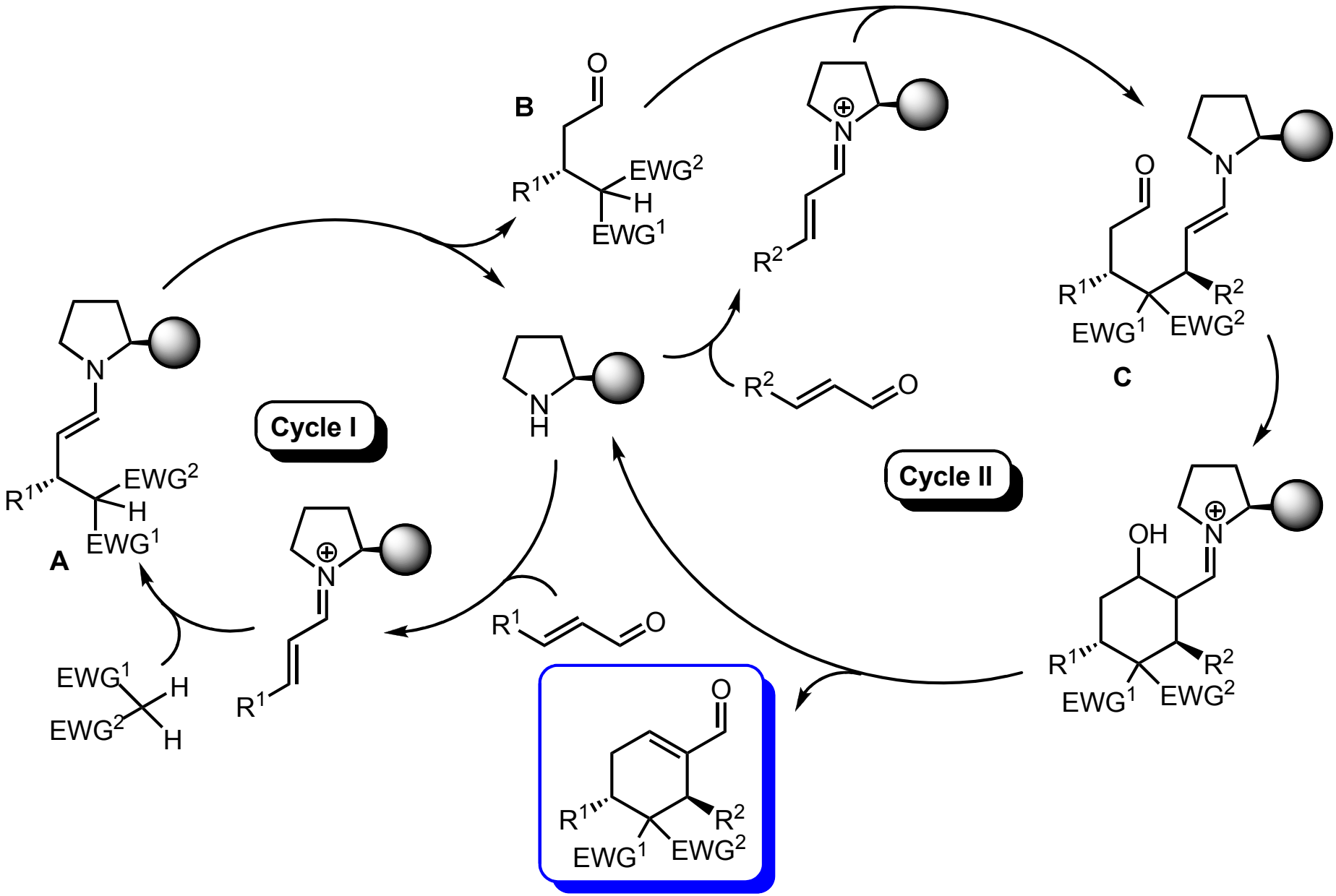
Catalytic Mode : Iminium-Iminium-Enamine

Reactions : Michael/ Michael/ Aldol

Efficiency : 2-3 new stereocenters , 3 new bonds

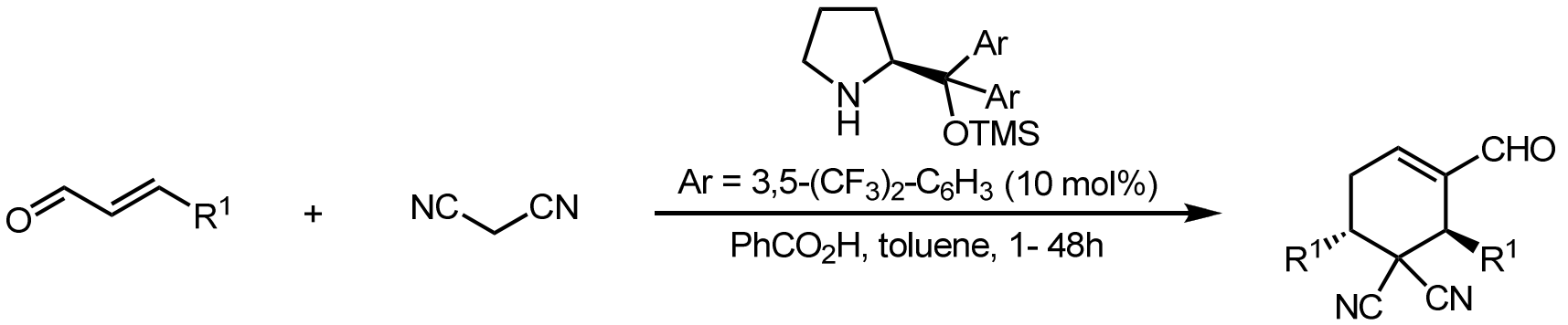
Jørgensen. K. A.; Carlone, A.; Cabera, S.; Marigo, M. *Angew. Chem. Int. Ed.* **2007,** *46*, 1101

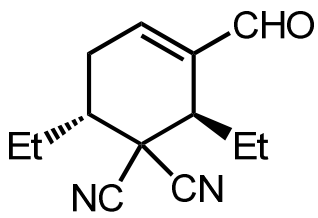
Proposed Catalytic Cycle



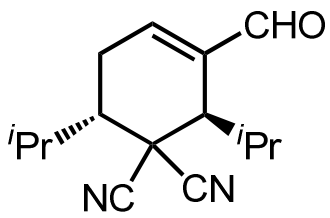
Jørgensen. K. A.; Carlone, A.; Cabera, S.; Marigo, M. *Angew. Chem. Int. Ed.* **2007,** *46*, 1101

Substrate Scope

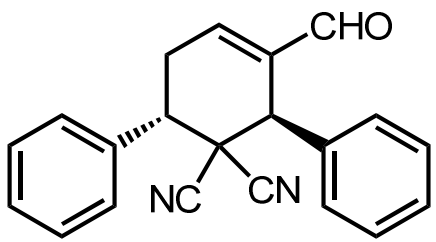




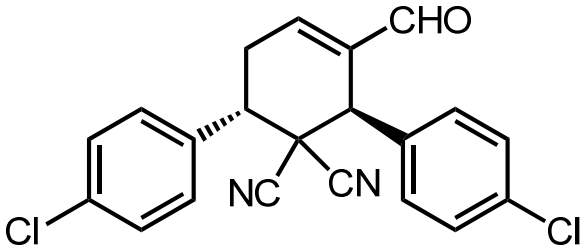
89% yield, **98%** *ee*



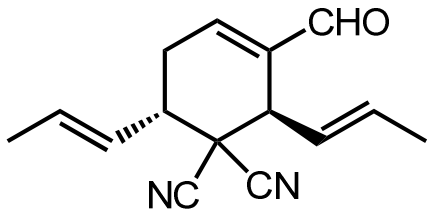
68% yield, >**99%** *ee*



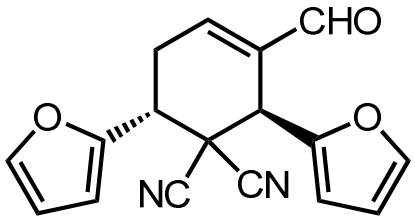
77% yield, >**99%** *ee*



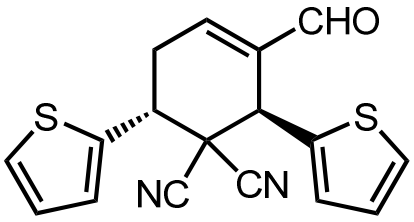
54% yield, >**99%** *ee*



80% yield, **97%** *ee*



57% yield, **98%** *ee*



66% yield, **97%** *ee*

Jørgensen. K. A.; Carlone, A.; Cabera, S.; Marigo, M. *Angew. Chem. Int. Ed.* **2007,** *46*, 1101

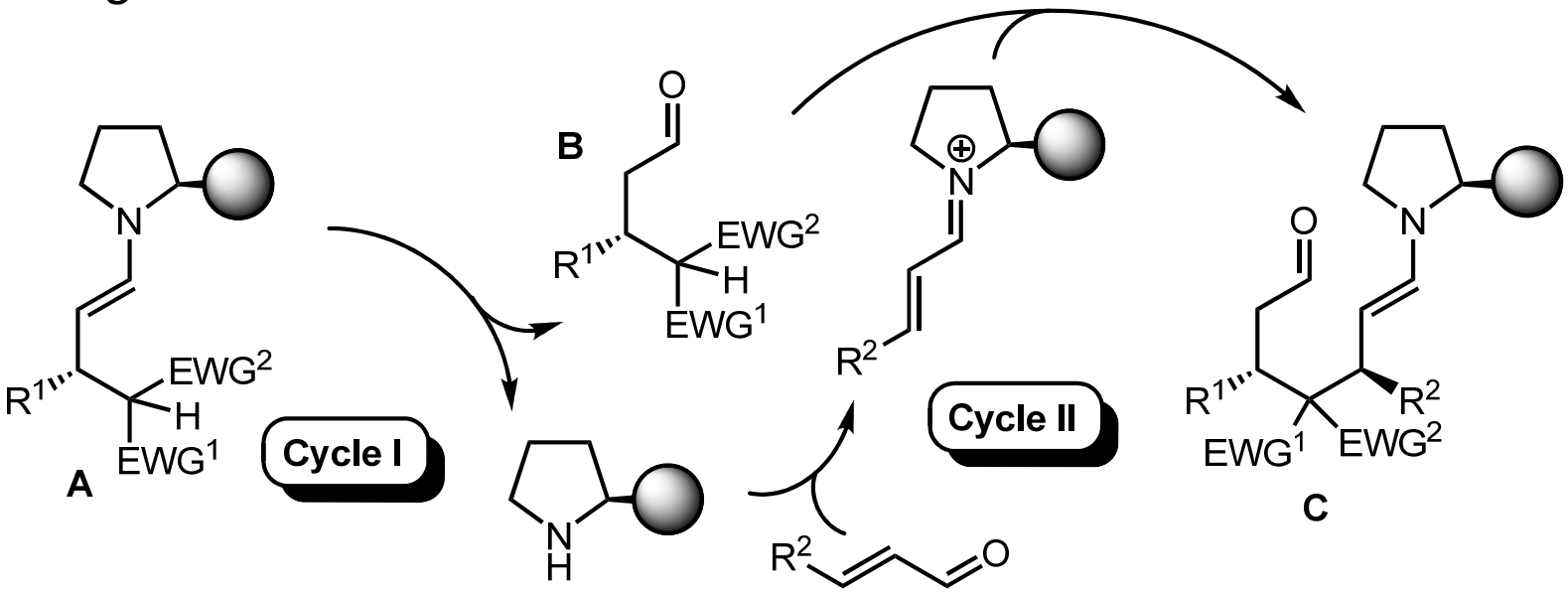
Substrate Scope

How about taking two different *α,β*-unsaturated aldehydes ?

Requirement: Controling the reaction sequence

- R^1- aldehyde to be unreactive enough in cycle II so that Cycle I would be completed prior to the beginning of the formation of **C.**

- R^2- aldehyde could be subsequently added and enter Cycle II together with **B.**



Jørgensen. K. A.; Carlone, A.; Cabera, S.; Marigo, M. *Angew. Chem. Int. Ed.* **2007,** *46*, 1101

Substrate Scope

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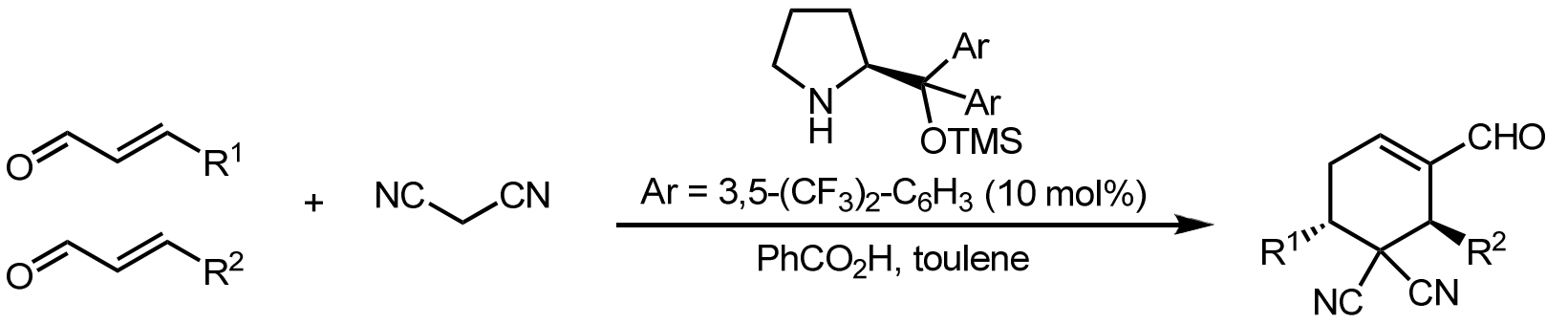
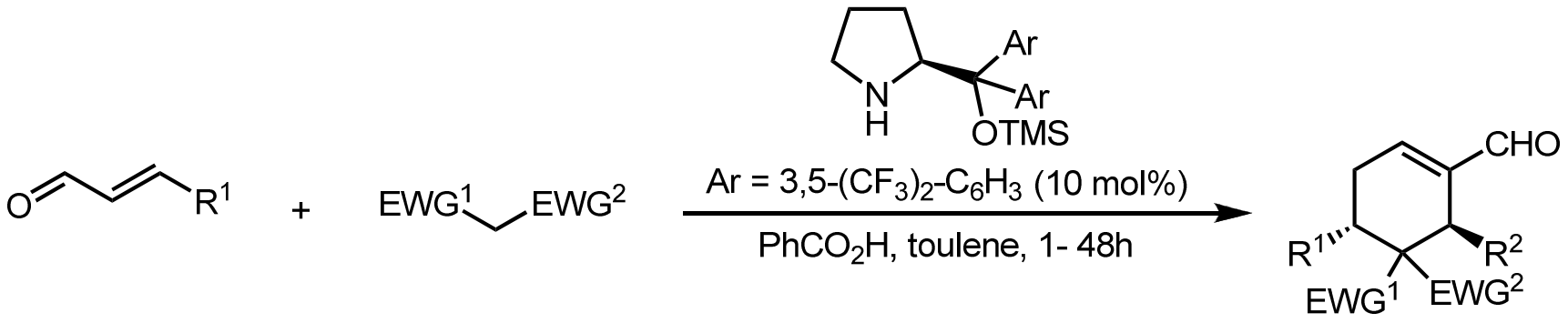
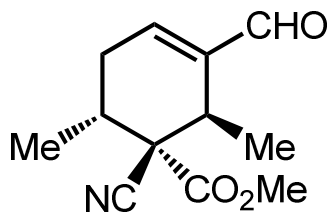


R^1	R^2	Yield(%)	*ee* %
^{i}Pr	Me	**51**	**97**
^{i}Pr	Ph	**52**	**>99**

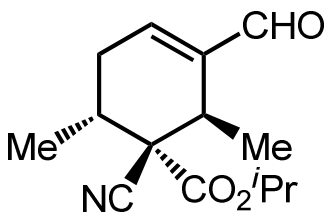
Jørgensen. K. A.; Carlone, A.; Cabera, S.; Marigo, M. *Angew. Chem. Int. Ed.* **2007,** *46*, 1101

Application: Generation of Quaternary Centres

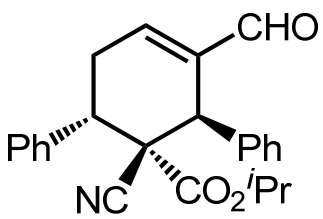




47% yield, **98%** *ee*
86/14 d.r.



40% yield, **99%** *ee*
90/10 d.r.



53% yield, >**99%** *ee*
98/2 d.r.

Better diastereo-control by increasing size of ester group

Jørgensen. K. A.; Carlone, A.; Cabera, S.; Marigo, M. *Angew. Chem. Int. Ed.* **2007,** *46*, 1101

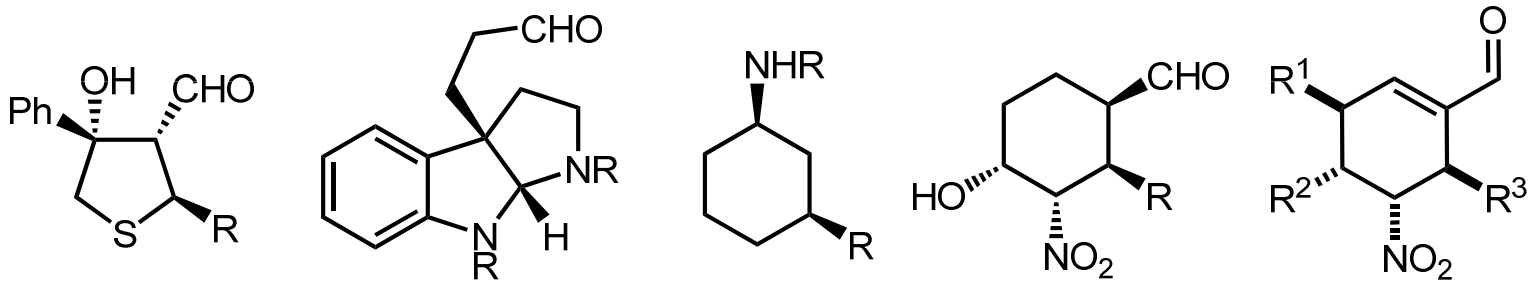
Quadruple Organocatalytic Cascade Reaction and A Cascade of Five

" MacMillan says that his group has now done a (as yet unpublished) quadruple organocascade in the lab, and is working on a cascade of five. But it isn't easy "

http://www.rsc.org/chemistryworld/restricted/2007/August/Atthetopofthecascade.asp

Conclusion

- Generation of new C-C bonds and more than 3 stereocenters in one pot .
- Shortest route to reach structural complexity from simple starting materials & catalysts.
- High diastereoselectivity and high enantioselectivity.
- High catalyst loading e.g. 10-20 mol%.



'One of my goals for the next few years is to try to convince the community that this is a reasonable thing, and we should be doing it. Once we make three, four, hopefully five natural products, I think then everyone will say that this is an exciting way to go.'

: MacMillan

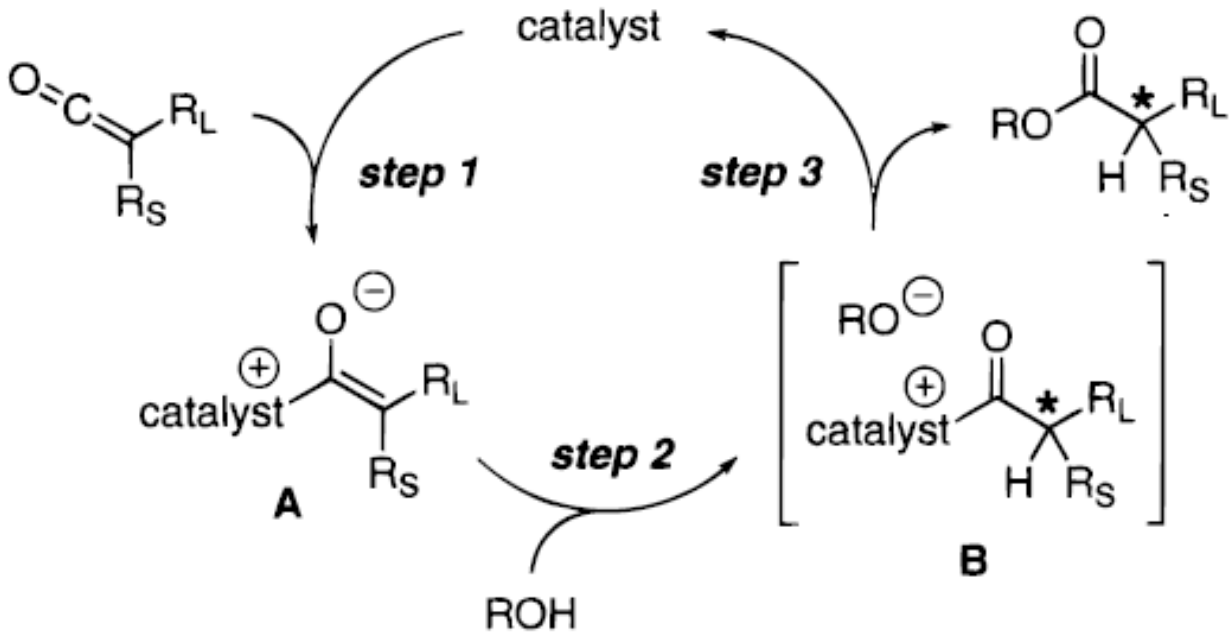
Acknowledgement

Dr. Wulff

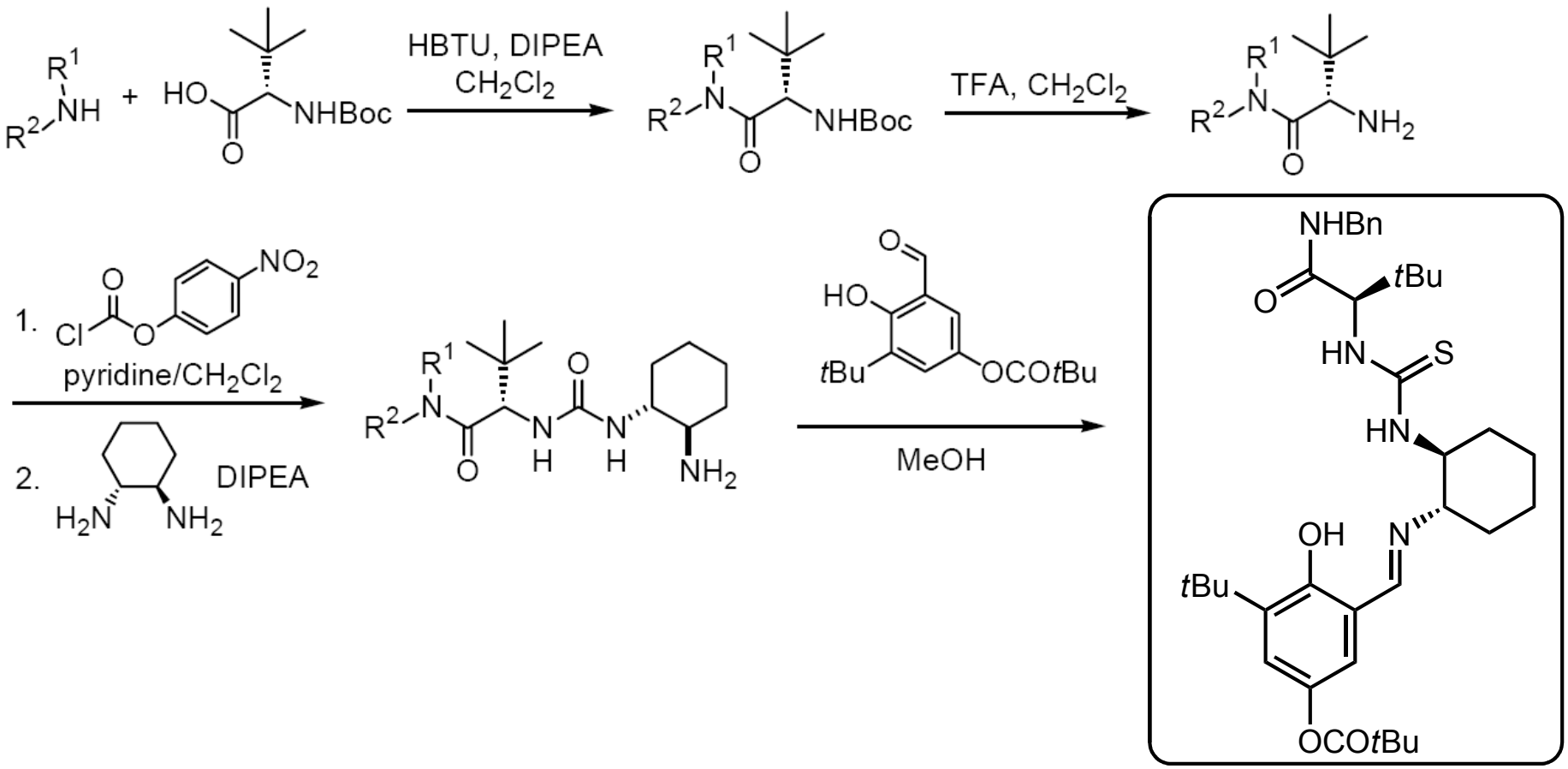
Dr. Walker Dr. Borhan Dr. Jackson

Zhenjie, Ding, Victor, Aman, Munmun, Li, Nilanjana,
Dima, Yong, Alex, Kostas

History: Addtion to Prochiral ketenes

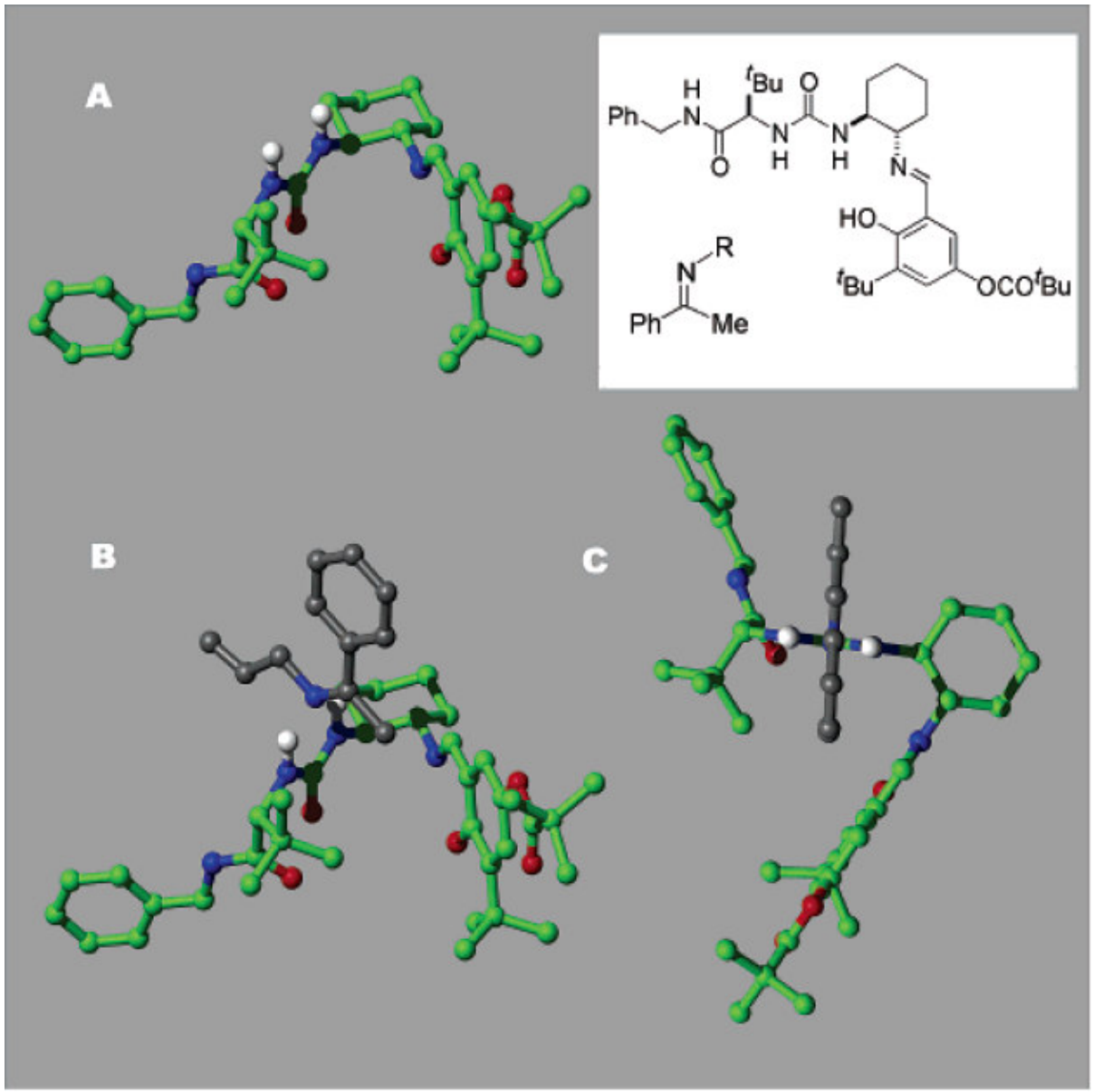


Industrial Appplication of Organocatalysis
Preparation of the Catalyst



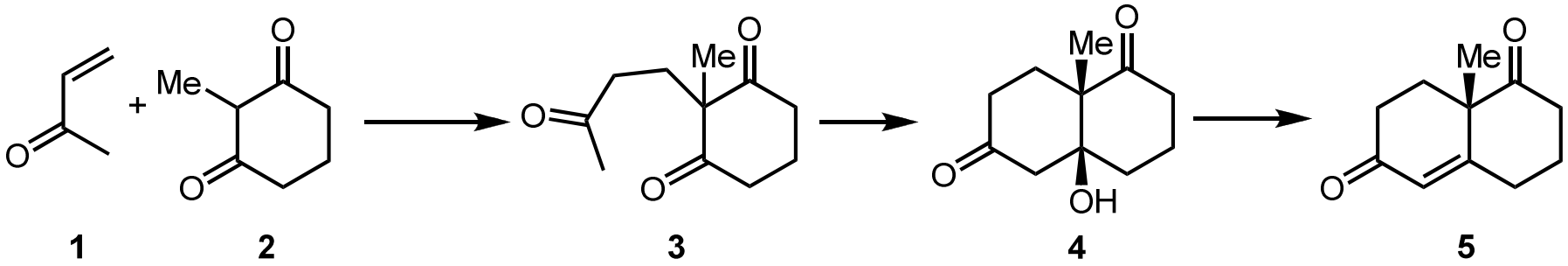
Jacobsen, E. N.; Vachal, P. *J. Am. Chem. Soc.* **2002**, *124*,10012

Industrial Appplication (Stereoselectivity)

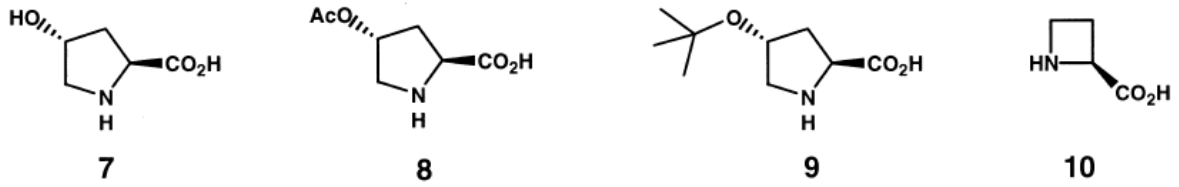


Jacobsen, E. N.; Vachal, P. *J. Am. Chem. Soc.* **2002**, *124*,10012

One-pot Robinson Annulation

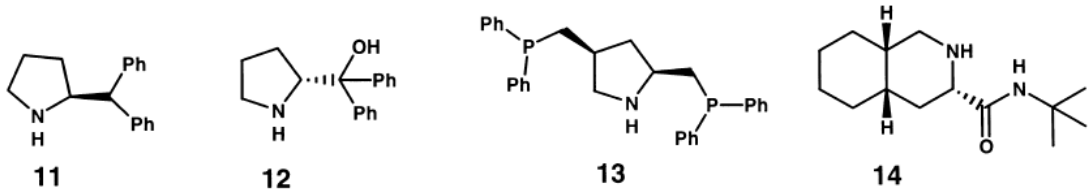


1 2 3 4 5



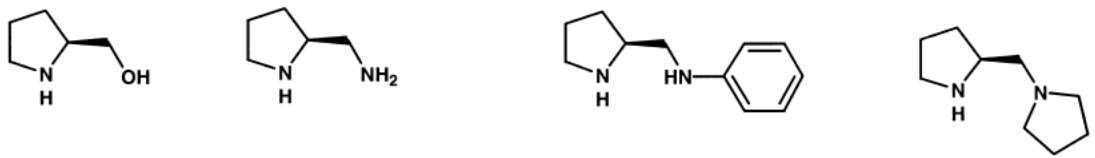
7 8 9 10

gives **5**



11 12 13 14

gives **3** only



15 16 17 18

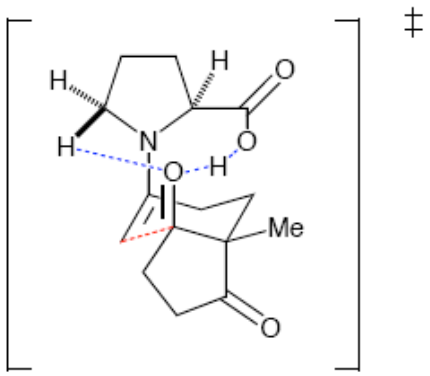
gives **4** only

The carboxylic acid functionality appears to be key to the dehydration step

Barbas, C. F.; Bui, T. *Tetrahedron Lett.* **2000**, *41,* 6951

Houk's Transition State

Houk, 2001 - 2003



- N-H---O hydrogen bond does not lower energy of transition state
- favorable O-H---O hydrogen bond
- additional NC-H---O hydrogen bond further stabilizes system
- reaction is first order in proline (supported by kinetic data) and no non-linear effect observed

Houk, K. *JACS* **2001**, *123*, 12911.
Houk, K., List, B. *JACS* **2003**, *125*, 16.

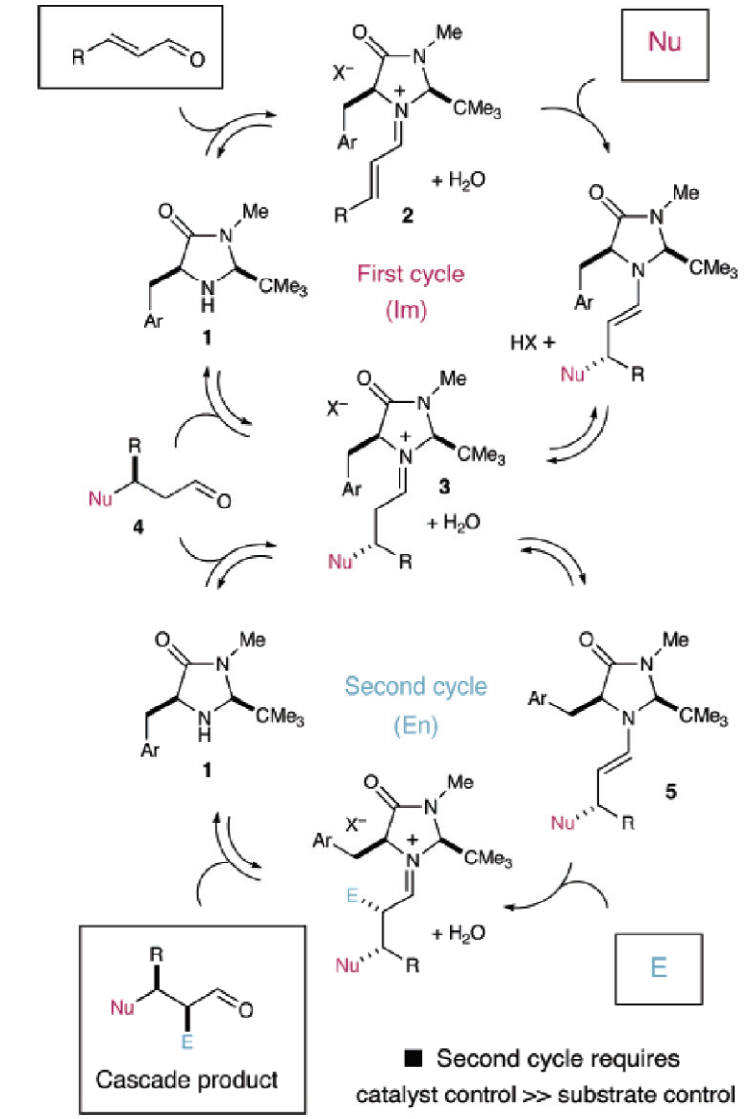
general hydrogen bond energies

O -H - - O 3.0-8.0 kcal
C -H - - O 0.5-3.8 kcal

for a discussion on R_3N^+-C-H---O=C bonds, see:
Houk, K. *JACS*, **2002**, *124*, 7163.

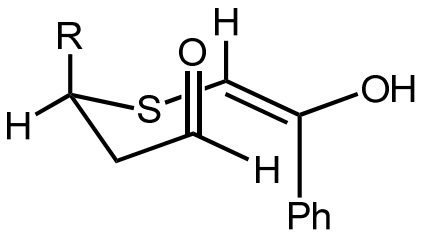
Enantioselective Organo-Cascade Catalysis

Scheme 1. Cascade Catalysis: Merged Iminium–Enamine Activation

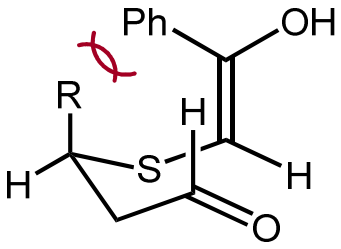


MacMillan, D. W. C.; Huang, Y.; Walji, A. M.; Larsen, C. H. *J. Am. Chem. Soc.* **2005**, *127*, 15051

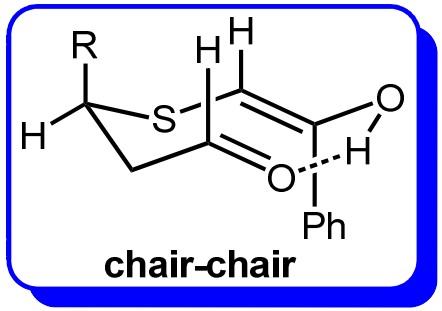
Possible Rationale for Stereochemical Outcome (Base Catalyzed)



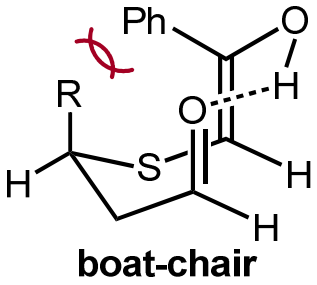
A



B

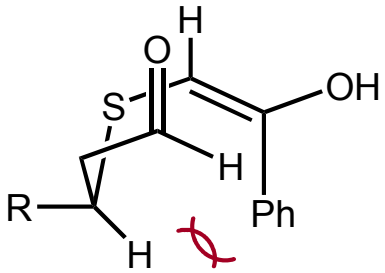


C

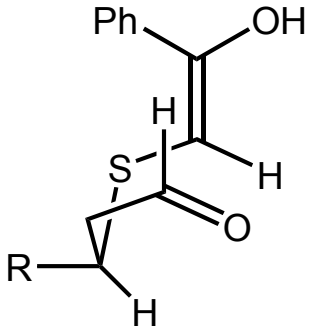


D

Axial



A



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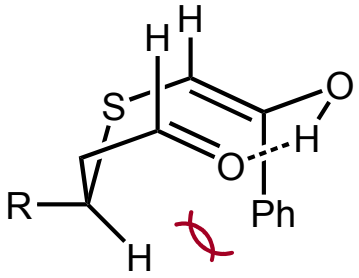
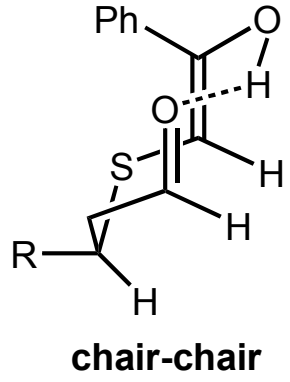


C



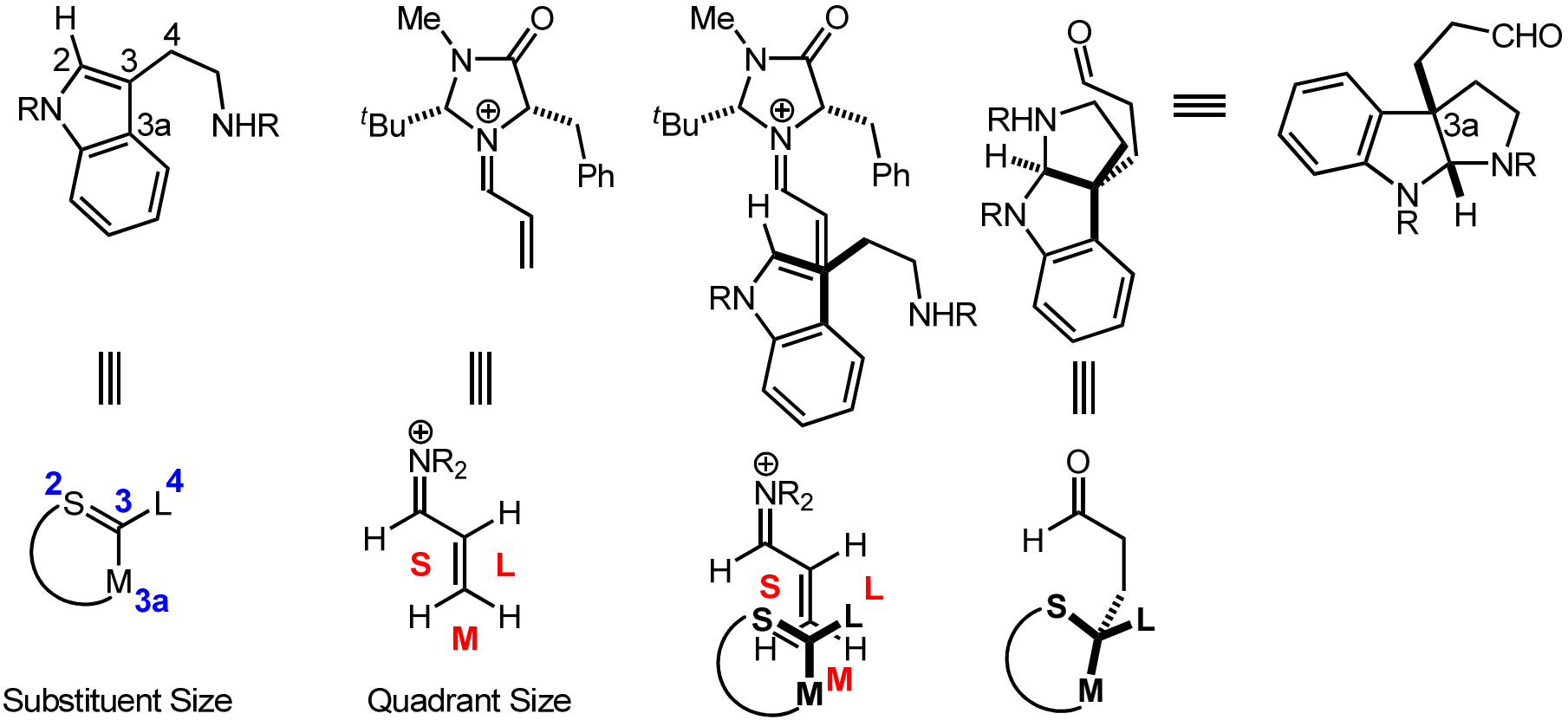
D

Equatorial

Evans, D. G.; Boeyens, J. C. *Acta. Cryst.* **1990**, *46*, 524

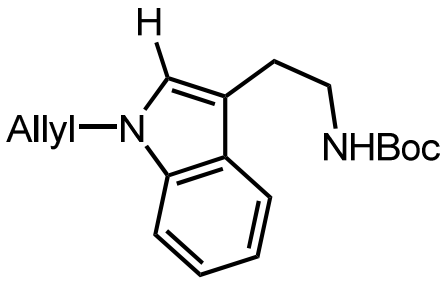
Humble, S.; Bouquant, J.; Portella, C.; Bouillon, J. *J. Org. Chem.* **2000**, *65*, 5823

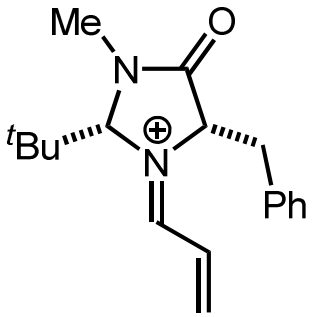
Stereochemical Rationale (High Dielectric Solvent)

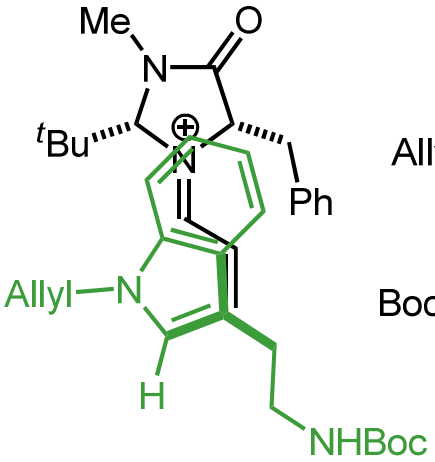


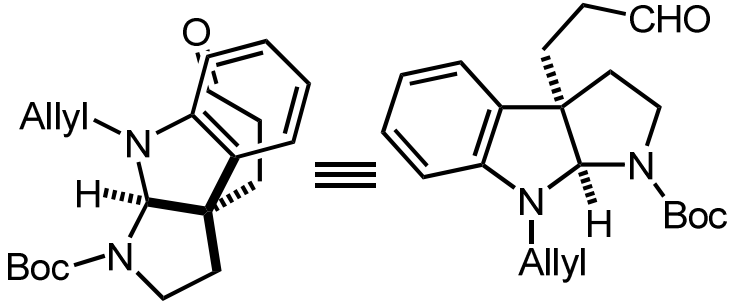
Austin. J. F., PhD Thesis, 2005, California Institute of Technology

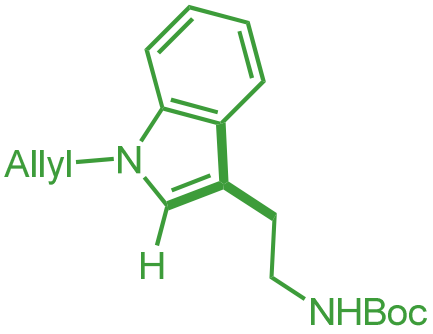
Stereochemical Rationale (Low Dielectric Solvent)



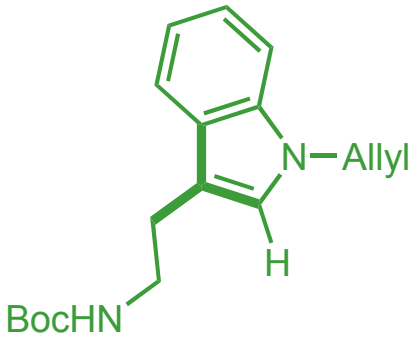


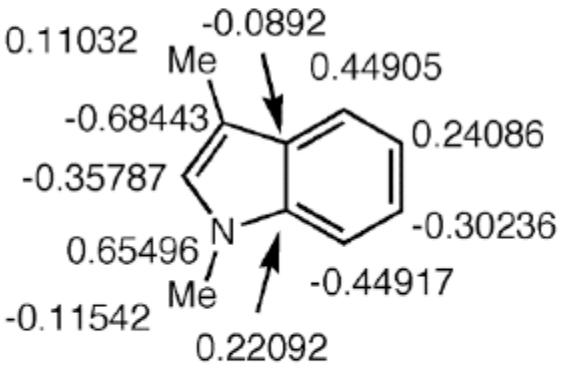




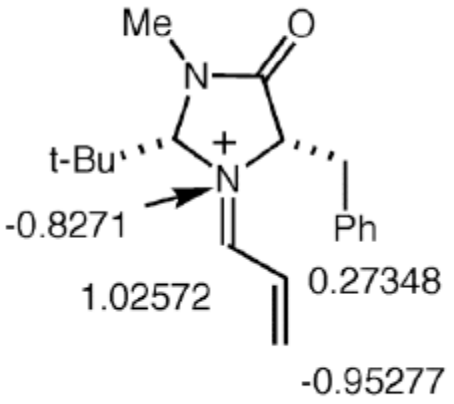


Vs





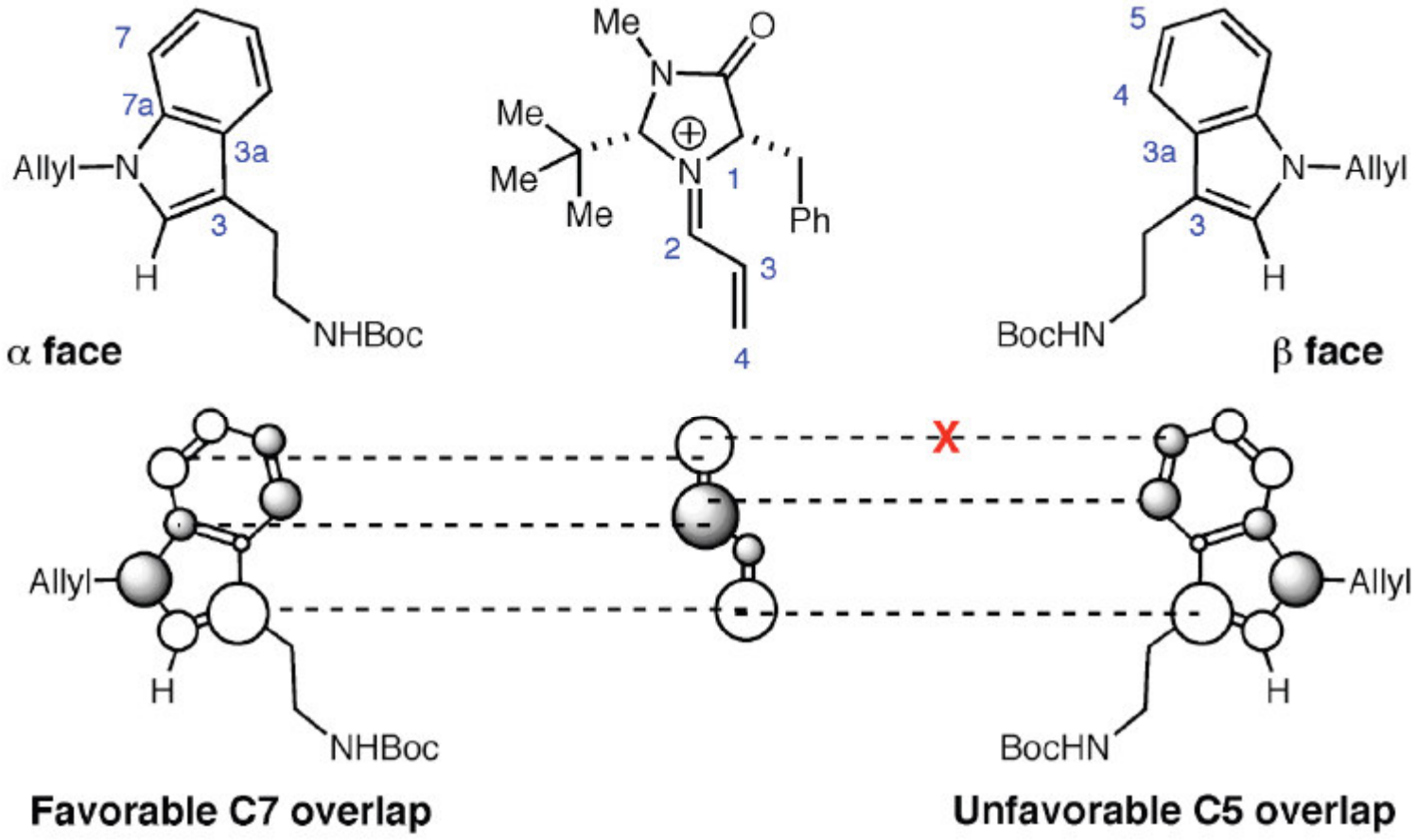
Frontier electron population for 1,3-dimethylindole HOMO



Frontier electron population for iminium LUMO

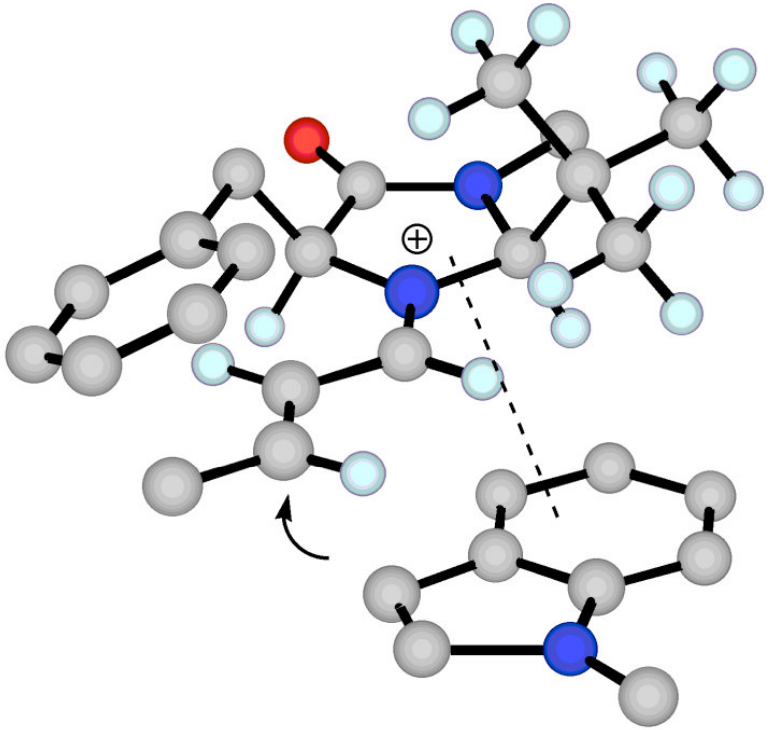
Austin. J. F., PhD Thesis, 2005, California Institute of Technology

Stereochemical Rationale (Low Dielectric Solvent)



Austin. J. F., PhD Thesis, 2005, California Institute of Technology

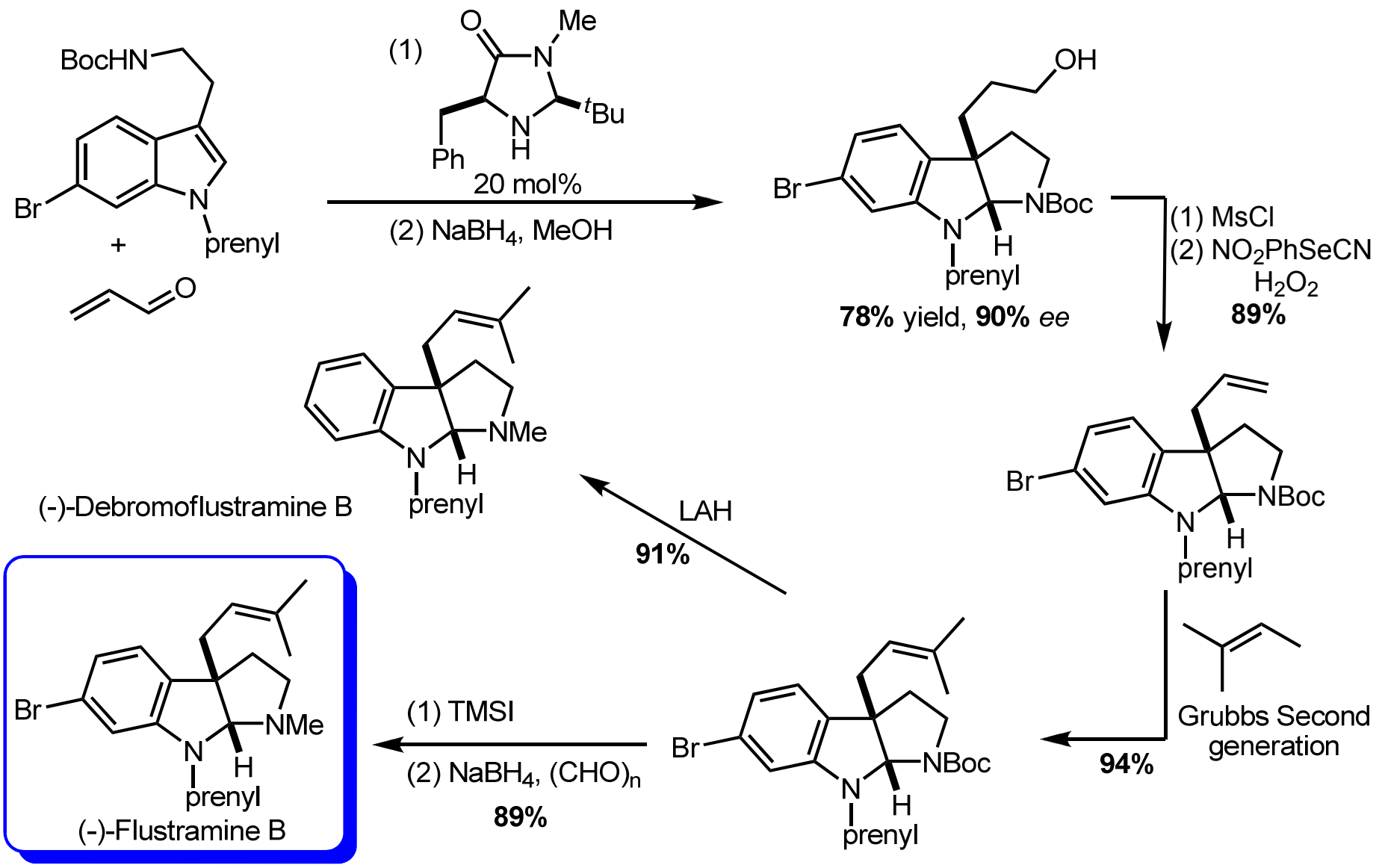
Transition State of Imidazolidinone Catalyst



MM3-4

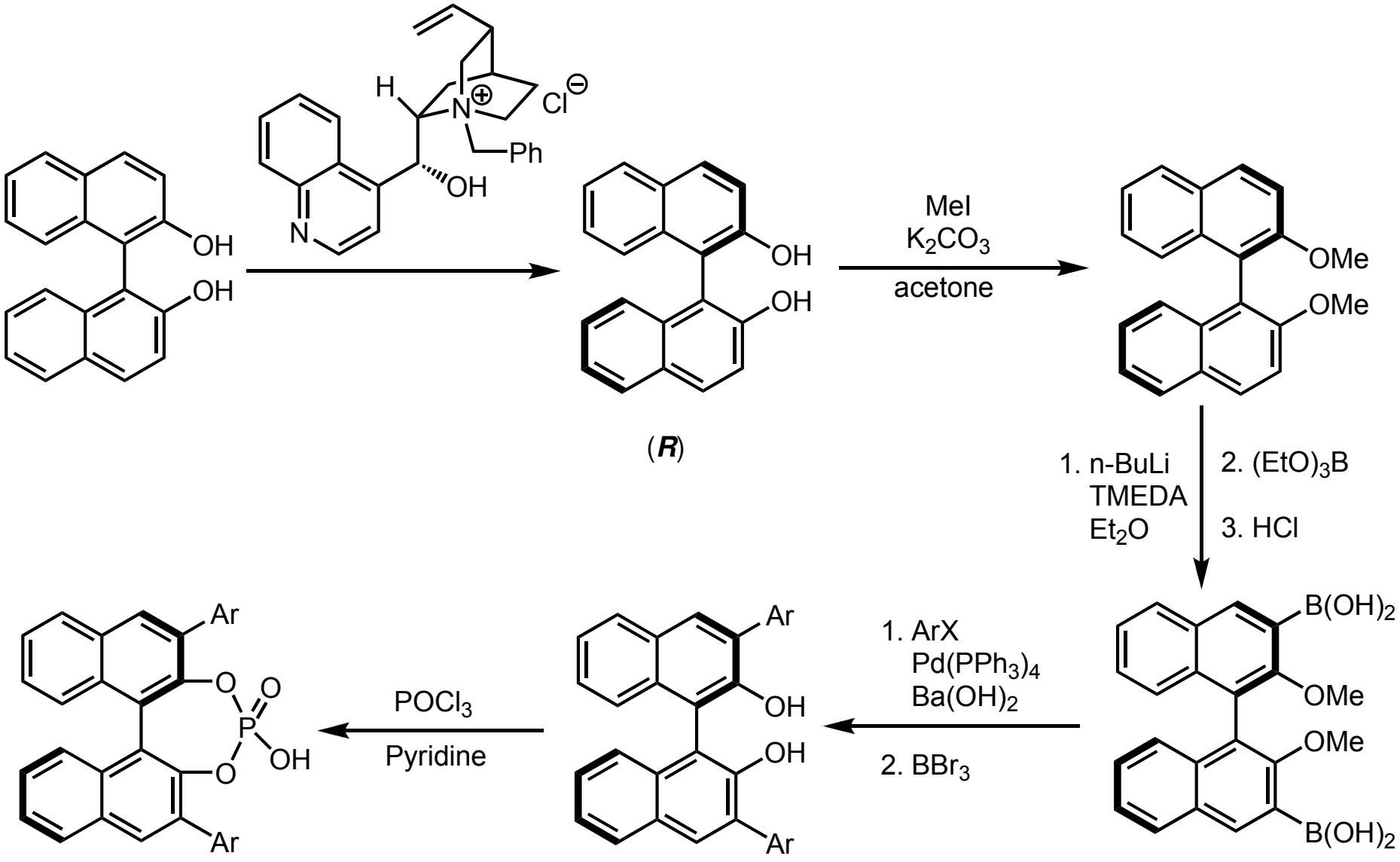
Increased *Si*-face coverage
Re-face addition unhindered
Increased substrate addition rate

Total Synthesis of (-) flustramine B



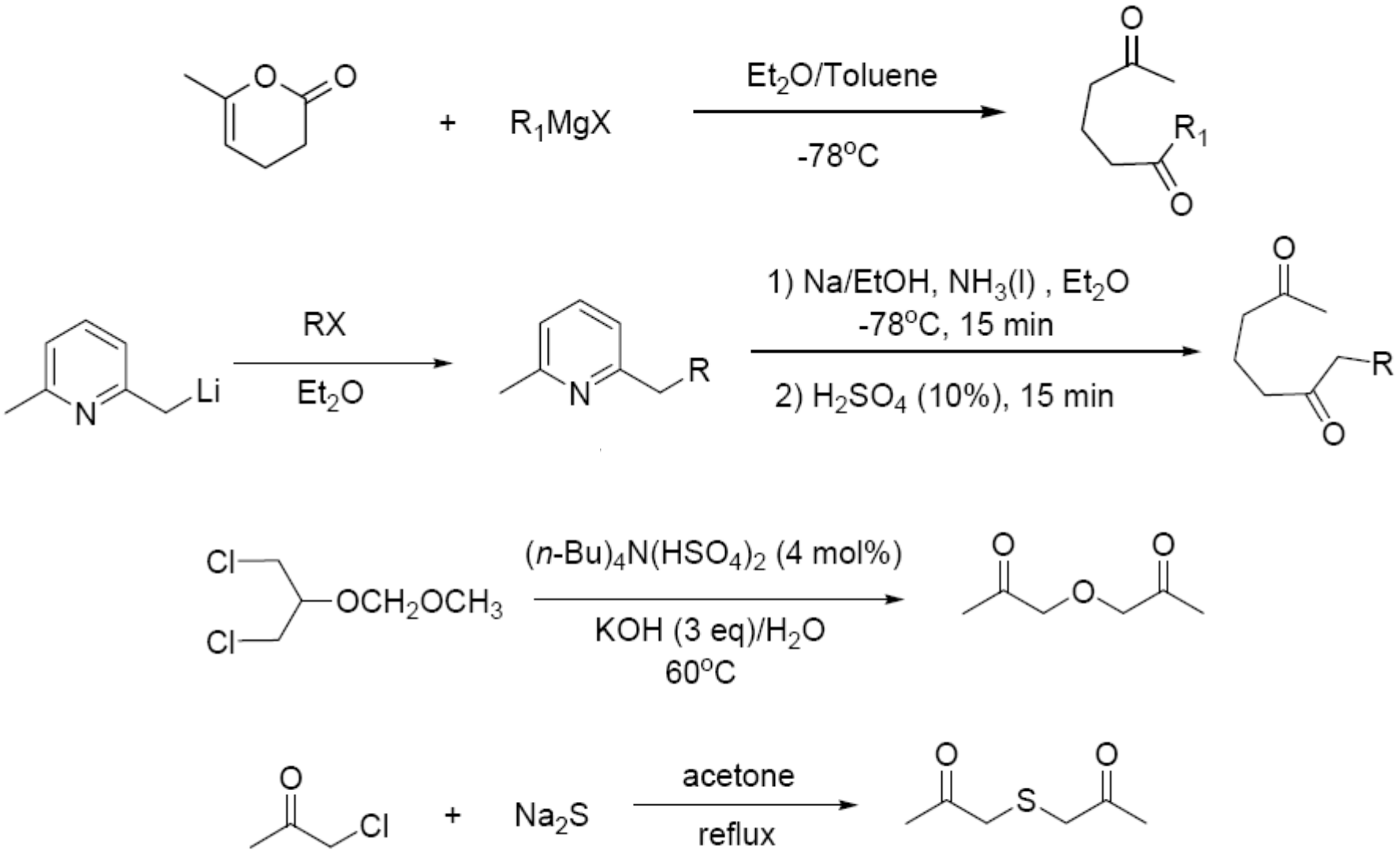
MacMillan *et.al., PNAS*, **2004**, 101, 5482.

Catalyst Preparation



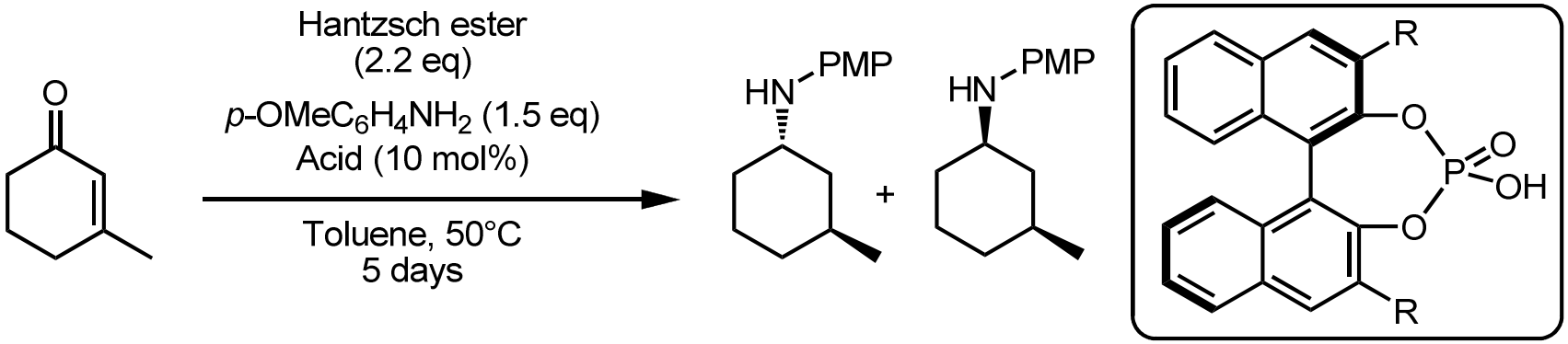
Wipf, P.; Jung, J. K. *J. Org. Chem.* **2000**, *65*, 6319

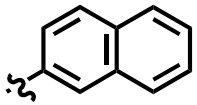
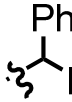
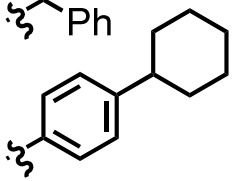
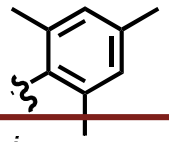
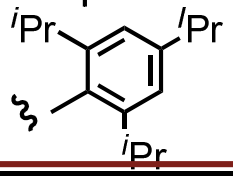
Diketone Preparation



List, B.; Zhou, J. *J. Am. Chem. Soc.* **2007**, *129*, 7498

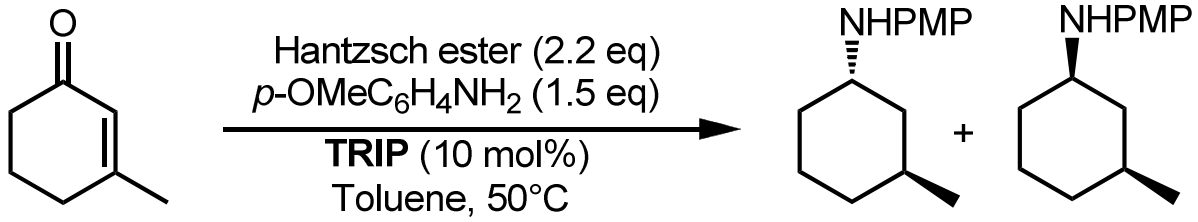
Reaction Optimization: Catalyst Screening



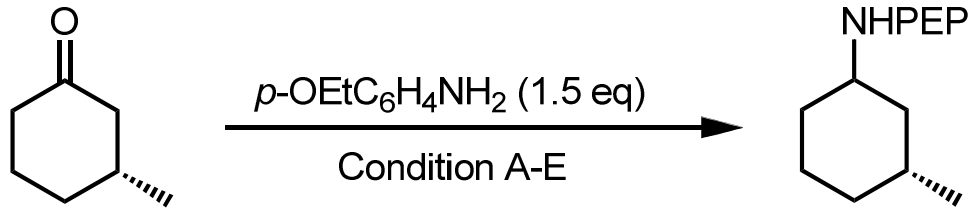
Entry	R	Conversion (%)	*dr (trans:cis)*	*er of cis*
1		80	72:28	55:45
2		100	64:46	50:50
3		50	65:35	50:50
4		80	60:40	51:49
5		80	80:20	51:49
6		100	67:33	79:21

List *et.al., JACS*, **2007**, 129, 7498.

Reaction Optimization: TRIP with Additive



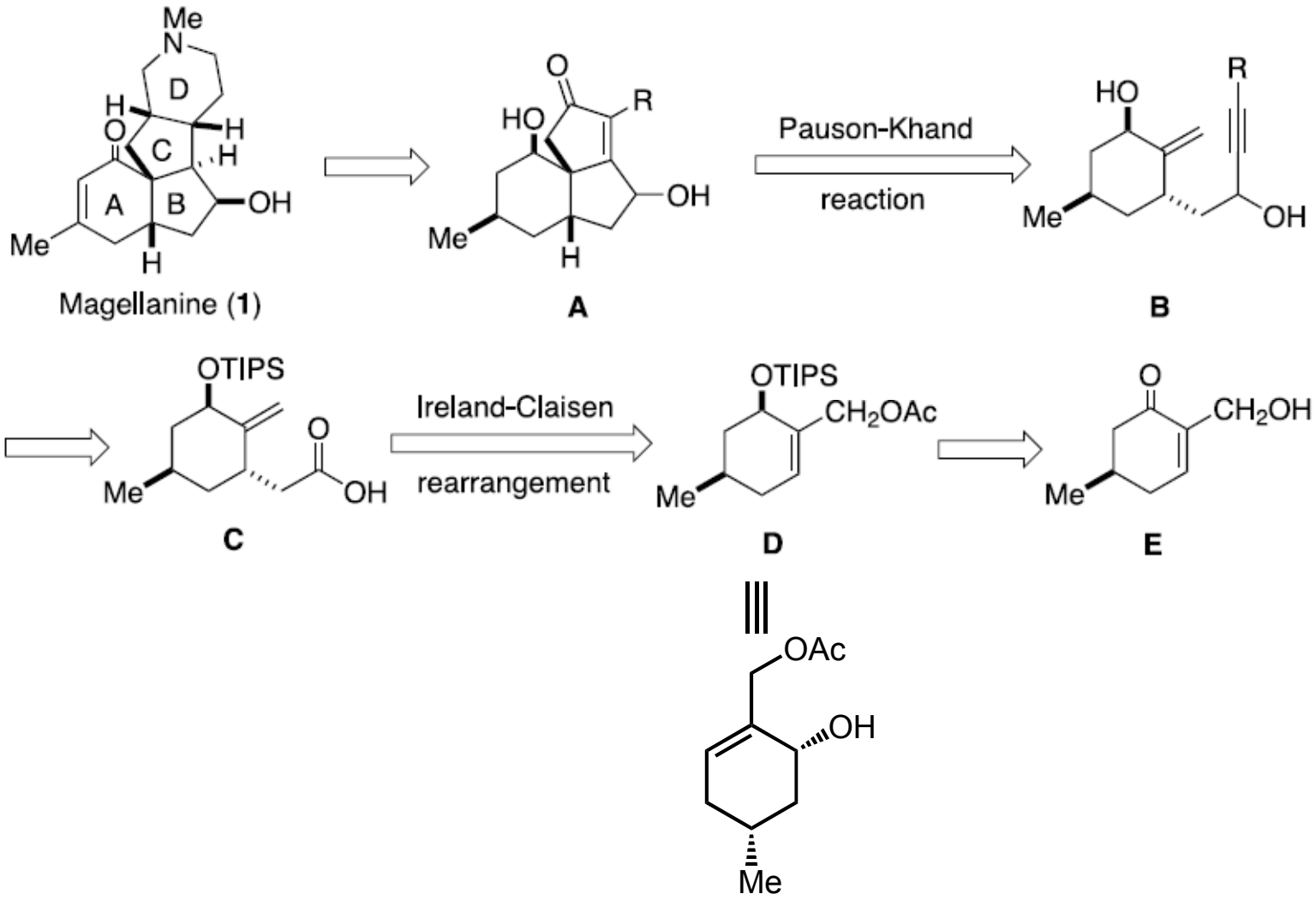
Entry	Additive	Time	Conversion (%)	*dr (trans:cis)*	*er of cis*
1	-	3 days	100	67:33	79:21
2	MS 5Å	1 days	100	24:76	87:13



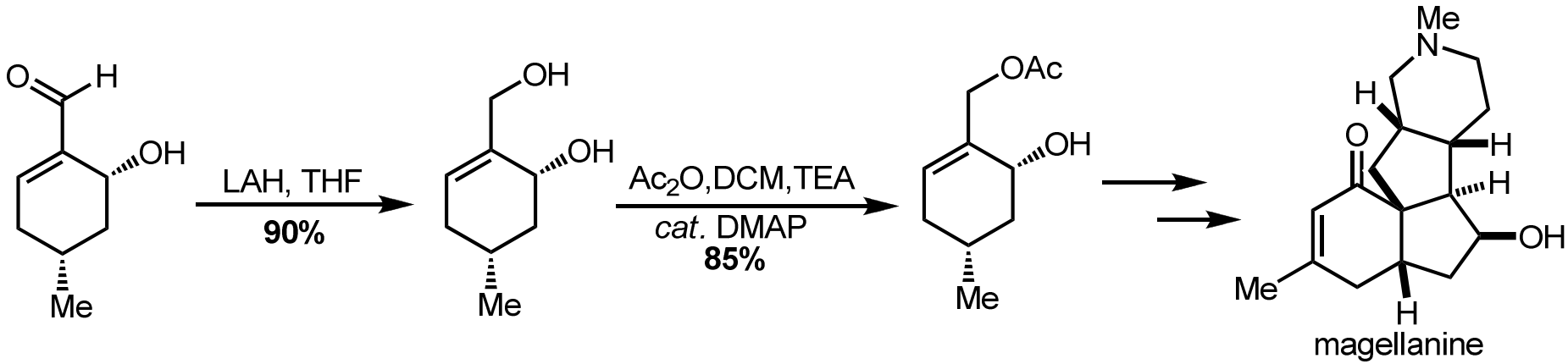
Condition	Yield (%)	*trans:cis*
A) TsOH (10 mol%, HE (1.2 eq), Cyclohexane/MS 5Å	89	3.6/1.0
B) *(S)*- **TRIP** (10 mol%, HE (1.2 eq), Cyclohexane/MS 5Å	91	1.0/6.0
C) *(R)*- **TRIP** (10 mol%, HE (1.2 eq), Cyclohexane/MS 5Å	82	1.0/1.2
D) $NaBH(OAc)_3$, HOAc/DCM, r.t.	94	3.7/1.0
E) 1) TiCl4/DCM, r.t; $NaBH_3CN$	91	1.2/1.0

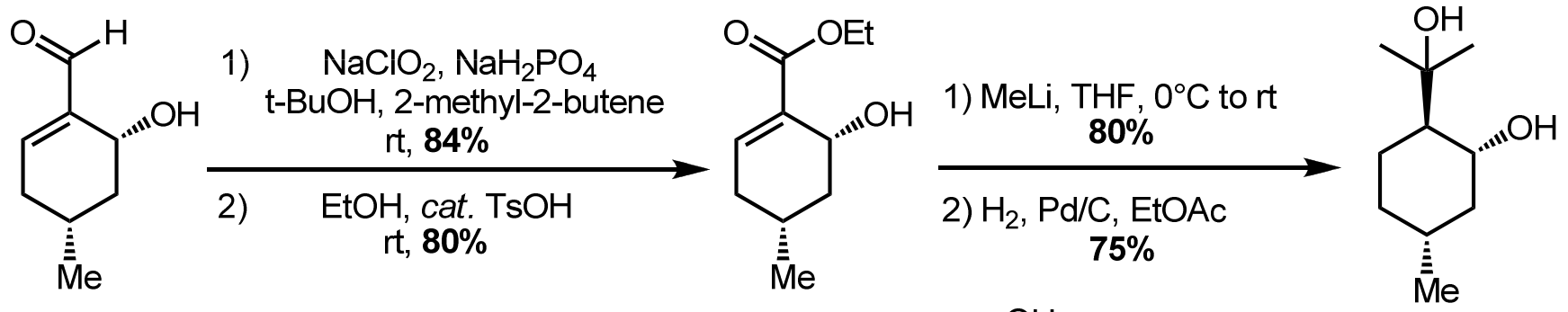
List *et.al., JACS*, **2007**, 129, 7498.

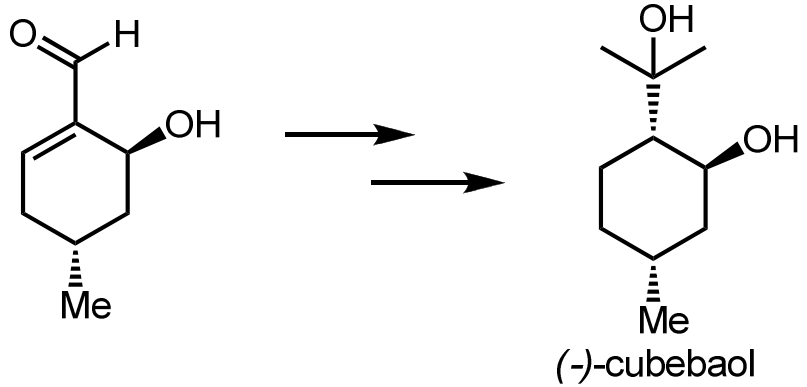
Retrosynthesis of Magellanine



Application to Total Synthesis

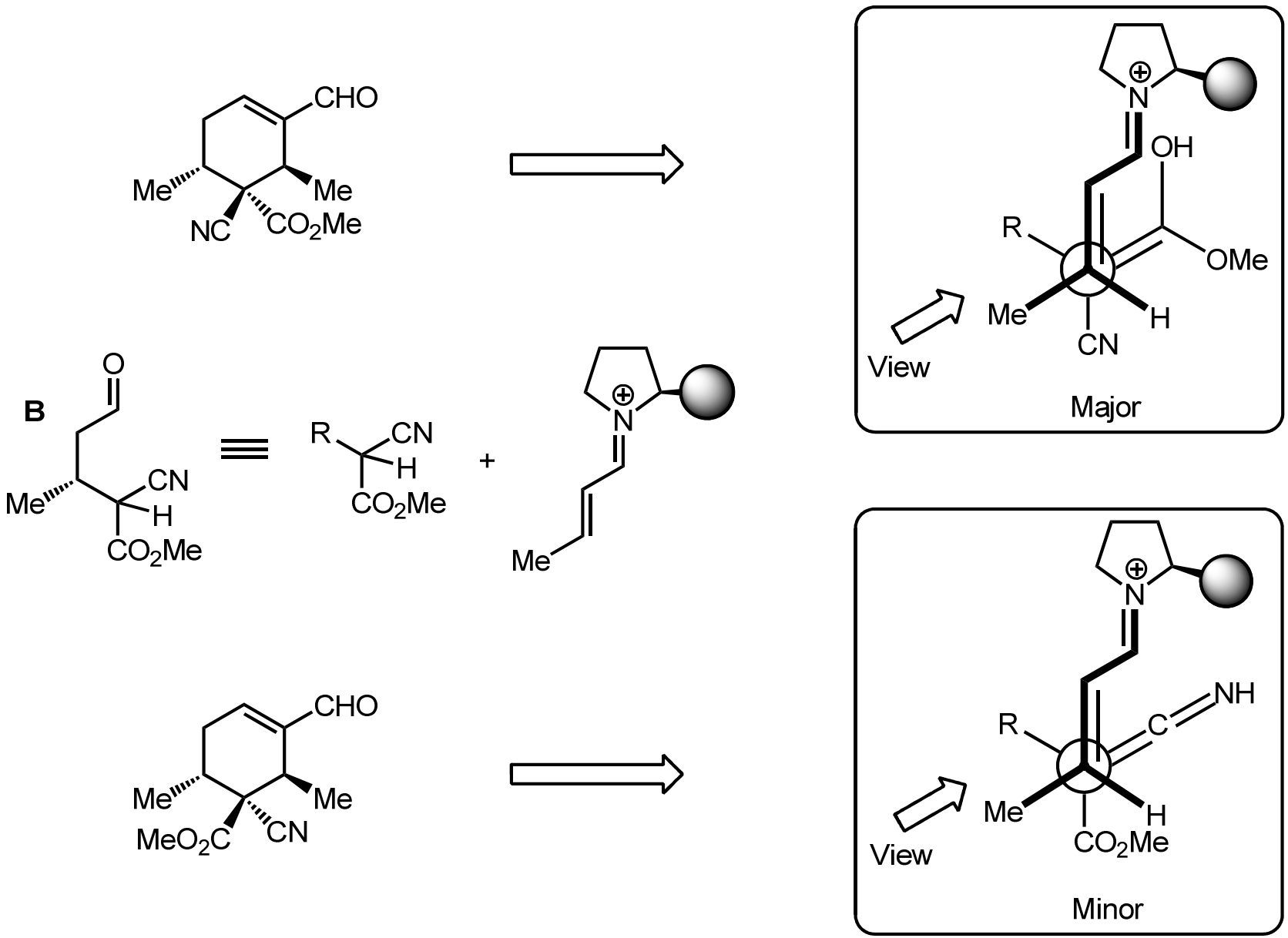






Hong, B.; Wu, M.; Tseng, H.; Liao, J. *Org. Lett.*, **2006**, *8*, 2217

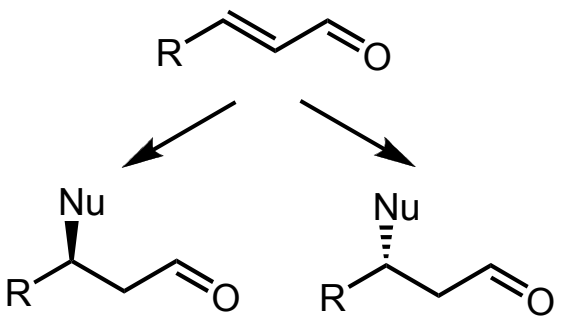
Quaternary Centres: Diastereocontrol



Jørgensen. K. A.; Carlone, A.; Cabera, S.; Marigo, M. *Angew. Chem. Int. Ed.* **2007,** *46*, 1101

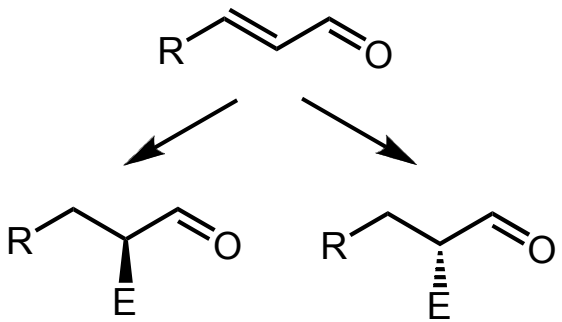
Enantioenrichment

Individual Asymmetric Reactions



9 80% ee 1

Iminium



9 80% ee 1

Enamine

However, you combine them..