Frontiers in Chemical Synthesis I
Stereochemistry

Seminar Program
May 1, BCH 3118

	Speaker	Title
May 1, 2012 - Morning		
Session I: (Chairman: Sophie Racine)		
8h30-9h45	Yvan Buslov	*Asymmetric Counteranion-Directed Cyclization Reactions*
9h45-11h00	Ahlin Joachim Sven Ernst	*Catalytic Enantioselective Isocyanide-Based Multicomponent Reactions*
11h00-12h15	Ugo Orcel	*Enantioselective Radical Reactions*
May 1, 2012 - Afternoon		
Session II: (Chairman: Ugo Orcel)		
13h30-14h45	Sophie Racine	*Enantioselective Synthesis of Beta-Lactams*
14h45-16h00	Ha minh Tu	*Catalytic Asymmetric Dearomatization Reactions*
16h00-17h15	Michele Boghi	*Synergism between Metals in Asymmetric Additions onto Carbonyl Compounds*

Asymmetric counteranion-directed cyclization reactions

Ivan Buslov

Frontiers in Chemical Synthesis: Stereochemistry

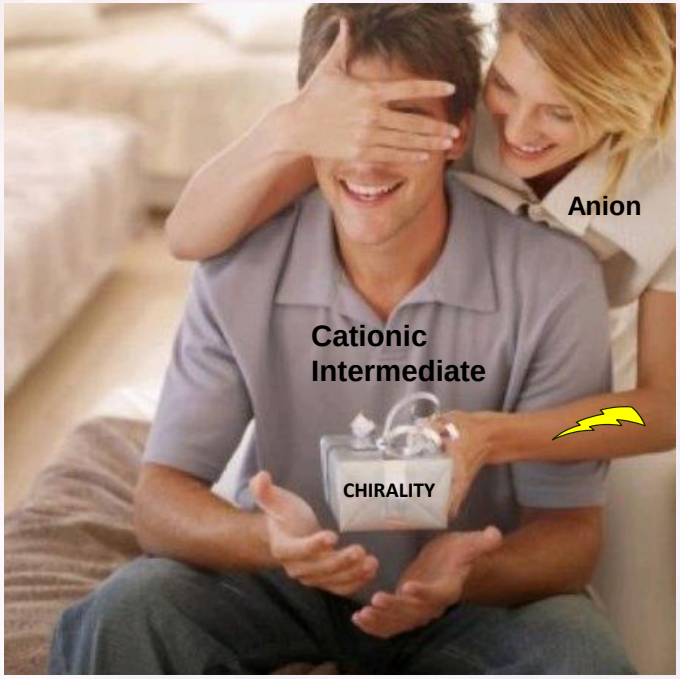
École Polytechnique Fédérale de Lausanne

1 May 2013

Plan of the Talk:

- Concept of ACDC
- First publications employing ACDC principle
- Development of ACDC (cyclization reactions)
- Conclusion and perspectives
- Questions

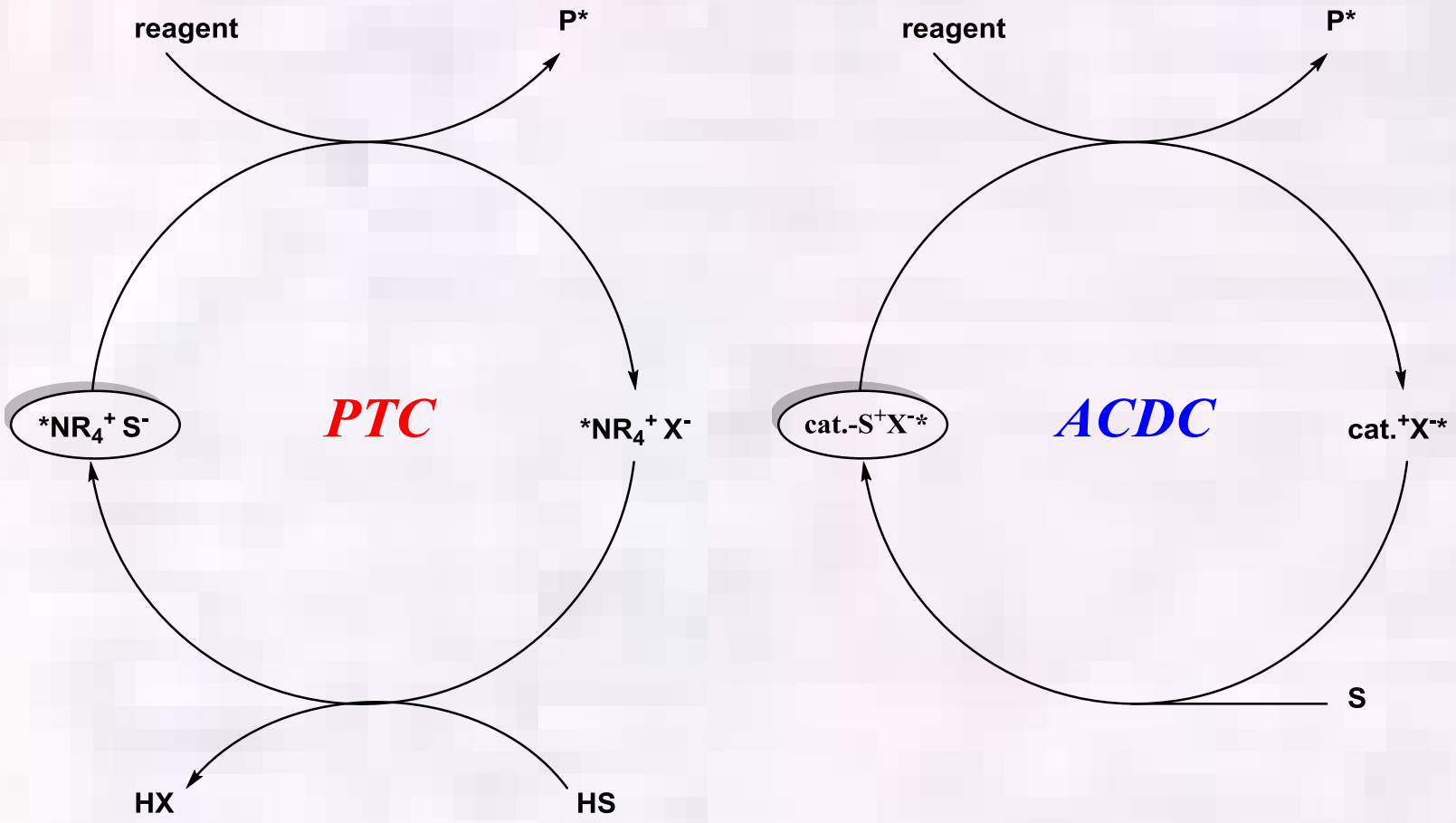
Definition of ACDC



"Asymmetric counteranion-directed catalysis (ACDC) refers to the induction of enantioselectivity in a reaction proceeding through a cationic intermediate by means of ion pairing with a chiral, enantiomerically pure anion provided by the catalyst "

M. Mahlau, B. List *Angew. Chem. Int. Ed.* **2013**, 52, 518 – 533

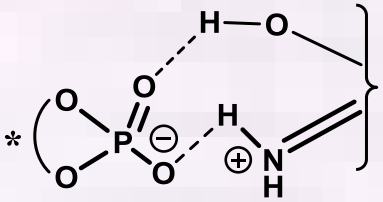
Comparison with Chiral Cation PTC



M. Mahlau, B. List *Angew. Chem. Int. Ed.* **2013**, 52, 518 – 533

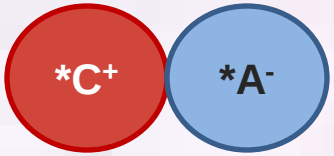
Ambiguous Cases

Brønsted acid catalysis: stabilization by hydrogen bonds



Transition-metal catalysis: difference between ACDC and anionic ligands

Combination of chirality in both the cationic and anionic moities



M. Mahlau, B. List *Angew. Chem. Int. Ed.* **2013**, 52, 518 – 533

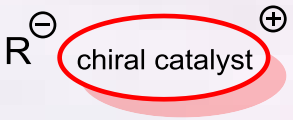
Place of ACDC

First example of chiral cation-directed catalysis - **1984**

First example of anion-directed catalysis - **2000**

ACDC

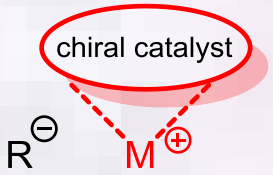
with charged catalyst



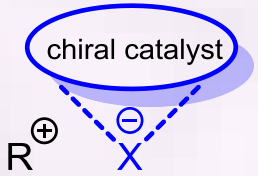
chiral cation-directed catalysis

chiral anion-directed catalysis

with neutral catalyst



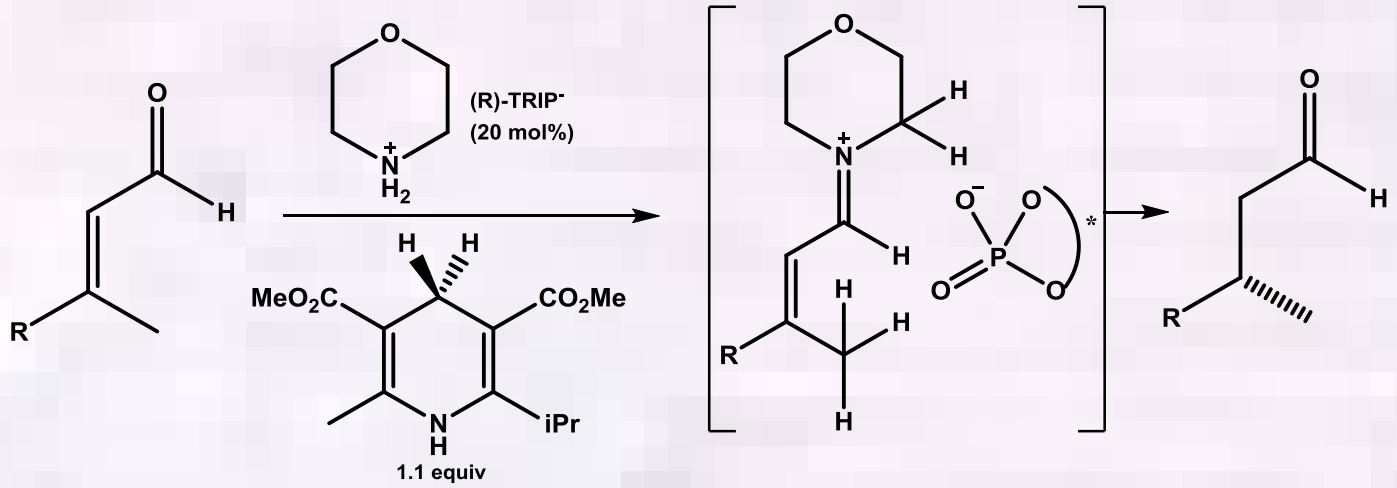
cation-binding catalysis



anion-binding catalysis

E.N. Jacobsen, K. Brak *Angew. Chem. Int.* **2013**, 52, 534-561

Advantages of ACDC



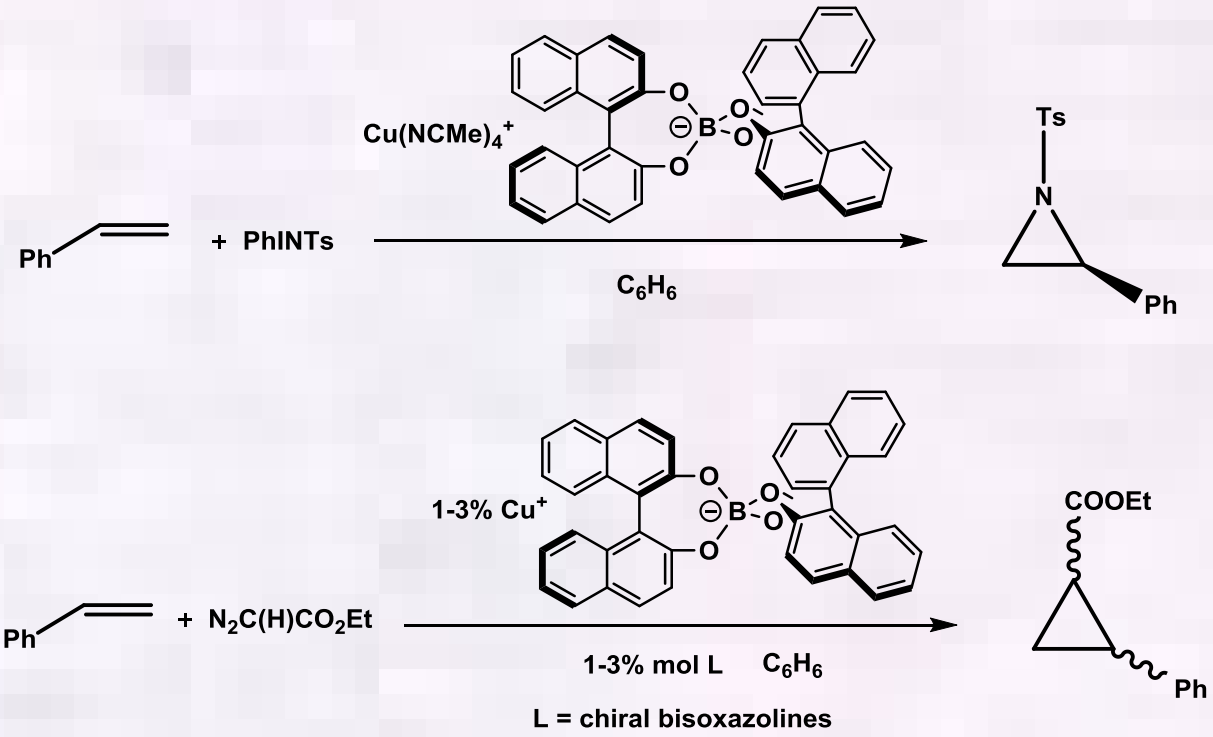
71% yield
e.r. 95:5

For the same reaction chiral secondary amine catalysis gave only moderate selectivity e.r. 70:30

S. Mayer, B. List, *Angew. Chem.* **2006**, 118, 4299 – 4301
S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan *J. Am. Chem. Soc.,* **2005 ,**127, 32-33

Pioneering Work

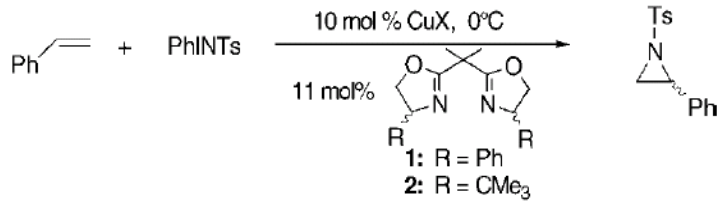
Aziridination and Cyclopropanation of Styrene



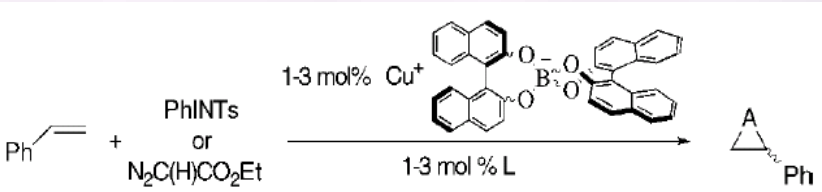
D.B. Llewellyn, D. Adamson, and B. A. Arndtsen *Org.Lett.* **2000,** 26, 4165-4168

Induction of Chirality

Chiral Ligand *vs* **Chiral Counteranion**



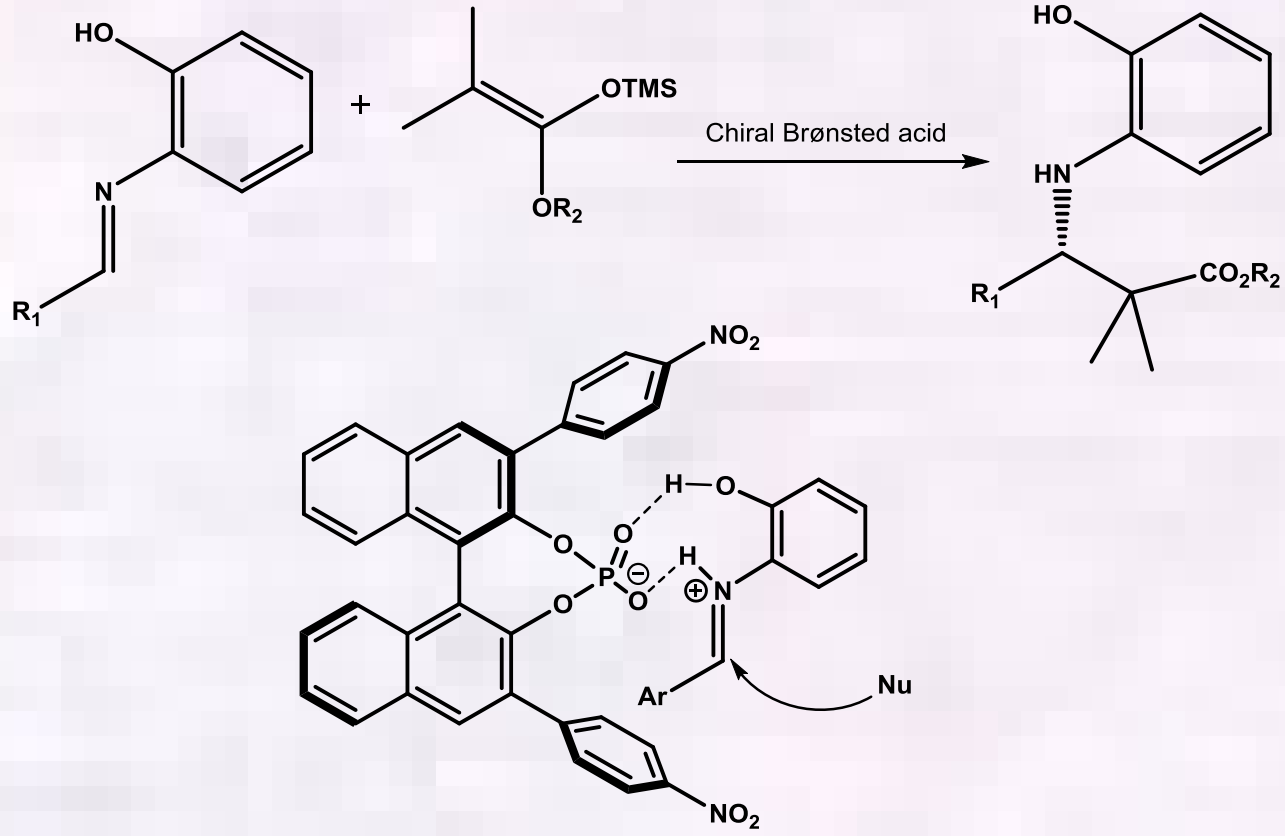
ligand	X	% ee (C_6H_6)[b]	% ee (MeCN)[b]
(*R*)-**1**	OTf	1 (*S*)	28 (*S*)
(*R*)-**1**	ClO_4	5 (*S*)	28 (*S*)
(*R*)-**1**	Cl	17 (*S*)	28 (*S*)
(*R*)-**1**	PF_6	33 (*S*)	28 (*S*)
(*S*)-**2**	OTf	66 (*R*)	2 (*R*)
(*S*)-**2**	ClO_4	57 (*R*)	2 (*R*)



entry	L	X	A	solvent	% ee[b]	yield, %
1	(*R*)-**1**	(*S*)-**3**	NTs	C_6H_6	22 (*S*)	75
2	(*R*)-**1**	(*R*)-**3**	NTs	C_6H_6	24 (*S*)	85
9	none	(*R*)-**3**	NTs	C_6H_6	7 (*R*)	86
10	none	(*S*)-**3**	NTs	C_6H_6	7 (*S*)	88
11	none	(*R*)-**3**	NTs	CH_2Cl_2	4 (*R*)	97
12	none	(*R*)-**3**	NTs	CH_3CN	<1	87

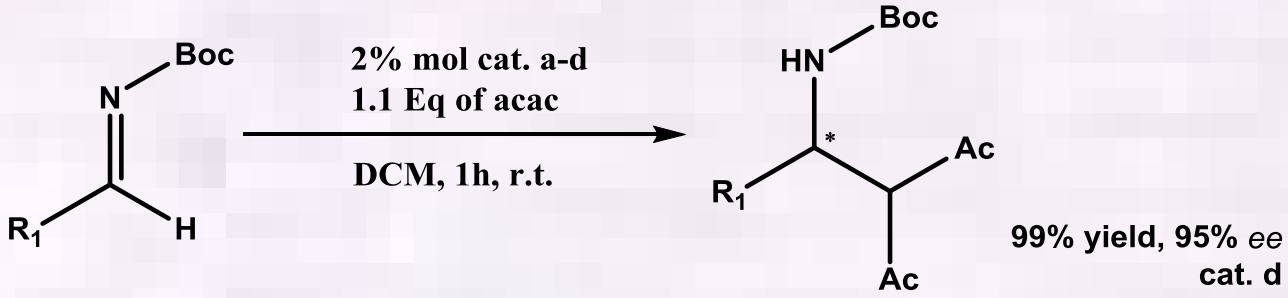
D.B. Llewellyn, D. Adamson, and B. A. Arndtsen *Org.Lett.* **2000,** 26, 4165-4168

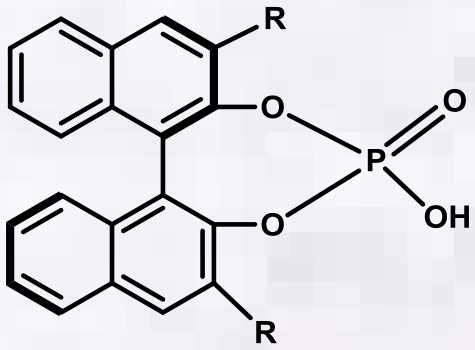
Akiyama's Work



T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, 116, 1592 – 1594

Terada's Work





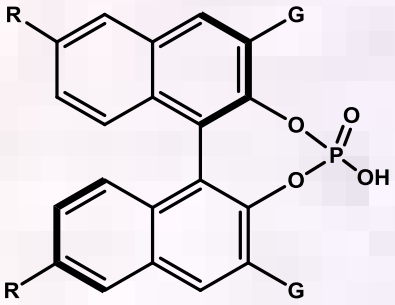
cat. a - R = H
b - R = Ph
c - R = 4-Biph
d - R = 4-(b-Naph)-C_6H_4

D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, 126, 5356 – 5357

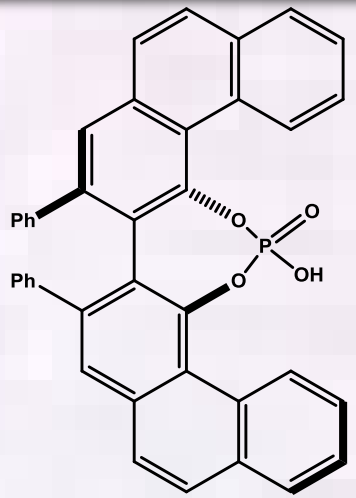
Selected Publications

- Brønsted Acid Catalysis
- Transition-Metal Catalysis
- Chiral Anion PTC
- Anion-binding Thiourias
- Sequential Catalysis

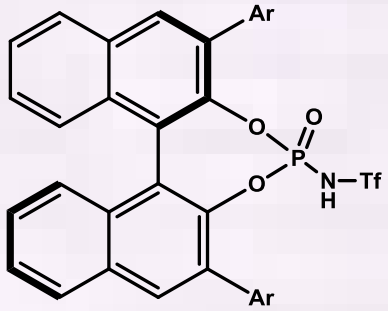
Chiral Brønsted Acids



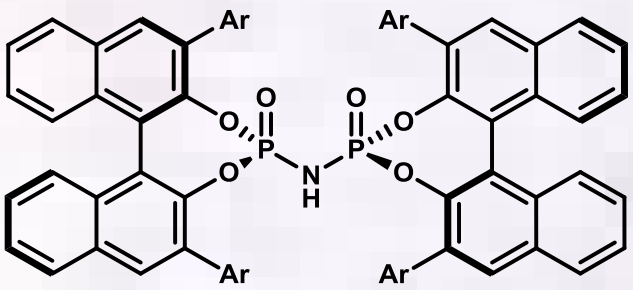
BINOL-derivatives



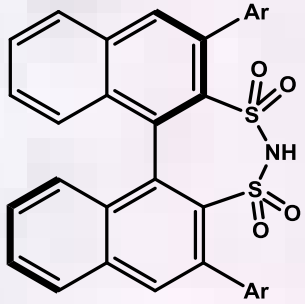
VAPOL-derivatives



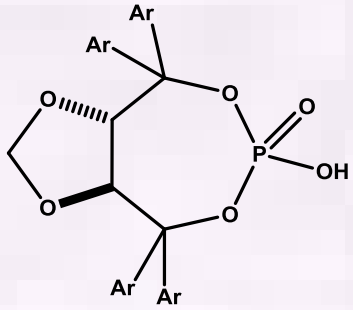
N-Triflylphosphoramidates



Imidodiphosphoric acids



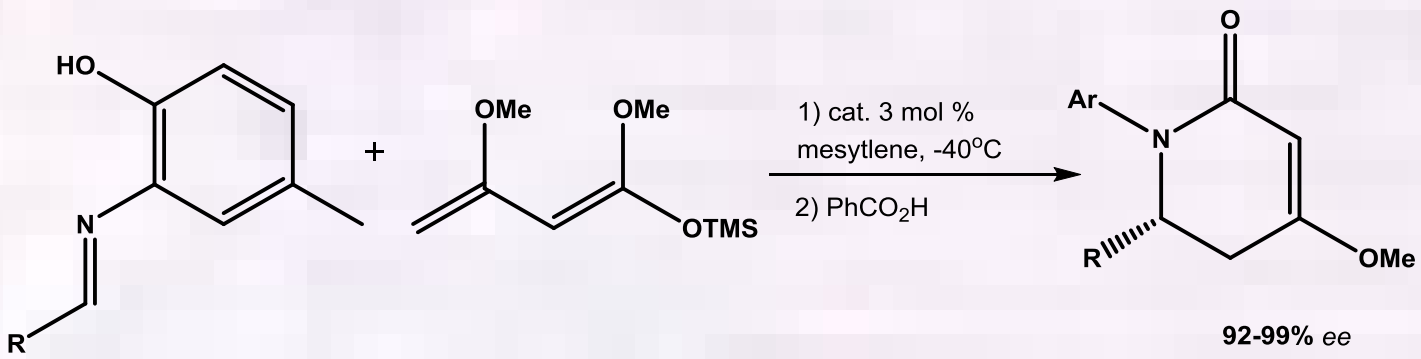
Disulfonimides



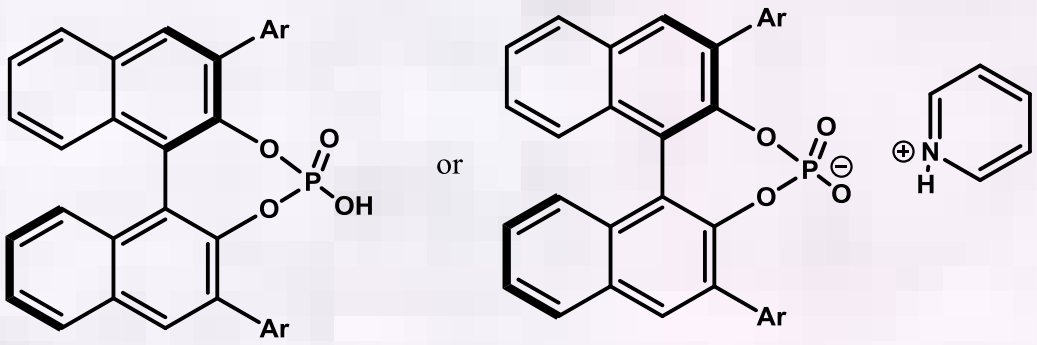
TADDOL-derivatives

Chiral Brønsted Acid Catalyzed Cyclizations

aza-Diels–Alder reaction of Brassard's diene with imines



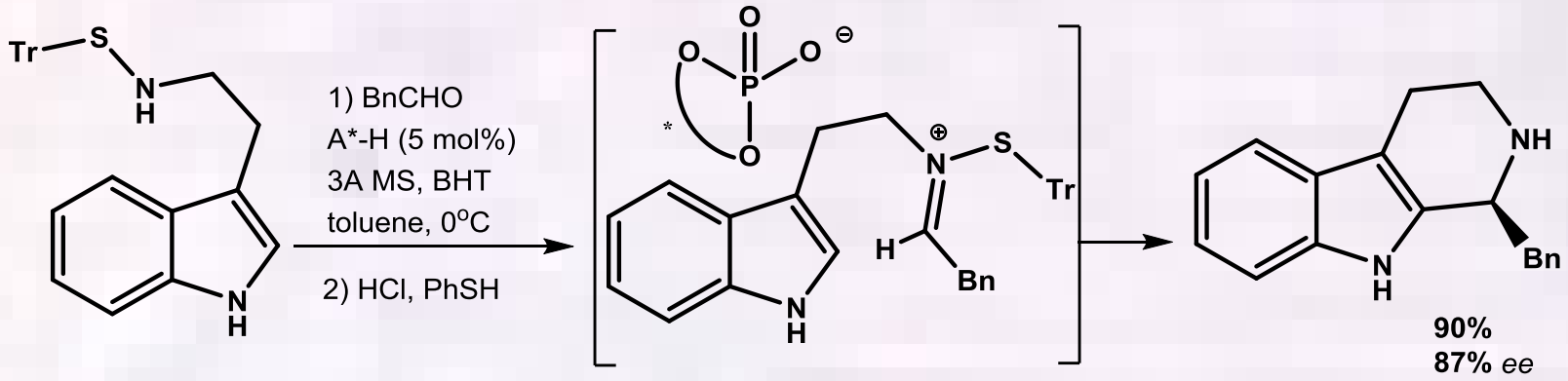
92-99% *ee*

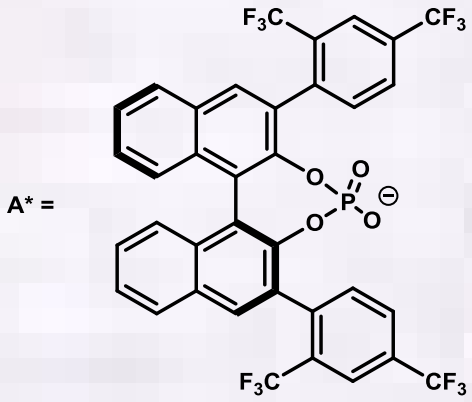


cat. Ar = 9-anthryl

J.Itoh, K.Fuchibe, and T. Akiyama *Angew. Chem.* **2006**, 118, 4914 –4916

Asymmetric Pictet-Spengler Reaction via Sulfenyliminium Ions

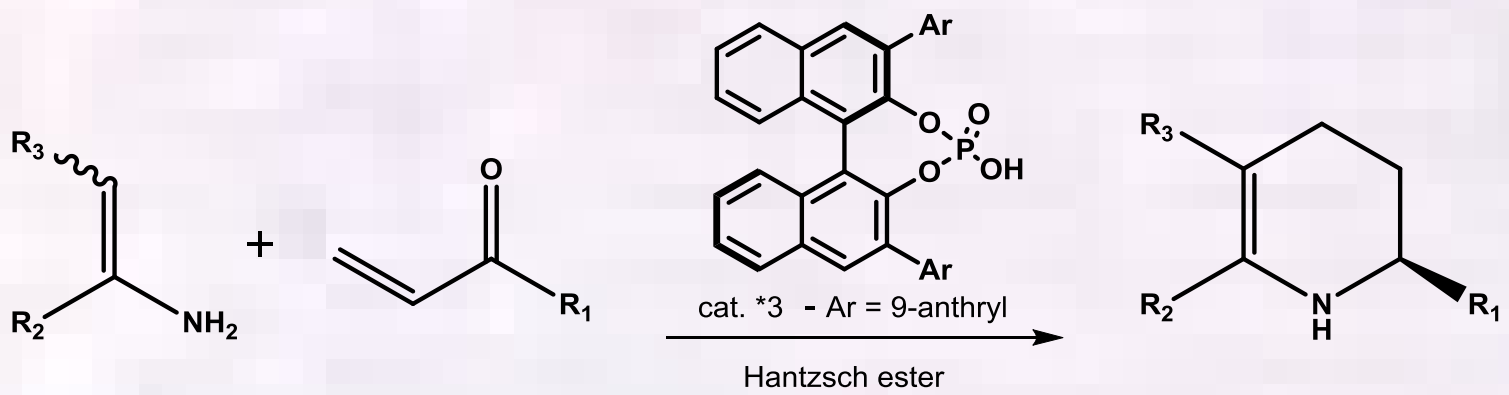


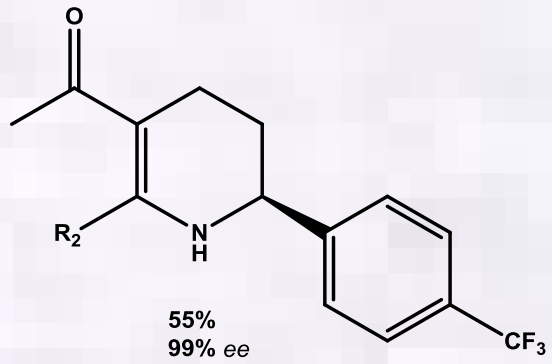


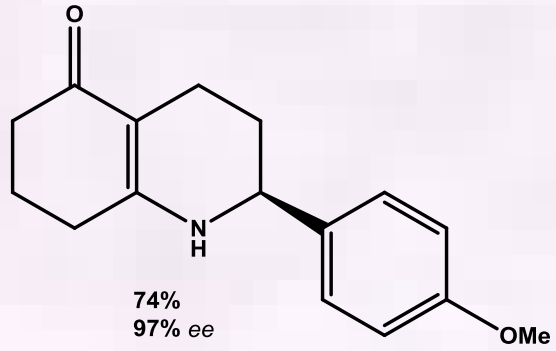
- Sulfenyl substituent stabilizes the intermediate iminium ion and favores Pictet–Spengler cyclization over undesired enamine formation
- Sulfenyl group is readily removable after the cyclization

M. J. Wanner, R. N. S. van der Haas, K. R. de Cuba, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem*. **2007**, 119, 7629 – 7631

Synthesis of Tetrahydropyridines and Azadecalinones

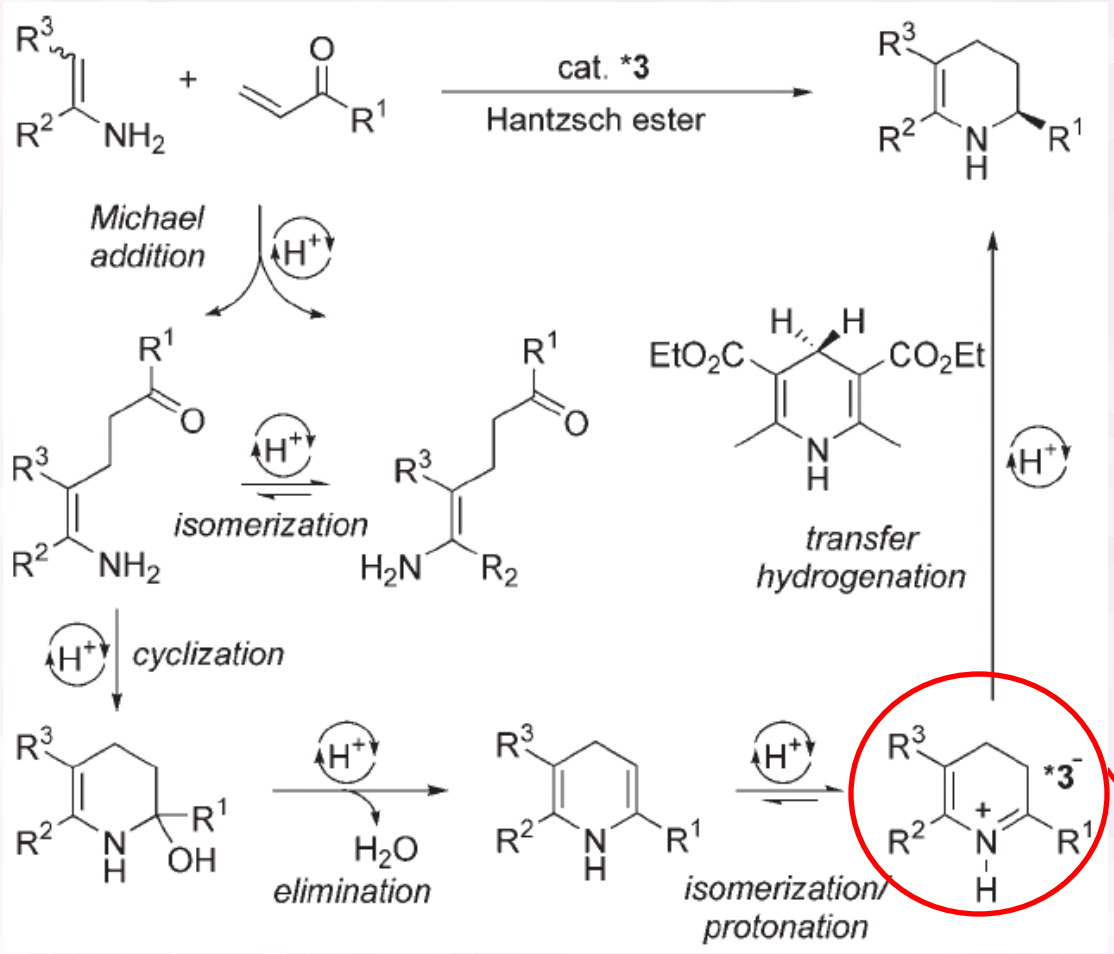


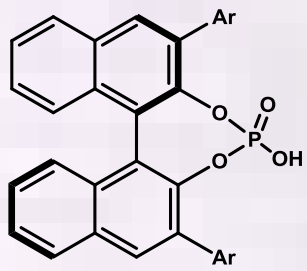




M. Rueping, A. P. Antonchick *Angew. Chem. Int. Ed.* **2008**, 47, 5836 –5838

Mechanism of Tetrahydropyridine Formation



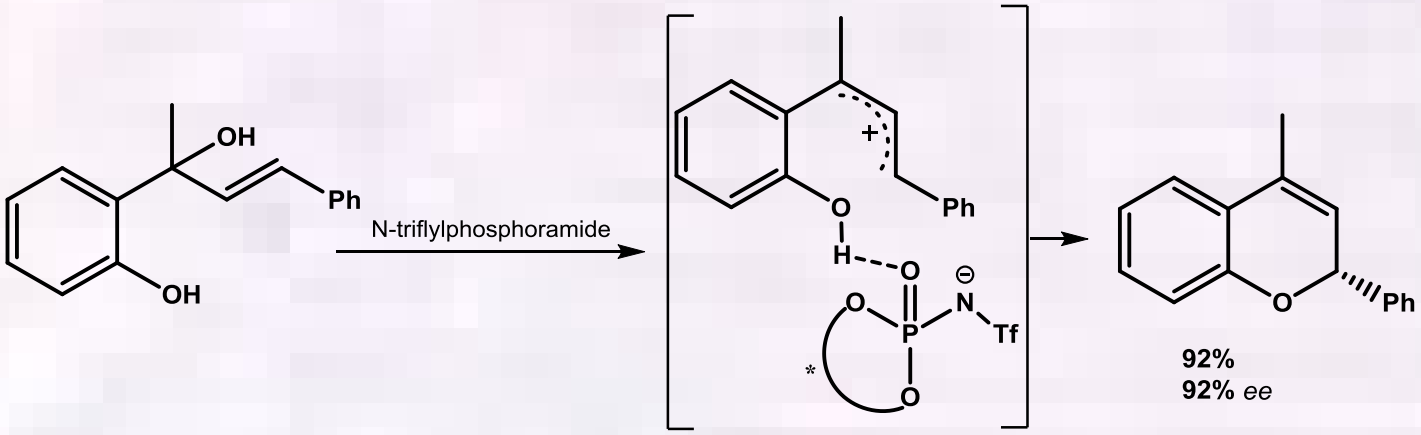


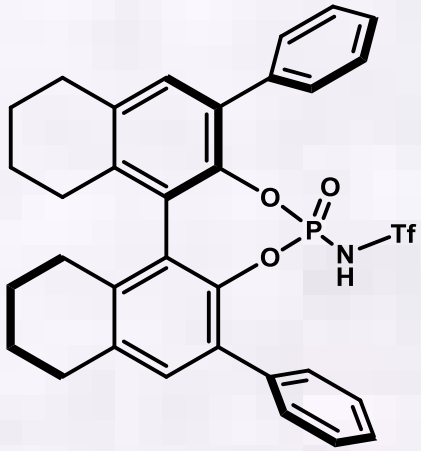
cat. *3 - Ar = 9-anthryl

Chiral anion induces enantioselective hydrogen transfer

M. Rueping, A. P. Antonchick *Angew. Chem. Int. Ed.* **2008**, 47, 5836 –5838

Allylic Alkylation Catalyzed by N-triflyl Phosphoramide





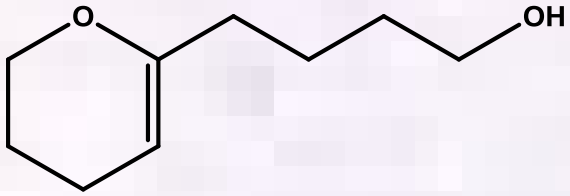
N-triflylphosphoramide

pKa = 6-7 (in MeCN)

for comparison pKa of chiral phosphoric acids in MeCN is 13-14

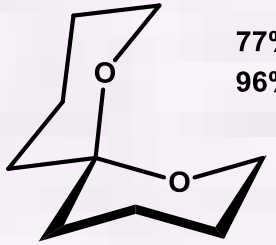
M. Rueping, U. Uria, M.-Y. Lin, I. Atodiresei, *J. Am. Chem. Soc*. **2011**, 133, 3732 – 3735

Enantioselective Spirocyclization by Imidodiphosphoric Acid



A*-H (5 mol%)

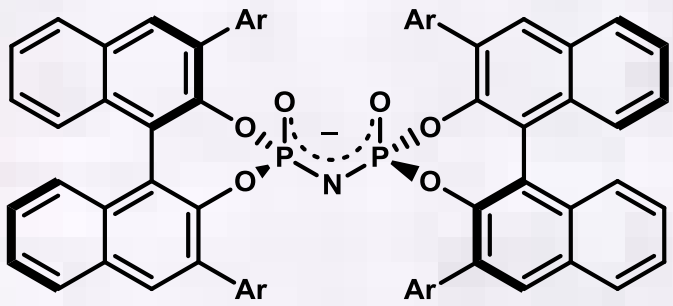
TBME, -25°C



77%

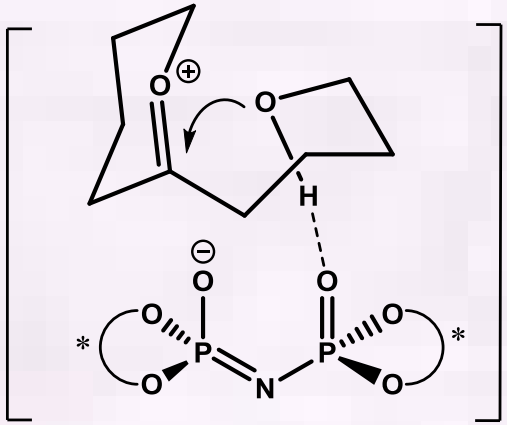
96% *ee*

(S) - olean



Ar = 2,4,6-trimethylbenzene

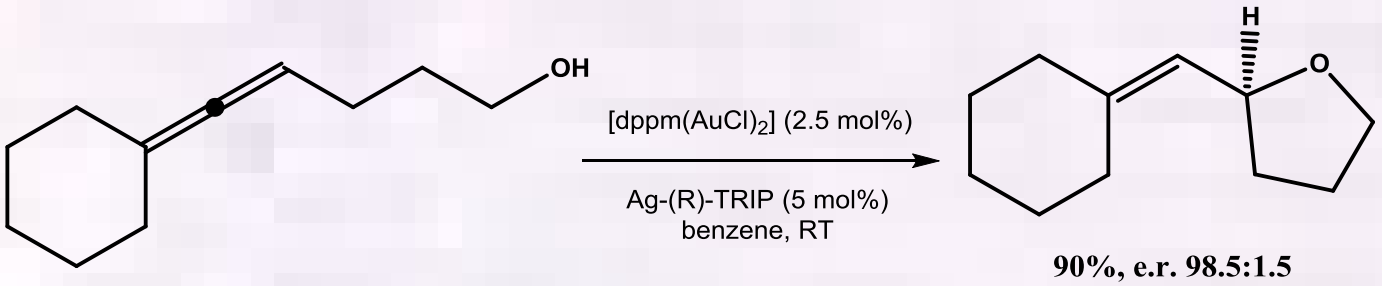
via



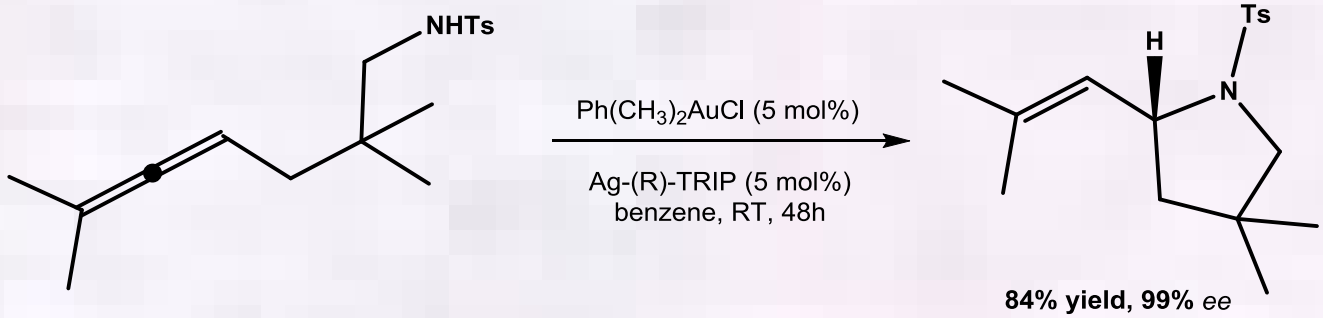
I. Čorić, B. List *Nature* **2012**, 483, 315 – 319

Transition-Metal Catalyzed Cyclizations

Gold-catalyzed Intramolecular Hydroalkoxylation



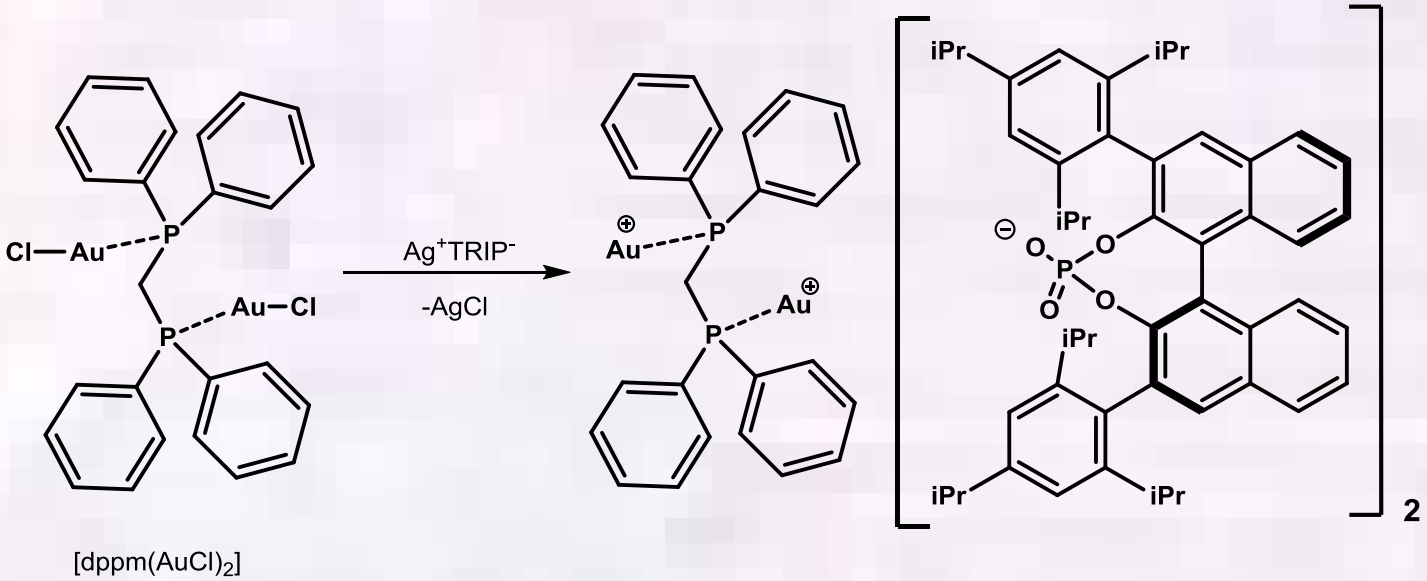
90%, e.r. 98.5:1.5



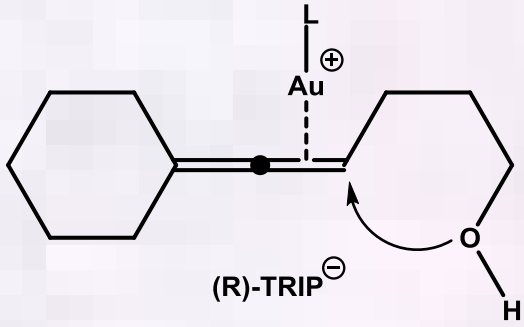
84% yield, 99% *ee*

G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, 317, 496 – 499

Complete Metal-Anion Separation



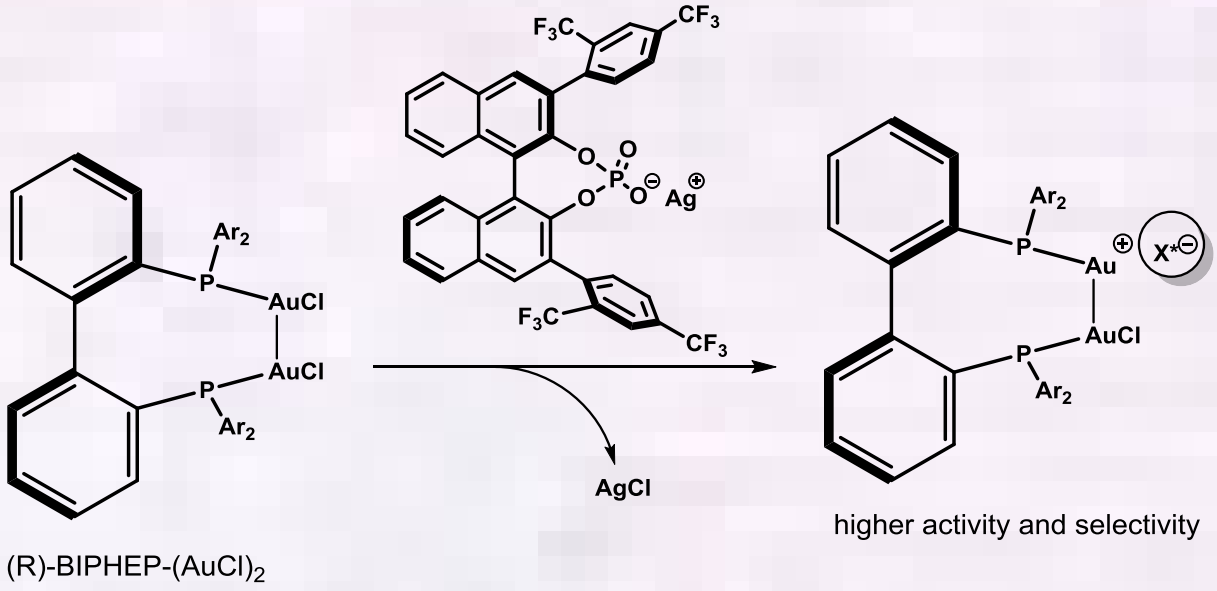
[dppm(AuCl)$_2$]



chiral ion-pair intermediate

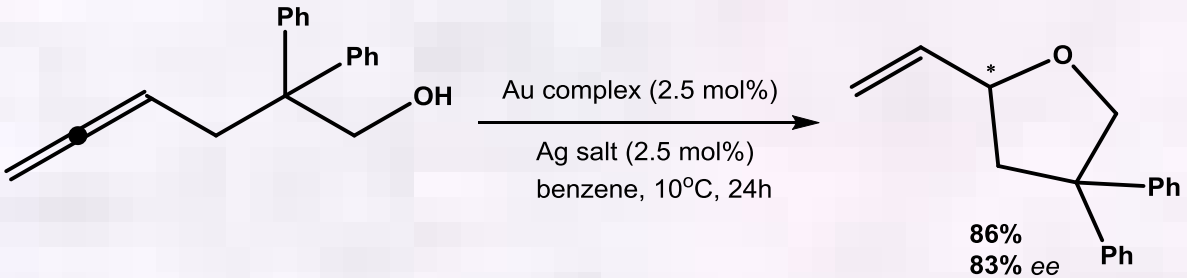
G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, 317, 496 – 499

Synergistic Effect: Combination of Enantiopure BIPHEP-Gold Complexes and Chiral Anions



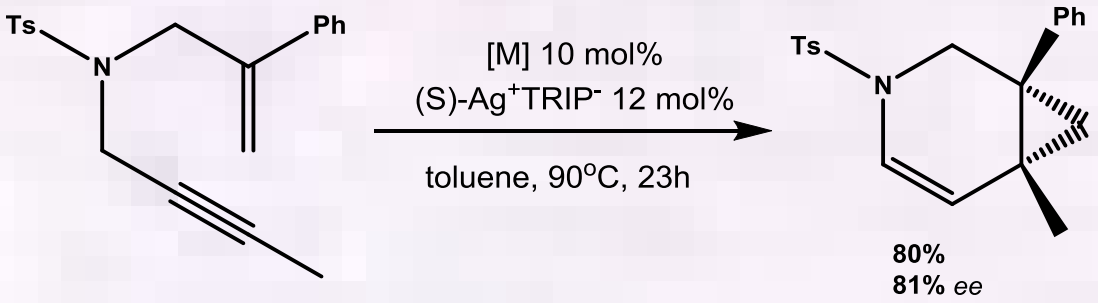
(R)-BIPHEP-$(AuCl)_2$

higher activity and selectivity



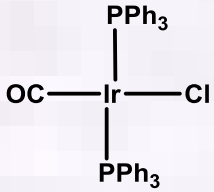
K. Aikawa, M. Kojima, K. Mikami, *Adv. Synth. Catal*. **2010**, 352, 3131 – 3135

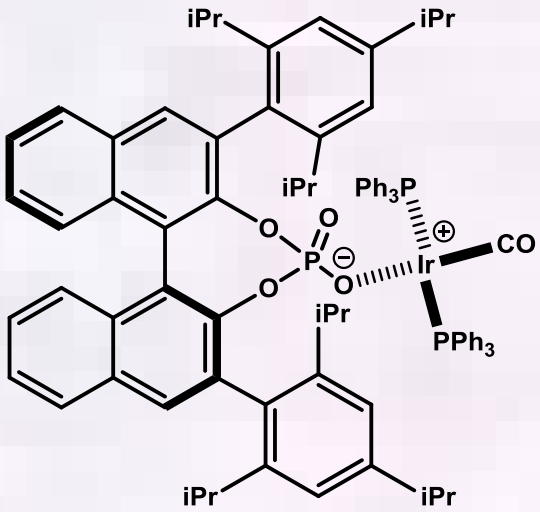
Carbocyclization of 1,6-Enynes by ACDC Strategy



80%
81% *ee*

[M] = Vaska's complex



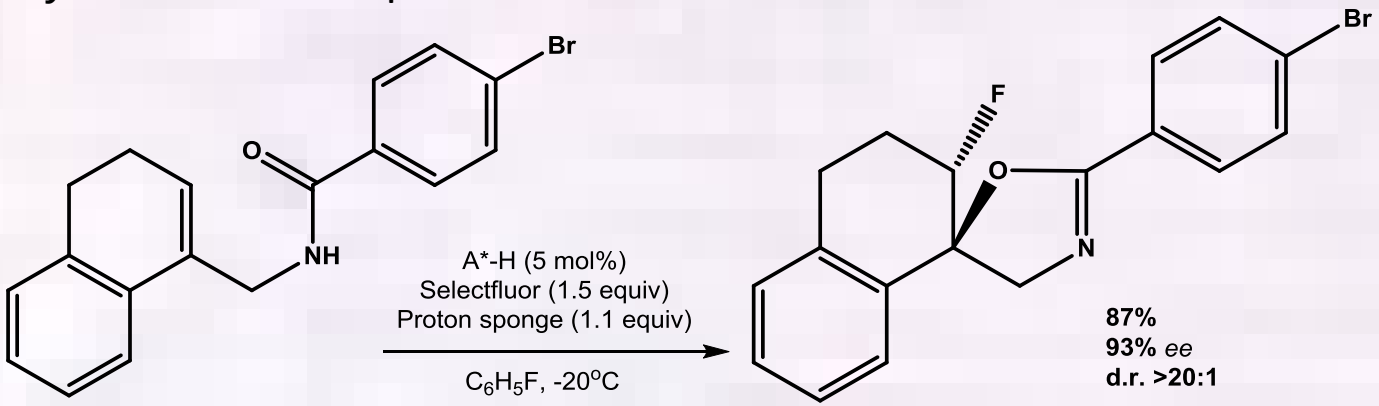


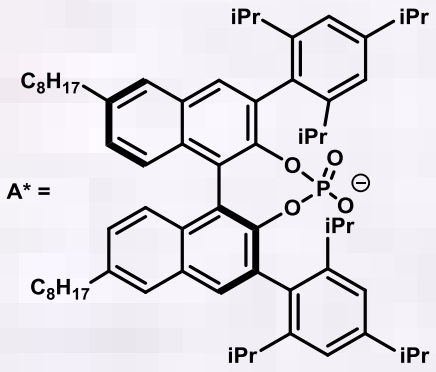
proposed active catalyst

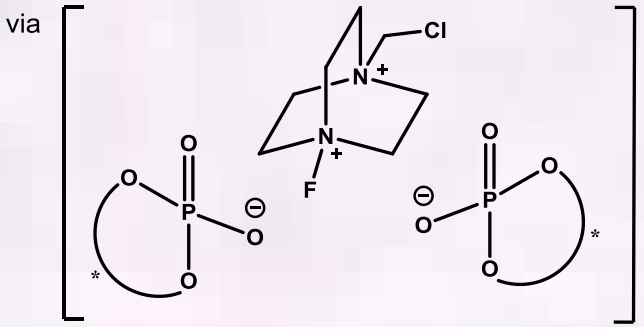
M. Barbazanges, M. Aug, J. Moussa, H. Amouri, C. Aubert, C.Desmartes, L. Fensterbank, V. Gandon, M. Malacria, C. Ollivier, *Chem. Eur. J.* **2011**, 17, 13789 – 13794

Chiral Anion PTC

Asymmetric Electrophilic Fluorination





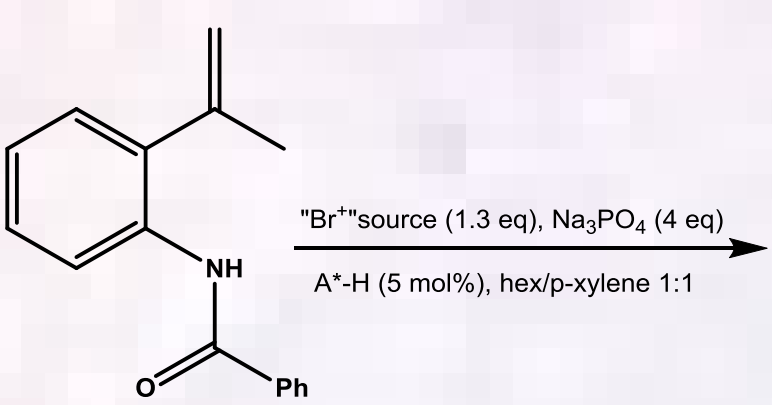


soluble in organic solvent

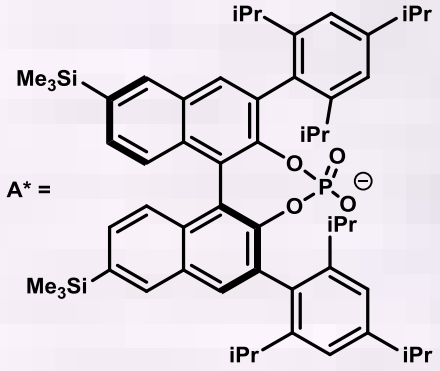
V. Rauniyar, A. D. Lackner, G. L. Hamilton, F. D. Toste, *Science,* **2011**, 334, 1681 – 1684

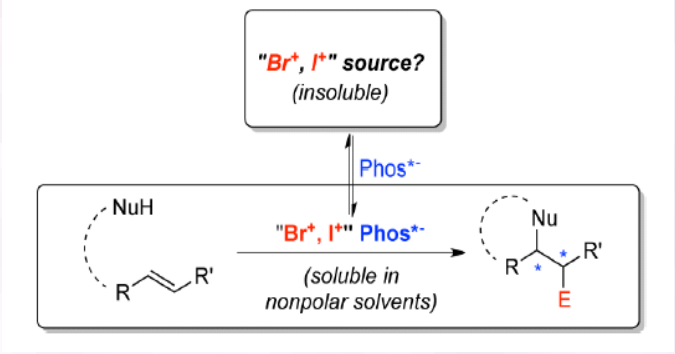
Chiral Anion PTC

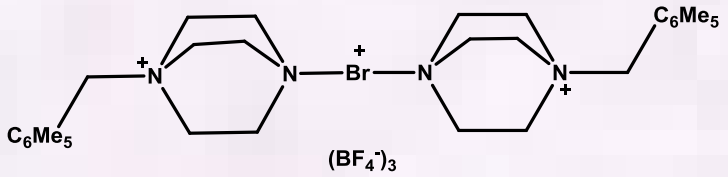
Enantioselective Halocyclization



82%
94% *ee*



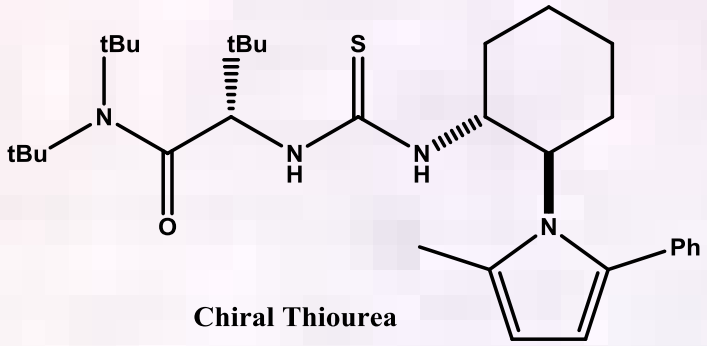




"Br+" source

Y.-M. Wang, J. Wu, Ch. Hoong, V. Rauniyar, F. D. Toste *J. Am. Chem. Soc.* **2012**, 134, 12928−12931

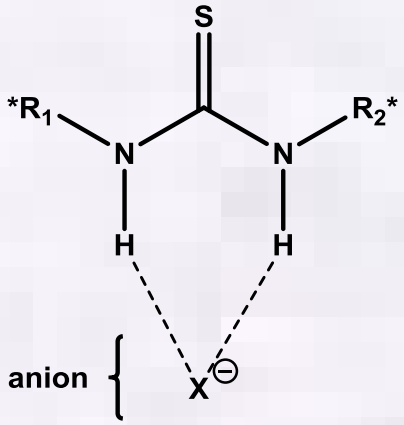
Anion-Binding Thioureas



Chiral Thiourea

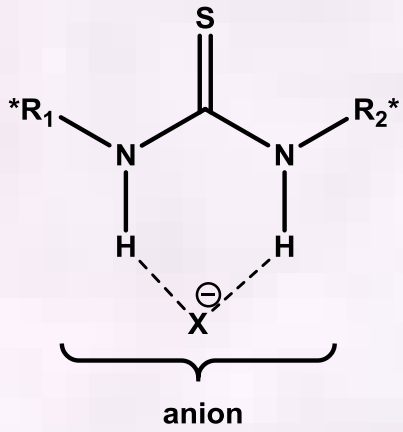
The classification of anion-binding catalysis depends on the definition

supramolecular complex



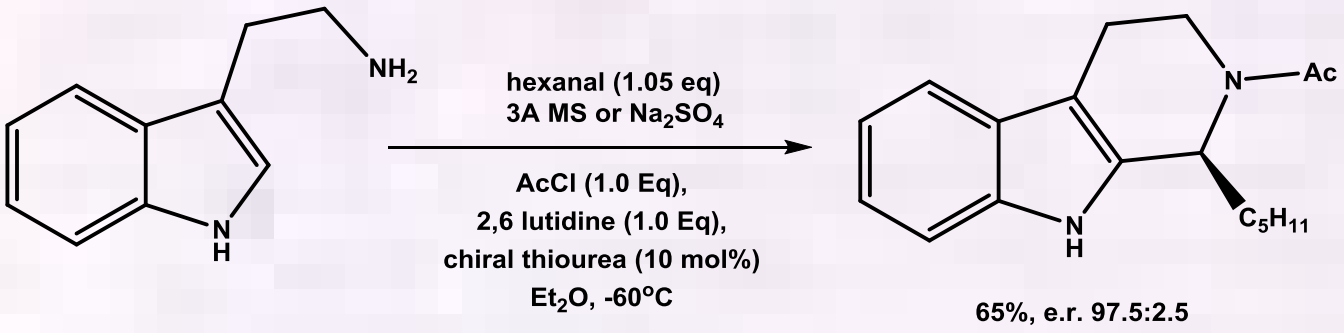
or

ACDC

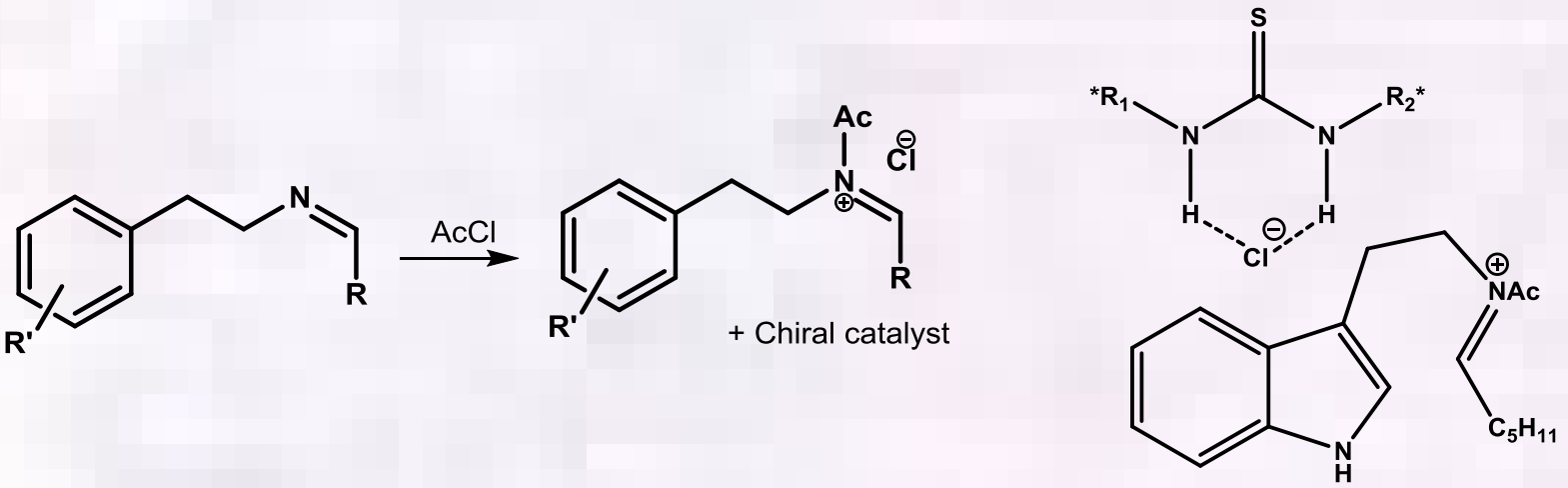


M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc*. **2004**, 126, 10558 – 10559

Enantioselective Catalytic Acyl-Pictet-Spengler Reaction

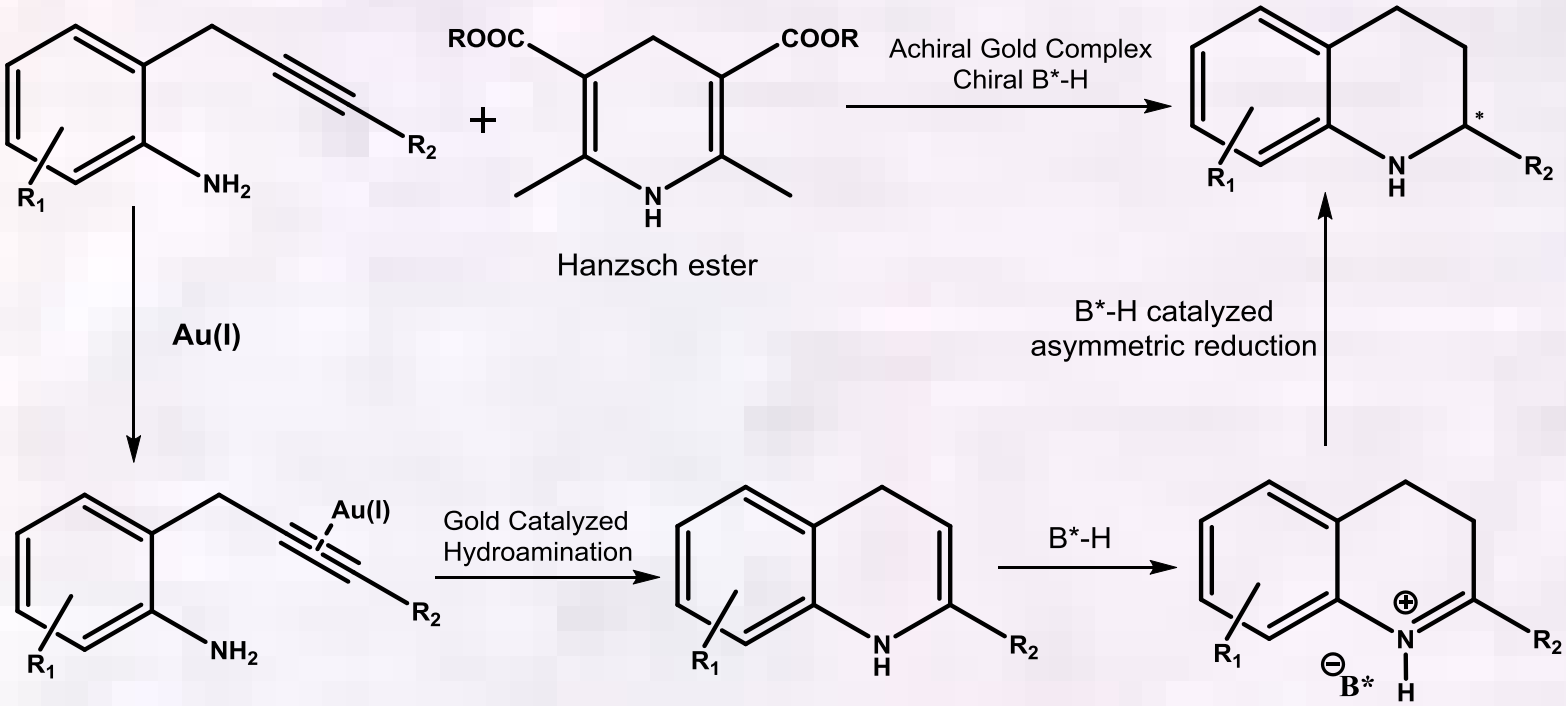


65%, e.r. 97.5:2.5



M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc*. **2004**, 126, 10558 – 10559

Consecutive Intramolecular Hydroamination/Asymmetric Transfer Hydrogenation



Z.-Y. Han, H. Xiao, X.-H. Chen, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, 131, 9182 – 9183

Perspectives

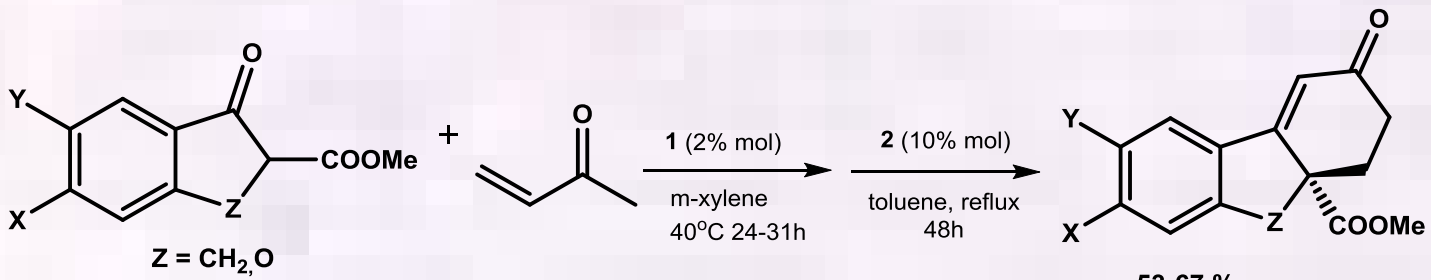
- ACDC gives better or at least complementary results than more traditional methods
- Combination with chiral cations seems to be very promising
- Cooperative and sequential catalysis
- Plethora of reactions proceeding through cationic intermediates
- Theoretic studies towards better understanding of reaction mechanisms will be essesntial for the progress

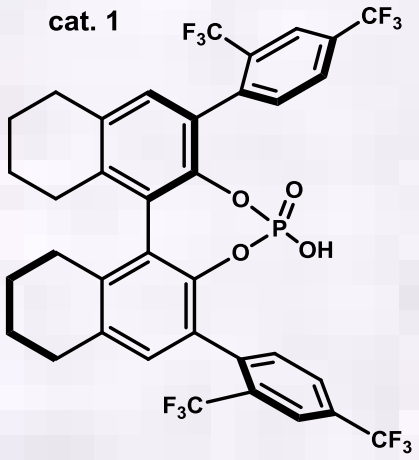
Questions

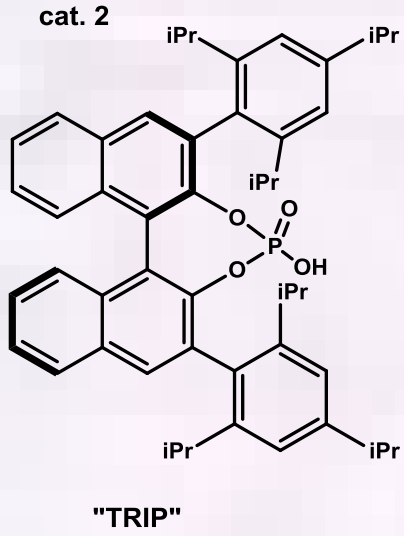
Why the reaction presented on the following slide cannot be regarded as ACDC?

Which types of reactions are going to be done by ACDC in the near future?

Enantioselective Robinson-Type Annulation Reaction

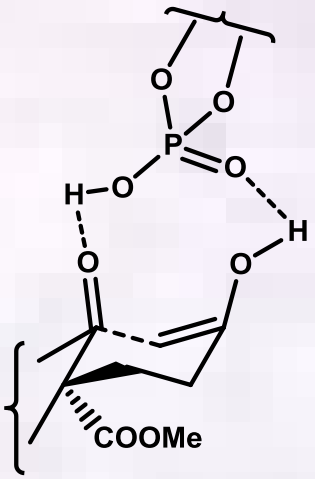






T. Akiyama, T.Katoh, and K. Mori *Angew. Chem. Int. Ed.* **2009**, 48, 4226 –4228

Mechanistic Aspect



Proposed transition state

The phosphoric acid hydrogen atom activates the ketone group by acting as a Brønsted acid and thus promotes the formation of an enol from the ketone unit. Covalent bonding is significant during the selectivity-determining step and the reaction cannot be classified as ACDC case

T. Akiyama, T.Katoh, and K. Mori *Angew. Chem. Int. Ed.* **2009**, 48, 4226 –4228

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Catalytic enantioselective isocyanide-based multicomponent reactions

Frontiers in Organic Chemistry Part III: Stereochemistry

Joachim S. E. Ahlin

1st Mai 2013

Cramer Group

Questions

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Question 1: Why is the approach for the introduction of chirality in IMCRs challenging?

- Question 2: In their catalytic enantioselective Passerini-type MCR leading to tetrazole derivatives, Zhu *et al.* eventually used the complex [(salen)Al^{III}Me] instead of [(salen)Al^{III}Cl]. Why? Can you think of a side reaction?

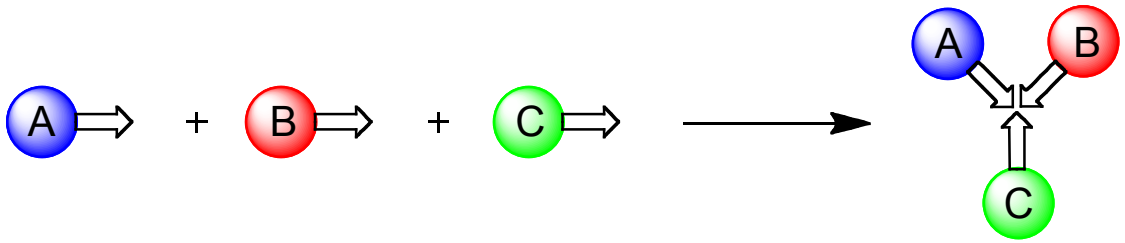
Table of Contents

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

Introduction

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Definition: Multicomponent Reactions (MCRs) are processes in which at least three starting compounds react in a single chemical step to afford products incorporating essentially all of the atoms of the reactants.



- MCRs should be distinguished from *domino*, *tandem*, *cascade*, *zipper* and *sequential component reactions*.

R. V. A. Orru *et al.*, *Chem. Soc. Rev.* **2012**, *41*, 3969–4009.
D. J. Ramon, M. Yus, *ACIE* **2005**, *44*, 1602–1634.
J. Zhu, H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, 2005.

Introduction

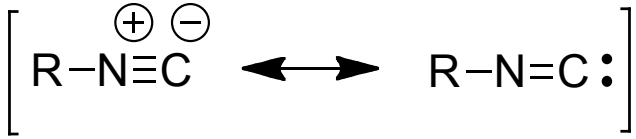
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Classification of MCRs:
- MCRs based on nucleophilic addition to imines
  - Strecker, Mannich, Biginelli, Petasis reaction
- Hantzsch MCR
- Isocyanide-based MCRs
  - Passerini, Ugi reaction
- Cycloaddition-based MCRs
  - Diels–Alder, Knoevenagel and 1,3-dipolar cycloaddition-based MCRs
- Michael addition-based MCRs

Introduction

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Isocyanide-based MCRs (IMCRs)

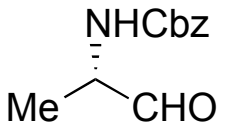


- Versatile reagents
- Diversity of bond forming processes
- Functional group tolerance
- High levels of chemo-, regio-, stereoselectivity often encountered.

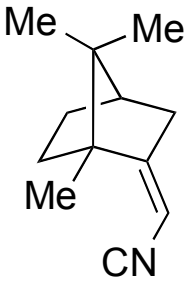
- Isocyanide reacts with both electrophiles and nucleophiles
- Readily availability of the isocyanides

Introduction

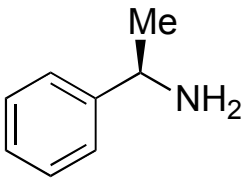
- Stereocontrol in IMCR:
  - Chiral aldehydes
  - Chiral isocyanides
  - Chiral carboxylic acids
  - Chiral amines
  - Chiral catalysts

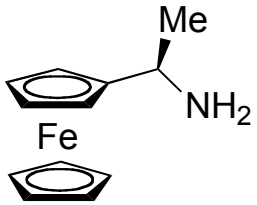


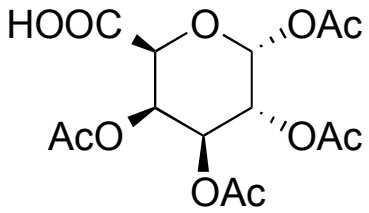
U. Schmidt, S. Weinbrenner, *Chem. Commun.* **1994**, 1003–1004.

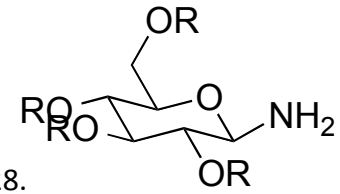


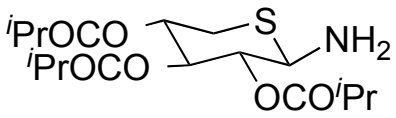
H. Bock, I. Ugi, *J. Prakt. Chem.* **1997**, *339*, 385–389.











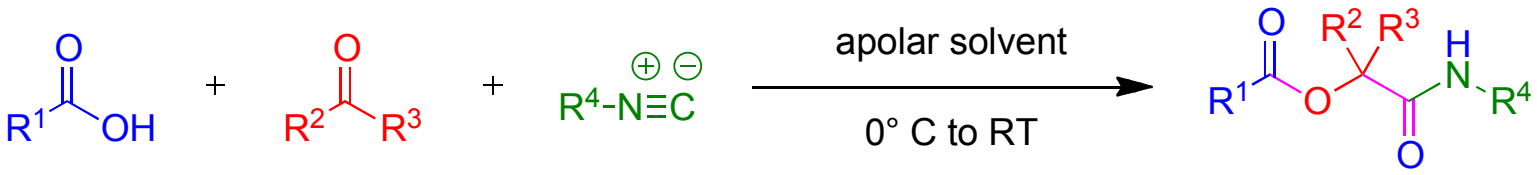
C. Lamberth *et al.*, *Synlett* **2003**, 1536–1538.

I. Ugi, G. Kaufhold, *Liebigs Ann. Chem.* **1967**, *709*, 11–28.
I. Ugi *et al.*, *JACS* **1971**, 1969–1972.
H. Kunz, W. Sager, *ACIE* **1987**, *26*, 557–559.
I. Ugi *et al.*, *Tetrahedron* **2002**, *58*, 6127–6133.

The Passerini MCR

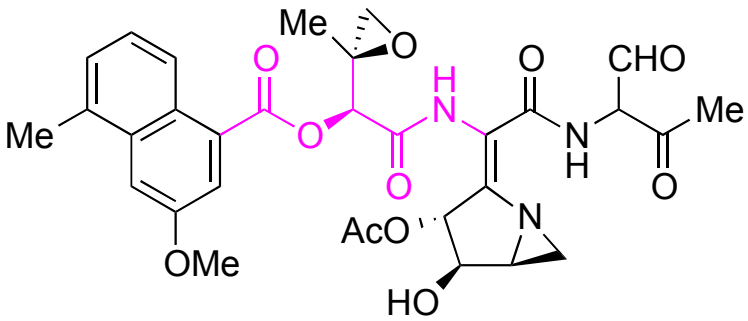
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- The Passerini three-component Reaction (P-3CR)



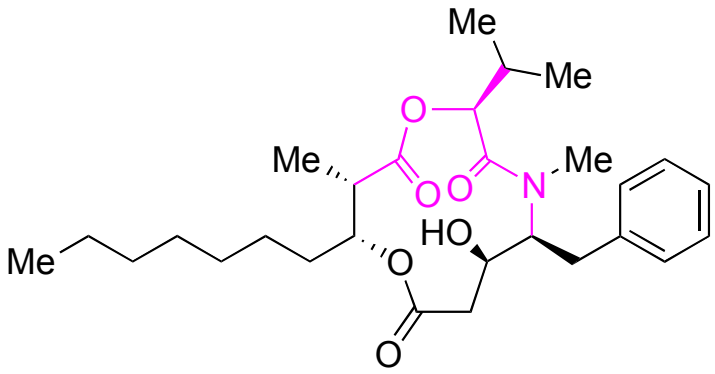
α-Acyloxycarboxamide

M. Passerini, *Gazz. Chim. Ital.* **1921**, *51*, 126–129; *Ibid.*, *51*, 181–189.



Azinomycin B

K. Nagaoka *et al.*, *J. Antibiot.* **1986**, *39*, 1527–1532.



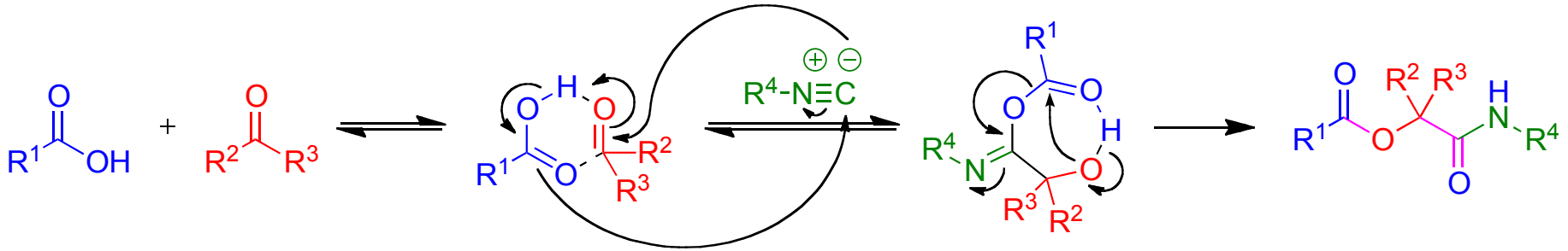
Hapalosin

R. E. Moore *et al.*, *JOC* **1994**, *59*, 7219–7226.

The Passerini MCR

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Plausible Mechanism:



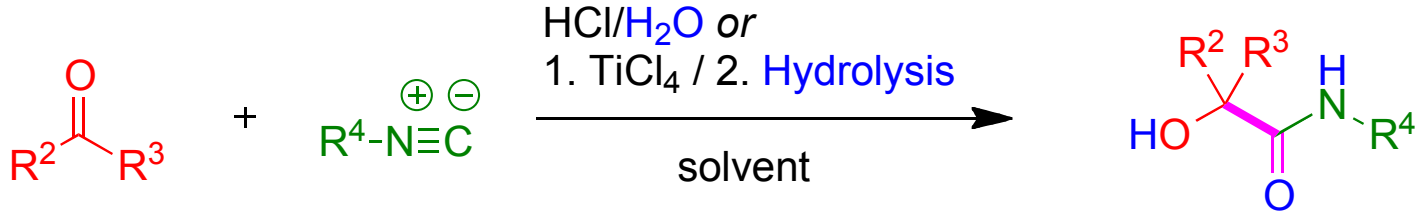
- Reaction is accelerated in apolar solvents
- Sterically hindered and α,β-unsaturated ketones do not react

M. Passerini, *Gazz. Chim. Ital.* **1922**, *52*, 432–435.
R. H. Baker, D. Stanonis, *JACS* **1951**, *73*, 699–702.
I. Ugi, R. Meyr, *Chem. Ber.* **1961**, *94*, 2229–2233.
I. Ugi, *ACIE* **1962**, *1*, 8–21.

The Passerini MCR

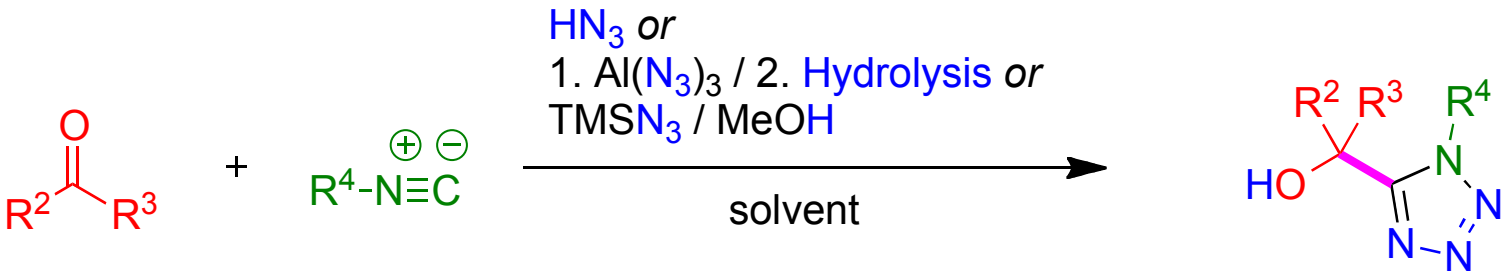
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Modifications



α-Hydroxycarboxamide

I. Hagedorn, U. Eholzer, *Chem. Ber.* **1965**, *98*, 936–940.
M. Schiess, D. Seebach, *Helv. Chim. Acta* **1983**, *66*, 1618–1623.
C. Floriani *et al.*, *Organometallics* **1993**, *12*, 2726–2736.

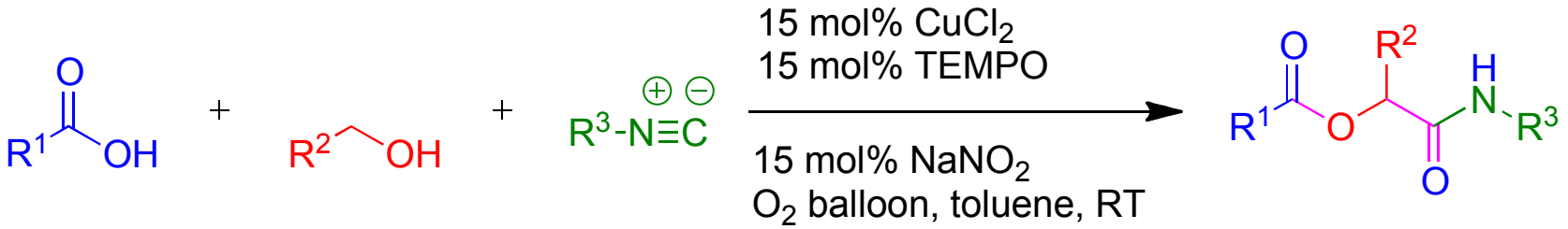


α-Hydroxyalkyltetrazole

I. Ugi, R. Meyr, *Chem. Ber.* **1961**, *94*, 2229–2233.
T. Nixey, C. Hulme, *TL* **2002**, *43*, 6833–6835.

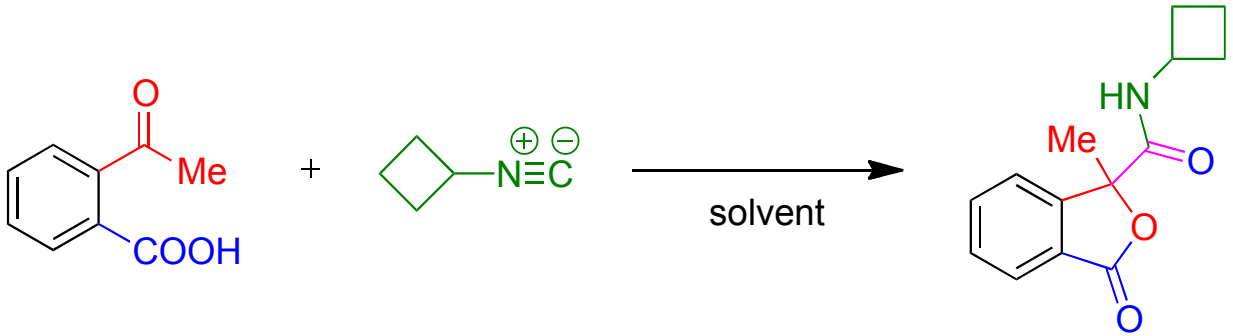
The Passerini MCR

- Modifications



α-Acyloxycarboxamide

J. Zhu *et al.*, *OL* **2010**, *12*, 1432–1435.



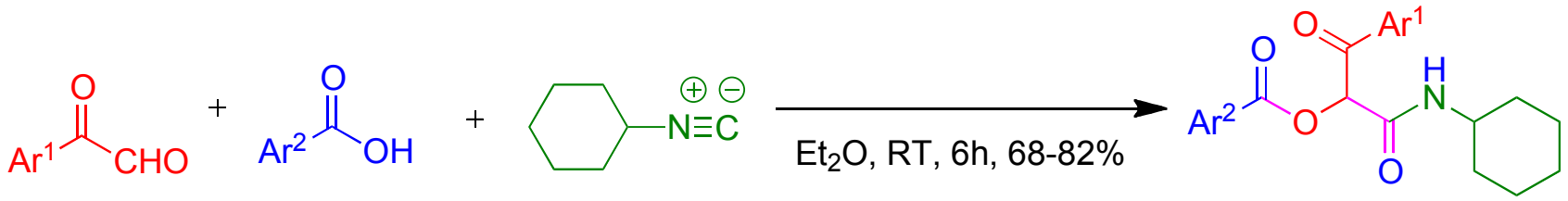
γ-lactone

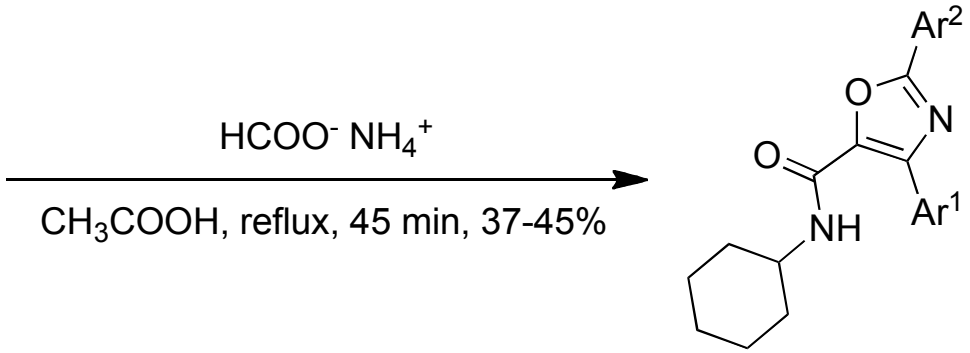
M. Passerini, *Gazz. Chim Ital*. **1923**, *53*, 331–333.

The Passerini MCR

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Modifications: accessing heterocycles





2,4,5-trisubstituted oxazoles

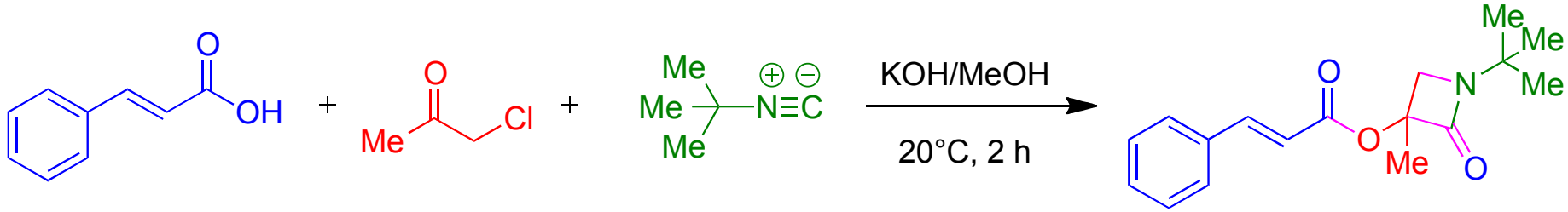
Ar^1 = Ph, *p*-ClPh
Ar^2 = Ph, *o*-ClPh, *o*-OHPh

S. Marcaccini et al., *Liebigs. Ann. Chem.* **1991**, 1107–1108.

The Passerini MCR

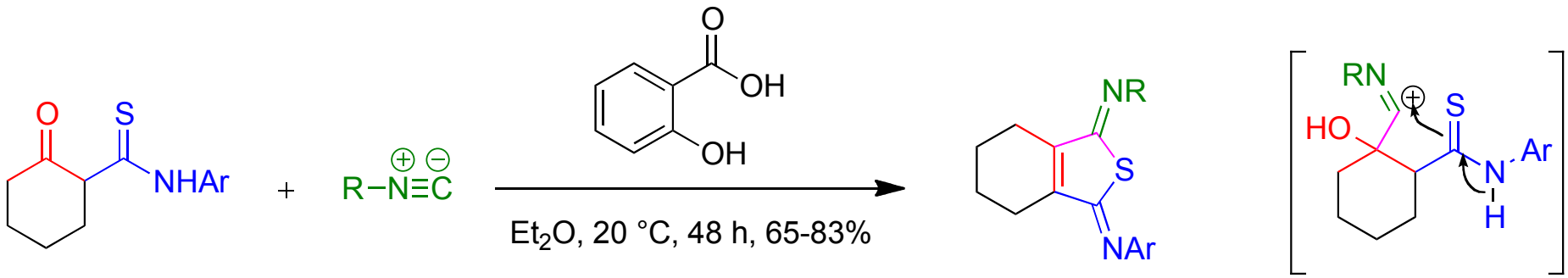
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Modifications: accessing heterocycles



3-Acyloxy-2-azetidinone

S. Sebti, A. Foucand, *Synthesis* **1983**, 546–549.



Benzo[c]thiophenes

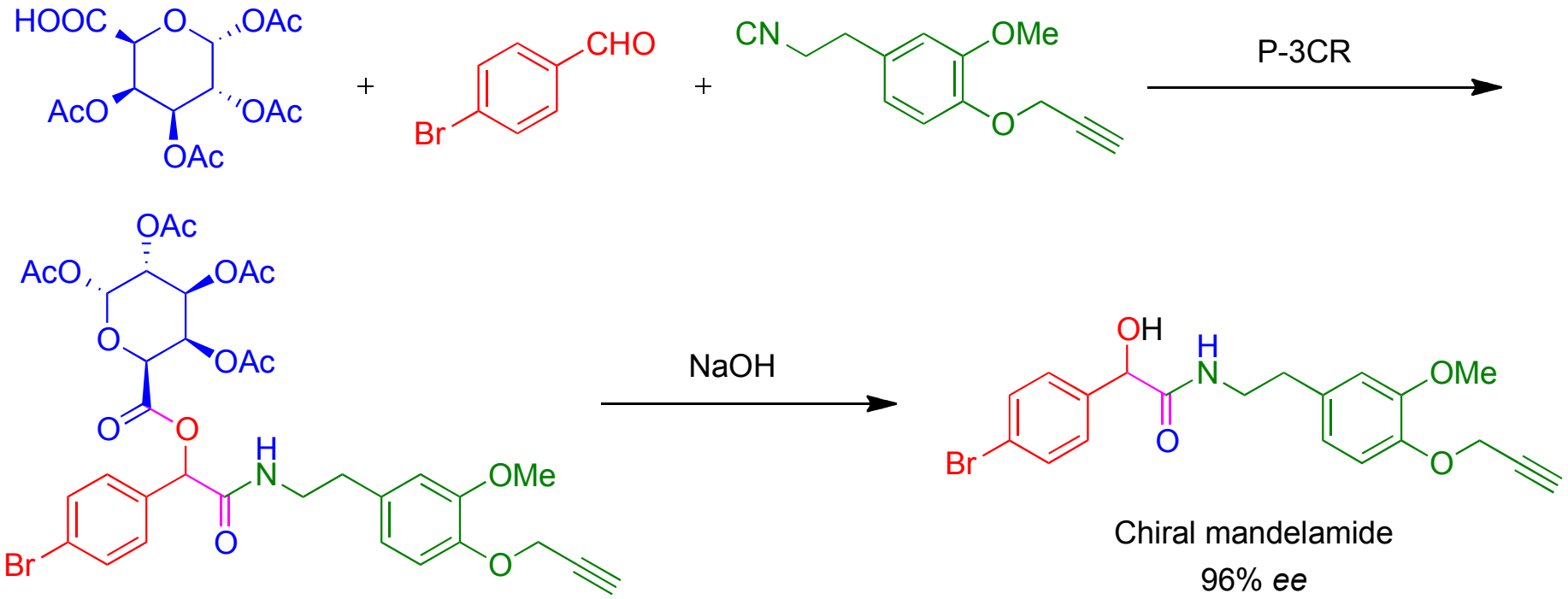
Ar = Ph, *p*-ClPh
R = Cy, Cyp, Bn, *p*-EtOPh

T. Torroba *et al.*, *J. Chem. Soc., Perkin Trans. 1* **1996**, 229–230.

Catalytic enantioselective Passerini MCR

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- First highly stereoselective Passerini MCR:



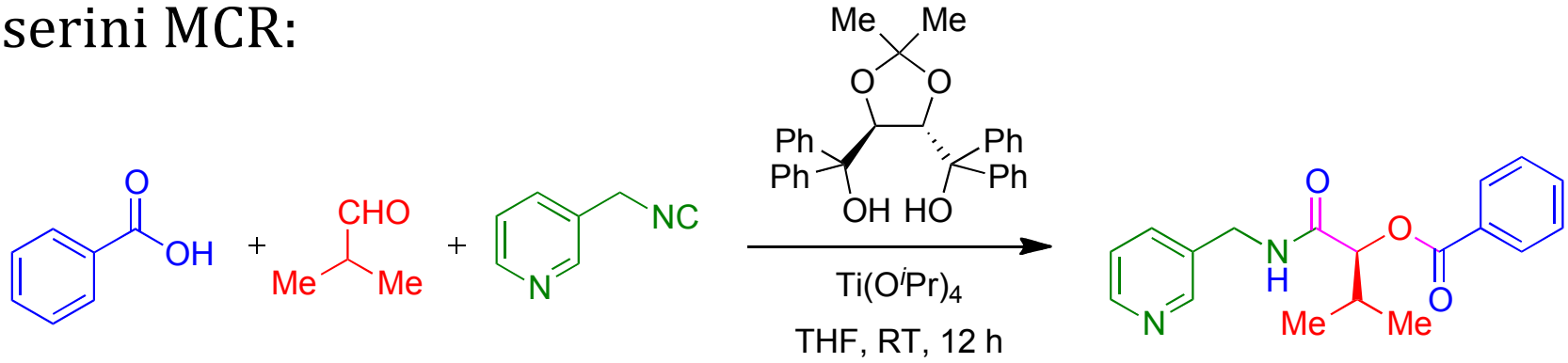
Chiral mandelamide
96% *ee*

C. Lamberth *et al.*, *Synlett* **2003**, 1536–1538.

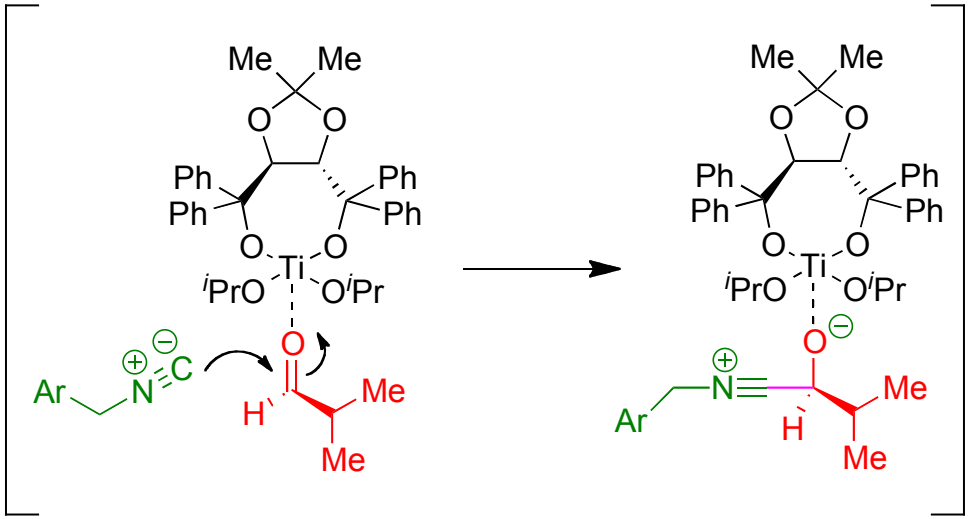
Catalytic enantioselective Passerini MCR

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- First "successful" enantioselective Lewis acid-promoted Passerini MCR:

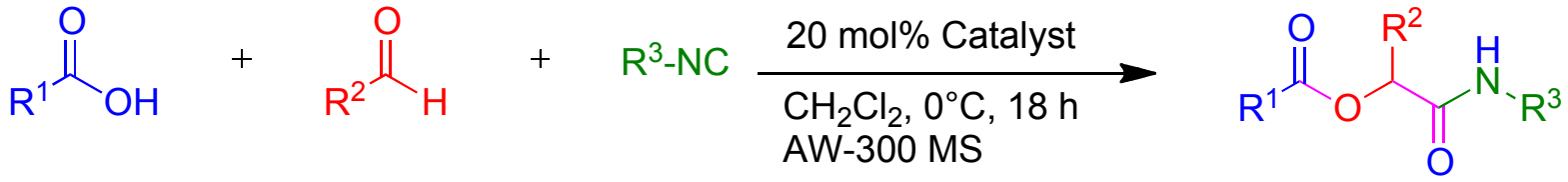


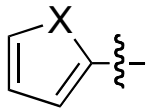
28%, 42% *ee*
76% without Lewis acid



A. Dömling *et al.*, *OL* **2003**, *5*, 4021–4024.

Catalytic enantioselective Passerini MCR

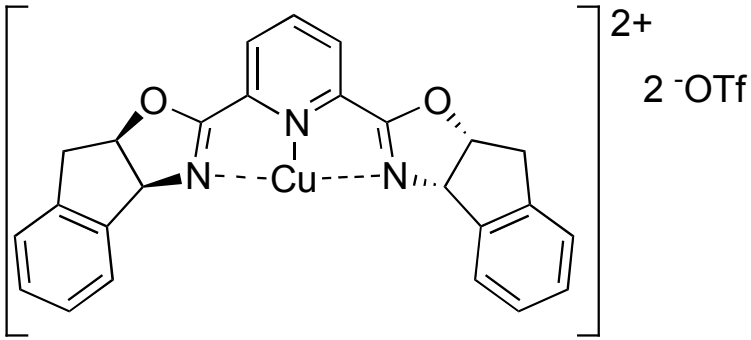


R^2 = CH_2OBn,  X = O, S

R^1 = Ph, Bn

R^3 = Bn, ^{t}Bu, *n*-Bu, *n*-pentyl, *p*-MeOPh

75-95%, 62-98% *ee*



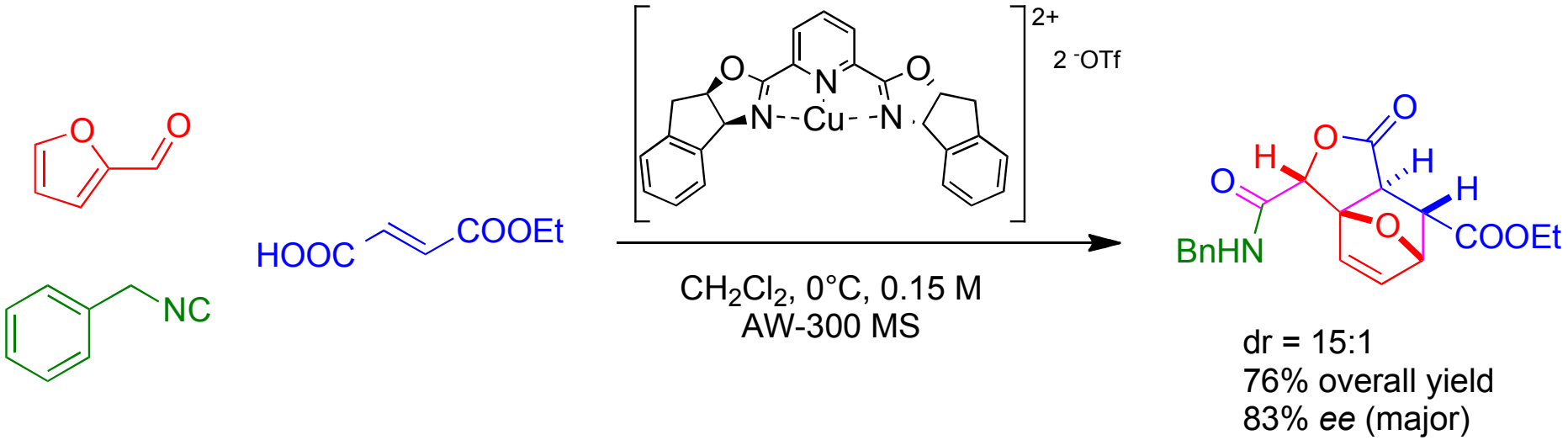
- Anhydrous conditions required
- Limited to bidentate aldehydes
- ^{t}BuNC / *p*-MeOPhNC afforded the best *ee*'s
- Lower *ee*'s with BnCOOH

S. L. Schreiber *et al.*, *OL* **2004**, *6*, 4231–4233.

Catalytic enantioselective Passerini MCR

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

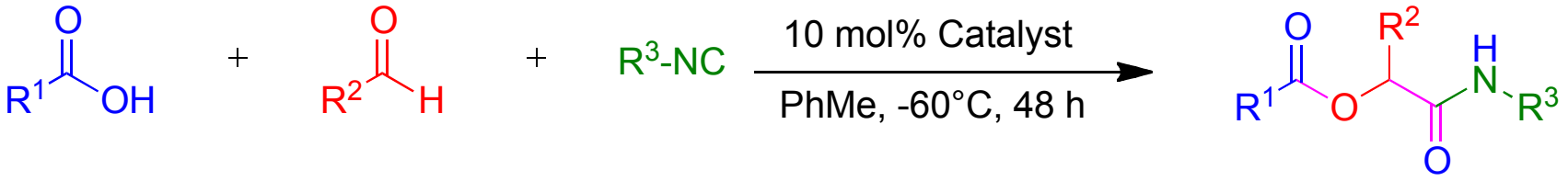
- Application: consecutive P-3CR/intramolecular Diels-Alder



dr = 15:1
76% overall yield
83% *ee* (major)

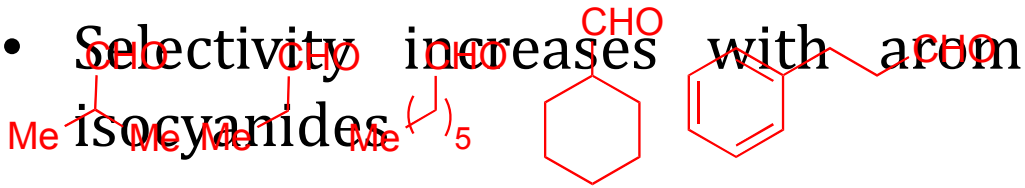
S. L. Schreiber *et al.*, *OL* **2004**, *6*, 4231–4233.

Catalytic enantioselective Passerini MCR

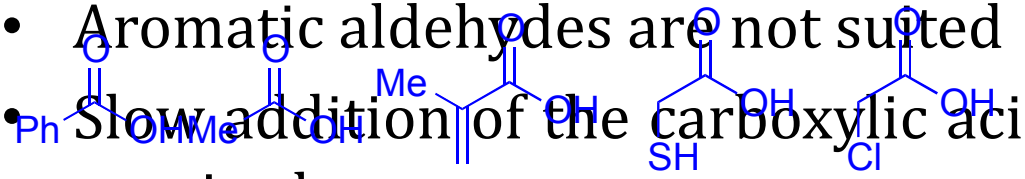


52-68%, 68->99% *ee*

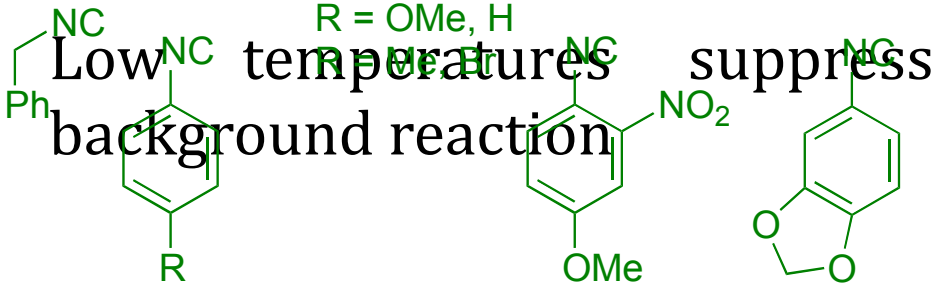
- Selectivity increases with aromatic isocyanides

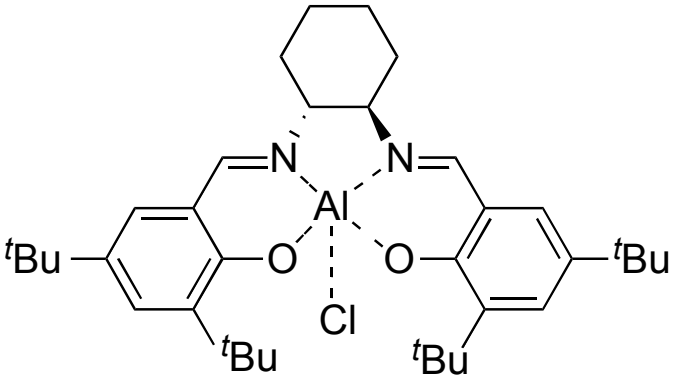


- Aromatic aldehydes are not suited
- Slow addition of the carboxylic acid is required



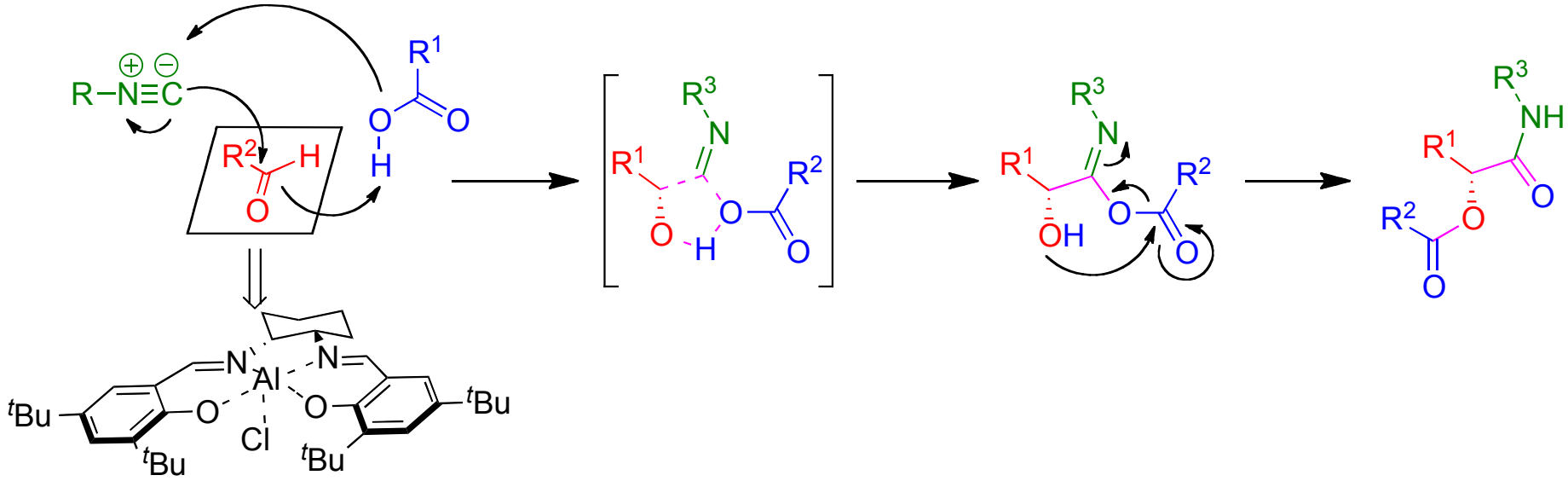
- Low temperatures suppress the background reaction





J. Zhu, M.-X. Wang *et al.*, *ACIE* **2008**, *47*, 388–391.

Catalytic enantioselective Passerini MCR



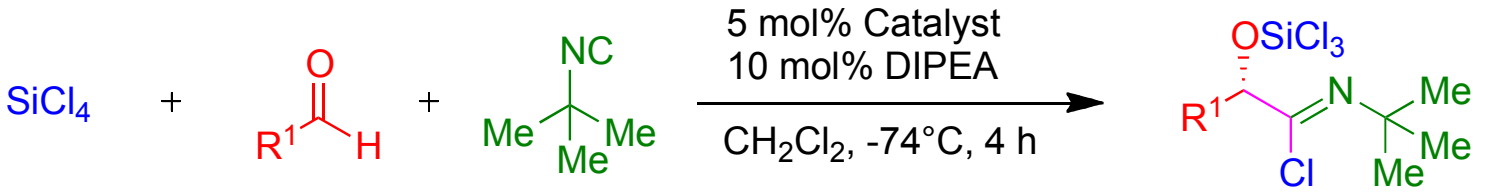
- Observed *S*-enantioselectivity: *Re*-face is attacked by the isocyanide.
- Structure of the acid influenced the enantioselectivity: carboxylic acid is involved in the C–C bond forming process.

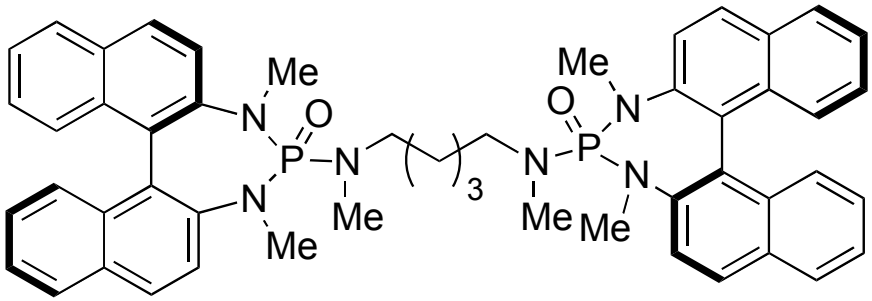
J. Zhu, M.-X. Wang *et al.*, *ACIE* **2008**, *47*, 388–391.

Catalytic enantioselective Passerini-type MCR

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- First catalytic enantioselective Passerini-type reaction



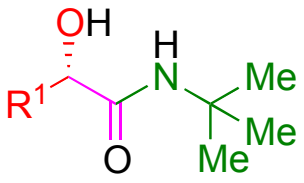


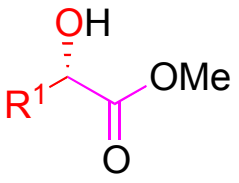
(*R*,*R*)

53-96%, 40->99% *ee*

aq. work-up

1. MeOH, -74°C, 40 min
2. aq. work-up





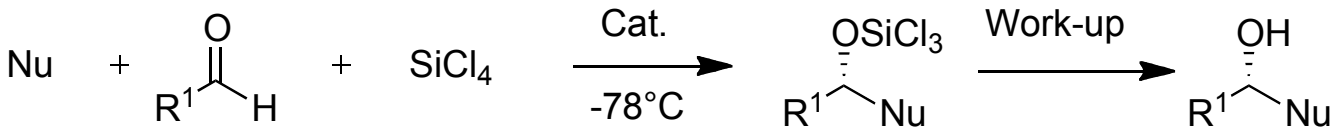
R^1 = Aryl, alkenyl, alkynyl, alkyl, heteroaryl

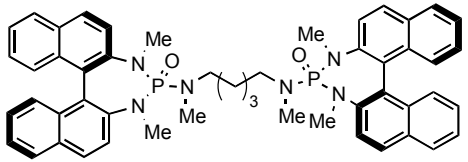
S. E. Denmark, Y. Fan, *JOC* **2005**, *70*, 9667–9676.

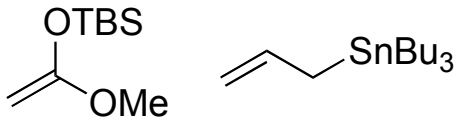
Catalytic enantioselective Passerini-type MCR

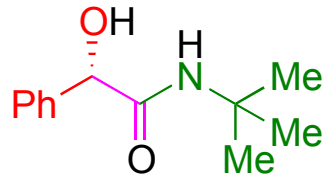
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Concept: Lewis Base activation of Lewis acid
  - Activation of a weak Lewis acid: a highly reactive and selective silyl cation is generated.





Nu = 



- Challenges: Achiral Background reaction
  - Slow addition of the isocyanide
  - Use of catalytic amounts of a base

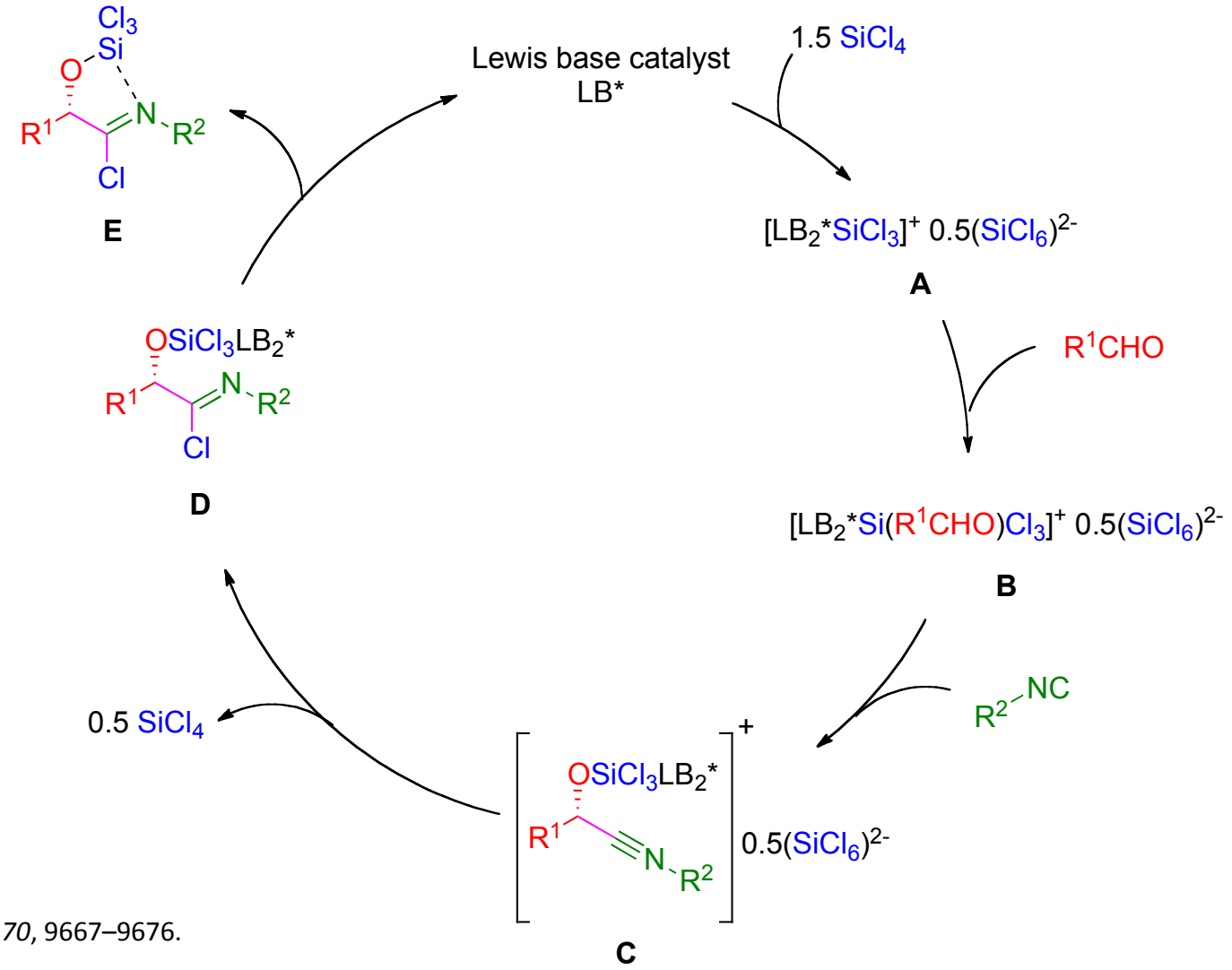
^{t}BuNC addition protocol	*er*
One-portion	90:10
Slow addition over 4 h	>99:1

S. E. Denmark, Y. Fan, *JOC* **2005**, *70*, 9667–9676.

Catalytic enantioselective Passerini-type MCR

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Mechanism

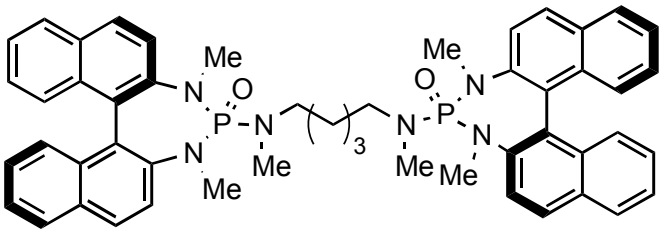


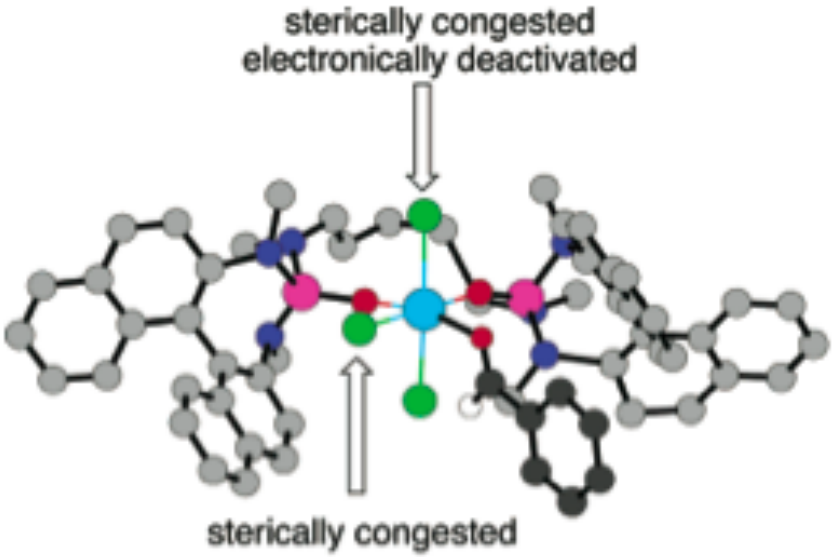
S. E. Denmark, Y. Fan, *JOC* **2005**, *70*, 9667–9676.

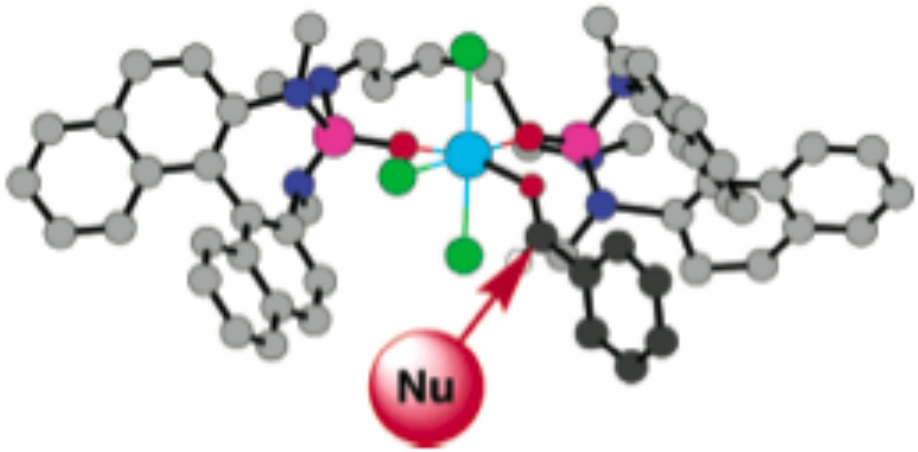
Catalytic enantioselective Passerini-type MCR

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Enantioselection: $[LB_2{*}Si(R^1CHO)Cl_3]^+ \ 0.5(SiCl_6)^{2-}$

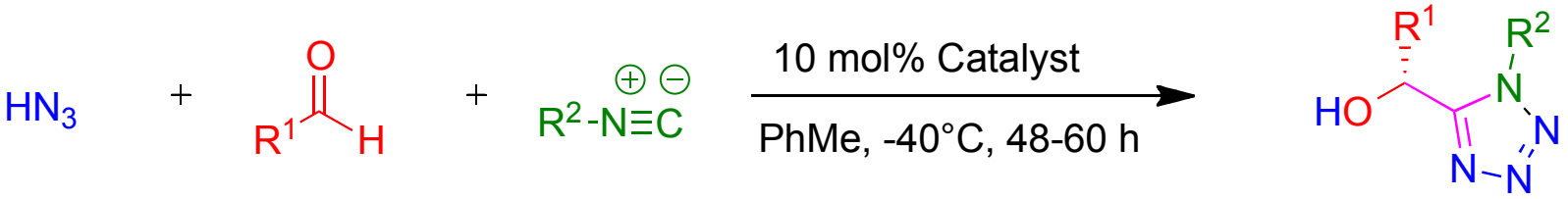






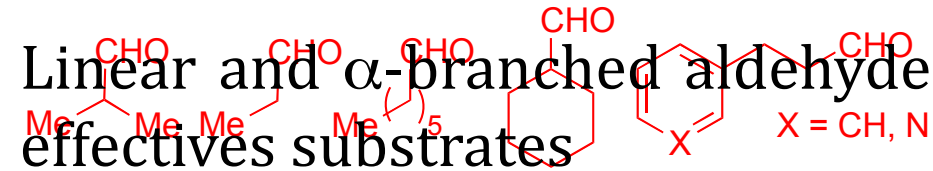
S. E. Denmark, Y. Fan, *JOC* **2005**, *70*, 9667–9676.

Catalytic enantioselective Passerini-type MCR

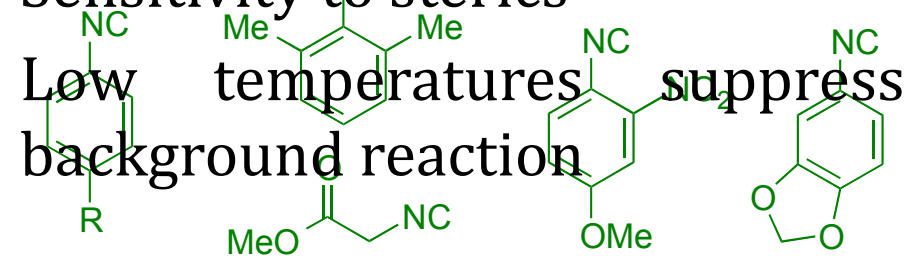


45-99%, 51->97% *ee*

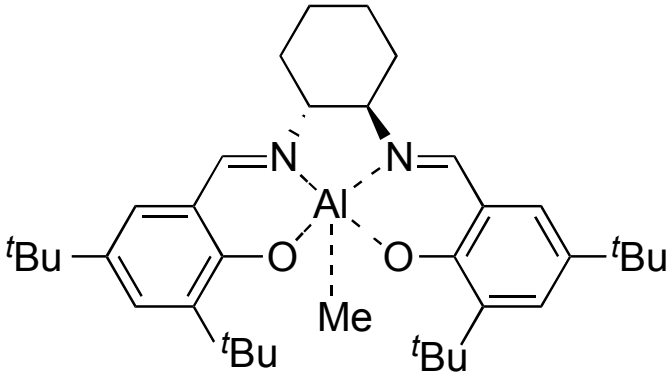
- Linear and α-branched aldehydes are effectives substrates



- Aromatic isocyanides with EWG or EDG well tolerated.
- Sensitivity to sterics
- Low temperatures suppress the background reaction

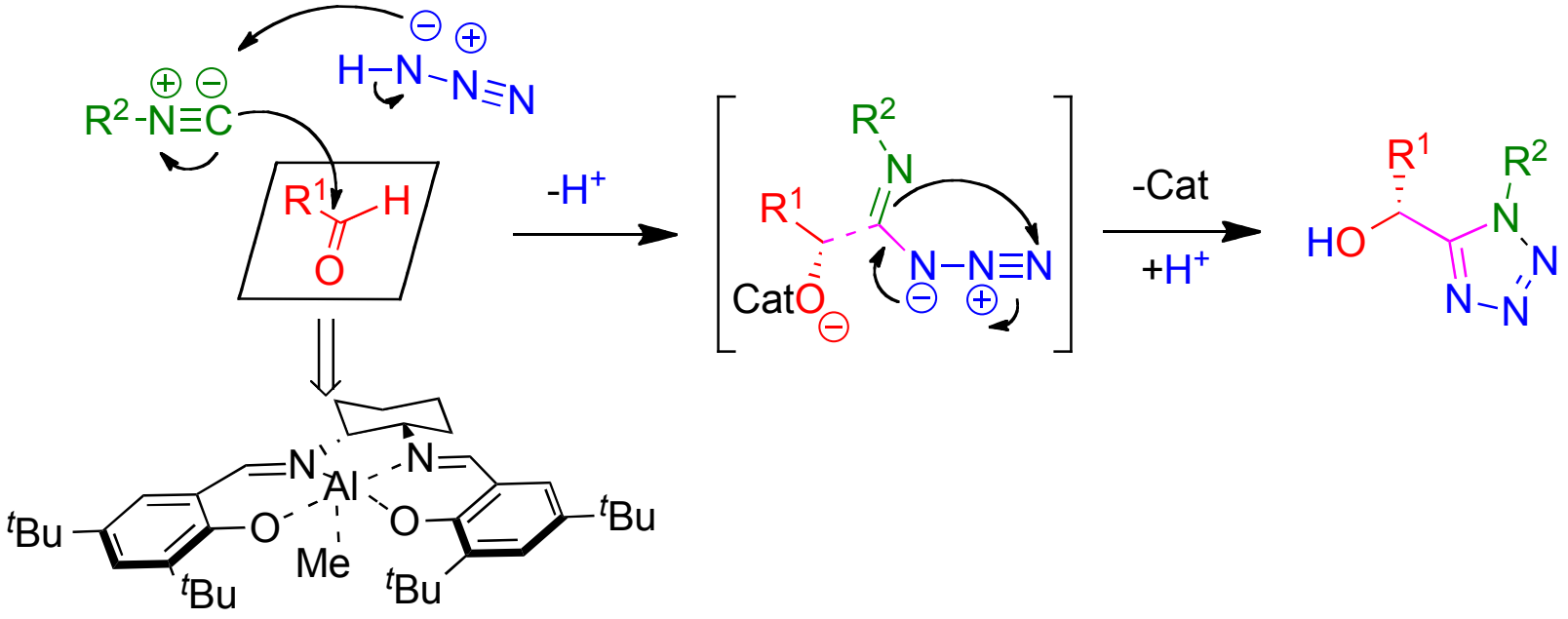


R = OMe, H, Me, Br, NMe_2



J. Zhu, M.-X. Wang *et al.*, *ACIE* **2008**, *47*, 9454–9457.

Catalytic enantioselective Passerini-type MCR



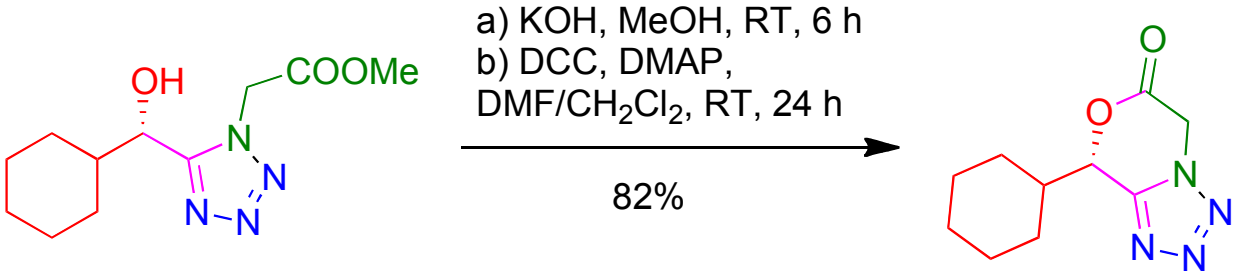
- Observed *S*-enantioselectivity: *Re*-face is attacked by the isocyanide.

J. Zhu, M.-X. Wang *et al.*, *ACIE* **2008**, *47*, 9454–9457.

Catalytic enantioselective Passerini-type MCR

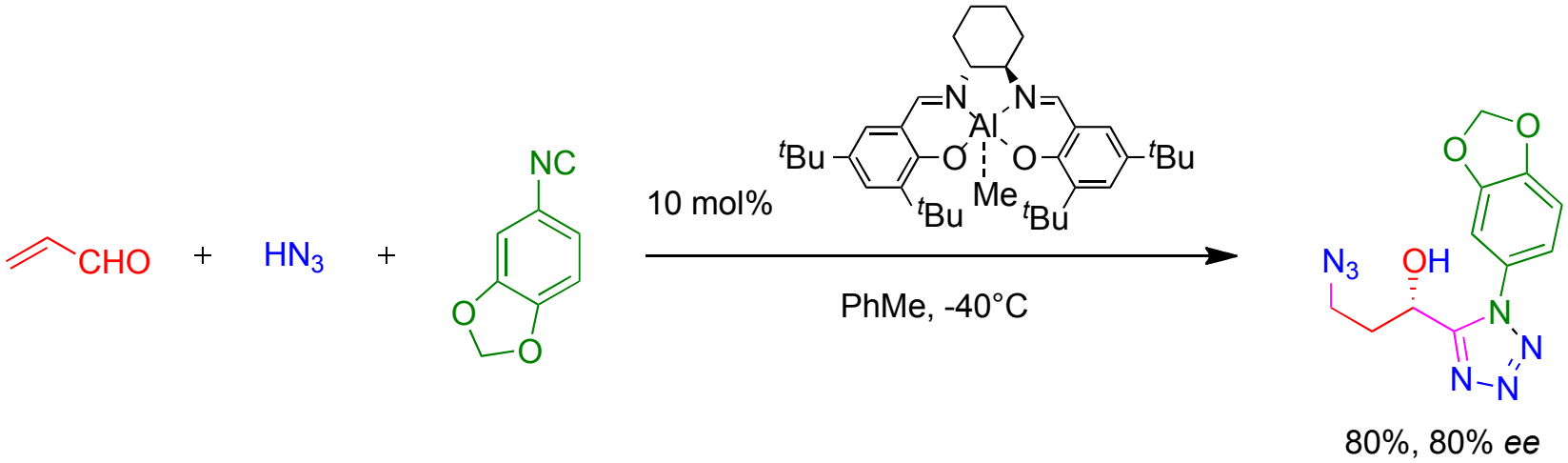
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Hydrolysis/Lactonization => Dipeptide mimics



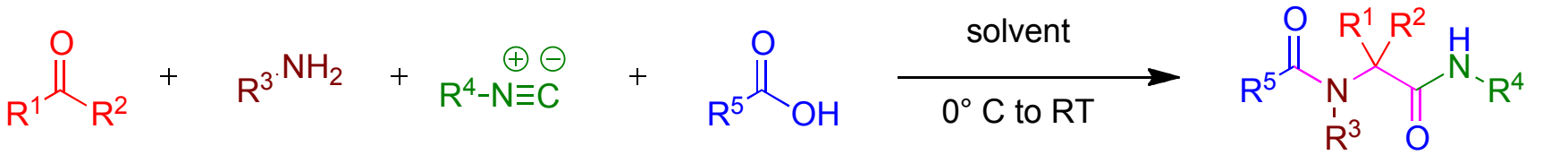
- Tandem Michael Addition/Enantioselective P-3CR

J. Zhu, M.-X. Wang *et al.*, *ACIE* **2008**, *47*, 9454–9457.

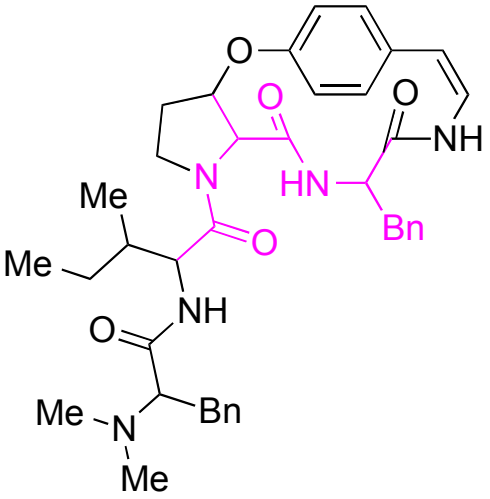


The Ugi MCR

- The Ugi-four component reaction (U-4CR)

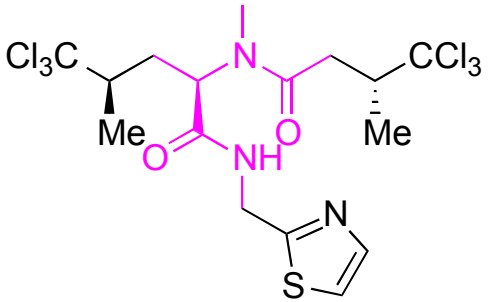


α-Acylaminocarboxamide



Amphibine B

R. Tschesche *et al.*,
Chem. Ber. **1972**, *105*, 3094–3105.



(+)-Demethylisidenine

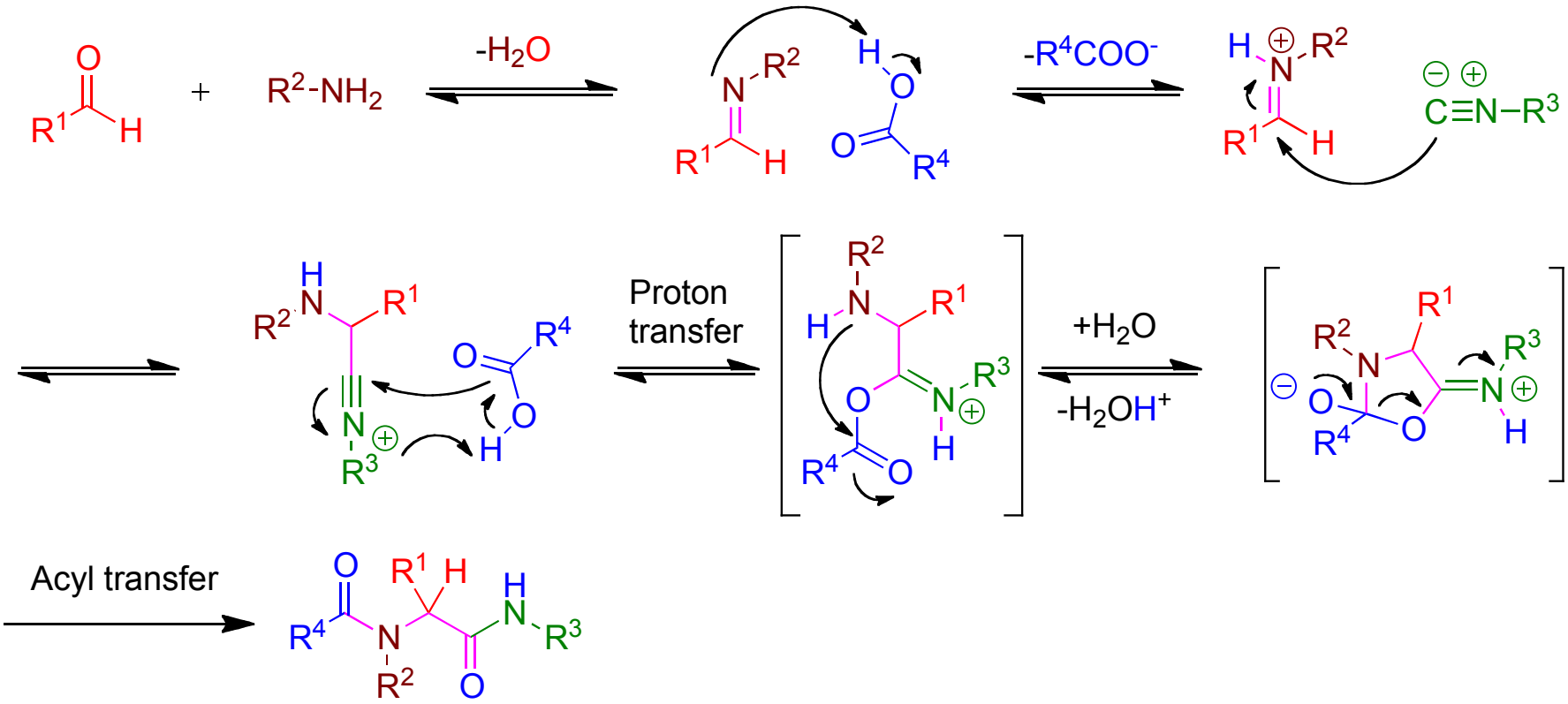
S. E. de Laszlo, P. G. Williard,
JACS **1985**, *107*, 199–203.

I. Ugi *et al.*, *Angew. Chem.* **1959**, *71*, 386.
I. Ugi, C. Steinbrückner, *Angew. Chem.* **1960**, *72*, 267–268.
I. Ugi, *Angew. Chem.* **1962**, *74*, 9–22.

The Ugi MCR

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Plausible Mechanism:

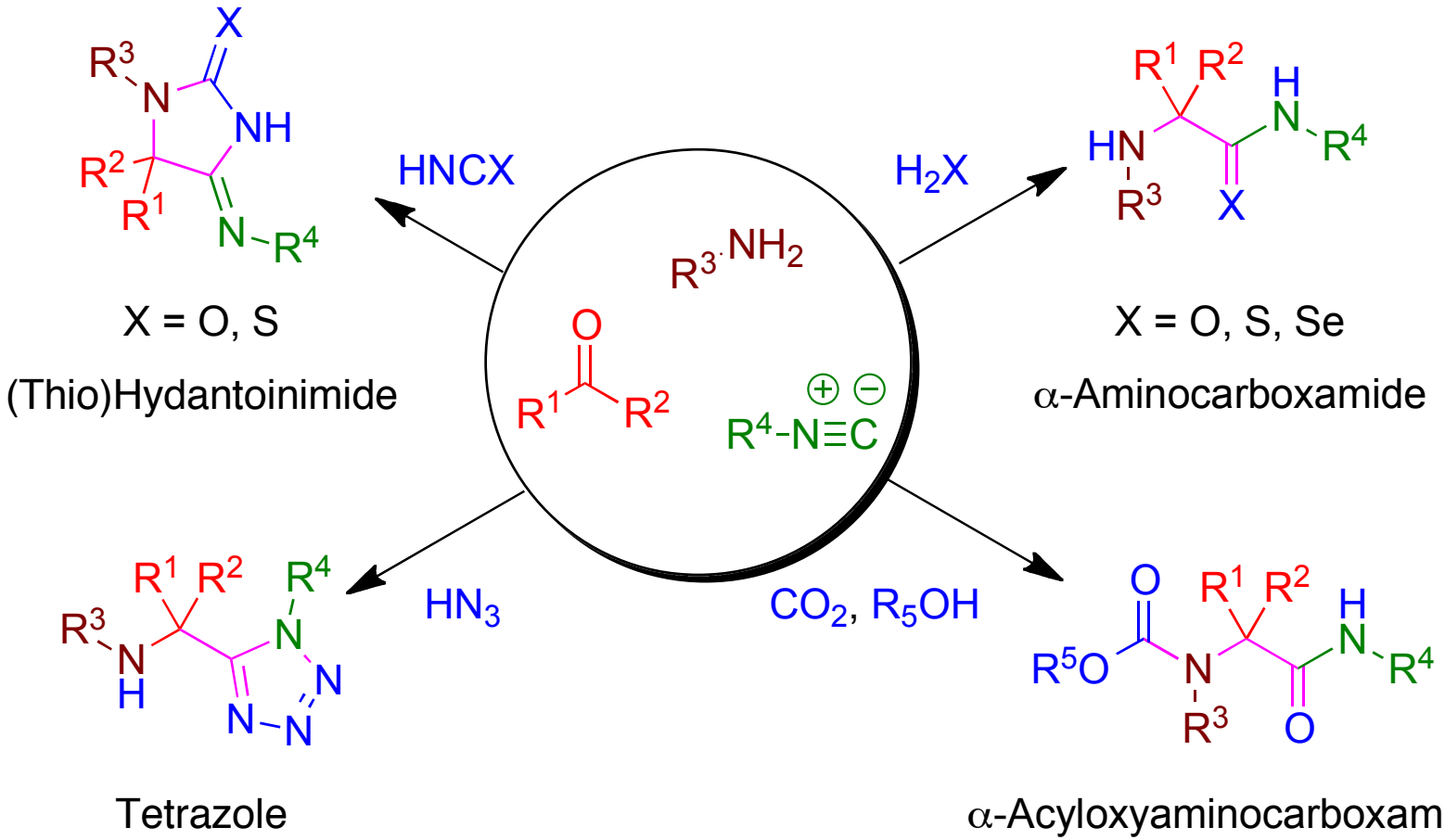


J. W. McFarland, *JOC* **1963**, *28*, 2179–2181.

I. Ugi, G. Kaufhold, *Liebigs Ann. Chem.* **1967**, *709*, 11–28.

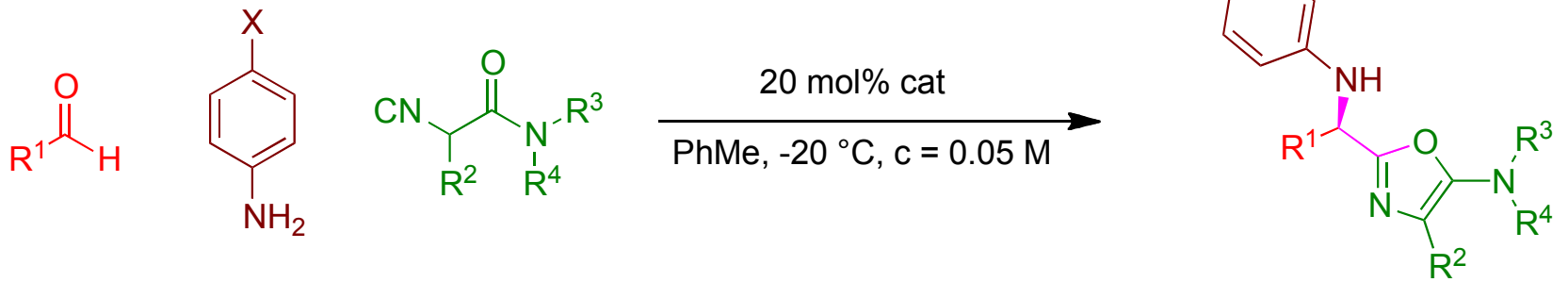
L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, Amsterdam, 2005, pp. 462–463.

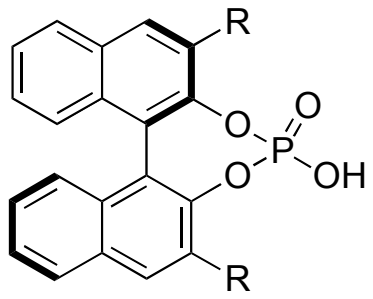
The Ugi MCR



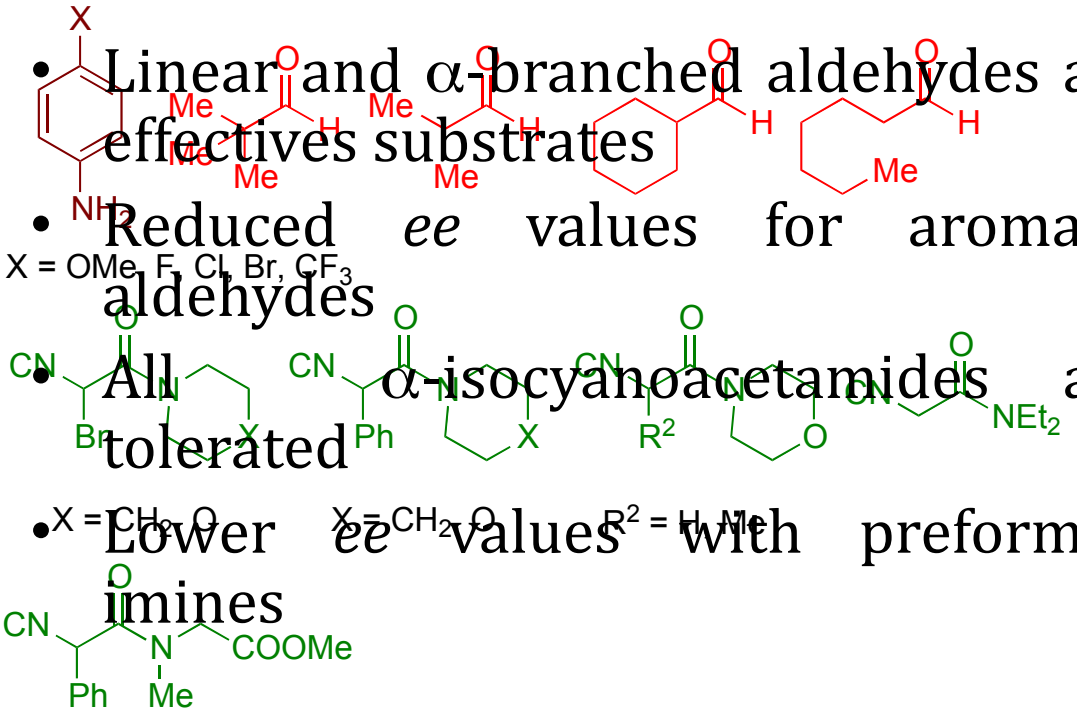
I. Ugi *et al.*, *Angew. Chem.* **1959**, *71*, 386.
I. Ugi, C. Steinbrückner, *Angew. Chem.* **1960**, *72*, 267–268.
I. Ugi, *Angew. Chem.* **1962**, *74*, 9–22.

Catalytic enantioselective Ugi-type MCR





- Linear and α-branched aldehydes are effectives substrates
- Reduced *ee* values for aromatic aldehydes
- All α-isocyanoacetamides are tolerated
- Lower *ee* values with preformed imines

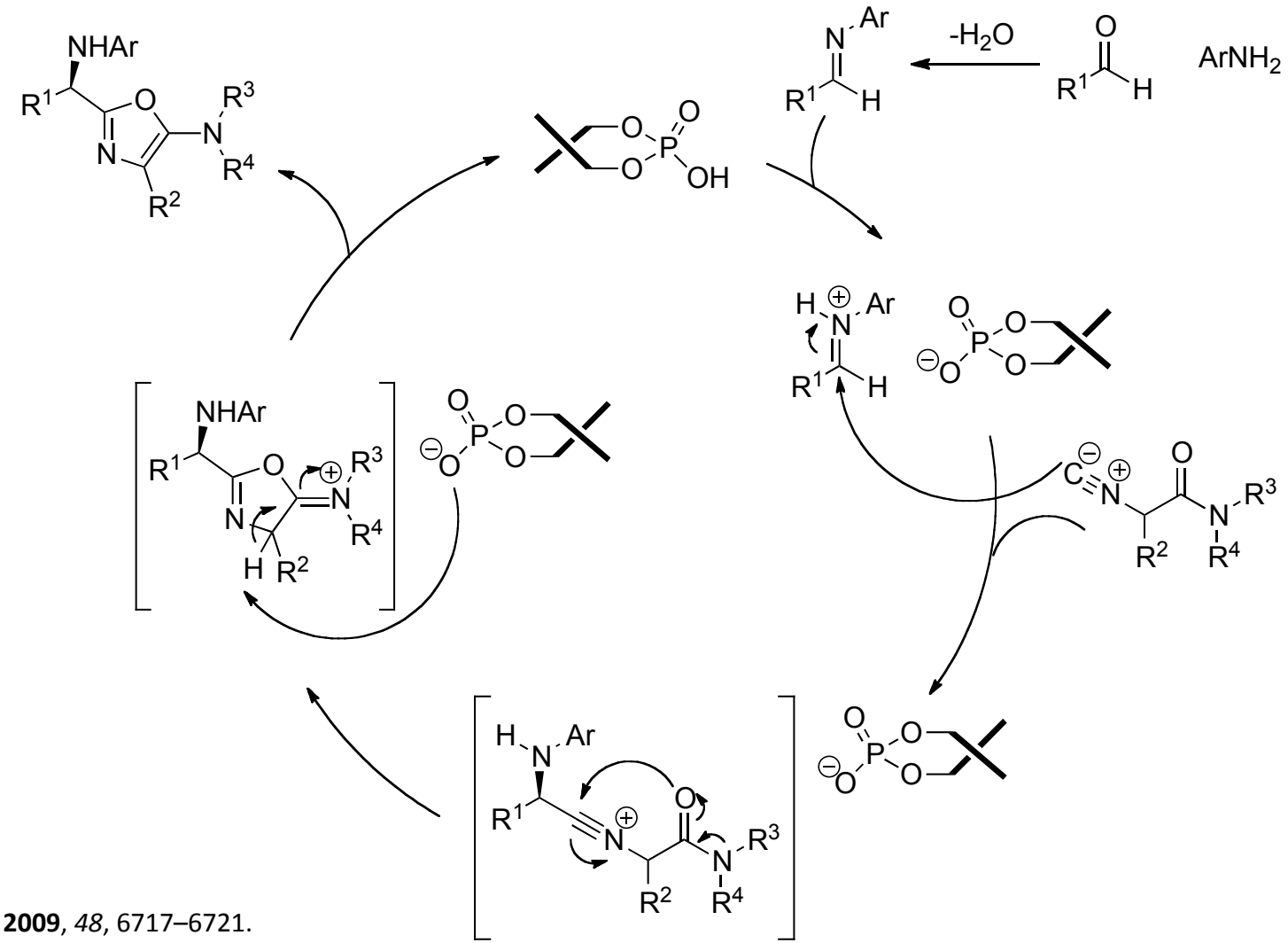


J. Zhu, M.-X. Wang *et al.*, *ACIE* **2009**, *48*, 6717–6721.

Catalytic enantioselective Ugi-type MCR

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Mechanism



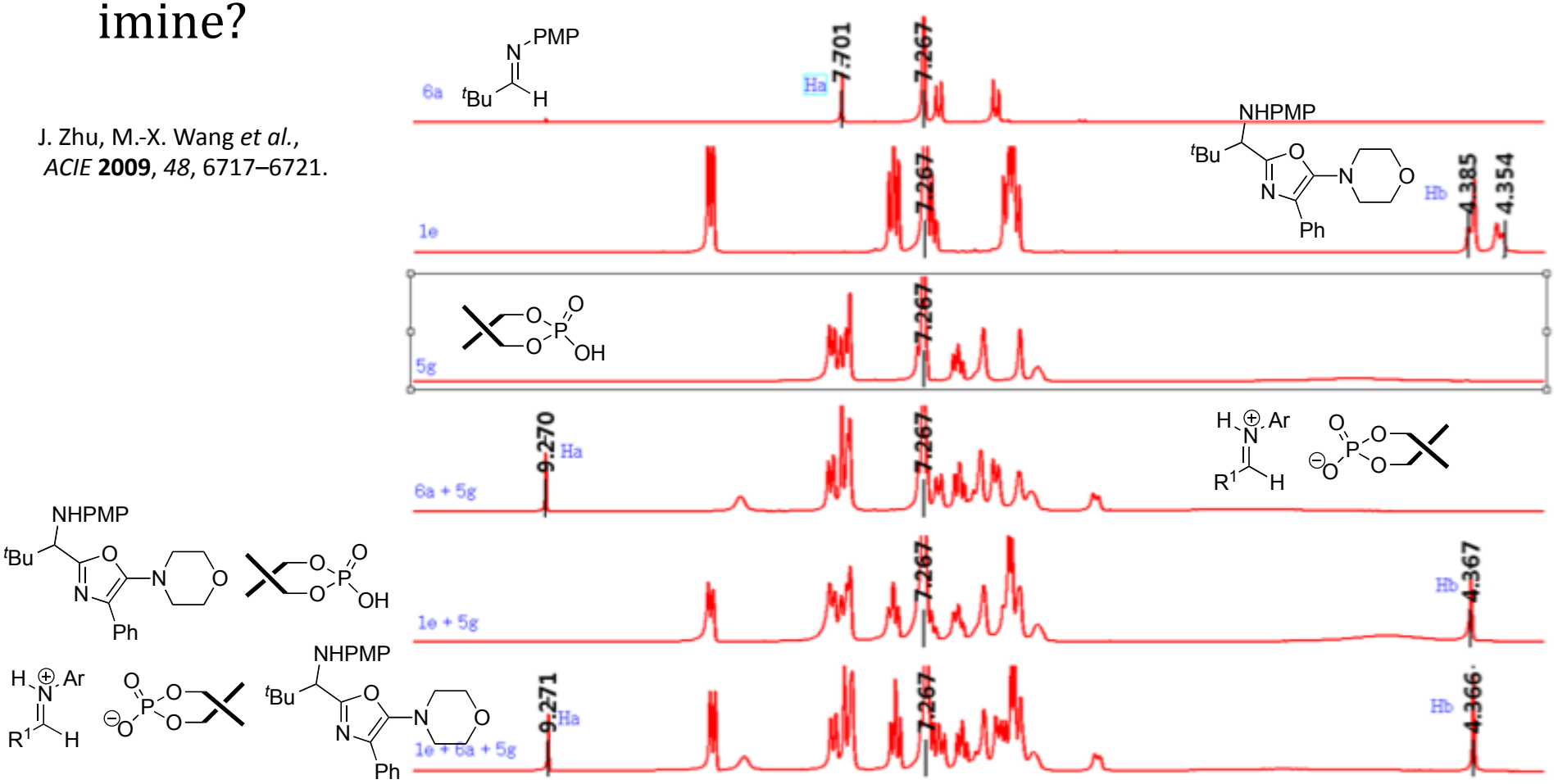
J. Zhu, M.-X. Wang *et al.*, *ACIE* **2009**, *48*, 6717–6721.

Catalytic enantioselective Ugi-type MCR

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Oxazole bear 3 basic nitrogen atoms. Competition with the imine?

J. Zhu, M.-X. Wang *et al.*, *ACIE* **2009**, *48*, 6717–6721.



Conclusion and Outlooks

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Main features of MCRs:

A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89.
S. S. van Berkel *et al.*, *EJOC* **2012**, 3543–3559.

  - Convergent processes
  - Short one-pot syntheses
  - Formation of several bonds in one operation.
  - Simple experimental procedures / mild reaction conditions
  - Achievement of high molecular brevity, diversity and complexity is possible
  - Starting materials are commercially available or easy prepared.

- Last decade: disclosure of several catalytic enantioselective MCRs

  - First catalytic enantioselective Biginelli (Zhu, 2005), Petasis (Schaus, 2008), Hantzsch (Gestwicki, 2009), Passerini (Schreiber, 2004) MCRs reported.

Conclusion and Outlooks

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

- Rapid access to new (chiral) compound libraries. => Diversity-oriented synthesis (DOS)
- A universal approach for the introduction of chirality in IMCRs is desirable
- Development of new (asymmetric) IMCRs / Development of catalytic enantioselective α-addition of isocyanides to aldehydes
- Development of a catalytic enantioselective Ugi MCR
- Combination with continuous flow chemistry
- Application in polymeric chemistry

A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89.
S. S. van Berkel *et al.*, *EJOC* **2012**, 3543–3559.
M. D. Burke, S. L. Schreiber, *ACIE* **2004**, *43*, 46–58.

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

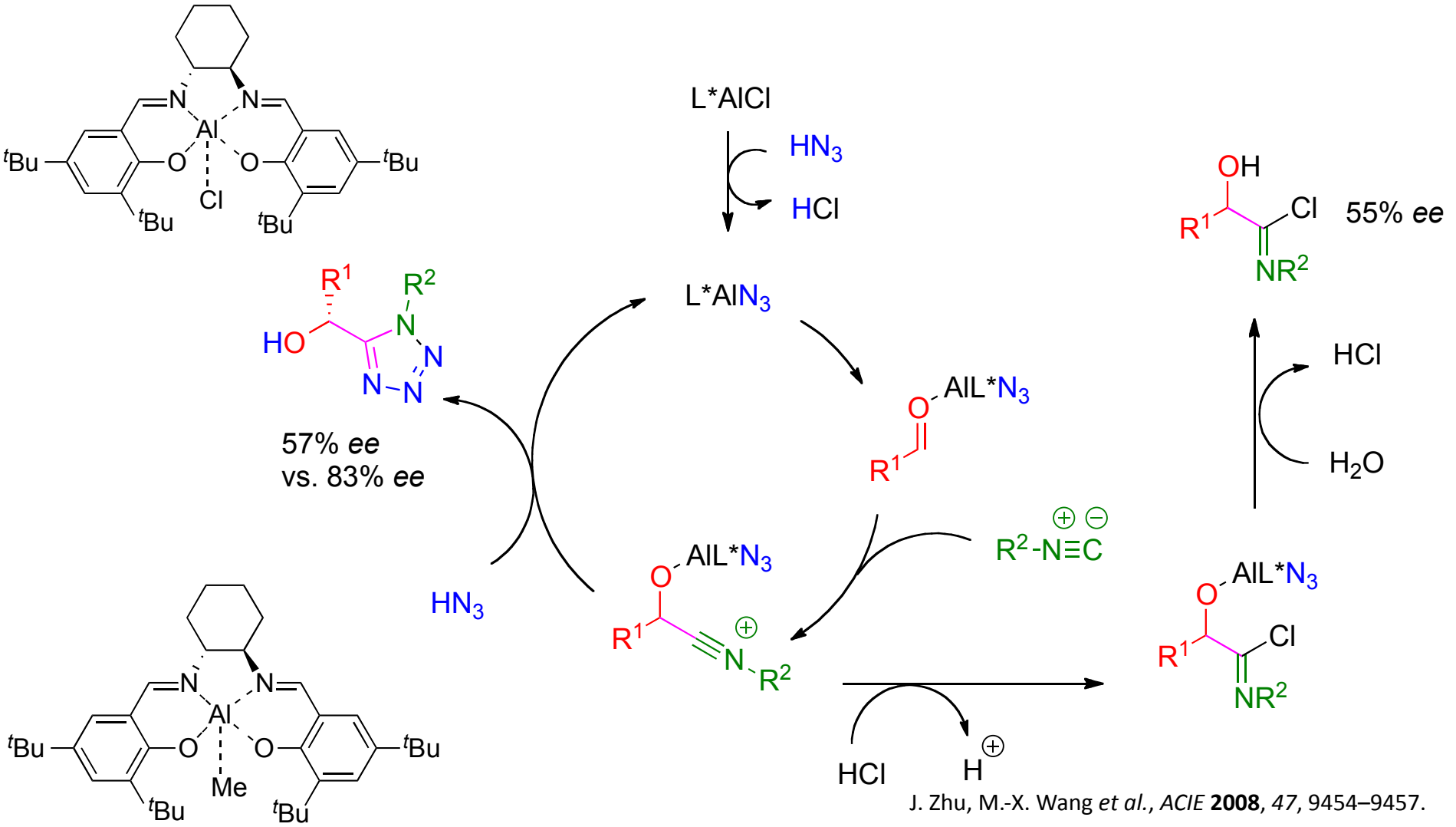
Thank you for your attention!

"*Since in this condensation reaction four components react with each other, the number of possible products is quite high. Already the use of ten of each component leads to* 10^4 *combinations*" (translated from German).

IVAR UGI

I. Ugi, C. Steinbrückner, *Chem. Ber.* **1961**, *94*, 734–742.
A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89.

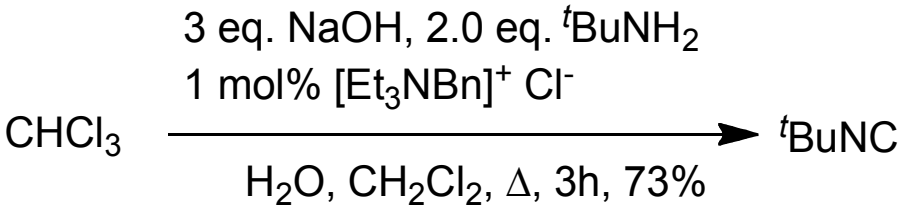
Catalytic enantioselective Passerini-type MCR



J. Zhu, M.-X. Wang *et al.*, *ACIE* **2008**, *47*, 9454–9457.

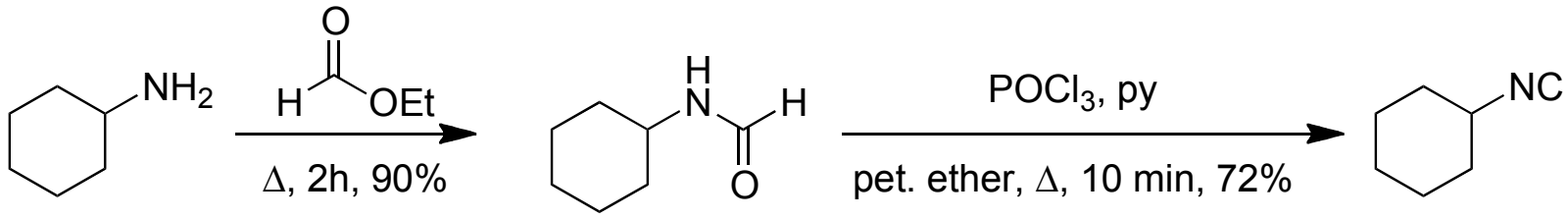
Isocyanides

- Synthesis of isocyanides:
  - Hofmann carbylamine synthesis



I. Ugi *et al.*, *ACIE* **1972**, *11*, 530–531.
W. P. Weber *et al.*, *Org. Synth.* **1988**, *Coll. Vol. 6*, 232; **1976**, *55*, 96.

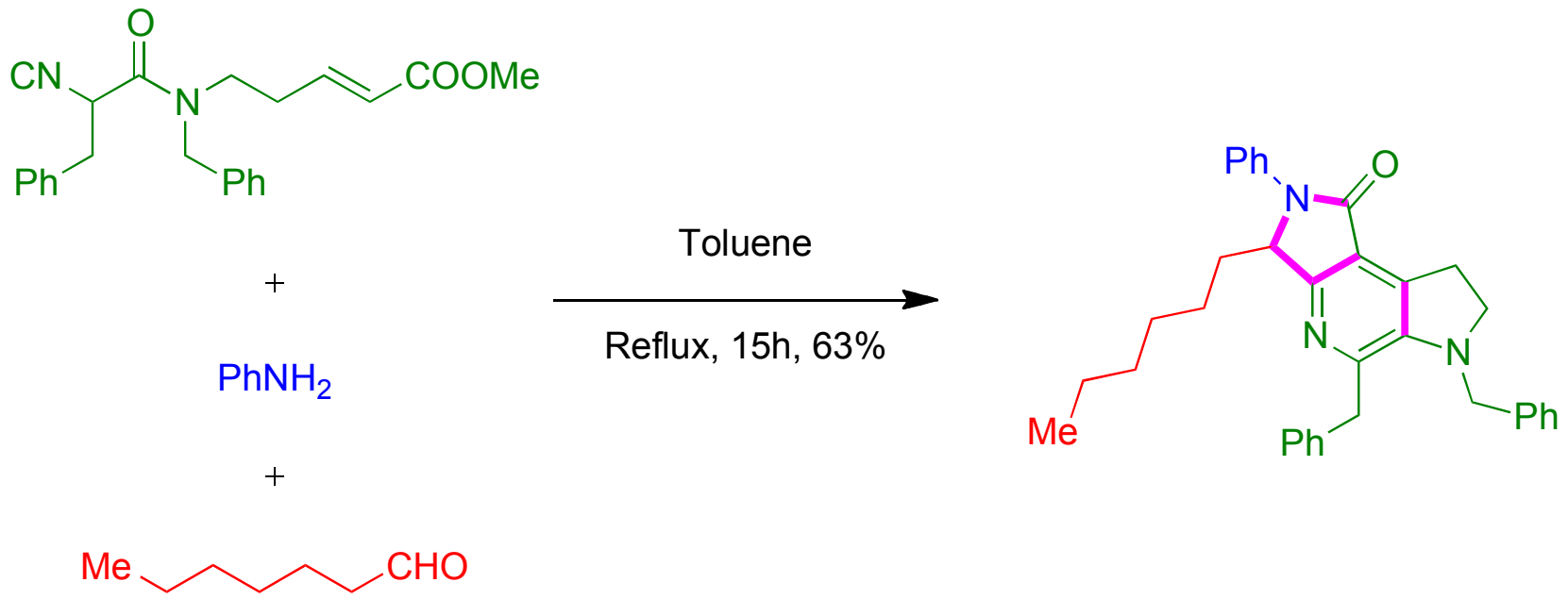
  - Dehydration of formamide



I. Ugi, R. Meyr, *Chem. Ber.* **1960**, *93*, 239–248.
I. Ugi *et al.*, *Org. Synth.* **1973**, *Coll. Vol. 5*, 300; **1961**, *41*, 13.

High bond forming efficiency

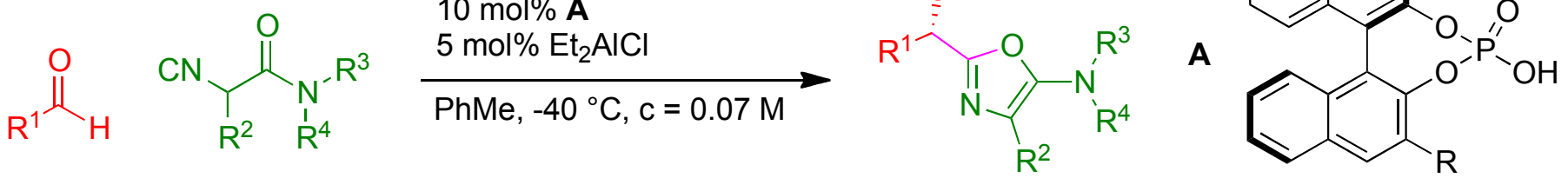
- High bond forming efficiency



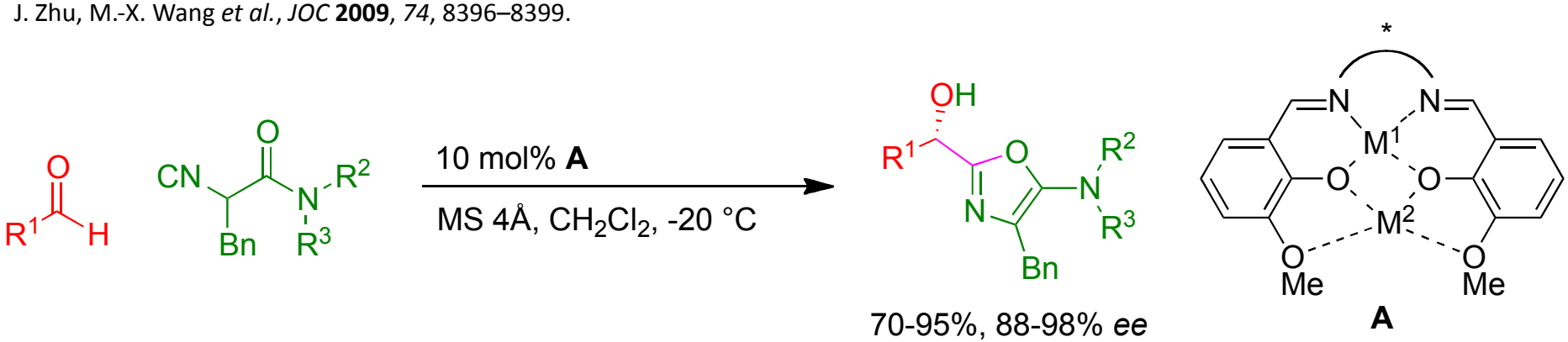
- 3 C–C-bonds and 2 C–N bonds formed

A. Fayol, J. Zhu, *OL* **2005**, *7*, 239–242.

Catalytic enantioselective α-addition of isocyanides to aldehydes



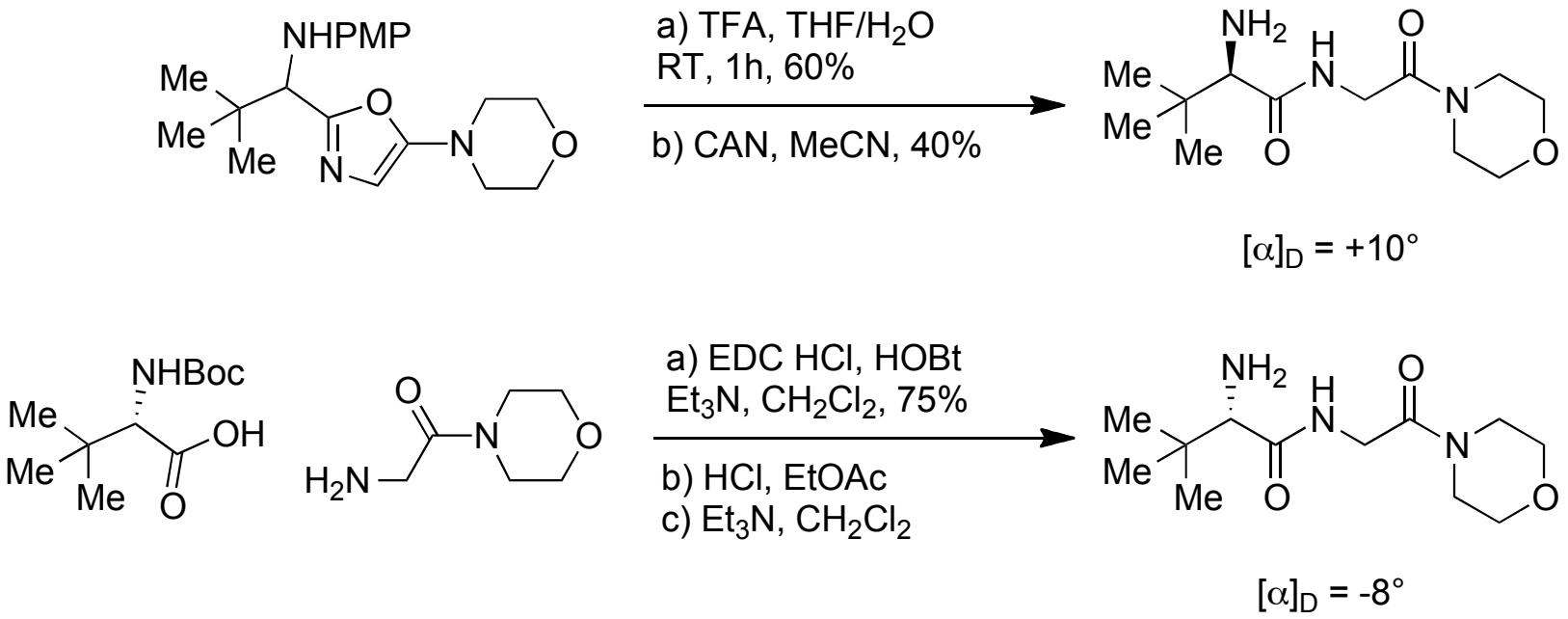
J. Zhu, M.-X. Wang *et al.*, *JOC* **2009**, *74*, 8396–8399.



S. Matsunaga, M. Shibasaki *et al.*, *JACS* **2009**, *131*, 8384–8385.

Catalytic enantioselective Ugi-type MCR

- Determination of the absolute configuration:



J. Zhu, M.-X. Wang *et al.*, *ACIE* **2009**, *48*, 6717–6721.

AMCR

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

- An asymmetric multicomponent reaction (AMCR) chiral or achiral reagents in a single vessel which have been added together (or nearly) to form stereoselectively a new chiral compound that contains portions of all the components, forming at least one new stereogenic element

- Challenges: Complexity of the reaction mechanism / background reaction / deactivation of the catalyst / catalyst turnover

Enantioselective Radical Reactions

Literature Talk

Ugo Orcel

May 2013

Outline

- Introduction to Radical Chemistry
- Chiral Lewis Acids
- Organocatalysis

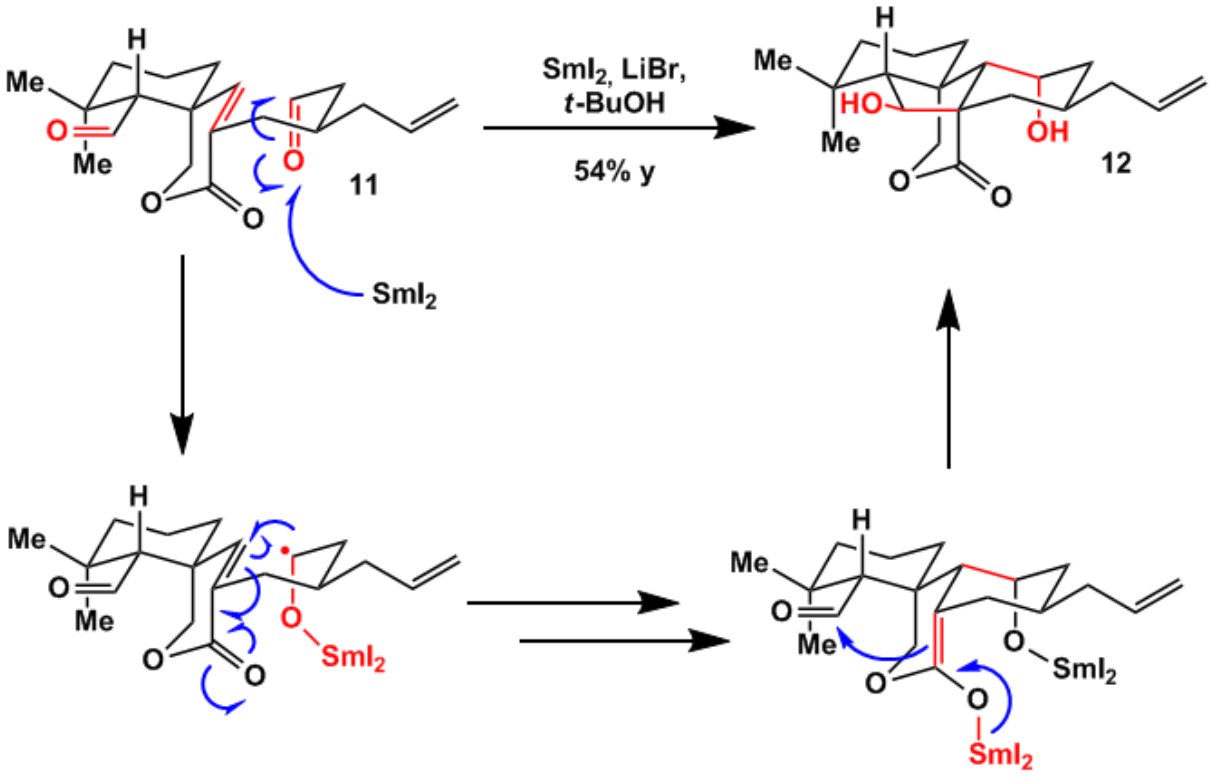
Importance

- Powerful and versatile reactions
- Mild conditions
- Compatible with many functional groups
- Early Transition State enables prediction of stereochemistry outcome

- Challenging
  - Planar stucture
  - Fast reactivity

Reisman's Maoecrystal TS

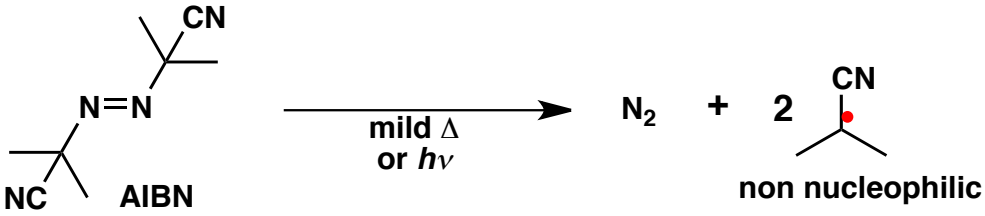
Diastereoselective Sm^{II}-mediated reductive cascade cyclization reaction:
2 new rings and 4 stereocenters formed highly selectively

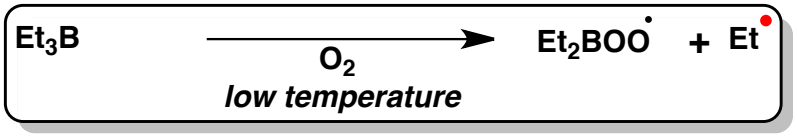


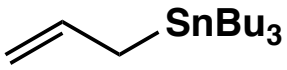
Reisman, *J. Am. Chem. Soc.*, **2011**, *133*, 14964

The Players

- Generation of Radicals:

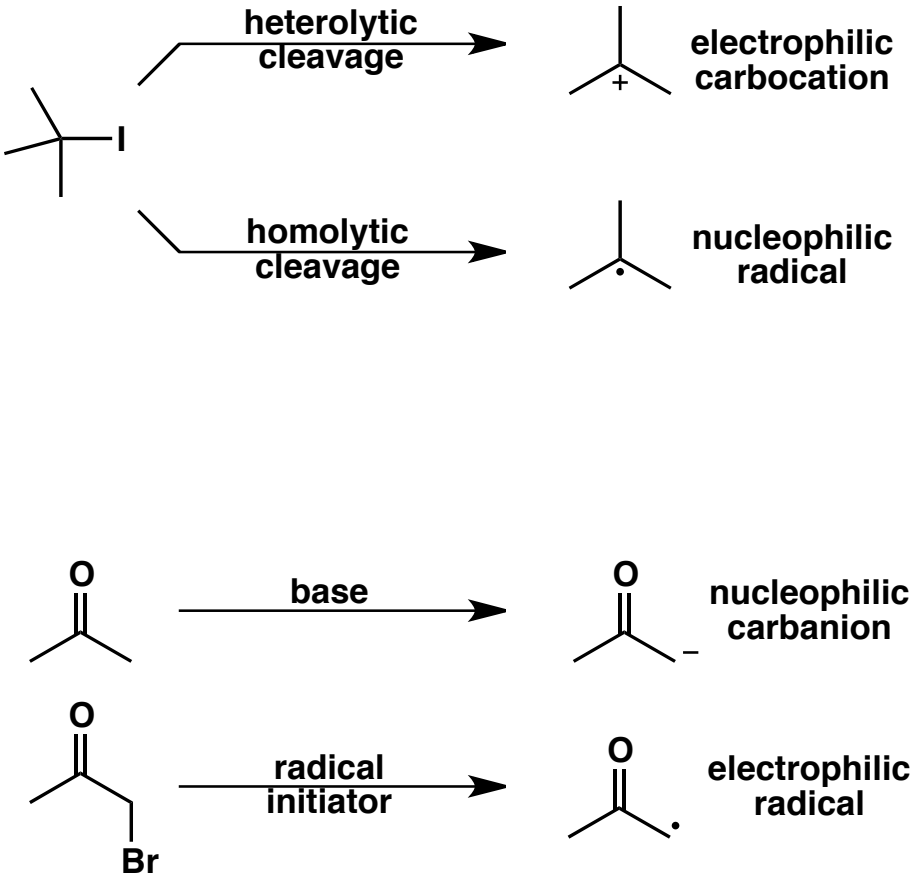




- Alkyl source: **Alkyl–Br** **Alkyl–I**  **$SnBu_3$**
- Stœchiometric H• donors: **Bu_3Sn-H, $(Me_3Si)_3$-H**
- SET stœchiometric metals: **Sm, Zn, Cu, Ag**
- SET catalytic metals: **Ru, Ir, Mn, Cu, V**

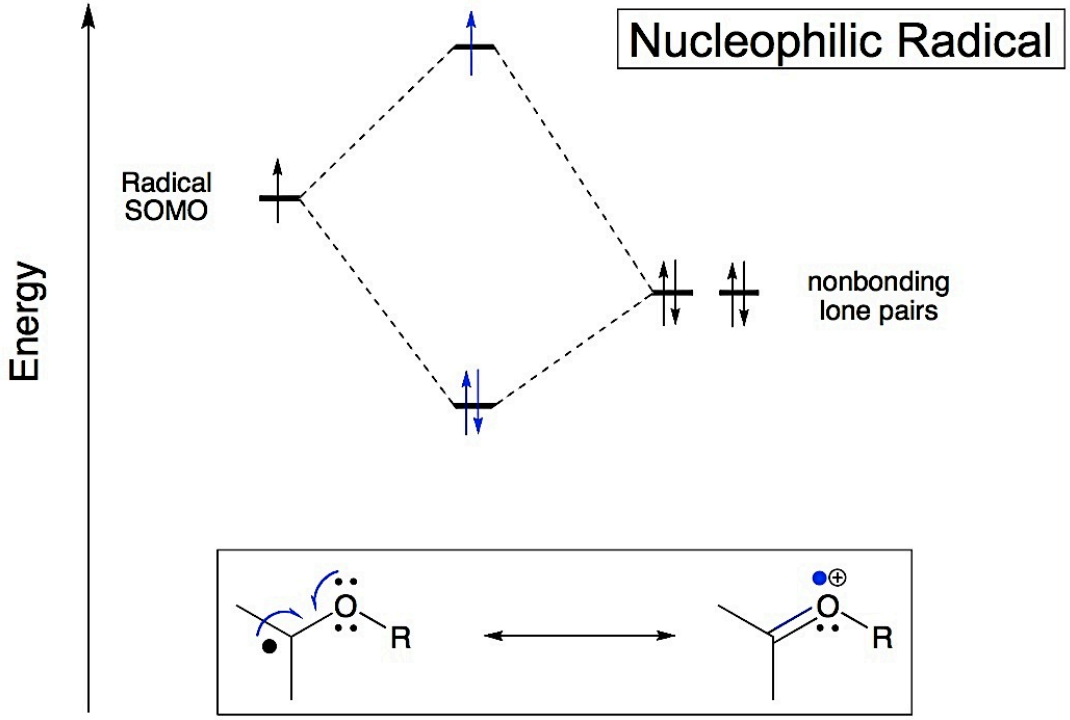
Type and Reactivity of free radicals

Reverseal of Reactivity



Stabilization of Radicals

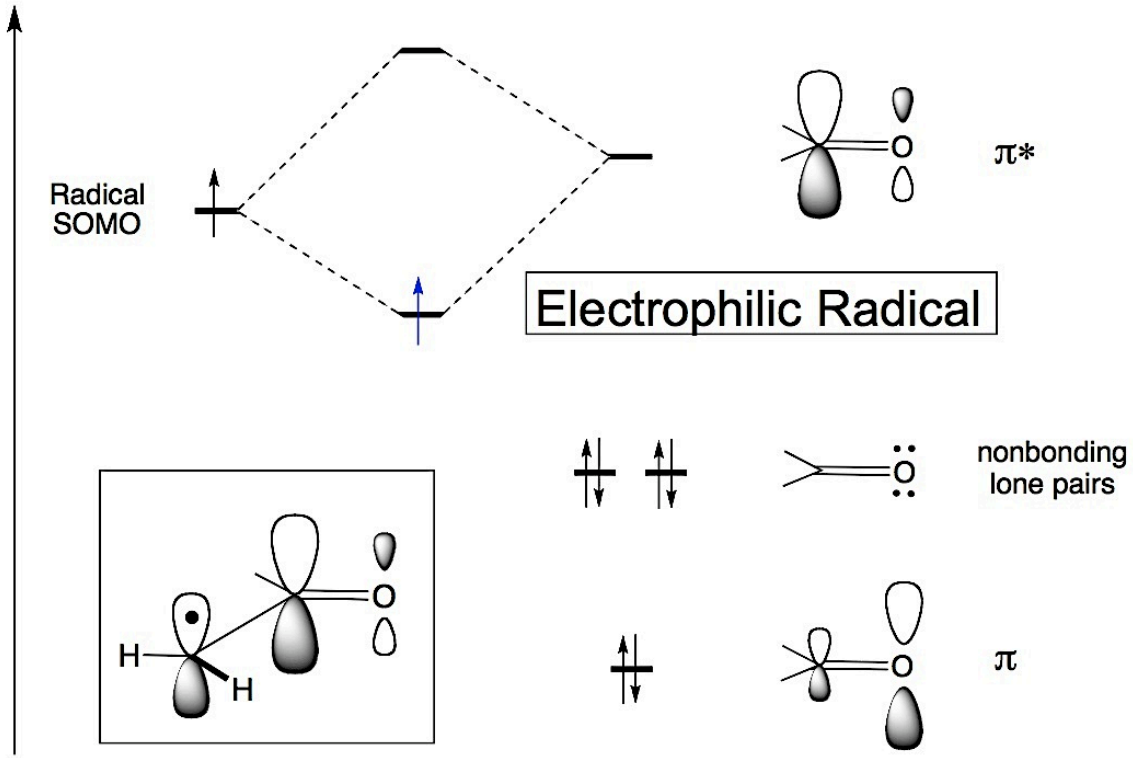
Electron Donating Group



ED groups both stabilize the radical and increase the energy of the SOMO

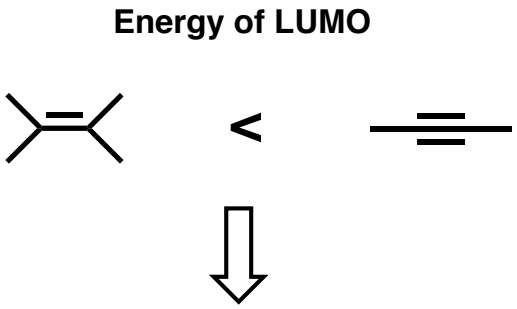
Type and Reactivity of free radicals

Electron Withdrawing Group



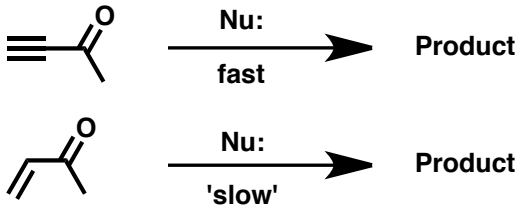
ED groups both stabilize the radical and lower the energy of the SOMO

Divergent Properties



Nucleophilic radicals react faster with alkenes

→ Early TS: SOMO-LUMO interaction



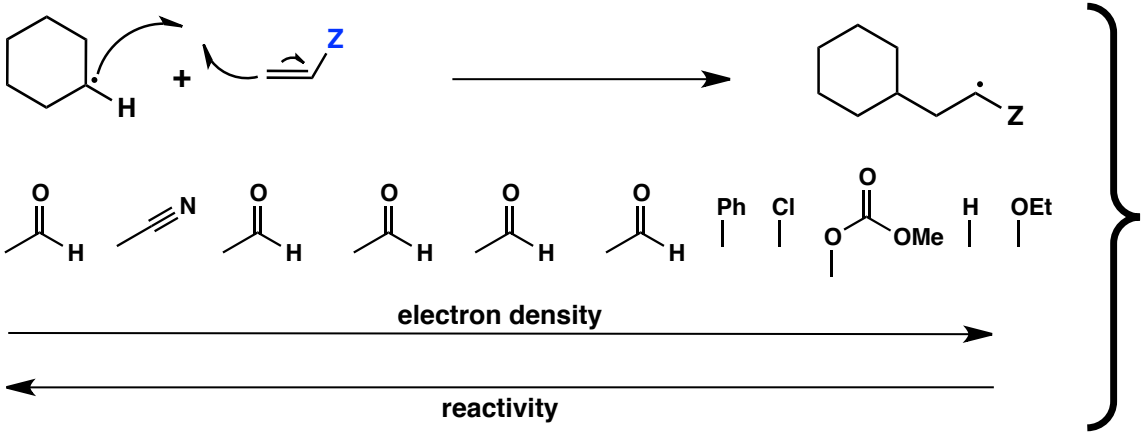
Ionic Nucleophiles react faster with alkynes

→ Late TS: rehybridization

Effect of Radical Acceptor's substituents

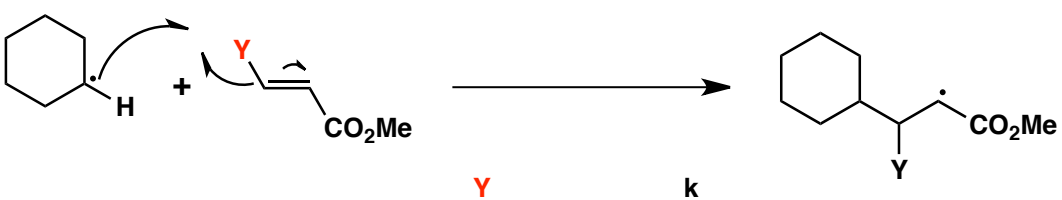
Reactivity of Alkyl Radicals

-Nature of the β-substituent



EWG increase:
-SOMO-LUMO interaction
-reaction rate

-Nature of the α-substituent



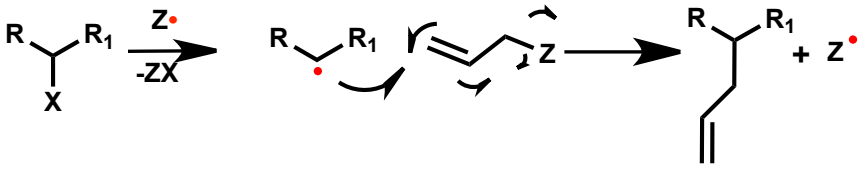
Y	k
H	1000
Me	11
Et	6.6
iPr	1.5
tBu	0.05

Strong steric effect

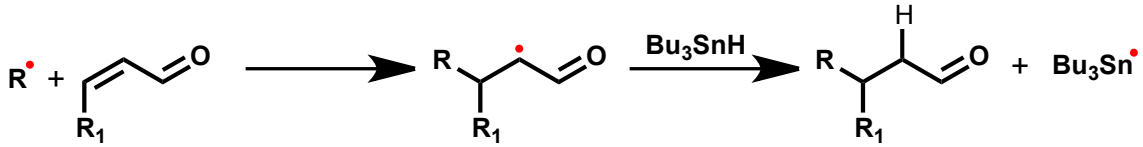
Reaction Type

- Atom transfer
  - Usually involve transfer of a Hydrogen or Halogen atom
  - Transfer of atom from a chain-transfer agent to a radical species to generate another radical

- Fragmentation
  - Usually: allylsilane and allylstannane
  - addition of radicals to a neutral molecule followed by β-elimination from the resulting radical generating an olefin



- Reductive alkylation
  - addition of radicals to carbon–carbon or carbon–heteroatom multiple bonds followed by trapping with a hydrogen atom source

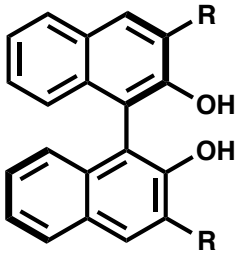


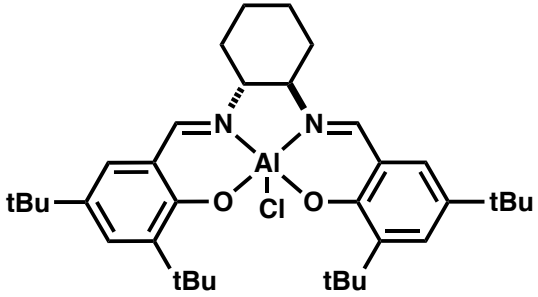
Chiral Lewis Acid

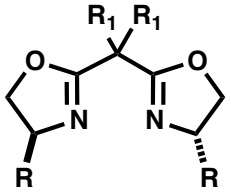
- The complexing chiral group must be fixed relative to the prochiral center
- The chiral group must shield one face of the radical or alkene
- Reactivity of the complex must exceed reactivity of the free substrate

Common Metals: **Mg, Zn, Al, Cu and lanthanides**

Common ligands:



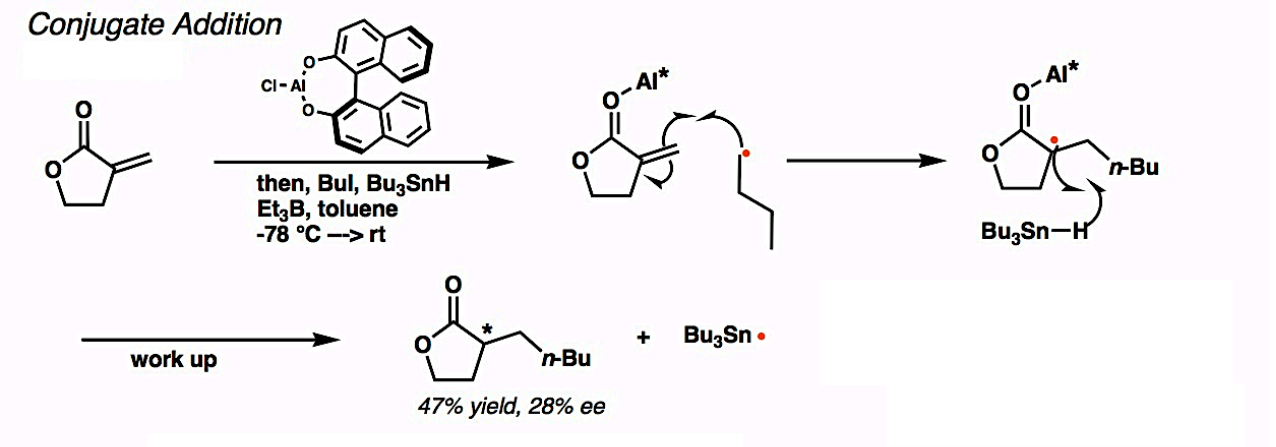




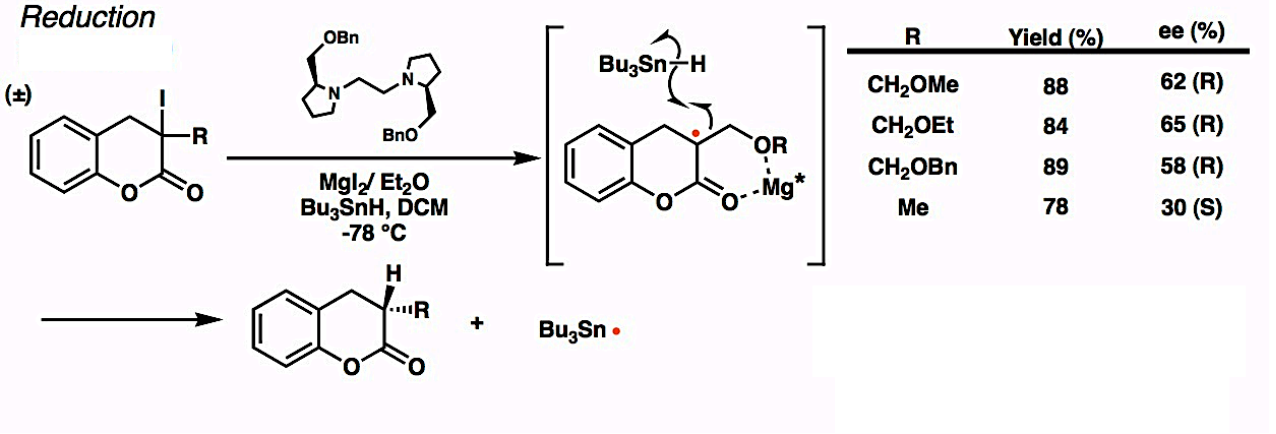
Cyclic Substrates

Enantioselective H transfer

Sato: 1st asymmetric exemple of radical addition



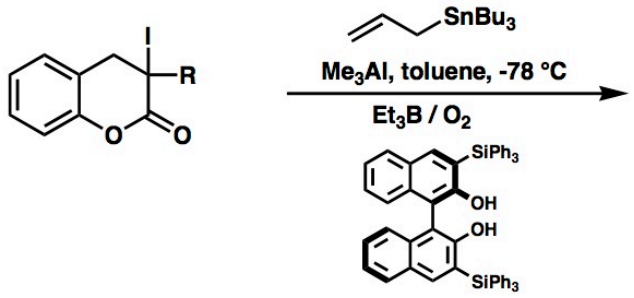
Murakata: 2-point binding chelation



R	Yield (%)	ee (%)
CH_2OMe	88	62 (R)
CH_2OEt	84	65 (R)
CH_2OBn	89	58 (R)
Me	78	30 (S)

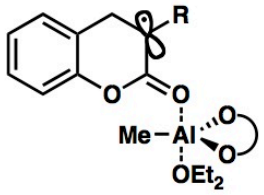
Sato, J. Org. Chem. **1995**, 60, 3576
Murakata, Tetrahedron **1999**, 55, 10295.

Quaternary Center Formation - Fragmentation



-no rxn w/o initiator
-no rxn w/ galvinoxyl radical inhibitor

R	LA (equiv.)	Additive	Yield (%)	ee (%)
Me	1.0	none	72	27
Me	1.0	Et_2O	84	81
CH_2OMe	1.0	none	75	-10
CH_2OMe	1.0	Et_2O	85	82
CH_2OMe	1.0	*i*-Pr_2O	83	43
CH_2OBn	1.0	Et_2O	76	91
CH_2OBn	0.2	Et_2O	73	82
CH_2OBn	0.1	Et_2O	78	71

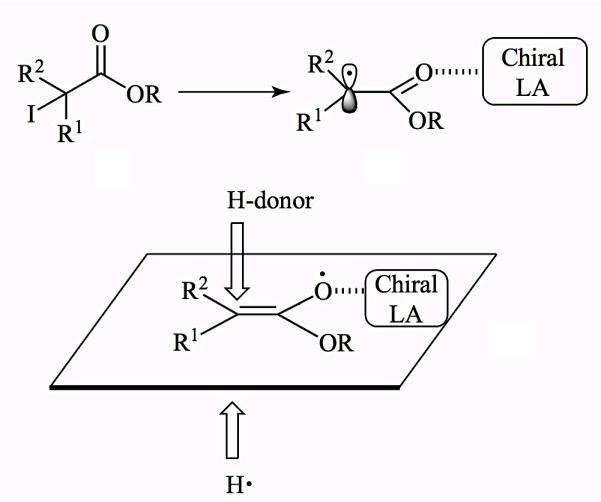


Ether additive influendes chiral sphere of catalyst.

Hoshino, JACS **1997**, 119, 11713

Acyclic Substrate

Acyclic systems are tougher to control

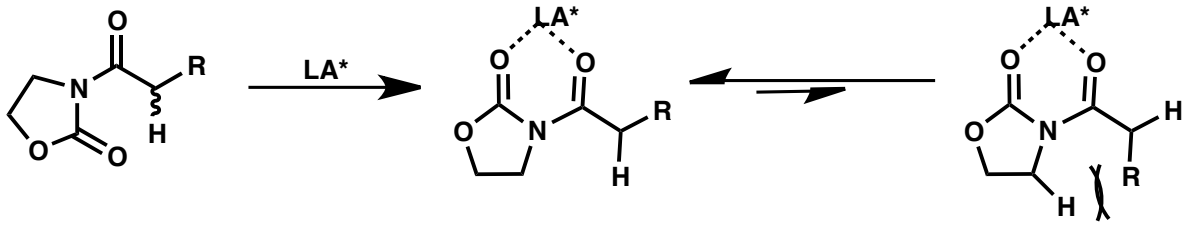


Rotamer control in radical transformations is important for selectivity:

Achiral auxiliaries: control rotamers of acyclic substrates via 2-point binding

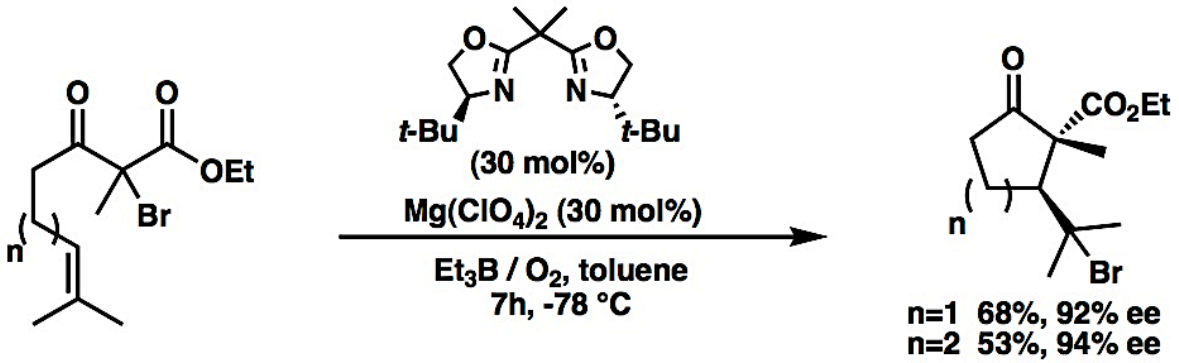
– Oxazolidinone templates

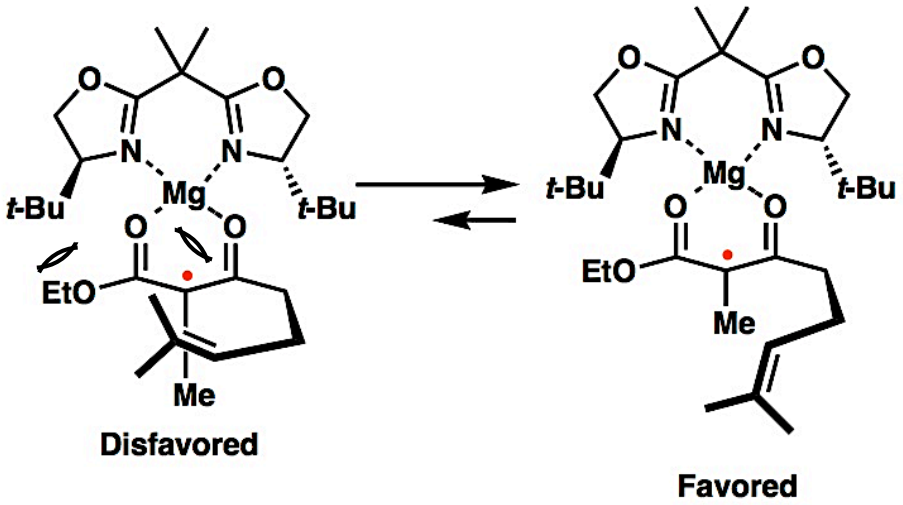
– **s-cis** favored due to A1,3 strain



Halogen Transfer Tandem Cyclization

Yang:





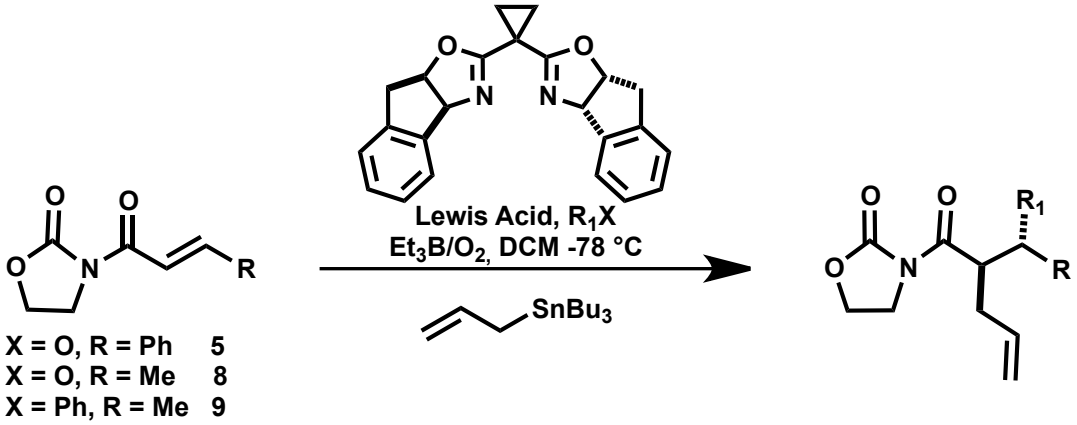
Yang, D. JACS **2001**, 123, 8612.

Tandem addition-fragmentation

Sibi

Two contiguous chiral center

Control of relative and absolute config.



X = O, R = Ph 5
X = O, R = Me 8
X = Ph, R = Me 9

β-carbon stereochemistry controls α-stereochemistry

Match/mismatch with ligands

Very good dr and ee with bulky radical

entry	sub.	R_1X	LA (0.3equiv)	yield (%)[a]	dr[b]	ee (%)[c]
1	**5**	$MeOCH_2Br$	MgI_2	80	20:1	72
2	**5**	EtI	MgI_2	79	32:1	77
3	**5**	c-HexI	MgI_2	80	60:1	92
4	**5**	*i*-PrI	MgI_2	93	37:1	93
5	**5**	*t*-BuI	MgI_2	84	99:1	97
6	**5**	*i*-PrI	$Cu(OTf)_2$	93[d]	30:1	−79
7	**5**	*t*-BuI	$Cu(OTf)_2$	90[d]	99:1	−96
8	**8**	EtI	$Mg(ClO_4)_2$	83	4:1	61
9	**8**	c-HexI	$Mg(ClO_4)_2$	83	4:1	62
10	**9**	EtI	$Mg(ClO_4)_2$	83	7:1	66
11	**9**	c-HexI	$Mg(ClO_4)_2$	84	7:1	69
12	**9**	$MeOCH_2Br$	$Mg(ClO_4)_2$	83	2.4:1	53
13	**9**	*i*-PrI	$Mg(ClO_4)_2$	84	7:1	76
14	**9**	*i*-PrI	$Cu(OTf)_2$	95[d]	10:1	−76
15	**9**	*t*-BuI	$Mg(ClO_4)_2$	85	19:1	92
16	**9**	*t*-BuI	$Cu(OTf)_2$	66[d]	50:1	−83

J. Am. Chem. Soc. **2001,** *123,* 9472

Chiral Lewis Acid

Very good asymmetric induction have been achieved

Major limitations:

High catalyst loading

Bulky radicals

Achiral auxiliauries

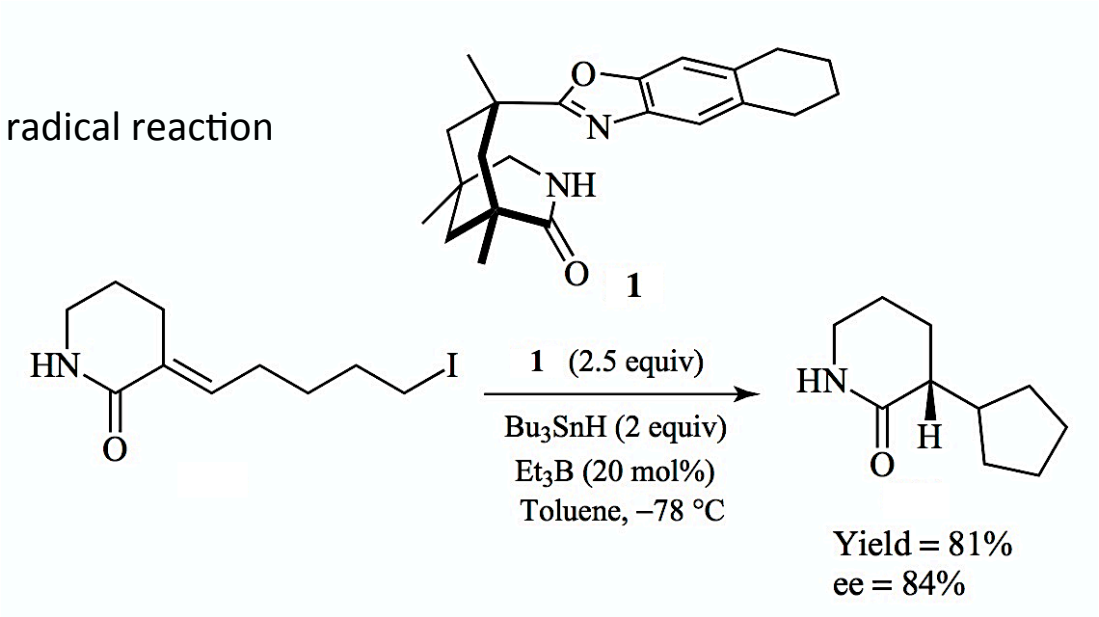
Tin reagents

Organocatalysis

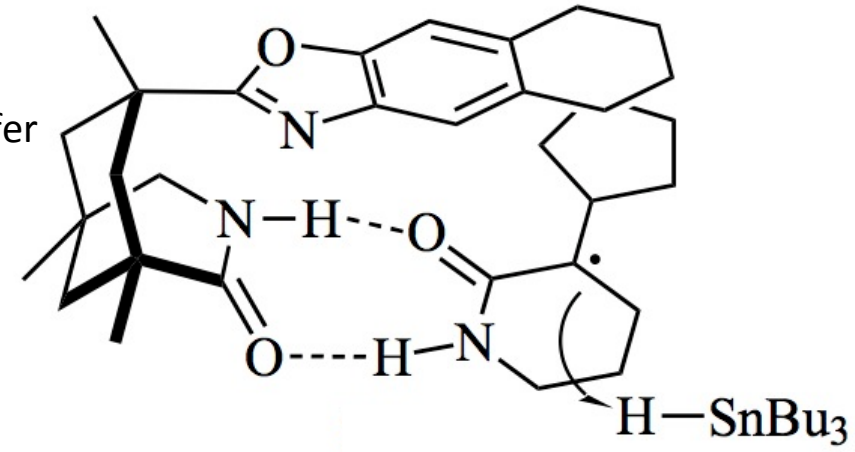
- Easy to handle
- Low cost
- Non toxic

N-H Bonding

Bach: earliest exemple of a radical reaction using an organic activator



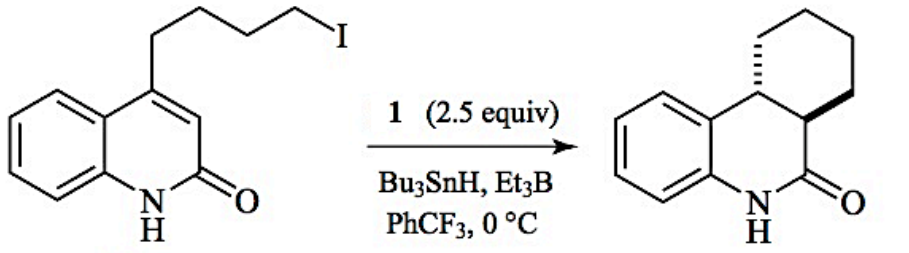
Organized structure: selective H transfer



T. Bach, *Angew. Chem. Int. Ed.*, 2004, **43**, 5849

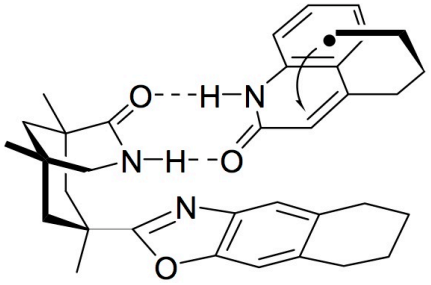
N-H Bonding

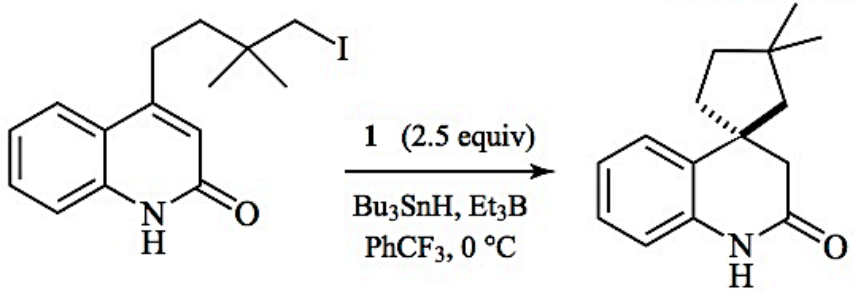
Similar conditions



Yield = 79%
ee = 99%
trans:cis = 88 : 12

via

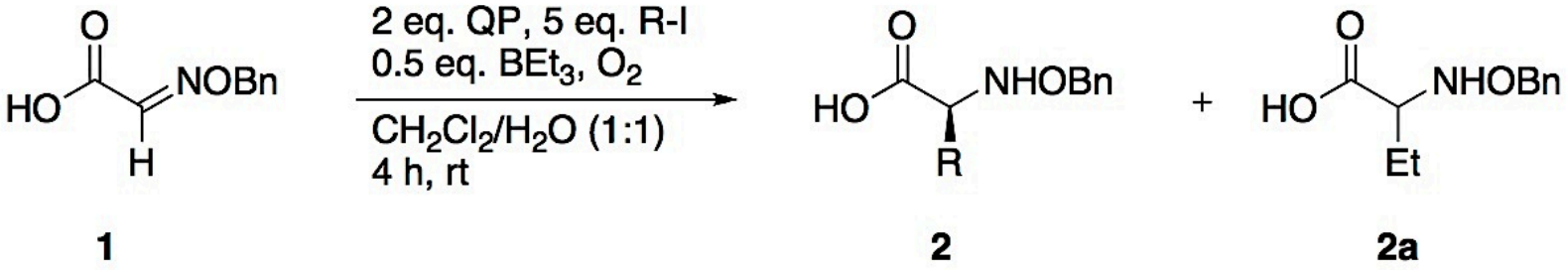




Yield = 66%
ee = 94%

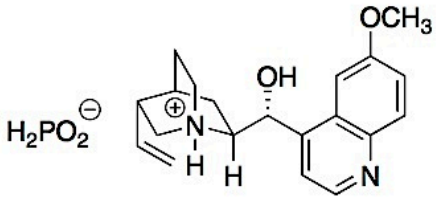
T. Bach, *Org. Lett.*, 2006, **8**, 3145

Chiral Bronsted Acid



1 **2** **2a**

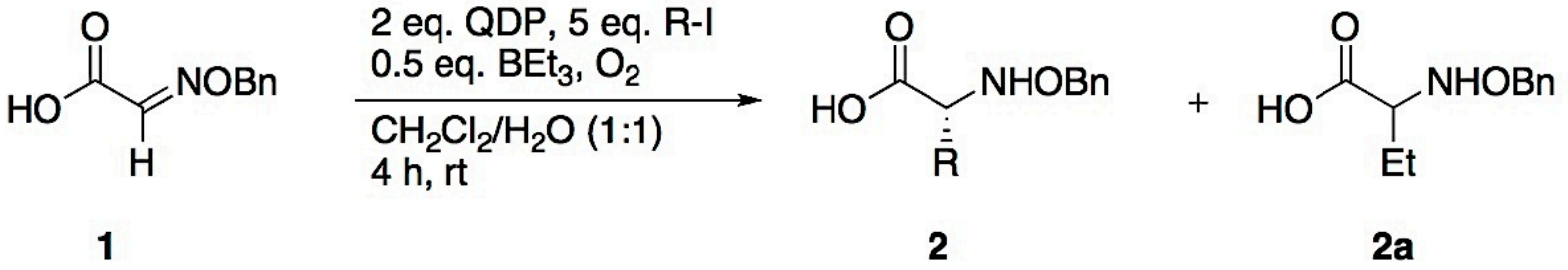
Entry	RI	Product	Isolated Yield (%)	**2a** Yield (%)	er of **2** *R* : *S*
1	*i*-Pr-I	**2b**	83	7	21 : 79
2	*c*-Hex-I	**2c**	80	10	21 : 79
3	*t*-Bu-I	**2d**	60	30	1 : >99
4	1-Ad-I	**2e**	45	35	1 : >99
5	*n*-Oct-I	**2f**	50	25	40 : 60



Quinine, QP

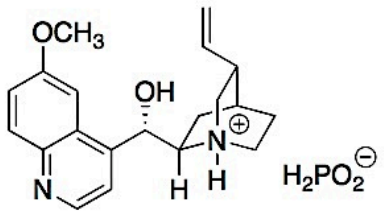
Cho, D.K.; Jang, D.O. Chem. Commun., **2006**, 5045-5047

Chiral Bronsted Acid



1 **2** **2a**

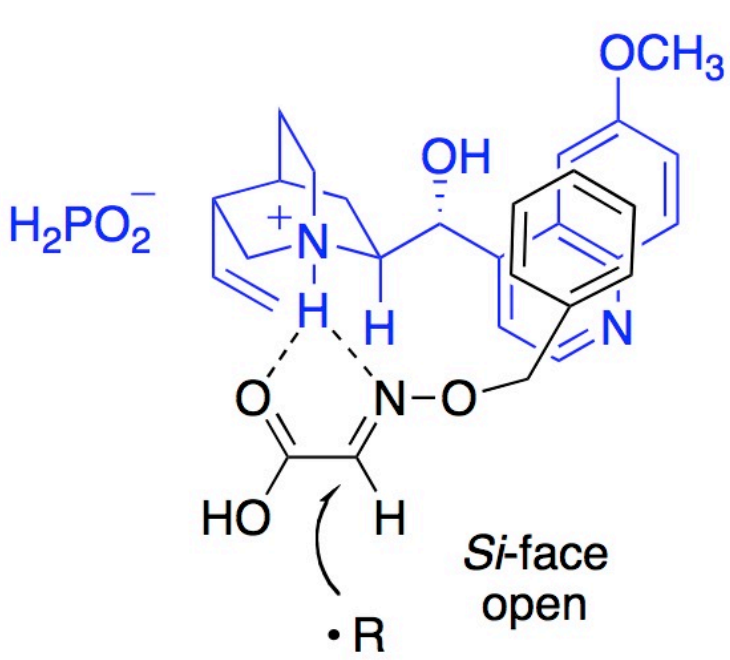
Entry	RI	Product	Isolated Yield (%)	**2a** Yield (%)	er of **2** *R* : *S*
1	*i*-Pr-I	**2b**	82	10	62 : 38
2	*c*-Hex-I	**2c**	82	9	72 : 28
3	*t*-Bu-I	**2d**	62	27	>99 : 1
4	1-Ad-I	**2e**	47	37	>99 : 1
5	*n*-Oct-I	**2f**	48	30	58 : 42

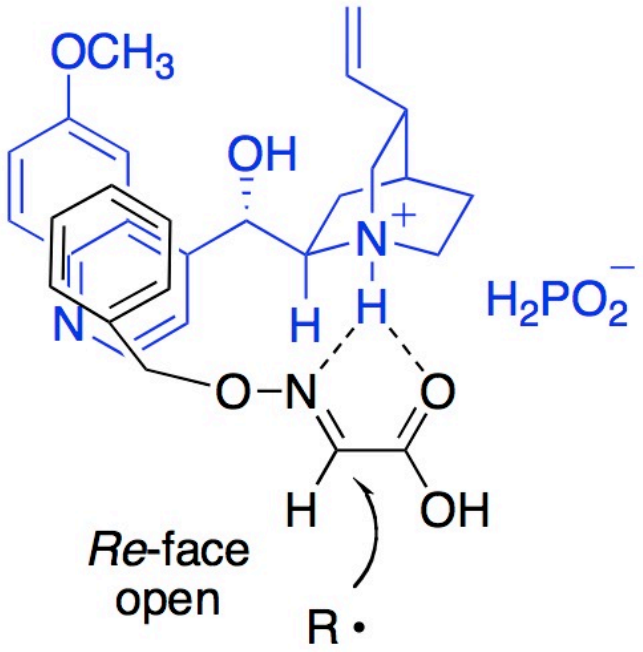


Quinidine, QDP

Cho, D.K.; Jang, D.O. Chem. Commun., **2006**, 5045-5047

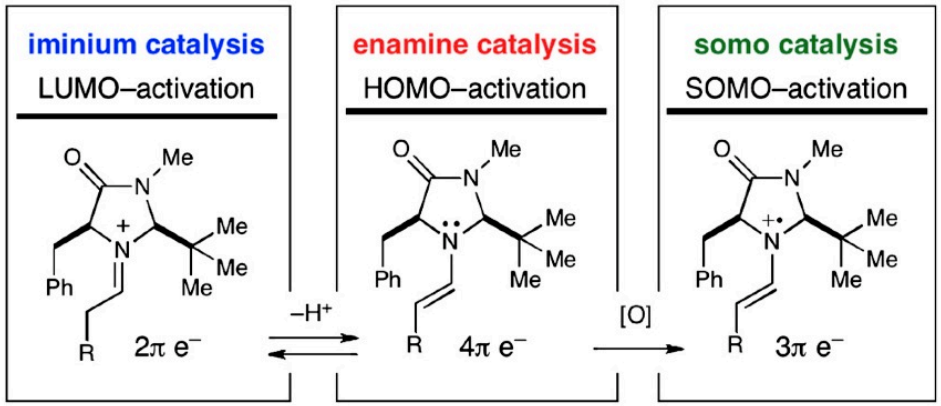
Model

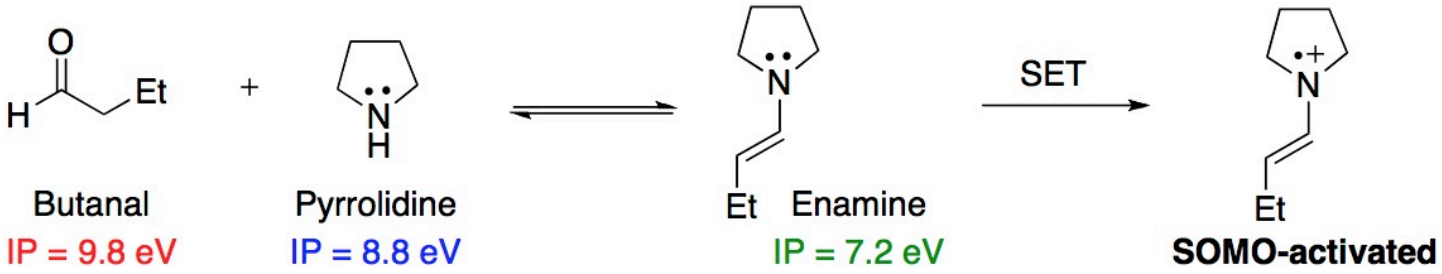


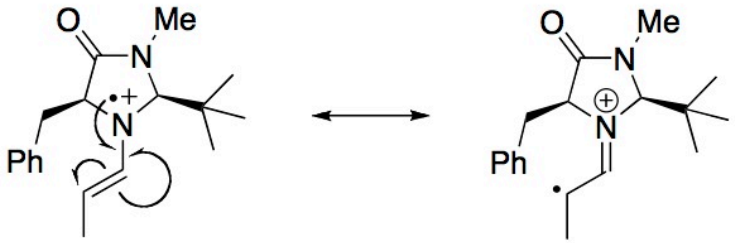


Cho, D.K.; Jang, D.O. Chem. Commun., **2006**, 5045-5047

MacMillan SOMO Catalysis - Hypothesis

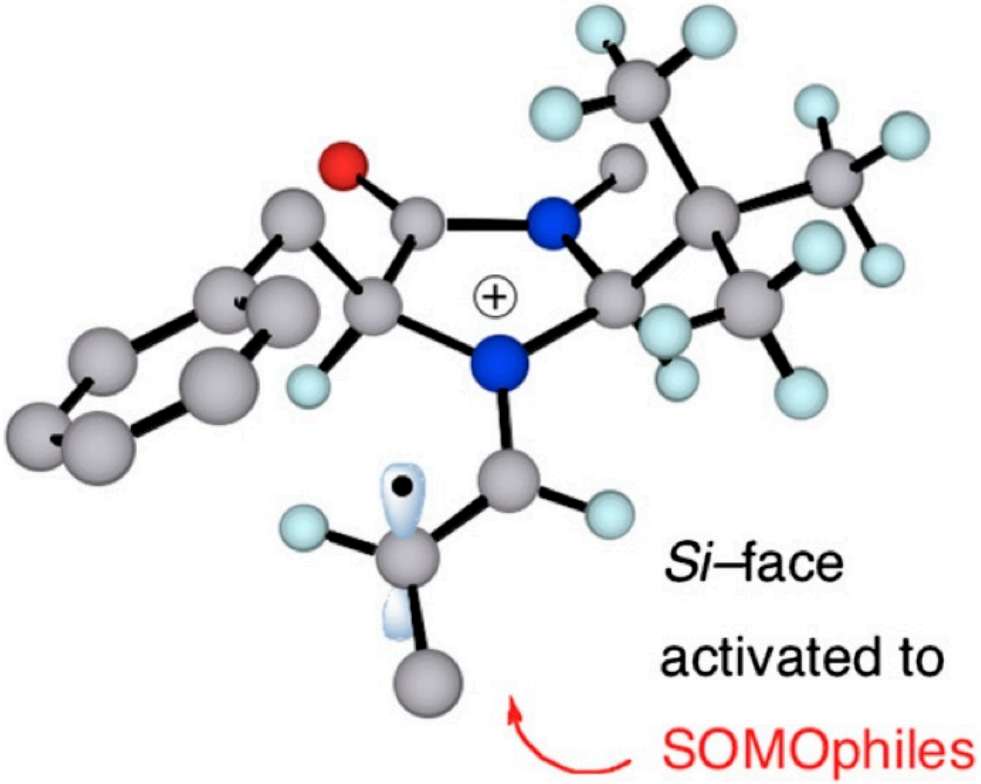






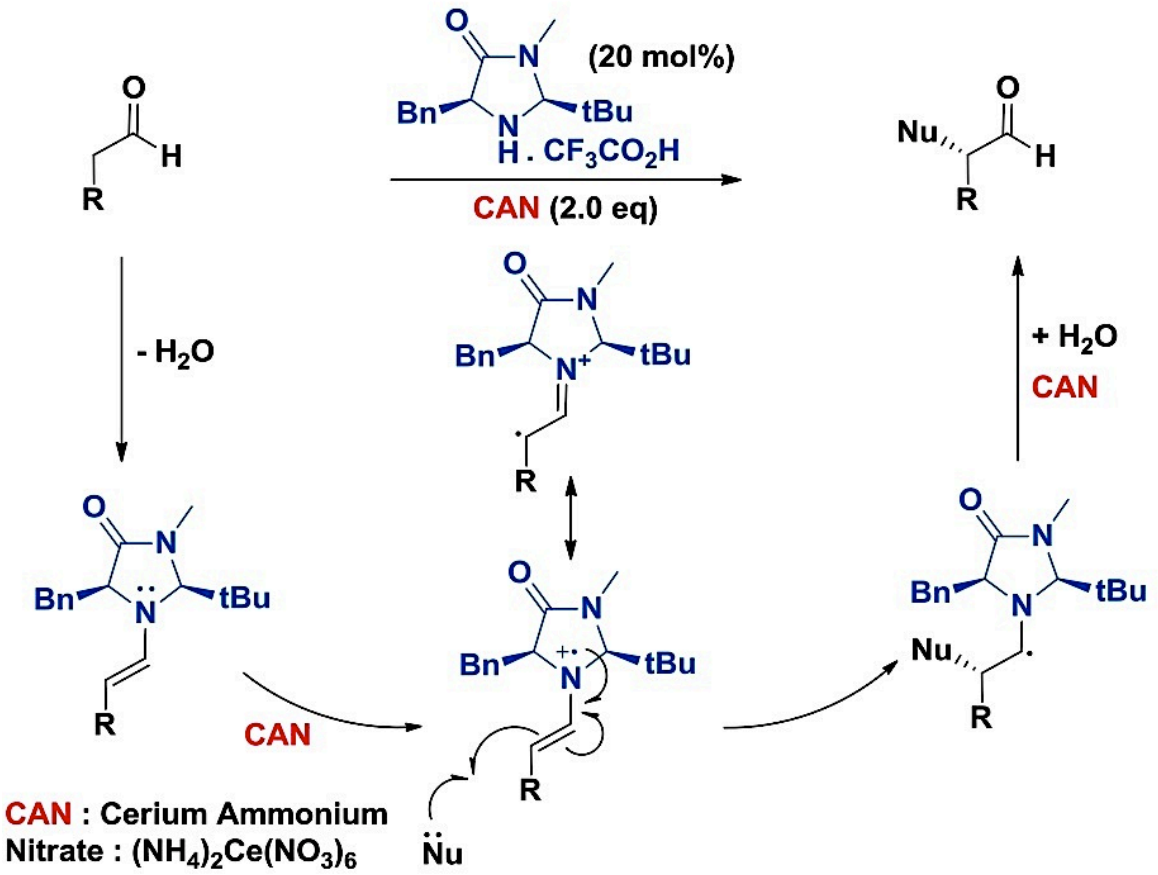
MacMillan, D.W.C. J. Am. Chem. Soc., **2007**, 129, 7004

MacMillan SOMO Catalysis



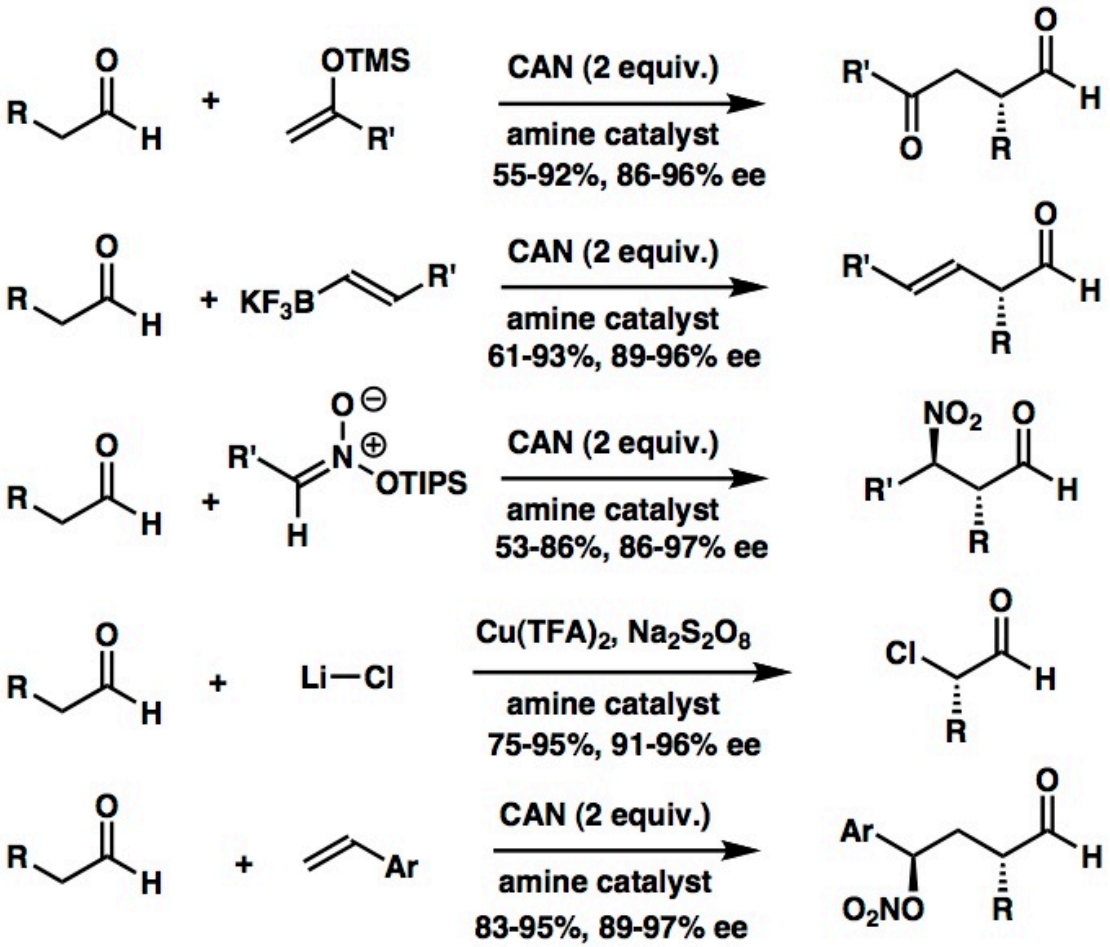
MacMillan, D.W.C. J. Am. Chem. Soc., **2007**, 129, 7004

MacMillan SOMO Catalysis

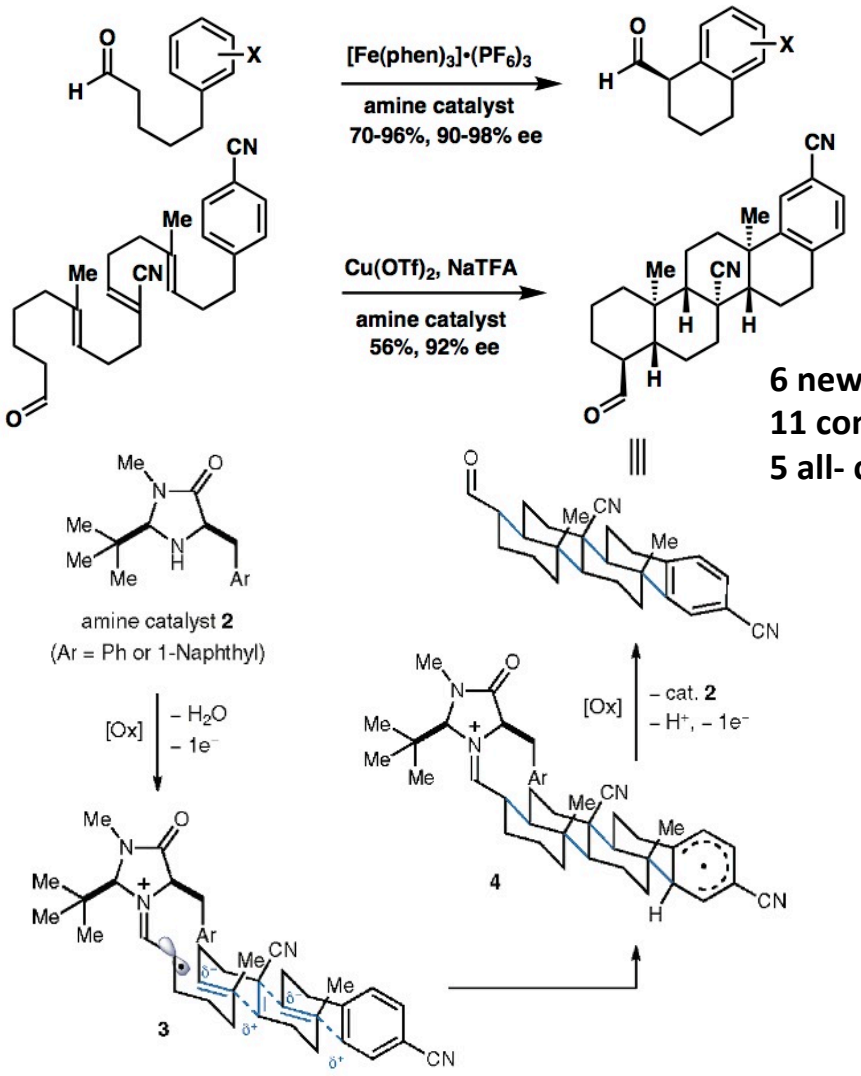


MacMillan, D.W.C. J. Am. Chem. Soc., **2007**, 129, 7004

Scope - intermolecular



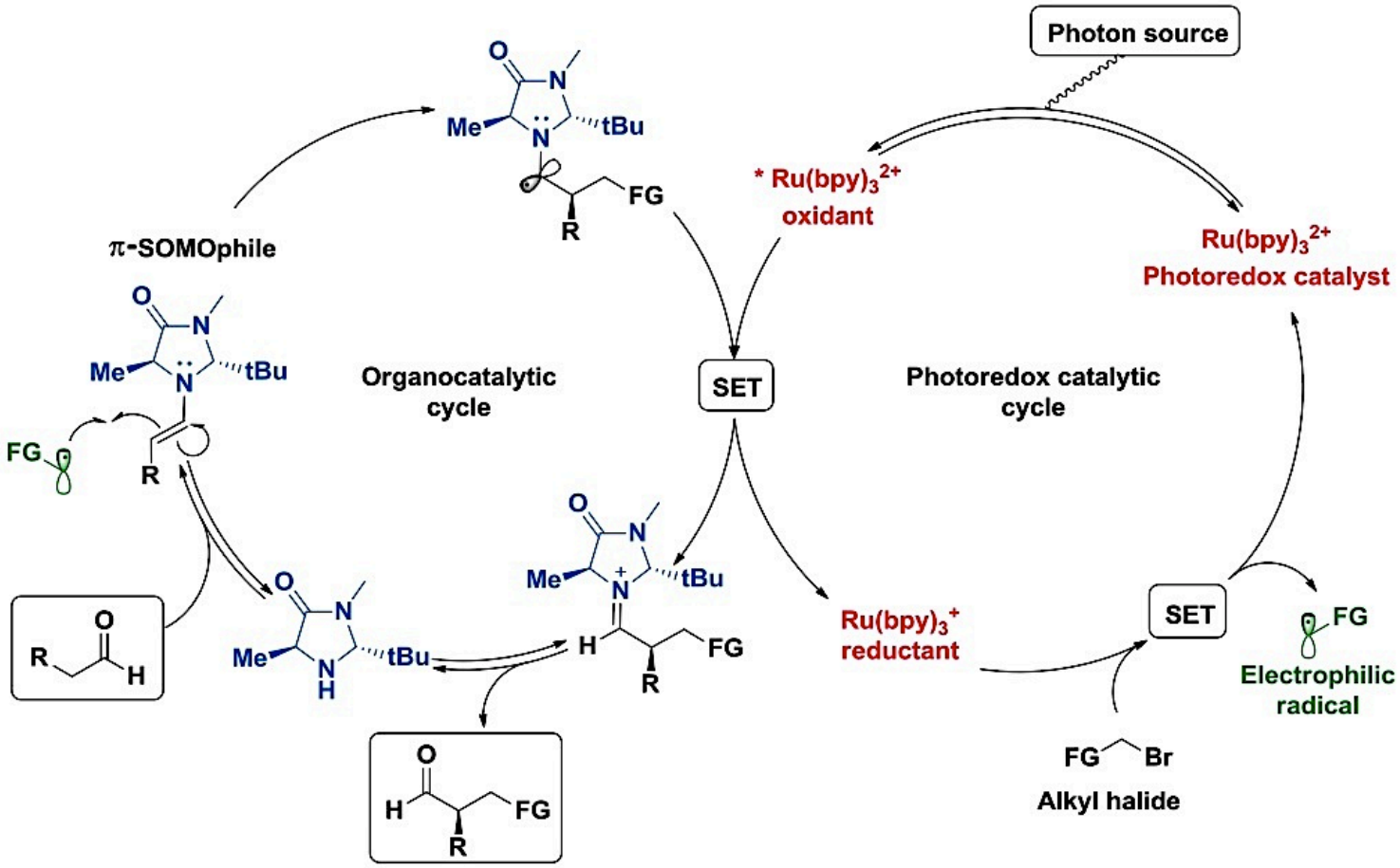
Scope - Intramolecular



6 new bonds
11 contiguous stereocenters
5 all- carbon quaternary stereocenters

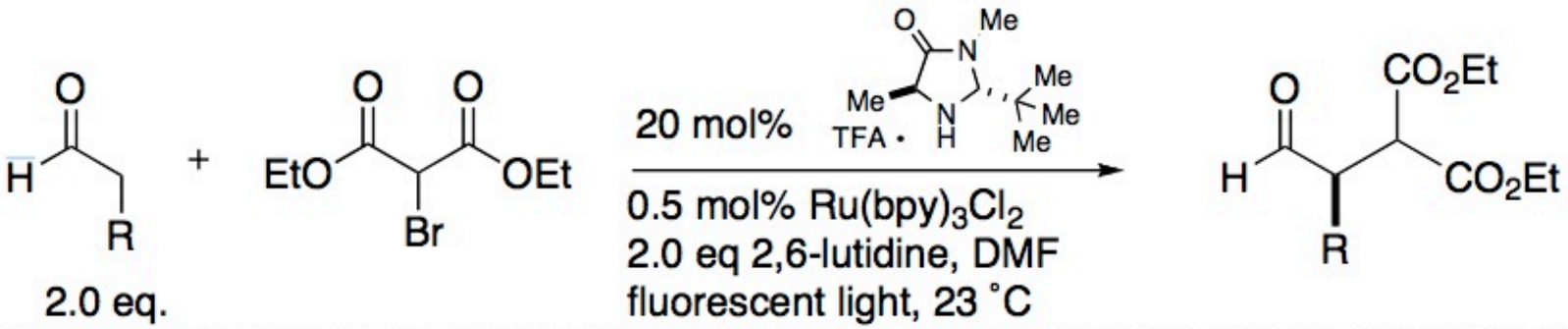
MacMillan, J. AM. CHEM. SOC. 2010, *132*, 5027

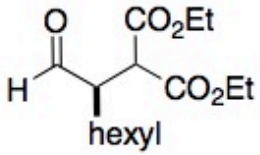
MacMillan Photoredox Catalysis



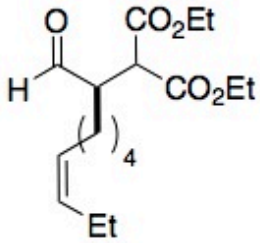
MacMillan, D.W.C. Science, **2008**, 322, 77

Scope

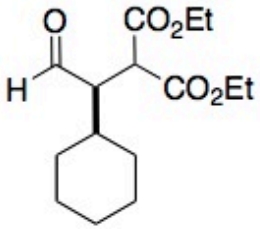




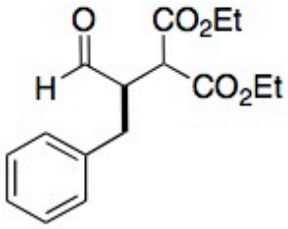
93% yield
90% ee



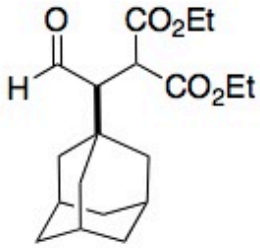
86% yield
90% ee



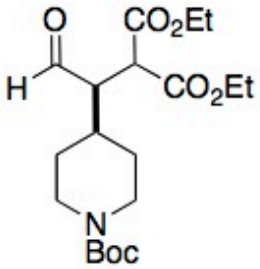
83% yield
95% ee



92% yield
90% ee



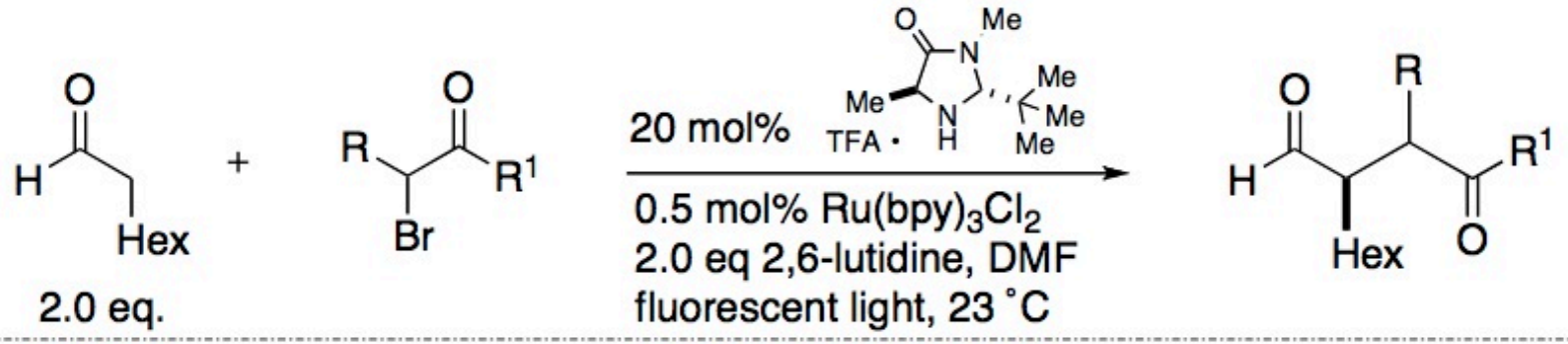
63% yield
93% ee

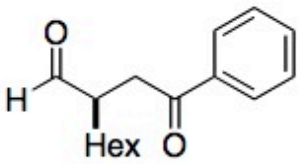


66% yield
91% ee

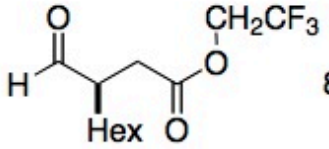
MacMillan, D.W.C. Science, **2008**, 322, 77

Scope

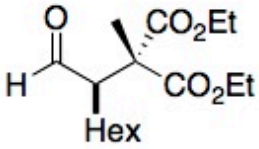




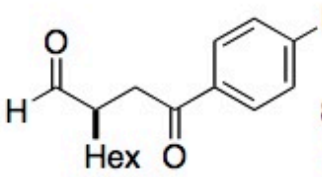
84% yield
96% ee



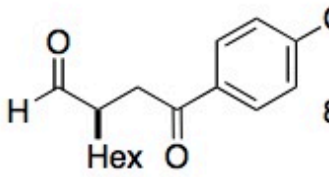
80% yield
92% ee



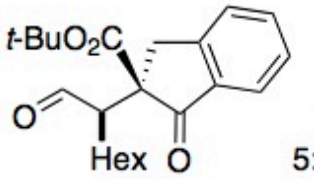
80% yield
88% ee



84% yield
95% ee



87% yield
96% ee



70% yield
5:1 dr, 99% ee

MacMillan, D.W.C. Science, **2008**, 322, 77

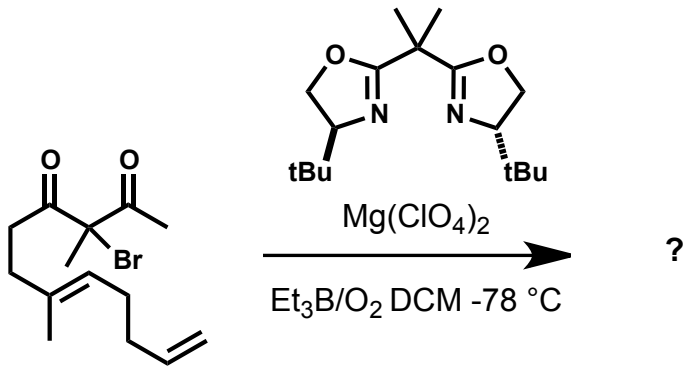
Conclusion

- Formation of C-H, C-X, and C-C bonds is possible
- Enantioselective radical reactions mediated by chiral Lewis acids still suffer from large catalyst loading and the need for toxic tin reagents
- Organocatalysts have made a significant impact on enantioselective radical chemistry and a good fraction of them can be considered ecofriendly
- Many areas left to explore
  - Introduction of more functional groups
  - Use in total synthesis

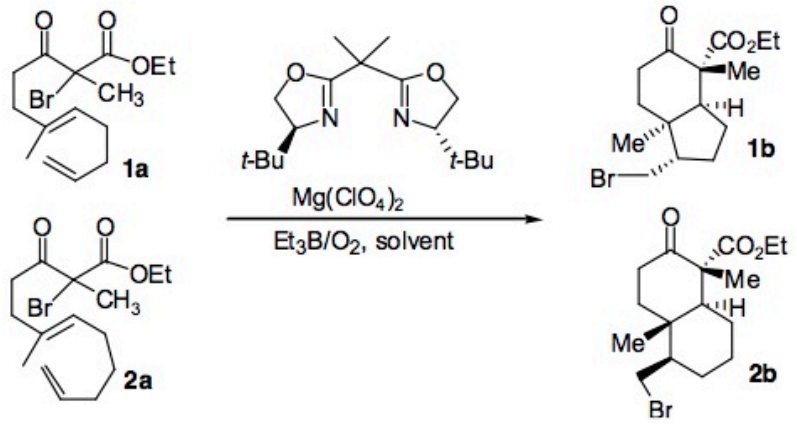
Questions

- What brings MacMillan photoredox catalysis to SOMO catalysis ?

- What is the product?



Tandem Atom Transfer Cyclizations



Entry	Substrate	T (°C)	Solvent	Product	Yield (%)	ee (%)
1	**1a**	-78	CH_2Cl_2	**2a**	41	13
2	**1a**	-78	CH_2Cl_2	**2a**	24	33
3	**2a**	-40	toluene	**2b**	23	82
4	**2a**	-20	toluene	**2b**	16	84

- Sets four stereocenters in one step with a single diastereomer observed

Yang, D.,, *Angew. Chem. Int. Ed.* **2002,** *41*, 3014

Enantioselective Synthesis of 1,2-Azetidinone

Sophie Racine

Laboratory of Catalysis and Organic Synthesis

http://isic.epfl.ch/lcso

Lausanne, May 1st.

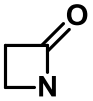
Questions

- Using the **Sharma's** methodology what kind of side product can you obtained (using oxalyl chloride)?

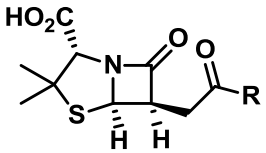
- Which methodology is for you most relevant?

Azetidine-2-one = β-Lactams

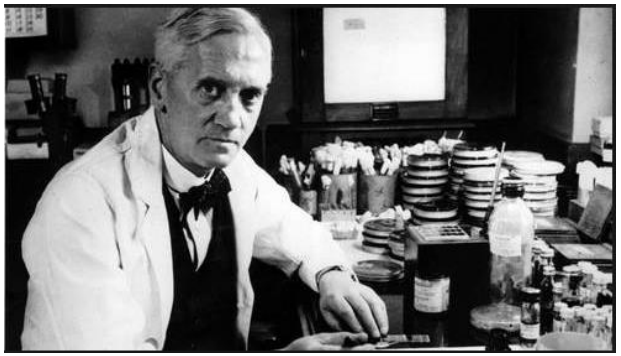
Azetidinone



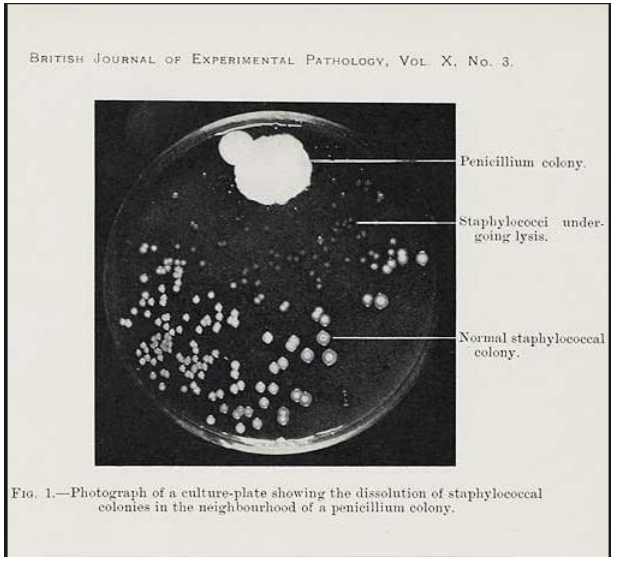
Penicillin



R = Bn penicillin G
= CH_2OPh penicillin V



Alexander Fleming, 1928
Nobel Prize 1945 (medicine)

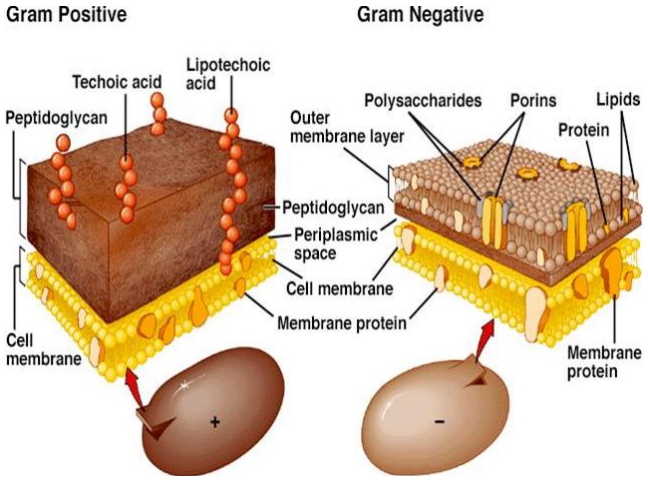


→ **Penicillin's discovery**

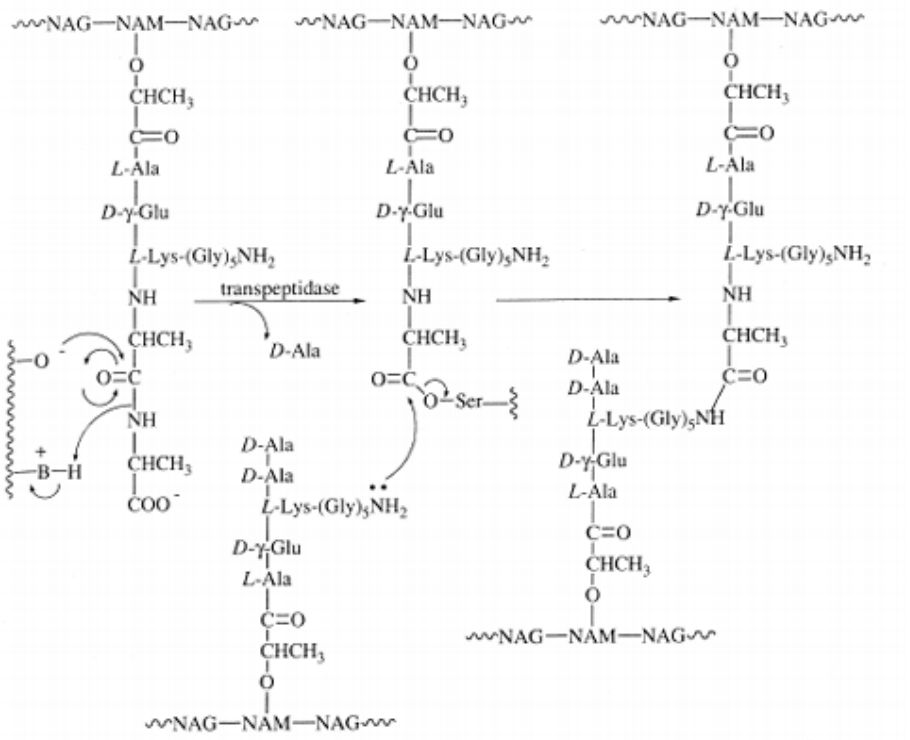
Penicillium mold vs
Staphylococcus Aureus

Mode of Action

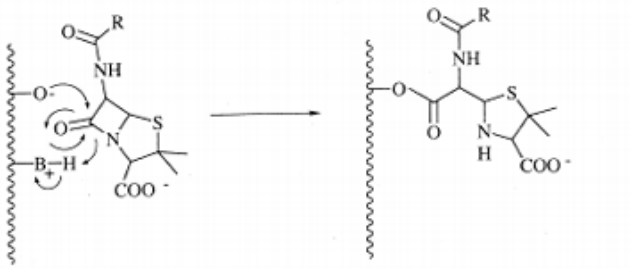
- Bacteria cell wall



- Peptidoglycans cross-linkage



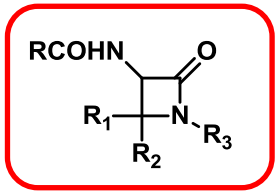
- Transpeptidase inhibition



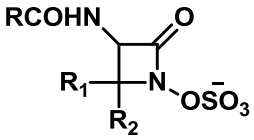
Silverman, R. B. *Medizinische Chemie für Organiker, Biochemiker und pharmazeutische Chemiker*; VCH: Weinheim [u.a.], 1995.

β-Lactams Classification

- Monocyclic β-lactams

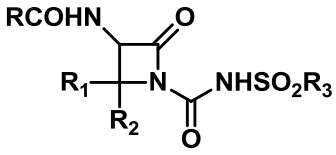


Monocarbams

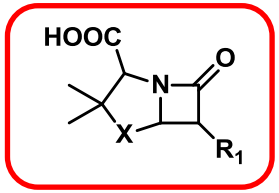


Monosulfactams

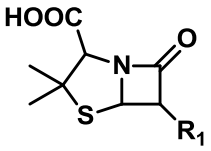
Monobactams



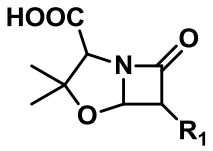
- Penams



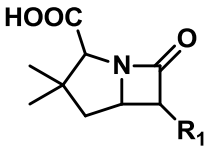
Penicillins



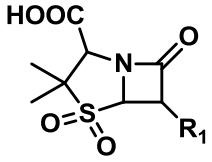
Oxapenams



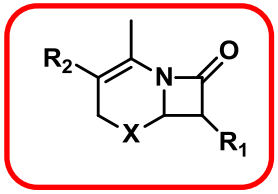
Carbapenams



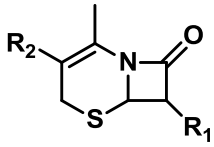
Sulbactams



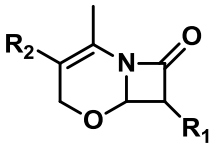
- Cephems



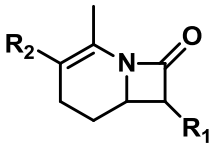
Cephalosporins



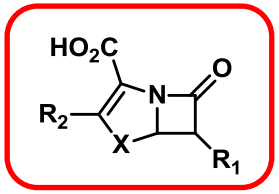
Oxacephems



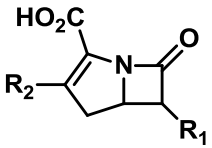
Carbacephem



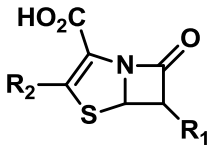
- Saturated Penams



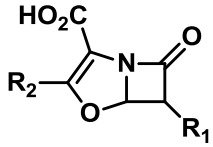
Carbapenems



Penems



Oxapenems



β-Lactams in numbers

- **Sales in 2000, $15 bilions** (antifungal and antiviral ± 3 billions)
  - $9.9 billions cephalosporin
  - $5 billions penicillin
- **50 marketed cephalosporins**
- **33,000 tons/year** (1960s 6,600 tons)
- Up to 400,000 liters batch
- **$10-20/kg** (1960s $300/kg)

TABLE WO-1 Burden of Multidrug-Resistant (MDR) Bacteria in the European Union, Iceland, and Norway, 2007

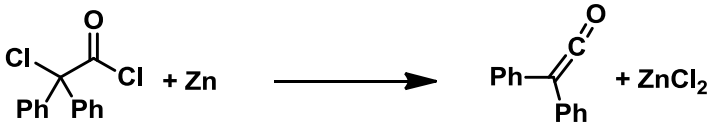
Human burden	
Infections (6 most frequent MDR bacteria, 4 main types of infection)	~400,000/year
Attributable deaths	~25,000/year
Extra hospital days	~2.5 million/year
Economic burden	
Extra in-hospital costs	~€900 million/year
Productivity losses	~€600 million/year

NOTE: Limitation: these are underestimates.
SOURCE: ECDC and EMEA (2009).

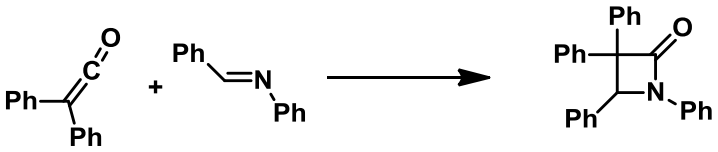
Elander, R. P. *Appl. Microbiol. Biotechnol.* 2003, *61*, 385–392.

First Synthesis of Azetidinone

- 1905 Ketene isolation & identification [1]



- 1907 Azetidinone synthesis [2]



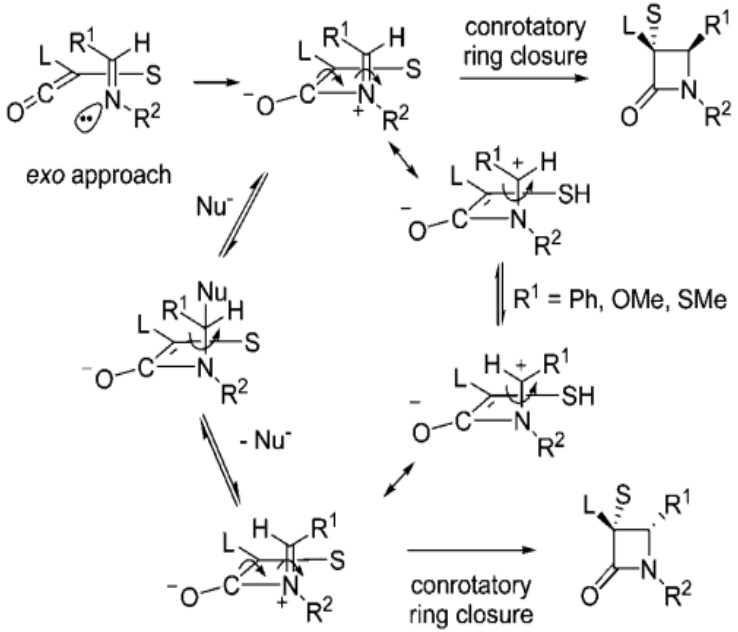
H. Staudinger, 1881-1965, ETHZ
1953 Nobel prize [3]

- Relative stereoselectivity was observed.
- Trans-product favored
- With cyclic imines Cis-product was exclusively isolated

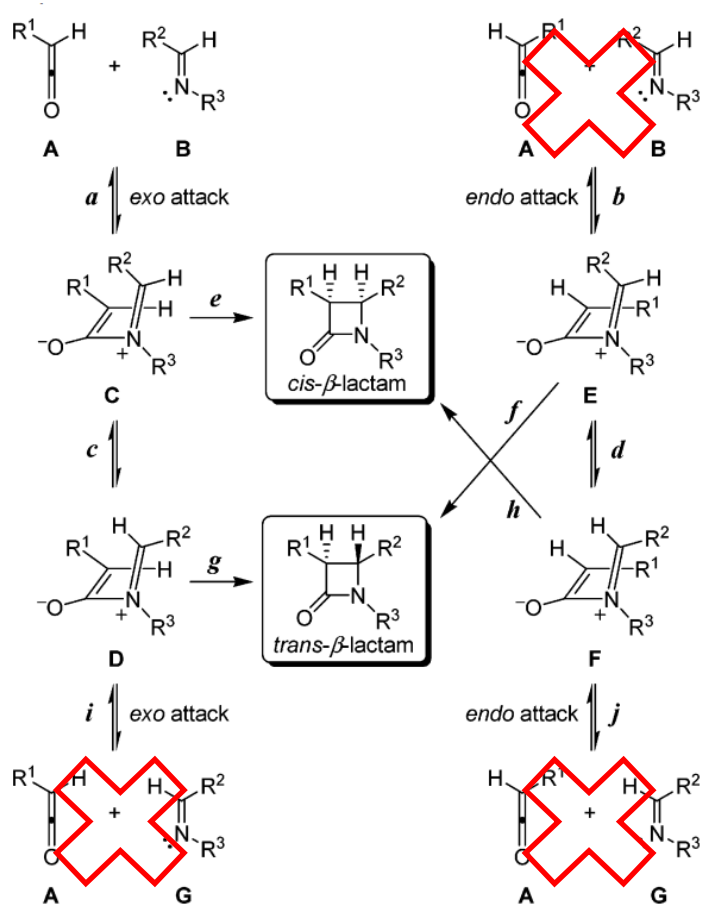
(1) Staudinger, H. *Ber. Dtsch. Chem. Ges.* 1905, *38*, 1735 - 1739. (2) Staudinger, H. *Justus Liebigs Ann. Chem.* 1907, *356*, 51-123.
(2) Tidwell, T. T. *Angewandte Chemie International Edition* 2008, *47*, 1016–1020.

Staudinger Reaction Mechanism

- Hegedus et al. 1991



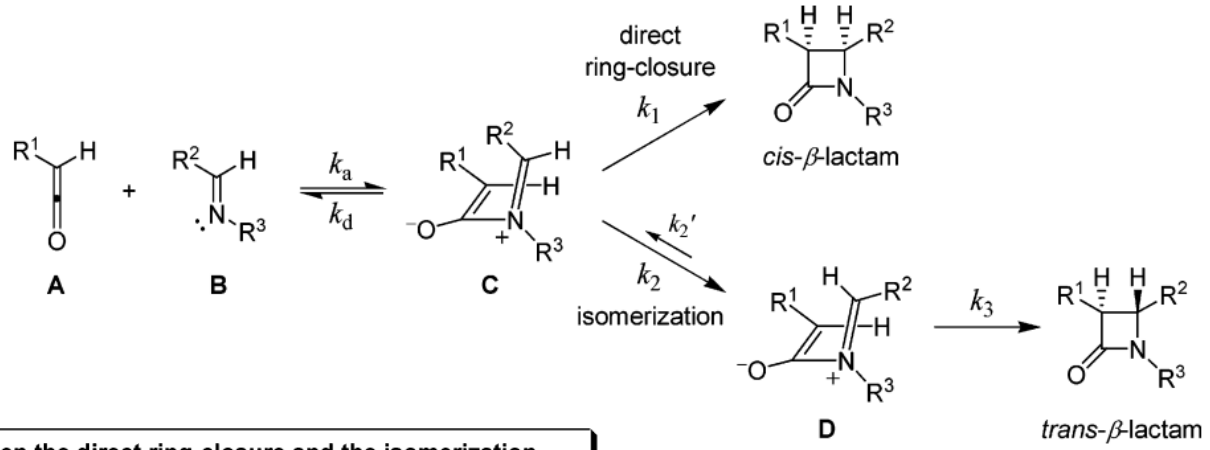
- Xu et al. 2006



[a] Only one enantiomer is drawn.

(1) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *Journal of the American Chemical Society* 1991, *113*, 5784–5791.
(2) Jiao, L.; Liang, Y.; Xu, J. *Journal of the American Chemical Society* 2006, *128*, 6060–6069.

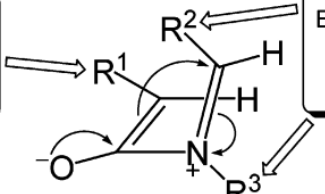
Staudinger Reaction Studies (Xu et al.)



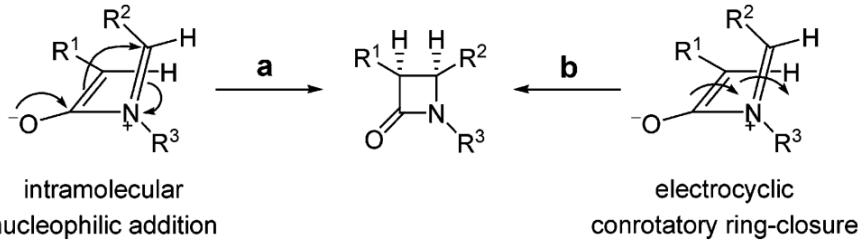
Competition between the direct ring-closure and the isomerization controls the relative stereoselectivity.

EDG can accelerate direct ring-closure (increase k_1)

EWG can accelerate both direct ring-closure and isomerization (increase both k_1 and k_2)



Bulky group can slow the isomerization (decrease k_2)



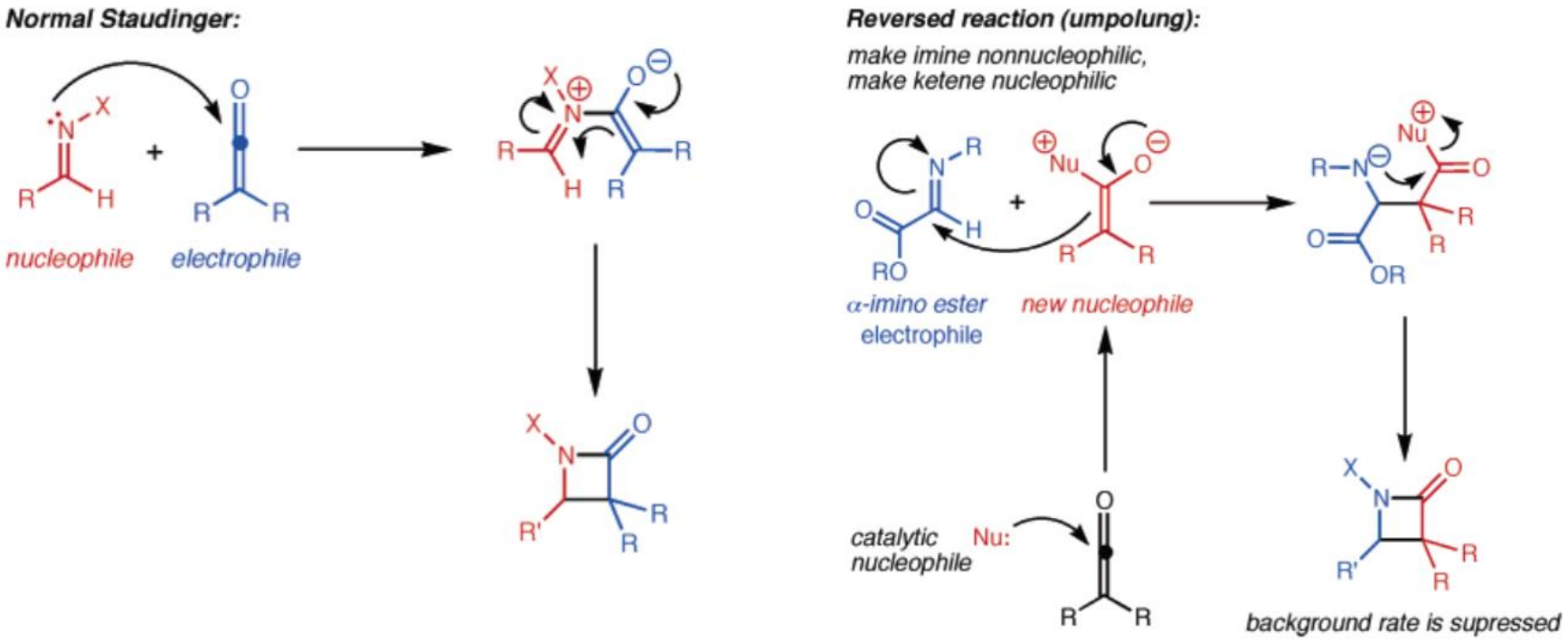
(1) Jiao, L.; Liang, Y.; Xu, J. *Journal of the American Chemical Society* 2006, *128*, 6060–6069.

Asymmetric Synthesis of azetidinone

- Chiral auxiliary based systems (Evans [a], Wagle [b])
- Doyle's rhodium-catalyzed C-H insertion into diazoacetamides.[c]
- Alper's rhodium-catalyzed ring expansion-carbonylation of aziridines[d]
- Tomioka's amine-catalyzed condensation of ester enolates and imines [e]
- Catalyzed Staudinger reaction
- Kinugasa reaction
- Aziridine enlargement

(a) Evans, D. A.; Sjogren, E. B. Tetrahedron Lett.1985, 26, 3783-3786. (b) Bose, A. K.; Manhas, M. S.; van der Veen, J. M.; Bari, S. S.; Wagle, D. R. *Tetrahedron*, 1992, 48, 4831-4844. (c) Doyle, M. P.; Kalinin, A. V. *Synlett*, 1995 ,10, 1075-1076. (d) Calet, S.; Urso, F.; Alper, H. *J. Am. Chem. Soc*. 1989, 111, 931-934. (e) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. A. *J. Am. Chem. Soc*. 1997, 119, 2060-2061

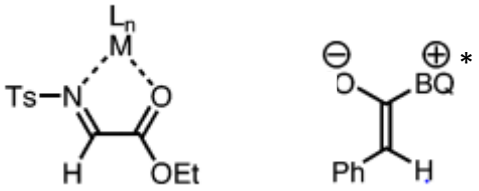
Staudinger Ümpolung General Mechanism



(1) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Accounts of Chemical Research* 2004, *37*, 592–600.

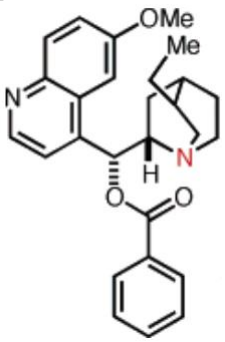
Staudinger Reaction between Zwitterionic Enolates and Imines (Lectka et al.)

- Lectka et al. strategy



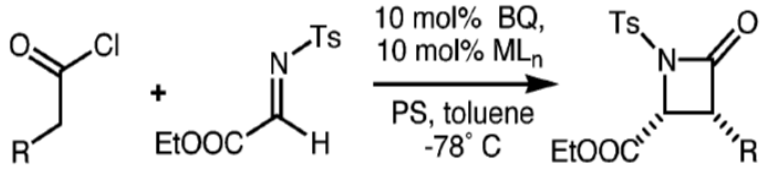
Bifunctional Lewis Acid-Nucleophile-Based Asymmetric Catalysis

BQ =



$MLn = In(OTf)_3$

- Lectka et al. 2003-2005



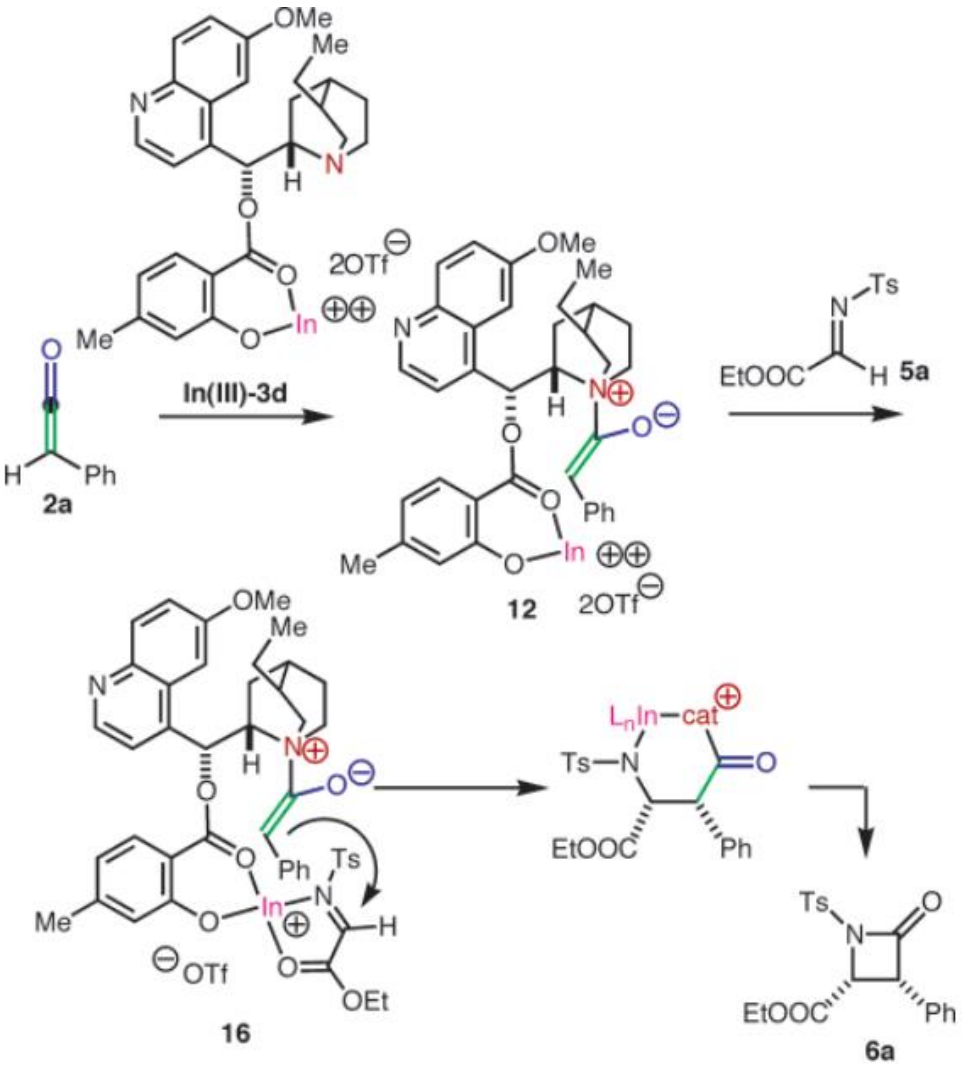
8 entries
9:1 to 60:1 d.r.
>96% e.e.
> 91% yield

(1) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *Journal of the American Chemical Society* 2005, *127*, 1206–1215.

(2) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Accounts of Chemical Research* 2003, *36*, 10–19.

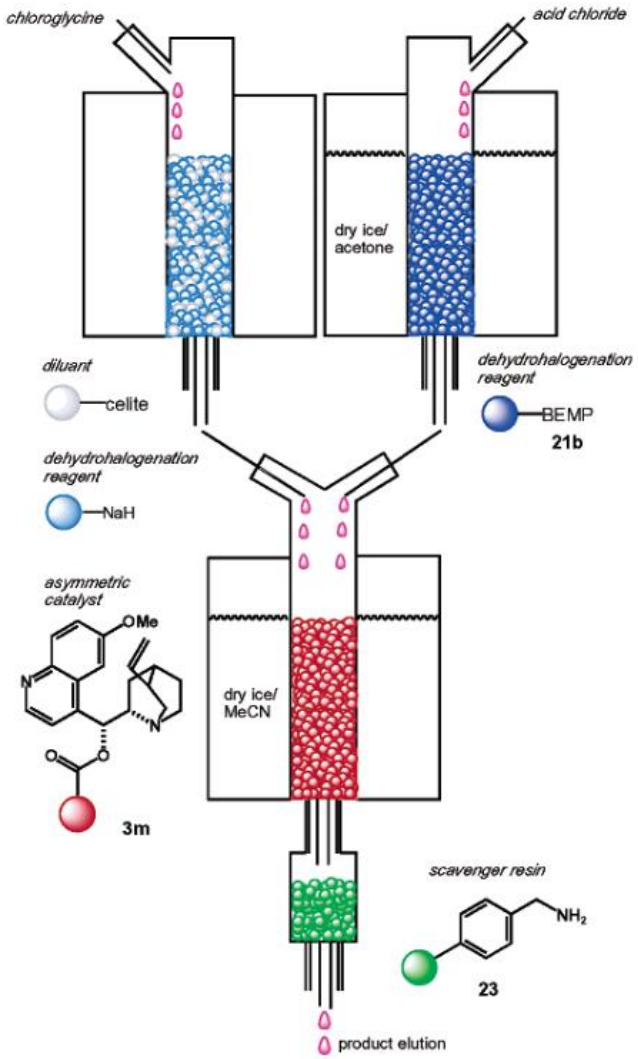
Staudinger Reaction between Zwitterionic Enolates and Imines Mechanism

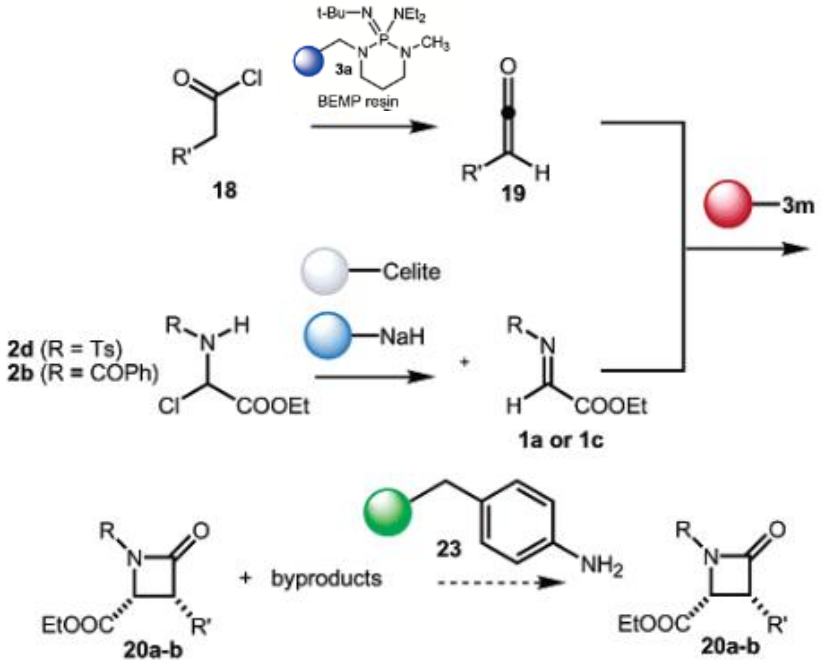
- Lectka et al. 2005



(1) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *Journal of the American Chemical Society* 2005, *127*, 1206–1215.

Solid Phase Synthesis of Azetidinone via Zwitterionic Enolates



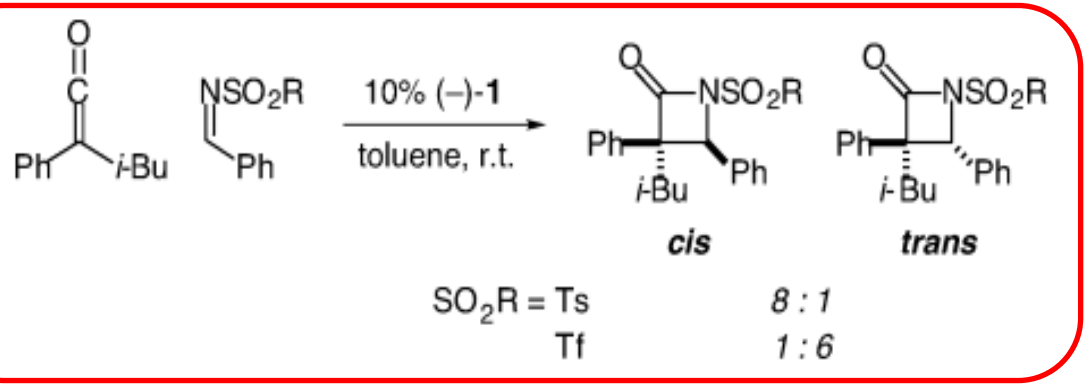


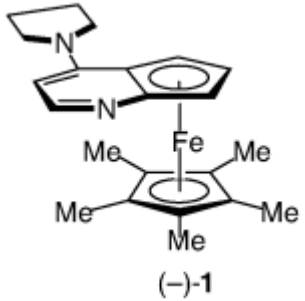
98/2 d.r.
>99% e.e.
62% yield

(1) Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J.; Lectka, T. *Organic Letters* 2000, *2*, 3963–3965.

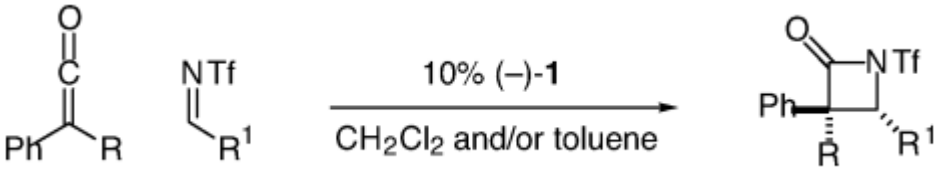
Staudinger Reaction for α,α- disubstituted Azetidinone Synthesis

- Fu et al. 2005, First Trans selective α-disubstuted Azetidinone





NTs
10:1 d.r.
89-98% e.e.

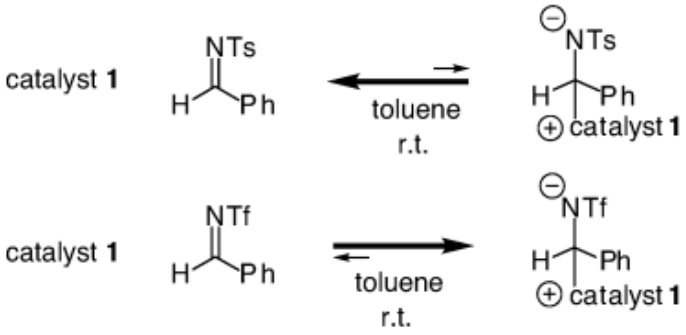


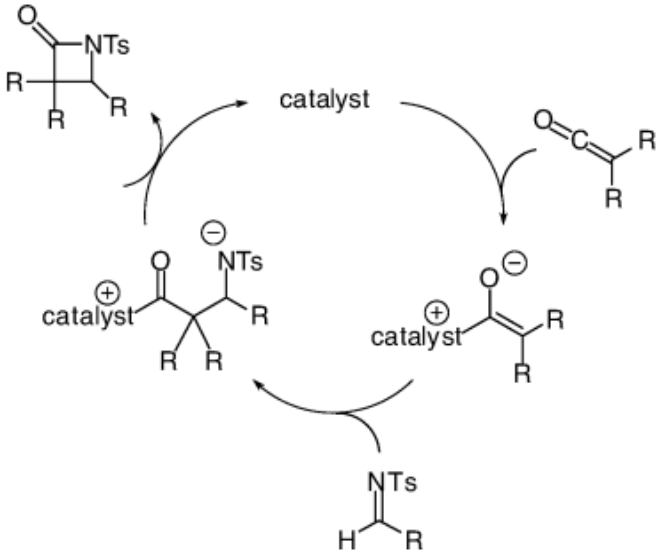
10 entries
80:20-98:2 d.r.
63-98% e.e.
90-89% yield

Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *Journal of the American Chemical Society* 2005, *127*, 11586–11587.

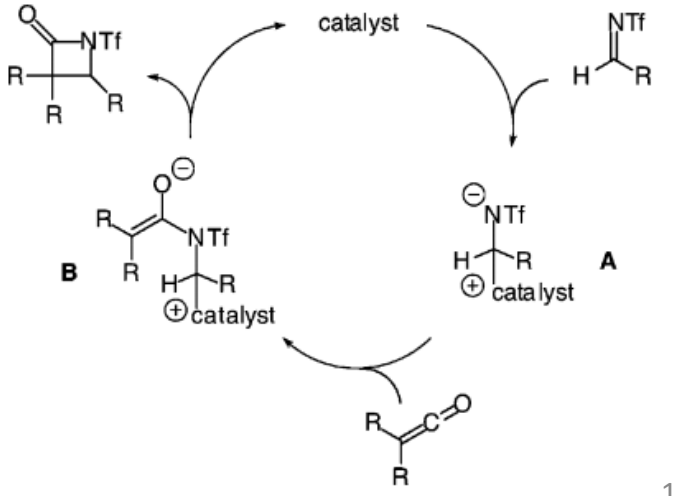
Staudinger Reaction for α,α- disubstituted Azetidinone Mechanism (Fu et al.)

«Umpolung» Staudinger
→ Cis





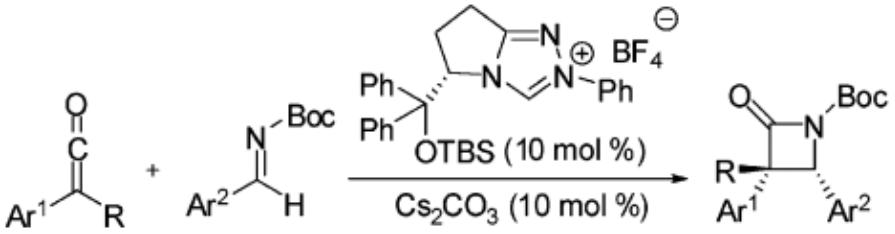
«Normal» Staudinger
→ Trans



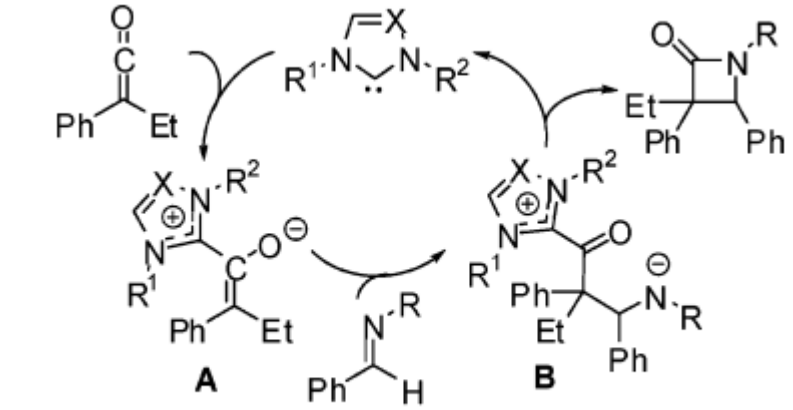
Lee, E. C.; Hodous, B. L.; Bergin, E.; Shih, C.; Fu, G. C. *Journal of the American Chemical Society* 2005, *127*, 11586–11587.

Staudinger NHC Catalyzed Reaction for α,α-disubstituted Azetidinone Synthesis

- Ye et al. 2008



13 entries
75:25-99:1 d.r.
91-99% e.e.
58-75% yield

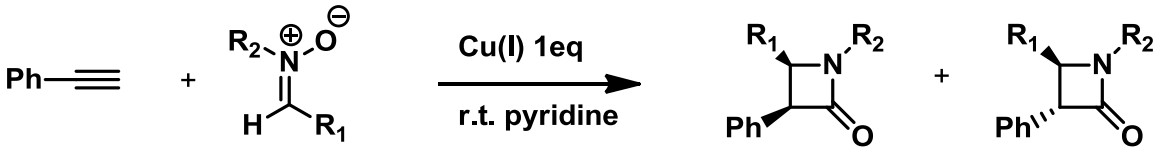


Mechanism A

Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Organic Letters* 2008, *10*, 277–280.

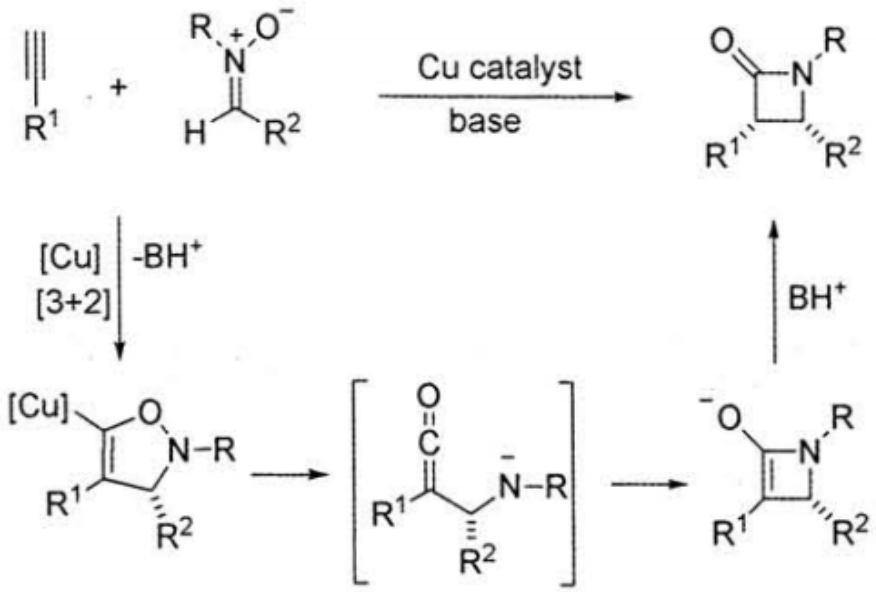
Copper(I) Phenylacetylide with Nitrones (Kinugasa reaction)

- Kinugasa et Hashimoto, 1972



Only one enantiomer is drawn

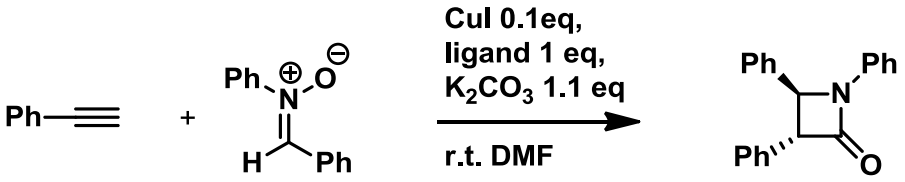
- Mechanism

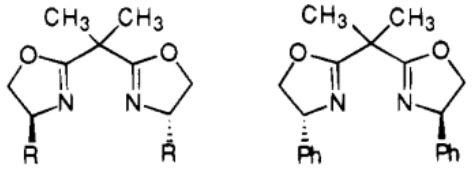


(1) Kinugasa, M.; Hashimoto, S. *Journal of the Chemical Society, Chemical Communications* 1972, 466.

Kinugasa reaction

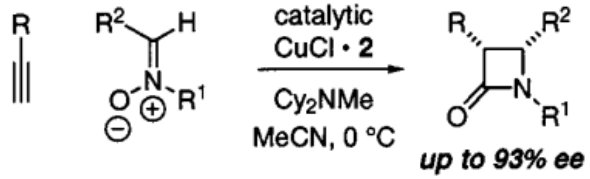
- Miura et al. 1995 First catalytic asymmetric Kinugasa reaction

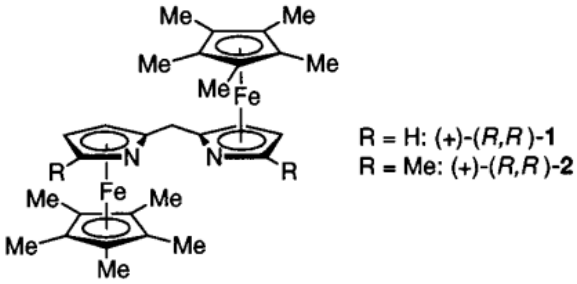




4 entries
2:1 d.r.
Max 57% e.e.
50% yield

- Fu et al., 2002





R 5 entries
>90:10 d.r.
>90% e.e.
45-65% yield

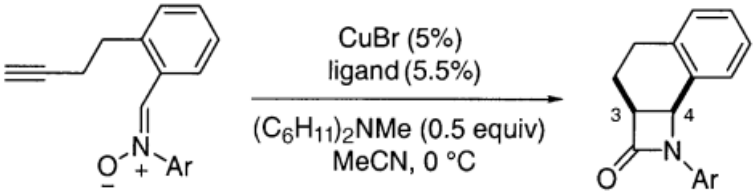
R_1 5 entries
>94:6 d.r.
67-85% e.e.
53-91% yield

R_2 5 entries
>91:9 d.r.
72-90% e.e.
42-57% yield

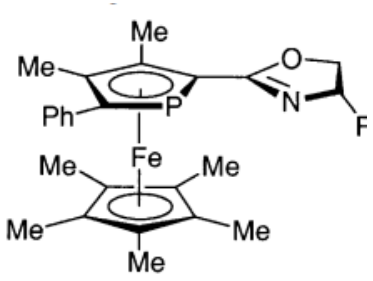
(1) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *The Journal of Organic Chemistry* 1995, *60*, 4999–5004
(2) Lo, M. M.-C.; Fu, G. C. *Journal of the American Chemical Society* 2002, *124*, 4572–4573.

Intramolecular Kinugasa

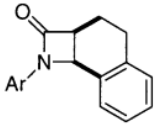
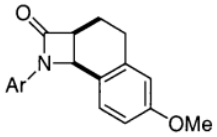
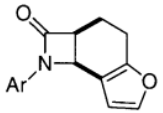
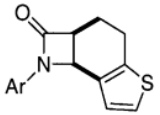
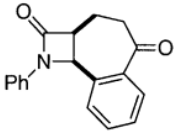
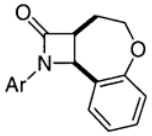
- Fu et al., 2003



Ar = *p*-carboethoxyphenyl



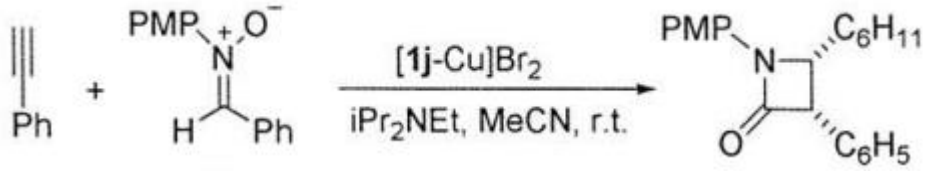
5a: R = *i*Pr; **5b**: R = *t*Bu

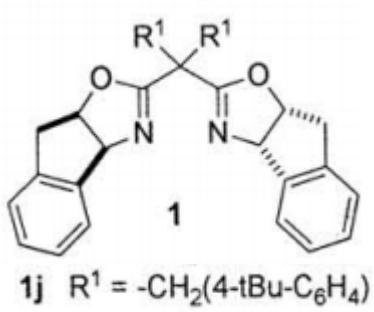
Entry	Product	Ligand	*ee* [%]	Yield [%]
1		**5a**	88	74
2		**5a**	86	60
3[b]		**5a**	90	46
4[b]		**5b**	90	64
5[b]		**5b**	85	53
6		**5b**	91	68

(1) Shintani, R.; Fu, G. C. *Angewandte Chemie International Edition* 2003, *42*, 4082–4085.

Kinugasa's Reaction

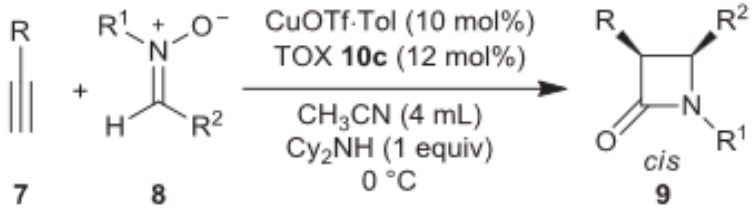
- Evans et al., 2007

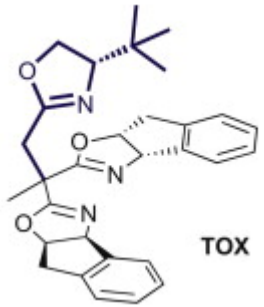




18 entries
>90:10 d.r.
>86% e.e.
41-72% yield

- Tang et al., 2012



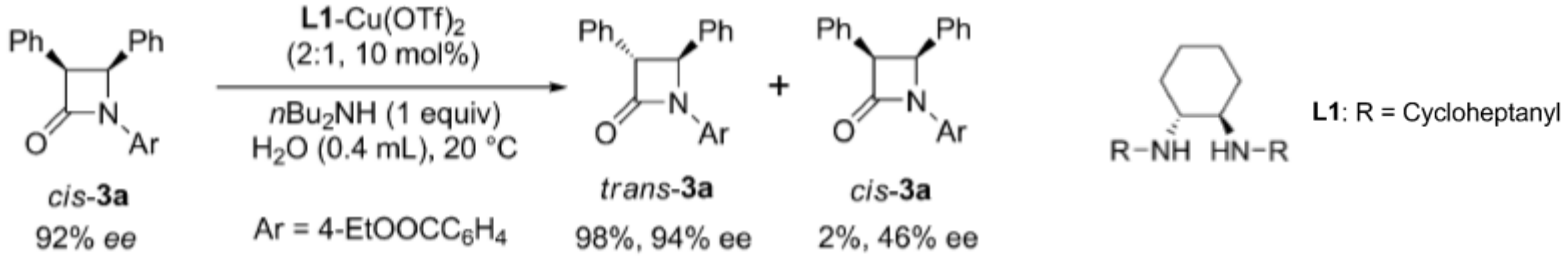


20 entries
>70:30 d.r.
>88% e.e.
34-98% yield

(1) *Asymmetric synthesis: the essentials*; Wiley-VCH: Weinheim, 2007.
(2) Chen, J.-H.; Liao, S.-H.; Sun, X.-L.; Shen, Q.; Tang, Y. *Tetrahedron* 2012, *68*, 5042–5045

Kinugasa's Reaction (Chen et al.) Access to Trans-Azetidinone

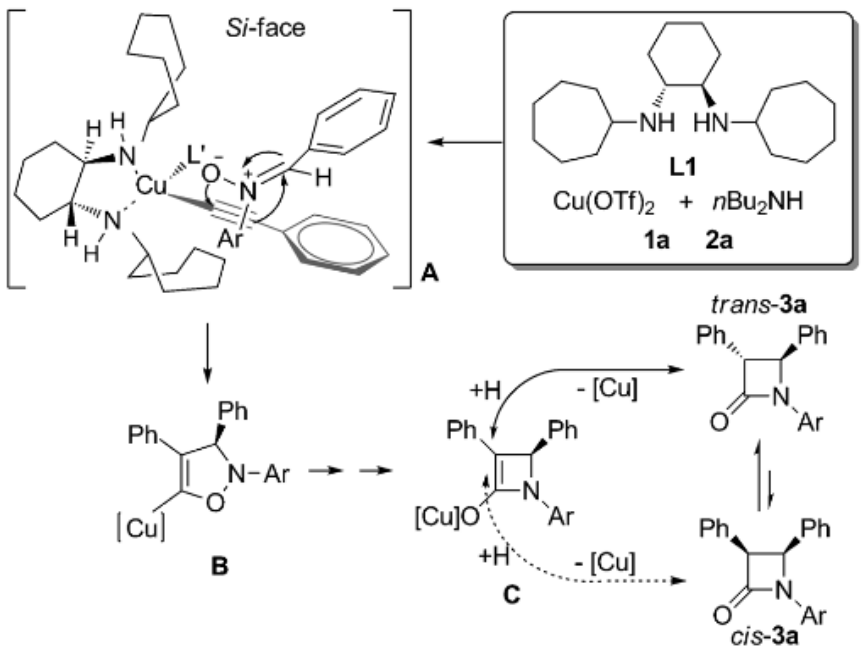
- Chen et al., 2013 Trans-azetidinone



Entry[a]	Solvent	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][c]
2	MeCN	88	83:17	78
3	BuOAc	97	76:24	85
4	CH_3NO_2	66	42:58	78
8[d]	water	90	99:1	91

Entry[a]	*T* [°C]	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][c]
1	35	84	96:4	75
2	20	90	99:1	91
3	0	83	42:58	95[d]

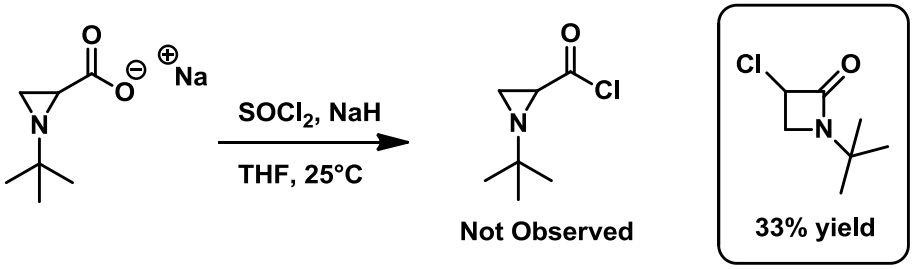
Entry[a]	*t*	Yield [%][b]	*trans*/*cis*[c]
1	5 min	83	38:62
2	10 min	84	42:58
3	1 h	84	41:59
4	4 h	90	56:44
5	8 h	91	76:24
6	24 h	91	>95:5



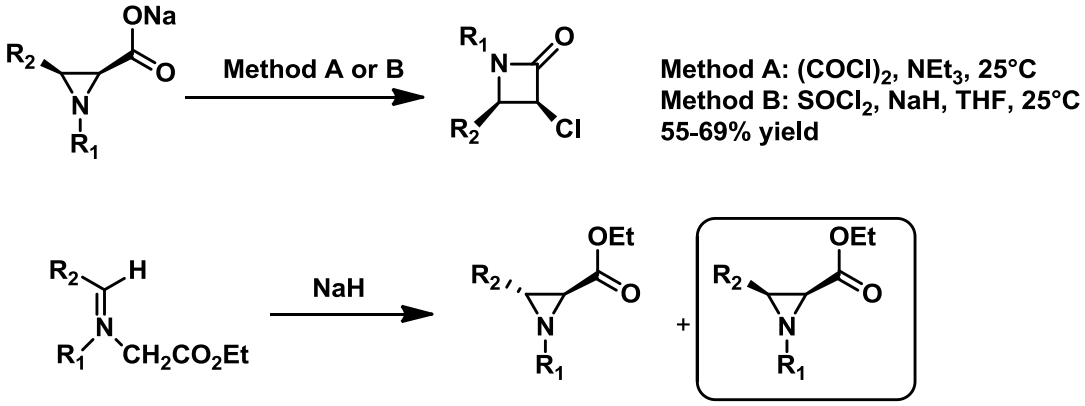
(1) Chen, Z.; Lin, L.; Wang, M.; Liu, X.; Feng, X. *Chemistry - A European Journal* 2013.

Ring Expension from Aziridine

- Firstly described by Deyrup and Clough 1969



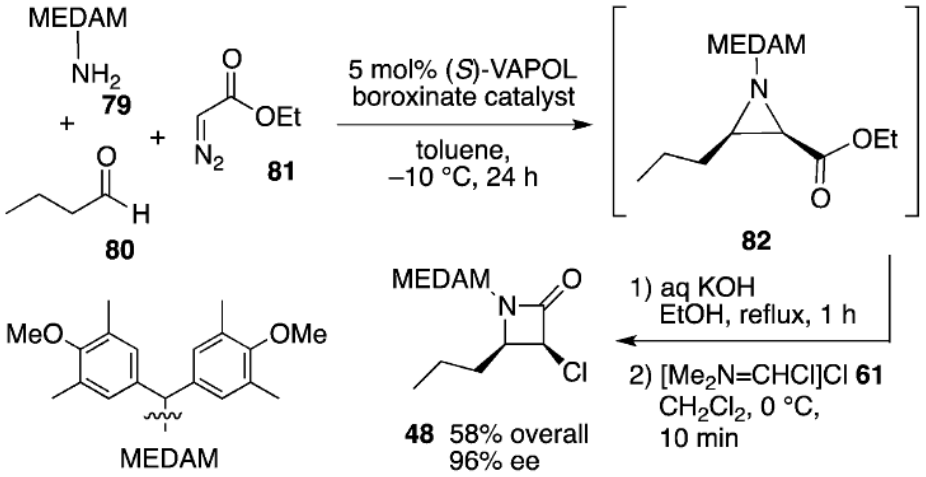
- Sharma et al. 2006

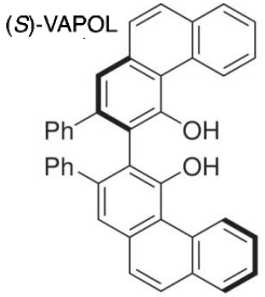


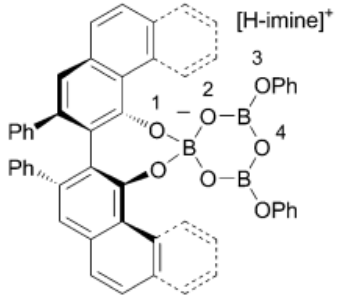
(1) Deyrup, J. A.; Clough, S. C. *Journal of the American Chemical Society* 1969, *91*, 4590–4591.
(2) Sharma, S. D.; Kanwar, S.; Rajpoot, S. *Journal of Heterocyclic Chemistry* 2006, *43*, 11–19.

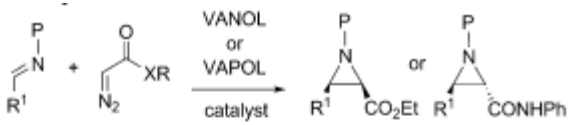
Ring Expension from Aziridine (Wulff et al.)

- Wulff et al. 2013







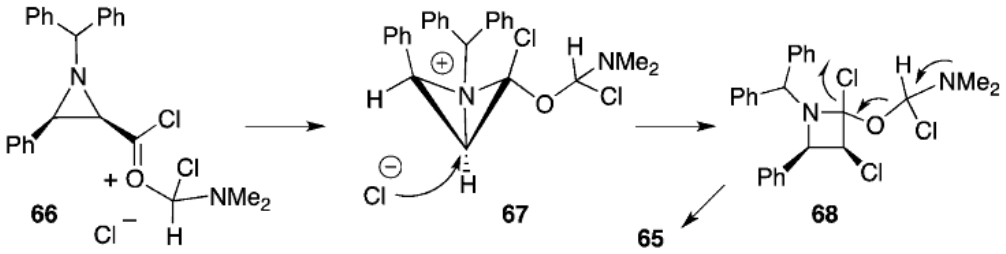


N-substituents (P)[a]	Aziridine	Ligand	Average yield [%]	Average *ee* [%][b]
(*R*)-α-methylbenzyl	*cis*	VAPOL	70[c,d]	100 (≥87)
	cis	VANOL	72[c,e]	100 (≥90)
	trans[f]	VAPOL	74	100 (≥90)
	trans[f]	VANOL	75	100 (≥90)
benzhydryl	*cis*	VAPOL	70	88
	cis	VANOL	77	88
DAM	*cis*	VAPOL	73	88
	cis	VANOL	78	85
BUDAM	*cis*	VAPOL	88	95
	cis	VANOL	90	94
MEDAM	*cis*	VAPOL	92	97
	cis	VANOL	91	96

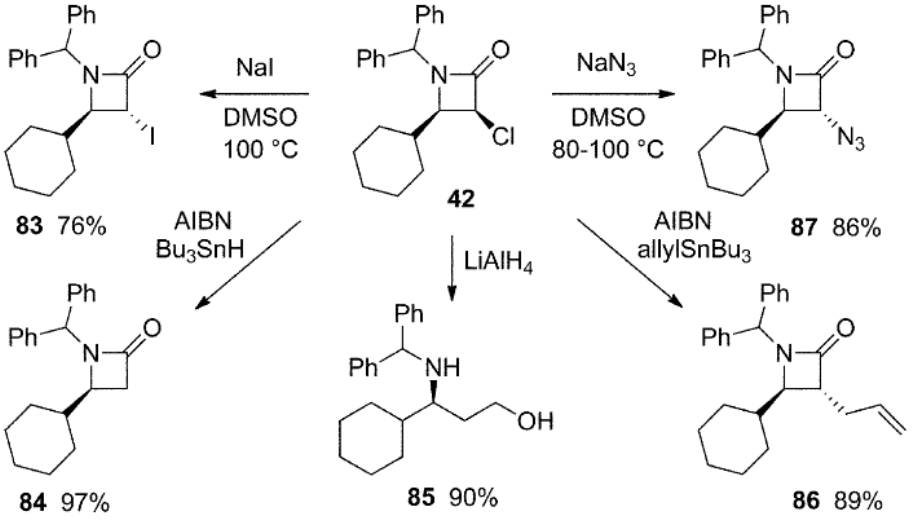
(1) Huang, L.; Zhao, W.; Staples, R. J.; Wulff, W. D. *Chemical Science* 2013, *4*, 622.
(2) Huang, L.; Zhang, Y.; Staples, R. J.; Huang, R. H.; Wulff, W. D. *Chemistry - A European Journal* 2012, *18*, 5302–5313

Ring Expension from Aziridine (Wulff et al.)

- Mechanism



- Further functionalization



(1) Huang, L.; Zhao, W.; Staples, R. J.; Wulff, W. D. *Chemical Science* 2013, *4*, 622.

Conclusions

- ***Cis*-trisubstituted** Azetidinone, enantioselectively obtained with;
  - **Lectka et al.** (bifunctional catalysis In(OTf)3 + Benzoylquinine) **Staudinger**
  - **Fu et al.** (planar-chiral bis(azaferrocene) + Cu(I)) **Kinugasa**
  - **Evans et al**. (bisoxazoline/Cu(II)) **Kinugasa**
  - **Tang et al**. (trisoxazoline/Cu(I)) **Kinugasa**

- ***Trans*-trisubstituted** Azetidinone, enantioselectively obtained with;
  - **Cheng et al.** (chiral secondary diamine/Cu(II)) **Kinugasa**

- ***Cis*-tetrasubstituted** Azetidinone, enantioselectively obtained with;
  - **Fu et al.** (PPY-ferrocene) **Staudinger**

- ***Trans*-tetrasubstituted** Azetidinone, enantioselectively obtained with;
  - **Fu et al.** (PPY-ferrocene) **Staudinger**
  - **Ye et al.** (NHC) **Staudinger**

- ***Cis*-trisubstituted and halogenated** Azetidinone, enantioselectively obtained with;
  - **Wulff et al. From azetidine enlargement**

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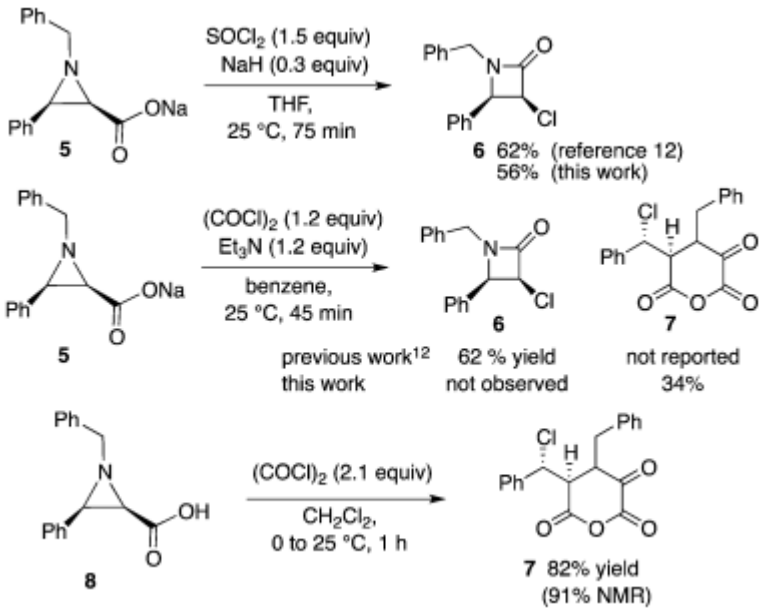
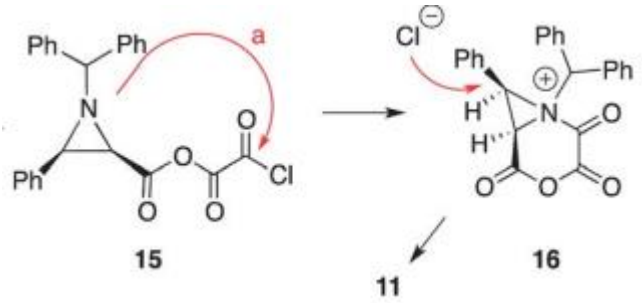
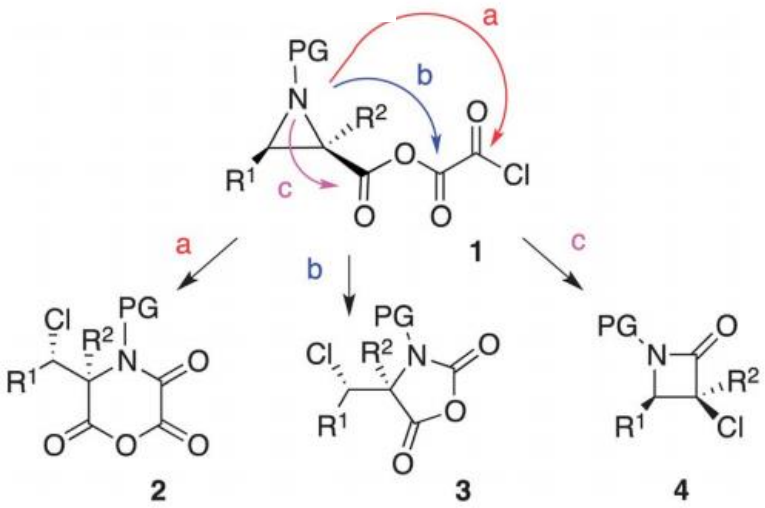
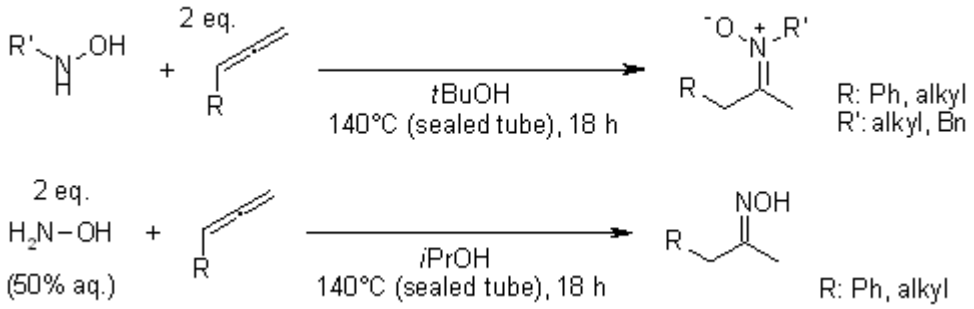
THANK YOU FOR YOUR ATTENTION

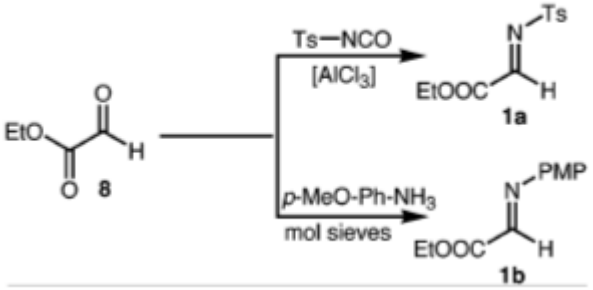

Ph
N
ONa
Ph
O
5
SOCl2 (1.5 equiv)
NaH (0.3 equiv)
THF,
25 °C, 75 min
Ph
N
O
Ph
Cl
6 62% (reference 12)
56% (this work)
(COCl)2 (1.2 equiv)
Et3N (1.2 equiv)
benzene,
25 °C, 45 min
Cl
H
7
previous work12
this work
62 % yield
not observed
not reported
34%
OH
8
(COCl)2 (2.1 equiv)
CH2Cl2,
0 to 25 °C, 1 h
7 82% yield
(91% NMR)

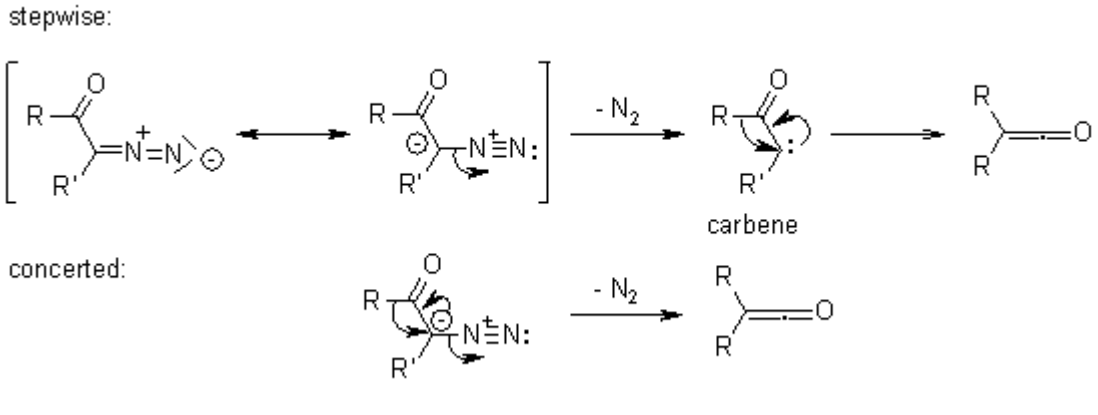

Ph
Ph
a
N
O
O
O
Cl
Ph
15
Cl
Ph
Ph
H
H
N
O
O
O
O
11
16

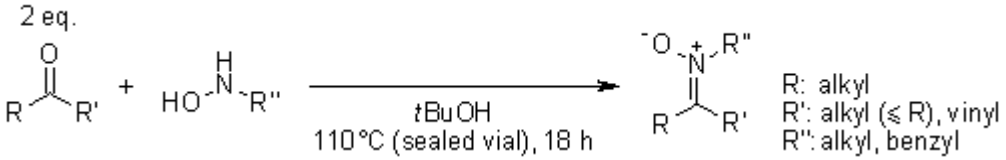

PG
N
R2
R1
a
b
c
O
O
O
Cl
1
a
b
c
Cl
PG
R2
N
R1
O
O
2
PG
Cl
R2
N
O
R1
O
O
3
PG
N
O
R2
R1
Cl
4



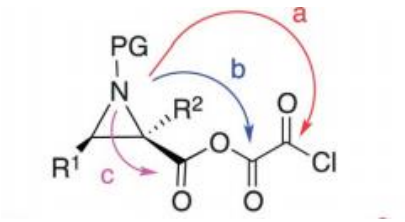
Scheme 2. Synthesis of α-Imino Esters

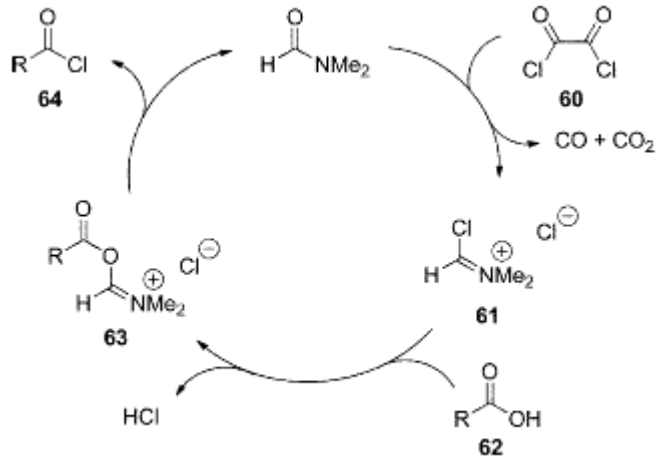






J. Y. Pfeiffer A. M. Beauchemin, *J. Org. Chem.*, **2009**, *74*, 8381-8383.
J. Moran, J. Y. Pfeiffer, S. I. Gorelsky, A. M. Beauchemin, *Org. Lett.*, **2009**, *11*, 1895-1898.


a
b
c
PG
N
R2
R1
O
O
Cl
O
O


R
Cl
64
H
NMe2
Cl
Cl
60
CO + CO2
Cl
H
NMe2
61
R
O
Cl
H
NMe2
63
HCl
R
OH
62

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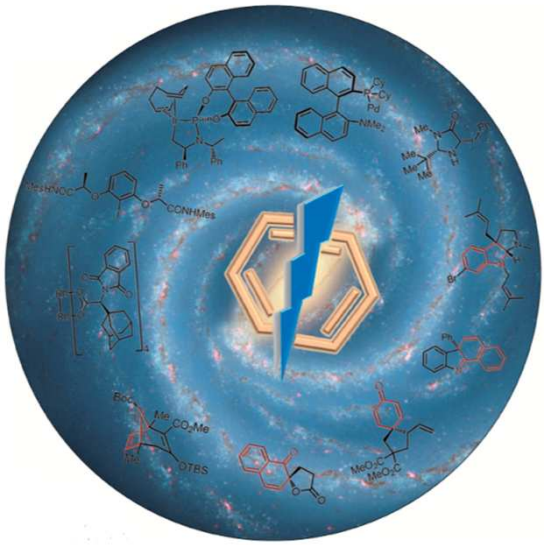
Catalytic Asymmetric Dearomatization Reactions

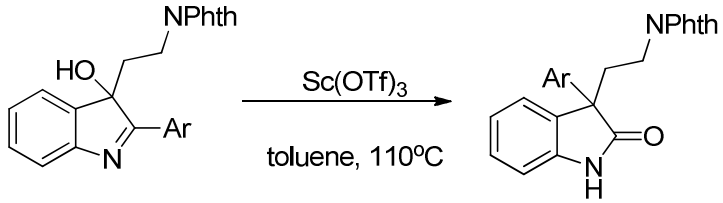


HA Minh Tu

Frontiers in Chemical Synthesis III: *Stereochemistry*
(Prof. Jérôme Waser, Prof. Xile Hu)

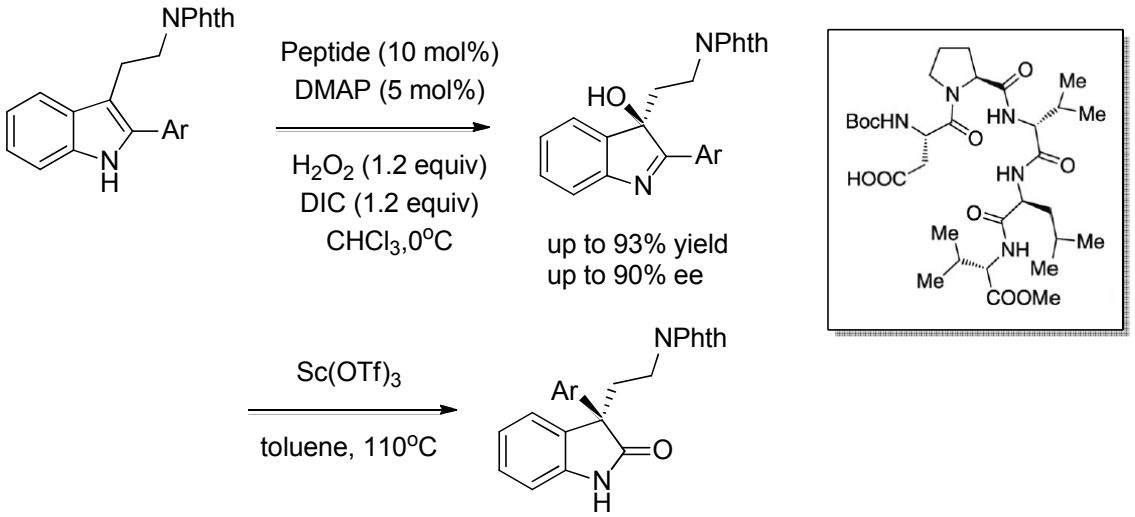
Questions

1. **This transformation was optimized to formation of oxidone**



In certain conditions, there is another product, which is that?

2. **In the oxidation protocol of 2-aryl-3-alkylindol by H2O2 catalyzed by chiral peptide (Movassaghi and Miller's work), aspartic residue is crucial factor. Can you suggest the intermediate and mechanism for this reaction?**



Outline

Introduction

Catalytic methods for asymmetric dearomatization

- Dearomatization by Oxidative reactions
- Dearomatization by Diels-Alder and related reactions
- Transition-Metal-Catalyzed reactions
- Dearomatization by Cascade sequences
- Nucleophilic dearomatization of electron-deficient aromatic rings
- Stepwise strategy
- Hydrogenation

Conclusion

Introduction

Catalytic Asymmetric Dearomatization Reactions are interesting…

- Product variety of ring systems
- Possible to form complex and unique structures
- Abundant of starting materials (aromatic rings)

Limitation

- Racemic product or low enantioselectivity
- Harsh conditions required

W. Zhang, C.-X. Zhuo, S. –L. You, *Angew. Chem. Int. Ed*, **2012**, 51, 12662

Introduction

Some pioneers in this field

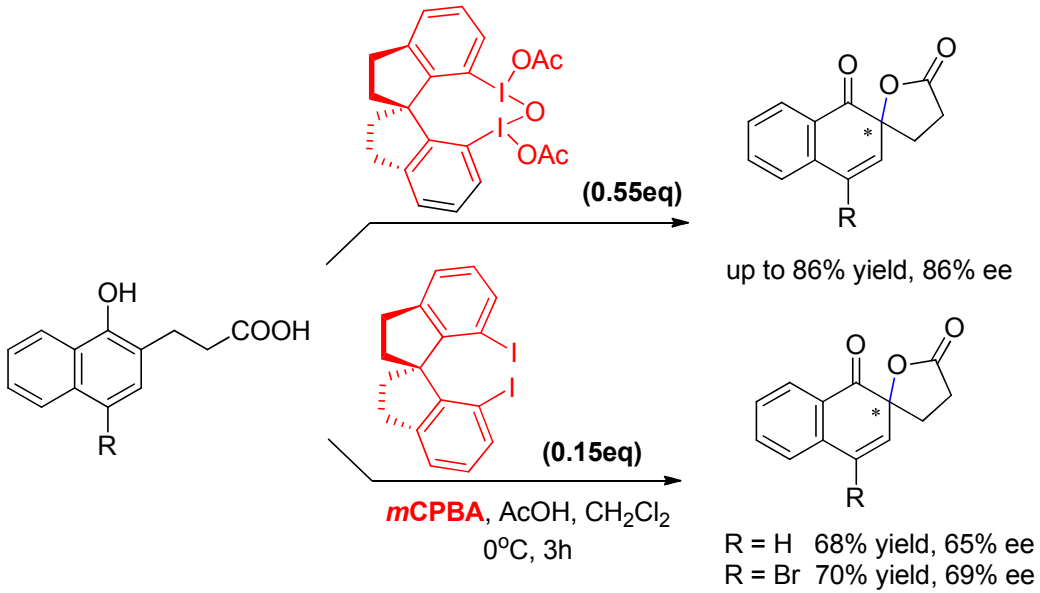
- John A. Porco Jr: Total synthesis using asymmetric dearomatization reactions
- Shu-Li You: Construct polycyclic scaffolds with quaternary centers and total synthesis by asymmetric dearomatization reactions
- Stéphane Quideau: hypervalent iodine-based methodologies for oxidative dearomatization

S. P. Roche, and J. A. Porco Jr., *Angew. Chem. Int. Ed*, **2011**, 50, 4068
W. Zhang, C.-X. Zhuo, S. –L. You, *Angew. Chem. Int. Ed*, **2012**, 51, 12662
L. Pouységu, D. Deffieux, S. Quideau, *Synlett*, **2008**, 4, 467

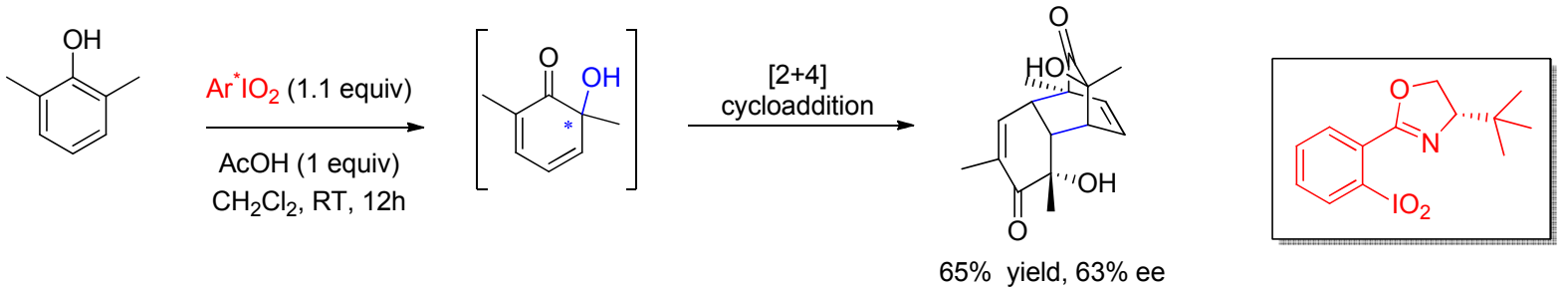
Oxidative dearomatization reactions

Compatible with: electron-rich arenes: phenols, indoles, pyroles
Oxidant: hypervalent iodine compounds, transition metal catalyst

Kita - 2008



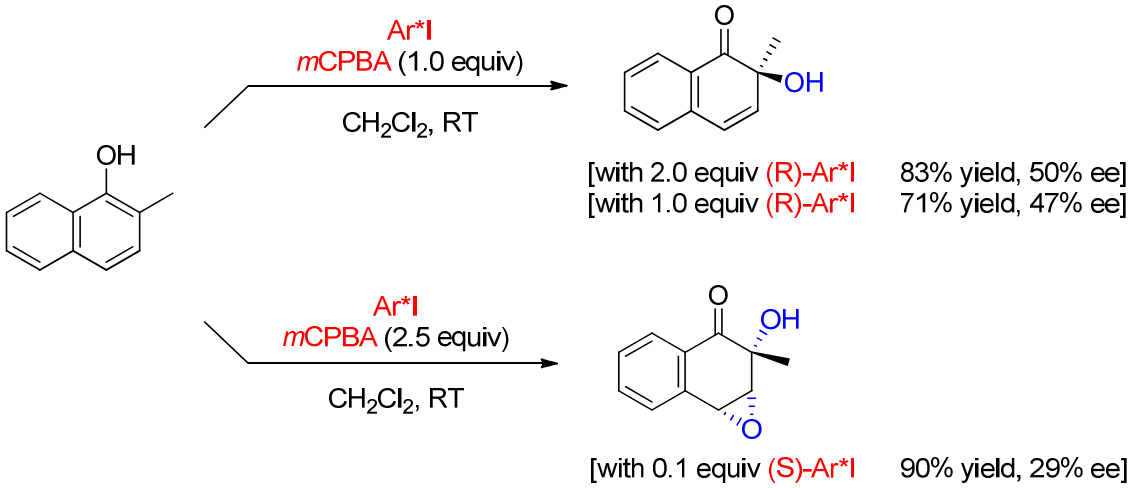
Boppisetti & Birman 2008



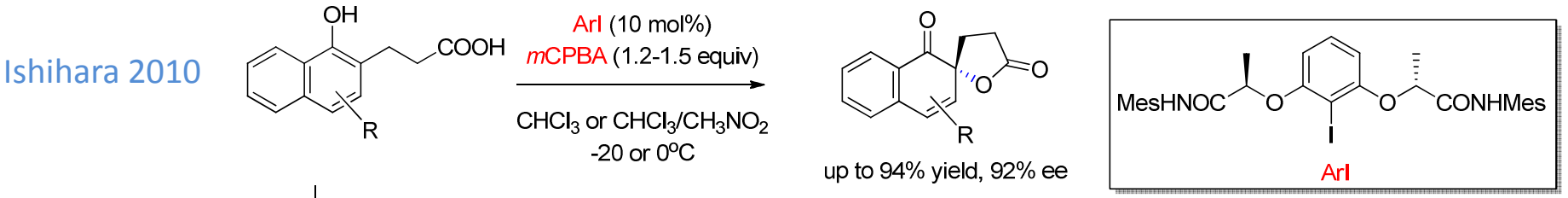
T. Dohi, A. Maruyama, N. Takenaga, K. Senami, S. Caemmerer and Y. Kita, *Angew. Chem. Int. Ed*, **2008**, 47, 3787
J. Boppisetti and V. Birman, *Org. Lett.*, **2009**, 11, 1221

Oxidative dearomatization reactions

Quideau 2009

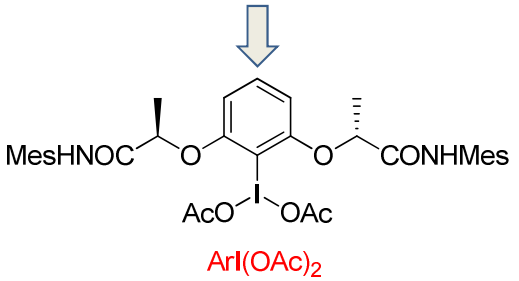


Ishihara 2010



ArI(OAc)$_2$ (1 equiv)
$CHCl_3$, -20°C

R	%Yield	%ee	R	%Yield	%ee
H	70	90	H	55	92
4-Me	85	89	4-Me	59	84
6-OMe	89	90	6-OMe	40	87
3-OMe	87	95	3-OMe	3	88

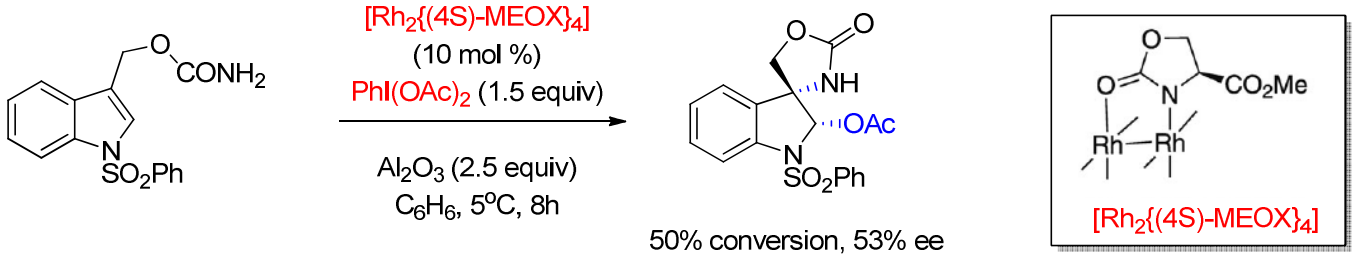


G. Lyvinec, M. Marguerit, K. Bathany, A. Chénedé, S. Quideau, *Angew. Chem. Int. Ed*, **2009**, 48, 4605

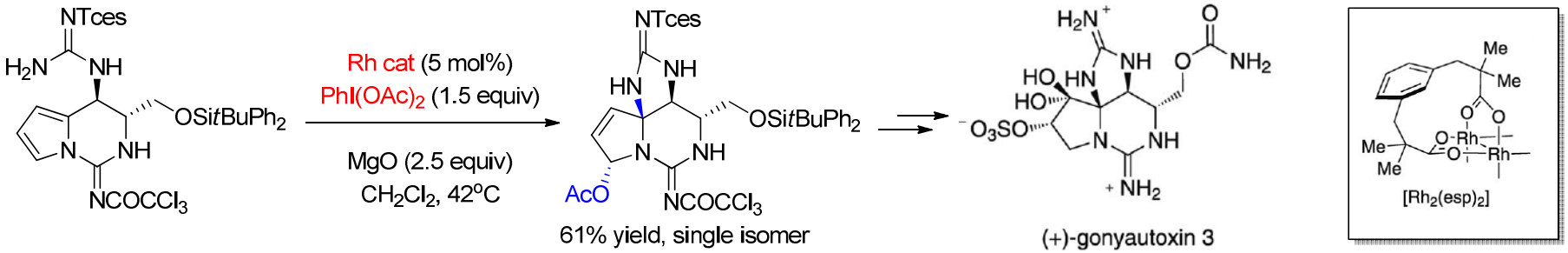
M. Uyanik, T. Yasui, and K. Ishihara, *Org. Lett.*, **2010**, 49, 2175

Oxidative dearomatization reactions

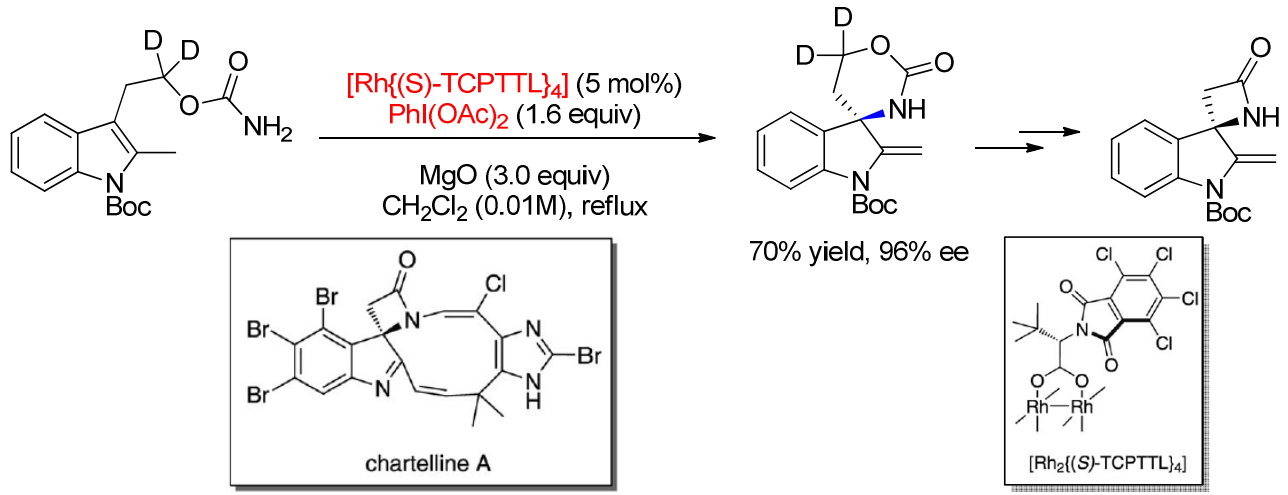
Che 2003



Mulcaphy &
Du Bois 2008



Iwabuchi 2009



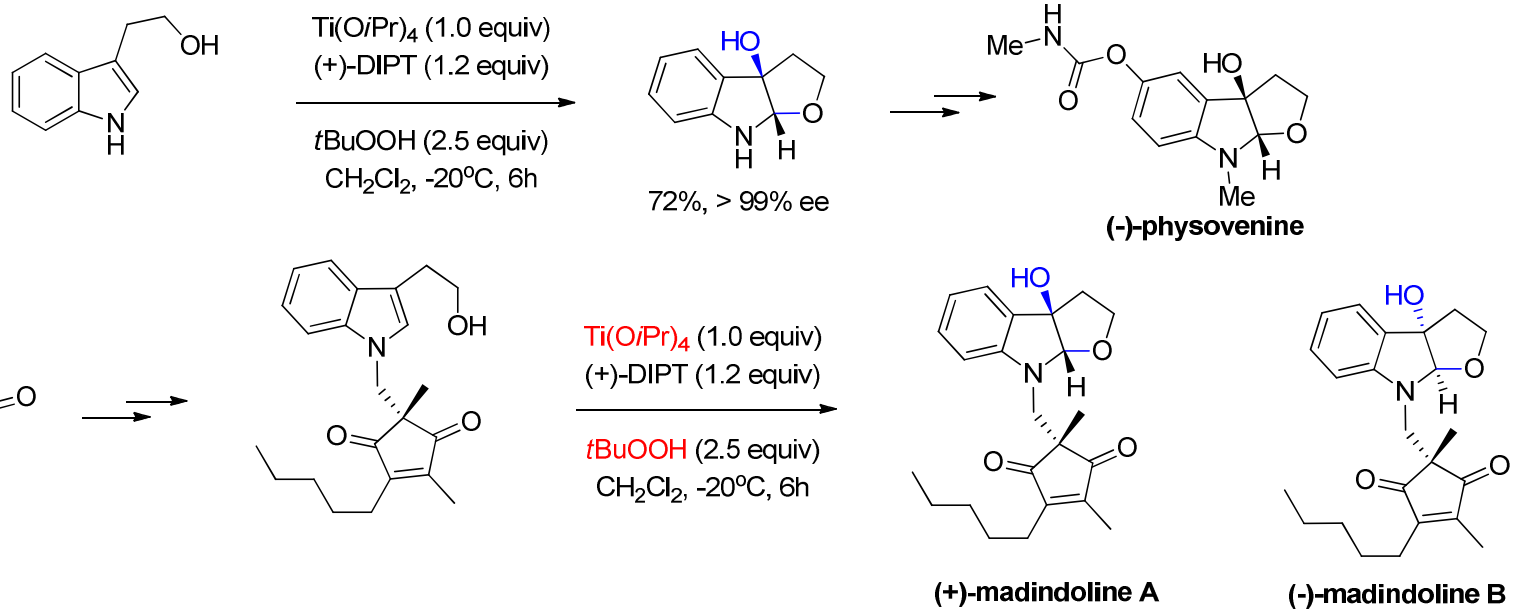
J. Liang, S-X. Yuan, P. W. Hong, Chi-Ming Che, *Tetrahedron Letters*, **2003**, 44, 5917

J. Mulcaphy, J. Du Bois, JACS, **2008**, 130, 12630

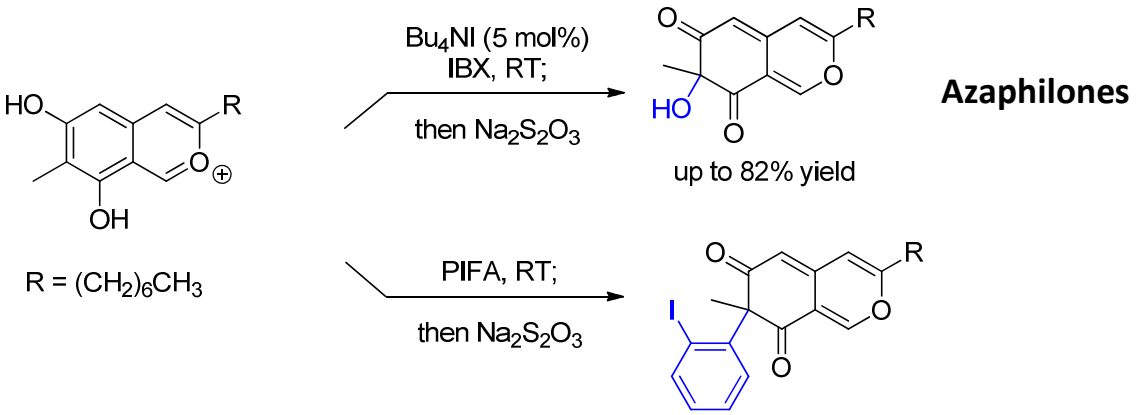
S. Sato, M. Shibuya, N. Kanoh, Y. Iwabuchi, *Chem. Comm.*, **2009**, 6264

Oxidative dearomatization reactions

Omura 2000



Porco 2004

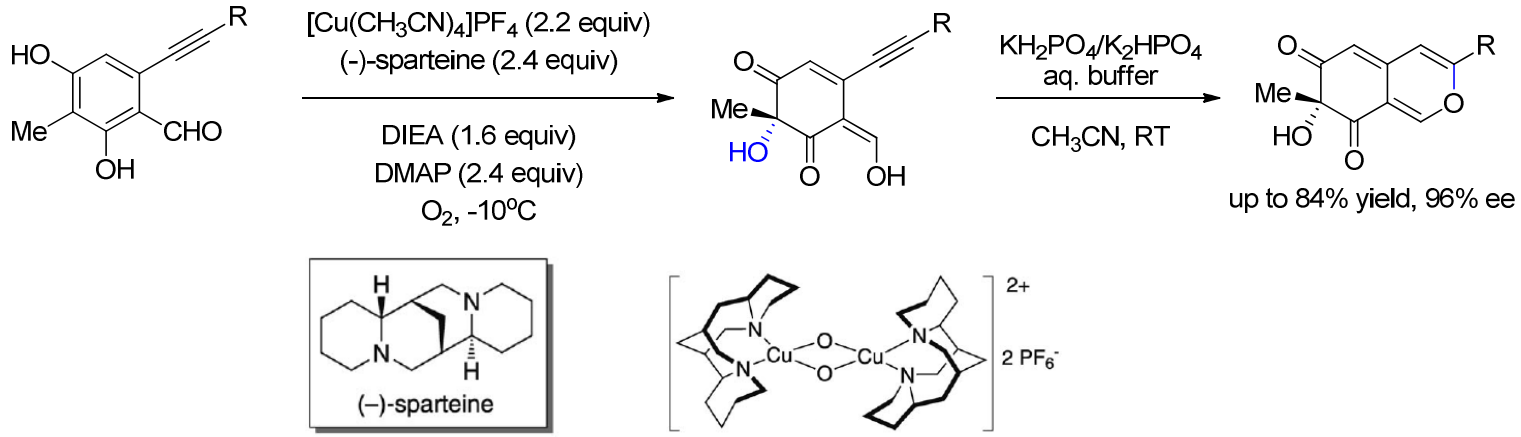


S. Omura et al., *Tetrahedron Letters*, **2000**, 46, 1459 and *JACS*, **2000**, 122, 2122

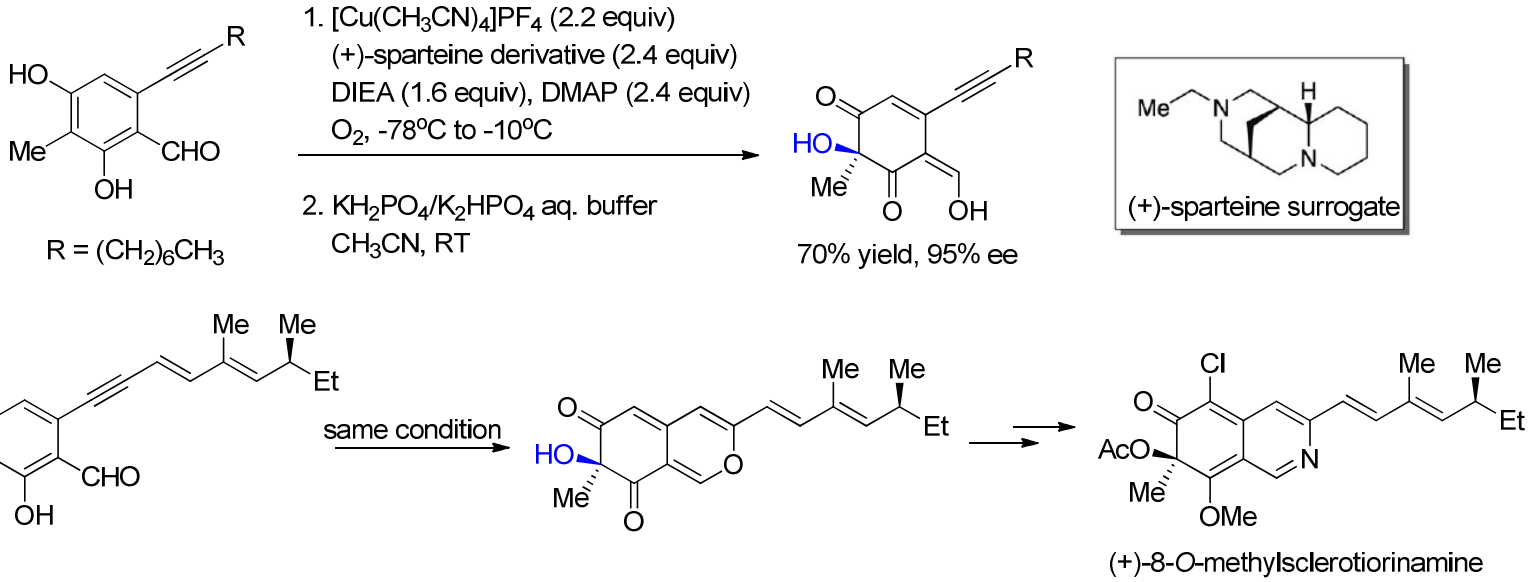
J. Zhu, A. Germain, and J. A. Porco Jr., *Angew. Chem. Int. Ed.*, **2004**, 43, 1239

Oxidative dearomatization reactions

Porco 2005



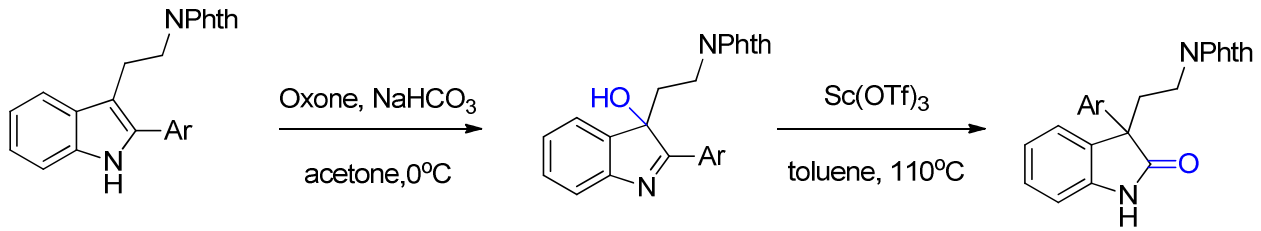
O' Brien 2011

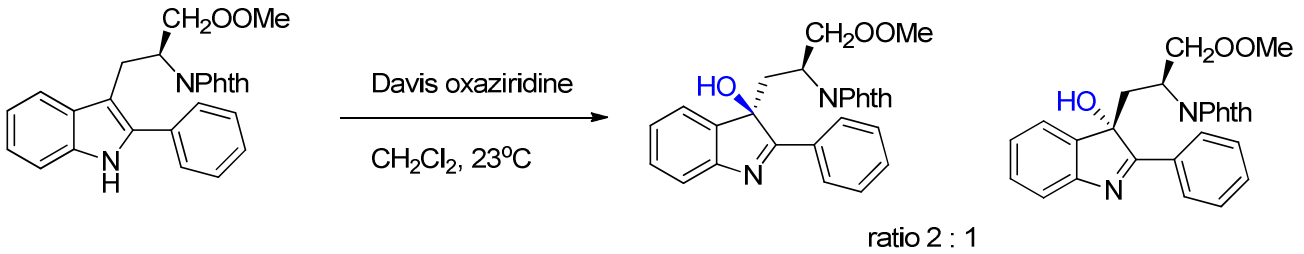


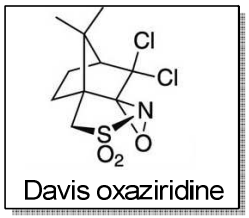
J. Zhu, N. Grigoriadis, J. P. Lee, and J. A. Porco Jr., *JACS*, **2005**, 127, 9342
A. Germain, D. Bruggemeyer, J. Zhu, C. Genet, P. O' Brien, and A. Porco Jr., *JOC,* **2011**, 76, 2577

Oxidative dearomatization reactions

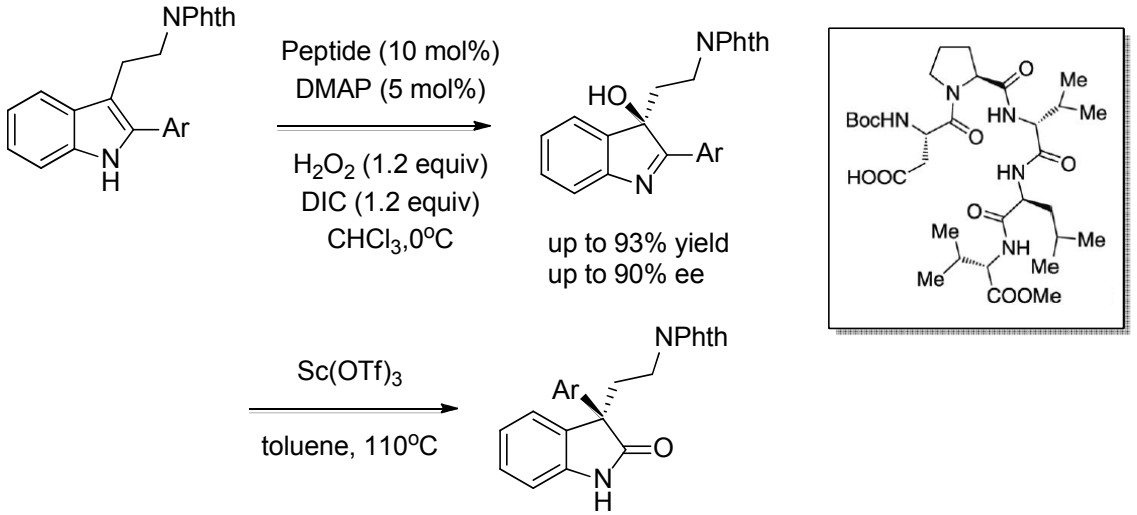
Movassaghi 2008







Movassaghi & Miller, 2011

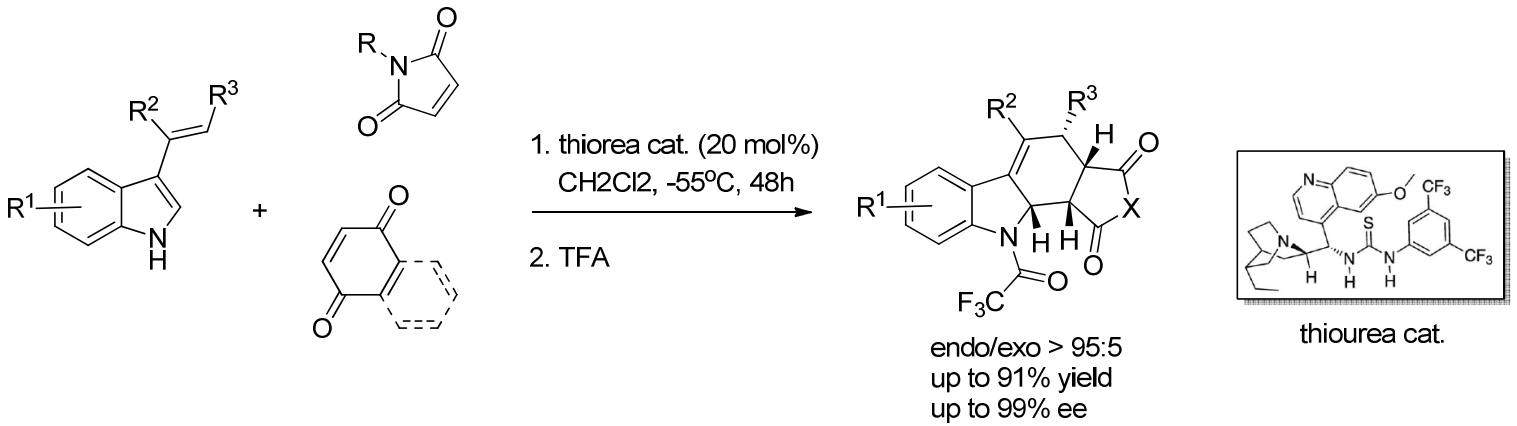


M. Schmidt, J. A. Ashenhurst, M. Movassaghi, *Org. Lett*, **2008**, 18, 4009

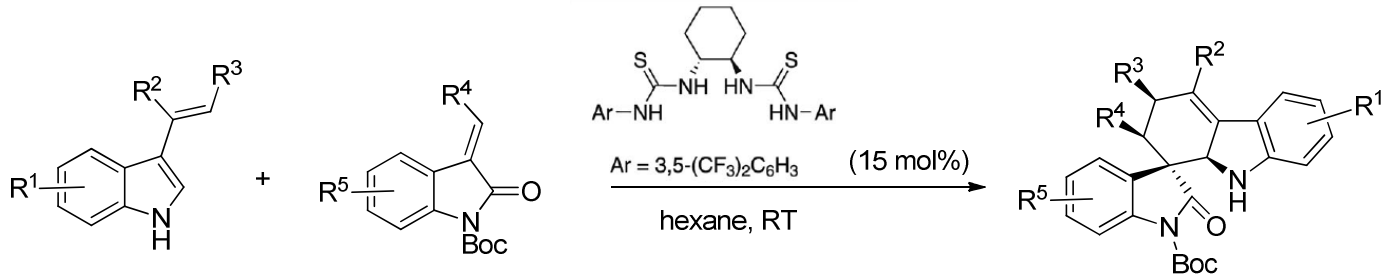
F. Kolundzic, M. Noshi, M. Tjanda, M. Movassaghi, and S. J. Miller, *JACS,* **2011**, 133, 9104

Dearomatization by Diels-Alder and Related reactions

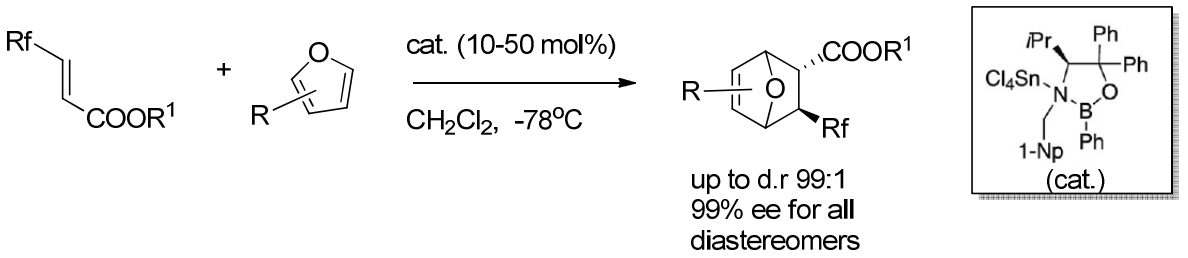
Bernadi & Ricci 2008



Barbas 2011



Futatsugi & Yamamoto 2010



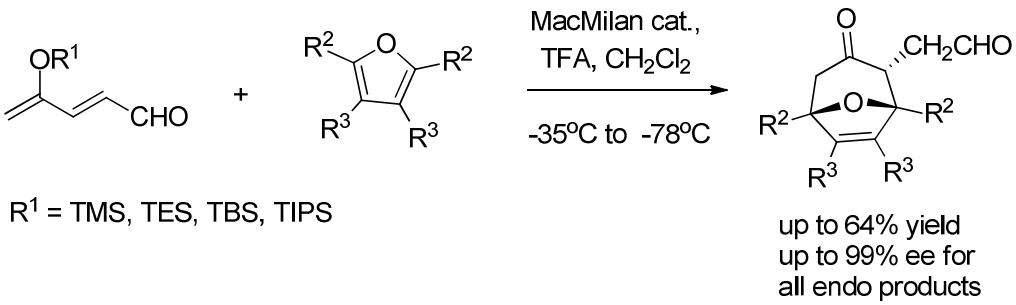
C. Gioia, A. Hauville, L. Bernardi, F. Fini, and A. Ricci, *Angew. Chem. Int. Ed*, **2008**, 47, 9236

B. Tan, G. Hernández-Torres, and C. F. Barbas, *JACS*, **2011**, 133, 12354

K. Shibatomi, K. Futatsugi, F. Kobayashi, S. Iwasa, and H. Yamamoto, *JACS,* **2010,** 132, 5625

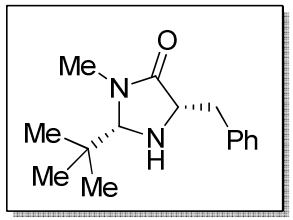
Dearomatization by Diels-Alder and Related reactions

Harmana 2003

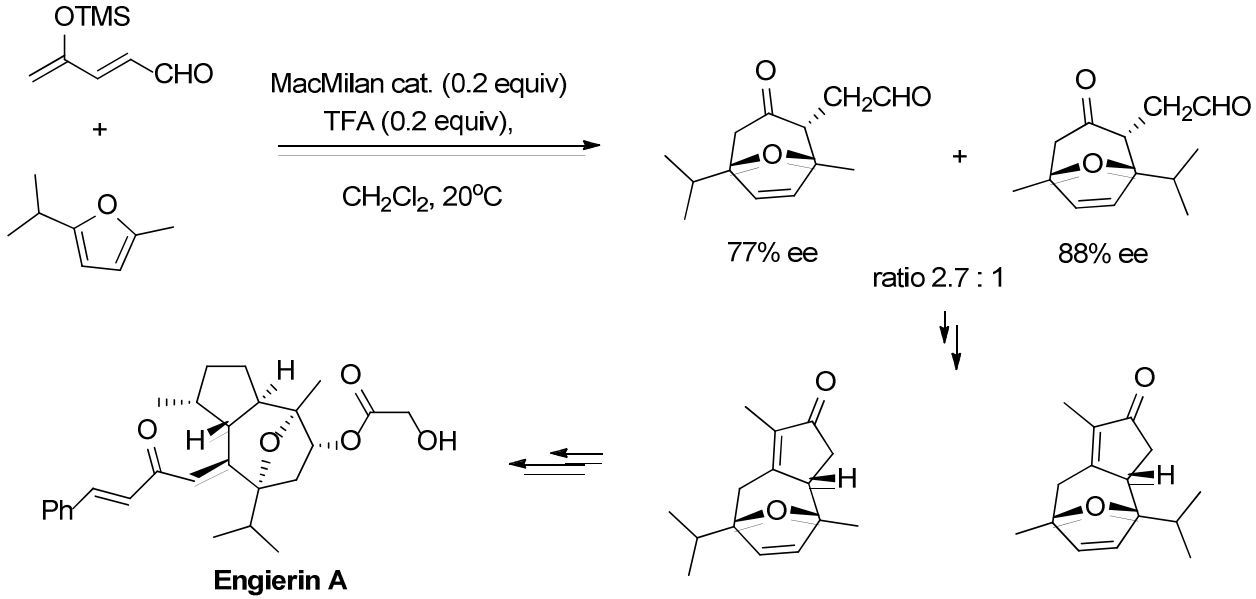


R^1 = TMS, TES, TBS, TIPS

up to 64% yield
up to 99% ee for
all endo products



Sun & Lin 2011

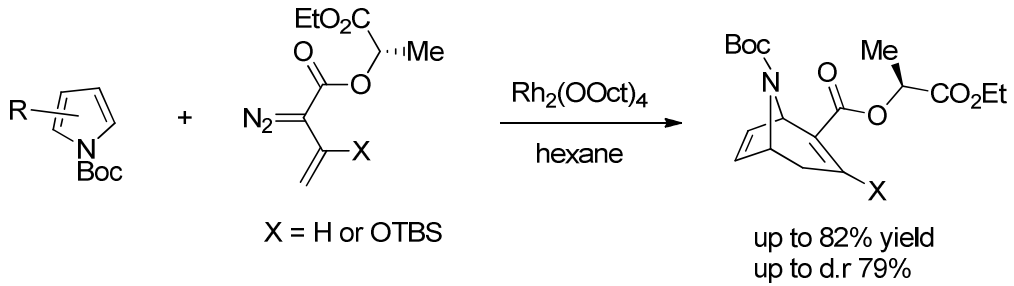


S. Ghosh, X. Hong, S. Wacharasindhu, P. Kirchhoefer, and M. Harmata, *JACS*, **2003**, 125, 2058

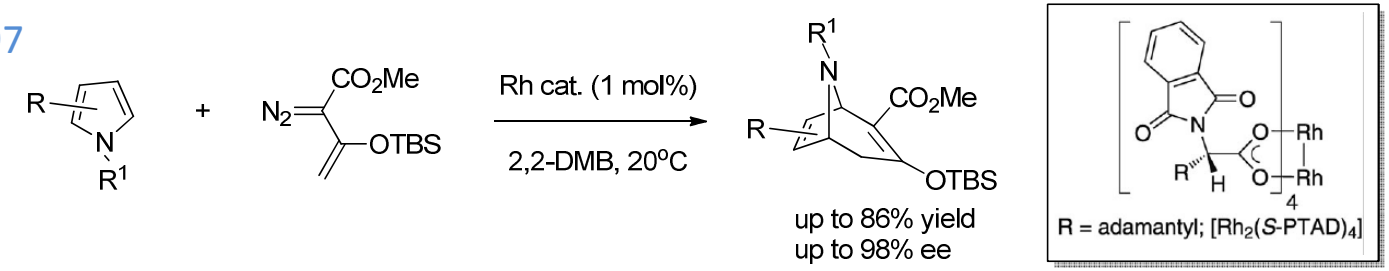
B-F. Sun, C-L. Wang, R. Ding, J-Y. Xu, G-Q. Lin, *Tetrahedron Lett.*, **2011**, 52, 2155

Dearomatization by Diels-Alder and Related reactions

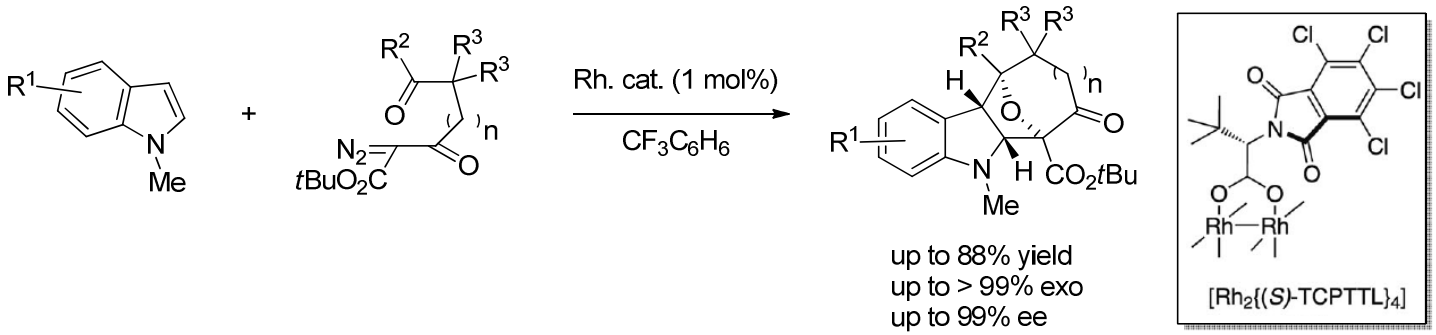
Reddy & Davies 2007



Reddy & Davies 1997



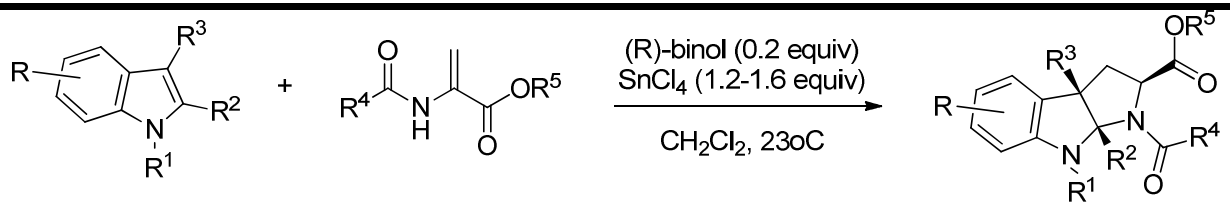
Hashimoto 2011



R. P. Reddy, H. M. Davies, *JACS*, **2007**, 129, 10312, and *JOC*, **1997**, 62, 1095
N. Shimada, T. Oohara, J. Krishnamurthi, H. Nambu, and S. Hashimoto, *Org. Lett.*, **2011**, 13, 6284

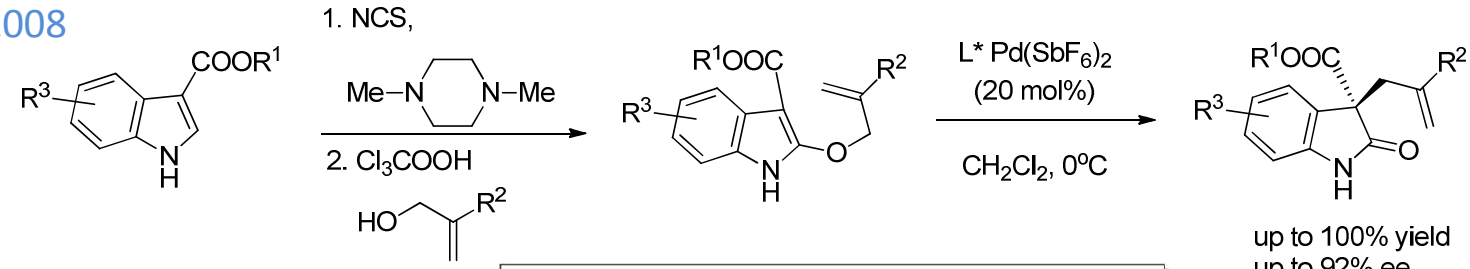
Dearomatization by Diels-Alder and Related reactions

Reisman 2010

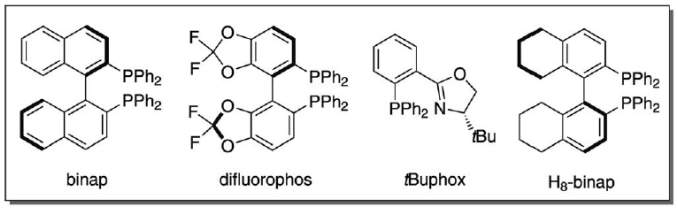


up to 93% yield
up to d.r > 18:1
up to 94% ee (major)
up to 91% ee (minor)

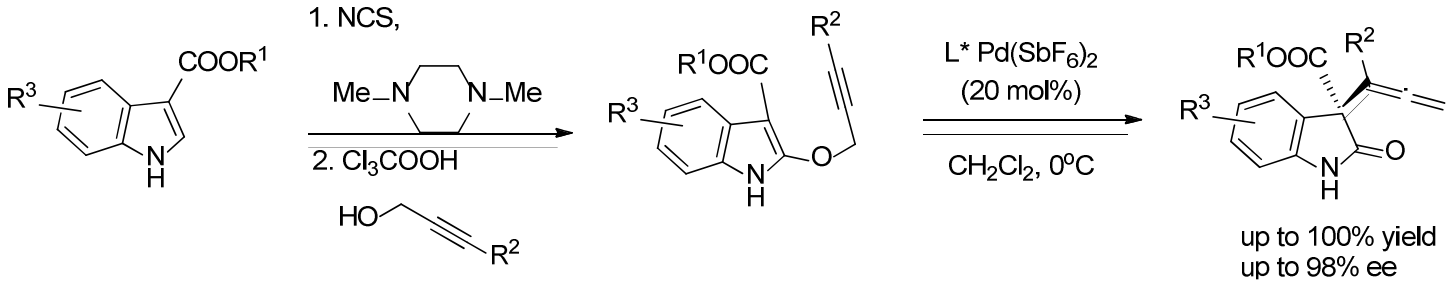
Linton and Kozlowski 2008



up to 100% yield
up to 92% ee



Linton and Kozlowski 2012

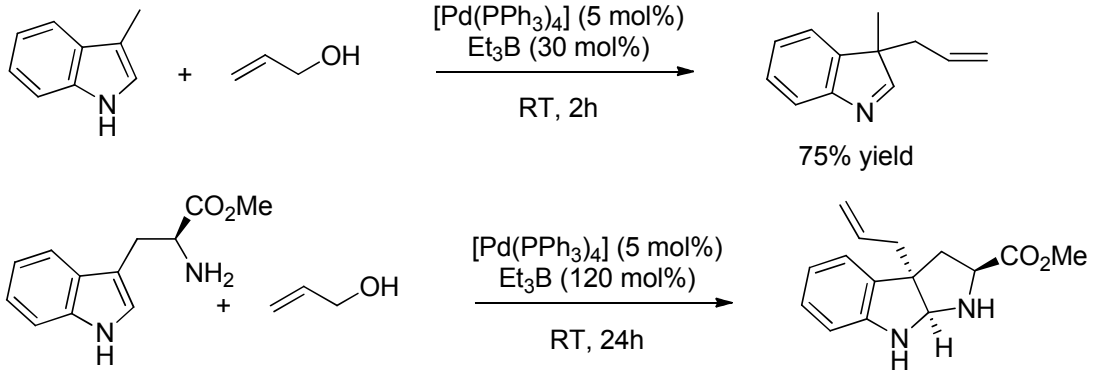


up to 100% yield
up to 98% ee

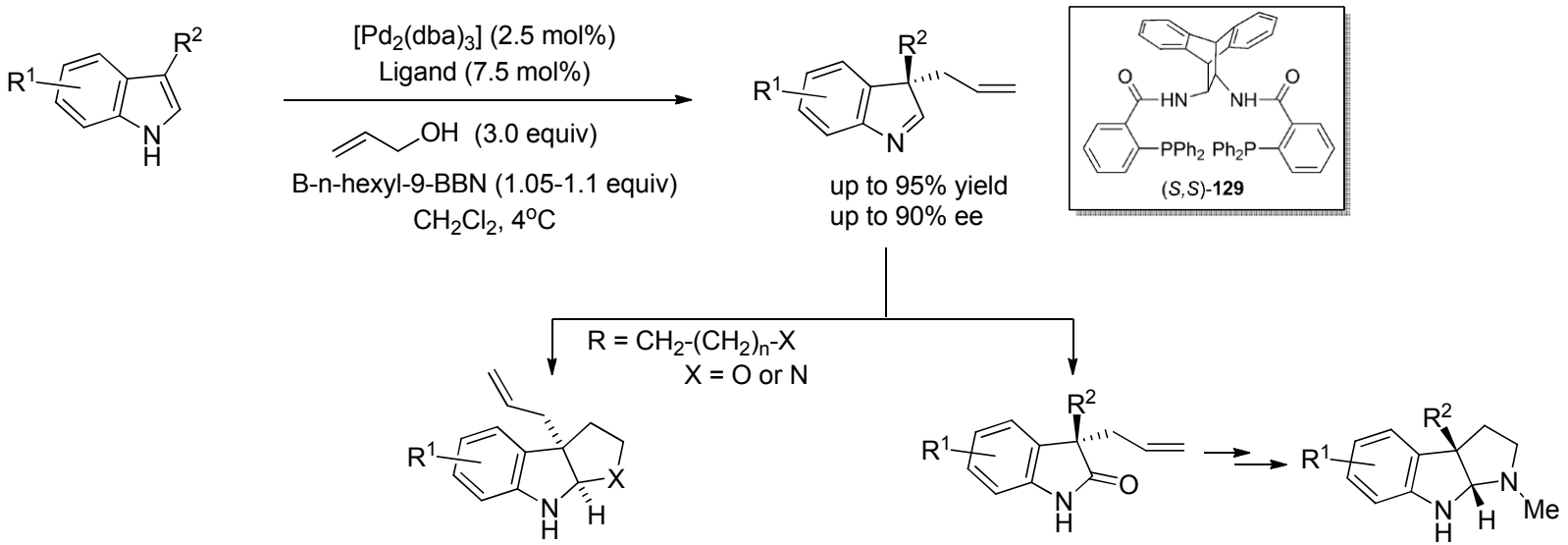
L. Repka, J. Ni, and S. E. Reisman, *JACS*, **2010**, 132, 14418
E. Linton, M. C. Kozlowski, *JACS*, **2008**, 130, 16163 and *Angew. Chem. Int. Ed.*, **2012,** 51, 2448

Transition-Metal-Catalyzed Dearomatization Reactions

Tamaru and Kimura 2005



Trost and Quancard 2005

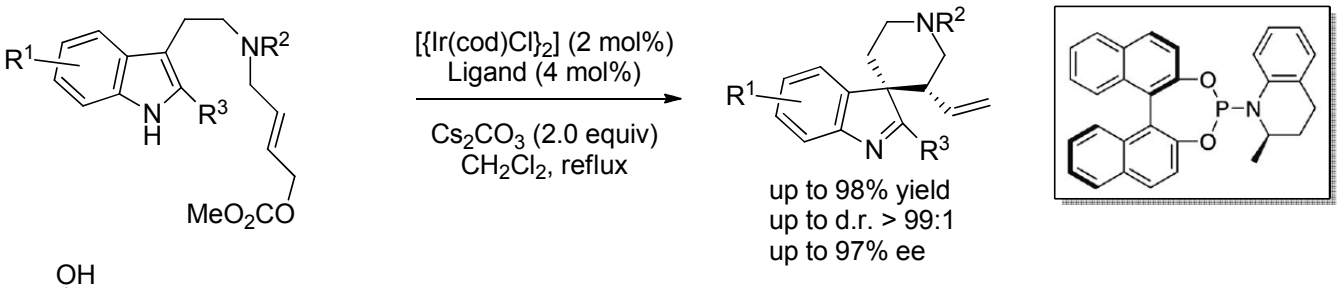


R. Mukai, M. Futamata, S. Tanaka, Y. Tamaru, and M. Kimura, *JACS*, **2005**, 127, 4592

J. Quancard, B. M. Trost, *JACS*, **2006**, 128, 6314

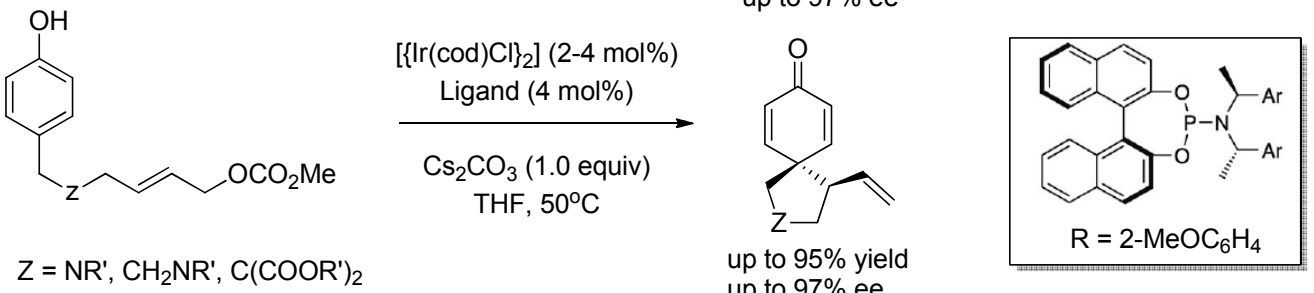
Transition-Metal-Catalyzed Dearomatization Reactions

You 2010

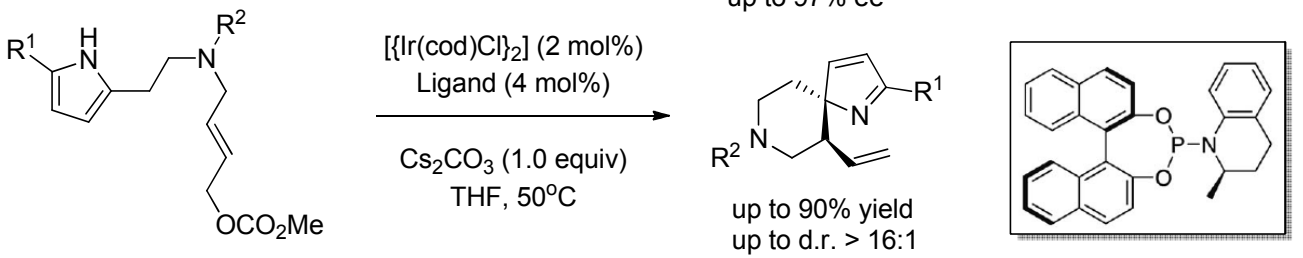


up to 98% yield
up to d.r. > 99:1
up to 97% ee

You 2011

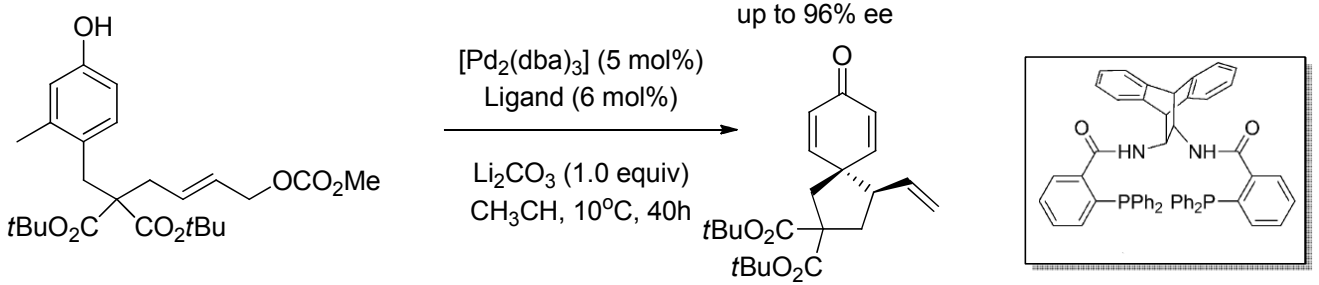


Z = NR', CH_2NR', $C(COOR')_2$



up to 90% yield
up to d.r. > 16:1
up to 96% ee

Hamada 2010



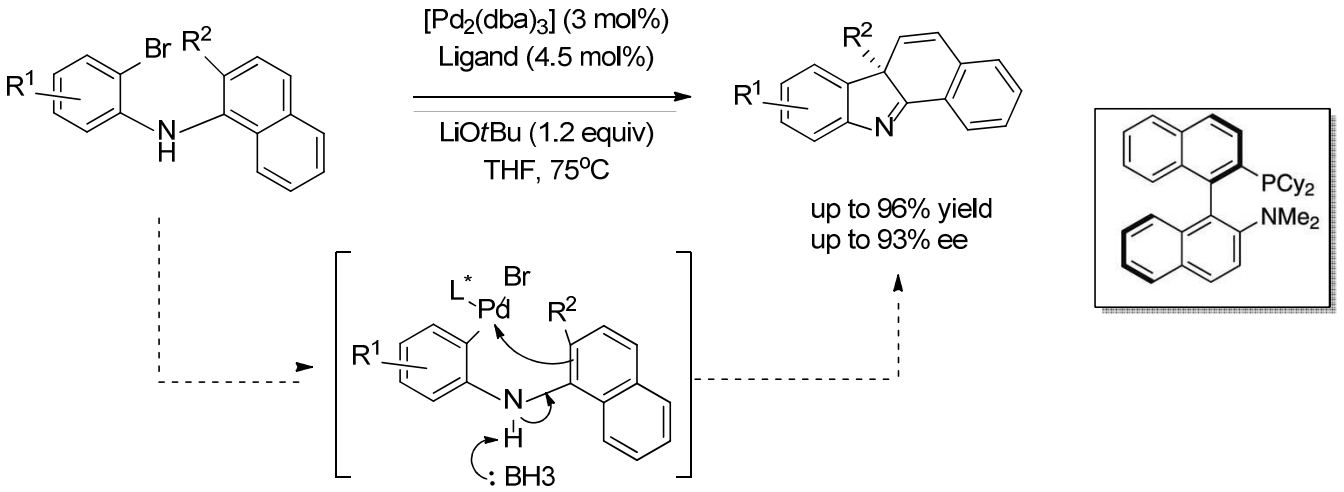
80% yield, d.r. 9.2:1, 89% ee

Q-F. Wu, H. He, W-B. Liu, S-L. You, *JACS*, **2010**, 132, 11418 and *Angew. Chem. Int. Ed*, **2011**, , 50, 4455

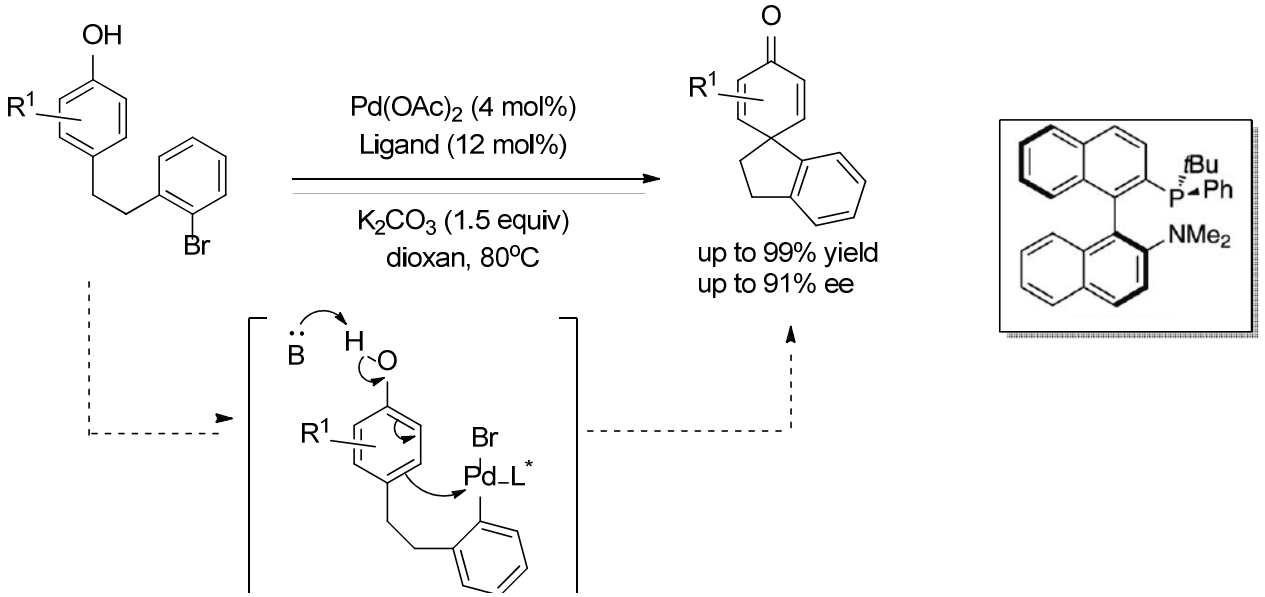
T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno, M. Kanematsu, and Y. Hamada, *Org. Lett.*, **2010**, 12, 5020

Transition-Metal-Catalyzed Dearomatization Reactions

Buchwald 2009

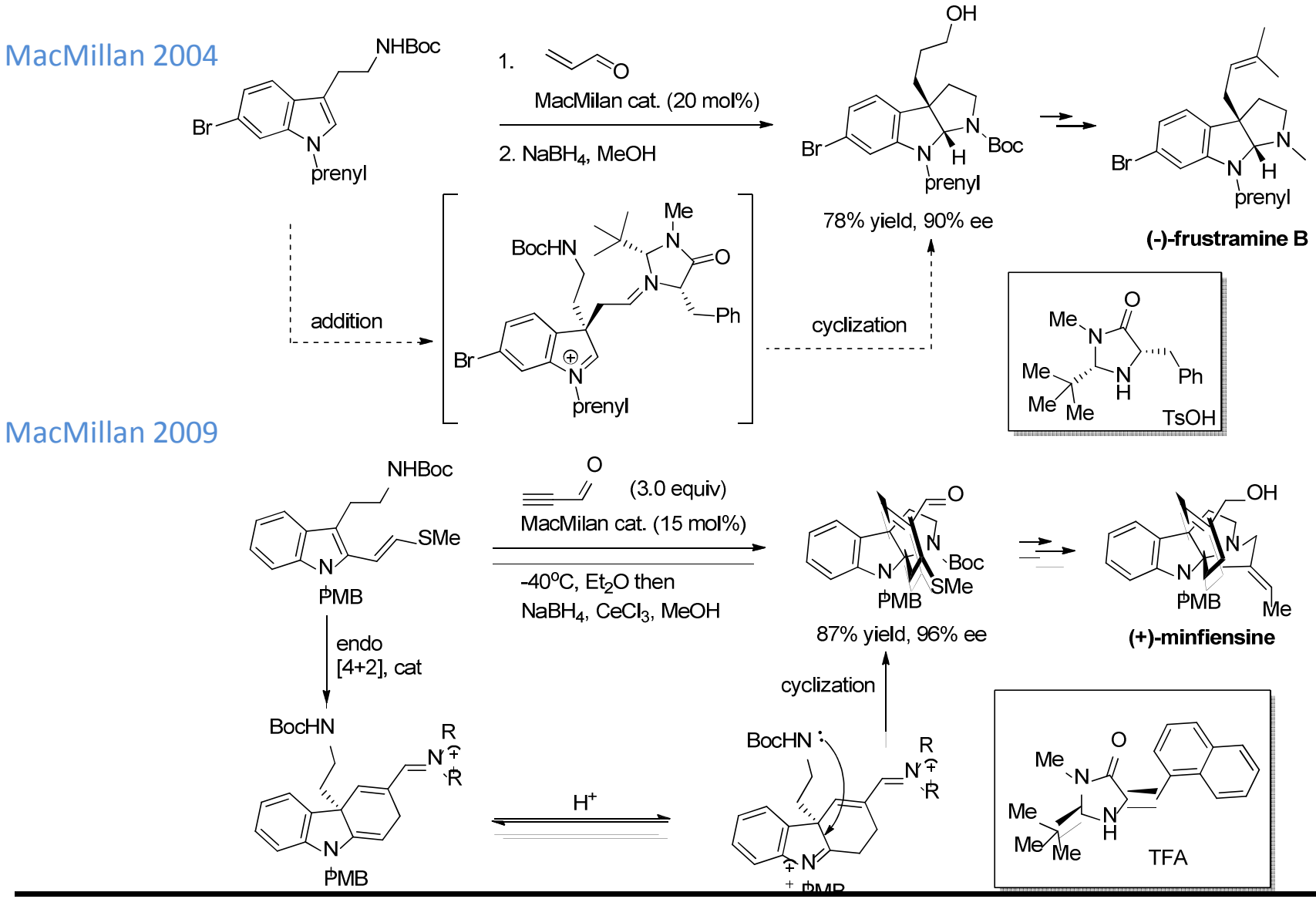


Buchwald 2011



J. Garcia-Fortanet, F. Kessler and S. L. Buchwald, *JACS*, **2009**, 131, 6676
S. Rousseaux, J. Garcia-Fortanet, M. A. Del Aguila Sanchez, and S. L. Buchwald, *JACS*, **2011**, 132, 9282

Cascade Asymmetric Dearomatization Sequences

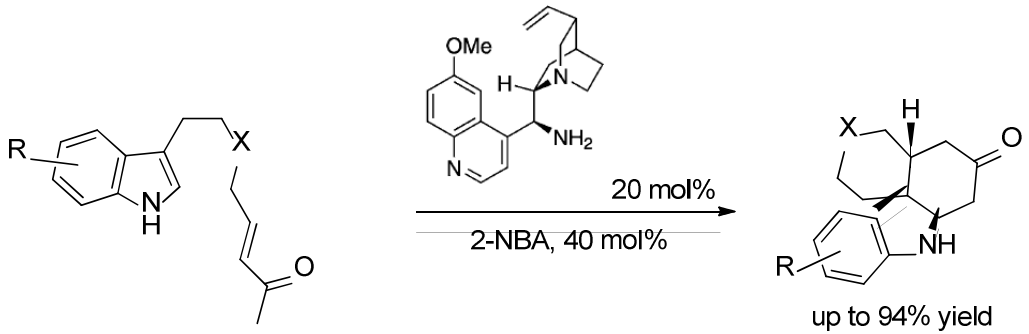


J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, 101, 5482–5487

S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, 131, 13606–13607

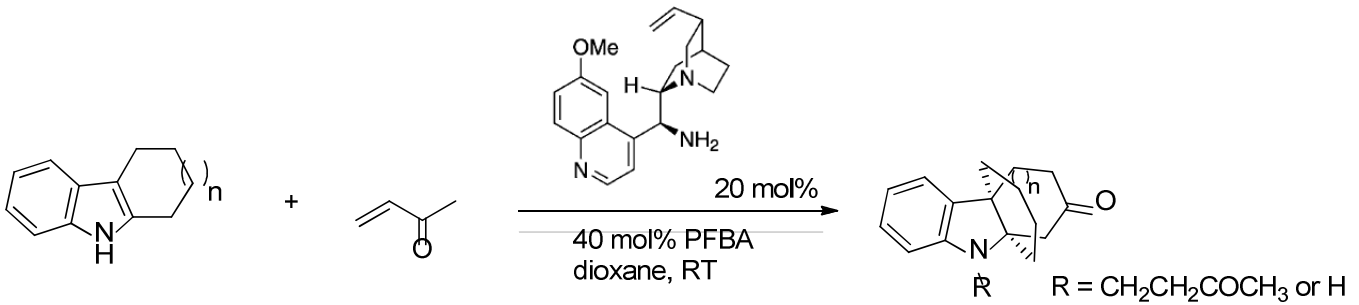
Cascade Asymmetric Dearomatization Sequences

You 2011



up to 94% yield
up to d.r. > 95:5
up to 99% ee

You 2012



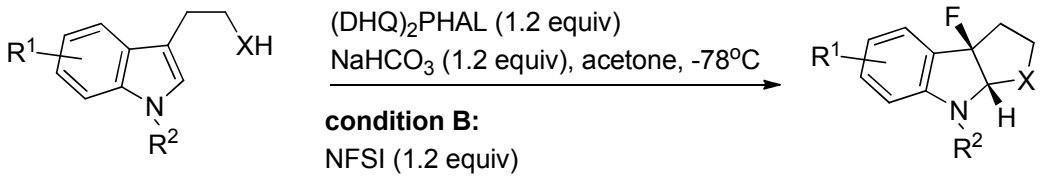
up to 98% yield
up to 98% ee

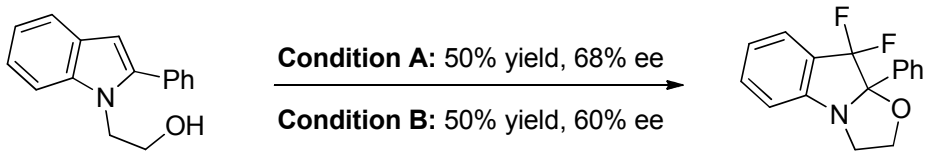
Michael/Manich cyclization cascade

Q. Cai, C. Zheng, S.-L. You, *Angew. Chem. Int. Ed.* **2011**, 50, 8665–8669
Q. Cai, S.-L. You, *Org. Lett.* **2012**, 14, 3040–3043.

Cascade Asymmetric Dearomatization Sequences

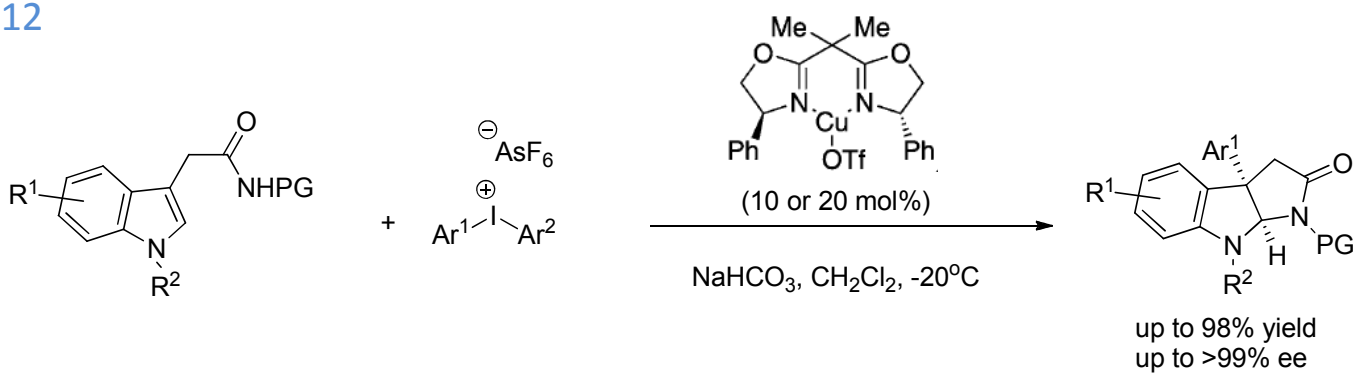
Gouverneur 2012





Fluorocyclization cascade

MacMillan 2012

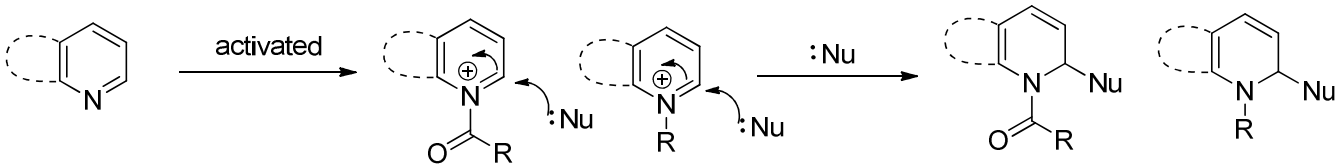


Arylation-cyclization cascade

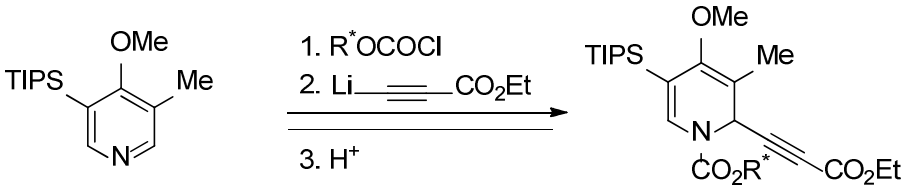
O. Lozano, G. Blessley, T. M. del Campo, A. Thompson,R. Borman, V. Gouverneur, *Angew. Chem. Int. Ed*, **2011**, 50, 8255
S. Zhu, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2012**, 134, 10815–10818.

Nucleophilic Dearomatization Reactions of Electron-Deficient Aromatic Rings

Electron-Deficient aromatic rings need to be activated

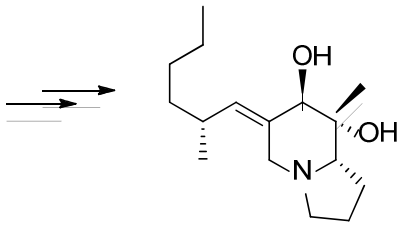


Comins 2001



70% yield, d.r. > 96%

R* = (+)-trans-2-(α-cumyl)-cyclohexyl

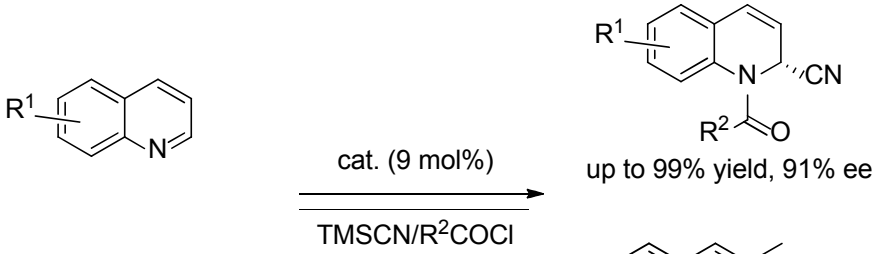


(+)-allopumiliotoxin 267A

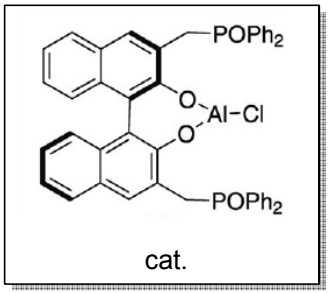
D. L. Comins, S. Huang, C. L. McArdle, C. L. Ingalls, *Org. Lett.* **2001**, 3, 469–471.

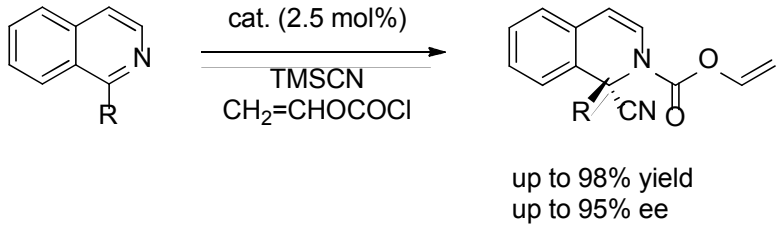
Nucleophilic Dearomatization Reactions of Electron-Deficient Aromatic Rings

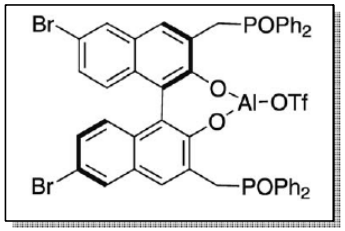
Shibasaki 2000



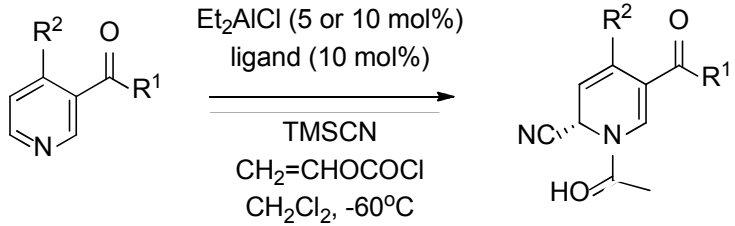
Shibasaki 2001

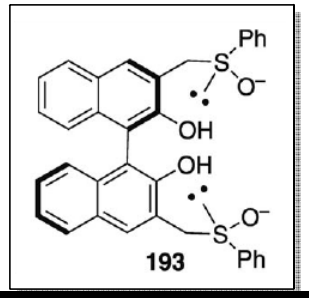






Shibasaki 2004

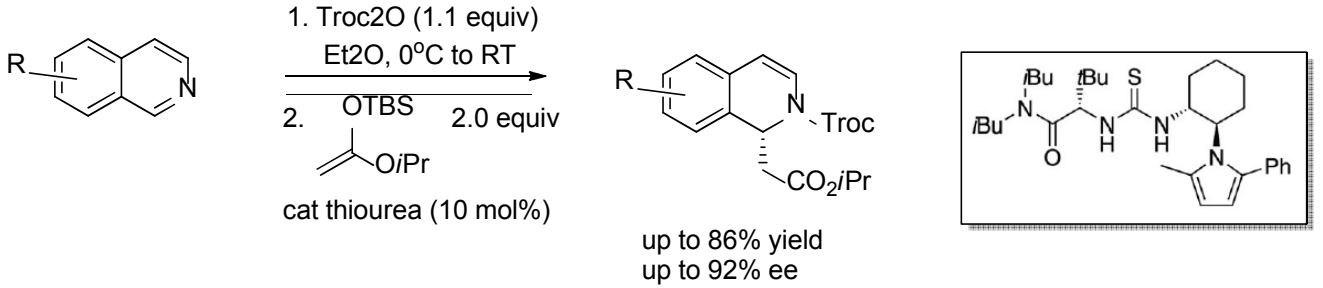




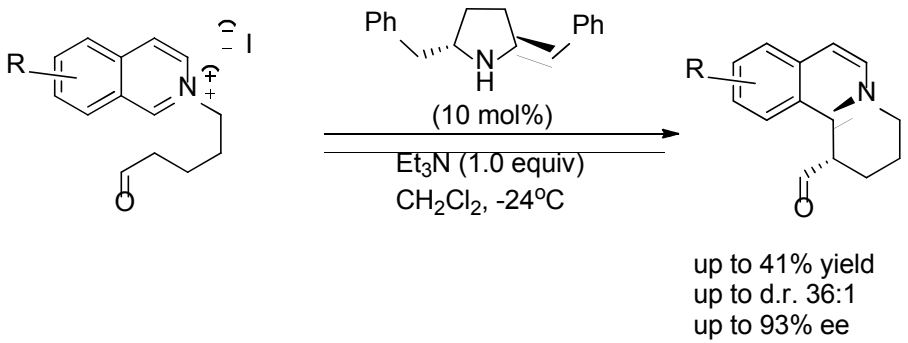
M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, 122, 6327–6328; J. Boppisetti and V. *E.* Ichikawa, M. Suzuki, K. Yabu, M. Albert, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, 126, 11808–11809

Nucleophilic Dearomatization Reactions of Electron-Deficient Aromatic Rings

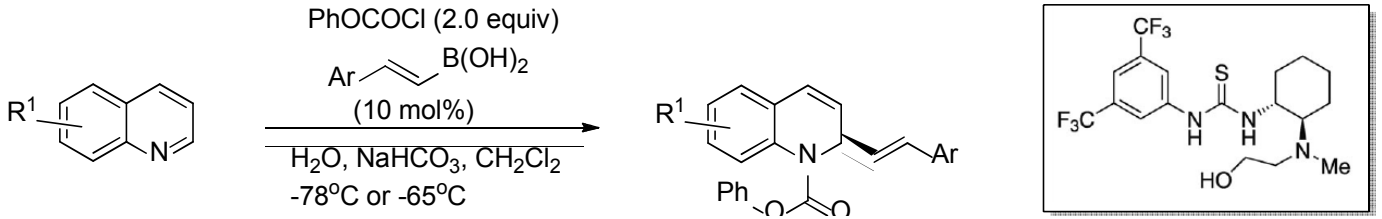
Jacobsen 2005



Jørgensen 2005



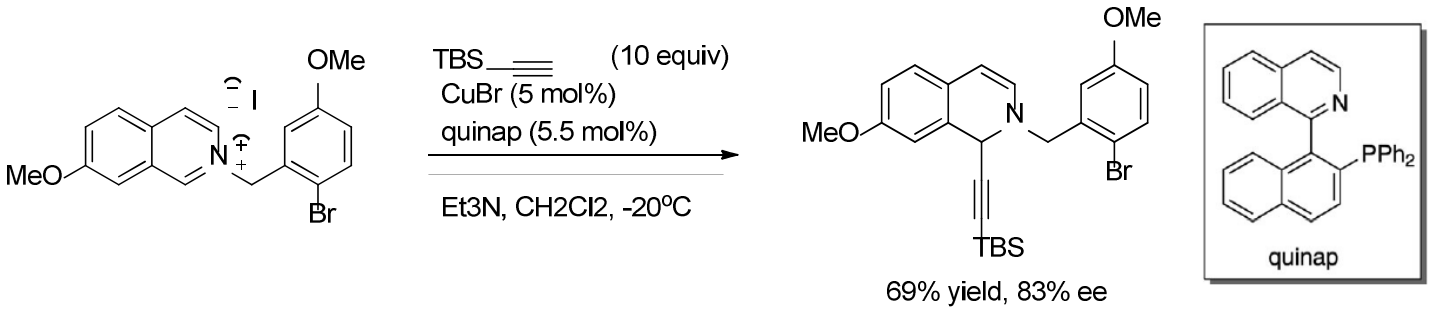
Takemoto 2007



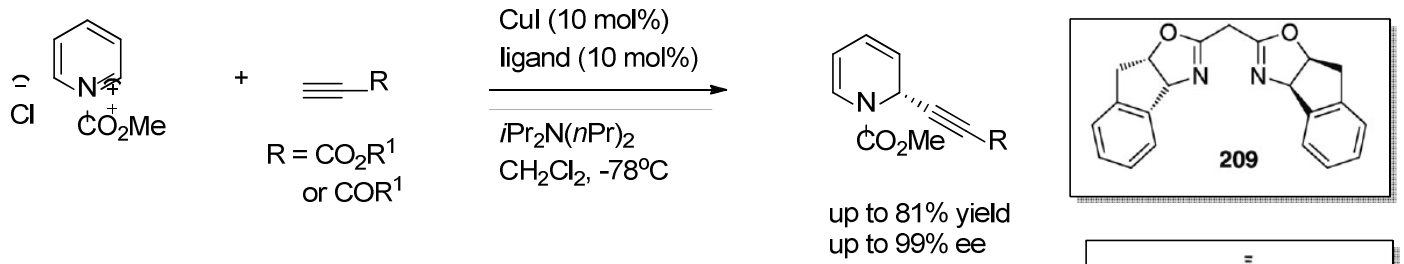
M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, 44, 6700–6704
K. Frisch, A. Landa, S. Saaby, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, 44, 6058–6063
Y. Yamaoka, H. Miyabe, Y. Takemoto, *J. Am. Chem. Soc.* **2007**, 129, 6686–6687.

Nucleophilic Dearomatization Reactions of Electron-Deficient Aromatic Rings

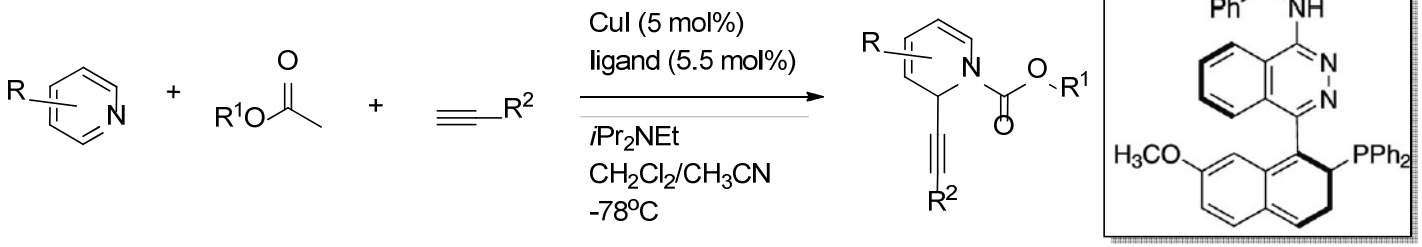
Taylor and Schreiber 2006



Ma 2007



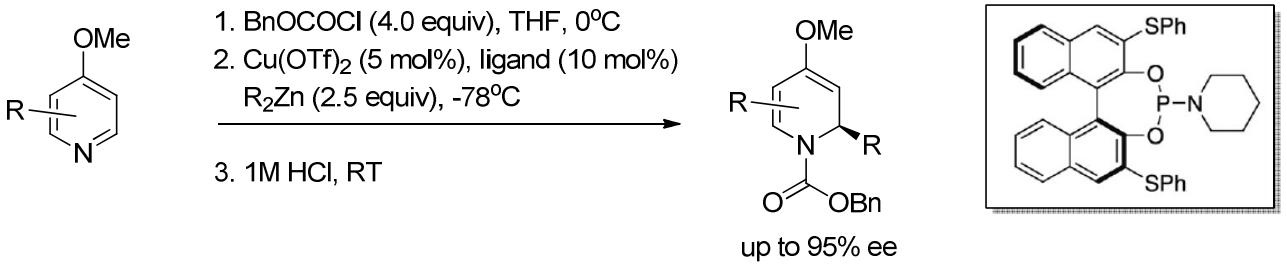
Arndtsen 2008



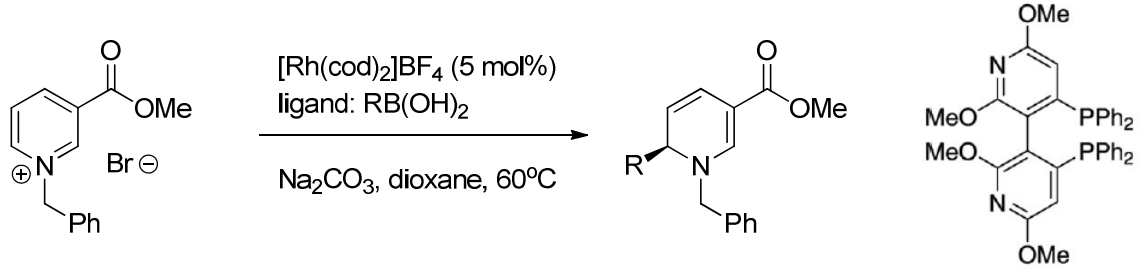
A. M. Taylor, S. L. Schreiber, *Org. Lett.* **2006,** 8, 143–146.
Z. Sun, S. Yu, Z. Ding, D. Ma, *J. Am. Chem. Soc.* **2007**, 129, 9300–9301
D. A. Black, R. E. Beveridge, B. A. Arndtsen, *J. Org. Chem.* **2008**, 73, 1906–1910.

Nucleophilic Dearomatization Reactions of Electron-Deficient Aromatic Rings

Feringa 2009



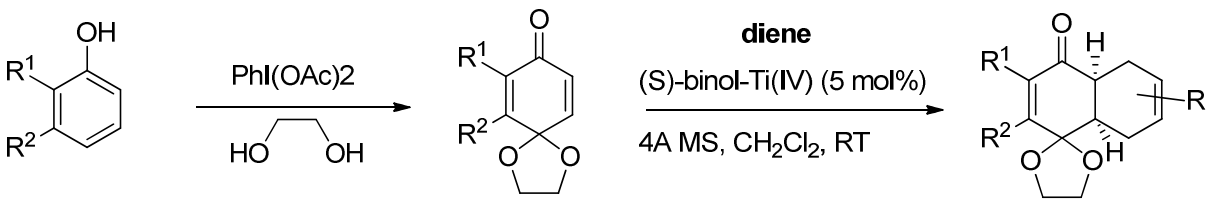
Nadeua 2011

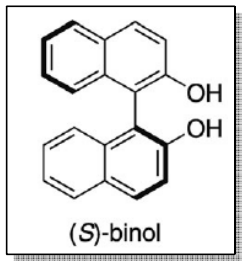


M. Á. Fernández, B. Maciá, M. G. Pizzuti, A. J. Minnaard, B. L. Feringa, *Angew. Chem. Int. Ed.* **2009**, 48, 9339–9341.
C. Nadeau, S. Aly, K. Belyk, *J. Am. Chem. Soc.* **2011**, 133, 2878–2880.

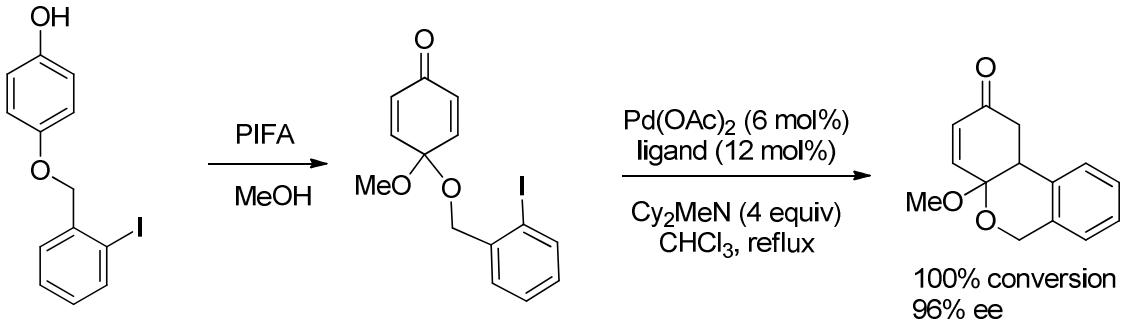
Stepwise strategy: Dearomatization/Asymmetric Catalysis

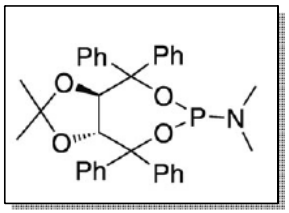
Corey 2001



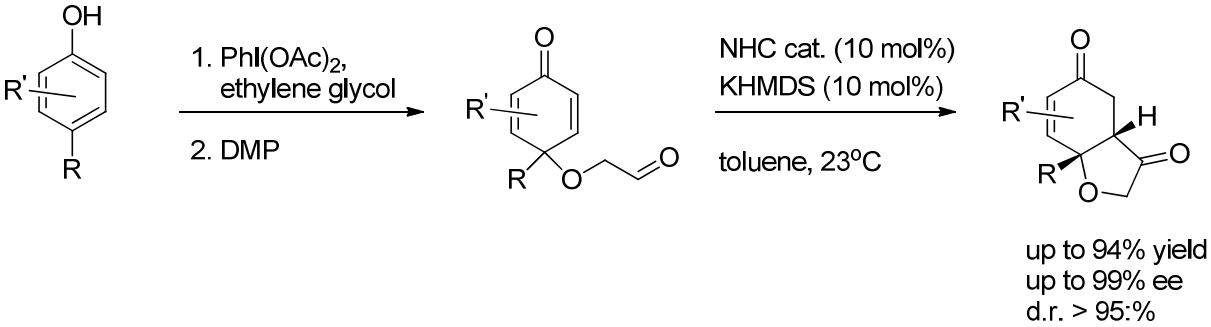


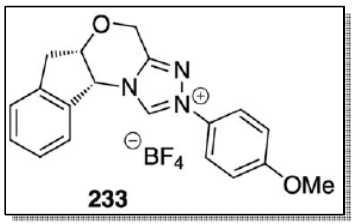
Feringa 2002





Liu and Rovis 2001

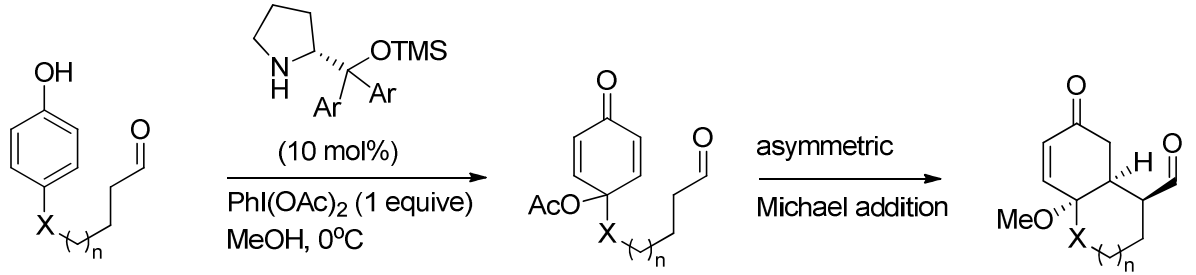




M. Breuning, E. J. Corey, *Org. Lett.* **2001**, 3, 1559–1562.
R. Imbos, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2002**, 124, 184–185
Q. Liu, T. Rovis, *J. Am. Chem. Soc.* **2006**, 128, 2552–2553;

Stepwise strategy: Dearomatization/Asymmetric Catalysis

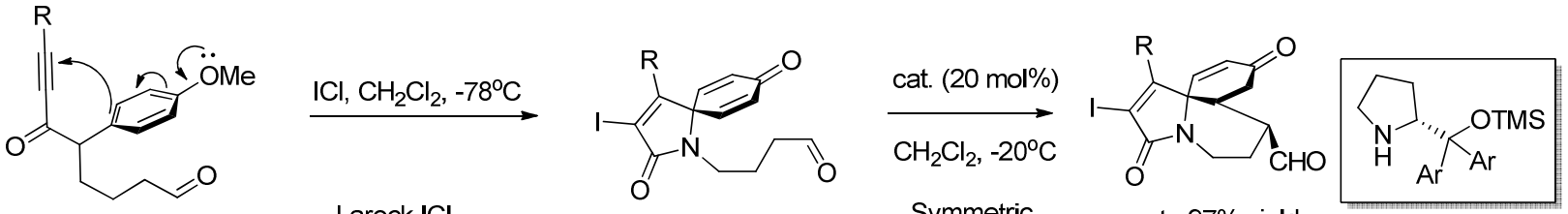
Gaunt 2008



X = C, O, NTs
n = 0, 1, 2

up to 84% yield
up to 99% ee
d.r. > 20:1

Gaunt 2011

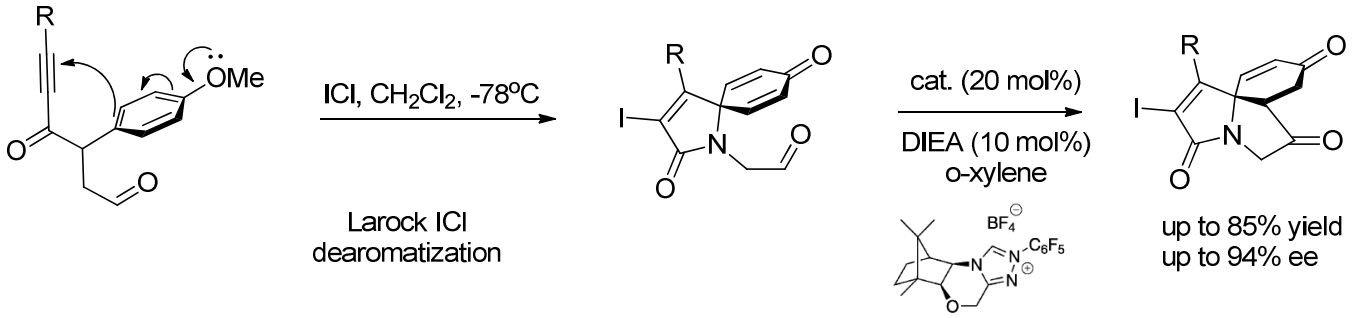


Larock ICl dearomatization

Symmetric Michael reaction

up to 97% yield
up to 97% ee
d.r. > 20:1

You 2012

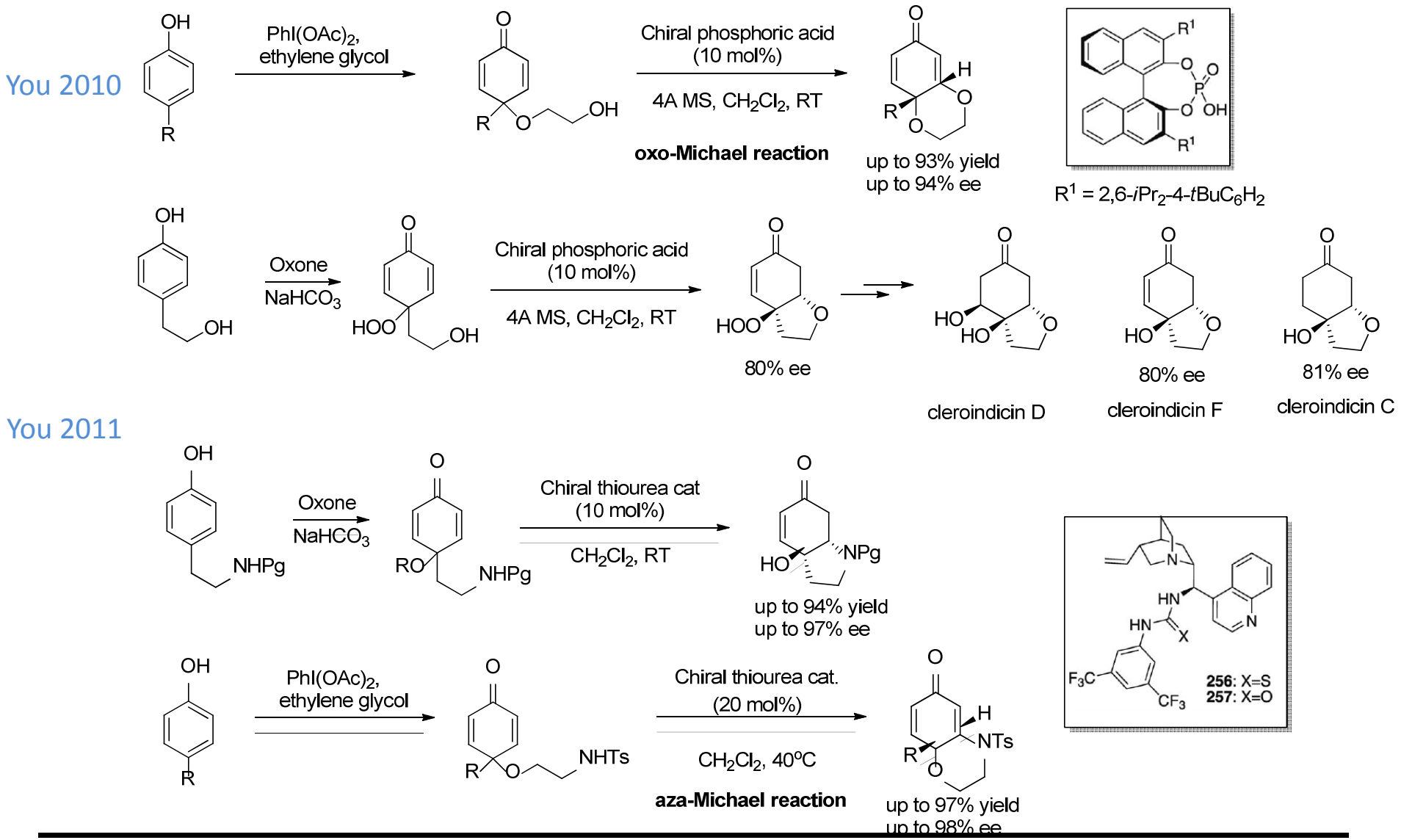


Larock ICl dearomatization

up to 85% yield
up to 94% ee

N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.* **2008,** 130, 404–405
R. Leon, A. Jawalekar, T. Redert, M. J. Gaunt, *Chem. Sci.* **2011**, 2, 1487–1490
M.-Q. Jia, S.-L. You, *Chem. Commun.* **2012**, 48, 6363–6365.

Stepwise strategy: Dearomatization/Asymmetric Catalysis



Q. Gu, Z.-Q. Rong, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2010**, 132, 4056–4057 and *Chem. Sci.* **2011**, 2, 1519–1522;

Conclusion

- **One of the most efficient methods**
- **Great potential as a practical application in synthesis of natural products**

However…

- **Limited to electron-rich aromatic rings**
- **Activation is necessary for electron-poor aromatic rings**
- **Simples arenes are not compatible**

THANK YOU FOR YOUR ATTENTION

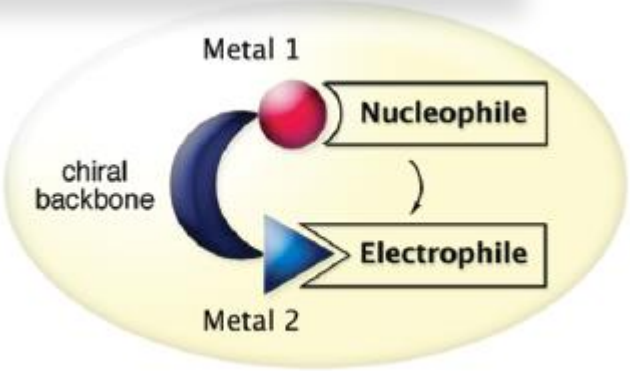
Frontiers in Chemical Synthesis III:
Stereochemistry

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Synergism between metals in asymmetric additions onto carbonyl compounds

Michele Boghi

2013



Outline

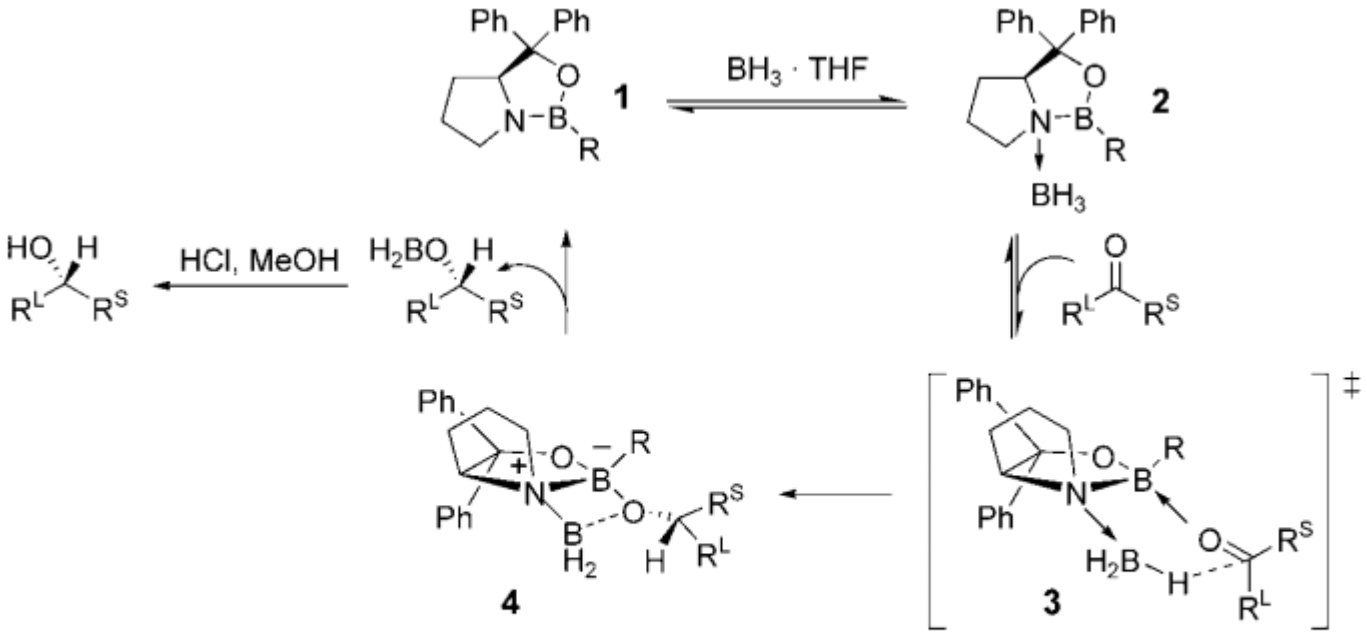
- **Introduction**
  - Dual Activation (electrophile/nucleophile)
  - Cooperative Bimetallic system

- **Types of bimetallic asymmetric catalysts**
  - Classification
  - Relevant examples

- **Catalytic Asymmetric Alkylation of Carbonyl Compounds**
  - *Noyori*
  - *Kozlowski*
  - *Shibasaki*

- **Catalytic Asymmetric Aldol, Mannich-type, 1,4-Addition Reactions**
  - *Trost*
  - *Shibasaki*

Borane-Mediated asymmetric **reduction** of carbonyl compounds (CBS reduction): excellent example of **dual activation**



Scheme 1. Proposed mechanism for the CBS reduction of ketones. R = H, *n*-alkyl, allyl, aryl, 3-phenylpropyl, cyclohexyl, β-branched substituents with or without stereogenic centers, trialkylsilyl methyl.

- BH_3 activated by the *N*-**Lewis Base** of the oxazaborilidine
- Carbonyl activated by the *B*-**Lewis Acid**
- Minimization of the the steric interactions between the R^L of the ketone and the R-oxazaborilidine via a 6-membered TS
- High chemo- and **stereo**- selectivity

The dual activation occurs at positions controlled by an asymmetric environment, and so nucleophiles react with electrophiles from a defined direction, resulting in high enantioselectivity.

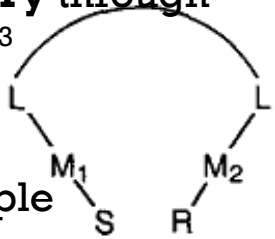
1) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**,109,7925-7926. (2) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, 37, 1987-2012.

Introduction

Conventional metal-based catalysts consist of a **single metal center** equipped with proper chiral ligands.

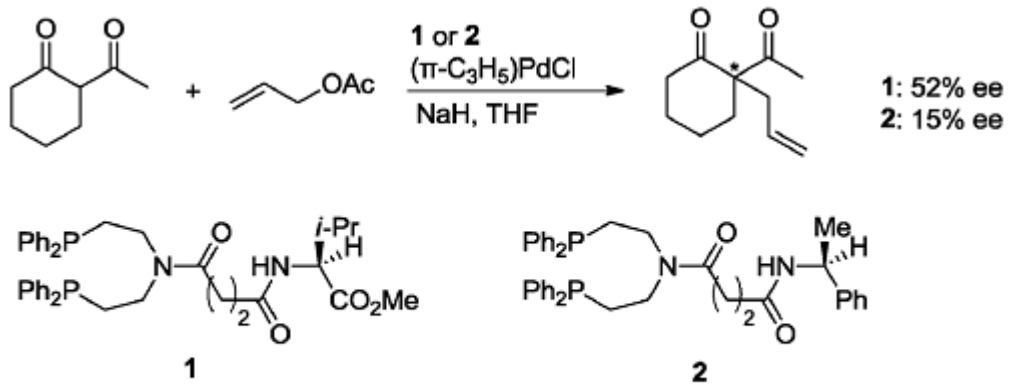
Single activation of one reactant is generally attributed to the observed catalytic activity

Synergistic, cooperative activation through multiple metal centers can be often found in enzyme biocataysts.[1] **Exceptional effiency and selectivity** can be obtained by holding **two** reaction partners in **optimal geometry** through **non-covalent** bonding inetractions.[2,3]



Simultaneously activation of multiple reacting species.

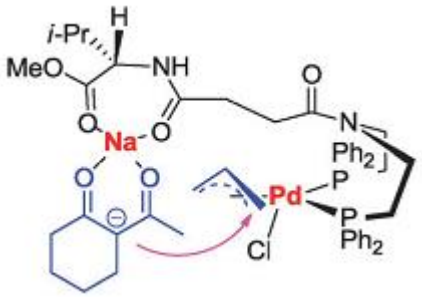
Pioneering work (Kumada): Asymmetric palladium catalyzed allylic alkylation of 1,3-diketone[4]



Scheme 1 Enantioselective allylic alkylation.

Additional chelation control unit, in the proper distance, of the nucleophile through the **alkali metal cation**.

Proposed mechanism



(1) E. K. van den Beuken and B. L. Feringa, *Tetrahedron*, **1998**, *54*, 12985–13011. (2) G. J. Rowlands, *Tetrahedron*, **2001**, *57*, 1865–1882. (3) J.-A. Ma and D. Cahard, *Angew. Chem., Int. Ed.*, **2004**, *43*, 4566–4583. (4) T. Hayashi, K. Kanehira, H. Tsuchiya and M. Kumada, *Chem. Commun.*, **1982**, 1162–1164

Types of bimetallic catalysts

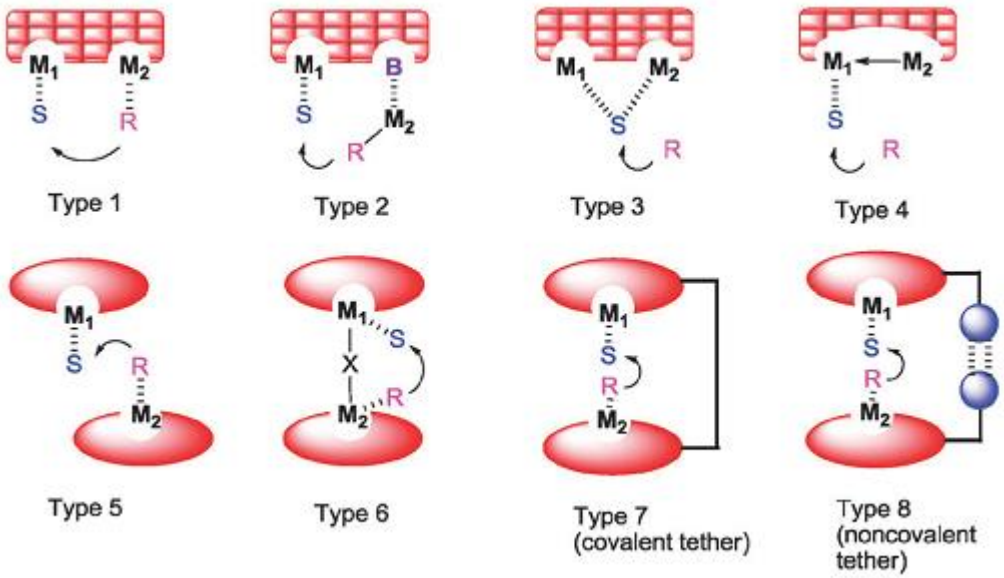
Metals used in bimetallic catalysis:

- **Alkali metals**
- **Transition metals**
- **Lanthanides**

The key to success for efficient catalysis is probably the **proper arrangement** of those metals in **close proximity** (3.5 – 6 Å)

From a **mechanistic** point of view, **one metal** plays a role as a **Lewis acid** for activating **electrophiles**, while the **other metal ion** serves as the **counterion** of **nucleophiles**.

From a **structural** point of view cooperative bimetallic catalysts can be classified into several **different types**.



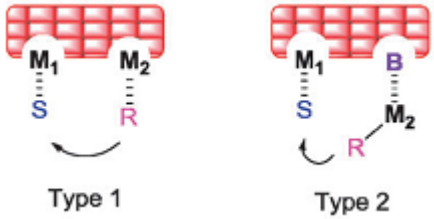
Type 1-4 host **two metals** in a **single** or fused **ligand frame**.

In **Type 5-8 two separate metal species** are involved in dual activation of both reaction partners.

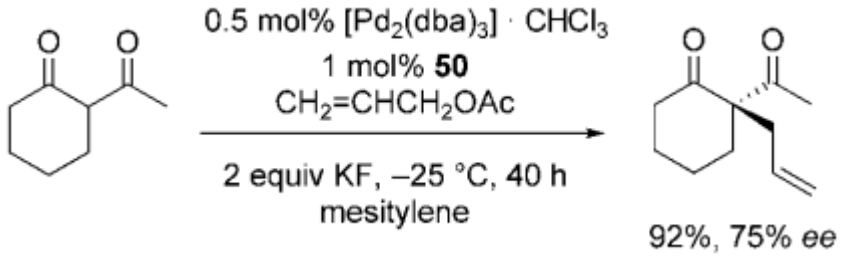
Park, J.; Hong, S.; *Chem. Soc. Rev.* **2012**, *41* (21), 6931-6943

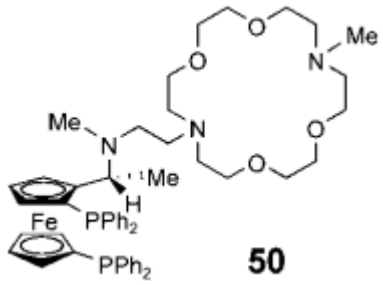
Types of bimetallic catalysts

<u>Single-framed bimetallic systems (Types 1 and 2):</u> *two metal centers are embedded in a single chiral ligand unit through direct complexation (type 1) or coordiantion of a basic site (type 2). Each metal activates different reactants (Nu/E).*



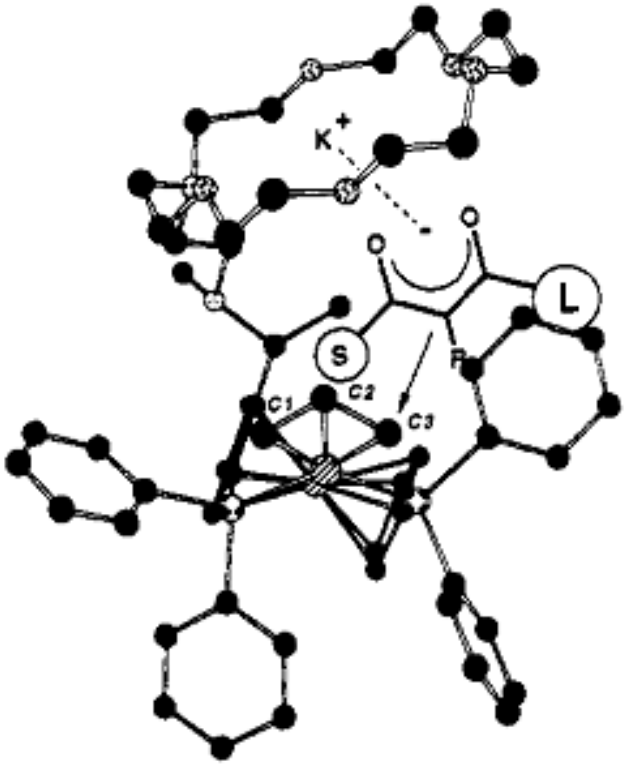
Pd-catalyzed asymmetric allylation of β-diketone enolates with the aid of a **chiral phospane ligand tethered to an azacrown ether.**





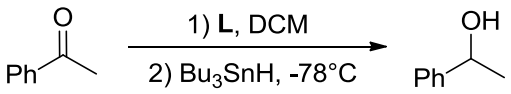
50

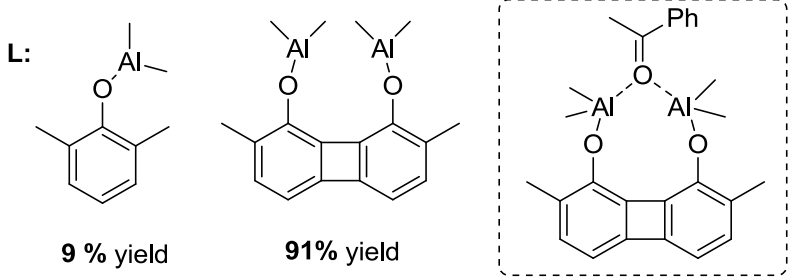
Double activation: for the electrophile by the palladium center and for the nucleophile by complexation of the cation.



Types of bimetallic catalysts

In type 3 bimetallic catalysts two metals **simultaneously activate one reactant.**[1]

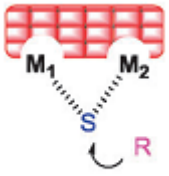




Bidentate organoaluminum Lewis acid

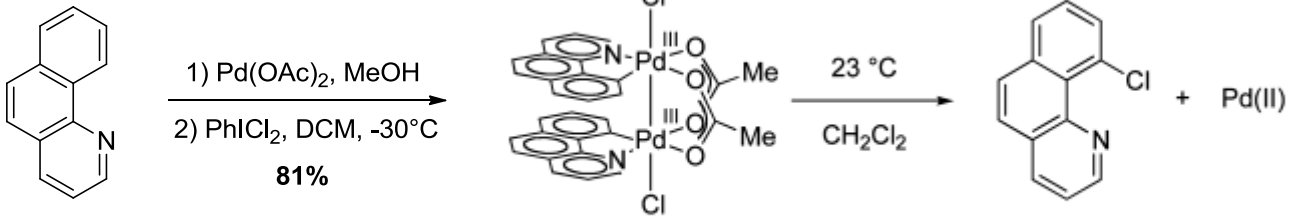
9 % yield

91% yield



Type 3

Type 4 bimetallic catalysts activate **one reactant by one metal**, however the other metal stabilizes the reacting metal through **metal-metal redox cooperation.** [2]

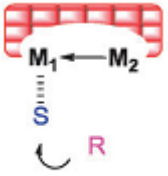


1

Pd-Pd: 2,57 A
stable below -30°C

2, 94%

3



Type 4

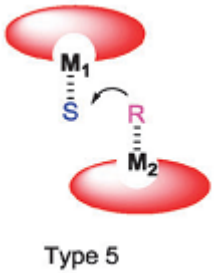
Reductive elimination from a dinuclear core with synergistic, bimetallic redox partecipation of both metals.

Types 3 and 4 approaches developped for non-chiral transformation, there is no reported example of asymmetric reactions.

(1) T. Ooi, M. Takahashi, M. Yamada, E. Tayama, K. Omoto and K. Maruoka, *J. Am. Chem. Soc.*, **2004**, *126*, 1150–1160. (2) D. C. Powers, D. Benitez, E. Tkatchouk, W. A. Goddard III and T. Ritter, *J. Am. Chem. Soc.*, **2010**, *132*, 14092–14103

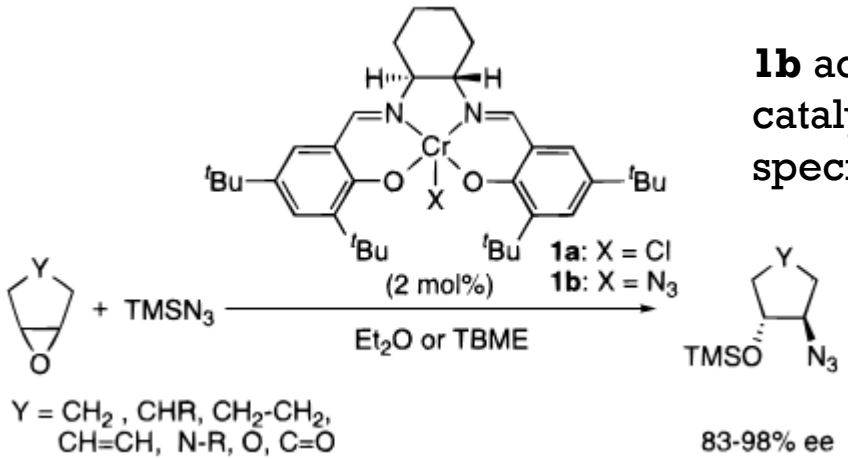
Types of bimetallic catalysts

Separate bimetallic systems (Type 5): *two metallic species are simultaneously involved in an enantioselective reaction. Identical or different metal species activate both nucleophile and electrophile.*

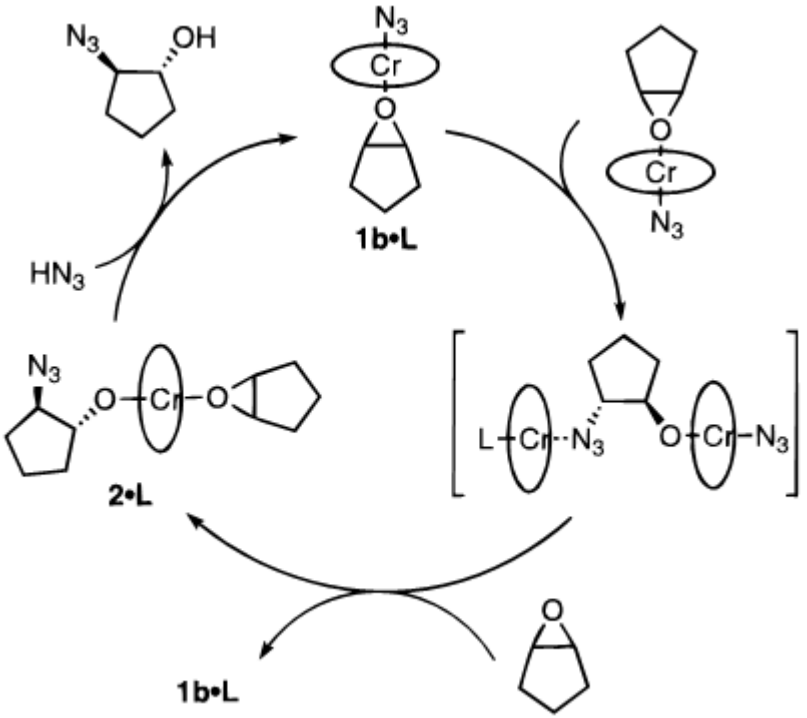


Type 5

(Salen)Cr(III) complexes catalyze asymmetric ring opening of *meso*-epoxide with $TMSN_3$ with high yield and enantioselectivity. Kinetic studies revealed the **second-order rate dependence** on a catalyst and significant **non-linear effects** were observed.



1b actual catalytic specie

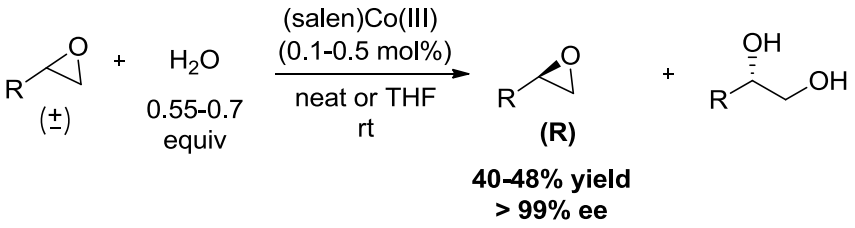


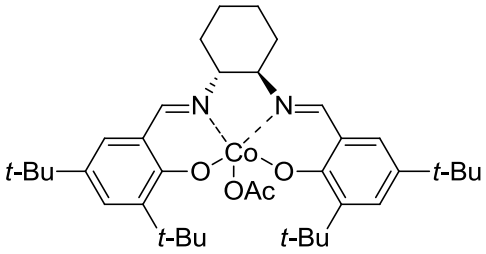
Bimetallic mechanism where **two distinct Cr** catalyst are involved.

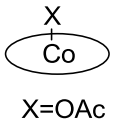
(1) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**,*117*, 5897-5898. (2) Hansen K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*,10924-10925. (3) Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*,10780-10781.

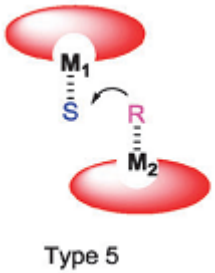
Types of bimetallic catalysts

(salen)Co(III) catalyst for hydrolytic kinetic resolution (HKR) of racemic epoxide with high selectivity factors ($k_{rel} = k_{fast} / k_{slow}$).



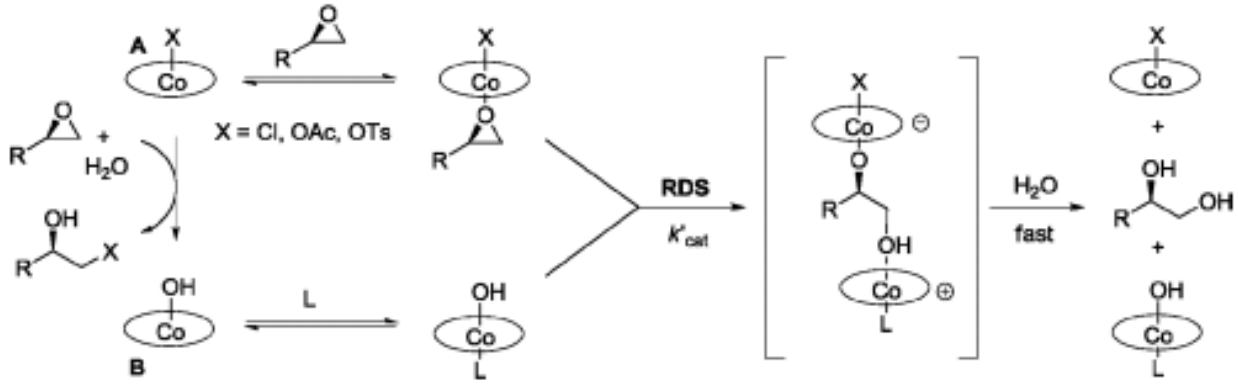






Second-order dependence on **cobalt** concentration suggests that two metal centers are involved in the rate-limitig TS. Dual activation mechanism: epoxide activated by one (salen)metal unit and cobalt hydroxide specie delivered by a second catalyst unit.

Maximum rate obtained when [A] = [B]. Ratio dependent on the nature of the counterion X.

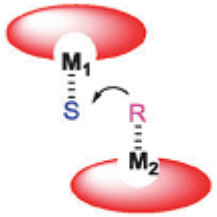


1) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**,*277*,936-938. (2) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. J. *Am. Chem. Soc.* **2002**, 124,1307-1315.(3) Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, 126,1360-1362.

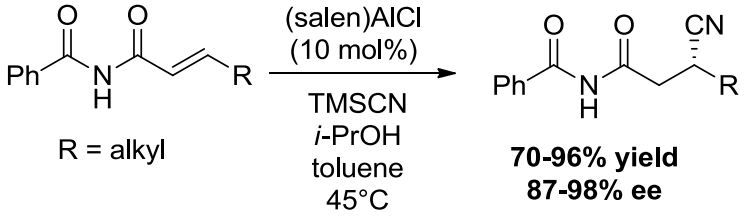
Type 5

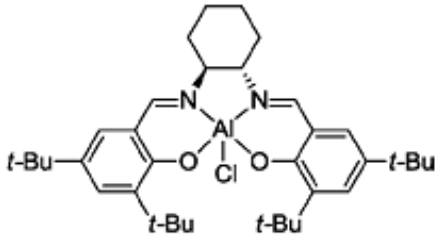
Types of bimetallic catalysts

Catalytic asymmetric conjugate addition reactions of cyanides to α,β-unsaturated imides.



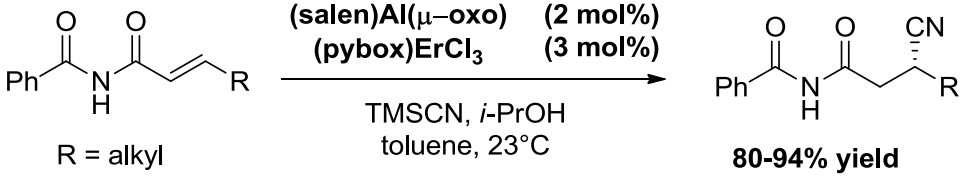
Type 5

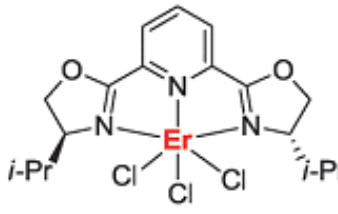




Homobimetallic patway: both cyanide and imide activated by (salen)AlCl

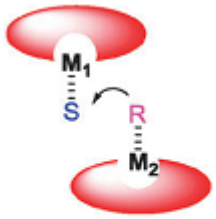
Combination of μ-oxo dimeric (salen)Aldimer (to activate the imide) and (pybox)$ErCl_3$ (to activate the cyanide) improves the catalytic system (dual activation). (salen)Al(μ-oxo)dimer alone can't activate the cyanide.



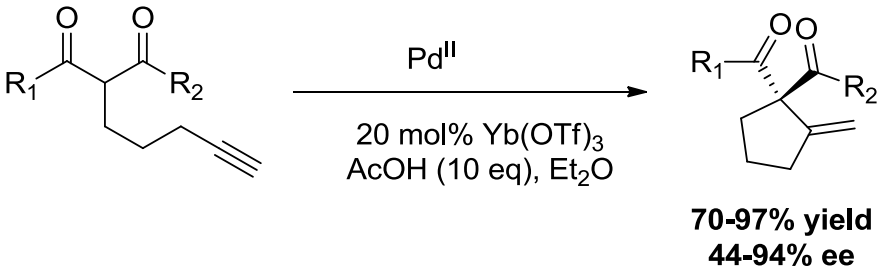


Types of bimetallic catalysts

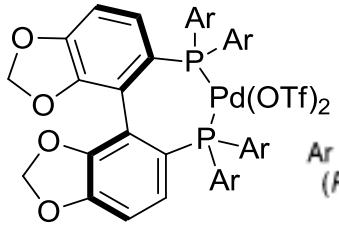
First **enantioselective intramolecular Conia-ene reaction** of β-dicarbonyl compounds and alkynes. The **Pd(II)/Yb(III) dual catalyst** system allows for the asymmetric sythesis of the carbon quaternary center.[1]



Type 5



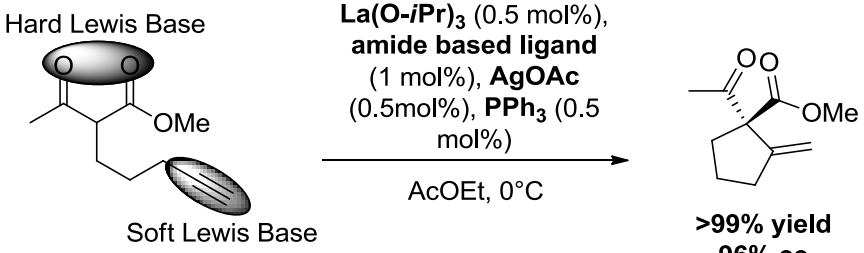
70-97% yield
44-94% ee



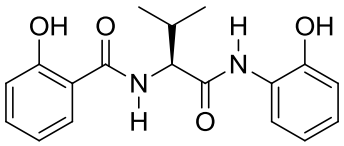
10 mol%

Ar = 3,5-di(*tert*-butyl)-4-methoxyphenyl: (*R*)-DTBM-SEGPHOS

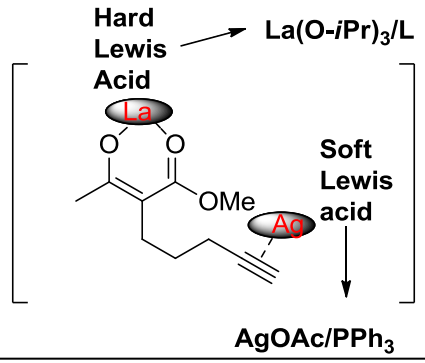
La-Ag heterobimetallic catalyst for asymmetric Conia-ene reactions. Cooperative activation by the hard Lewis acid and the Sof lewis acid crucial for reactivity and selectivity.[2]



>99% yield
96% ee



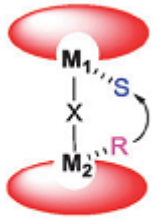
Amide based ligand



(1) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168-17169. (2) A. Matsuzawa, T. Mashiko, N. Kumagai and M. Shibasaki, *Angew. Chem., Int. Ed.*, **2011**, *50*, 7616–7619.

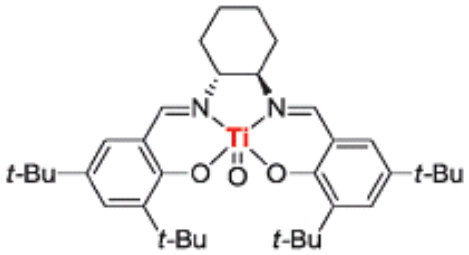
Types of bimetallic catalysts

Bridged bimetallic systems: *In type 6 two chiral metallic units are connected by μ-oxo or halide bridges.*



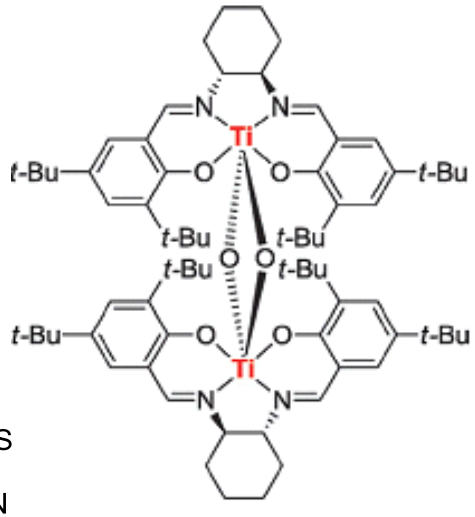
Type 6

TMSCN addition to carbonyl compounds *via* bimetallic activation: the bridge *μ-oxo titanium species is the actual precatalyst (simultaneously activates both the carbonyl and the TMSCN).*

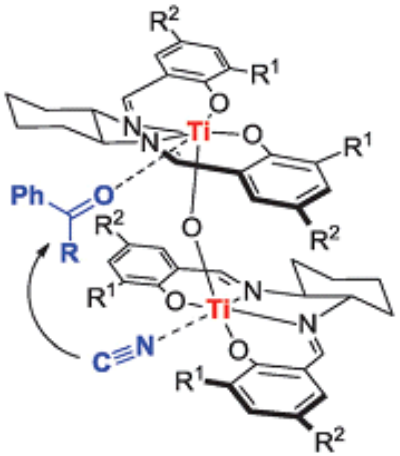


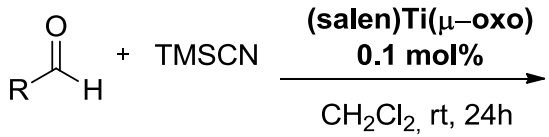
catalytically inactive

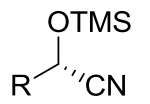
in solution



catalytically active





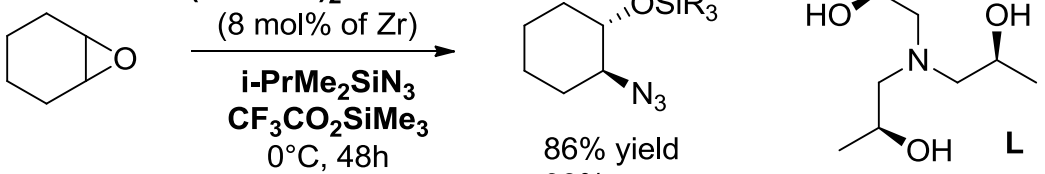


100% conv
52-92% ee

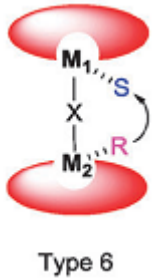
Y. N. Belokon', S. Caveda-Cepas, B. Green, N. S. Ikonnikov, V. N. Khrustalev, V. S. Larichev, M. A. Moscalenko, M. North, C. Orizu, V. I. Tararov, M. Tasinazzo, G. I. Timofeeva and L. V. Yashkina, *J. Am. Chem. Soc.*, **1999**, *121*, 3968–3973.

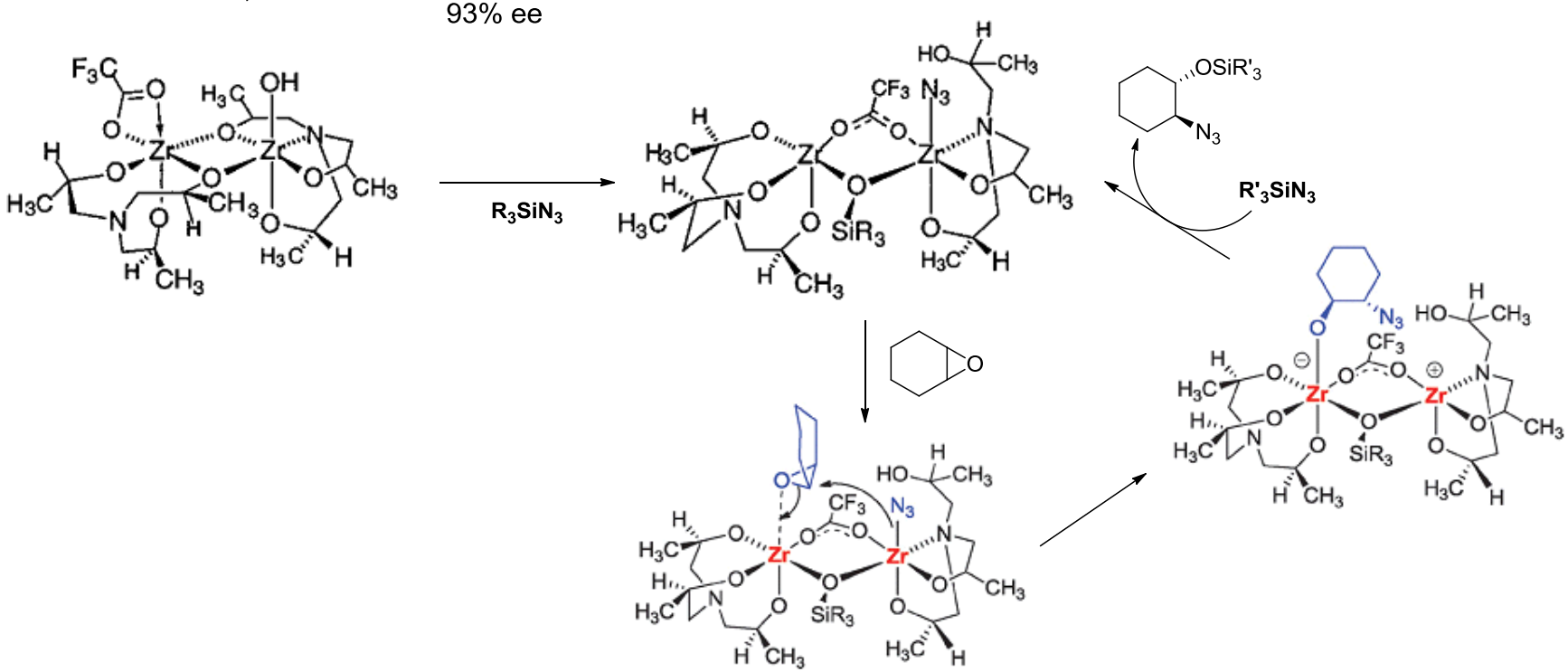
Types of bimetallic catalysts

Highly enantioselective additon of azide to *meso*-epoxide in the presence of chiral zirconium complex.



Two zirconium metals are involved in the stereoselective TS

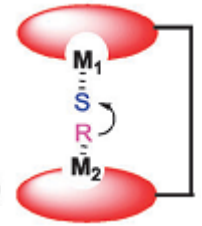




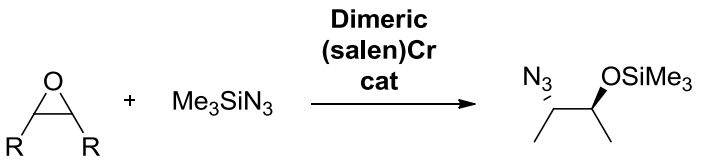
(1) W. A. Nugent, *J. Am. Chem. Soc.*, **1992**, *114*, 2768–2769. (2) B. W. McCleland, W. A. Nugent and M. G. Finn, *J. Org. Chem.*, **1998**, *63*, 6656–6666

Types of bimetallic catalysts

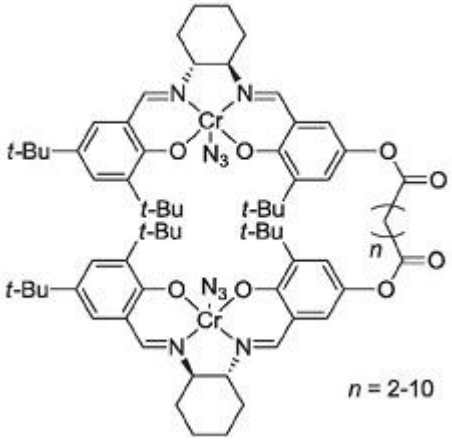
Tethered bimetallic systems (covalent approach): *In type 7 two (or more) catalytic units are linked through an appropriate linker or merging within a single framwork.*

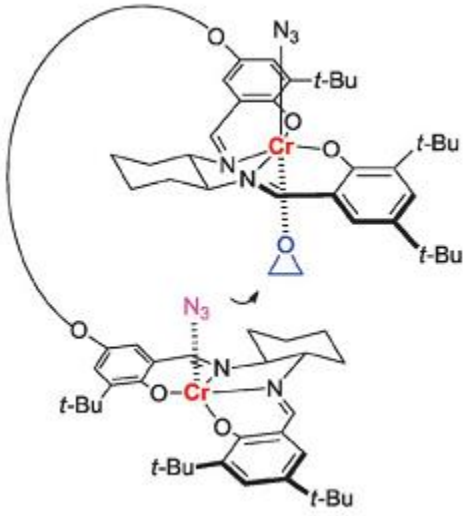


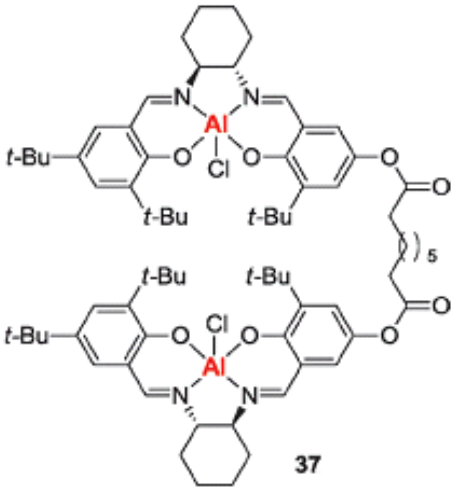
Type 7
(covalent tether)

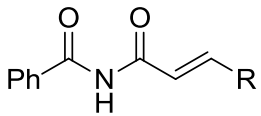


n = 5 displayed maximum value of k_{intra} and enantioselectivity



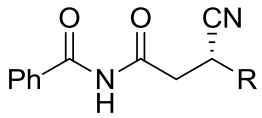






Dimer (salen)AlCl
(2.5 mol%)

TMSCN
i-PrOH
toluene



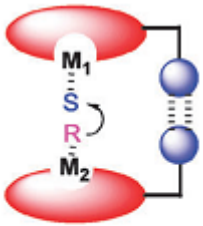
91-99% yield
84-96% ee

Covalently tethered dinuclear (salen)Al catalyst: intramolecular patway dominates over the second-order (intermolecular) component (kinetic studies)

(1) R. G. Konsler, J. Karl and E. N. Jacobsen, *J. Am. Chem. Soc.*, **1998**, *120*, 10780–10781. (2) C. Mazet and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, **2008**, *47*, 1762–1765

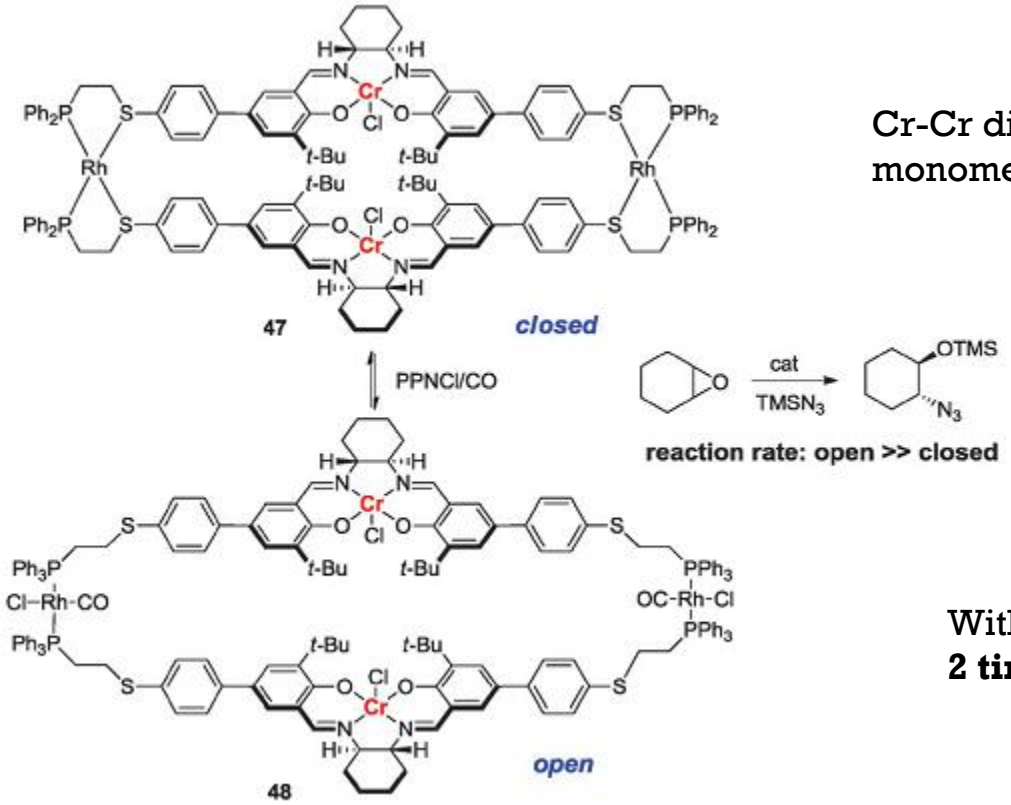
Types of bimetallic catalysts

Tethered bimetallic systems (supramolecular approach): *In type 8 two catalytic units are linked through a reversible metal-coordination or non-covalent bonding interaction such as hydrogen bonding.*



Type 8 (noncovalent tether)

*R*eversible nature supramolecular catalyst → allosteric regulation



Cr-Cr distance = 5A. Rate **20 times faster** than monomeric (salen)Cr(III).

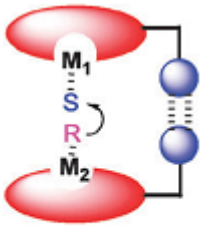
Switchable structural motifs

With external ligands (Cl^- and CO) **2 times faster** than the close one

N. C. Gianneschi, P. A. Bertin, S. T. Nguyen, C. A. Mirkin, L. N. Zakharov and A. L. Rheingold, *J. Am. Chem. Soc.*, **2003**, *125*, 10508–10509

Type 8

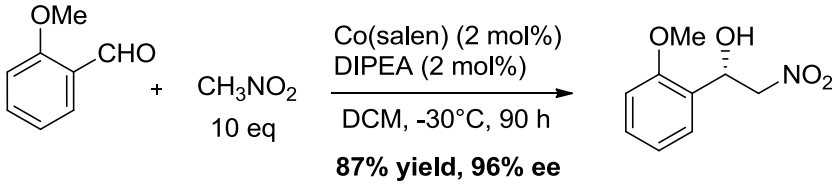
Types of bimetallic catalysts



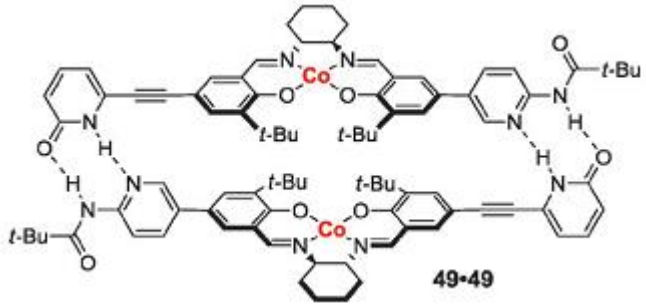
Type 8 (noncovalent tether)

Chiral homodimeric bimetallic system which can be **self-assembled** through self-complementary **hydrogen bonding** interactions.

This catalyst displays superior reactivity and selectivity in the asymmetric Henry reaction compared to the simple unfunctionalized (salen)Co catalyst.



Simple monomeric **(salen)Co cat: 11% yield, 55% ee**

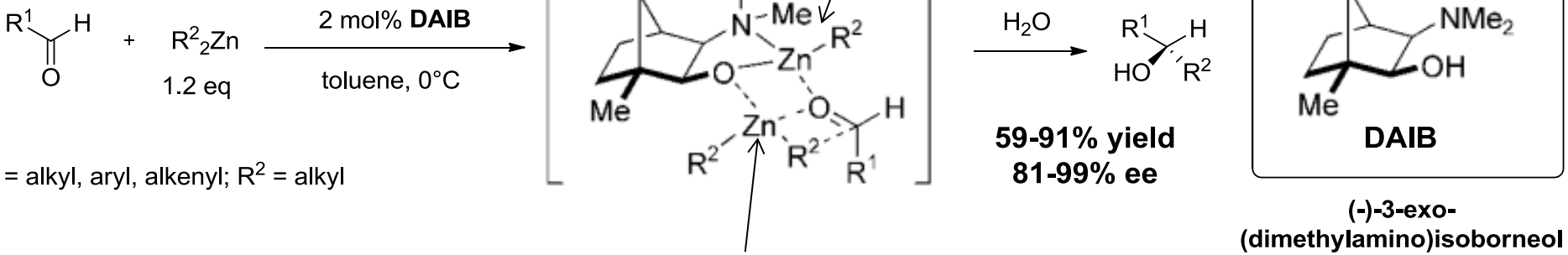


Structure confirmed by X-ray analysis and ^{1}H-NMR studies kinetic 2° order

Alkylation of Carbonyls

Catalytic asymmetric alkylation of carbonyls compounds: First example of highly enantioselective alkylation of aldehydes with Et_2Zn, catalyzed by (-)-DAIB.

Bimetallic TS → high catalytic activity and excellent enantioselectivity



Lewis acid (activates the aldehyde), catalytic, Zn alkoxide

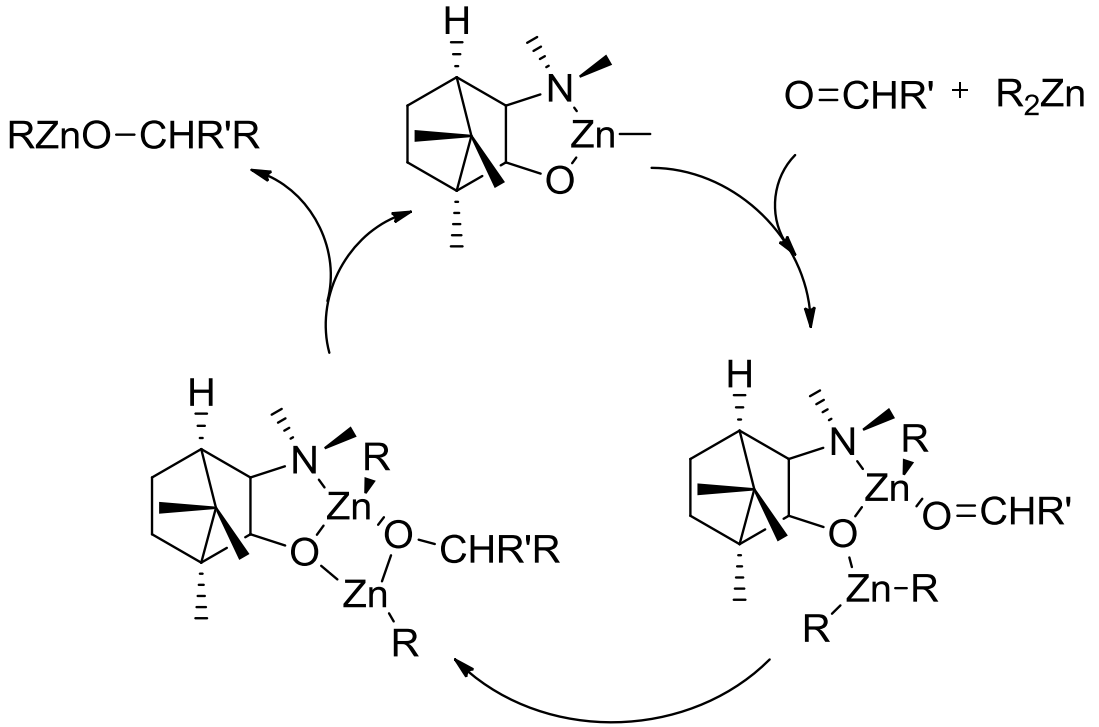
R^1 = alkyl, aryl, alkenyl; R^2 = alkyl

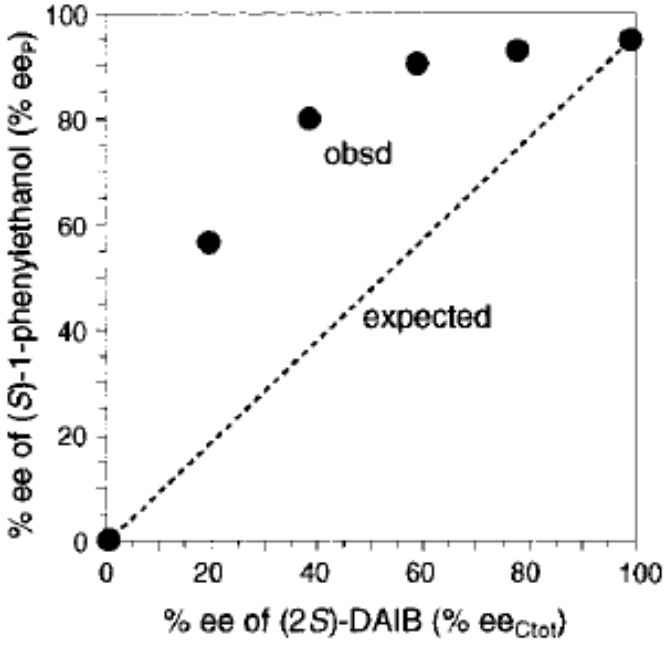
Stoichiometric, **coordinates the Lewis basic oxygen atom** which activates and directs the addition

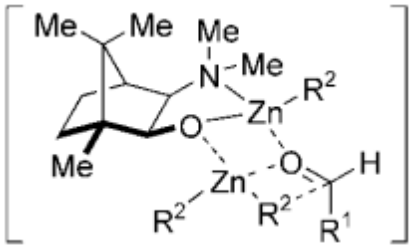
(1) M. Kitamura, S. Suga, K. Kawai and R. Noyori, *J. Am. Chem. Soc.,* **1986**, *108*, 6071–6072; (2) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. J. *Am. Chem. Soc.* **1998**, *120*, 9800-9809; (3) Rasmussen, T.; Norrby, P. O. *J. Am. Chem. Soc*. **2003**, *125*, 5130-5138.

Alkylation of Carbonyls

Catalytic asymmetric alkylation of carbonyls compounds





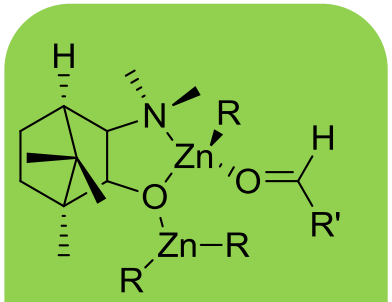


Non linear effect: asymmetric amplification

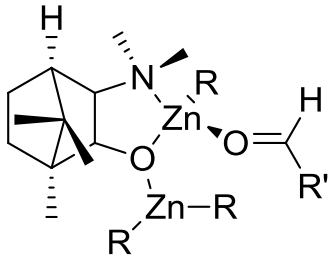
(1) M. Kitamura, S. Suga, K. Kawai and R. Noyori, *J. Am. Chem. Soc.,* **1986**, *108*, 6071–6072; (2) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. J. *Am. Chem. Soc.* **1998**, *120*, 9800-9809; (3) Rasmussen, T.; Norrby, P. O. *J. Am. Chem. Soc*. **2003**, *125*, 5130-5138.

Alkylation of Carbonyls

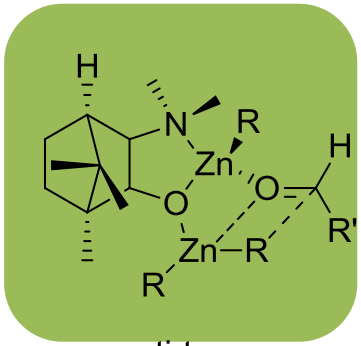
Catalytic asymmetric alkylation of carbonyls compounds:



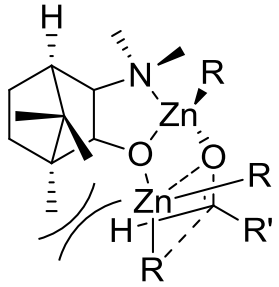
Zn(R)-trans



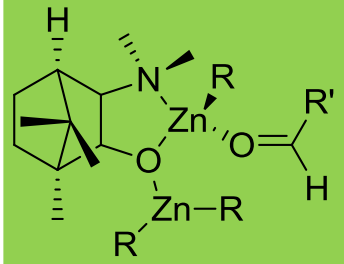
Zn(S)-trans



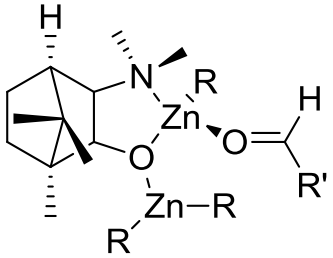
anti-trans



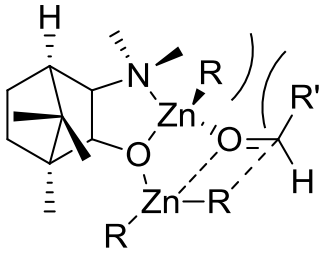
syn-trans



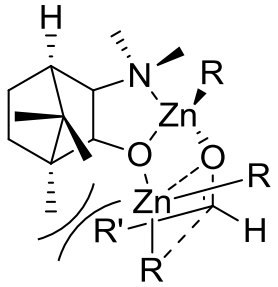
Zn(R)-cis



Zn(S)-cis

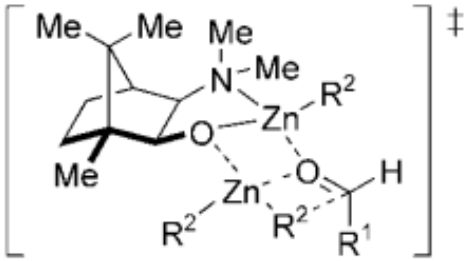


anti-cis



syn-cis

Different coordination modes of the aldehydes to the catalyst. Alkoxide-O > aldehyde-O > N > R

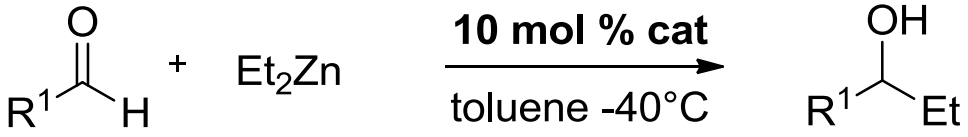


Tricyclic transition states for the Zn(R) face. Syn and anti define the relationship between the transferring alkyl and the bidentate ligand. Cis and trans define which aldehyde lone pair coordinates the catalytic zinc

(1) M. Kitamura, S. Suga, K. Kawai and R. Noyori, *J. Am. Chem. Soc.*, **1986**, *108*, 6071–6072; (2) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800-9809; (3) Rasmussen, T.; Norrby, P. O. *J. Am. Chem. Soc*. **2003**, *125*, 5130-5138.

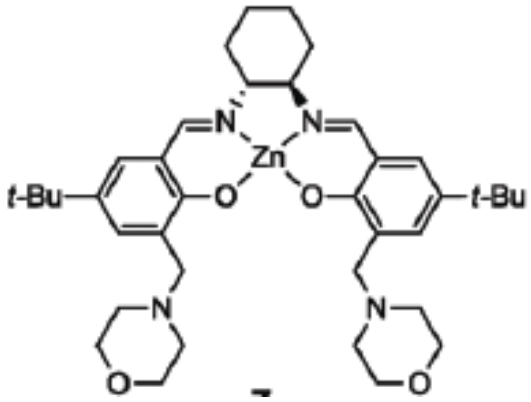
Alkylation of Carbonyls

Lewis acid/base bifunctional salen catalyst for highly efficient enantioselective addition of Et_2Zn to aldehydes.

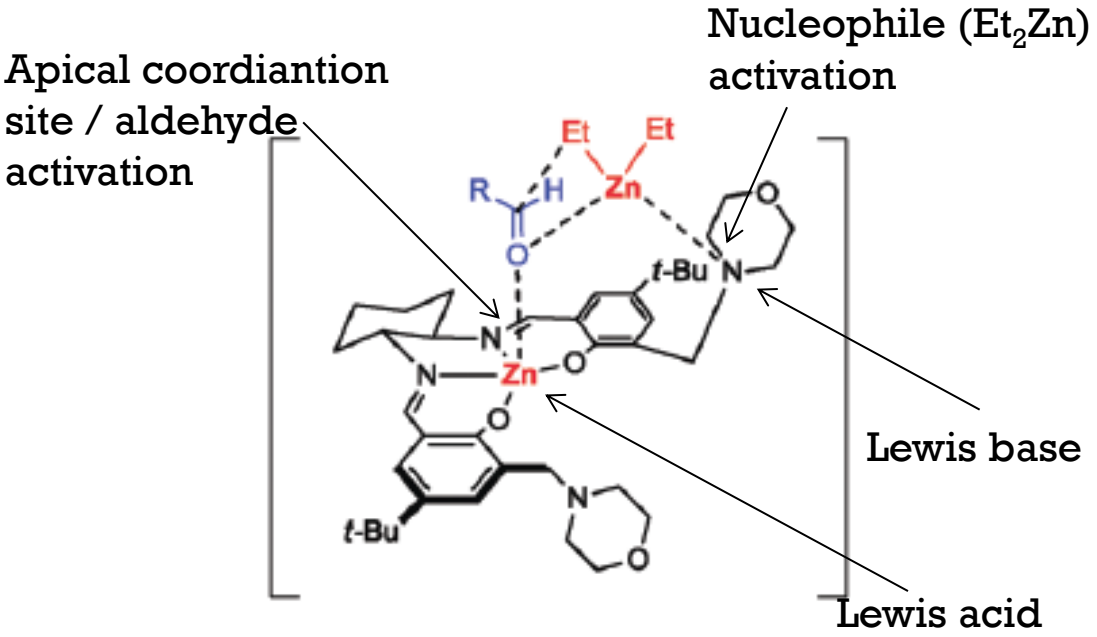


R^1 = alkyl, cyclohexyl, aryl

75 - 91% ee
78 - 99% yield



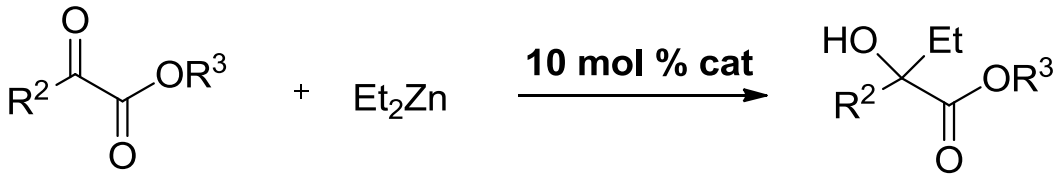
(N,N'-bis(salicylidene)ethylenediamine)



(1) E. F. DiMauro, M. C. Kozlowski, *Org. Lett*. **2001**, *3*, 3053 – 3056; (2) E. F. DiMauro, M. C. Kozlowski, *J. Am. Chem. Soc.* **2002**, *124*, 12668 – 12669; (3) E. F. DiMauro, M. C. Kozlowski, *Org. Lett.* **2002**, *4*, 3781 – 3784.

Alkylation of Carbonyls

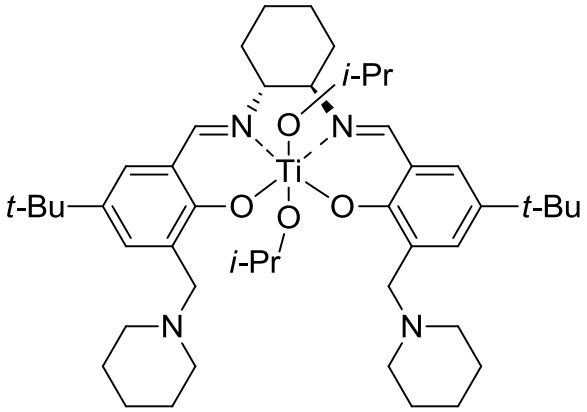
First enantioselective addition of Et_2Zn to α-ketoesters by using bifunctional salen catalyst.

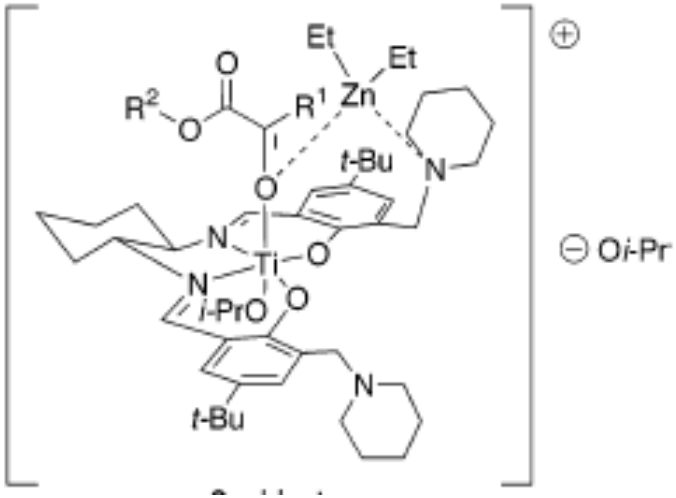


R^2 = alkyl, aryl
R^3 = alkyl, benzyl

up to 78% ee
up to 99% yield

Issues addressed with **α-ketoesters** : catalyst must accelerate the addition faster than uncatalyzed racemic addition and reduction.

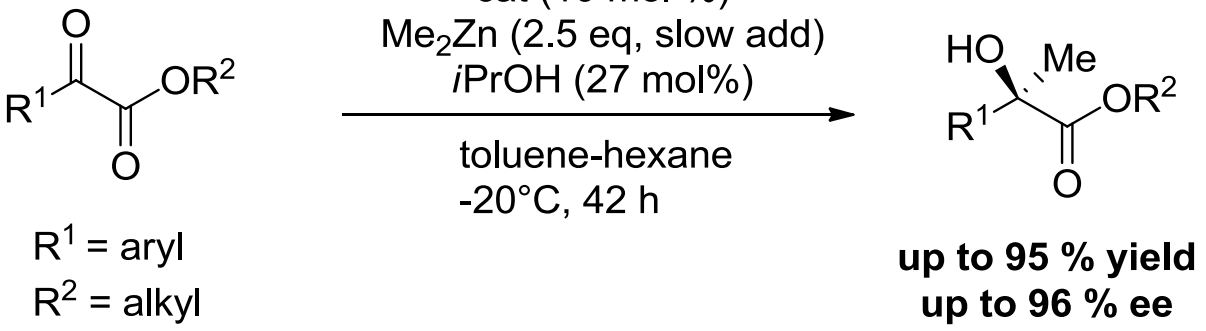




(1) E. F. DiMauro, M. C. Kozlowski, *Org. Lett*. **2001**, *3*, 3053 – 3056; (2) E. F. DiMauro, M. C. Kozlowski, *J. Am. Chem. Soc.* **2002**, *124*, 12668 – 12669; (3) E. F. DiMauro, M. C. Kozlowski, *Org. Lett.* **2002**, *4*, 3781 – 3784.

Alkylation of Carbonyls

Proline-derived ligand for enantioselective addition of Me_2Zn to α-ketoesters.



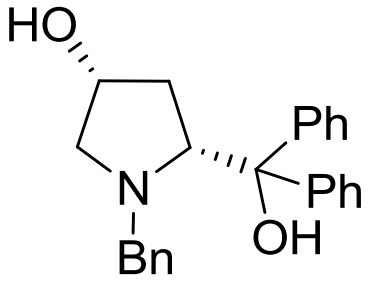
R^1 = aryl
R^2 = alkyl

up to 95 % yield
up to 96 % ee

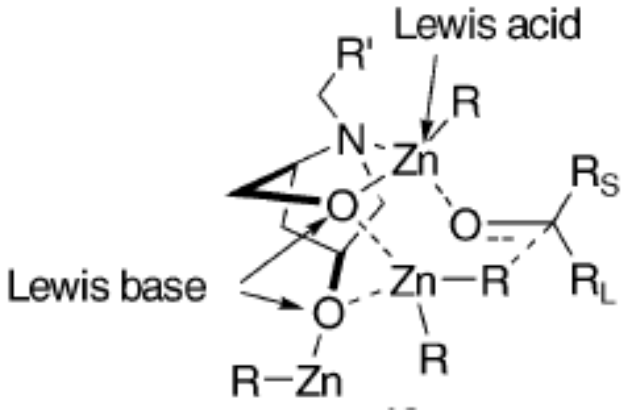
Linear effect in presence of the alcohol.

↓

Monomeric form as active catalytic specie



cat

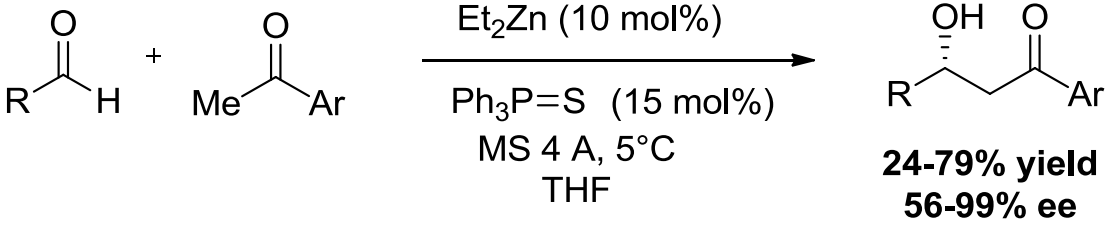


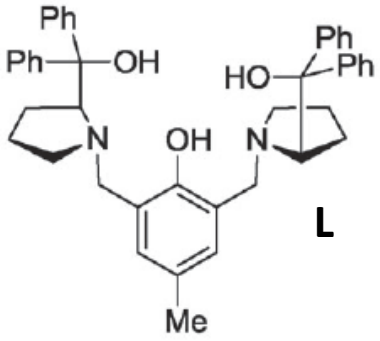
Nucleophile activated by an additional Lewis base (Zinc alkoxide more electron-donating)

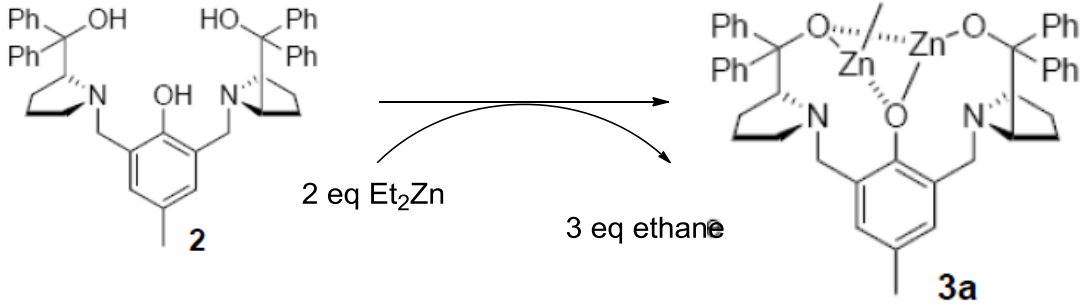
K. Funabashi, M. Jachmann, M. Kanai and M. Shibasaki, *Angew. Chem., Int. Ed.*, **2003**, *42*, 5489–5492.

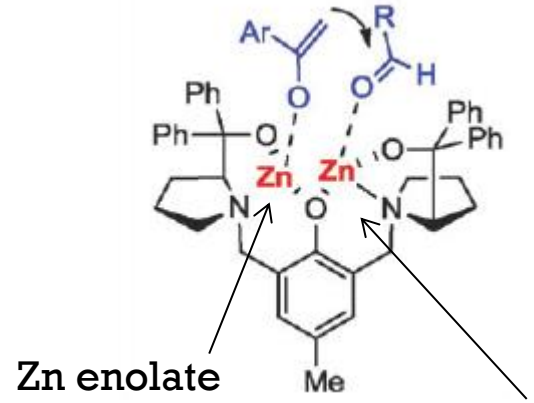
Catalytic Asymmetric Aldol

Dinuclear Zinc catalyst (chiral ProPhenol/Zn) for enantioselective direct aldol reactions





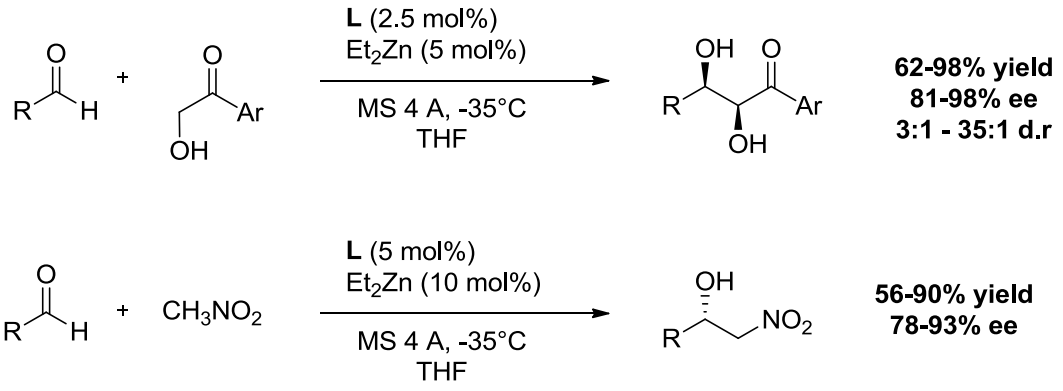


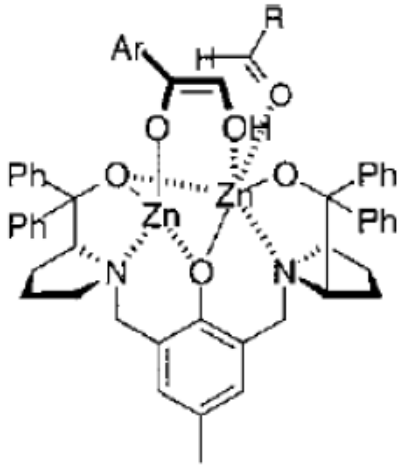


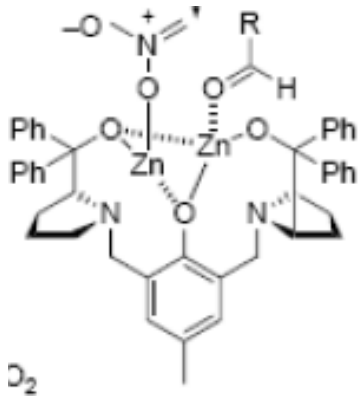
(1) B . M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003–12004; (2) B. M. Trost, H. Ito, E. R. Silcoff, *J. Am. Chem. Soc.* **2001**, *123*, 3367–3368; (3) B . M. Trost, V. S. C. Yeh, *Angew. Chem.* **2002**, *114*, 889-891; (4) *Angew. Chem. Int. Ed.* **2002**, *41*, 861 – 863; (5) B . M. Trost, V. S. C. Yeh, H. Ito, N. Bremeyer, *Org. Lett.* **2002**, *4*, 2621 – 2623.

Catalytic Asymmetric Aldol

Dinuclear Zinc catalyst (chiral ProPhenol/Zn) for enantioselective direct aldol and nitro-aldol.



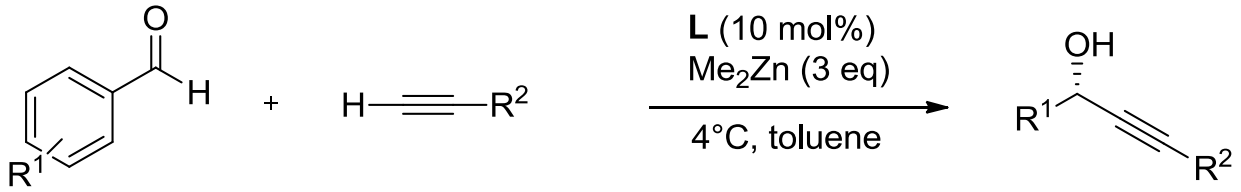




1) B . M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003–12004; (2) B. M. Trost, H. Ito, E. R. Silcoff, *J. Am. Chem. Soc.* **2001**, *123*, 3367–3368; (3) B . M. Trost, V. S. C. Yeh, *Angew. Chem.* **2002**, *114*, 889-891; (4) *Angew. Chem. Int. Ed.* **2002**, *41*, 861 – 863; (5) B . M. Trost, V. S. C. Yeh, H. Ito, N. Bremeyer, *Org. Lett.* **2002**, *4*, 2621 – 2623.

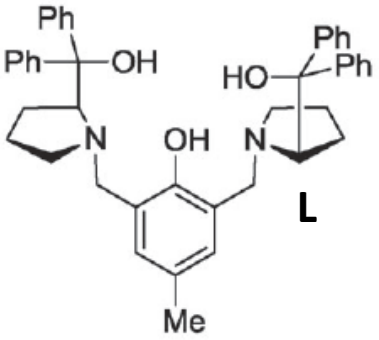
Catalytic Asymmetric Aldol

Dinuclear Zinc catalyze Asymmetric Alkynylation of aldehydes

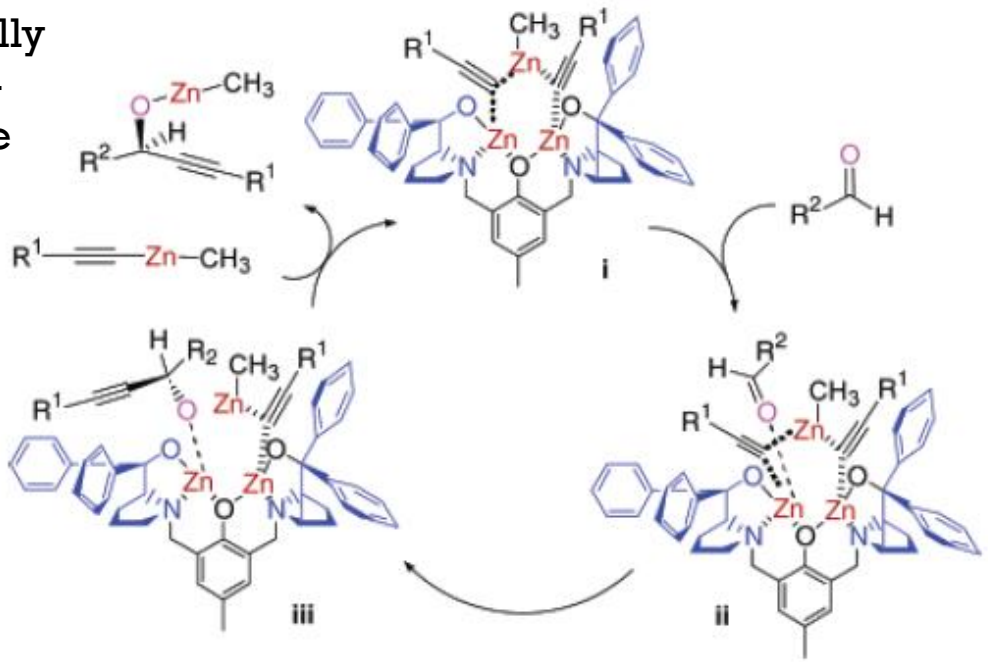


-R^1 = -NO_2, -H, -(2-naphth), -OMe, -furyl
-R^2 = -Ph, -TMS, -CH_2OCH_3, -CO_2Et

74-95% yield
68-97% ee



Conditions successfully applied also with α,β-unsaturated aldehyde

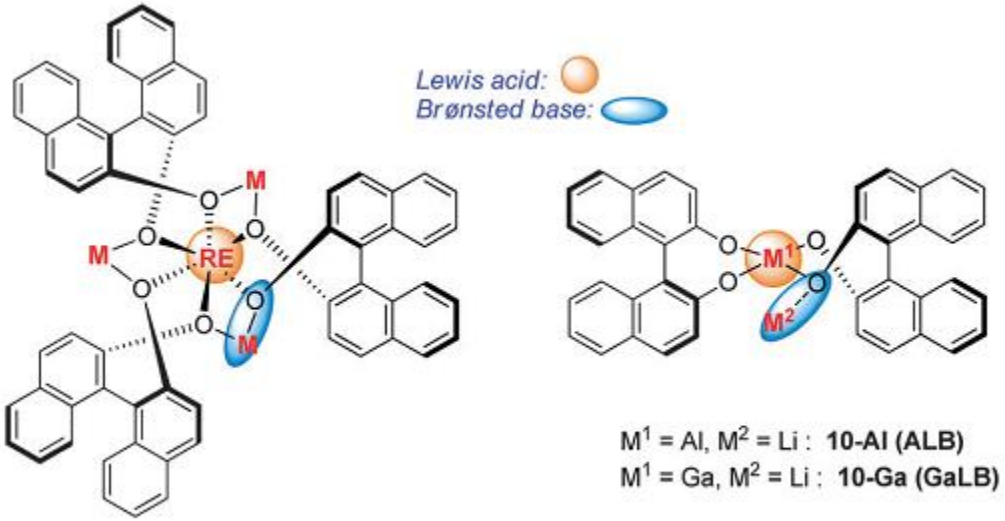


- Coordination of 2 equiv of zinc alkynylide
- Coordination of the aldehyde to the most sterically accessible site forms intermediate
- Alkyne transfer sets the stereochemistry
- Transmetalation to another zinc alkynylide forms the alkoxide product

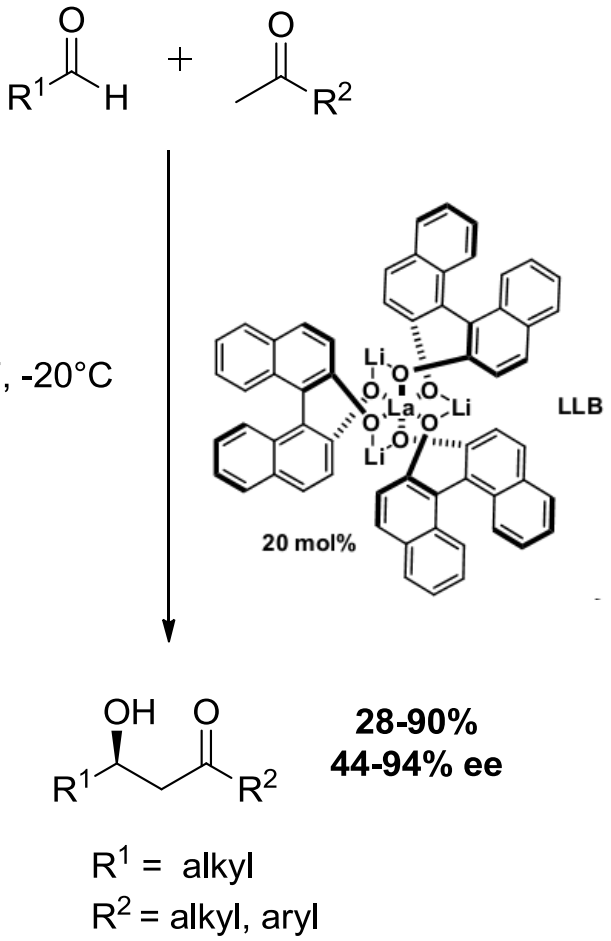
B. M. Trost, *J. Am. Chem. Soc.*, **2006**, *128*, 8–9

Catalytic Asymmetric Aldol

BINOL-based heterobimetallic catalysts that contain one rare earth metal (RE) , three alkali metals (M) and three 1,1'-bis-2-naphtols for asymmetric direct aldols, nitroaldols, aza-Henry and conjugate additions.



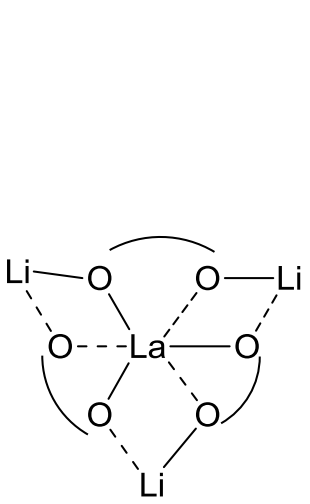
Structure proved by NMR, MS and X-ray (on an analogue)



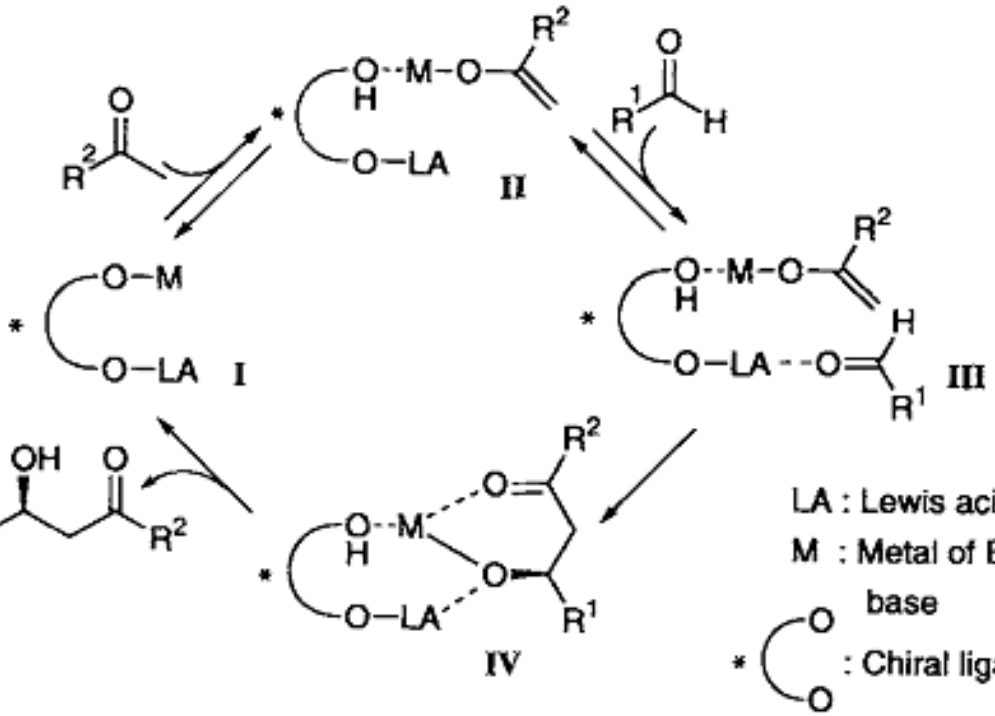
(1) Y. M. A. Yamada, N. Yoshikawa, H. Sasai and M. Shibasaki, *Angew. Chem., Int. Ed.*, **1997**, *36*, 1871–1873; (2) M. Shibasaki, M. Kanai, S. Matsunaga and N. Kumagai, *Acc. Chem. Res.*, **2009**, *42*, 1117–1127.

Catalytic Asymmetric Aldol

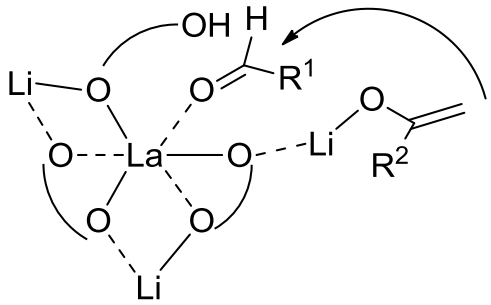
Mechanism of the direct aldol with LBB (REMB)



LBB enolate



coordination of the aldehyde in a chiral enviroment (proved by NNMR studies)

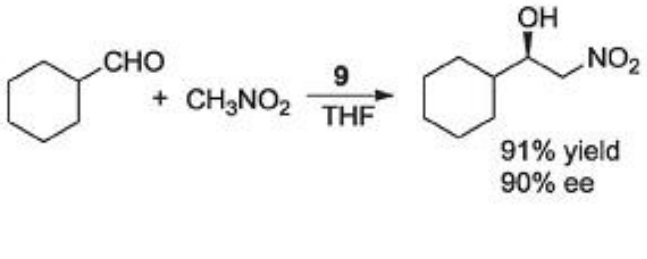


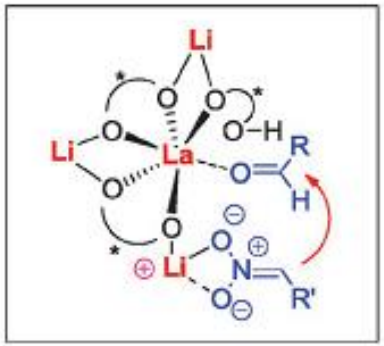
(1) Y. M. A. Yamada, N. Yoshikawa, H. Sasai and M. Shibasaki, *Angew. Chem., Int. Ed.*, **1997**, *36*, 1871–1873; (2) M. Shibasaki, M. Kanai, S. Matsunaga and N. Kumagai, *Acc. Chem. Res.*, **2009**, *42*, 1117–1127.

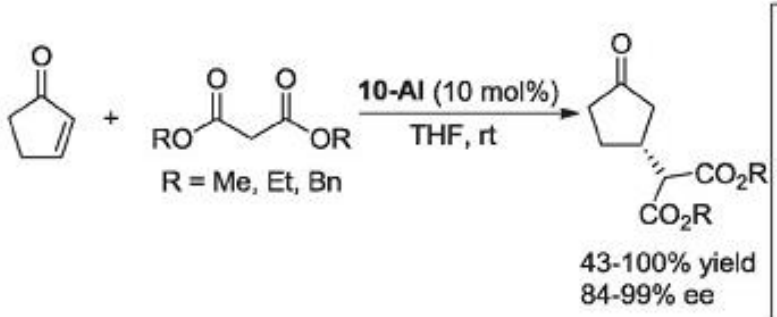
Catalytic Asymmetric Aldol-type

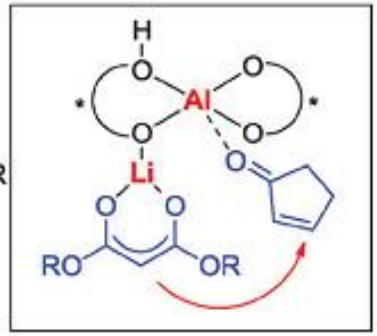
Further example of BINOL-based bimetallic catalysts:

- Nitro aldol reaction (LLB)
- Conjugate addition of cyclopentenone of malonates (BINOL-derived aluninum alkali metal)

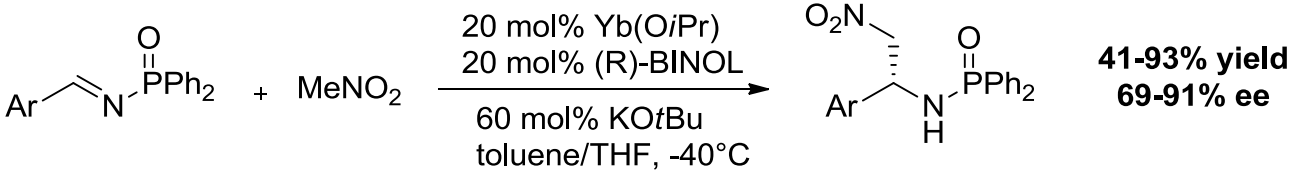








First Example of Asymmetric Nitro-Mannich reaction:

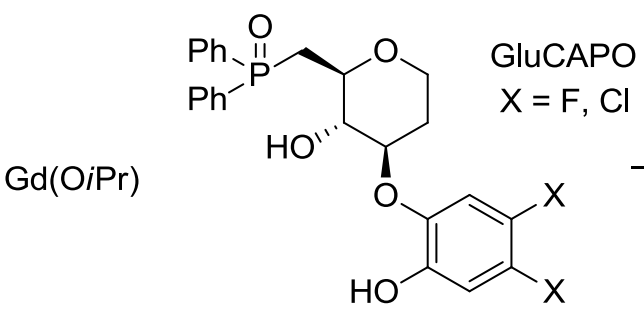


(1) Y. M. A. Yamada, N. Yoshikawa, H. Sasai and M. Shibasaki, *Angew. Chem., Int. Ed.*, **1997**, *36*, 1871–1873; (2) M. Shibasaki, M. Kanai, S. Matsunaga and N. Kumagai, *Acc. Chem. Res.*, **2009**, *42*, 1117–1127.

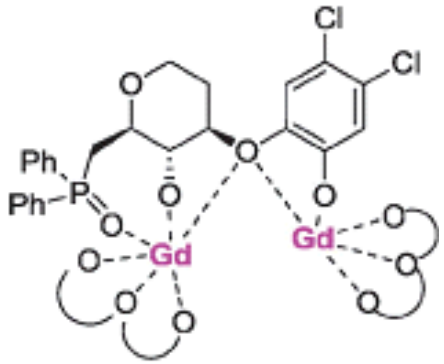
Shibasaki

Catalytic Asymmetric Strecker

Gadolinium complex with D-glucose-derived ligand (GluCAPO) for asymmetric Strecker reaction of ketimines with TMSCN with high enantioselectivities. Used also for cyanosilylation of ketone and ring opening reactions of meso-aziridines with TMSCN and $TMSN_3$.

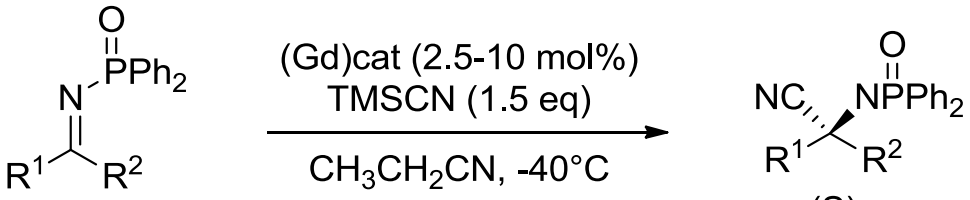


2 **3**

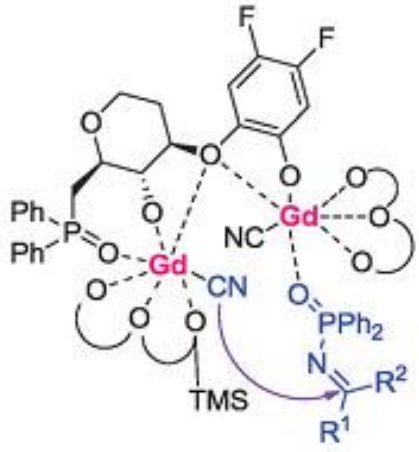


Active catalyst found by mechanistic and ESI studies.

Cristalized 4:5 complex (μ-oxo bridge)



58-100% yield
51-98% ee

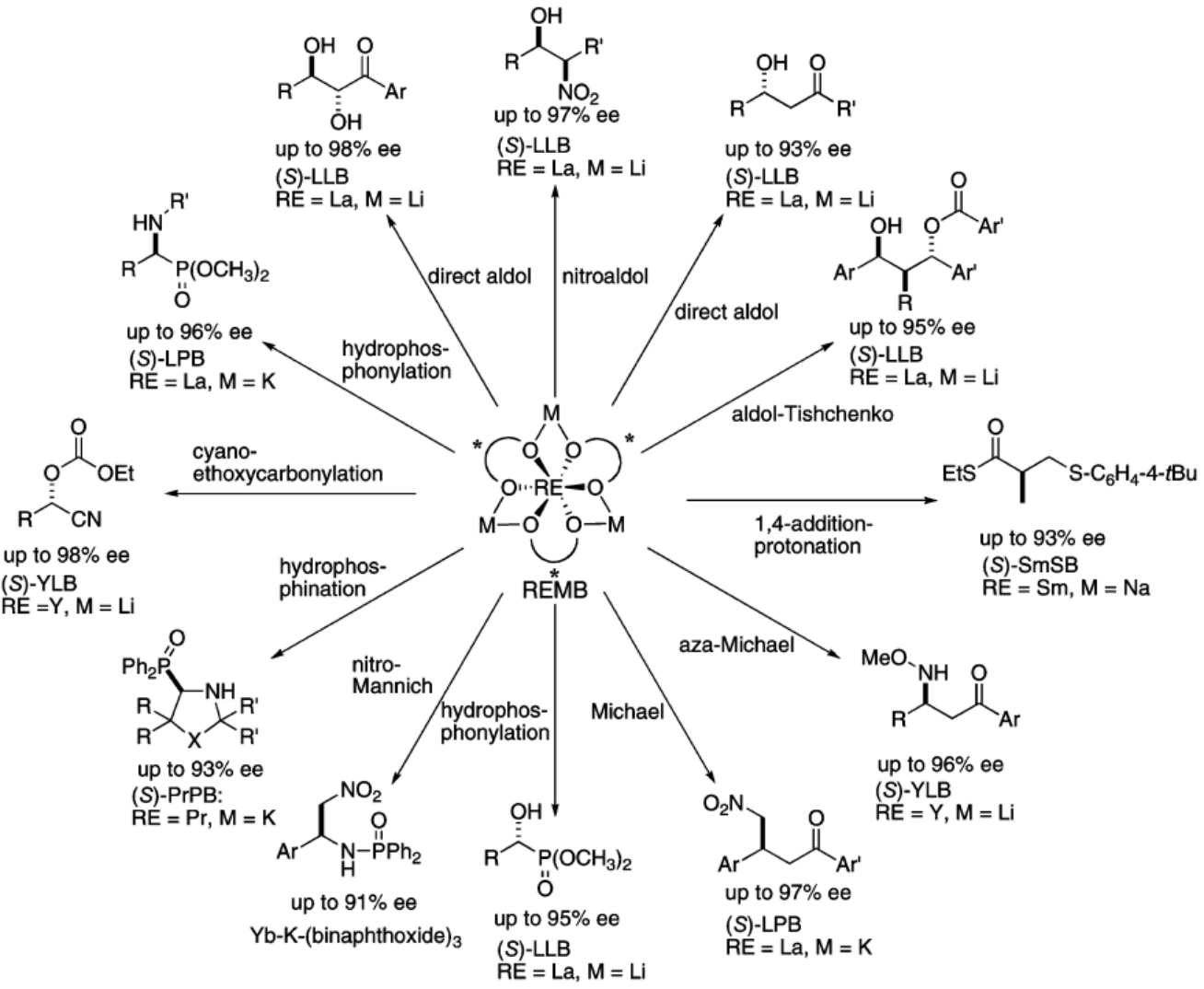


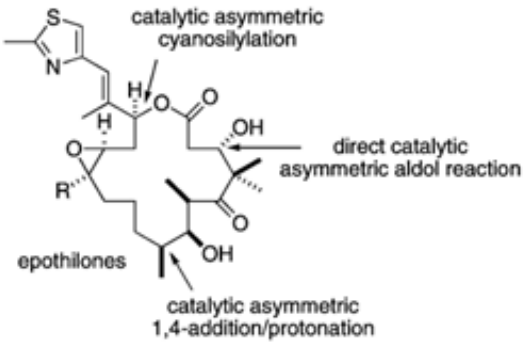
Proposed mechanism

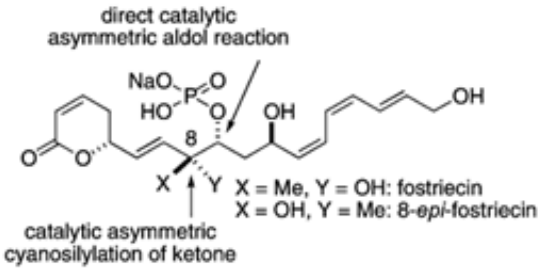
(1) Y. M. A. Yamada, N. Yoshikawa, H. Sasai and M. Shibasaki, *Angew. Chem., Int. Ed.*, **1997**, *36*, 1871–1873; (2) M. Shibasaki, M. Kanai, S. Matsunaga and N. Kumagai, *Acc. Chem. Res.*, **2009**, *42*, 1117–1127.

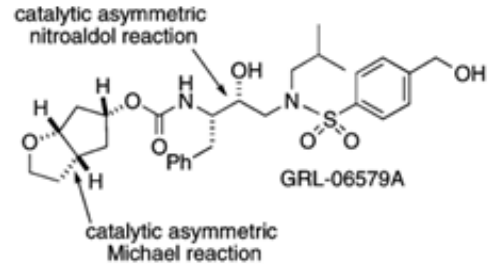
Conclusion

Representative catalytic asymmetric reactions promoted by REMB complexes







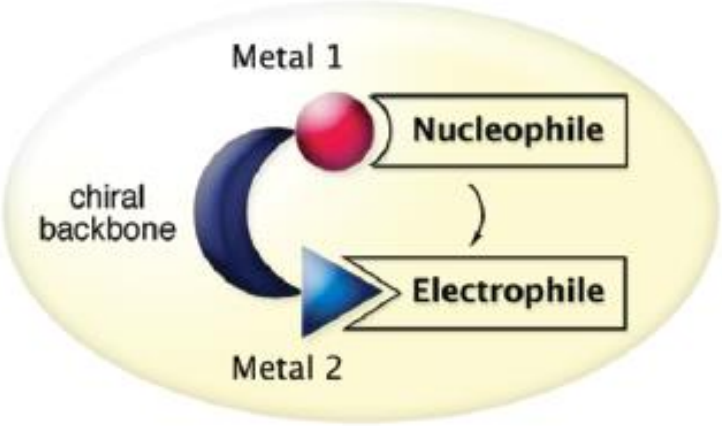


(1) Y. M. A. Yamada, N. Yoshikawa, H. Sasai and M. Shibasaki, *Angew. Chem., Int. Ed.*, **1997**, *36*, 1871–1873; (2) M. Shibasaki, M. Kanai, S. Matsunaga and N. Kumagai, *Acc. Chem. Res.*, **2009**, *42*, 1117–1127.

Frontiers in Chemical Synthesis III: Stereochemistry

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

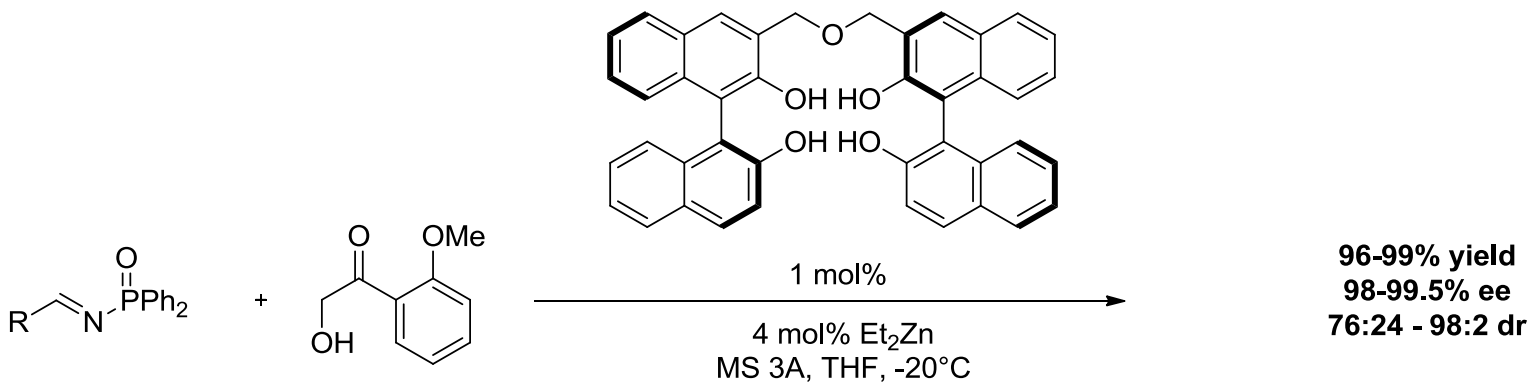
Thanks!!

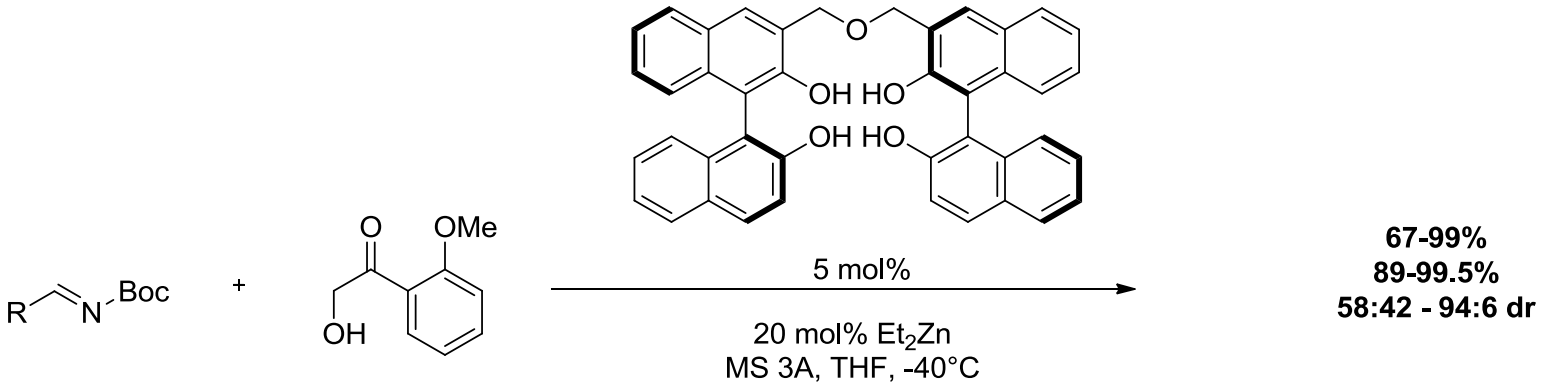


Michele Boghi

2013

Questions?

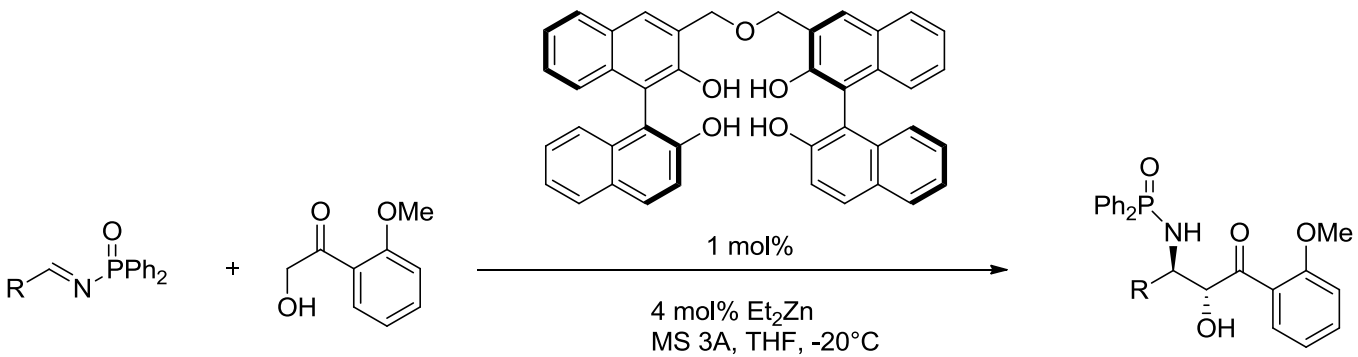


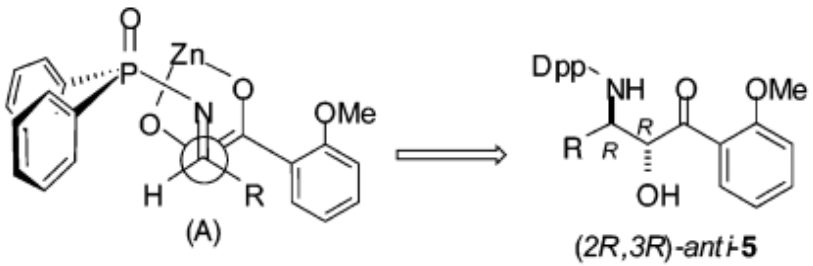


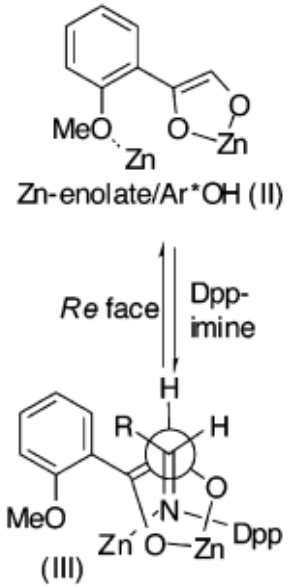
This specific Et_2Zn/Linked BINOL complex favores the attack selectively from the *Re* face of the 'nuclephile'.

M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126,* 8777-8785.

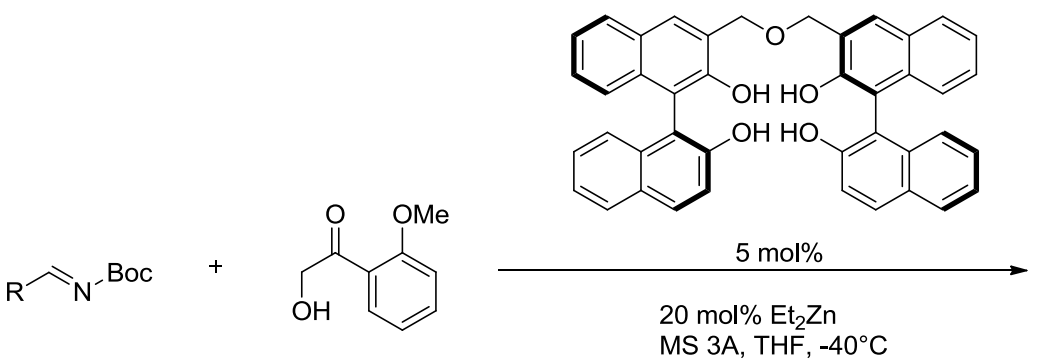
Answer

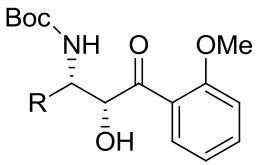

1 mol%
4 mol% Et2Zn
MS 3A, THF, -20°C
96-99% yield
98-99.5% ee
76:24 - 98:2 dr


(A)
(2R,3R)-anti-5

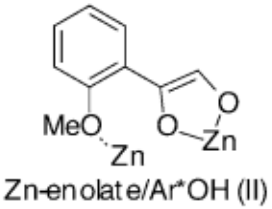

Zn-enolate/Ar*OH (II)
Re face
Dpp-imine
(III)

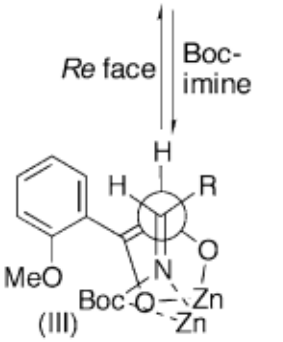
Answer

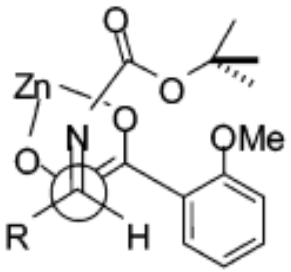




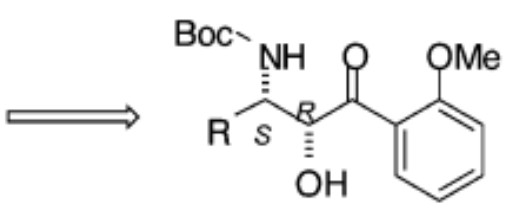
67-99%
89-99.5%
58:42 - 94:6 dr







(B)



(2*R*,3*S*)-*syn*-**6**

M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8777-8785.