Frontiers in Chemical Synthesis II
Stereoselective Synthesis

Seminar Program
May 20, BCH 5310
May 22, BCH 5310

	Speaker	**Title**
	May 20, 2019, BCH 5310	
	Session I: (Bastian Muriel)	
8h15-9h15	Teerawat Songsichan	*Transition-Metal-Catalyzed Asymmetric Hydrogenation of Unsaturated Carboxylic Acids*
9h15-10h15	Eliott Le Du	*Magnesium-Catalyzed Asymmetric Transformations*
10h15-11h15	Philipp Seeberger	*Asymmetric Hydrogenation Reactions catalysed by Frustrated Lewis Pairs*
	May 20, 2019, BCH 5310	
	Session II: (Vitalii Smal)	
13h15-14h15	Sung Hwan Park	*Enantioselective Catalysis with Chiral Phosphoramides*
14h15-15h15	Serhii Shyshkanov	*Memory of chirality*
15h15-16h15	Bastian Muriel	*Catalytic Enantioselective [2+2] Cycloadditions*
	May 22, 2019, BCH 5310	
	Session III: (Philipp Seeberger)	
8h15-9h15	Ashis Das	*Rhodium-catalyzed Asymmetric Synthesis of Heterocycles; Recent Developments*
9h15-10h15	Vitalii Smal	*Catalytic enantioselective C-C activation applied to total synthesis*
10h15-11h15	Kristers Ozols	*Selected Examples of Catalytic Asymmetric Umpolung of Imines and Carbonyl Compounds*

Magnesium-Catalyzed Asymmetric Transformations

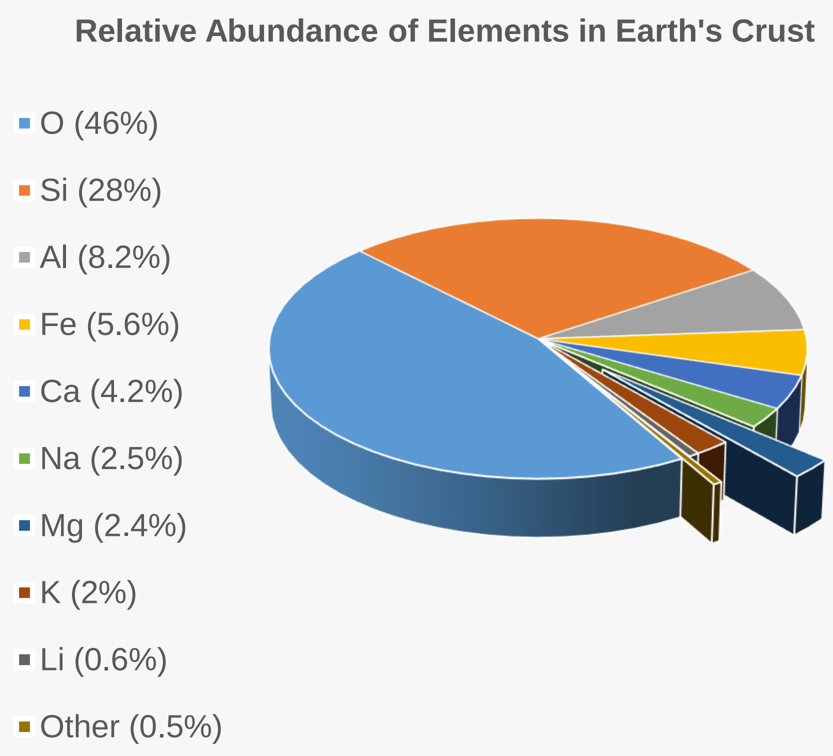
Frontiers in Chemical Synthesis III: Stereochemistry

Eliott Le Du
20/05/2019

Ecole Polytechnique Fédérale de Lausanne
Laboratory of Catalysis and Organic Synthesis (LCSO)

Introduction

- Eighth most abundant element in Earth's crust
- Cheap, readily available metal
- Biocompatible, less harmful for environment



Introduction

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- Biocompatible, less harmful for environment

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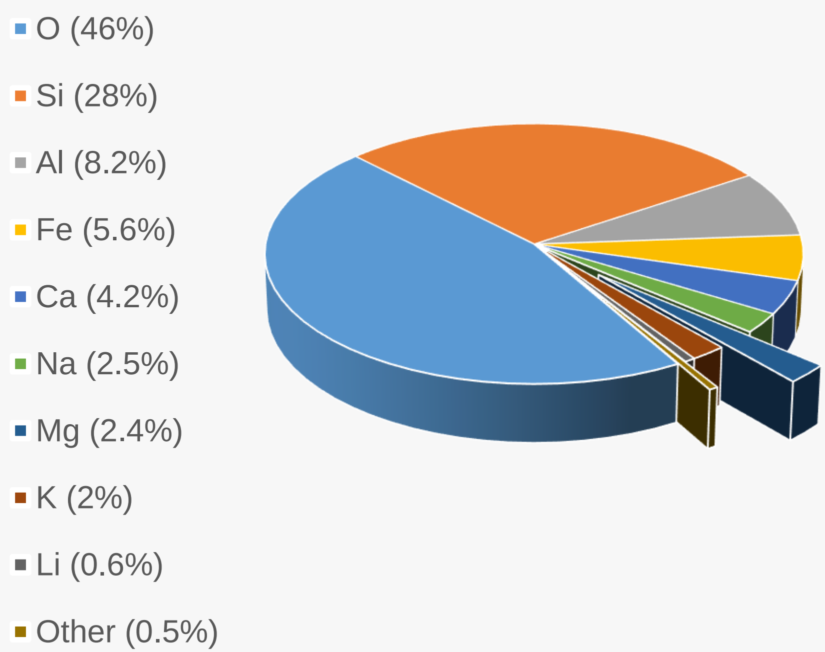
- Green sustainable chemistry

Relative Abundance of Elements in Earth's Crust



Introduction

- Electronic configuration: $1s_2 2s_2 2p_6 3s_2$
- Only two easily accessible oxidation states 0 and +II
- Low electronegativity: formation of strong Brønsted bases (Grignard reagent, Nobel Prize 1912)
- Moderate Lewis acidity

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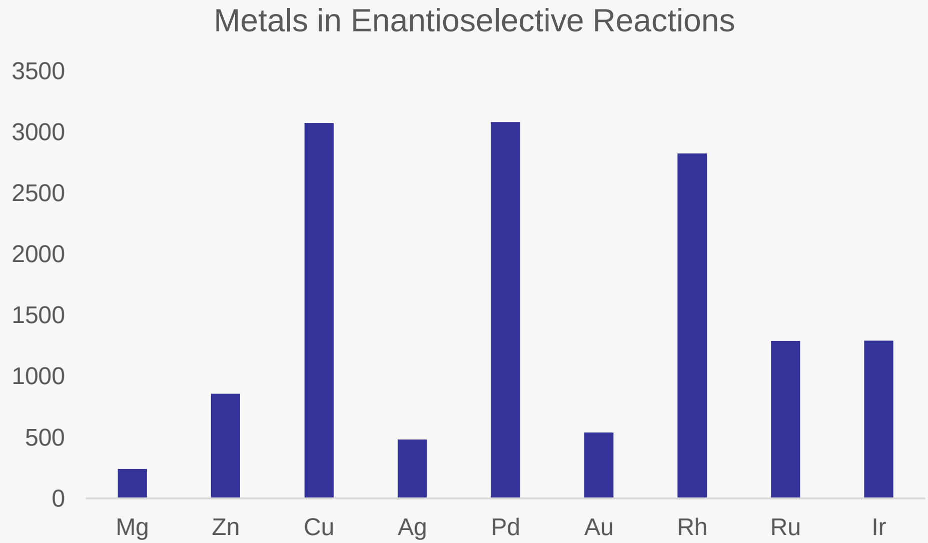
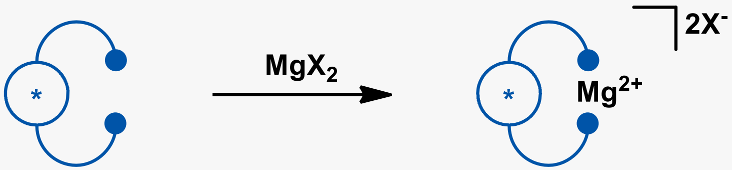
Different strategies to use Magnesium in asymmetric transformation



Scifinder 19.05.2019

Types of Magnesium Catalysts

Starting from a Mg(II) salt



- Tunable chiral backbone
- Coordination: tetrahedral or octahedral geometries
- Lewis acidity

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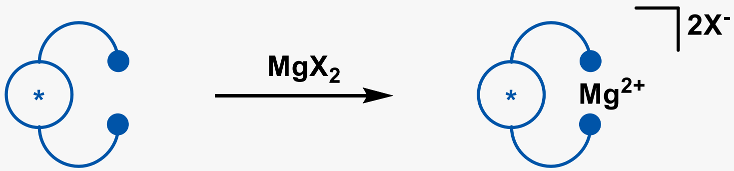

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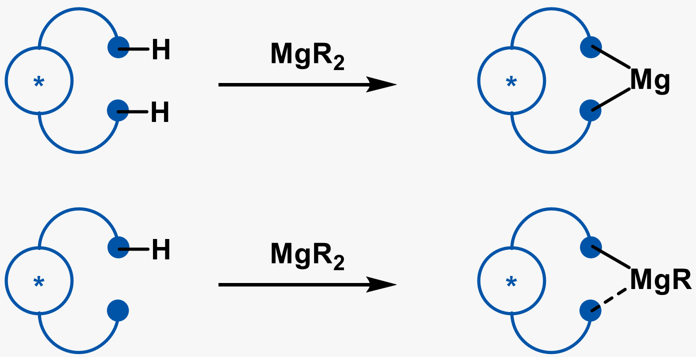
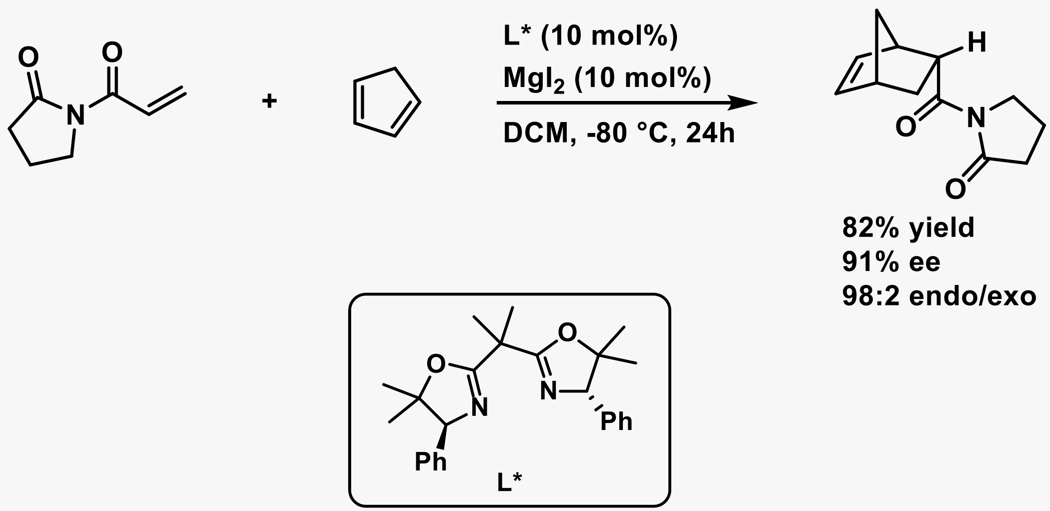
Generating *in-situ* a Mg(II) catalyst



- Tunable chiral backbone
- Covalent bonds with Mg
- Lewis acidity / Brønsted basicity

Coordinated Mg(II) Salt: Diels-Alder Reaction

- Seminal work by Corey and Ishihara (1992):



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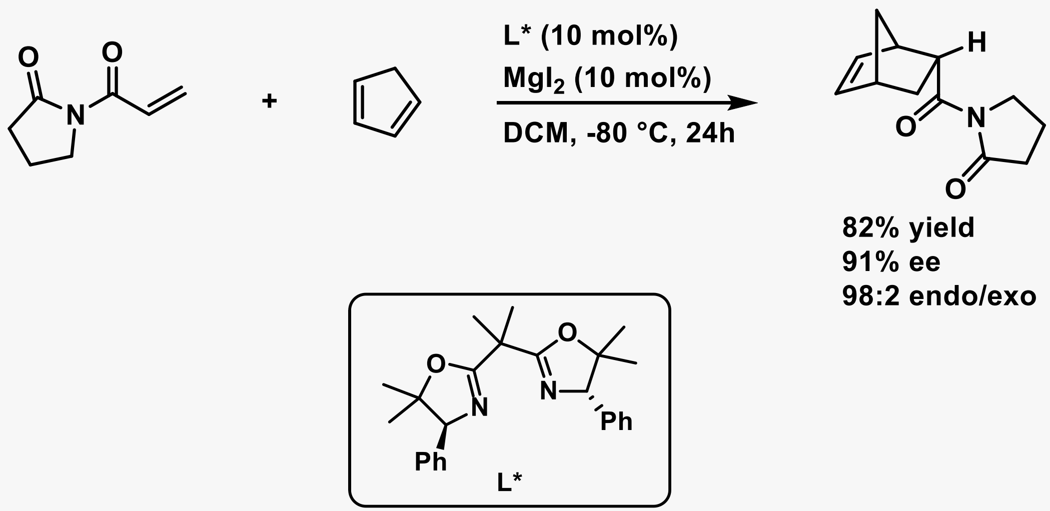
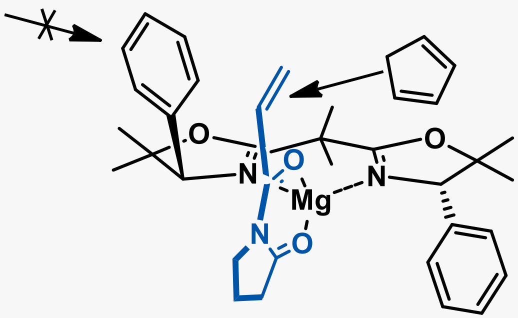


- Model for selectivity:



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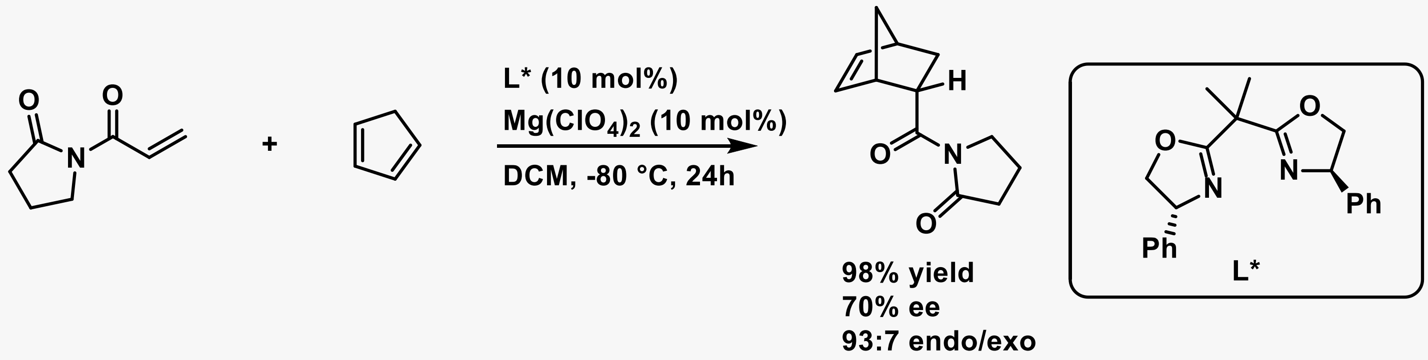
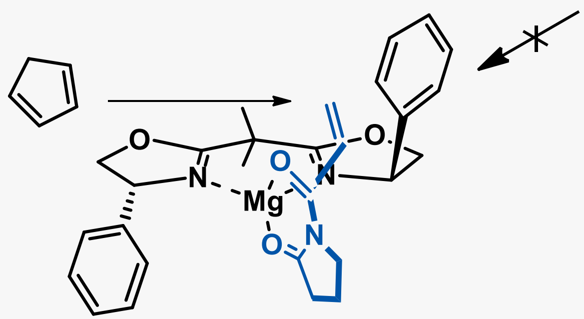
Coordinated Mg(II) Salt: Diels-Alder Reaction

- Mechanistic investigation:



- Model for selectivity:
  - No additive
  - No Non-Linear Effect



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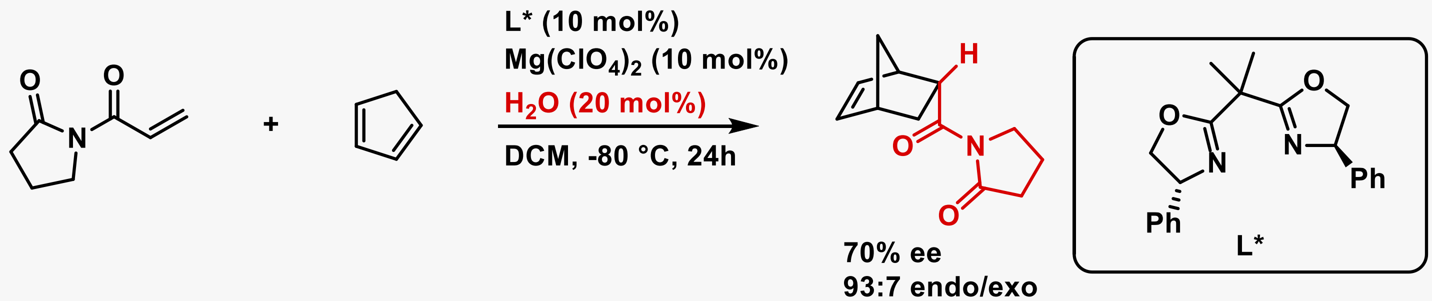

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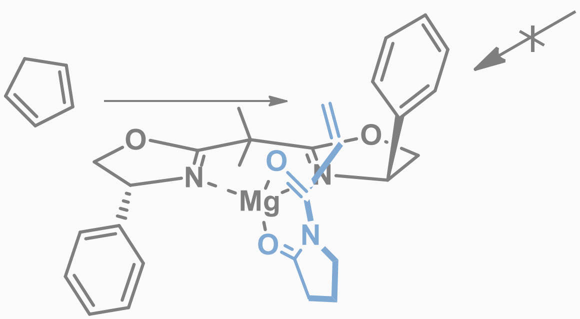
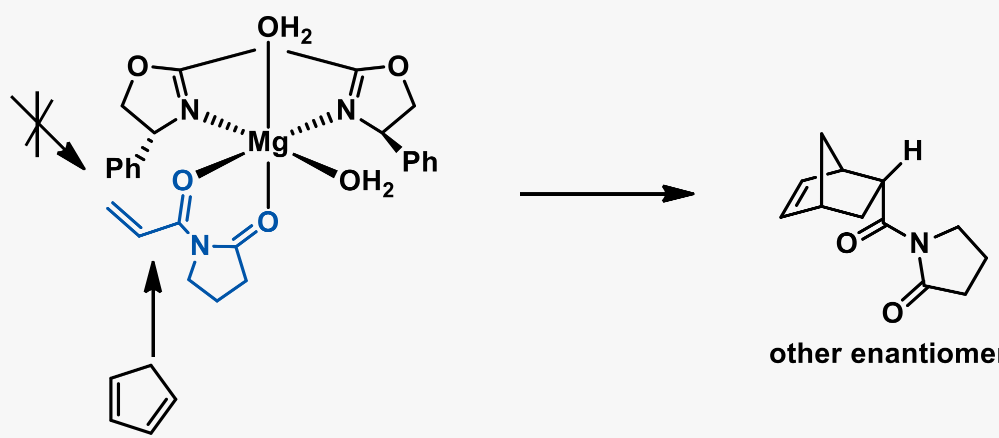


- 2.0 equiv. of water
- No Non-Linear Effect
- Octahedral geometry
- Other enantiomer with same ligand



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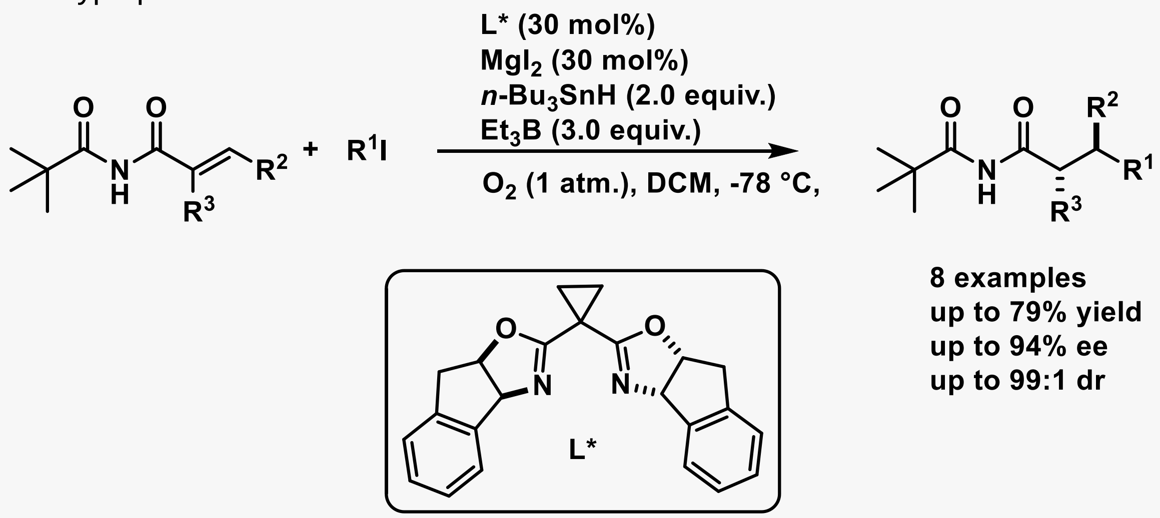
Coordinated Mg(II) Salt: Radical Reactions

➢ Synthesis of *anti*-aldol-type products:



8 examples
up to 79% yield
up to 94% ee
up to 99:1 dr

Sibi, M. P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* **2005**, 2390.

Coordinated Mg(II) Salt: Radical Reactions

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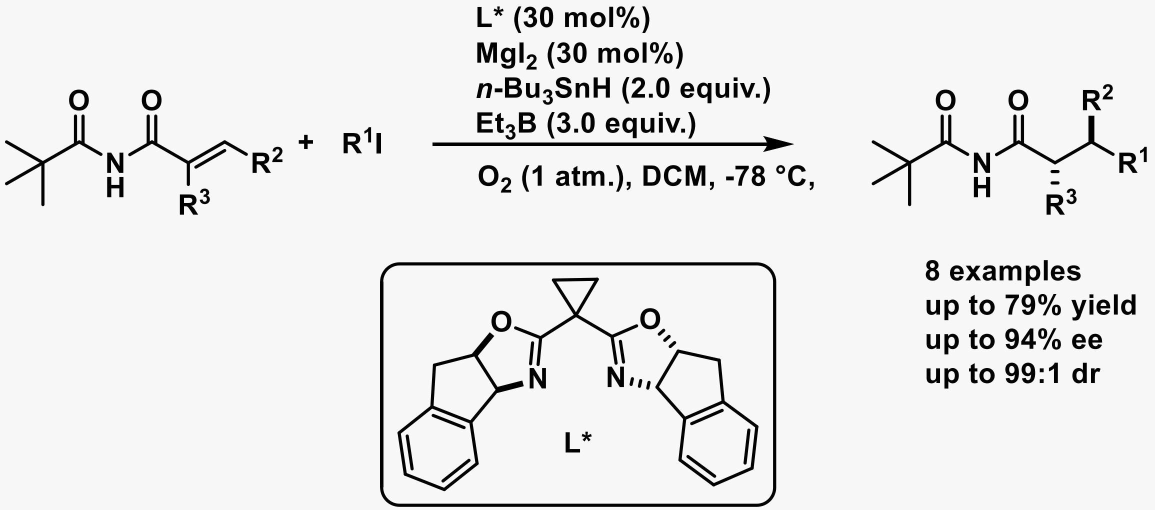
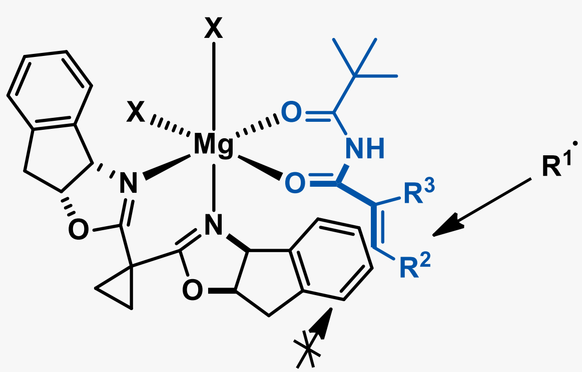
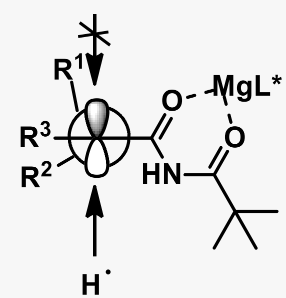


- Model for selectivity:

Addition to β-carbon



Addition to α-carbon

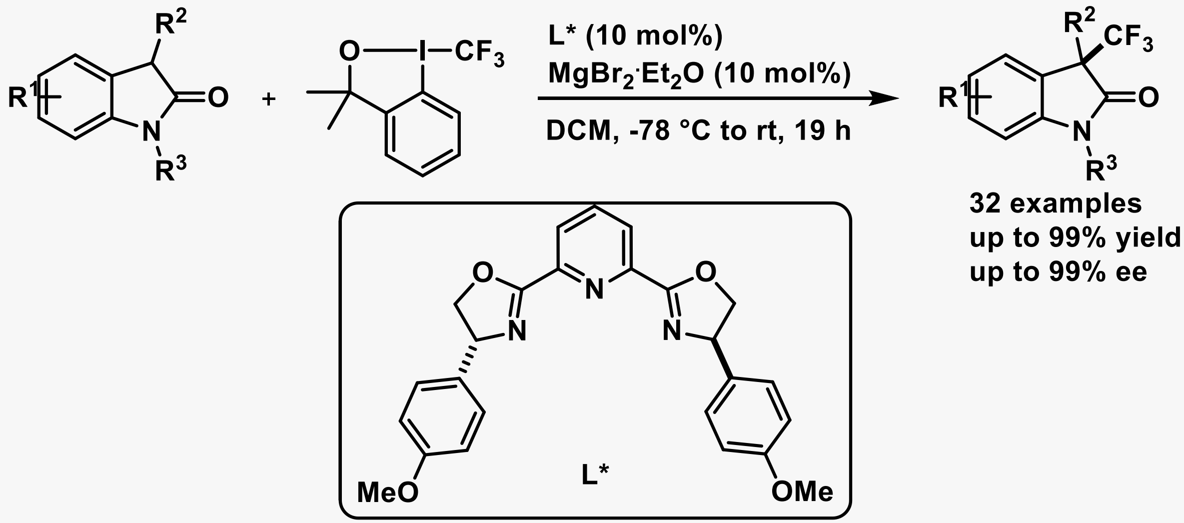


- Not controlled by ligand
- Insensitive to R^2

Sibi, M. P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* **2005**, 2390.

Coordinated Mg(II) Salt: Radical Reactions

- Generation of enantioenriched quaternary carbon centers:



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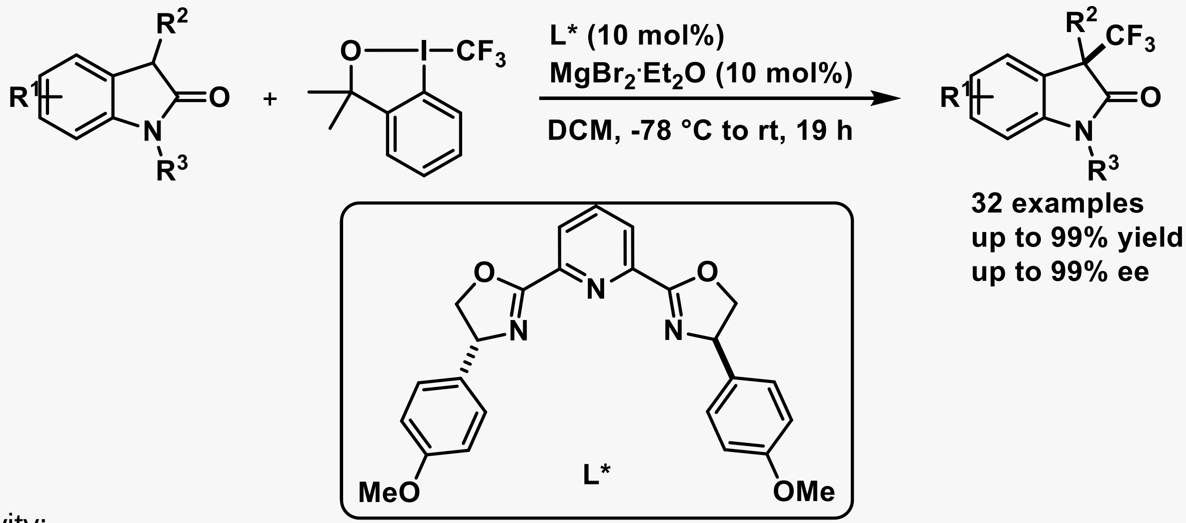

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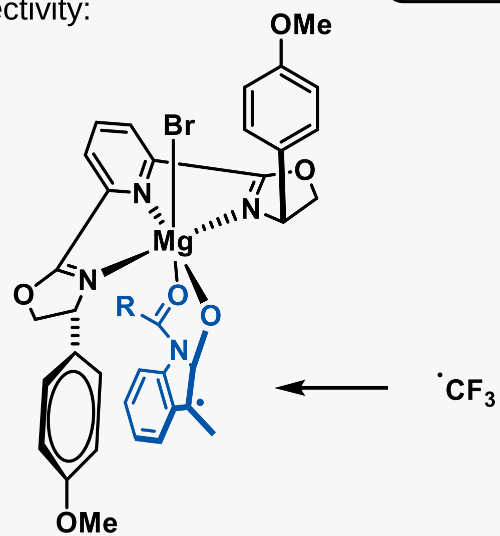


➢ Activation of Togni's reagent through proton transfer

➢ Reduction of Togni's reagent (SET to enolate)

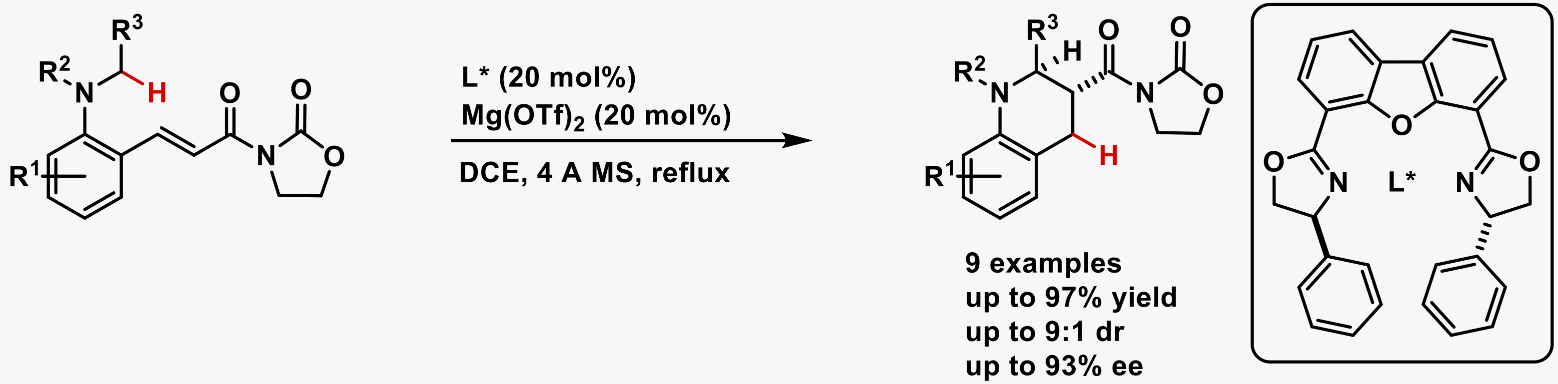
➢ Liberation of CF_3 radical

➢ Potential π- π stacking interaction

Calvo, R.; Comas-Vives, A.; Togni, A.; Katayev, D. *Angew. Chem. Int. Ed.* **2019**, 1447.

Coordinated Mg(II) Salt: Hydride Shift / Cascade

- 1st Catalytic enantioselective hydride shift / ring closure cascade reaction:



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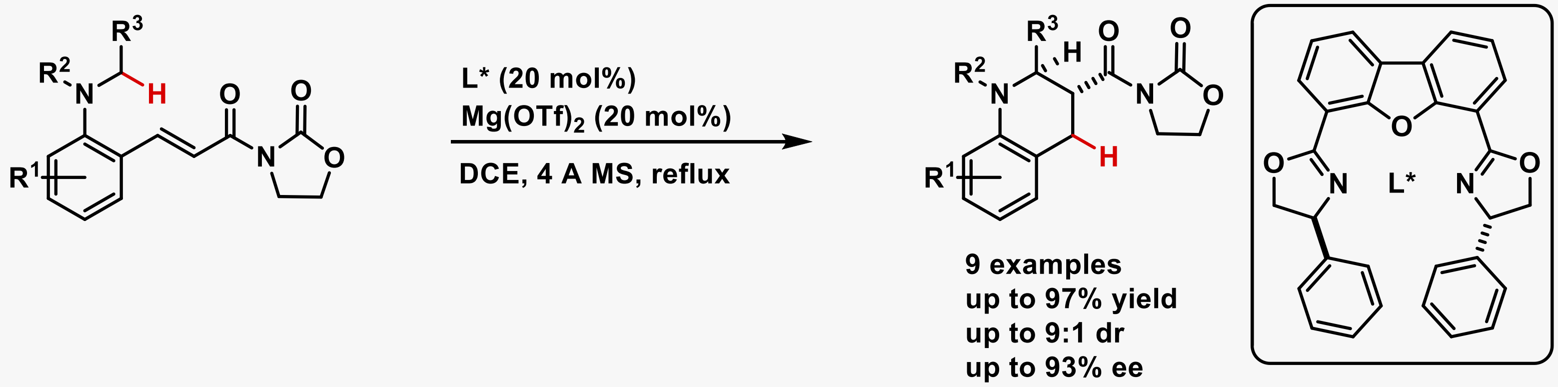

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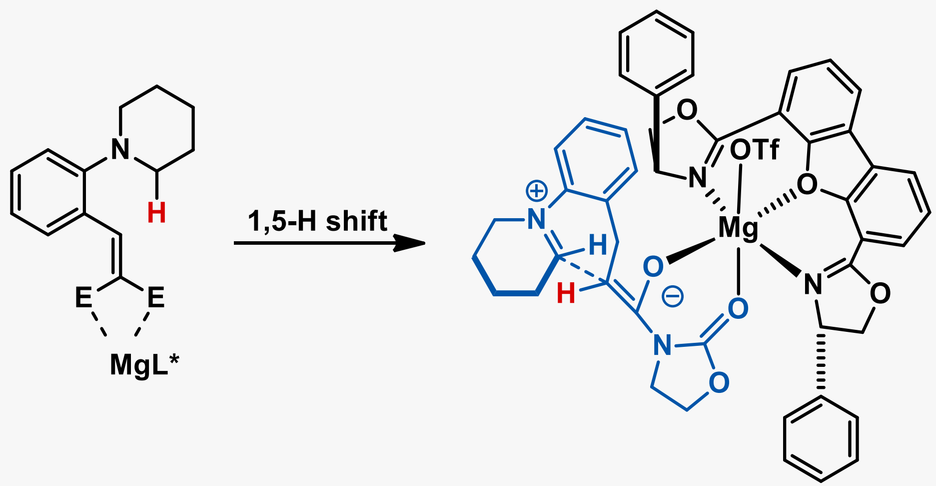

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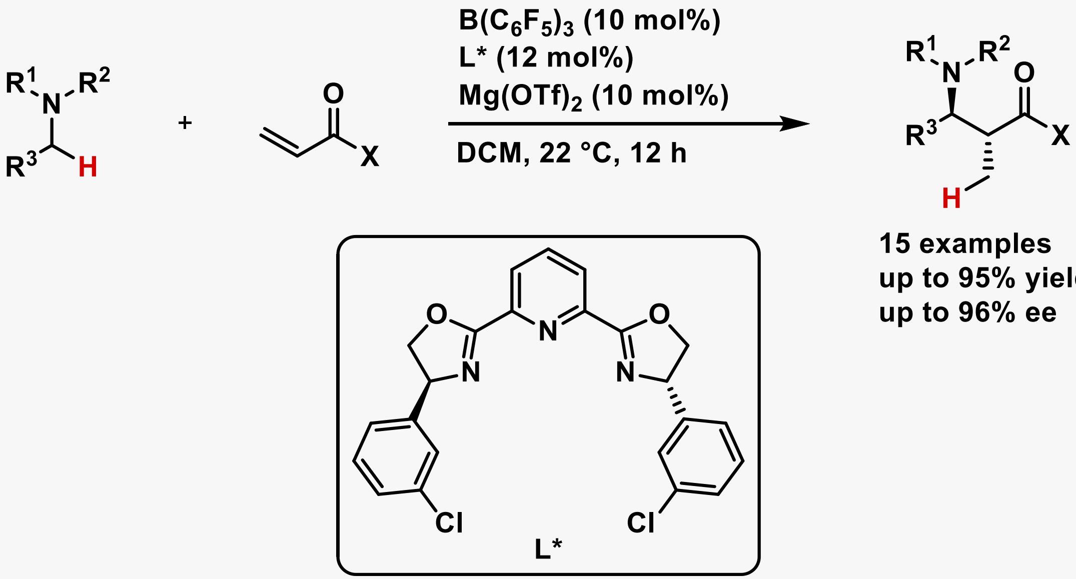
Coordinated Mg(II) Salt: Hydride Shift / Cascade

➢ Cooperative action of chiral and achiral Lewis acid catalysts



15 examples
up to 95% yield
up to 96% ee

Shang, M.; Chan, J. Z.; Cao, M.; Chang, Y.; Wang, Q.; Cook, B.; Torker, S.; Wasa, M. *J. Am. Chem. Soc.* **2018**, 10593.

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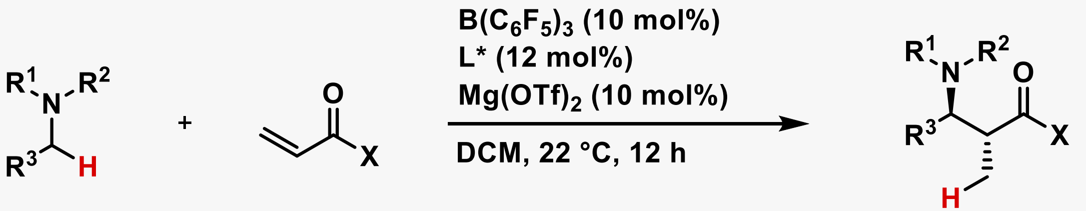

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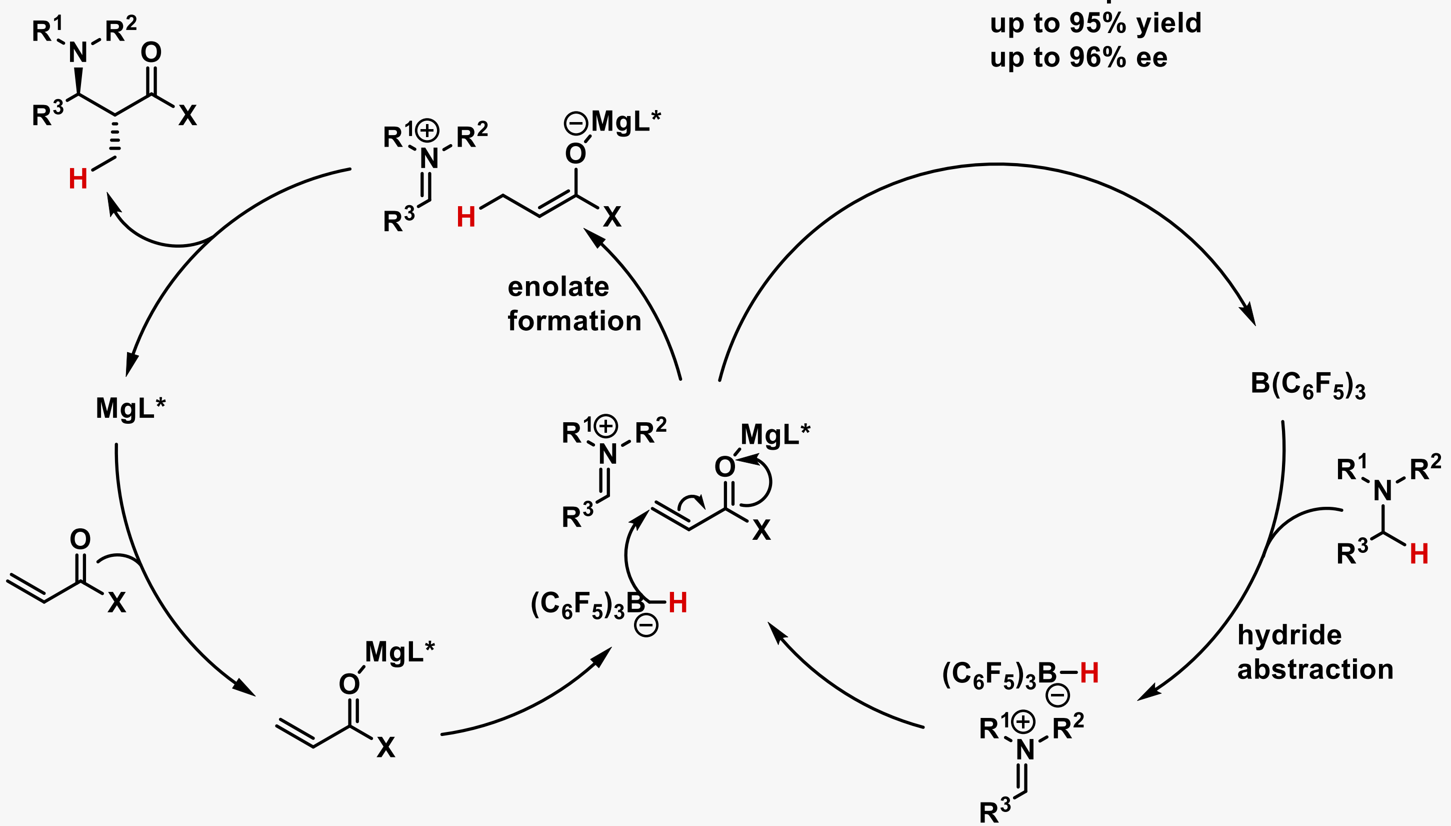
- Mechanism



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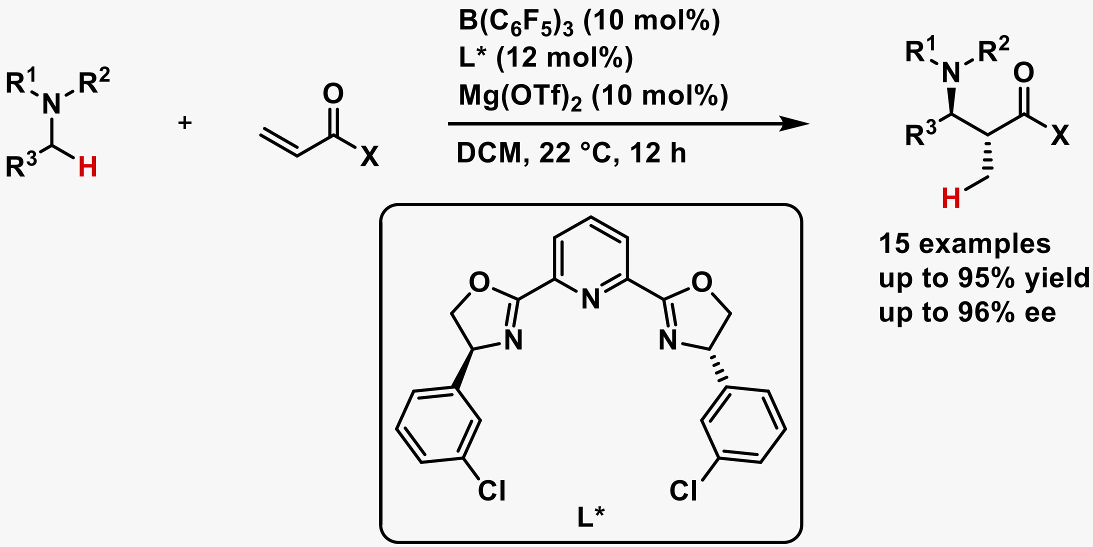

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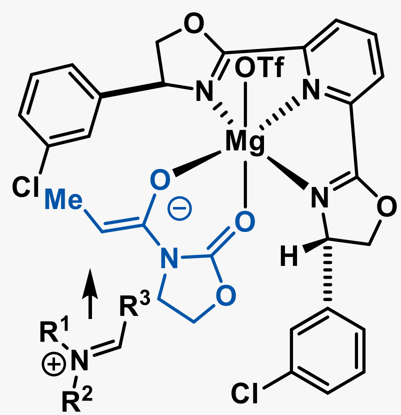
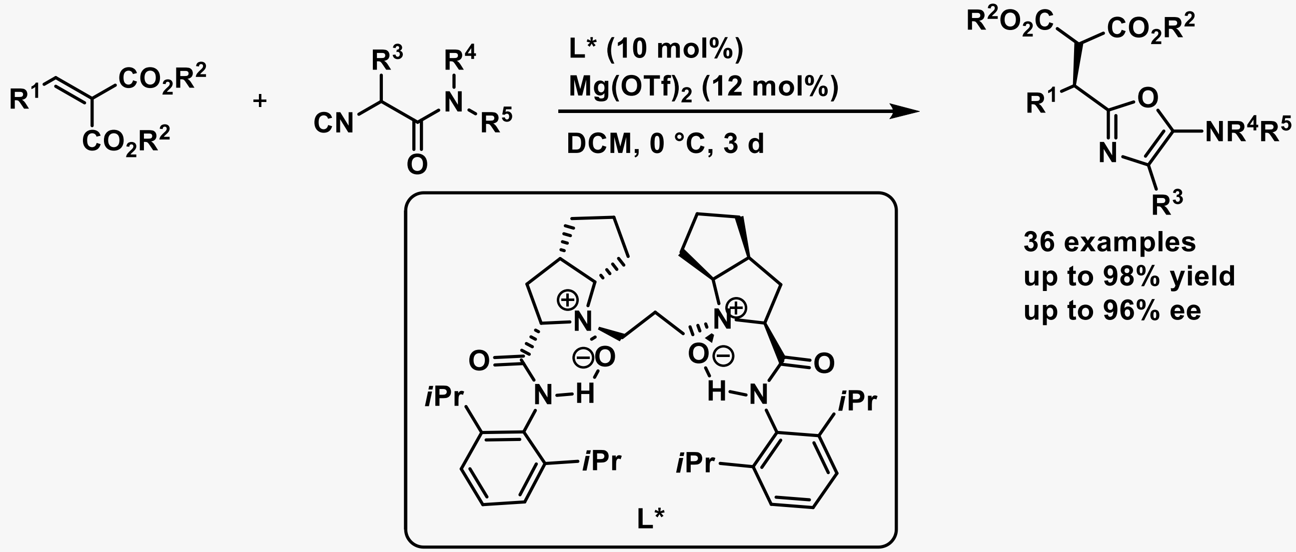


Coordinated Mg(II) Salt: Addition of Isocyanides

- α-addition of isocyanides to alkylydene malonates:



Luo, W.; Yuan, X.; Lin, L.; Zhou, P.; Liu, X.; Feng, X. *Chem. Sci.* **2016**, 4736.

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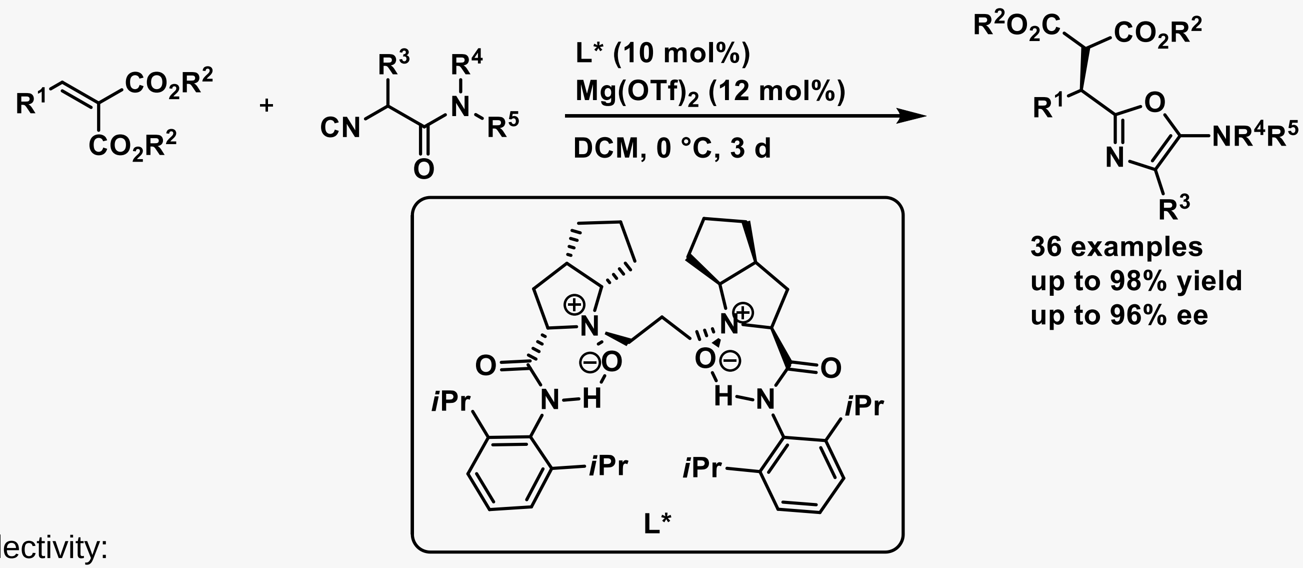

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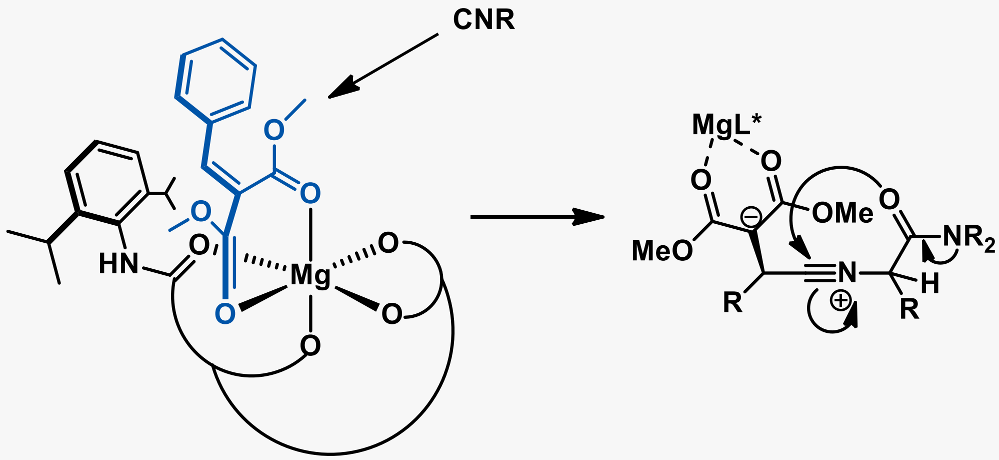

- N,N dioxide ligands: octahedral geometry
- Potential π- π stacking interaction

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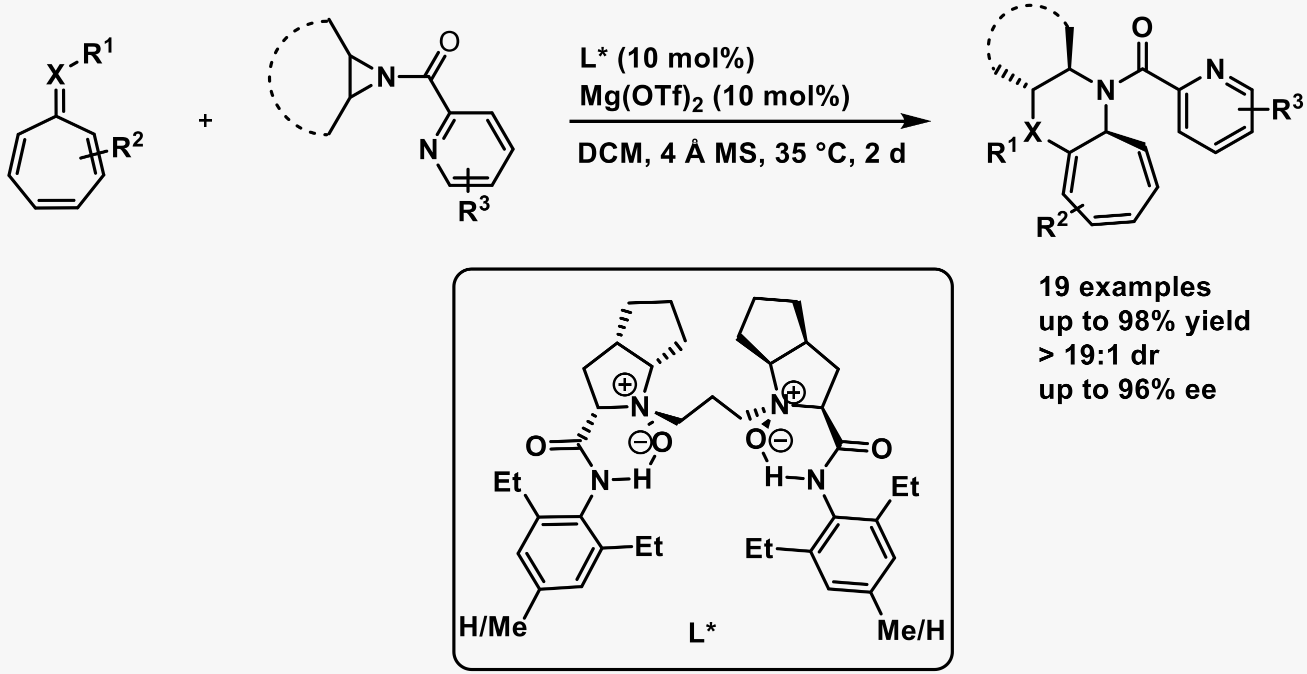
Coordinated Mg(II) Salt: Desymmetrization

- asymmetric catalytic strategy for [8+3] cycloaddition of azaheptafulvenes or tropones with *meso*-aziridine:



19 examples
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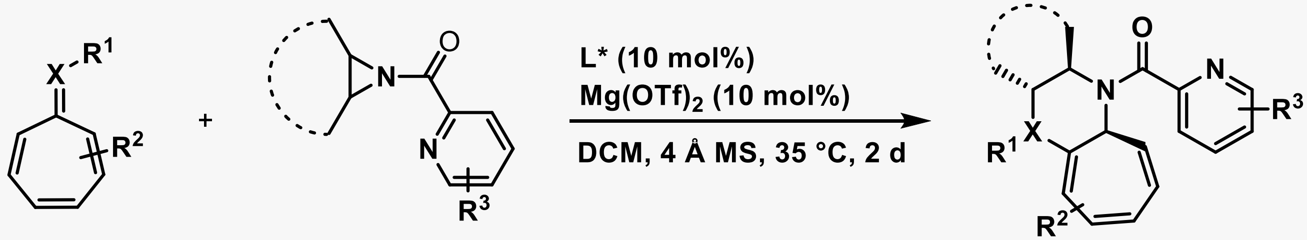

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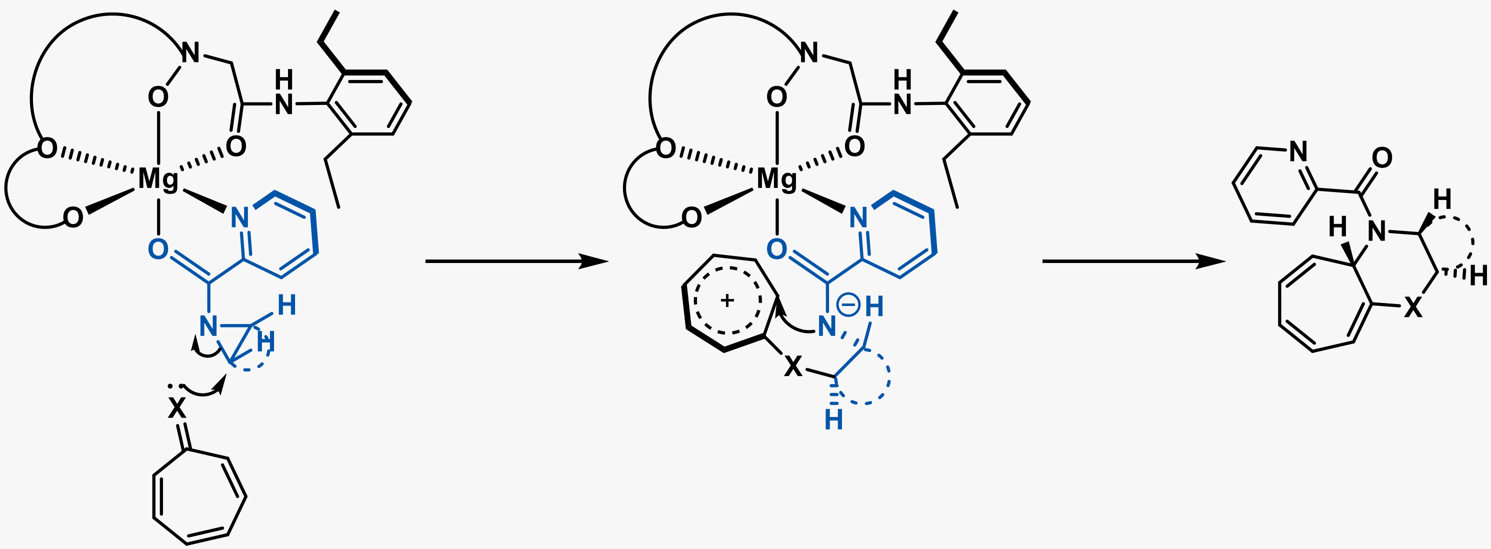

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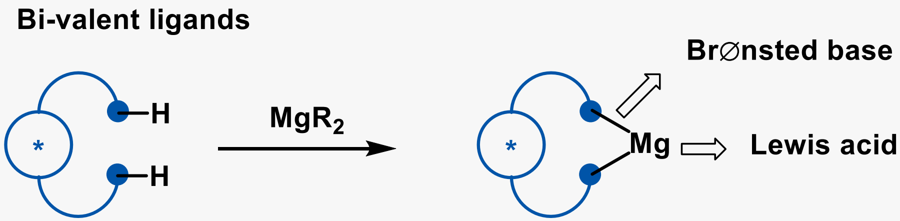
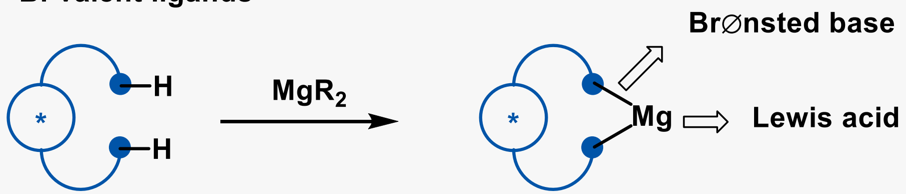
In-Situ Generated Mg(II) Catalyst



- Possibility to add coordinating additives

In-Situ Generated Mg(II) Catalyst

Bi-valent ligands



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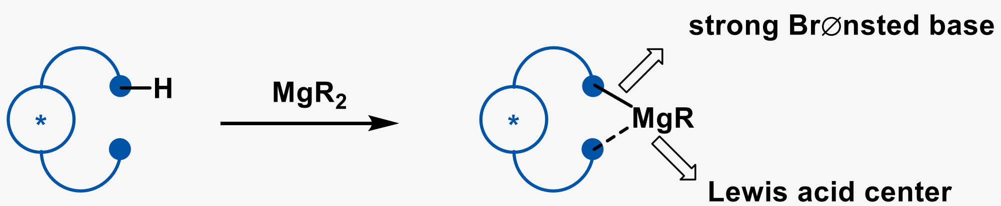

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In-Situ Generated Mg(II) Catalyst

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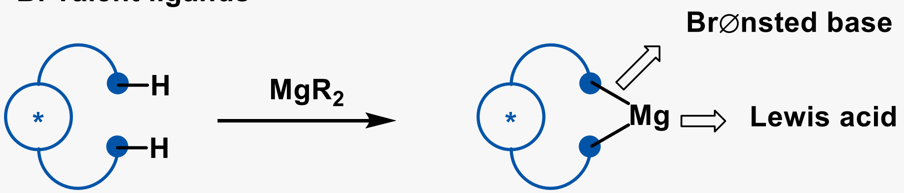

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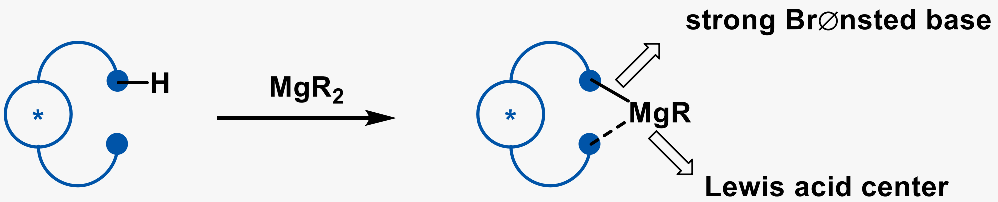

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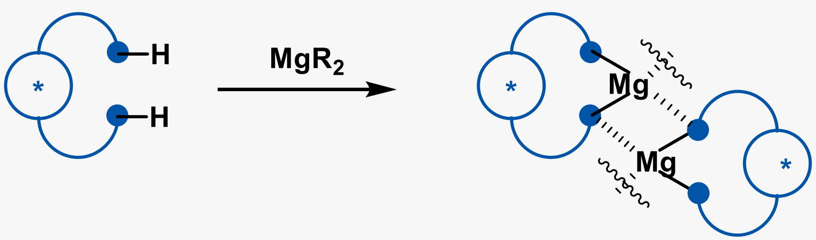
Polymetallic magnesium catalysis



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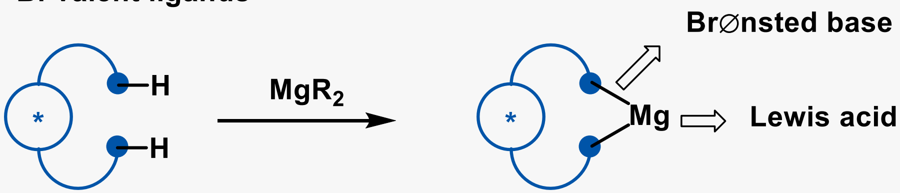

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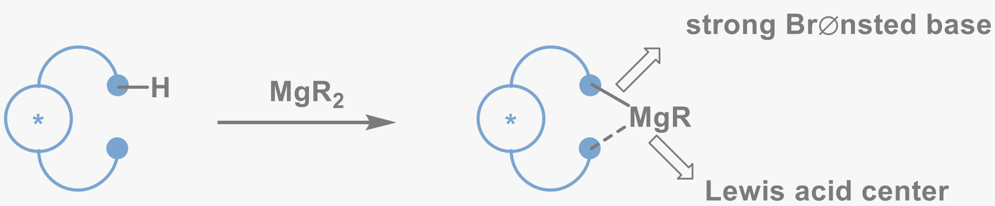

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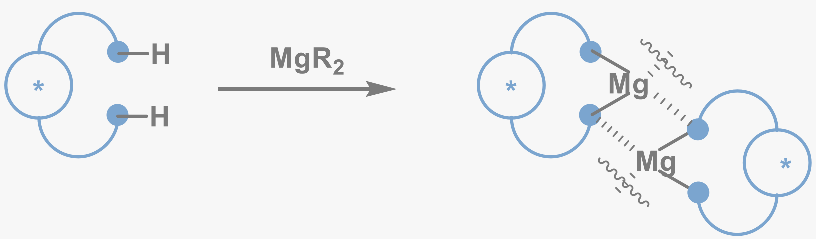
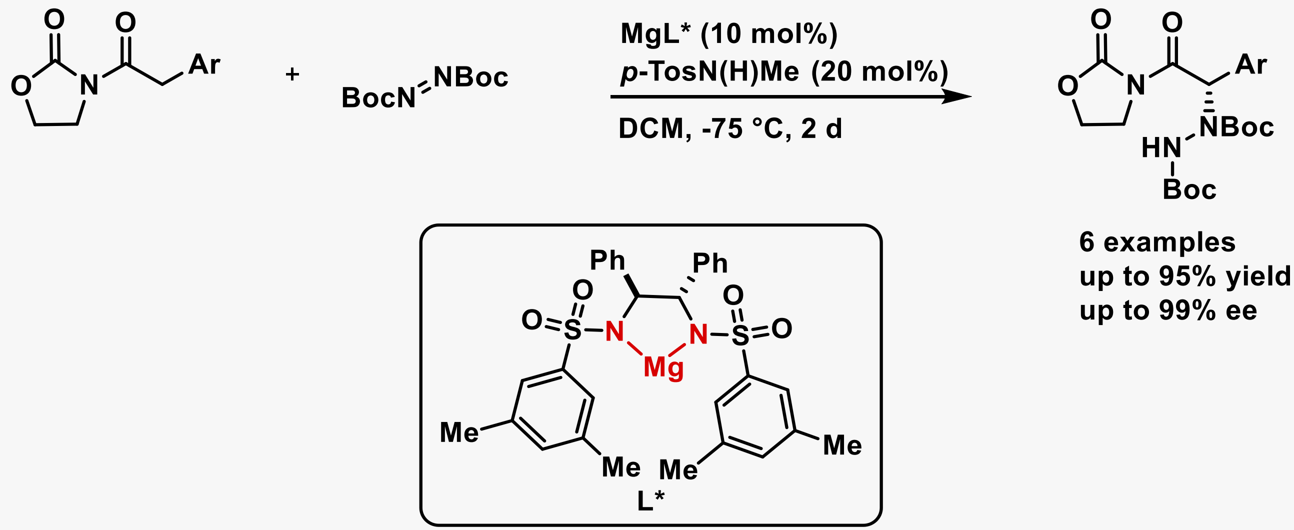


In-Situ Generated Mg(II) Catalyst

- Seminal work by Evans and Nelson (1997)



6 examples
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Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, 6452.

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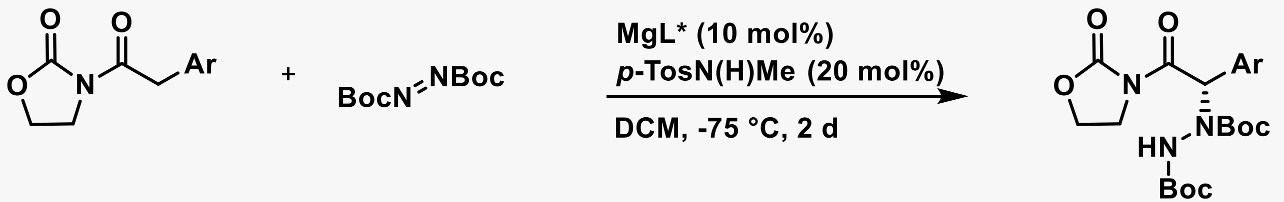

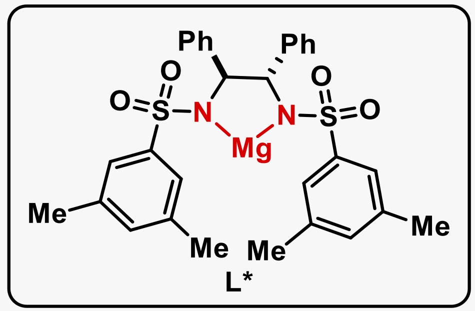

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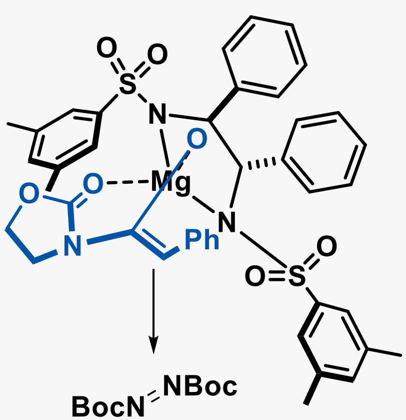

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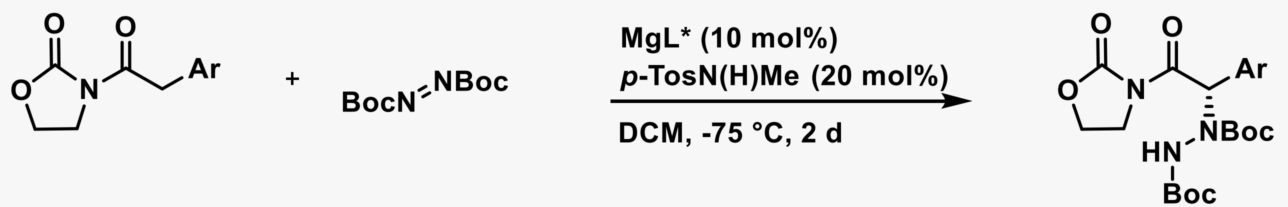

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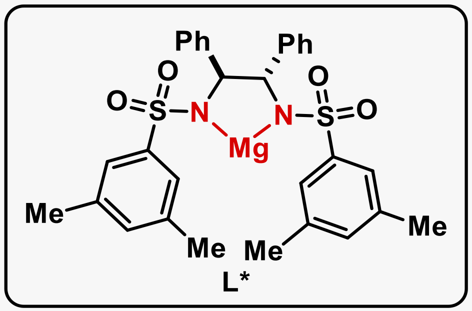
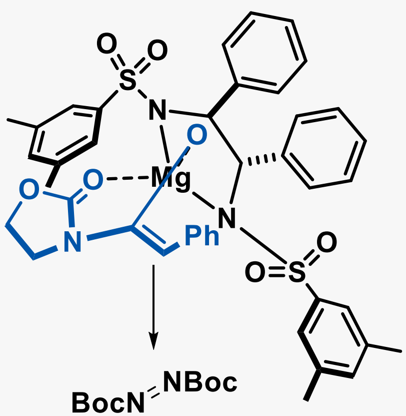
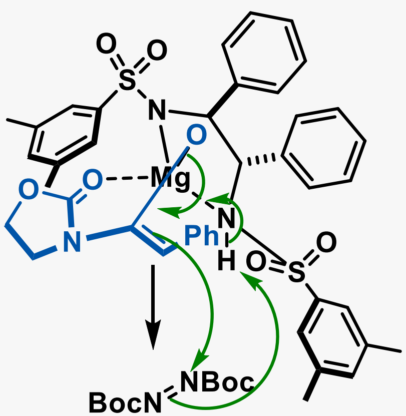


- Model for selectivity:

- Proposed:



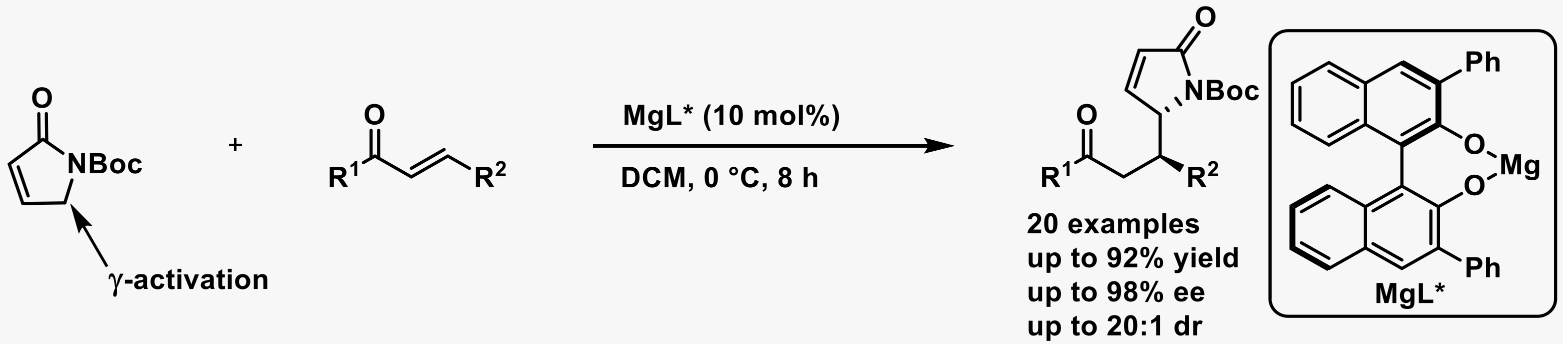
- Alternative:



Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, 6452.

In-Situ Generated Mg(II) Catalyst

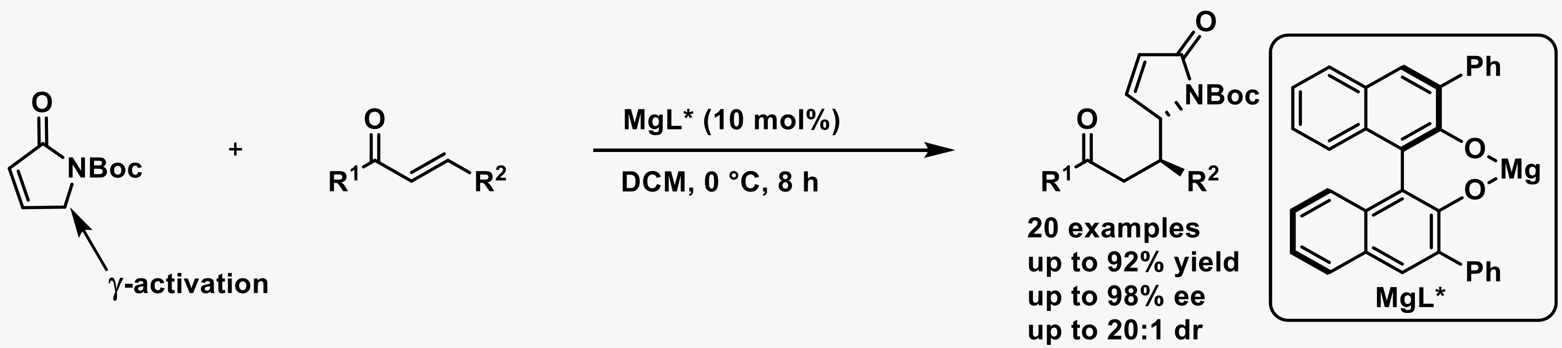
➢ Asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactam:

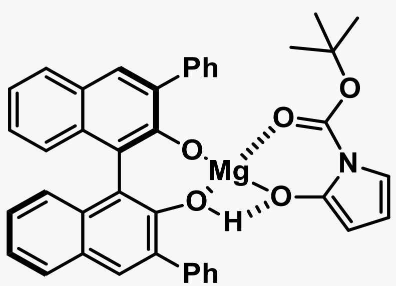


(1) Lin, L.; Zhang, J.; Ma, X.; Fu, X.; Wang, R. *Org. Lett.* **2011**, 6410.

In-Situ Generated Mg(II) Catalyst

➢ Asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactam:

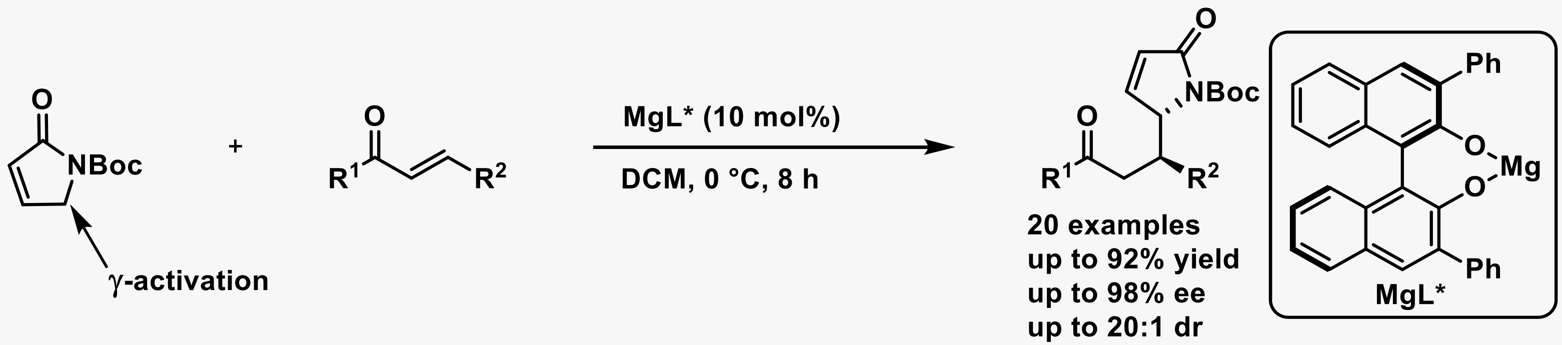




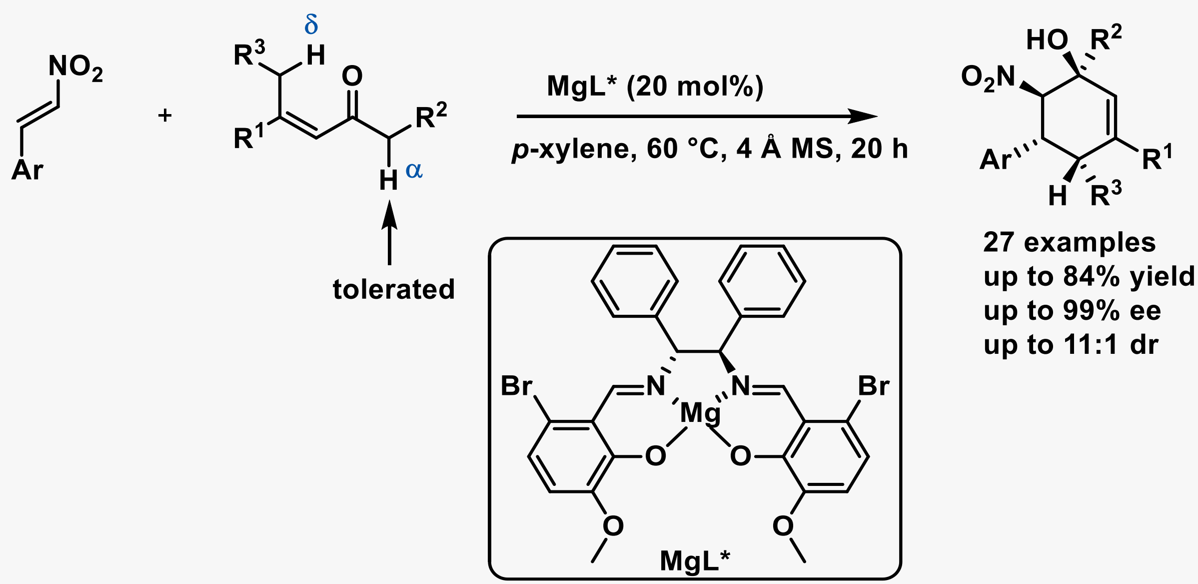
(1) Lin, L.; Zhang, J.; Ma, X.; Fu, X.; Wang, R. *Org. Lett.* **2011**, 6410.

In-Situ Generated Mg(II) Catalyst

- Asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactam:



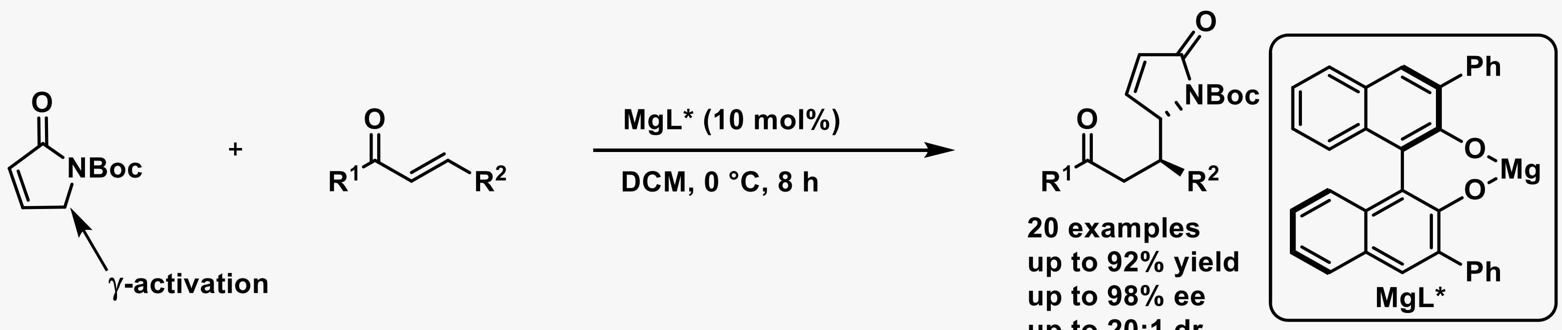
- γ-Functionalization of linear α,β-unsaturated ketones:



(1) Lin, L.; Zhang, J.; Ma, X.; Fu, X.; Wang, R. *Org. Lett.* **2011**, 6410. (2) Yang, D.; Wang, L.; Han, F.; Zhao, D.; Zhang, B.; Wang, R. *Angew. Chem. Int. Ed.* **2013**, 6739.

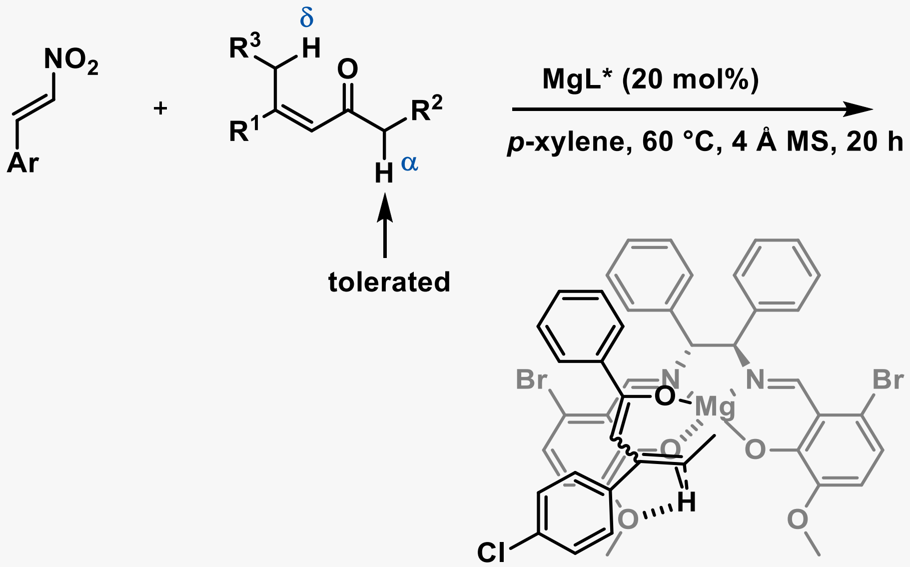
In-Situ Generated Mg(II) Catalyst

- Asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactam:



20 examples
up to 92% yield
up to 98% ee
up to 20:1 dr

- γ-Functionalization of linear α,β-unsaturated ketones:

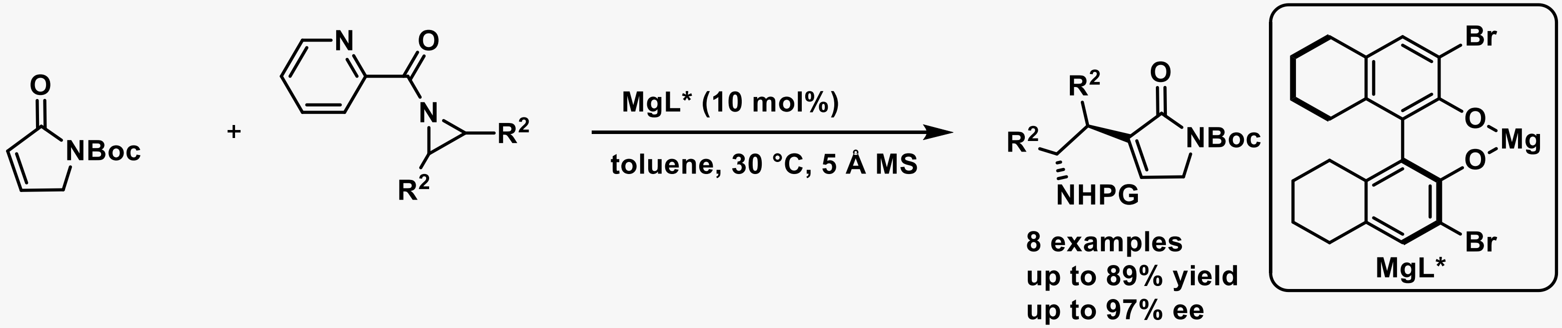


27 examples
up to 84% yield
up to 99% ee
up to 11:1 dr

(1) Lin, L.; Zhang, J.; Ma, X.; Fu, X.; Wang, R. *Org. Lett.* **2011**, 6410. (2) Yang, D.; Wang, L.; Han, F.; Zhao, D.; Zhang, B.; Wang, R. *Angew. Chem. Int. Ed.* **2013**, 6739.

In-Situ Generated Mg(II) Catalyst

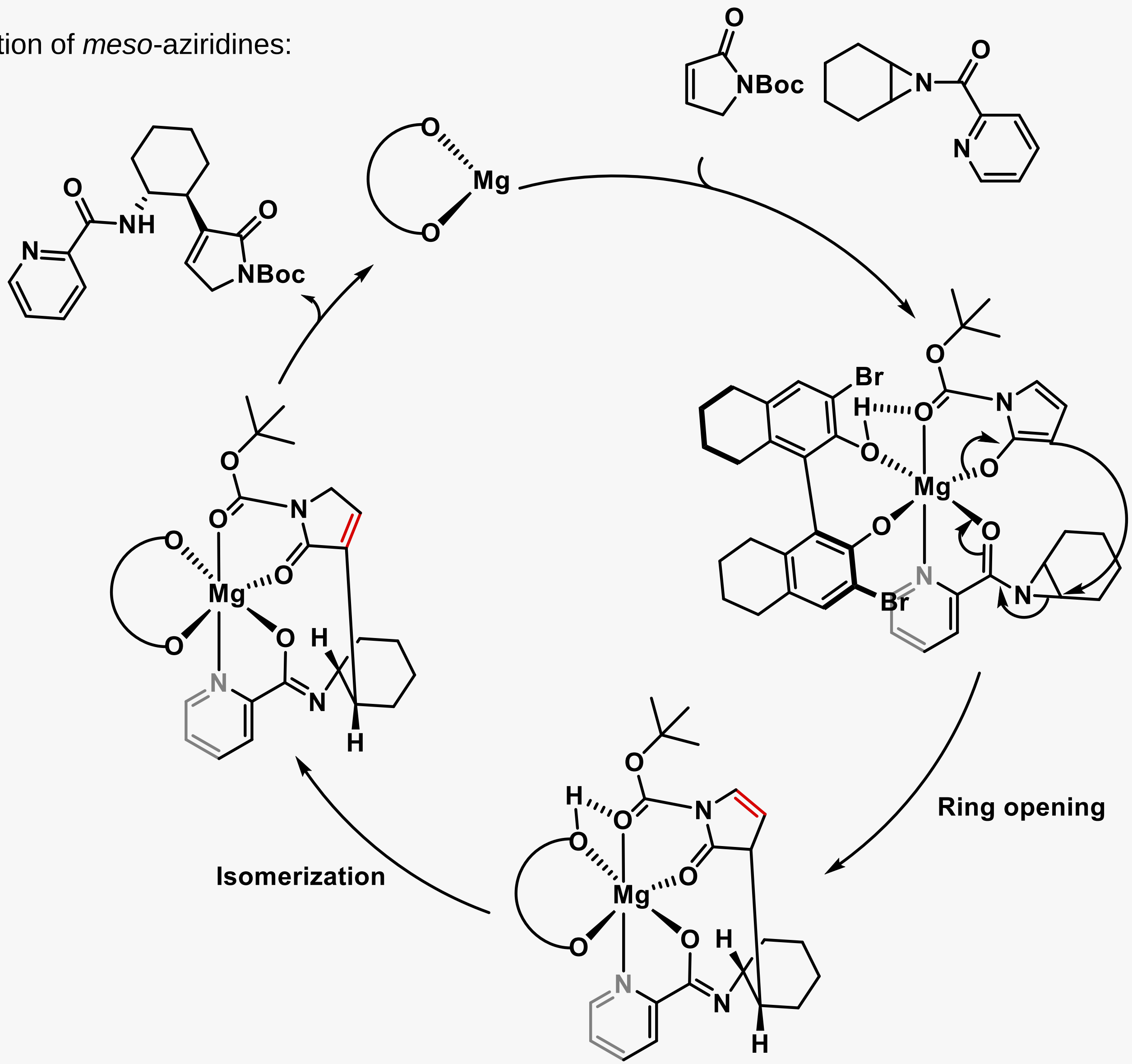
➢ Desymmetrization of *meso*-aziridines:



Li, D.; Wang, Y.; Wang, L.; Wang, J.; Wang, P.; Wang, K.; Lin, L.; Liu, D.; Jiang, X.; Yang, D. *Chem. Commun.* **2016**, 9640.

In-Situ Generated Mg(II) Catalyst

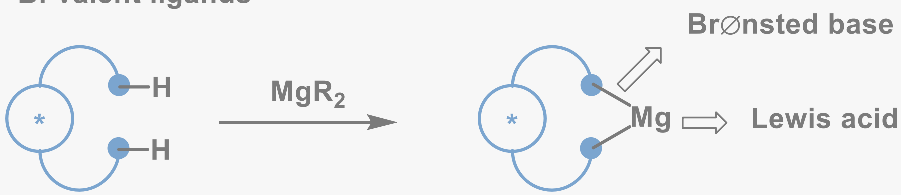
- Desymmetrization of *meso*-aziridines:



Li, D.; Wang, Y.; Wang, L.; Wang, J.; Wang, P.; Wang, K.; Lin, L.; Liu, D.; Jiang, X.; Yang, D. *Chem. Commun.* **2016**, 9640.

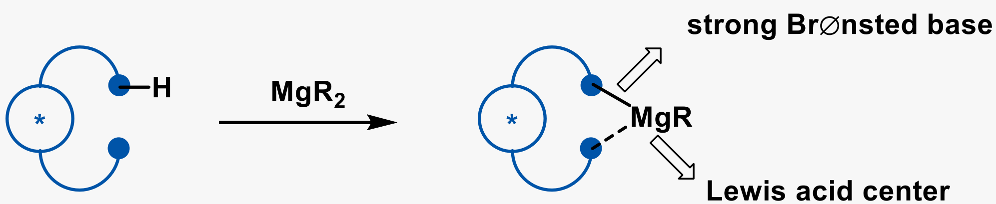
In-Situ Generated Mg(II) Catalyst

Bi-valent ligands



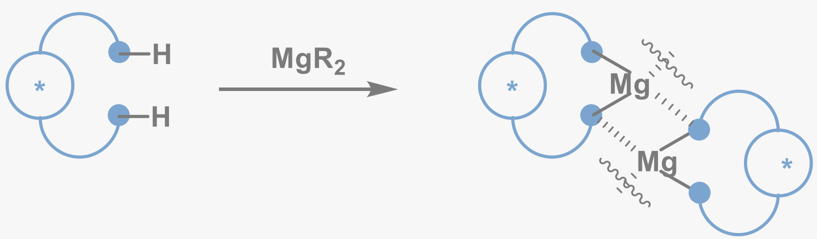
- Possibility to add coordinating additives

Mono-valent ligands



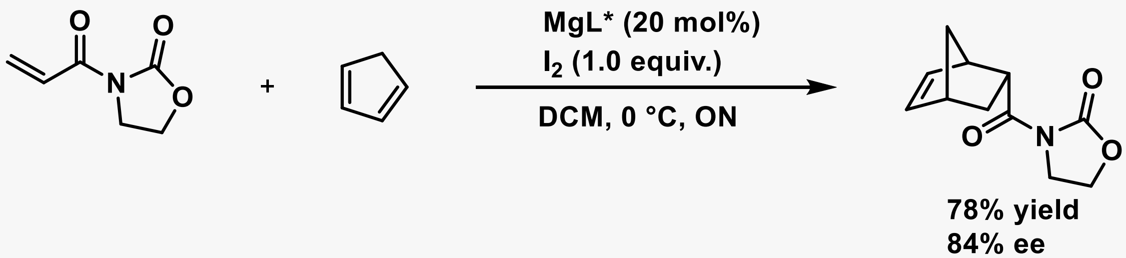
- Possibility to add covalently bonding additives

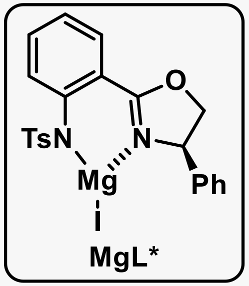
Polymetallic magnesium catalysis



In-Situ Generated Mg(II) Catalyst

➢ Early works on *in-situ* magnesium catalysis with mono-covalent ligands:





(1) Fujisawa, T.; Ichiyanagi, T.; Shimizu, M. *Tetrahedron Lett.* **1995**, 5031.

In-Situ Generated Mg(II) Catalyst

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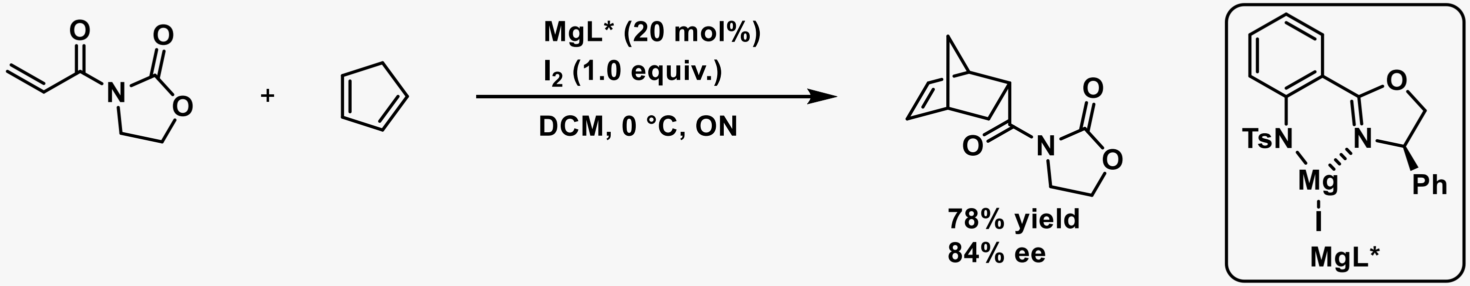
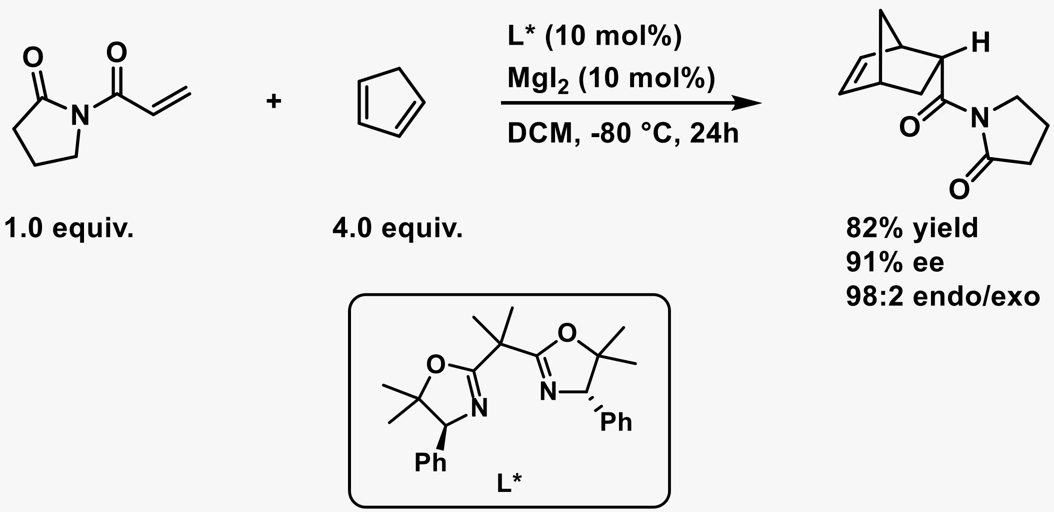


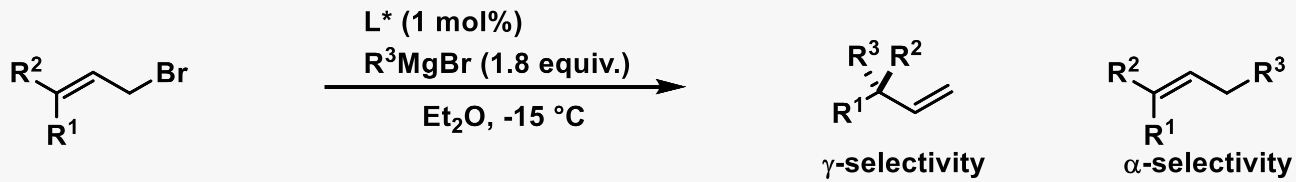
➢ Corey and Ishihara (1992):

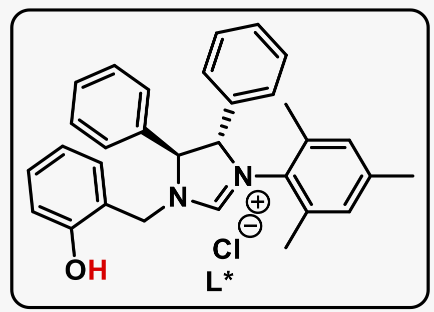


(1) Fujisawa, T.; Ichiyanagi, T.; Shimizu, M. *Tetrahedron Lett.* **1995**, 5031. (2) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, 6807.

In-Situ Generated Mg(II) Catalyst

- Mg-mediated asymmetric allylic alkylation



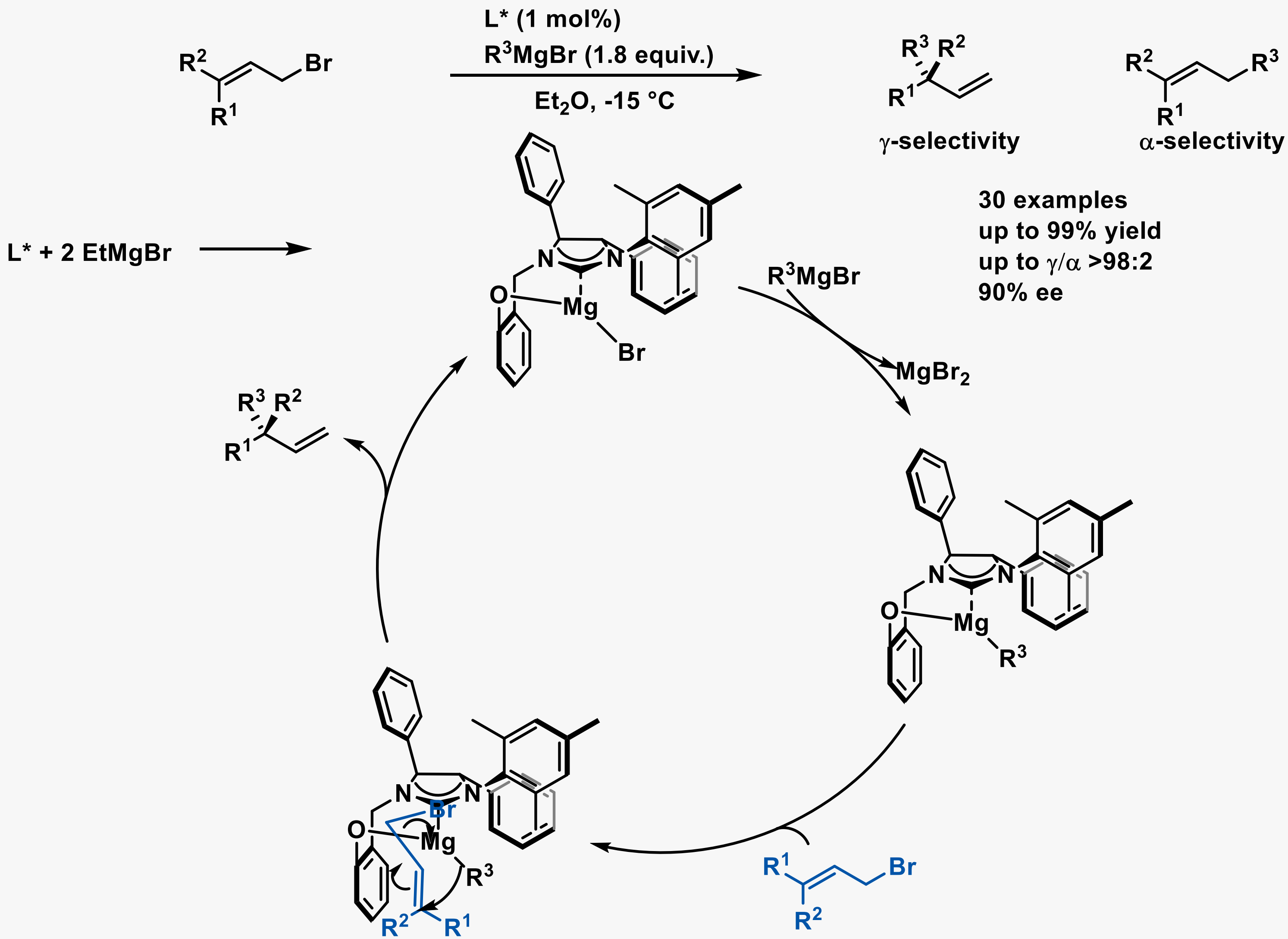


30 examples
up to 99% yield
up to γ/α >98:2
90% ee

(1) Jackowski, O.; Alexakis, A. *Angew. Chem. Int. Ed.* **2010**, 3346. (2) Grassi, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2013**, 13642.

In-Situ Generated Mg(II) Catalyst

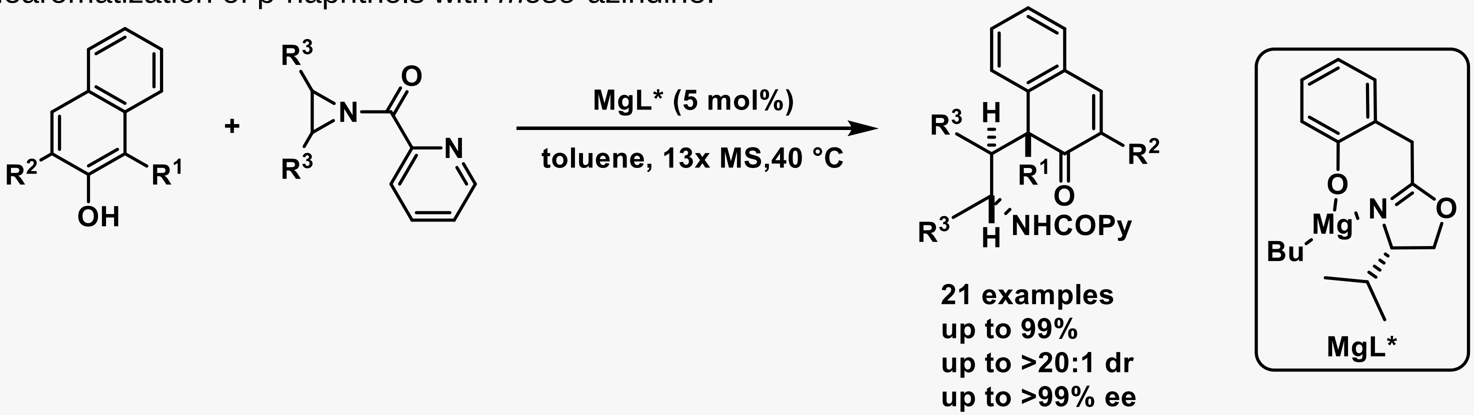
- Mg-mediated asymmetric allylic alkylation



(1) Jackowski, O.; Alexakis, A. *Angew. Chem. Int. Ed.* **2010**, 3346. (2) Grassi, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2013**, 13642.

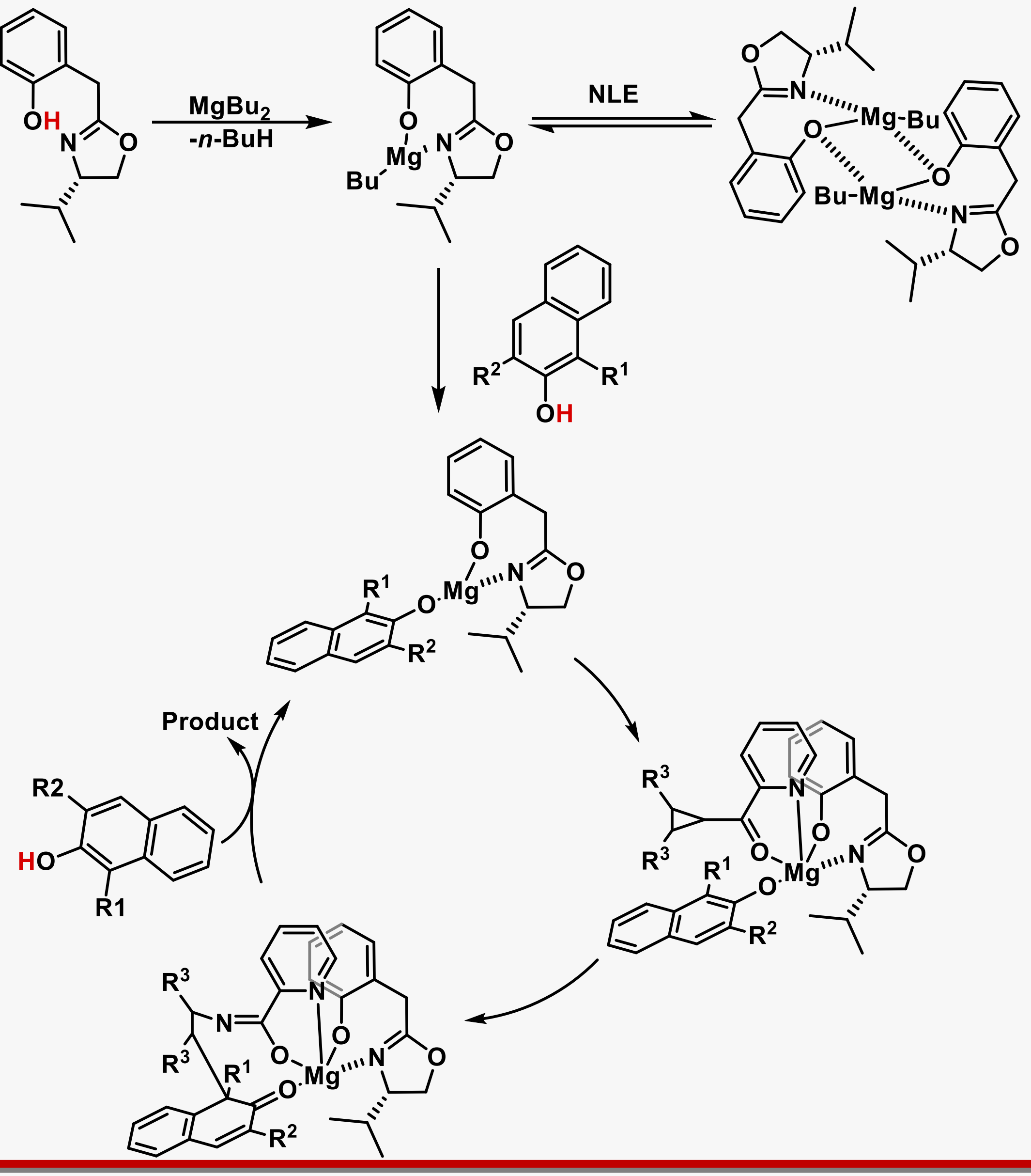
In-Situ Generated Mg(II) Catalyst

- Enantioselective dearomatization of β-naphthols with *meso*-aziridine:



Yang, D.; Wang, L.; Han, F.; Li, D.; Zhao, D.; Wang, R. *Angew. Chem. Int. Ed.* **2015**, 2185.

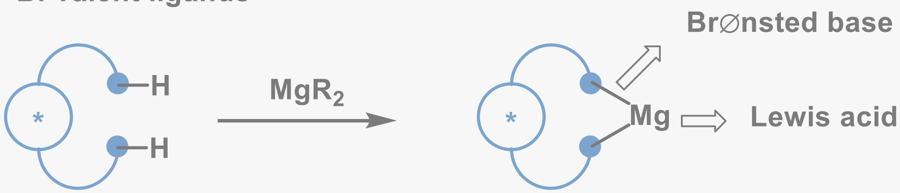
In-Situ Generated Mg(II) Catalyst



Yang, D.; Wang, L.; Han, F.; Li, D.; Zhao, D.; Wang, R. *Angew. Chem. Int. Ed.* **2015**, 2185.

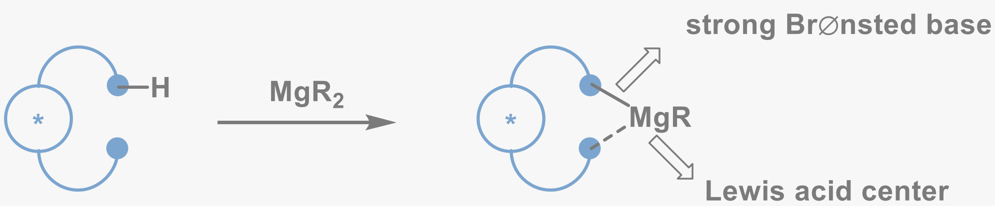
In-Situ Generated Mg(II) Catalyst

Bi-valent ligands



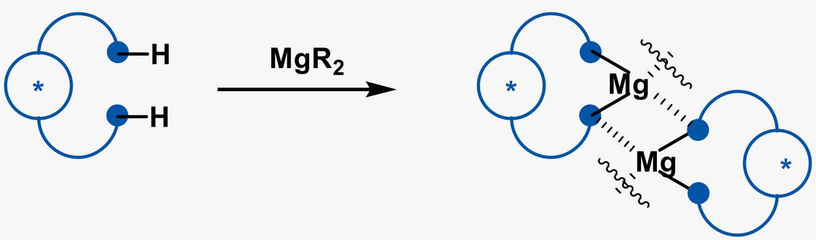
- Possibility to add coordinating additives

Mono-valent ligands



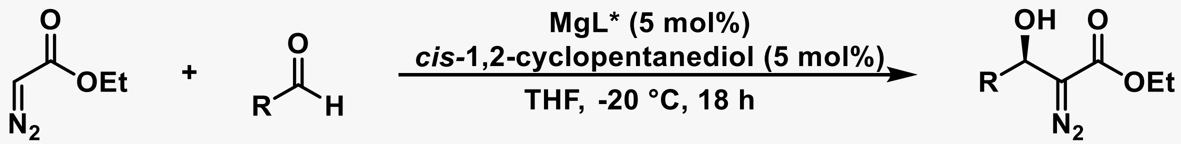
- Possibility to add covalently bonding additives

Polymetallic magnesium catalysis

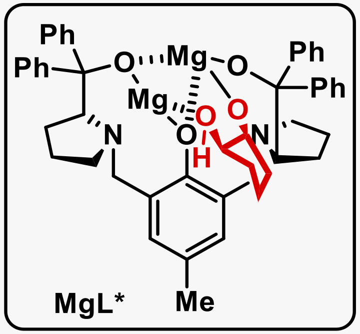


In-Situ Generated Mg(II) Catalyst

- Enantioselective addition of ethyl diazoacetate to aldehydes:

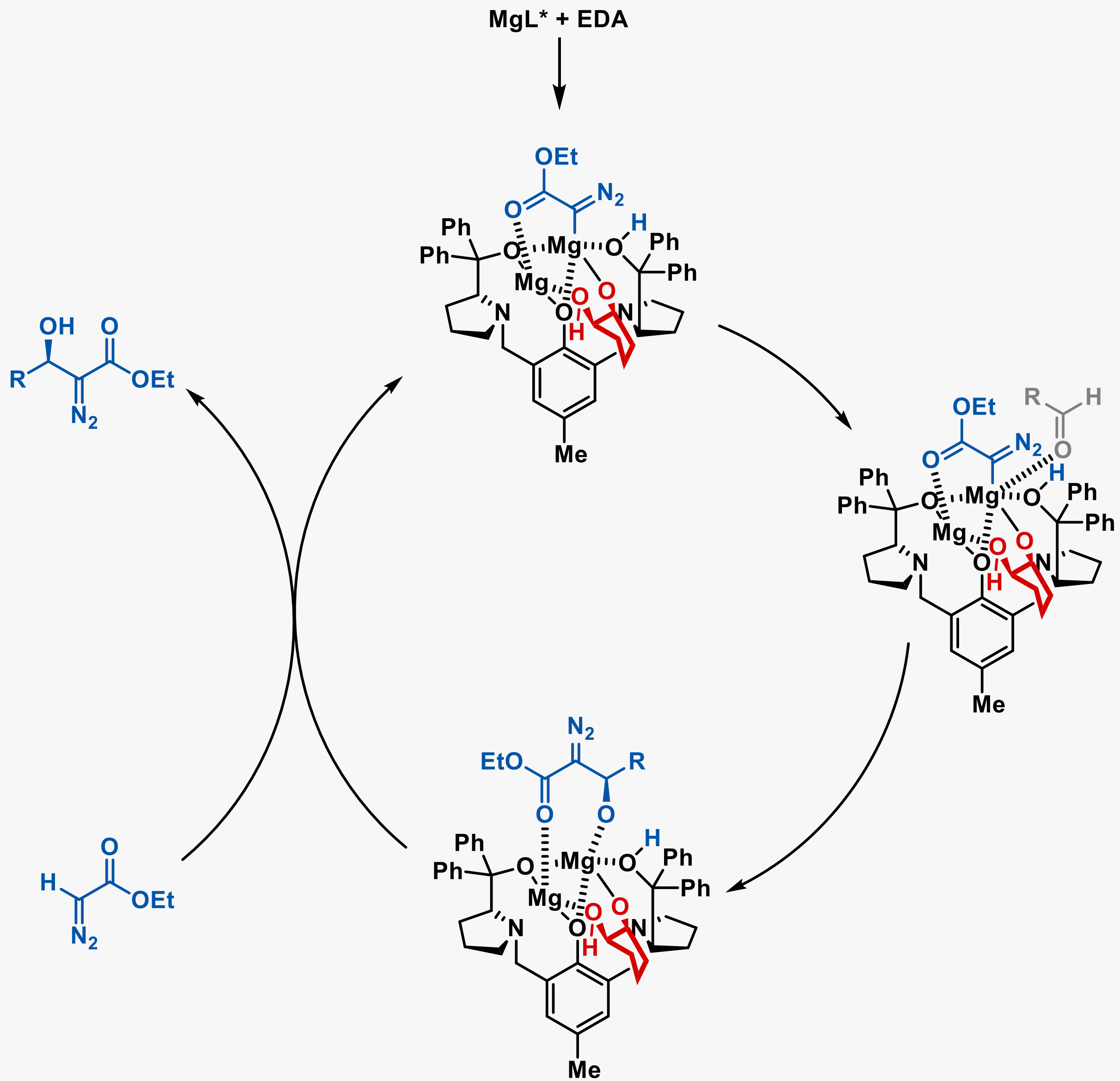


29 examples
up to 95% yield
up to >99% ee



(1) Trost, B. M.; Malhotra, S.; Fried, B. A. *J. Am. Chem. Soc.* **2009**, 1674. (2) Trost, B. M.; Malhotra, S.; Koschker, P.; Ellerbrock, P. *J. Am. Chem. Soc.* **2012**, 2075.

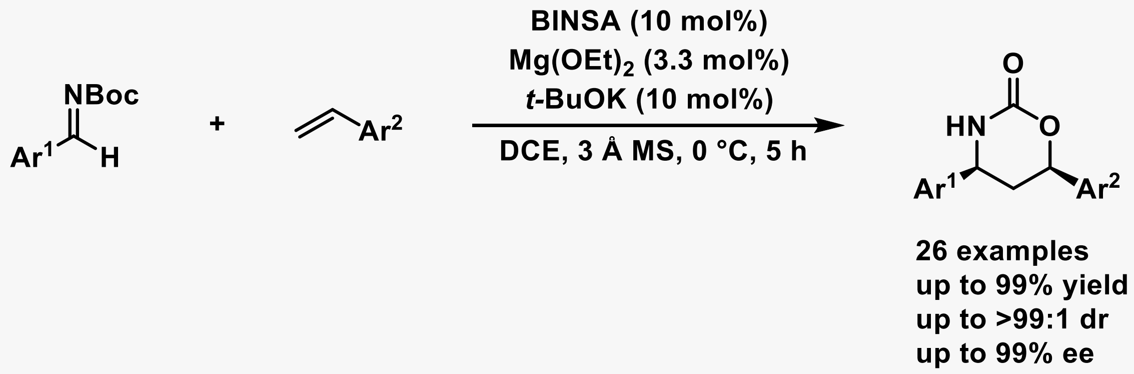
In-Situ Generated Mg(II) Catalyst



(1) Trost, B. M.; Malhotra, S.; Fried, B. A. *J. Am. Chem. Soc.* **2009**, 1674. (2) Trost, B. M.; Malhotra, S.; Koschker, P.; Ellerbrock, P. *J. Am. Chem. Soc.* **2012**, 2075.

In-Situ Generated Mg(II) Catalyst

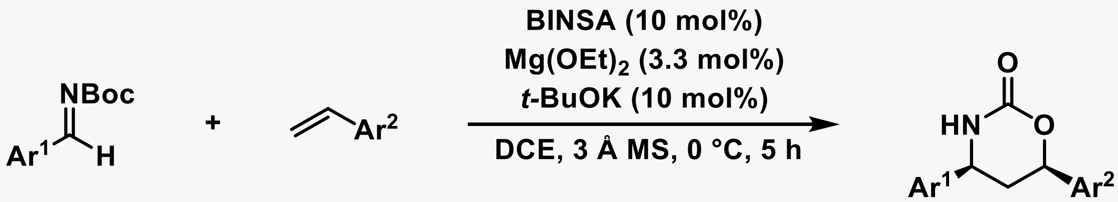
➢ Enantioselective cycloaddition of styrenes with aldimines:

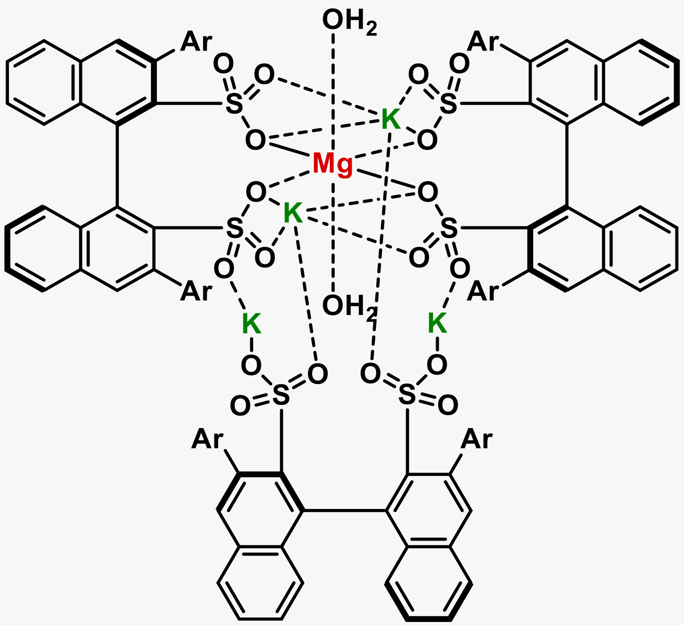


Hatano, M.; Nishikawa, K.; Ishihara, K. *J. Am. Chem. Soc.* **2017**, 8424.

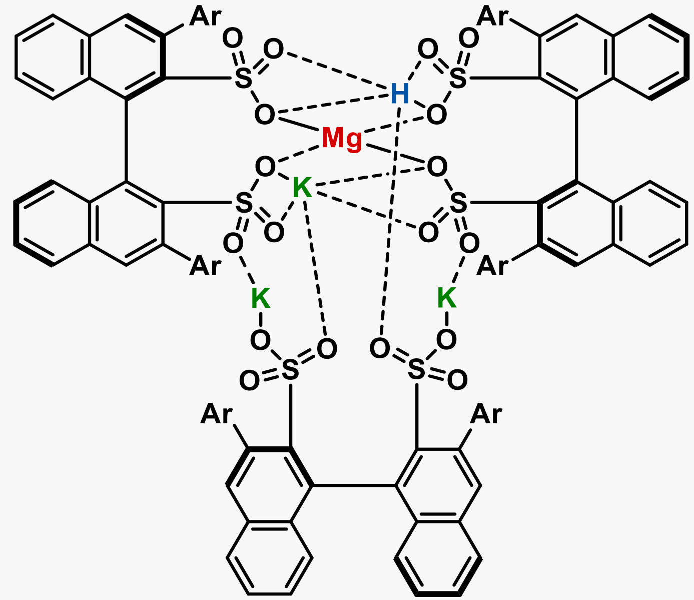
In-Situ Generated Mg(II) Catalyst

- Enantioselective cycloaddition of styrenes with aldimines:





X-ray analysis
3:1:4 complex BINSA/Mg/K
unreactive

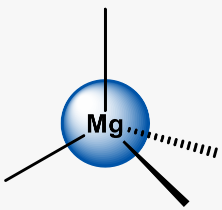


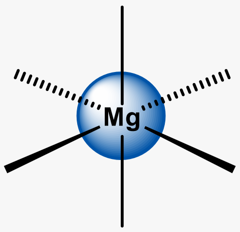
proposed active catalyst
3:1:3 complex
position of H^+ not determined

Hatano, M.; Nishikawa, K.; Ishihara, K. *J. Am. Chem. Soc.* **2017**, 8424.

Conclusion

- Fixed Mg(II) salts:
  - Chiral Lewis Acid
  - Monomeric Catalysts
  - Tetrahedral or Octahedral Geometry



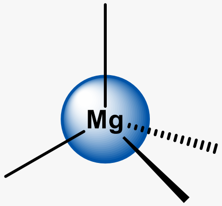


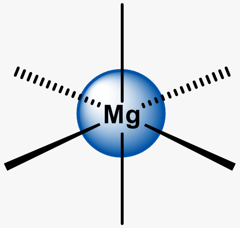
- *In-situ* Generated Mg(II) Catalysts:
  - Bifunctional Catalytic Activities
  - Tendency to Polymerization
  - Tunable Reactivity

Conclusion

➢ Fixed Mg(II) salts:

- ➢ Chiral Lewis Acid
- ➢ Monomeric Catalysts
- ➢ Tetrahedral or Octahedral Geometry



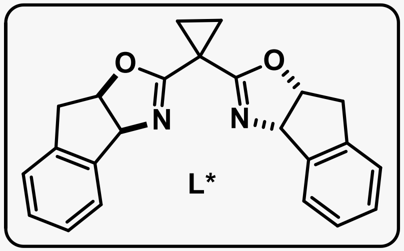


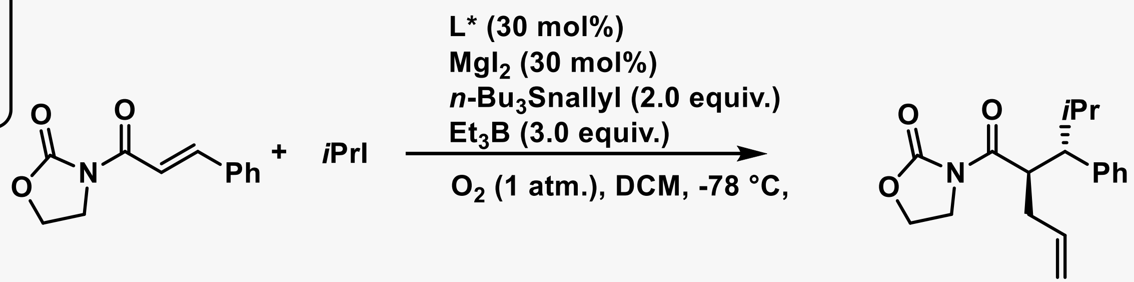
➢ *In-situ* Generated Mg(II) Catalysts:

- ➢ Bifunctional Catalytic Activities
- ➢ Tendency to Polymerization
- ➢ Tunable Reactivity

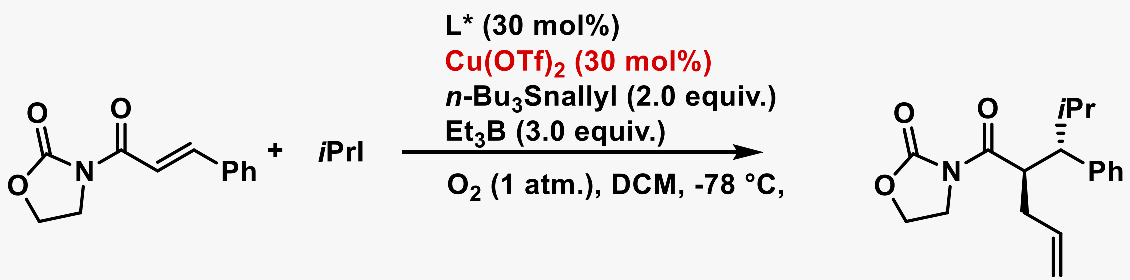
Thank you for your attention

Exercises





93% yield
37:1 dr
93% ee

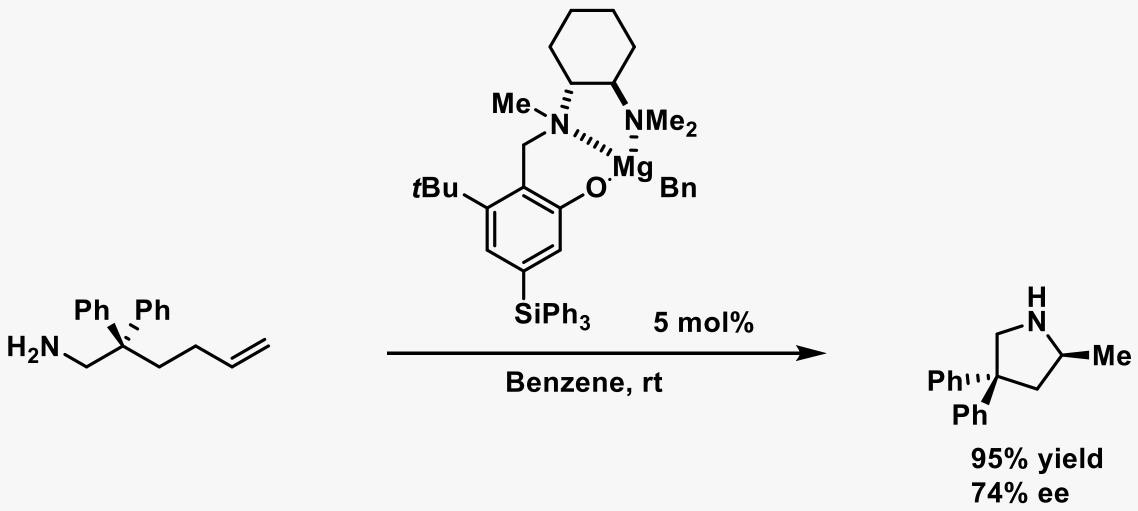


93% yield
30:1 dr
-79% ee

- How to explain the reversal of stereochemistry?

Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, 9472.

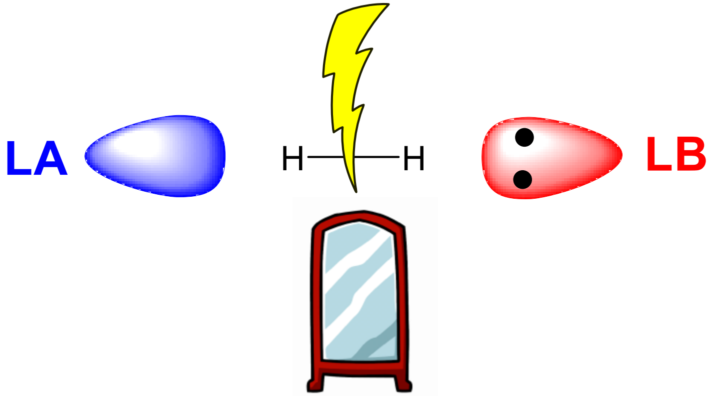
Exercises



- Mechanism?

Zhang, X.; Emge, T. J.; Hultzsch, K. C. A *Angew. Chem. Int. Ed.* **2012**, 394.

Asymmetric Hydrogenation Reactions catalysed by Frustrated Lewis Pairs



Frontiers in Chemical Synthesis II

Stereoselective Synthesis

Table of contents

1. Introduction
2. Hydrogenation reactions with FLPs
3. Asymmetric hydrogenations with FLPs
4. Conclusion

Very Few Asymmetric Catalytic Hydrogenations Have Been Applied in Industry

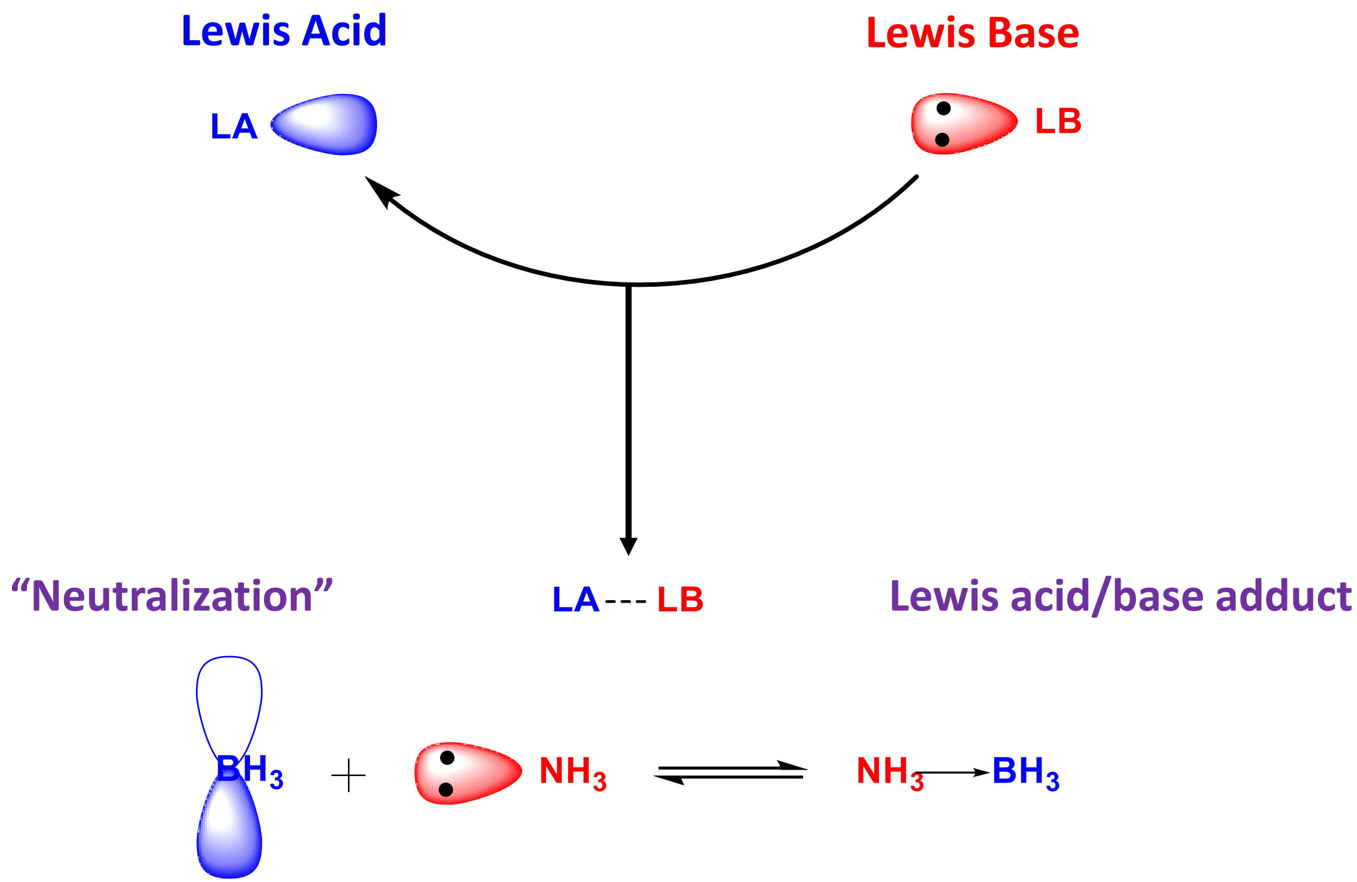
Statistics for the industrial application of enantioselective catalytic reactions

Transformation	Production		Pilot		Bench scale
	>5 t/y	<5t/y	>50 k	<50 kg	
Hydrogenation of enamides	1	1	2	6	4
Hydrogenation of C=C-COOR and C=C-CH-OH	1	0	3	4	6
Hydrogenation of other C=C	1	0	1	2	2
Hydrogenation of α- and β-functionalized C=O	2	2	3	6	4
Hydrogenation/reduction of other C=O	0	0	0	1	4
Hydrogenation of C=N	1	0	1	0	0
Dihydroxylation of C=C	0	1	0	0	4
Epoxidation of C=C and oxidation of sulfide	2	1	2	0	2
Isomerization etc.	2	0	3	0	1

M. Thommen, H.-U. Blaser in *Phosphorus Ligands in Asymmetric Catalysis*, ed. A. Börner, Wiley-VCH, 2008

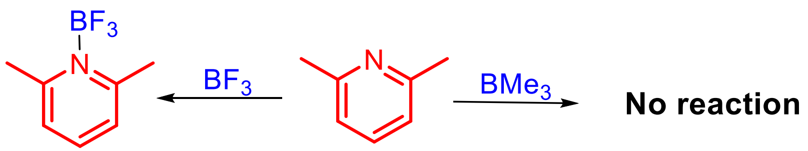
Lewis acids and bases

- Gilbert N. Lewis in 1923



Steric hindrance

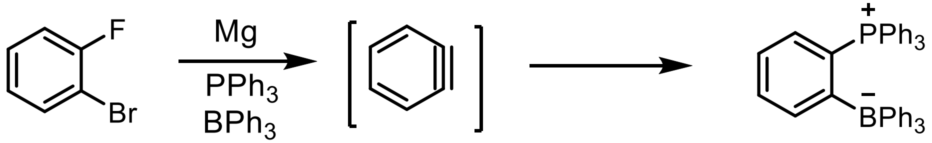
- Brown, 1942:



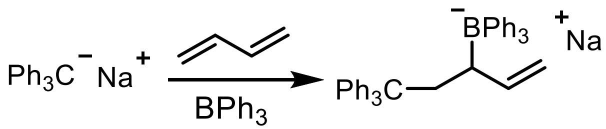
Steric conflict due to o-Me of lutidine

Non-quenched Lewis pair

- Wittig and Benz, 1959:



- Tochtermann:

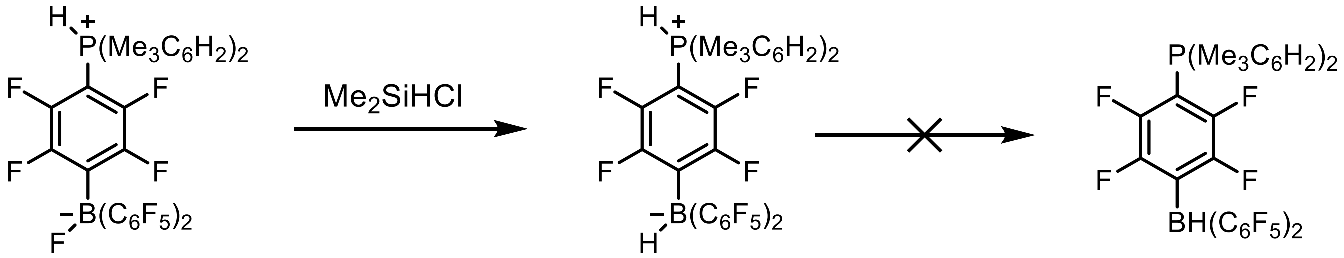


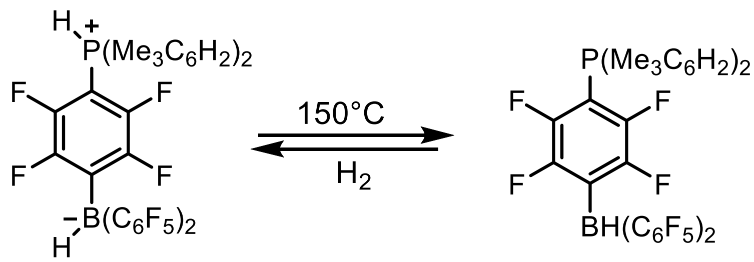
"Antagonistisches Paar"

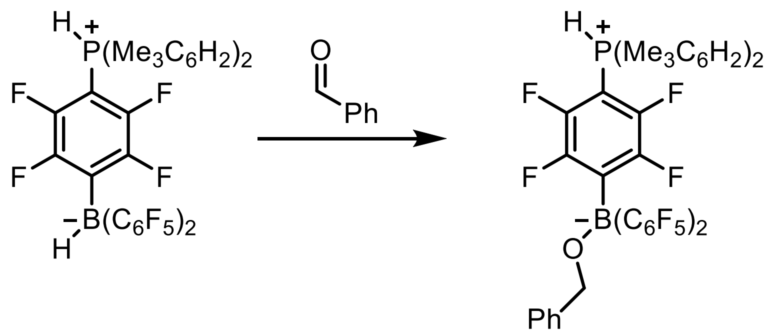
Brown, H. C.; Schlesinger, H. I. *JACS*, **1942**, *64*, 325-329; Wittig, G.; Benz, E. *Chem. Ber.*, **1959**, *92*, 1999-2013; *W. Tochtermann, Angew. Chem. 1966, 78, 355–375.*

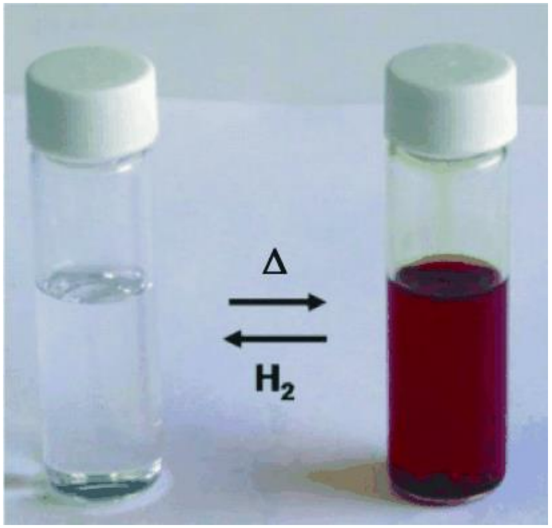
H_2 activation by FLPs

- Stephan, 2006





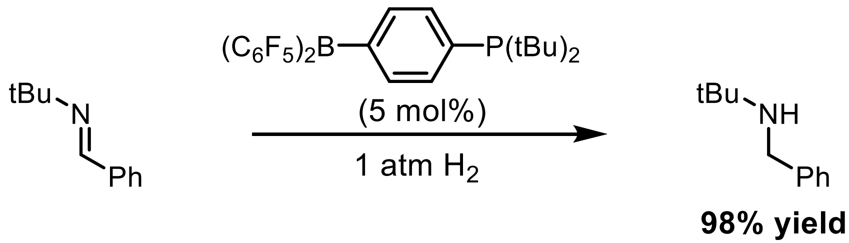




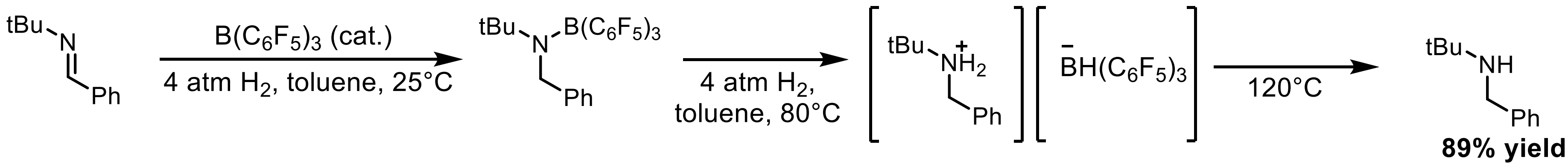
Welch, G. C.; San Juan, R. R.; Masuda, J. D.; Stephan, D. W. *Science*, **2006**, *314*, 1124-1126.

Catalytic H_2 activation by FLPs

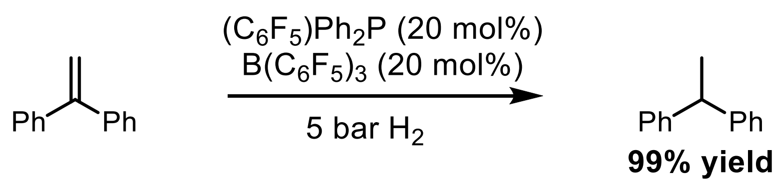
- Stephan, 2007:



- Stephan, 2008:

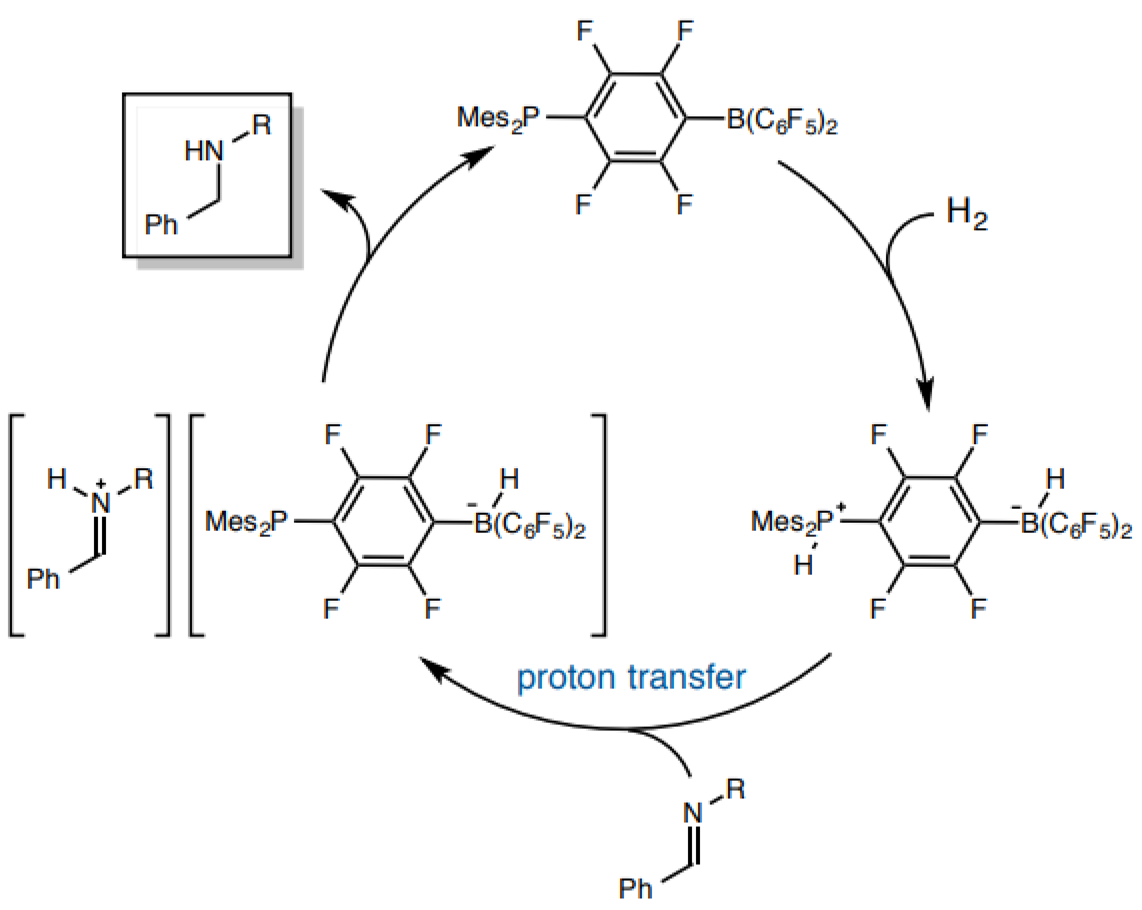


- Stephan, 2012:



Chase, P.A.; Welch, G. C.; Jurca, T.; Stephan, D. W. *ACIE*, **2007**, *46*, 8050-8053; Greb, L.; Ona-Burgos, P.; Chase, P. A.; Jurca, T.; Stephan, D. W. *Chem. Comm.*, **2008**, 1701-1703; Schirmer, B.; Grimme, S.; Stephan, D. W.; Paradies, J. *ACIE*, **2012**, *51*, 10164-10168.

General Mechanism



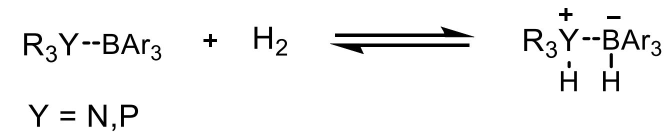
Proton transfer precedes hydride delivery

Chase, P. A.; Welch, C.; Jurca, T.; Stephan, D. W. *ACIE*, **2007**, *46*, 8050-8053.

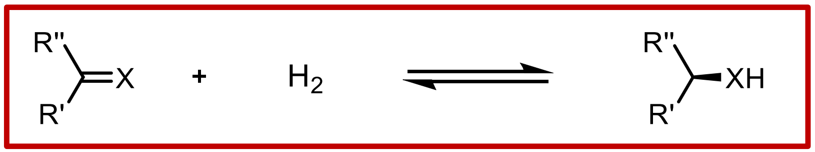
Enantioselective hydrogenation

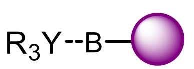
Challenges

- Synthesis of chiral boranes
- Creation of «enantioinducing» environment

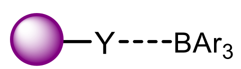


Modes of enantioinduction

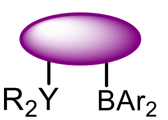




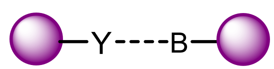
Mode I: chiral borane



Mode II: Chiral Lewis Base

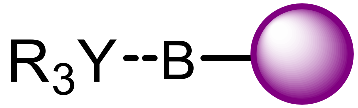


Mode III: Intramolecular FLP catalyst

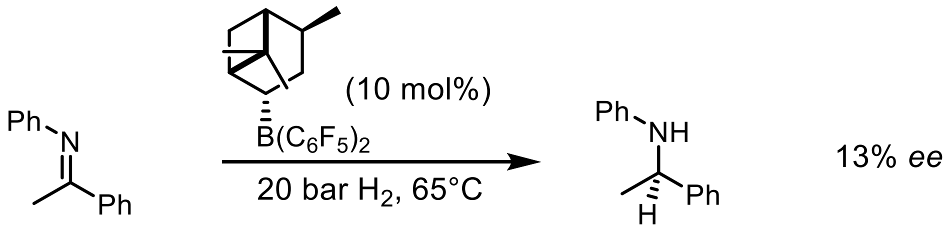


Mode IV: chiral FLP

Mode I: Chiral Borane



- Borane involved in stereodefining hydride transfer
- Required Lewis acidity limits substituents
- Klankermeyer, 2008:

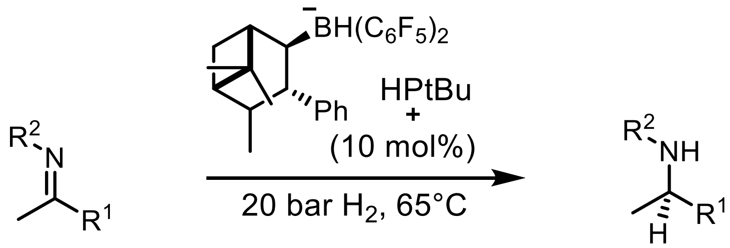


- 1st enantioselective example for FLP reduction
- α-pinene derived borane
- Bulky imine required

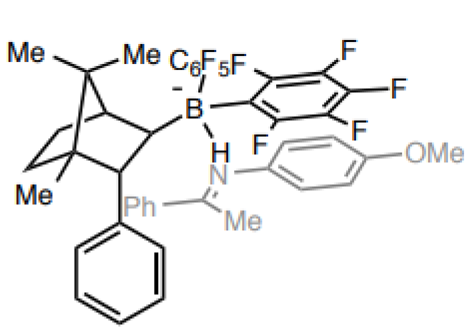
D. Chen, J. Klankermayer, *Chem. Commun.* **2008**, 2130–2131

Mode I: Chiral Borane

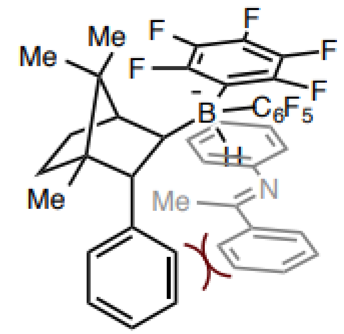
- Klankermeyer, 2010:



6 aryl subst. examples up to 99% yield
up to 83% *ee*



favored approach

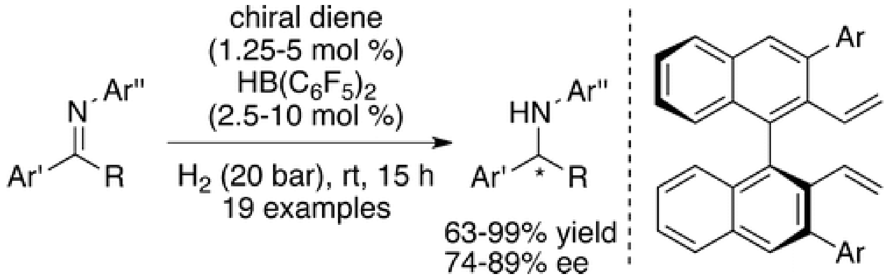


disfavored approach

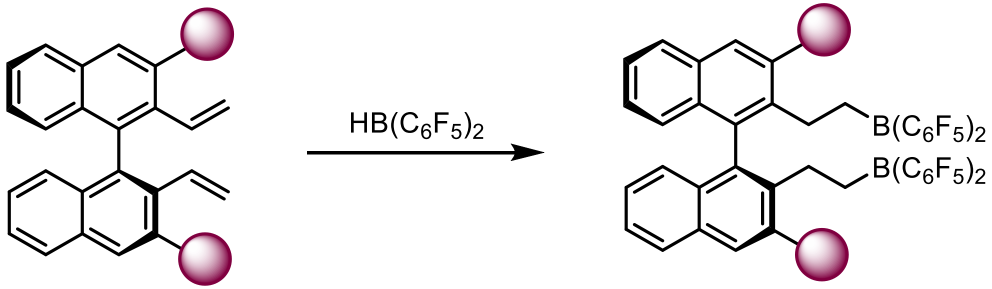
Chen, D.; Wang, Y.; Klankermayer, J. *ACIE*, **2010**, *49*, 9475.

Mode I: Chiral Borane

- Du, 2013:



- *In situ* generation of chiral borane *via* hydroboration
- Tuneable ligand
- Avoids purification of borane catalyst

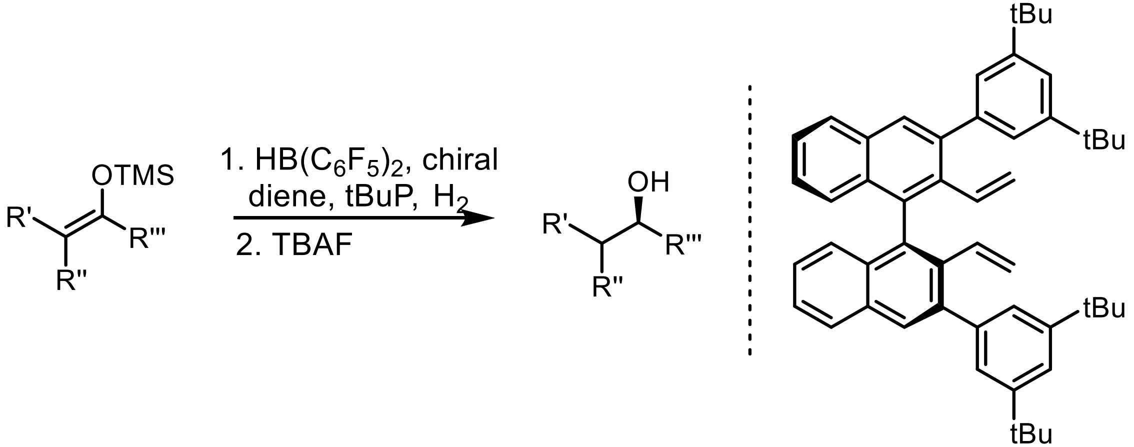


Liu, Y.; Du, H. *JACS,* **2013**, *135*, 6810.

Mode I: Chiral Borane

Synthesis of chiral alcohols

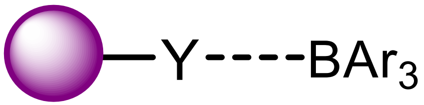
- No direct reduction of ketones
- FLP reduction examples limited to imines
- Du, 2014:



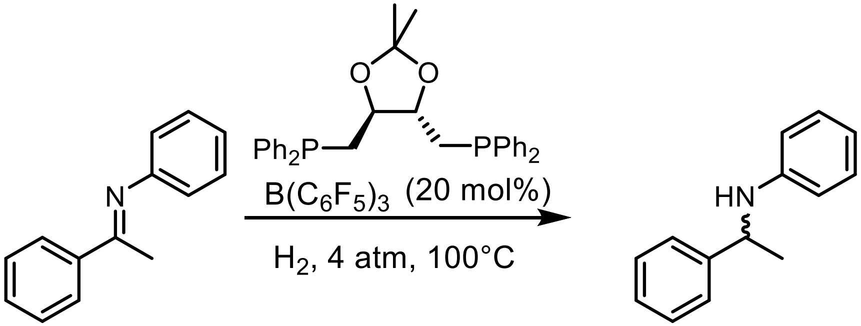
93-99% yields
88 up to >99% *ee*

Wei, S.; Du, H. *JACS,* **2014**, *136*, 12261.

Mode II: Chiral Lewis base



- Huge potential due to reported chiral phosphone ligands
- Challenges:
    1. Competing with substrate as Lewis Base
    2. Proton transfer from LB not stereodefining
- Stephan, 2011:



99% yield, 25% *ee*

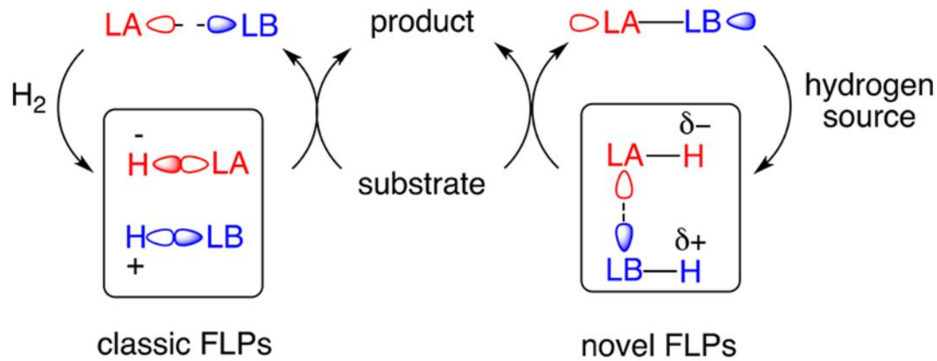
➡ Best result after testing a range of chiral phosphines

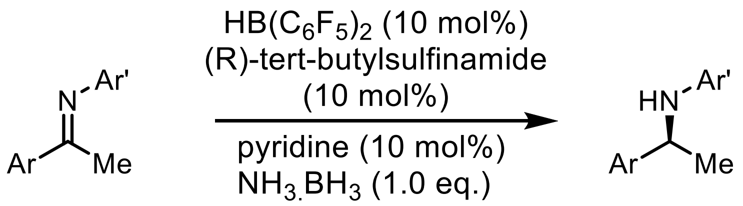
Stephan, D. W.; Greenberg, S.; Graham, T. W.; Chase, P.; Hastie, J. J.; Geier, S. J.; Farrell, J. M.; Brown, C. C.; Heiden, Z. M.; Welch, G. C.; Ullrich, M. *Inorganic Chemistry* **2011**, *50*, 12338.

Mode II: Chiral Lewis Base

Novel FLPs

- Du, 2016:



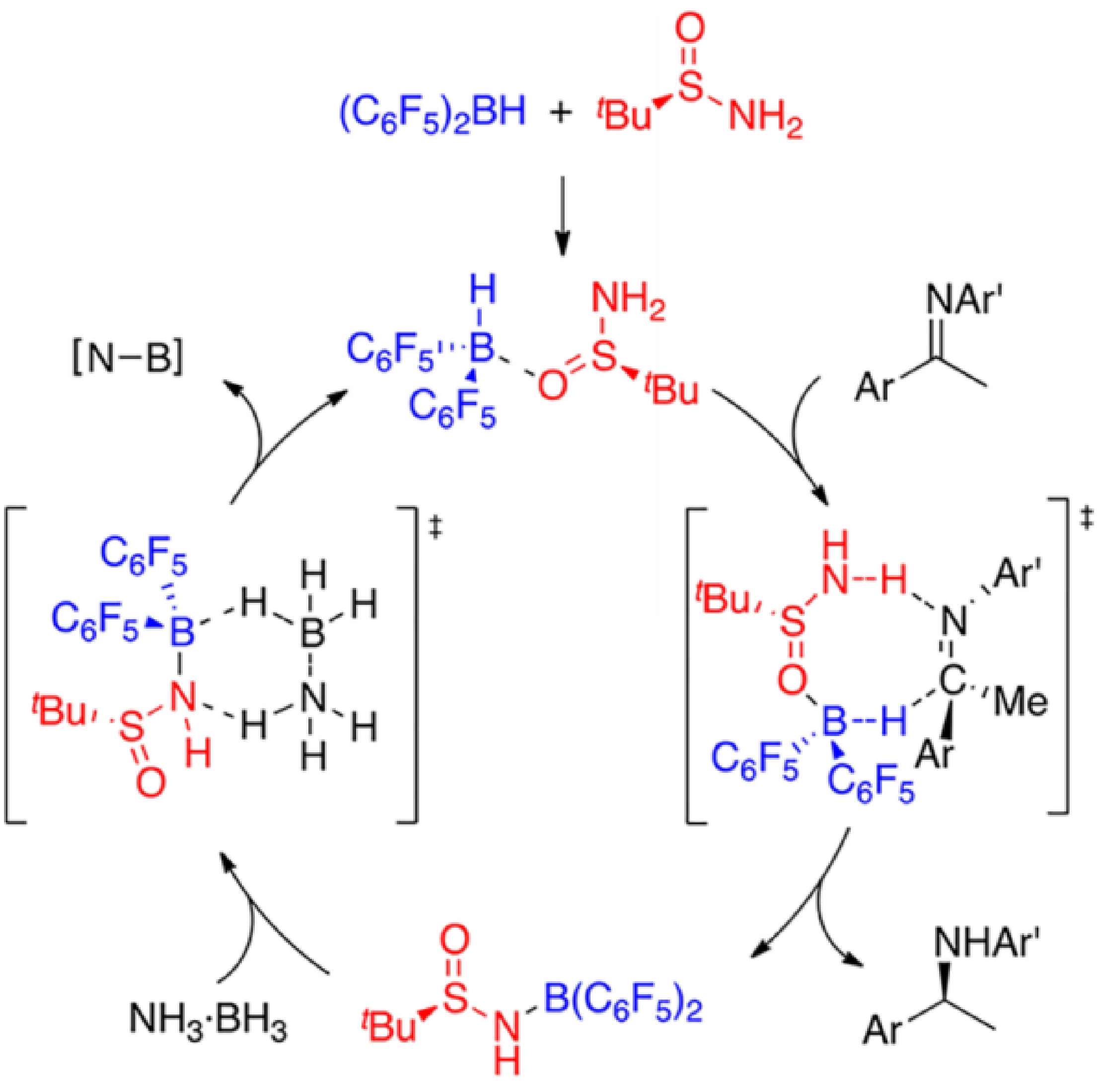


up to 99% yield, up to 95% *ee*

- **Allows application of chiral Lewis Base**
- NH_3.BH_3 better hydrogen source than H_2 (only 10% conversion)

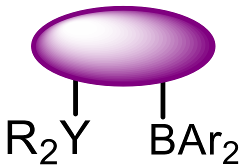
Li, S.; Li, G.; Meng, W.; Du, H. *JACS,* **2016**, *138*, 12956.

Mechanism

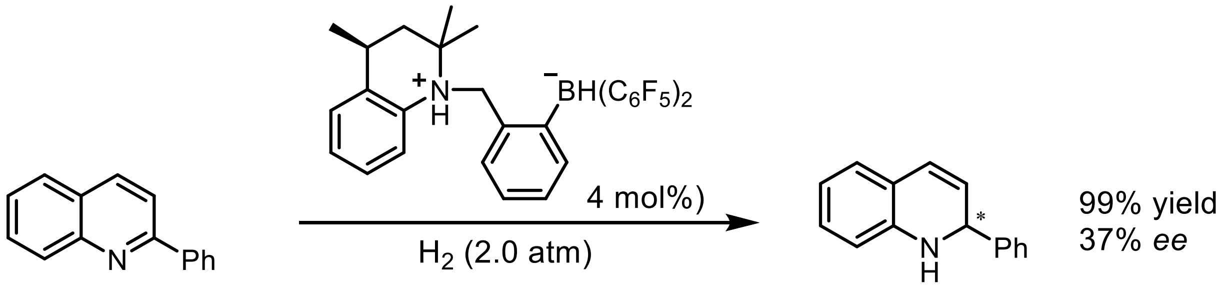


Li, S.; Li, G.; Meng, W.; Du, H. *JACS,* **2016**, *138*, 12956.

Mode III: Intramolecular FLP catalyst



- Repo, 2011:

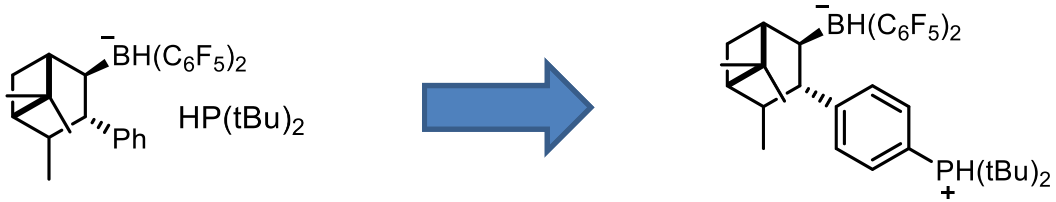


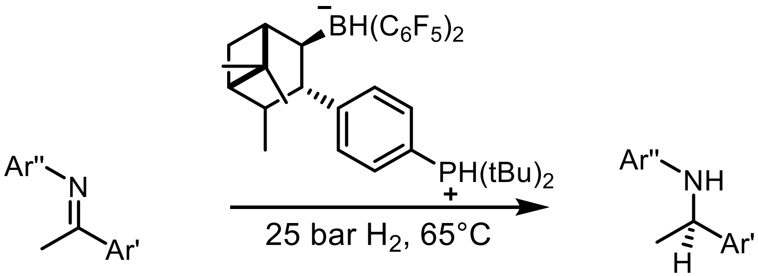
- Investigated broad range of substrates
  → Inherently low enantioselectivity
  → Chiral amine as Lewis Base

V. Sumerin, K. Chernichenko, M. Nieger, M. Leskelä, B. Rieger, T. Repo, *Adv. Synth. Catal.* 2011, **353**, 2093–2110.

Mode III: Intramolecular FLP catalyst

- Klankermeyer, 2012:





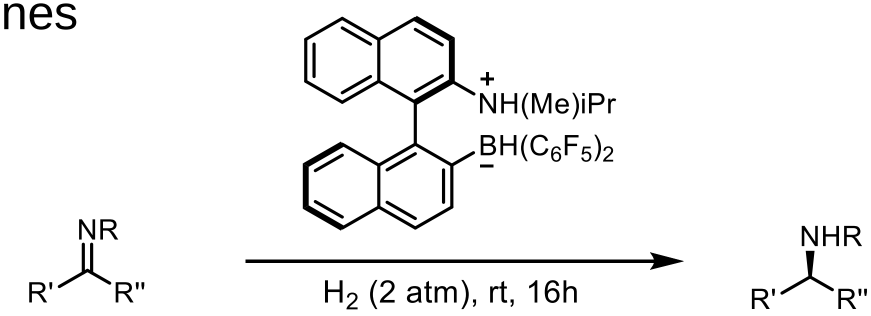
9 aryl subst. examples up to 99% yield
up to 76% *ee*

- Zwitterionic catalyst could be isolated and purified *via* column chromatography
- Reusable catalyst (4 cycles)

G. Ghattas, D. Chen, F. Pan, J. Klankermayer, *Dalton Trans.* 2012, **41**, 9026–9028.

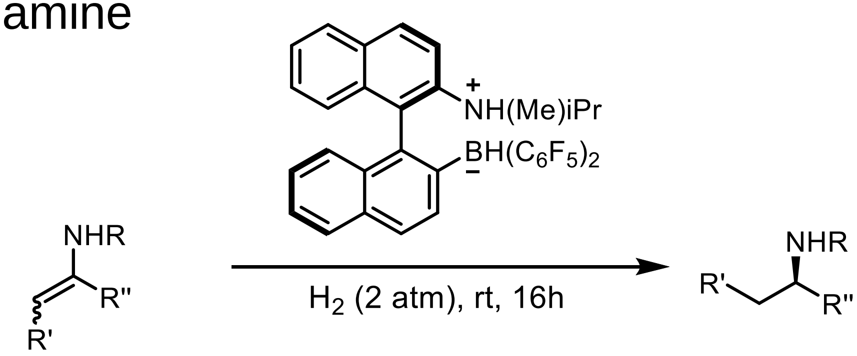
Mode III: Intramolecular FLP catalyst

- Repo, 2015:
  - Imines



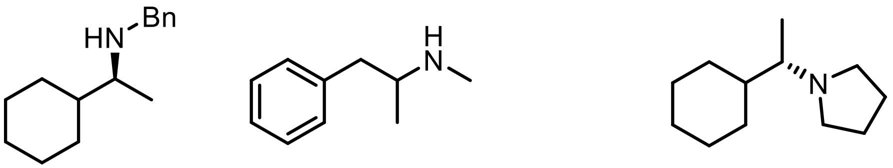
R, R', R" = aryl, alkyl
up to 99% yield
up to 83% *ee*

  - Enamine



R, R', R" = aryl, alkyl
up to 99% yield
up to 99% *ee*

- Successful reduction of enamines
- Selection of aliphatic substrates

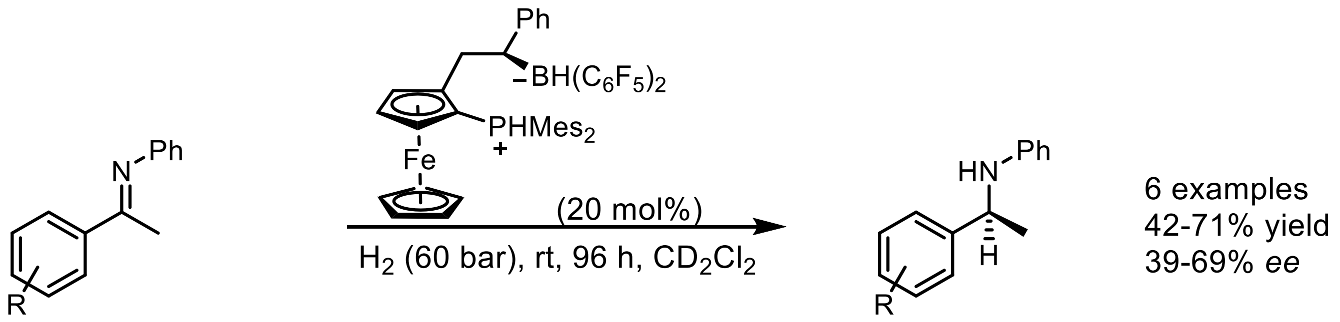


34% *ee* 32% *ee* 85% *ee*

Lindqvist, M.; Borre, K.; Axenov, K.; Kótai, B.; Nieger, M.; Leskelä, M.; Pápai, I.; Repo, T. *JACS,* **2015**, *137*, 4038

Mode III: Intramolecular FLP catalyst

- Erker, 2017:



- Modest yields and enantiocontrol
- Different type of catalyst
- Potentially easily modifiable class
- Easy purification

Ye, K.-Y.; Wang, X.; Daniliuc, C. G.; Kehr, G.; Erker, G. *Eur.J. Inorg. Chem.*, **2017**, *2017*, 368.

Advantages

- 3 modes of FLP catalysed asymmetric hydrogenations
- Excellent yields and selectivities for reduction of aromatic imines
- Reported methods for reduction of enol ethers and enamines

Drawbacks

- Only few examples for aliphatic imines
- Many methods require high temperature and pressure
- Lower selectivities than transition-metal catalysed methods
- Purification of catalysts

Future outlook

- Expanded scope for aliphatic imines
- Development of asymmetric methods for carbonyls and alkenes
- Development of Mode IV catalysts

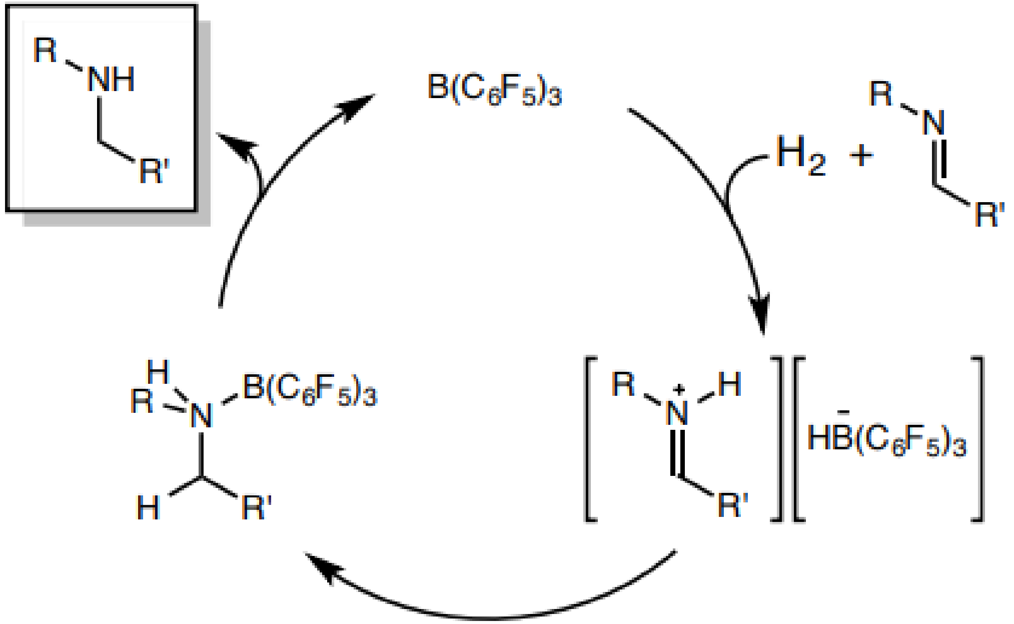
Thank you for your attention!

Questions

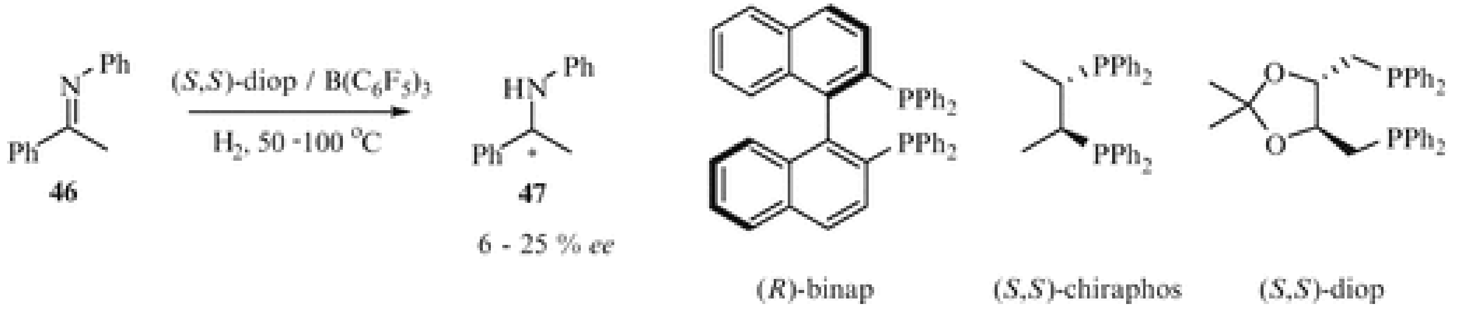
1. What limits the enantioselectivities and potential ligands for Mode II type FLP catalysts?

2. Why are there limited options for the use of chiral Lewis Acids in Mode I type catalysts? What properties are important?

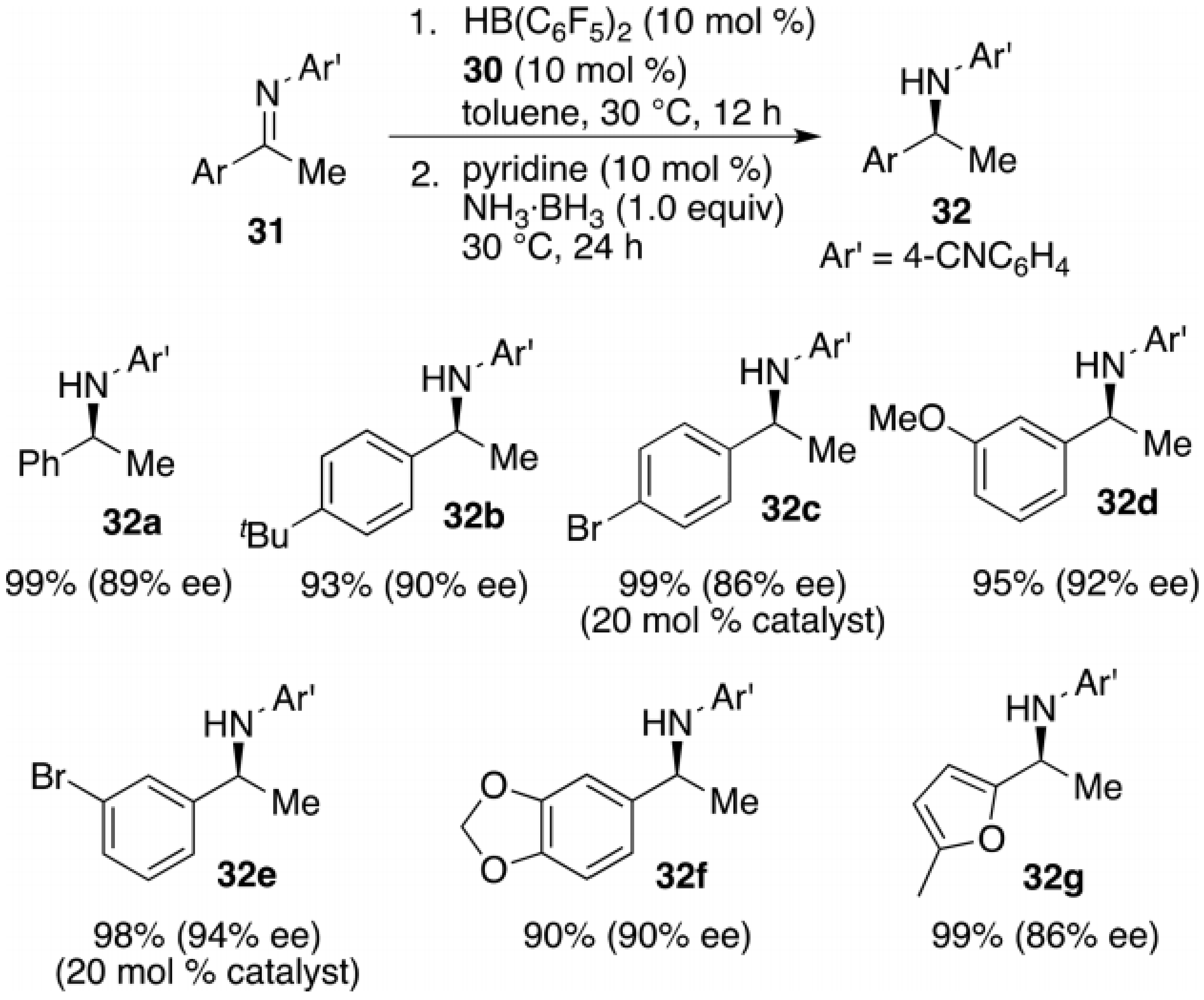
Backup: substrate as LB



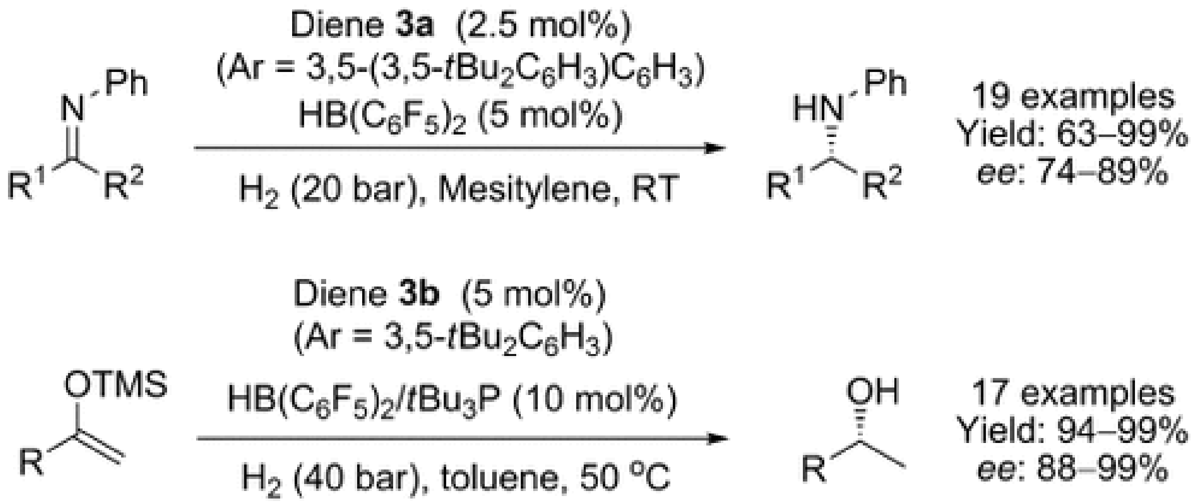
Backup


Ph
N
Ph
46
(S,S)-diop / B(C6F5)3
H2, 50 -100 °C
HN
Ph
Ph
*
47
6 - 25 % ee
PPh2
PPh2
(R)-binap
PPh2
PPh2
(S,S)-chiraphos
O
O
PPh2
PPh2
(S,S)-diop

Asymmetric transfer hydrogenation

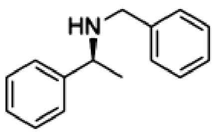


Cp *in situ* hydroboration

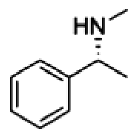


Chiral molecular tweezers

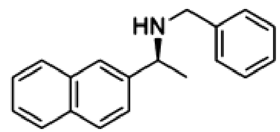
Imines



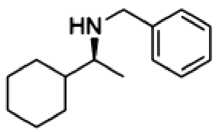
11[a]
94, (80), 83% ee (*S*)



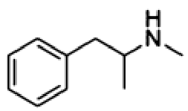
12[b]
99, (92), 75% ee (*R*)



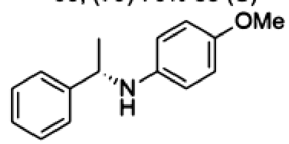
13[c]
93, (79) 76% ee (*S*)



14[a]
97, (79), 34% ee (S)

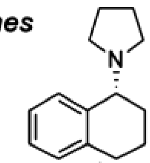


15[e]
97, (72), 32% ee[f] (n.d.)

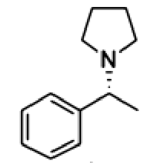


16[g]
53, (34), 36% ee (*S*)

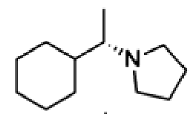
Enamines



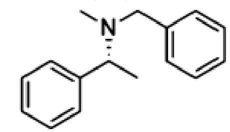
17[d]
99, (95), 99% ee (*R*)[19]



18[d]
99, (81), 95% ee (*R*)



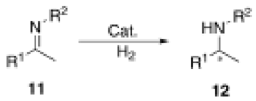
19[b]
99, (42), 85% ee[h] (*S*)



20[a]
99, (85), 47% ee (*R*)

First asymmetric FLP

Table 1. Hydrogenation catalyzed by chiral FLP salts.



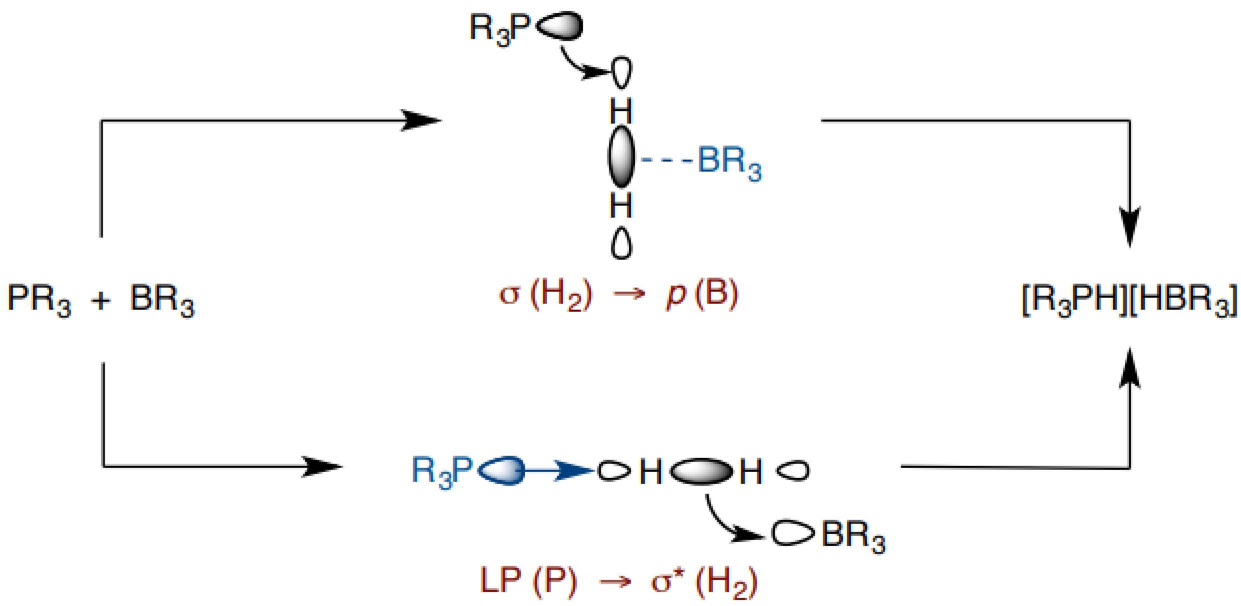
11a: R^1 = Ph, R^2 = Ph
11b: R^1 = Ph, R^2 = 2-Me-C_6H_4
11c: R^1 = Ph, R^2 = 2,6(Me$_2$CH)C_6H_3
11d: R^1 = 4-MeO-C_6H_4, R^2 = Ph
11e: R^1 = Ph, R^2 = 4-MeO-C_6H_4
11f: R^1 = 2-Naphthyl, R^2 = Ph
11g: R^1 = 2-Naphthyl, R^2 = 4-MeO-C_6H_4

Entry[a]	Substrate	Catalyst	Yield [%][c]	*ee* [%][d]
1	**11 a**	**9**/**10**=1:1	>99	20 (*S*)
2	**11 a**	**9**	>99	48 (*S*)
3	**11 a**	**10**	95	79 (*R*)
4[b]	**11 b**	**10**	37	74 (−)
5[b]	**11 c**	**10**	0	–
6	**11 d**	**10**	96	81 (−)
7	**11 e**	**10**	>99	81 (*R*)
8	**11 f**	**10**	93	80 (−)
9	**11 g**	**10**	96	83 (+)

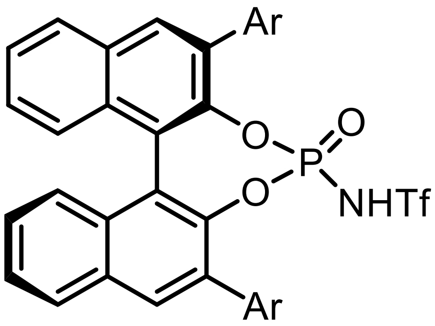
Electron transfer model

$$t\mathrm{Bu_3P} + \mathrm{B(C_6F_5)_3} \xrightarrow[\text{1 atm}]{\mathrm{H_2}} [t\mathrm{Bu_3PH}][\mathrm{HB(C_6F_5)_3}]$$

$$\mathrm{Mes_3P} + \mathrm{B(C_6F_5)_3} \xrightarrow[\text{1 atm}]{\mathrm{H_2}} [\mathrm{Mes_3PH}][\mathrm{HB(C_6F_5)_3}]$$



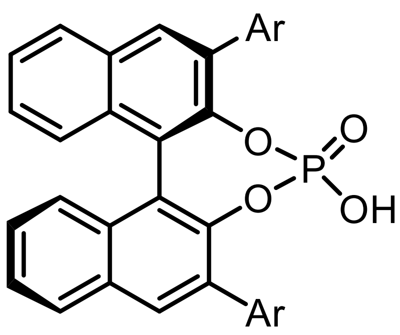
Asymmetric catalysis of Brønsted acid, focused on phosphoramide catalyst

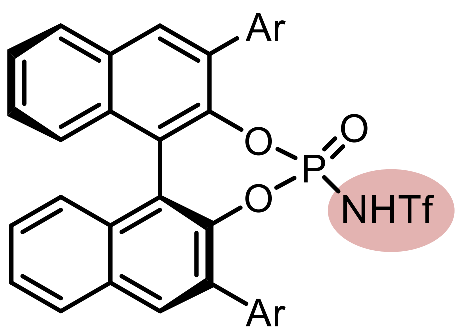


Sung Hwan Park

20.05.2019

History



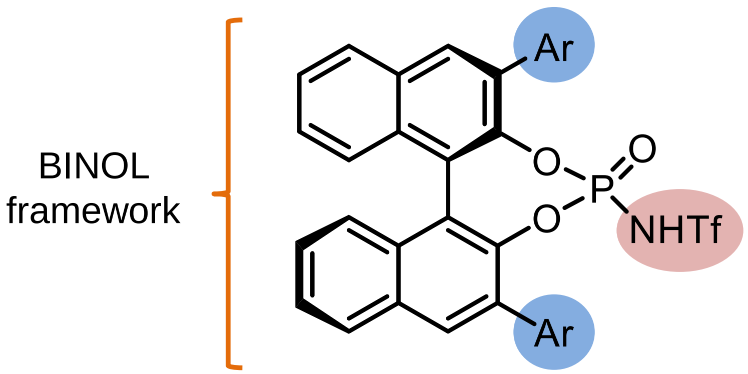


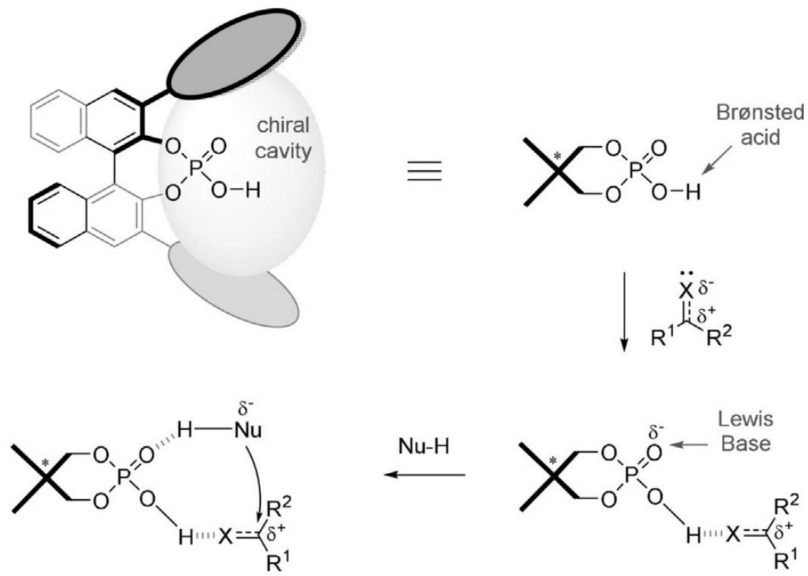
- Akiyama and Terada (2004)
- Electrophile
  aldimine, ketimine, aziridine

- Yamamoto (2006)
- Stronger acidity
  than BINOL based phosphoric acid (BPA)

T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566 – 1568
D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356 – 5357
D. Nakashima, H. Yamamoto *J. Am. Chem. Soc.* **2006**, *128*, 9626 – 9627

Structure

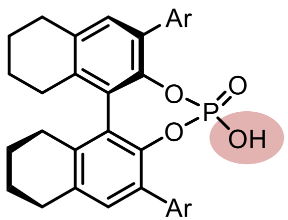


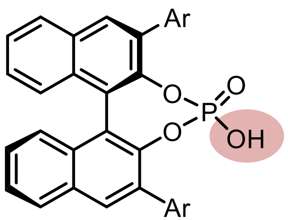


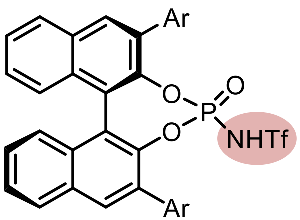
- **Yamamoto** (2006)
- **Stronger acidity**
  than BINOL based phosphoric acid (BPA)
- **BINOL** framework
  tunable axial chirality (dihedral angle)
- **Ar** substituents
  tunable steric and electronic effect

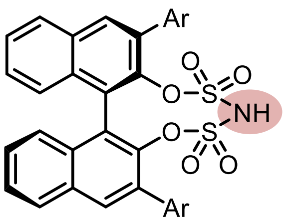
D. Nakashima, H. Yamamoto *J. Am. Chem. Soc.* **2006**, *128*, 9626 – 9627
Image from *Chem. Eur. J.* **2018**, *24*, 3925 – 3943

N-triflylphosphoramide (NTPA)









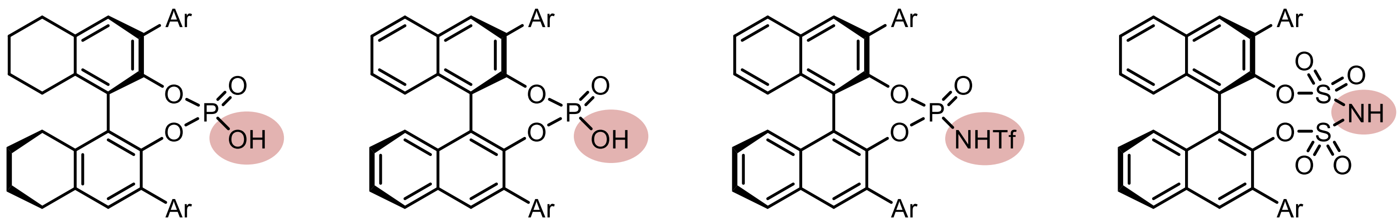
pK_a(MeCN)	14	13.3	6.4	5.2

- pKa's of common acid in MeCN

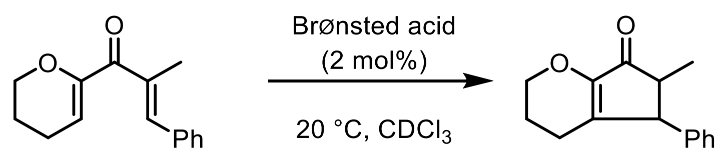
acid	pK_a in MeCN
saccharin	14.6
picric acid	11.0
HCl	10.3
TsOH	8.5
4-$NO_2C_6H_4$-SO_3H	6.7
HBr	5.5

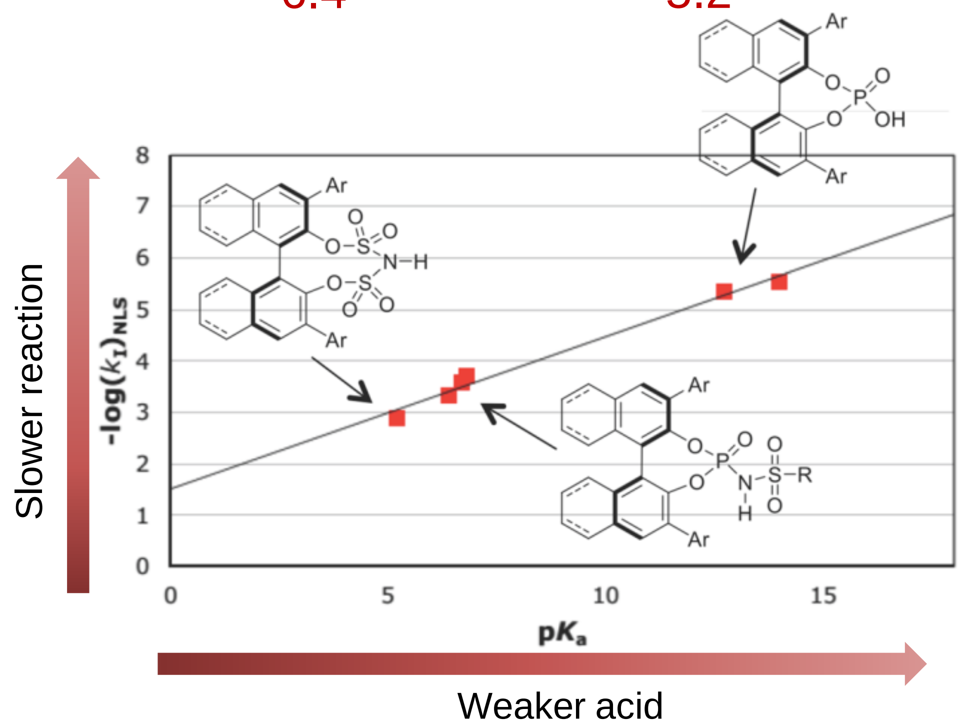
D. Parmar, E. Sugiono, S. Raja, M. Rueping *Chem. Rev.* **2014**, *114*, 9047 – 9153

N-triflylphosphoramide (NTPA)



pK$_a$(MeCN) 14 13.3 6.4 5.2

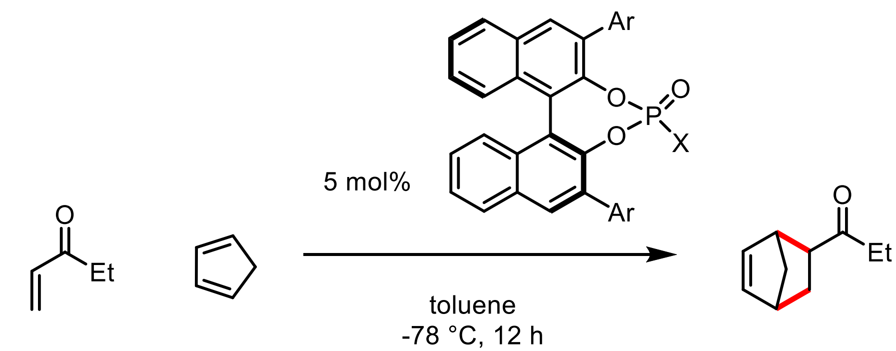




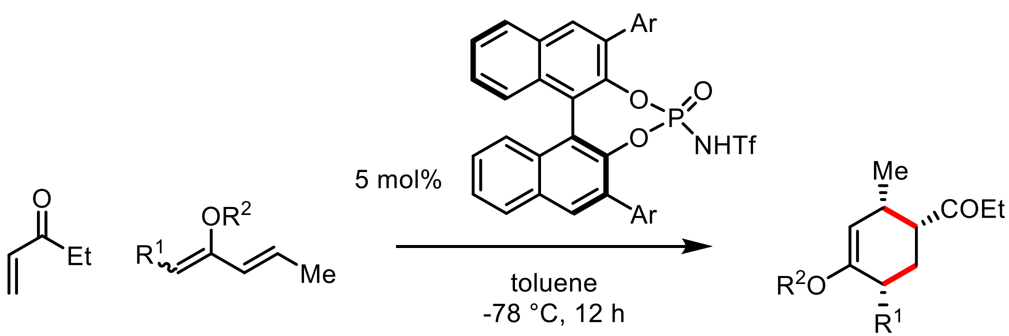
K. Kaupmees, N. Tolstoluzhsky, S. Raja, M. Rueping, I. Leito *Angew. Chem., Int. Ed.* **2013**, *52*, 11569 – 11572
D. Parmar, E. Sugiono, S. Raja, M. Rueping *Chem. Rev.* **2014**, *114*, 9047 – 9153

Diels-Alder Reaction

- NTPA-Catalyzed Enantioselective Diels–Alder Reaction



	Ar	X	Yield	*ee*
1	Ph	OH	0%	
2	Ph	NHTf	91%	9% (*S*)
3	2,4,6-*i*$Pr_3C_6H_2$	NHTf	86%	32% (*R*)



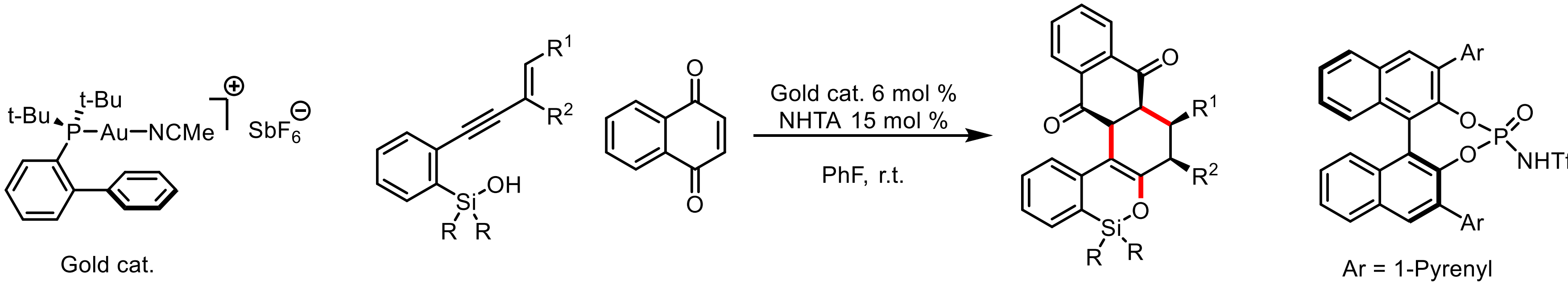
Ar = 2,4,6-*i*$Pr_3C_6H_2$

43%-quant. yield
82-92% *ee*

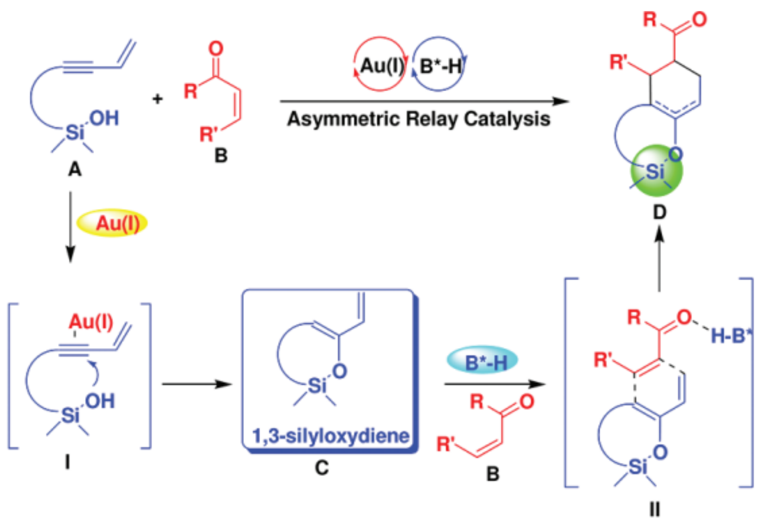
	R^1	R^2	Yield	*ee*
1	H	TIPS	43%	88%
2	Me	TIPS	95%	92%
3	Bn	TIPS	99%	85%
4	$HO-C_6H_4-CH_2$	TIPS	35%	82%
5	$MOMO-C_6H_4-CH_2$	TIPS	99%	87%
6	Me	TBS	43%	92%

D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626 – 9627

- Asymmetric Diels–Alder Reaction using Gold/NTPA Relay Catalysis



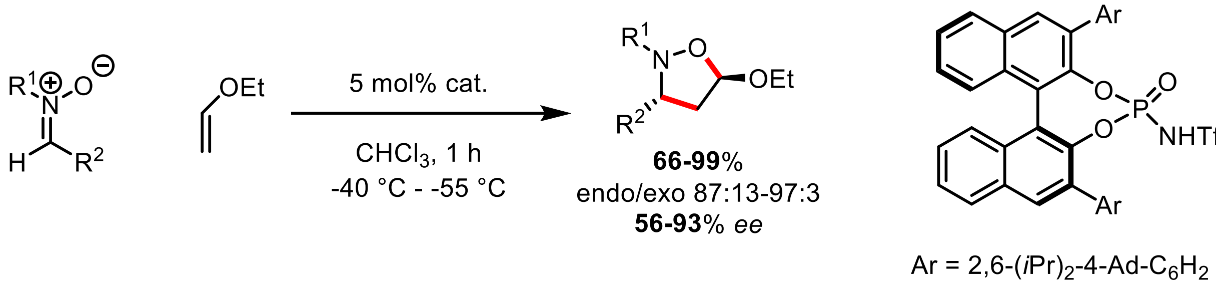
67-98% yield
87-96% *ee*
15 examples



	R^1	R^2	R	Yield	*ee*
1	Ph	H	Ph	95%	94%
2	4-MeC_6H_4	H	Ph	70%	96%
3	4-MeOC_6H_4	H	Ph	72%	92%
4	4-FC_6H_4	H	Ph	98%	95%
5	H	Me	Ph	67%	91%
6	H	n-Bu	Ph	94%	91%
7	Ph	H	Me	90%	95%

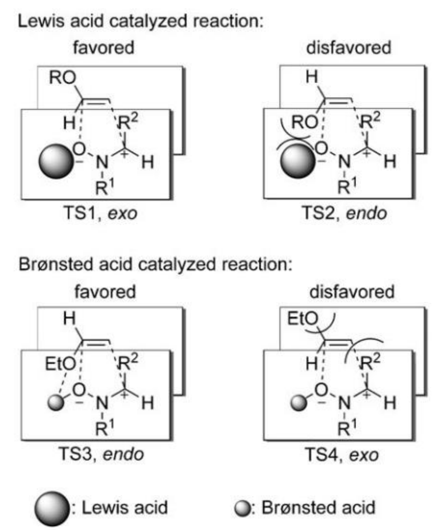
Z.-Y. Han, D.-F. Chen, Y.-Y. Wang, R. Guo, P.-S. Wang, C. Wang, L.-Z. Gong *J. Am. Chem. Soc.* **2012**, *134*, 6532 – 6535

- NTPA-Catalyzed Enantioselective 1,3-Dipolar Cycloaddition



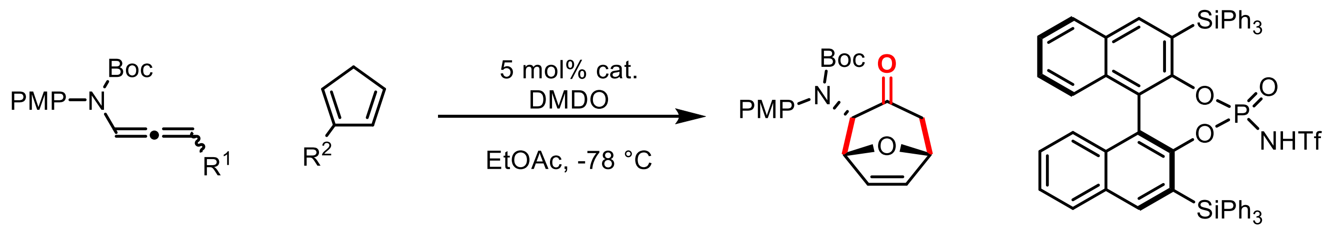
	R^1	R^2	Yield	*endo:exo*	*ee*
1	Ph	4-ClPh	95%	97:3	90%
2	Ph	4-CF_3Ph	69%	96:4	92%
3	4-ClPh	Ph	92%	96:4	84%
4	4-ClPh	4-ClPh	74%	96:4	90%
5	4-ClPh	4-CF_3Ph	66%	93:7	93%
6	4-ClPh	4-NO_2Ph	98%	89:11	92%
7	4-ClPh	2-furyl	95%	93:7	89%
8	4-ClPh	2-thienyl	>99%	96:4	92%

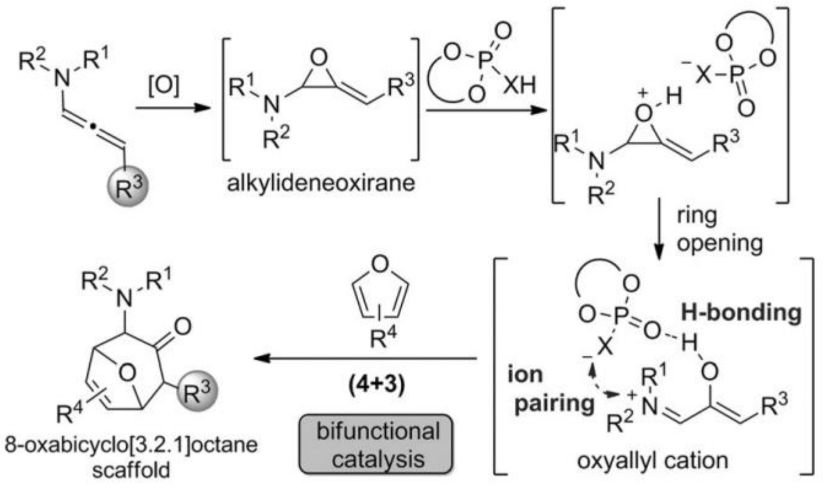
- Rationalization of Stereoselectivity



P. Jiao, D. Nakashima, H. Yamamoto, *Angew. Chem. Int. Ed.* **2008**, *47*, 2411 – 2413

- NTPA-Catalyzed Enantioselective [4+3] Cycloaddition

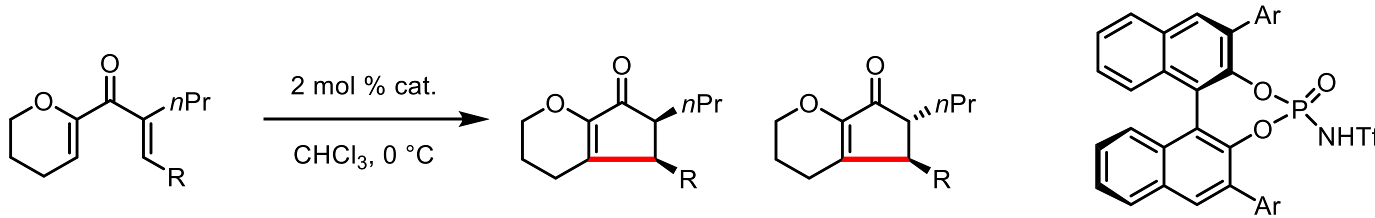




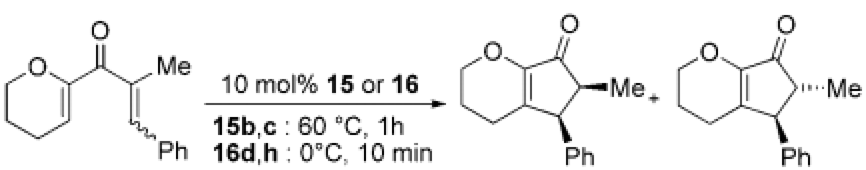
	R^1	R^2	Yield	*ee*	*rr*
1	H	H	71%	83%	
2	H	Me	72%	82%	14:1
3	H	Et	66%	76%	10:1
4	Me	Me	86%	82%	15:1
5	Et	CH_2OTIPS	82%	94%	
6	*c*-Hex	CH_2OTIPS	87%	>98%	

L. Villar, U. Uria, J. I. Martinez, L. Prieto, E. Reyes, L. Carrillo, J. L. Vicario *Angew. Chem. Int. Ed.* **2017**, *56*, 10535 – 10538

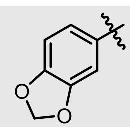
- NTPA-Catalyzed Nazarov cyclization



Ar = 9-phenanthryl

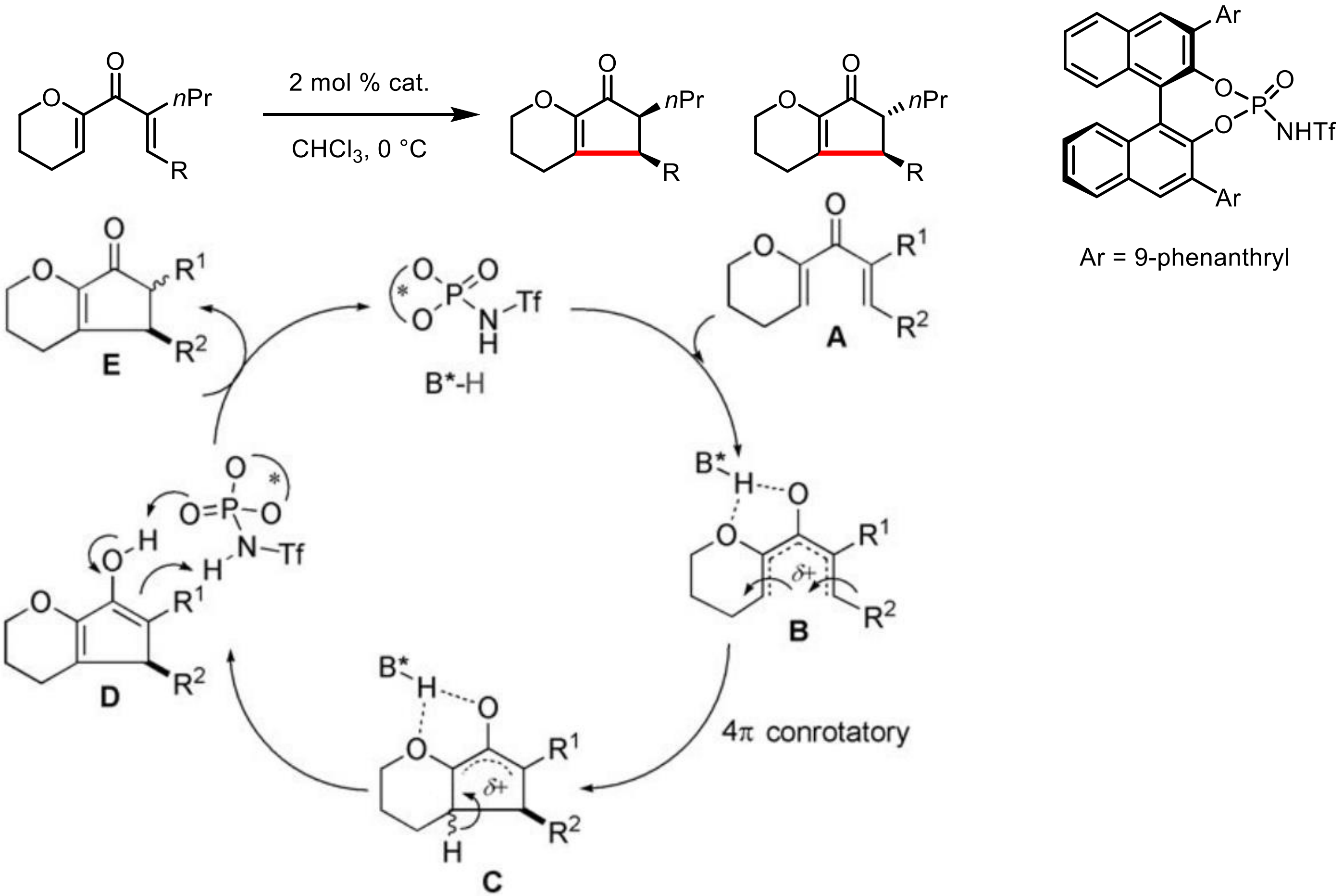


		cis-25a	:	*trans*-25a
a)	BPA **15c** (Ar = 1-naphthyl)	2.3 (81% *ee*)	:	1 (55% *ee*)
b)	BPA **15b** (Ar = 9-anthryl)	3.4 (82% *ee*)	:	1 (60% *ee*)
c)	NTPA **16h** (Ar = 1-naphthyl)	5.2 (83% *ee*)	:	1 (96% *ee*)
d)	NTPA **16d** (Ar = 9-phenanthryl)	7 (86% *ee*)	:	1 (94% *ee*)
e)	NTPA **16d** (2 mol%) (Ar = 9-phenanthryl)	6 (87% *ee*)	:	1 (95% *ee*)

	R	Yield	cis/ trans	*ee* (cis)	*ee* (trans)
1	Ph	85%	3.2:1	93%	91%
2	4-MePh	77%	2.6:1	91%	90%
3		83%	1.5:1	87%	92%
4	3-BrPh	72%	3.7:1	90%	91%
5	4-BrPh	87%	4.6:1	92%	92%

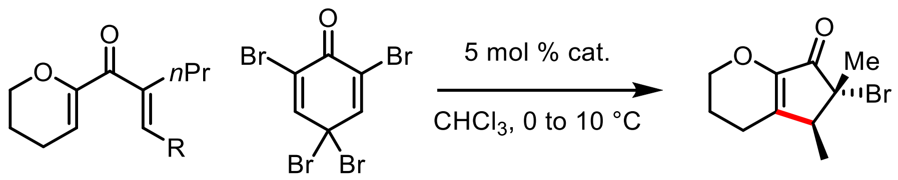
M. Rueping, W. Ieawsuwan, A. P. Antonchick, B. J. Nachtsheim, *Angew. Chem. Int. Ed.* **2011**, *50*, 6706–6720

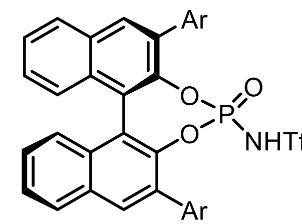
- NTPA-Catalyzed Nazarov cyclization



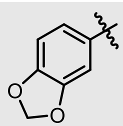
M. Rueping, W. Ieawsuwan, A. P. Antonchick, B. J. Nachtsheim, *Angew. Chem. Int. Ed.* **2011**, *50*, 6706–6720

- NTPA-Catalyzed Nazarov cyclization/Bromination Cascade

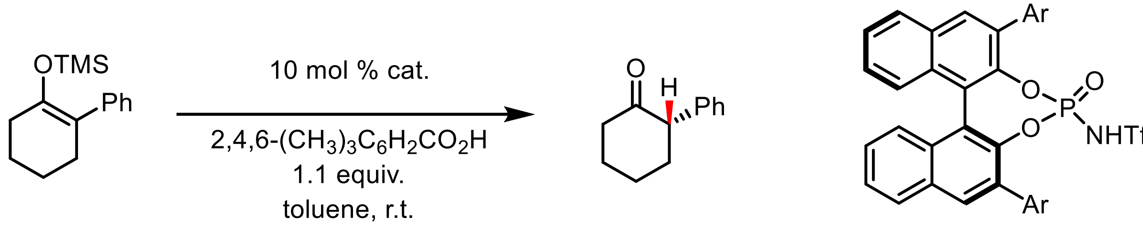




Ar = 9-phenanthryl

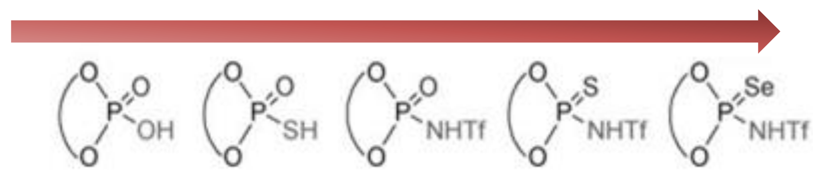
	R	Yield	cis/ trans	*ee*
1	Ph	66%	2:1	89%
2	4-FPh	50%	20:1	94%
3		43%	8:1	92%
4	4-MePh	61%	1.7:1	92%
5	2-Naph	63%	4.8:1	94%

- NTPA-Catalyzed Enantioselective Protonation



Ar = 2,4,6-(iPr)$_3$C$_6$H$_2$

Stronger acid

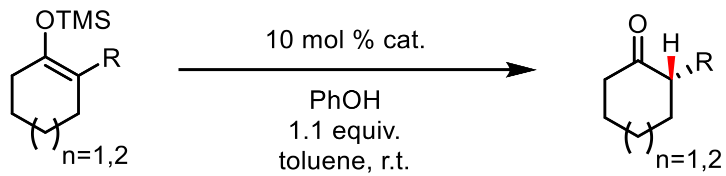


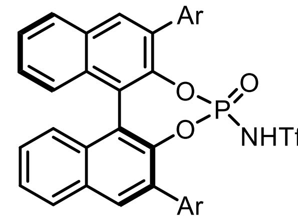
cat	*ent*-**15d**	*ent*-**15e**	*ent*-**16b**	*ent*-**16l**	*ent*-**16n**
t (h)	96	96	4.5	3.5	3.5
yield	0	traces	98%	97%	97%
ee	-	-	54%	78%	72%

C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246–9247

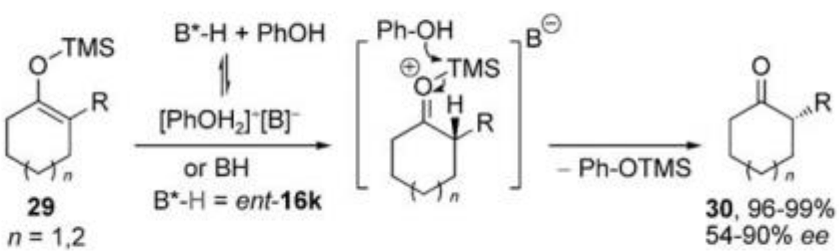
Enantioselective Protonation

- NTPA-Catalyzed Enantioselective Protonation





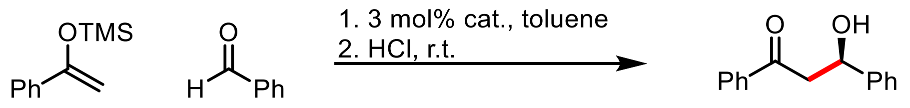
Ar = 4-*t*Bu-2,6-*i*$Pr_2C_6H_2$

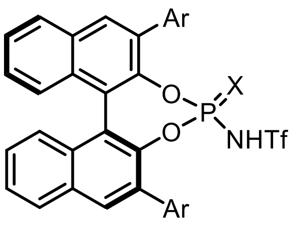


	n	R	Yield	*ee*
1	1	Ph	97%	82%
2	1	4-MeOPh	98%	84%
3	1	4-ClPh	95%	84%
4	1	Bn	97%	54%
5	1	*c*-Hex	96%	64%
6	1	2-Naph	99%	86%
7	2	Ph	99%	88%
8	2	2-Naph	97%	90%

C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246–9247

- Brønsted acid Catalyzed Mukaiyama Aldol Reaction

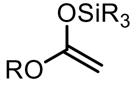




- Catalyst Optimization

	X	Ar	t	Yield	*ee*
1	O	2,4,6-*i*$Pr_3C_6H_2$	r.t.	0%	-
2	S	2,4,6-*i*$Pr_3C_6H_2$	r.t.	96%	14%
3	S	2,6-*i*Pr_3-4-(9-anthryl)C_6H_2	r.t.	96%	34%
4*	S	2,6-*i*Pr_3-4-(9-anthryl)C_6H_2	-86 °C	95%	84%

* 1mol% cat., toluene/hexane 1:1

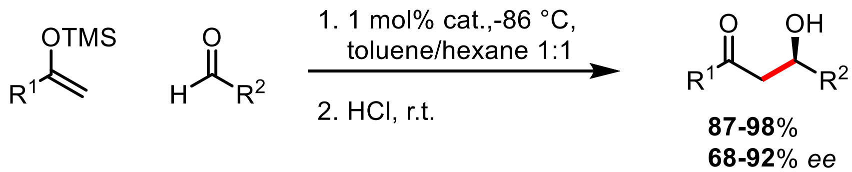


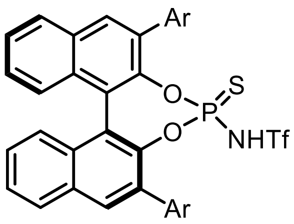
silyl ketene acetal

C. H. Cheon, H. Yamamoto, *Org. Lett.* **2010**, *12*, 2476 – 2479

Mukaiyama Aldol Reaction

- Brønsted acid Catalyzed Mukaiyama Aldol Reaction





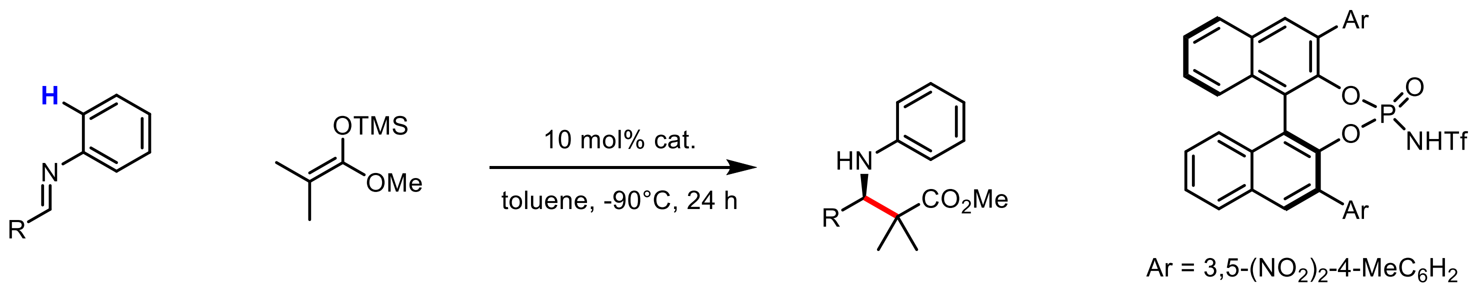
Ar = 2,6-iPr$_2$-4-(9-anthryl)C$_6$H$_2$

	R1	R2	Yield	*ee*
1	Ph	Ph	95%	84%
2	Ph	4-OMePh	96%	84%
3	Ph	4-ClPh	93%	80%
4	Ph	2-thienyl	92%	70%
5	4-MeOPh	Ph	97%	84%
6	2-MeOPh	Ph	98%	80%
7	2-Naph	Ph	94%	84%

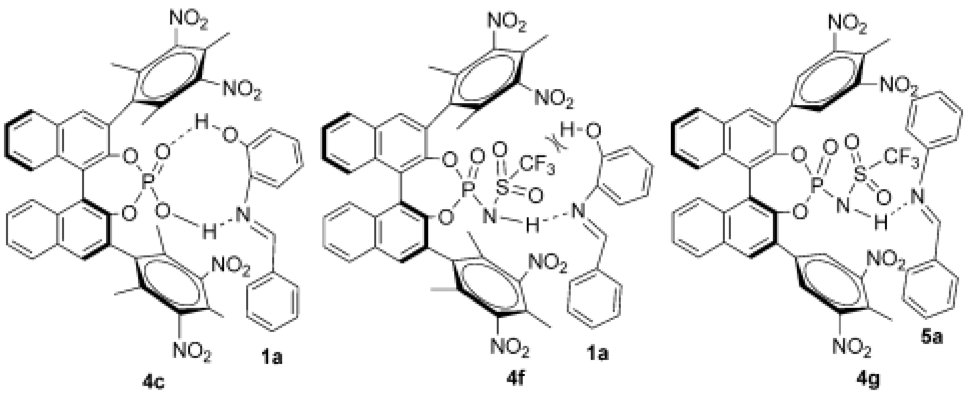
C. H. Cheon, H. Yamamoto, *Org. Lett.* **2010**, *12*, 2476 – 2479

Mukaiyama-Mannich Reaction

- Brønsted acid Catalyzed Mukaiyama-Mannich Reaction



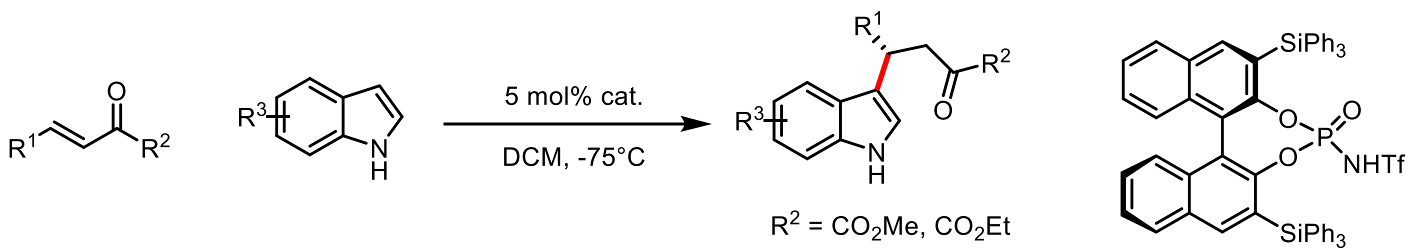
	R	Yield	*ee*
1	Ph	96%	94%
2	4-MeC_6H_4	95%	90%
3	4-$MeOC_6H_4$	95%	95%
4	4-$CF_3C_6H_4$	99%	91%
5	4-BrC_6H_4	80%	90%
6	1-Naph	82%	93%
7	2-thienyl	94%	92%
8	n-Pr	98%	80%



F. Zhou, H. Yamamoto, *Angew. Chem. Int. Ed.* **2016**, *55*, 8970 – 8974

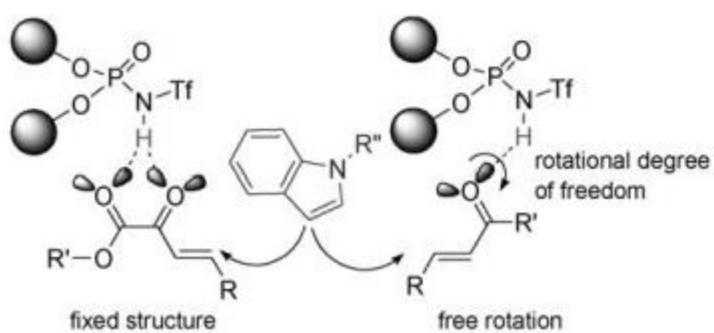
Friedel-Crafts Alkylation

- 1,4-Addition of Indoles to α,β-Unsaturated Carbonyl Compounds



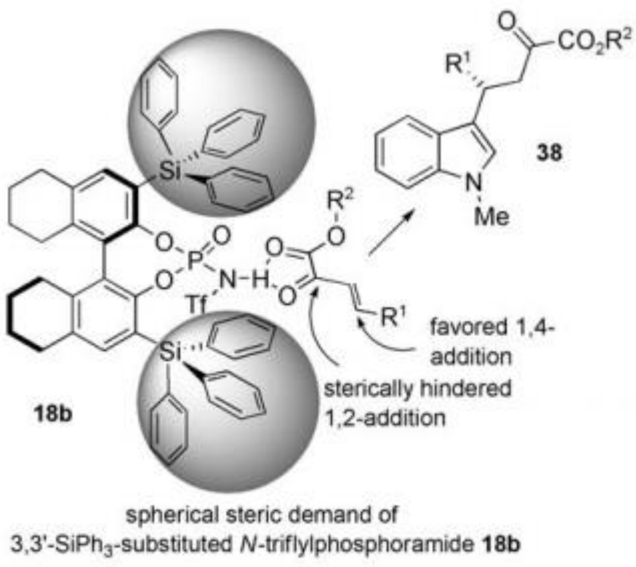
	R^1	R^2	R^3	Yield	*ee*
1	Ph	CO_2Me	H	62%	88%
2	Ph	CO_2Me	5-Br	43%	86%
3	Ph	CO_2Me	7-Me	78%	84%
4	4-ClPh	CO_2Me	H	65%	88%
5	4-MeOPh	CO_2Me	H	88%	86%
6	4-MePh	CO_2Me	H	69%	92%
7	2-Naph	CO_2Me	H	70%	90%
8	Ph	Me	H	45%	14%

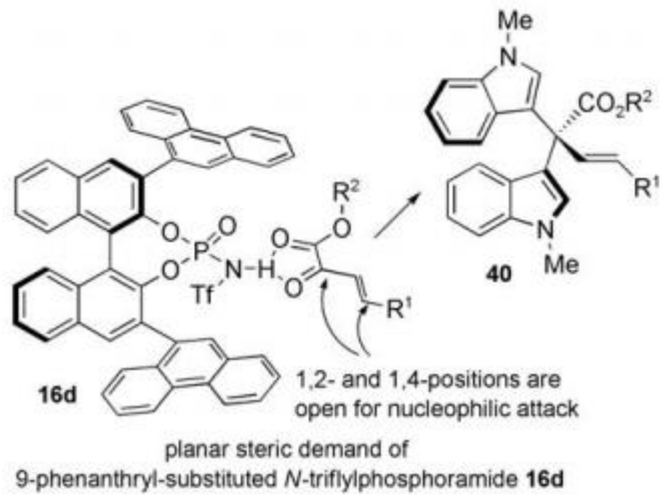
- Rationalization of Poor Enantioselectivity of Ketones



M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem. Int. Ed.* **2008**, *47*, 593 – 596

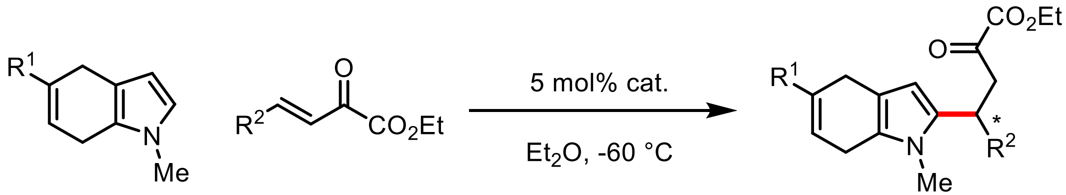
- 1,4-Addition of Indoles to α,β-Unsaturated Carbonyl Compounds



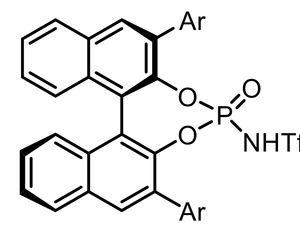


Friedel-Crafts Reaction

- Friedel–Crafts Reaction of 4,7-Dihydroindoles

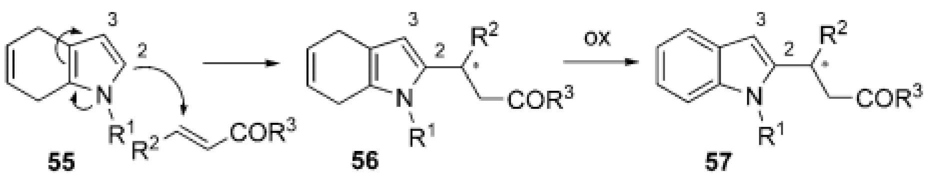


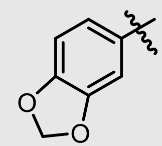
59-96%, **91-98**% *ee*



Ar = 2,4,6-(iPr)$_3$C$_6$H$_2$

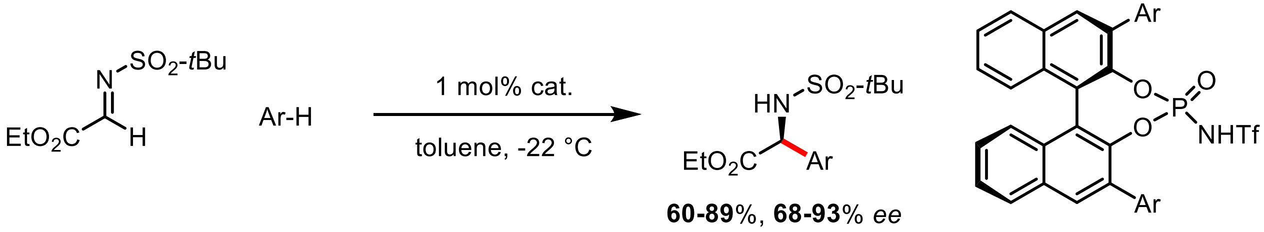
2-Alkylation of indole



	R¹	R²	Yield	*ee*
1	H	Ph	96%	98%
2	H	4-MePh	59%	87%
3	H		82%	97%
4	H	3-NO_2Ph	66%	93%
5	H	2-furyl	89%	96%
6	H	2-thienyl	96%	98%

Friedel-Crafts Reaction

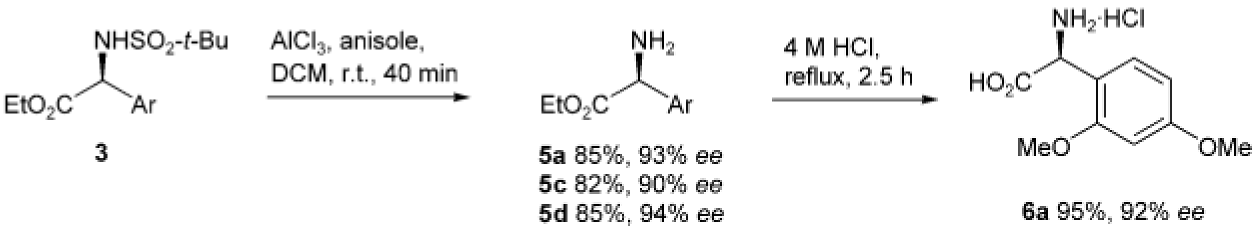
- Friedel–Crafts Reaction of Glyoxylate Imines for a Synthesis of Arylglycines



Ar = 2,4,6-(iPr)$_3$C$_6$H$_2$

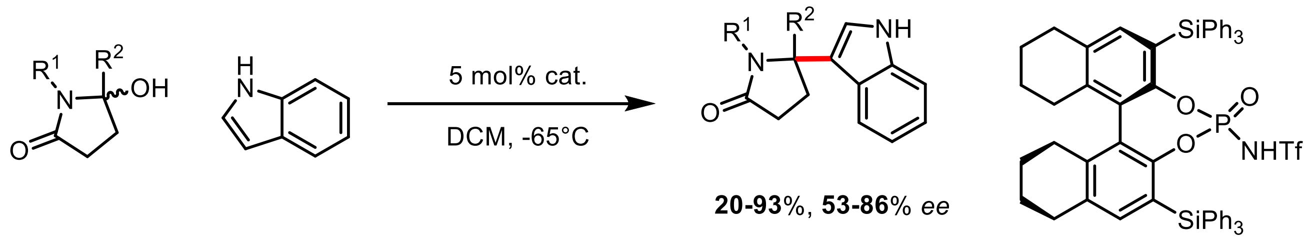
	Ar	Yield	*ee*
1	2,4-(MeO)$_2$Ph	76%	93%
2	3,4-(MeO)$_2$Ph	87%	82%
3	4-(MeO)-Ph	62%	91%
4	4-(MeO)-Naph	74%	96%
5	2-(MeO)-Naph	89%	87%

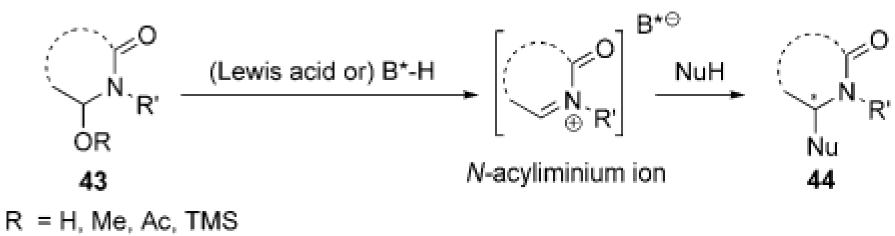
- Deprotection and Hydrolysis



D. Enders, M. Seppelt, T. Beck, *Adv. Synth. Catal.* **2010**, *352*, 1413 – 1418

- Nucleophilic Addition to N-Acyliminium Ions

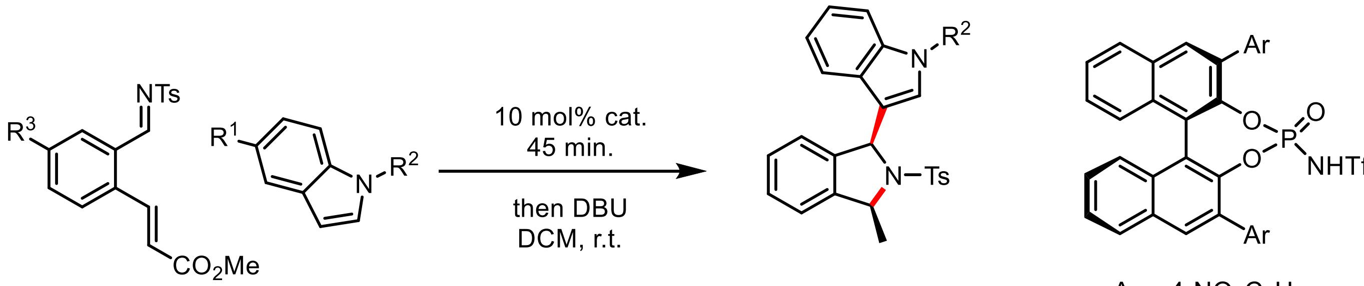




	R^1	R^2	Yield	*ee*
1	PMB	Me	54%	86%
2	Bn	Me	61%	84%
3	Bn	Et	54%	71%
4	Bn	C_3H_7	93%	55%
5	Bn	Bu	58%	84%
6	Bn	Bn	39%	63%

M. Rueping, B. J. Nachtsheim, *Synlett* **2010**, 119 – 122

- Domino aza-Friedel-Crafts/aza-Michael Reaction for an Isoindoline Synthesis

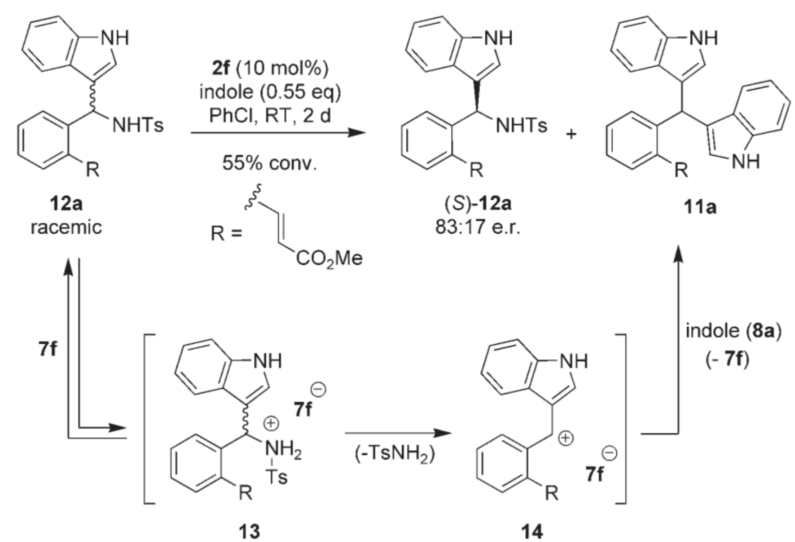


71-99%, **22-90**% *ee*

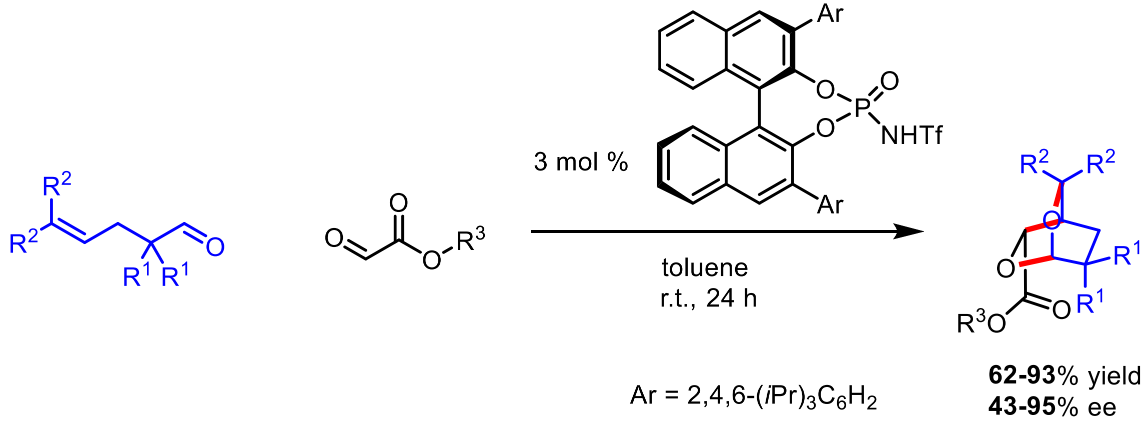
Ar = 4-$NO_2C_6H_4$

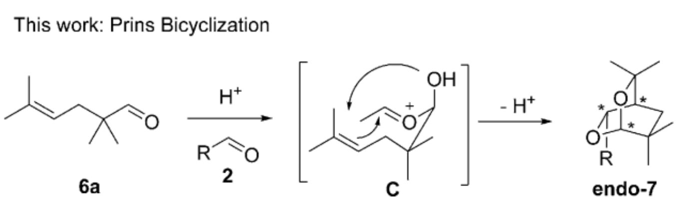
- Stereoablative Kinetic Resolution

	R^1	R^2	R^3	Yield	*ee*
1	H	H	H	94%	90%
2	Br	H	H	99%	88%
3	MeO	H	H	93%	52%
4	CO_2Me	H	H	71%	72%
5	H	H	F	75%	95%
6	MeO	H	F	82%	76%



- NTPA-Catalyzed Enantioselective Prins Bicyclization



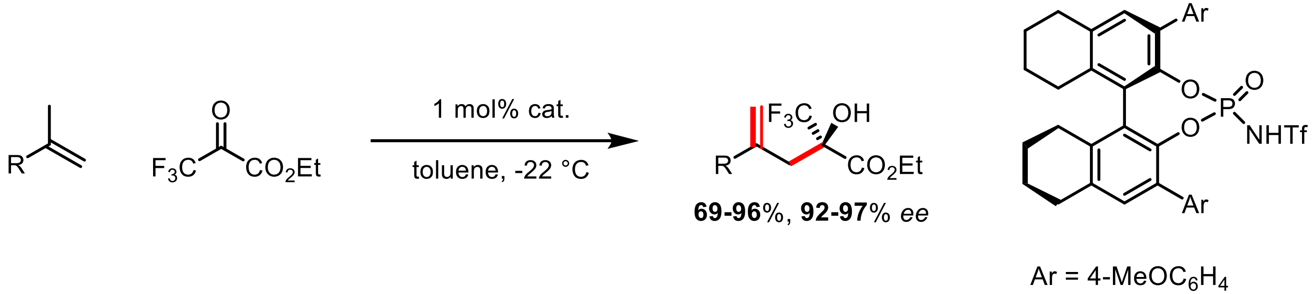


	R¹	R²	R³	Yield	*ee*
1	Me	Me	Et	85%	86%
2	Me	Me	*i*Pr	72%	95%
3	Me	Me	*t*Bu	70%	92%
4	Me	Me	Bn	93%	87%
5	-($(CH_2)_3$)-	Me	Et	83%	88%
6	-($(CH_2)_3$)-	Me	*t*Bu	80%	89%

J. Liu,L. Zhou,C. Wang, D. Liang, Z. Li, Y. Zou, Q. Wang, A. Goeke *Chem. Eur. J.* **2016**, *22*, 6258–6261

Carbonyl-Ene Reaction

- Carbonyl-Ene Reaction for Synthesis of Homo-allylic Alcohol

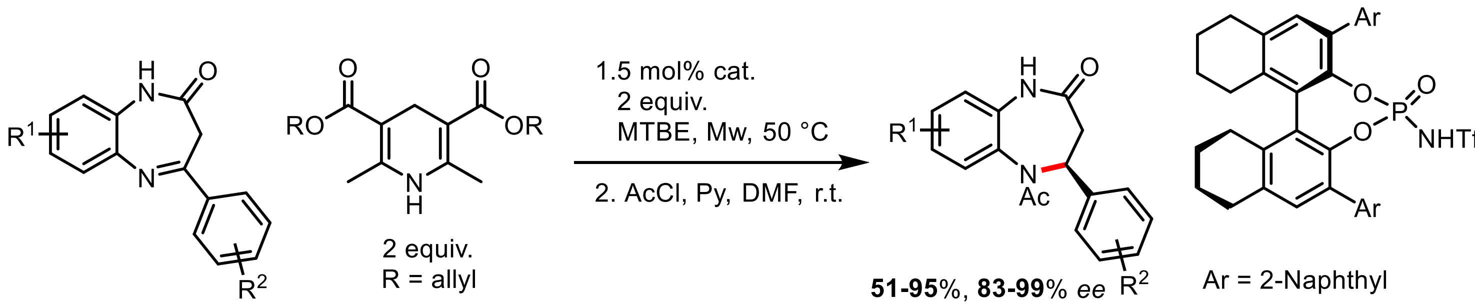


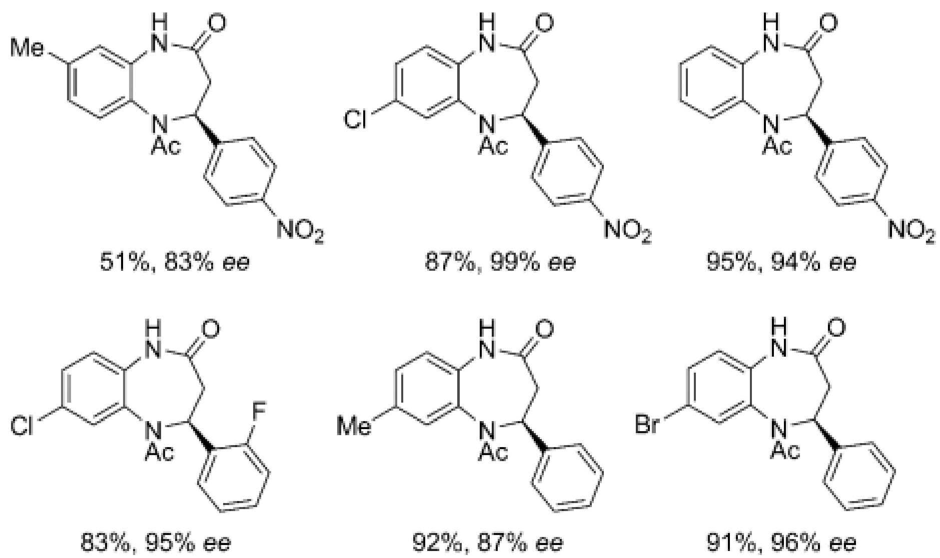
	R	Yield	*ee*
1	Ph	76%	96%
2	4-MeOPh	69%	92%
3	4-MePh	92%	96%
4	3-MePh	91%	96%
5	4-EtPh	96%	95%
6	4-FPh	88%	92%
7	2-Naph	95%	95%
8	biphenyl	87%	97%
9	4-*t*BuPh	83%	94%

M. Rueping, T. Theissmann, A. Kuenkel, R. M. Koenigs, *Angew. Chem. Int. Ed.* **2008**, *47*, 6798 – 6801

Reduction

- Reduction of Imine for Synthesis of Benzodiazepinone

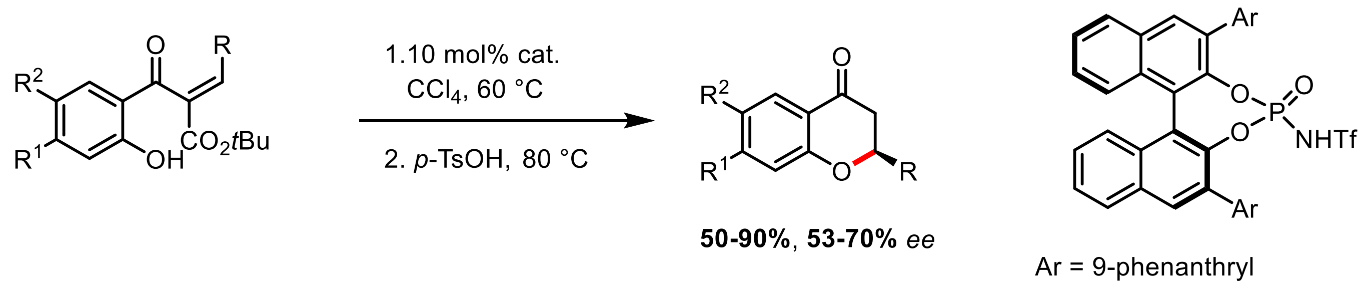




M. Rueping, E. Merino, R. M. Koenigs, *Adv. Synth. Catal.* **2010**, *352*, 2629 – 2634

Michael Addition

- oxa-Michael Addition for Synthesis of flavanones

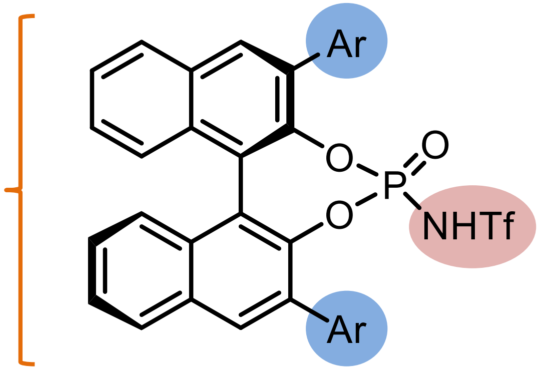


	R	R^1	R^2	Yield	*ee*
1	Ph	H	H	82%	55%
2	4-BrPh	H	H	84%	70%
3	4-NO_2Ph	H	H	50%	53%
4	4-MePh	H	H	90%	63%
5	Ph	-$(CH_2)_4$-		90%	66%

Z. Feng, M. Zeng, Q.-L. Xu, S.-L. You, *Chin. Sci. Bull.* **2010**, *55*, 1723 – 1725

Conclusion

BINOL framework

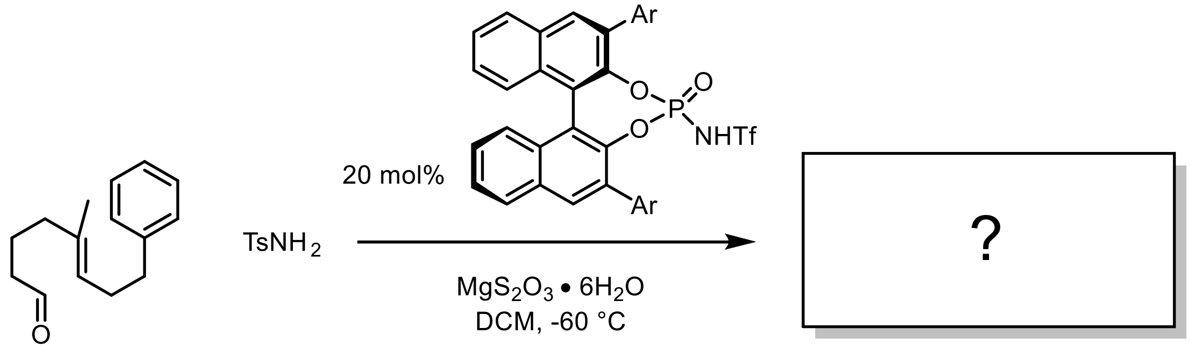


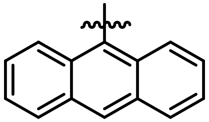
- BINOL based N-triflylphosphoramide
  Chiral Brønsted acid catalyst

- Useful for activating carbonyl compounds and imines

- Many enantioselective version of Cycloaddition, Nazarov reaction, Mukaiyama aldol reaction and Friedel-Crafts reactions are developed with chiral phosphoramide.

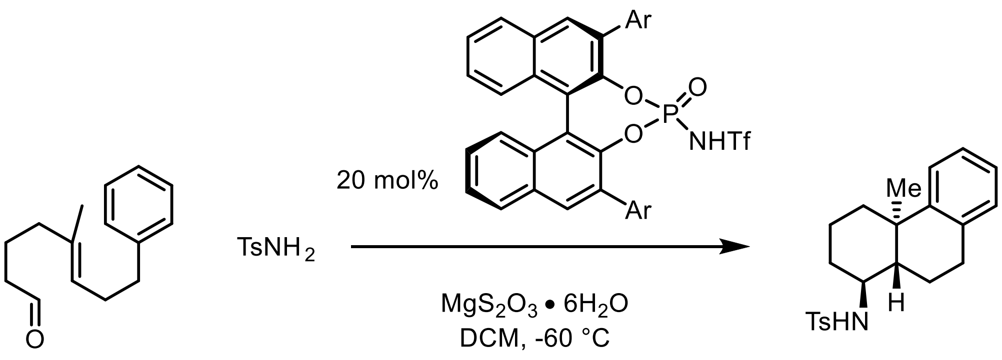
- Estimate the product with stereochemistry

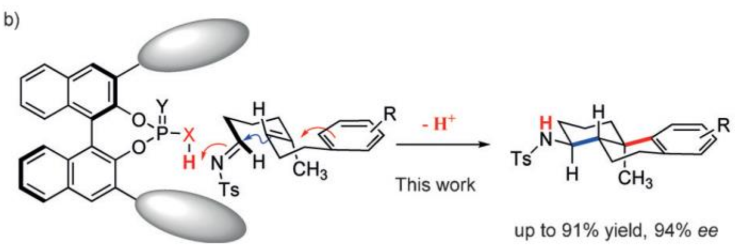


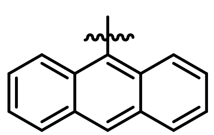
Ar = 

Answer

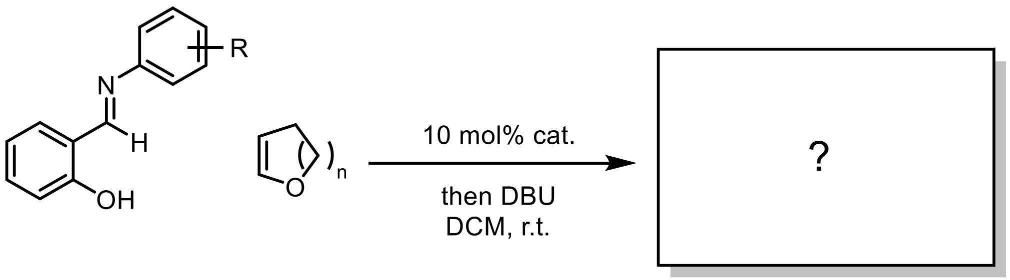
- Estimate the product with stereochemistry





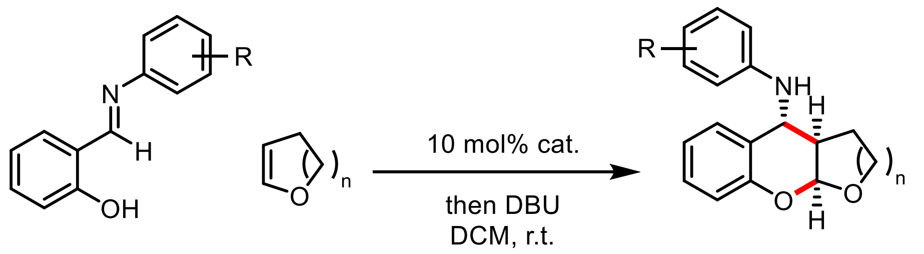
Ar = 

Domino Mannich/ketalization Reaction

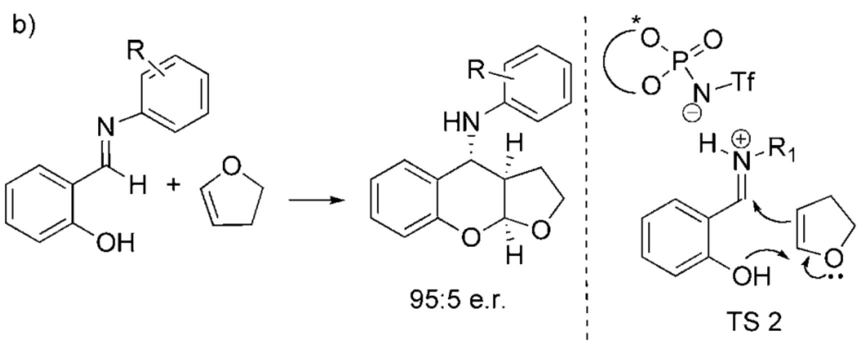


Domino Mannich/ketalization Reaction

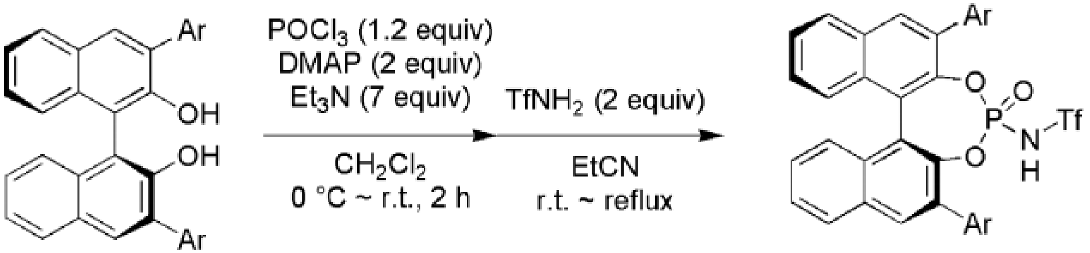
- Domino Mannich/ketalization for benzopyran synthesis



n=1	n=2
51-89%	59-71%
74-96% *ee*	86-95% *ee*
d.r. = 1.15:1 - 2.2:1	d.r. = 4.3:1 - 33:1

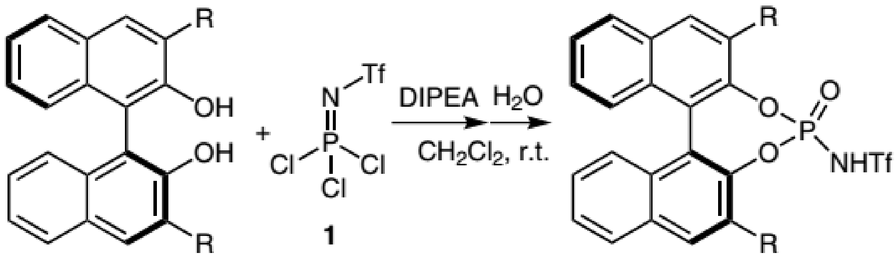


- Synthesis of a N-triflylphosphoramide (NTPA)

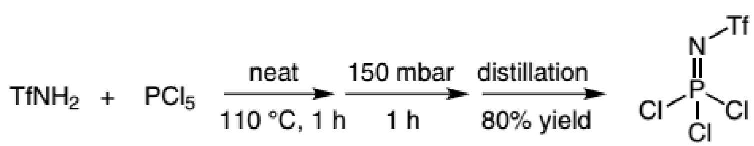


2: Ar = Ph
3: Ar = 1,3,5-(i-Pr)$_3C_6H_2$

D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626 – 9627



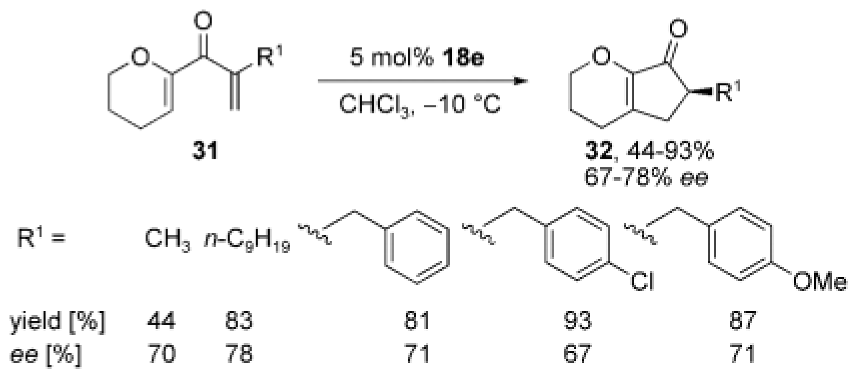
2a–g **6a–g**



1

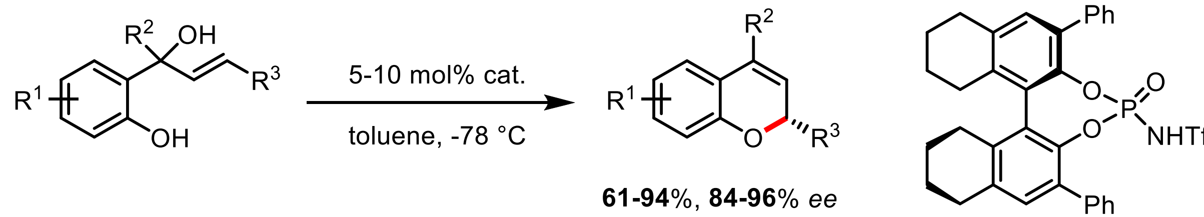
S. Lee, P. S. J. Kaib, B. List *Synlett* **2017**, *28*, 1478 – 1480

- NTPA-Catalyzed Nazarov Cyclization/Protonation



cat structure 필요

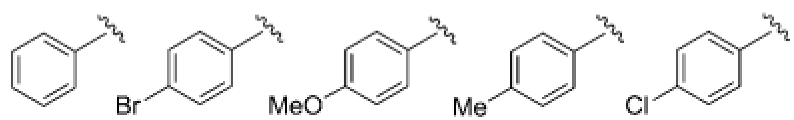
- Asymmetric Allylic Alkylation



R^2 = Me
R^1 = H, R^3 =

R^2 = Me
R^1 = 7-F, R^3 =

R^2 = Et
R^1 = H, R^3 =



yield [%]	92	80	91	94	71
ee [%]	92	94	90	92	96

Catalytic Enantioselective [2+2] Cycloadditions: Synthesis of Cyclobutanes

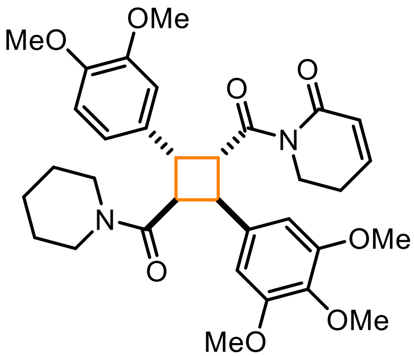
Frontiers in Chemical Synthesis III: Stereochemistry

Bastian MURIEL

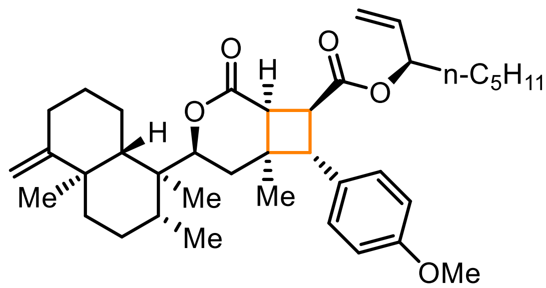
Big Talk, 20/05/2019

Ecole Polytechnique Fédérale de Lausanne
Laboratory of Catalysis and Organic Synthesis (LCSO)

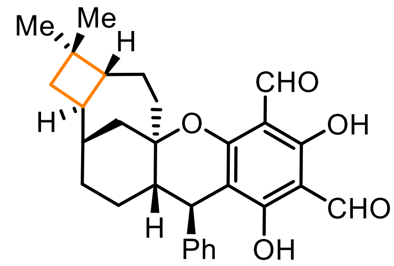
Cyclobutane-containing Bioactive Natural products



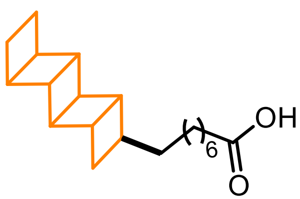
Piperaborenine B
Cytotoxic activity



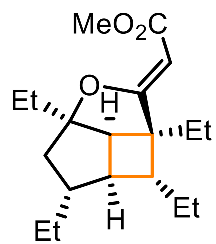
Scopariusicide A
Immunosuppressive activity



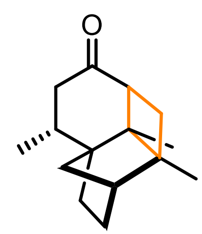
Psiguadial B
Antiproliferative activity



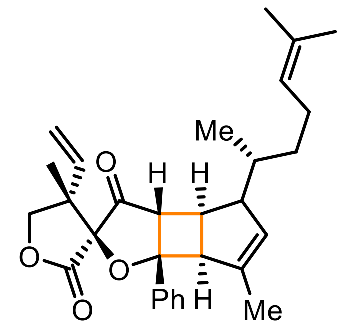
Pentacycloanammoxic acid
Annamox process biomarker



Hippolachnin A
Antifungal activity



Solanascone
Antibacterial activity



Biyouyanagin A
HIV replication inhibitor

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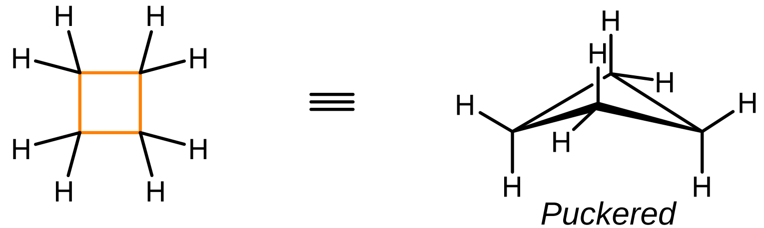
(1) M. Weng, P. Lu, *Org. Chem. Front.*, **2018**, *5*, 254–259. (2) V. M. Dembitsky, *J. Nat. Med.*, **2008**, *62*, 1–33.

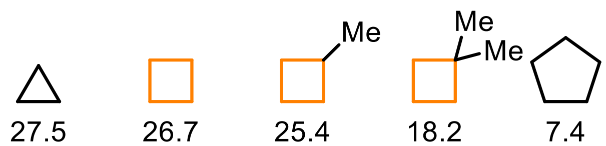
Structure and Importance

Conformation[1]

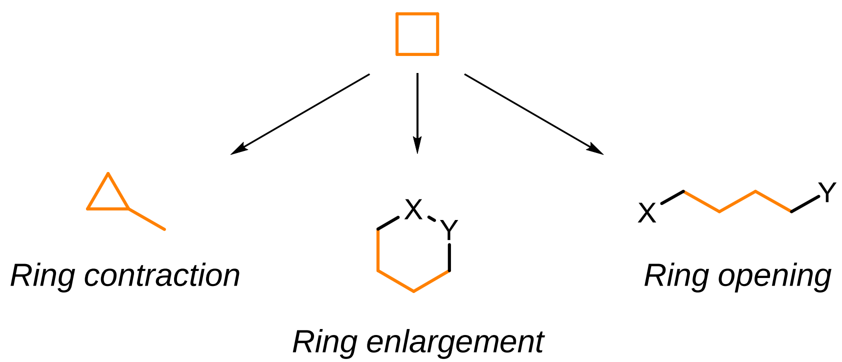


Minimized eclipsing interactions of C-H bonds

Ring Strain (kcal.mol^{-1})[2]

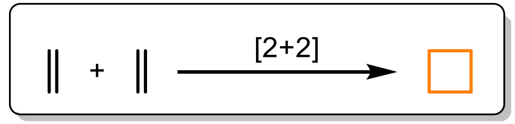


Highly Reactive Synthetic Intermediates[3]

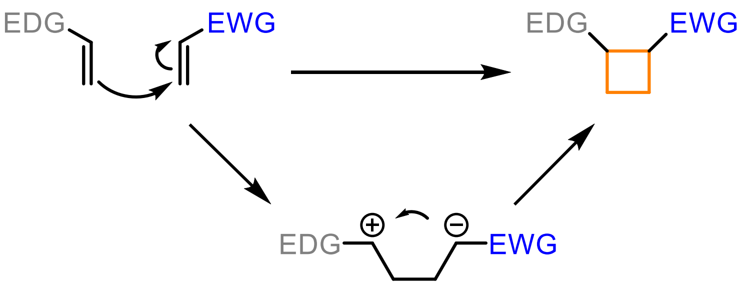


(1) F. A. Cotton, B. A. Frenz, *Tetrahedron*, **1974**, *30*, 1587-1594. (2) J. C. Namyslo, D. E. Kaufmann, *Chem. Rev.*, **2003**, *103*, 1485−1537. (3) E. Lee-Ruff, G. Mladenova, *Chem. Rev.*, **2003**, *103*, 1449−1483.

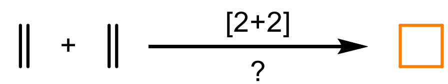
[2+2] Cycloadditions: Straightforward Access to Cyclobutanes



Polarized

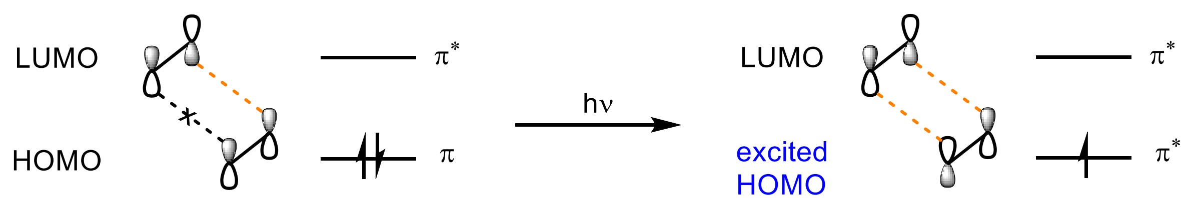


Non Polarized



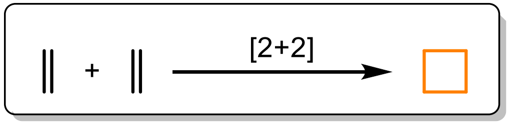
Thermal

Photochemical



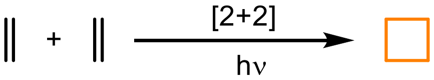
(1) N. Hoffmann, *Chem. Rev.*, **2008**, *108*, 1052–1103.

Catalytic Enantioselective [2+2] Cycloadditions

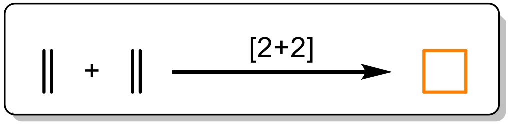


Polarized

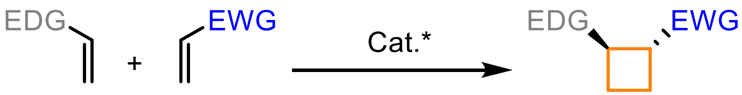
Photochemical



Catalytic Enantioselective [2+2] Cycloadditions



Polarized

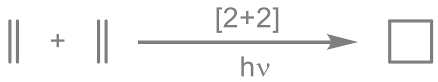


I/ Lewis Acid Catalysis

II/ Amine Catalysis

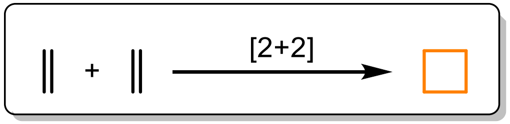
III/ Gold Catalysis

Photochemical



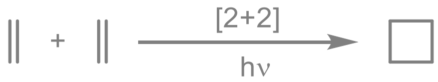
(1) Y. Xu, M. L. Conner, M. K. Brown, *Angew. Chem. Int. Ed.*, **2015**, *54*, 11918-11928. (2) S. Poplata, A. Tröster, Y.-Q. Zou, T, Bach, *Chem. Rev.*, **2016**, *116*, 9748-9815.

Catalytic Enantioselective [2+2] Cycloadditions



Polarized

Photochemical



I/ Lewis Acid Catalysis

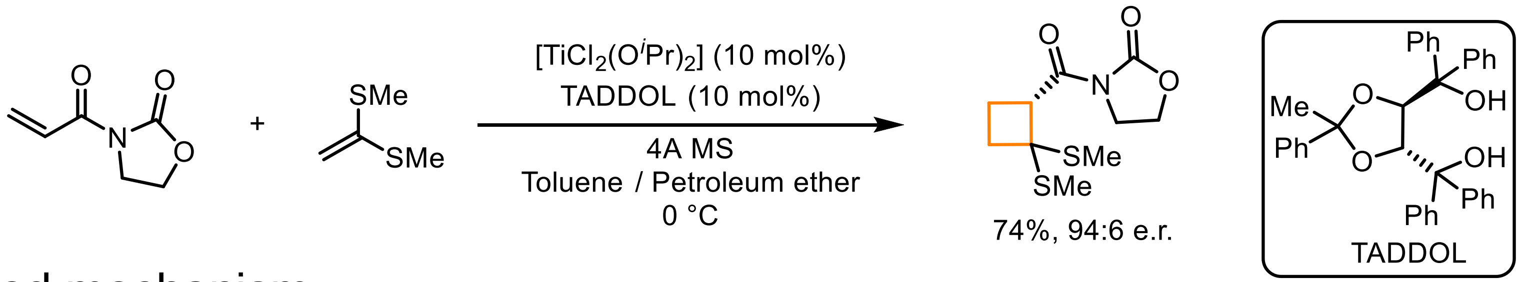
II/ Amine Catalysis

III/ Gold Catalysis

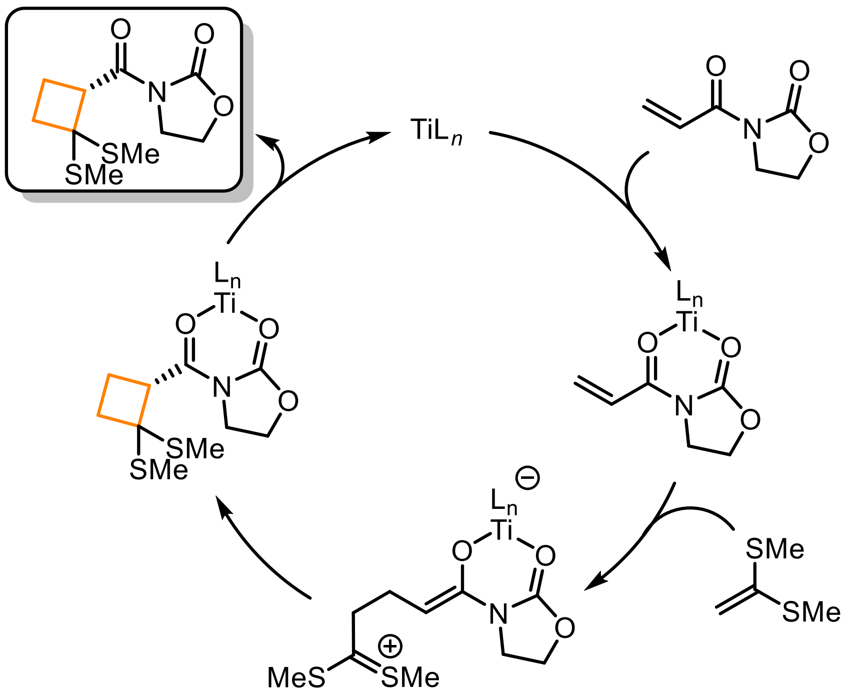
(1) Y. Xu, M. L. Conner, M. K. Brown, *Angew. Chem. Int. Ed.*, **2015**, *54*, 11918-11928. (2) S. Poplata, A. Tröster, Y.-Q. Zou, T, Bach, *Chem. Rev.*, **2016**, *116*, 9748-9815.

I/ Lewis Acid Catalysis: Ti-TADDOL

First example of lewis acid catalyzed enantioselective [2+2] cycloaddition



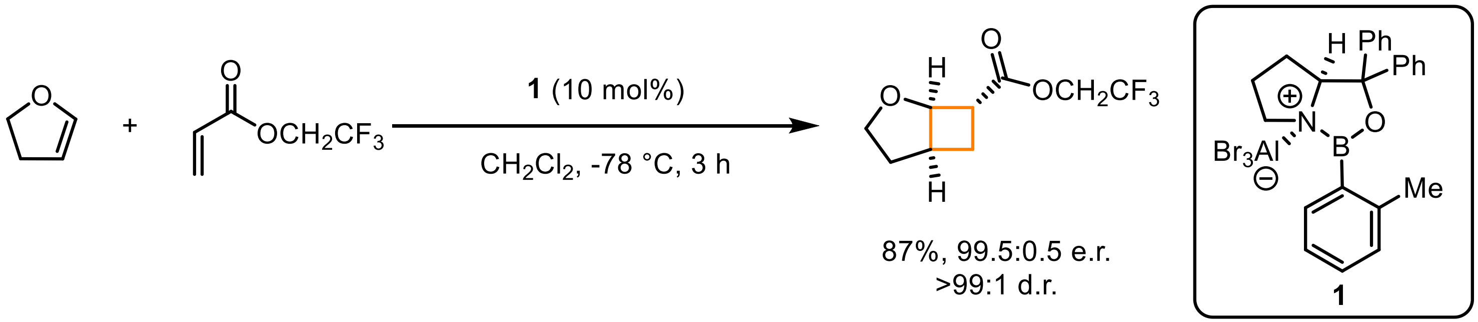
Proposed mechanism



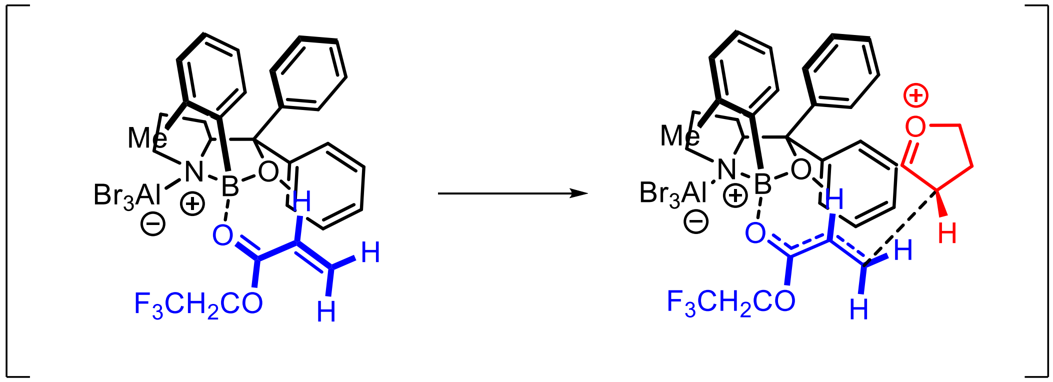
(1) Y. Hayashi, K. Narasaka, *Chem. Lett.*, **1989**, 793–796. (2) Y.-I. Ichikawa, A. Narita, A. Shiozawa, Y. Hayashi, K. Narasaka, *J. Chem. Soc. Chem. Commun.*, **1989**, 1919–1921.

I/ Lewis Acid Catalysis: oxazaborolidines

Enantioselective [2+2]-Cycloaddition of Trifluoroethyl Acrylate to Enol Ethers



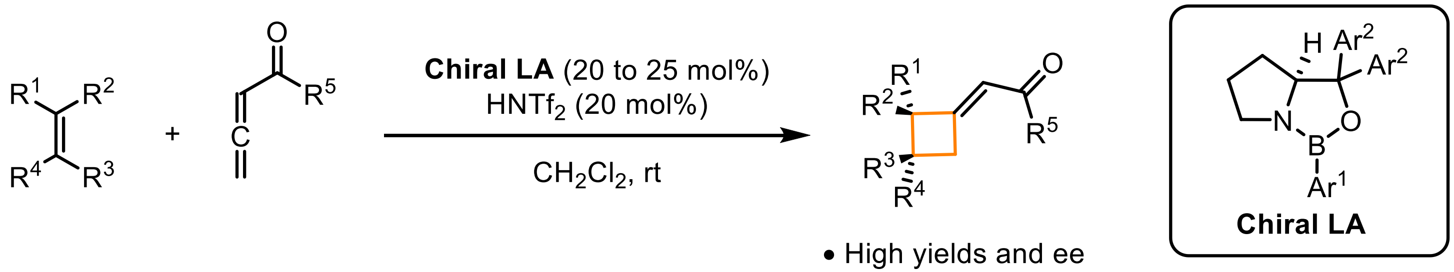
Proposed model for the stereochemical outcome



(1) E. Canales, E. J. Corey, *J. Am. Chem. Soc.*, **2007**, *129*, 12686 –12687. (2) E. J Corey, *Angew. Chem. Int. Ed.*, **2009**, *48*, 2100 – 2117.

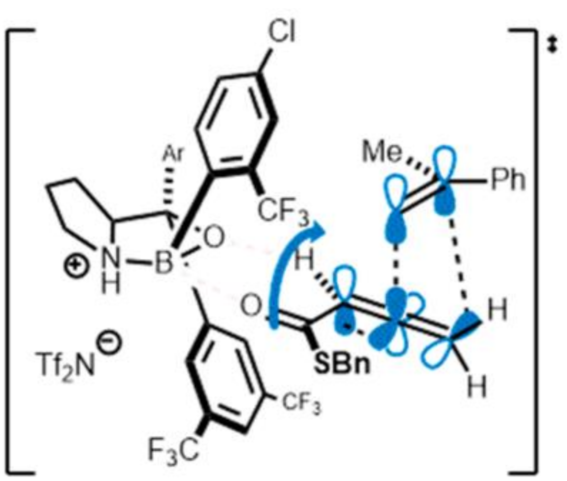
I/ Lewis Acid Catalysis: oxazaborolidines

Allenoates in Enantioselective [2+2] Cycloadditions[1,2,3]

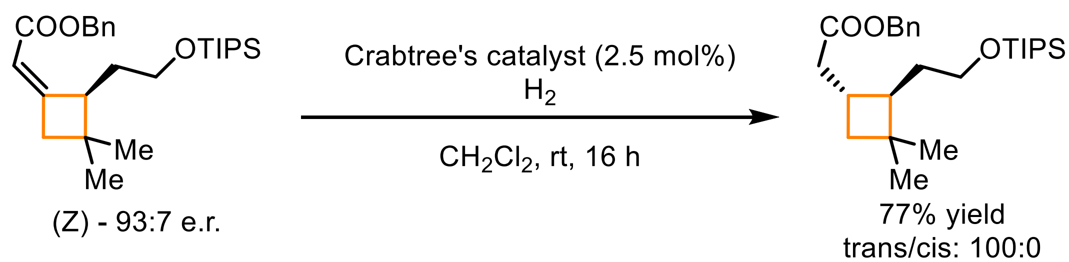


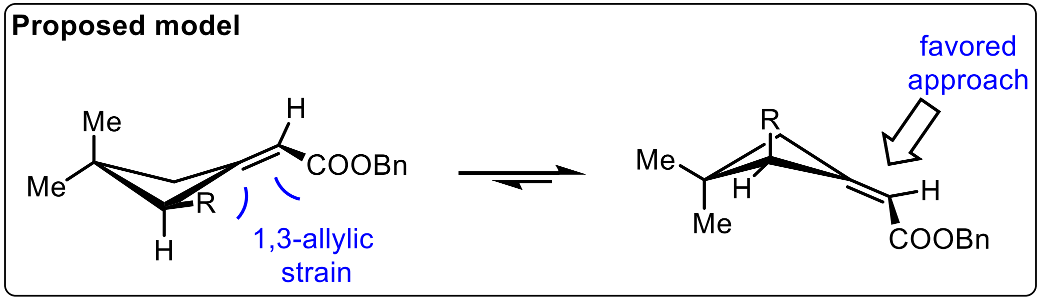
- High yields and ee
- Broad alkene scope
- Non activated alkenes suitable
- Regioselective

Proposed concerted asynchronous mechanism[3]



Conjugate Reduction[2]

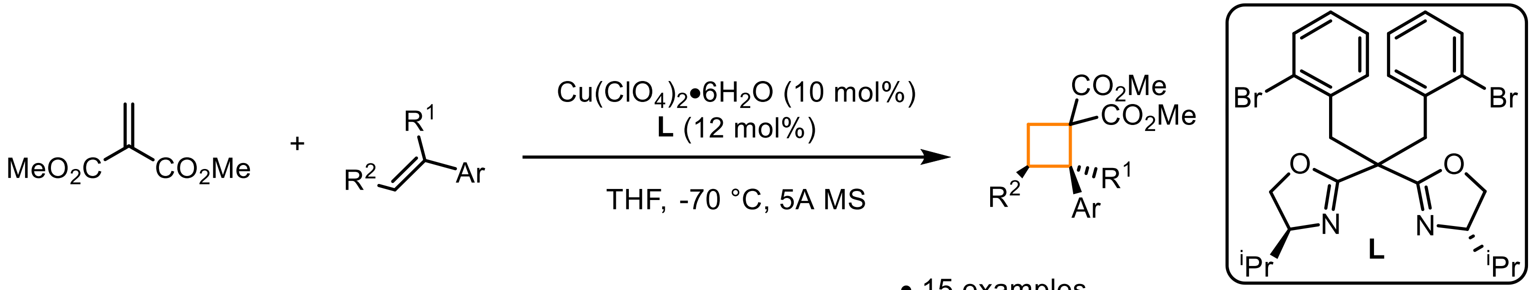




(1) M. L. Conner, Y. Xu, M K. Brown, *J. Am. Chem. Soc.,* **2015**, *137*, 3482. (2) J. M. Wiest, M. L. Conner, M. K. Brown, *Angew. Chem., Int. Ed.,* **2018**, *57*, 4647.
(3) J. M Wiest, M. L. Conner, K. M. Brown, *J. Am. Chem. Soc.*, **2018**, *140*, 15943−15949.

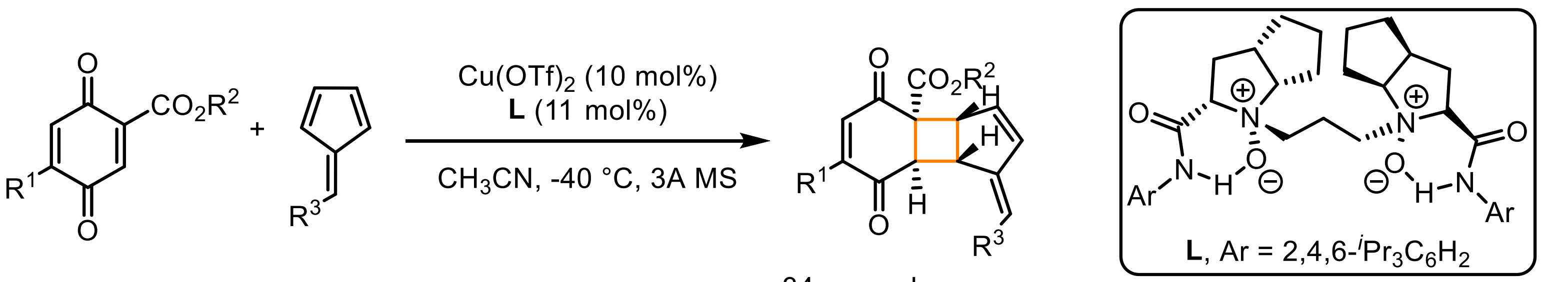
I/ Lewis Acid Catalysis: Copper

First enantioselective synthesis of donor-acceptor (DA) cyclobutanes[1]



- 15 examples
- Up to 92% yield
- > 99:1 d.r. and *ee* up to >99%

Quinone-Fulvene [2+2] cycloaddition[2]

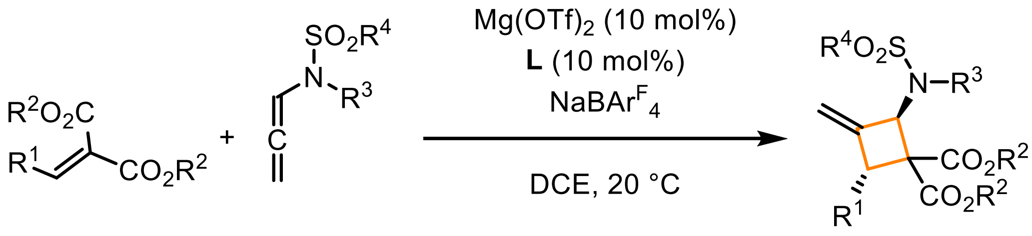


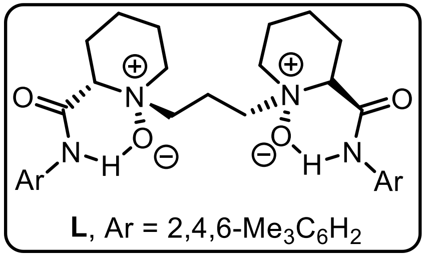
- 34 examples
- Up to 83% yield, 98:2 d.r. and 99:1 *e.r.*

(1) J-L. Hu, L-W. Feng, L. Wang, Z. Xie, Y. Tang, X. Li, *J. Am. Chem. Soc.*, **2016**, *138*, 13151−13154. (2) H. Zheng, C. Xu, Y. Wang, T. Kang, X. Liu, L. Lin, X. Feng, *Chem. Commun.*, **2017**, *53*, 6585-6588.

I/ Lewis Acid Catalysis: Magnesium

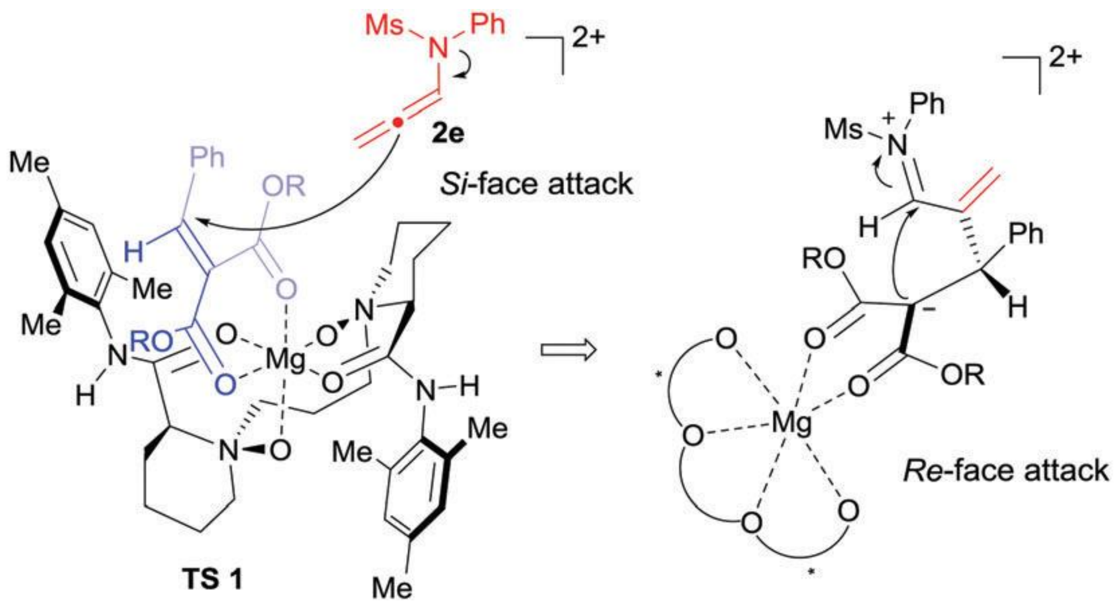
Asymmetric synthesis of aminocyclobutanes from *N*-allenamides





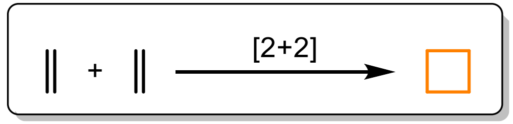
- 32 examples
- Up to 99% yield, >95:5 d.r. and 96% *ee*.

Proposed transition state

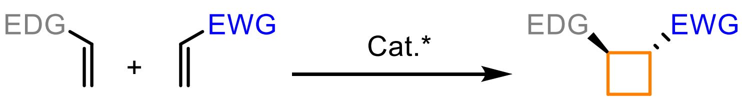


(1) X. Zhong, Q. Tang, P. Zhou, Z. Zhong, S. Dong, X. Liu, X. Feng, *Chem. Commun.,* **2018**, *54*, 10511-10514.

Catalytic Enantioselective [2+2] Cycloadditions



Polarized

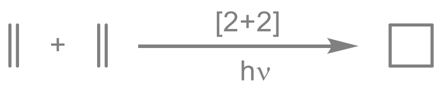


I/ Lewis Acid Catalysis

II/ Amine Catalysis

III/ Gold Catalysis

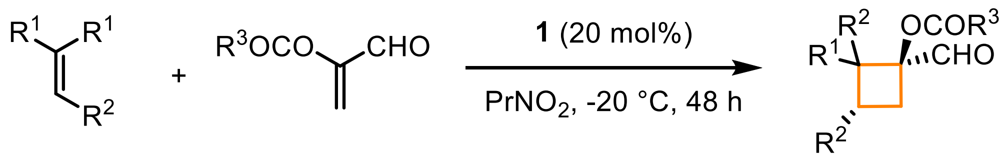
Photochemical

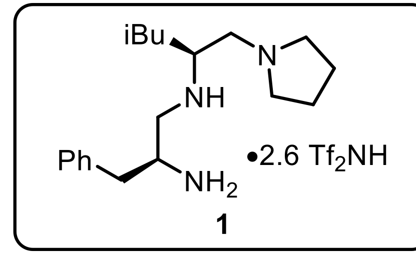


(1) Y. Xu, M. L. Conner, M. K. Brown, *Angew. Chem. Int. Ed.*, **2015**, *54*, 11918-11928. (2) S. Poplata, A. Tröster, Y.-Q. Zou, T, Bach, *Chem. Rev.*, **2016**, *116*, 9748-9815.

II/ Amine Catalysis: Iminium

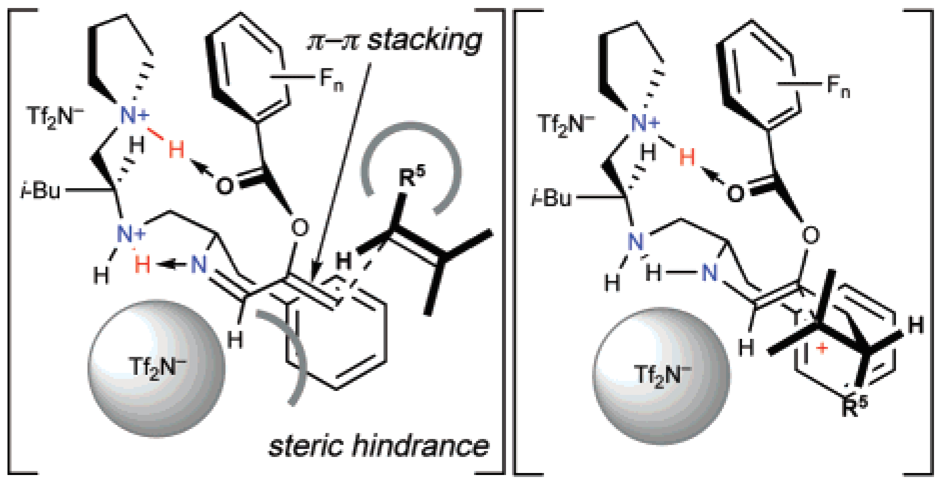
Unactivated Alkenes with α-Acyloxyacroleins Catalyzed by Chiral Organoammonium Salts[1]





- 17 examples
- Up to 80% yield, 95:5 d.r. and 95% *ee.*

Proposed Transition State

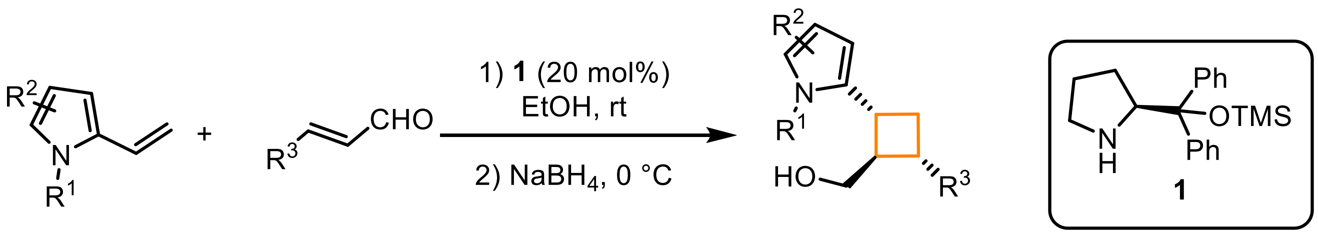


TS-9 TS-10

(1) K. Ishihara, K. Nakano, *J. Am. Chem. Soc.*, **2007**, *129*, 8930-8931.

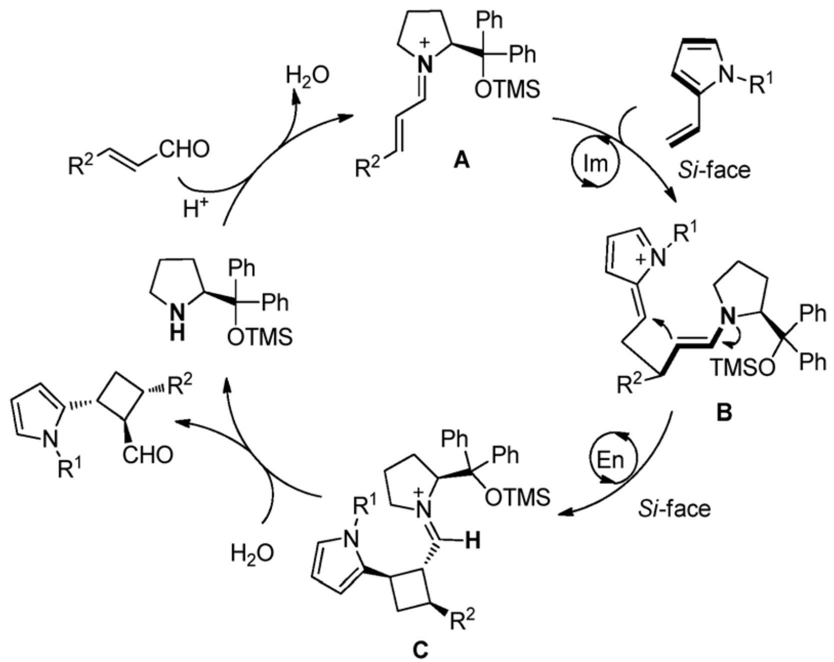
II/ Amine Catalysis: Iminium

Vinylogous Friedel–Crafts alkylation for the synthesis of pyrrole substituted cyclobutanes[1]



- 17 examples
- Up to 79% yield and 98% *ee.*
- d.r > 99:1

Proposed mechanism



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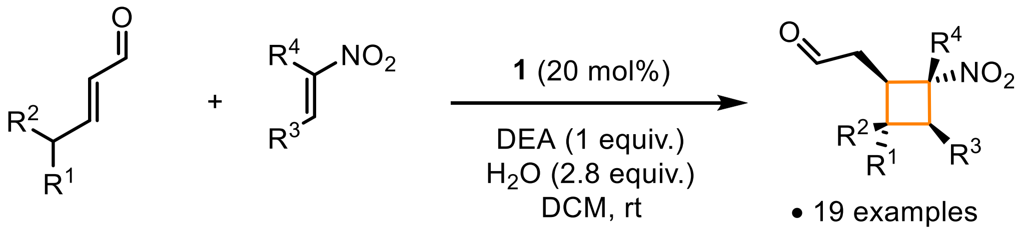
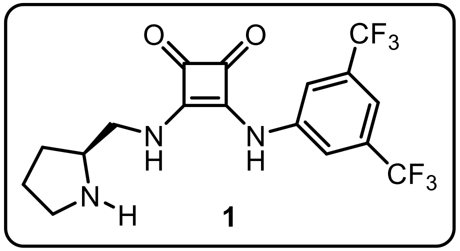
(1) G-J. Duan, J-B. Ling, W-P. Wang, Y-C. Luo, P-F. Xu, *Chem. Commun.,* **2013**, *49*, 4625-4627

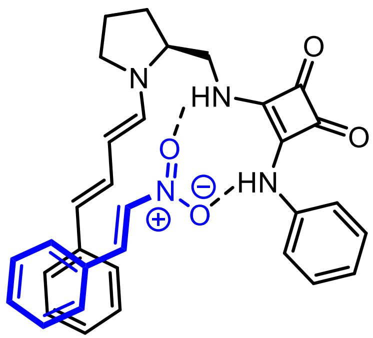
II/ Amine Catalysis: Enamine

Bifunctional H-Bond Directing Enamine Catalysis[1]

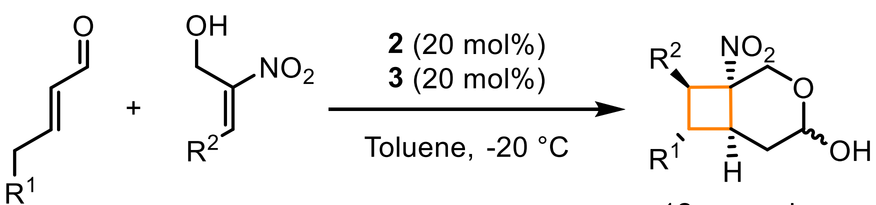


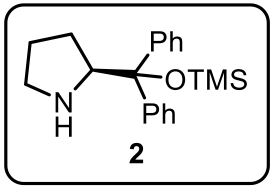


- 19 examples
- Up to 93% yield and 99% *ee.*
- d.r > 20:1

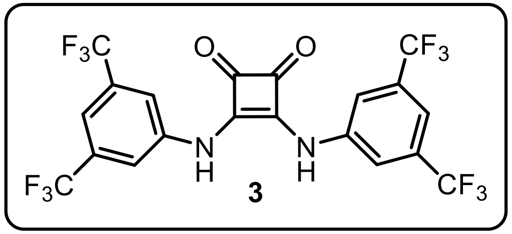


Cooperative Dienamine/Hydrogen-Bonding Catalysis





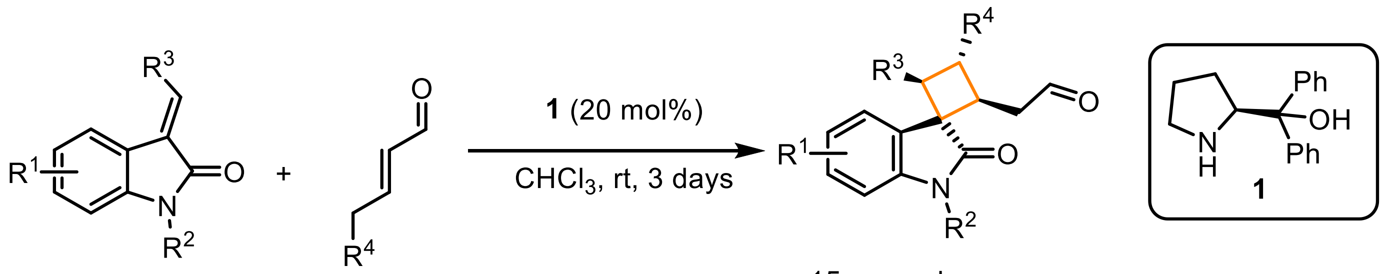
- 12 examples
- Up to 91% yield and 94% *ee*



(1) Ł. Albrecht, G. Dickmeiss, F. C. Acosta, C. Rodriguez-Escrich, R. L. Davis, K. A. Jørgensen, *J. Am. Chem.Soc.*, **2012**, *134*, 2543−2546. (2) G. Talavera, E. Reyes, J. L. Vicario, L. Carrillo, *Angew. Chem. Int. Ed.*, **2012**, *124*, 4180-4183.

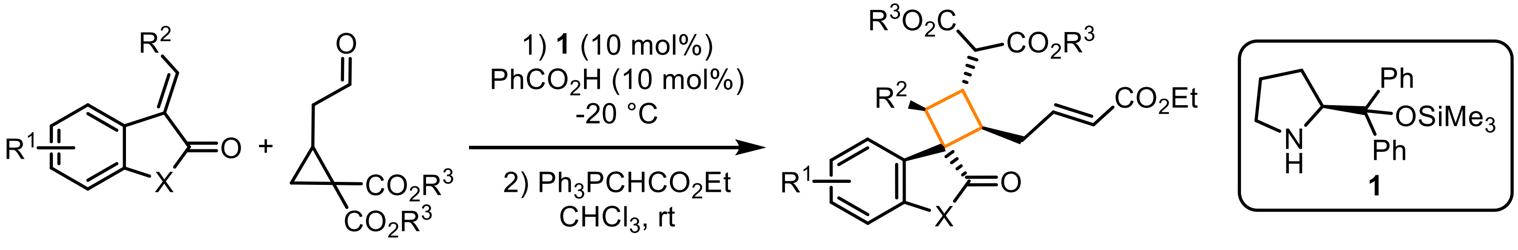
II/ Amine Catalysis: Recent Developments

Access to spiro-cyclobutyl oxindoles[1]



- 15 examples
- Up to 82% yield, 19:1 d.r and 97% *ee.*

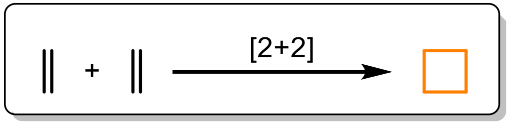
From Cyclopropylacetaldehyde[2]



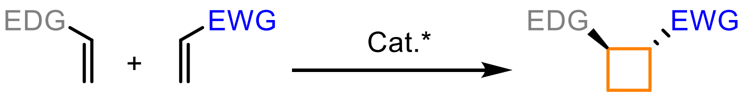
- 14 examples
- Up to 86% yield, >25:1 d.r and 97% *ee.*

(1) L.-W. Qi, Y. Yang, Y.-Y. Gui, Y. Zhang, F. Chen, F. Tian, L. Peng, L.-X. Wang, *Org. Lett.*, **2014**, *16*, 6436–6439. (2) K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund, K. A. Jørgensen, *J. Am. Chem. Soc.*, **2015**, *137*, 1685-1691.

Catalytic Enantioselective [2+2] Cycloadditions



Polarized

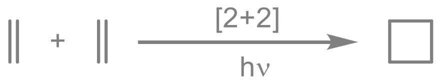


I/ Lewis Acid Catalysis

II/ Amine Catalysis

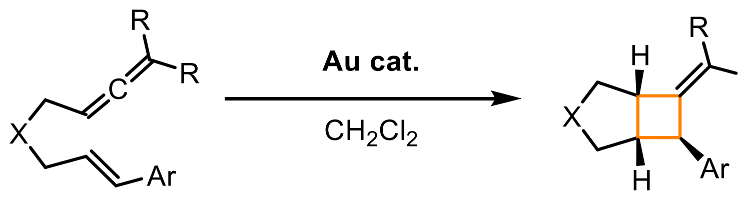
III/ Gold Catalysis

Photochemical

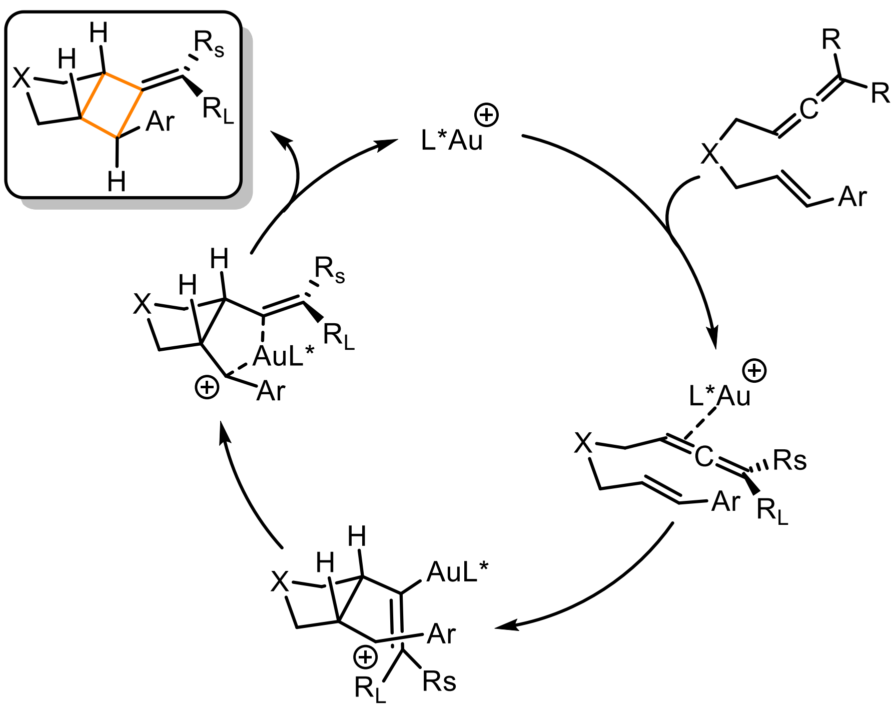


(1) Y. Xu, M. L. Conner, M. K. Brown, *Angew. Chem. Int. Ed.*, **2015**, *54*, 11918-11928. (2) S. Poplata, A. Tröster, Y.-Q. Zou, T, Bach, *Chem. Rev.*, **2016**, *116*, 9748-9815.

II/ Gold Catalysis: Early efforts, Intramolecuar [2+2]

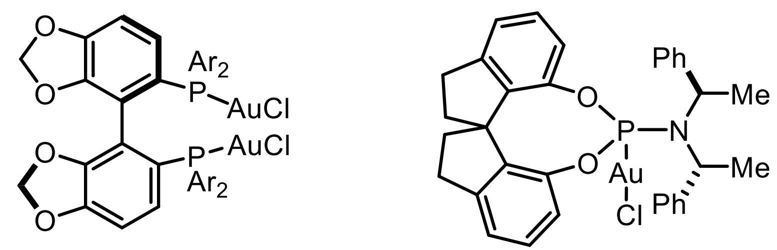


Mechanism



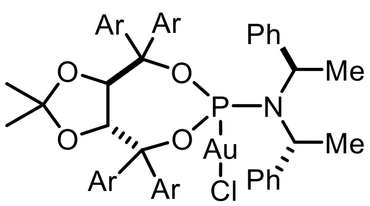
Gold catalysts

Toste[1,3]



Ar = 3,5-t-Bu$_2$-(CH$_3$O)-C$_6$H$_2$

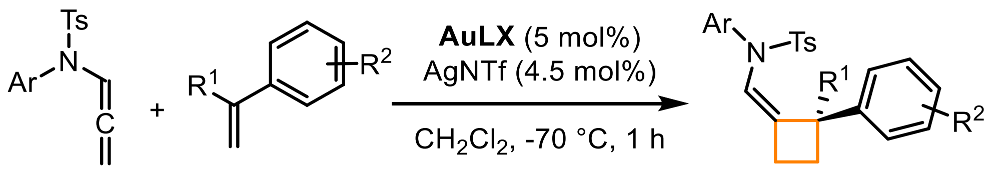
Fürstner[2,4]



(1) M. R. Luzung, P. Mauleýn, F. D. Toste, *J. Am. Chem. Soc.*, **2007**, *129*, 12402-12403.. (2) H. Teller, S. Flîgge, R. Goddard, A. Fürstner, *Angew. Chem. Int. Ed.*, **2010**, *49*, 1949–1953. (3) A. Z. Gonz.lez, D. Benitez, E. Tkatchouk, W. A. Goddard III, F. D. Toste, *J. Am. Chem. Soc.*, **2011**, *133*, 5500–5507. (4) H. Teller, M. Corbet, L. Mantilli, G. Gopakumar, R. Goddard, W. Thiel, A. Fürstner, *J. Am. Chem. Soc.*, **2012**, *134*, 15331-15342.

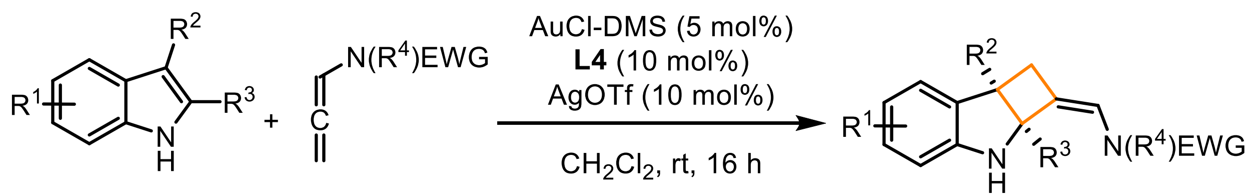
II/ Gold Catalysis: Intermolecular [2+2]

N-Allenylsulfonamides with Vinylarenes[1]

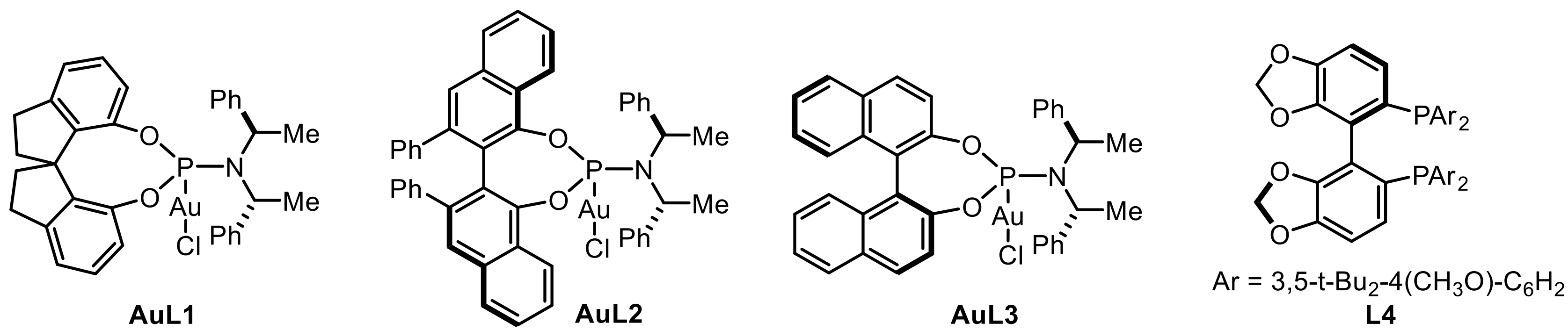


- 21 examples
- Up to 95% yield and 95% *ee.*

Dearomative [2+2]-cycloaddition between indoles and allenamides[2]

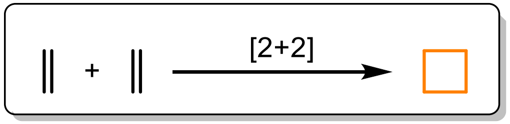


- 16 examples
- Up to 96% yield, 20:1 d.r and 99% *ee.*



(1) S. Suarez-Pantiga, C. Hernandez-D.az, E. Rubio, J. M. Gonzalez, *Angew. Chem. Int. Ed.,* **2012**, *51*, 11552-11555. (2) M. Jia, M. Monari, Q.-Q. Yang, M. Bandini, *Chem. Commun.*, **2015**, *51*, 2320–2323.

Catalytic Enantioselective [2+2] Cycloadditions



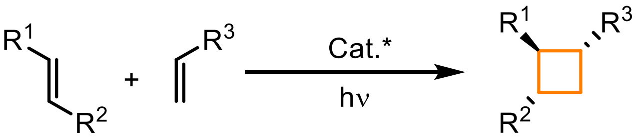
Polarized

I/ Lewis Acid Catalysis

II/ Amine Catalysis

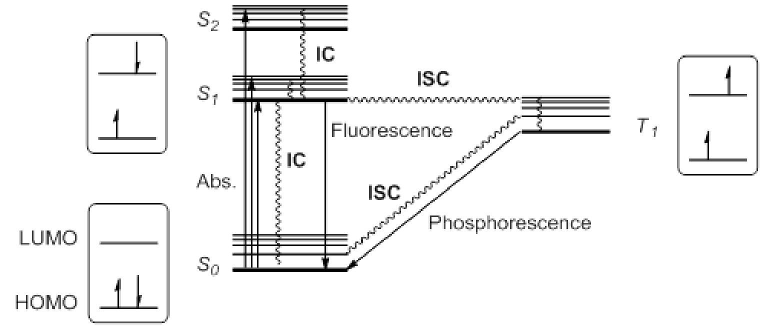
III/ Gold Catalysis

Photochemical

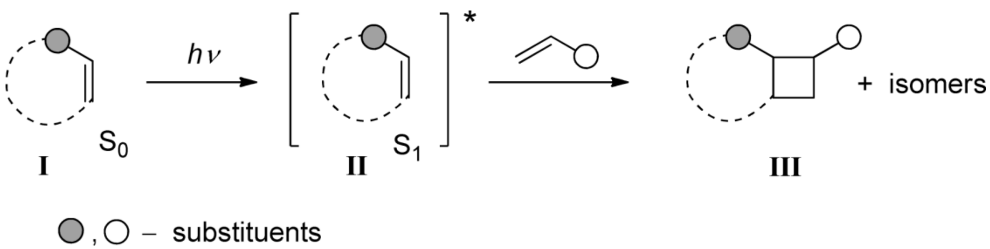


(1) Y. Xu, M. L. Conner, M. K. Brown, *Angew. Chem. Int. Ed.*, **2015**, *54*, 11918-11928. (2) S. Poplata, A. Tröster, Y.-Q. Zou, T, Bach, *Chem. Rev.*, **2016**, *116*, 9748-9815.

I/ Photocycloaddition: S_1 VS T_1



[2 + 2] Photocycloaddition of an Olefin I via its **First Excited Singlet State II (S_1)**

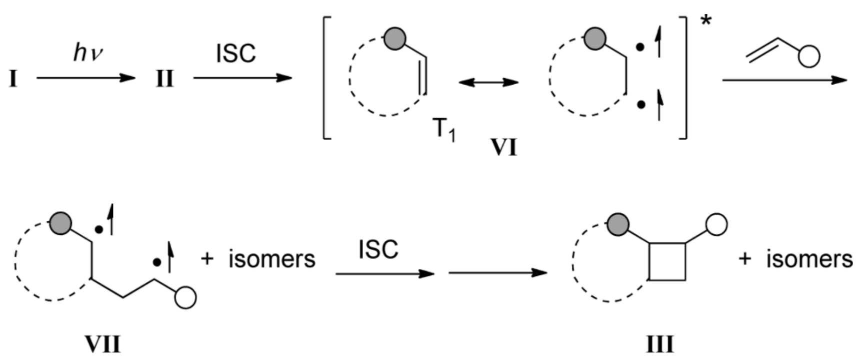


Limitations:

Many substrates have a high S_1 state: Difficult excitation with commercial irradiation sources

S_1 is short lived because of fluorescence and IC: Rapid relaxation to the ground state making difficult intermolecular cycloadditions

[2 + 2] Photocycloaddition of an Olefin I via its **First Excited Triplet State VI (T_1)**

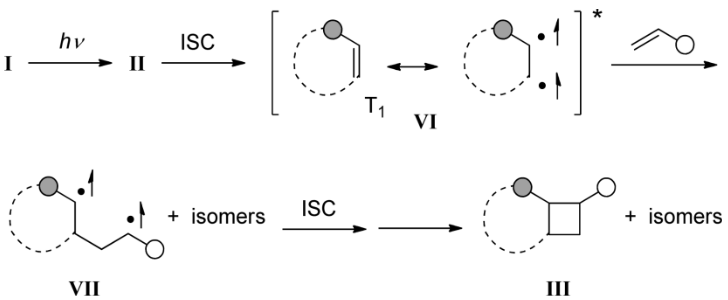


Long lifetime allows intermolecular attack of another olefin generating a 1,4-diradical intermediate (VII)

(1) S. Poplata, A. Tröster, Y.-Q. Zou, T, Bach, *Chem. Rev.*, **2016**, *116*, 9748-9815.

I/ Photocycloaddition: Role of a catalyst

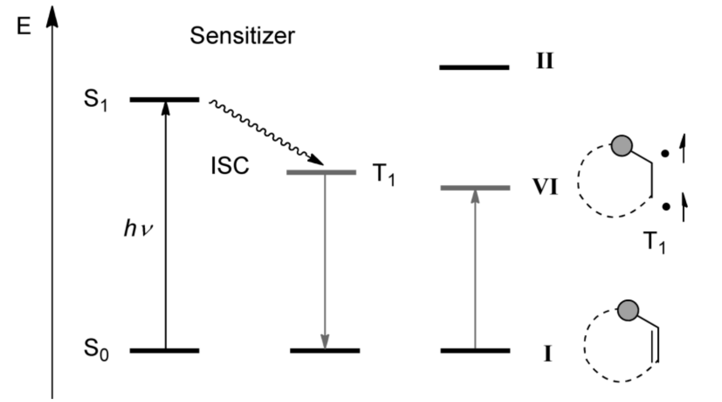
Direct absorption



Catalyst:

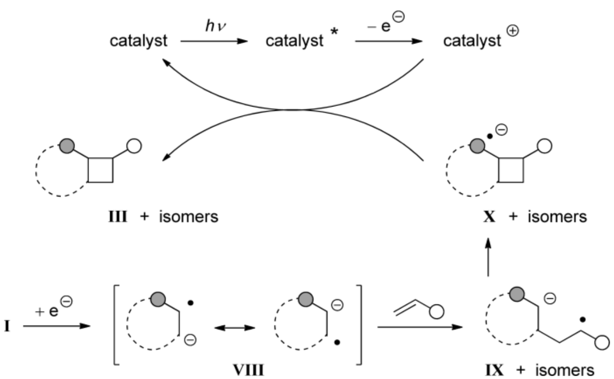
- Lowers T_1
- Stabilizes T_1
- Shifts the absorption wavelength of the olefin

Energy tranfer



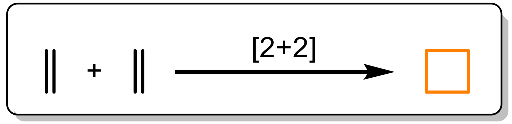
Photoexcited catalyst (sensitizer) transfers energy to the olefin

SET (single electron transfer)



(1) S. Poplata, A. Tröster, Y.-Q. Zou, T, Bach, *Chem. Rev.*, **2016**, *116*, 9748-9815.

Catalytic Enantioselective [2+2] Cycloadditions



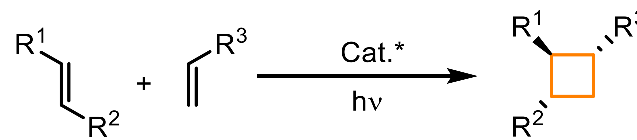
Polarized

I/ Lewis Acid Catalysis

II/ Amine Catalysis

III/ Gold Catalysis

Photochemical



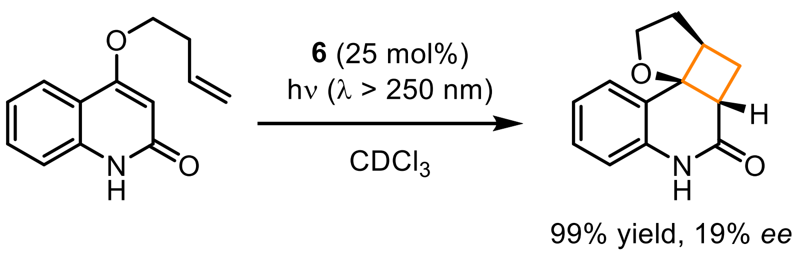
I/ H-bonding catalysts

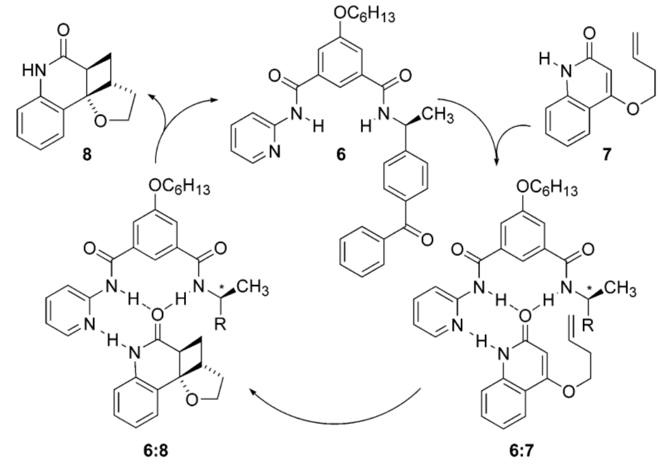
II/ Lewis acid catalysts

(1) Y. Xu, M. L. Conner, M. K. Brown, *Angew. Chem. Int. Ed.*, **2015**, *54*, 11918-11928. (2) S. Poplata, A. Tröster, Y.-Q. Zou, T, Bach, *Chem. Rev.*, **2016**, *116*, 9748-9815.

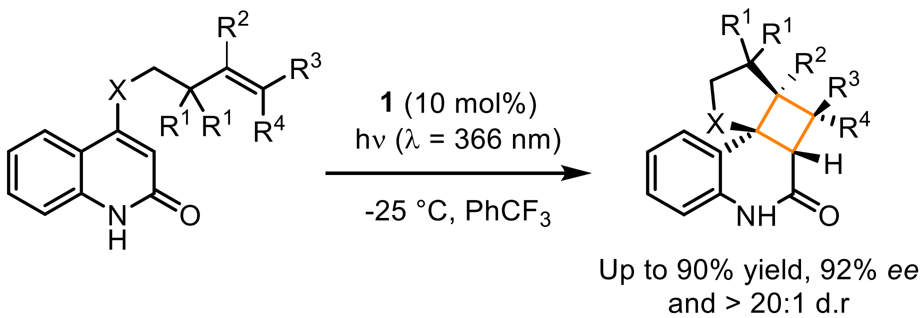
I/ Photocycloaddition: H-bonding catalysis

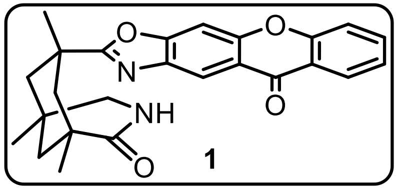
Early efforts: H-bonding chiral sensitizer[1]





Energy transfer from a xanthone-based chiral sensitizer with a H-bonding motif[2,3,4]

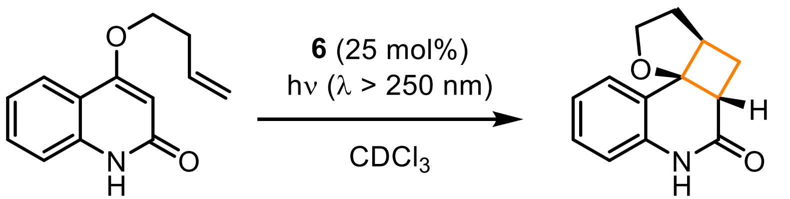




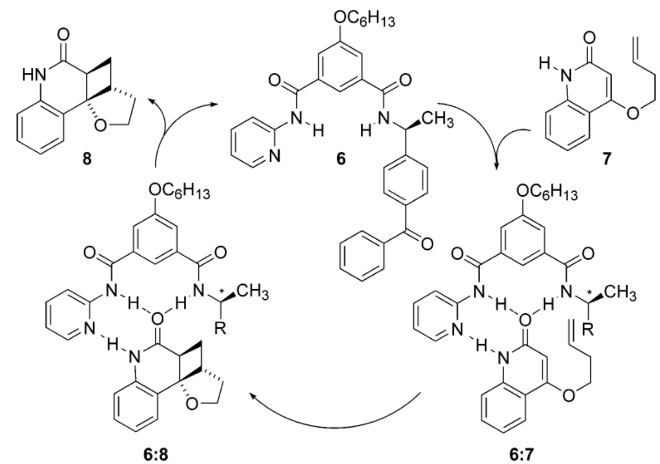
(1) D. F. Cauble, V. Lynch and M. J. Krische, *J. Org. Chem.*, **2003**, *68*, 15-21; (2) C. Müller, A. Bauer, T. Bach, *Angew. Chem. Int. Ed.,* **2009**, *48*, 6640-6642; (2) C. Müller, A. Bauer, M. M. Maturi, M. C. Cuquerella, T. Bach, *J. Am. Chem. Soc.,* **2011**, *133*, 16689-16697; (3) M. M. Maturi, M. Wenninger, R. Alonso, A. Bauer, A. Pöthig, E. Riedle, T. Bach, *Chem. Eur. J.*, **2013**, *19*, 7461-7472.

I/ Photocycloaddition: H-bonding catalysis

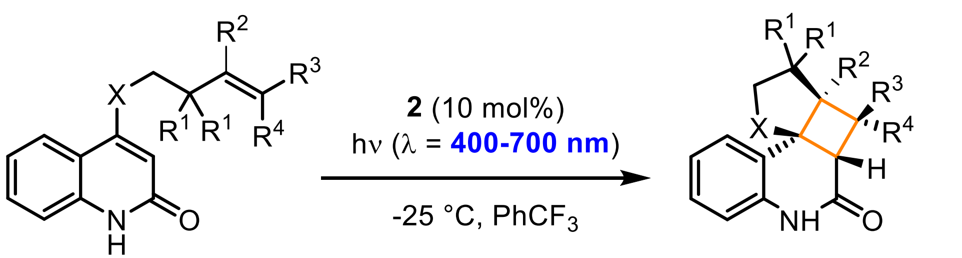
Energy transfer from a xanthone-based chiral sensitizer with a H-bonding motif[1]



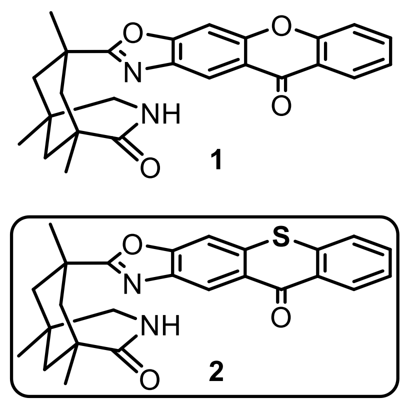
99% yield, 19% *ee*



Energy transfer from a **thio**xanthone-based chiral sensitizer with a H-bonding motif[5]



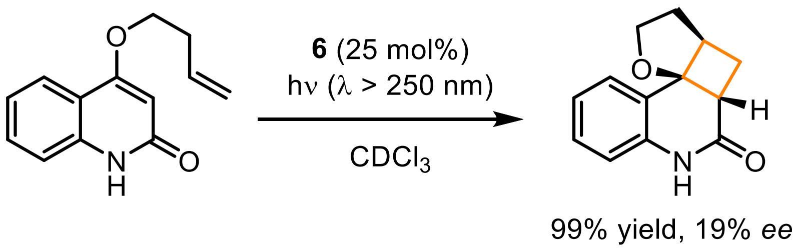
Up to 90% yield, 92% *ee*
and > 20:1 d.r

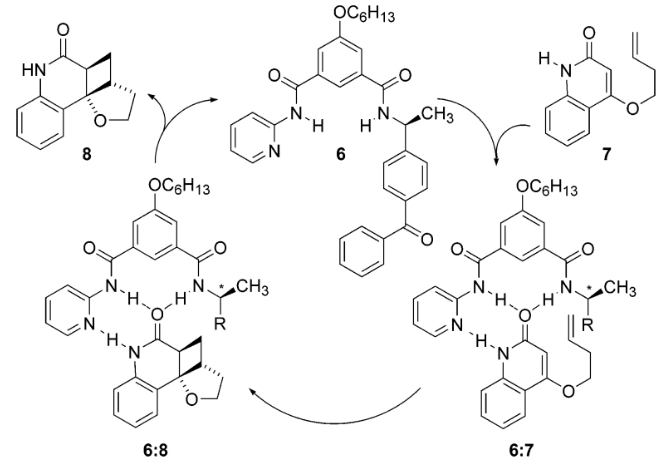


(1) D. F. Cauble, V. Lynch and M. J. Krische, *J. Org. Chem.*, **2003**, *68*, 15-21; (2) C. Müller, A. Bauer, T. Bach, *Angew. Chem. Int. Ed.,* **2009**, *48*, 6640-6642; (2) C. Müller, A. Bauer, M. M. Maturi, M. C. Cuquerella, T. Bach, *J. Am. Chem. Soc.,* **2011**, *133*, 16689-16697; (3) M. M. Maturi, M. Wenninger, R. Alonso, A. Bauer, A. Pöthig, E. Riedle, T. Bach, *Chem. Eur. J.*, **2013**, *19*, 7461-7472. (5) R. Alonso, T. Bach, *Angew. Chem. Int. Ed.,* **2014**, *126*, 4457-4460;.

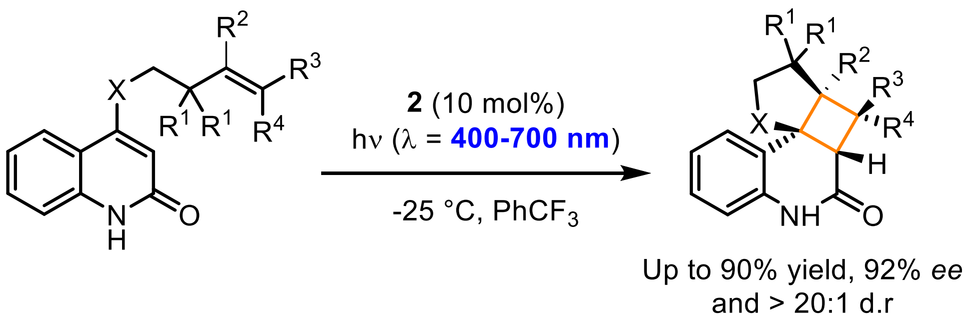
I/ Photocycloaddition: H-bonding catalysis

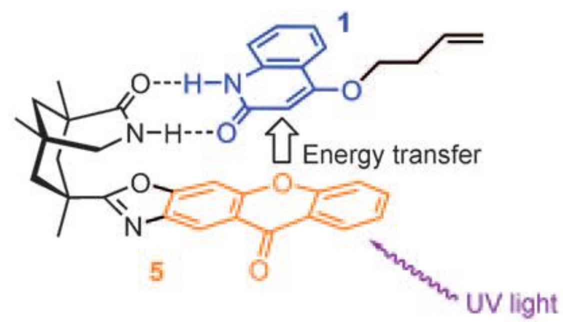
Energy transfer from a xanthone-based chiral sensitizer with a H-bonding motif[1]





Energy transfer from a **thio**xanthone-based chiral sensitizer with a H-bonding motif[5]

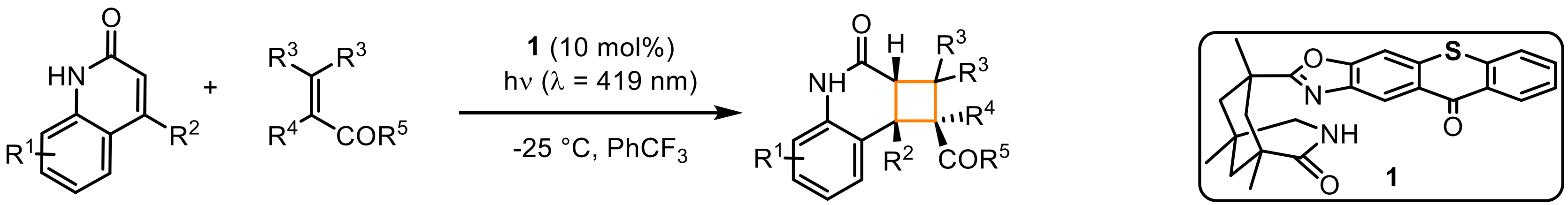




(1) D. F. Cauble, V. Lynch and M. J. Krische, *J. Org. Chem.*, **2003**, *68*, 15-21; (2) C. Müller, A. Bauer, T. Bach, *Angew. Chem. Int. Ed.,* **2009**, *48*, 6640-6642; (2) C. Müller, A. Bauer, M. M. Maturi, M. C. Cuquerella, T. Bach, *J. Am. Chem. Soc.,* **2011**, *133*, 16689-16697; (3) M. M. Maturi, M. Wenninger, R. Alonso, A. Bauer, A. Pöthig, E. Riedle, T. Bach, *Chem. Eur. J.*, **2013**, *19*, 7461-7472. (5) R. Alonso, T. Bach, *Angew. Chem. Int. Ed.,* **2014**, *126*, 4457-4460;.

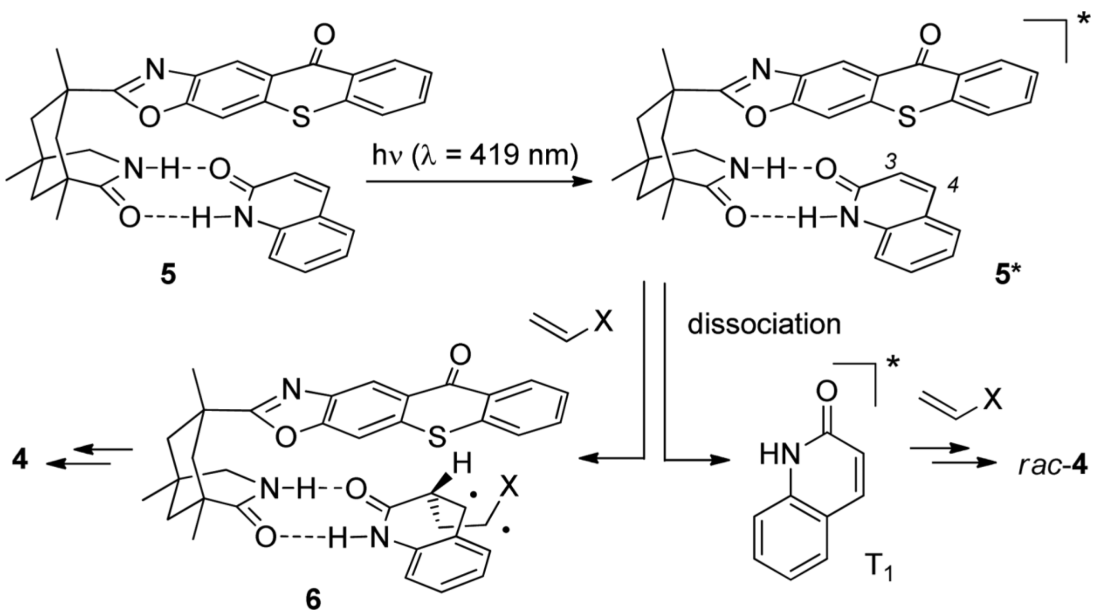
I/ Photocycloaddition: H-bonding catalysis

Intermolecular [2+2] photocycloaddition of quinolones and electron poor olefins



Up to 94% yield, 95% *ee*
and > 20:1 d.r

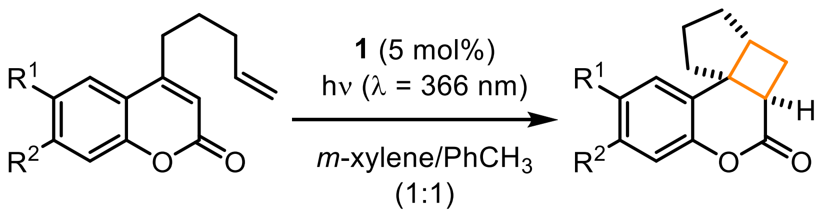
Mechanism



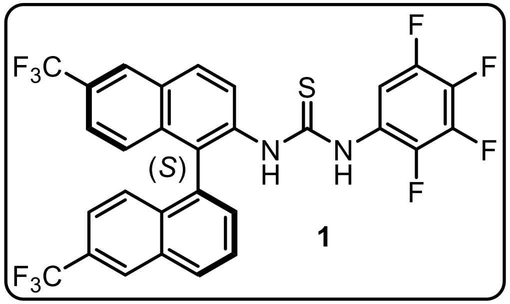
(1) A. Tröster, R. Alonso, A. Bauer, T. Bach, *J. Am. Chem. Soc.,* **2016**, *138*, 7808-7811.

I/ Photocycloaddition: H-bonding catalysis

Direct absorption with H-bonding photocatalysts: Thioureas[1,2]

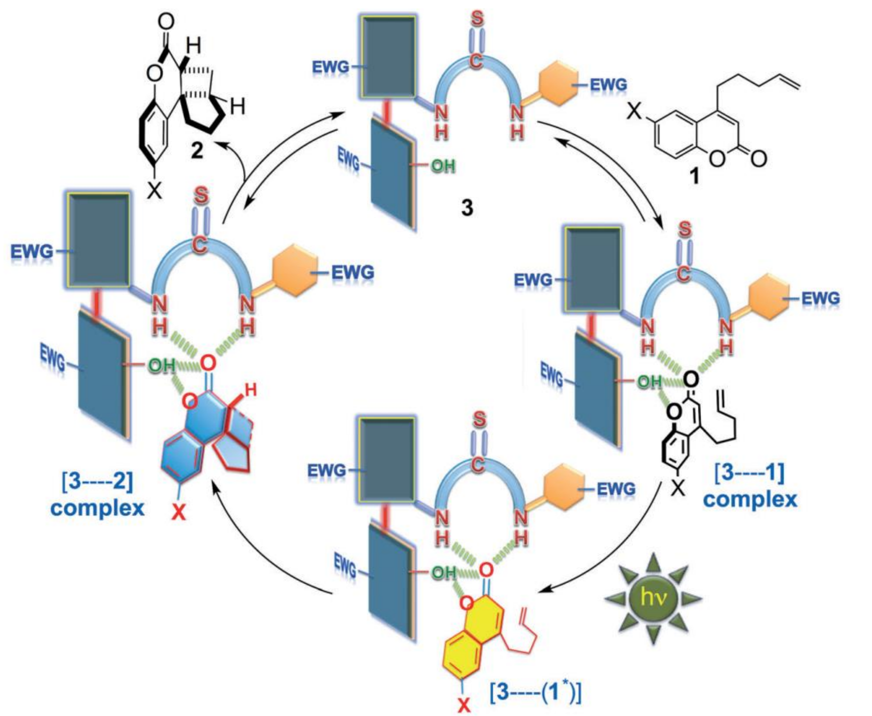


Limited scope, up to 84% yield, 82% *ee*



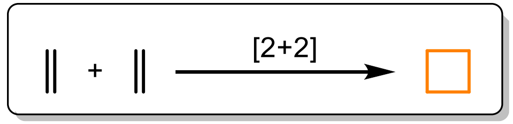
1

Mechanism



(1) N. Vallavoju, S. Selvakumar, S. Jockusch, M. P. Sibi, J. Sivaguru, *Angew. Chem. Int. Ed.,* **2014**, *53*, 5604 –5608; (2) N. Vallavoju, S. Selvakumar, S. Jockusch, M. T. Prabhakaran, M. P. Sibi, J. Sivaguru, *Adv. Synth. Catal.,* **2014**, *356*, 2763 – 2768.

Catalytic Enantioselective [2+2] Cycloadditions



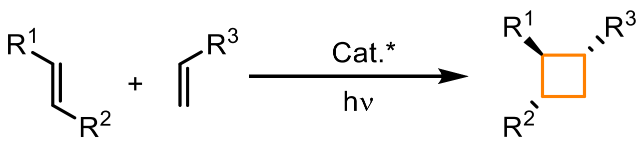
Polarized

I/ Lewis Acid Catalysis

II/ Amine Catalysis

III/ Gold Catalysis

Photochemical



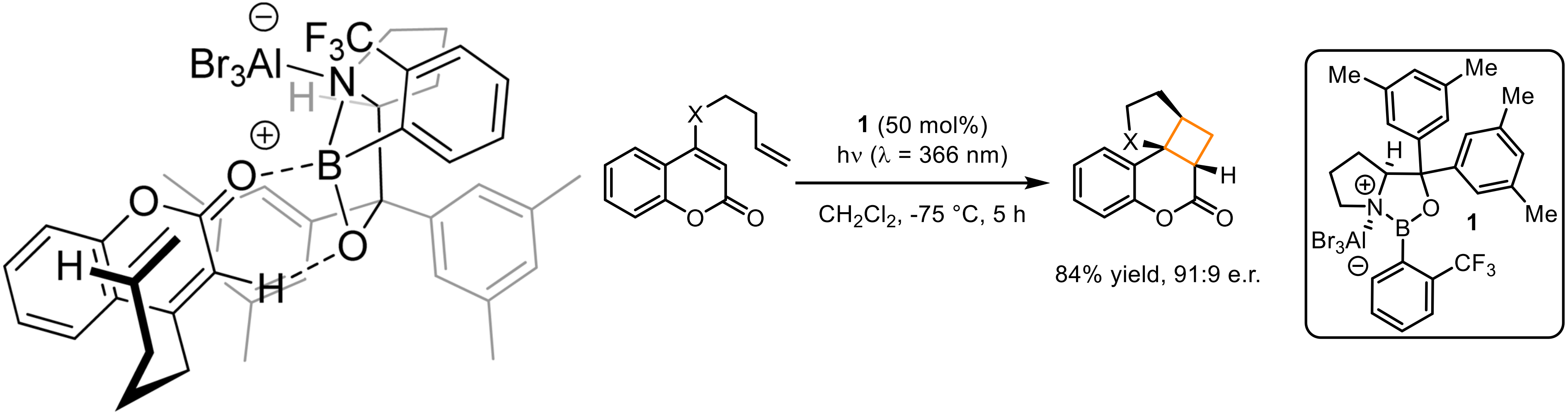
I/ H-bonding catalysts

II/ Lewis acid catalysts

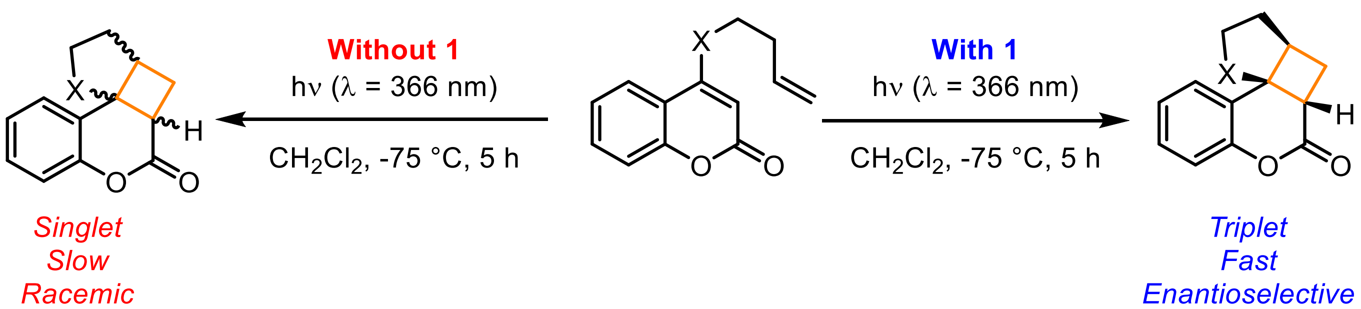
(1) Y. Xu, M. L. Conner, M. K. Brown, *Angew. Chem. Int. Ed.*, **2015**, *54*, 11918-11928. (2) S. Poplata, A. Tröster, Y.-Q. Zou, T, Bach, *Chem. Rev.*, **2016**, *116*, 9748-9815.

II/ Photocycloaddition: Lewis acid catalysis

Enantioselective photocycloaddition of 4-substituted coumarins[1,2]



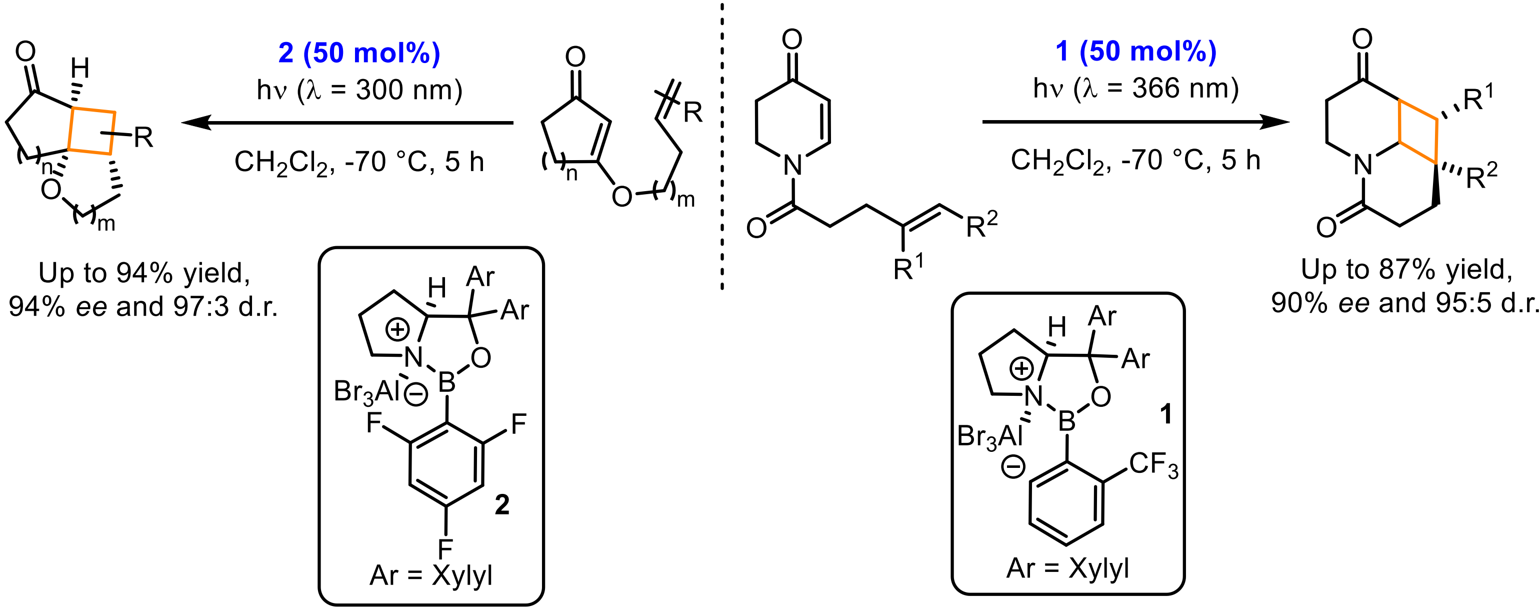
Role of the catalyst[3]



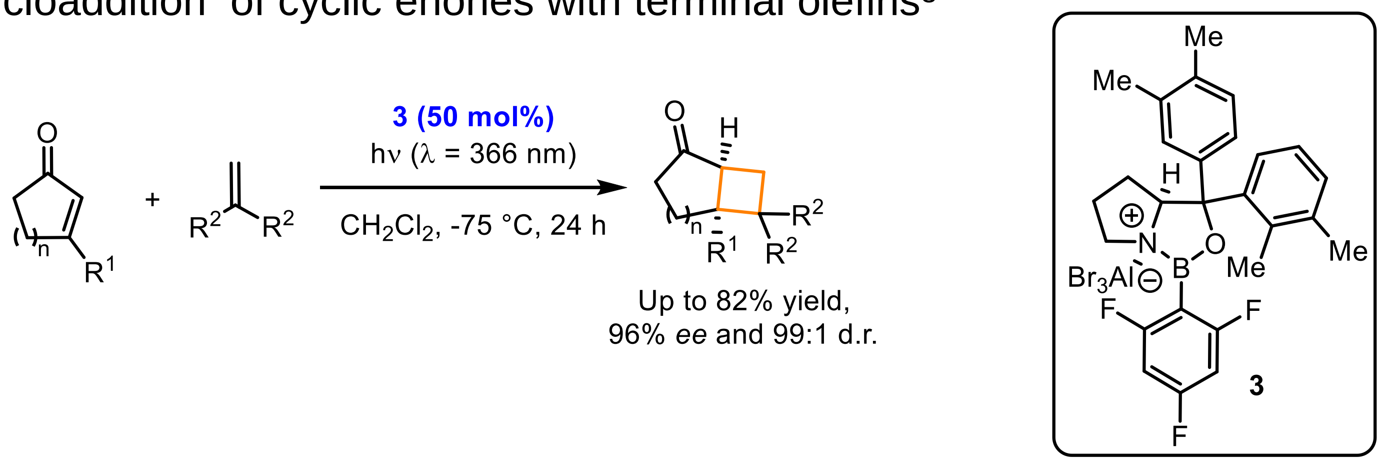
(1)) H. Guo, E. Herdtweck, T. Bach, *Angew. Chem. Int. Ed.*, **2010**, *49*, 7782–7785; (2) R. Brimioulle, H. Guo, T. Bach, *Chem. Eur. J.*, **2012**, *18*, 7552-7560. (3) R. Brimouille, A. Bauer, T. Bach, *J. Am. Chem. Soc.*, **2015**, *137*, 5170−5176.

II/ Photocycloaddition: Lewis acid catalysis

Extension to cycloalkenones and dihydropyridones[1,2]



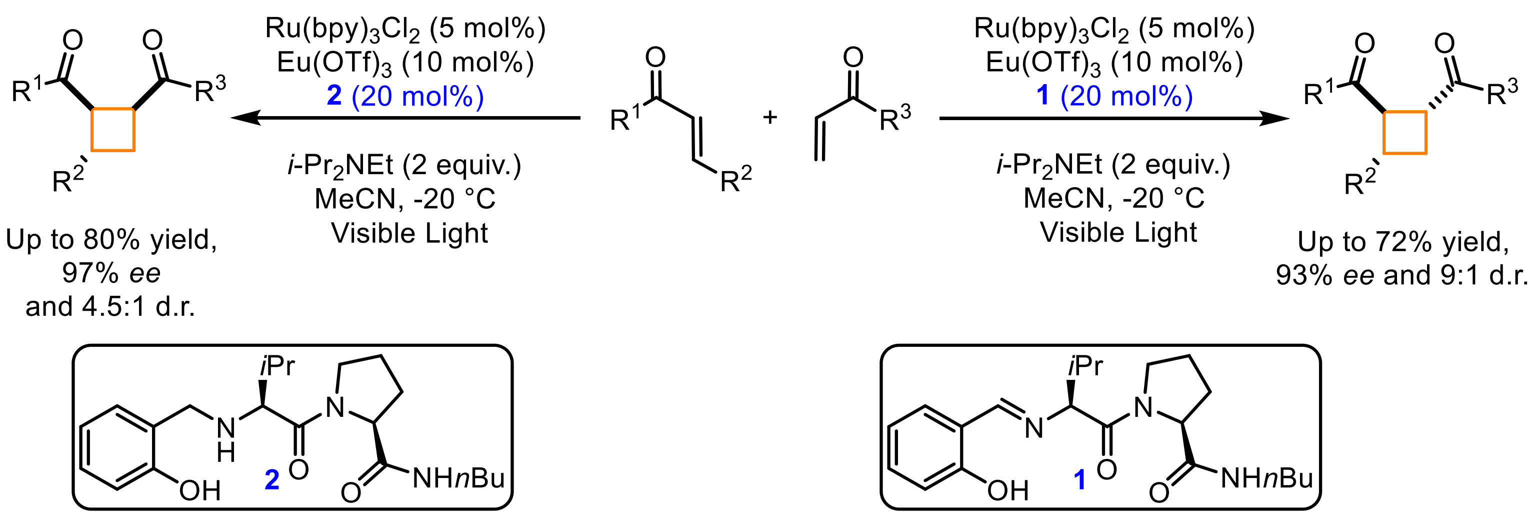
Intermolecular photocycloaddition of cyclic enones with terminal olefins[3]



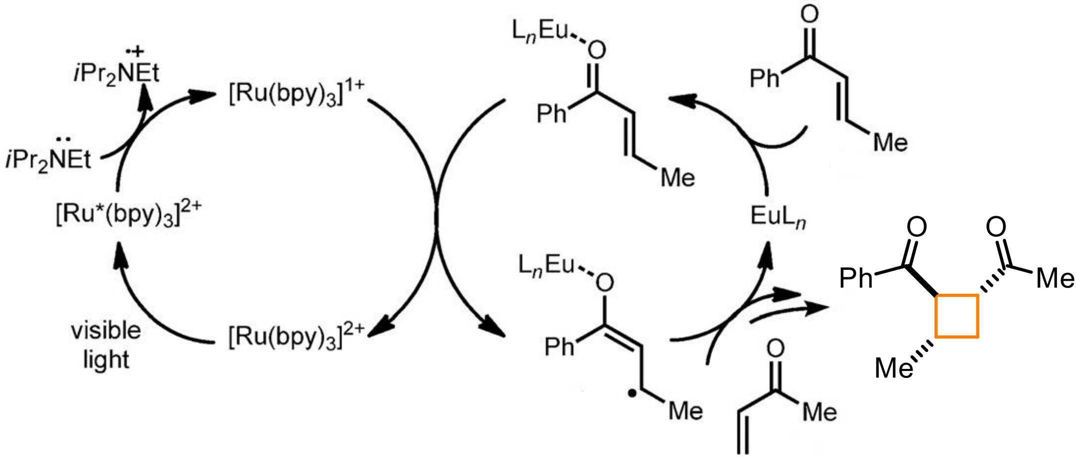
(1)) 33 R. Brimioulle, T. Bach, *Science*, **2013**, *342*, 840-843; (2) R. Brimioulle, T. Bach, *Angew. Chem., Int. Ed.*, **2014**, *53*, 12921-12924; (3) S. Poplata, T. Bach, *J. Am. Chem. Soc.*, **2018**, *140*, 3228−3231.

II/ Photocycloaddition: Lewis acid catalysis

Electron transfer for the enantioselective [2+2] of unsaturated carbonyls by dual Catalysis[1]



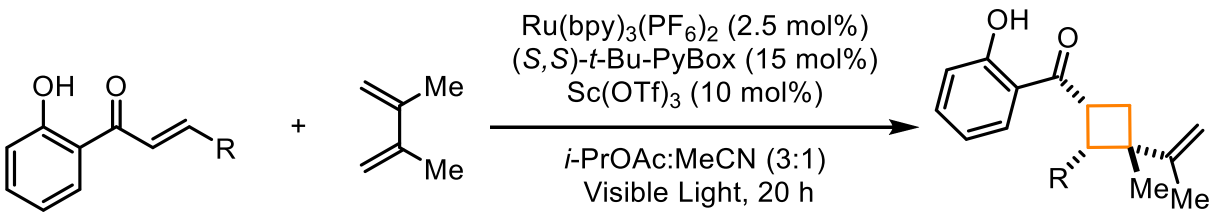
Mechanism



(1) J. Du, K. L. Skubi, D. M. Schultz, T. P. Yoon, *Science*, **2014**, *344*, 392–396.

II/ Photocycloaddition: Lewis acid catalysis

Lewis acid-mediated lowering of the triplet energy of 2'-hydroxychalcone[1]



Up to 86% yield,
94% *ee* and 4:1 d.r.

Lewis acid–promoted decrease in triplet energy (E_T)

E_T(exp) = 54 kcal/mol

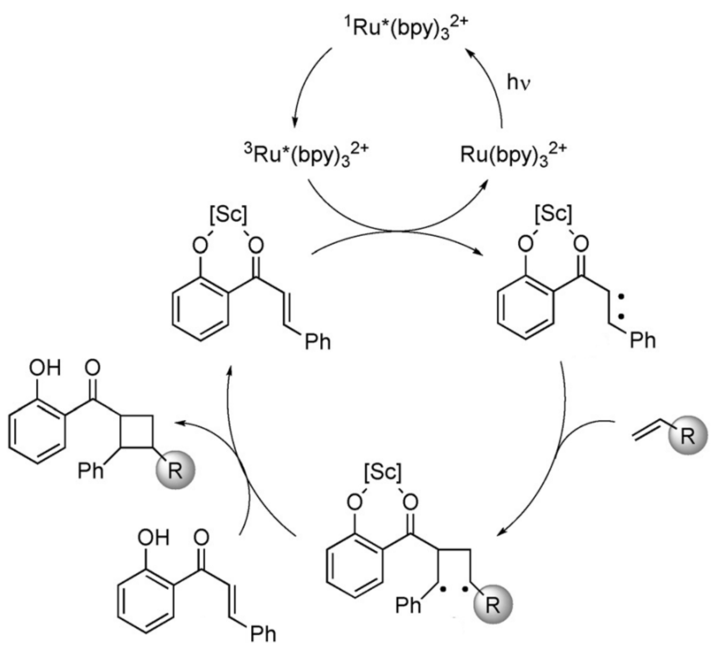
E_T(calc) = 51 kcal/mol

E_T(exp) = 33 kcal/mol

E_T(calc) = 32 kcal/mol

Triplet energy transfer from $Ru(bpy)_3^{2+}$ (E_T = 46 kcal/mol) feasible

Proposed mechanism

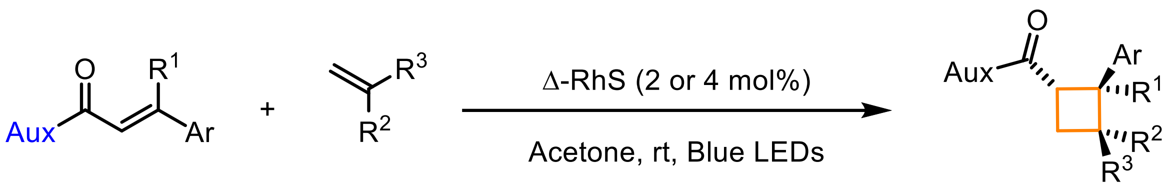


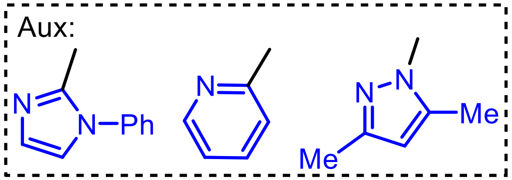
Scope extended to styrenes[2]

(1) T. R. Blum, Z. D. Miller, D. M. Bates, I. A. Guzei, T. P. Yoon, *Science*, **2016**, *354*, 1391-1395; (2) Z. D. Miller, B. J. Lee, T. P. Yoon, *Angew. Chem., Int. Ed.*, **2017**, *129*, 12053-12057.

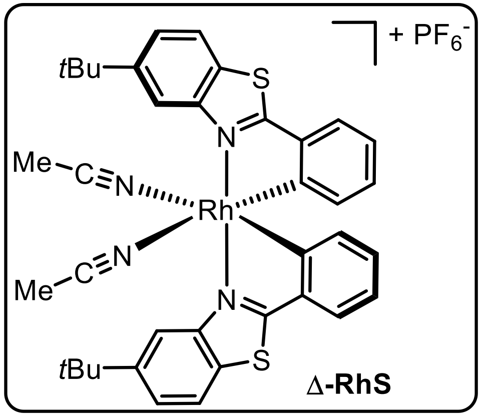
II/ Photocycloaddition: Lewis acid catalysis

Direct Visible Light excitation of a metal-substrate complex[1]

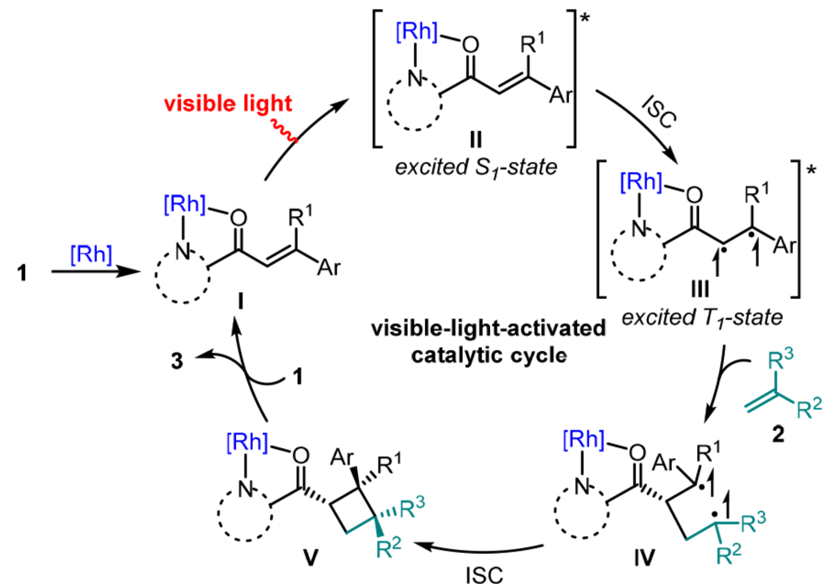




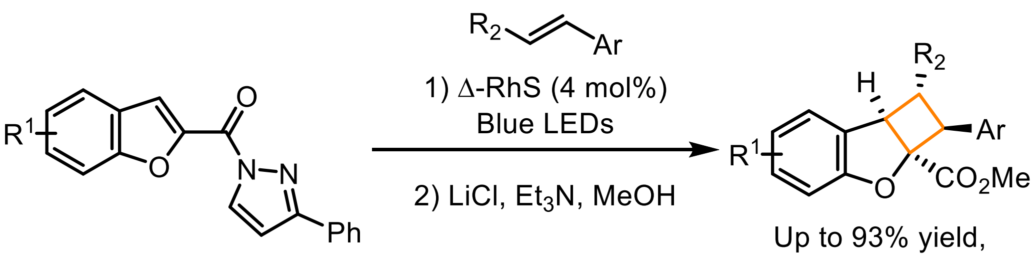
Up to 99% yield,
99% *ee* and 20:1 d.r.



Proposed mechanism



Extension to asymmetric dearomatization[2]

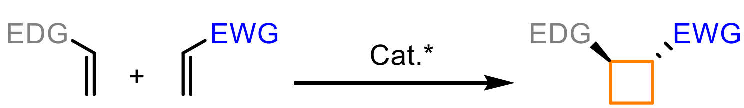


Up to 93% yield,
99% *ee* and > 20:1 d.r.

(1) X. Huang, T. R. Quinn, K. Harms, R. D. Webster, L. Zhang, O. Wiest, E. Meggers, *J. Am. Chem. Soc.*, **2017**, *139*, 9120−9123; (2) N. Hu, H. Jung, Y. Zheng, J Lee, L. Zhang, Z. Ullah, X. Xie, K. Harms, M.-H. Baik, E. Meggers, *Angew. Chem. Int. Ed.*, **2018**, *57*, 6242 –6246.

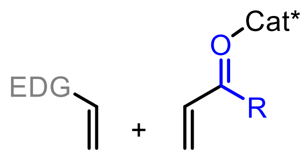
Conclusion

Polarized

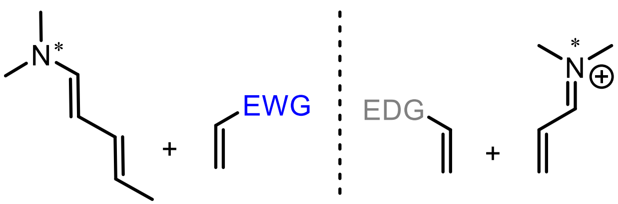


HOMO or LUMO activation by a chiral catalyst

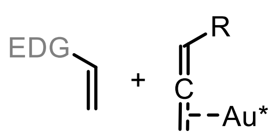
I/ Lewis Acid Catalysis



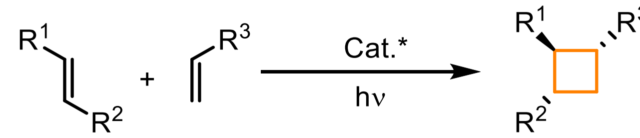
II/ Amine Catalysis



III/ Gold Catalysis

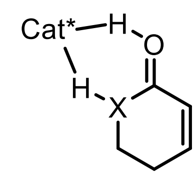


Photochemical

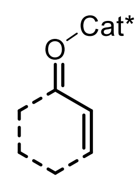


Ground-state pre-association with a chiral catalyst to facilitate the photo-activation step

I/ H-bonding catalysts



II/ Lewis acid catalysts

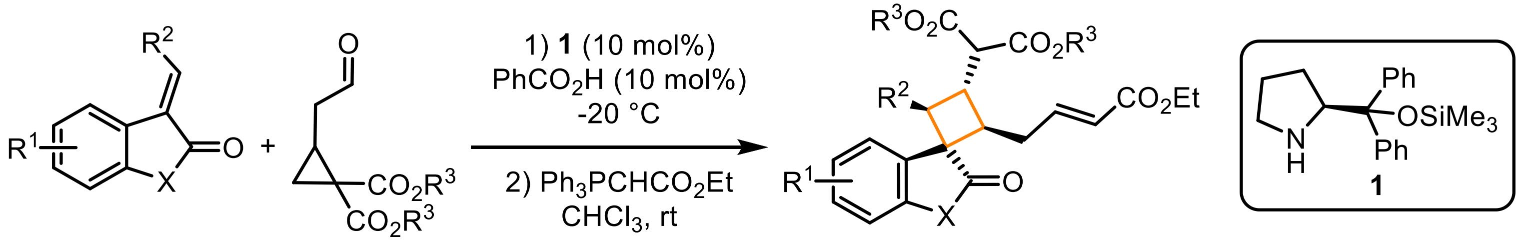


Many areas left to explore:

- **Extention to weakly / non polarized alkenes**
- **Application in total synthesis**

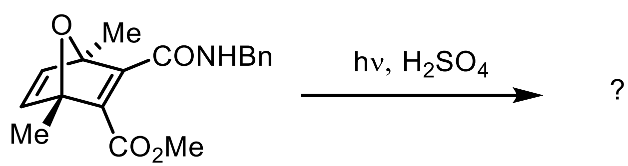
Questions

- Propose a Mechanism for this transformation[1]



- 14 examples
- Up to 86% yield, >25:1 d.r and 97% *ee.*

- What is the product ?[2]

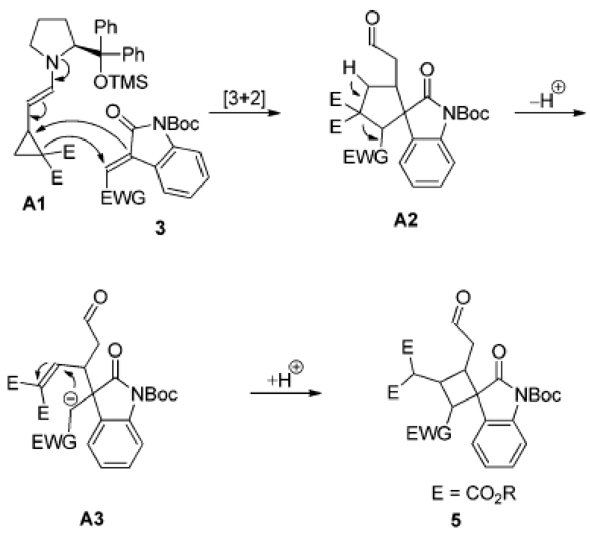


75% *ee*

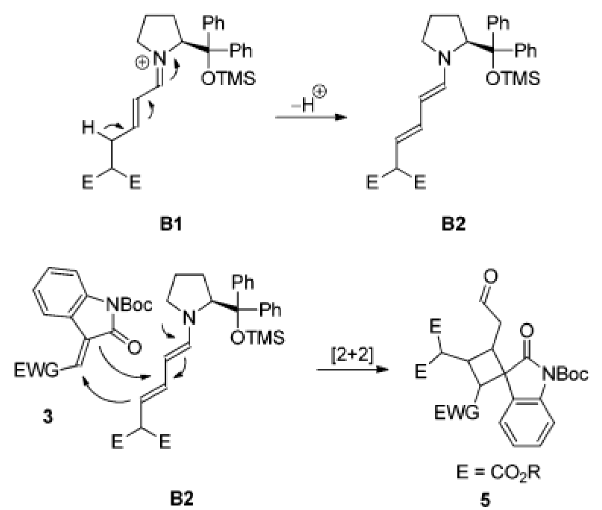
(1) K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund, K. A. Jørgensen, *J. Am. Chem. Soc.,* **2015**, *137*, 1685-1691. (2) P. S. Baran, K. Li, D. P. O'Malley, C. Mitsos, *Angew. Chem. Int. Ed.*, **2006**, *45*, 249 –252.

Answers

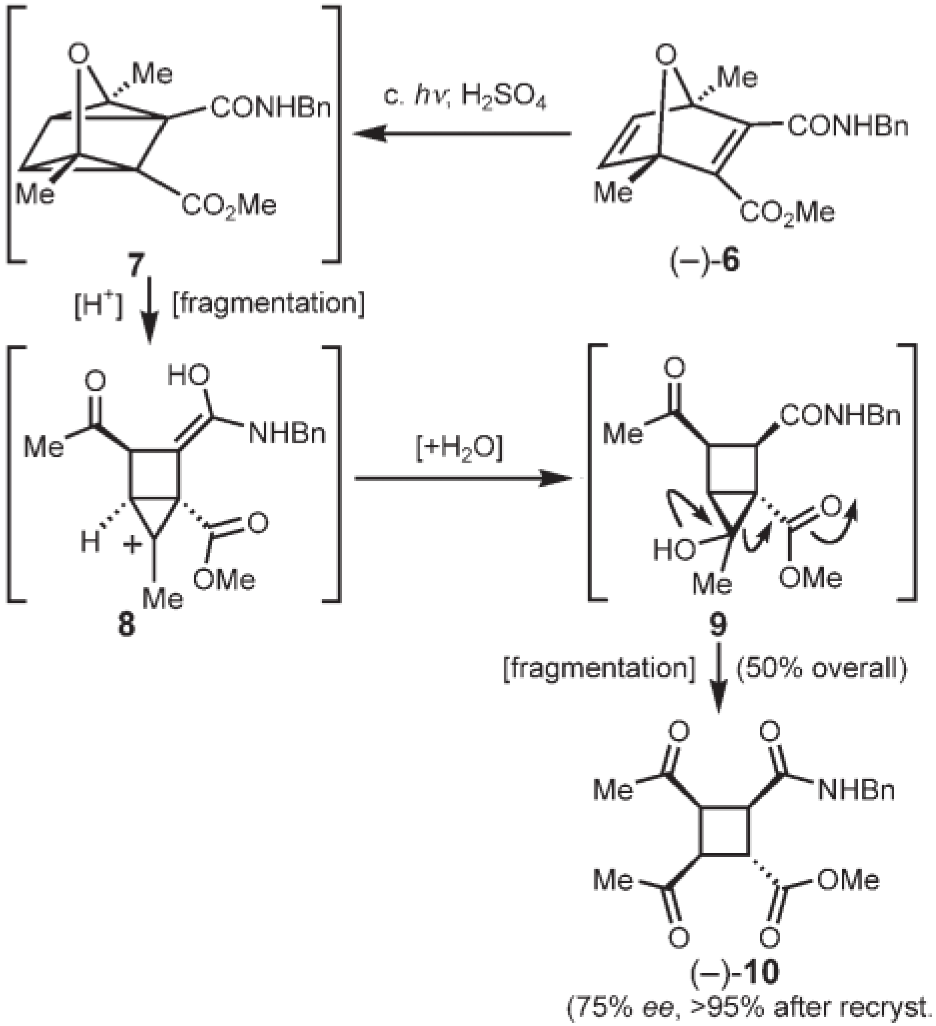
b) Mechanistic proposal based on [3+2]-cycloaddition and ring-contracting rearrangement



c) Mechanistic proposal based on dienamine-mediated [2+2]-cycloaddition



Answers



Me
CONHBn
Me
CO2Me
7
c. hv, H2SO4
O
Me
CONHBn
Me
CO2Me
(–)-6
[H+]
[fragmentation]
O
HO
Me
NHBn
H
+
O
OMe
Me
8
[+H2O]
O
Me
CONHBn
O
HO
Me
OMe
9
[fragmentation]
(50% overall)
O
O
Me
NHBn
Me
OMe
O
O
(–)-10
(75% ee, >95% after recryst.)

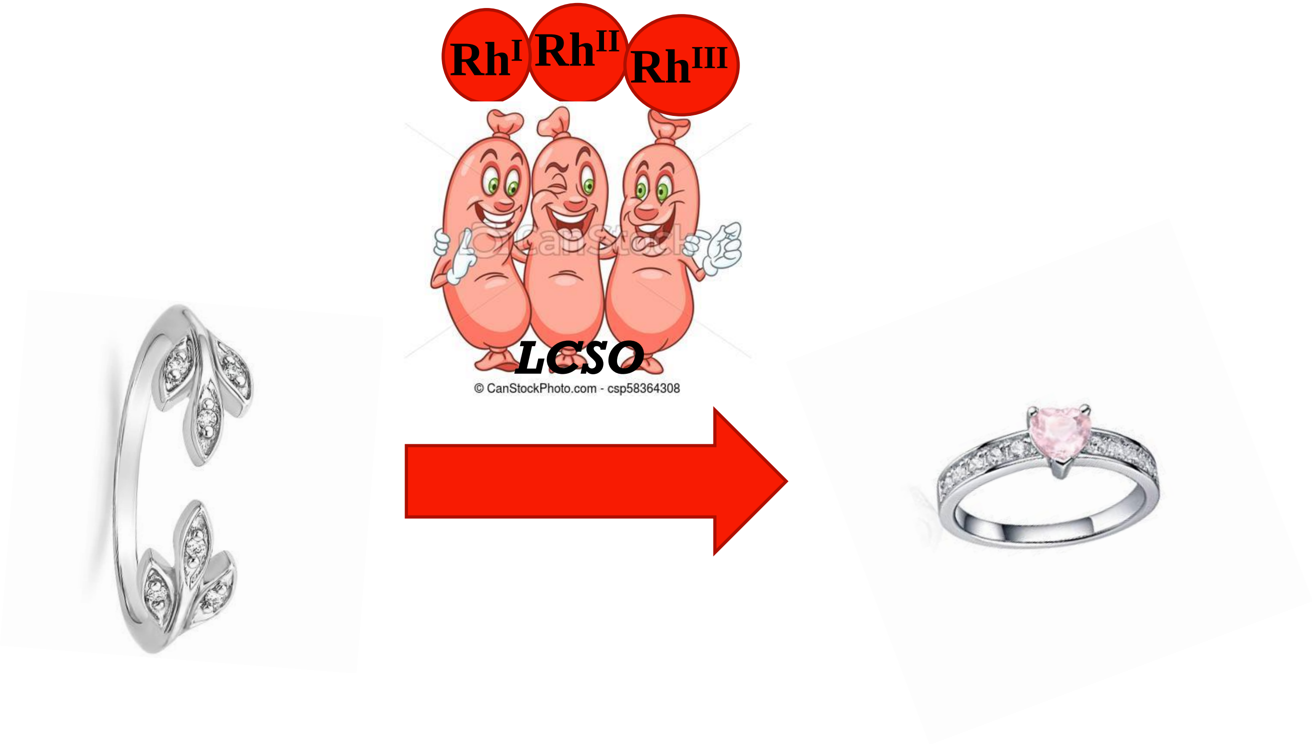
Rhodium catalysed Asymmetric synthesis of Heterocycles; recent advancements

Frontiers in Organic Synthesis, Part III Stereochemistry

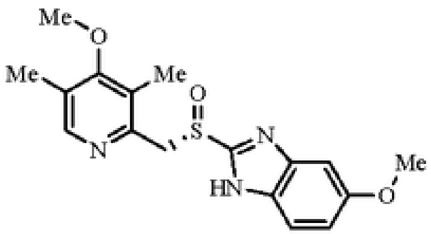
Presented by
Ashis Das

22.05.2019

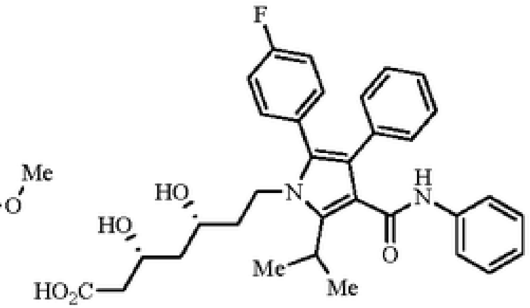
Ecole polytechnique fédérale de Lausanne


Rh^{I}
Rh^{II}
Rh^{III}
LCSO
© CanStockPhoto.com - csp58364308

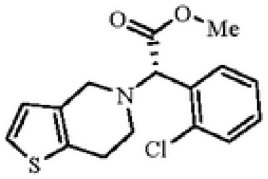
Introduction



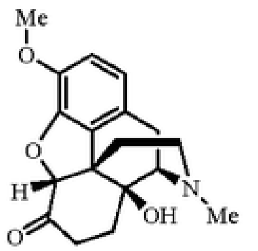
Nexium (Esomeprazole)
Antiulcerant



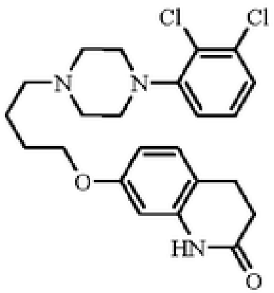
Lipitor (Atorvastatin)
Cholesterol/triglyceride regulator



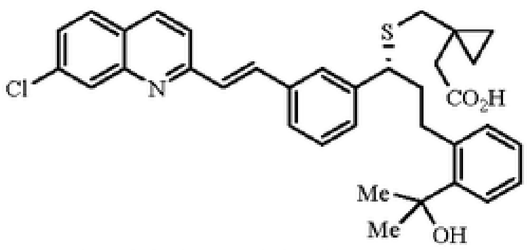
Plavix (Clopidogrel)
Platelet aggregation inhibitor



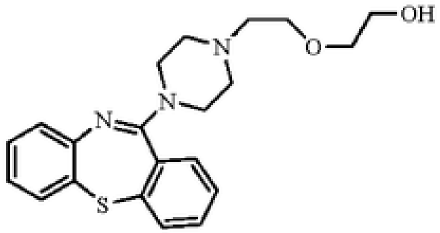
Oxycontin (Oxycodone)
Analgesic



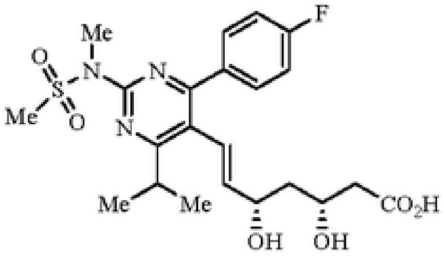
Abilify (Aripiprazole)
Antipsychotic



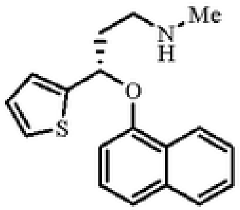
Singulair (Montelukast)
Antiasthmatic



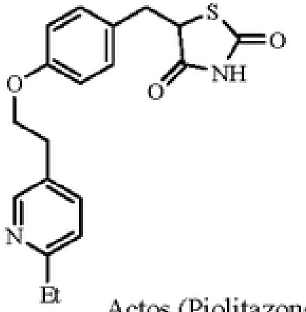
Seroquel (Quetiapine)
Antipsychotic



Crestor (Rosuvastatin)
Cholesterol/triglyceride regulator



Cymbalta (Duloxetine)
Antidepressant



Actos (Piolitazone)
Antidiabetic

- Rh(I)-Catalyzed ene –type cyclization of 1,6-enynes
- Rh(I) catalysed cyclization of alkynals and alkynones
- Rh(I)/Rh(III)-catalysed C-H functionalization
- Rh(II) carbenoid and nitrenoid insertion
- Rh(I)-catalysed ring opening reaction via C-C bond activation
- Rh(I)-catalysed arylboron addition/cyclization
- Miscellaneous

Rh(I)-Catalyzed ene –type cyclization of 1,6-enynes

Rh(I) catalysed cyclization of alkynals and alkynones

Rh(I)/Rh(III)-catalysed C-H functionalization

Rh(II) carbenoid and nitrenoid insertion

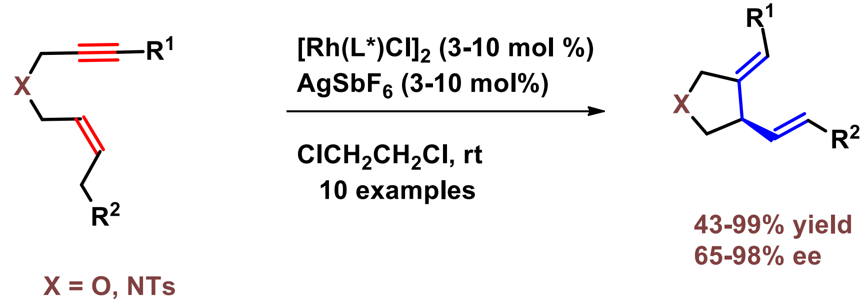
Rh(I)-catalysed ring opening reaction via C-C bond activation

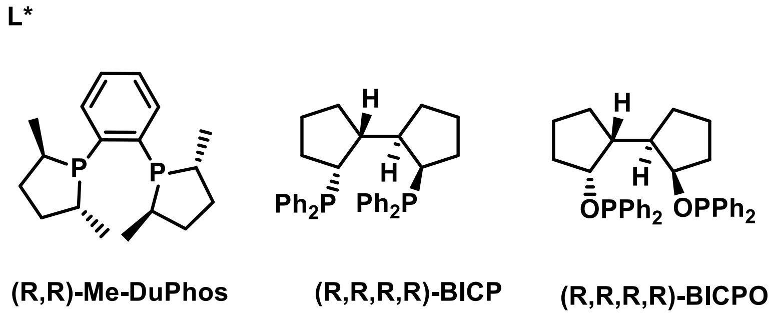
Rh(I)-catalysed arylboron addition/cyclization

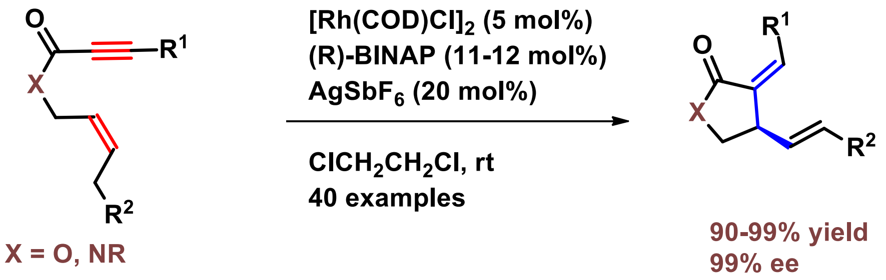
Miscellaneous

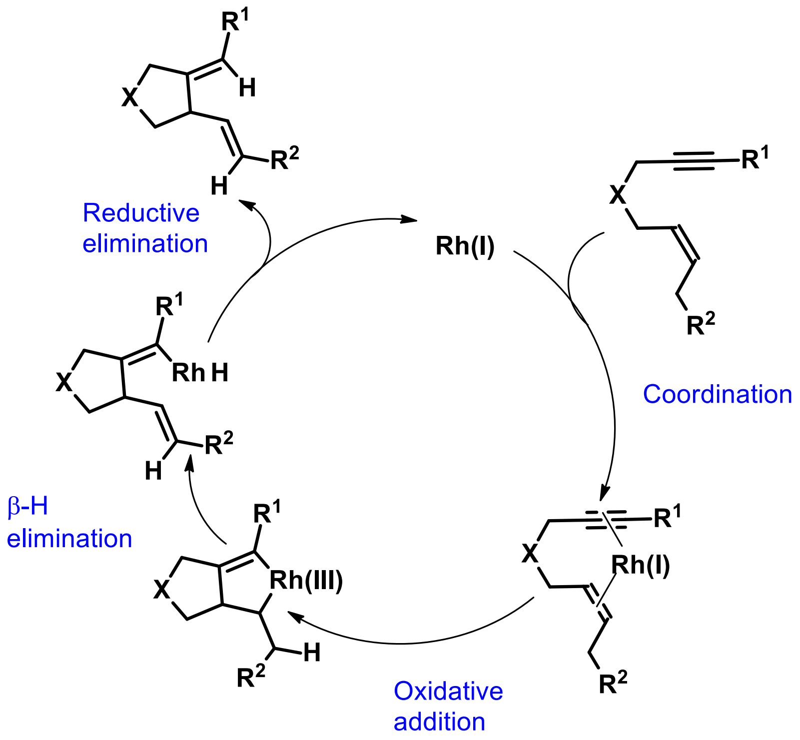
Rh(I)-Catalyzed ene –type cyclization of 1,6-enynes

Alder-ene cycloisomerization





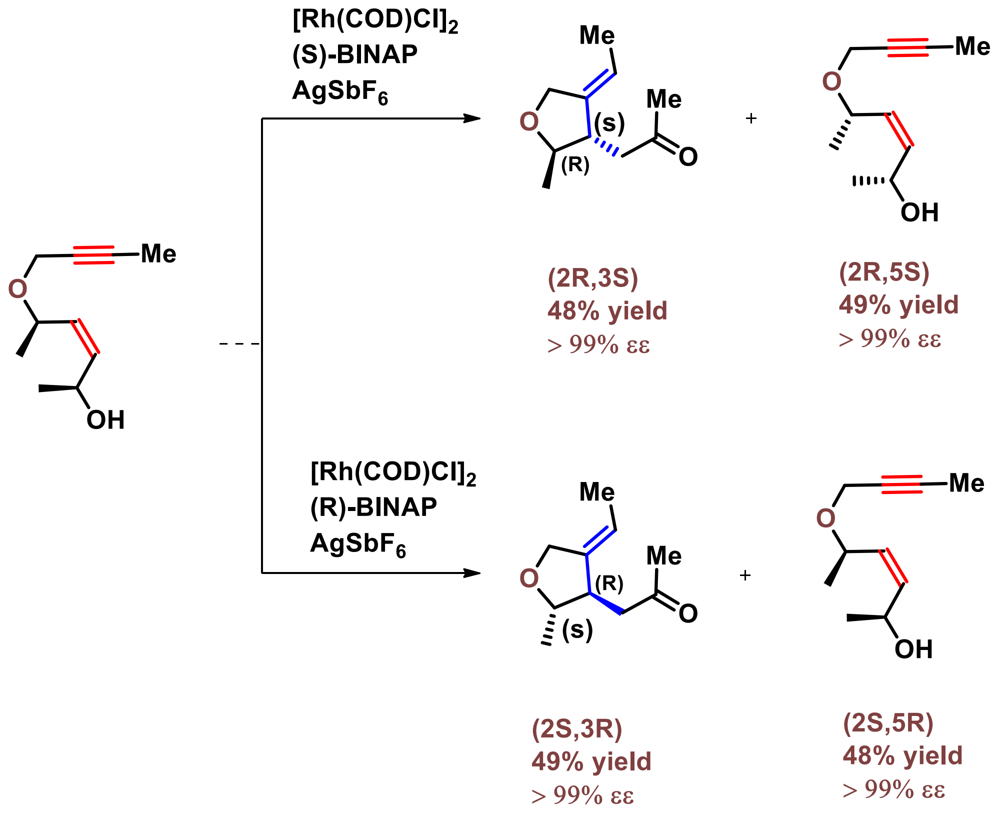


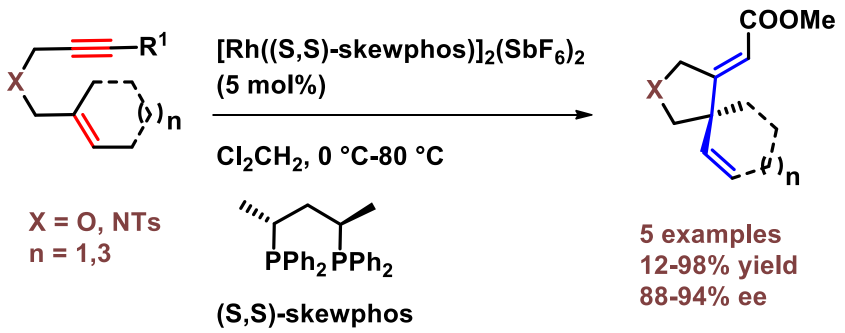


P. Cao and X. Zhang, *Angew. Chem., Int. Ed.*, **2000**, *39*, 4104–4106;
(a) A. Lei, M. He and X. Zhang, *J. Am. Chem. Soc.*, **2002**, *124*, 8198–8199; (b) A. Lei, J. P. Waldkirch, M. He and X. Zhang, *Angew. Chem., Int. Ed.*, **2002**, *41*, 4526–4529; For reviews of transition-metal-catalyzed cycloisomerization of 1,n-enynes, G. C. Lloyd-Jones, *Org. Biomol. Chem.*, **2003**, *1*, 215–236;

Rh(I)-Catalyzed ene –type cyclization of 1,6-enynes

Alder-ene cycloisomerization

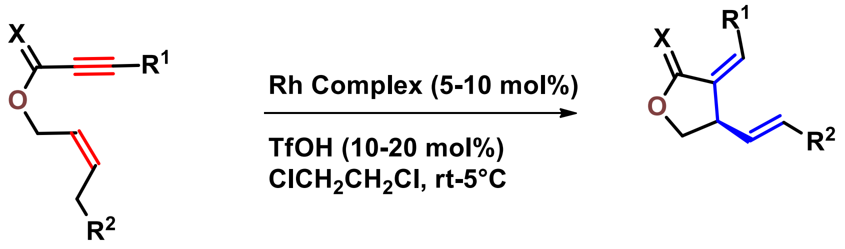




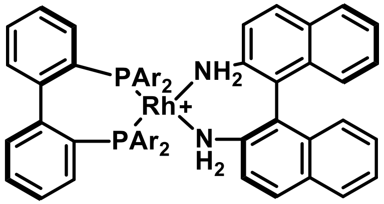
X. Zhang, A. Lei and M. He, *J. Am. Chem. Soc*., **2003**, *125*, 11472–11473.

(a) K. Mikami, Y. Yusa, M. Hatano, K. Wakabayashi and K. Aikawa, *Chem. Commun*., **2004**, 98–99; (b) K. Mikami, Y. Yusa, M. Hatano, K. Wakabayashi and K. Aikawa, *Tetrahedron*, **2004**, *60*, 4475–4480.

Alder-ene cycloisomerization



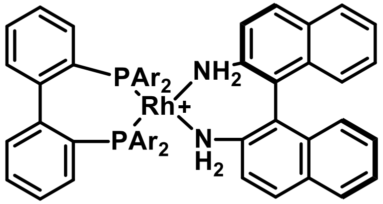
R^1 = Me, , Ar; R^2 = alkyl; X = H, O



Ar = 3,5-dimethylphenyl

(R)-DM-BIPHEP-Rh/(R)-DABN

4 examples
20-99% yield
88-96% ee

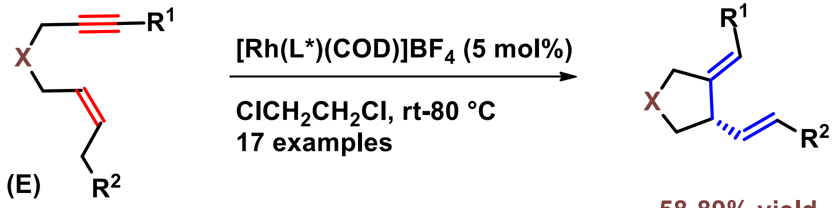


$SbF6^-$

BIPHEP-Rh/(S)-NOBIN

3 examples
70-99% yield
92-98% ee

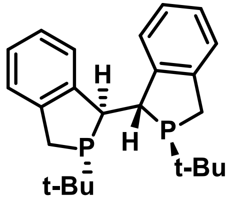
No TfOH was required



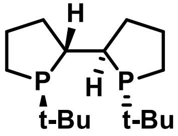
X = O, NTs, etc.

58-89% yield
61->99% ee

L*



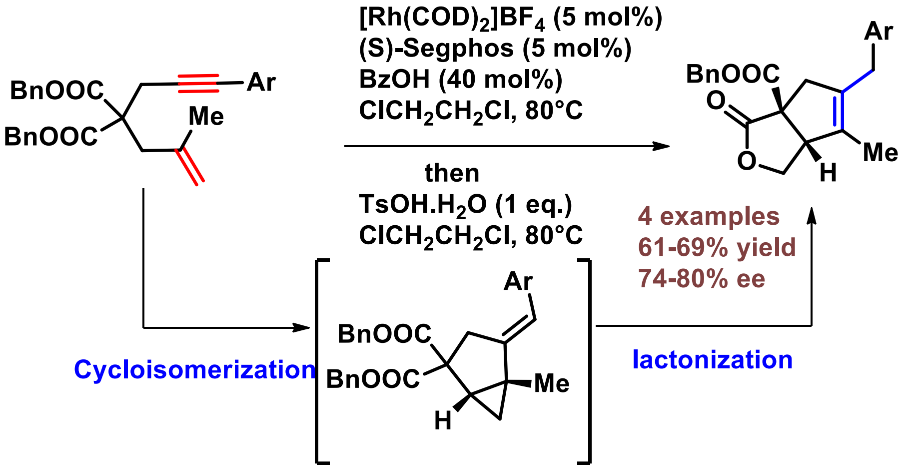
(Sc,Rp)-DuanPhos

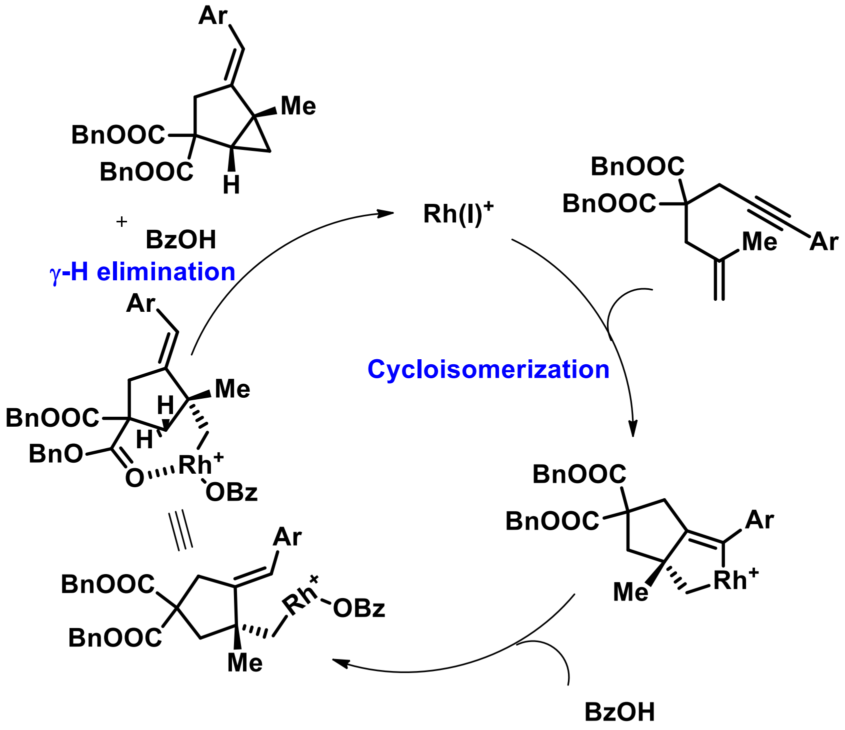


(S,s,R,R)-TangPhos

(a) K. Mikami, S. Kataoka, Y. Yusa and K. Aikawa, *Org. Lett.*, **2004**, *6*, 3699–3701. (b) K. Mikami, S. Kataoka and K. Aikawa, *Org. Lett.*, **2005**, *7*, 5777–5780.
X. Deng, S.-F. Ni, Z.-Y. Han, Y.-Q. Guan, H. Lv, L. Dang and X.-M. Zhang, *Angew. Chem., Int. Ed.*, **2016**, *55*, 6295– 6299.

Alder-ene cycloisomerization

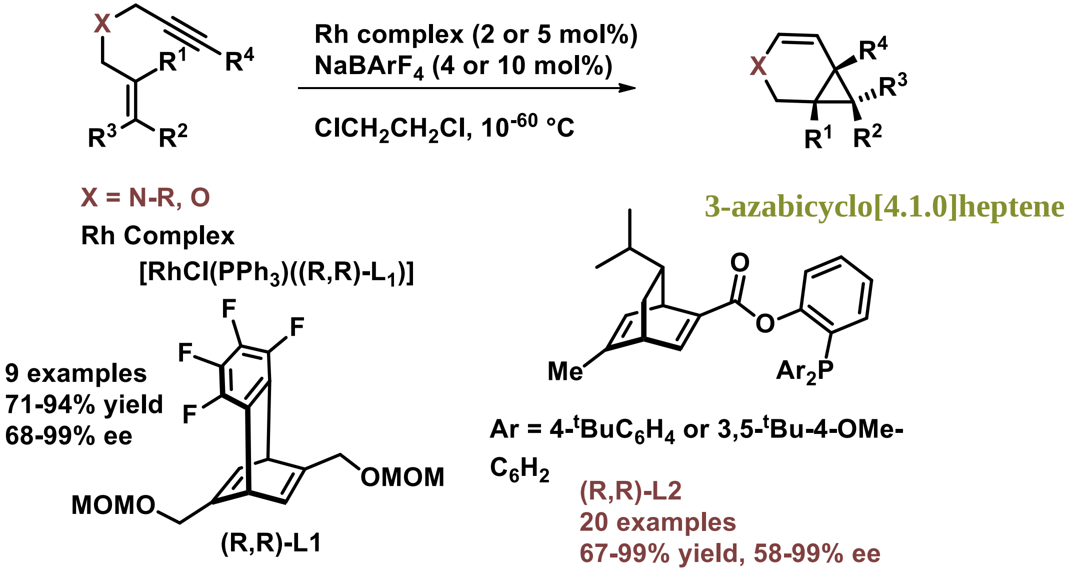


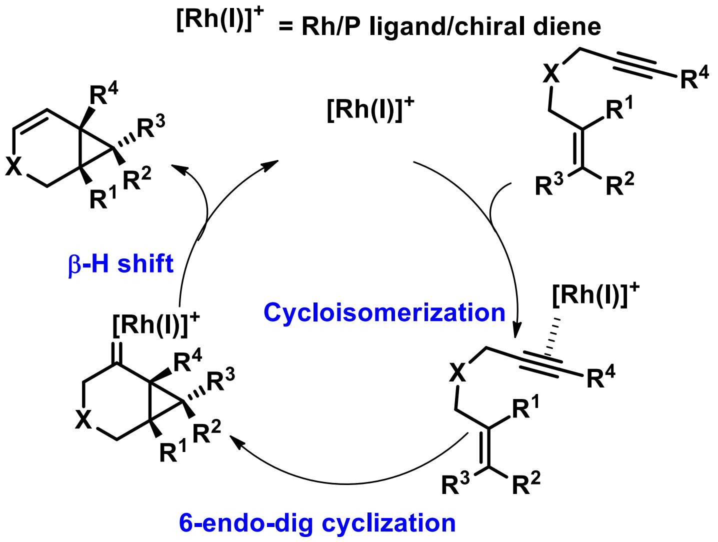


K. Masutomi, K. Noguchi and K. Tanaka, *J. Am. Chem. Soc*., **2014**, *136*, 7627–7630.

Rh(I)-Catalyzed ene –type cyclization of 1,6-enynes

Alder-ene cycloisomerization





Rh–bisphosphine complex coordinated by PPh_3 was found to be totally inactive towards this reaction

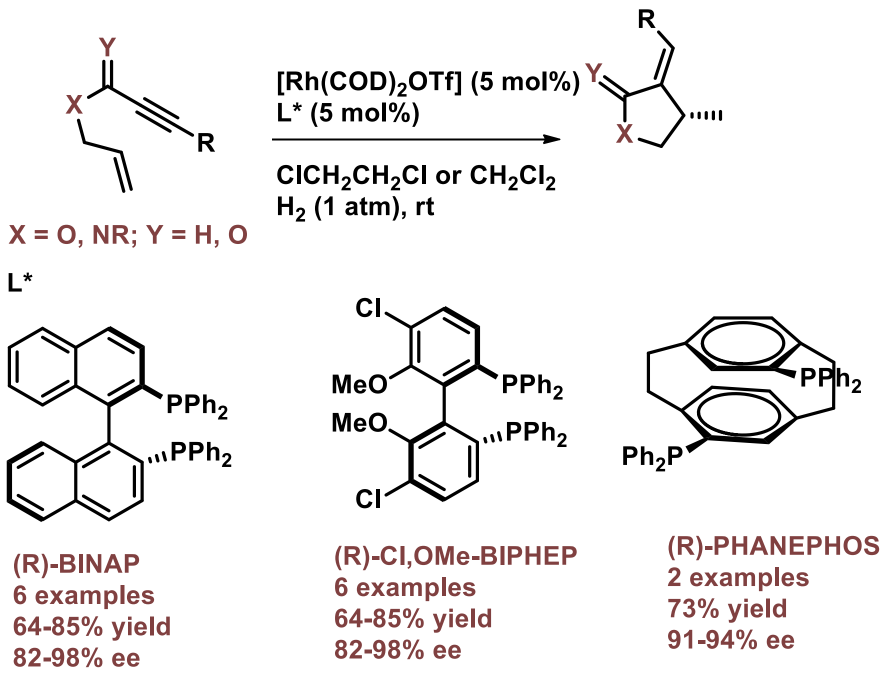
Less hindered and less electron donating character for diene ligand

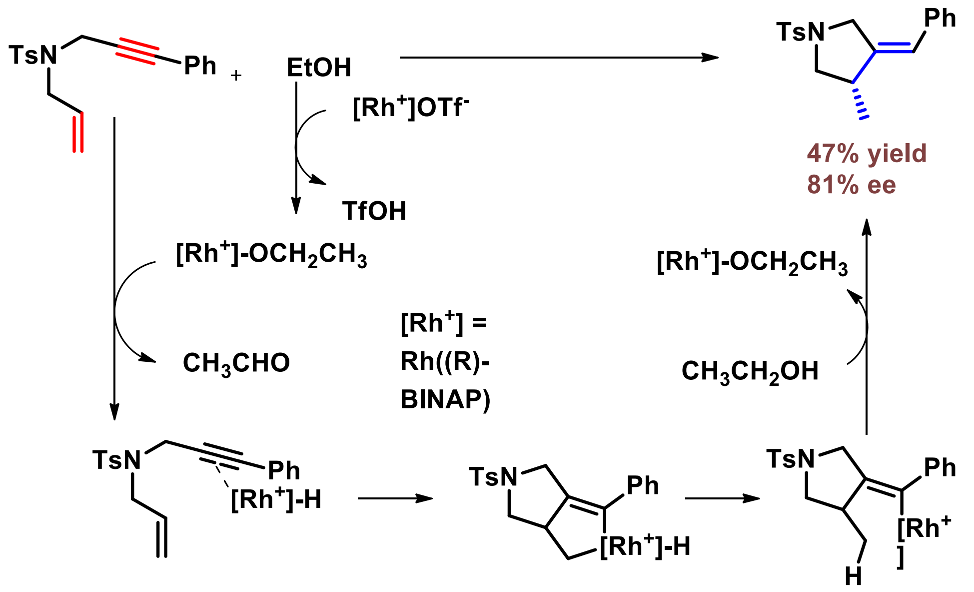
Overcomes Limited substrate scope and enyne oligomerisation due to dissociation of PPh_3

T. Nishimura, T. Kawamoto, M. Nagaosa, H. Kumamoto and T. Hayashi, *Angew. Chem., Int. Ed.*, **2010**, *49*, 1638–1641.

T. Nishimura, Y. Maeda and T. Hayashi, *Org. Lett.*, **2011**, *13*, 3674–3677.

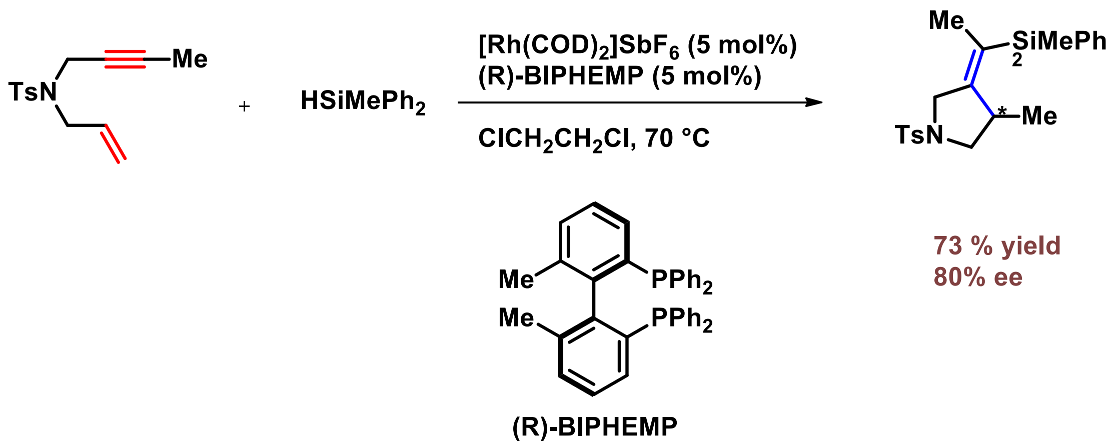
Reductive cyclization

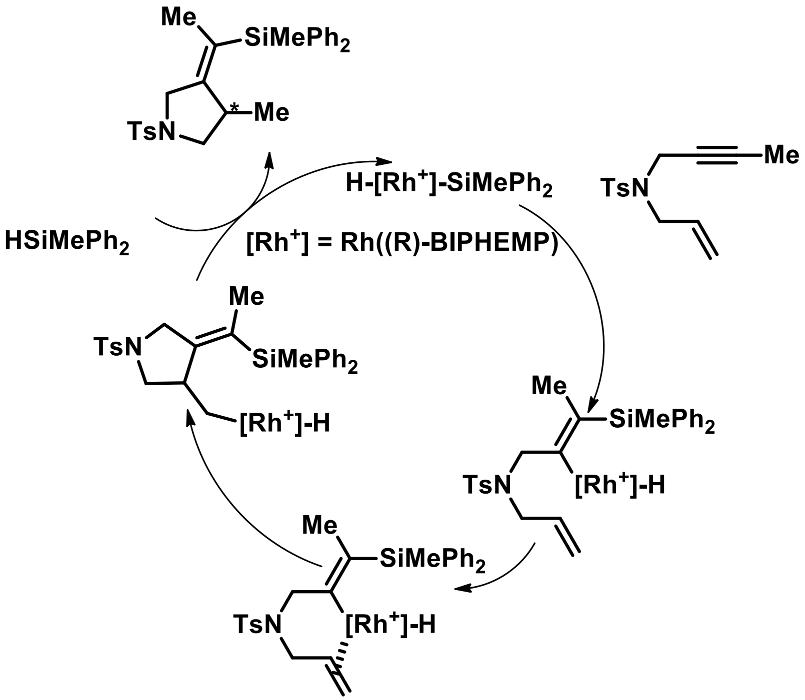




H.-Y. Jang, F. W. Hughes, H. Gong, J. Zhang, J. S. Brodbelt and M. J. Krische, *J. Am. Chem. Soc.*, **2005**, *127*, 6174– 6175.
J. H. Park, S. M. Kim and Y. K. Chung, *Chem. – Eur. J.*, **2011**, *17*, 10852–10856.

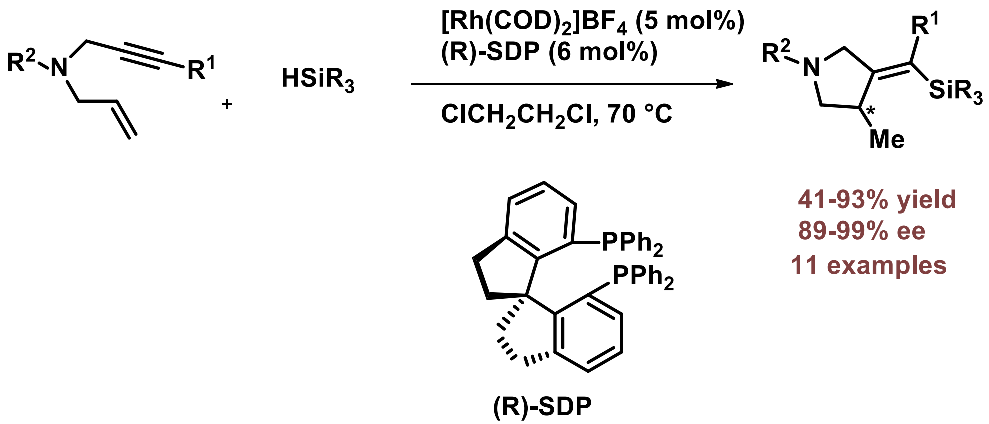
Reductive cyclization

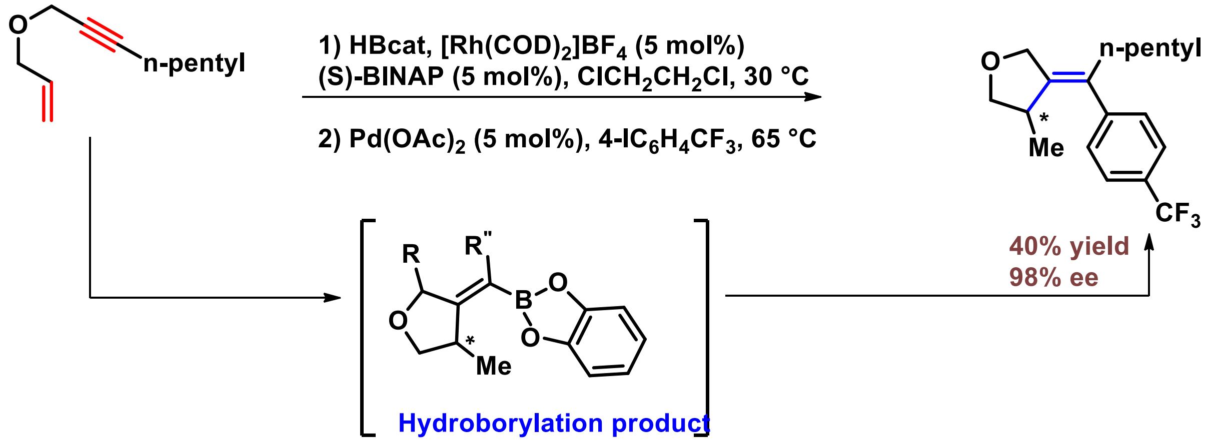




H. Chakrapani, C. Liu and R. A. Widenhoefer, *Org. Lett.*, **2003**, *5*, 157–159.

Reductive cyclization





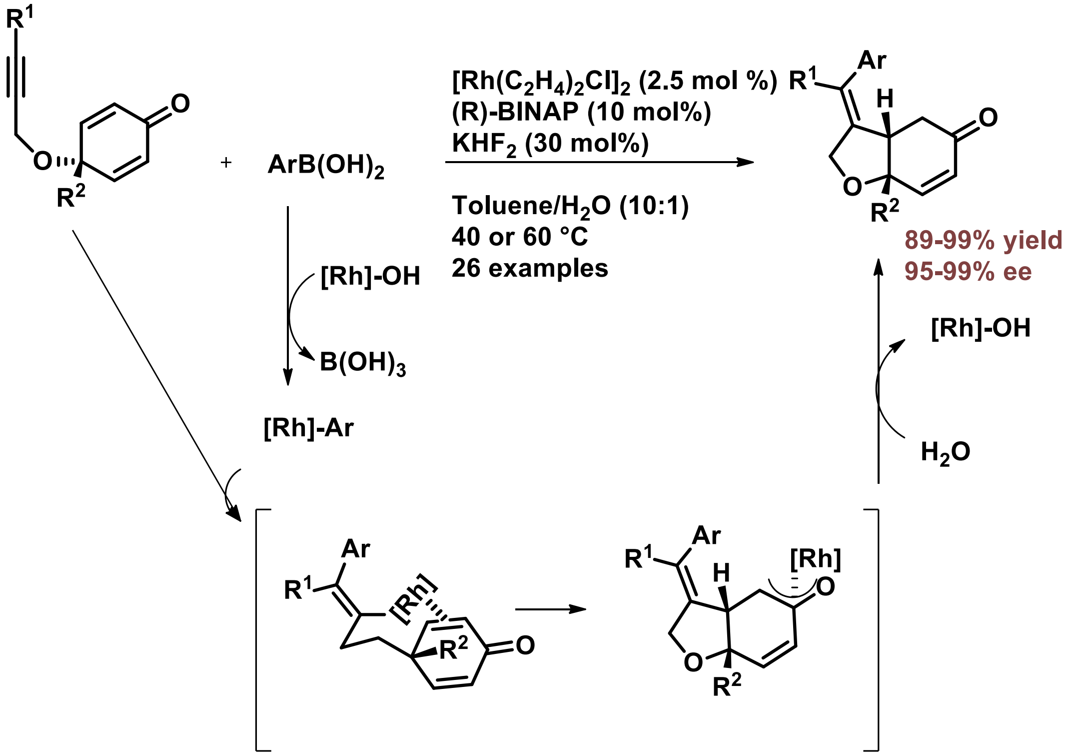
the 1,6-enynes bearing a phenyl group attached to the alkyne or alkene terminus can only afford a trace amount of silylcyclization products.

Catecholborane was confirmed to be the optimal borylating agent

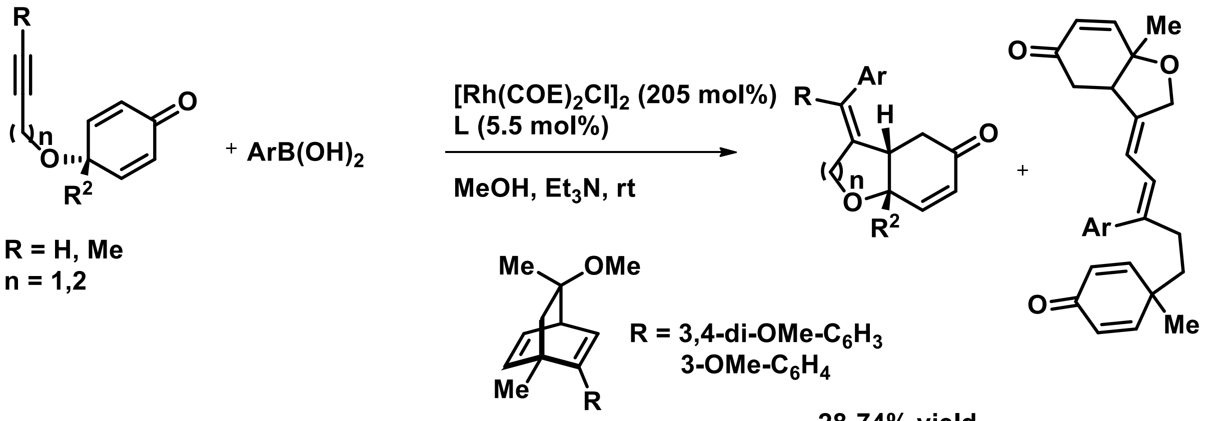
In addition, 1,6-enynes bearing a terminal C–C triple bond or a substituted C–C double bond and 1,7-enynes could not be tolerated

B.-M. Fan, J.-H. Xie, S. Li, L.-X. Wang and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, **2007**, *46*, 1275–1277.
R. E. Kinder and R. A. Widenhoefer, *Org. Lett.*, **2006**, *8*, 1967–1969.

Arylative cyclization



Rh retains +1 oxidation state



28-74% yield
48-90% ee
23 examples

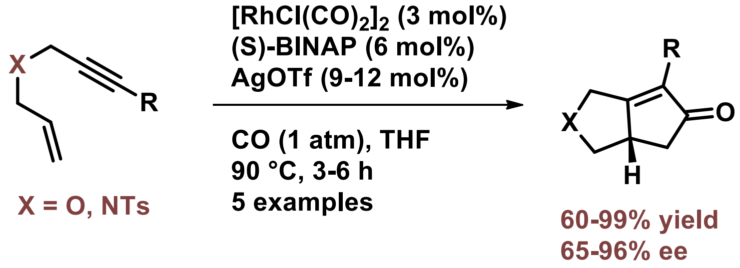
C_1 symmetric chiral diene

Phosphine ligands, decomposition of starting material

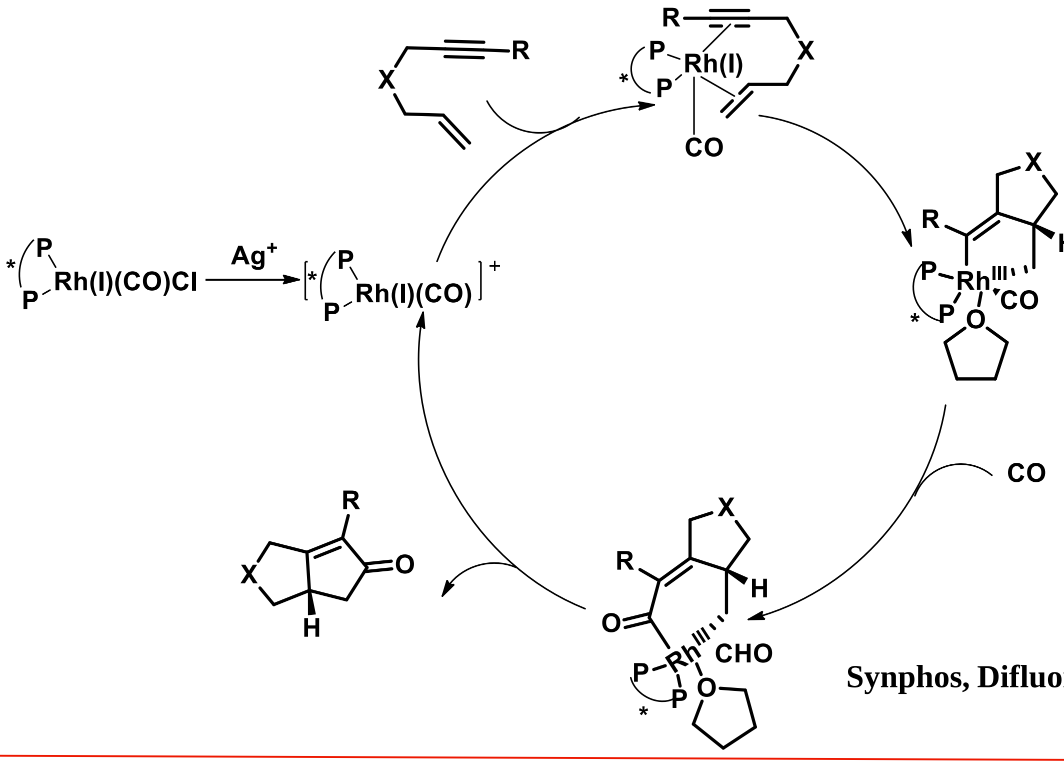
1,2-carborhodation via syn-addition of aryl-Rhodium species

Z.-T. He, B. Tian, Y. Fukui, X. Tong, P. Tian and G.-Q. Lin, *Angew. Chem., Int. Ed.*, **2013**, *52*, 5314–5318.
J. Keilitz, S. G. Newman and M. Lautens, *Org. Lett.*, **2013**, *15*, 1148–1151.

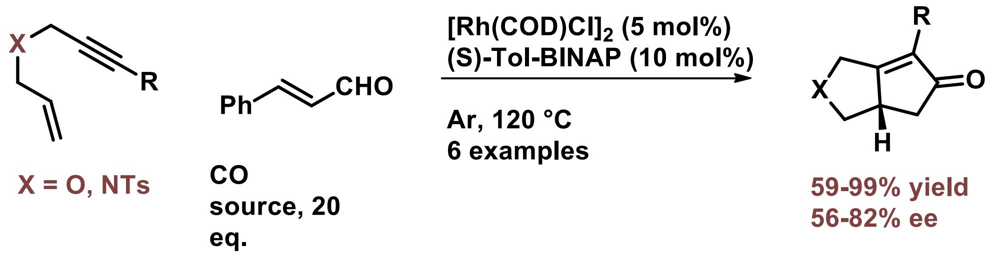
Intramolecular Pauson-Khand-type reaction

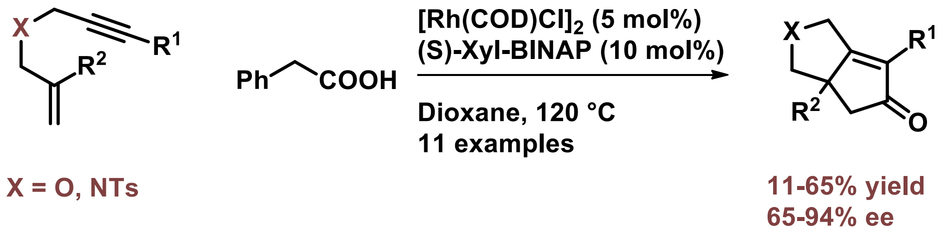


CO pressure,
Enantioselectivity
Dihedral angle of ligands
Electron density of alkyne



Synphos, Difluorphos better reactivity





(a) N. Jeong, B. K. Sung and Y. K. Choi, *J. Am. Chem. Soc.*, **2000**, *122*, 6771–6772; (b) N. Jeong, B. K. Sung, J. S. Kim, S. B. Park, S. D. Seo, J. Y. Shin, K. Y. In and Y. K. Choi, *Pure Appl. Chem.*, **2002**, *74*, 85–91.
(b) T. Shibata, N. Toshida and K. Takagi, *Org. Lett.*, **2002**, *4*, 1619–1621; (b) T. Shibata, N. Toshida and K. Takagi, *J. Org. Chem.*, **2002**, *67*, 7446–7450.
(c) H. W. Lee, A. S. C. Chan and F. Y. Kwong, *Chem. Commun.*, **2007**, 2633–2635.

Rh(I)-Catalyzed ene –type cyclization of 1,6-enynes

Rh(I) catalysed cyclization of alkynals and alkynones

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Rh(II) carbenoid and nitrenoid insertion

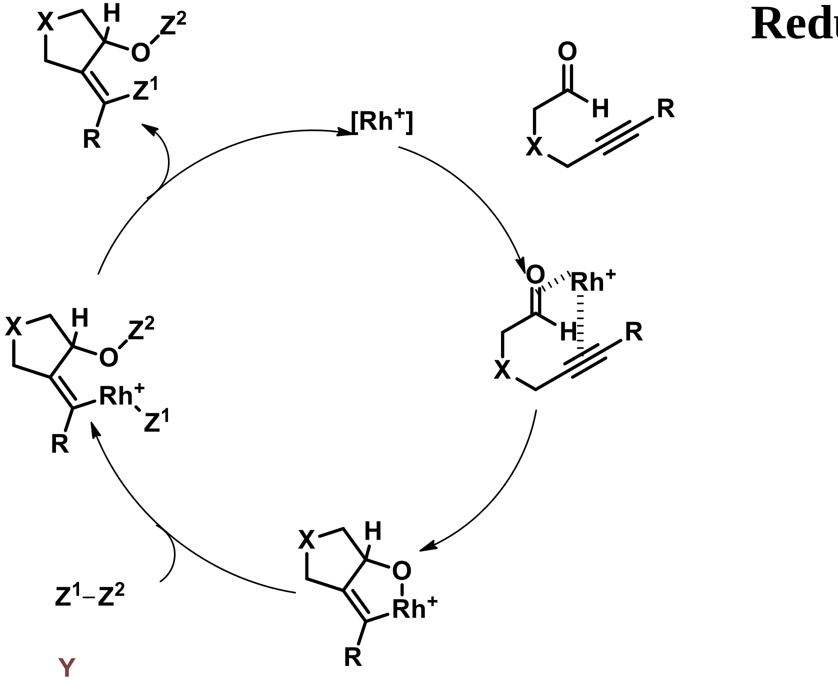
Rh(I)-catalysed ring opening reaction via C-C bond activation

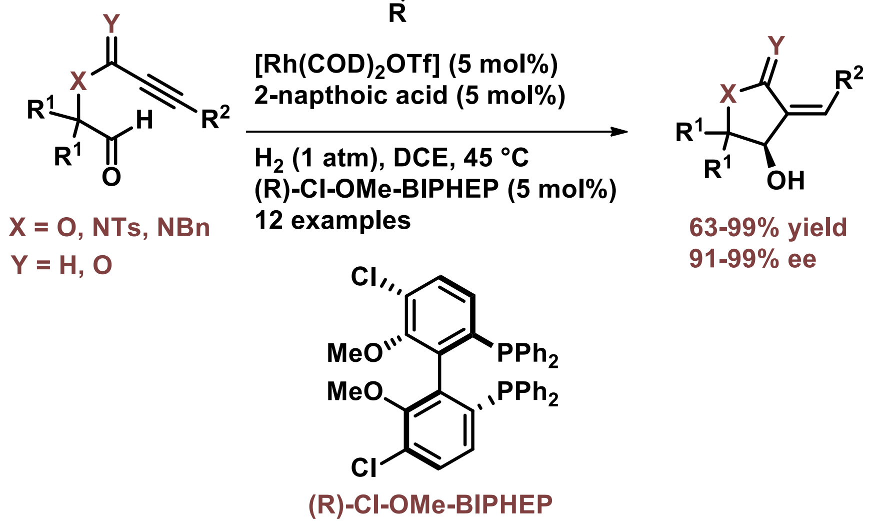
Rh(I)-catalysed arylboron addition/cyclization

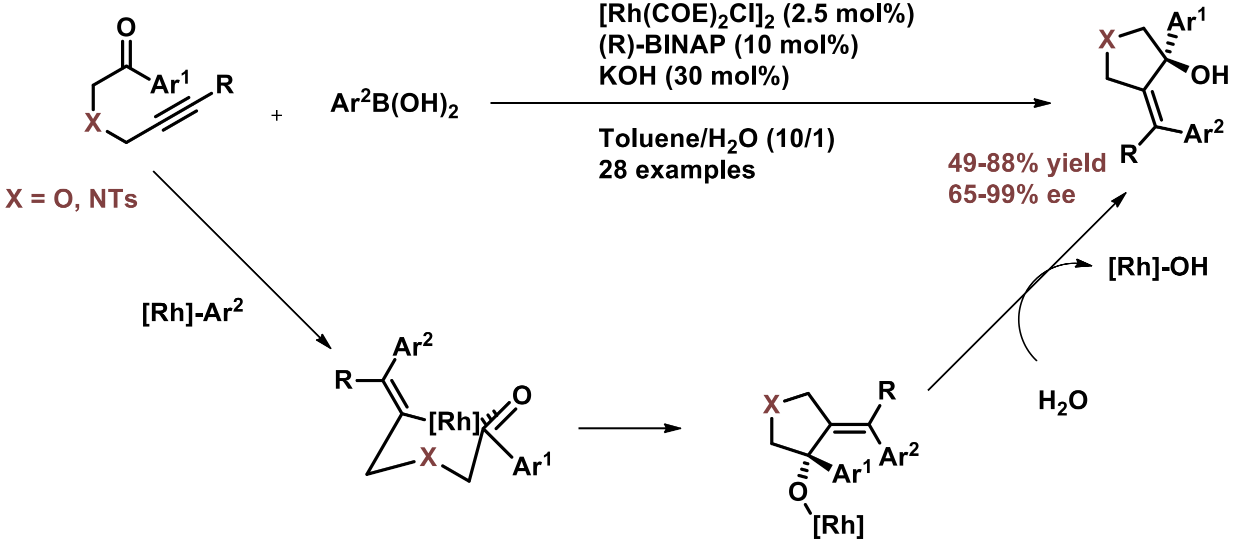
Miscellaneous

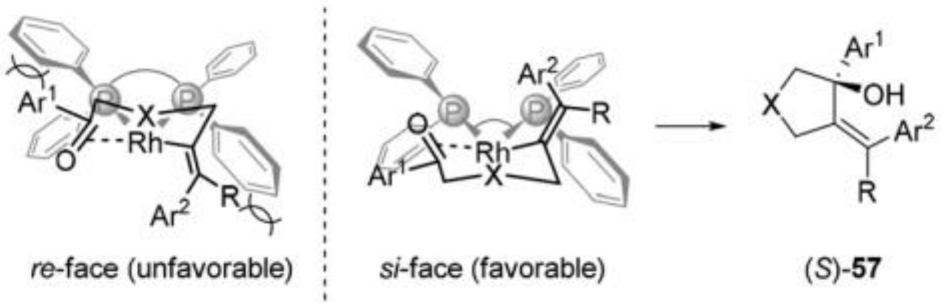
Rh(I) catalysed cyclization of alkynals and alkynones

Reductive cyclization of 5-alkynals



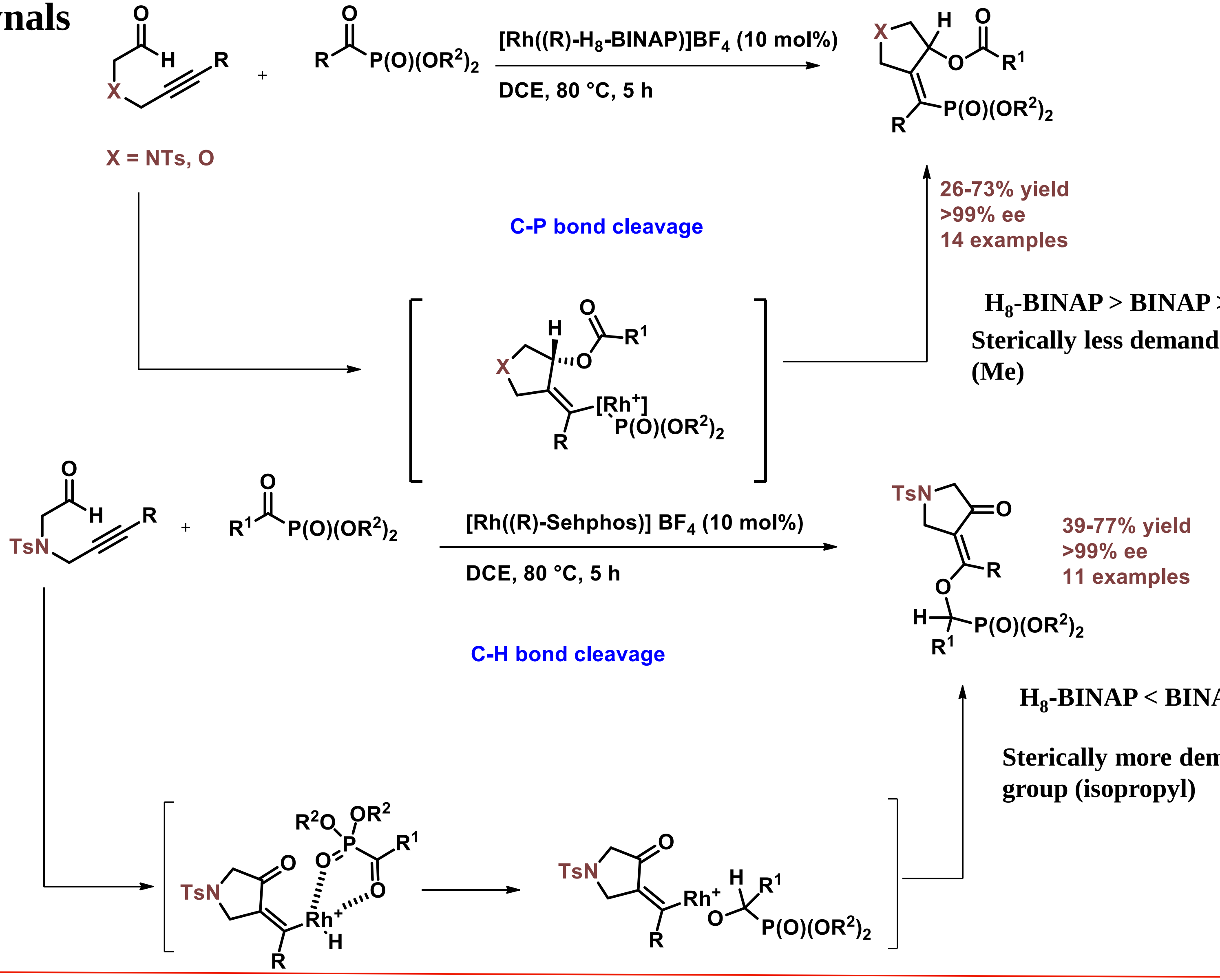






(a) J. U. Rhee and M. J. Krische, *J. Am. Chem. Soc.*, **2006**, *128*, 10674–10675; (b) J. U. Rhee, R. A. Jones and M. J. Krische, *Synthesis*, **2007**, 3427–3430.
Y. Li and M.-H. Xu, *Org. Lett.*, **2014**, *16*, 2712–2715.

Reductive cyclization of 5-alkynals



H$_8$-BINAP > BINAP > Segphos

Sterically less demanding alkoxy group (Me)

H$_8$-BINAP < BINAP < Segphos

Sterically more demanding alkoxy group (isopropyl)

K. Masuda, N. Sakiyama, R. Tanaka, K. Noguchi and K. Tanaka, *J. Am. Chem. Soc.*, **2011**, *133*, 6918–6921.

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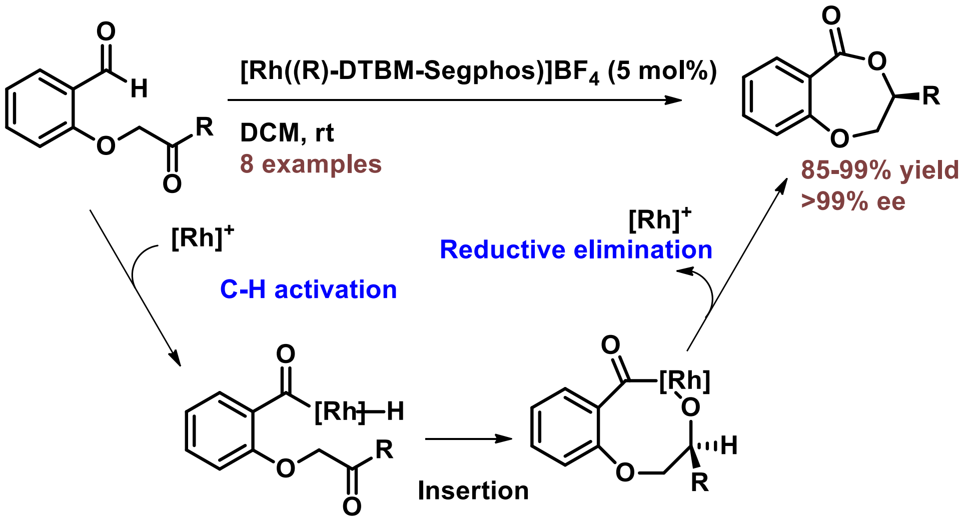
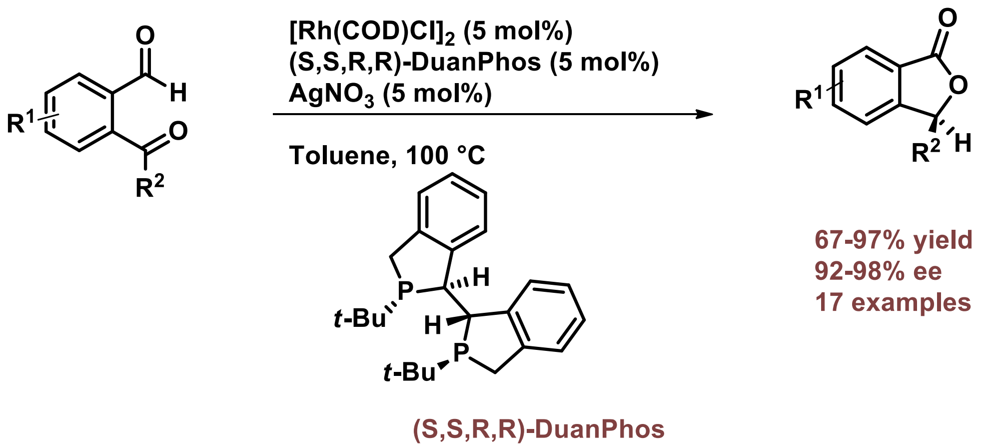
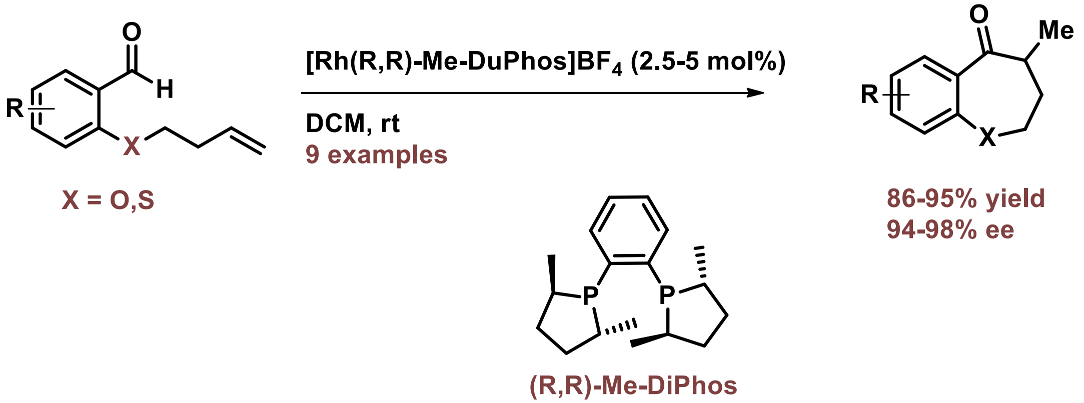
- Miscellaneous

Rh(I)/Rh(III)-catalysed C-H functionalization

Intramolecular hydroacylation of ketones and alkenes





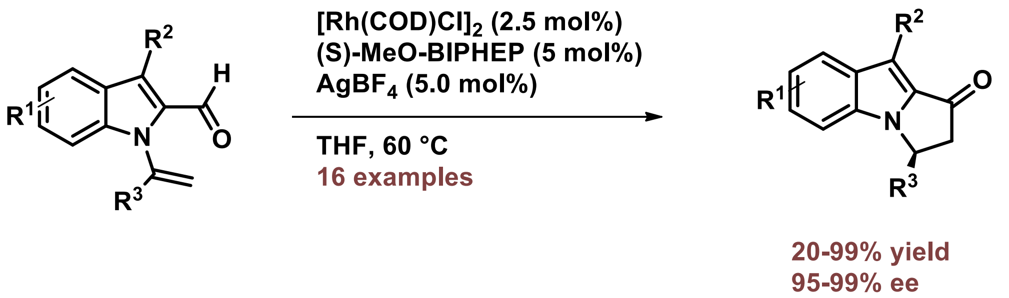


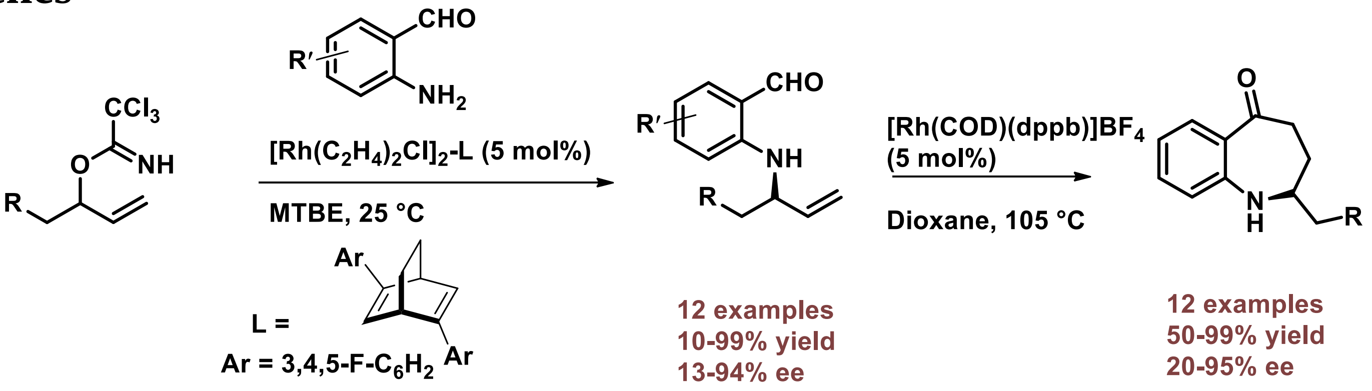
(a) Z. Shen, H. A. Khan and V. M. Dong, *J. Am. Chem. Soc*., **2008**, *130*, 2916–2917; (b) Z. Shen, P. K. Dornan, H. A. Khan, T. K. Woo and V. M. Dong, *J. Am. Chem. Soc*., **2009**, *131*, 1077–1091.
D. H. T. Phan, B. Kim and V. M. Dong, *J. Am. Chem. Soc*., **2009**, *131*, 15608–15609.
M. M. Coulter, P. K. Dornan and V. M. Dong, *J. Am. Chem. Soc*., **2009**, *131*, 6932–6933.

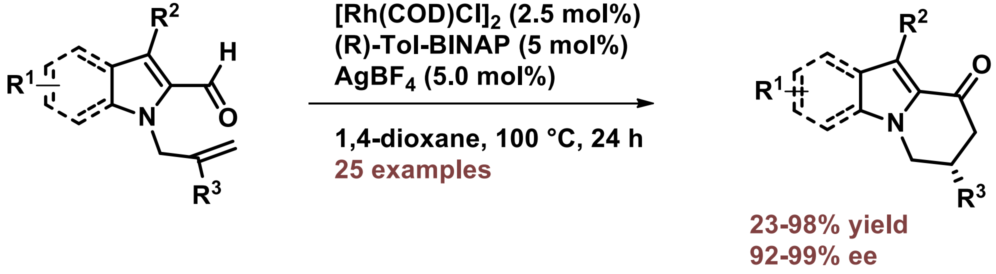
Rh(I)/Rh(III)-catalysed C-H functionalization

LCSO

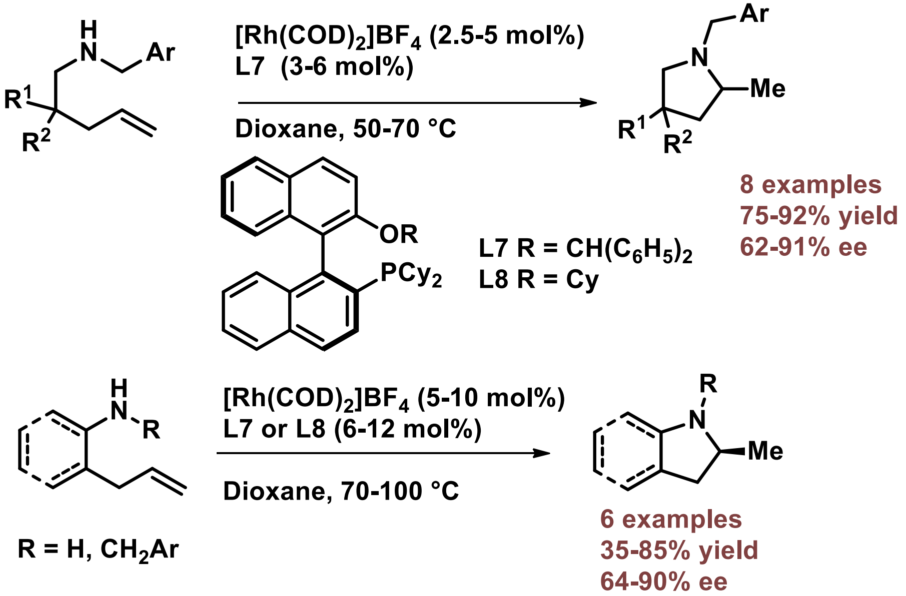
Intramolecular hydroacylation of ketones and alkenes







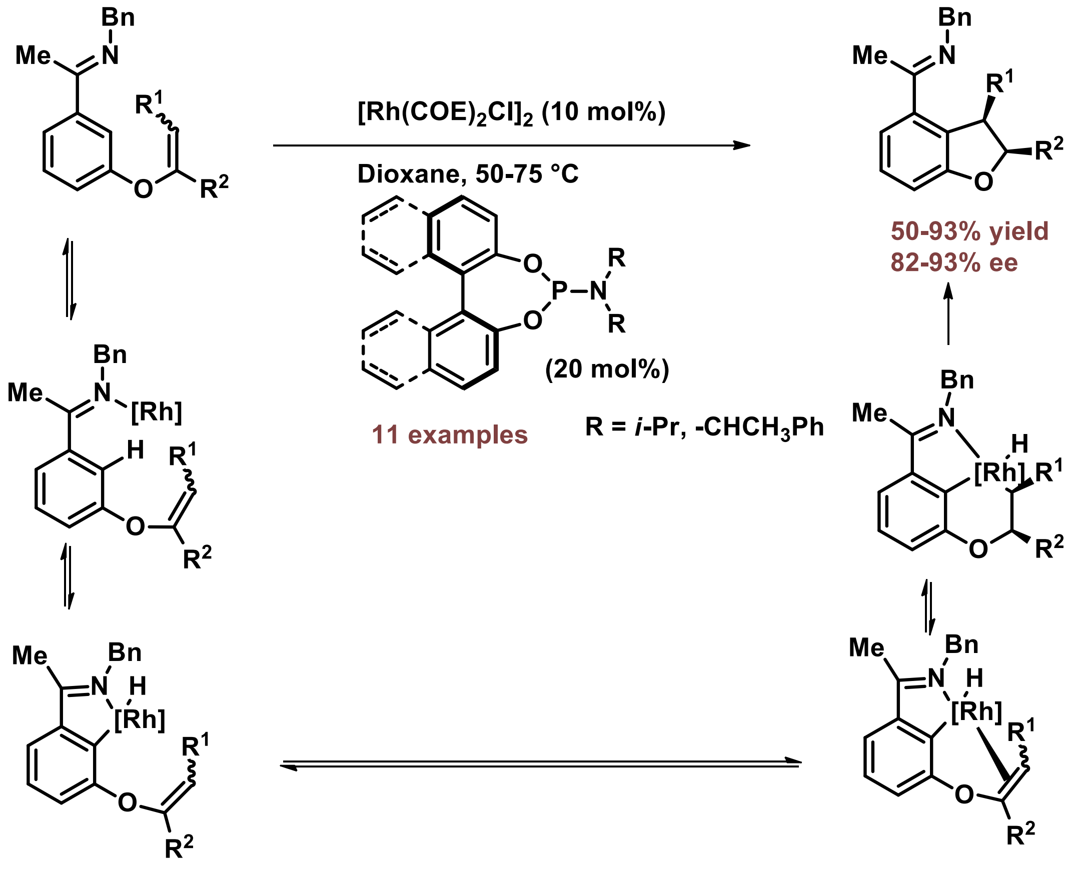
Intramolecular hydroamination of alkenes



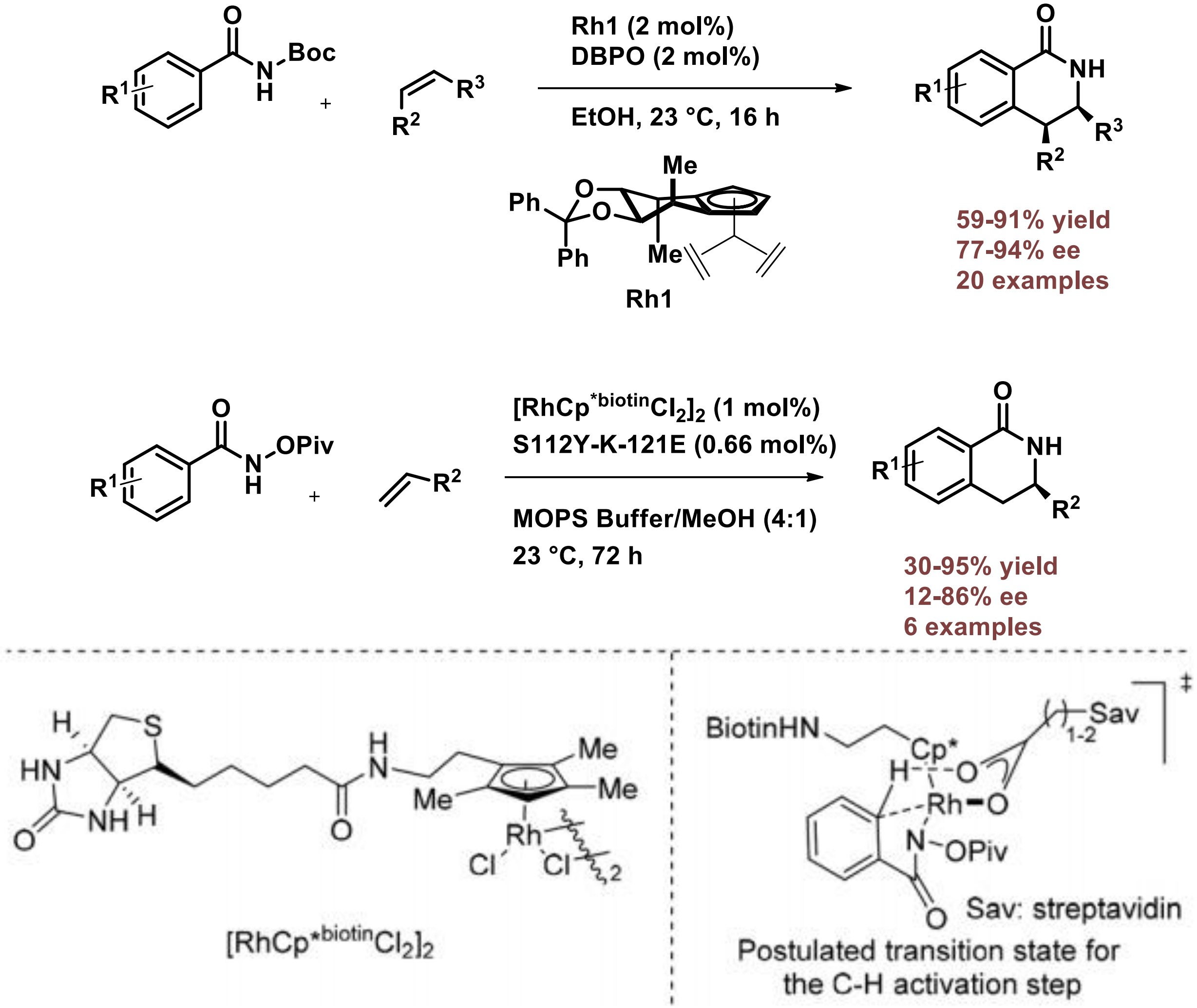
(a) A. Ghosh and L. M. Stanley, *Chem. Commun.*, **2014**, *50*, 2765–2768; (b) X.-W. Du, A. Ghosh and L. M. Stanley, *Org. Lett.*, **2014**, *16*, 4036–4039.
J. S. Arnold, E. T. Mwenda and H. M. Nguyen, *Angew. Chem., Int. Ed.*, **2014**, *53*, 3688–3692.
X. Shen and S. L. Buchwald, *Angew. Chem., Int. Ed.*, **2010**, *49*, 564–567.

Rh(I)/Rh(III)-catalysed C-H functionalization

Intramolecular hydroarylation of alkenes



Cp*Rh(III) catalysed C-H activation

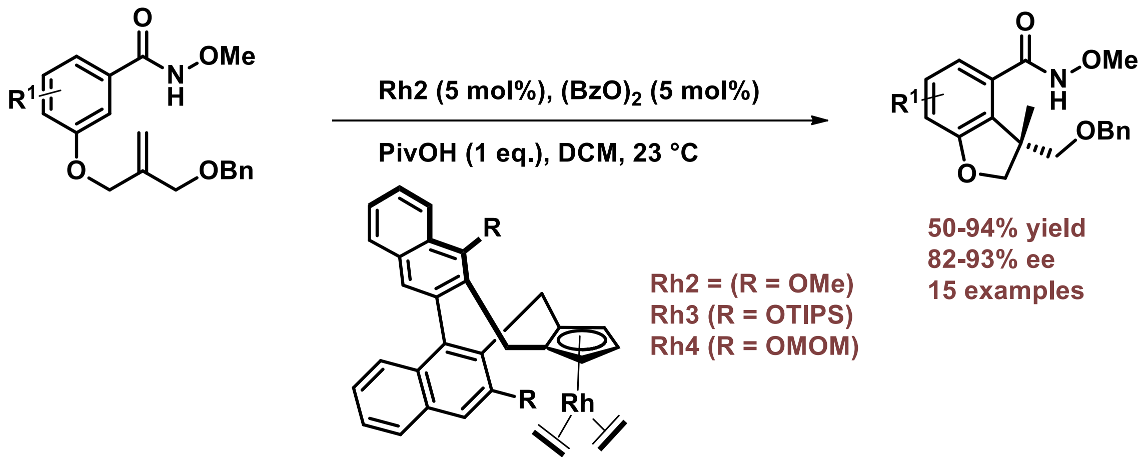


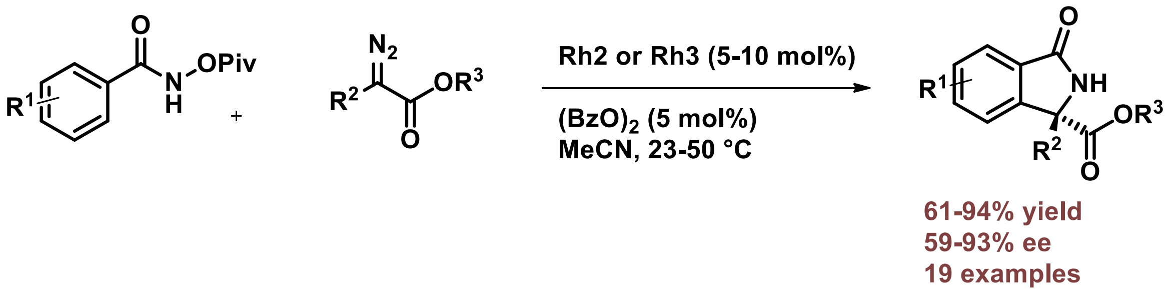
(a) R. K. Thalji, J. A. Ellman and R. G. Bergman, *J. Am. Chem. Soc.*, **2004**, *126*, 7192–7193; (b) H. Harada, R. K. Thalji, R. G. Bergman and J. A. Ellman, *J. Org. Chem.*, **2008**, *73*, 6772–6779.

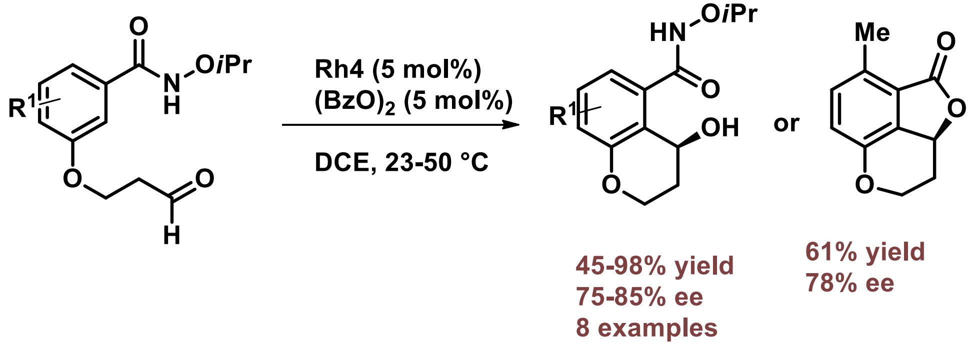
B. Ye and N. Cramer, *Science*, **2012**, *338*, 504–506.

T. K. Hyster, L. Knçrr, T. R. Ward and T. Rovis, *Science*, **2012**, *338*, 500–503.

Rh(I)/Rh(III)-catalysed C-H functionalization

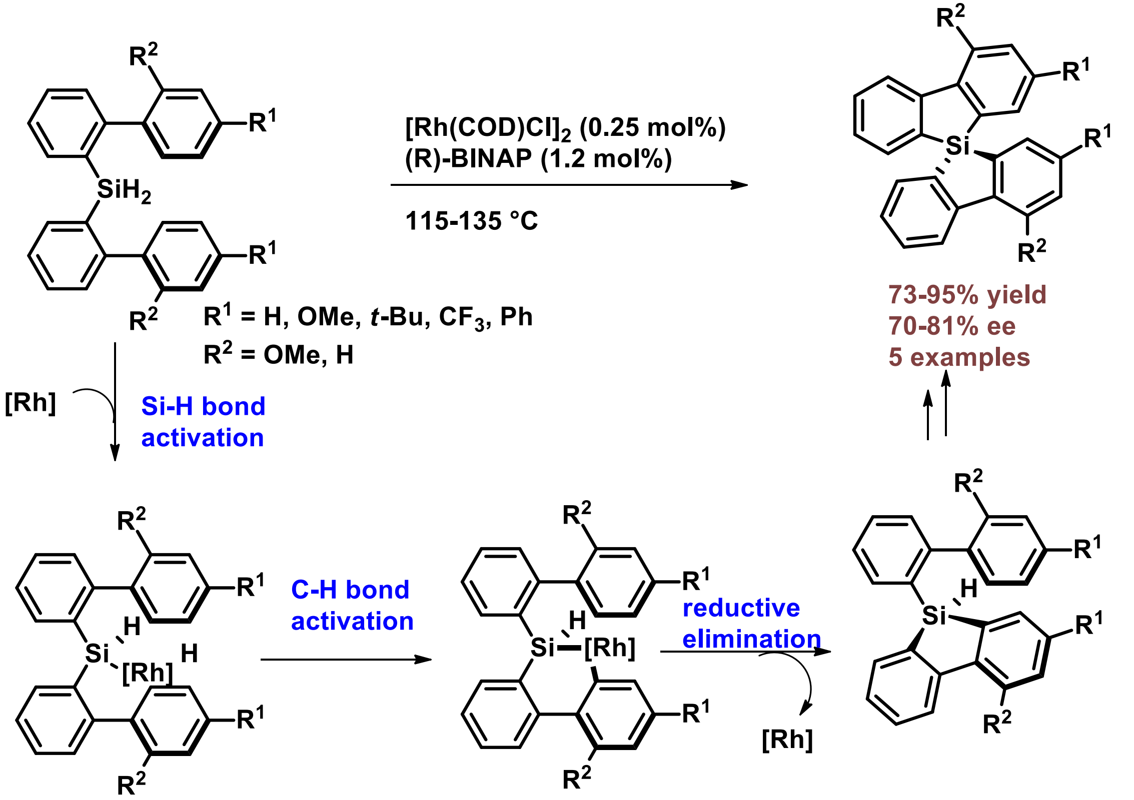






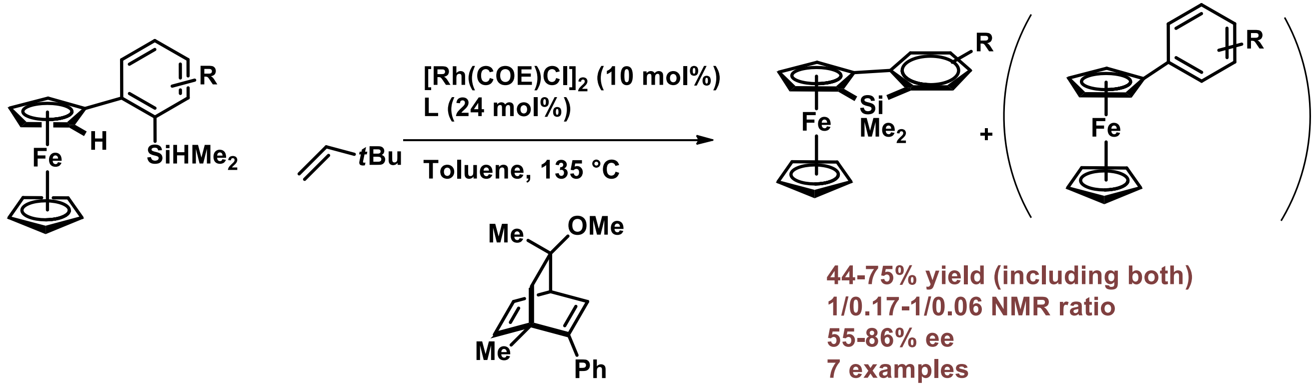
B. Ye, P. A. Donets and N. Cramer, *Angew. Chem., Int. Ed.*, **2014**, *53*, 507–511.

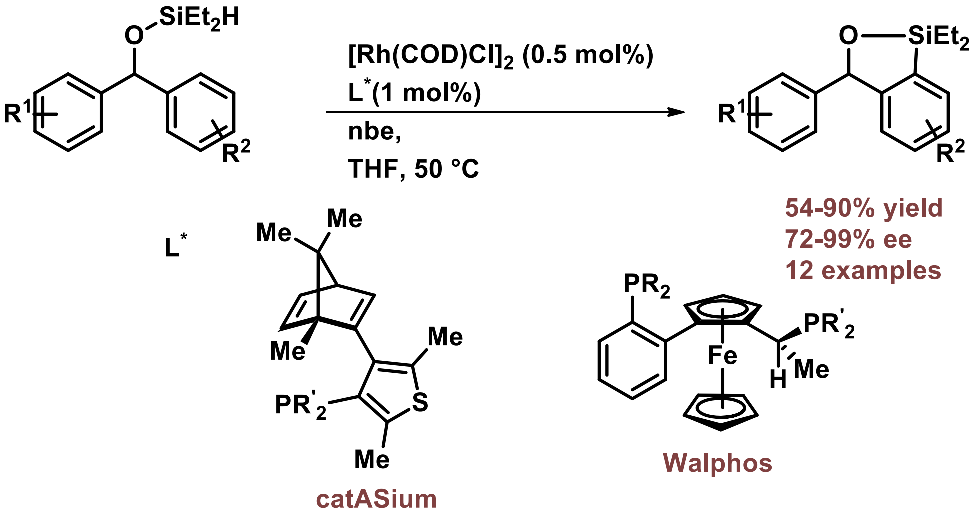
Intramolecular C-H silylation

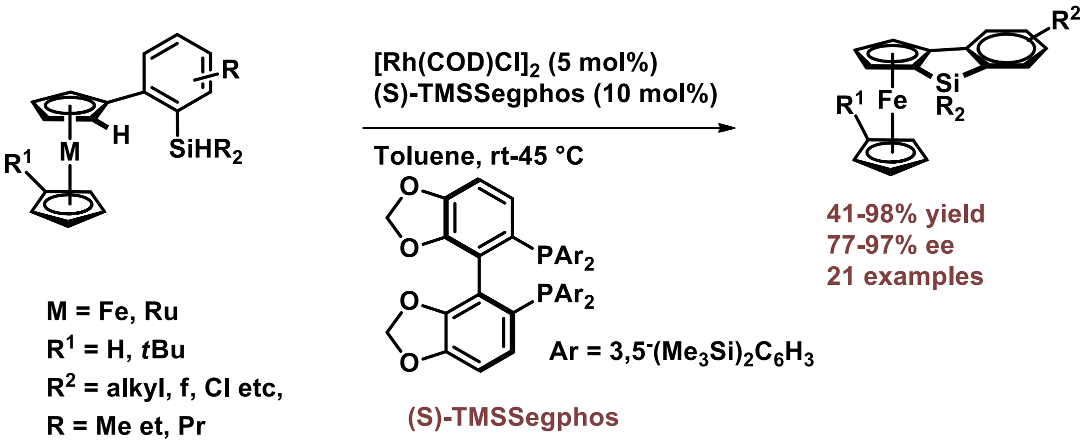


Y. Kuninobu, K. Yamauchi, N. Tamura, T. Seiki and K. Takai, *Angew. Chem., Int. Ed.*, **2013**, *52*, 1520–1522

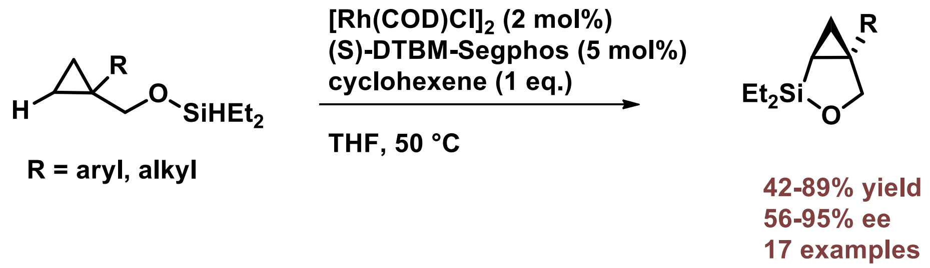
Intramolecular C-H silylation







M = Fe, Ru
R^1 = H, *t*Bu
R^2 = alkyl, f, Cl etc,
R = Me et, Pr



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T. Lee and J. F. Hartwig, *Angew. Chem., Int. Ed.*, **2016**, *55*, 8723–8727.

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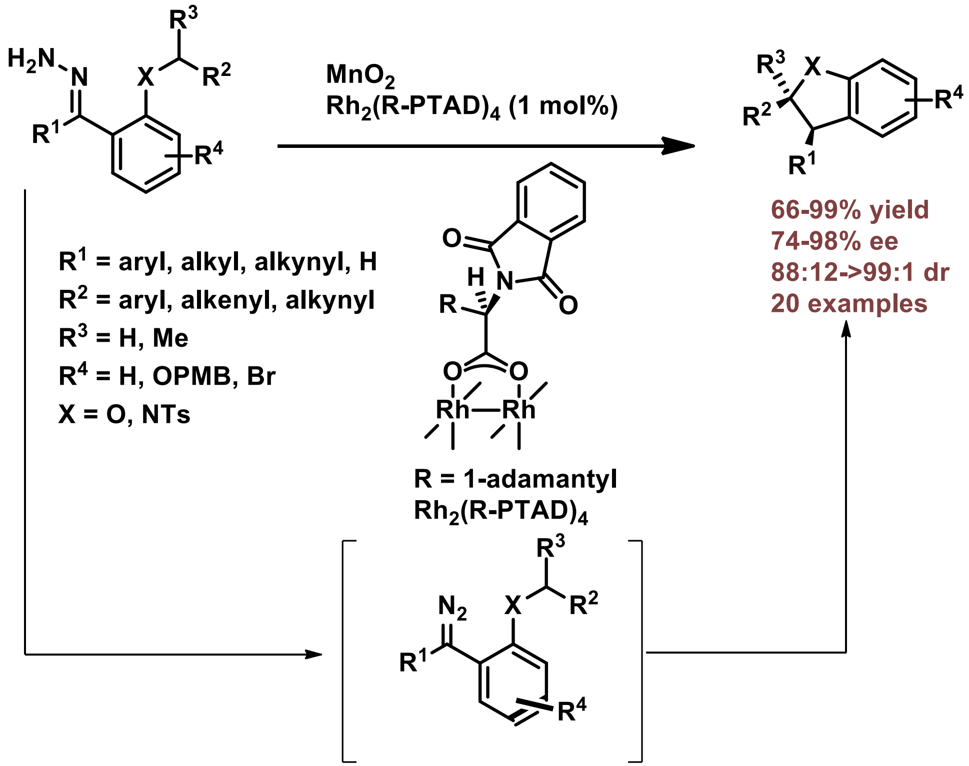
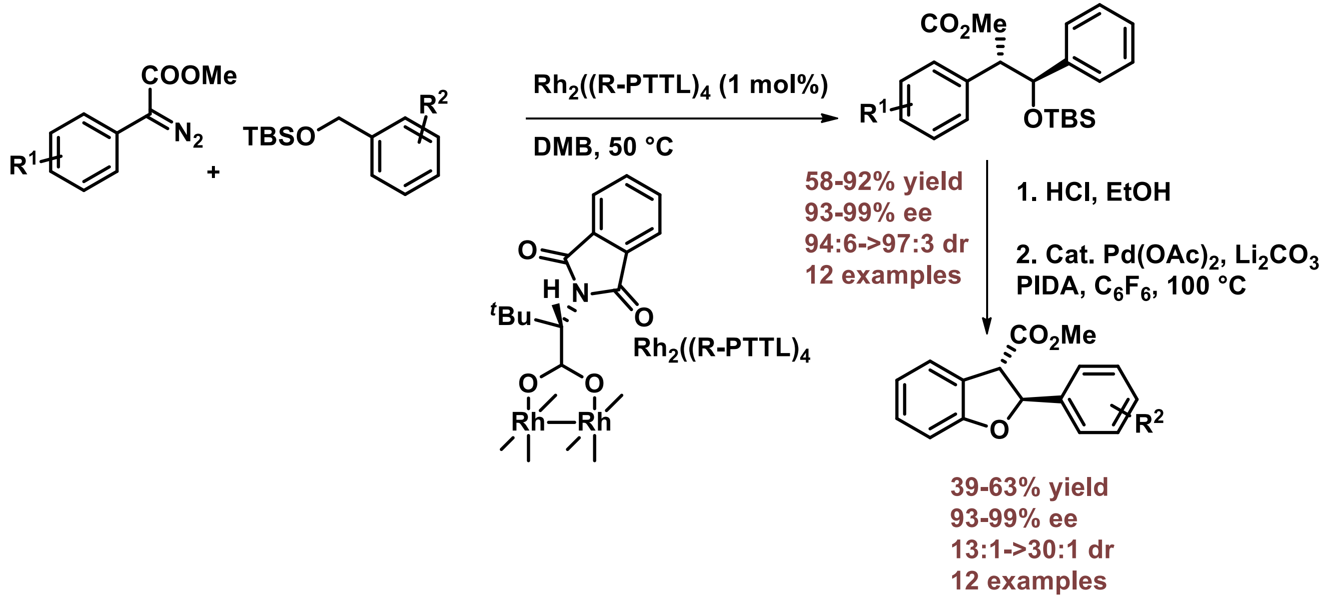
Carbene insertion





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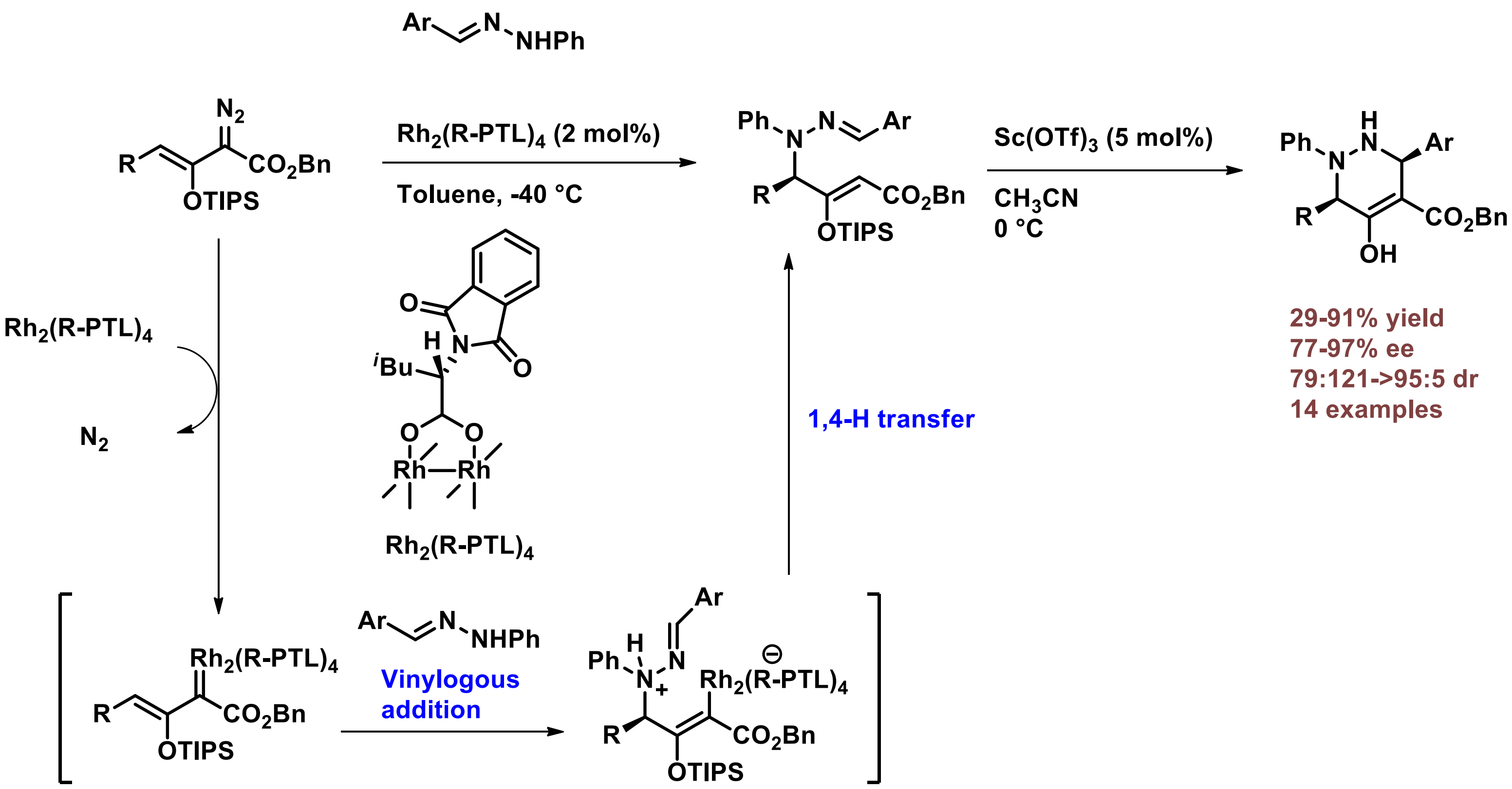
Carbene insertion



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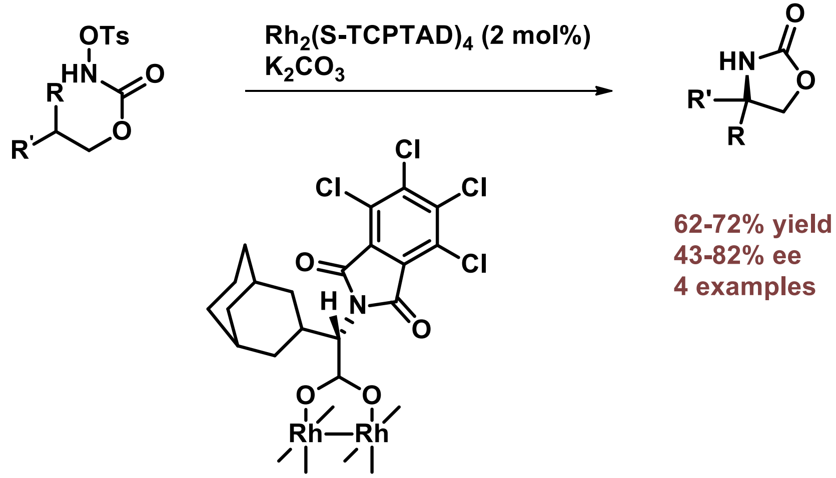

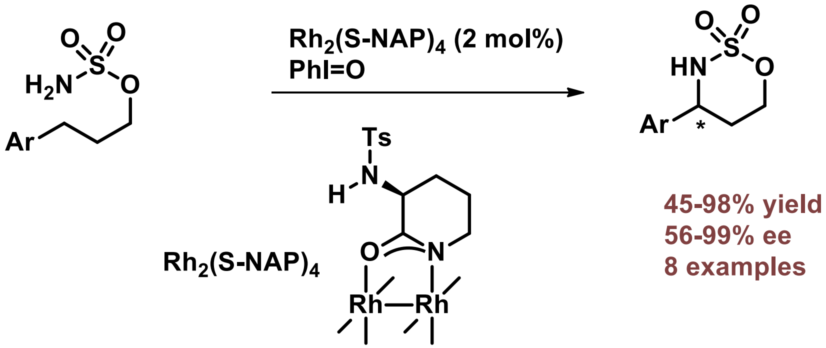

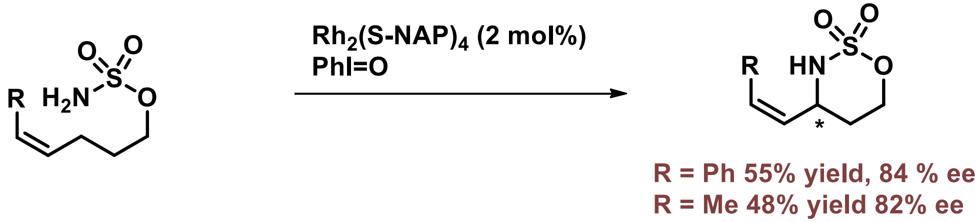

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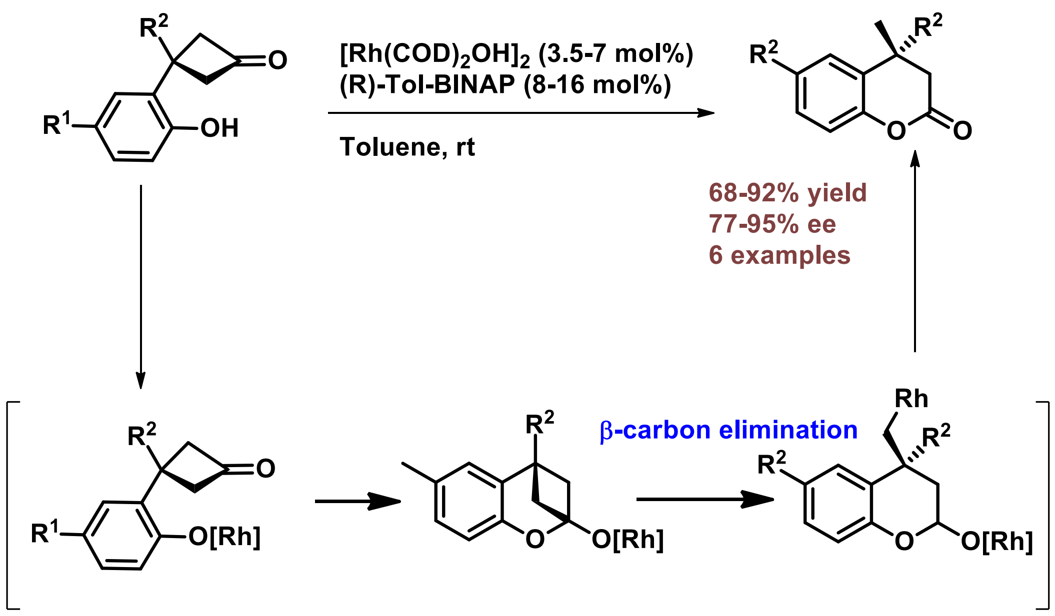
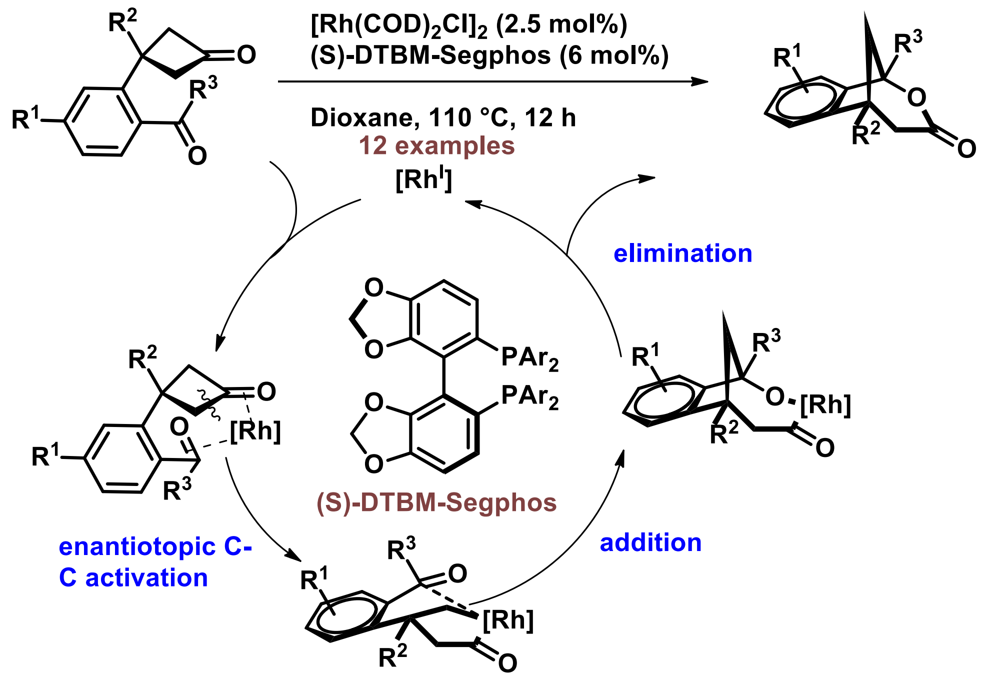
Rh(I)-catalysed ring opening reaction via C-C bond activation





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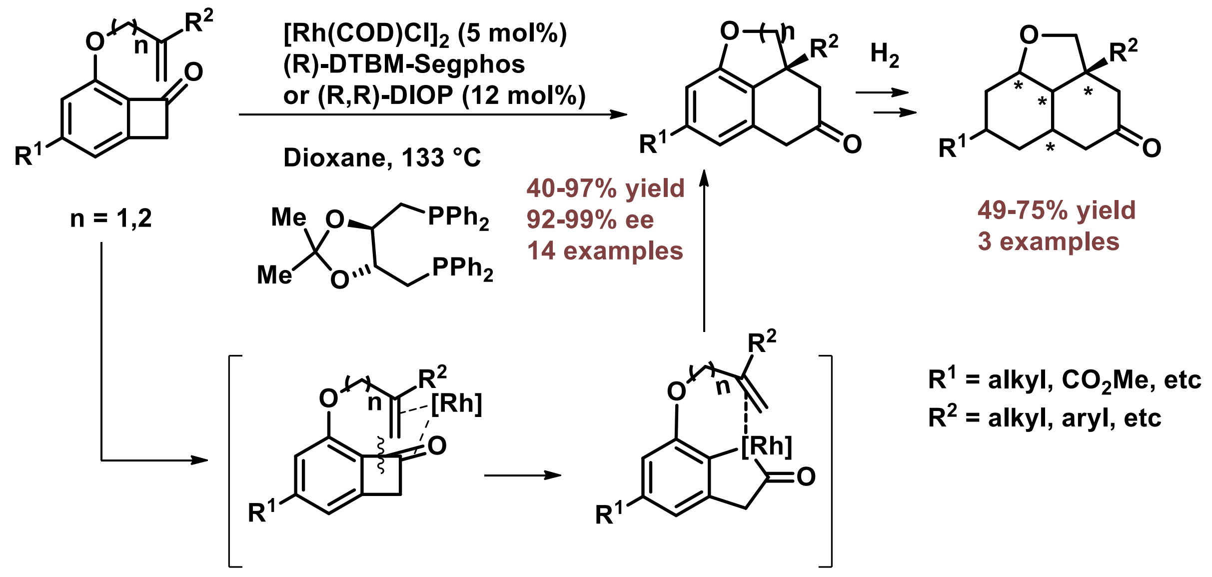
Rh(I)-catalysed ring opening reaction via C-C bond activation



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- Rh(I)-Catalyzed ene –type cyclization of 1,6-enynes
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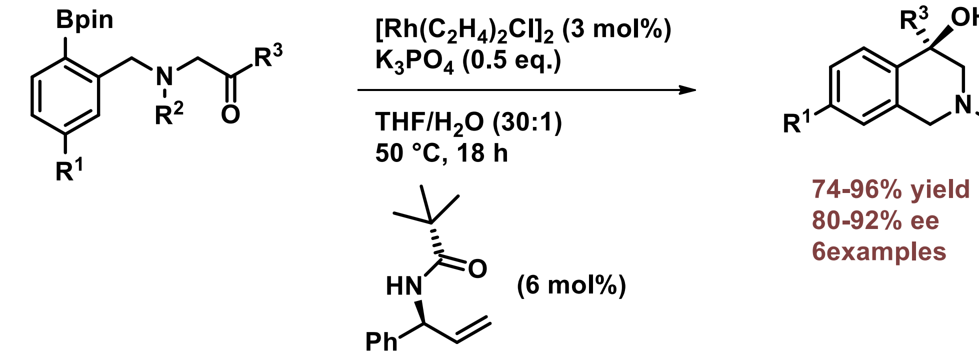
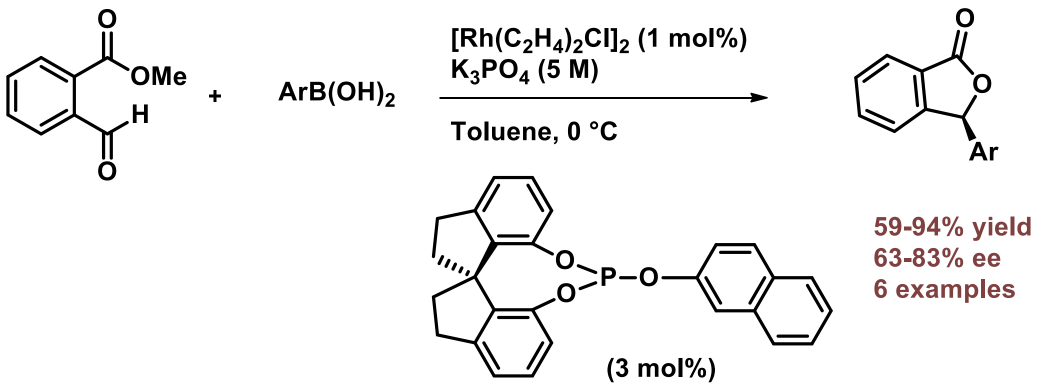
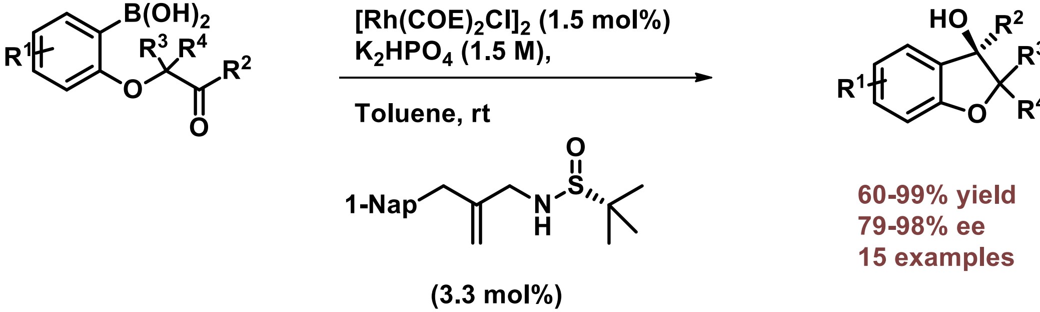
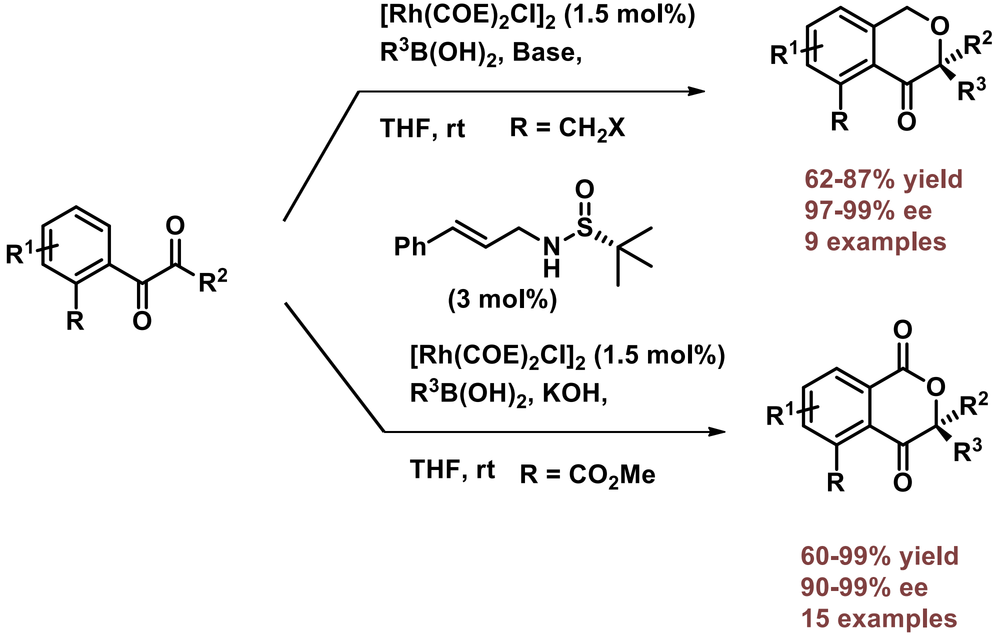
Rh(I)-catalysed arylboron addition/cyclization









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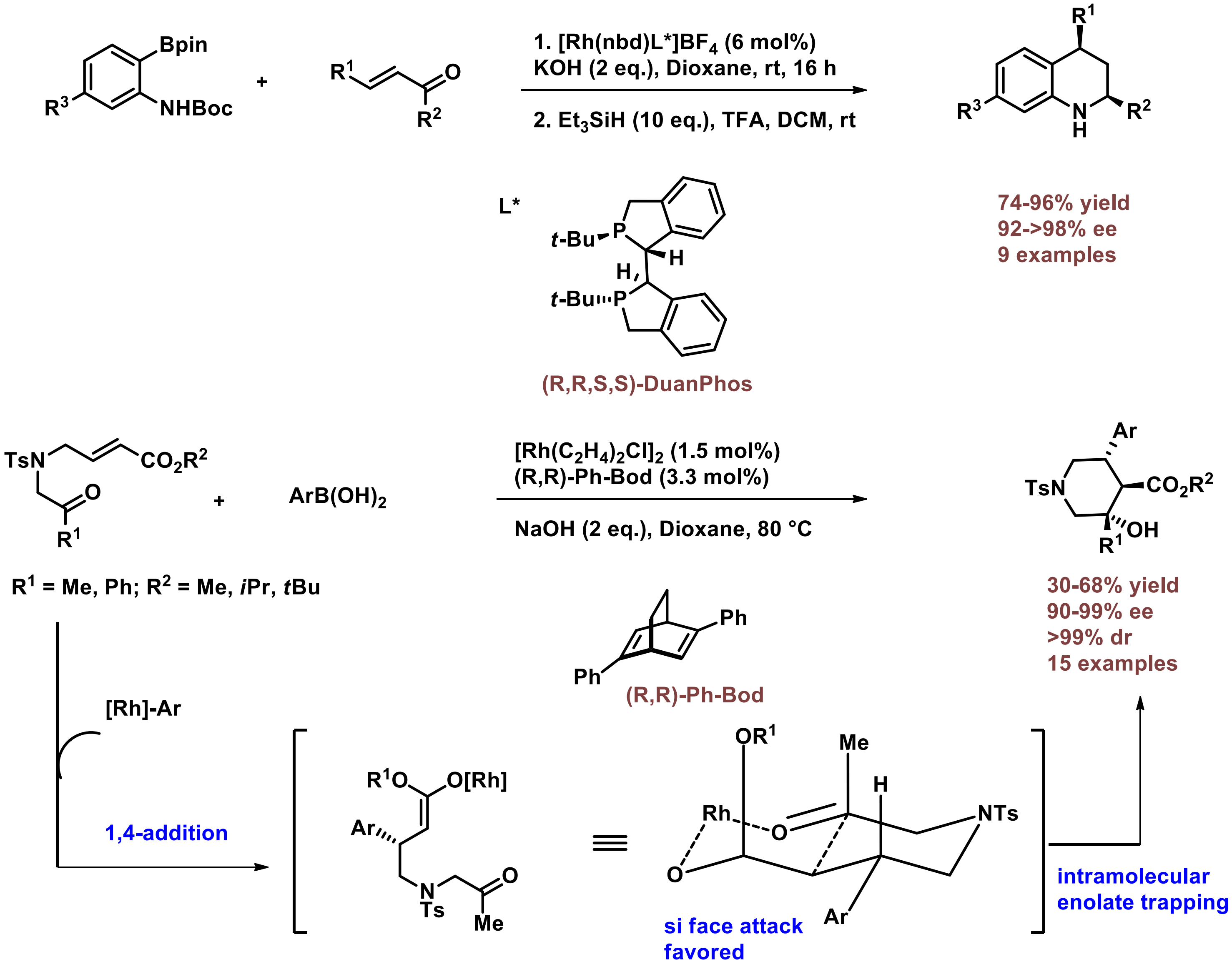
Rh(I)-catalysed arylboron addition/cyclization



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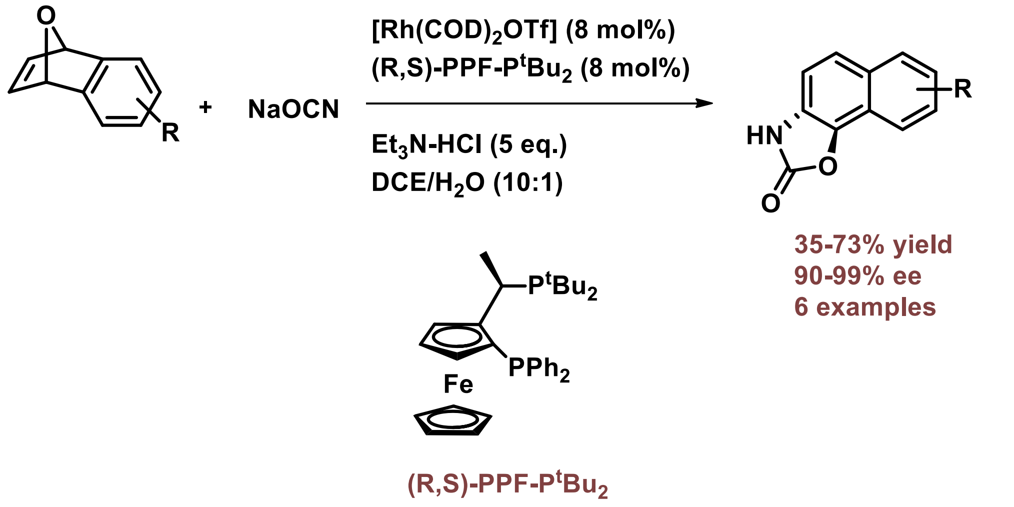
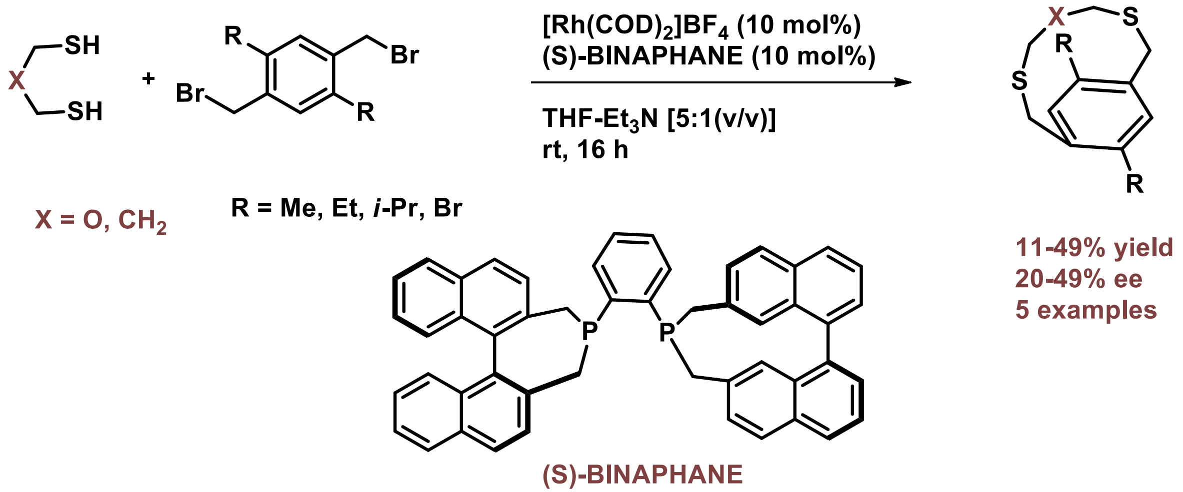
Miscellaneous





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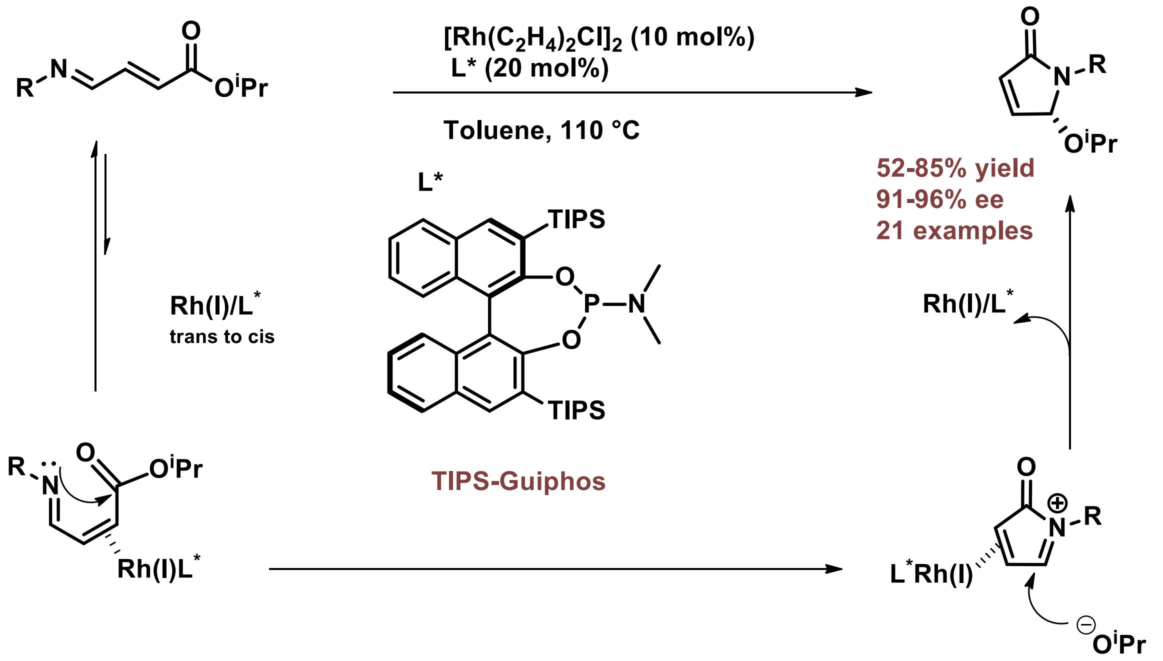
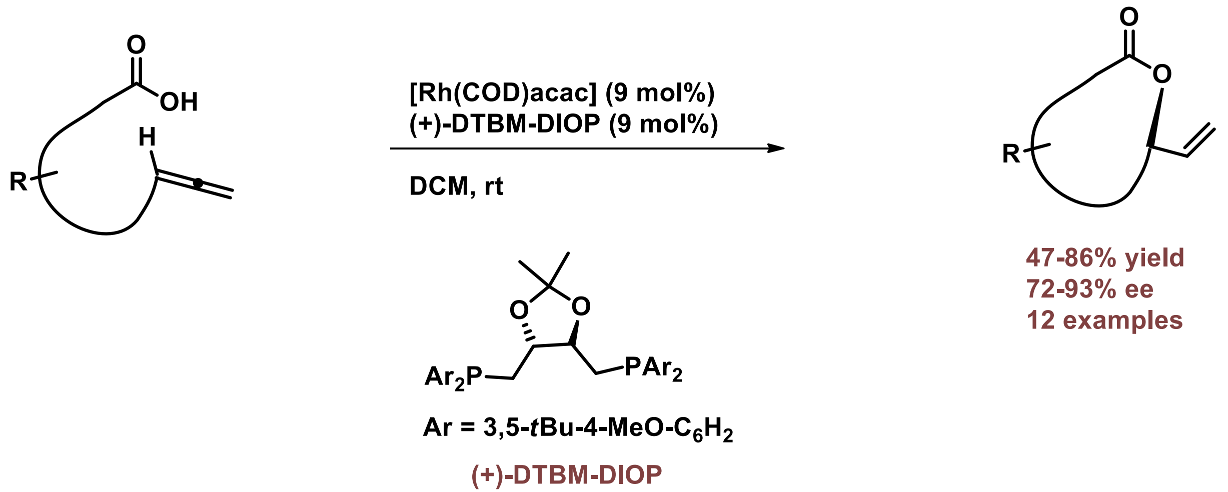
Miscellaneous





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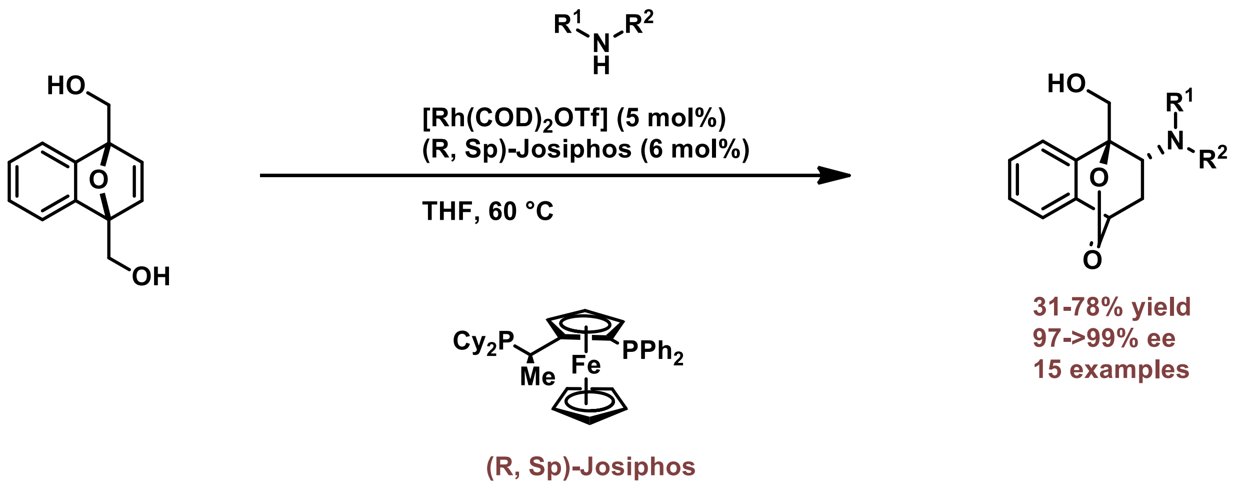
Conclusions

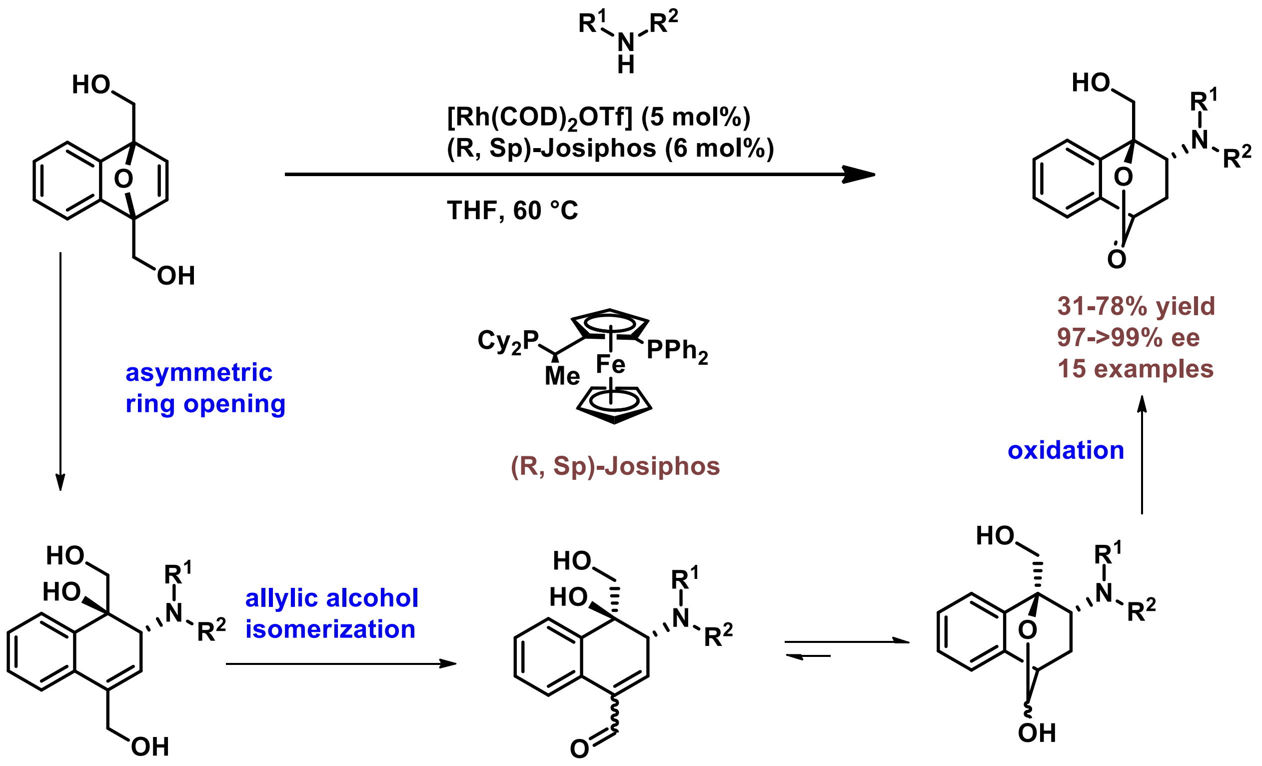
- **Asymmetric transformation catalysed by Rh(I) complexes with various diphosphines, phosphoramidites, diene or heteroatom-olefin ligands, synthesis of chiral heterocycles.**
- **Rh(II) complexes with carboxylate and carboxamidate ligand are explored in carbenoid and nitrenoid chemistry.**
- **Rh(III) complexes are less explored due to lack of design of chiral Cp ligands.**


Thank You
For Your Atten



Explain the Mechanism ??

Rh(I)-catalysed ring opening reaction via C-C bond activation



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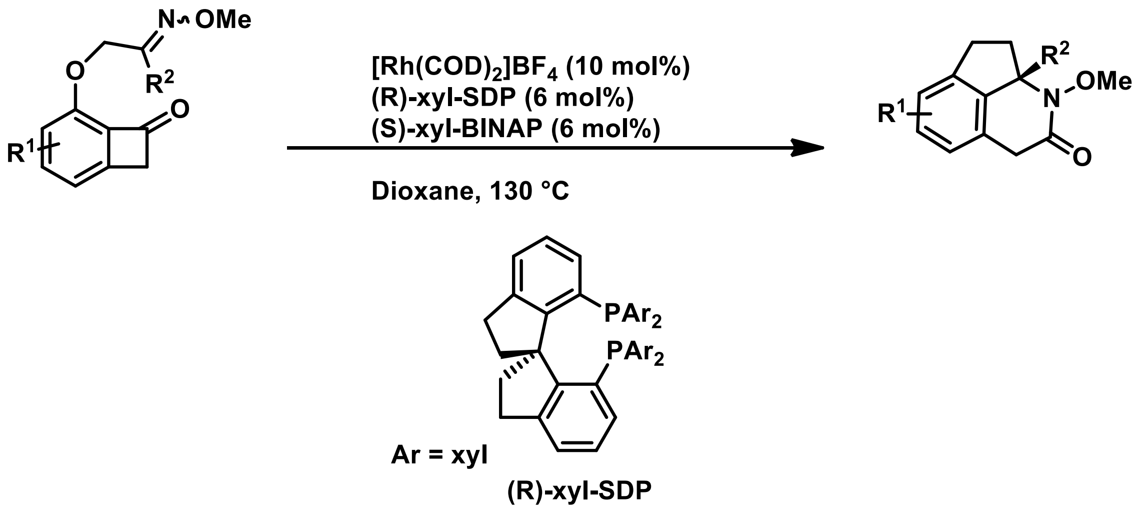
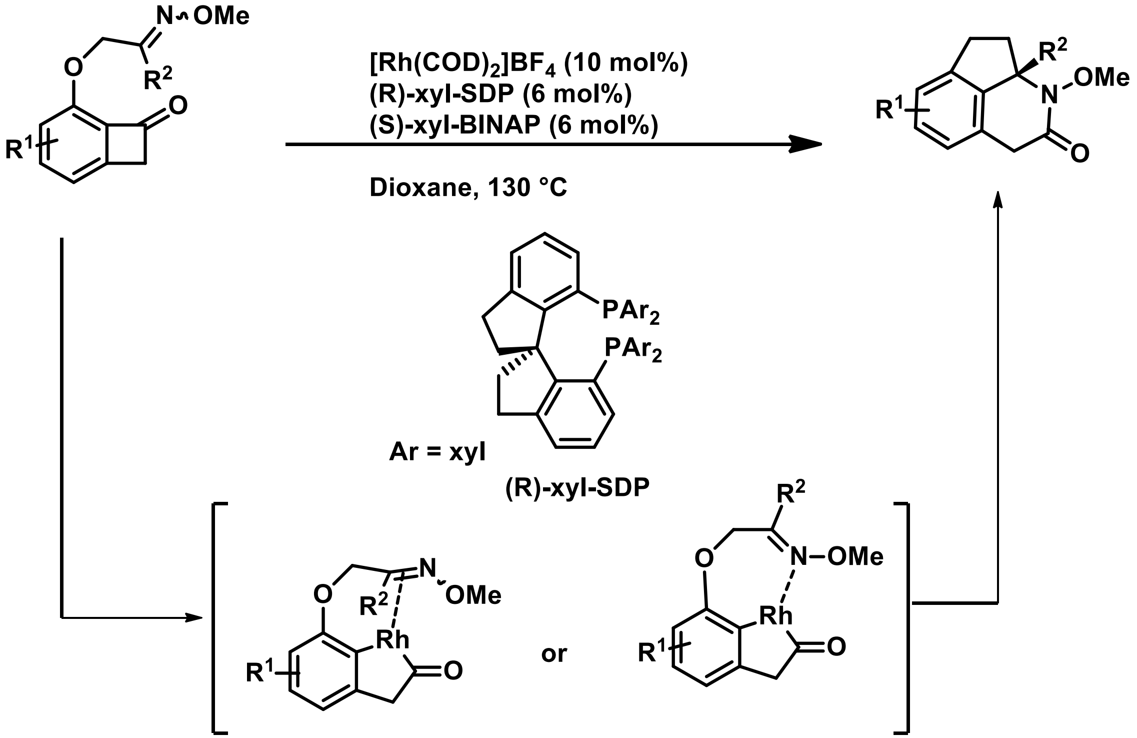
Problem



Explain the Mechanism ??

L. Deng, T. Xu, H. Li and G. Dong, *J. Am. Chem. Soc.*, **2016**, *138*, 369–374.

Solution



L. Deng, T. Xu, H. Li and G. Dong, *J. Am. Chem. Soc.*, **2016**, *138*, 369–374.

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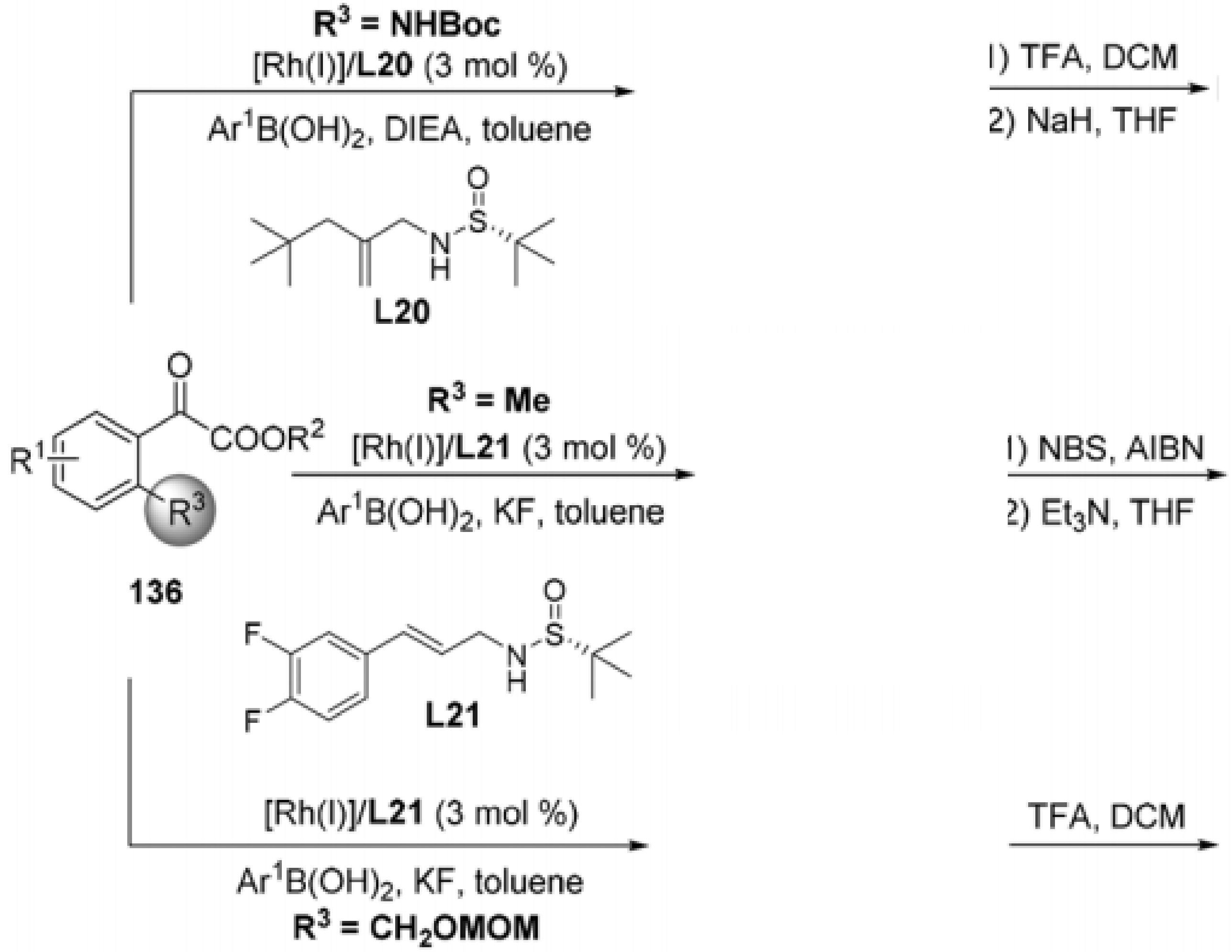


R3 = NHBoc
[Rh(I)]/L20 (3 mol %)
Ar1B(OH)2, DIEA, toluene
L20
1) TFA, DCM
2) NaH, THF
R3 = Me
[Rh(I)]/L21 (3 mol %)
Ar1B(OH)2, KF, toluene
COOR2
136
L21
1) NBS, AIBN
2) Et3N, THF
[Rh(I)]/L21 (3 mol %)
Ar1B(OH)2, KF, toluene
R3 = CH2OMOM
TFA, DCM

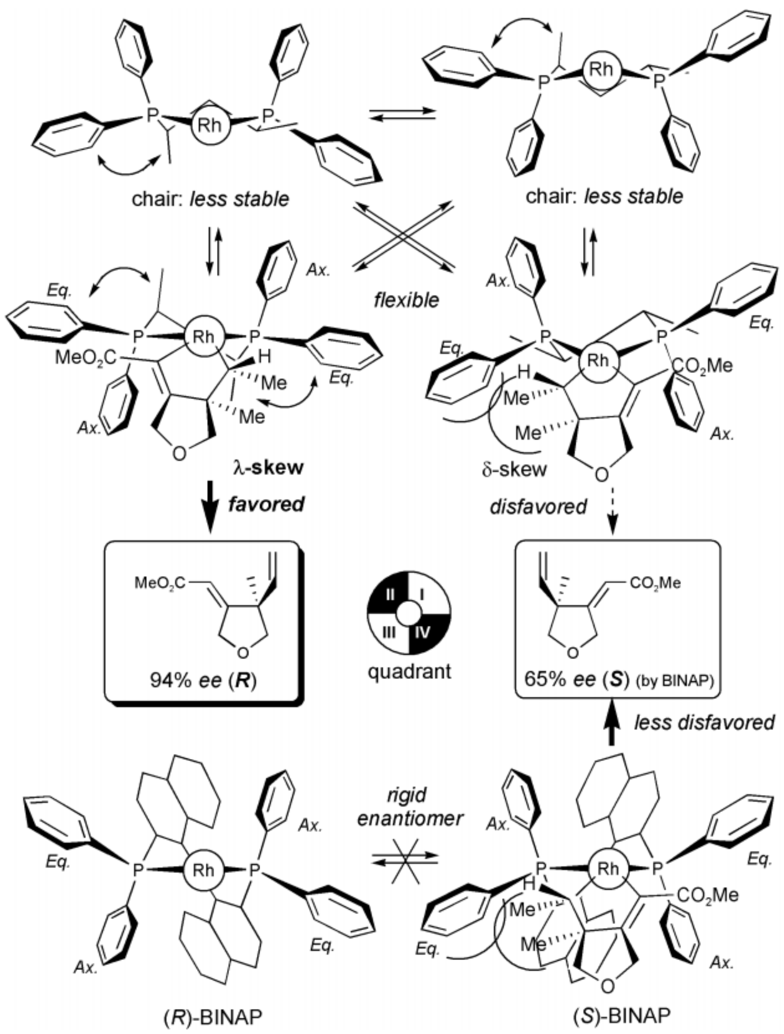
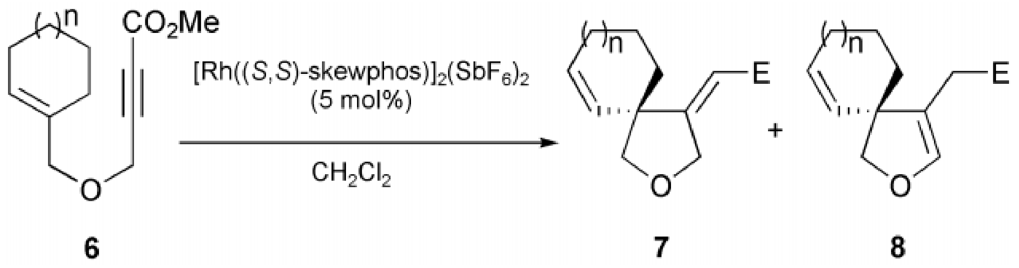


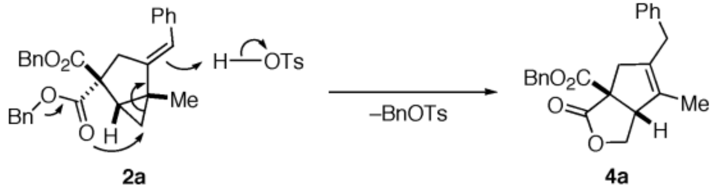
Table 2 Enantioselective spiro cyclization catalyzed by a cationic (*S,S*)-skewphos rhodium(I) complex



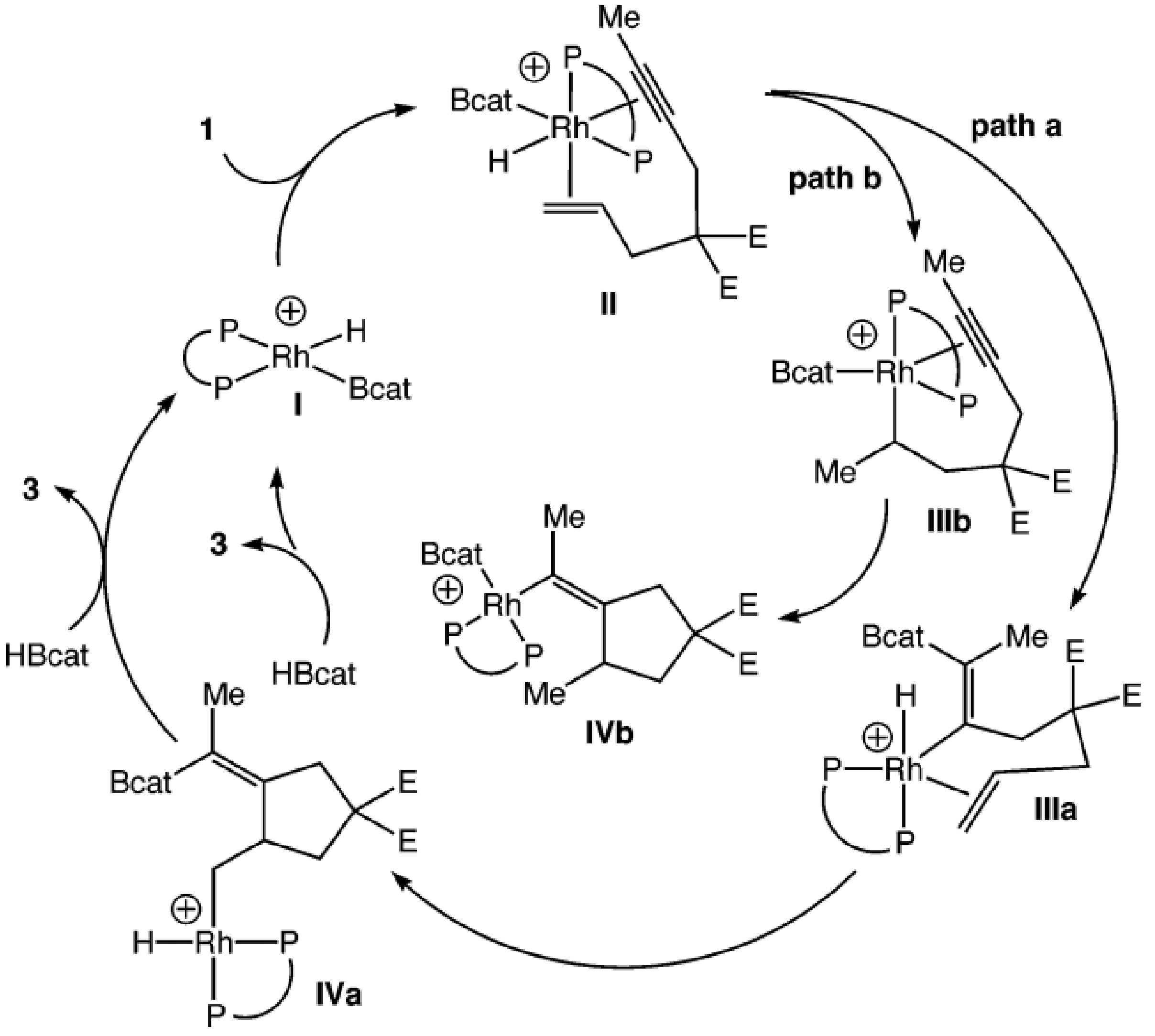
Entry	Substrate (*n*)	*T* [°C]	Reaction time	Yield (%) 7[a]	Yield (%) 8[a]
1	**6a** (1)	r.t.	46 h	53 (88)	16 (97)
2	**6a** (1)	80	40 min	4 (67)	44 (91)
3	**6b** (3)	80	40 min	6 (79)	55 (79)
4	**6b** (3)	40	17 h	12 (88)	51 (88)

[a] Ee (%) in parentheses.

Scheme 6

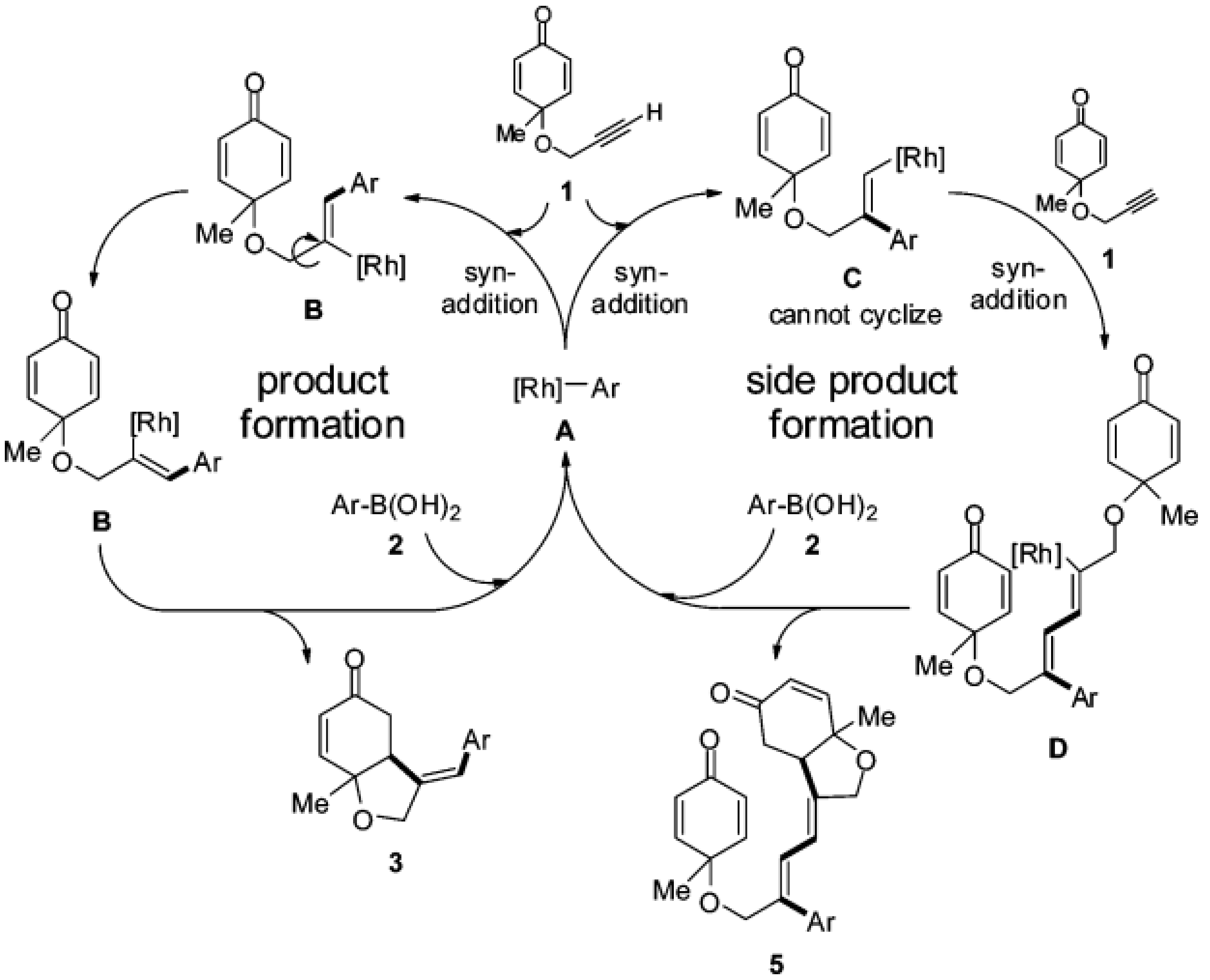


Scheme 3

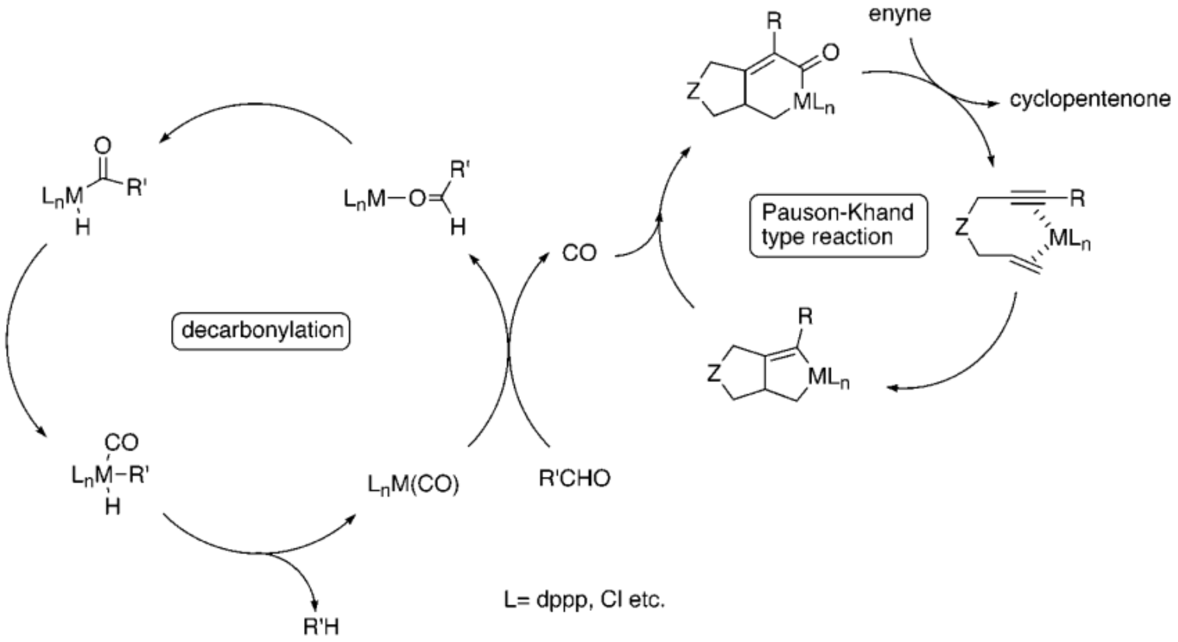


1
Me
P
Bcat
Rh
H
P
E
E
II
path b
path a
Me
P
Bcat
Rh
P
Me
E
E
IIIb
P
Rh
H
P
Bcat
I
3
3
HBcat
HBcat
Me
Bcat
Rh
P
P
E
E
Me
IVb
Bcat
Me
E
E
H
P
Rh
P
IIIa
Me
Bcat
E
E
H
Rh
P
P
IVa

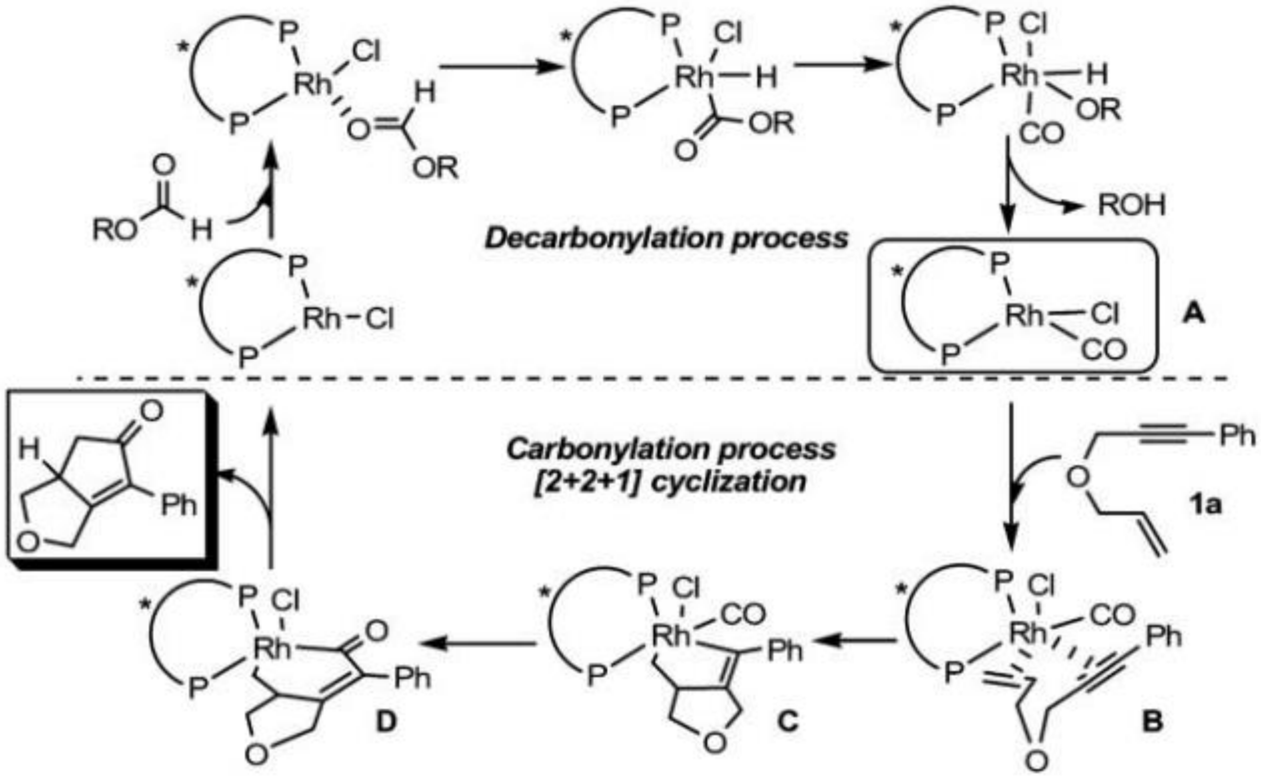
Scheme 3. Proposed Catalytic Cycle

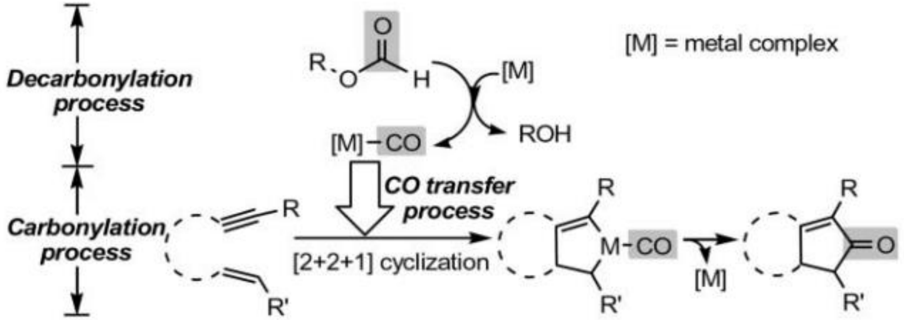


Scheme 1



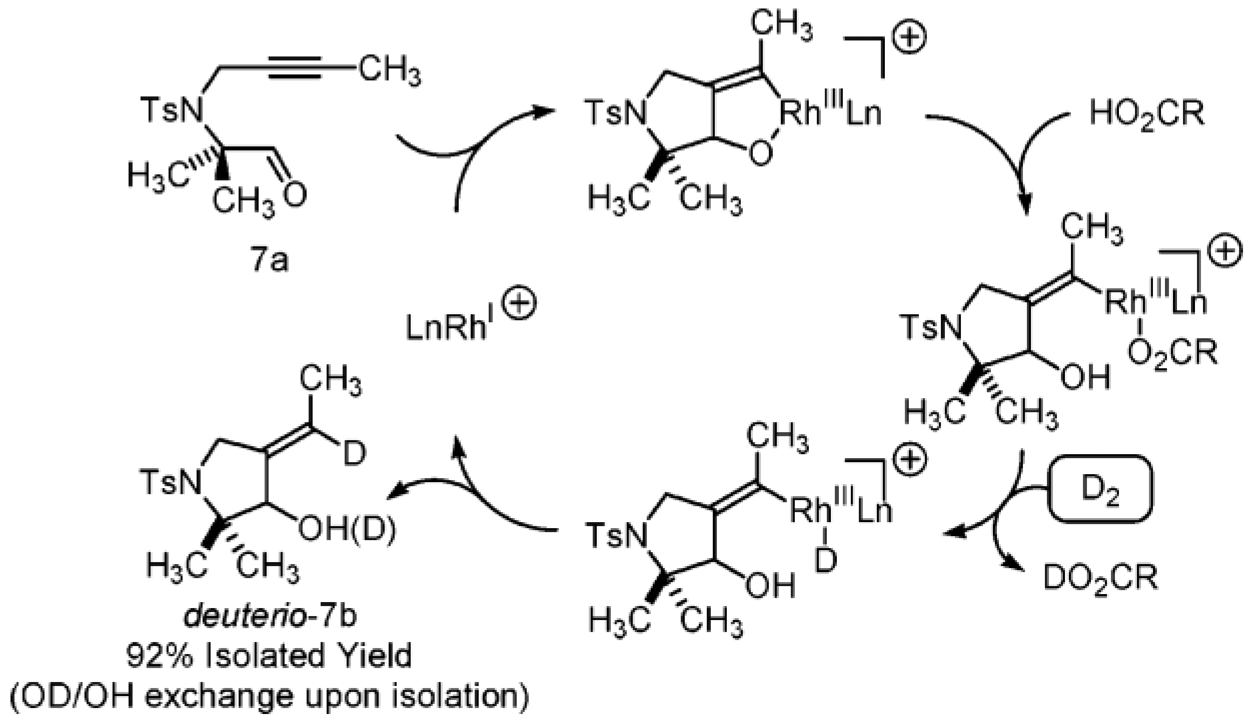
decarbonylation
Pauson-Khand type reaction
enyne
cyclopentenone
CO
R'CHO
R'H
L= dppp, Cl etc.





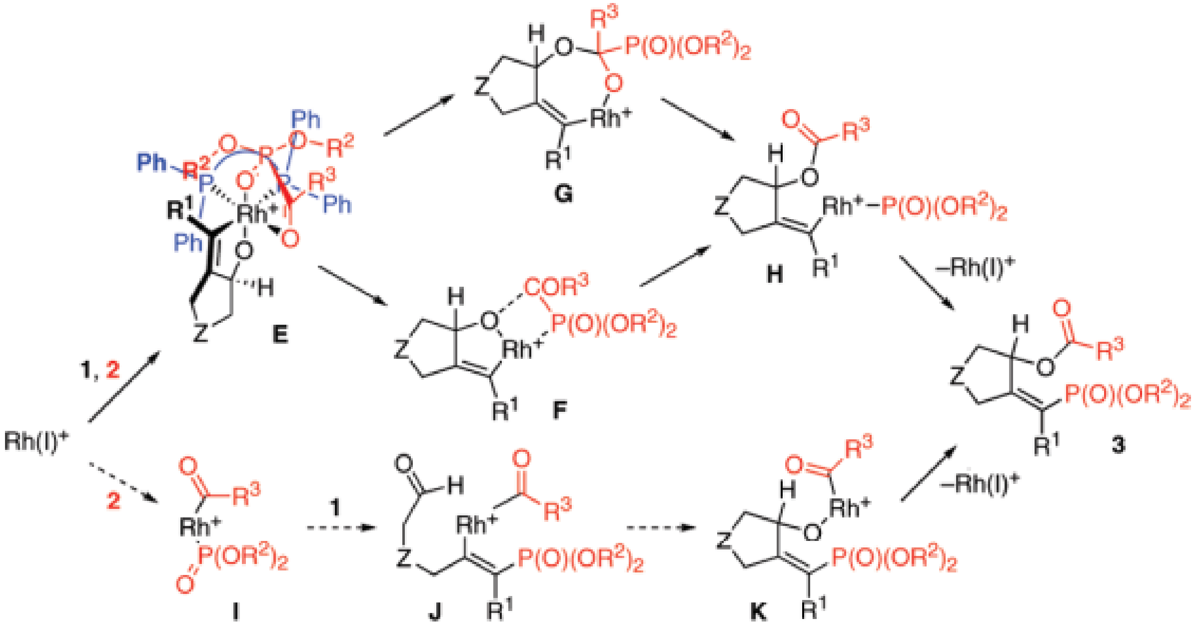
Scheme 1 Cooperative dual catalysis.

Scheme 1. Plausible Catalytic Cycle as Supported by ^{2}H-Labeling

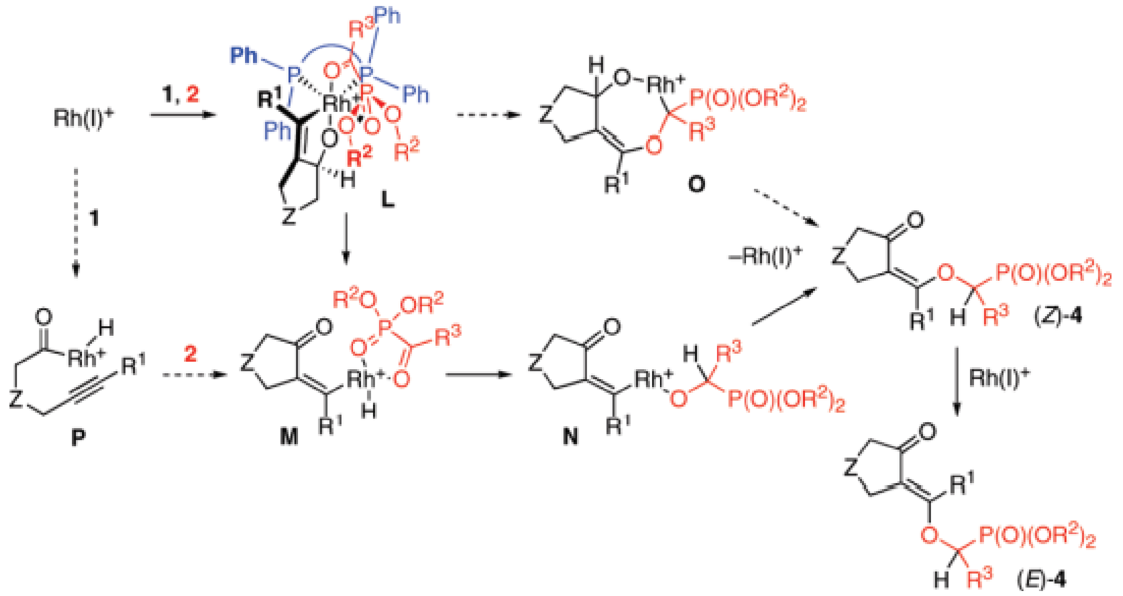


ABSTRACT: It has been established that a cationic rhodium(I)/(*R*)-H_8-BINAP or (*R*)-Segphos complex catalyzes two modes of enantioselective cyclizations of γ-alkynylaldehydes with acyl phosphonates via C−P or C−H bond cleavage. The ligands of the Rh(I) complexes and the substituents of both γ-alkynylaldehydes and acyl phosphonates control these two different pathways.

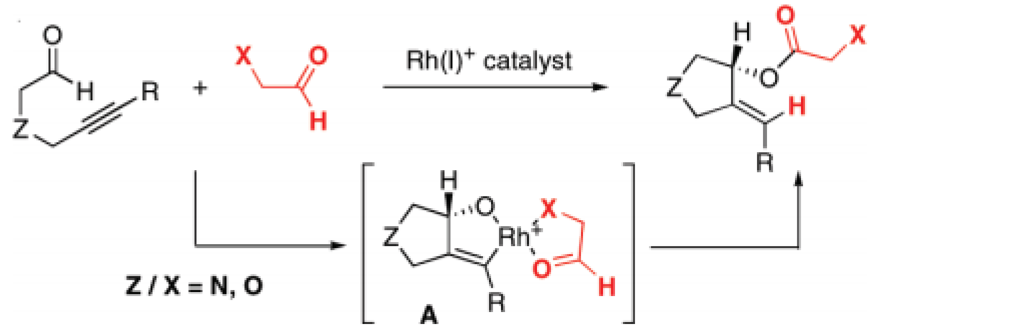
Scheme 4. Possible Mechanism for Formation of 3[a]



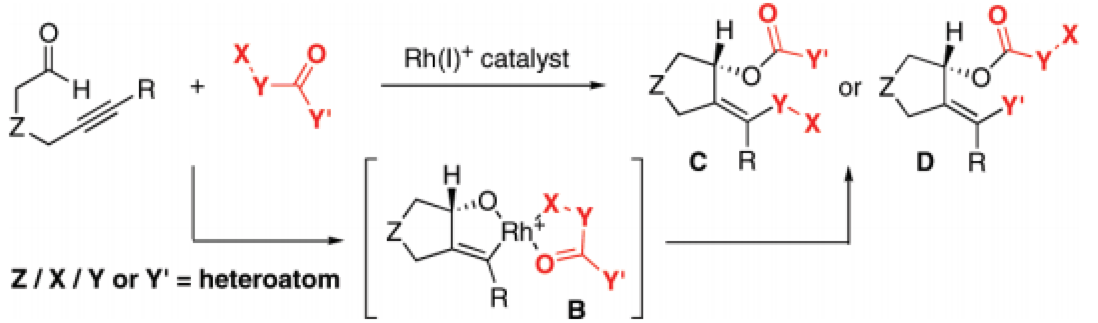
Scheme 5. Possible Mechanism for Formation of 4[a]



Scheme 1



Scheme 2



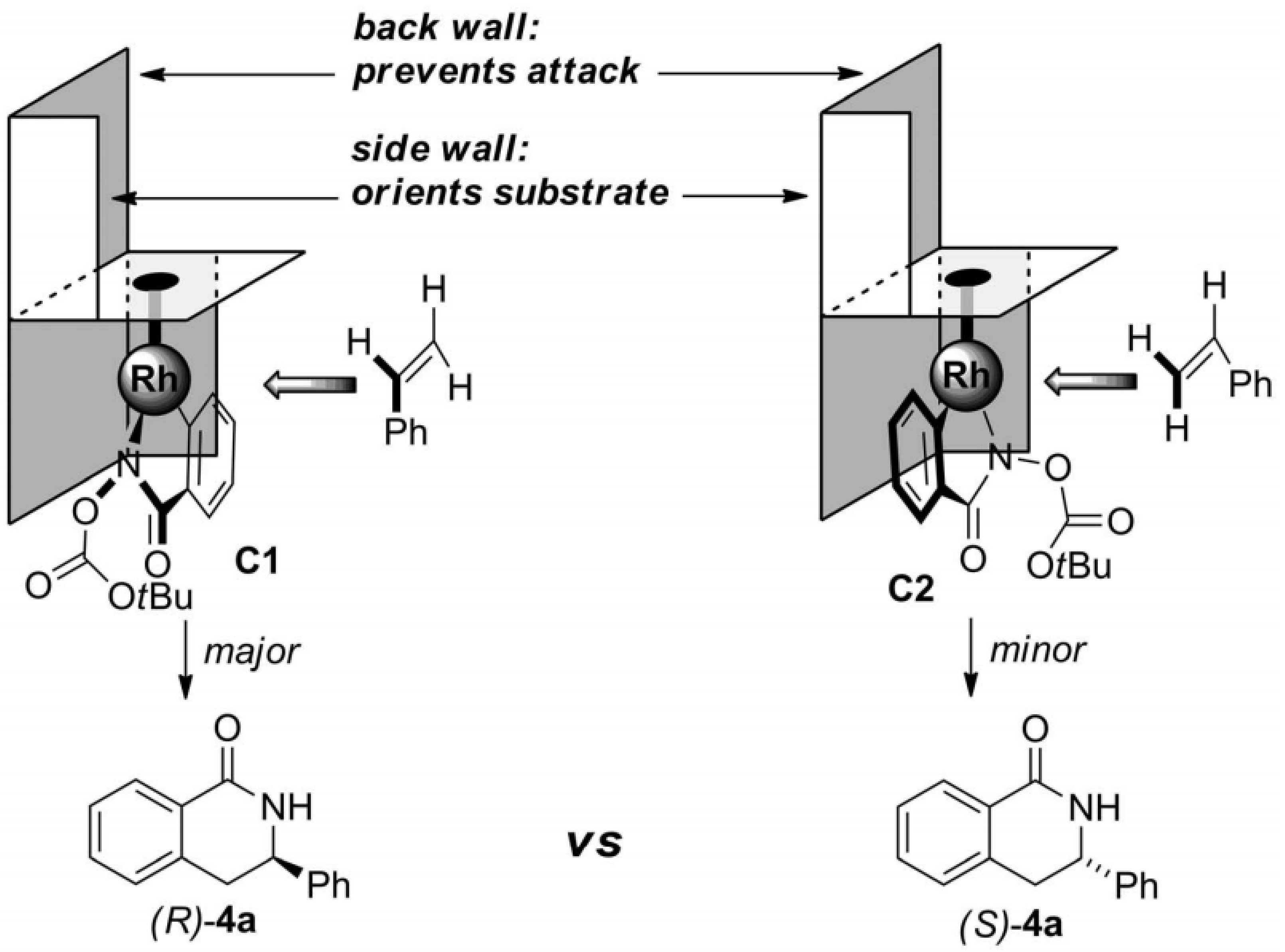
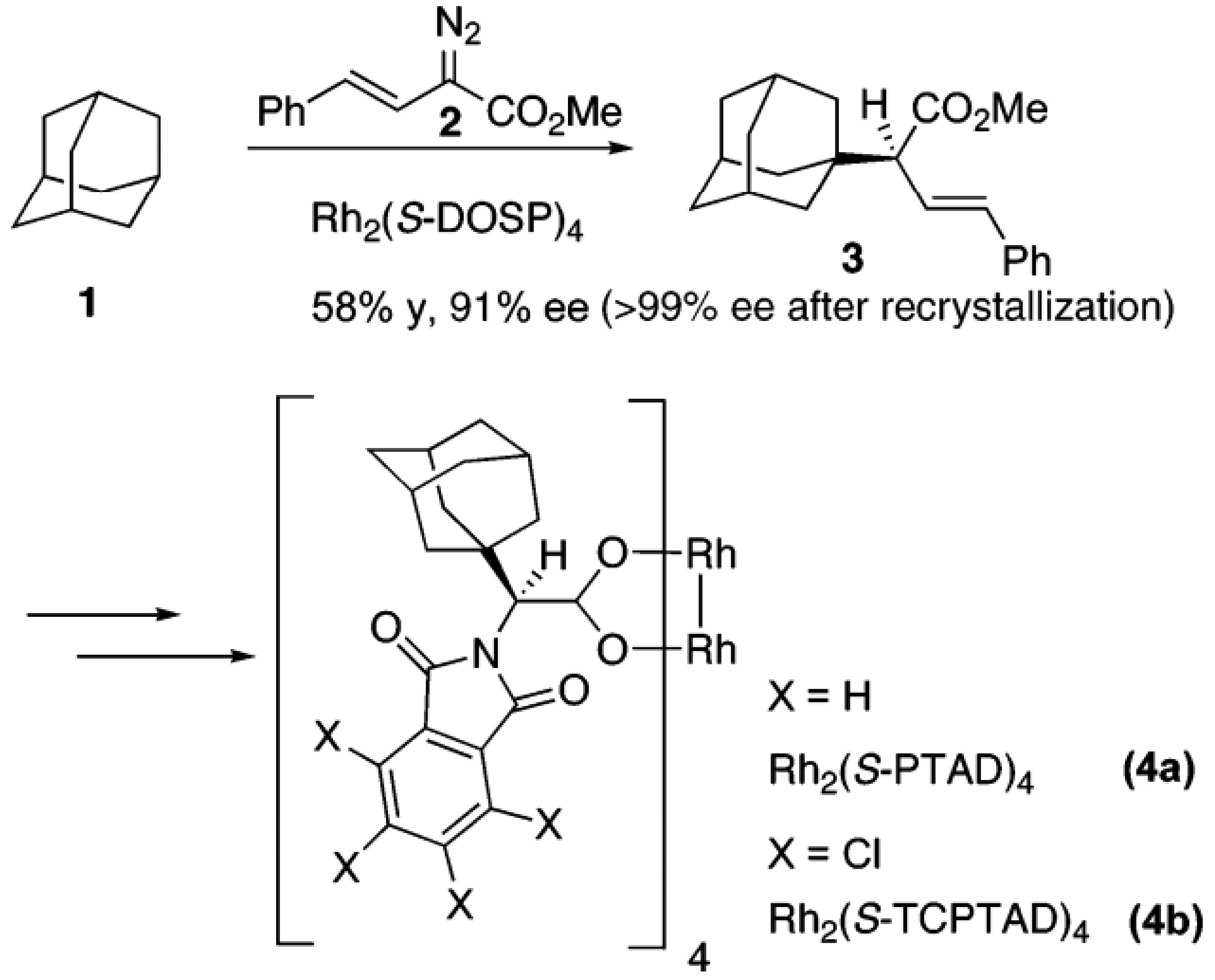


Fig. 3. Postulated model for the stereochemical preference with complex **1c**.

Scheme 2. Synthesis of Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-TCPTAD)$_4$



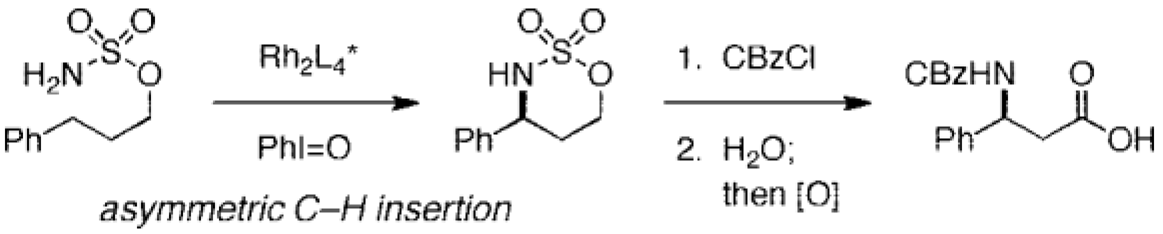
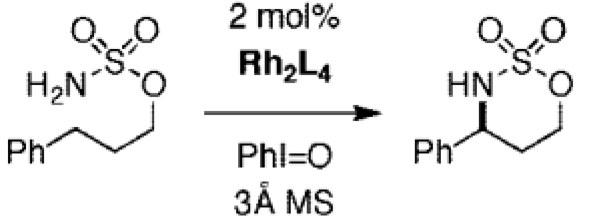
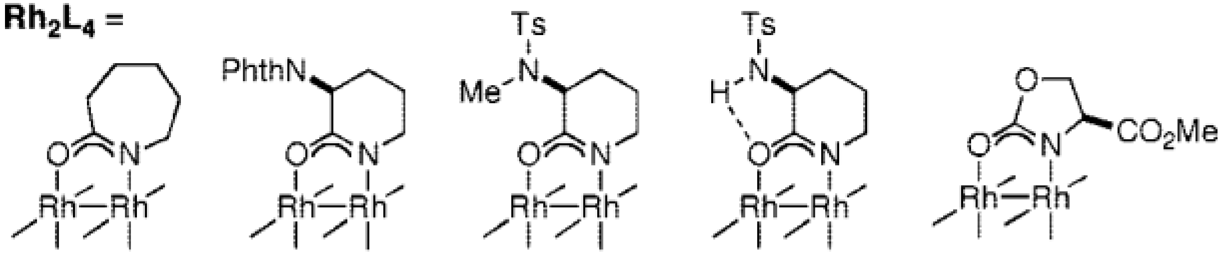


Figure 1. Optically active amine derivatives through C−H amination.



Rh_2L_4	$E_{ox}^{(II/II\rightarrow II/III)}$	% yield	% ee
1	11 mV	< 5	–
2	120 mV	22	54
3	242 mV	< 5	nd
4	**330 mV**	**85**	**92**

Rh_2L_4 =



1 **2** **3** **4** **5**

Figure 2. Evaluating catalyst performance for C−H amination.

Catalytic enantioselective C-C activation applied to total synthesis

Frontiers in Organic Chemistry
Part III: Stereochemistry
(Prof. Jérôme Waser, Prof. Xile Hu)

Session III
May 22, 2019

Vitalii Smal

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2. Enantioselective C – C activation of strained molecules:
   - 2.1. Via oxidative addition
     - 2.1.1. Oxidative addition to cyclopropane derivatives
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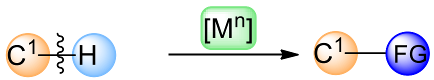
   - 2.2. Via β-carbon elimination
     - 2.2.1. β-carbon elimination of cyclobutanole derivatives
3. Enantioselective C – C activation of unstrained molecules:
   - 3.1. Oxidative addition to C – CN bonds
   - 3.2. β-carbon elimination of tertiary alcohols
4. Conclusion.
5. Questions.

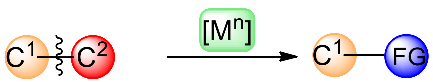
1. Introduction

Direct functionalization of C-C and C-H bonds = streamlined access to complex targets

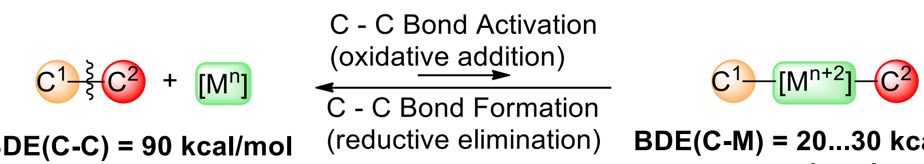
C - H bond activation: well establsihed



C - C bond activation: less developed



Problem: thermodynamic preference of C-C bond formation



BDE(C-C) = 90 kcal/mol per bond

BDE(C-M) = 20...30 kcal/mol per bond

<u>Other difficult points in C-C activation:</u>

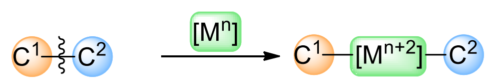
1. Highly directed nature of the bond, less favorable orbital interaction with TM.
2. High steric encumbrance.
3. C-C bond are statistically less abundant than C-H.

<u>Basic strategy:</u>

1. Increase the energy state of the starting materials.
2. Lower the energy state of the C – C bond cleaved complexes

<u>Main Mechanisms of C – C activation:</u>[1-3]

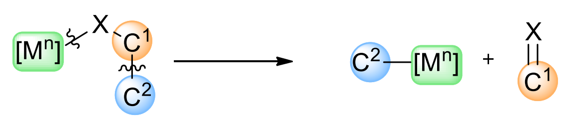
Path A: Oxidative Addition



<u>Can be favoured by:</u>

1) Strain release (small rings);
2) Aromatization of the product;
3) Presence of a proximal directing group (chelation assistance)

Path B: β-Carbon Elimination

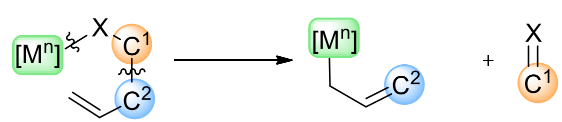


X = C,N,O

<u>Can be favoured by:</u>

1) Strain release;
2) Formation of strong C=X bond;

Path C: Retro-Allylation

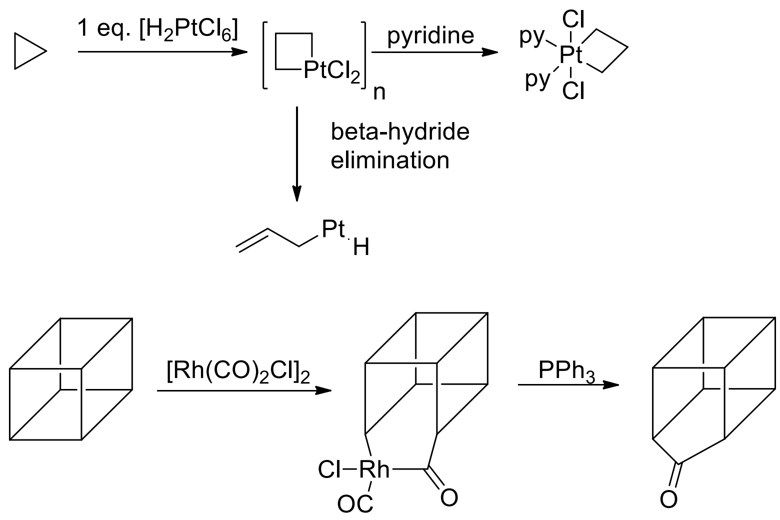


(1) L. Souillart, N. Cramer *Chem. Rev*. **2015**, *115*, 9410. (2) F. Chen, T. Wang, N. Jiao *Chem. Rev*. **2014**, *114*, 8613. (3) G. Fumagalli, S. Stanton, J.F. Bower *Chem. Rev*. **2017**, *117*, 9404.

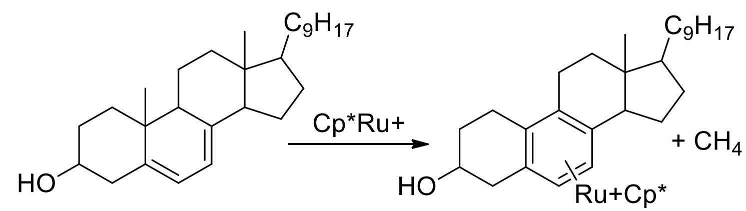
1. Introduction

Pioneering examples of C – C activation:[1-4]

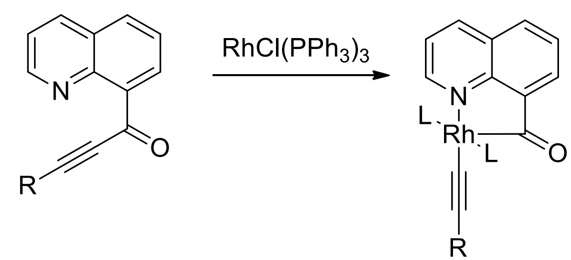
1) Strained starting materials:[1,2]



2) Aromatization:[3]



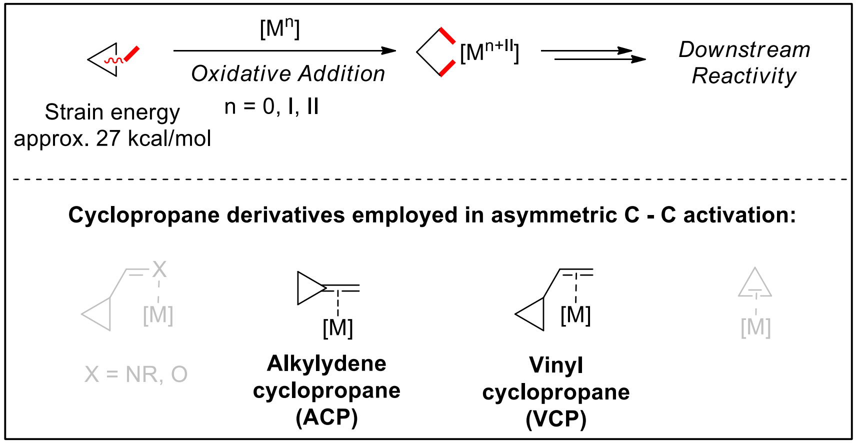
3) Chelation assistance:[4]



(1) C.F.H Tipper *J. Chem. Soc.* **1955,** 2043. (2) D.M. Adams, J. Chatt, R.G. Guy, N. Sheppard *J. Chem. Soc.* **1961,** 738. (3) L. Cassar, P.E. Eaton, J. Halpern *J. Am. Chem. Soc.* **1970,** *92*, 3515. (4) J.W. Suggs, S.D. Cox *J. Organomet. Chem.* **1981**, *221*, 199.

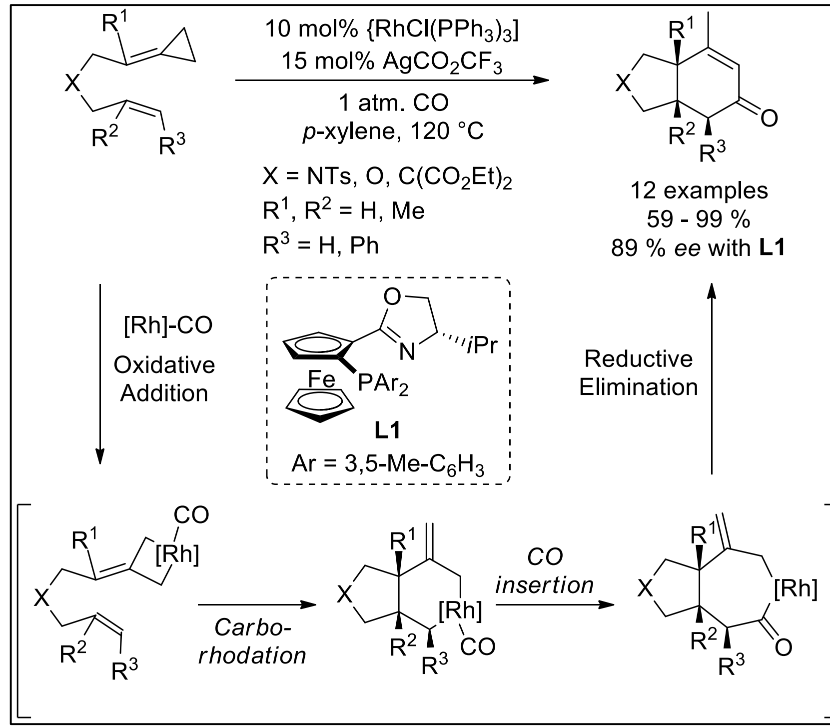
2. Enantioselective C – C activation of strained molecules

2.1.1. Oxidative addition to cyclopropane derivatives.



- Selective activation of the distal C – C bond of ACP
- Carborhodation is a rate-determining step
- Without chiral ligand, reaction provides *cis*-bicycles in high dr.

Rh-catalyzed [3+2+1] carbocyclization:[1]

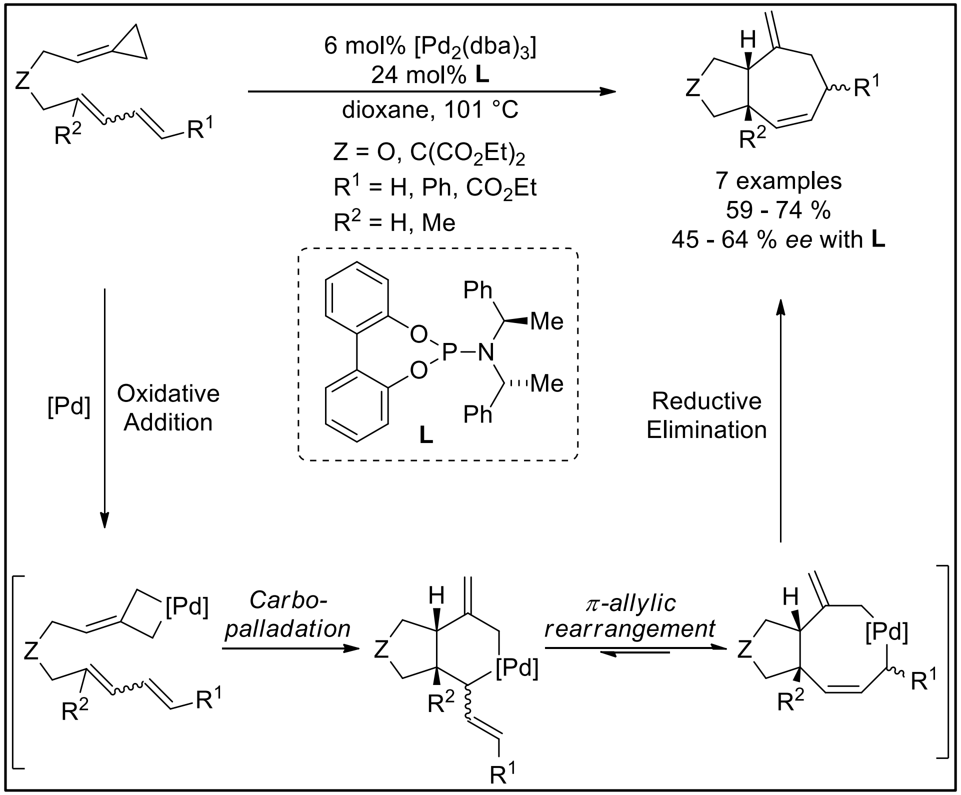


(1) S. Mazumder, D. Shang, D.E. Negru, M.-H. Baik, P.A. Evans *J. Am. Chem. Soc.* **2012,** *134,* 20569.

2. Enantioselective C – C activation of strained molecules

2.1.1. Oxidative addition to cyclopropane derivatives.

Pd-catalyzed [4+3] cycloaddition of ACP:[1]



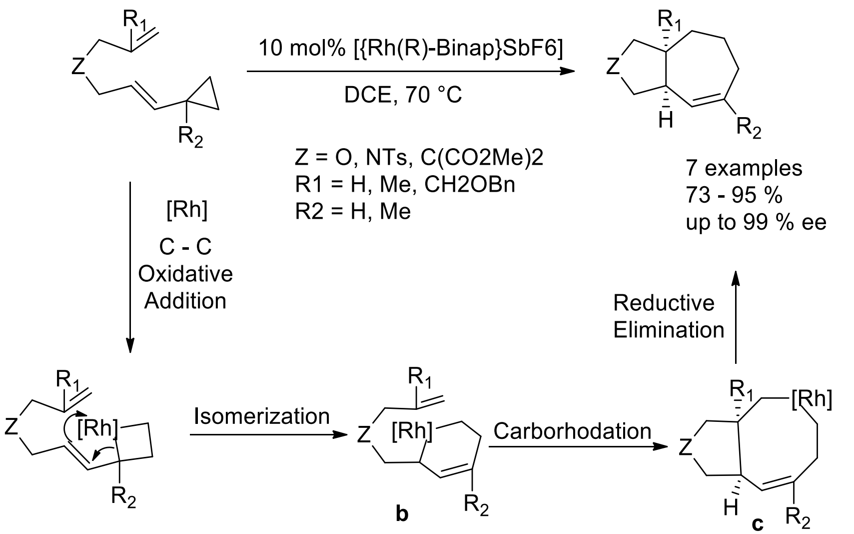
- Selective activation of the distal C – C bond of ACP
- Reductive elimination is preceded by π-allylic rearrangement; order of steps is controlled by ligand

(1) M. Gulias, J. Duran, F. Lopez, L.Castedo, J.L. Mascarenas *J. Am. Chem. Soc.* **2007,** *129,* 11026.

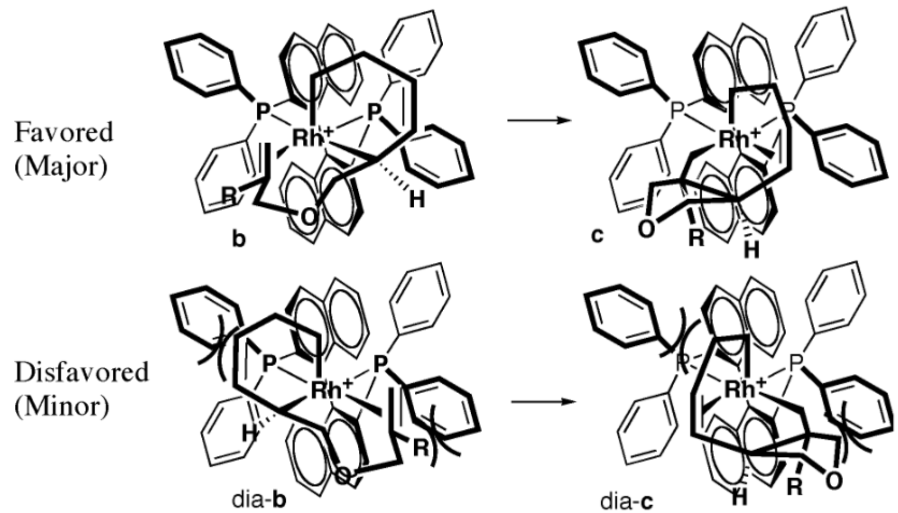
2. Enantioselective C – C activation of strained molecules

2.1.1. Oxidative addition to cyclopropane derivatives.

Rh-catalyzed [5+2] cycloaddition of vinylcyclopropanes:[1]



Selectivity model:



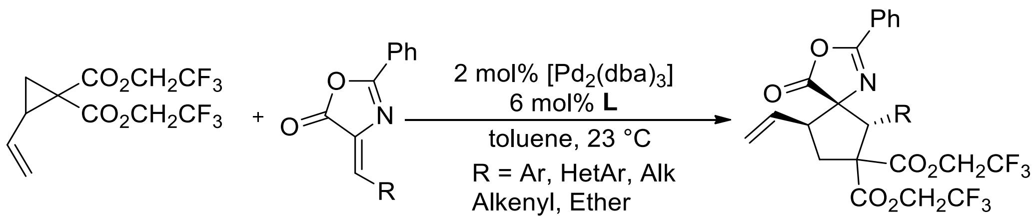
- VCP serves as a **5-carbon synthon**
- Good reactivity and enantioselectivity for alkene-substituted VCP's
- The catalytic system could not give high ee with alkyne substrates

(1) P. A. Wender, L. O. Haustedt, J. Lim, J. A. Love, T.J. Williams, J.-Y. Yoon *J. Am. Chem. Soc.* **2006**, *128*, 6302.

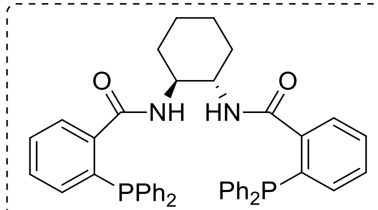
2. Enantioselective C – C activation of strained molecules

2.1.1. Oxidative addition to cyclopropane derivatives.

Trost: Pd-catalyzed [3+2] cycloaddition of donor-acceptor VCP's and azlactones[1]



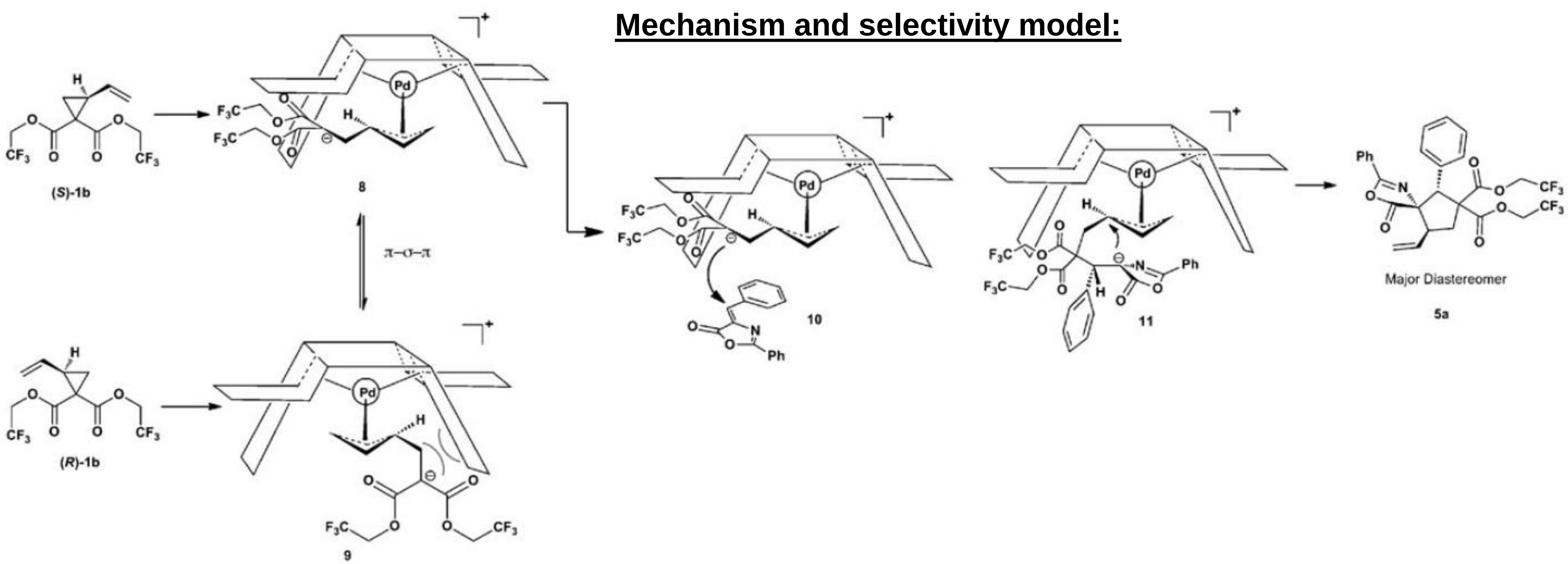
13 examples
63 - 87 %
63 - 98 % ee
up to 19:1 d.r.



L

- VCP serves as a **<u>3-carbon synthon</u>**
- Use of fluorinated ester groups is needed for high yield and ee

<u>Mechanism and selectivity model:</u>

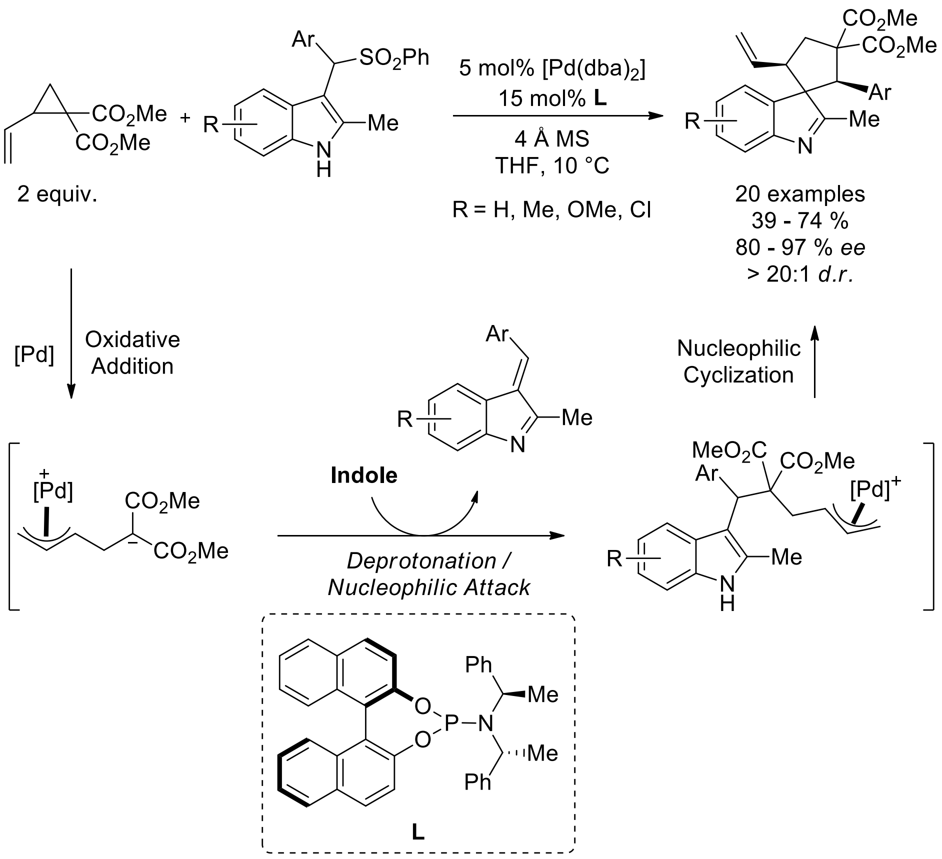


(1) B.M. Trost, P.J. Morris *Angew. Chem., Int. Ed.* **2011,** *50,* 6167.

2. Enantioselective C – C activation of strained molecules

2.1.1. Oxidative addition to cyclopropane derivatives.

He and Liu: Pd-catalyzed [3+2] cycloaddition of donor-acceptor VCP's and imines[1]



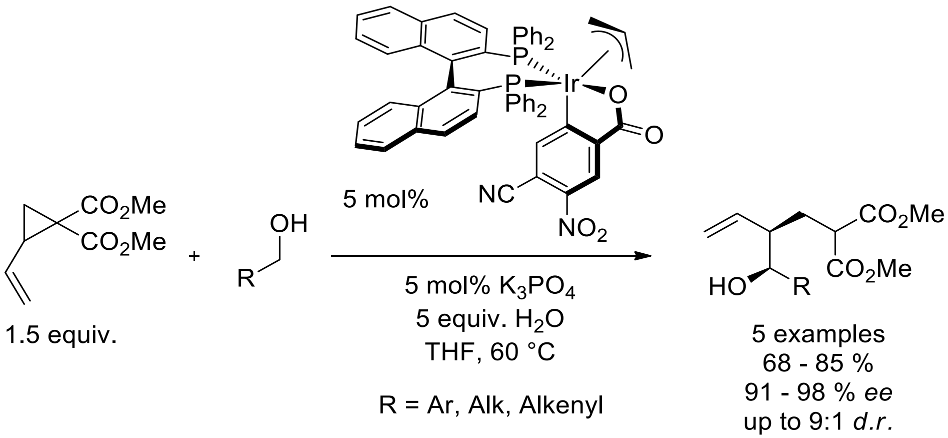
- Imine is formed *in situ* by N-deprotonation of the corresponding indole
- VCP serves as a 3-carbon synthon
- Products – chiral spiroindolenines

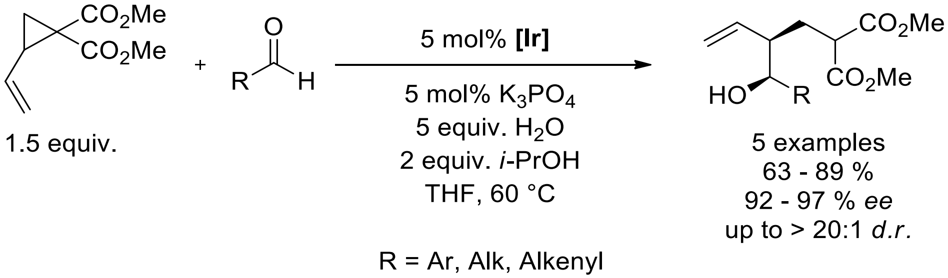
(1) Z.-S. Liu, W.-K. Li, T.-R. Kang, L. He, Q.-Z. Liu.*Org. Lett.* **2015,** *41,* 150.

2. Enantioselective C – C activation of strained molecules

2.1.1. Oxidative addition to cyclopropane derivatives.

Krieshe: Ir-catalyzed allylation of aldehydes[1]

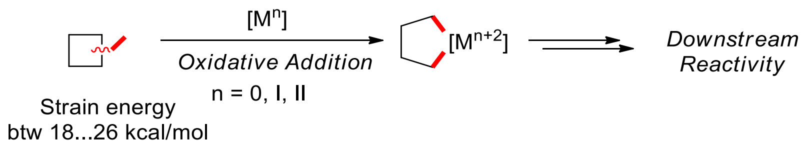




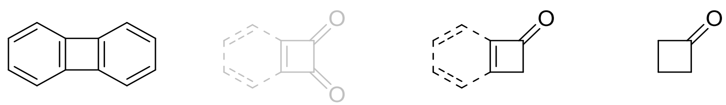
- C – C activation leads to nucleophilic π-allyl iridium - umpolung
- Aldehyde can be also generated from corresponding primary alcohol via β-H elimination on Ir

(1) J. Moran, A. G. Smith, R. M. Carris, J. S. Johnson, M. J. Krische *J. Am. Chem. Soc.* **2011**, *133*, 18618.

2.1.2. Oxidative addition to cyclobutane derivatives

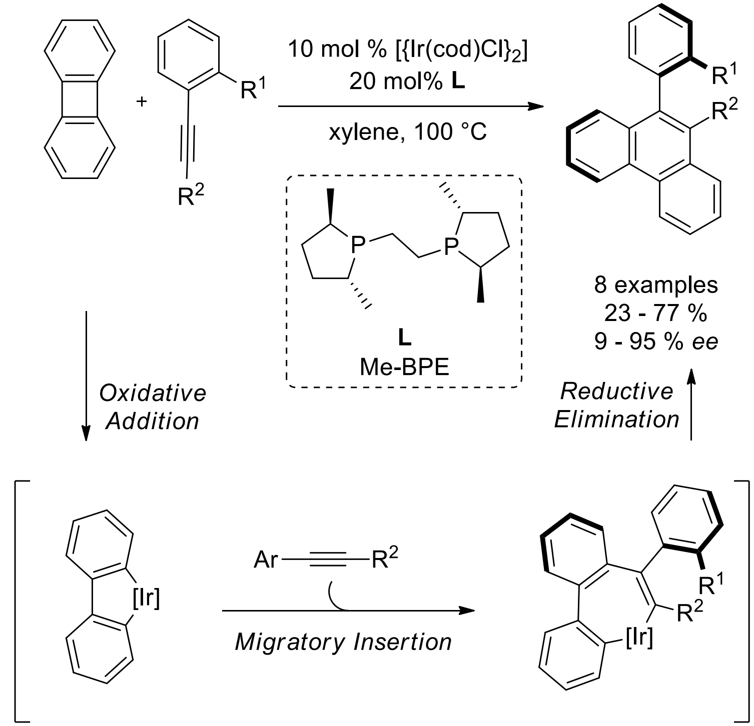


Cyclobutane derivatives employed in asymmetric C - C activation



- Construction of axial chirality via C – C activation
- ee is very dependent on substitution of the alkyne

Ir-catalyzed [4+2] cycloaddition of biphenylene with alkynes:[1]



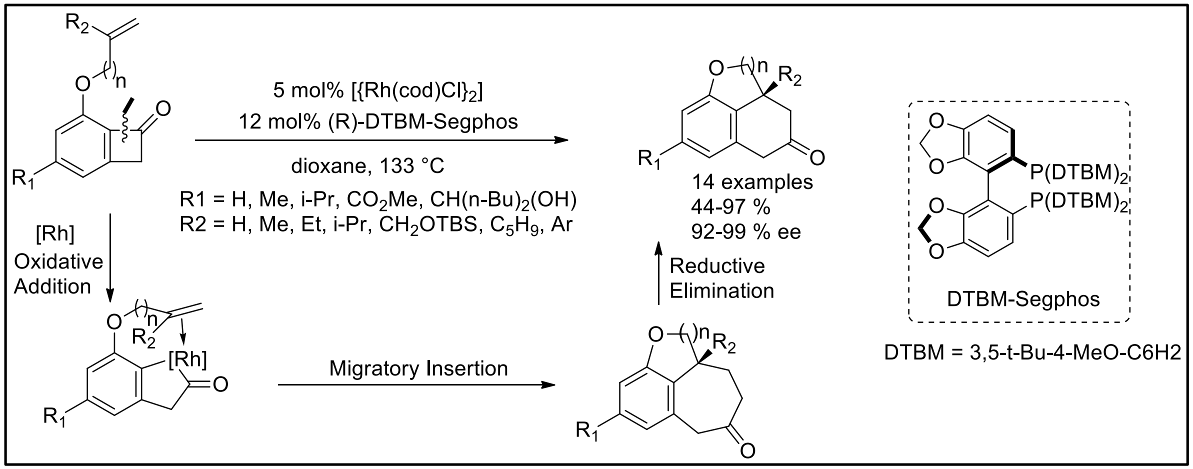
R^1 = Me, OMe, CF_3
R^2 = Me, CH_2OMe, CH_2OTBS, 4-OMe-C_6H_5, 4-CO_2Et-C_6H_5

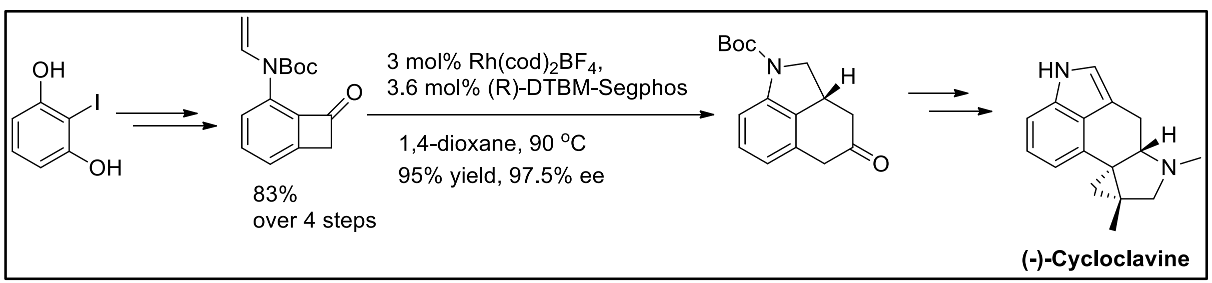
(1) T. Shibata, G. Nishizawa, K. Endo *Synlett* **2008**, 765.

2. Enantioselective C – C activation of strained molecules

2.1.2. Oxidative addition to cyclobutane derivatives

Dong: Rh-catalyzed carboacylation of olefins initiated by C – C activation of cyclobutenone[1]
(“cut and sew” process)





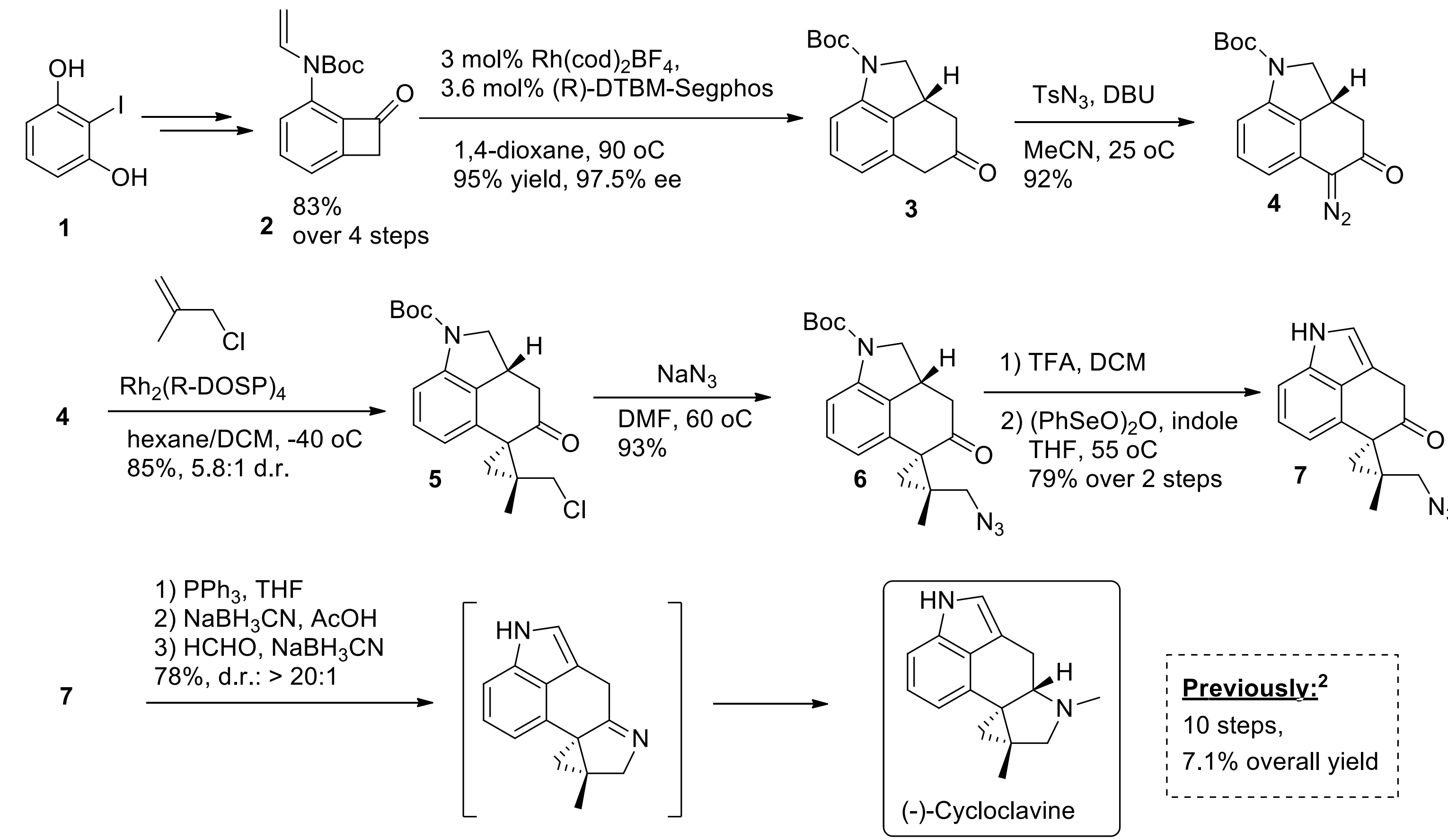
- Use of bidentate ligand with large bite angle helps to minimize decarbonylation of the starting material
- Insertion of terminal, di- or trisubstituted olefins is well tolerated
- The aromatic ring in the product can be further reduced giving saturated polycycles with 4 contiguous stereocenters
- This methodology was further expanded to afford chiral fused indolines and total synthesis of (–)-Cycloclavine A

(1) Xu, T.; Ko, H. M.; Savage, N. A.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 20005.

2. Enantioselective C – C activation of strained molecules

2.1.2. Oxidative addition to cyclobutane derivatives

Dong: asymmetric C – C activation as a key step in total synthesis of (–)-Cycloclavine[1]



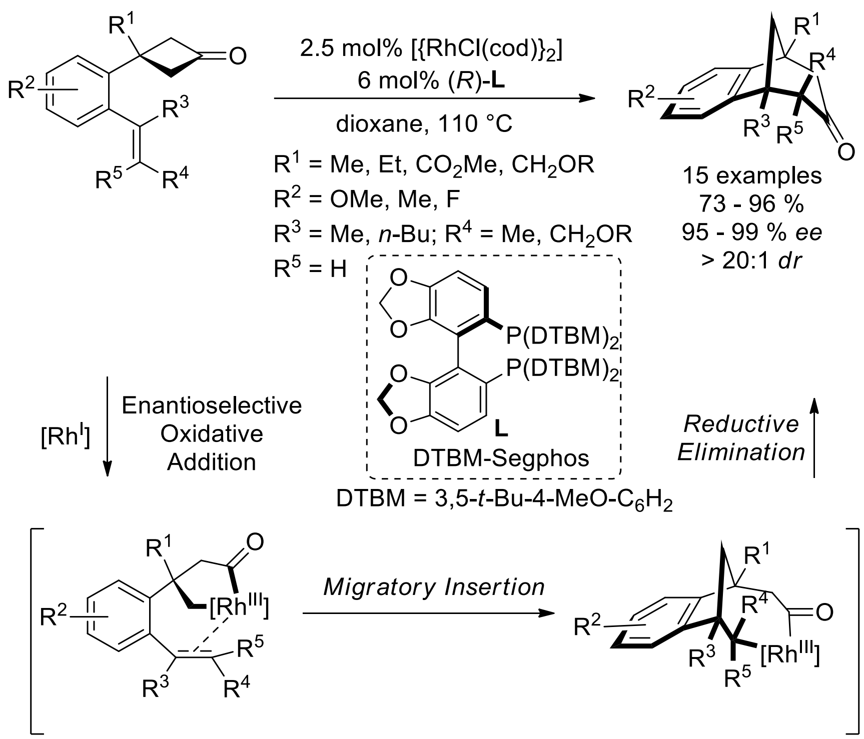
10 steps starting from **1**
30% overall yield

(1) L. Deng, M. Chen, G. Dong *J. Am. Chem. Soc.* **2018,** *140,* 9652. (2) S.R. McCabe, P. Wipf *Angew. Chem. Int. Ed.* **2017**, *56*, 324.

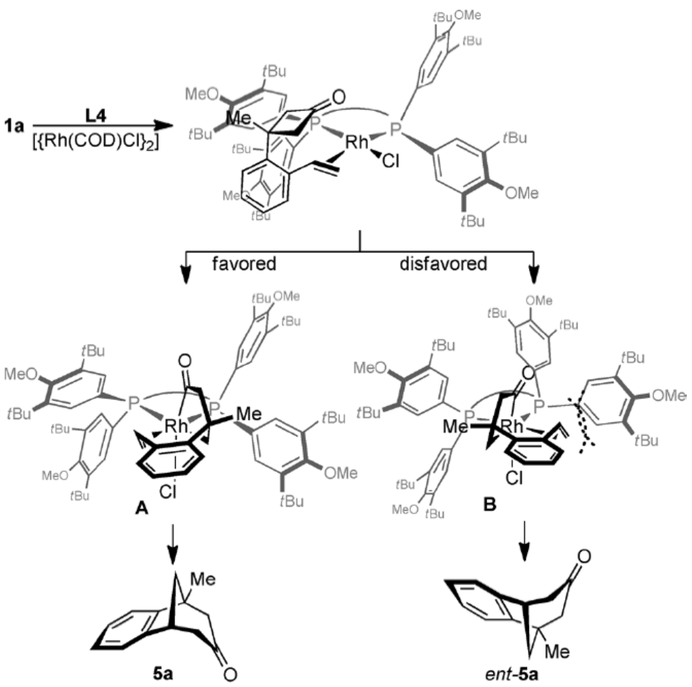
2. Enantioselective C – C activation of strained molecules

2.1.2. Oxidative addition to cyclobutane derivatives

Cramer: asymmetric C – C activation of cyclobutanones[1]



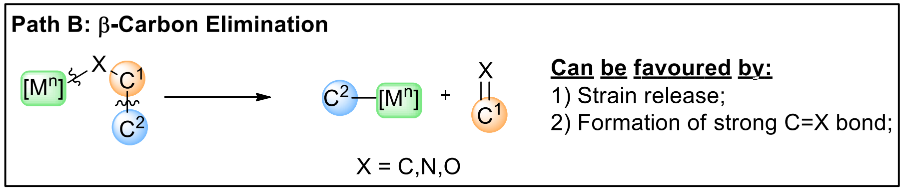
Selectivity model:



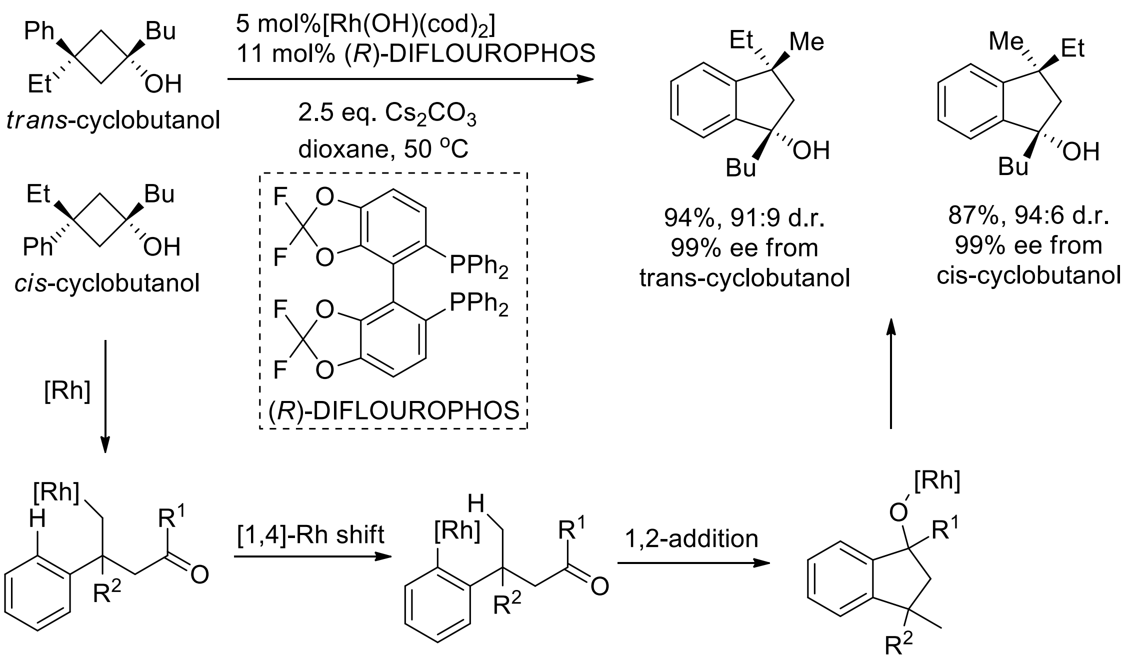
(1) L. Souillart, E. Parker, N. Cramer *Angew. Chem., Int. Ed.* **2014,** *53,* 3001.

2. Enantioselective C – C activation of strained molecules

2.2.1. β-carbon elimination of cyclobutanole derivatives



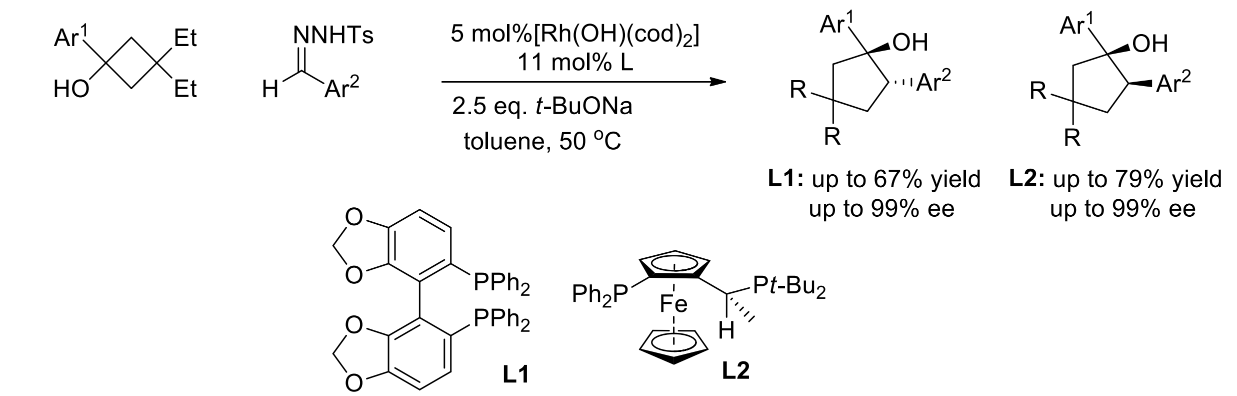
Cramer: C – C/C – H activation sequence of cyclobutanones[1]



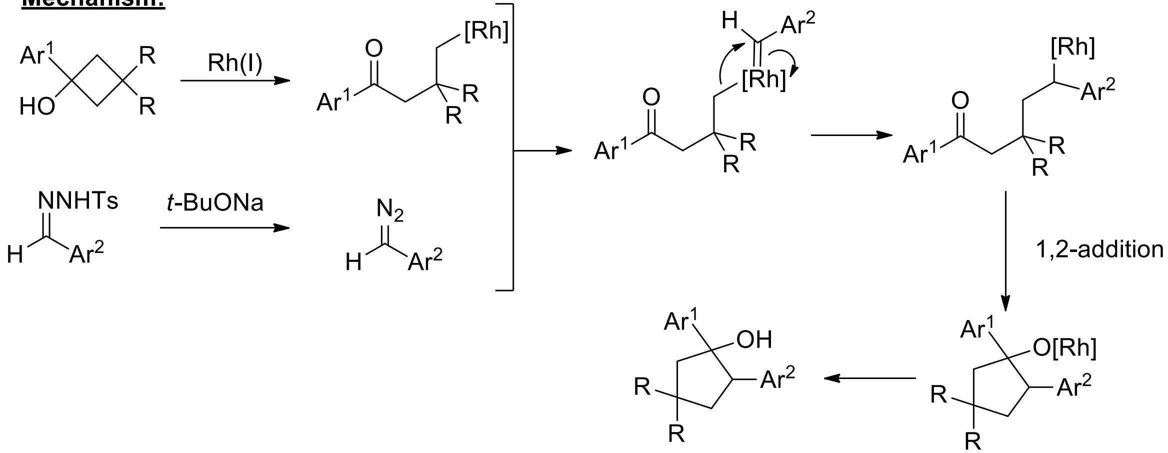
(1) T. Seiser, O. A. Roth, N. Cramer *Angew. Chem., Int. Ed.* **2009,** *48*, 6320.

2.2.1. β-carbon elimination of cyclobutanole derivatives

Murakami: combining β-carbon elimination with carbene insertion[1]



Mechanism:

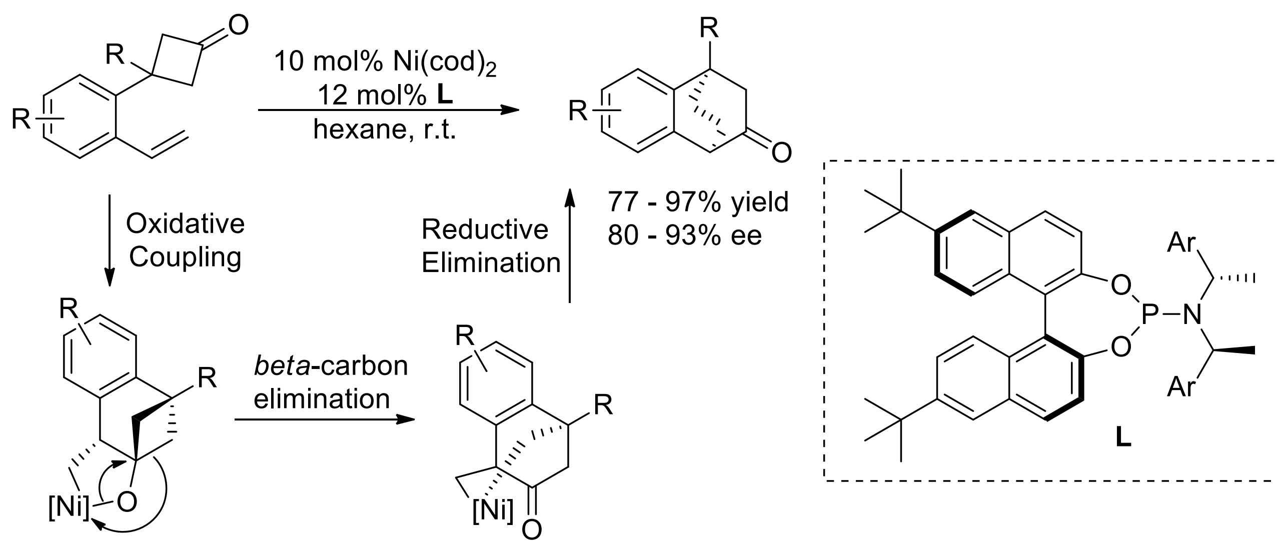


(1) A. Yada, S. Fujita, Murakami M. *J. Am. Chem. Soc.* **2014,** *136*, 7217.

2. Enantioselective C – C activation of strained molecules

2.2.1. β-carbon elimination of cyclobutanole derivatives

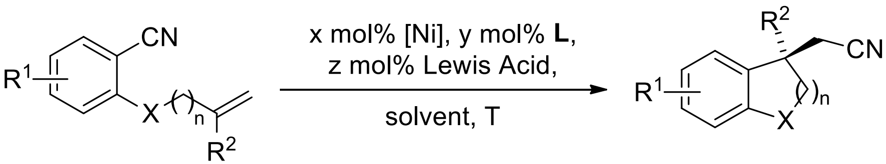
Murakami: Ni-catalyzed intramolecular [4+2] cycloaddition of cyclobutanones with styrenes[1]



(1) L. Liu, N. Ishida, M. Murakami *Angew. Chem., Int. Ed.* **2012,** *51,* 2485.

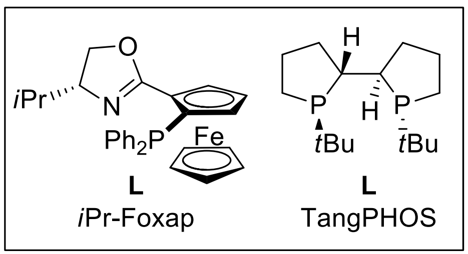
3. Enantioselective C – C activation of unstrained molecules:

3.1. Oxidative addition to C – CN bonds[1,2]



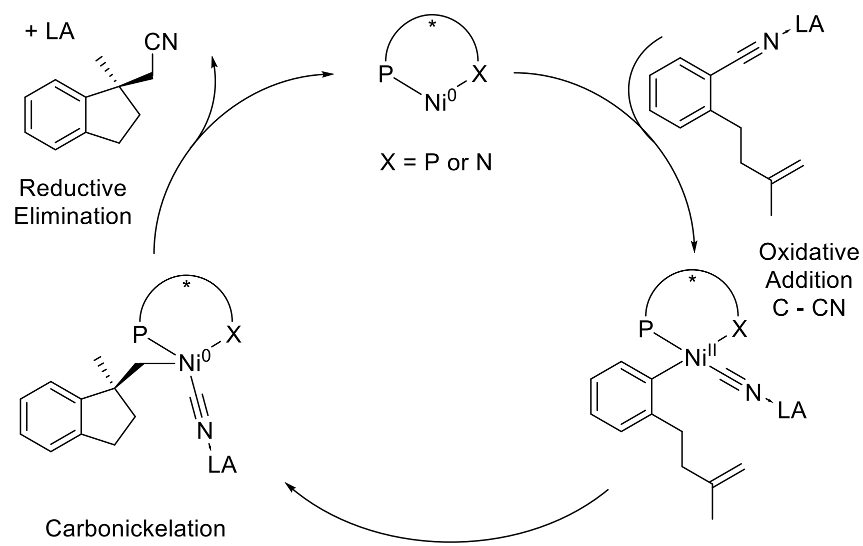
47 - 85 %
up to 97 % *ee*

R^1 = F, Cl, OMe
R^2 = Alk, Ar
X = CH_2, O, NR
n = 1, 2



Component	Jacobsen	Nakao
[Ni]	10 mol% $NiCl_2{\cdot}DME$ + 20 mol% Zn^0	10 mol% $[Ni(cod)_2]$
L	TangPHOS	*i*Pr-Foxap
Lewis Acid	BPh_3	Me_2AlCl
solvent	toluene	DME
T, °C	105	100

Catalytic Cycle:

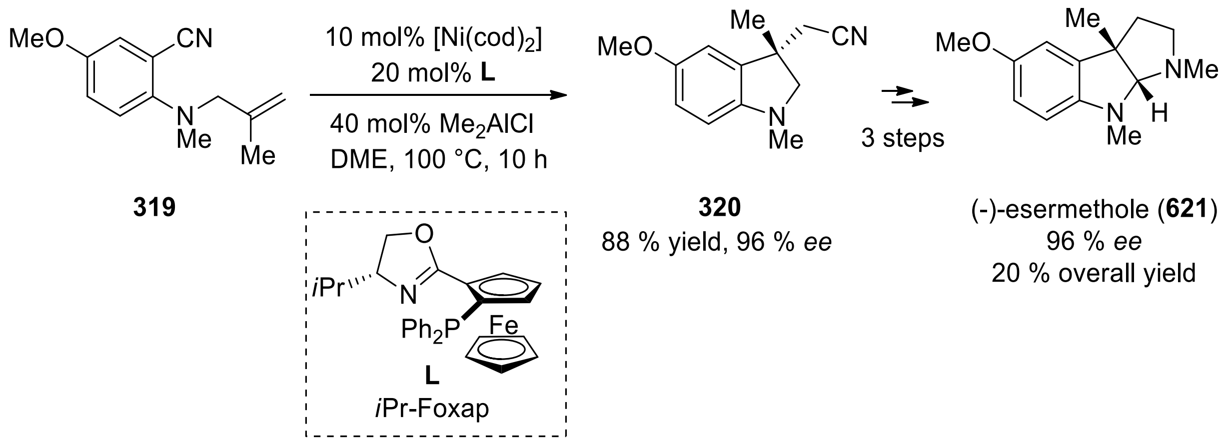


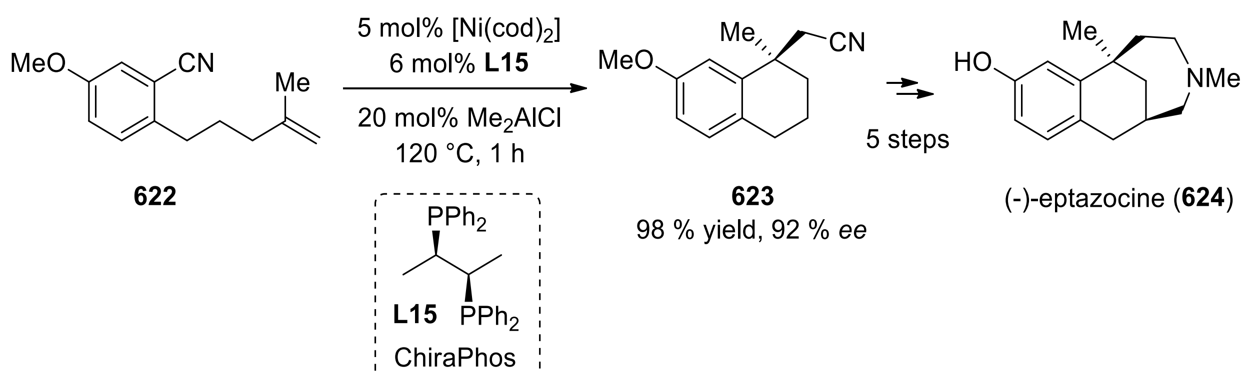
(1) Y. Nakao, S. Ebata, A. Yada, T. Hiyama, M. Ikawa, S. Ogoshi *J. Am. Chem. Soc*. **2008**, *130*, 12874. (2) M.P. Watson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 12594.

3. Enantioselective C – C activation of unstrained molecules:

3.1. Oxidative addition to C – CN bonds

Applications in total synthesis[1]



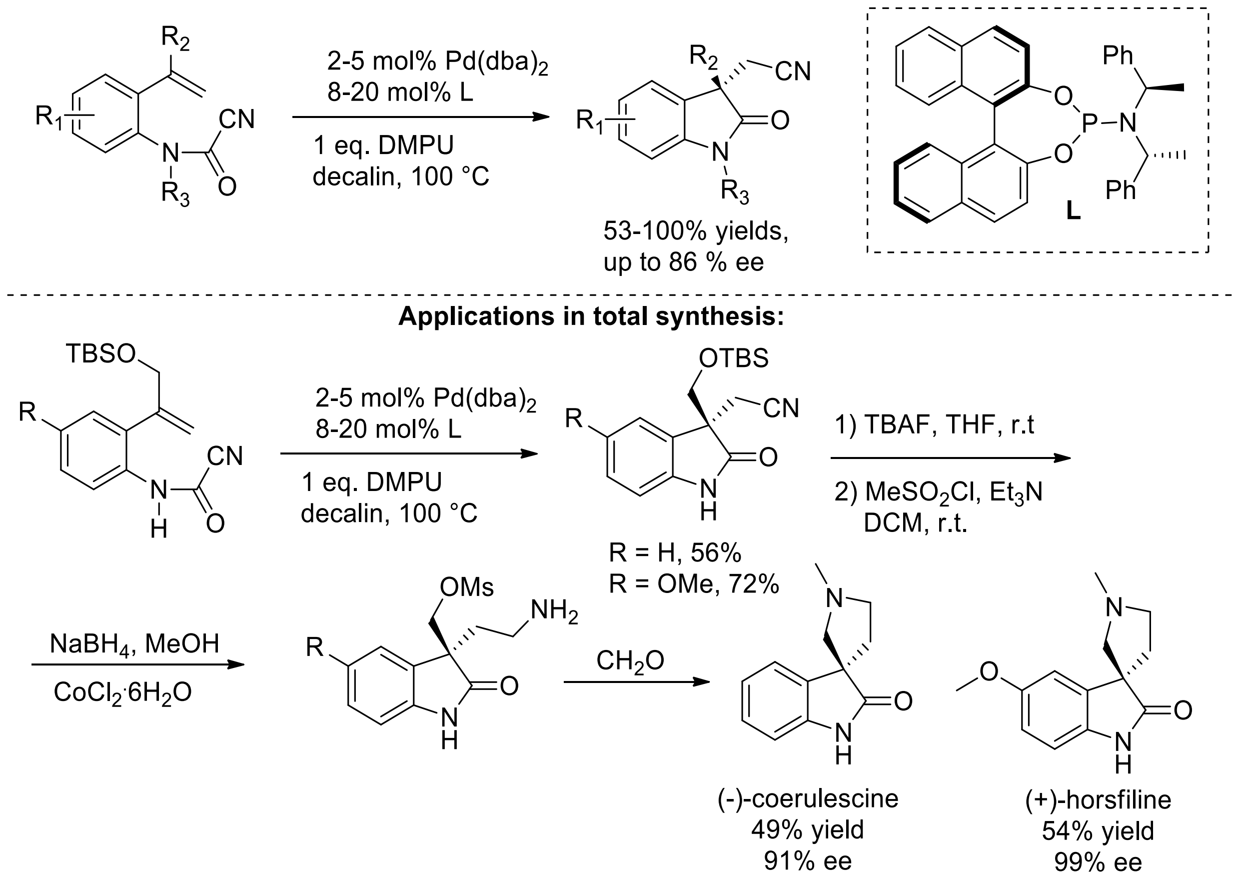


(1) Y. Nakao, S. Ebata, A. Yada, T. Hiyama, M. Ikawa, S. Ogoshi *J. Am. Chem. Soc*. **2008**, *130*, 12874

3. Enantioselective C – C activation of unstrained molecules:

3.1. Oxidative addition to C – CN bonds

Douglas: Pd-catalyzed cyanoamidation[1]

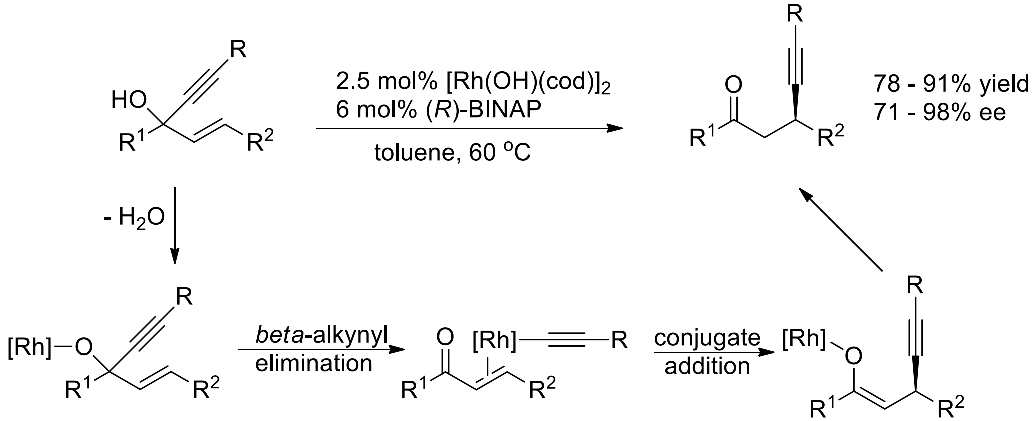


(1) V.J.Reddy C.J. Douglas *Org. Lett.*, **2010**, *12* 952.

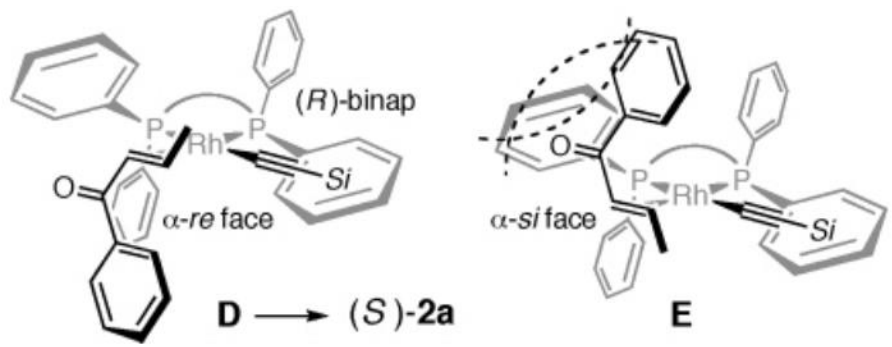
3. Enantioselective C – C activation of unstrained molecules:

3.2. β-carbon elimination of tertiary alcohols

Hayashi: Rh-catalyzed Asymmetric Rearrangement of Alkynyl Alkenyl Carbinols[1]



Selectivity model:

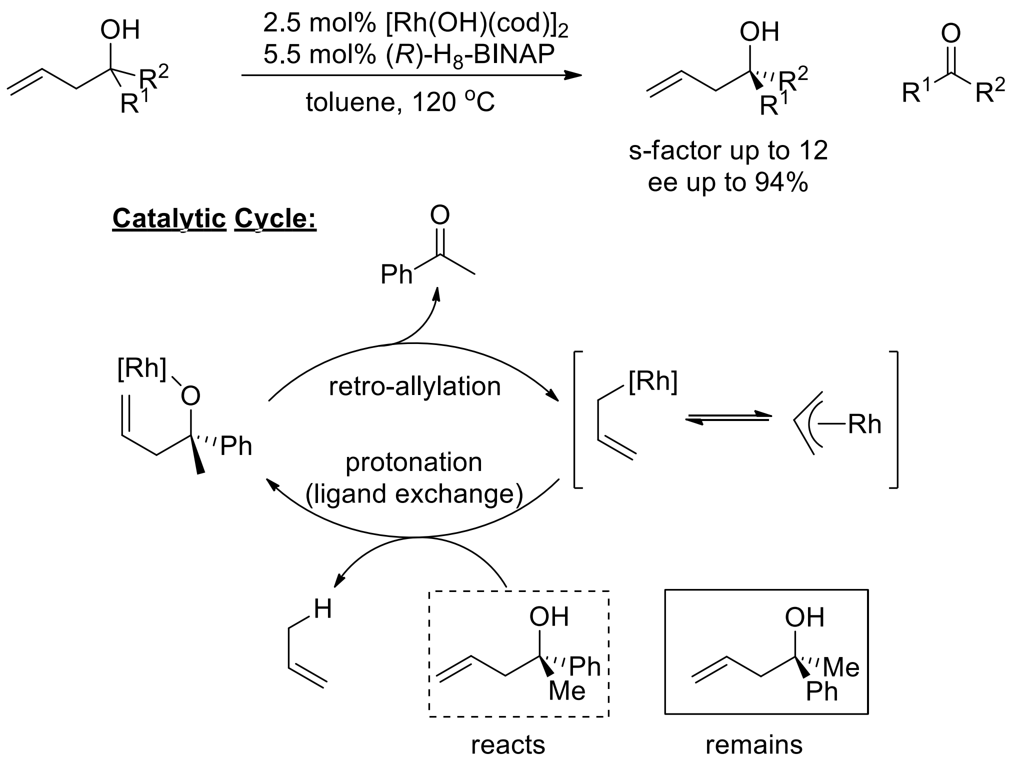


(1) T. Nishimura, T. Katoh, K. Takatsu, R. Shintani, T. Hayashi *J. Am. Chem. Soc.*, **2007**, *129*, 14158.

3. Enantioselective C – C activation of unstrained molecules:

3.2. β-carbon elimination of tertiary alcohols

Hayashi: Rh-catalyzed Kinetic Resolution of Tertiary Homoallyl Alcohols[1]



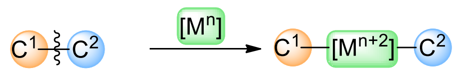
(1) R. Shintani, K. Takatsu, T. Hayashi *Org. Lett.,* **2008**, *10*, 1191.

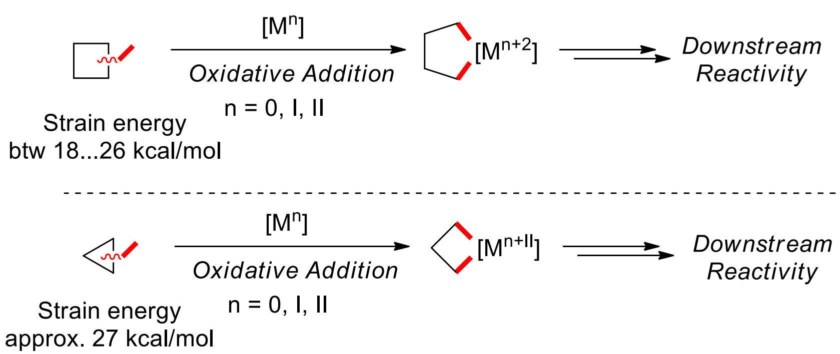
4. Conlcusions

Enantioselective C – C activation:

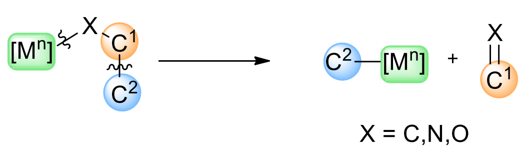
Strained molecules

Path A: Oxidative Addition



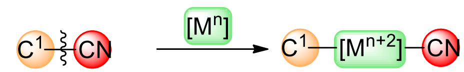


Path B: β-Carbon Elimination - ring-opening of cyclobutanols



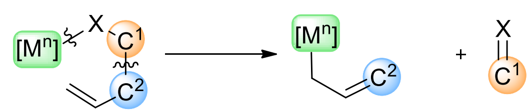
Unstrained molecules

Path A: Oxidative Addition to C-CN bonds



Path B: β-Carbon Elimination

Path C: Retro-Allylation



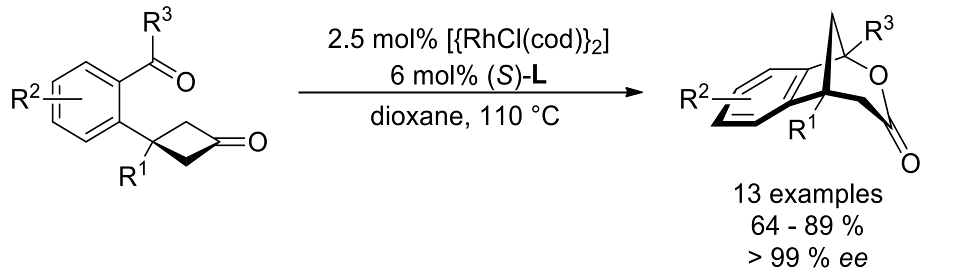
- Catalytic asymmetric C – C functionalization can be used as a key step in total synthesis, however only a handful of examples reported so far

The End

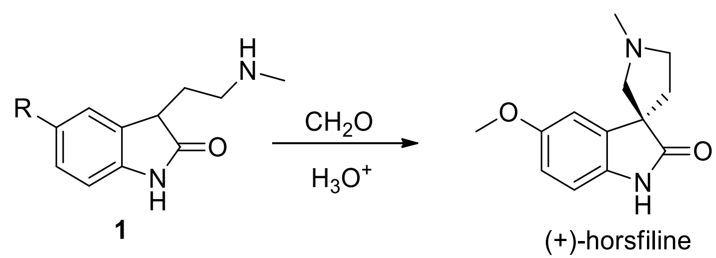
Thank you for attention!

Questions

1) Draw the mechanism for the following transformation:



2) In principle, horsfiline-type skeleton could be assembled via acid-catalyzed Mannich reaction of oxoindole 1. Draw the mechanism of such process and discuss its stereochemical aspects



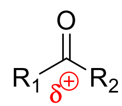
Selected Examples of Catalytic Asymmetric Umpolung of Imines and Carbonyl Compounds

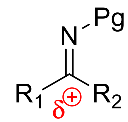
Frontiers in Chemical Synthesis II

Stereoselective Synthesis

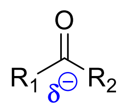
Background

Reactivity towards nucleopiles: well established

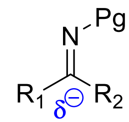




Catalytic asymmetric *umpolung* reactivity towards electrophiles: underdeveloped



In this presentation:
NHC-catalyzed Stetter reaction



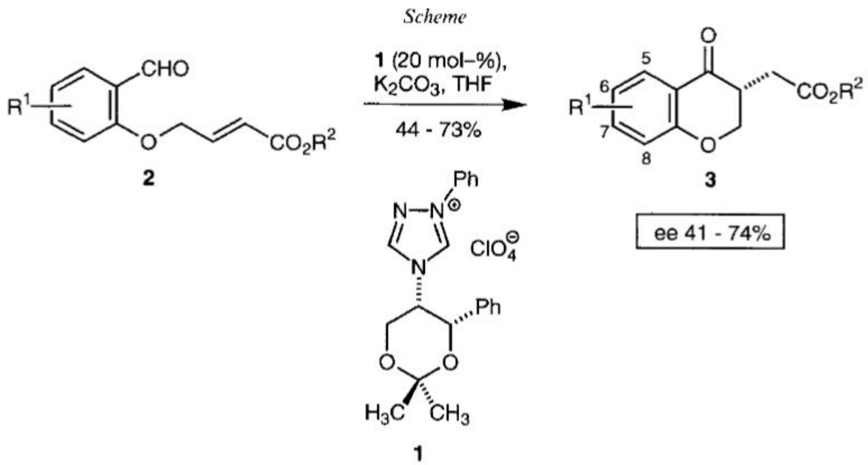
In this presentation:
miscellaneous appoaches

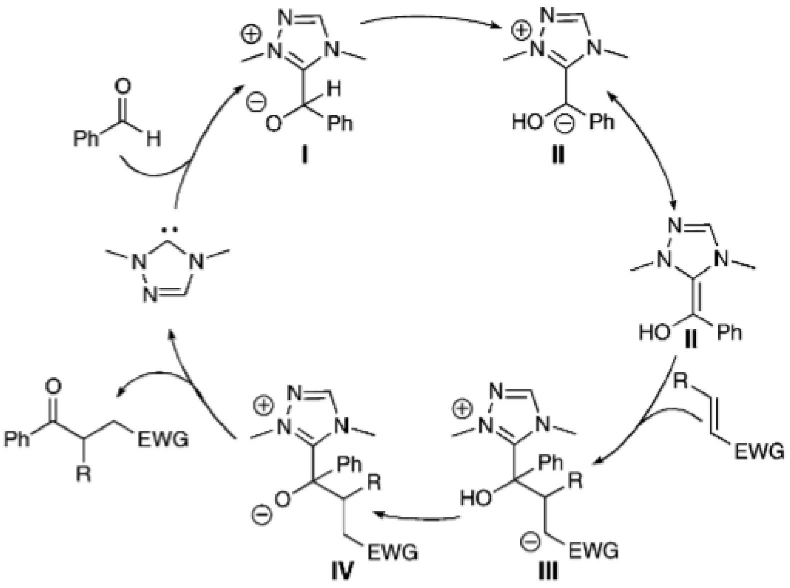
Catalytic Asymmetric Stetter Reaction

Intramolecular Developments

Asymmetric Catalytic Stetter Reaction

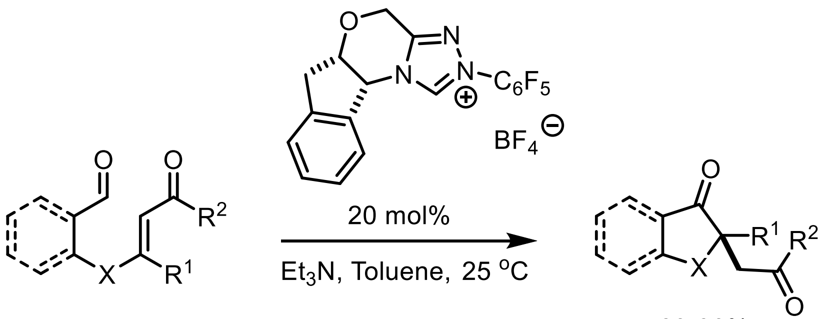
Seminal work:





Enders *et al*. *Helv. Chim. Acta.* **1996**, *79*, 1899.

Asymmetric Catalytic Stetter Reaction



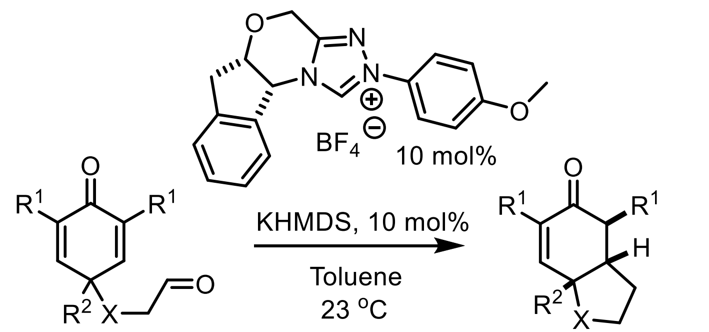
X = CH_2, O, S, NAc, SO_2

R^1 = alkyl, Ph; for H, rapid degradation of *ee*.

R^2 = alkyl, alkyloxy

60-90%
up to 99% *ee*

Rovis *et al. J. Am. Chem. Soc*. **2004**, *126*, 8876.
Rovis *et al. Tetrahedron.* **2006**, *62*, 11477.
Rovis *et al. J. Org. Chem*. **2007**, *73*, 2033.



R^1 = H, Alkyl, alkyloxy

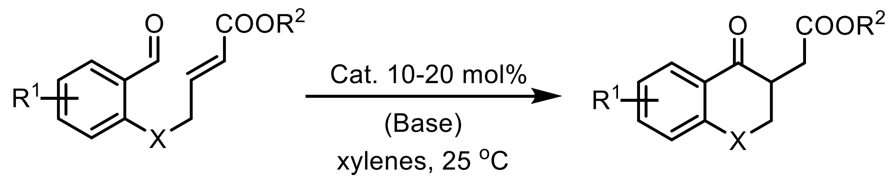
R^2 = Alkyl

X = O, CH_2

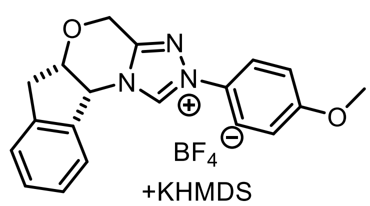
60-86% yield
up to 99% *ee*
Up to 3 stereoceneters

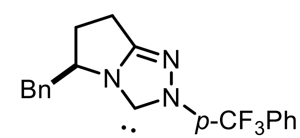
Rovis *et al. J. Am. Chem. Soc*. **2006**, *128*, 2552.
Rovis *et al. Org. Proc. Res. Dev*. **2007**, *11*, 598.

Asymmetric Stetter Reaction: Chromones

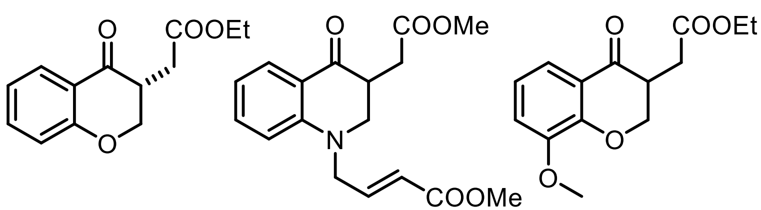


6-*exo-trig* less facile than 5-*exo-trig*
Low *ees* for R^1 = EWG
X = CH_2, N(Alk), O, S



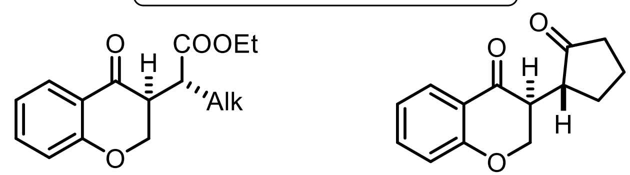


Prepared *in situ* prior reaction



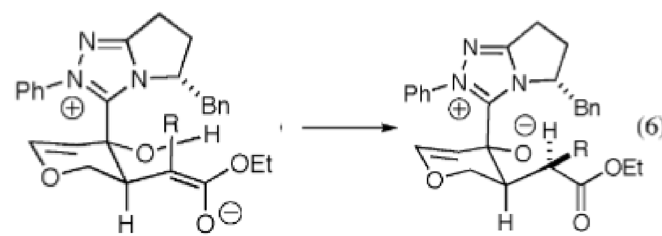
94%, 94% *ee* | 72%, 84% *ee* | 95%, 87% *ee*

Rovis *et al. J. Am. Chem. Soc.* **2002**, *124*, 10298.



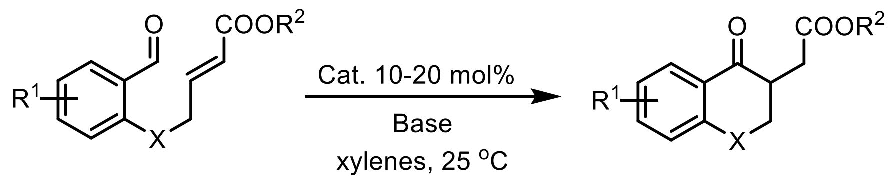
Alk = Me, 94%, 95% *ee*, 30:1 *dr.*
Alk = Bn, 80%, 84% *ee*, 20:1 *dr.*

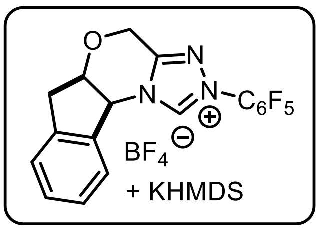
80%, 95% *ee*, 18:1 *dr.*

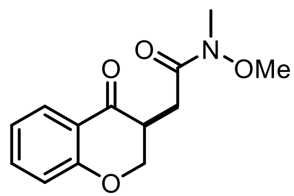


Rovis *et al. J. Am. Chem. Soc.* **2005**, *127*, 6284.

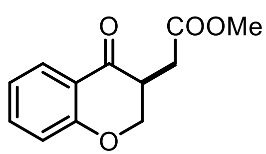
Asymmetric Stetter Reaction: Chromones



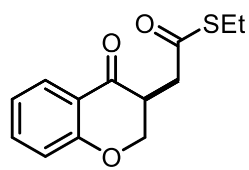




94%, 92% *ee*

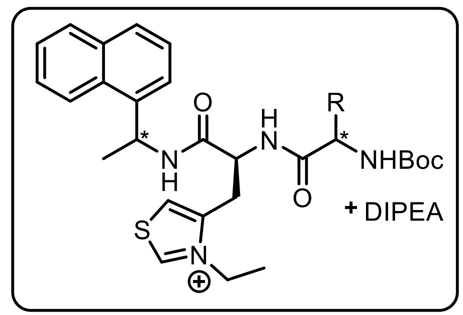


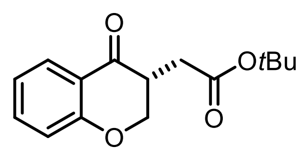
From *Z*-alkene: 80%, 22% *ee*
From *E*-alkene: 94%, 95% *ee*



85%, 70% *ee*

Rovis *et al. J. Org. Chem*. **2007**, *73*, 2033

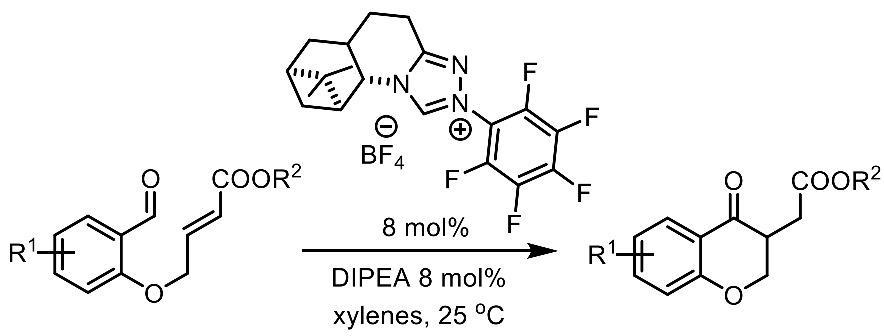




67%, 73% *ee*

Miller *et al. Chem. Commun.* **2005**, 195.

Asymmetric Stetter Reaction: Chromones



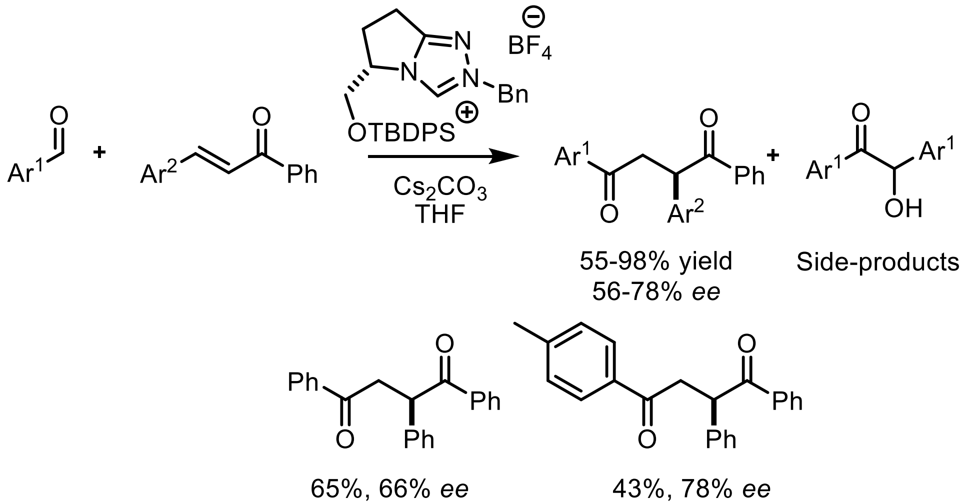
Pinene-based catalyst delivers product in excellent yields and *ee*s up to 98%

Rafiński *et al*. *ACS Catal*. **2014**, *4*, 1404.

Asymmetic Stetter Reaction

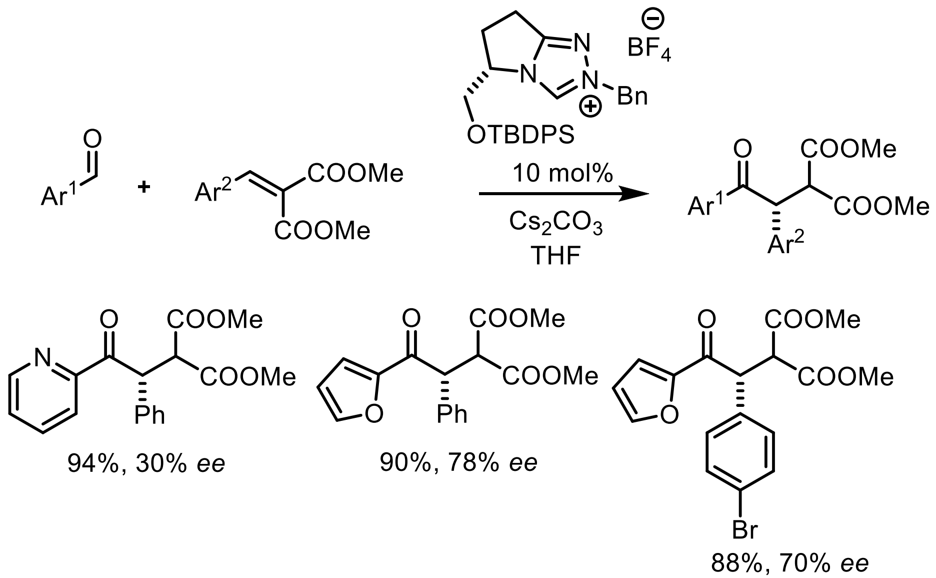
Intermolecular Reactions

Intermolecular reactions: First reports



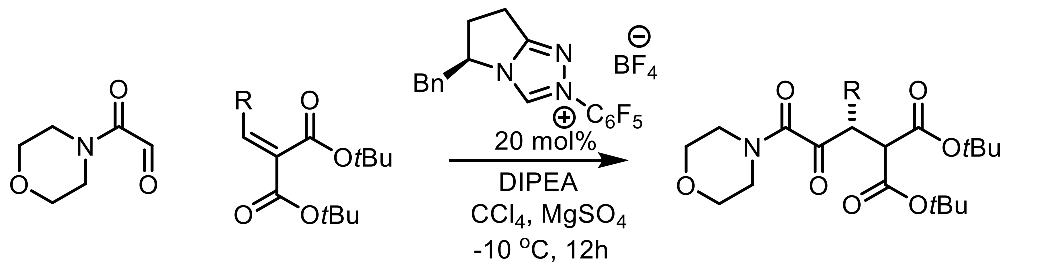
Enders *et al*. *Chem. Commun*. **2008**, 3989.

Intermolecular reactions: First reports



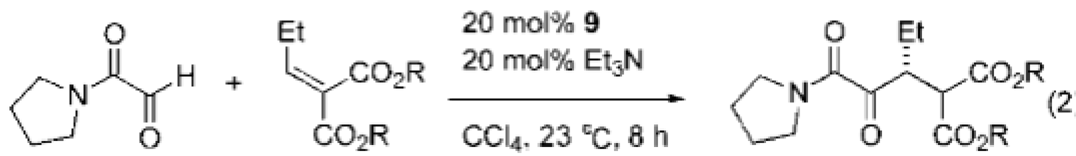
Asymmetric Catalytic Stetter Reaction

Intermolecular reactions



R = 1° alkyl (50-97%, 80-90% *ee*)

- R = 1° alkyl (50-97%, 80-90% *ee*)
- low temperature, hindered base to avoid racemization



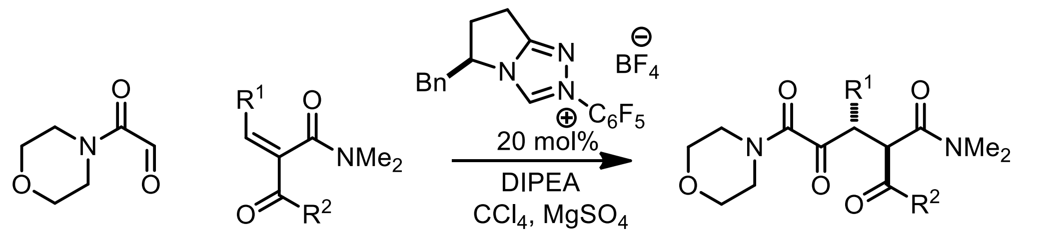
6d **12a-c**

13a R = Me : 52%, 51%ee
13b R = ^{i}Pr : 54%, 75% ee
13c R = ^{t}Bu : 51%, 81% ee

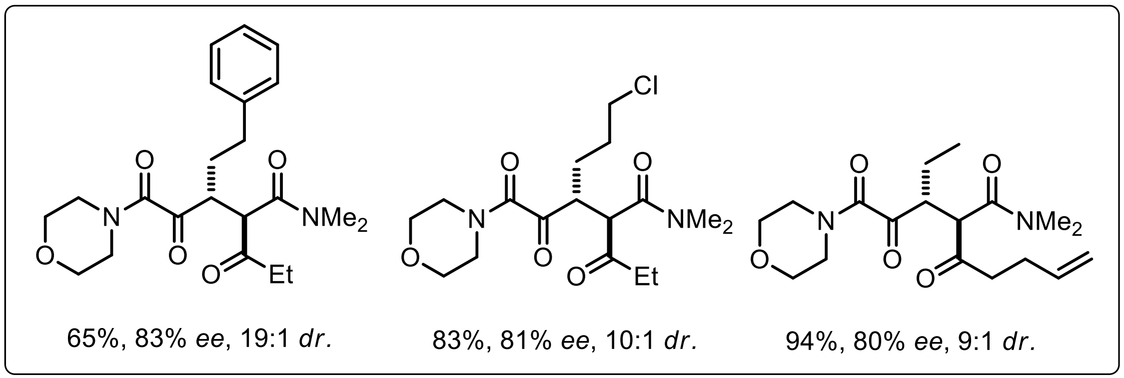
Rovis *et al*. *JACS,* **2008**, *130*, 14066.

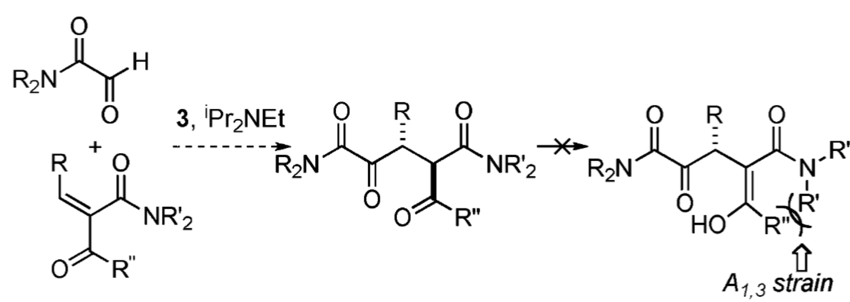
Asymmetric Catalytic Stetter Reaction

Intermolecular reactions

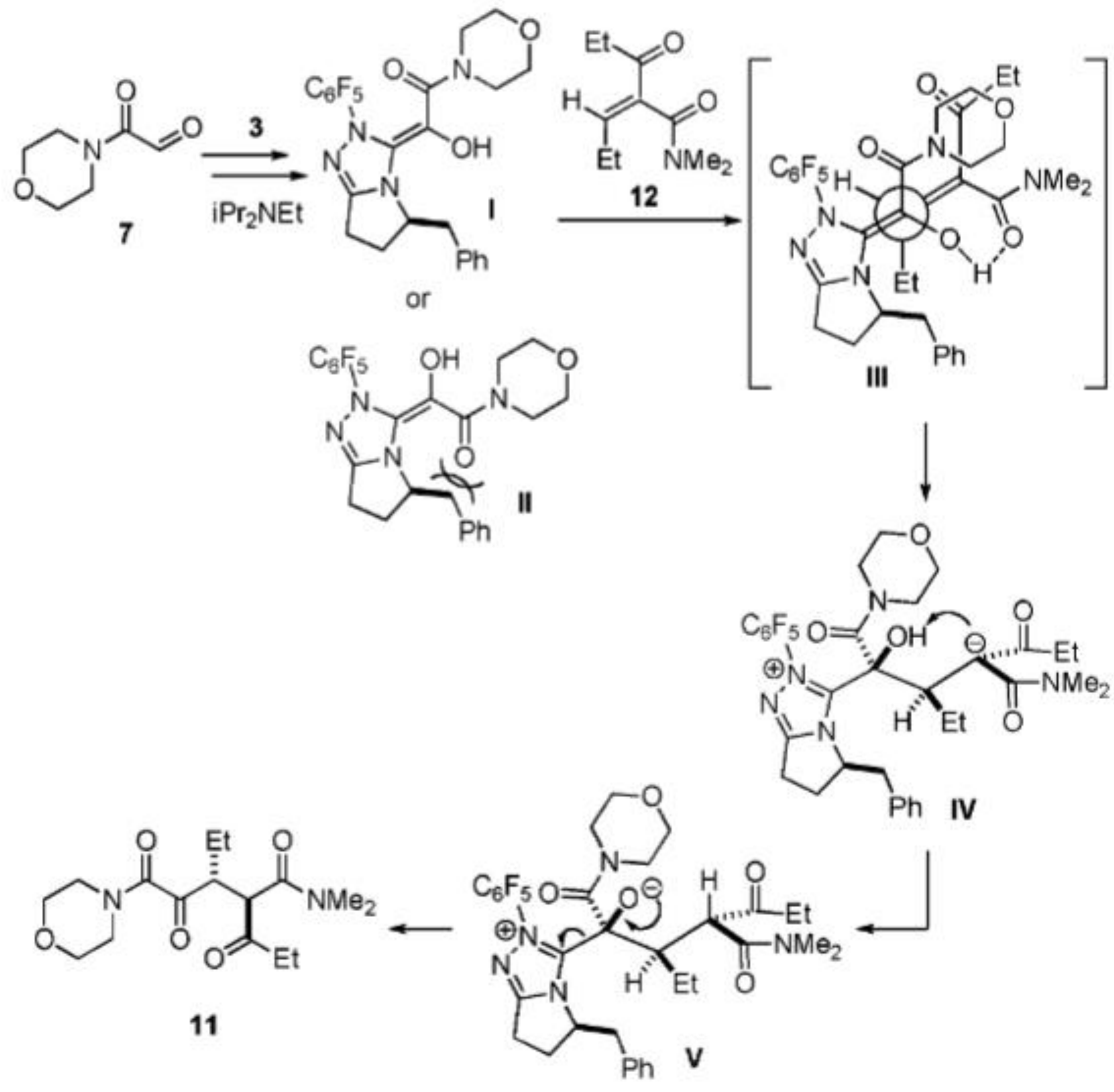


Two stereocenters
R = 1° alkyl (44-95%, 81-94% *ee*)



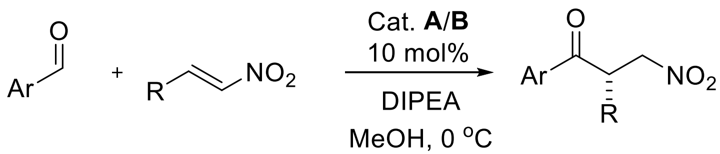


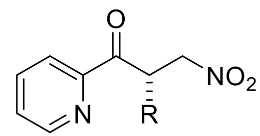
Detailed Reaction Mechanism



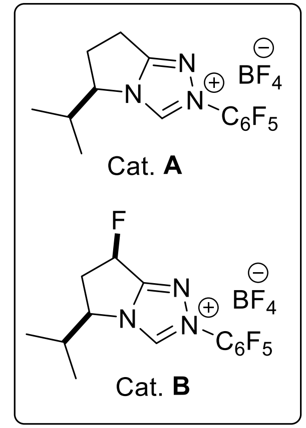
Asymmetric Catalytic Stetter Reaction

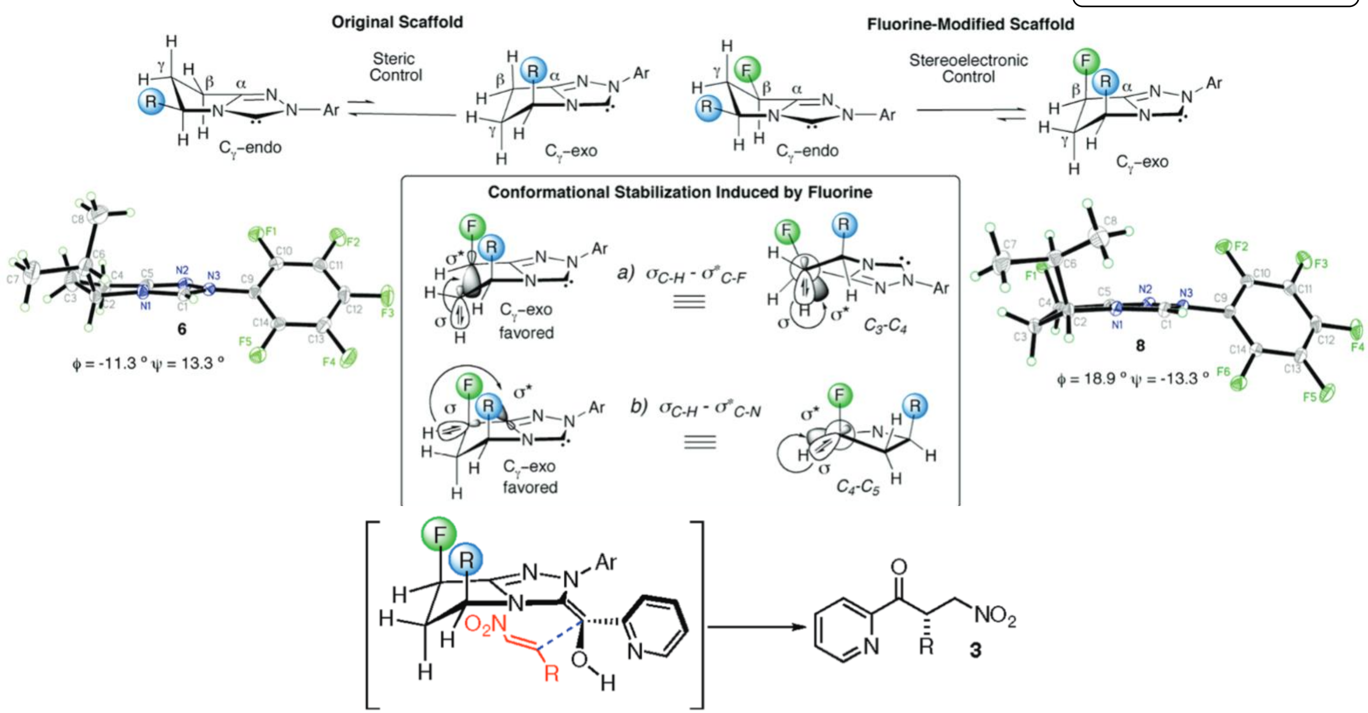
Intermolecular reactions





Cat. **A**: 90%, 88% *ee*
Cat. **B**: 95%, 95% *ee*

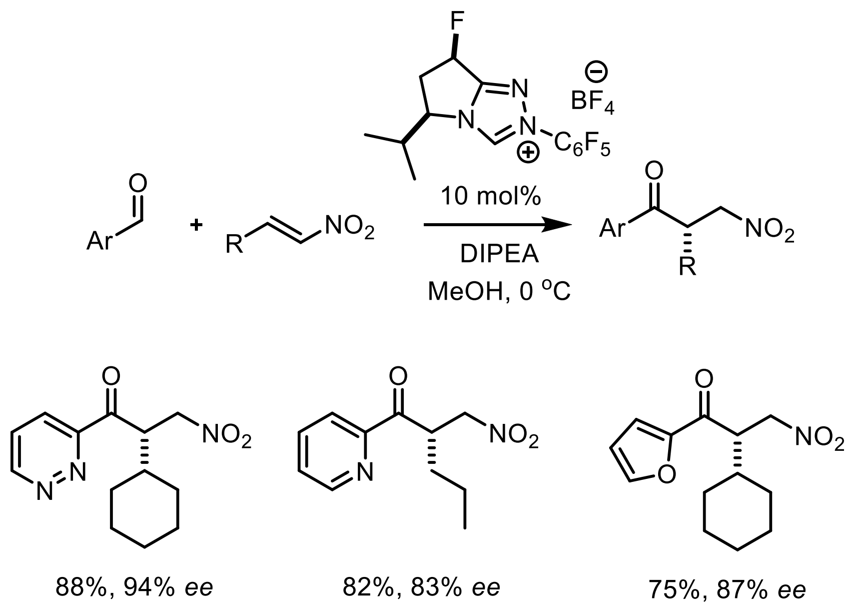




Rovis *et al*. *J. Am. Chem. Soc.* **2009**, *131*, 10872.

Asymmetric Catalytic Stetter Reaction

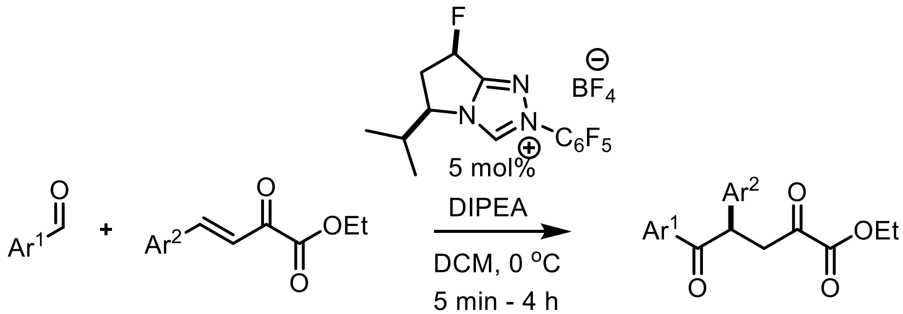
Intermolecular reactions

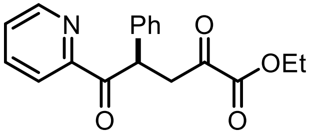


Rovis *et al*. *J. Am. Chem. Soc.* **2009**, *131*, 10872.

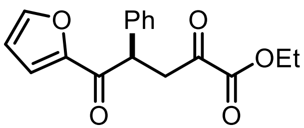
Asymmetric Catalytic Stetter Reaction

Intermolecular reactions

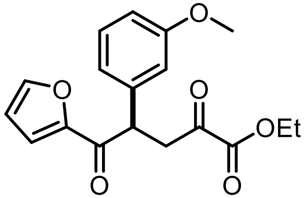




88%, 91% *ee*



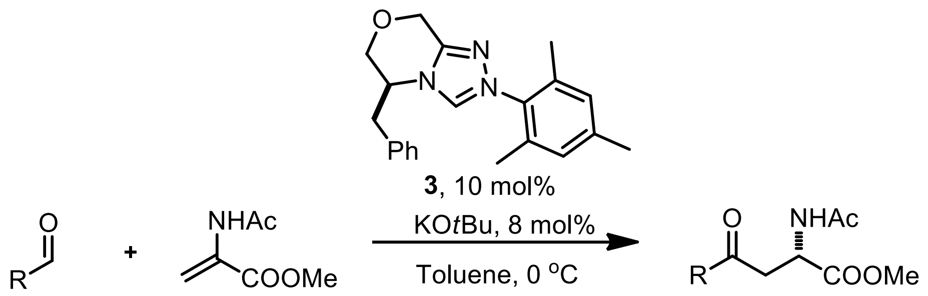
92%, 90% *ee*

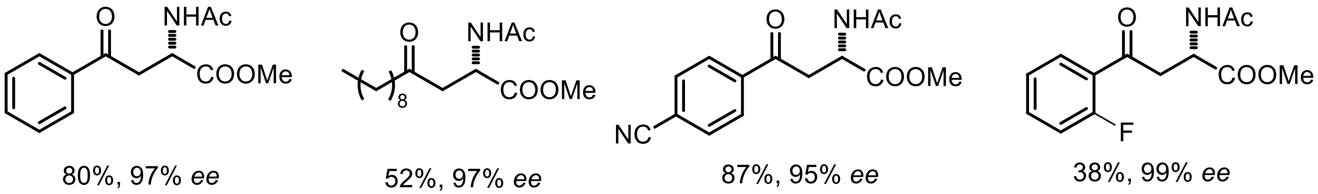


96%, 90% *ee*

Asymmetric Catalytic Stetter Reaction

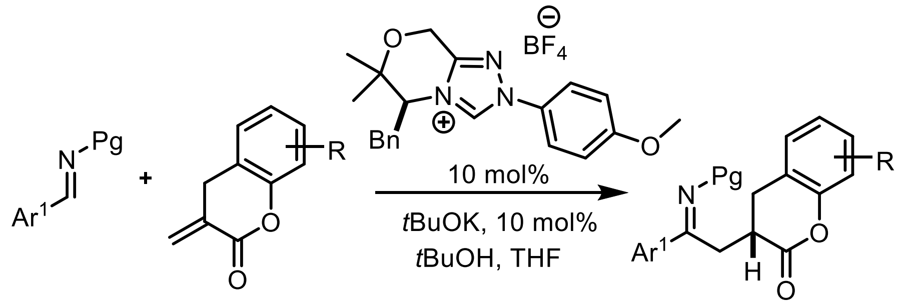
Intermolecular reactions



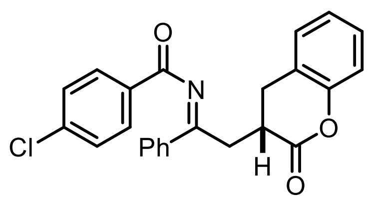


Catalytic Asymmetric Umpolung of Imines

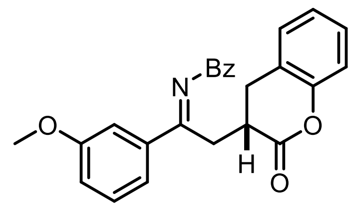
Asymmetric Aza-Stetter Reaction



50-88% yield
over 96% *ee*



60%, 96% *ee*

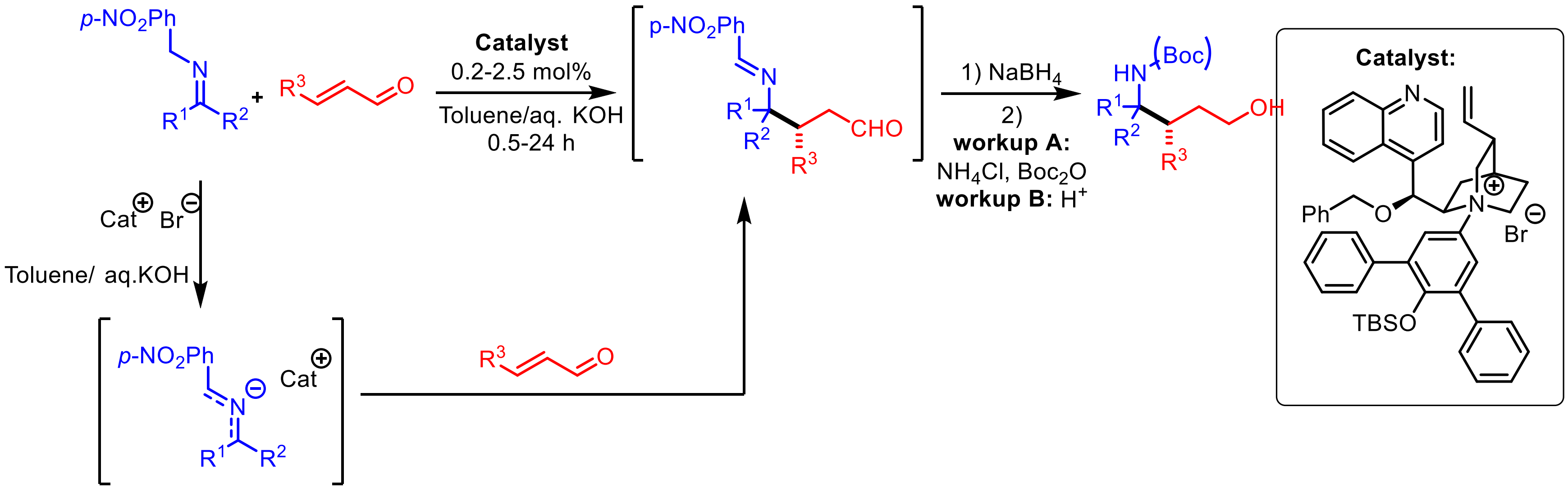


80%, 98% *ee*

- Only chromanone Michael acceptors demonstrated (otherwise imine dimerization).
- Alkyl imines rearrange to enamines.
- Highest yields with electron-rich imines

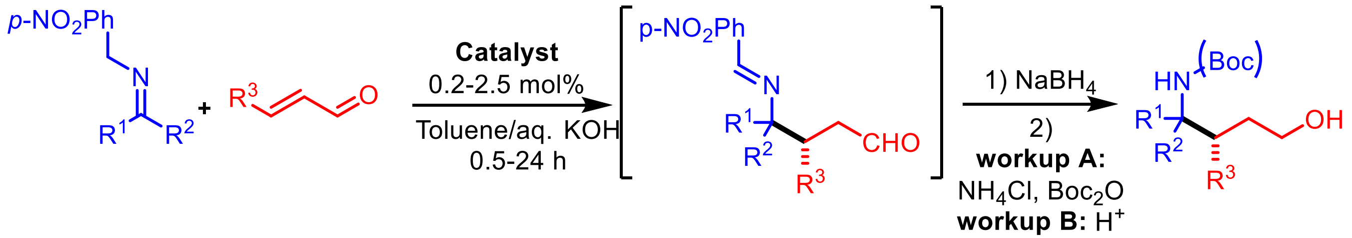
Lupton, *Angew. Chem*. **2019**, *131*, 4047.

Chiral Phase-Transfer Catalysis

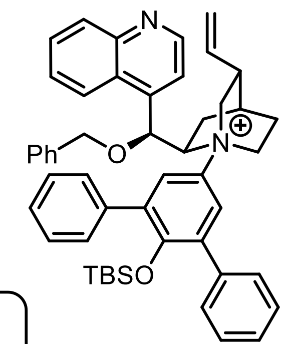


Deng *et al.* *Nature*. **2015**, *523*, 445.

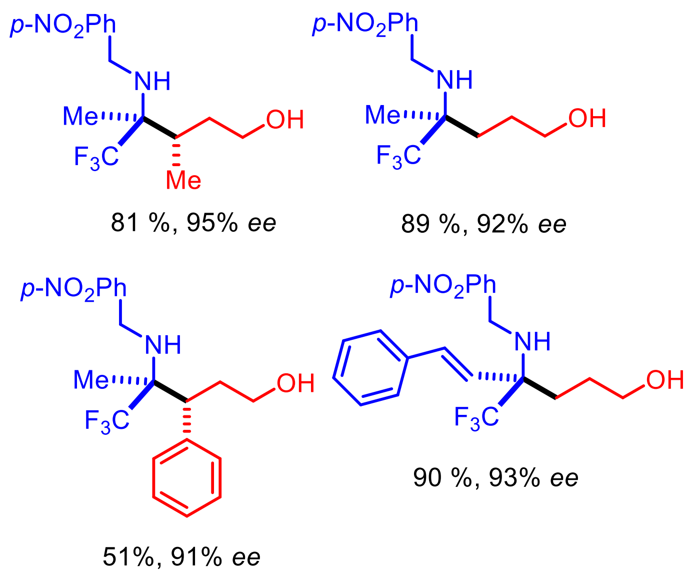
Chiral Phase-Transfer Catalysis



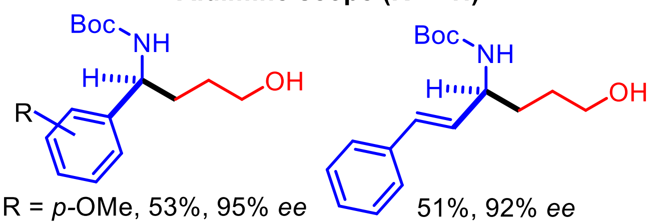
Catalyst:



Trifluormethyl imine scope ($R^1 = CF_3$)



Aldimine scope (R^2 = H)

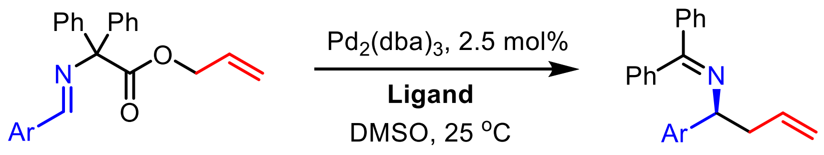


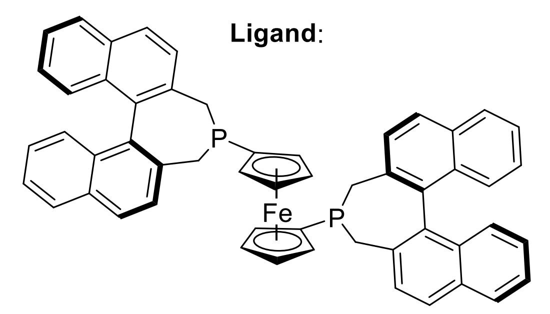
R = *p*-OMe, 53%, 95% *ee*
R = H, 55%, 93% *ee*
R = *o*-Br, 52%, 95% *ee*
R = *p*-COOMe, 53%, 90% *ee*

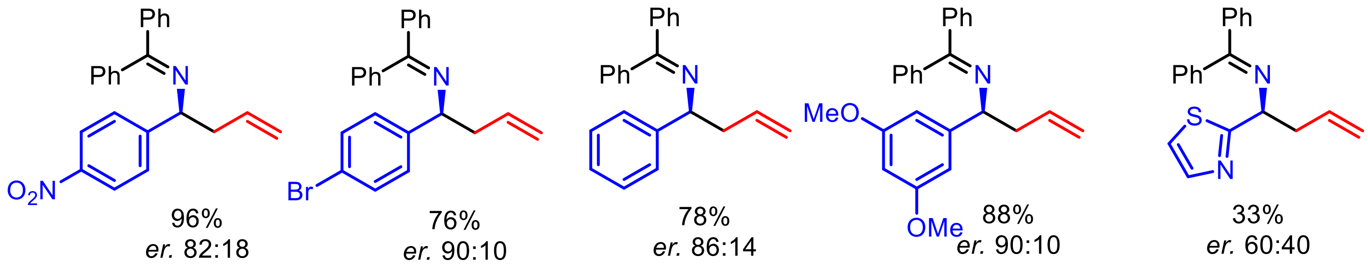
No R= alkyl imines

Deng *et al. Nature*. **2015**, *523*, 445.

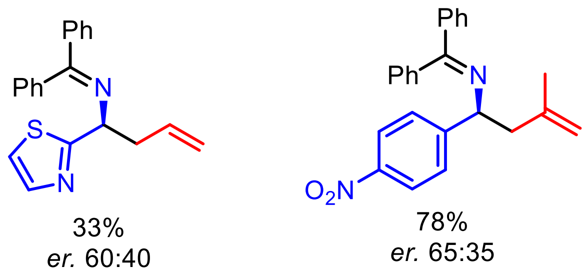
Decarboxylative allylation



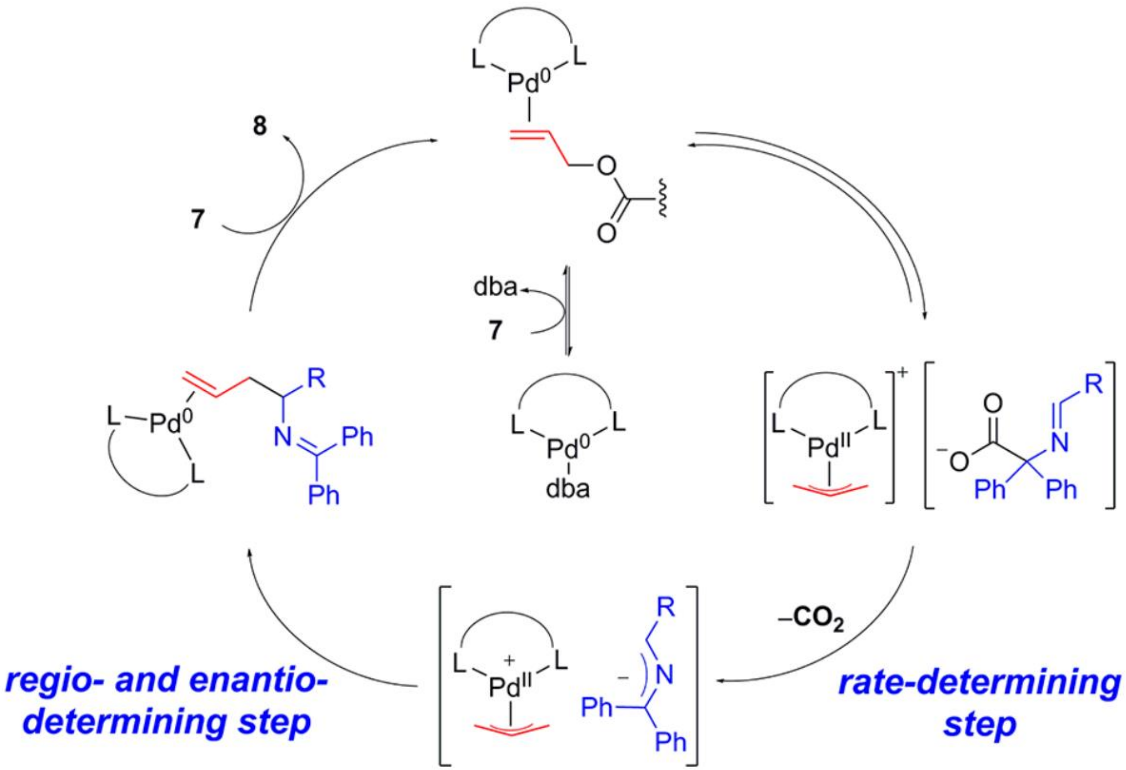




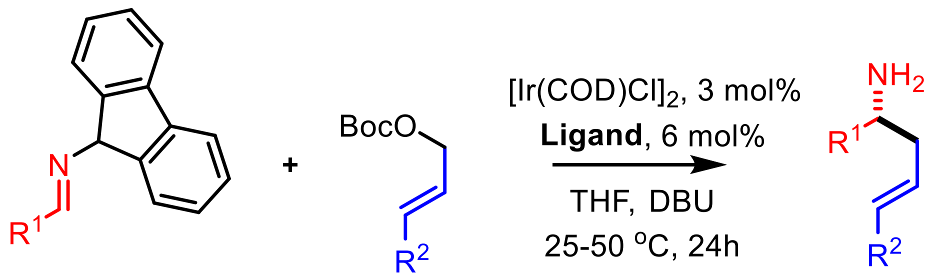
Problematic substrates:

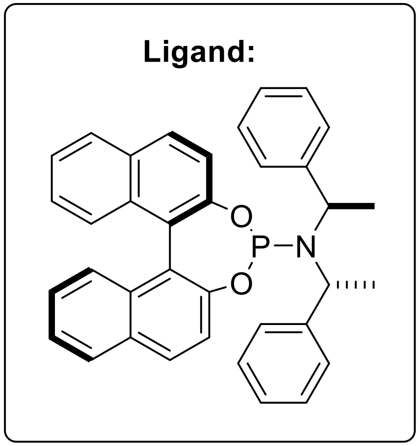


Mechanistic proposal



Ir-Catalyzed Allylation



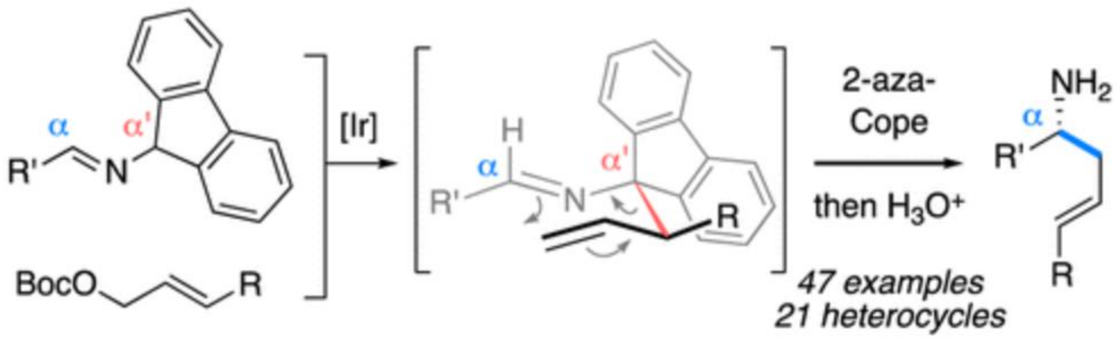


70-95% yield, 90-99% *ee*

Alkyl, aryl substituents well tolerated;

No 2-substituted allyl-systems,

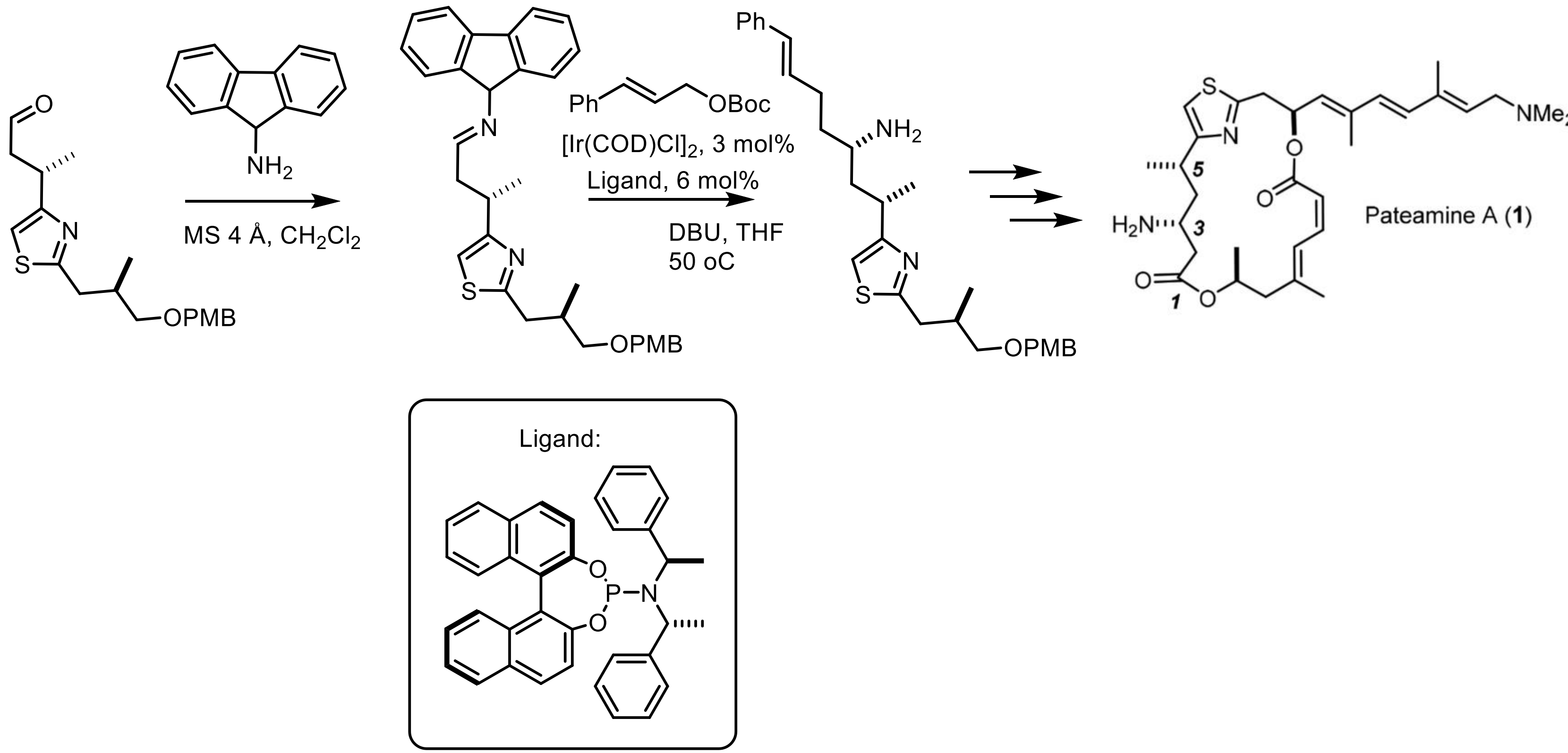
Mechanistic proposal:



Could be isolated if R = Alk

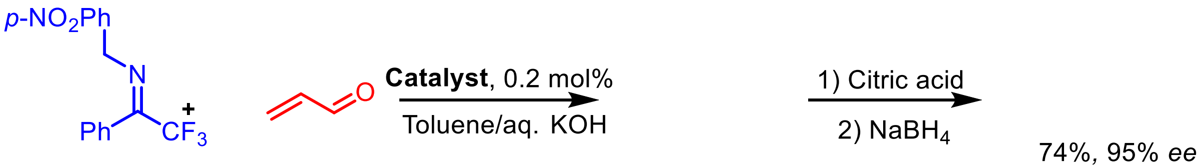
Rearrangement demends heating

Application in Total Synthesis

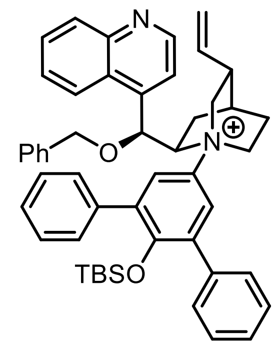


Thank you for your attention

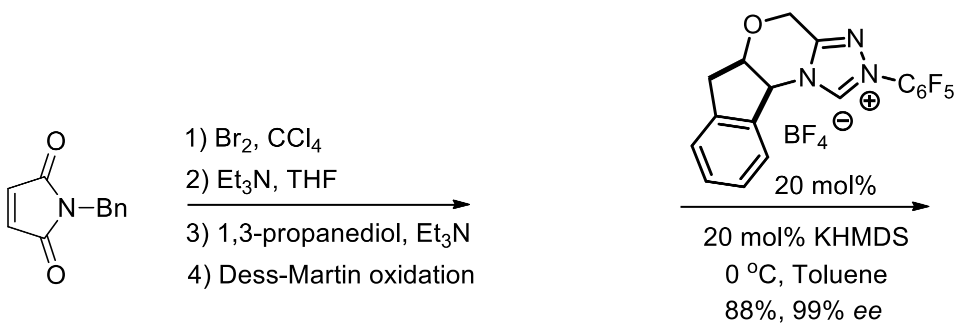
Exercise 1



Catalyst:

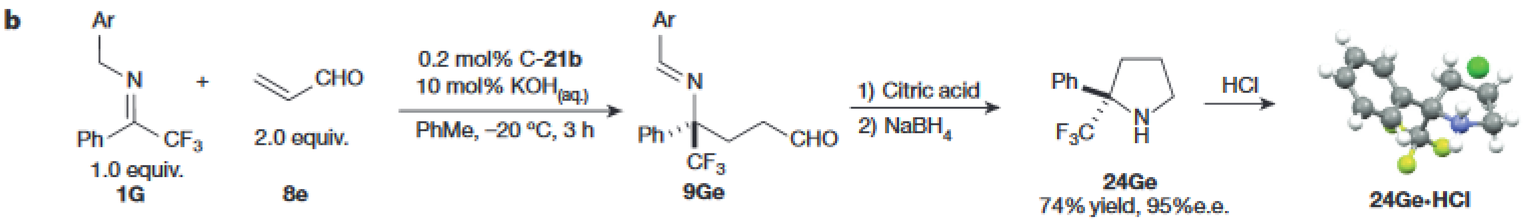


Exercise 2

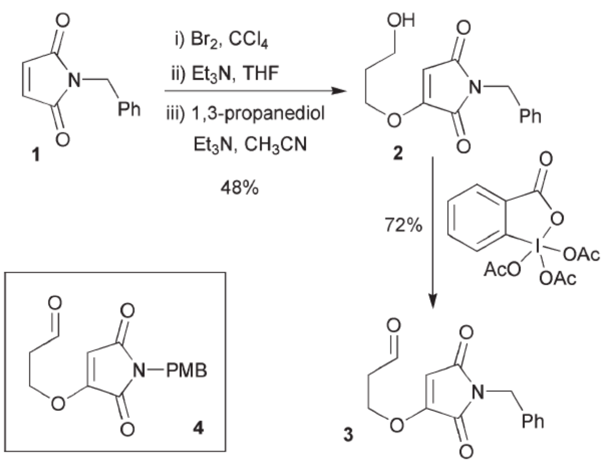


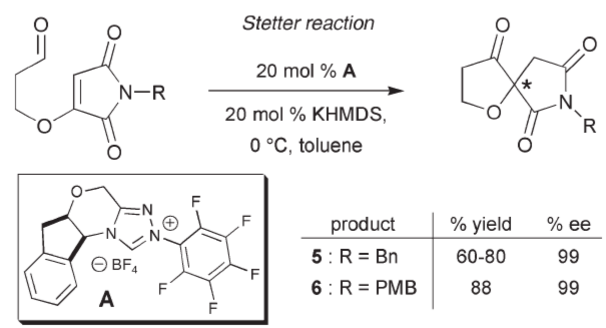
Solutions

Exercise 1



Exercise 2





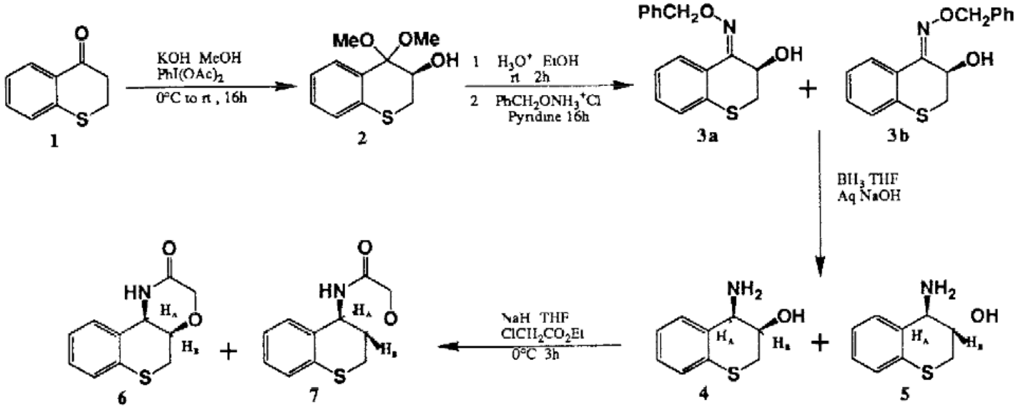
product	% yield	% ee
5 : R = Bn	60-80	99
6 : R = PMB	88	99

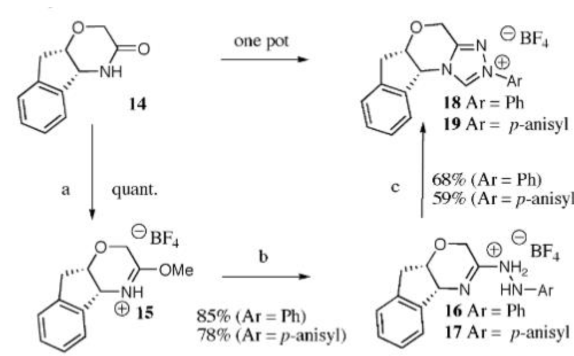
Scheme 3 Key catalytic asymmetric Stetter reaction.

Rovis *et al*. *Chem. Commun*., **2008**, 730.

Preparation of NHC Precursors

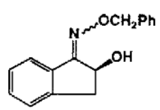
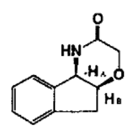
Scheme I





[a] (a) $Me_3O^+BF_4^-$, CH_2Cl_2, 23 °C, 12 h; (b) phenylhydrazine or *p*-anisylhydrazine, 23 °C, 30 min; (c) PhCl, $HC(OEt)_3$, 110 °C, 12 h.

Table I Reduction Of O-benzyl oxime with BH_3 THF[a]

Entry	Substrate (Yield)		Ratio of aminoalcohol[b] Cis/Trans (Yield)[c]	Oxazinone	Coupling (J_{AB})
3		(73%)	88 12 (81%)		3 9 Hz

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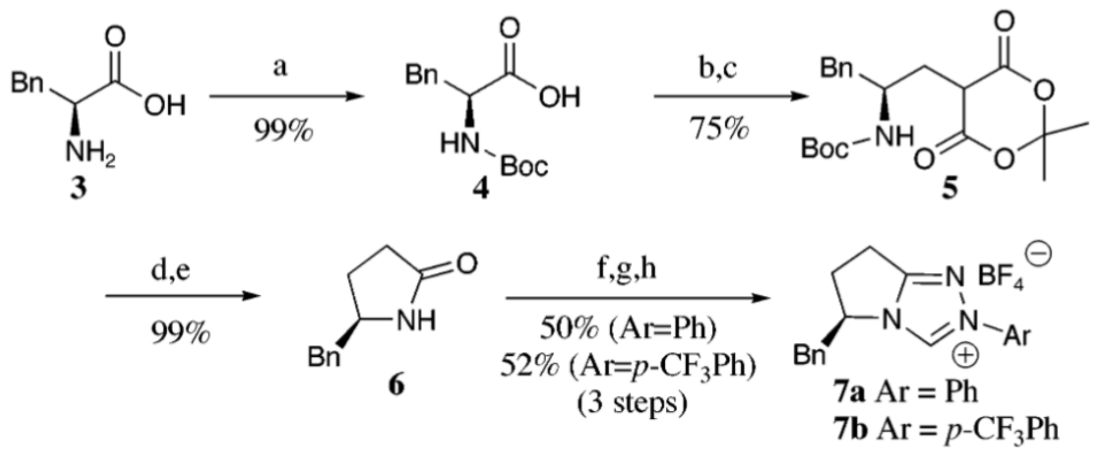
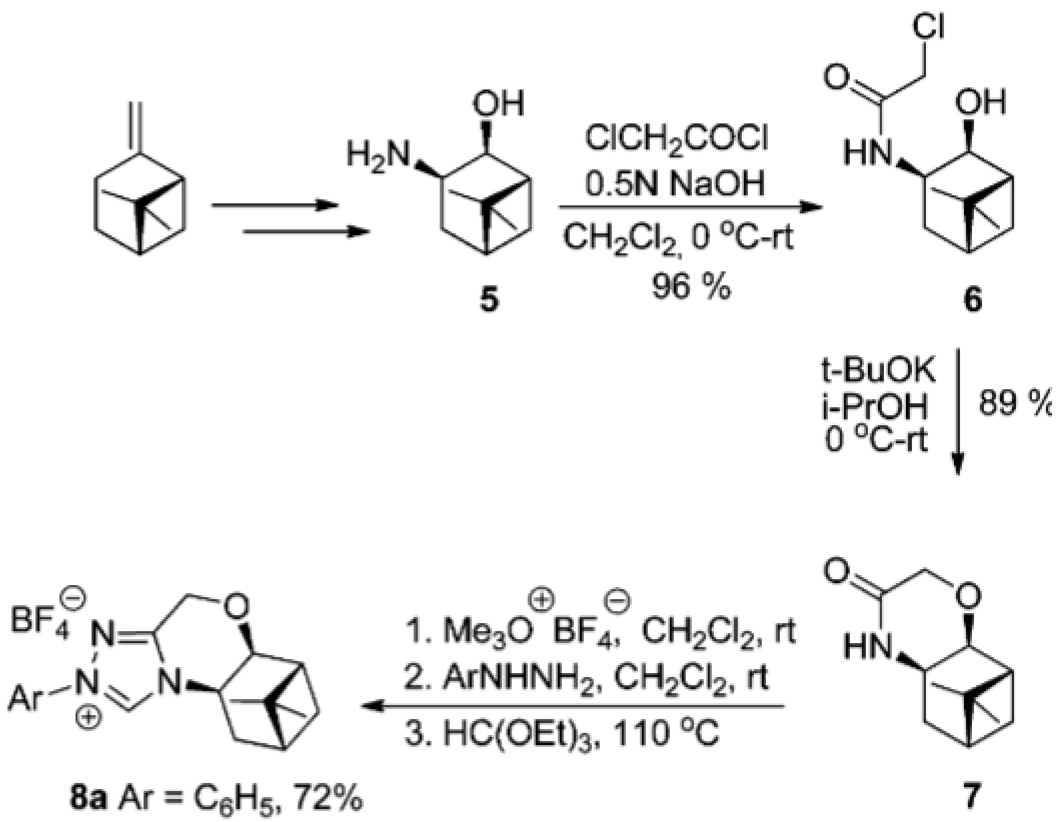
Preparation of NHC Precursors



[a] (a) Boc_2O, NaOH, THF/H_2O, 23 °C; (b) Meldrum's acid, DMAP, DCC, CH_2Cl_2, 0 °C; (c) AcOH, $NaBH_4$, CH_2Cl_2, 0 °C; (d) toluene, 110 °C; (e) TFA, CH_2Cl_2, 0 °C; (f) $Me_3O+BF_4^-$, CH_2Cl_2, 23 °C; (g) phenylhydrazine or 4-(trifluoromethyl)phenylhydrazine, 23 °C; (h) MeOH, $CH(OMe)_3$, 80 °C or MeOH, $CH(OEt)_3$, 110 °C.

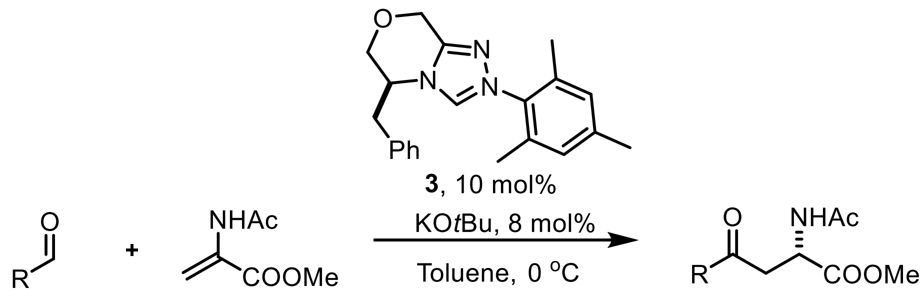
Rovis, *J. Org. Chem.*, **2005**, *70*, 5725.

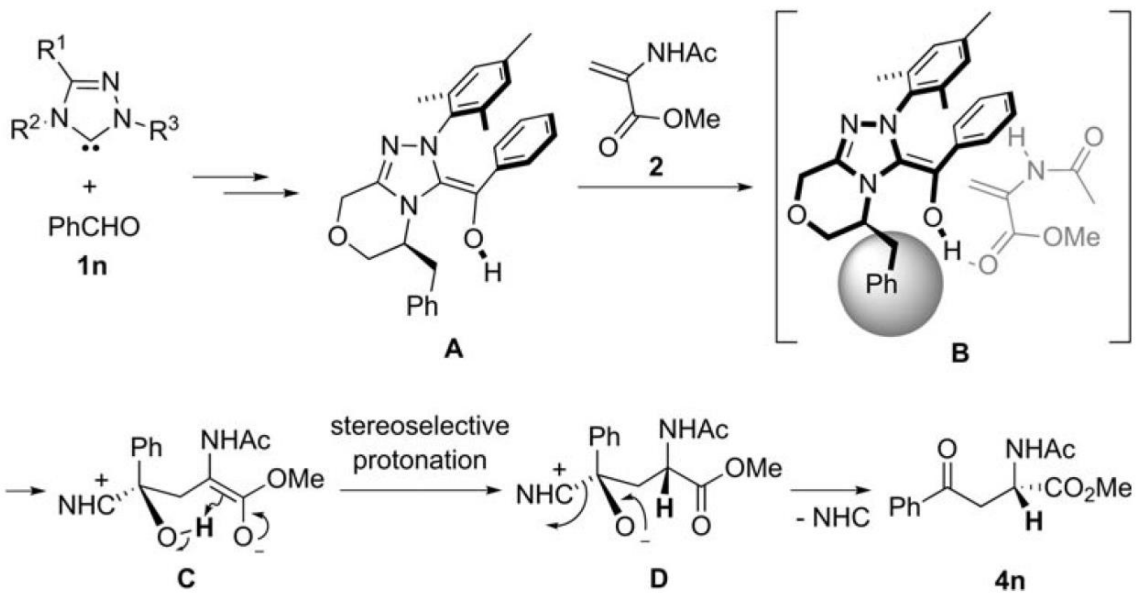
Preparation of NHC Precursors



8a Ar = C_6H_5, 72%
8b Ar = C_6F_5, 66%
8c Ar = 2,4,6-$(CH_3)_3C_6H_2$, 75%

Rovis, *J. Org. Chem.*, **2005**, *70*, 5725.





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