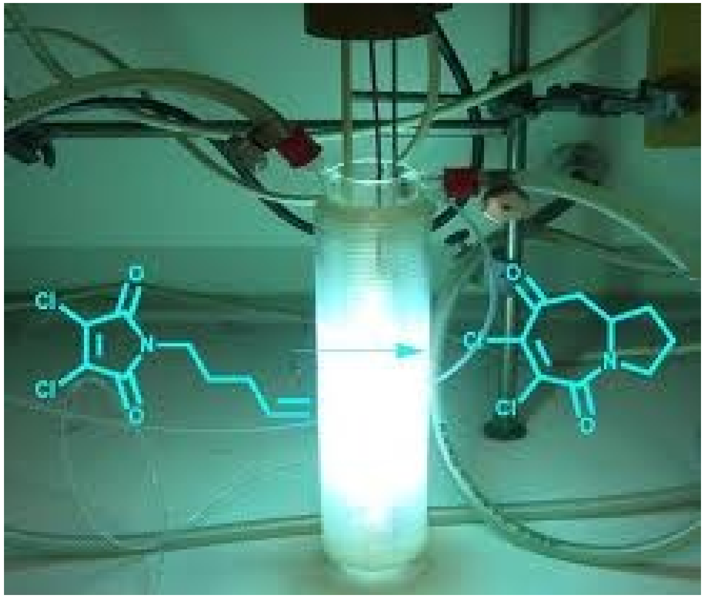
Frontiers in Chemical Synthesis I
Towards Sustainable Chemistry

Seminar Program
June 6-7, BCH 3118

	Speaker	**Title**
June 6, 2011		
Session I: New Technologies for Organic Chemistry (Chairman: Stefano Nicolai)		
9h30-10h45	Filippo De Simone	*Flow Chemistry in Organic Synthesis*
10h45-12h00	Weija Gan	*Design of Ligands for Metal-Catalyzed Reactions in Water*
Session II: Functionalization of Olefins and C-H bonds (Chairman: Jean-Baptiste Gualtierotti)		
13h30-14h45	Ala Bunescu	*Palladium-Catalyzed C-H Amination*
14h45-16h00	Laetitia Souillart	*Late Stage C-H Activation in Protecting Group Free Total Synthesis*
16h00-17h15	Baihua Ye	*Rhodium-Catalyzed Hydroamination of Olefins*
June 7, 2011		
Session III: Organocatalysts and Radicals (Chairman: Filippo De Simone)		
8h15-9h30	Thomas Buyck	*Organocatalysis by N-Heterocyclic Carbenes*
9h30-10h45	Florian De Nanteuil	*Cooperative Catalysis: Organocatalysts and Metals*
10h45-12h00	Jean-Baptiste Gualtierotti	*Metal and Enlightenment, Radical Pathways toward Complex Structures*
Session IV: Metal Catalysis (Chairman: Baihua Ye)		
13h30-14h45	Pablo Marcelo Perez Garcia	*Enantioselective Reactions Catalyzed by Iron Complexes*
14h45-16h00	Daniel Lamey	*Gold Nanoparticles for Heterogenous Catalysis in Organic Chemistry*
16h00-17h15	Stefano Nicolai	*Rhodium-Catalyzed Cycloaddition Reactions*

Flow Chemistry in Organic Synthesis

Litterature Talk



Filippo De Simone

EPFL

6 June 2011

1) Try to identify the limitations of flow chemistry

2) In witch context flow chemistry is advantageous?

Table of contents

Flow chemistry

Microfluidics (10^{-9} to 10^{-18} L)

Control of concentration in space/time

Molecular analysis
(GC, HPLC, CE)

- Small volume
- Low cost
- Short analysis time

Biodefence

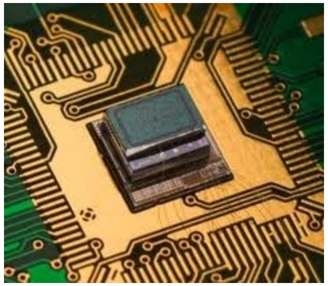
1990 Microfluidic detector
(for chemical and biological threats)

Academic interest

Molecular biology

DNA sequencing

Microelectronics



Microelectronics
Technologies

(DARPA = Defense Advanced Research Projects Agency from US Department of Defense

G. M. Whiteside, *Nature*, **2006**, *442*, 368.

From batch to flow

- Superior heat and mass transfer rates (hight surface/volume ratio)
- Easy scale up (bigger or multi columns)
- Safe use of extreme pressures and temperatures
- Precise control of conditions
- Reduced chemical exposion and waste
- Ideal for fast reactions, esothermic reactions, instable intermediate

Microfluidic and Minifluidic

Microfluidic (ø 10-500 µm)

- 🟢 High heat transfer
- 🟢 Efficient mixing
- 🔴 Low flow capacity
- 🔴 High pressure drop
- 🔴 Tendency to block

Minifluidic (ø >0.5mm)

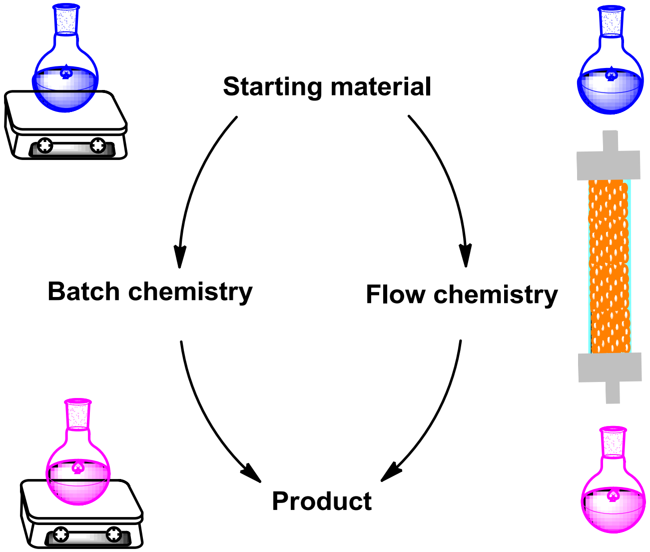
- 🟢 High flow capacity
- 🟢 Low pressure drop
- 🟢 No blocking
- 🟢 Multigrams-multikilogram scale
- 🟢 Packed reactors
- 🔴 Lower heat transfer

A. Kirschning, *Chem. Comm*, **2011**, 4583.

From batch to flow

Stoichiometry
Concentration / Volumetric ratio

- Batch Volume
- Concentration
- Reaction time



Starting material

Batch chemistry

Flow chemistry

Product

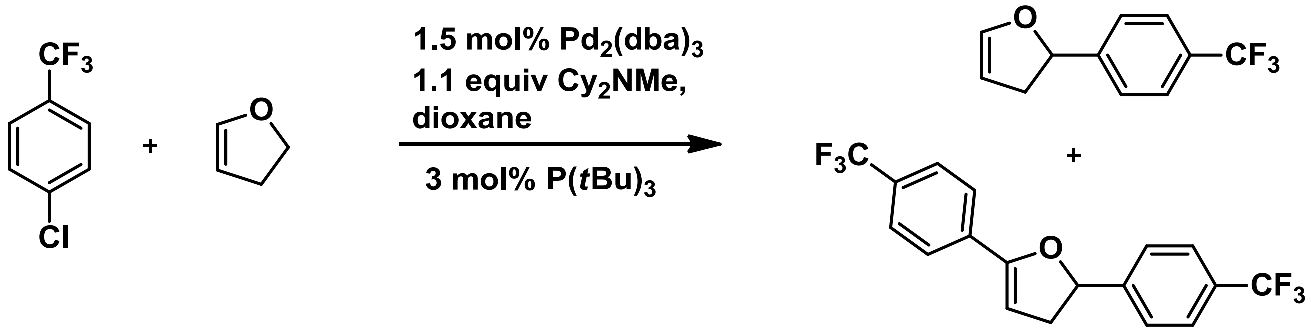
Stoichiometry
Concentration / Flow rate

- Reactor Volume
- Residence time
- Operation time

EtOH → AcOH	**Industrial batch process**	**Flow microreactor**
Residence time (s)	1760	3
Conversion (%)	30/90	>99
Reaction volume (cm^3)	2900	3
Throughput (cm^3/h)	5930	4300
Space-time yield (h^{-1})	0.7-2.0	500

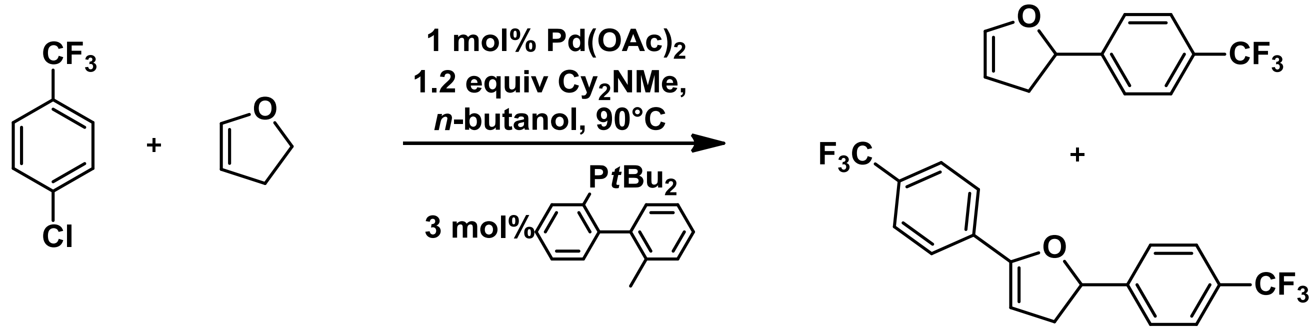
A. Kirschning, *Chem. Comm*, **2011**, 4583. H.Lowe, *Chem. Eng. Technol.*,**2005**, *28*, 267.

From batch to flow
Heck reaction



- Side biaryl compound
- Formation of black Pd
- Insoluble ammonium salt

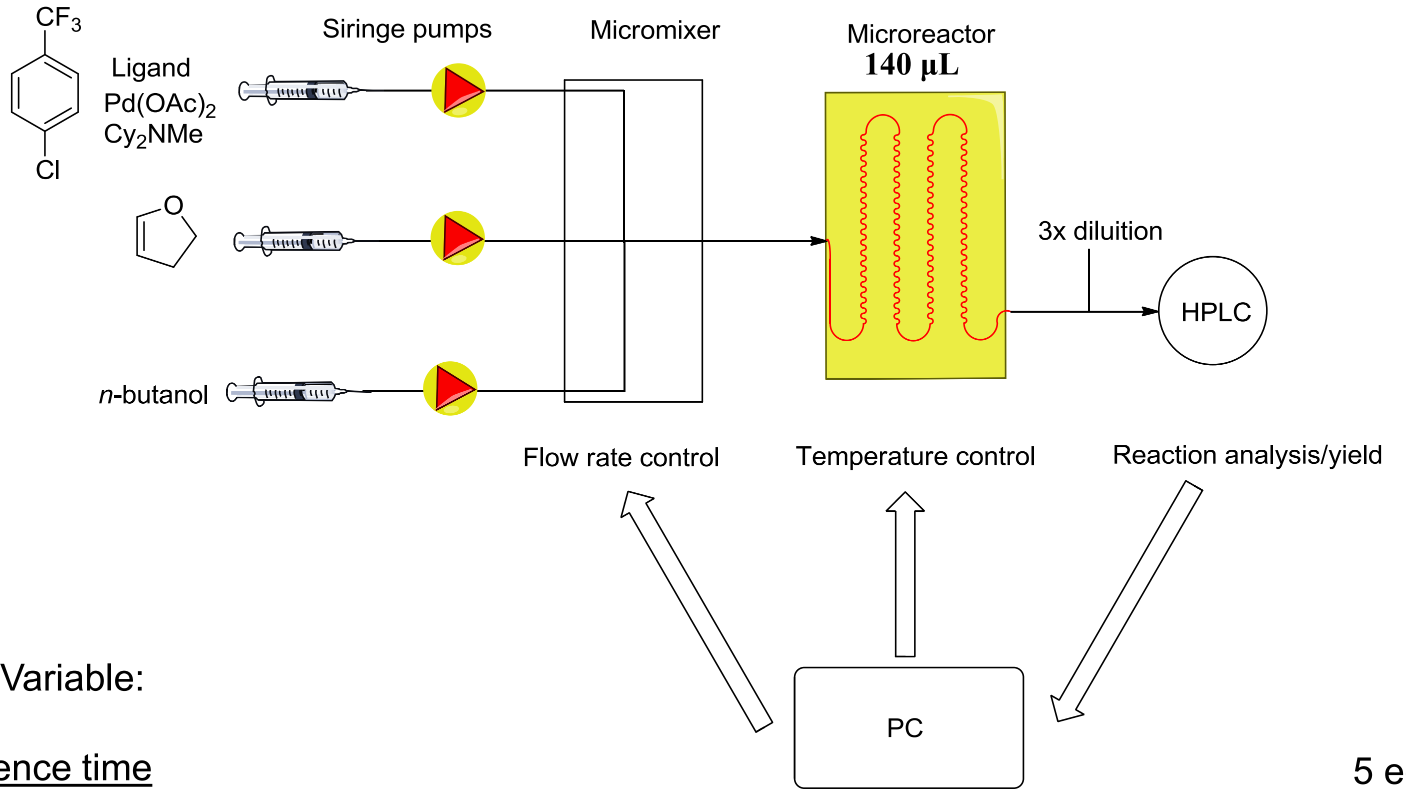
G. C. Fu, *JACS* **2001**, *123*, 6989.



S. L. Buchwald and K. F. Jensen, *ACIE,* **2010**, *49*, 7076.

From batch to flow
Heck reaction

Self optimization



Variable:

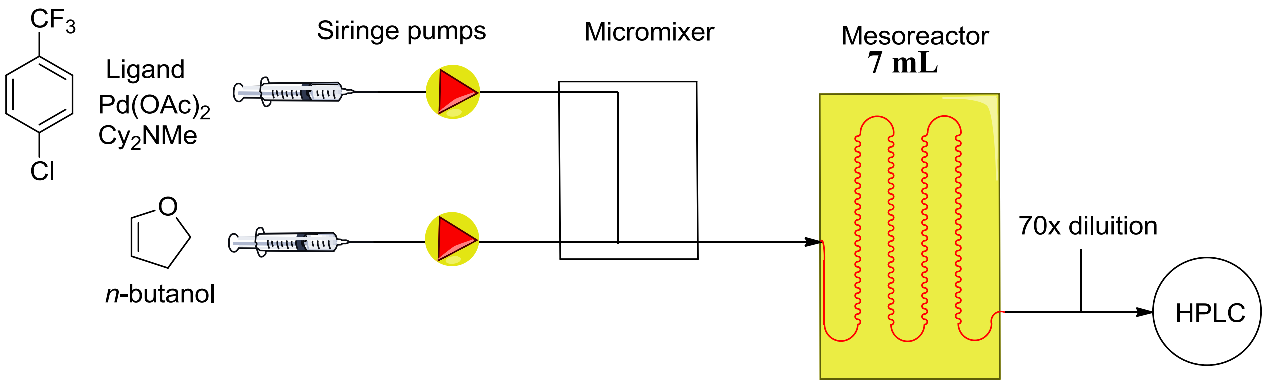
- Residence time
- Equivalents of alchene
- Concentration
- Catalyst loading
- Ph value
- Ionic strenght

5 eq of alchene
6 gr of aryl chloride
Yield 83%
Process time 20 min

S. L. Buchwald and K. F. Jensen, *ACIE,* **2010**, *49*, 7076.

From batch to flow
Heck reaction

Scale up

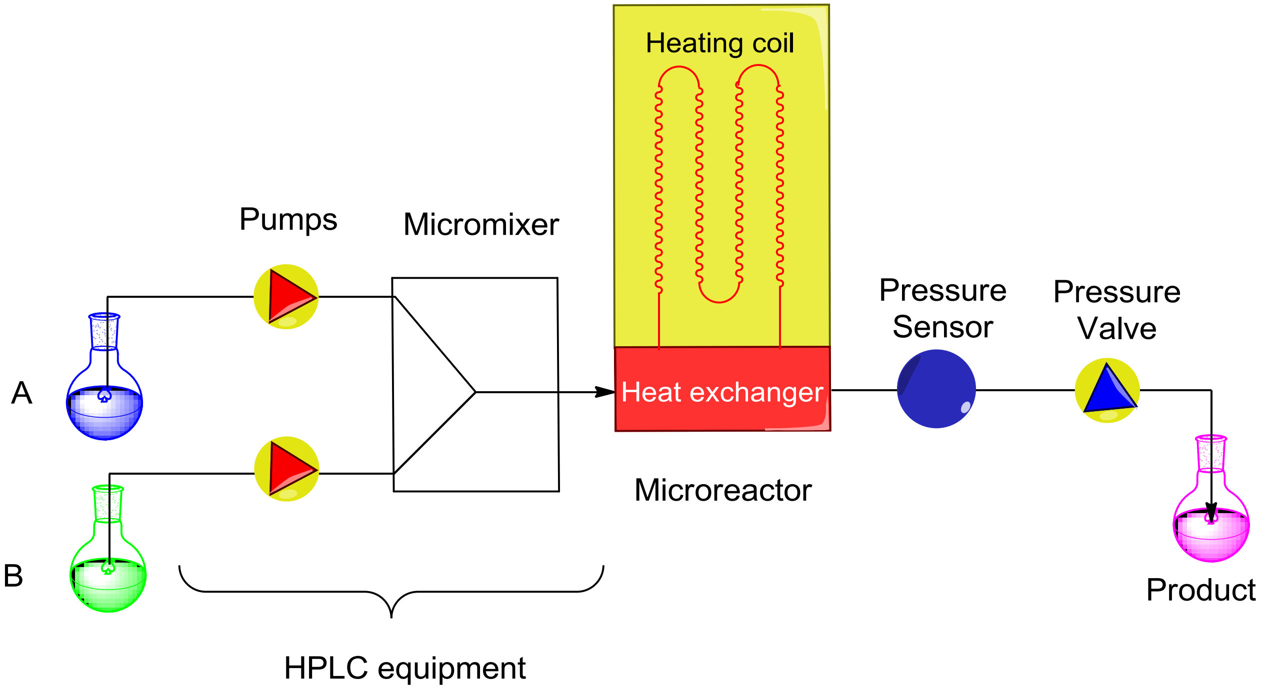


Concentration of alchene adjusted manually
No feedback control
Comparison with microscale

5 eq of alchene
26.9 g of product
Yield 80%
Process time 2 hours

S. L. Buchwald and K. F. Jensen, *ACIE,* **2010**, *49*, 7076.

High Temperature/Pressure Conditions

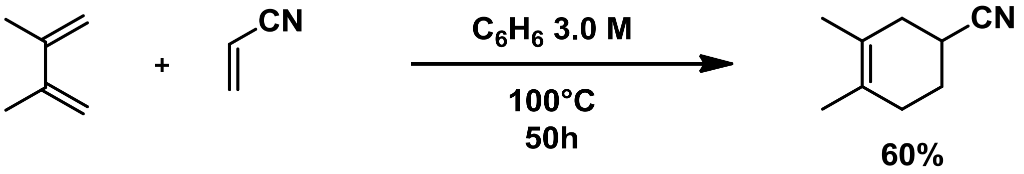


Steal microreactor:

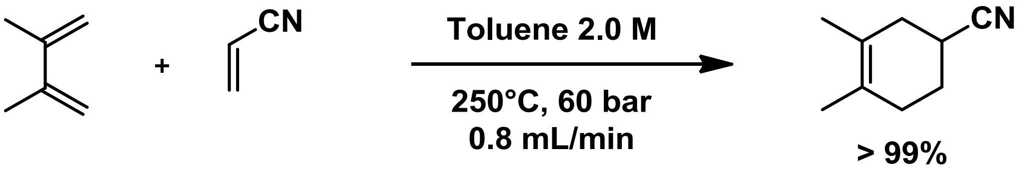
- Pressure up to 200 bar
- Temperature > 300°C
- Rapid heating and cooling
- Easily scale-up

C. O. Kappe, *Eur. J. Org. Chem.*, **2009**, 1321

High Temperature/Pressure Conditions



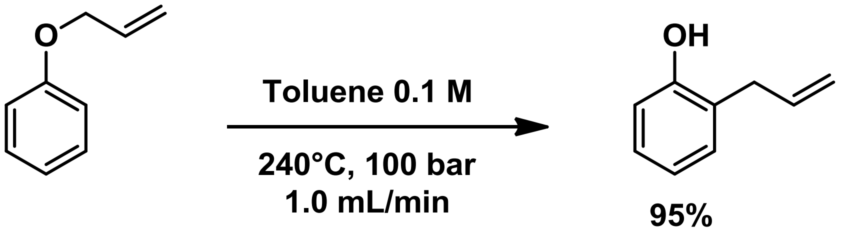
Li, Y.; Padias, A. B.; Hall, H. K., Jr. *J. Org. Chem.* **1993**, *58*, 7049**.**



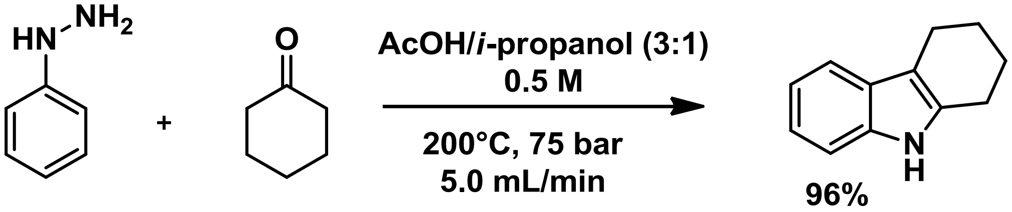
Also:
MeCN 36 bar
THF 42 bar
DME 33 bar

T. N. Glasnov and C. O. Kappe, *Eur. J. Org. Chem.*, **2009**, 1321

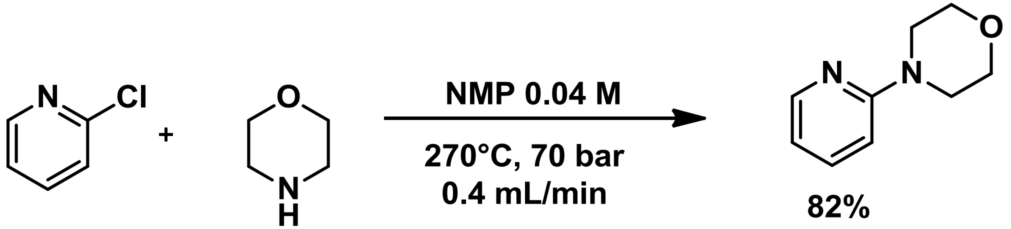
High Temperature/Pressure Conditions



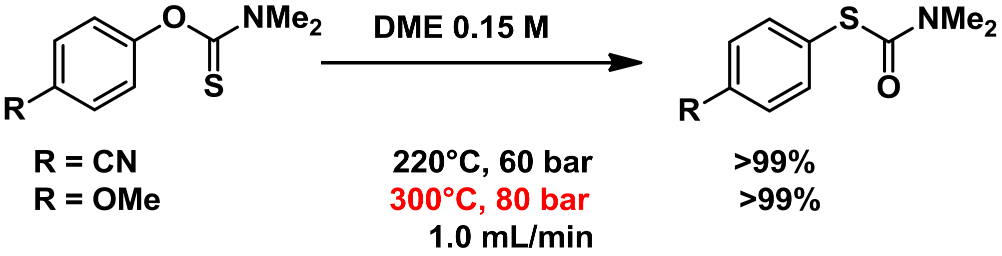
- Claisen rearrangement



- Indole Fisher synthesis



- S_NAr of inactivated Ar



R = CN
R = OMe

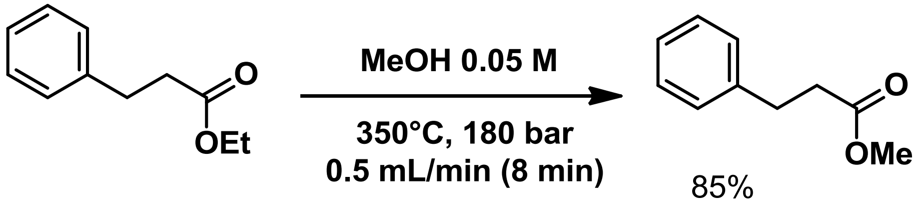
220°C, 60 bar
300°C, 80 bar
1.0 mL/min

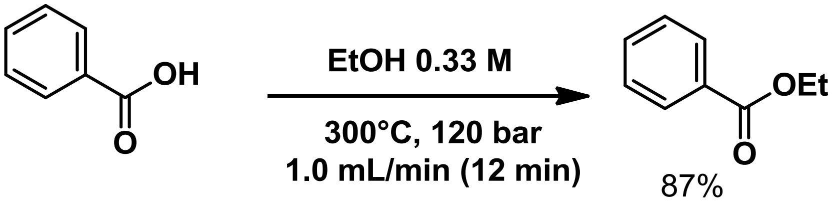
>99%
>99%

- Newman-Kwart rearrangement

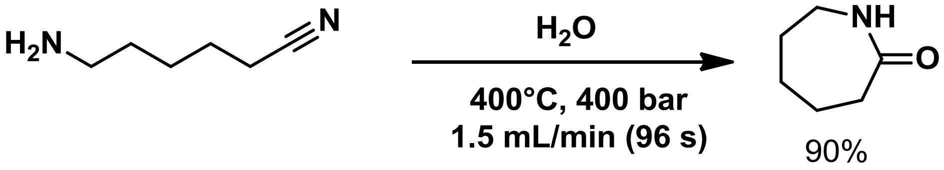
T. N. Glasnov and C. O. Kappe, *Eur. J. Org. Chem.*, **2009**, 1321

Supercritical Conditions



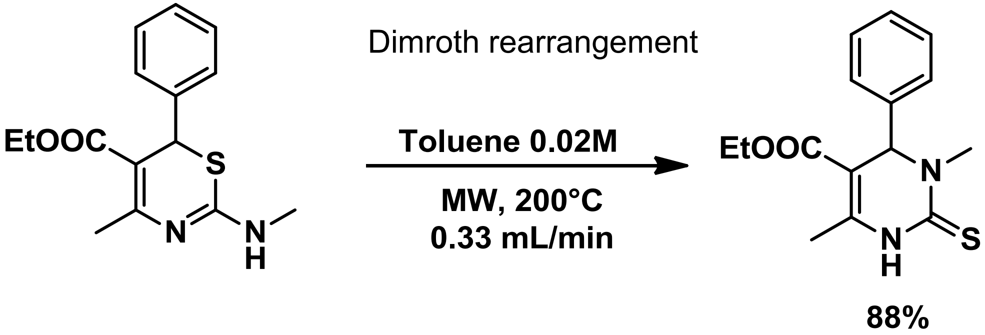


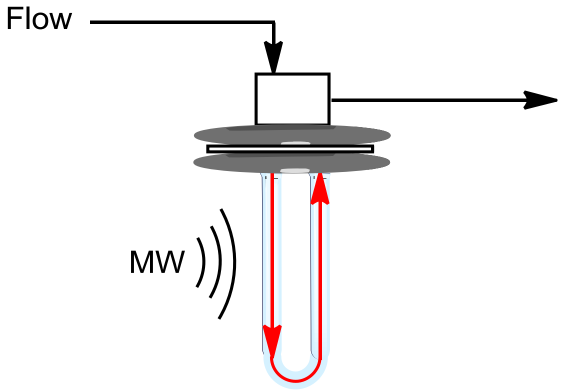
C. O. Kappe, *Eur. J. Org. Chem.*, **2009**, 1321

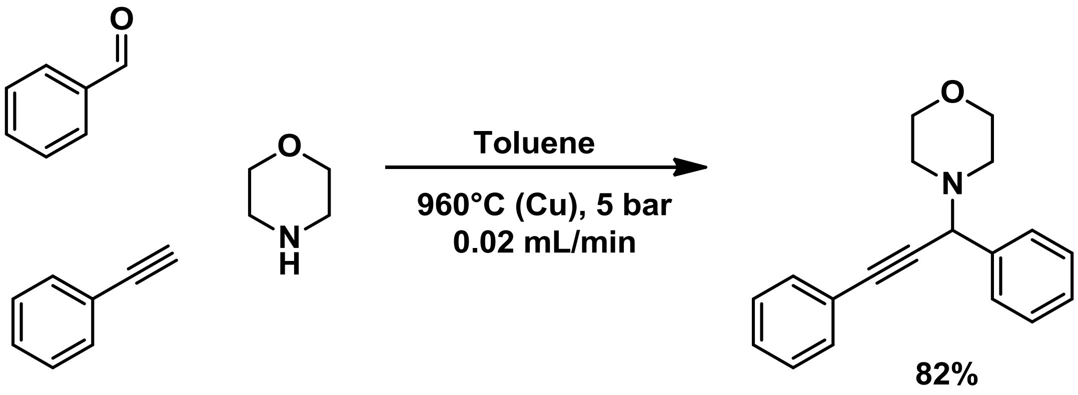


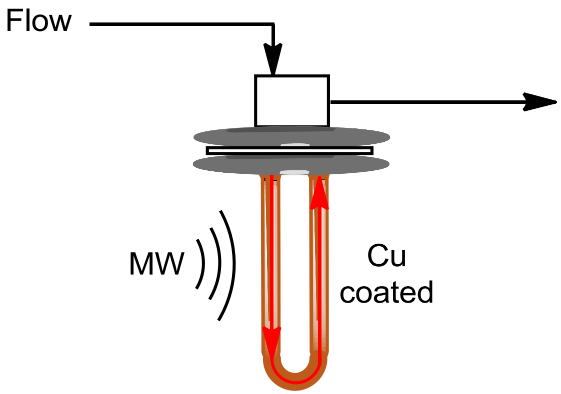
M. Poliakoff, *Green Chem.,* **2008**, *10*, 98.

Microwave-assisted synthesis





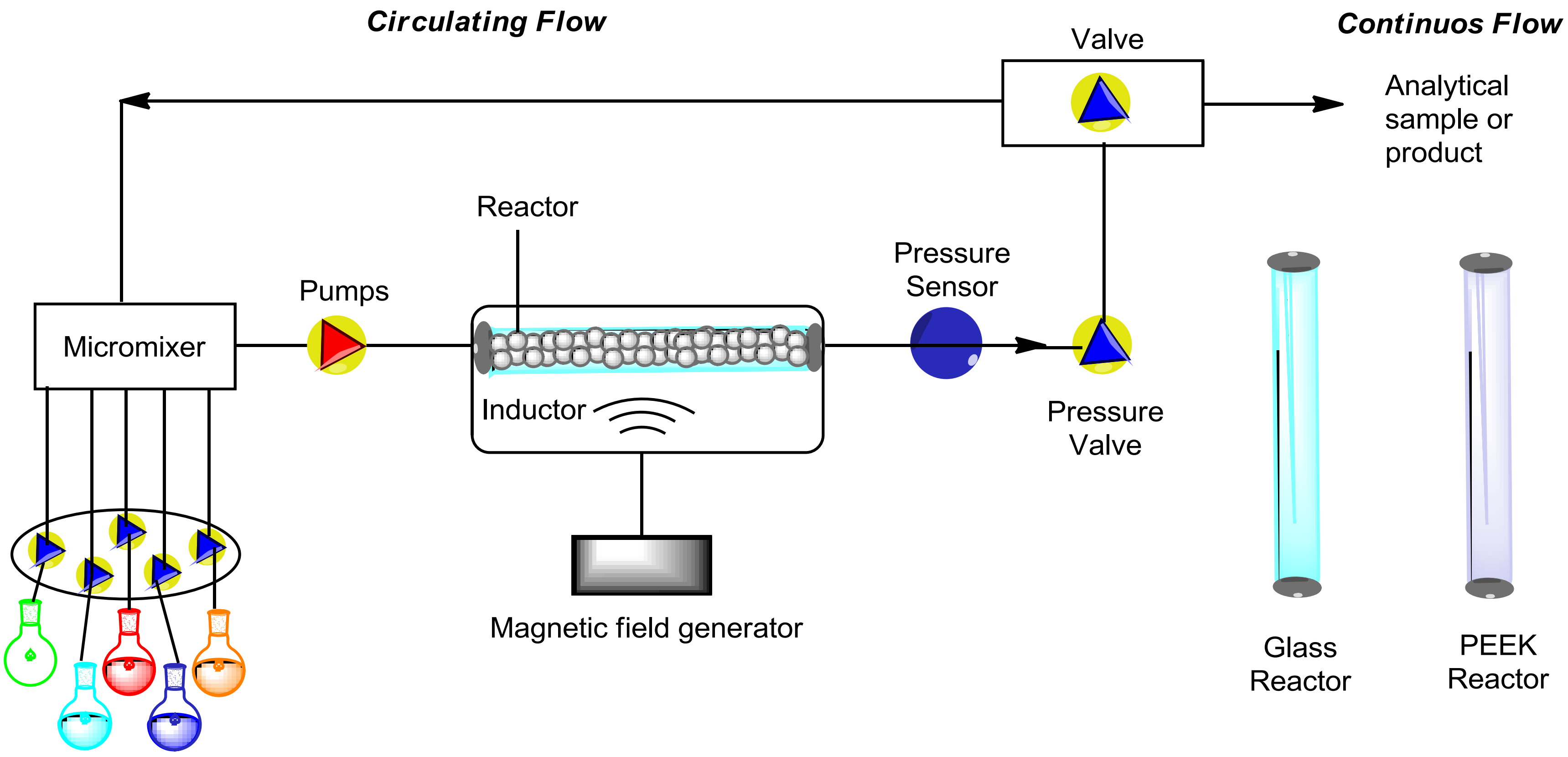




C. O. Kappe, QSAR Comb. Sci., **2006**, *25*, 509.

M. G. Organ, *Chem. Eur. J.,* **2010**, *16*, 126

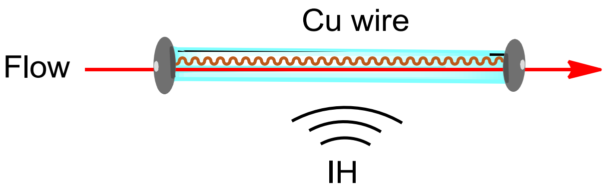
Inductively hated flow reactor

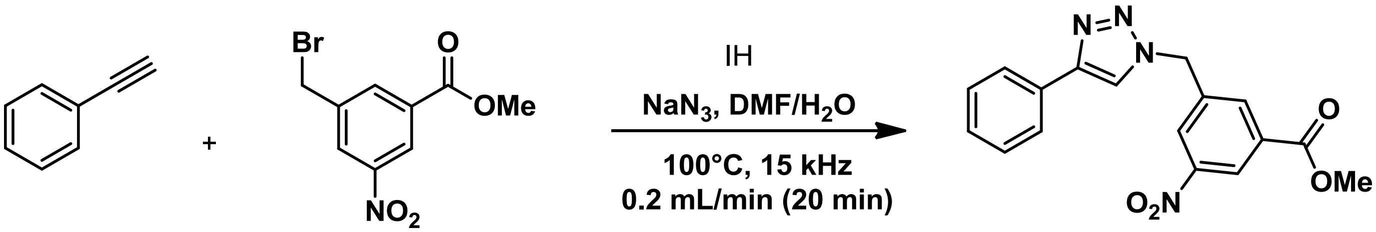


● Superparamagnetic particle

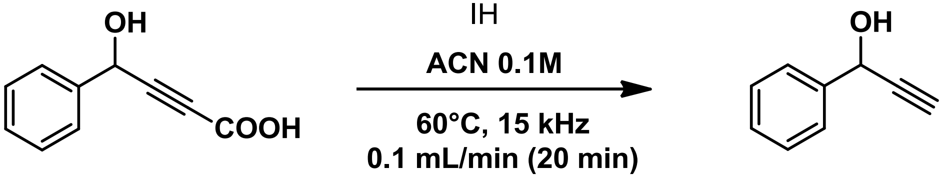
PEEK (polyether ether ketone)

Inductively hated flow reactor



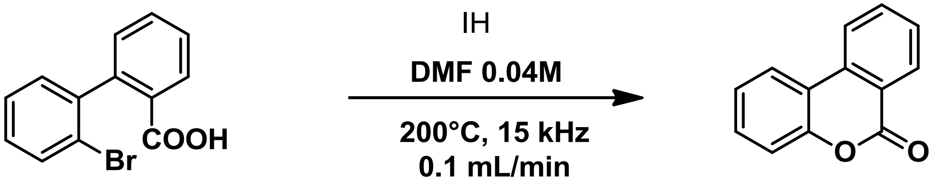


Flow 99%
Batch no conversion



Flow 93%
Batch 99% (3h)

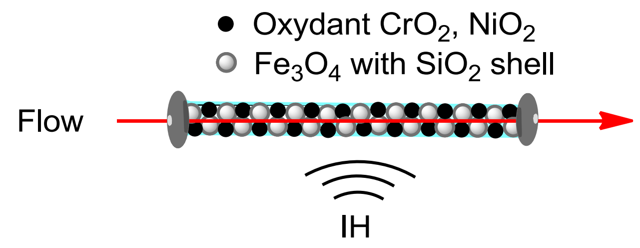
PEEK reactor



Flow 95%
Batch 77% (2.5h)

A. Kirschning, *Synlett*, **2010**, 2009.

Inductively hated flow reactor

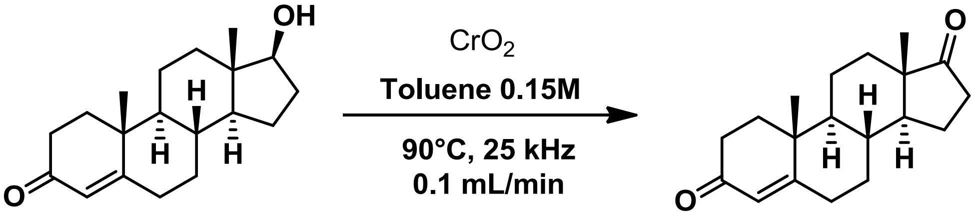


● Oxydant CrO_2, NiO_2

● Fe_3O_4 with SiO_2 shell

Flow

IH

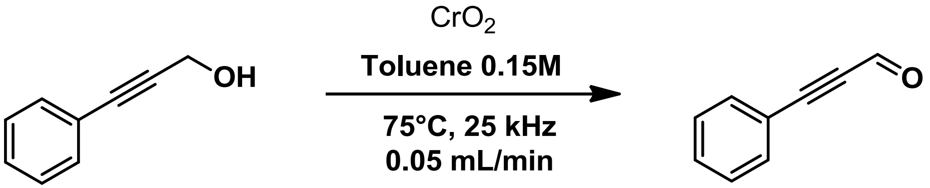


CrO_2

Toluene 0.15M

90°C, 25 kHz
0.1 mL/min

Flow 95%
Batch 95% (22h)

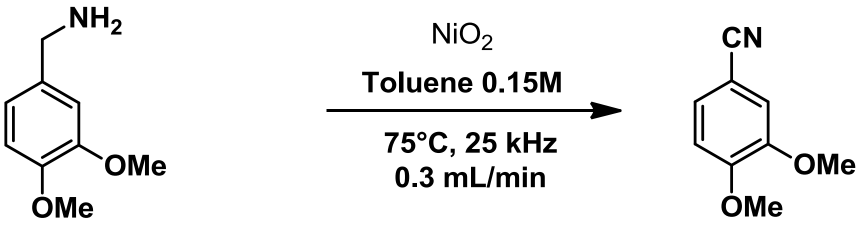


CrO_2

Toluene 0.15M

75°C, 25 kHz
0.05 mL/min

Flow 93%
Batch 46% (7h)



NiO_2

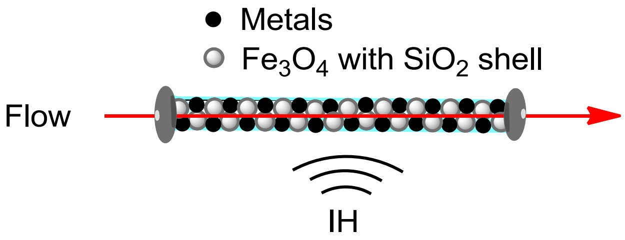
Toluene 0.15M

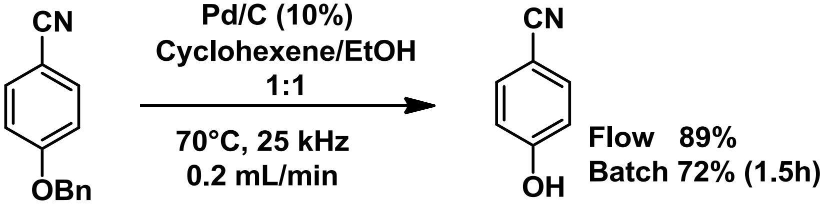
75°C, 25 kHz
0.3 mL/min

Flow 82%
Batch 70% (4h)

A. Kirschning, *Chem. Eur. J.*, **2010**, 4372.

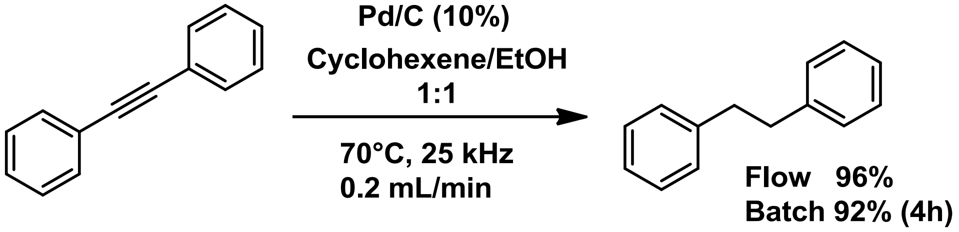
Inductively hated flow reactor





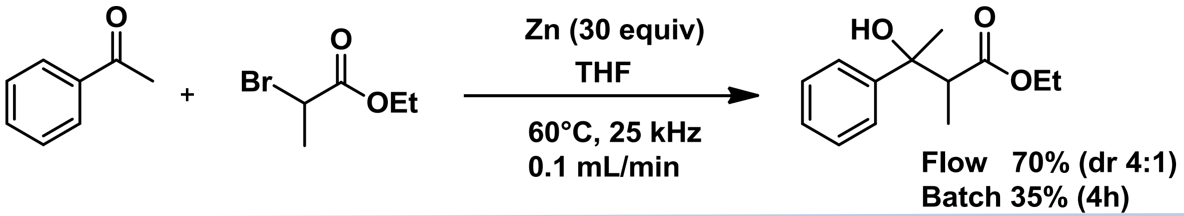
Flow 89%
Batch 72% (1.5h)

- Hydrogenolysis



Flow 96%
Batch 92% (4h)

- Reduction

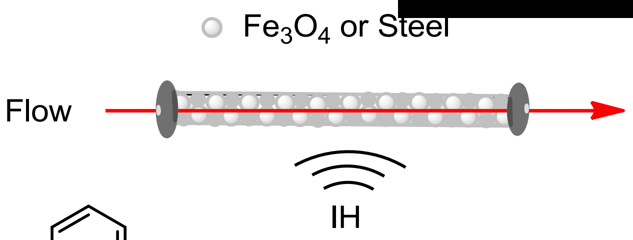


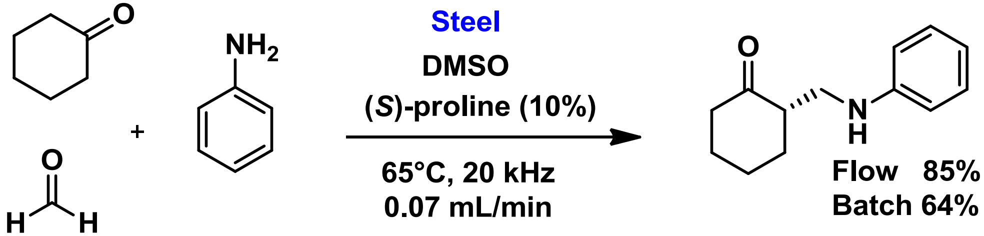
Flow 70% (dr 4:1)
Batch 35% (4h)

- Reformatzky

A. Kirschning, *Chem. Eur. J.*, **2011**, 1884.

Inductively hated flow reactor
Multi-component reactions

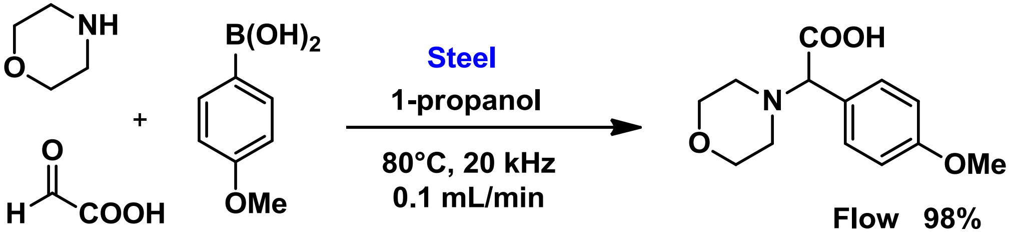




Steel
DMSO
(*S*)-proline (10%)
65°C, 20 kHz
0.07 mL/min

Flow 85% (88% ee)
Batch 64% (92% ee) (1 h)

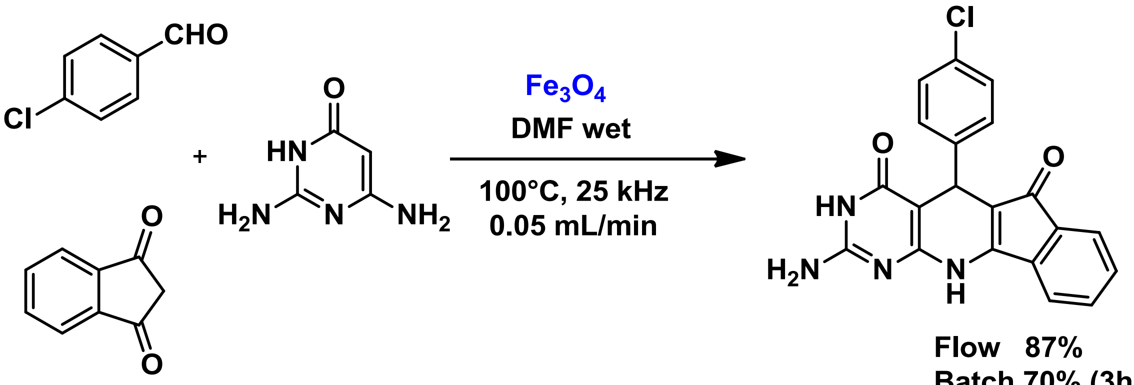
- Mannich



Steel
1-propanol
80°C, 20 kHz
0.1 mL/min

Flow 98%
Batch 77% (40 min)

- Petasis



Fe_3O_4
DMF wet
100°C, 25 kHz
0.05 mL/min

Flow 87%
Batch 70% (3h)

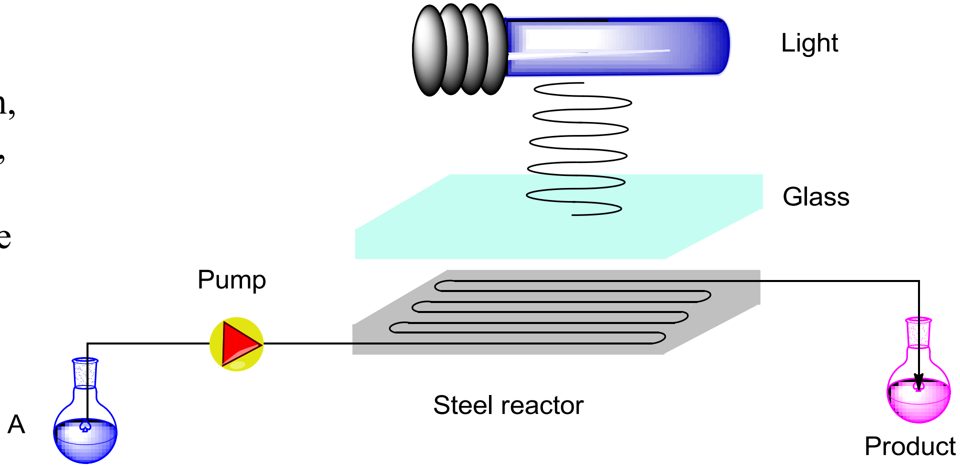
- MCR

A. Kirschning, *Chem. Eur. J.*, **2011**, 1884.

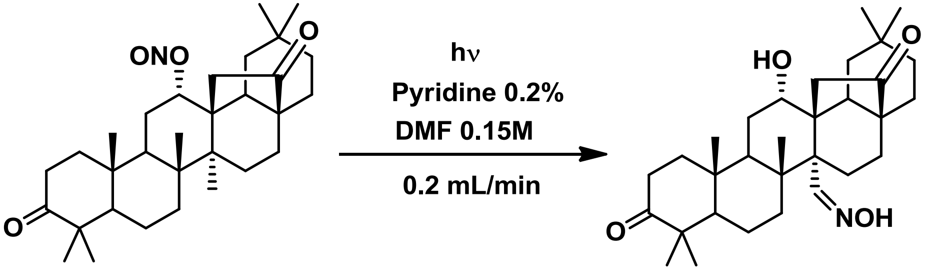
Flow and photochemistry

Burton reaction

Micro flow
1000 µm width,
107 µm depth,
2.2 m length
0.2 mL volume



Mini flow
1000 µm width,
500 µm depth,
0.5 m length
4 mL volume



- **Micro flow condition (10 mL)**
- **15 W black light or LED**
- **Pyrex glass**
- **71% yield**
- **mg scale, 0.05 mL/h**
- **6-12 min residence time**

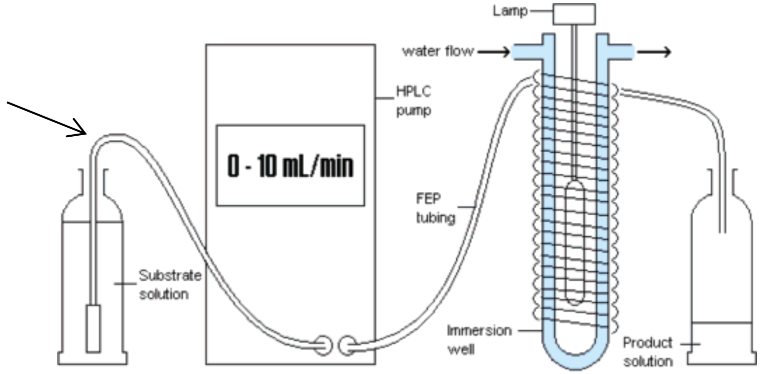
- **Mini flow condition**
- **15 W black light (6x)**
- **Pyrex glass**
- **61% yield**
- **5.3 g (HPLC) 40 h of flow**
- **20 min residence time**

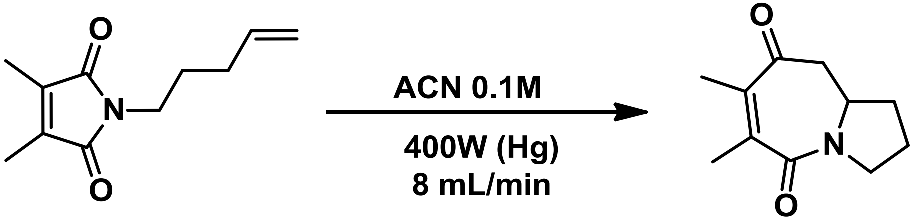
I. Ryu, *Tetrahedron*, **2009**,*65*, 1593.

Flow and photochemistry

Photocycloadditions

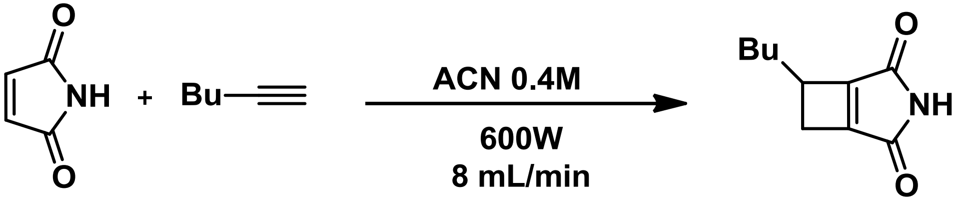
Fluorinated ethylpropylene





80%
178 gr

- [5 + 2]

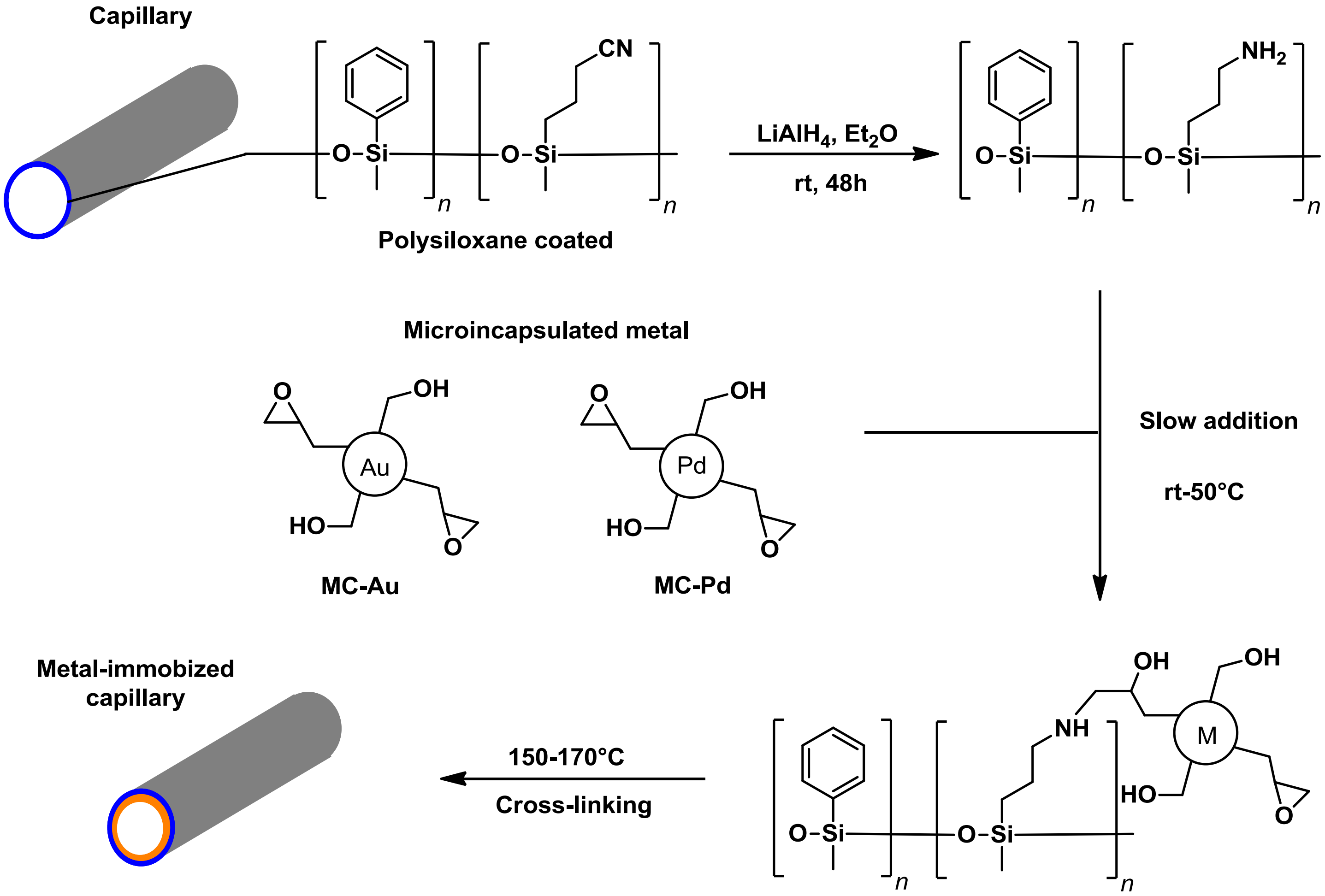


83%
685 gr

- [2 + 2]

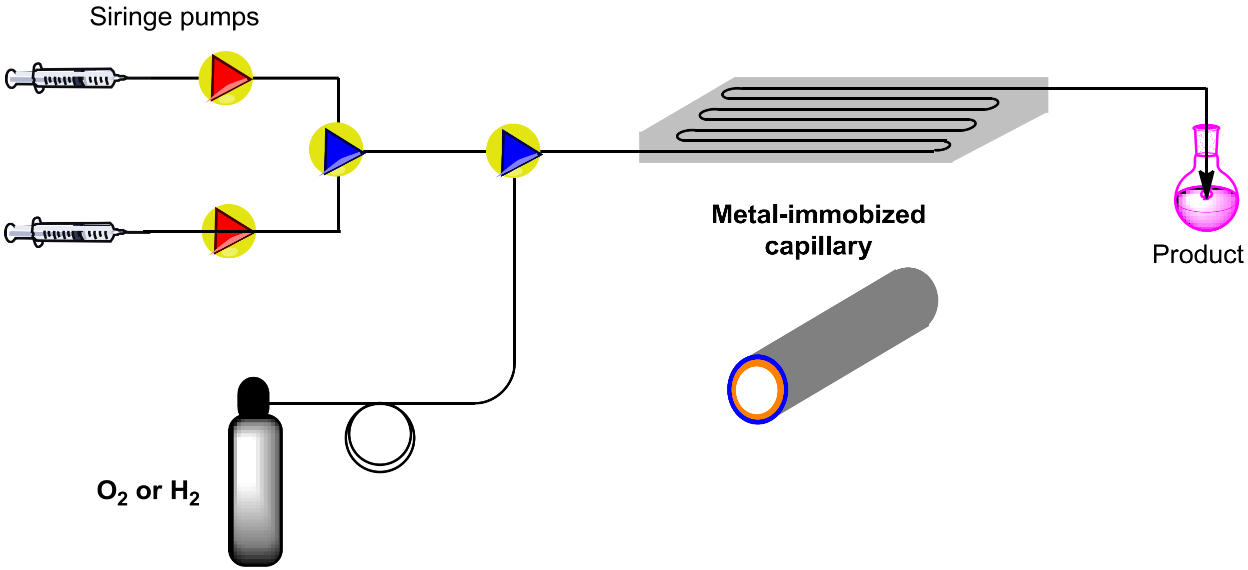
M. B. Berry and K. I. Booker-Milburn, *J. Org. Chem*., **2005**, *70*, 7558.

Flow on supported catalysts



S. Kobayashi, *Science* **2004**, *304*, 1305 S. Kobayashi, *ACIE* **2009**, *48*, 4744

Flow on supported catalysts

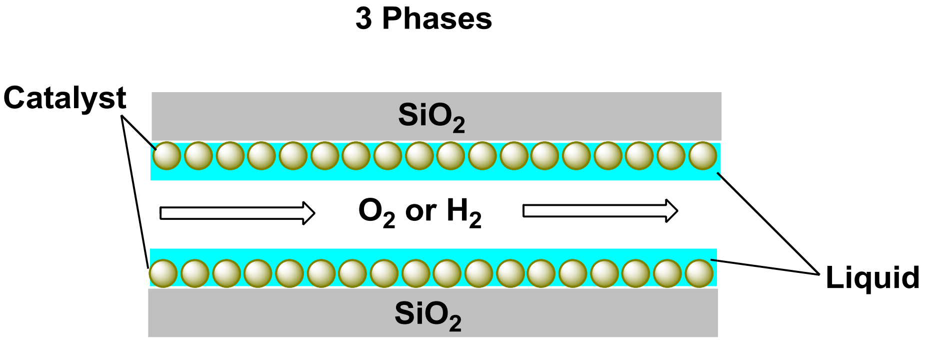


Siringe pumps

Metal-immobized capillary

Product

O_2 or H_2



3 Phases

Catalyst

SiO_2

O_2 or H_2

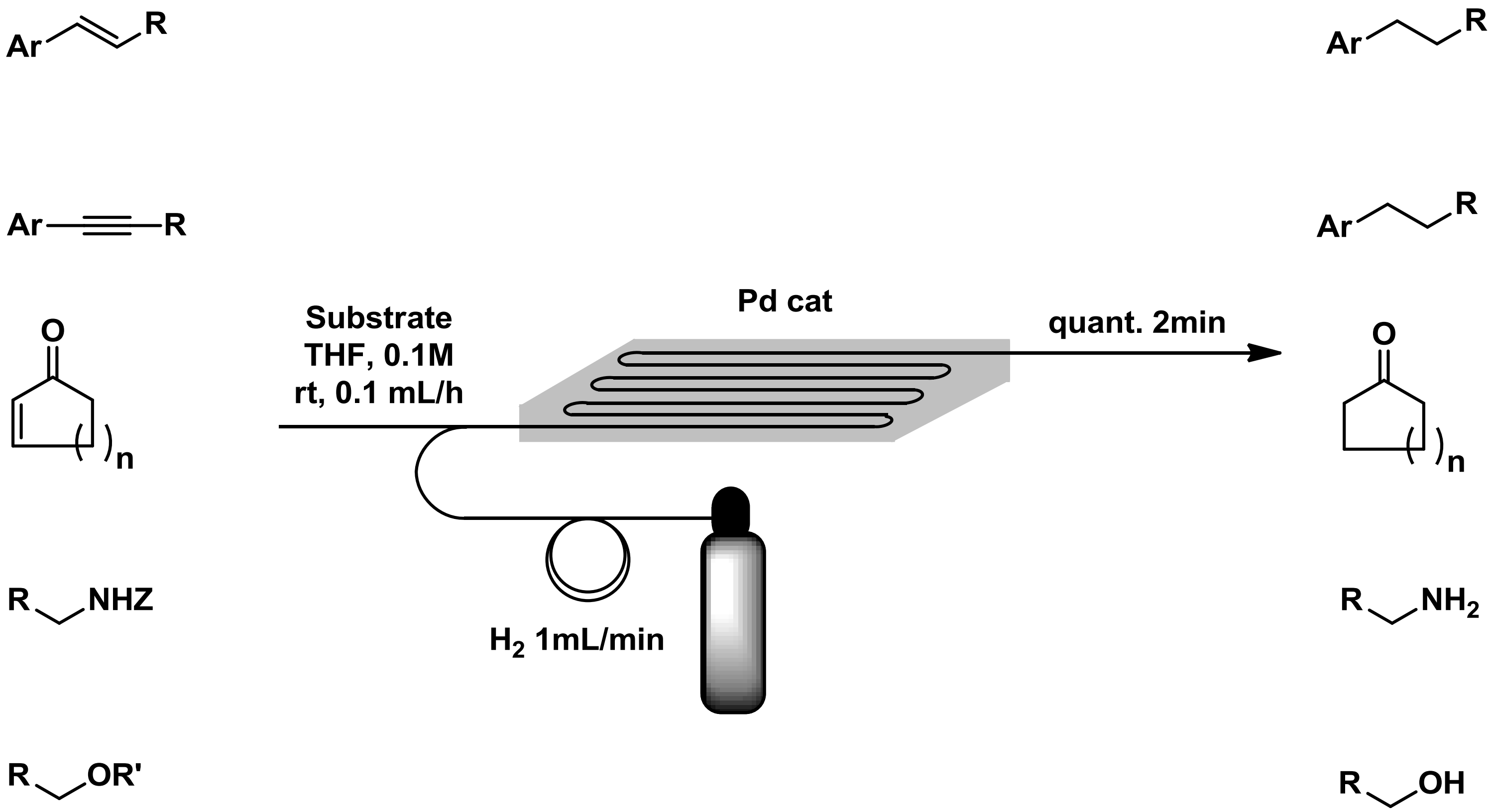
Liquid

SiO_2

S. Kobayashi, *Science* **2004**, *304*, 1305   S. Kobayashi, *ACIE* **2009**, *48*, 4744

Flow on supported catalysts

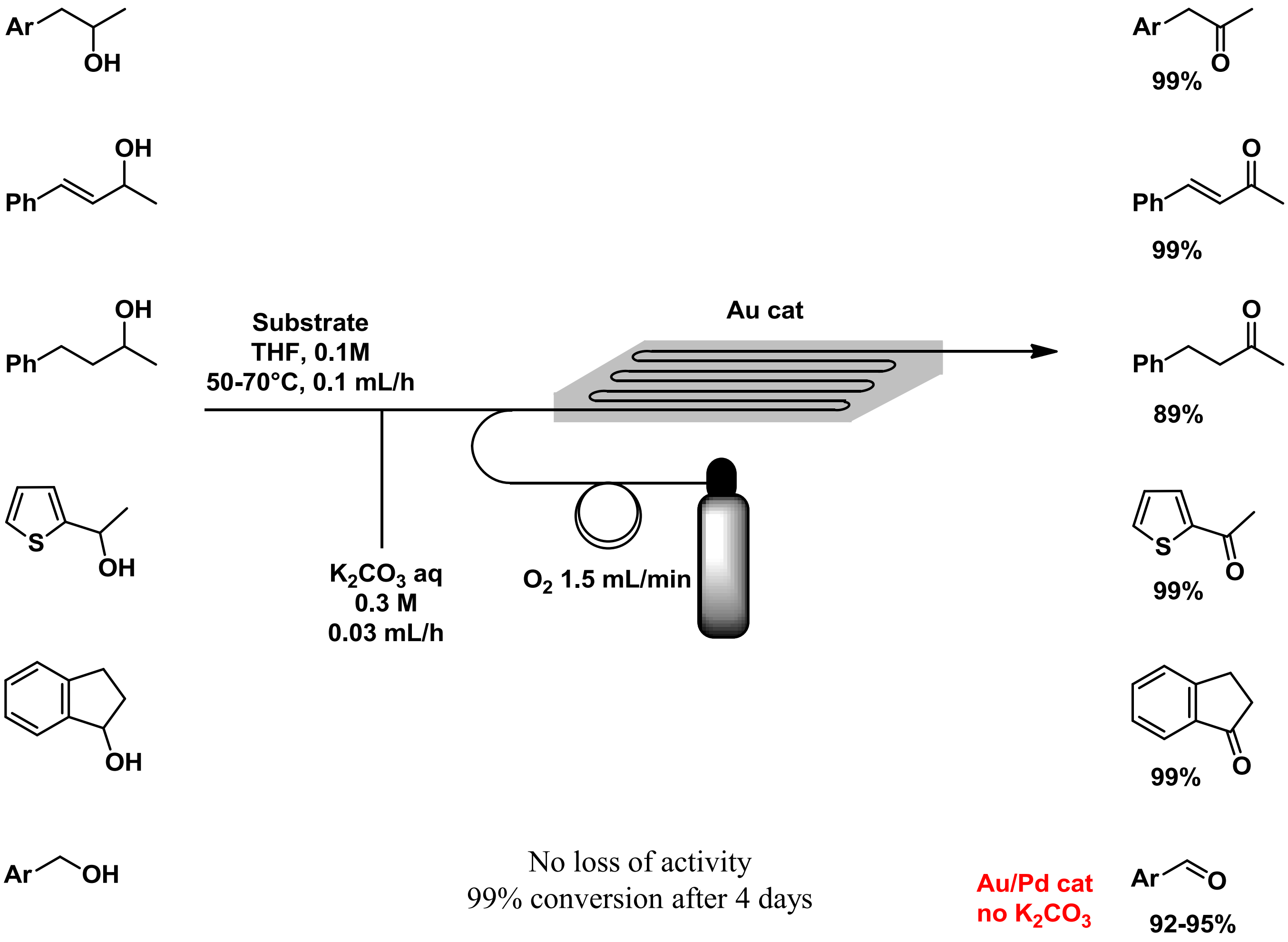
Hydrogenation



S. Kobayashi, *Science* **2004**, *304*, 1305

Flow on supported catalysts

Oxidation



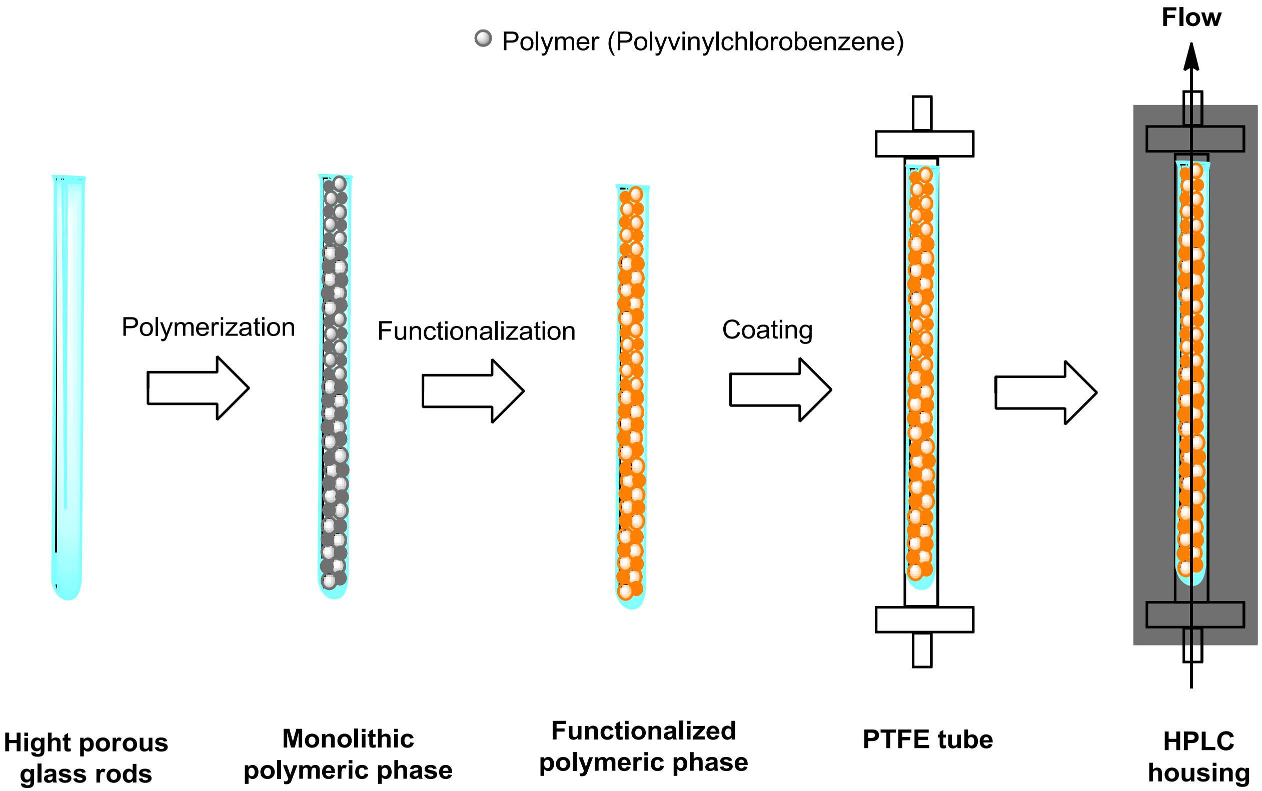
No loss of activity
99% conversion after 4 days

Full conversion in flow

S. Kobayashi, *ACIE* **2009**, *48*, 4744

Flow synthesis throw solid phase reagents

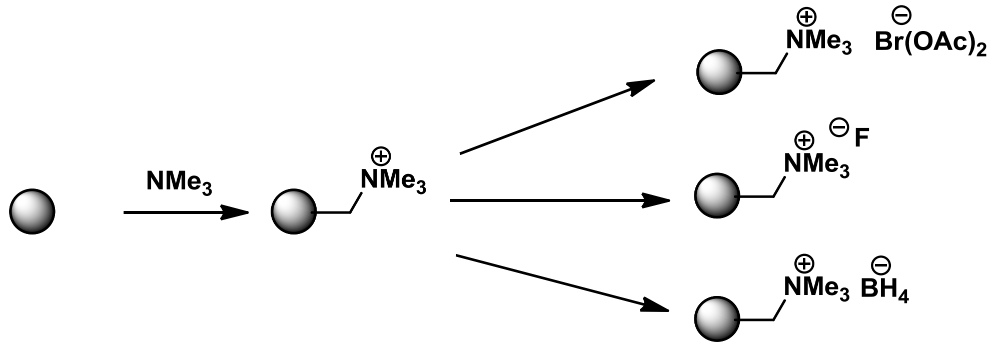
PASSflow
Polymer Assisted Solution-phase Synthesis

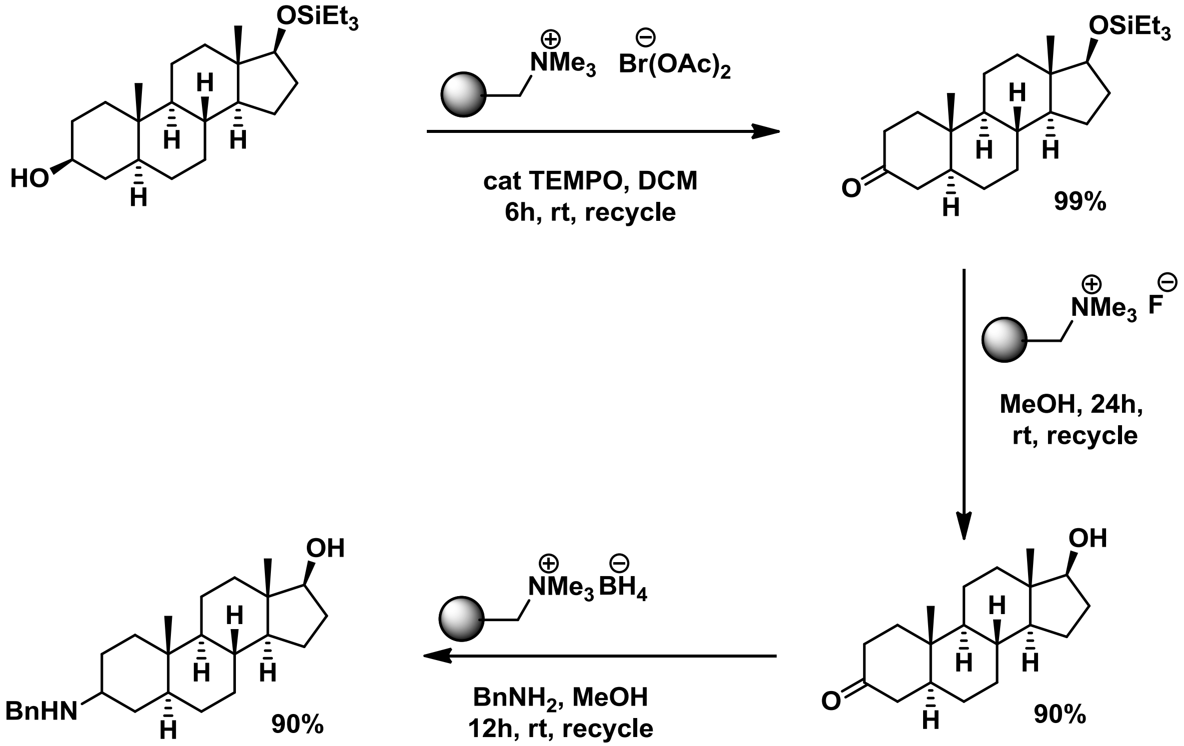


- **Homogeneus surface**
- **Hight pressure drop avoided**
- **HPLC system used**
- **Wide functionalization**

A. Kirschning, *ACIE,* **2001**, 3995.

Flow synthesis throw solid phase reagents

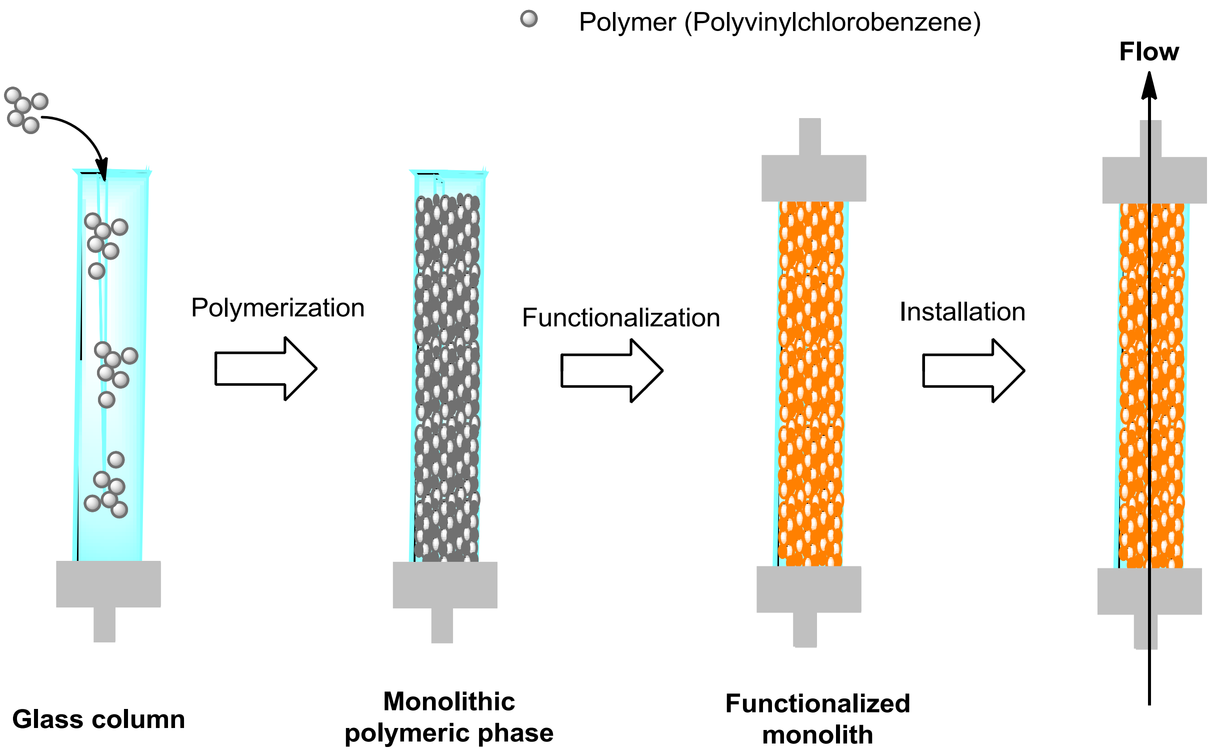




A. Kirschning, *ACIE,* **2001**, 3995.

Flow synthesis throw solid phase reagents

Curtius Rearrangement



● Polymer (Polyvinylchlorobenzene)

Flow

Polymerization

Functionalization

Installation

Glass column

Monolithic polymeric phase

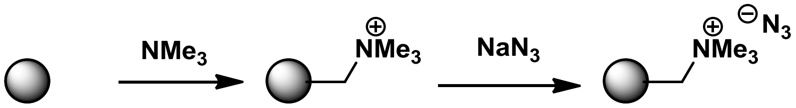
Functionalized monolith

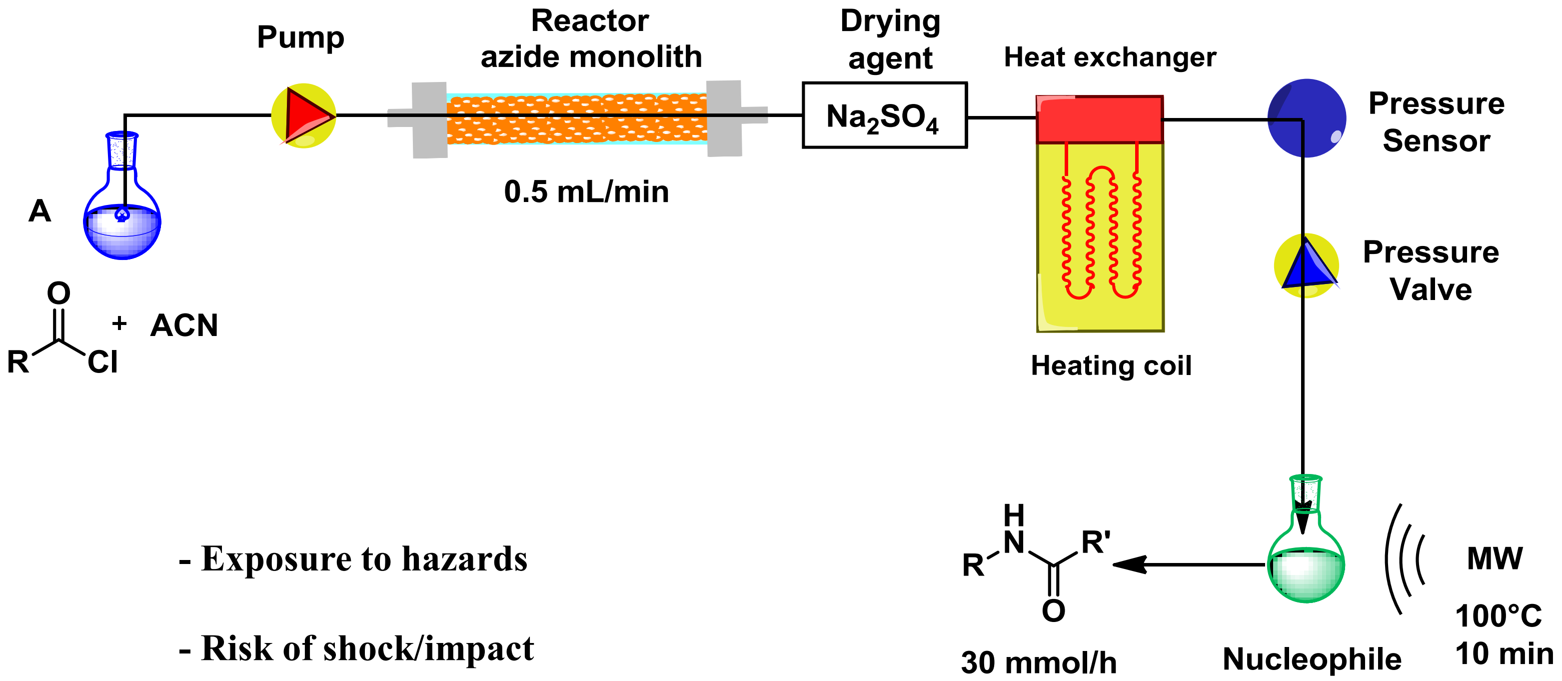
- **Control of pore dimension**
- **Micro- and mini-flow system**
- **Easy to scale up**
- **Wide functionalization**

S. V. Ley, *Org. Biomol. Chem.*, **2008**, 1578.

Flow synthesis throw solid phase reagents

Curtius Rearrangement





- Exposure to hazards

- Risk of shock/impact

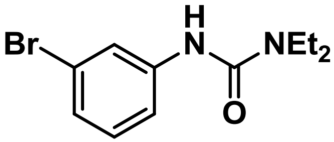
\+ Multiple usage

\+ Easy regenaration

S. V. Ley, *Org. Biomol. Chem.*, **2008**, 1578.

Flow synthesis throw solid phase reagents

Curtius Rearrangement



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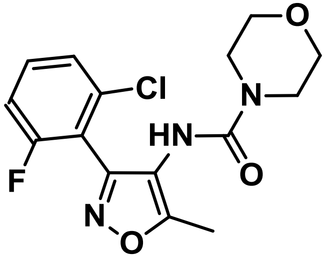

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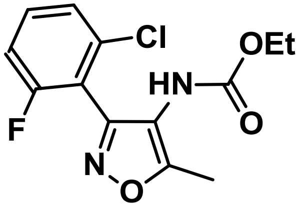

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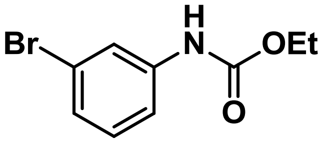

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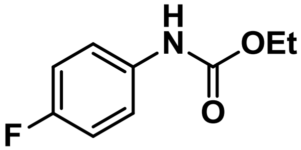

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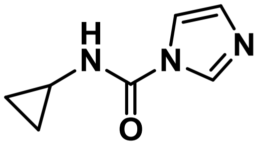

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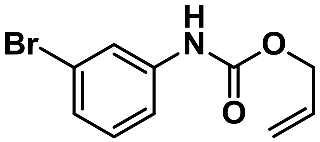

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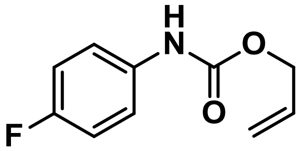

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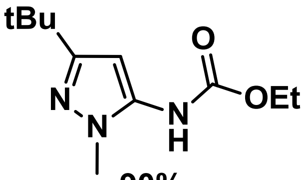
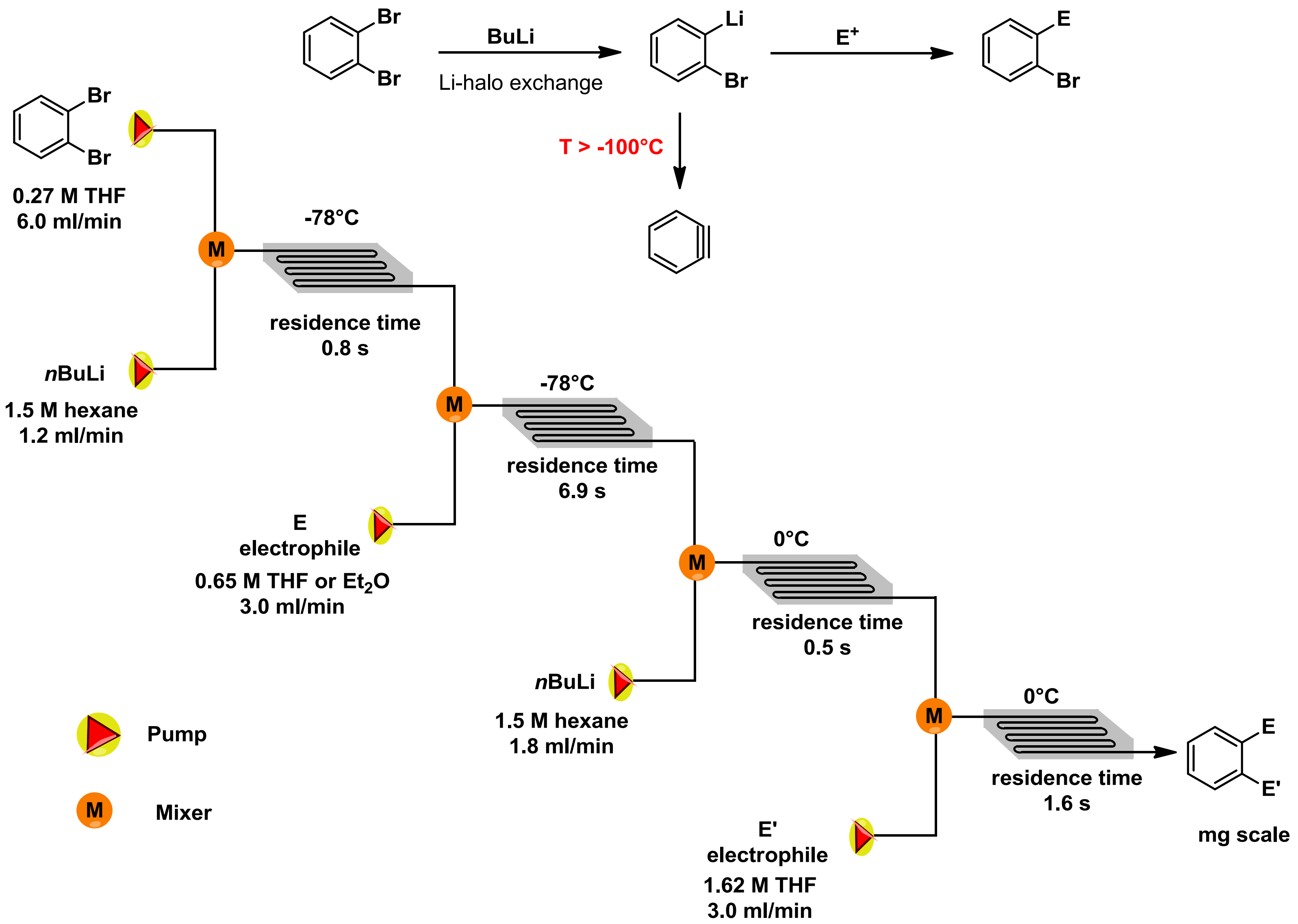


90%

S. V. Ley, *Org. Biomol. Chem.*, **2008**, 1578.

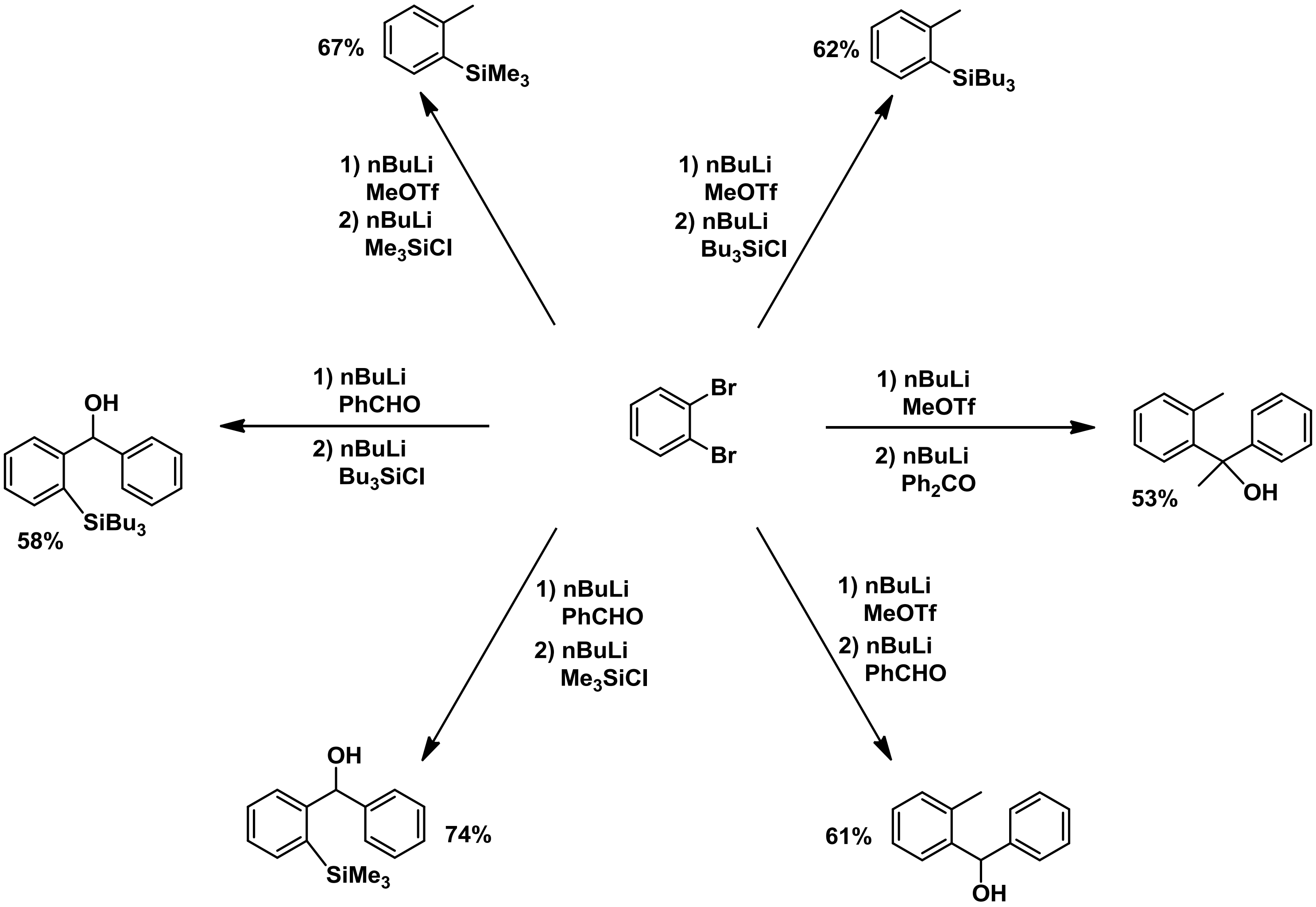
Multi step flow synthesis

Continuos Flow



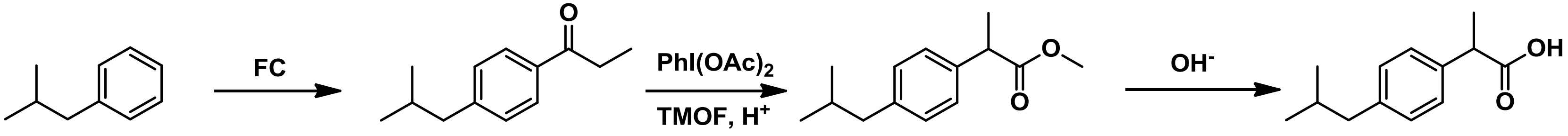
J.-I. Yoshida, *JACS*, **2007**, *129*, 3046.

Multi step flow synthesis

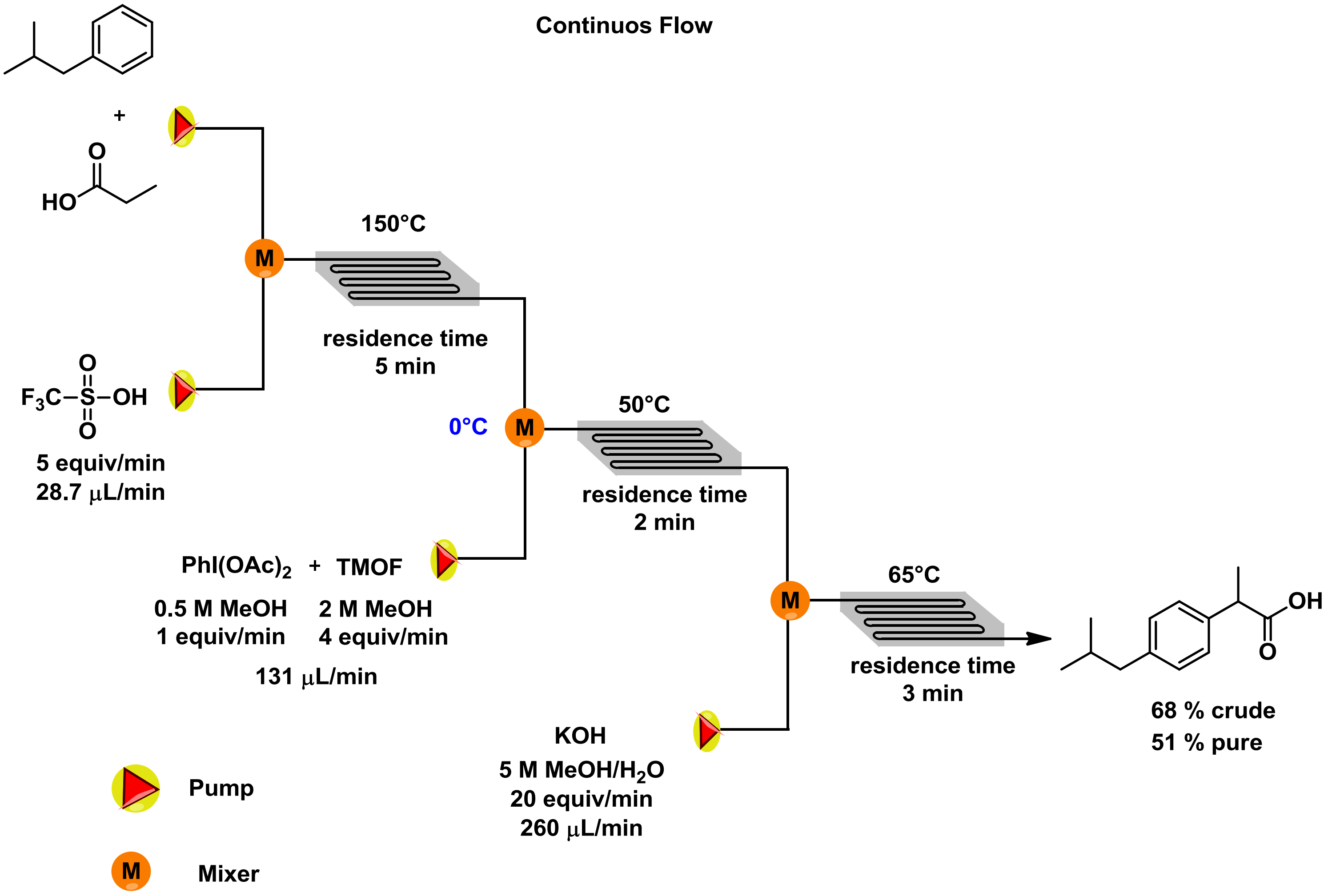


J.-I. Yoshida, *JACS*, **2007**, *129*, 3046.

Multi step flow synthesis



Continuos Flow



5 equiv/min
28.7 μL/min

150°C
residence time
5 min

0°C

50°C
residence time
2 min

PhI(OAc)$_2$ + TMOF
0.5 M MeOH 1 equiv/min
2 M MeOH 4 equiv/min
131 μL/min

65°C
residence time
3 min

KOH
5 M MeOH/H$_2$O
20 equiv/min
260 μL/min

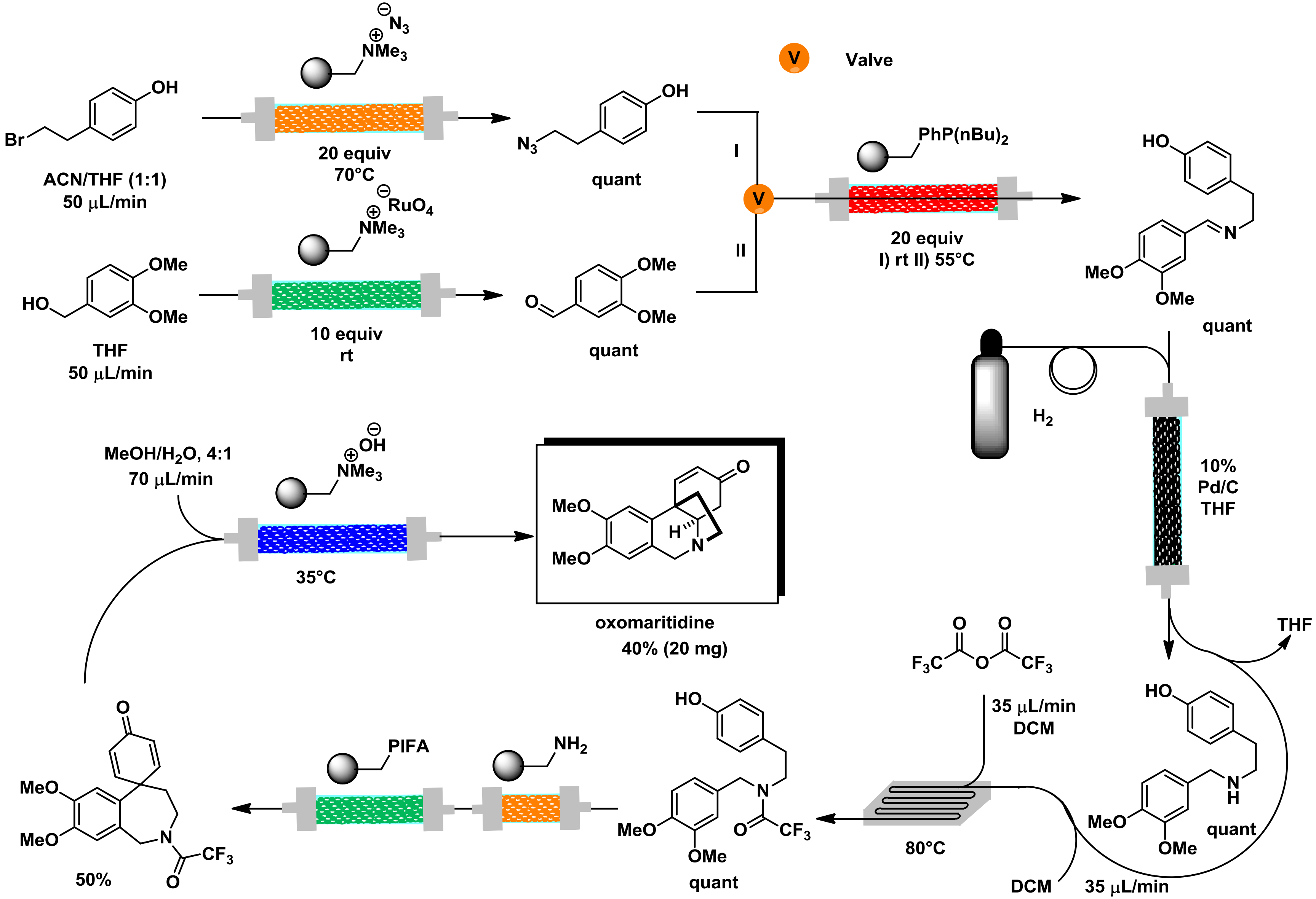
68 % crude
51 % pure

Pump

Mixer

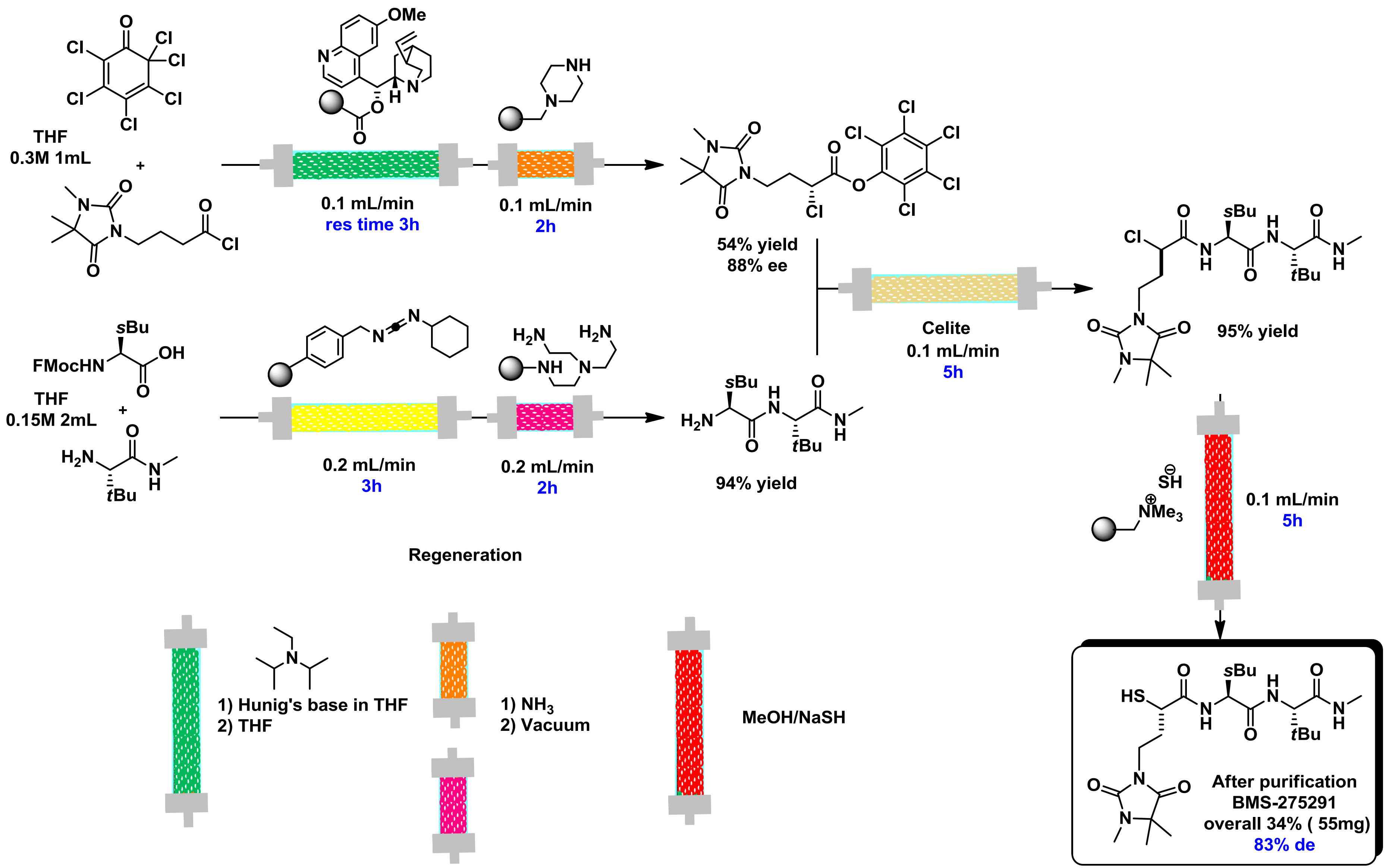
D. T. McQuade, *ACIE*, **2009**, *48*, 8547.

Multi step flow synthesis



S. V. Ley, *Chem. Commun.*, **2006**, 2566.

Multi step flow synthesis



T. Lectka, *Org. Lett.*, **2005**, *7*, 3009.

Conclusion

- Flow chemistry high potential to improve synthesis process
- Flow chemistry: safe, time saving and easy scale up
- Progress needed in multi reactor assembly
- Collaboration between Chemists and Engineers are essential

DESIGN AND APPLICATION OF HYDROPHILIC LIGANDS FOR AQUEOUS-PHASE METAL-CATALYZED ORGANIC REACTIONS

Weijia GAN
06 Jun 2011

Questions?

- How to improve the mass transport issue in aqueous-biphasic system?

- How the hydrophilic functionalities could influence the ligand properties (water solubility, steric and electronic effects)?

Outline

- Introduction
  - Why and how to use water as the solvent for organic reactions

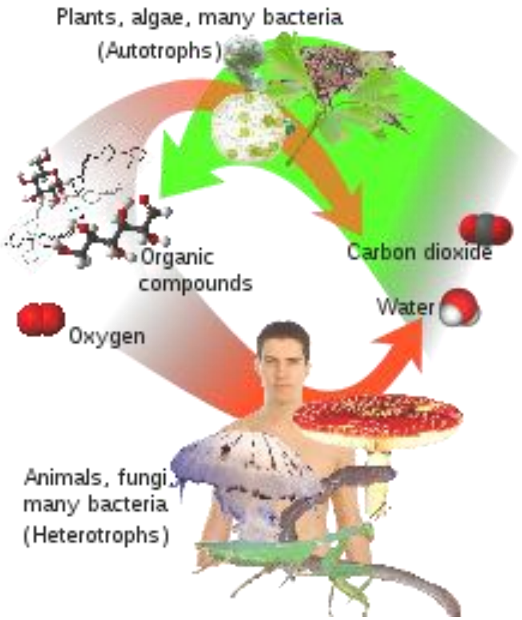
- Strategies to perform organic reaction in water using hydrophilic ligands
  - Examples of aqueous-phase hydroformylation

- Examples of the application of the hydrophilic ligands on some typical organic reactions
  - Hydrogenation; metathesis; cross-coupling; oxidation; etc.

- Conclusions and perspectives

Solvent of life - water

- Water covers more than 70.9% of the earth’s surface and makes up about 60% of the mass of the human body.



- Water plays an important role in the world economy as it functions as solvent for a wide variety of chemical substances and facilitates industrial cooling and transportation.

Organic solvents vs. water

Organic solvents

- Dissolve a wide range of organic compounds
- A variety of options and properties
- Volatile and easily removed
- Toxic, inflammable, nonrenewable, low heat capacities, etc.

Water

- Nontoxic
- Nonflammable
- High heat capacity
- Relatively inexpensive
- Green solvent
- Poor solvent for most organic molecules
- Highly reactive with many reagents.

Homogeneous metal catalyzed reactions

- Homogeneous catalysts offer unparalleled degrees of selectivity and tunability from

Pioneering industrial processes:

Wacker oxidation; olefin hydroformylation

Modern processes:

asymmetric hydrogenation; Pd-catalyzed cross-coupling; olefin metathesis, etc.

- Similar solubility characteristics of the catalyst and product – **how to recover the metal from the product?**

How to recover the catalyst?

Catalyst immobilization

- To heterogenize the homogeneous catalyst by attaching it to a solid support, allowing the catalyst to be recovered in the same way as traditional heterogeneous catalysts.
- Synthetically challenging
- Decreased activity and selectivity
- Metal leaching

Organic immiscible solvents

- To constrain the catalytic species in an organic immiscible liquid, allowing the reaction to proceed by stirring the immiscible phases.
- Retain the reactivity and selectivity properties
- Good activities when sufficient interaction between the substrate phase and catalyst phase provided
- Simple decantation separation
- water, fluorous solvents, supercritical CO_2, and ionic liquids

Water as an organic immiscible solvent

- Proven track record of using water in industrial catalytic processes: **Wacker oxidation; Rhône-Poulenc hydroformylation of propene**.
- Poor solvent for most organic molecules
  - The hydrophilic catalysts and hydrophobic products strongly partition into their relative phase;
  - Phase separation can be easily achieved upon completion of reaction.
- Green solvent
  - Water in its pure form is completely benign;
  - Significant savings in the use of solvents and energy in the purification process can be realized by simplifying the separation → low E-factor (kg of waste/kg of product).
- Water becomes waste itself once contacted with organic materials; its high heat capacity makes purification by distillation an energy intensive process.

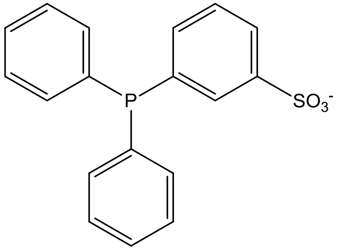
Water effect on chemical reactivity and selectivity

- Accelerating reactions through hydrophobic effect (organic reactants in water attempt to minimized their interaction with water), favoring reactions with negative volumes of activation;
- The Lewis-basic nature of water leads in some cases to accelerated reactions;
- Water is highly polar and provides effective solvation for ionic species, leading to solvent separated ions;
- Providing the opportunity to finely tune pH;
- Serving as an acid, base, nucleophilic reagent, and even a hydrogen source.

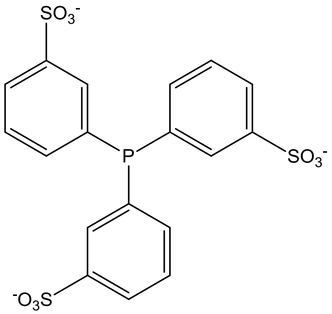
Reactions in water can in some cases proceed **much differently** than they do in traditional organic solvents.

Design of hydrophilic ligands

- Suitable hydrophilic functionality:
  - Partition into aqueous phase;
  - Providing the necessary steric and electronic properties to provide desired catalyst stability, activity and selectivity.
- Attaching water-solubilizing groups to known hydrophobic ligands:
  - Most common ionic substituents: $-SO_3^-$, $-COO^-$, $-PO_3^{2-}$, $-NMe_3^+$
  - Non-ionic hydrophilic substituents: polyol, carbonhydrate, polyether



L1: *m*TPPMS

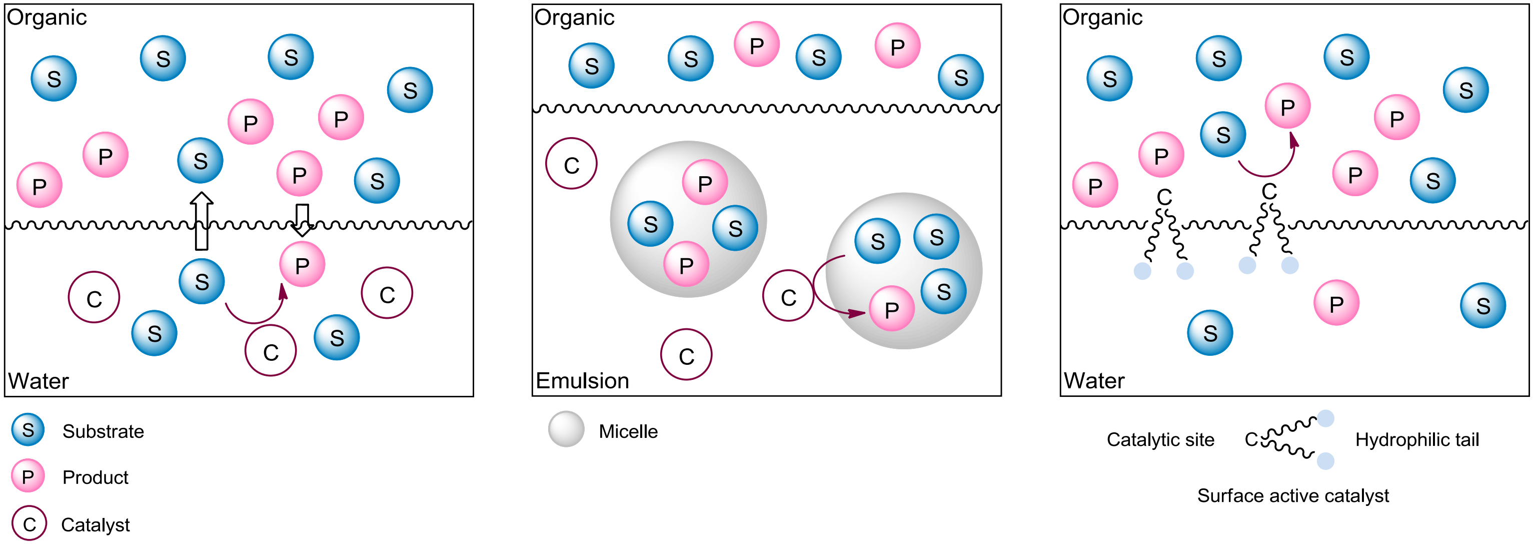


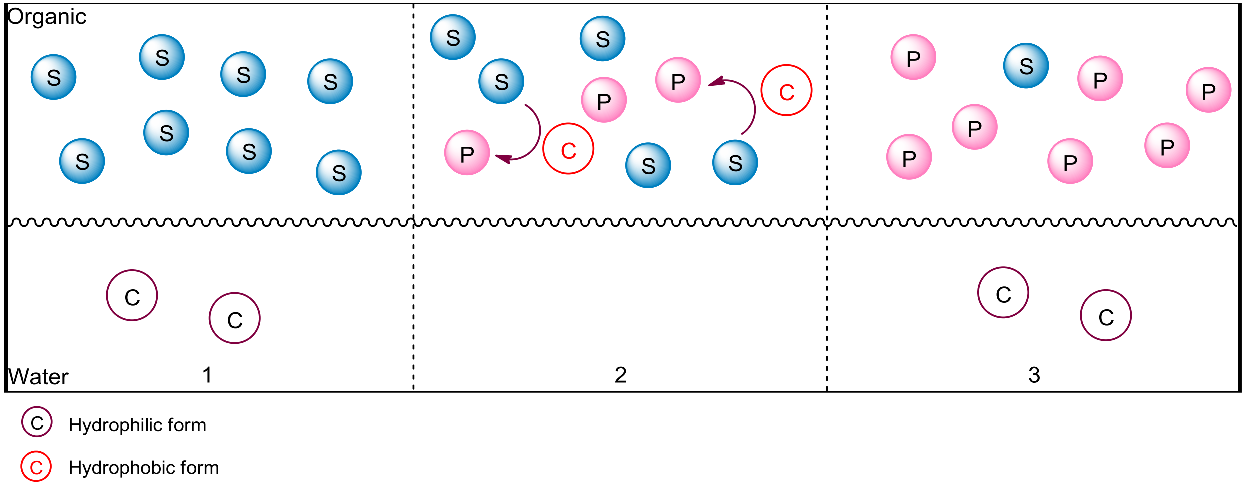
L2: *m*TPPTS

A major challenge in aqueous-biphasic catalysis is to bring the water soluble catalyst into contact with the hydrophobic substrate and other reagents.

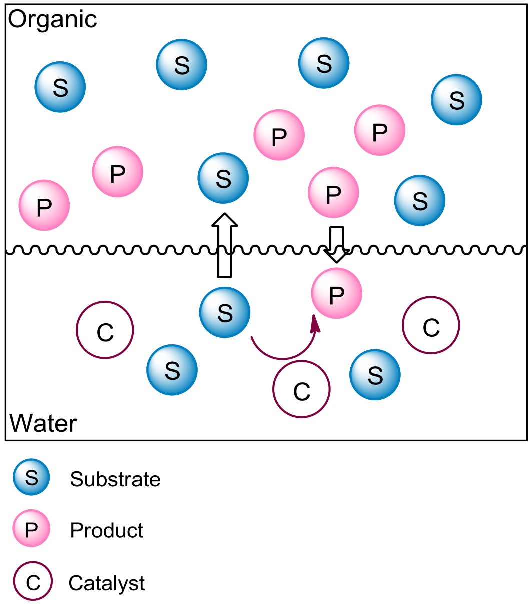
S. Ahrland, et al. *J. Chem. Soc.*, **1958**, 276.
E. G. Kuntz, French Patent, 2,314,910, **1975**.

Possible modes for aqueous-biphasic catalysis





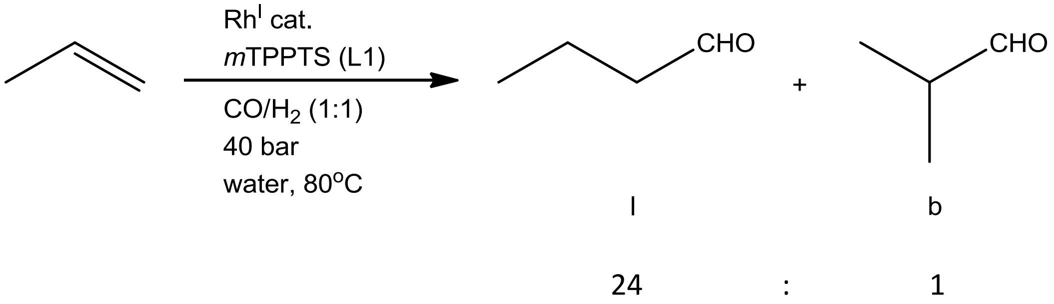
For molecules with some degree of water solubility



- The reaction can occur in the aqueous bulk through interaction of the water-soluble catalyst with the substrate dissolved in water.

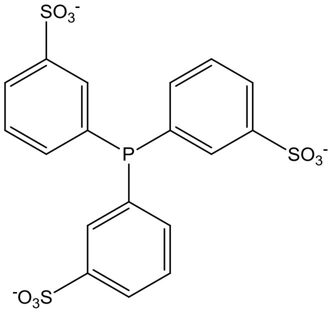
Starting point of aqueous-phase catalysis: Rhône-Poulenc process

- Hydroformylation of Propene: Co → Rh



95%, 4 h

Two-phase upon completion

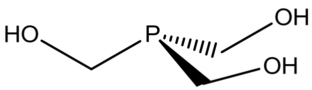


L2: *m*TPPTS

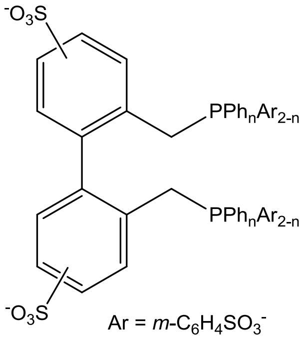
This process was commercialized in a plant in Oberhausen, Germany in 1984. Initial capacity was 100,000 tons/year.

E. G. Kuntz, *CHEMTECH,* **1987**, *17*, 570.
E. G. Kuntz, French Patent, 2,314,910, **1975**.
E. G. Kuntz, French Patent, 2,349,562, **1976**.

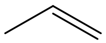
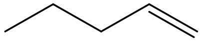
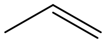
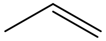
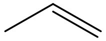
Other hydrophilic ligands applied to the hydroformylation of lower olefins



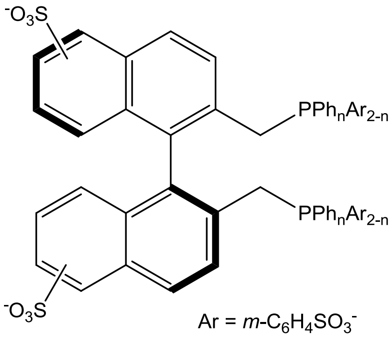
L3: THMP



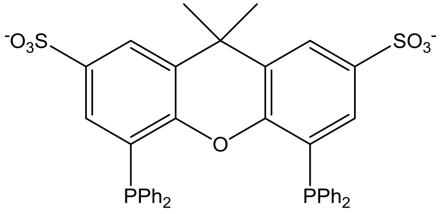
L4: BISBIS

Catalyst (Rh)	Substrate	l/b	Recyclability
L2 *m*TPPTS		24:1	Industrial process
L3		0.75:1	-
L4		97:3	-
L5		98:2	Constant conversion over 2 month period
L6		30:1 *	5 cycles in the absence of CO

* Results obtained under low pressure (10 bar CO/H_2) when **L1** gave the l/b ration of 16:1.



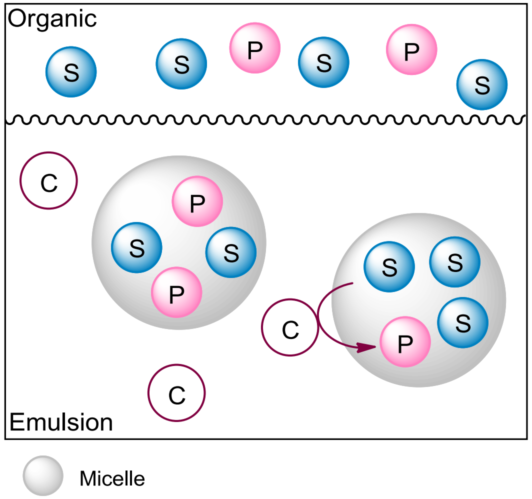
L5: BINAS



L6: Xantphos-S

A. Fukuoka, et al. *Chem. Commun.* **1999**, 489.
W. A. Herrmann, et al. *J. Mol. Catal.* **1992**, *73*, 191.
W. A. Herrmann, et al. *J. Mol. Catal. A,* **1995**, *97*, 65.
H. Bahrmann, et al. *J. Mol. Catal. A,* **1997**, *116*, 49.
M. Kranenburg, et al. *Organometallics.* **1995**, *14*, 3081.

For molecules less soluble in water



- To use water miscible organic co-solvents to increase the solubility of the hydrophobic substrate in the aqueous solution;
- To use surfactants or phase transfer agents to carry the organic reagent into the aqueous phase by formation of water-soluble micelles with hydrophobic interiors.

Strategies for hydroformylation of higher olefins

- To use a water-miscible organic co-solvent to increase the solubility of the alkene in the aqueous phase or of the catalyst in the organic phase

Catalyst	**Substrate**	**Solvent**	**Reaction condition**	**Conversion**
Rh-*m*TPPTS	1-dodecene	H_2O	2 h, 100°C	No conversion
		ethanol/H_2O 1/1		25%
		propanol/H_2O 1/1		42%
	1-octene	H_2O	15 h, 80°C	24%
		methanol/H_2O 1/1	10 h, 80°C	90%

- The linear selectivity decreased
- Catalyst leaching into the organic phase
- Undesirable reactions, such as acetal formation

H. Chen, et al. *J. Mol. Catal. A,* **1999**, *149*, 1.
F. Monteil, et al. *J. Organomet. Chem.* **1994**, *480*, 177.
P. Purwanto, et al. *Catal. Today,* **1995**, 135.

Strategies for hydroformylation of higher olefins

- To use surfactants to provide micelles to make the hydrophobic substrate dispersed in the aqueous phase, increasing the water/organic interfacial area significantly

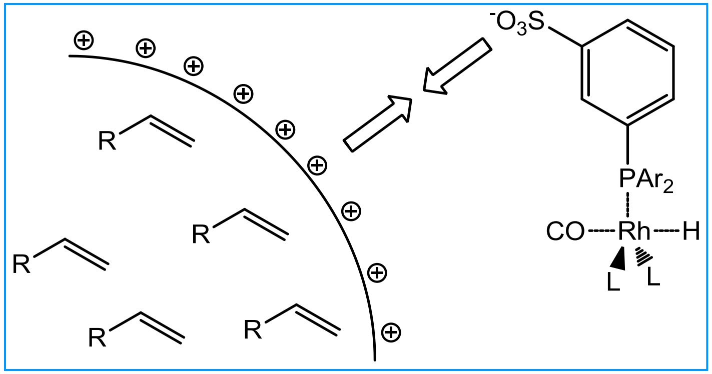
Catalyst	Substrate	Surfactant	Reaction condition	Conversion
Rh-*m*TPPTS	1-dodecene	No surfactant	2 h, 100°C	No conversion
		Cationic surfactant CTAB		61%
		Dicationic surfactant		78% - 85%
		Neutral surfactant Tween 20 and Spam 40		3 - 4%
		Anionic surfactant SDS		No conversion

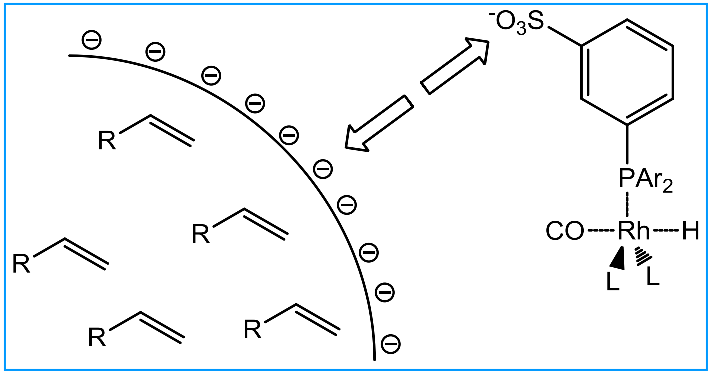
- The linear selectivity was higher than using co-solvent
- Complicated phase separation

H. Chen, et al. *J. Mol. Catal. A,* **1999**, *149*, 1.
M. Li, et al. *J. Mol. Catal. A,* **2005**, *235*, 130.
F. Monteil, et al. *J. Organomet. Chem.* **1994**, *480*, 177.
P. Purwanto, et al. *Catal. Today,* **1995**, 135.

Micelle surface

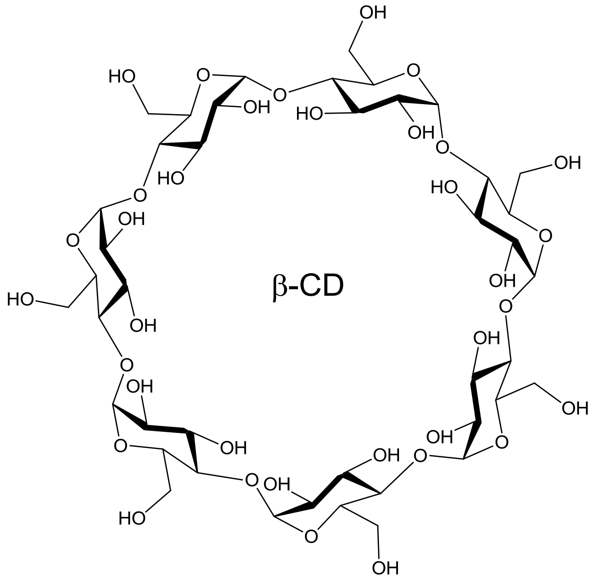
- The cationic surfactants play more than just a simple role of forming micelles

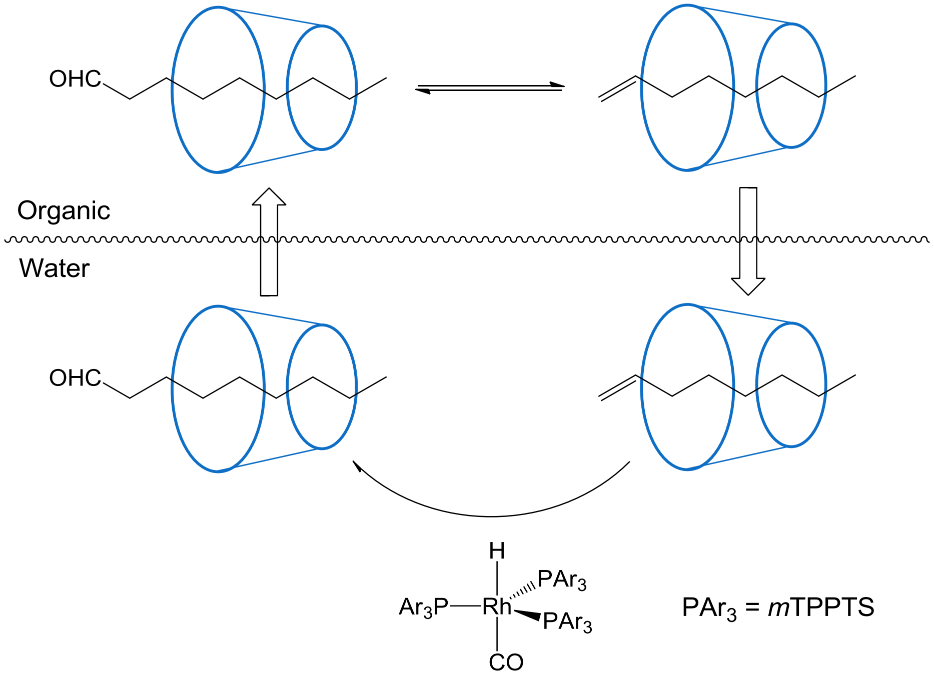




Strategies for hydroformylation of higher olefins

- To use cyclodextrins (CD) as inverse phase transfer catalysts



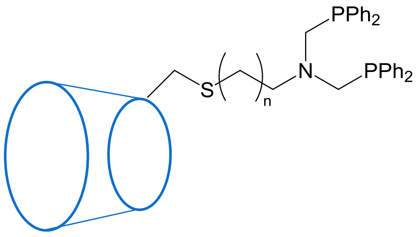


Strategies for hydroformylation of higher olefins

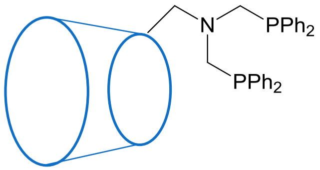
- The degree of methylation is an important parameter in these systems. Methylated CD has surface-active behavior and lower stability of the aldehyde inclusion complex.

Catalyst	Substrate	Surfactant	Reaction condition	Conversion	Aldehyde selectivity
Rh-*m*TPPTS	1-decene	No CD	18 h, 80°C	< 1%	-
		β-CD		6%	90%
		Dimethylated β-CD		51%	90%
		Randomly methylated β-CD (12.6 methyl/CD)	8 h, 80°C	100%	95%
Rh-L7/L8	1-octene		18 h, 80°C	100%	> 99%

- The steric congestion of CD-supported olefin can also increase linear selectivity in some cases.



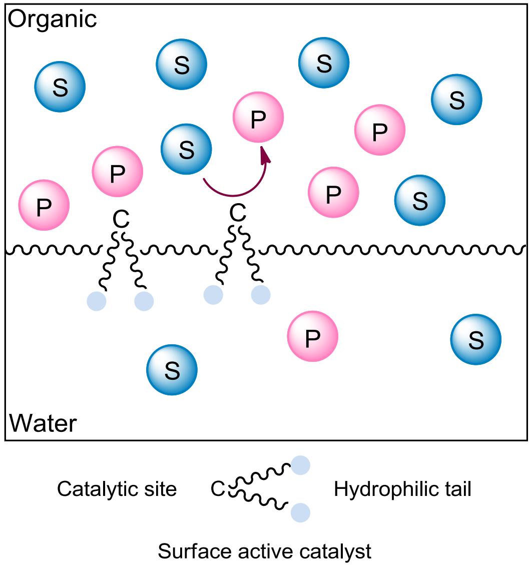
L7



L8

E. Monflier, et al. *Tetrahedron Lett,* **1995**, *36*, 9481.
M. Dessoudeix, et al. *Eur. J. Inorg. Chem.* **2001**, 1797.
E. Monflier, et al. *Angew. Chem. Int. Ed.,* **1995**, *34*, 2269.
M. Reetz, et al. *Angew. Chem. Int. Ed.,* **1997**, *36*, 865.

For molecules less soluble in water – surface active ligands

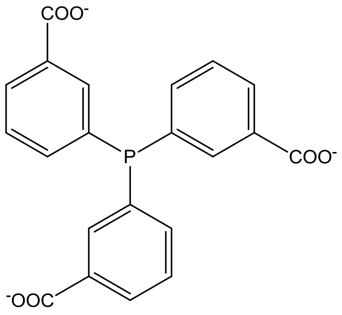


- Surfactant-like structures with long aliphatic tails connected to an hydrophilic functionality; the metal coordination site is placed on the hydrophobic end of the ligand;
- In some cases the ligand itself can form micelles, in addition to supporting the metal catalyst.

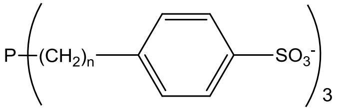
Strategies for hydroformylation of higher olefins

- The development of ligands that can act as surfactants themselves

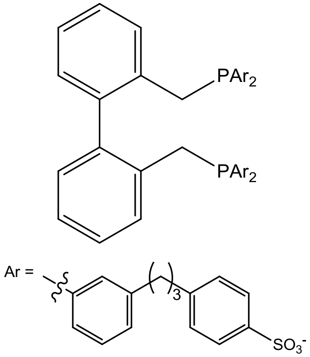
Catalyst (Rh)	Substrate	Reaction condition	Conversion	Aldehyde selectivity	l/b
***m*TPPTS**	1-octene	3 h, 80°C	2%	45%	2.8 : 1
L9 *m*TPPTC			94%	87%	2.3 : 1
L10 (n=3)		10 h, 120°C	85% yield		8 : 1
L11		5 h, 120°C	73% yield		94 : 6
L12 (n=6)		24 h, 120°C	97% yield		98 : 2



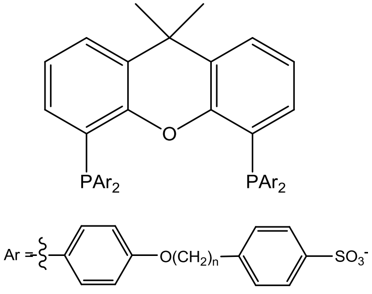
L9: *m*TPPTC



L10



L11

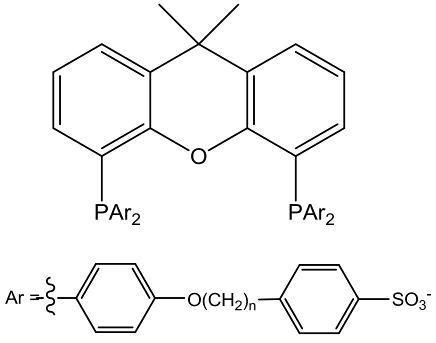


L12

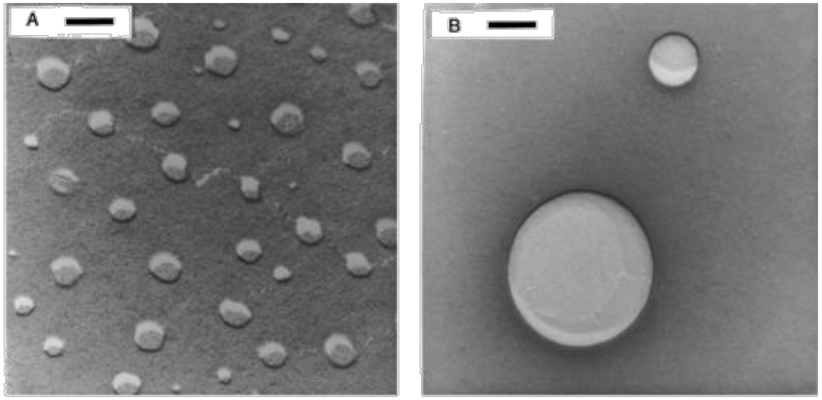
S. Tilloy, et al. *Adv. Synth. Catal.*, **2006**, *348*, 1547.
T. Bartik, et al. *J. Mol. Catal.*, **1994**, *88*, 43.
H. Ding, et al. *J. Mol. Catal. A*, **1997**, *124*, 21.
M. S. Goedheijt, et al. *J. Am. Chem. Soc.*, **2000**, *122*, 1650.

Vesicles formed by ligands

- Electron microscopy pictures showed the vesicles formed by L12 in aqueous solution.
  - A. A uniform distribution of vesicles of L12 (n=3);
  - B. A large and an average sized vesicle formed by L12 (n=6).



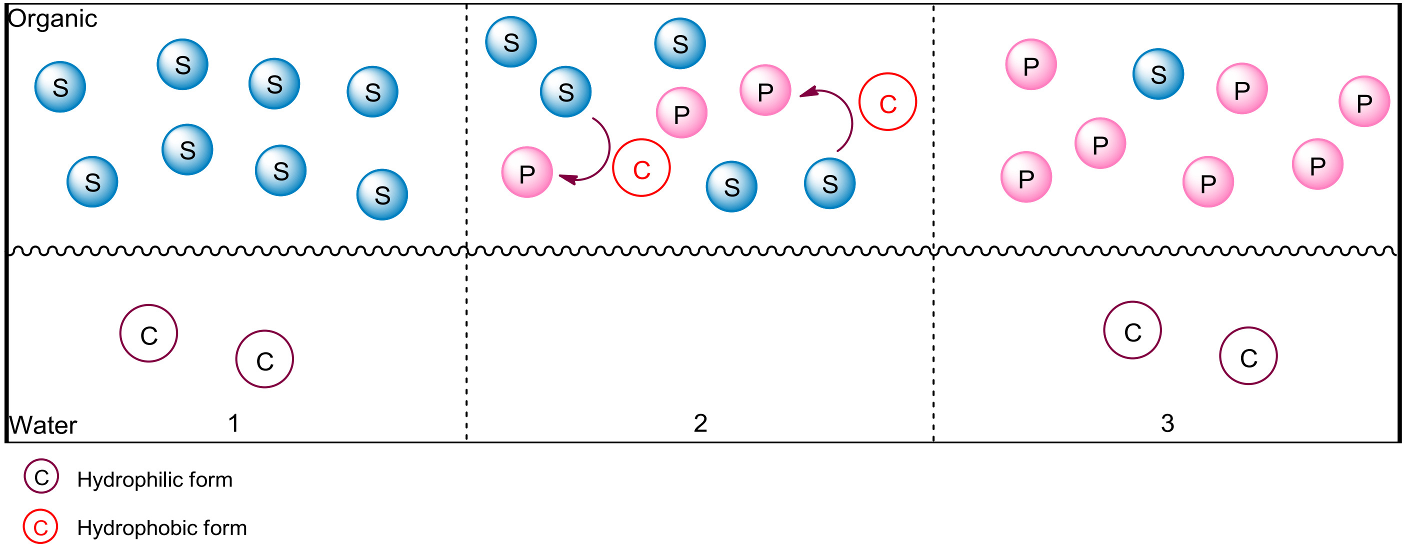
L12



M. S. Goedheijt, et al. *J. Am. Chem. Soc.*, **2000**, *122*, 1650.

Aqueous-biphasic catalysis - Mass transport issue

- The ideal catalyst would have controllable solubility properties.

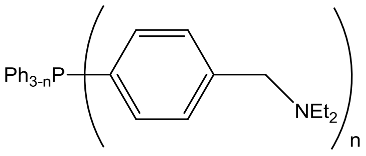


- To carry out the reaction using an ionic ligand in a polar solvent under homogeneous conditions. Upon completion, water can be added to give a biphasic mixture with the products in the organic phase and the catalyst in the aqueous phase;

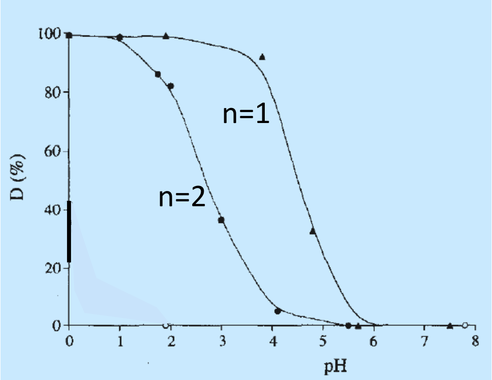
- To design ligands with adjustable solvent properties: by changing a reaction variable (pH or Temperature), the catalyst partitions into the organic phase to provide high activity; at the end of reaction, the conditions are changed back to allow easy separation

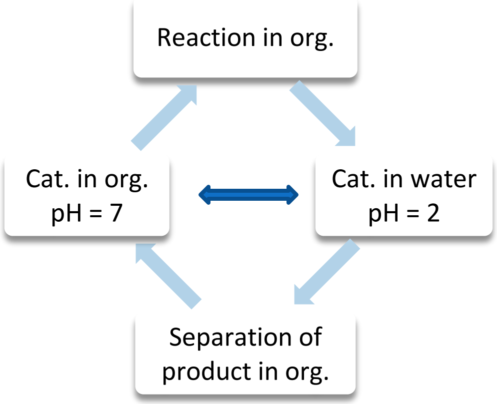
pH responsive ligands for Rh-catalyzed hydroformylation of 1-octene

- Amine-functionalized ligands has pH-controlled phase preference



L13





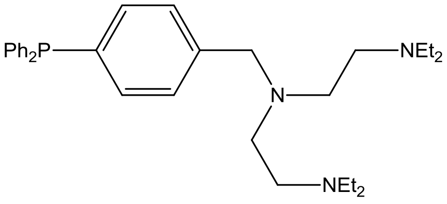
Reaction in org.

Cat. in water
pH = 2

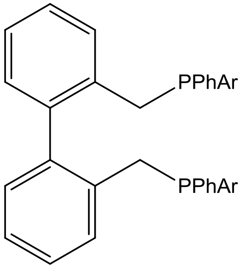
Separation of
product in org.

Cat. in org.
pH = 7

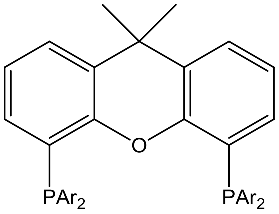
  - Activity nearly identical to PPh_3 in toluene;
  - The recovered catalyst retained 98.5% of Rh and 86% of its original activity. The loss of activity is likely due to decomposition of the catalyst under the strongly acidic and basic conditions used for recovery.



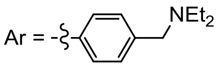
L14



L15

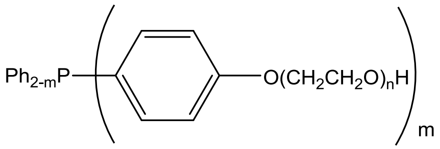


L16

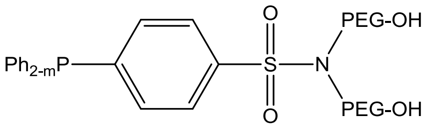


A. Buhling, et al. *J. Mol. Catal. A,* **1995**, *98*, 69.
A. Buhling, et al. *J. Mol. Catal. A,* **1997**, *116*, 297.
M. Karlsson, et al. *J. Chem. Soc. Dalton Trans.,* **1999**, 4187.
A. Buhling, et al. *J. Chem. Soc. Dalton Trans.,* **1996**, 2143.
A. Buhling, et al. *Organometallics.* **1997**, *16*, 3027.

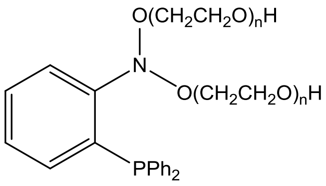
PEG-substituted ligands with inverse temperature-dependent solubility



L17



L18



L19

m	n	Cloud point (°C)
1	8	26
	16	52
	25	75
2	15	55
	20	71
3	18	95

	T (°C)	Aldehyde yield	l/b
Rh-L18 catalyzed hydroformylation of 1-decene, time 5h	70	10.4%	160 : 1
	80	26.4%	1.42 : 1
	90	81.7%	0.98 : 1
	100	95.6%	0.64 : 1

- For Rh-L19, the TOF was 418 h^{-1} at 100°C; at room temperature, the catalyst located exclusively in the aqueous phase, which could be used for 20 reaction cycles with only 5% loss in activity.

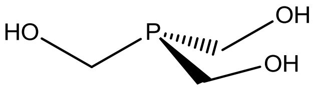
A. Jin, et al. *J. Mol. Catal. A,* **1997**, *116*, 55.
J. Jiang, et al. *J. Mol. Catal. A,* **2001**, *171*, 85.
C. Liu, et al. *J. Mol. Catal. A,* **12003**, *1198*, 23.

Examples of the application of hydrophilic ligands

- Aqueous-phase hydrogenation
- Aqueous-phase olefin metathesis
- Aqueous-phase palladium-catalyzed cross-coupling
- Aqueous-phase catalytic oxidation
- Substrate partitioning-controlled reaction in aqueous phase.

Olefin hydrogenation

- One of the earliest examples of the use of a hydrophilic ligand for aqueous-phase catalysis : to use Rh-THMP catalyzing the hydrogenation of 1-octene in ethanol (rapid hydrogenation) and water (no activity).



L3: THMP

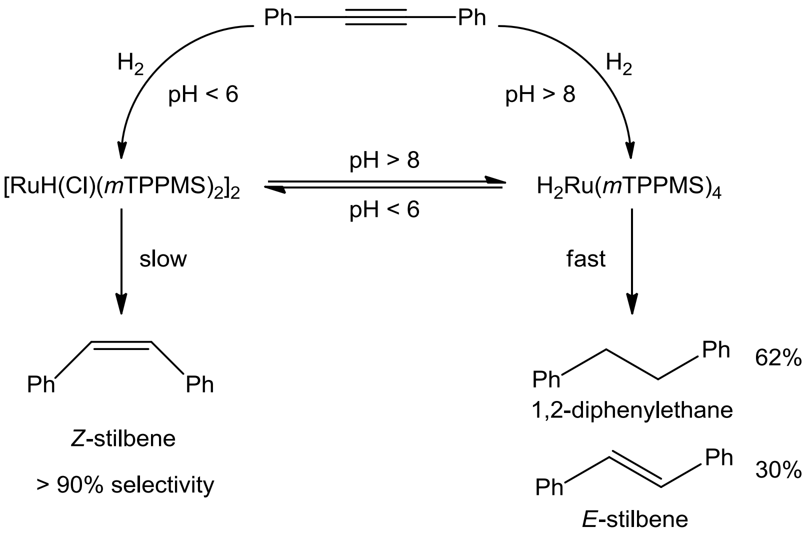
"We conclude that these complexes show no obviously useful catalytic properties"

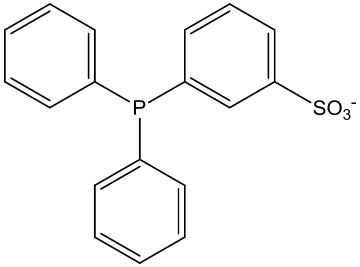
- THMP complexes of ruthenium and iridium have shown modest activity in some hydrogenation and hydroformylation reactions in water.

J. Chatt, et al. *J. Chem. Soc. Dalton Trans.,* **1973**, 2021.
A. Fukuoka, et al. *Chem. Commun.* **1999**, 489.

Ru-*m*TPPMS catalyzed hydrogenation

- Early examples of alkene hydrogenation in aqueous-biphasic systems by Manassen, Joó and Wilkinson.
- pH-dependent hydrogenation by [$RuCl_2$(*m*TPPMS$)_2]_2$



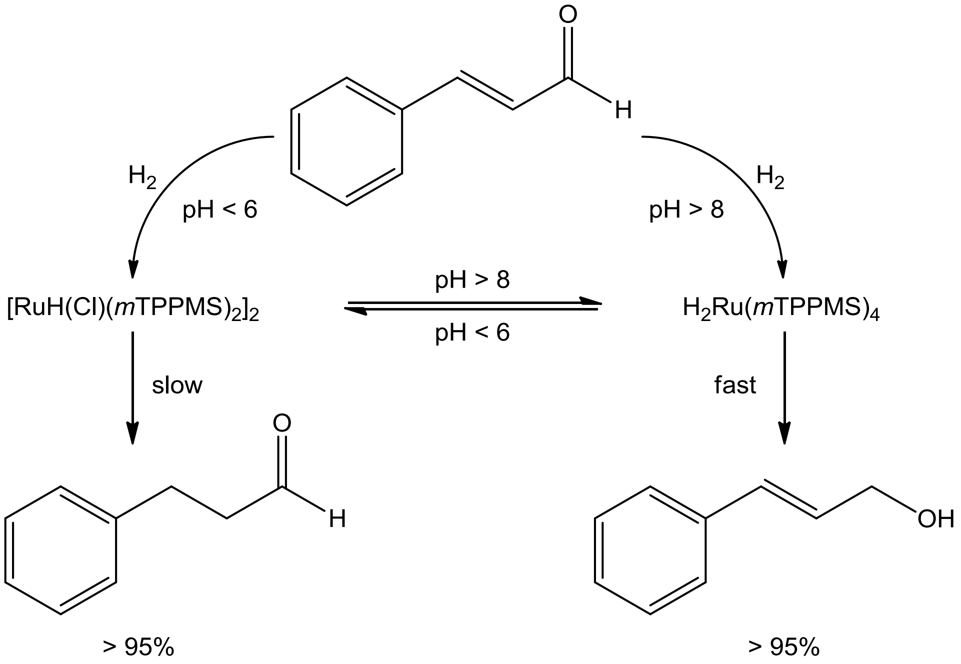


L1: *m*TPPMS

Y. Dror, et al. *J. Mol. Catal.* **1977**, *2*, 219.
F. Joó, et al. *Inorg. Chim. Acta.*, **1977**, *25*, L61.
A. F. Borowski, et al. *Nouv. J. Chim.*, **1978**, *2*, 137.
H. H. Horváth, et al. *React. Kinet. Catal. Lett.*, **2005**, *85*, 355.
F. Joó, et al. *Angew. Chem. Int. Ed.*, **1998**, *37*, 969.

pH-dependent hydrogenation of cinnamaldehyde

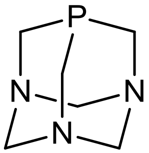
- Hydrogenation of α, β-unsaturated aldehydes, such as cinnamaldehyde, can give the **unsaturated allylic alcohol** by reduction of aldehyde; the **saturated aldehyde** by reduction of alkene; or the **fully reduced saturated alcohol.**
- Hydrogenation of cinnamaldehyde under comparable conditions in toluene using Ru/PPh_3 complexes give low selectivity with the fully reduced alcohol being the major product in most cases.



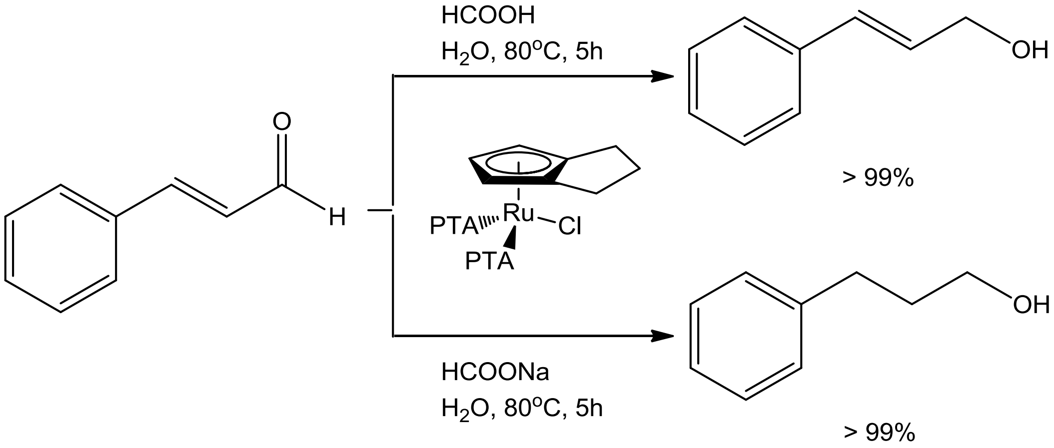
F. Joó, et al. *Angew. Chem. Int. Ed.*, **1998**, *37*, 969.

pH-dependent hydrogenation of cinnamaldehyde

- ☐ The product selectivity for cinnamaldehyde reduction under transfer hydrogenation conditions was found to be dependent on the reaction pH when using Cp/Dp-Ru-PTA complexes



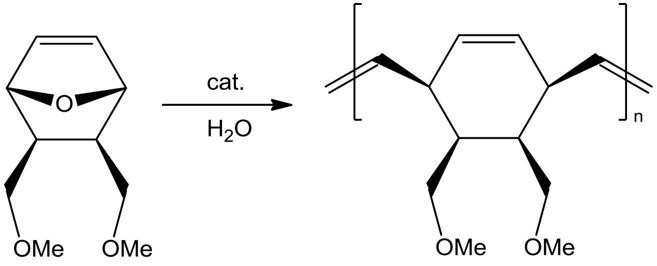
L20: PTA



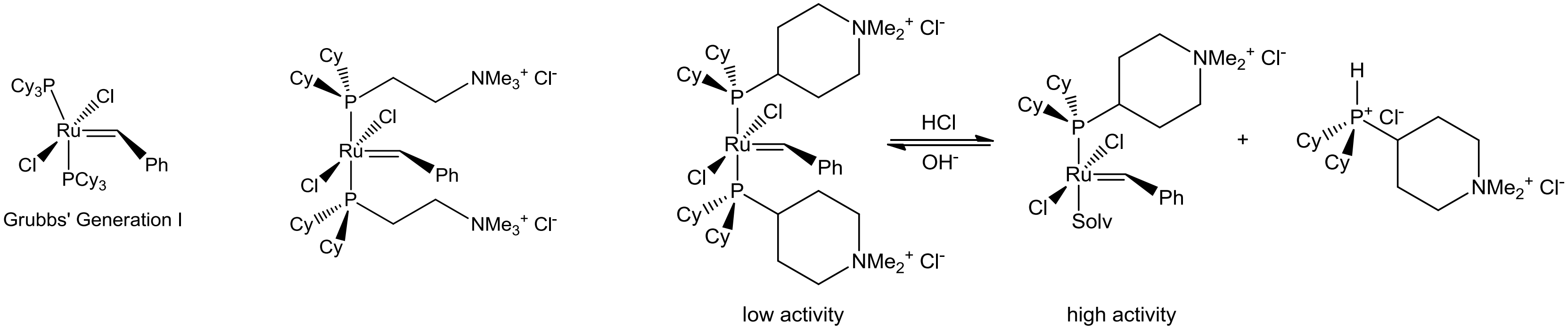
C. A. Mebi, et al. *Organometallics.* **2007**, *26*, 429.

Metathesis

- The molybdenum complexes developed by Schrock are sensitive to water; the ruthenium catalysts developed by Grubbs are quite stable in water.
- The first examples of water-soluble olefin metathesis: ring opening metathesis polymerization of functionalized oxanorbornene.

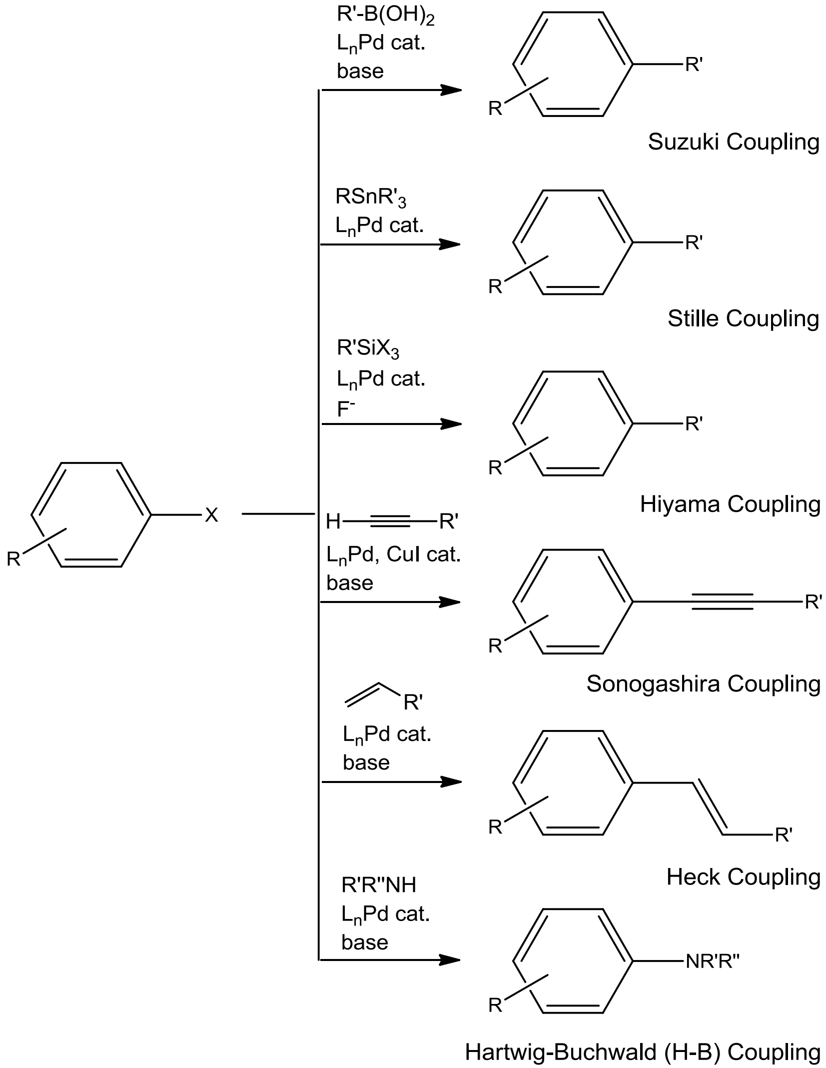


D. M. Lynn, et al. *J. Am. Chem. Soc.,* **2000**, *122*, 6601.
D. M. Lynn, et al. *J. Am. Chem. Soc.,* **1998**, *120*, 1627.



  - Addition of acid to complexes resulted in loss of a phosphine ligand to give a highly active ROMP catalyst.

Aqueous-phase Pd-catalyzed cross-coupling



- The history of using aqueous solvent systems in Pd-catalyzed cross-coupling goes back to the early development of the Suzuki coupling, which utilized aqueous base to activate the organoboron nucleophile.

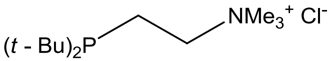
- The first example of the use of a water-soluble ligand for Pd-catalyzed cross-coupling in water was reported by Casalnuovo in 1990:

  Using Pd-*m*TPPMS catalyst for the cross-coupling of aryl iodides and activated aryl bromides in H_2O/CH_3CN.

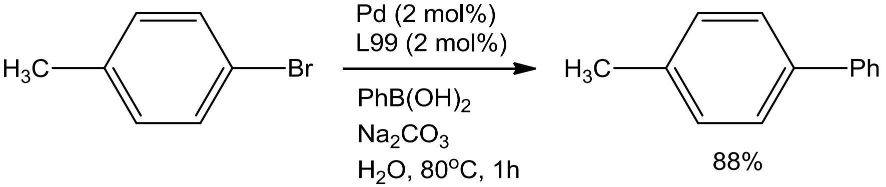
N, Miyaura, et al. *J. Am. Chem. Soc.*, **1985**, *107*, 972.
A. L. Casalnouvo, et al. *J. Am. Chem. Soc.*, **1990**, *112*, 4324.

Aqueous-phase Pd-catalyzed cross-coupling

- Sterically demanding trialkylphosphines provide effective catalysts for a range of coupling reactions of aryl bromides and chlorides. Catalyst derived from *t*-Bu-Amphos and $Pd(OAc)_2$ gave good activity for Suzuki, Sonogashira and Heck couplings of aryl bromides in aqueous-biphasic reactions.



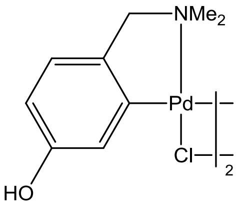
L21: *t*-Bu-Amphos



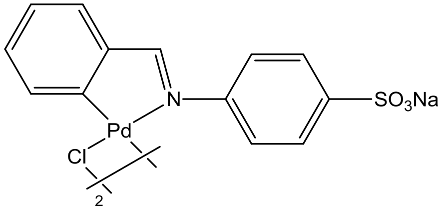
88%

Pd = $Pd(OAc)_2$

3 cycles



4 cycles



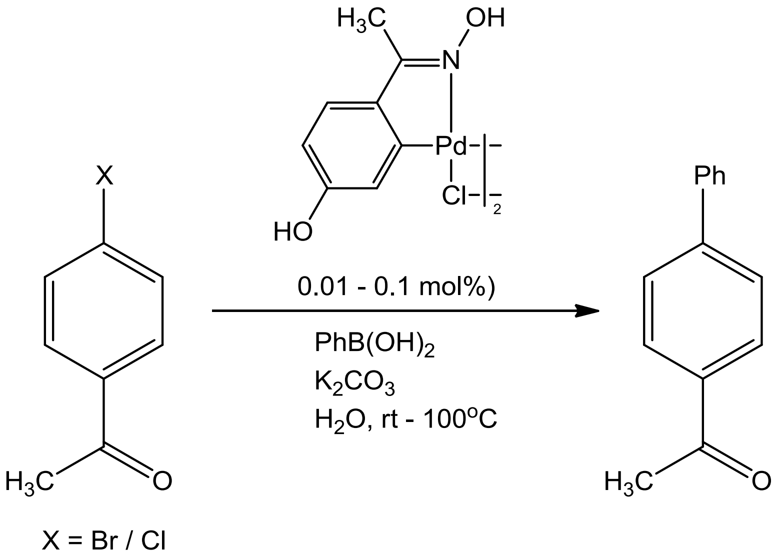
11 cycles

- The *t*-Bu-Amphos/$Pd(OAc)_2$ system gave turnover values of 730,000 mol/mol of Pd at 80°C for the coupling of 4-bromotoluene and phenylboronic acid.
- Using hydrophilic palladacycles in combination with *t*-Bu-Amphos gave a highly stable catalyst systems.

R. Huang, et al. *Organometallics,* **2006**, *25*, 4105.

Pd-catalyzed cross-coupling with hydrophilic nitrogen ligands

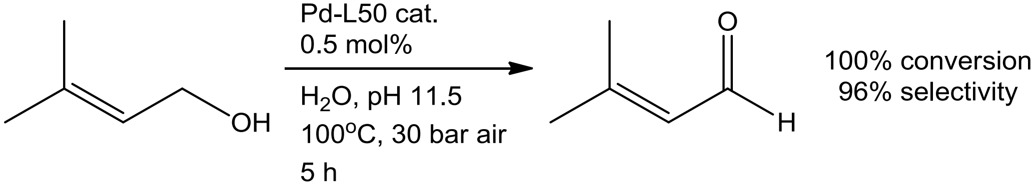
- Palladacyclic complexes showed significant promise as catalyst precursors in cross-coupling of aryl bromides and chlorides reactions.

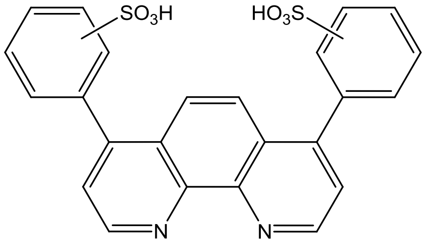


L. Botella, et al. *Angew. Chem. Int. Ed.*, **2002**, *41*, 179.
L. Botella, et al. *J. Organomet. Chem.*, **2002**, *663*, 46.

Aqueous-phase catalytic oxidation

- Water is an attractive solvent for metal catalyzed oxidations as the oxidants and their byproducts are often water-soluble, which allows them to be easily separated from the organic product;
- These reactions typically rely on hydrophilic nitrogen-based ligands.





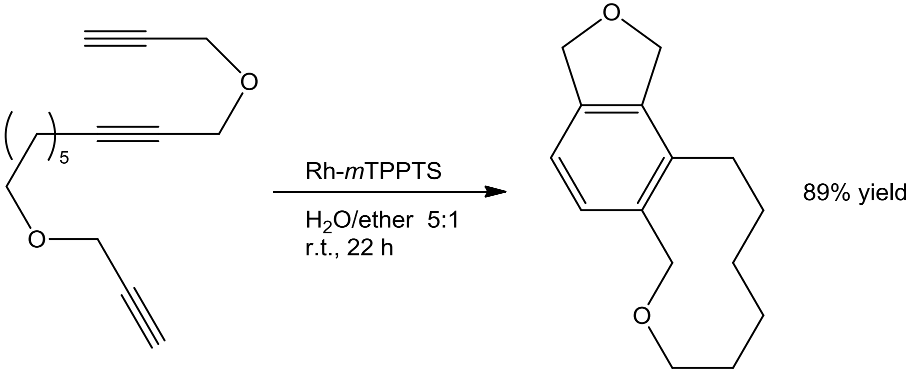
L22

- Because oxygen is more soluble in water than nitrogen, nitrogen diluted oxygen (8% O_2, not explosive in combination with organic materials) was used at high pressure.

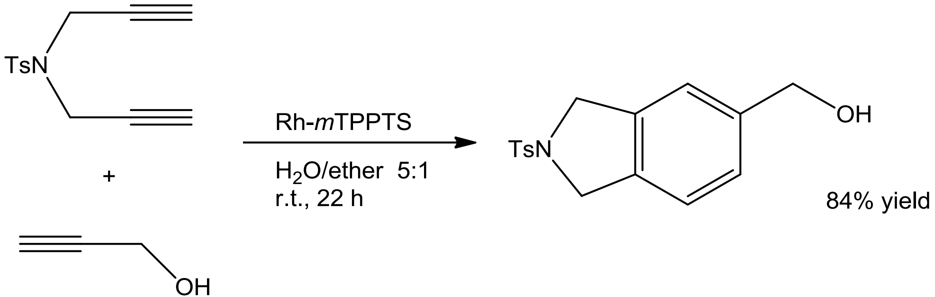
G. -J. ten Brink, et al. *Science,* **2000**, *287*, 1636.

Selective cycloisomerization controlled by substrate partitioning

- Cyclization of triynes to give polycyclic arenes typically are carried out under ultradilute conditions to avoid intermolecular reactions; by using a water-soluble catalyst, the [2+2+2] cyclization would occur in the aqueous phase where the concentration of the substrate would be low.

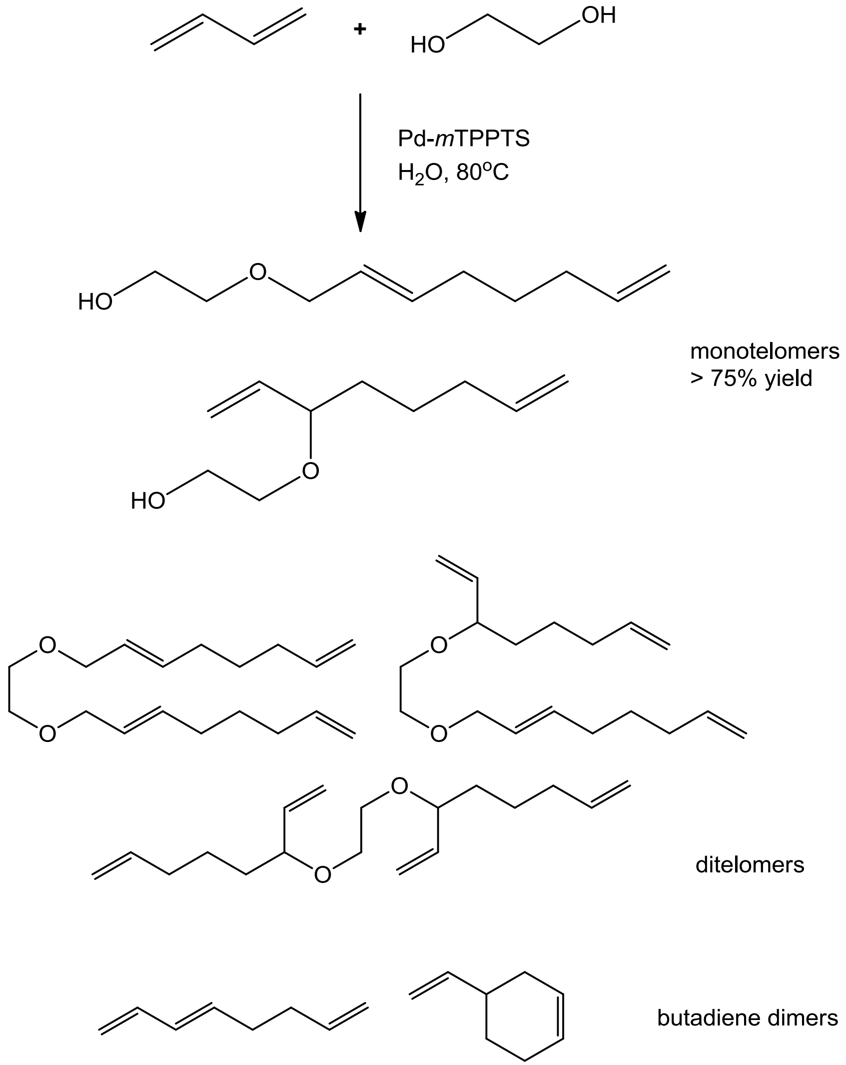


- The intermolecular [2+2+2] cyclization of a diyne and propargyl alcohol often fives low yields due to oligomerization of the diyne.



H. Kinoshita, et al. *J. Am. Chem. Soc.*, **2003**, *125*, 7784.

Telomerization of butadiene with ethylene glycol in water



- Telomerization of butadiene with ethylene glycol using Pd/PPh_3 give 50-60% selectivity for the monotelomers.
- The high selectivity was believed to be due to the low solubility of the product in water, which prevented further reaction to give ditelomeric products.
- The catalyst can be recycled up to six times with only slight loss of activity.

A. Behr, et al. *Green Chem.*, **2003**, *5*, 198.

Conclusions and perspectives

- Since the report of the Rhône-Poulenc aqueous-phase hydroformylation process, nearly any catalytic reaction involving late transition metals can be adapted to the use of water as a solvent provided the reagents themselves are water stable;

- The majority of hydrophilic ligands developed are based on known hydrophobic ligands. Most commonly ionic and non-ionic hydrophilic substituents have been attached, providing the necessary solubility and steric and electronic properties;

- There remain few examples of industrial processes that use water-soluble catalyst systems, thus further effort is needed develop industrially viable systems. These must be demonstrated to be economically advantageous over current processes.

Conclusions and perspectives

- The major drivers/advantages to develop aqueous-phase catalysts:
  - The aqueous-phase catalyst systems can simplify the separation of the catalytic active species from the hydrophobic product stream, which is of significant importance for industrial application. The expensive and rare metals can be recovered and the products have low levels of metal or ligand derived impurities;
  - Water is potentially a more environmentally benign solvent than traditional organic solvents. Issues related to handling water contaminated with organic impurities must be addressed. Thus aqueous-phase catalyst systems that provide comparable activity and selectivity to homogeneous processes have the potential to provide significant savings if implemented;
  - Another advantage is the ability to use water's unique properties to fundamentally change the nature of the reaction, e.g. the formation of macrocycles in water.

Conclusions and perspectives

- One of the key questions is how does water affect the fundamental organometallic reaction steps that make up catalytic cycles. By better understanding the role of water in catalytic processes, and how this differs from typical organic solvents, the unique properties of water can be better utilized. In this way, not only can water be used as a substitute for organic solvents, but it can be used to create new types reactivity or selectivity.

- While continuing the development of new ligand architectures and adapting new reactions to the aqueous phase, fundamental studies of organometallic reactivity related to catalysis in aqueous environments will be critical to the rational development of novel aqueous-phase catalytic reactions.

Palladium Catalyzed C-H Amination

Presented by Ala Bunescu: 1st year PhD student, LSPN, EPFL
PhD supervisor : Prof. Jieping Zhu

Questions:

- What is the mechanism of C-H amination?
- What are the limits of C-H amination?

Plan

1. Introduction

2. Pd-Catalyzed direct C-H amination: Mechanistic overview

3. Examples found in literature:
    - Mechanistical pathway
    - Type of oxidant: internal/external
    - Type of C-H bond: sp^3, allylic, aromatic
    - Inter/Intra Molecular C-H amination

Pd-Catalyzed direct C-H functionalization

Advantages:

- Atom economy /low energy starting material
- Direct route to complex product
- An alternative approach for Buchwald-Hartwig Amination

Desavantages:

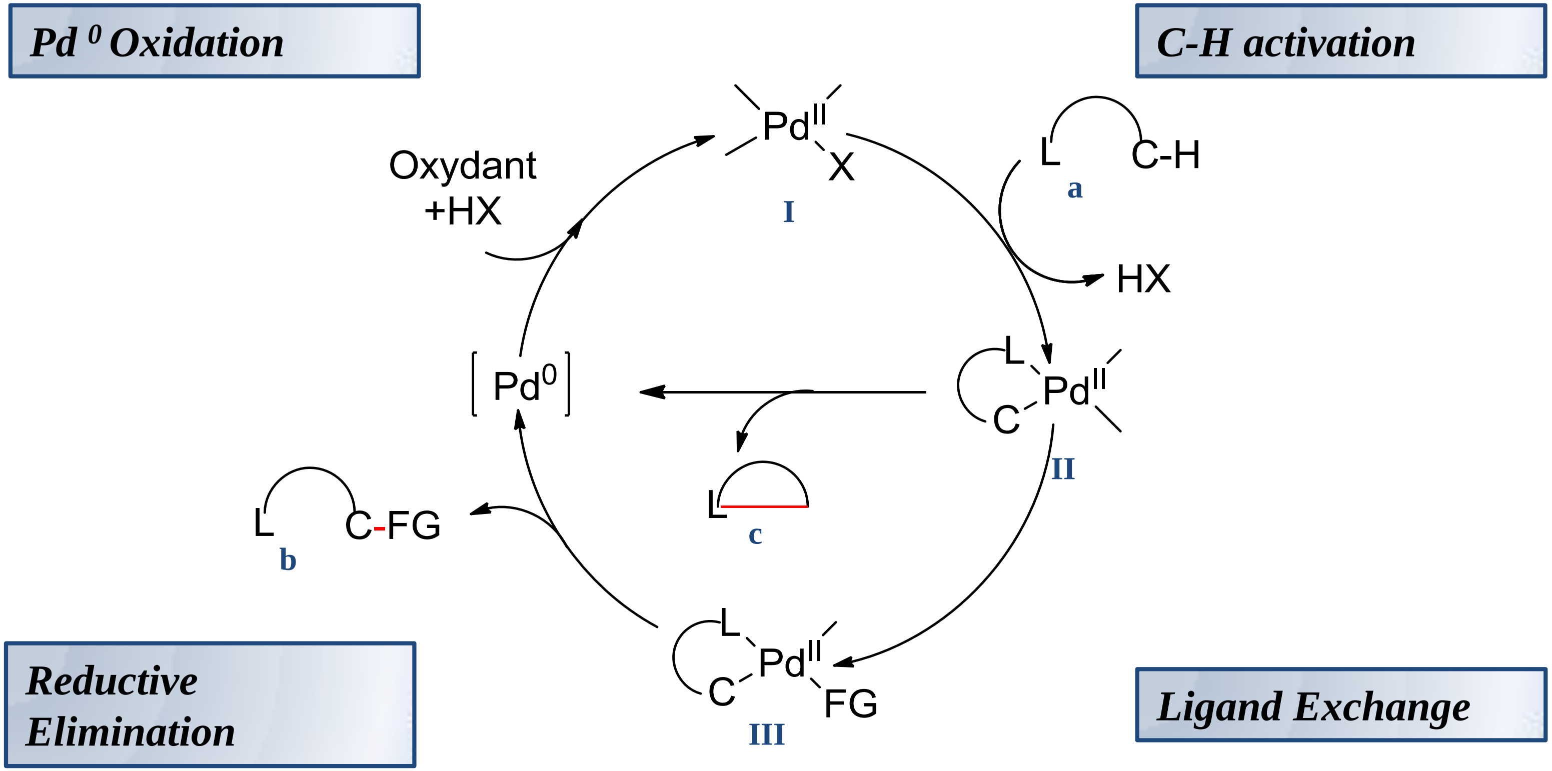
- Inert nature of most C-H carbon bonds: harsh conditions
- Requirement of site selectivity: directory group

Pd-Catalyzed direct C-H amination: Mechanistical Overview

- Reductive functionalization pathway
- Electrophilic functionalization pathway
- C-H activation

Reductive Functionalization Pathway

- Pd $^{II/0}$ Catalytic Cycle



Pd ⁰ Oxidation

C-H activation

Reductive Elimination

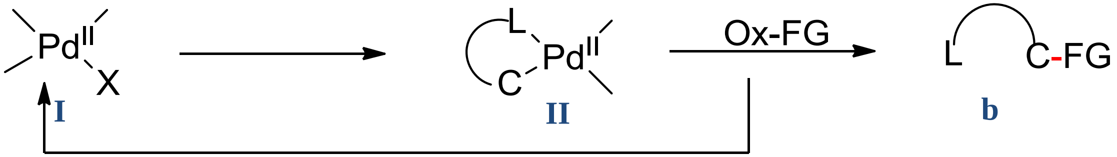
Ligand Exchange

Electrophilic Functionalization Pathway

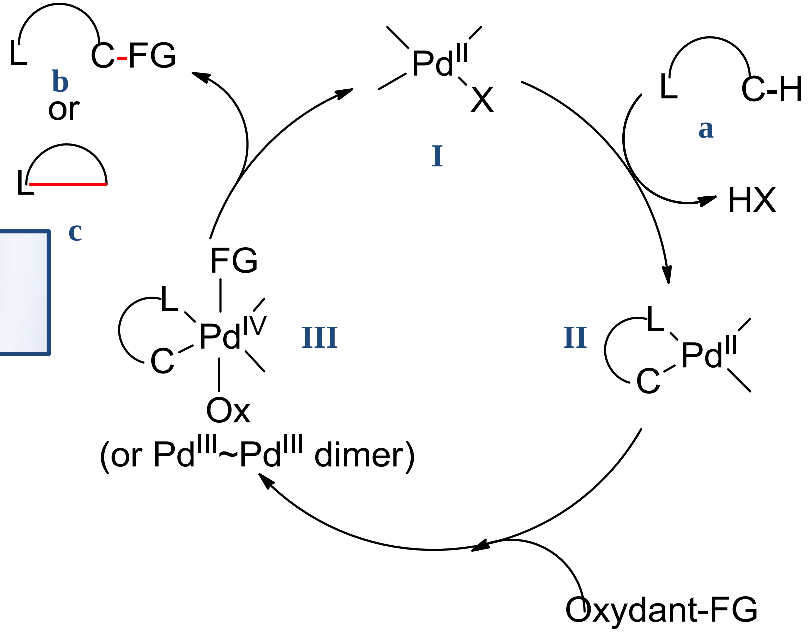
- **Direct electrophilic Functionalization of Paladacycle:**

C-H activation

Direct Electrophilic cleavage



- **One or Two electron Oxidation of Palladacycle:**



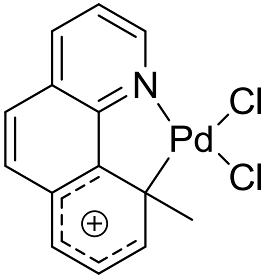
C-H activation

Reductive Elimination

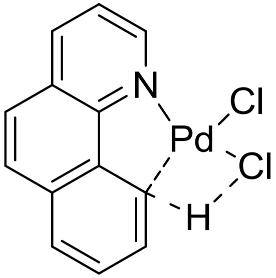
Pd(II) oxidation :

- Two / one electron oxidant
- Internal oxidant /external oxidant

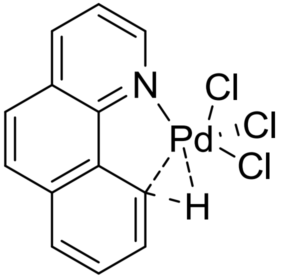
Transition states for C-H activation : DFT calculation



I



II

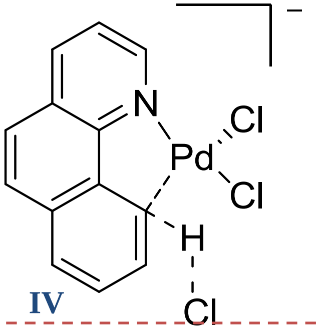


III

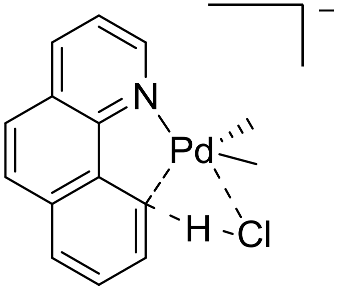
Electrophilic Activation (metal arenium): Th. instable via DFT calculation

Intra-deprotonation From C-H agostic form: 32kcal/mol

Oxidative addition: 23kcal/mol



IV



V

Deprotonation (external base) 15.6kcal/mol

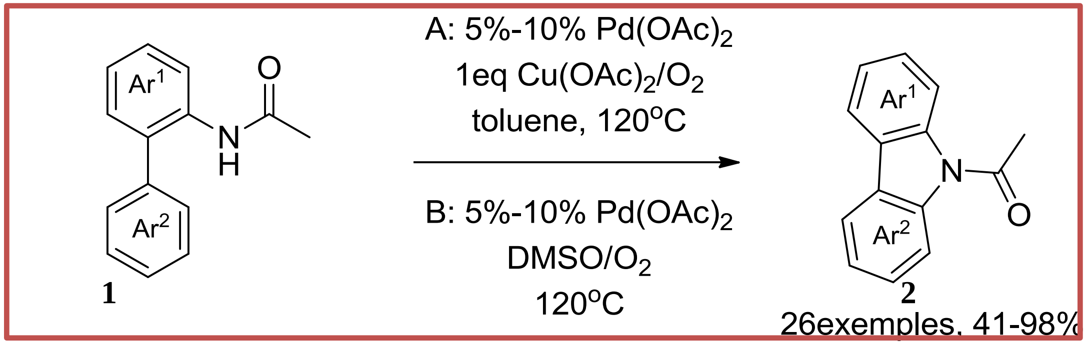
Intra-deprotonation (internal base) 15.1kcal/mol

Cundary, T. *Organometallics*, Vol. 29, No. 4, **2010**, 821

Examples: Type of Mechanism

- Pd(0)/Pd(II): 2 examples
- Pd(II)/Pd(IV): 2 examples
- Nitrene insertion: 1 example

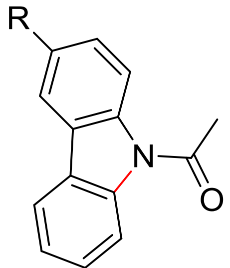
C-H Amination to carbazole: Pd(0)/Pd(II)



1

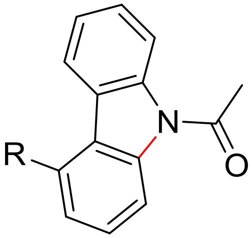
2

26exemples, 41-98%



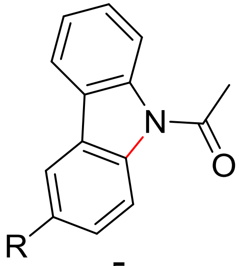
3

R: OMe (92%)
F (94%)
CF_3 (88%)



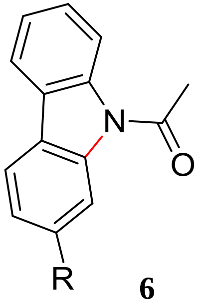
4

R: OMe (81%)
F (78%)
CF_3 (95%)



5

R: Me (82%)
OMe (41%)
CF_3 (86%)
CO_2Me (99%)

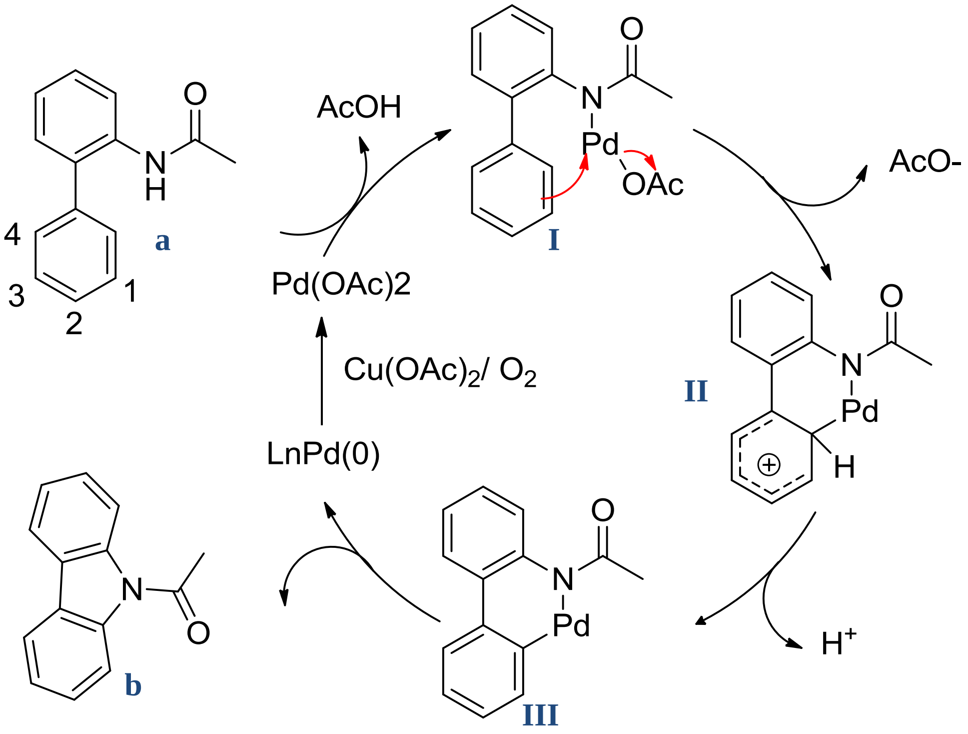


6

R: OMe (97%)
F (87%)
CF_3 (94%)
SMe (82%)[b]
NO_2 (72%)[b]

Buchwald, S.L. *J. Am. Chem.Soc.*, **2005**, 127, 14560-14561
Buchwald, S.L. *J. Org. Chem.*, **2008**, 73,7603-7610

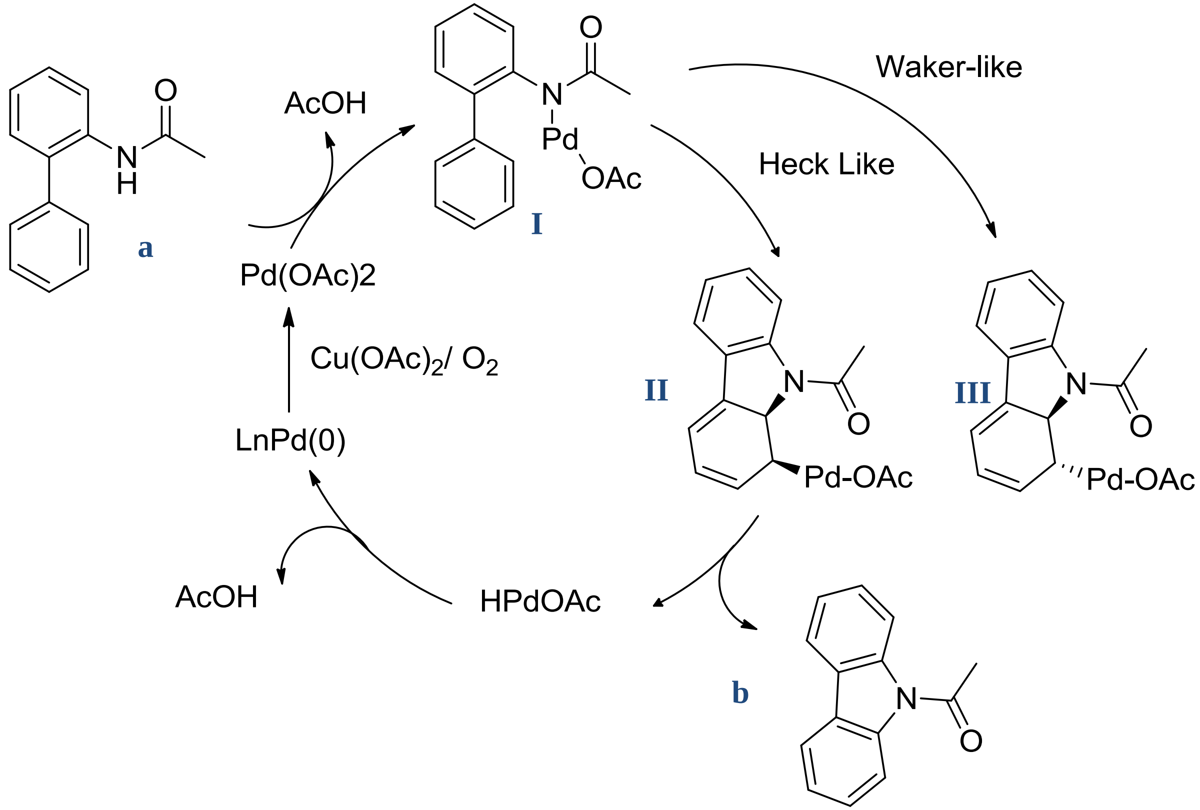
Initial Proposed Pathway



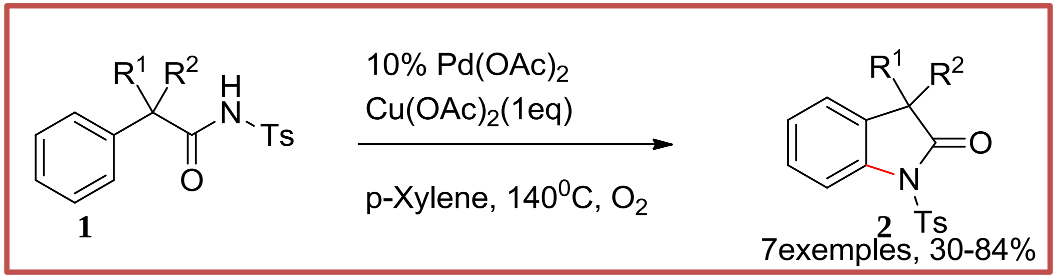
Experimental observation:

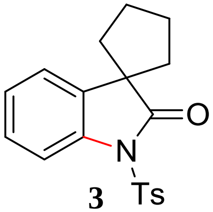
- OMe group in position 3 give just 41% yield
- At lower temperature just 2’-acetamino- 4-metoxybiphenyl cyclizide in73% (inductive effect of MeO)

Alternative Pathway



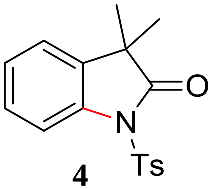
C-H amination to oxindole: Pd(0)/Pd(II)





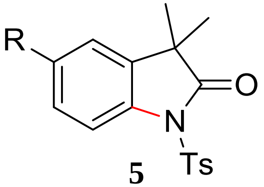
3

84%



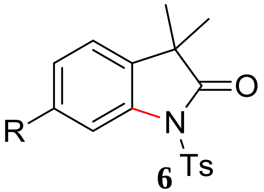
4

82%



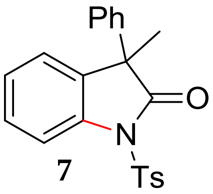
5

R : OMe (30%)
Cl (63%)



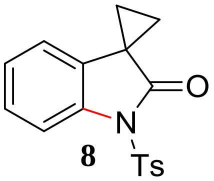
6

R : OMe (61%)
Cl (65%)



7

97%



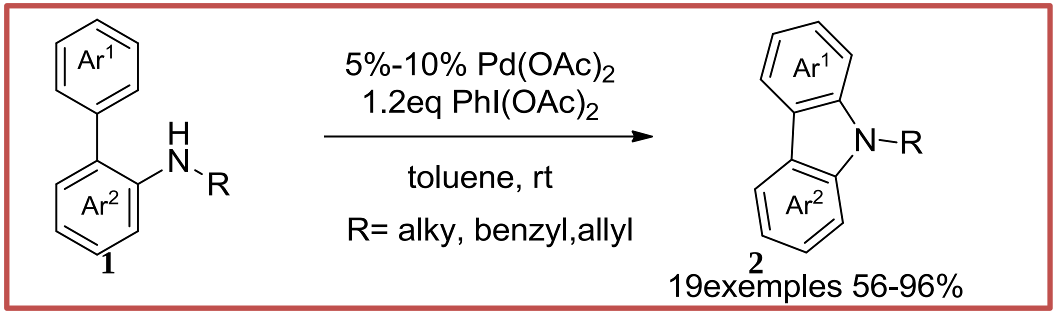
8

39%

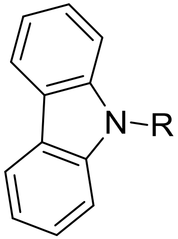
- Non-substituted substrates failed: Thorpe- Ingold effect
- PMB instead Ts group: no reaction
- MeO in 4 retarded the process : no S_EAr for C-H activation
- Proposed mechanism: via six membered palladacycle in Pd(0)/Pd(II)

Murakami, M. *Chemistry Lett*., **2009**, 38, 328-329

Oxidative Pd(II) C-H Bond Amination to Carbazole

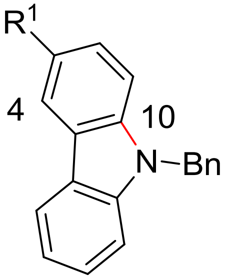


Scope of reaction



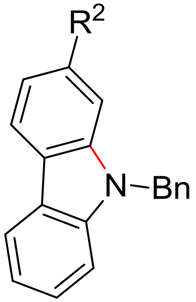
3

R^a: Bn (96%)
i-Pr (96%)
Allyl (79%)
Me (80%)



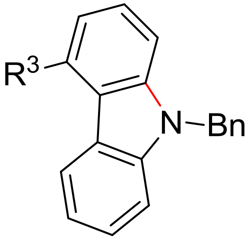
4

R^1: OMe (85%)^b
Me (86%)^{b,a}
F (79%)
CO_2Me(95%)^a



5

R^2: OMe (81%)
CO_2Me(94%)



6

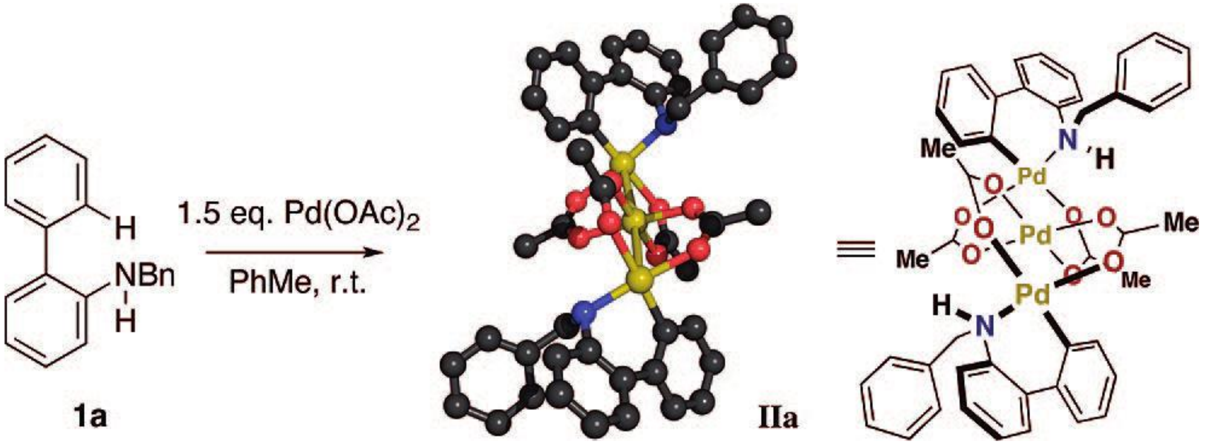
R^3: Me (56%)*
OMe(75%)

[a] Use of 1eq of AcOH

[b] Mixture C10/C4 carbazole isomer

Gaunt,M. *J.Am.Chem.Soc*, **2008**, *130*, 16184–16186

Proposed Mechanism: Pd(II)/Pd(IV)

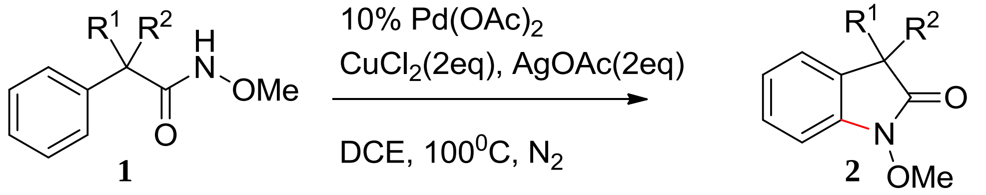


Experimental observation:

- Electron rich substrate react faster: -electrophilic mechanism
  -stronger interaction of C-H with the metal
- X ray of **IIa** : trinuclear complex
- **IIa** can be transformed to the carbazole: $PhI(OAc)_2$, PhMe, rt
- No oxidation in DMSO or in presence of coordinating additive (Py) : monomeric paladacycle

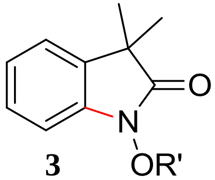
Pd(II) C-H Activation to β, γ, δ-lactame

γ, δ-lactame :



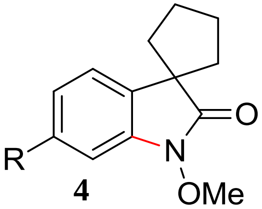
10% Pd(OAc)$_2$
CuCl$_2$(2eq), AgOAc(2eq)
DCE, 100^{0}C, N$_2$

19 exampels, 58-94%



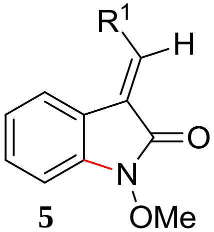
3

R^1: OMe(94%)
OBn(95%)



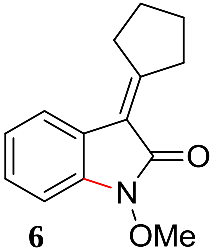
4

R: OMe(90%)
Cl (88%)
F(86%)



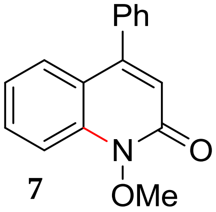
5

R^1: Ph (58%)
Et (60%)
iPr (62%)



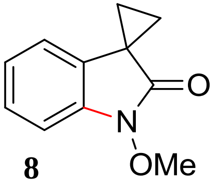
6

78%



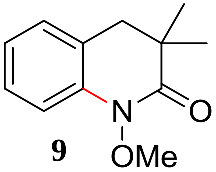
7

91%



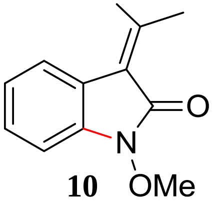
8

88%



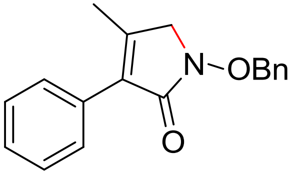
9

72%



10

Sp^2 CH 72%



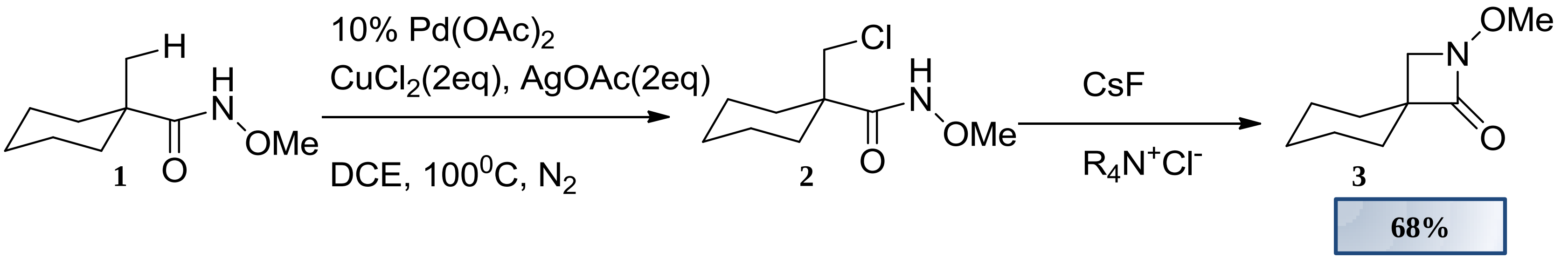
11

Sp^3 CH 68%

Yu, J.-Q. *J.Am.Chem. Soc.* **2008**, 130, 14058–14059

Pd(II) C-H Activation to β, γ, δ-lactame

β-lactame



1

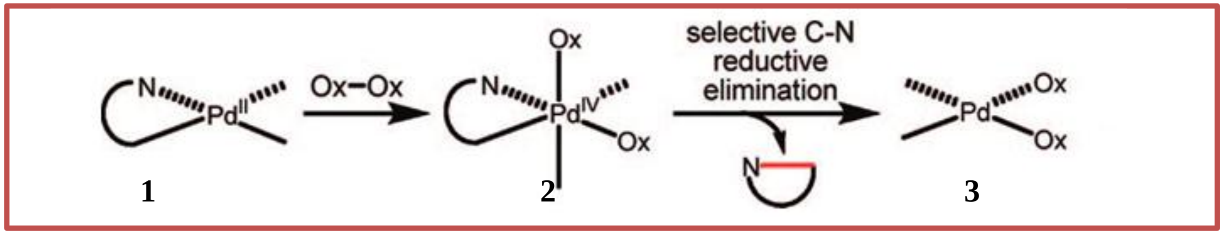
2

3

68%

- One-pot procedure
- Reductive elimination of R-Cl from five membered palladacycle
- Strained transition state

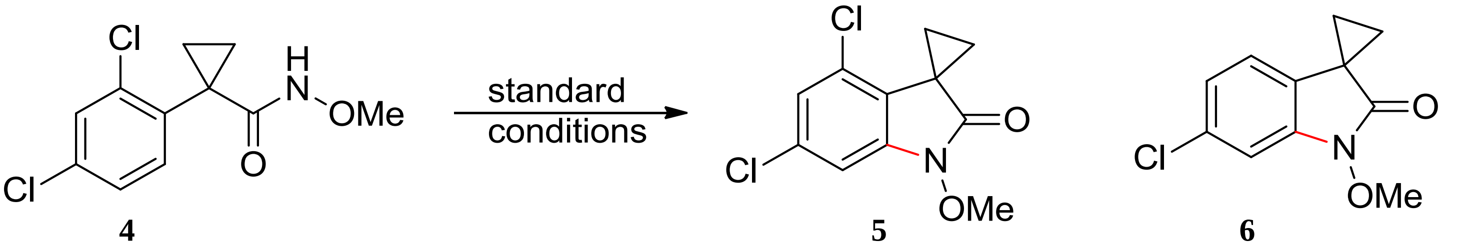
Proposed Mechanism: Pd(II)/Pd(IV)



1 2 3

Experimental observation/ hypothesis

- Using PhI(OAc)$_2$ give 10% of desired oxindole
- CuCl$_2$ source of Cl^{+} : 1ē or 2ē ?
- PdCl$_2$ ligand exchange with AgOAc
- Sequential chlorination –amination excluded:

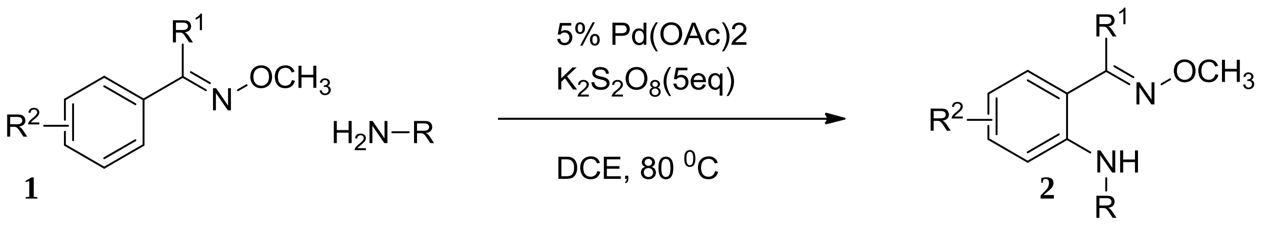


4 5 6

40%

Not observed

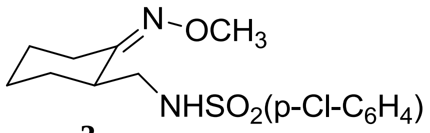
C-H activation via nitrene insertion



R: CO_2CH_3, $COCF_3$, CO_2tBu, SO_2CH_3, $SO_2(p\text{-}Cl\text{-}C_6H_4)$

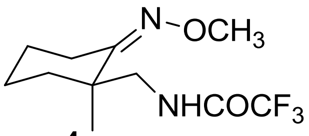
15exampels, 68-96%

- **Sp3 C-H amination**



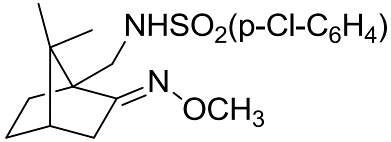
3

88%



4

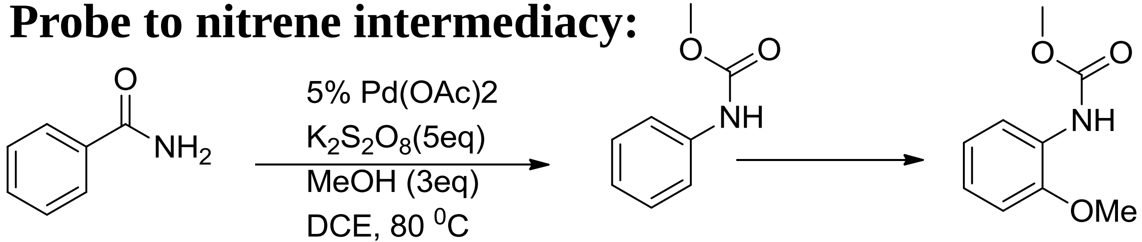
89%



5

93%

- **Probe to nitrene intermediacy:**



6 **7** **8**

1) **Oxidation to form nitrene**
2) **Curtius Rearrangement to isocyanate**
3) **Pd-catalyzed o-methoxylation**

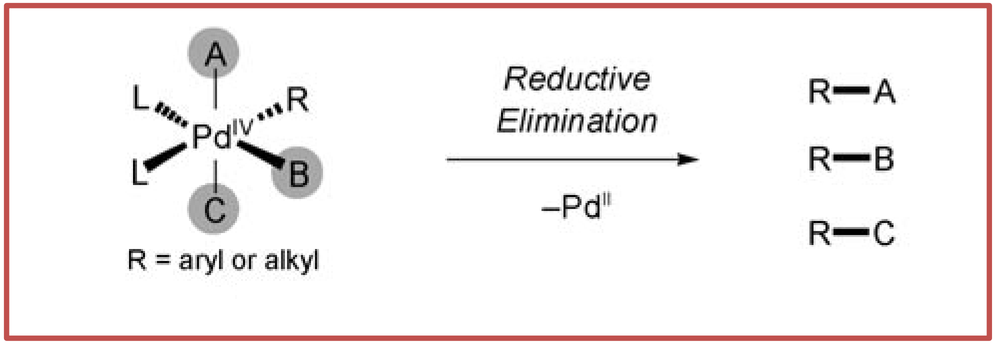
- **Proposed mechanism:** cyclopalladation then nitrene insertion into Pd-C bond or Pd(II) nitrene. Pd(II)/Pd(IV) is not excluded

Chi-Ming Che *J.Am. Chem. Soc*, **2006**, *128,* 9048-9049

Examples: Type of oxidant

- External Oxidant:
  - ✓ bystanding oxidant: definition
  - ✓ F^+ :baystanding oxidant
  - ✓ Example1: Indoline synthesis via Pd(II)/Pd(IV)
- Internal Oxidant:
  - ✓ Example1: N-Nosyl carbamate
  - ✓ Example2: Oxime esters

External Oxidant Pd(II)/Pd(IV)



- Octahedral Pd IV: lack of selectivity
- Bystanding oxidant : *“A reagent that participates in electron transfer to increase the oxidation state of a transition metal species but is not incorporated into the final product during subsequent reductive elimination”*
- Why F^+ bystanding oxidant?

Yu J.-Q. *Angew. Chem. Int. Ed.* **2011**, 50, 1478 – 1491

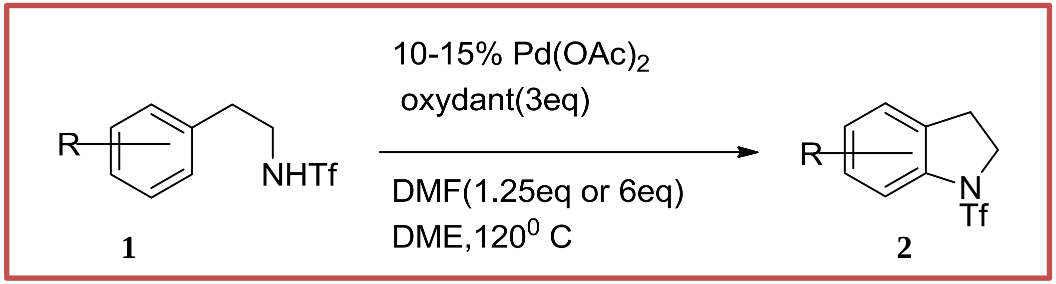
F+: Bystanding Oxidants in Pd(II)/Pd(IV) Catalysis

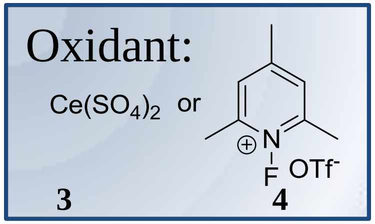
- Cl_2, $CuCl_2$, NCS, NBS, NIS, IOAc, and $PhICl_2$ source of X^+ : halogenating agent C-H activation reactions

- F^+ more problematic:

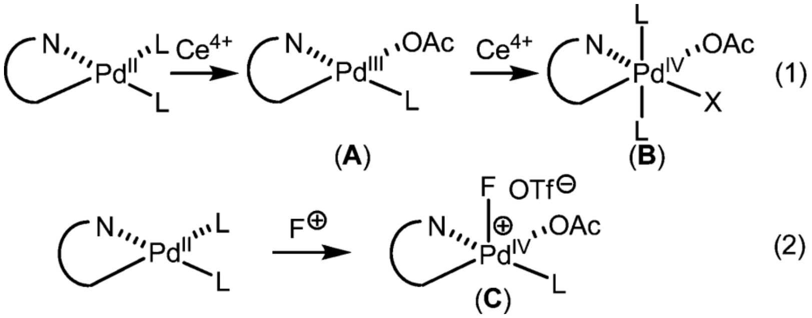
  - F^+ reagent : strong sigma donor ligand hamper the C-H activation
  - Highly electronegative, low polarizability : attenuate the reductive elimination

C-H amination using F^+ and Ce^{4+} as oxidant: Indoline synthesis



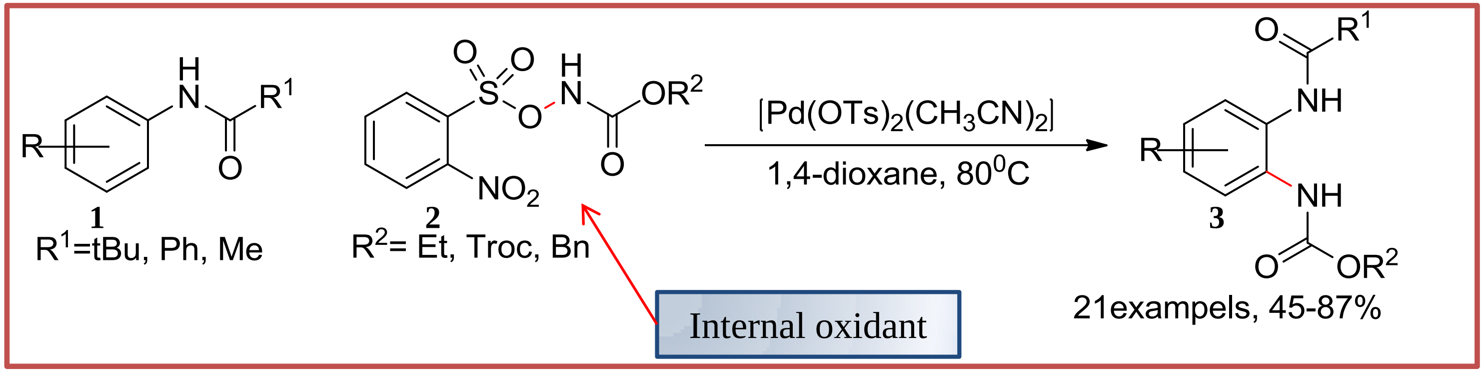


- Using classical oxidation agent ($CuCl_2$, NCS, NBS, NIS, IOAc) give halogenation/ acetoxylation side product
- 22 examples, yield 53-91% when F^+ (two electron oxidant) is used: large number of functionalities are tolerated (Br,Cl, F, CN, NO_2…), quinoline low yield
- 9 examples, yield 40-80% when $Ce(SO_4)_2$



Yu J., Q. *J. Am. Chem. Soc.*, **2009**, 131, 10806–10807

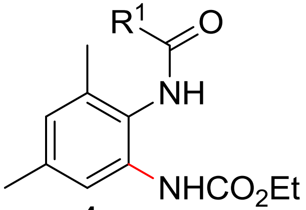
External-oxidant free oxidative amination:



1 R^1=tBu, Ph, Me

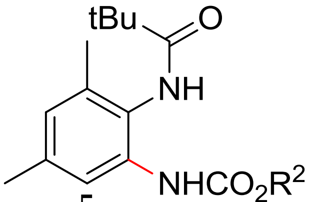
2 R^2= Et, Troc, Bn

3 21exampels, 45-87%



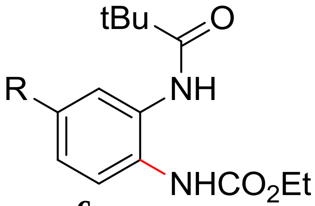
4

R^1: t-Bu (84%)
Me (52%)
Ph (57%)



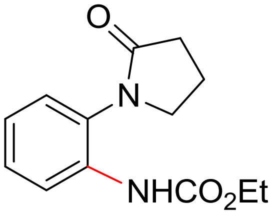
5

R^2: Troc (87%)
Bn (70%)



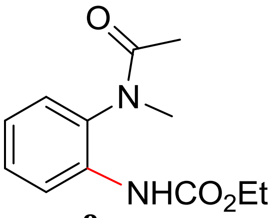
6

R: OMe (45%)
F (66%)
Br(68%)



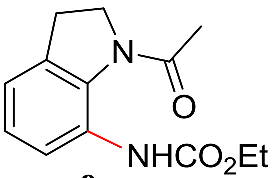
7

85%



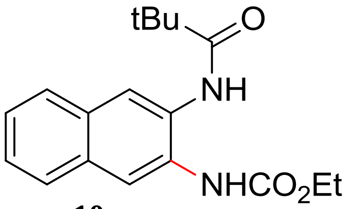
8

72%



9

68%

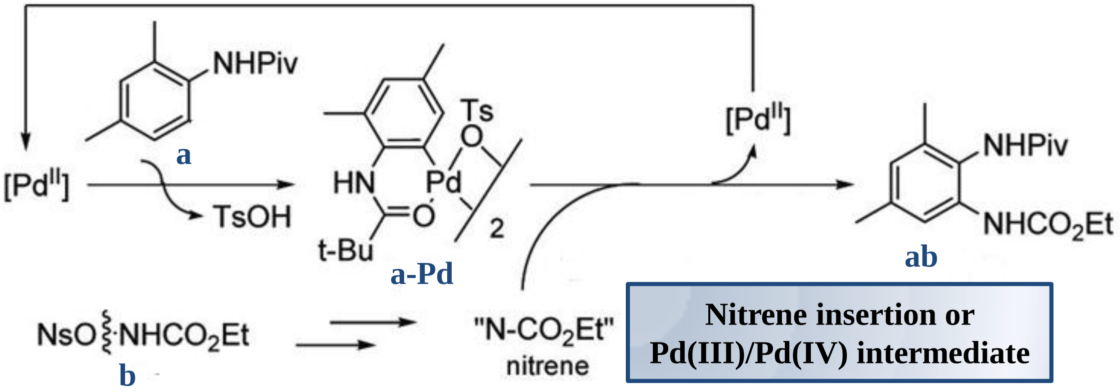


10

72%

Yu, J. M., *J. Am. Chem. Soc.*, **2010,** 132, 12862–12864

Proposed mechanism: Pd(II)/Pd(IV) or nitrene:

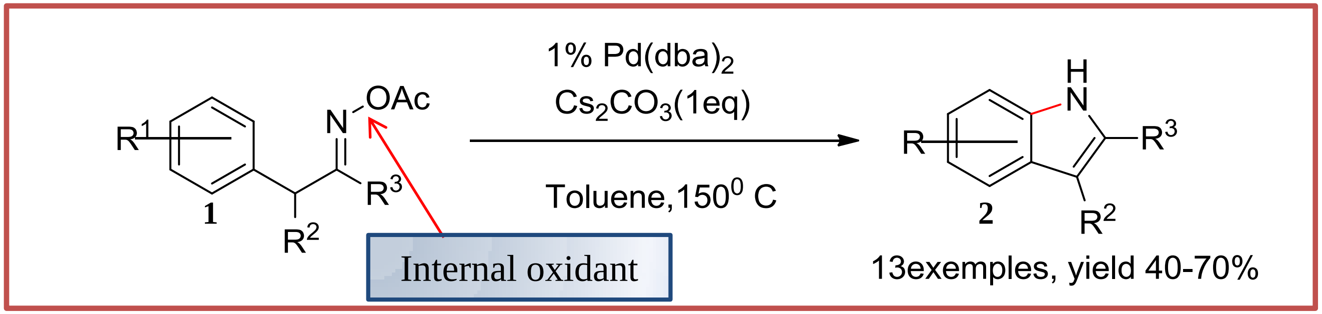


Nitrene insertion or Pd(III)/Pd(IV) intermediate

Experimental observation:

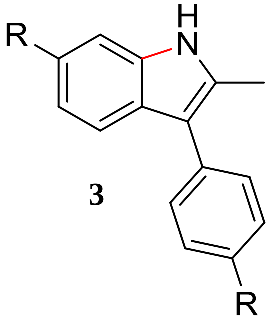
- Isotope effect (k_H/k_D) =3.7
- Stoichiometric amidation of cyclopaladated intermediate afford 45% of **ab**
- Anilide stabilized reactive intermediary species
- Treating **a-Pd**, **a** with **b** in presence of K_2CO_3(generate nitrene) give 74% desired compound

External-oxidant free oxidative amination: Indole synthesis

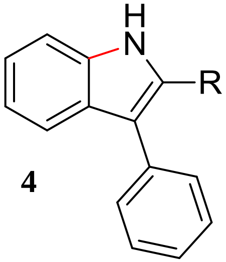


Internal oxidant

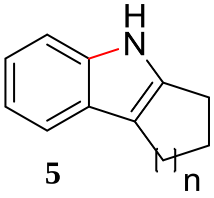
13exemples, yield 40-70%



3



4



5

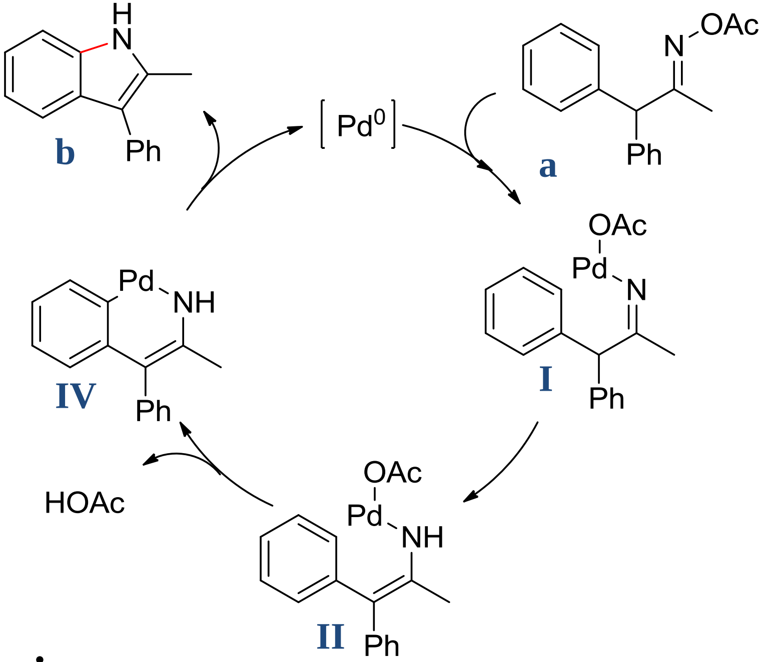
R^1: Me (65%)
F (61%)
Cl (63%)
Br(60%)
OMe(40%)

R^1: Me (65%)
Et (51%)

n=1(41%)
n=2 (51%)

Hartwig J., F. *J. Am. Chem. Soc.*, **2010**, 132, 3676–3677

Proposed mechanism Pd(0)/Pd(II)



C-N bond reductive elimination

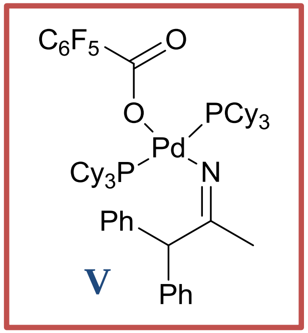
N-O bond oxidative addition

Tautomerization

C-H activation

Experimental observation:

- Complex **V** was isolated (X-Ray structure)
- Complex (1%) catalyzed the reaction with **a** in 58%
- By heating **V** indole **b** is obtained in 31%



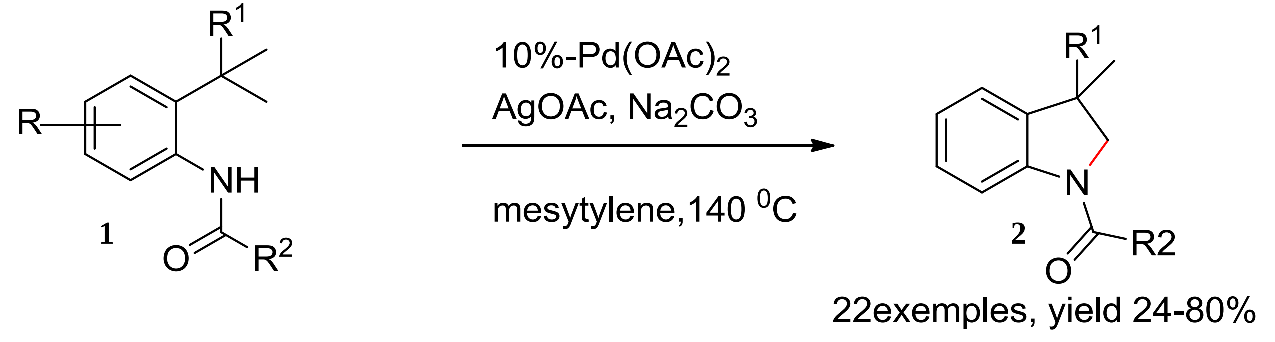
V

Type of C-H bond

- C(sp^3)-H
- Allylic
- Aromatic

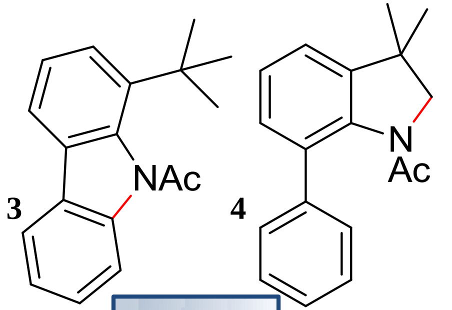
Note : Pd(II) catlyzed addition of nitrogen nucleophiles to the alkene is not included in this talk

Sp3-CH Amination : from aniline to indoline



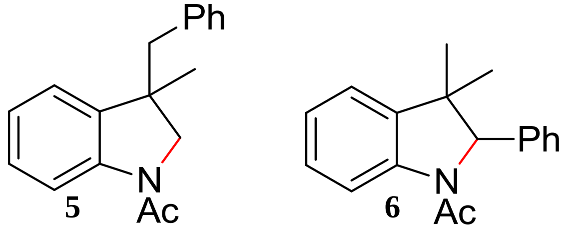
22exemples, yield 24-80%

C(sp^3)-H vs C(sp^2)-H

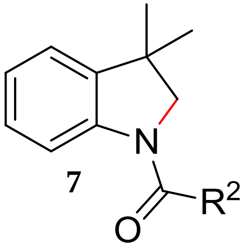


39 :0%

C(sp^3)-H vs benzylic C-H



48:52

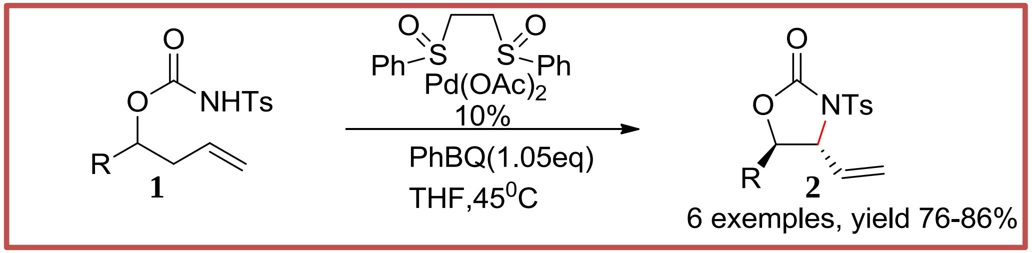


R^2: H(73%)
Me(80%)
Et (59%)
iPr(24%)

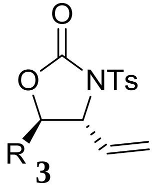
- Large variety of groups is tolerated: Cl, OMe, CHO, ketone…

Glorius, *F. Angew. Chem. Int. Ed.*, **2009**, 48, 6892 –6895

Allylic intramolecular C-H amination: syn-1,3 and 1,2-Aminoalcohols



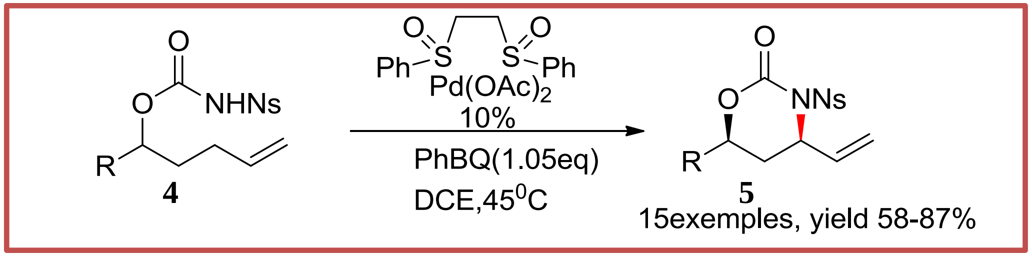
6 exemples, yield 76-86%



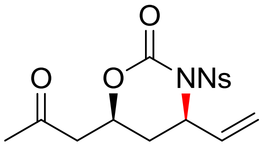
3

R: iPr (76%,7/1*)
tBu (8%, 18/1)
nPr (59%, 1.6/1)

*dr (anti:syn)

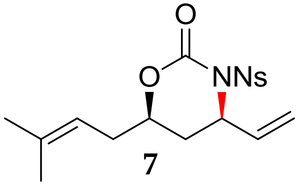


15exemples, yield 58-87%



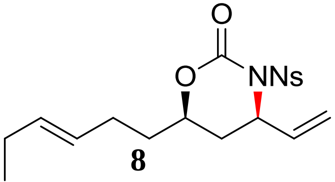
6

76%, 3.4/1



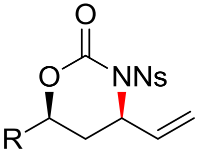
7

67%, 4.5/1



8

76%, 3.4/1



9

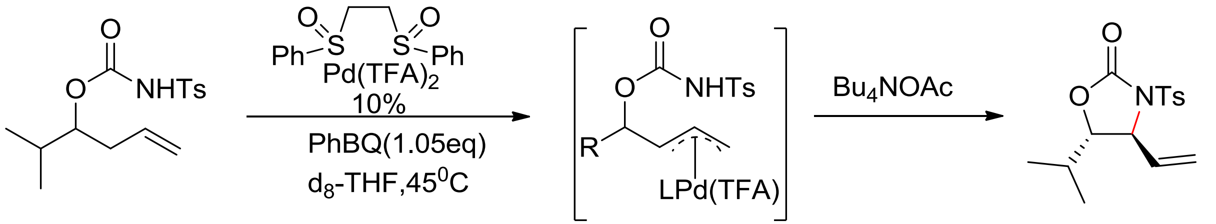
R: *i*Pr (80%, 6/1)
***t*Bu (84%, 6.3/1)**
Et (87%, 4.3/1)

White,C. *J.Am.Chem.Soc.*, **2007**, *129*, 7274-7276; White,C. *J.Am.Chem.Soc.*, **2009**, *131*, 11707-11711

Stoichiometric allylic amination: Hegedus,L.S. *J. Am. Chem. SOC.* **1981,** *103*, 3037 ; Trost, B.M. *Tetrahedron*, **1977**, 33, 2615

Possible mechanism:

- Allylic C-H amination / isomerization of double bond followed by aminopalladation

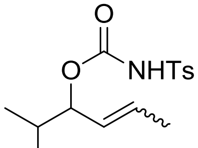


1

61% **2** by NMR

75% **3** dr 6/1

- Alkene **4** give very poor yield (9% for Z, 20% for E)



4

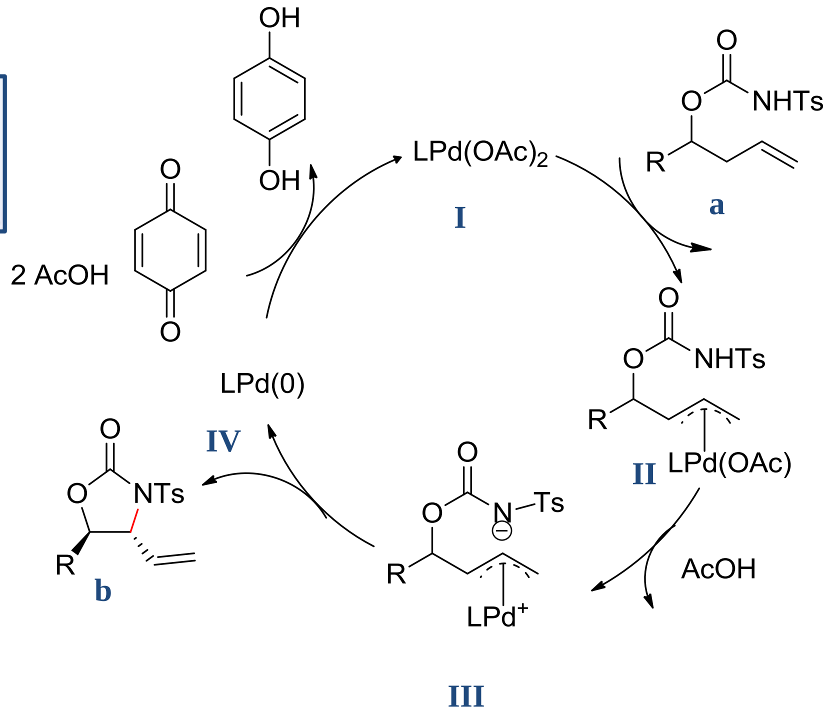
Proposed mechanism:

Catalyst and endogenous base regeneration

Electrophilic C-H cleavage

Nucleophilic functionalization

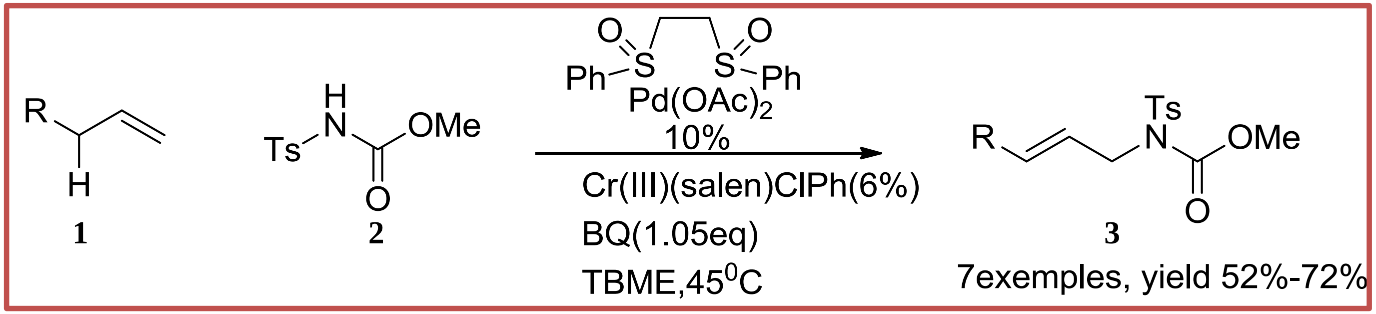
Acid/Base exchange



Allylic intermolecular C-H amination

Heterobimetallic catalysis :

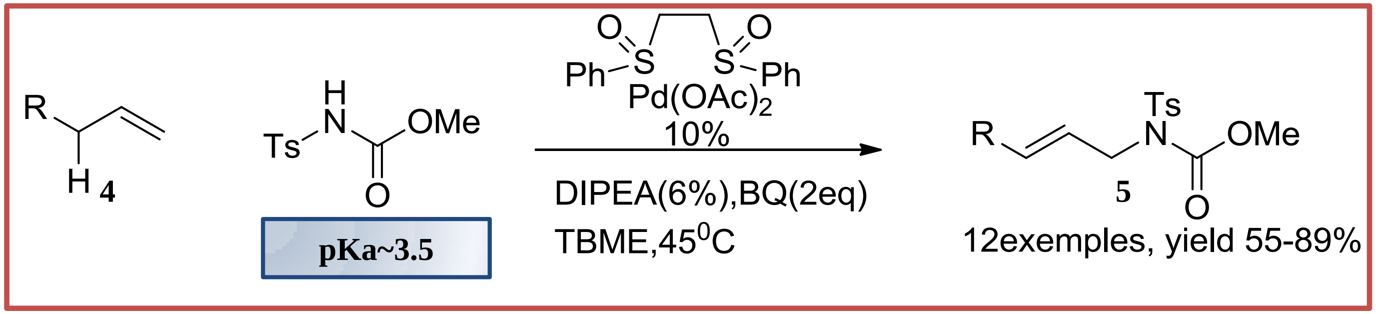
- Lewis Acid catalysis Cr bind to BQ –π-Allyl complex increasing his electrophilicity



7exemples, yield 52%-72%

Bronsted base activation :

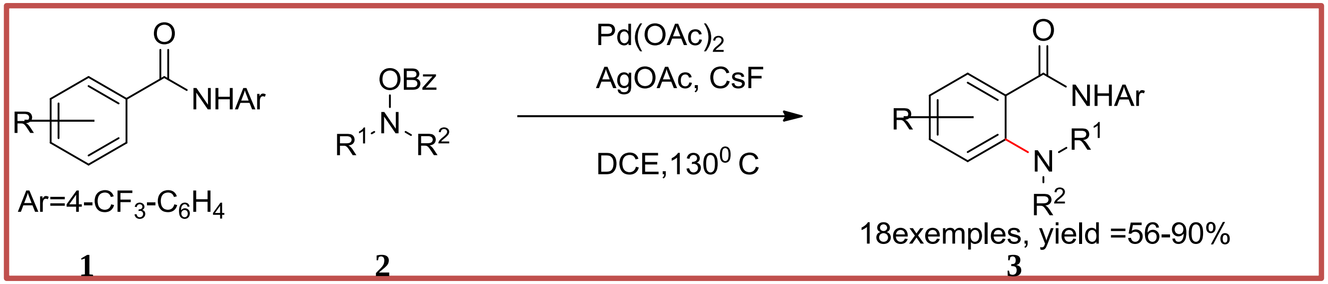
- Exogenous base will increase the concentration of deprotonated nucleophile nitrogen

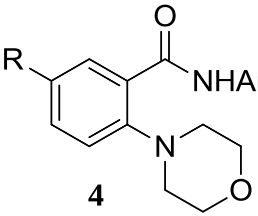


12exemples, yield 55-89%

White, C. *J.Am.Chem.Soc.*, **2008**, *130*, 3316-3318
White, C. *J.Am. Chem. Soc.*, **2009**, *131*, 11701–11706

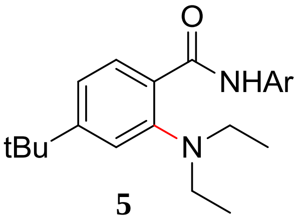
Aromatic intramolecular amination with amine





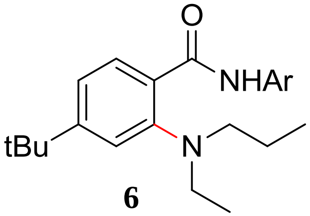
4

R: OMe (79%)
Br (56%)
Cl (60%)
Me(82%)



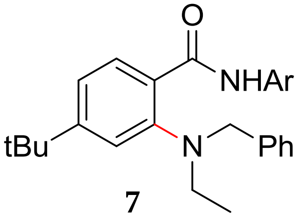
5

73%



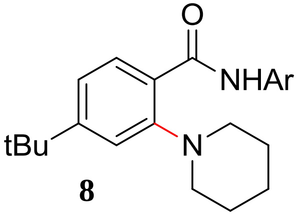
6

80%



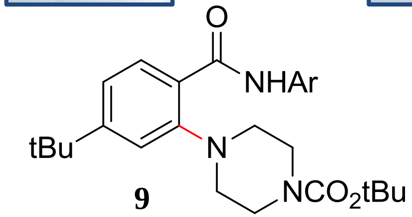
7

75%



8

97%



9

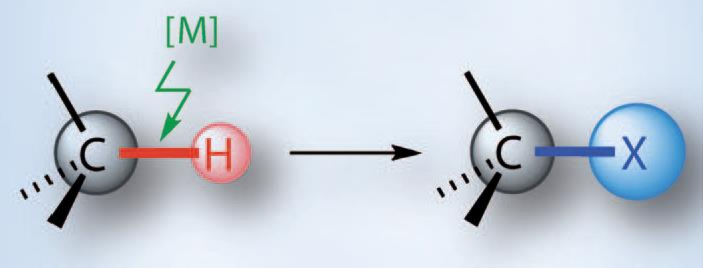
78%

- No external oxidant is required
- Reaction work as well with amine in presence of benzoyl peroxide
- CsF as base, cycloppaladation, Pd(II)/Pd(IV) or electrophilic amination
- Pd(dba)$_2$ catalyzed as the reaction: N-O bond oxidative addition

Jin-Quan Yu, JACS, 2011

Thank you for your attention!

Late stage
transition metal catalyzed
C-H functionalization
in total synthesis

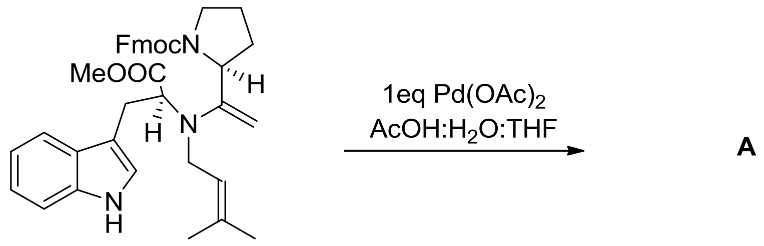


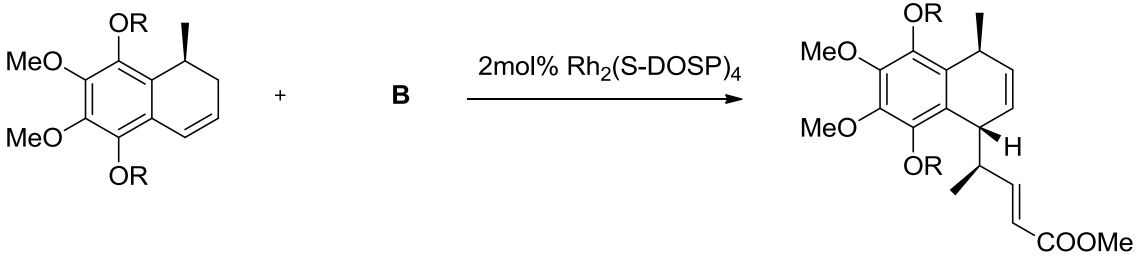
Laetitia Souillart

06.06.11

Questions

Complete the following syntheses:





Introduction to the concept of « economy »

- Hendrickson “ideal synthesis”[1]:

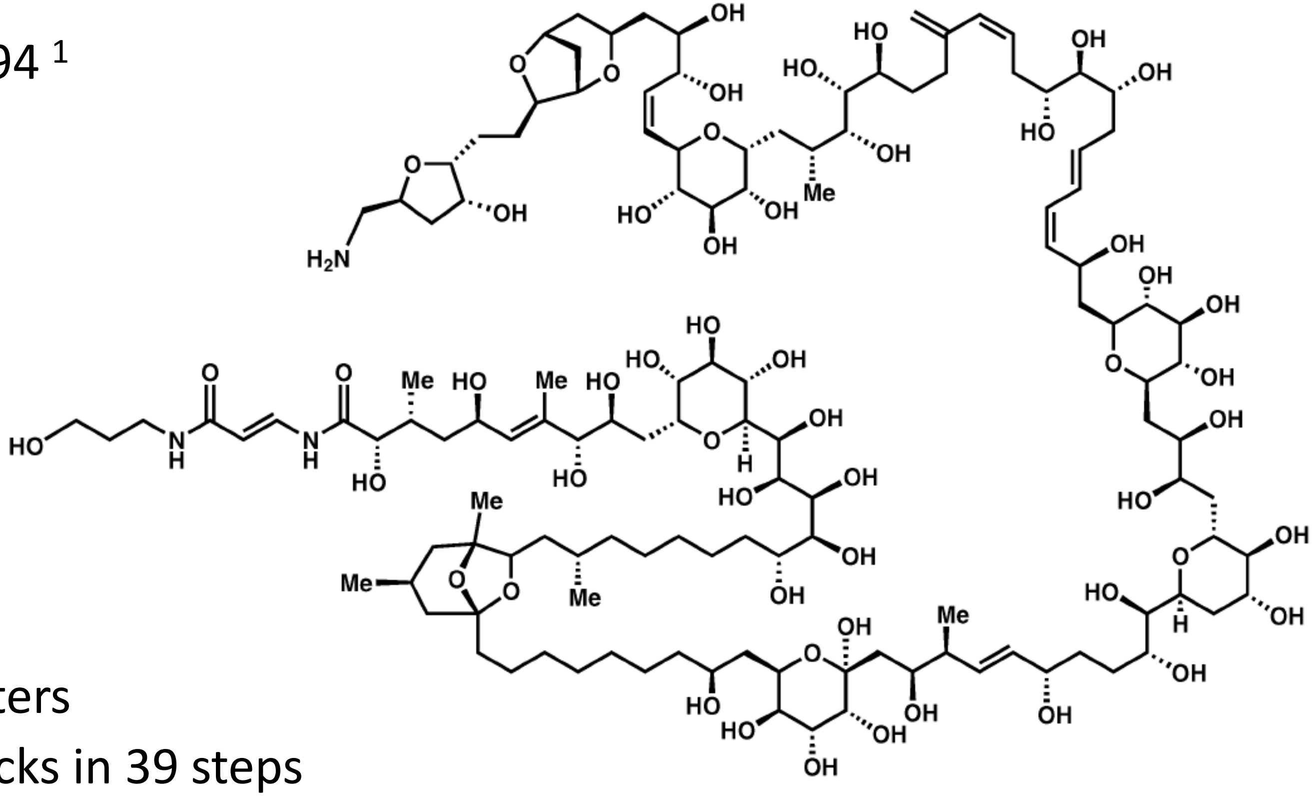
“ The ideal synthesis creates a complex molecule from available small molecules … linking them together in a sequence only of successive construction reactions involving no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality.”

---

1. Hendrickson, *JACS*, **1975**, 97, 5784-5800

Introduction to the concept of « economy »

Palytoxin, Kishi, 1994 [1]



64 stereogenic centers

from 7 building blocks in 39 steps

(11 skeleton forming, 15 refunctionalization, 13 protecting group management steps)

→ far away from Hendrickson’s « ideal synthesis »

---

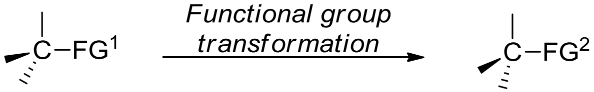
[1] Y. Kishi, *JACS*, **1994**, 116, 11205-11206

C-H bond functionalization

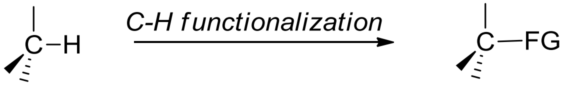
- Formally, any retrosynthetic disconnection resulting in a C-H synthon in a C-H bond functionalization [1]

- Generally, restricted to “inert” C-H bonds

- Traditional approach:



- C-H functionalization:



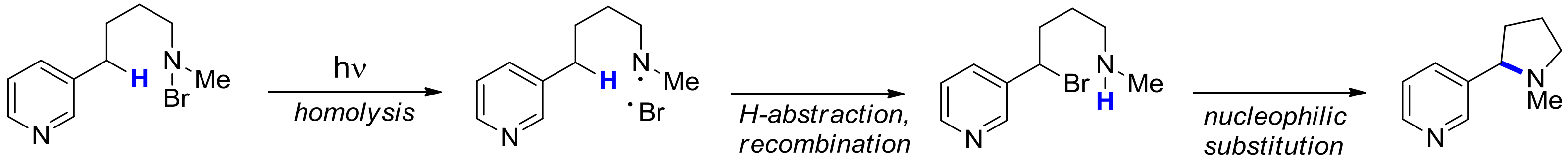
→ C-H bonds are omnipresent so that methods must be selective
→ Methods must be tolerant to the other functionalities to be applied at a late stage

---

1. P. Baran, *Chem. Soc. Rev.*, **2011**, 40, 1976-1991

Pioneering work

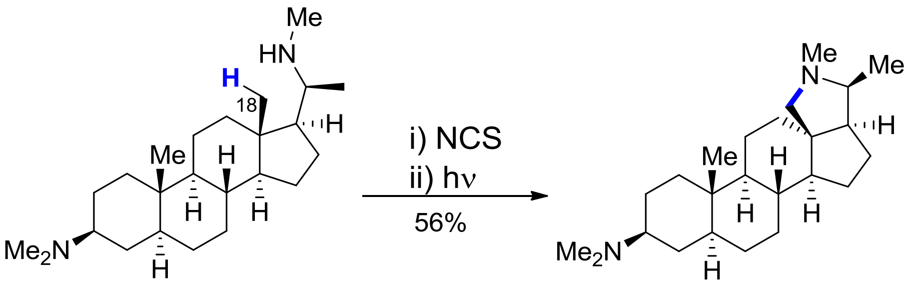
- 1909: Nicotine, Löffler [1]



nicotine

- earliest example of C–H functionalization in total synthesis
- one single step

- 1958: Dihydroconessine, Corey [2]



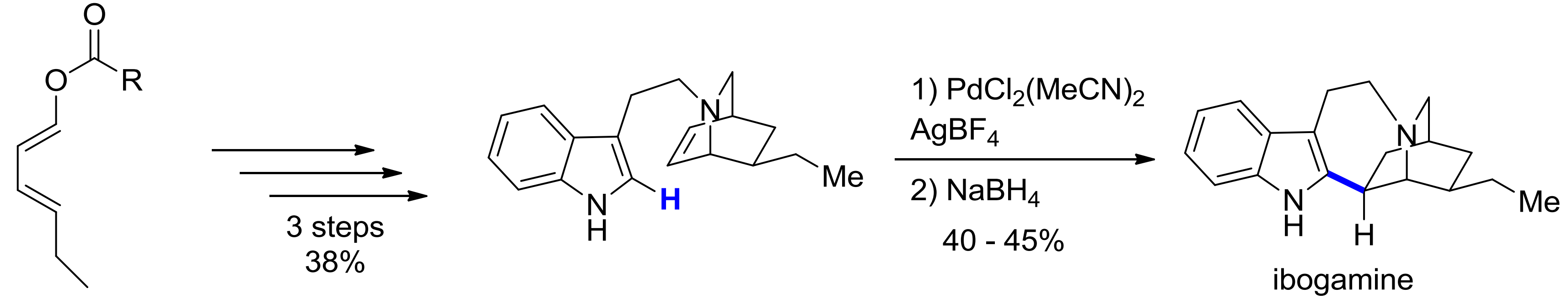
dihydroconessine

---

1. K. Löffler , *Ber.*, **1909**, 42, 3431-3438
2. E.J. Corey, *J.A.C.S.*, **1958**, 80, 2905-2906

Pioneering work

- 1978: Ibogamine, Trost [1]



- earliest example of transition metal catalyzed C–H activation in total synthesis
- stoichiometric quantities of palladium and silver salts
- 4 steps; 17% overall yield

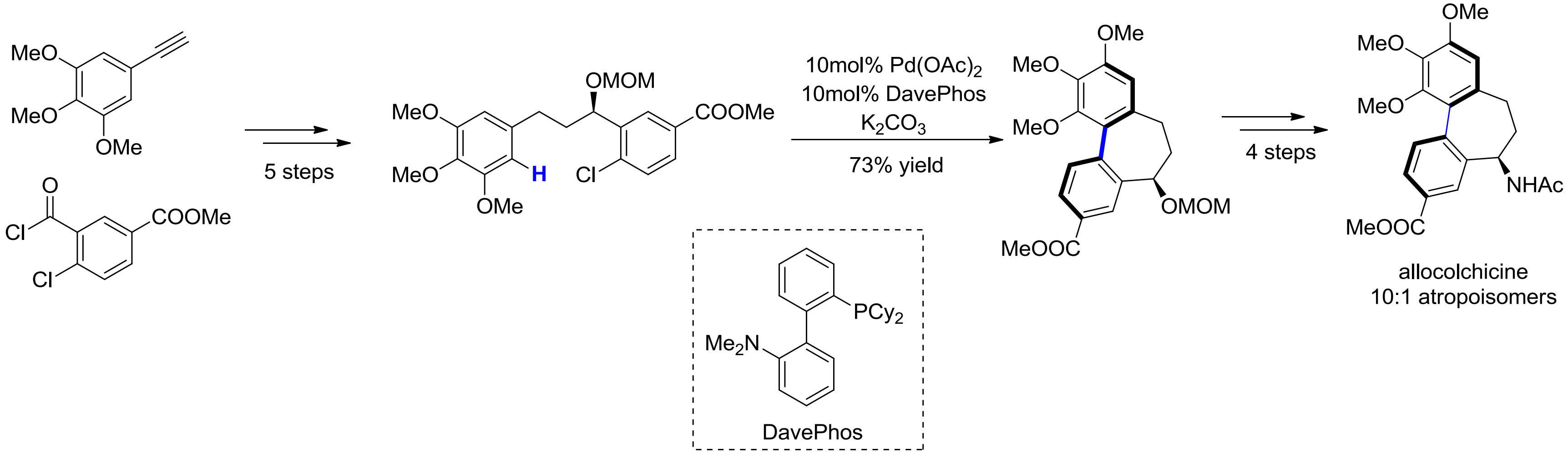
(previous synthesis by Ziegler[2] was 14 steps and overall yield <1%)

---

1. B.M. Trost, *J.A.C.S.*, **1978**, 100, 3930-3931
2. E. Ziegler, *J.A.C.S.*, **1965**, 87, 2073-2075

Recent developments

- 2005: Allocolchicine, Fagnou [1]



- intramolecular direct arylation of aryl chloride
- 10 steps, 24% overall yield

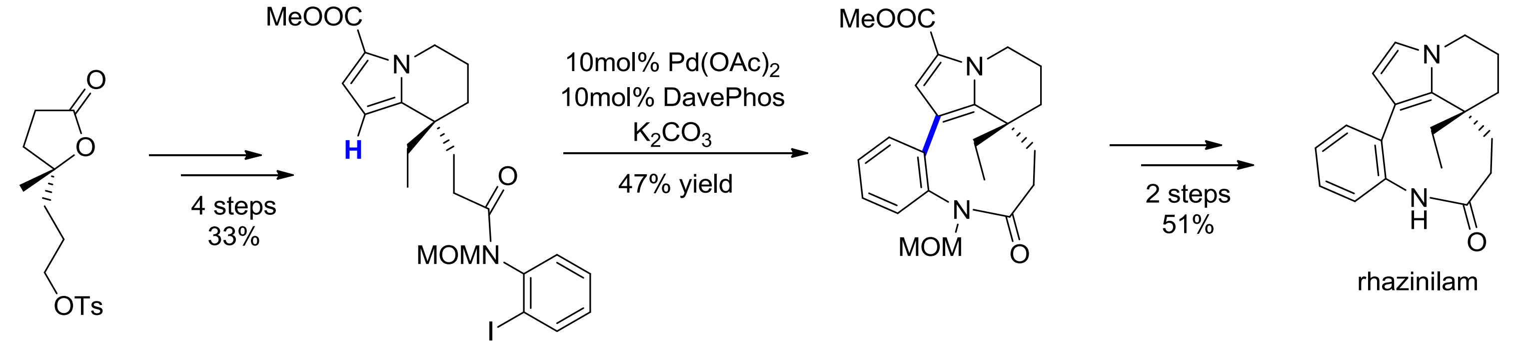
(previous synthesis by Wulff [2] was 14 steps, 7% overall yield)

---

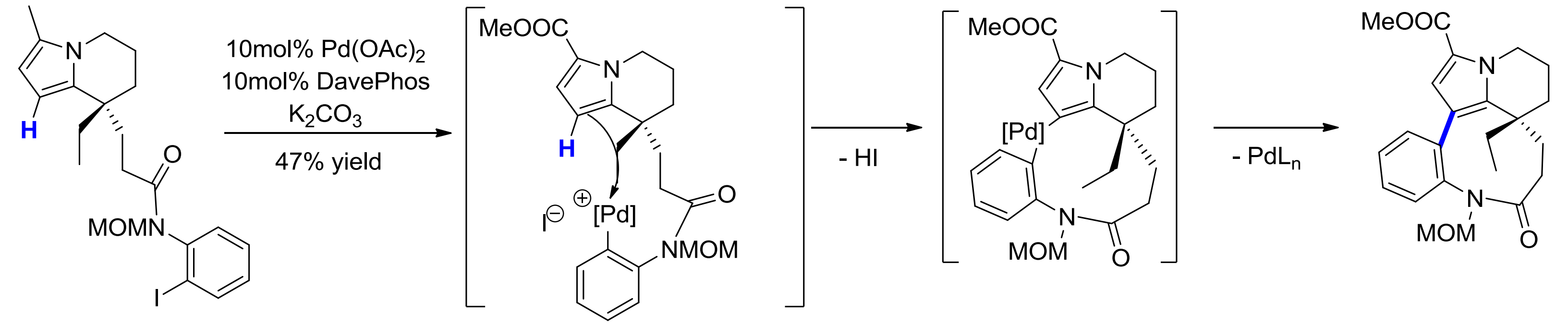
1. K. Fagnou, *Org. Lett.*, **2005**, 7, 2849-2852
2. W. D. Wulff , *J. Org. Chem.*, **2003**, 68, 5826-5831

Recent developments

- 2005: Rhazinilam, Trauner [1]



- Palladium(II)-catalyzed intramolecular direct arylation
- 7 steps, 8% overall yield



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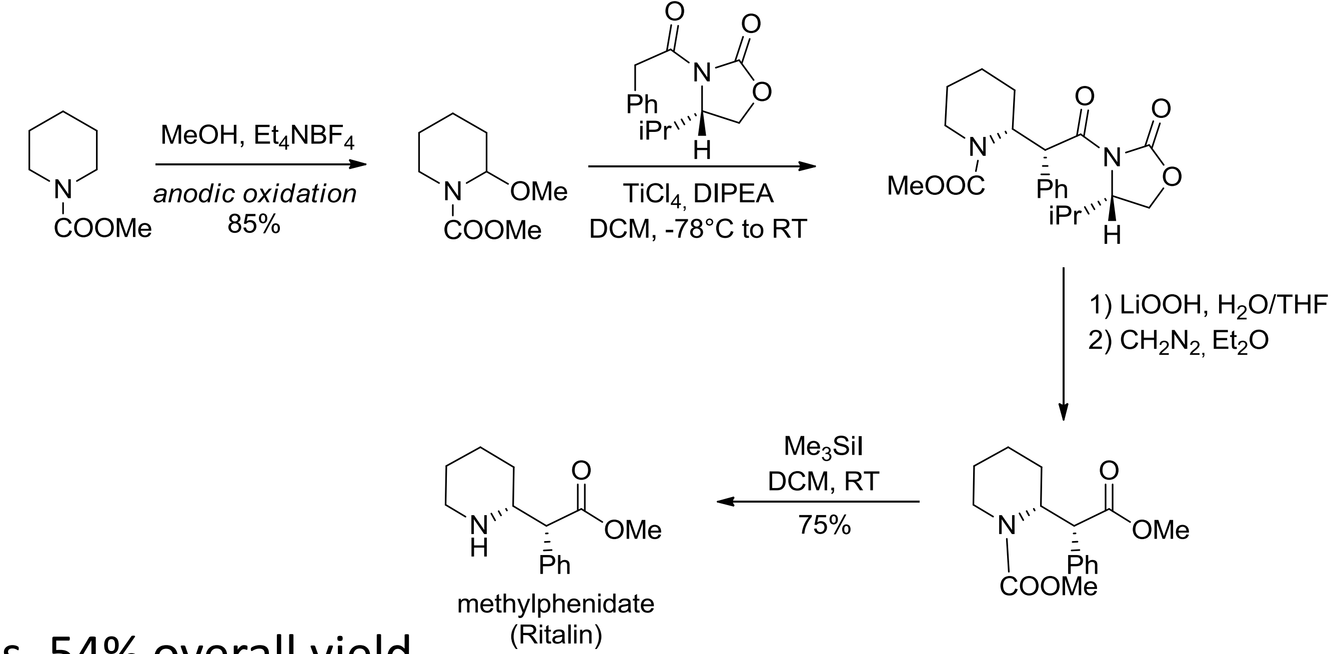
1. D. Trauner, *Org. Lett.*, **2005**, 7, 5207-5209

Recent developments

- 2004: Methylphenidate (Ritalin), Davies [1]

- Previous synthesis, 1999, Matsumura [2]



5 steps, 54% overall yield

95% de, >99% ee

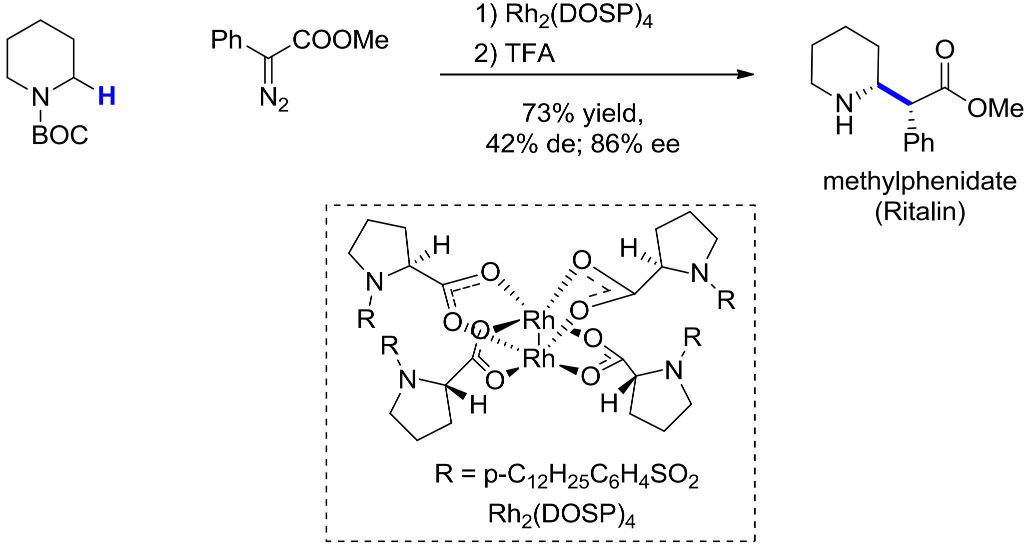
Stoichiometric amount of Evans chiral auxiliary

---

1. H.M.L. Davies, *Bioorg. Med. Chem. Lett.*, **2004**, 14, 1799-1802
2. Y. Matsumura, *Org. Lett.*, **1999**, 1, 175-178

Recent developments

- 2004: Methylphenidate (Ritalin), Davies [1]



Rhodium(II)-catalyzed intermolecular C–H insertion

2 steps, 73% yield

42% de, 86% ee

---

1. H.M.L. Davies, *Bioorg. Med. Chem. Lett.*, **2004**, 14, 1799-1802

Recent developments

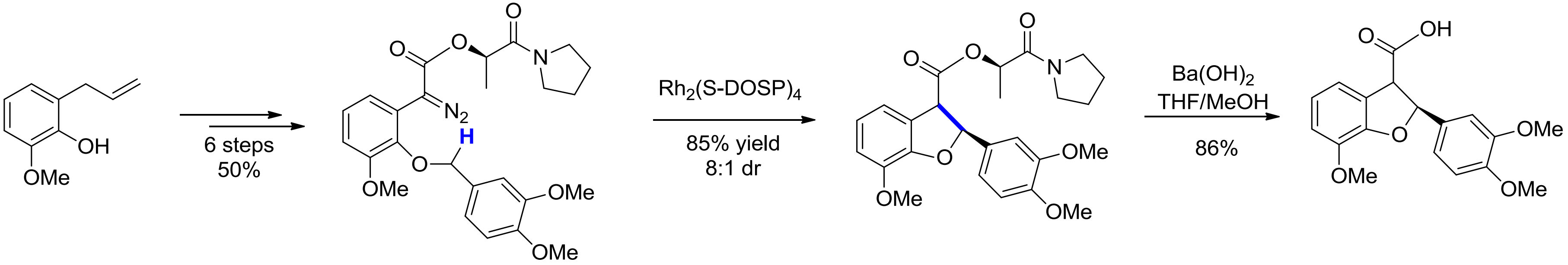
- 2011: Lithospermic acid, J.Q. Yu[1]

- 2005: Ellman[2]: 14 steps, 6% overall yield
- 2011: J.Q. Yu: 13 steps, 10% overall yield

2 key C-H functionalization reactions

First key step:

Rhodium(II)-catalyzed intermolecular C–H insertion using Davies' conditions[3]



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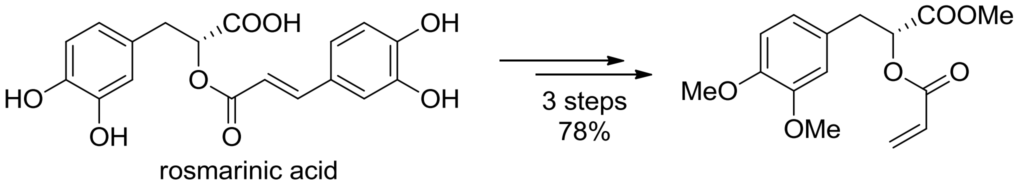
1. J. Q. Yu, *J.A.C.S.*, **2011**, 133, 5765-5769
2. J. A. Ellman, *J.A.C.S.*, **2005**, 127, 13496
3. H.M.L. Davies, *Bioorg. Med. Chem. Lett.*, **2004**, 14, 1799-1802

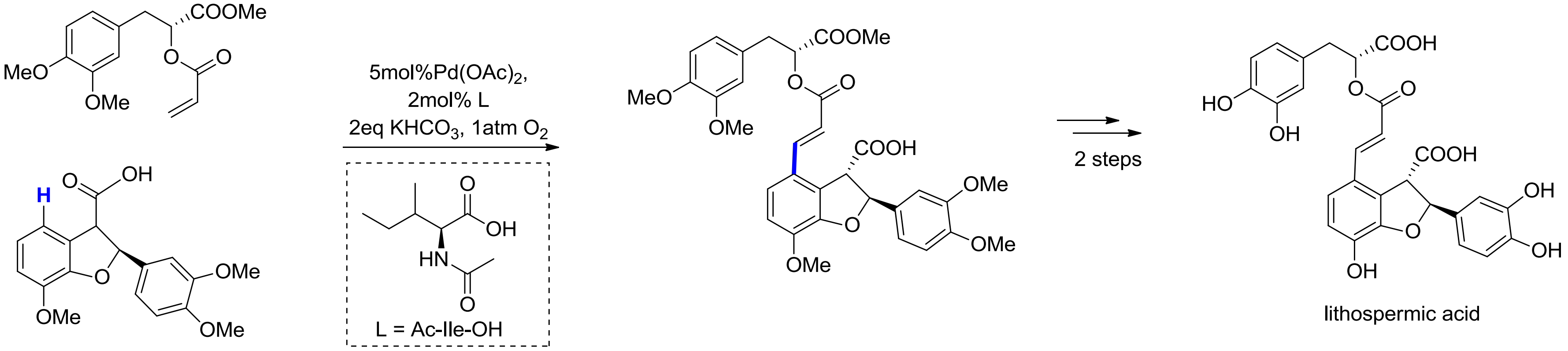
Recent developments

- 2011: Lithospermic acid , J.Q. Yu[1]

Second key step:

Palladium(II)-catalyzed intermolecular C-H olefination





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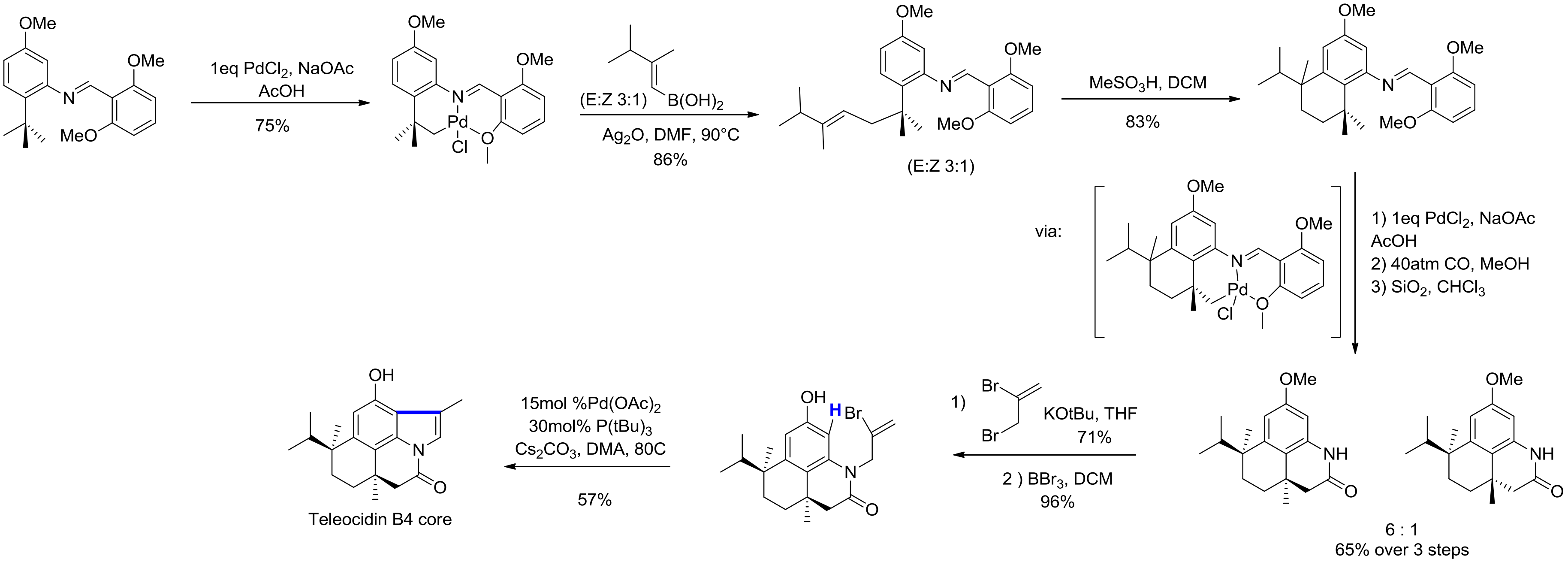
1. J. Q. Yu, *J.A.C.S.*, **2011**, 133, 5765-5769

Recent developments

- 2002: core of Teleocidin B4, Sames [1]

- 9 steps including 4 C-C bond forming step including:
  - a palladium(II) catalyzed intramolecular alkenylation
  - two tandem cycles of directed C-h bond functionalization of t-Bu group



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1. D. Sames, *J.A.C.S.*, **2002**, 124, 11856-11857

Conclusion and outlook

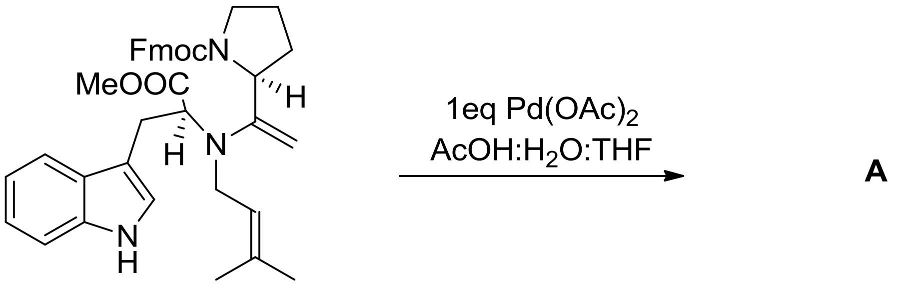
- Advantages of applying C-H functionalization to total synthesis:

  - Atom economy
  - Step economy
  - Redox economy

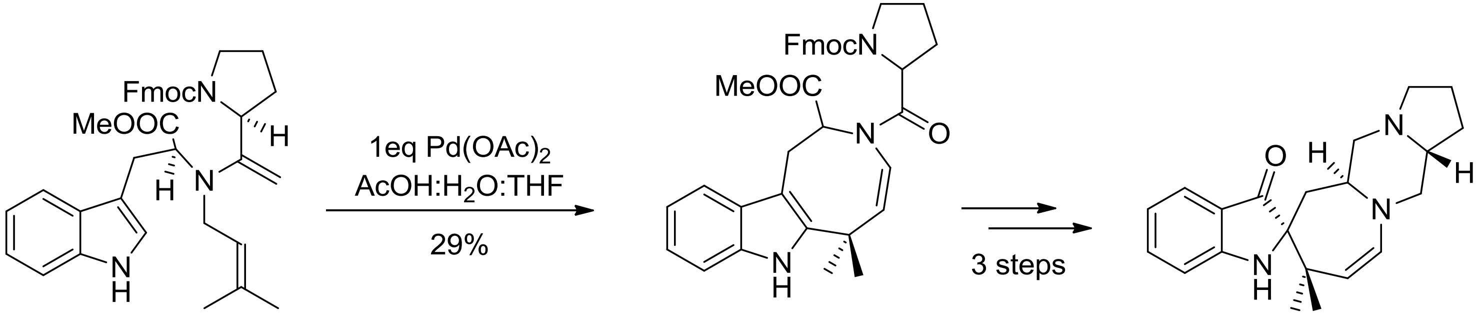
- New methods for functionalizing C-H bonds rapidly growing leading to new retrosynthetic disconnections

→ C-H bond is a new function

Questions



- Corey's hydratoaustamide synthesis[1]:



hydratoaustamide

- Indole is palladated at C-2 position (similar to Trost's ibogamine synthesis)

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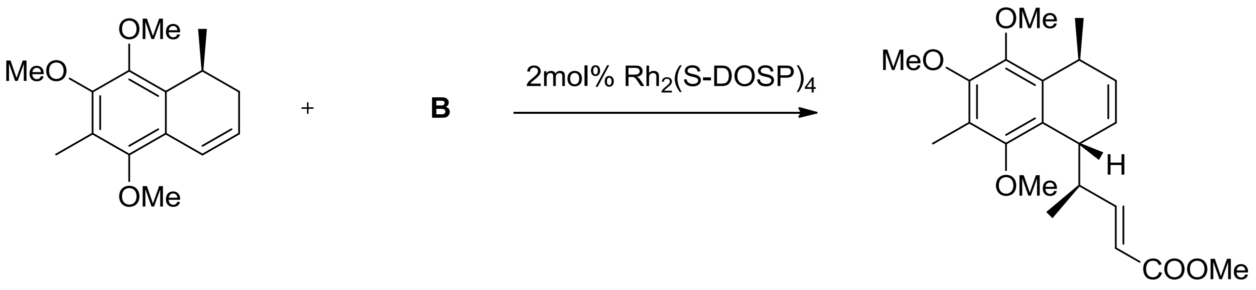
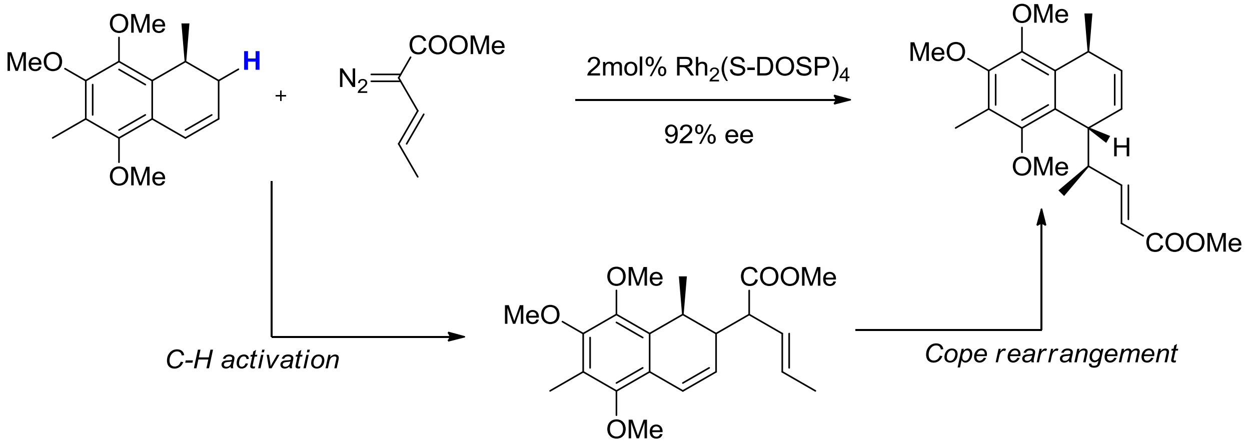
[1] Corey, *J.A.C.S.*, **2002**, 124, 7904-7905

Solutions to questions



- Davies' Elisapterosin synthesis[1]:



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[1] Davies, *J.A.C.S.*, **2006**, 128, 2485-2490

Rhodium-catalyzed hydroamination of olefin

Baihua YE

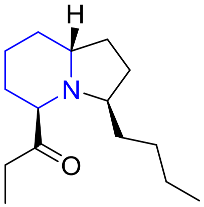
06/06/2011

Summary

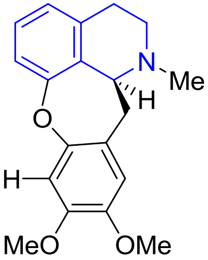
1. Introduction
2. Rhodium-catalyzed intermolecular hydroamination
    - 2.1. Rh-catalyzed hydroamination of ethylene
    - 2.2. Rh-catalyzed hydroamination of norbornene
    - 2.3. Rh-catalyzed hydroamination of aryl olefin
3. Rhodium-catalyzed intramolecular hydroamination
    - 3.1. Markovnikov cyclization
    - 3.2. Anti-Markovnikov cyclization
4. Enantioselective intramolecular hydroamination
5. Conclusion and Outlook

1. Introduction

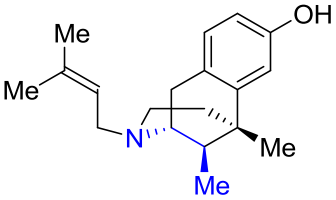
The ubiquity of nitrogen-containing compounds in naturally occurring and biologically active molecules



(Myrmicaria Alkaloid)[a]



(+)-Cularine
(Cularine alkaloid) [b]



(-)-Pentazocine[c]
(Opium alkaloid)

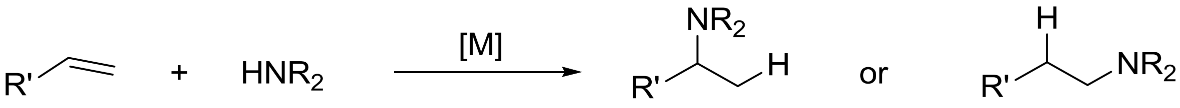
Hydroamination[d]: Direct formation of C-N bonds from amine and alkene or alkyne

- One of the simplest and most atom-economical methods
- From the inexpensive starting materials to the nitrogen heterocycles.

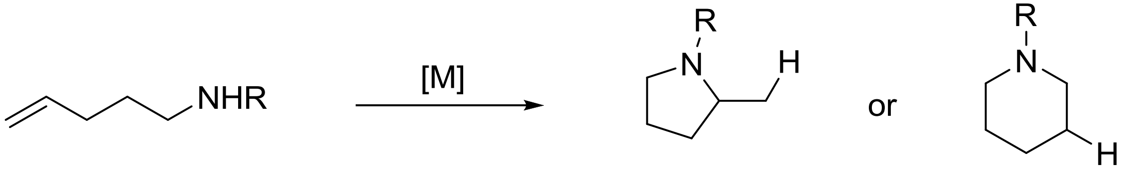
[a] *Nat. Prod. Rep*. **2000**, 17, 435
[b] *Chem. Rev.* **2004**, 104, 3341
[c] *JACS* **2003**, 8744
[d] *ChemCatChem* **2010**, 2, 1192

1. Introduction

Intermolecular



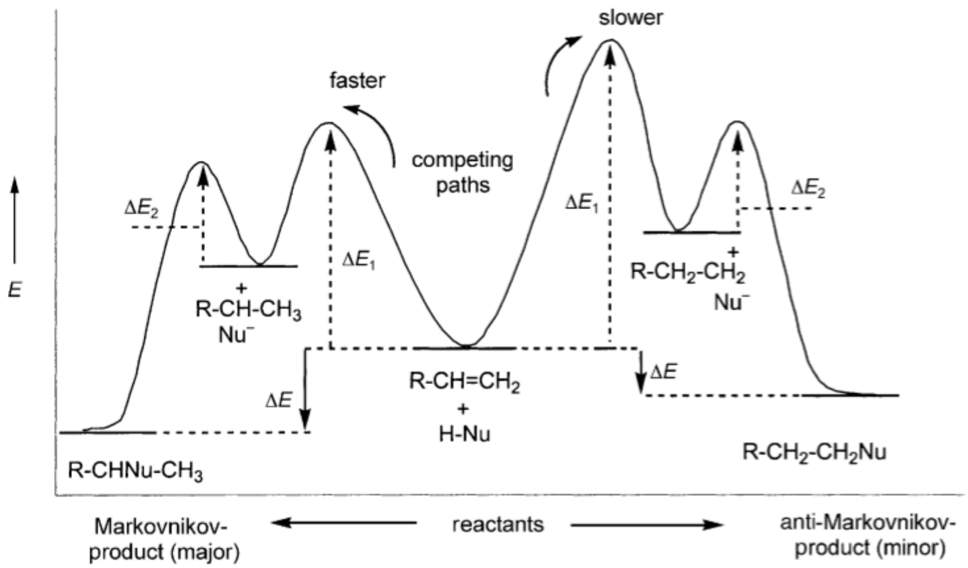
Intramolecular



Markovnikov product

anti-Markovnikov product

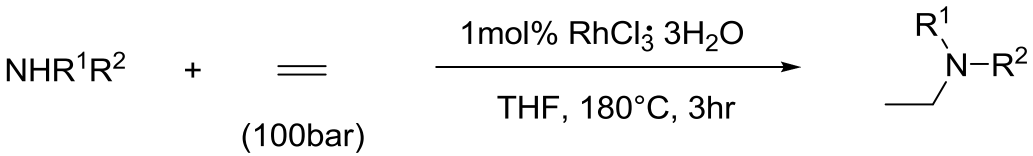
Energy diagram of the addition of H-Nu to olefins[a]

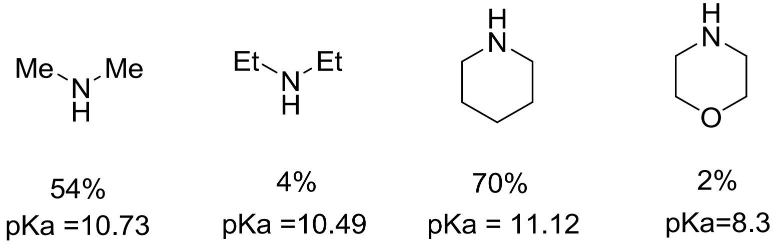


[a] *Angew. Chem. Int. Ed.* **2004**, 3368

2.1. Rh-catalyzed hydroamination of ethylene

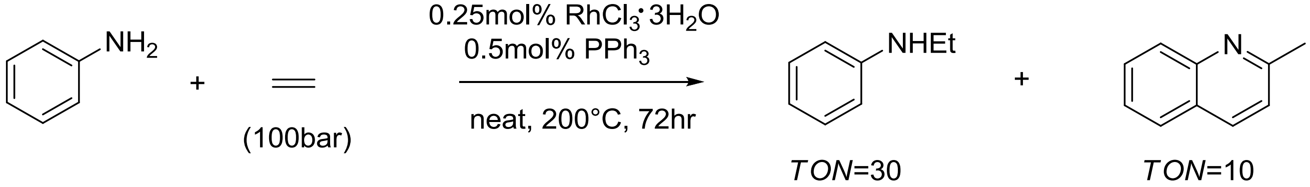
Coulson[a], 1970: First example of a homogeneous transition metal-catalyzed hydroamination





- Steric hindrance
- Basicity (or nucleophilicity)

Diamond[b], 1979: subsequent investigation

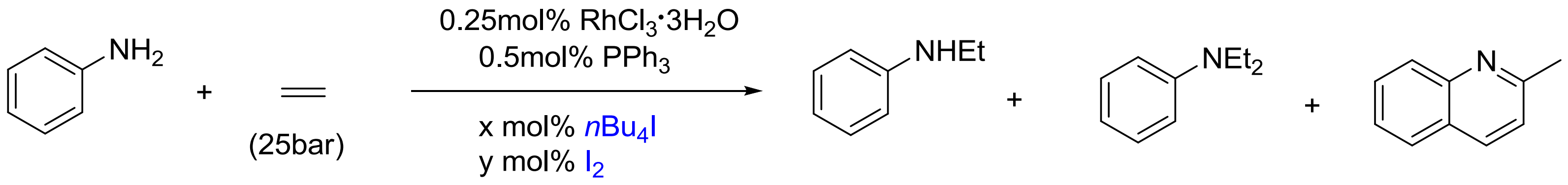


- 10% overall yield
- Main side reaction: the dimerization of ethylene to butene

[a] *Tetrahedron Lett*. **1971**, 429
[b] *JACS*. **1979**, 490

2.1. Rh-catalyzed hydroamination of ethylene

Brunet[a]: more active catalytic system



A **B** **C**

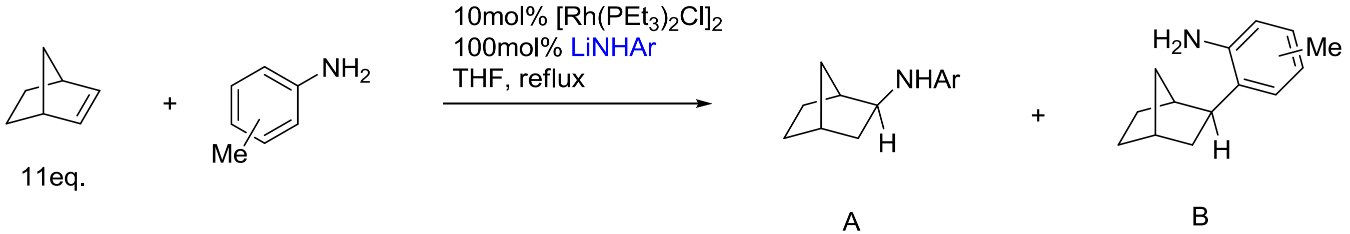
2.5mol% $n$$Bu_4I$	0.5mol% I_2	*TON*=152	*TON*=52	*TON*=0
38mol% $n$$Bu_4I$	0.5mol% I_2	*TON*=21	*TON*=230	*TON*=3

- About 65% overall yield
- Increase of catalytic efficiency
- Basicity: diethylaniline>ethylaniline

[a] *Organometallics* **2007**, 5264

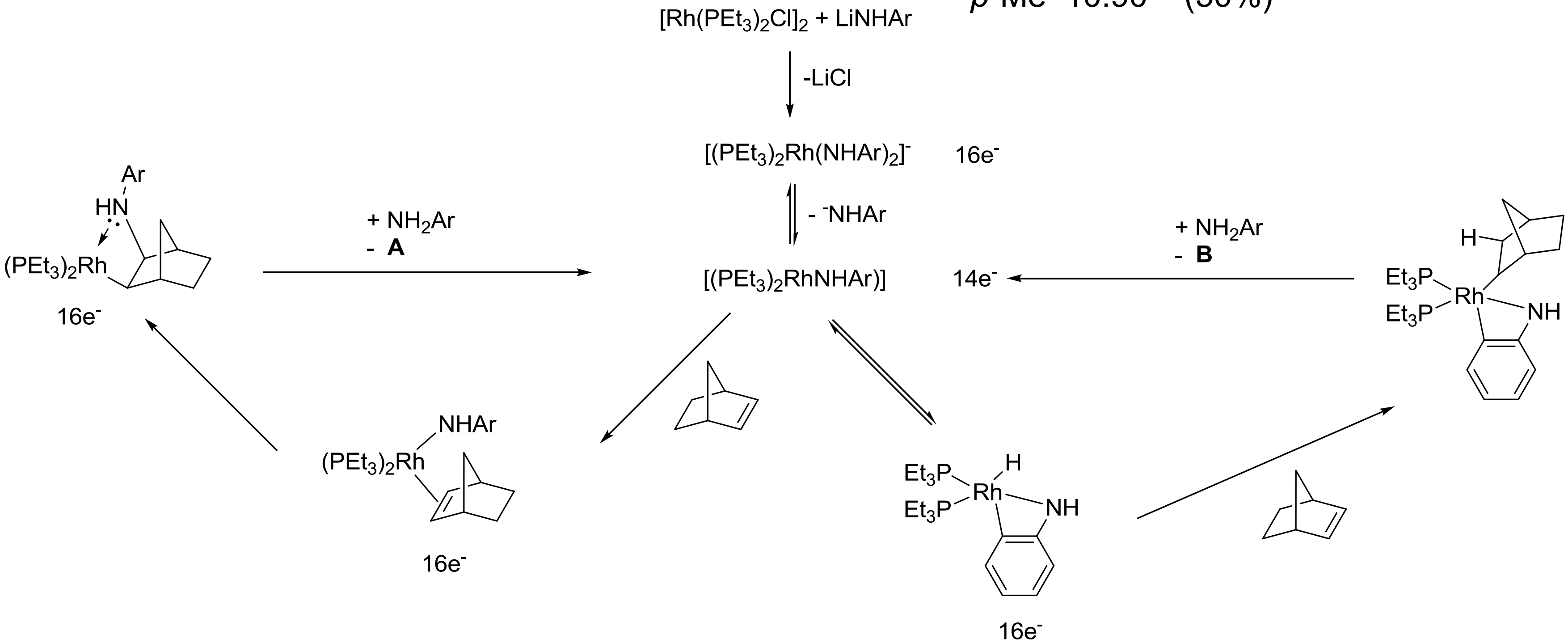
2.2. Rh-catalyzed hydroamination of norbornene

Brunet[a]: norbornene



	A:B	
o-Me	0:100	(95%)
m-Me	40:60	(50%)
p-Me	10:90	(50%)

Hypothesized mechanism:

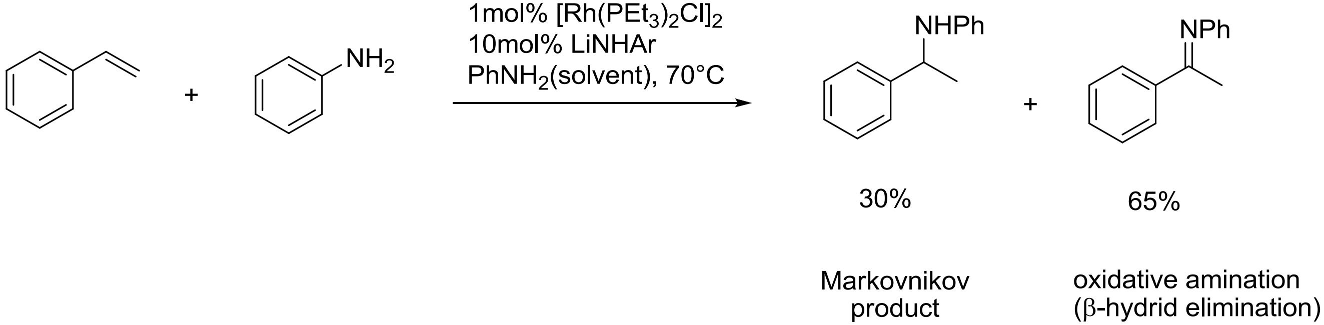


Orthometallation

[a] *J. OrganoM. Chem.* **1994**, 221

2.3. Rh-catalyzed hydroamination of aryl olefin

Brunet[a]: Styrene



1mol% $[Rh(PEt_3)_2Cl]_2$
10mol% LiNHAr
$PhNH_2$(solvent), 70°C

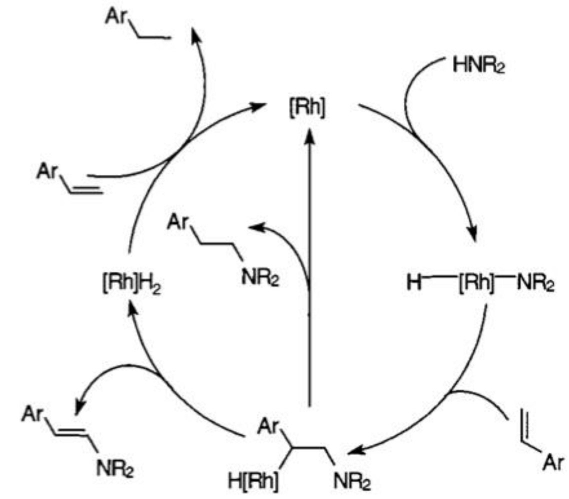
30%

65%

Markovnikov product

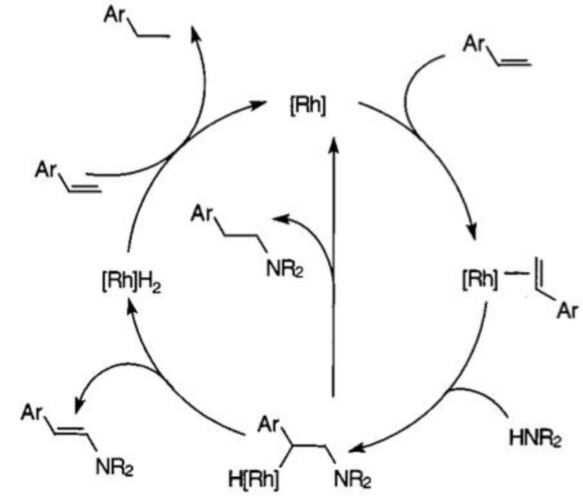
oxidative amination (β-hydrid elimination)

N-H oxidative addition



Ar = Aryl; R'= Alkyl

Nucleophilic attack on coordinated alkene



Ar = Aryl; R= Alkyl

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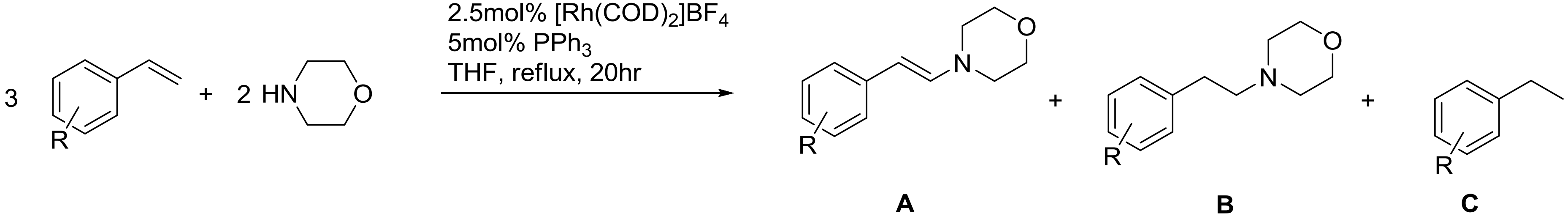
[a] *Tetrahedron Lett.* **1993**, 3877

2.3. Rh-catalyzed hydroamination of aryl olefin

Beller[b]: anti-Markovnikov product



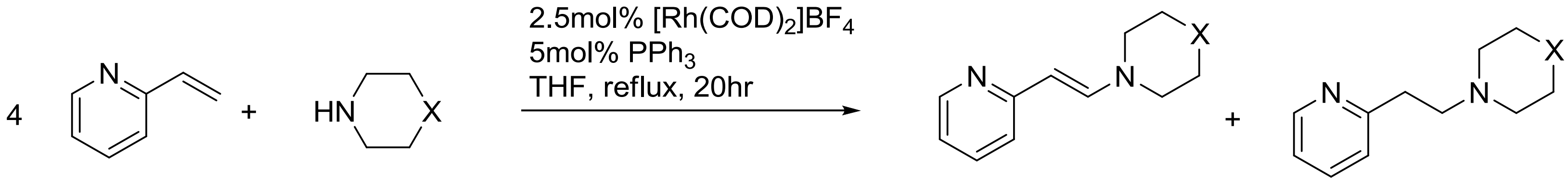
	A	**B**	**C**	**A/B**
R=H	74%	14%	84%	5.3
R=4-Me	76%	15%	99%	5.1
R=2-Me	27%	6%	20%	4.5
R=4-OMe	50%	12%	47%	4.2
R=4-F	60%	19%	85%	3.1
R=4-CF_3	21%	2%	9%	10.5

Electronic and steric factors of aryl olefin

[b] *Chem. Eur. J.* **1999**, 5

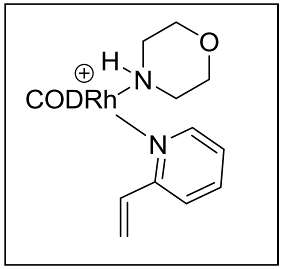
2.3. Rh-catalyzed hydroamination of aryl olefin

Beller[a]: vinyl pyridine



A' **B'**

	A'	B'
X=C	47% (2%)	53% (97%)
X=O	2%	98%
X=S	<1%	98%
X=NPh	8%	91%

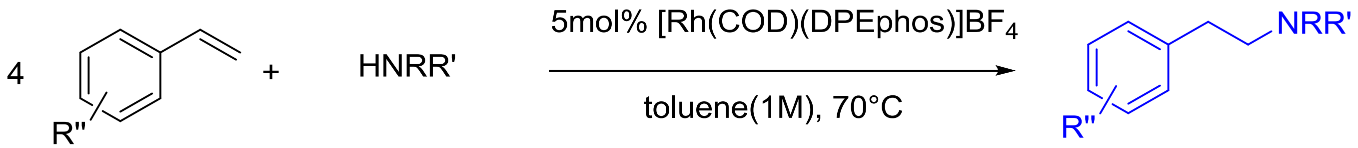


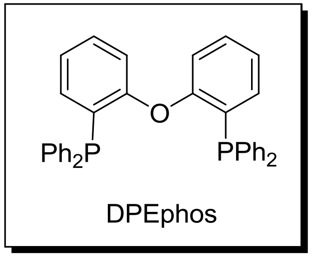
- Increased amount of PPh$_3$ leads to enamine product.
- Coordination of N-atom of pyridine to Rh metal center leads a decreased in a electron density of vinyl group (Micheal acceptor).
- Mechanism: N-H oxidative addition

[a] *Eur. J. Inorg. Chem.* 1999, 1121

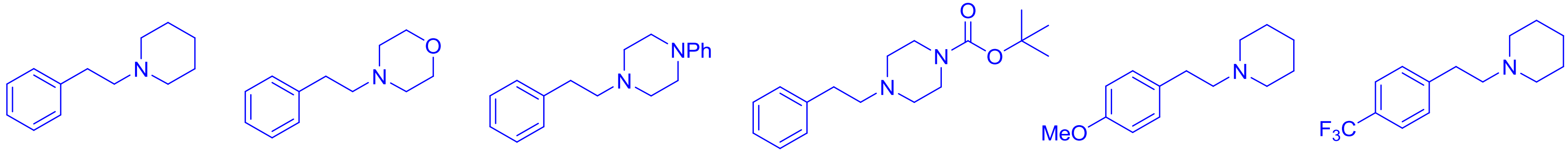
2.3. Rh-catalyzed hydroamination of aryl olefin

Hartwig[a] : Anti-Markovnikov addition of aliphatic amine on aryl olefin



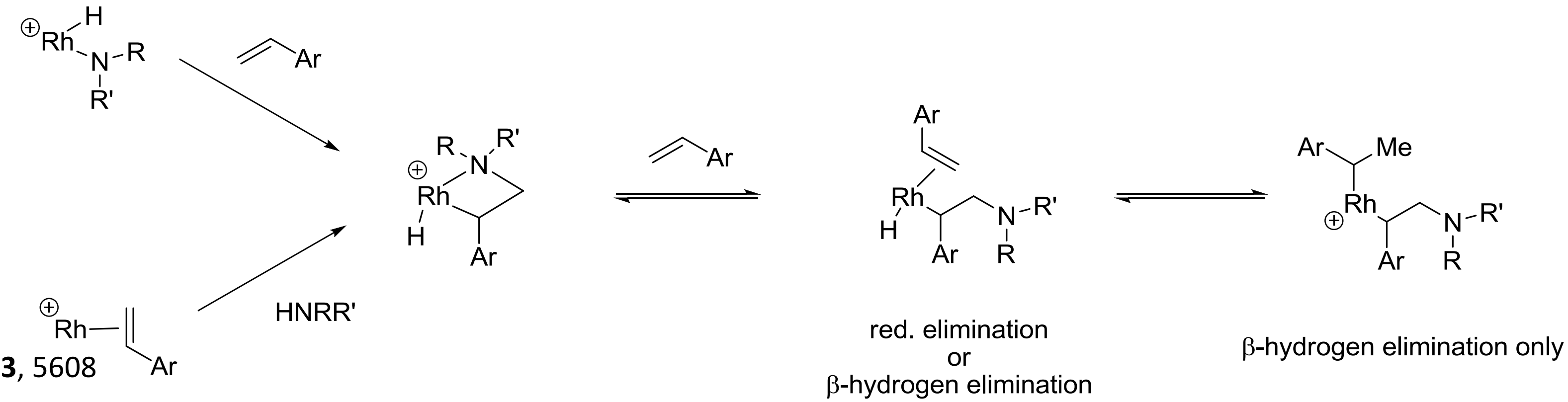


DPEphos



isolated yield (amine:enamine)	57% 63:37	71% 75:25	58% 86:14	53% 96:4	71% 85:15	41% 57:43

Excess equivalent of aryl olefin is essential:



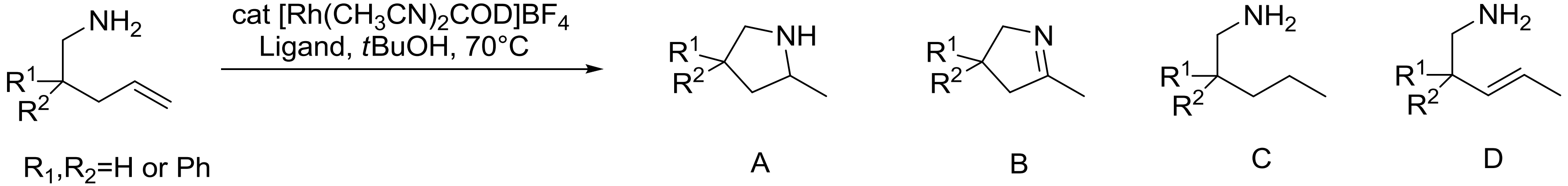
red. elimination
or
β-hydrogen elimination

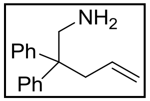
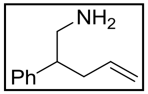
β-hydrogen elimination only

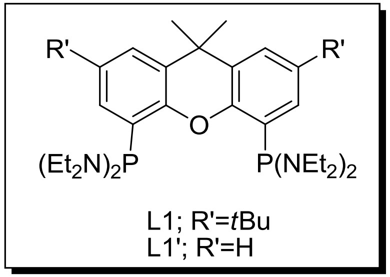
[a]*JACS*. **2003**, 5608

3.1. Intramolecular hydroamination- Markovnikov cyclization

Hartwig[a]: Primary Aminoalkene: initial results



SM	mol % [Rh]	Ligand	time(h)	conversion (%)	A	B	C	D
	1	L1	2	100	87%	5%	5%	3%
	1	L1'	2	100	83%	8%	8%	1%
	3	L1	15	100	78%	9%	9%	2%
	3	L1'	15	100	83%	7%	7%	3%



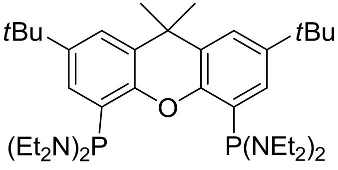
L1; R'=tBu
L1'; R'=H

- Markovnikov product
- Geminal disubstitution on the alkyl linker
- *t*-Bu group on the xanthene backbond had little effect on the reactivity or selectivity of the catalyst

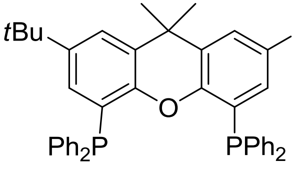
[a] *JACS*, **2010**, 13813; *JACS*, **2008**, 1570

3.1. Intramolecular hydroamination- Markovnikov cyclization

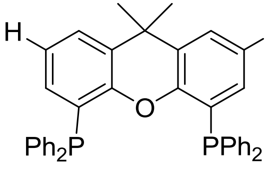
Investigation of suitable substitution on the Xantphos[a]:



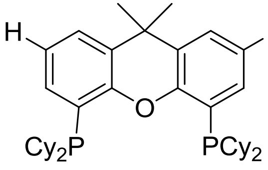
L1



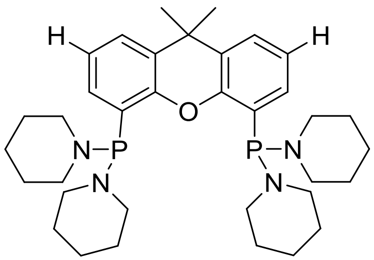
L2



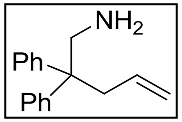
L2'



L3



L4

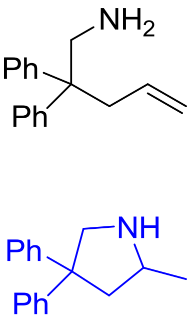
SM	mol % [Rh]	Ligand	time(h)	conversion (%)	A	B	C	D
	1	L1	2	100	87%	5%	5%	3%
	3	L2	2	83	18%	2%	0%	80%
	3	L2'	2	62	10%	2%	0%	88%
	3	L3	2	47	50%	25%	25%	3%
	3	L4	2	100	70%	12%	12%	6%

[a] *JACS*, **2010**, 13813; *JACS*, **2008**, 1570

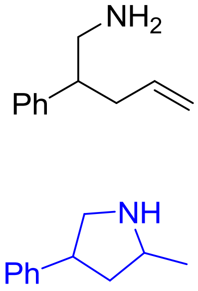
3.1. Intramolecular hydroamination- Markovnikov cyclization

Scope of Rh-Catalyzed Hydroamination of primary and secondary amines

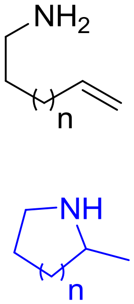
Catalytic loading 1-18mol%



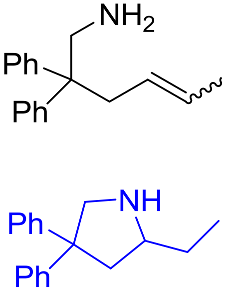
80%



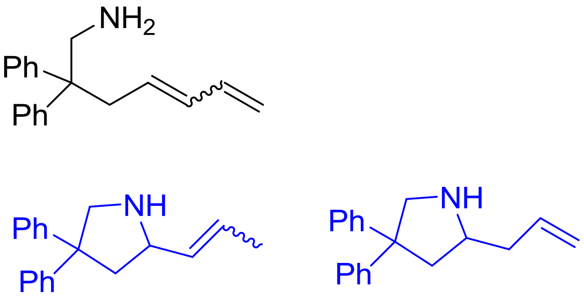
60%
1.3:1



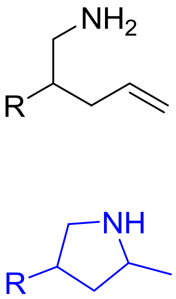
n=1; 76%
n=2; 77%



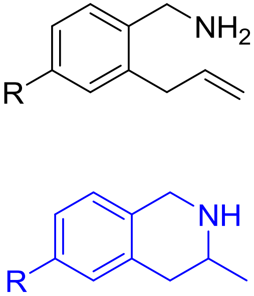
40%



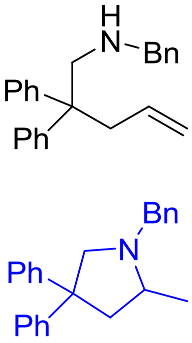
64%



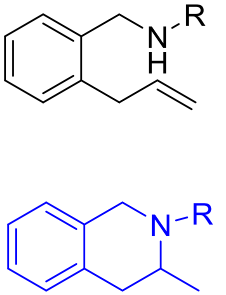
R=OTBDPS; 71%; 1.6:1
R=4-(CO_2Me)C_6H_4; 64%; 1.6:1
R=4-(CH_2CN)C_6H_4; 79%; 1.5:1
R=4-(CH_2OH)C_6H_4; 56%; 1.1:1



R=H; 87%
R=Cl; 84%



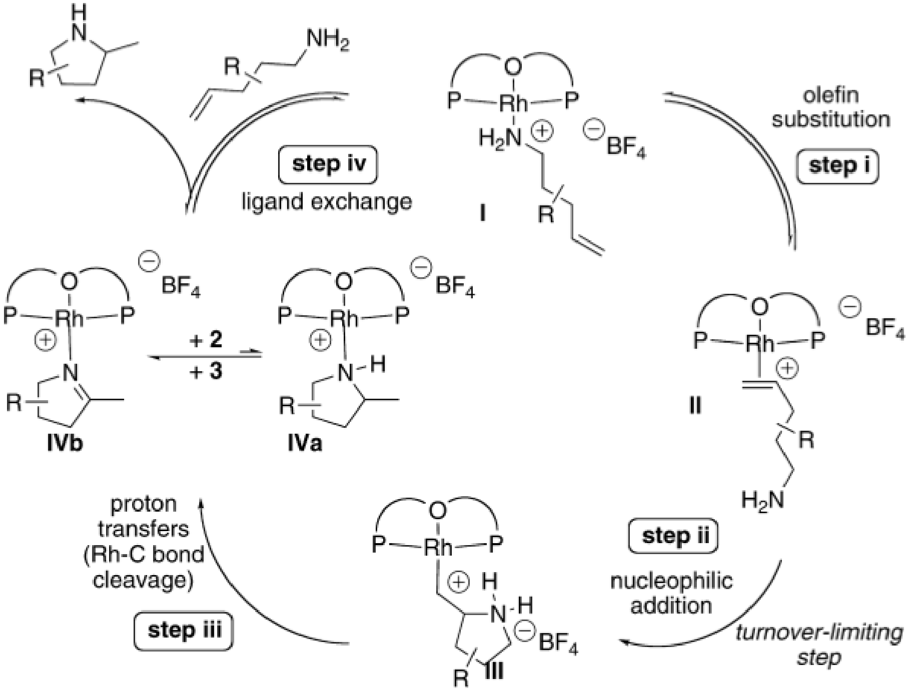
83%

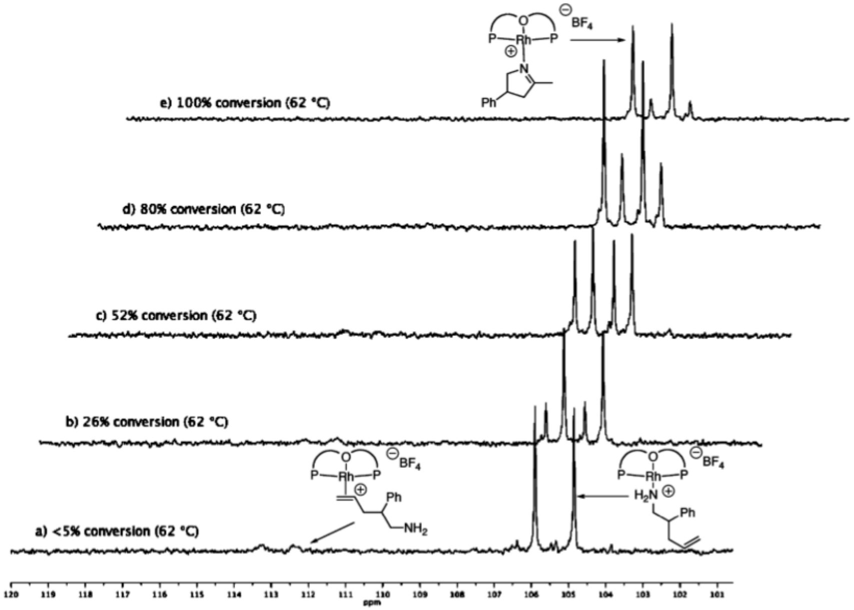


R=iPr; 78%
R=Bn; 86%

3.1. Intramolecular hydroamination- Markovnikov cyclization

Proposed mechanism[a]





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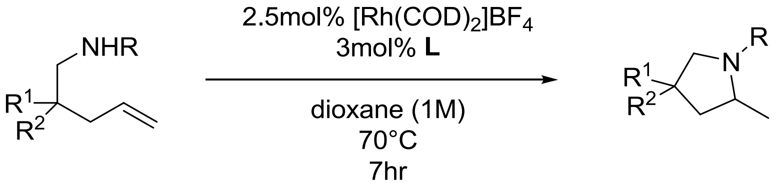
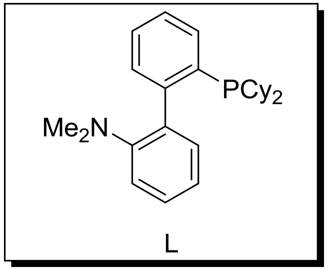
[a] *JACS*, **2010**, 13813; *JACS*, **2008**, 1570

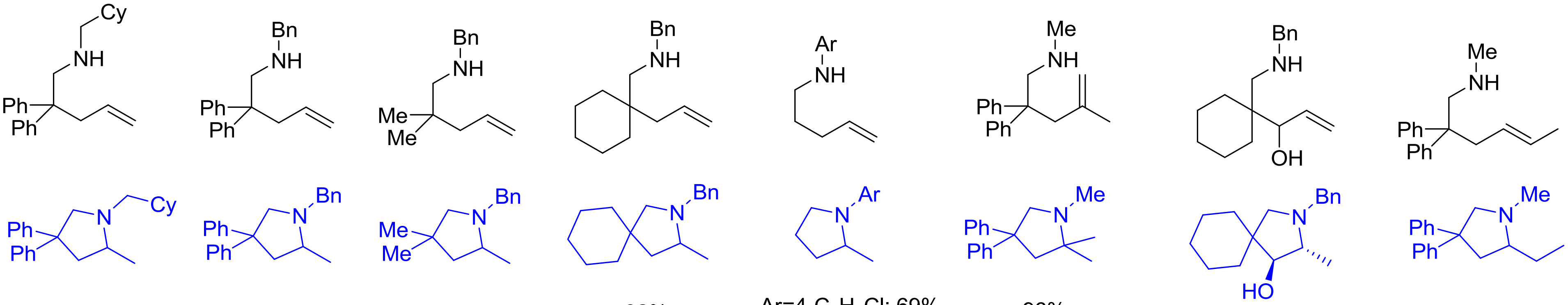
3.1. Intramolecular hydroamination- Markovnikov cyclization

Hartwig[a]:biarylphosphine ligand





Secondary amines:



91%

91%

83%

92%

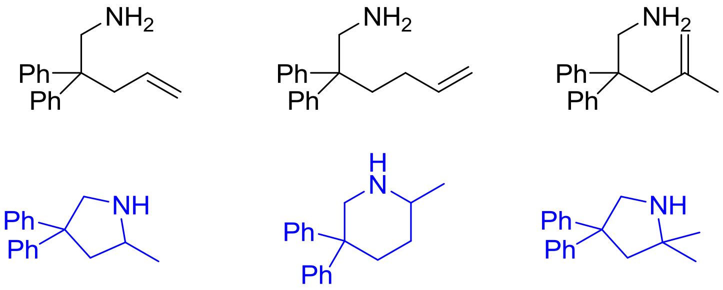
Ar=4-C_6H_4Cl; 69%
Ar=4-C_6H_4CN; 62%
Ar=4-$C_6H_4CO_2Me$; 69%

96%

65% (11:1)

76% (100°C)

Primary amines:



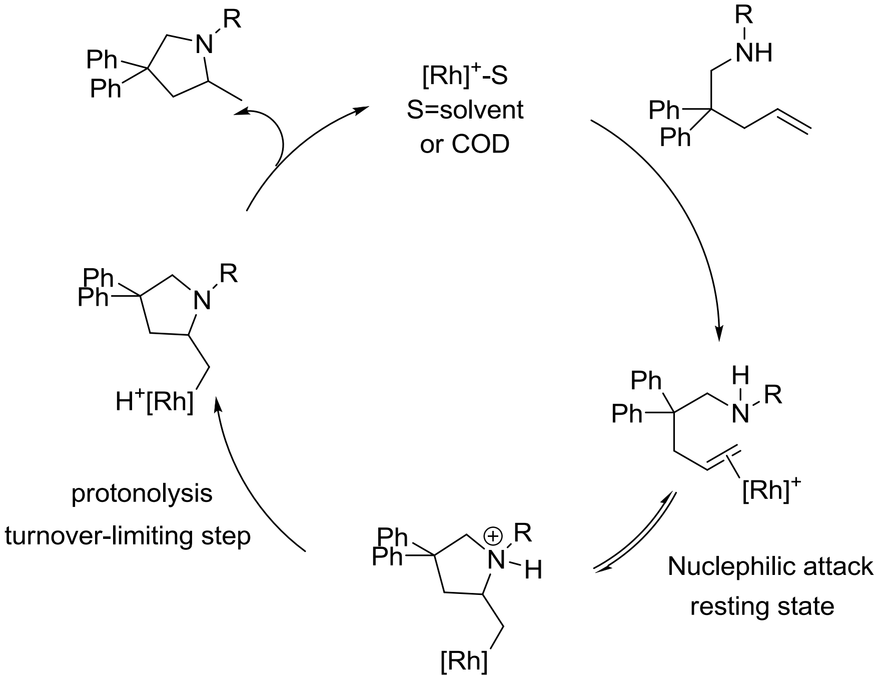
83%

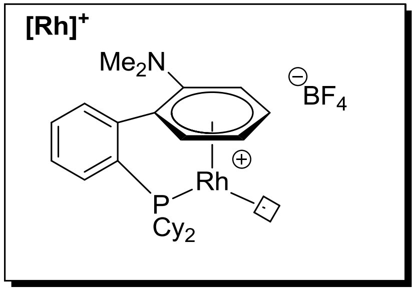
84%

96%

[a]*JACS*. **2008**, 130, 1570; *JACS*, **2011**, 2772

3.1. Intramolecular hydroamination- Markovnikov cyclization

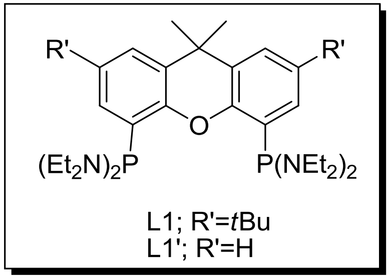


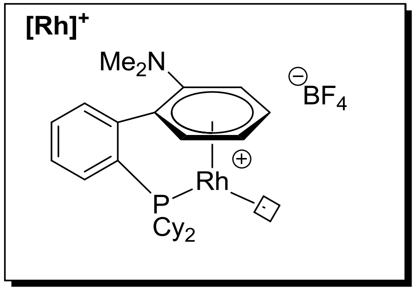


Nucleophilic attack generates a coordinatively saturaed, 18-electrons aminoalkyl complex

➡ Disfavor β–hydrogen elimination

3.1. Intramolecular hydroamination-Markovnikov cyclization





•Advantage :

Primary and secondary amines

Mild condition

High degree of tolerance for polar functional group

Aminophosphine groups on ligand are involved in creating the high rates and selectivity

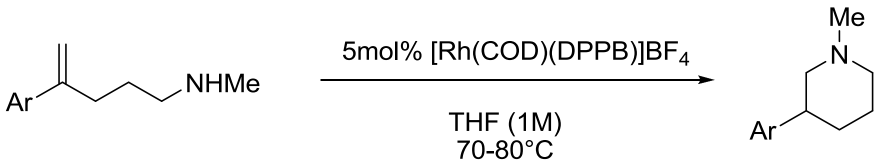
•Limitation

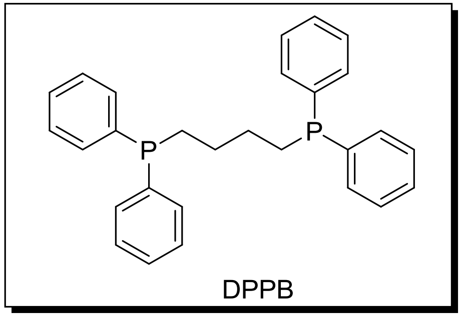
Basic amine is required

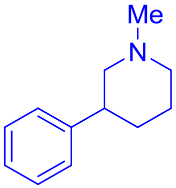
Five to six-membered rings of Markovnikov product

3.2. Intramolecular hydroamination-Anti-Markovnikov cyclization

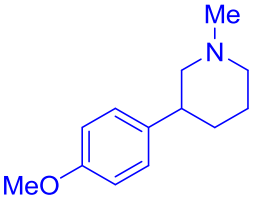
Hartwig[a]: Anti-Markovnikov piperidine:



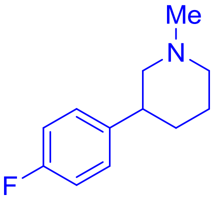




76%

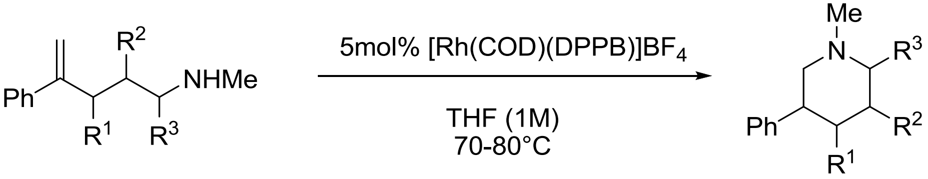


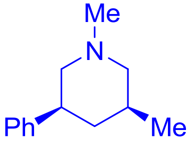
78%



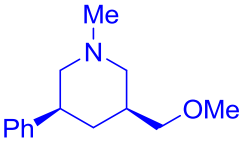
78%

1-4% enamine only each case

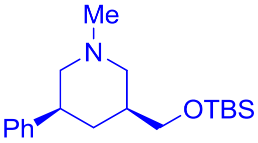




78%
(94/6)



87%
(95/5)



74%
100/0

High diastereoselectivity to *cis* product

No product detected if R_1,R_3 =H.

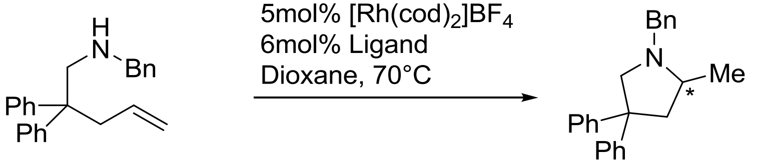
Mechanism unkown yet.

---

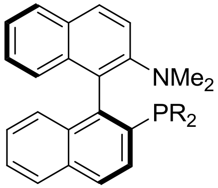
[a]*JACS*. **2006**, 6042

4. Enantioselective intramolecular hydroamination

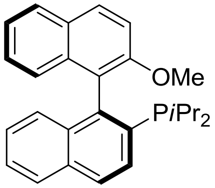
Buchwald[a]: first Rh-catalyzed asymmetric intramolecular addition of amines to olefins



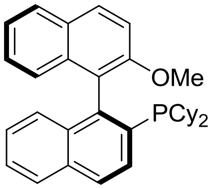
Ligand development:



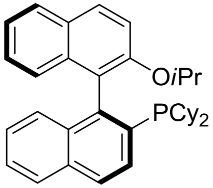
L1: R=Cy, 95%, 38%ee(S)
L2: R=*i*Pr, 83%, 20%ee(S)
L3: R=*t*Bu, 8%, n.d.



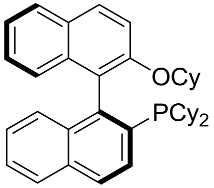
L4: 94%; 42%ee(S)



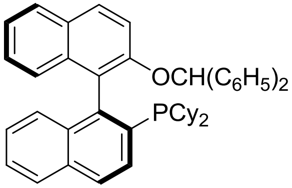
L5: 96%; 53%ee(S)



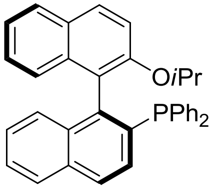
L6: 98%; 70%ee(S)



L7: 95%; 75%ee(S)



L8: 94%; 80%ee(S)



L9: 9%; n.d.

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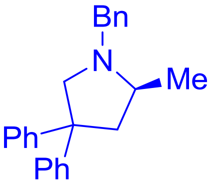
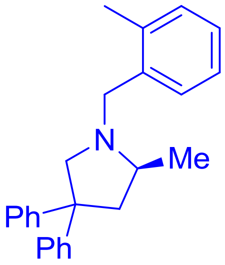
[a] *Angew. Chem. Int. Ed.* **2010**, 564

4. Enantioselective intramolecular hydroamination

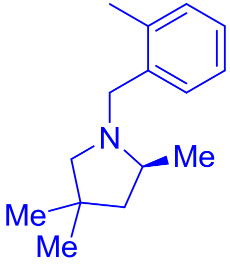
Scope of Rh-catalyzed enantioselective intramolecular hydroamination of aminoalkene with ligand L8



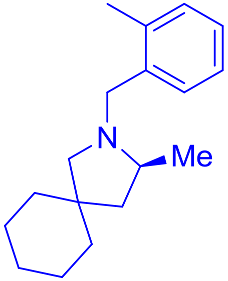
91%
80%ee(S)



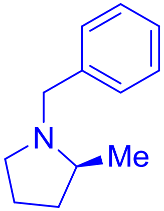
92%
84%ee(S)



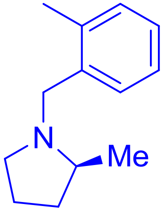
70%
62%ee(S)



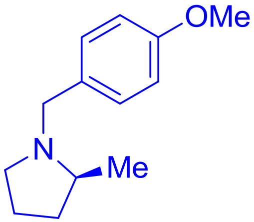
80%
63%ee(S)



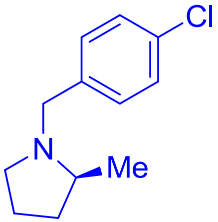
48%
90%ee(S)



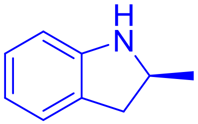
50%
86%ee(S)



35%
85%ee(S)



61%
85%ee(S)



85%
64%ee(S)

Unprotected aminoolefins exhibited poor reactivity; 2-allylaniline is the exceptional

5. Conclusion and Outlook

- Rhodium-mediated catalyst have been employed successfully in addressing specific challenges for both the inter- and intramolecular variants of the alkene hydroamination reaction.

- Important contributions towards anti-Markovnikov additions in the intermolecular hydroamination.

- Phosphine ligand can modulate either Markovnikov or anti-Markovnikov addtions.

- No Rh-catalyzed asymmetric intermolecular hydroamination yet.

- Scope of substrate is still limited.

LABORATOIRE DE SYNTHESE
ET PRODUITS NATURELS

N-Heterocyclic carbenes :
A powerful tool in organic synthesis

Thomas BUYCK
PhD Student in Prof. Zhu Group,
LSPN, EPFL

Frontiers in Chemical Synthesis

June 6th, 2011

LABORATOIRE DE SYNTHESE
ET PRODUITS NATURELS

Questions

I. Why is this type of catalysis important ?

II. What is the name of the reactive specie in all the presented reactions ?

Plan

Introduction

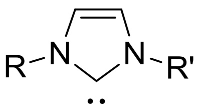
I. Benzoin condensation and Stetter reaction

II. Homoenolate reactivity

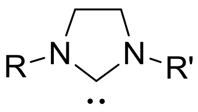
III. Miscellanous reactions

Introduction

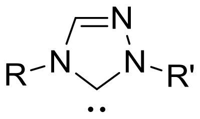
N-Heterocyclic carbenes



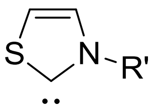
Imidazolylidene



Imidazolinylidene



Triazolylidene



Thiazolylidene

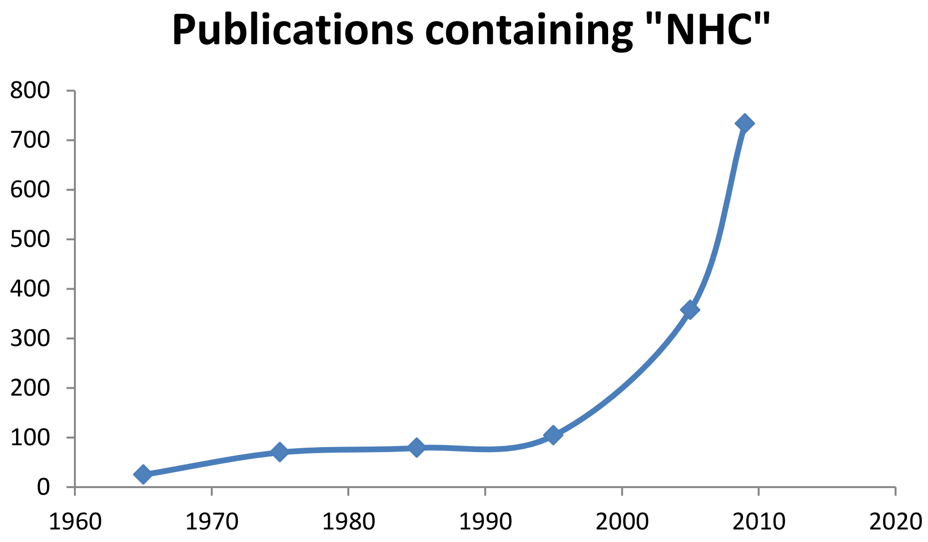
- Alternative to metal catalysed reactions
- Cheaper and more environment friendly

New field in organic chemistry

LABORATOIRE DE SYNTHESE
ET PRODUITS NATURELS

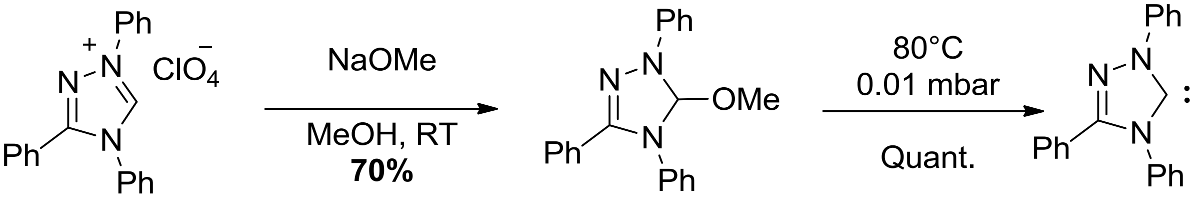
Introduction

Explosion in this field during the last decade



Introduction

Multigram scale synthesis of carben by Enders

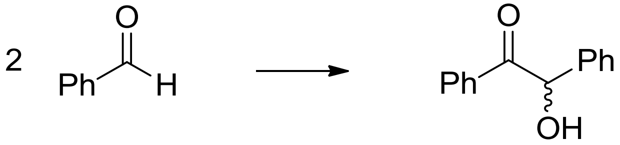


Commercially available from Acros® 195 CHF/g

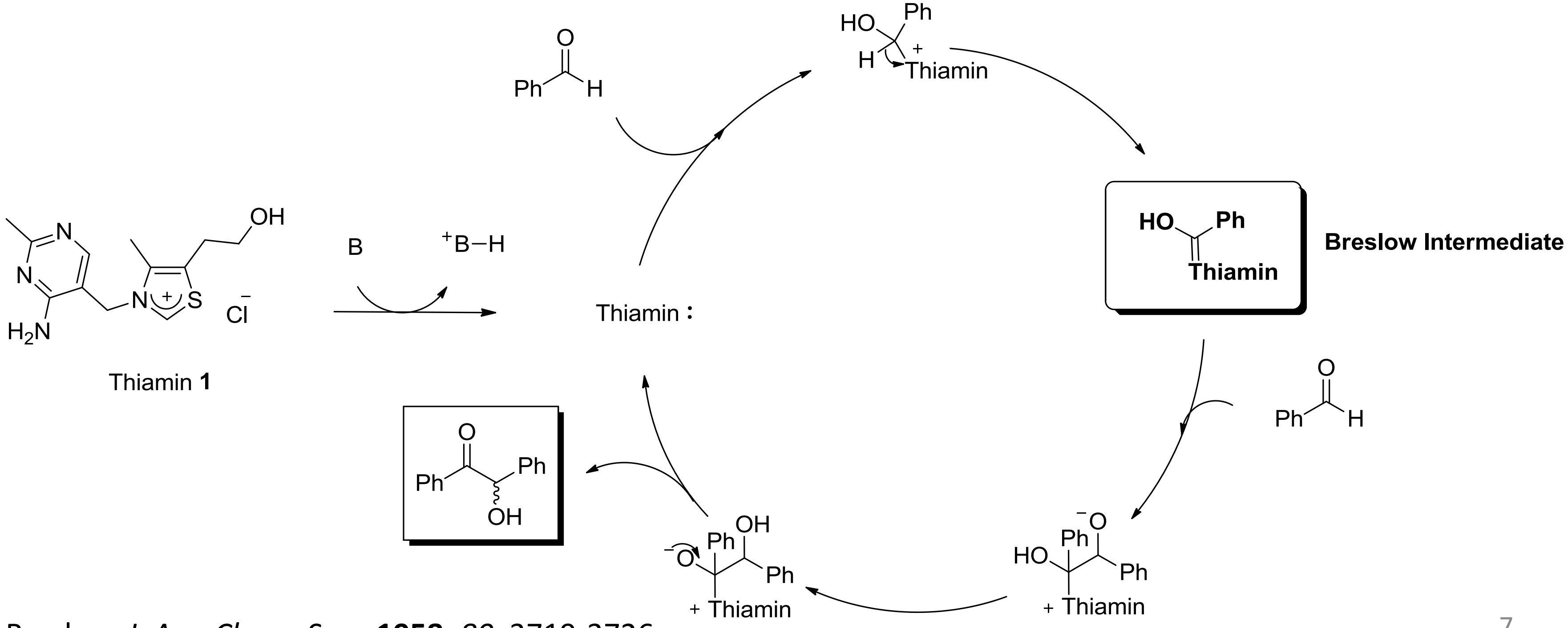
D. Enders, *Synthesis*, **2003**, 1292-1295

Benzoin Condensation

Autocondensation of benzaldehyde



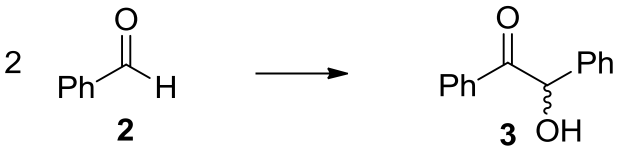
F. Wöhler, J. Liebig, *Ann. Pharm.*, **1832**, *3*, 249-282 ; T. Ukai, *J. Pham Soc. Jpn*, **1943**, *63*, 296-300



R. Breslow, *J. Am. Chem. Soc.*, **1958**, *80*, 3719-3726

Benzoin Condensation

Creation of a stereogenic center



2

3

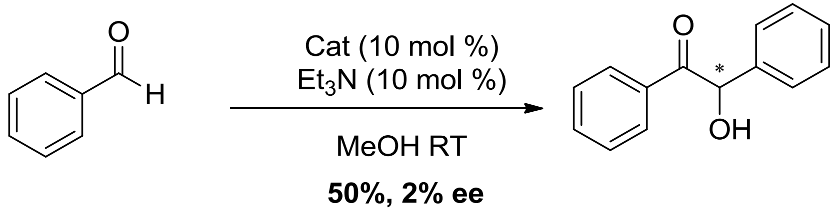
How to control the selectivity of this reaction to obtain a single enantiomer ?

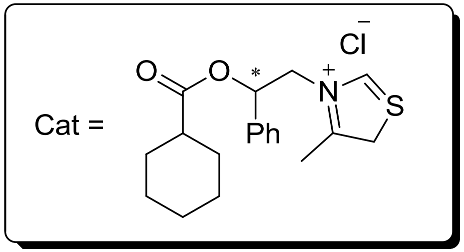
D. Enders, T. Balensiefer, *Acc. Chem. Res.*, **2004**, *37*, 534-541

Benzoin Condensation

Enantiomeric version

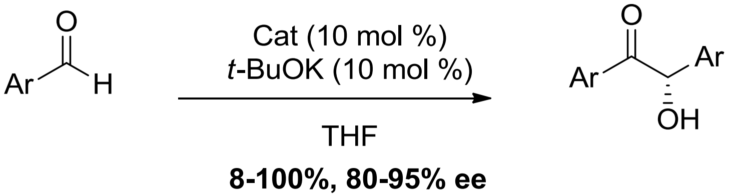
First example in 1966 by Sheehan

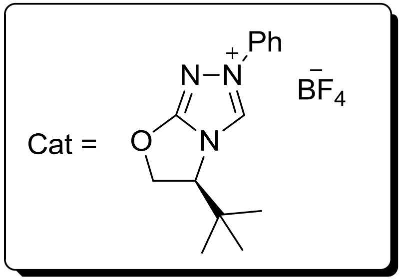




J. Sheehan, *J. Am. Chem. Soc.*, **1966**, *88*, 3666-3667

Enders published in 2002 a more efficient method

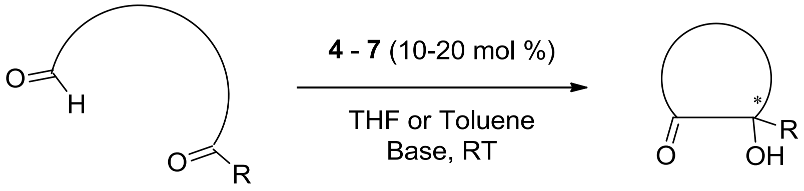




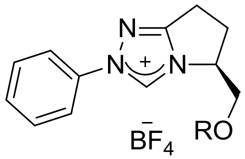
D. Enders, *Angew. Chem. Int. Ed.*, **2002**, *41*, 11743-1745

Benzoin Condensation

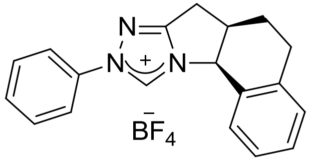
Enantiomeric version



Enders et al.

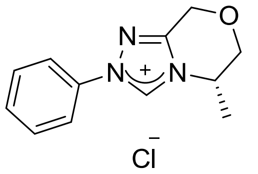


4a, R = TBS
4b, R = TIPS

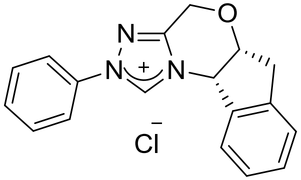


5

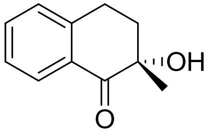
Suzuki et al.



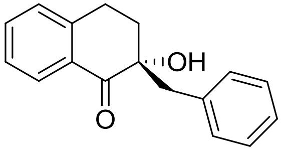
6



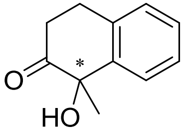
7a, R = OMe
7b, R = H



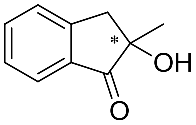
93%, 94% ee



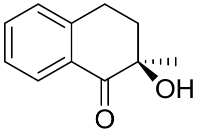
90%, 63% ee **4b**
43%, 93% ee **5**



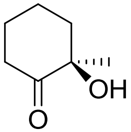
68%, 67% ee



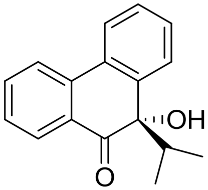
95%, 74% ee



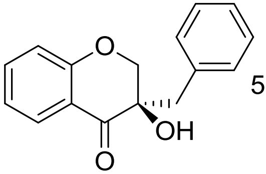
70%, 96% ee



44%, 96% ee



74%, 85% ee

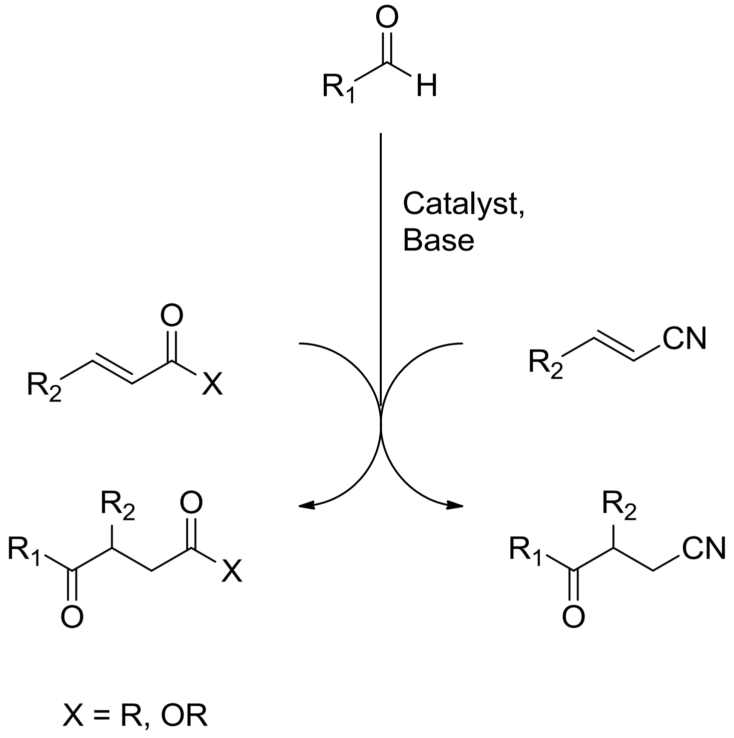


56%, 88% ee

D. Enders, *Angew. Chem. Int. Ed.*, **2006**, *45*, 1463-1467 ; K. Suzuki, *Angew. Chem. Int. Ed.*, **2006**, *45*, 3492-3494

Stetter reaction

In the early 70's Stetter described a new reaction usefull to create 1,4 dicarbonyl



Catalyst :

- CN^- (1973)
- Thiazolium salt (1976)

H. Stetter, *Angew. Chem. Int. Ed.*, **1973**, *12*, 81 ; H. Stetter, *Angew. Chem. Int. Ed.*, **1976**, *15*, 639-712

LABORATOIRE DE SYNTHESE
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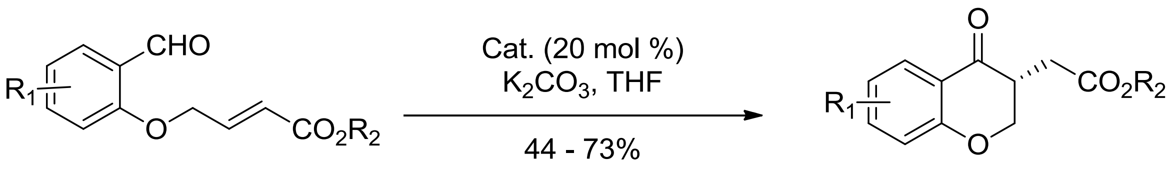
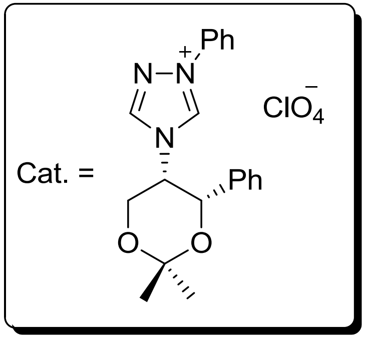
Stetter reaction

Enantiomeric version

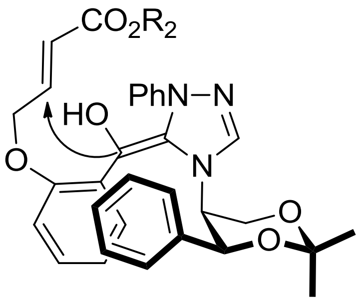
First example in 1996 by Enders



41 - 74% ee



Model explaining the facial selectivity



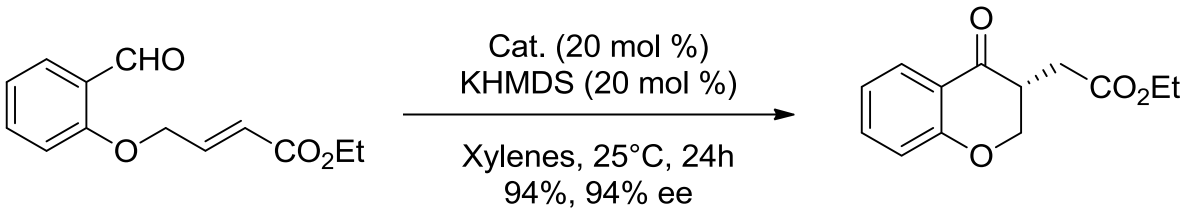
Re-face shielded by Phenyl group

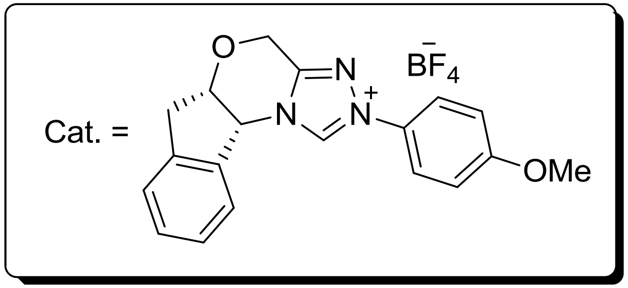
D. Enders, *Helv. Chim. Acta.*, **1996**, *79*, 1899-1902

Stetter reaction

Enantiomeric version

The second example is published only in 2002 by Rovis



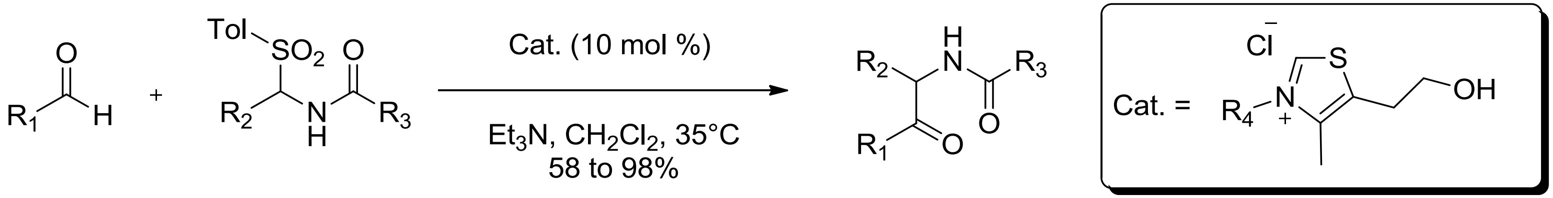


T. Rovis, *J. Am. Chem. Soc.*, **2002**, *124*, 10298-10299 ; T. Rovis, *J. Am. Chem. Soc.*, **2005**, *127*, 6284-6289

Stetter reaction

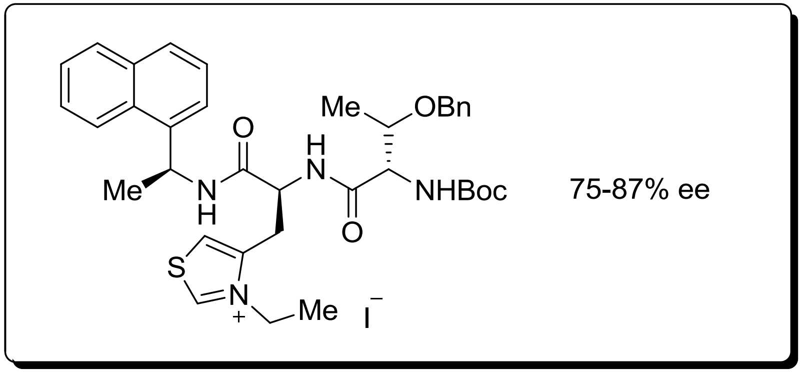
Extension of the scope

Merck published in 2001 an Aldehyde-Imine Cross-Coupling



J. A. Murry, D. E. Franz, *J. Am. Chem. Soc.*, **2001**, *123*, 9696-9697

Enantiomeric version is described by the group of Miller in 2005

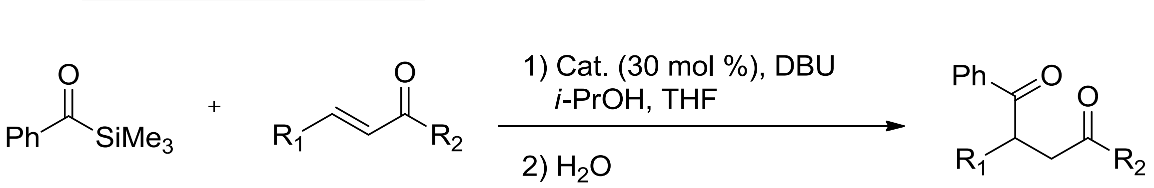


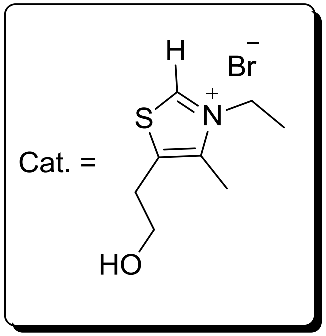
S. J. Miller, *J. Am. Chem. Soc.*, **2005**, *127*, 1654-1655

Stetter reaction

Extension of the scope

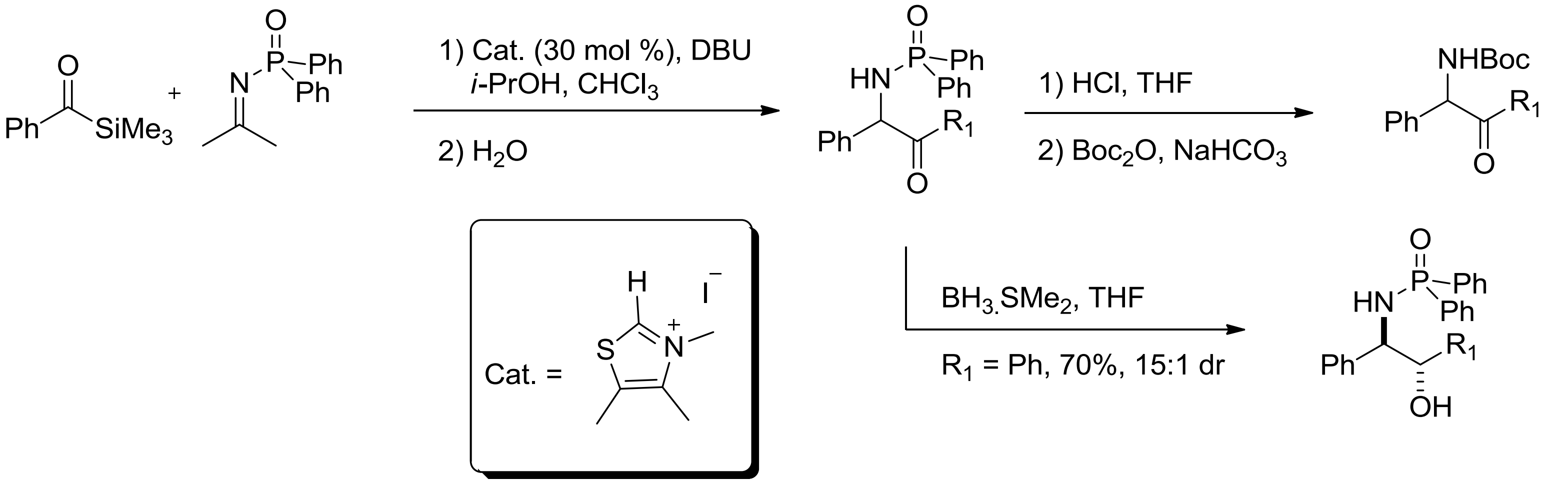
Sila-Stetter reaction





K. A. Scheidt, *J. Am. Chem. Soc.*, **2004**, *126*, 2314-2315

Addition of acylsilanes to Imines

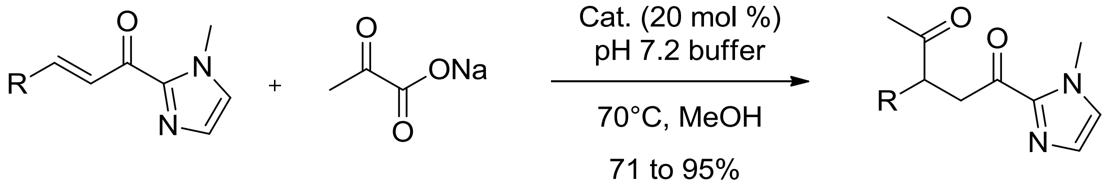


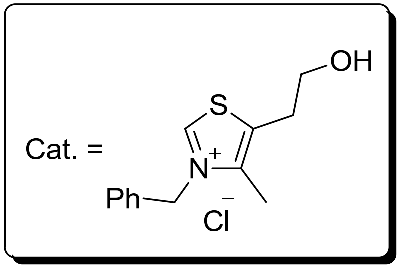
K. A. Scheidt, *Org. Lett.*, **2004**, *6*, 4363-4366

Stetter reaction

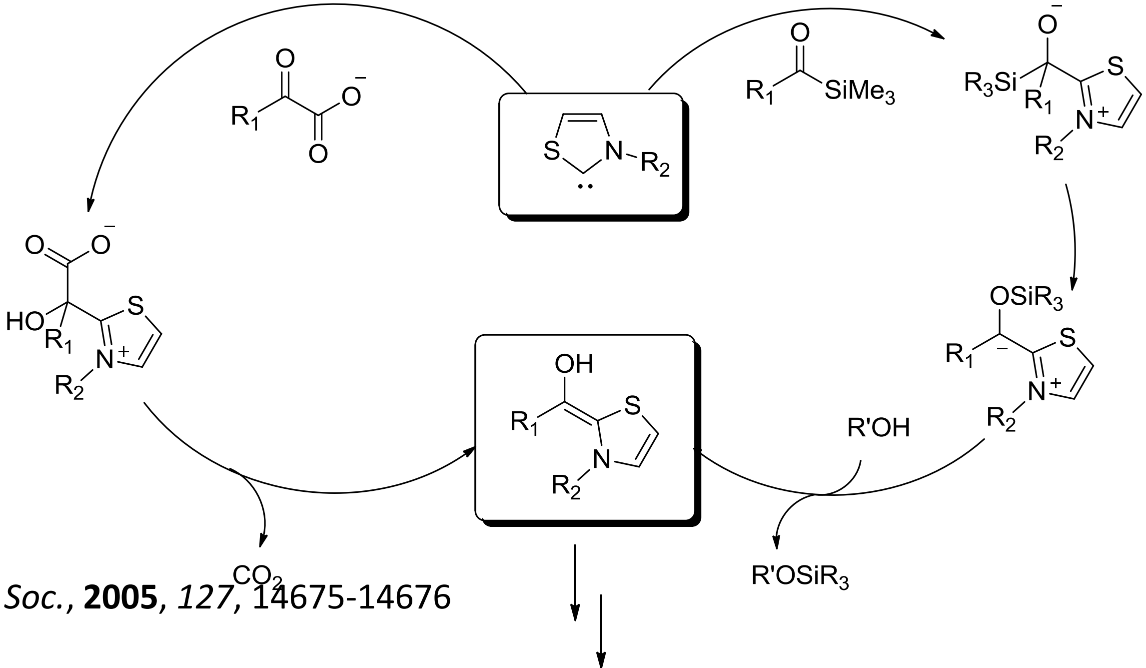
Extension of the scope

Keto carboxylate as acyl anion precursor





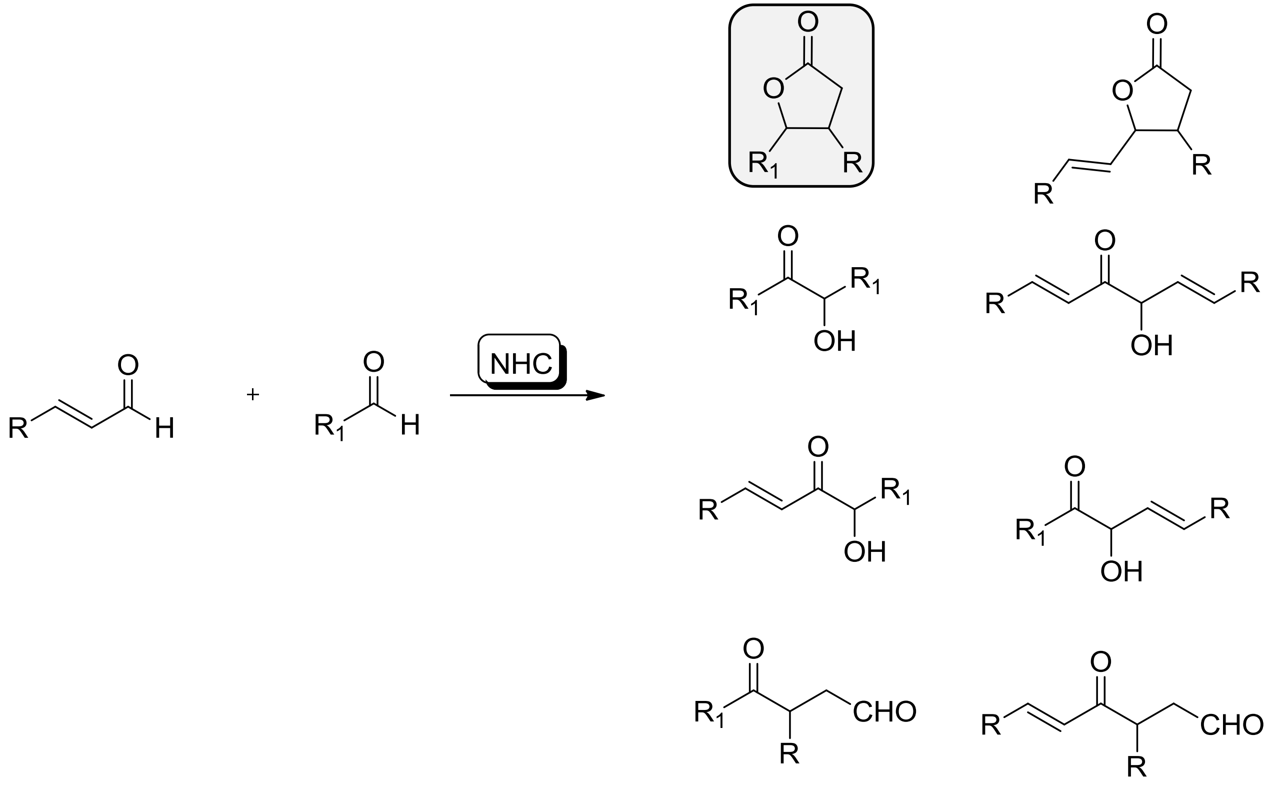
Generation of acyl anion equivalent



K. A. Scheidt, *J. Am. Chem. Soc.*, **2005**, *127*, 14675-14676

Homoenolates

In 2004, Glorius and Bode reported independently a new reaction



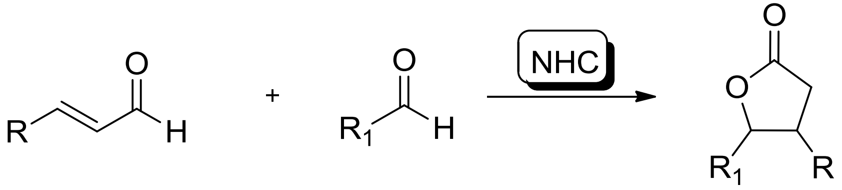
Homobenzoin products

Crossbenzoin products

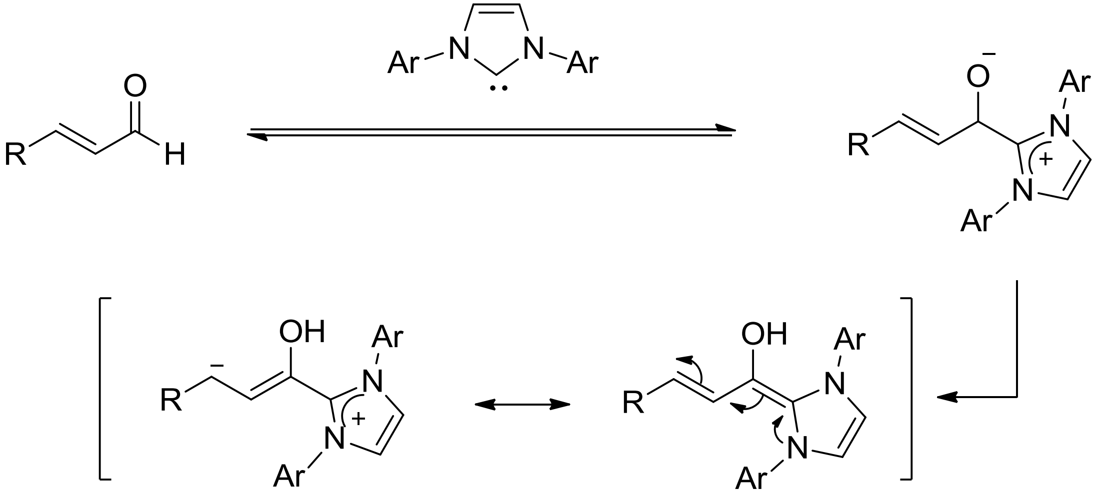
Stetter products

F. Glorius, *Angew. Chem. Int. Ed.*, **2004**, *43*, 6205-6208 ; J. Bode, *J. Am. Chem. Soc.*, **2004**, *126*, 14370-14371

Homoenolates



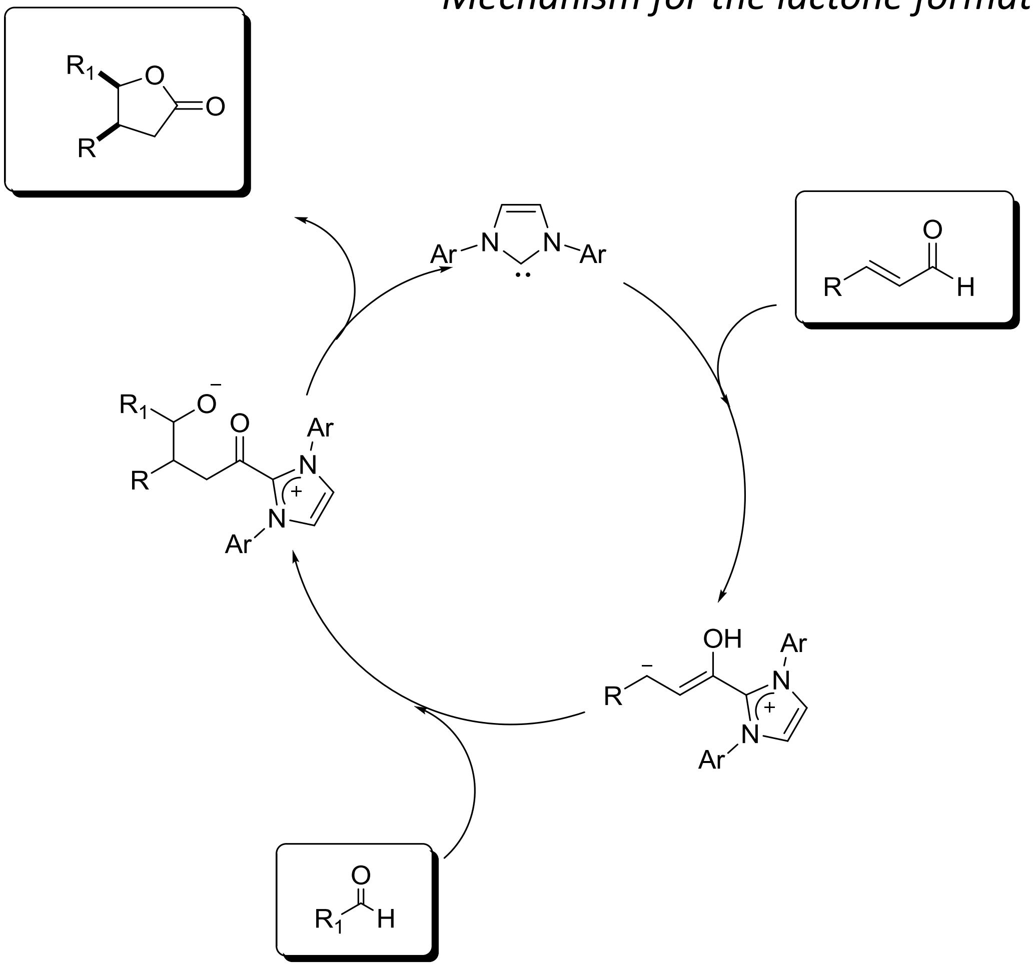
Homoenolate formation

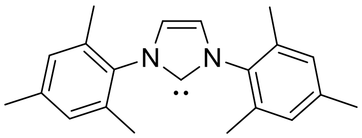


F. Glorius, *Angew. Chem. Int. Ed.*, **2004**, *43*, 6205-6208 ; J. Bode, *J. Am. Chem. Soc.*, **2004**, *126*, 14370-14371

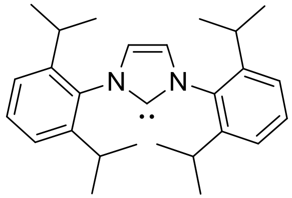
Homoenolates

Mechanism for the lactone formation

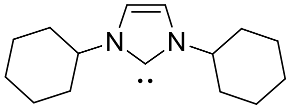




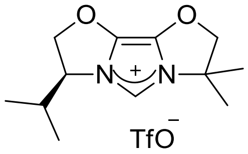
IMes



IPr unselective



ICy unreactive



Enantiomeric version

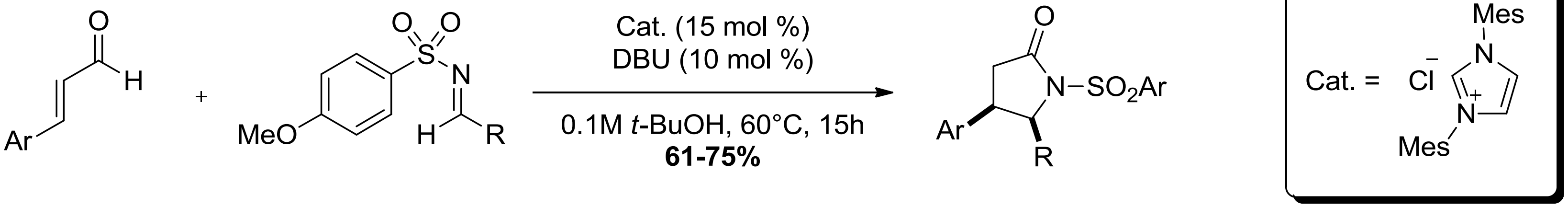
Enantiomeric version but with only 25% ee

F. Glorius, *Angew. Chem. Int. Ed.*, **2004**, *43*, 6205-6208 ; J. Bode, *J. Am. Chem. Soc.*, **2004**, *126*, 14370-14371

Homoenolates

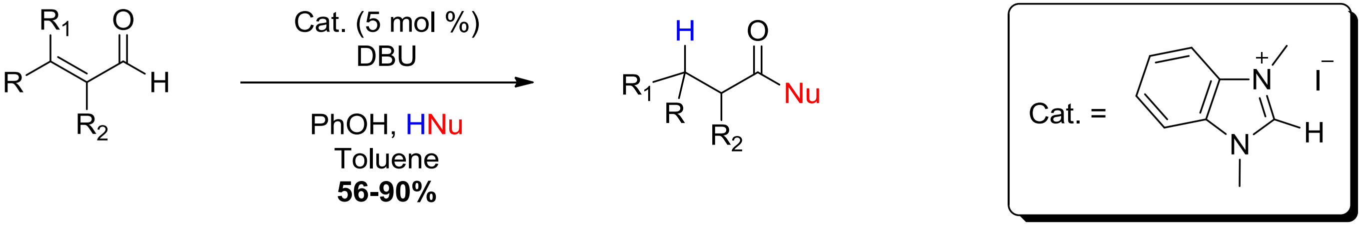
Electrophile diversification

- N-Sulfonylimines



J. Bode, *Org. Lett*, **2005**, *7*, 3131-3134

- Proton trapping followed by addition of a Nucleophile

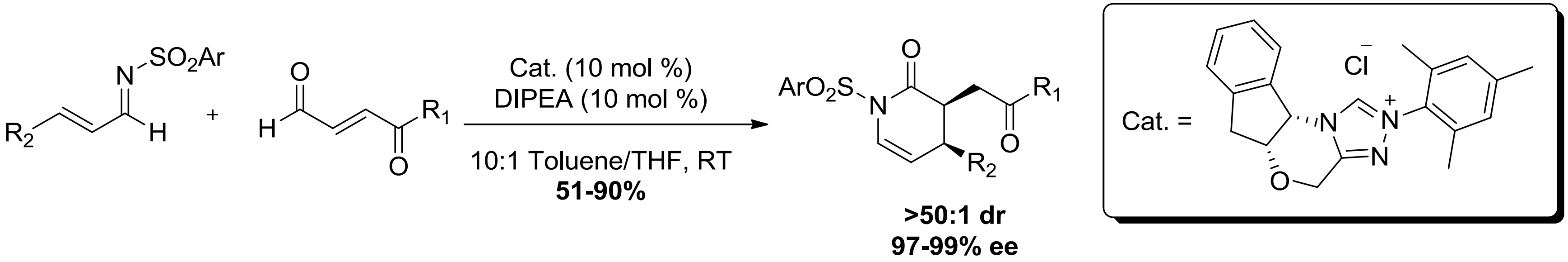


K. A. Scheidt, *Org. Lett*, **2005**, *7*, 905-908

Homoenolates

Electrophile diversification

- Azadiene Diels-Alder reaction



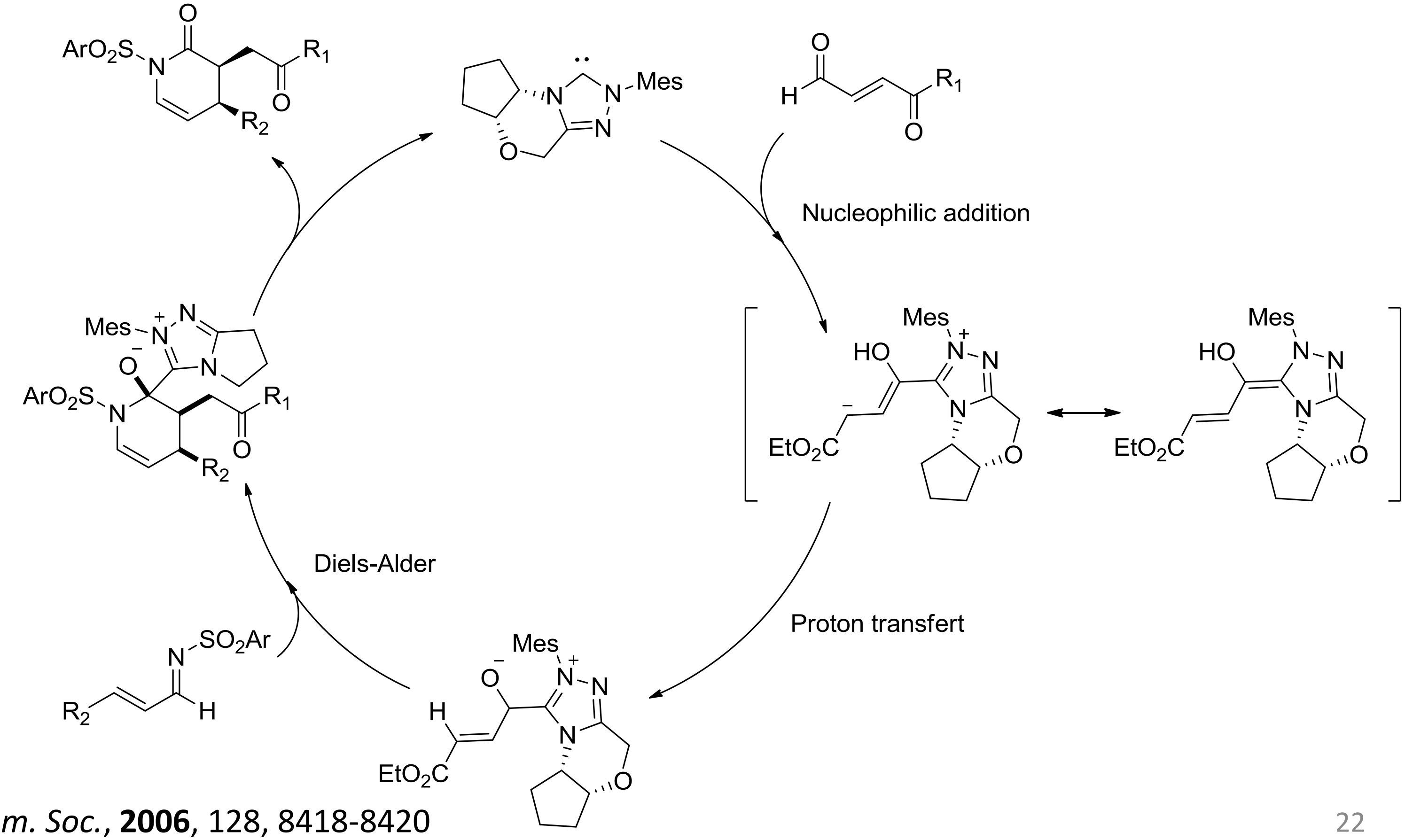
J. Bode, *J. Am. Chem. Soc.*, **2006**, 128, 8418-8420

LABORATOIRE DE SYNTHESE
ET PRODUITS NATURELS

Homoenolates

Electrophile diversification

- Azadiene Diels-Alder reaction

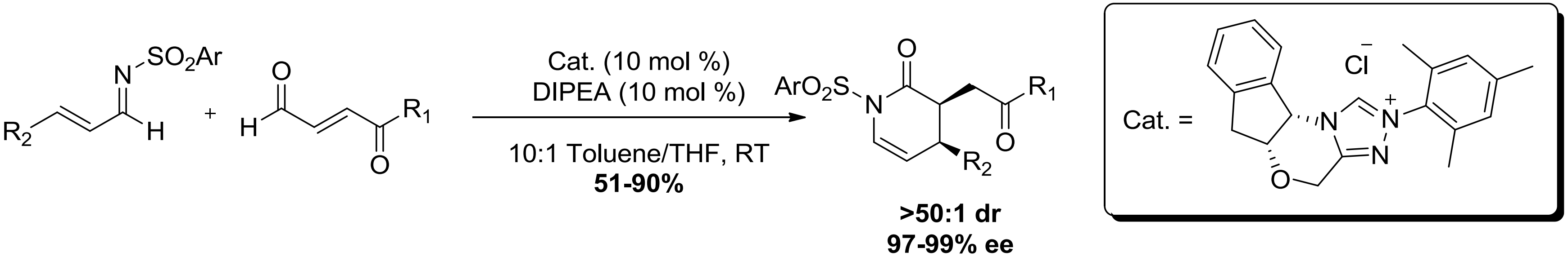


J. Bode, *J. Am. Chem. Soc.*, **2006**, 128, 8418-8420

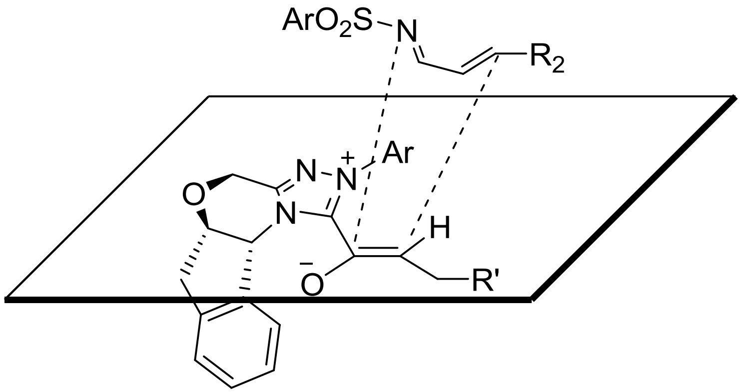
Homoenolates

Electrophile diversification

- Azadiene Diels-Alder reaction



Model explaining the selectivity

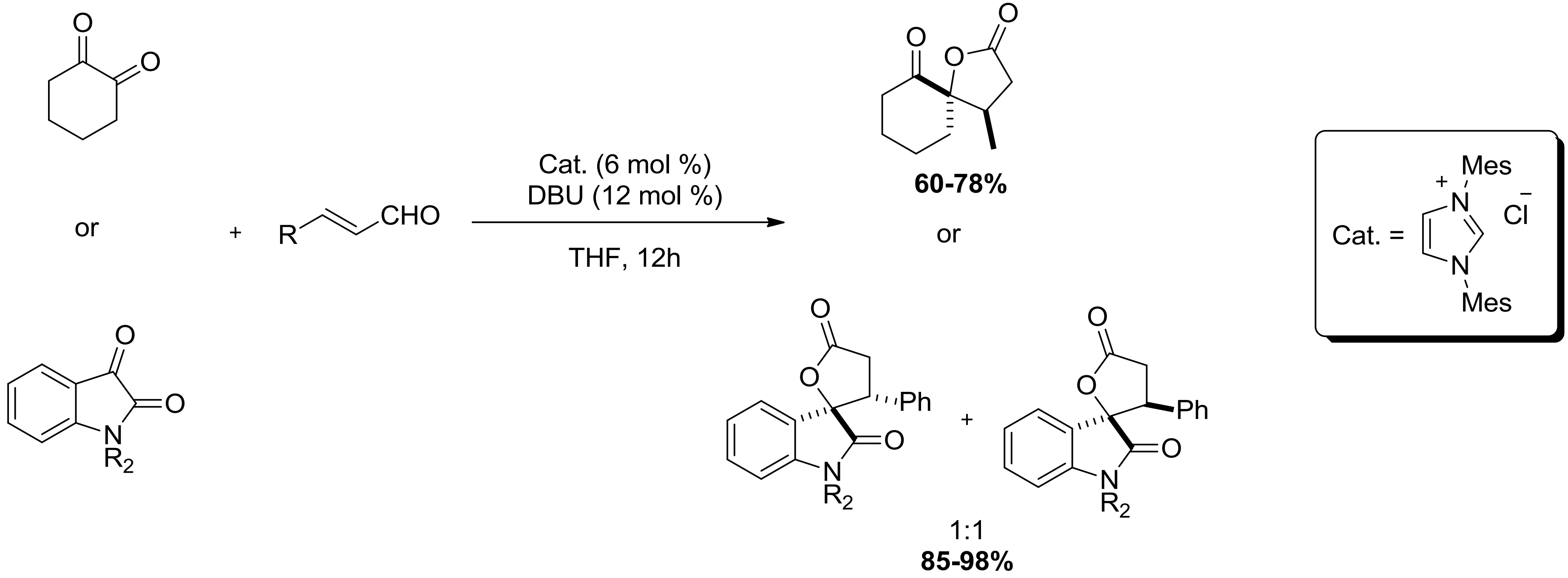


J. Bode, *J. Am. Chem. Soc.*, **2006**, 128, 8418-8420

Homoenolates

Electrophile diversification

- 1,2-Dicarbonyl Compounds

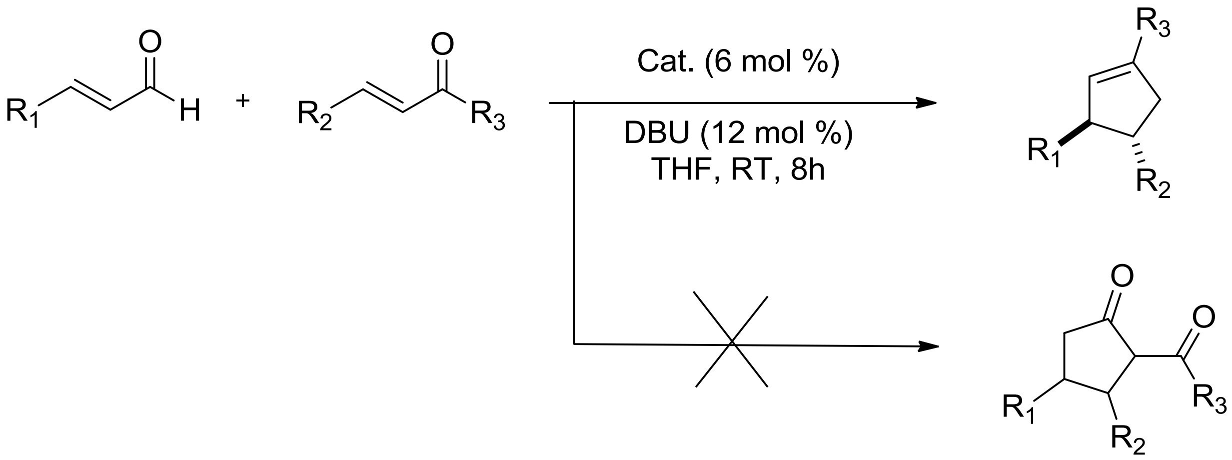


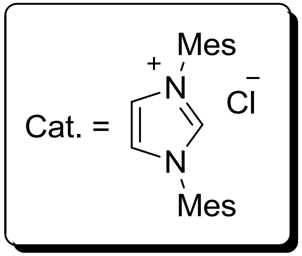
V. Nair, *Org. Lett*, **2006**, *8*, 507-509

Homoenolates

Electrophile diversification

- <u>α,β unsaturated ketone</u>

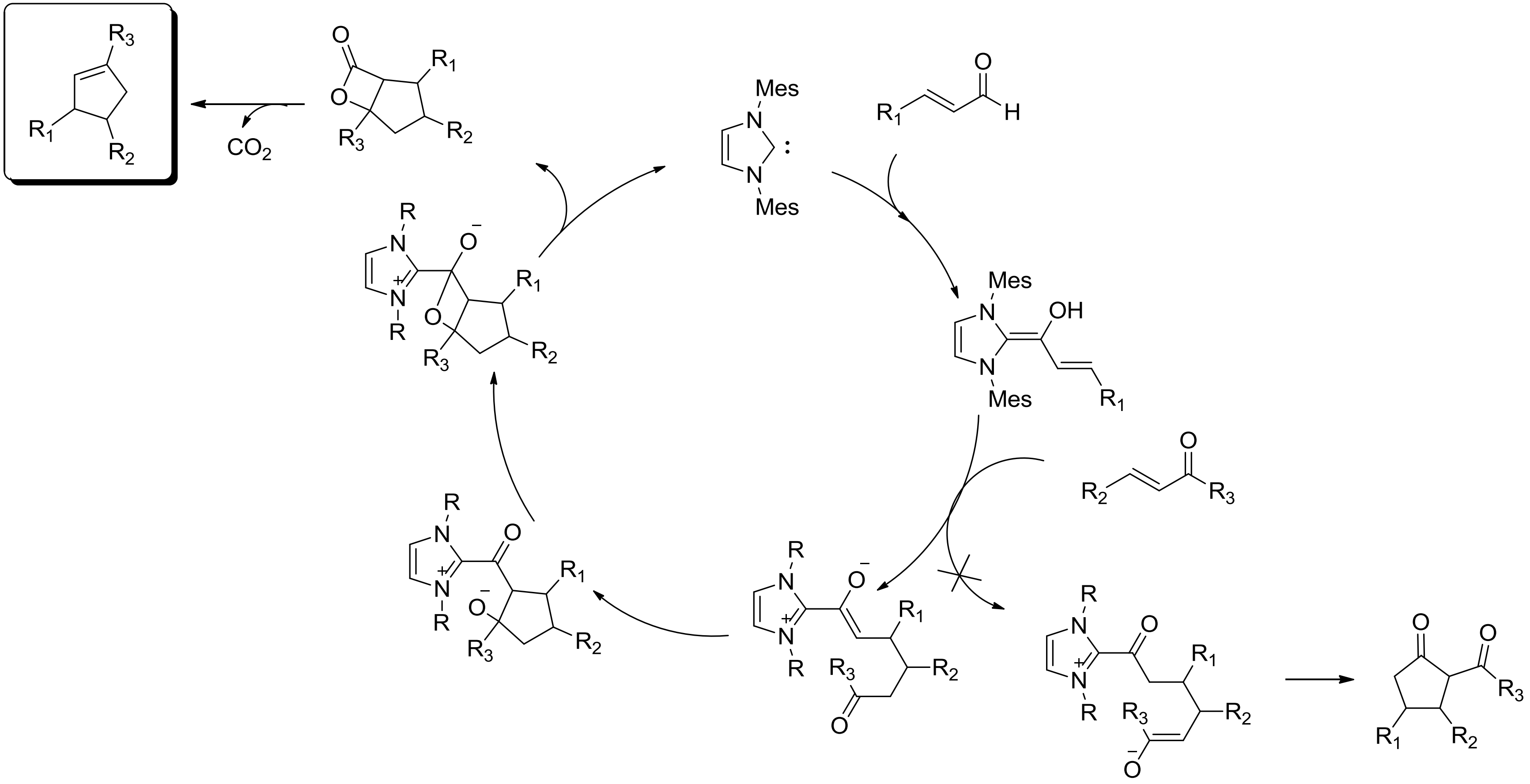




V. Nair, *J. Am. Chem. Soc.*, **2006**, 128, 8736-8737

Homoenolates

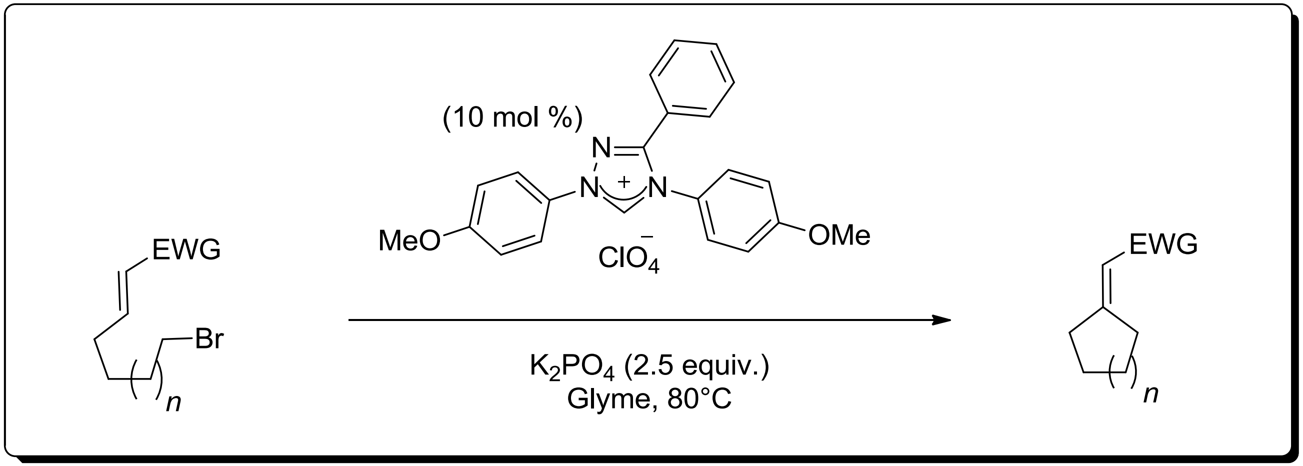
Mechanism to form the cyclopentene

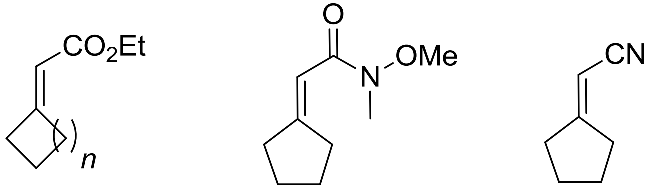


V. Nair, *J. Am. Chem. Soc.*, **2006**, 128, 8736-8737

Homoenolates

Intramolecular alkylation of α β unsaturated ester





n = 1, 48%
n = 2, 94%
n = 3, 81%

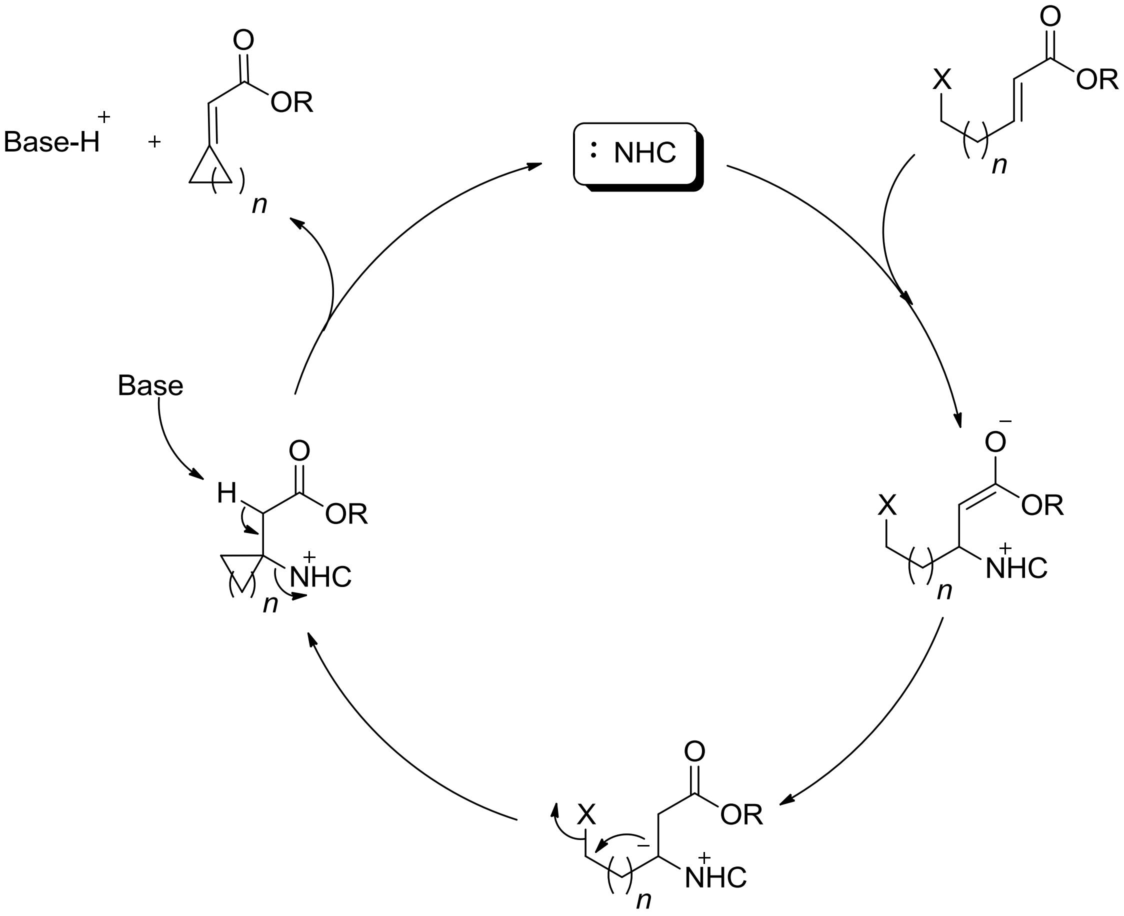
68%

71%

G. C. Fu, *J. Am. Chem. Soc.*, **2006**, 128, 1472-1473

Homoenolates

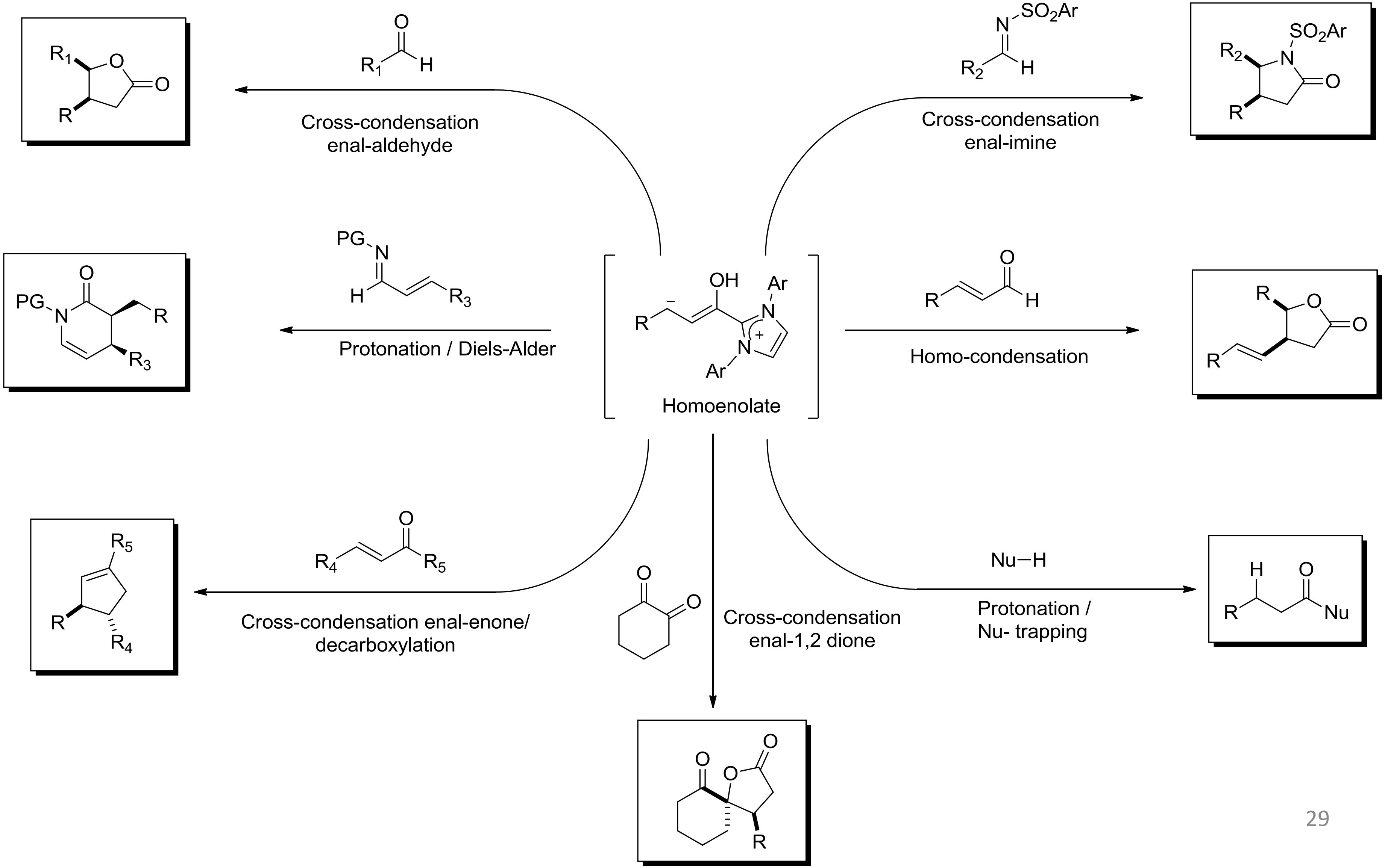
Homoenolates obtention via α β unsaturated ester



G. C. Fu, *J. Am. Chem. Soc.*, **2006**, 128, 1472-1473

LSPN
LABORATOIRE DE SYNTHESE
ET PRODUITS NATURELS

Homoenolates



Cross-condensation enal-aldehyde

Cross-condensation enal-imine

Protonation / Diels-Alder

Homoenolate

Homo-condensation

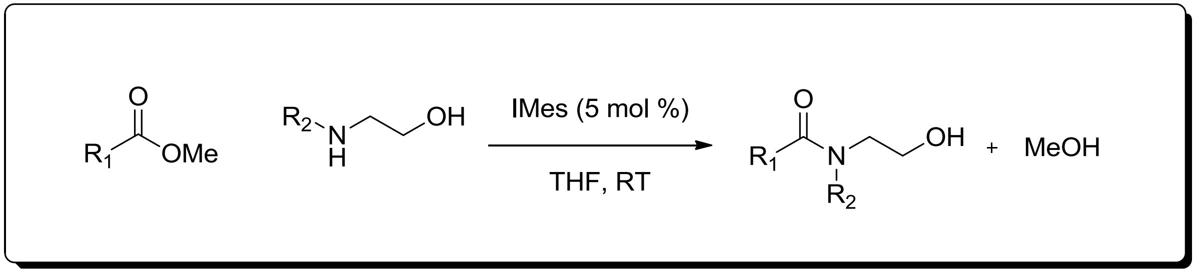
Cross-condensation enal-enone/ decarboxylation

Cross-condensation enal-1,2 dione

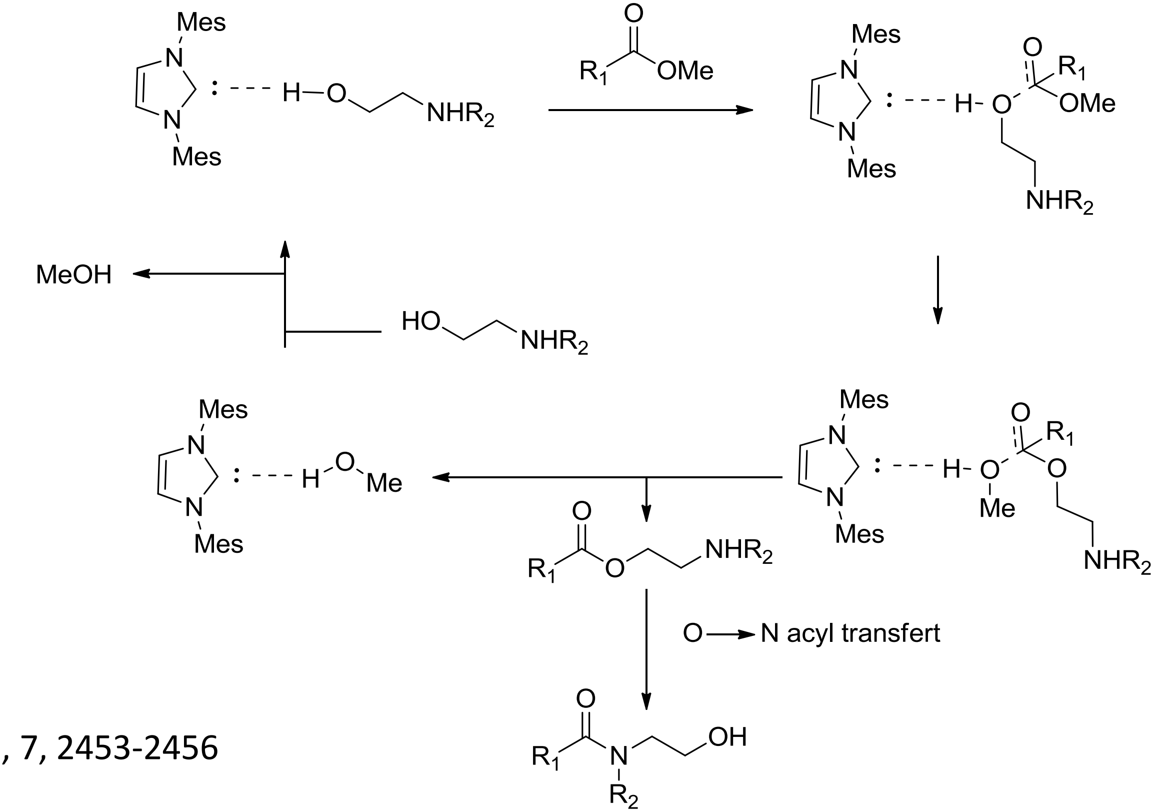
Protonation / Nu- trapping

Trans-esterification

Amide formation



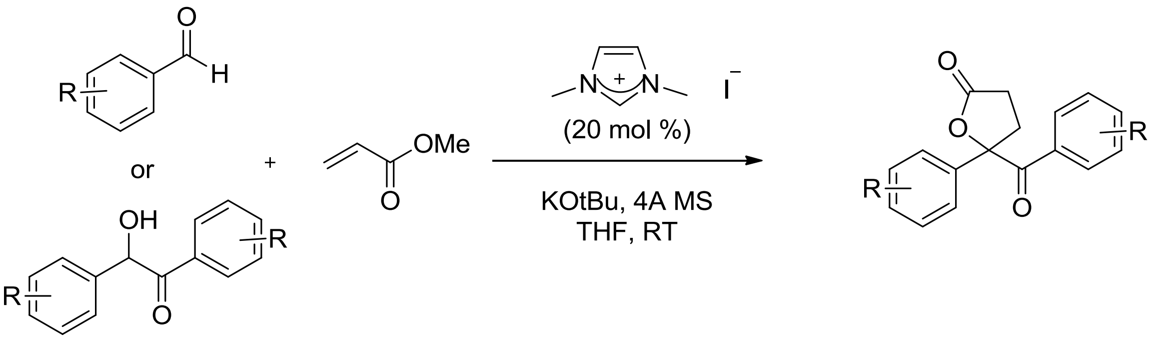
Proposed mechanism



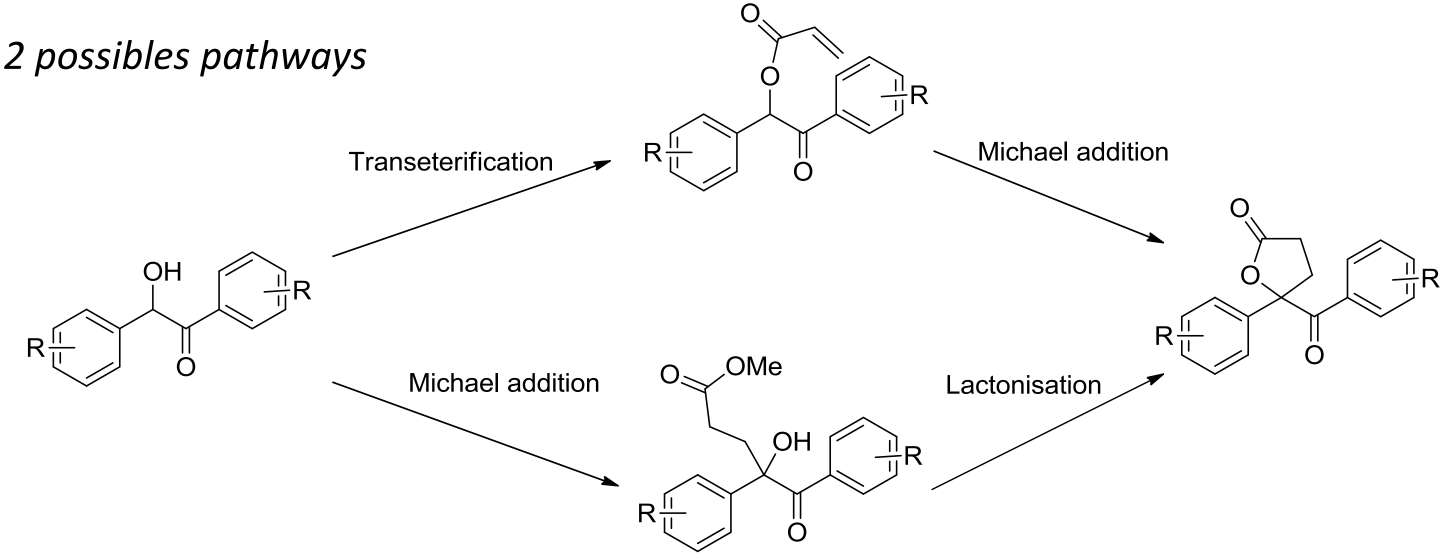
M. Movassaghi, *Org. Lett.*, **2005**, 7, 2453-2456

Trans-esterification

γ-butyrolactone formation



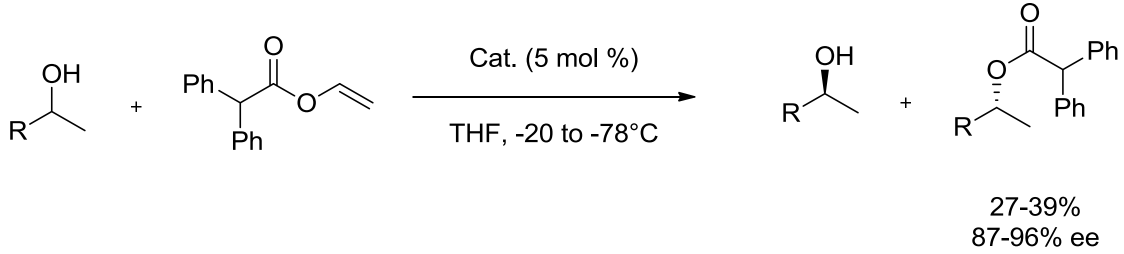
2 possibles pathways

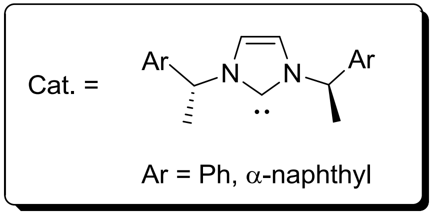


H. Zhai, *Org. Lett.*, **2005**, 7, 3769-3771

Acylation reaction

Kinetic resolution with chiral NHCs



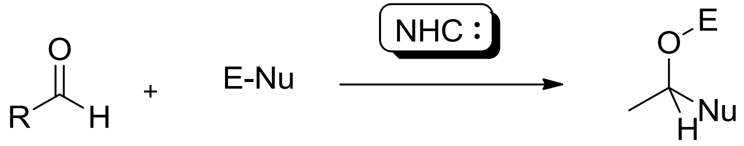


Need to have a hindered acylating agent

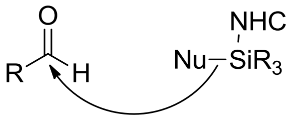
K. Maruoka, *Org. Lett.*, **2005**, 7, 1347-1349

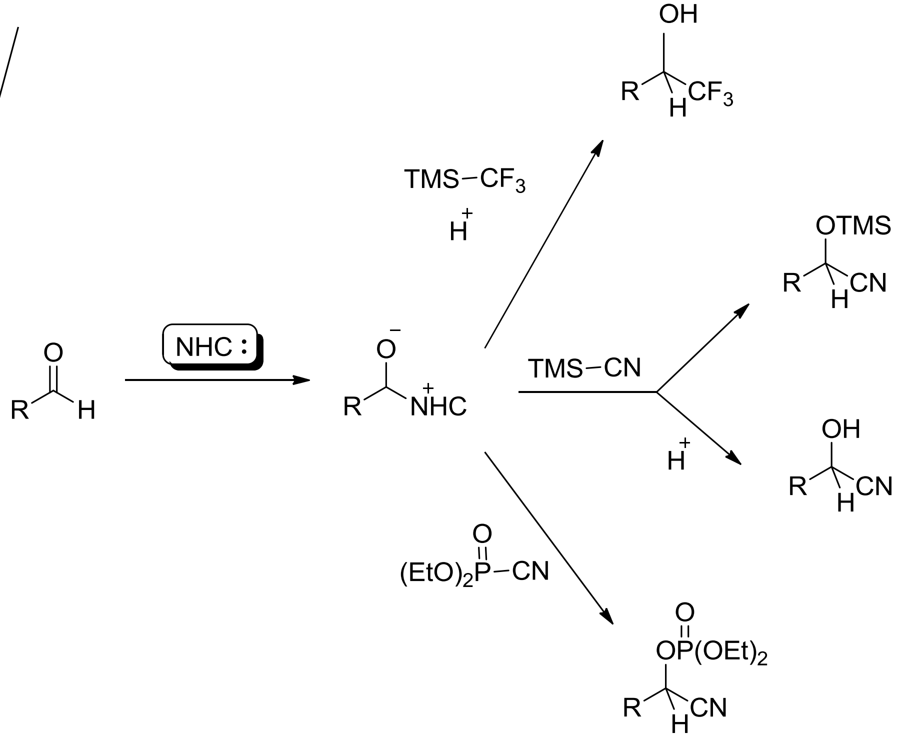
1,2-Addition reactions

Reaction with E-Nu

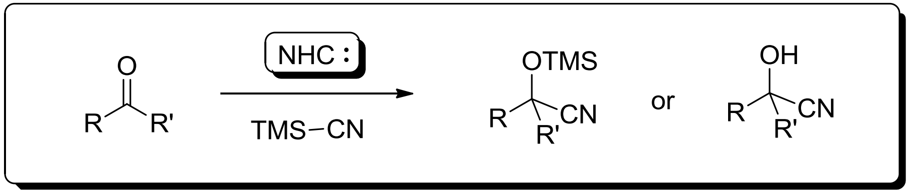


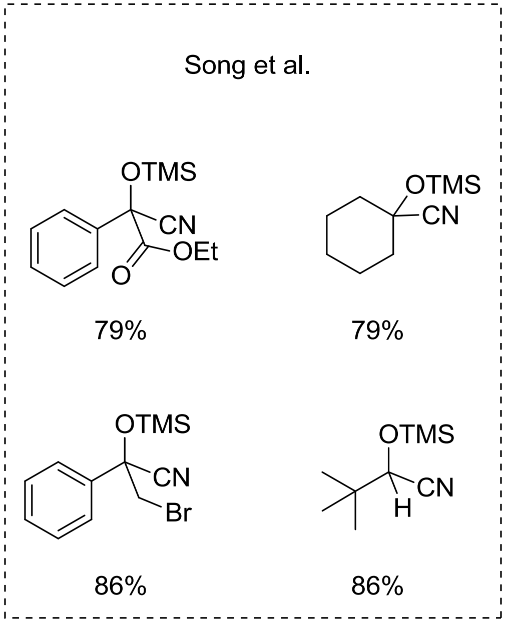
Possible activation by NHC

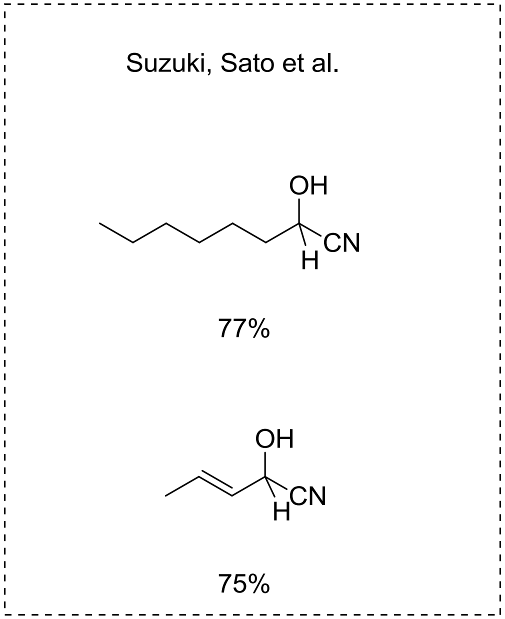


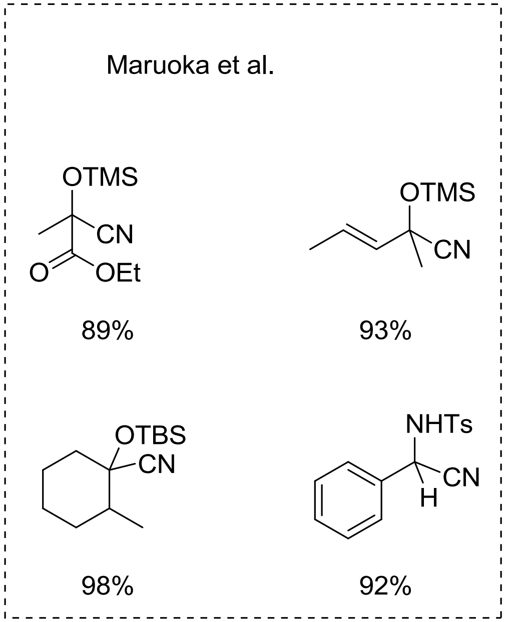


1,2-Addition reactions









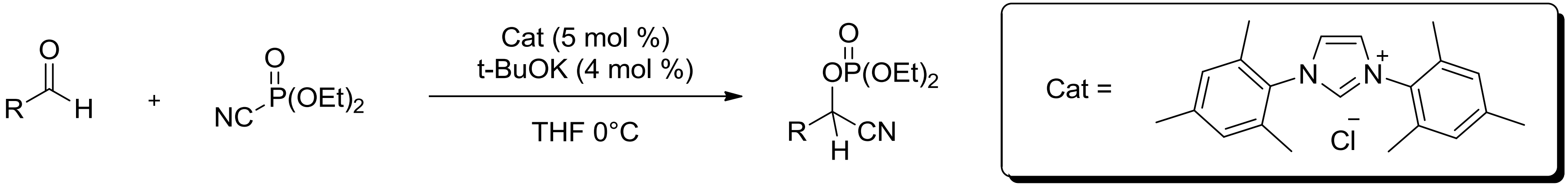
- Ketone
- Enal
- Imine
- α-ester

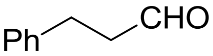
Asymetric version was tried by Suzuki and Sato with a poor ee 22%

D. H. Song, *Synth. Commun.*, **2004**, 34, 2973-2980 ; Y. Suzuki, M. Sato, *Tetrahedron*, **2006**, 62, 4227-4231 ;
K. Maruoka, *Tetrahedron Lett.*, **2006**, 47, 4615-4618

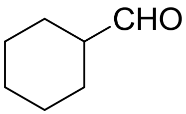
1,2-Addition reactions

Cyanophosphorylation of aldehyde

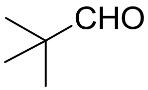




91%

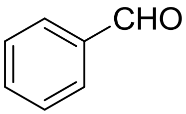


94%

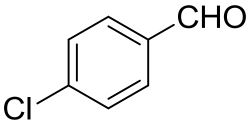


98%

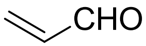
Reaction time less than 5 min



94%



92%

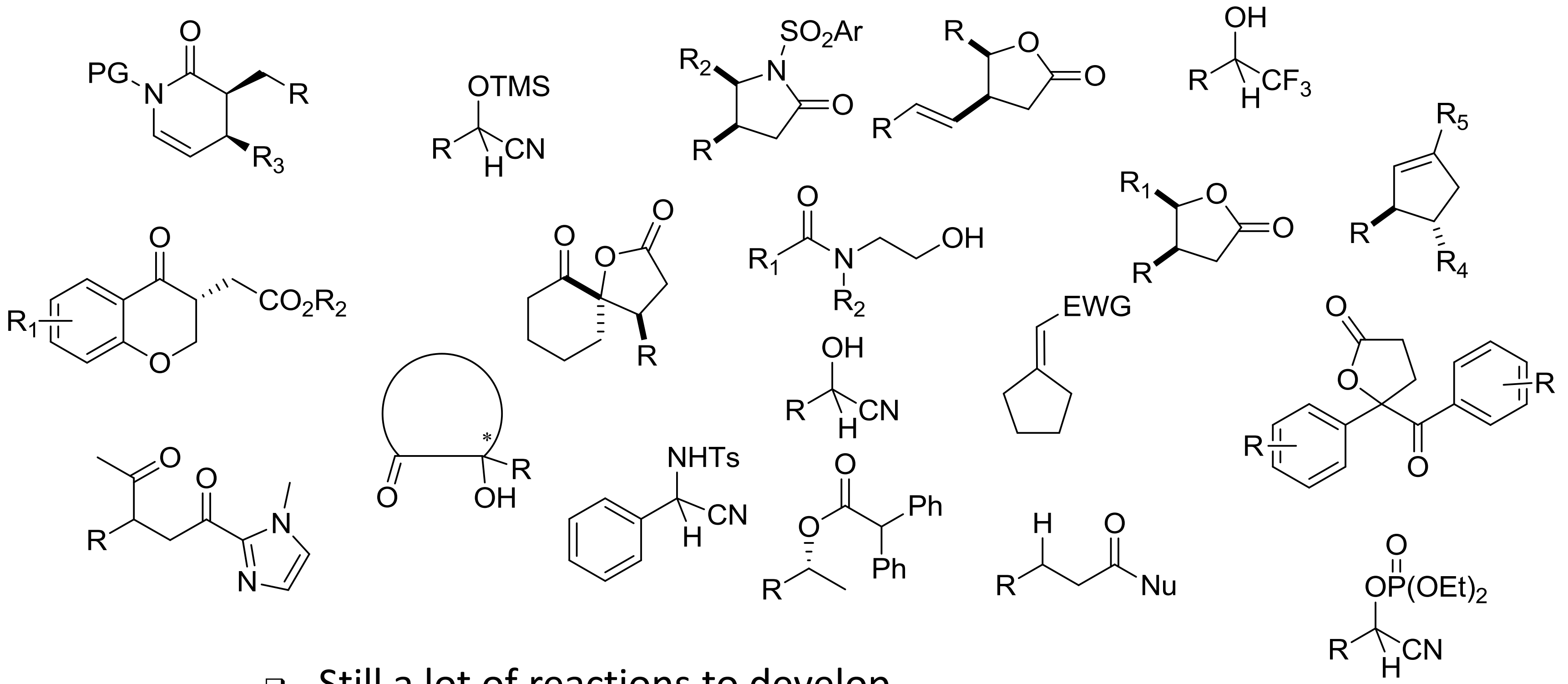


90%

K. Kondo, T. Aoyama, *Chem. Pharm. Bull.*, **2006**, *54*, 397-398

Conclusion

NHC as an organocatalyst allows access to a wide diversity of molecules



- ❑ Still a lot of reactions to develop
- ❑ Enantiomeric version of homoenolate reaction to upgrade

Conclusion

Questions

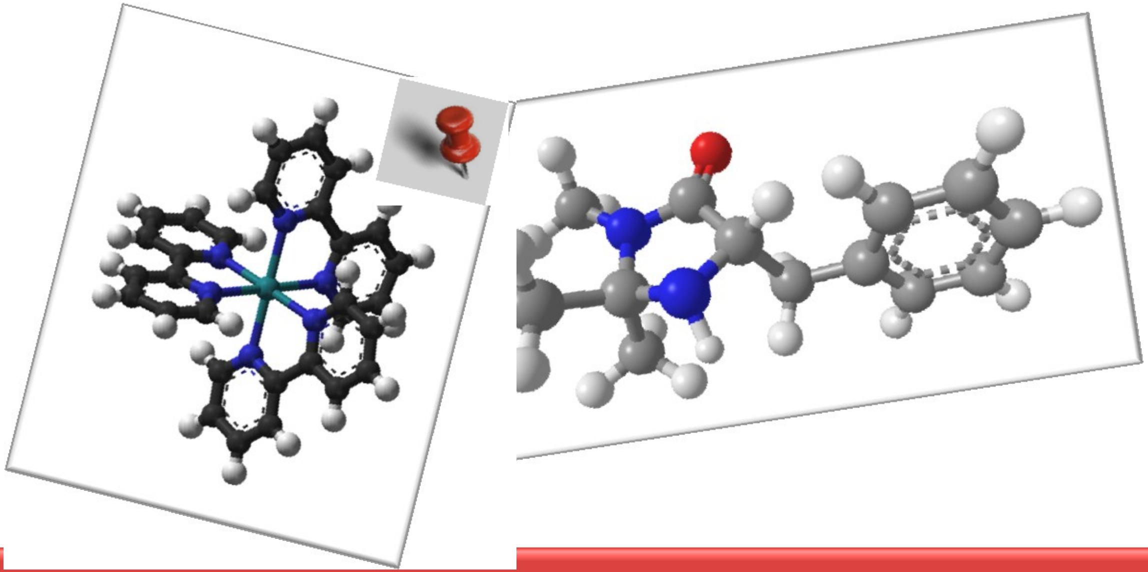
Reviews :

- <u>N-Heterocyclic carbenes as organocatalysts</u>

N. Marion, S. Díez-González*, and S. P. Nolan*, *Angew. Chem. Int. Ed.*, **2007**, *46*, 2988-3000

- <u>Nucleophilic cabenes in asymetric organocatalysis</u>

D. Enders*, T. Balensiefer, *Acc. Chem. Res.*, **2004**, *37*, 534-541



Cooperative catalysis between metals and organocatalysis

LITERATURE TALK

Florian de Nanteuil

EPFL 2011

Questions

- What is the difference in terms of reactivity between the MacMillan SOMO and Photoredox-catalysis?
- In the case of a cationic-gold complex, why the chiral-counteranion strategy is particularly interesting in order to induce chirality?

Sustainable Chemistry

"meets the needs of the present without compromising the ability of future generations to meet their own needs."[1]

Catalysis

Renewable Feedstock

Atom Economy

Energy Efficiency

Minimum Waste

Design for Degradation

Efficient Isolation Process

Synthetic methods

1.United Nations. 1987. "Report of the World Commission on Environment and Development." General Assembly Resolution 42/187, 11 December 1987

Anastas, P. T.; Warner, J. C.*; Green Chemistry: Theory and Practice*, Oxford University Press: New York, **1998**, p.30

Sustainability in organic chemistry

Atom Economy

RedOx Economy

E-Factor

Function oriented Synthesis

Metal Free

- Cascade/Domino
- Organocatalysis
- Direct Functionalisation
- Carbocyclisations
- Radical transformations
- C-C/C-H functionalisation
- Photoredox
- New technologies (MW, flow chem …)

Catalysis

1836, Berzelius

Lower Activation Energy = Enhancement of the rate of a reaction - Unblock a reaction

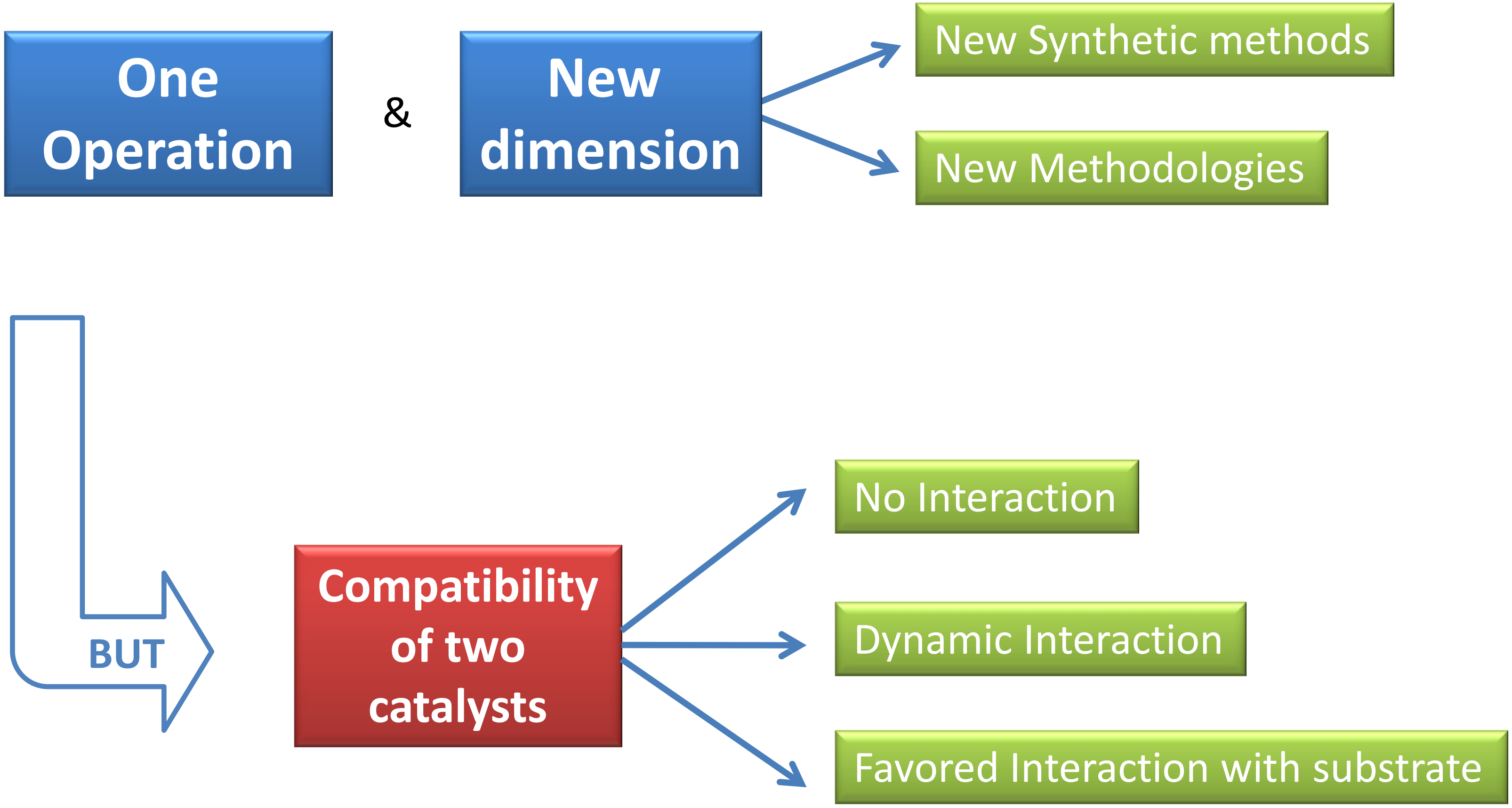
Catalytic amount

- Less waste
- Fewer atoms
- Less energy

Control

- Activity
- Regioselectivity
- Stereoselectivity

Two catalysts?



One Operation & **New dimension**

- New Synthetic methods
- New Methodologies

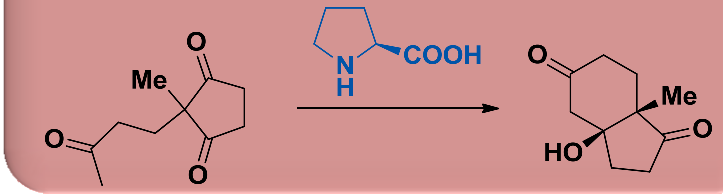
BUT

Compatibility of two catalysts

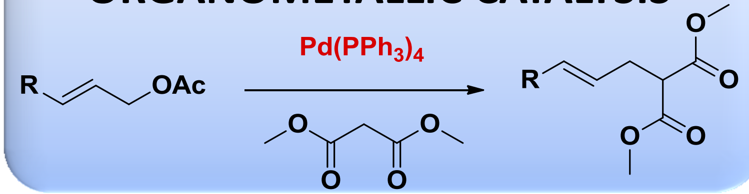
- No Interaction
- Dynamic Interaction
- Favored Interaction with substrate

Cooperative catalysis

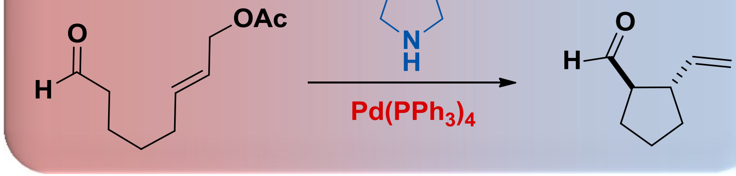
ORGANOCATALYSIS



ORGANOMETALLIC CATALYSIS



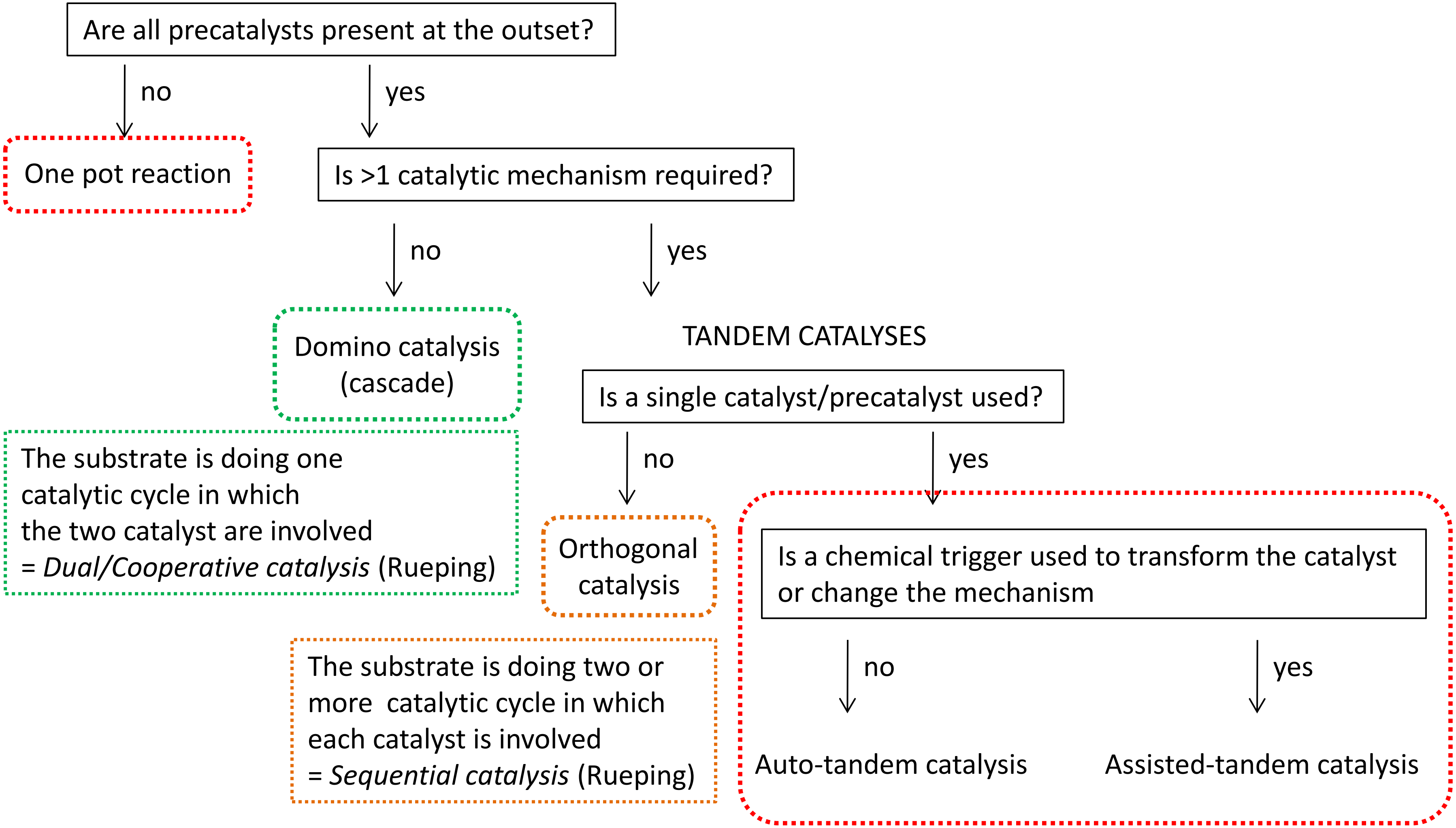
COOPERATIVE CATALYSIS



REVIEWS :

Chem. Soc. Rev., **2009**, 38, 2745-2755
Chem. Eur. J. **2010**, 16, 9350 – 9365
Eur. J. Org. Chem. **2010**, 2999–3025

Content



Are all precatalysts present at the outset?

no

One pot reaction

yes

Is >1 catalytic mechanism required?

no

Domino catalysis (cascade)

The substrate is doing one catalytic cycle in which the two catalyst are involved
= *Dual/Cooperative catalysis* (Rueping)

yes

TANDEM CATALYSES

Is a single catalyst/precatalyst used?

no

Orthogonal catalysis

The substrate is doing two or more catalytic cycle in which each catalyst is involved
= *Sequential catalysis* (Rueping)

yes

Is a chemical trigger used to transform the catalyst or change the mechanism

no

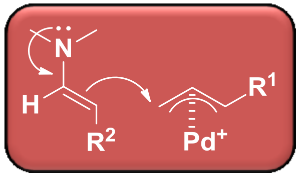
Auto-tandem catalysis

yes

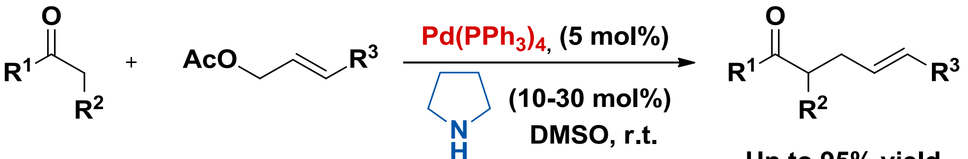
Assisted-tandem catalysis

D.E. Fogg, E.N. dos Santos, *Coord. Chem. Rev.* **2004**, 248, 2365–2379
Rueping et al. *Chem. Eur. J.* **2010**, 16, 9350 – 9365

Amine - Transition metal



Cordova - 2006



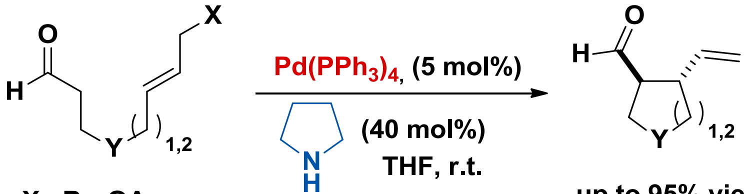
$Pd(PPh_3)_4$, (5 mol%)

(10-30 mol%)

DMSO, r.t.

Up to 95% yield

Saicic - 2007



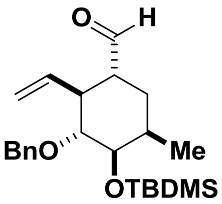
X= Br, OAc
Y= CH_2, NTs, $C(COOEt)_2$

$Pd(PPh_3)_4$, (5 mol%)

(40 mol%)

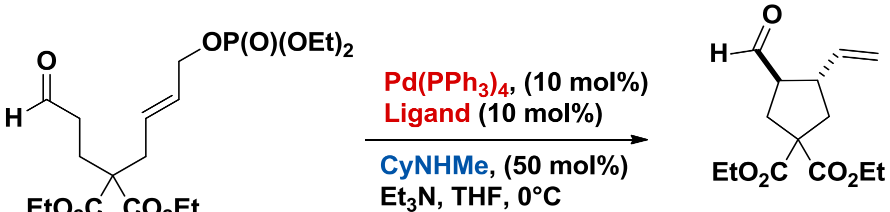
THF, r.t.

up to 95% yield
up to 13:1 dr



95%
7:1

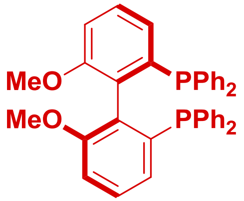
Saicic - 2009



$Pd(PPh_3)_4$, (10 mol%)
Ligand (10 mol%)

CyNHMe, (50 mol%)
Et_3N, THF, 0°C

76% yield,, 7.4:1 dr, 98% ee

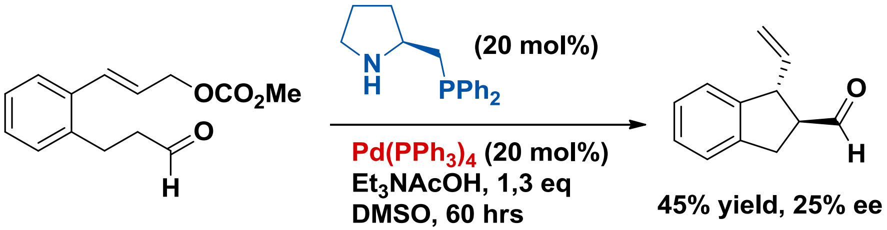


L = (R)-Ph-MeOBIPHEP

I. Ibrahem , A. Córdova , *Angew. Chem. Int. Ed.* **2006** , 45 , 1952 –1956
F. Bihelovic , R. Matovic , B. Vulovic , R. N. Saicic , *Org. Lett*. **2007** , *9* , 5063 –5066
B. Vulovic , F. Bihelovic , R. Matovic , R. N. Saicic , *Tetrahedron* **2009** , 65 , 10485 –10494

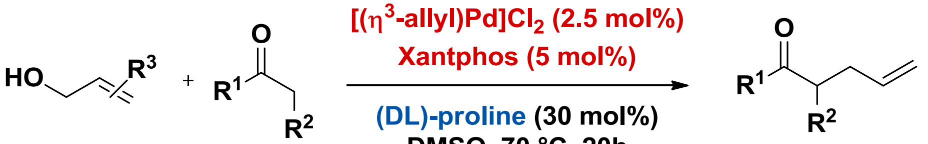
Amine - Transition metal

Tomioka – 2008



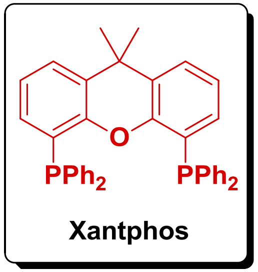
45% yield, 25% ee

Breit – 2009

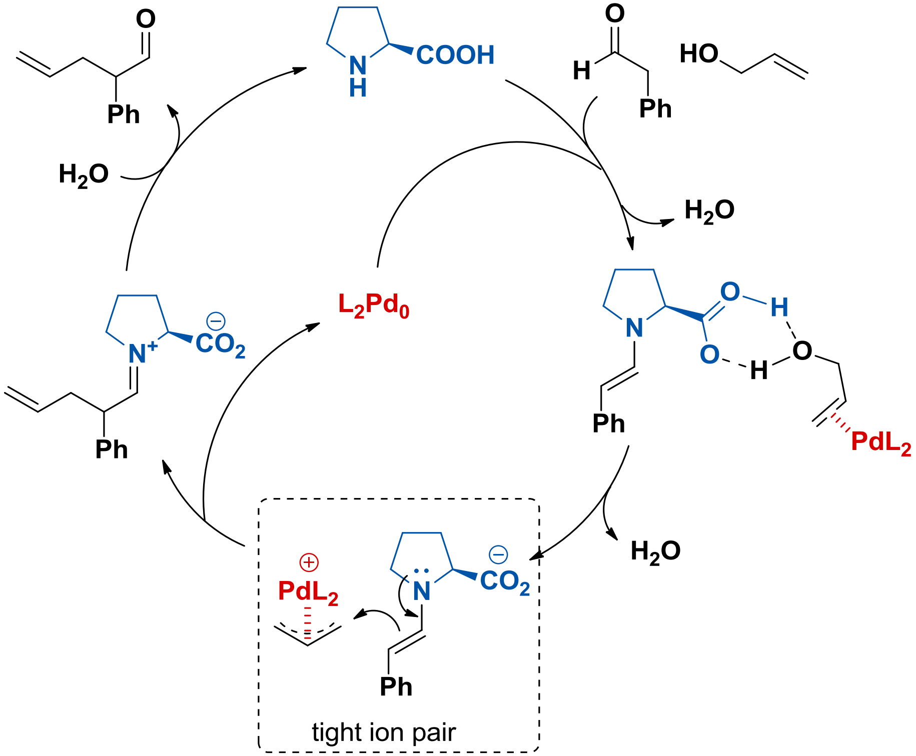


R1 = H, alkyl; R2 = alkyl
R3 = H, Ph

up to 96% yield

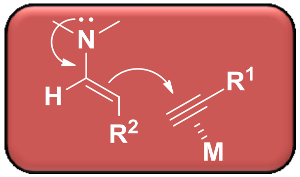


Xantphos

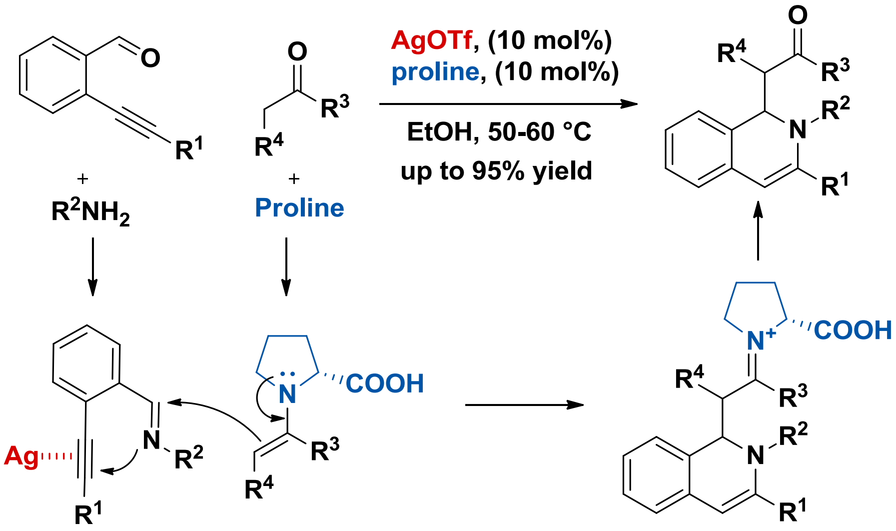


T. Sato , K. Tomioka , *Heterocycles* **2009** , 77 , 587 –593 .
I. Usui , S. Schmidt , B. Breit , *Org. Lett*. **2009** , 11 , 1453 –1456 .

Amine - Transition metal

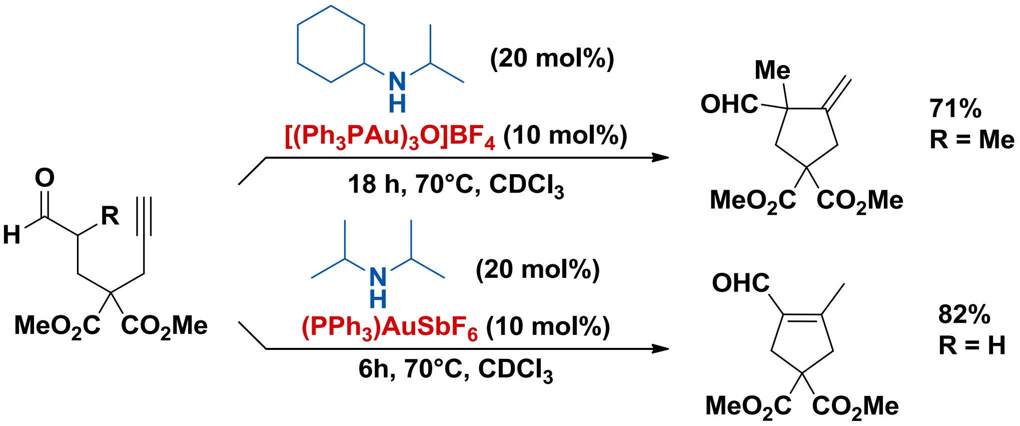


Wu - 2007



R^1 = Ar, cyclopropyl, n-Bu,TMS; R^2 = Ar; R^3 = alkyl; R^4 =H, alkyl

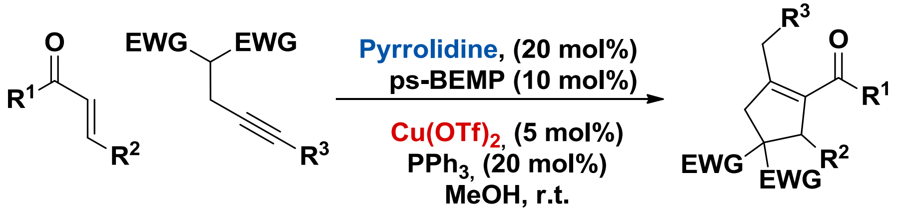
Kirsch - 2008

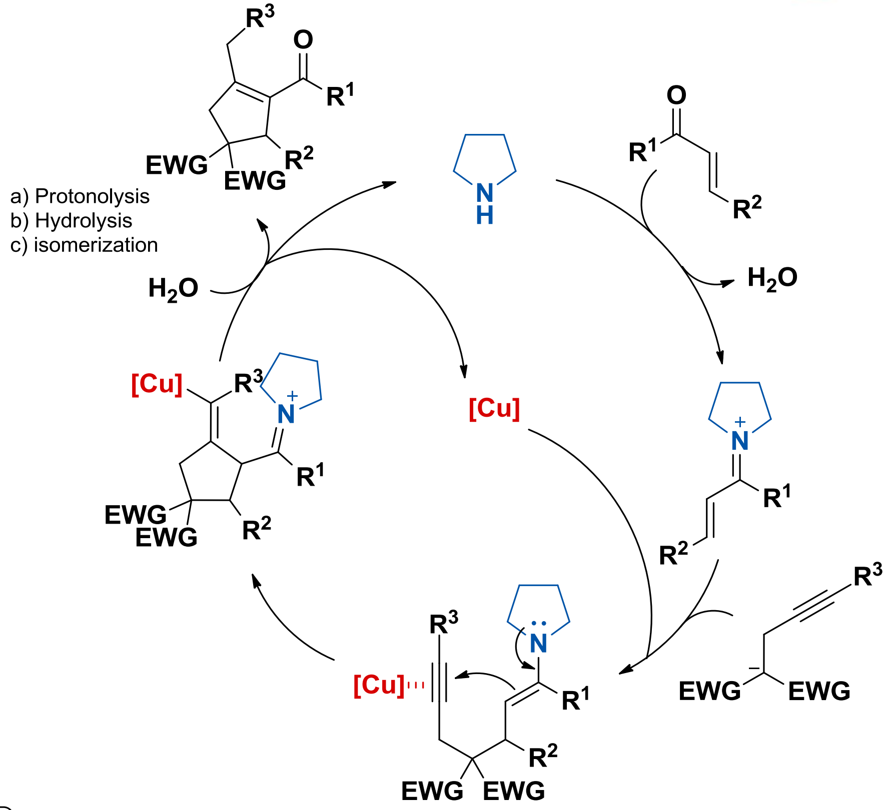


Q. Ding , J. Wu , *Org. Lett*. **2007** , 9 , 4959 –4962
J. T. Binder , B. Crone , T. T. Haug , H. Menz , S. F. Kirsch , *Org. Lett*. **2008** , 10 , 1025 –1028

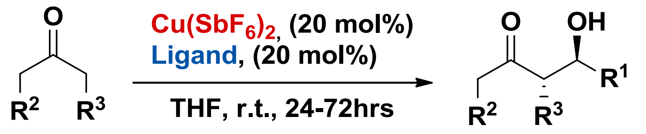
Amine - Transition metal

Dixon - 2008

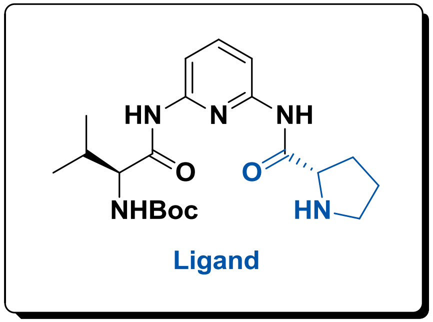




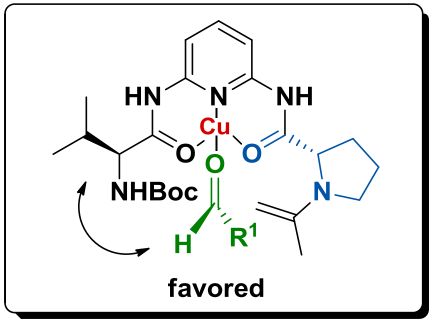
Whang - 2009



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



Ligand

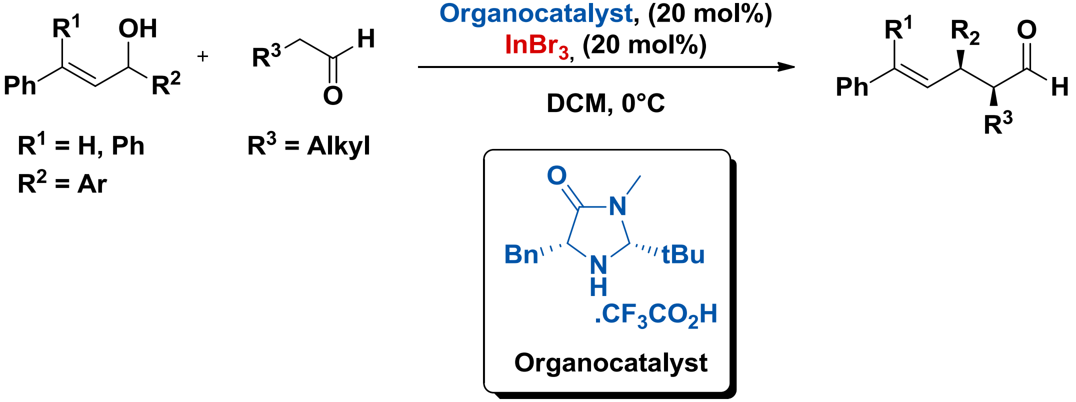


favored

T. Yang , A. Ferrali , L. Campbell , D. J. Dixon , *Chem. Commun*. **2008** , 2923 –2925
Z. Xu , P. Daka , I. Budik , H. Wang , F.-Q. Bai , H.-X. Zhang , *Eur. J. Org. Chem*. **2009** , 4581 –4585

Amine - Transition metal

Cozzi - 2010

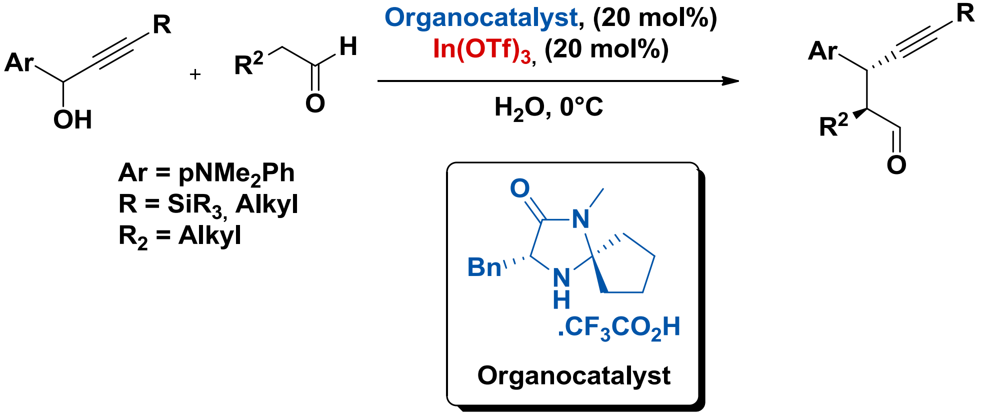


R^1 = H, Ph
R^2 = Ar

R^3 = Alkyl

Up to 90% yield
Up to 20:1 dr
Up to 99% ee *syn*
Up to 87% ee *anti*

Cozzi - 2011



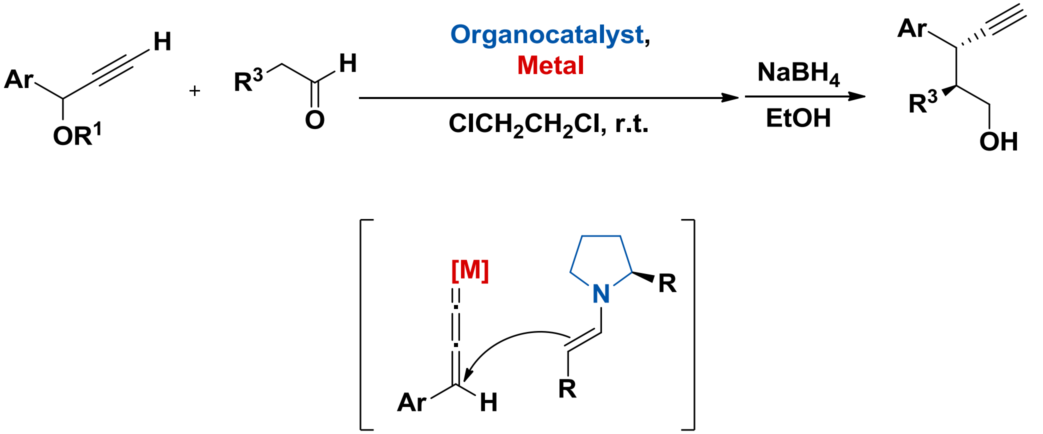
Ar = $pNMe_2Ph$
R = SiR_3, Alkyl
R_2 = Alkyl

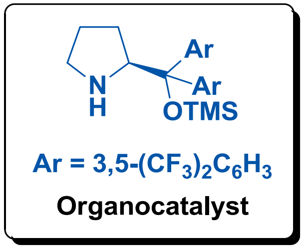
Up to 98% yield
Up to 6.7:1 dr
Up to 99% ee *anti*
Up to 99% ee *syn*

Capdevila M.G., Benfatti F., Zoli L., Stenta M., Cozzi P. G. *Chem. Eur. J.* **2010**, 16, 11237
Sinisi R., Vita M. V., Gualandi A., Emer E., Cozzi P. G. *Chem. Eur. J.* **2011**, ASAP

Amine - Transition metal

Nishibayashi – 2010/2011





Ar = 3,5-$(CF_3)_2C_6H_3$

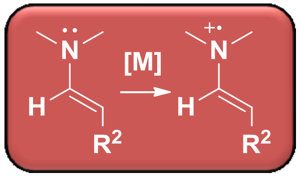
Organocatalyst

R_1 = H, [M] = [{Cp*RuCl(SMe)}$_2$], (5 mol%)
Organocatalyst, (5 mol%)
Up to 93% yield
Up to 3.3:1 dr
Up to 99% ee *syn*
Up to 95% ee *anti*

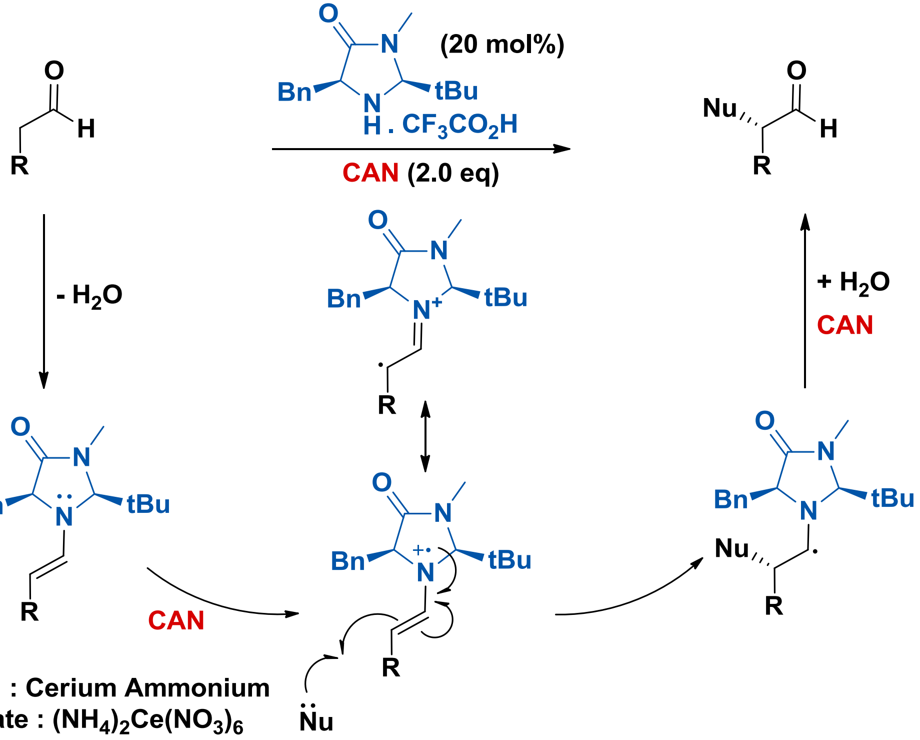
R_1 = COR^{2,} [M] = CuOTf.0.5$C_6H_{6,}$ *rac*-BINAP, (5 mol%)
Organocatalyst, (5 mol%)
Up to 64% yield
Up to 3.5:1 dr
Up to 99% ee *syn*
Up to 98% ee *anti*

Ikeda M., Miyake Y., Nishibayashi Y. *Angew. Chem. Int. Ed*. **2010**, 49, 7289
Yoshida A., Ikeda M., Hattori G., Miyake Y., Nishibayashi Y. *Org. Lett*. **2011**, 13, 592

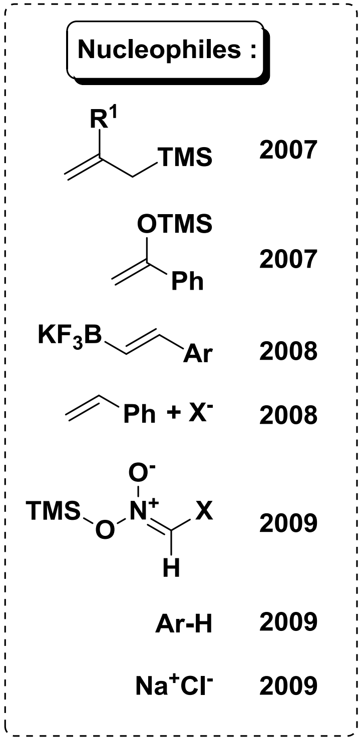
Amine – Oxidant metal



MacMillan – SOMO catalysis



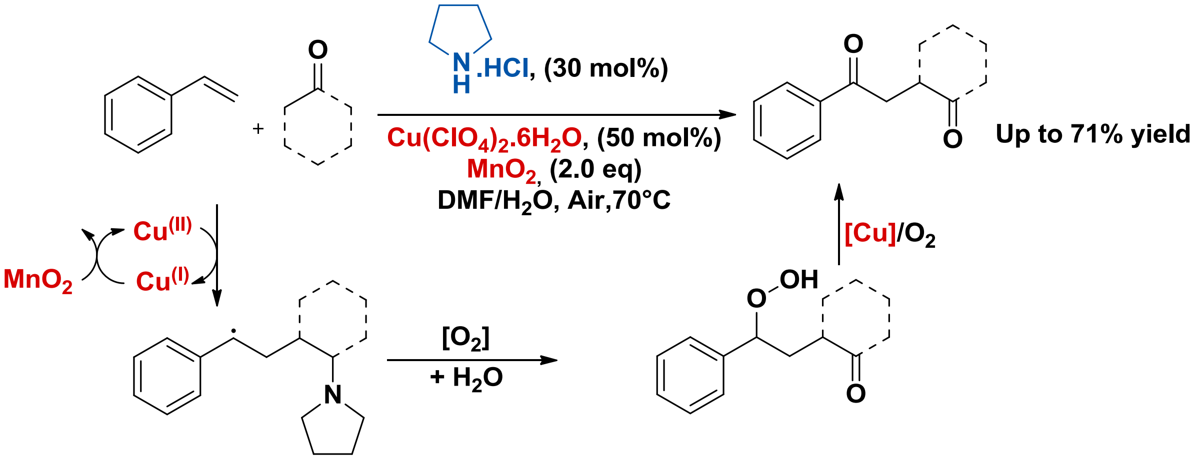
CAN : Cerium Ammonium Nitrate : $(NH_4)_2Ce(NO_3)_6$



TJ. J. Devery III, J. C. Conrad, D. W. C. MacMillan, R. A. Flowers II *Angew. Chem. Int. Ed*. **2010**, 49, 6106-6110

Amine – Oxidant metal

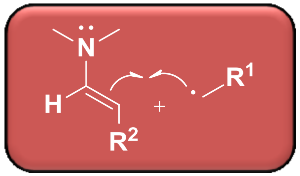
Huang - 2010



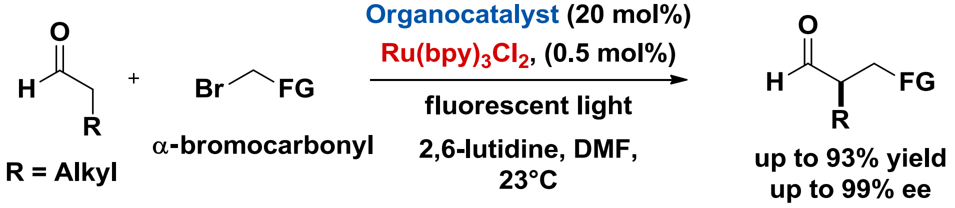
Xie J., Huang Z. Z., *Chem. Commun.* **2010**, 46, 1947

Amine – Photoactivated metal

MacMillan – Photoredox catalysis



2008



R = Alkyl

α-bromocarbonyl

Organocatalyst (20 mol%)

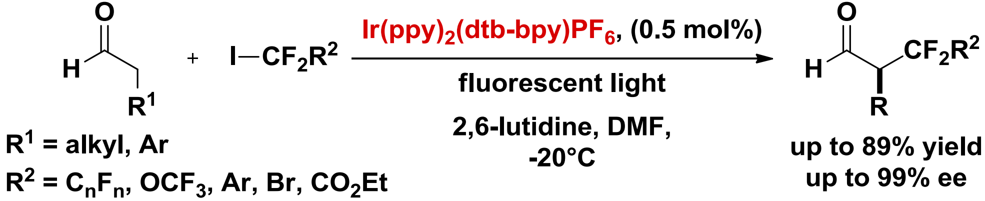
$Ru(bpy)_3Cl_2$, (0.5 mol%)

fluorescent light

2,6-lutidine, DMF, 23°C

up to 93% yield
up to 99% ee

2009



R^1 = alkyl, Ar

R^2 = C_nF_n, OCF_3, Ar, Br, CO_2Et

Organocatalyst (20 mol%)

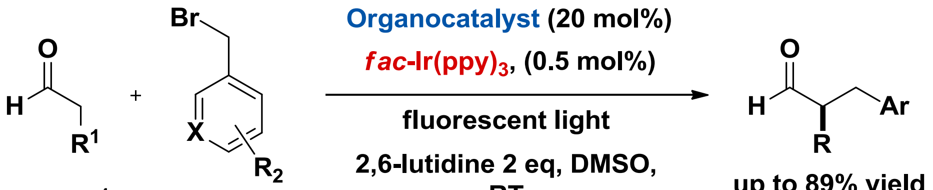
$Ir(ppy)_2(dtb\text{-}bpy)PF_6$, (0.5 mol%)

fluorescent light

2,6-lutidine, DMF, -20°C

up to 89% yield
up to 99% ee

2010



R^1 = alkyl
R^2 = EWG,
X = C, N

Organocatalyst (20 mol%)

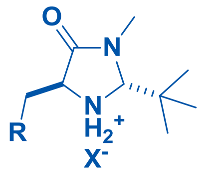
fac-$Ir(ppy)_3$, (0.5 mol%)

fluorescent light

2,6-lutidine 2 eq, DMSO, RT

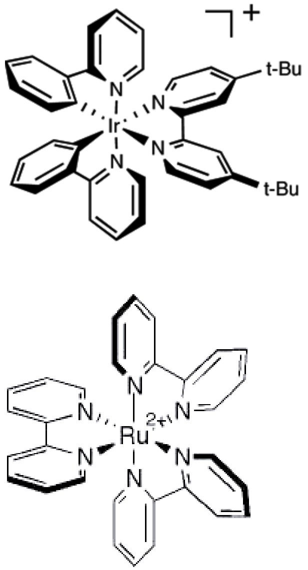
up to 89% yield
up to 99% ee

Organocatalyst



Photocatalysts

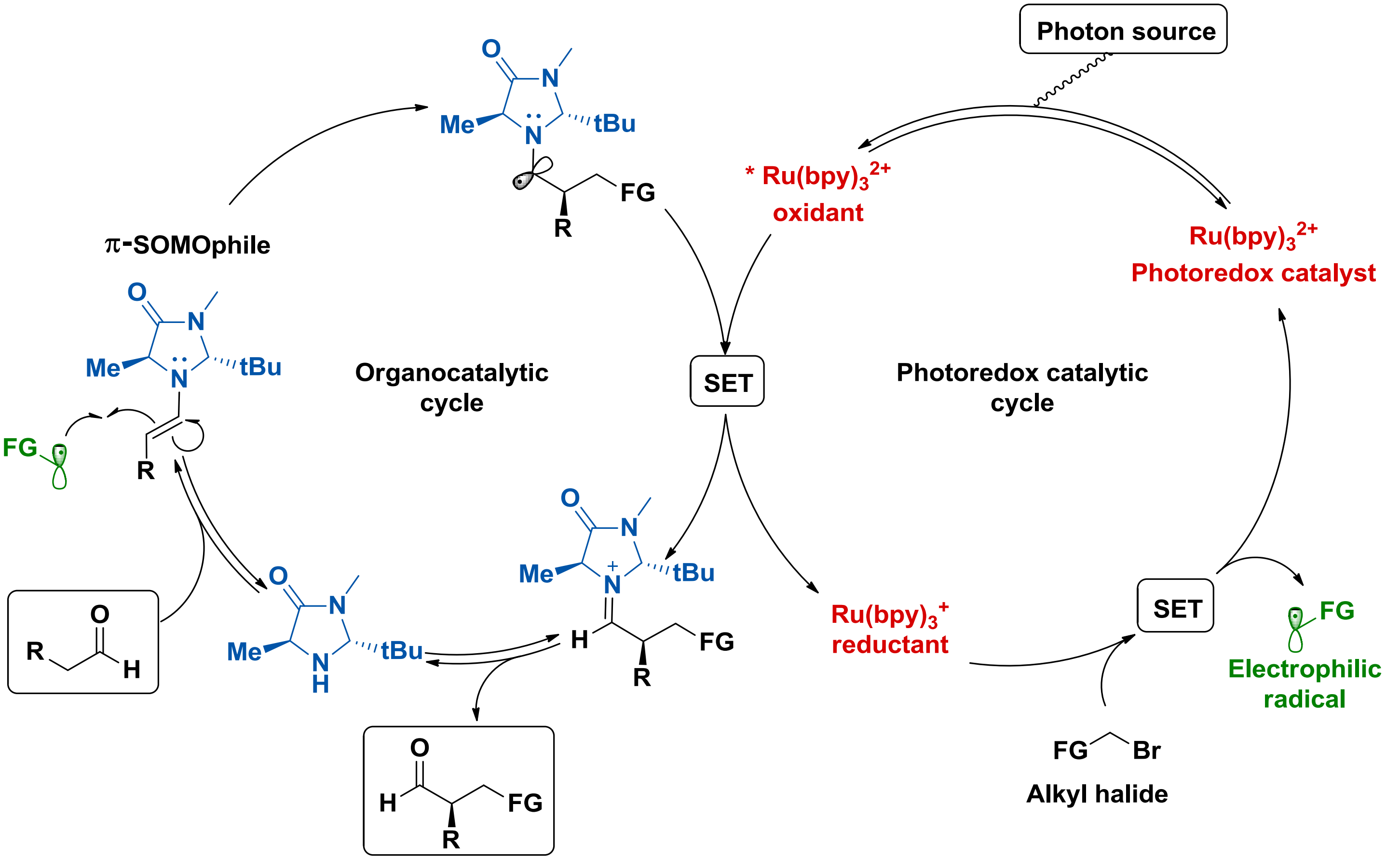
pictures from original document

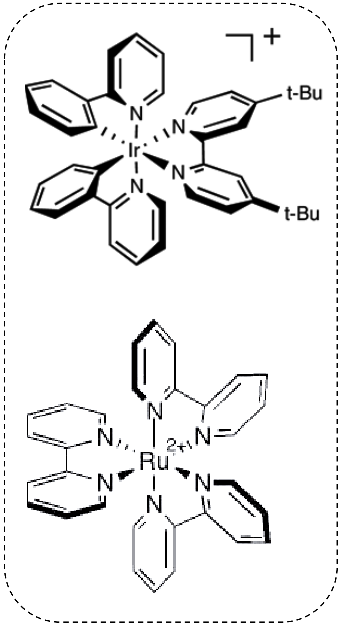


D. A. Nicewicz , D. W. C. MacMillan , *Science* **2008** , 322 , 77 –80
D. A. Nagib , M. E. Scott , D. W. C. MacMillan , *J. Am. Chem. Soc.* **2009** , 131 , 10875 –10877
H.-W. Shih, M. N. Vander Wal, R. L. Grange, D. W. C. MacMillan *J. Am. Chem. Soc.* **2010**, 132, 13600-13603

Amine – Photoactivated metal

MacMillan – Photoredox catalysis

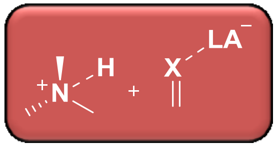




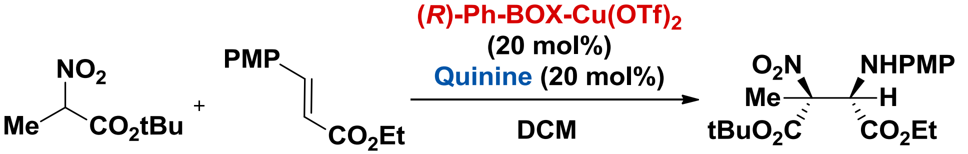
Ru and Ir catalysts

pictures from original document

Brønsted base – Lewis acid

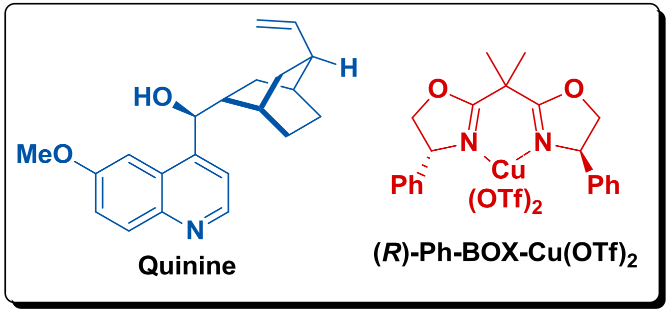


Jørgensen – 2005



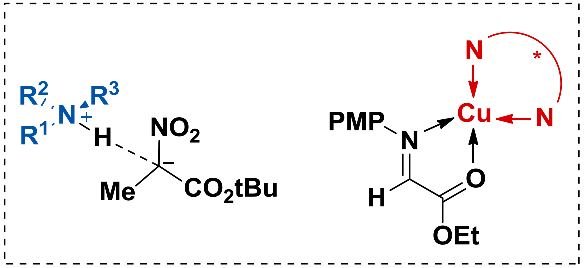
(*R*)-Ph-BOX-Cu(OTf)$_2$ (20 mol%)
Quinine (20 mol%)
DCM

90% yield
98% ee
14:1 dr

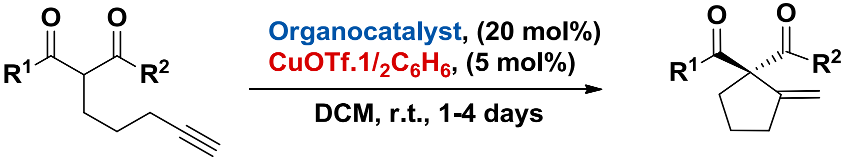


Quinine

(*R*)-Ph-BOX-Cu(OTf)$_2$

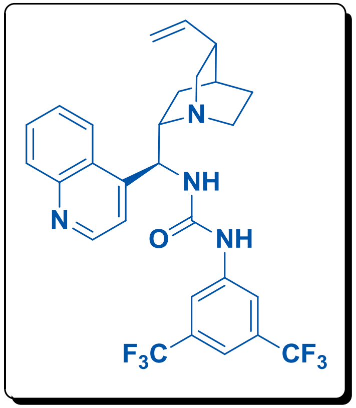


Dixon – 2009

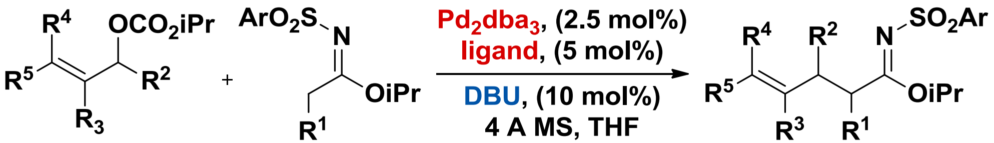


Organocatalyst, (20 mol%)
CuOTf.1/$_2$C$_6$H$_6$, (5 mol%)
DCM, r.t., 1-4 days

98% yield
93% ee

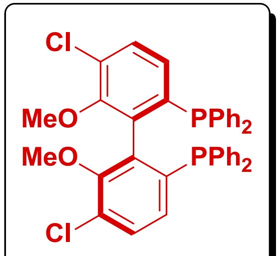


Kobayashi – 2008



Pd$_2$dba$_3$, (2.5 mol%)
ligand, (5 mol%)
DBU, (10 mol%)
4 A MS, THF

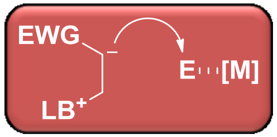
Up to 99% yield



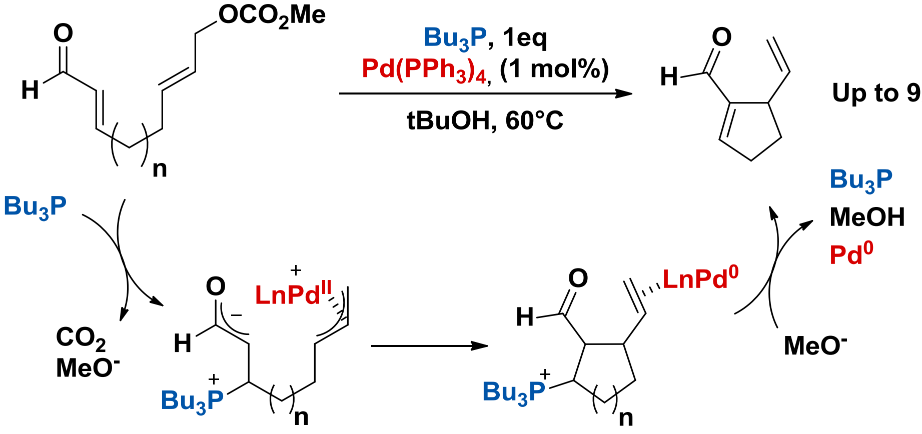
Ligand

K. R. Knudsen , K. A. Jørgensen , *Org. Biomol. Chem.* **2005** , 3 , 1362 – 1364
T. Yang , A. Ferrali , F. Sladojevich , L. Campbell , D. J. Dixon , *J. Am. Chem. Soc.* **2009** , 131 , 9140 – 9141
S. B. J. Kan , R. Matsubara , F. Berthiol , S. Kobayashi , *Chem. Commun.* **2008** , 6354 – 6356 .

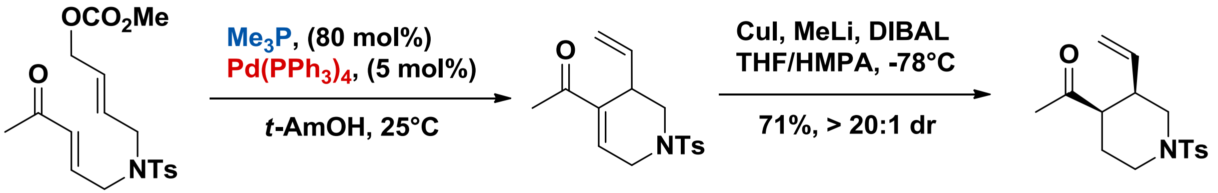
Lewis base – Transition metal



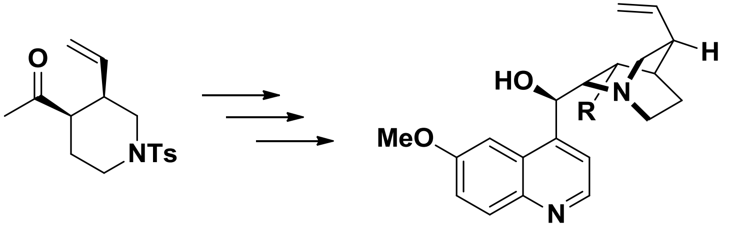
Krische – 2003



Up to 92% yield



Krische – 2008
Total synthesis of Quinine

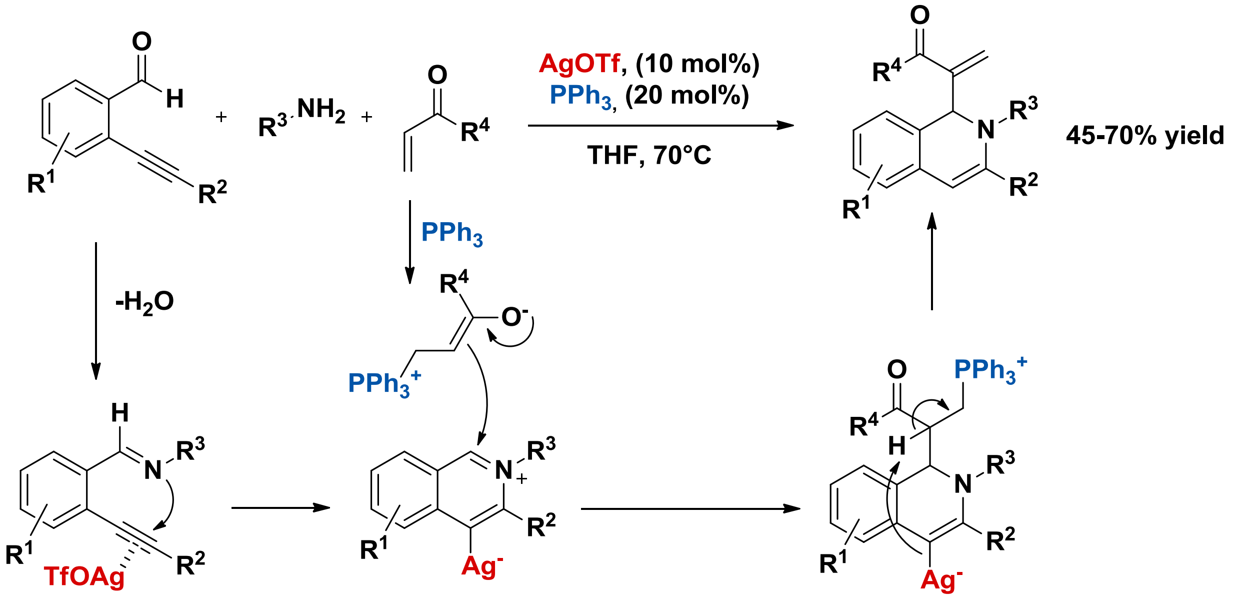


R = H: Quinine
R = OH: 7-Hydroxyquinine

B. G. Jellerichs , J.-R. Kong , M. J. Krische , *J. Am. Chem. Soc.* **2003** , 125 , 7758 –7759
P. Webber , M. J. Krische , *J. Org. Chem.* **2008** , 73 , 9379 –9387

Lewis base – Transition metal

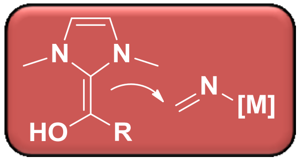
Wu – 2009



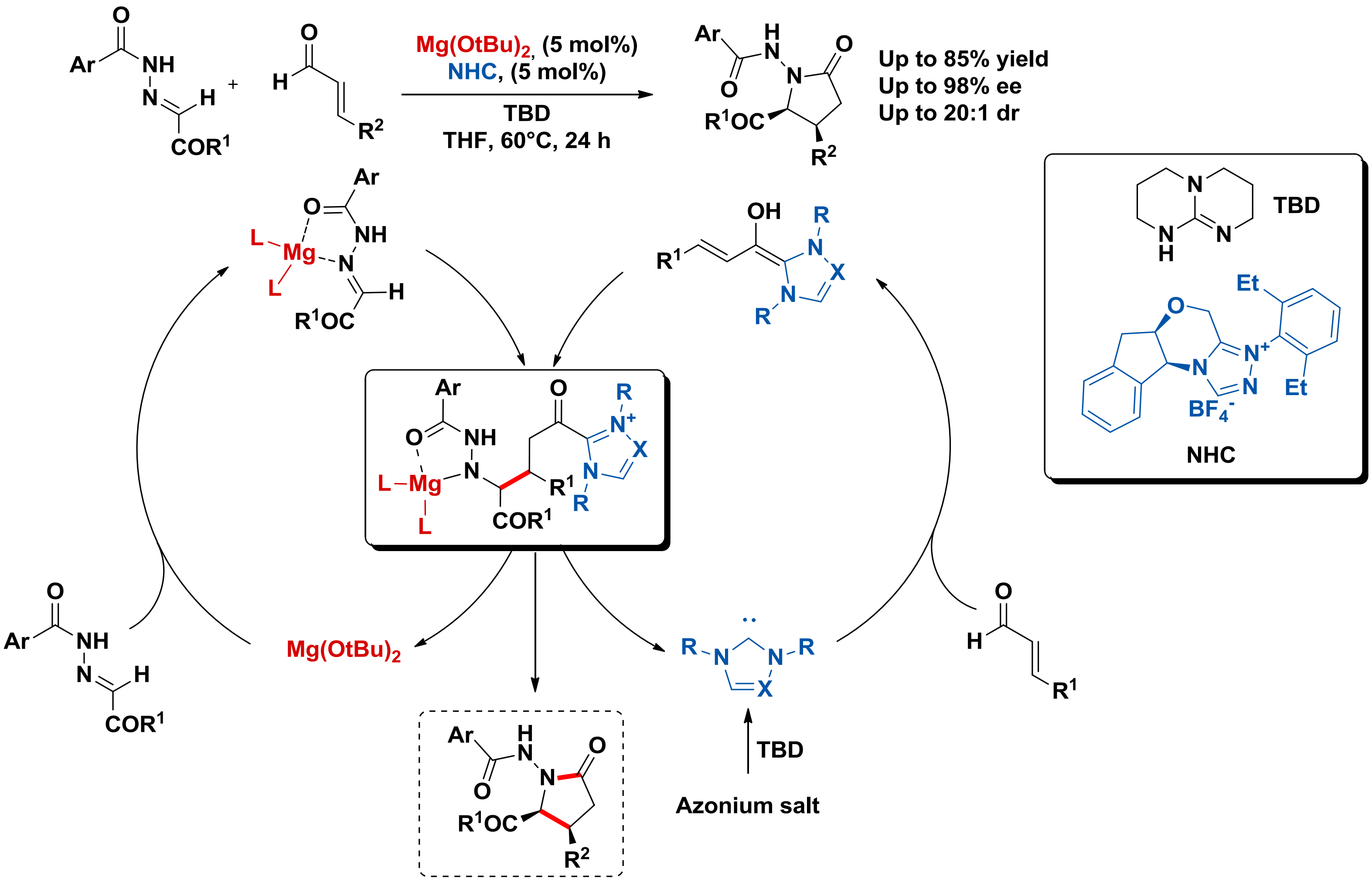
R^1 = H, F, OMe
R^2 = Ph, nBu, cyclopropyl
R^3 = Ar

S. Ye , J. Wu , *Tetrahedron Lett.* **2009** , 50 , 6273 –6275

NHC– Transition metal



Scheidt – 2010

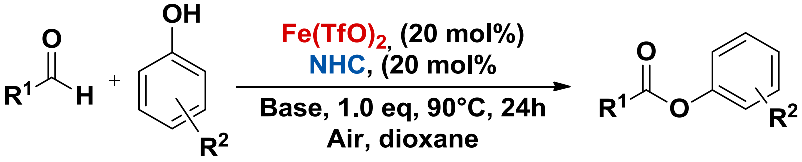


Up to 85% yield
Up to 98% ee
Up to 20:1 dr

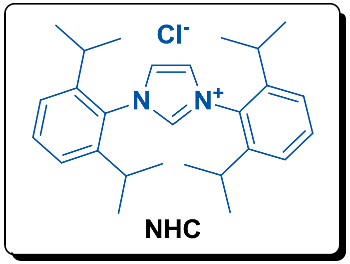
Raup D., Cardinal-David B., Holte D., Scheidt K. A. *Nat. Chem.* **2010**, 2, 766

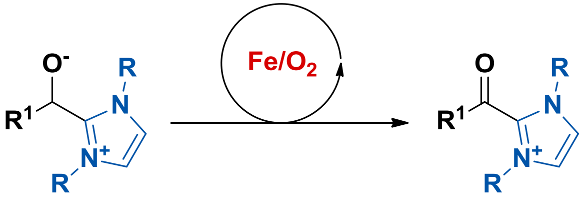
NHC– Transition metal

Gois – 2011



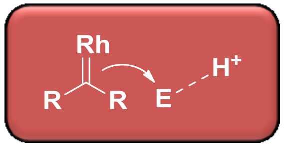
R^1 = Ar, cynnamyl
R^2 = H, Me, EWG



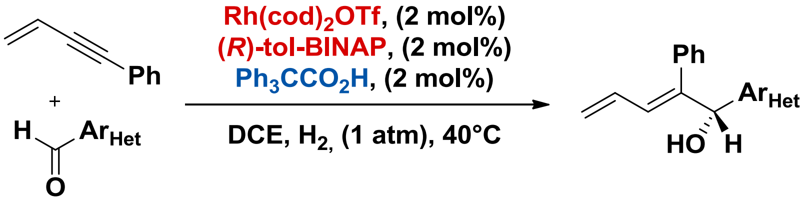


Reddy R. S., Rosa J. N., Veiros L. F., Caddick S., Gois P. M. P. *Org. Biomol. Chem.* **2011,** 9, 3126

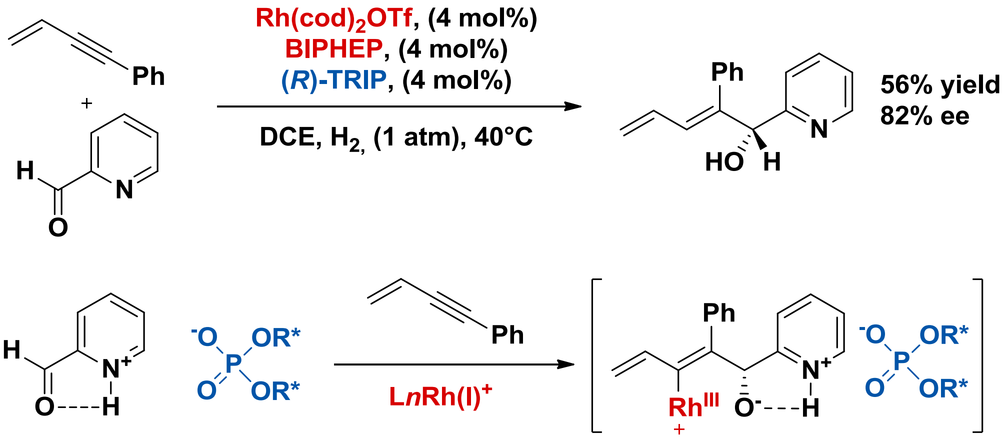
Brønsted acid– Rhodium carbene



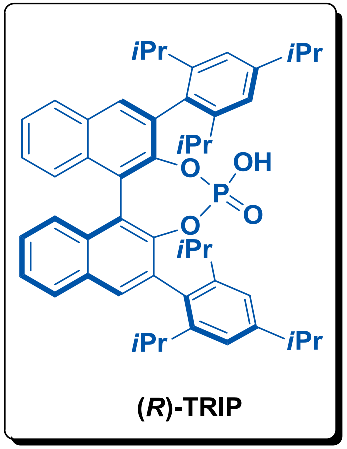
Krische – 2006



Up to 98% yield
Up to 99% ee



56% yield
82% ee

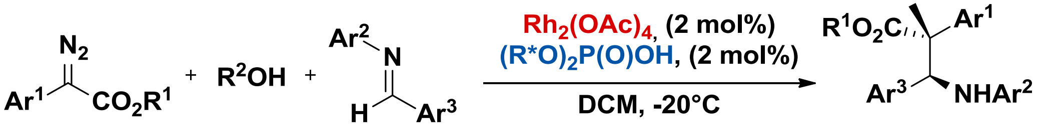


(*R*)-TRIP

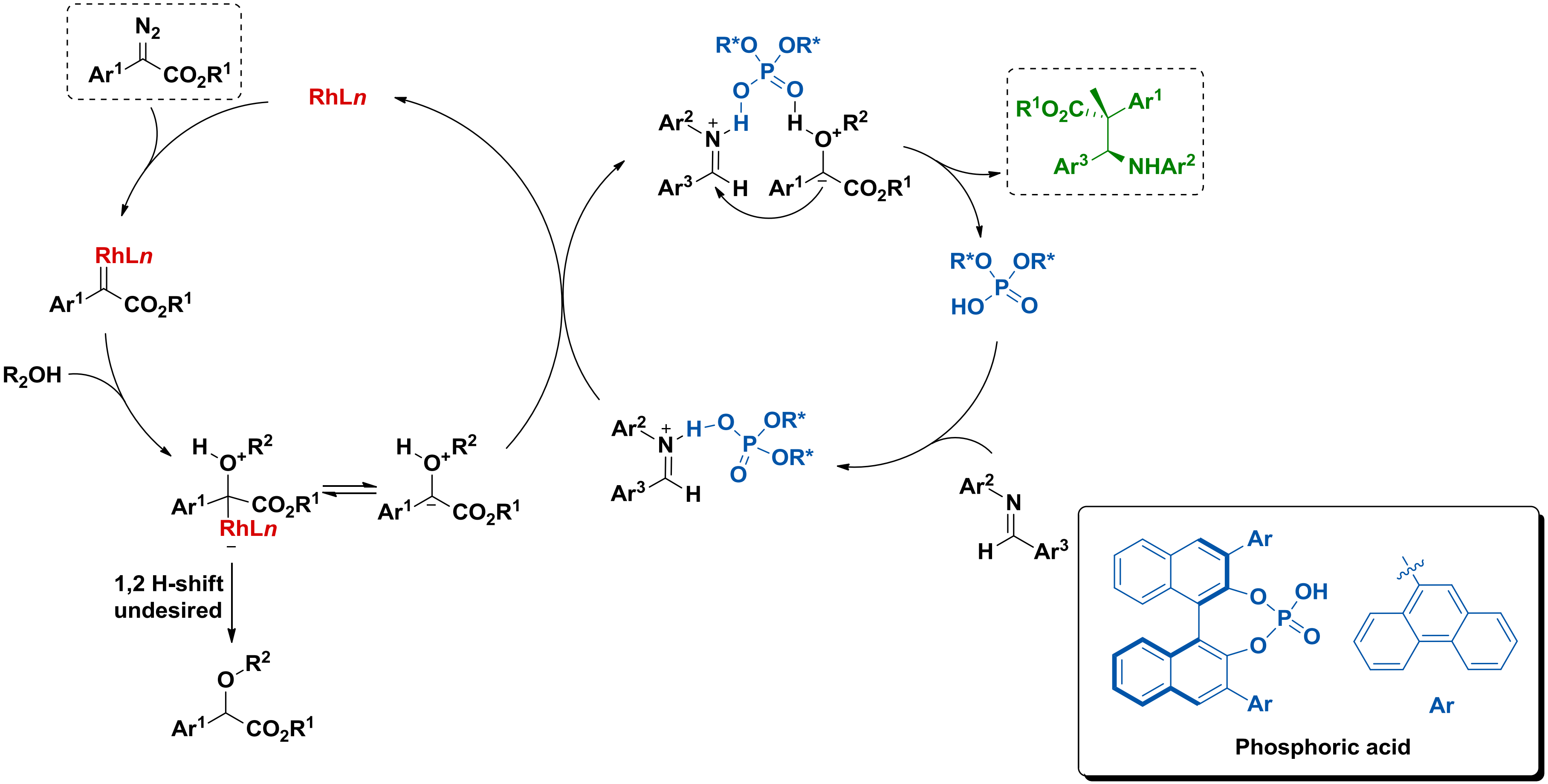
V. Komanduri , M. J. Krische , *J. Am. Chem. Soc.* **2006** , 128 , 16448 –16449 .

Brønsted acid– Rhodium carbene

Gong, Hu – 2008



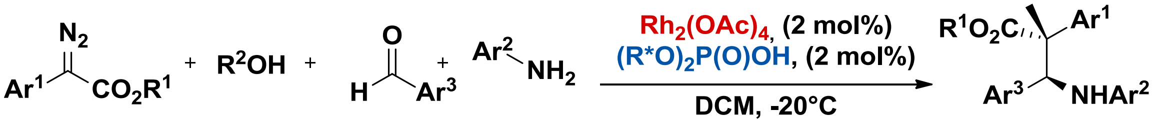
Up to 98% yield
Up to >99:1 dr
Up to 99% ee



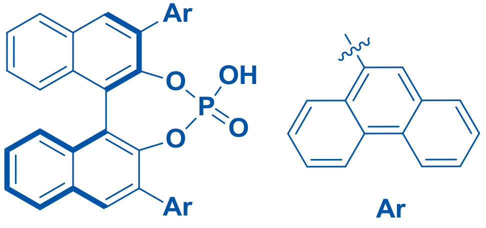
W.-H. Hu , X.-F. Xu , J. Zhou , W.-J. Liu , H.-X. Huang , J. Hu , L.-P. Yang , L.-Z. Gong , *J. Am. Chem. Soc.* **2008** , 130 , 7782 –7783 .

Brønsted acid– Rhodium carbene

Hu – 2008



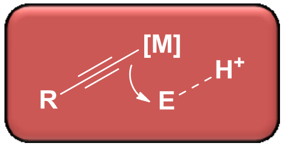
Up to 98% yield
Up to >99:1 dr
Up to 99% ee



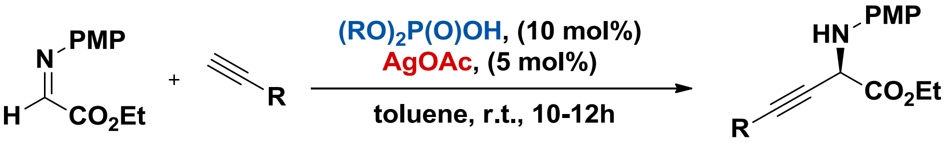
Phosphoric acid

X.-F. Xu , J. Zhou , L.-P. Yang , W.-H. Hu , *Chem. Commun*. **2008** , 6564 –6566

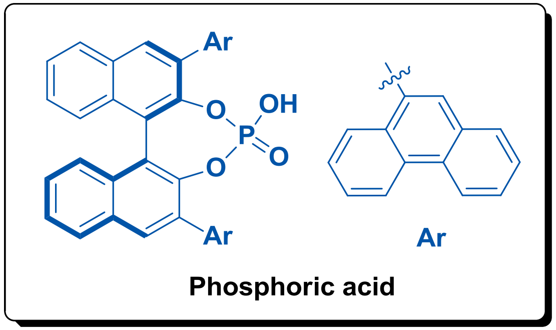
Brønsted acid– Transition metal



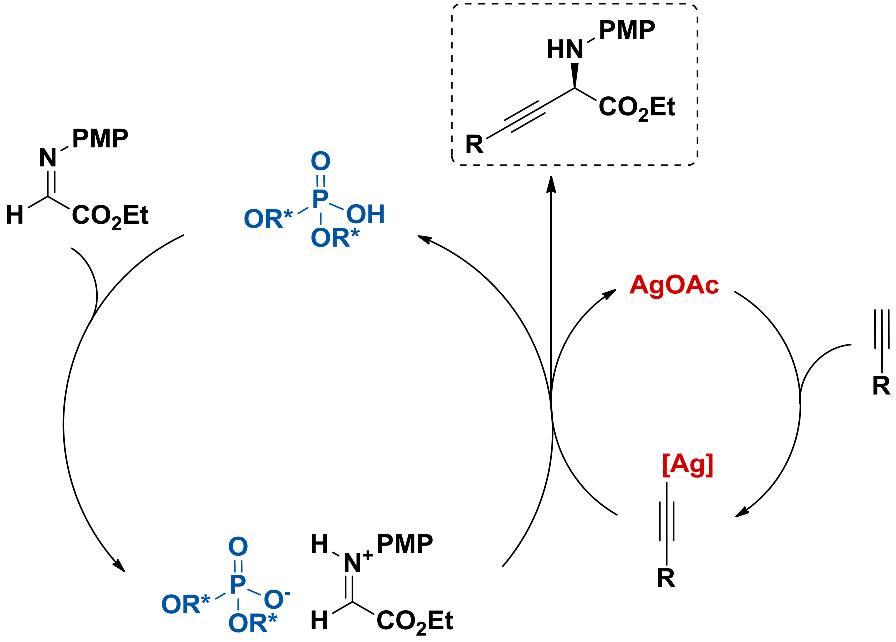
Rueping – 2007

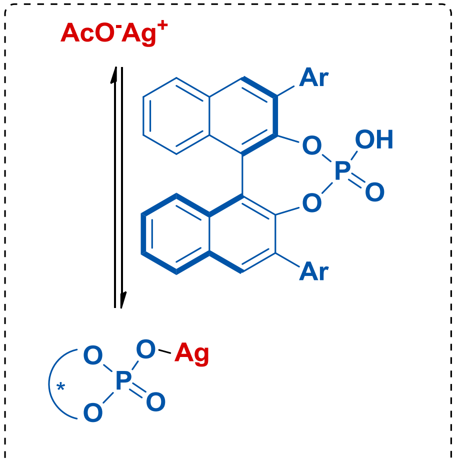


Up to 90% yield
Up to 92% ee



Phosphoric acid



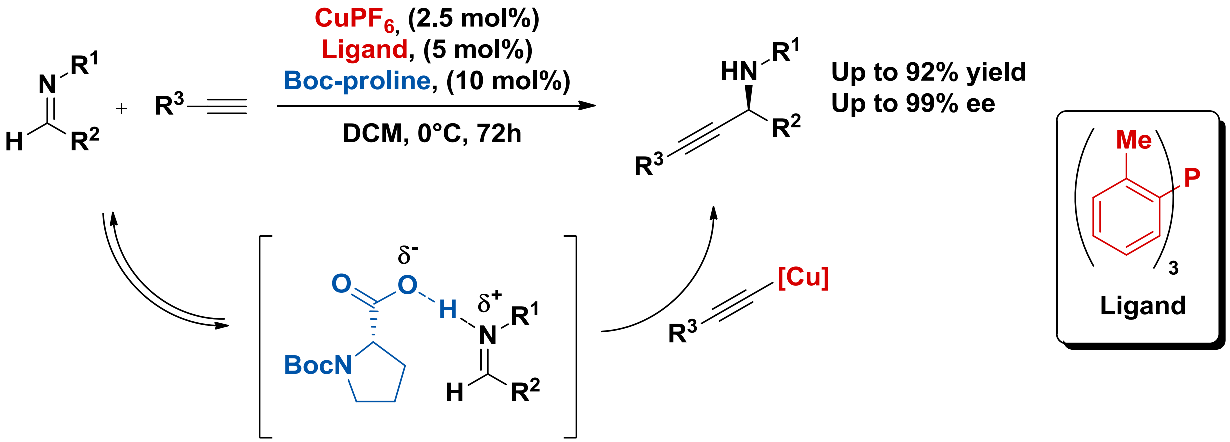


Alternative stereocontrol pathway

M. Rueping , A. P. Antonchick , C. Brinkmann , *Angew. Chem. Int. Ed*. **2007** , 46 , 6903 –6906

Brønsted acid– Transition metal

Arndsten – 2009

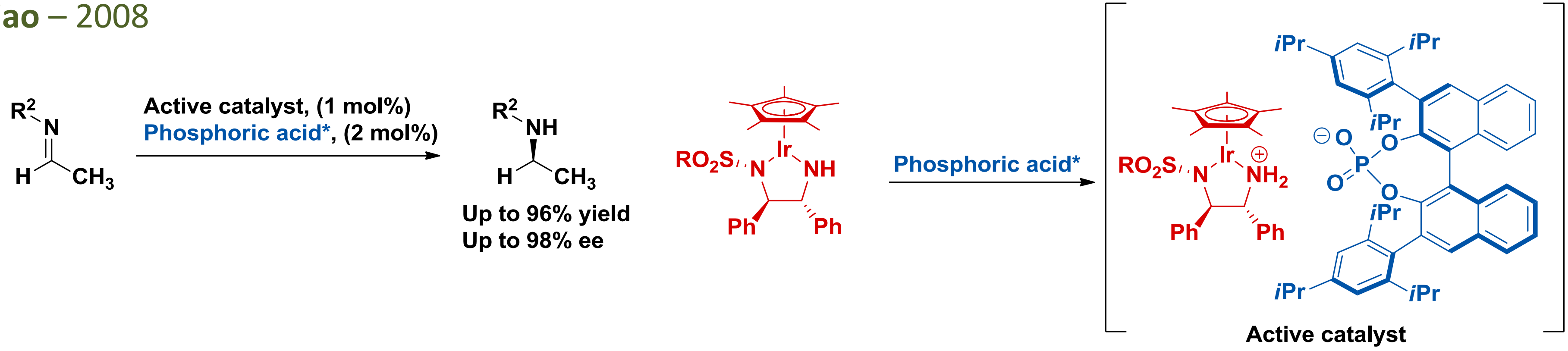


Up to 92% yield
Up to 99% ee

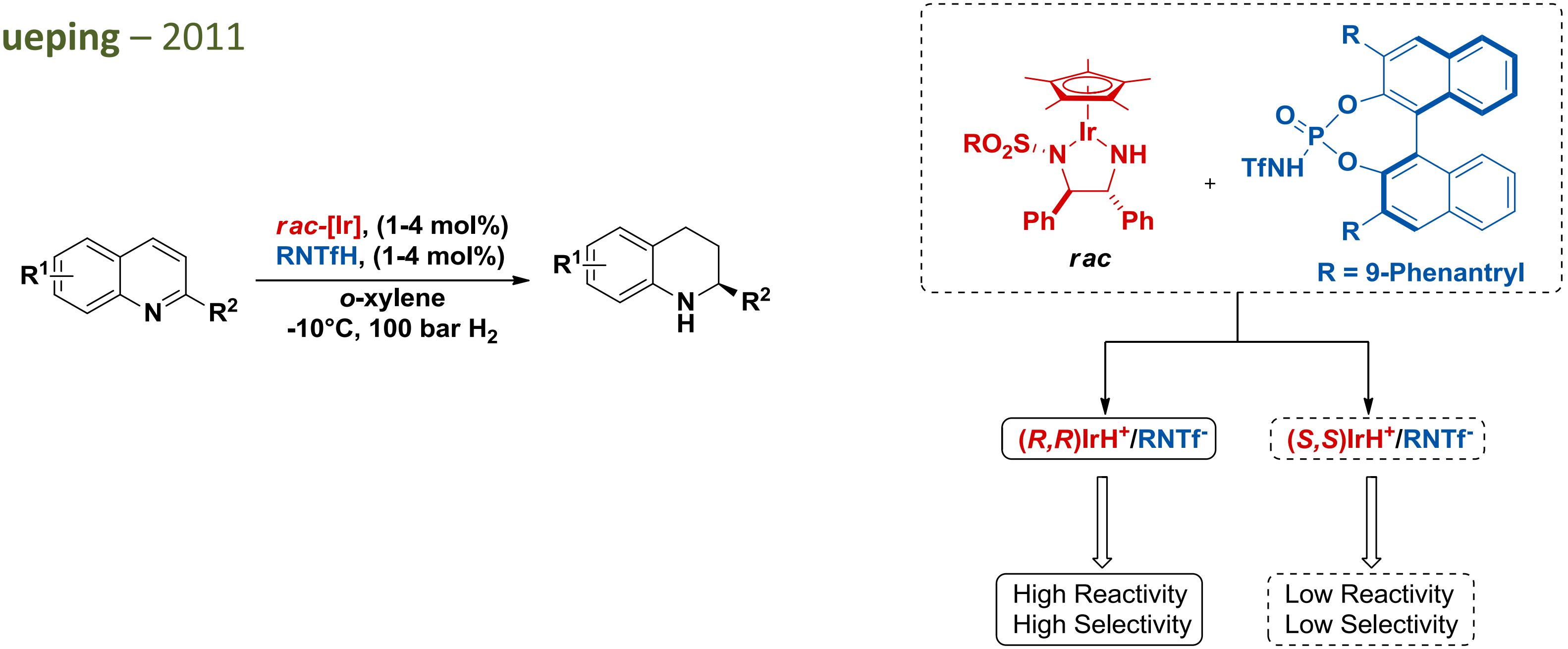
Y. Lu , T. C. Johnstone , B. A. Arndtsen , *J. Am. Chem. Soc.* **2009** , 131 , 11284 –11285
HIGHLIGHT : Pedro de Armas, David Tejedor, Fernando García-Tellado *Angew. Chem. Int. Ed*. **2010**, 49, 1013 – 1016

Brønsted acid– Transition metal

Xiao – 2008



Rueping – 2011

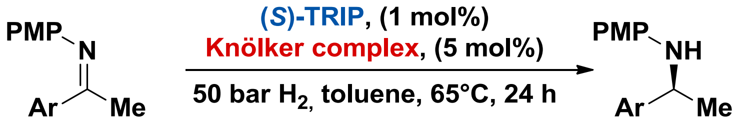


Li C., Wang C., Villa-Marcos B., Xiao J. *J. Am. Chem. Soc.* **2008**, 130, 14450

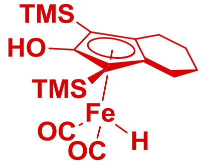
Magnus Rueping, René M. Koenigs, *Chem. Commun*., **2011**, 47, 304-306

Brønsted acid– Transition metal

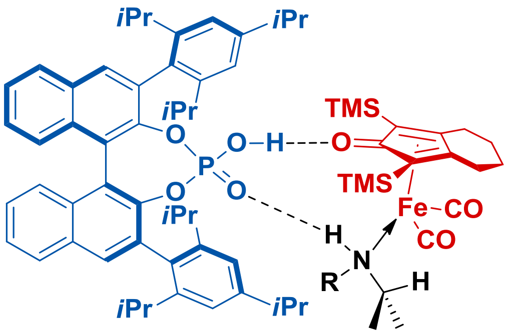
Beller – 2011



Up to 99% yield
Up to 98% ee



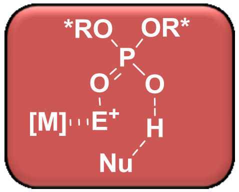
Knölker complex



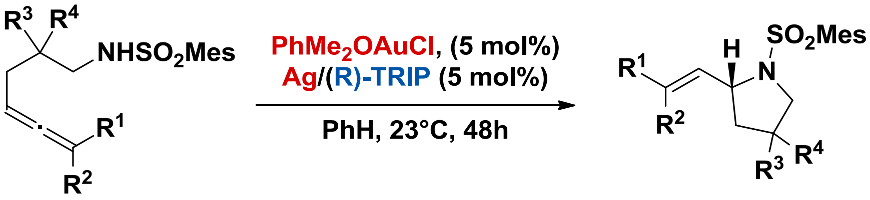
Proposed intermediate

Zhou S., Fleischer S., Junge K., Beller M. *Angew. Chem. Int. Ed.* **2011**, 50, 5120

Brønsted acid– Transition metal

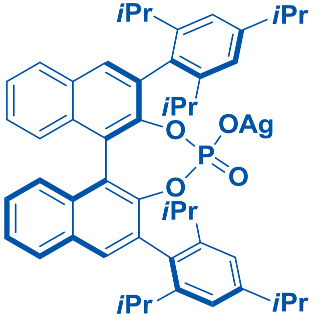


Toste – 2007

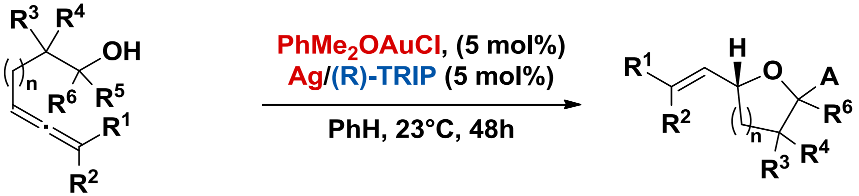


$R^1 = R^2 =$ alkyl
$R^3 = R^4 =$ H, alkyl

Up to 97% yield
Up to 98% ee



Ag-(*R*)-TRIP



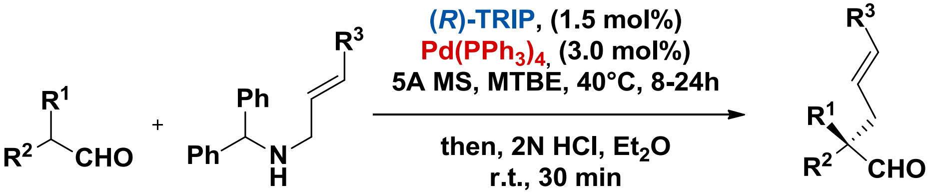
$R^1 = R^2 =$ alkyl
$R^3 = R^4 =$ H, Me
$R^5 = R^6 =$ H, Me

Up to 91% yield
Up to 99% ee

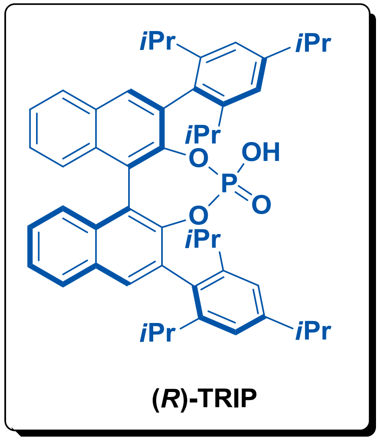
G. L. Hamilton , E. J. Kang , M. Mba , F. D. Toste , *Science* **2007** , 317 , 496 –499 .

Brønsted acid– Transition metal

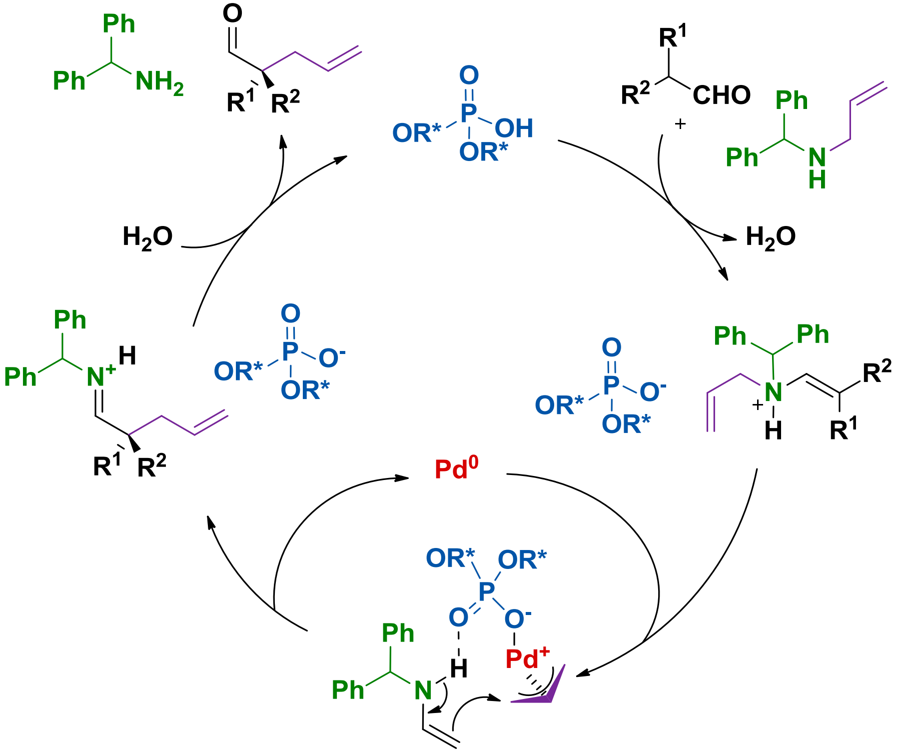
List – 2007



Up to 90% yield
Up to 97% ee



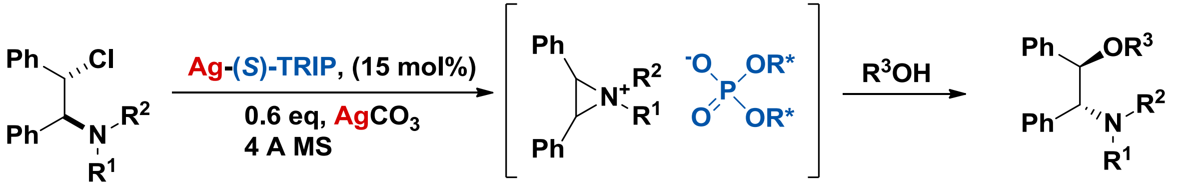
(R)-TRIP



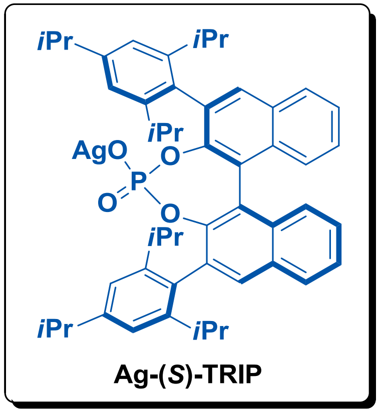
S. Mukherjee , B. List , *J. Am. Chem. Soc.* **2007** , 129 , 11336 –11337

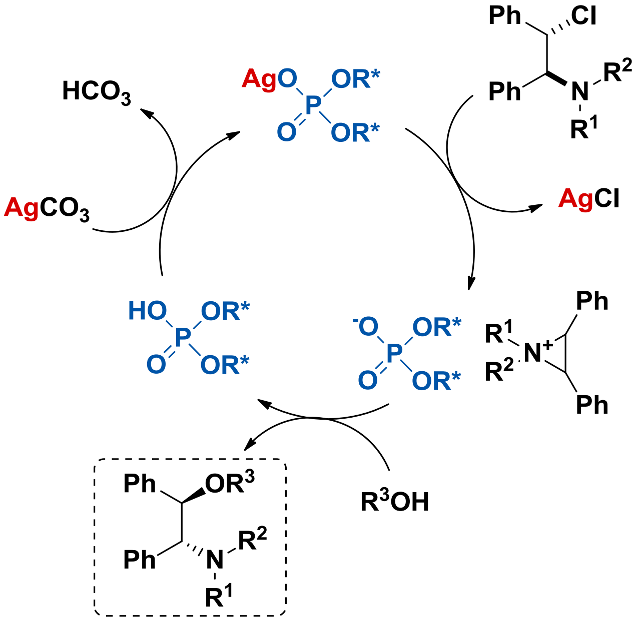
Brønsted acid– Transition metal

Toste – 2008



Up to 95% yield
Up to 99%ee

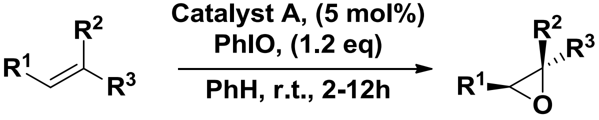




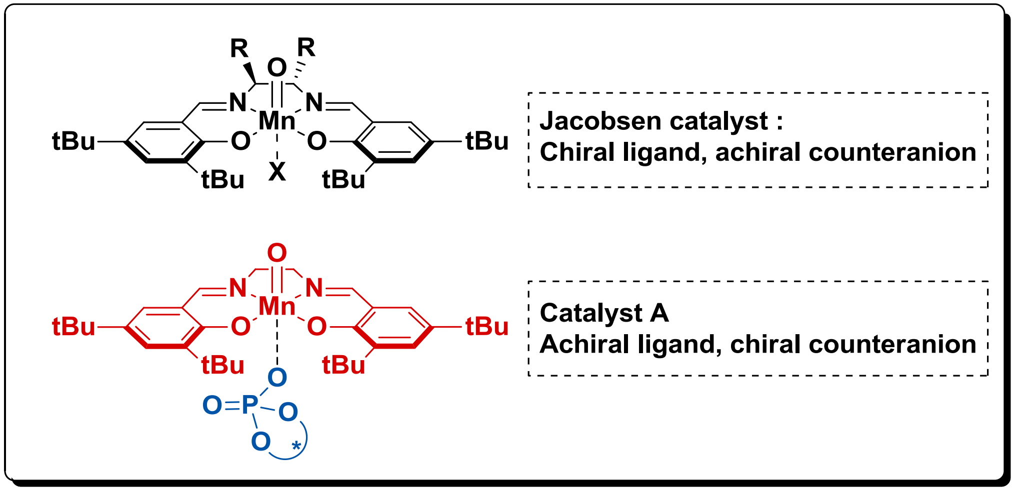
G. L. Hamilton, T. Kanai, F. D. Toste, *J. Am. Chem. Soc*. **2008**, 130, 14984–14985.

Brønsted acid– Transition metal

List – 2010



Up to 98% yield
Up to 96% ee



Jacobsen catalyst :
Chiral ligand, achiral counteranion

Catalyst A
Achiral ligand, chiral counteranion

Sc, Inanaga, ***fluorination***
Yb, Inanaga, ***Michael addition***
Li, Ishiara, ***cyanosilation***
Fe, Huang, ***Friedel-Craft***
Mg, Luo, ***Friedel-Craft***
Zn, Charette, ***Cyclopropanation***
Cu, Shi, ***diamination***
Na, Feng, ***cyanosilation***
Ca, Ishiara, ***Mannich***

S. Liao, B. List, *Angew. Chem.* **2010**, 122, 638–641;
Rueping et al. *Chem. Eur. J.* **2010**, 16, 9350 – 9365

Perspectives

-Attractive concept

-Simplifying catalyst evaluation

-Reactive intermediates present in low concentration

-Lot of combinations that have to be discovered

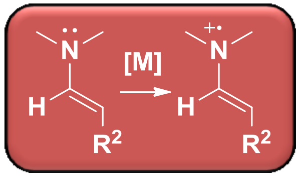
- Mechanistic studies

Thank you for your attention

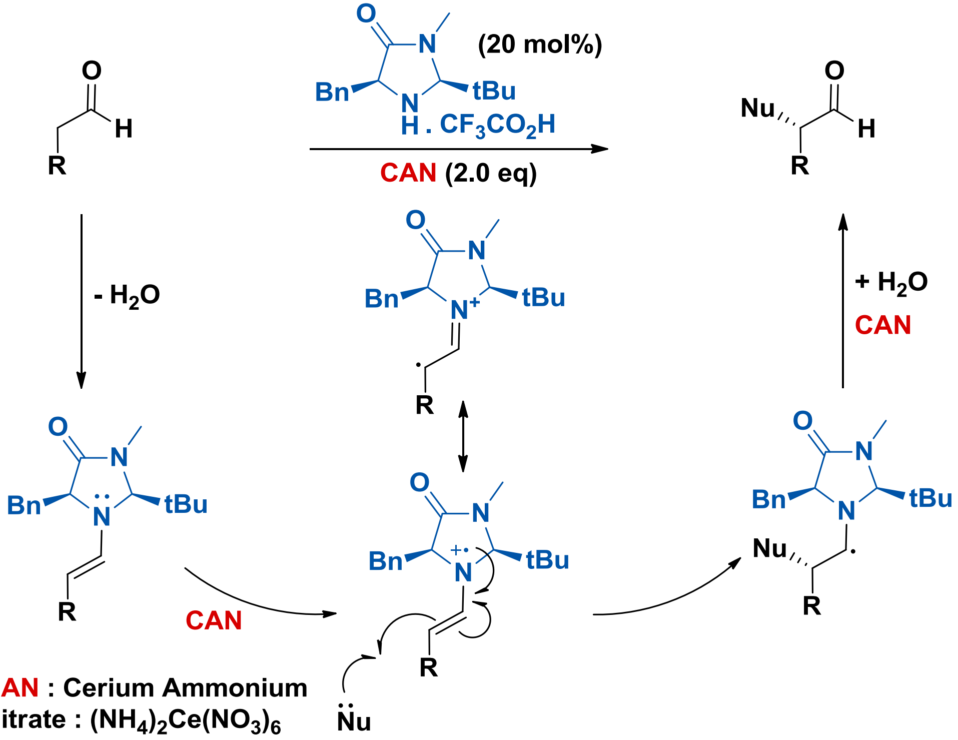
Questions

- 1: What is the difference of reactivity between the MacMillan SOMO and Photoredox-catalysis?
- In the case of a cationic-gold complex, why the chiral-counteranion strategy is particularly interesting in order to induce chirality?

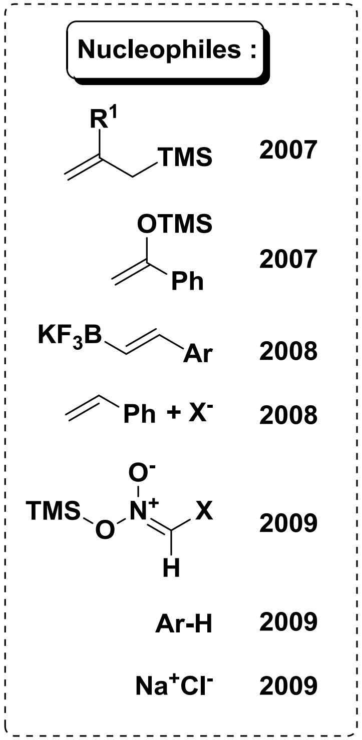
Amine – Oxidant metal



MacMillan – SOMO catalysis



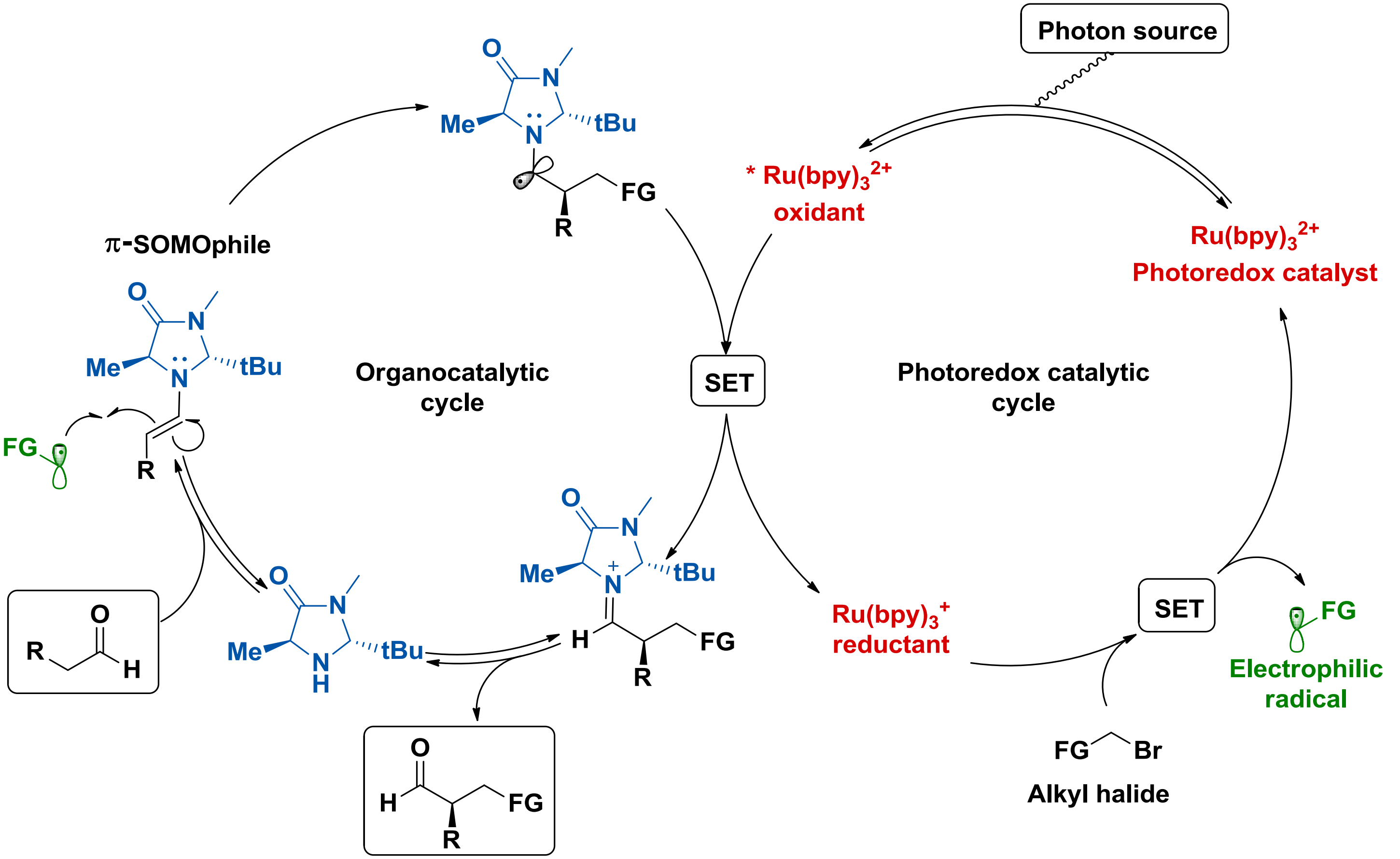
CAN : Cerium Ammonium Nitrate : $(NH_4)_2Ce(NO_3)_6$

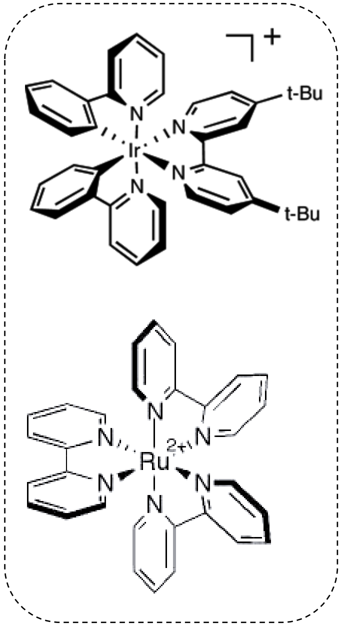


TJ. J. Devery III, J. C. Conrad, D. W. C. MacMillan, R. A. Flowers II *Angew. Chem. Int. Ed*. **2010**, 49, 6106-6110

Amine – Photoactivated metal

MacMillan – Photoredox catalysis





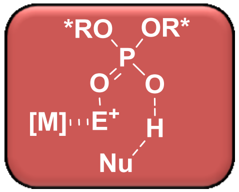
Ru and Ir catalysts

pictures from original document

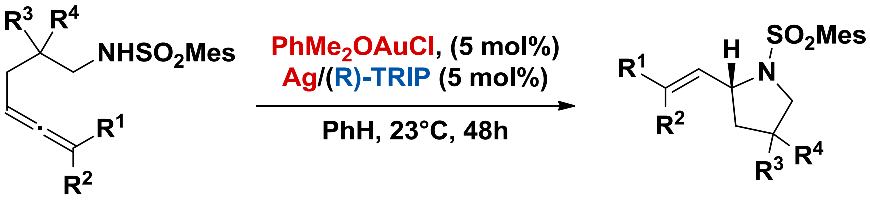
Questions

- What is the difference of reactivity between the MacMillan SOMO and Photoredox-catalysis?
- In the case of a cationic-gold complex, why the chiral-counteranion strategy is particularly interesting in order to induce chirality?

Brønsted acid– Transition metal

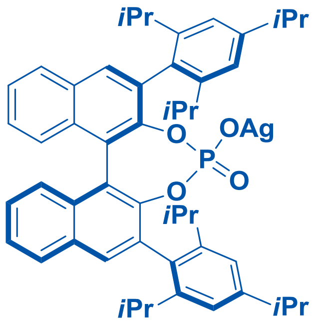


Toste – 2007

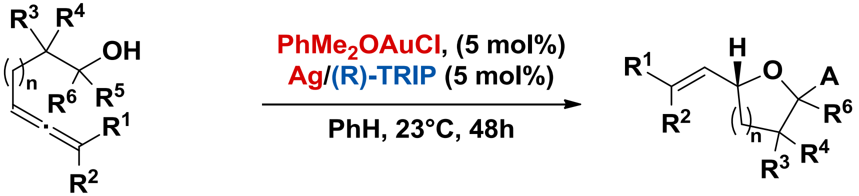


$R^1 = R^2$ = alkyl
$R^3 = R^4$ = H, alkyl

Up to 97% yield
Up to 98% ee



Ag-(*R*)-TRIP



$R^1 = R^2$ = alkyl
$R^3 = R^4$ = H, Me
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Up to 91% yield
Up to 99% ee

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

LABORATOIRE DE SYNTHESE
ET PRODUITS NATURELS

ENLIGHTENMENT, RADICAL PATHWAY TOWARDS COMPLEX STRUCTURES

Jean-Baptiste Gualtierotti

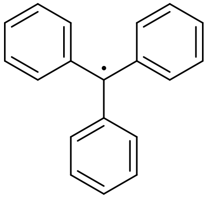
FRONTIERS IN CHEMICAL SYNTHESIS: TOWARDS SUSTAINABLE CHEMISTRY

SESSION III: ORGANOCATALYSTS AND RADICALS

LAYOUT

- **Historical Background**
- **Methods for the formation of complex structures through total synthesis**
  - Photo-cycloadditions
  - Photo-rearrangements
  - Norrish 1 and 2
  - Photo-extrusion
  - Photo-oxidation
  - Photo-protecting groups
- **Summary and questions**

PRIMARY RADICALS



- ***Gomberg (U. of Michigan 1900): first who recognized he had stumbled the evidence of a free radical***

- ***1911 enough evidence for the community to accept their existence***

- **Giacomo Ciamician, by some called the father of photochemistry, proposed the concept of solar energy as green source to replace societies dependency on coal (1912)**

- ***1929: Paneth and*** **Hofeditz produced the methyl free radical, CH_3**

- **In 1933, Morris Kharasch and his student, Frank Mayo, invoked a free-radical mechanism and discovered "the peroxide effect"**

- ***Evolved towards plastic, understanding of many processes (ie oxidative stress) and so on***

- ***1970's and onwards: truly used in synthesis i.e Barton reaction in steroid synthesis***

On the arid lands there will spring up industrial colonies without smoke and without smokestacks;
forests of glass tubes will extend over the plains and glass buildings will rise everywhere;
inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants,
but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature,
for nature is not in a hurry and mankind is.

Giacomo Ciamician *science* **36,** 385***,* 1912**

A SINGULAR ENTITY

Advantageous over ionic counterparts

- More FG tolerant
- Lesser pH dependence
- Potential cascade reactions
- Can acess congested «areas»

In addition light based chemistry

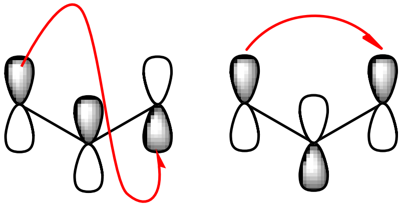
$$\text{Atom economy} = \frac{Mw\ product}{\sum Mw\ reactants}$$

Mw light << Standard reagents

$$\text{E factor} = \frac{m\ overall\ waste}{m\ \ product}$$

Light waste?

Photochemical reactions lead to a reversal of terminal symmetry relation-ships and reversal of stereospecificity Woodward-Hoffmann rules

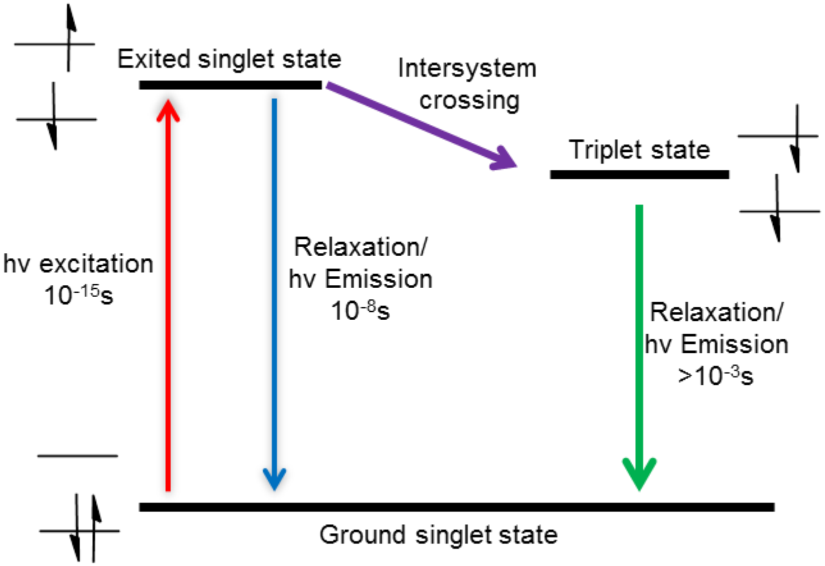


Thermal [1.3] antarafacial sigmatropic shift

Photo [1.3] superafacial sigmatropic shift

PHOTO-EXCITATION PATHWAYS

Simplified Jablonski diagram:



Exited singlet state

Intersystem crossing

Triplet state

hv excitation 10^{-15}s

Relaxation/ hv Emission 10^{-8}s

Relaxation/ hv Emission $>10^{-3}$s

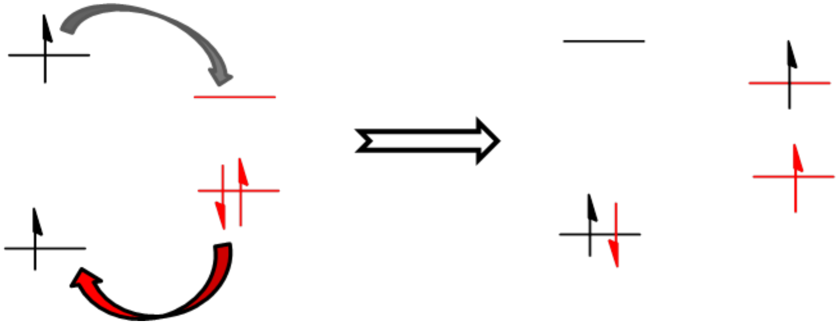
Ground singlet state

Quantum yield:

$$\Phi = \frac{Nbre\ events}{Nbre\ of\ photons\ absorbed}$$

Sensitization by energy transfer

Dexter or FRET mechanism



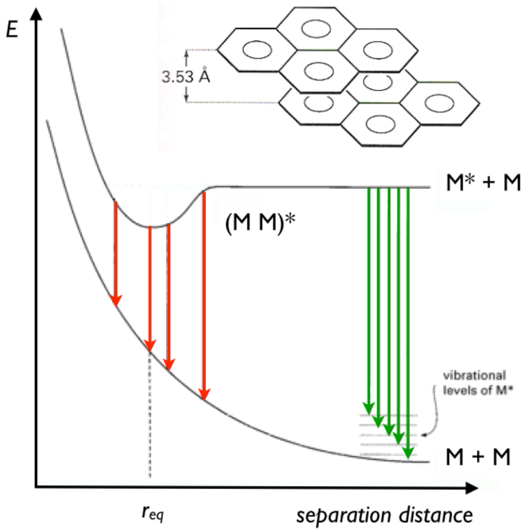
Donor: sensitizer

Acceptor: substrate

EXIPLEX

Complex formed by the stabilizing interactions between ground state molecule and exited state molecule

M + M*: eximer
M + N*: exiplex



TOWARDS COMPLEX STRUCTURES THROUGH RADICALS

Questions

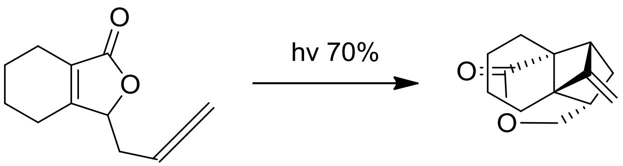
How to control the formation of an intermediate singlet or triplet state?

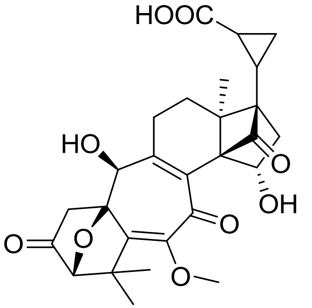
What reaction media are available for the following reactions?

2+2 CYCLOADDITIONS

Most common photochemical reaction, based on excitation to the reactive long lived ππ* triplet (biradical) state

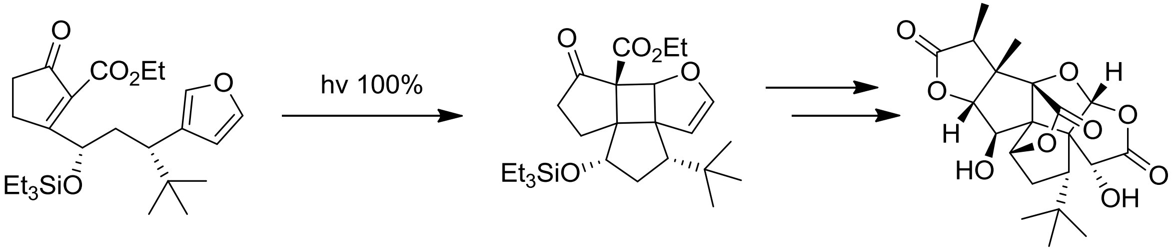
Photosensitivisation oft needed for ISC





Solanoclepin A

Buu Hue, B. T.; Dijkink, J.; Kuiper, S.; van Schaik, S.; van Maarseveen, J. H.; Hiemstra, H *Eur. J. Org. Chem*. **2006,** 127-137.

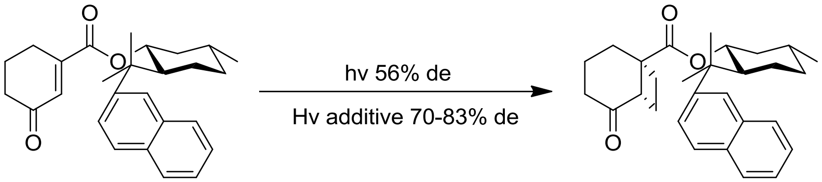


Ginkgolide B 1

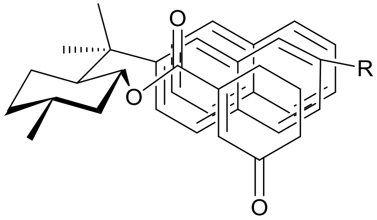
Crimmins, Michael T.; Pace, Jennifer M.; Nantermet, Philippe G.; Kim-Meade, Agnes S.; Thomas, James B.; Watterson, Scott H.; Wagman, Allan S.. *J. Am. Chem. Soc.* **2000,** *122*, 8453-8463

2+2 CYCLOADDITIONS

Additives to enhance diaselectivity



Major isomer



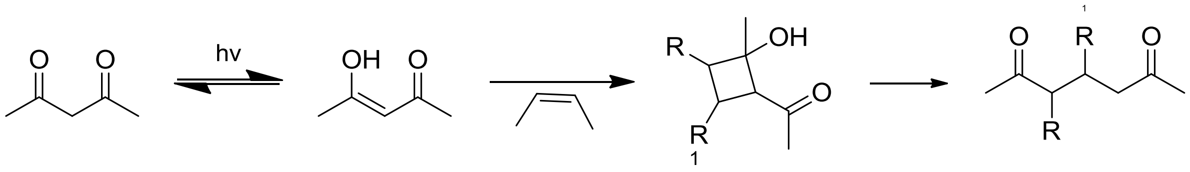
exiplex intermediate

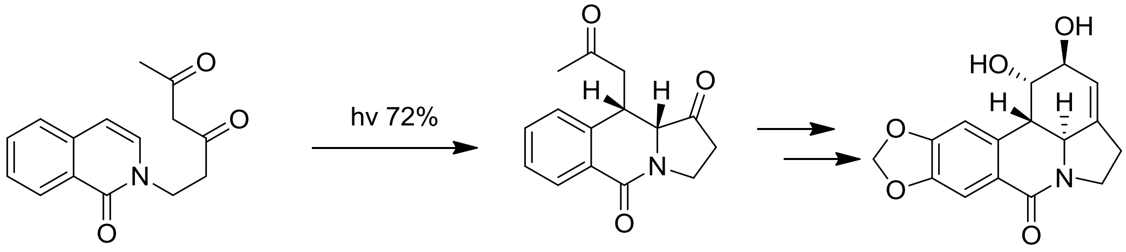
Tsutsumi, K.; Nakano, H.; Furutani, A.; Endou, K.; Merpuge, A.; Shintani, T.; Morimoto, T.; Kakiuchi, K., *J. Org .Chem* **2004,** *69* (3), 785-789.

2+2 CYCLOADDITIONS

De Mayo varient

Enol followed by retro-aldol





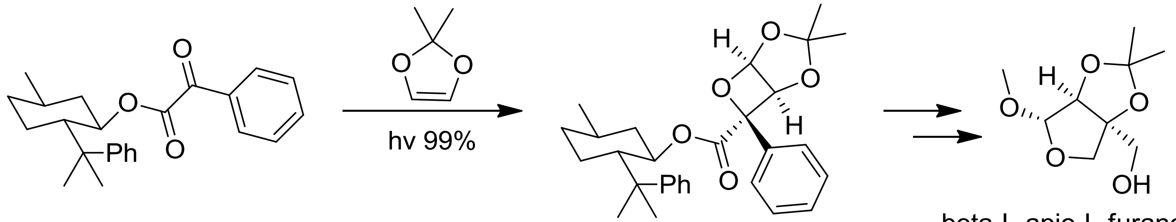
(-)-Lycorine

David E. Minter and, Christopher D. Winslow *J.Org.Chem* **2004** *69* (5), 1603-1606

2+2 CYCLOADDITIONS

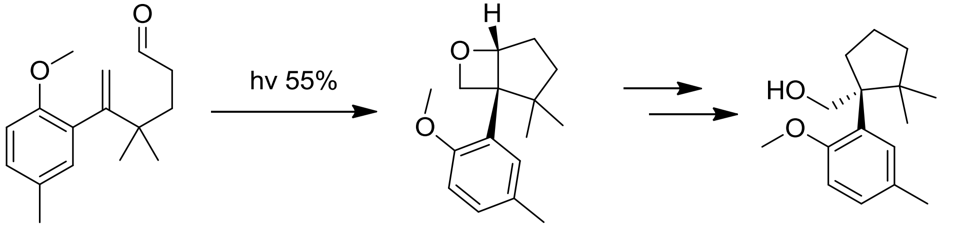
Paternó-Büchi varient

Hetero 2+2 cycloadditon, passing through triplet nπ* or ππ* carbonyl biradical



beta-L-apio-L-furanoside

Nehrings, A.; Scharf, H.-D.; Runsink, J., *Angew Chem* **1985,** *97* (10), 882-883.



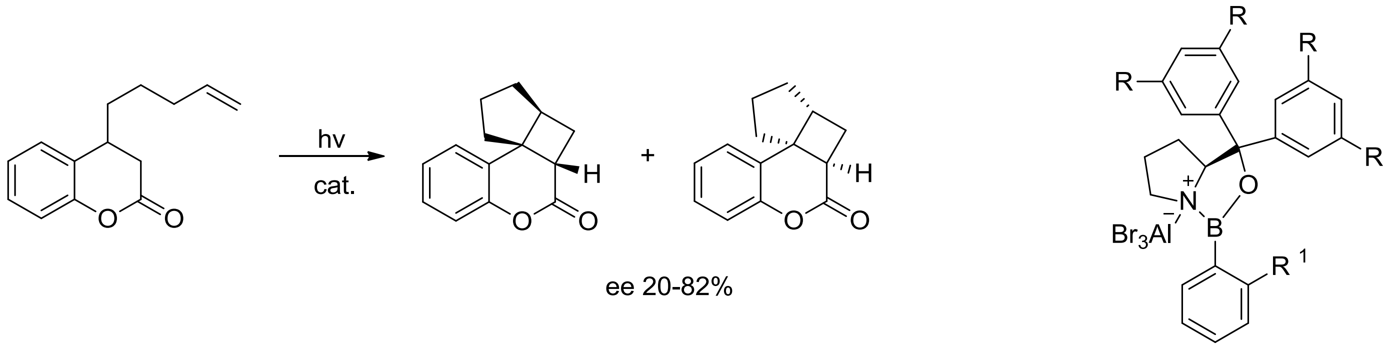
(+/-)-herbertendiol

Boxall, Richard J.; Ferris, Leigh; Grainger, Richard S. *Synlett* **2004** 2379-2381

2+2 CYCLOADDITIONS

Paternó-Büchi varient

Efforts to reach stero-control have been made



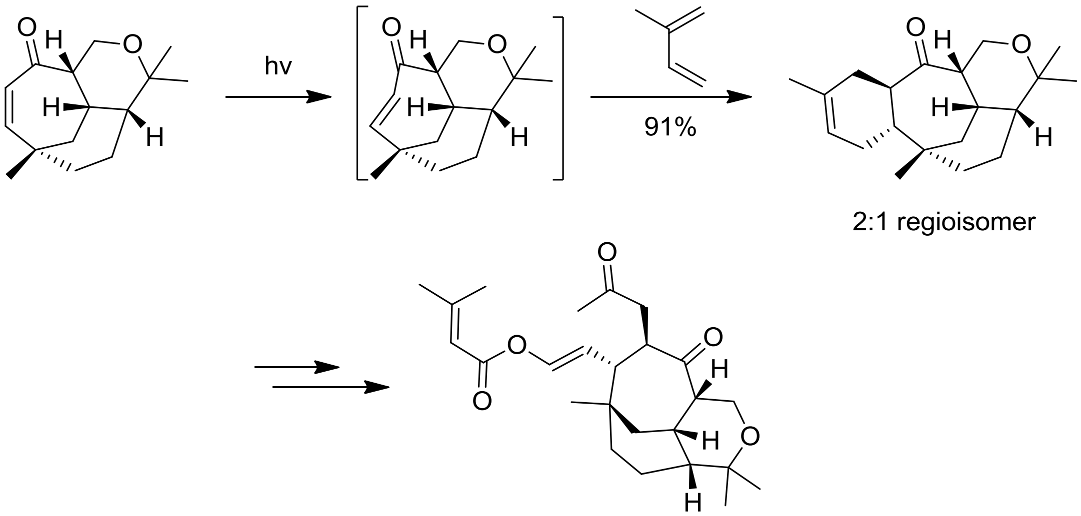
ee 20-82%

Guo, H.; Herdtweck, E.; Bach, T., *Angew. Chem. Int. Ed.* **2010,** *49* (42), 7782-7785.

4+2 CYCLOADDITIONS

Rarer: photoexcitation dealigns orbitals

Some examples exist: based on photoswitching rather than photoactivation

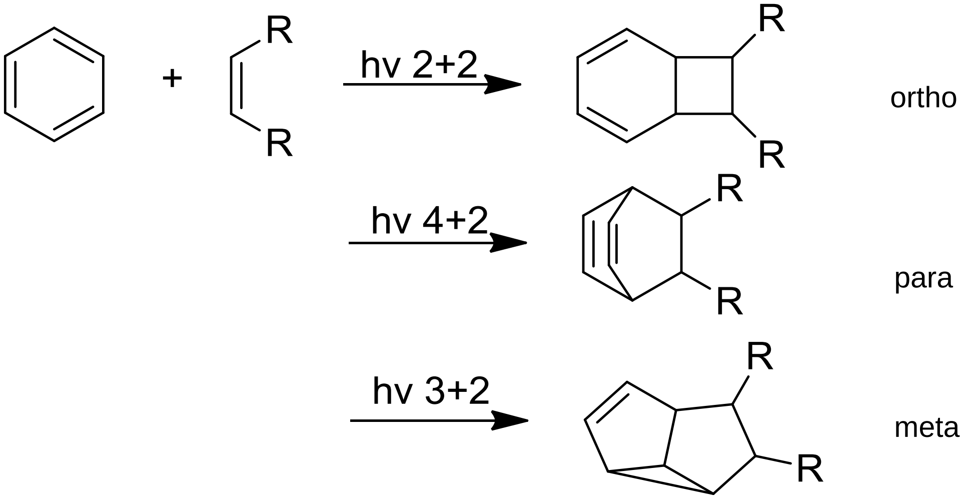


(+/-)-5-epi-10-epi-vibsarin E

Davies, H. M. L.; Loe, Ø.; Stafford, D. G., *Org Let* **2005,** *7* (25), 5561-5563.

PHOTOCYCLOADDITIONS

Additions on aromatic cores leading to the loss of aromaticity



Intra/inter selectivity:

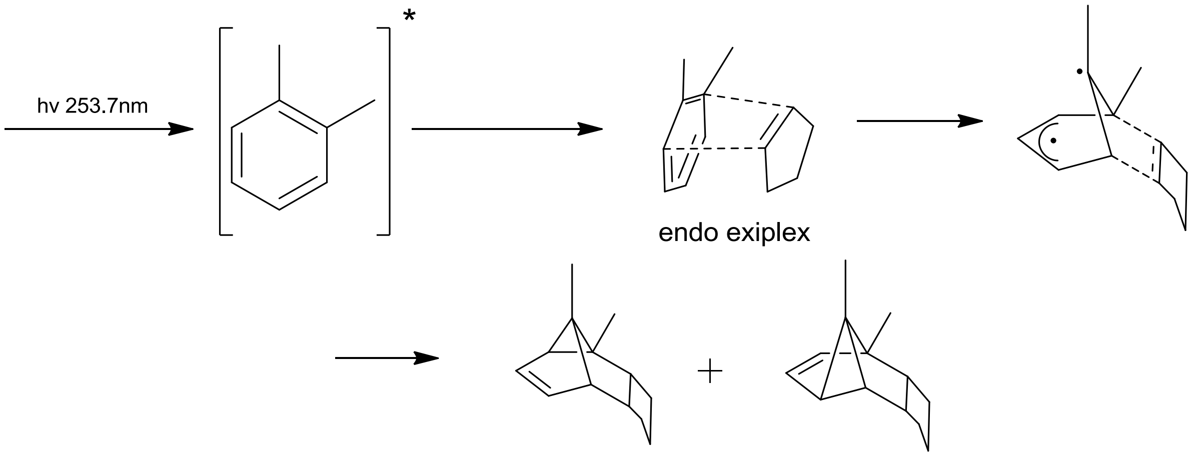
Regioselective issues: Controllable by tethering and substituant optimisation

Steroselective issues: endo prefered

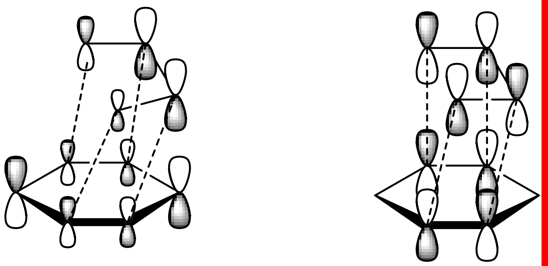
Facial selectivity: Structure dependent

PHOTOCYCLOADDITIONS

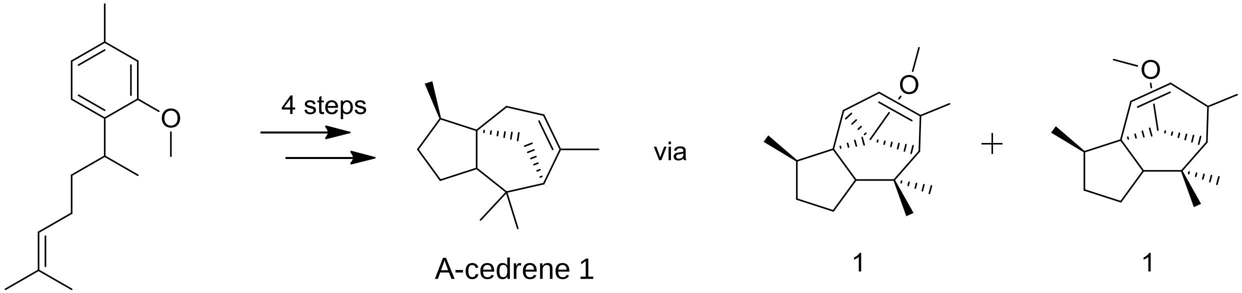
Meta-photocycloaddition



1 1.36



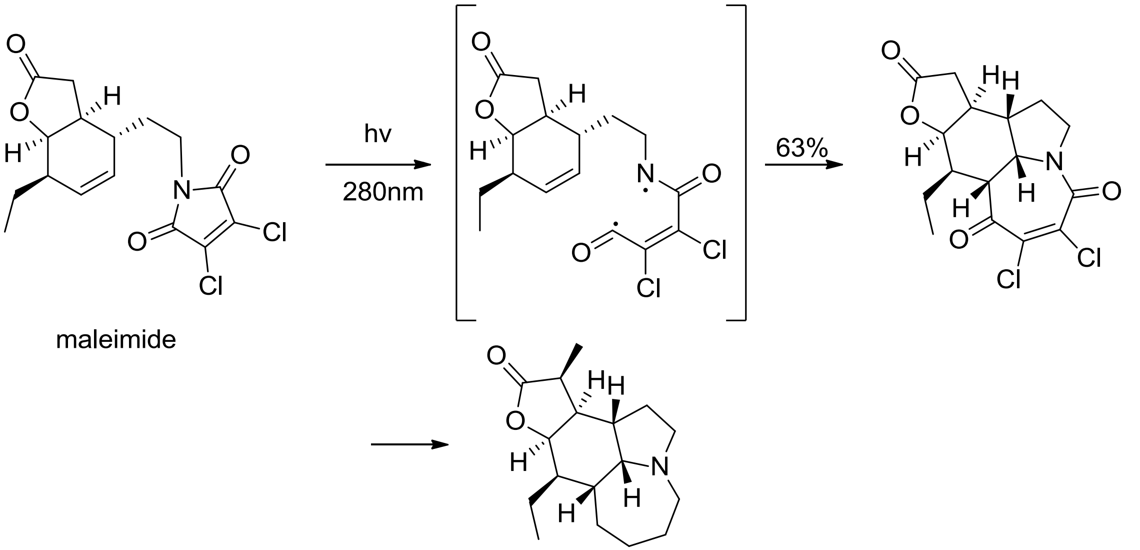
Endo selectivity



Howbert J.J. Wender P.A., *J. Am. Chem. Soc,* **103**, 688-690

Deicated review: Chappell, D.; Russell, A. T., *Organic & Biomolecular Chemistry* **2006,** *4* (24), 4409-4430.

5+2 PHOTOCYCLOADDITIONS



maleimide

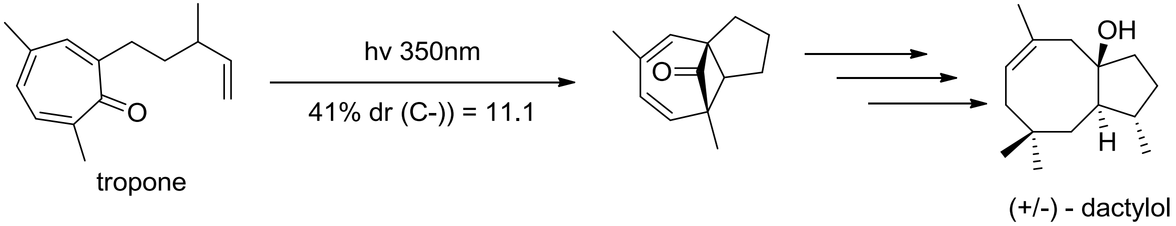
(+/-) - neostenine

Unusual intramolecular reaction, protecting group free

Lainchbury, M. D.; Medley, M. I.; Taylor, P. M.; Hirst, P.; Dohle, W.; Booker-Milburn, K. I., *J. Org. Chem*. **2008,** *73* (17), 6497-6505.

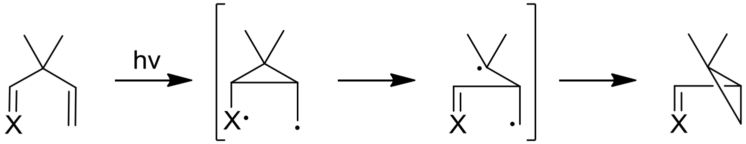
6+2 PHOTOCYCLOADDITIONS

6 + 2 also exists, although rare in synthesis

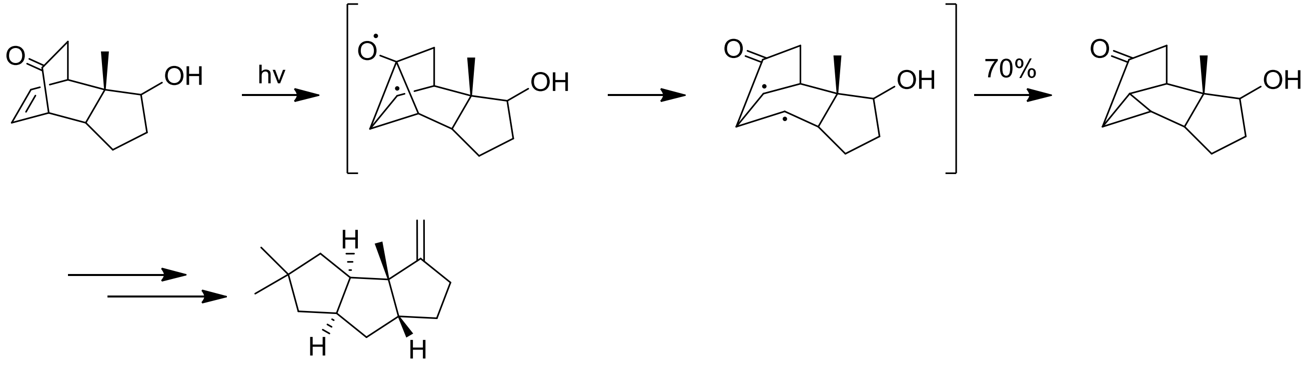


Feldman, K. S.; Wu, M. J.; Rotella, D. P., *J.Am.Chem.Soc* **1990,** *112* (23), 8490-8496.

PHOTO-REARANGEMENTS



X = CH2 Di-π-methane rearangement
X = O Oxa-Di-π-methane rearangement

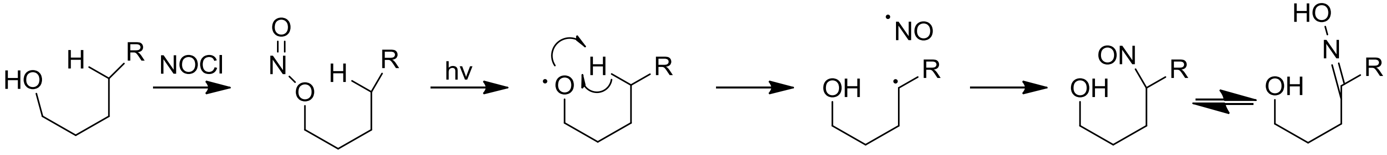


(+/-)-hirsutine

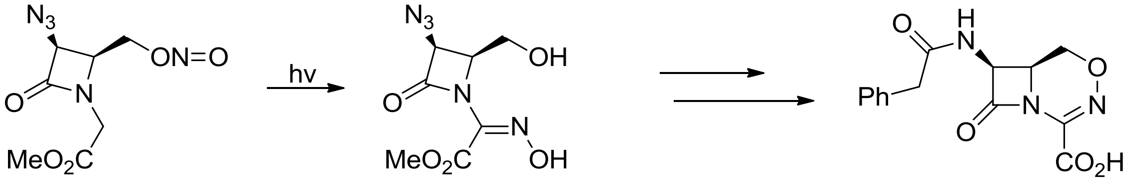
Singh, V.; Sahu, P. K.; Mobin, S. M., *Tetrahedron* **2004,** *60* (44), 9925-9930

PHOTO-REARANGEMENTS

Barton Nitrite ester reaction



5 hydrogen abstraction



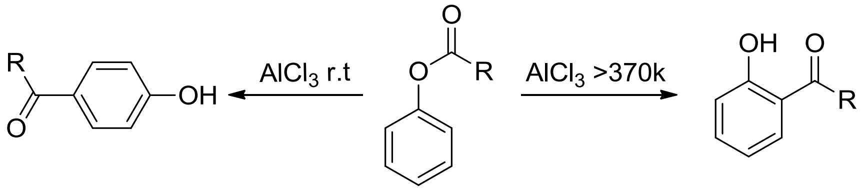
1-Dethia-3-aza-1-carba-2-oxacephem

Hakimelahi G.H., Li P., Moosavi-Movahedi A., Chamani J., Khodarahmi G. A., Ly T. W., Valiyev F., Leong M. K., Hakimelahi S., Shia K. Chao I. *Org. Biomol. Chem.*, 2003, **1**, 2461-2467

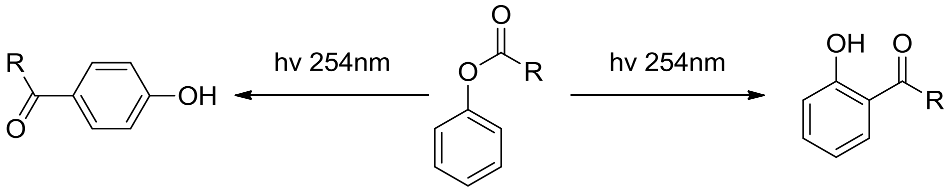
Similar to the Hofmann-Löffler-Freytag Reaction, amine instead of alcohol

PHOTO-FRIES REARANGEMENT

Strong lewis acid

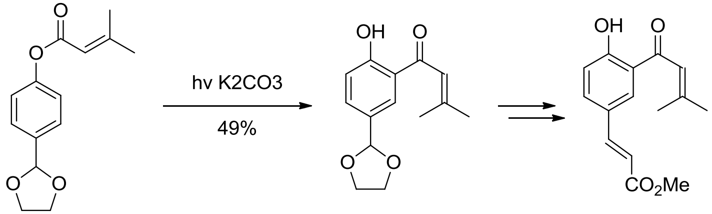


Mild alternative



Through homolitical cleavage
of the ester bond

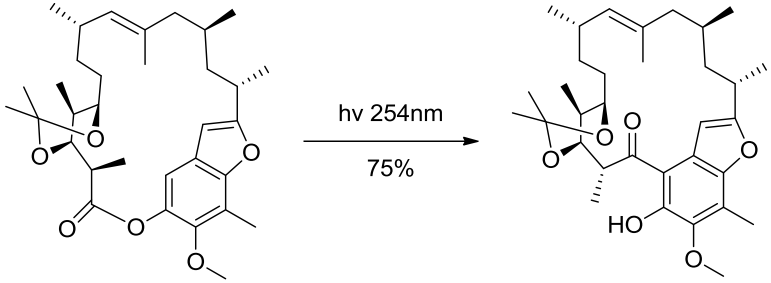
Regioselectivity dependant
on substituded positions



Capillarol

«standard» reaction did not work

Okada K., Suzuki R., Yokota T. *Biosci. Biotechnol, Biochem*. **1999**, 63, 257-260

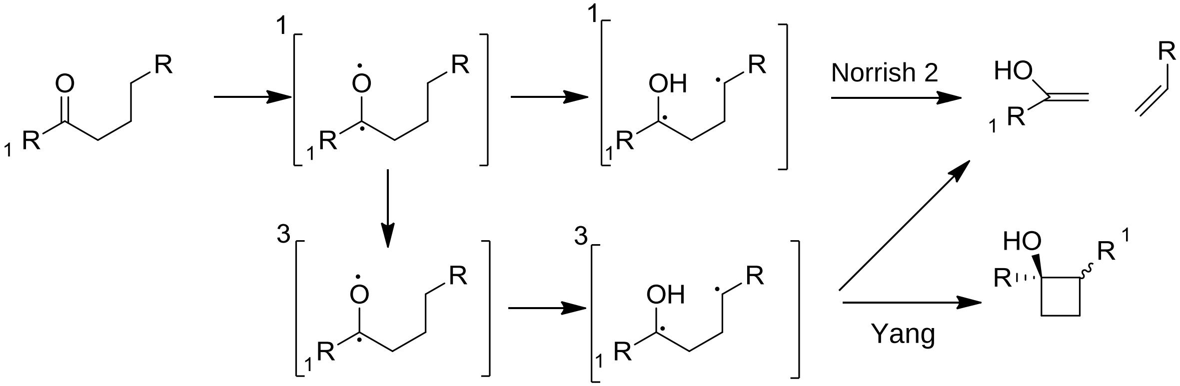


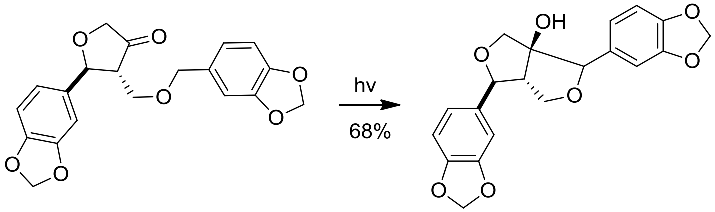
(-)-kendomycin

Standard Fries in general requires unencumbered arenes

Magauer, T.; Martin, H. J.; Mulzer, J., Angew Chem. Int. Ed. **2009,** *48* (33), 6032-6036.

NORRISH-YANG REACTION

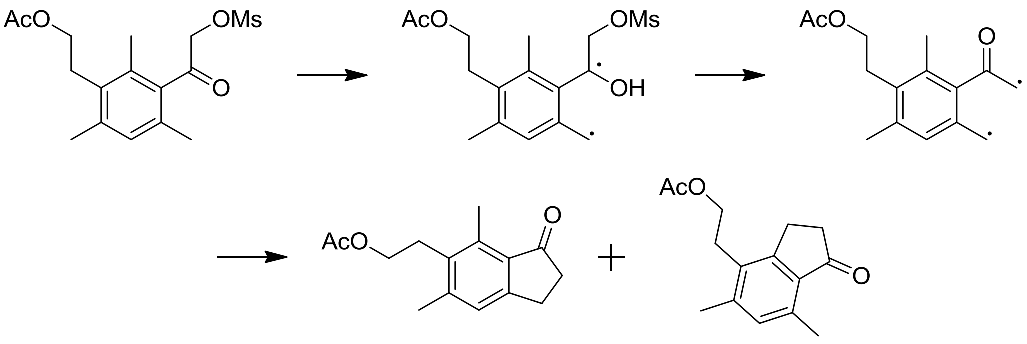




(+/-)-paulownin

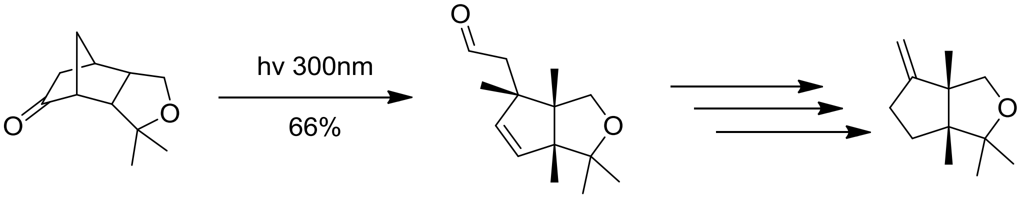
Kraus, G. A.; Chen, L., *J. Am. Chem. Soc* **1990,** *112* (9), 3464-3466.

Wessig, P; Teubner, J *Synlett* **2006,** 1543-1546



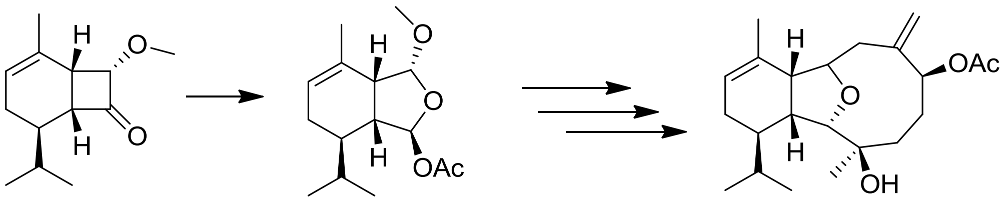
pterosin B

NORRISH CLEAVAGE



(+)-hop ether

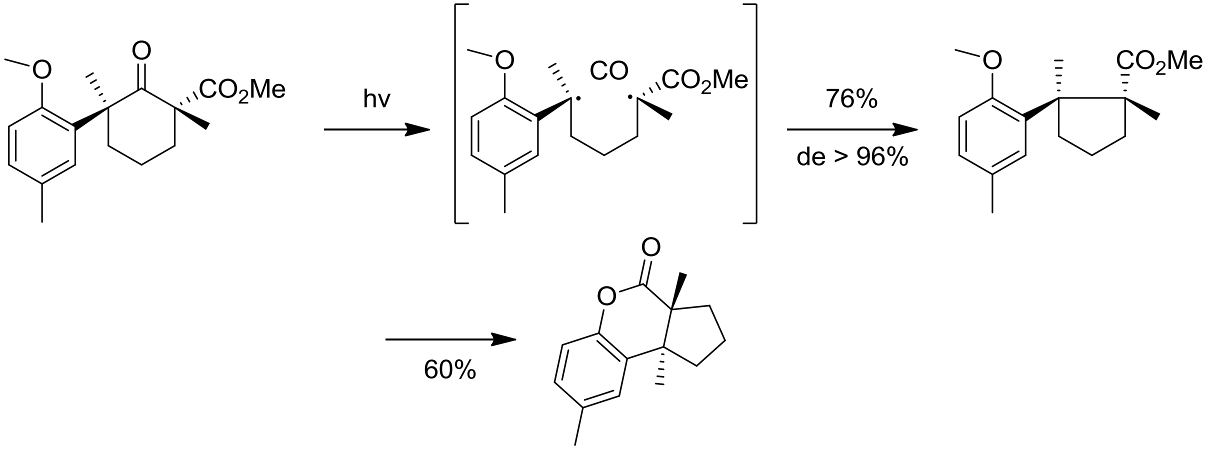
C.-H Lin, Y.-L. Su, H.-M. Tai, *Heterocycles* **2006**, 68, 771-777



(-)-deacetoxyalcyonin

Molander, G. A.; St. Jean, D. J.; Haas, J., *J. Am. Chem. Soc* **2004,** *126* (6), 1642-1643.

PHOTOEXTRUSION

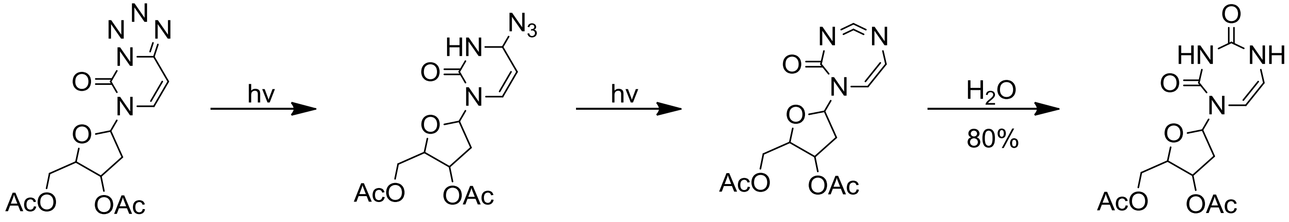


(+/-)-herbertenolide

Cyclic ketone double alpha cleavage

Veerman, M.; Resendiz, M. J. E.; Garcia-Garibay, M. A., *Org Lett* **2006,** *8* (12), 2615-2617.

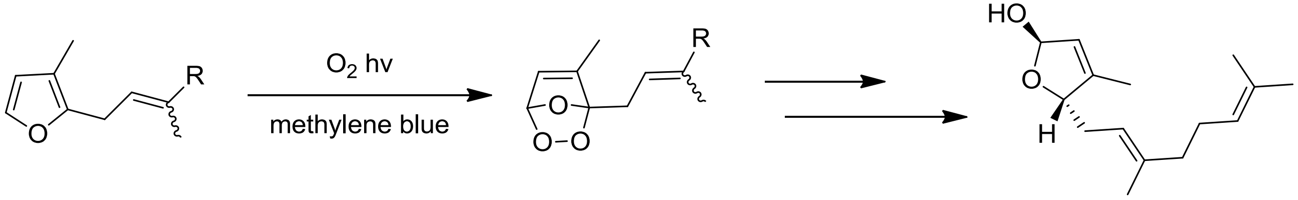
Tetrazo-option also known



PHOTOOXYDATION

Singlet oxygen is far more reactive than ground state triplet oxygen

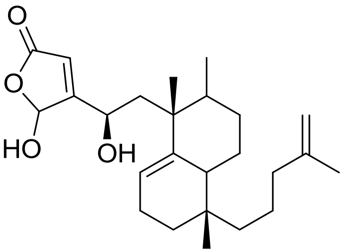
Easy oxidation, sunlight is sufficient.



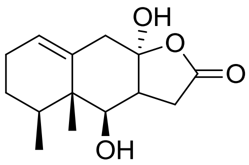
Litseaverticillol A

Vassilikogiannakis, G.; Margaros, I.; Montagnon, T.; Stratakis, M., *Chem.–Eur. J.* **2005,** *11* (20), 5899-5907.

Photo-oxydation of furans gave several natural products



Cladocorane A



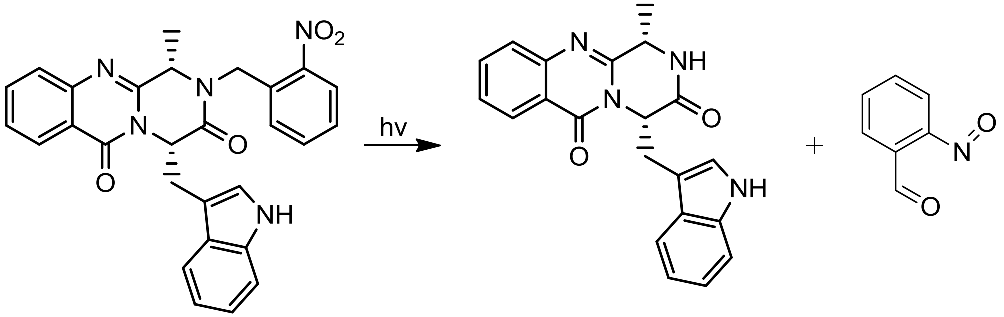
(+/-)-Toluccanolide C

Miyaoka, H.; Yamanishi, M.; Kajiwara, Y.; Yamada, Y., *J Org Chem* **2003,** *68* (9), 3476-3479.

Mace, L. H.; Shanmugham, M. S.; White, J. D.; Drew, M. G. B., *Org. Biomol. Chem.* **2006,** *4* (6), 1020-1031.

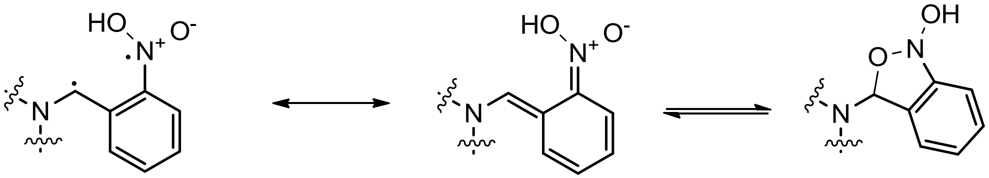
PROTECTING GROUPS

Cleavage by light avoids reagents and is rapid and clean



ent-fumiquinazoline

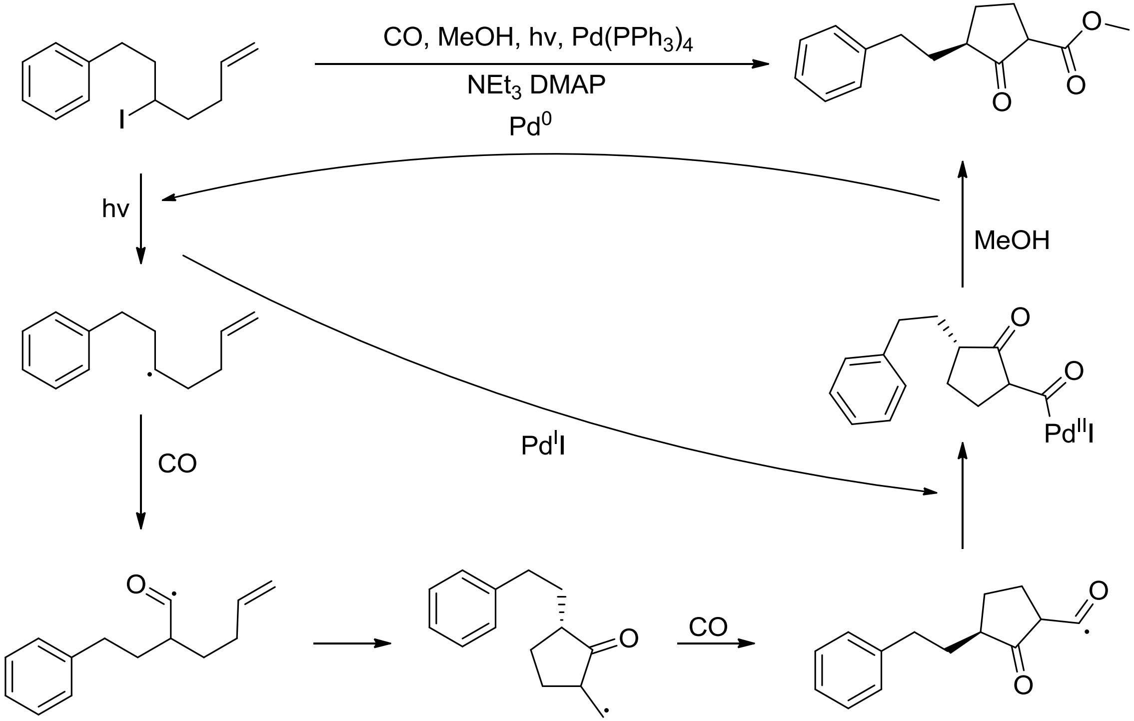
via



Snider, B. B.; Busuyek, M. V., *Tetrahedron* **2001,** *57* (16), 3301-3307.

PHOTOCHEMICAL MCR

Light as an auxillary for radical chemistry



Ryu, I.; Kreimerman, S.; Araki, F.; Nishitani, S.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M., *J. Am. Chem. Soc* **2002,** *124* (15), 3812-3813.

Recent similar work by Corey R. J. Stephenson on light photoredox catalysis

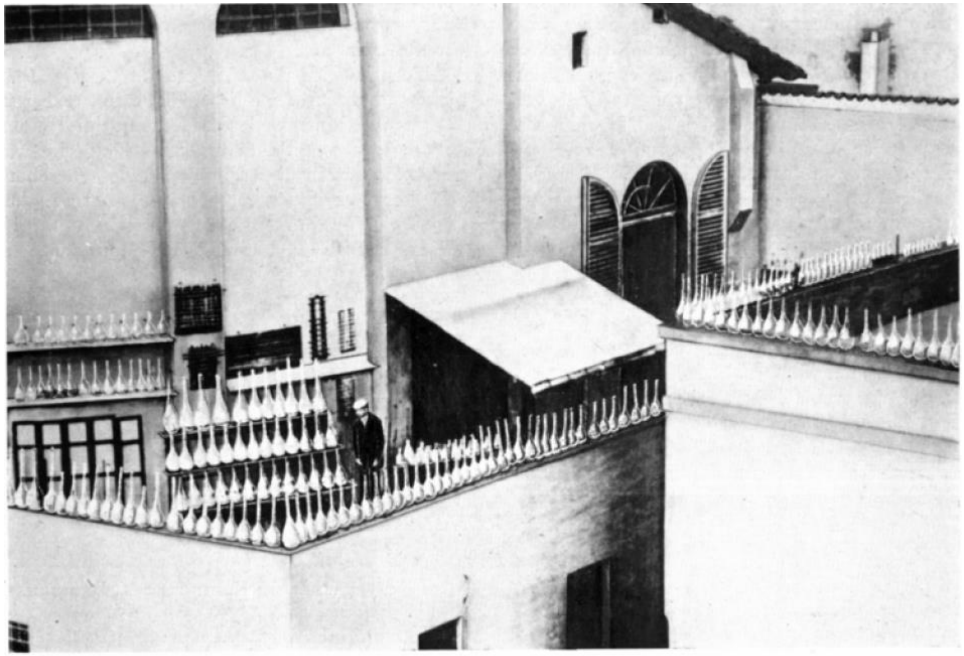
SUMMARY

Many structures are accessible through photo-induced radical reactions

Oft in greener conditions, even at times in crystal phase

Sensitizers, additives and carefully chosen substituents can induce selectivity on several levels

Questions?



Ciamician *passant en revue les centaines de flacons exposés au soleil sur le toit de son laboratoire.*

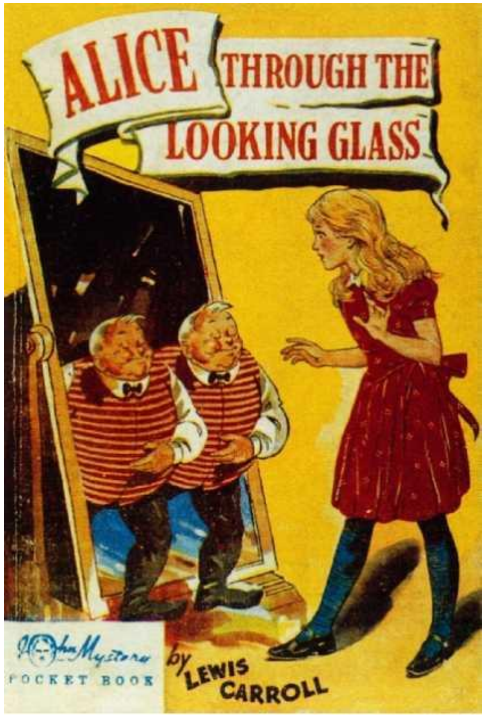
Enantioselective Reactions Catalyzed by Iron Complexes

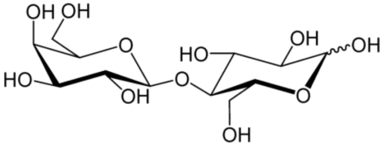
Pablo Pérez

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

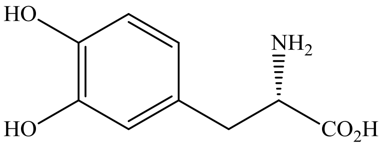
General Introduction

"How would you like to live in Looking-glass House Kitty? I wonder if they'd give you milk in there? Perhaps looking glass milk isn't good to drink.." Lewis Carroll, *Through the looking-glass and what Alice found there*, Macmillan, 1872

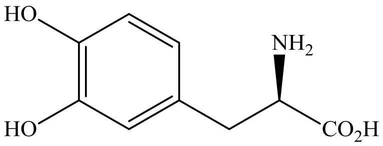




D-lactose



(*S*)-dopa
Restores nerve function

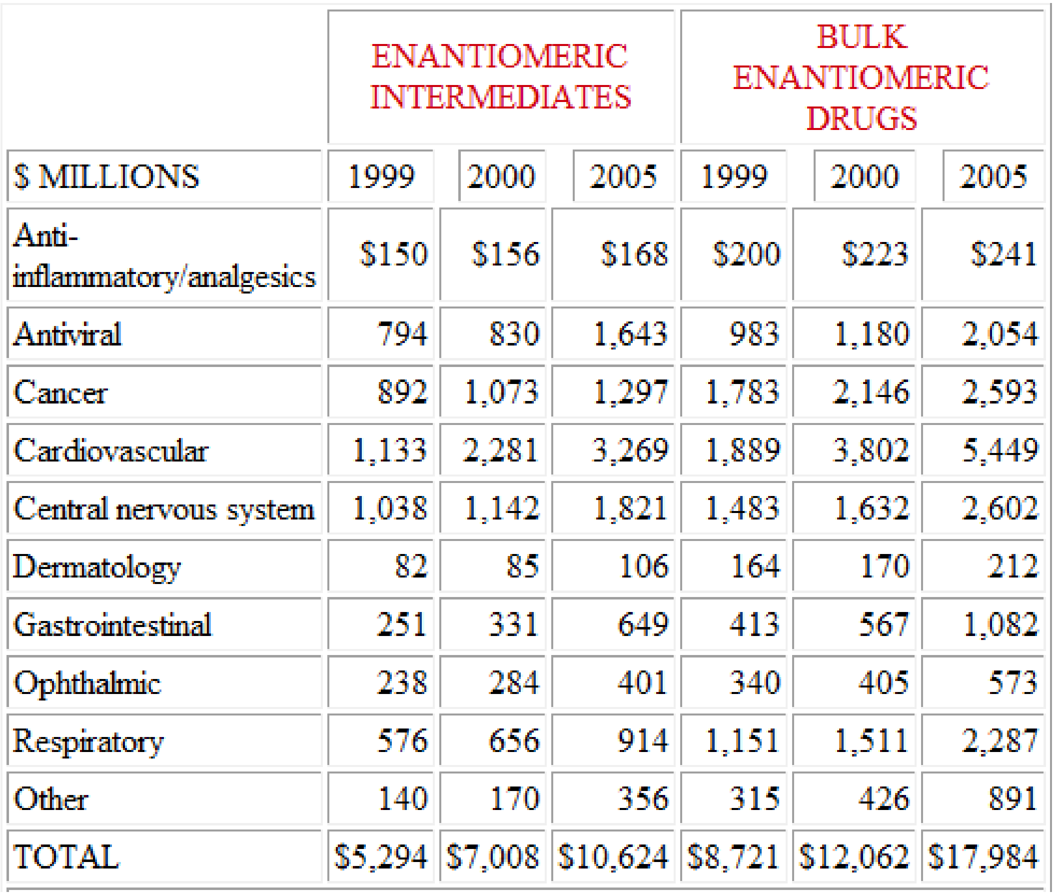


(*S*)-dopa
toxic

General Introduction

Chiral Components

Sales of enantiomeric intermediates and single-enantiomer drugs are up



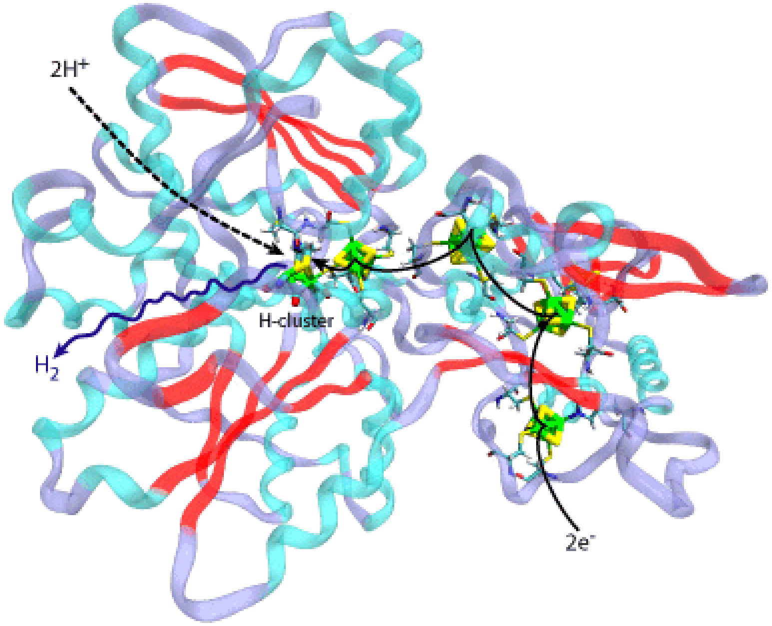
	ENANTIOMERIC INTERMEDIATES			BULK ENANTIOMERIC DRUGS		
$ MILLIONS	1999	2000	2005	1999	2000	2005
Anti-inflammatory/analgesics	$150	$156	$168	$200	$223	$241
Antiviral	794	830	1,643	983	1,180	2,054
Cancer	892	1,073	1,297	1,783	2,146	2,593
Cardiovascular	1,133	2,281	3,269	1,889	3,802	5,449
Central nervous system	1,038	1,142	1,821	1,483	1,632	2,602
Dermatology	82	85	106	164	170	212
Gastrointestinal	251	331	649	413	567	1,082
Ophthalmic	238	284	401	340	405	573
Respiratory	576	656	914	1,151	1,511	2,287
Other	140	170	356	315	426	891
TOTAL	$5,294	$7,008	$10,624	$8,721	$12,062	$17,984

S. C. Stinson *Chem. Eng. News.* **2001**, *79*(40), 79

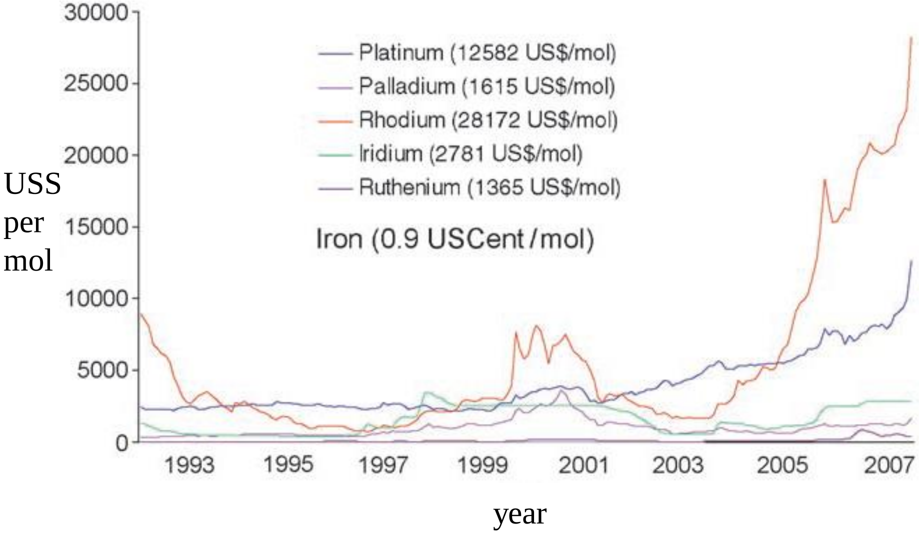
General Introduction

Why to do catalysis with Iron?

Biological iron-based catalysts



Market prices of transition metals



M. Beller *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 3317

Large use of iron as catalyst in organic chemistry

- Addition Reactions.
- Substitution Reactions.
- Cycloadditions.
- Hydrogenations.
- Isomerizations and Rearrangements
- Polymerizations
- Other (Sulfide oxidations, CO insertions, Baeyer Villiger Reactions, etc)

C. Bolm *Chem. Rev.* **2004**, *104*, 6217

- Carbon – heteroatom bond forming processes.
- Heteroatom – heteroatom bond forming processes.

C. Bolm *Chem. Soc. Rev.* **2008**, *37*, 1108

Goal of the talk: Try to give a summary of principal enantiomeric synthesis applications of iron catalysis.

Organization

- Addition Reaction: *Asymmetric Michael Reaction.*
  Asymmetric Olefin cis-*Dihydroxylation*
  Asymmetric Epoxidation

- Substitution Reactions: *Stereoselective Allylic Alkylation.*

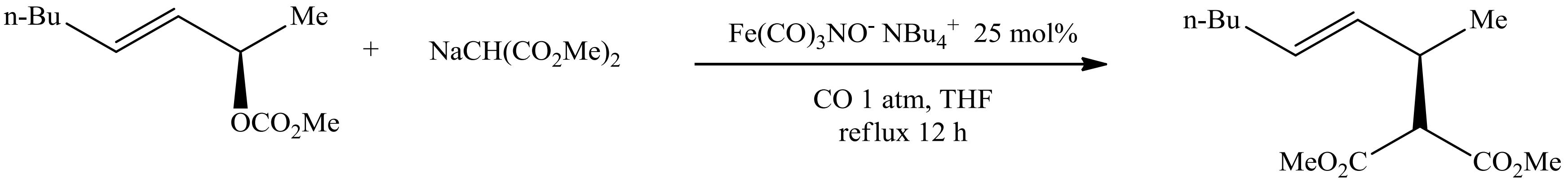
- Cycloadditions: *Asymmetric Diels – Alder Reaction,*
  Asymmetric 1,3-Dipolar Cycloaddition

- Hydrogenations: *Asymmetric Hydrogenation of Ketones.*
  Asymmetric Transfer Hydrogenation of Imines.

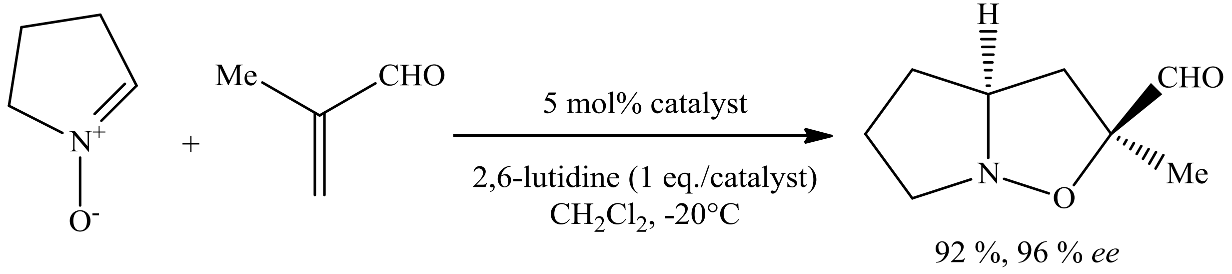
- Other: *Asymmetric Sulfide Oxidation,*
  Enantioselective O-H bond insertions,
  Selective Aliphatic C-H Oxidation Reaction,
  Enantioriched Cross-coupling of 2-Naphtols.

Questions

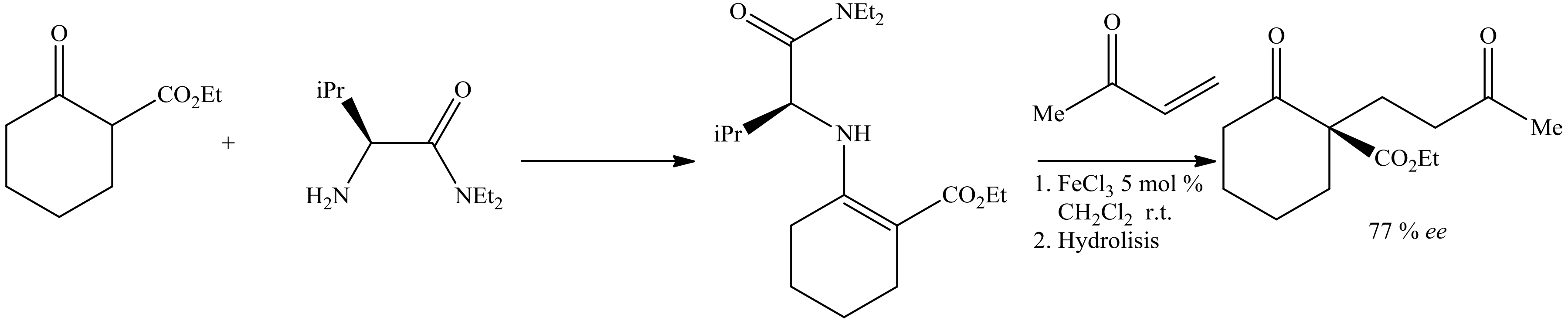
1. For the following reaction, during the catalytic cycle, the alkene double bond is sigma or pi coordinated to the iron?



2. For the following reaction analyzing the structure of the product, the nitrone approach preferentially the C_{alpha}-*Si*-face or the C_{alpha}-*Re*-face of the enal?



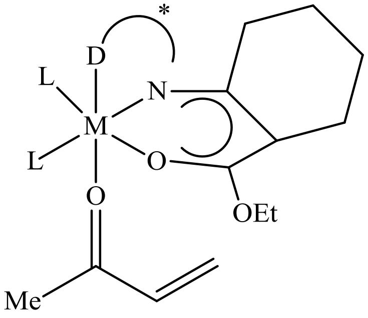
Asymmetric Michael Reaction



1. $FeCl_3$ 5 mol %
   CH_2Cl_2 r.t.
2. Hydrolisis

77 % *ee*

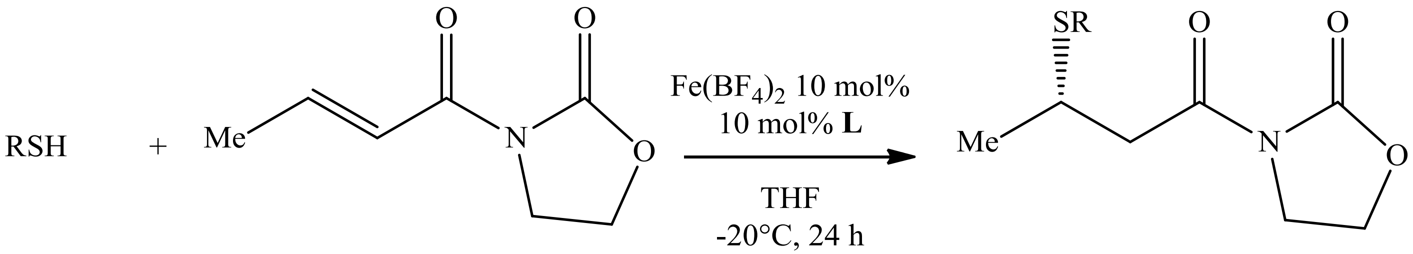
Intermediate Proposed:



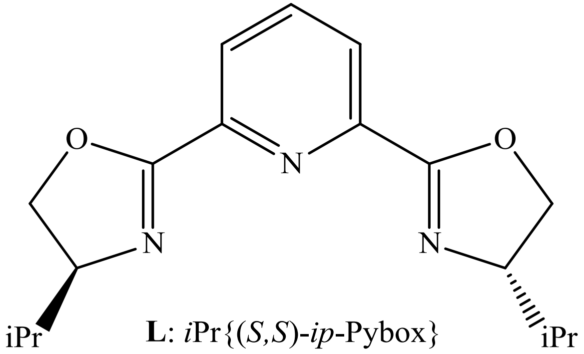
J. Christoffers *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 2752

Asymmetric Michael Reaction

C-S bond formation



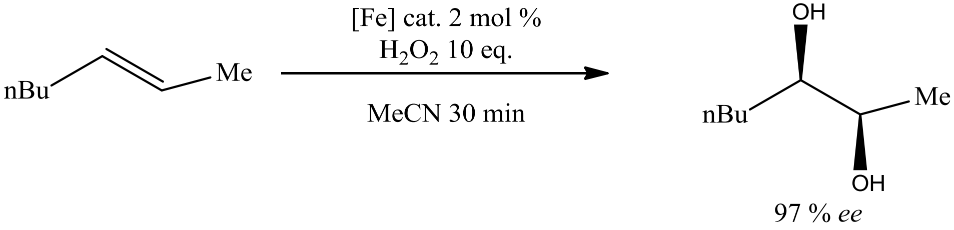
R: Ph	86 %, 90 % *ee*
R: *o*-Tolyl	92 %, 95 % *ee*
R: 2-Naphthyl	96 %, 89 % *ee*

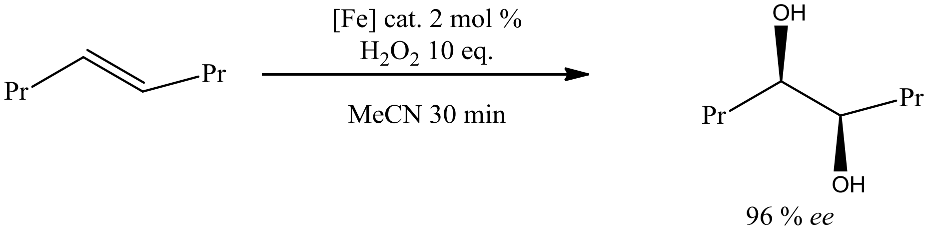


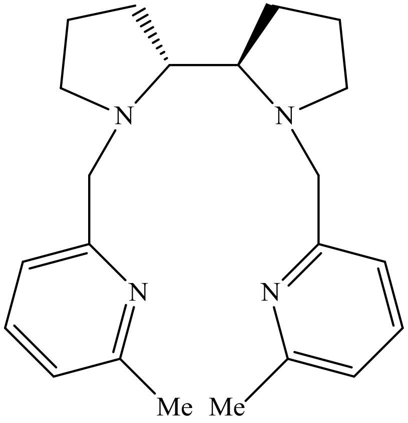
L: *i*Pr{(*S*,*S*)-*ip*-Pybox}

T. Itoh *et al. Tetrahedron Letters* **2007**, *48*, 6480

Asymmetric Olefin *cis*-Dihydroxylation

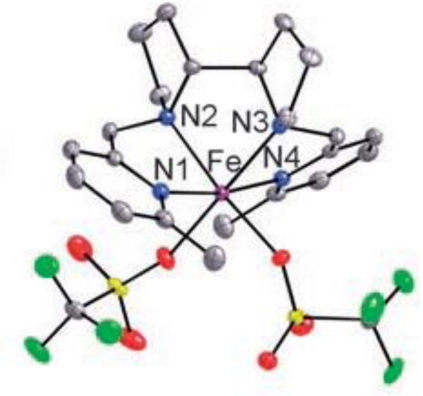






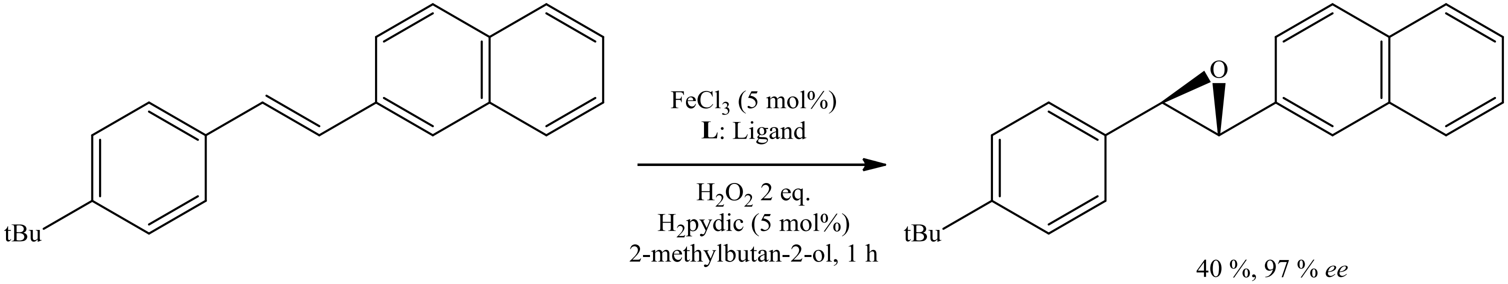
Chiral Ligand: 6-Me_2-BPBP

[Fe^{II}(6-Me_2-BPBP)(OTf)$_2$]



L. Que *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 1887

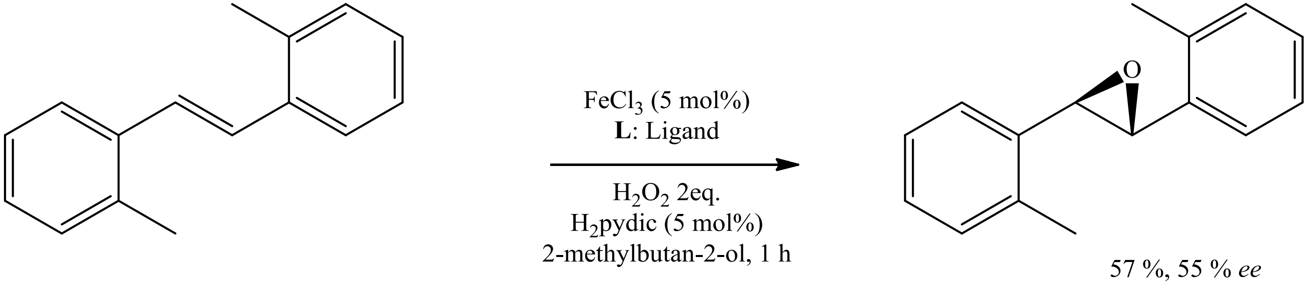
Asymmetric Epoxidation



$FeCl_3$ (5 mol%)
L: Ligand

H_2O_2 2 eq.
H_2pydic (5 mol%)
2-methylbutan-2-ol, 1 h

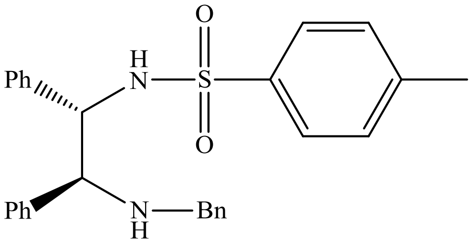
40 %, 97 % *ee*



$FeCl_3$ (5 mol%)
L: Ligand

H_2O_2 2eq.
H_2pydic (5 mol%)
2-methylbutan-2-ol, 1 h

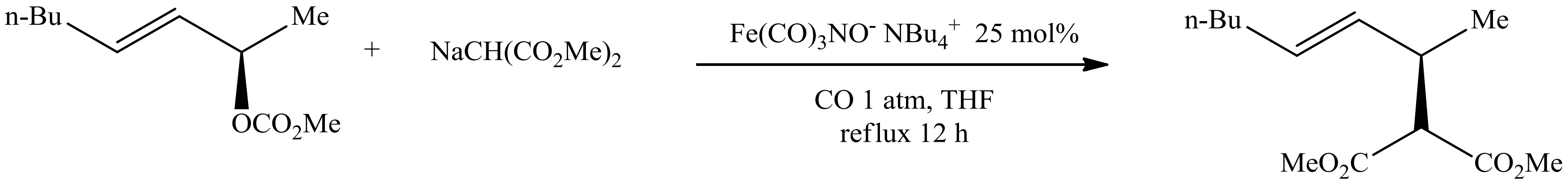
57 %, 55 % *ee*



L: Ligand

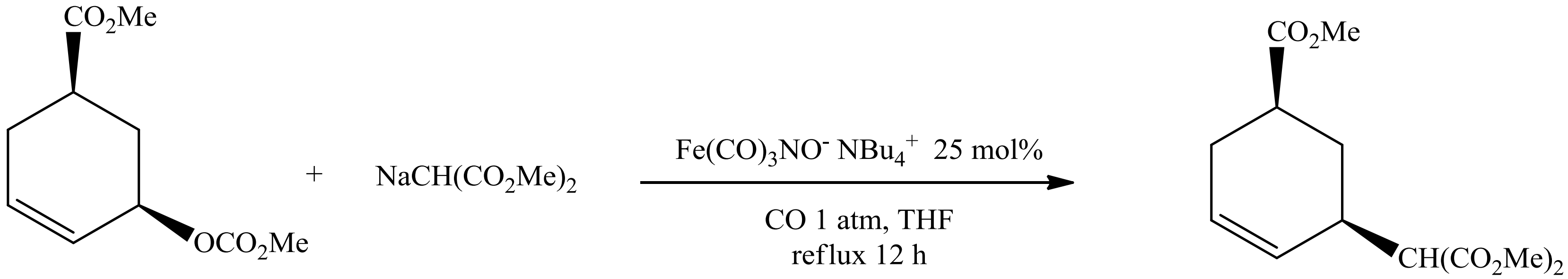
M. Beller *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 7293

Stereoselective Allylic Alkylation



$Fe(CO)_3NO^- NBu_4^+$ 25 mol%

CO 1 atm, THF
reflux 12 h

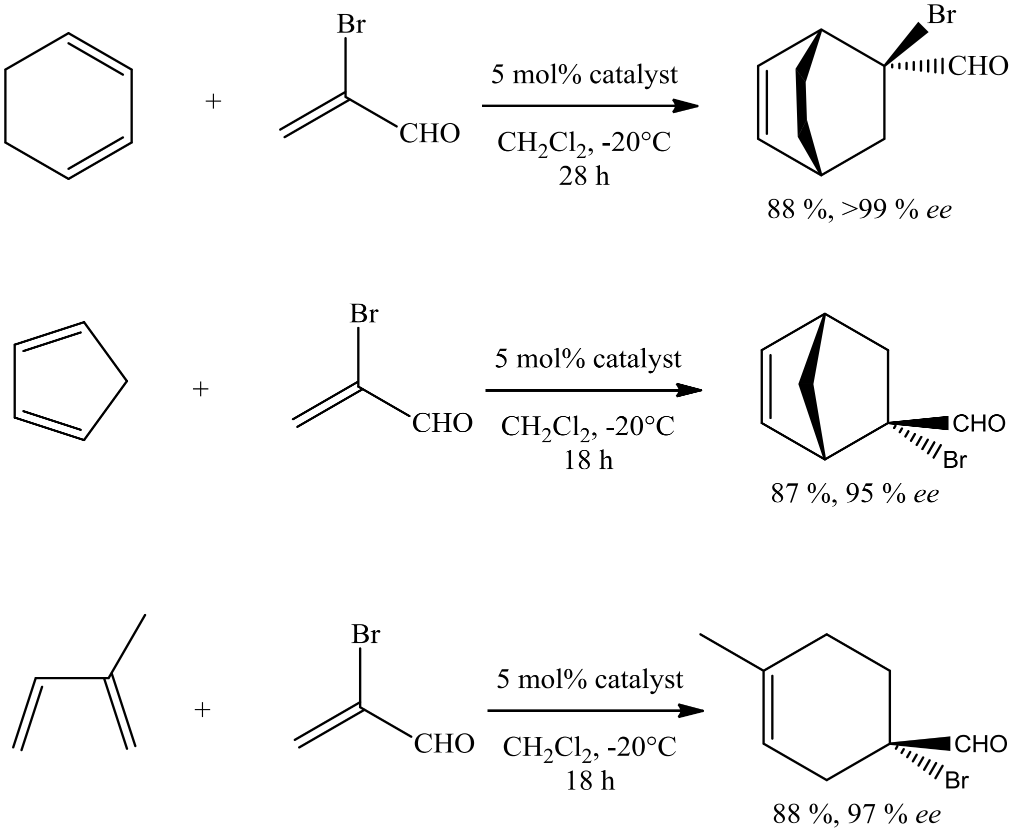


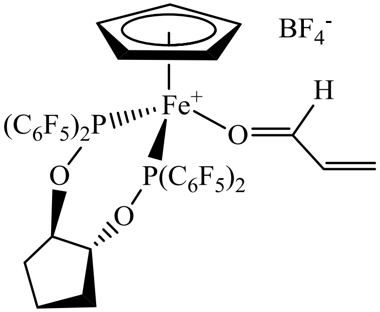
$Fe(CO)_3NO^- NBu_4^+$ 25 mol%

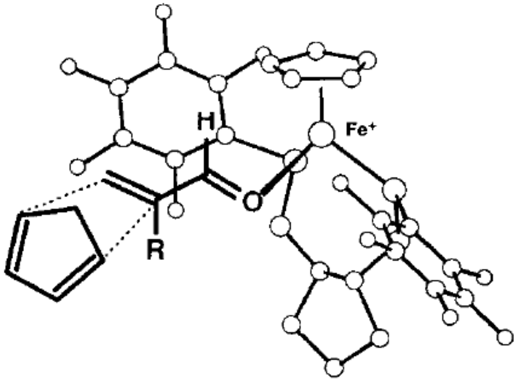
CO 1 atm, THF
reflux 12 h

Y. Xu *et al. J. Org. Chem.* **1987**, *52*, 974

Asymmetric Diels – Alder Reactions

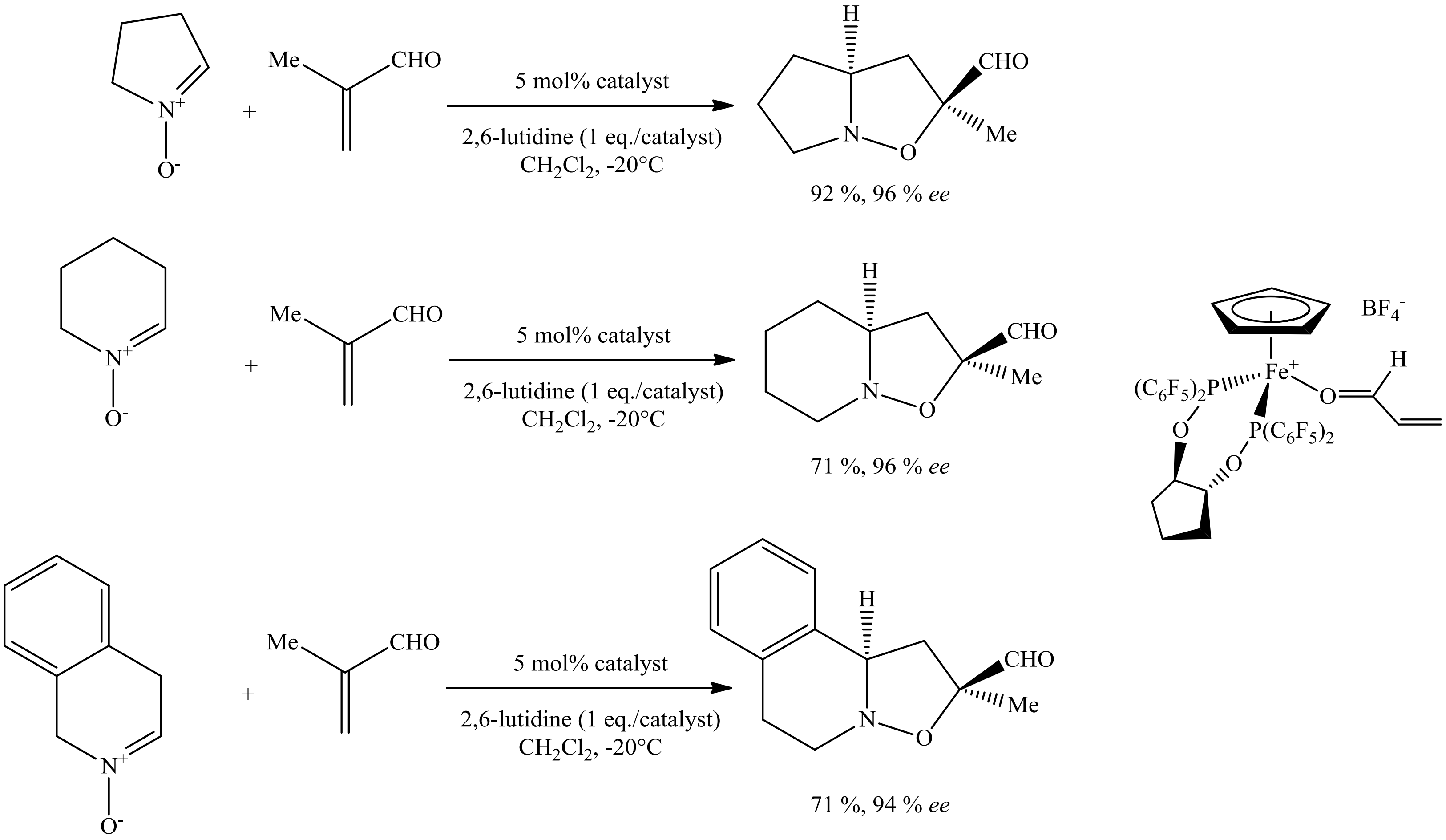






E. P. Kündig *et al. Angew. Chem. Int. Ed.* **1994**, *33*, 1856

Asymmetric 1,3-Dipolar Cycloaddition



5 mol% catalyst

2,6-lutidine (1 eq./catalyst)
CH_2Cl_2, -20°C

92 %, 96 % *ee*

5 mol% catalyst

2,6-lutidine (1 eq./catalyst)
CH_2Cl_2, -20°C

71 %, 96 % *ee*

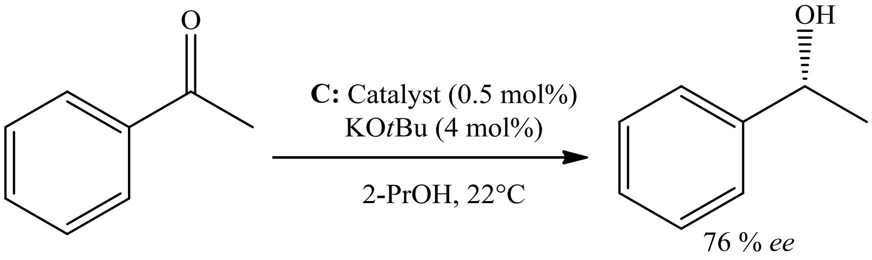
5 mol% catalyst

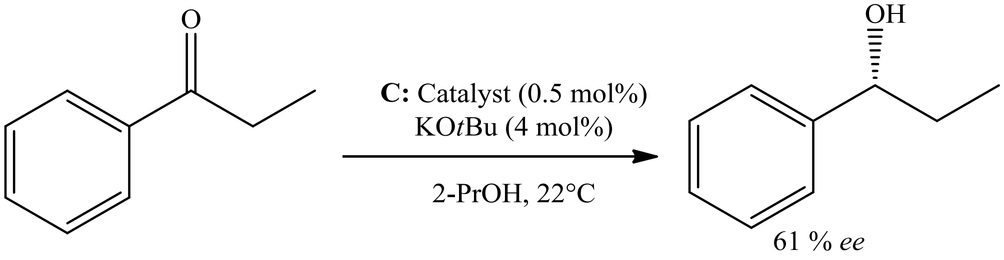
2,6-lutidine (1 eq./catalyst)
CH_2Cl_2, -20°C

71 %, 94 % *ee*

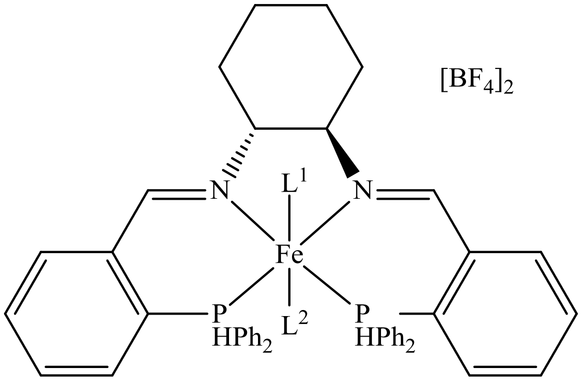
E. P. Kündig *et al. J. Am. Chem. Soc.* **2002**, *124*, 4968

Asymmetric Transfer Hydrogenation of Ketones





C: Catalyst

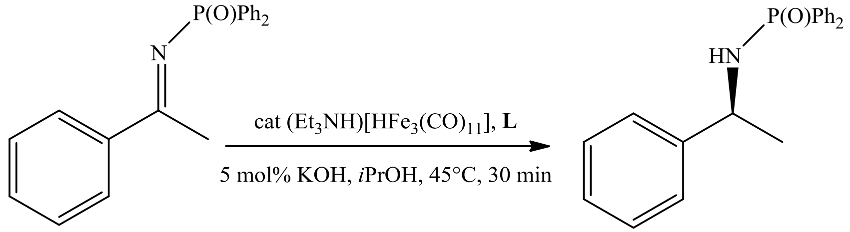


L^1: MeCN; L^2: CO

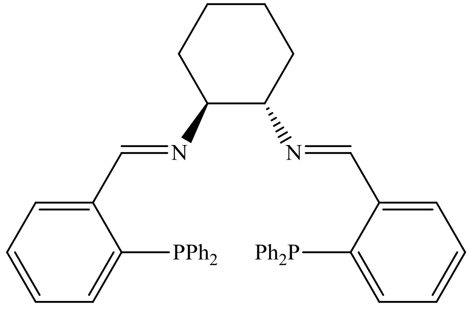
13 examples all *ee* around to 35%

R. H. Morris *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 940

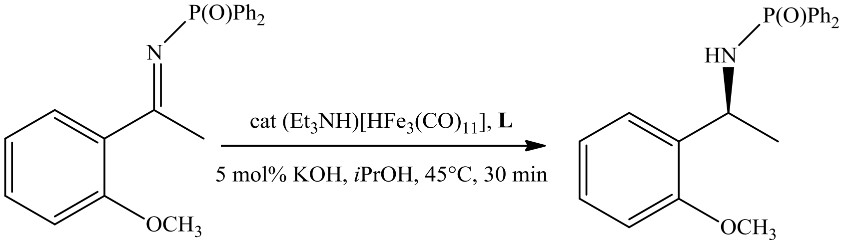
Asymmetric Transfer Hydrogenation of Imines



87 %, 96% *ee*

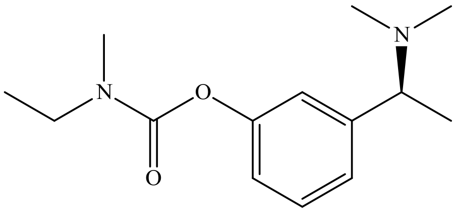


L: Ligand

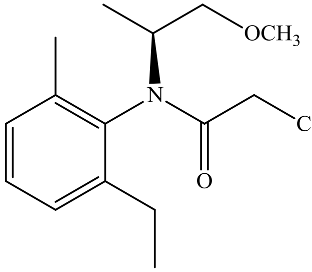


94 %, 96% *ee*

Applications:



Rivastigmine

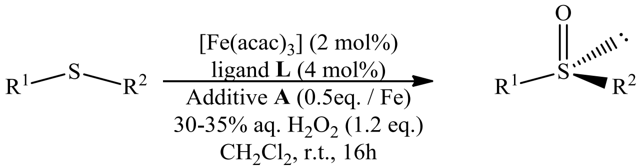


Metolachlor

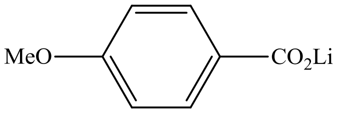
17 examples all *ee* up to 90%

M. Beller *et al. Angew. Chem. Int. Ed.* **2010**, *49*, 8121

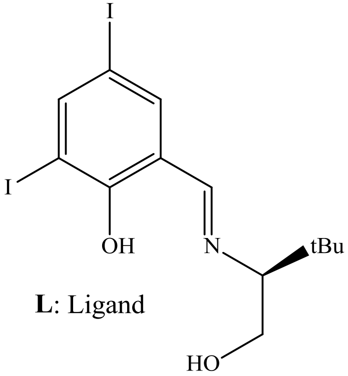
Asymmetric Sulfide Oxidation



R^1: Ph R^2: Me	63 %, 90 % *ee*
R^1: 4-BrC_6H_4 R^2: Me	59 %, 94 % *ee*
R^1: 2-naphthyl R^2: Me	67 %, 95 % *ee*

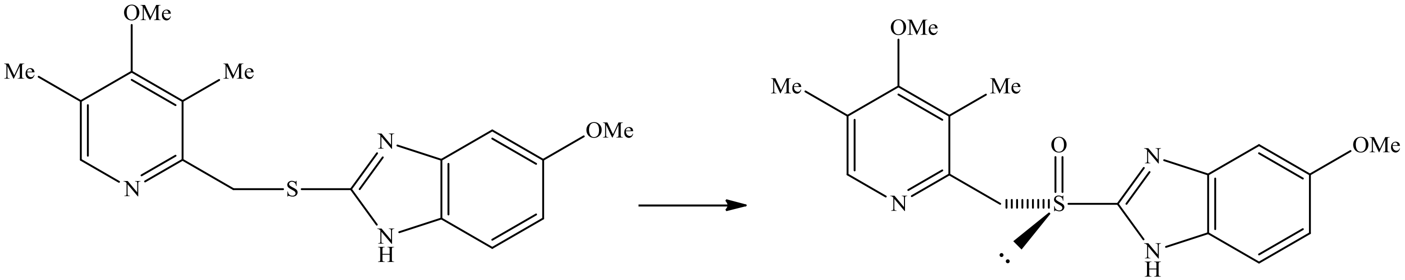


A: Additive



L: Ligand

Useful reaction in pharmaceutical industry:

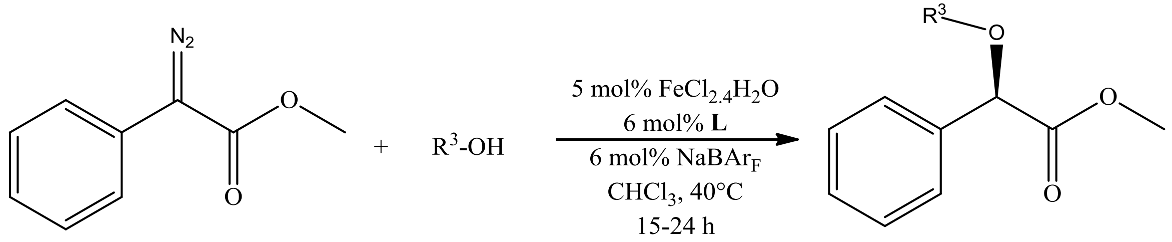


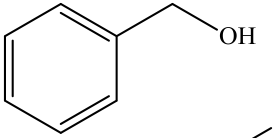
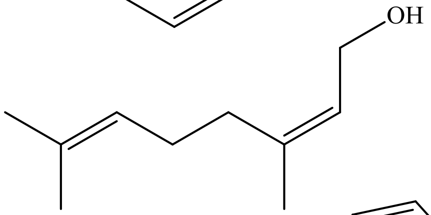
Esomeprazole
(94 % *ee*)

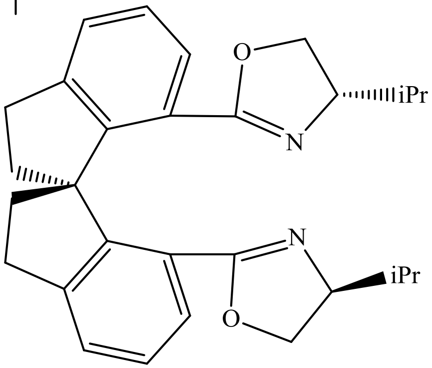
C. Bolm *et al. Chem. Eur. J.* **2005**, *11*, 1086

Enantioselective O-H bond insertions

Alcohol insertion



*n*BuOH	93 %, 98 % *ee*
MeOH	85 %, 96 % *ee* (69 % *ee*)
	94 %, 98 % *ee* (77 % *ee*)
	88 %, 95 % *ee*



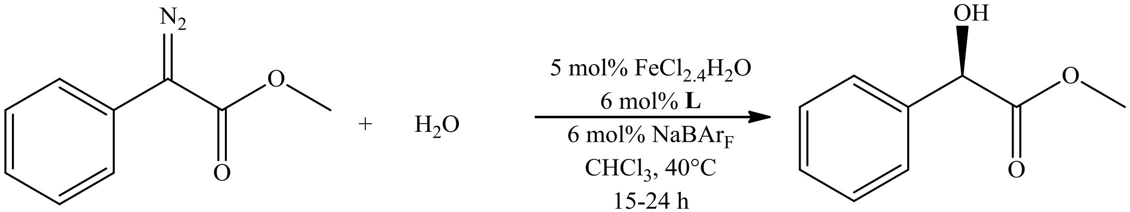
L: Spirobox

15 examples all *ee* up to 90%

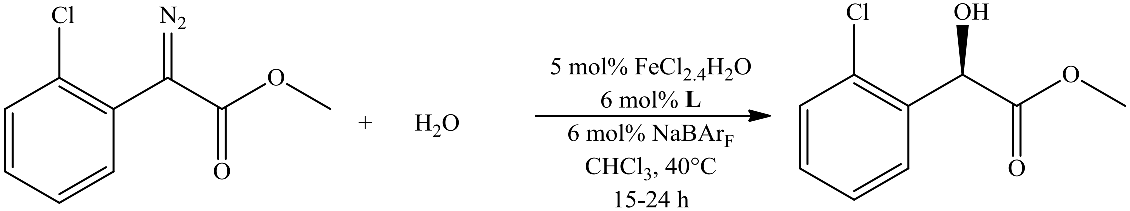
Qi-Lin Zhou *et al. Nature Chemistry* **2010**, *2*, 546

Enantioselective O-H bond insertions

Water insertion



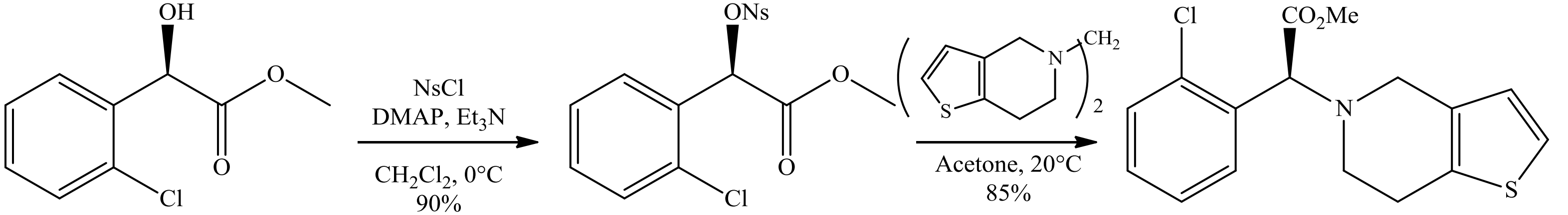
90 %, 95 % *ee*



92 %, 95 % *ee*

92 % *ee* with 1 mol% of catalyst

Clopidogrel: Platelet aggregation inhibitor



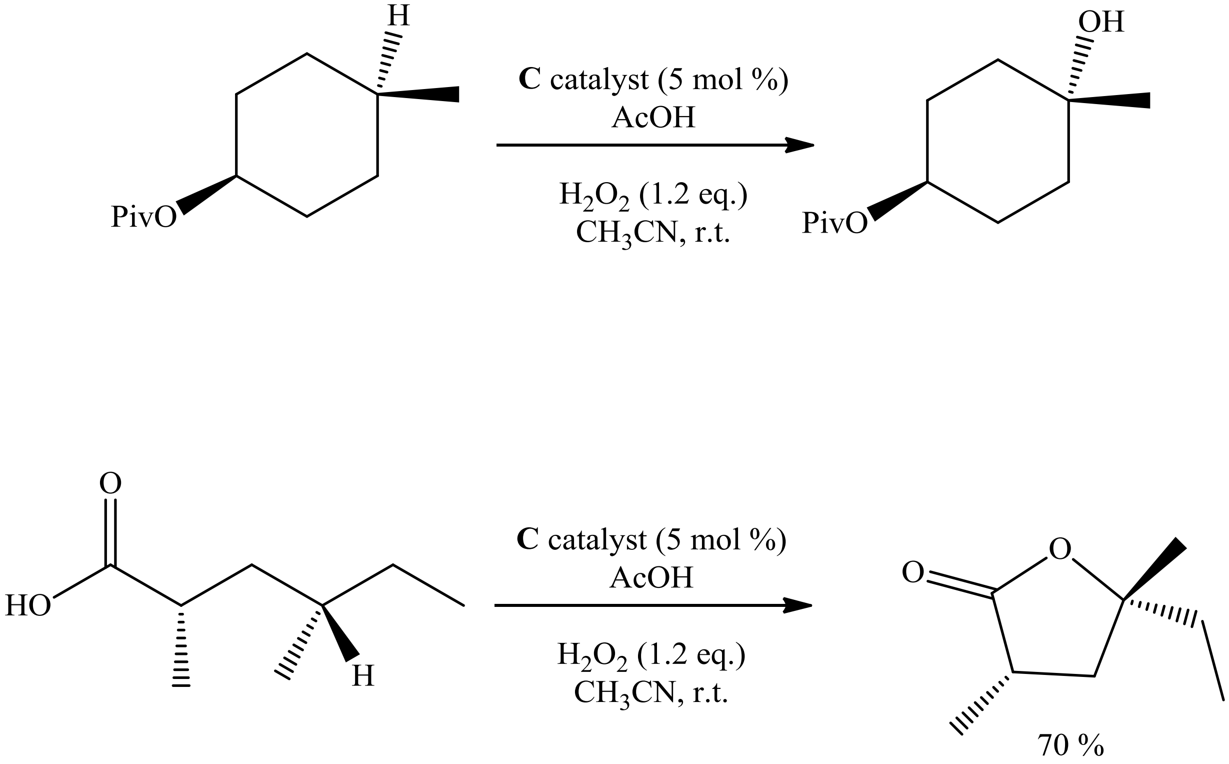
95 % *ee*

93 % *ee*

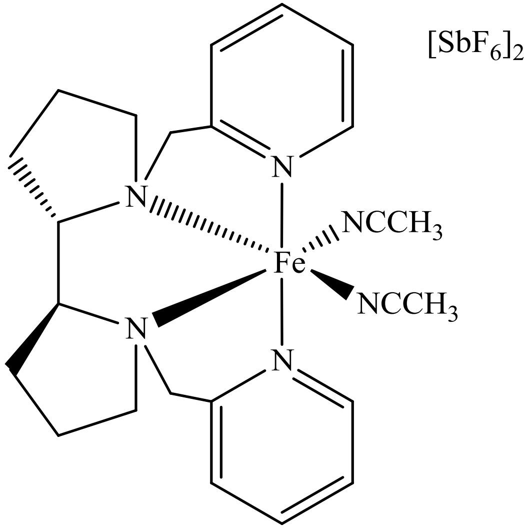
17 examples all *ee* up to 90%

Qi-Lin Zhou *et al. Nature Chemistry* **2010**, *2*, 546

Selective Aliphatic C-H Oxidation Reaction

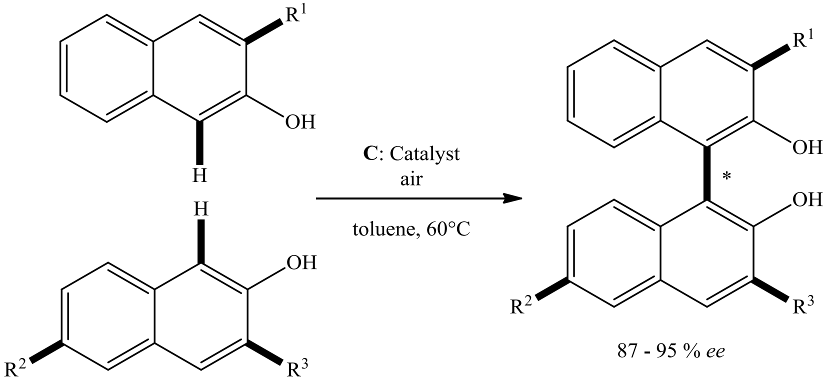


C: Catalyst



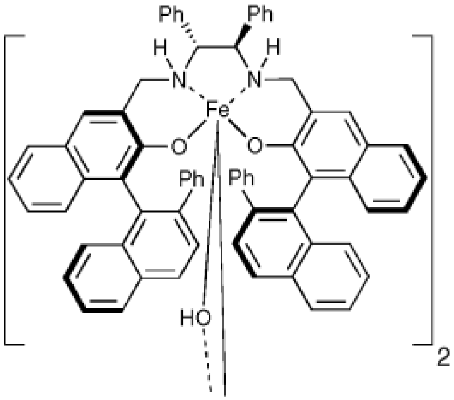
C. White *et al.* *Science* **2007**, *318*, 783

Enantioriched Cross-coupling of 2-Naphtols



R^1: electron-donating group
R^2: electron-withdrawing group of H
R^3: H or electron-withdrawing (or less donating) group

C: Catalyst



T. Katsuki *et al. J. Am. Chem. Soc.* **2010**, *132*, 13633

Conclusions

- Iron is a very interesting option for a catalyst center due to its ready availability, environmental friendliness and low market price.

- It has been shown that iron is useful for several kinds of enantiomeric reactions showing generally a high enantioselectivity.

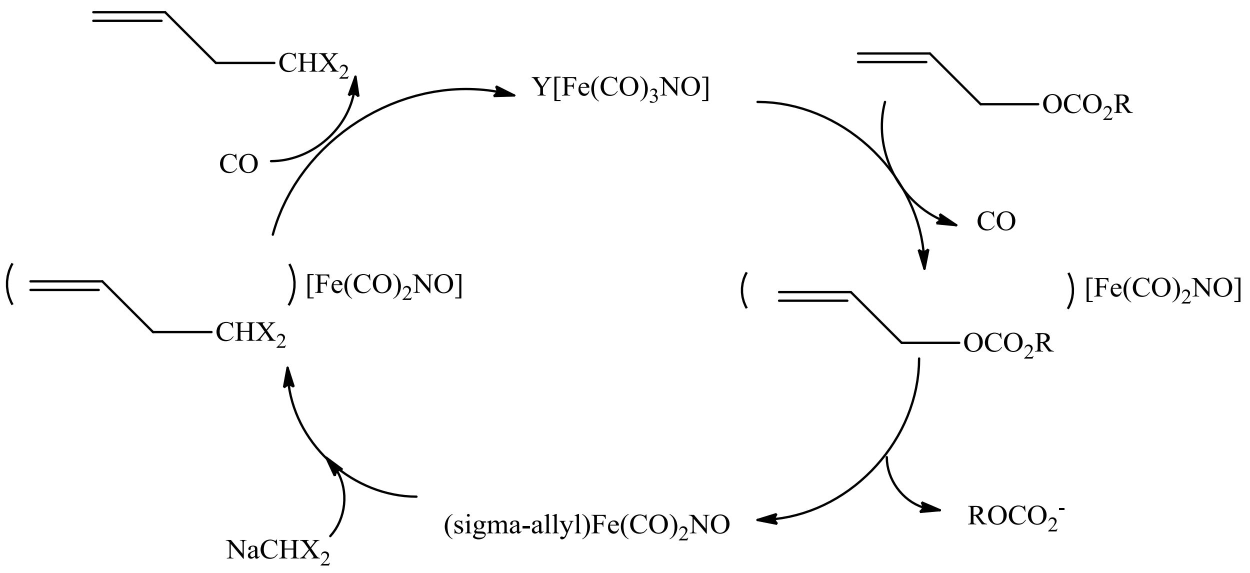
- It is hoped that the methodologies will be more developed to be applied in more “real synthesis”.

- The understanding of the catalysis mechanism is crucial for the improvement of catalyst activity and productivity.

Stereoselective Allylic Alkylation

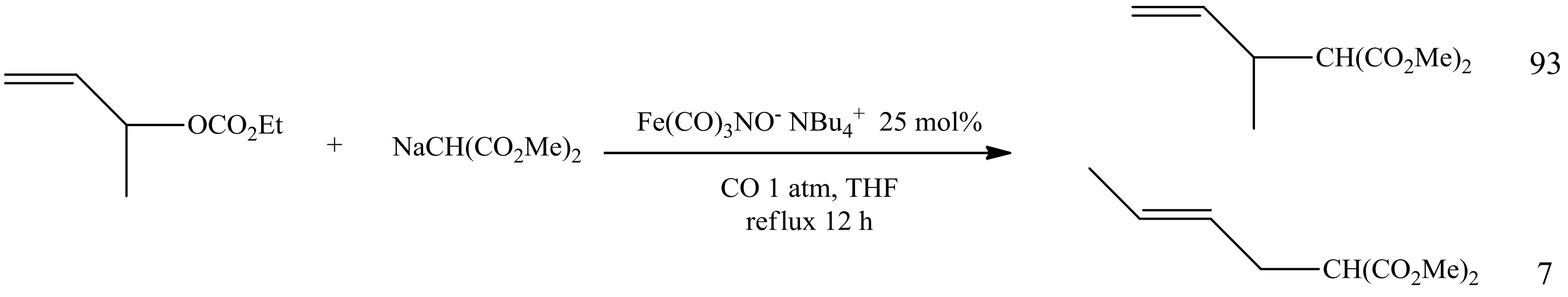
Question 1

Proposed mechanism:



Y = Bu$_4$N$^+$

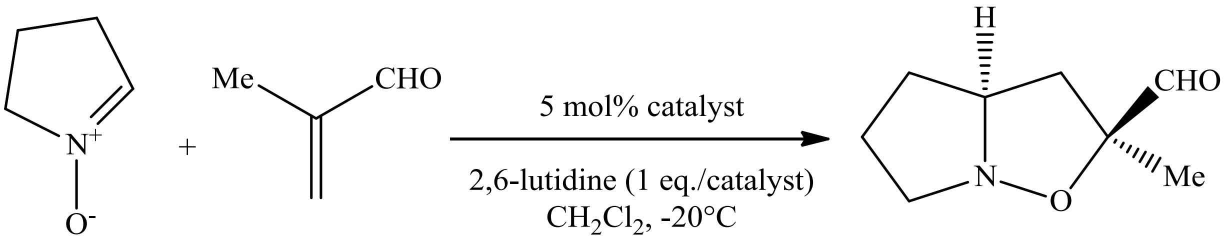
Pi to Sigma allyl coordination:



Y. Xu *et al. J. Org. Chem.* **1987**, *52*, 974

Asymmetric 1,3-Dipolar Cycloaddition

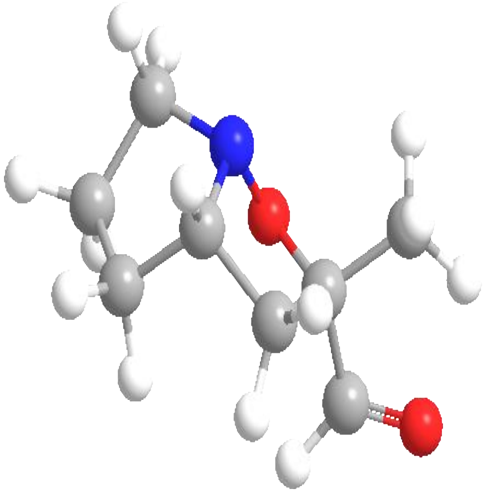
Question 2

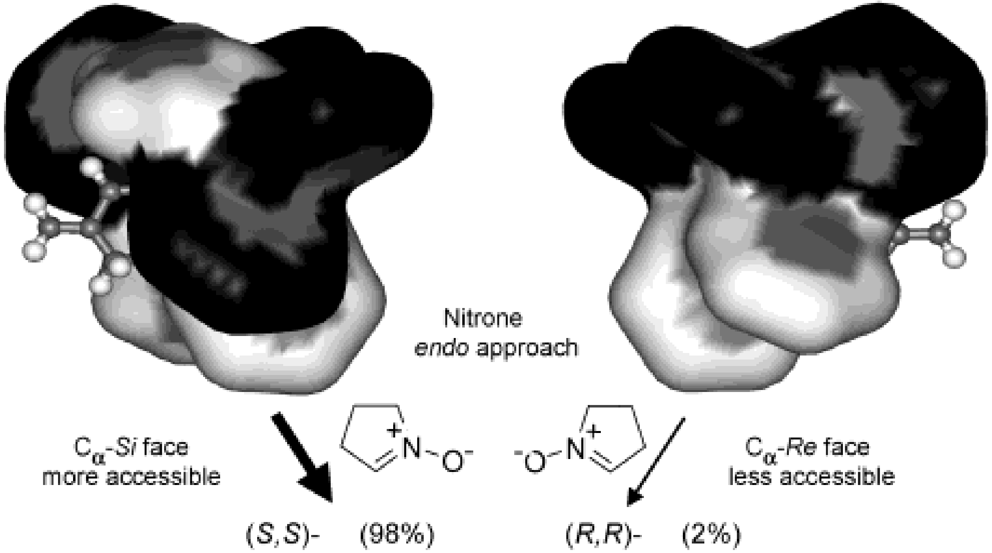


5 mol% catalyst

2,6-lutidine (1 eq./catalyst)
CH_2Cl_2, -20°C

92 %, 96 % *ee*





E. P. Kündig *et al. J. Am. Chem. Soc.* **2002**, *124*, 4968

Questions

The intramolecular Rh(I) catalyzed [5+2] carbocyclization of alkene-tethered VCPs is a highly diastereoselective reaction:the cis isomer is always the only one or the major one to be observed, for what concern the bridges-bond in the obtained bicyclic cycloadduct.
How could this outcome be justified?

Sterical effects can explain the feasibility of the intermolecular Rh(I) catalyzed [5+2] carbocyclization with 1-alkyl substituted VCPs (favoring the preorganization). An alkoxy or siloxy group on the same position can also favor the reactivity in intermolecular systems, by lowering the energy of TS3 (transition state for the rate determing step). How could this effect be rationalized?

Frontiers in Chemical Synthesis:
Towards Sustainable Chemistry
June 6-7, 2011

Rhodium(I)-Catalyzed Carbocyclization Reactions

A Straightforward Access to Medium-Size Rings

Stefano Nicolai

Outline

Introduction

- Cycloaddition vs Metal-Catalyzed Carbocyclizations

Synthesis of 7-Membered Rings: Rh(I) Catalyzed [5+2] Carbocyclisations

- Catalytic systems
- Regio/Stereoselectivity
- Applications in Total synthesis

Synthesis of 8-Membered Rings:

- Rh(I) Catalysed [4+2+2] Carbocyclisation Reactions
- Rh(I) Catalysed [6+2] Carbocyclisation Reactions

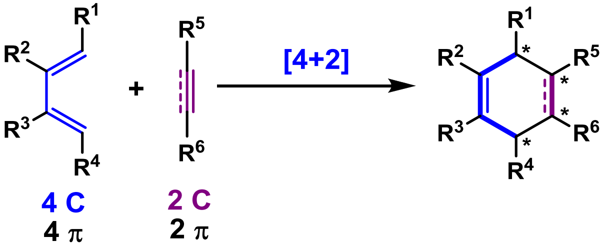
Conclusions

Cycloaddition Reactions: Effective Synthetic Tools towards Complexity

- ***Simultaneous formation of multiple σ-bonds***
- ***Possible control on Regio- and Stereo Selectivity***
- ***Complex cyclic systems accessible in a convergent way***

Highly Step-Economical Reactions

***Diels-Alder Cycloaddition:** a Classical Model*



Newly formed in one step:

- ***2 σ-bonds***
- ***Up to 4 stereocenters***

***HOMO – LUMO MATCHING** required for reactivity*

D.-A. Cyclodditon Limitation:

→ ***Electronically dissimilar components required;***

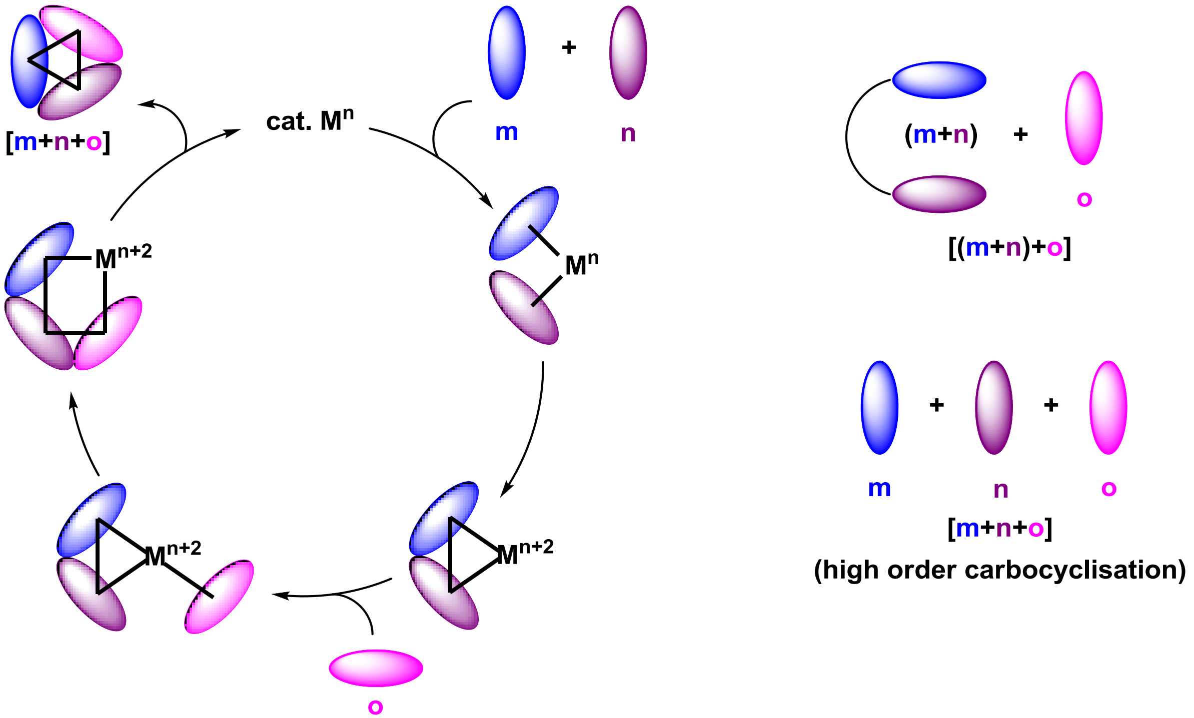
→ ***Low Rate or no reactivity;***

→***Forcing conditions.***

Transition Metal Catalyzed Carbocyclisation Reactions

Formal Cycloaddition processes:

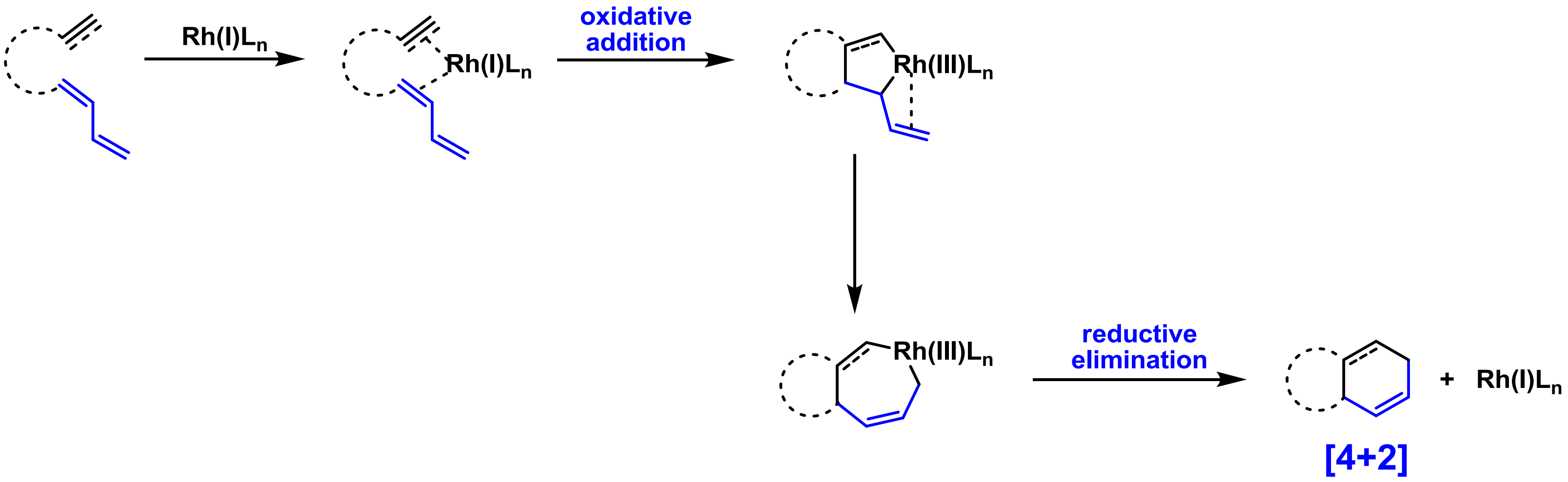
- *Coordination/Activation of two unsaturated units m, n;*
- *Oxidative Cyclisation → Metallacycle formation.*
- *Interception of unsaturated unit o;*
- *Reductive elimination → Cycloadduct release.*



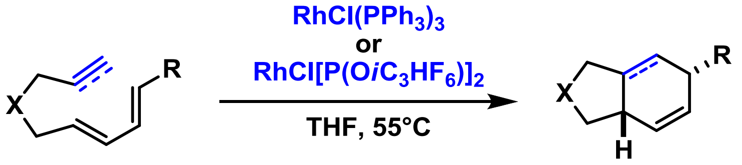
Most commonly used metal: Ni, Co, Ru, Rh, Pd

***Rh:** High versatility; high FG tolerance; compatible with mild conditions*

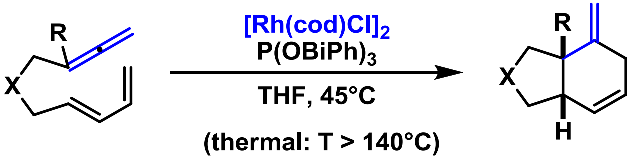
Rhodium-Catalyzed [4+2] Carbocyclization: "Diels-Alder" with unactivated substrates

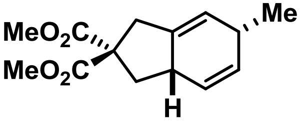


Ene-, Yne-Diene [4+2] *(Livinghouse, 1990)*

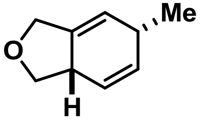


Allene-Diene [4+2] *(Wender, 1995)*

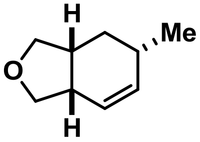




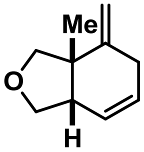
87%



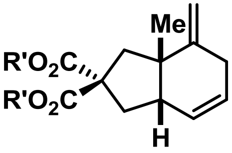
96%



96%
(only *cis*)



98%
(only *cis*)

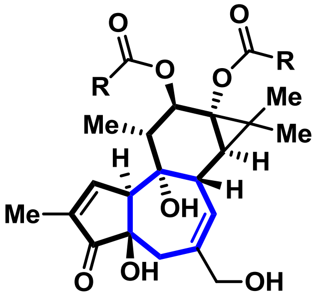


94%
(only *cis*)

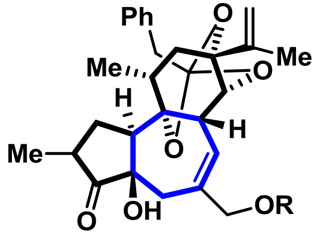
Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.*, **1990**, *112*, 4965, Jolly, R. S.; Wender., P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.*, **1995**, *117*, 1843.

Medium Size Membered Rings: Targets for Cycloadditions?

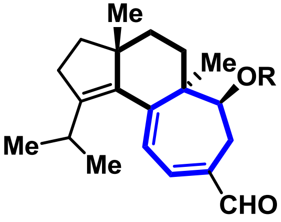
***Cycloeptanoyds* and *Cyclooctanoids*: widely present in bio- and pharmacologically active compounds**



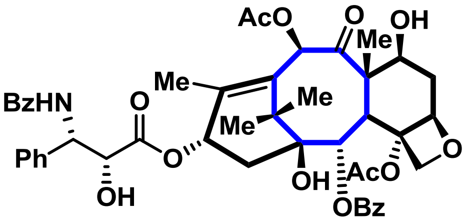
Phorbol Esters
(Tumor promoters)



Resiniferatoxin
(Lead for treating of chronic pain)



Allocyantines
(Nerve Growth Factor Promoters)

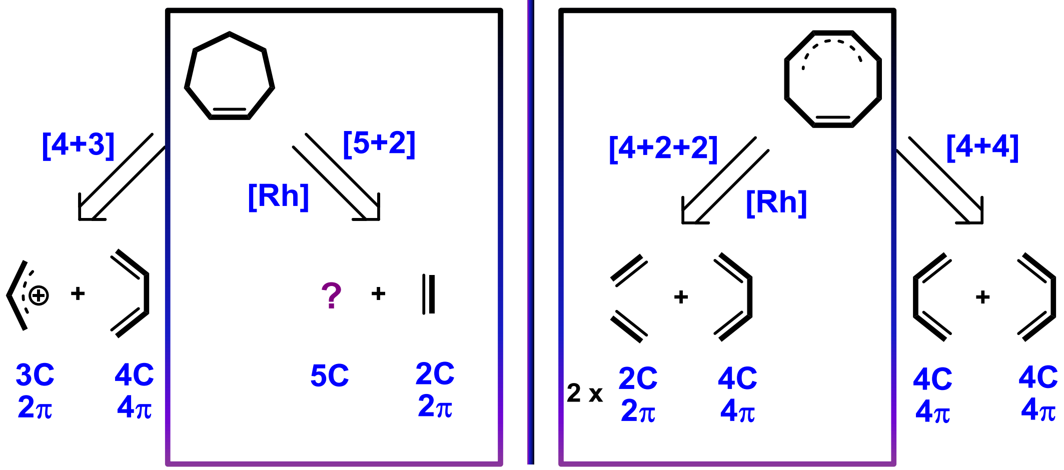


Taxol
(Antitumor agent)

7-Membered Rings

Homologs of 6 membered rings

8-Membered Rings



[4+3]

[5+2]

[Rh]

3C 2π + 4C 4π

? +

5C 2C 2π

[4+2+2]

[Rh]

2 x 2C 2π + 4C 4π

[4+4]

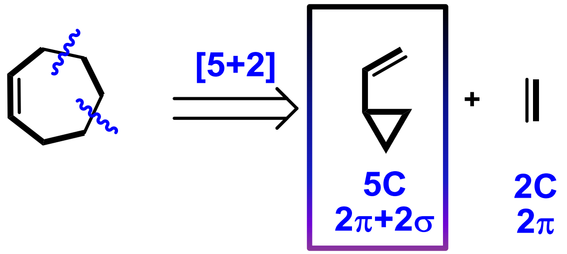
4C 4π + 4C 4π

- ***Allyl cations***
- ***M-allyl complexes***

Ni-Catalysis

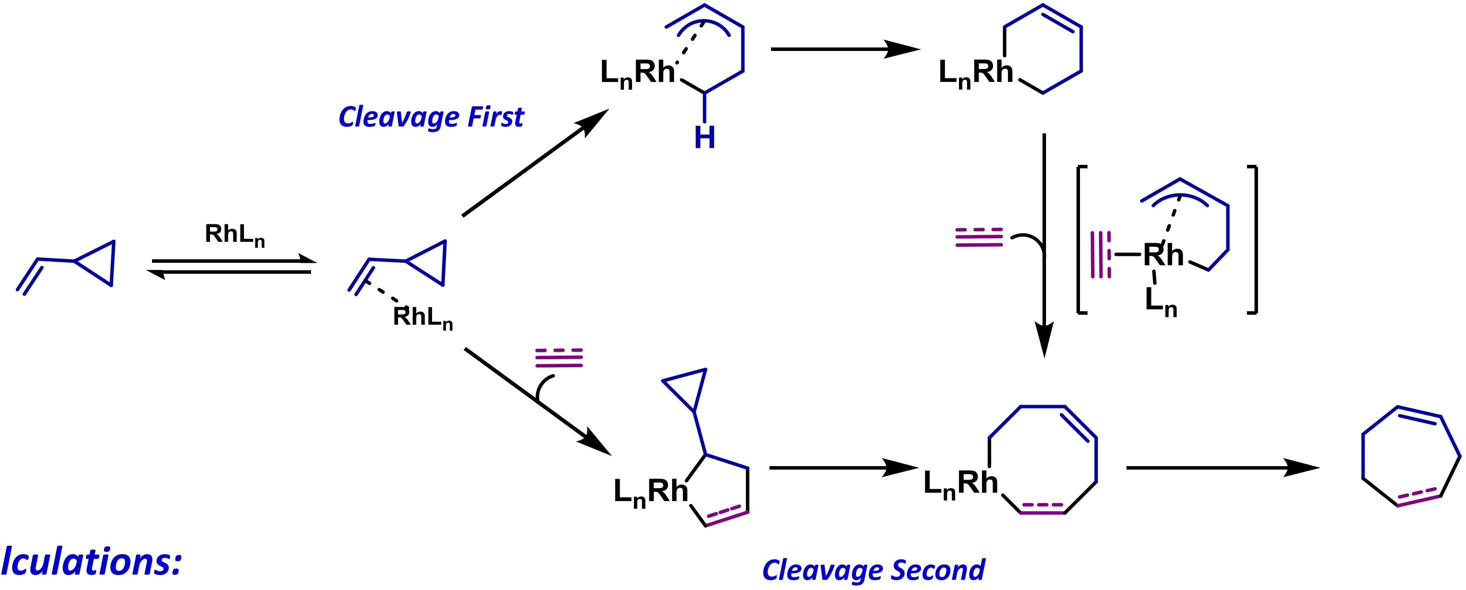
For a recent review on [4+3] cycloadditions: Harmata, M. *Chem. Comm.* **2010**, *46*, 8886.

Aiming to [5+2] Carbocyclizations: Vinylcyclopropanes (VCPs)



***VCPs:* potential homologs of dienes:**

- ***Kinetically stable (high $\Delta G^{\ddagger}$ for thermal isomerisation);***
- ***C=C available for metal coordination;***
- ***Strained Cyclopropane available for cleavage upon activation;***
- ***Isomerization to dienes/cyclopentene is known to be promoted by Rh(I)****



DFT calculations:

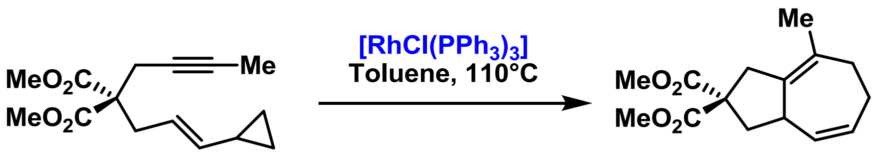
Intramolecular: Cleavage Second

Intermolecular: Cleavage First

Yu, Z.-X.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 9154; *Salomon, R. G.; Salomon, M. F.; Kachinski, J. L. C. *J. Am. Chem. Soc.* **1977**, *99*, 1043

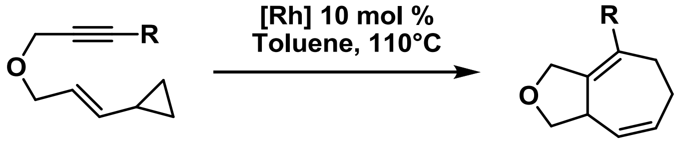
Intramolecular [5+2] Cycloadditions of VCPs

Discovery of the Reaction: Tethered Alkynes and Alkenes

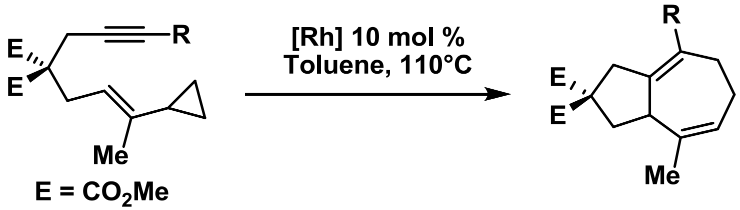


A: [Rh] 10 mol%
→ 84% (after 48h)

B: [Rh]/AgOTf 0.5 mol%
→ 83% (after 20 min)

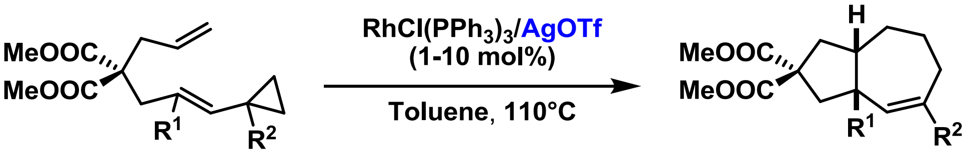


R = Me	**(1.5 h)**	**88%**
R = TMS	**(3.5 h)**	**83%**
R = CO_2Me	**(1.25 h)**	**74%**
R = Ph	**(1.5 h)**	**80%**



E = CO_2Me

R = H	**(48 h)**	**82%**
R = Me	**(48 h)**	**89%**
R = CO_2Me	**(16 h)**	**74%**

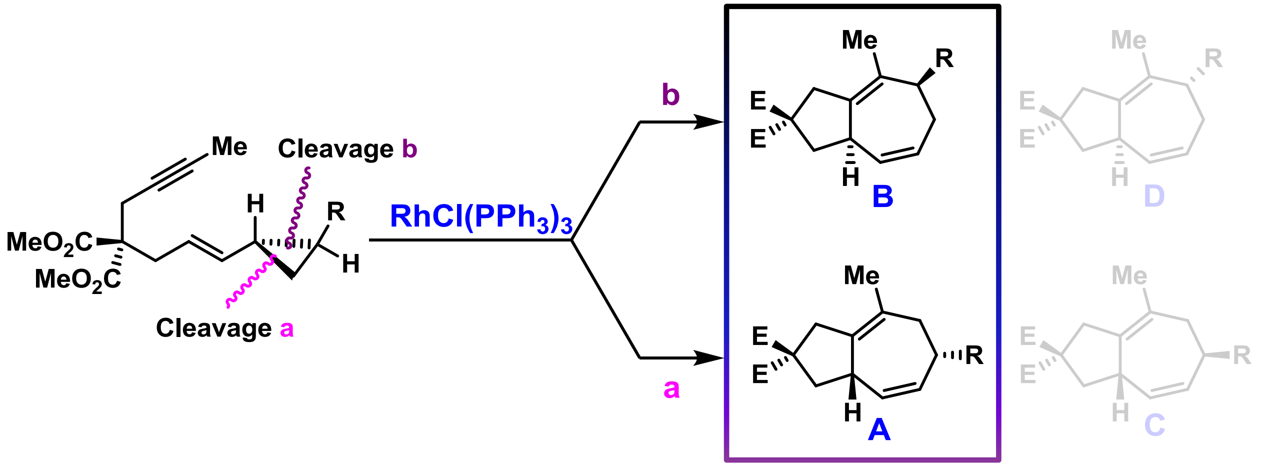


$R^1 = R^2$ = H	**90%**
R^1 = H, R^2 = Me	**90%**
R^1 = Me, R^2 = H	**92%**

(only *cis* junction)

Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843; Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 1940.

Regioselectivity and Diastereoselectivity in the Intramolecular [5+2] Cycloaddition

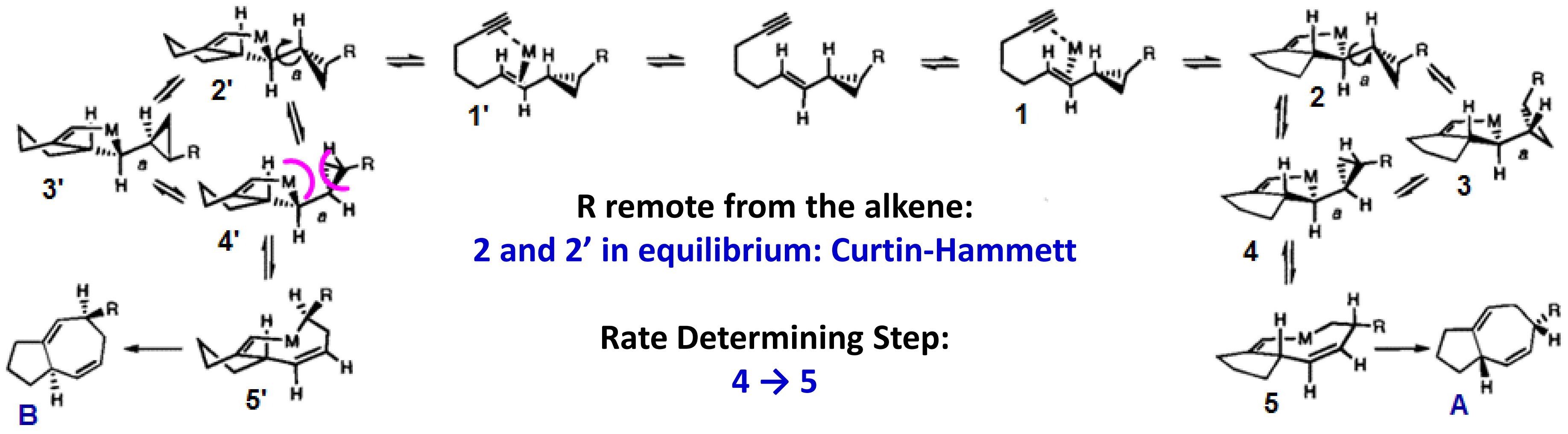


Stereochemistry of VCP translated to the cycloadduct (no C/D)

A usually favored over B (with bulky R: d.r. > 20:1)

Cleavage b

Cleavage a



R remote from the alkene:

2 and 2’ in equilibrium: Curtin-Hammett

Rate Determining Step:

4 → 5

Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Amer. Chem. Soc.* **1999**, *121*, 10442; (Picture taken from the same article and modified); Wender, P. A.; Dyckman, A. J. *Org. Lett.* **1999**, *1*, 2089.

Improved Catalytic Systems: $[Rh(CO)_2Cl]_2$

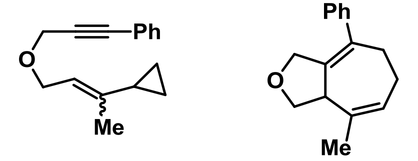
Wilkinson Catalyst ***$[RhCl(PPh_3)_3]$*:**

- ***High temperatures required;***
- ***Not generally applicable***

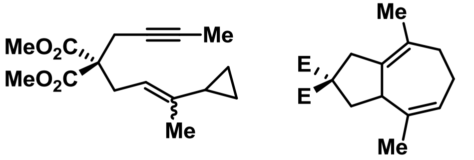
(No Reactivity or isomerisation depending on thether and VCP)

Wender, 1998: $[Rh(CO)_2Cl]_2$

- ***Less sterically encumbered;***
- ***Requires milder conditions in related additions.***

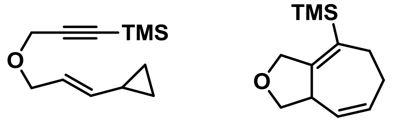


5% $[Rh(CO)_2Cl]_2$	**110°C, 20 min**	**80%**
10% $RhCl(PPh_3)_3$ 10% AgOTf	110°C	-

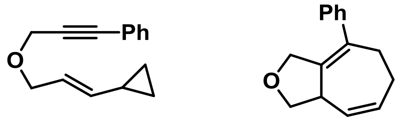


5% $[Rh(CO)_2Cl]_2$	**110°C, 3 h**	**84%**
10% $RhCl(PPh_3)_3$	110°C, 48 h	mix.

Improved reactivity with « problematic substrates »



5% $[Rh(CO)_2Cl]_2$	**30°C, 14 h**	**78%**
10% $RhCl(PPh_3)_3$	110°C, 3.5 h	83%



5% $[Rh(CO)_2Cl]_2$	**30°C, 14 h**	**80%**
10% $RhCl(PPh_3)_3$	110°C, 1,5 h	80%

Milder conditions generally possible

No reactivity observed with alkenes and terminal alkynes

Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164.

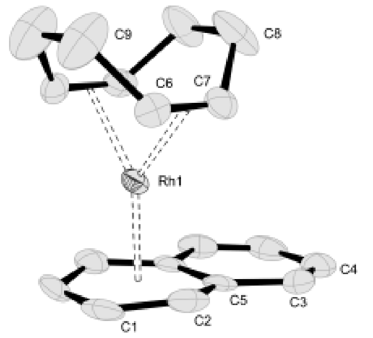
Other Catalyst Systems: $[(C_{10}H_8)Rh(cod)]^+$

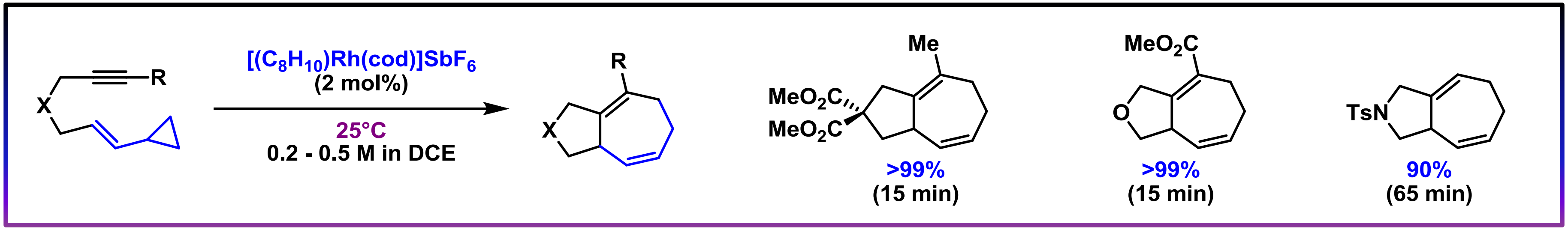
Chung, 1999: $[(C_{10}H_8)Rh(cod)]BF_4$

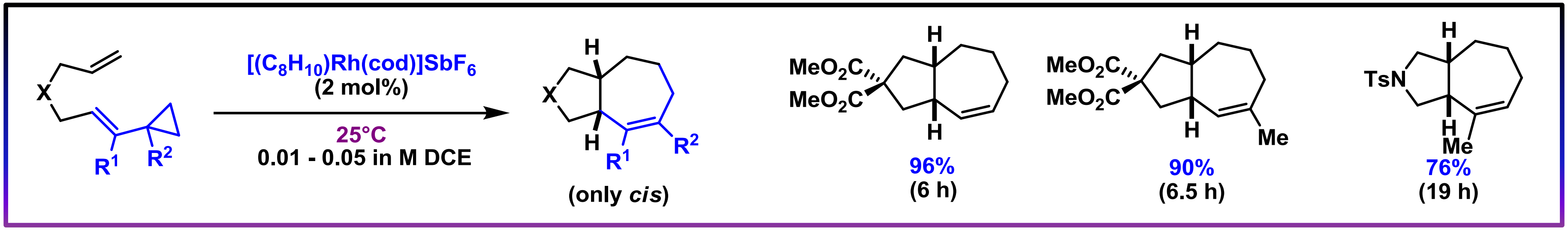
efficient catalyst for [4+2] cycloadditions of dienes and alkynes.

Wender, 2002: $[(C_{10}H_8)Rh(cod)]SbF_6$

- *readily prepared from* $[RhCl(cod)_2]$, $AgSbF_6$ *and naphthalene;*
- *air stable at rt, catalytic activity is retained for long times;*



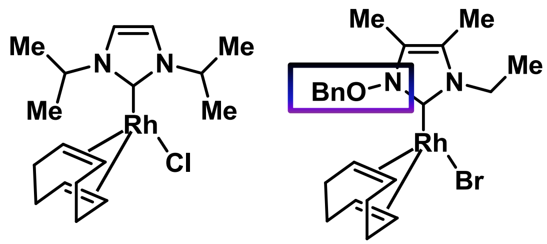




- *More general catalytic system than Wilkinson catalyst and* $[Rh(CO)_2Cl]_2$*;*
- *Effective under mild conditions.*

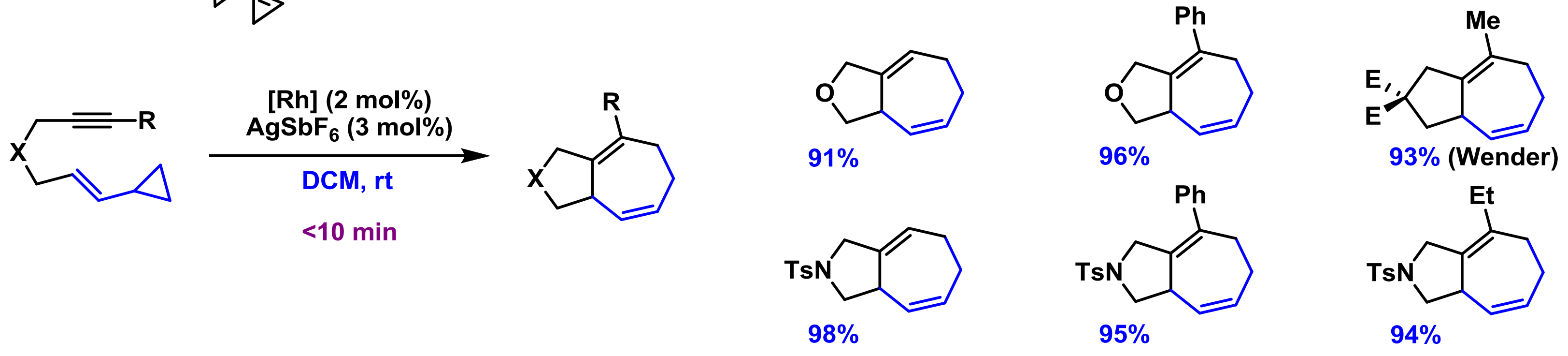
Paik, S.-J.; Son, S. U.; Chung, Y. K. *Org. Lett.* **1999**, *1*, 2045; Wender, P. A.; Williams, T. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 4550.

A Further Improvement: Rhodium-NHCs

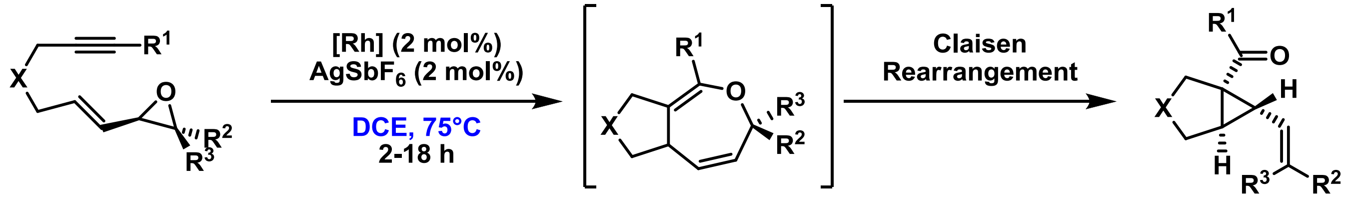


Chung (2006): first use of Rh-NHC for [4+2] and [5+2]

Wender (2007): tuning of NHC σ-donor properties by *heteroatom on N*.



Vinylic Oxiranes: Synthesis of [3.1.0] Hexanes by Hetero-[5+2] Cycloaddition/Claisen Rearrangement



X = C(CO_2Me), O, NTs
R^1= Ar

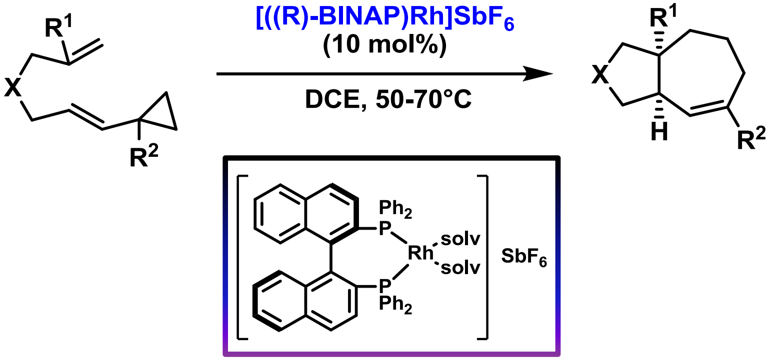
47-94%

Zhang et al. *J. Am. Chem. Soc.* **2011**, *133*, 7304.

Lee, S. I.; Park, S. Y.; Park, J. H.; Jung, I. G.; Choi, S. Y.; Chung, Y. K.; Lee, B. Y. *J. Org. Chem* **2006**, *71*, 91;
Gómez, F. J.; Kamber, N. E.; Deschamps, N. M.; Cole, A. P.; Wender, P. A.; Waymouth, R. M. *Organometallics* **2007**, *26*, 4541.

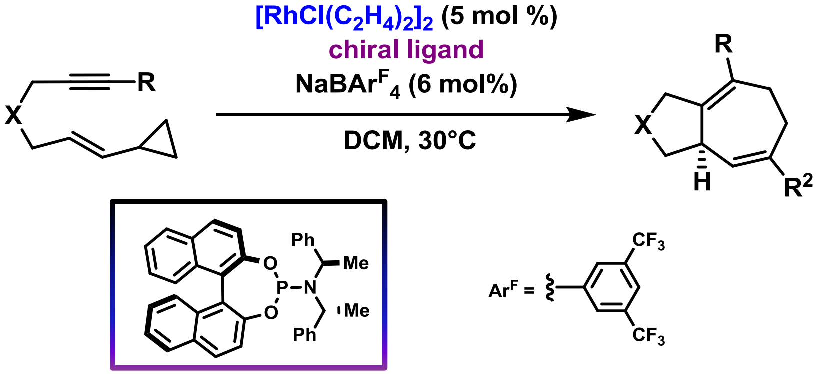
Asymmetric Rh-Catalyzed [5+2] Cycloaddition of VCPs

Wender (2006): Alkene-VCPs

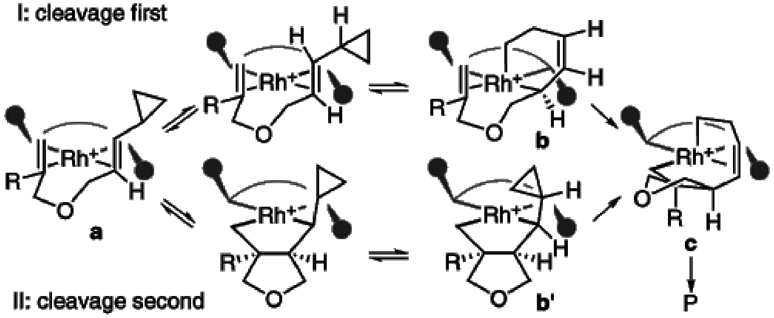


X	R^1	R^2	Yield	ee
$C(CO_2Me)_2$	*H*	*H*	*73%*	*52%*
	Me	*H*	*72%*	*>95%*
	CH_2OBn	*H*	*80%*	*>99%*
	H	*Me*	*92%*	*95%*
NTs	*H*	*H*	*90%*	*96%*

Hayashi (2009): Alkyne-VCPs



X	R	Yield	ee
$C(CO_2Me)_2$	Ph	82	83%
NTs	Ph	88%	99%
	Me	87%	>99.5%
	H	53%	92%
O	CH_2CH_2Ph	90%	95%

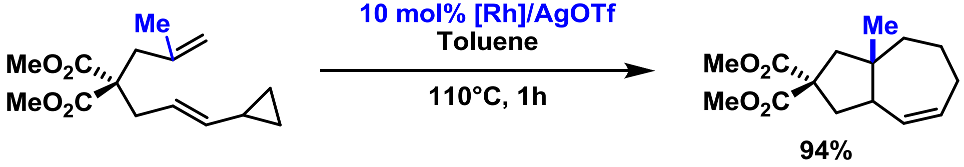


Wender, P. A.; Haustedt, L. O.; Lim, J.; Love, J. A.; Williams, T. J.; Yoon, J.-Y. *J. Am. Chem. Soc.* **2006**, *128,* 6302; (Pictures taken from the same article); Shintani, R.; Nakatsu, H.; Takatsu, K.; Hayashi, T. *Chem. Eur. J.* **2009,** *15,* 8692.

Reaction with Tethered Allenes

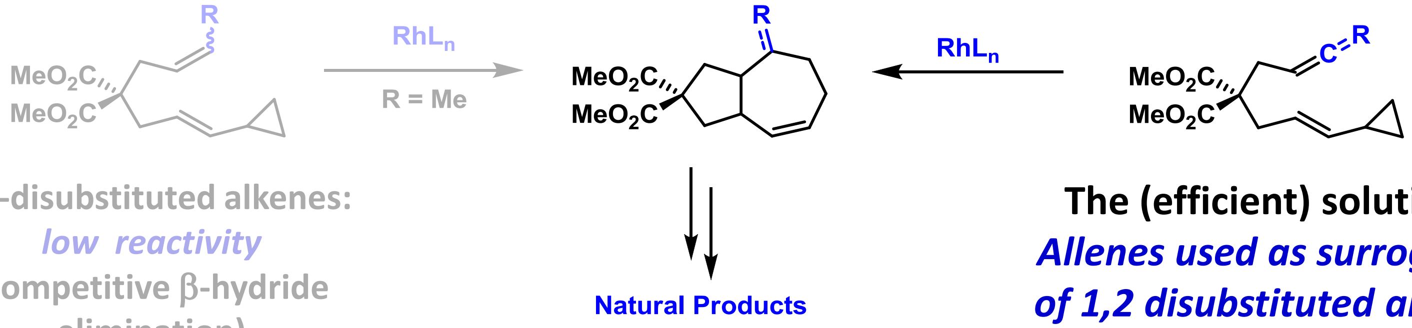
1,1-disubstituted alkenes:

good reactivity observed



10 mol% [Rh]/AgOTf
Toluene
110°C, 1h

94%



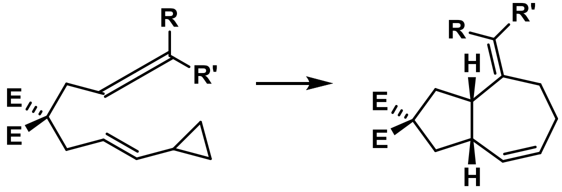
1,2-disubstituted alkenes:

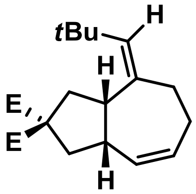
low reactivity

(competitive β-hydride elimination)

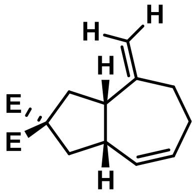
The (efficient) solution:

Allenes used as surrogates of 1,2 disubstituted alkenes

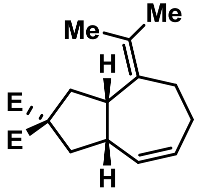




1 mol% $RhCl(PPh)_3$
PhMe, 110°C, 5h
96%



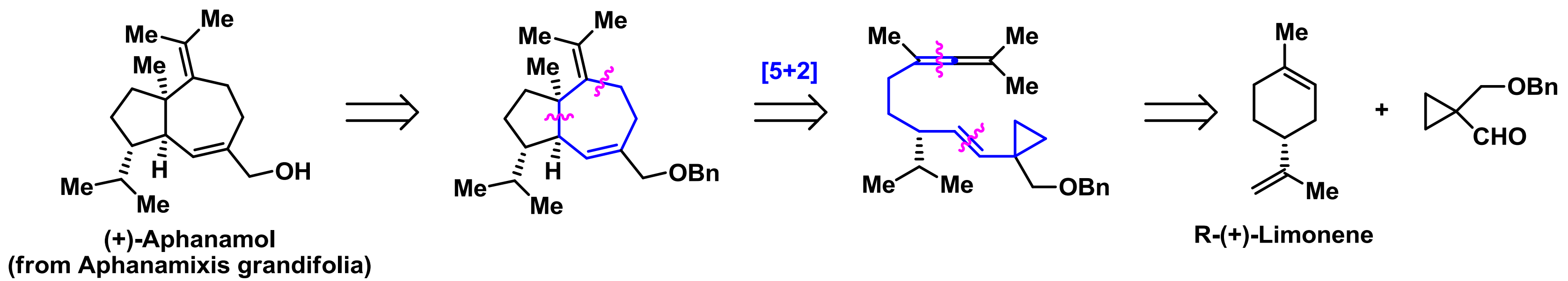
5 mol% $[Rh(CO)_2Cl]_2$
DCE, 90°C, 3.5 h
83% (cis:trans > 20:1)



10 mol% $[Rh(CO)_2Cl]_2$
PhMe, 90°C, 0.75 h
90% (cis:trans > 10:1)

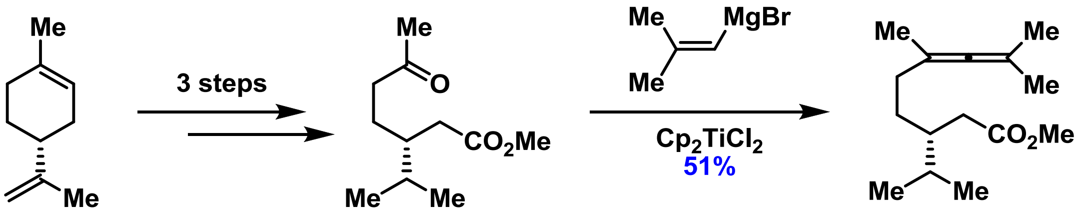
Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem.Soc.* **1999**, *121*, 5348.

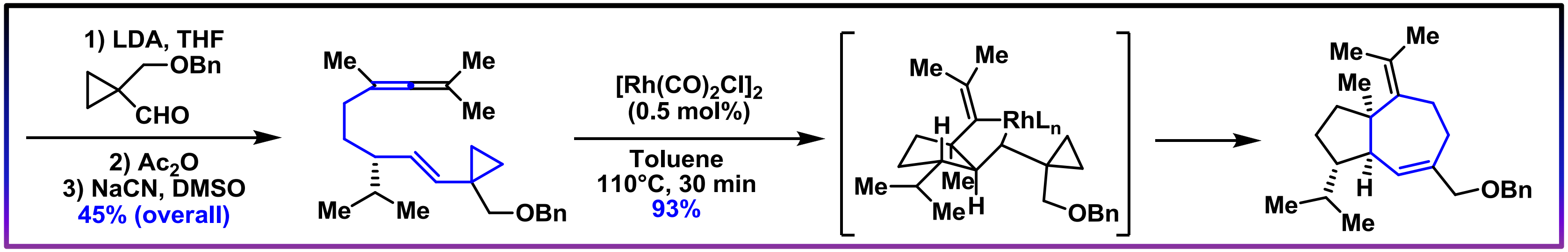
Total Synthesis of (+)-Aphanamol (Wender)

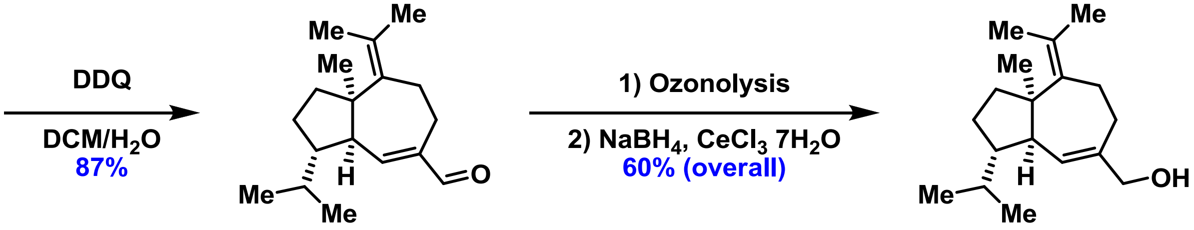


(+)-Aphanamol
(from Aphanamixis grandifolia)

R-(+)-Limonene

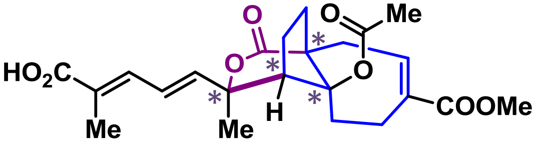




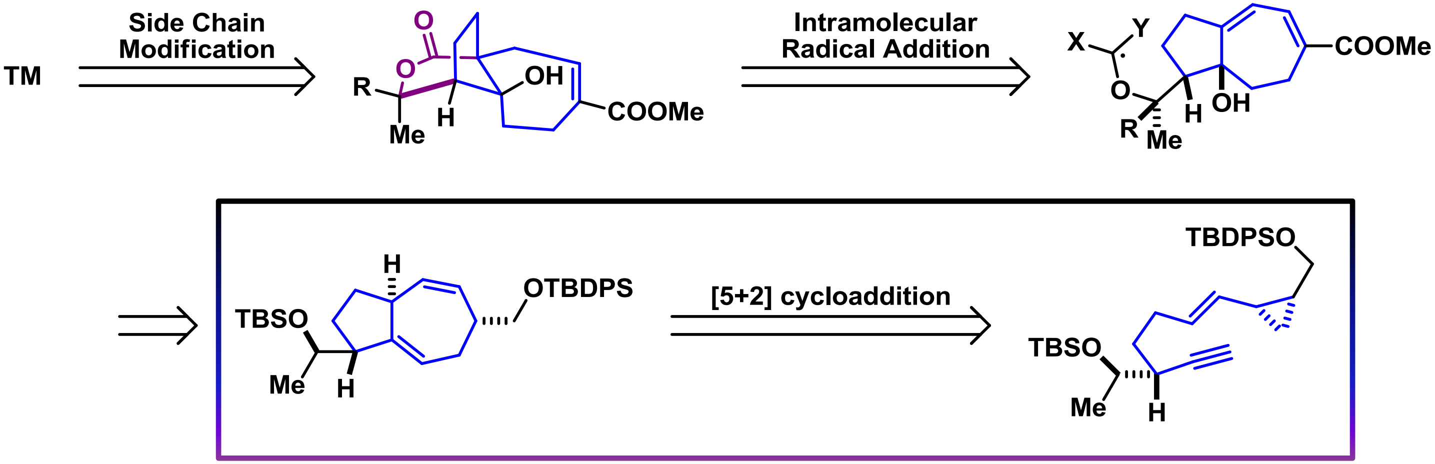


Wender, P. A.; Zhang, L. *Org. Lett.* **2000**, *2*, 2323.

Total Synthesis of (-)-Pseudolaric Acid B (Waser, Trost)

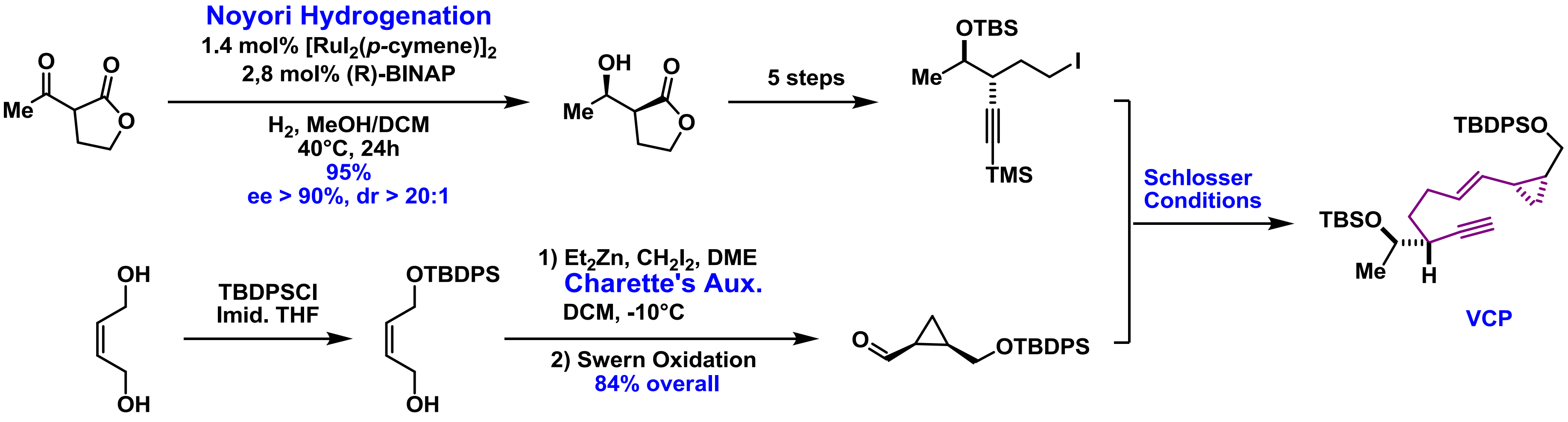


- ***Proved antifungal, antifertility and citotoxic activity; potential application for cancer therapy.***
- ***Complex multifunctionalized triyclic core; four contiguous stereocenters (one quaternary).***
- ***Fused [5 – 7] ring system (polyhydroazulene): Target for [5+2] cycloaddition.***



Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc*. **2007**, *129*, 14556; Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2008**, *130*, 16424.

(-)-Pseudolaric Acid B: [5+2] Cycloaddition



Noyori Hydrogenation

1.4 mol% $[RuI_2(p\text{-cymene})]_2$

2,8 mol% (R)-BINAP

H_2, MeOH/DCM

40°C, 24h

95%

ee > 90%, dr > 20:1

5 steps

TBDPSCl

Imid. THF

1) Et_2Zn, CH_2I_2, DME

Charette's Aux.

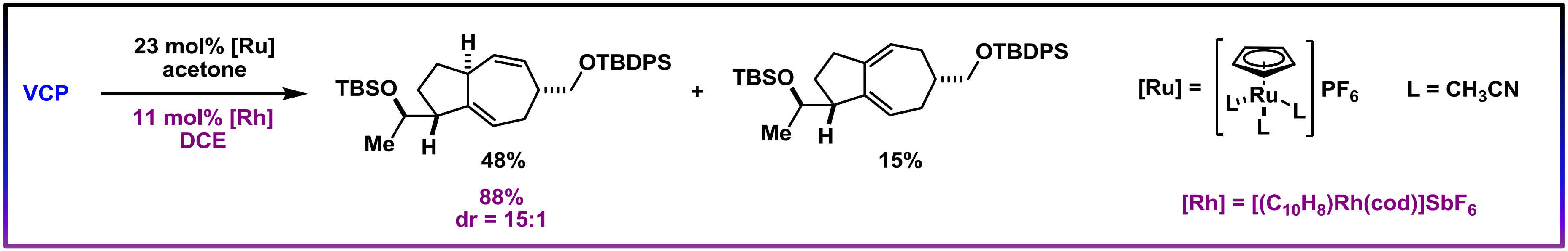
DCM, -10°C

2) Swern Oxidation

84% overall

Schlosser Conditions

VCP



VCP

23 mol% [Ru]

acetone

11 mol% [Rh]

DCE

48%

88%

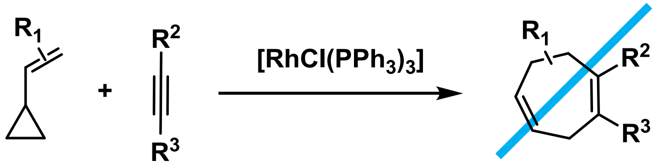
dr = 15:1

15%

[Ru] = $\left[\text{CpRu}(L)_3\right]PF_6$ L = CH_3CN

[Rh] = $[(C_{10}H_8)Rh(cod)]SbF_6$

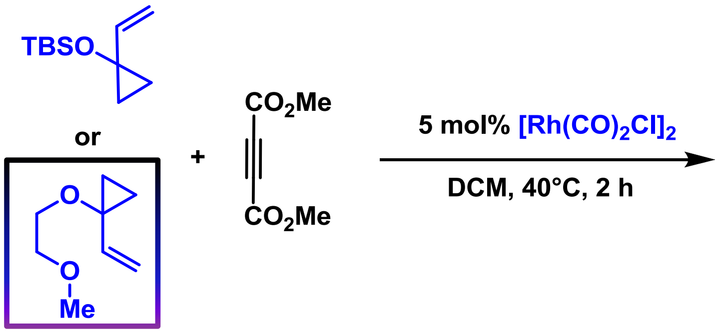
Intermolecular [5+2] cycloaddition of VCPs and alkynes

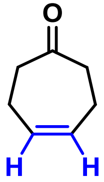


- ***No reactivity***
- ***Isomerization of the VCP***
- ***Trimerization of the alkyne***

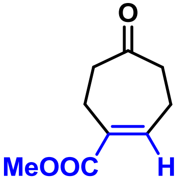
Previously observed: ***Increase of intramolecular reactivity with O-substituted VCPs;***

$[Rh(CO)_2Cl]_2$ effective with unreactive substrates.

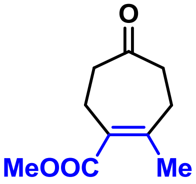




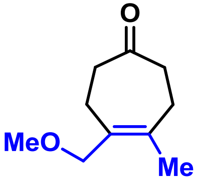
75% (2h)
(with TBSO-VCP
79%, 3h)



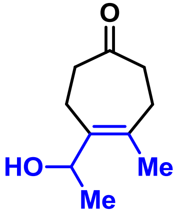
84%, 10 min
(with TBSO-VCP:
93%, 2h)



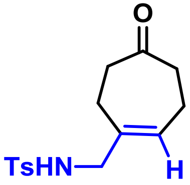
81% (2h)
(with TBSO-VCP:
92%, 1.5h)



94% (30 min)
(with TBSO-VCP:
88%,1.5h)



89% (12 min)

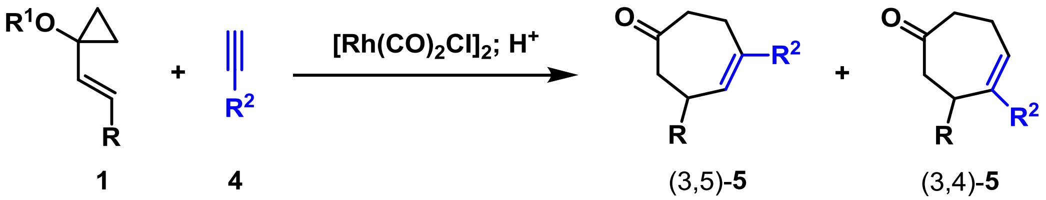


87% (15 min)

Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120, 10976;* Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Scanio, M. J. C. *Org. Lett.* **2000**, *2*, 1609.

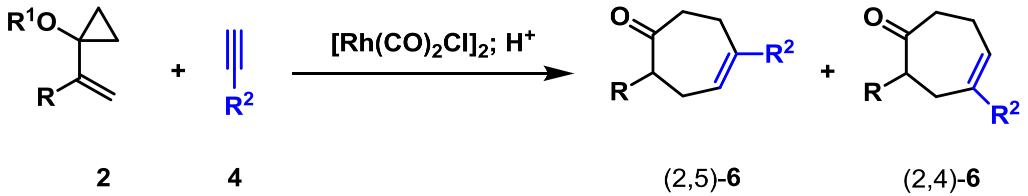
Intermolecular [5+2] Cycloadditions with Substituted VCPs: Regioselectivity

No tether present → two possible orientations for interception of monosubtituted alkynes.



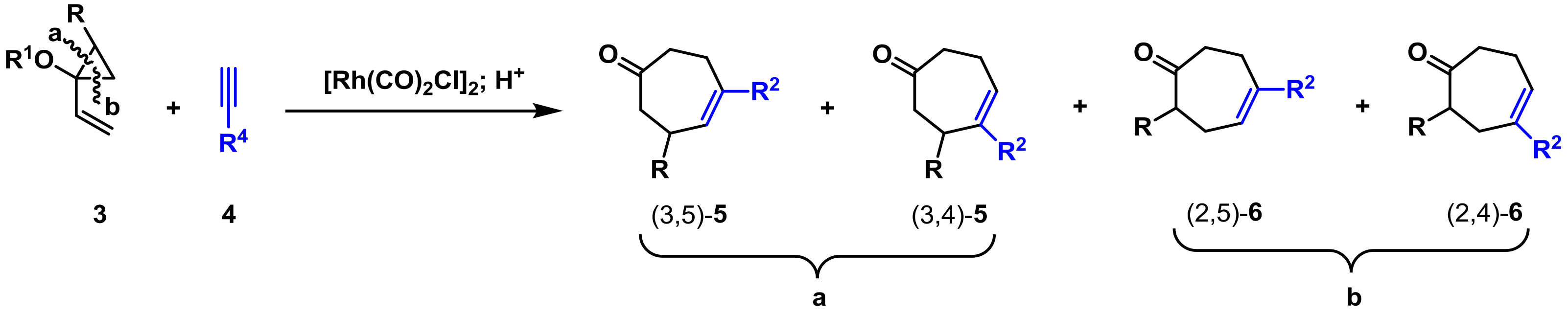
(3,5)-**5** ***strongly favored with all alkynes***;

(3,4)-**5** ***never observed***.



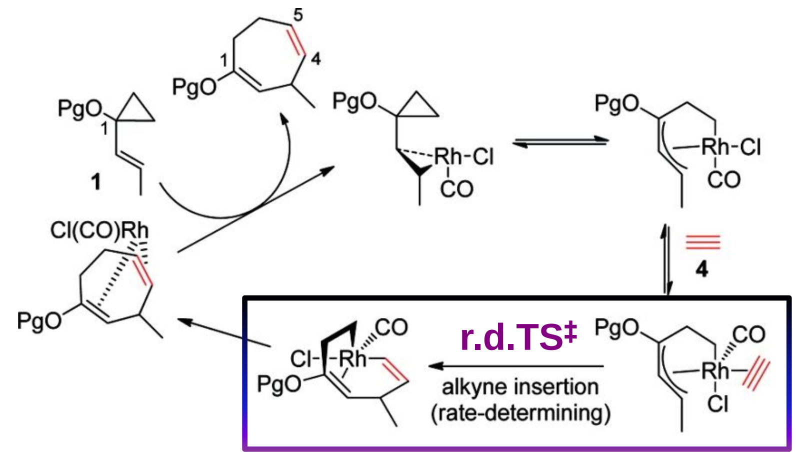
(2,5)-**6** ***favored with most alkynes***;

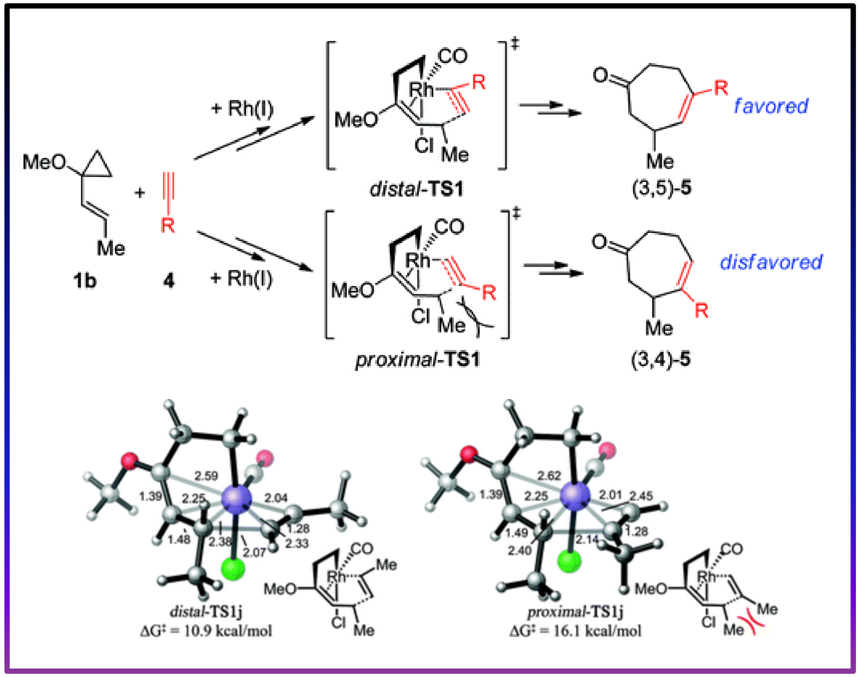
(2,4)-**6** ***less unfavored or dominating if R^4 is small and EWG***

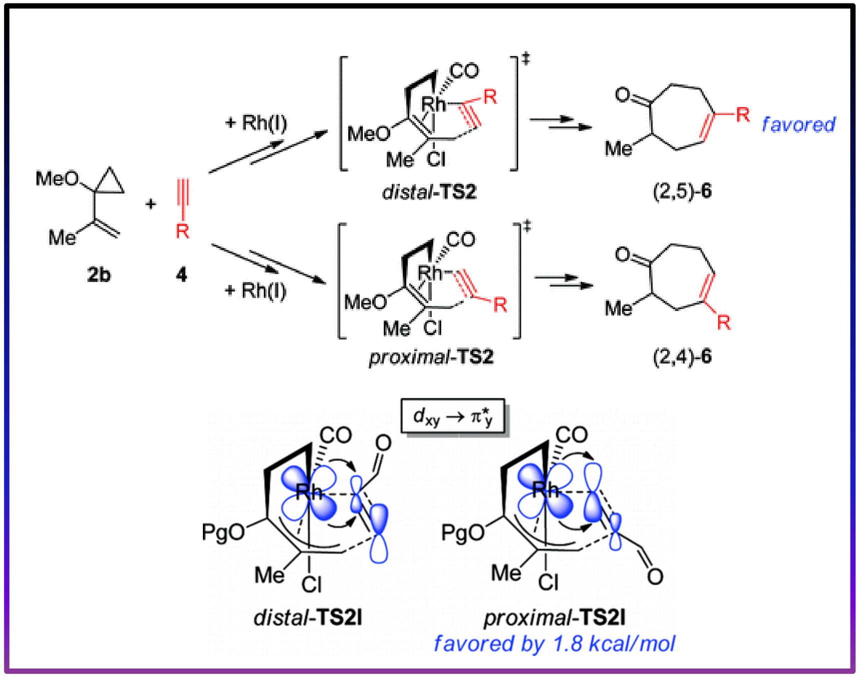


(2,4)-**6** ***selectively formed if R^4 is large and not strongly EWG***; (3,4)-**5** ***never observed***

Intermolecular [5+2] Cycloadditions with Substituted VCPs: Regioselectivity

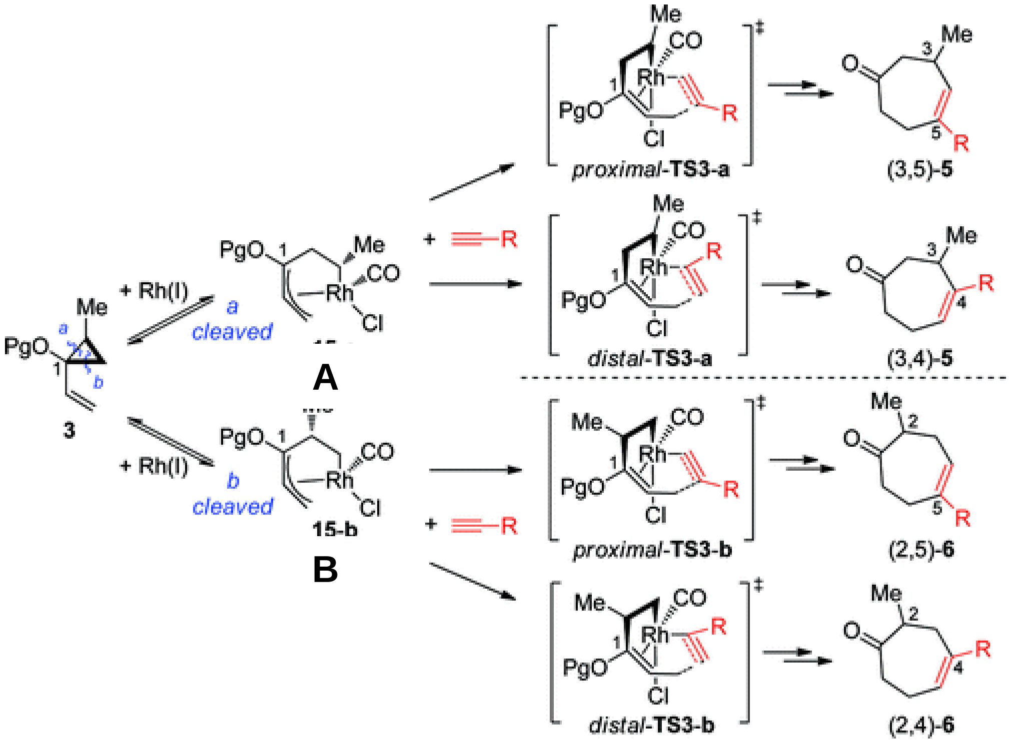






Liu, P.; Sirois, L. E.; Cheong, P. H.-Y.; Yu, Z.-X.; Hartung, I. V.; Rieck, H.; Wender, P. A.; Houk, K. N., *J. Am. Chem. Soc*. **2010**, *132,* 10127 (Pictures taken from the same article).

Intermolecular [5+2] Cycloadditions with Substituted VCPs: Regioselectivity



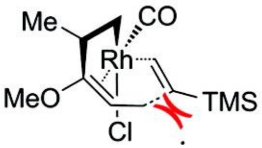
Low activation barriers for cleavage of both bonds ***a*** and ***b*** in VCP cyclopropyl:

Cleavage of Cyclopropyl bonds reversible

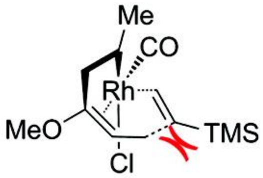
Metallacycles A and B in equilibrium

Curtin-Hammett conditions applied

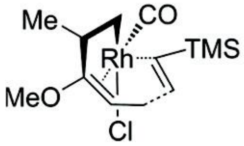
Example: R on alkyne large and electron-donating (TMS): ***Sterical Effect Dominating***



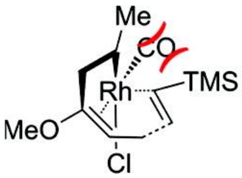
distal **TS3-a**:
ΔG*= 13.9 kcal/mol



Proximal **TS3-a**:
ΔG*= 15.1 kcal/mol



Distal **TS3-b**:
ΔG*= 12.1 kcal/mol

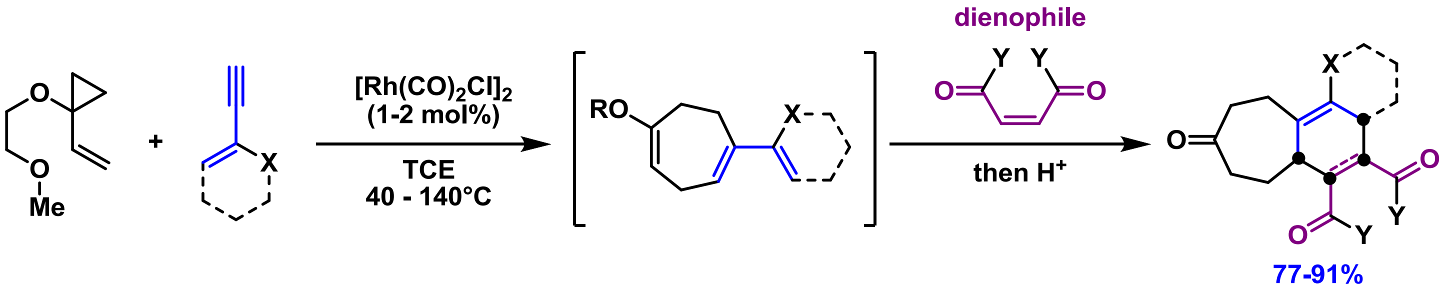


Proximal **TS3-b**:
ΔG*= 14.3 kcal/mol

Liu, P.; Sirois, L. E.; Cheong, P. H.-Y.; Yu, Z.-X.; Hartung, I. V.; Rieck, H.; Wender, P. A.; Houk, K. N.*, J. Amer. Chem. Soc.* **2010**, *132,* 10127; (picture takene from the same paper).

Aiming to Step-Economy: Intermolecular [5+2] Cycloadditions in Cascade Reactions

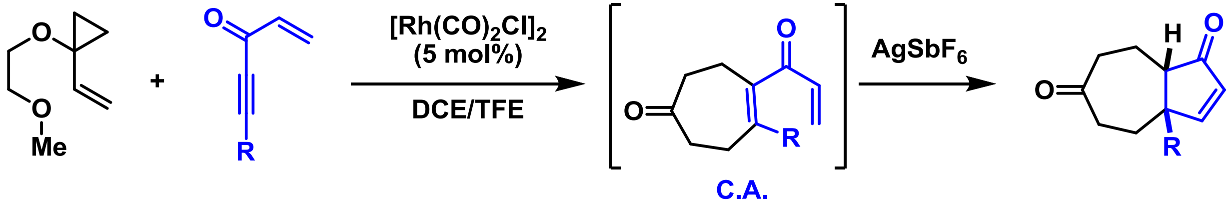
Serial [5+2]/[4+2] Cycloaddition Reactions

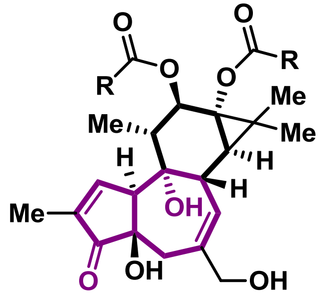


Complete Chemoselectivity
for the alkyne over the alkene

- Tricyclic system
- Up to four stereocenters

Serial [5+2] Cycloaddition/Nazarov Cyclisation



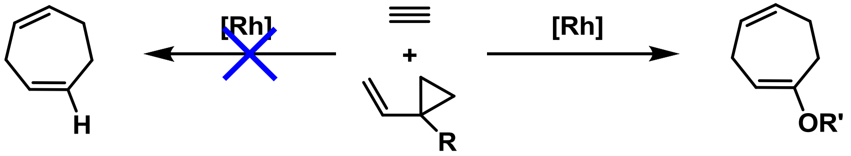


Phorbol Esters

- *Sequence (two-flask): $[Rh(CO)_2Cl]_2$ → isolation of C.A. → $AgSbF_6$*
- *Sequence (one-flask, two catalysts): $[Rh(CO)_2Cl]_2$ → $AgSbF_6$ (68-82% yields)*
- *Cascade (one flask, one catalyst): $[Rh(CO)_2Cl]_2/AgSbF_6$ (56-95% yields)*

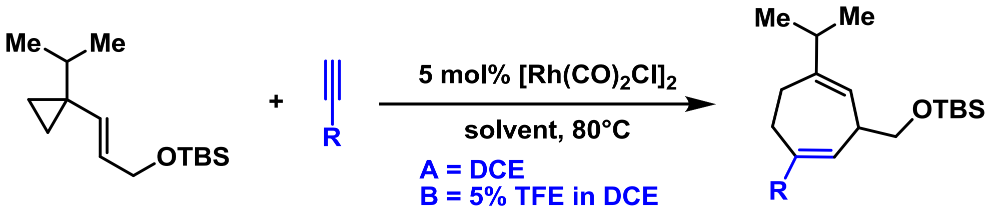
Wender, P. A.; Gamber, G. G.; Scanio, M. J. C. *Angew. Chem. Int. Ed.* **2001**, *40*, 3895; Wender, P. A.; Stemmler, R. T.; Sirois, L. E. *J. Amer. Chem. Soc.* **2010**, *132*, 2532.

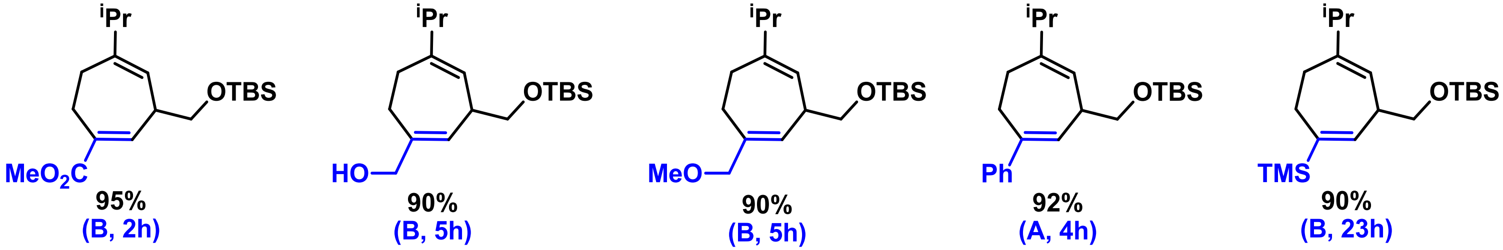
[5+2] Cycloadditions with Unactivated, Alkyl-Substituted VCPs (I)



Heteroatom required to allow intermolecular [5+2]cycloaddition ?

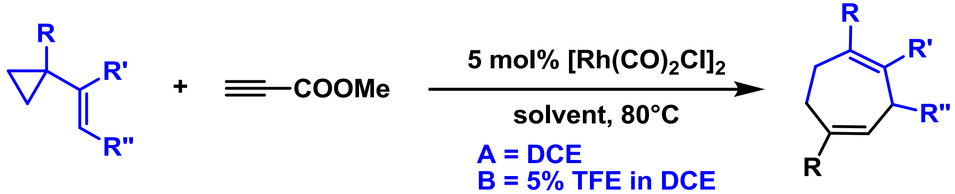
Reactivity also observed with alkyl geminally substituted VCPs!



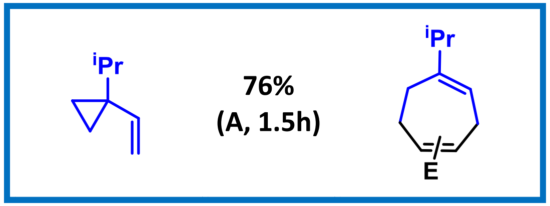


Wender, P. A.; Barzilay, C. M.; Dyckman, A. J. *J. Chem. Amer. Soc.* **2001**, *123*, 179.

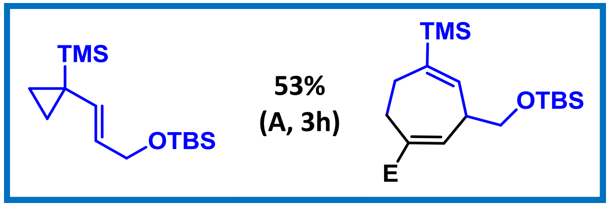
[5+2] Cycloadditions with Unactivated, Alkyl-Substituted VCPs (II)



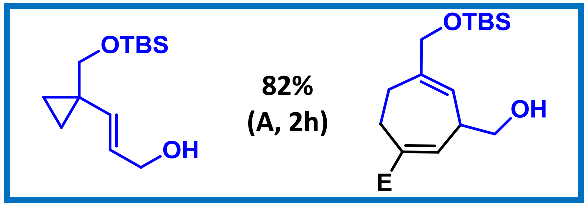
A = DCE
B = 5% TFE in DCE



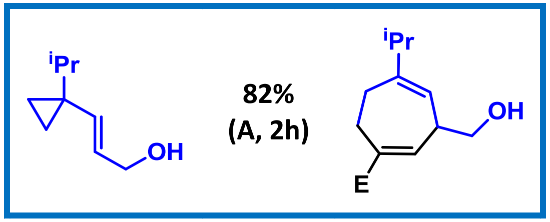
76%
(A, 1.5h)



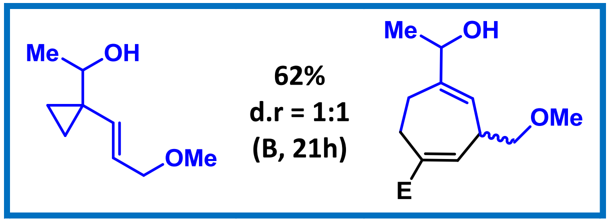
53%
(A, 3h)



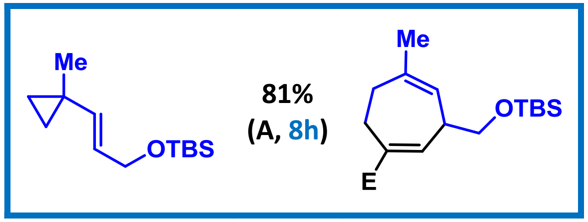
82%
(A, 2h)



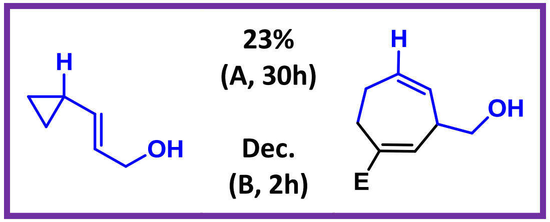
82%
(A, 2h)



62%
d.r = 1:1
(B, 21h)

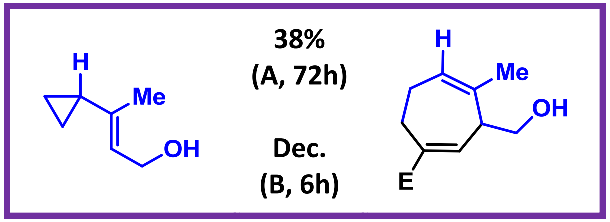


81%
(A, 8h)



23%
(A, 30h)

Dec.
(B, 2h)



38%
(A, 72h)

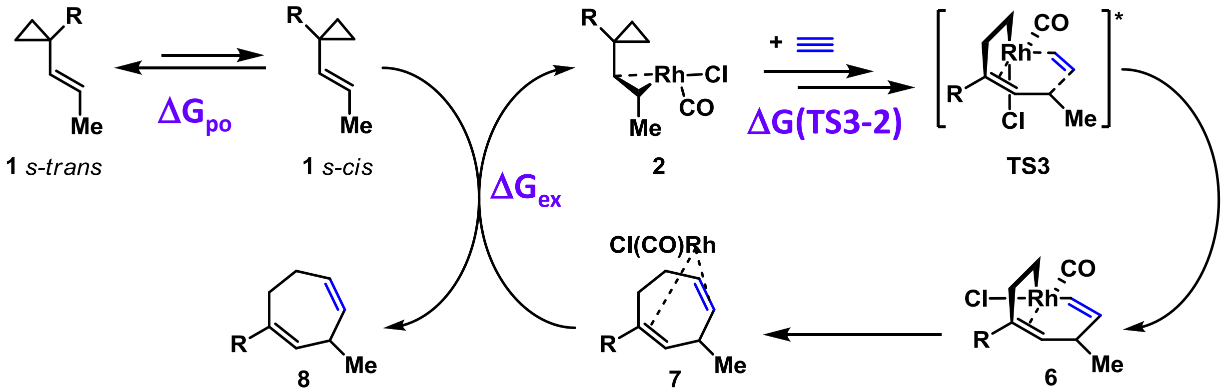
Dec.
(B, 6h)

Low yields or decompositions for unsubstituted cyclopropyls

With monosubstituted alkynes: High (>10:1) to complete regioselectivity observed.

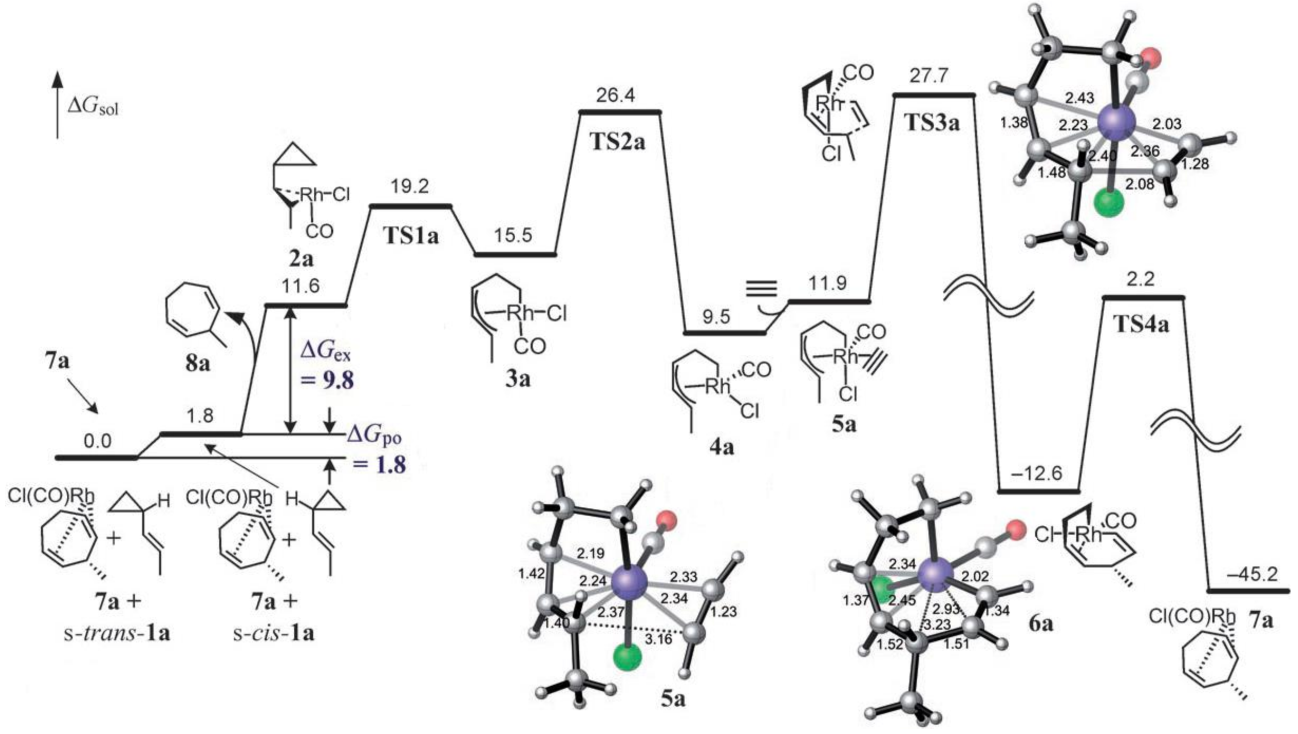
Wender, P. A.; Barzilay, C. M.; Dyckman, A. J. *J. Chem. Am. Soc.* **2001**, *123*, 179.

Intermolecular Reactivity: Effect of Substituents on VCP-C^1



R = H (a)
Me
*i*Pr
OMe

Reactivity increase



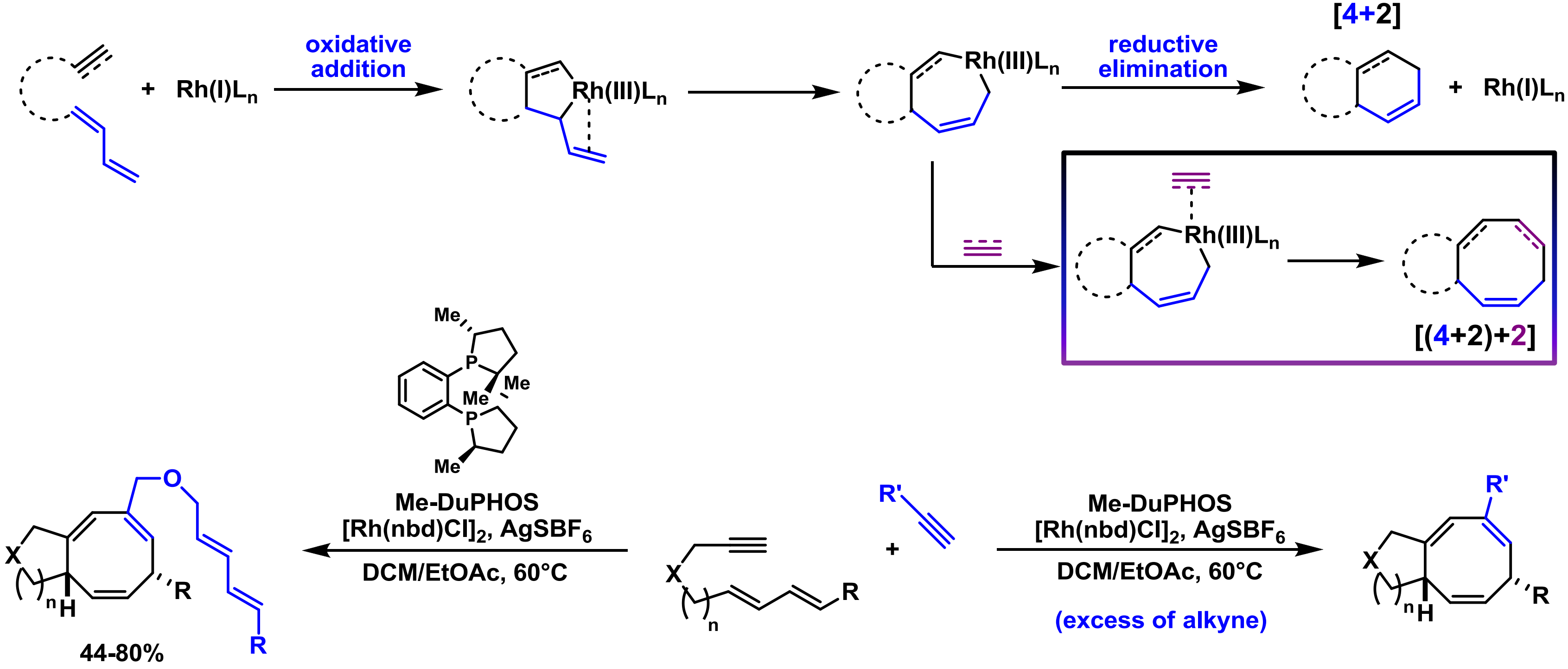
$\Delta G^{\ddagger}=\Delta G_{po}+\Delta G(TS3\text{-}2)+\Delta G_{ex}$

- Bulky R reduces **ΔG_{po}**
- R = OR' reduces **ΔG(TS3-2)**
- **ΔGex** lowly influent

Liu, P.; Cheong, P. H.-Y.; Yu, Z.-X.; Wender, P. A.; Houk, K. N. *Angew. Chem. Int. Ed.* **2008**, *47,* 3939;
(Picture taken from the same article).

Rhodium-Catalyzed [(4+2)+2] Cycloaddition

Gilbertson: Alkyne Interception by [4+2]



oxidative addition

reductive elimination

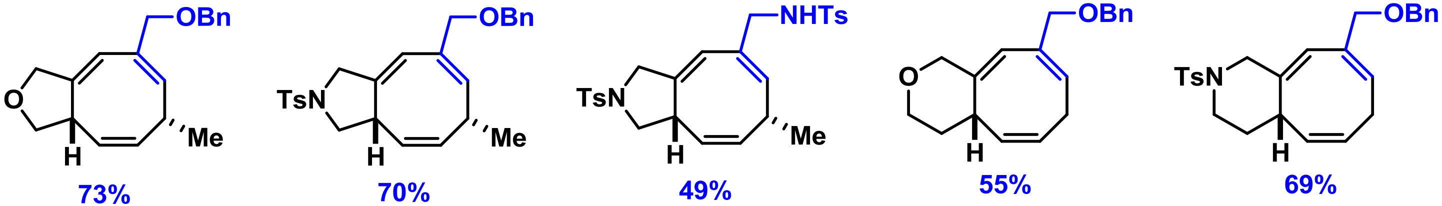
[4+2]

[(4+2)+2]

Me-DuPHOS
$[Rh(nbd)Cl]_2$, $AgSBF_6$
DCM/EtOAc, 60°C

Me-DuPHOS
$[Rh(nbd)Cl]_2$, $AgSBF_6$
DCM/EtOAc, 60°C
(excess of alkyne)

44-80%



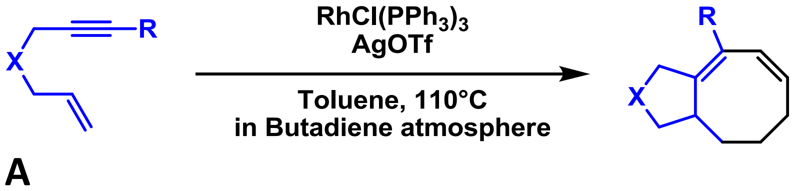
73% 70% 49% 55% 69%

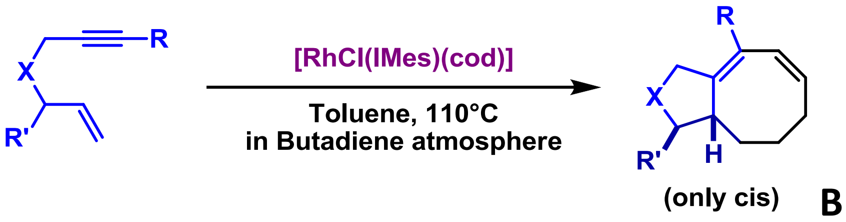
(mixture of regioisomers in both cases)

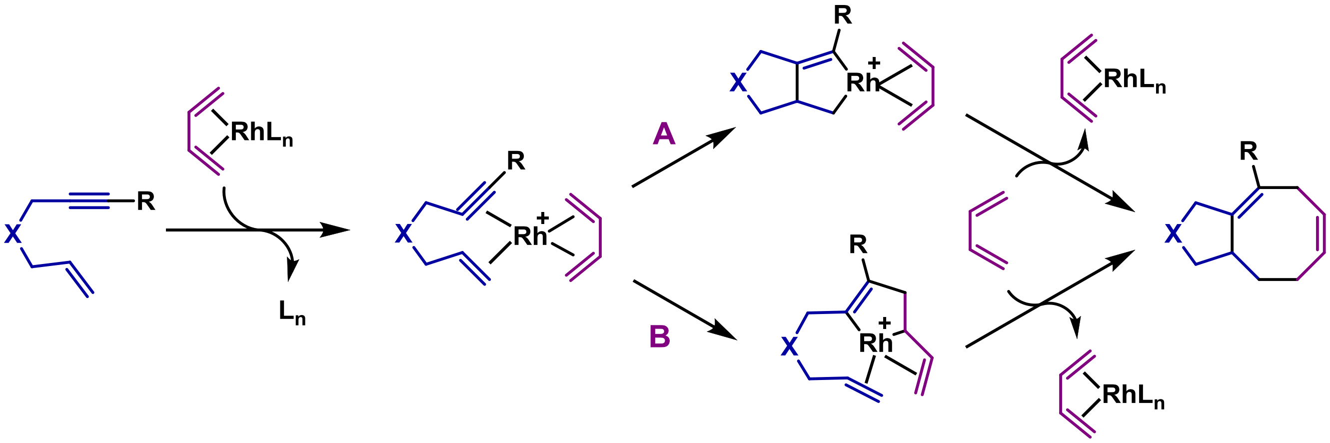
Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784.

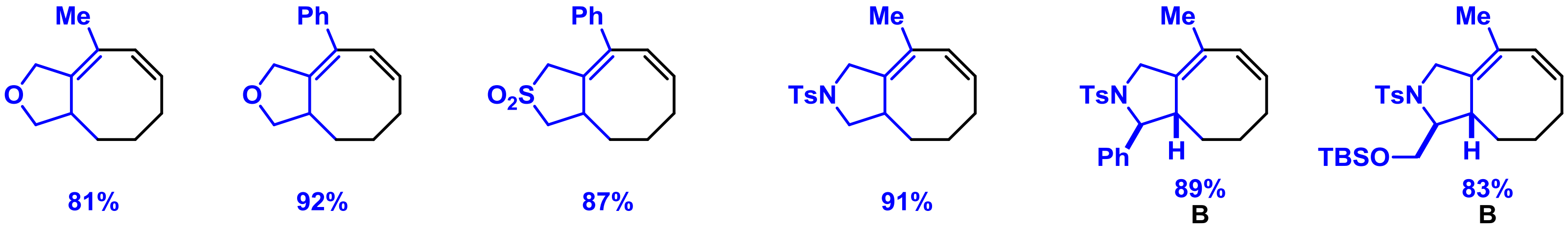
Rhodium-Catalyzed [4+(2+2)] Cycloaddition

Evans: Carbocyclization by interception of butadiene.





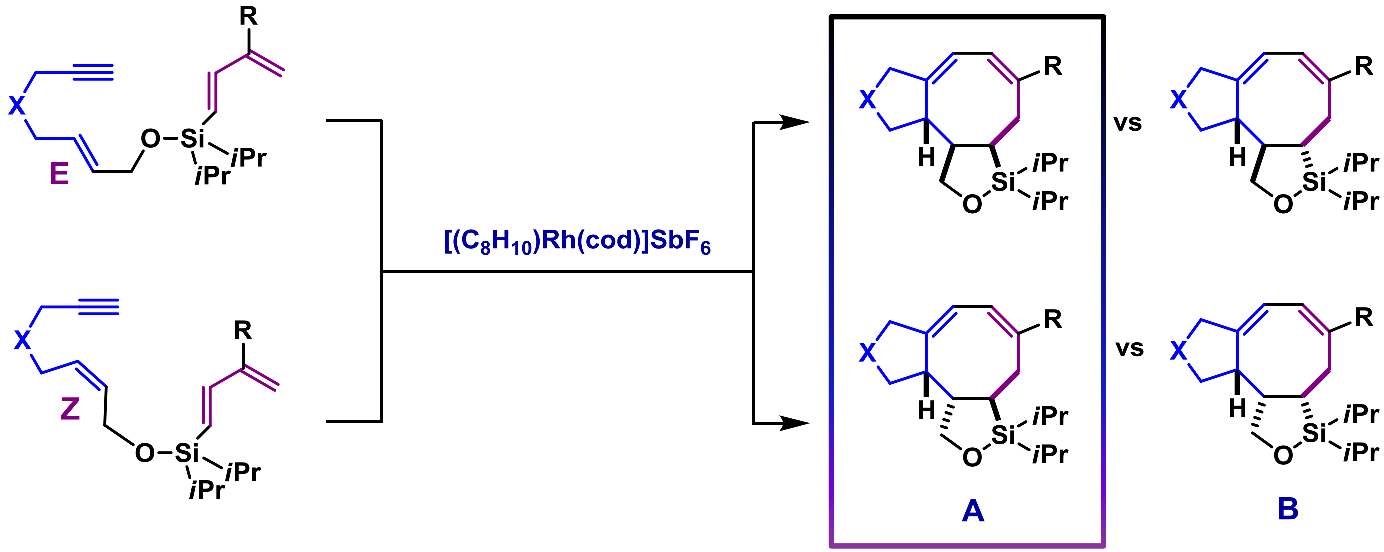


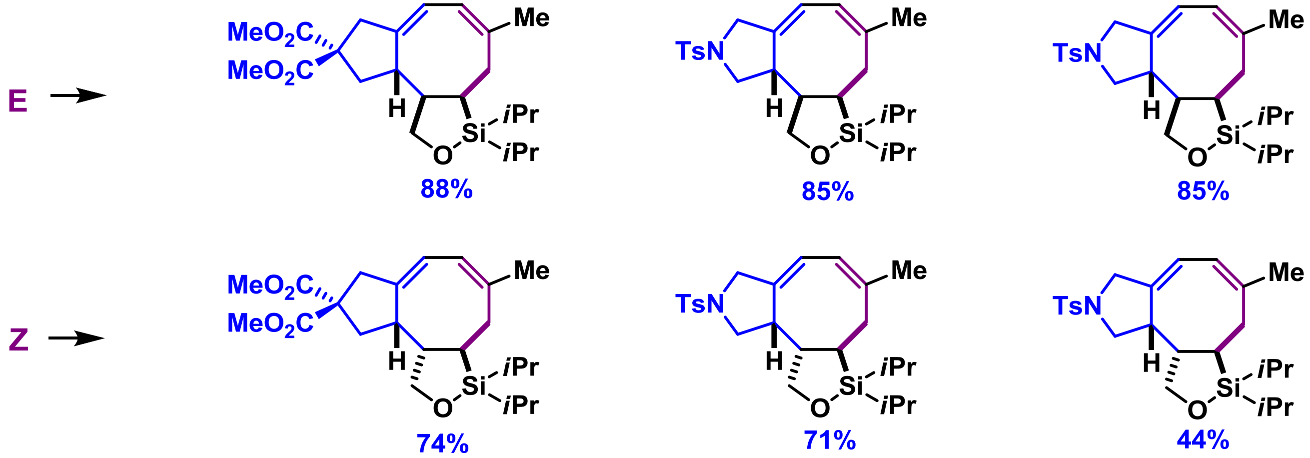


A) Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2002**, *124*, 8783; B) Evans. P. A.; Baum, E. W.; Fazal, A. N.; Pink, Maren *Chem. Comm.* **2005**, 63.

Rhodium-Catalyzed [4+(2+2)] Cycloaddition

Evans: Temporary Silicon-Tethered Rh(I) Catalyzed [4+(2+2)] Carbocyclisation Reactions

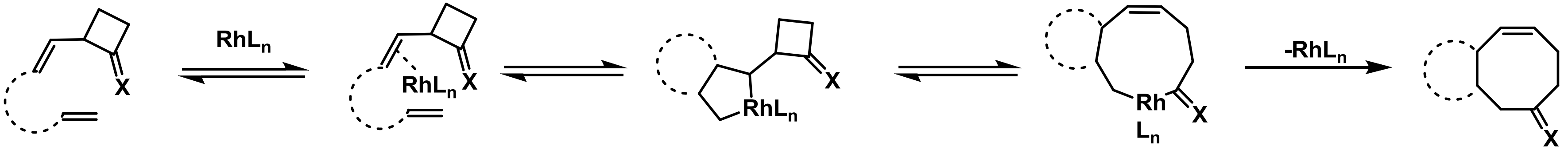




Evans, P. A.; Baum, E. W. *J. Am. Chem. Soc.* **2004**, *126*, 8783

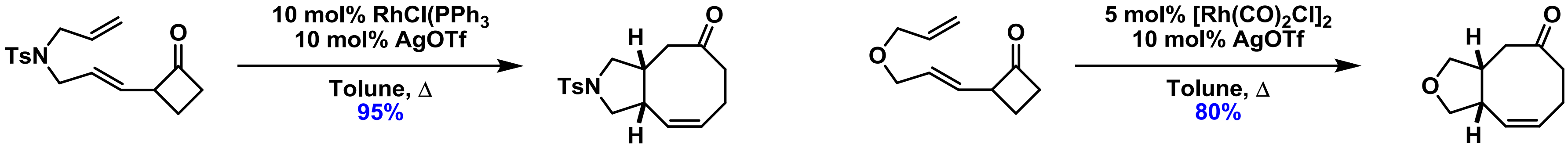
[6+2] Cycloadditions of Vinylcyclobutanones

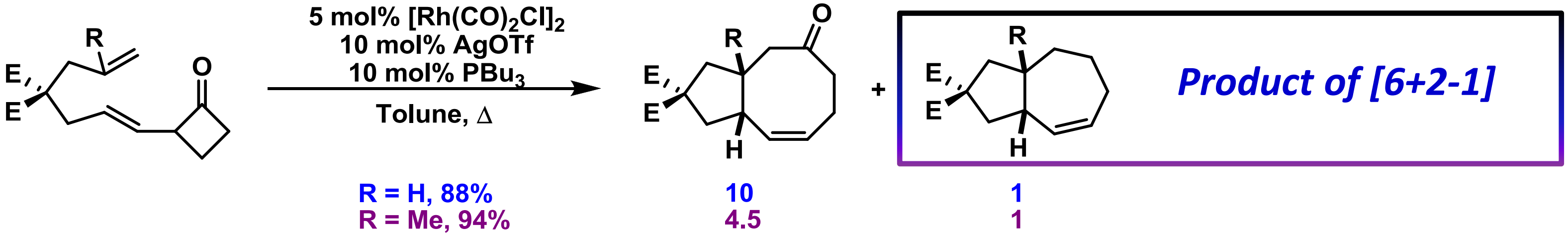
Strain energies similar in simple Cyclopropane and Cyclobutane (27 kcal/mol vs 26 kcal/mol).



No reactivity observed with Vinylcyclobutanes

- VCPs reactivity tunable by substitution of the Cyclopropane subunit;
- Rh known to be able to efficiently insert Cyclobutenones (ring expansion) (Libeskind).*

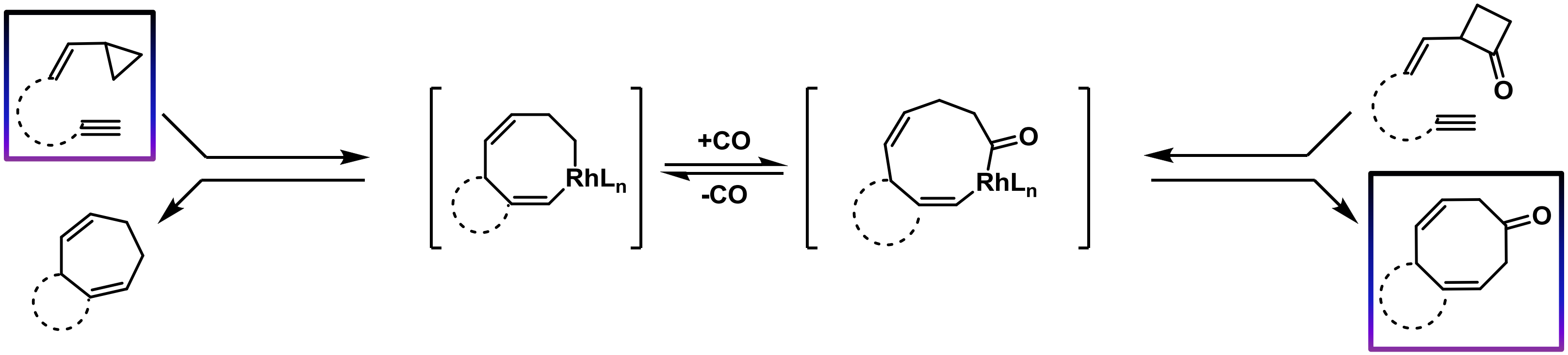


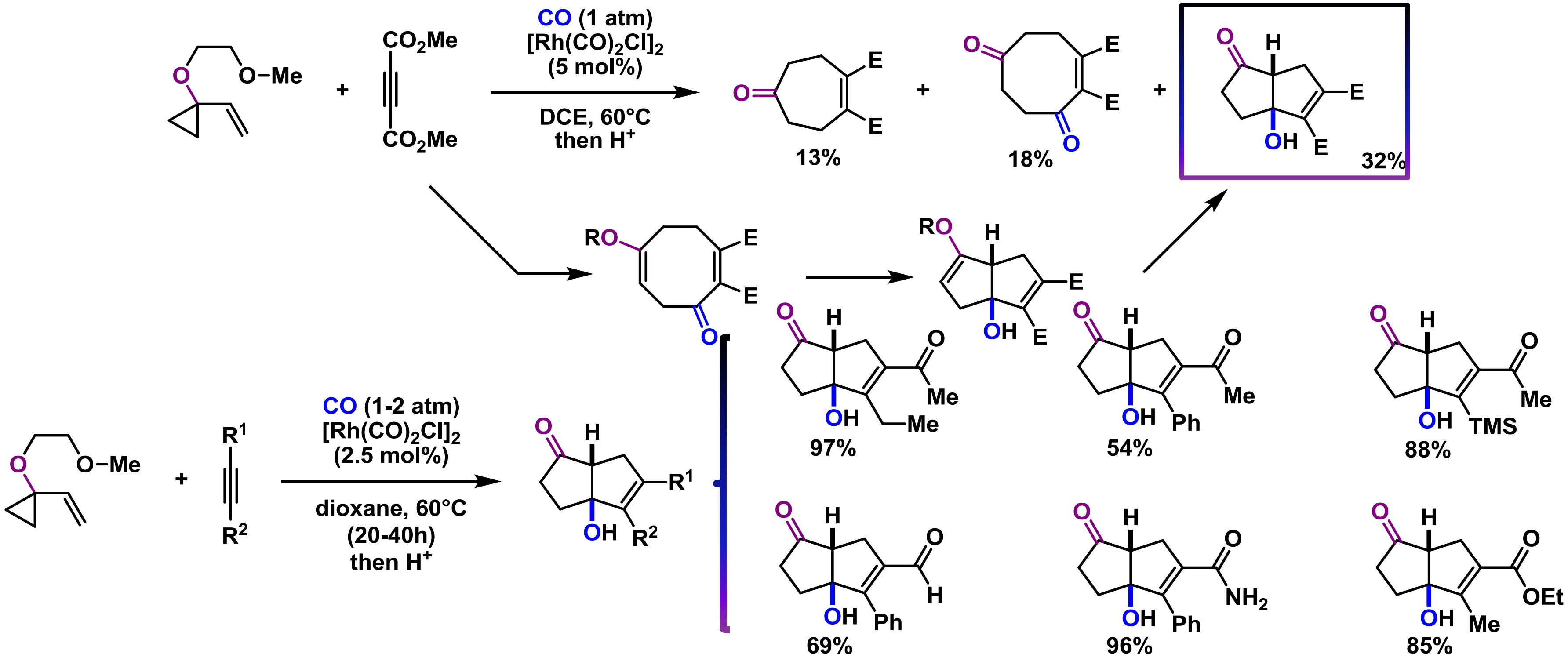


Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815;

* Huffman, M. A.; Liebeskind, L. S. . *J. Am. Chem. Soc.* **1993**, *115*, 4895.

Multicomponent [5+2+1] Cycloadditions of VCPs, alkynes and CO





Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876.

Conclusions

Carbocyclization Reactions:
An effective alternative to « thermal » cycloaddition reaction with unactivated substrates.

Rh(I) Catalyzed [5+2] Cycloadditions:

- **Easy access to 7-membered rings by reaction of VCPs with alkynes, alkenes, allenes;**
- **Intramolecular and Intermolecular versions optimized;**
- **Good FG tolerance;**
- **High Regio- and Diastereoselectivities;**
- **Key step in total syntheses.**

Rh(I) Catalazed Carbocyclization to generate 8-Memberd Rings

Possible Future Developments:

- **Further efforts towards Asymmetry?**
- **Hetero Cycloadditions;**
- **Applications to more complex systems and in total synthesis.**