Frontiers in Chemical Synthesis III
Stereochemistry

Seminar Program
April 14-15, 2016, BCH4310/5310

	Speaker	**Title**
April 14, 2016, BCH 4310: Session I Chair: Nicolas Gaeng		
13h30-14h30	Yang Sun	*Ruthenium Catalyzed Asymmetric Transfer Hydrogenation*
14h30-15h30	Franck Le Vaillant	*Towards a More Sustainable Asymmetric Catalysis with Iron-based Complexes: Progress since 2011*
15h30-16h30	Raphael Beltran	*Major Developments in Rh-catalyzed Asymmetric 1,4-Addition of Boron Species to Enones*
16h30-17h30	Cyril Piemontesi	*Asymmetric Pictet-Spengler Reactions*
April 15, 2016, BCH 5310: Session II Chair: Franck Le Vaillant		
8h30-9h30	Nicolas Gaeng	*Chiral Sulfoxides as Ligands in Asymmetric Catalysis*
9h30-10h30	Marta Falcone	*Chiral Heterobimetallic Lanthanoid Complexes in Asymmetric Catalysis*
10h30-11h30	Lionel Schouwey	*Catalyst Design: from Proline to more Efficient and Enantioselective Derivatives*

Ruthenium-Catalyzed Transfer Hydrogenation

Frontiers in Chemical Synthesis: Stereochemistry

Yang Sun

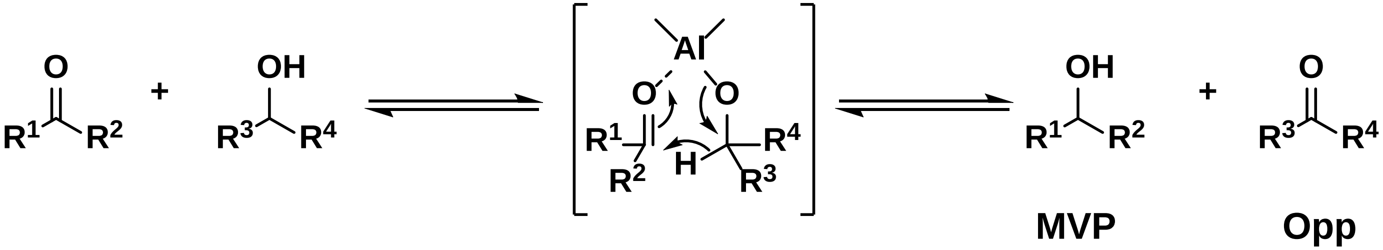
Lausanne, 14th April 2016

Outline

- Introduction
- Noyori’s ligand for ATH
- The development of Noyori’s ligand
- ATH in water and ionic liquid

Introduction of catalytic Transfer Hydrogenation

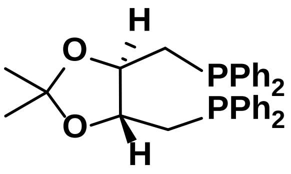
Meerwein-Pondorff-Verley reduction & Oppenauer oxidation



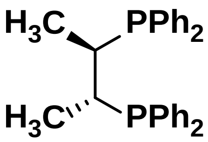
H. Meerwein, R. Schmidt, *Liebigs. Ann. Chem.* **1925**, *444,* 221;
A. Verley, *Bull. Soc. Chim. Fr.* **1925**, 37, 537;
W. Pondorff, *Angew. Chem.* **1926**, *39*, 138;
R. V. Oppenauer, *Rec. Trav. Chim.* **1937**, *56*, 137.

The early stage Ruthenium-catalyzed asymmetric version of transfer hydrogenation

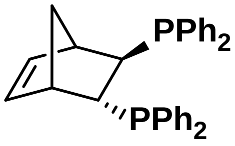
- Examples of phosphorus ligands



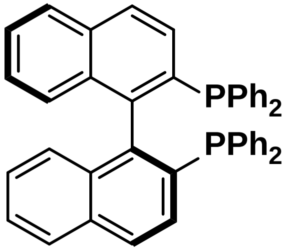
(*R*,*R*)-(-)-DIOP



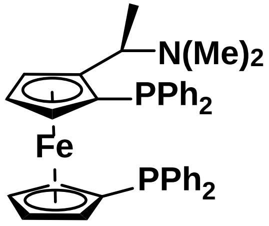
(*R*,*R*)-(+)-CHIRAPHOS



(*R*,*R*)-(-)-NORPHOS



(*S*)-(-)-BINAP



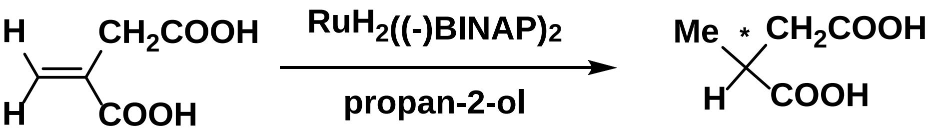
(*R*,*S*)-(-)-BPPFA

G. Yassinovich, G. Mestroni, S. Gladiali, *Chem. Rev*. **1992**, *92*, 1051.

Introduction of catalytic Transfer Hydrogenation

The early stage Ruthenium-catalyzed asymmetric version of transfer hydrogenation

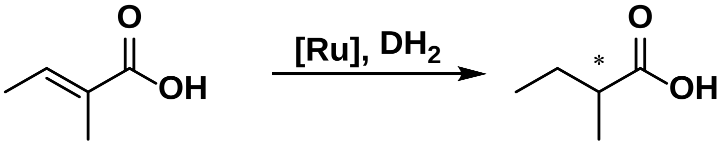
- The achievements of TH with phosphorus ligands

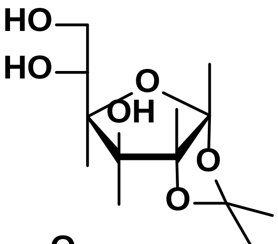
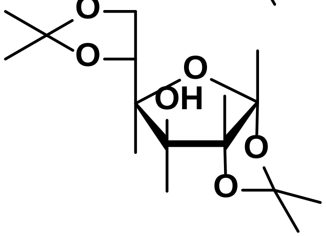


yield: 100%
ee: 97%

G. Yassinovich, G. Mestroni, S. Gladiali, *Chem. Rev*. **1992**, *92*, 1051.

- The influence of other chiral sources (Hydrogen donors)

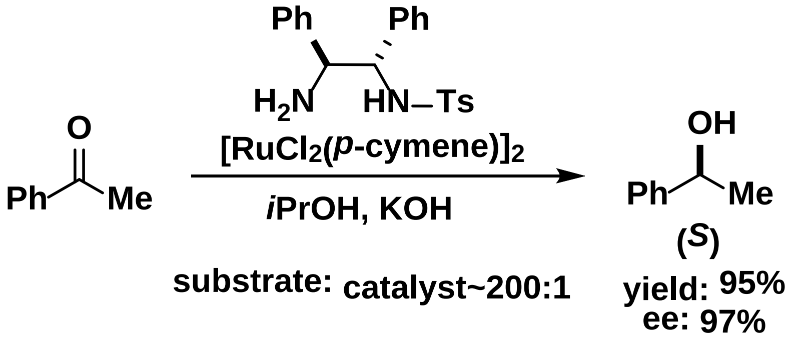


DH_2	**cat.**	**ee(%)**
	$[RuCl_2(PPh_3)_3]$	8.9 (*R*)
	$[Ru_2Cl_4((-)\text{-DIOP})_3]$	22.5 (*R*)
	$[Ru_2Cl_4((+)\text{-DIOP})_3]$	3.9 (*S*)
	$[RuCl_2(PPh_3)_3]$	6.7 (*R*)
	$[Ru_2Cl_4((-)\text{-DIOP})_3]$	12.9 (*R*)
	$[Ru_2Cl_4((+)\text{-DIOP})_3]$	6.4 (*R*)

G. Descotes, D. Sinou, *Tetrahydron Lett.* **1976**, 4083.

The important improvement by Noyori

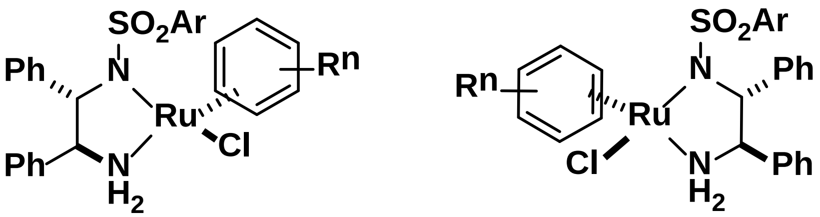
- Examples



S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 7562.

- Origin of stereoselectivity

diamine ligands



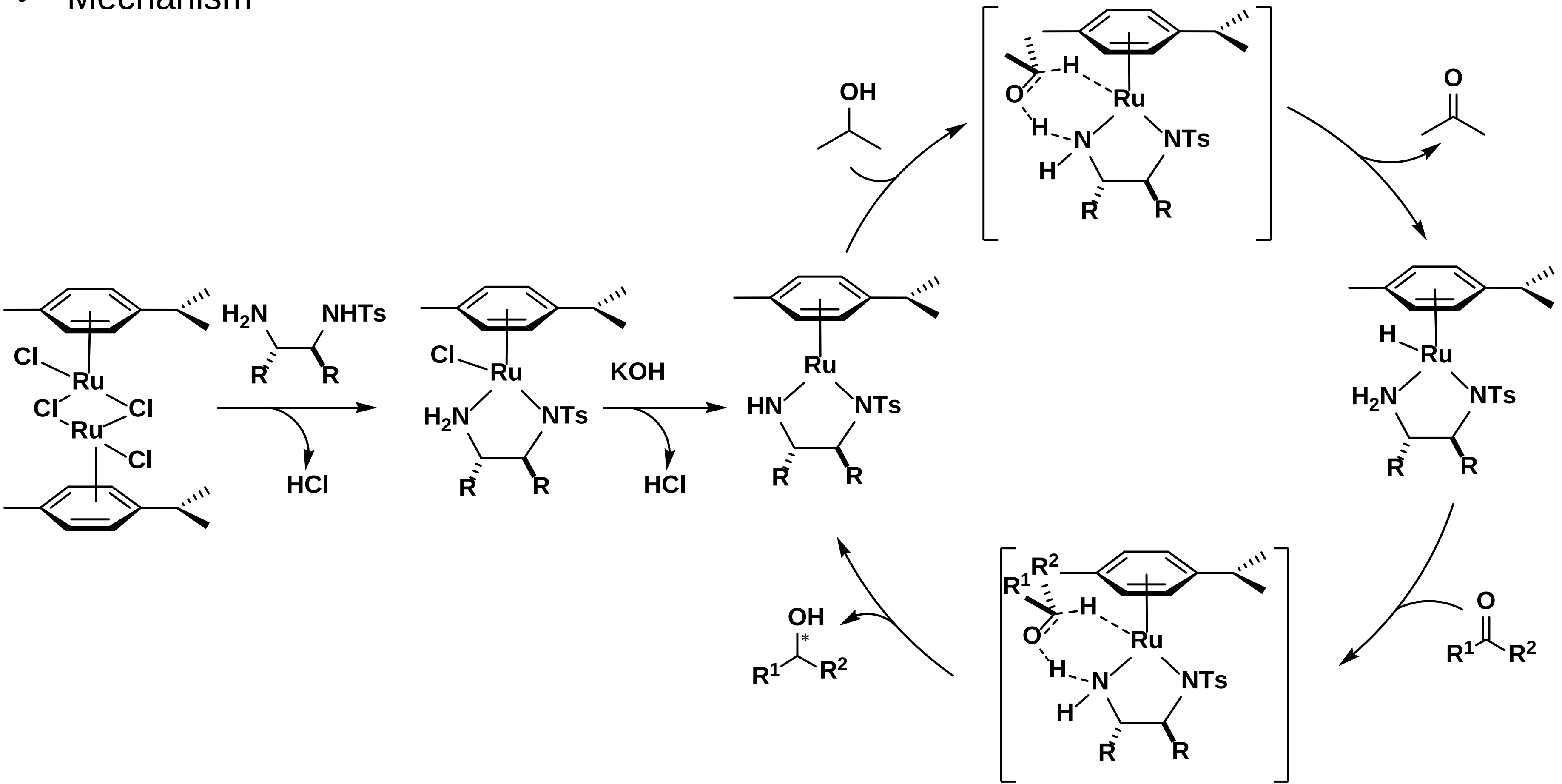
Ar= 4-$CH_3C_6H_4$, 2,4,6-$(CH_3)_3C_6H_2$
η^6-arene= mesitylene, *p*-cymene, benzene

amino alcohol ligands

R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97.

The important improvement by Noyori

- Mechanism



- Hydrogen donor

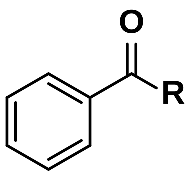
Isopropanol or formic acid/trimethylamine
corresponding product: acetone/ CO_2

S. Gladiali, E. Alberico, Chem. Soc. Rev., 2006, 35, 226.

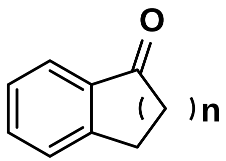
The important improvement by Noyori

- Scope

➢ Mainly aryl-alkyl ketones (alkyl-alkynyl ketones)

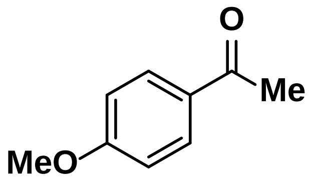


R= Me >99% yield, 98% ee
R= Et 96% yield, 97% ee
R= *i*Pr 41% yield, 83% ee
R= *t*Bu <1% yield

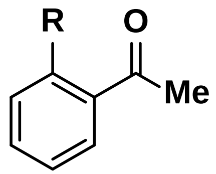


n= 1
*i*PrOH: 45% yield, 91% ee
HCOOH/NEt_3: >99% yield, 99% ee

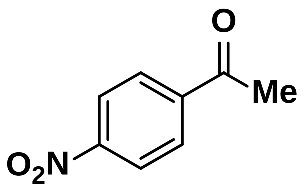
n= 2
*i*PrOH: 65% yield, 97% ee
HCOOH/NEt_3: >99% yield, 99% ee



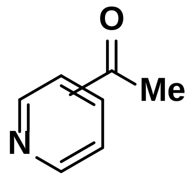
*i*PrOH: 53% yield, 72% ee
HCOOH/NEt_3: >99% yield, 97% ee



R= Me 53% yield, 91% ee
R= OMe 24% yield, 89% ee



100% yield, 86% ee



2-acetylpyridine: 99% yield, 91% ee
3-acetylpyridine: 99% yield, 89% ee
4-acetylpyridine: 99% yield, 92% ee

–Alkyl group: Not sterically bulky
–Aryl group: High oxidation potential prefered

o-Subtituteddifficult

Electron withdrawing groups erode stereoselectivity

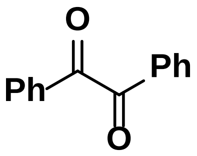
Heteroaromaticgroups tolerated

R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97.
K. Okano, K. Murata, T. Ikariya, *Tetrahedron Lett.* **2000**, *41*, 9277.

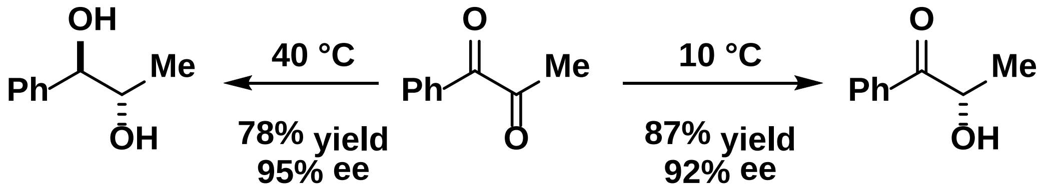
The important improvement by Noyori

- Diketones and β–keto esters

1,2-diketone



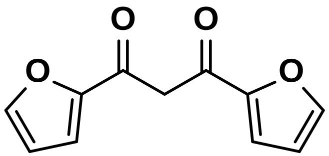
***anti: syn*= 98.6:1.4**
100% yield, >99% ee



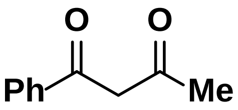
78% yield
95% ee

87% yield
92% ee

1,3-diketone

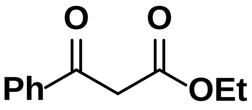


***anti: syn*= 95:5**
85% yield

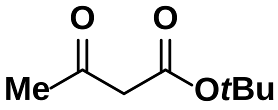


***anti: syn*= 56:42**
79% yield

β-keto ester mono reduction

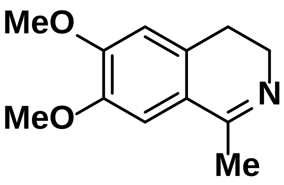


99% yield
94% ee

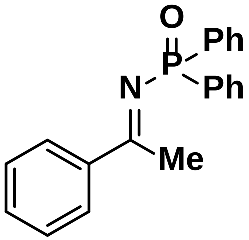


99% yield
68% ee

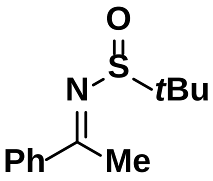
- Imines



>99% yield
95% ee



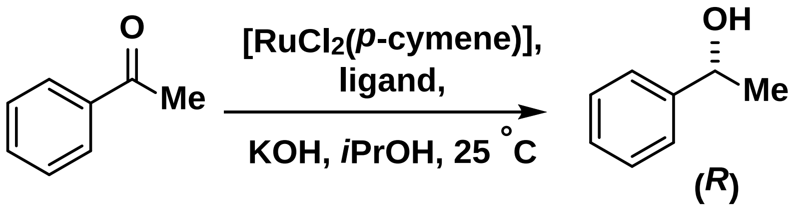
87% yield
82% ee

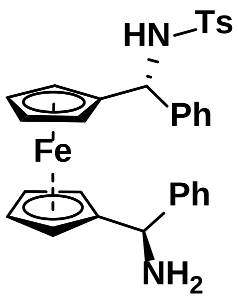


97% yield
97% ee

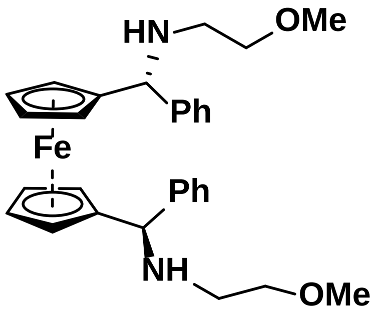
R. Noyori *et al.*, *Org. Lett.* **1999**, *1*, 1119;
T. Ikariya *et al.*, *Org. Lett.* **2000**, *2*, 3833;
P. I. Dalko et al., *Tetrahedron Lett.* **2001**, *42*, 5005;
R. Noyori *et al., J. Am. Chem. Soc*. **1996**, *118*, 4916;
M. Yus *et al., Chem. Eur. J*. **2012**, *18*, 1969;
M. Yus *et al., Appl. Sci.* **2012**, *2*, 1;
F. Foubelo *et al., Chem. Rec*. **2015**, *15*, 907.

Ferrocynl diamine Ligands

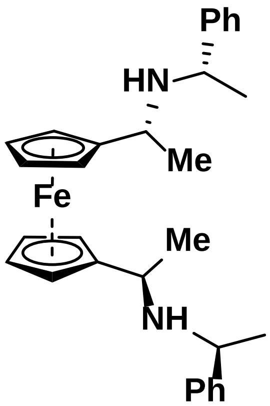




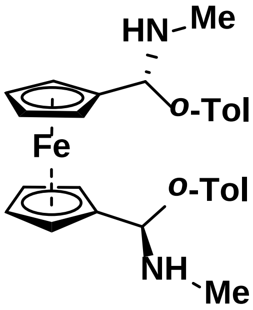
98% yield, 71% ee
95% yield, 80% ee



38% yield, 35% ee



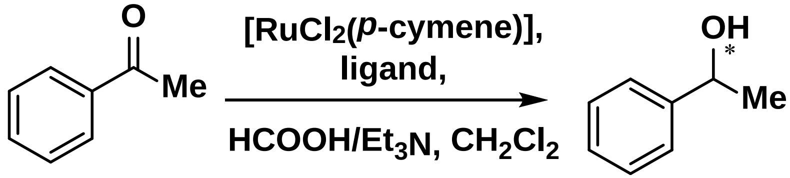
45% yield, 31% ee

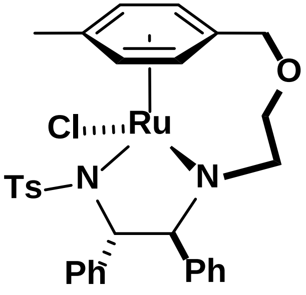


97% yield, 80% ee

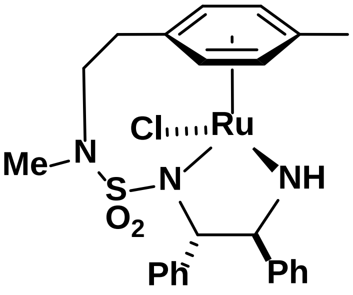
L. Schwink *et al.*, *Tetrahedron: Asymmetry* **1998**, *9*, 1143.

Other diamine/amino alcohol Ligands

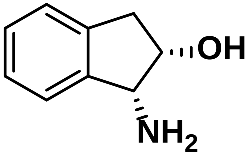




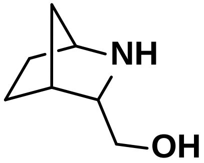
99% yield, 99% ee



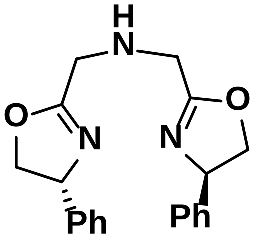
100% yield, 99.9% ee



70% yield, 91% ee



92% yield, 95% ee

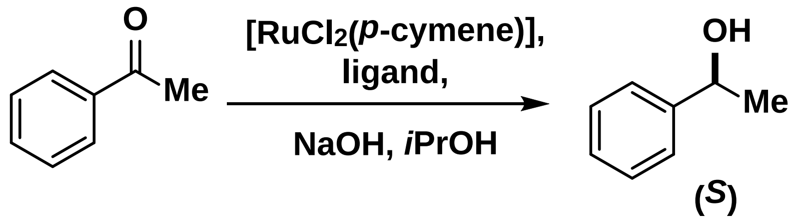


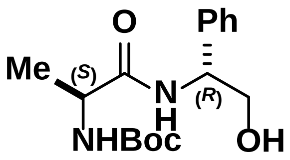
81% yield, 98% ee

M. Wills *et al., Catal. Sci. Technol.*, **2012**, *2*, 406;
X. Zhang *et al., J. Am. Chem. Soc*. **1998**, *120*, 3817.

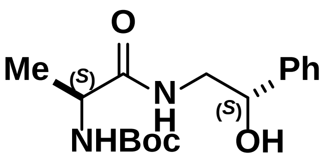
Amino Acid-Based Ligands

- Boc group & free hydroxyl group crucial

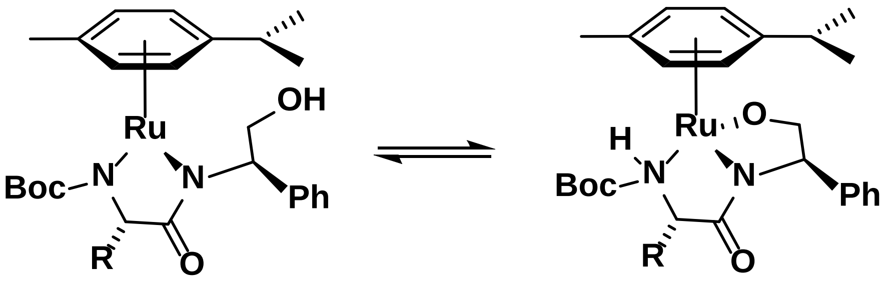




95% yield, 93% ee



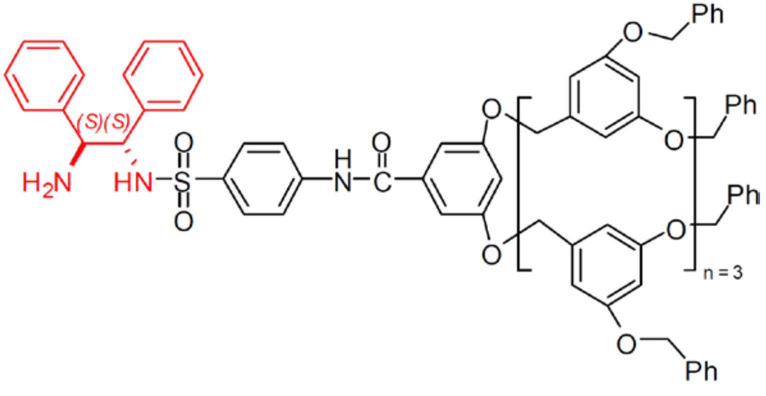
91% yield, 94% ee

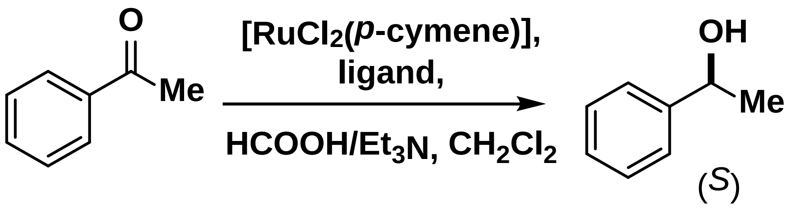


H. Adolfsson *et al., Chem. Eur. J.* **2003**, *9*, 4031;
H. Adolfsson *et al., Chem. Eur. J.* **2004**, *10*, 294.

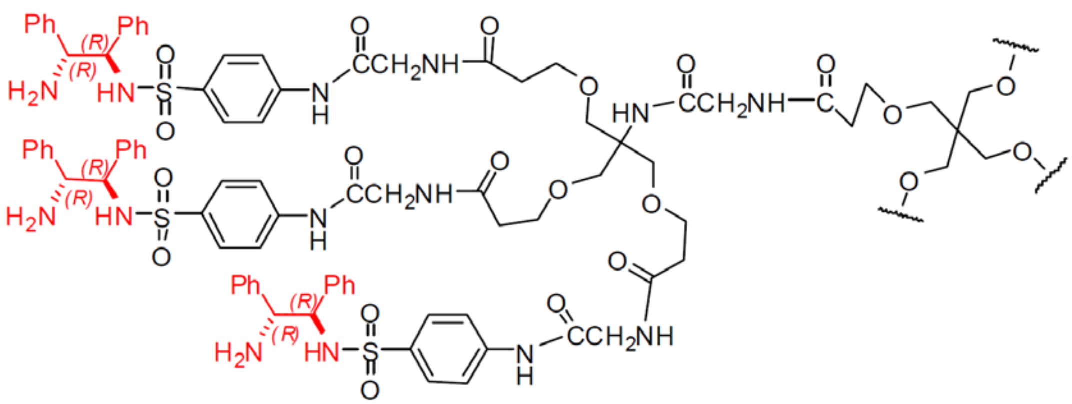
Dendimer-bound diamine ligands

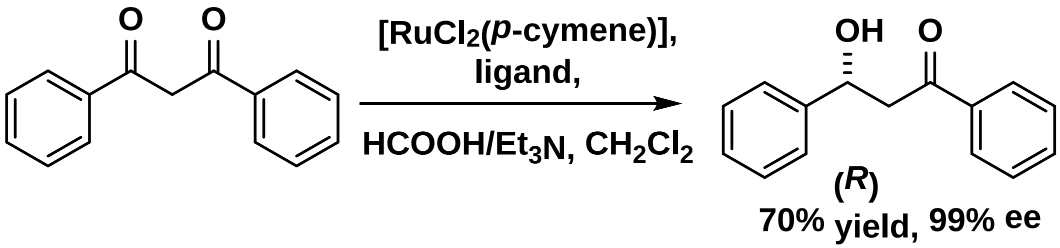
- Immobilization on supporting apparatus can allow for recovery
- For ATH, two classes of dendrimersinitially tested





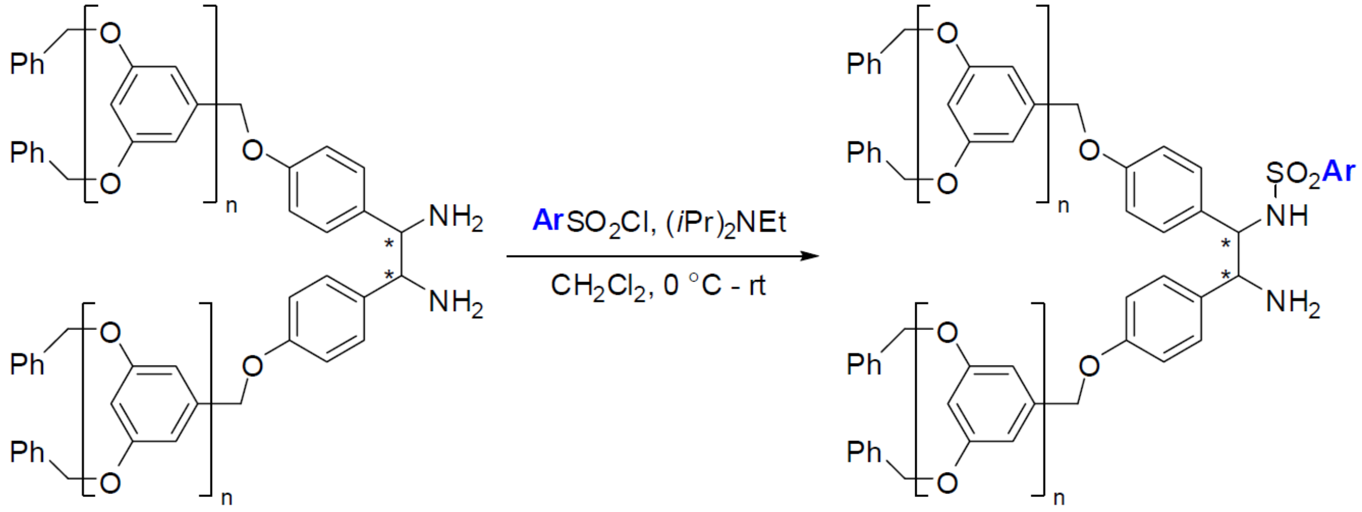
Run #	t (h)	Conversion (%)	*ee* (%)
1	20	98	96.5
2	20	92	96.6
3	25	87	96.8
4	30	85	96.7
5	40	73	96.3
6	40	52	87

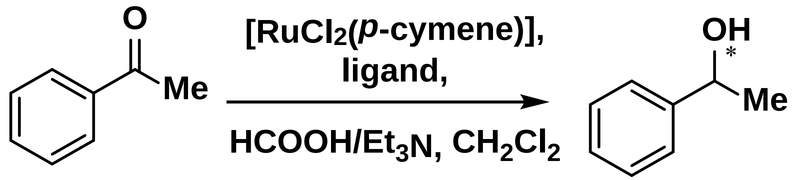




A. S. C. Chan *et al., Chem Commun*. **2001**, 1488;
A. S. C. Chan *et al.,J. Org. Chem.* **2002**, *67*, 5301.

Dendimer-bound diamine ligands

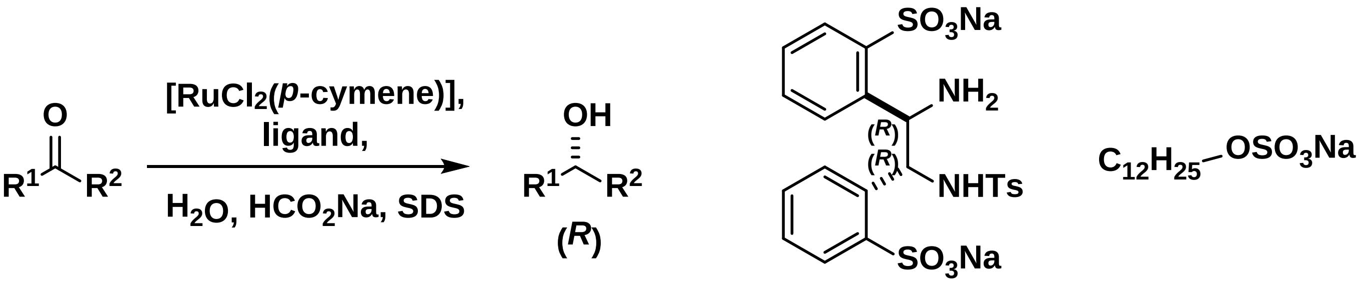




n	Ar	Configuration	time (h)	Conversion (%)	*ee* (%)	Configuration
0	4-$CH_3C_6H_4$	(*R*,*R*)	20	95	96.8	*R*
1	4-$CH_3C_6H_4$	(*R*,*R*)	20	>99	96.6	*R*
2	4-$CH_3C_6H_4$	(*R*,*R*)	20	97.1	96.1	*R*
				(95.4, 90.2, 83.7, 71.2)	(97.5, 97.2, 97.5, 97.0)	
3	4-$CH_3C_6H_4$	(*R*,*R*)	20	75	94.6	*R*
2	2,4,6-Et_3-C_6H_2	(*S*,*S*)	20	93.0	91.7	*S*
2	2,4,6-*i*Pr_3-C_6H_2	(*S*,*S*)	20	91.7	92.8	*S*
2	1-naphthyl	(*S*,*S*)	20	>99	96.3	*S*

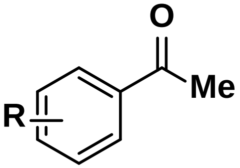
J. Deng *et al., Tetrahedron: Asymmetry*. **2005**, *16*, 2525.

Asymmetric transfer hydrogenation in water

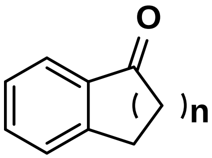


ligand

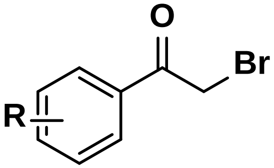
SDS



R	yield	ee
p-Me	94%	94%
p-F	88%	92%



n	yield	ee
1	66%	83%
2	21%	98%

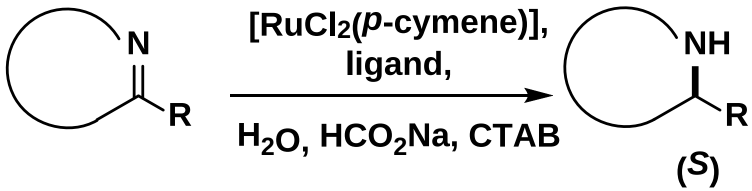


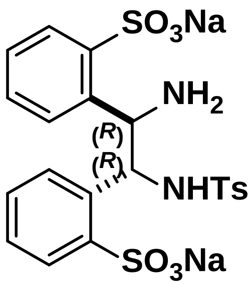
R	yield	ee
H	87%	94%
NO_2	58%	84%

Recyclability posiible: retention of stereoselevitivy, loss of conversion (99% → 75%)

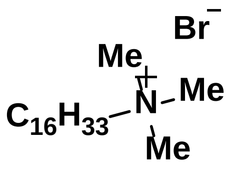
J. Deng *et al.*, *Org. Lett.* **2003**, *5*, 2103.

Asymmetric transfer hydrogenation in water

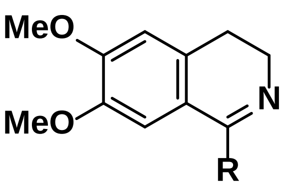




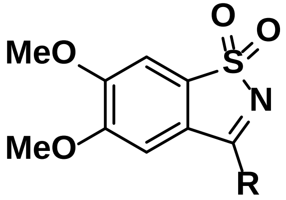
ligand



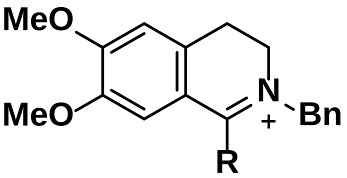
CTAB



R	yield	ee
Me	97%	95%
Et	68%	92%
*i*Pr	90%	90%



R	yield	ee
Me	97%	65%
*t*Bu	95%	94%
Recycle experiment	97%	94%
	95%	94%
	96%	94%
	85%	94%

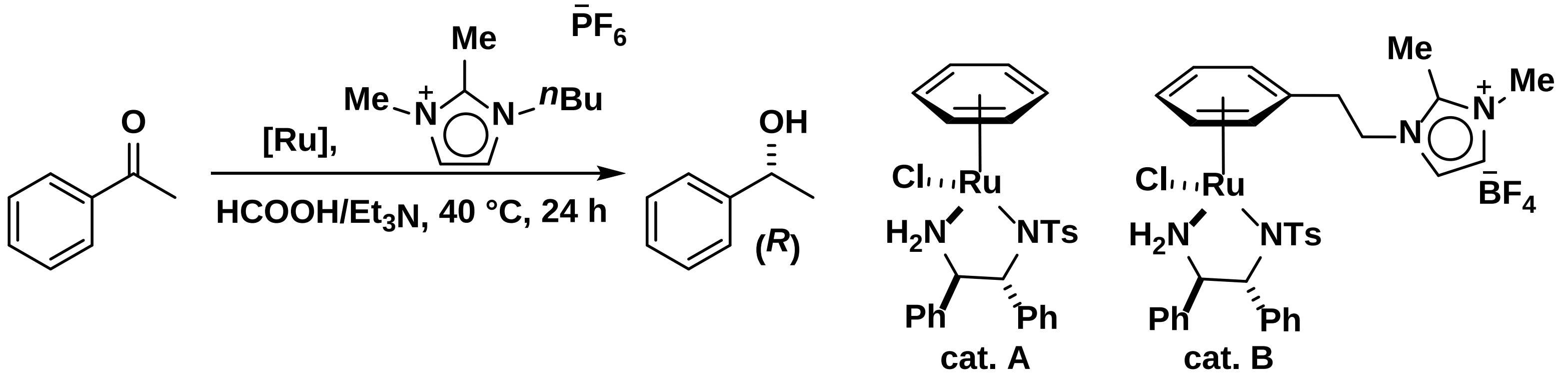


R	yield	ee
Me	85%	90%
Ph	94%	95%

Acyclic imines unsuccessful

J. Deng *et al.*, *Chem. Commun.* **2006**, 1766.

Asymmetric transfer hydrogenation in ionic liquid

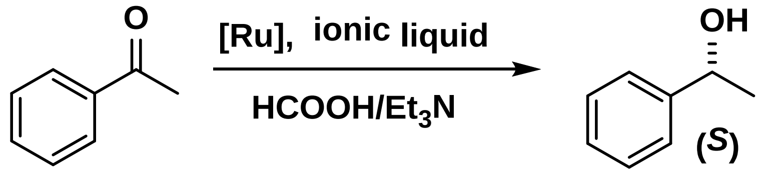


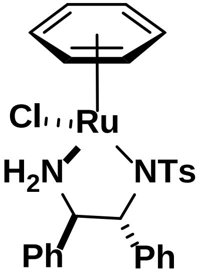
Cycle #	Catalyst **A** (% yield, % *ee*)	Catalyst **B** (% yield, % *ee*)
1	>99%, 99%	>99%, 99%
2	>99%, 99%	>99%, 99%
3	>99%, 99%	80%, 99%
4	99%, 99%	45%, 99%
5	96%, 99%	

Cycle #	R =	Conversion (%)	*ee* (%)
1	*o*-Me	72%	97%
2	*p*-Cl	99%	95%
3	H	99%	99%
4	H	98%	99%
1	Acetophenone	99%	97%
2	Tetralone	99%	97%
3	Benzaldehyde	90%	N/A

P. J. Dyson *et al.*, *J. Am. Chem. Soc.* **2004**, *126*, 8114.

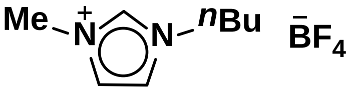
Asymmetric transfer hydrogenation in ionic liquid



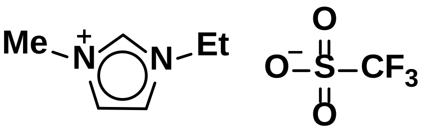


cat. A

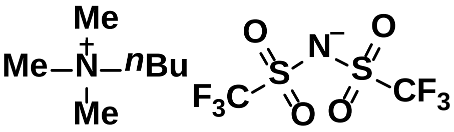
Ionic Liquid	Cycle #	Time (h)	Conversion (%)	*ee* (%)	
[bmim][BF$_4$]		40	<1	-	Hydrophilic Ionic Liquids
[bmim][MeSO$_4$]		48	19	85	
[emim][OTf]		24	0	-	
[bmim][PF$_6$]	1	31	97	96	Hydrophobic Ionic Liquids
	2	50	92	95	
	3	95	46	89	
[bmim][NTf$_2$]	1	27	98	96	
	2	21	58	96	
[tmba][NTf$_2$]	1	26	98	97	
	2	41	99	97	
	3	94	99	97	
	4	50	56	96	



[bmim][BF$_4$]



[emim][OTf]



[tmba][NTf$_2$]

Hydrophilic ILs inhibit reaction.

Hydrophobic Ils slow reaction, but good ee.

M. Vaultier *et al.*, *Arkivoc.* **2006**, *152*.

Conclusion and outlook

Conclusion

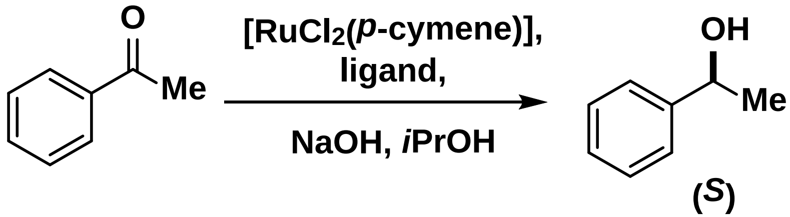
- Ruthenium-catalyzed ATH is very an efficient methodology
- Role of solvent in transition state may be significant
- Various ligands are suitable for ATH, such diamines, amino alcohol
- Catalyst can be recovered and reused
- ATH can be run in water or ionic liquid

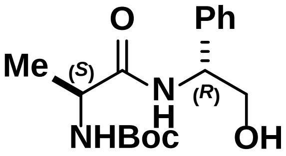
Future directions:

- Increase substrate: catalyst ratio
- Expand scope
- Improve recoverability further

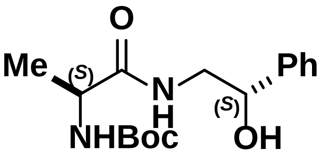
Questions

1) How to explain the relationship between the configurations of the ligand and the configuration of the product?



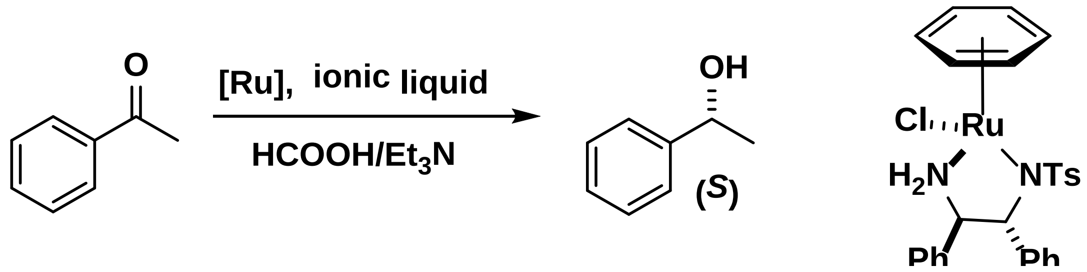


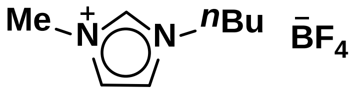
95% yield, 93% ee



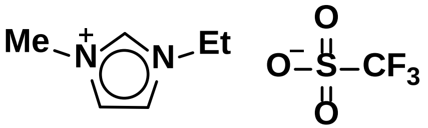
91% yield, 94% ee

Asymmetric transfer hydrogenation in ionic liquid

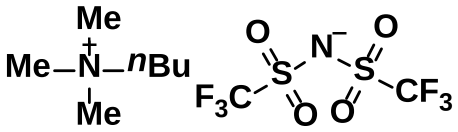




[bmim][BF$_4$]



[emim][OTf]



[tmba][NTf$_2$]

Ionic Liquid	Cycle #	Time (h)	Conversion (%)	*ee* (%)	
[bmim][BF$_4$]		40	<1	-	Hydrophilic Ionic Liquids
[bmim][MeSO$_4$]		48	19	85	
[emim][OTf]		24	0	-	
[bmim][PF$_6$]	1	31	97	96	Hydrophobic Ionic Liquids
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	3	95	46	89	
[bmim][NTf$_2$]	1	27	98	96	
	2	21	58	96	
[tmba][NTf$_2$]	1	26	98	97	
	2	41	99	97	
	3	94	99	97	
	4	50	56	96	

Hydrophilic ILs inhibit reaction.
Hydrophobic Ils slow reaction,
but good ee.
Why?

M. Vaultier *et al.*, *Arkivoc.* **2006**, *152*.

Thanks for your kind attention !

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Towards a more sustainable asymmetric catalysis using Iron-based complexes:

Progress since 2011 in hydrogenation and heteroatoms transfer

Franck Le Vaillant

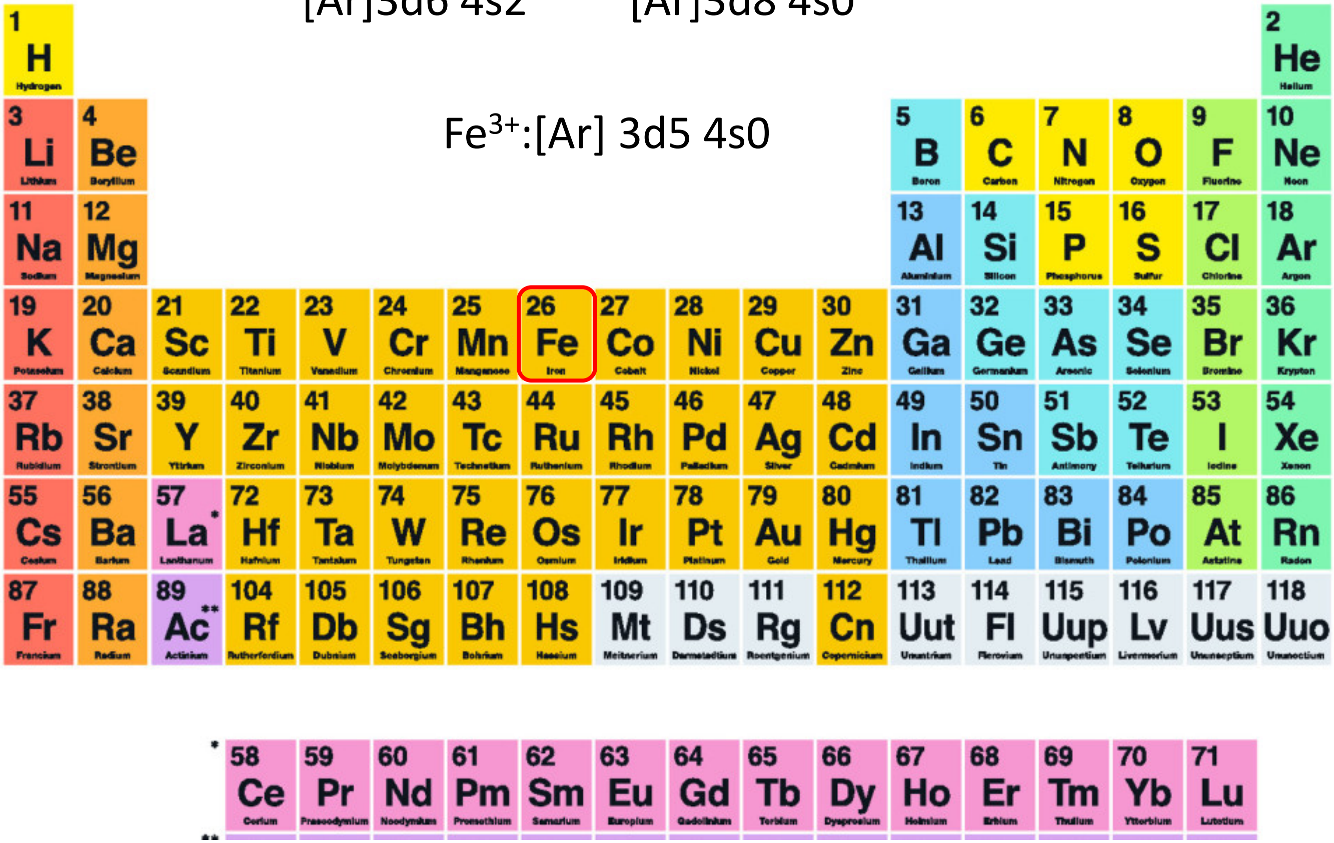
Laboratory of Catalysis and Organic Synthesis (LCSO)

2nd Year PhD Student, Prof. J. Waser Group

Frontiers in Organic Chemistry, EPFL, April 14th 2016

Table of contents

1. Introduction



[Ar]3d6 4s2 [Ar]3d8 4s0

Fe^{3+}:[Ar] 3d5 4s0

1 H																	2 He
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba	57 La*	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
87 Fr	88 Ra	89 Ac**	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Uut	114 Fl	115 Uup	116 Lv	117 Uus	118 Uuo

*	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu
**														

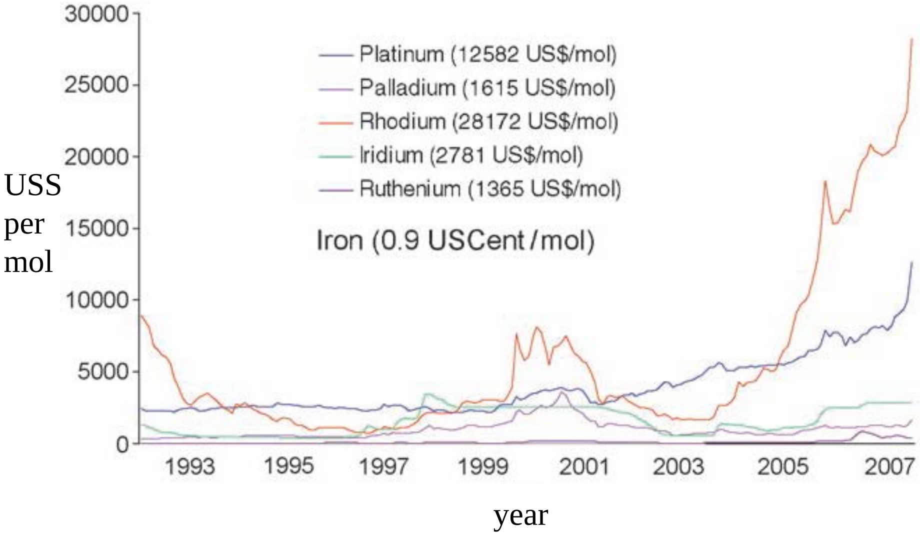
Common oxidation state: -II, -I, 0, +II, +III, +VI

Often in octahedral structure in complexes

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

1. Introduction

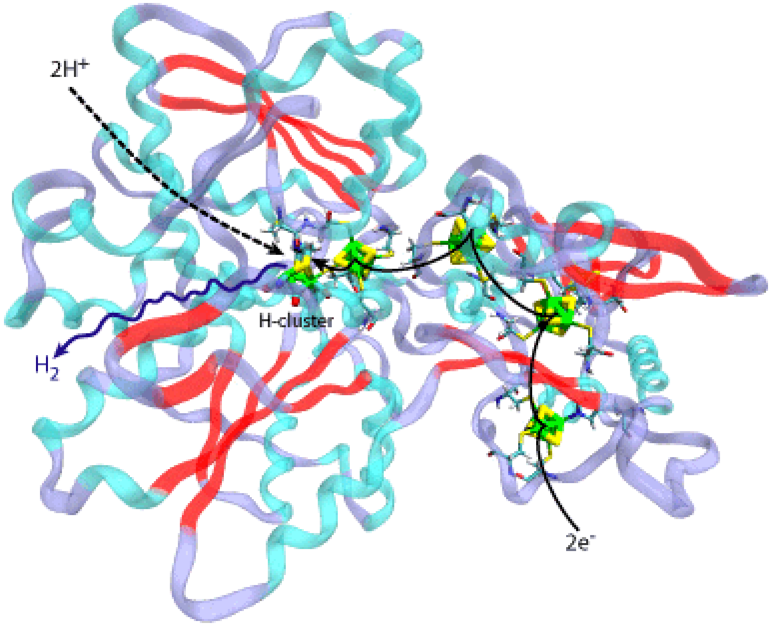
Market prices of transition metals



IRON = MOST ABUNDANT METAL ON EARTH = CHEAP

(~4.7 wt % of Earth’s crust)

Biological iron-based catalysts



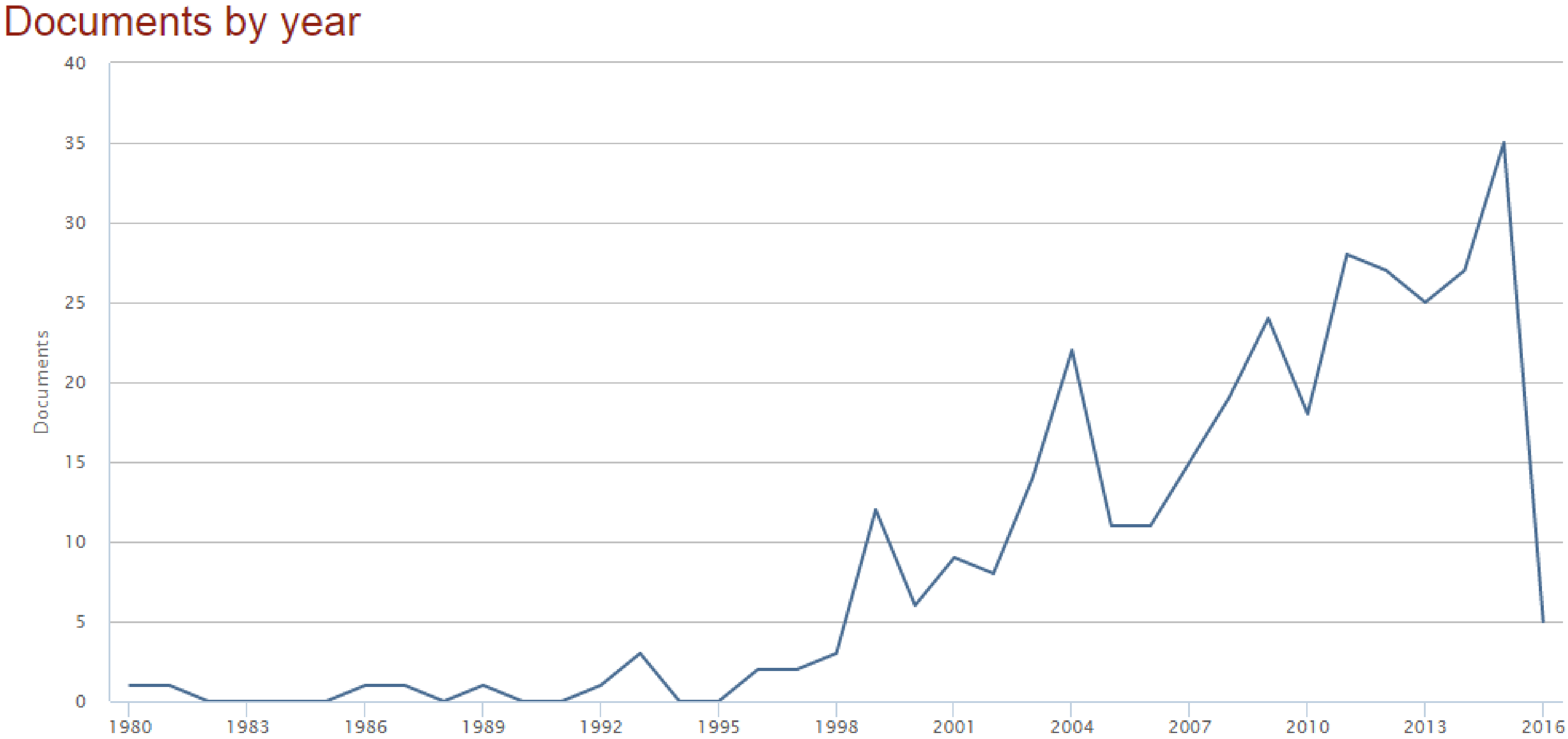
IRON = LOW TOXICITY = BENIGN FOR HUMANS

1) M. Beller *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 3317
2) Kovuru Gopalaiah, *Chem. Rev.* **2013**, *113*, 3248−3296

1. Introduction

Asymmetric iron catalysis : 332 results

1980 – 2010 : 182 results
2011 – 2016 : 150 results



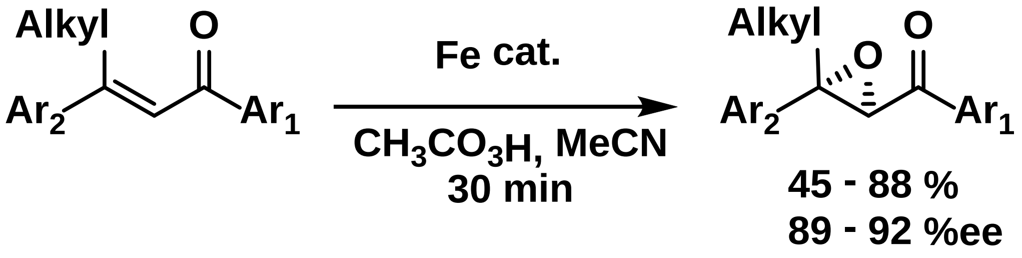
Goal of the talk: Introduction to asymmetric iron catalysis and why it is more and more relevant nowadays

Scopus data base.

QUESTIONS

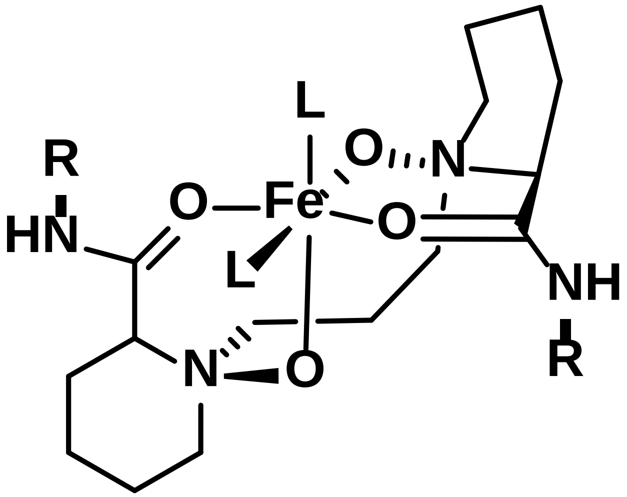
QUESTION 1

Explain why the epoxidation of β-β disubstituted olefins is challenging, and why the method described is efficient.



QUESTION 2

In the haloamination of alkenes, try to draw the transition state using the geometry of this ligand to explain the *anti* selectivity of the product.

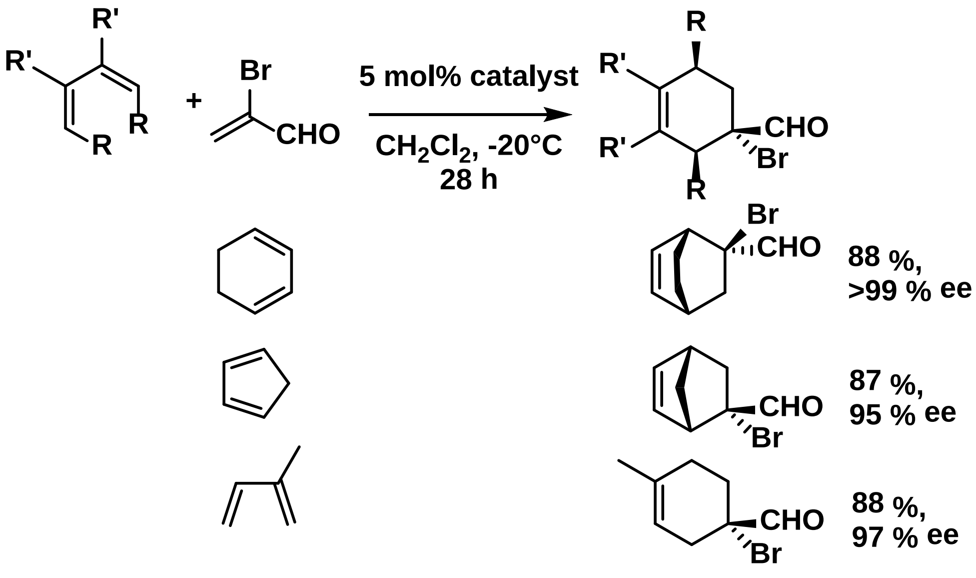


2. State of the art before 2011

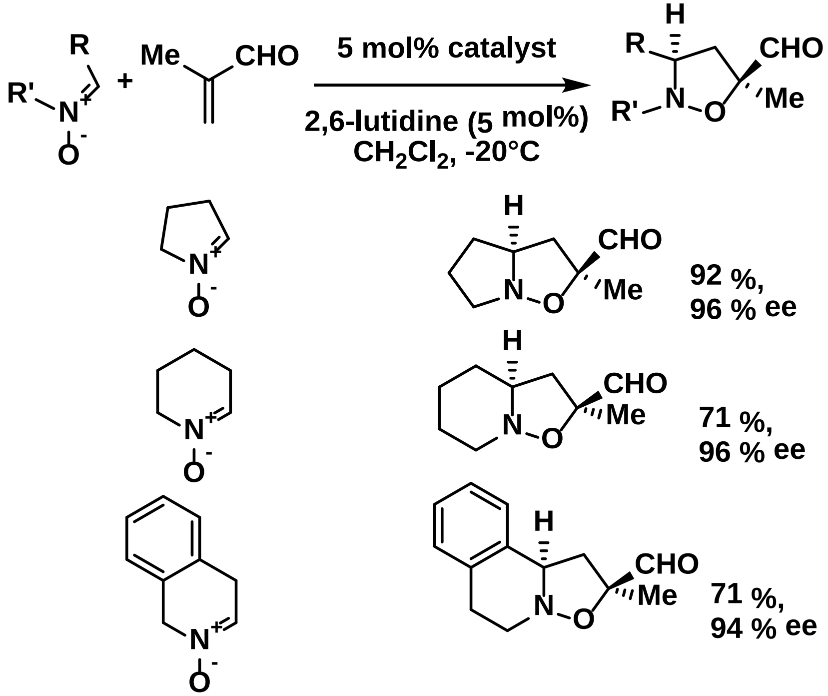
2.a. Asymmetric Cycloaddition

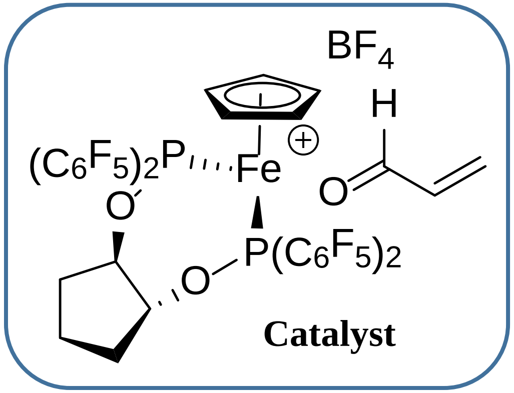
State of the art
before 2011

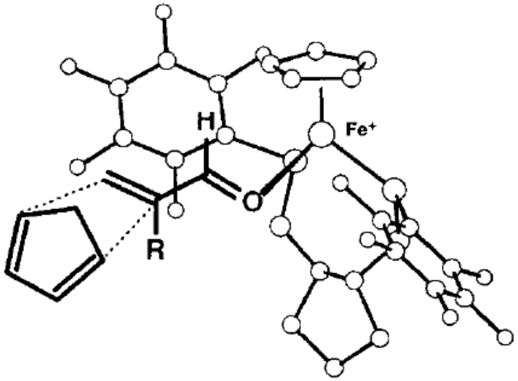
Diels – Alder



1,3-Dipolar Cycloaddition with Nitrone



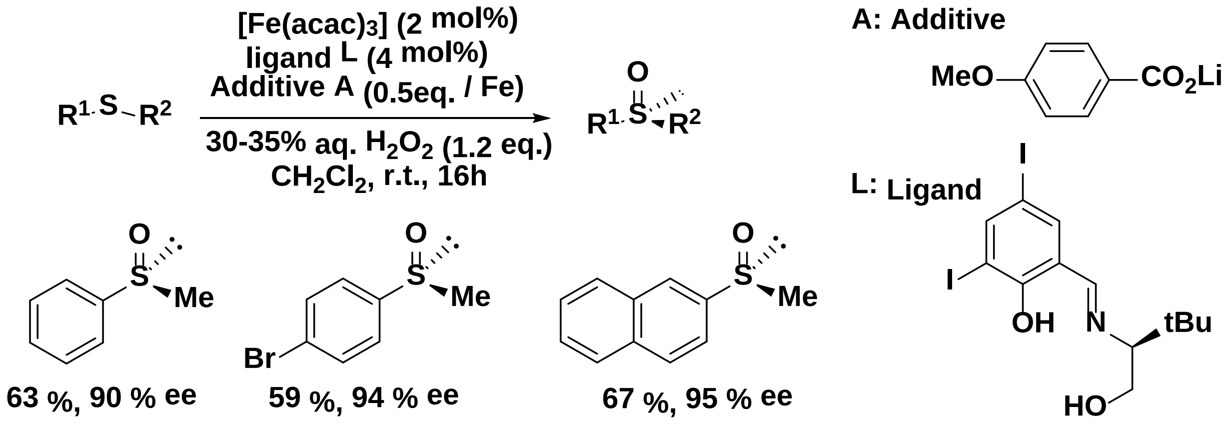




1) E. P. Kündig *et al. Angew. Chem. Int. Ed.* **1994**, *33*, 1856
2) E. P. Kündig *et al. J. Am. Chem. Soc.* **2002**, *124*, 4968

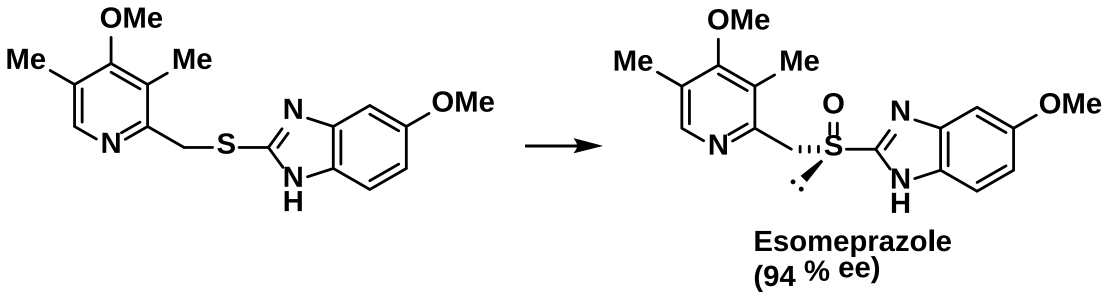
2.b. Asymmetric Sulfide Oxidation to Sulfoxide

State of the art before 2011



Prof. Carlsten Bolm

Useful reaction in pharmaceutical industry:



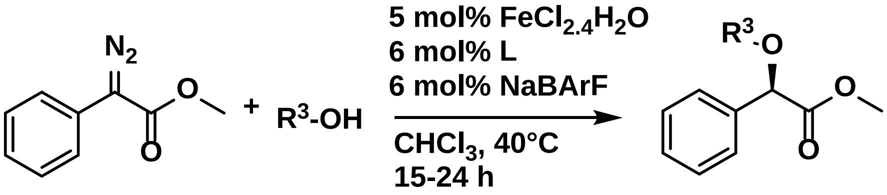
> “While the number of [enantioselective] reactions is still limited, these results constitute the basis of a promising new area of research.”

1) C. Bolm *et al. Chem. Eur. J.* **2005**, *11*, 1086
2) J. Legros, J. Le Paih, L. Zani, C. Bolm *Chem. Rev.* **2004**, *104*, 6217

2.c. Enantioselective O-H bond insertions

State of the art
before 2011

Alcohol insertion

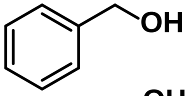


5 mol% $FeCl_{2.4}H_2O$
6 mol% L
6 mol% NaBArF

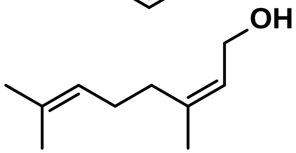
$CHCl_3$, 40°C
15-24 h

n-BuOH 93 %, 98 % ee

MeOH 85 %, 96 % ee (69 % ee with Cu)



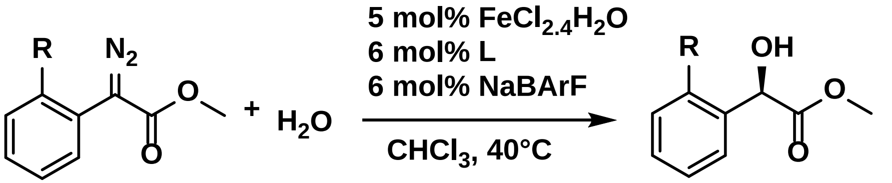
94 %, 98 % ee (77 % ee with Cu)



88 %, 95 % ee

15 examples, all *ee* up to 90%

Water insertion



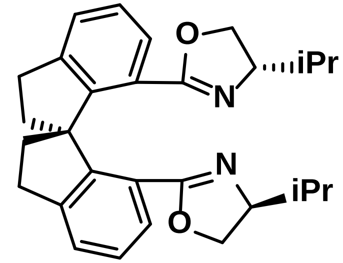
5 mol% $FeCl_{2.4}H_2O$
6 mol% L
6 mol% NaBArF

$CHCl_3$, 40°C

R = H 90 %, 95 % ee

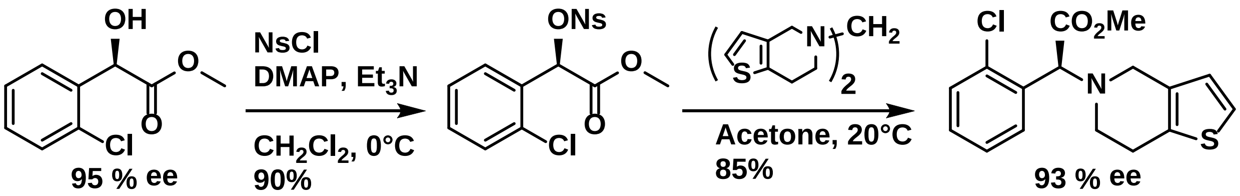
R = Cl 92 %, 95 % ee
92 % ee
with 1 mol% of cat.

17 examples, all *ee* up to 90%



L: Spirobox

Clopidogrel: Platelet aggregation inhibitor



95 % ee

NsCl
DMAP, Et_3N

CH_2Cl_2, 0°C
90%

Acetone, 20°C
85%

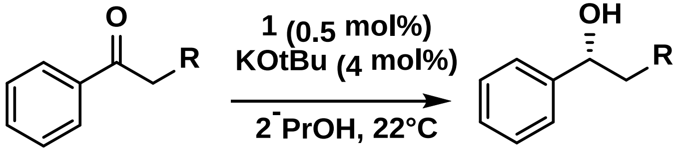
93 % ee

S.-F. Zhu, Y. Cai, H.-X. Mao, J.-H. Xie, Q.-L. Zhou, *Nature Chemistry* **2010**, *2*, 546

2.d. Asymmetric Transfer Hydrogenation

State of the art before 2011

Ketones

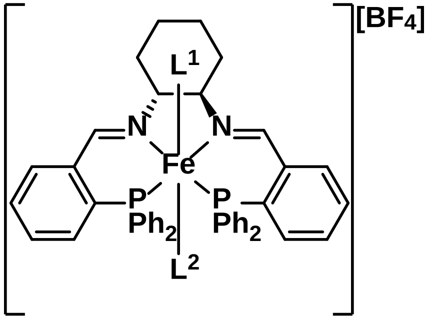


R = H 95% conv., 33 % ee

R = Me 95% conv., 61 % ee

13 examples with ee around 35%

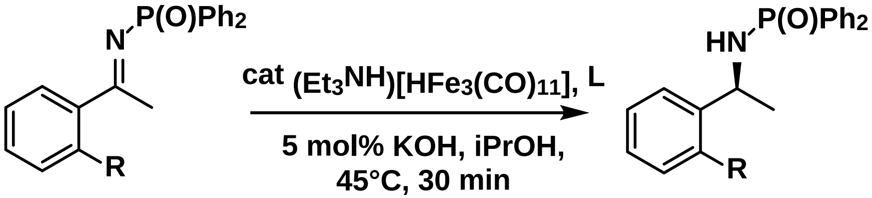
1



L1: MeCN; L2: CO

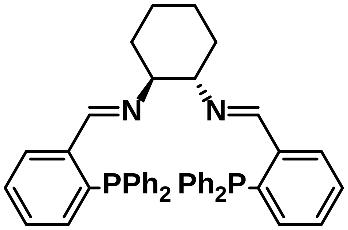
Prof. Robert. H. Morris

Imines



R = H : 87 %, 96% ee
R = OMe : 94 %, 96% ee

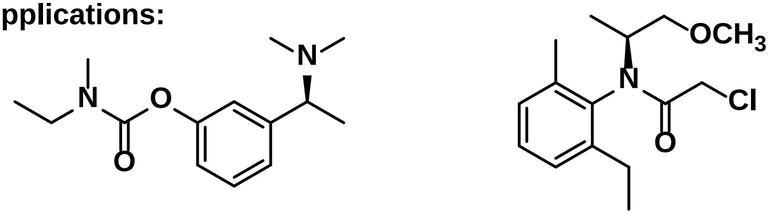
17 examples all ee up to 90%



L: Ligand

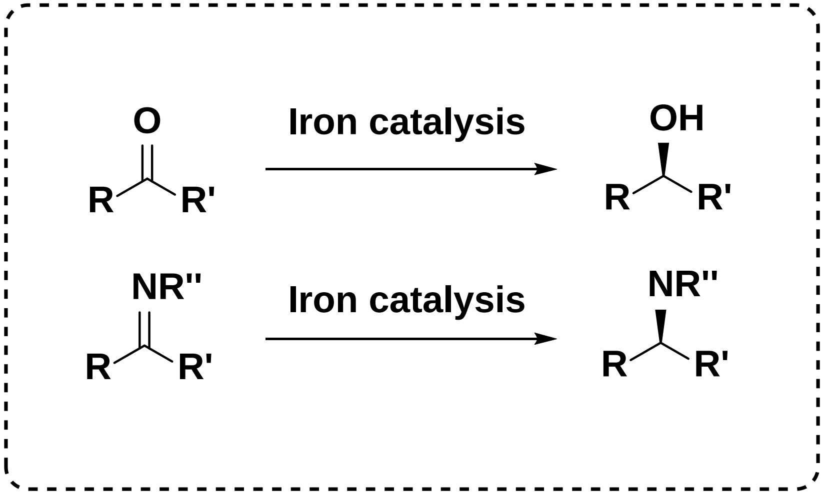
Prof. Matthias Beller

Applications:



1) C. Sui-Seng, F. Freutel, A. J. Lough, R. H. Morris, *Angew. Chem. Int. Ed.* **2008**, *47*, 940
2) M. Beller *et al.* *Angew. Chem. Int. Ed.* **2010**, *49*, 8121

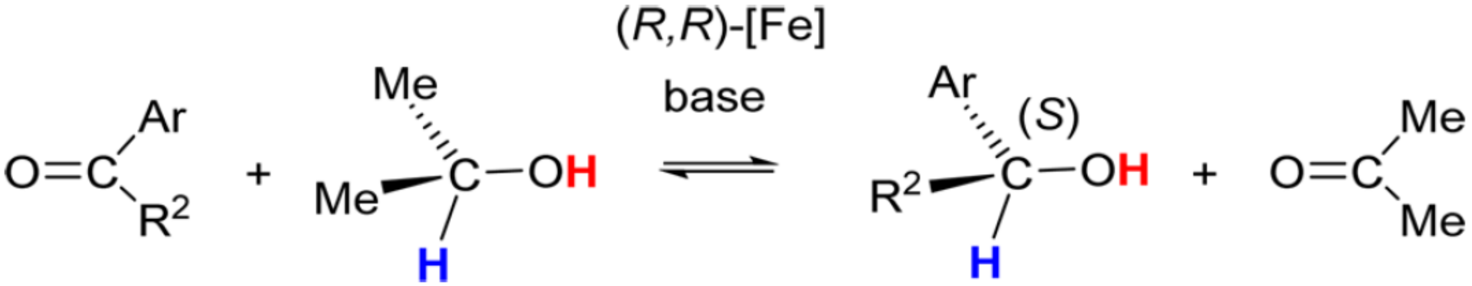
3. Reduction of Ketones and Imines



Progress since 2011

3.a. Asymmetric Reduction of Ketones and Imines

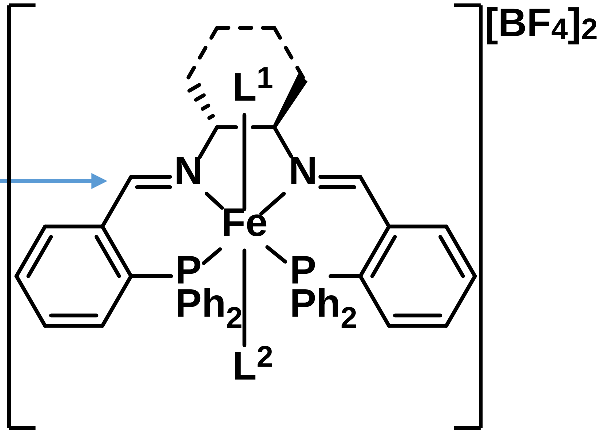
Asymmetric Transfer Hydrogenation (ATH)



- 6 membered ring more flexible

- Allow ligand dissociation under reducing conditions

1



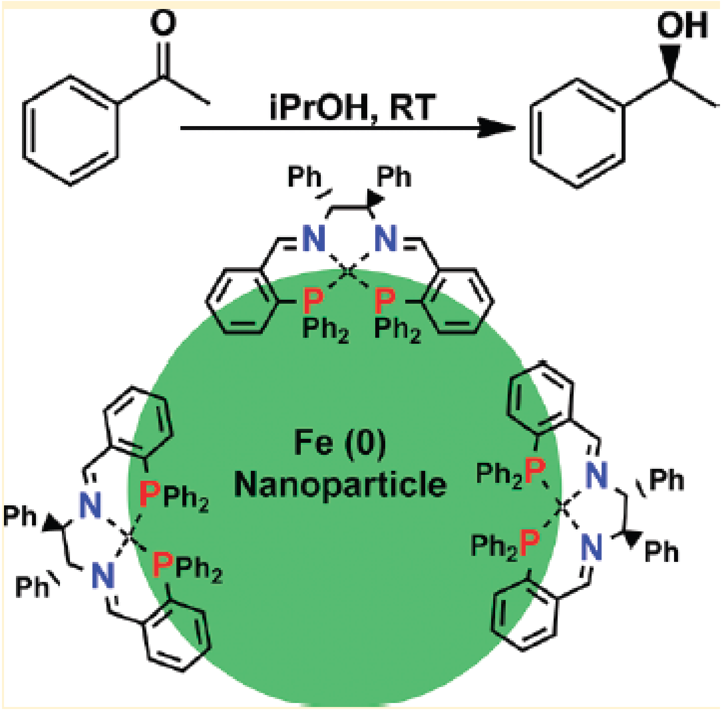
L1: MeCN; L2: CO

First generation

Weiwei Zuo *et al. Science* **342**, 1080 (2013);
P. E. Sues, K. Z. Demmans and R. H. Morris, *Dalton Trans*., **201**4, *43*, 7650–7667
Weiwei Zuo & Robert H Morris**,** *Nature Protocols*, **2015,** *10*, 2, 241-257

3.a. Asymmetric Reduction of Ketones and Imines

The actual active species is a functionalized chiral iron NPs



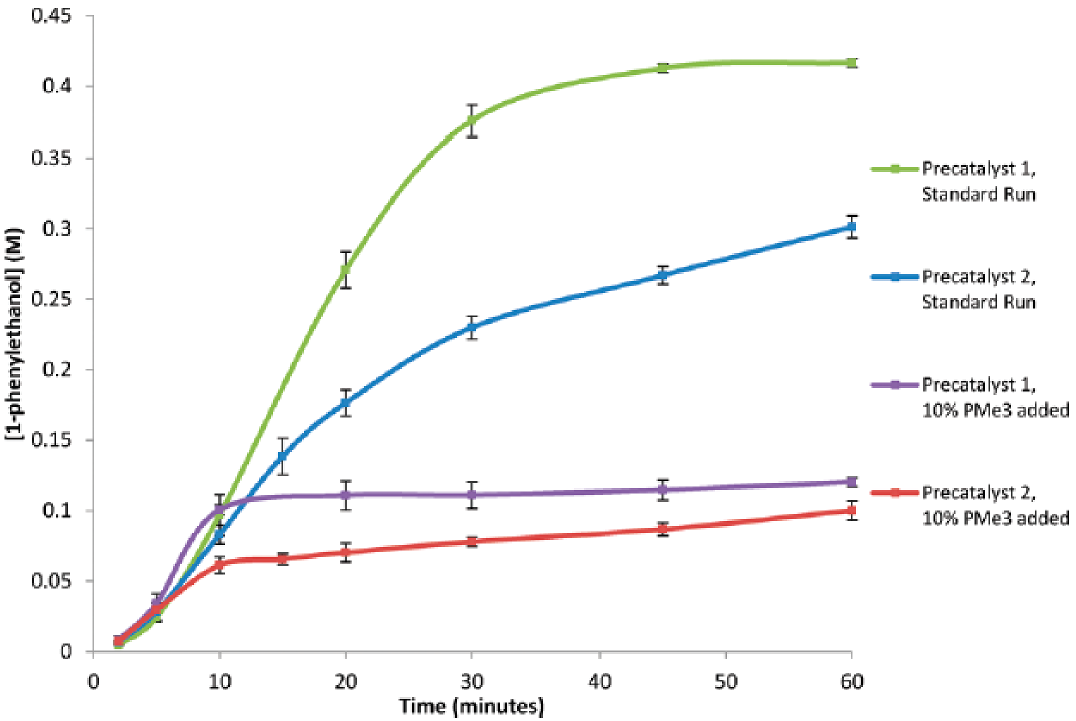


Figure 1. Standard catalytic runs using **1** and **2**, and poisoning runs using **1** and **2** and 10% PMe_3 added at *t* = 10 min.

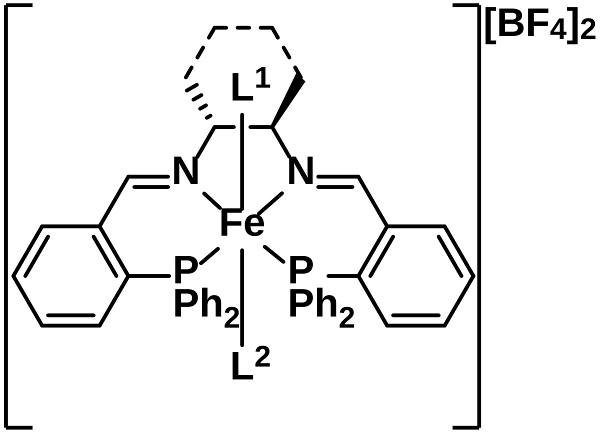
Experiment with poisonous PR3 addition

J. F. Sonnenberg, N. Coombs, P. A. Dube, R. H. Morris , *J. Am. Chem. Soc*. **2012**, *134*, 5893−5899

3.a. Asymmetric Reduction of Ketones and Imines

Asymmetric Transfer Hydrogenation (ATH)

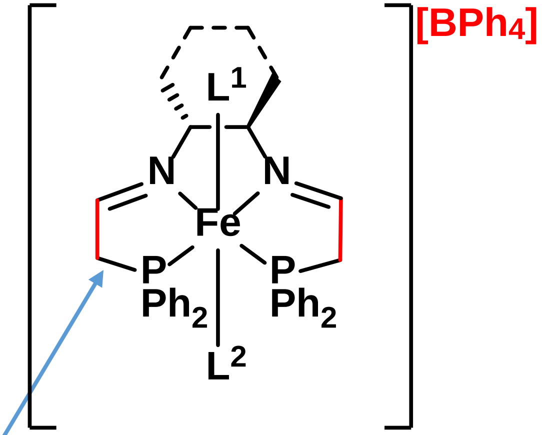
1



L1: MeCN; L2: CO

First generation

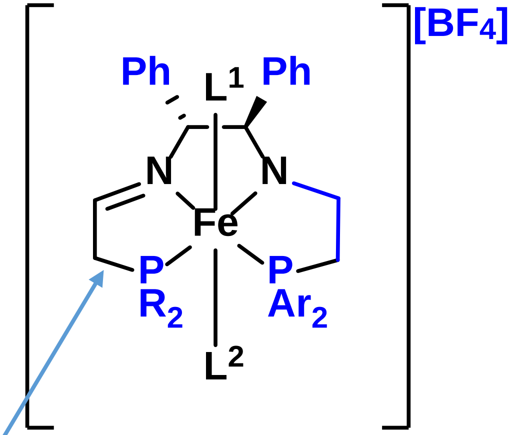
2



L1: Br$^-$; L2: CO

Second generation

3



L1: Cl$^-$; L2: CO

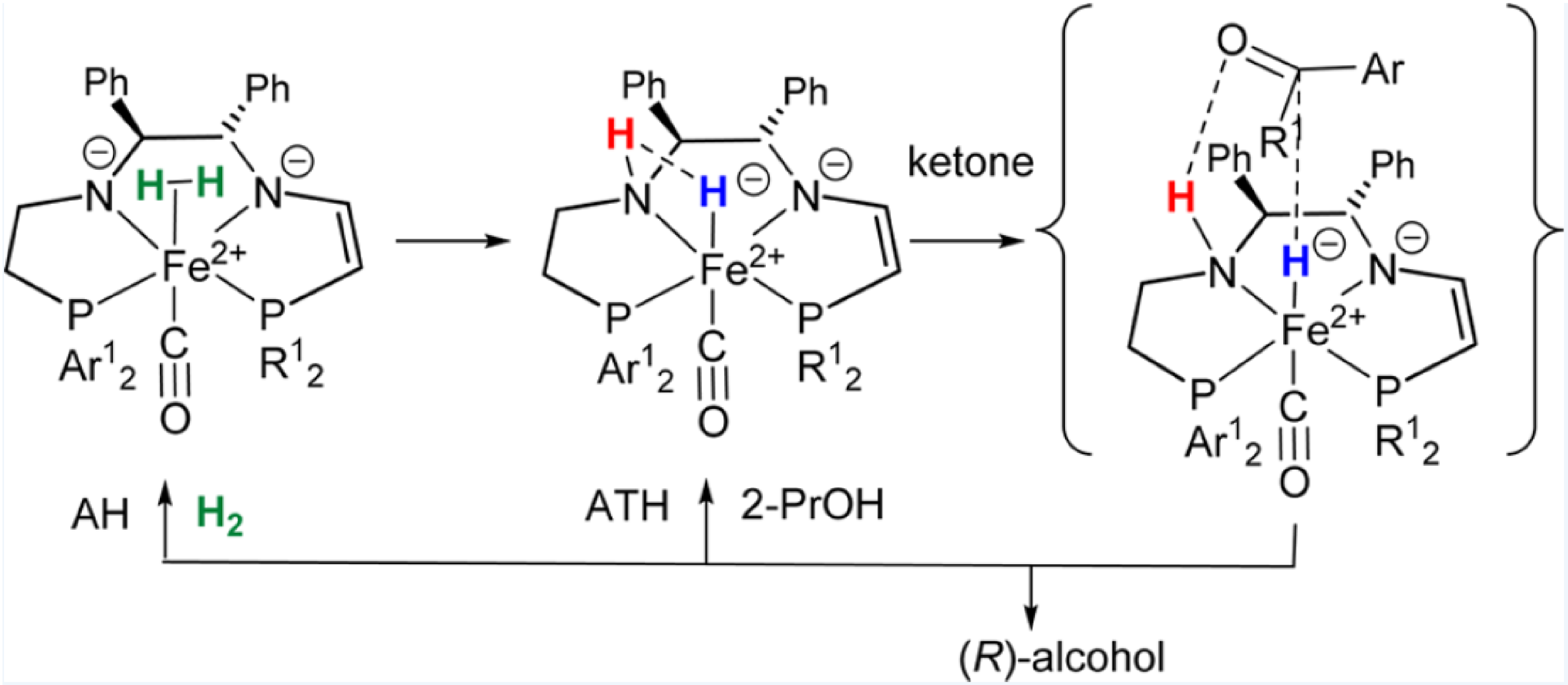
Third generation

5 membered ring
More robust catalyst

Only one side of the catalyst
can be reduced
No more induction

Weiwei Zuo *et al.* *Science* **342**, 1080 (2013);
P. E. Sues, K. Z. Demmans and R. H. Morris, *Dalton Trans*., **2014**, *43*, 7650–7667
Weiwei Zuo & Robert H Morris**,** *Nature Protocols***, 2015,** *10*, 2, 241-257

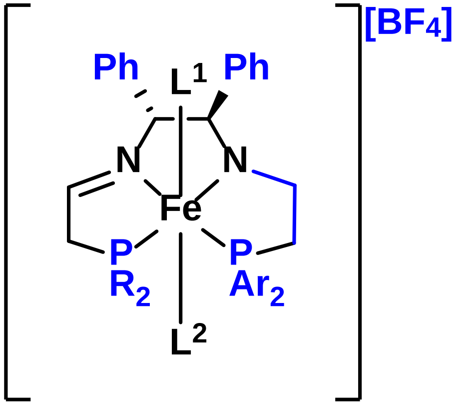
3.a. Asymmetric Reduction of Ketones and Imines



1) Weiwei Zuo *et al.* *Science* **342**, 1080 (2013);
2) R. H. Morris, *Acc. Chem. Res*. **2015**, *48*, 1494-1502

3.a. Asymmetric Reduction of Ketones and Imines

3



L1: Cl^-; L2: CO

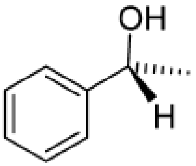
Third generation

(*S*,*S*)-3a R^1 = Cy, Ar^1 = Ph

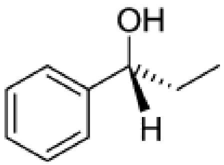
(*S*,*S*)-3b R^1 = Ar^1 = 3,5-$Me_2C_6H_3$

(*S*,*S*)-3c R^1 = Ar^1 = Ph

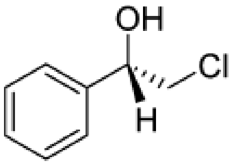
(*S*,*S*)-3d R^1 = 4-MeC_6H_4, Ar^1 = Ph



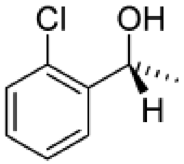
73%
98% ee (*R*)
(*S*,*S*)-3a



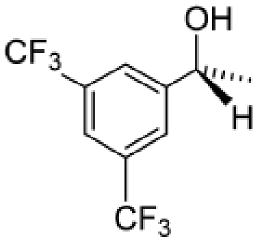
80%
94% ee (*R*)
(*S*,*S*)-3a



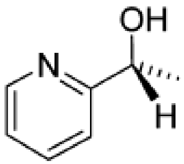
98%
99% ee (*R*)
(*S*,*S*)-3a



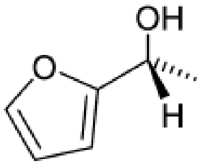
99%
94% ee (*R*)
(*S*,*S*)-3a



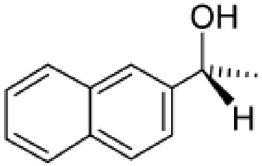
100%
98% ee (*R*)
(*S*,*S*)-3b



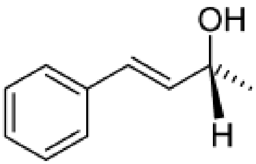
99%
34% ee (*R*)
(*S*,*S*)-3a



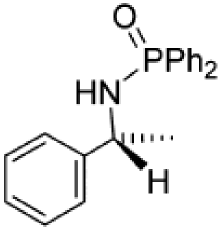
84%
51% ee (*R*)
(*S*,*S*)-3c



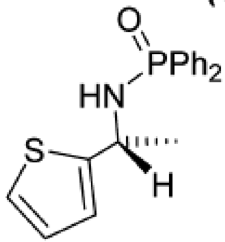
84%
83% ee (*R*)
(*S*,*S*)-3c



55%
40% ee (*R*)
(*S*,*S*)-3c



100%
99% ee (*R*)
(*S*,*S*)-3c



100%
99% ee (*R*)
(*S*,*S*)-3c

1) Weiwei Zuo *et al. Science* **342**, 1080 (2013);
2) R. H. Morris, *Acc. Chem. Res*. **2015**, *48*, 1494-1502

3.b. Asymmetric Reduction of Ketones

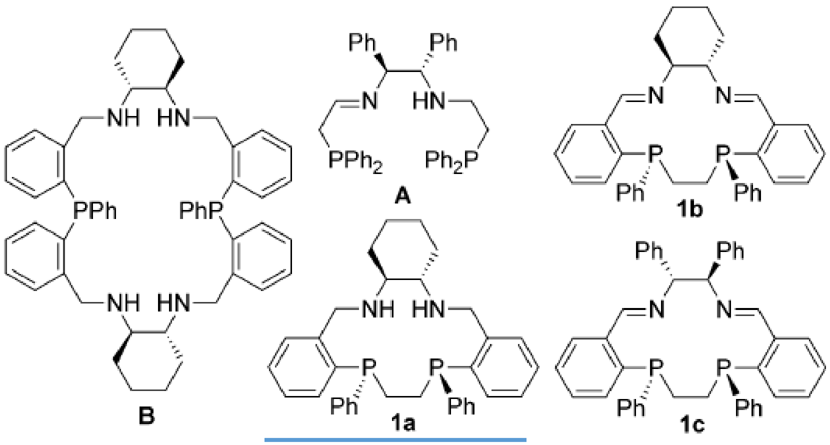
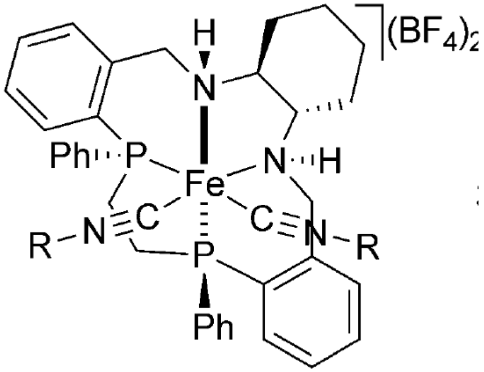


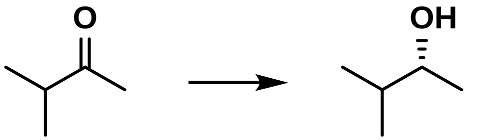
Figure 1. Open-chain PNNP ligand A and macrocyclic analogues.

Macrocyclic structure : prevent NP formation



CO / MeCN => RNC where R = CEt$_3$ or NiPr$_2$

Alkylarylketones : 25 examples
(66 – 99 % yield, 76 – 99 % ee)



99 %, 24 %ee

R. Bigler, R. Huber, A. Mezzetti, *Angew. Chem. Int. Ed.* **2015**, *54*, 5171 –5174

4. Reactivity towards alkenes

a) Epoxidation

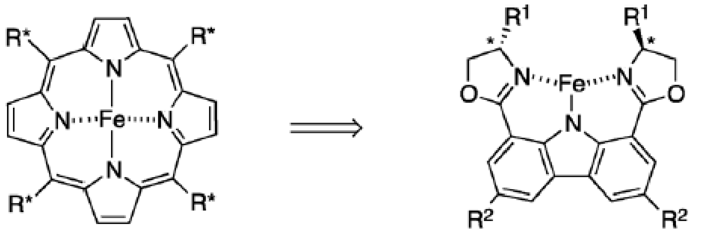
b) Aminohydroxylation

c) Haloamination

d) Hydroboration

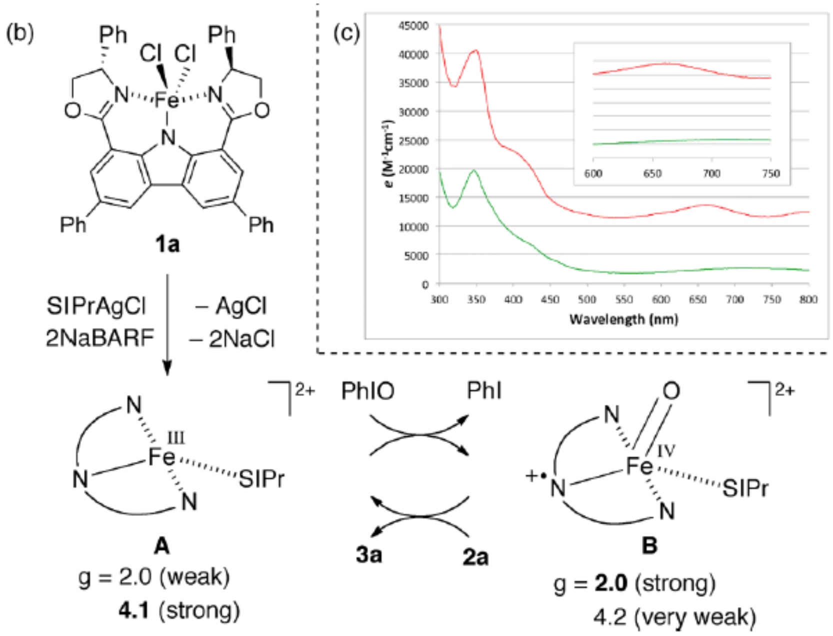
4.a. Asymmetric Epoxidation

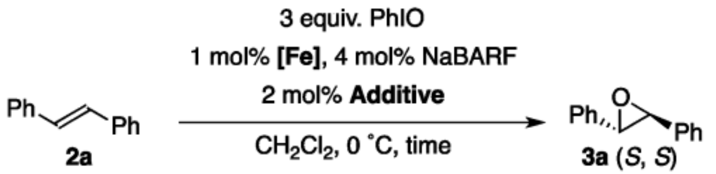
Non-Heme Iron(III) Complex with Porphyrin-like Properties



porphyrin (tetradentate)
(difficult design and preparation)

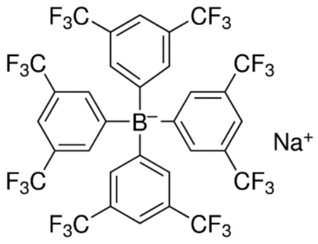
carbazole-based tridentate
(easy preparation with high diversity)





1a **1b** FeCl$_2$(BOPA) SIPrAgCl

entry	complex	additive	time (min)	yield (%)[a]	ee (%)[b]
1	1a	None	30	35	83
2[c]	1a	None	60	trace	NA[d]
3	1a	SIPrAgCl	60	55	88
4	1b	SIPrAgCl	60	trace	NA[d]

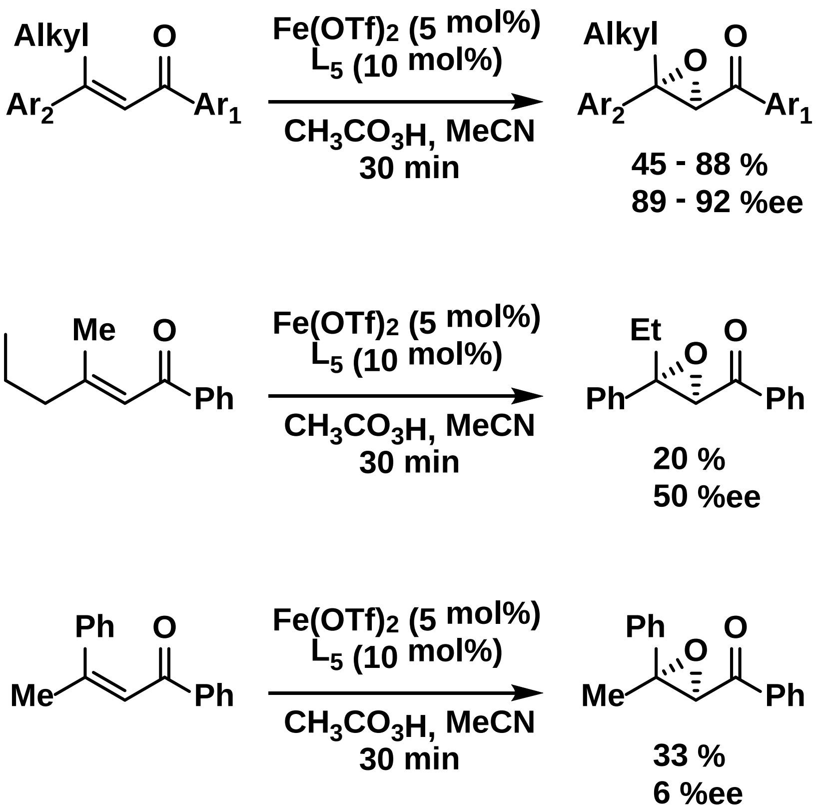


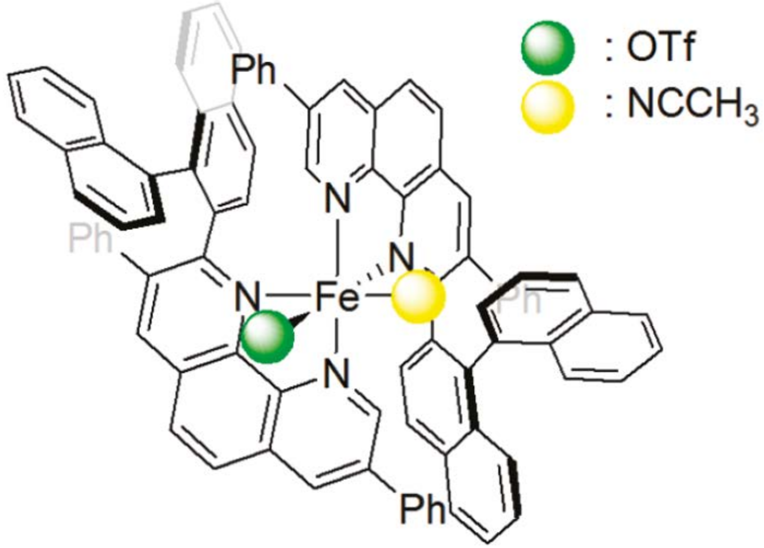
NaBARF

T. Niwa, M. Nakada, *J. Am. Chem. Soc.* **2012**, *134*, 13538−13541

4.a. Asymmetric Epoxidation of Enones

Challenging epoxidation of β,β disubstituted olefin



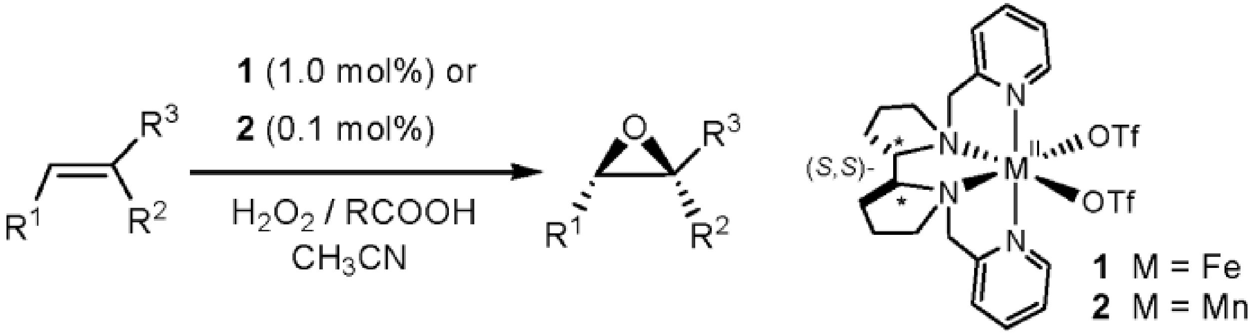


Question: explain why it is challenging, and why this method is efficient.

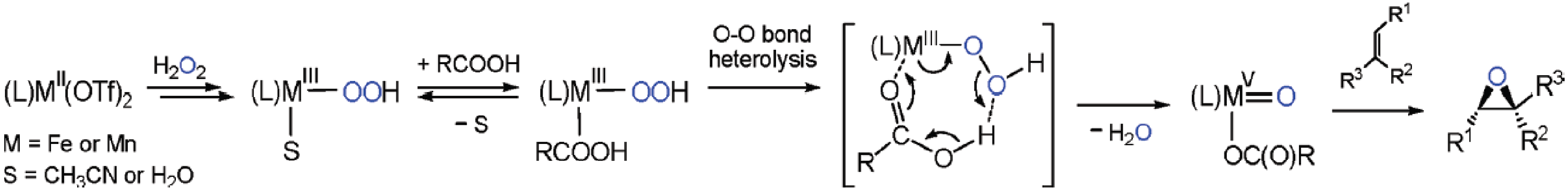
Y. Nishikawa, H. Yamamoto, *J. Am. Chem. Soc*. **2011**, *133*, 8432–8435

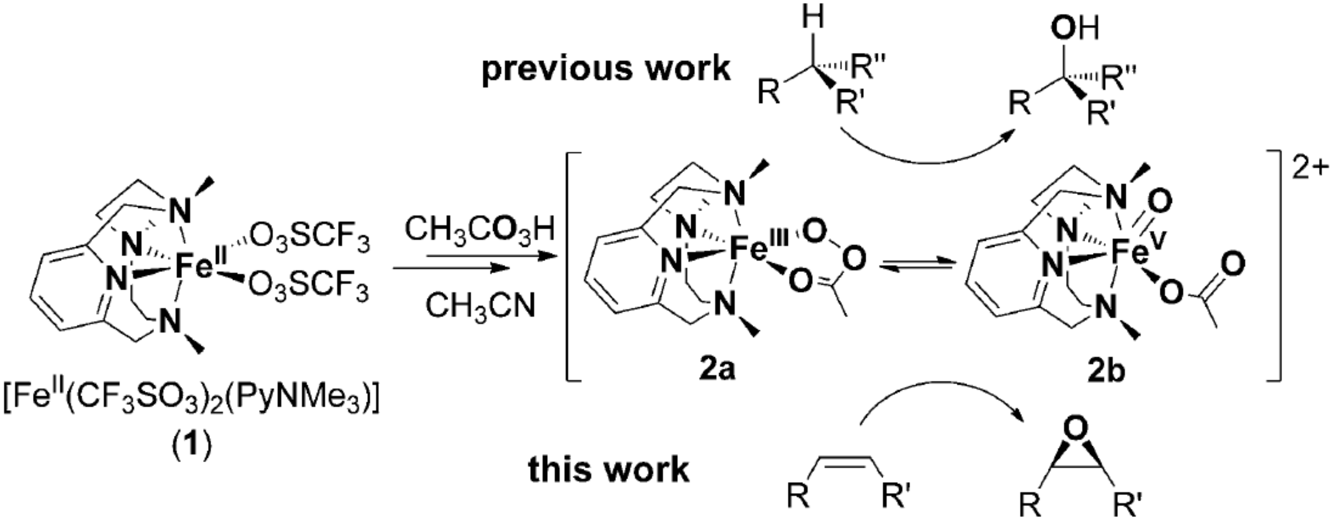
4.a. Asymmetric Epoxidation

Reactivity of alkenes



33 to 99 % yield
37 – 93 % ee

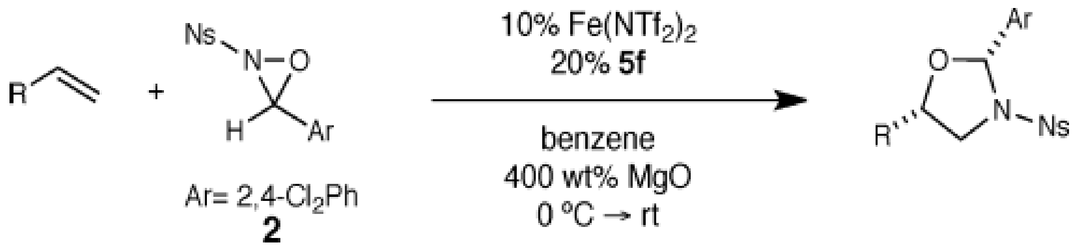




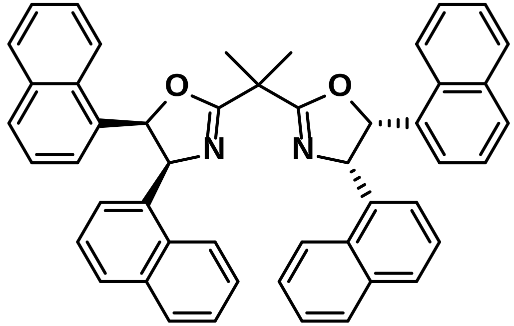
Miquel Costas, ACIE, early view 13/04/16

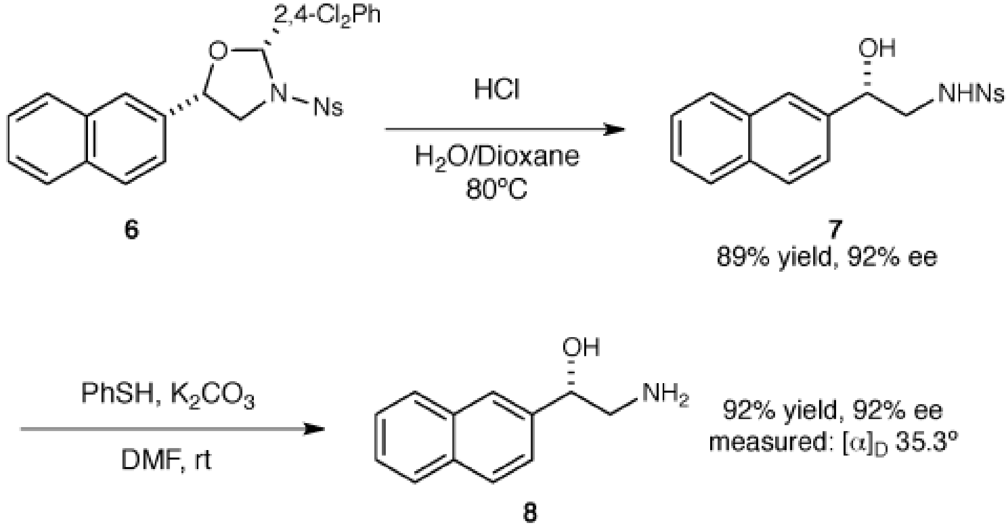
O. Y. Lyakin, R. V. Ottenbacher, K. P. Bryliakov, E. P. Talsi, *ACS Catal*. **2012**, *2*, 1196−1202

4.b. Asymmetric Intermolecular Aminohydroxylation



5f



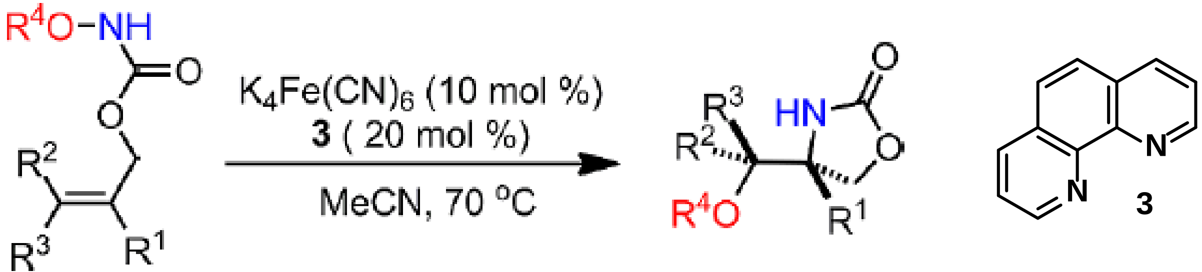


Synthesis of enantioenriched 1,2 aminoalcohol

Kevin S. Williamson and Tehshik P. Yoon, *J. Am. Chem. Soc.* **2012**, *134*, 12370−12373

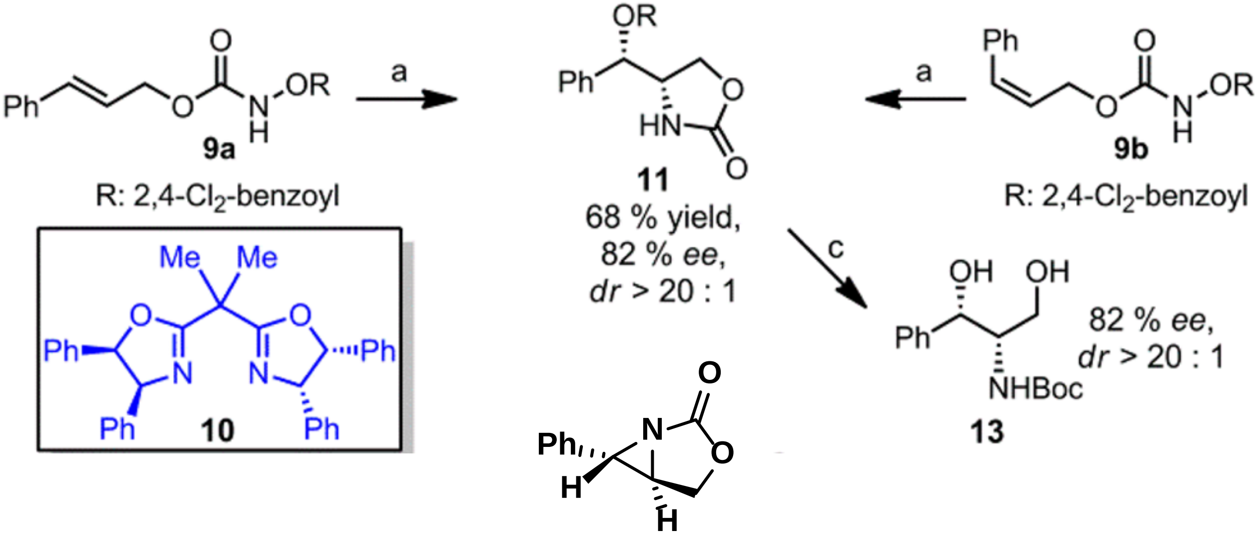
4.b. Asymmetric Intramolecular Aminohydroxylation

Diastereoselective



16 examples
dr 2:1 to >20:1

Enantioselective



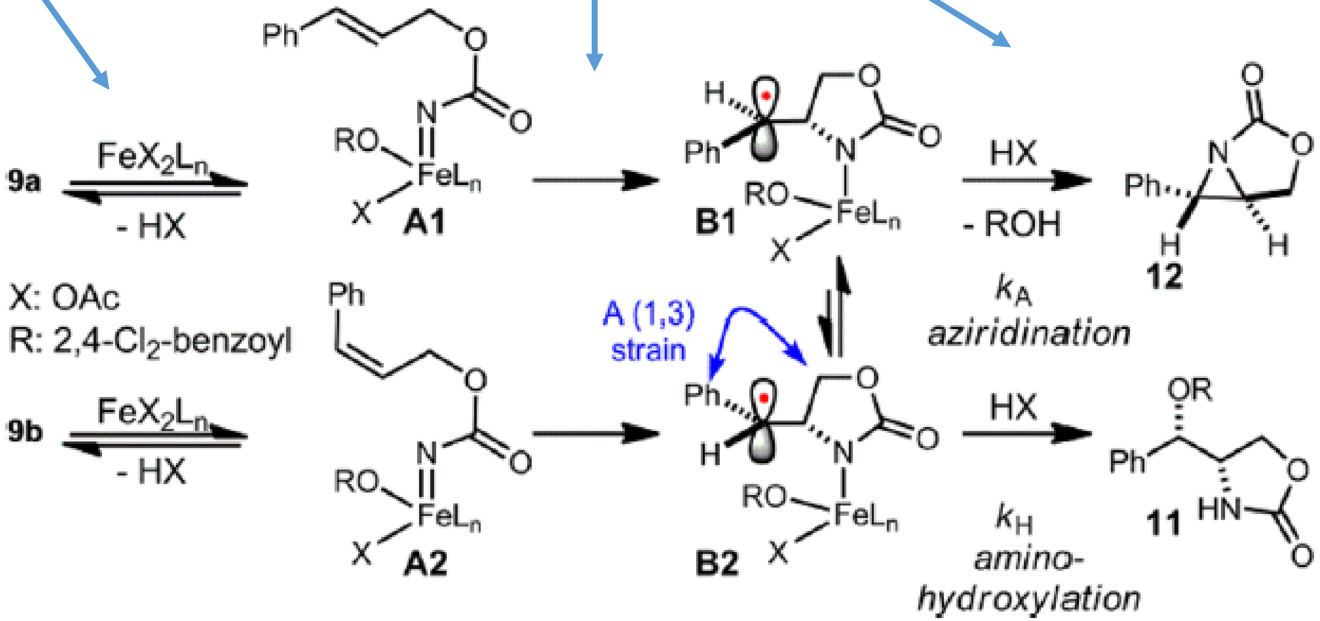
Aziridine side product

G.-S. Liu, Y.-Q. Zhang, Y.-A. Yuan, H. Xu, *J. Am. Chem. Soc*. **2013**, *135*, 3343−3346

4.b. Asymmetric Intramolecular Aminohydroxylation

N-O insertion

radical attack

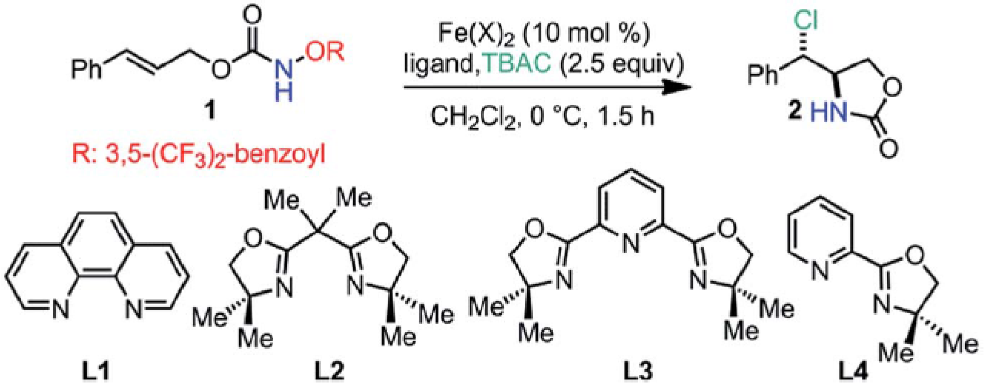


Equilibrium controled by counterion and ligand combination

G.-S. Liu, Y.-Q. Zhang, Y.-A. Yuan, H. Xu, *J. Am. Chem. Soc*. **2013**, *135*, 3343−3346

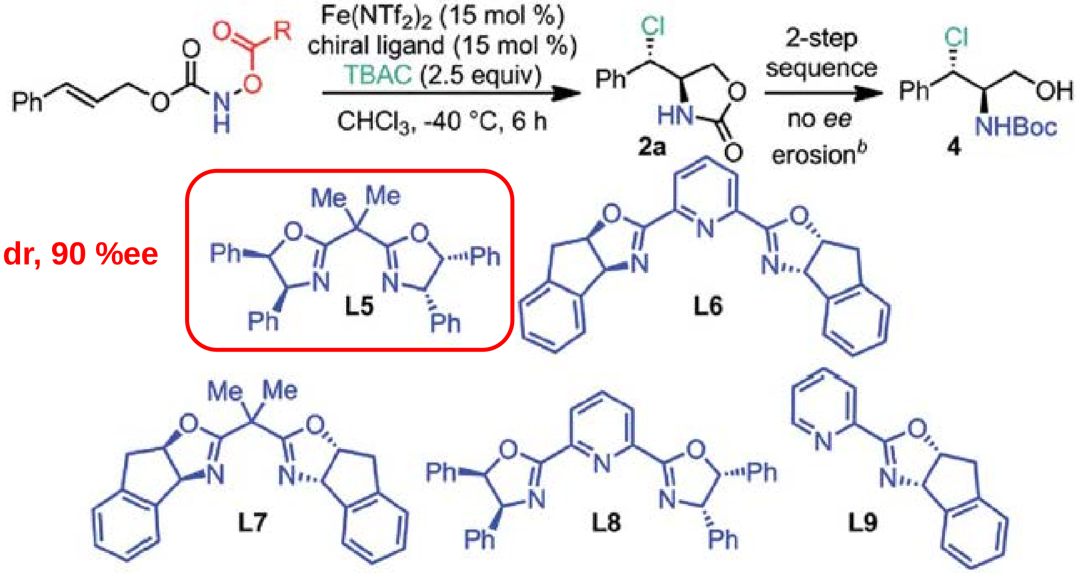
4.c. Asymmetric Intramolecular Aminochlorination

Diastereoselective



86 %, >20:1 82 %, 0.83:1 34 %, 0.25:1 75 %, 1.8:1

Enantioselective

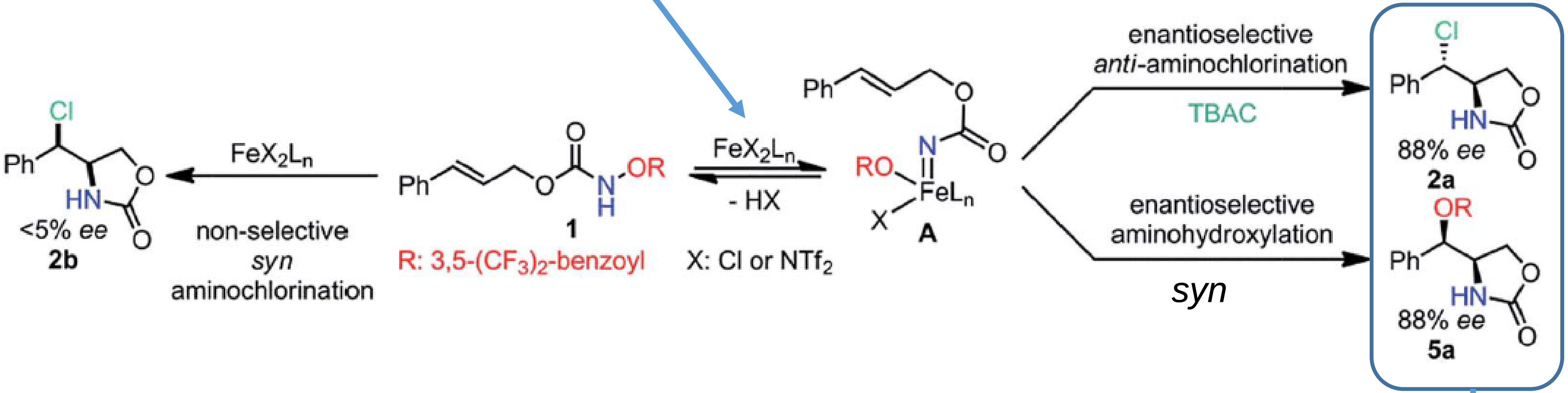


51 %, 11:1 dr, 90 %ee

C.-L. Zhu, J.-S. Tian, Z.-Y. Gu, G.-W. Xing, H. Xu, *Chem. Sci.*, **2015**, *6*, 3044–3050

4.c. Asymmetric Intramolecular Aminochlorination

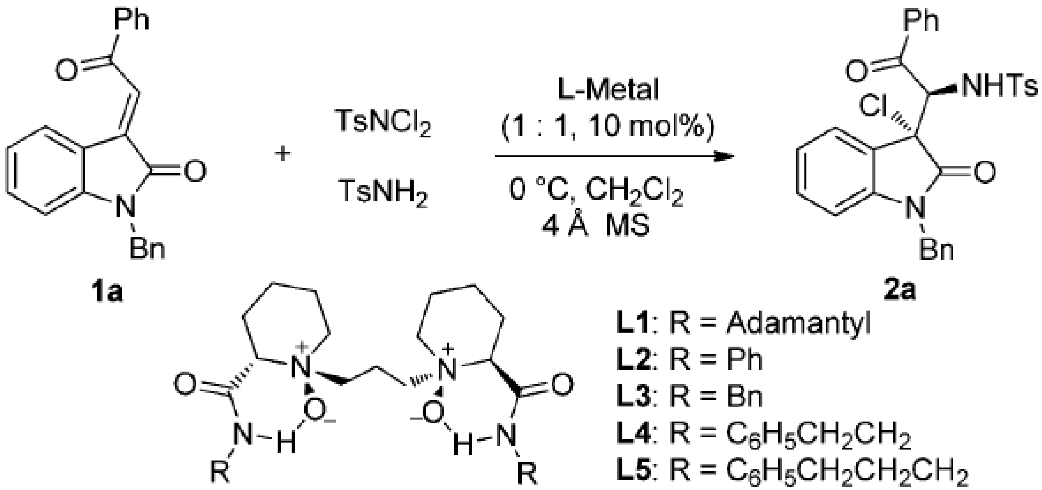
Reversible N-O cleavage



Same ee:
the radical amination is the rate and ee determining step !

C.-L. Zhu, J.-S. Tian, Z.-Y. Gu, G.-W. Xing, H. Xu, *Chem. Sci.*, **2015**, *6*, 3044–3050

4.c. Asymmetric haloamination of alkenes



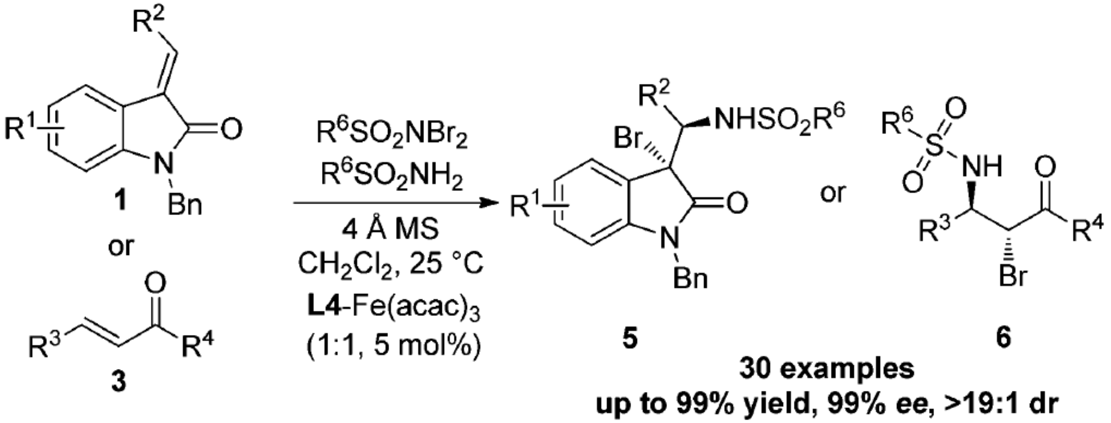
L1: R = Adamantyl
L2: R = Ph
L3: R = Bn
L4: R = $C_6H_5CH_2CH_2$
L5: R = $C_6H_5CH_2CH_2CH_2$

Entry[a]	Metal	Ligand	Yield of 2a[b] (%)	ee of 2a[c] (%)	dr of 2a[d] (*anti* : *syn*)
1	Fe(acac)$_3$	**L1**	40	7	>19 : 1
2	Fe(acac)$_3$	**L2**	88	96	>19 : 1
3	Fe(acac)$_3$	**L3**	99	97	>19 : 1
4	Fe(acac)$_3$	**L4**	99	99	>19 : 1
5	Fe(acac)$_3$	**L5**	98	97	>19 : 1

18 examples, 90 – 99 % yield, 93 – 99 %ee, >19:1 dr

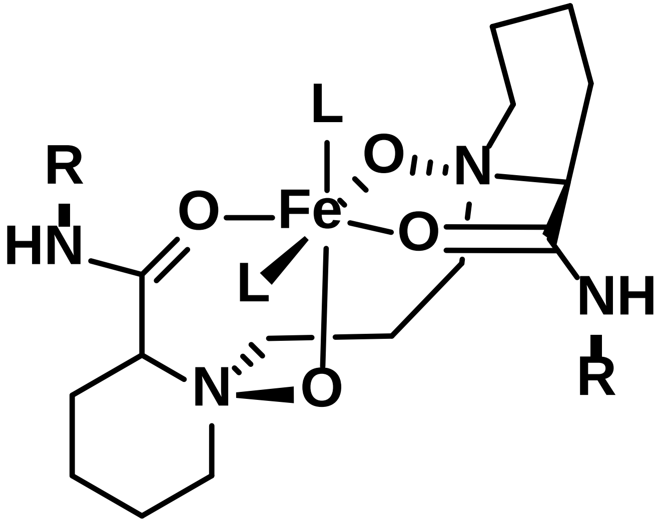
Y. Cai, X. Liu, P. Zhou, Y. Kuang, L. Lin, X. Feng, *Chem. Commun.,* 2013, **49**, 8054--8056

4.c. Asymmetric haloamination of alkenes



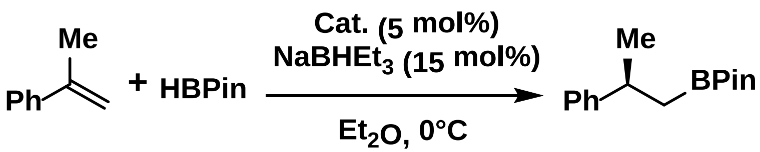
QUESTION ??

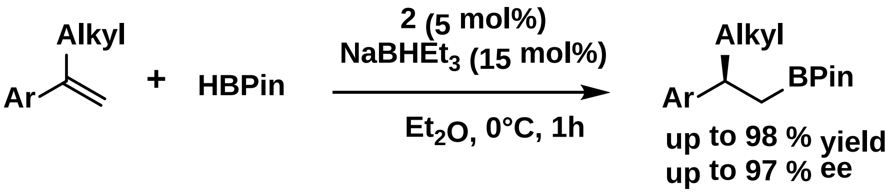
Draw the transition state using the geometry of this ligand to explain the *anti* selectivity



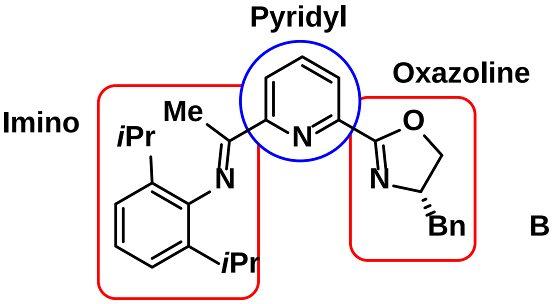
Y. Cai, X. Liu, P. Zhou, Y. Kuang, L. Lin, X. Feng, *Chem. Commun.*, 2013, **49**, 8054--8056

4.d. Asymmetric Hydroboration



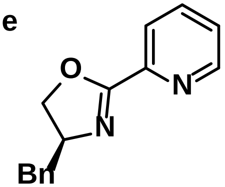


up to 98 % yield
up to 97 % ee



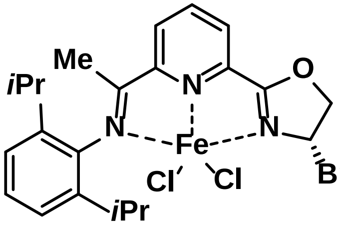
1 - IPO

with Ir or Ru: nr



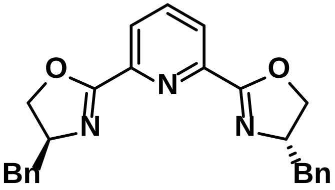
3

< 5 %, - %ee



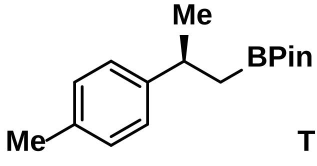
2

98 %, 96 %ee

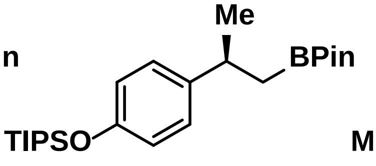


4 - PyBox

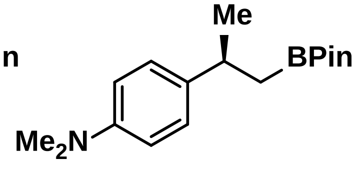
6 %, - %ee



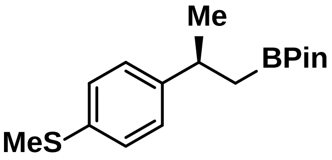
93 %, 90 %ee



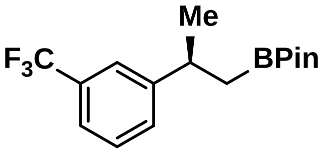
88 %, 95 %ee



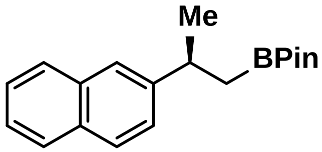
88 %, 95 %ee



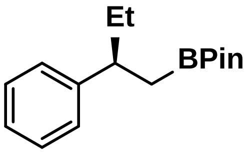
77 %, 96 %ee



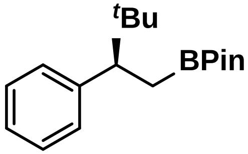
61 %, 92 %ee



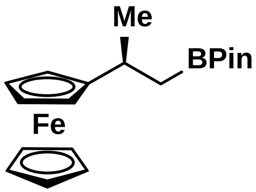
93 %, 95 %ee



91 %, 93 %ee



69 %, 87 %ee



47 %, 97 %ee

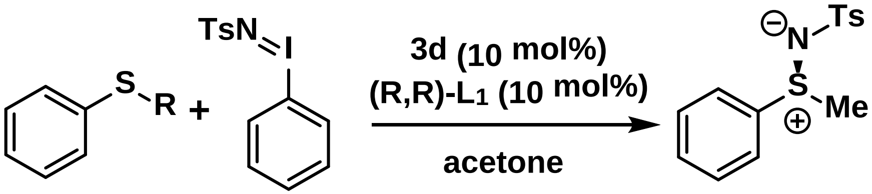
- High regio- and enantioselectivities
- Glove box not necessarily required
- PyOX and PyBox doesn't work

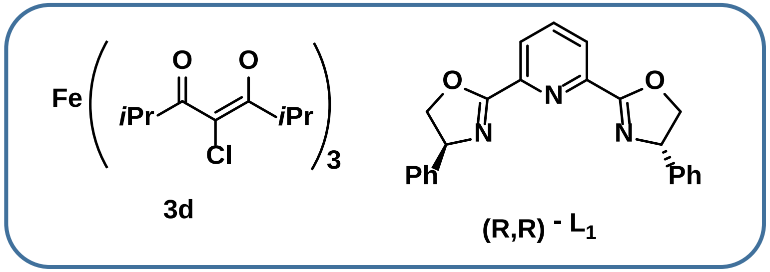
J. Chen, T. Xi, Z. Lu, *Org. Lett.* **2014**, *16*, 6452−6455

5. Heteroatoms transfers using hypervalent iodine reagents

- Sulfimides synthesis by nitrene transfer
- Azidation of β-ketoesters and oxindoles

5.a. Enantioselecive Nitrene Transfer to Sulfides





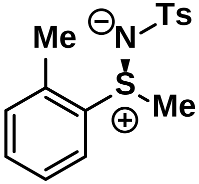
3d

(R,R) - L_1

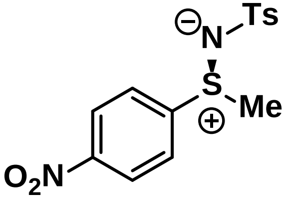
R = linear alkyl chain:
from C1 to C8: 80 to 98 %, 86 to 90 % ee

R = C14H29 : 23 %, 82 % ee

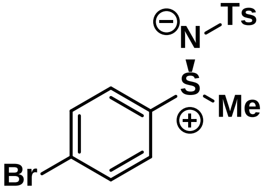
R = iPr : 49 %, 60 % ee



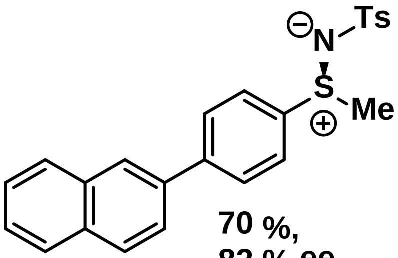
91 %, 84 % ee



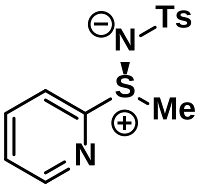
82 %, 66 % ee



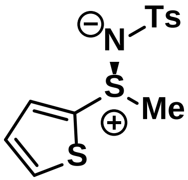
97 %, 86 % ee



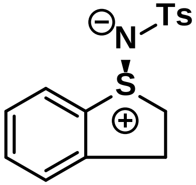
70 %,
82 % ee



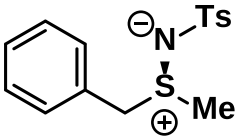
81 %, 84 % ee



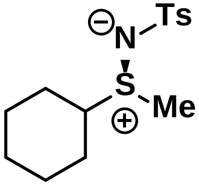
49 %, 86 % ee



91 %, 84 % ee



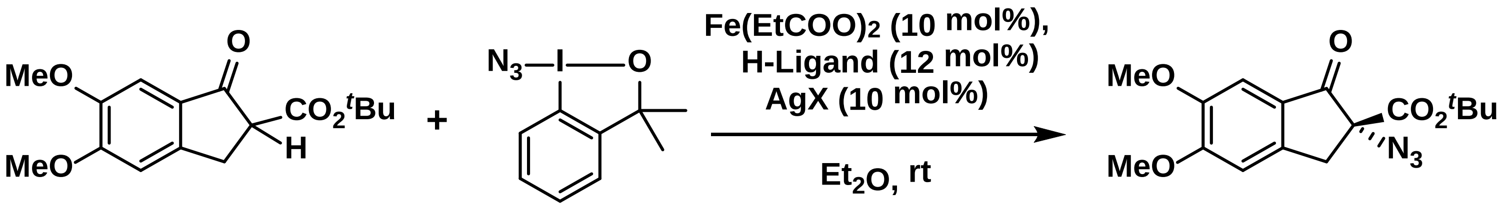
55 %, 10 % ee

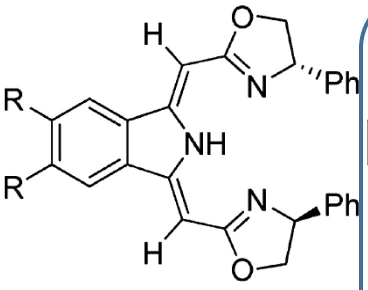


47 %, 66 % ee

J. Wang, M. Frings, C. Bolm, *Angew. Chem. Int. Ed.* **2013**, *52*, 8661 –8665

5.b. Asymmetric Azidation of *β*-ketoesters



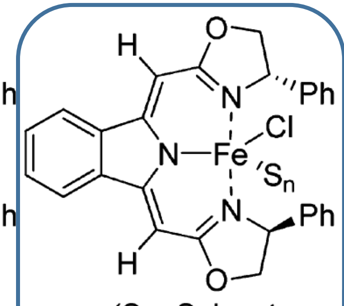


boxmi (2)

R = Me, **2a**

R = Ph, **2b**

R = H, **2c**

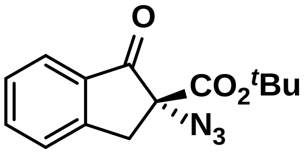


(S = Solvent, n = 1 or 2)

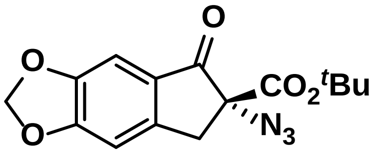
6a

AgOOCR (**7**)

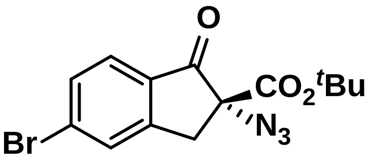
	R
7a	CF_2CF_3
7b	Ph
7c	4-MeO-C_6H_4
7d	4-NO_2-C_6H_4
7e	C_6F_5
7f	2-Naphthyl



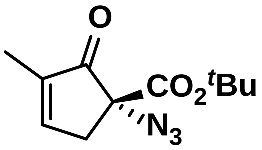
89 %, 93 % ee



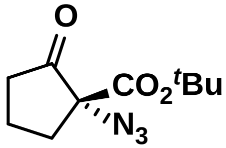
85 %, 93 % ee



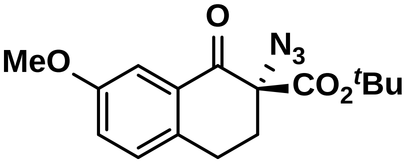
87 %, 90 % ee



89 %, 92 % ee



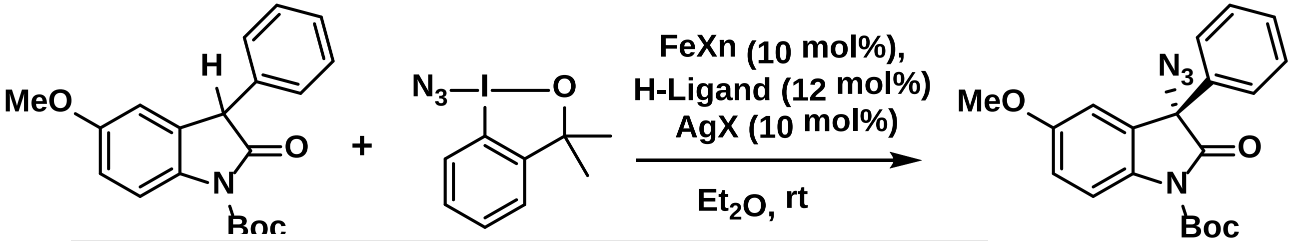
87 %, 69 % ee



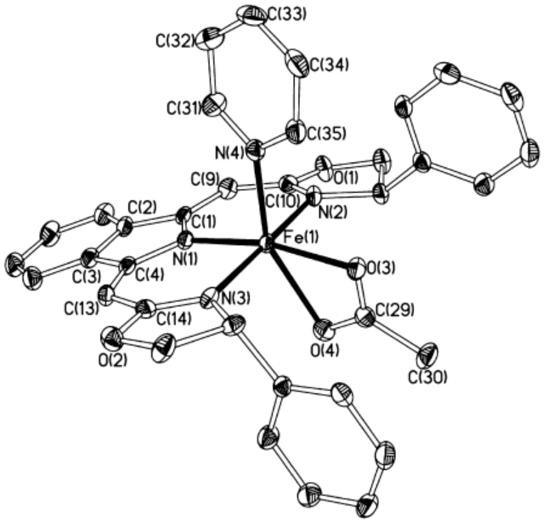
88 %, 76 % ee

Q.-H. Deng, T. Bleith, H. Wadepohl, L. H. Gade, *J. Am. Chem. Soc.* **2013**, *135*, 5356−5359

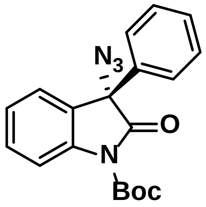
5.b. Asymmetric Azidation of Oxindoles



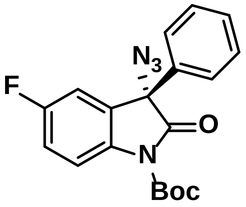
entry	MXn	H-Lig	AgX	solvent	T	t (h)	yield (%)[a]	ee (%)[b]
1	**6a**	–	**7d**	Et_2O	rt	36	86	78
2	**3**	**2c**	–	Et_2O	rt	36	87	91
3	**3**	**2c**	–	THF	rt	36	84	84
4	**3**	**2a**	–	Et_2O	rt	36	84	90
5	**3**	**2c**	–	Et_2O	0 °C	48	51	69



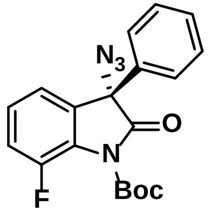
- In situ generation of the catalyst is better
- No silver salt needed



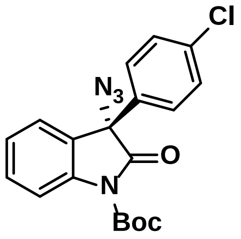
85 %, 91 % ee



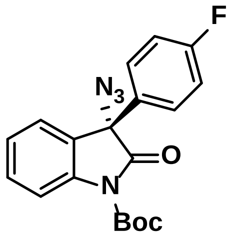
90 %, 91 % ee



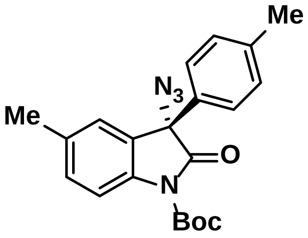
85 %, 91 % ee



85 %, 94 % ee



89 %, 90 % ee



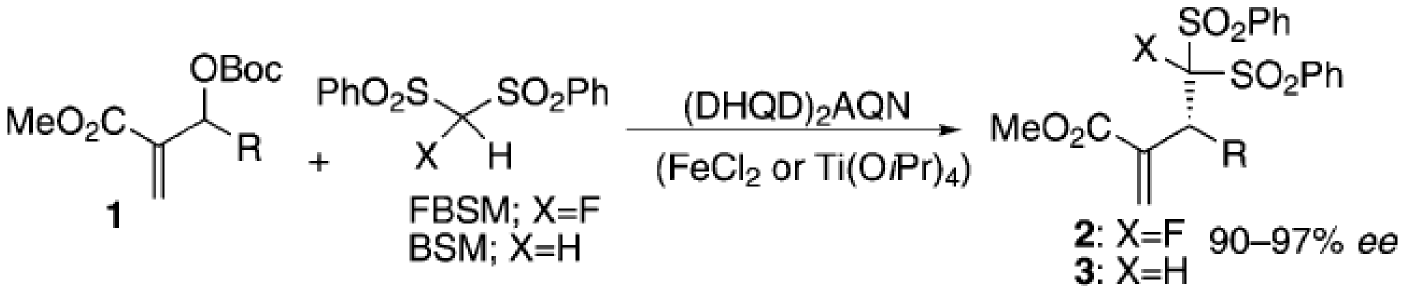
88 %, 90 % ee

Q.-H. Deng, T. Bleith, H. Wadepohl, L. H. Gade, *J. Am. Chem. Soc*. **2013**, *135*, 5356−5359

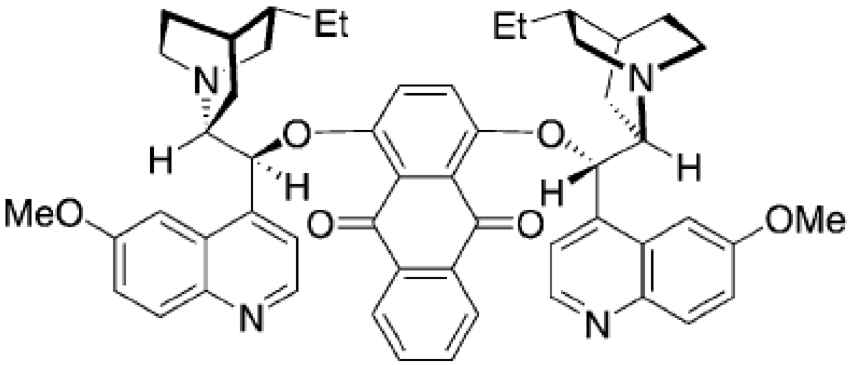
6. Achiral Iron Complexes

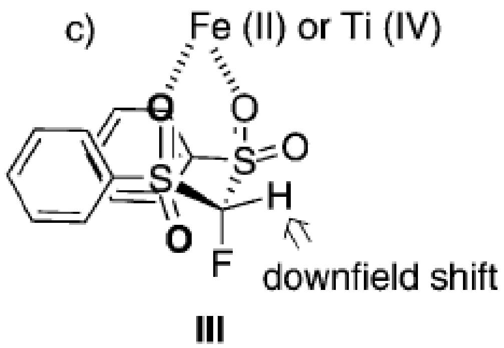
6.a. Dual Catalysis with Organocatalyst

Asymmetric Allylic Monofluoromethylation and Methylation of Morita–Baylis–Hillman Carbonates with FBSM and BSM by Cooperative Cinchona Alkaloid/$FeCl_2$ Catalysis



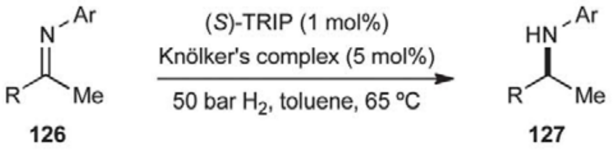
(DHQD)$_2$ AQN =





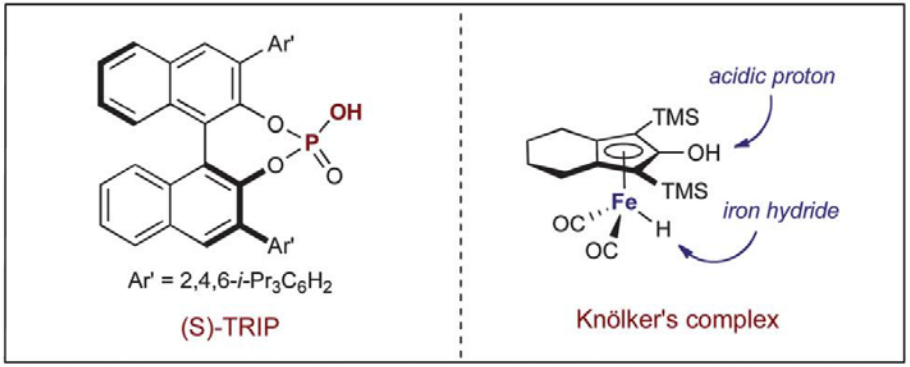
T. Furukawa, J. Kawazoe, W. Zhang, T. Nishimine, E. Tokunaga, T. Matsumoto, M. Shiro, N. Shibata, *Angew. Chem. Int. Ed.* **2011**, *50*, 9684 –9688

6.b. Asymmetric reduction of imines

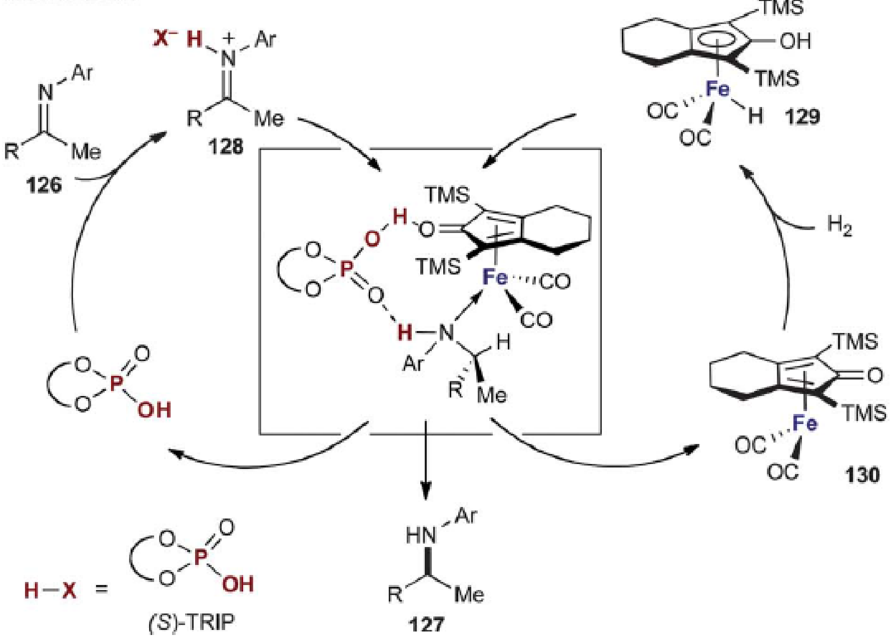


R = aryl 67-93%
80-98% ee

R = alkyl 69-94%
67-83% ee

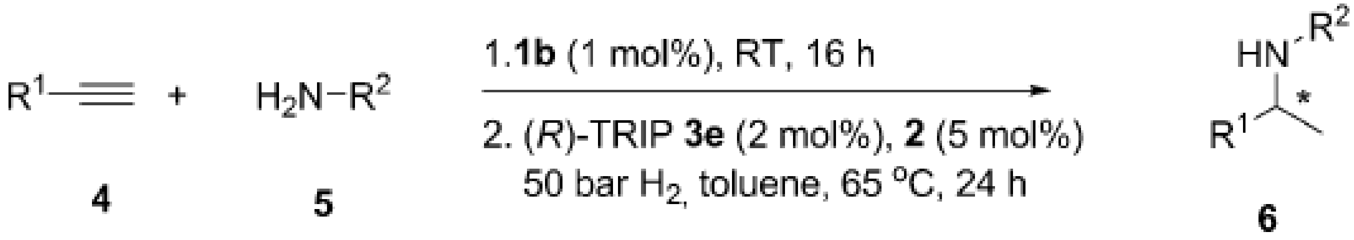


Mechanism:

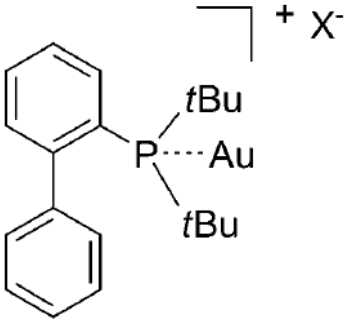


1) S. Zhou, S. Fleischer, K. Junge, M. Beller, *Angew. Chem., Int. Ed.*, **2011**, *50*, 5120–5124
2) M. Darwish, M. Wills, *Catal. Sci. Technol.*, **2012**, *2*, 243–255
3) A. E. Allen, David W. C. MacMillan, *Chem. Sci.*, **2012**, *3*, 633–658

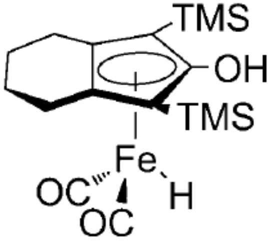
6.c. Asymmetric Hydroamination of Alkynes



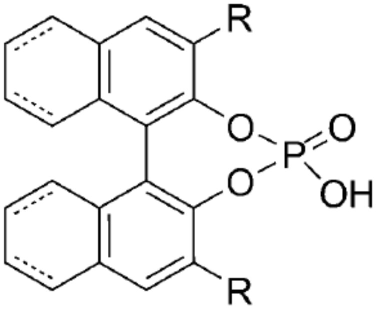
4 **5** **6**



1a: X = Cl
1b: X = BF_4



2

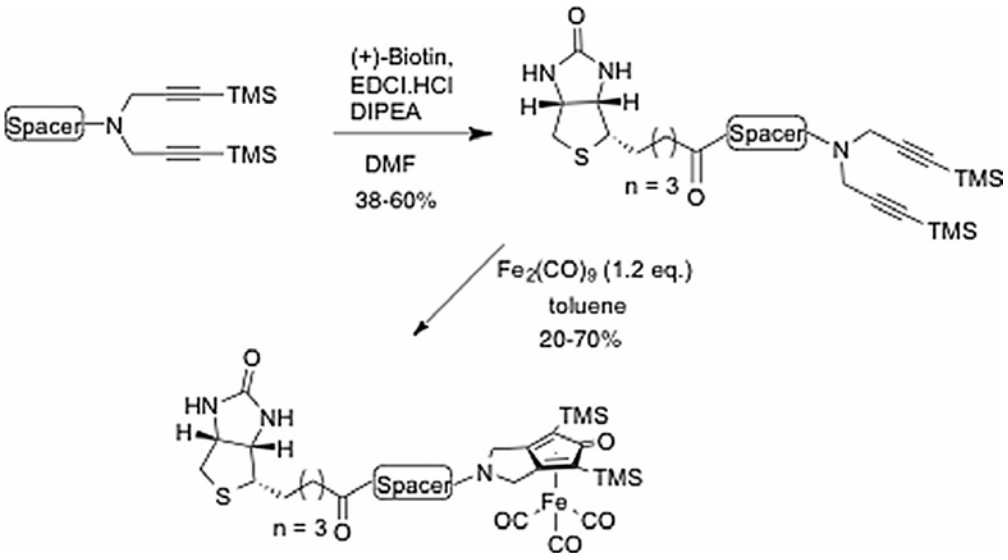


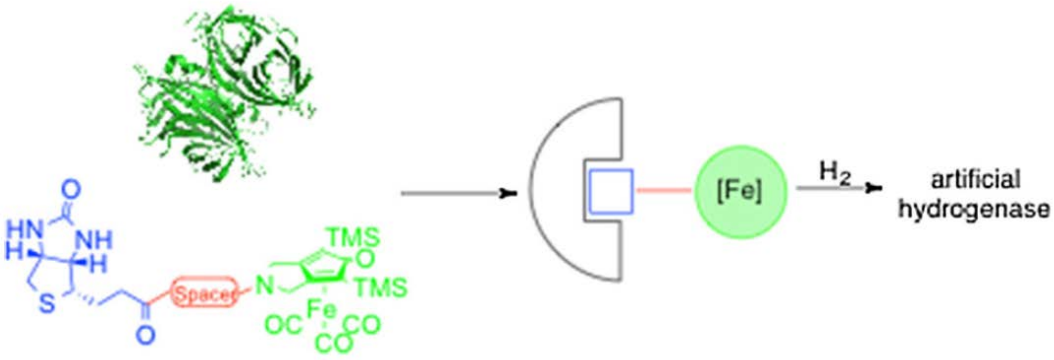
3

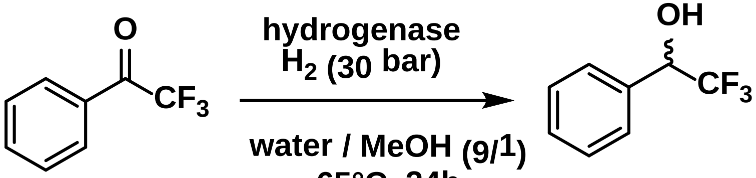
S. Fleischer, S. Werkmeister, S. Zhou, K. Junge, M. Beller, *Chem. Eur. J.* **2012**, *18,* 9005 – 9010

6.d. Artificial metalloenzymes

Achiral Cyclopentadienone Iron Tricarbonyl Complexes Embedded in Streptavidin

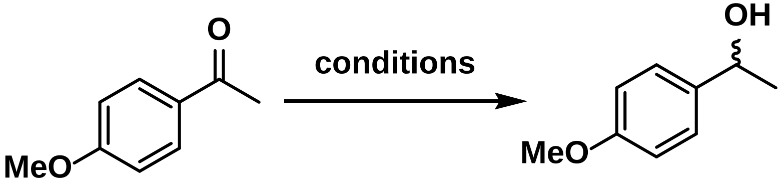






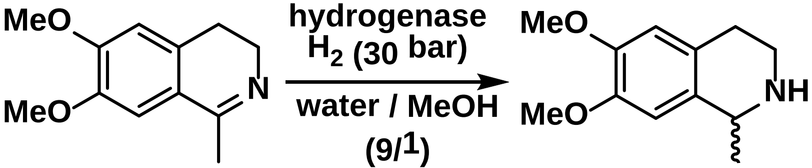
5 mol% hydrogenase
H_2 (30 bar)
water / MeOH (9/1)
65°C, 24h

100 % yield
9 % ee



conditions

conv. 26 %
34 % ee



5 mol% hydrogenase
H_2 (30 bar)
water / MeOH (9/1)
75°C, 18h

conv. 12% yield
9 % ee

D. S. Mérel, S. Gaillard, T. R. Ward, J-L. Renaud, *Catal Lett,* **2016**, *146,* 564–569

Outlook

- Decrease catalyst loading (often 5-10 mol%)
- Recyclability (if NP, by using magnets)
- More diversity of the ligand classes
  Mostly Box, PyBox, SpiroBox, Porphyrin
- New chiral ferrocene based ligands
- Domino reaction (>2 bonds formation)
- Asymmetric transformations in aqueous media
- C-C bond formation (Carbocyclization, Cyclopropanation, Mukaiyama, Grignards…)

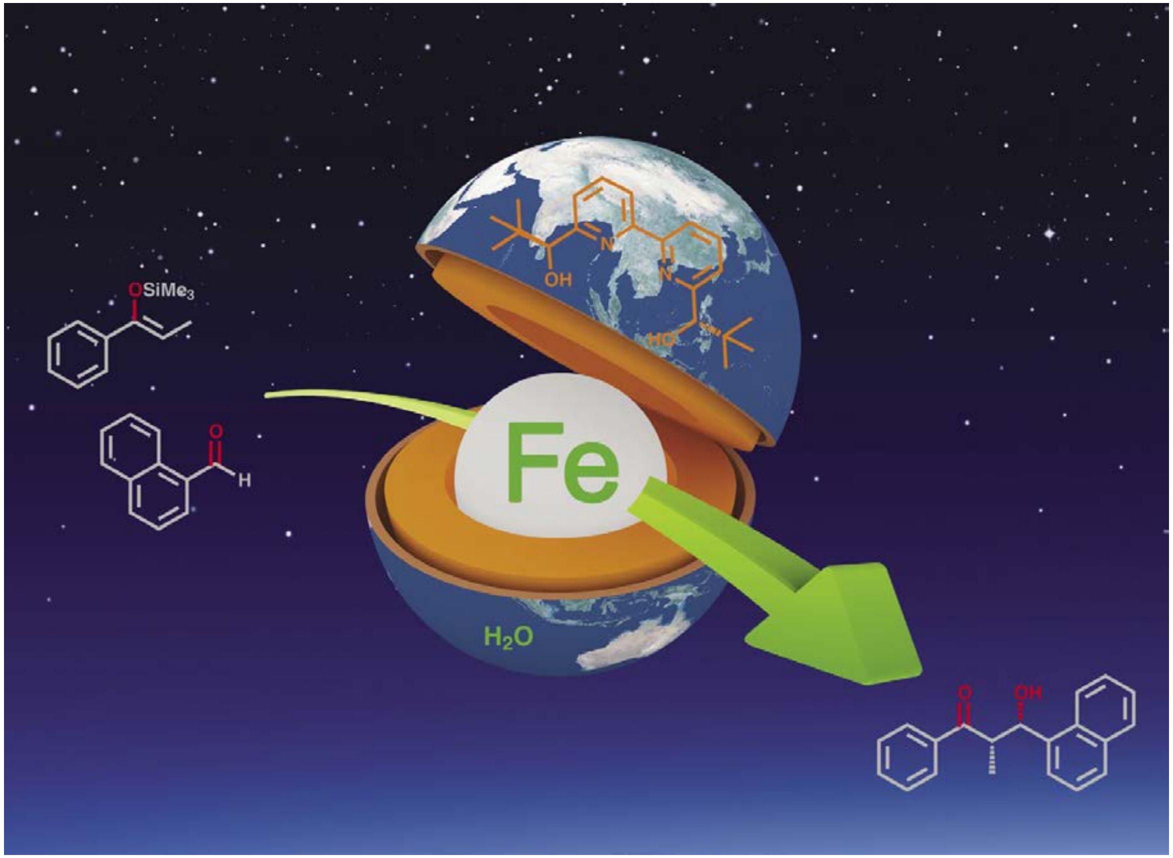
Conclusion

Fe–H	**Fe=O**	**Fe=NR**	**$Fe{=}CR_2$**
Iron hydride	**Oxo-iron**	**Iron-Nitrenoid**	**Iron carbene**

Most abundant metal on earth

Low toxicity

Cheap



Efficient

Various types of transformations

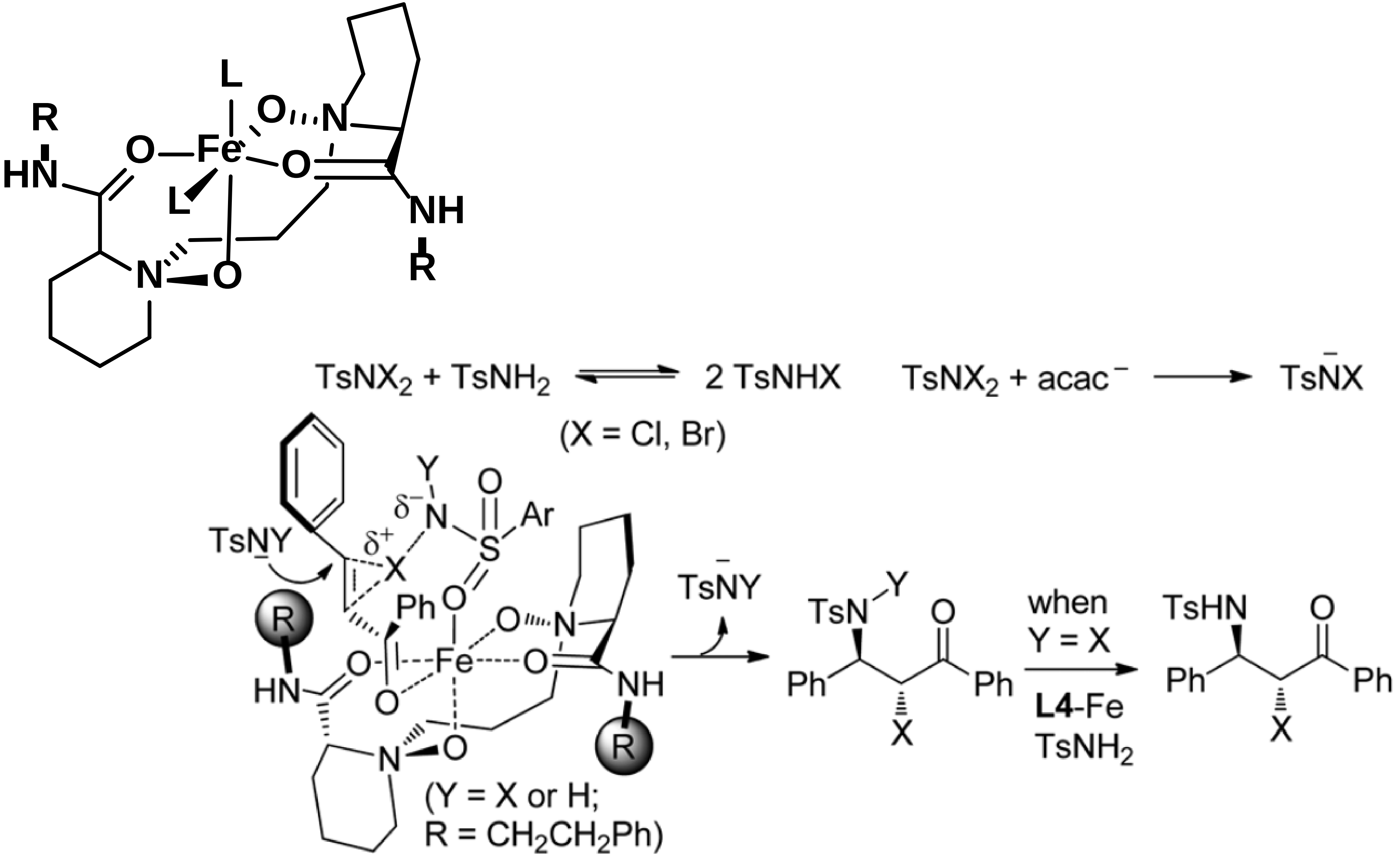
High chemo- and stereo selectivity

Aqueous media tolerated

Cover: T. Ollevier *et al.*, *Chem. Commun.*, 2012, **48**, 2289

Thank you for your attention

Asymmetric haloamination of alkenes

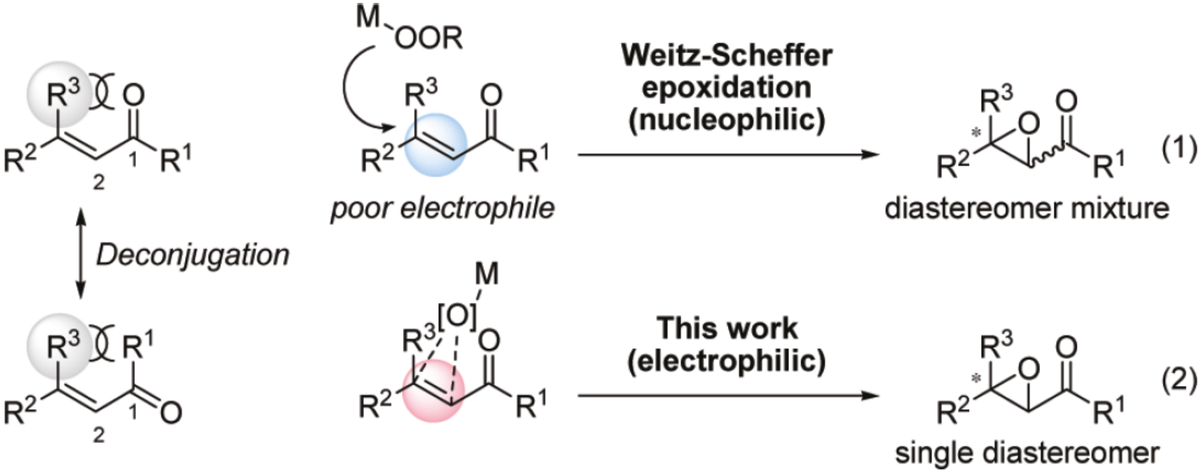


Y. Cai, X. Liu, P. Zhou, Y. Kuang, L. Lin, X. Feng, *Chem. Commun.,* 2013, **49**, 8054--8056

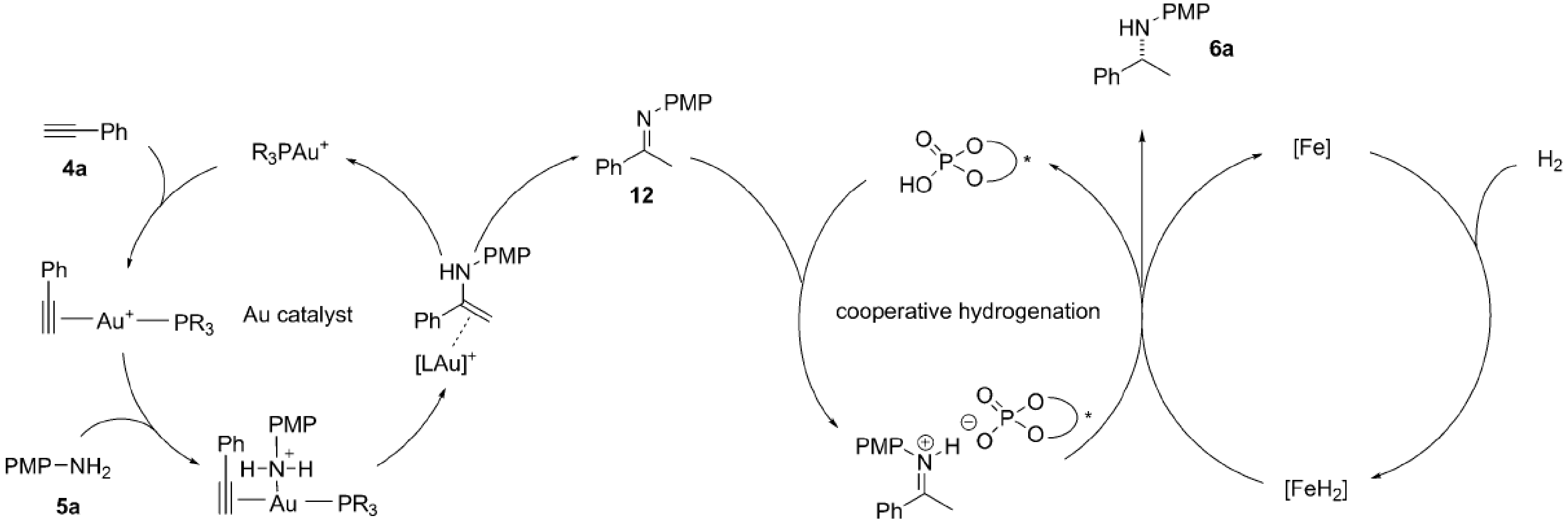
Asymmetric Epoxidation of Alkenes

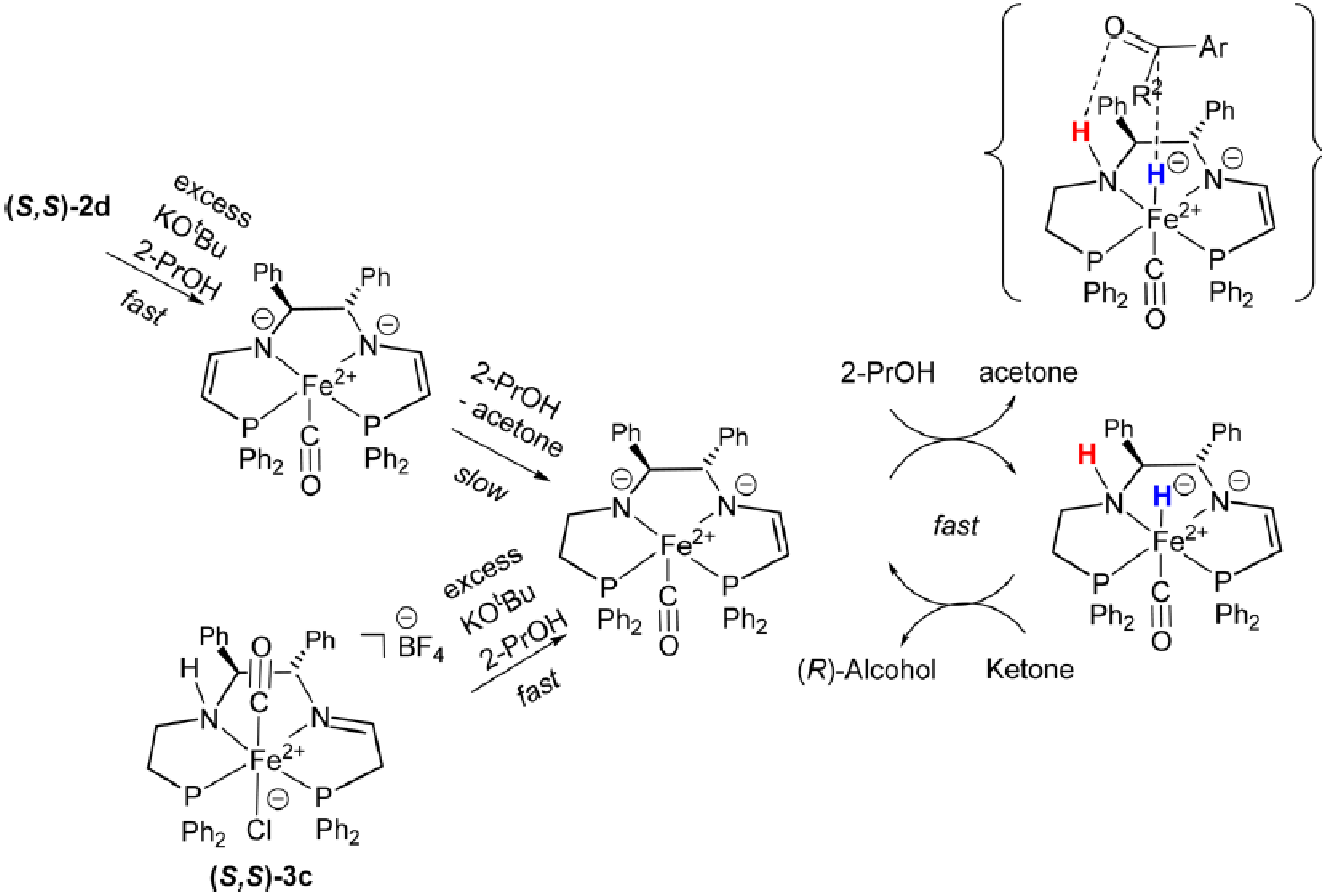
More nucleophilic

Steric

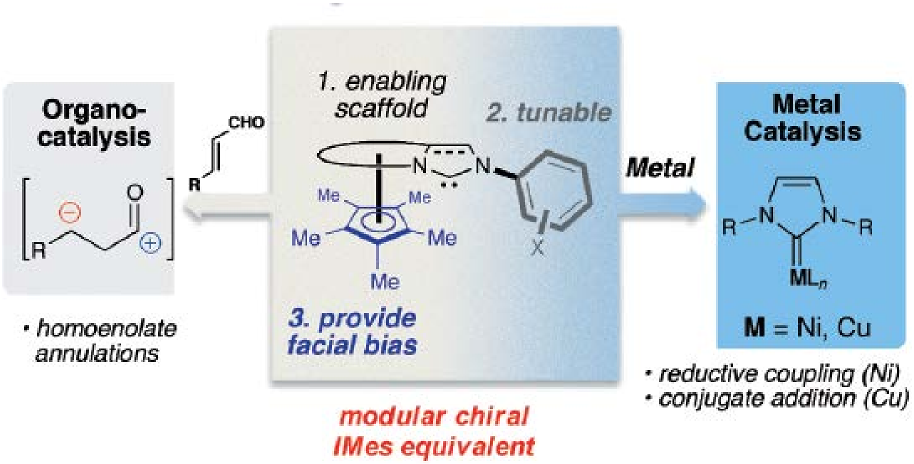


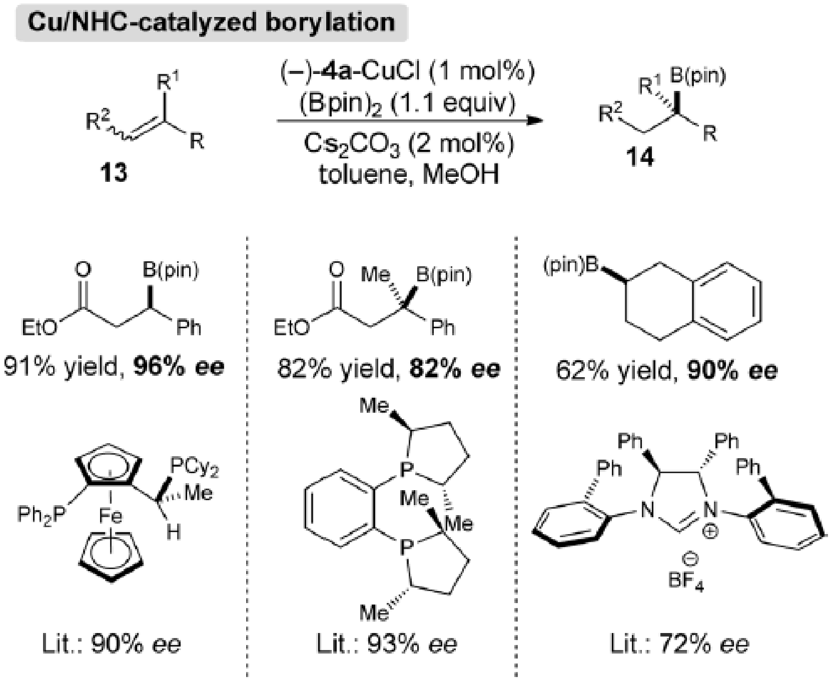
Yasuhiro Nishikawa and Hisashi Yamamoto, *J. Am. Chem. Soc*. **2011**, *133*, 8432–8435

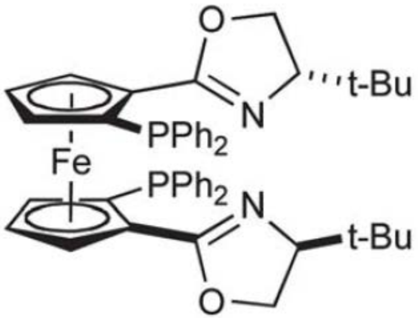

Ph
4a
R3PAu+
Ph
Au+ — PR3
Au catalyst
PMP−NH2
5a
Ph
PMP
H−N−H
Au — PR3
HN PMP
Ph
[LAu]+
N PMP
Ph
12
HN PMP
Ph
6a
O
P
HO
O
O
*
cooperative hydrogenation
PMP
N
H
Ph
O
P
O
O
O
*
[Fe]
H2
[FeH2]

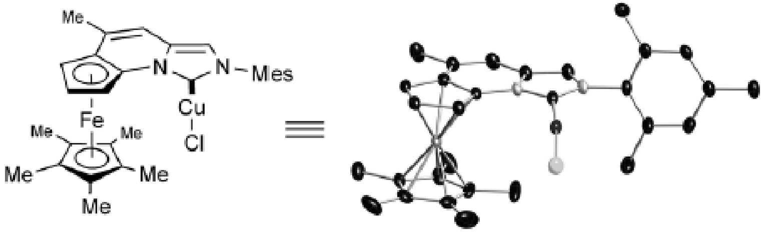

(S,S)-2d
excess KO^{t}Bu
2-PrOH
fast
2-PrOH
- acetone
slow
excess KO^{t}Bu
2-PrOH
fast
BF_4^-
(S,S)-3c
2-PrOH
acetone
fast
(R)-Alcohol
Ketone
Ph
N
Fe^{2+}
P
Ph$_2$
C
O
Cl
H
Ar
R^2

Ligand design









(–)-4a-CuCl X-Ray

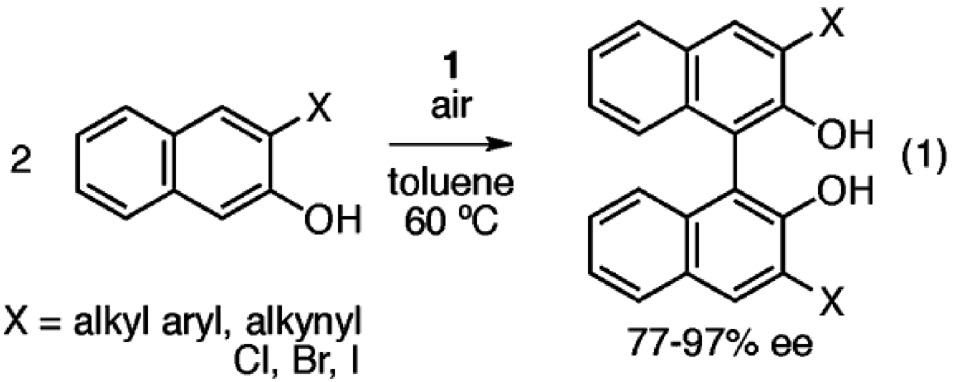
C. T. Check, K. P. Jang, C. B. Schwamb, A. S. Wong, M. H. Wang, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2015**, *54*, 4264 –4268

6. Asymmetric Oxidative Transformation of 2-Naphtols

- Coupling
- Dearomatization
- Spirocyclization

Asymmetric Oxidative Coupling of 2-Naphtols (AOC)

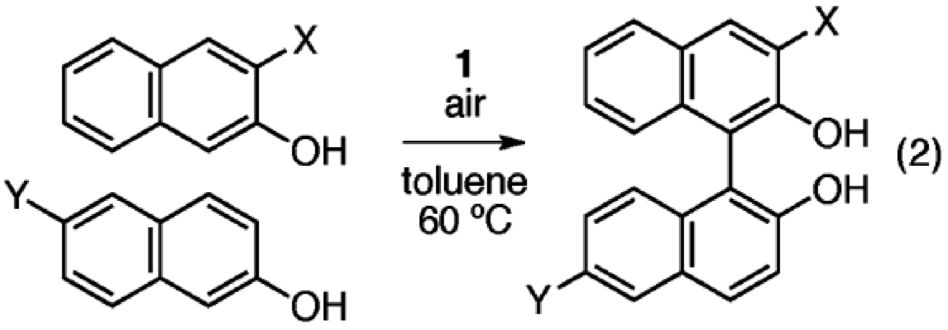
Efficient chiral BINOL synthesis



X = alkyl aryl, alkynyl
Cl, Br, I

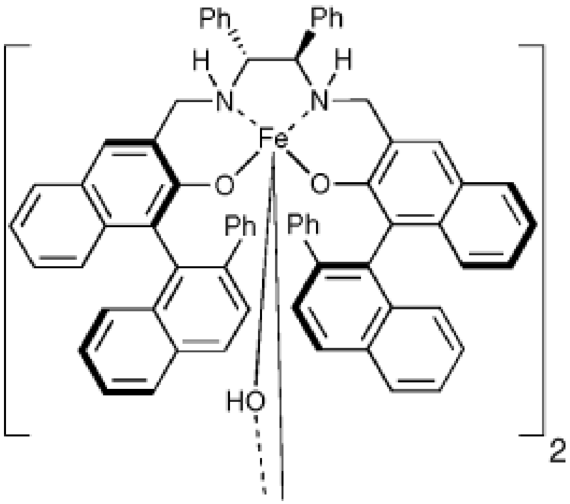
77-97% ee

Prof. T. Katsuki



Y = CO_2Me, Ac, CN, CH=O

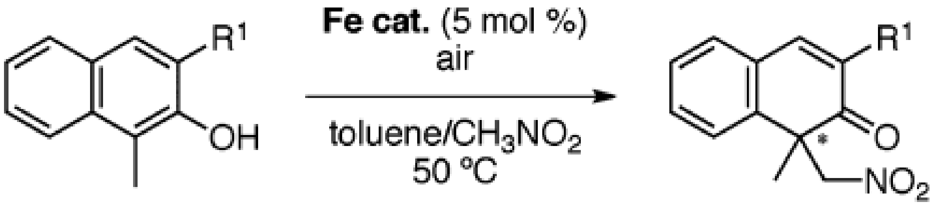
87-95% ee



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

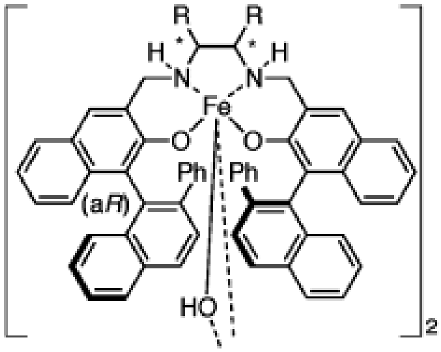
Asymmetric Oxidative Dearomatization of 2-Naphtols (AOD)

With nitroalkanes



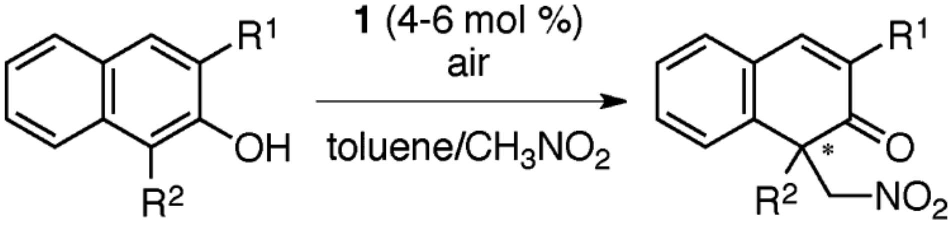
entry	R^1	cat.	yield (%)[b]	ee (%)[c]
1	Me	1	90	90 (+)
2	Me	2	trace	n.d.
3	Me	3	61	80 (+)
4	Me	4	48	84 (−)
5	Me	1	n.r.	–
6	H	1	23[i]	34 (+)

Under Ar



Fe(salan) cat.

1: (a*R*, *R*), R = Ph, **3**: (a*R*, *R*), R = -$(CH_2)_4$-
2: (a*R*, *S*), R = Ph, **4**: (a*R*, *S*), R = -$(CH_2)_4$-



5 **6**

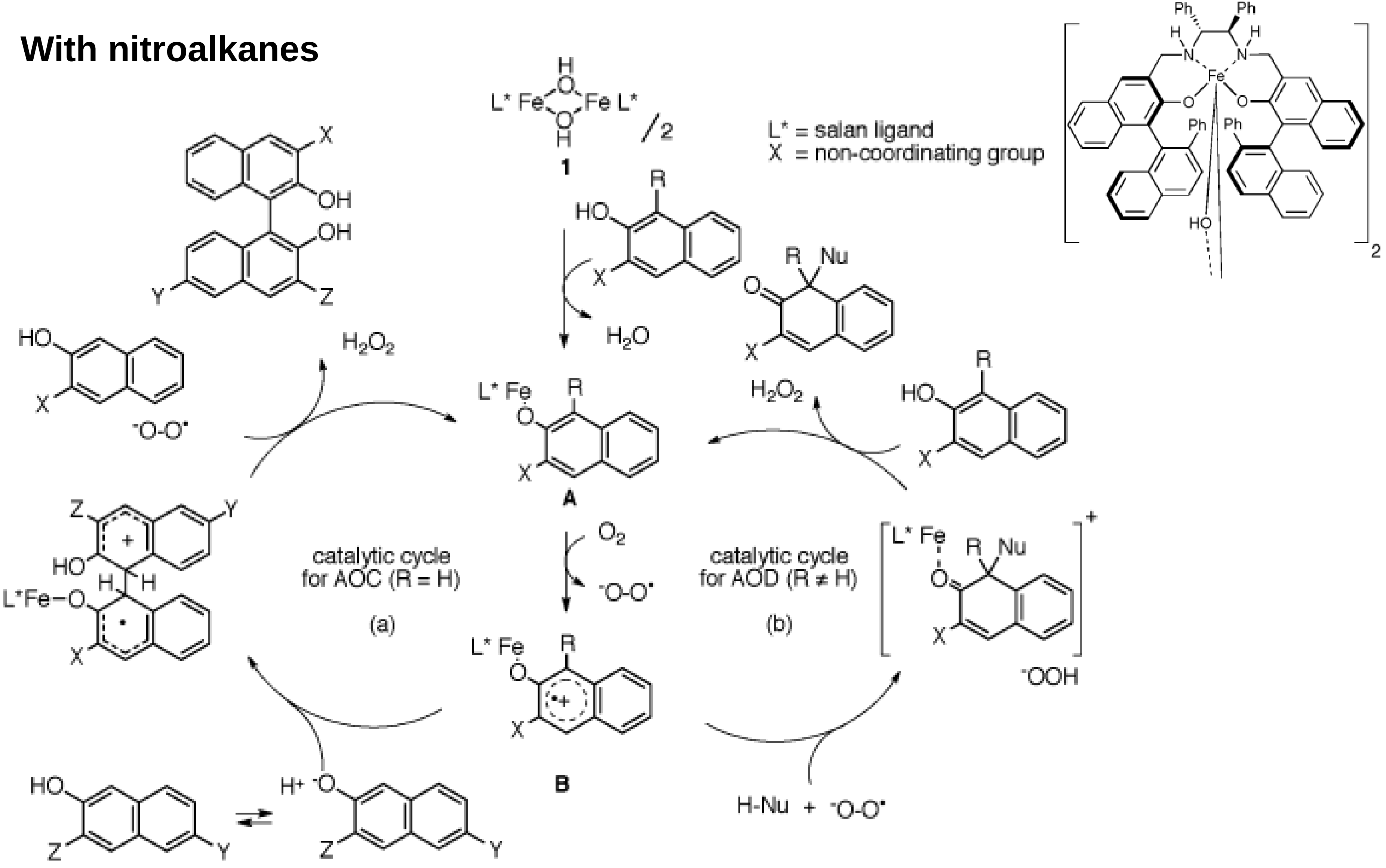
75 to 92 % yield
88 to 96 % ee

R1 = alkyl, allyl, alknynyl, aromatic, halogen,
R2 = alkyl

T. Oguma, T. Katsuki, *J. Am. Chem. Soc.* **2012**, *134*, 20017−20020

AOC and AOD of 2-Naphtols

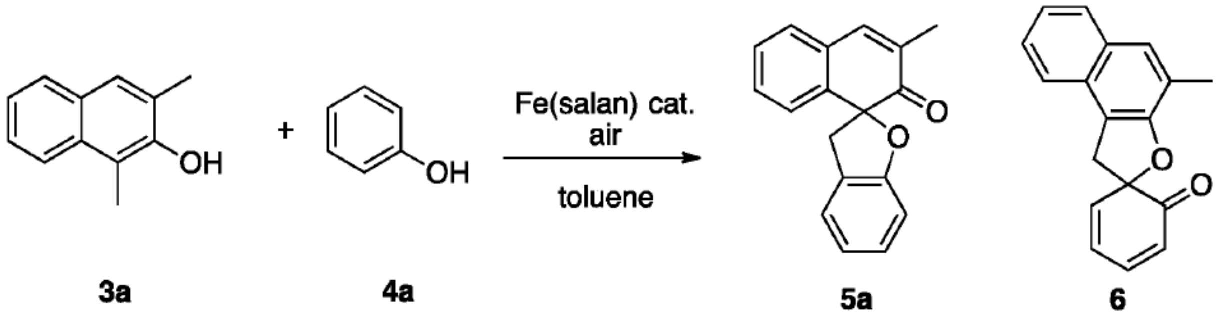
With nitroalkanes

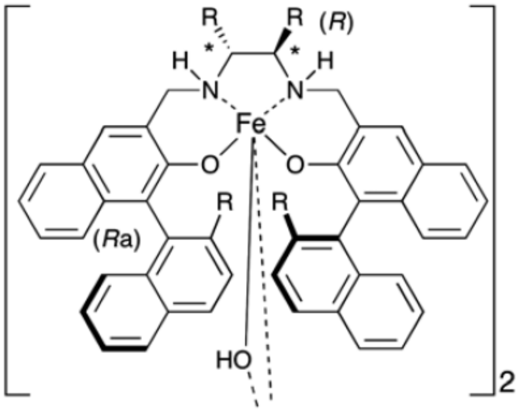


Z = X or H, Y = EWG or H

AOD by spirocyclization

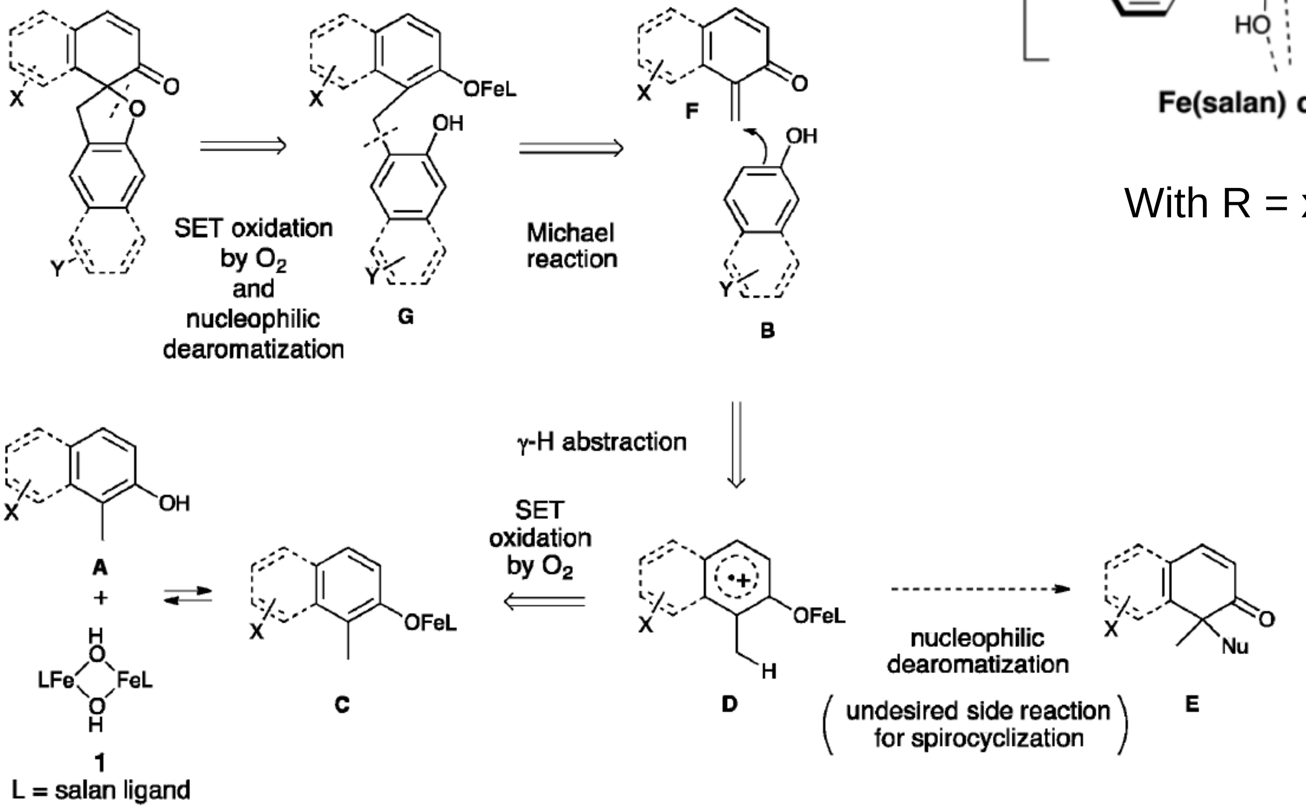
C-C bond formation





Fe(salan) catalyst

With R = xylyl



Chem. Commun., 2014, 50, 5053 Takuya Oguma[ab] and Tsutomu Katsuki

Major developments in Rh-catalyzed asymmetric 1,4-addition of boron species to enone

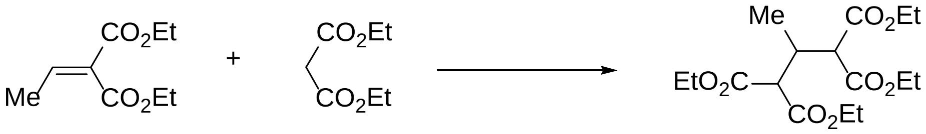
BY RAPHAËL BELTRAN

Table of contents

- Introduction
- First non-asymmetric & asymmetric 1,4 addition
- Mechanistic studies
- Evolution of chiral ligands
- Application in total synthesis
- Conclusion

Origins of conjugated addition

- First example of carbon nucleophile adding to an electron-deficient double bond

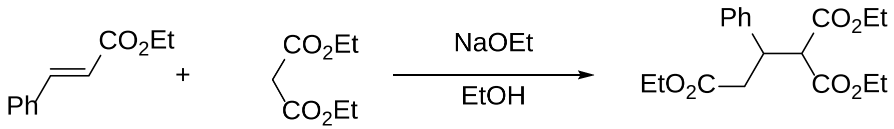


ethylidene malonate

diethyl malonate

Komnenos, T. *Liebigs Ann. Chem*· **1883**, *218*, 145.

- Michael systematically investigated the reaction of stabilized anions with α,β-unsaturated systems



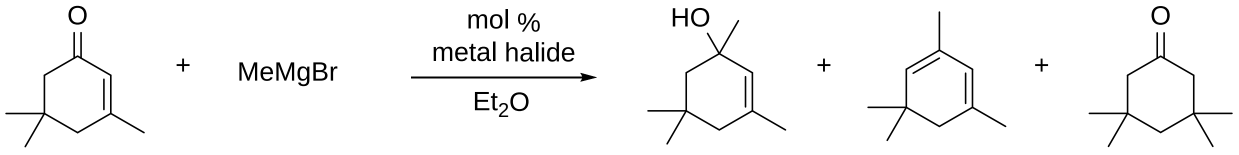
ethyl cinnamate

diethyl malonate

Michael, A. *J. Prakt. Chem./Chem.-Ztg*· **1887**, *35* ,349.

Origins of conjugated addition

- First conjugated addition to enone



isophorone

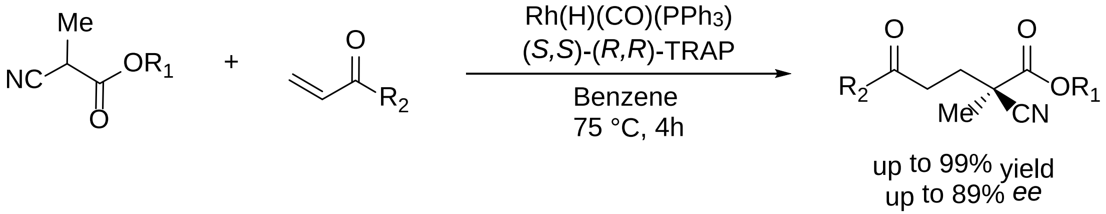
None	67.2 %	23.6 %	-
1.0 CuCl	6.9 %	-	82.5 %

Kharasch, M. S, Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308

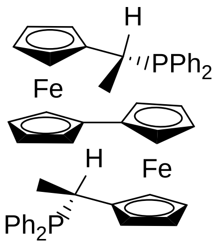
- Beginning of a vast number of studies with organometallic reagents.

First enantioselective 1,4-addition using Rh

- α-cyano carboxylate with vinyl ketone or acrolein



up to 99% yield
up to 89% *ee*



(*S*,*S*)-(*R*,*R*)-TRAP

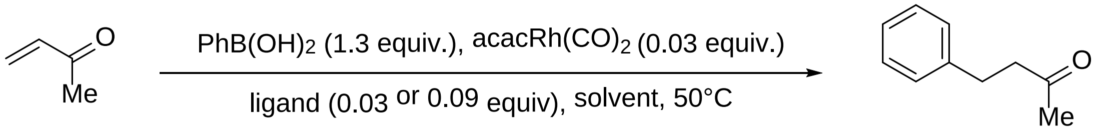
Y. Ito, *J. Am. Chem. Soc.*, **1992**, *114*, 8295

- TRAP ligand designed by the same group. Both planar chiralities & stereogenic centers.

First 1,4 addition of boronic acid

- 1,4-addition of aryl-boronic acids to α,β- unsaturated ketones using a phosphine-rhodium complex as a catalyst system.

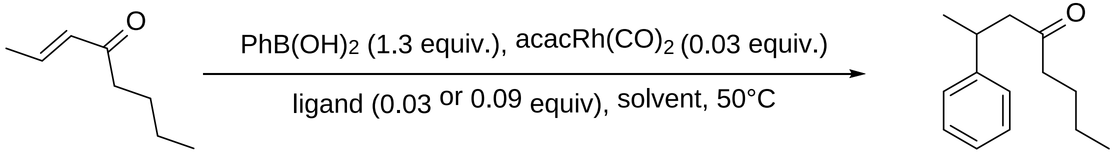
Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.



$PhB(OH)_2$ (1.3 equiv.), $acacRh(CO)_2$ (0.03 equiv.)

ligand (0.03 or 0.09 equiv), solvent, 50°C

entry	ligand	solvent	yield
1	PBu_3	DMF/H_2O	93
2	PPh_3	DMF/H_2O	83
3	dppe	DMF/H_2O	70
4	dppp	DMF/H_2O	97
5	dppb	DMF/H_2O	99
6	dppb	DMF	91



$PhB(OH)_2$ (1.3 equiv.), $acacRh(CO)_2$ (0.03 equiv.)

ligand (0.03 or 0.09 equiv), solvent, 50°C

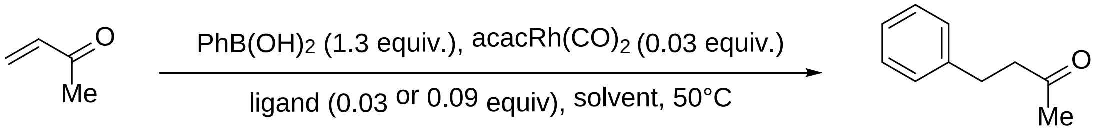
entry	ligand	solvent	yield
1	PPh_3	DMF/H_2O	0
2	dppe	DMF/H_2O	0
3	dppp	DMF/H_2O	19
4	dppb	DMF/H_2O	28
5	dppb	$toluene/H_2O$	34
6	dppb	$cyclohexane/H_2O$	61
7	dppb	$MeOH/H_2O$	96
8	dppb	MeOH	0

- Suggesting that the reaction is accelerated upon the increase of the P-Rh-P angles: dppb>dppp>dppe

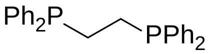
First 1,4 addition of boronic acid

- 1,4-addition of aryl-boronic acids to α,β- unsaturated ketones using a phosphine-rhodium complex as a catalyst system.

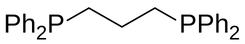
Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.



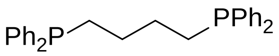
entry	ligand	solvent	yield
1	PBu_3	DMF/H_2O	93
2	PPh_3	DMF/H_2O	83
3	dppe	DMF/H_2O	70
4	dppp	DMF/H_2O	97
5	dppb	DMF/H_2O	99
6	dppb	DMF	91



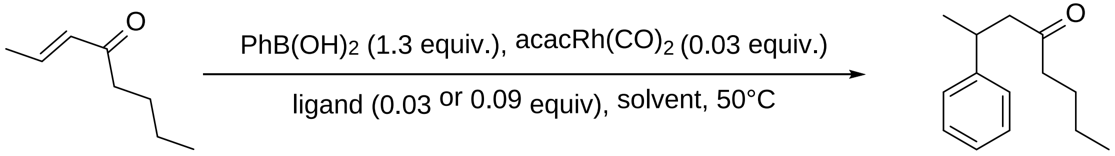
dppe



dppp



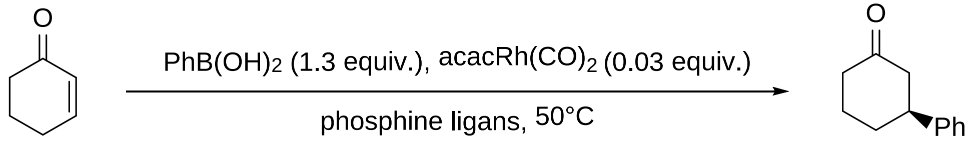
dppb



entry	ligand	solvent	yield
1	PPh_3	DMF/H_2O	0
2	dppe	DMF/H_2O	0
3	dppp	DMF/H_2O	19
4	dppb	DMF/H_2O	28
5	dppb	toluene/H_2O	34
6	dppb	cyclohexane/H_2O	61
7	dppb	$MeOH/H_2O$	96
8	dppb	MeOH	0

- Suggesting that the reaction is accelerated upon the increase of the P-Rh-P angles: dppb>dppp>dppe
- Electron-withdrawing & -donating groups: No difference. Ortho substituents strongly retarded the addition.

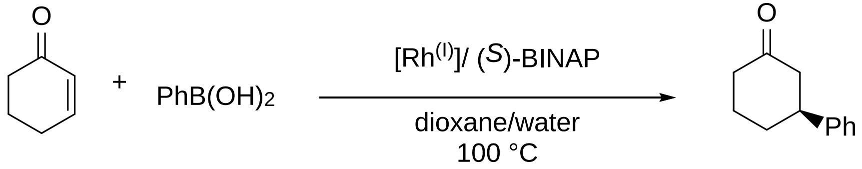
First asymmetric 1,4-addition of boronic acid



Very slow reaction with any chiral ligands examined.

Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

- What about the catalytic species?



entry	Rhodium complex	Equiv. $PhB(OH)_2$	Yield	*ee*
1	$[Rh(acac)(CO)_2]$	1.4	15	*43*
2	$[Rh(acac)(C_2H_4)_2]$	1.4	64	*97*
3	[Rh(acac)(*S*)-BINAP)]	1.4	64	*97*
4	$[Rh(acac)(C_2H_4)_2]$	2.5	93	*97*

$Rh(acac)(CO)_2 \xrightarrow[C_6D_6]{(S)\text{-binap}} Rh(acac)[(S)\text{-binap}]$ + unidentified species

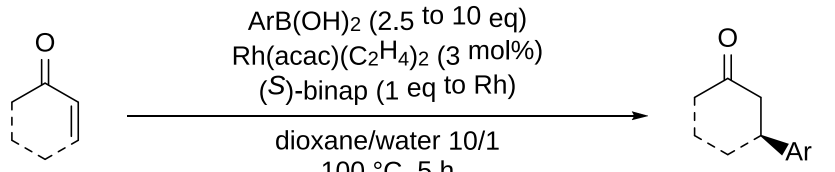
lower reactivity & selectivity attributed to the formation of this mixture

$Rh(acac)(C_2H_4)_2 \xrightarrow[C_6D_6]{(S)\text{-binap}} Rh(acac)[(S)\text{-binap}]$

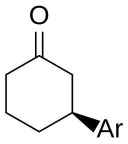
quantitative

this complex showed the same catalytic activity and stereoselectivity as the in situ generated catalyst
conclusion: Rh(acac)[(S)-binap] is a catalytically active species or a key precursor

First asymmetric 1,4-addition of boronic acid

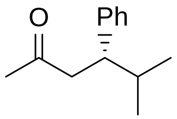


up to 99 %
up to 99 *ee*

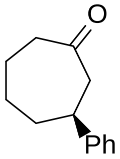


Ar=	
4-MeC_6H_4	97% *ee*
4-CF_3-C_6H_4	99%*ee*
3-OCH_3-C_6H_4	96% *ee*
3-ClC_6H_4	96% *ee*

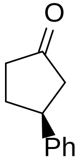
- ➢ Generation of Rh(acac)[(*S*)-binap]
- ➢ High reaction temperature (100 °C). Less than 60 °C < 3% yield.
- ➢ Enantioselectivity constant between 40 and 120°C
- ➢ Mixture of dioxane and water in a ratio of 10 to 1
- ➢ Broad scope, linear & cyclic enones.



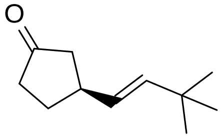
82%
97% *ee*



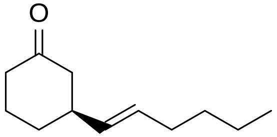
51%
93% *ee*



93%
97% *ee*



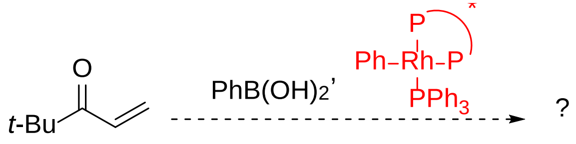
64%
96% *ee*

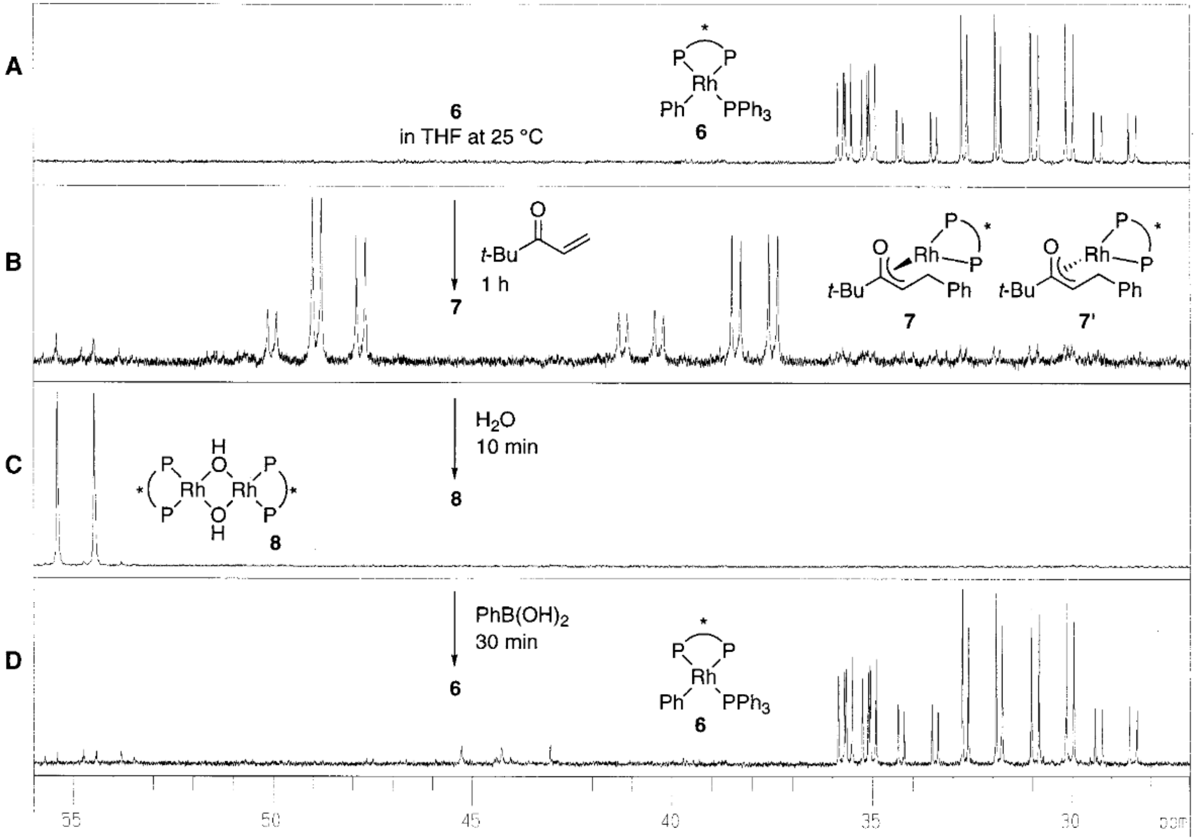


76%
91% *ee*

Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

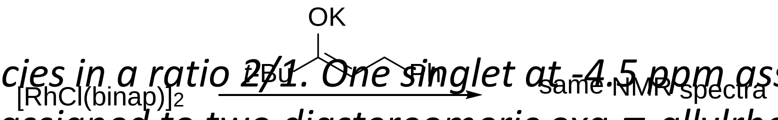
Mechanistic studies





Three ddd, characteristic of square-planar Rh complex with 3 unequivalent phosphorus atoms

Two new species in a ratio 2/1. One singlet at -4.5 ppm assignable to PPh_3. This isomers assigned to two diastereomeric oxa-π-allylrhodium complexes



according to procedure in *Organometallics*, **1994**, *13*, 890.

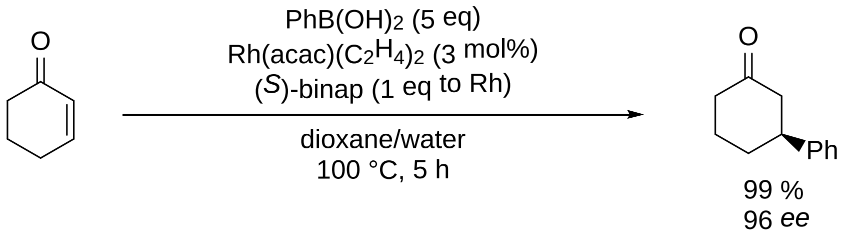
Immediate generation of a new rhodium species assigned to be hydroxorhodium. Nb, the singlet for free PPh_3 stay at the same high field

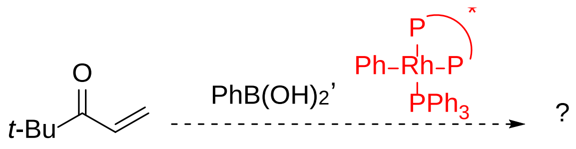
$\frac{1}{2}[Rh(OH)(cod)]_2 \xrightarrow[\text{benzene}]{(S)\text{-binap}} \frac{1}{2}[Rh(OH)(binap)]_2$

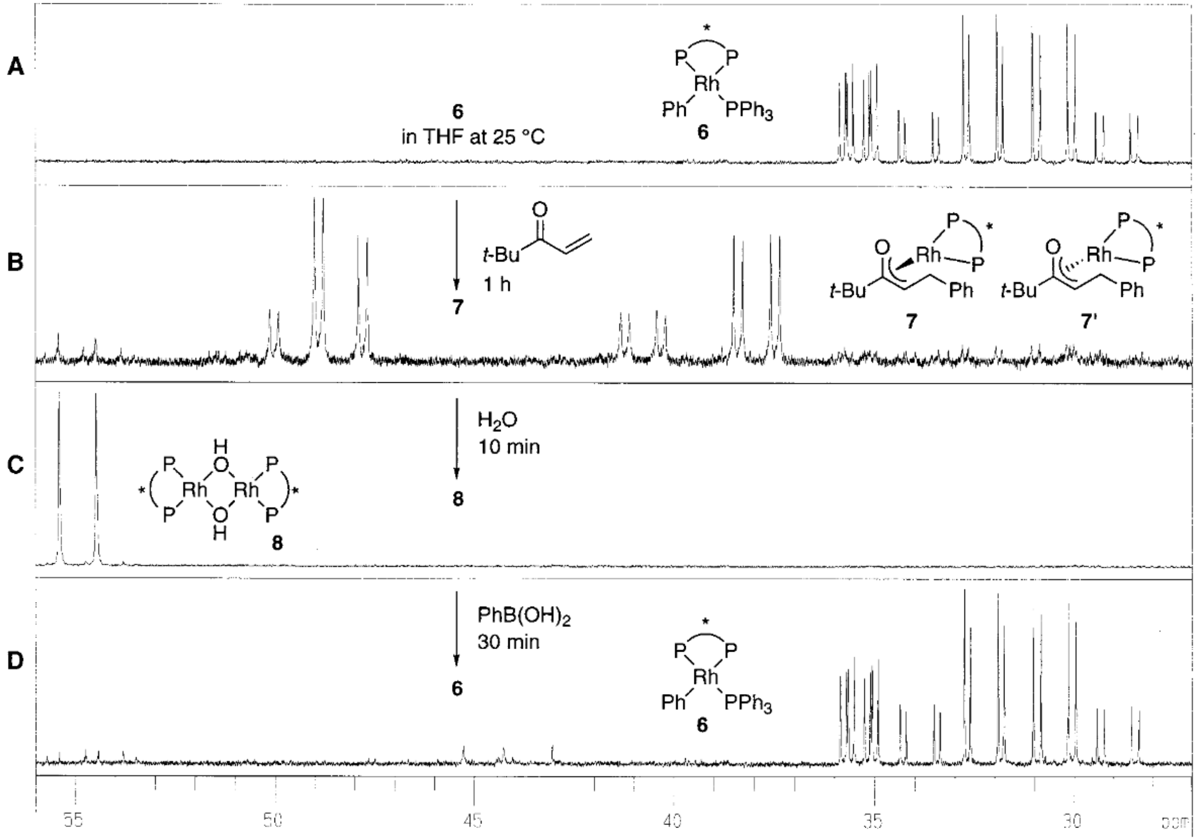
Transmetalation of a phenyl group from boron to rhodium species 8. Quite fast at 25 °C

PPh_3 which was free in step B & C came back to the rhodium at the transmetalation

Mechanistic studies







Three ddd, characteristic of square-planar Rh complex with 3 unequivalent phosphorus atoms

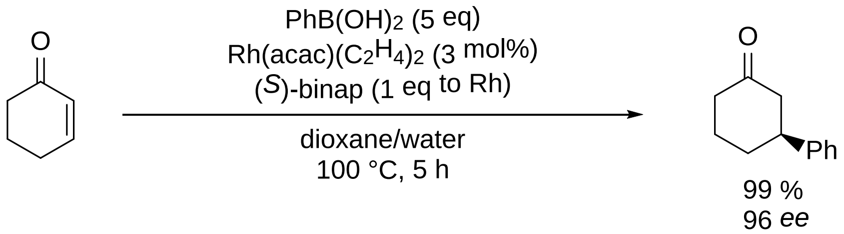
Two new species diastereomeric oxa-π-allylrhodium complexes

Immediate generation of a new rhodium species: hydroxorhodium.

Transmetalation of a phenyl group to rhodium specie.
Done at 25 °C

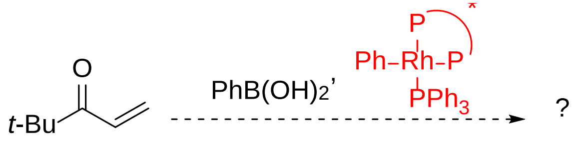
T. Hayashi, *J. Am. Chem. Soc.*, **2002**, *124*, 5052

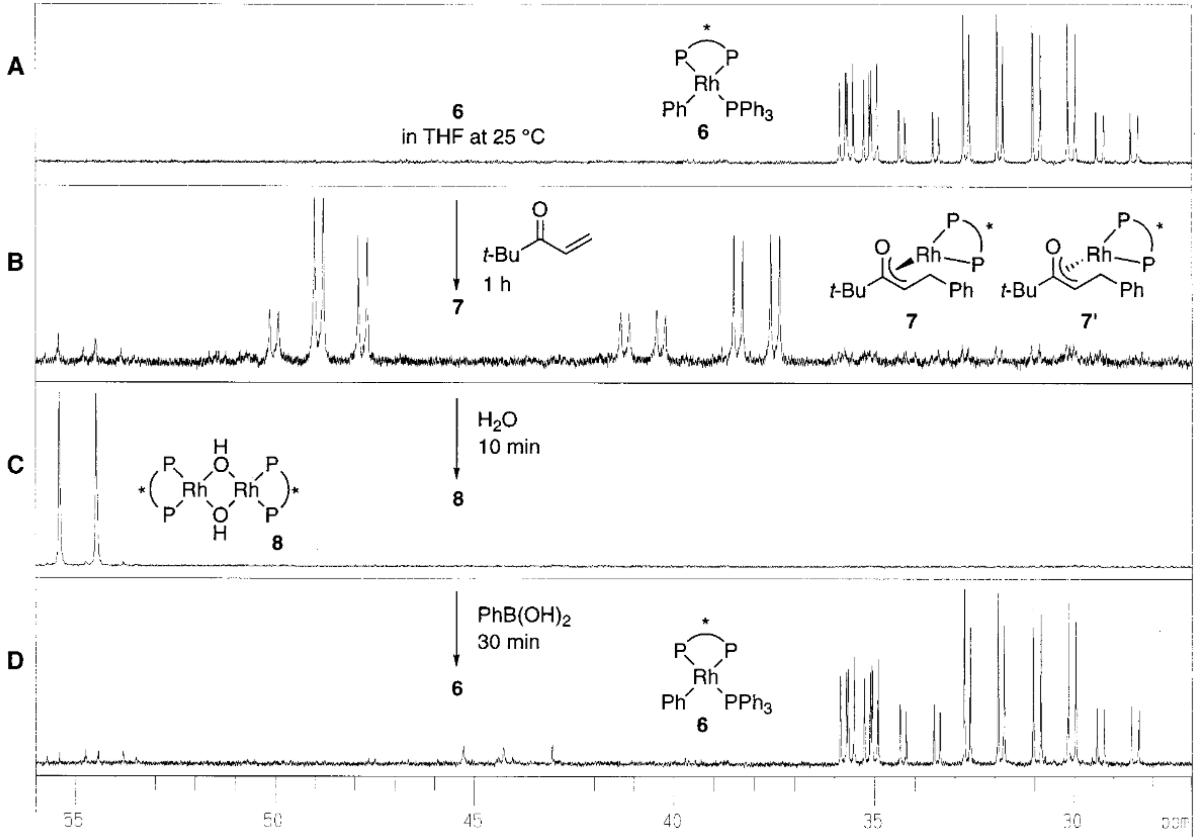
Mechanistic studies

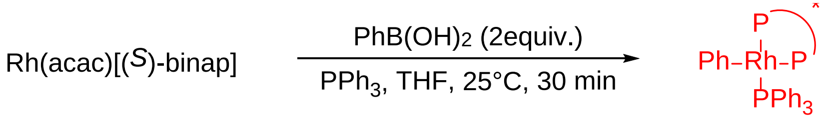


$PhB(OH)_2$ (5 eq)
$Rh(acac)(C_2H_4)_2$ (3 mol%)
(*S*)-binap (1 eq to Rh)
dioxane/water
100 °C, 5 h

99 %
96 *ee*

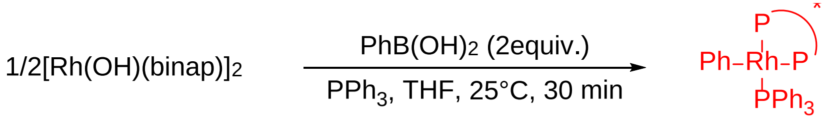






Rh(acac)[(*S*)-binap] $\xrightarrow[PPh_3\text{, THF, 25°C, 30 min}]{PhB(OH)_2\text{ (2equiv.)}}$ Ph–Rh(P–P*)(PPh$_3$)

25°C for 30 min	<8% conv.
80°C for 20 min	>90% conv.

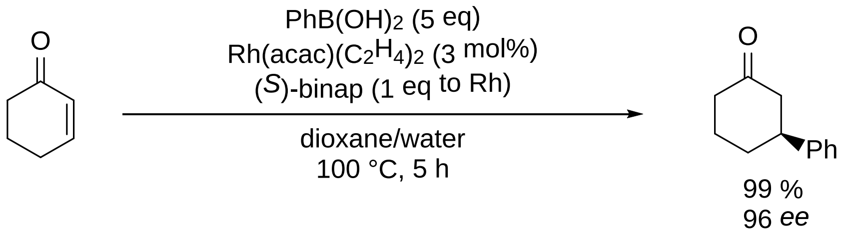


1/2[Rh(OH)(binap)]$_2$ $\xrightarrow[PPh_3\text{, THF, 25°C, 30 min}]{PhB(OH)_2\text{ (2equiv.)}}$ Ph–Rh(P–P*)(PPh$_3$)

>99% conversion

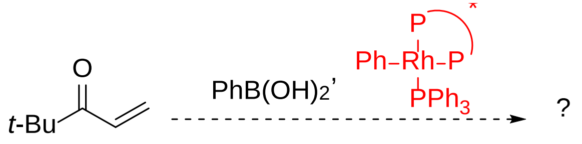
T. Hayashi, *J. Am. Chem. Soc.*, **2002**, *124*, 5052

Mechanistic studies



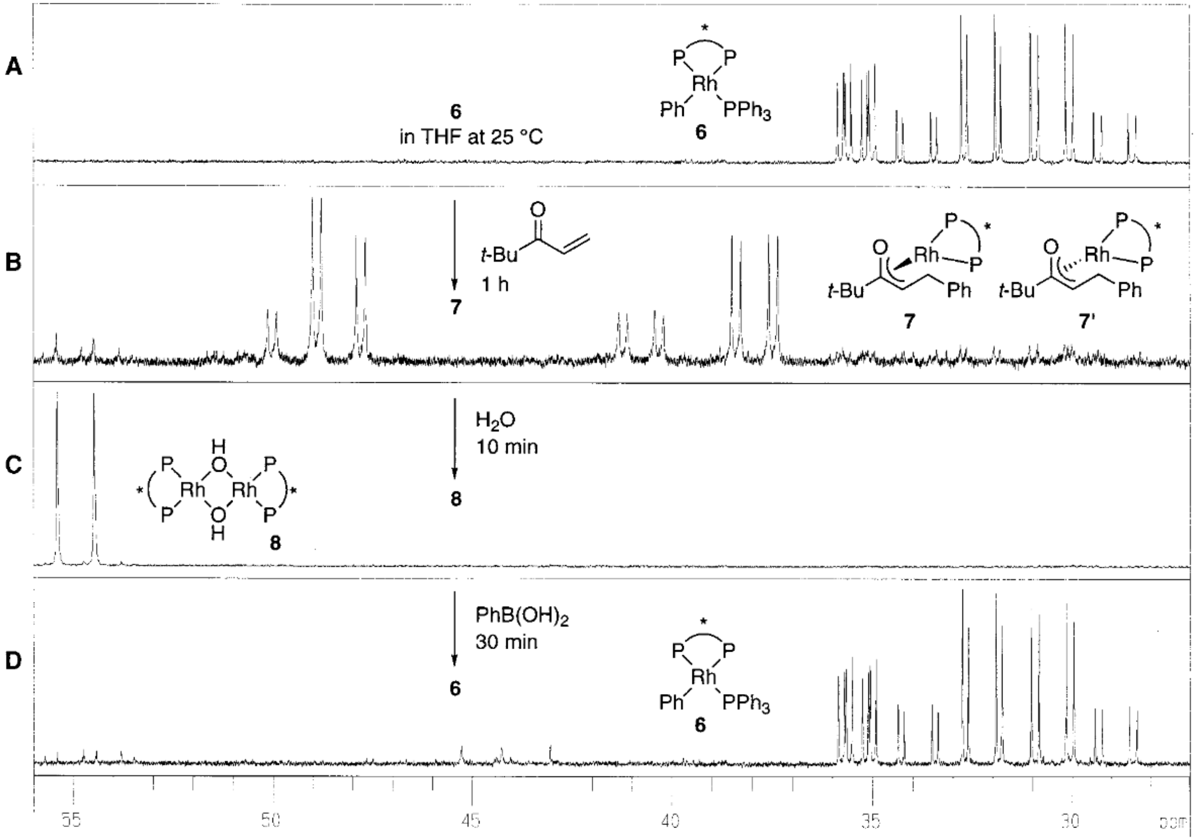
$PhB(OH)_2$ (5 eq)
$Rh(acac)(C_2H_4)_2$ (3 mol%)
(*S*)-binap (1 eq to Rh)
dioxane/water
100 °C, 5 h

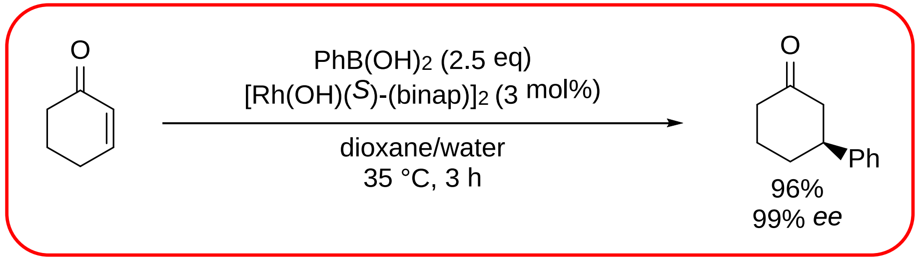
99 %
96 *ee*



$PhB(OH)_2$'

?



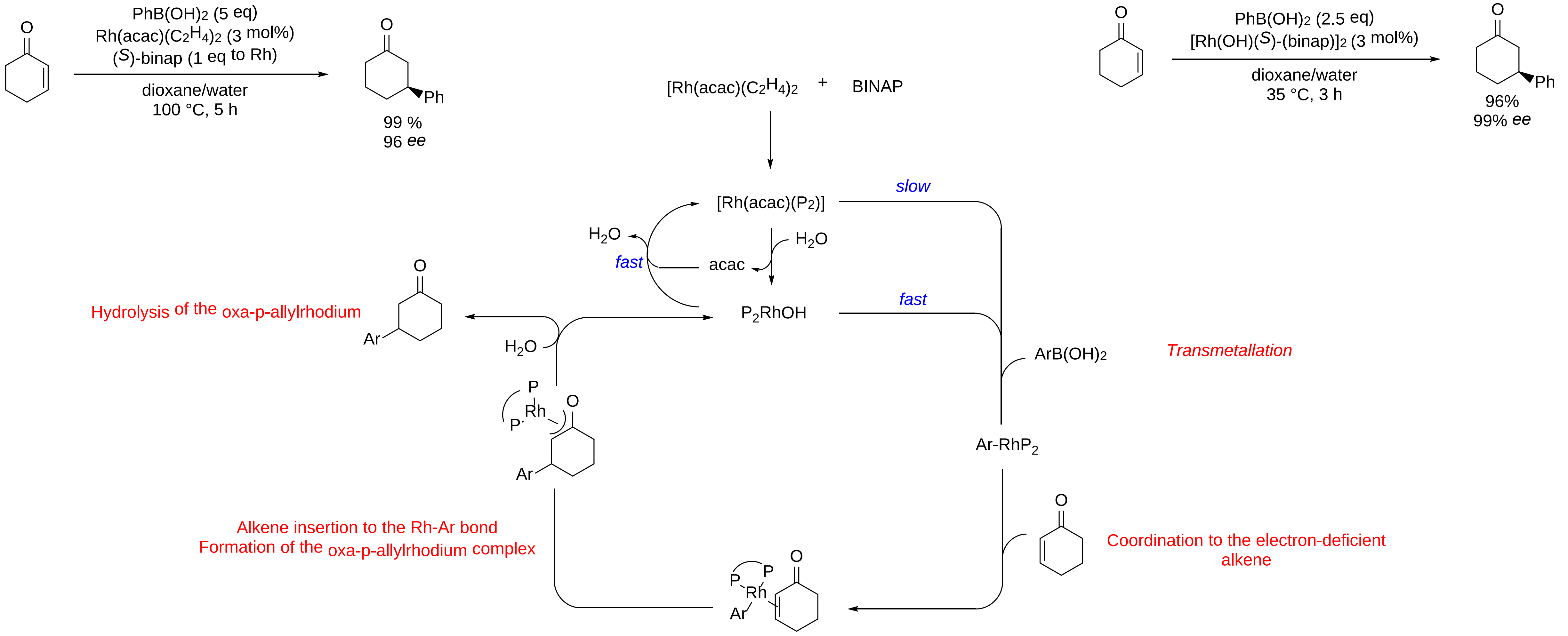


$PhB(OH)_2$ (2.5 eq)
$[Rh(OH)(S)\text{-}(binap)]_2$ (3 mol%)
dioxane/water
35 °C, 3 h

96%
99% *ee*

T. Hayashi, *J. Am. Chem. Soc.*, **2002**, *124*, 5052

Mechanistic studies



Hydrolysis of the oxa-p-allylrhodium

Transmetallation

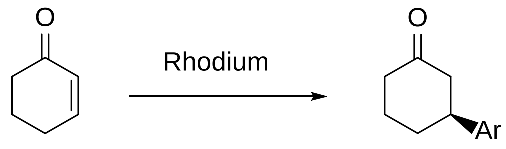
Alkene insertion to the Rh-Ar bond
Formation of the oxa-p-allylrhodium complex

Coordination to the electron-deficient alkene

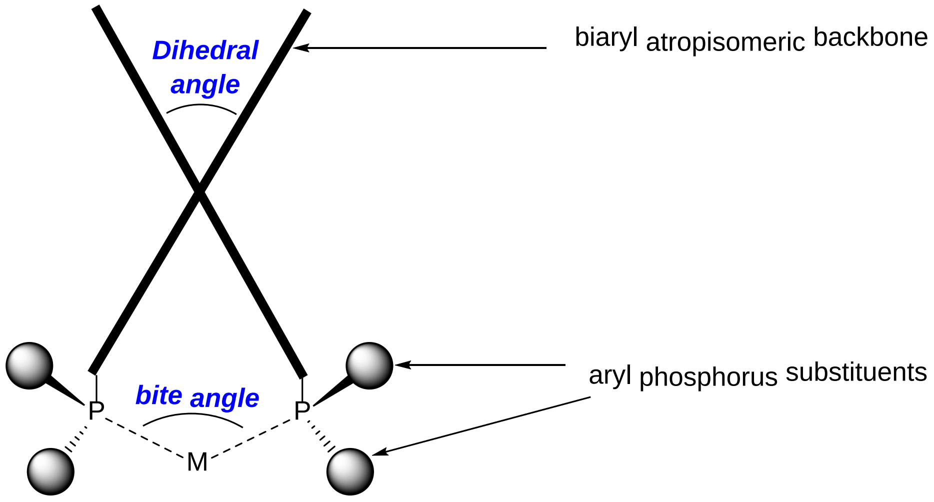
M. Lautens, Chem. Rev., **2003**, *103*, 169

Evolution of Chiral Ligands

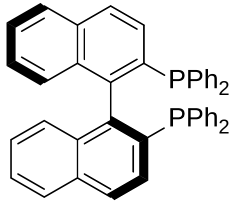
Bisphosphine ligands



- Based on chiral BINOL, play with atropisomeric (such as BINAP) to get high *ee* in 1,4-addition reactions



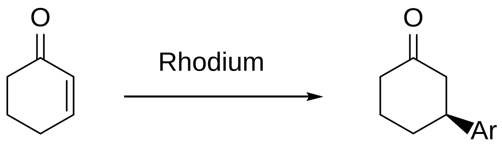
Genaral stereoelectronic tunable features of a C2-symetric atropisomeric diphosphane

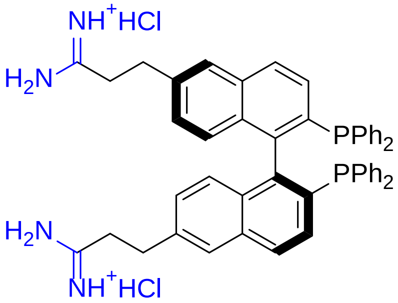


(*S*)-BINAP
96%
99% *ee*

R. Noyori. *J. Am. Chem. Soc.*, **1980**, *27*, 7932

Bisphosphine ligands

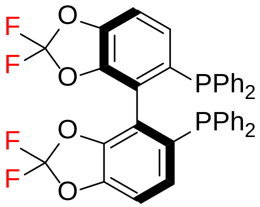




***digm*-BINAP**
94%
98% *ee*

Designed for aqueous conugated addition with two guanidine salt

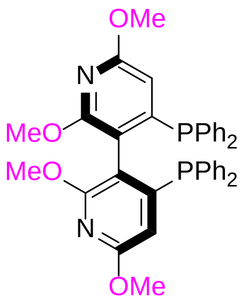
R. Amengual, V. Michelet, J.-P. Genet, *Synlett*, **2002**, *11*, 1791



DIFLUORPHOS
98%
99% *ee*

bi(difluorobenzodioxole) motif afford narrow dihedral angle and unusal p-acidity

S. Jeulin, J.P. Genet, *Angew. Chem. Int. Ed.*, **2004**, *43*, 320.

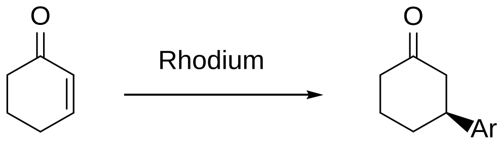


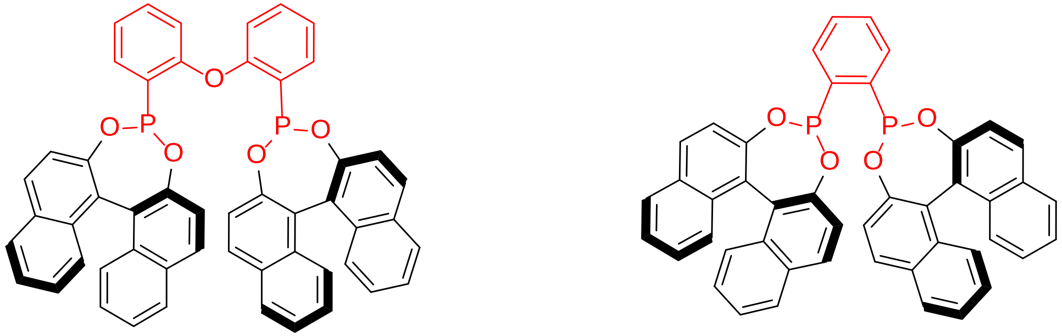
(*S*)-P-Phos
99%
95% *ee*

ortho group block the acces of the nitrogen to the Rh

J. Wu, A. S. C. Chan, *Accounts of Chemical Research*, **2006**, *39*, 711

Bisphosphine ligands





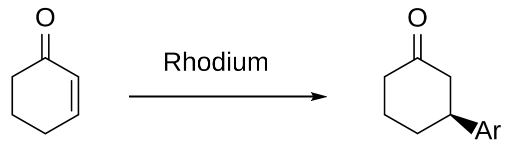
BINOL-based diphosphonites

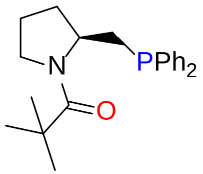
quant. 96% *ee*	100 99% *ee*

Achiral backbone determines the degree of enantioselectivity

M.T. Reetz, *Organic Letters*, **2001**, *3*, 4083

Monodentate ligands

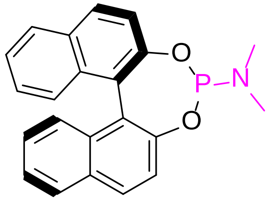




Amidomonophosphine
99%
96% *ee*

Phosphorus atom strongly bonds to rhodium and the amide carbonyl oxygen is coordinatively labile.

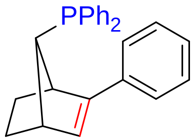
K. Tomioka, *J. Am. Chem. Soc.*, **2002**, *124*, 8932.



H_8-MonoPhos
97%
92% *ee*

Excellent ligands for conjugated- additions. Ease of preparation and structural flexibility by varying the amine.

B. L. Feringa, *Organic Letters*, **2003**, *5*, 681



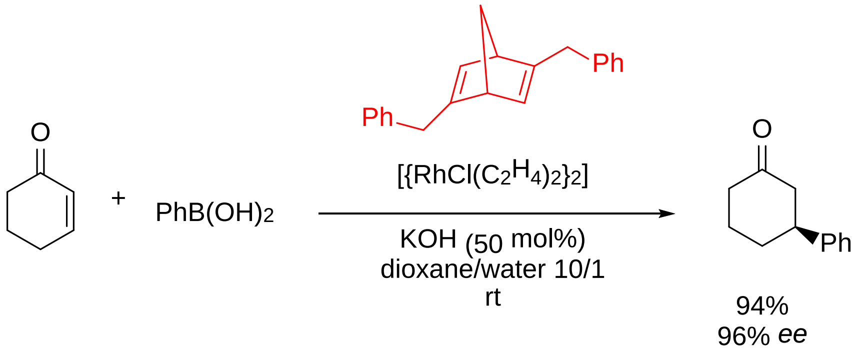
Alkene-phosphine
94%
93% *ee*

Combine advantages of phosphine: Good coordination Diene: Good rigidity. Ideal chiral environment around rhodium

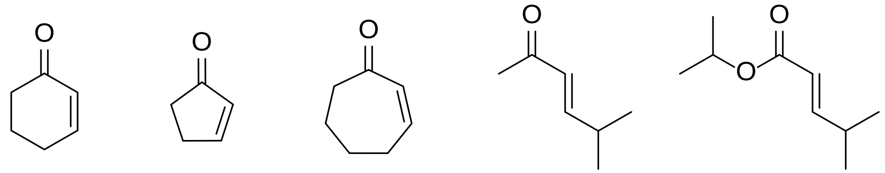
W. L. Duan, T. Hayashi, *J. Am. Chem. Soc.*, **2007**, *129*, 2130

Chiral diene ligands

- Second major class of metal complex for asymmetric conjugated addition.



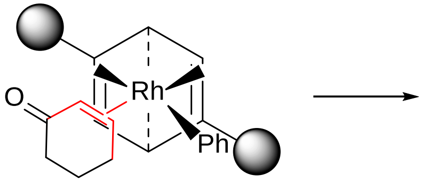
T. Hayashi, *J. Am. Chem. Soc.*, **2003**, *125*, 11508



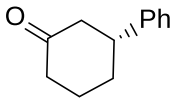
Excellent yield & *ee*

Chiral diene ligands

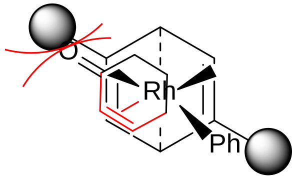
- Chirality is controlled by the size of the substituents attached to the double bond.



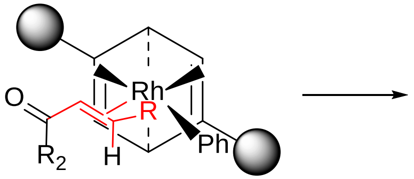
Coordination to *Re* face
favored



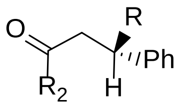
R product



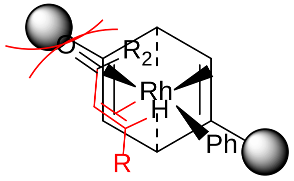
Coordination to *Si* face
disfavored



Coordination to *Re* face
favored



R product

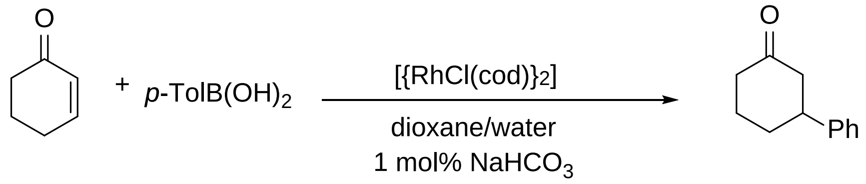


Coordination to *Si* face
disfavored

T. Hayashi, *J. Am. Chem. Soc.*, **2003**, *125*, 11508

Chiral diene ligands

- Importance of dienes as ligands.

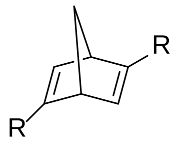


entry	Mol % catalyst	T [°C]	t [h]	Yield [%]	*TON*
1	0.01	90	16	98	*9800*
2	0.005	90	24	67	*13400*
3	0.005	90	36	97	*18400*
4	0.001	100	36	97	*97000*
5	0.0005	100	36	96	*192000*
6	0.0002	100	36	75	*375000*

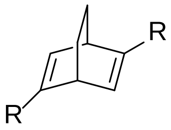
R. Itooka, N. Miyaura, *Chem. Lett.*, **2001**, 722

Chiral diene ligands

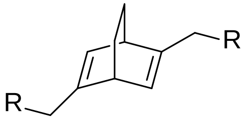
- Range of chiral diene ligands



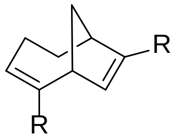
Hayashi



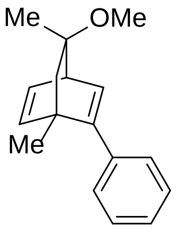
Hayashi



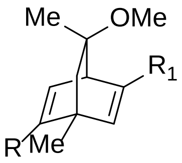
Hayashi



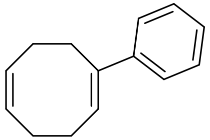
Hayashi



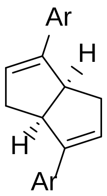
Carreira



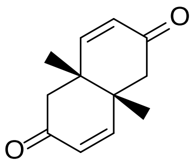
Carreira



Grützmacher



Xu, Lin, Laschat

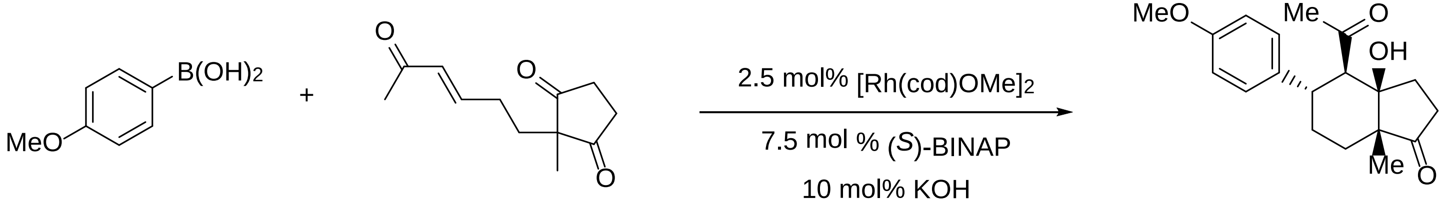


Trauner

Table of contents

Application in total synthesis

- Enantioselective approach



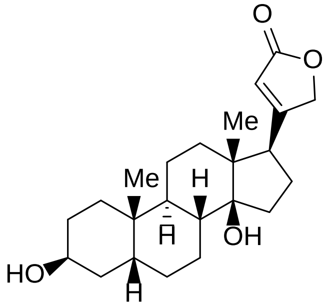
2.5 mol% $[Rh(cod)OMe]_2$

7.5 mol % (*S*)-BINAP

10 mol% KOH

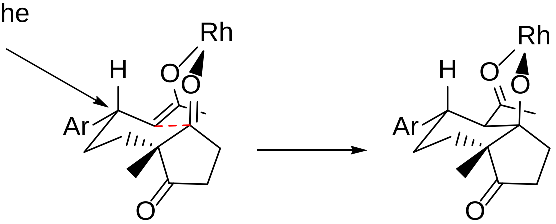
dioxane/H_2O, 95 °C

80% yield
>99:1 de, 92% *ee*



digitoxigenin

M. J. Krishe, *J. Am. Chem. Soc.*, **2003**, *125*, 1110

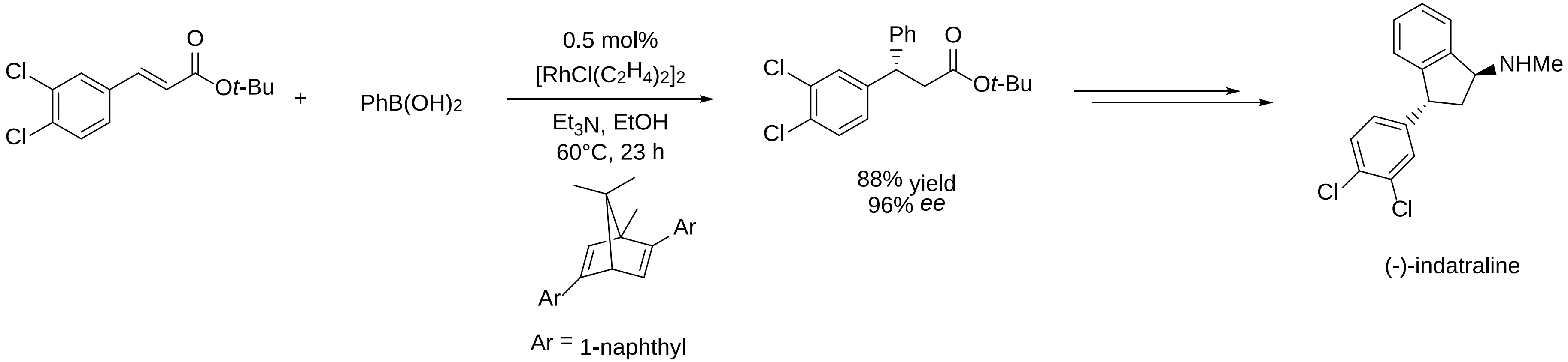


established by the
1,4 addition

Control of 4 contigous stereocenters

Application in total synthesis

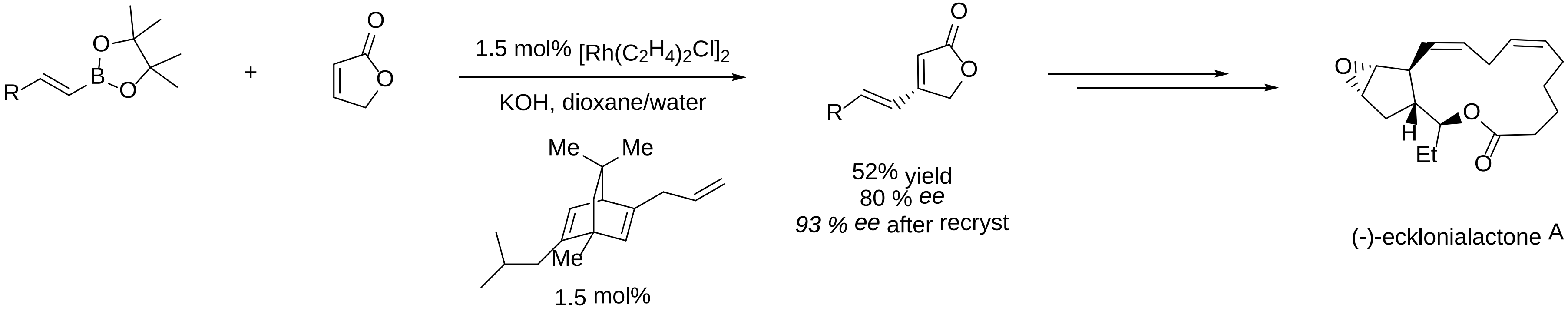
- Enantioselective approach for the synthesis of (-)-indatraline



H. L. Wu, *Chem. - Eur. J.*, **2011**, *17*, 11405

Application in total synthesis

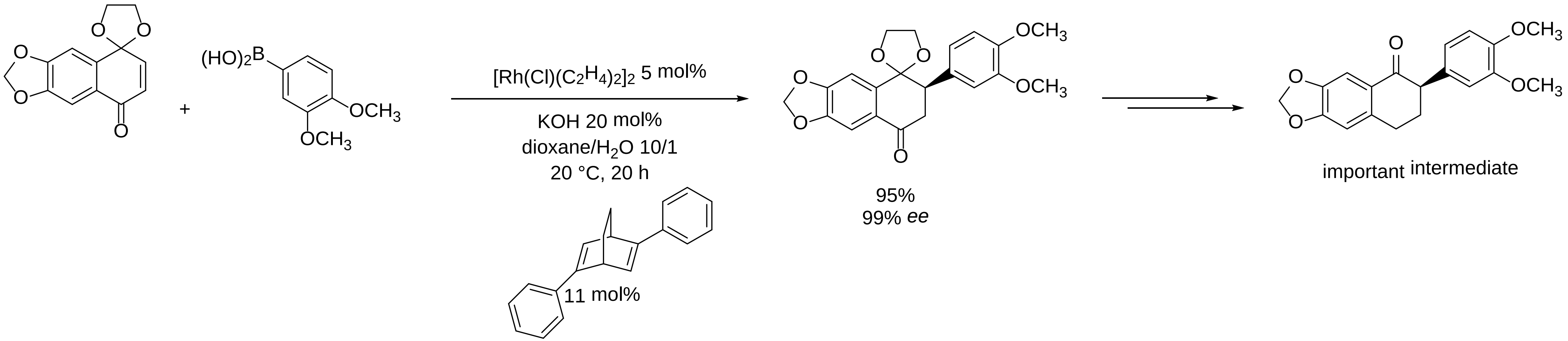
- Enantioselective approach for the synthesis of (-)-ecklonialactone A



A. Fürstner, *J. Am. Chem. Soc*. **2010**, *132*, 11042

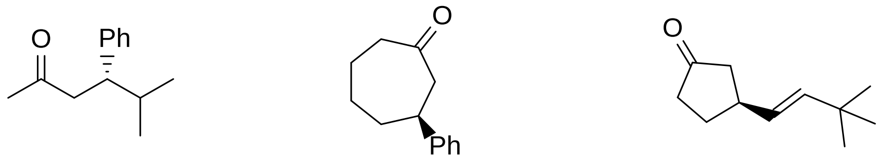
Application in total synthesis

- Enantioselective approach for important intermediate in alkaloids

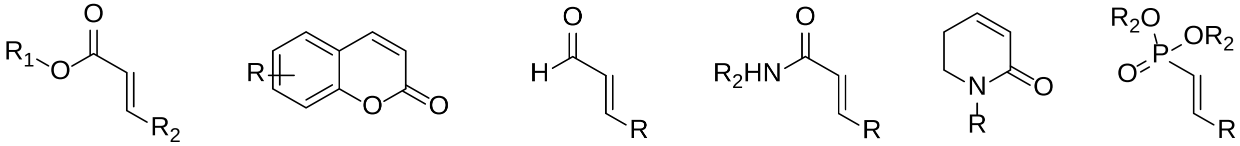


Conclusion

- Developments
  - Racemic, first asymmetric, pre-catalyst/active species, mechanism, evolution of ligands.
- Many advantages to create a new carbon-carbon bond with this reaction
  - Very high enantioselectivity
  - Very good yield
  - Carried out in aqueous solvent
  - Variety of sp^2 carbon group (aryl and alkenyl group) can be introduced



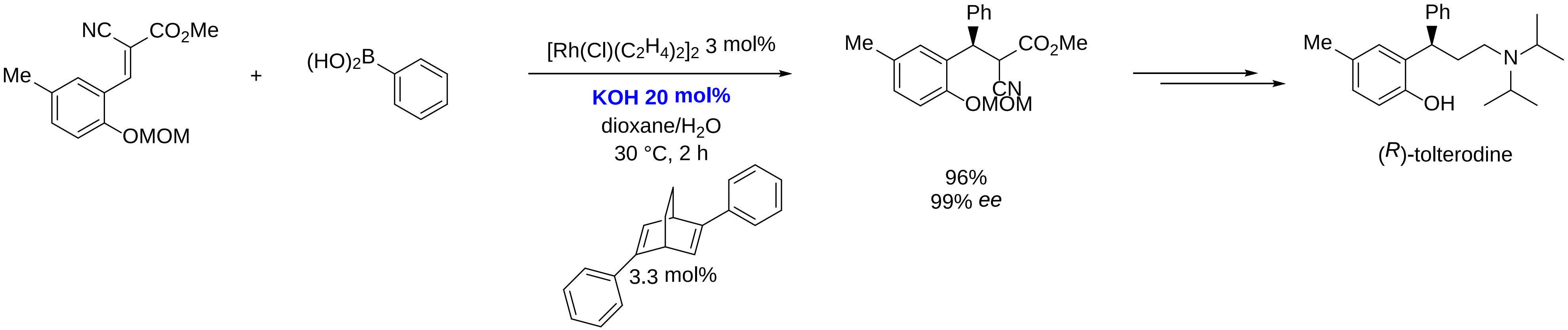
  - Various type of olefins (ketone, esters, amide etc.)



Questions?

Application in total synthesis

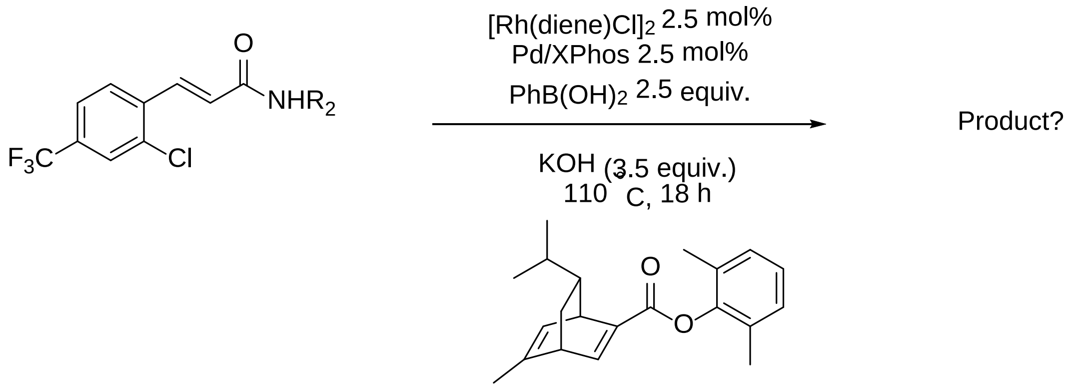
- Enantioselective approach of (*R*)-Tolterodine



T. Hayashi, *Org. Lett.*, **2008**, *10*, 589

Application in domino process

- Enantioselective approach for synthesis of dihydroquinolinones

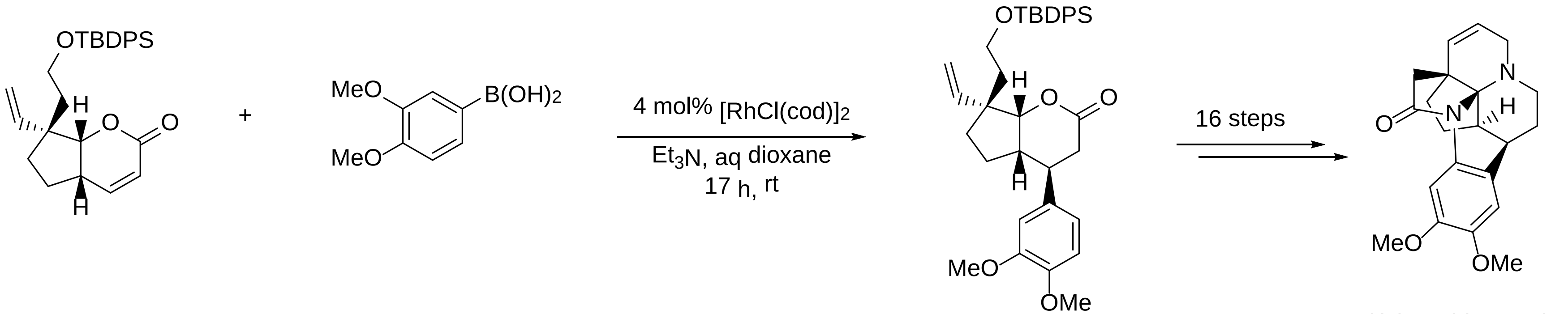


M. Lautens, *Angew. Chem. Int. Ed.*, **2014**, *53*, 13850

Thank you!

Application in total synthesis

- Diastereoselective approach with the 1st total synthesis of (−)-Isoschizogamine

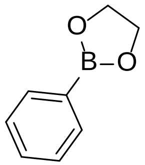


93 %
one diastereoisomer

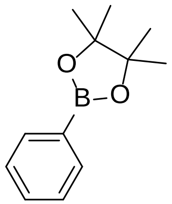
(-)-isoschizogamine

N. Hayashi, T. Fukuyama, *J. Am. Chem. Soc.*, **2012**, *134*, 11995

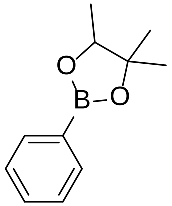
Boron



Glycol

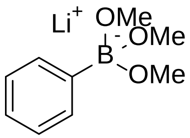


pinacol

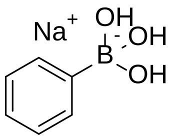


2-methyl-2,4-pentanediol

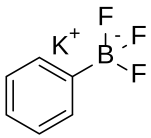
Not so efficient



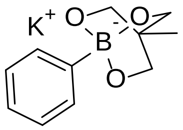
Hayashi



Cammidge



Vedjes

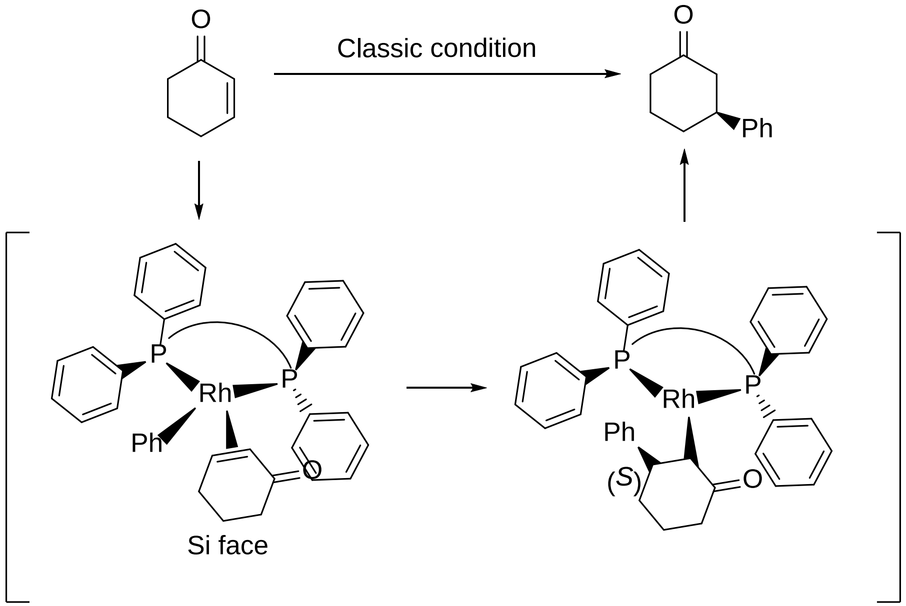


Miyaura

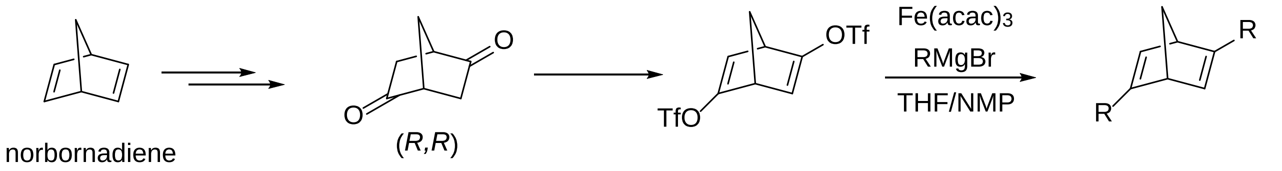
Very efficient

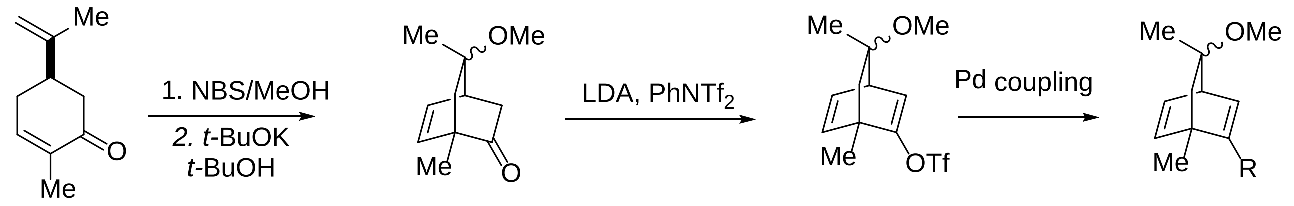
Model with phosphine ligands

- Diene: steric difference, space discrimination around the central metal.
- Phosphine: Conformation differentiation.

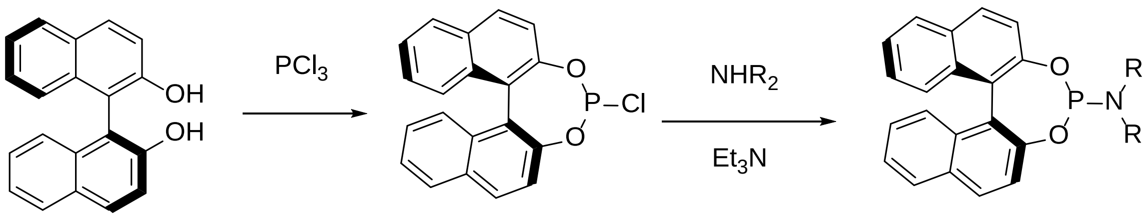


Chiral diene

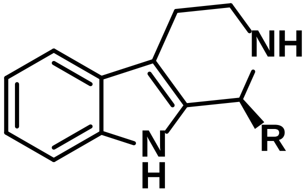




Phosphoramidites



The Asymmetric Pictet-Spengler Reaction



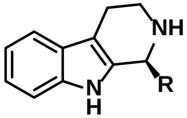
Frontiers in Chemical Synthesis III: Stereochemistry

Cyril Piemontesi – 14.04.2016

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Laboratory of Synthesis and Natural Products (LSPN)

Content



Content - Precisions

Only enantioselective transformations (no diastereoselective induction)

Only “chemical” reactions (no biocatalyzed reactions)

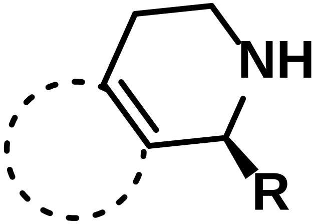
Only «aza» PS (no oxygen or other heteroatom-based PS)

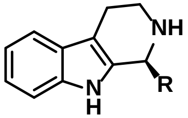
Not all the literature present, mainly based on seminal works (methodology)

No application in total synthesis of natural products or drugs

Classified regarding the nature of the nucleophile and of the substituent of the amine

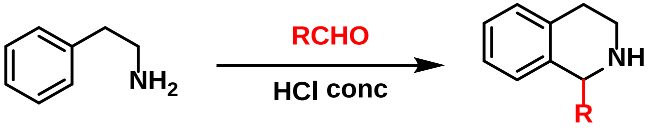
Introduction



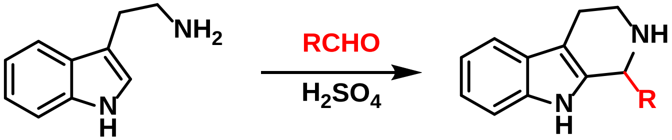


Pictet-Spengler reaction - Discovery

Discovered in 1911 by Pictet (Swiss chemist!) and Spengler in Geneva[1]
Initially with phenylethylamine and an aldehyde (or an acetal)
Only 17 years later: PS with tryptamine (Tatsui)[2]
52’000 results in Google (391’000 for Wittig reaction) but as important



Pictet and Spengler - 1911



Tatsui - 1928

In nature: Pictet-Spenglersases (see slide “importance”)

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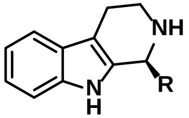
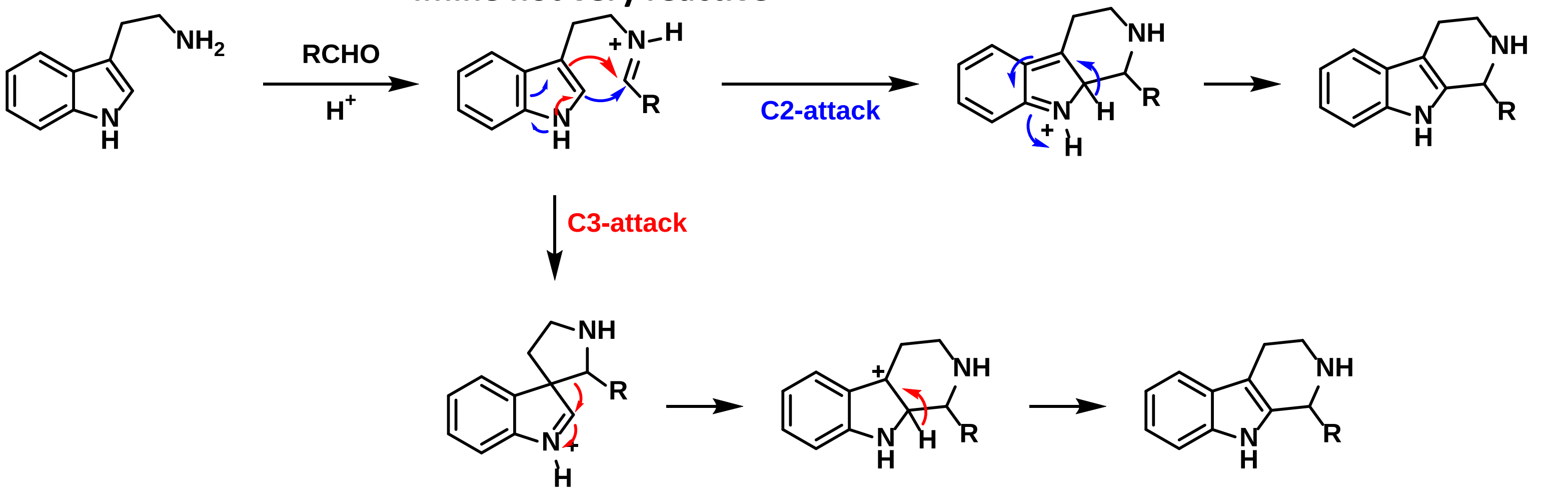
1. Pictet, A.; Spengler, T. *Ber. dtsch. Chem. Ges.* **1911**, *44*, 2030.
2. Tatsui, G. *J. Pharm. Soc. Jpn.* **1928**, *48*, 92.



Pictet-Spengler reaction - Mechanism

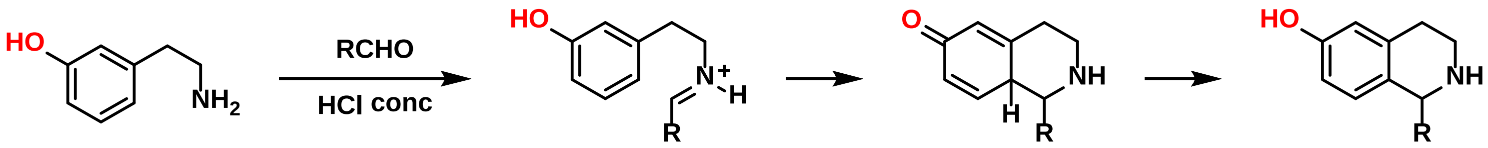
2 different mechanisms commonly accepted
Very hard to discriminate between the two (fast rearomatization)

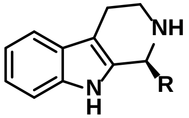
Imine not very reactive



Wagner-Meervein

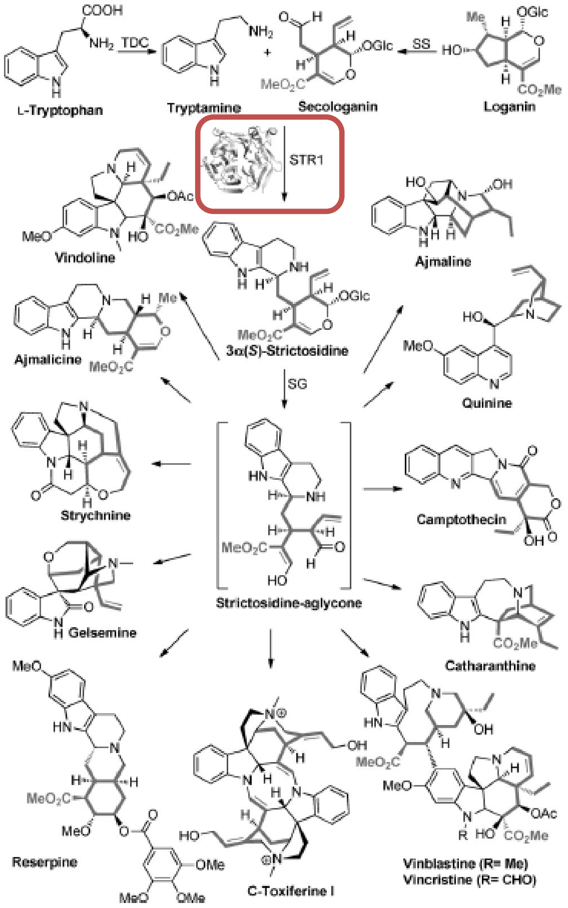
Electron-rich aromatics react faster (good for the yield, bad for the ee)

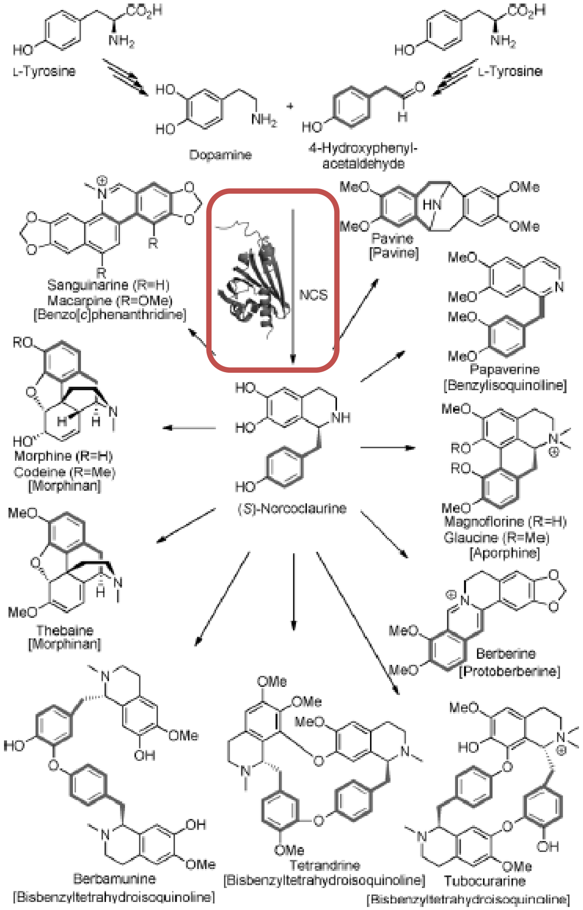




Pictet-Spengler reaction - Importance

Use for the synthesis of 1,2,3,4-tetrahydro-β-carboline and 1,2,3,4-tetrahydroisoquinoline





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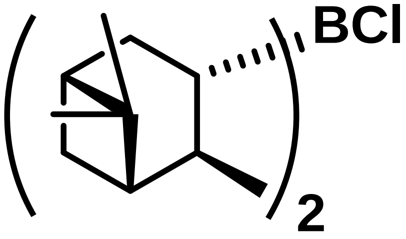
1. Review of PS in nature: Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 8538.

Stoichiometric Lewis Acid

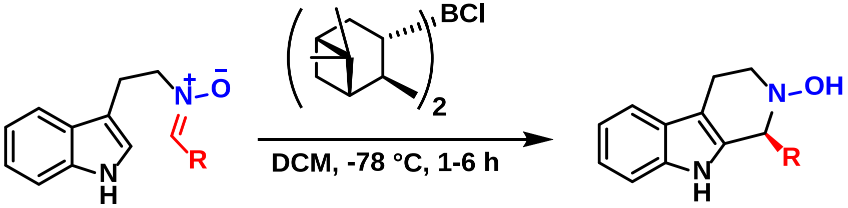


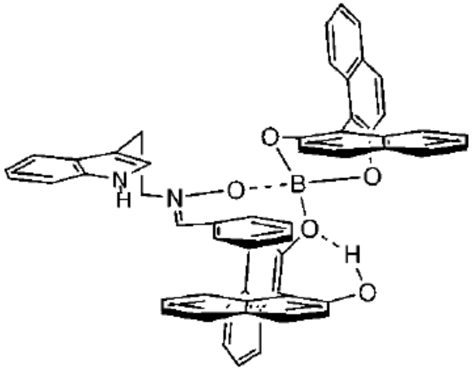
Indole – C3 linker – Stoichiometric LA

First example of reagent controlled PS: using (Ipc)$_2$BCl (1.9 equiv)[1] and nitrones

Working with aromatic (neutral or rich) R, generally 70-90% ee

Aliphatic aldehyde give poor ee (35%), electron poor aryl give no ee



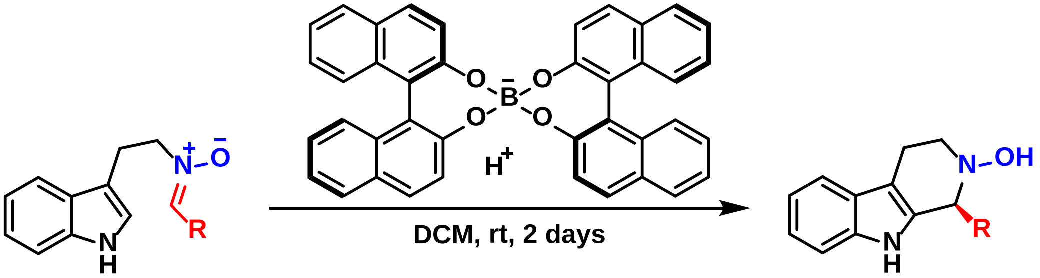


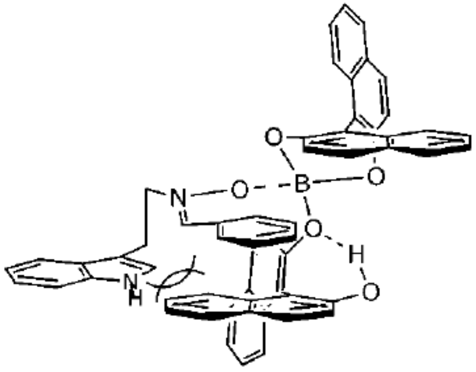
Transition State-A: *re*-Face Attack

Second generation using BINOL ligand (2 equiv boron) [2]

Can now give better ee with electron poor aromatic aldehyde (75%)

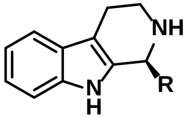
Catalytic gave good yield but very poor ee





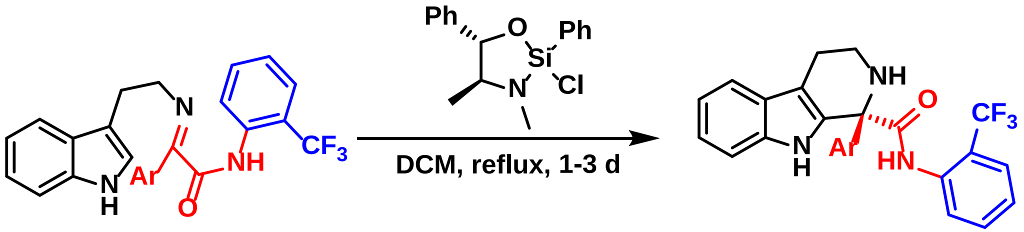
Transition State-B: *si*-Face Attack

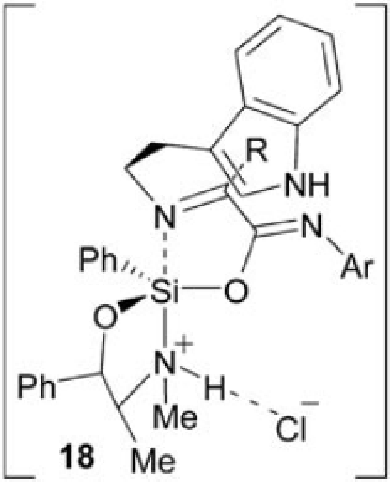
1. Kawate, T.; Yamada, H.; Soe, T.; Nakagawa, M. *Tetra. Asym.* **1996**, *7*, 1249.
2. Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. *J. Org. Chem.* **1998**, *63*, 6348.



Indole – C3/C4/N1 linker – Stoichiometric LA

2nd example of reagent controlled PS (1.3 to 2 equiv silane)[1,2]
Aromatic on the amide crucial for the yield (C_6H_6=0% vs 65%)
Also work with aliphatic ketone and can form the imine *in situ*
In general 80-95% ee
Iso-PS also possible with C4 and N1 linker





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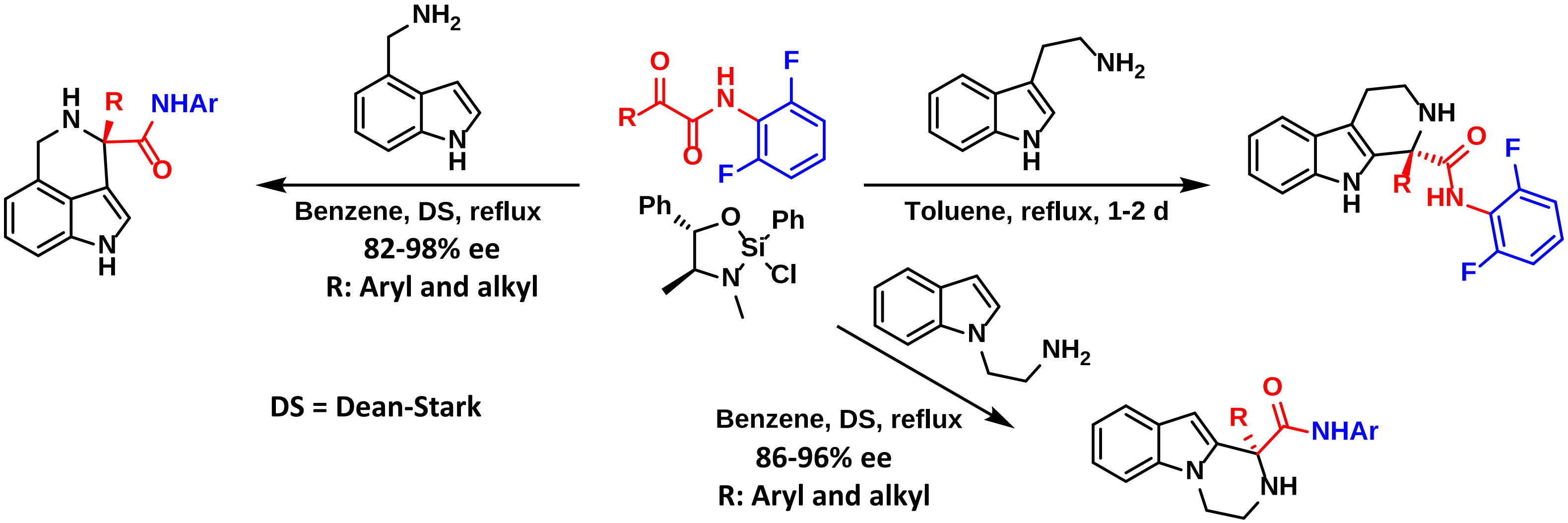


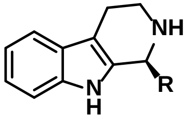
Benzene, DS, reflux
82-98% ee
R: Aryl and alkyl

Toluene, reflux, 1-2 d

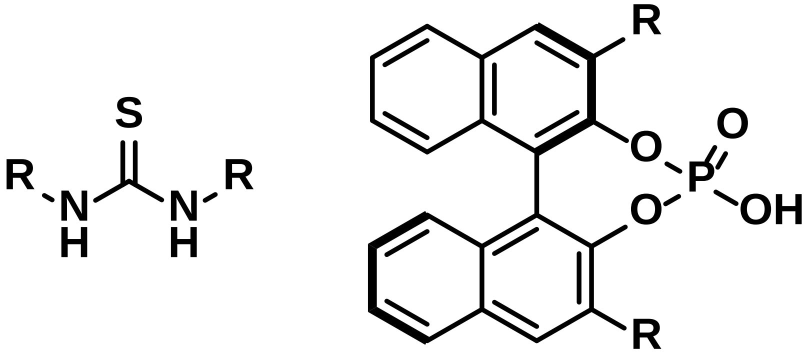
DS = Dean-Stark

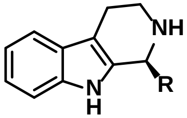
Benzene, DS, reflux
86-96% ee
R: Aryl and alkyl

1. Bou-Hamdan, F. R.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2009**, *48*, 2403.
2. Schönherr, H.; Leighton, J. L. *Org. Lett.* **2012**, *14*, 2610.



Seminal works on catalytic enantioselective PS





Indole – C3 linker – Catalytic BA

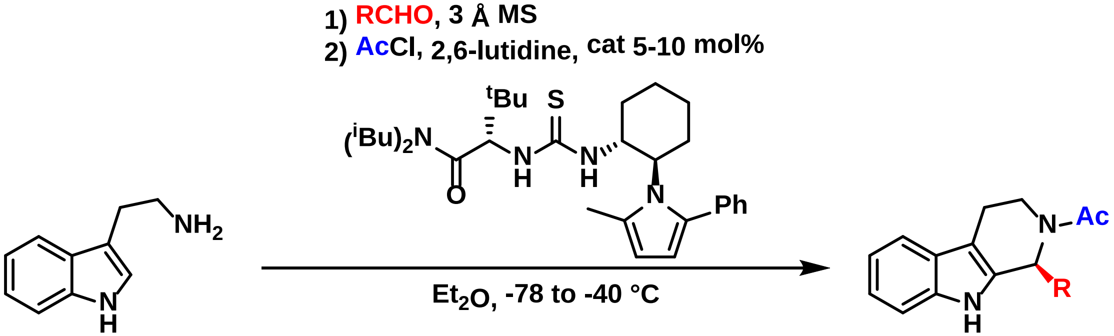
1st example of catalytic enantioselective PS[1]

N-acyl iminium very reactive compare to iminium

Thiourea catalyst gave 85-93% ee

Only aliphatic aldehydes + acetylated (AcCl crucial) tryptamine

Catalyst got *S*-acetylated at the required temperature for aromatic aldehyde (>-30 °C)



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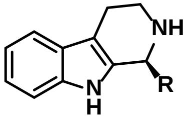
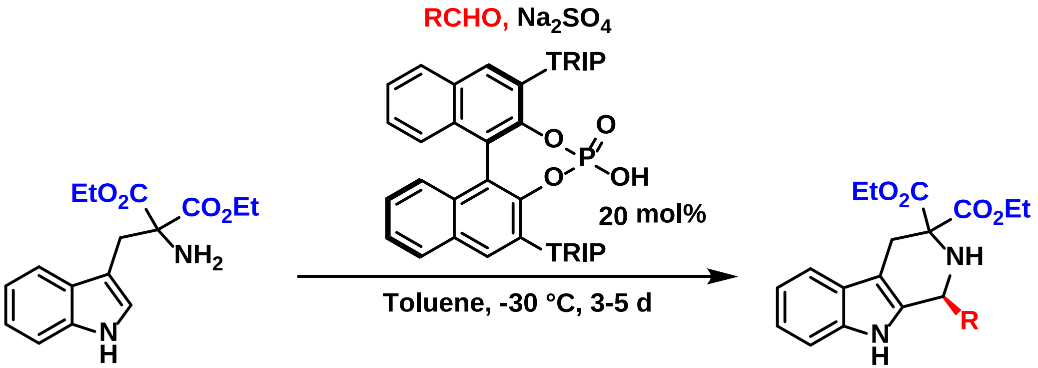
1. Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.



Indole – C3 linker – Catalytic BA

1st example of catalytic enantioselective PS catalyzed by BPA[1]
BPA catalyst gave 62-96% ee
Only aliphatic and electron-poor aromatic aldehydes (vs Jacobsen)
gem-disubstituted tryptamine required



Why is the *gem*-disubstitution required and
what would be the reaction outcome without it (with propanal)?

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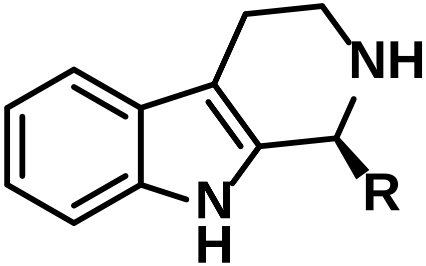
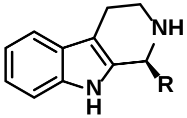
1. Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086.

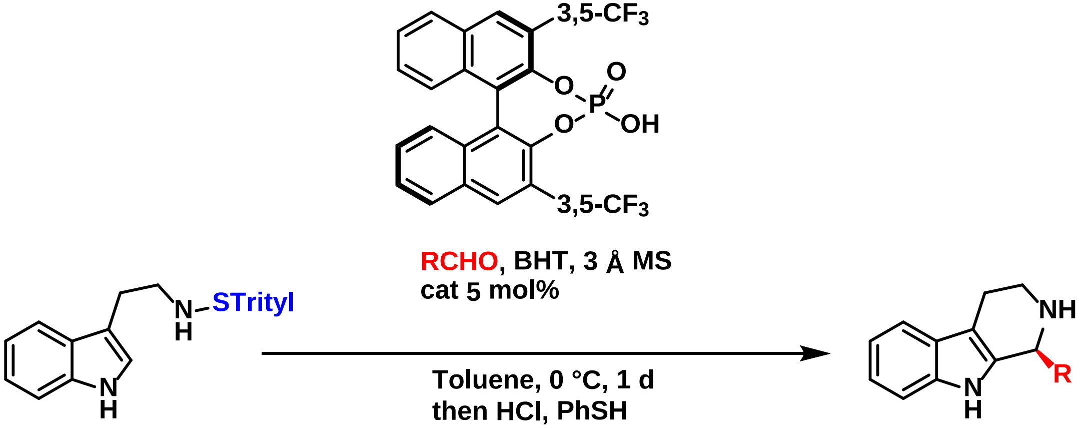
Indole as nucleophile





Indole – C3 linker – N-S

BPA in low catalyst loading (5 mol%)[1]
Sulphenyl stabilized the iminium (favor PS vs enamine formation)
BHT as radical scavenger to avoid product decomposition (homolytic cleavage)
Aliphatic and aromatic aldehyde tolerated
72-87% ee except acetaldehyde (30%)



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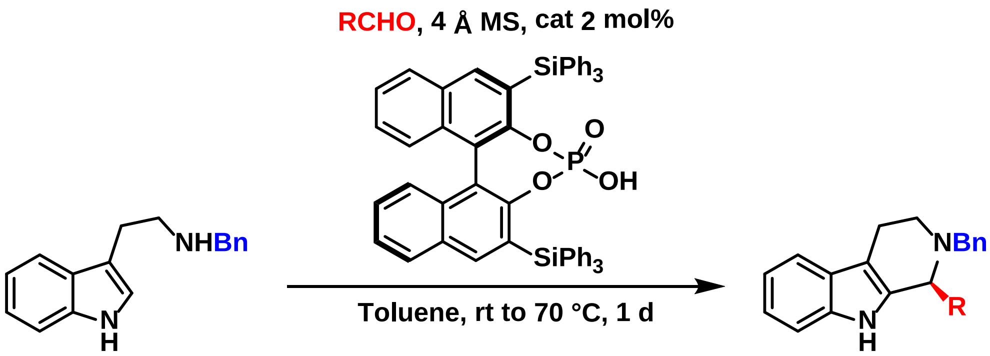
1. Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 7485.

Indole – C3 linker – Nalkyl

BPA in low catalyst loading[1]

Aliphatic and aromatic aldehyde tolerated in 61-87% ee

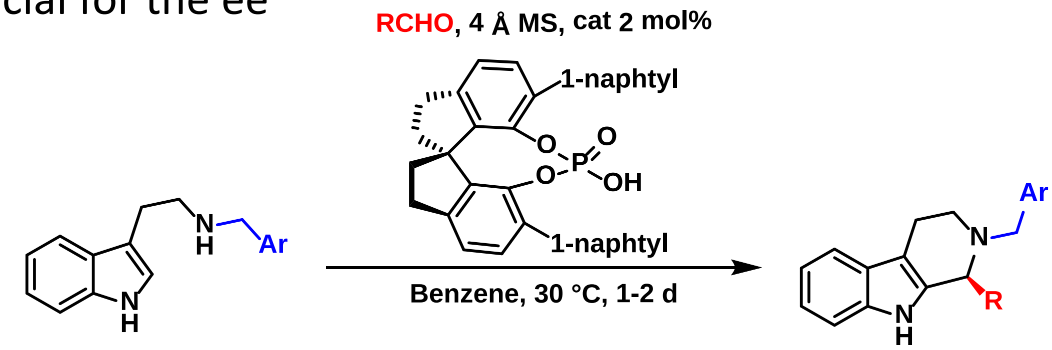


SPA in low catalyst loading (1st example with SPA). Much better than BPA (yield + ee)[2]

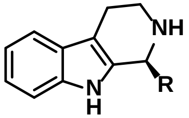
Various aryl group tolerated

Aliphatic and aromatic aldehyde tolerated with 90-98% ee

NH of the indole crucial for the ee

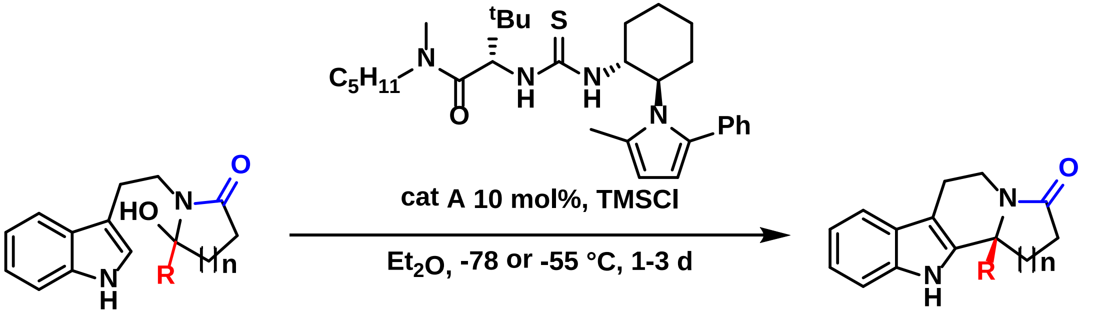


1. Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405.
2. Huang, D.; Xu, F.; Lin, X.; Wang, Y. *Chem. Eur. J.* **2012**, *18*, 3148.

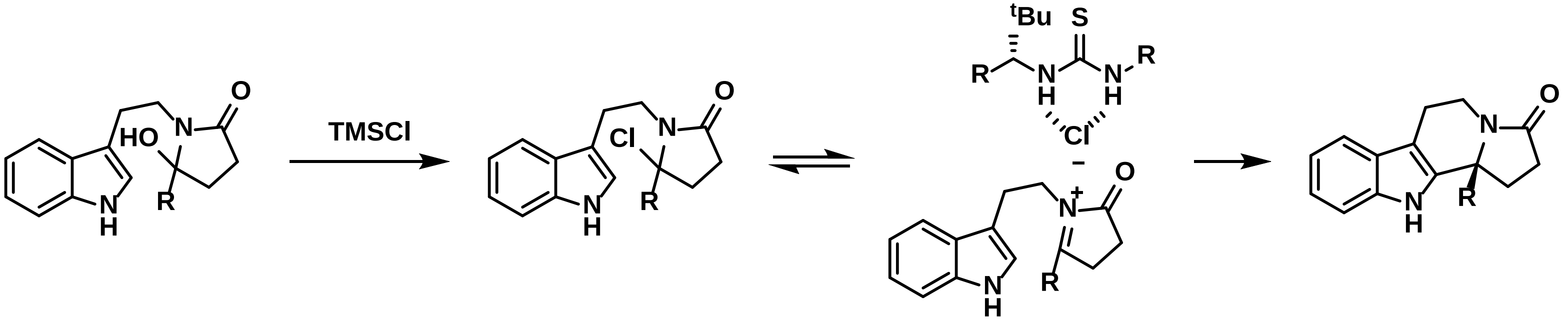


Indole – C3 linker – NAcyl

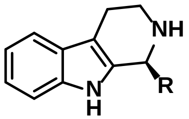
From hydroxylactame with thiourea catalysis
TMSCl for the formation of the iminium
R = alkyl or aryl / n = 1 or 2 with 81-99% ee



S$_N$1 + Asymmetric Counteranion Directed Catalysis mechanism
ee depends on the size of the counter anion (Cl: 97, Br: 68 and I: <5% ee)



1. Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404.



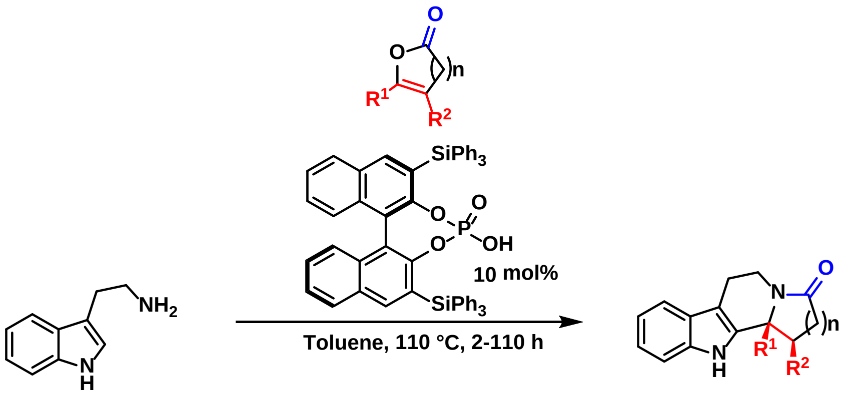
Indole – C3 linker – NAcyl

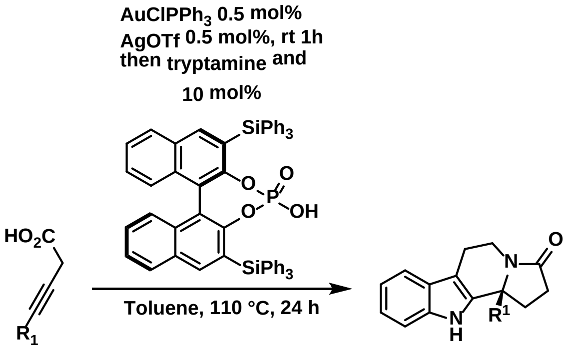
R^1 = alkyl or aryl / R^2 = H or EWG / n = 1 or 2 with 72-99% ee[1]

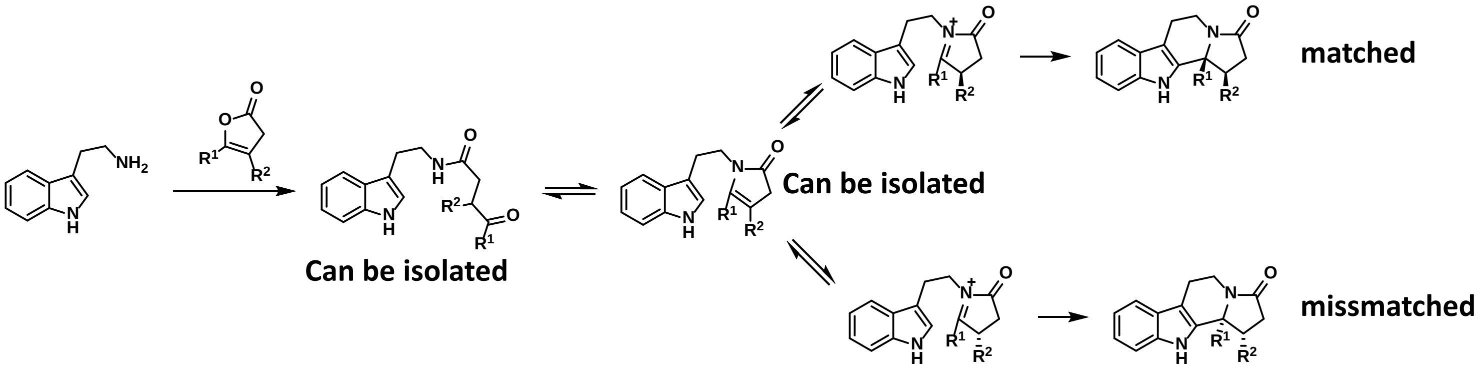
Compatible with the enol lactone-forming gold(I)-catalyzed cycloisomerization of alkynoic acids

Can go down to 1 mol% catalyst loading

One single diastereoisomer (*cis*)







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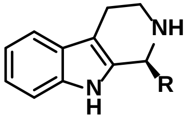
1. Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796.



Indole – C3 linker – NAcyl

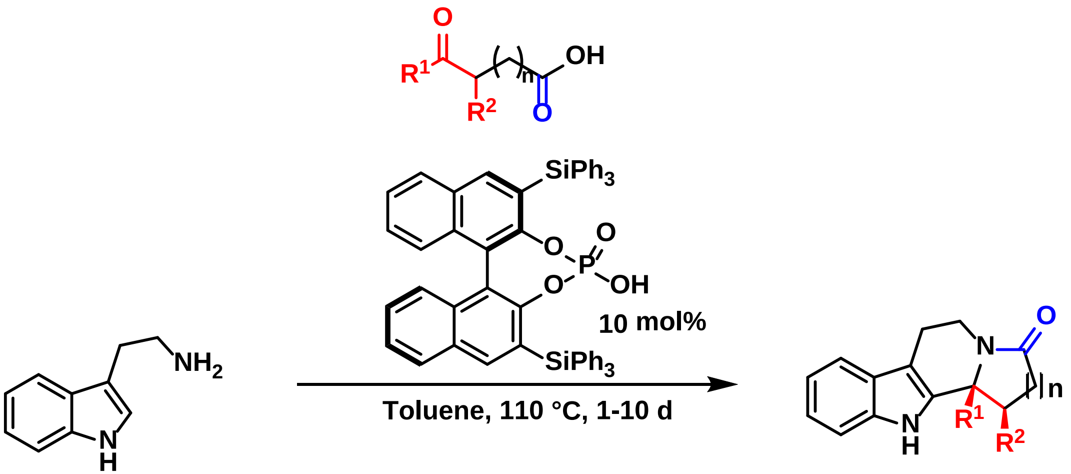
From the open form of the lactone before[1]

R^1 = alkyl or aryl / R^2 = alkyl or EWG / n = 1 or 2 with 68-98% ee

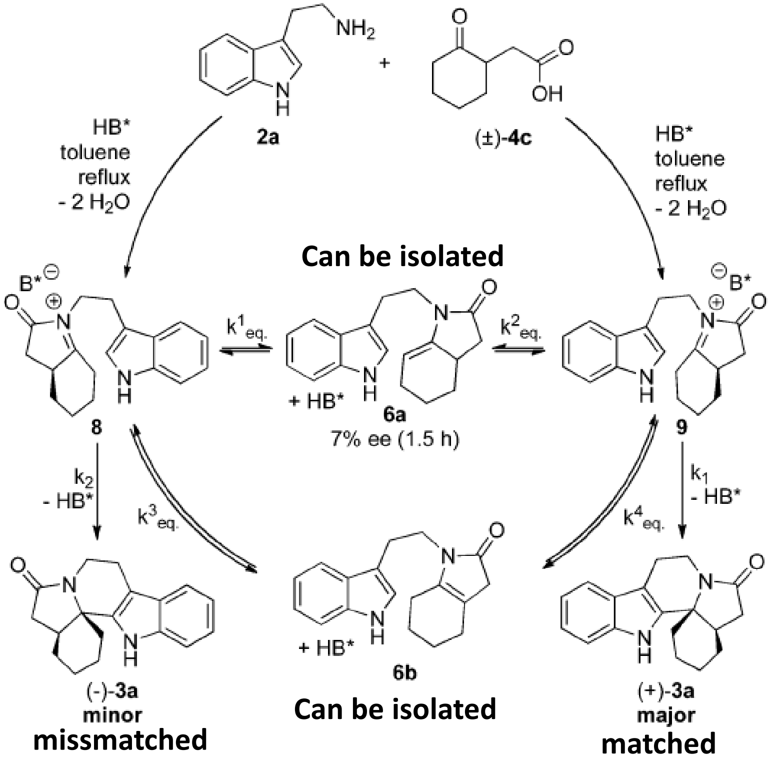
One single diastereoisomer (*cis*)

Dynamic kinetic asymmetric cyclization

$k^1_{eq}, k^2_{eq}, k^3_{eq}, k^4_{eq} >> k_1 > k_2$



Scheme 6. Postulated Origins of Stereocontrol in the Reaction Cascade via a Dynamic Kinetic Asymmetric Cyclization



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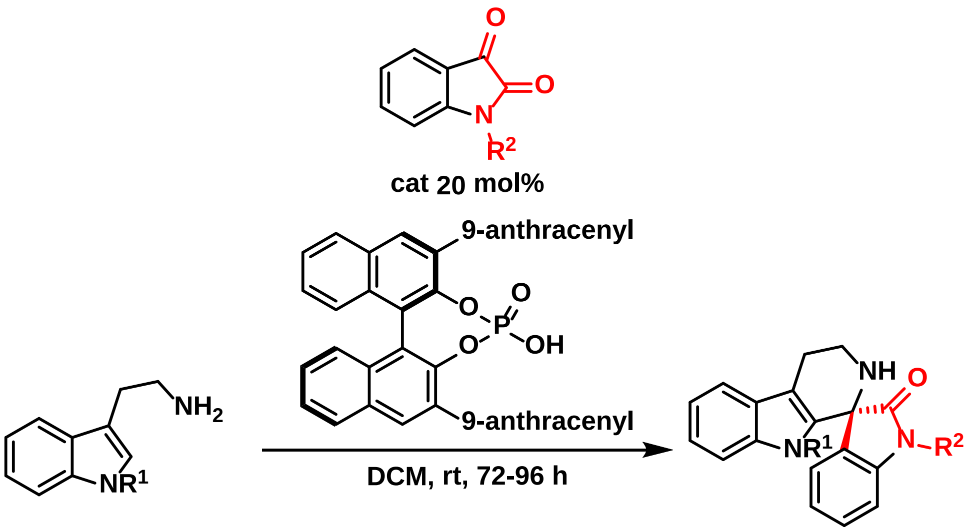
1. Holloway, C. A.; Muratore, M. E.; Storer, R. I; Dixon, D. J. *Org. Lett.* **2010**, *12*, 4720.

Indole – C3 linker – NH_2



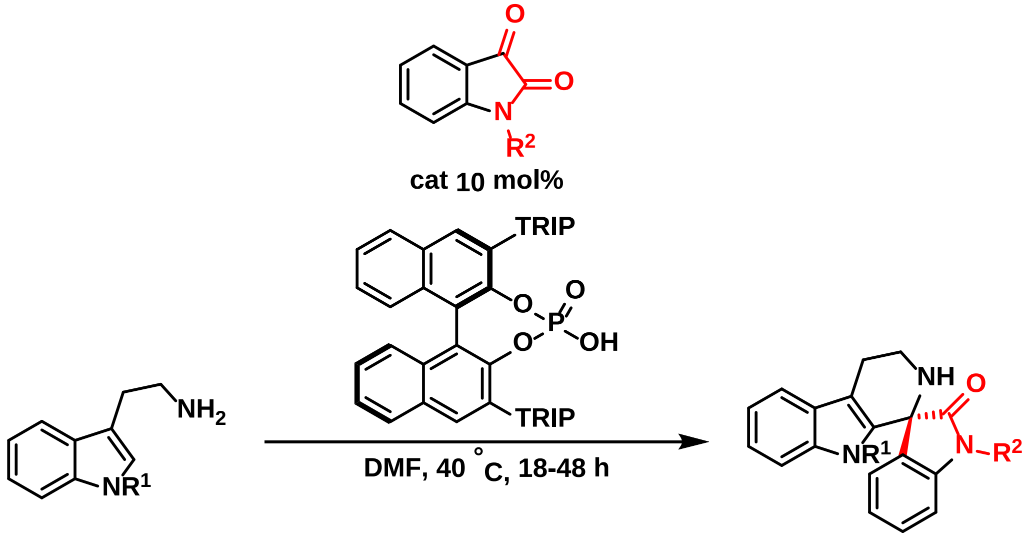
With isatine (reactive ketone)

R^1 = H and R^2= H, alkyl, aryl

Very sensitive to the substituent on the tryptamine

0-94% ee[1]

Sn and Sc Box and Pybox gave poor ee



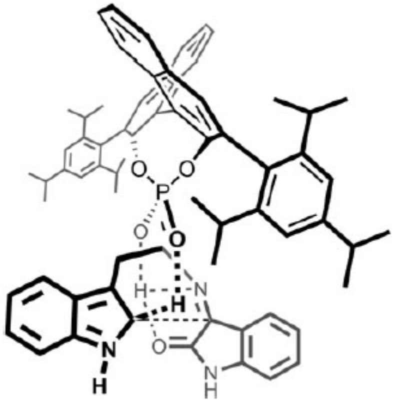
With isatine (reactive ketone)

R^1 = H, Me (!!) and R^2= H, alkyl

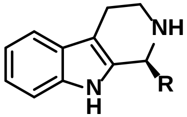
Not sensitive at all to water

DMF as solvent

71-95% ee[2]



1. Badillo, J. J.; Silva-García, A.; Shupe, B. H.; Fettinger, J. C.; Franz, A. K. *Tetrahedron Lett.* **2011**, *52*, 5550.
2. Duce, S.; Pesciaioli, F.; Gramigna, L.; Bernardi, L.; Mazzanti, A.; Ricci, A.; Bartoli, G.; Bencivennia, G. *Adv. Synth. Catal.* **2011**, *353*, 860.



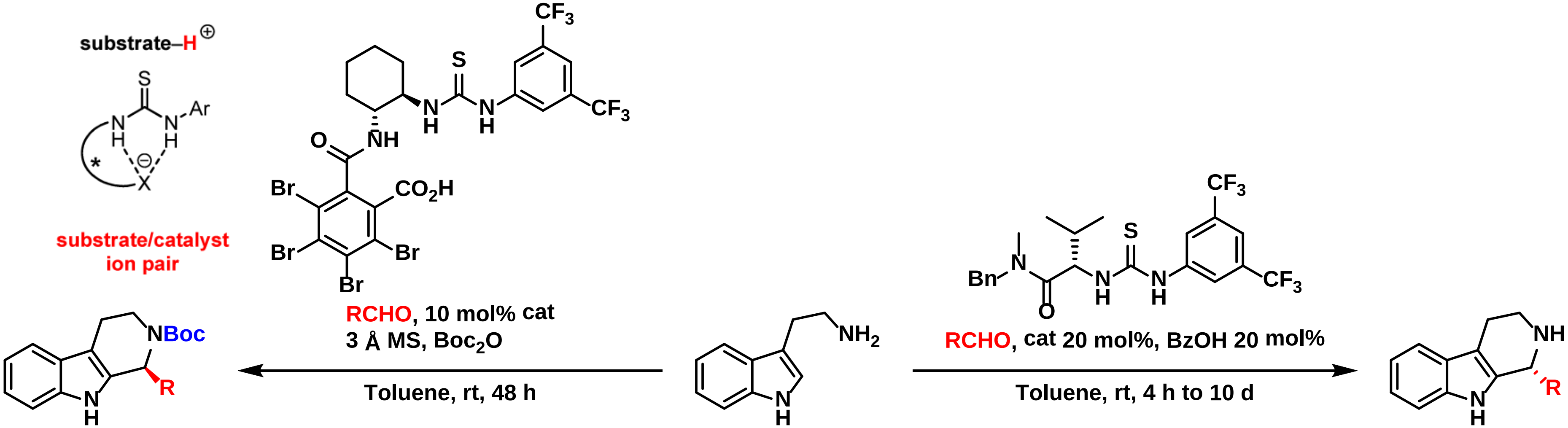
Indole – C3 linker – NH_2

With thiourea:

R = alkyl and aryl with 86-99% ee[1]

Acid not required for aliphatic aldehyde if tryptamine rich enough (slower but higher ee)

Very slow if not electron rich tryptamine



With thiourea-acid catalyst:

R = aryl only with 32-92% ee[2] and much faster than Jacobsen

In situ Boc protection of the product to avoid product inhibition (otherwise add malonic acid)

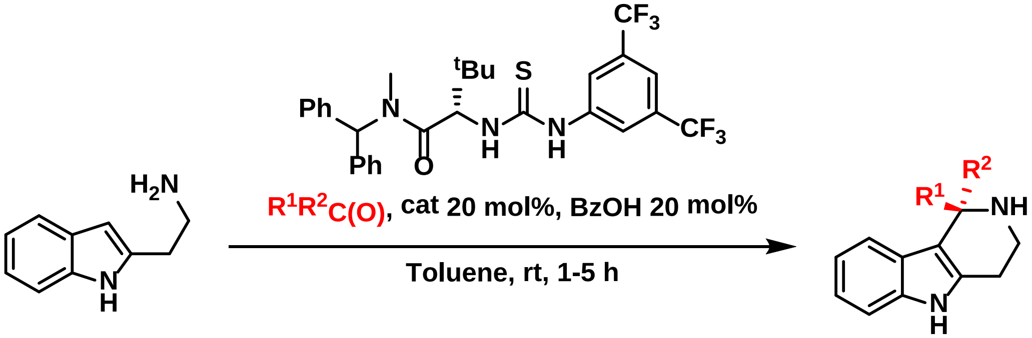
1. Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887.
2. Mittal, N.; Sun, D. X.; Seidel, D. *Adv. Org. Lett.* **2014**, *16*, 1012.

Indole – C2, C4, N1 linker

Synthesis of tetrahydro-γ-carboline (drug discovery)[1]

Work with aliphatic and aromatic aldehyde with 79-95% ee

1 example with ketone



Direct *in situ* Boc protection + trituration afforded all examples in >99% ee without column

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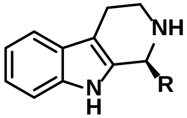
1. Lee, Y.; Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 5564.



Indole – C2, C4, N1 linker

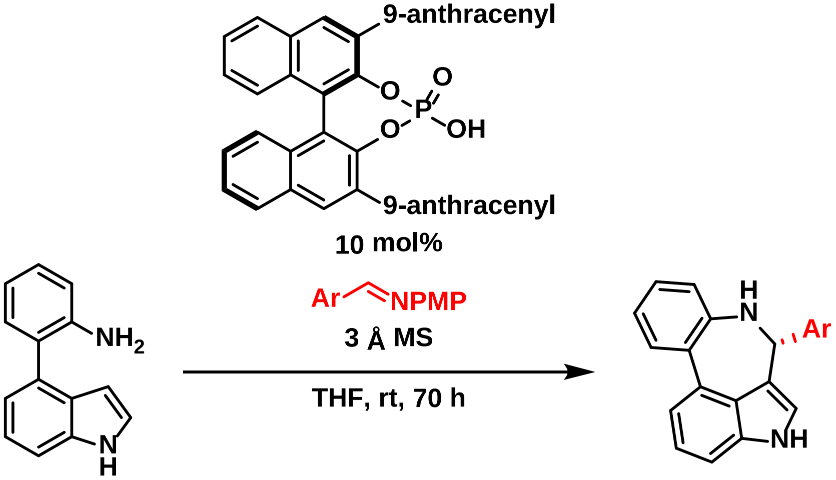
1st example of 7-membered ring formation via PS[1]

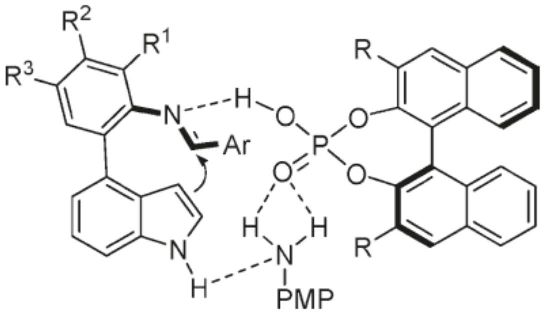
Work with electron poor and rich aromatic imine in 84-91% ee

For the same example imine vs aldehyde: 90 vs 83% ee

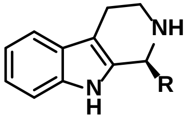
1 example with 7-aza-indole but work only with aldehyde (0% vs 77% yield, 90% ee)

NH of the indole required for the ee (not for the yield)





[1] Cheng, D.-J.; Wu, H.-B.; Tian, S.-K. *Org. Lett.* **2011**, *13*, 5636.

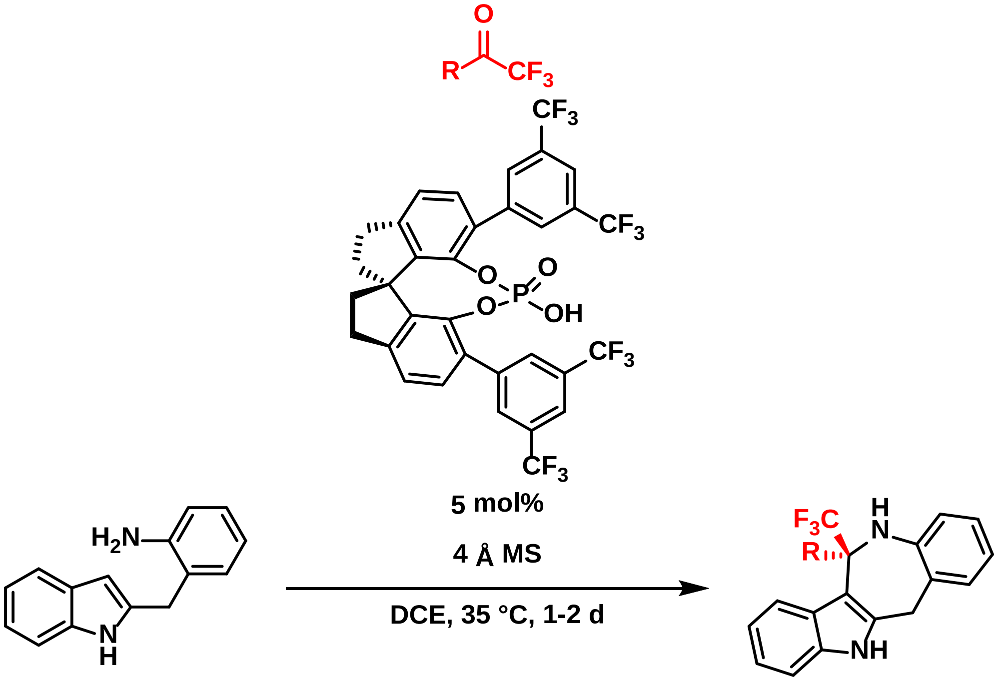


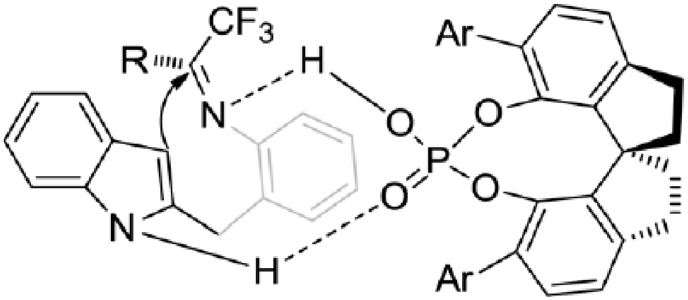
Indole – C2, C4, N1 linker

Synthesis of 7-membered ring with quaternary stereocenters bearing a CF_3 moiety[1]

Work with electron poor and rich aromatic ketone with 87-99% ee

NH of the indole required for the ee





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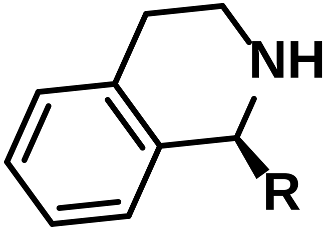
1. Li, X.; Chen, D.; Gu, H.; Lin, X. *Chem. Commun.* **2014**, *50*, 7538.

Phenyl as nucleophile



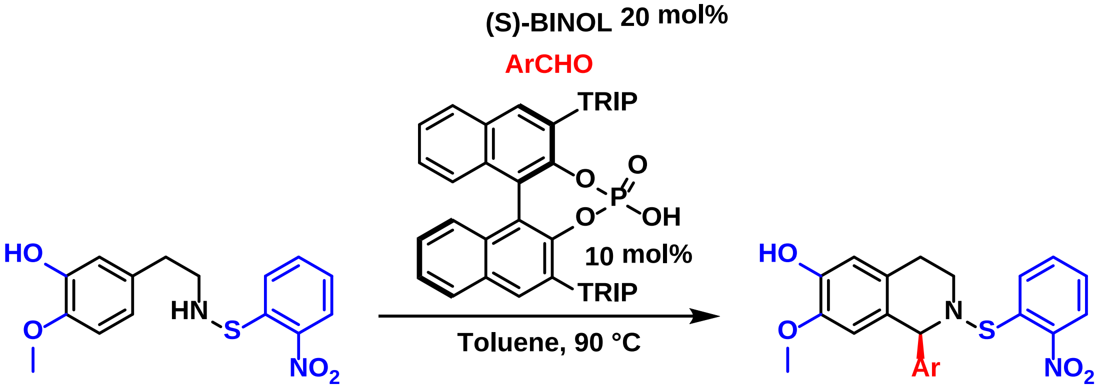
Phenyl

BPA in combination with BINOL ligand for the synthesis of tetrahydroisoquinolines

Nps give a good para/ortho ratio compare to H, Me, Bn + 24-86% ee

Work with electron poor and rich aromatic aldehyde + aliphatic one

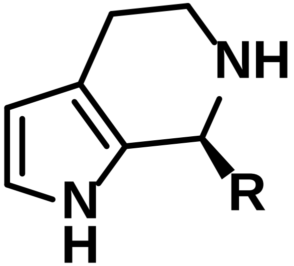
One hydroxyl group on the aryl is not enough

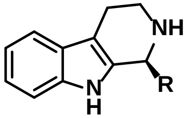


Why is enantioselective reaction harder to develop with phenylethylamine compared to tryptamine?

1. Mons, E.; Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2014**, *79*, 7380.

Pyrrole as nucleophile



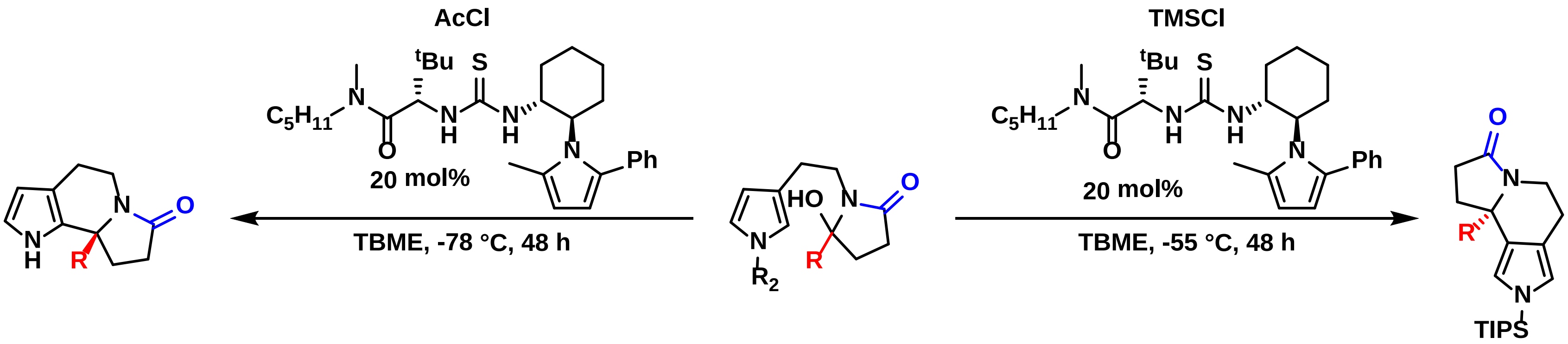


Pyrrole

C2 or C4 attack depending on the substitution of the pyrrole and on the LA used[1]

For C4 attack: 70-97% ee.
Use TIPS as steric bulk to prevent C2 attack
Catalyst influence the regioselectivity too. 3:1 vs >50:1 C4/C2 with catalyst

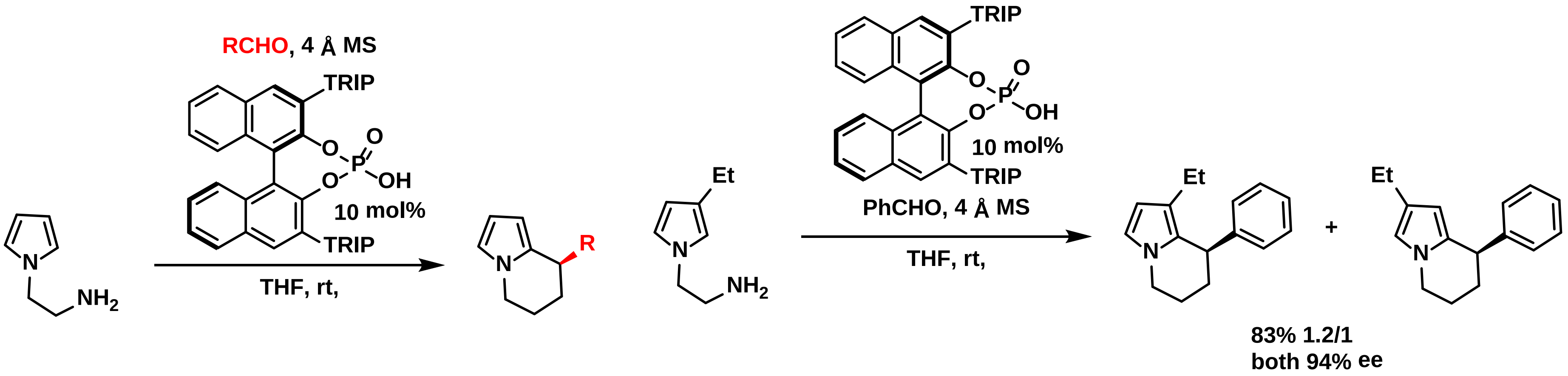
For C2 attack: 52-93% ee
For both R = aliphatic, aromatic or H



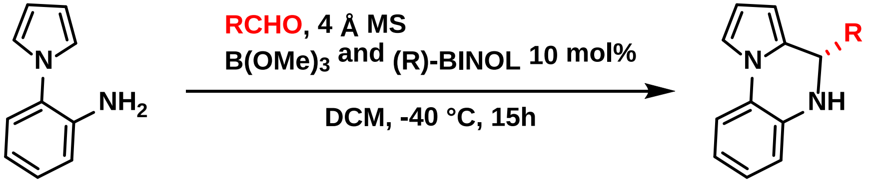
1. Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577.

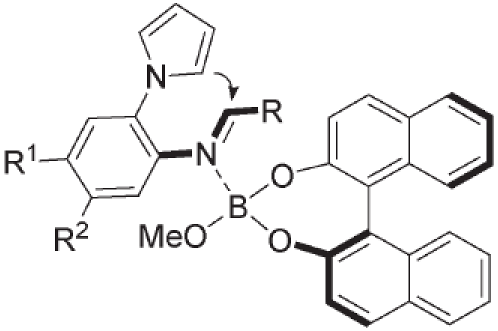
Pyrrole

Synthesis of 1,2,3,4-Tetrahydropyrrolo[1,2-a]pyrazines[1]
Branched aliphatic and aromatic aldehyde tolerated in 65-94% ee
BPA also influence the regioselectivity (10:1 C2/C5 without catalyst)



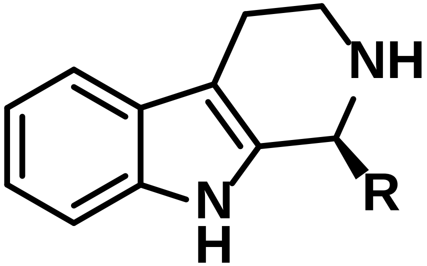
Boron-BINOL complex better than BPA[2]
Aliphatic and aromatic aldehyde in 72-95% ee

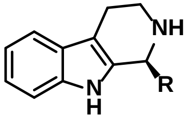




1. He, Y.; Lin, M.; Li, Z.; Liang, X.; Li, G.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4490.
2. Li, Y.; Su, Y.-H.; Dong, D.-J.; Wua, Z.; Tian, S.-K. *RSC Adv.* **2013**, *3*, 18275.

Conclusion





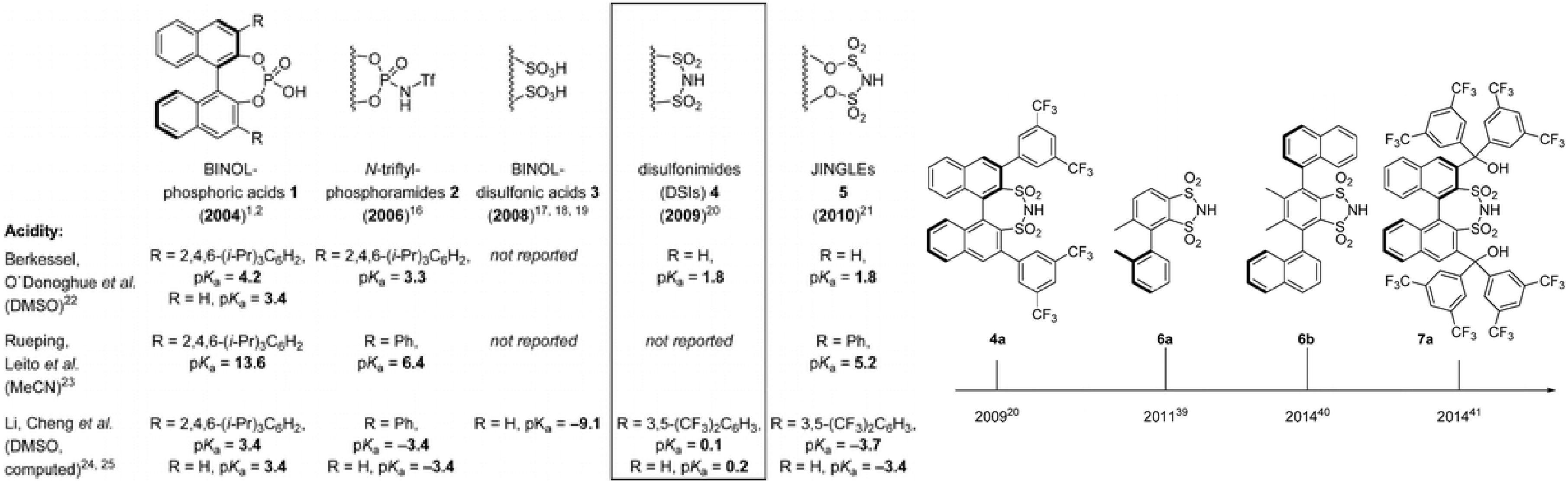
Conclusion and outlook

- PS very usefull reaction and tolerant to many variations

- Missing method for the use of NH_2-tryptamine and for phenylethylamine
- Ketone not well tolerated in the scope for the electrophiles except when “cheating”

- Be able to lower the catalyst loading as well as the time of the reaction

- Use of catalytic Lewis acid or of stronger chiral acid



	BINOL-phosphoric acids **1** (2004)[1,2]	*N*-triflyl-phosphoramides **2** (2006)[16]	BINOL-disulfonic acids **3** (2008)[17, 18, 19]	disulfonimides (DSIs) **4** (2009)[20]	JINGLEs **5** (2010)[21]
Acidity:					
Berkessel, O´Donoghue *et al.* (DMSO)[22]	R = 2,4,6-(i-Pr)$_3$C$_6$H$_2$, pK_a = **4.2** R = H, pK_a = **3.4**	R = 2,4,6-(i-Pr)$_3$C$_6$H$_2$, pK_a = **3.3**	*not reported*	R = H, pK_a = **1.8**	R = H, pK_a = **1.8**
Rueping, Leito *et al.* (MeCN)[23]	R = 2,4,6-(i-Pr)$_3$C$_6$H$_2$ pK_a = **13.6**	R = Ph, pK_a = **6.4**	*not reported*	*not reported*	R = Ph, pK_a = **5.2**
Li, Cheng *et al.* (DMSO, computed)[24, 25]	R = 2,4,6-(i-Pr)$_3$C$_6$H$_2$, pK_a = **3.4** R = H, pK_a = **3.4**	R = Ph, pK_a = **−3.4** R = H, pK_a = **−3.4**	R = H, pK_a = **−9.1**	R = 3,5-(CF$_3$)$_2$C$_6$H$_3$, pK_a = **0.1** R = H, pK_a = **0.2**	R = 3,5-(CF$_3$)$_2$C$_6$H$_3$, pK_a = **−3.7** R = H, pK_a = **−3.4**

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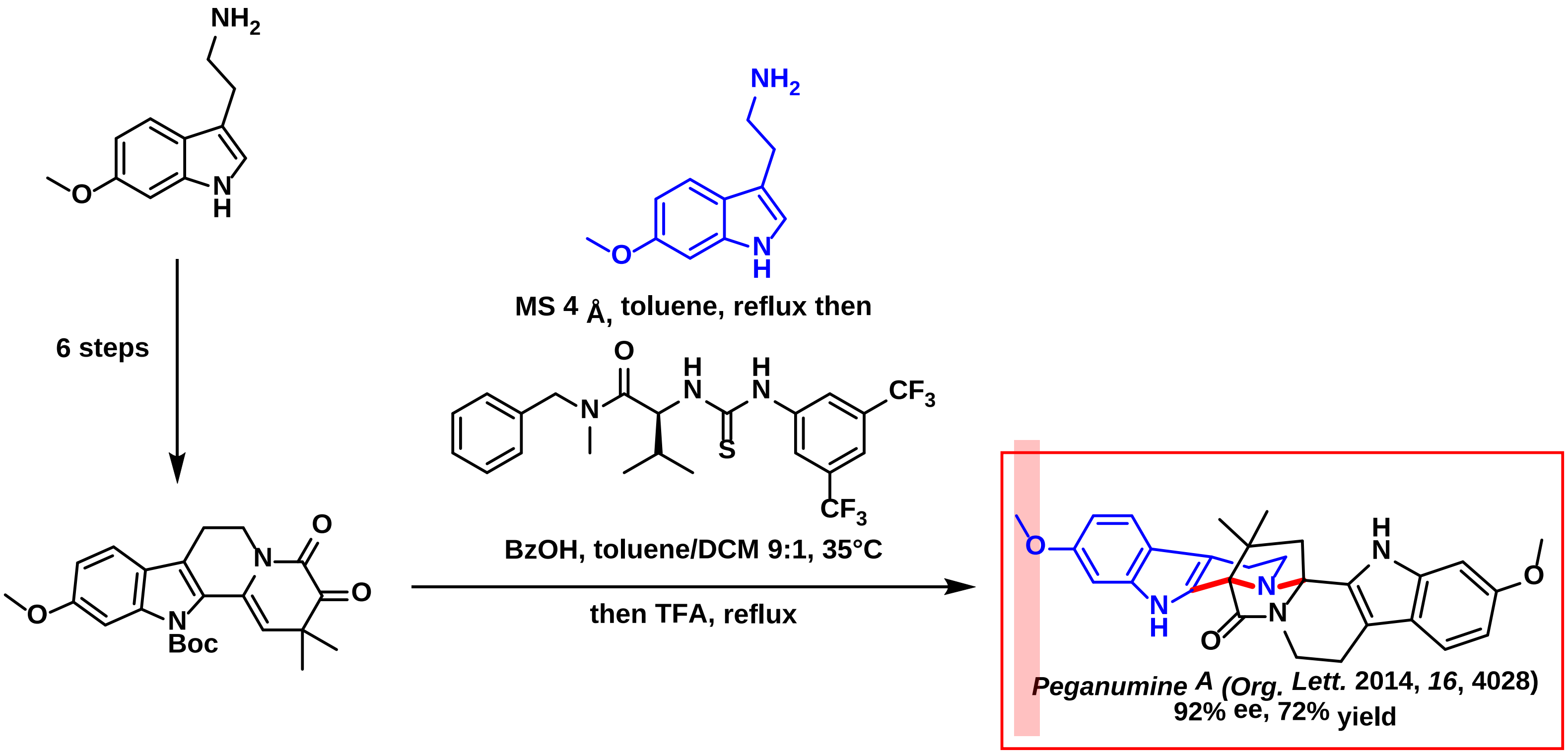
1. James, T.; van Gemmeren, M.; List, B. *Chem. Rev.* **2015**, *115*, 9388.

Conclusion and outlook

But nevertheless a useful method… :)



6 steps

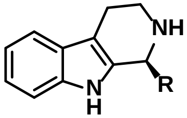
MS 4 Å, toluene, reflux then

BzOH, toluene/DCM 9:1, 35°C

then TFA, reflux

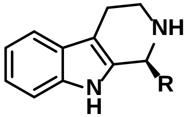
Peganumine A (*Org. Lett.* 2014, *16*, 4028)
92% ee, 72% yield

1. Piemontesi, C.; Wang, Q.; Zhu, J. *Unpublished results*



Conclusion and outlook

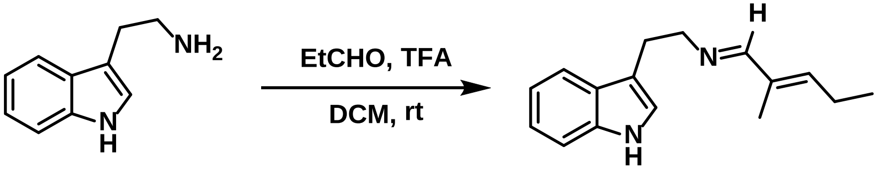
Answers



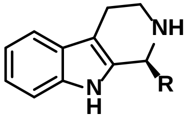
Answers

Why is the *gem*-disubstitution required and
what would be the reaction outcome without it?

gem-disubstituted tryptamine required for the Thorpe-Ingold effect + for steric reason



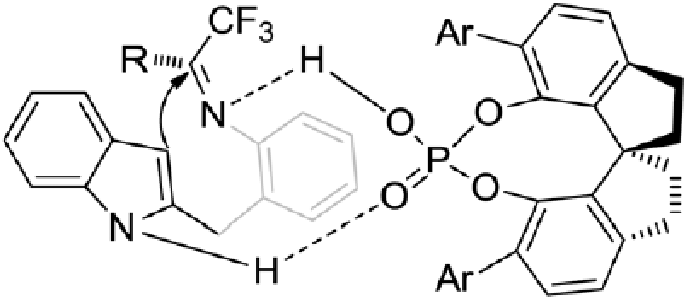
Side-reaction



Answers

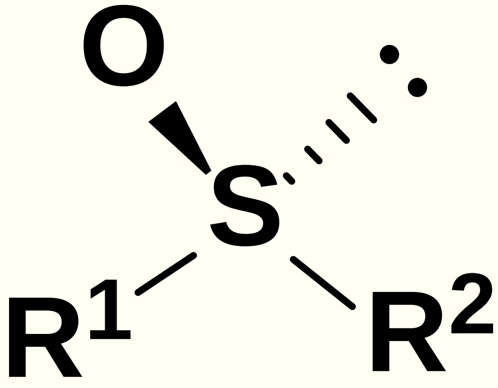
Why is enantioselective reaction harder to develop with phenylethylamine compared to tryptamine?

No “binding point” compare to tryptamine



Frontier in Organic Chemistry

CHIRAL SULFOXIDES AS LIGAND IN ASYMMETRIC CATALYSIS



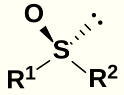
by Nicolas Gaeng

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Lausanne, April 15th 2016

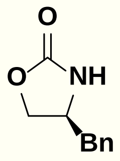
Outline

- Introduction
    - Structure and bonding of chiral sulfoxides
    - History, pioneer work
- Preparation of chiral sulfoxides
- Chiral sulfoxides as ligands
    - S/N ligands
    - S/P ligands
    - S/S ligands
    - S/Olefin ligands
    - S/Cp ligands
- Conclusion and outlook

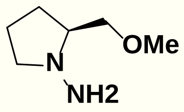


Introduction – Asymmetric Synthesis

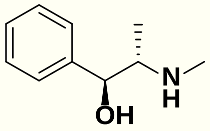
- Chiral auxiliaries
    - Evans' oxazolidones



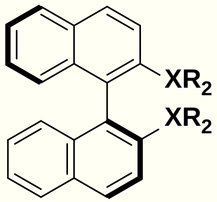
    - Enders' hydrazines



    - Pseudoephedrine

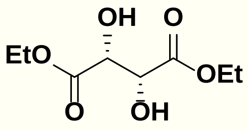


- Asymmetric catalysis
    - BINAP / BINOL

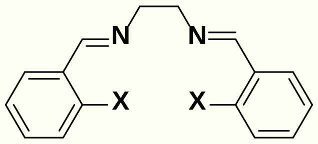


X = O, P

    - Diethyl tartrate

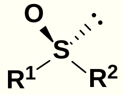


    - Salen-derived



X = O, P

Step and atom economic

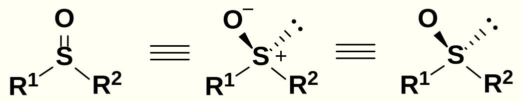


P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40 – 49.

Introduction – Structure and Bonding of Chiral Sulfoxides

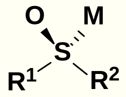
- Chiral information is at the sulfur atom

  → Enantiodiscrimination is close to the metal center

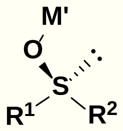


- Sulfoxides can bind through «soft» sulfur or «hard» oxygen atoms

M = 2nd and 3rd row

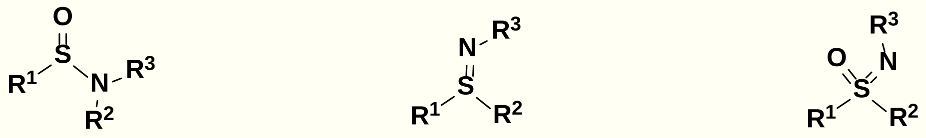


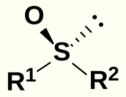
vs



M’ = 1st row

- Sulfoxides can be derivatized into sulfinamides, sulfilimines and sulfoximines

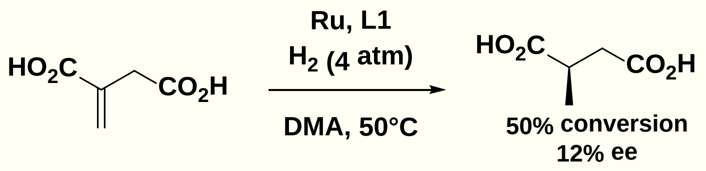




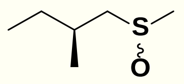
E. Alessio, *Chem. Rev.* **2004**, *104*, 4203 – 4242.

Introduction – History

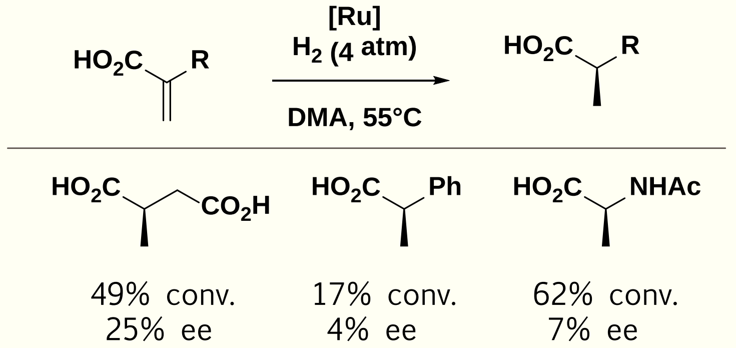
- First report on chiral sulfoxides by James in 1976



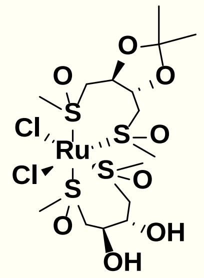
L1



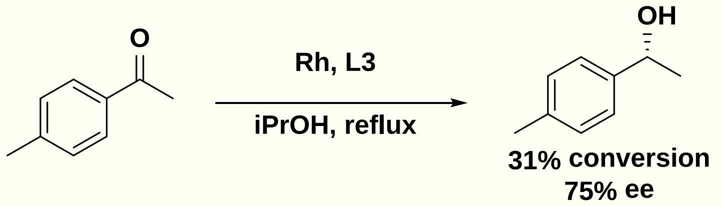
- Second generation, in 1977, with tartrate-derived backbone



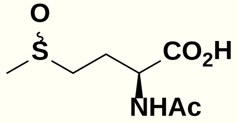
[Ru]

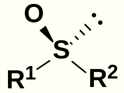


- Third generation, in 1986, with free carboxylate and EW-nitrogen protected group



L3

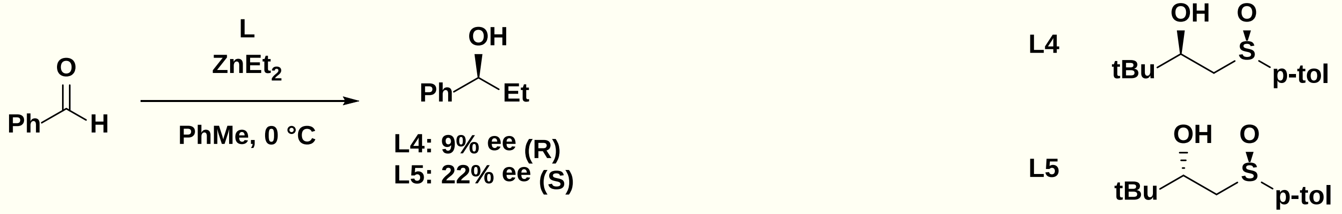




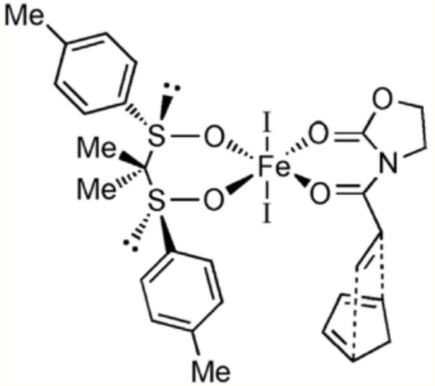
B. R. James, R. S. McMillan, K. J. Reimer, *J. Mol. Catal. A-Chemical* **1976**, *1*, 439 – 441.
B. R. James, R. S. McMillan, *Can. J. Chem*. **1977**, *55*, 3927 – 3932.
P. Kvintovics, B. R. James, B. Heil, J. *Chem. Soc. Chem.Commun*. **1986**, 1810 – 1811.

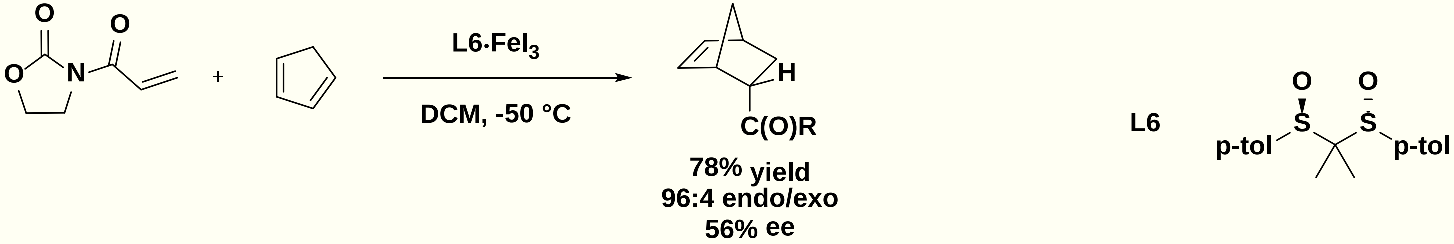
Introduction – History

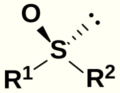
- First single sulfur epimers ligands were developopped by Carreño, in 1993



- First chiral sulfoxide ligand with a chirality on the sulfur atom only, by Khiar in 1993







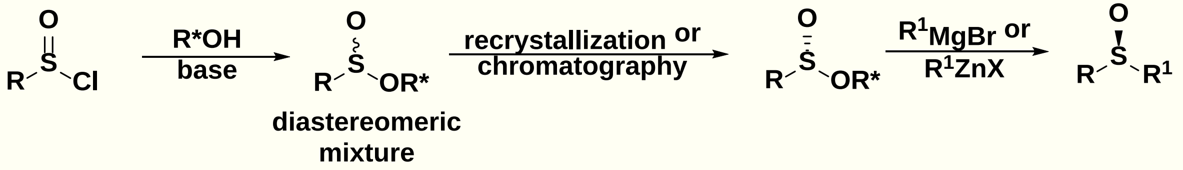
M. C. Carreño, J. L. Garcia Ruano, M. Carmen Maestro, L. M. Martin Cabrejas, *Tetrahedron: Asymmetry* **1993**, *4*, 727 – 734.
N. Khiar, I. Fernndez, F. Alcudia, *Tetrahedron Lett.* **1993**, *34*, 123 – 126.

Preparation of Chiral Sulfoxides

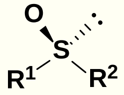
- Synthesis of chiral sulfoxides is still relevant as they show strong biological activity

- Many different variants for the synthesis but two main strategies are mostly used

- Chiral oxysulfinyl intermediate followed by an addition of an organometallic reagent
    - By Andersen in 1962



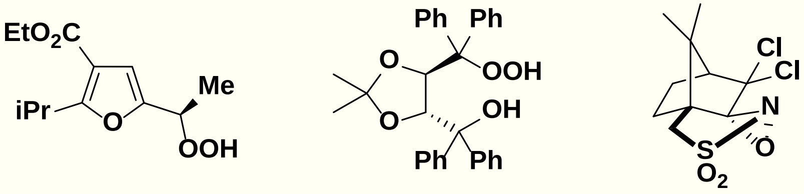
R*OH = (-)-menthol or any



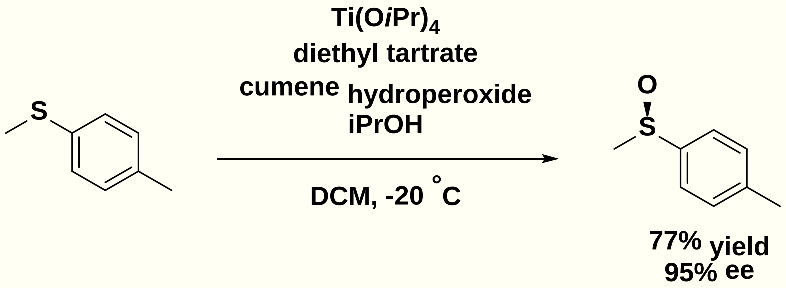
E. Wojaczynska, J.Wojaczynski, *Chem. Rev.* **2010**, *110*, 4303 – 4356.

Preparation of Chiral Sulfoxides

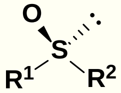
- Enantioselective oxidation of prochiral sulfides using chiral oxidants
  - By Takata in 1986



- First report of a transition-metal-catalyzed enantioselective sulfide oxidation
  - By Kagan in 1996



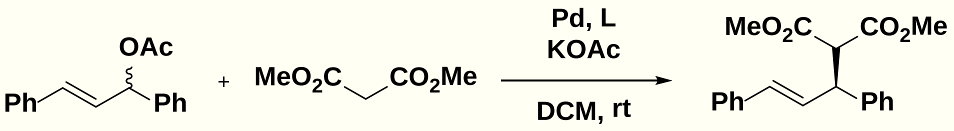
- Disadvantage of the oxidation is its limited scope

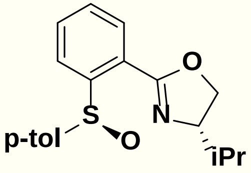


E. Wojaczynska, J.Wojaczynski, *Chem. Rev.* **2010**, *110*, 4303 – 4356.

Chiral Sulfoxides as Ligand – S/N Ligands

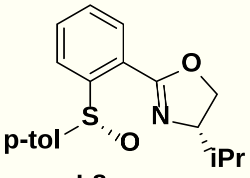
- First ligands investigated by Williams in 1994, containing a sulfoxide-oxazolidine
  - Palladium-Catalyzed Asymmetric Allylic Alkylation (AAA)





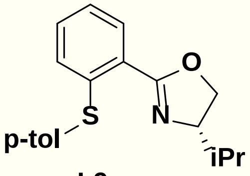
L7

96% yield
88% ee



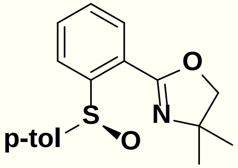
L8

42% yield
55% ee



L9

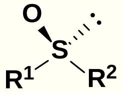
69% conversion
93% ee



L10

60% yield
49% ee

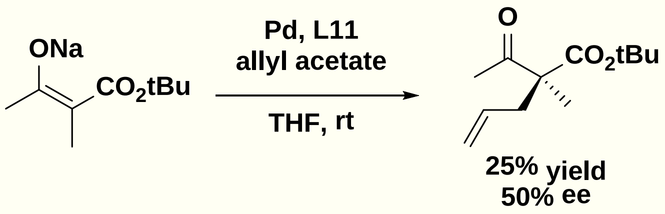
- Clear matched/mismatched effect between L7 and L8
- Sulfoxide not necessary for the enantioselectivity (L9)
- Removing the chirality on the backbone (L10) lowers the reactivity and enantioselectivity



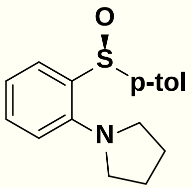
J. V. Allen, J. F. Bower, J. M. J. Williams, *Tetrahedron: Asymmetry* **1994**, *5*, 1895 – 1898.

Chiral Sulfoxides as Ligand – S/N Ligands

- First chiral ligand at the sulfur atom only in the Pd-catalyzed AAA by Hiroi in 1997

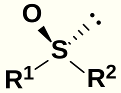


L11



- First and only example of S/N ligand with prochiral nucleophile

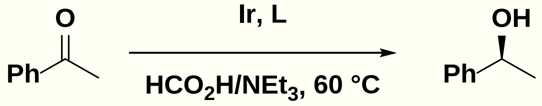
- Switching solvent from THF to 1,2-dimethoxyethane reversed the absolute configuration
  - Can be a powerful trick

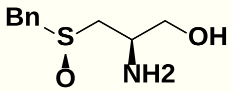


K. Hiroi, Y. Suzuki, *Heterocycles* **1997**, *46*, 77 – 81.

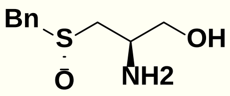
Chiral Sulfoxides as Ligand – S/N Ligands

- First report of chiral sulfoxide used in an asymmetric carbonyl addition
  - Ir-catalyzed transfer hydrogenation by Leeuwen in 2000

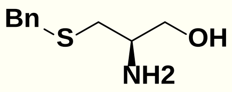




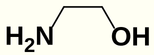
L12
56% conversion
27% ee (R)



L13
99% conversion
65% ee (S)



L14
69% conversion
12% ee (S)

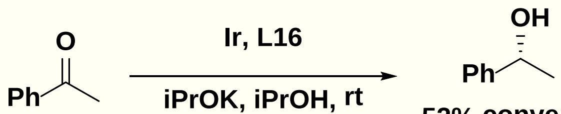


L15
n.r.
n/a

- Matched/mismatched effect between L12 and L13

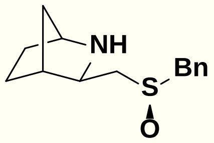
- Sulfide diminishes the enantioselectivity. Must bind to Ir through the sulfur atom

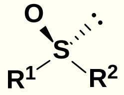
- Andersson in 2003



52% conversion
80% ee

L16

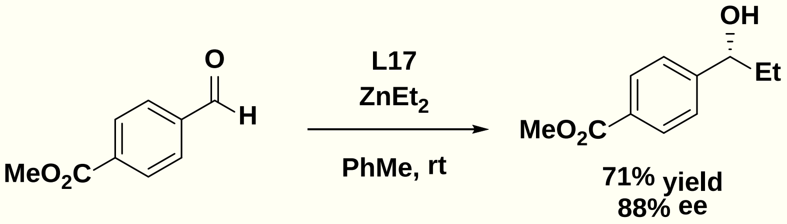


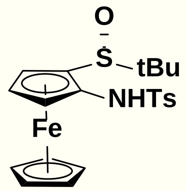


D. G. I. Petra, P. C. J. Kamer, A. L. Spek, H. E. Schoemaker, P.W. N. M. van Leeuwen, *J. Org. Chem.* **2000**, *65*, 3010 – 3017.
J. K. Ekegren, P. Roth, K. Kllstrçm, T. Tarnai, P. G. Andersson, *Org. Biomol. Chem.* **2003**, *1*, 358 – 366.

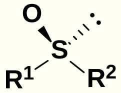
Chiral Sulfoxides as Ligand – S/N Ligands

- Ferrocene-based S/N ligands were developed by Carretero in 2001
    - Asymmetric addition onto benzaldehyde derivatives



L17


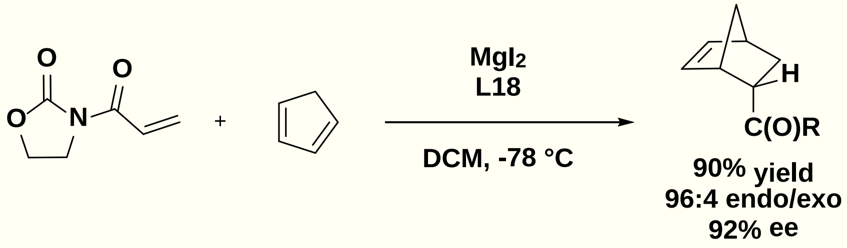
- Chirality elements on the ferocene unit and the sulfoxide
- Sulfide or sulfone gave similar result for the enantioselectivity
- Sulfone slow down the reaction → sulfur must bind to the metal center



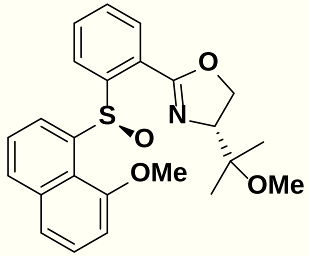
J. Priego, O. Garca MancheÇo, S. Cabrera, J. C. Carretero, *Chem. Commun.* **2001**, 2026 – 2027.

Chiral Sulfoxides as Ligand – S/N Ligands

- Following the work of Khiar, Hiroi reported, in 2001, a new oxazolidine-sulfoxide ligand
  - Mg-catalyzed asymmetric Diels-Alder reaction

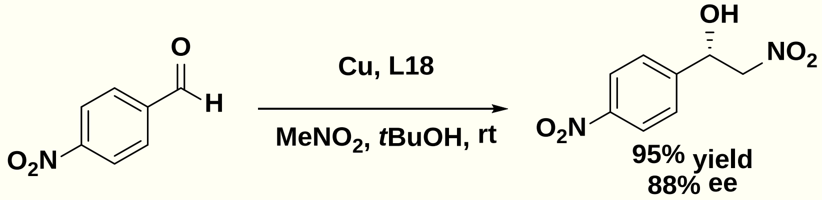


L18

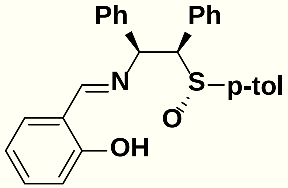


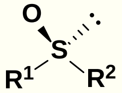
- Both chirality elements must be present

- In 2012, Xiao studied a new class of ligand, based on a salen-derived imine-sulfoxide
  - Cu-catalyzed asymmetric Henry reaction



L19

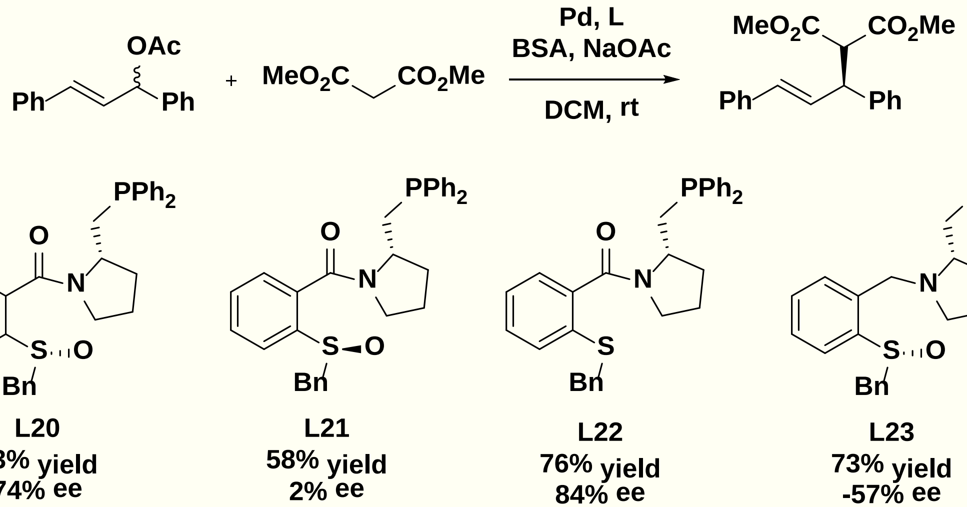




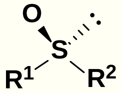
K. Hiroi, K. Watanabe, I. Abe, M. Koseki, *Tetrahedron Lett.* **2001**, *42*, 7617 – 7619.
H.-G. Cheng, L.-Q. Lu, T. Wang, J.-R. Chen, W.-J. Xiao, *Chem. Commun.* **2012**, *48*, 5596 – 5598.

Chiral Sulfoxides as Ligand – S/P Ligands

- Hiroi also worked on the development of S/P sulfoxide ligands in the AAA reaction
  - Firsts report was in 1999 based on proline



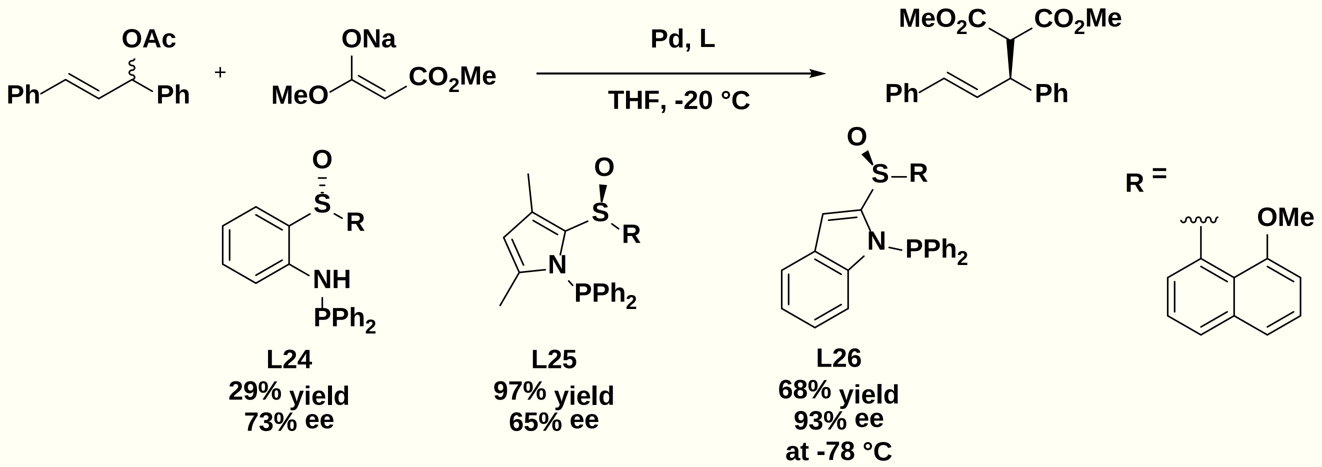
- Matched/mismatched effect between L20 and L21
- Sulfide gave a more efficient reaction reactivity and selectivity → diastereoselective binding
- Amine reversed selectivity → nitrogen is basic enough to coordinate the metal



K. Hiroi, Y. Suzuki, I. Abe, *Chem. Lett.* **1999**, 149 – 150.
Y. Suzuki, I. Abe, K. Hiroi, *Heterocycles* **1999**, *50*, 89 – 94.
K. Hiroi, Y. Suzuki, I. Abe, *Tetrahedron: Asymmetry* **1999**, *10*, 1173 – 1188.

Chiral Sulfoxides as Ligand – S/P Ligands

- Hiroi's second-generation aminophosphine-sulfoxide ligands with only sulfur chirality

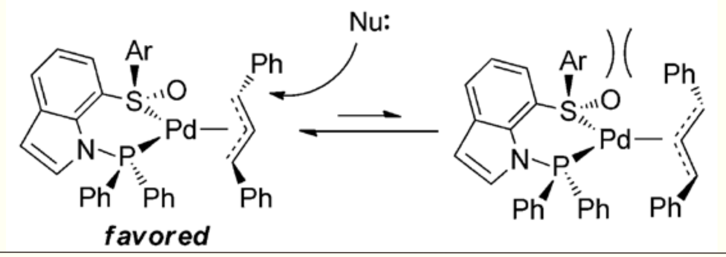


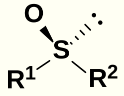
L24
29% yield
73% ee

L25
97% yield
65% ee

L26
68% yield
93% ee
at -78 °C

- Including the nitrogen in a heteroaromatic increases the reactivity → better π-backbonding
- More active ligand allowed to cool down the reaction, increasing the enantioselectivity

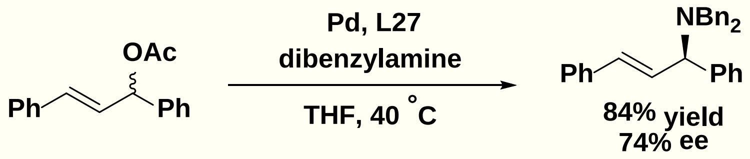




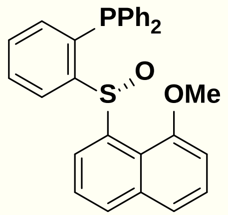
K. Hiroi, I. Izawa, T. Takizawa, K. Kawai, *Tetrahedron* **2004**, *60*, 2155 – 2162.

Chiral Sulfoxides as Ligand – S/P Ligands

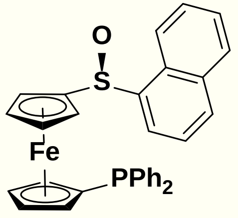
- Hiroi's third-generation ligands lack the nitrogen linker, increasing their potency



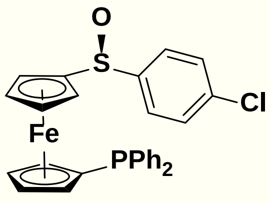
L27



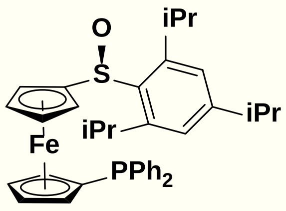
- Toru developed non-planar ferrocene S/P ligands for Pd-AAA



L28
68% ee

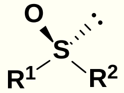


L29



L30

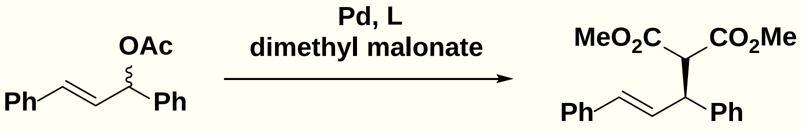
- L28 gave lower ee than L27. EWG (L29) slower the reactivity and L30 shut it down, but…

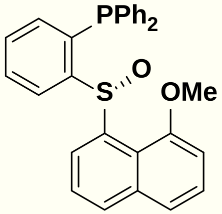


K. Hiroi, Y. Suzuki, I. Abe, R. Kawagishi, *Tetrahedron* 2000, *56*, 4701 – 4710.
S. Nakamura, T. Fukuzumi, T. Toru, *Chirality* 2004, *16*, 10 – 12.

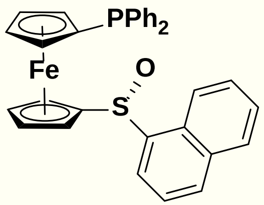
Chiral Sulfoxides as Ligand – S/P Ligands

- Comparison between Hiroi's and Toru's ligands





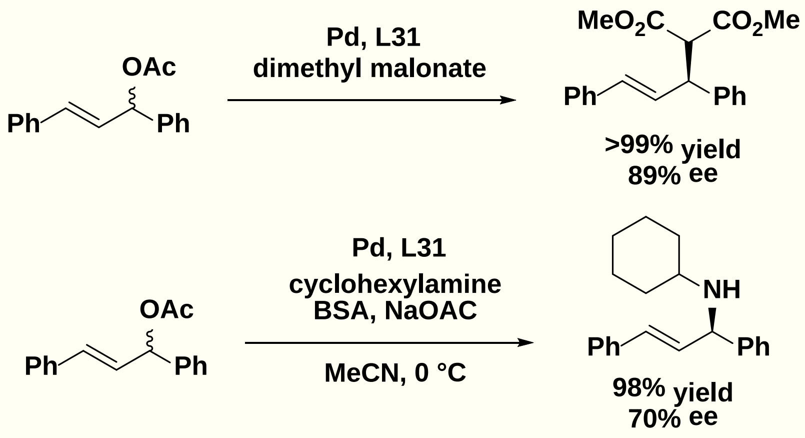
L27
75% yield
75% ee (S)



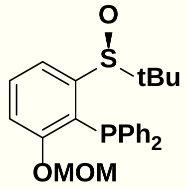
L28
96% yield
68% ee (R)

Chiral Sulfoxides as Ligand – S/P Ligands

- Most effective S/P ligands for the AAA were developed by Liao in 2009
  - Based on the Hiroi scaffold

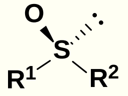


L31



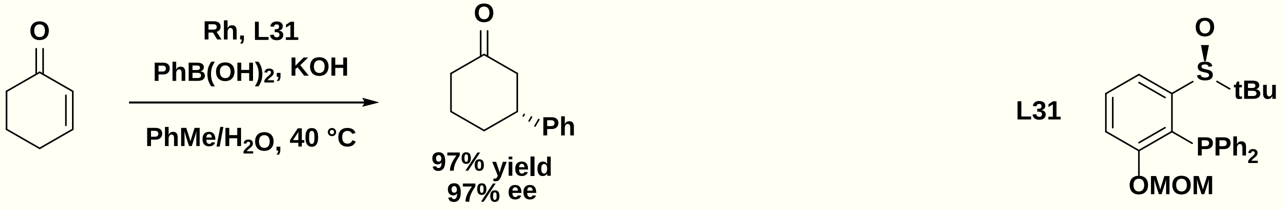
- The bulky alkyl sulfoxide substituent as well as the EDG-substituent on the aromatic ring creates a positive effect on the reactivity and enantioselectivity

J. Chen, F. Lang, D. Li, L. Cun, L. Zhu, J. Deng, J. Liao, *Tetrahedron: Asymmetry* **2009**, *20*, 1953 – 1956.

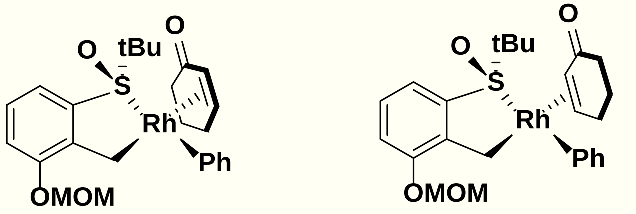


Chiral Sulfoxides as Ligand – S/P Ligands

- Liao's tert-butylsulfinyl-phosphine ligand was used in conjugated addition in 2010



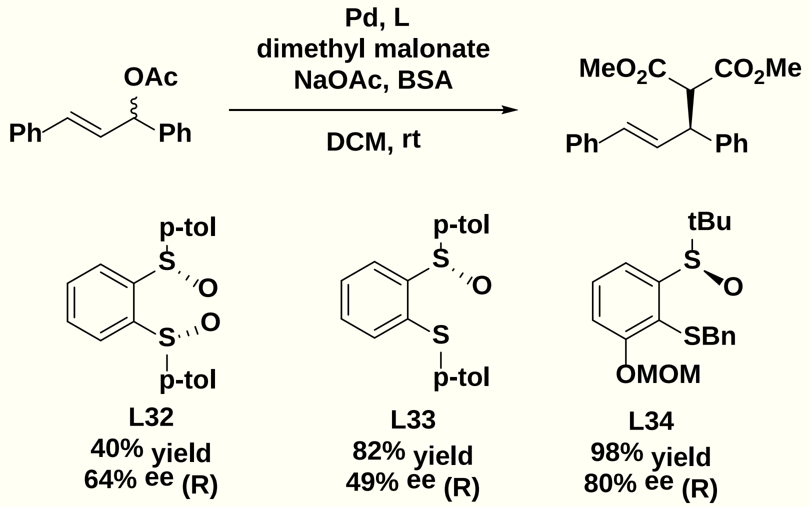
- Similar or best results when using 2-nitrostyrenes
- Importance of the donating group on the aryl
- BINAP gave low enantioselectivity (10% ee)
- *re* face is favored → steric hinderance



F. Lang, D. Li, J. Chen, J. Chen, L. Li, L. Cun, J. Zhu, J. Deng, J. Liao, *Adv. Synth. Catal.* **2010**, *352*, 843 – 846

Chiral Sulfoxides as Ligand – S/S Ligands

- In 1995, Shibasaki was the first to report a S/S chiral sulfoxide ligand only at the sulfur atom

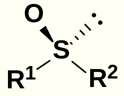


L32
40% yield
64% ee (R)

L33
82% yield
49% ee (R)

L34
98% yield
80% ee (R)

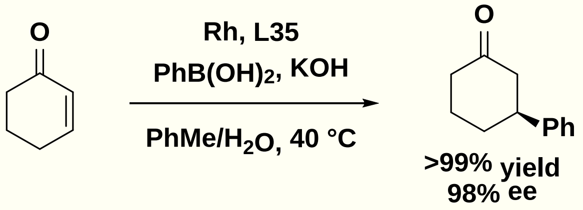
- Sulfoxide-sulfide ligand is more reactive but less selective
- In 2011, Liao reported the use of L34 as a powerful ligand for this transformation
- Both epimers on the sulfoxide give the same product → no explanation



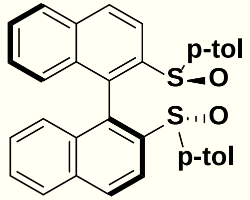
R. Tokunoh, M. Sodeoka, K. Aoe, M. Shibasaki, *Tetrahedron Lett.* **1995**, *36*, 8035 – 8038.
J. Liu, G. Chen, X. Jing, J. Liao, *Tetrahedron: Asymmetry* **2011**, *22*, 575 – 579.

Chiral Sulfoxides as Ligand – S/S Ligands

- Major breakthrough was made by Dorta in 2008 for the Hayashi reaction
  - First example of exceptional reactivity and enantioselectivity using chiral sulfoxides as ligand

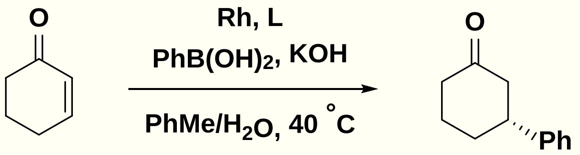


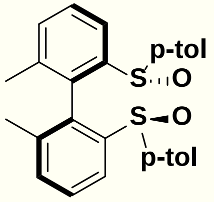
L35



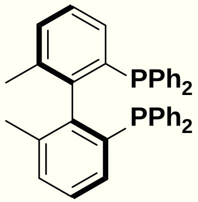
- Reaction tolerates variety of nucleophiles, but the enones were limited

- 2010, new discovery of a more reactive ligand (L36), more σ-donating than (S)-biphemp

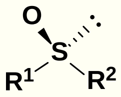




L36
98% yield
98% ee



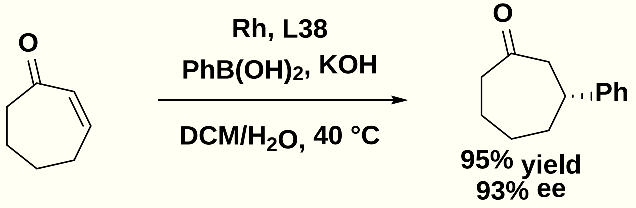
L37
58% yield
90% ee



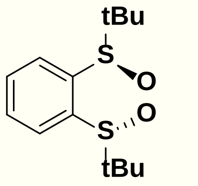
R. Mariz, X. Luan, M. Gatti, A. Linden, R. Dorta, *J. Am. Chem. Soc.* 2008, *130*, 2172 – 2173.
R. Mariz, A. Poater, M. Gatti, E. Drinkel, J. J. Brgi, X. Luan, S. Blumentritt, A. Linden, L. Cavallo, R. Dorta, *Chem. Eur. J.* 2010, *16*, 14335 – 14347

Chiral Sulfoxides as Ligand – S/S Ligands

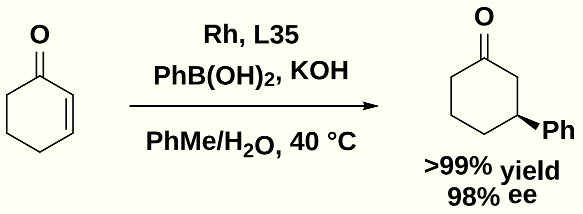
- Great discovery by Liao in 2010 regarding the understanding of sulfoxides' chirality



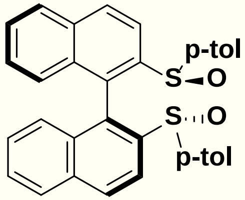
L38



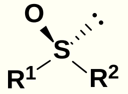
- Tolerant to a broad scope of nucleophiles and (acyclic) acceptors



L35



- Same chirality at the sulfoxides gives different enantiomer
  → axial chirality of the linker is dominant over the chiral sulfoxides

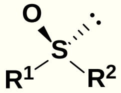


J. Chen, J. Chen, F. Lang, X. Zhang, L. Cun, J. Zhu, J. Deng, J. Liao, *J. Am. Chem. Soc.* **2010**, *132*, 4552 – 4553.

Chiral Sulfoxides as Ligand – S/S Ligands

- Following Liao's work, Dong, in 2011, reported a new type of chiral bis(sulfoxide) ligand

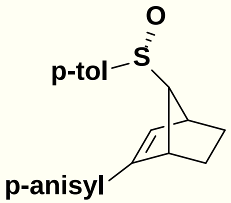
- When using L40, the opposite enantiomer was found and the selectivity was low



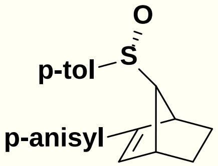
P. K. Dornan, P. L. Leung, V. M. Dong, *Tetrahedron* **2011**, *67*, 4378 – 4384.

Chiral Sulfoxides as Ligand – S/Olefin Ligands

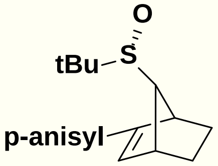
- Most recent discoveries includ an olefin as second coordinating group
- In 2011, four groups reported independently a new class of chiral sulfoxides used in a Hayashi reaction
- The first one, Knochel, based his design on a norbornene scaffold



L41
98% yield
92% ee (S)

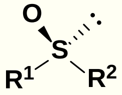


L42
87% yield
92% ee (R)



L43
no reaction

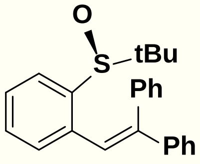
- Two diastereoisomers L41 and L42 gave two different enantiomer products
- Increasing the size of the sulfoxide substituent shut down the reactivity → importance of sulfoxide binding



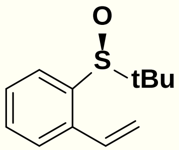
T. Thaler, L.-N. Guo, A. K. Steib, M. Raducan, K. Karaghiosoff, P. Mayer, P. Knochel, *Org. Lett.* **2011**, *13*, 3182 – 3185.

Chiral Sulfoxides as Ligand – S/Olefin Ligands

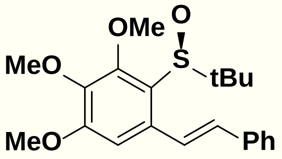
- Xu’s ligands, based on Liao’s work, contain the chiral information at the sulfur atom only
  - *tert*-butyl substituent of the sulfoxide was tolerated as the steric bulk of the ligand is smaller than norbornene



L44
no reaction



L45
98% yield
8% ee (S)

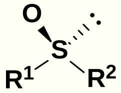


L46
99% yield
95% ee (R)

- Trisubstituted olefin ligand led to no reaction as the hindrance prevent the metal to coordinate the alkene

- L45 gave a good reactivity, however, no concrete enantioselectivity was observed

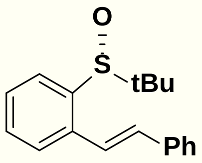
- Increasing the steric bulk to a disubstituted olefin provided excellent results



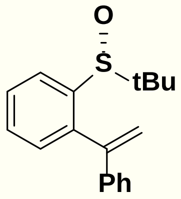
W.-Y. Qi, T.-S. Zhu, M.-H. Xu, *Org. Lett.* **2011**, *13*, 3410 – 3413.

Chiral Sulfoxides as Ligand – S/Olefin Ligands

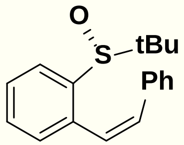
- Finally, Liao published his own *tert*-butyl sulfoxide-olefin ligands



L47
97% yield
97% ee (S)

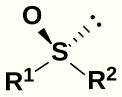


L48
98% yield
95% ee (R)



L49
98% yield
35% ee (R)

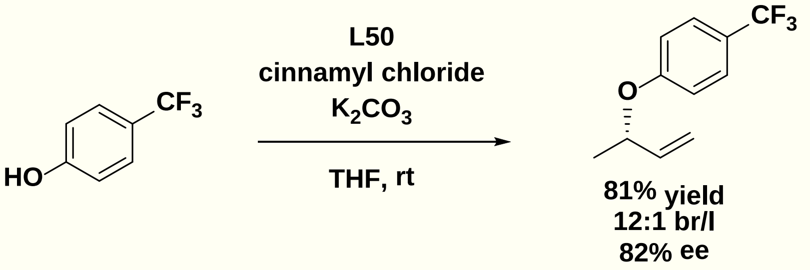
- L47 gave excellent results and yielded to the (S)-product
- Surprisingly, switching the substituent to a 1,1-disubstituted olefin reversed the enantioselectivity
- The (Z)-isomer (L49) gave also the reversed, however lower, selectivity → steric hindrance



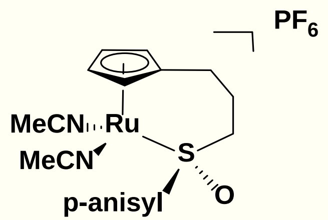
G. Chen, J. Gui, L. Li, J. Liao, *Angew. Chem. Int. Ed.* **2011**, *50*, 7681 – 7685

Chiral Sulfoxides as Ligand – S/Cp Ligands

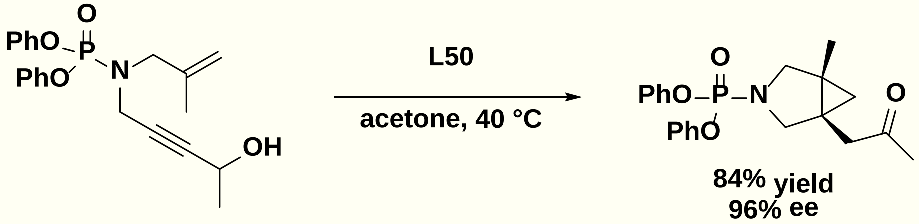
- Trost recently reported, in 2013, a novel class of Cp-sulfoxide ligands
    - Ru-catalyzed AAA



L50



    - First enantioselective Ru-catalyzed enyne cycloisomerization



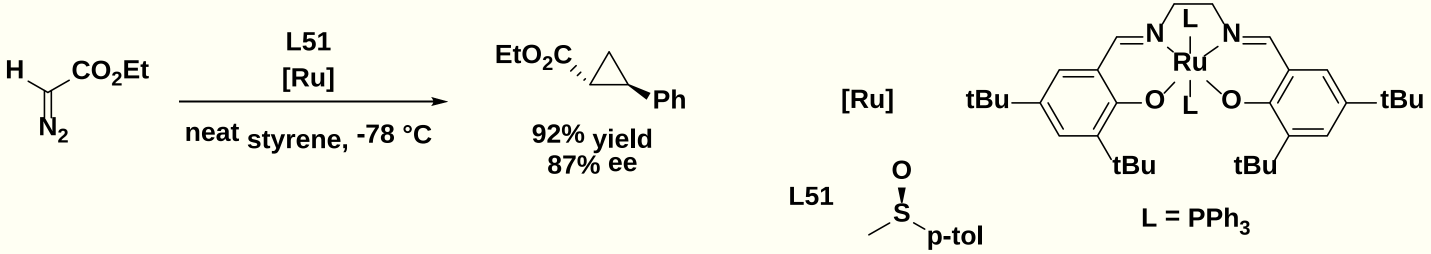
- BINAP and Feringa's ligands led to no reaction

B. M. Trost, M. Rao, A. P. Dieskau, *J. Am. Chem. Soc.* **2013**, *135*, 18697 – 18704

Chiral Sulfoxides as Ligand – Monodentate Ligand

- Since the original ligand by James, in 1976, most of the new class are bidentate

- In 2005, Nguyen used for the first time a monodentate chiral sulfoxide for asymmetric catalysis



- «Chiral amplification»: chiral sulfoxides with achiral salen ruthenium catalyst allow an asymmetry

- Chiral additive induce a conformational change in the structure of the salen moiety → asymmetry

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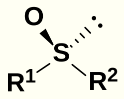
J. A. Miller, B. A. Gross, M. A. Zhuravel, W. Jin, S. T. Nguyen, *Angew. Chem. Int. Ed.* **2005**, *44*, 3885 – 3889

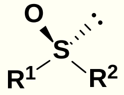


Conclusion and Outlook

- In the last 40 years, the field has grown considerably
- Subtle but powerful ligands
- Sulfoxide-olefin ligands can reverse the enantioselectivity using different substituents

- Scope of the reactions is limited

- However, recent reports show promising results for new cycloaddition (ACIE, ASAP)

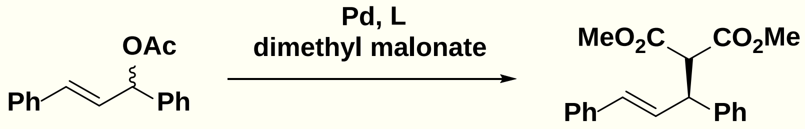


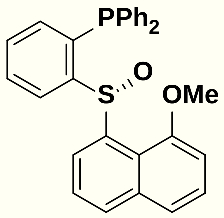
B. M. Trost, M. Rao, *Angew. Chem. Int. Ed.* **2015**, *54*, 5026–5043.

Thank you for your attention

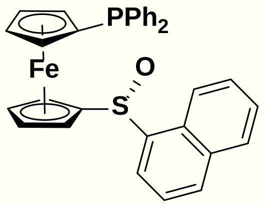
Chiral Sulfoxides as Ligand – S/P Ligands

- Comparison between Hiroi's and Toru's ligands



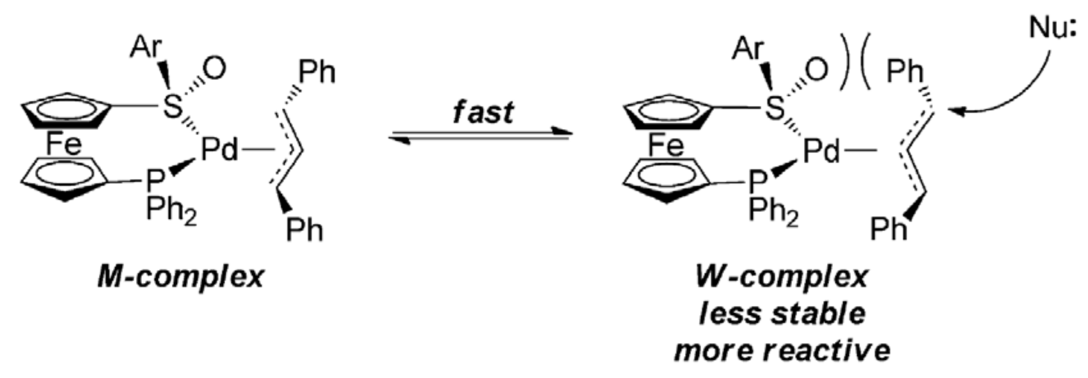


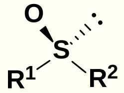
L27
75% yield
75% ee (S)



L28
96% yield
68% ee (R)

- Curtin-Hammett





Chiral Sulfoxides as Ligand – S/S Ligands

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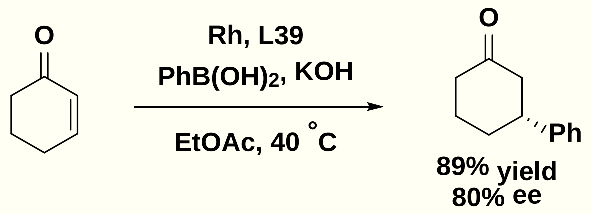
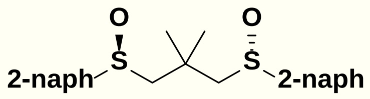
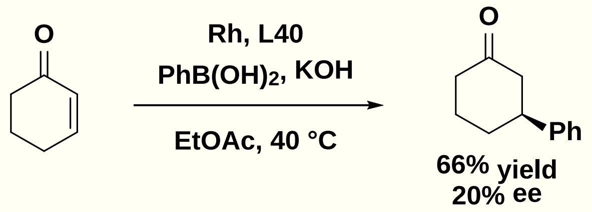


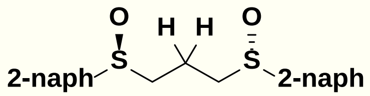
L39



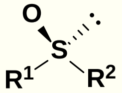
- When using L40, the opposite enantiomer was found and the selectivity was low



L40



- Thorpe-Ingold effect
- 6-membered-ring Rh-sulfoxide chelates are not optimal



Frontiers in organic chemistry: Stereochemistry

Chiral Heterobimetallic Lanthanoid Complexes: Highly Efficient Multifunctional Catalysts

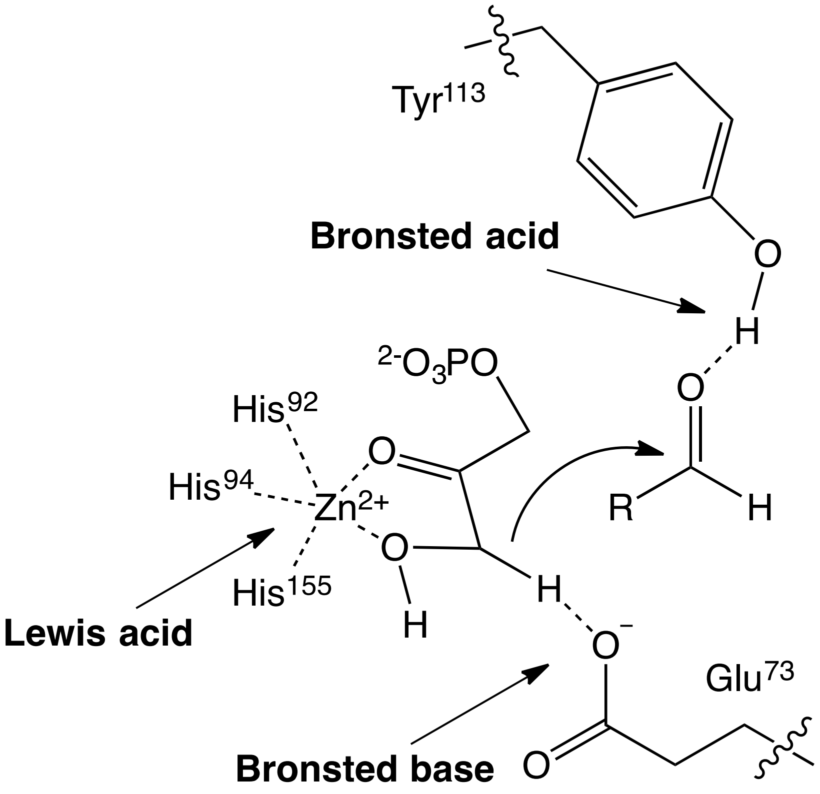
Marta Falcone

14/04/2016

ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Cooperative calatysis for atom economy

Postulated acid and base cooperative mechanism of class II aldolase.

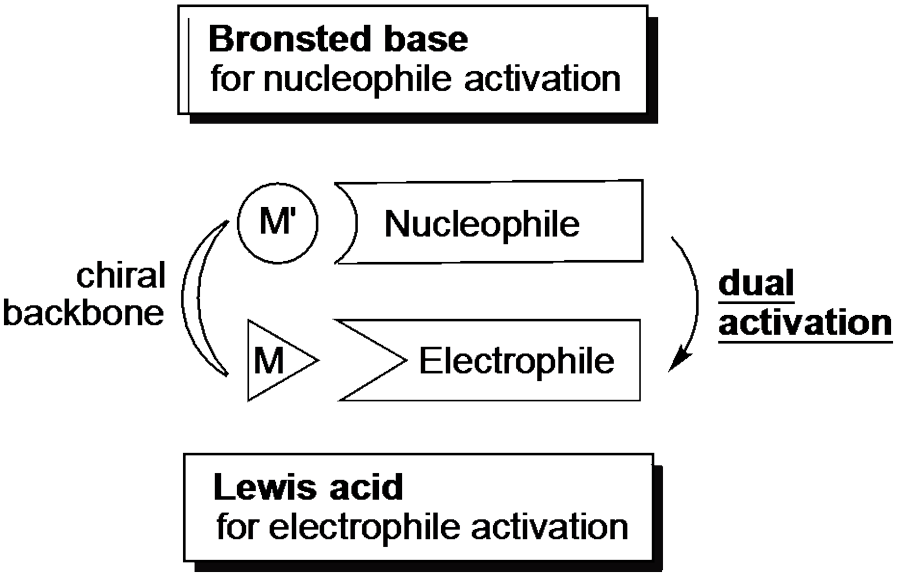


Bronsted acid

Lewis acid

Bronsted base

Chiral Heterobimetallic Catalysts



Bronsted base
for nucleophile activation

Nucleophile

chiral
backbone

Electrophile

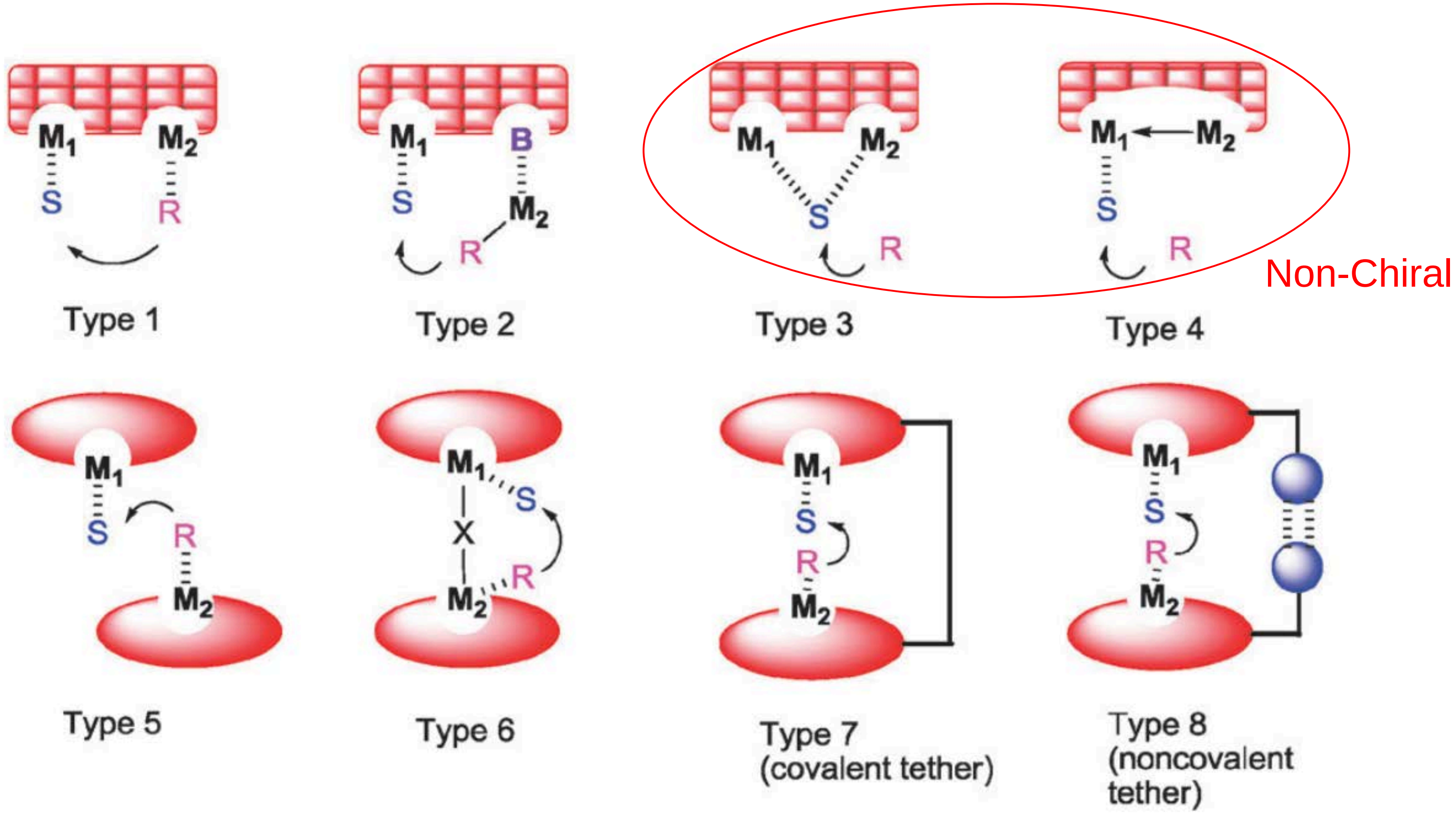
dual
activation

Lewis acid
for electrophile activation

Enzyme Catalysis in Organic Synthesis, ed. P. T. Anastas and R. H. Crabtree, Wiley-VCH, Weinheim, **2009**

Bimetallic cooperative catalysts

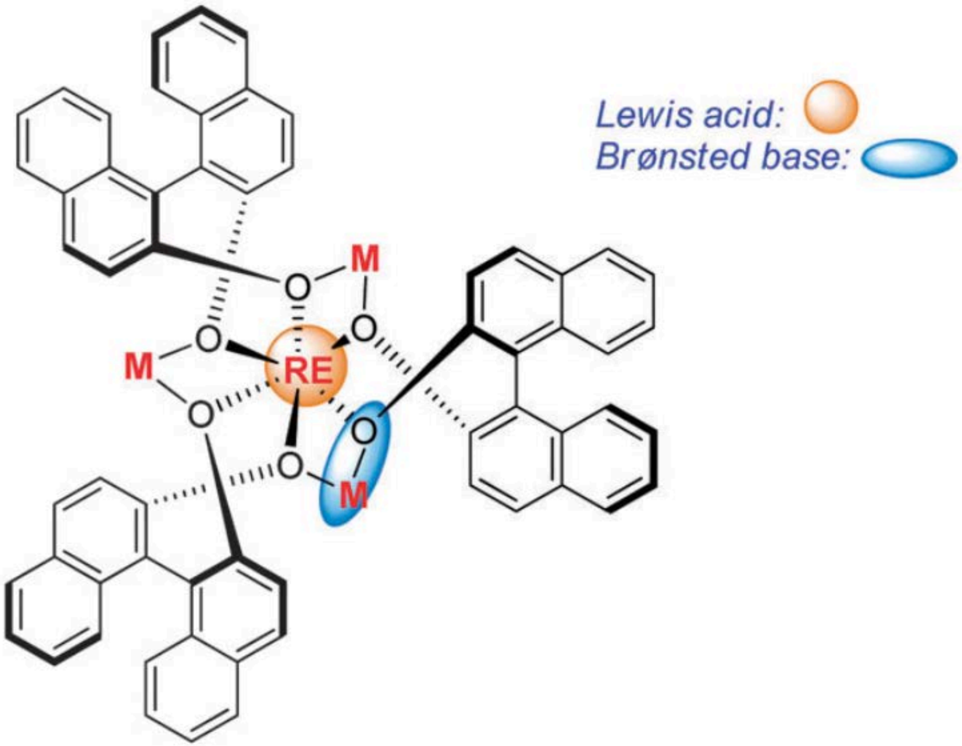
- Alkali metals
- Transition metals
- Lanthanide metals



Non-Chiral

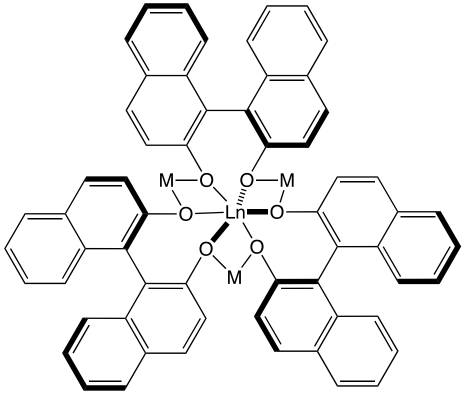
Jongwoo Park and Sukwon Hong, *Chem. Soc. Rev.*, **2012**, *41*, 6931

BINOL-based heterobimetallic catalysts



RE = La, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Yb, Y
M = Li, Na, K

Applications of heterobimetallic lanthanoid complexes in asymmetric catalysis



(R)-LnMB

Asymmetric C-C bond formation:

- Nitroaldol reaction
- Aldol reaction
- Michael addition reaction
- Diels-Alder reaction

Asymmetric C-O bond formation:

- Epoxidation of enones

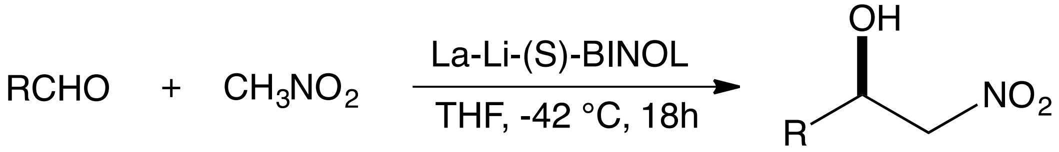
Chiral Heterobimetallic
Lanthanoid Catalysts
LnMB

Asymmetric C-P bond formation:

- Hydrophosphonylation of aldehydes
- Hydrophosphonylation of imines

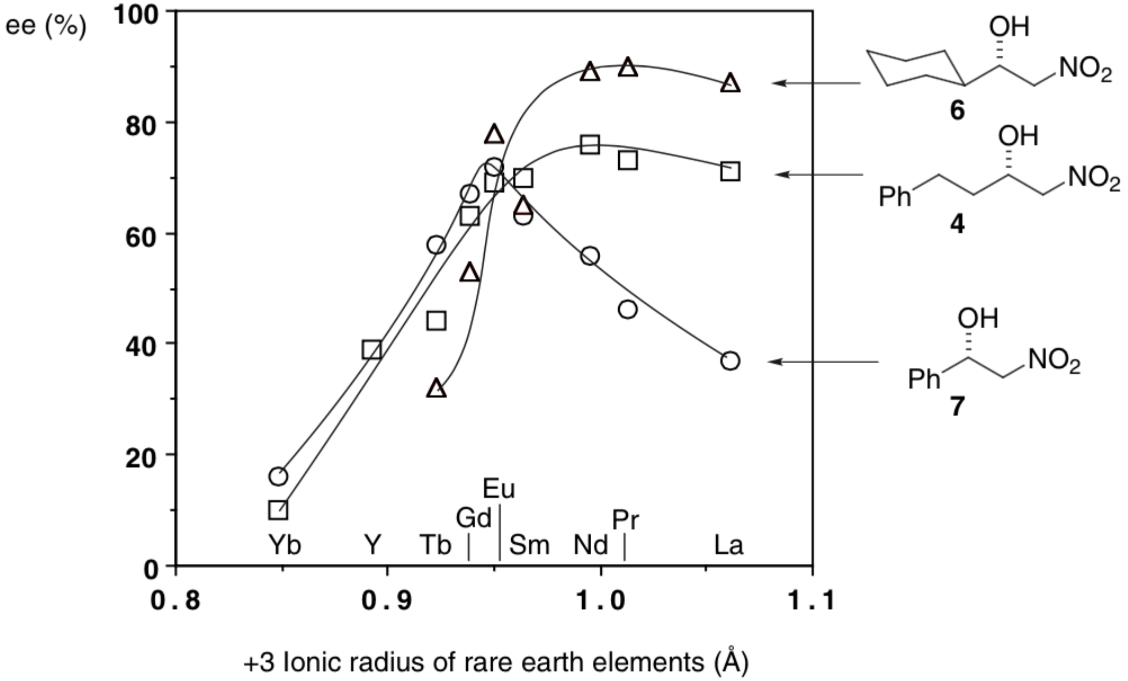
C-C Bond Formation using LnMB

Nitroaldol Reaction



R_1 = $PhCH_2CH_2$ 79% (73% ee)
R_2 = *i*Pr 80% (85% ee)
R_3 = cyclohexyl 91% (90% ee)

Effect of the ionic radii of rare earth elements on the enantioselectivity

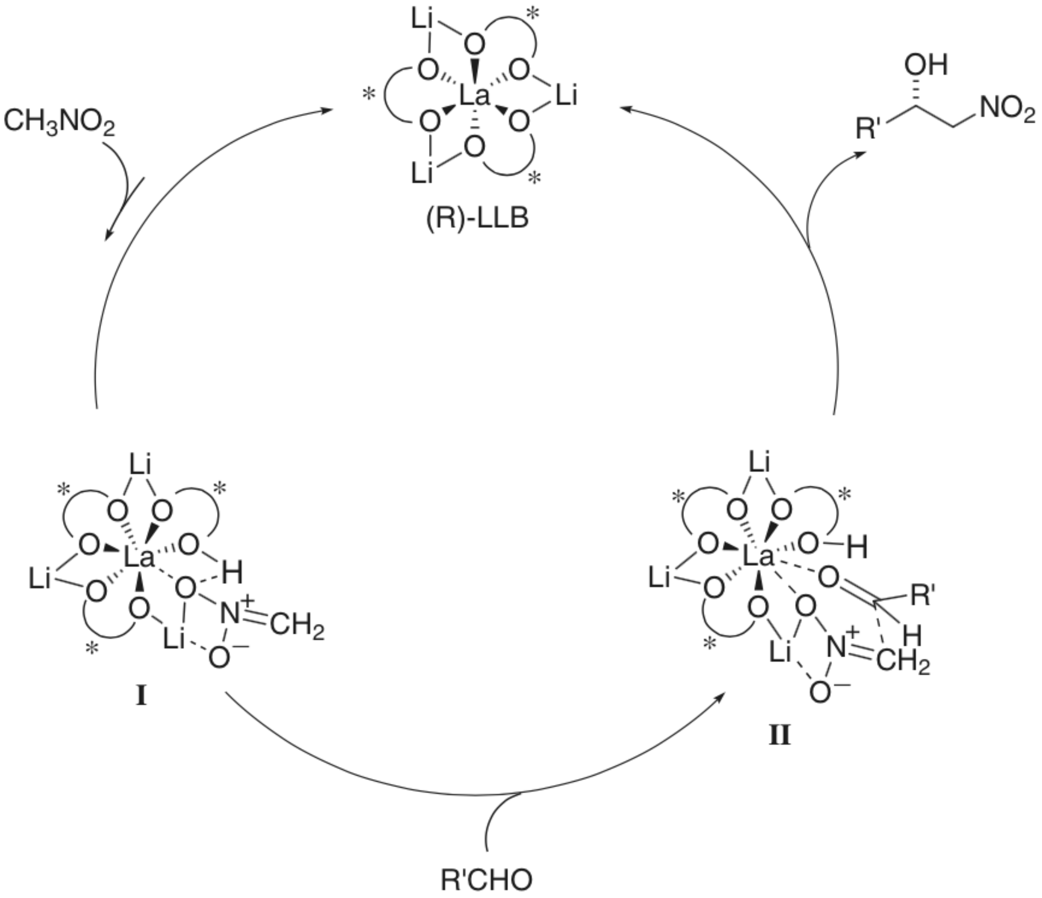


Sasai H, Suzuki T, Arai S, Arai T, Shibasaki M, *J Am Chem Soc*, **1992,** 114, 4418

C-C Bond Formation using LnMB

Nitroaldol Reaction

Proposed mechanism for catalytic nitroaldol reactions with nitromethane



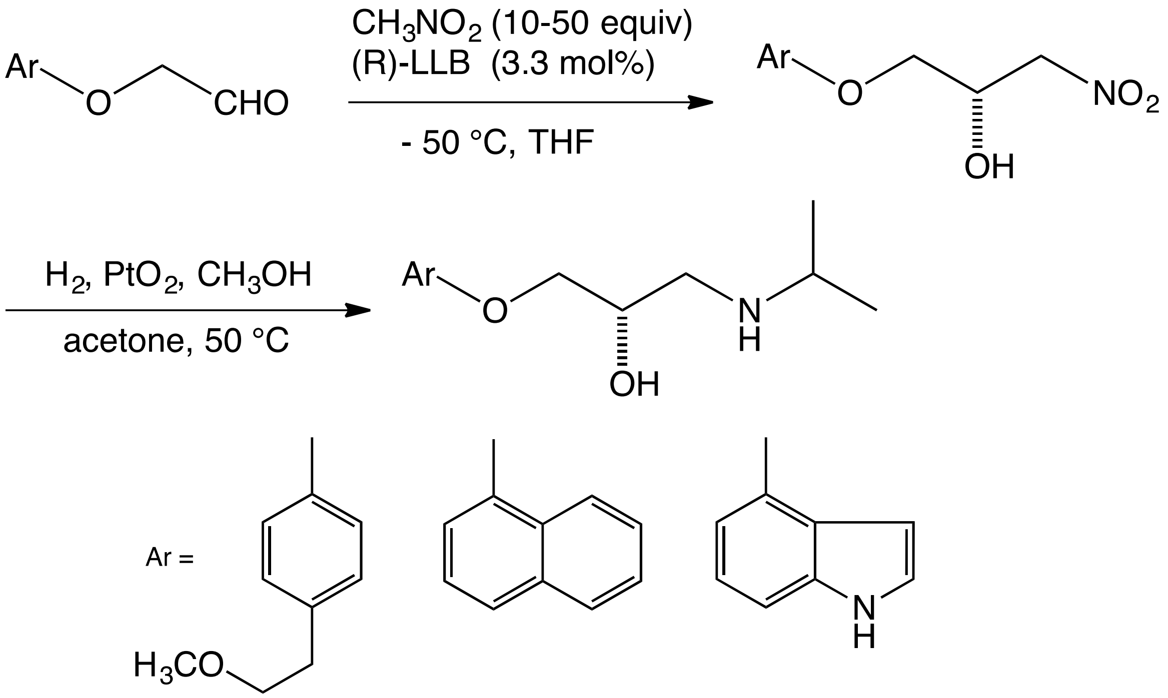
Shibasaki M, Sasai H, Arai T (1997) Angew Chem 109:1290; Angew Chem Int Ed Engl, 36:1236

C-C Bond Formation using LnMB

Nitroaldol Reaction

Enantioselective catalytic nitroaldol reaction

Synthesis of betablockers



(S) Configuration
Si face attack

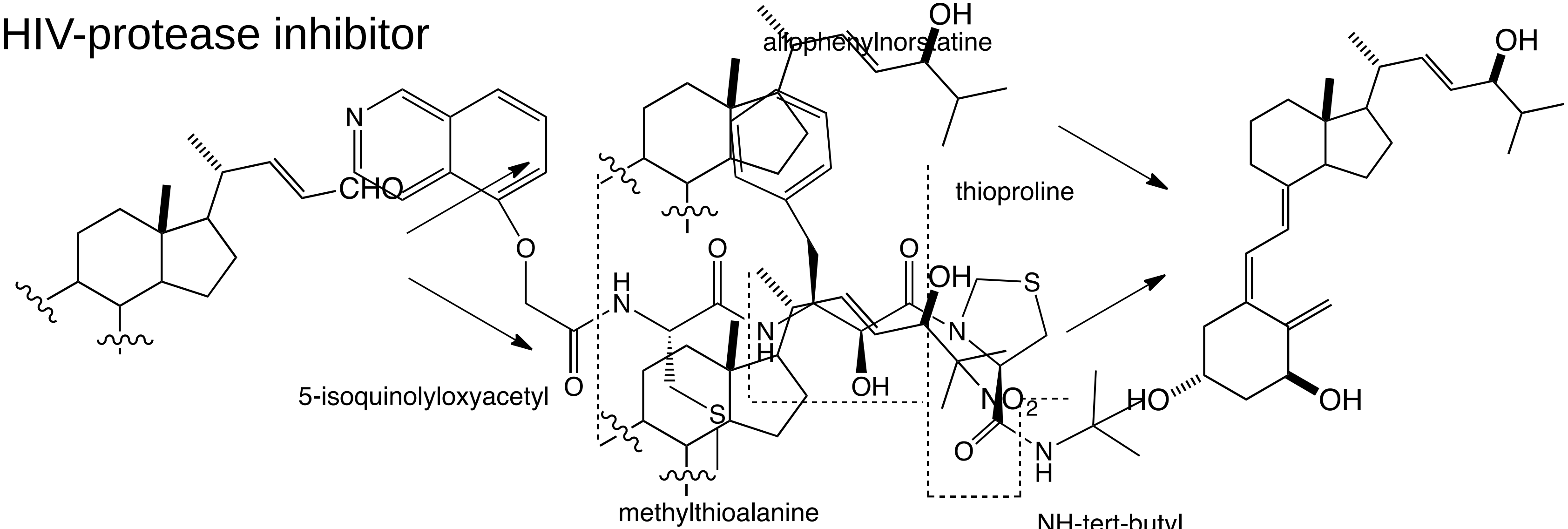
Sasai H, Suzuki T, Itoh N, Arai S, Shibasaki M (1993) Tetrahedron Lett 34:2657

C-C Bond Formation using LnMB

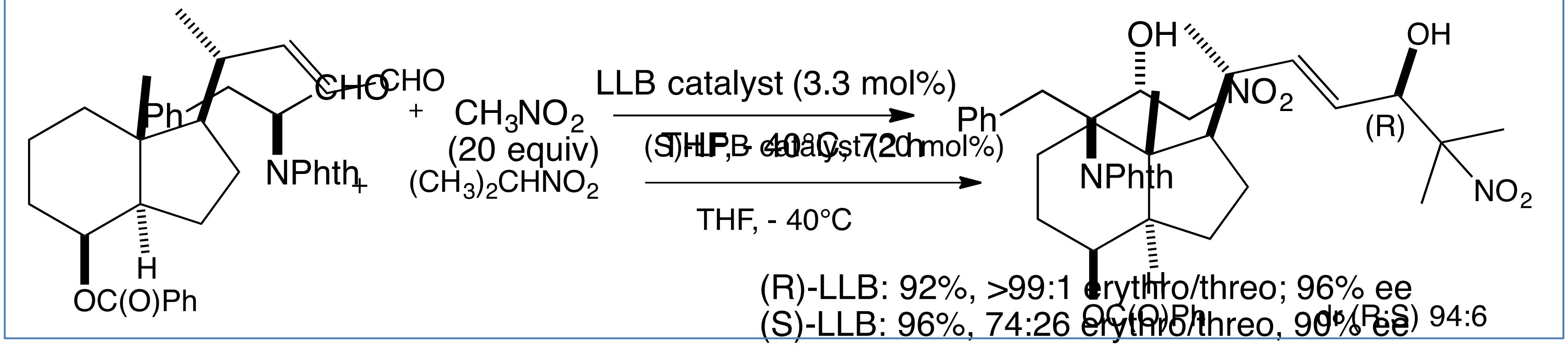
Nitroaldol Reaction

Diastereoselective catalytic nitroaldol reaction

HIV-protease inhibitor



hydroxyvitamin D_3



CH_3NO_2 (20 equiv)

LLB catalyst (3.3 mol%)

THF, - 40°C, 72 h

$(CH_3)_2CHNO_2$

(S)-LLB catalyst (20 mol%)

THF, - 40°C

(R)-LLB: 92%, >99:1 erythro/threo; 96% ee

(S)-LLB: 96%, 74:26 erythro/threo, 90% ee

dr (R:S) 94:6

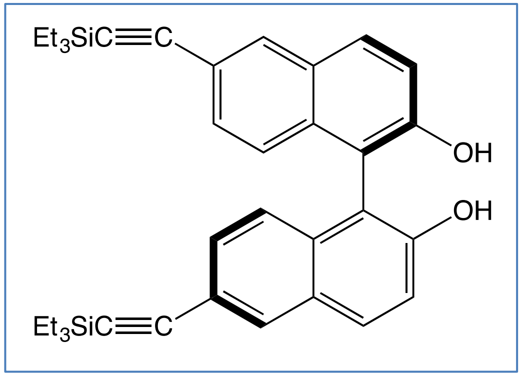
Oshida J, Okamoto M, Azuma S, Tanaka T (1997) Tetrahedron Asymmetry 8:2579

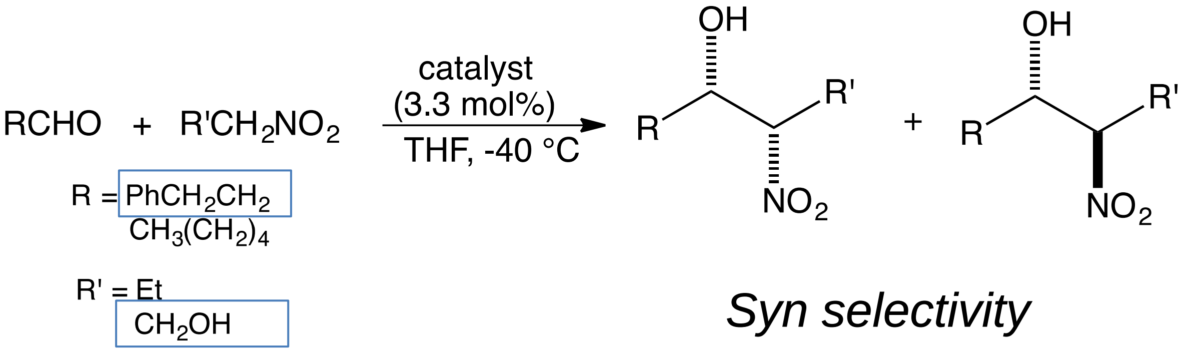
SasaiH,KimWS,SuzukiT,ShibasakiM,MitsudaM,HasegawaJ,OhashiT (1994) Tetrahedron Lett 35:6123

C-C Bond Formation using LnMB

Nitroaldol Reaction

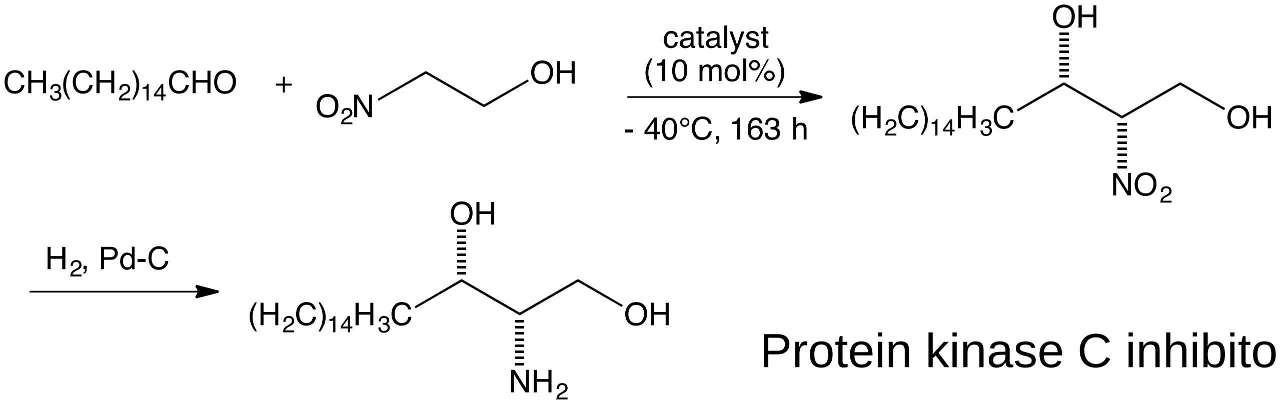
Diastereoselective nitroaldol reaction from prochiral materials





Syn selectivity

92:8

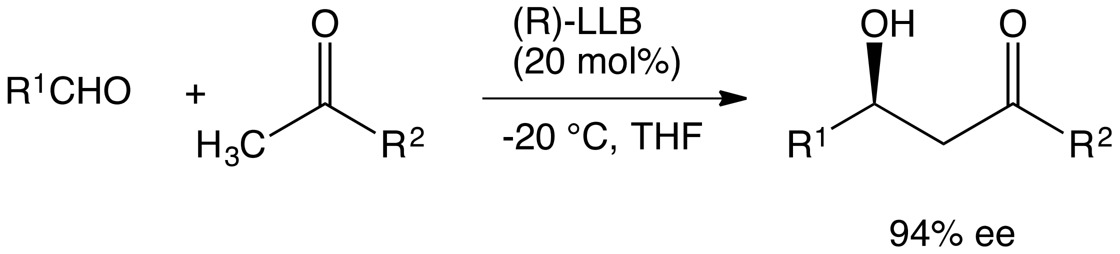


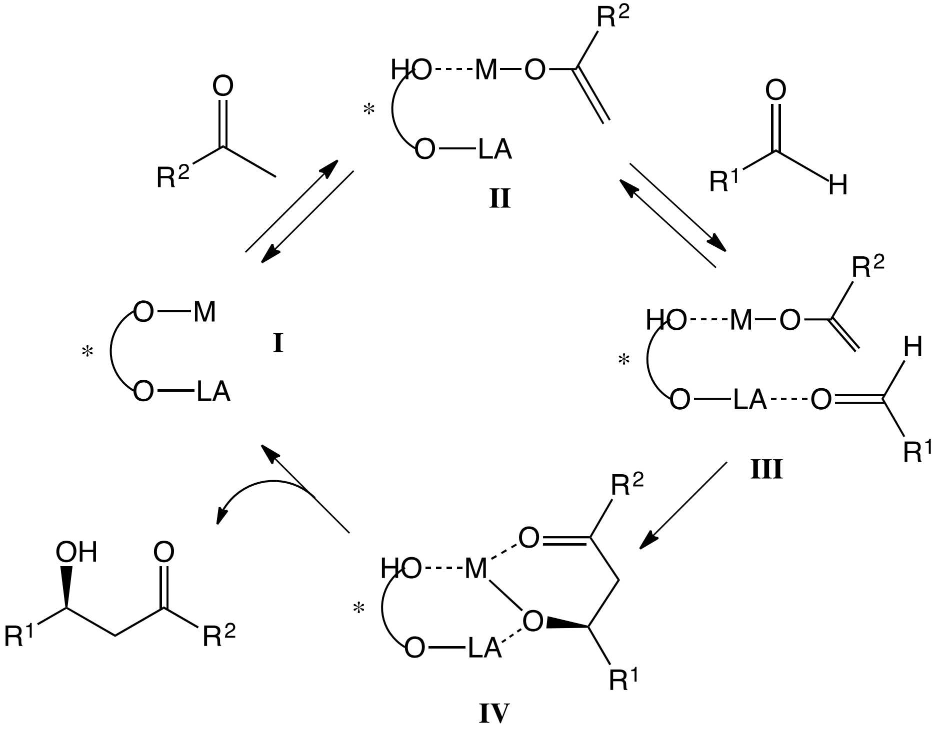
Protein kinase C inhibitor

Sasai H, Tokunaga T, Watanabe S, Suzuki T, Itoh N, Shibasaki M (1995) J Org Chem 60:7388

C-C Bond Formation using LnMB

Direct aldol Reaction



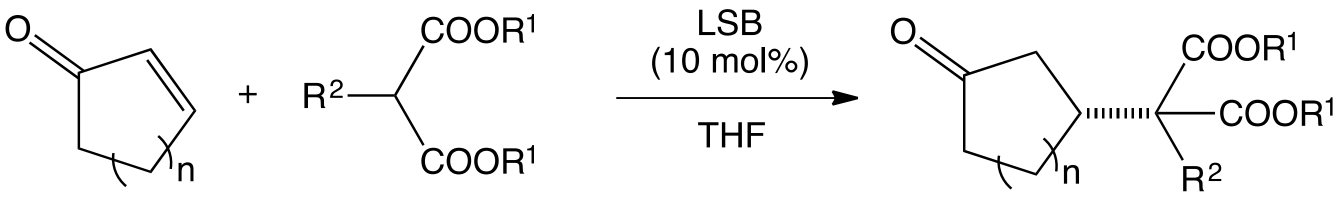


LA = Lewis Acid
M = Metal of Bronsted base

Yamada YMA, Yoshikawa N, Sasai H, Shibasaki M (1997) Angew Chem 109:1942; Angew Chem Int Ed Engl 36:1871

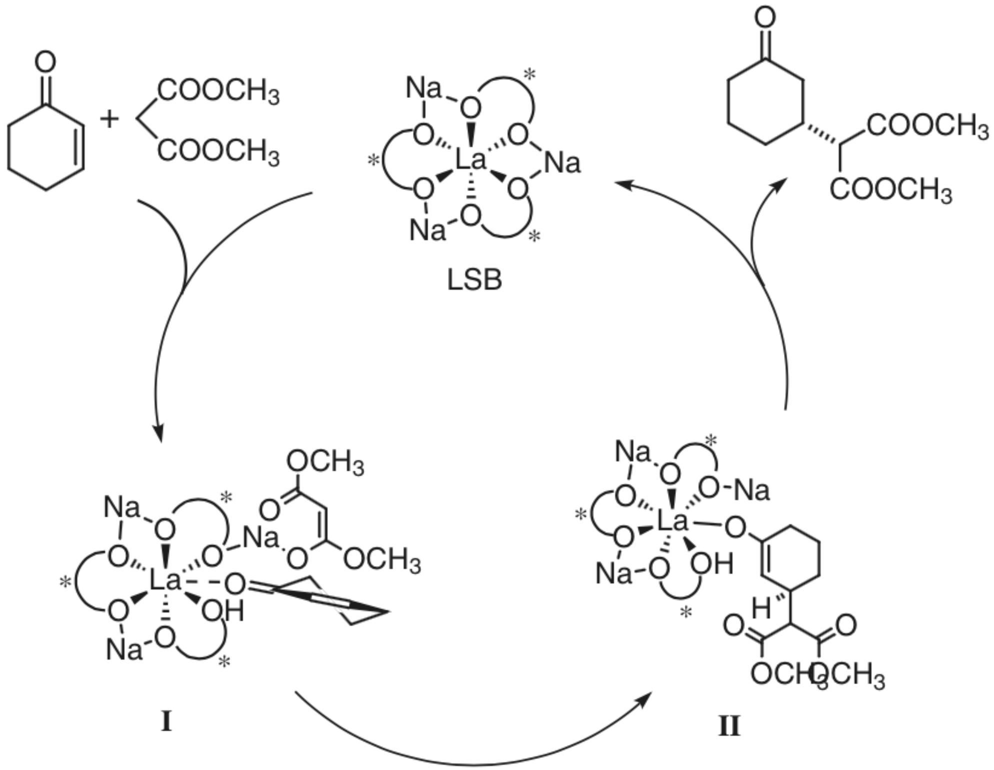
C-C Bond Formation using LnMB

LnSB-catalyzed asymmetric Michael addition



n = 1,2

^{1}H-NMR:
PrSB large shift of alfa proton of cyclohexenone
EuSB no changes



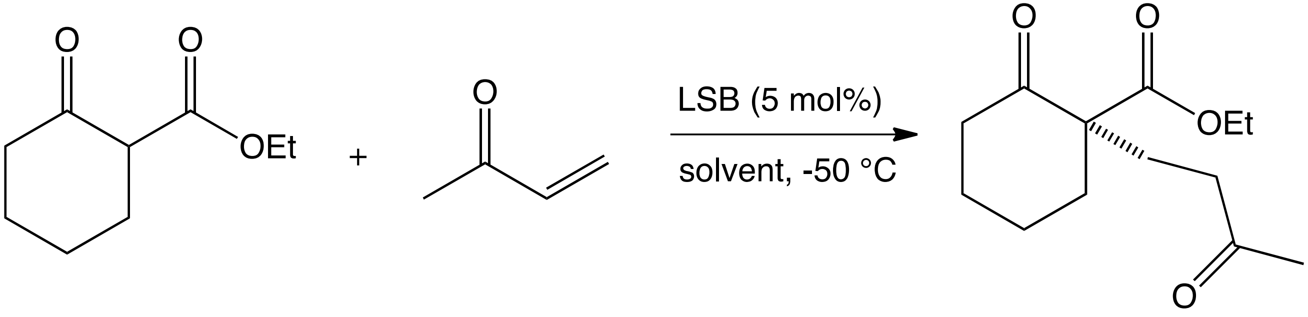
LSB vs LLB

Sasai H., Arai T., Satow Y., Houk K. N., Shibasaki M., *J Am Chem Soc*, **1995**, 117, 6194

C-C Bond Formation using LnMB

LnSB-catalyzed asymmetric Michael addition

Importance of solvent with beta-keto ester



Malonates vs
beta-keto ester

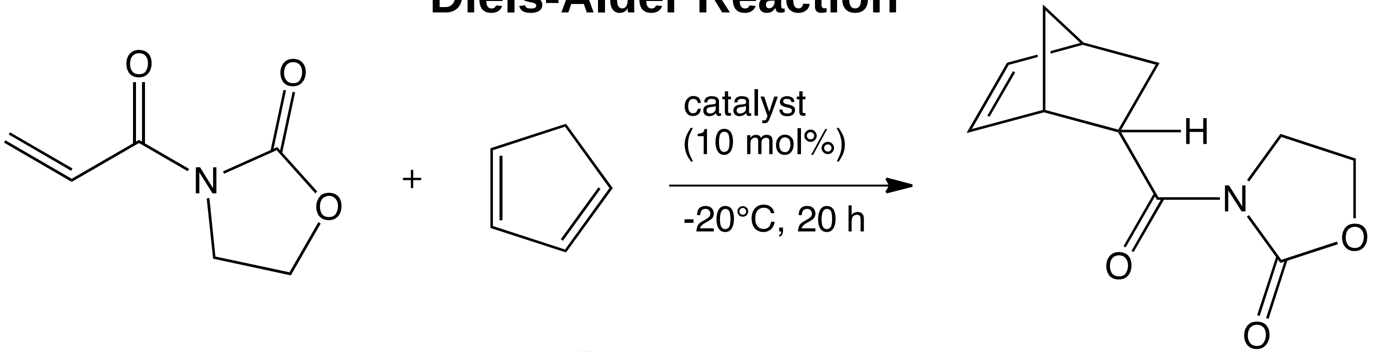
THF → very low ee

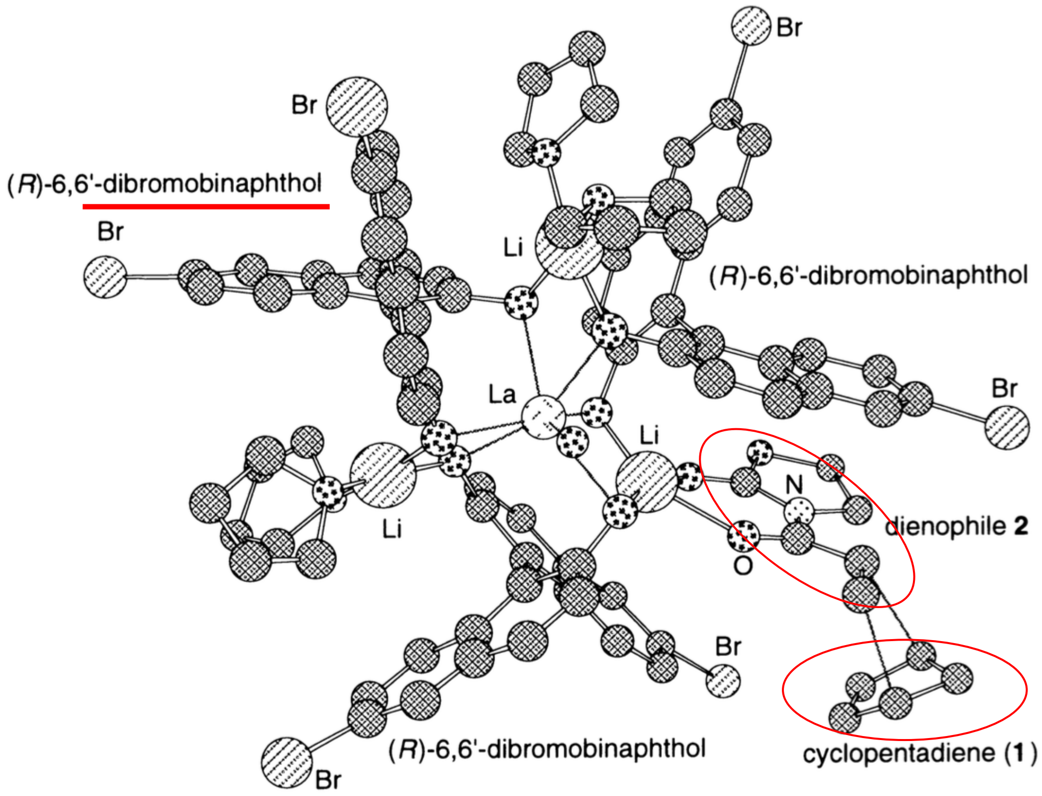
solvent	yield	ee
toluene	83%	25%
toluene (slow addition of Nu)	76%	89%
CH_2Cl_2	89%	91%

Sasai H ,Emori E, Arai T, Shibasaki M, *Tetrahedron Lett.*, **1996**, 37, 5561

C-C Bond Formation using LnMB

Diels-Alder Reaction





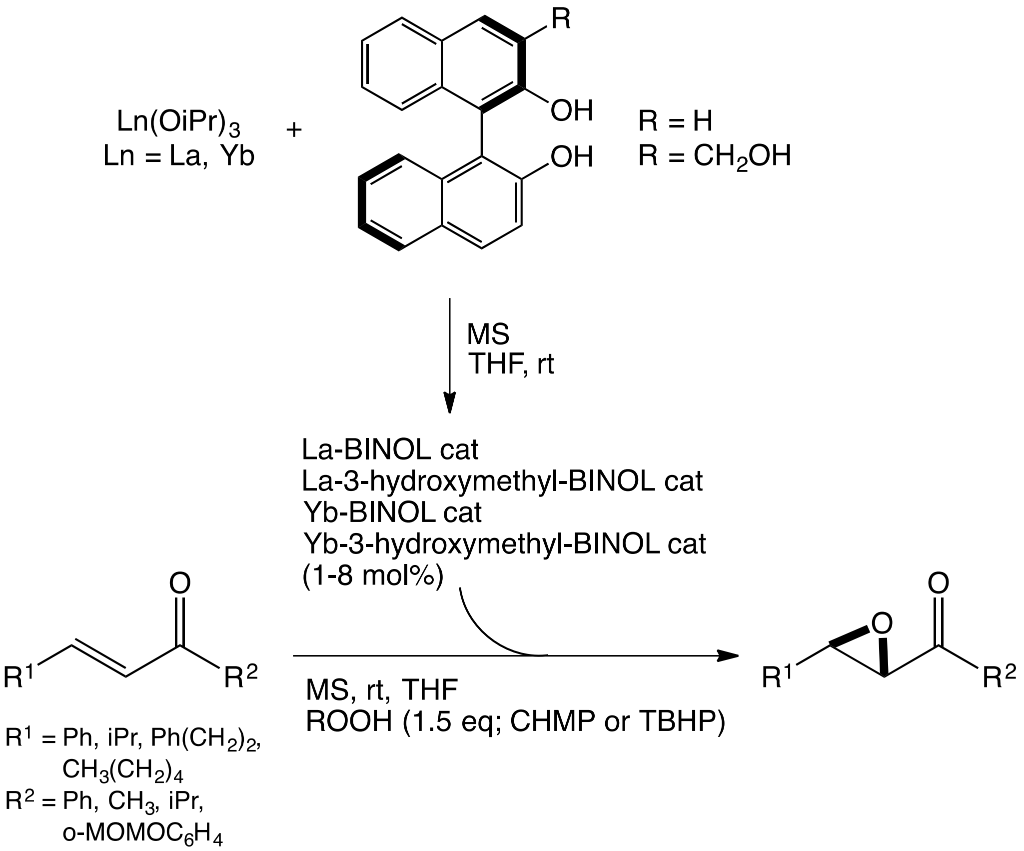
Mechanism for enantioselection:

LLB as Lewis acidic catalyst
Through Lithium

Morita T, Arai T, Sasai H, Shibasaki M (1998) Tetrahedron: Asymmetry 9:1445i

C-O Bond Formation

Epoxidation of enones

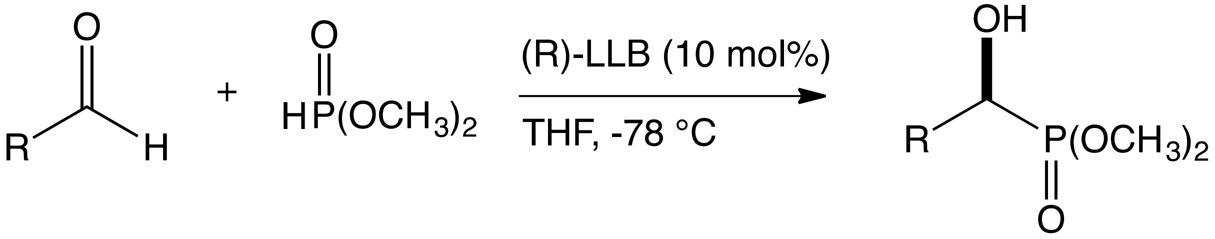


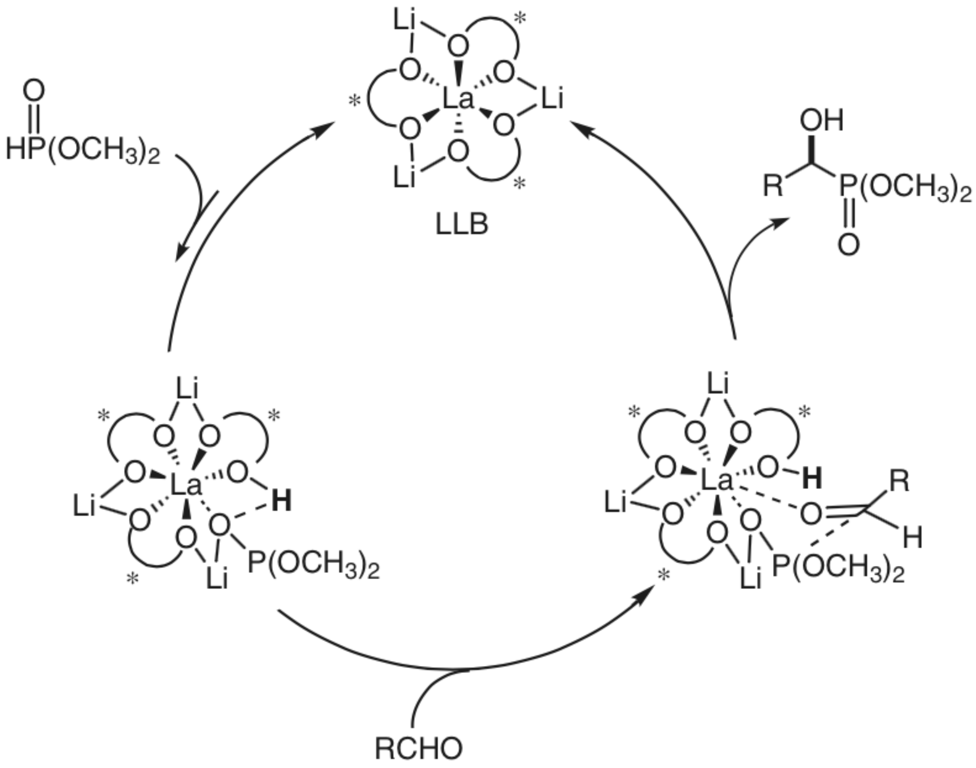
Alkali metal free → Oligomeric structure: Ln-alkoxide moiety as Bronsted base
Ln metal ion as Lewis acid

Bougauchi M, Watanabe S, Arai T, Sasai H, Shibasaki M (1997) J Am Chem Soc, 119:2329

C-P Bond Formation using LnMB

Hydrophosphonylation of aldehydes





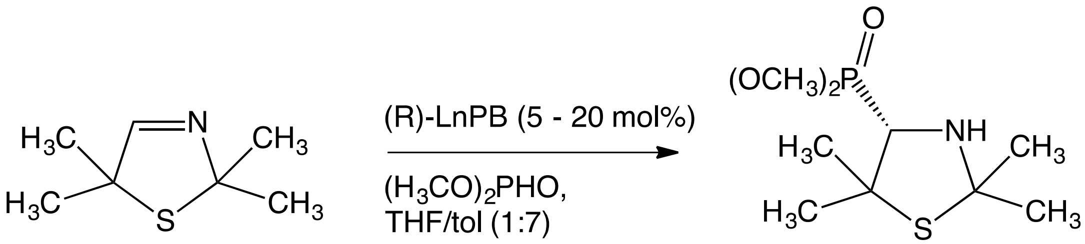
Good results with p-methoxybenzaldehyde

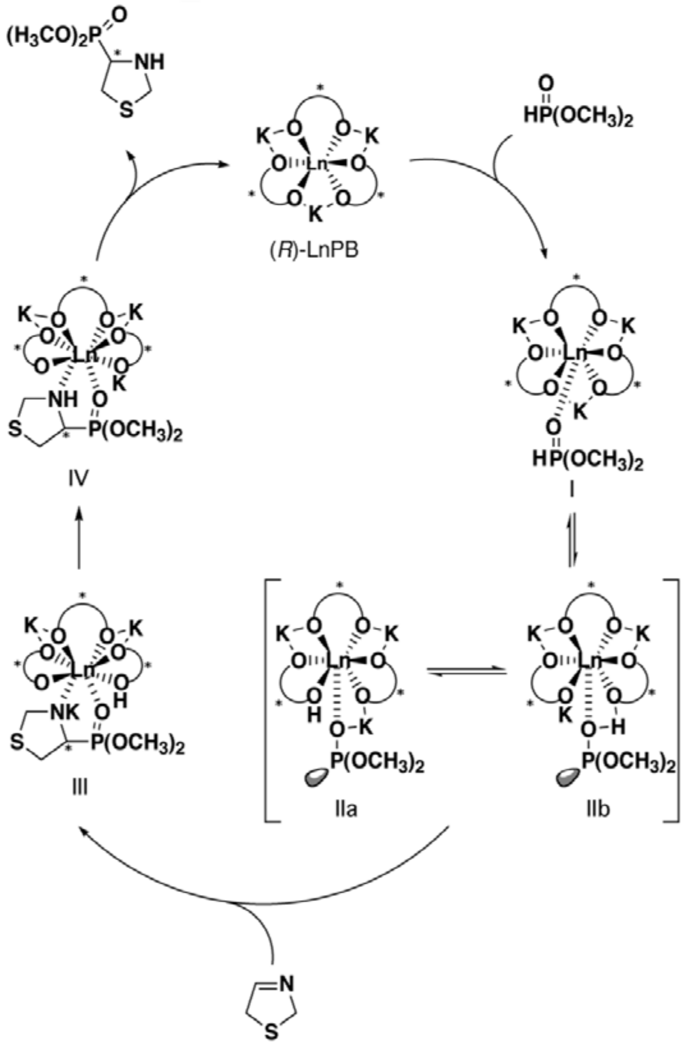
Slow addition of reactive aldehydes

Sasai H, Bougauchi M, Arai T, Shibasaki M, 1997 Tetrahedron Lett 38:2717

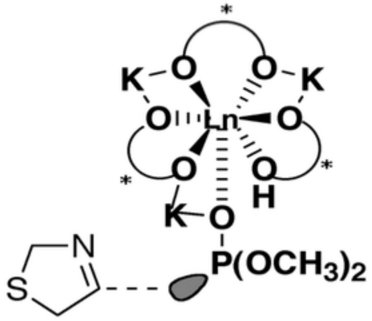
C-P Bond Formation using LnMB

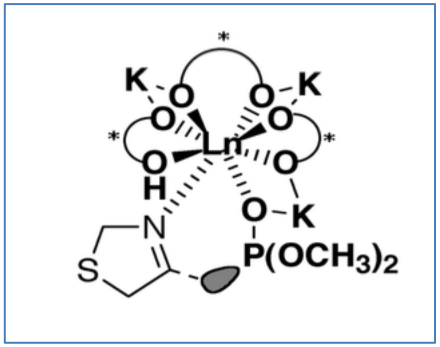
Hydrophosphonylation of imines





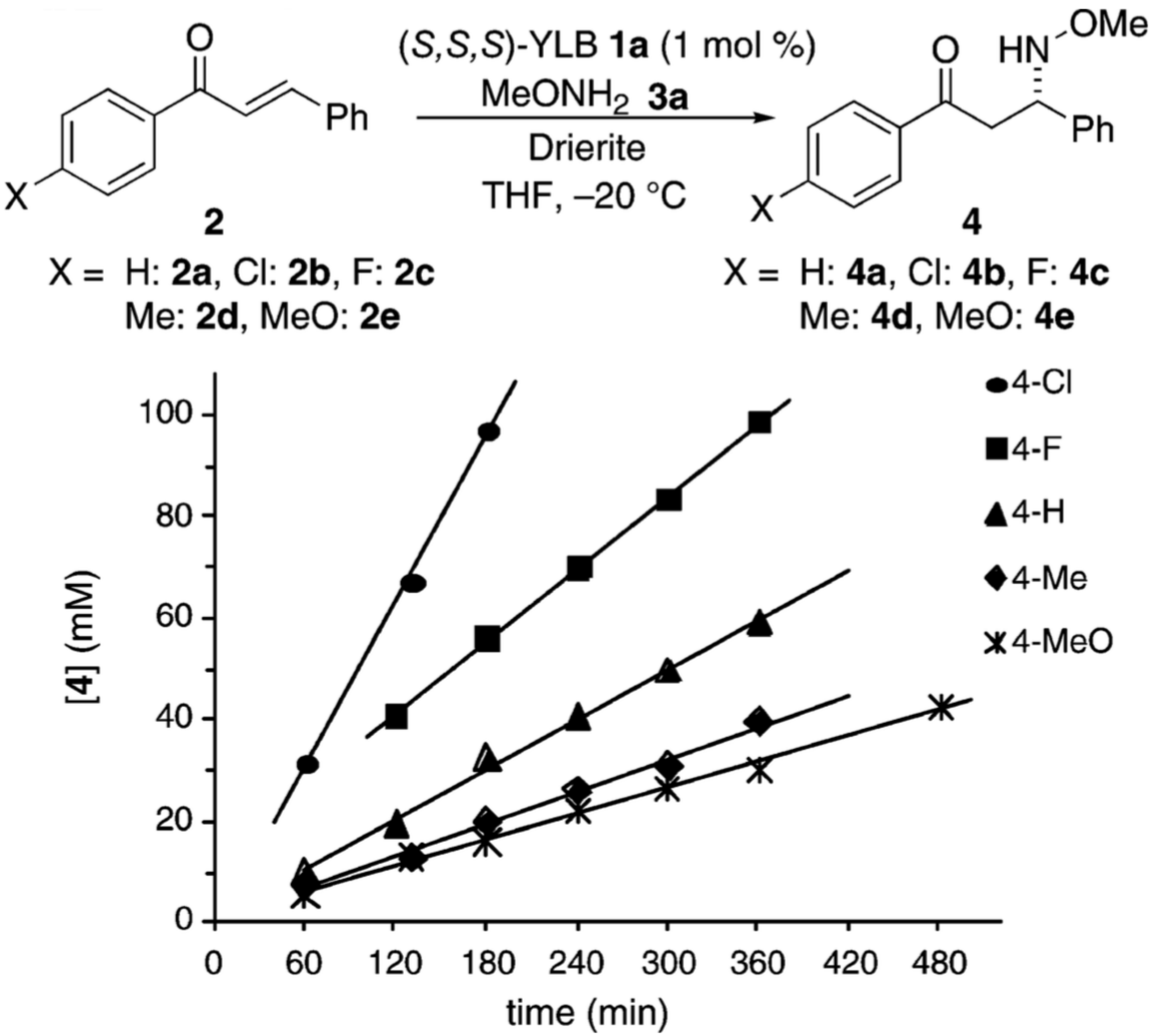
Addition step





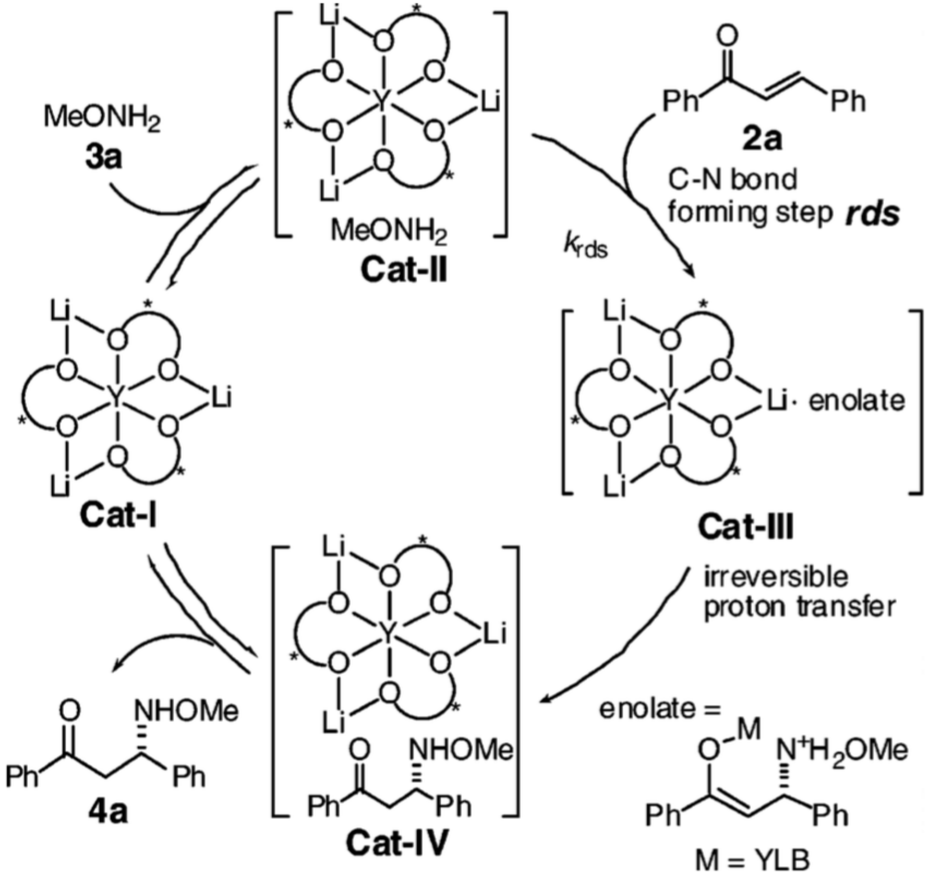
Gröger H, Saida Y, Arai S, Martens J, Sasai H, Shibasaki M, *Tetrahedron Lett.*, **1996**, *37*, 9291

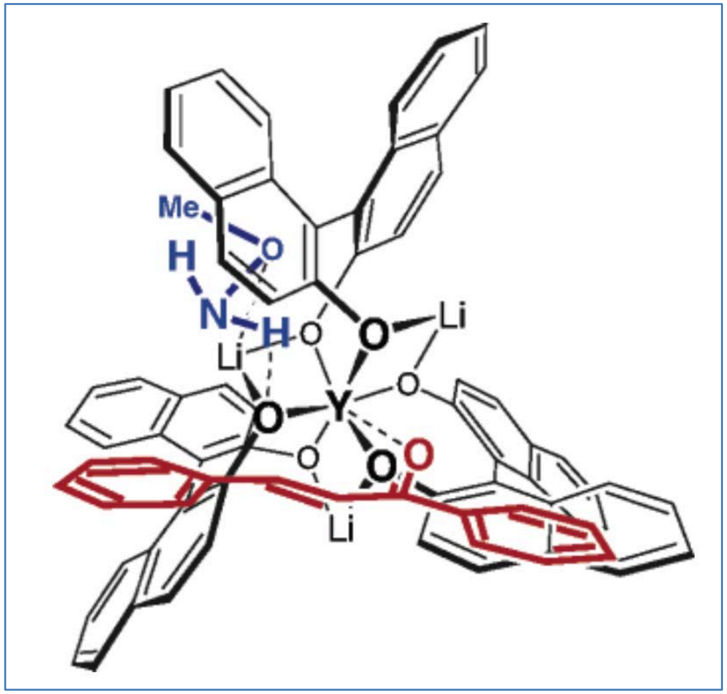
Lewis acid - Lewis acid cooperative catalysis



M. Shibasaki, *J. Am. Chem. Soc.*, **2005**, *127*, 13419

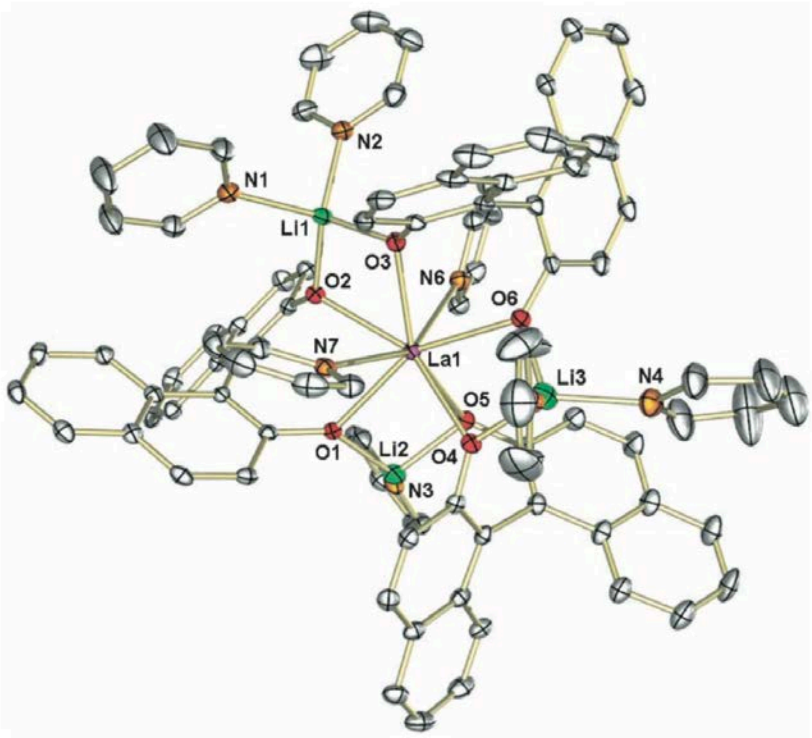
Lewis acid - Lewis acid cooperative catalysis



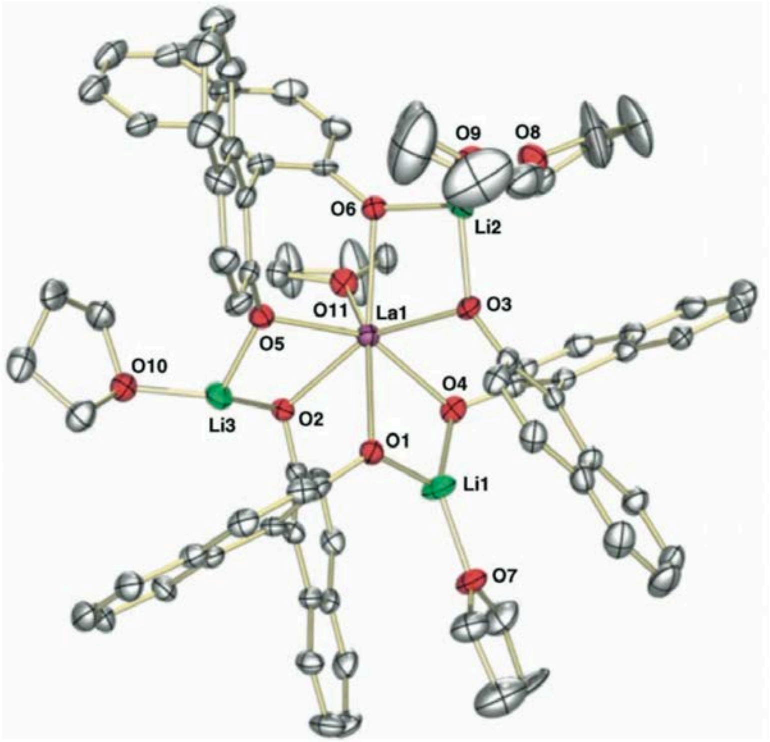


M. Shibasaki, *J. Am. Chem. Soc.*, **2005**, *127*, 13419

Lewis acid - Lewis acid cooperative catalysis



$[Li_3(py)_5(binolate)_3La(py)_2]$

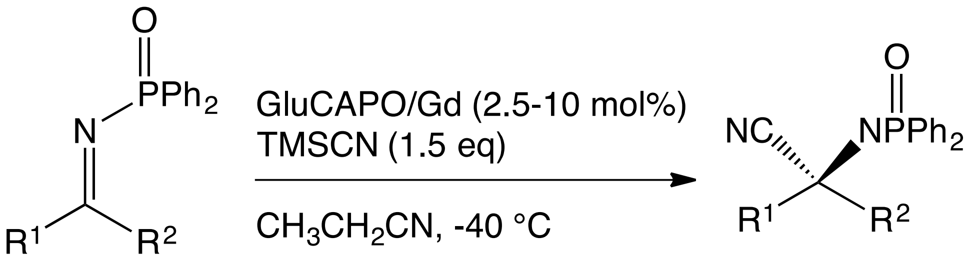


Structure of $[Li_3(thf)_4(binolate)_3La(thf)]$

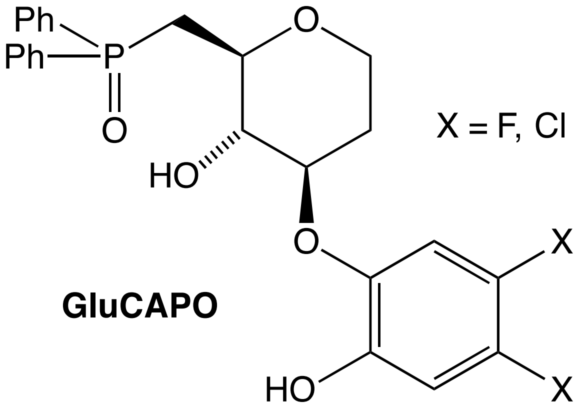
P. J. Walsh, *Angew. Chem., Int. Ed.,* **2006**, *45*, 2549

Bimetallic catalyst Ln-Ln

Catalytic Enantioselective Strecker Reaction of Ketoimines



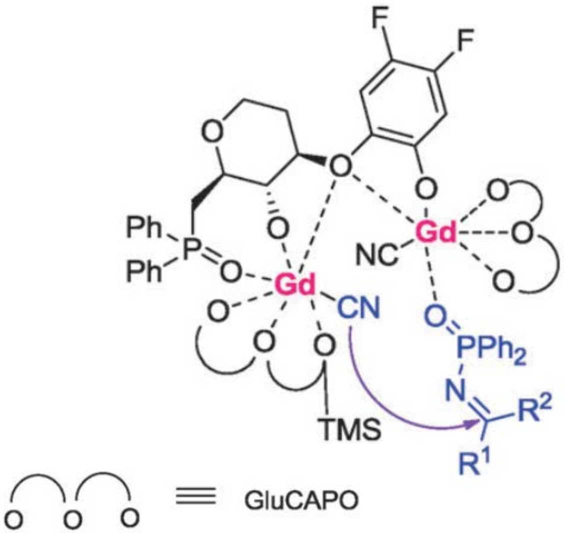
(S)-compound
58-100% yield
51-98% ee



GluCAPO

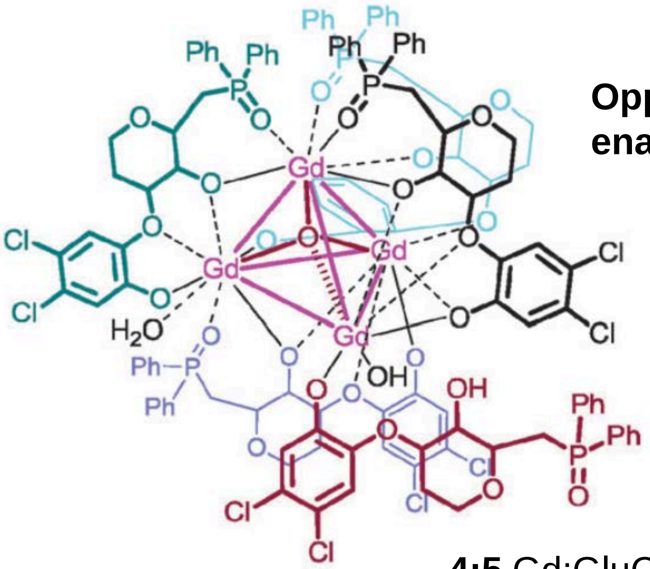
X = F, Cl

Bimetallic activation proposed



2:3 Gd:GluCAPO

Crystalized species



Opposite enantioselection

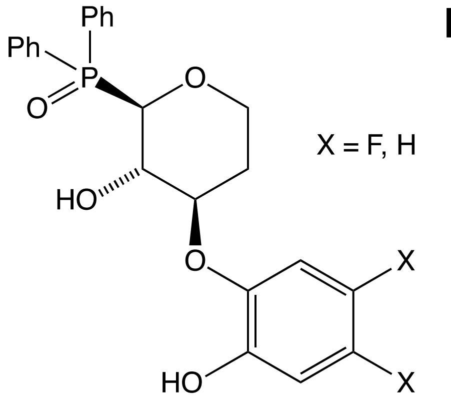
4:5 Gd:GluCAPO

S. Masumoto, H. Usuda, M. Suzuki and M. Shibasaki, *J. Am. Chem. Soc.*, **2003**, *125*, 5634

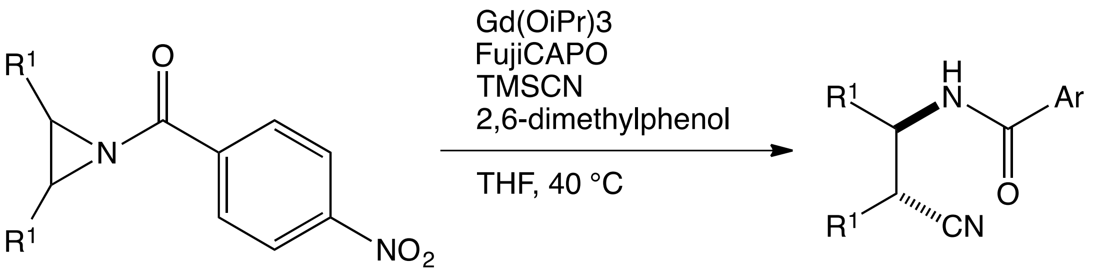
Bimetallic catalyst Ln-Ln

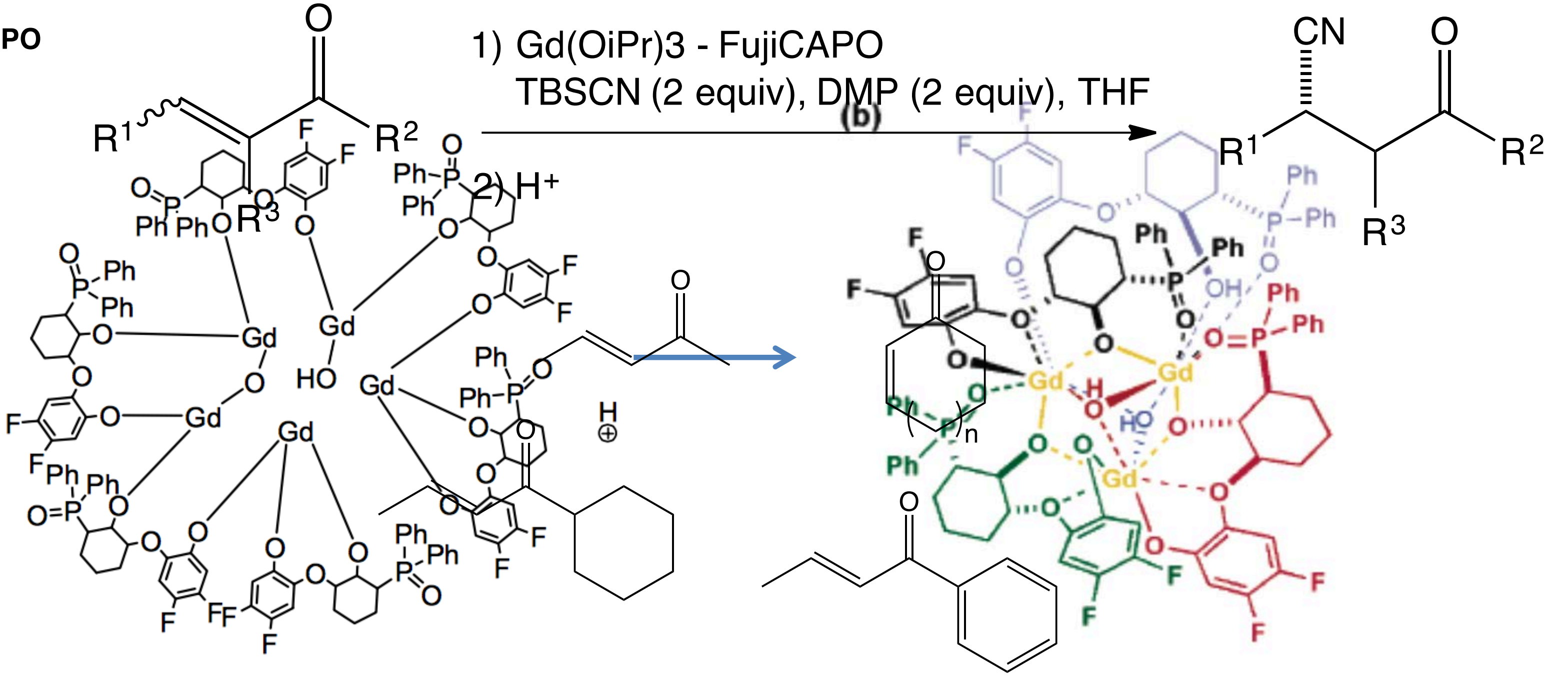
Ring-Opening Reaction of meso-Aziridines

Conjugate addition of Cyanide to enones



FujiCAPO





Reverse enantioselectivity respect to GluCAPO

I. Fujimori, T. Mita, K. Maki, M. Shiro, A. Sato, and M. Shibasaki, *J. Am. Chem. Soc.*, **2006**, 128, 16438

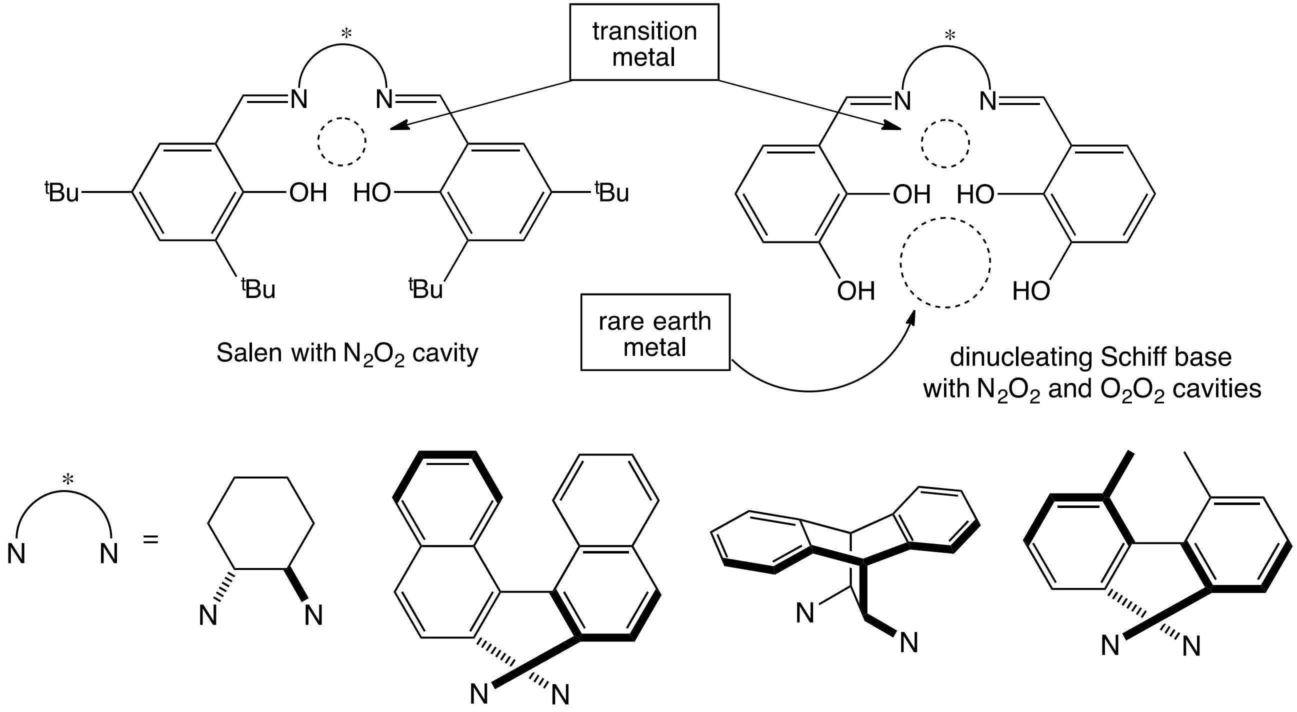
M. Shibasaki, *J. Am. Chem. Soc.*, **2008**, 130, 6072

Bimetallic catalyst with Schiff base ligands

BINOL-based ligands: alkali metals, rare earth metals, group 13 metals, Zn

Mn, Co, Ni, Cu not suitable

Salen complexes


transition metal

rare earth metal

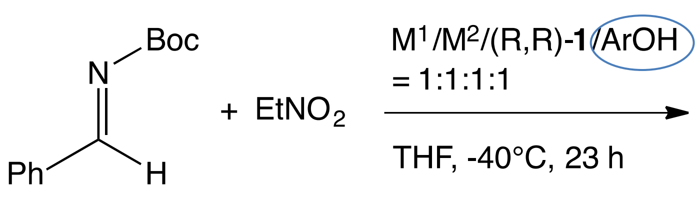
Salen with N_2O_2 cavity

dinucleating Schiff base with N_2O_2 and O_2O_2 cavities

The positions of the two metals affect the reactivity and stereoselectivity

Bimetallic catalyst with Schiff base ligands

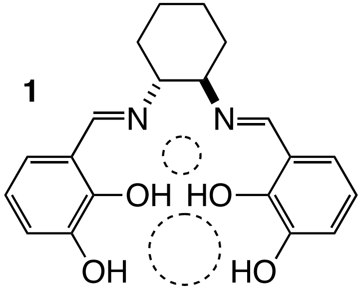
aza-Henry reaction



$M^1/M^2/(R,R)$-**1**/ArOH = 1:1:1:1

THF, -40°C, 23 h

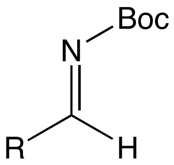
1



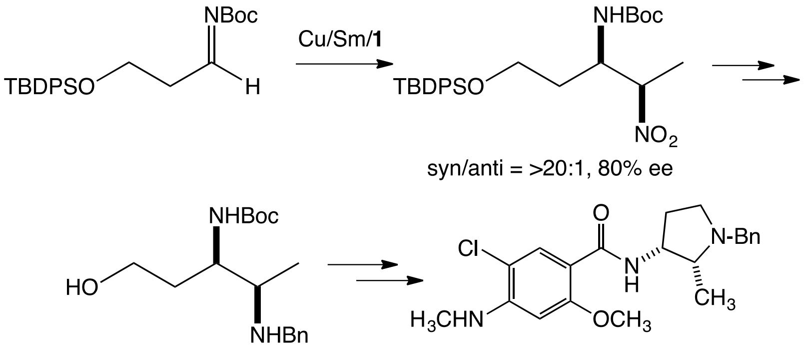
M^1= Cu(OAc)$_2$, Zn(OAc)$_2$, Mg(OAc)$_2$, Ni(OAc)$_2$
M^2= La, Pr, Sm, Eu, Dy(O-iPr)$_3$
>20:1 *syn*-selectivity, 80%ee

beta-silyloxy-substituted aliphatic imine

Substrate



R = C_6H_5, 4-Me-C_6H_4, 3-Me-C_6H_4, 4-Cl-C_6H_4, 2-Naphthyl, isobutyl

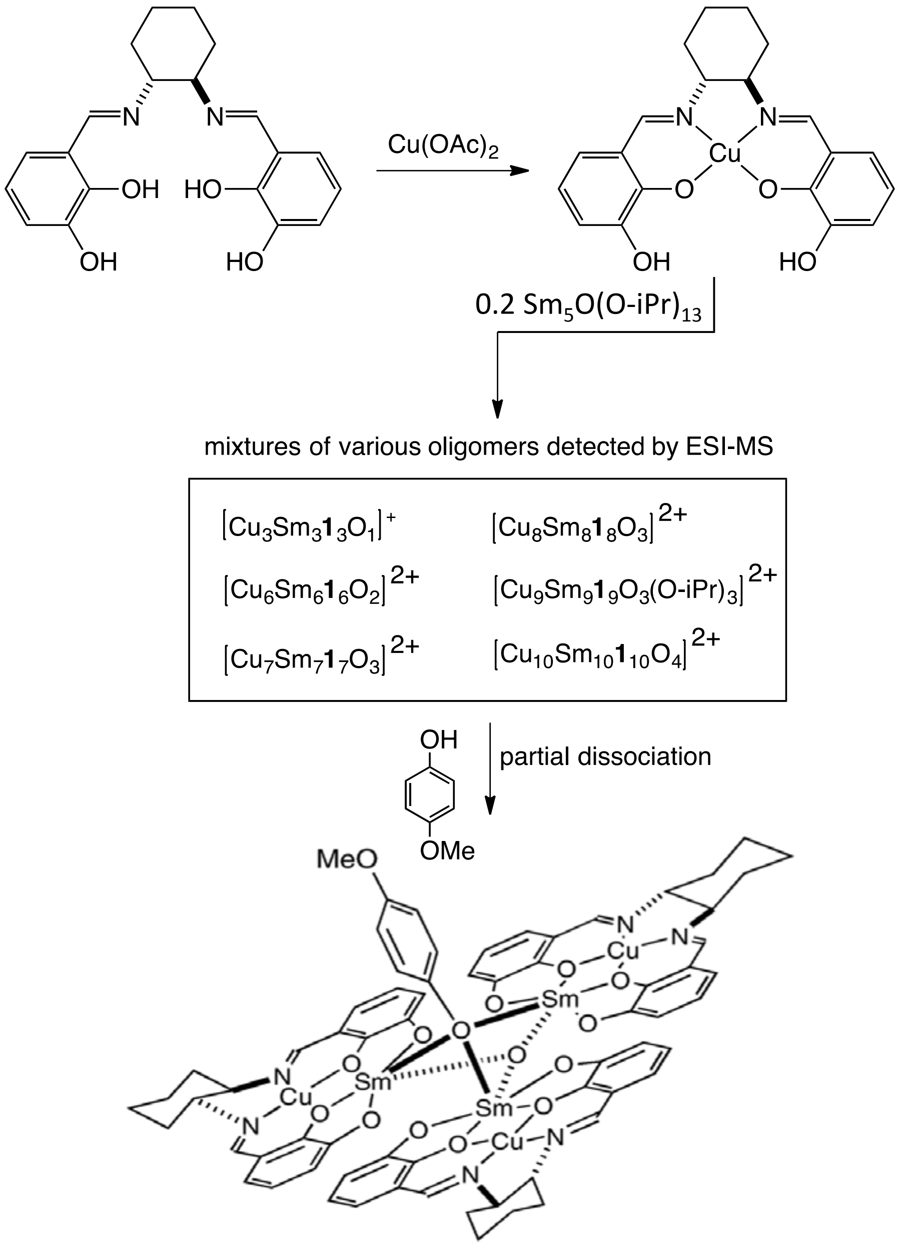


syn/anti = >20:1, 80% ee

nemonapride (antipsychotic agent)

S. Handa, V. Gnanadesikan, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, **2007**, *129*, 4900
S. Handa, V. Gnanadesikan, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, **2010**, *132*, 4925.

Bimetallic catalyst with Schiff base ligands



mixtures of various oligomers detected by ESI-MS

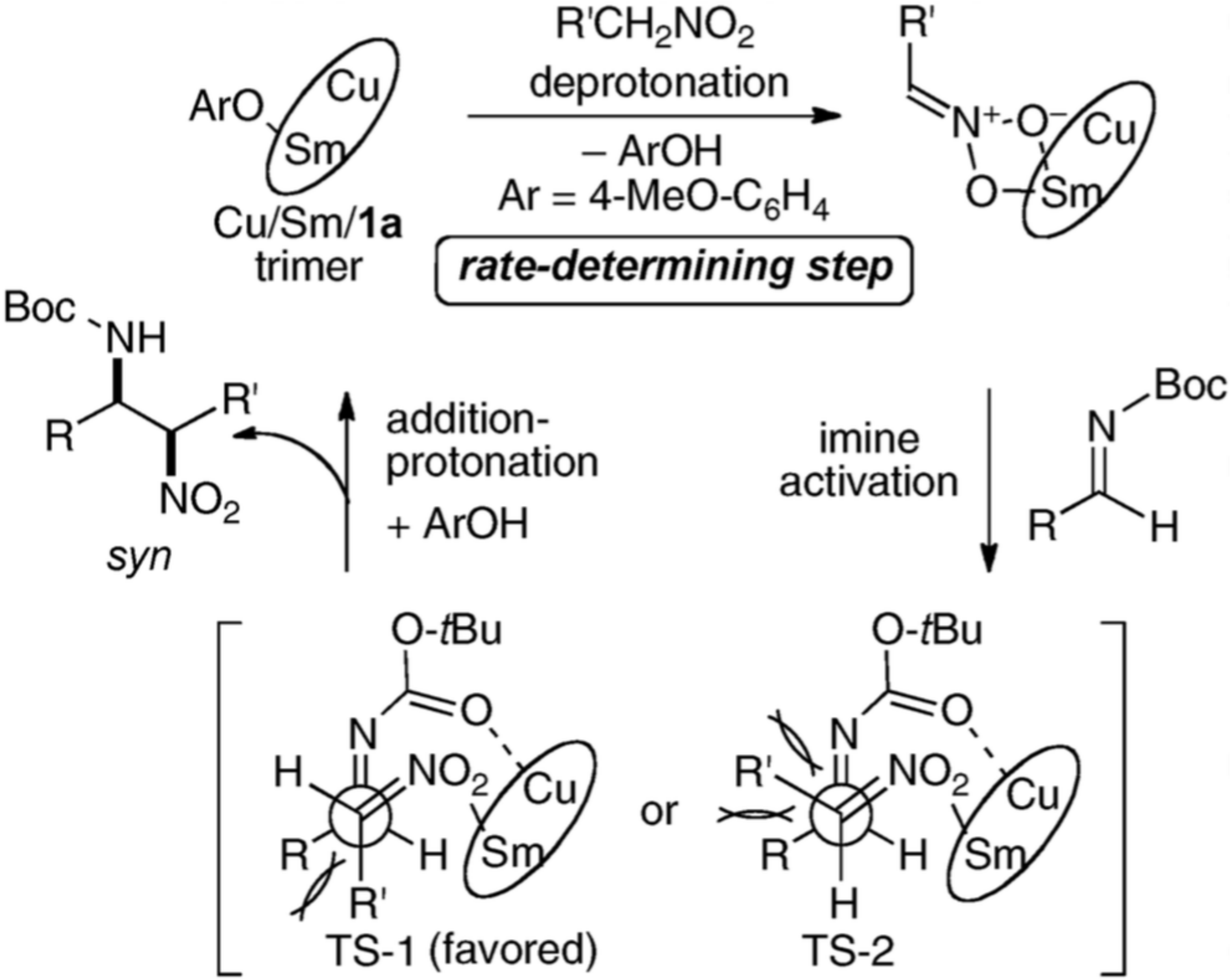
$[Cu_3Sm_3\mathbf{1}_3O_1]^+$ $[Cu_8Sm_8\mathbf{1}_8O_3]^{2+}$

$[Cu_6Sm_6\mathbf{1}_6O_2]^{2+}$ $[Cu_9Sm_9\mathbf{1}_9O_3(O\text{-}iPr)_3]^{2+}$

$[Cu_7Sm_7\mathbf{1}_7O_3]^{2+}$ $[Cu_{10}Sm_{10}\mathbf{1}_{10}O_4]^{2+}$

S. Handa, V. Gnanadesikan, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, **2010**, *132*, 4925.

Bimetallic catalyst with Schiff base ligands

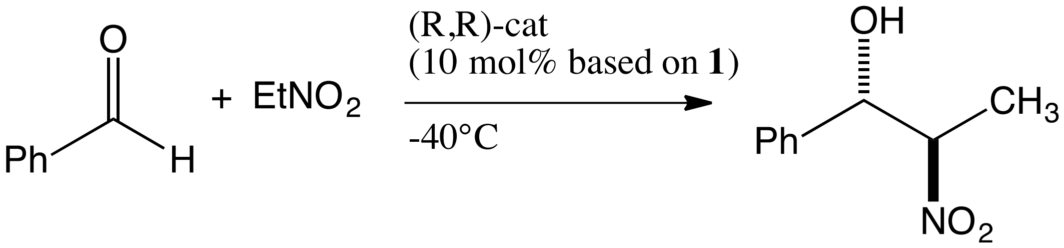


S. Handa, V. Gnanadesikan, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, **2010**, *132*, 4925.

Bimetallic catalyst with Schiff base ligands

Changing metals and phenol

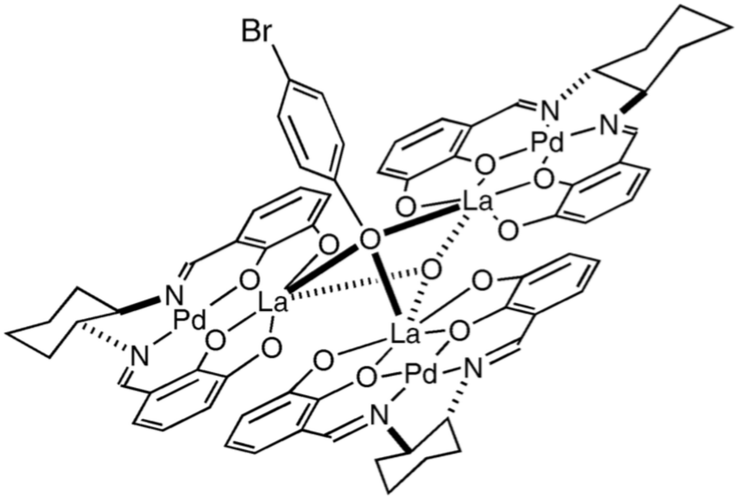
Catalyst tuning for anti-selective Henry reaction



Cu/Sm/**1**/4-*tert*-Bu-phenol: 33% yield, 1% ee, anti/syn = 2.3:1

VS

Pd/La/**1**/4-Br-phenol: 92% yield, 84% ee, anti/syn = 19:1

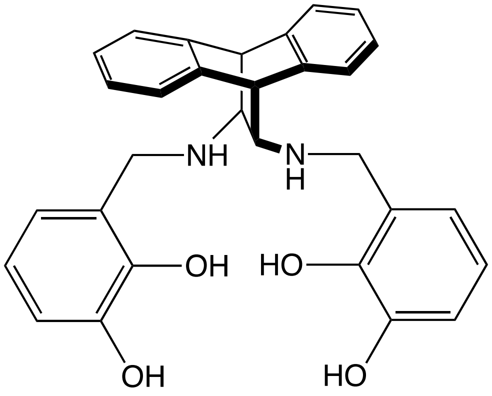


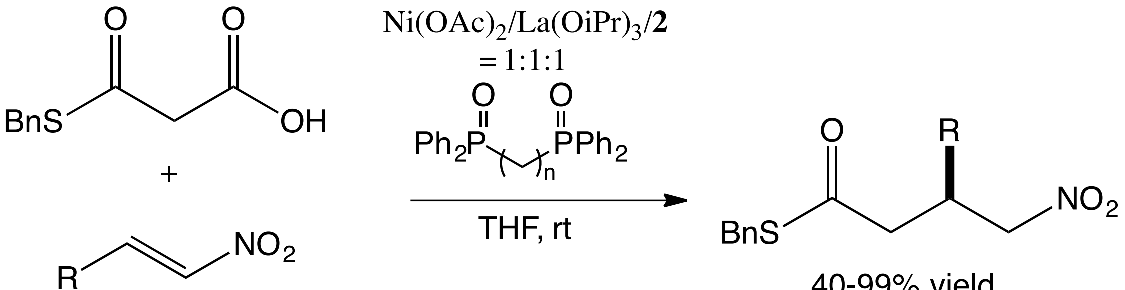
T. Ogawa, N. Kumagai and M. Shibasaki, *Angew. Chem., Int. Ed.*, **2013**, *52*, 6196

Bimetallic catalyst with Schiff base ligands

1,4 addition followed by decarboxylation

2

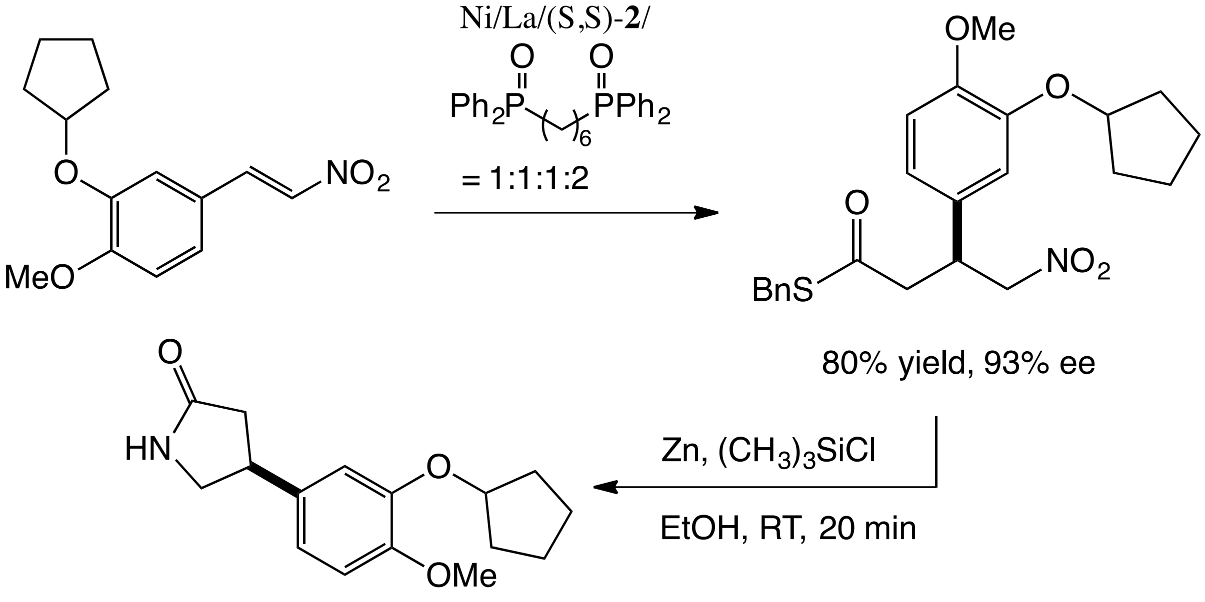




40-99% yield
66-92% ee

R = aryl, heteroaryl,
alkenyl, alkyl

Application to catalytic asymmetric synthesis of rolipram



80% yield, 93% ee

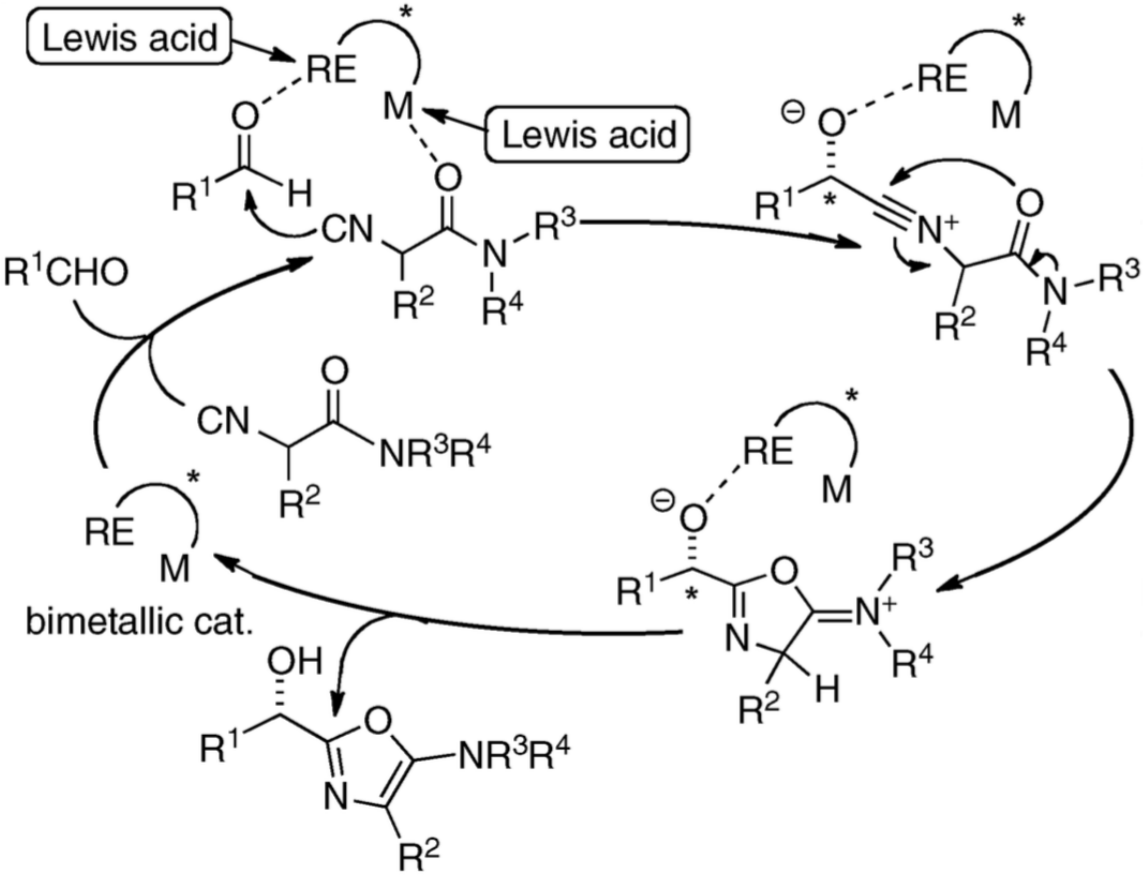
(S)-rolipram

M. Furutachi, S. Mouri, S. Matsunaga and M. Shibasaki, Chem.– Asian. J., **2010**, 5, 2351.

Bimetallic catalyst with Schiff base ligands

Heterobimetallic catalysts containing cationic rare earth metal as a Lewis acid unit

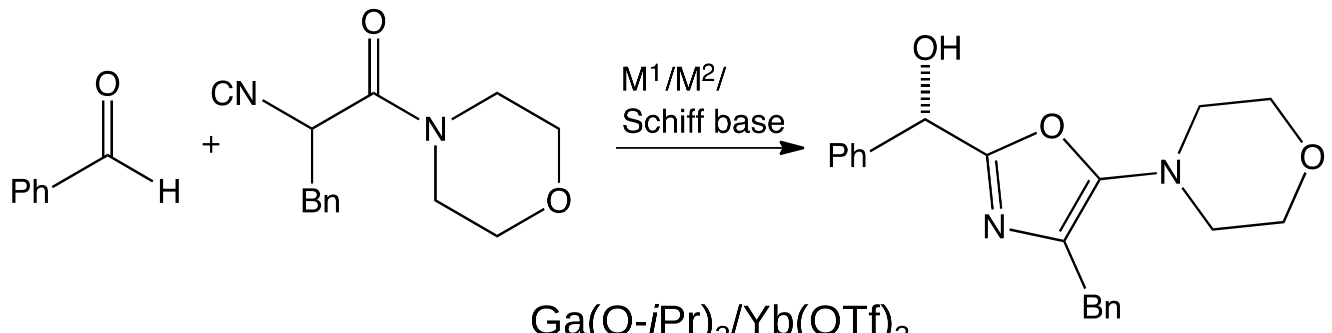
alfa-additions of alfa-isocyanoacetamides



S.-X. Wang, M.-X. Wang, D.-X. Wang and J. Zhu, Org. Lett., 2007, 9, 3615; (b) S.-X. Wang, M.-X. Wang, D.-X. Wang and J. Zhu, Eur. J. Org. Chem., **2007**, 4076.

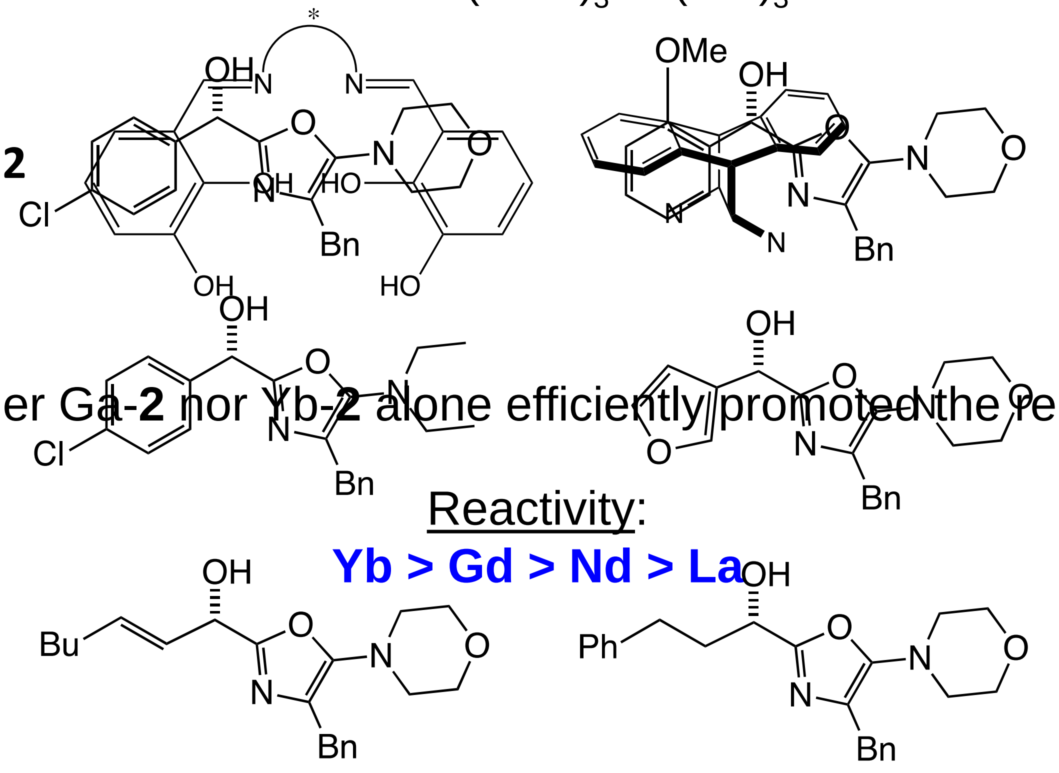
27 A review on the utility of isocyanide in organic synthesis: A. Do¨mling, Chem. Rev., **2006**, 106, 17

Bimetallic catalyst with Schiff base ligands



$Ga(O\text{-}iPr)_3/Yb(OTf)_3$

2



Neither Ga-**2** nor Yb-**2** alone efficiently promoted the reaction

Reactivity:

Yb > Gd > Nd > La

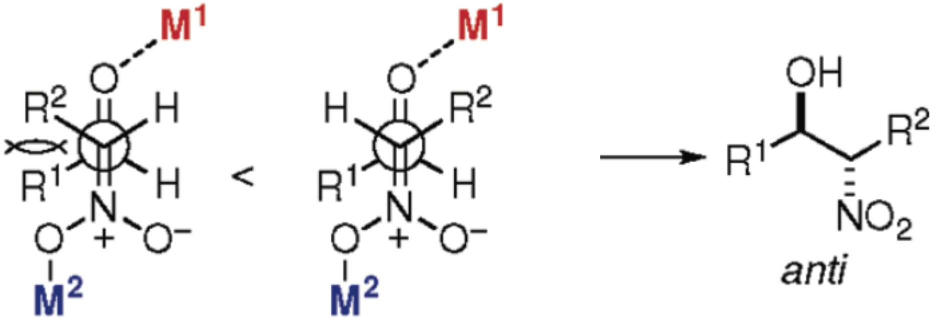
H. Tsuruta, K. Yamaguchi and T. Imamoto, Chem. Commun., **1999**, 1703

H. Mihara, Y. Xu, N. E. Shepherd, S. Matsunaga and M. Shibasaki, J. Am. Chem. Soc., **2009**, 131, 8384

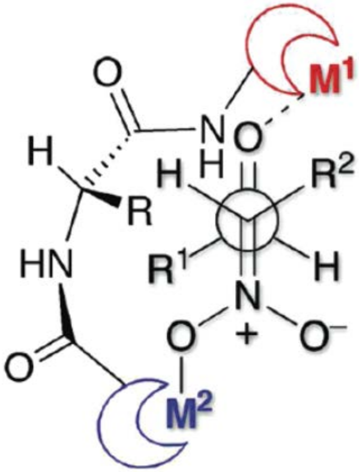
Amide-Based Ligand for a Heterobimetallic System

anti-Selective Nitroaldol Reaction

Aniparallel transition state



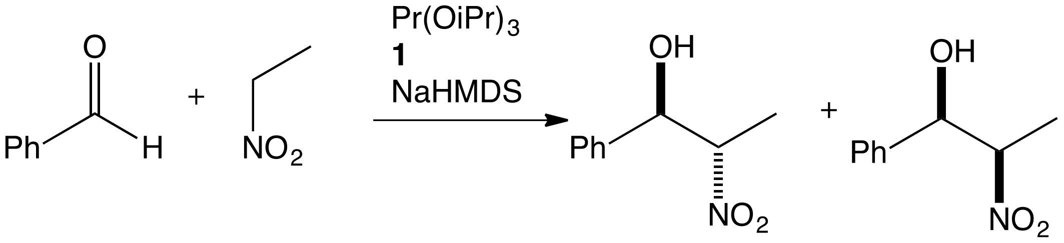
Ligand?

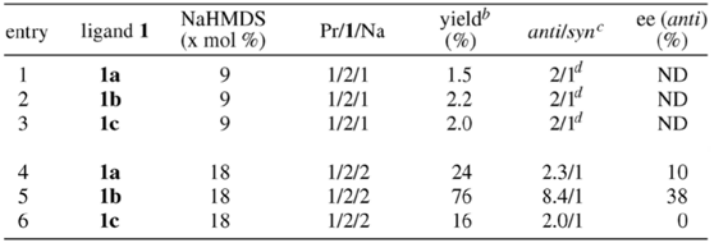


M. Shibasaki, *J. Am. Chem. Soc.*, **2009**, *131*, 13860

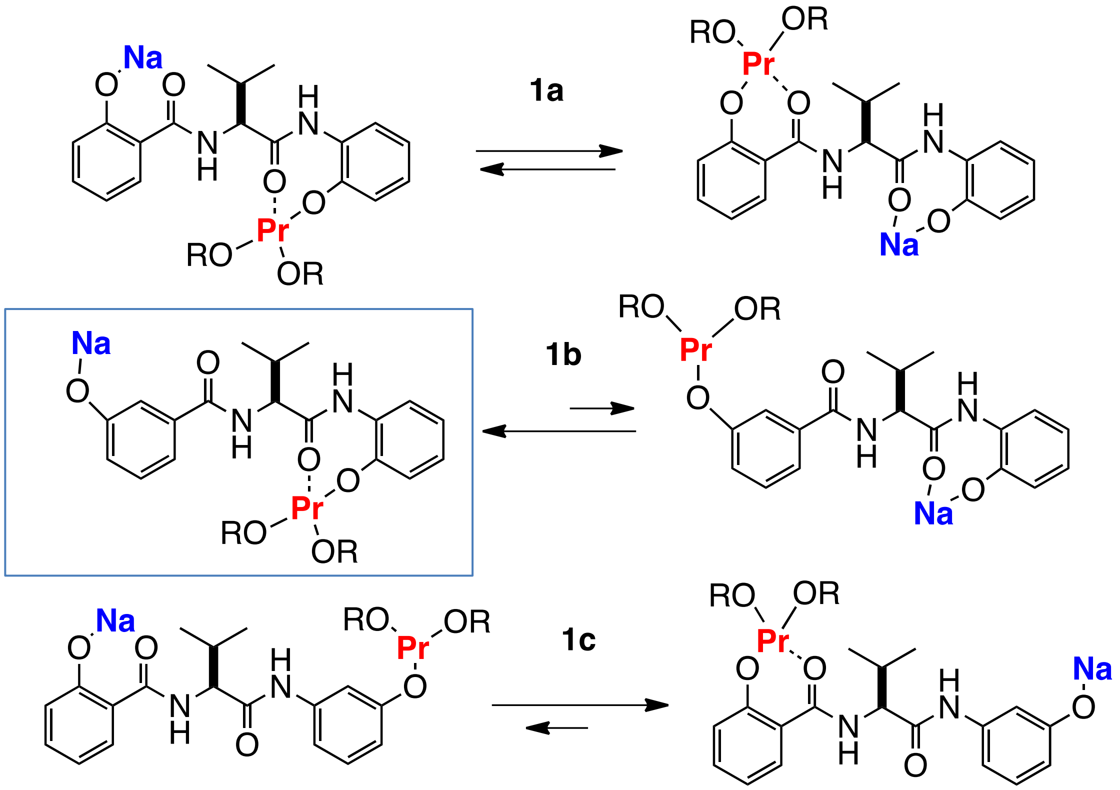
Amide-Based Ligand for a Heterobimetallic System

anti-Selective Nitroaldol Reaction



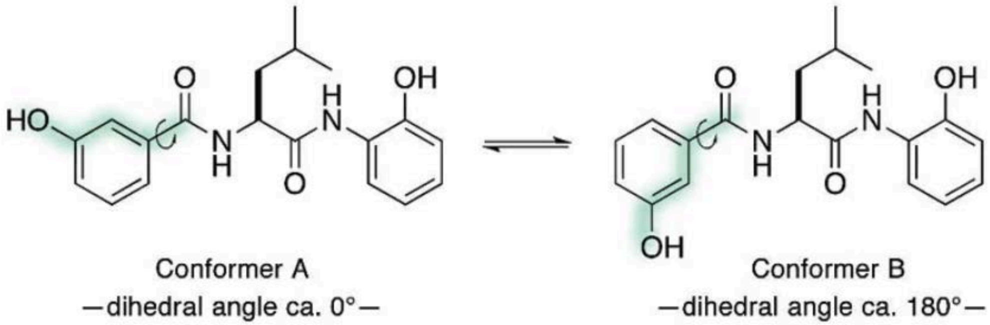


entry	ligand **1**	NaHMDS (x mol %)	Pr/**1**/Na	yield[b] (%)	*anti*/*syn*[c]	ee (*anti*) (%)
1	**1a**	9	1/2/1	1.5	2/1[d]	ND
2	**1b**	9	1/2/1	2.2	2/1[d]	ND
3	**1c**	9	1/2/1	2.0	2/1[d]	ND
4	**1a**	18	1/2/2	24	2.3/1	10
5	**1b**	18	1/2/2	76	8.4/1	38
6	**1c**	18	1/2/2	16	2.0/1	0

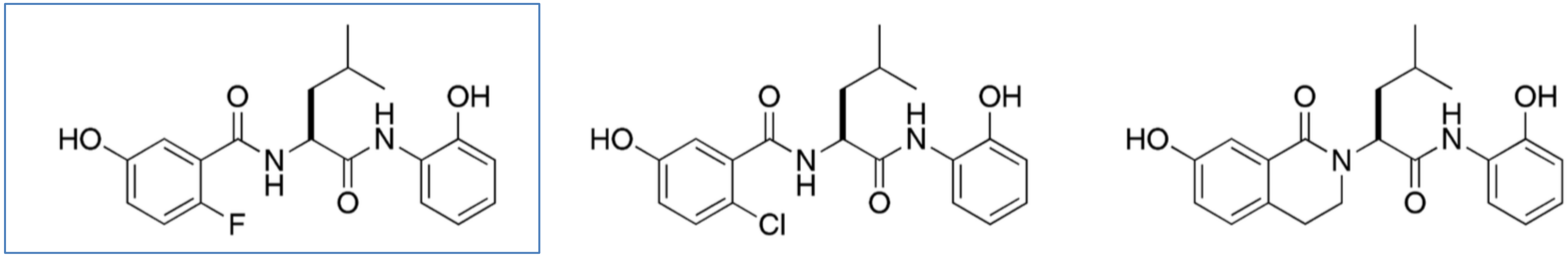


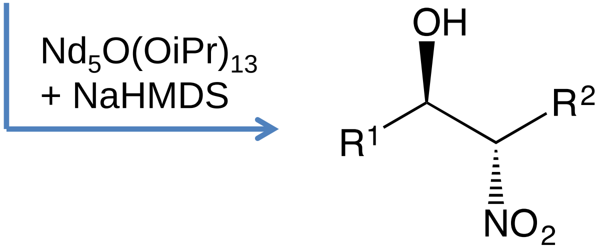
M. Shibasaki, *J. Am. Chem. Soc.*, **2009**, *131*, 13860

Amide-Based Ligand for a Heterobimetallic System



Restriction of bond rotation



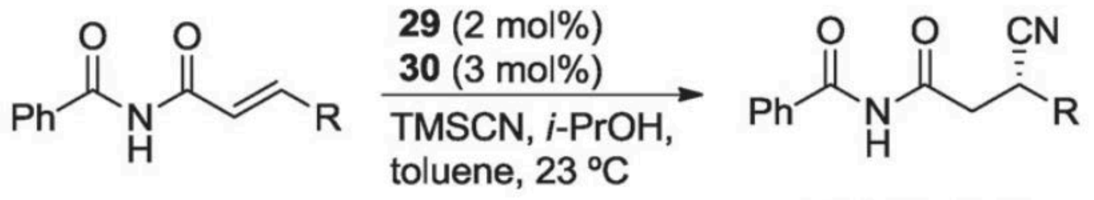


97% yield, 19:1 anti:syn
73% ee

M. Shibasaki, *J. Am. Chem. Soc.*, **2009**, *131*, 13860

Separate bimetallic systems (Type 5)

Cooperative Dual metal catalysis



R = alkyl

80-94% yield
93-97% ee

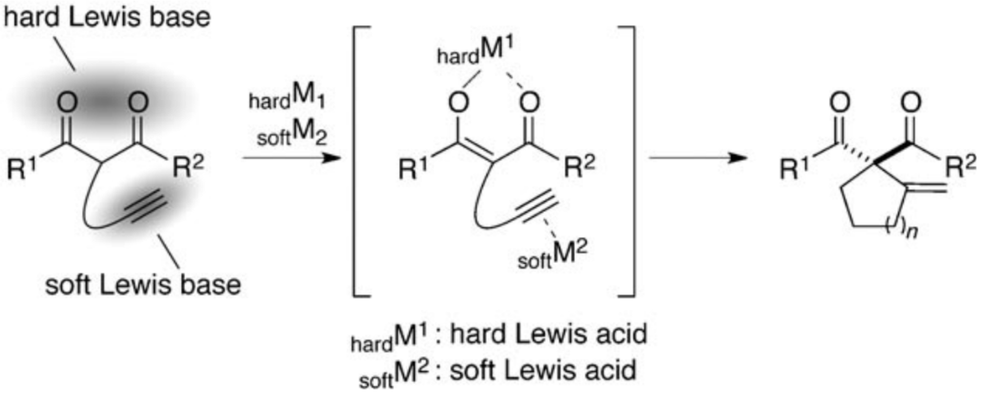
29

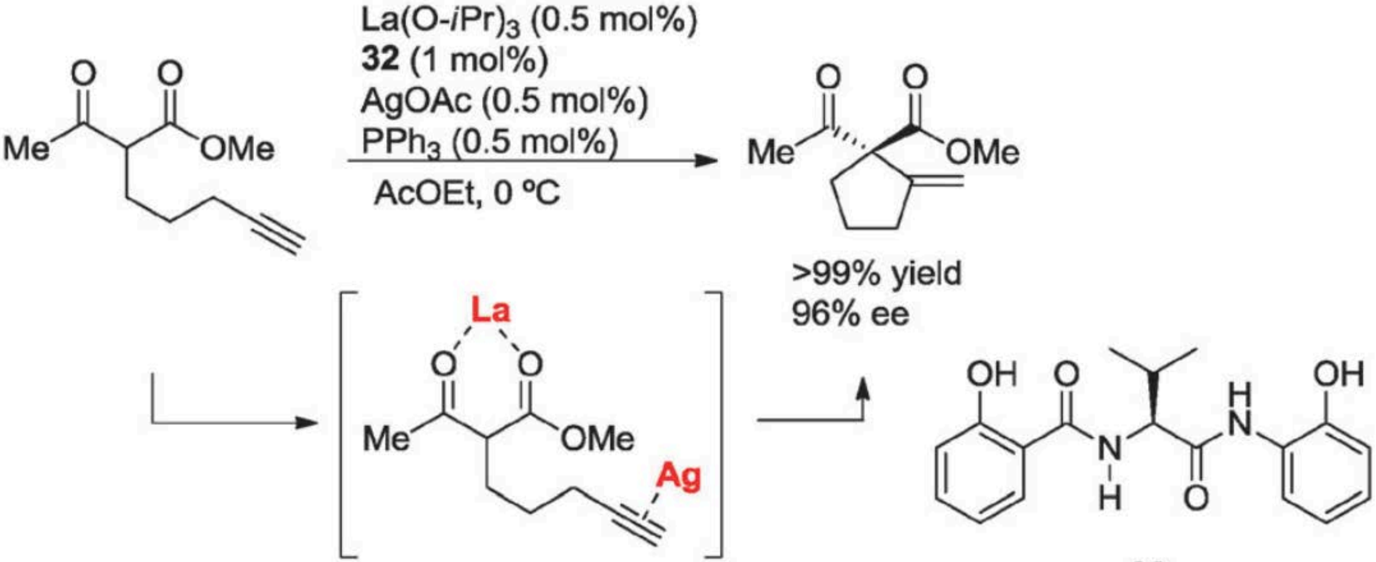
30

G. M. Sammis, H. Danjo and E. N. Jacobsen, J. Am. Chem. Soc., 2004, 126, 9928–9929

Separate bimetallic systems (Type 5)

Cooperative Dual metal catalysis: Conia-Ene Reaction

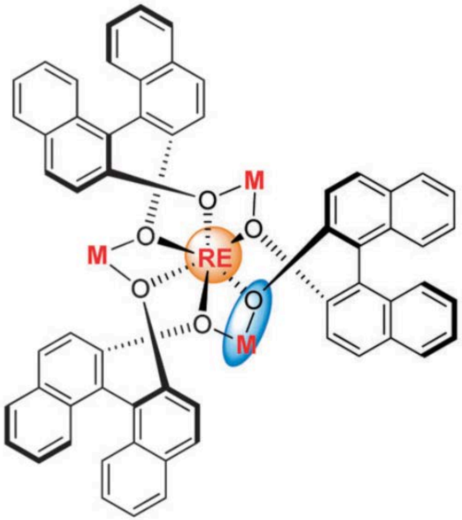




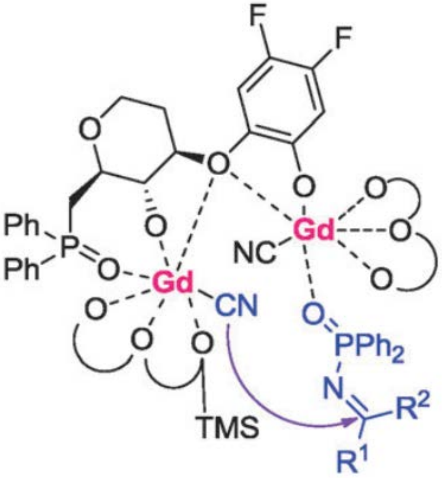
32

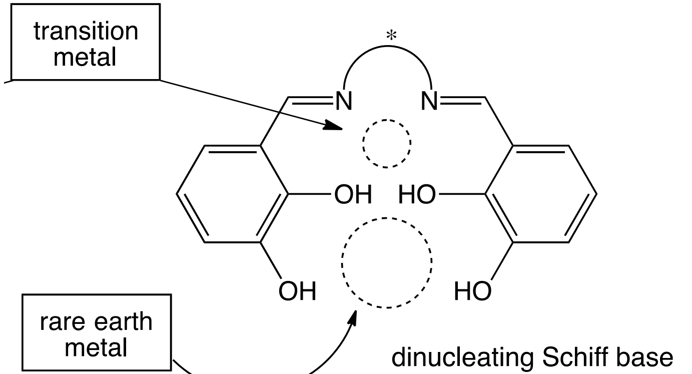
A. Matsuzawa, T. Mashiko and M. Shibasaki, *Angew. Chem., Int. Ed.*, **2011**, *50*, 7616

CONCLUSION

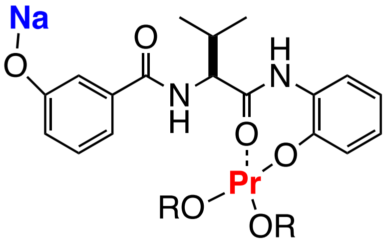


RE = La, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Yb, Y
M = Li, Na, K





dinucleating Schiff base
with N_2O_2 and O_2O_2 cavities

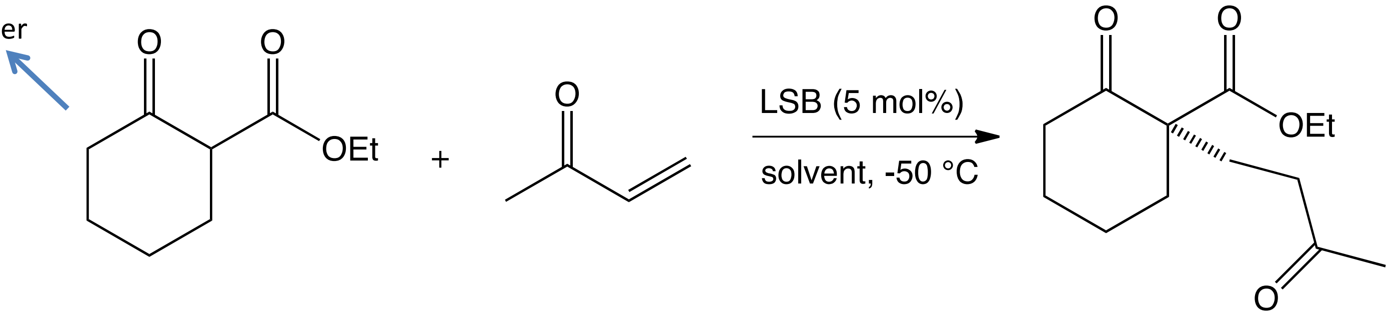


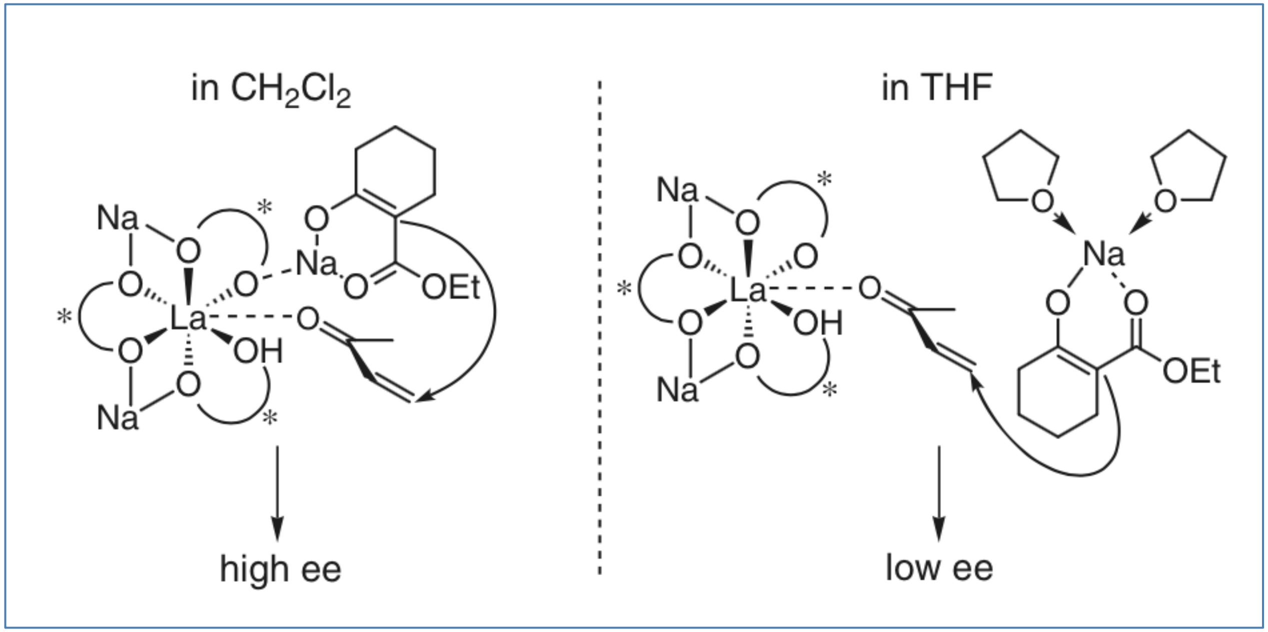
Thank you for your kind attention!!

Question 1

Why with malonate THF can be used as solvent and with beta-keto ester CH_2Cl_2 is chosen?

Malonates vs
beta-keto ester

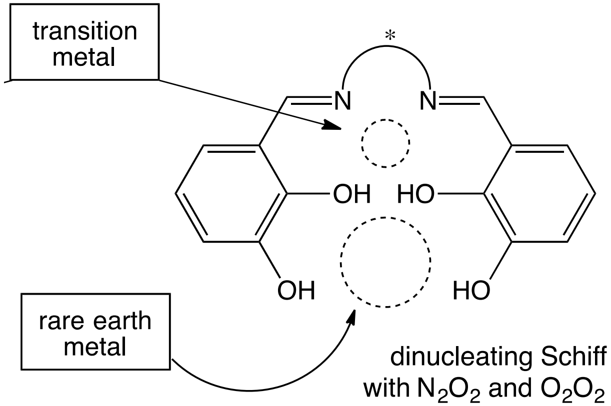




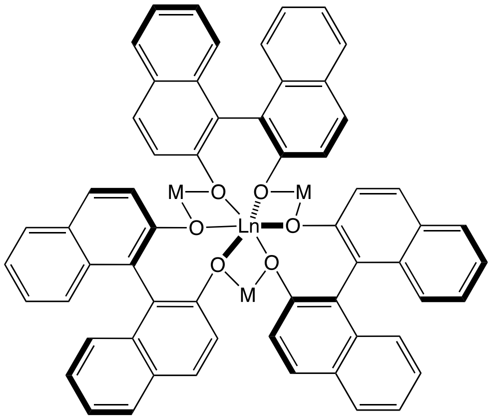
solvent	yield	ee
toluene	83%	25%
toluene (slow addition of Nu)	76%	89%
CH_2Cl_2	89%	91%

Question 1

Why Sm-OAr can act as a Brοnsted base with nitroalkane?



dinucleating Schiff base with N_2O_2 and O_2O_2 cavities



(R)-LnMB

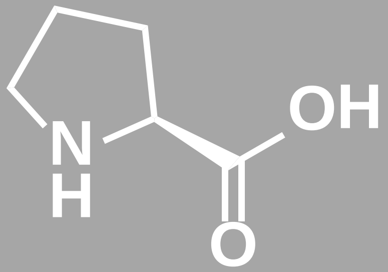
ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

Frontiers in Organic Synthesis

Stereochemistry

14.04.2016

Catalyst design: From proline to more efficient and enantioselective derivatives



Lionel Schouwey

14.03.2017

Plan of the presentation

Dual activation

- Context
- Most common proline-catalysed reactions
- Catalyst modifications
    - Acid modifications
    - Core modifications
    - Industrial applications
- Conclusions
- Questions

Questions

- Why free alcohol on prolinol catalyst decrease generally the reactivity?
- Why Nitro-Michael reactions are generally highly selective?
- What is important in order to have a good enantioselectivity? (catalytic cycle)

Why Proline is attractive as catalyst

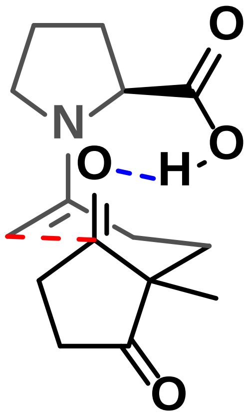
Organocatalysis

- Cheap
- Available from nature in two enantiomers
- Small molecule – water soluble
- Non-Metallic + non toxic
- No need of inert conditions

- Amino-acid but:
- Rigide five members ring
- Secondary amine
- Isoelectric point at pH = 6.30

- Dual activation modes
- HOMO-raising by enamine formation
- LUMO-lowering with the hydrogen bonding
- Directing group

- Drawback
- Solubility
- High catalyst loading



Hajos-Parrish-Eder-Sauer-Wiechert reaction transition state
List-Houk Mechanism

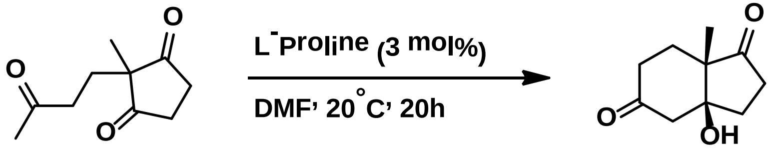
List B. Et al. *J. Am. Chem. Soc.* **2000**, *122, 10*, 2395

Proline-catalyzed Reactions

ESWHP reaction – Aldol reaction – Mannich reaction

Hajos-Parrish-Eder-Sauer-Wiechert reaction

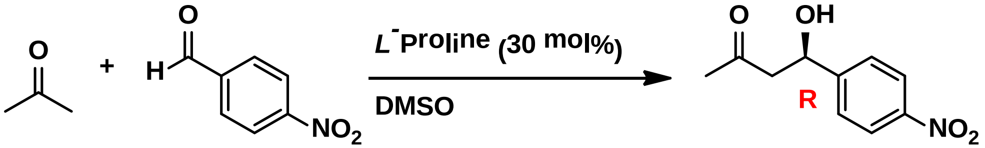
a)



Quantitative
ee = 93%

Aldol reaction

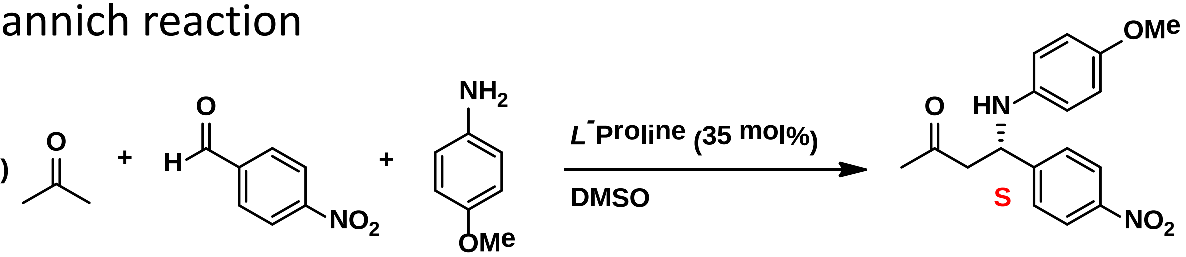
b)



y = 68%
ee = 76%

Mannich reaction

c)



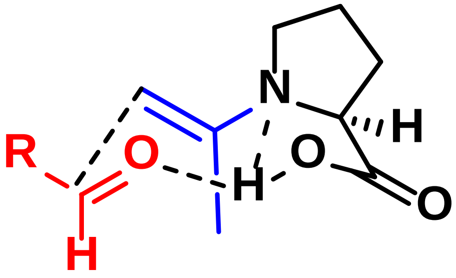
y = 50%
ee = 94%

a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, *10*, 496 / Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615
b) C. F. Barbas, R. A. Lerner, B. List, *J. Am. Chem. Soc.* **2000,** *122*, 2395
c) B. List, *J. Am. Chem. Soc.* **2000,** *122*, 9336

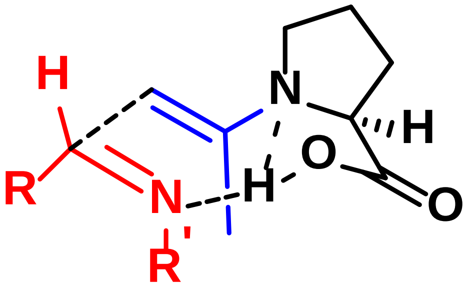
Aldol reaction – Mannich reaction

Selectivity

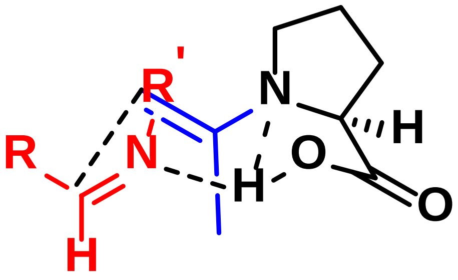
Aldol reaction intermediate



Mannich reaction intermediate



Z - Si face

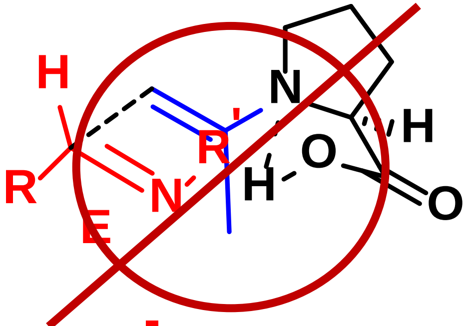


Z - Re face

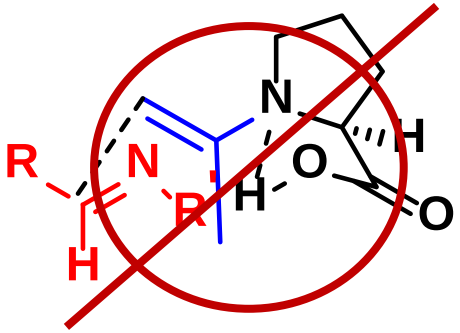
- R group in equatorial

- In case of Mannich:

- Avoid interaction between R' and proline
- E imine don't allow hydrogen bonding



E - Si face



E - Re face

C. F. Barbas, R. A. Lerner, B. List, *J. Am. Chem. Soc.* **2000,** *122*, 2395

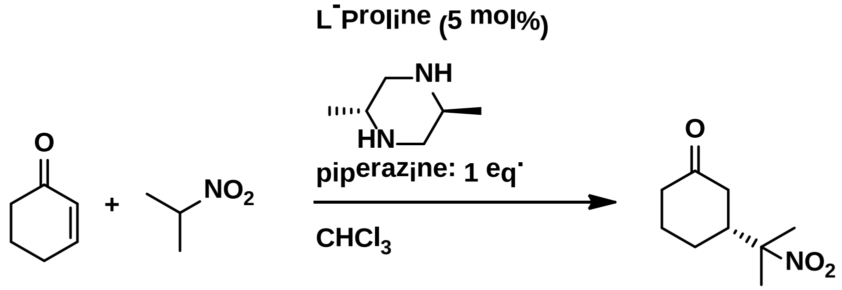
B. List, *J. Am. Chem. Soc.* **2000,** *122*, 9336

Proline-catalyzed Reactions

Michael Addition

Nitro - Michael addition reaction

d)

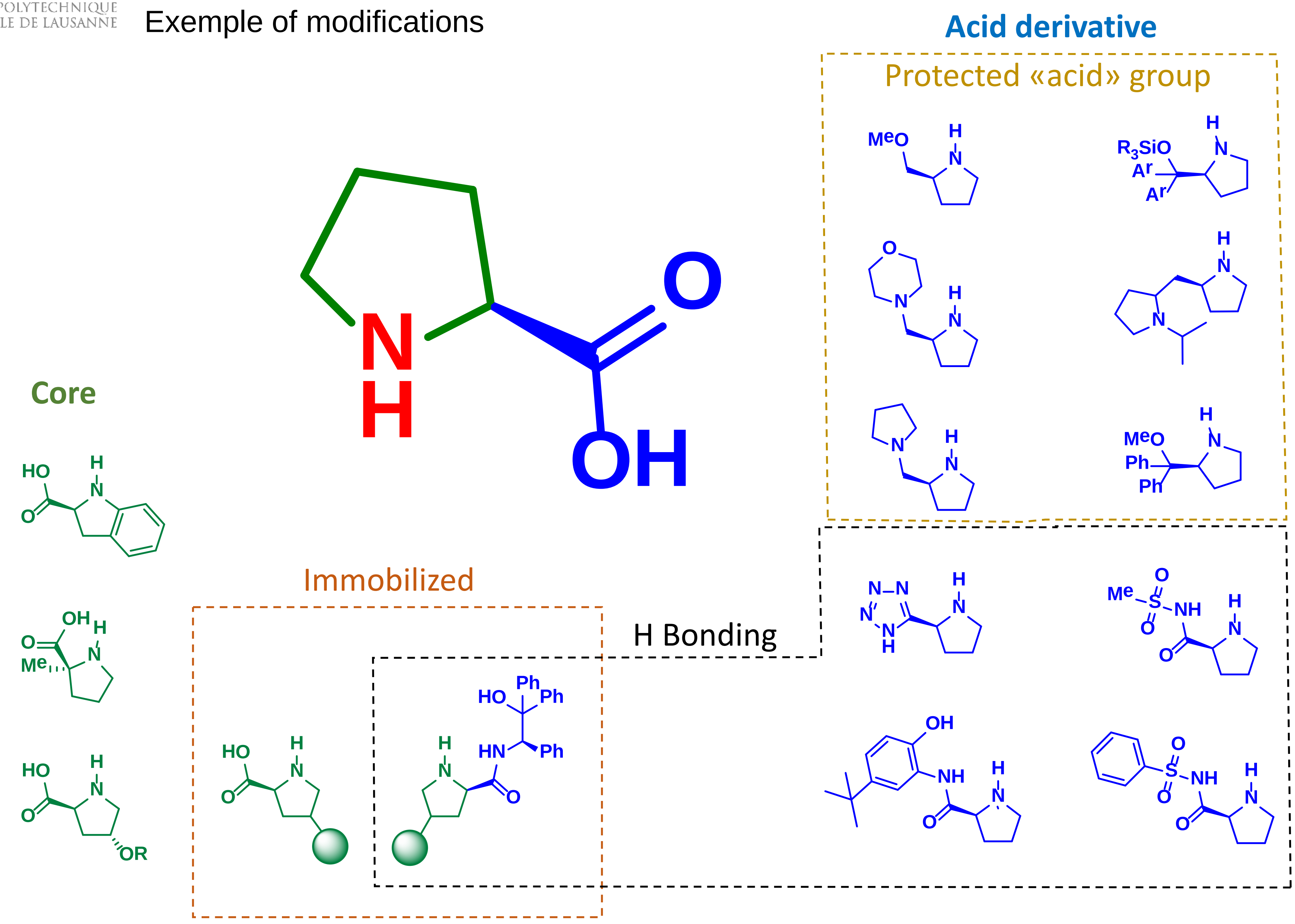


y = 88%
ee = 93%

d) V. Pham, S. Hannessian, *Org. Lett.* **2000,** *2*, 2975

Proline-Derivatives

Exemple of modifications



Acid derivative

Protected «acid» group

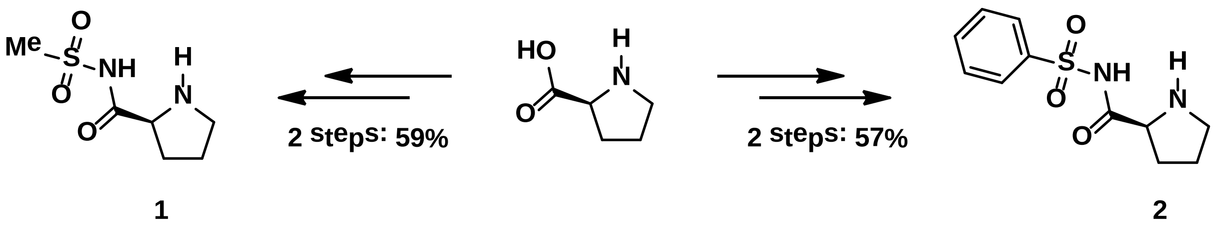
Core

Immobilized

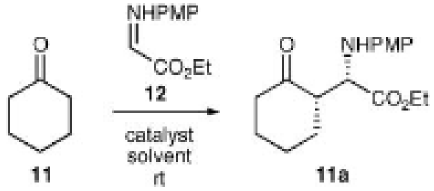
H Bonding

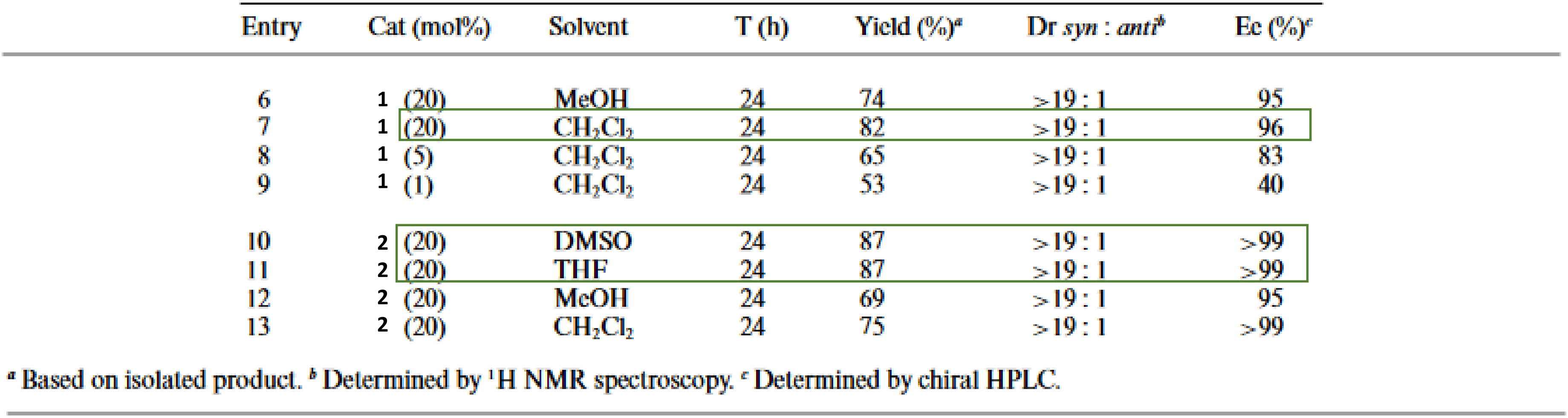
Acid group substitution: Acyl sulfonamide

Acid group modification



- Goal of modifications:
- Overcome solubility problems of proline (DMSO, MeOH and H_2O only)
- Stay in pKa range of acid
- Lower the catalyst loading





Entry	Cat (mol%)	Solvent	T (h)	Yield (%)[a]	Dr *syn* : *anti*[b]	Ee (%)[c]
6	1 (20)	MeOH	24	74	>19 : 1	95
7	1 (20)	CH_2Cl_2	24	82	>19 : 1	96
8	1 (5)	CH_2Cl_2	24	65	>19 : 1	83
9	1 (1)	CH_2Cl_2	24	53	>19 : 1	40
10	2 (20)	DMSO	24	87	>19 : 1	>99
11	2 (20)	THF	24	87	>19 : 1	>99
12	2 (20)	MeOH	24	69	>19 : 1	95
13	2 (20)	CH_2Cl_2	24	75	>19 : 1	>99

[a] Based on isolated product. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral HPLC.

J.A. Cobb, D. M. Shaw, D. A, Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005,** *3*, 84

Acid group substitution: Acyl sulfonamide

Acid group modification

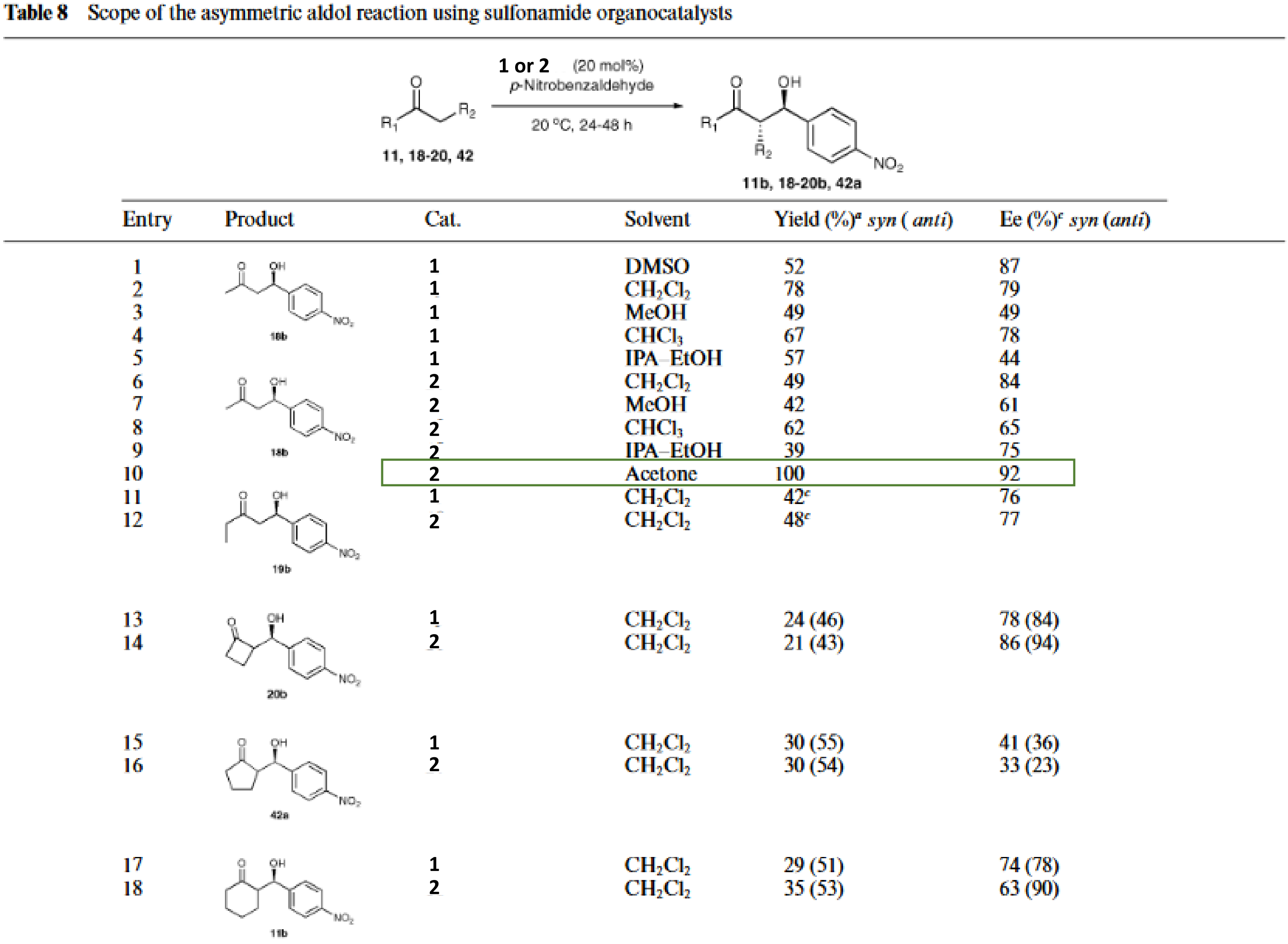


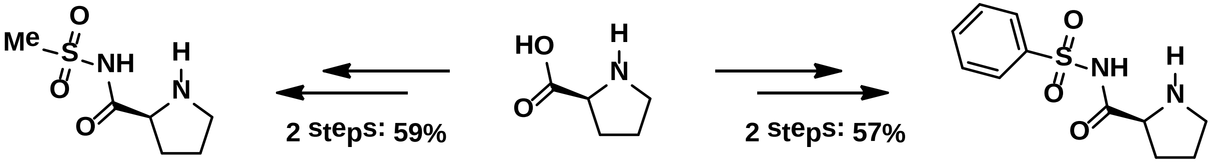
Table 8 Scope of the asymmetric aldol reaction using sulfonamide organocatalysts

Entry	Product	Cat.	Solvent	Yield (%)^a *syn* (*anti*)	Ee (%)^c *syn* (*anti*)
1	18b	1	DMSO	52	87
2		1	CH_2Cl_2	78	79
3		1	MeOH	49	49
4		1	$CHCl_3$	67	78
5		1	IPA–EtOH	57	44
6	18b	2	CH_2Cl_2	49	84
7		2	MeOH	42	61
8		2	$CHCl_3$	62	65
9		2	IPA–EtOH	39	75
10		2	Acetone	100	92
11	19b	1	CH_2Cl_2	42^c	76
12		2	CH_2Cl_2	48^c	77
13	20b	1	CH_2Cl_2	24 (46)	78 (84)
14		2	CH_2Cl_2	21 (43)	86 (94)
15	42a	1	CH_2Cl_2	30 (55)	41 (36)
16		2	CH_2Cl_2	30 (54)	33 (23)
17	11b	1	CH_2Cl_2	29 (51)	74 (78)
18		2	CH_2Cl_2	35 (53)	63 (90)

J.A. Cobb, D. M. Shaw, D. A, Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005,** *3*, 84

Acid group substitution: Acyl sulfonamide

Acid group modification



1 2

- Conclusions:

- Allow the use of less polar solvents / no reaction with *L*-proline

- No improvement of the reaction time / same range as proline
- ee drops when the catalyst loading in decreased
- No nitro-Michael reaction possible with 1 and 2

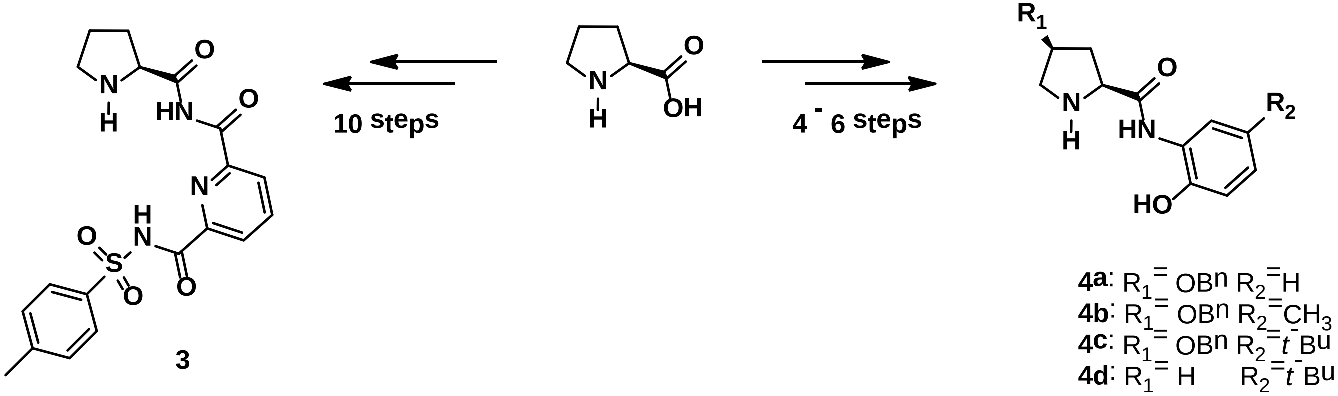
Reaction	catalyst	Solvent	Yield range	ee range
Mannich	1	MeOH, DCM	74-82	95-96
	2	DMSO, THF, MeOH, DCM	69-87	95-99
Aldol reaction	1	DMSO, DCM, MeOH, Chloroform, IPA-EtOH	52-78	44-87
	2	DCM, MeOH, Chloroform, IPA-EtOH, Acetone	39-100	61-92

In green: Best solvent for this reaction system

J.A. Cobb, D. M. Shaw, D. A, Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005,** *3*, 84

Acid group substitution: multidentate chelate

Enzyme mimeting



4a: $R_1 = OBn$ $R_2 = H$
4b: $R_1 = OBn$ $R_2 = CH_3$
4c: $R_1 = OBn$ $R_2 = t\text{-}Bu$
4d: $R_1 = H$ $R_2 = t\text{-}Bu$

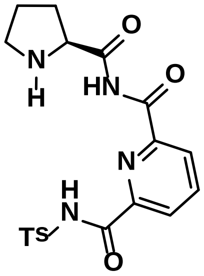
- Goal of modifications:
- Mimic the catalytic manner of enzyme
- Enhance solubility:
  - 3) organic solvents
  - 4a-d) Pure water as solvent without surfactant
- Lower the catalyst loading
- 4a-d) Use of small ketone excess

Cat. 3) L. Wang, R. Tang, H. Yang, J. Korean Chem. Soc. **2013,** *57*, *5*, 591
Cat 4a-d) S-P. Zhang, X-K. Fu, S-D. Fu, *Tetrahedron Lett*. **2009**, *50*, 1173

Acid group substitution: multidentate chelate

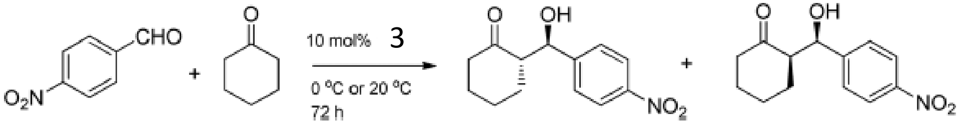
3 Dentate catalyst

Aldol reaction



3

Table **1.** Primary selection of solvent employed in aldol reaction.[a]



Entry	Solvent	Time (h)	Temperature (°C)	Yield[b] (%)	Dr[c] (anti/syn)	Ee[c] (%) (anti)
1	MeOH	72	20	22	62:38	21(84)[d]
2	DCM	72	20	76	72:28	85
3	$CHCl_3$	72	20	26	74:26	48
4	DMF	72	20	19	68:32	28
5	DCE	72	20	54	87:13	68
6	Water	72	20	30	54:46	13(62)[d]
7	Neat	72	20	84	63:37	76
8	DMSO	72	20	43	49:51	47
9	*n*-hexane	72	20	Trace	–	–
10	DCM	120	0	57	69:31	80
11	DCE	120	0	44	66:34	75

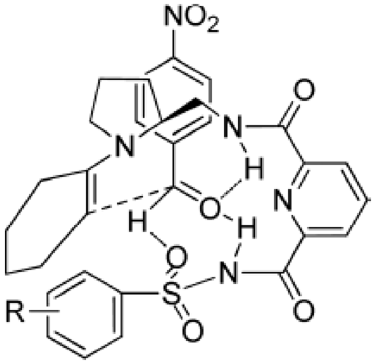
[a] All the reactions were performed with 1.0 mmol of *p*-nitrobenzaldehyde, 1.0 mL of cyclohexanone, 10 mol.% catalyst **12a**, at 0 °C or 20 °C.

[b] Isolated yield.

[c] Determined by chiral HPLC for *anti*-diastereomer.

[d] Enantiomeric excess determined by chiral HPLC for *syn*-diastereomer.

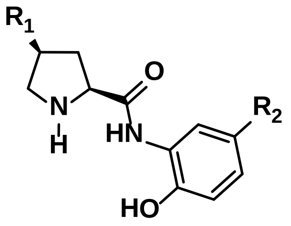
- Try to use additive:
    - Increase of yield with Benzyl acid and $ZnCl_2$
    - Drop of the ee
- 10 mol% catalyst only
- Ketone / aldehyde ratio 1:1



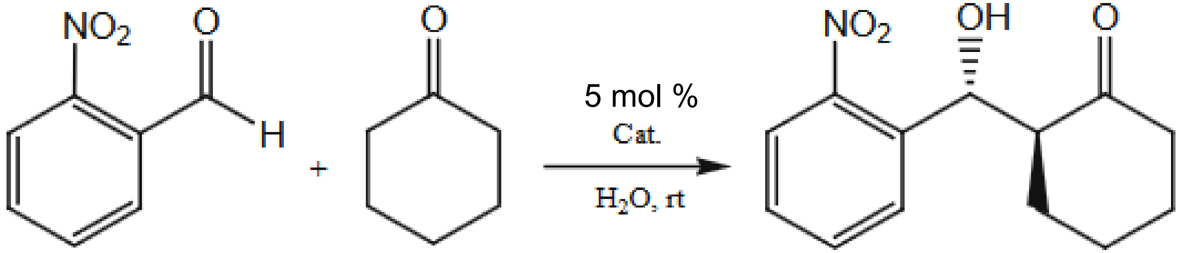
L. Wang, R. Tang, H. Yang, J. Korean Chem. Soc. **2013,** *57*, *5*, 591

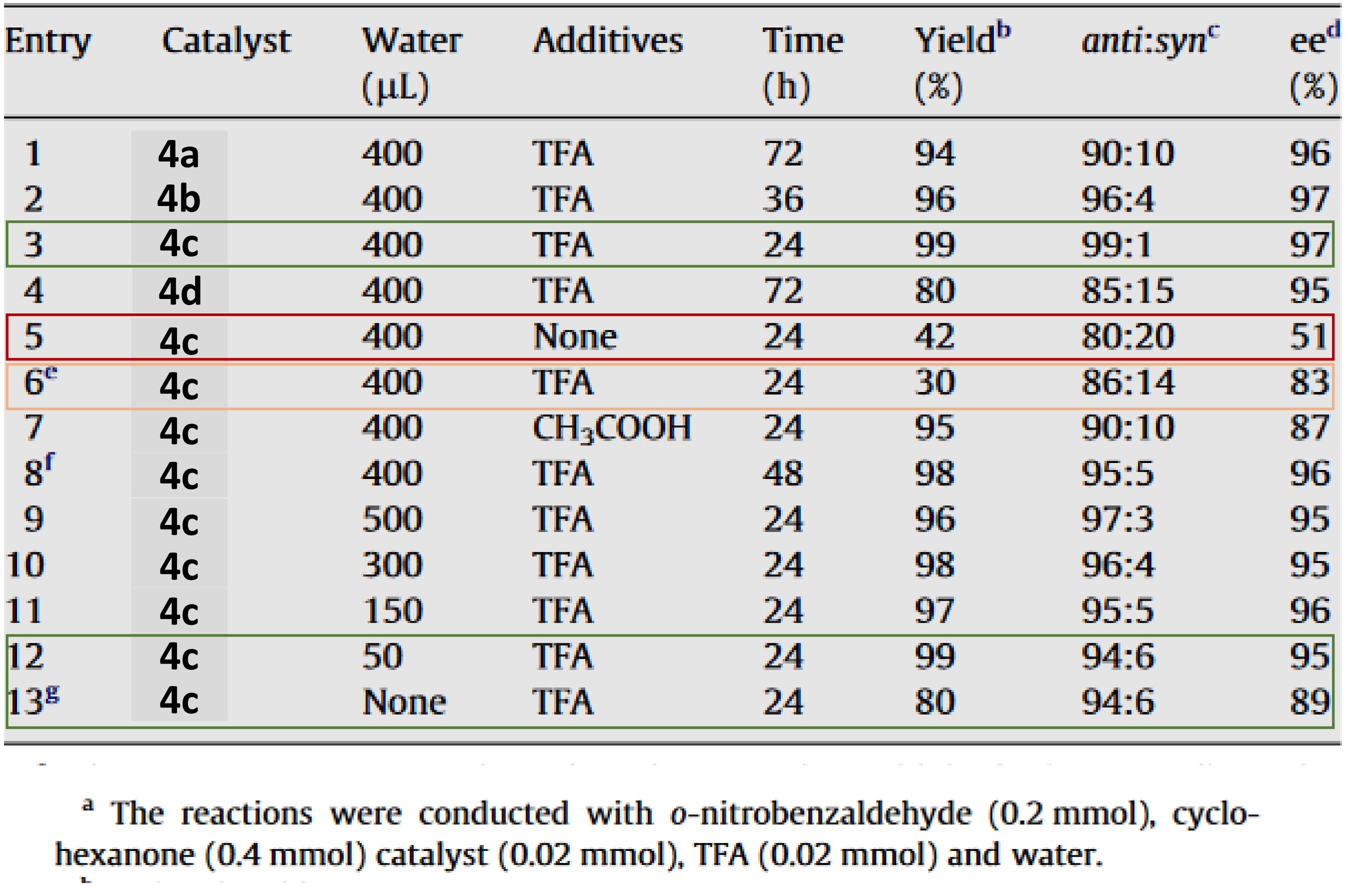
Acid group substitution: multidentate chelate

2 dentate catalyst



4a: R_1 = OBn R_2 = H
4b: R_1 = OBn R_2 = CH_3
4c: R_1 = OBn R_2 = *t* Bu
4d: R_1 = H R_2 = *t* Bu





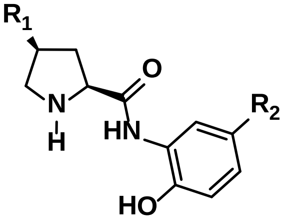
Entry	Catalyst	Water (µL)	Additives	Time (h)	Yield[b] (%)	*anti*:*syn*[c]	ee[d] (%)
1	**4a**	400	TFA	72	94	90:10	96
2	**4b**	400	TFA	36	96	96:4	97
3	**4c**	400	TFA	24	99	99:1	97
4	**4d**	400	TFA	72	80	85:15	95
5	**4c**	400	None	24	42	80:20	51
6[e]	**4c**	400	TFA	24	30	86:14	83
7	**4c**	400	CH_3COOH	24	95	90:10	87
8[f]	**4c**	400	TFA	48	98	95:5	96
9	**4c**	500	TFA	24	96	97:3	95
10	**4c**	300	TFA	24	98	96:4	95
11	**4c**	150	TFA	24	97	95:5	96
12	**4c**	50	TFA	24	99	94:6	95
13[g]	**4c**	None	TFA	24	80	94:6	89

[a] The reactions were conducted with *o*-nitrobenzaldehyde (0.2 mmol), cyclohexanone (0.4 mmol) catalyst (0.02 mmol), TFA (0.02 mmol) and water.

S-P. Zhang, X-K. Fu, S-D. Fu, *Tetrahedron Lett*. **2009**, *50*, 1173

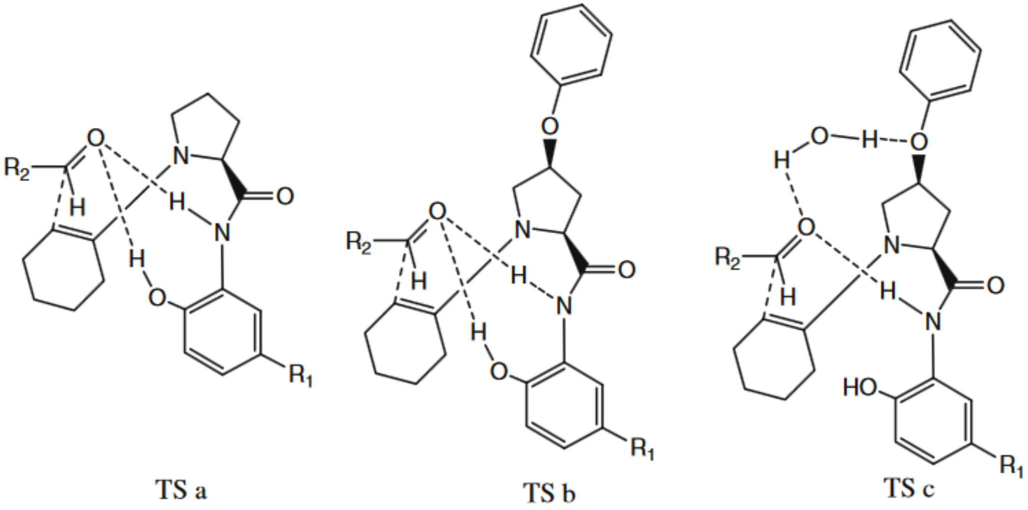
Acid group substitution: multidentate chelate

Enzyme mimeting



4a: R_1= OBn R_2=H
4b: R_1= OBn R_2=CH_3
4c: R_1= OBn R_2=*t* Bu
4d: R_1= H R_2=*t* Bu

- Large scope with excellent reactivity and selectivity
- Cat. TFA (5 mol%) as additive increase yield and ee
- 5 mol % catalyst
- Work for pure water / even concentrated or neat
- 2 equivalent of ketone
- Water molecule seems to add a chelating point
- Still slow reactions (24h) even if rate increased with R_1 = OBn



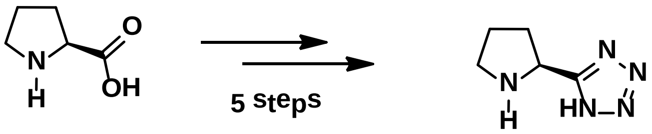
TS a TS b TS c

Scheme 3. Proposed transition structures.

S-P. Zhang, X-K. Fu, S-D. Fu, *Tetrahedron Lett*. **2009**, *50*, 1173

Acid group substitution: Tetrazole

Used as bioisosteres for carboxylic acid in med. Chem.



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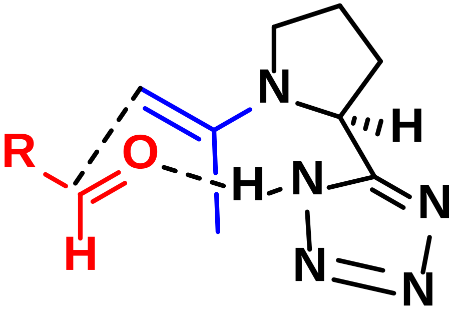
- Goal of modifications:

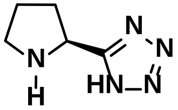
- Great solubility
- Tetrazole often used as carboxylic acid substitute in med. chem
- Lower the catalyst loading



J.A. Cobb, D. M. Shaw, D. A, Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005,** *3*, 84

Acid group substitution: Tetrazole

Mannich reaction



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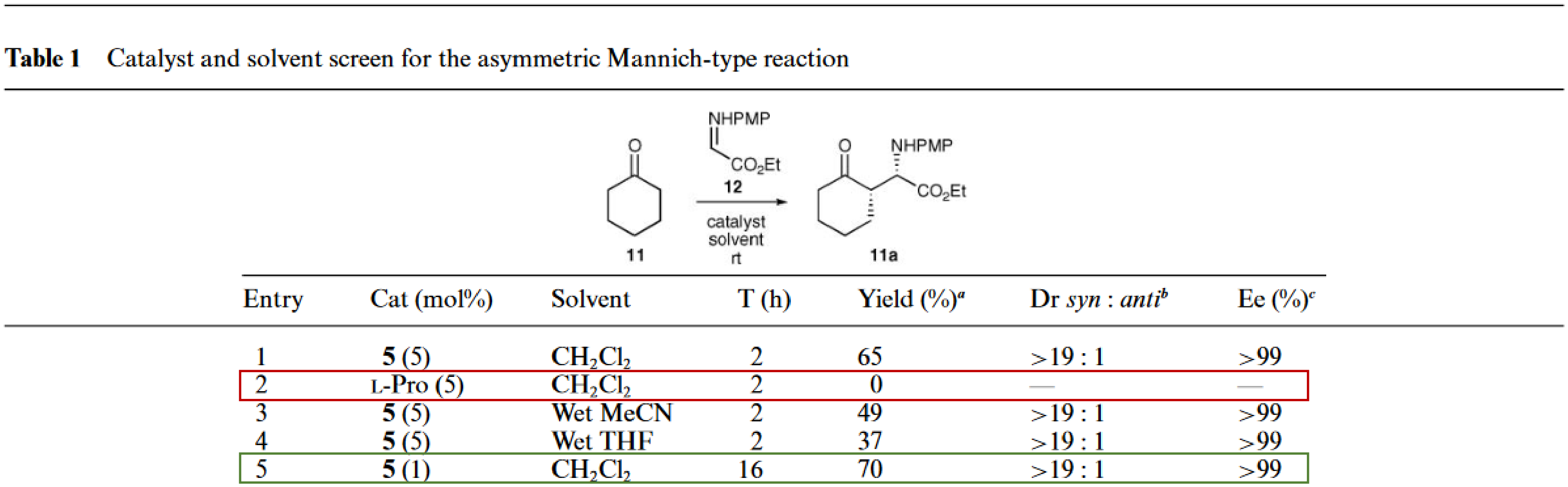


Table 1 Catalyst and solvent screen for the asymmetric Mannich-type reaction

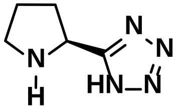
Entry	Cat (mol%)	Solvent	T (h)	Yield (%)[a]	Dr *syn* : *anti*[b]	Ee (%)[c]
1	**5** (5)	CH_2Cl_2	2	65	>19 : 1	>99
2	L-Pro (5)	CH_2Cl_2	2	0	—	—
3	**5** (5)	Wet MeCN	2	49	>19 : 1	>99
4	**5** (5)	Wet THF	2	37	>19 : 1	>99
5	**5** (1)	CH_2Cl_2	16	70	>19 : 1	>99

- Mannich reaction
- Low loading -> excellent ee
- Solubility in MeCN, THF, DCM
- Short reaction time with 5 mol%

J.A. Cobb, D. M. Shaw, D. A, Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005,** *3*, 84

Acid group substitution: Tetrazole

Nitro-Michael



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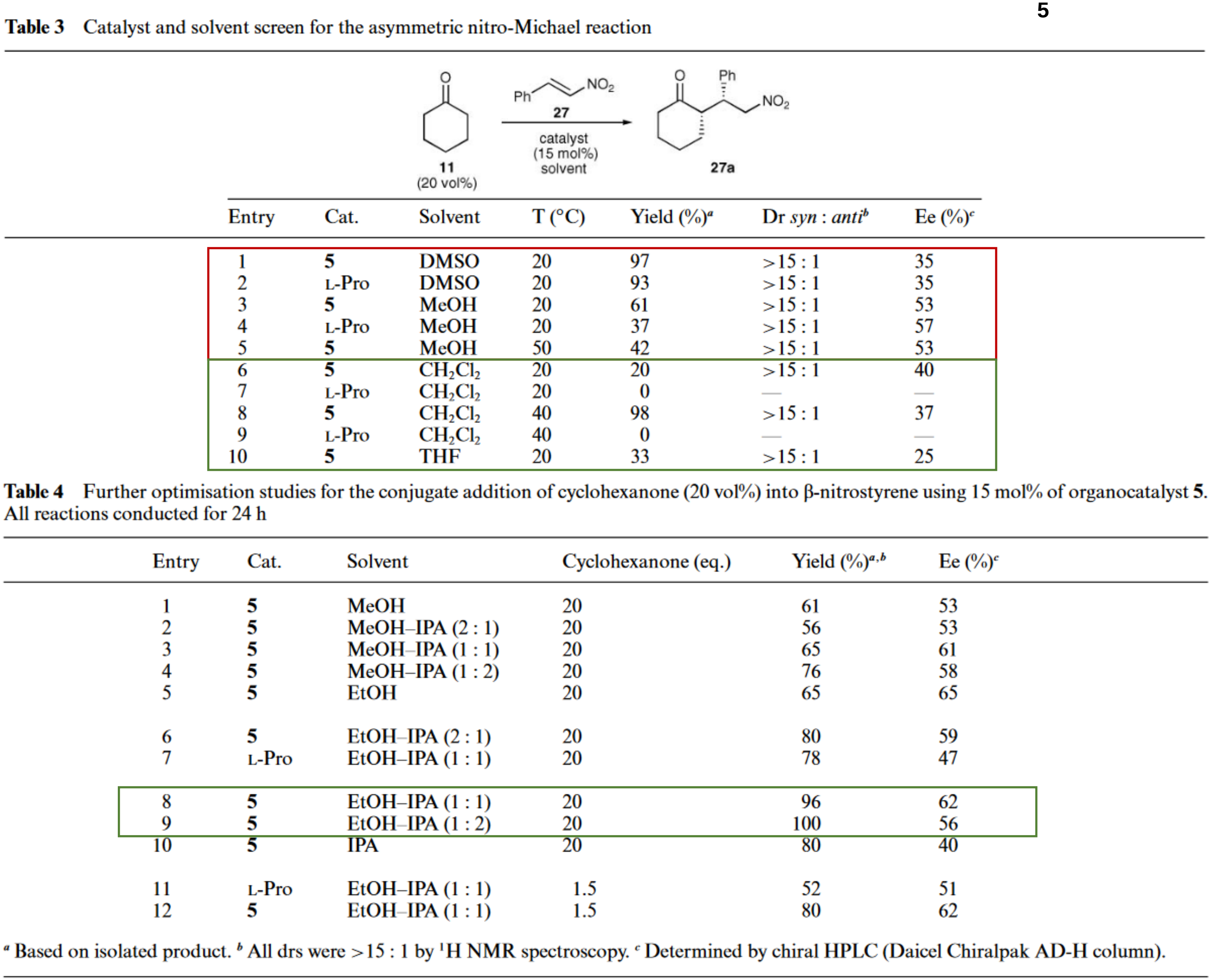


Table 3 Catalyst and solvent screen for the asymmetric nitro-Michael reaction

Entry	Cat.	Solvent	T (°C)	Yield (%)[a]	Dr *syn* : *anti*[b]	Ee (%)[c]
1	**5**	DMSO	20	97	>15 : 1	35
2	L-Pro	DMSO	20	93	>15 : 1	35
3	**5**	MeOH	20	61	>15 : 1	53
4	L-Pro	MeOH	20	37	>15 : 1	57
5	**5**	MeOH	50	42	>15 : 1	53
6	**5**	CH_2Cl_2	20	20	>15 : 1	40
7	L-Pro	CH_2Cl_2	20	0	—	—
8	**5**	CH_2Cl_2	40	98	>15 : 1	37
9	L-Pro	CH_2Cl_2	40	0	—	—
10	**5**	THF	20	33	>15 : 1	25

Table 4 Further optimisation studies for the conjugate addition of cyclohexanone (20 vol%) into β-nitrostyrene using 15 mol% of organocatalyst **5**. All reactions conducted for 24 h

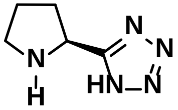
Entry	Cat.	Solvent	Cyclohexanone (eq.)	Yield (%)[a,b]	Ee (%)[c]
1	**5**	MeOH	20	61	53
2	**5**	MeOH–IPA (2 : 1)	20	56	53
3	**5**	MeOH–IPA (1 : 1)	20	65	61
4	**5**	MeOH–IPA (1 : 2)	20	76	58
5	**5**	EtOH	20	65	65
6	**5**	EtOH–IPA (2 : 1)	20	80	59
7	L-Pro	EtOH–IPA (1 : 1)	20	78	47
8	**5**	EtOH–IPA (1 : 1)	20	96	62
9	**5**	EtOH–IPA (1 : 2)	20	100	56
10	**5**	IPA	20	80	40
11	L-Pro	EtOH–IPA (1 : 1)	1.5	52	51
12	**5**	EtOH–IPA (1 : 1)	1.5	80	62

[a] Based on isolated product. [b] All drs were >15 : 1 by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC (Daicel Chiralpak AD-H column).

J.A. Cobb, D. M. Shaw, D. A, Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005,** *3*, 84

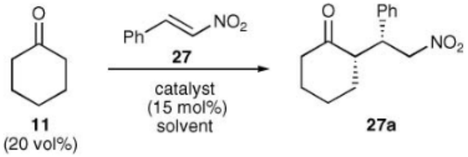
Acid group substitution: Tetrazole

Nitro-Michael



5

Table 3 Catalyst and solvent screen for the asymmetric nitro-Michael reaction

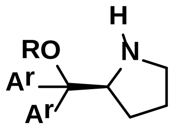


- Nitro-Michael
- Loading 15-25 mol%
- Moderate ee
- Proline give better results in polar solvent
- Impossible reaction with other catalyst in organic solvent
- Use of DCM, IPA, THF
- Work also with less ketone equivalent

J.A. Cobb, D. M. Shaw, D. A, Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005,** *3*, 84

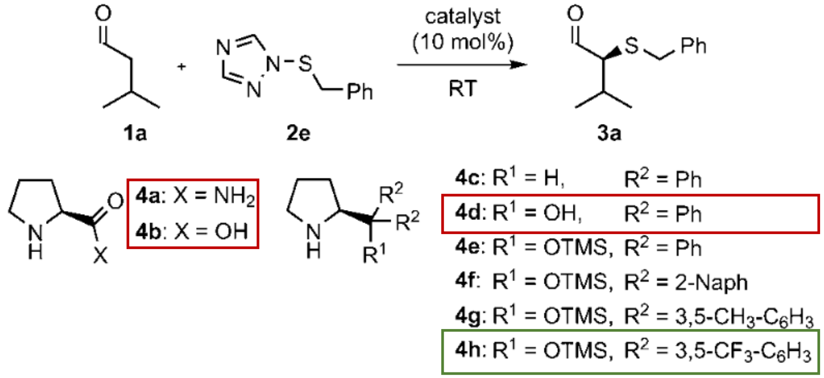
Proline Modification

Prolinol derivative



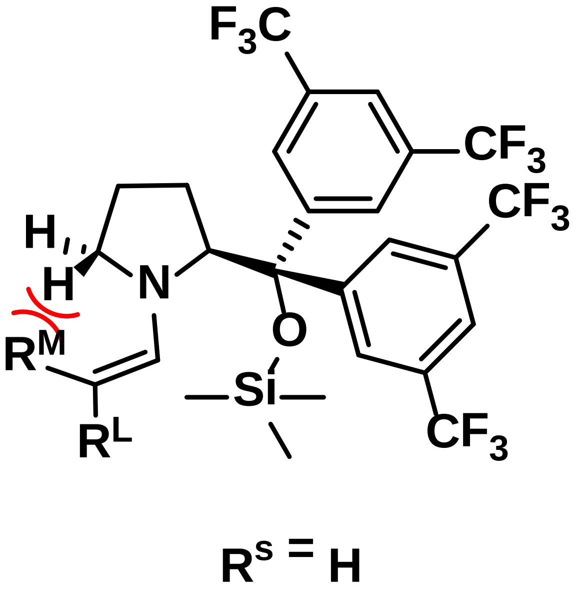
R = H, Me, TMS,

Ar = Ph, Napht, 3,5-(CH_3)-C_6H_3, 3,5-(CF_3)-C_6H_3



Entry	4	Solvent	Yield [%][b]	*ee* [%][c]
1	a	DMSO	–[d,e]	–
2	a	Et_2O	5	18
3	a	CH_2Cl_2	7	22
4	a	toluene	30	25
5	b	toluene	16	0
6	c	toluene	56[e]	52[f]
7	d	toluene	–[d]	–
8	e	toluene	90	77
9	f	toluene	75[e]	84
10	g	toluene	73[e]	90
11	h	toluene	90	98
12[g]	h	toluene	90	96
13[h]	h	toluene	90	90

- No more hydrogen bonding possible
  - - Loss of the hydrogen bond
  - - No more activation of electrophile
  - - Controlled by steric shielding



M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen , *Angew.Chem.Int.Ed.* **2005**, *44*, 794

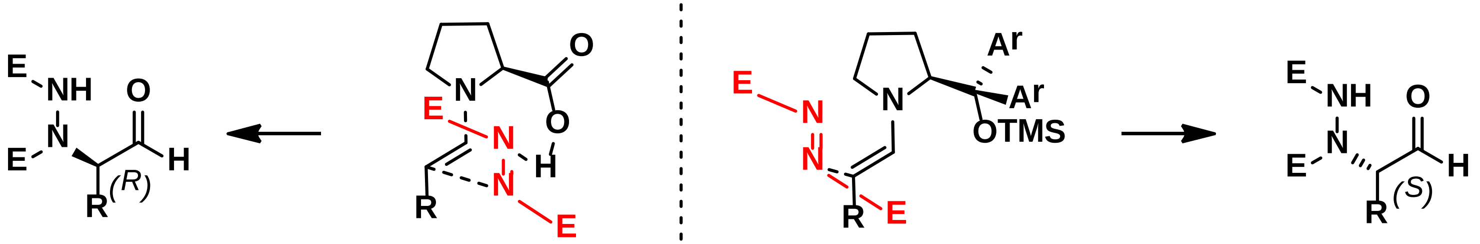
Prolinol

Comparution with proline

- Proline:
- H bonding / low steric hindrance:
  - → Good for hydrogen-bond acceptor substrates
  - → Bad for poor H-bond acceptors

- Hindered-Prolinol
- No H bonding* / High steric hindrance
  - → Good for steric controlled reactions
  - → Bad for H-bond acceptors substrates

- * Free alcohol: Could give good stereocontrol some times, but generally very low turnover!



From above
Re - Face

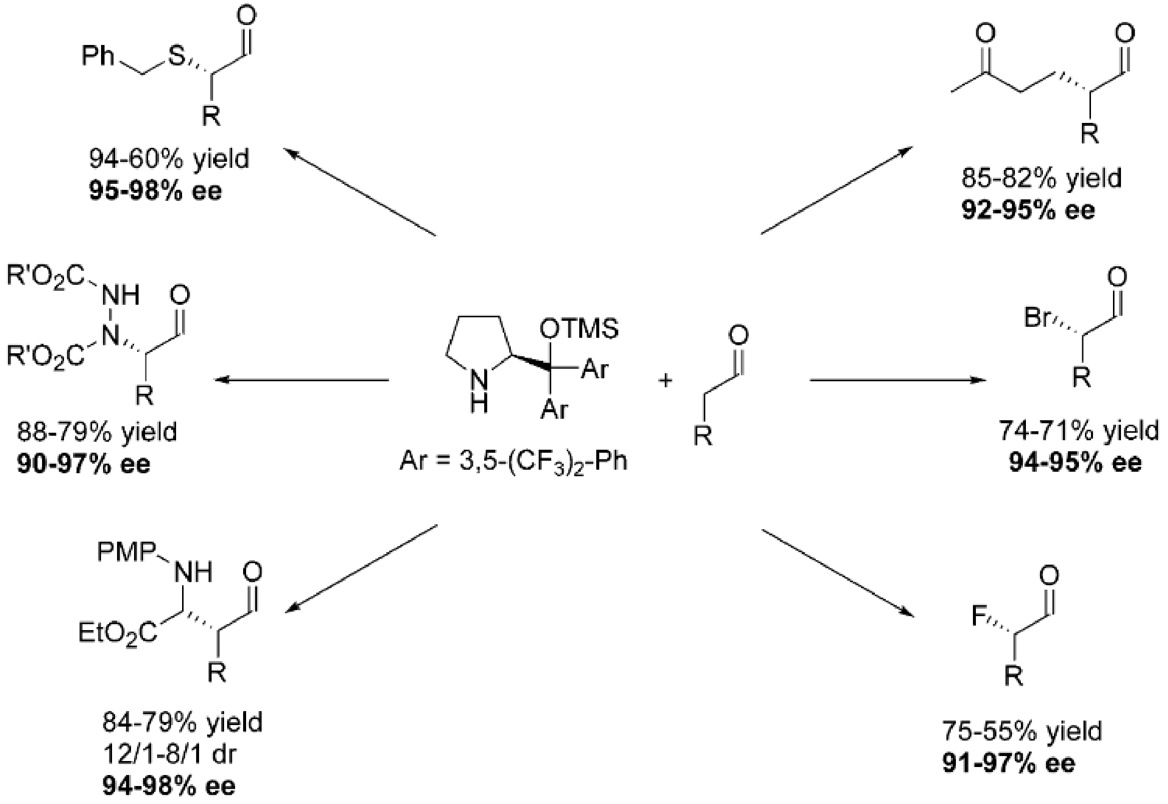
From below
Si - Face

J. Franzen, M. Marigo, T. C. Wabnitz, D. Fielenbach, A. Kjaersgaard, K. A. Jørgensen , *J. Am. Chem. Soc.* **2005**, *127*, 18296

Prolinol

Reactivity and selectivity examples

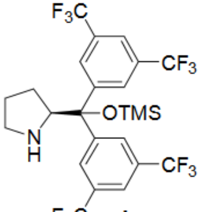
Scheme 1. Highly Enantioselective α-Functionalizations of Aldehydes Catalyzed by the α,α-Diarylprolinol Silyl Ether



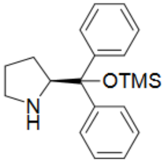
J. Franzen, M. Marigo, T. C. Wabnitz, D. Fielenbach, A. Kjaersgaard, K. A. Jørgensen , *J. Am. Chem. Soc.* **2005**, *127*, 18296

Prolinol

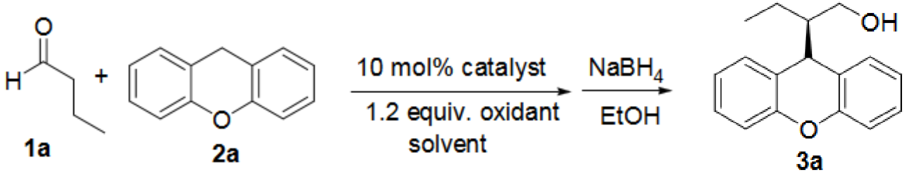
Dehydrogenative alpha-alkylation



I



II



Entry[a]	Oxidant	Solvent	Catalyst	Yield[b]/%	ee[c]/%
1	CAN	CH_2Cl_2	**I**	Trace	—
2	$FeCl_3$	CH_2Cl_2	**I**	Trace	—
3	$Cu(OAc)_2$	CH_2Cl_2	**I**	Trace	—
4	IBX	CH_2Cl_2	**I**	Trace	—
5[d]	O_2	CH_2Cl_2	**I**	Trace	—
6[d]	O_2	CH_2Cl_2	**II**	58	0
7	DDQ	CH_2Cl_2	**I**	50	72
8	DDQ	$MeNO_2$	**I**	42	94
9	DDQ	$CHCl_3$	**I**	62	92
10	DDQ	Toluene	**I**	18	—
11	DDQ	THF	**I**	17	—
12[e]	DDQ	$CHCl_3$	**I**	51	—
13[f]	DDQ	$CHCl_3$	**I**	29	—
14[g]	DDQ	$CHCl_3$	**I**	23	—
15	DDQ	$CHCl_3$	**II**	27	57

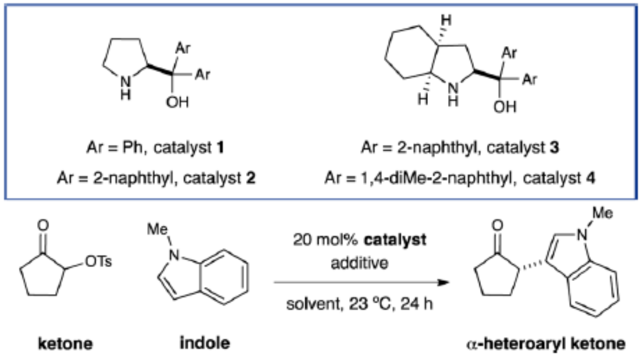
[a] Reactions were performed with **1a** (0.8 mmol), **2a** (0.2 mmol) and **I** (0.02 mmol) in 2 mL solvent at room temperature. [b] Isolated yield by column chromatography. [c] *ee* was determined by chiral HPLC on a chiral stationary phase. [d] 20 mol% catalyst and 20 mol% TfOH was used. [e] 1.5 equiv. DDQ was used. [f] 0 ℃ for 12 h. [g] 10 ml% 4-$NO_2C_6H_5CO_2H$ was added.

F. Huang, L. Xu, J. Xiao, *Chin. J. Chem.* **2012**, *30*, 2721

Prolinol

Oxy-allyl cation catalysis

Table 1. Initial Studies and Reaction Optimization

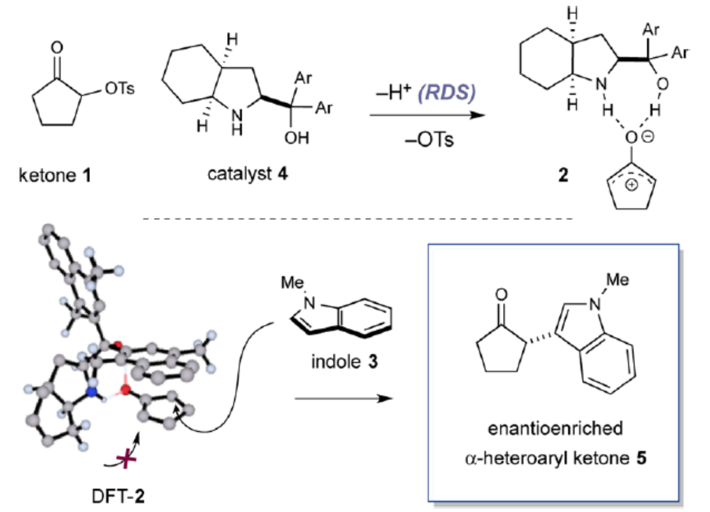


entry	catalyst	solvent	additive	yield[a]	ee[b]
1	1	C_6H_6	K_2HPO_4	58%	37%
2	2	C_6H_6	K_2HPO_4	50%	55%
3	3	C_6H_6	K_2HPO_4	54%	73%
4	3	1:1 C_6H_6/C_6F_6	K_2HPO_4	55%	79%
5	3	C_6F_6	K_2HPO_4	33%	81%
6[c]	4	C_6F_6	K_2HPO_4, H_2O[d]	91%	92%
7	none	C_6F_6	K_2HPO_4, H_2O[d]	0%	–
8	4	C_6F_6	H_2O	4%	–

[a] Yield determined by ^{1}H NMR. [b] Enantioselectivities determined by chiral HPLC. [c] Reaction time of 48 h. [d] 1 equiv of H_2O.

- Unprotected prolinol
  - Base needed
- Not via iminium / enamine formation
- Stabilisation of the cation by π interaction with an aromatic ring of catalyst

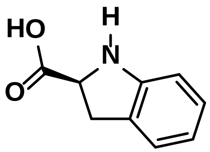
Scheme 3. Proposed Mechanism of the Substitution Reaction



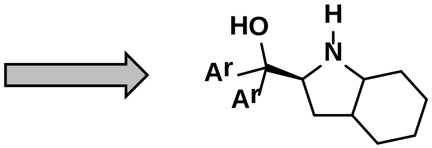
C. Liu, E. Z. Oblak, M. N. Vander Wal, A. K. Diliger, D. K. Almstead, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, *138*, 2134

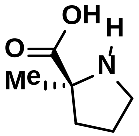
Core modifications

Exemple of modifications

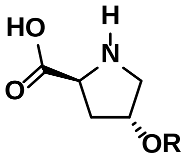


- Rigidity / Bulkiness

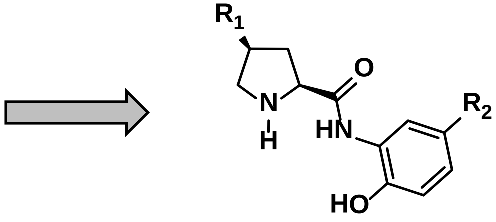


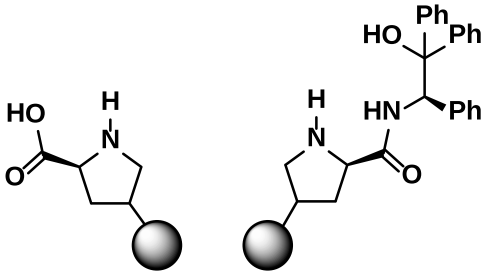


- Alpha-position from the acid



- Solubility / interaction

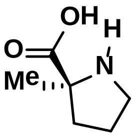


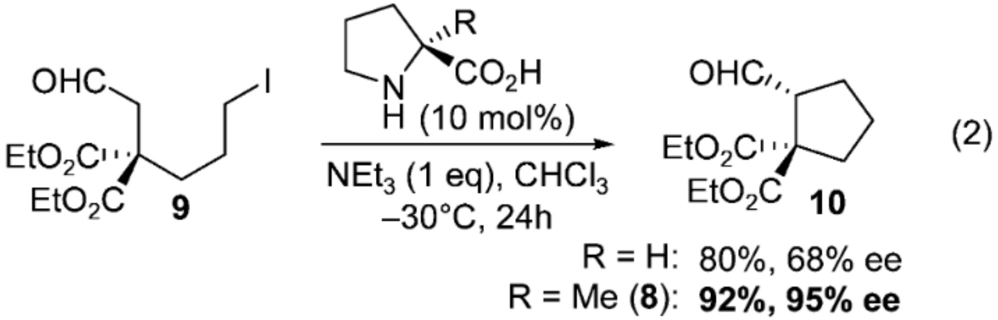


- Immobilized catalyst

Core modification

Alpha-position from the acid

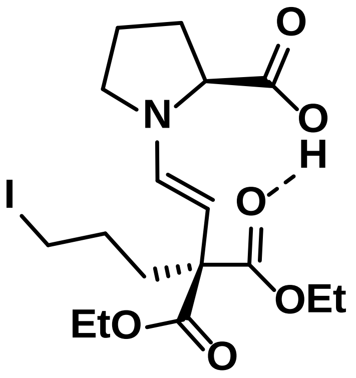




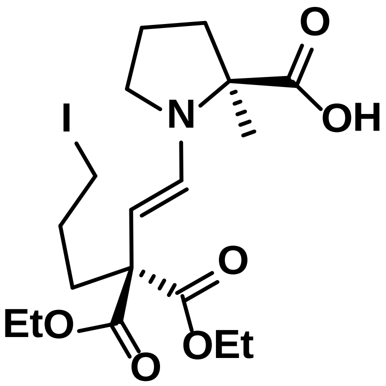
R = H: 80%, 68% ee

R = Me (**8**): **92%, 95% ee**

- Help to shift the *anti*-enamine formation



Syn

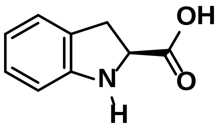


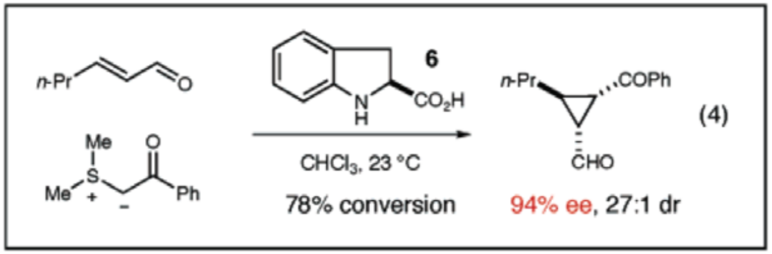
Anti

N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126, 2*, 450

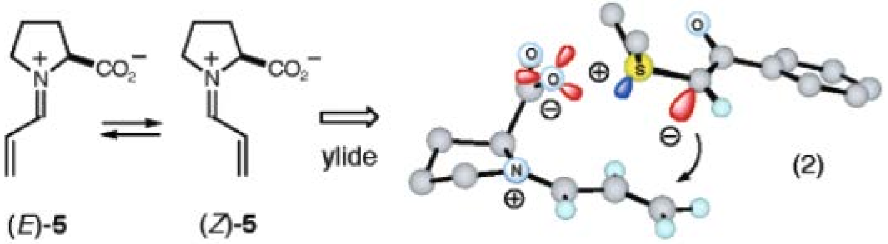
Core modification

Fused ring catalyst for cyclopropanation





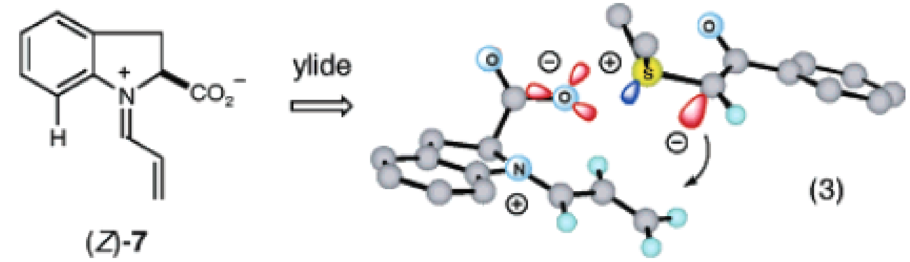
With proline: Conversion = 72% / ee = 46%



zwitterionic iminium
poor iminium control

directed electrostatic activation
good reactivity, low % ee

- With proline: Directed by carboxylate
- No E / Z selectivity
- Poor ee



van der Waals forces lead to
selective (Z)-iminium formation

retain electrostatic activation
good reactivity, high % ee

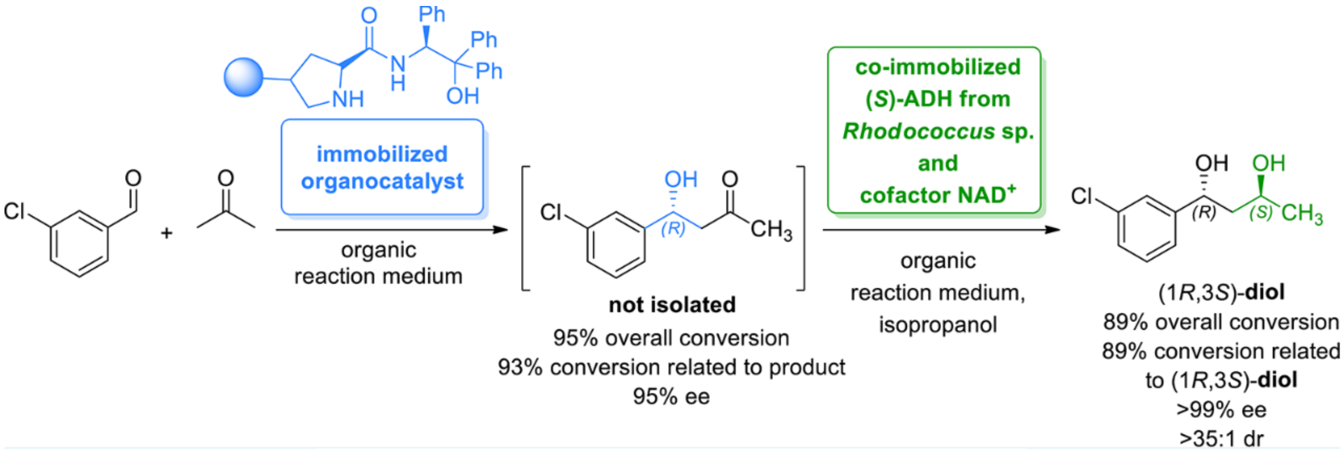
- Aromatic ring favors the Z iminium
- Minimize Van der Waals interaction between aryl hydrogen and olefin

R. K. Kunz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127, 3240*

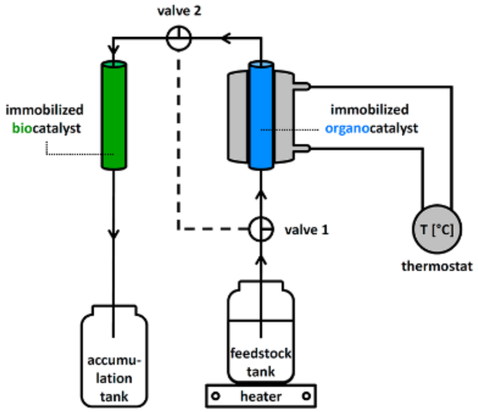
Core modification

Immobilized catalyst

- Reuse catalyst → high loading of proline? No problem!
- Green chemistry : industrial applications
- Design installation / applications
- Add novel proprieties



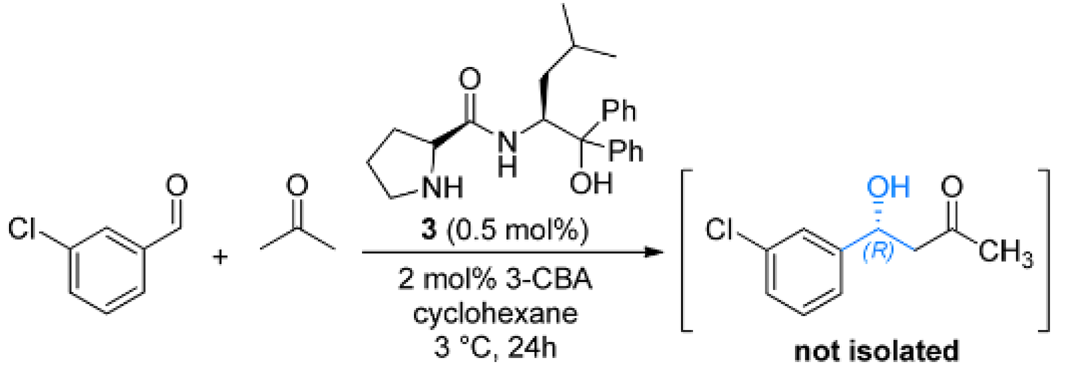
(B) Process with immob. catalysts separated in different compartments



M. Heidlindemann, G. Rulli, A. Berkessel, W. Hummel, H. Gröger, *ACS Catal.*. **2014**, *4*, 1099

Online-immobilized reactions

Immobilized catalyst



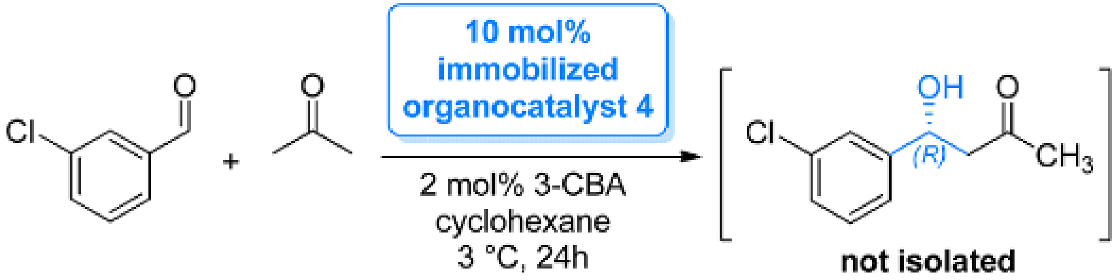
not isolated

(*R*)-**1**

95% overall conversion

93% conversion related to (*R*)-**1**

95% ee



not isolated

(*R*)-**1**

95% overall conversion

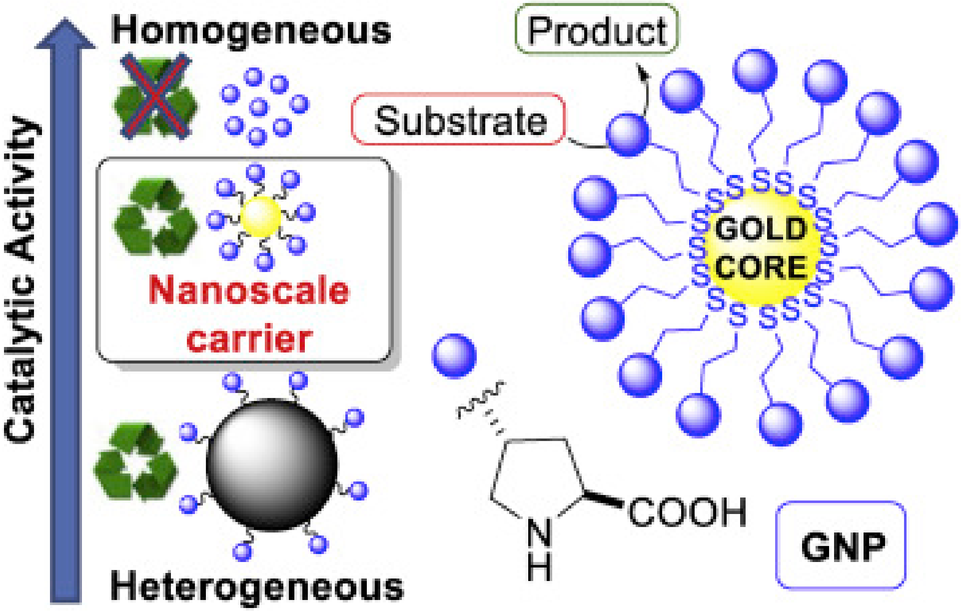
93% conversion related to (*R*)-**1**

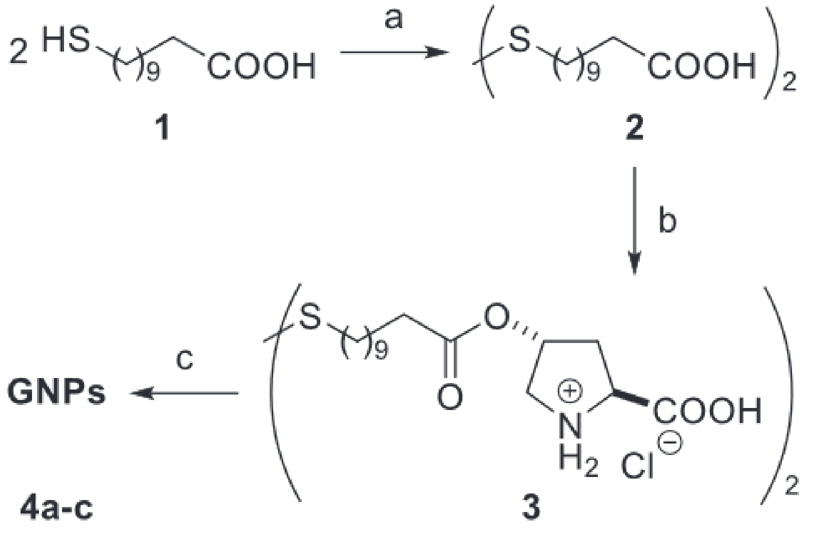
95% ee

M. Heidlindemann, G. Rulli, A. Berkessel, W. Hummel, H. Gröger, *ACS Catal.*. **2014**, *4*, 1099

Hetero – Homogeneous catalysis

Proline-coated GNP





(a) i) NaOH, H_2O_2, H_2O, rt, 1 h, ii) HCl, rt, 0.5 h, 86%
(b) i) $(COCl)_2$, CH_2Cl_2, rt, 3 h,
ii) 4-hydroxy-L-proline, TFA, rt, 16 h, 81%
(c) $HAuCl_4$, $NaBH_4$, DMSO, rt, 24 h 53%

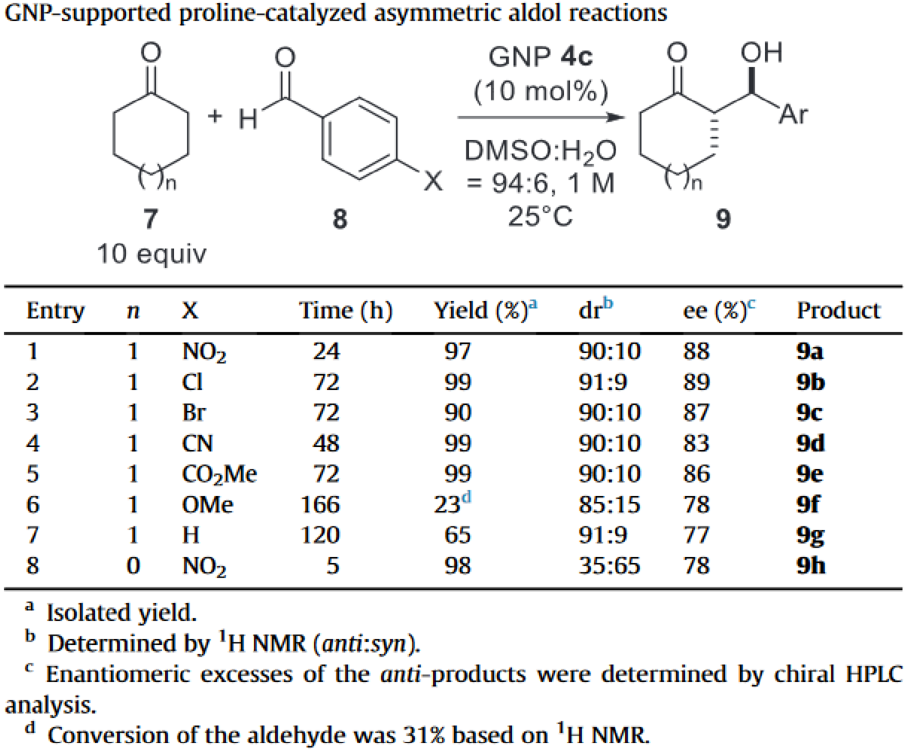
P. L. Soti, H. Yamashita, K. Sato, T. Narumi, M. Toda, n. Watanabe, G. Marosi, N. Mase, *Tetrahedron.* **2016**, *72*, 1984

Hetero – Homogeneous catalysis

Proline-coated GNP

- Screening

GNP-supported proline-catalyzed asymmetric aldol reactions



7 10 equiv

8

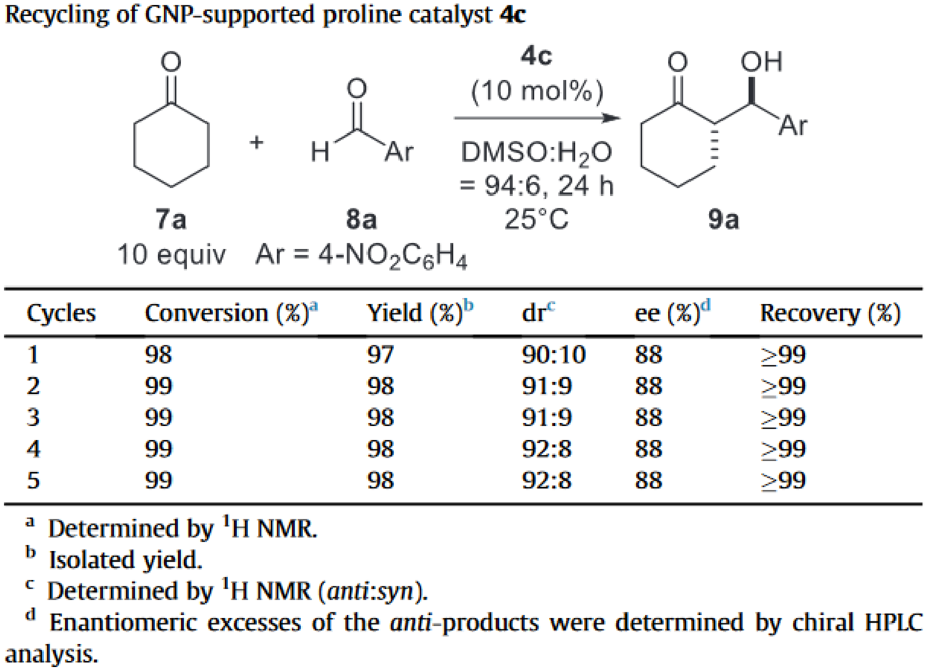
9

Entry	*n*	X	Time (h)	Yield (%)[a]	dr[b]	ee (%)[c]	Product
1	1	NO_2	24	97	90:10	88	**9a**
2	1	Cl	72	99	91:9	89	**9b**
3	1	Br	72	90	90:10	87	**9c**
4	1	CN	48	99	90:10	83	**9d**
5	1	CO_2Me	72	99	90:10	86	**9e**
6	1	OMe	166	23[d]	85:15	78	**9f**
7	1	H	120	65	91:9	77	**9g**
8	0	NO_2	5	98	35:65	78	**9h**

[a] Isolated yield.
[b] Determined by ^{1}H NMR (*anti*:*syn*).
[c] Enantiomeric excesses of the *anti*-products were determined by chiral HPLC analysis.
[d] Conversion of the aldehyde was 31% based on ^{1}H NMR.

- Reuse NP
(filtration + drying only)

Recycling of GNP-supported proline catalyst **4c**



7a 10 equiv

8a Ar = 4-$NO_2C_6H_4$

9a

Cycles	Conversion (%)[a]	Yield (%)[b]	dr[c]	ee (%)[d]	Recovery (%)
1	98	97	90:10	88	≥99
2	99	98	91:9	88	≥99
3	99	98	91:9	88	≥99
4	99	98	92:8	88	≥99
5	99	98	92:8	88	≥99

[a] Determined by ^{1}H NMR.
[b] Isolated yield.
[c] Determined by ^{1}H NMR (*anti*:*syn*).
[d] Enantiomeric excesses of the *anti*-products were determined by chiral HPLC analysis.

P. L. Soti, H. Yamashita, K. Sato, T. Narumi, M. Toda, n. Watanabe, G. Marosi, N. Mase, *Tetrahedron.* **2016**, *72*, 1984

Conclusions

Proline modularity

- L-Proline gave very good results
  - But in certain conditions only
- Limitations:
  - Solubility
    - Substitution of acid group
    - Additions of group on the core
  - Face selectivity
    - Increase steric hindrance on core
    - Substitute acid group
    - Add directing/repulsing group on core
  - Reactivity
    - Substitute acid group
    - Protect alcohol group
    - Linked to solubility
  - Enantioselectivity
    - Linked to face selectivity
    - Fine tuning
  - catalyst loading
    - Linked to reactivity
    - Make it reusable (heterogeneous cat.)
    - Fine tuning
- Some solutions has to be found

Conclusions

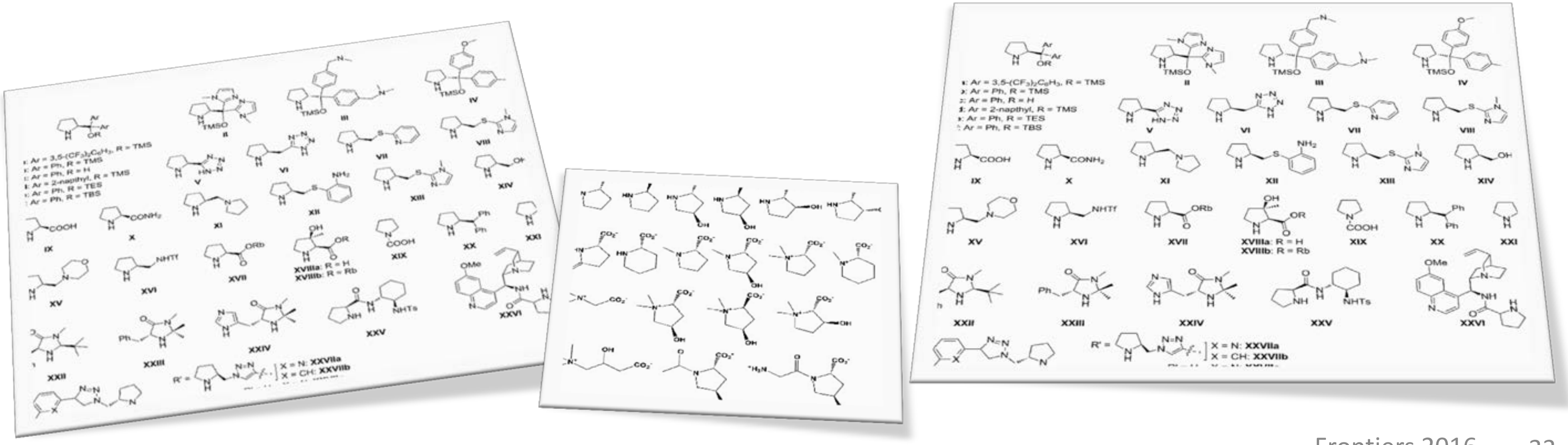
Proline modularity

No universal catalyst

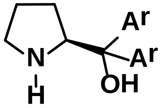
Reaction / substrate dependant

Many different structure possible and reported

- Heterocycle
- Substituted amine
- Different size of ring
- Etc…



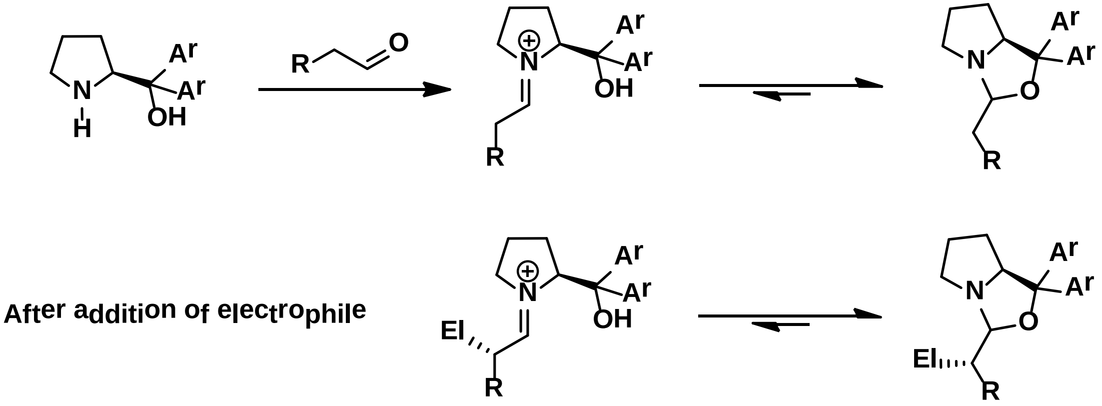
Questions



- Why free alcohol on prolinol catalyst decrease generally the reactivity?
- Why Nitro-Michael reactions are generally highly selective?
- What is important in order to have a good facial selectivity? (catalytic cycle)

Questions

- Formation of stable hemiaminal species



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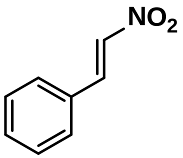
Questions



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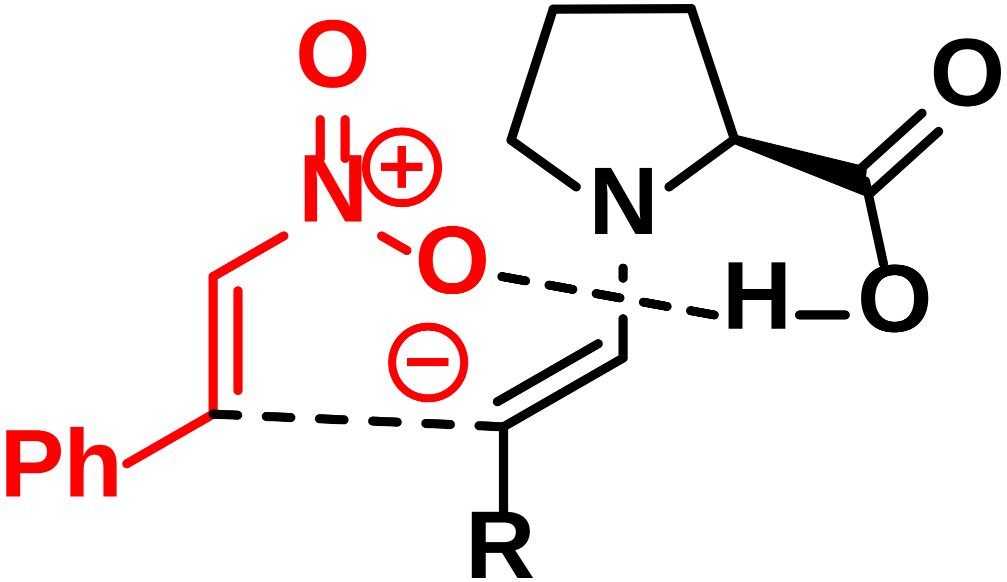
- Why Nitro-Michael reactions are generally highly selective?

- What is important in order to have a good facial selectivity? (catalytic cycle)

Questions



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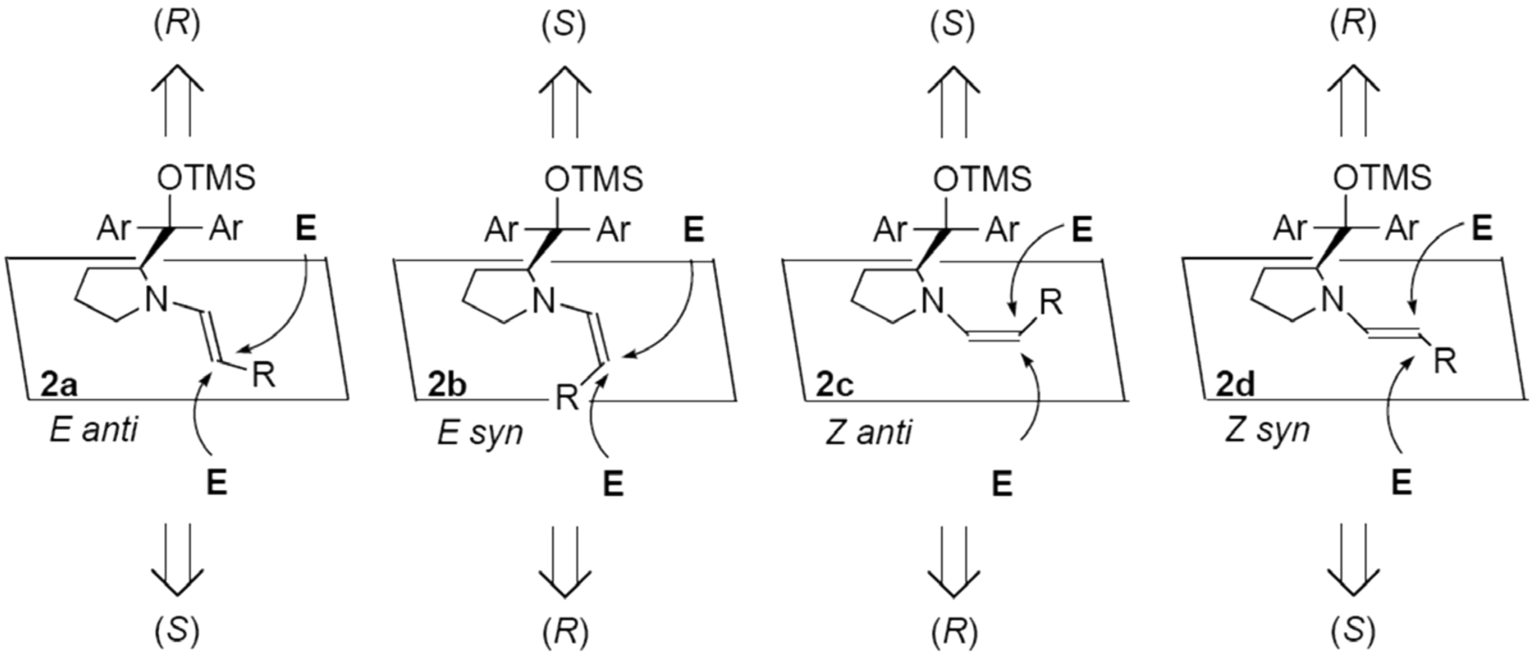

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