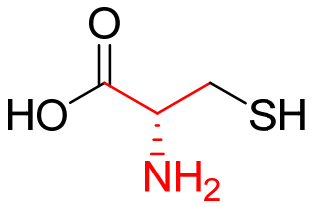
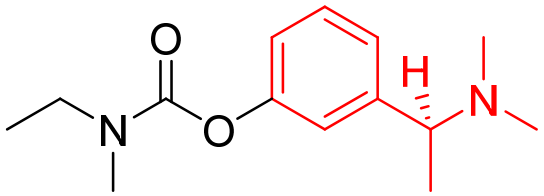
Chiral Amines

Chiral amine: Ubiquitous structure motif of natural products, drugs.



(R)-Cysteine

Non-essential amino acid



(S)-Rivastigmine

Trade name: Exelon
Treatment of dementia - Alzheimer's disease

Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.;* Springer: New York, **2004**; Suppl. 1, p 43
Nicholas J Turner, *Nature Chemical Biology* **5**, 567 - 573

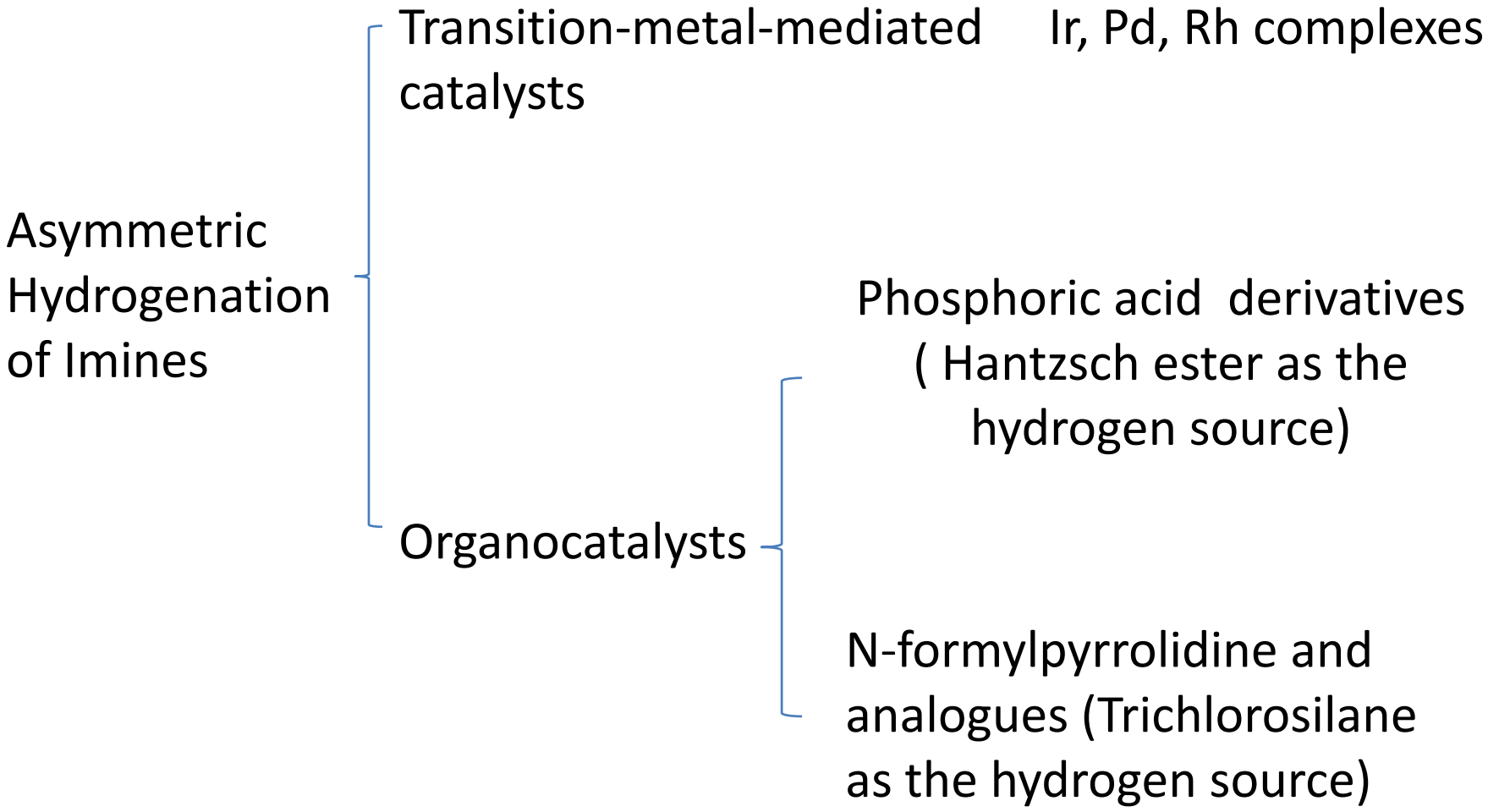
Synthetic Methods for Chiral Amines

- Asymmetric Hydrogenation of Imines
- Asymmetric Hydrogenation of Enamides
- Asymmetric Amination of Ketones
- Amine Alkylation to a Chiral Alkyl Halides

Asymmetric hydrogenation is important in research and industry.

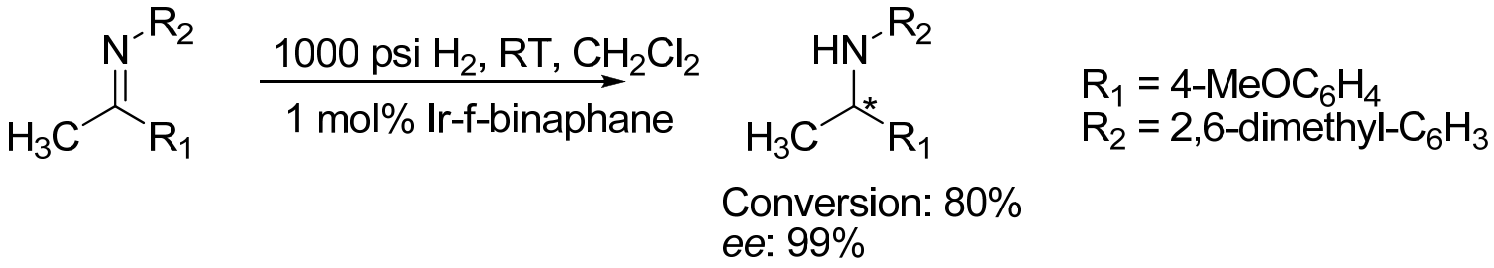
D. Xiao, and X. Zhang, *Angew. Chem. Int. Ed.* **2001**, *40*, 3425
Anna Trifonova, Jarle S. Diesen, and Pher G. Andersson. *Chem. Eur. J.* **2006**, *12*, 2318 – 2328

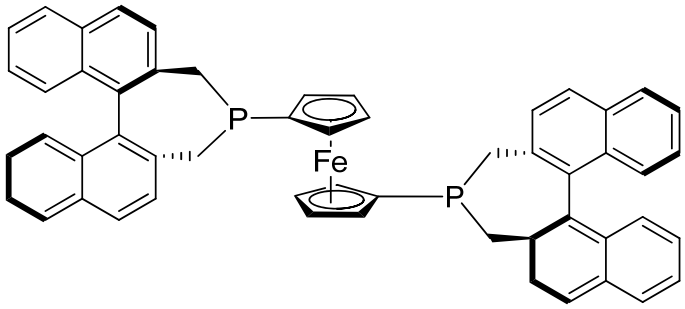
Asymmetric Hydrogenation of Imines



Transition Metal Catalyst

Many transition metals can be used for imine hydrogenation.
Ir complexes are currently the most prevalent.





(R,R)-f-binaphane

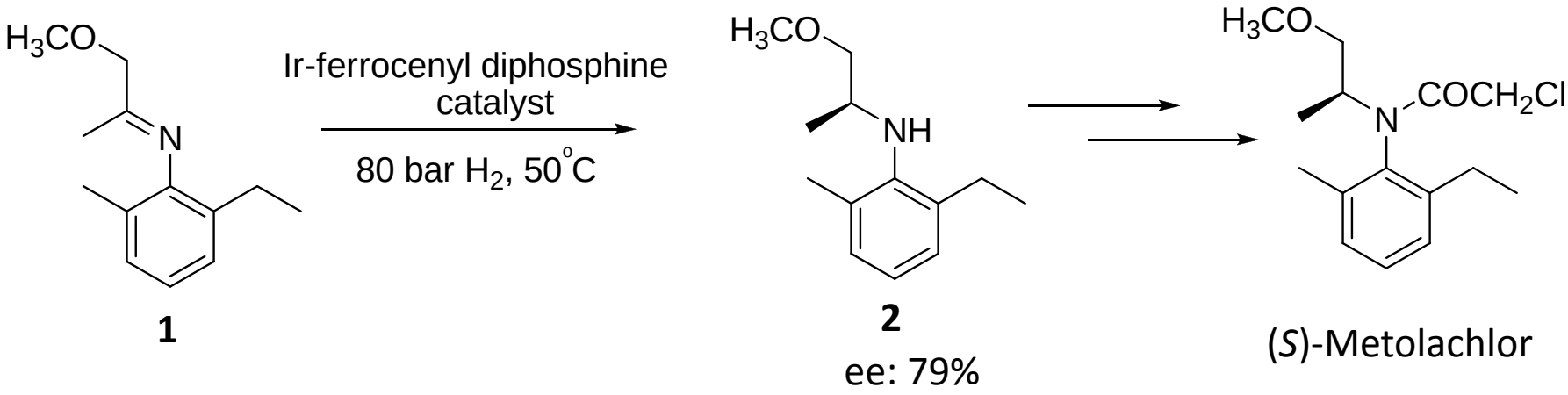
Anna Trifonova, Jarle S. Diesen, and Pher G. Andersson. *Chem. Eur. J.* **2006**, *12*, 2318 – 2328

J. C. Cobley, J. P. Henschke*, Adv. Synth. Catal.* **2003**, *345*, 195.

V. I. Tararov,R. Kadyrov, T. H. Riermeier, C. Fischer, A. Borner, *Adv. Synth. Catal*. **2004**, *346*, 2004

Industrial Applications: Synthesis of (S)-Metolachlor

Trade name: Dual Magnum (a popular herbicide)



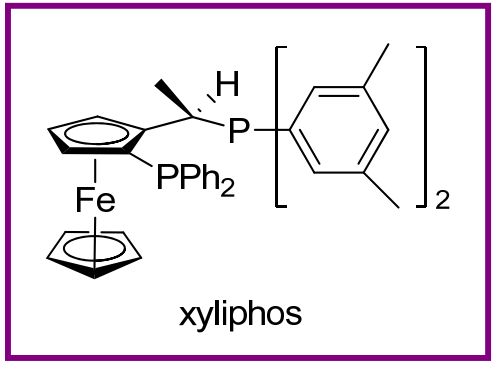
1

2

ee: 79%

(*S*)-Metolachlor

Ligand structure:

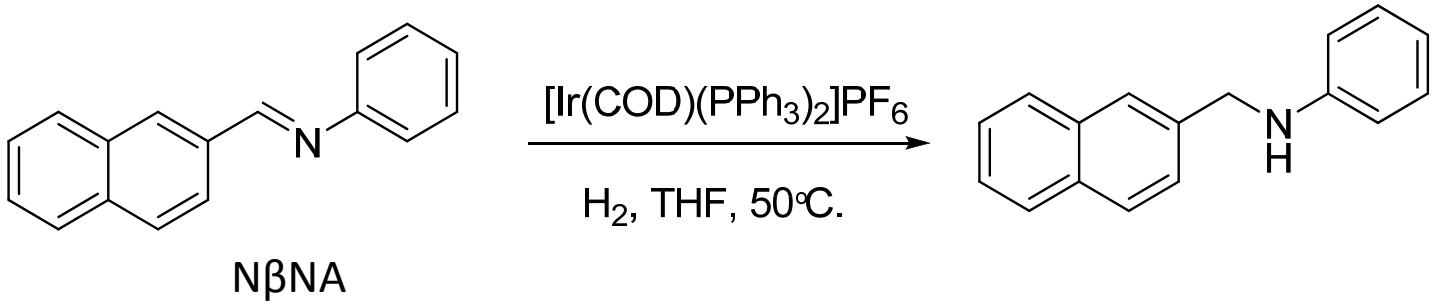


xyliphos

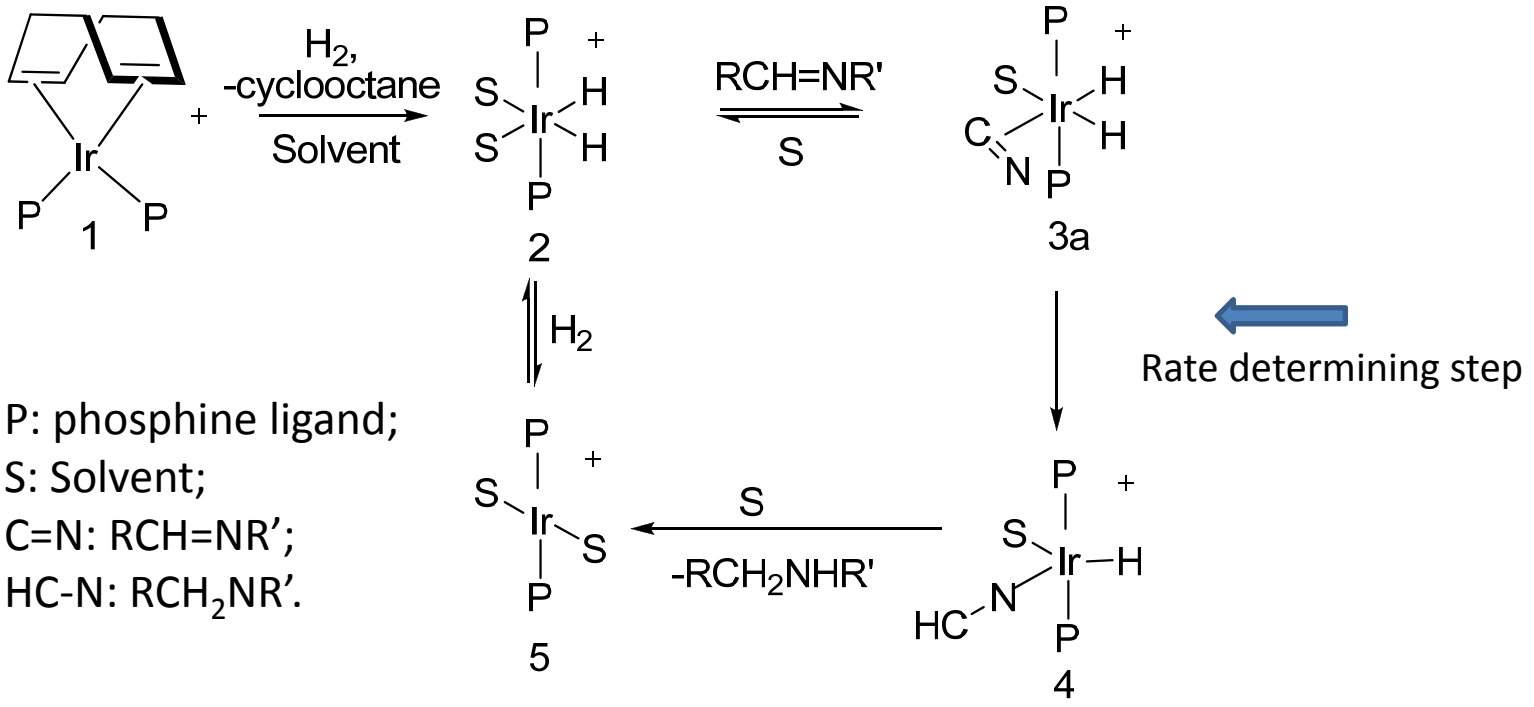
Turnover: > 1000,000
Scale: > 10,000 t/y

H.-U. Blaser, R. Hanreich, H.-D. Schneider, F. Spindler, B. Steinacher in *Asymmetric Catalysis on Industrial Scale* (Eds.: H.-U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**, pp 55– 70

Proposed Catalytic Cycle for Ir Catalyzed Imine Hydrogenation



NβNA

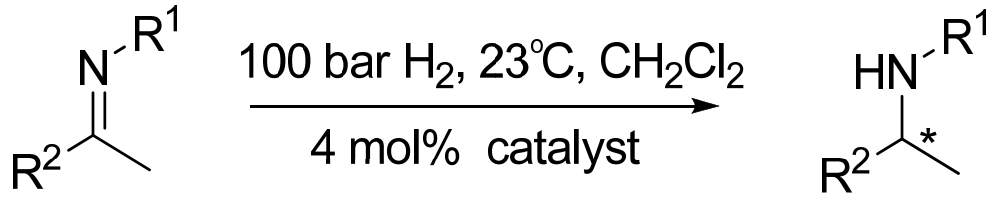


P: phosphine ligand;
S: Solvent;
C=N: RCH=NR';
HC-N: RCH_2NR'.

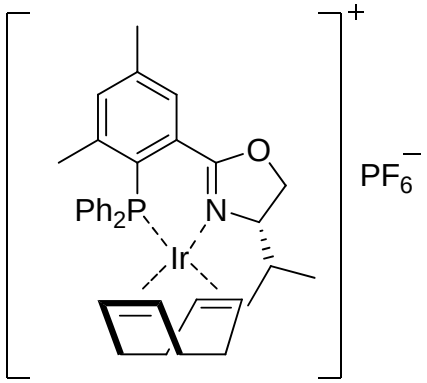
Calculated rate constant: k_{cat} = 2.8x 10^3 $M^{-2}s^{-1}$

Herrera, V.; Munoz, B.; Landaeta, V.; Canudas, N. *J. Mol. Catal.* **2001,** *174,* 141**.**

Pfaltz's Catalyst in Asymmetric Hydrogenation of Imines



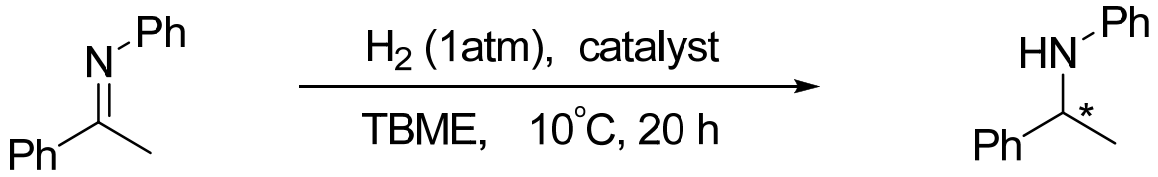
Catalyst



Entry	R^1	R^2	Conversion/%	*ee*/%
1	Ph	Ph	100	71
2	Bn	2-naphthyl	100	69
3	Bn	Ph	100	76

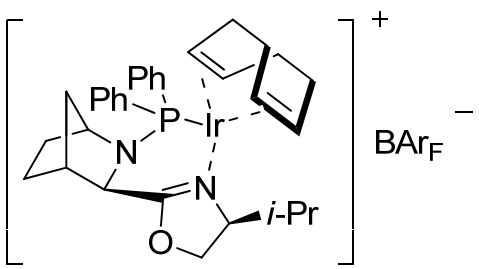
P. Schnider, G. Koch, R. Prétôt, G. Wang, F. Bohnen, C. Krüger, A. Pfaltz, *Chem. Eur. J.* **1997**, *3*, 887

Introducing a Bulkier Scaffold to Increase *ee*

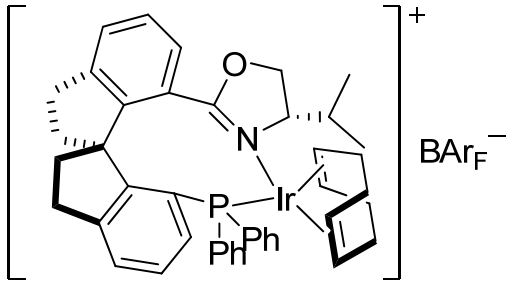


TBME: methyl t-Butyl ether

Entry	Catalyst	Catalyst Loading (mol%)	*ee*/%
1	1	0.5	90
2	2	1	93



1



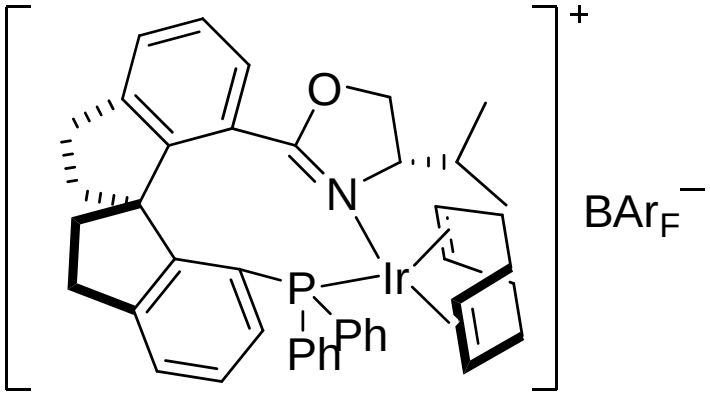
2

BAr_F^-: $B(3,5\text{-}(CF_3)_2C_6H_3)_4^-$

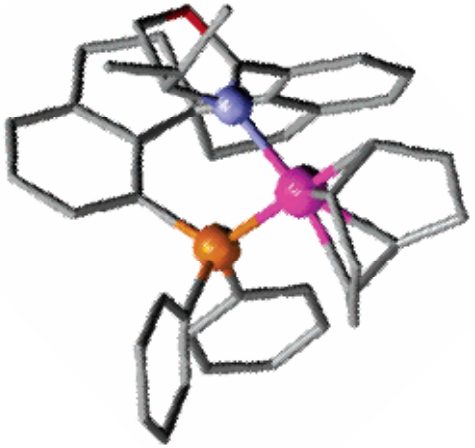
Shou-Fei Zhu, Jian-Bo Xie, Yong-Zhen Zhang, Shen Li, and Qi-Lin Zhou, *J. Am. Chem. Soc*. **2006**, *128*, 12886-12891

Crystal Structure of the Catalyst

Catalyst



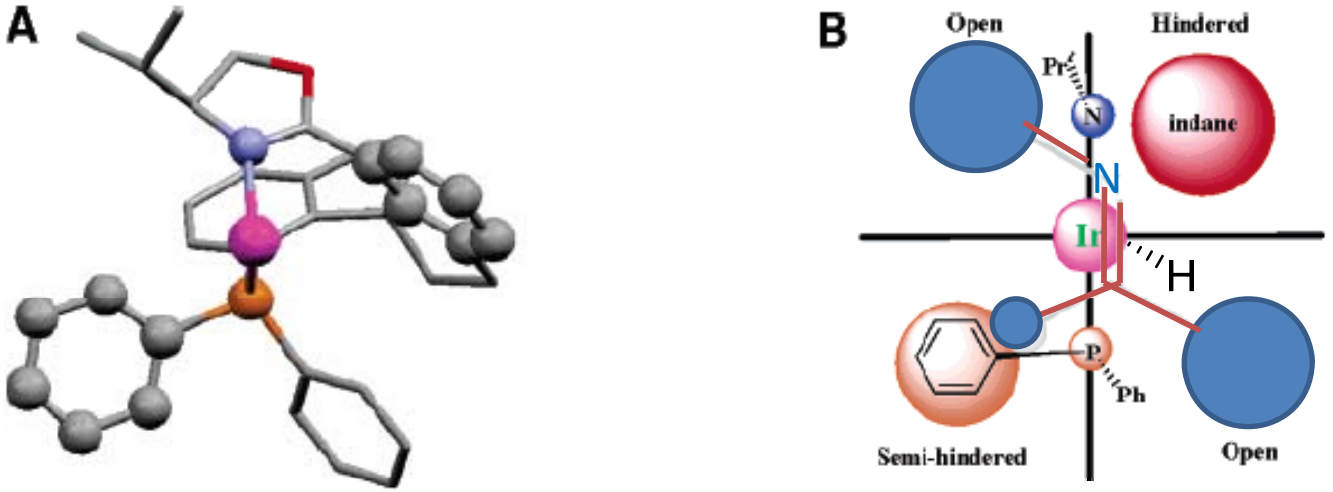
Crystal structure



BAr_F^- and hydrogen atoms omitted for clarity

Shou-Fei Zhu, Jian-Bo Xie, Yong-Zhen Zhang, Shen Li, and Qi-Lin Zhou, *J. Am. Chem. Soc*. **2006**, *128*, 12886-12891

Proposed Model for Stereochemistry

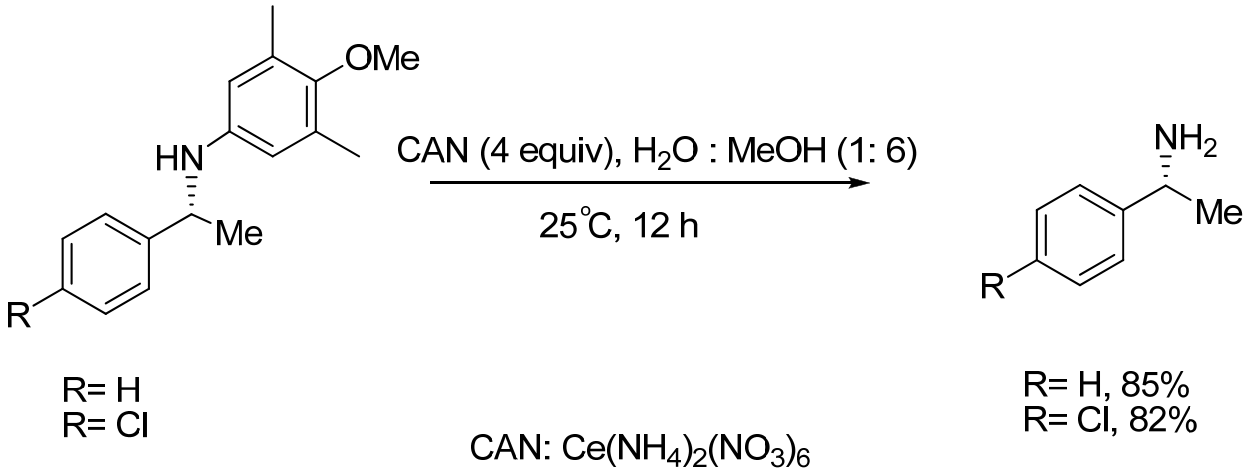


The hydride has to attack from the *Si* face, giving amines with R configuration.

Shou-Fei Zhu, Jian-Bo Xie, Yong-Zhen Zhang, Shen Li, and Qi-Lin Zhou, *J. Am. Chem. Soc*. **2006**, *128*, 12886-12891

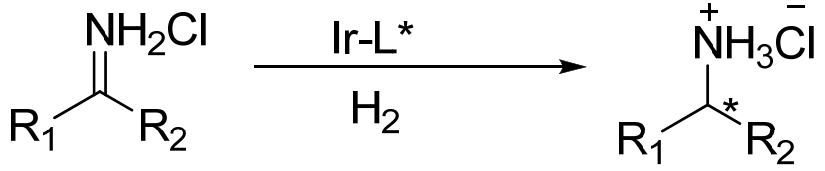
N-aryl Group Cleavage

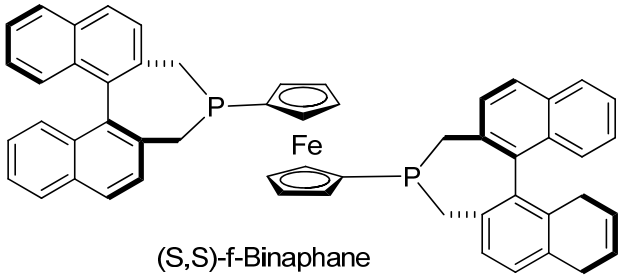
Only N-aryl groups with methoxy groups can be easily cleaved.



Murthy N. Cheemala and Paul Knochel. *Org. Lett.* **2007**, *9*, 3089

Hydrogenation of Unprotected Imines



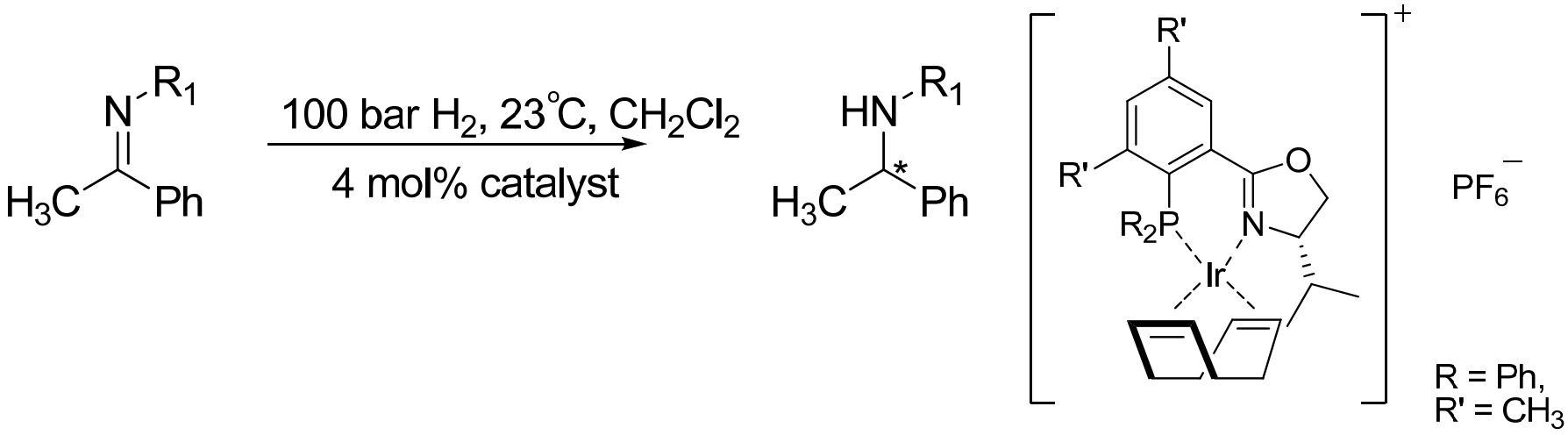


Ligand

Entry	R_1	R_2	Yield/%	*ee*/%
1	Ph	Me	93	93(R)
2	Ph	Et	92	86(R)
3	Ph	*n*-Bu	92	88(R)
4	4-$MeOC_6H_4$	Me	95	93(R)
5	4-ClC_6H_4	Me	95	94(R)

G.Hou, F. Gosselin, W. Li, J. C. McWilliams, Y. Sun, M. Weisel, Paul D. O'Shea, C. Chen, Ian W. Davies, and X. Zhang, *J. Am. Chem. Soc*. **2009***, 131,* 9882–9883

Hydrogenation of N-Alkyl Imines



Entry	R_1	Conversion/%	*ee*/%
1	Me	100	58
2	*n*Bu	100	75

P. Schnider, G. Koch, R. Prétôt, G. Wang, F. Bohnen, C. Krüger, A. Pfaltz, *Chem. Eur. J.* **1997**, *3*, 887

Drawbacks of transition metal catalysts:

- Expensive;
- Toxicity;
- Metal Leaching problem.

Cheaper and ‘greener’ organocatalysts:

•Phosphoric acid derivatives + Hantzsch ester (hydrogen source)

•N-formylpyrrolidine and analogues + trichlorosilane (hydrogen source)

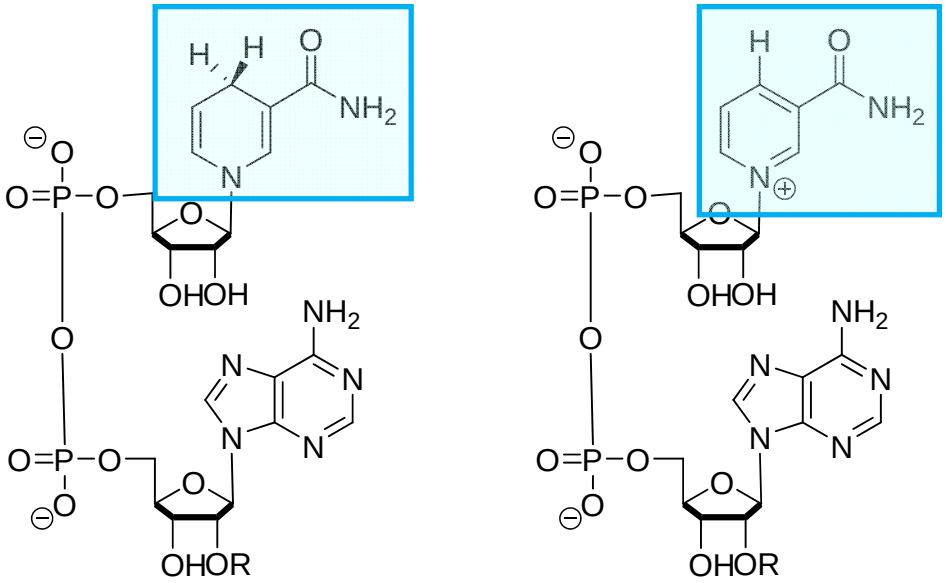
In vivo oxidoreductions

The use of Hantzsch esters as the hydrogen source was inspired by the interconversion of NAD(P)H and NAD(P)$^+$ which are the key compounds for *in vivo* oxidoreductions.

NADH: Nicotinamide adenine dinucleotide

NADPH: nicotinamide adenine dinucleotide phosphate

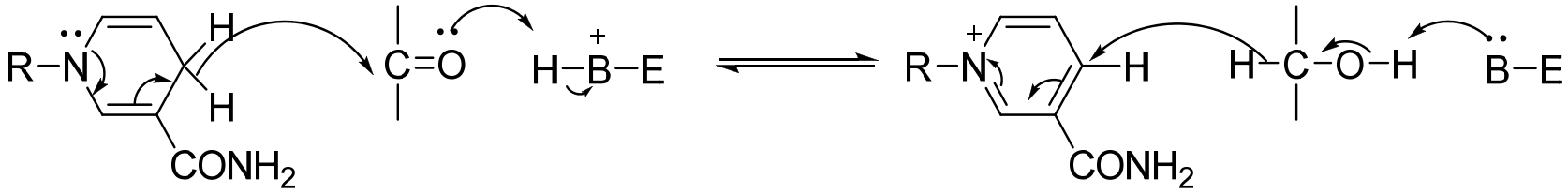
Structure of NAD(P)H and NAD(P)$^+$



Tommaso Marcelli, Peter Hammar, and Fahmi Himo. *Chem. Eur. J.* **2008**, *14*, 8562 – 8571

P. A. Frey, A. D. Hegeman, *Enzymatic Reaction Mechanisms*, Oxford University Press, New York, **2007**, Chapter 3

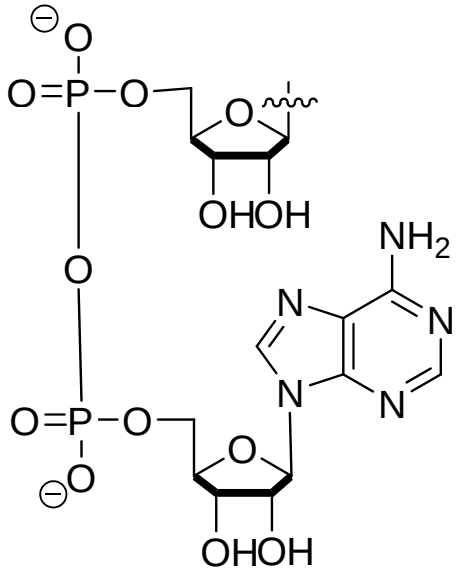
Scheme for *in vivo* Oxidoreduction



NADH

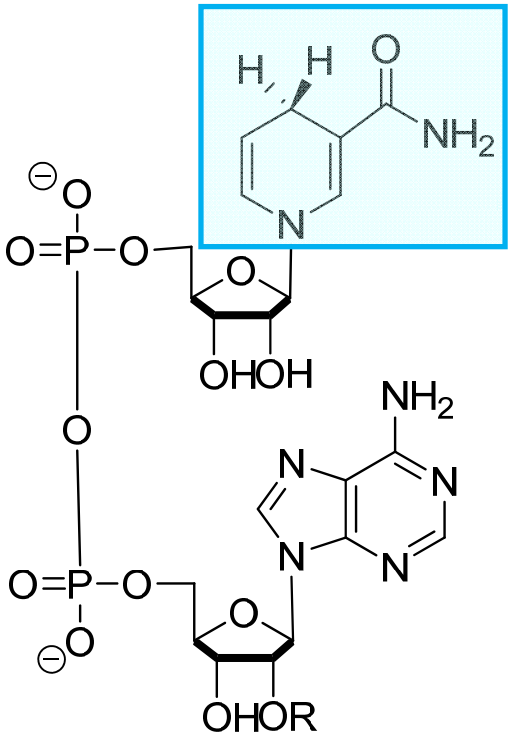
R:

NAD+

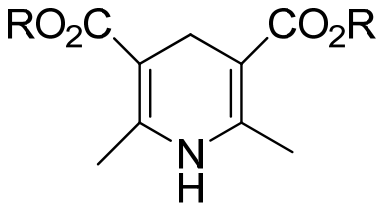


P. A. Frey, A. D. Hegeman, Enzymatic Reaction Mechanisms, Oxford University Press, New York, 2007, Chapter 3

Hantzsch esters: mimics of NAD(P)H



NADH: R=H
NADPH: R=PO_3^{2-}



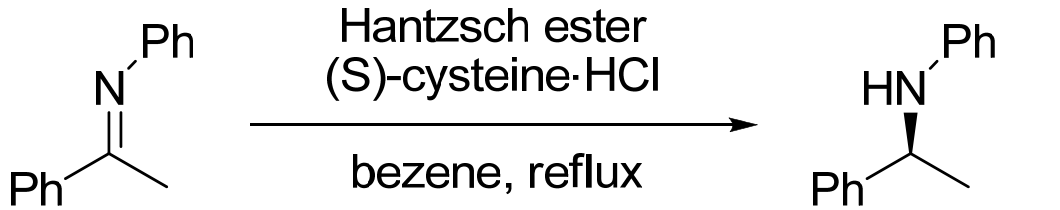
Hantzsch ester

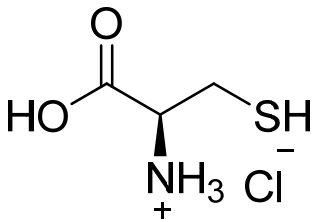
R = Me, Et

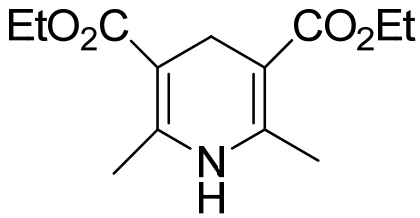
Hantzsch esters: mimics of NAD(P)H

Tommaso Marcelli, Peter Hammar, and Fahmi Himo. *Chem. Eur. J.* **2008**, 14, 8562 – 8571

First Enantioselective Hydrogenation using Hantzsch Ester

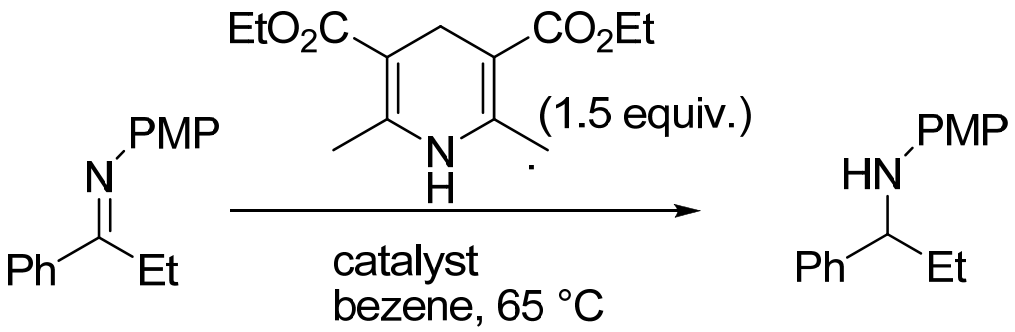






S. Singh, U. K. Batra, *Ind. J. Chem., Sect. B.* **1989**, *28*, 1–2.

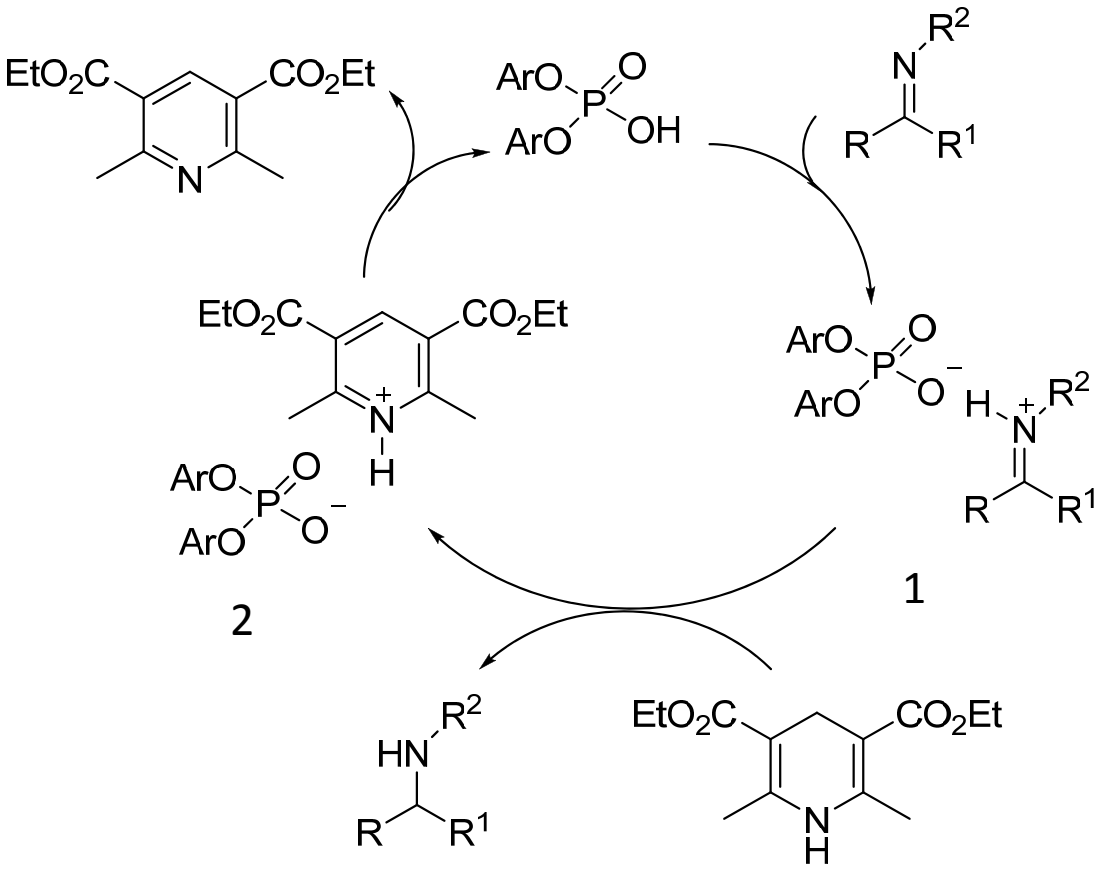
Diphenyl Phosphate is the Best Brønsted Acid



Entry	Brønsted acid	mol% of acid	Yield(%)
1	HCl	10	41
2	TFA	10	74
3	HBF_4	10	71
4	Diphenyl phosphate	10	82
5	Diphenyl phosphate	5	76
6	None	none	0

M. Rueping, C. Azap, E. Sugiono, T. Theissmann, *Synlett*, **2005**, 2367 – 2369

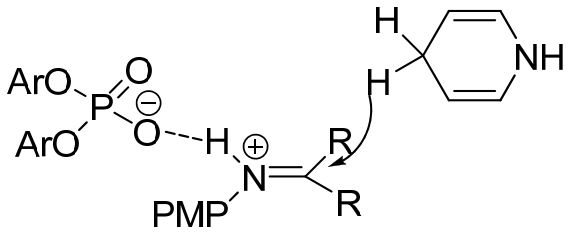
Catalytic Cycle



Major driving force is the formation of stable pyridine derivatives.

M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781 –3783

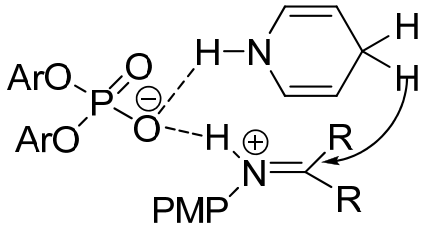
Why is Diphenyl Phosphate Better than Other Acids ?



10 kcal/mol

c

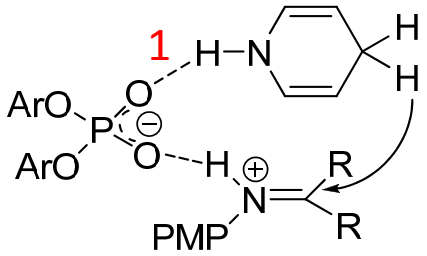
c) Bronsted acid pathway



6 kcal/mol

b

b) mono-coordinated Lewis base/Bronsted acid pathway,



0 kcal/mol

a

a) Di-coordinated Lewis base/Bronsted acid pathway,

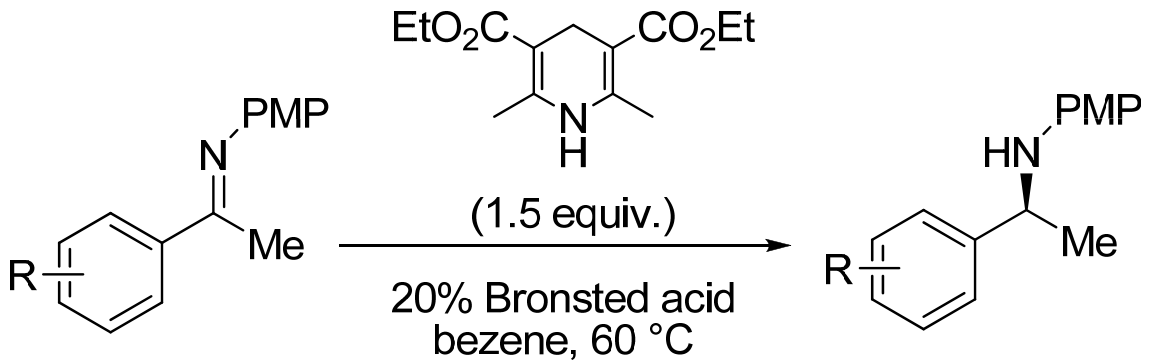
Diphenyl phosphate functions as a Brønsted acid and a Lewis base.

H-bond 1 stabilizes the developing positive charge on the nitrogen atom of the Hantzsch ester;

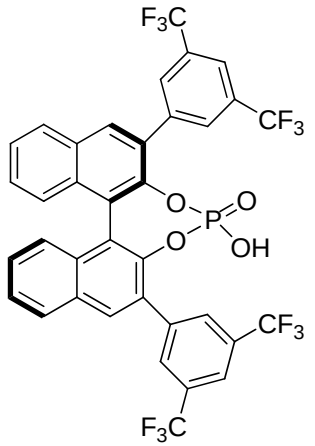
Protonation of the imine lowers the energy barrier for hydride transfer.

Tommaso Marcelli, Peter Hammar, and Fahmi Himo. *Chem. Eur. J.* **2008**, *14*, 8562 – 8571

Chiral Phosphoric Acid Catalyzed Hydrogenation of Imines



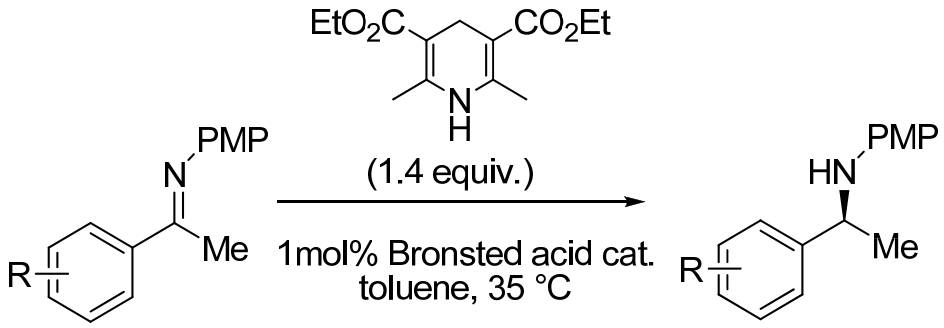
Brønsted acid



Entry	R	Yield(%)	*ee*/%
1	H	76	74
2	2-F	82	84
3	2-CH_3	74	78
4	4-CH_3	91	78
5	4-MeO	76	72

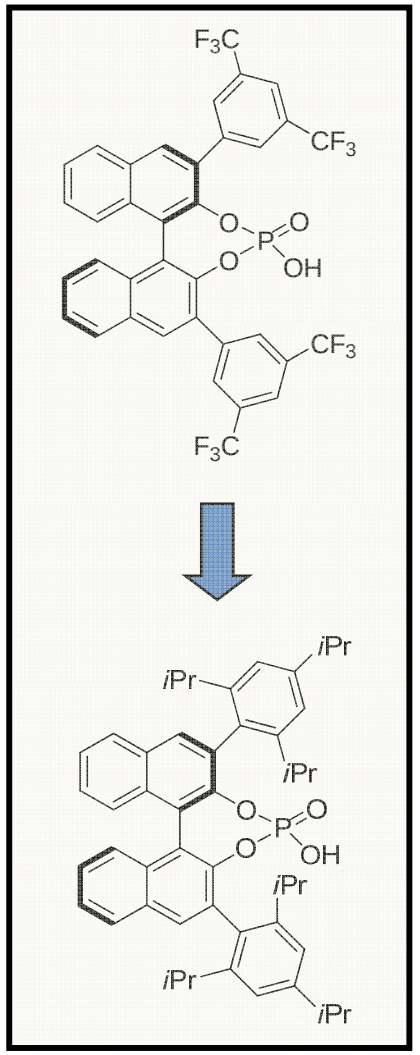
M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781 –3783

In Pursuit of a Better Catalyst



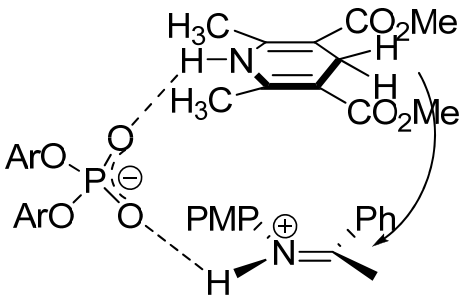
Entry	R	Yield(%)	*ee*(%)
1	H	96	88
2	2-F	95	85
3	2-Me	91	93
4	4-NO_2	96	80
5	4-Me	98	88

catalyst

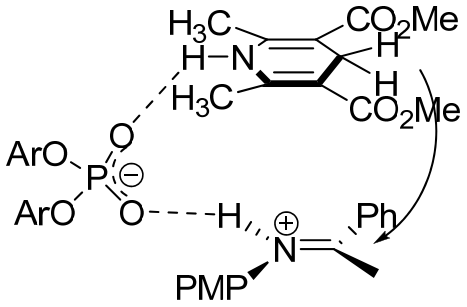


S. Hoffmann, A. Majeed Seayad, B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 7424 –7427

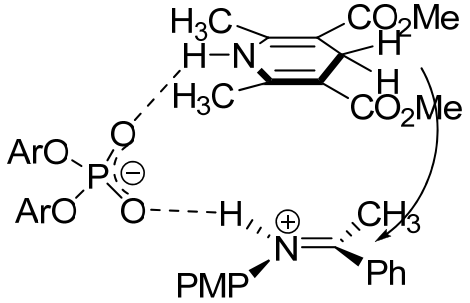
Origin of Stereochemistry



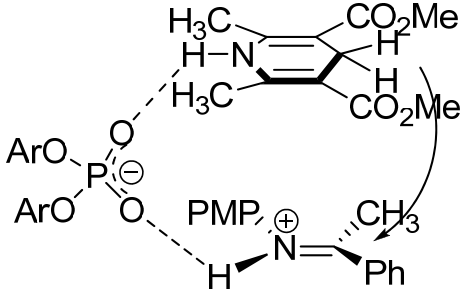
Z imine,
hydride attack Re face
0 kcal/mol.



E imine,
hydride attack Re face
2.6 kcal/mol



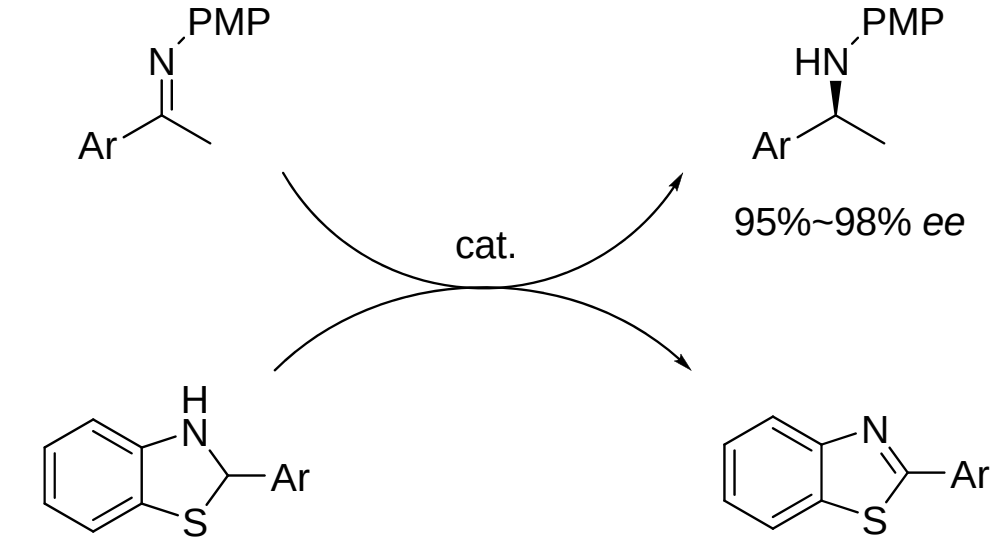
Z imine,
hydride attack Si face
2.3 kcal/mol



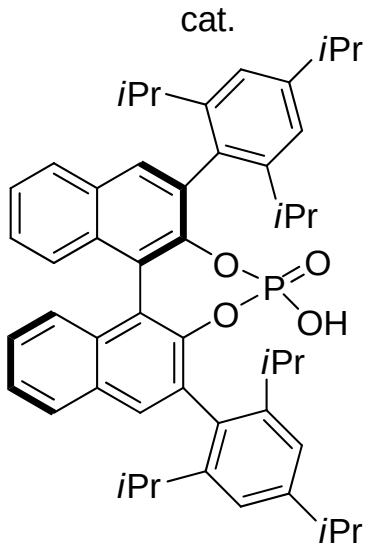
E imine,
hydride attack Si face
2.3 kcal/mol

Tommaso Marcelli, Peter Hammar, and Fahmi Himo, *Chem. Eur. J.* **2008**, *14*, 8562 – 8571

Benzothiazoline: Surrogate of Hantzsch Ester



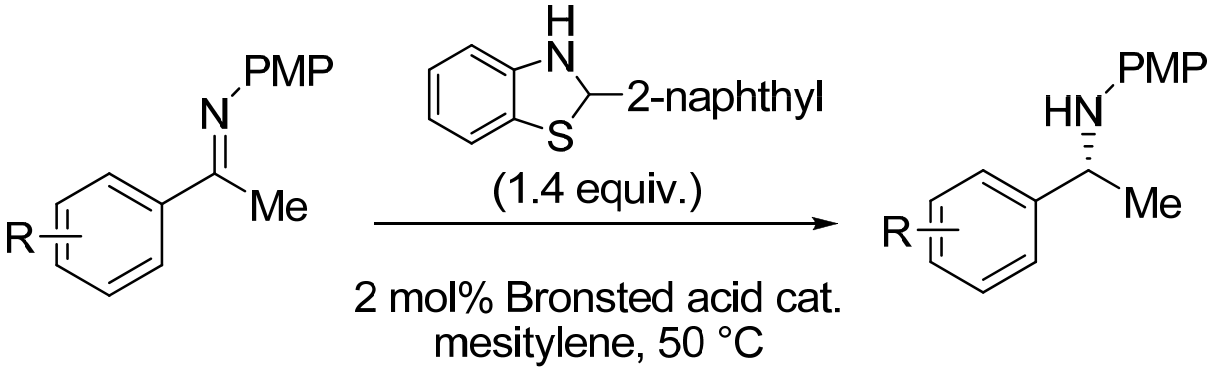
benzothiazoline benzothiazole

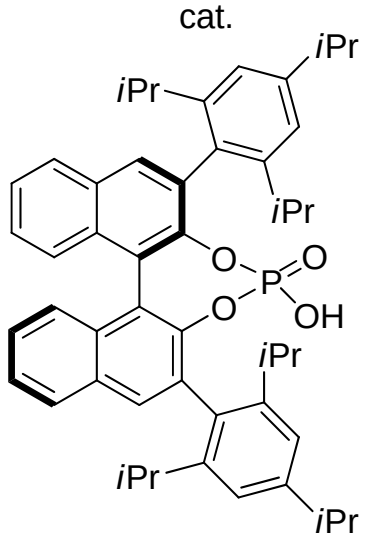


Driving force: formation of a stable benzothiazole.

Chen Zhu and Takahiko Akiyama, *Org. Lett.,* **2009**, *11*, 4180

Substrate Scope

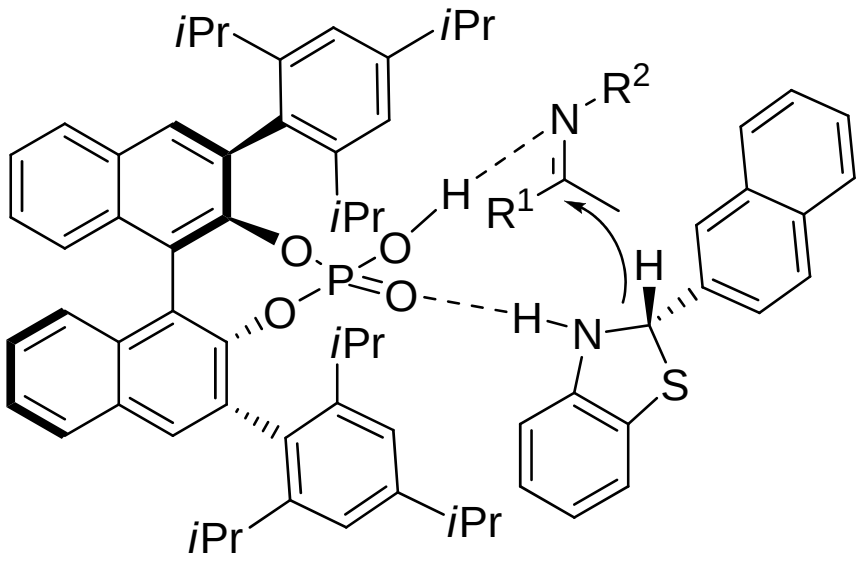




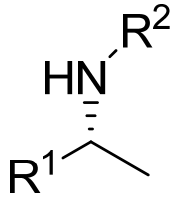
Entry	R	Yield(%)	*ee*/%
1	H	90	98
2	4-F	92	98
3	4-NO_2	86	95
4	4-Me	93	98
5	4-MeO	84	98

Chen Zhu and Takahiko Akiyama *Org. Lett.,* **2009**, *11*, 4180

Proposed Transition State

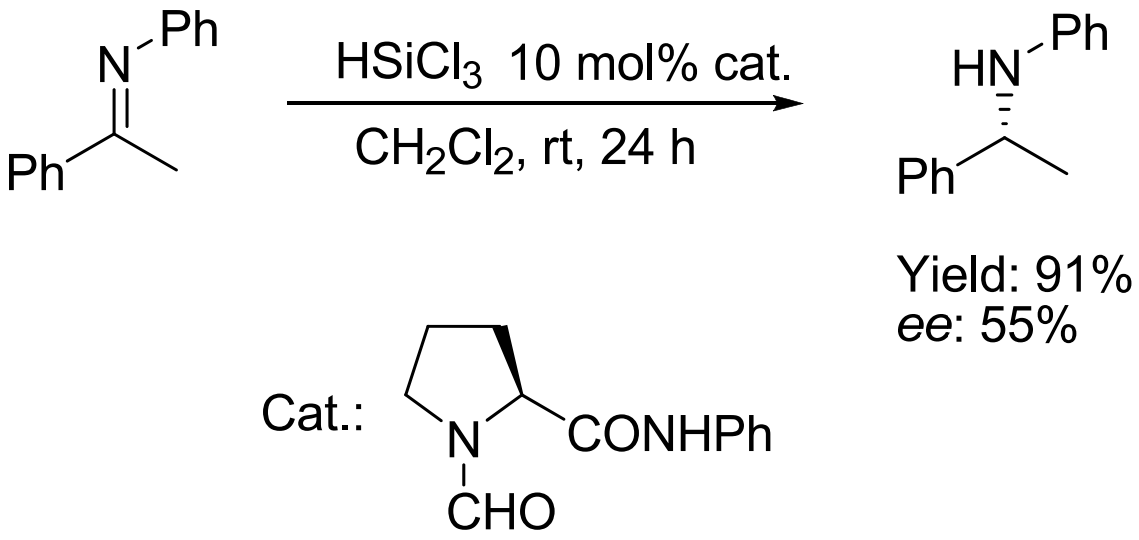


Hydride attack at the *Si* face gives the *R* amine.



Chen Zhu and Takahiko Akiyama *Org. Lett.,* **2009**, 11, 4180

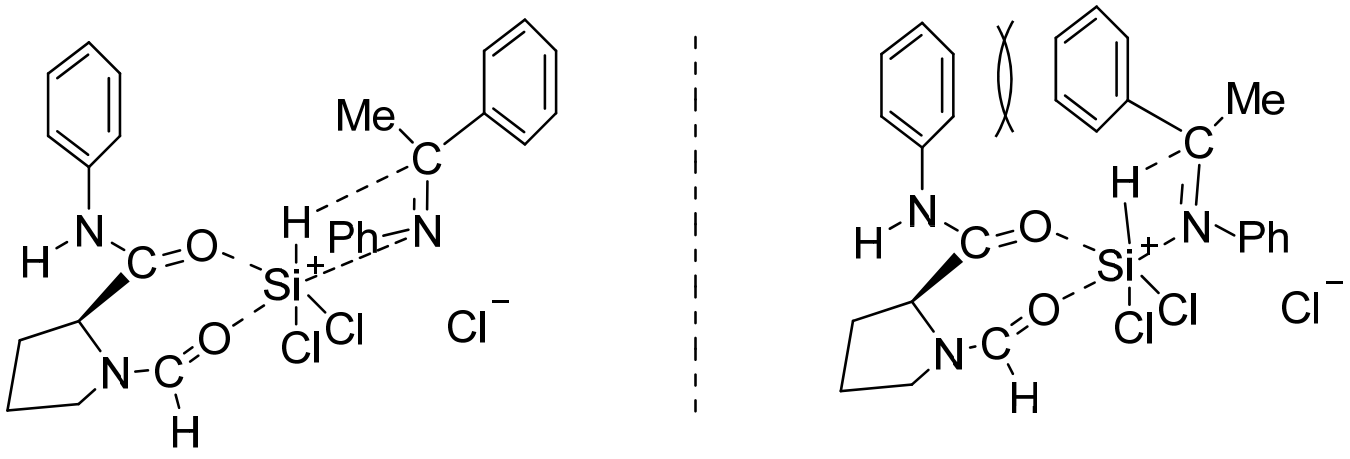
First Stereoselective Reduction of Imines Using Trichlorosilane



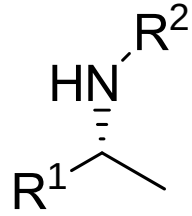
N-formylpyrrolidine

Iwasaki, F.; Omonura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, *42*, 2525

Proposed Transition States for Asymmetric Reduction

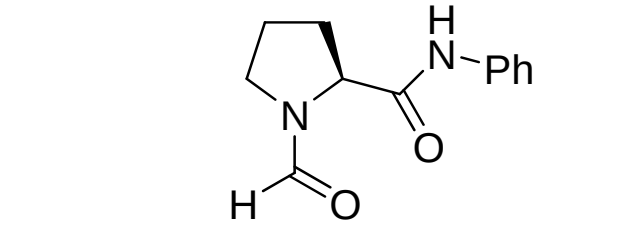


Steric effect dominates,
(R)-amine is the major product

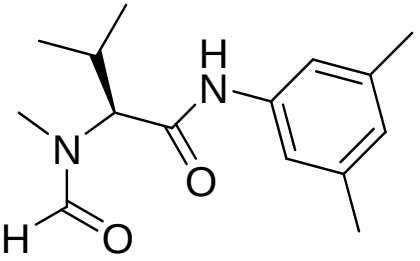


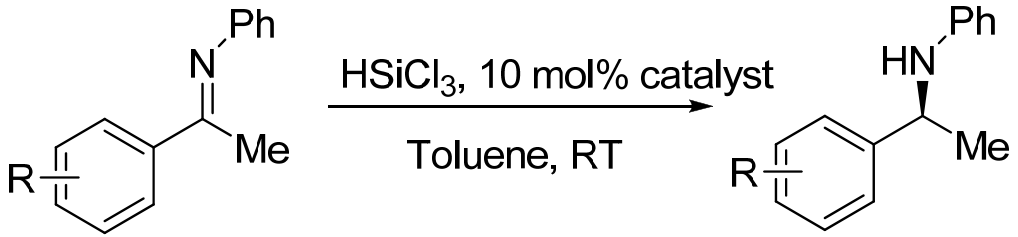
Iwasaki, F.; Omonura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, *42*, 2525

Replacing the Rigid Cyclic Ring with an Isopropyl Group



Highest ee: 55%

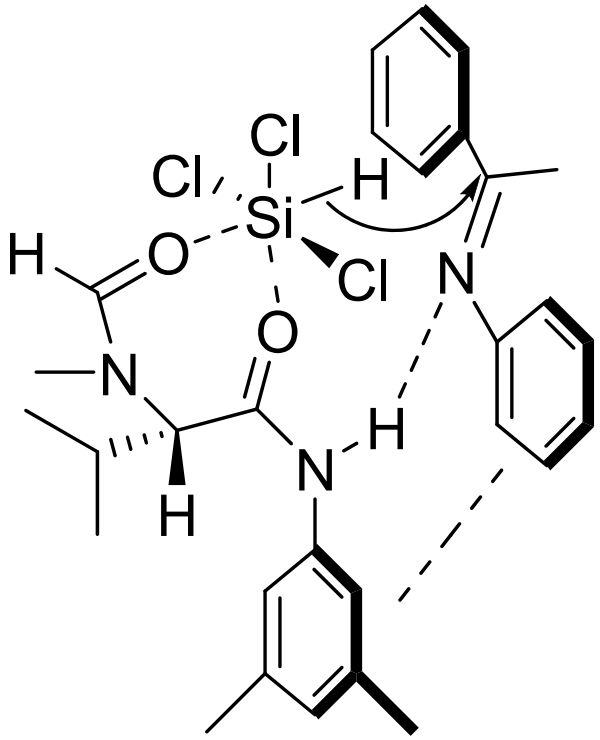




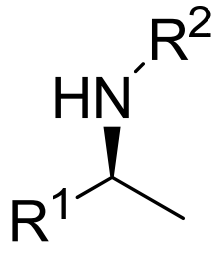
Entry	R	Yield(%)	*ee*/%
1	H	81	92
2	4-MeO	86	85
3	4-CF_3	86	89

Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Kocovsky, P. *Org. Lett.* **2004**, *6*, 2253.

Proposed Transition State

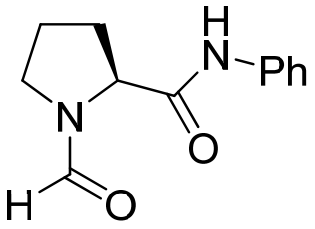


π-π interaction dominates,
(S)-amine is the major product

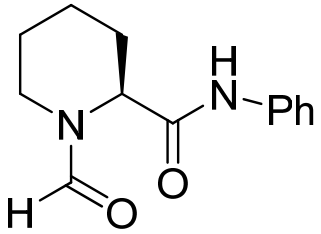


Malkov, A. V.; Mariani, A.; MacDougall, K. N.; Kocovsky, P. *Org. Lett.* **2004**, *6*, 2253

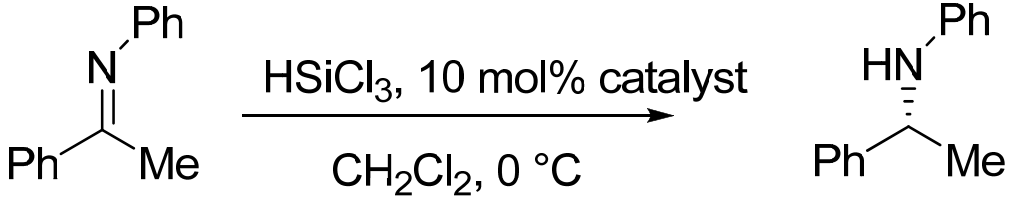
Replacing the 5-membered Ring with a Less rigid 6-membered Ring



1



2

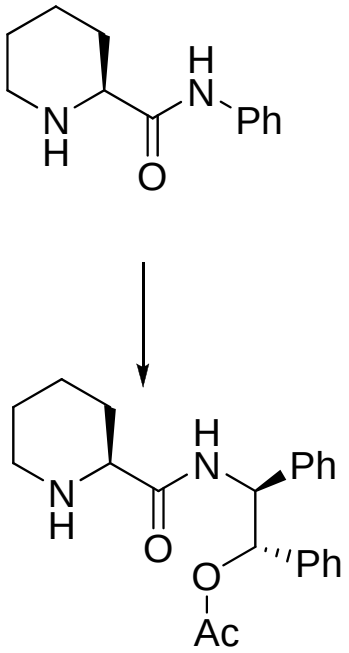


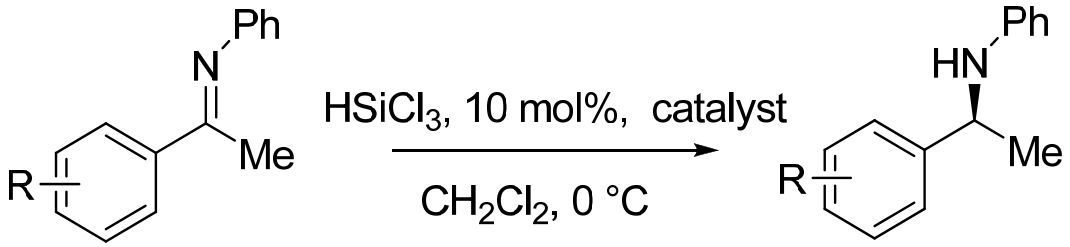
Catalyst	Yield(%)	*ee*/%
1	75[a]	59[a]
2	94	73

a: The yield and *ee* were measured at 0 °C; at RT, the values were 91 % yield and 55 5 *ee* .

Z. Wang, X. Ye, S. Wei, P. Wu, A. Zhang and J. Sun, *Org. Lett.*, **2006**, *8*, 999.

Further Improvement of the 6-membered Ring Catalyst

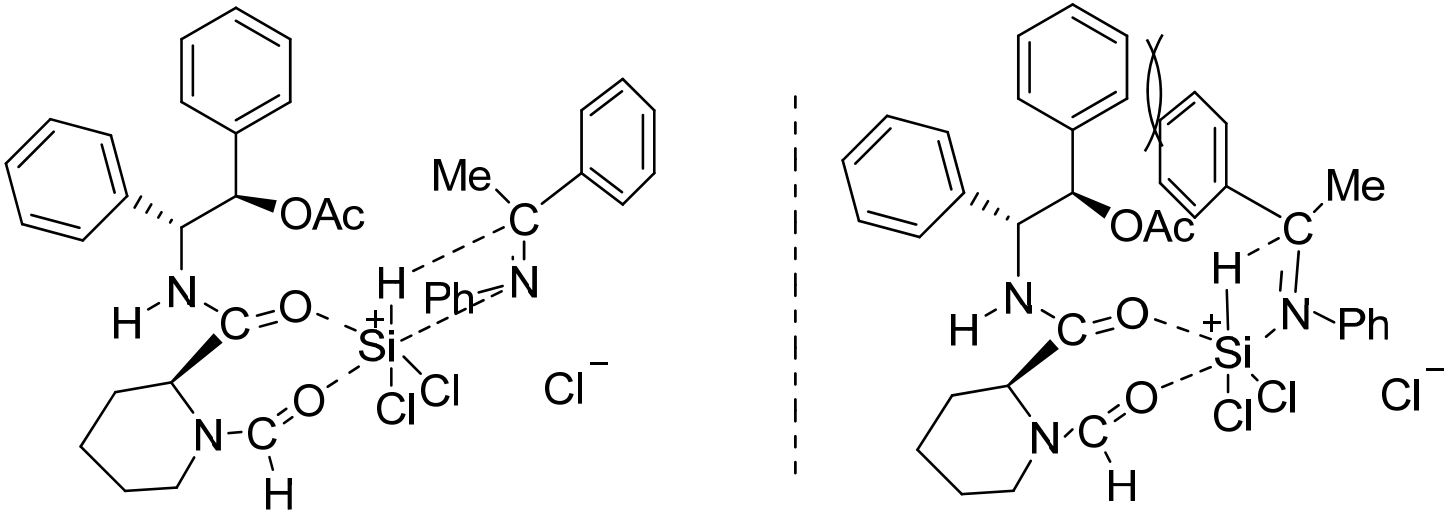




Entry	R	Yield(%)	*ee*/%
1	H	97	95
2	4-NO_2	96	95
3	4-MeO	95	93

Z. Wang, X. Ye, S. Wei, P. Wu, A. Zhang and J. Sun, *Org. Lett.*, **2006**, *8*, 999

Proposed Transition States for Asymmetric Reduction



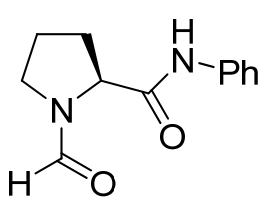
Steric effects become more predominant, leading to higher *ee*

(R)-amine is the major product

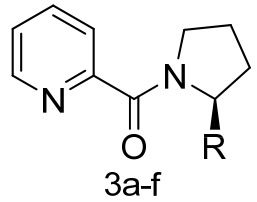
Iwasaki, F.; Omonura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, *42*, 2525

Catalyst Without a Formyl Group

Catalyst

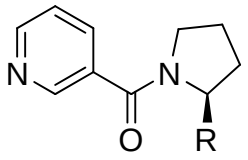


1

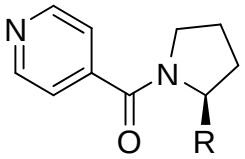


3a-f

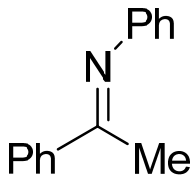
a, R= H; b, R= CO_2Me
c, R= CONHPh; d, R= CONHNaph-1
e, R= CPh_2OH; f, R= $CHPh_2$

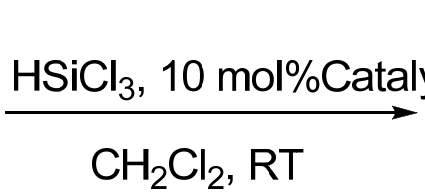


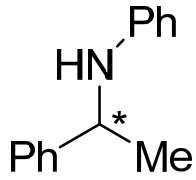
3h



3i







Entry	Catalyst	R	Yield(%)	*ee*/%	Configuration
1	-	-	18	-	-
2	3h	H	12	-	-
3	3i	H	21	-	-
4	3a	H	83	-	-
5	3b	CO_2Me	85	20	R
6	3c	CONHPh	76	18	S
7	3d	CONHNaph-1	96	25	R
8	3e	CPh_2OH	86	73	S
9	3f	$CHPh_2$	75	13	R
10	1	-	91	55	R

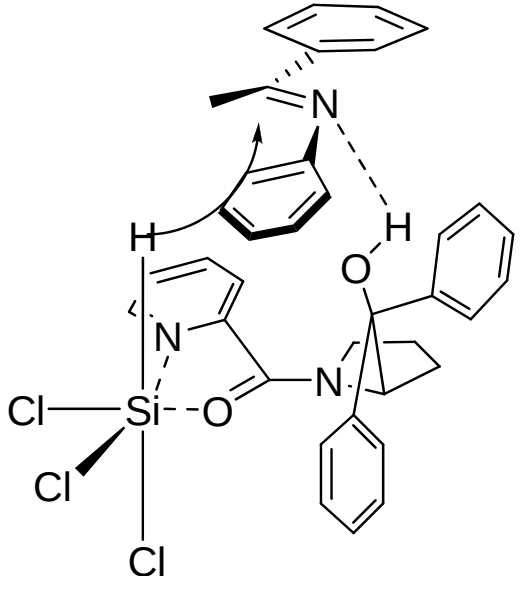
N atom participates in activation

C=O of R doesn't help

OH directs the hydride attacking face

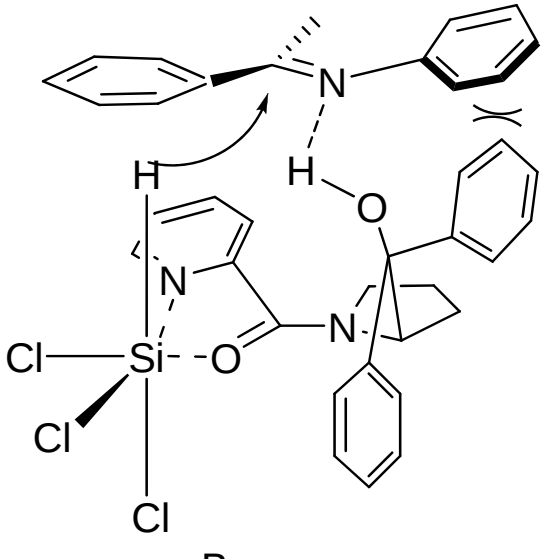
O. Onomura, Y. Kouchi, F. Iwasaki, Y. Matsumura. *Tetrahedron Lett*. **2006**, *47*, 3751

Proposed Reaction Mechanism



A

(S)-amine



B

(R)-amine

(S)-amine is the major product

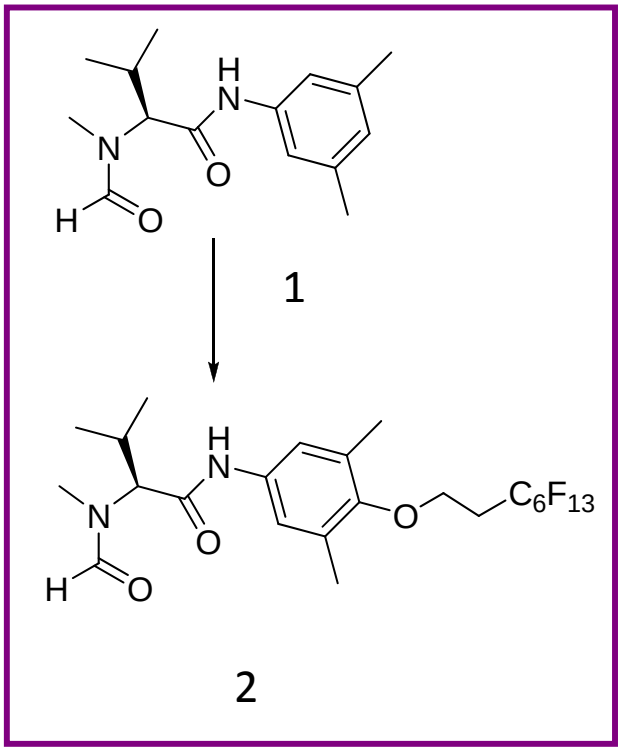
O. Onomura, Y. Kouchi, F. Iwasaki, Y. Matsumura. *Tetrahedron Lett*. **2006**, *47*, 3751

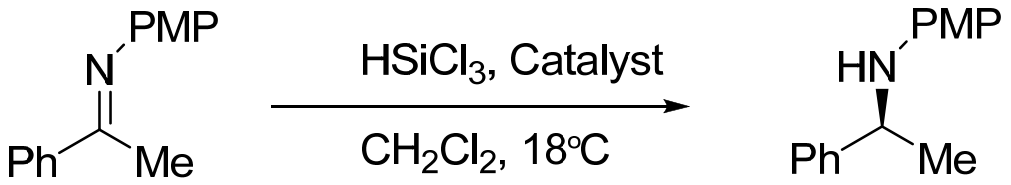
Separation and regeneration of organocatalysts remain difficult tasks.

Three solutions to this problem:

- Introduce a fluorous tag on the catalyst;
- Attach the catalyst to a solid support;
- Immobilize the catalyst onto a nanoparticle.

Introducing a Fluorous Tag





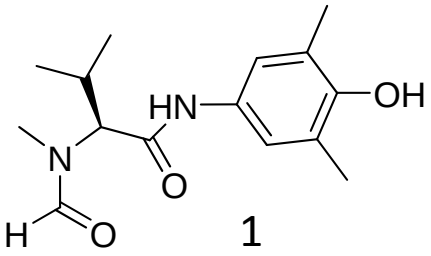
Catalyst (run)	Yield (%)	*ee*/%	Separation
1 (10 mol%)	85	91	Column chromatography
2(1) (10 mol%)	90	91	Filtered through a pad of fluorous silica gel
2(2)	88	88	
2(3)	86	88	

fluorous silica gel: silica gel with a fluorocarbon bonded phase, used in separation of fluorous and non-fluorous compounds.

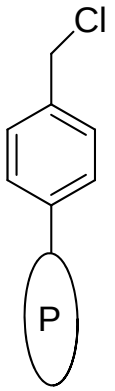
Malkov, A. V.; Figlus, M.; Stoncius, S.; Kocovsky, P. *J. Org. Chem*. **2007**, *72*, 1315

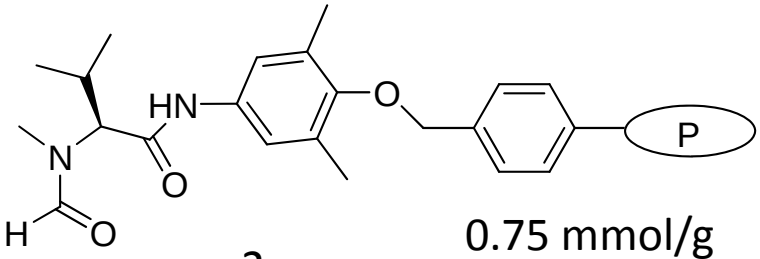
Gladysz, J. A.; Curran, D. P.; Horvath, I. T. *Handbook of Fluorous Chemistry;* Wiley: New York,2004

Attaching the Catalyst to a Solid Polymer Support



1

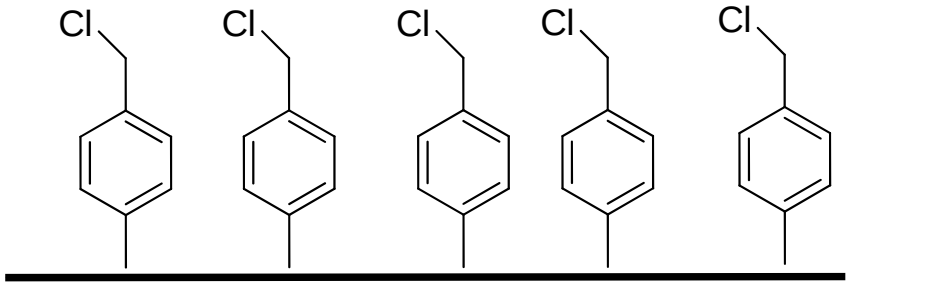




2

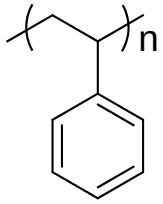
0.75 mmol/g

Reaction condition: CsOH, DMF, 60 °C, 48h.



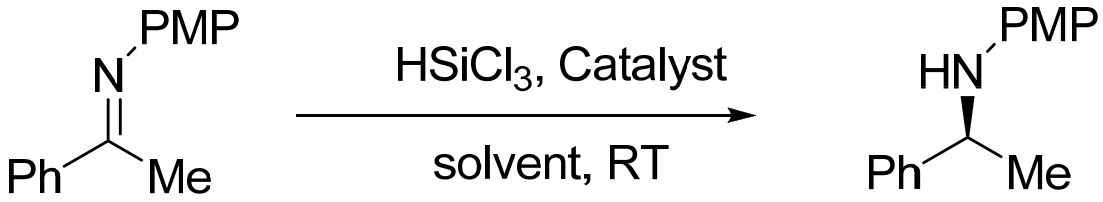
Chloromethyl Polystyrene Resin

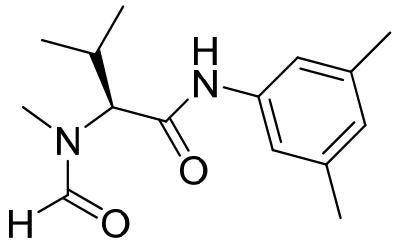
Polystyrene:



Malkov, A. V.; Figlus, M.; Kocovsky, P. *J. Org. Chem*. **2008**, *73*, 3985

Hydrogenation of Imines





1

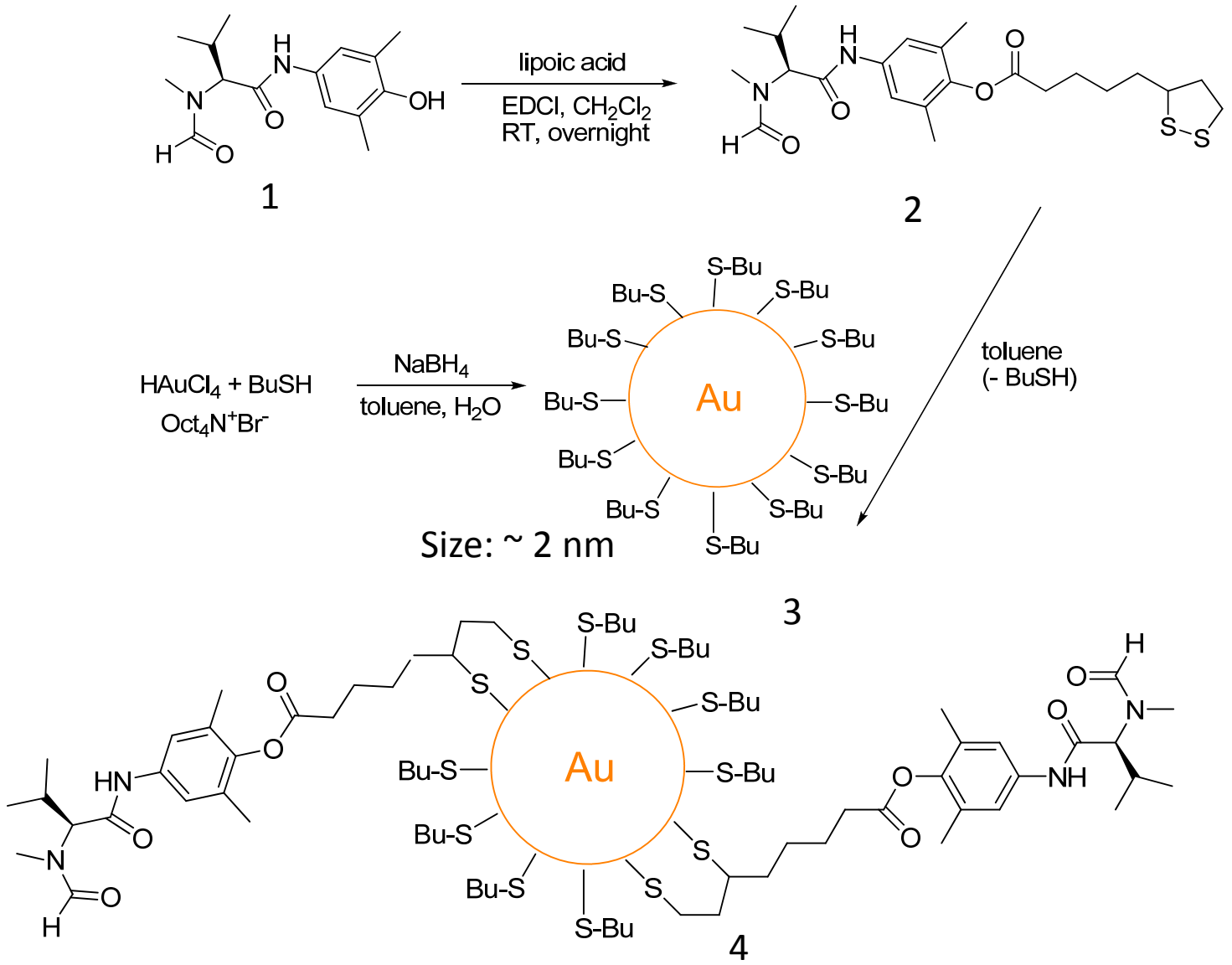
2: polymer supported catalyst

Entry	Catalyst	Solvent	Run	Yield(%)	*ee*/%
1	1 (10 mol%)	toluene	1	85	91
2	2 (25 mol%)	$CHCl_3$	1	80	76
3	2	$CHCl_3$	2	81	82
4	2	$CHCl_3$	3	82	81
5	2	$CHCl_3$	4	80	82
6	2	$CHCl_3$	5	81	82
7	2	$CHCl_3$	6	78	81

Regenerate the catalyst: wash with toluene, CH_2Cl_2, MeOH, Et_2O, respectively.

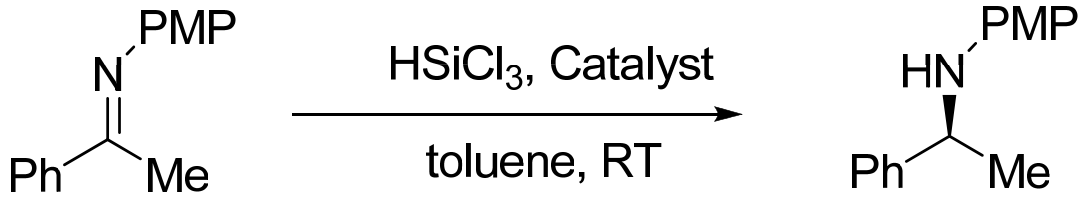
Malkov, A. V.; Figlus, M.; Kocovsky, P. *J. Org. Chem*. **2008**, *73*, 3985

Immobilizing the Catalyst to a Au Nanoparticle

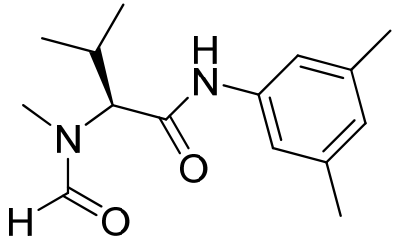


Malkov, A. V.; Figlus, M.; Cooke, G.; Caldwell, S. T.; Kocovsky, P. *Org. Bionol. Chem*. **2009**, *7*, 1878

Hydrogenation of Imine



0.2 mmol



1

2: (nanoparticle supported catalyst)

Entry	Catalyst	Run	Yield(%)	*ee*/%
1	1 (10 mol%)	1	85	91
2	2 (100 mg)	1	90	84
3	2	2	92	82
4	2	3	92	80
5	2	4	89	68

Regenerate the catalyst: wash with methanol, repeated centrifugation.

Malkov, A. V.; Figlus, M.; Cooke, G.; Caldwell, S. T.; Kocovsky, P. *Org. Bionol. Chem*. **2009**, *7*, 1878

Conclusion

Ir complexes catalyze asymmetric imine hydrogenation in high yields and ee's.

However, the high cost of Ir metal and costly ligand synthesis are major challenges.

‘Greener’ and cheaper organocatalysts that provide comparable results to Ir complexes are viable alternatives to imine hydrogenation.