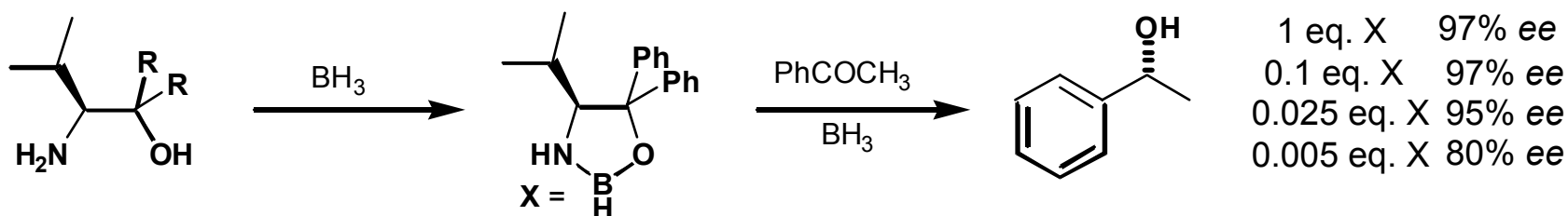


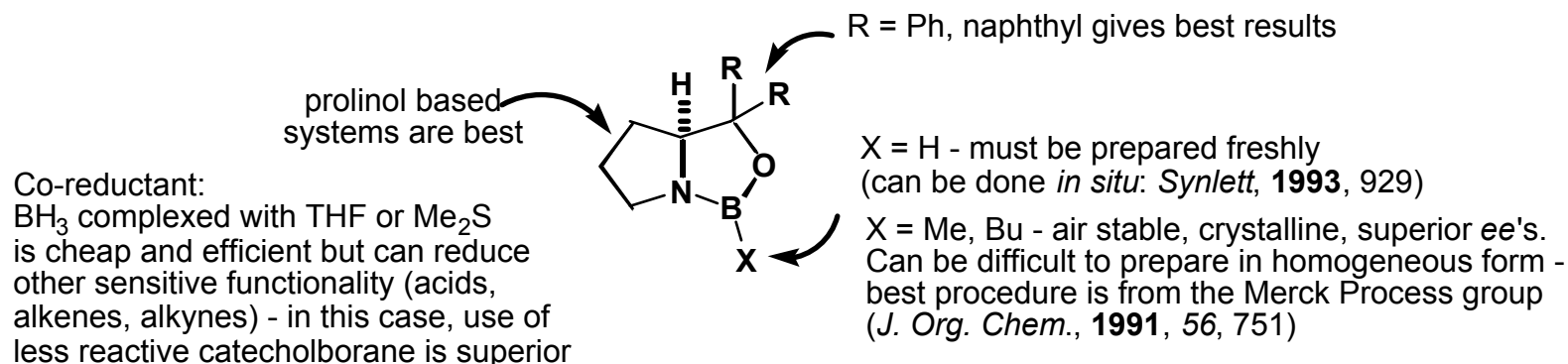
## Oxazaborolidines as catalysts for reduction of ketones with borane

- Itsuno found that the combination of chiral amino alcohols (such as valinol) and  $\text{BH}_3$  reduced ketones asymmetrically and more quickly than  $\text{BH}_3$  alone; Corey discovered that the mixture formed an oxazaborolidine, which was not itself a reducing agent, but which activated borane towards the reduction of ketones even at sub-stoichiometric levels:



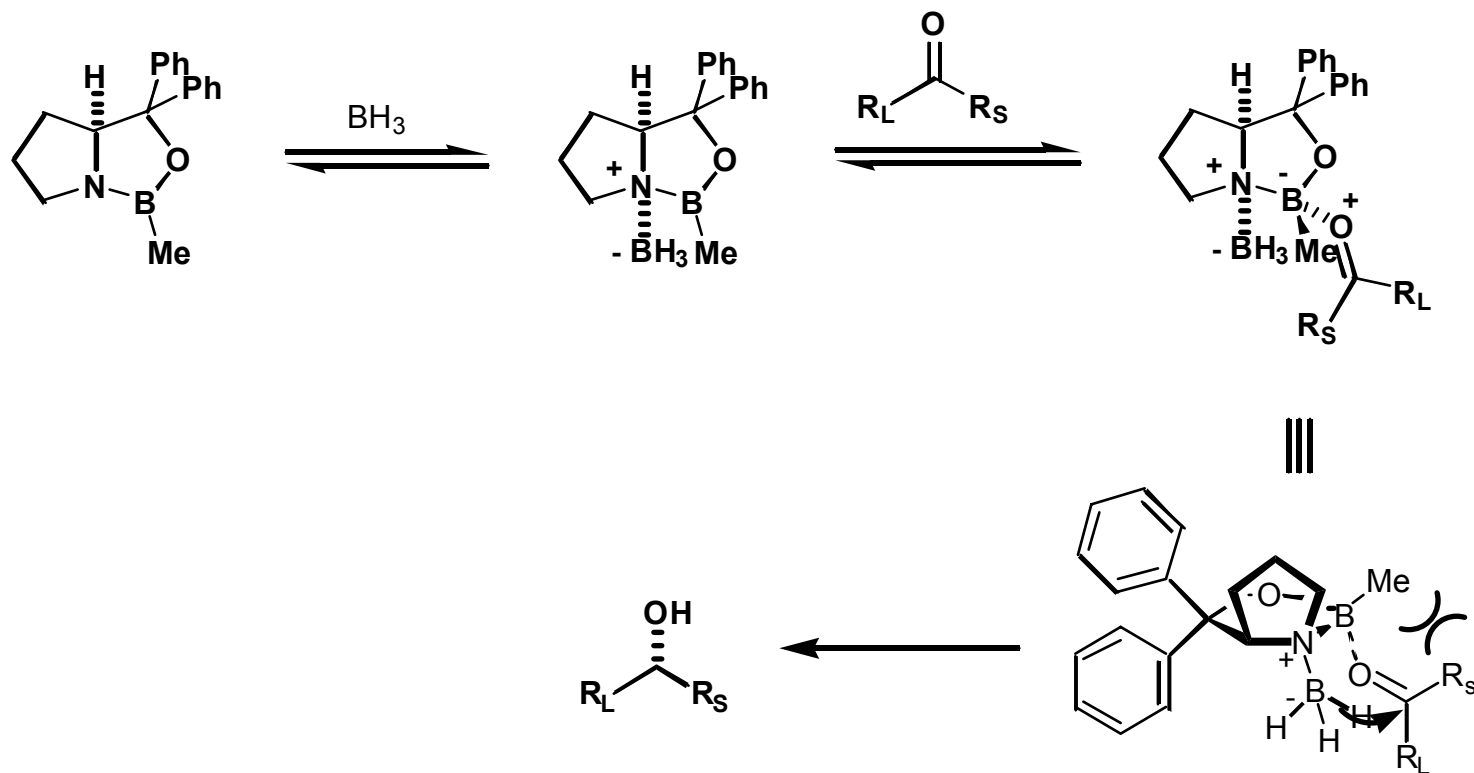
Corey, *J. Am. Chem. Soc.*, **1987**, 109, 5551; Itsuno, *Perkin Trans. 1*, **1983**, 1673; *Chem. Commun.*, **1983**, 469

- optimisation of the ligand followed; arriving at the following system:



Review of oxazaborolidine reductions: Corey, *Angew. Chem., Int. Ed. Engl.*, **1998**, 37, 1986

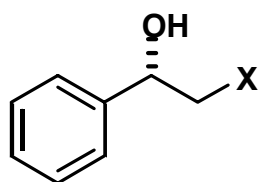
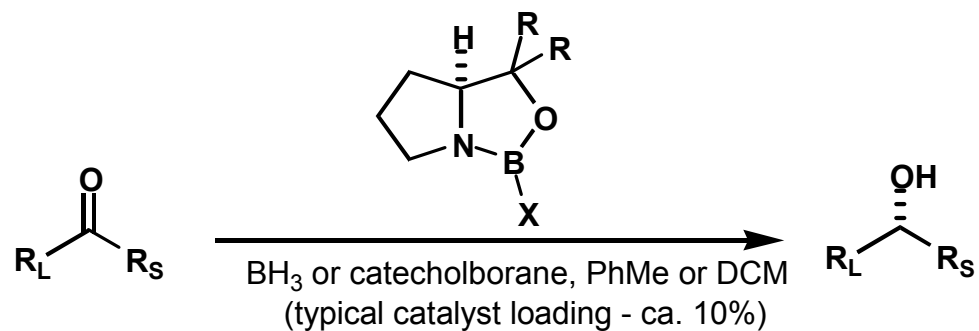
## Mechanism of catalytic asymmetric reduction with oxazaborolidines



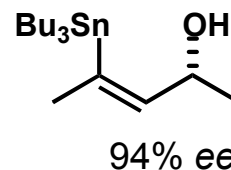
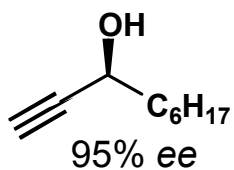
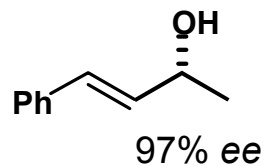
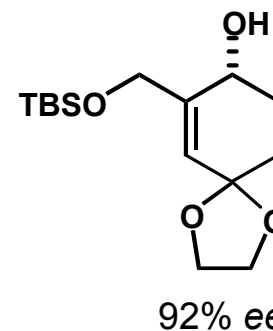
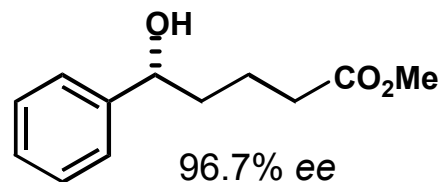
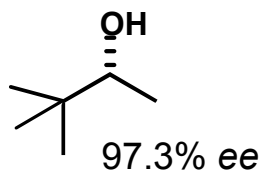
Catalyst performs three roles:

- activates borane as reducing agent through coordination of Lewis basic nitrogen
- activates carbonyl towards reduction through coordination to Lewis acidic boron
- pre-organises substrates for intramolecular hydride delivery in asymmetric environment

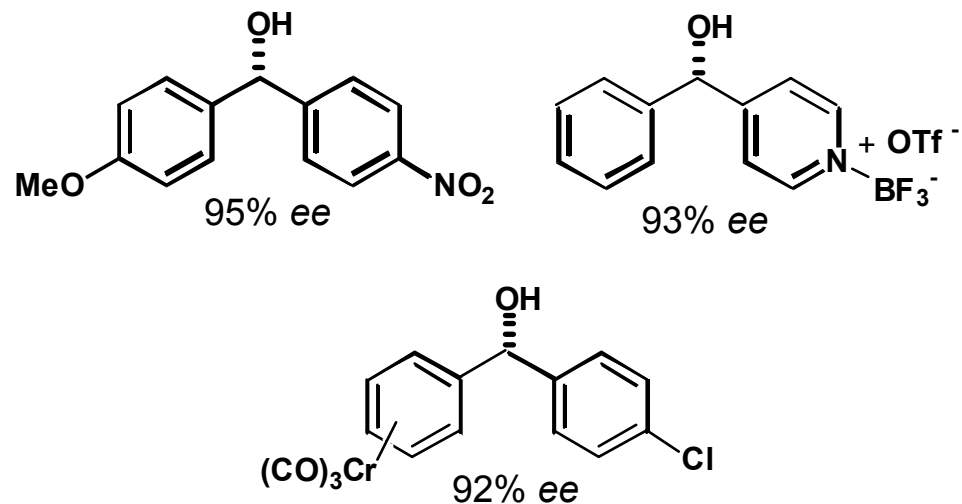
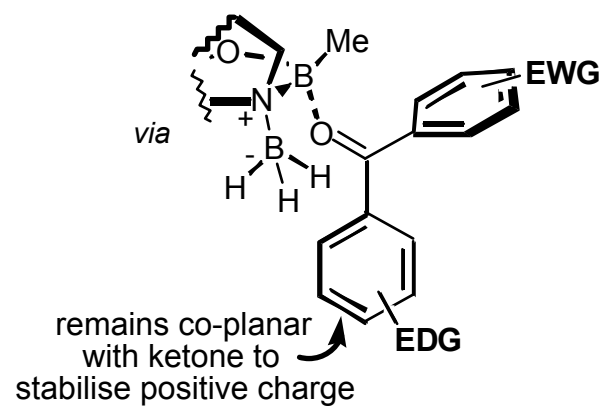
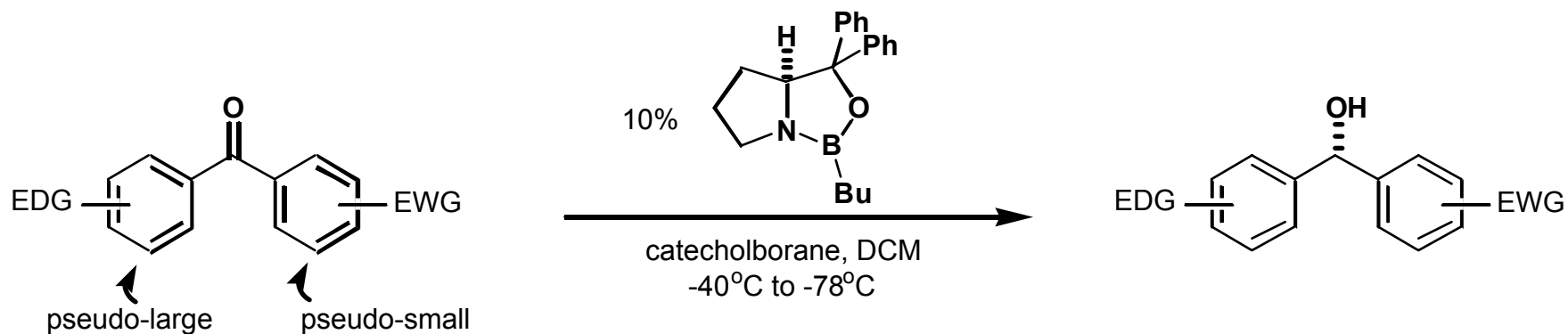
## Scope of catalytic asymmetric reduction with oxazaborolidines



X = H 96.5% ee  
X = Me 96.7% ee  
X = Cl 95.3% ee

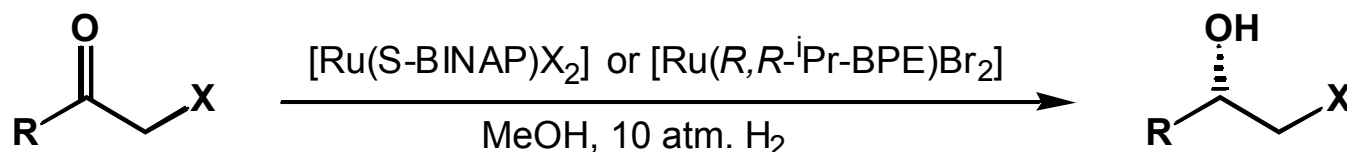


## Electronic effects in the reduction of diaryl ketones

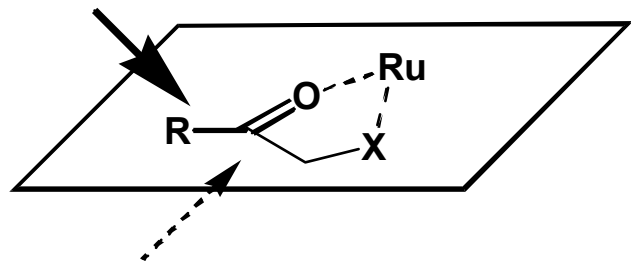


## Asymmetric reduction of functionalised ketones

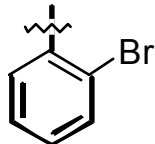
- ruthenium dihalide - BINAP complexes efficiently reduce ketones provided there is a  $\beta$ - or  $\gamma$ -heteroatom to coordinate the catalyst. In reality, a range of heteroatom containing functional groups will suffice. Ru-BPE catalysts are also efficient, but only for  $\beta$ -ketoesters



(S)-BINAP



(R)-BINAP

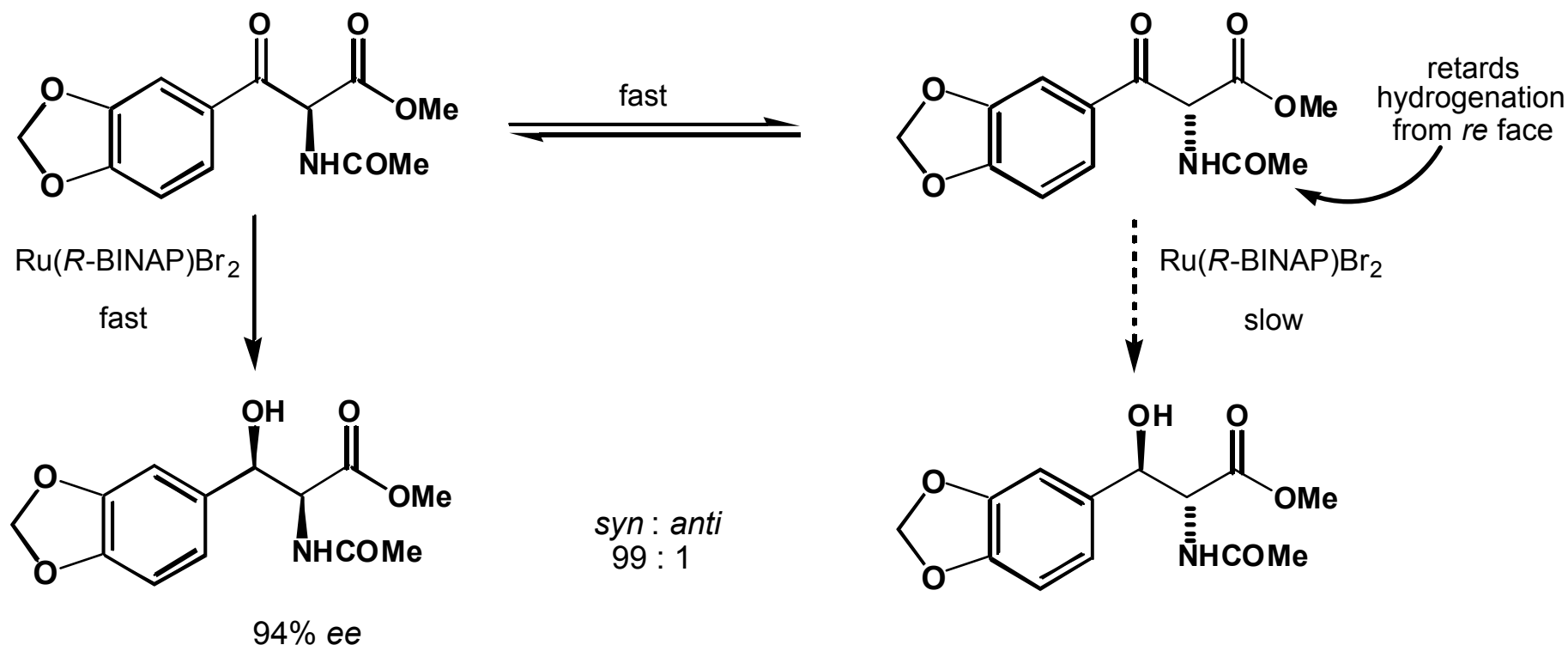
R	X	ee	
		BINAP	BPE
Me	NMe <sub>2</sub>	96	--
Ph	NMe <sub>2</sub>	95	--
Me	CH <sub>2</sub> OH	98	--
Me	CO <sub>2</sub> Me	99	99.3
(CH <sub>2</sub> )CH=Me <sub>2</sub>	CO <sub>2</sub> Me	98	--
CH <sub>2</sub> Cl	CO <sub>2</sub> Et	97	76
Me		92	--

Ru BINAP: R. Noyori, H. Takaya, *J. Am. Chem. Soc.*, **1987**, 109, 5856; *J. Am. Chem. Soc.*, **1988**, 110, 629

Ru-BPE: M. J. Burk, *J. Am. Chem. Soc.*, **1995**, 115, 4423

## Dynamic kinetic resolution in the asymmetric reduction of $\beta$ -ketoesters

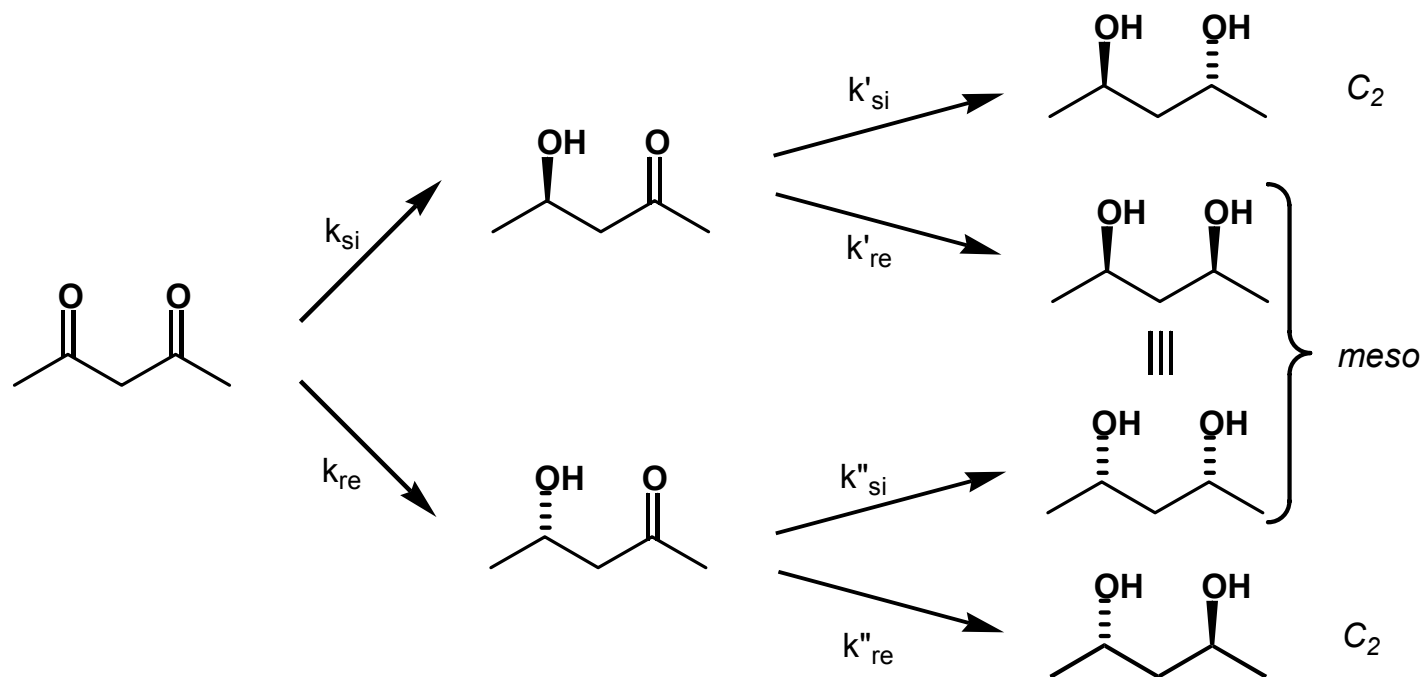
- $\beta$ -ketoesters are particularly good substrates for reduction by both ruthenium dihalide - BINAP and ruthenium dihalide - DuPHOS/BPE complexes (see previous slide)
- substituted  $\beta$ -ketoesters are usually epimerising rapidly in alcoholic solution; since the presence of a substituent *syn* to the face of the ketone undergoing reduction will dramatically slow that reduction, one can perform a dynamic kinetic resolution of racemic  $\beta$ -ketoesters and thus gain an extra asymmetric centre!



Ru BINAP: R. Noyori, H. Takaya, *J. Am. Chem. Soc.*, **1988**, 110, 629  
Ru-BPE: M. J. Burk, *J. Am. Chem. Soc.*, **1995**, 115, 4423

## Reduction of symmetrical $\beta$ -diketones: self-enhancing enantioselectivity

- Since the second reduction of a  $\beta$ -diketone also proceeds with reagent controlled enantioselectivity, there is an in-built enhancement of enantioselectivity in their reduction. The production of the *meso* diastereomer serves to 'correct' any reduction from the 'wrong' face in the first reaction. In the extreme case where  $k_{\text{re}} = k'_{\text{re}} = k''_{\text{re}}$ , and  $k_{\text{si}} = k'_{text{si}} = k''_{\text{si}}$ , then even if the first step only proceeds with 9:1 selectivity (80% ee) then the  $C_2$  product is formed in an enantiomeric ratio of 81:1, ie 97.5% ee. In actual fact, a favourable 'doublediscrimination' occurs which pushes the ee even higher

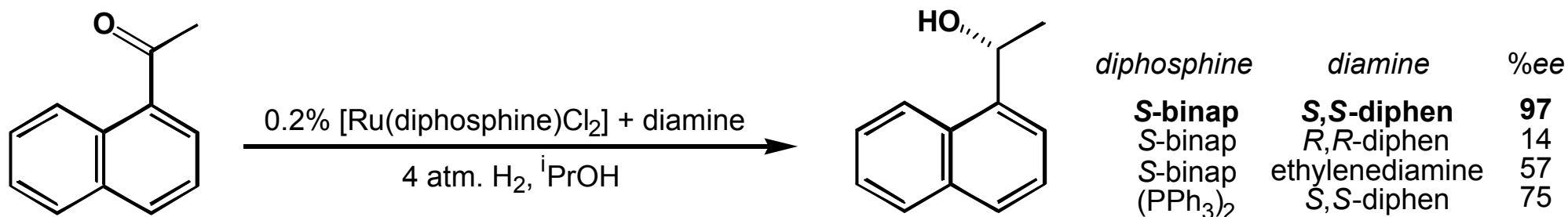


eg 0.05% [Ru(R-BINAP)Cl<sub>2</sub>],  
72 atm. H<sub>2</sub>, MeOH  
100%, >99% ee

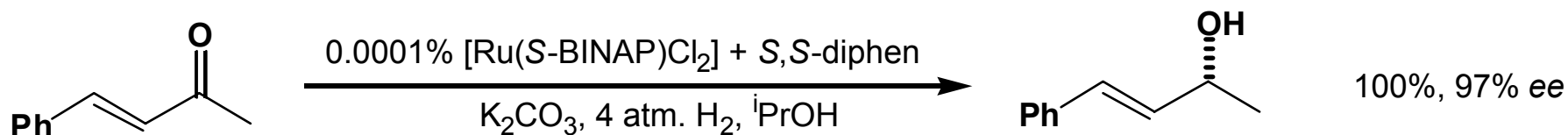
R. Noyori, H. Takaya, *J. Am. Chem. Soc.*, **1988**, 110, 629

## Catalytic asymmetric hydrogenation of unfunctionalised ketones

- this is not a well developed area, despite much effort. Ruthenium biphosphine complexes are poor catalysts for ketone reduction, but it was found that the addition of diamines to these complexes increases the rate of hydrogenation ca. 300 fold. Use of chiral biphosphines and chiral diamines in tandem leads to a synergistic effect and the attainment of high ee's



- catalyst system works for a range of aromatic and alkenyl ketones in 86-100% ee

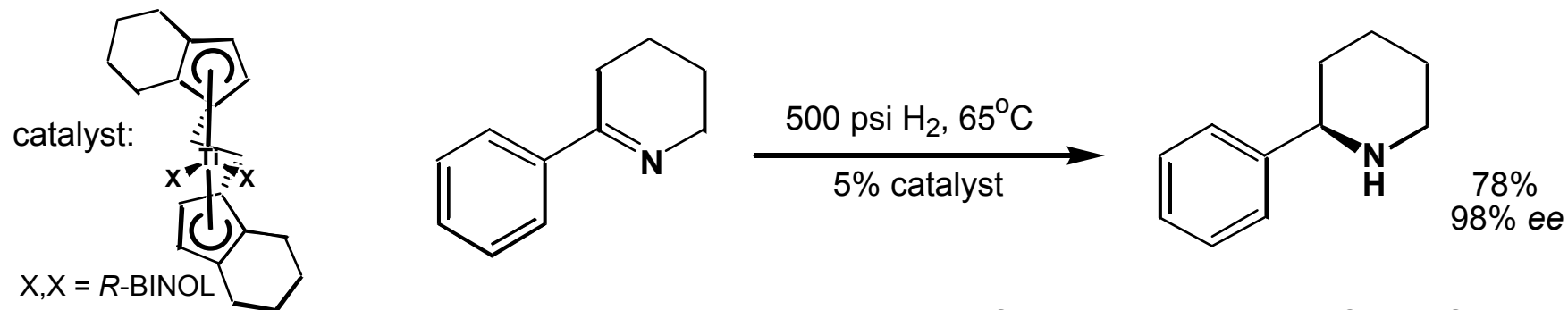


diphen = 1,2-diphenylethylenediamine



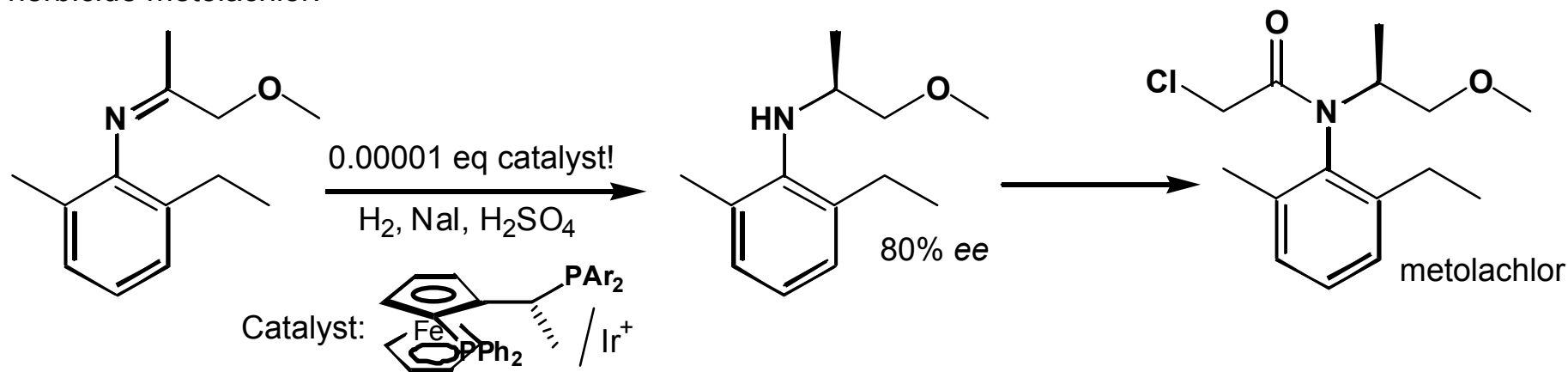
## Catalytic asymmetric hydrogenation of imines

- The hydrogenation of imines is better developed than for ketones, and can be achieved with a range of catalysts.
- Cyclic imines are reduced in high optical purity by titanocene catalysts amongst others.



S. L. Buchwald, *J. Am. Chem. Soc.*, **1994**, 116, 8952

- The reduction of acyclic imines is trickier, but this forms the basis of the Ciba-Geigy industrial synthesis of the herbicide metolachlor:

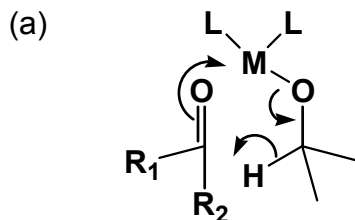


A. Togni, *Angew. Chem., Int. Ed. Engl.*, **1996**, 35, 1475 and refs therein

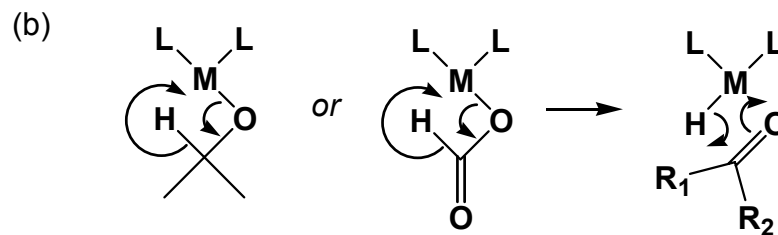
# Asymmetric Transfer Hydrogenation of Ketones

Reduction with the aid of a hydrogen donor in the presence of a catalyst

Reviews: Wills, *Tetrahedron Asymmetry*, **1999**, 10, 2045; Noyori, *Acc. Chem. Res.* **1997**, 30, 97.



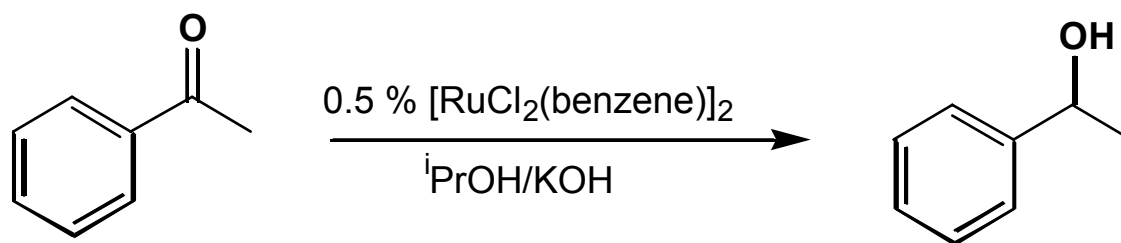
Meerwein-Ponndorf-Verley type  
(main group or lanthanide metals)



Metal hydride type:  
transition metals, <sup>i</sup>PrOH or formate  
as reductant

## Metal hydride mediated transfer hydrogenation

- since typical classes of transition metal ligand (phosphines, pyridines, oxazoles) did not provide a catalyst capable of delivering high ee's across a range of substrates, Noyori screened several achiral additives for their effect on the rate of transfer hydrogenation with a Ru catalyst



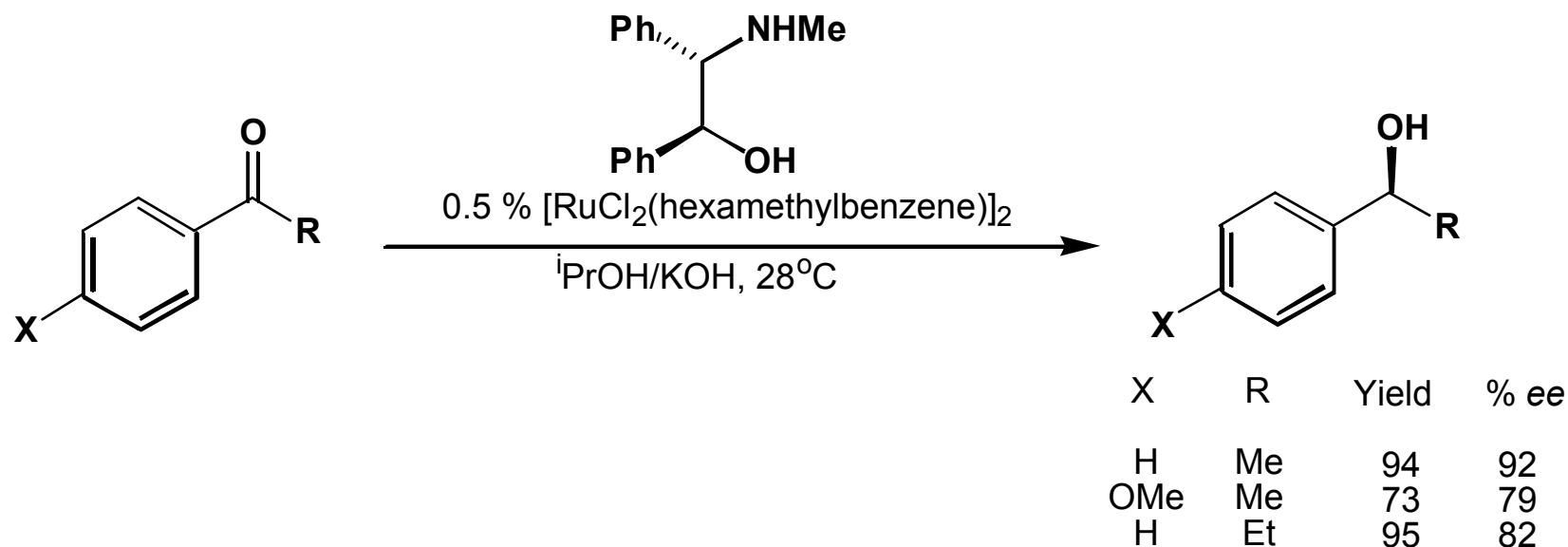
Additive	relative rate
none	1
$\text{HOCH}_2\text{CH}_2\text{OH}$	3.3
$\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$	0.3
$\text{HOCH}_2\text{CH}_2\text{NH}_2$	76
$\text{TsNHCH}_2\text{CH}_2\text{NH}_2$	29

- amino alcohols and monotosylated diamines demonstrate significant ligand accelerated catalysis

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

## Amino alcohols as ligands for asymmetric transfer hydrogenation

- Noyori screened a range of ligands for their ability to accelerate the transfer hydrogenation of ketones, and found that monotosylated diamines and amino alcohols gave good accelerations
- a range of chiral amino alcohols have proved to be competent ligands for asymmetric transfer hydrogenation, provided they comprise either a primary or secondary amine (tertiary amines do not work)

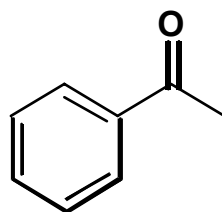
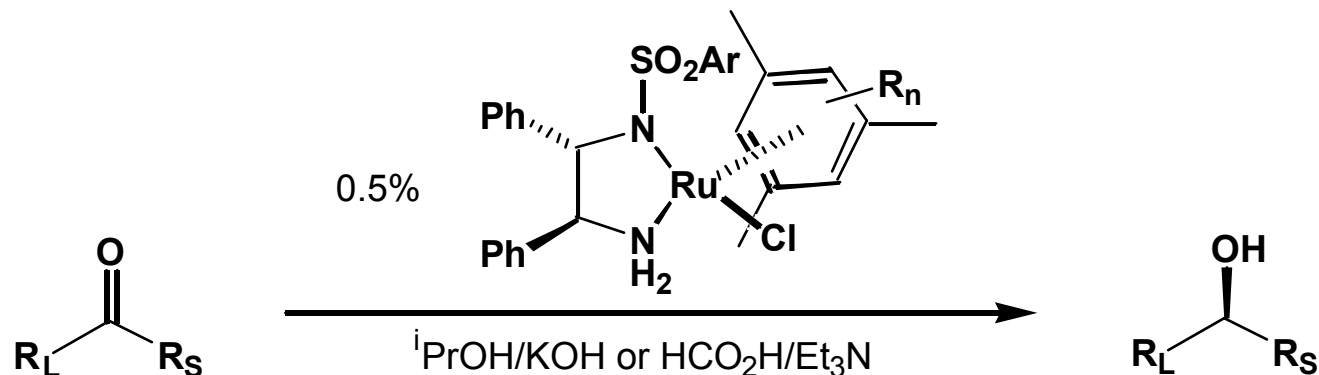


- high ee's are obtained for many arylalkylketones, but those with electron rich aryl groups or benzocycloalkanones suffer from reversibility of the reaction and give lower ee's
- amino alcohols in general are not compatible ligands for use with the irreversible hydride donor formic acid

R. Noyori, *J. Chem. Soc., Chem. Commun.*, **1996**, 233  
For a review of the development of the ligands, see: R. Noyori, *Acc. Chem. Res.*, **1997**, 30, 97

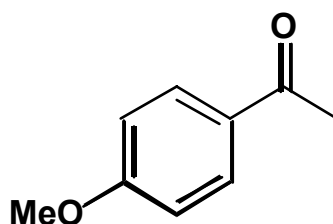
## Monotosylated diamines as formic acid tolerant ligands for transfer hydrogenation

- although slightly less reactive than the amino alcohols, monotosylated diamines have proven to be a more useful ligand system for ruthenium based transfer hydrogenations

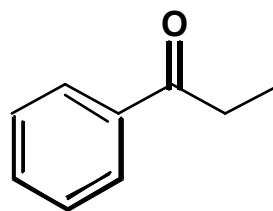


$iPrOH/KOH$   
 $HCO_2H/Et_3N$

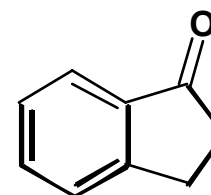
97% ee  
98% ee



72% ee  
97% ee



97% ee  
97% ee



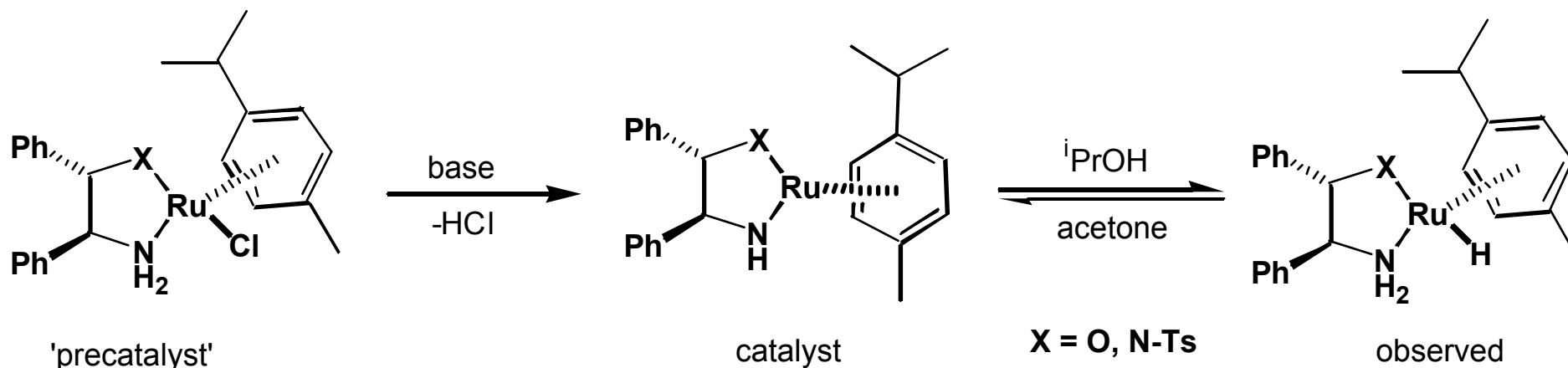
91% ee  
99% ee

- compatibility with the formic acid system allows the efficient reduction even in readily reversible systems

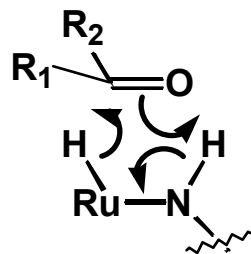
R. Noyori, *J. Am. Chem. Soc.*, **1995**, 117, 7562; *J. Am. Chem. Soc.*, **1996**, 118, 2521

## Hydride transfer mechanism demonstrated for both classes of ligands

- need for at least one free hydrogen on the amine is explained by the formation of the true catalytic species by loss of HCl from the 'precatalyst'

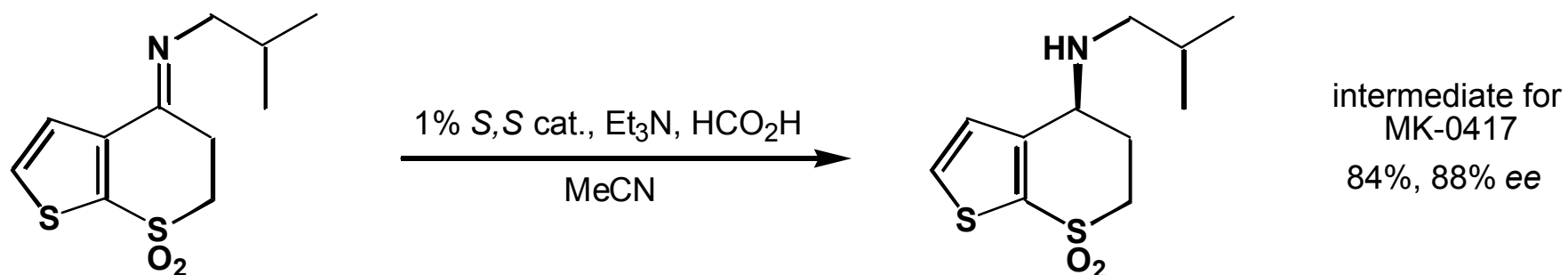
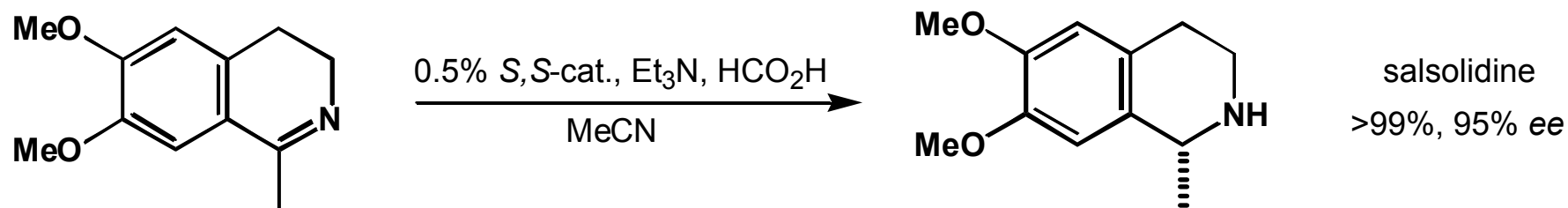


- also believed that the N-H bond participates in the hydride transfer step:

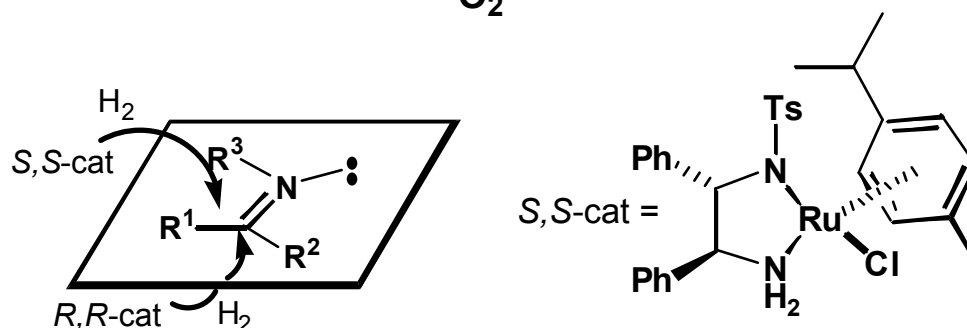


Monotosylated diamines: R. Noyori, *Angew. Chem., Int. Ed. Engl.*, **1997**, 36, 285  
 Amino alcohols: P. G. Andersson, *J. Am. Chem. Soc.*, **1999**, 121, 9580; M. Wills, *Chem. Commun.*, **2000**, 99

## Asymmetric transfer hydrogenation of imines



- ketimines are 1000 times more reactive than ketones under these conditions, which implies that a catalytic asymmetric reductive amination might be feasible!



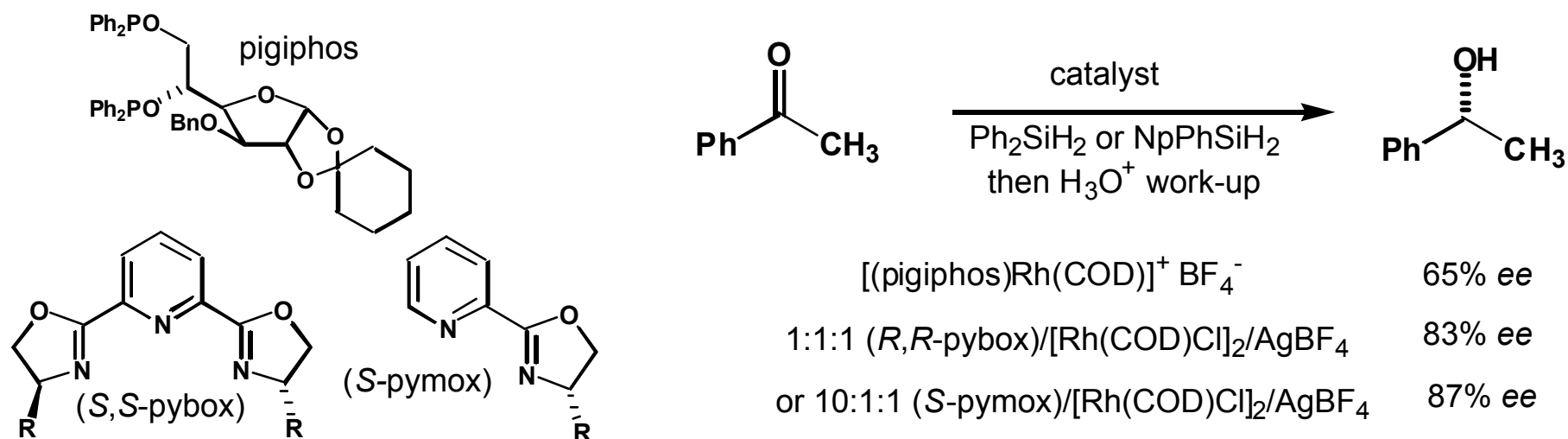
R. Noyori, *J. Am. Chem. Soc.*, **1996**, *118*, 4916





## Hydrosilylation of imines/ketones provides an alternative to hydrogenative reduction

- addition of  $\text{H-SiR}_3$  across a ketone or imine generates the corresponding silyl ether/amine, which can be readily cleaved to reveal the parent alcohol or amine; silanes are safe, easy to handle reducing agents.
- early work focused on the use of chiral phosphines, with only moderate success. A breakthrough came with the discovery that pyridyl monooxazoline (pymox) and pyridyl bisoxazoline (pybox) ligands give good enantioselectivities in conjunction with cationic rhodium (I) species - note the importance of ligand stoichiometry though.

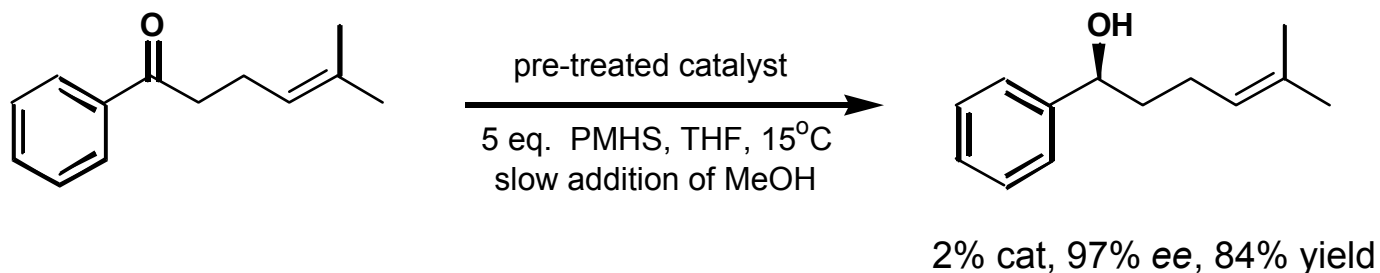
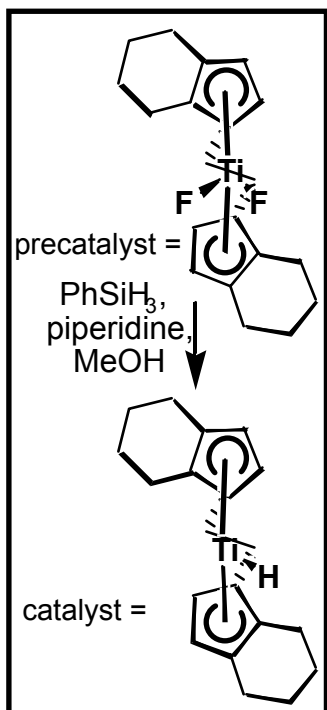


- one drawback is the use of relatively expensive silanes - eg  $\text{PhSiH}_2 = \text{£}275$  per mole (Aldrich)

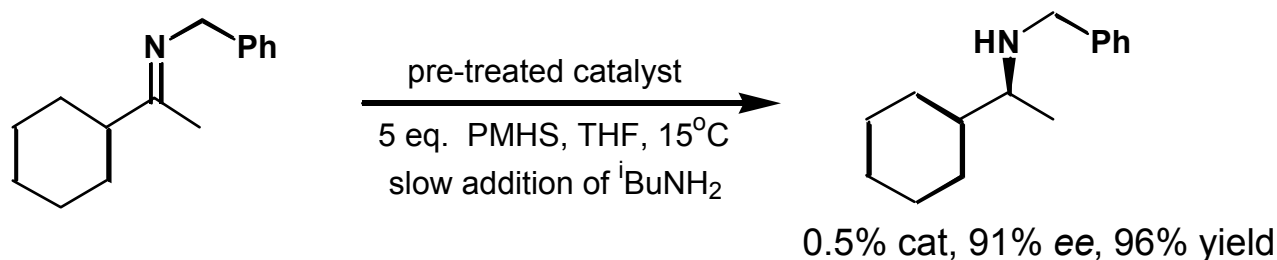
H. Nishiyama, *Organometallics*, **1991**, 10, 560; H. Brunner, *Tetrahedron Asymm.*, **1991**, 2, 919

## Asymmetric hydrosilylation of ketones and imines using cheap siloxanes

- poly(methylhydrosiloxane) is a cheap by-product of the polysiloxane industry (ca. £9 per 'mole' - Aldrich)
- pre-activated titanocene catalysts are very effective at asymmetric hydrosilylation using PMHS
- works for aryl and alkenyl ketones; not so efficient for dialkyl ketones



- works for a range of imines as well (better at handling dialkyl imines than dialkyl ketones)



- alcohol/amine additives speed up catalytic cycle (lower loadings, higher ee's)