

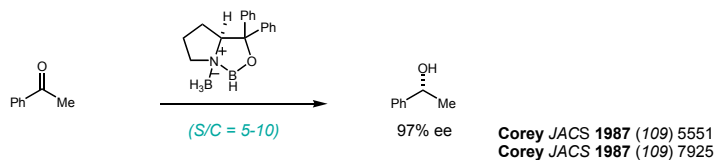
## Catalyst Directed Asymmetric Hydrogenation of Carbonyls

Mike Brochu  
MacMillan Group Meeting  
March 31, 2004

- Homogeneous Hydrogenation
- Hydride Transfer
- Bifunctional Catalysis

## Reduction of Carbonyls Introduction

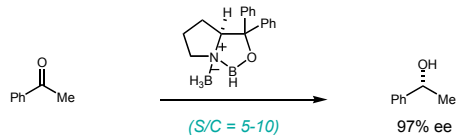
- Oxazaborolidine structure based catalysts



## Reduction of Carbonyls

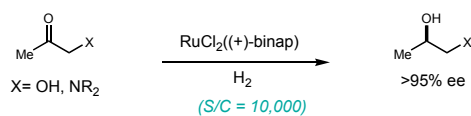
### Introduction

#### ■ Oxazaborolidine structure based catalysts



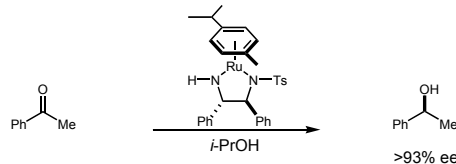
97% ee  
Corey JACS 1987 (109) 5551  
Corey JACS 1987 (109) 7925

#### ■ Homogeneous hydrogenation - bifunctional catalysis



>95% ee  
Noyori ACIEE 2001 (40) 40

#### ■ Transfer hydrogenation - bifunctional catalysis

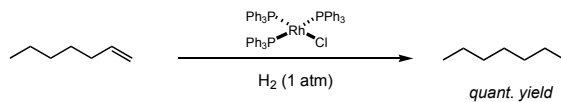


Noyori JOC 2001 (66) 7931

## History of Asymmetric Hydrogenation I

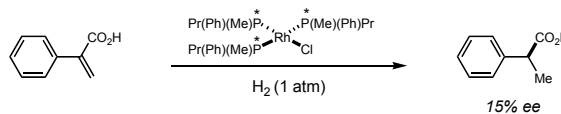
### Olefin reductions

#### ■ Wilkinson's catalyst capable of achiral olefin hydrogenations



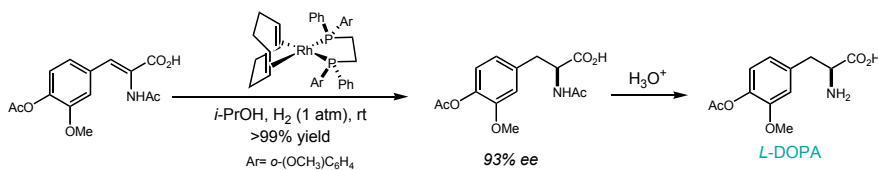
Wilkinson J. Chem Soc. (A) 1966, 1711

#### ■ First report of asymmetric hydrogenation came from William Knowles



Knowles Chem. Commun. 1968, 1445

#### ■ Monsanto Chemical Company produces L-DOPA



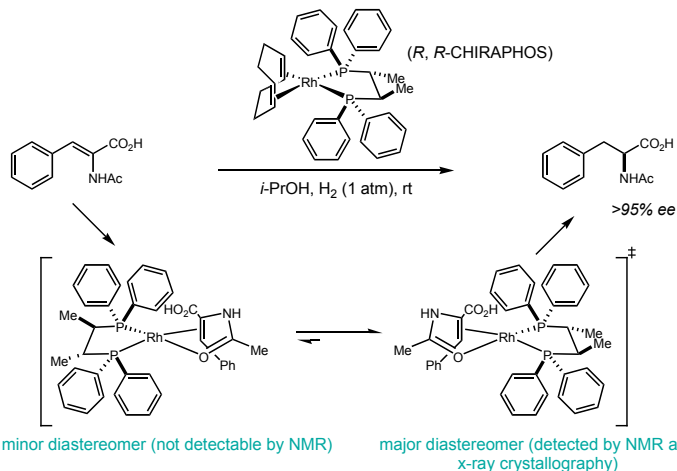
Knowles JACS 1975 (97) 2567

#### ■ First demonstration of a chiral metal complex transferring chirality to a non-chiral substrate with high ee

#### ■ Limited substrate scope

**History of Asymmetric Hydrogenation II**  
**Origin of asymmetric induction in Knowles' system**

- Chelation of carbonyl from acylamino group energetically stabilizes one diastereomeric transition state

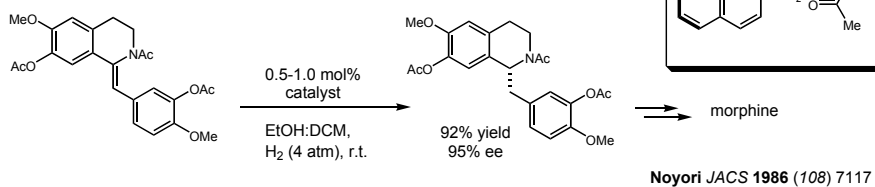


- Minor diastereomer is 580 fold more reactive towards  $\text{H}_2$  oxidative addition - leads to 60:1 product ratio

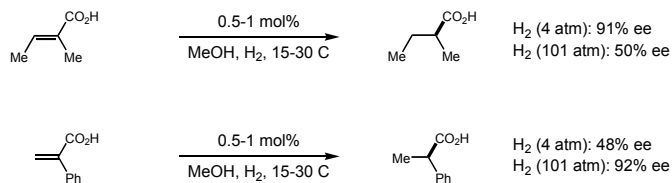
Halpern Science 1982 (217) 401

**History of Asymmetric Hydrogenation III**  
**Olefin reductions**

- Noyori develops *BINAP*-Ru complex



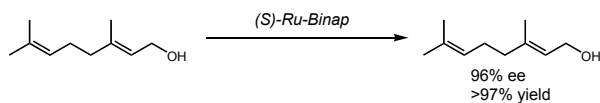
- *BINAP*-Ru shows improved substrate scope



- First demonstration of high asymmetric induction of substrates lacking an acylamino group
- No trend observed between  $\text{H}_2$  pressure and enantioselectivity and no rationale given

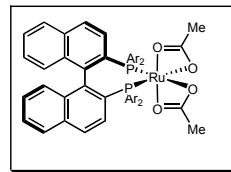
History of Asymmetric Hydrogenation IV  
Olefin reductions

■ Hydrogenation of allylic and homoallylic alcohols



*bis-homoallylic and higher analogues are not hydrogenated*

Noyori JACS 1987 (109) 1596



■ Can Ru-Binap catalysts be applied to ketone hydrogenations?

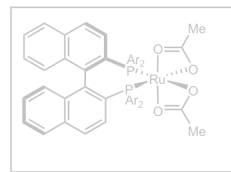
History of Asymmetric Hydrogenation IV  
Olefin reductions

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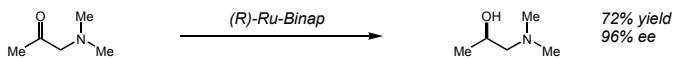
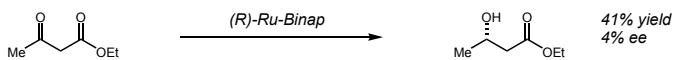


*bis-homoallylic and higher analogues are not hydrogenated*

Noyori JACS 1987 (109) 1596



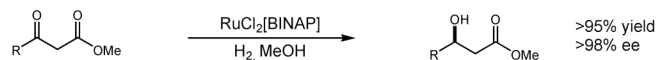
■ Can Ru-Binap catalysts be applied to ketone hydrogenations?



■ Ru-hydride of Binap dicarboxylate catalysts are not hydridic enough in character

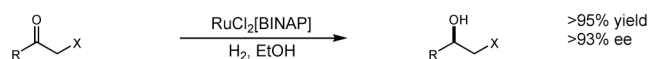
### Substrate-Directed Ketone Hydrogenation Pioneering work from Noyori

- Halogen containing Ru-Binap complexes are capable of reducing keto-esters



Noyori JACS 1987 (109) 5856

- Scope quickly expanded to include functionalized ketones



R = C<sub>6</sub>H<sub>5</sub>, Alkyl, CH<sub>2</sub>OAr  
X = OH, OMe, CO<sub>2</sub>Me, NMe<sub>2</sub>, Br, COSMe, CONMe

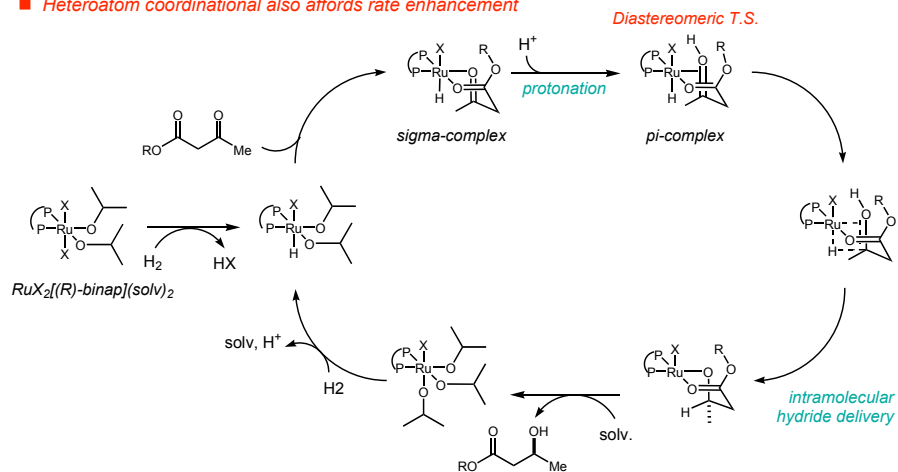
Noyori JACS 1988 (110) 829

- Reactions require forcing pressures of H<sub>2</sub> (50-100 psi commonly required)
- Ru(II) -BINAP dicarboxylate catalysts were ineffective for ketone hydrogenations.

Why are functionalities close to carbonyls required?

### Substrate-Directed Ketone Hydrogenation Mechanism

- Functional group chelation stabilizes one diastereomeric transition state
- Heteroatom coordinational also affords rate enhancement

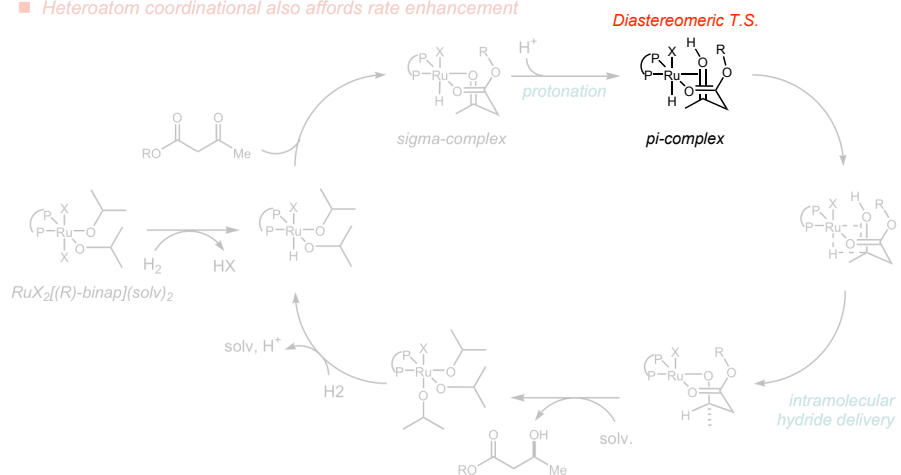


- Small amount of acid dramatically improves reaction efficiency
- Protonation of keto-oxygen increases electrophilicity of carbonyl carbon and facilitates hydride delivery

Noyori ACIEE 2001 (40) 40

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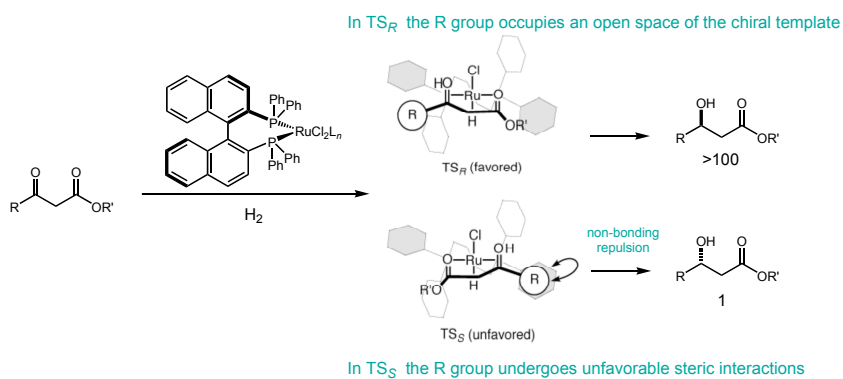


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Noyori *ACIEE* 2001 (40) 40

### Ru-BINAP Catalyzed Asymmetric Hydrogenation Enantiodetermining Transition States

- Diastereomeric chelate rings are present in stereodetermining hydride-transfer step

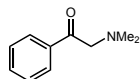


- Enantio-discrimination driven by non-bonding interactions between equatorial phenyl rings and R group

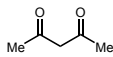
Noyori *ACIEE* 2001 (40) 40

### Ru-BINAP Catalyzed Asymmetric Hydrogenation Reaction scope and application

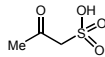
- Variety of functional groups are tolerable



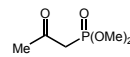
amino ketones  
100% conv.  
95% ee



diketones  
100% conv.  
100% ee  
99:1 anti:syn

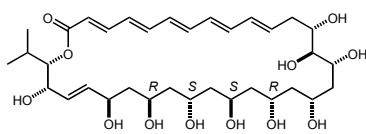


keto sulfonates  
100% conv.  
97% ee

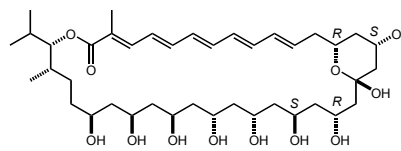


keto phosphonates  
100% conv.  
98% ee

- Synthetic Applications of asymmetric hydrogenations



(+)-mycoticin



roflumycoin

- Stereocenters set by asymmetric hydrogenation are marked

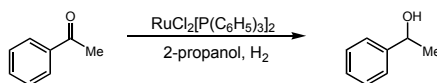
Schreiber JACS 1993 (115) 3360  
Rychnovsky JACS 1997 (119) 2058

Can Simple Ketones be Asymmetrically Hydrogenated?

Chelation traditionally required for rate enhancement and selectivity

### Ruthenium Catalyzed Hydrogenation of Simple Ketones Noyori has breakthrough result

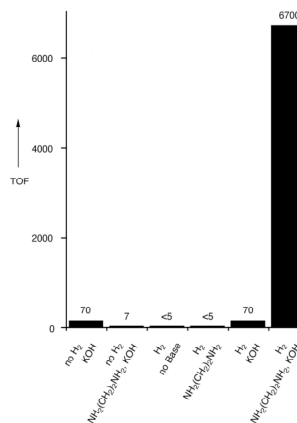
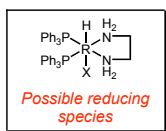
- Ruthenium is traditionally a poor metal for carbonyl hydrogenation



Ethylene diamine and KOH enormously accelerated hydrogenation

*N,N,N',N'*-tetramethylethylenediamine is totally ineffective

NH proton was postulated to act as a hydrogen bond donor



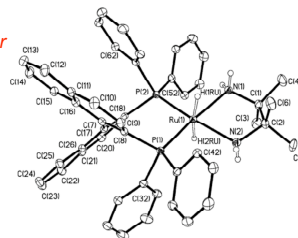
- Diamine ligand and inorganic base increase reactivity of Ru-catalyzed carbonyl hydrogenation

### Asymmetric Hydrogenation of Ketones in the Diamine-BINAP System Catalytic cycle

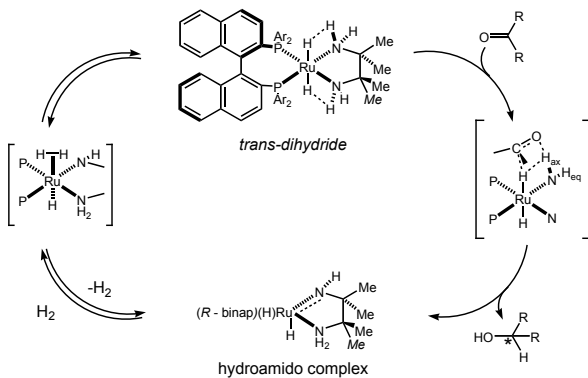
- Hydrogenation occurs through direct hydride and proton transfer

Ru-H<sup>+</sup>...H<sub>ax</sub>-N distances are at the outer limit of protonic-hydric or dihydrogen bonding. (2.4 Å)

Ru-H bond weakened by high trans influence of hydride which explains the reactivity of hydric hydride toward ketones.



Proposed mechanism involves concerted transfer of hydric Ru-H and protic N-H to the ketone via a 6-membered pericyclic TS.



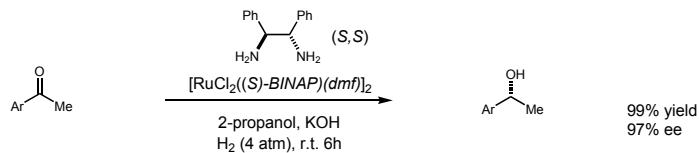
**Trans effect:** labilization of ligands *trans* to other ligands, typically those with a strong sigma-bonding character.

Hydroamido complex rapidly splits H<sub>2</sub> under normal reaction conditions

Morris JACS 2001 (123) 7473

### Asymmetric Hydrogenation Ligands can impart chirality

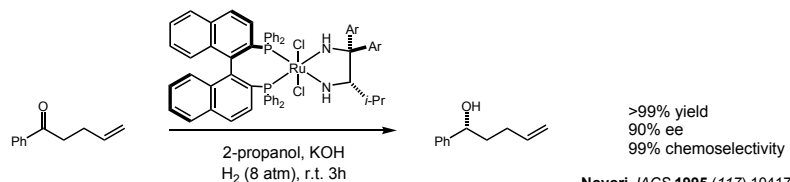
- Chiral diamine ligands influence reaction selectivity



Running reaction with diamine antipode affords product with 14% ee

Noyori JACS 1995 (117) 2675

- Diamine-BINAP catalyst selective for carbonyls over olefins



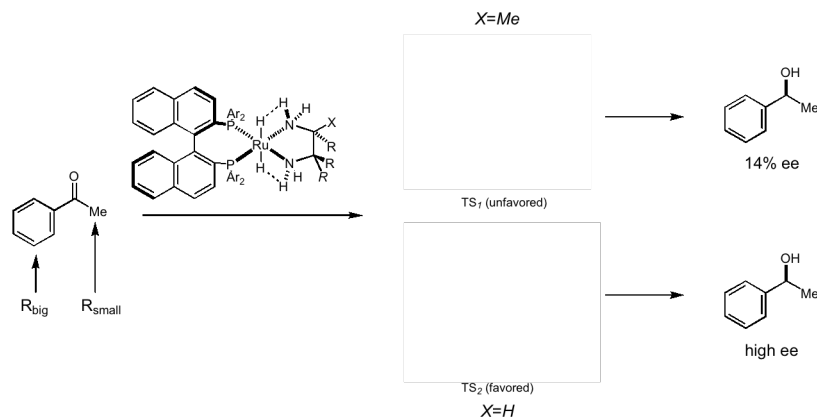
Presence of diamine and inorganic base essential for excellent chemoselectivity



### Asymmetric Hydrogenation of Ketones in the Diamine-BINAP System Enantiodetermining Transition States

- Diastereomeric transition states are present in dihydride delivery step

In TS<sub>1</sub>, unfavorable steric interference results in a less active and selective system



In TS<sub>2</sub> R<sub>big</sub> wants to orient away from binap backbone and axial phenyl

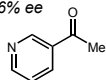
Morris JACS 2001 (123) 7473

### Asymmetric Hydrogenation Diamine-BINAP system tolerates broad substrate scope

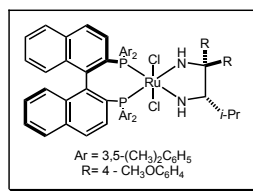
- Change of chiral diphosphine increases enantioselectivities for many substrates

#### Heteroaromatic Ketone Reduction

>96% conv.  
99.6% ee

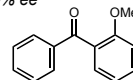


24 h.; 30 C; 8 atm H<sub>2</sub>  
(S/C)= 2,000



#### bis-Aryl ketone Reduction

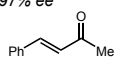
100% conv.  
99% ee



15 h.; 30 C; 8 atm H<sub>2</sub>  
(S/C)= 13,000

#### Enone Reduction

100% conv.  
97% ee



43 h.; 30 C; 80 atm H<sub>2</sub>  
(S/C)= 100,000

#### Cyclopropyl Reduction

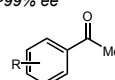
96% conv.  
95% ee



12 h.; 30 C; 10 atm H<sub>2</sub>  
(S/C)= 11,000

#### Aryl Ketone Reduction

>99.7% conv.  
>99% ee



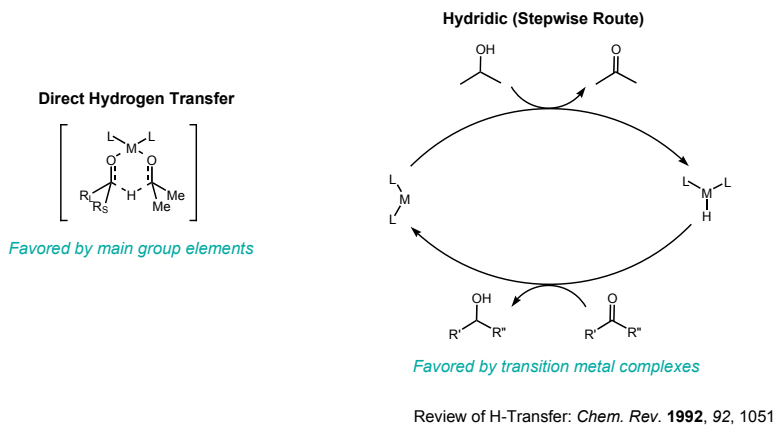
4-10 h.; 30 C; 8-10 atm H<sub>2</sub>  
R=F, Cl, Br, I, CF<sub>3</sub>, C(O)OR,  
NO<sub>2</sub>, NH<sub>2</sub> in m-, p-, o- positions

- New ligands also show wider scope for aryl ketones

Noyori JACS 1998 (120) 13529  
Noyori ACIEE 2001 (40) 40

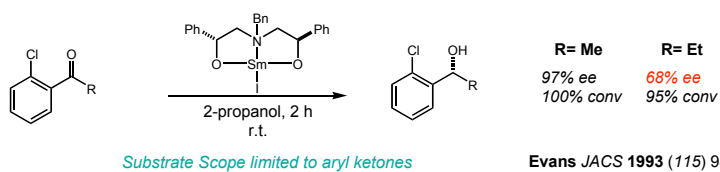
## Asymmetric Hydrogen Transfer Reactions Introduction

- The reduction of multiple bonds by a metal catalyst with the aid of a hydrogen donor is known as hydrogen transfer
- Hydrogen transfer is advantageous on account of increased safety and chemical flexibility
- Two mechanistic pathways exist in hydrogen transfer reactions

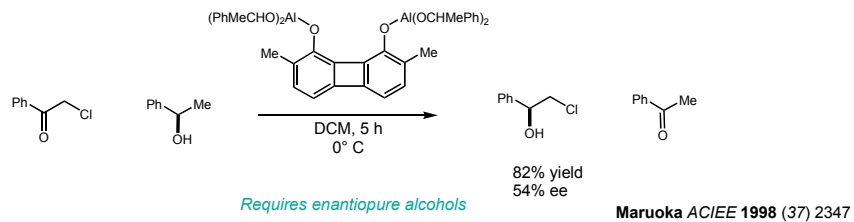


## Asymmetric Hydrogen Transfer Reactions Meerwein-Ponndorf-Verley Reduction

- Evans develops a chiral samarium catalyst for MPV reaction



- Maruoka develops a bidentate aluminum system

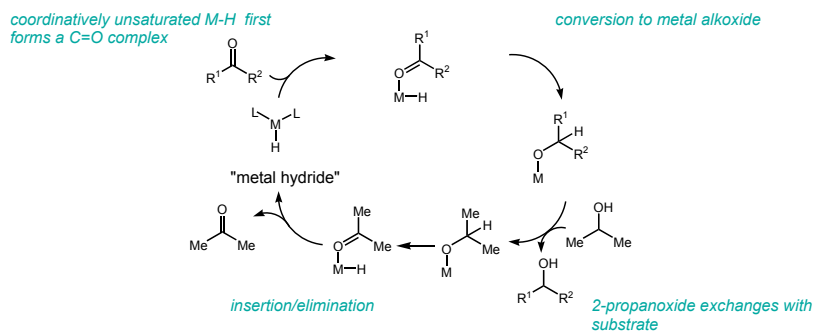


- Also reports of Lanthanide catalyzed system

### Asymmetric Hydrogen Transfer Reactions "Classical" Mechanism

- Hydric route favored by transition metal complexes thought to proceed via stepwise T.S.
- Hydride delivered to substrate by reactive metal hydride species

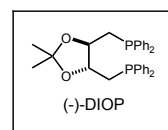
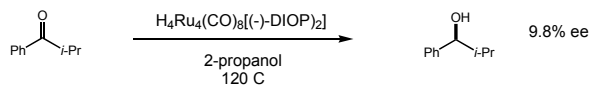
#### Hydric (Stepwise Route)



- Nature of base should effect reaction rate by increasing concentration of alkoxide in solution
- Chiral H-donors have only a marginal effect on enantioselectivity in these processes

### Ruthenium and Rhodium mediated Asymmetric Hydrogen Transfer Reactions Phosphine ligands

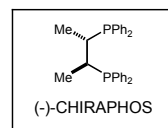
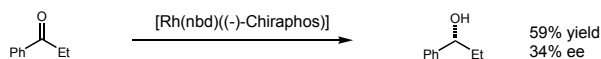
#### Ruthenium



*J. Organomet. Chem.* **1980** 73

Most transfer hydrogenations require temperatures above 150 C with ee's below 50%

#### Rhodium

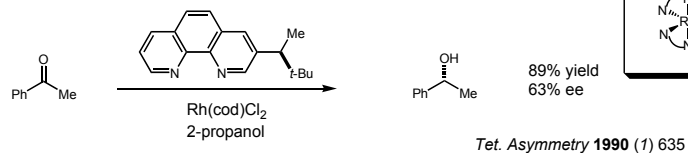


*J. Organomet. Chem.* **1986** 292

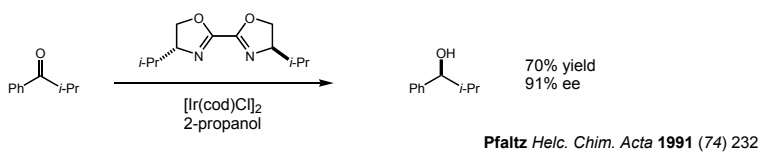
Typical ketone hydrogenations afford 10% ee or less

### Asymmetric Hydrogen Transfer Reactions Nitrogen-ligand systems

- Phenanthroline ligands afford moderate selectivities



- Pfaltz's bioxazole ligands can achieve high selectivities

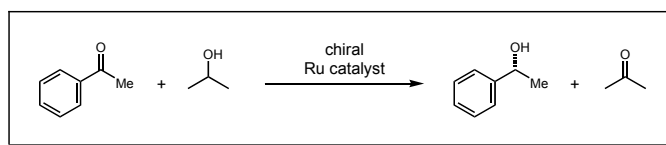


Typical substrates have ee's below 60%

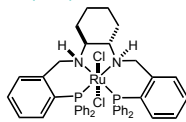
- Iridium systems may undergo MVP type mechanism

### Asymmetric Transfer Hydrogenations Noyori has breakthrough result

- Structurally similar salen-derived catalysts provide drastically different results



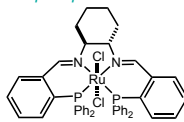
diphosphine/diamine



1

93% yield  
93% ee  
r.t. 5 h

diphosphine/diimine



2

3% yield  
18% ee  
r.t. 48 h

- Lack of amine N-H in 2 makes catalyst much less effective

### Asymmetric Transfer Hydrogenations Effect of ligand on reactivity

- Amine ligand has a marked effect on reactivity and extent of enantioselectivity

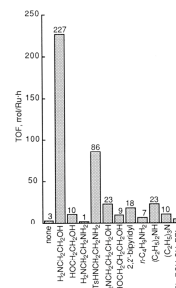
Ethylenediamine (TOF=1) less reactive than no ligand (TOF=3)

N-Tosylated ethylenediamine second fastest catalyst (TOF=86)

Amino alcohol has the fastest reaction rate (TOF=227)

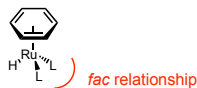
Presence of a primary or secondary amine end is crucial for catalytic activity: dimethylamino analogues are totally unreactive

Noyori JOC 2001 (66) 7931



- Move away from phosphine ligands: Arene ligands are electronically desirable

Spectator ligands automatically occupy three adjacent coordination sites of Ru in an octahedral environment; thereby leaving three sites with a fac relationship for other functions



### Asymmetric Transfer Hydrogenations Effect of ligand on reactivity

- Amine ligand has a marked effect on reactivity and extent of enantioselectivity

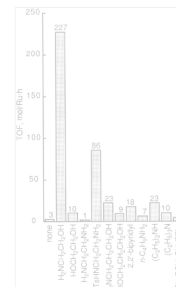
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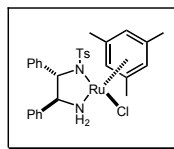
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Noyori JOC 2001 (66) 7931

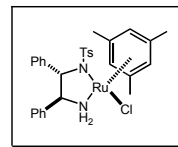


- Move away from phosphine ligands: Arene ligands are electronically desirable

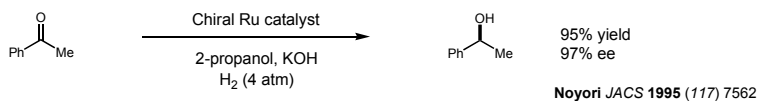
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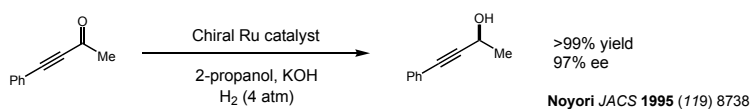
### Asymmetric Transfer Hydrogenation Away from BINAP



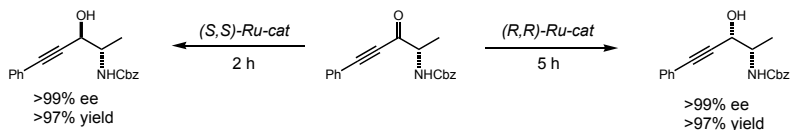
- Chiral amine ligand affords sufficient enantiofacial discrimination



- Methodology extendable to acetylinic ketones

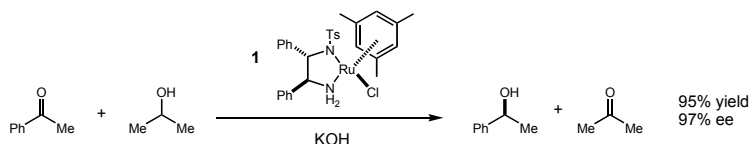


- Resident stereogenicity has little impact on reaction selectivity



### Asymmetric Transfer Hydrogenation Solution for reversibility problem

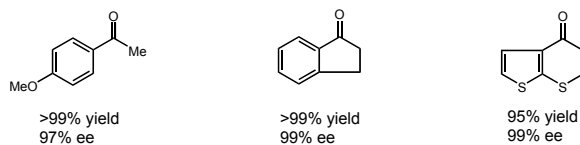
- Structural similarity of product and 2-propanol frequently deteriorates enantiomeric purity



- Azeotropic mixture of formic acid and triethyl amine makes reaction irreversible

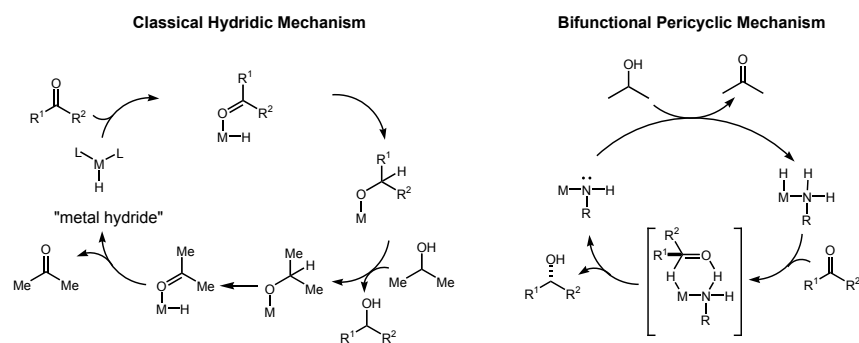


New conditions allow for higher yields, higher substrate concentrations (2-10 M vs. <0.1 M) and wider substrate scope



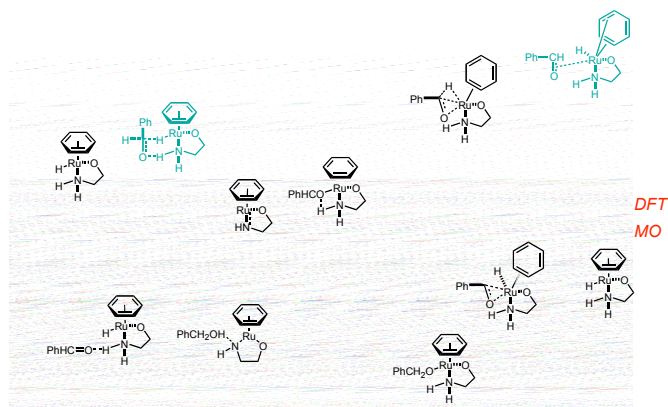
### Asymmetric Transfer Hydrogenations Mechanism "Revisited"

- Prior results on the effects of primary and secondary amine ligands cause mechanistic questioning.



### Theoretical Study on Catalytic Cycle of Asymmetric Transfer Hydrogenations Energy Diagrams of pericyclic and elimination/insertion mechanisms

- MO and DFT calculations show pericyclic mechanism to be more energetically favorable



- Neither carbonyl oxygen nor alcoholic oxygen interact with metal center during pericyclic mechanism

Noyori JACS 2000 (122) 1466

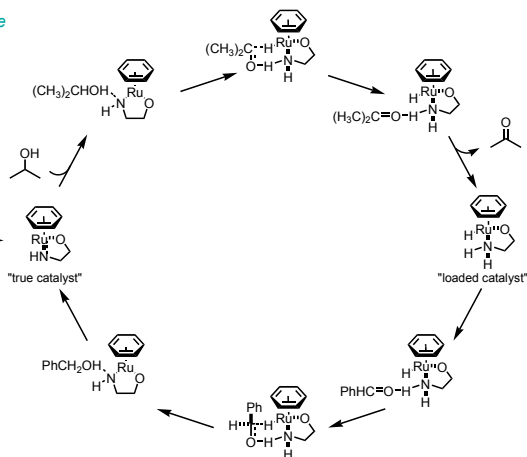
### Asymmetric Transfer Hydrogenation Proposed Catalytic cycle

- Theoretical calculations indicate novel catalytic pathway

All pathways are reversible

Base required for "true catalyst" formation not for improving alkoxide ion concentration

Preformed complexes of "true catalyst" do not exhibit rate depreciation in the absence of base



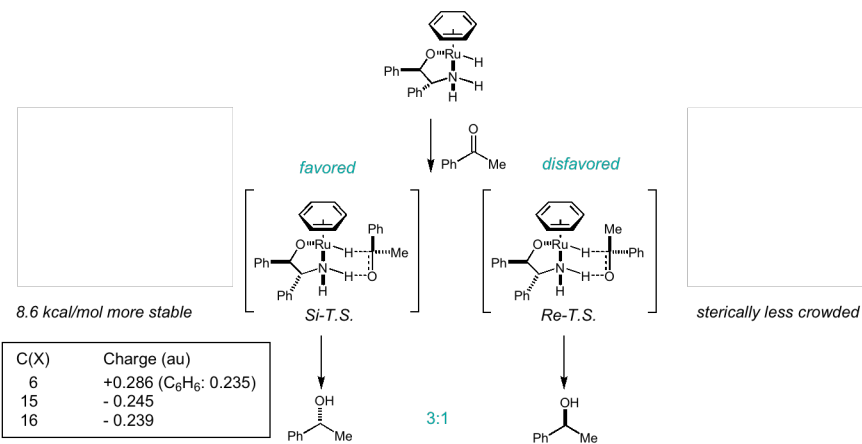
Hydride delivery occurs through a pericyclic mechanism via a 6-membered T. S.

- Ruthenium and amine ligand simultaneously participate in forward and reverse steps

Noyori JACS 2000 (122) 1466

### Origins of Enantioselectivity in Asymmetric Transfer Hydrogenation DFT Calculations

- CH- $\pi$  attractive interaction between C(sp<sup>2</sup>)H of benzene ligand and  $\pi$  system stabilizes T.S.



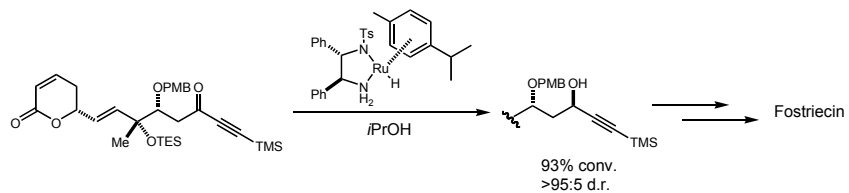
- $\pi$ -donation of benzene to Ru enhances positive charge on C(sp<sup>2</sup>)H
- Explains lower enantioselectivities of EWG's on aryl moiety of substituent

Noyori ACIEE 2001 (40) 2818



## Asymmetric Transfer Hydrogenation Synthetic Applications

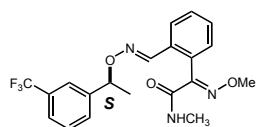
### ■ Jacobsen's synthesis of Fostriecin



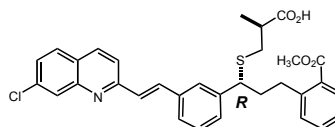
Control of relative stereochemistry of 1,3 diol unit through choice of catalyst enantiomer

Jacobsen *ACIEE* 2001 (113) 3779

### ■ Methodology useful in synthesis of biologically active compounds



96% yield, 91% ee  
*MA-20565*  
(herbal fungicide)



68% yield, 92% ee  
*L-699,392*  
(LTD4 antagonist)

## Conclusions

- Asymmetric hydrogenation of prochiral ketones is a highly efficient method for obtaining a range of optically pure alcohols in high ee and yield.
- Bifunctional catalytic systems have been developed to overcome reactivity limitations of transition metals for the hydrogenation of simple ketones.
- Transfer hydrogenation is a desirable alternative for the asymmetric reduction of simple ketones due to increased safety and high selectivities.