



**Named reactions:**

# The Noyori Asymmetric Hydrogenation

**Shyam Sundar Samanta**

**September, 18<sup>th</sup> 2012.**

2001 Nobel Prize in Chemistry – Asymmetric Catalysis



William S. Knowles  
1/4 of the prize  
USA

St. Louis, MO, USA

b. 1917



Ryoji Noyori  
1/4 of the prize  
Japan

Nagoya University  
Nagoya, Japan

b. 1938



K. Barry Sharpless  
1/2 of the prize  
USA

The Scripps  
Research Institute  
La Jolla, CA, USA

b. 1941

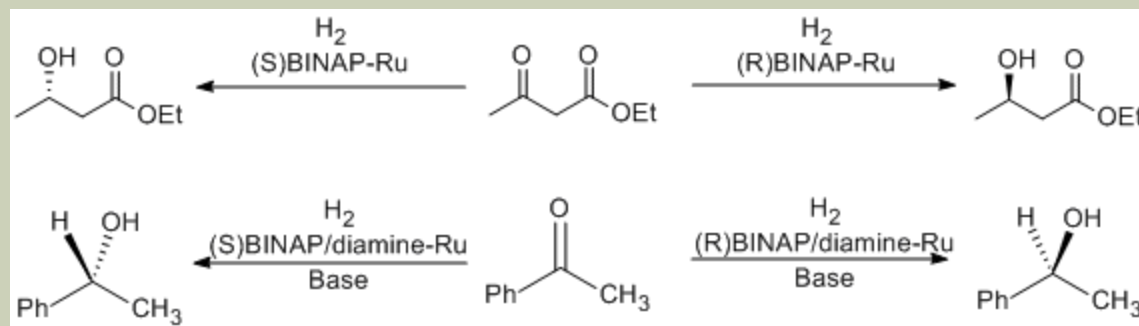


*"for their work on chirally catalysed hydrogenation and oxidation reactions"*

# The Noyori Asymmetric Hydrogenation : *Introduction :*

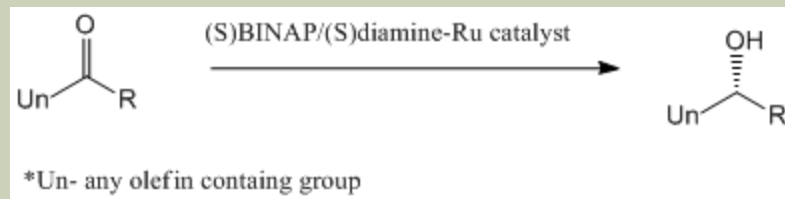


➤ **Noyori asymmetric hydrogenation of ketones** is a chemical reaction for the enantioselective hydrogenation of **ketone, aldehydes, and imines**.



➤ BINAP-Ru catalyst is used for the asymmetric hydrogenation of functionalized ketones and BINAP/diamine-Ru catalyst is used for the asymmetric hydrogenation of simple ketones.

➤ This system also had **chemoselectivity** on C=O bond over the C=C bond.

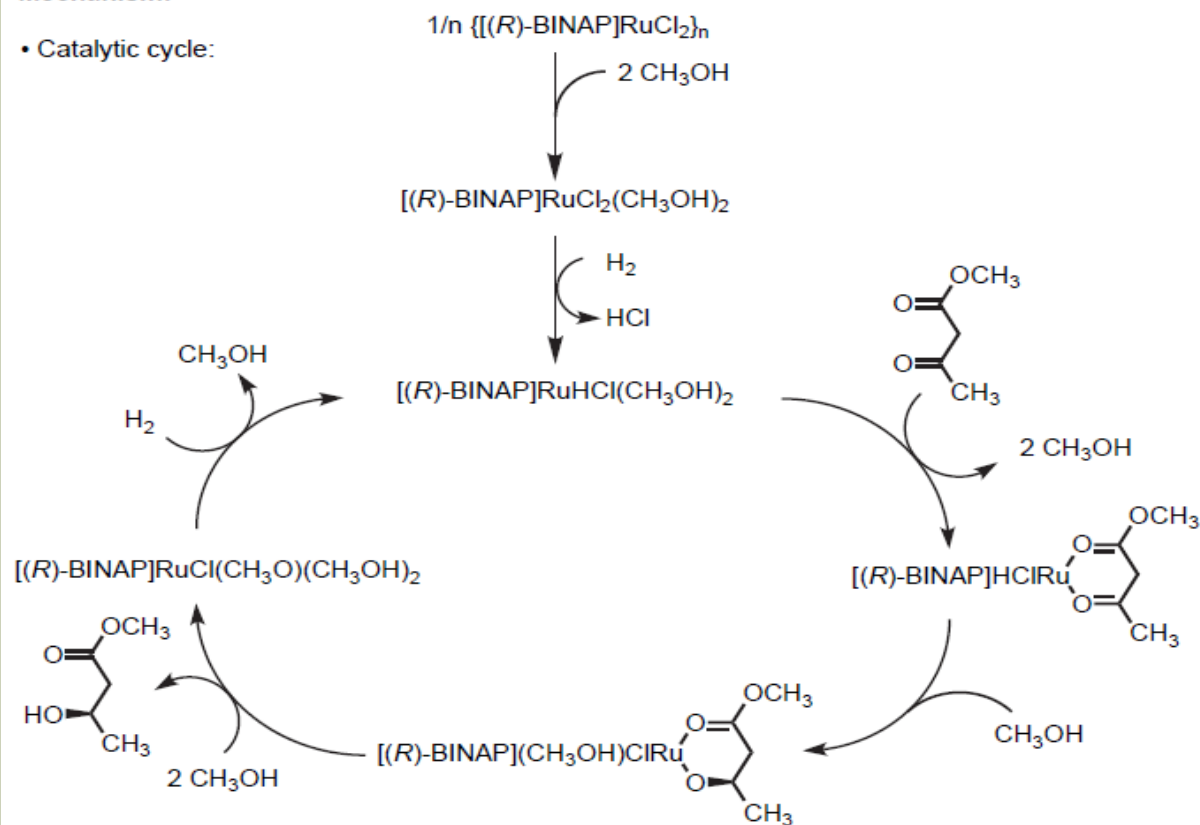


# The Noyori Asymmetric Hydrogenation : Mechanism :



## Mechanism:

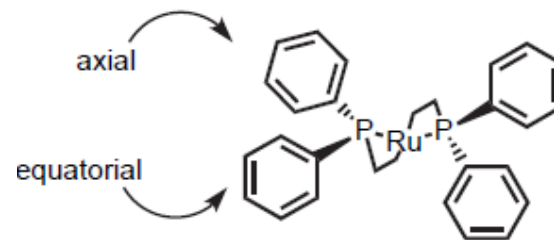
- Catalytic cycle:



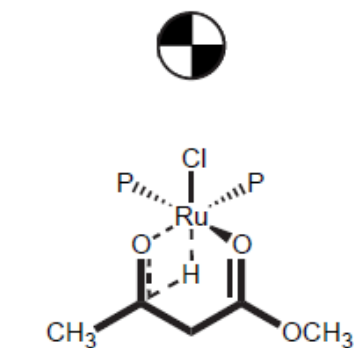
# The Noyori Asymmetric Hydrogenation :



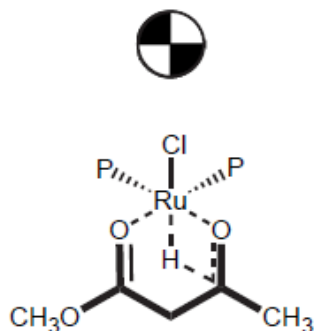
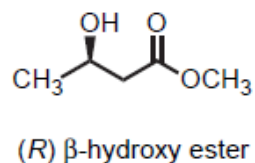
- A crystal structure of  $\text{Ru}(\text{OCOCH}_3)_2[(S)\text{-BINAP}]$  revealed that the rigid BINAP backbone forces the phenyl rings attached to phosphorous to adopt the conformation depicted here (the naphthyl rings are omitted for clarity).



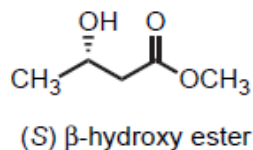
$\text{Ru}(\text{OCOCH}_3)_2[(S)\text{-BINAP}]$



$(R)\text{-BINAP}$



$(R)\text{-BINAP}$



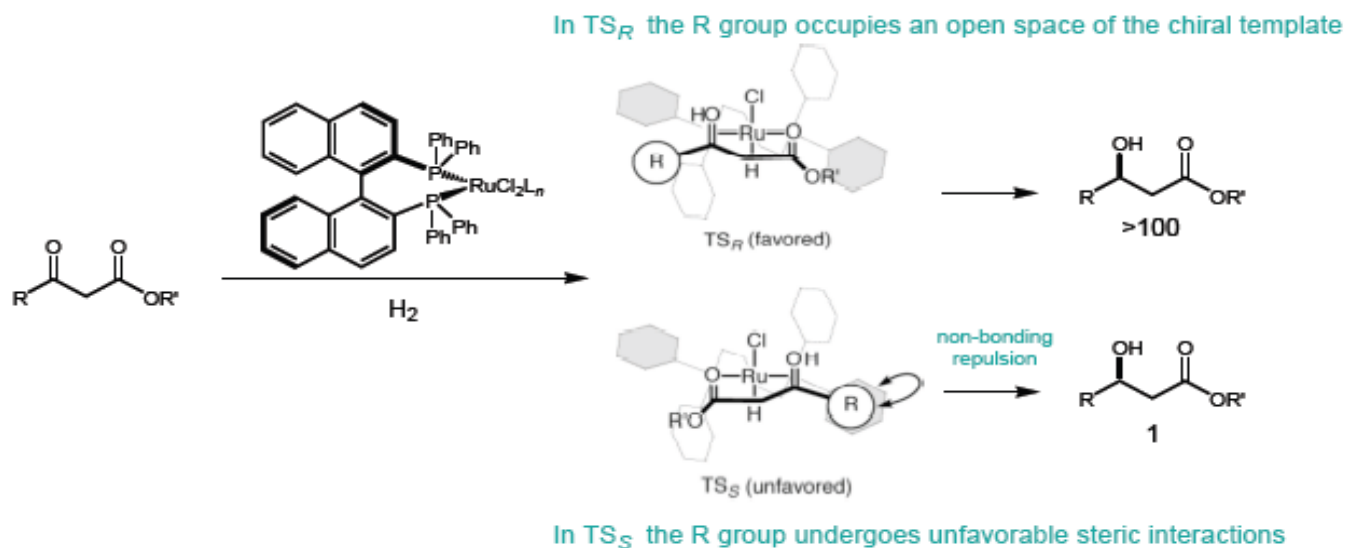
Of the two possible diastereomeric transition states for complexes with  $(R)\text{-BINAP}$  shown below, the one leading to the  $(R)$   $\beta$ -hydroxy ester allows the approach of the ketone at an unhindered quadrant (as represented by the light lower left quadrant of the circle).

# RU-BINAP CATALYZED ASYMMETRIC HYDROGENATION ENANTIODETERMINING TRANSITION STATES



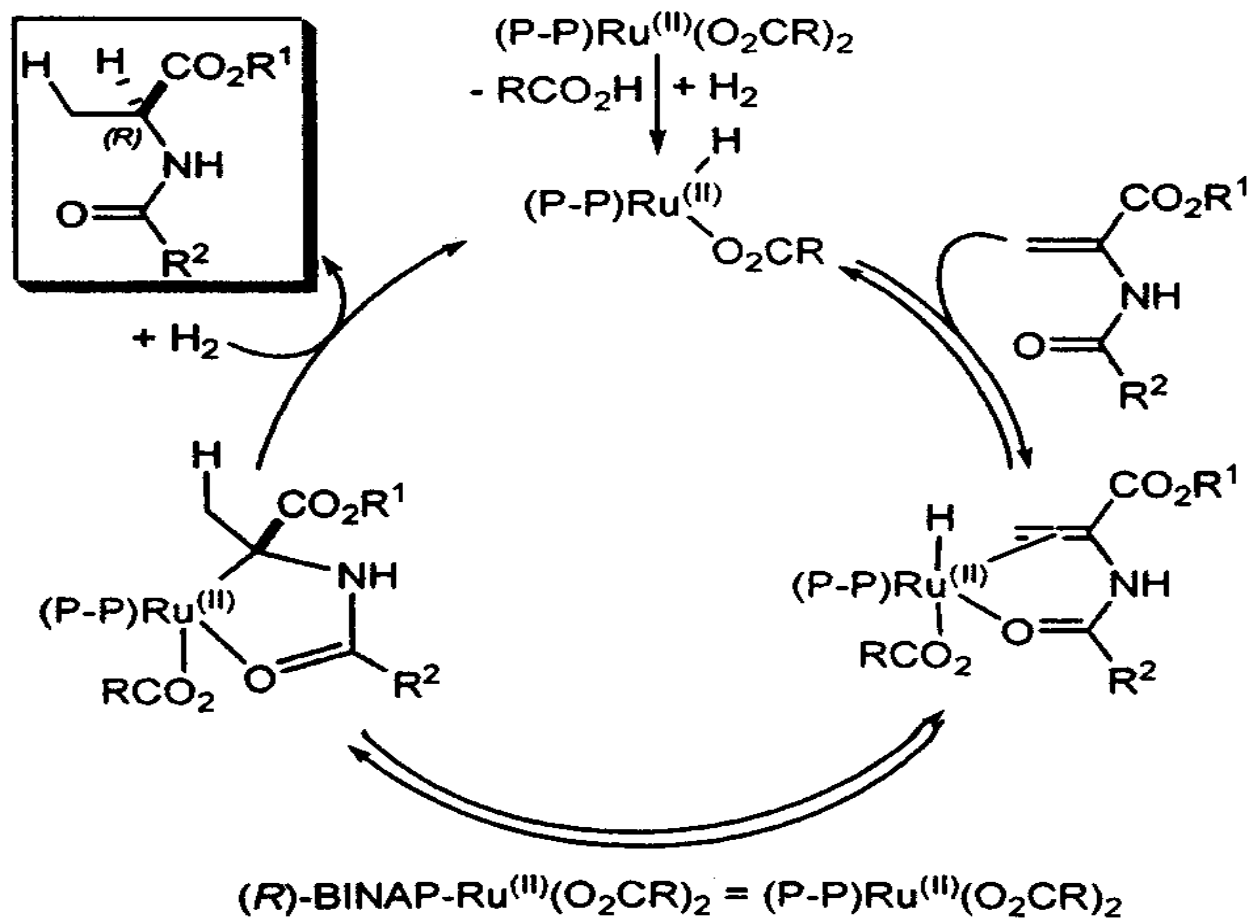
## Ru-BINAP Catalyzed Asymmetric Hydrogenation Enantiodetermining Transition States

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



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

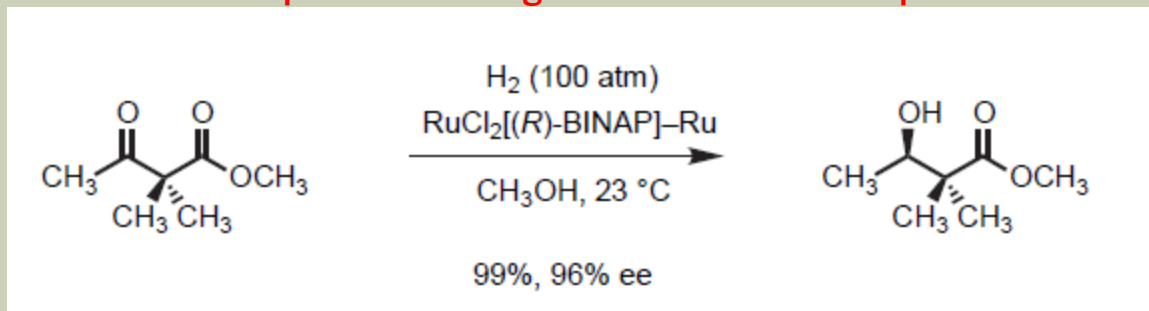
The Noyori Asymmetric Hydrogenation :  
Mechanism :



# The Noyori Asymmetric Hydrogenation : Mechanism Evidence :

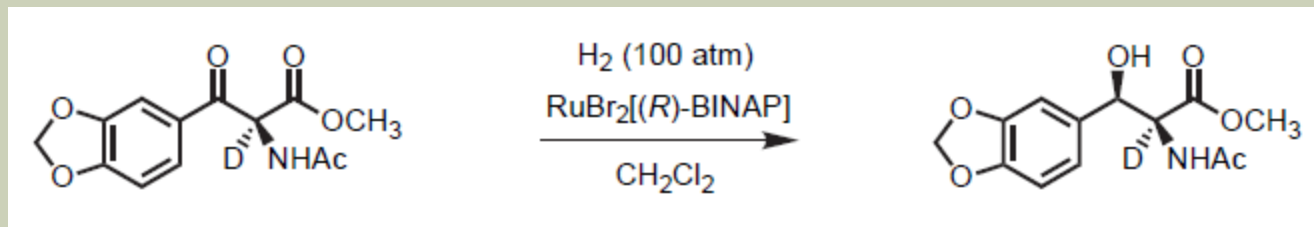


- Evidence that the reduction proceeds through the keto form of the  $\beta$ -keto ester.



Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345–350.

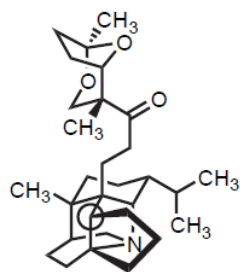
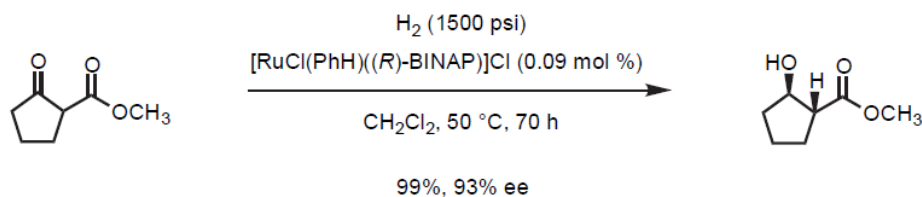
- However, pathways that involve hydrogenation of the enol form of other  $\beta$ -keto esters cannot be ruled out.
- The use of a deuterated substrate provides further evidence that the reduction proceeds through the keto tautomer. Enolization is rapid, so the deuterium is lost quickly. However, when the reaction was stopped at 1.3% conversion, the hydroxy ester product retained 80% of the deuterium at C-2, and no deuterium was incorporated at C-3.



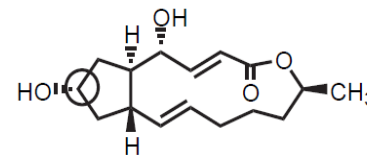
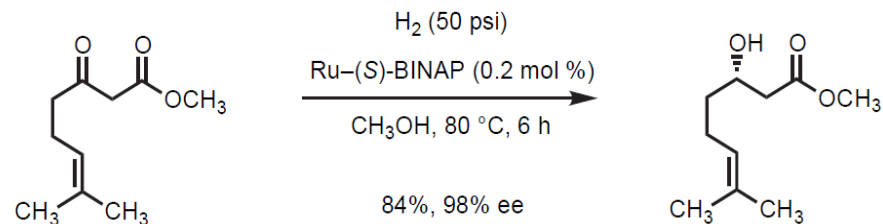
Noyori, R.; Ikeda, T.; Okhuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.



# The Noyori Asymmetric Hydrogenation : *Synthetic applications.*



(+)-Codaphniphylline

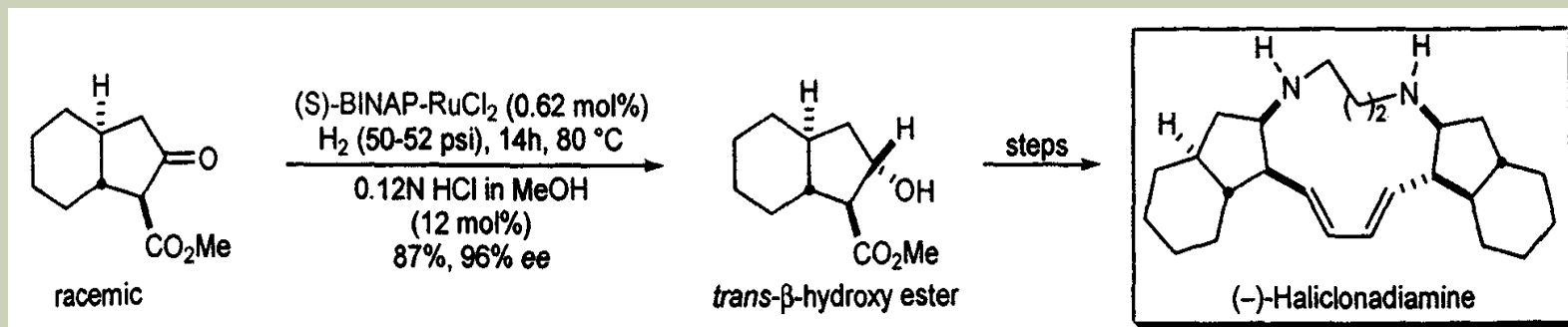


(+)-Brefeldin A

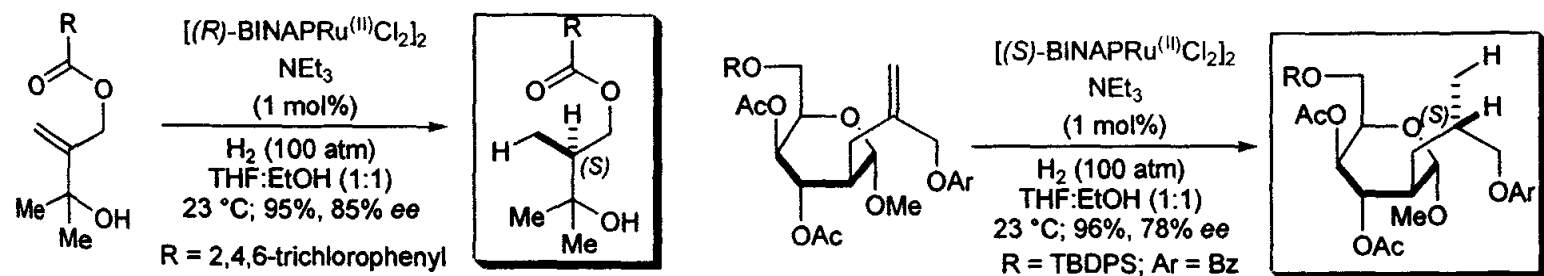
Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120–1130.

Taber, D. F.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639–6645.

# The Noyori Asymmetric Hydrogenation : *Synthetic applications.*



Taber, D. F., Wang, Y. Synthesis of (-)-Haliciondiamine. *J. Am. Chem. Soc.* **1997**, *119*, 22-26.



Shimizu, H., Shimada, Y., Tomita, A., Mitsunobu, O. Pronounced enhancement of stereoselectivity in asymmetric hydrogenation of 2-substituted 2-propen-1-ols by transient acylation. *Tetrahedron Lett.* **1997**, *38*, 849-852.