Catalyst Directed Asymmetric Hydrogenation of Carbonyls

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MacMillan Group Meeting
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- Homogeneous Hydrogenation
- Hydride Transfer
- Bifunctional Catalysis

Reduction of Carbonyls
Introduction

- Oxazaborolidine structure based catalysts

\[ \text{Ph Me OH} \rightarrow \text{Ph Me CH}_2\text{N} \]

(S/C = 5-10)

97% ee (S/C = 5-10)

Corey JACS 1987 (109) 5551
Corey JACS 1987 (109) 7925
Reduction of Carbonyls

Introduction

- Oxazaborolidine structure based catalysts

![Structure](image)

(S/C = 5-10) Corel JACS 1987 (109) 5551
Corel JACS 1987 (109) 7623

- Homogeneous hydrogenation - bifunctional catalysis

![Structure](image)

RuCl₂((+)-binap) (S/C = 10,000) Noyori ACIE 2001 (40) 40

- Transfer hydrogenation - bifunctional catalysis

![Structure](image)

Noyori JOC 2001 (66) 7931

History of Asymmetric Hydrogenation

- Wilkinson's catalyst capable of achiral olefin hydrogenations

![Structure](image)

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

- First report of asymmetric hydrogenation came from William Knowles

![Structure](image)

Knowles Chem. Commun. 1968, 1445

- Monsanto Chemical Company produces L-DOPA

![Structure](image)

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

![Chemical reaction diagram]

- Minor diastereomer is 580 fold more reactive towards H₂ oxidative addition - leads to 60:1 product ratio

Halpern, Science 1982 (217) 401

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**History of Asymmetric Hydrogenation III**

*Olefin reductions*

- Noyori develops BINAP-Ru complex

![Chemical reaction diagram]

- BINAP-Ru shows improved substrate scope

- First demonstration of high asymmetric induction of substrates lacking an acylamino group
- No trend observed between H₂ pressure and enantioselectivity and no rationale given

Noyori, JACS 1986 (108) 7117

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Noyori, JOC 1987 (52) 3174
History of Asymmetric Hydrogenation IV
Olefin reductions

1. Hydrogenation of allylic and homoallylic alcohols

- (S)-Ru-Binap

\[ \text{cis-2,3-Dialkoxy-1-propene} \rightarrow \text{cis-2,3-Dialkoxy-2-propene} \]

96% ee > 97% yield

(bis-homoallylic and higher analogues are not hydrogenated)

Noyori JACS 1987 (109) 1596

2. Can Ru-Binap catalysts be applied to ketone hydrogenations?

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

\[ \text{MeOEt} \quad \text{MeOEt} \quad \text{Me} \quad \text{Me} \quad \text{OEt} \]

Hydride of Binap dicarboxylate catalysts are not hydridic enough in character

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

\[ \text{MeOEt} \quad \text{MeOEt} \quad \text{Me} \quad \text{Me} \quad \text{OEt} \]

41% yield
4% ee

72% yield
96% ee

Hsitory of Asymmetric Hydrogenation IV
Olefin reductions

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

\[ \text{MeOEt} \quad \text{MeOEt} \quad \text{Me} \quad \text{Me} \quad \text{OEt} \]

41% yield
4% ee

72% yield
96% ee

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

- Can Ru-Binap catalysts be applied to ketone hydrogenations?
Substrate-Directed Ketone Hydrogenation
Pioneering work from Noyori

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

![Chemical structure](image_url)

$\text{R} = \text{C}_4\text{H}_4\text{R}, \text{Alkyl}, \text{CH}_3\text{OAr}$

$\text{X} = \text{OH}, \text{OMe}, \text{CO}_2\text{Me}, \text{NMMe}_2, \text{Br, COSMe, CONMe}$

- Reactions require forcing pressures of $\text{H}_2$ (50-100 psi commonly required)
- $\text{Ru(II)}$ -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

![Mechanism diagram](image_url)

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

Noyori JACS 1987 (109) 5856
Noyori JACS 1988 (110) 629
Noyori ACIEE 2001 (40) 40
Substrate-Directed Ketone Hydrogenation
Mechanism

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

Diastereomeric T.S.

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

RuBINAP Catalyzed Asymmetric Hydrogenation
Enantiodetermining Transition States

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

In TS_R the R group occupies an open space of the chiral template

In TS_S the R group undergoes unfavorable steric interactions

- 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
- Keto sulfonates: 100% conv., 97% ee
- Keto phosphonates: 100% conv., 98% ee

- Synthetic Applications of asymmetric hydrogenations

- (+)-mycosicin
- Rofamycin

- Stereocenters set by asymmetric hydrogenation are marked

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'-tetramethylethenediamine 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' – H_2 - N distances are at the outer limit of protonic-hydridic or dihydrogen bonding. (2.4 Å)
  - Ru-H bond weakened by high trans influence of hydride which explains the reactivity of hydridic hydride toward ketones.

![Diagram of catalytic cycle](image)

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

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

Morris, JACS 2001 (123) 7473

Asymmetric Hydrogenation
Ligands can impart chirality

- Chiral diamine ligands influence reaction selectivity
  - 2-propanol, KOH
  - H_2 (4 atm), r.t. 6h

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

Noyori, JACS 1995 (117) 10417
Asymmetric Hydrogenation of Ketones in the Diamine-BINAP System

- Diastereomeric transition states are present in dihydride delivery step

\[ X^\text{Me} \]

\[ X^=\text{H} \]

In TS\text{I}, unfavorable steric interference results in a less active and selective system

- In TS\text{II}, \( \text{R}_{\text{Me}} \) 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\text{2} (S/C) = 2,000

**Enone Reduction**

- 100% conv.
- 97% ee
- 43 h; 30 C; 80 atm H\text{2} (S/C) = 100,000

**Cyclopropyl Reduction**

- 96% conv.
- 95% ee
- 12 h; 30 C; 10 atm H\text{2} (S/C) = 11,000

**Bis-Aryl Ketone Reduction**

- 100% conv.
- 99% ee
- 15 h; 30 C; 8 atm H\text{2} (S/C) = 13,000

**Arly Ketone Reduction**

- >99.7% conv.
- >99% ee
- 4-10 h; 30 C; 8-10 atm H\text{2} (S/C) = 20-70

**New ligands also show wider scope for aryl ketones**

Noyori JACS 1998 (120) 13529
Noyori ACS 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.

![Diagram of Direct Hydrogen Transfer](image)

**Favored by main group elements**

Hyridic (Stepwise Route)

![Diagram of Hyridic Route](image)

**Favored by transition metal complexes**

Review of H-Transfer: Chem. Rev. 1992, 92, 1051

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**Asymmetric Hydrogen Transfer Reactions**

**Meerwein-Ponndorf-Verley Reduction**

- Evans develops a chiral samarium catalyst for MPV reaction
  
  ![Evans's Catalyst](image)

  **Substrate Scope limited to aryl ketones**

  Evans JACS 1993 (115) 9800

- Maruoka develops a bidentate aluminum system
  
  ![Maruoka's Catalyst](image)

  **Requires enantiopure alcohols**

  Maruoka ACIEE 1998 (37) 2347

- Also reports of Lanthanide catalyzed system
Asymmetric Hydrogen Transfer Reactions

"Classical" Mechanism

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

Hydridic (Stepwise Route)

 coordinatively unsaturated M-H first forms a C=O complex

*metal hydride*

insertion/elimination

2 propanoxide exchanges with substrate

- 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**

  \[
  \text{Ph}-\text{H} + \text{H}_2\text{Ru(CO)}_2[(-)-\text{DIOP}] \rightarrow \text{Ph}-\text{OH} \quad 9.8\% \text{ ee}
  \]

  J. Organomet. Chem. 1980 73

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

- **Rhodium**

  \[
  \text{Ph}-\text{Et} + [\text{Rh(nbd)}[(-)-\text{Chiraphos}]] \rightarrow \text{Ph}-\text{OH} \quad 59\% \text{ yield} \quad 34\% \text{ ee}
  \]

  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
  
  ![Structural formula](image)

  89% yield
  63% ee

  Tet. Asymmetry 1990 (1) 635

- Pfaltz's bixazole ligands can achieve high selectivities
  
  ![Structural formula](image)

  70% yield
  91% ee


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
  
  ![Structural formula](image)

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

  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: dimethylaminooxalides 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

Noyori JOC 2001 (66) 7931
Asymmetric Transfer Hydrogenation
Away from BINAP

- Chiral amine ligand affords sufficient enantiofacial discrimination

![Chemical structure 1](image1)

Chiral Ru catalyst
2-propanol, KOH
H₂ (4 atm)

95% yield
97% ee

Noyori JACS 1995 (117) 7562

- Methodology extendable to acetylenic ketones

![Chemical structure 2](image2)

Chiral Ru catalyst
2-propanol, KOH
H₂ (4 atm)

>99% yield
97% ee

Noyori JACS 1995 (119) 8738

- Resident stereogenicity has little impact on reaction selectivity

![Chemical structure 3](image3)

(S,S)-Ru-cat
2 h

>99% ee
>97% yield

(R,R)-Ru-cat
5 h

>99% ee
>97% yield

Asymmetric Transfer Hydrogenation
Solution for reversibility problem

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

![Chemical structure 4](image4)

KOH

>95% yield
97% ee

Noyori JACS 1996 (118) 2521

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

![Chemical structure 5](image5)

HCO₂H-TEA

>99% yield
98% ee

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

![Chemical structure 6](image6)

>99% yield
96% ee

95% yield
99% ee
Asymmetric Transfer Hydrogenations
Mechanism "Revisited"

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

Classical Hydridic Mechanism

Bifunctional Pericyclic Mechanism

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
Theoretical calculations indicate novel catalytic pathway. All pathways are reversible.

Preformed complexes of "true catalyst" do not exhibit rate depression 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.

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

- CH-π attractive interaction between C(sp²)H of benzene ligand and π system stabilizes T.S.

8.6 kcal/mol more stable

\[ \text{C}(X) \quad \text{Charge (au)} \]
\[ 6 \quad +0.280 \quad (C_6H_5) \quad 0.235 \]
\[ 15 \quad -0.245 \]
\[ 16 \quad -0.239 \]

- π-donation of benzene to Ru enhances positive charge on C(sp²)H

Explains lower enantioselectivities of EWGs on aryl moiety of substituent.

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Noyori JACS 2000 (122) 1466

Noyori ACIEE 2001 (40) 2818
Asymmetric Transfer Hydrogenation
Synthetic Applications

- Jacobsen’s synthesis of Fostriecein
  
  Control of relative stereochemistry of 1,3 dial 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.