Activation Modes Are Enabled by Privileged Catalyst Architectures
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Activation Modes Are Enabled by Privilegded Catalyst Architectures

Catalysis Platform / Concept

Activation Modes

Catalyst Design

Privilegded Architecture

Chiral Pool

Chemical Methodology

New Reactions – Enabling Valuable Bond Disconnections

Previous Lecture

This Lecture – Broadened Activation Themes

- Enamine
  - Proline-derived

- Iminium
  - Imidazolidinone

- Electrophile Activation
  - DMAP
  - Carbene

- Nucleophile Activation
  - Acids and Phase Transfers
Phase Transfer Catalysis (PTC)

Begining with Makosza and Brandstrom, Stark coined the term phase transfer catalysis


An alternative solution to the heterogeneity problem, phase-transfer catalysis, is introduced here. Reaction is brought about by the use of small quantities of an agent which transfers one reactant across the interface into the other phase so that reaction can proceed. The
"The phenomenon of rate enhancement of a reaction between chemical species located in different phases by addition of a small quantity of an agent (called the 'phase-transfer catalyst') that extracts one of the reactants, most commonly an anion, across the interface into the other phase so that reaction can proceed..." – IUPAC Gold book
Pioneering Studies at Merck

- In 1984 researchers at Merck published their work towards asymmetric alkylation.
Pioneering Studies at Merck

In 1984 researchers at Merck published their work towards asymmetric alkylations.

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\[
\text{CHO} \quad \text{Cl}_{2} \quad \text{O} \quad \text{MeO} \quad \text{MeCl} \quad 10 \text{ mol} \% \text{ cat} \\
50\% \text{aq NaOH} \\
toluene \\
20^\circ \text{C}, 18 \text{ h} \\
95\% \text{ yield} \\
92\% \text{ ee}
\]

\[
\text{H-bond / ion pair} \\
\text{\pi-stack}
\]

Asymmetric Phase Transfer Catalysis

The catalyst controls the orientation of the enolate alkylation


Glycine Imine Ester

Organic

Aqueous
Asymmetric Phase Transfer Catalysis

The catalyst controls the orientation of the enolate alkylation

Asymmetric Phase Transfer Catalysis

The catalyst controls the orientation of the enolate alkylation

Asymmetric Phase Transfer Catalysis

The catalyst controls the orientation of the enolate alkylation

Asymmetric Phase Transfer Catalysis

The catalyst controls the orientation of the enolate alkylation

Switching Enantioselectivity Using Pseudoenantiomers

Catalyst diastereomers give rise to the opposite product configuration.

\[
\text{PhCH}_2\text{Br} \quad 10 \text{ mol} \% \text{ cat} \\
\text{50\% aq KOH} \\
\text{toluene} \\
\text{20 °C, 18 h}
\]

\[
\begin{align*}
\text{cat A} & \quad 77\% \text{ yield} \\
& \quad 86\% \text{ ee} \\
\text{cat B} & \quad 85\% \text{ yield} \\
& \quad 94\% \text{ ee}
\end{align*}
\]

\[
\begin{align*}
\text{A From cinchonine} & \\
\text{B From cinchonidine}
\end{align*}
\]

Advances in Catalyst Design

Catalysts have been benchmarked using the benzylation of glycine imine:

\[
\text{PhCH}_2\text{Br} \quad \text{10 mol \% cat} \\
\text{50\% aq KOH} \\
\text{toluene} \\
\text{20 \degree C, 18 h}
\]

\[
\text{Ph} - \text{N} - \text{CO} - \text{Ot-Bu} \text{→ Ph} - \text{N} - \text{CO} - \text{Ot-Bu}
\]

\[
\text{Ar} = \text{Ph} \\
\text{O'Donnell 1989} \\
\text{10 mol \%} \\
\text{75\% yield, 66\% ee}
\]

Advances in Catalyst Design

Catalysts have been benchmarked using the benzylation of glycine imine:

Ph\(\text{CH}_2\text{Br}\) 10 mol % cat
50% aq KOH
toluene 20 \(^\circ\text{C}, 18 \text{ h}\)

\[
\text{Ph} = \text{Ph}
\]
\[
\text{Cocatalyst:}
\]

Ar = Ph  
O'Donnell 1989  
10 mol %  
75% yield, 66% ee

R = allyl  
Lygo, Corey 1997  
10 mol %  
87% yield, 94% ee

Advances in Catalyst Design

Catalysts have been benchmarked using the benzylation of glycine imine:

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\text{PhCH}_2\text{Br} \quad 10 \text{ mol } \% \text{ cat} \\
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\text{toluene} \\
\text{20 }^\circ\text{C, 18 h}
\]

\[
\begin{align*}
\text{Ph} & \text{N} \text{C} \text{O} \text{Ot-Bu} \\
\text{Ph} & \text{N} \text{C} \text{O} \text{Ot-Bu}
\end{align*}
\]

Ar = Ph
O'Donnell 1989
10 mol %
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\[
\begin{align*}
\text{Ar} & = \text{Ph} \\
\text{O} & = \text{Ph} \\
\text{R} & = \text{allyl}
\end{align*}
\]

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Advances in Catalyst Design

- Catalysts have been benchmarked using the benzylation of glycine imine:

\[
\text{Ph-CH}_2\text{Br} \quad \text{10 mol % cat} \quad \text{50% aq KOH} \quad \text{toluene} \quad 20 \degree \text{C, 18 h}
\]

- Ar = Ph
  - O'Donnell 1989
  - 10 mol %
  - 75% yield, 66% ee

- R = allyl
  - Lygo, Corey 1997
  - 10 mol %
  - 87% yield, 94% ee

- \text{Ar} = \text{Ph}
  - Maruoka 1999
  - 1 mol %
  - 91% yield, 98% ee

- \text{Cocatalyst: 18-crown-6}

- \text{Ar} = \text{Ph}
  - Maruoka 2005
  - 0.05 mol %
  - 0.05 mol % 18-crown-6
  - 90% yield, 98% ee

The PTC Activation Mode Beyond Alkylation Reactions

- PTC activation of carbonyls has enabled the development of many different asymmetric reactions.

![Chemical structures and reactions](image)

- 90% 98% ee glycine–alkylation

- 85%, 98% ee glycine alkylation–allylation

- 85%, 91% ee glycine–Michael

- 83% 96:4 anti, 98% ee glycine–aldol

- 95%, 9:1 syn 82% ee glycine–Mannich

- 78%, 85% ee β-ketoester SN_Ar

The PTC Activation Mode Beyond Alkylation Reactions

PTC activation of carbonyls has enabled the development of many different asymmetric reactions.

- **94%, 94% ee**
  Strecker

- **99%, 96% ee**
  enone epoxidation

- **70%, 81% ee**
  Darzens epoxidation

- **94%, 84% ee**
  β-ketoester fluorination

- **99%, 92% ee**
  β-ketoester amination

- **79%, 84% ee**
  aziridation

Phase Transfer Catalysis

- Since the original reports the area continues to be a strong sector of organocatalysis research.
- ISI web of knowledge references containing the key phrase "phase transfer catalysis" total 3698.

Dolling’s (+)-indacrinone synthesis:
Carbenes as Organocatalysts

- Carbenes were long suspected as catalytic intermediates
Carbenes as Organocatalysts

Carbenes were long suspected as catalytic intermediates

Carbenes as Organocatalysts

Carbenes were long suspected as catalytic intermediates.

Thiazolium Salt of Thiamine Coenzyme (vitamin B₁)  Nature's Carbene Organocatalyst
Carbenes as Organocatalysts

- Carbenes were long suspected as catalytic intermediates

![Thiazolium Salt of Thiamine Coenzyme (vitamin B₁)](image1)

![Nature's Carbone Organocatalyst](image2)

- For many years a carbene catalyst for the enantioselective benzoin condensation was elusive

![Benzoin Product](image3)

![Breslow-type Intermediate](image4)
Carbenes as Organocatalysts

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![Thiazolium Salt of Thiamine Coenzyme (vitamin B₁)](image1)
![Nature's Carbone Organocatalyst](image2)

- For many years a carbene catalyst for the enantioselective benzoin condensation was elusive
- The newly proposed intermediate exhibits umpolung reactivity

![electrophilic](image3)
![Breslow-type Intermediate](image4)
![acyl anion synthon](image5)
Carbenes as Organocatalysts

- Carbenes were long suspected as catalytic intermediates

\[
\begin{align*}
\text{Thiazolium Salt of Thiamine Coenzyme (vitamin B_1)} &\quad \text{Nature's Carbone Organocatalyst} \\
\text{HOC} &\quad \text{Me} \\
\text{H_2N} &\quad \text{H_2N} \\
\text{Me} &\quad \text{Me} \\
\end{align*}
\]

- For many years a carbene catalyst for the enantioselective benzoin condensation was elusive

- The newly proposed intermediate exhibits umpolung reactivity

\[
\begin{align*}
\text{Ph} &\quad \text{Ph} \\
\text{HOC} &\quad \text{cat} \\
\text{H} &\quad \text{H} \\
\text{N} &\quad \text{N} \\
\text{R} &\quad \text{R} \\
\text{Ph} &\quad \text{Ph} \\
\text{OH} &\quad \text{OH} \\
\end{align*}
\]

- Before we can get new reactions
  we need better catalysts
**Carbenes as Organocatalysts**

- Carbenes were long suspected as catalytic intermediates

![Thiazolium Salt of Thiamine Coenzyme (vitamin B₁)](image1) → ![Nature's Carbone Organocatalyst](image2)

- For many years a carbene catalyst for the enantioselective benzoin condensation was elusive

- The newly proposed intermediate exhibits umpolung reactivity

![electrophilic](image3) → ![Breslow-type Intermediate](image4) → ![acyl anion synthon](image5)

Before we can get new reactions we need better catalysts

novel reactivity patterns
Carbenes as Organocatalysts

- Isolated in 1991 by Arduengo while working at DuPont


- In 1995 Enders and Teles develop stable triazole-based carbenes

Preparation, Structure, and Reactivity of 1,3,4-Triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene, a New Stable Carbene**

Dieter Enders,* Klaus Breuer, Gerhard Raabe, JanRunsink, J. Henrique Teles,* Johann-Peter Melder, Klaus Ebel, and Stefan Brode

Asymmetric Carbene Catalysts

The genesis of a new platform for asymmetric catalysis

1966 Sheehan Hunneman

22% ee

1997 Leeper

80% ee

2002 Enders

83% 90% ee

2002 Chiral triazole are made and are efficient and selective for the benzoin condensation

Carbenes: Generic Activation Platform

- It was soon realized that carbenes activate carbonyls for a number of useful reactions.

Breslow-type Nucleophile

- Alkene geometry controlled by bulky group
- Re face shielded by t-Bu
- Generically activated towards electrophiles
Recent Advance in Carbene Catalysis

After the initial disclosures in the 1990’s the Stetter reaction has been championed by Rovis

Recent Advance in Carbene Catalysis

After the initial disclosures in the 1990's the Stetter reaction has been championed by Rovis


The Rovis catalyst design has been proven to be excellent for many more reactions

Beyond the Stetter and Bezoin Reactions

Azadiene Diels–Alder

Beyond the Stetter and Bezoin Reactions

■ Azadiene Diels–Alder

Beyond the Stetter and Bezoin Reactions

Azadiene Diels–Alder

Substrate Activation Towards New Reactivity

- α-chloraldehydes provide access to alternate manifolds for e.g. esterification

\[
\begin{align*}
\text{α-chloraldehyde} & \quad \text{alcohol} \\
\text{ester} & \quad 10 \text{ mol}\% \quad \text{NEt}_3
\end{align*}
\]

Substrate Activation Towards New Reactivity

α-chloroaldehydes provide access to alternate manifolds for e.g. esterification

**Substrate Activation Towards New Reactivity**

- \( \alpha \)-chloroaldehydes provide access to alternate manifolds for e.g. esterification

\[
\begin{align*}
\text{H} & \quad \text{Ph} \\
\text{Cl} & \\
\text{H} & \quad \text{Ph} \\
\text{Cl} & \\
\text{Cl} & \quad \text{OH} \\
\text{Ph} & \quad \text{Cl} & \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

\( \alpha \)-chloroaldehyde  alcohol

\[
\begin{align*}
\text{10 mol \%} \\
\text{NEt}_3
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{O} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

ester

- Oxy Diels–Alder reaction

\[
\begin{align*}
\text{H} & \quad \text{Ph} \\
\text{O} & \\
\text{Cl} & \\
\text{Cl} & \\
\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{N} & \quad \text{N} \\
\text{Mes} & \quad \text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{0.5 mol \%} \\
\text{EtOAc, NEt}_3
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Ph} \\
\text{CO}_2\text{Me} & \quad \text{Ph}
\end{align*}
\]

88\%, >20:1 dr, 99\% ee

Hydrogen-Bonding Catalysis

H-bond catalysis

~30 new reactions
Jacobsen–Akiyama

Hydrogen-Bonding Catalysis

H-bond catalysis

~30 new reactions

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Hydrogen-Bonding Catalysis

~30 new reactions
Jacobsen–Akiyama

Addition of Aromatic Thiols to Conjugated Cycloalkenones, Catalyzed by Chiral β-Hydroxy Amines. A Mechanistic Study on Homogeneous Catalytic Asymmetric Synthesis

Henk Hiemstra and Hans Wynberg


Hydrogen-Bonding Catalysis

Addition of Aromatic Thiols to Conjugated Cycloalkenones, Catalyzed by Chiral β-Hydroxy Amines. A Mechanistic Study on Homogeneous Catalytic Asymmetric Synthesis

Henk Hiemstra and Hans Wynberg*

Contribution from the Laboratory of Organic Chemistry, The University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands. Received February 25, 1980

Early examples using cinchonia alkaloids as H-bonding catalysts

Early Examples of Hydrogen Bonding Catalysis

A small dipeptide was designed by Inoue to mimic oxynitrilase

![Dipeptide structure](image)

HCN

2 mol %, toluene, –20 °C

97%, 97% ee

Early Examples of Hydrogen Bonding Catalysis

A small dipeptide was designed by Inoue to mimic oxynitrilase

Early Examples of Hydrogen Bonding Catalysis

A small dipeptide was designed by Inoue to mimic oxynitrilase

\[
\begin{align*}
\text{HCN} & \quad \xrightarrow{2 \text{ mol } \% \text{, toluene, } -20 \degree C} \quad \text{PhCN} \\
\text{Ph} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

Asymmetric Strecker reaction using Corey's guanidine H-bonding catalyst

\[
\begin{align*}
\text{HCN} & \quad \xrightarrow{10 \text{ mol } \% \text{, toluene, } -40 \degree C} \quad \text{PhCN} \\
\text{Ph} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

Discovery of Acid Mediated Strecker Reactions – Jacobsen Thioureas

- Parallel synthetic ligand libraries were evaluated with various metals

Schiff Base Catalysts for the Asymmetric Strecker Reaction Identified and Optimized from Parallel Synthetic Libraries

Matthew S. Sigman and Eric N. Jacobsen

Department of Chemistry and Chemical Biology
Harvard University, Cambridge, Massachusetts 02138

Received January 13, 1998

Discovery of Acid Mediated Strecker Reactions – Jacobsen Thioureas

- Parallel synthetic ligand libraries were evaluated with various metals

- Modified Schiff bases were prepared in a combinatorial fashion on a solid support

Discovery of Acid Mediated Strecker Reactions – Jacobsen Thioureas

- Parallel synthetic ligand libraries were evaluated with various metals

![Chemical structure]

- Modified Schiff bases were prepared in a combinatorial fashion on a solid support

![Chemical structure]

Discovery of Acid Mediated Strecker Reactions – Jacobsen Thioureas

The structure was quickly optimized to provide an efficient Strecker catalyst

Systematic optimization

Catalyst Lead

New Catalyst

The structure was quickly optimized to provide an efficient Strecker catalyst.

Systematic optimization

New Catalyst

Catalyst Lead

TBSCN

2 mol % cat

toluene, –78 °C

TFA

78% conv 91% ee

How Do These New Catalysts Function?

- Knock-out studies show that the urea functional group is essential
- Hydrogen bonding established as the activation mode

**How Do These New Catalysts Function?**

- Knock-out studies show that the urea functional group is essential
- Hydrogen bonding established as the activation mode
- Weaker product binding enables turnover

DFT and NMR Studies:

\[
\begin{align*}
\text{MeNH}_2\text{NMe} & \quad \text{MeNH}_2\text{NMe} \\
\text{MeNH} & \quad \text{MeNH} \\
X = \text{O} & \quad -8.5 \text{ kcal/mol} \\
X = \text{S} & \quad -10 \text{ kcal/mol}
\end{align*}
\]

\[
\begin{align*}
\text{MeNH}_2\text{NMe} & \quad \text{MeNH}_2\text{NMe} \\
\text{MeNH} & \quad \text{MeNH} \\
\text{MeNH} & \quad \text{MeNH} \\
\text{MeNH} & \quad \text{MeNH} \\
\text{MeCN} & \quad \text{MeCN} \\
\text{MeCN} & \quad \text{MeCN} \\
-5.0 \text{ kcal/mol} & \quad -6.3 \text{ kcal/mol}
\end{align*}
\]

Urea Stereochemical Model

With a better understanding of how these catalysts work new reaction methods can be developed

Strecker reaction with aldimine or ketoimine

\[
\begin{align*}
\text{HCN} & \quad \overset{1 \text{ mol} \% \text{ cat}}{\longrightarrow} & \text{t-Bu} \quad \overset{\text{toluene, } -78^\circ\text{C}}{\longrightarrow} & \text{F}_3\text{C} \quad \overset{\text{TFA}}{\longrightarrow} & \text{t-Bu} \\
\text{N} & \quad \text{Ph} & \quad \text{CN} & & \\
\end{align*}
\]

\( R = H \) 99\% ee
\( R = \text{Me} \) 86\% ee

Urea Catalyzed Reactions

Enantioselective Mannich Reaction

\[
\begin{align*}
\text{Boc} & \quad \text{OTBS} \\
\text{H} & \quad \text{i-Pr}
\end{align*}
\]

5 mol % cat
–40 °C
toluene, 48 h

90% conv, 91% ee

Urea Catalyzed Reactions

- **Enantioselective Mannich Reaction**

  ![Mannich Reaction Scheme](image1)

  Boc\(\text{NH}^+\)Ph + OTBS + 5 mol % cat \(-40 ^\circ C\) in toluene, 48 h → i-PrO\(\text{CO}^+\)\(\text{NH}\)Boc

  90% conv, 91% ee


- **Enantioselective Acyl Pictet–Spengler Reaction**

  ![Pictet–Spengler Reaction Scheme](image2)

  ![Pictet–Spengler Reaction Scheme](image3)

  10 mol % cat \(\text{Ac-Cl}\) in lutidine, \(-78 ^\circ C\) → 81% conv, 93% ee

**Urea Catalyzed Reactions**

**Enantioselective Aza-Henry Reaction**

![Chemical reaction diagram]

10 mol % cat
4 °C
toluene, i-Pr$_2$NEt
4 Å MS

>95% conv, 91% ee
15:1 syn

Urea Catalyzed Reactions

■ Enantioselective Aza-Henry Reaction

\[
\text{Boc}_2N + \text{EtNO}_2 \rightarrow \text{BocNH}_2\text{NO}_2
\]

10 mol % cat
4 °C
toluene, i-Pr\textsubscript{2}NEt
4 Å MS

>95% conv, 91% ee
15:1 syn


■ Enantioselective Hydrophosphorylation

\[
\text{Ar} = 2\text{-nitrophenyl}
\]

10 mol % cat
4 °C
Et\textsubscript{2}O

87% yield, 98% ee

**Bifunctional Urea Catalysts**

- **Enantioselective Michael Addition**

  ![Chemical Reaction](image)

  \[ \text{EtO}_2\text{C} \rightarrow \text{OEt} \quad \text{Ph} \rightarrow \text{NO}_2 \quad 10 \text{ mol}\% \text{ cat} \]

  Toluene, 23 °C

- **Both thiourea and tertiary amine are needed**

  ![Structural Formulas](image)

  - AcHN\(\text{NMMe}_2\)
  - 14%, 35% ee
  - 10 mol % NEt\(3\)
  - 57%, 0% ee
  - 86%, 93% ee

Bifunctional Urea Catalysts

- Enantioselective Michael Addition

![Chemical reaction](image)

- Both thiourea and tertiary amine are needed

![Chemical structures](image)

Urea Catalyzed Double Michael Cascade

- Enantioselective Double Michael Addition

\[
\text{Me} = \text{Ph} \rightarrow \text{Ph} = \text{Me}
\]

10 mol % cat

\text{toluene, } -20 ^\circ \text{C}

87% yield

>99% de

92% ee

\text{catalyst} =

Rawal's Discovery of H-Bonding Catalyzed Diels–Alder


- Observed that the hetero Diels–Alder reaction is accelerated in alcohol solvent
Rawal's Discovery of H-Bonding Catalyzed Diels–Alder


- Observed that the hetero Diels–Alder reaction is accelerated in alcohol solvent
- This observation was turned into an asymmetric reaction using a chiral H-donor catalyst

Mechanism of Rawal's H-Bonding Diels–Alder Reaction

Is single or double point activation in operation?

Mechanism of Rawal's H-Bonding Diels–Alder Reaction

Is single or double point activation in operation?

Chiral Phosphoric Acids

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- Long used for chiral resolutions

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- Long used for chiral resolutions
- Used as a ligand for Lewis acid catalysis

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- Long used for chiral resolutions
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- 2004 Terada and Akiyama use as Brønsted acid catalyst

**Chiral Phosphoric Acids**

- Long used for chiral resolutions
- Used as a ligand for Lewis acid catalysis
- 2004 Terada and Akiyama use as Brønsted acid catalyst
- Size of R group very important for enantioselectivity

![Chemical Structure of Chiral Phosphoric Acids]

\[
\text{R = } \begin{cases} 
H & 92\% \text{ yield} \quad 12\% \text{ ee} \\
\text{Ph} & 95\% \text{ yield} \quad 56\% \text{ ee} \\
\text{N-Ph} & 88\% \text{ yield} \quad 90\% \text{ ee} \\
\text{N-N} & 99\% \text{ yield} \quad 95\% \text{ ee}
\end{cases}
\]

New Reactivity – Imine Amination

Boc-imine $\rightarrow$ tosyl-amine

No known reaction
metal or organocatalytic

enantioenriched aminal
(differentially protected)

New Reactivity – Imine Amination

\[
\begin{align*}
\text{Boc-imine} & \quad \text{H}_2\text{N-Ts} & \quad \rightarrow & \quad \text{enantioenriched aminal} \\
\text{tosyl-amine} & & & \text{(differentially protected)}
\end{align*}
\]

\[
\begin{align*}
\text{No known reaction} & \quad \text{metal or} \\
& \quad \text{organocatalytic}
\end{align*}
\]

\[
\text{(S)-VAPOL}
\]

5 mol % cat
\[
\text{Et}_2\text{O, 1 h, 21 °C}
\]
86% yield
93% ee

Consideration of priviledged architecture and stereogenicity

Friedel–Crafts

\[
\text{Me}_2\text{N} \quad \text{O}\text{Me} \\
\text{CO}_2\text{Et}
\]

Transfer Hydrogenation

\[
\text{Me}
\]

\[
\text{H} \quad \text{Me}
\]

- Perhaps the most important stereogenicity for biomedical applications

biomedically relevant center

\[
\text{NH}_2
\]

Amine conjugate addition

\[
93–97\% \text{ ee}
\]
There are vast technologies for the construction of amine stereogenicity

- Favourite: Ellman imine, most general–dogma breaking

\[ \text{tert-butanesulfinamide} \quad \text{DIBAL} \quad 20:1 \text{ dr, 86% yield} \]
There are vast technologies for the construction of amine stereogenicity!

- Favourite: Ellman imine, most general–dogma breaking

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{S} & \quad \text{N} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{SR} & \quad & \quad & \\
\text{Me} & \quad \text{Me} & \quad & \quad & \quad & \\
\text{Me} & \quad \text{Me} & \quad & \quad & \quad & \\
\end{align*}
\]

\[
\text{DIBAL} \quad \rightarrow \\
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{S} & \quad \text{N} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{SR} & \quad & \quad & \\
\text{Me} & \quad \text{Me} & \quad & \quad & \quad & \\
\text{Me} & \quad \text{Me} & \quad & \quad & \quad & \\
\end{align*}
\]

*tert*-butanesulfinamide

20:1 dr, 86% yield

- Reductive Amination: Simultaneous fragment coupling and C–N bond formation

\[
\begin{align*}
\text{F} & \quad \text{Me} & \quad \text{O} & \quad \text{Me} \\
\text{NH}_2 & \quad \text{N} & \quad \text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{Me} & \quad \text{NH} & \quad \text{Me} & \quad \text{Me} & \quad \text{O} \\
\end{align*}
\]

fragment 1        fragment 2        no enantioselective catalytic reductive amination-coupling
**Organic Catalyzed Reductions in Biological Systems**

- NADH: Nature's Reduction (Hydrogenation) Reagent (Coenzyme)

![Diagram showing organic catalyzed reductions in biological systems](image)

Selective reduction of pyruvate imines to create amino acids

Could this organocatalytic sequence be utilized in the reduction of carbon–carbon double bonds?
Organic Catalyzed Reductions in Laboratory Systems

- Hantzsch ester as a useful surrogate for NADH reductions in the lab

\[
\begin{align*}
\text{acetophenone} & \quad \text{NADH analog} \\
\text{NH}_2R & \quad \text{phenylethyl amine}
\end{align*}
\]

H-bonded or Bronsted acid
organic iminium reduction

Can we translate a biochemical concept to a laboratory reaction
Can we develop a useful transformation on the basis of established Bronsted acid catalysts
Organic Catalyzed Reductions in Laboratory Systems

- Hantzsch ester as a useful surrogate for NADH reductions in the lab

\[
\begin{align*}
\text{acetophenone} & \quad \text{NADH analog} & \quad \text{phenylethyl amine} \\
& \quad \text{NH}_2R \\
& \quad \text{catalyst}
\end{align*}
\]

H-bonded or Bronsted acid
organic iminium reduction

catalyst

Can we translate a biochemical concept to a laboratory reaction
Can we develop a useful transformation on the basis of established Bronsted acid catalysts
Organocatalysis and the advent of Bronsted Acid/H-bonded catalysis

Pioneers

- Jacobsen
- Rawal
- Yamamoto
- Schaus
- Akiyama, Terada
Organocatalysis and the advent of Bronsted Acid/H-bonded catalysis

Organocatalysis and the advent of Bronsted Acid/H-bonded catalysis

acetophenone

NH₂PMP

80°C, toluene
20 mol% catalyst

Pioneers

Jacobsen
Rawal

Yamamato

Schaus

Akiyama, Terada
Organocatalysis and the advent of Bronsted Acid/H-bonded catalysis

acetophenone

\[ \text{NH}_2\text{PMP} \]
\[ 80^\circ\text{C}, \text{toluene} \]
\[ 20 \text{ mol\% catalyst} \]

Pioneers

Jacobsen
No reaction

Rawal
No reaction

Schaus
No reaction

Akiyama, Terada
43\% yield
7\% ee
Attempts to develop a Bronsted Acid Catalyst for Reductive Amination

acetophenone

NH₂PMP

80°C, toluene
20 mol% catalyst

7% ee
Attempts to develop a Bronsted Acid Catalyst for Reductive Amination

acetophenone

\[
\text{NH}_2\text{PMP} \quad 80^\circ\text{C, toluene} \quad 20 \text{ mol\% catalyst} \quad \text{7\% ee}
\]

\[
\begin{array}{c}
\text{H} & \text{H} \\
\text{MeO}_2\text{C} & \text{Me} \\
\text{Me} & \text{CO}_2\text{Me}
\end{array}
\quad \rightarrow 
\begin{array}{c}
\text{H} \\
\text{Me}
\end{array}
\]
Attempts to develop a Bronsted Acid Catalyst for Reductive Amination

acetophenone

\[
\text{MeO}_2\text{C} \quad \text{H} \quad \text{H} \quad \text{CO}_2\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{N}\quad \text{Me} \\
\text{O} 
\]

\[
\text{NH}_2\text{PMP} \quad 80^\circ\text{C}, \text{ toluene} \quad 20 \text{ mol}\% \text{ catalyst} \\
\text{MeO} 
\]

\[
\text{NHPMP} 
\]

\[
\text{NHPMP} 
\]

\[
\text{Ph(NO}_2)_2 
\]

\[
\text{Ph(CF}_3)_2 
\]

\[
\text{2-Nap} 
\]

\[
\text{H} 
\]

\[
\text{43} 
\]

\[
\text{7} 
\]

\[
\text{Ph(NO}_2)_2 
\]

\[
\text{45} 
\]

\[
\text{16} 
\]

\[
\text{Ph(CF}_3)_2 
\]

\[
\text{39} 
\]

\[
\text{65} 
\]

\[
\text{2-Nap} 
\]

\[
\text{56} 
\]

\[
\text{40} 
\]
Attempts to develop a Bronsted Acid Catalyst for Reductive Amination

\[ \text{Acetophenone} \rightarrow \begin{array}{c}
\text{NH}_2\text{PMP} \\
80^\circ\text{C}, \text{toluene} \\
20 \text{ mol}\% \text{ catalyst}
\end{array} \rightarrow \text{Product} \]

7% ee

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>Ph(NO_2)_2</td>
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</tr>
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<td>65</td>
</tr>
<tr>
<td>2-Nap</td>
<td>56</td>
<td>40</td>
</tr>
<tr>
<td>Ph_3Si</td>
<td>90</td>
<td>85</td>
</tr>
</tbody>
</table>
The impact of additives and temperature on the reductive amination

80°C, toluene MeO MeNHPMP NH₂PMP NH₂PMP NH₂PMP

What is the scope of this transformation with respect to ketones?

What is the impact of the water biproduct?
The impact of additives and temperature on the reductive amination

80°C, toluene
20 mol% cat

What is the impact of the water biproduct

<table>
<thead>
<tr>
<th>additive</th>
<th>Time</th>
<th>Yield</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>--</td>
<td>28 h</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>H₂O (1eq)</td>
<td>72 h</td>
<td>35</td>
<td>77</td>
</tr>
<tr>
<td>H₂O (2eq)</td>
<td>72 h</td>
<td>&lt;10</td>
<td>72</td>
</tr>
<tr>
<td>MgSO₄</td>
<td>20 h</td>
<td>79</td>
<td>83</td>
</tr>
<tr>
<td>Na₂SO₄</td>
<td>36 h</td>
<td>83</td>
<td>85</td>
</tr>
<tr>
<td>5A mol sieves</td>
<td>6 h</td>
<td>85</td>
<td>90</td>
</tr>
</tbody>
</table>

What is the scope of this transformation with respect to ketones?
The scope of the reductive amination with respect to aryl ketones

40°C, toluene
10 mol% cat
5A mol sieves

Scope of the ketone component

(o) 83% ee
(m) 95% ee
(p) 94% ee
60-85% yield

90% ee
77% yield

85% ee
75% yield

95% ee
75% yield

95% ee
71% yield

96% ee
73% yield

Are there other systems that are successful in this transformation?
The scope of the reductive amination

\[
\begin{align*}
\text{R} & \quad \text{MeO}_2C\text{H} - \text{NH}_2P\text{MP} - \text{HCO}_2\text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

40°C, toluene
10 mol% cat
5A mol sieves

Scope of the ketone-ketimine component

97% ee
82% yield
The scope of the reductive amination

40°C, toluene
10 mol% cat
5A mol sieves

Scope of the ketone-ketimine component

97% ee
82% yield

79% ee
27% yield
The scope of the reductive amination

40°C, toluene
10 mol% cat
5A mol sieves

Scope of the ketone-ketimine component

97% ee
82% yield

79% ee
27% yield

Stereochemical models are in accord with the observed reactivity
MM3-Calculation提供良好的对不对称环境预测
MM3-Calculations Provide Good Prediction of Asymmetric Environment

![Chemical Reaction Diagram]

**MM3-structure**  **X-ray structure**  Crystal grown in toluene at –20 °C in glove box
The scope of the reductive amination

40°C, toluene
10 mol% cat
5A mol sieves

Scope of the ketone-ketimine component

97% ee
82% yield

79% ee
27% yield

Stereochemical models are in accord with the observed reactivity
The scope of the reductive amination

40°C, toluene
10 mol% cat
5A mol sieves

Scope of the ketone-ketimine component

97% ee
82% yield

79% ee
27% yield

Stereochemical models are in accord with the observed reactivity
The scope of the reductive amination

\[ \text{R} \quad \text{MeO}_2 \text{C} \quad \text{Me} \quad \text{NH} \quad \text{NH}_2 \text{PMP} \quad \text{NH} \quad \text{R} \]

40°C, toluene
10 mol% cat
5A mol sieves

catalyst

Scope of the ketone-ketimine component

- Si-face exposed
- Si-face blocked

Stereochemical models are in accord with the observed reactivity
The scope of the reductive amination

40°C, toluene, 10 mol% cat, 5A mol sieves
to methyl versus ethyl ketones

Scope of the ketone-ketimine component

- 93% ee, 87% yield for ethyl ketones
- ND% ee, <15% yield for methyl ketones

Stereochemical models are in accord with the observed reactivity
The scope of the reductive amination

40°C, toluene
10 mol% cat
5A mol sieves

Scope of the ketone-ketimine component

Stereochemical models are in accord with the observed reactivity
The scope of the reductive amination

40°C, toluene
10 mol% cat
5A mol sieves

Scope of the ketone-ketimine component

Me vs Et on the same substrate

Stereochemical models are in accord with the observed reactivity
The scope of the reductive amination: alkyl ketones

NH₂PMP
40°C, toluene
10 mol% cat
5A mol sieves

Scope of the alkyl ketone component

91% ee
71% yield
The scope of the reductive amination: alkyl ketones

40°C, toluene
10 mol% cat
5A mol sieves

Scope of the alkyl ketone component

91% ee 71% yield
86% ee 49% yield
86% ee 50% yield
91% ee 72% yield
94% ee 75% yield
92% ee 68% yield

This reductive amination process appears to be general for methyl ketones
The scope of the reductive amination: aryl amines

\[
\text{RNH}_2 \rightarrow \text{RNHR}
\]

40°C, toluene
10 mol% cat
5A mol sieves

Scope of the amine component

- **93% ee, 73% yield**
- **95% ee, 55% yield**
- **90% ee, 92% yield**
- **93% ee, 90% yield**
- **91% ee, 70% yield**
- **90% ee, 75% yield**

Activation Modes Are Enabled by Privileged Catalyst Architectures

Catalysis Platform / Concept

Activation Modes Are Enabled by Priviledged Catalyst Architectures

Catalysis Platform / Concept

Activation Modes

Activation Modes Are Enabled by Privileged Catalyst Architectures

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Catalysis Platform / Concept

Chemical Methodology

Activation Modes

Catalyst Design

H-Bonding, Brønsted Acids

Carbene, Phase Transfer

Privileged Architecture

Chiral Pool

Novel Reactivity

Activation Modes Are Enabled by Priviledged Catalyst Architectures

Catalysis Platform / Concept

Chemical Methodology

Activation Modes

Catalyst Design

- H-Bonding, Brønsted Acids
- Carbene, Phase Transfer

Priviledged Architecture

Chiral Pool

Novel Reactivity

Valuable New Bond Disconnections