Activation Modes Are Enabled by Priviledged Catalyst Achitectures

Activation Modes

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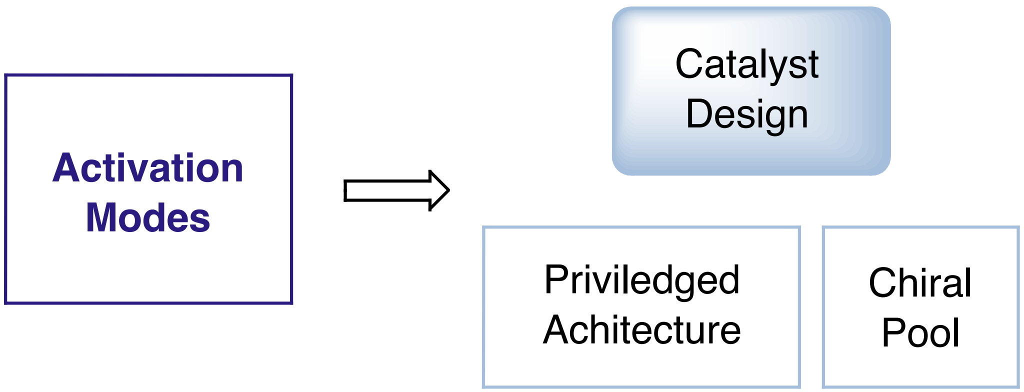

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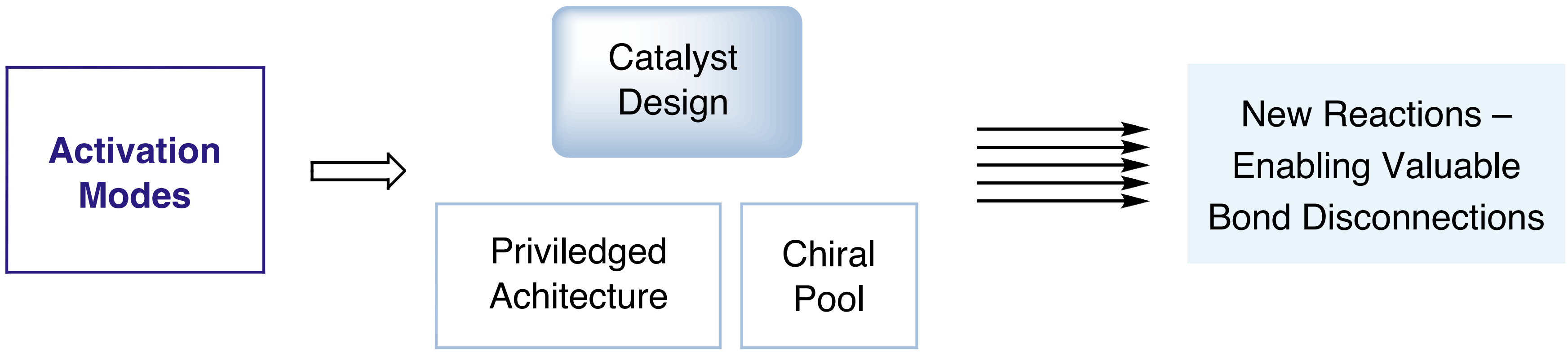
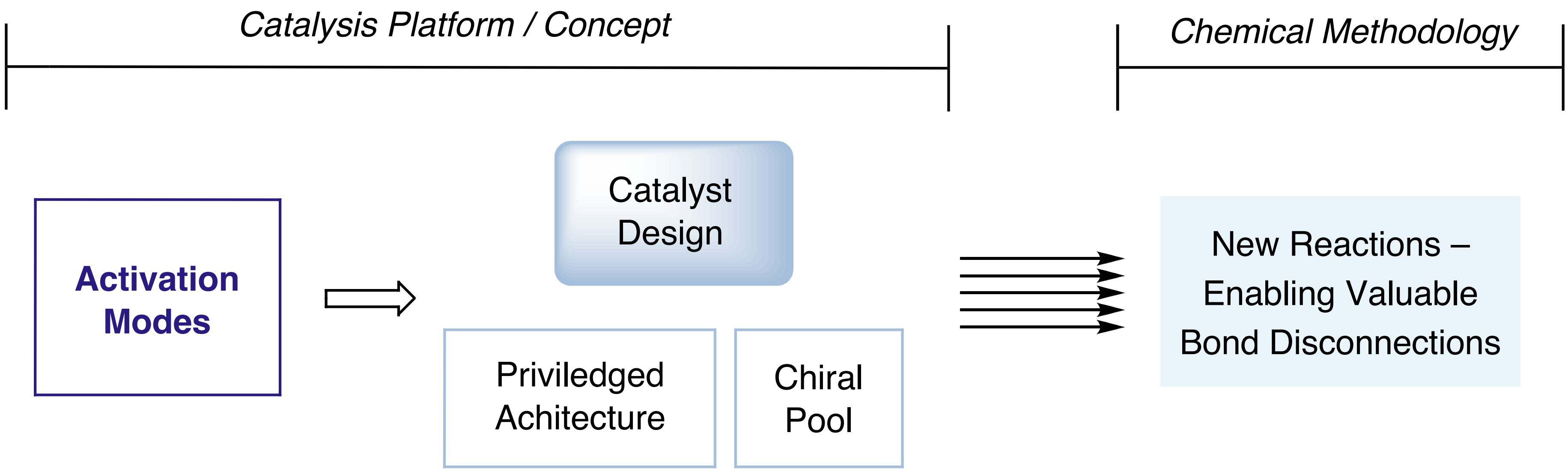


Activation Modes Are Enabled by Priviledged Catalyst Achitectures



Activation Modes Are Enabled by Priviledged Catalyst Achitectures

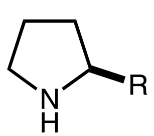
Catalysis Platform / Concept — *Chemical Methodology*

Activation Modes ⇒ Catalyst Design; Priviledged Achitecture; Chiral Pool → New Reactions – Enabling Valuable Bond Disconnections

Previous Lecture

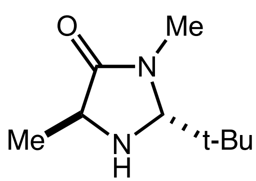
This Lecture – Broadened Activation Themes

■ Enamine



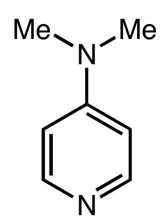
Proline-derived

■ Iminium

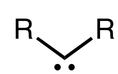


Imidazolidinone

■ Electrophile Activation

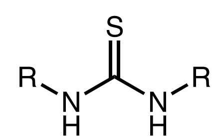


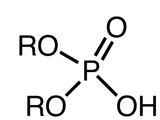
DMAP



Carbene

■ Nucleophile Activation

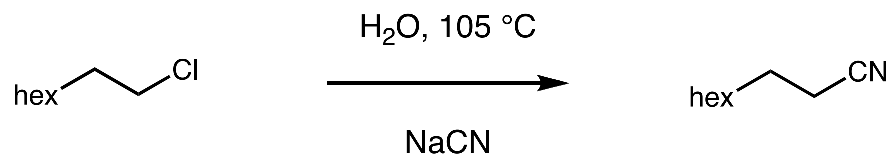




$\oplus$ NR_4

Acids and Phase Transfers

Phase Transfer Catalysis (PTC)



No Reaction

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

Starks, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 195.

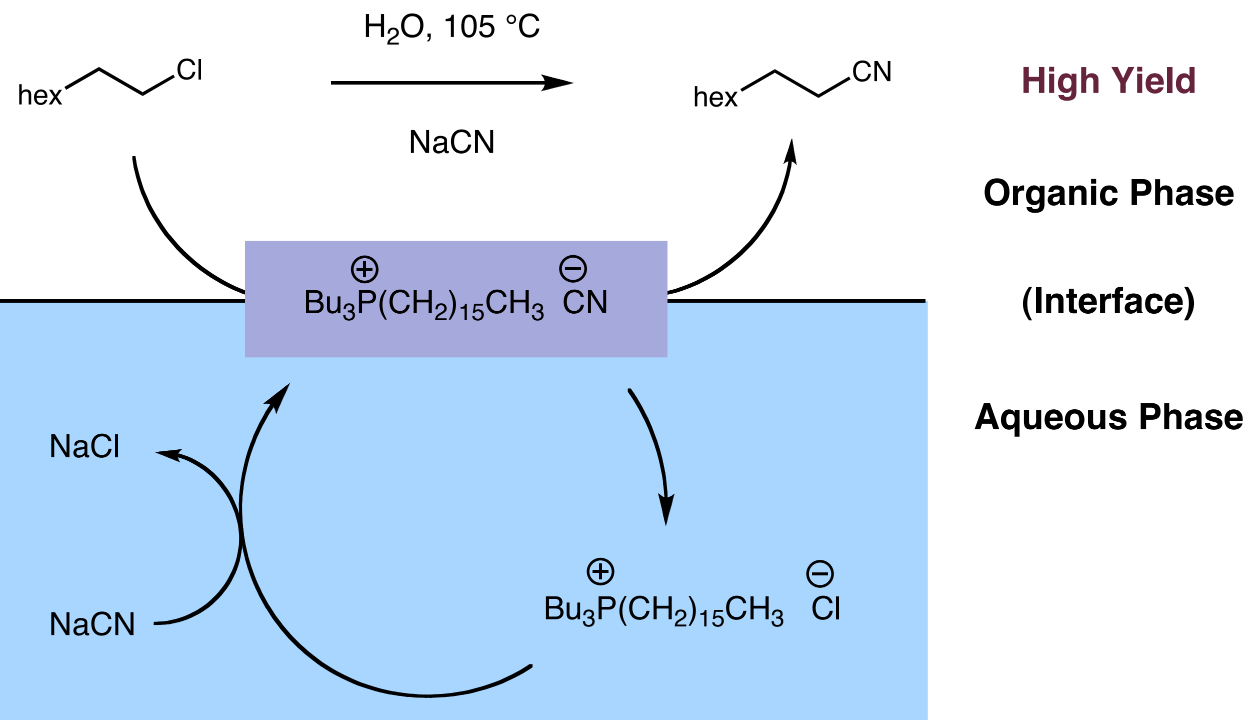
Phase-Transfer Catalysis. I. Heterogeneous Reactions Involving Anion Transfer by Quaternary Ammonium and Phosphonium Salts

Charles M. Starks

Contribution from the Petrochemical Research Division, Continental Oil Company, Ponca City, Oklahoma 74601.
Received February 12, 1970

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

Phase Transfer Catalysis (PTC)



"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 alkylations

Efficient Catalytic Asymmetric Alkylations. 1. Enantioselective Synthesis of (+)-Indacrinone via Chiral Phase-Transfer Catalysis

Ulf-H. Dolling,* Paul Davis, and Edward J. J. Grabowski

Merck Sharp & Dohme Research Laboratories
Merck & Co., Inc., Rahway, New Jersey 07065

Received September 26, 1983

We wish to report the first efficient, catalytic, enantioselective alkylation in the asymmetric synthesis of the new uricosuric (+)-indacrinone (**5**) (MK-0197)[4] via chiral phase-transfer catalysis. Methylation of 0.61 g of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone (**1**)[4a] with 0.7 g of CH_3Cl in toluene/50% aqueous NaOH (25 mL/5mL) using 0.11 g of *N*-(*p*-(trifluoromethyl)benzyl)cinchoninium bromide as phase-transfer catalyst at 20 °C for 18 h produced (*S*)-(+)-6,7-dichloro-5-methoxy-2-methyl-2-phenyl-1-indanone (**2**) in up to 92% ee in 95% yield.[5] Subsequent O-demethylation ($AlCl_3$, toluene, 45 °C), giving **3**, followed by O-alkylation with ethyl chloroacetate (K_2CO_3, NaI, toluene, reflux), giving **4**, hydrolysis (toluene, NaOH, reflux), acidification (HCl), and crystallization (CH_2Cl_2) afforded the S-(+)-enantiomer[4d] of **5** in 63% isolated yield (overall from **1**), identical in all respects with resolved material[4a,d] (Scheme I).

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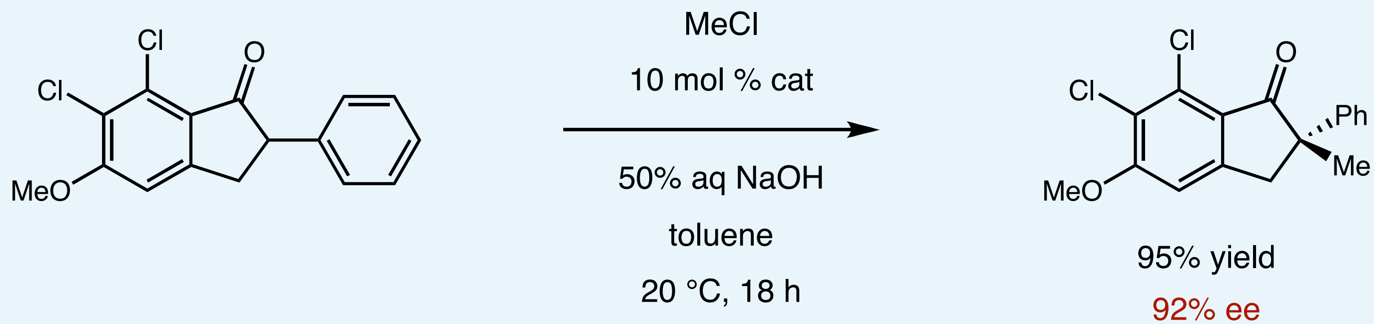

Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.

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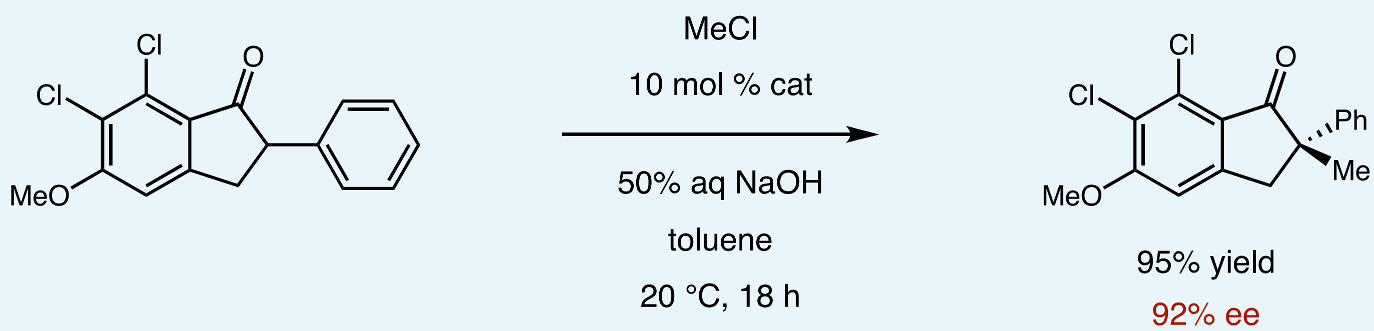

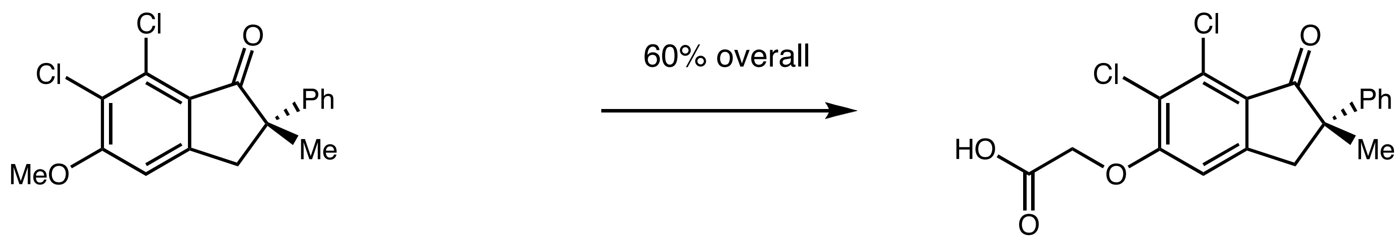

(+)-indacrinone

MK-0197

Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.

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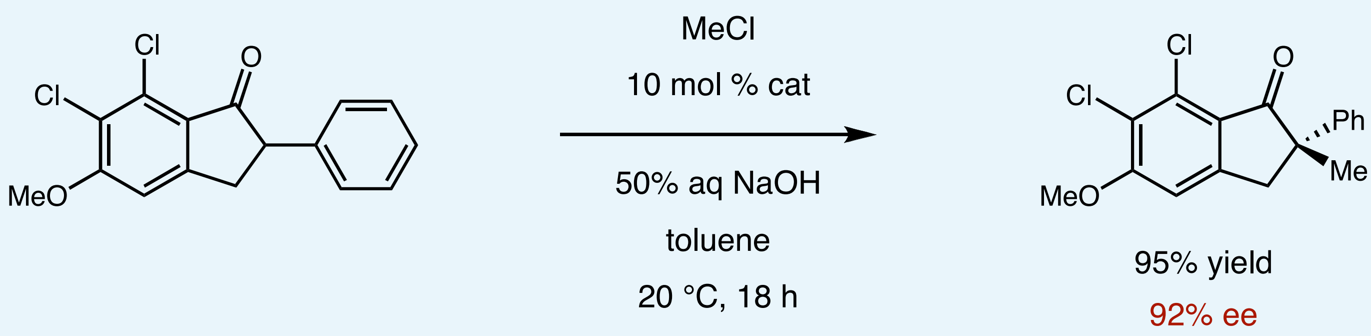
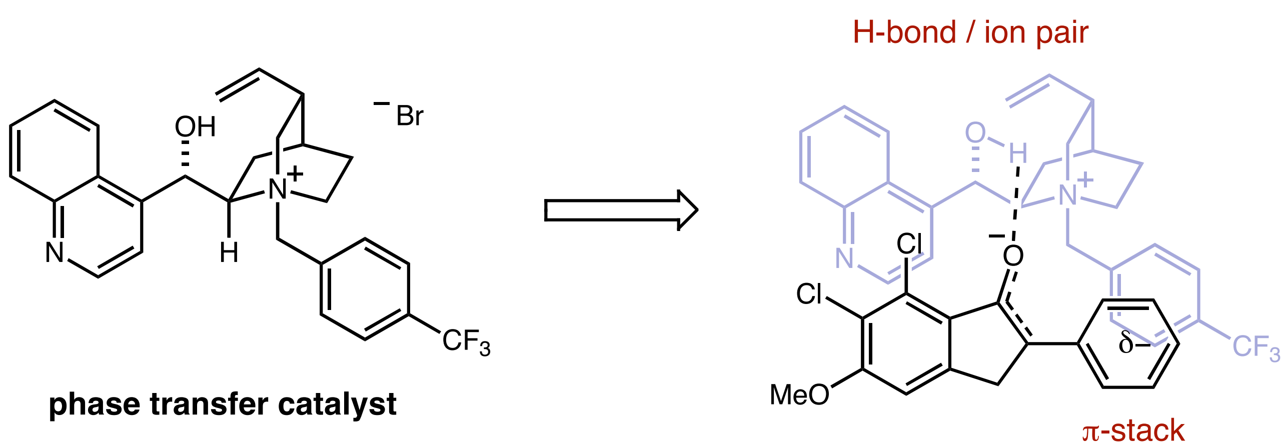




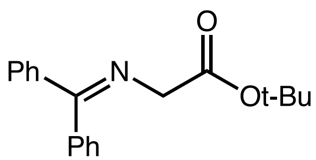
phase transfer catalyst

Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.

Asymmetric Phase Transfer Catalysis

■ The catalyst controls the orientation of the enolate alkylation

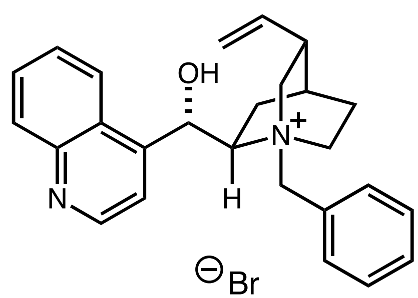
Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518.



Glycine Imine Ester

Organic

Aqueous



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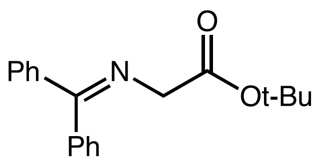

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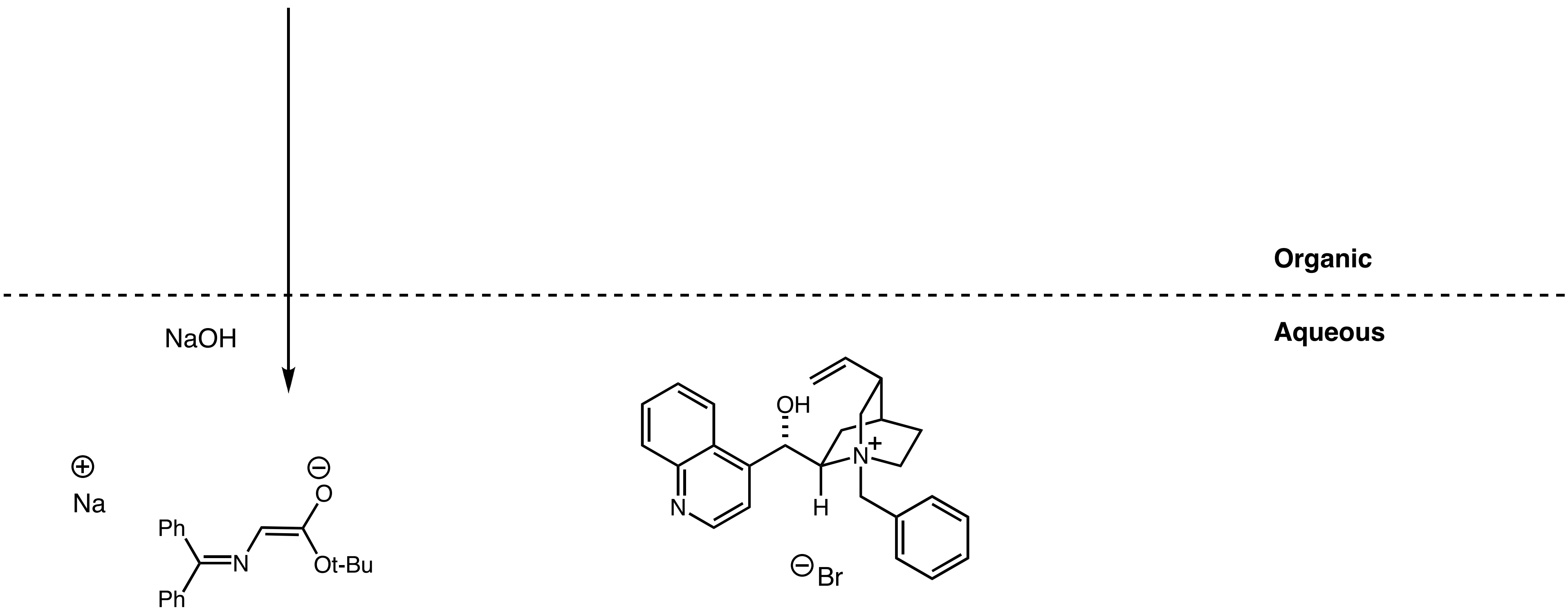

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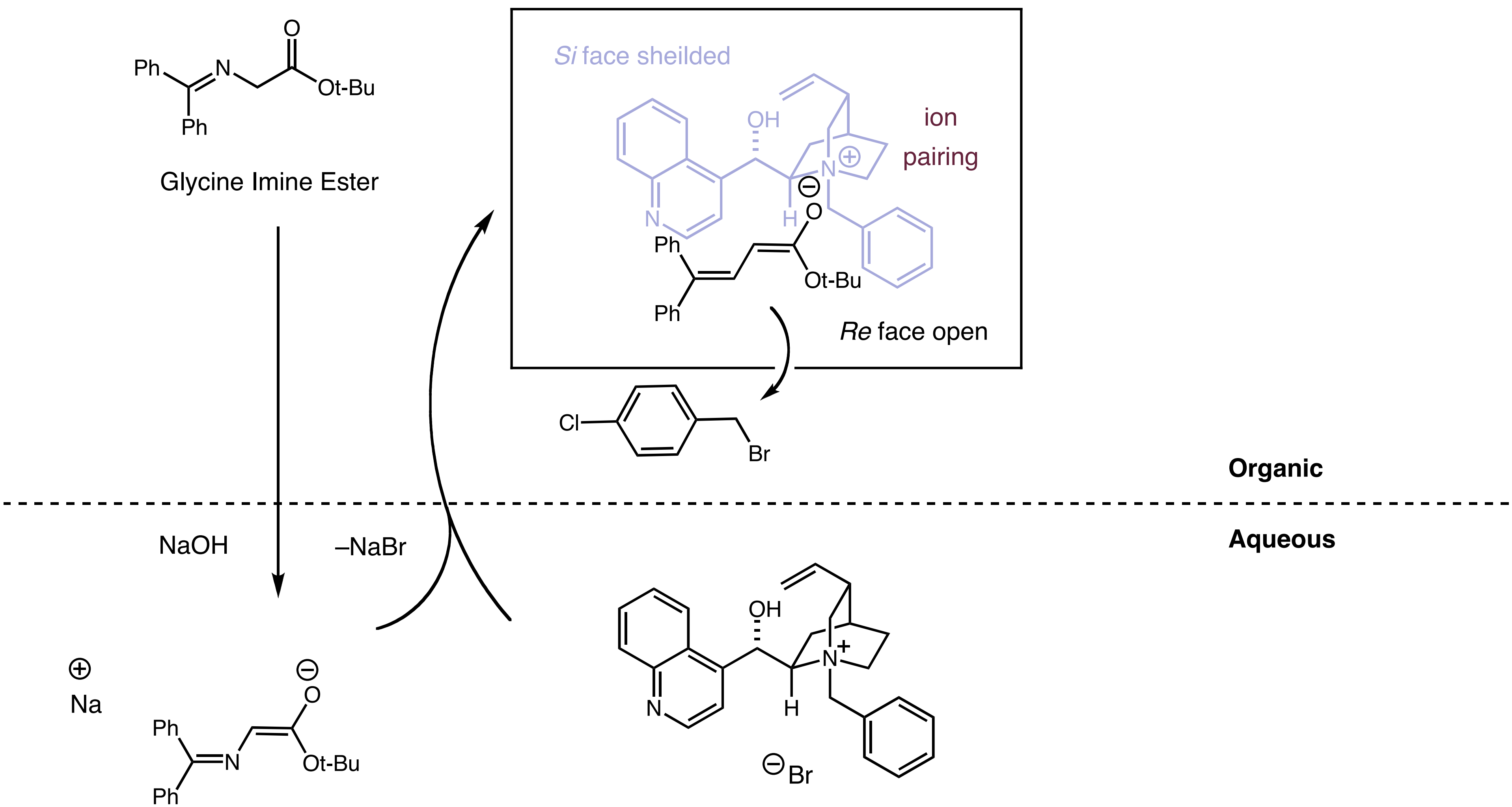

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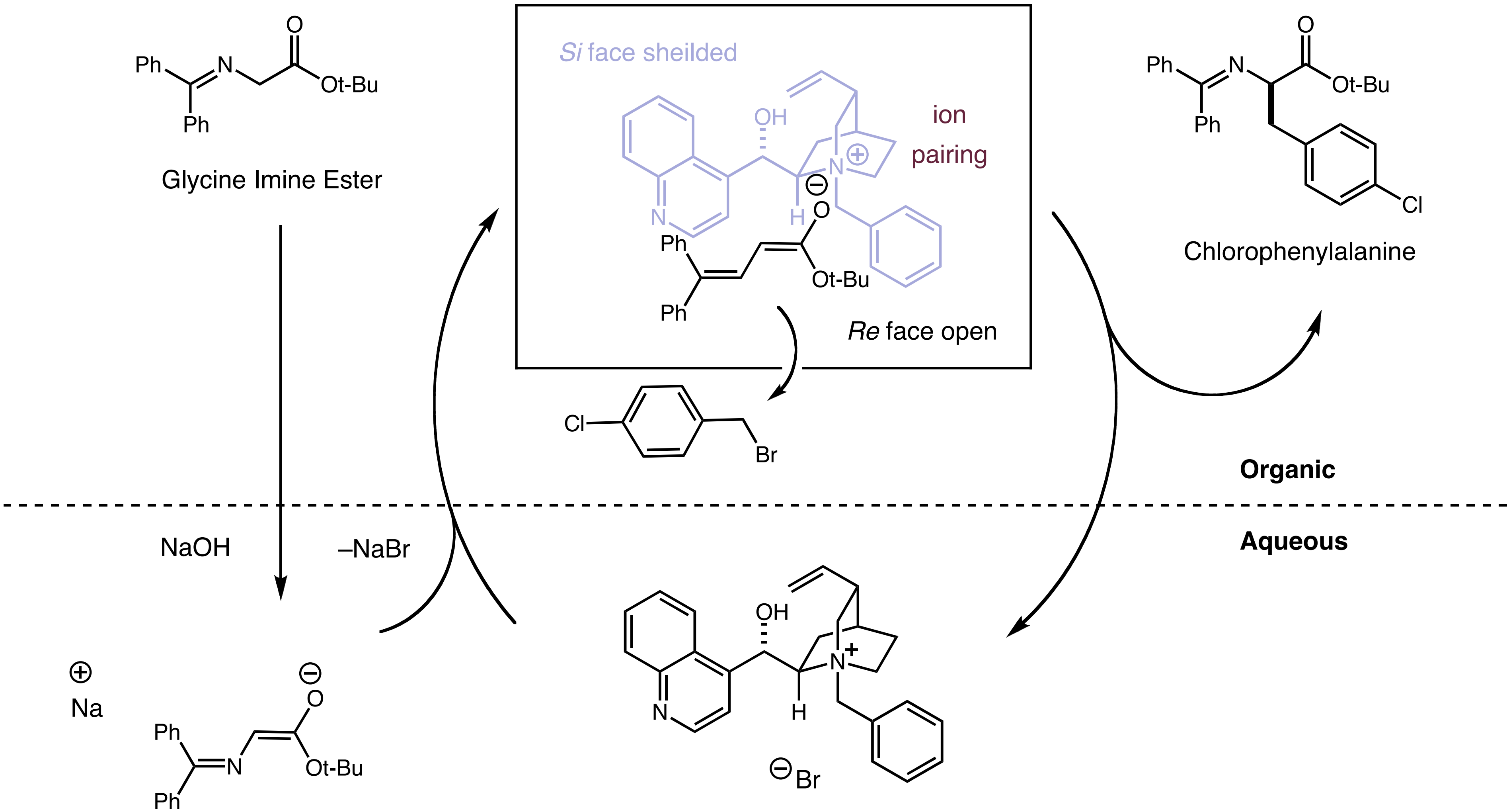

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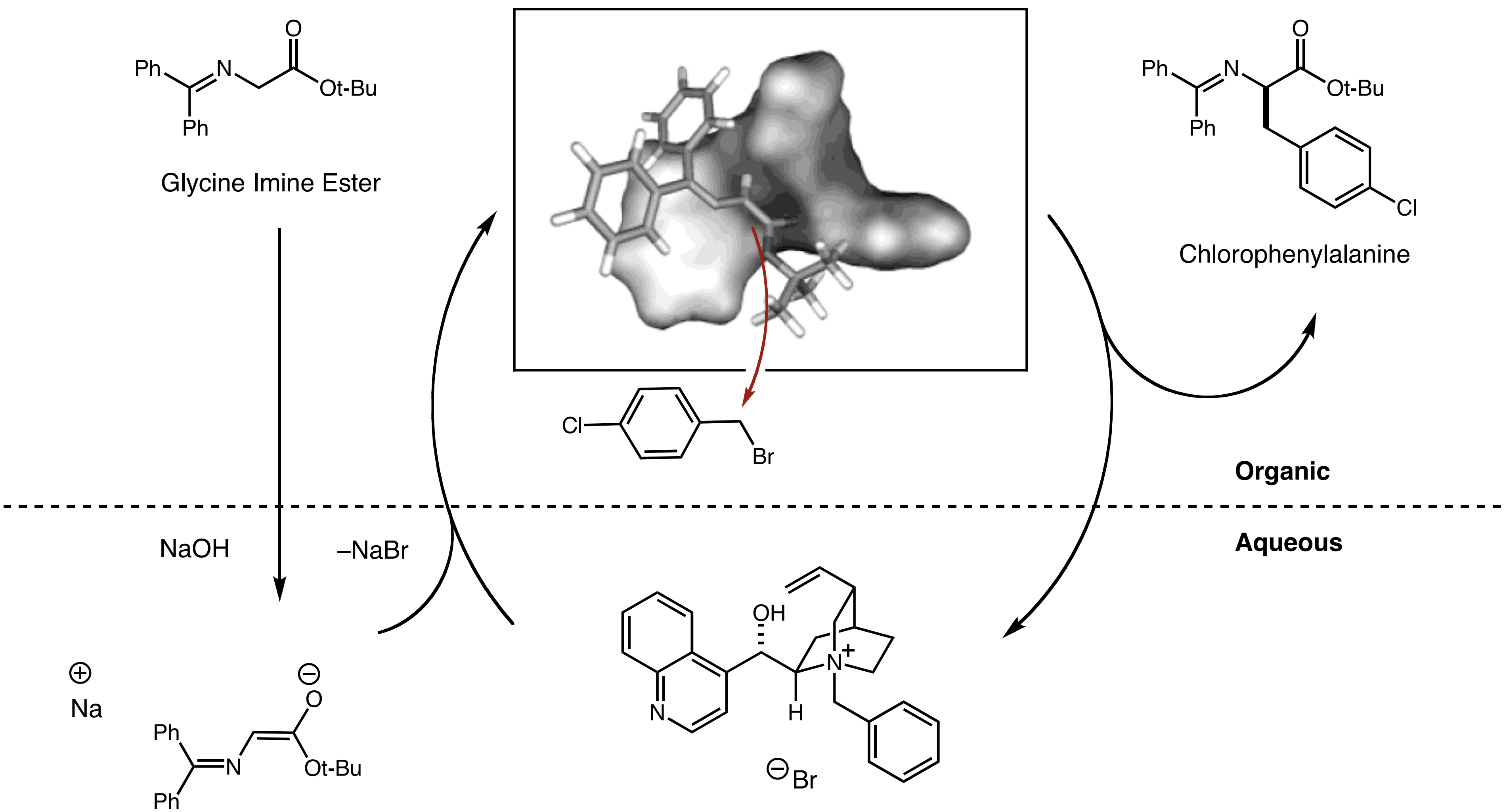
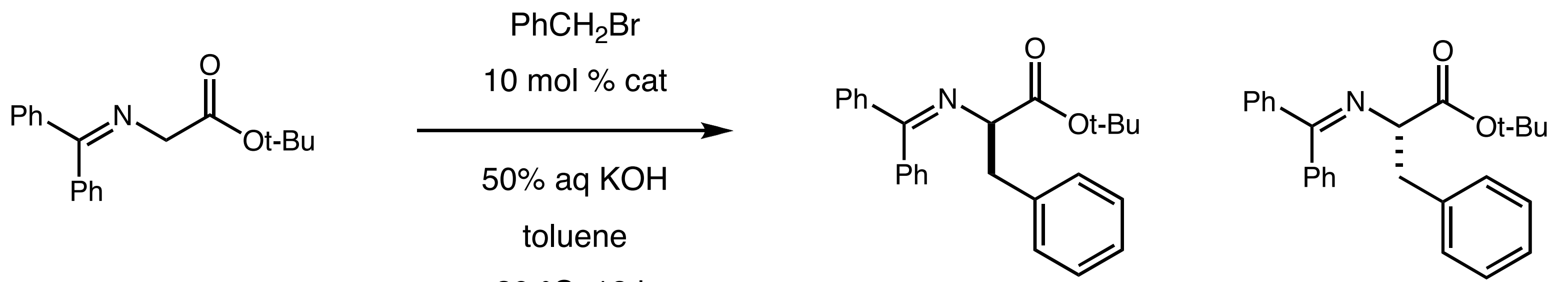


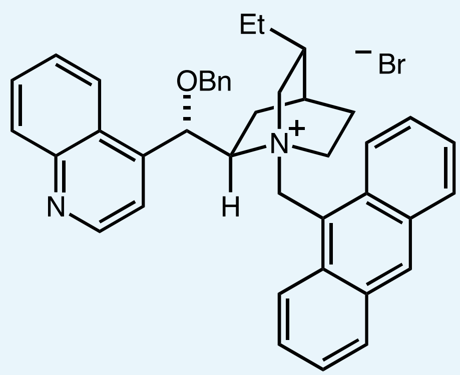
Switching Enantioselectivity Using Pseudoenantiomers

■ Catalyst diastereomers give rise to the opposite product configuration

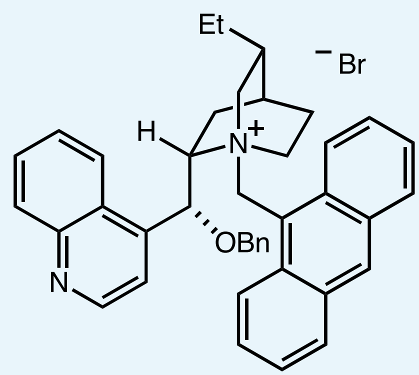


cat **A**
77% yield
86% ee

cat **B**
85% yield
94% ee



A From cinchonine

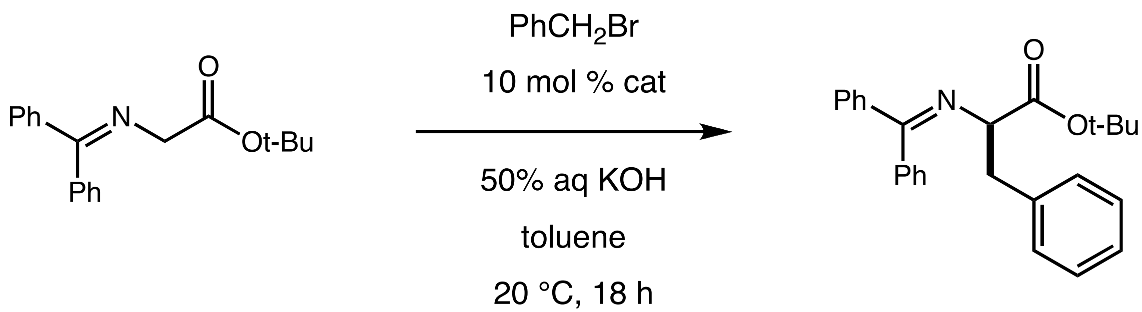


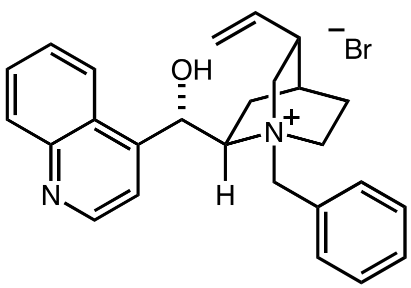
B From cinchonidine

Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518.

Advances in Catalyst Design

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





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

Shirakawa, S.; Marouka, K. *Catalytic Asymmetric Synthesis.* Hoboken: Wiley, 2010.

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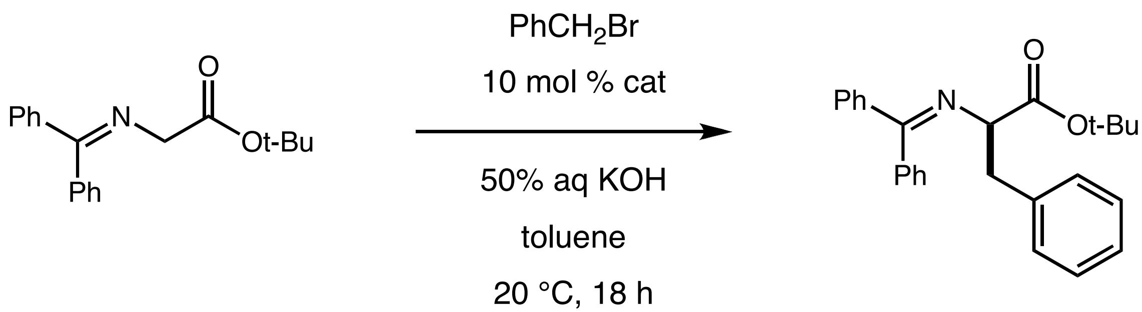

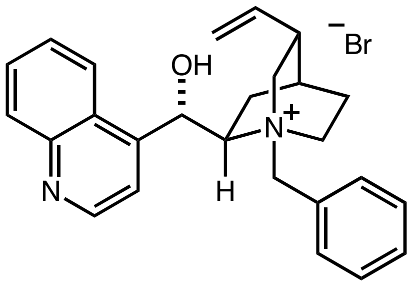

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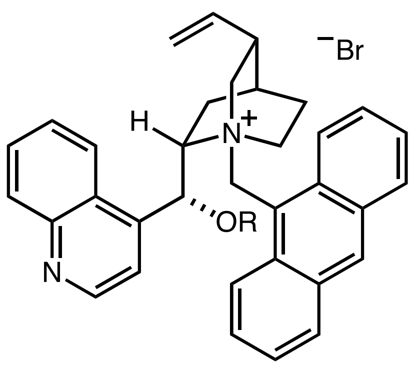

R = allyl
Lygo, Corey 1997
10 mol %
87% yield, 94% ee

Shirakawa, S.; Marouka, K. *Catalytic Asymmetric Synthesis.* Hoboken: Wiley, 2010.

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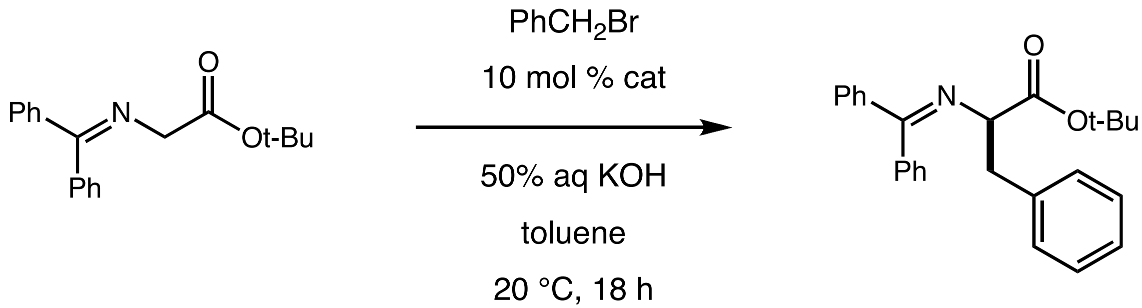

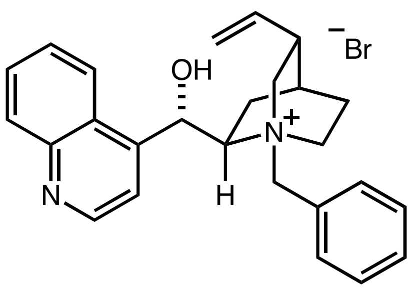

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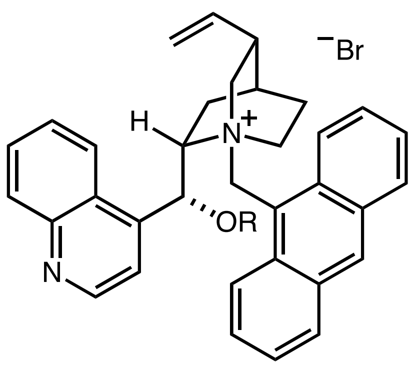

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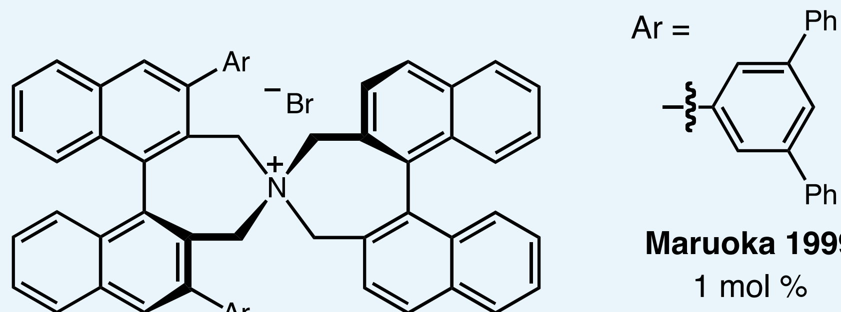

Maruoka 1999
1 mol %
91% yield, 98% ee

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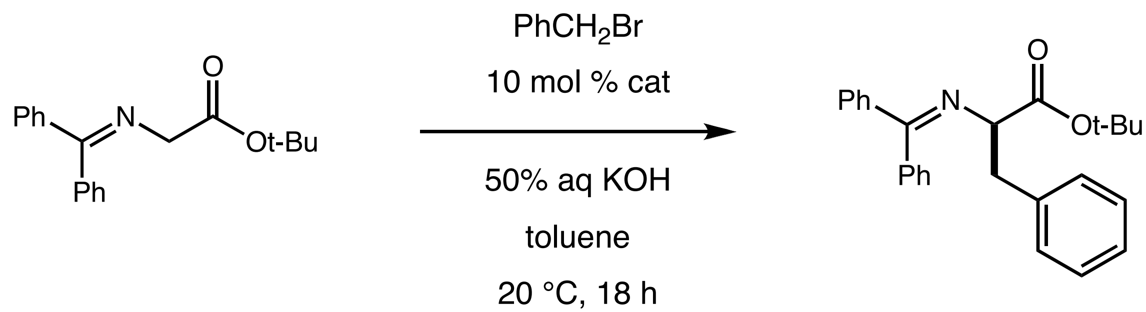

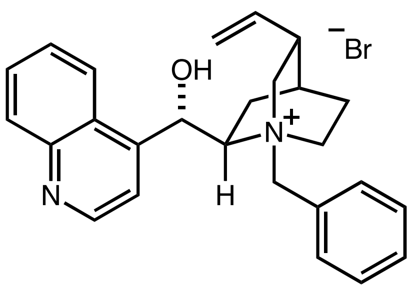

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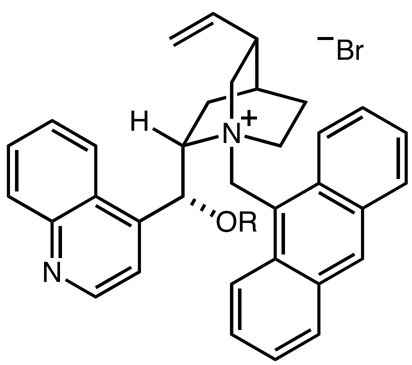

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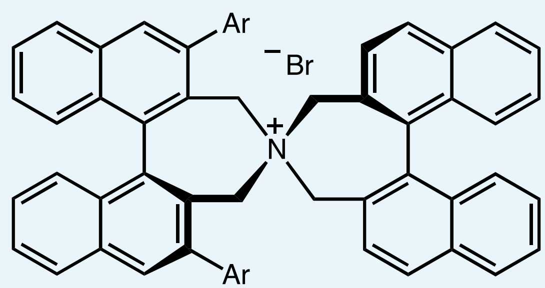
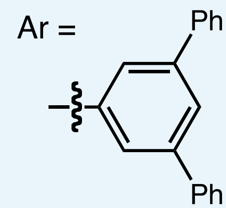
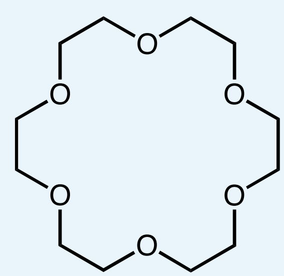




Maruoka 1999
1 mol %
91% yield, 98% ee

Cocatalyst:
18-crown-6

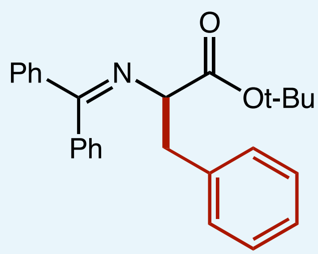


Maruoka 2005
0.05 mol %
0.05 mol % 18-crown-6
90% yield, 98% ee

Shirakawa, S.; Marouka, K. *Catalytic Asymmetric Synthesis.* Hoboken: Wiley, 2010.

The PTC Activation Mode Beyond Alkylation Reactions

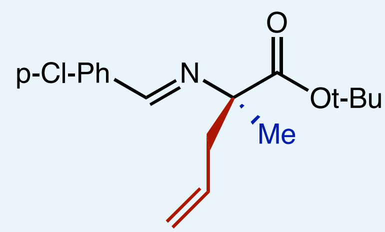
■ PTC activation of carbonyls has enabled the developement of many different asymmetric reactions



90%, 98% ee

glycine–alkylation

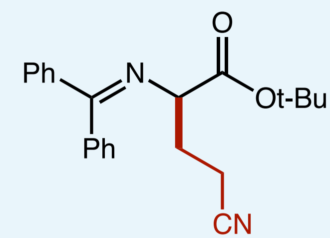
Angew. Chem. Int. Ed. **2005**, *44* , 625.



85%, 98% ee

glycine alkylation–allylation

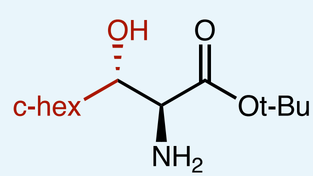
J. Am. Chem. Soc. **2000**, *122*, 5228.



85%, 91% ee

glycine–Michael

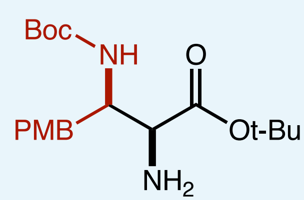
Org. Lett. **2000**, *2*, 1097.



83% 96:4 anti, 98% ee

glycine–aldol

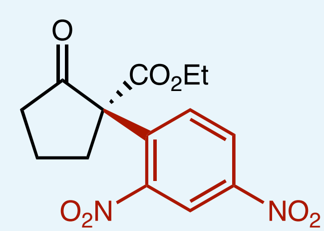
J. Am. Chem. Soc. **2004**, *126*, 9685.



95%, 9:1 syn 82% ee

glycine–Mannich

Angew. Chem. Int. Ed. **2005**, *44*, 4564.



78%, 85% ee

β-ketoester SN_{Ar}

J. Org. Chem. **2006**, *71*, 4980.

Recent review: Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.

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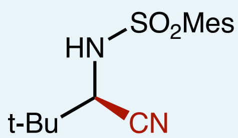
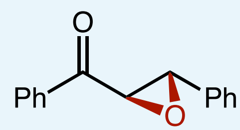


94%, 94% ee

Strecker

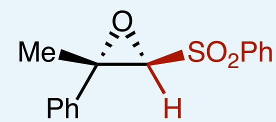
J. Am. Chem. Soc. **2006**, *128*, 2548.



99%, 96% ee

enone epoxidation

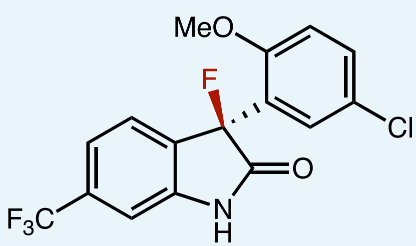
J. Am. Chem. Soc. **2004**, *126*, 6844.



70%, 81% ee

Darzens epoxidation

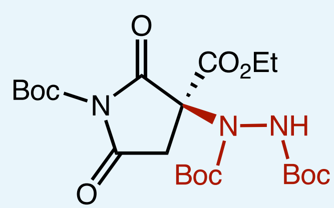
Tetrahedron **2002**, *58*, 1407.



94%, 84% ee

β-ketoester fluorination

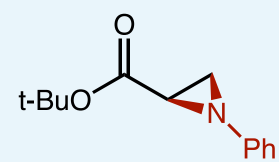
J. Org. Chem. **2003**, *68*, 2494.



99%, 92% ee

β-ketoester amination

Angew. Chem. Int. Ed. **2008**, *47*, 9466.



79%, 84% ee

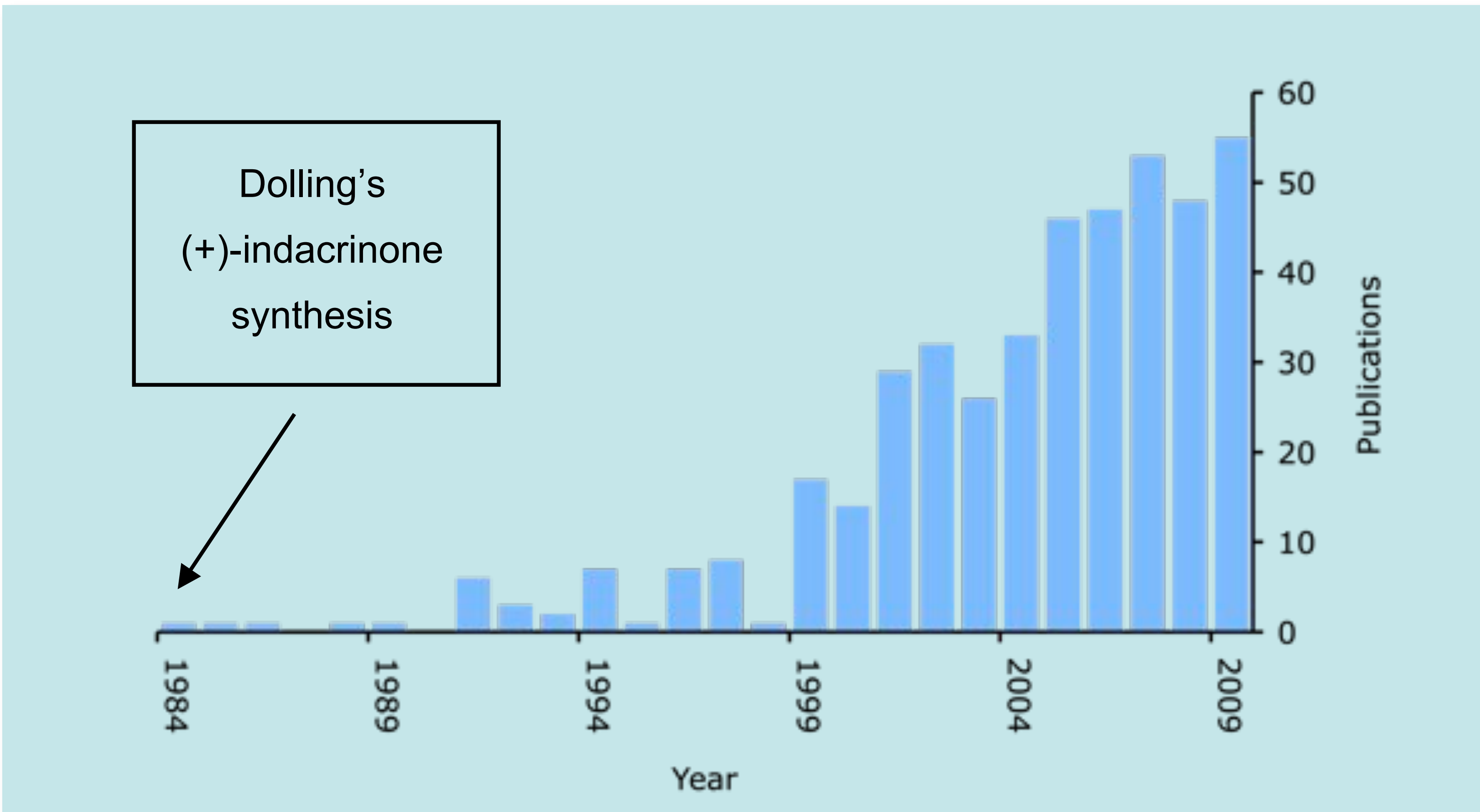
aziridation

Synthesis **2005**, 2022.

Recent review: Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.

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



Carbenes as Organocatalysts

- Carbenes were long suspected as catalytic intermediates

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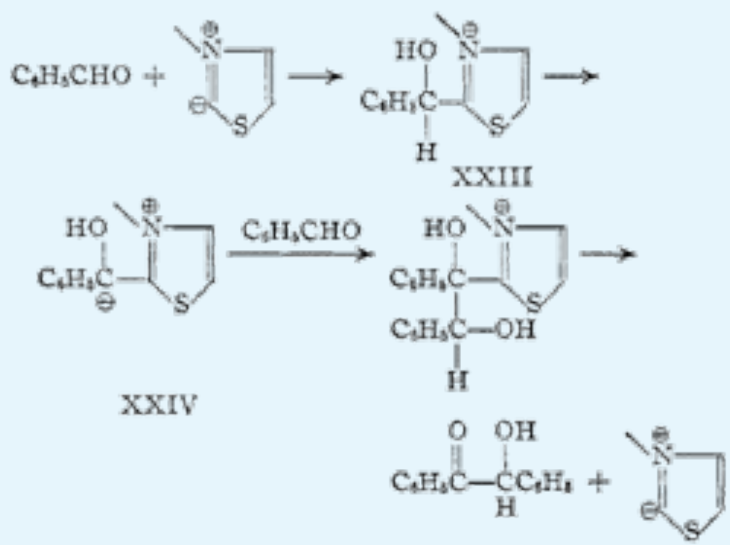
Breslow, R. *J. Am. Chem. Soc.* **1958**, *14*, 3719.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

On the Mechanism of Thiamine Action. IV.[1] Evidence from Studies on Model Systems

BY RONALD BRESLOW

RECEIVED JANUARY 14, 1958



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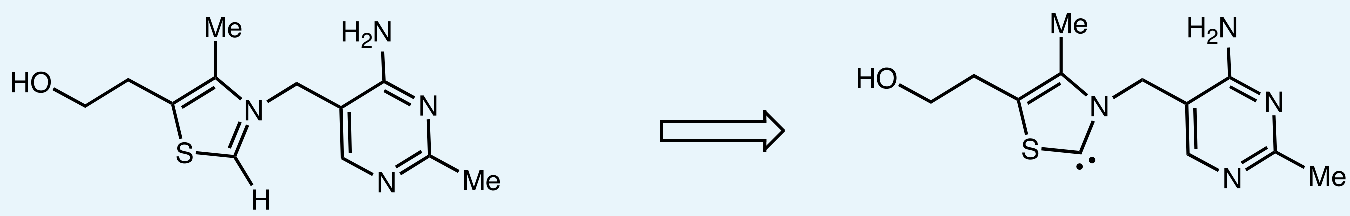

Thiazolium Salt of Thiamine Coenzyme (vitamin B_1)

Nature's Carbene Organocatalyst

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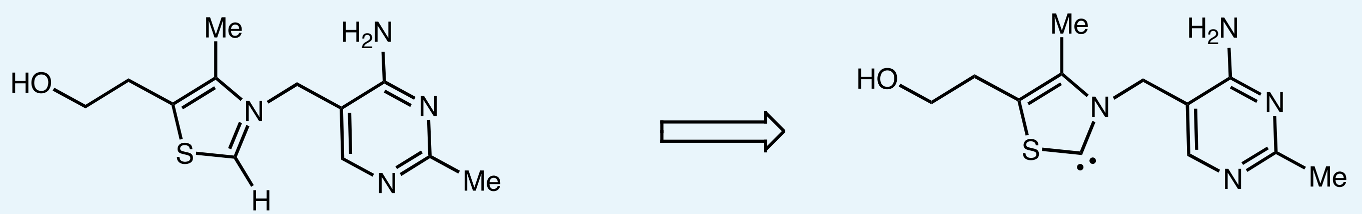

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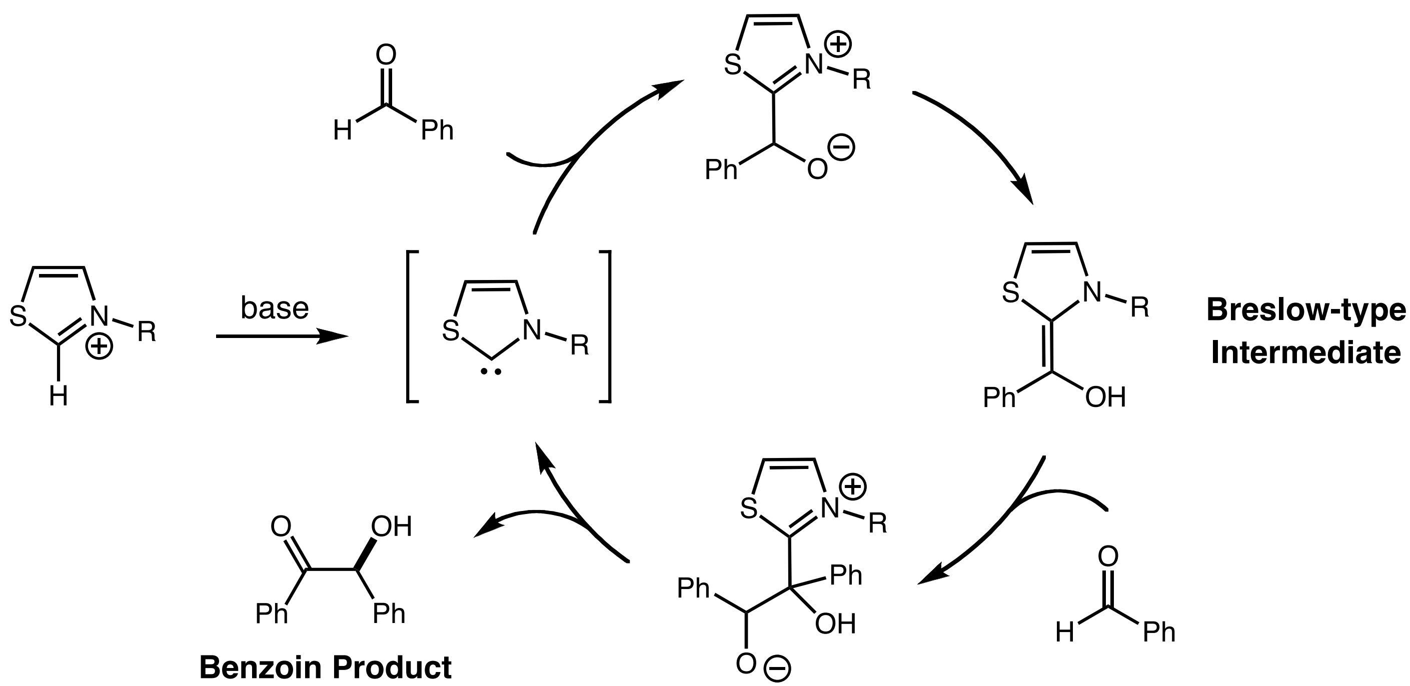

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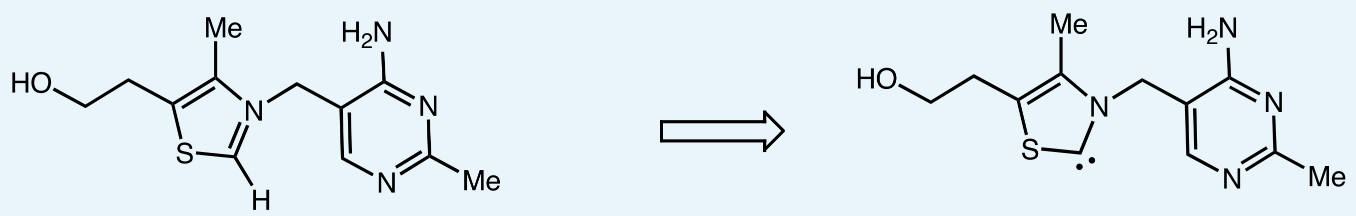

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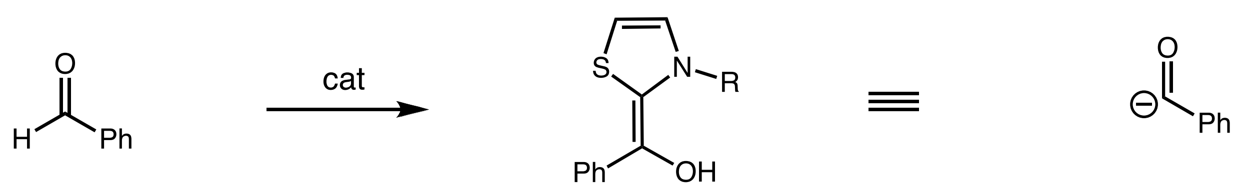

electrophilic

Breslow-type Intermediate

acyl anion synthon

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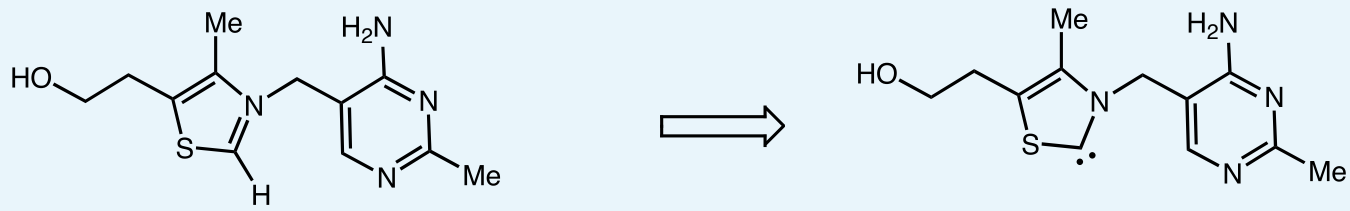

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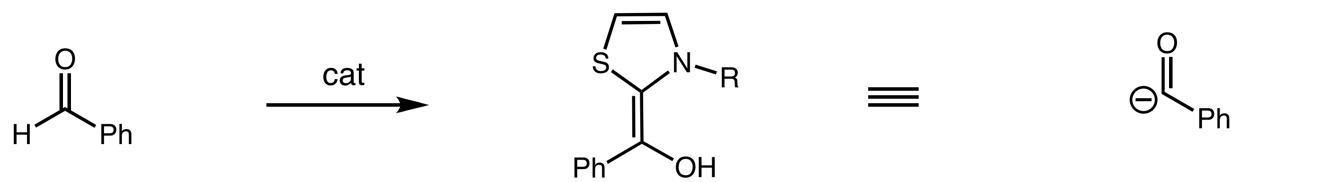

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Before we can get new reactions we need better catalysts

Carbenes as Organocatalysts

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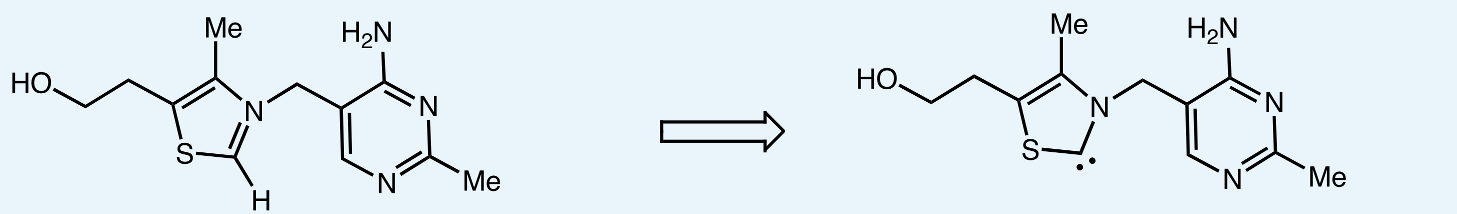

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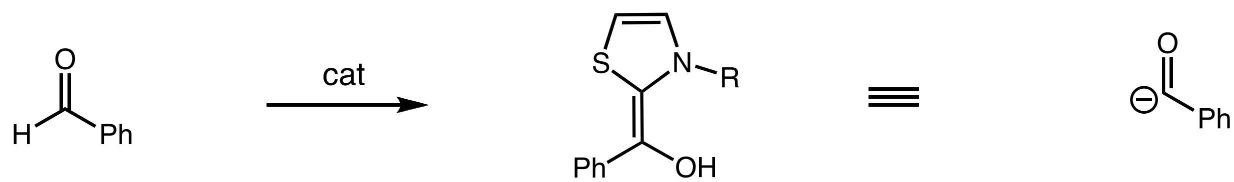

electrophilic

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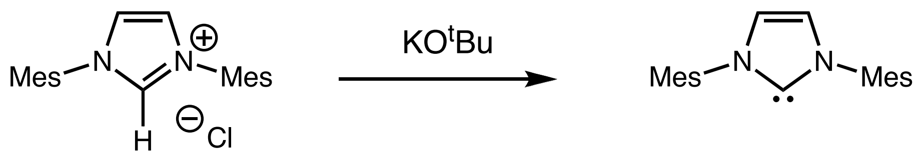
Before we can get new reactions we need better catalysts

novel reactivty patterns

Carbenes as Organocatalysts

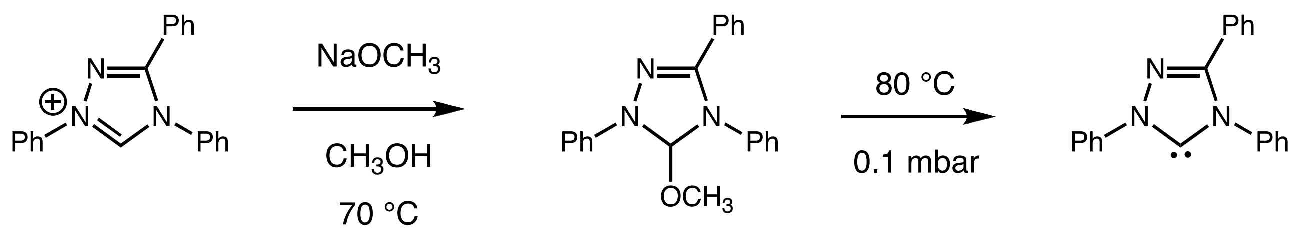
- Isolated in 1991 by Arduengo while working at DuPont



Bulky groups prevent dimerization

Arduengo III, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

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

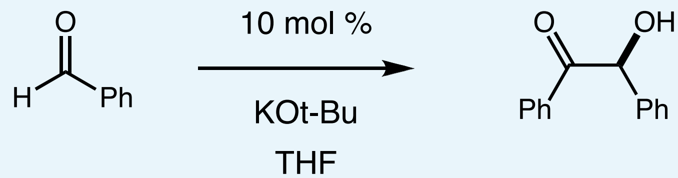


Preparation, Structure, and Reactivity of 1,3,4-Triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene, a New Stable Carbene**

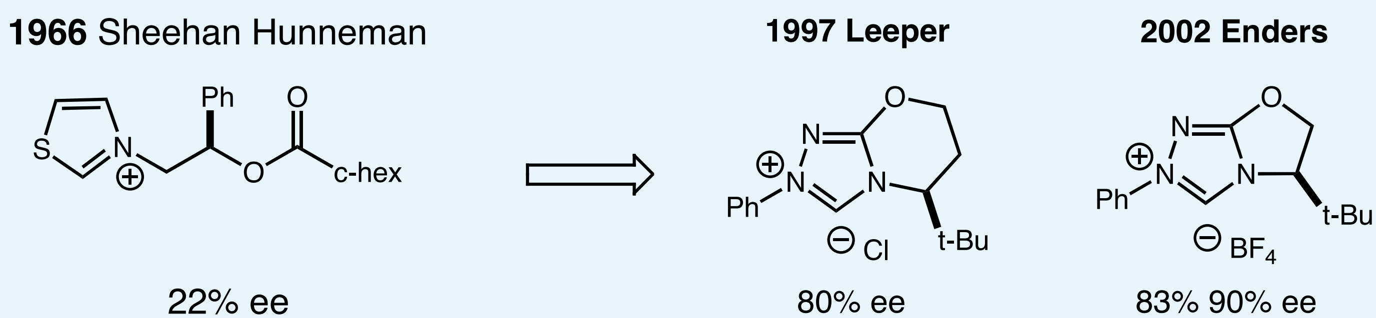
Dieter Enders,* Klaus Breuer, Gerhard Raabe, Jan Runsink, J. Henrique Teles,* Johann-Peter Melder, Klaus Ebel, and Stefan Brode

Angew. Chem. Int. Ed. **1995**, *34*, 1021.

Asymmetric Carbene Catalysts



■ The genesis of a new platform for asymmetric catalysis



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

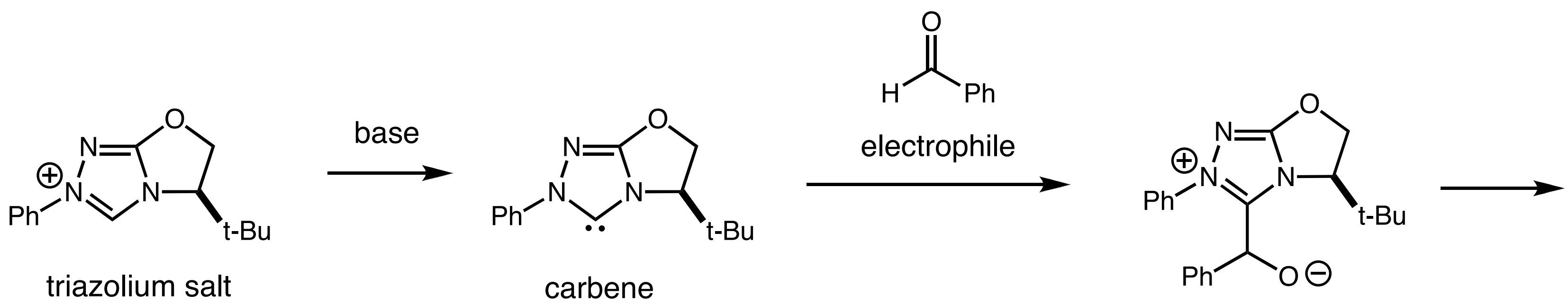
Sheehan, J.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666.

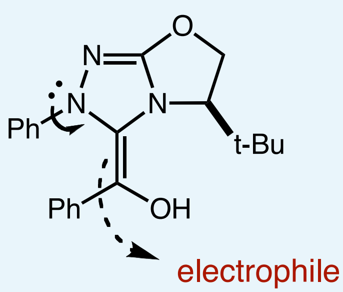
Knight, R. L.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3611.

Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743.

Carbenes: Generic Activation Platform

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



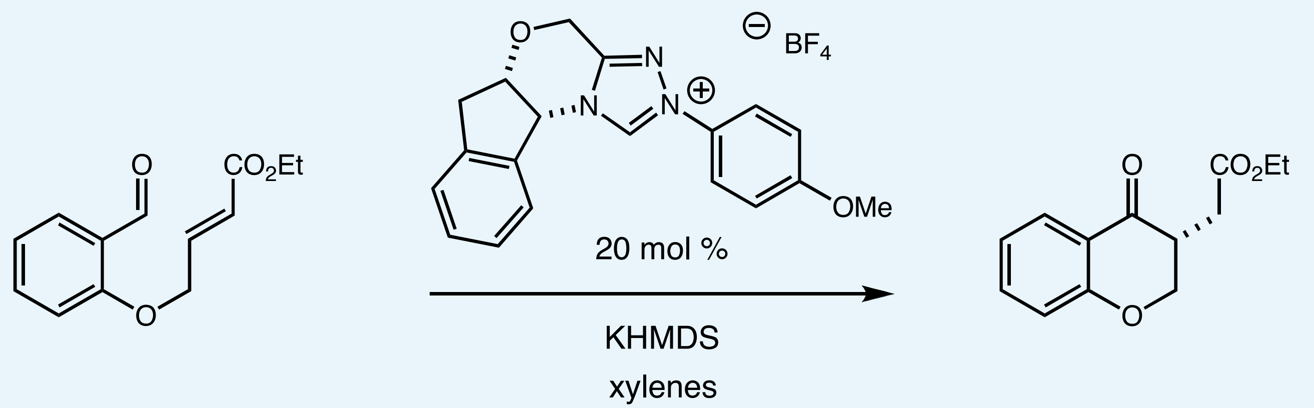


Breslow-type Nucleophile

- 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



Rovis 2002

94% yield

94% ee

Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am Chem. Soc.* **2002**, *124*, 10298.

J|A|C|S

COMMUNICATIONS

Published on Web 08/10/2002

A Highly Enantioselective Catalytic Intramolecular Stetter Reaction

Mark S. Kerr, Javier Read de Alaniz, and Tomislav Rovis*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received June 21, 2002

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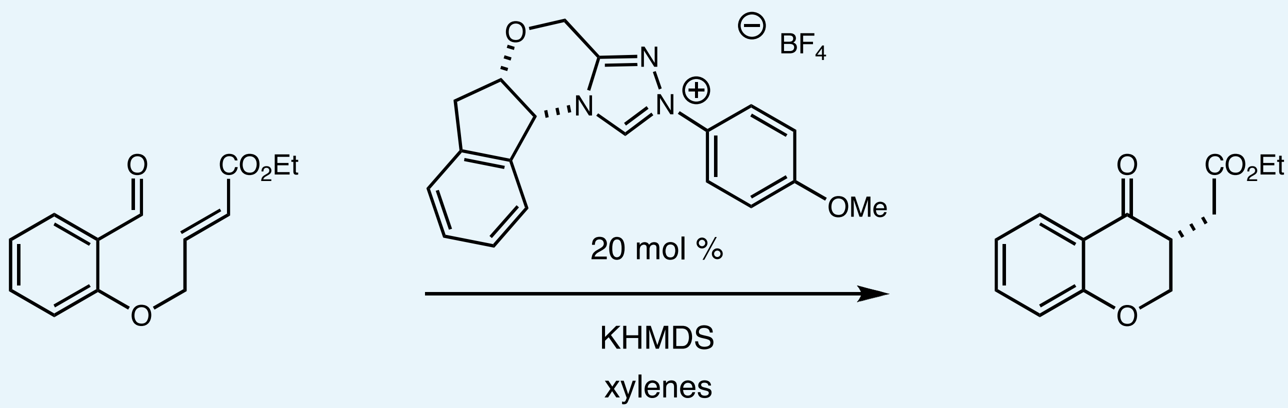

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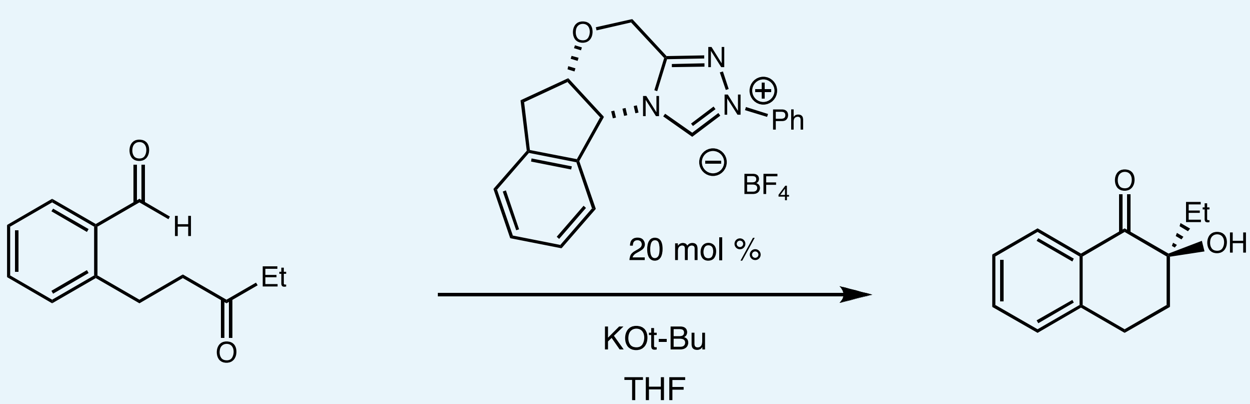
- The Rovis catalyst design has been have been proven to be excellent for many more reactions



Enders 2006

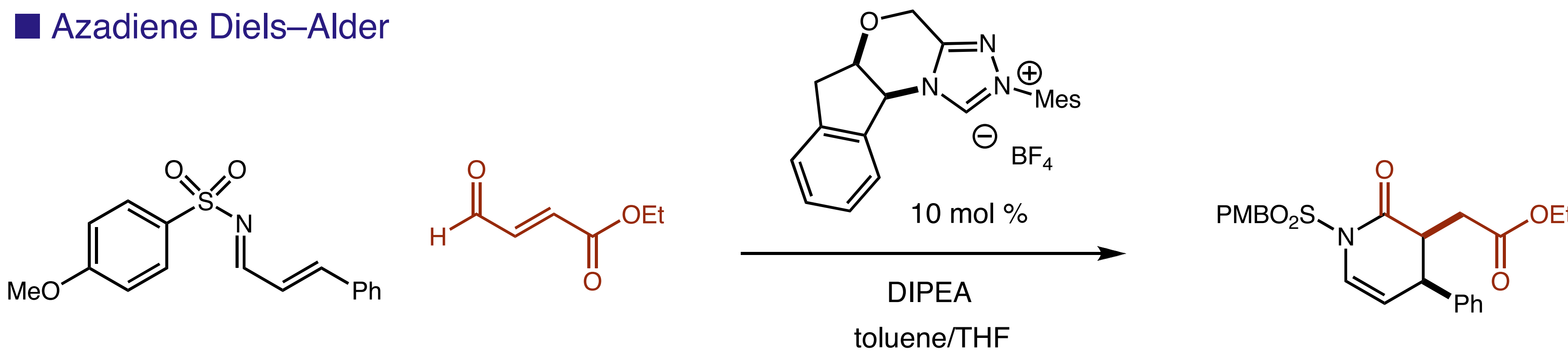
88% yield

94% ee

Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431.

Beyond the Stetter and Bezoin Reactions

■ Azadiene Diels–Alder



90%, 50:1 dr 99% ee

Bode 2006

He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

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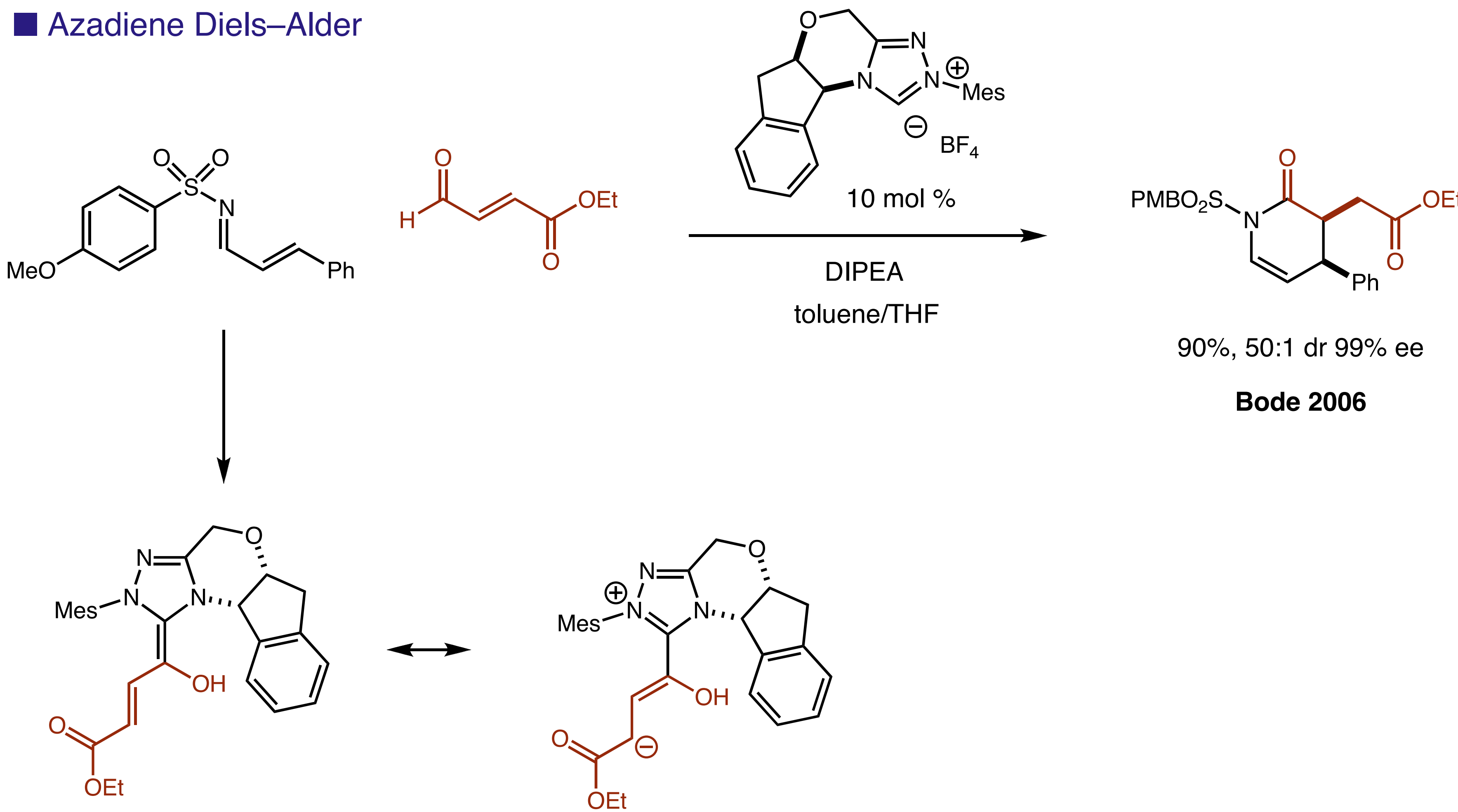

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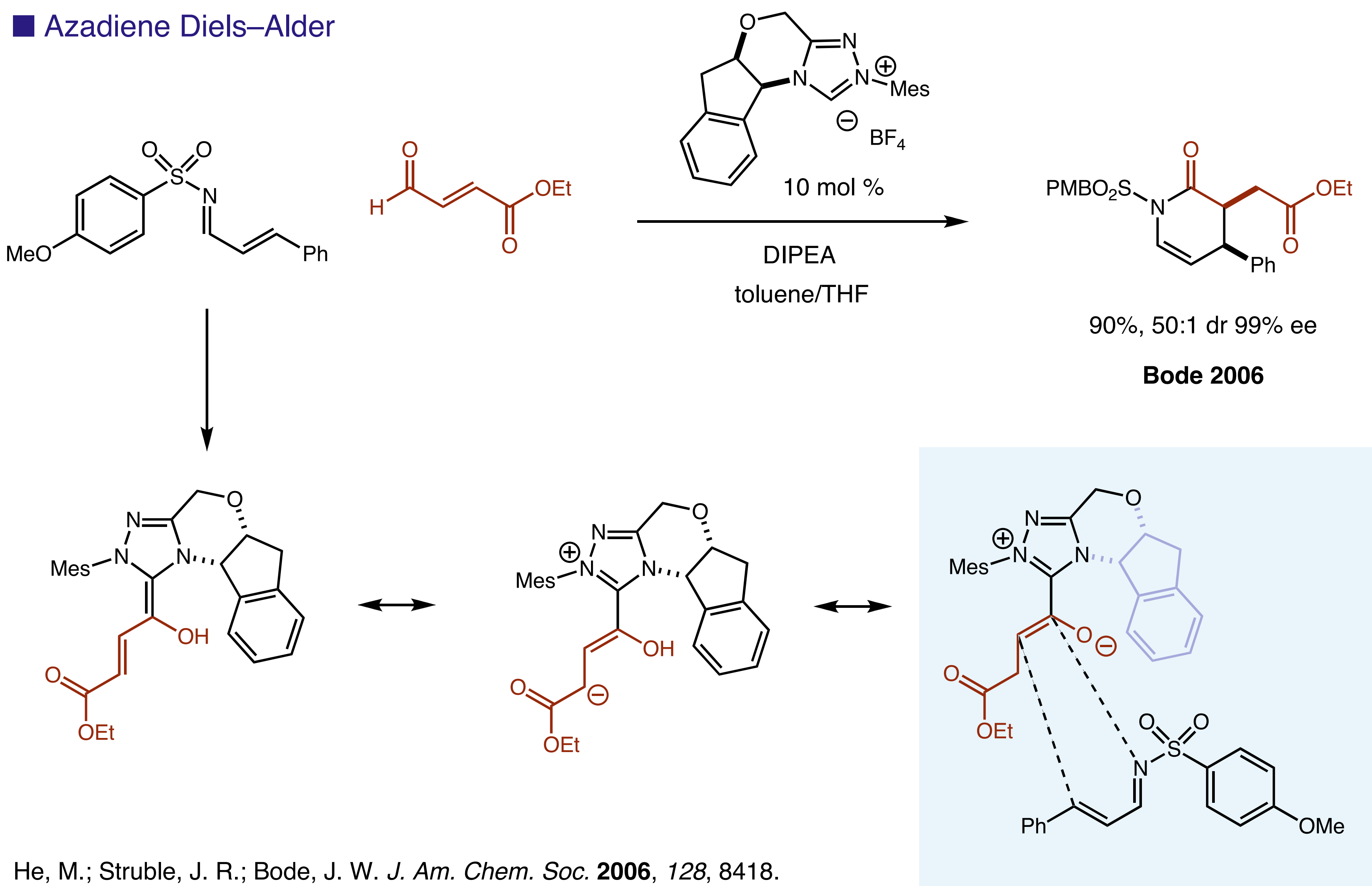

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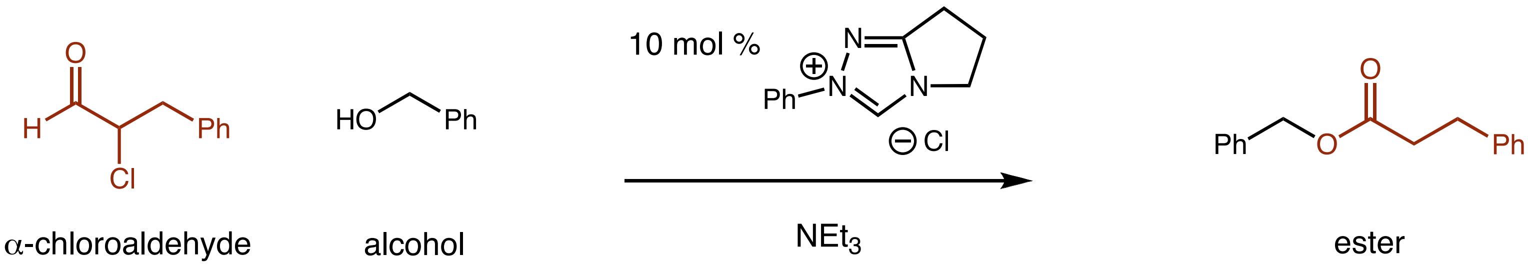
Substrate Activation Towards New Reactivity

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



Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518. He, M.; Uc, G. J.; Bode, J. W. *J Am. Chem. Soc.* **2006**, *128*, 15088.

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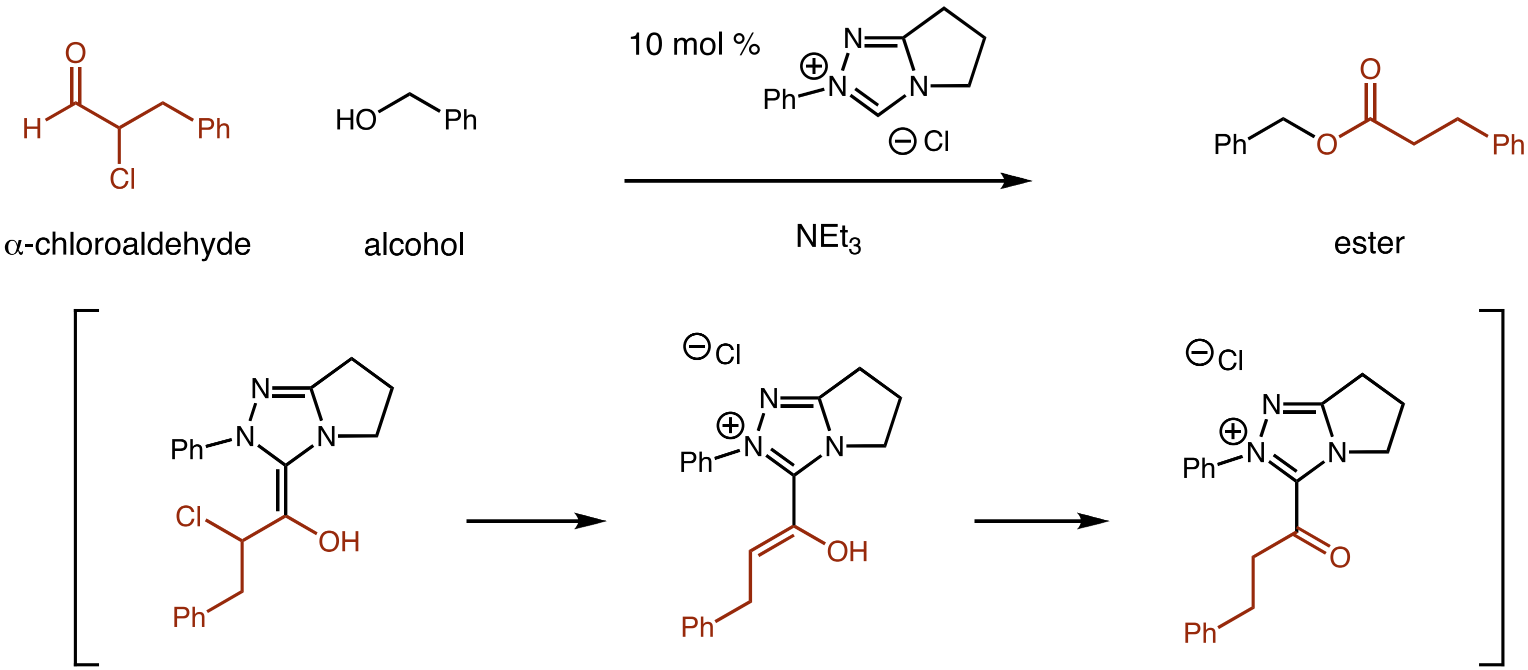

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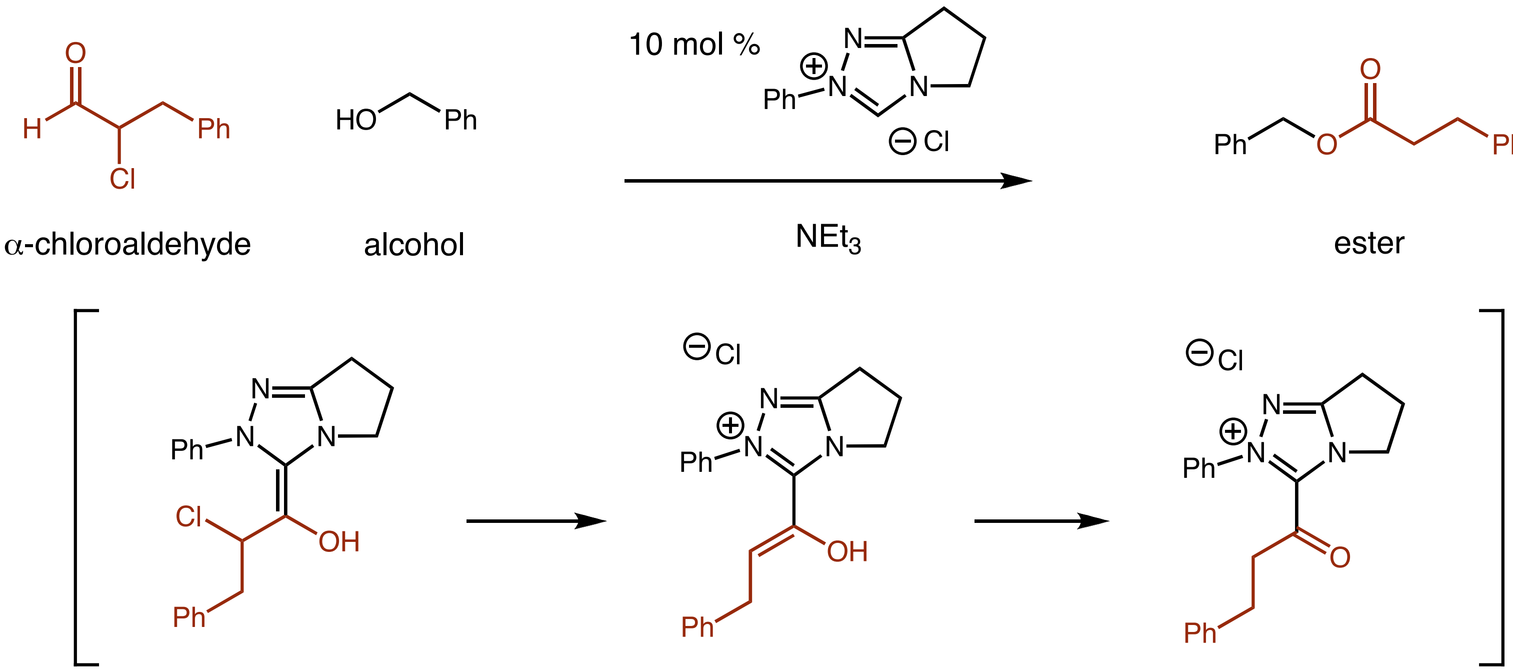
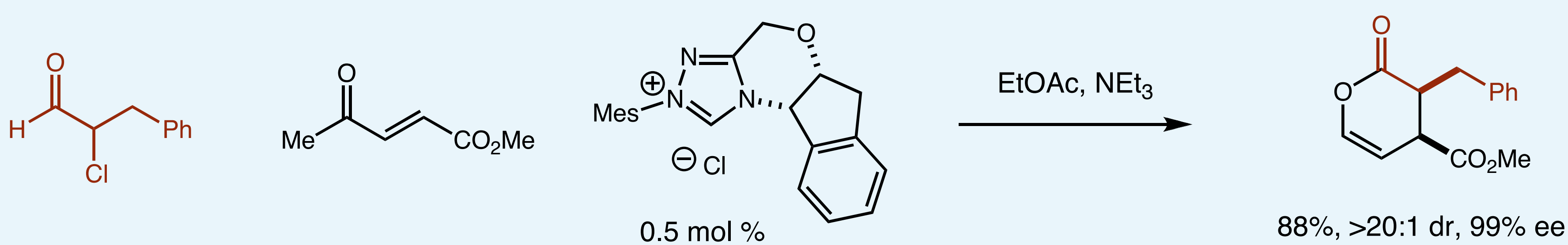


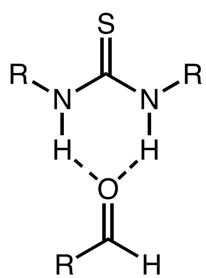
■ Oxy Diels–Alder reaction



Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518. He, M.; Uc, G. J.; Bode, J. W. *J Am. Chem. Soc.* **2006**, *128*, 15088.

Hydrogen-Bonding Catalysis

H-bond catalysis



~30 new reactions

Jacobsen–Akiyama

Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.

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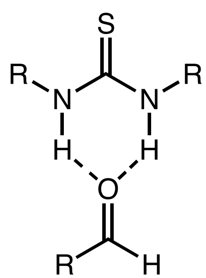

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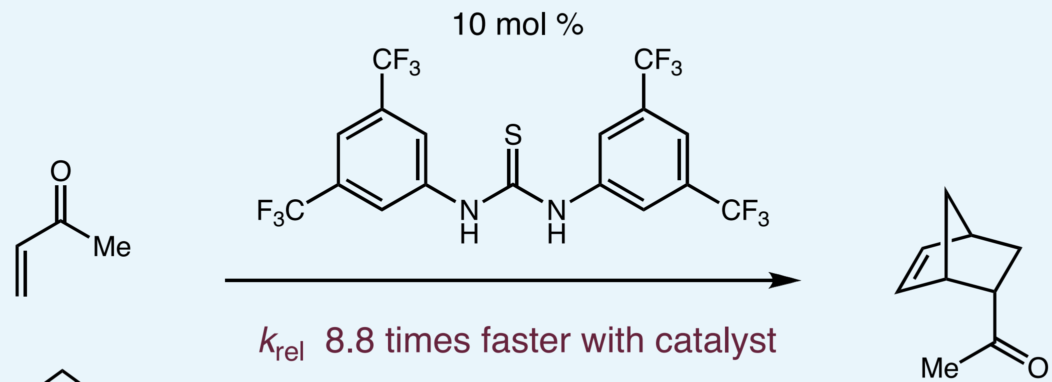

- Typically a 2-20 kcal/mol interaction
- Activates electrophiles

Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407.

Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.

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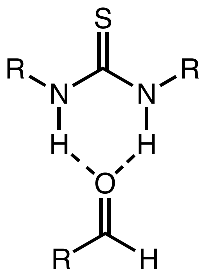

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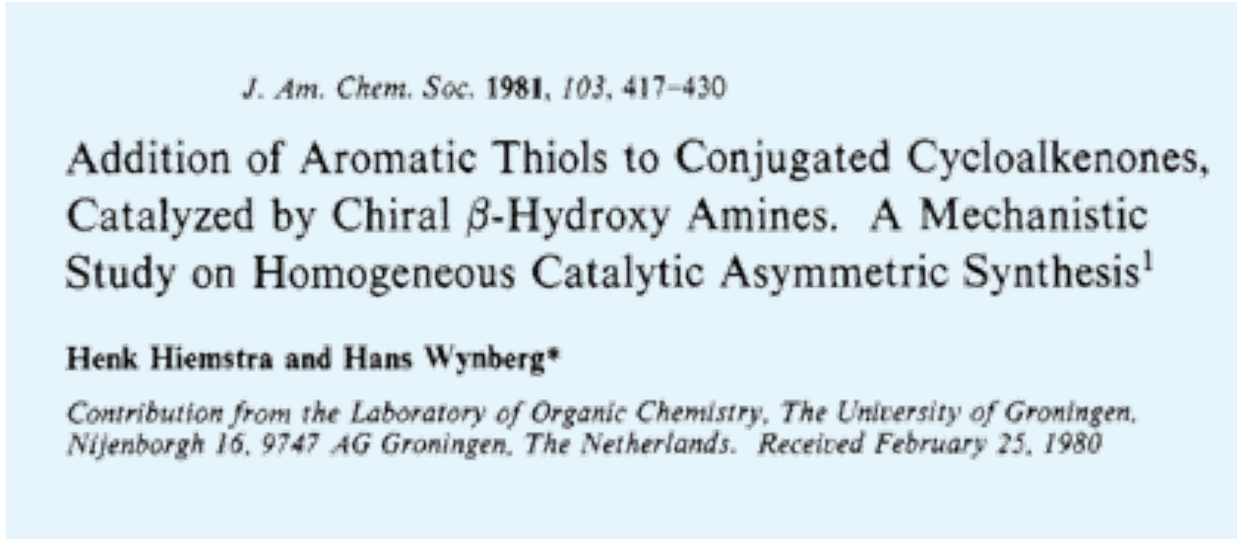

J. Am. Chem. Soc. **1981**, *103*, 417–430

Addition of Aromatic Thiols to Conjugated Cycloalkenones, Catalyzed by Chiral β-Hydroxy Amines. A Mechanistic Study on Homogeneous Catalytic Asymmetric Synthesis[1]

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*

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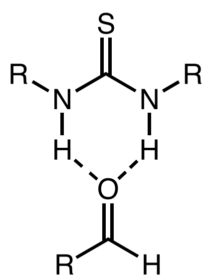

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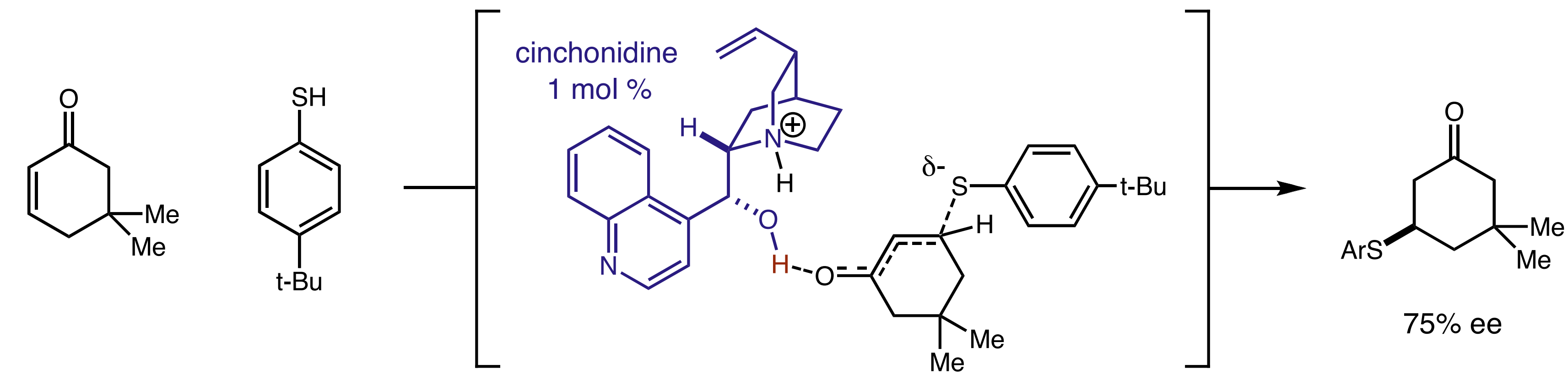
■ Early examples using cinchonia alkaloidsas H-bonding catalysts



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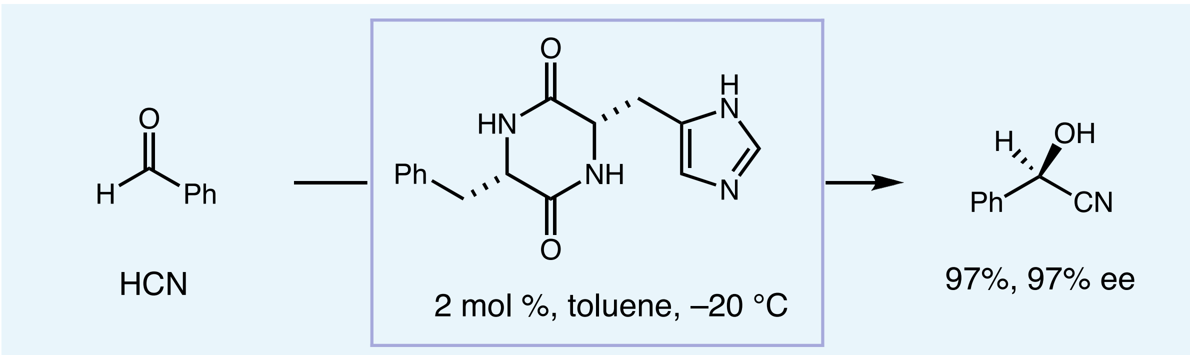
Early Examples of Hydrogen Bonding Catalysis

- A small dipeptide was designed by Inoue to mimic oxynitrilase



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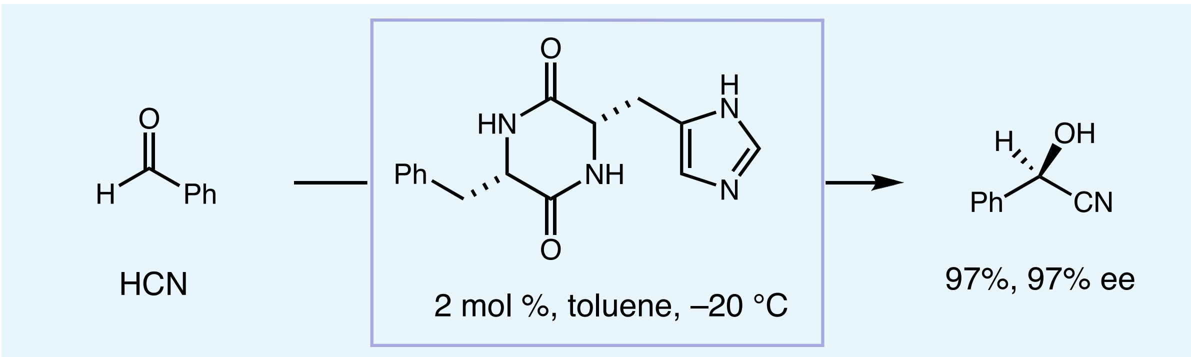

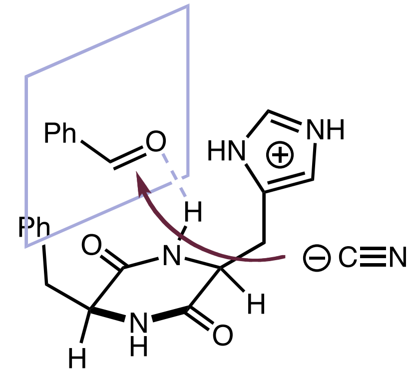

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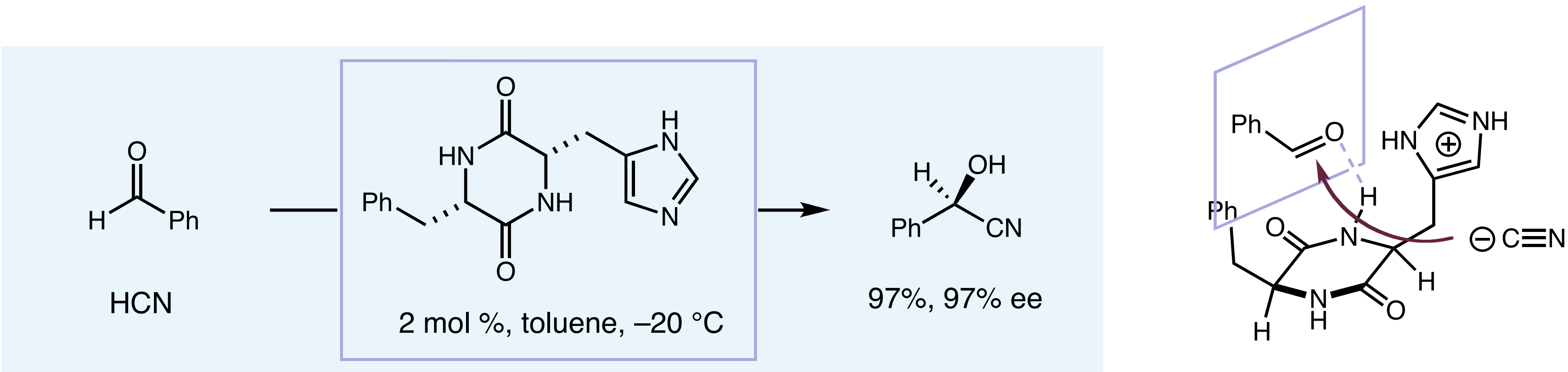
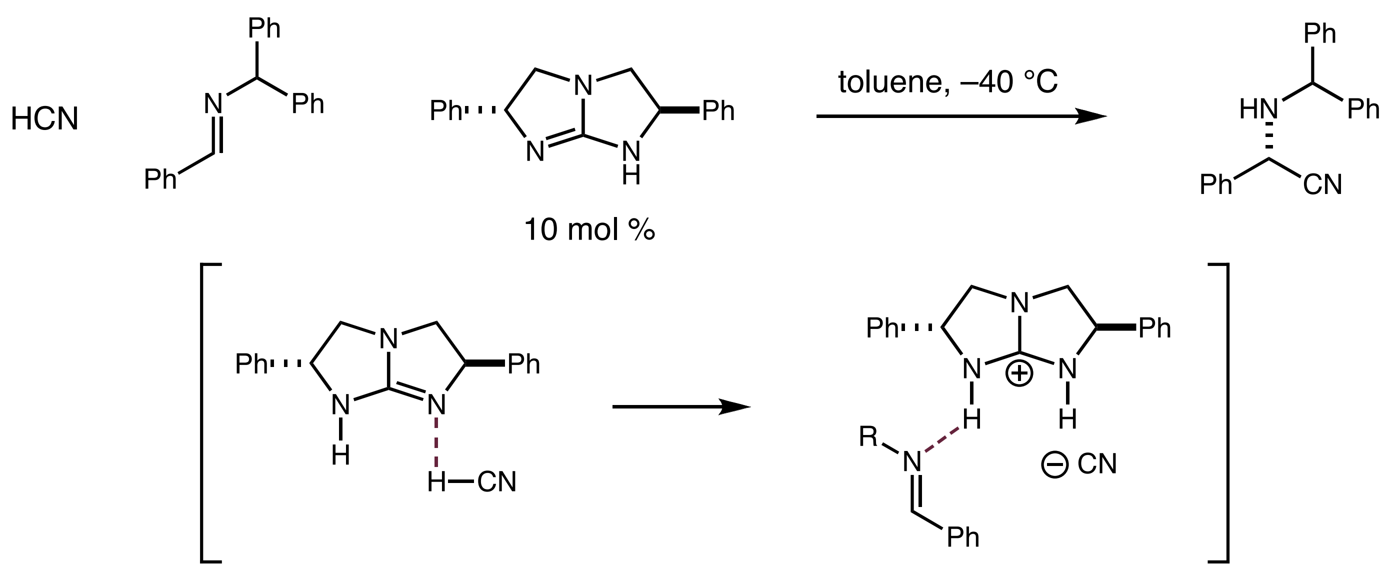


■ Asymmetric Strecker reaction using Corey's guanidine H-bonding catalyst



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Discovery of Acid Mediated Strecker Reactions – Jacobsen Thioureas

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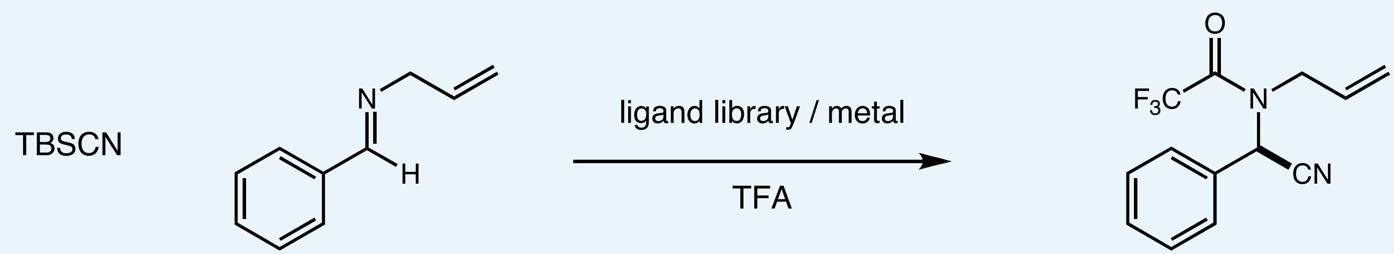

Schiff Base Catalysts for the Asymmetric Strecker Reaction Identified and Optimized from Parallel Synthetic Libraries

Matthew S. Sigman and Eric N. Jacobsen*

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

Received January 13, 1998

Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

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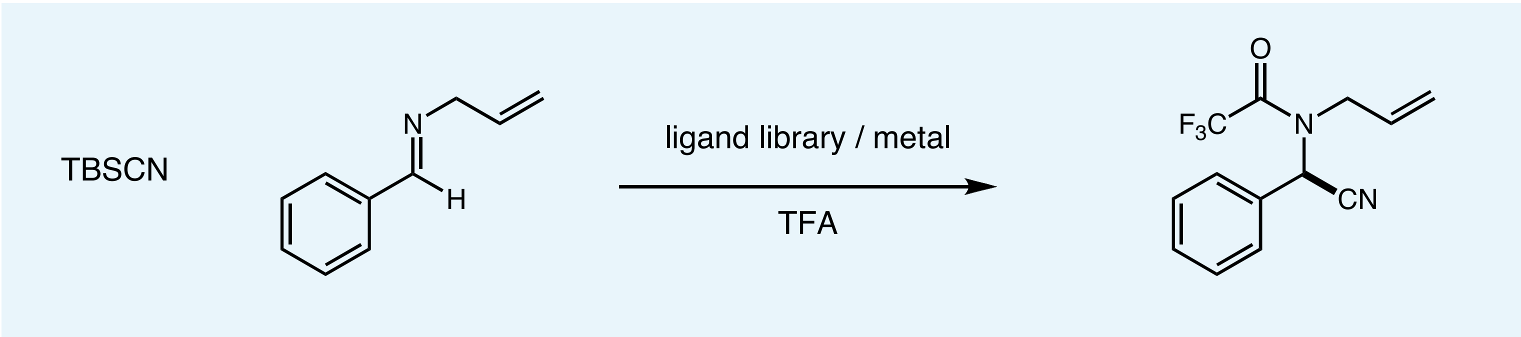

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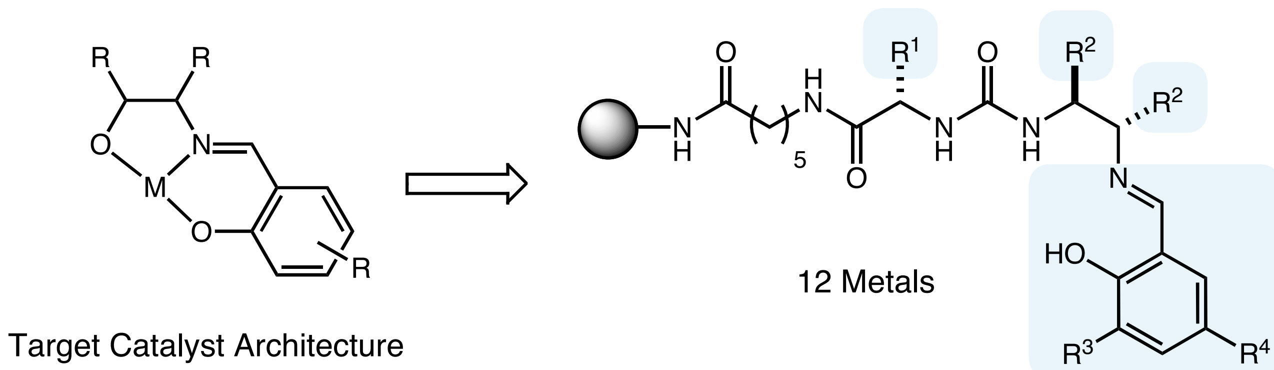

Ru

69% conv 13% ee

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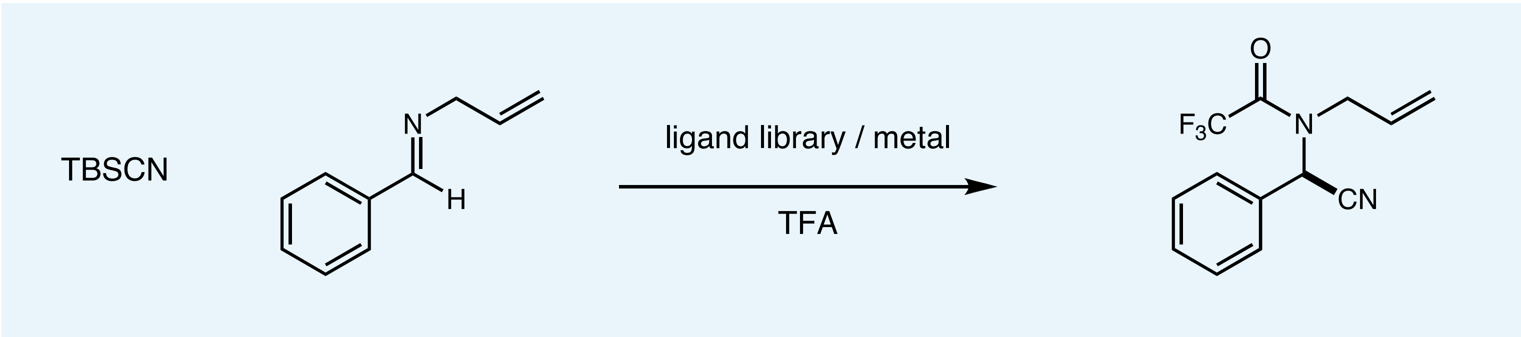

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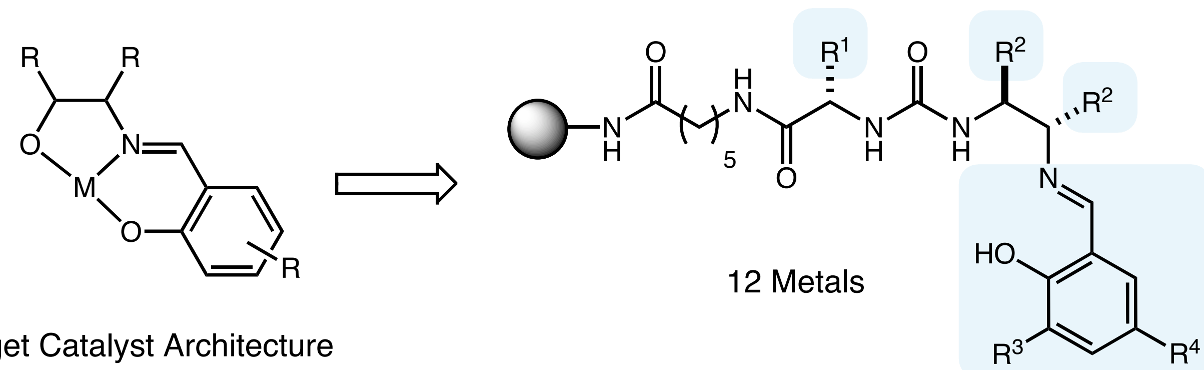

Target Catalyst Architecture

Ru

69% conv 13% ee

No Metal

59% conv 19% ee

Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

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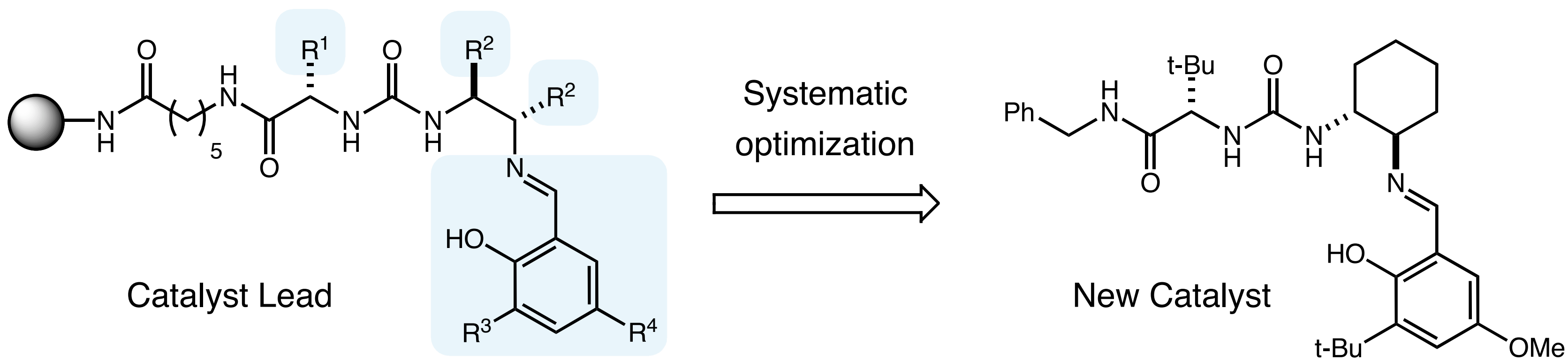

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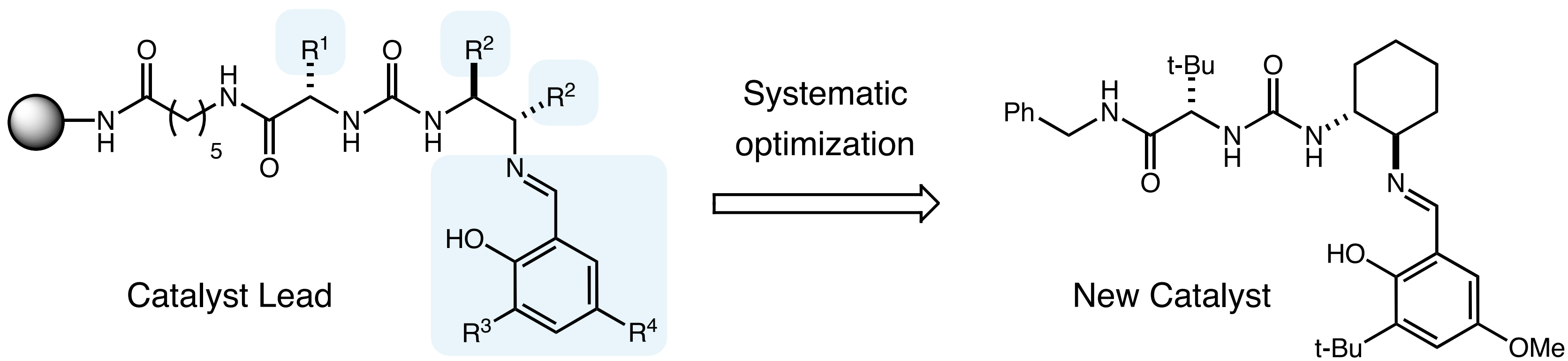
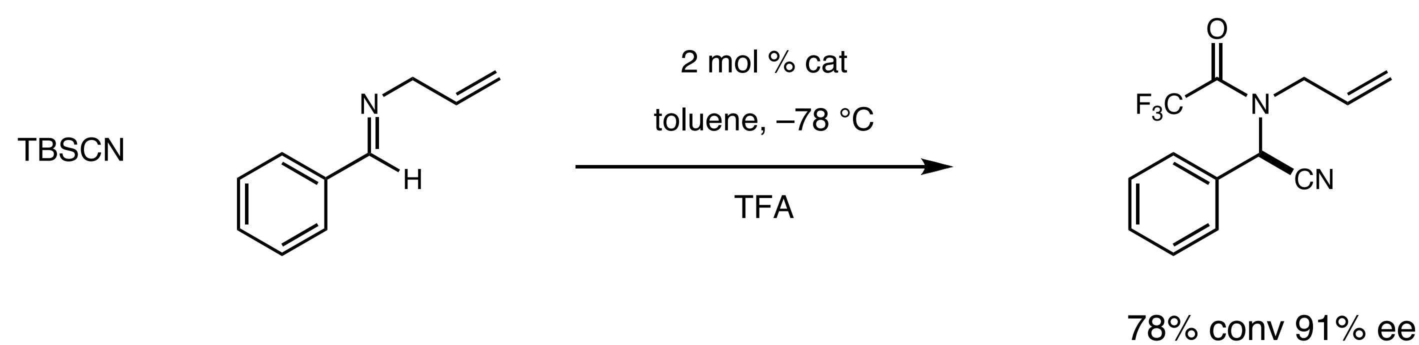
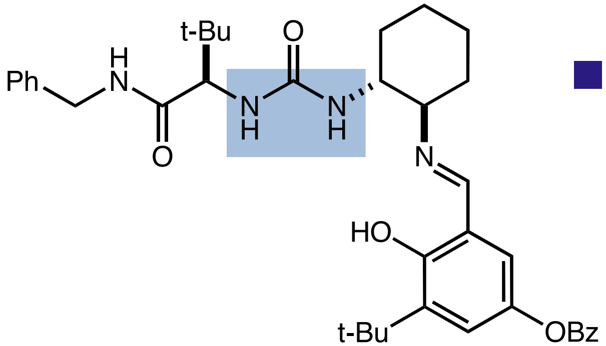
■ The structure was quickly optimized to provide an efficient Strecker catalyst





Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

How Do These New Catalysts Function?

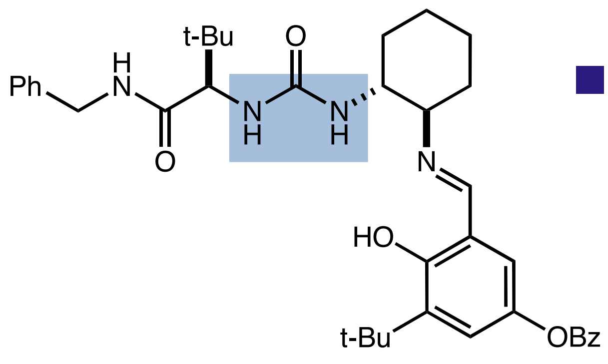


■ Knock-out studies show that the urea functional group is essential

■ Hydrogen bonding established as the activation mode

Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *120*, 10012.

How Do These New Catalysts Function?

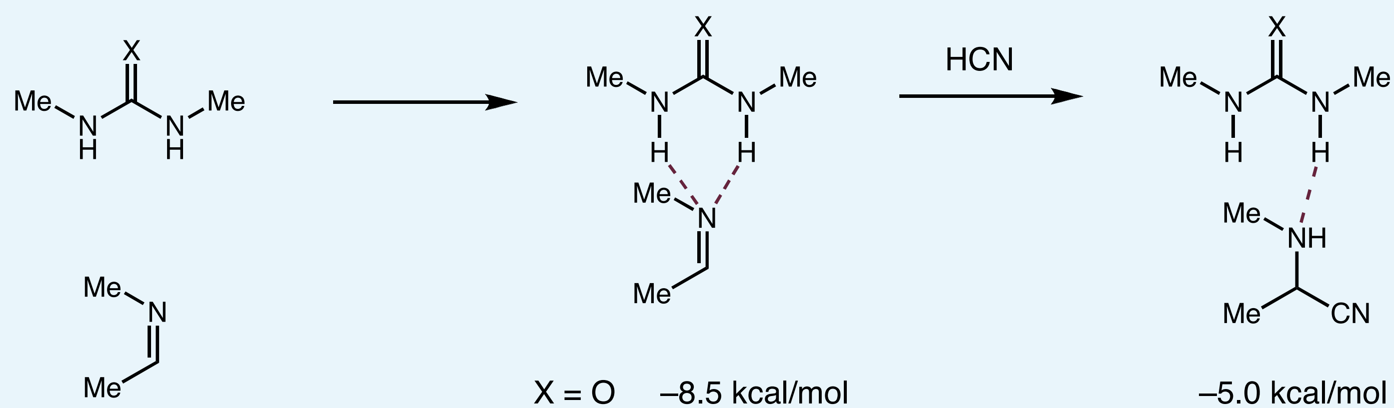


■ Knock-out studies show that the urea functional group is essential

■ Hydrogen bonding established as the activation mode

■ Weaker product binding enables turnover

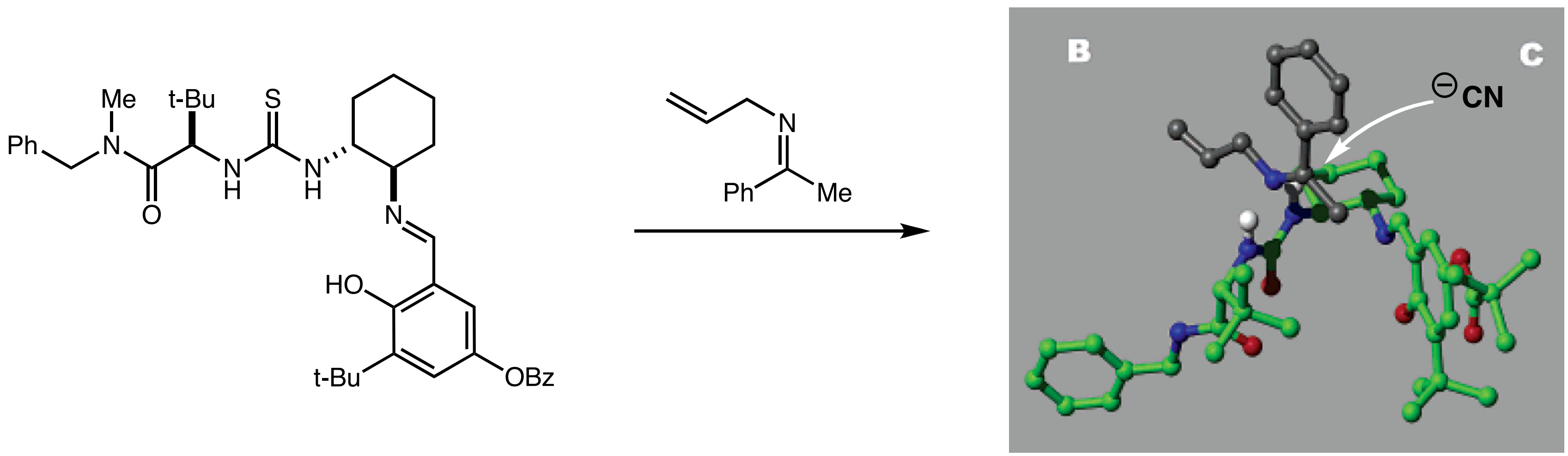
DFT and NMR Studies:



X = O	–8.5 kcal/mol	–5.0 kcal/mol
X = S	–10 kcal/mol	–6.3 kcal/mol

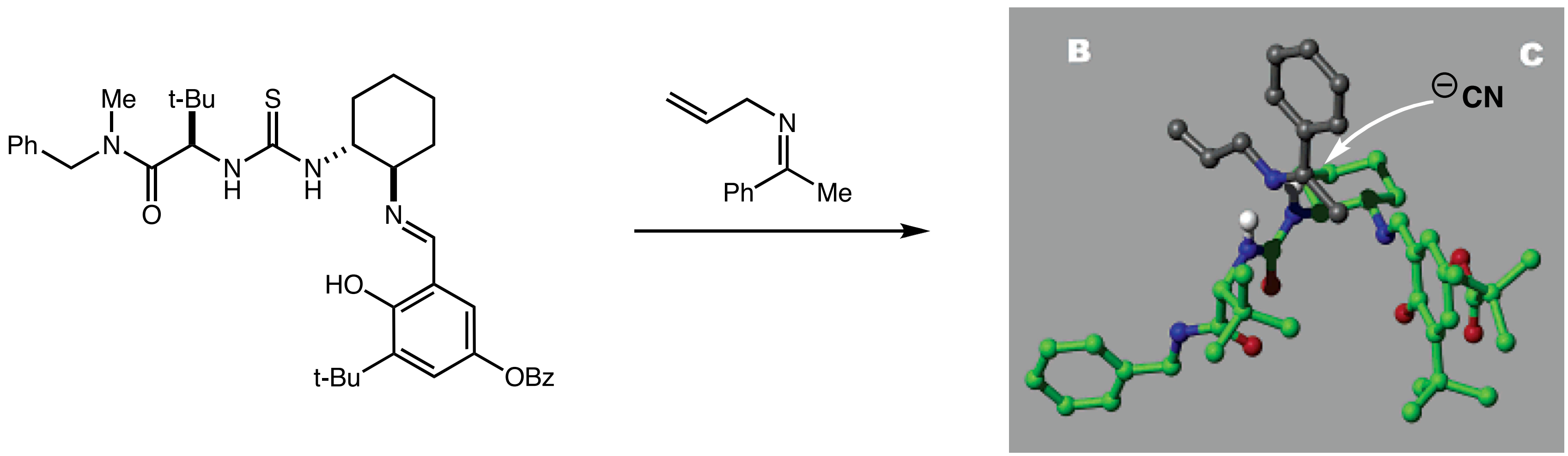
Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *120*, 10012.

Urea Stereochemical Model



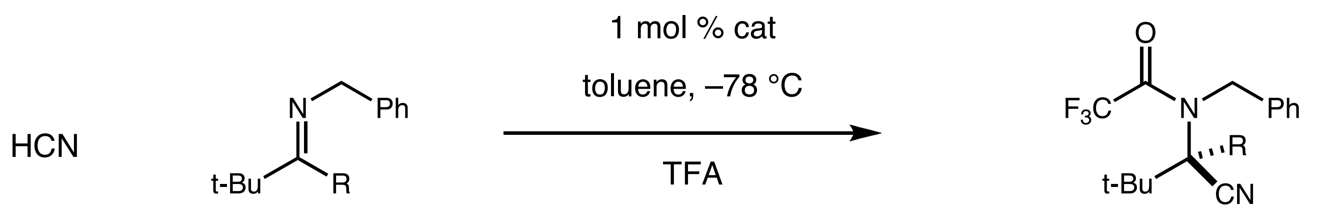
Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *120*, 10012.

Urea Stereochemical Model



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

Strecker reaction with aldimine or ketoimine



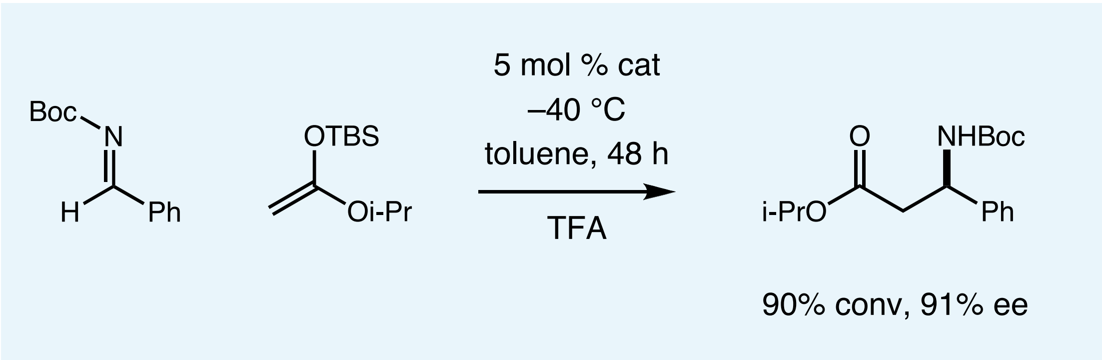
R = H 99% ee

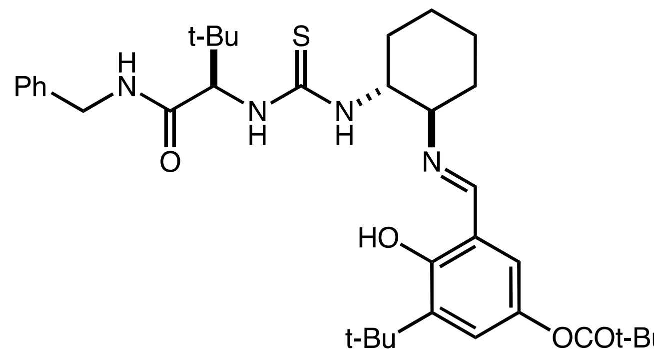
R = Me 86% ee

Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *120*, 10012.

Urea Catalyzed Reactions

Enantioselective Mannich Reaction

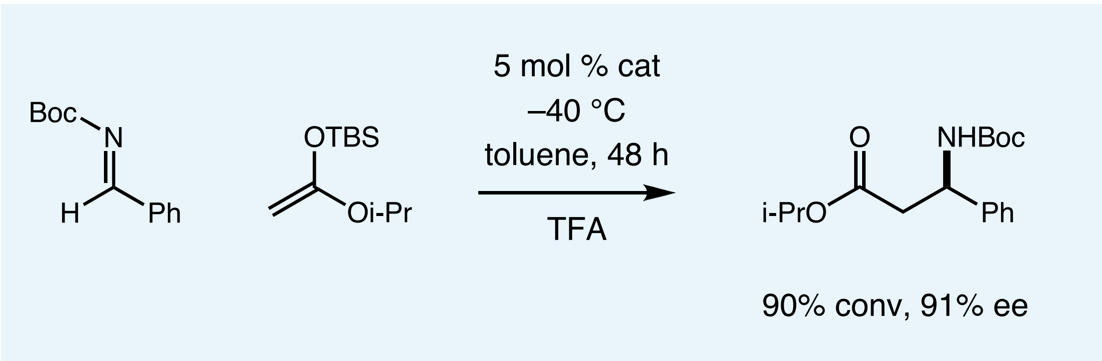


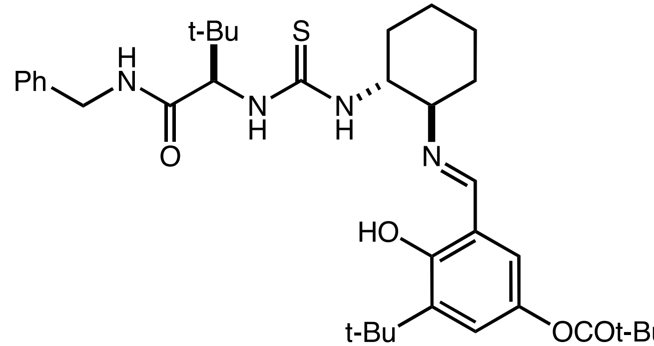


Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

Urea Catalyzed Reactions

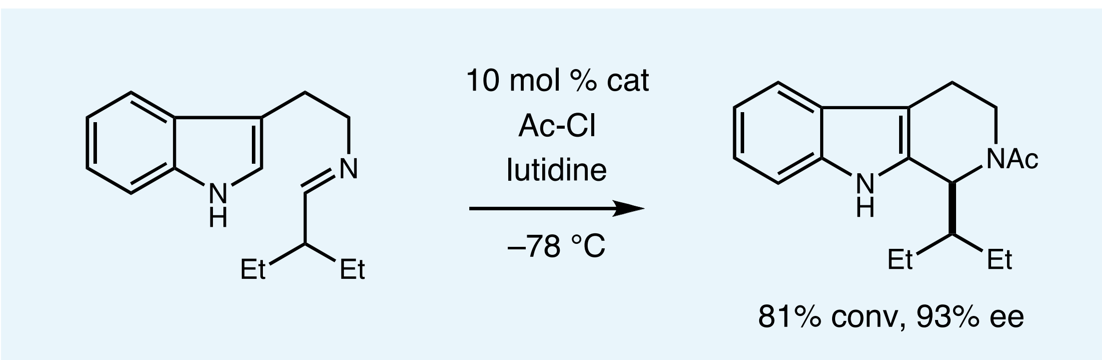
Enantioselective Mannich Reaction

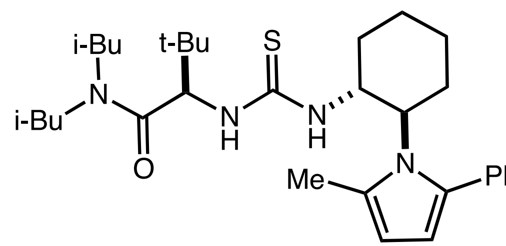




Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

Enantioselective Acyl Pictet–Spengler Reaction

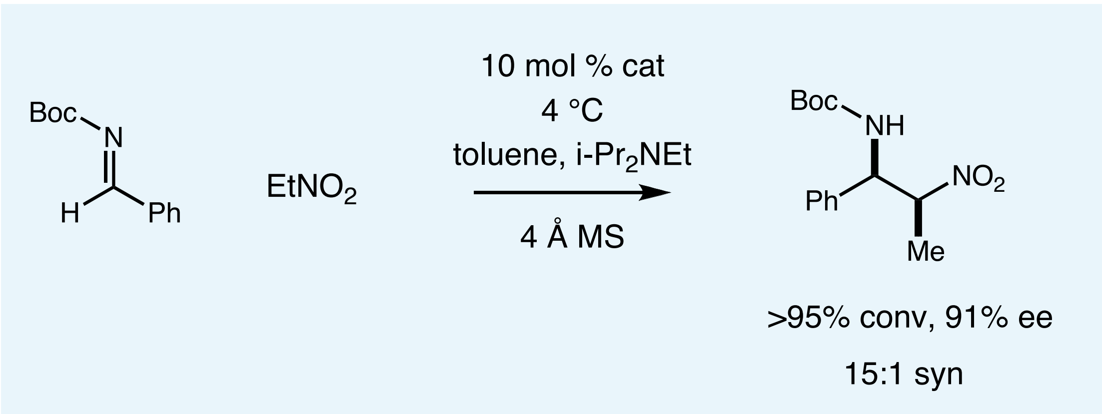


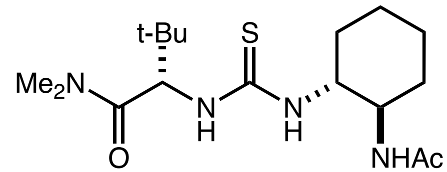


Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.

Urea Catalyzed Reactions

Enantioselective Aza-Henry Reaction

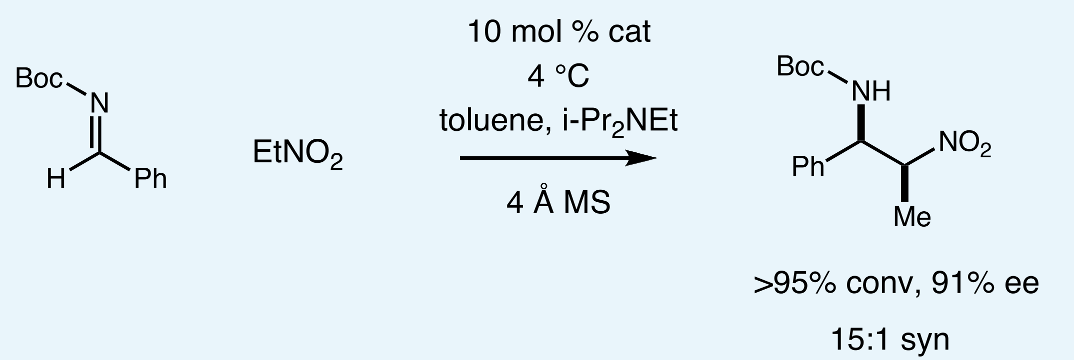


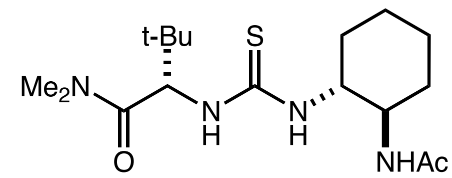


Yoon, T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *124*, 466.

Urea Catalyzed Reactions

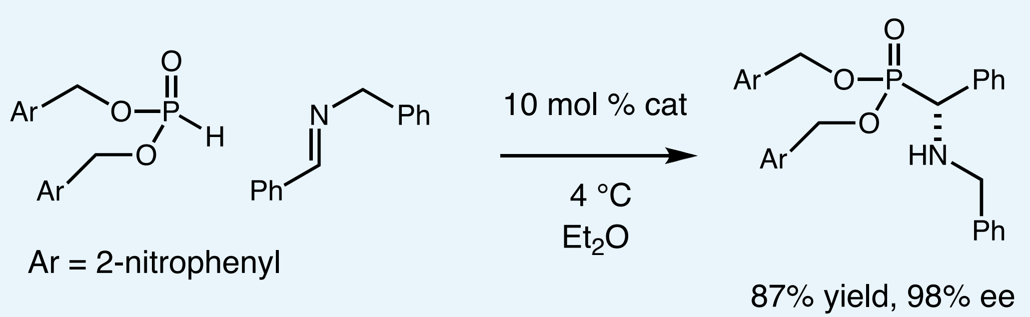
Enantioselective Aza-Henry Reaction

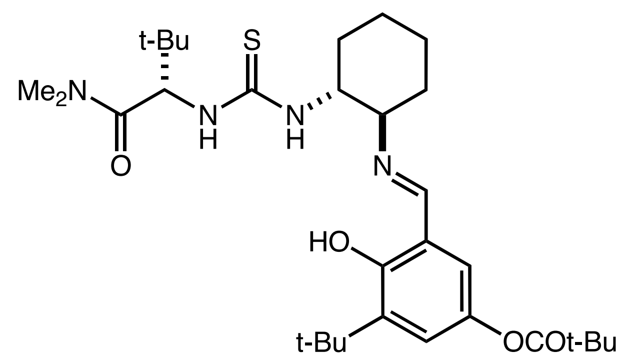




Yoon, T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *124*, 466.

Enantioselective Hydrophosphorylation

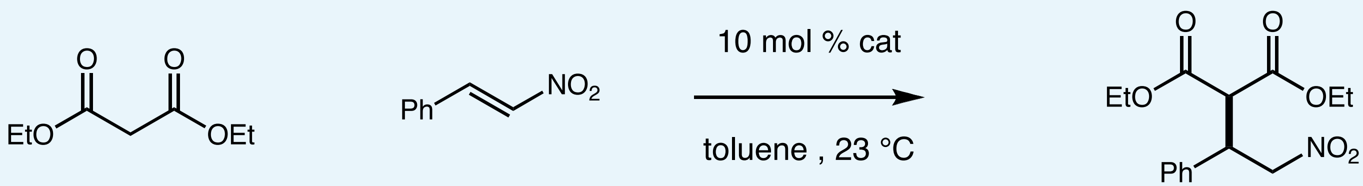




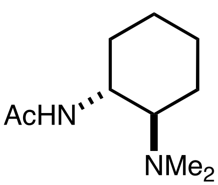
Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102.

Bifunctional Urea Catalysts

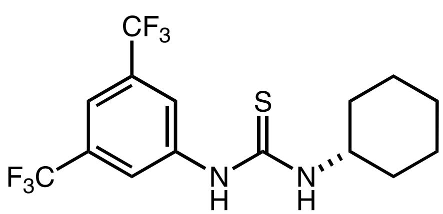
■ Enantioselective Michael Addition



■ Both thiourea and tertiary amine are needed

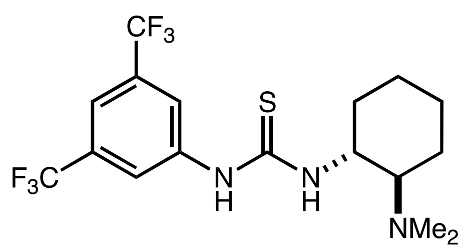


14%, 35% ee



10 mol % NEt_3

57%, 0% ee

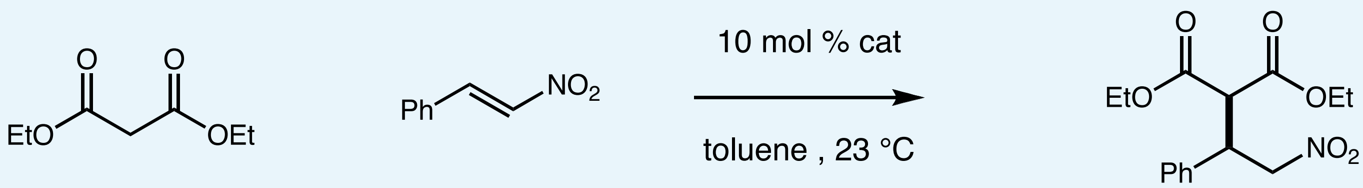


86%, 93% ee

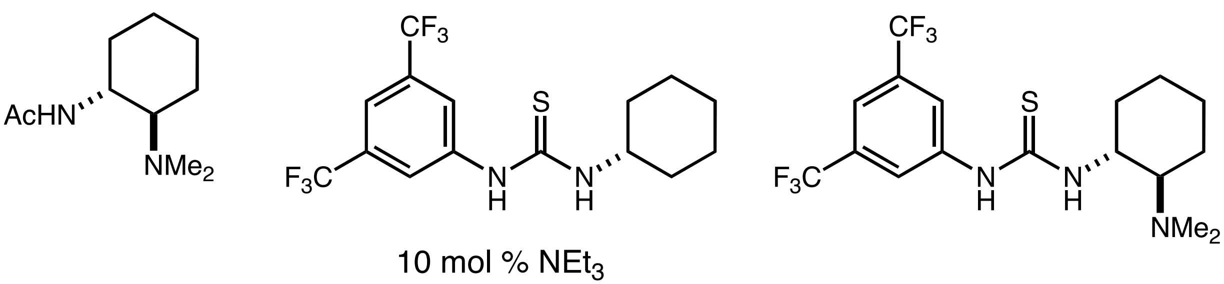
Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *128*, 12672.

Bifunctional Urea Catalysts

■ Enantioselective Michael Addition



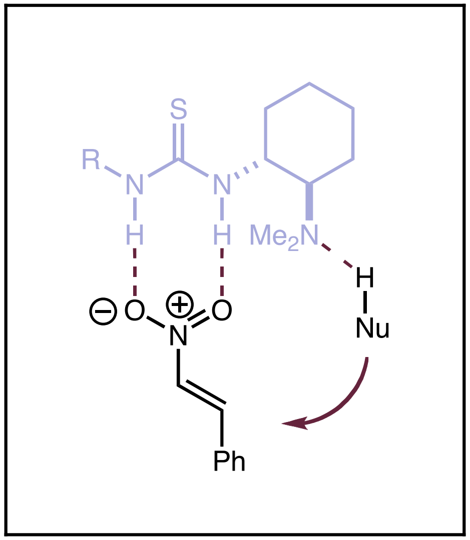
■ Both thiourea and tertiary amine are needed



14%, 35% ee

57%, 0% ee

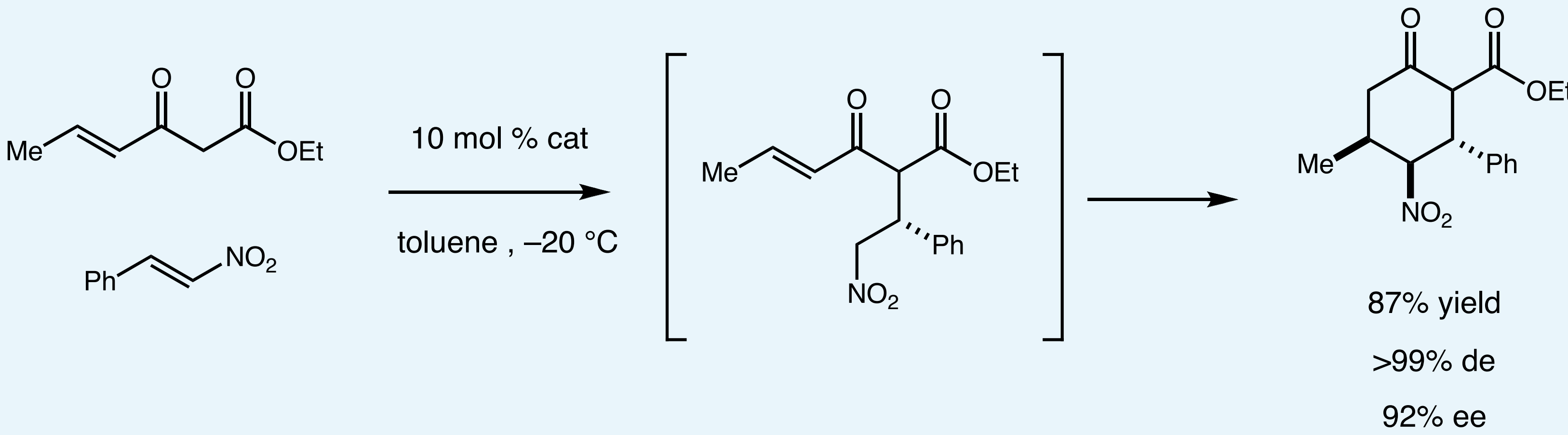
86%, 93% ee



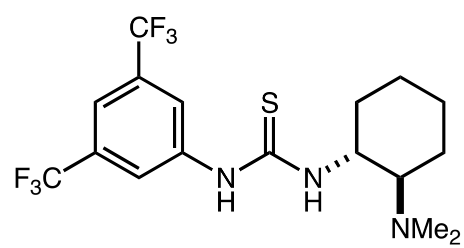
Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *128*, 12672.

Urea Catalyzed Double Michael Cascade

■ Enantioselective Double Michael Addition

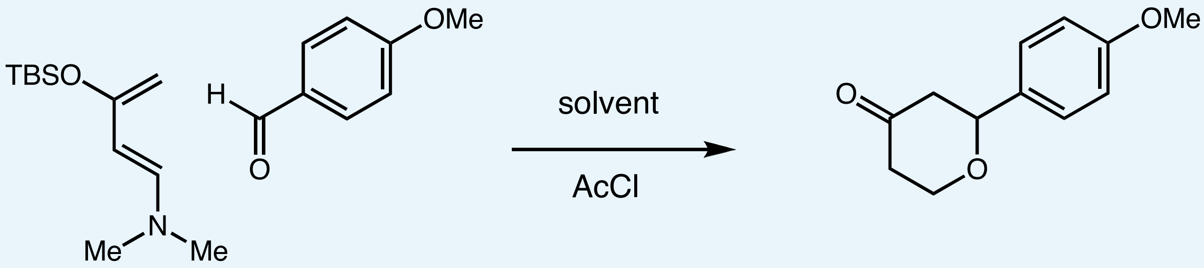


catalyst =



Hoashi, Y.; Yabuta, T.; Takemoto, Y. *Tettrahdron Lett.* **2003**, *45*, 9185.

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

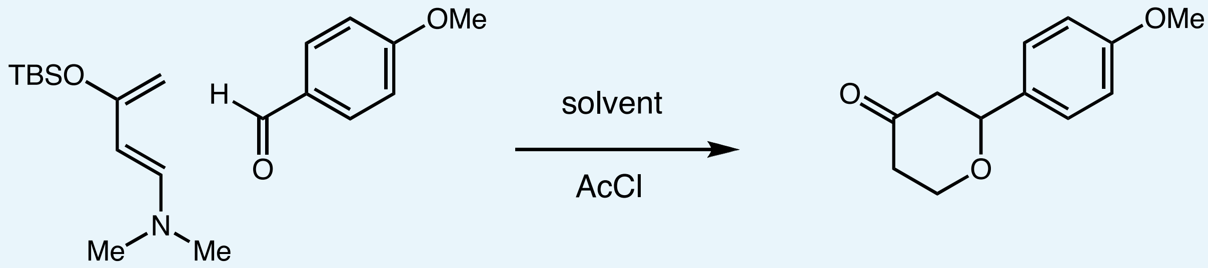


solvent	k_{rel}
THF	1
Benzene	1.3
t-BuOH	280
i-PrOH	630

Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662.

■ Observed that the hetero Diels–Alder reaction is accelerated in alcohol solvent

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



solvent	k_{rel}
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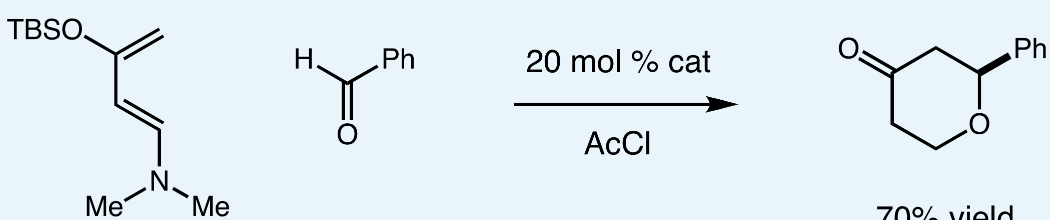
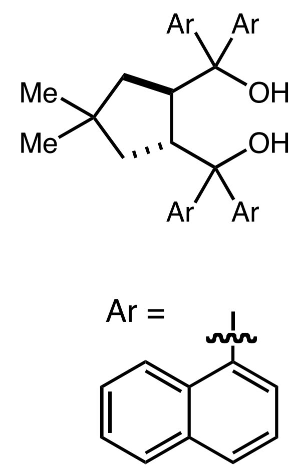
Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662.

- 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



70% yield

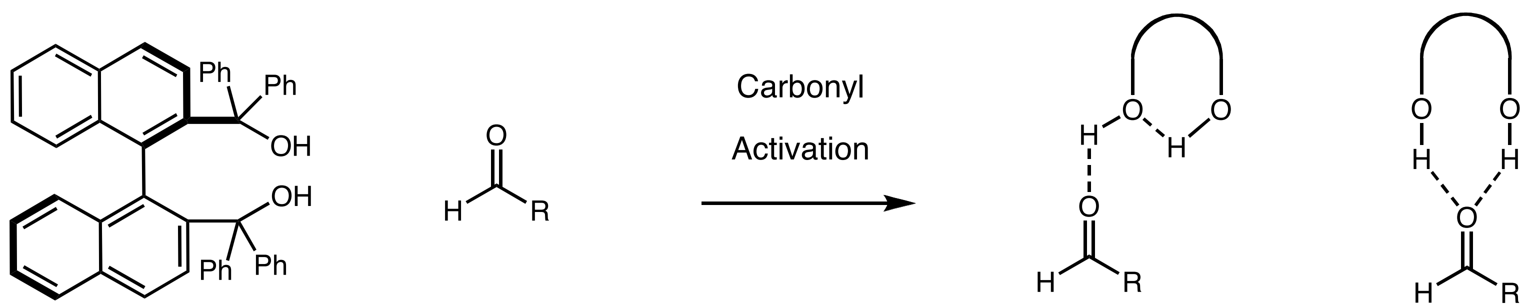
99% ee



Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.

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

- Is single or double point activation in operation?



Single or Double–point activation

Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.

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

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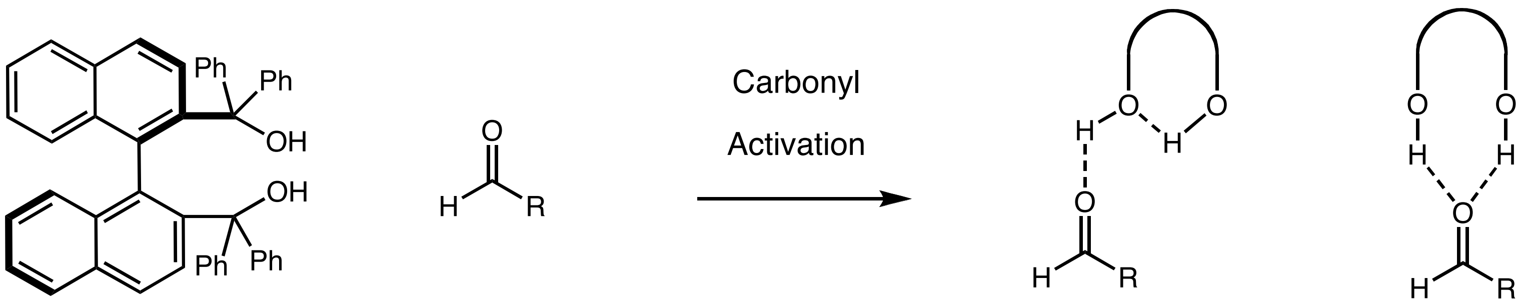
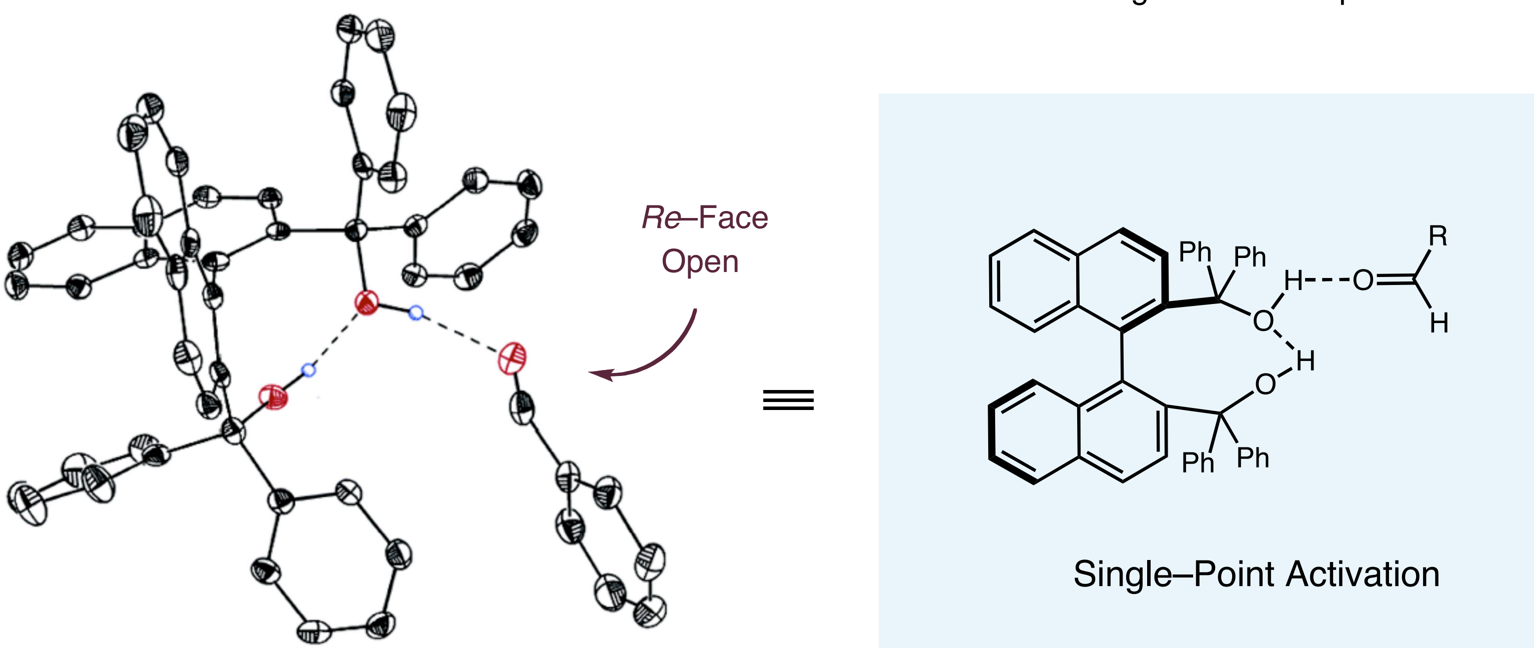
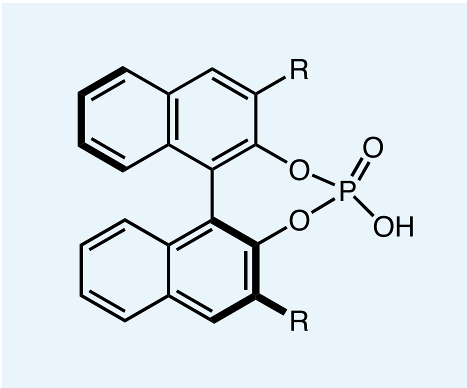


Single or Double–point activation



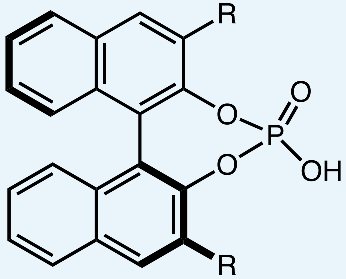
Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.

Chiral Phosphoric Acids



Akiyama, T.; Itoh, K.; Yokota, K.; Fuchibe, K. *Angew Chem. Int. Ed.* **2004**, *43*, 1566.
Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

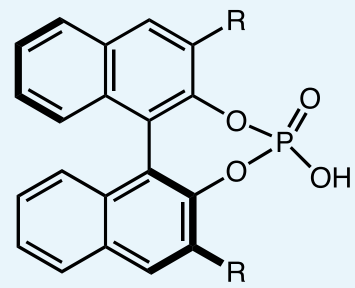
Chiral Phosphoric Acids



- Long used for chiral resolutions

Akiyama, T.; Itoh, K.; Yokota, K.; Fuchibe, K. *Angew Chem. Int. Ed.* **2004**, *43*, 1566.
Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

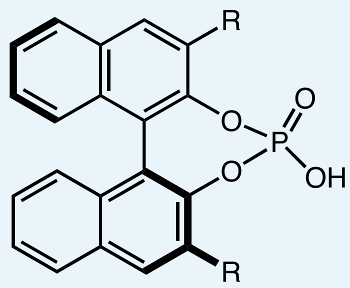
Chiral Phosphoric Acids



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

Akiyama, T.; Itoh, K.; Yokota, K.; Fuchibe, K. *Angew Chem. Int. Ed.* **2004**, *43*, 1566.
Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

Chiral Phosphoric Acids



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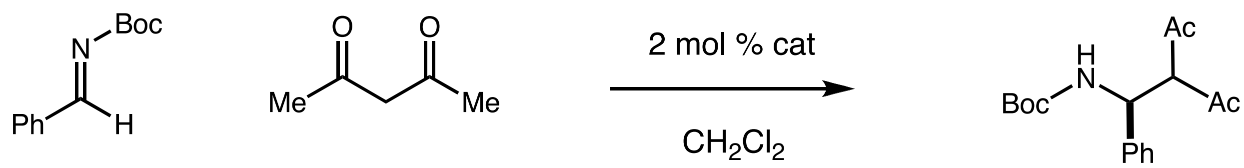
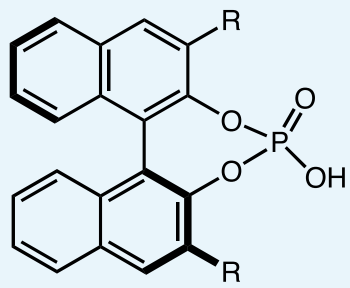
- 2004 Terada and Akiyama use as Brønsted acid catalyst

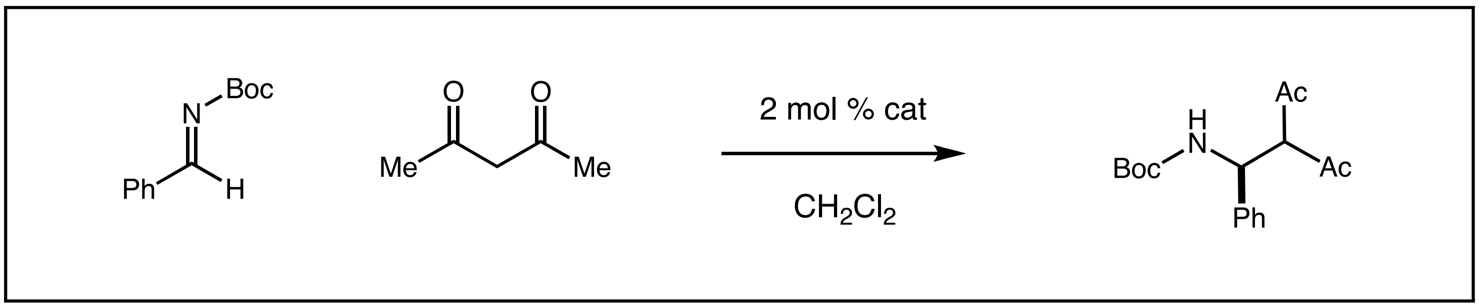


Akiyama, T.; Itoh, K.; Yokota, K.; Fuchibe, K. *Angew Chem. Int. Ed.* **2004**, *43*, 1566.
Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

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

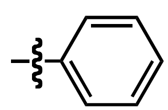


R =

H

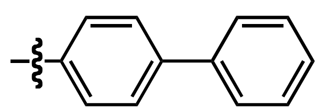
92% yield
12% ee

R =



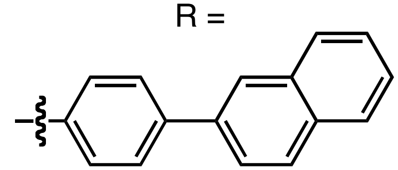
95% yield
56% ee

R =



88% yield
90% ee

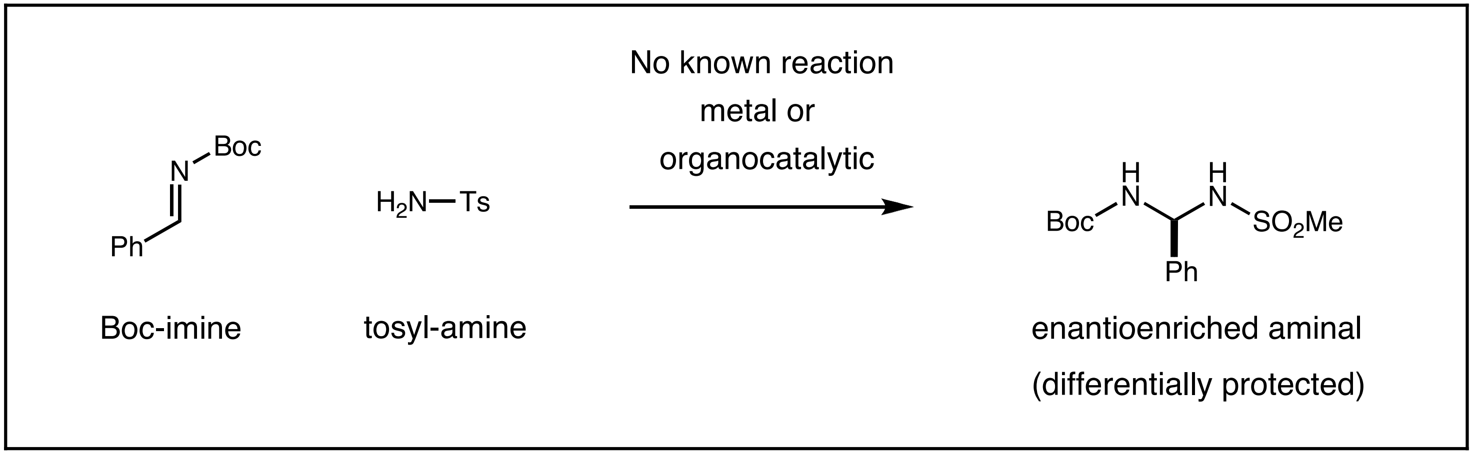
R =



99% yield
95% ee

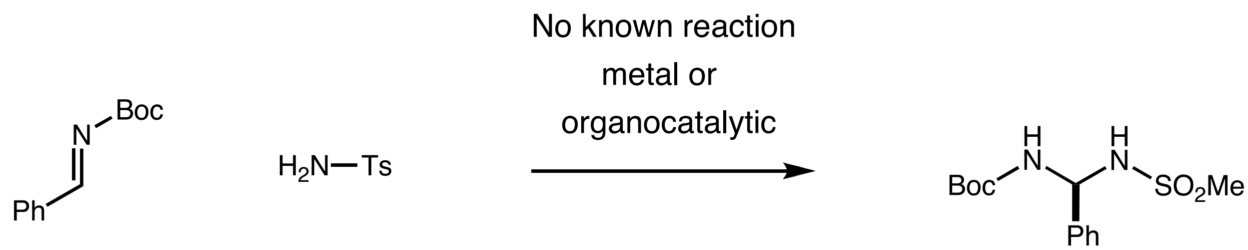
Akiyama, T.; Itoh, K.; Yokota, K.; Fuchibe, K. *Angew Chem. Int. Ed.* **2004**, *43*, 1566.
Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

New Reactivity – Imine Amination



Rowlan, G. B.; Zang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696.

New Reactivity – Imine Amination

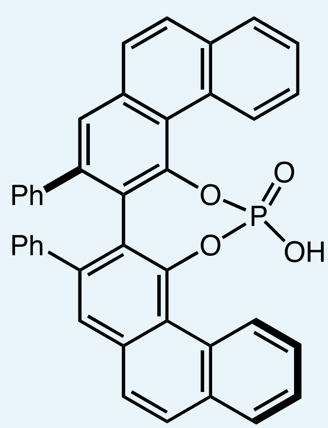


Boc-imine

tosyl-amine

enantioenriched aminal

(differentially protected)



(S)-VAPOL

5 mol % cat

Et_2O, 1 h, 21 °C

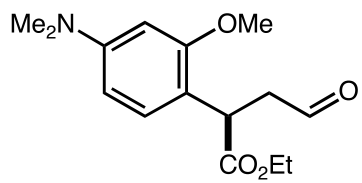
86% yield

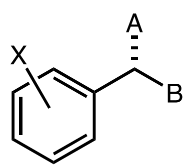
93% ee

Rowlan, G. B.; Zang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696.

Consideration of priviledged architecture and stereogenicity

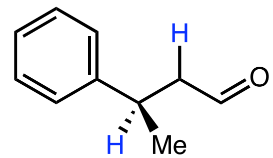
Friedel–Crafts

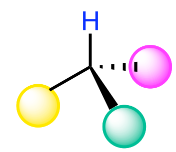




important chiral synthon

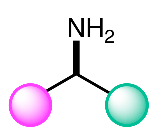
Transfer Hydrogenation





important chiral synthon

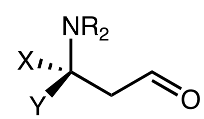
- Perhaps the most important stereogenicity for biomedical applications



biomedically relevant center

⇒

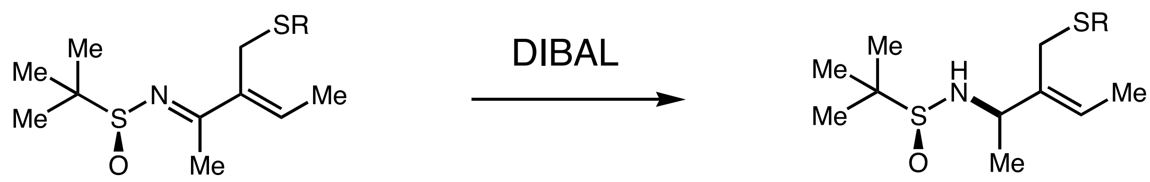
Amine conjugate addition



93–97% ee

There are vast technologies for the construction of amine stereogenicity

- Favourite: Ellman imine, most general–dogma breaking

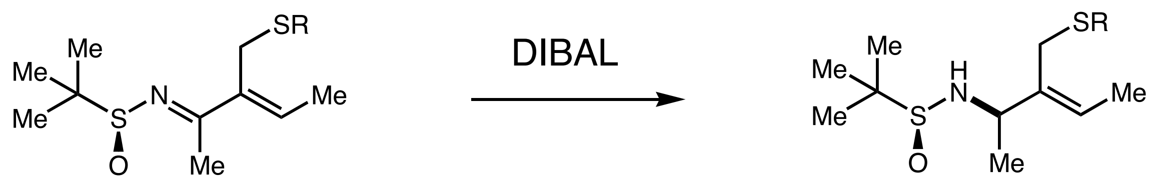


tert-butanesulfinamide

20:1 dr, 86% yield

There are vast technologies for the construction of amine stereogenicity

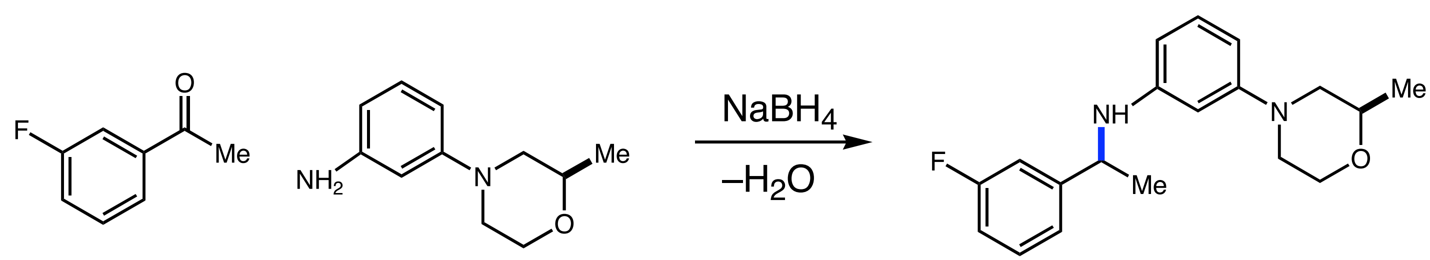
■ Favourite: Ellman imine, most general–dogma breaking



tert-butanesulfinamide

20:1 dr, 86% yield

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



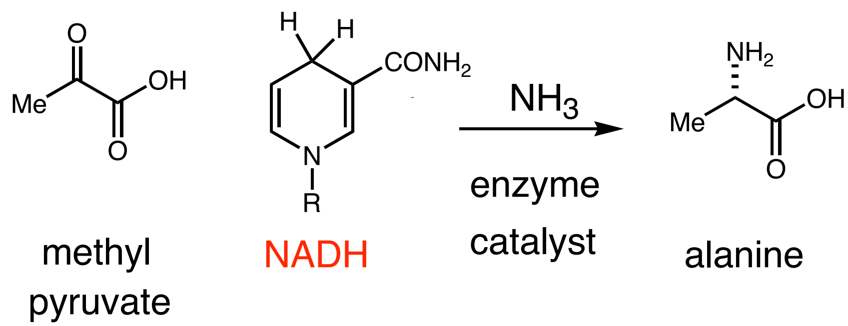
fragment 1

fragment 2

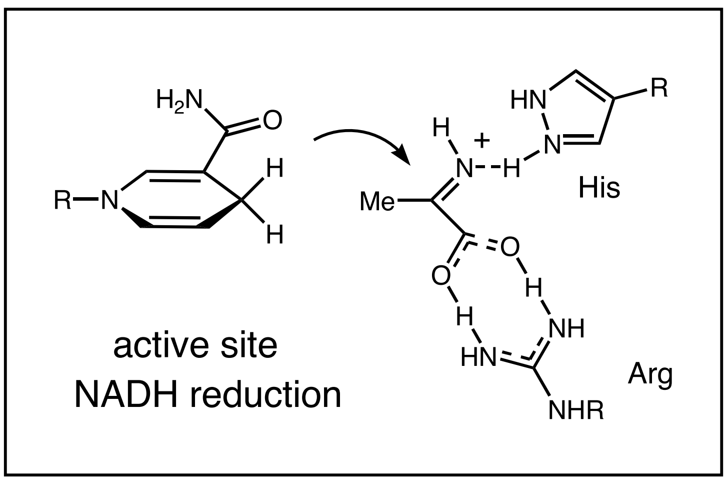
no enantioselective catalytic reductive amination-coupling

Organic Catalyzed Reductions in Biological Systems

■ NADH: Natures Reduction (Hydrogenation) Reagent (Coenzyme)



alanine transferase

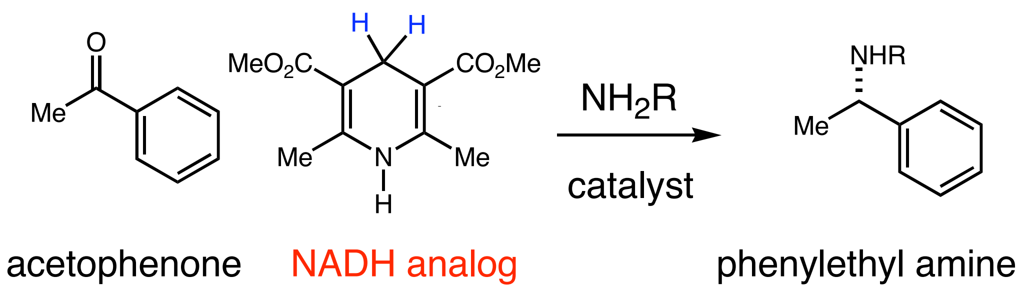


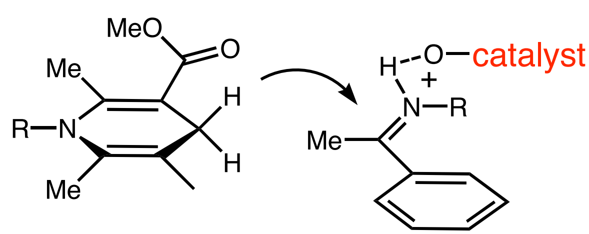
Selective reduction of pyruvate imines to create amino acids

Could this organocatalytic sequence be utilized in the redution of carbon–carbon double bonds

Organic Catalyzed Reductions in Laboratory Systems

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





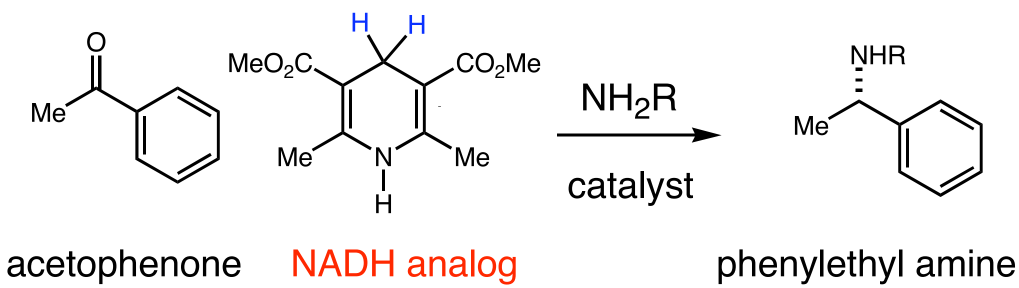
H-bonded or Bronsted acid organic iminium reduction

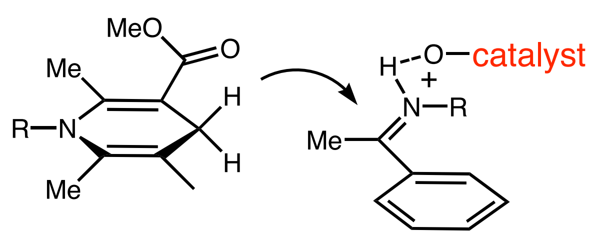
Can we translate a biochemical concept to a laboratory reaction

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

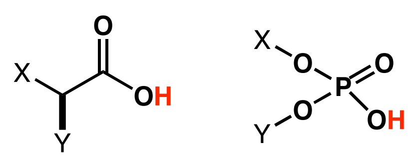




H-bonded or Bronsted acid

organic iminium reduction

catalyst



simple carboxylic

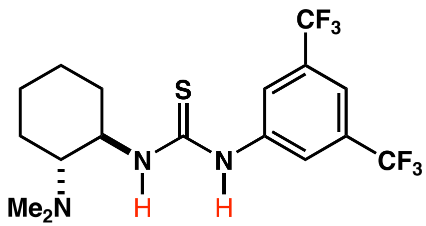
or phosphonic acids

Can we translate a biochemical concept to a laboratory reaction

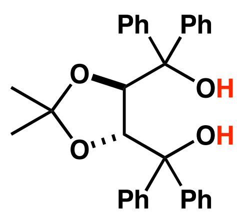
Can we develop a useful transformation on the basis of established Bronsted acid catalysts

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

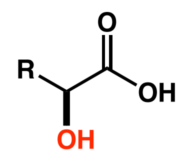
■ Pioneers



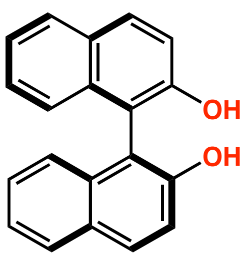
Jacobsen



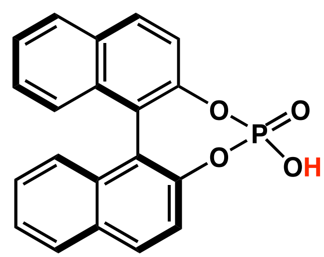
Rawal



Yamamoto

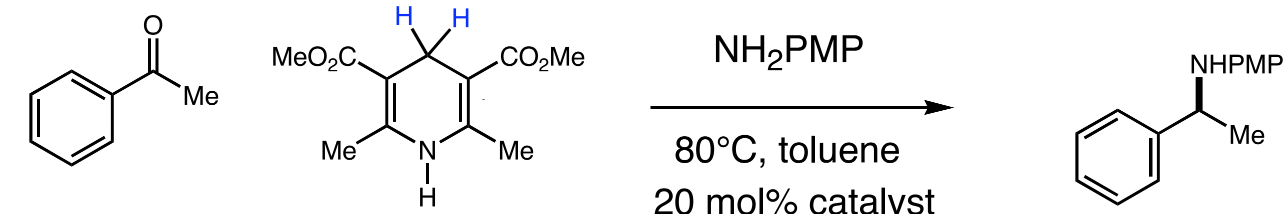


Schaus



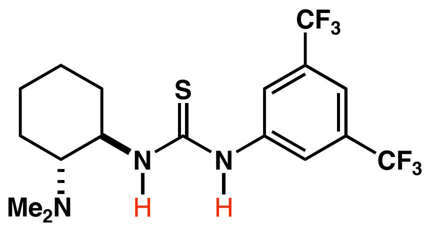
Akiyama, Terada

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

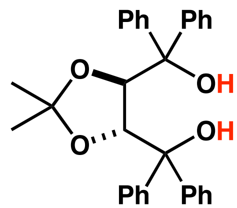


acetophenone

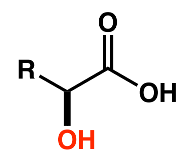
Pioneers



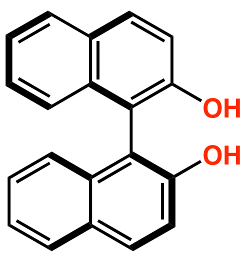
Jacobsen



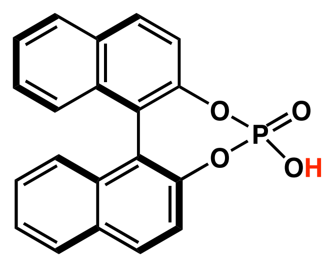
Rawal



Yamamoto

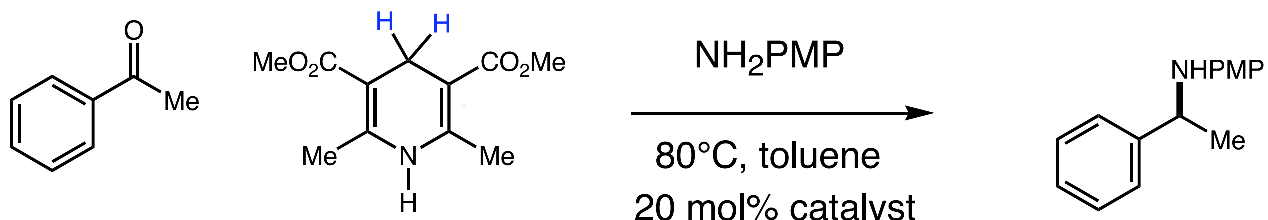


Schaus



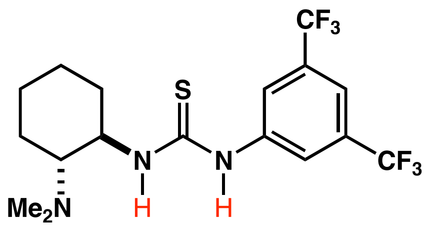
Akiyama, Terada

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



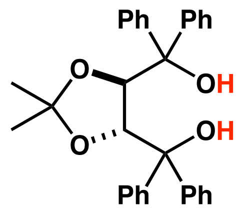
acetophenone

Pioneers



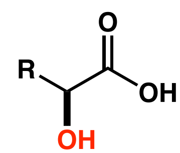
Jacobsen

No reaction



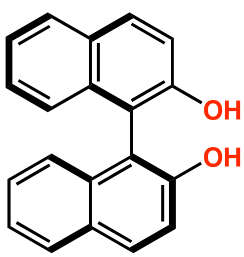
Rawal

No reaction



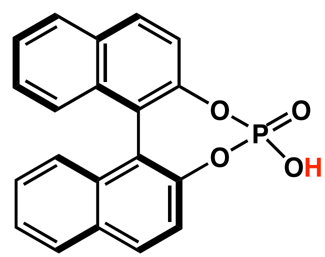
Yamamoto

No reaction



Schaus

No reaction

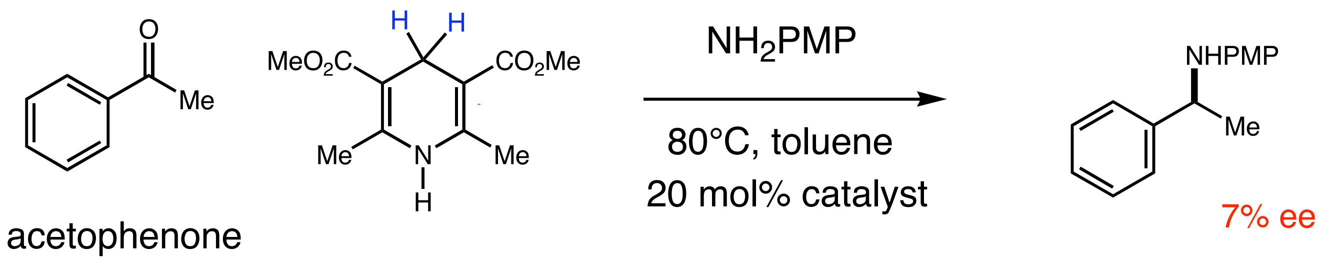


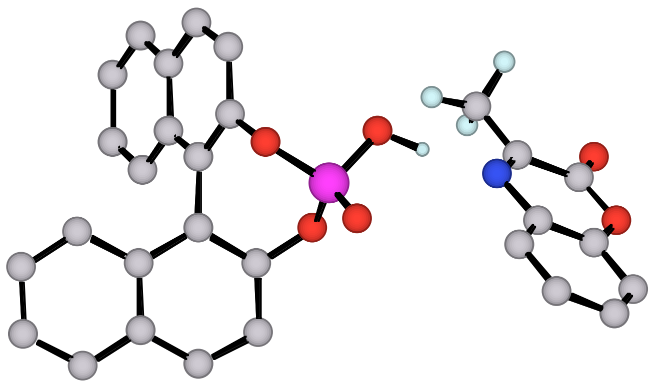
Akiyama, Terada

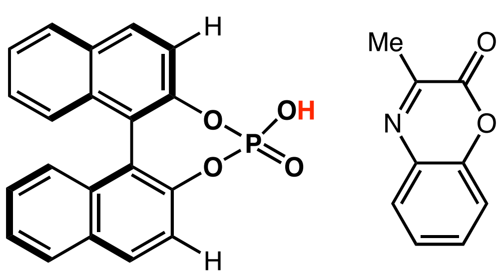
43% yield

7%ee

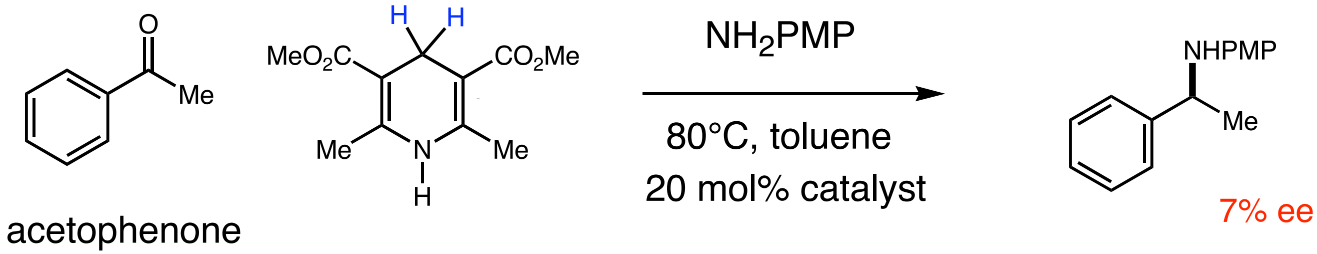
Attempts to develop a Bronsted Acid Catalyst for Reductive Amination

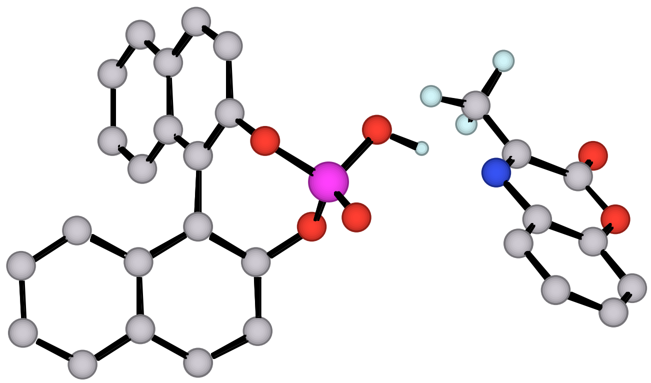


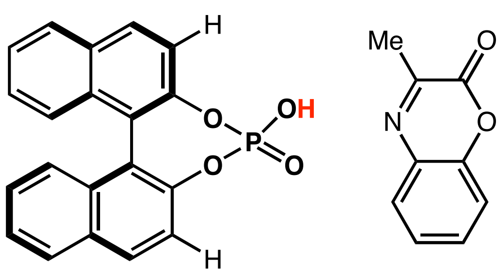


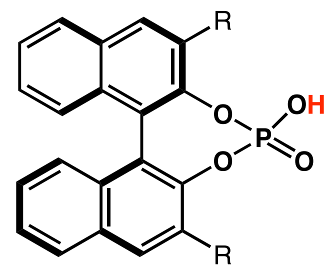


Attempts to develop a Bronsted Acid Catalyst for Reductive Amination



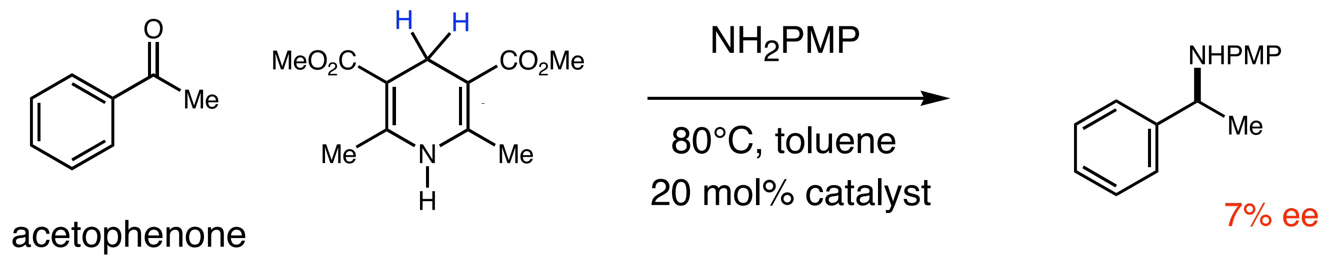


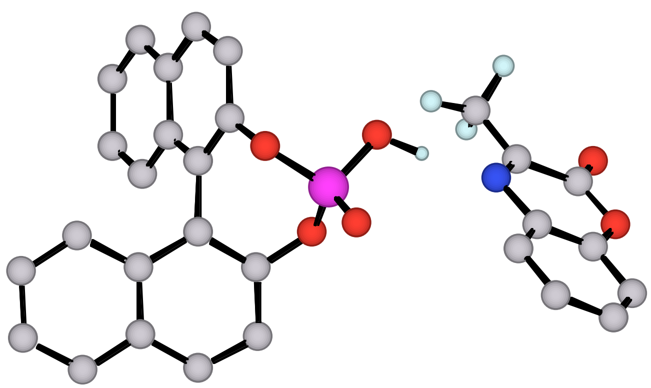


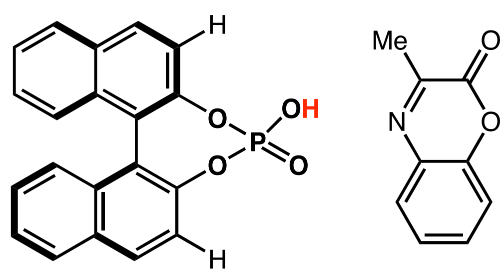


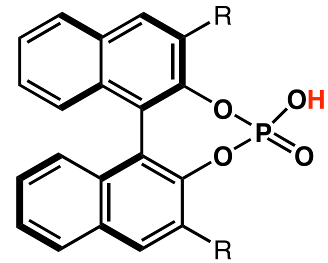
R	Yield	%ee

Attempts to develop a Bronsted Acid Catalyst for Reductive Amination



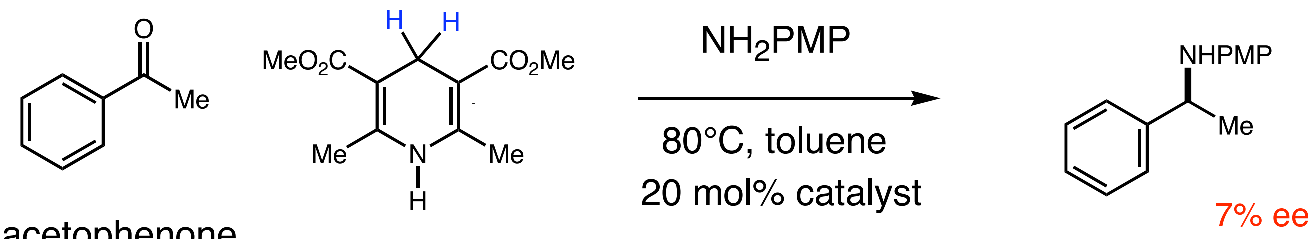




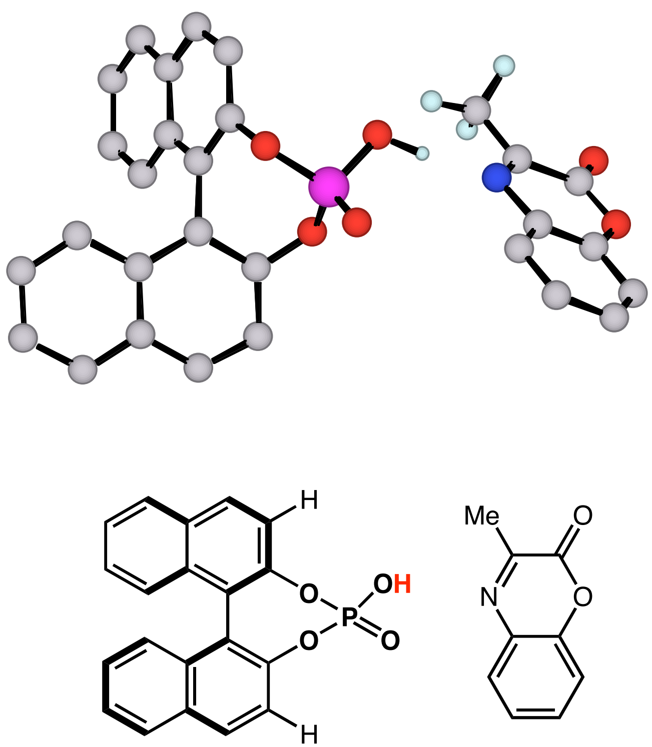


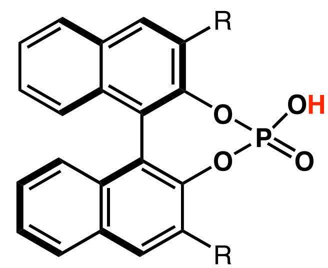
R	Yield	%ee
H	43	7
$Ph(NO_2)_2$	45	16
$Ph(CF_3)_2$	39	65
2-Nap	56	40

Attempts to develop a Bronsted Acid Catalyst for Reductive Amination



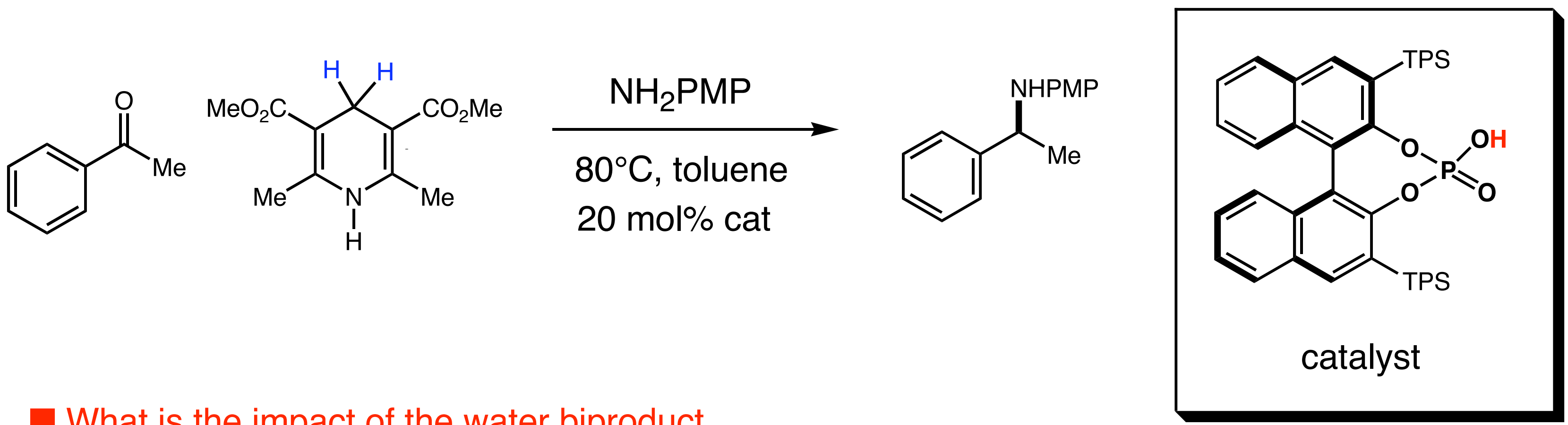
acetophenone





R	Yield	%ee
H	43	7
$Ph(NO_2)_2$	45	16
$Ph(CF_3)_2$	39	65
2-Nap	56	40
Ph_3Si	90	85

The impact of additives and temperature on the reductive amination

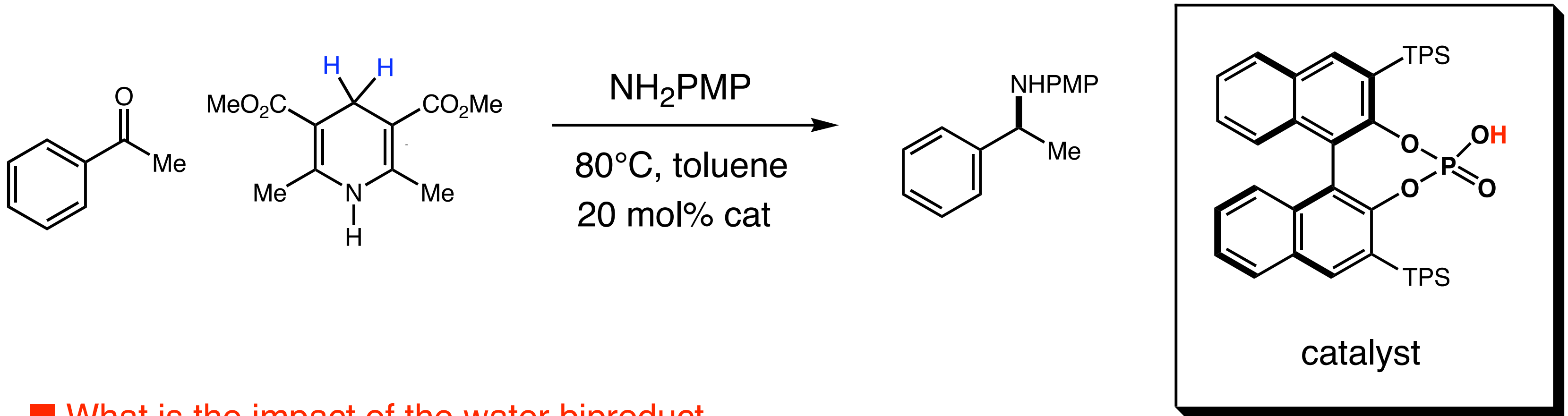


■ What is the impact of the water biproduct

additive	Time	Yield	%ee
--	28 h	90	85
H_2O (1eq)	72 h	35	77
H_2O (2eq)	72 h	<10	72
$MgSO_4$	20 h	79	83
Na_2SO_4	36 h	83	85

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

The impact of additives and temperature on the reductive amination



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additive	Time	Yield	%ee
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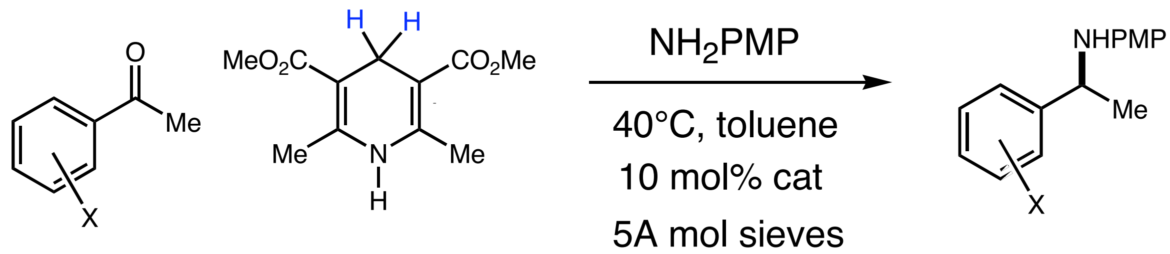
H_2O (1eq)	72 h	35	77
H_2O (2eq)	72 h	<10	72
$MgSO_4$	20 h	79	83
Na_2SO_4	36 h	83	85
5A mol sieves	6 h	85	90

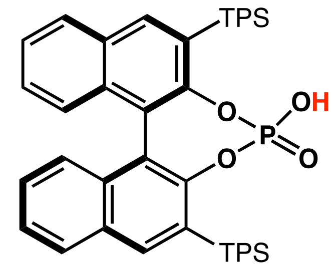
⇨

Temp	Time	Yield	%ee
80°	6 h	85	90
60°	22 h	90	93
40°	36 h	86	95

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

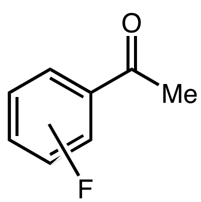
The scope of the reductive amination with respect to aryl ketones



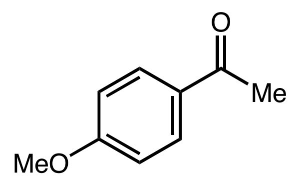


catalyst

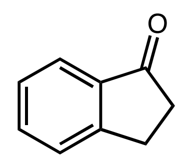
■ Scope of the ketone component



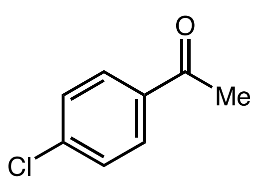
(o) 83% ee
(m) 95% ee
(p) 94% ee
60-85% yield



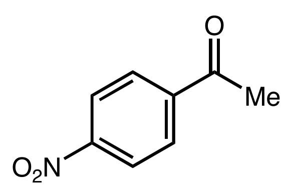
90% ee
77% yield



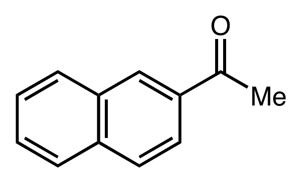
85% ee
75% yield



95% ee
75% yield



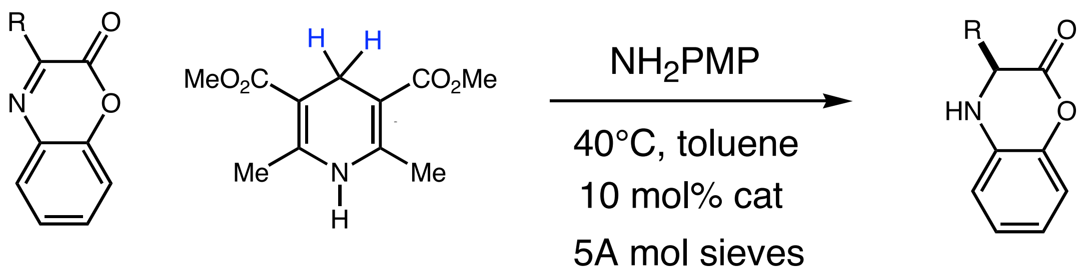
95% ee
71% yield

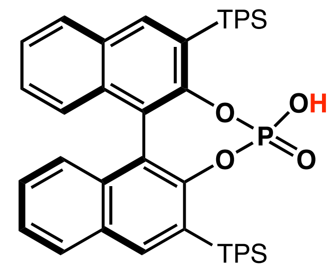


96% ee
73% yield

■ Are there other systems that are successful in this transformation?

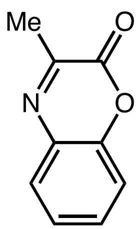
The scope of the reductive amination





catalyst

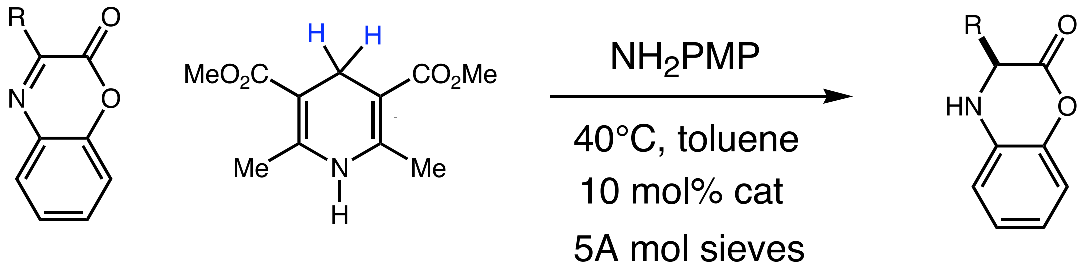
■ Scope of the ketone-ketimine component

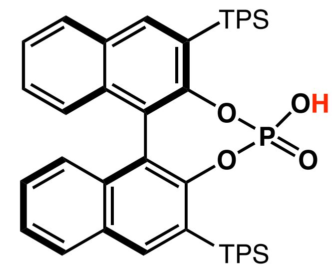


97% ee

82% yield

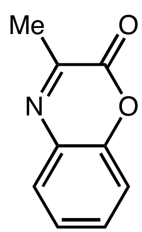
The scope of the reductive amination





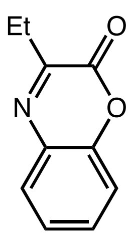
catalyst

Scope of the ketone-ketimine component



97% ee

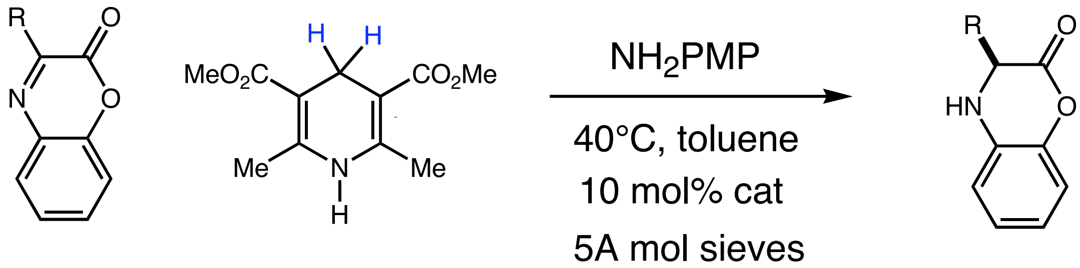
82% yield

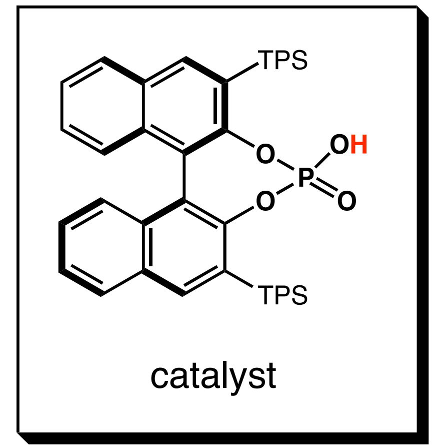


79% ee

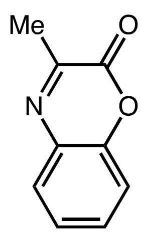
27% yield

The scope of the reductive amination

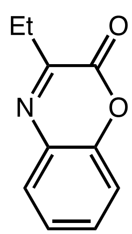




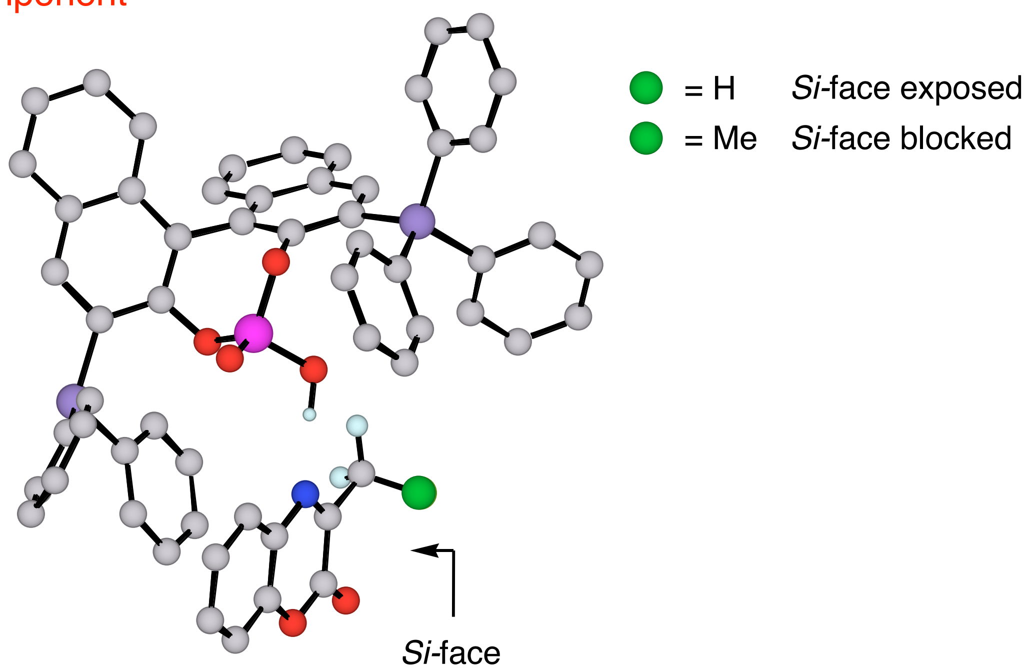
■ Scope of the ketone-ketimine component



97% ee
82% yield

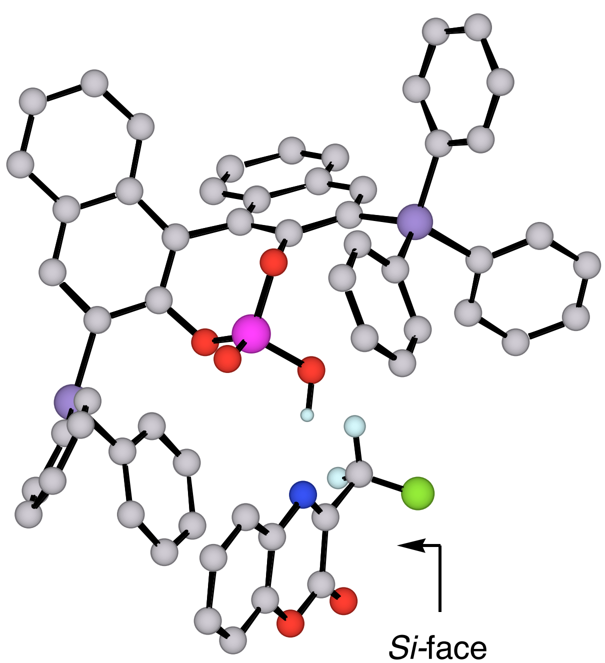


79% ee
27% yield



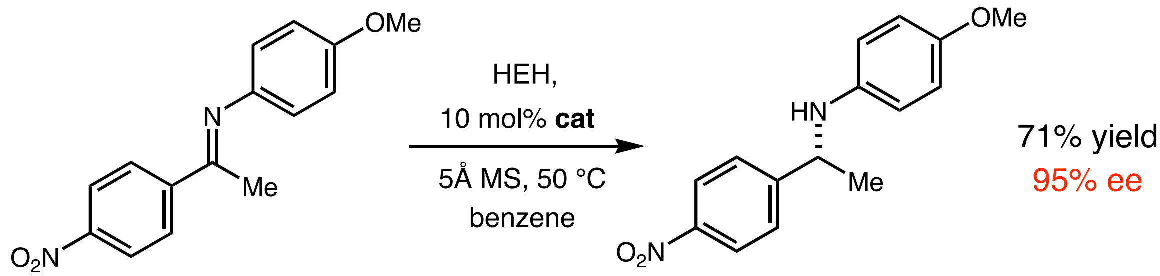
■ Stereochemical models are in accord with the observed reactivity

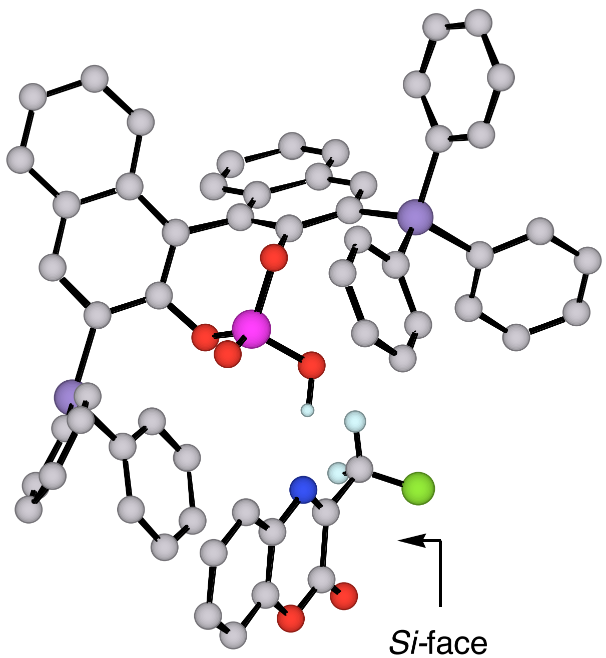
MM3-Calculations Provide Good Prediction of Asymmetric Environment

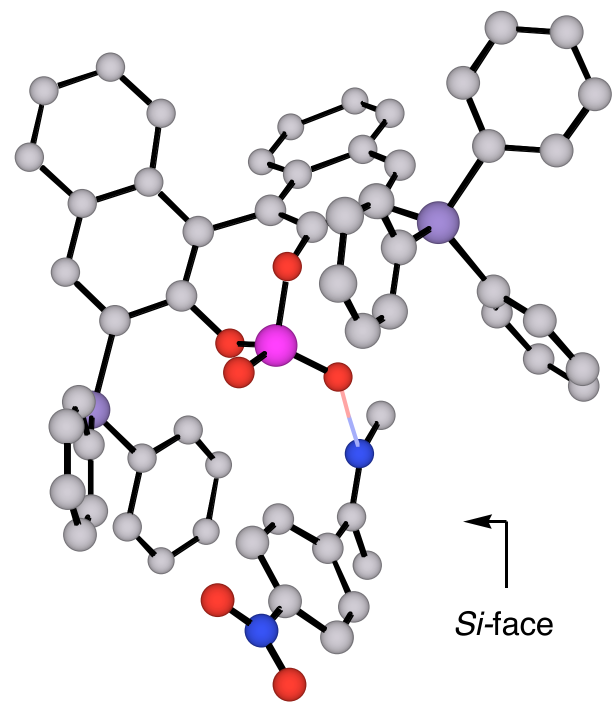


MM3-structure

MM3-Calculations Provide Good Prediction of Asymmetric Environment



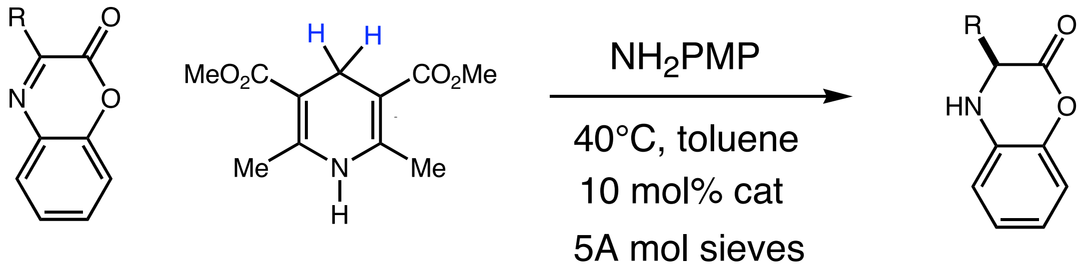


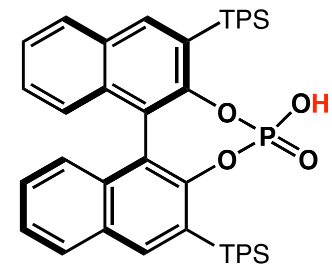


MM3-structure

X-ray structure Crystal grown in toluene at –20 ˚C in glove box

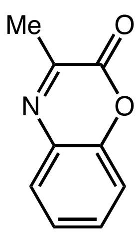
The scope of the reductive amination



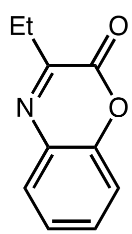


catalyst

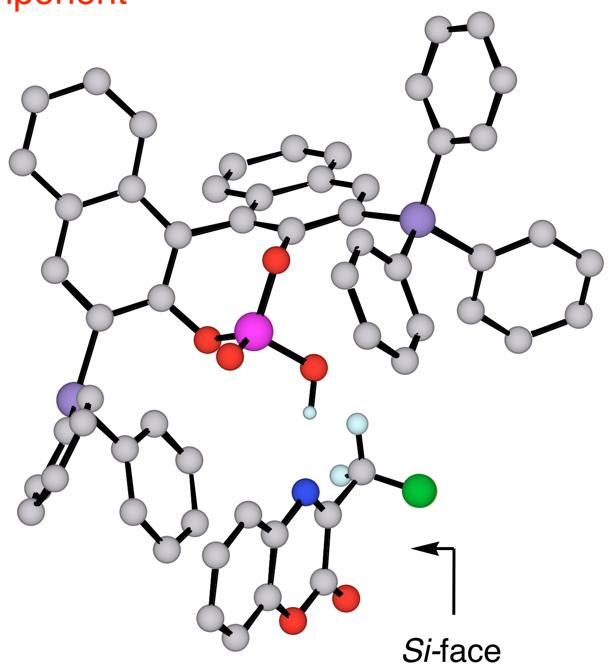
■ Scope of the ketone-ketimine component



97% ee
82% yield



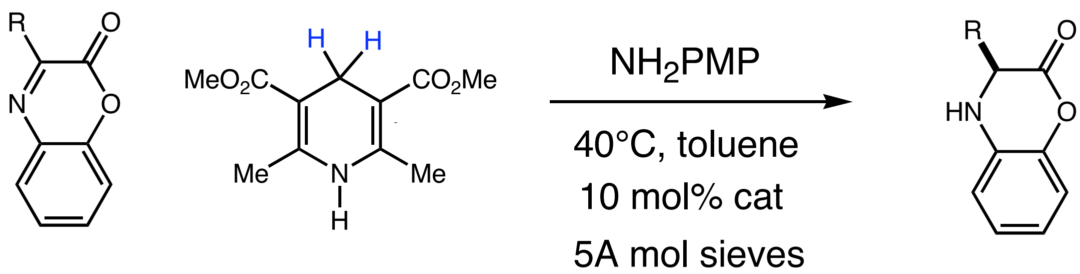
79% ee
27% yield

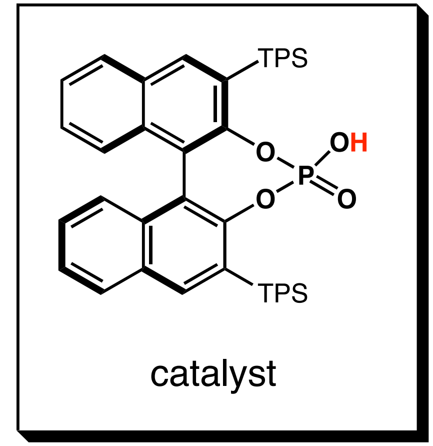


= H *Si*-face exposed
= Me *Si*-face blocked

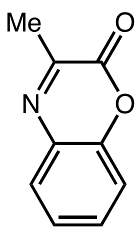
■ Stereochemical models are in accord with the observed reactivity

The scope of the reductive amination

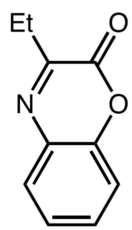




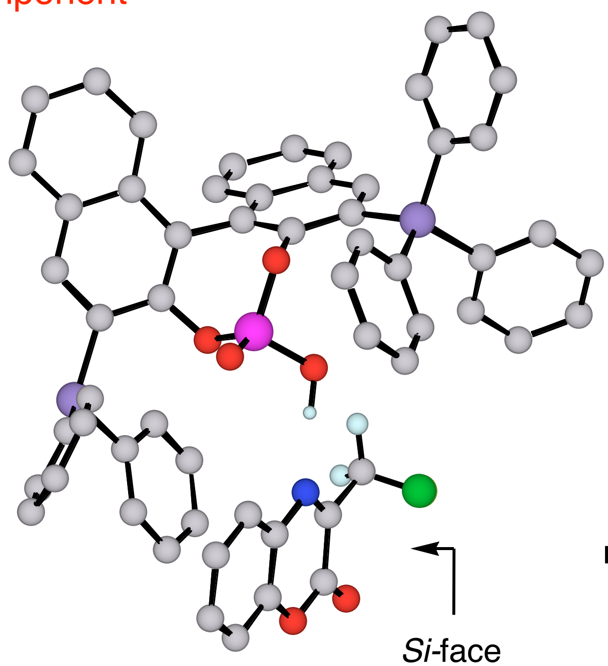
■ Scope of the ketone-ketimine component



97% ee
82% yield



79% ee
27% yield

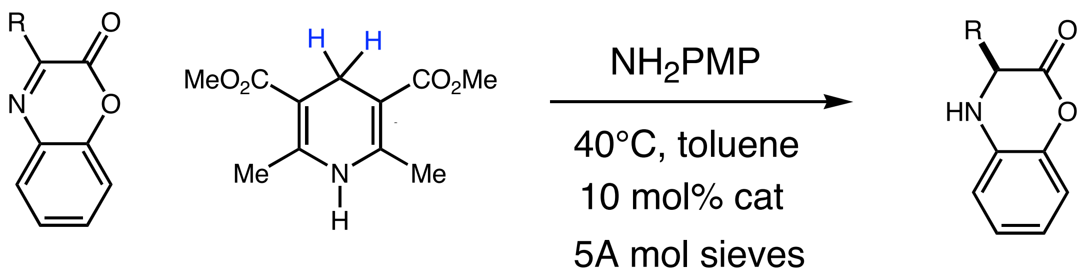


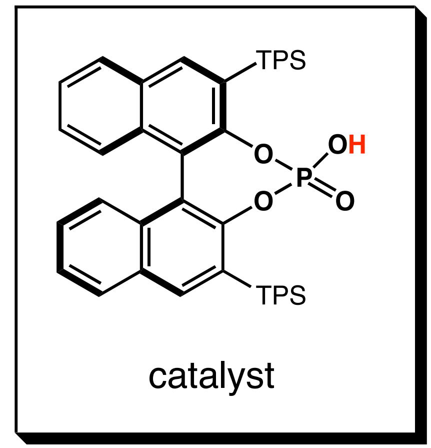
● = H *Si*-face exposed
● = Me *Si*-face blocked

⇨ **selective for methyl versus ethyl ketones**

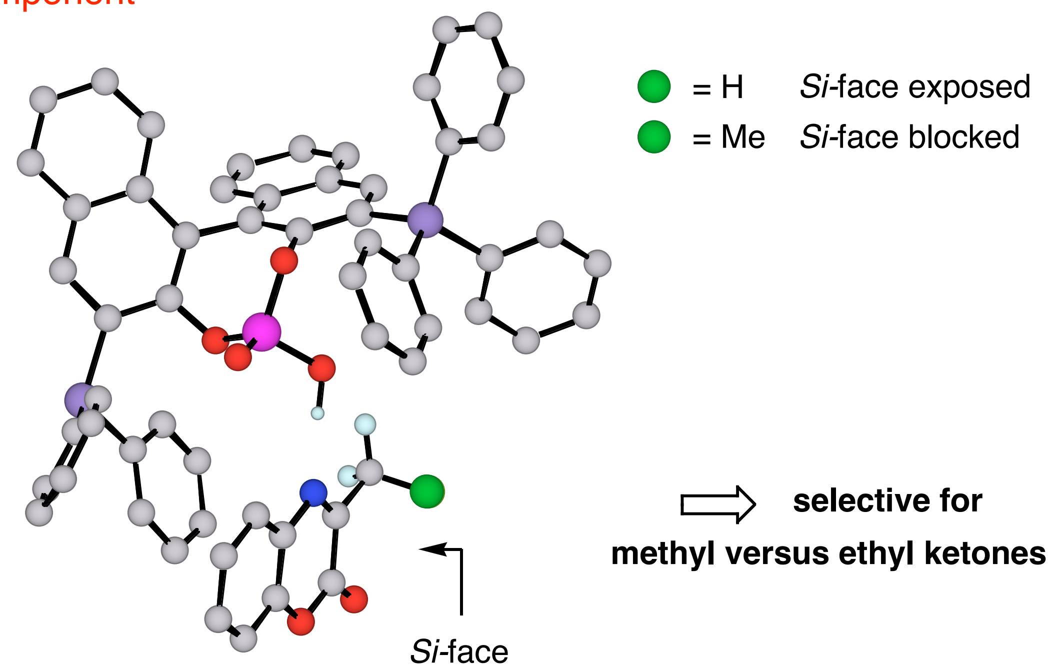
■ Stereochemical models are in accord with the observed reactivity

The scope of the reductive amination



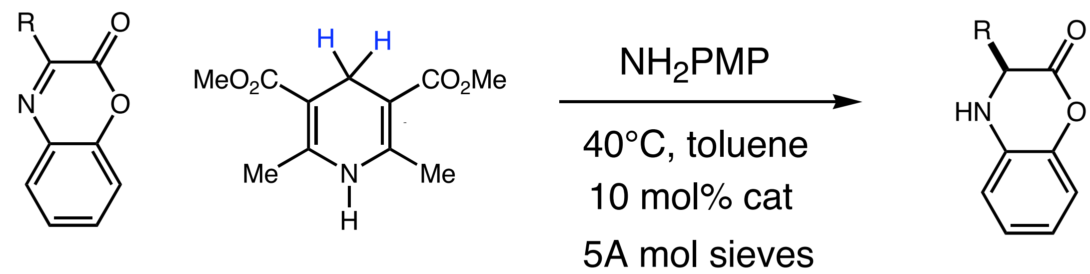


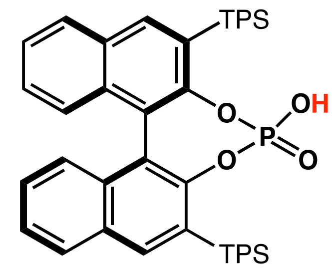
■ Scope of the ketone-ketimine component



■ Stereochemical models are in accord with the observed reactivity

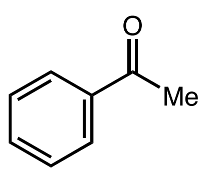
The scope of the reductive amination





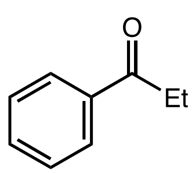
catalyst

■ Scope of the ketone-ketimine component



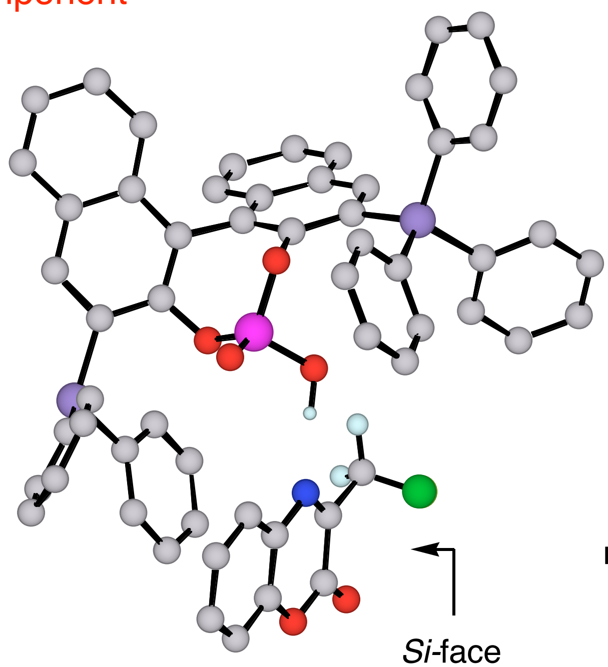
93% ee

87% yield



ND % ee

<15% yield



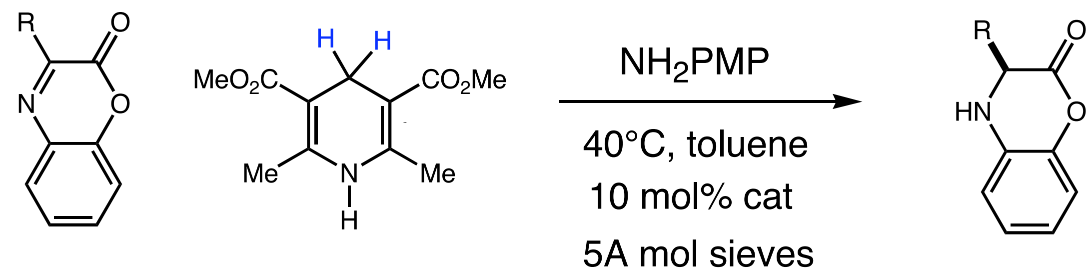
● = H *Si*-face exposed

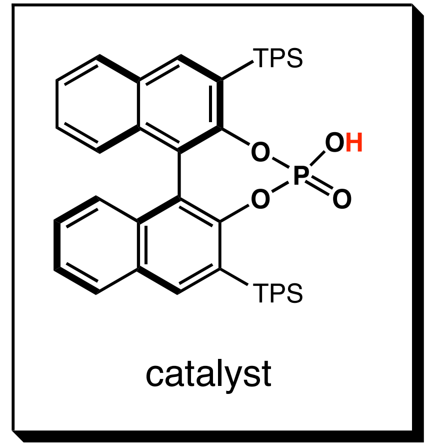
● = Me *Si*-face blocked

⇨ **selective for methyl versus ethyl ketones**

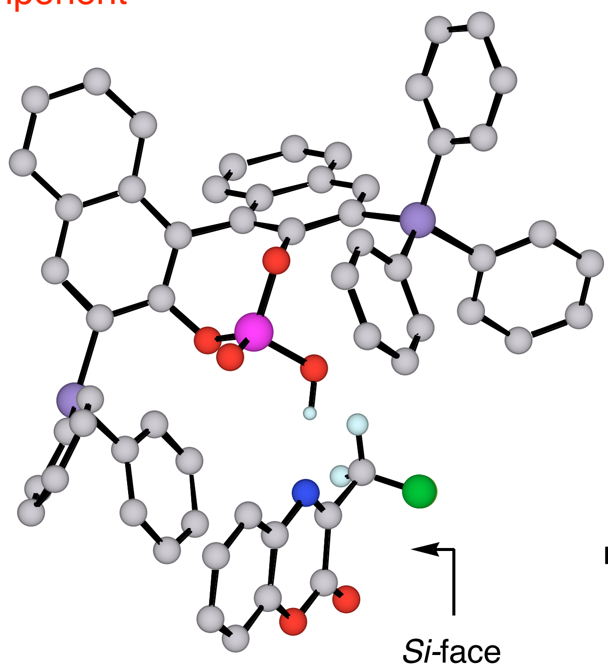
■ Stereochemical models are in accord with the observed reactivity

The scope of the reductive amination





■ Scope of the ketone-ketimine component



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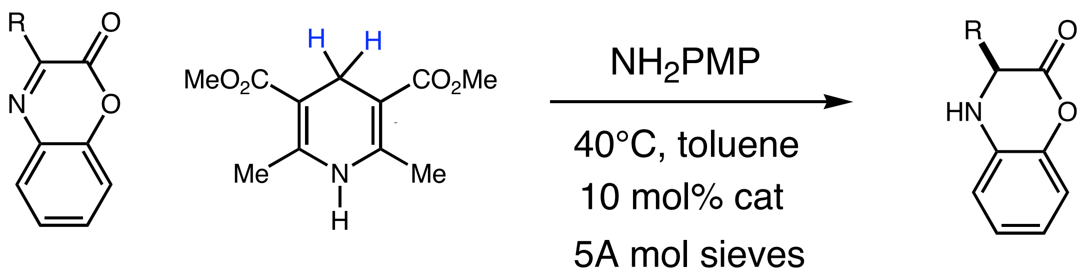
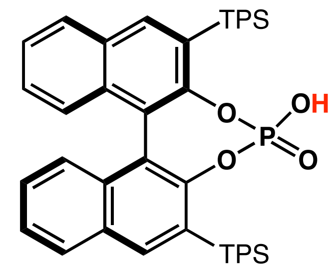
■ Stereochemical models are in accord with the observed reactivity

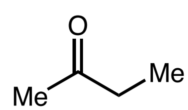
The scope of the reductive amination





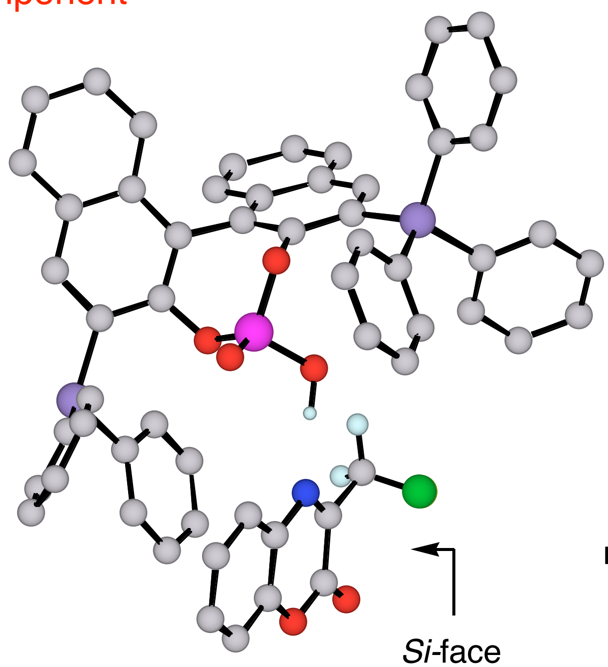
catalyst

■ Scope of the ketone-ketimine component



2-butanone

Me vs Et
on the same substrate

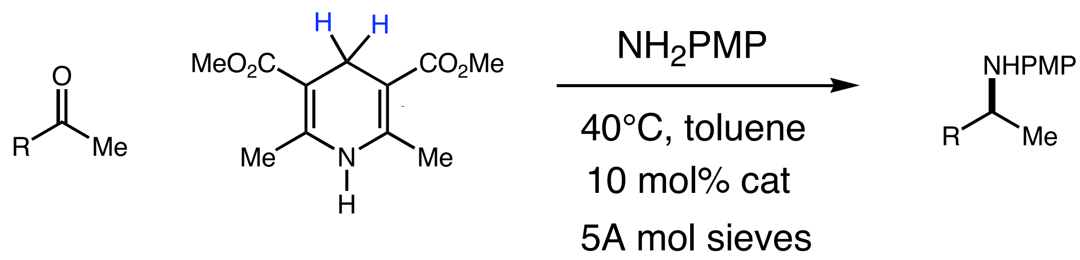


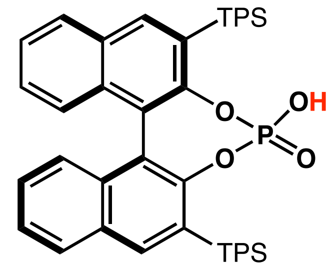
● = H *Si*-face exposed
● = Me *Si*-face blocked

⇨ **selective for**
methyl versus ethyl ketones

■ Stereochemical models are in accord with the observed reactivity

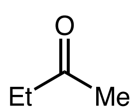
The scope of the reductive amination: alkyl ketones





catalyst

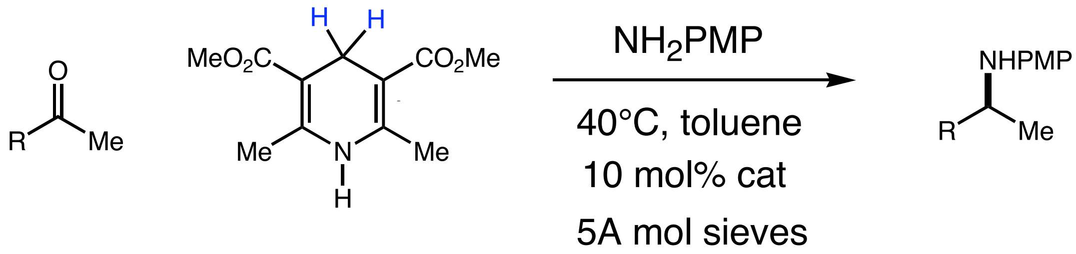
■ Scope of the alkyl ketone component

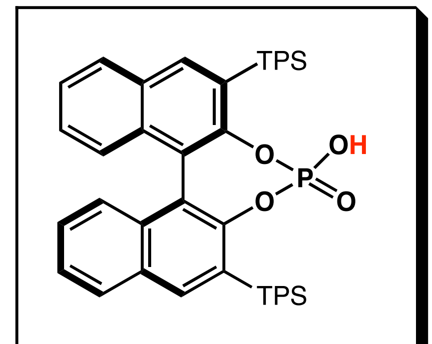


91% ee

71% yield

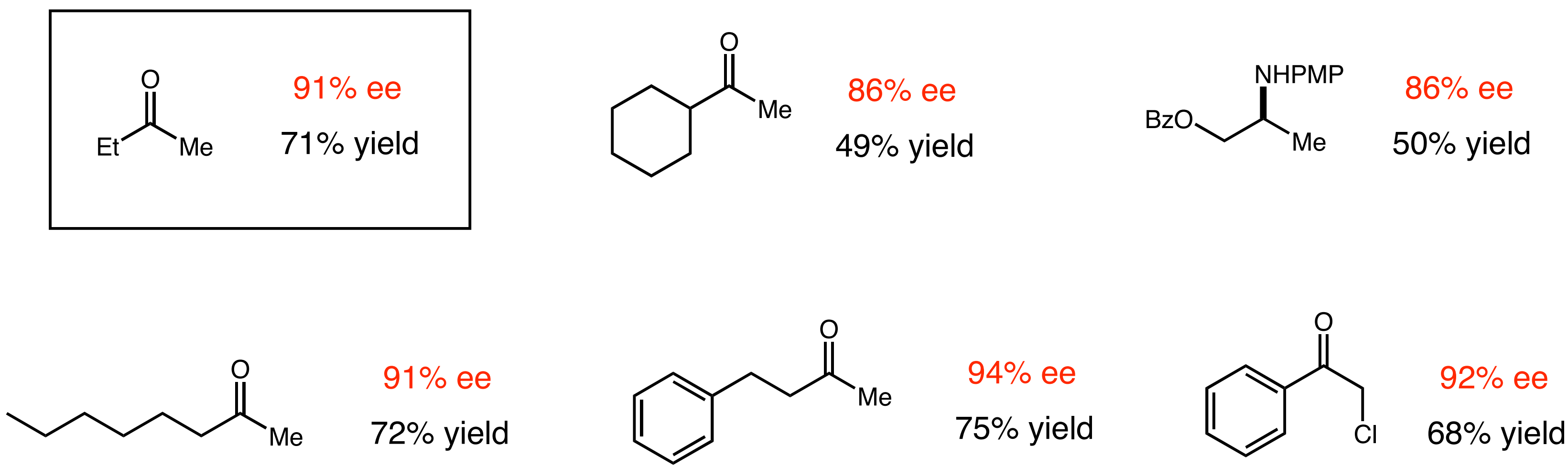
The scope of the reductive amination: alkyl ketones





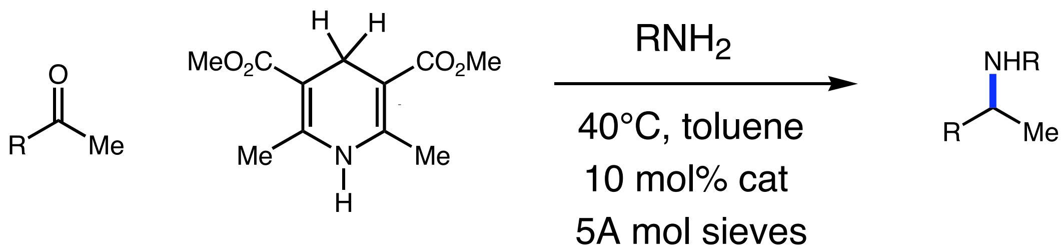
catalyst

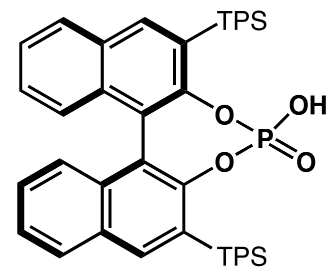
■ Scope of the alkyl ketone component



■ This reductive amination process appears to be general for methyl ketones

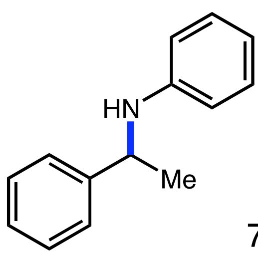
The scope of the reductive amination: aryl amines





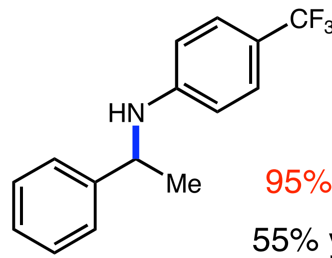
catalyst

■ Scope of the amine component



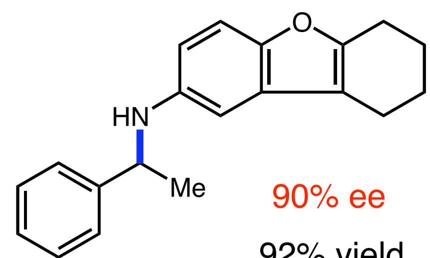
93% ee

73% yield



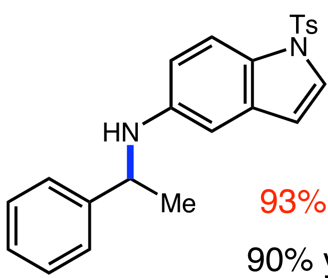
95% ee

55% yield



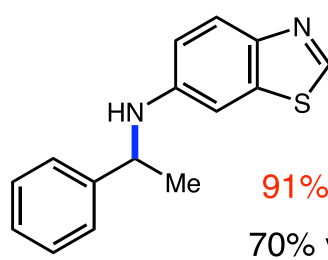
90% ee

92% yield



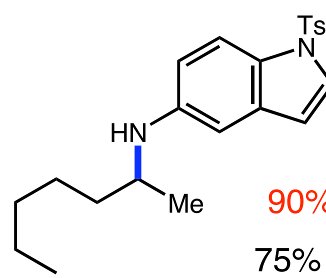
93% ee

90% yield



91% ee

70% yield



90% ee

75% yield

With Storer, Carrera, Ni. *J. Am. Chem. Soc.* **2006,** *128*, 84

Activation Modes Are Enabled by Priviledged Catalyst Achitectures

Catalysis Platform / Concept

MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

Activation Modes Are Enabled by Priviledged Catalyst Achitectures

Catalysis Platform / Concept

Activation Modes

MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

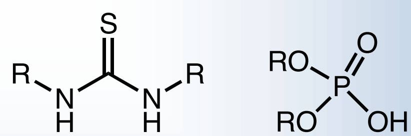
Activation Modes Are Enabled by Priviledged Catalyst Achitectures

Catalysis Platform / Concept

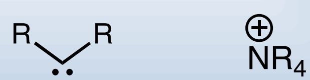
Activation Modes

⇒

Catalyst Design



H-Bonding, Brønsted Acids



Carbene, Phase Transfer

MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

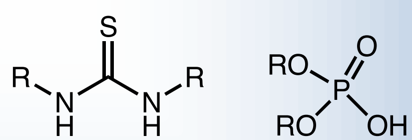
Activation Modes Are Enabled by Priviledged Catalyst Achitectures

Catalysis Platform / Concept

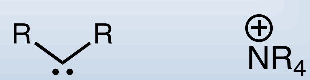
Activation Modes

⇨

Catalyst Design



H-Bonding, Brønsted Acids



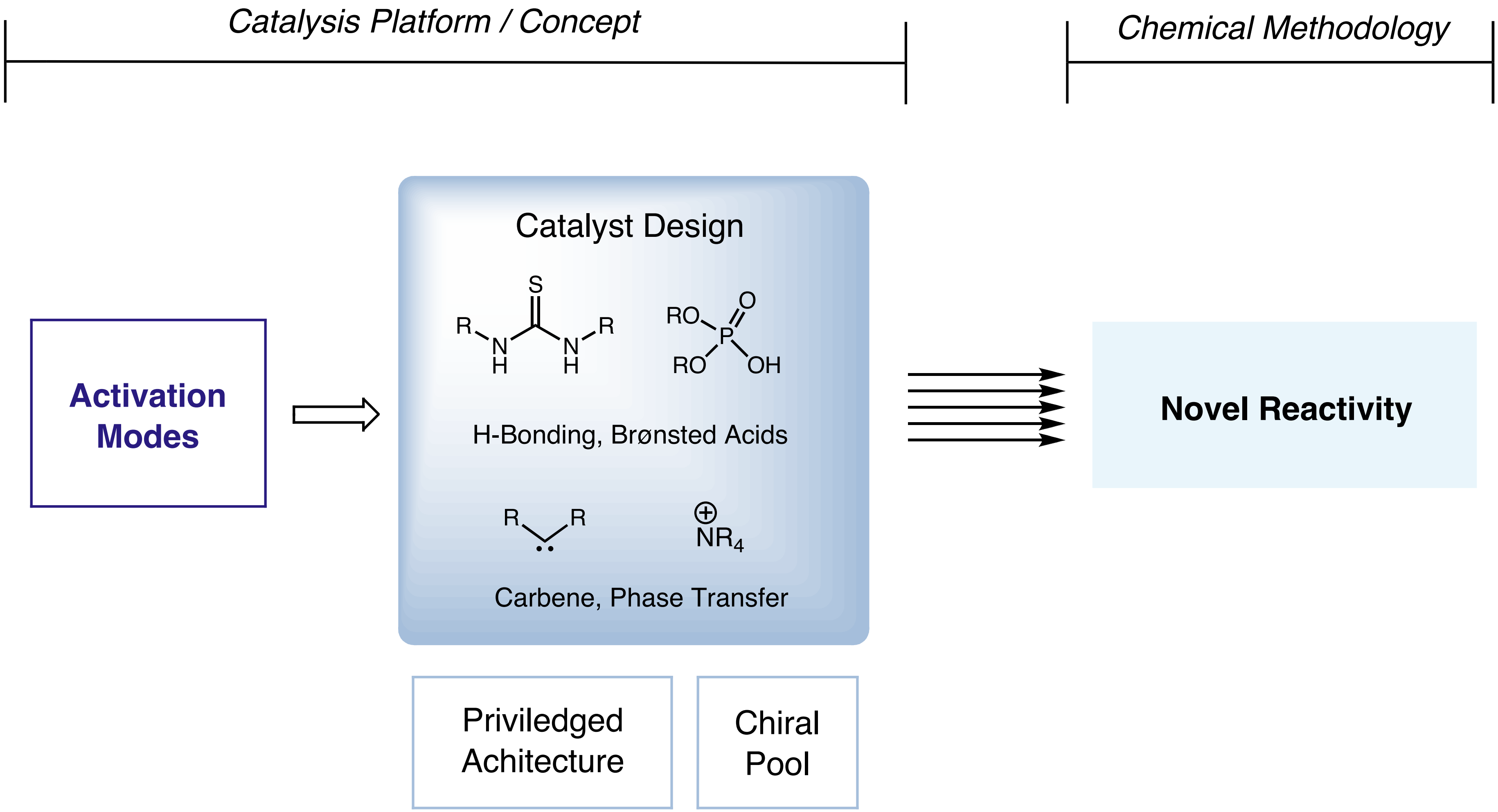
Carbene, Phase Transfer

Priviledged Achitecture

Chiral Pool

MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

Activation Modes Are Enabled by Priviledged Catalyst Achitectures



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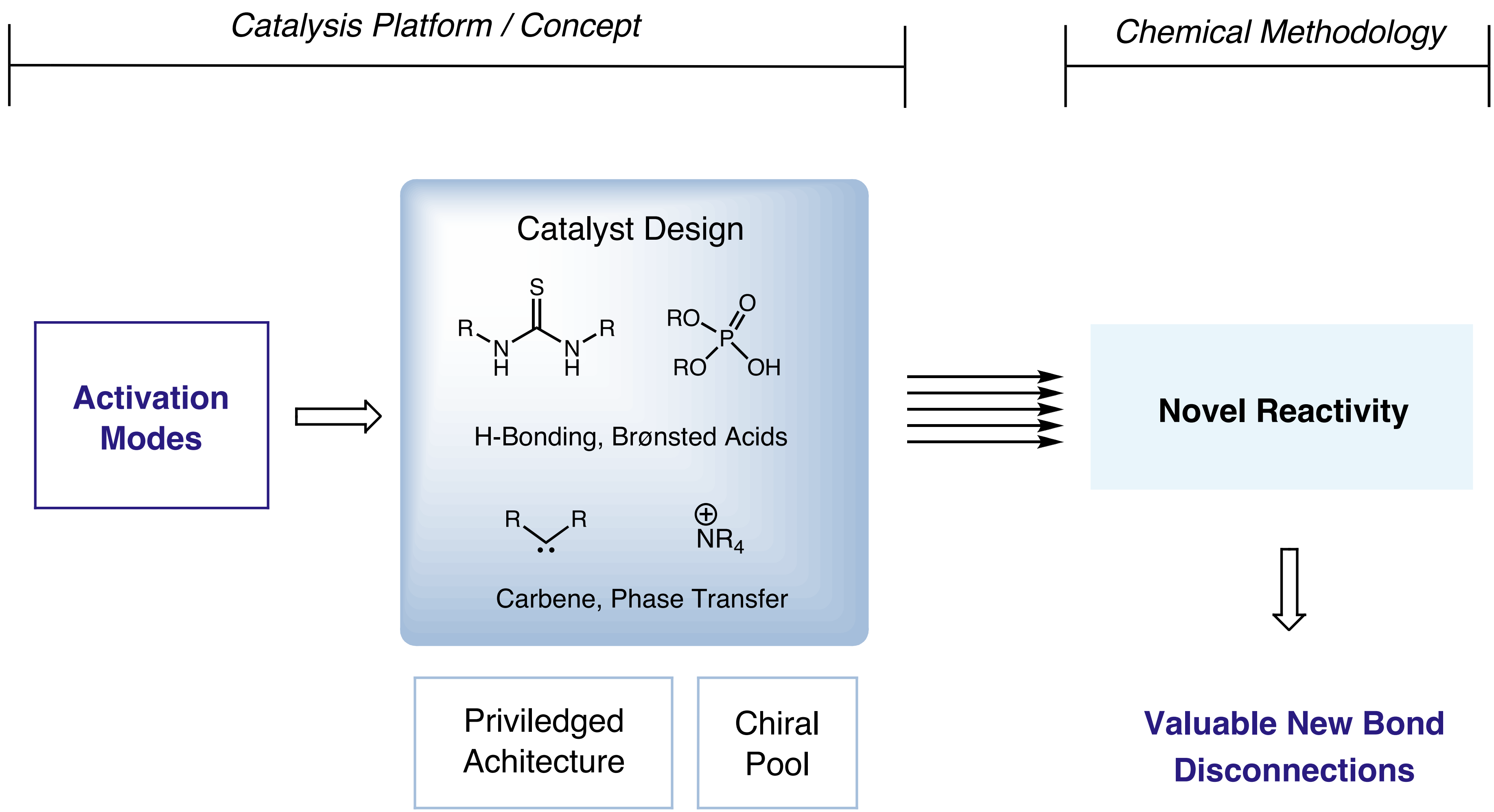
Activation Modes Are Enabled by Priviledged Catalyst Achitectures



MacMillan, D. W. C. *Nature* **2008**, *455*, 304.