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GIESSEN

Organocatalytic Additions to C=X Bonds (X=O, C, and NR)

Zhiguo Zhang

09.05.2008, Gießen

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Overview

- Introduction
- Design and synthesis of thiourea-based organocatalysts
- Applications of thiourea-based organocatalysts
  - Organocatalytic reductions
  - Cyanosilylation of ketone
  - Hydrophosphonylation
- Asymmetric reduction of ketimines with $HSiCl_3$

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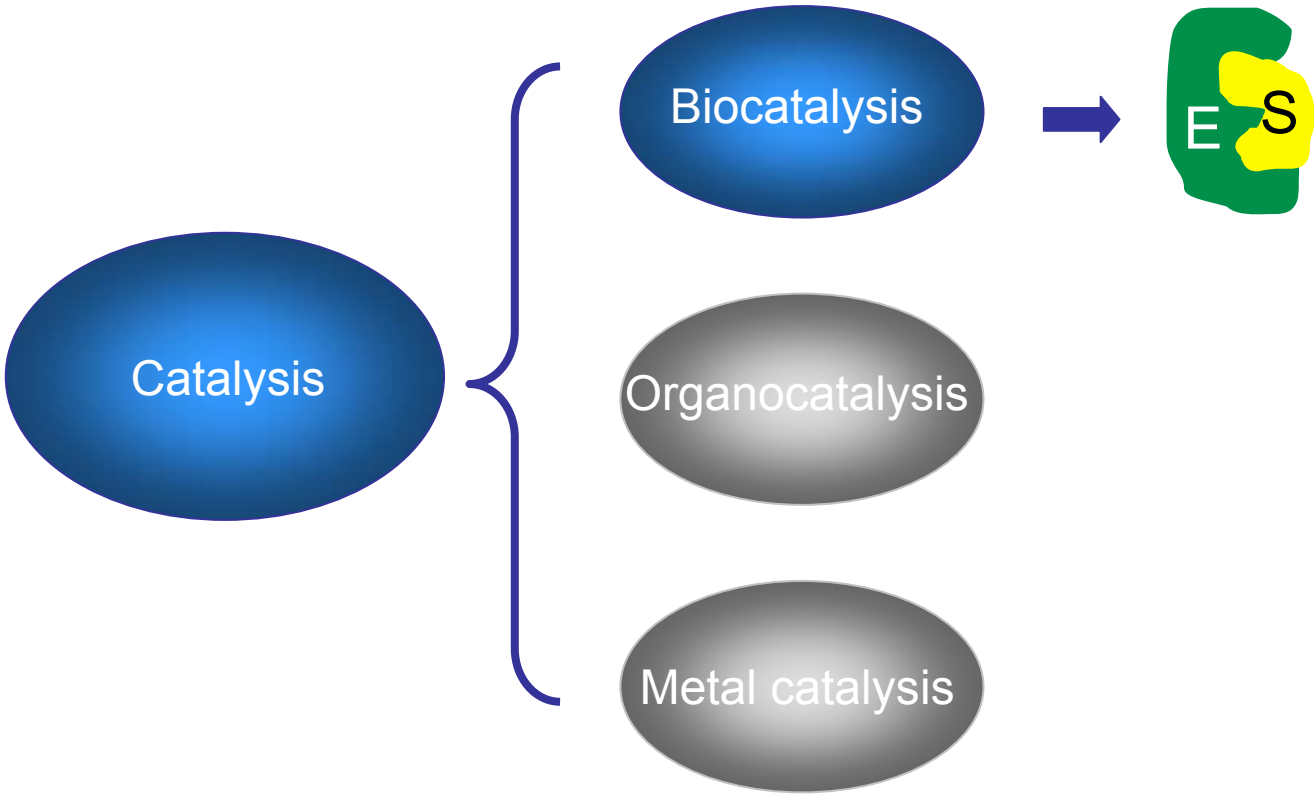
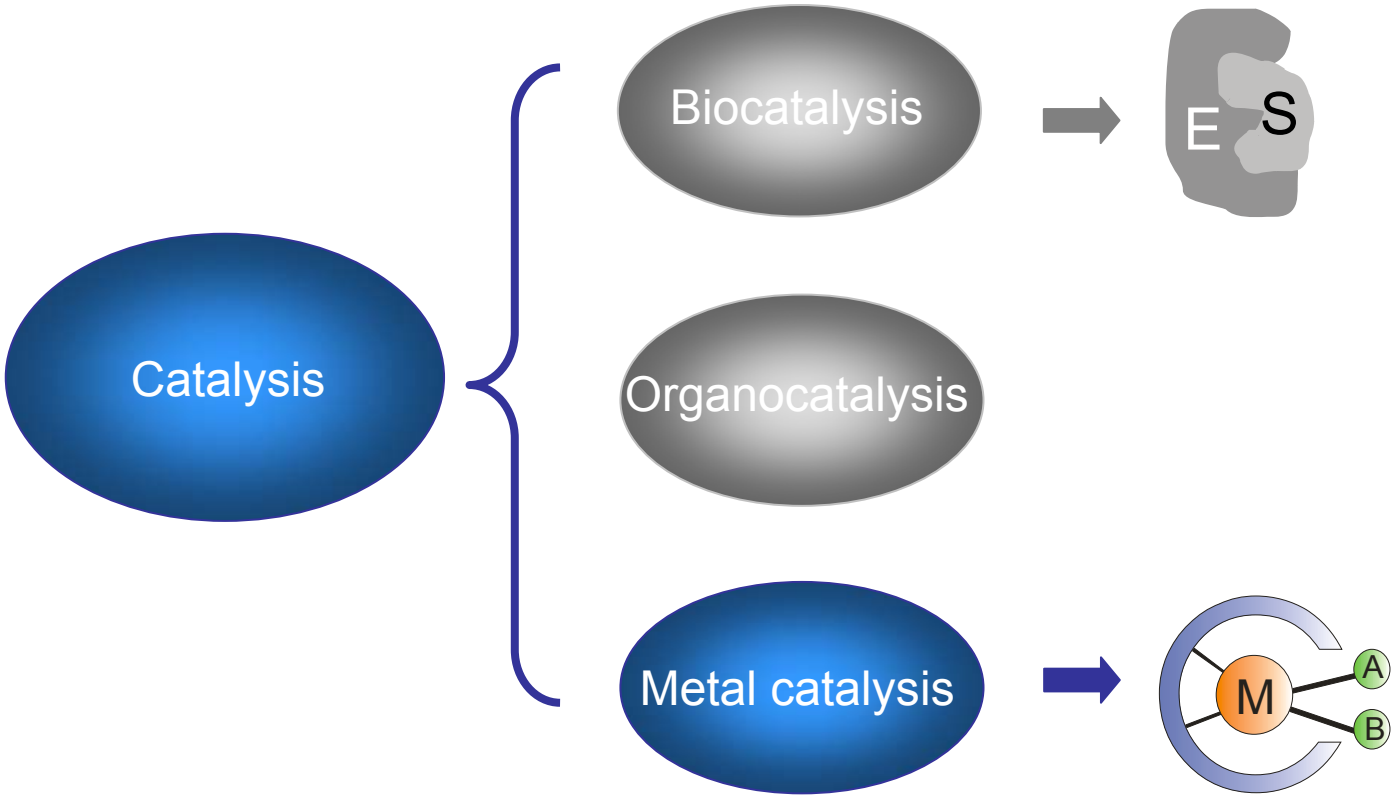
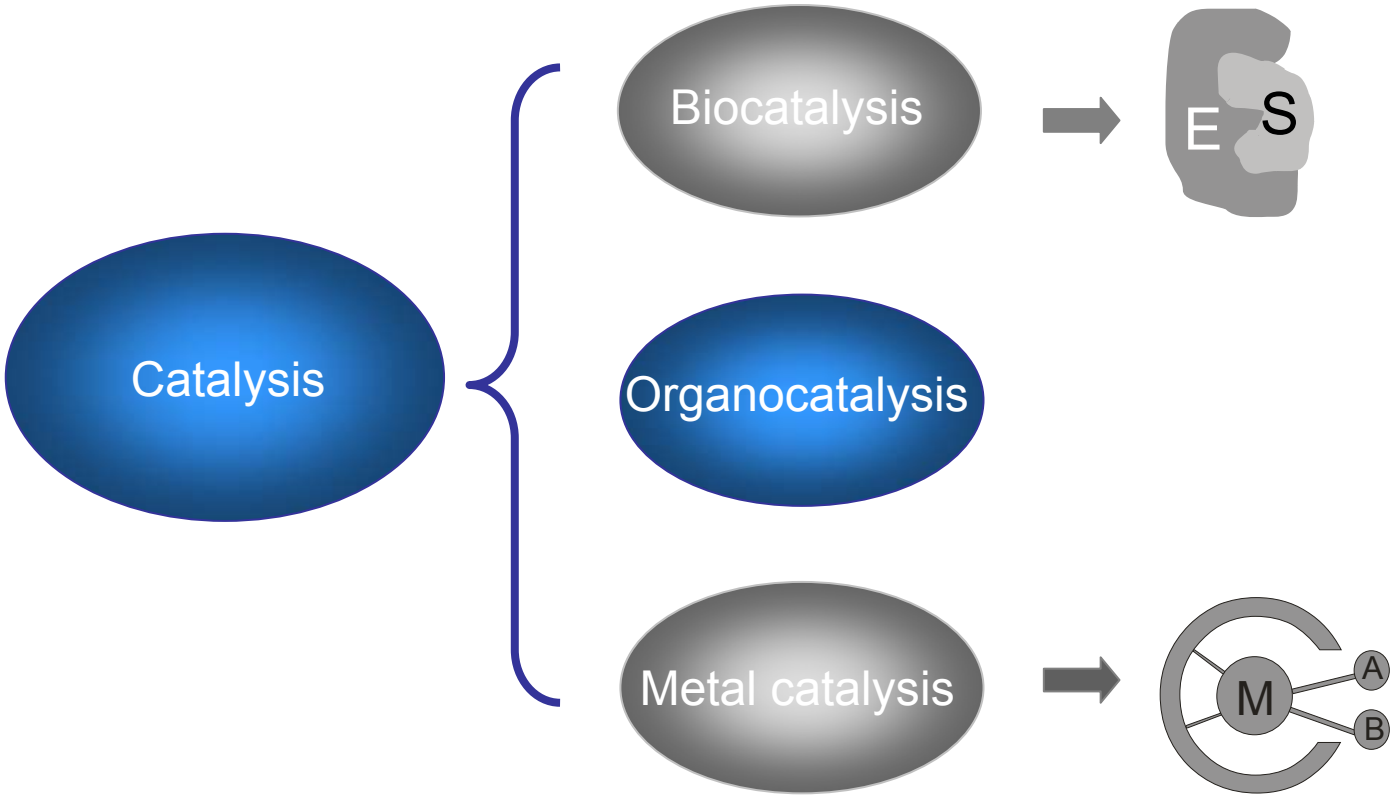
Introduction



Introduction



Introduction



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Introduction

Organocatalysis: the acceleration of chemical reactions with a sub-stoichiometric amount of organic molecules, which do not contain an active metal reaction center.

Comparison of three kinds of catalysis:

Type	Advantages	Disadvantages
Metal catalysis	Wide substrate scope High reactivity	Tedious process Potential heavy metal pollution
Biocatalysis	High catalytic activity High selectivity	Limited substrate scope
Organocatalysis	**Operational simplicity, inexpensive, readily available, robust, environmentally friendly**	

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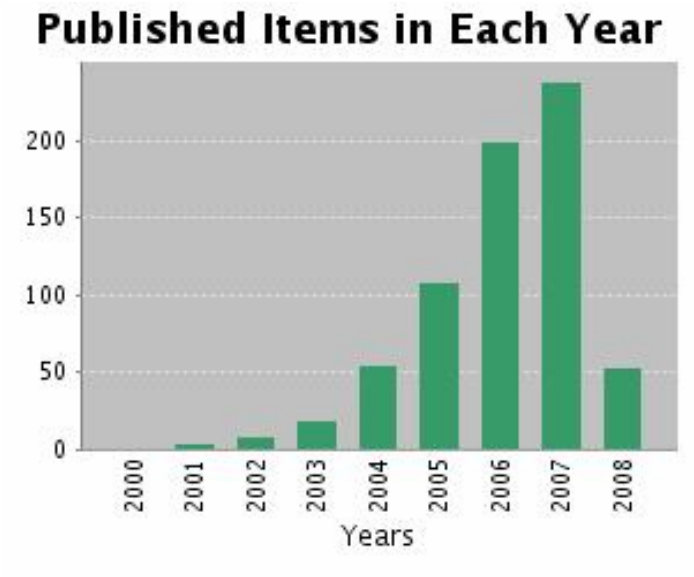
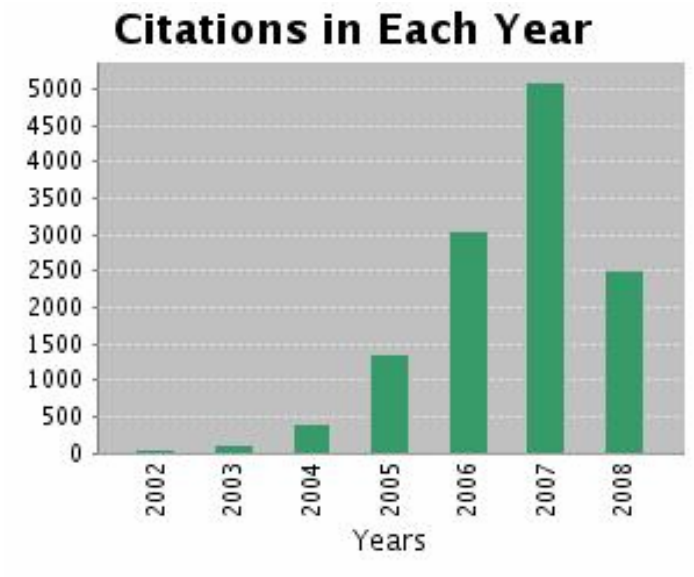
Introduction

The tendency of the term “organocatalysis”





- citation report on the topic “organocatalysis” in web of science since the year 2000

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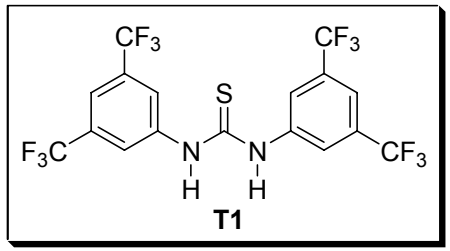
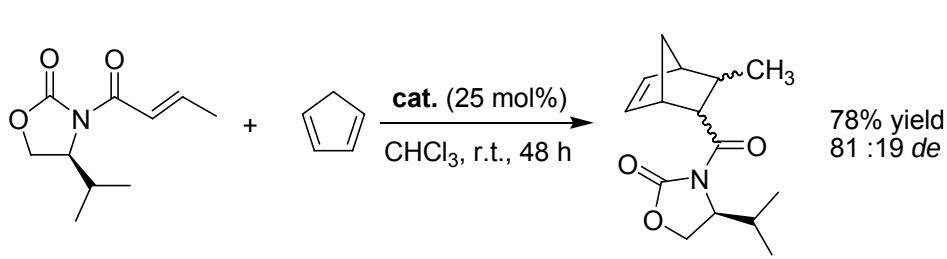
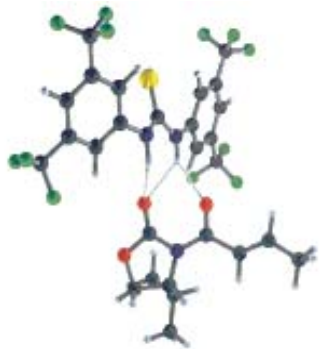
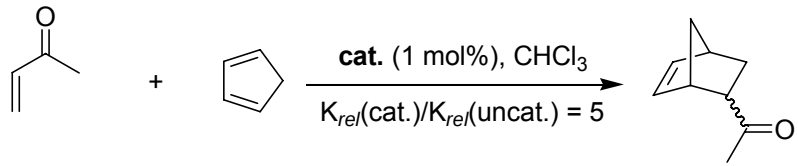
Introduction



T1







A. Wittkopp, P. R. Schreiner, In *The Chemistry of Dienes and Polymers*, **2000**, 1029.
P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217.
A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407.
P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289.

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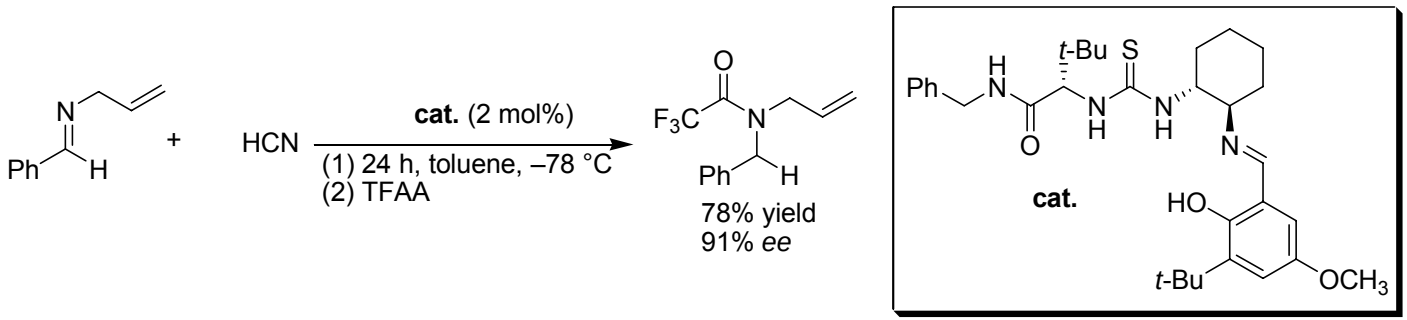
Introduction



E. N. Jacobsen, *et al., J. Am. Chem. Soc.* **1998**, *120*, 4901.
B. List, *et al., J. Am. Chem. Soc.* **2000**, *122*, 2395.
D. W. C. MacMillan, *et al., J. Am. Chem. Soc.* **2000**, *122*, 4243.

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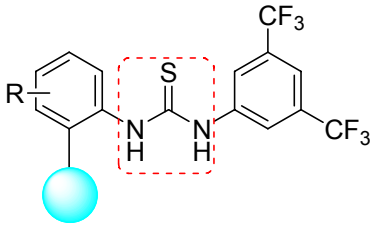
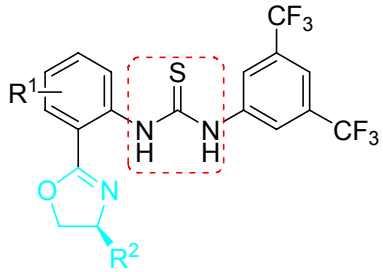
Design and Synthesis of Potential Catalysts

Strategy 1:

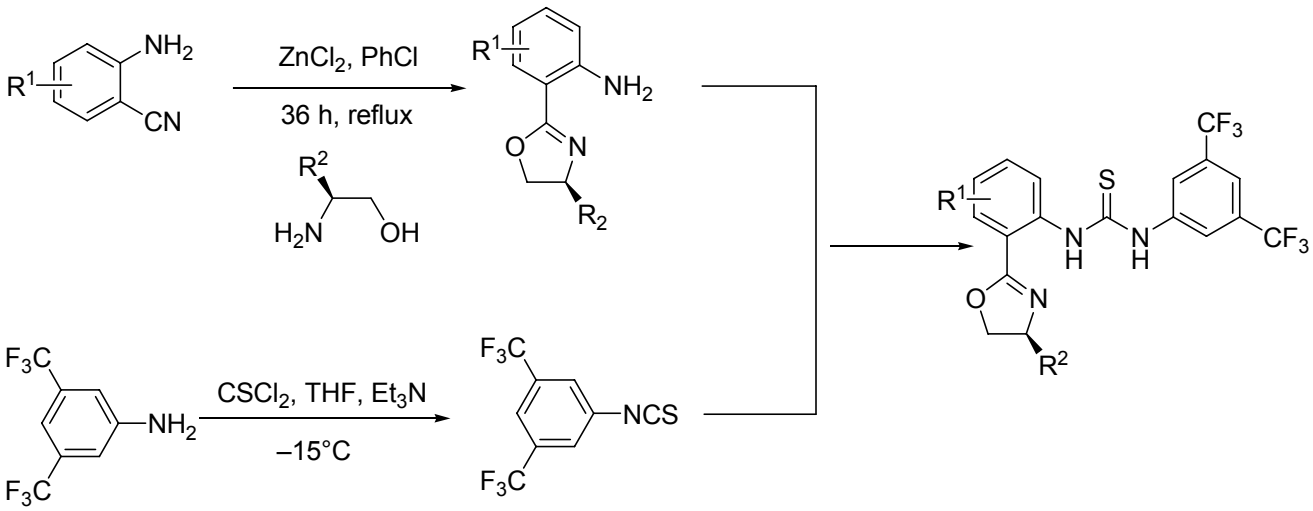


chiral modules



R^1 = H, 3,5-di-CF_3,
R^2 = H, methyl, *i*-propyl,
2-butyl, *t*-butyl, benzyl

Synthetic route:



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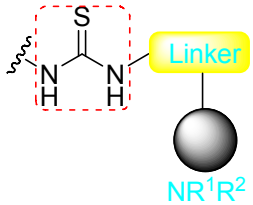
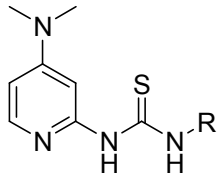
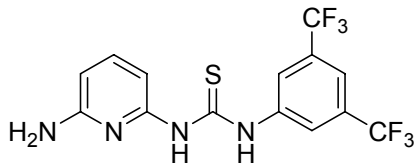
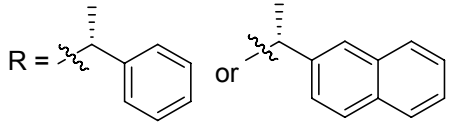
Design and Synthesis of Potential Catalysts

Strategy 2:

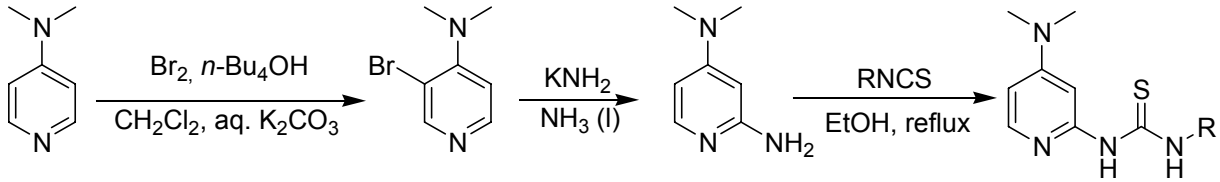


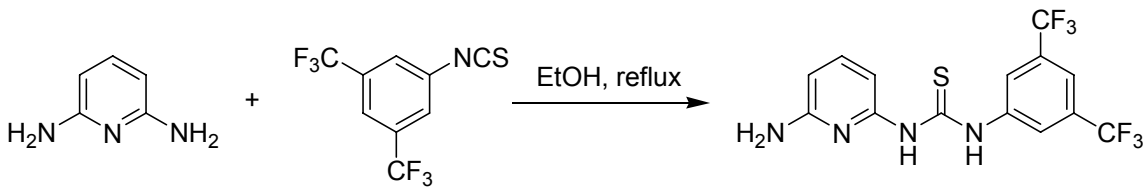






Synthetic route:





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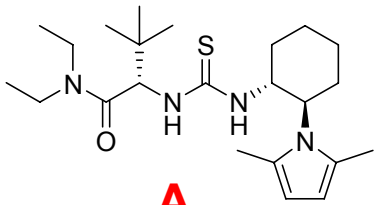
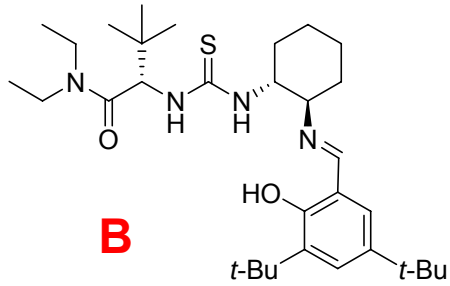
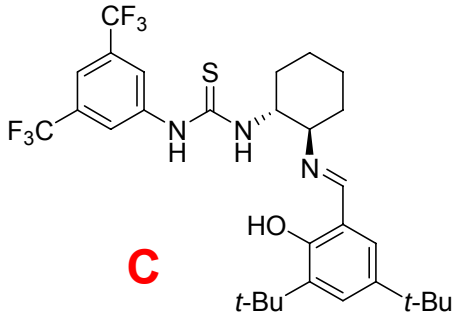
Design and Synthesis of Potential Catalysts

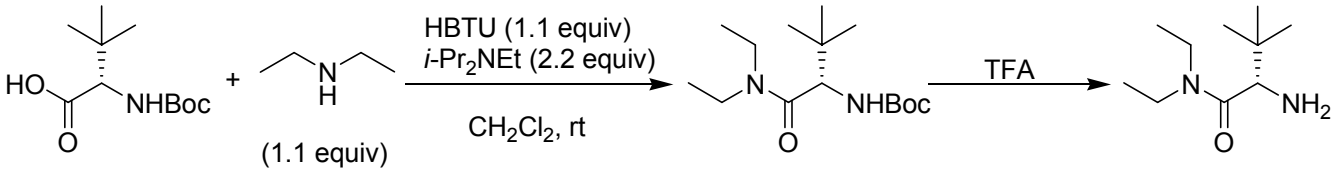
Strategy 3:

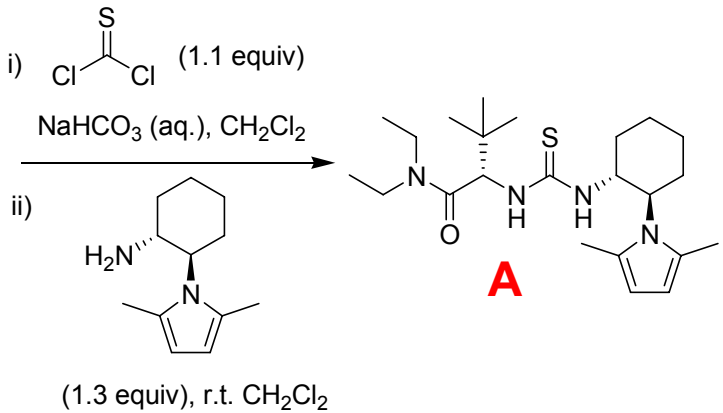






Synthetic route for A:





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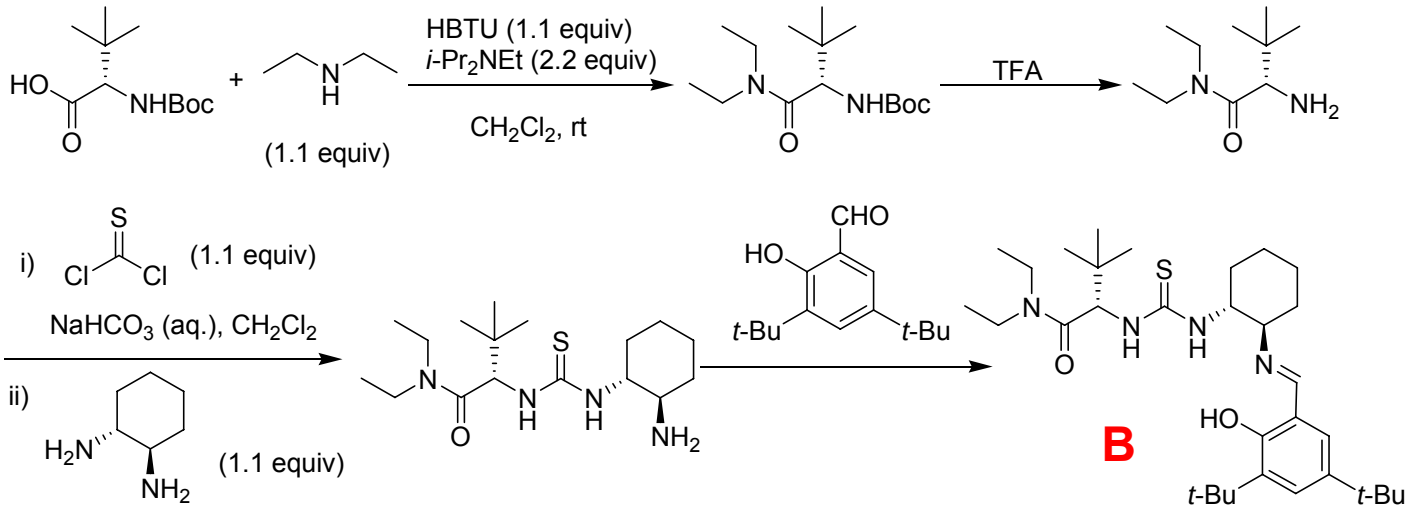
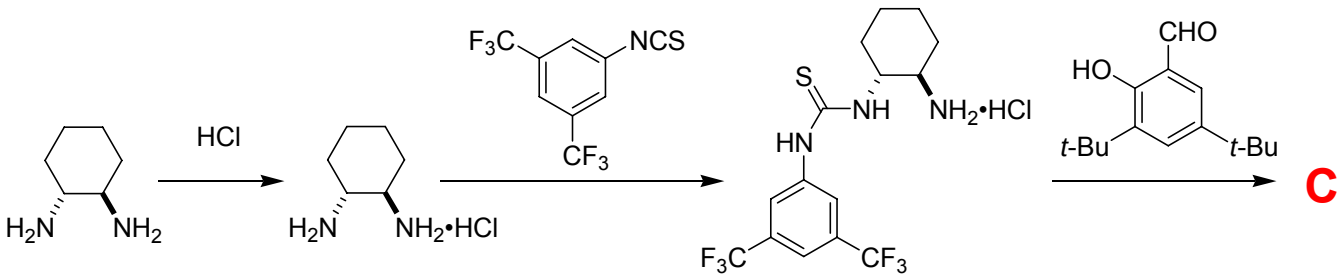
Design and Synthesis of Potential Catalysts

Synthetic route for B:



Synthetic route for C:



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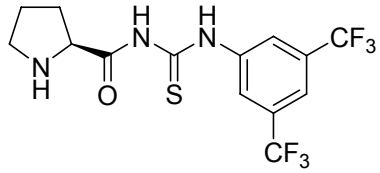
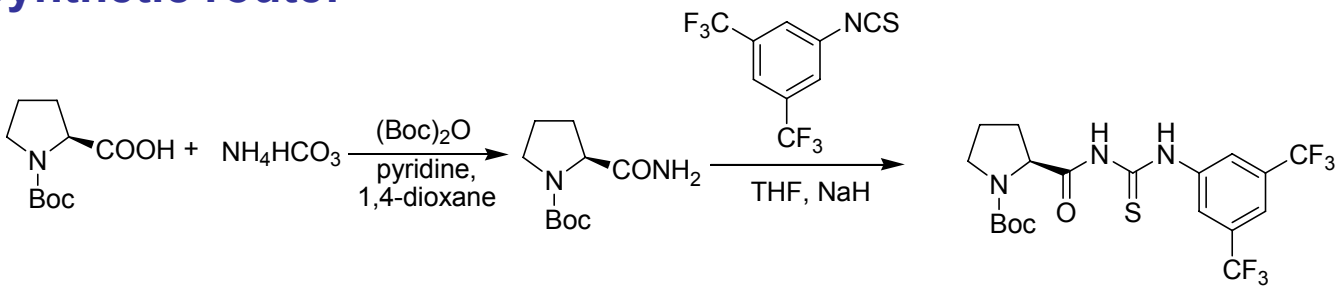
Design and Synthesis of Potential Catalysts

Strategy 4:



Synthetic route:



Boc deprotection (all failed):

1. 25% TFA (v/v) in DCM.
2. 98% H_2SO_4 in DCM.
3. 2 M HCl in AcOEt.
4. CAN in acetone at 0 °C.
5. $BiCl_3$ in CH_3CN/H_2O.
6. 25% TFA in DCM and scavengers ($S(CH_3)_2$)

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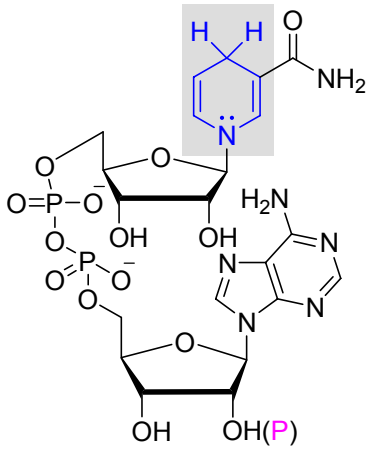
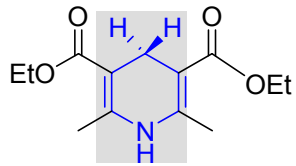
Applications: Oganocatalytic Reductions

Biomimetic concepts:



NADH (NADPH)

Nature's Reduction Cofactor



Hantzsch ester

Biomimetic Reduction Agent

A. Hantzsch, *Justus Liebigs Ann. Chem.*, **1882**, *215*, 1
B. Alberts, *et al.*, *Molecular Biology of the Cell*, **2002**, 3rd ed.

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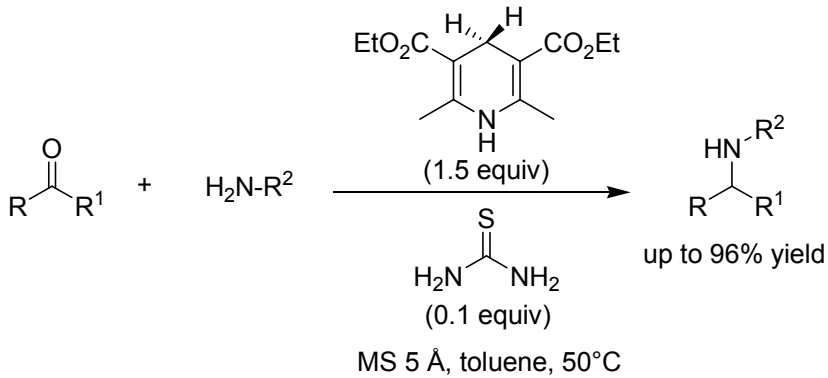
Thiourea-Catalyzed Transfer Hydrogenation of Aldimines

Reports from Menche group:



D. Menche, *et al*., *Org. Lett*. **2006**, *8*, 741.
D. Menche, *et al*., *Synlett* **2006**, 841.
D. Menche, et al., *Tetrahedron Lett.* **2007**, *48*, 365.
D. Menche, et al., *Bioorg. Med. Chem.* **2007**, *15*, 7311.

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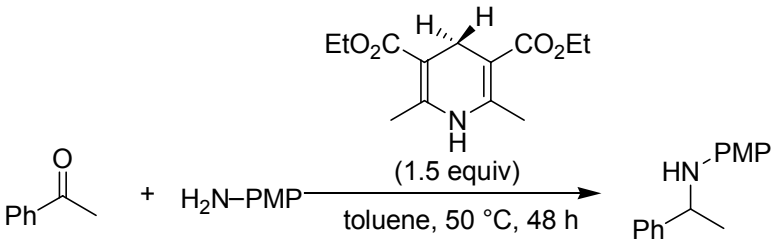
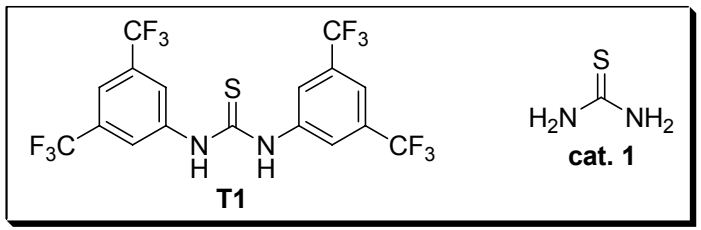
Thiourea-Catalyzed Transfer Hydrogenation of Aldimines





Entry	Conditions	Yield
1	**T1** (10 mol%), MS 5 Å (activated)	trace
2	**cat. 1** (10 mol%), MS 5 Å (activated)	trace
3	MS 5 Å (unactivated)	89%
4	MS 5 Å (unactivated)	(<5%)*

* The unreproducible result from Menche group

Z. Zhang, P. R. Schreiner, *Synlett* **2007**, 1455. **Highlight**: *Synfacts* **2007**, 988.

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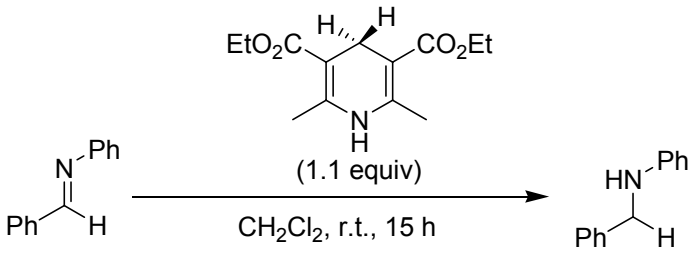
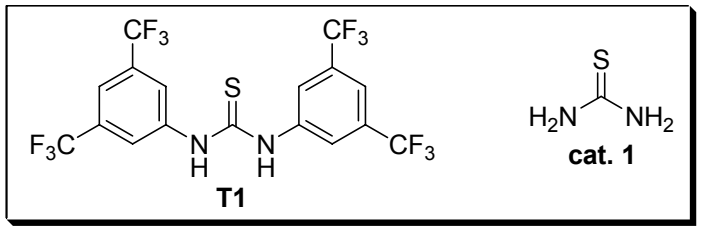
Thiourea-Catalyzed Transfer Hydrogenation of Aldimines





Entry	Conditions	Yield
1	**T1** (10 mol%)	91%
2	**cat. 1** (10 mol%)	trace
3	**T1** (0.1 mol%), 60 h	87%

Z. Zhang, P. R. Schreiner, *Synlett* **2007**, 1455. **Highlight**: *Synfacts* **2007**, 988.

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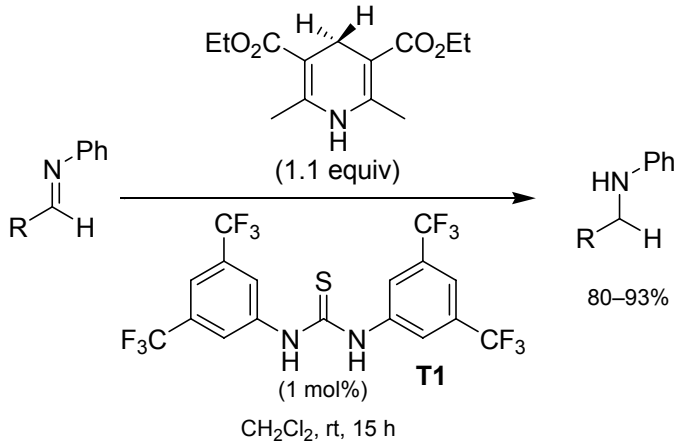
Summary 1



Conclusions:

- The results reported by Menche group were challenged.
- Thiourea-catalyzed transfer hydrogenation of aldimines was firstly reported.

Z. Zhang, P. R. Schreiner, *Synlett* **2007**, 1455. **Highlight**: *Synfacts* **2007**, 988.

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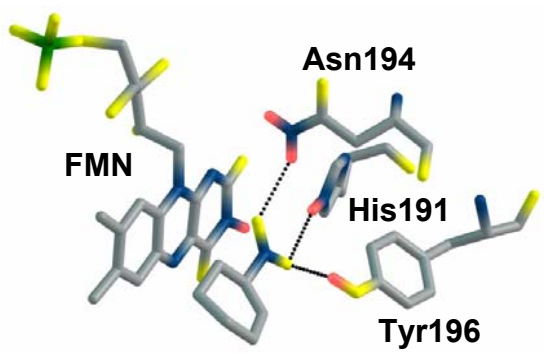
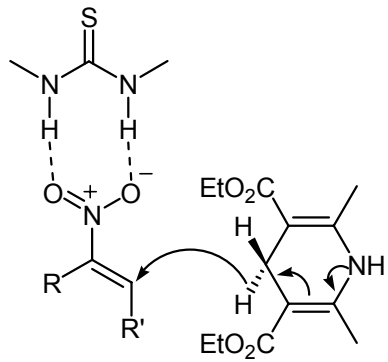
Organocatalytic Biomimetic Reduction of Conjugated Nitroalkenes



A



B

A: Key interaction between the Old Yellow Enzyme (OYE) and nitrocyclohexene (PDB 1OYE)

B: mode of the thiourea-catalyzed biomimetic reduction of conjugated nitroalkenes

Z. Zhang, P. R. Schreiner, *Synthesis* **2007**, 2559.

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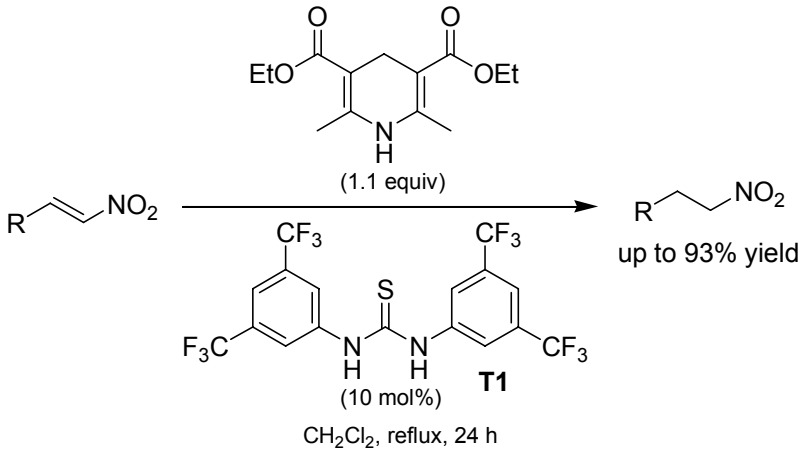
Summary 2



Conclusions:

- Various aliphatic and aromatic nitroalkenes can be reduced to their corresponding products using this biomimetic method.

Z. Zhang, P. R. Schreiner, *Synthesis* **2007**, 2559.

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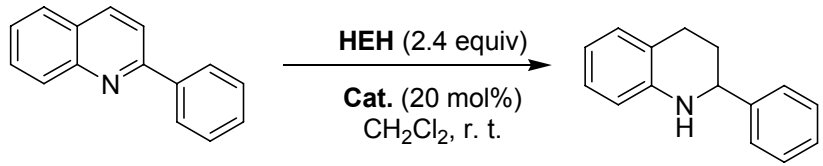
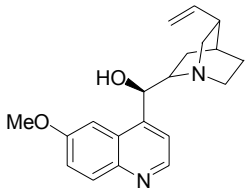
Reduction of Quinoline with Organic Salts



Entry	Quinine	Acids	Ratio	Conversion (%)	*ee* (%)
1		H_3PO4	1:1	0	-
2		*p*-toluenesulfonic acid	1:1	100	1.2
3		L-(+)-tartaric acid	1:1	80	0
4		L-(+)-tartaric acid	2:1	trace	-
5		L-(+)-lactic acid	1:1	trace	-
6		TFA	1:1	trace	-
7		(1*S*)-(+)-CSA	1:1	100	0

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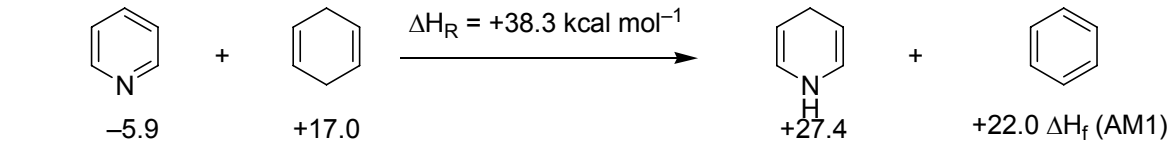
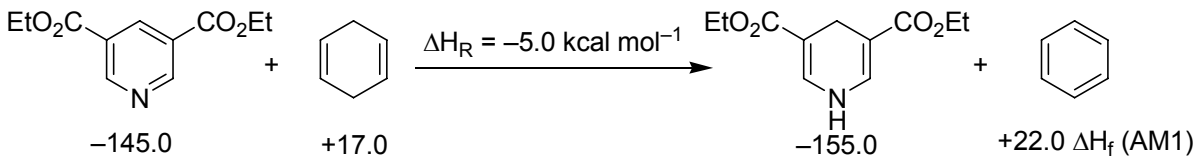
Attempts to Regenerate Hantzsch Ester





*Chemical calculation of the enthalpy by Prof. Schreiner

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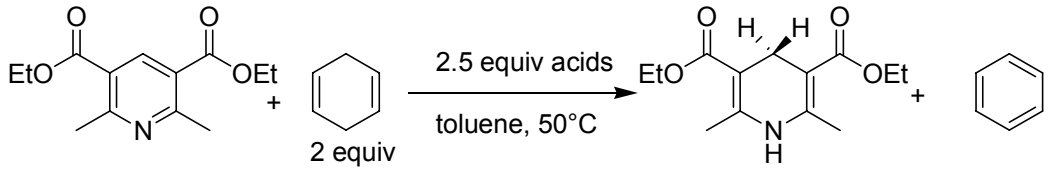
Attempts to Regenerate Hantzsch Ester



entry	acid	yield
1	CH_3COOH	-
2	HCl	-
3	CF_3COOH	-
4	H_3PO4	-
5	P-TSA	-
6	CSA	-
7	$HClO_4$	-
8	HBF_4	-

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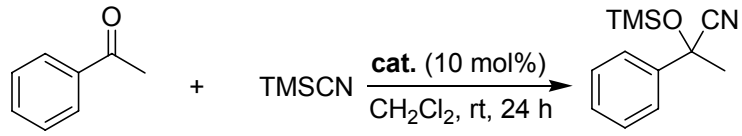
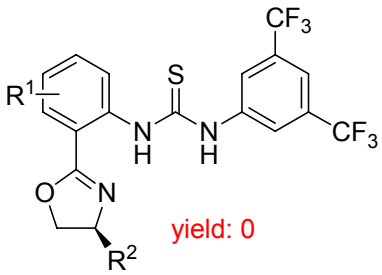
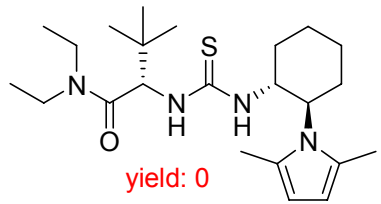
Applications: Cyanosilylation of Ketone



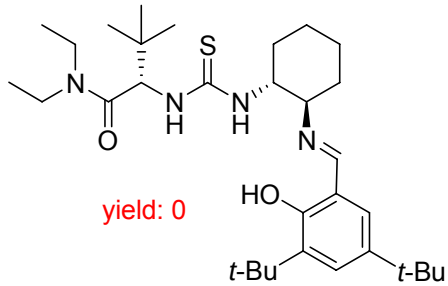


yield: 0

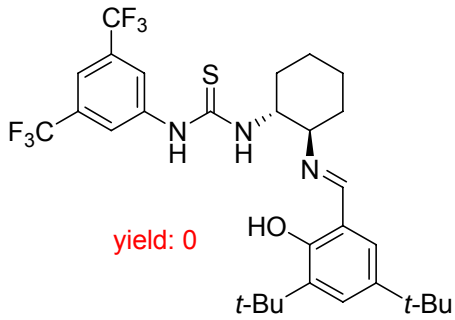
R^1 = H, 3,5-di-CF_3,
R^2 = H, methyl, *i*-propyl, 2-butyl, *t*-butyl, benzyl



yield: 0



yield: 0



yield: 0

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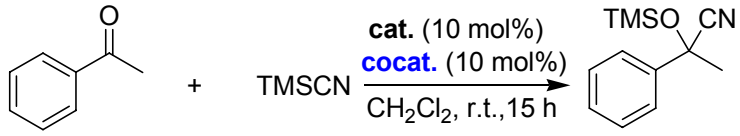
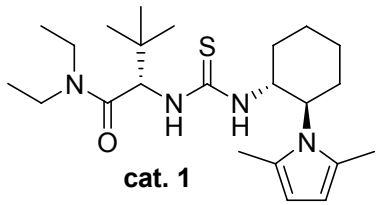
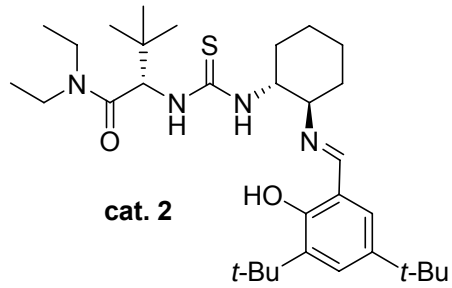
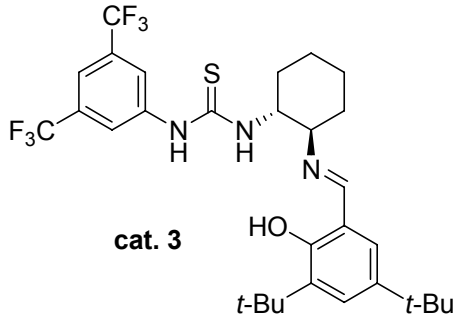
Applications: Cyanosilylation of ketone



cocat.: LiOH, NaOH, CaH, KOH, $LiOPr^i$, $LiOH \cdot H_2O$, NaOMe, Ph_3PO, *n*-BuLi







Entry	Catalyst	Cocatalyst	Conversion (%)	*Ee* (%)
1	**cat. 1**	**LiOH**	100	0
2	**cat. 2**	**LiOH**	100	0
3	**cat. 3**	**LiOH**	80	36%
4	**cat. 3**	***n*-BuLi**	100	0
5	**-**	***n*-BuLi**	100	0

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Summary 3

- Structures bearing a thiourea functionality and phenolate in a chiral scaffold were firstly demonstrated as catalysts for cyanosilylation of acetophenone, yielding the product with up to 36% *ee*.
- Several bases such as *n*-BuLi alone can promote the cyanosilylation of acetophenone.

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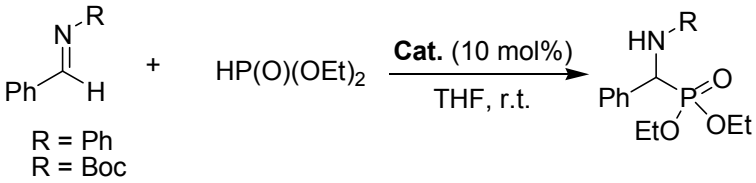
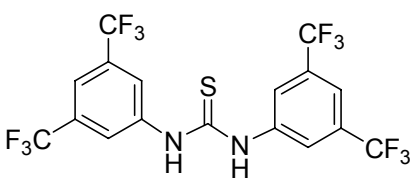
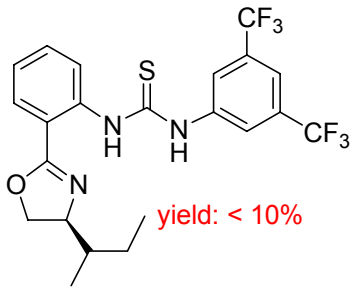
Hyrophosphonylations

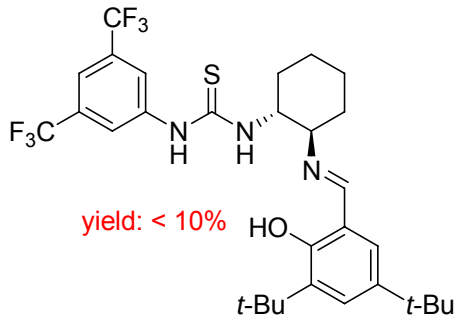




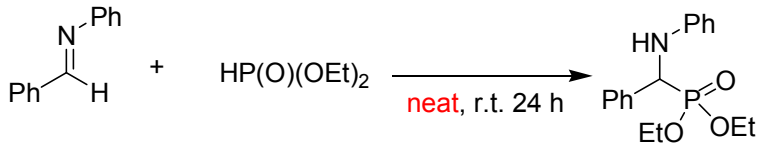
yield: < 10%



yield: < 10%



yield: < 10%



87% yield

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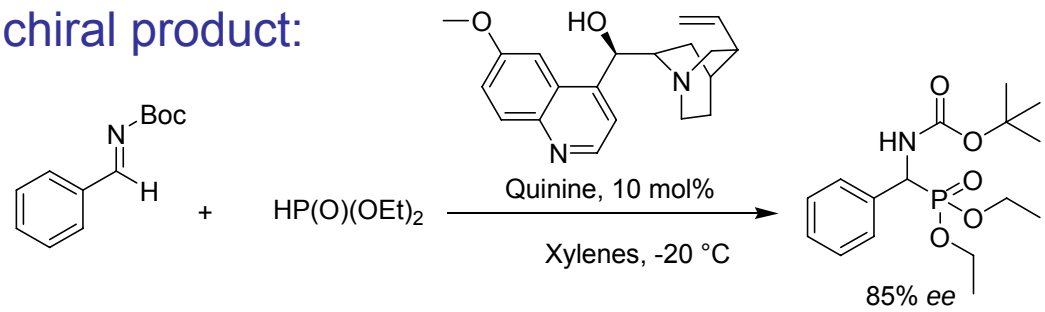
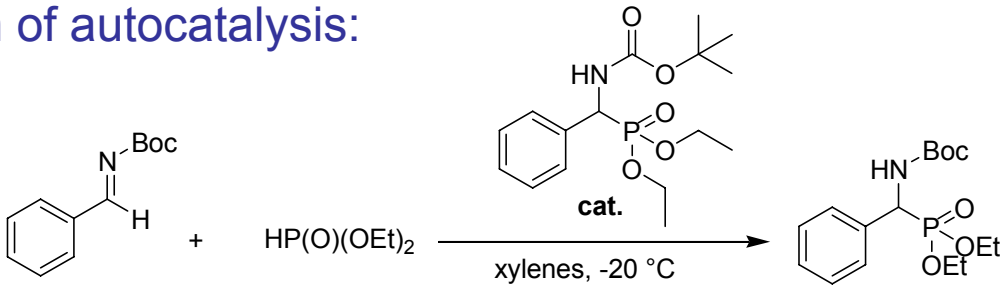
Hyrophosphonylations

Synthesis of chiral product:



Investigation of autocatalysis:



Entry	Catalyst (mol%)	Yield (%)	*ee* (%)
1	30	3	60
2	20	6	56
3	10	21	28
4	1	27	11

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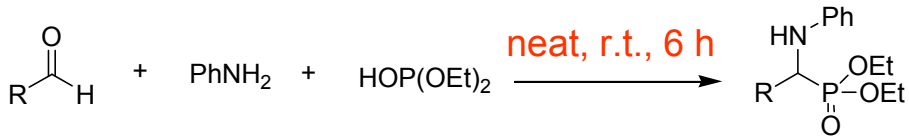
One-pot Synthesis of α-amino Phosphonates



Entry	R	Yield (%)
1	Ph	89
2	4-NO_2Ph	86
3	4-BrPh	82
4	4-OHPh	78

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Summary 4

- The designed thioureas are generally inefficient for hydrophosphonylation of imines.
- No evidence for autocatalysis.
- One-pot reaction of aldehydes, amines, and diethylphosphite proceeded smoothly to afford the corresponding α-amino phosphonates under neat conditions without the involvement of any catalyst and solvent.

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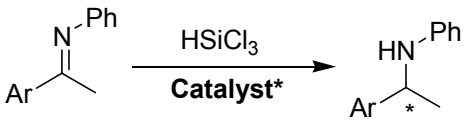
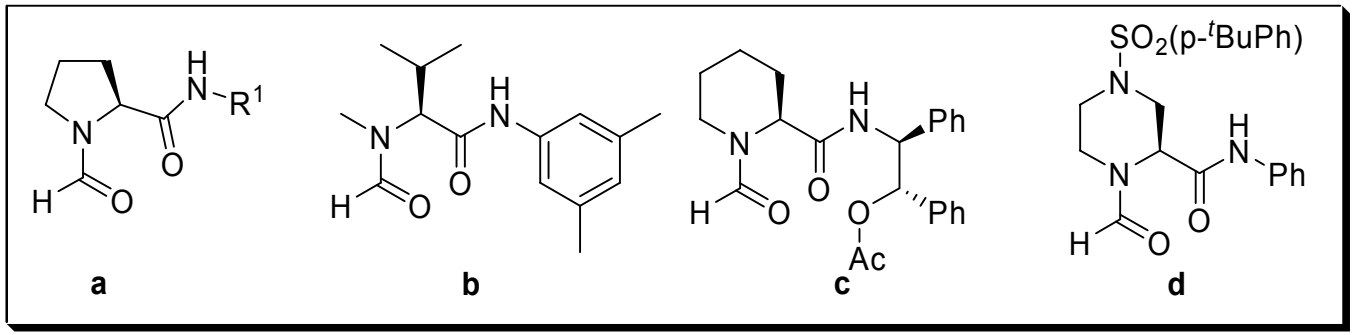
Asymmetric Organocatalyzed Reduction of Ketimines with $HSiCl_3$



a: up to 66% ee
b: up to 92% ee
c: up to 96% ee
d: up to 97% ee



F. Iwasaki, *et al.*,*Tetrahedon Lett*. **2001**, *42*, 2525
A. V. Malkov, *et al*., *Org. Lett.* **2004**, *6*, 2253
Z. Wang, *et al*., *Org. Lett.* **2006**, *8*, 999
Z. Wang, *et al*., *Org. Lett.* **2006**, *8*, 3045

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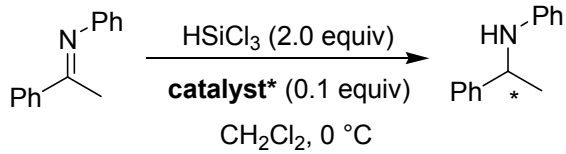
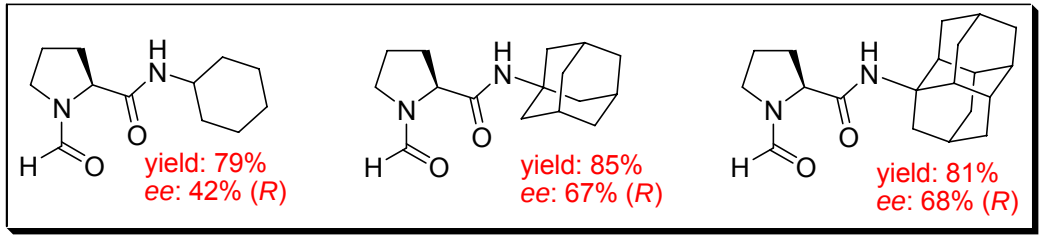
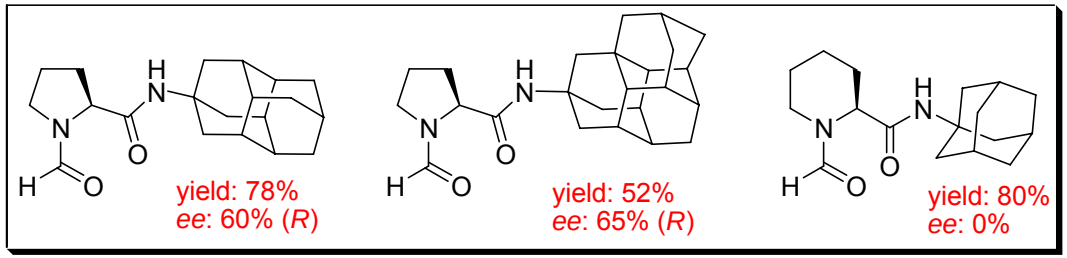
Synthesis and Screening of Potential Catalysts







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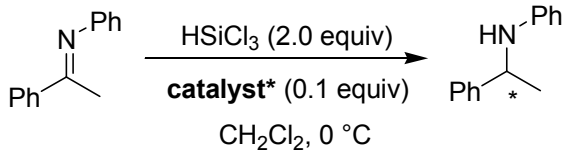
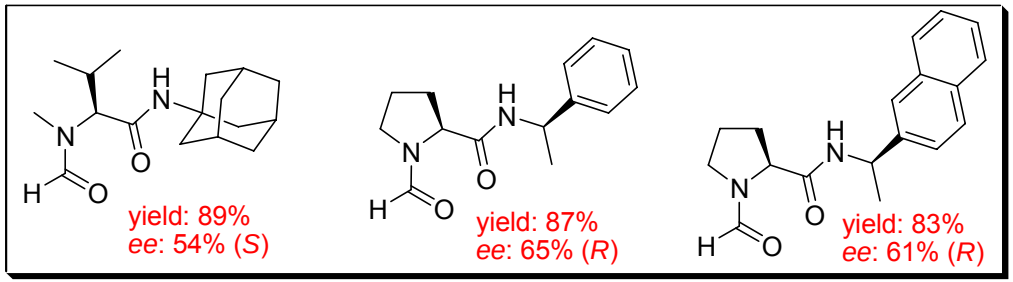
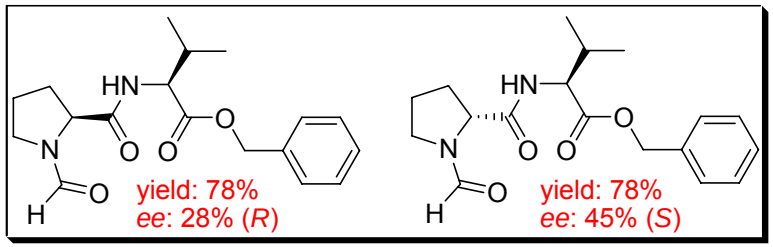
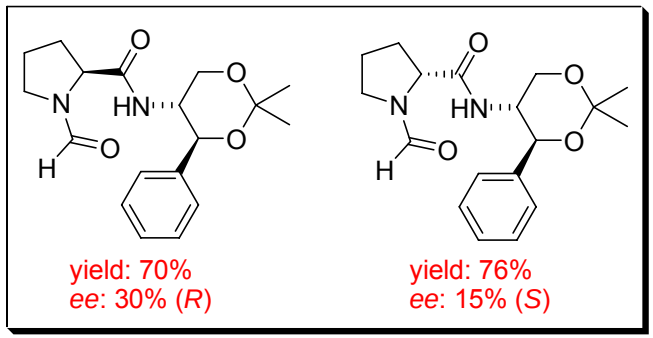
Synthesis and Screening of Potential Catalysts









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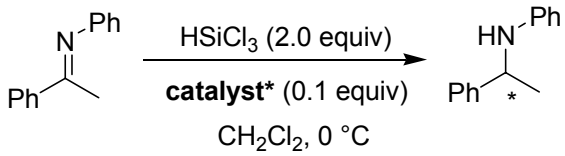
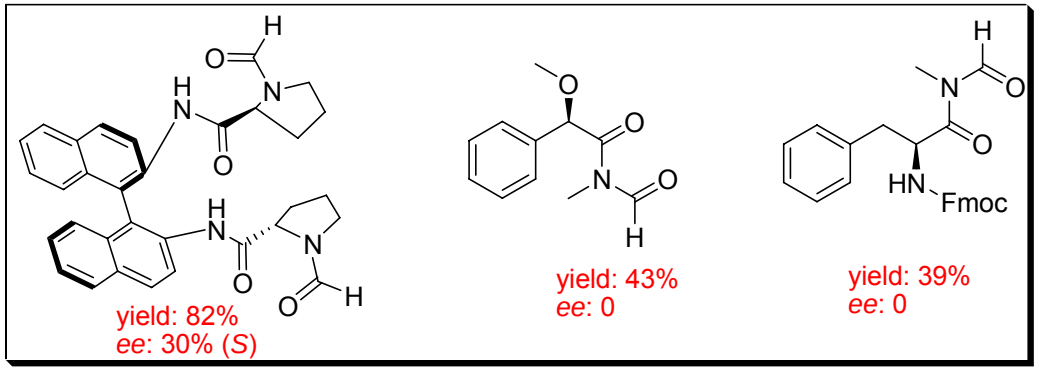
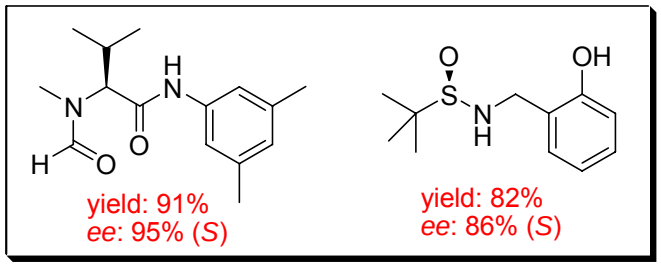
Synthesis and Screening of Potential Catalysts







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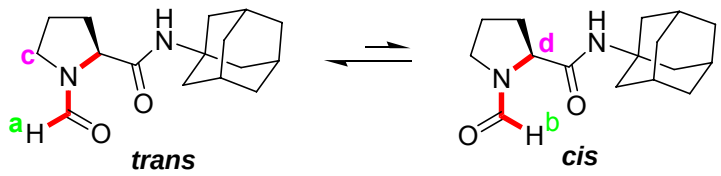
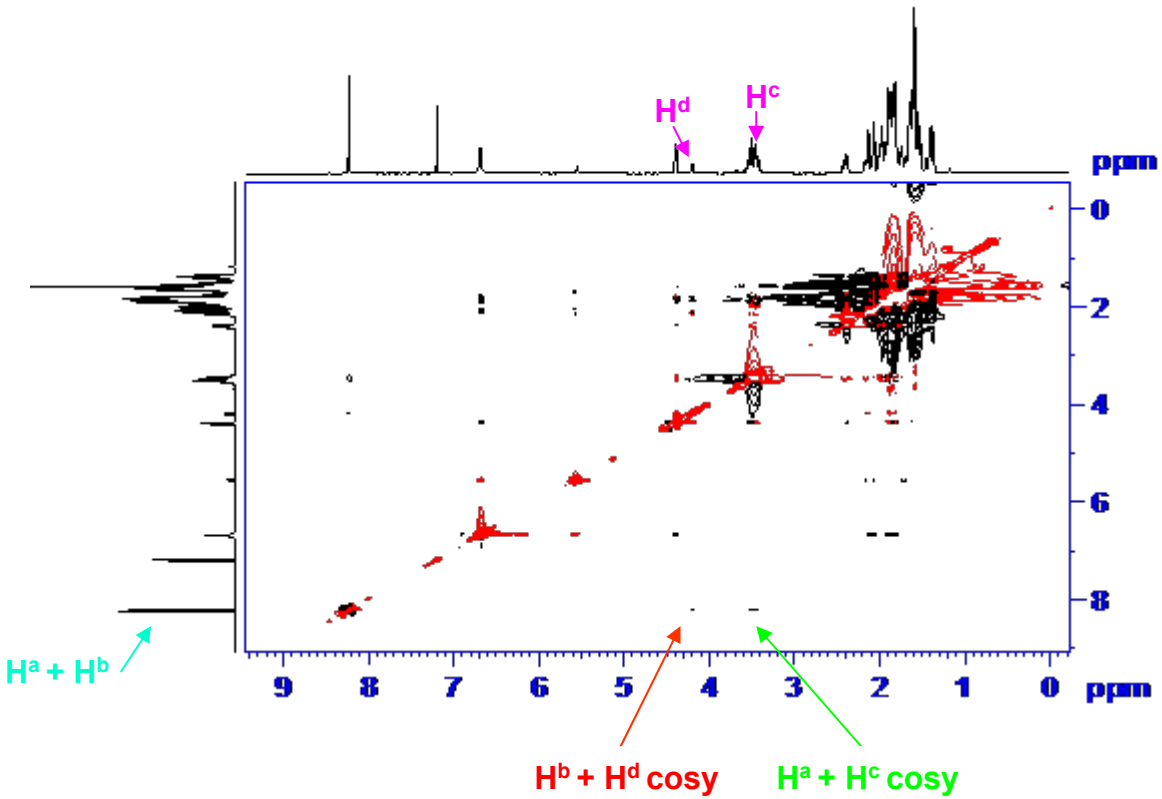
Structure Features





ROESY spectrum

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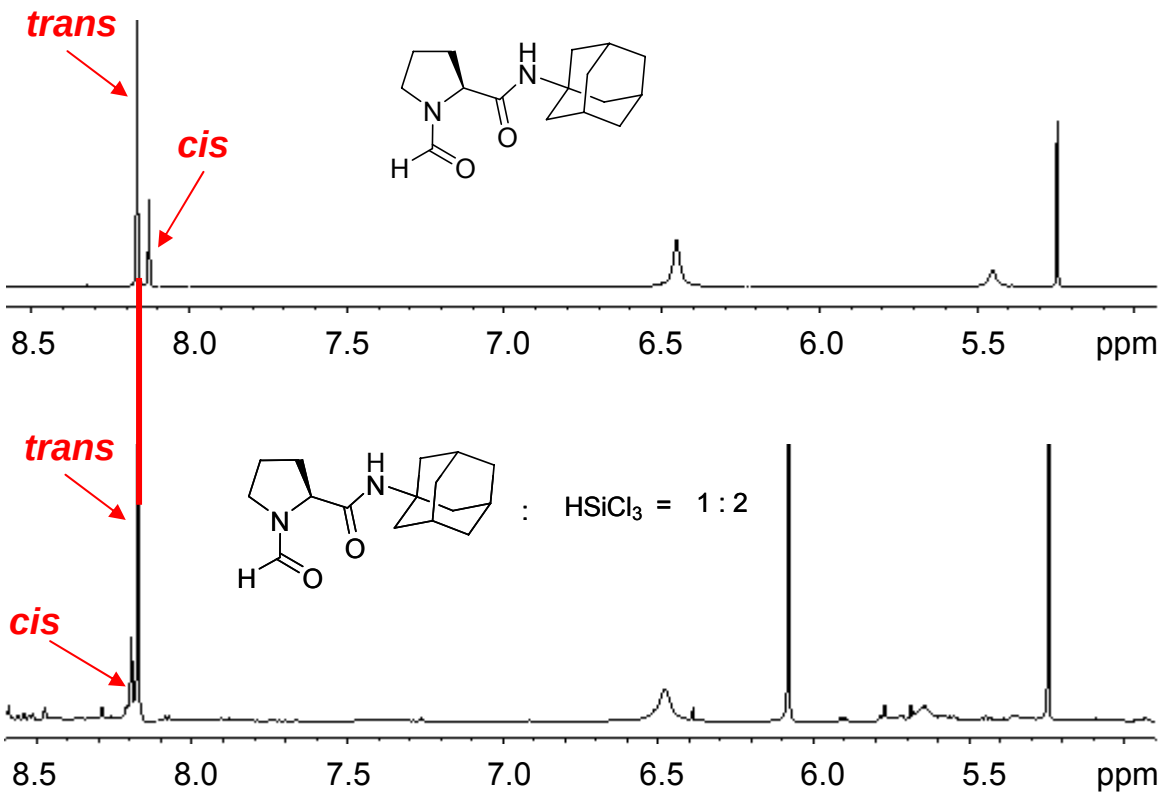
Mechanism Consideration

Determination of reaction intermediate by ^{1}H-NMR:



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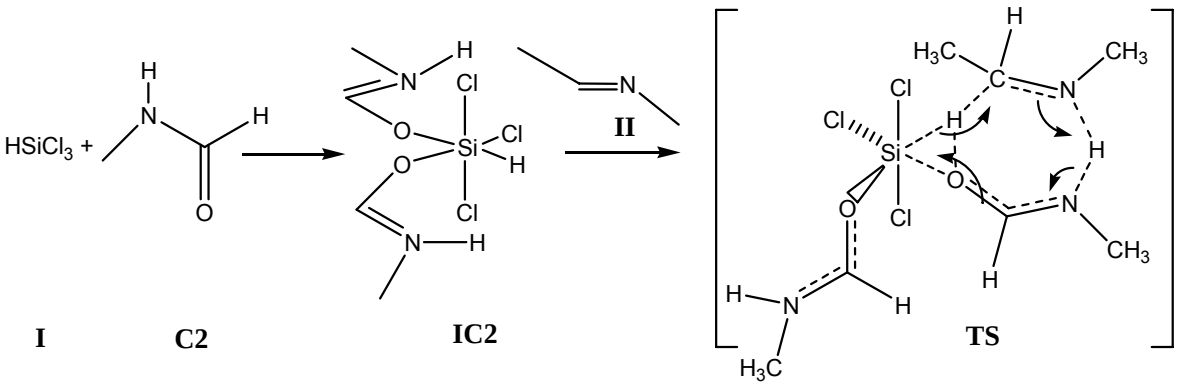
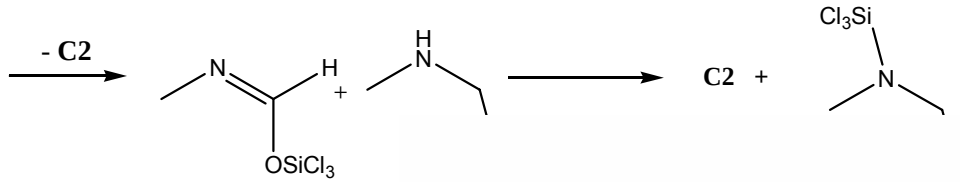
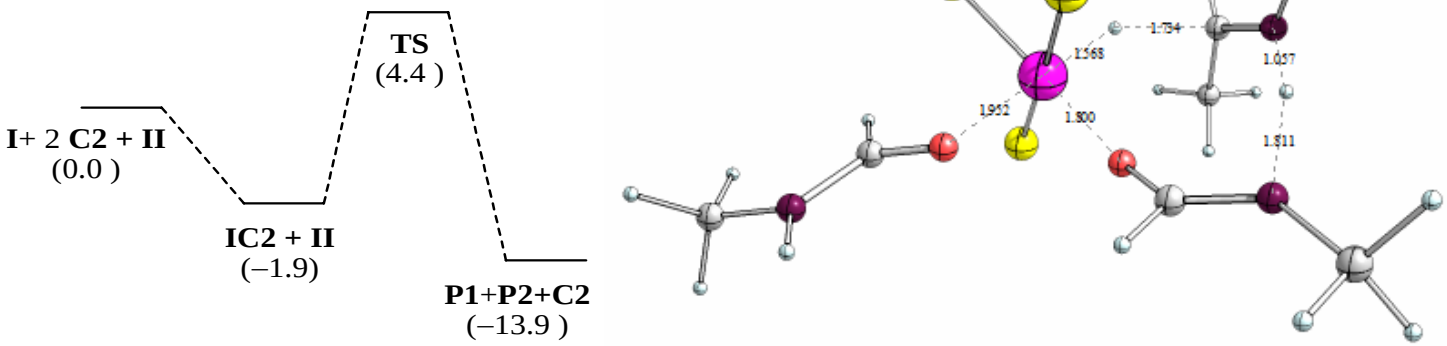
Proposed transition state by chemical computation: (Dr. P. Rooshenas)







Computed potential hyper surface for the MFA- catalyzed reduction of II with I (relative ΔH_o values computed at B3PW91/cc-pvdz level of the theory are given in kcal/mol). The optimized geometries **TS** at B3PW91/cc-pvdz.

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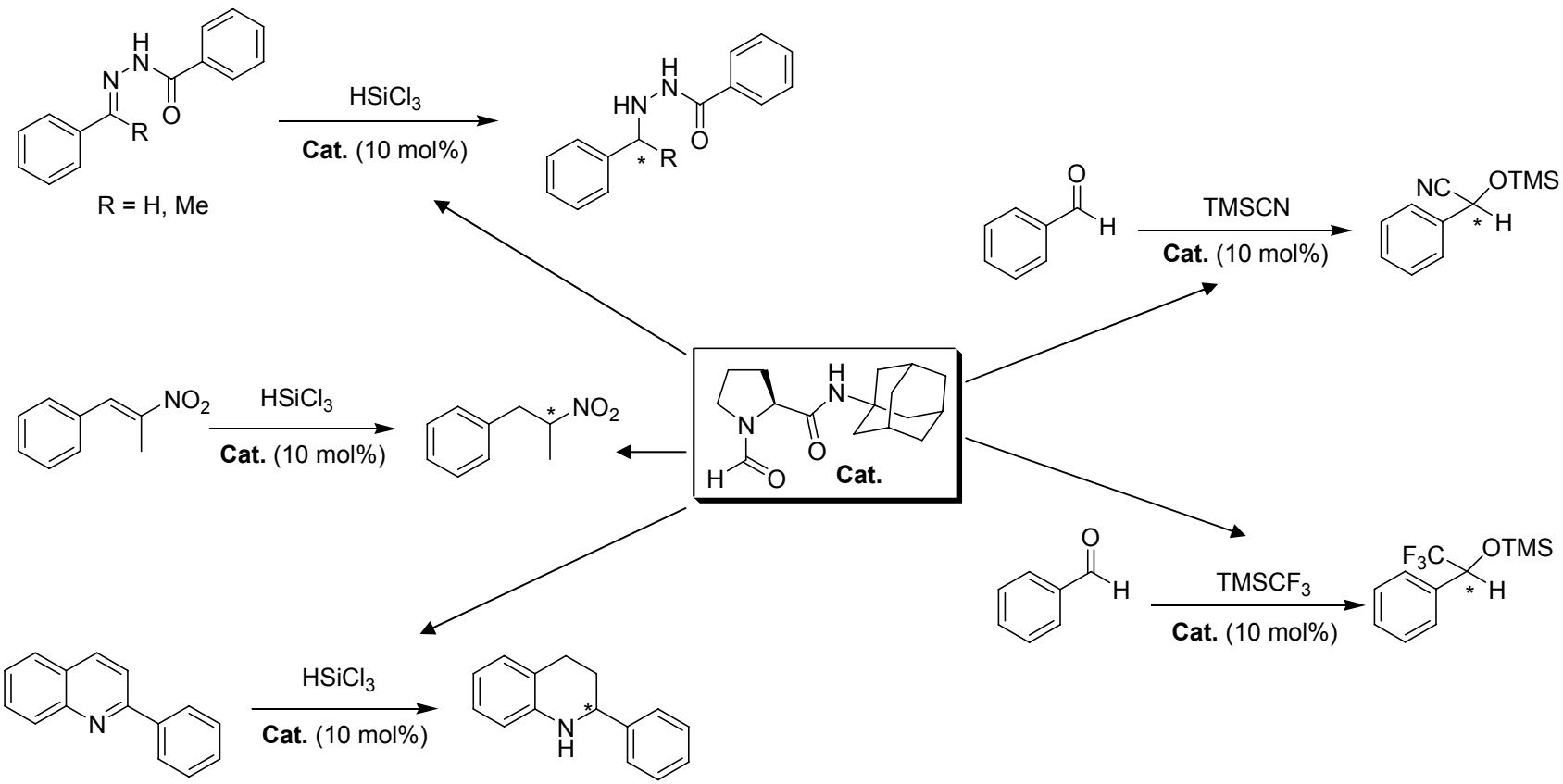
Other Attempts



No catalytic effect was observed in those reactions!!

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Summary 5

- 16 novel chiral *N*-formamides were designed and prepared.
- *ee* up to 68% for reduction of ketimine with our promoters was so far obtained.
- Two reported protocols were reproduced as control experiments.
- Investigation of the mechanism and development of more efficient catalysts is still in progress.

Z. Zhang, P. R. Schreiner, *manuscript in preparation*

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organokatalyse