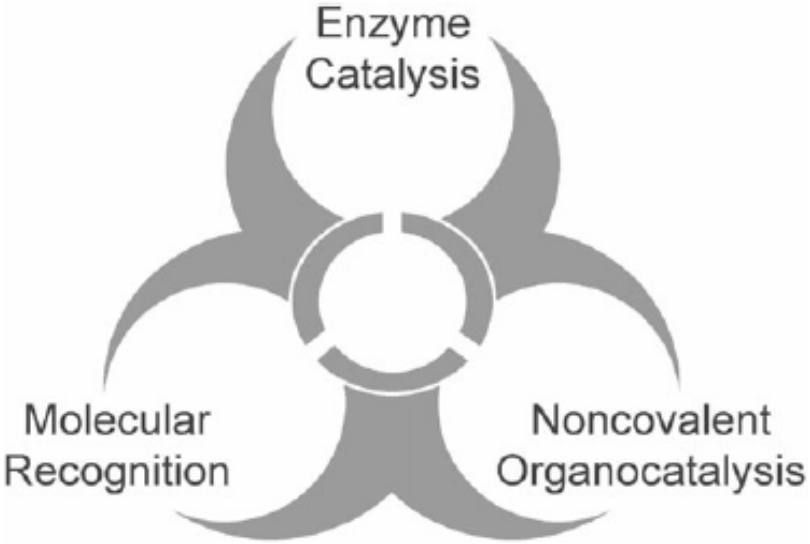
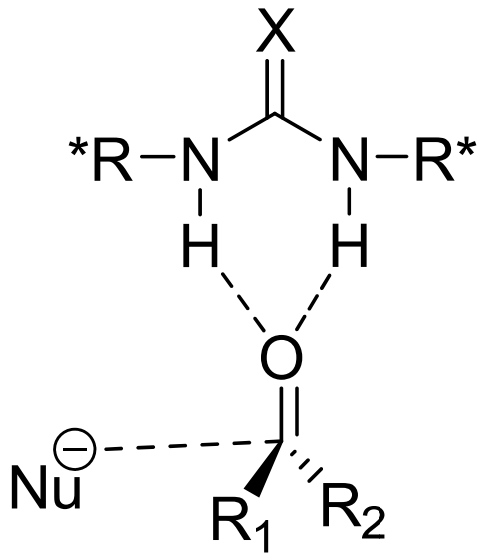
Organocatalysis Mediated by (Thio)urea Derivatives

--A kind of Small-Molecule H-Bond Donors

By Chaoren Shen





X=O,S

Peter R. Schreiner
Chem. Soc. Rev., 2009, **38**, 1187–1198

1. The Origin of (Thio)urea Catalyst Derivatives

2.Brief Introduction to the Pioneers in This Filed

3. Catalyst And Asymmetric Catalytic Reaction

4.Application in the total synthesis and industry

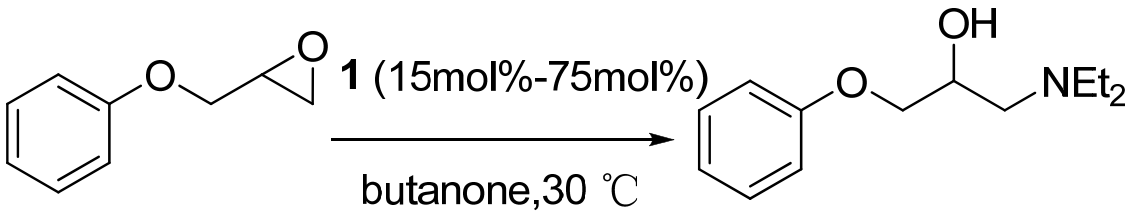
5.Conclusion

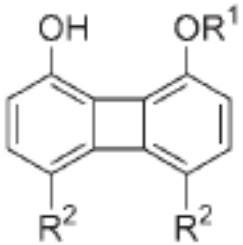
1.The Origin of the Catalyst

Seminal Studies

Hine and Kelly's poineering work:

Established that general acid catalysis by conformationally restricted metal-free diprotic acids is a valid strategy upon which to base organocatalyst design.

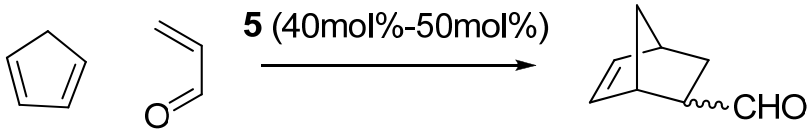




1 $R^1 = H, R^2 = H$
4 $R^1 = Me, R^2 = H$
5 $R^1 = H, R^2 = NO_2$

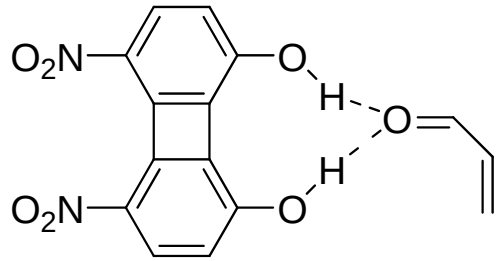
catalyst	pK_a	k_{rel}
phenol	9.98	1.0
m-nitrophenol	8.40	2.4
p-nitrophenol	7.15	2.8
catechol	9.49	2.0
4	9.15	1.2
1	8.00	12.5

J. Hine, *J. Am. Chem. Soc.*,**1984**, 106, 7980.



the promotion of the D-A reaction between cyclopentadiene and unsaturated aldehydes by 3,6-dipropylderivatives of **5**

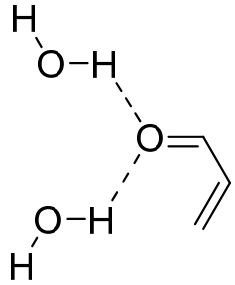
T. R. Kelly, *Tetrahedron Lett*. **1990**, 31,3381



Kelly proposed the mechanism of double hydrogen-bond donation to the dienophile

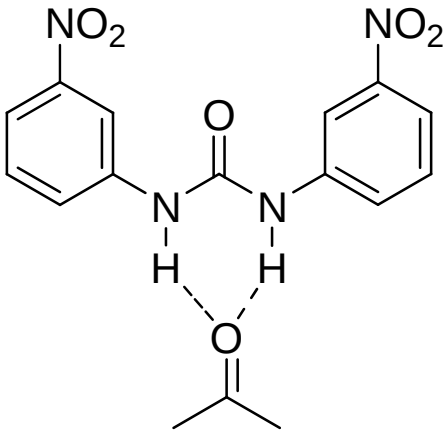
One year later, Jorgensen confirmed the proposition from Kelly

Solvent Effects on a Diels-Alder Reaction from Computer Simulations
W. L. Jorgensen, *J. Am. Chem. Soc.* **1991**, 113, 7430.



Jorgensen's hydration model

Effects of Hydration on the Claisen Rearrangement of Allyl Vinyl Ether from Computer Simulations
W. L. Jorgensen, *J. Am. Chem. Soc.* **1992**, 114,10966.



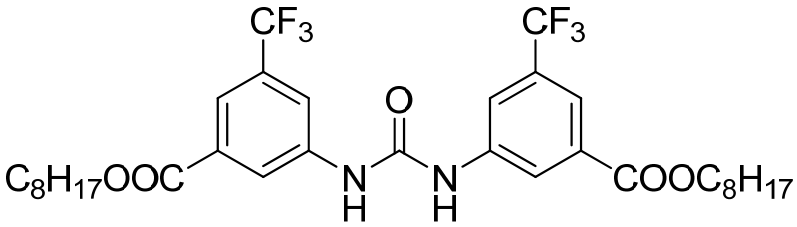
M. C. Etter, *J. Am. Chem. Soc.* **1988**, 110, 5896
M. C. Etter, *J. Am. Chem. Soc.* **1990**, 112, 8415

Etter's Important Observation:
Hydrogen bond-directed co-crystallisation of N,N'-diarylureas (in particular 3,3'-dinitrocarbanilide) with compounds incorporating a wide variety of Lewis basic functional groups, such as nitroaromatics, ethers, ketones and sulfoxides. The donation of two hydrogen bonds by a single urea molecule to the Lewis base was implicated.

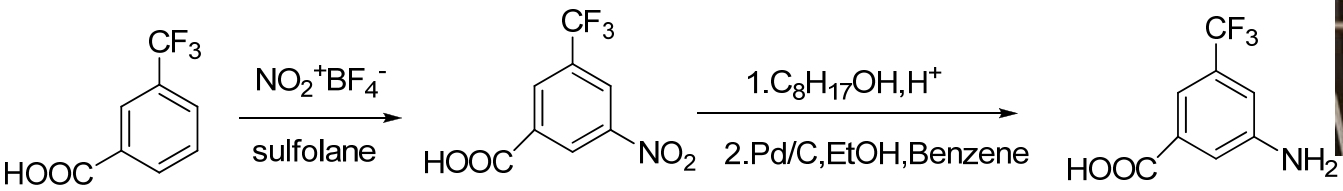
A crystal structure of an unstable N,N'-[bis-(α -tosylbenzyl)urea–acetone hydrogen-bonded adduct had been previously obtained: *J. Chem. Soc. Perkin Trans. 2* ,1976, 483.

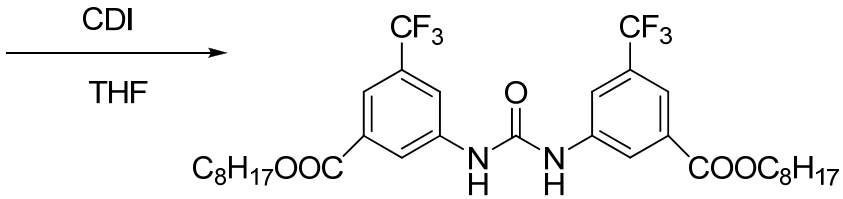
This is the basis for the development of urea-based organocatalysts!

The first example of urea-based organocatalyst



Dennis P. Curran
J. Org. Chem. 1994,**59**, 3259-3261

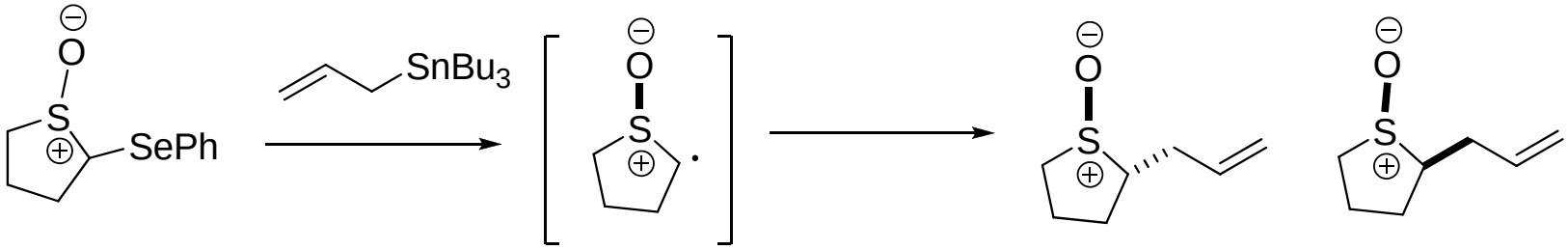




The choice of functionality installed on the diarylurea backbone:

1.lipophilic side chains were utilised to improve solubility in common organic solvents

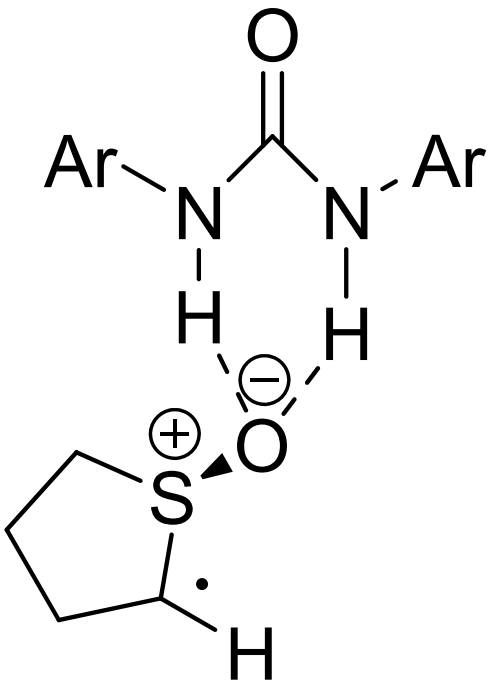
2.-CF3 is an more electron-withdrawing group than -NO2

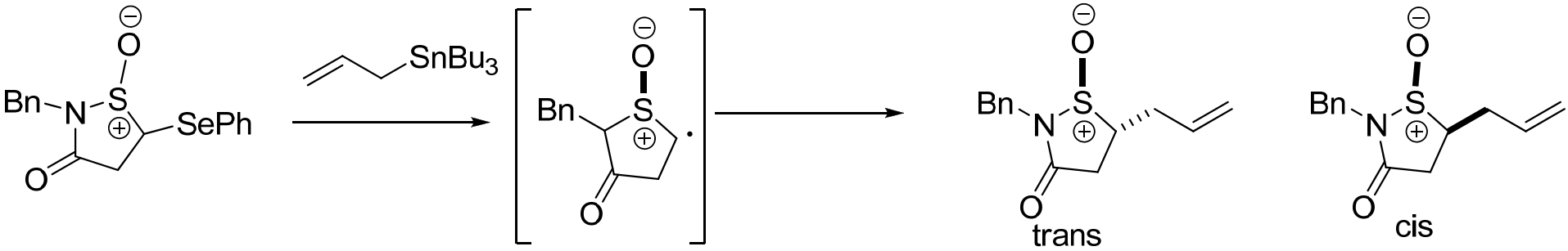


trans/cis=6.6:1

trans cis

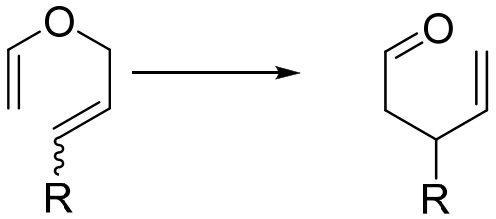
entry	solvent	additive	7-*trans*/7-*cis* (yield, %)
1	benzene[a]	none	2.5/1 (60)
2	CH_2Cl_2[a]	none	5.5/1 (62)
3	CH_3CH_2OH[b]	none	4.9/1 (87)
4	CH_3CO_2H[b]	none	6.7/1 (51)
5	CF_3CH_2OH[b]	none	8.1/1 (83)
6	THF[a]	none	2.2/1 (36)
7	THF[a]	LiCl (0.5 M)	5.8/1 (25)
8	THF[a]	$ZnBr_2$ (0.5 M)	8.0/1 (60)
9	THF[a]	$BF_3{\cdot}Et_2O$ (0.5 M)	4.5/1 (73)
10	benzene[a]	1 (0.2 equiv)	3.7/1 (57)
11	benzene[a]	1 (0.6 equiv)	5.8/1 (72)
12	benzene[a]	1 (1.0 equiv)	7.0/1 (81)





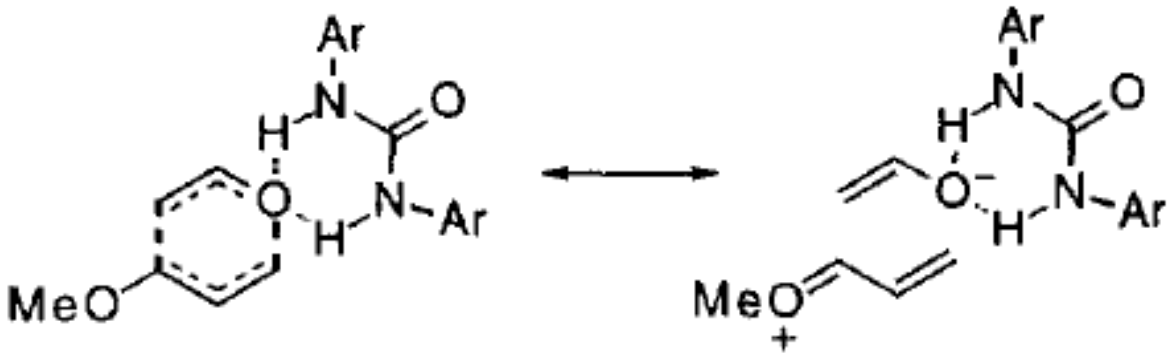
entry	solvent	additive	9b-*trans*/9b-*cis*[b] (yield, %)[c]
1	benzene	none	5.3/1 (59)
2	EtOH	none	9.8/1 (63)
3	benzene	TFE (1.0 equiv)	7.1/1 (61)
4	benzene	TFE (5 equiv)	10.3/1 (63)
5	benzene	1 (0.25 equiv)	7.1/1 (70)
6	benzene	1 (0.5 equiv)	11.3/1 (72)
7	benzene	1 (1.0 equiv)	14.1/1 (72)

Claisen rearrangement



a:R=Ph (All ***E***)
b:R=Me(***E/Z***=6.6:1)

Substrate	T (°C)	equiv **1a**	k (x 10^{-5} s^{-1})	k_{rel}
5a	100	none	0.4	1
5a	100	0.2	0.7	1.7
5a	100	0.5	1.3	3.1
5a	100	1.0	1.8	4.2
----	----	----	----	----
5b	80	none	0.6	1
5b	80	0.1	1.6	2.7
5b	80	0.4	3.1	5.0
5b	80	1.0	13.7	22.4



bis-hydrogen bonded transtion state

Tetrahedron Lett. 1995, **36**, 6647.

2.Brief Introduction to the Pioneers in This Filed

Eric Jacobsen

Albrecht Berkessel

Yoshiji Takemoto

Carlos F. Barbas

Eric Jacobsen

Education:
1978-1982: New York University, New York, New York.
Degree awarded: B.S. in Chemistry
Research advisor (1981-1982): Professor Yorke E. Rhode

1982-1986: University of California, Berkeley, California.
Degree awarded: Ph.D.
Research advisor: Professor Robert G. Bergman
Thesis title: Synthesis and Reactions of Dinuclear Transition Metal Complexes Containing Bridging Ligands Relevant to Heterogeneous Catalysis

1986-1988: National Institutes of Health Postdoctoral Fellow
Massachusetts Institute of Technology, Cambridge, Massachusetts.
Research advisor: Professor K. Barry Sharpless
Development of the osmium-catalyzed asymmetric dihydroxylation reaction

Empolyment:1993-present: Harvard University
Professor (July 1993-June 2001)
Sheldon Emery Professor of Chemistry (July 2001-present)

1988-1993: University of Illinois at Urbana-Champaign
Assistant Professor (June 1988-September 1991)
Associate Professor (September 1991-June 1993)

Consulting: Firmenich, Geneva, Switzerland, since 2009 (consultant)

Importaant Awards and Honors:
ACS H.C. Brown Award for Synthetic Methods (2008)
Van't Hoff Prize (1998)
Thieme-IUPAC Award in Synthetic Organic Chemistry (1996)
Arthur C. Cope Scholar (1994)

Member, Editorial Board: Advanced Synthesis and Catalysis, Science of Synthesis
Editorial Advisory Board: Journal of Organic Chemistry, Synthesis, Synlett, Organic Letters, Journal of Combinatorial Chemistry, Journal of Molecular Catalysis, Current Opinion in Drug Discovery & Development, Chemistry: An Asian Journal

Yoshiji Takemoto

Education
Bachelor: Osaka University, Faculty of Pharmaceutical Sciences (1983)
Master: Osaka University, Faculty of Pharmaceutical Sciences (1985)
Ph.D.: Osaka University, Faculty of Pharmaceutical Sciences (1988)
Postdoctoral Fellow: Florida State University, Department of Chemistry (Prof. R. A. Holton), 1988-1989, Sagami Chemical Research Center (Dr. S. Terashima), 1989-1990

Academic Position
Research Associate, Osaka University, Faculty of Pharmaceutical Sciences (1990-1998)
Associsate Professor, Kyoto University, Graduate School of Pharmaceutical Sciences (1998-2000)
Professor, Kyoto University, Graduate School of Pharmaceutical Sciences (2000-present)

Research Interests:
1. Development of new enantio- and stereoselective synthetic methods involving transition-metal catalysts.
2. Development of environmentally friendly synthetic methods for process chemistry.
3. Total synthesis of biologically important synthetic and natural products.
4. Synthetic studies on multi-functional heterocyclic compounds and their use as drug-templates

Albrecht Berkessel

1955: born in Saarlouis
1976-82: studies in chemistry (Diploma) at the Universität Saarbrücken
1985: PhD Universität Würzburg (Prof. W. Adam)
1985-86: post-doc at Columbia University, New York, USA (Prof. R. Breslow)
1990: habilitation at the Universität Frankfurt (Prof. G. Quinkert)
1992-97: associate professor at the Universität Heidelberg
since 1997: full professor at the Universität zu Köln

visiting profesor at the University of Wisconsin, Madison, USA (1995)
lecturer scholarship of the Fonds der Chemischen Industrie (1991-96)
yearly award in chemistry of the Akademie der Wissenschaften zu Göttingen (1995)
visiting professor at the Australian National University, Canberra (2000)
visiting professor at Chuo University, Tokyo, Japan (2007)
visiting professor at the National University of Singapore (2007)

Author Profile

C. F. Barbas III

*The author presented on this page has recently published his **10th article** since 2000 in Angewandte Chemie:* "*anti*-Selective Asymmetric Michael Reactions of Aldehydes and Nitroolefins Catalyzed by a Primary Amine/Thiourea": H. Uehara, C. F. Barbas III, *Angew. Chem.* **2009**, *121*, 10032–10036; *Angew. Chemie. Int. Ed.* **2009**, *48*, 9848–9852.

Carlos F. Barbas III

Date of birth:	November 5, 1964
Position:	Kellogg Professor of Chemistry and Molecular Biology, The Scripps Research Institute (USA)
Education:	1981–1985 BS degree in Chemistry and Physics, Eckerd College, Florida (USA) 1985–1989 PhD with Chi-Huey Wong, Texas A&M University (USA) 1989–1991 Postdoc with Richard Lerner and Steven Benkovic, The Scripps Research Institute (USA)
Professional associations:	ACS; Fellow of the AAAS; Protein Society; Director of Cold Spring Harbor Laboratory Annual Course on "Phage Display Of Proteins & Peptides"; Board of Consulting Editors for Bioorganic & Medicinal Chemistry Letter and Bioorganic & Medicinal Chemistry; American Society for Microbiology; International Advisory Editorial Board for Chemical Society Reviews; Editorial Board, MedChemComm; Founder of the biotechnology companies Prolifaron, CovX, and Zyngenia and inventor of their underlying core technologies
Awards:	**2009** Arthur C. Cope Scholar Award; **2009** Tetrahedron Young Investigator Award—Bioorganic & Medicinal Chemistry; Since **2003**, ISI Highly Cited Researcher; **2000** Co-recipient of the Presidential Green Chemistry Challenge Award; **1993–1997** Investigator Award, Cancer Research Institute; **1992–1995** Scholar of The American Foundation for AIDS Research
Current research interests:	Advancing the science of therapeutic antibodies, vaccines, zinc-finger technology, and asymmetric catalysis with organic molecules through studies at the interfaces of chemistry, biology, and medicine; Chemical reactivity and molecular recognition; Development of new classes of drugs and vaccines for cancer and HIV-1
Hobbies:	Travel, hiking, scuba diving, snow boarding, anything with my children

My biggest inspiration is … the life work of Paul Ehrlich.

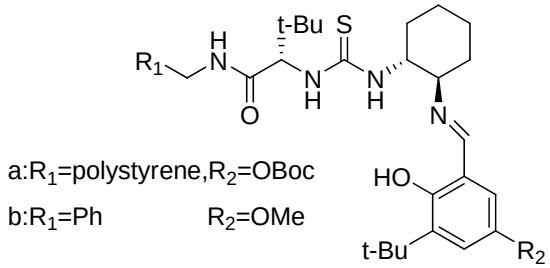
My favorite subject at school was … science of course.

A good work day begins with … an espresso and the New York Times.

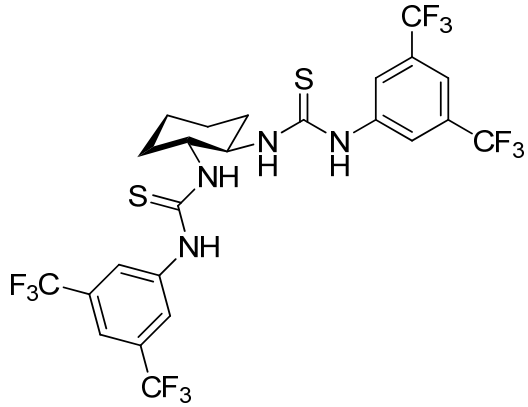
The biggest problem that scientists face is … educating the public and lobbying governments to fund science properly.

3.Catalyst And Asymmetric Catalytic Reaction

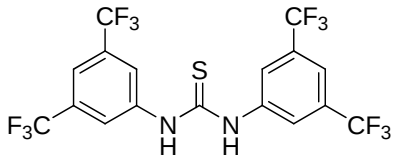
concept for catalyst development.



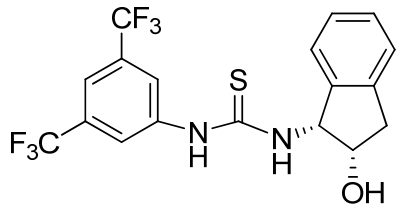
1998:Jacobsen's chiral (polymer-bound) Schiff base thiourea derivative
J. Am. Chem. Soc. 1998, 120, 4901-4902; *Angew. Chem. Int. Ed*. 2000, 39, 1279-1281



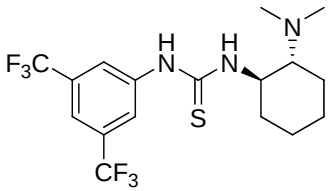
2004: Nagasawa's chiral bis-thiourea organocatalyst
Tetrahedron Letters, 2004, 45, 5589-5592



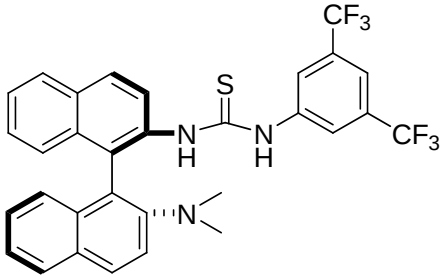
2001: Schreiner's N,N'-bis[3,5-bis(trifluoromethyl)phenyl thiourea
Org. Lett. 2002, 4, 217-220; *Chem. Eur. J*. 2003, 9, 407-414



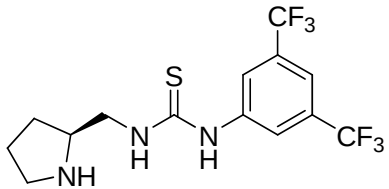
2005: Ricci's chiral thiourea derivative with additional hydroxy-group
Angew. Chem. Int. Ed. 2005, 44, 6576-6579



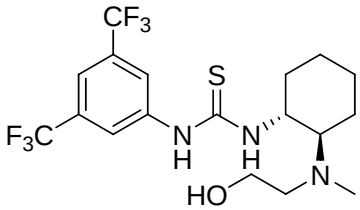
2003: Takemoto's bifunctional chiral thiourea derivative
J. Am. Chem. Soc. 2003, 125, 12672-12673



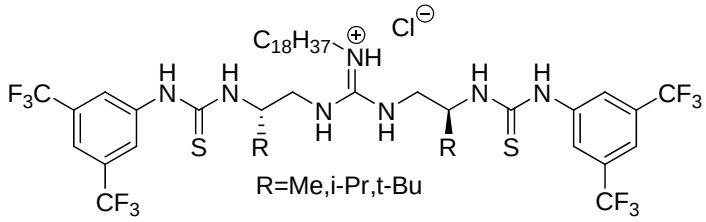
2005: Wei Wang's bifunctional binaphthyl-thiourea derivative
Org. Lett. 2005, 7, 4293-4296



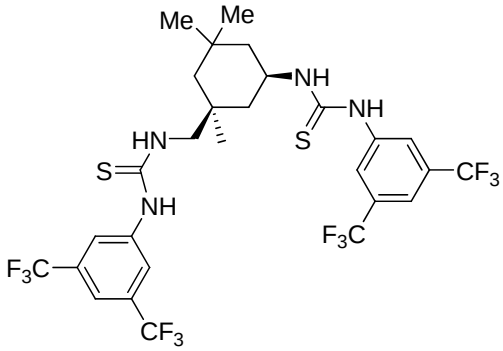
2006: Yong Tang's chiral bifunctional pyrrolidine-thiourea
Org. Lett. 2006, 8, 2901-2904



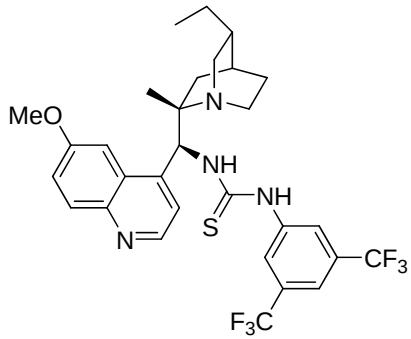
2007: Takemoto's chelating bifunctional hydroxy-thiourea
J. Am. Chem. Soc. 2007, 129, 6686-6687



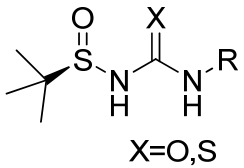
2005: Nagasawa's bifunctional thiourea functionalized guanidine
Adv. Synth. Catal. 2005, 347, 1643-1648



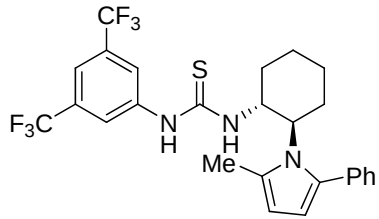
2006: Berkessel's chiral isophoronediamine-derived bisthiourea derivative
Org. Lett. 2006, 8, 4195-4198

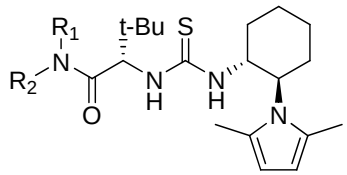


2005: Soos's and Connon's bifunctional thiourea funtionalized Cinchona alkaloid
Org. Lett. 2005, 7, 1967-1969,*Angew. Chem. Int. Ed*. 2005, 44, 6367-6370

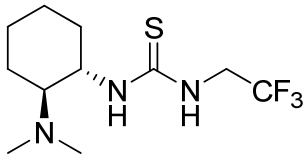


2007:Ellman's N-Sulfinyl Urea Organocatalyst
J. Am. Chem. Soc., 2007,129, 15110-15111

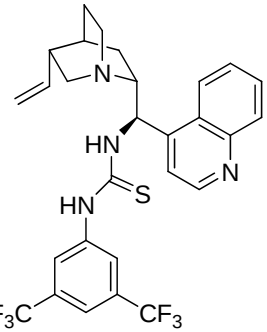




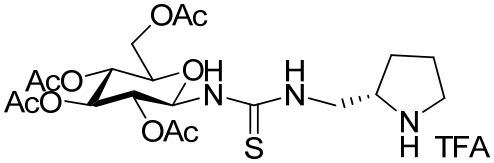
2004:Jacobsen's chiral bifuntional pyrrole-thiourea



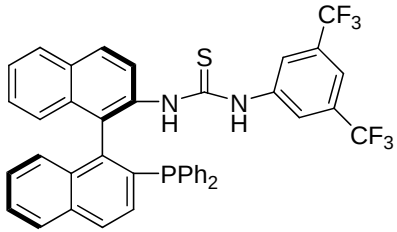
2009:Jin-Pei Cheng's Chiral Alkyl-Substituted Thiourea Catalyst
Adv. Syn. Catal. 2010,352,416-424



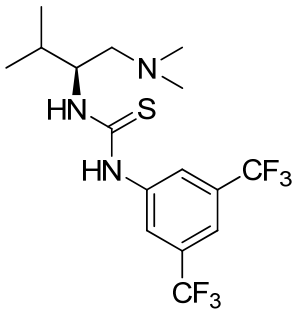
2005:Dixon's bifunctional cinchonine derivative
Chem. Commun., 2005,4481-4483;*Chem. Commun*., 2006, 1191-1193



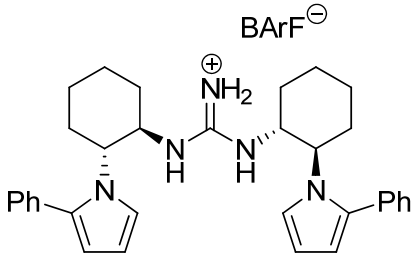
2009:Zhenghong Zhou's chiral glucose-based bifunctional secondary amine-thiourea catalyst
Org. Biomol. Chem., 2009, 7, 3141-3147



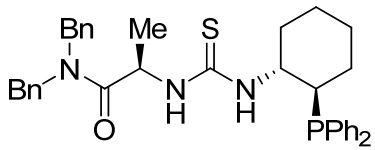
2007:Min Shi's Chiral Thiourea-Phosphine Organocatalyst
Adv. Synth. Catal. 2007, 349, 2129-2135



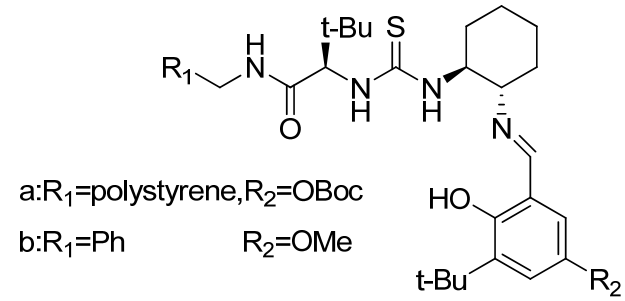
2008:Rafael Pedrosa's Bifunctional Chiral Urea and Thiourea Derivatives
Chem. Eur. J. 2008,14,5116-5119



2008:Jacobsen's Guanidinium BArF catalysts
J. Am. Chem. Soc. 2008, 130, 9228-9229



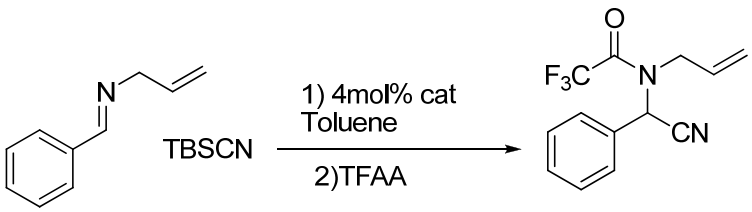
2008:Jacobsen's chiral phosphinothiourea catalysts
J. Am. Chem. Soc. 2008, 130,5660-5661

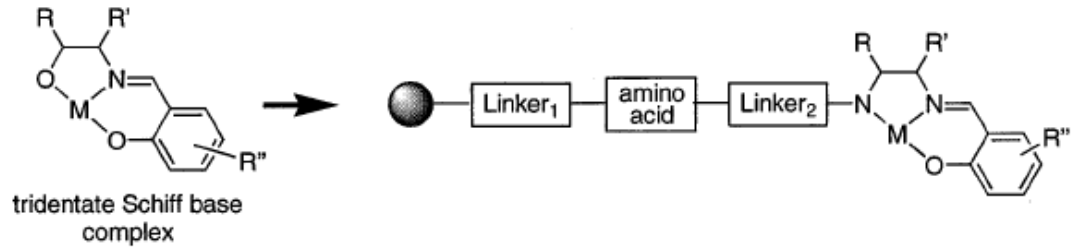


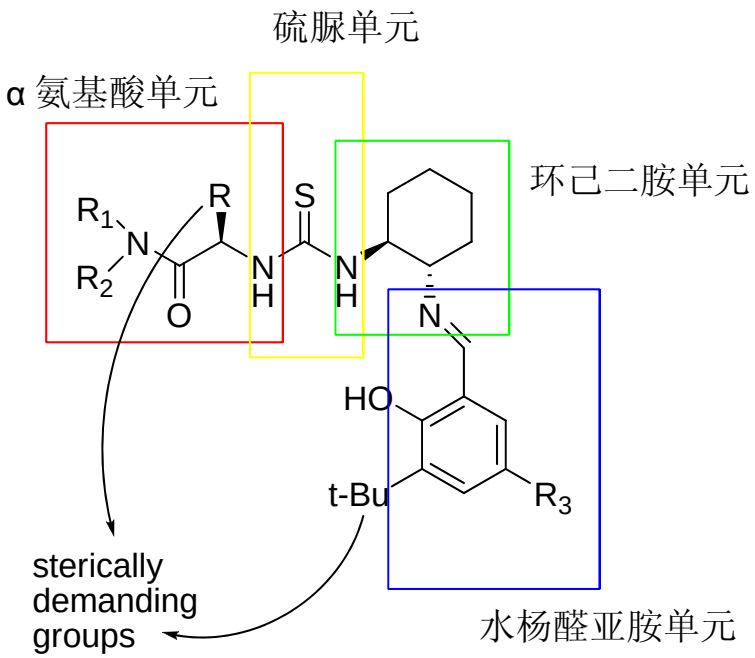
1998:Jacobsen's chiral (polymer-bound) Schiff base thiourea derivative
J. Am. Chem. Soc. 1998, 120, 4901-4902; *Angew. Chem. Int. Ed*. 2000, 39, 1279-1281

Combinatorial chemistry

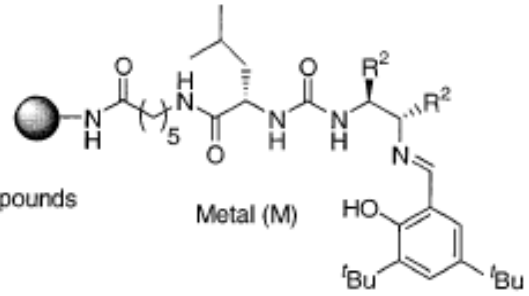
Article Title: Schiff Base Catalysts for the Asymmetric Strecker Reaction Identified and Optimized from Parallel Synthetic Libraries







Library 1

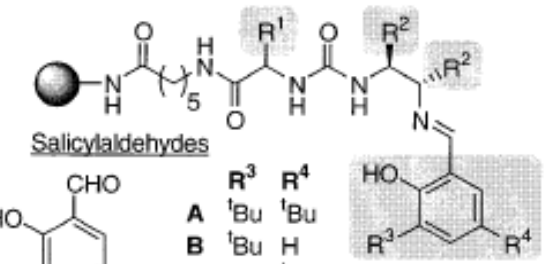


Library Size : 12 Compounds

Metal (M)

M	None	Ti	Mn	Fe	Ru	Co	Cu	Zn	Gd	Nd	Yb	Eu
e (%)	19	4	5	10	13	0	9	1	2	3	0	5
conv.(%)	59	30	61	69	63	68	55	91	95	84	94	34

Library 2



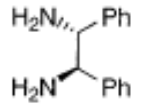
Amino Acid

Leu, D-Leu, His

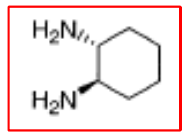
Phg (Phenylglycine)

Diamines

DP



CH

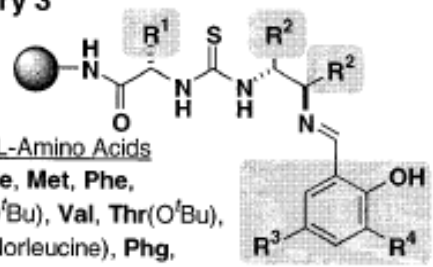


Salicylaldehydes

	R^3	R^4
A	^{t}Bu	^{t}Bu
B	^{t}Bu	H
C	H	^{t}Bu
D	^{t}Bu	OMe
E	Br	Br
F	^{t}Bu	NO_2

Library Size: 48 Compounds

Library 3



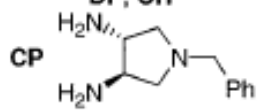
L-Amino Acids

Leu, Ile, Met, Phe,
Tyr (O^{t}Bu), **Val, Thr**(O^{t}Bu),
Nor (Norleucine), **Phg,**
Chg (Cyclohexylglycine),
***t*-Leu** (*tert*-Leucine)

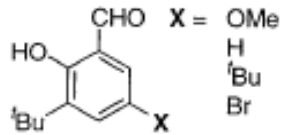
(*R, R*)-Diamines

DP, CH

CP



Salicylaldehydes

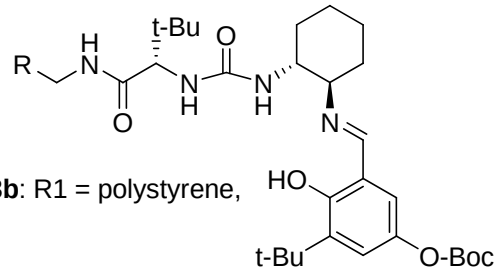


X = OMe, H, ^{t}Bu, Br

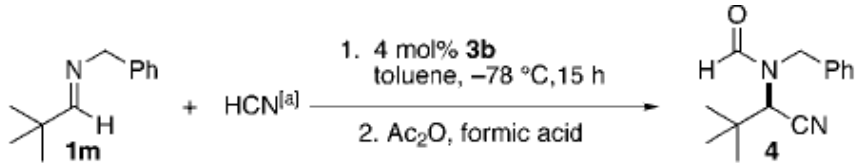
Library Size: 132 Compounds

A General Catalyst:

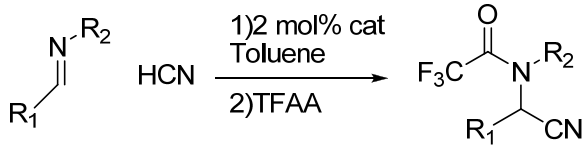
hydrogencyanide to imines and Ketoimines

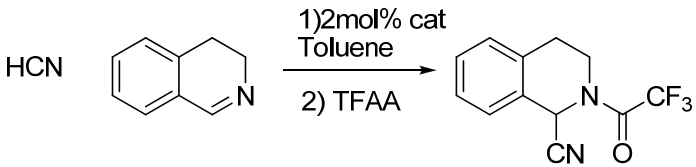


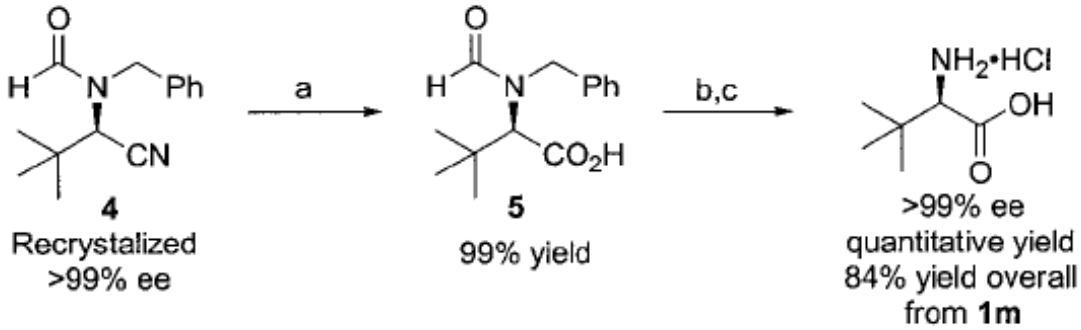
3b: R1 = polystyrene,



Cycle[b]	Yield [%][c]	*ee* [%]
1	97	92
2	98	93
3	98	93
4	97	93
5	97	92
6	96	93
7	98	93
8	97	93
9	98	93
10	98	93

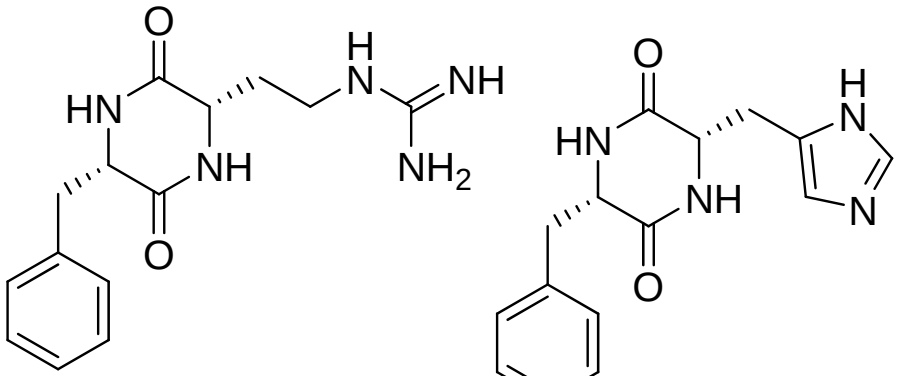






Scheme 2. Hydrolysis and deformylation of **4**. a) 65% (w/v) H_2SO_4, 45 °C, 20 h; b) HCl (conc.), 70 °C, 12 h; c) H_2, Pd/C, MeOH.

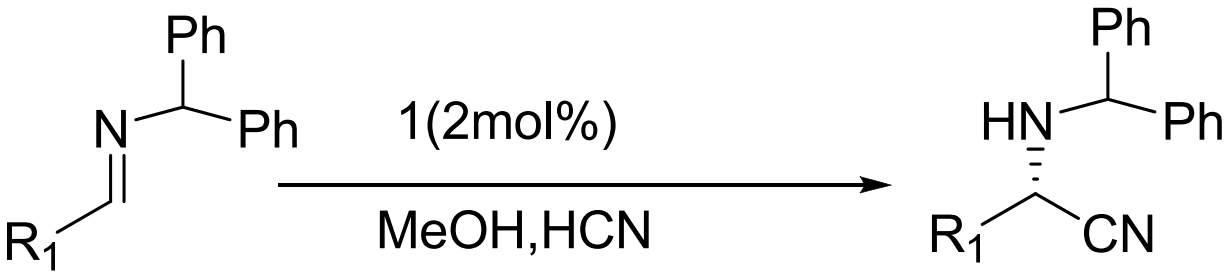
Mark Lipton*,*J. Am. Chem. Soc.* **1996,** *118,* 4910-4911



1

2

2 fails to afford any asymmetric induction in the mechanistically similar Strecker synthesis,

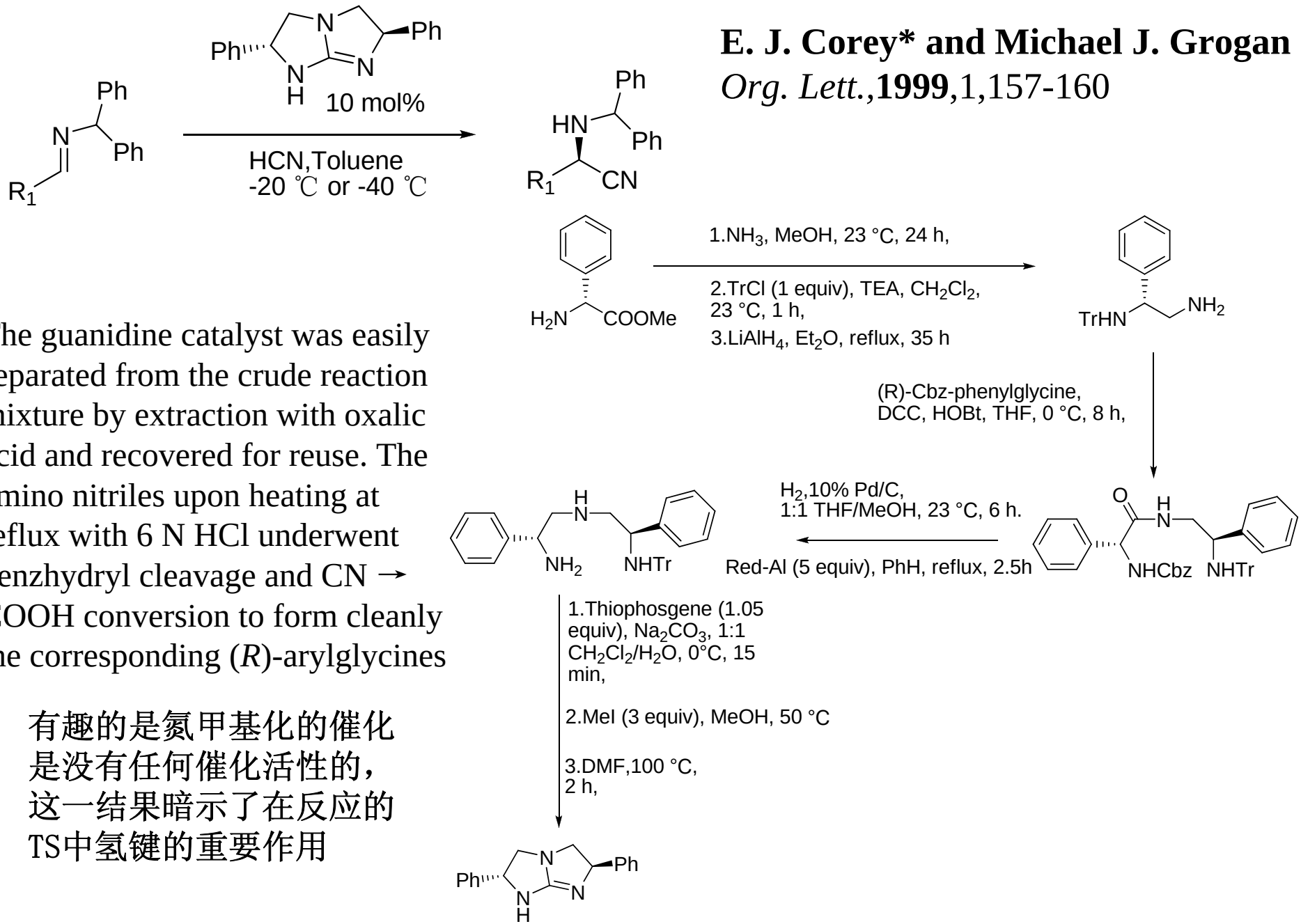


Substrate range:aromatic,heteraromatic,aliphatic

LIPTON小组试图在此二肽催化剂存在下使用苯甲醛、氨和氰化物进行直接的Strecker反应，得到的却是外消旋的氨基腈。

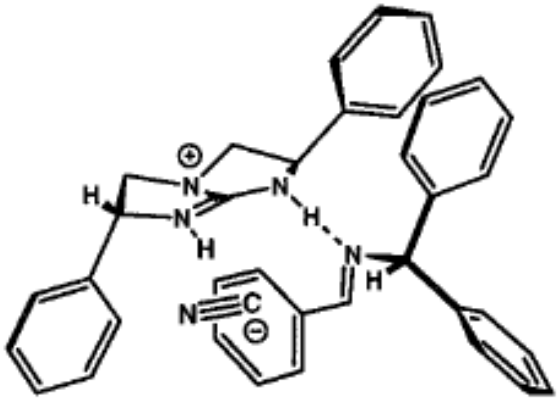
E. J. Corey* and Michael J. Grogan

Org. Lett.,**1999**,1,157-160

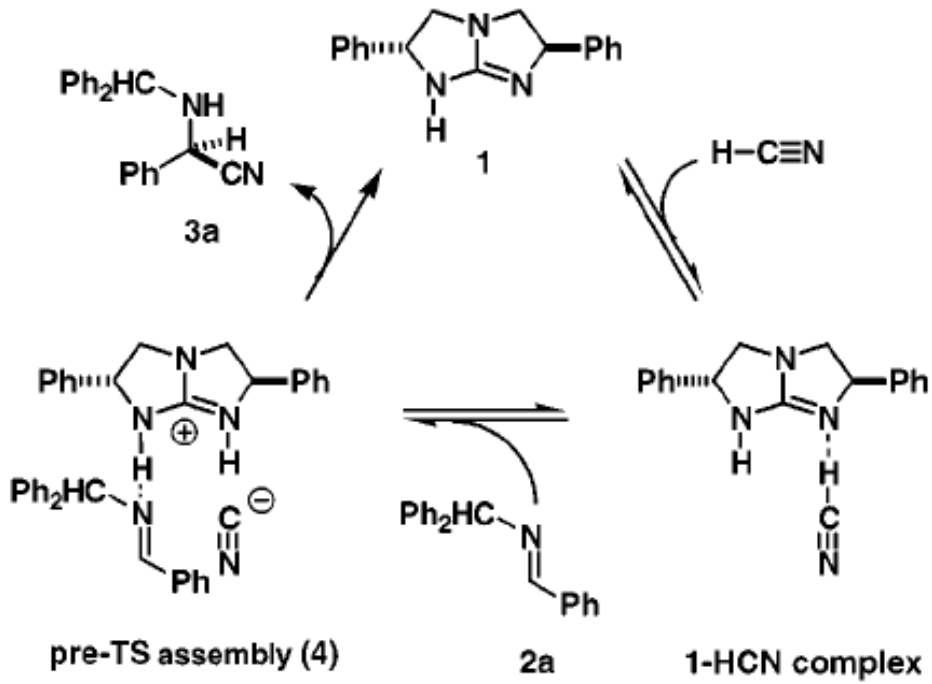


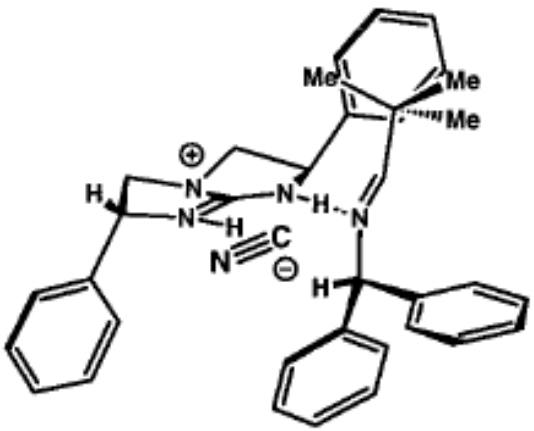
The guanidine catalyst was easily separated from the crude reaction mixture by extraction with oxalic acid and recovered for reuse. The amino nitriles upon heating at reflux with 6 N HCl underwent benzhydryl cleavage and CN → COOH conversion to form cleanly the corresponding (*R*)-arylglycines

有趣的是氮甲基化的催化是没有任何催化活性的，这一结果暗示了在反应的TS中氢键的重要作用



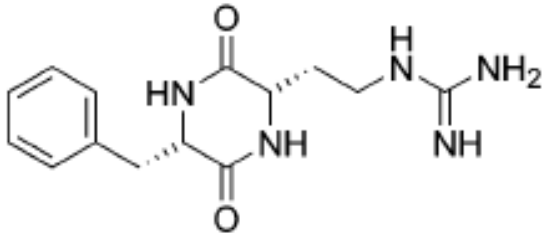
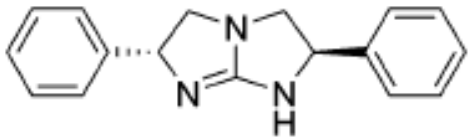
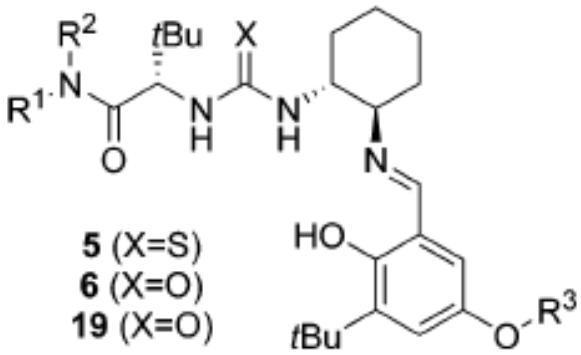
4





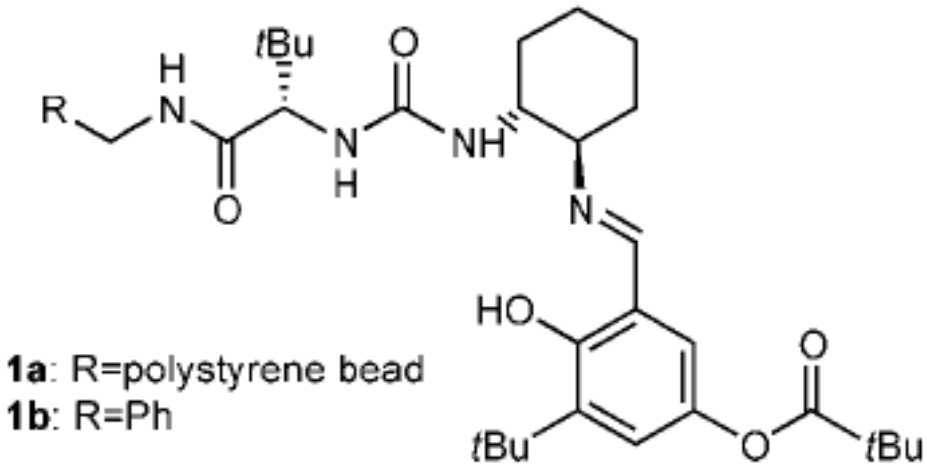
5

The inversion of product configuration from *R* for aromatic imines to *S* for aliphatic imines indicates that alkyl groups incur steric repulsions in the vacant quadrant of guanidine where an imine aryl or a benzhydryl phenyl gains van der Waals attractions.

catalyst structure	substrate range	catalytic amount	range of yield [%]	range of ee [%]
 **3**	aromatic aldimines (not NO_2- subst. and heteroatoms)	2 mol%	82-97	80-99
 **4**	aromatic, aliphatic aldimines	10 mol%	80-99	50-88
 **5** (X=S) **6** (X=O) **19** (X=O)	aromatic, aliphatic aldimines and ketimines	1-2 mol%	65-98 45-100	77-99 42-95

Compared with Resin-bound catalyst 1a,the homogeneous analogue 1b was found to display substantially higher reactivity and to induce slightly improved enantioselectivity((1-3% ee)

But the the homogeneous analogue was more difficult to prepare than resin-bound

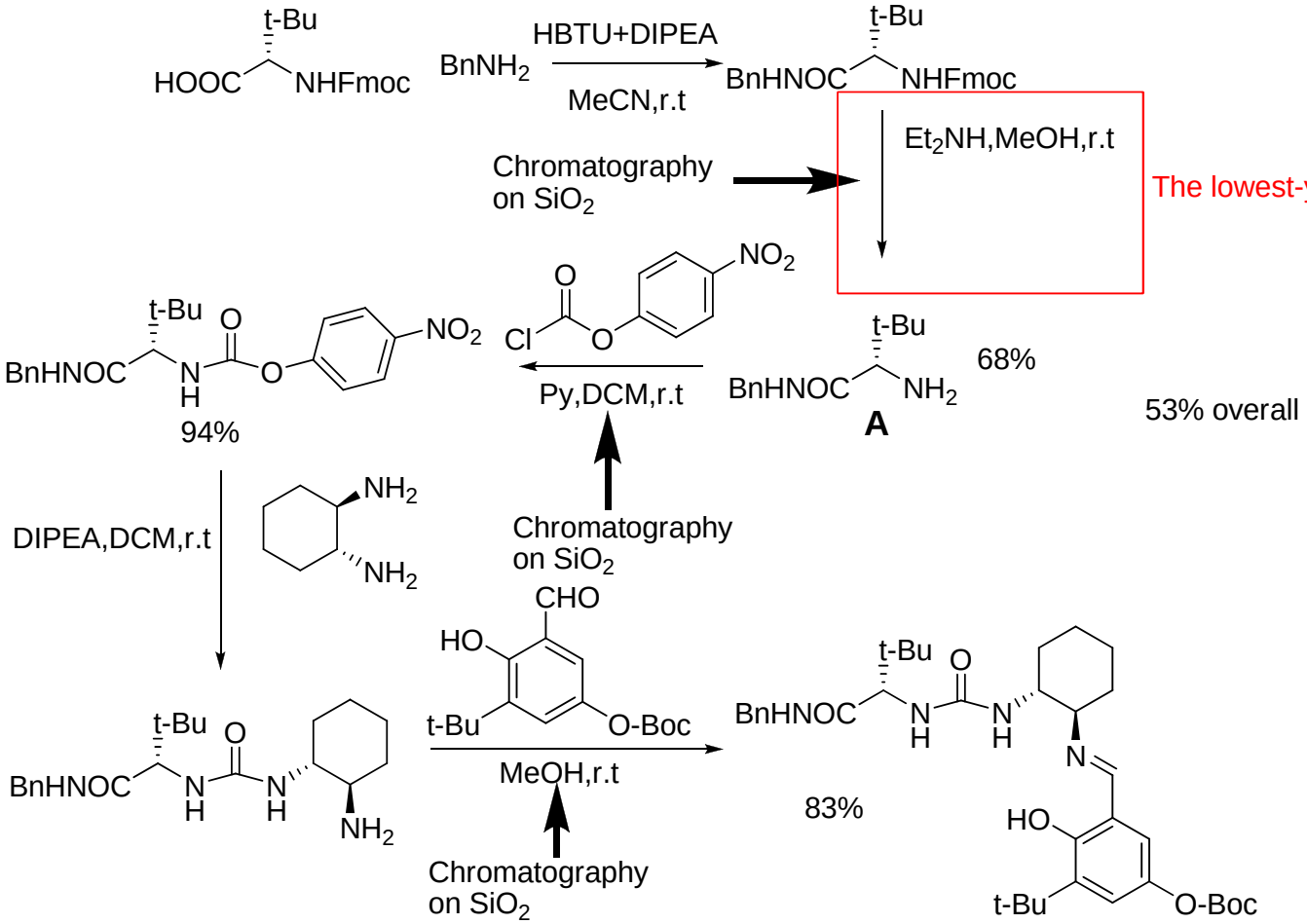


1a: R=polystyrene bead
1b: R=Ph

Practical Synthesis of Catalyst

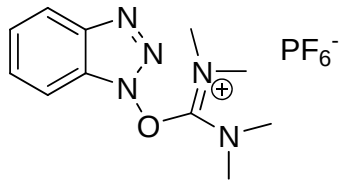
Adv. Synth. Catal. 2001,**343**,197-200

Original synthesis of Catalyst

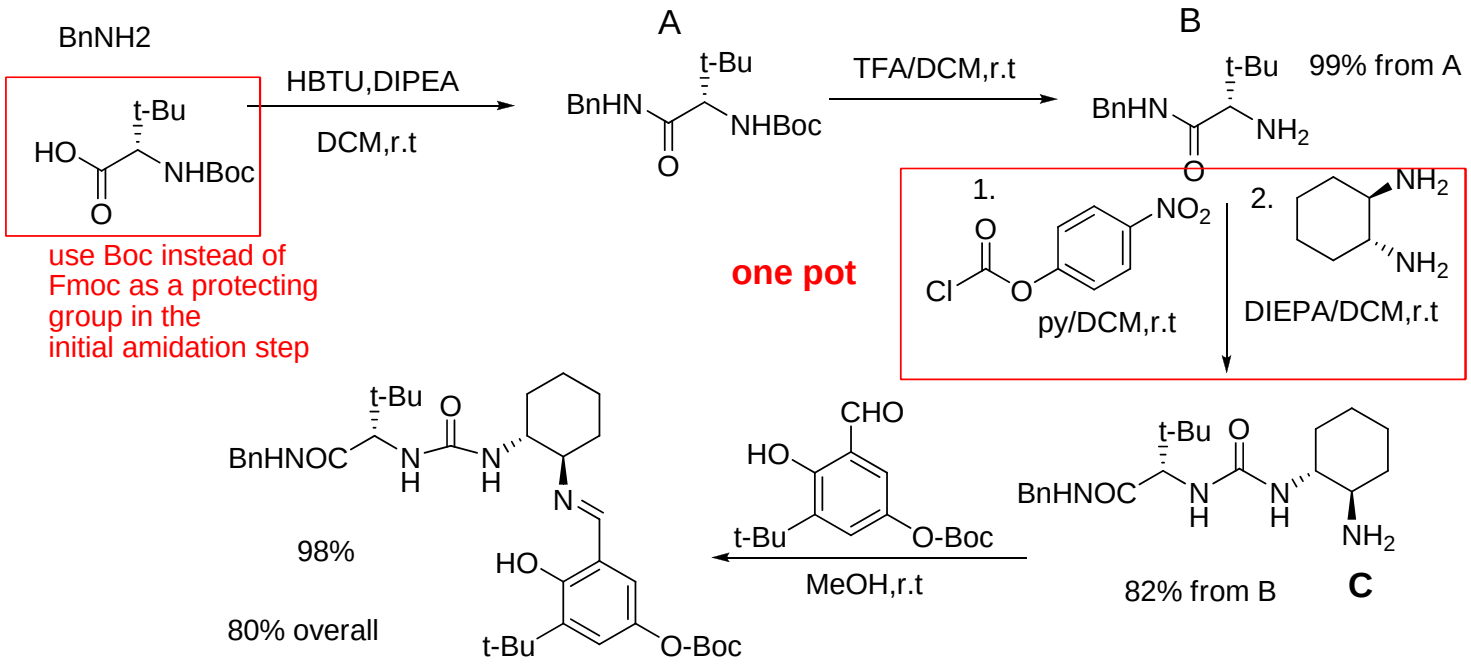


1.The product A underwent degradation in the presence of diethylamine during solvent removal.
2.Chromatography on silica gel was necessary to remove the dibenzofulvene byproduct.

HBTU:苯并三氮唑-N,N,N',N'-四甲基脲六氟磷酸盐
DIPEA:N,N-二异丙基乙胺



Optimized synthesis of Catalyst



Reaction of B with 4-nitrophenyl chloroformate proceeded with high selectivity and the crude product was shown to be >94% pure by H NMR analysis.

Since both this and the subsequent urea-forming reaction are conducted under basic conditions, they investigated the possibility of carrying out the reactions sequentially in one pot, ideally with the same base for both reactions.

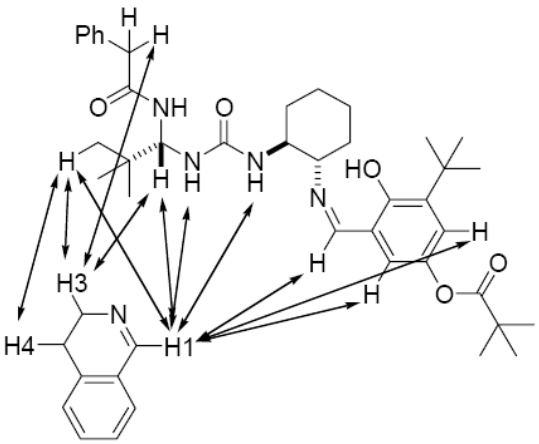
They ultimately observed that the one-pot procedure was indeed possible, although best results were obtained using pyridine for formation of carbamate and DIPEA for generation of urea **C**. Combining both reactions into a one-pot arrangement made it possible to avoid isolation and purification of the sensitive intermediate

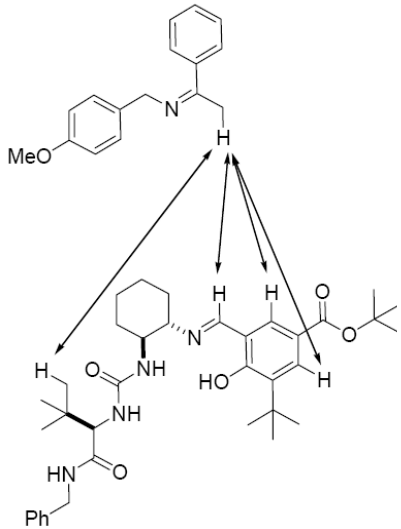
The crude product mixture of **C** was washed with aqueous sodium hydroxide to remove the 4-nitrophenol by product, leaving behind the product **C** contaminated with DIPEA, pyridine, unreacted excess diamine, and tetramethylurea. All of the components except **C** proved to be soluble in hexanes. Thus, after solvent removal, the crude solid residue was washed with hexanes to afford **C** in high purity and in 82% yield

Mechanism

J. Am. Chem. Soc. **2002**, 124, 10012-10014

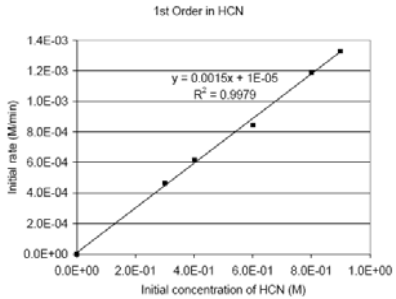
Structure-Based Analysis and Optimization of a Highly Enantioselective Catalyst for the Strecker Reaction

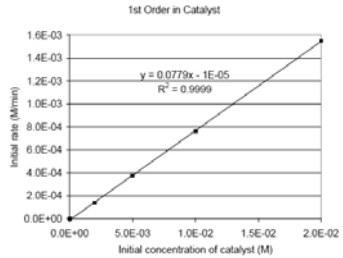


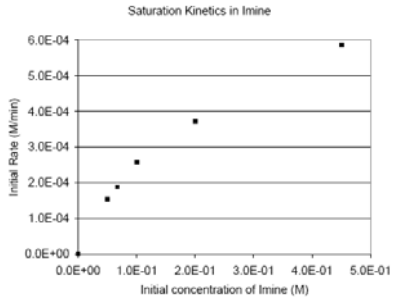


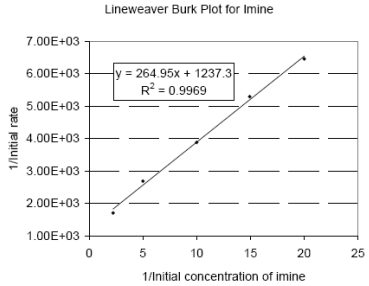
From Supportting Information

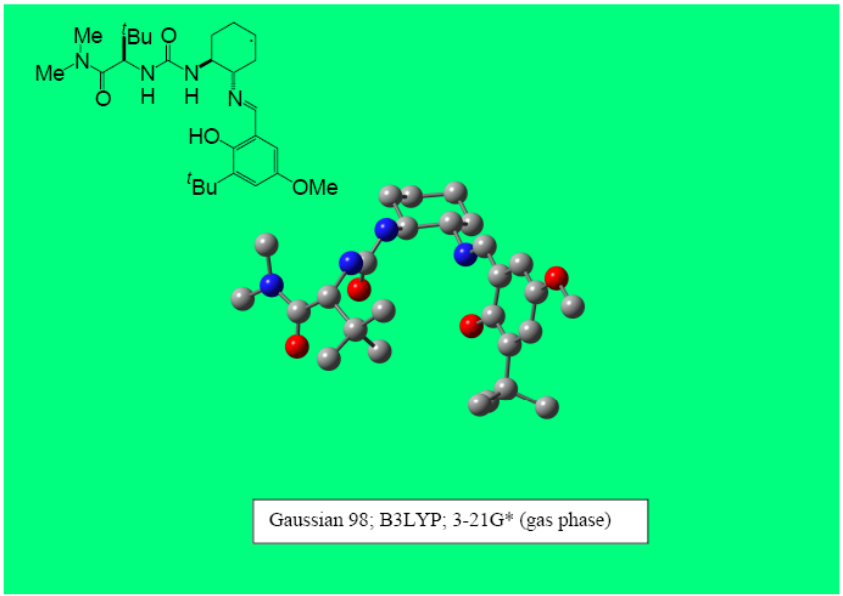
Reaction kinetics were investigated using React-IR instrument











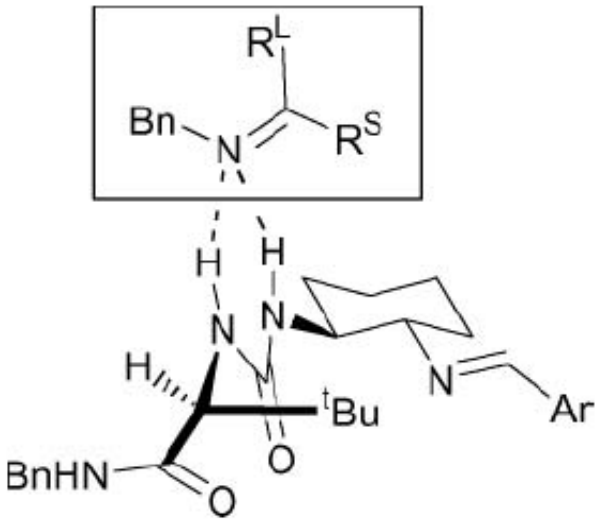
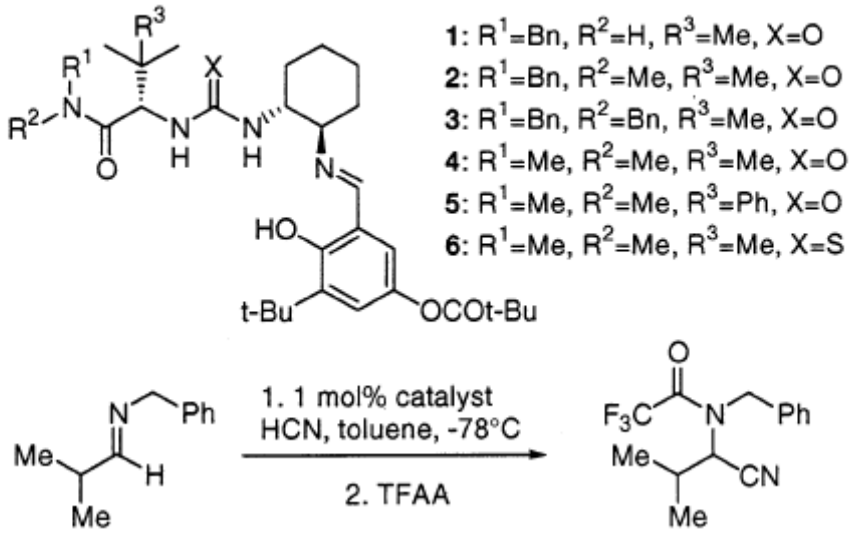


Table 1. Model-Driven Optimization of Catalyst **1**



Replacement of the urea with a thiourea group led to a measurable improvement in enantioselectivity.

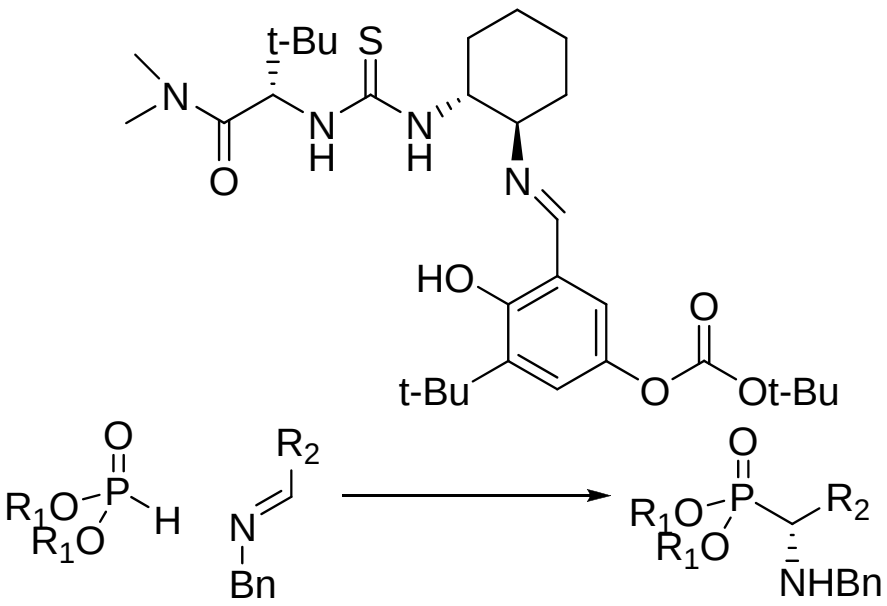
Through this mechanismdriven optimization exercise, catalyst **6** was identified as the most enantioselective Strecker catalyst prepared to date.

Following Improvement and More Work

1. Continue to Develop the catalyst
2. Develop various reactions and wide its application in natural product synthesis
3. Deeply Investigate the mechanism of reactions

J. Am. Chem. Soc. **2002**, 124, 12964-12965
J. Am. Chem. Soc. **2004**, 126, 4102-4103
J. Am. Chem. Soc. **2004**, *126*, 10558-10559
J. Am. Chem. Soc. **2005**, 127, 8964-8965
J. Am. Chem. Soc. **2006**, 128, 7170-7171
J. Am. Chem. Soc. **2007**, 129, 15872-15883
J. Am. Chem. Soc. **2008**, 130,5660-5661
J. Am. Chem. Soc., ***2008***, 130, 7198–7199
Synlett,**2003**,1919-1922
Org. Lett. **2008**, *10*, 1577–1580 (Total Synthesis of (+)-Yohimbine, acyl-Pictet-Spengler reaction)
Org. Lett.,**2009**,*11*, 887-890
Angew. Chem., Int. Ed. **2009**, *48*, 6446–6449

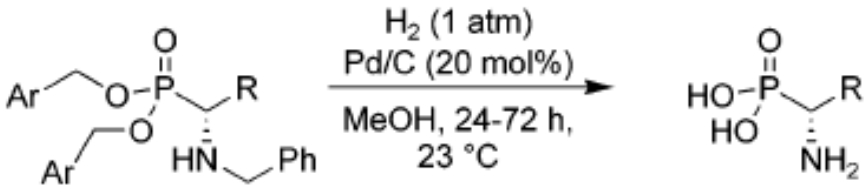
“Scaleable catalytic asymmetric Strecker syntheses of unnatural α-amino acids,” *Nature* **2009**, *461*, 968–970
“Bifunctional Asymmetric Catalysis with Hydrogen Chloride: Enantioselective Ring Opening of Aziridines Catalyzed by a Phosphinothiourea,” *Synlett* **2009**, 1680–1684 (Special Cluster Issue on Cooperative Catalysis).
“Asymmetric Cooperative Catalysis of Strong Brønsted Acid-Promoted Reactions Using Chiral Ureas,” *Science* **2010**, *327*, 986–990.



Hydrophosphonylation of Imines

J. Am. Chem. Soc. **2004**, 126, 4102-4103

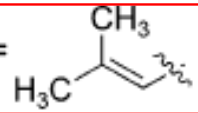
Synthesis of R-Amino Phosphonic Acids



Ar = 2-nitrophenyl

4a: R = Ph (98% *ee*)

4b: R = 3-pentyl (96% *ee*)

4f : R = 

(99% *ee*)

5a: R = Ph
(87% yield, 97% *ee*)

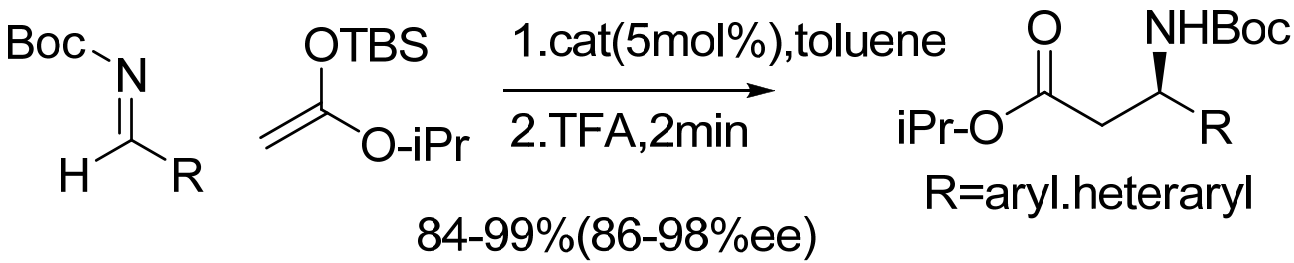
5b: R = 3-pentyl
(89% yield, 96% *ee*)

5f : R = *i*-Bu [(*R*)-Leu^P]
(93% yield, 98% *ee*)

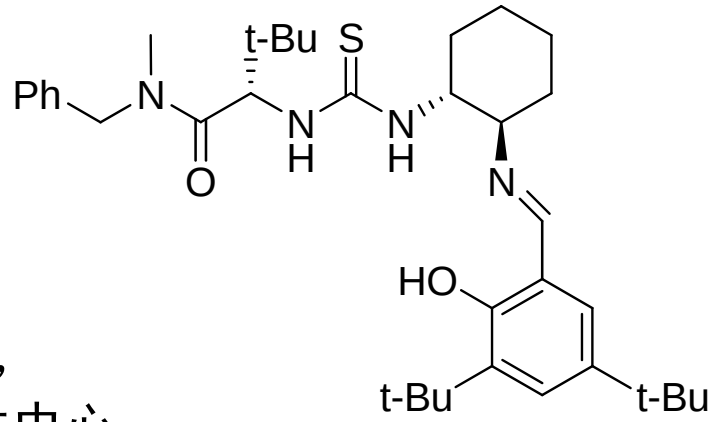
α -amino phosphonate **4f** was prepared on a one-gram scale and recrystallized to 99% ee. Subjecting adduct **4f** to the deprotection conditions resulted in concomitant hydrogenation of the olefin to provide (*R*)-LeuP **5f**, the R-amino phosphonic acid analogue of leucine and a known inhibitor（抑制剂） of leucine amino peptidase

J. Am. Chem. Soc. **2002**, 124, 12964-12965

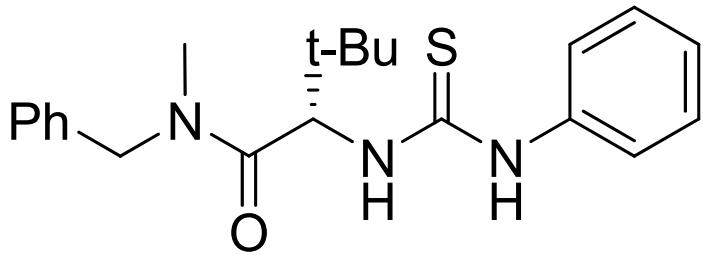
Mannich Reactions:Synthesis of a-Aryl-a-Amino Acid



84-99%(86-98%ee)

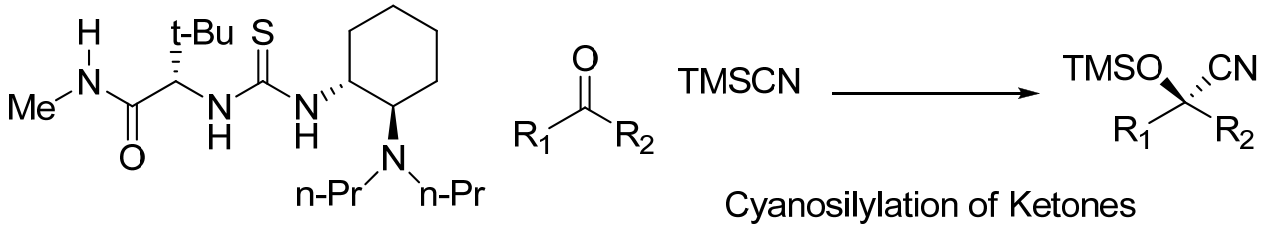


Jacobsen集中精力再次对催化剂进行了优化，
比之前的硫脲催化剂少一半的分子量和立体中心



100% yield
94 ee%

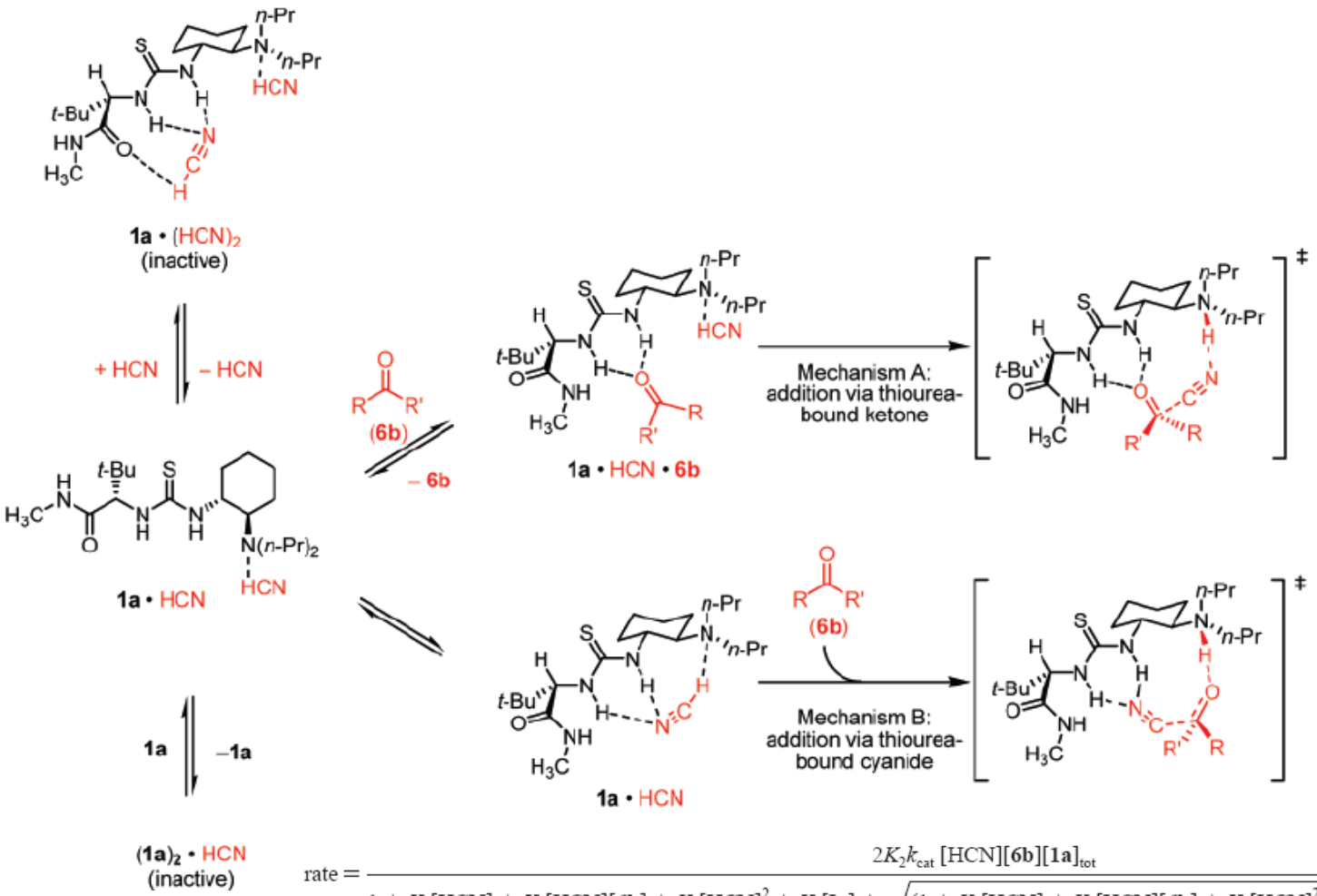
Synlett,**2003**,1919-1922



Cyanosilylation of Ketones

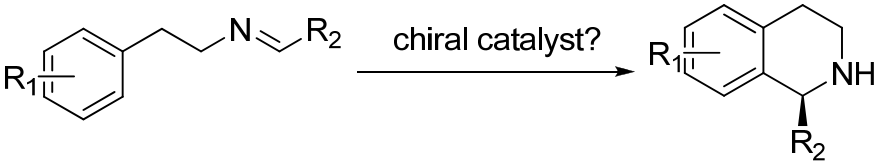
ee range from 91% to 98%

J. Am. Chem. Soc. **2005**, 127, 8964-8965

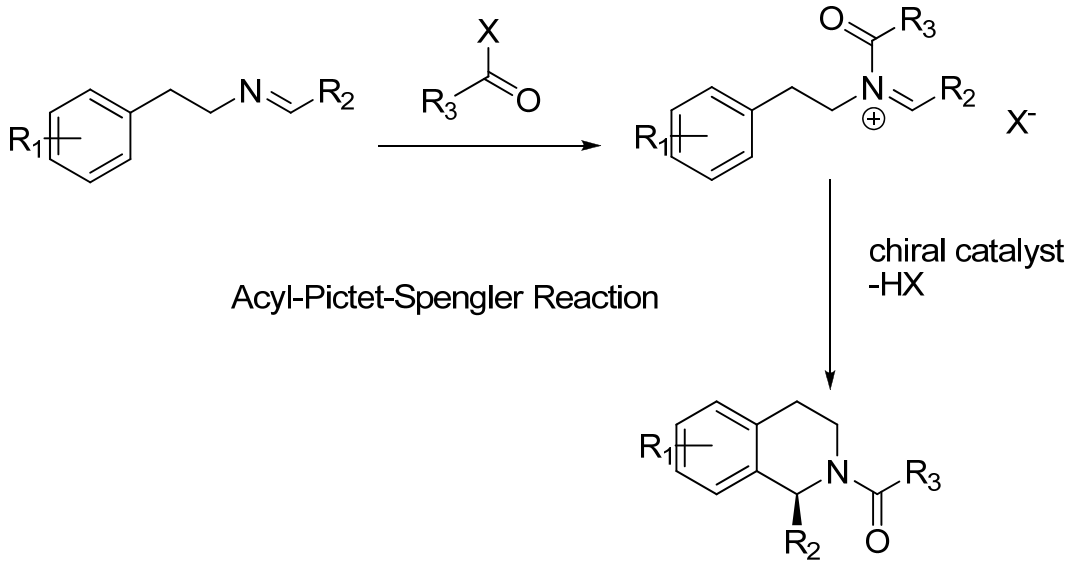


$$\text{rate} = \frac{2K_2k_{cat}\,[\text{HCN}][\mathbf{6b}][\mathbf{1a}]_{tot}}{1 + K_1[\text{HCN}] + K_2[\text{HCN}][\mathbf{6b}] + K_3[\text{HCN}]^2 + K_5[\text{In}] + \sqrt{(1 + K_1[\text{HCN}] + K_2[\text{HCN}][\mathbf{6b}] + K_3[\text{HCN}]^2 + K_5[\text{In}])^2 + 8K_3[\text{HCN}][\mathbf{1a}]_{tot}}}$$

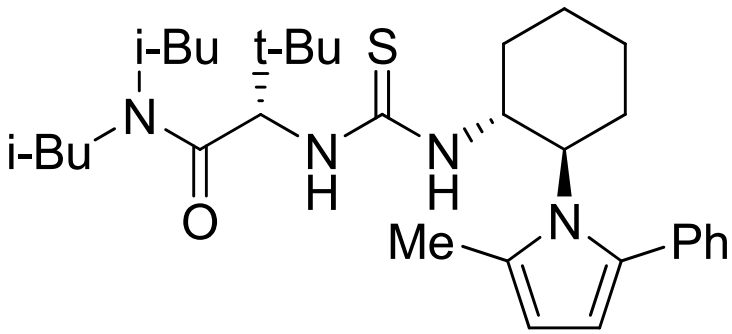
J. Am. Chem. Soc. **2007**, 129, 15872-15883

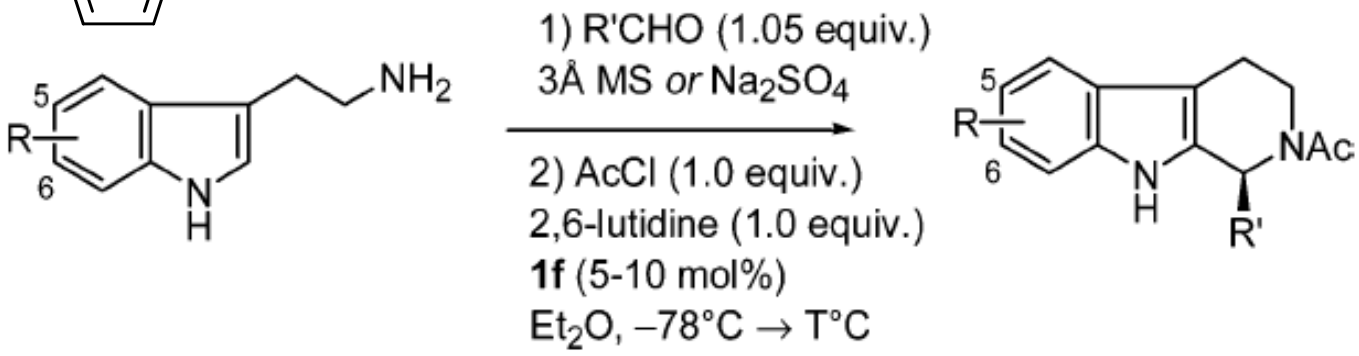


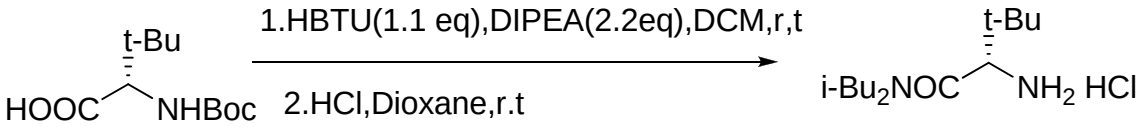
J. Am. Chem. Soc. **2004**, *126*, 10558-10559

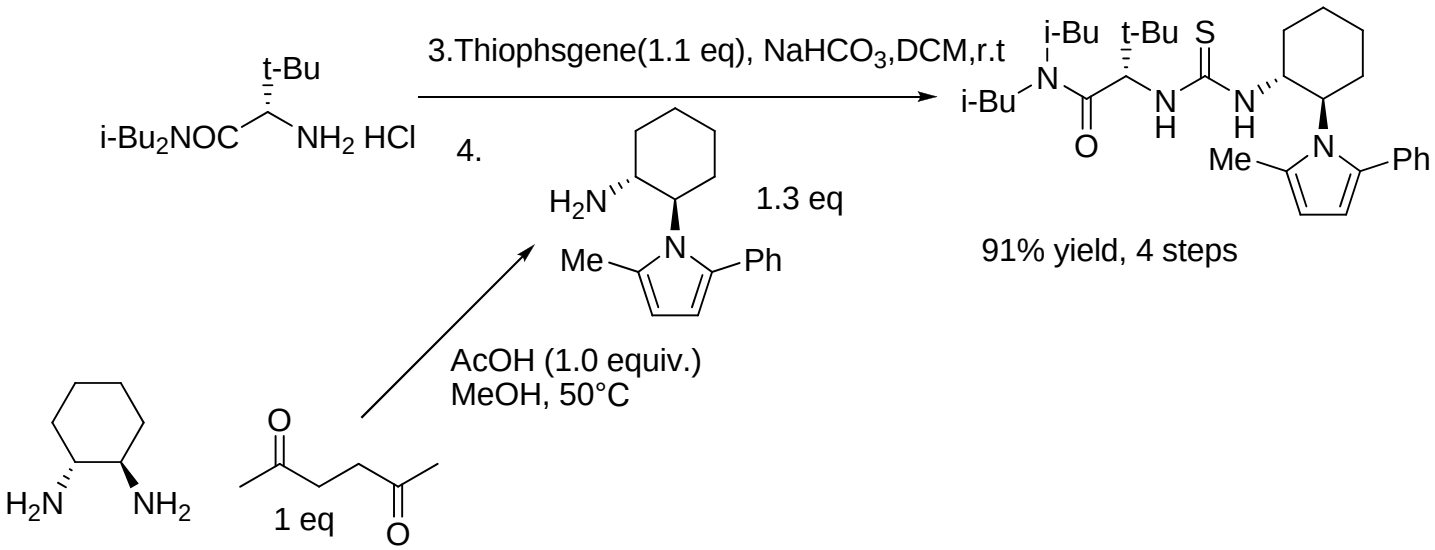


The challenge of developing an asymmetric catalytic variant of the Pictet-Spengler reaction appears to be associated with the low reactivity of the imine substrate. Most often, strong Brønsted acids are employed to promote the racemic pathway; the few reported examples of Lewis acid catalysis involve highly reactive agents, unmodified by donor ligands. In addition, high reaction temperatures are often required. They were thus not surprised to discover that a screen of potential chiral catalysts for this transformation did not afford any useful leads: all compounds tested were inactive except at high temperatures, and no enantiomerically enriched products were obtained under any conditions. These results led their to conclude that the exploration of more reactive variants of the Pictet-Spengler reaction, which could proceed under relatively mild conditions, might be key to the development of an enantioselective,catalytic process







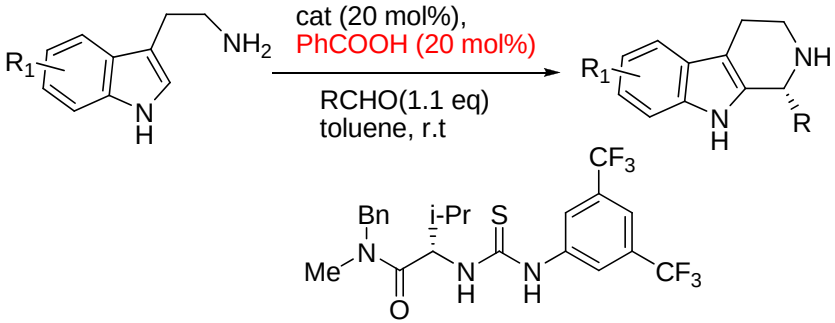


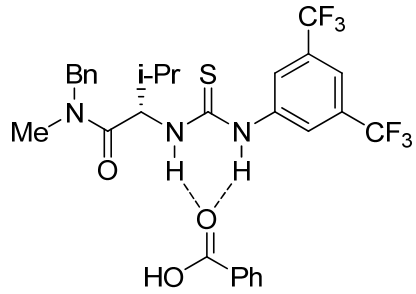
91% yield, 4 steps

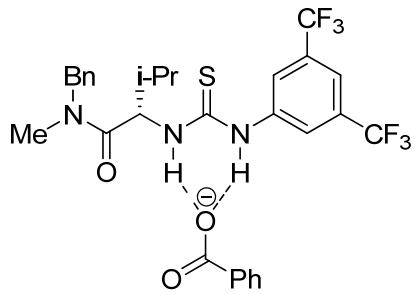
Protio-Pictet-Spengler Reaction

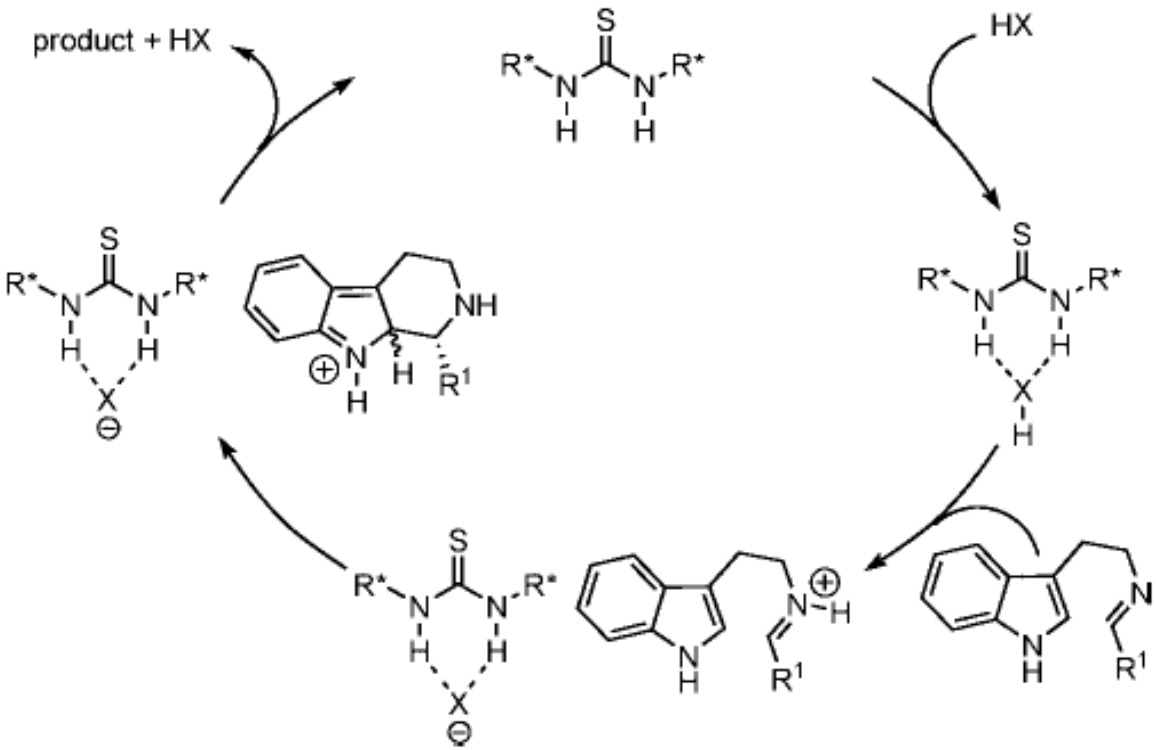
Weak Brønsted Acid-Thiourea Co-catalysis

Org. Lett.,**2009**,*11*, 887-890





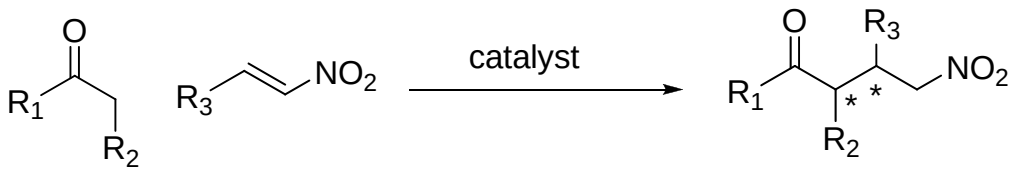


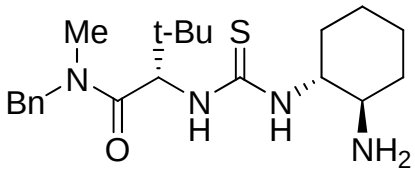


Additions of Ketones to Nitroalkenes

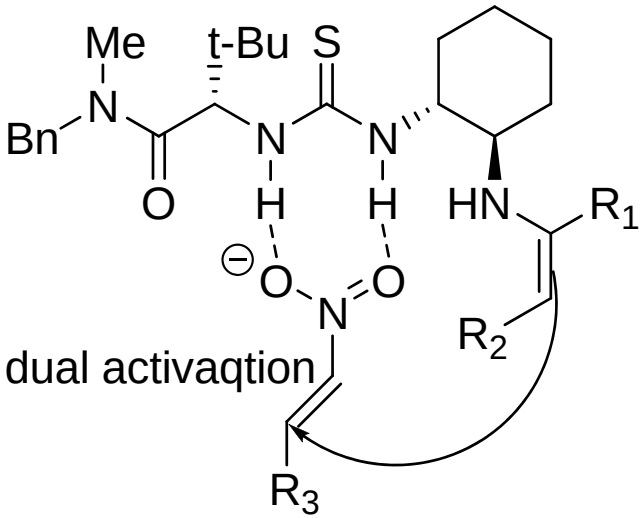
J. Am. Chem. Soc. **2006**, 128, 7170-7171

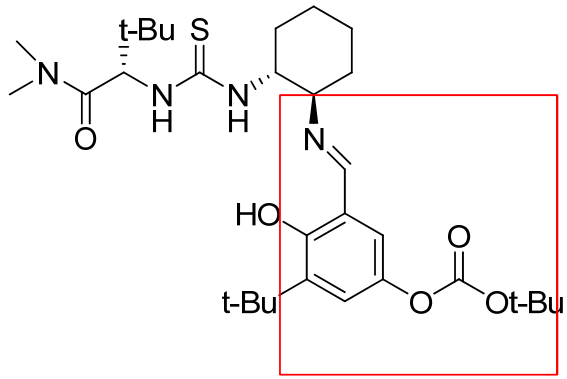
Before this article， the substrates used in their reactions are somewhat restricted to aldimines and ketomines. This limitation was over come by them in this article

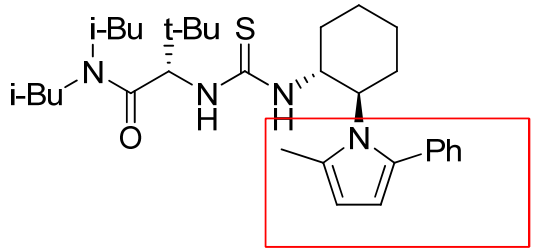




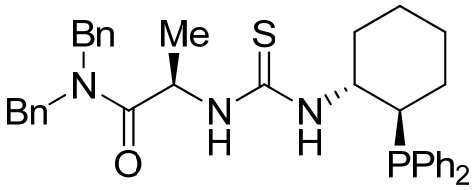
94-99 ee%





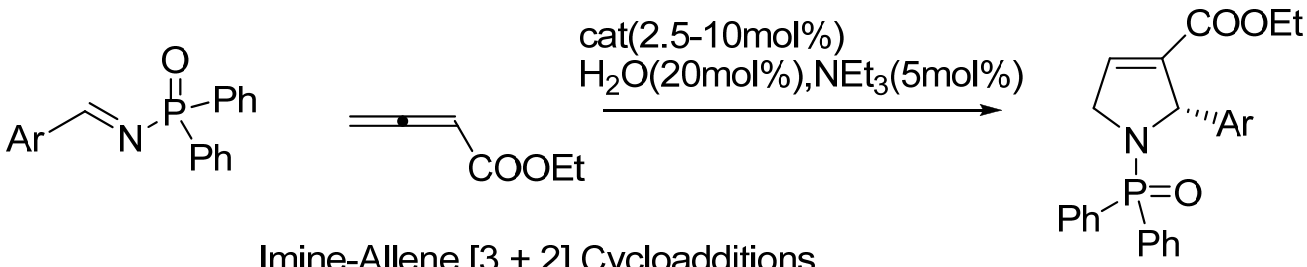


This part is replaced with a functional group

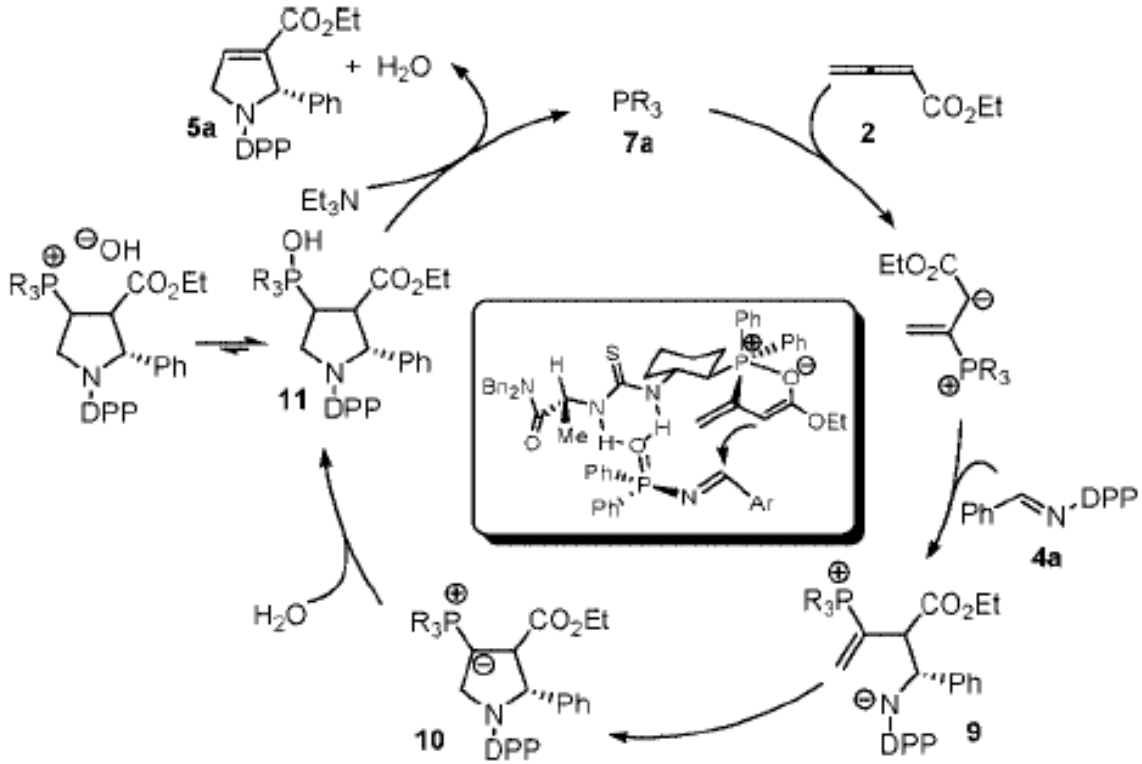


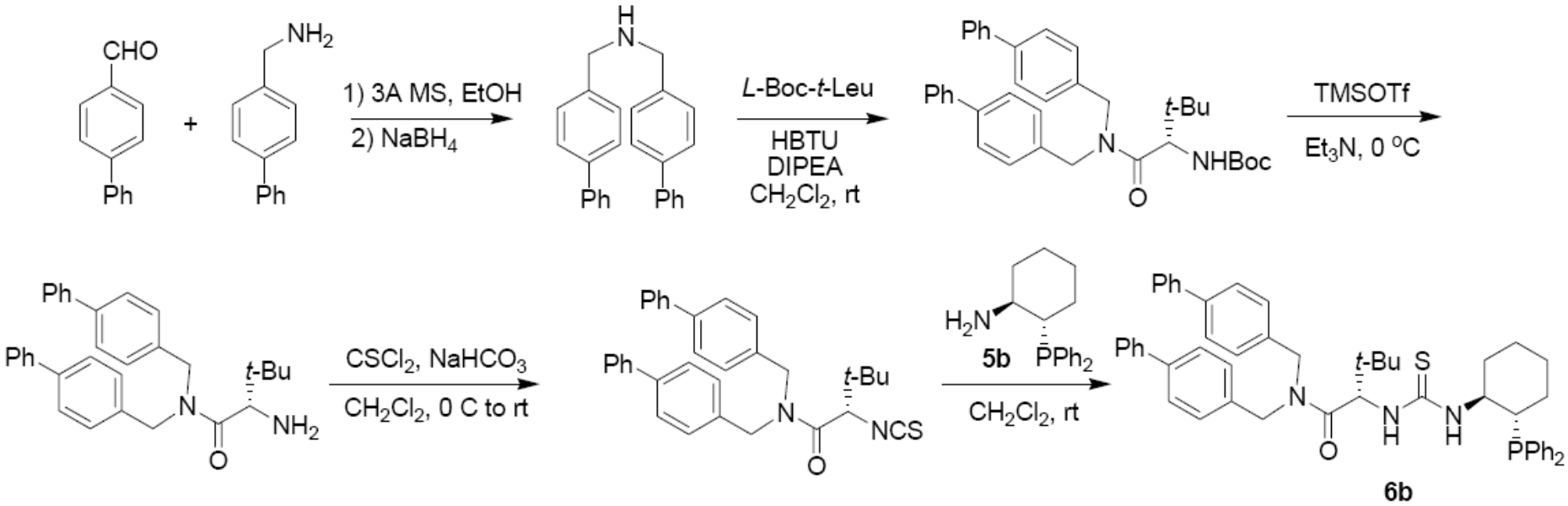
2008:Jacobsen's chiral phosphinothiourea catalysts

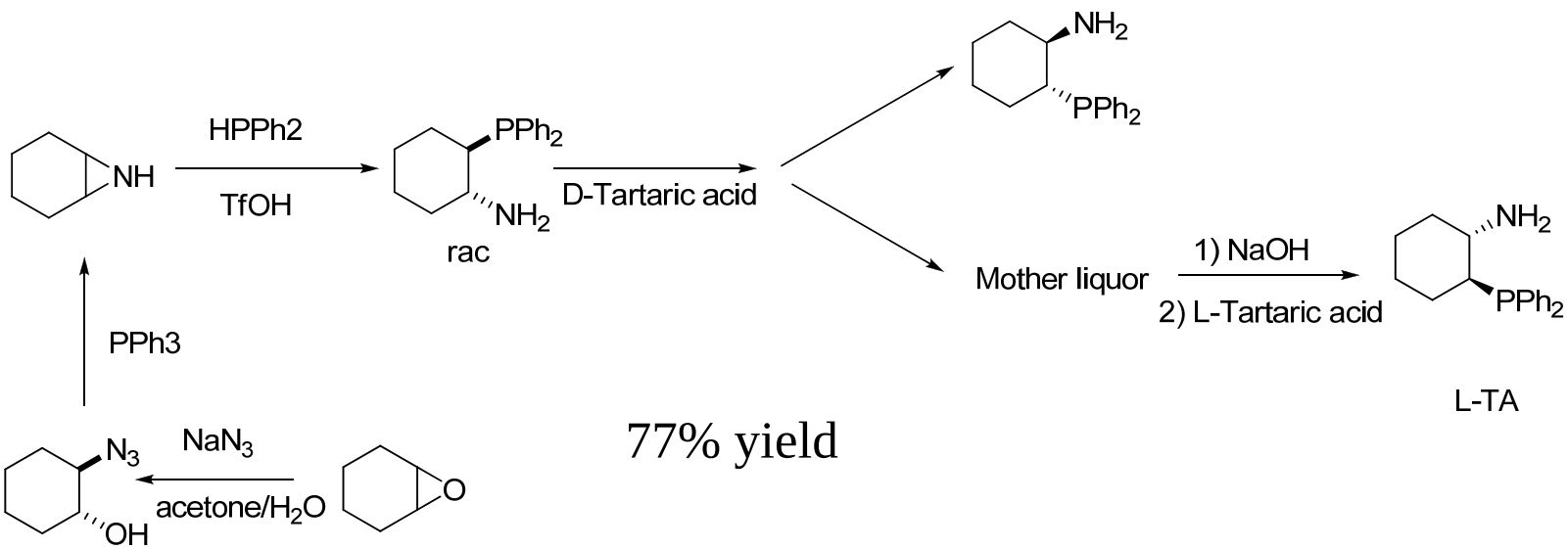
J. Am. Chem. Soc. 2008, 130,5660-5661



Imine-Allene [3 + 2] Cycloadditions

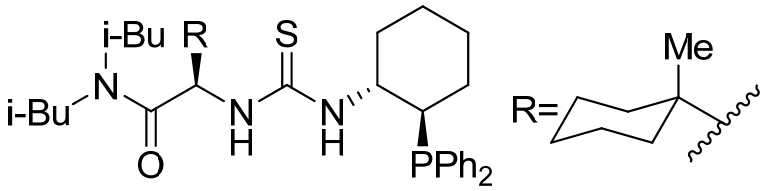


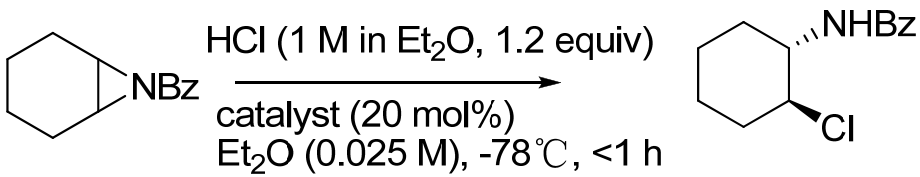

CHO
Ph
NH2
Ph
1) 3A MS, EtOH
2) NaBH4
H
N
Ph
Ph
L-Boc-t-Leu
HBTU
DIPEA
CH2Cl2, rt
Ph
Ph
t-Bu
N
O
NHBoc
TMSOTf
Et3N, 0 °C
Ph
Ph
t-Bu
N
O
NH2
CSCl2, NaHCO3
CH2Cl2, 0 C to rt
Ph
Ph
t-Bu
N
O
NCS
H2N
PPh2
5b
CH2Cl2, rt
Ph
Ph
t-Bu
S
N
O
N
H
N
H
PPh2
6b

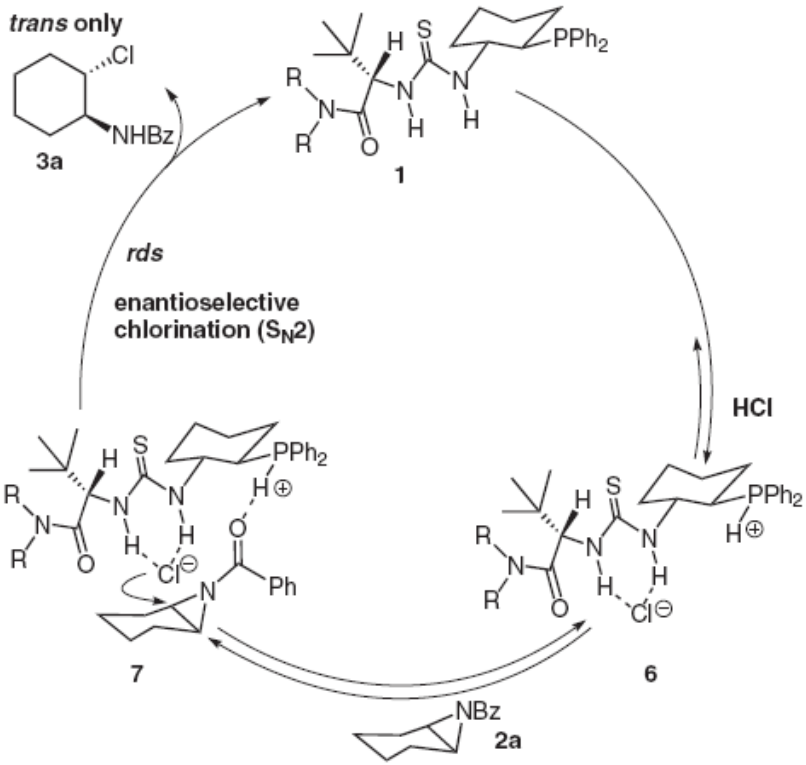

NH
HPPh2
TfOH
PPh2
NH2
rac
D-Tartaric acid
NH2
PPh2
Mother liquor
1) NaOH
2) L-Tartaric acid
NH2
PPh2
L-TA
PPh3
N3
OH
NaN3
acetone/H2O
O

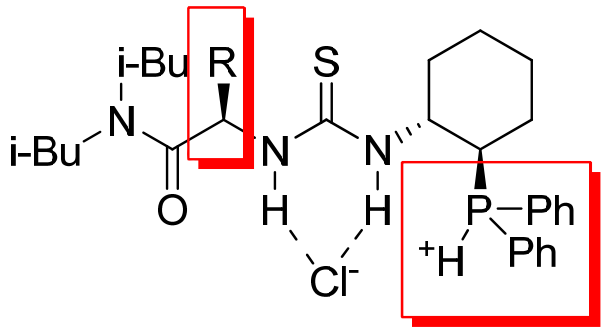
77% yield

Synlett **2009**, 1680–1684 (Special Cluster Issue on Cooperative Catalysis).







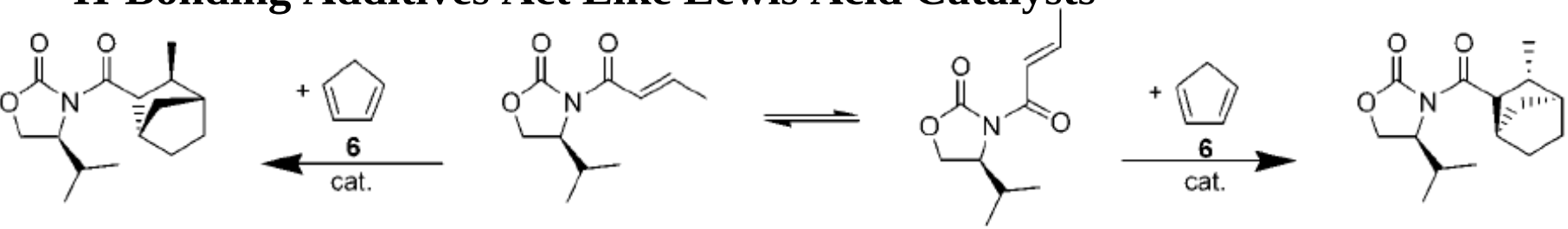


Concentration of HCl

Peter R. Schreiner,*Org. Lett.*,**2002**,4,217-220

The double hydrogen-bonding motif

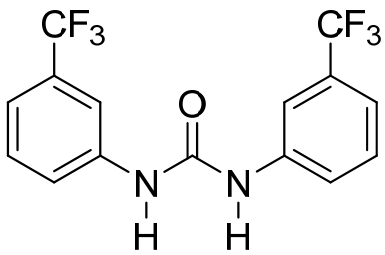
H-Bonding Additives Act Like Lewis Acid Catalysts



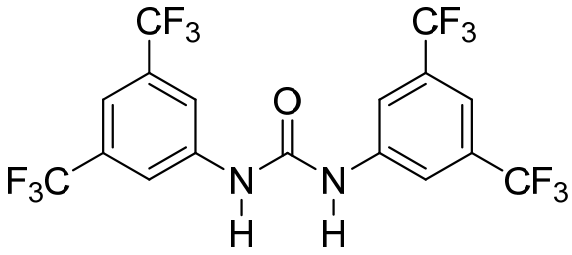
7 **4** **4'** **7'**

entry	catalyst	catalyst concn (rel to **4**)/solvent	T [°C]	t [h]	yield [%]	**7**:**7′**
1		0/benzene	130	96	55	36:64
2	$AlCl_3$	25 mol %/$CHCl_3$	−78	1	95	92:8
3	$TiCl_4$	25 mol %/$CHCl_3$	−78	1	92	89:11
4	**3e**	25 mol %/$CHCl_3$	23	48	74	77:23
5	**3f**	25 mol %/$CHCl_3$	23	48	78	81:19

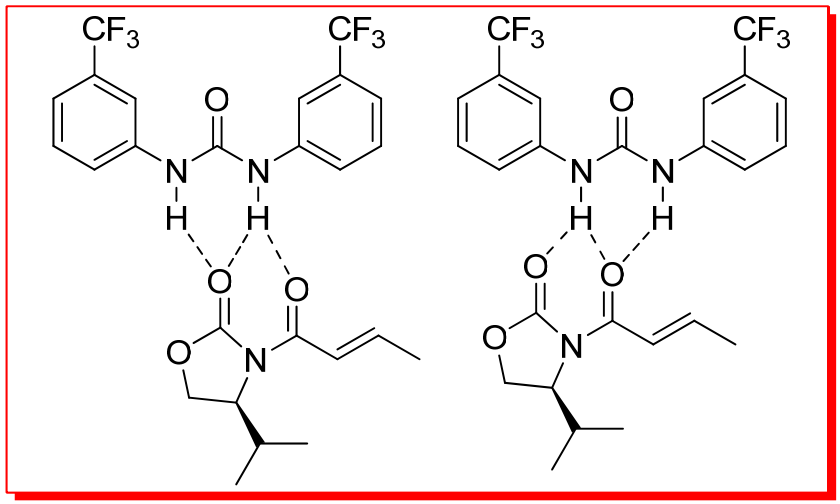
[a] Yields and product ratios were determined by NMR integration of the reaction mixtures.[16]

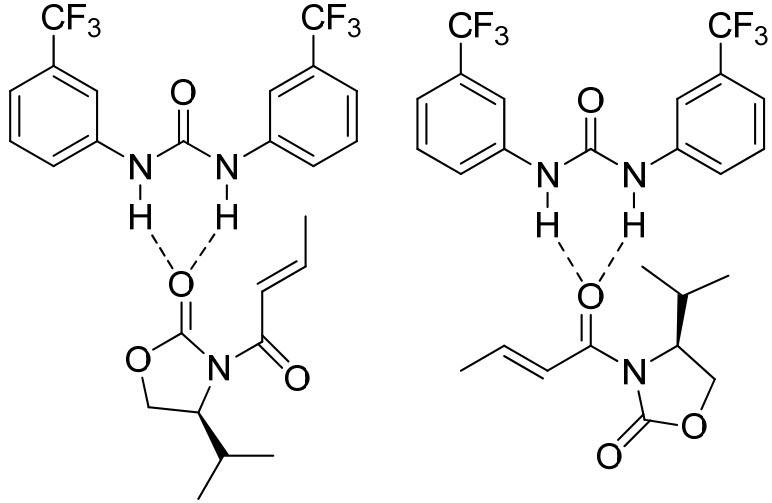


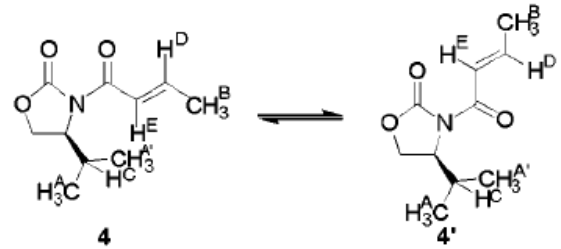
3e



3f







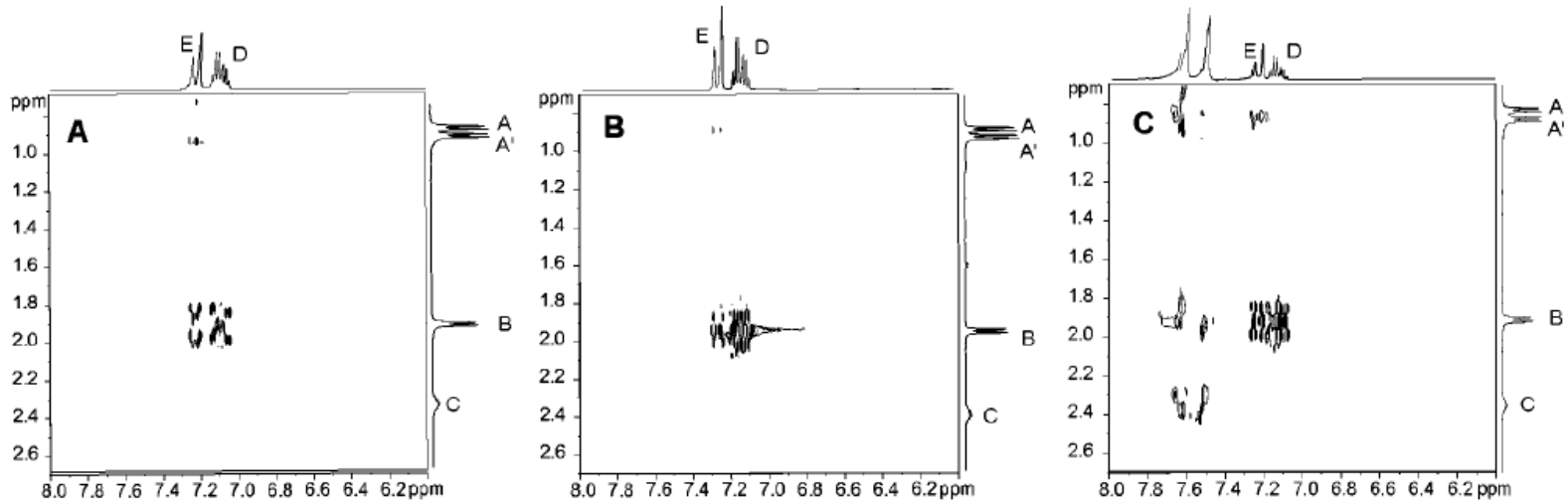
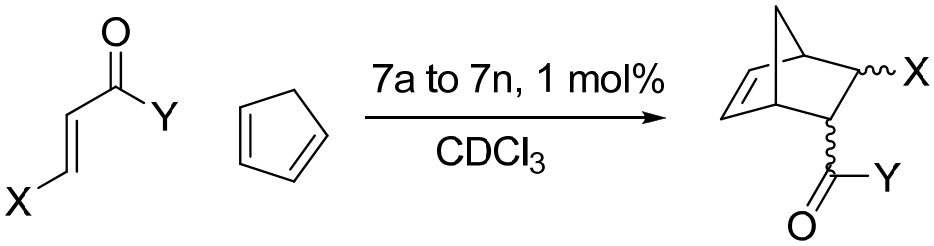
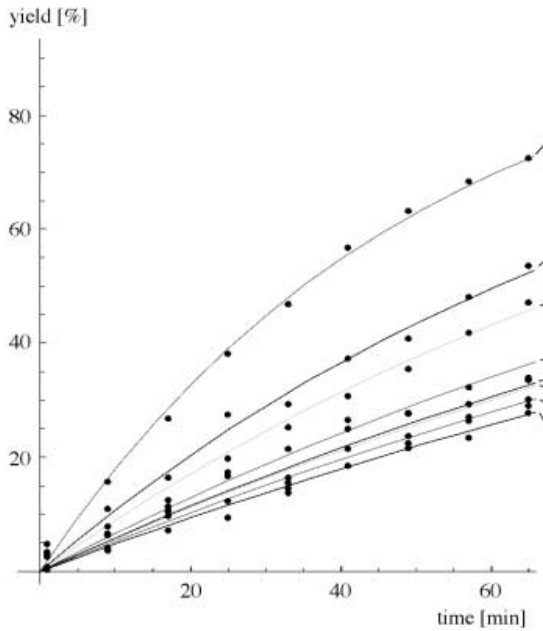


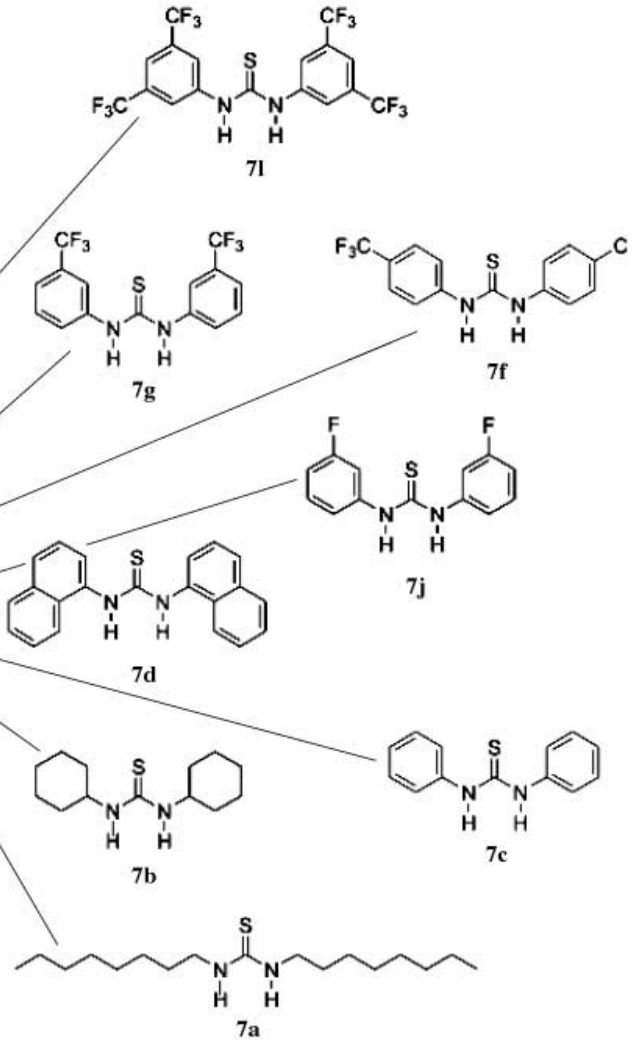
Figure 1. ^{1}H NOE spectra of pure **4** (A), a 1:1 mixture of **4** and $AlCl_3$ (B), and a 1:1 mixture of **4** and **3e** (C).

Chem. Eur. J. 2003, 9,407-414

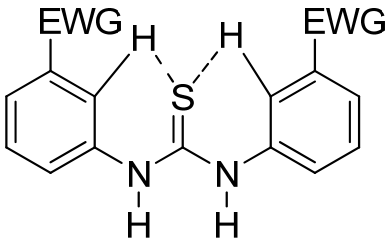


thiourea derivatives with rigid electron-withdrawing aromatic substituents are the most effective H-bonding catalysts for Diels-Alder reactions considered in the present study

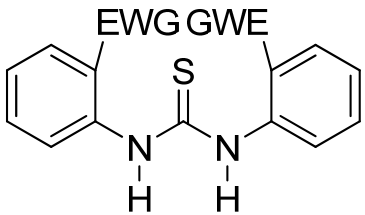


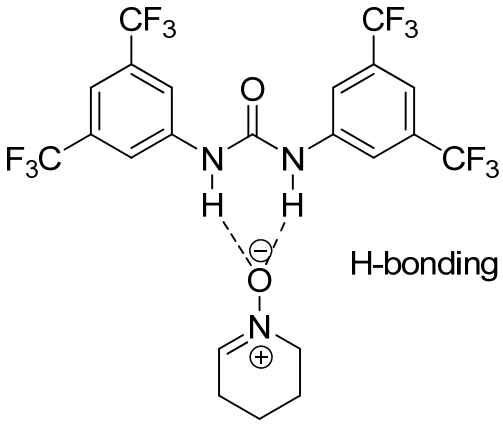


attractive S...H interaction



repulsive S...EWG interaction

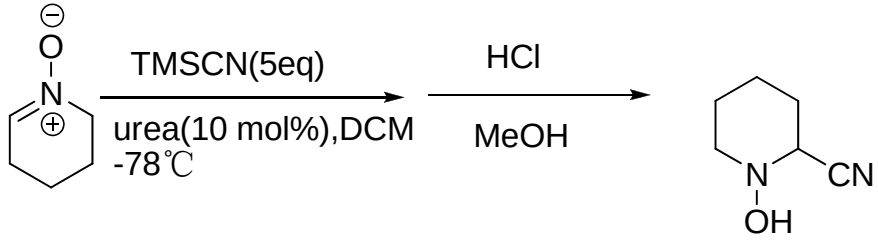




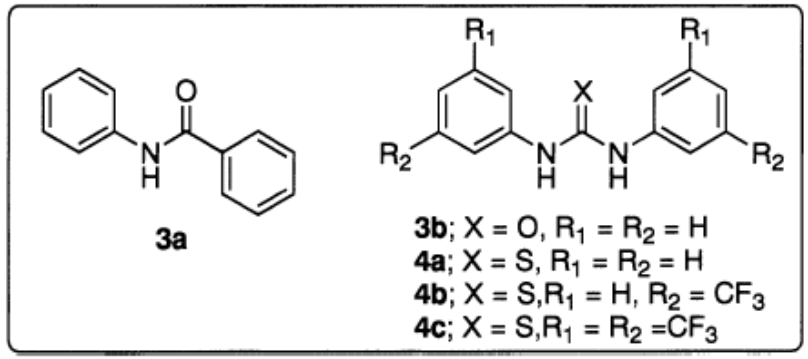
H-bonding activation

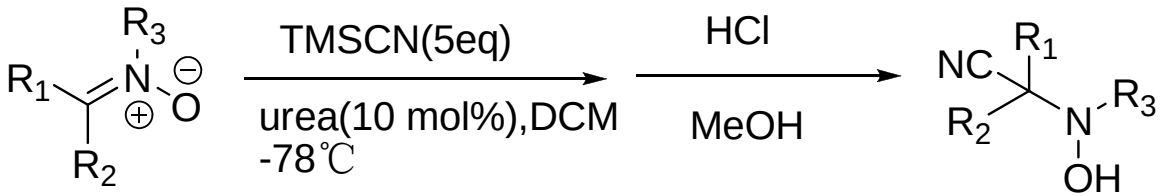
Yoshiji Takemoto

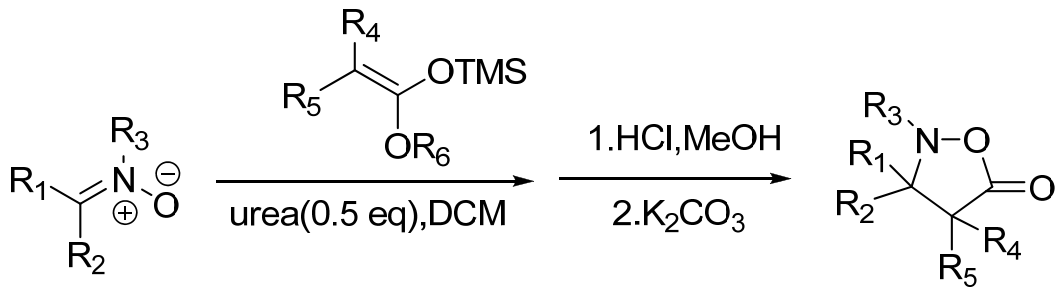
Tetrahedron Letters, **2003**,44,2817–2821

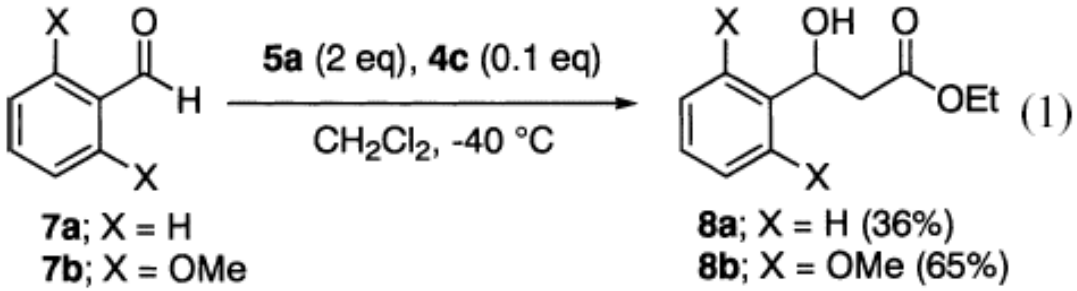


entry	urea	time (min)	cy (%)
1	-	300	79
2	**3a**	180	83
3	**3b**	90	77
4	**4a**	45	81
5	**4b**	15	75
6	**4c**	15	81



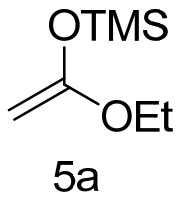




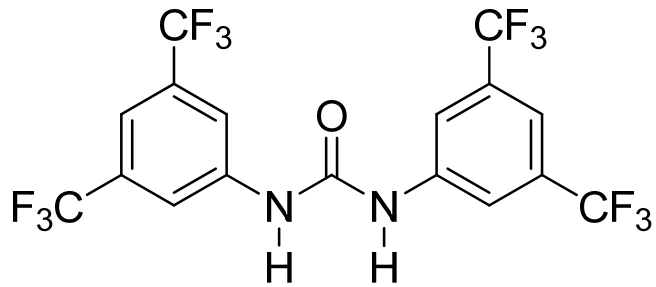


7a; X = H
7b; X = OMe

8a; X = H (36%)
8b; X = OMe (65%)

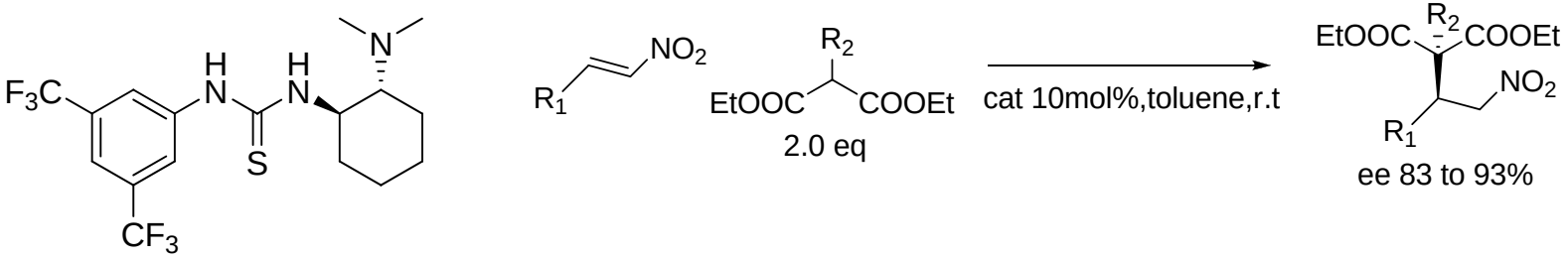


5a



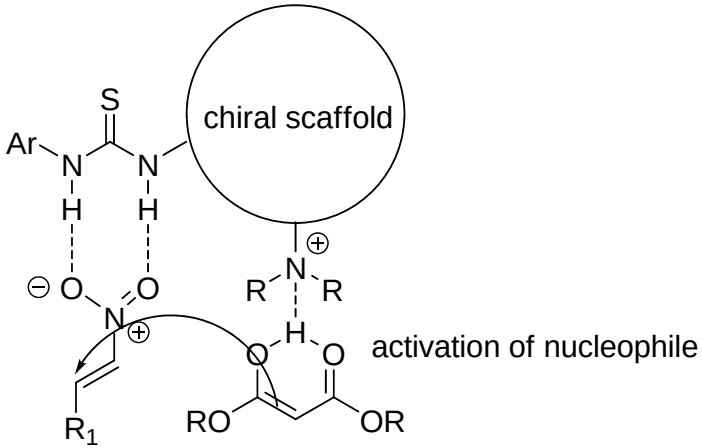
4c

At this stage, the reason is not clear, but we now assume that both oxygens of the carbonyl and methoxy groups of **7b** might coordinate to thiourea **6c** to form a highly activated intermediate.

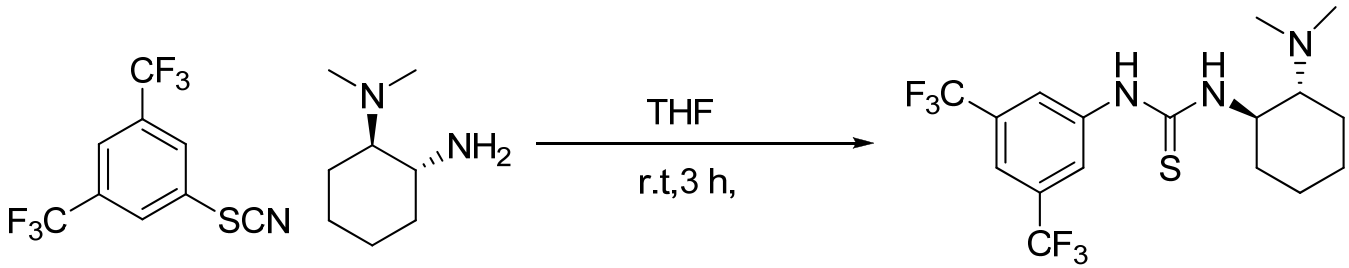


2003: Takemoto's bifunctional chiral thiourea derivative

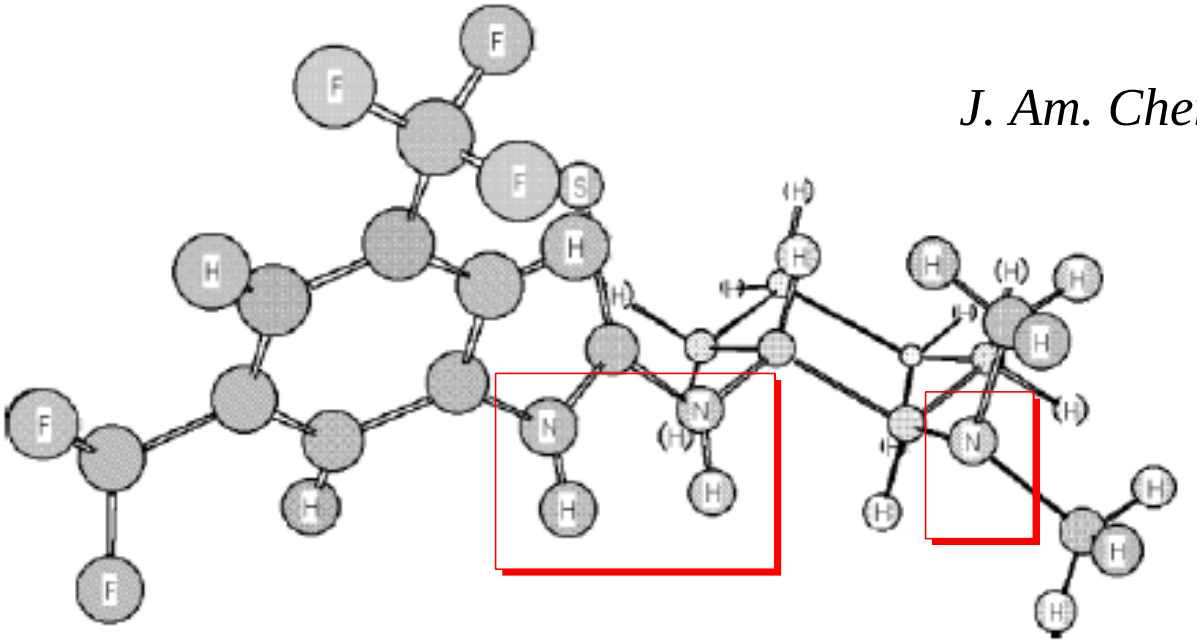
J. Am. Chem. Soc. 2003, 125, 12672-12673



activation of electrophile

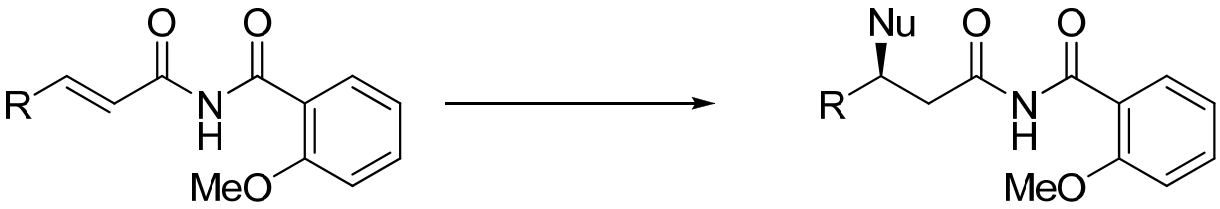


J. Am. Chem. Soc. **2005**, 127, 119-125

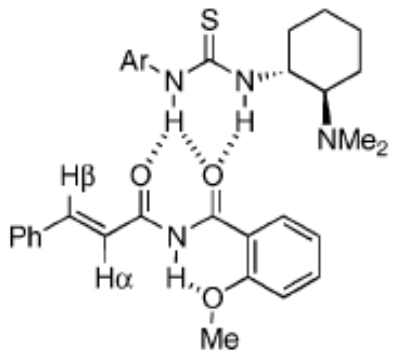


the X-ray crystallography of Takemoto's bifunctional thiourea catalyst indicates that amino groups and thiourea N–H orient towards the same direction . Therefore, nucleophiles can approach nitroolefins in an ideal way, when both thiourea and amino group interact with nitroolefin and nucleophile, respectively. This hypothesis agrees with their experimental result

J. Am. Chem. Soc. **2006**, 128, 9413-9419



Nu=CH_3NO_2,$CH_2(CN)_2$,CH(CN)COOMe



δ (NH): 10.24 (10.22)

δ (Hα): 8.04 (8.06)

δ (Hβ): 8.23 (8.30)

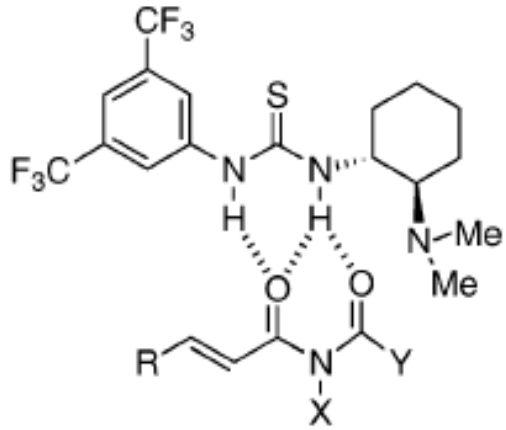
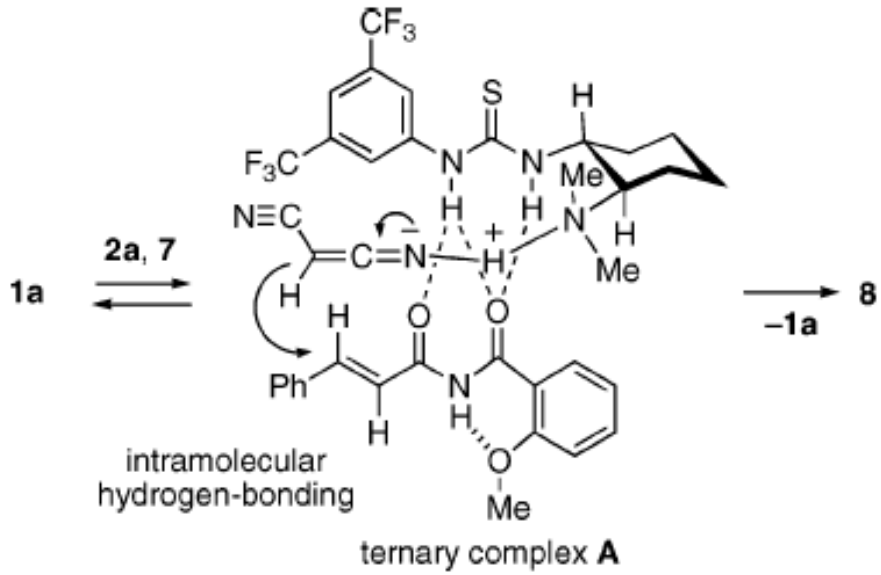


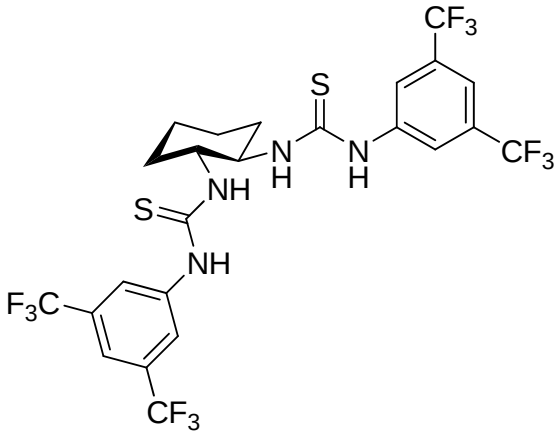
Figure 2. ^{1}H NMR of a 1:1 mixture of **1a** and **7A** in toluene-d_8 (0.02 M) (the values in parentheses are chemical shifts of **7A** without **1a**).

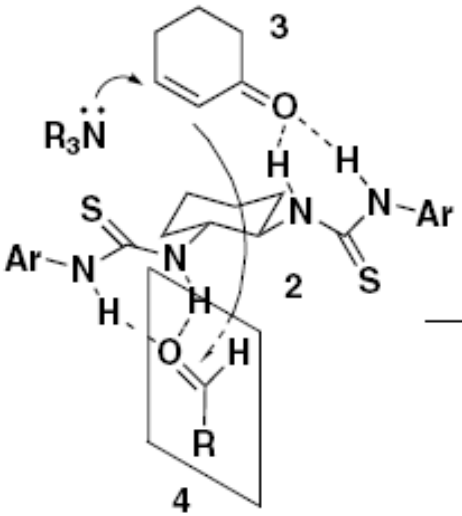


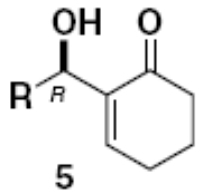
Kazuo Nagasawa

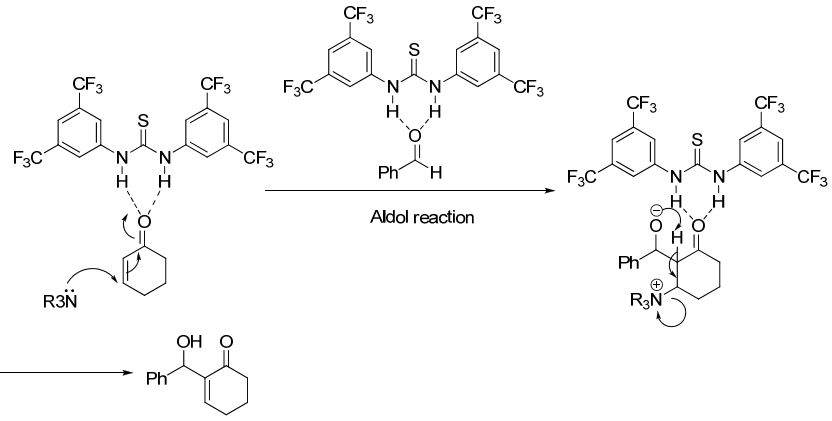
Tetrahedron Letters, **2004**, 45, 5589-5592

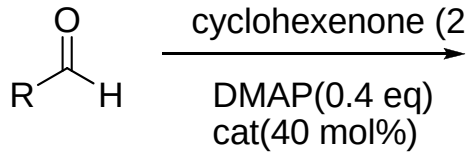
Baylis–Hillman Reaction

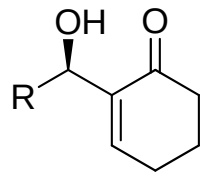




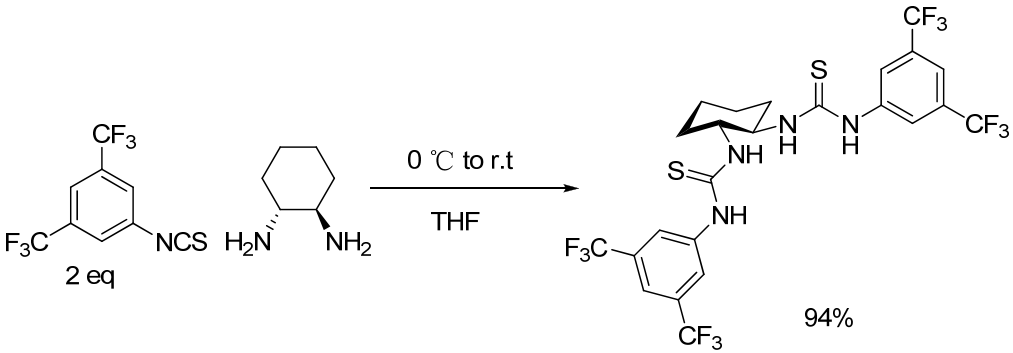




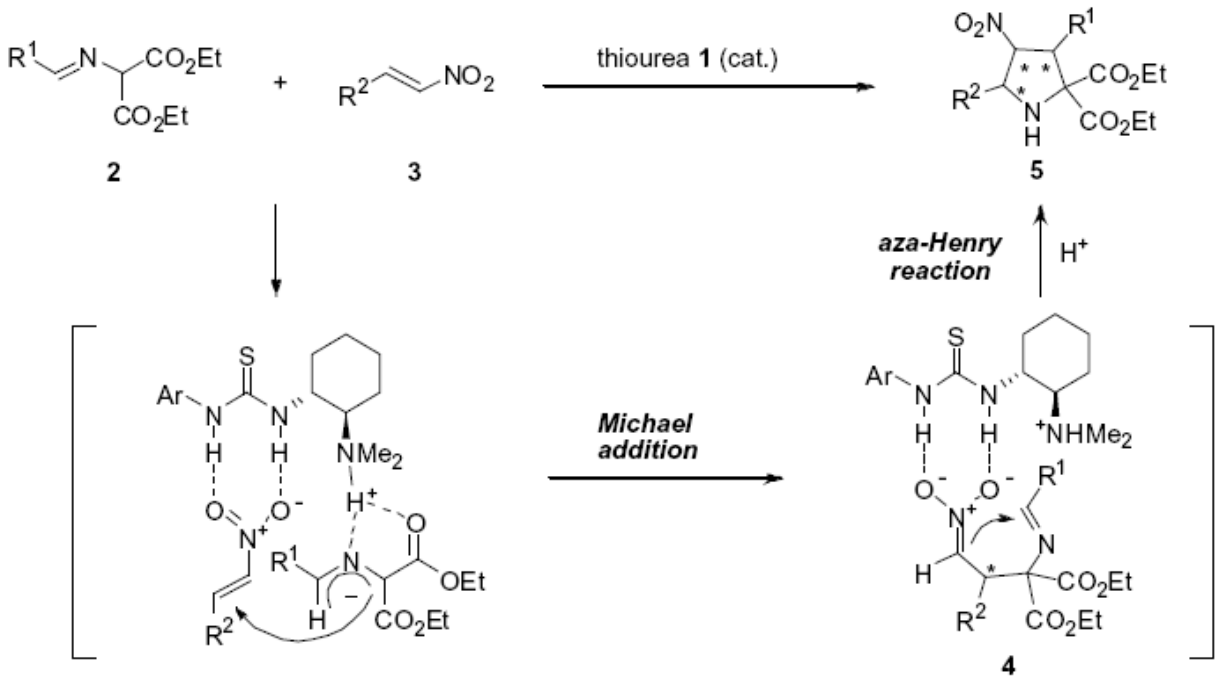


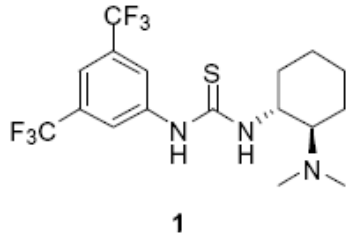


up to 90% ee



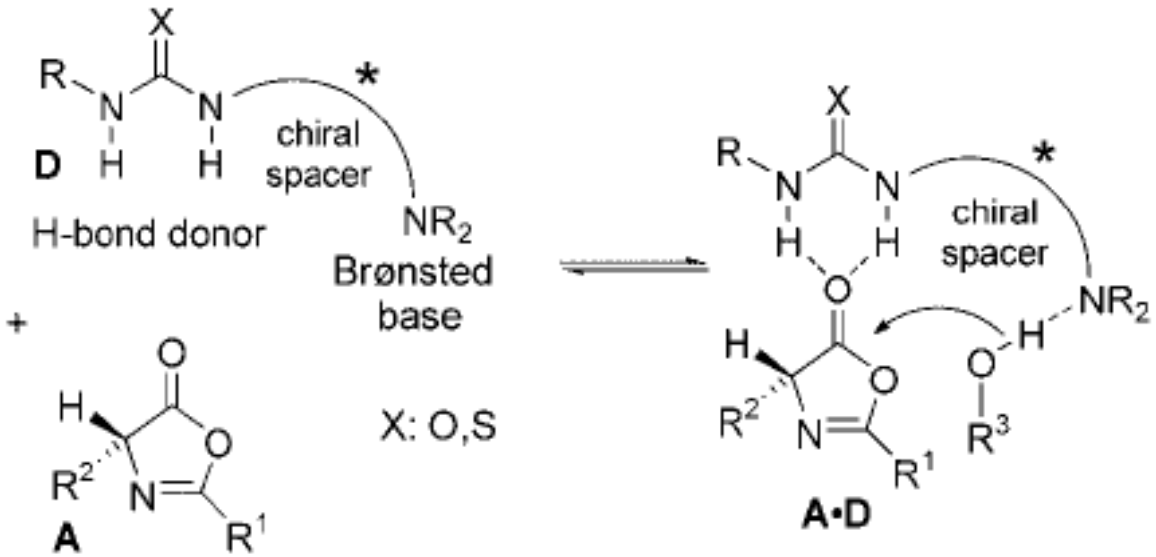
Tetrahedron Letters, 2008,49 , 6910–6913





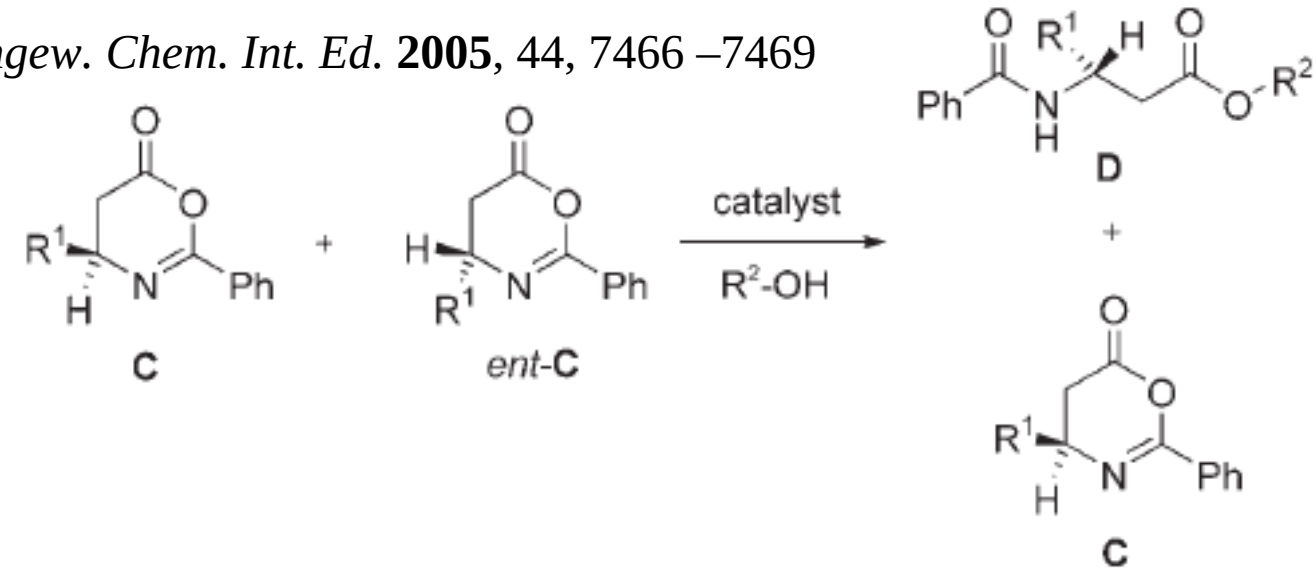
Dynamic Kinetic Resolution of Azlactones

Albrecht Berkessel
Angew. Chem. Int. Ed. **2005**, 44, 807 –811



Kinetic Resolution of Oxazinones

Angew. Chem. Int. Ed. **2005**, 44, 7466 –7469

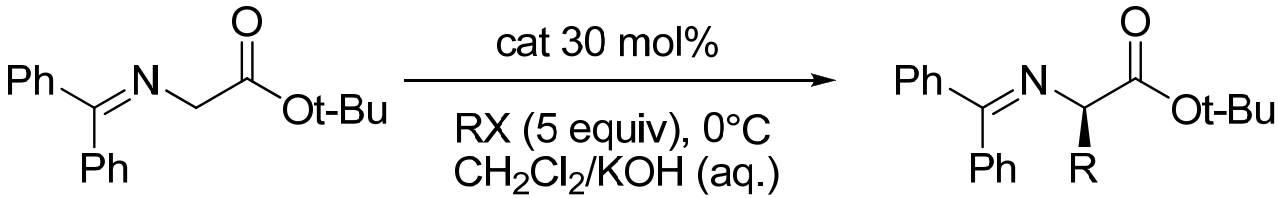


C2-Symmetric Chiral Pentacyclic Guanidine

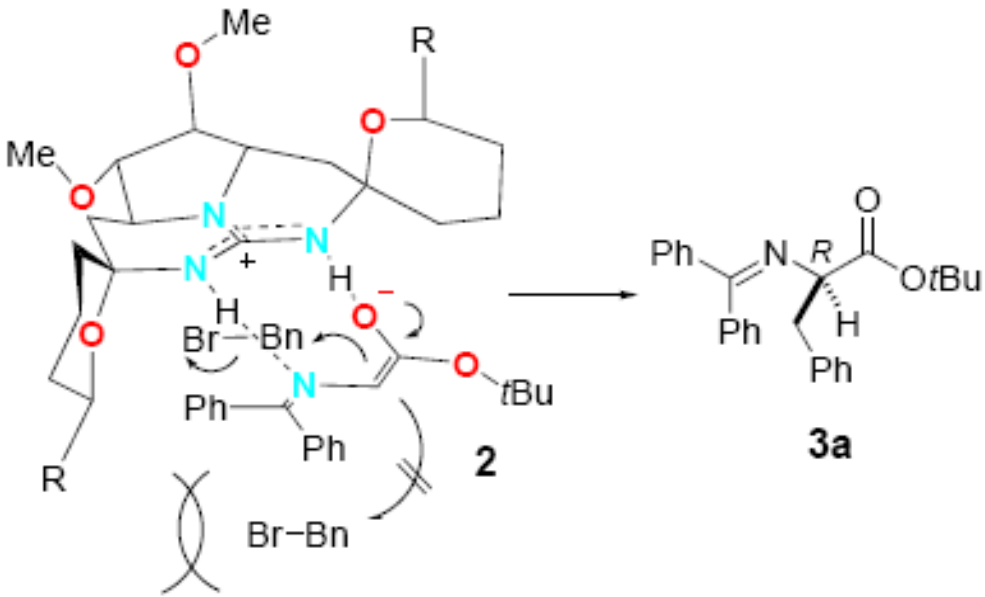
Kazuo Nagasawa

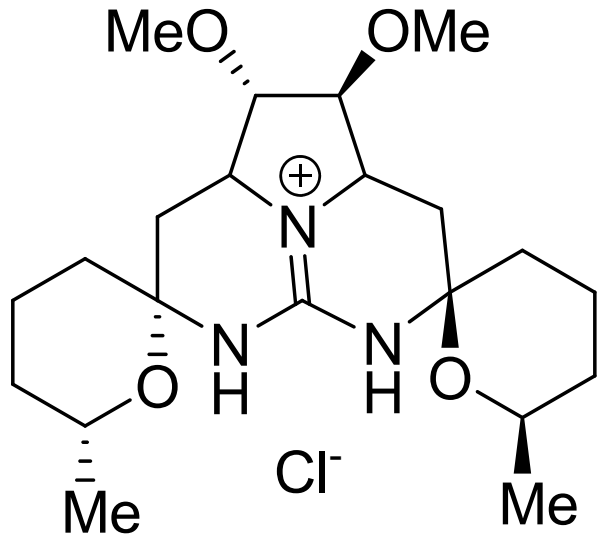
Angew. Chem. Int. Ed., **2002**, 41,2832-2834

Phase-Transfer Catalyst

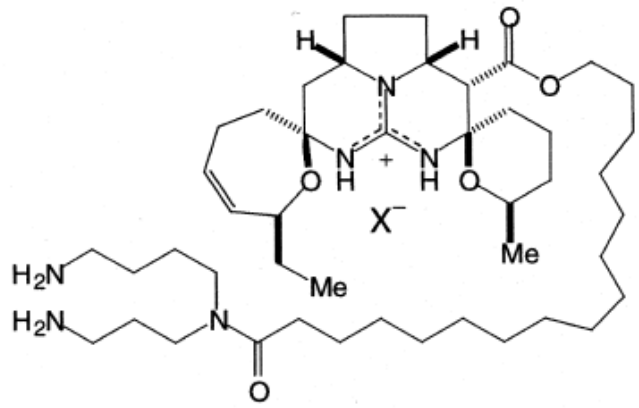


ee from 79% to 90%

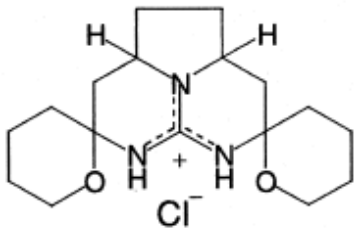




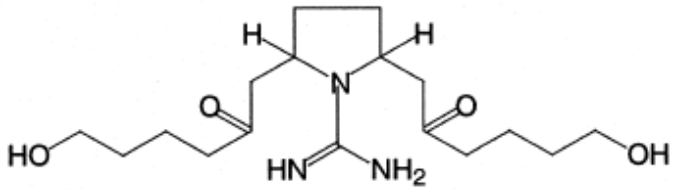
This catalyst's structure was inspired by the marine guanidine alkaloid Ptilomycalin A and its analogs.
Ptilomycalin A were isolated from the Caribbean sponge ***Ptilocaulis***



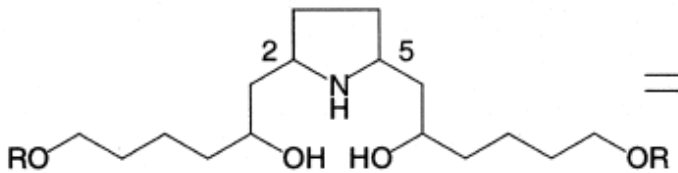
Ptilomycalin A (1)



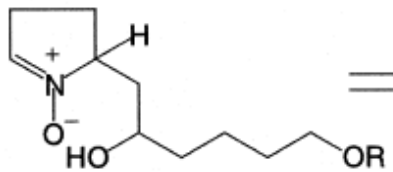
3



4



5



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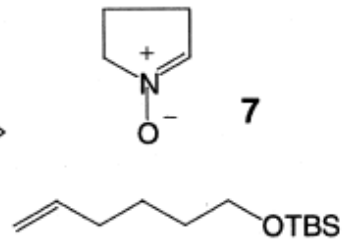
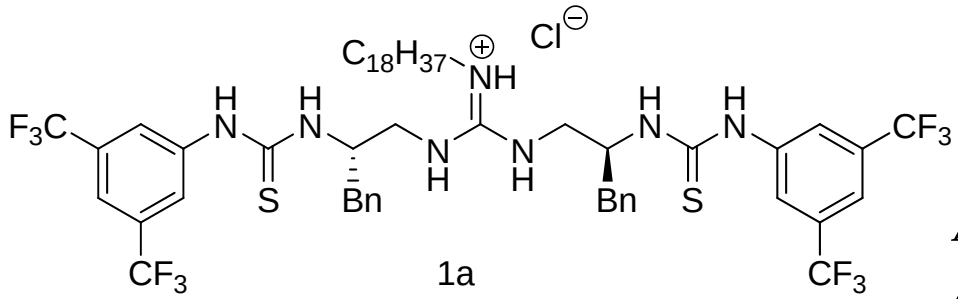
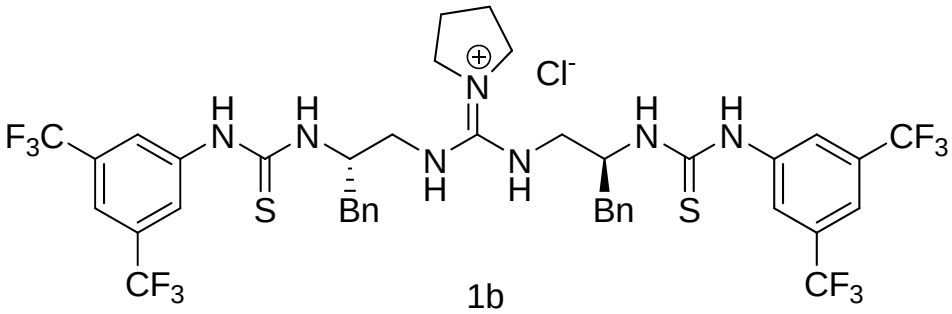
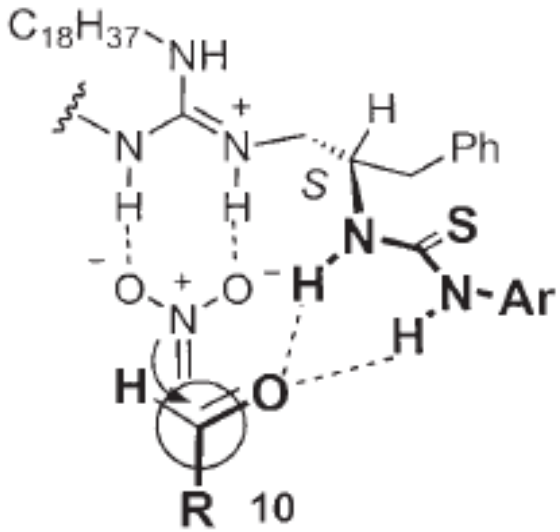


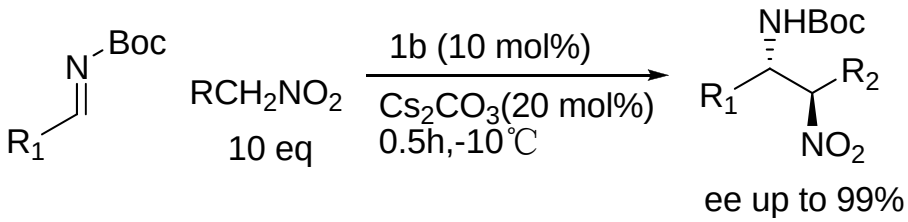
8

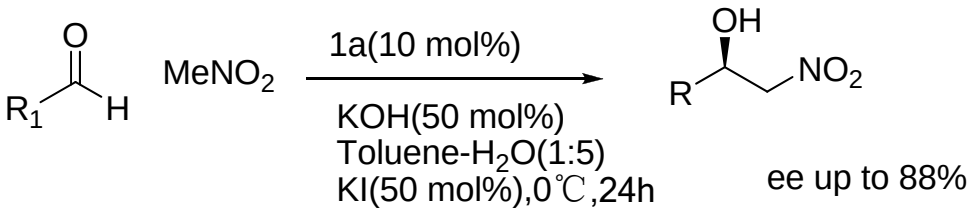


Adv. Synth. Catal. **2005**, 347, 1643 – 1648
Adv. Synth. Catal. **2009**, 351, 345 – 347



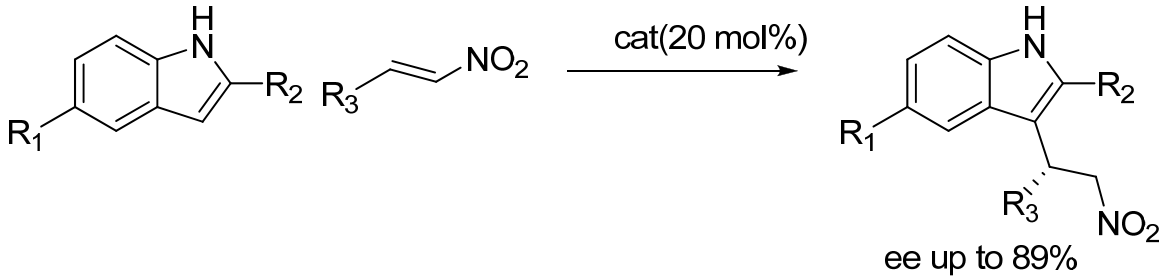


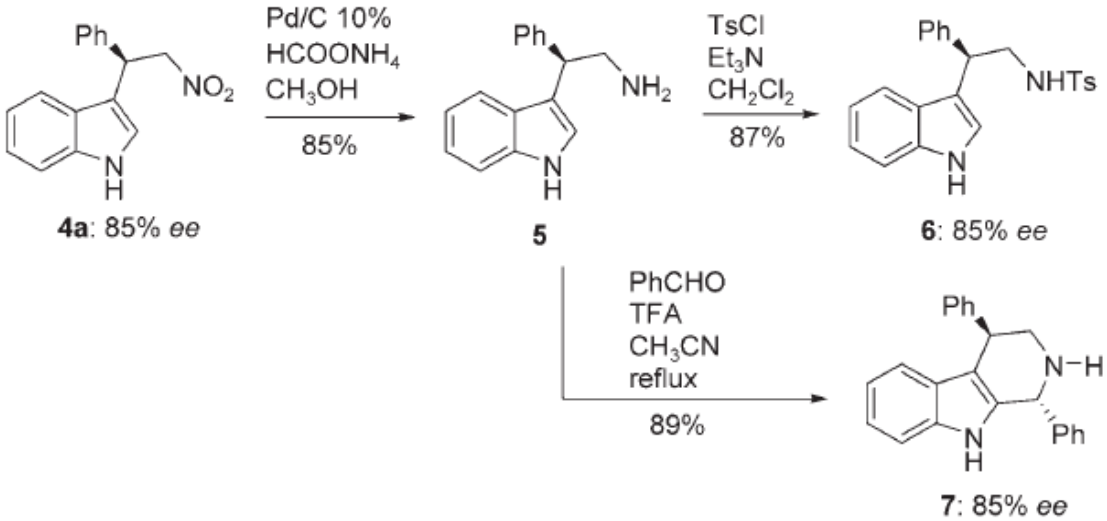




Alfredo Ricci

Angew. Chem. Int. Ed. **2005**, 44, 6576 –6579



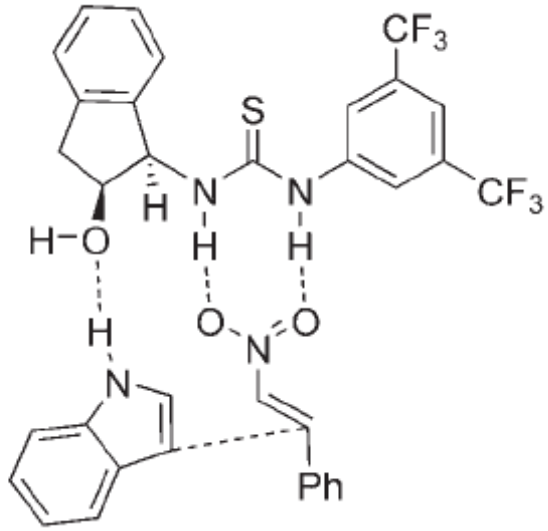


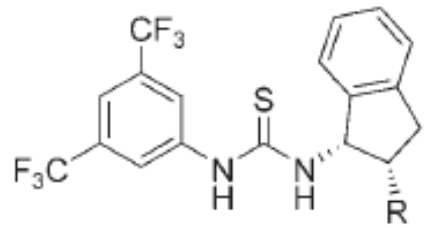
4a: 85% *ee*

5

6: 85% *ee*

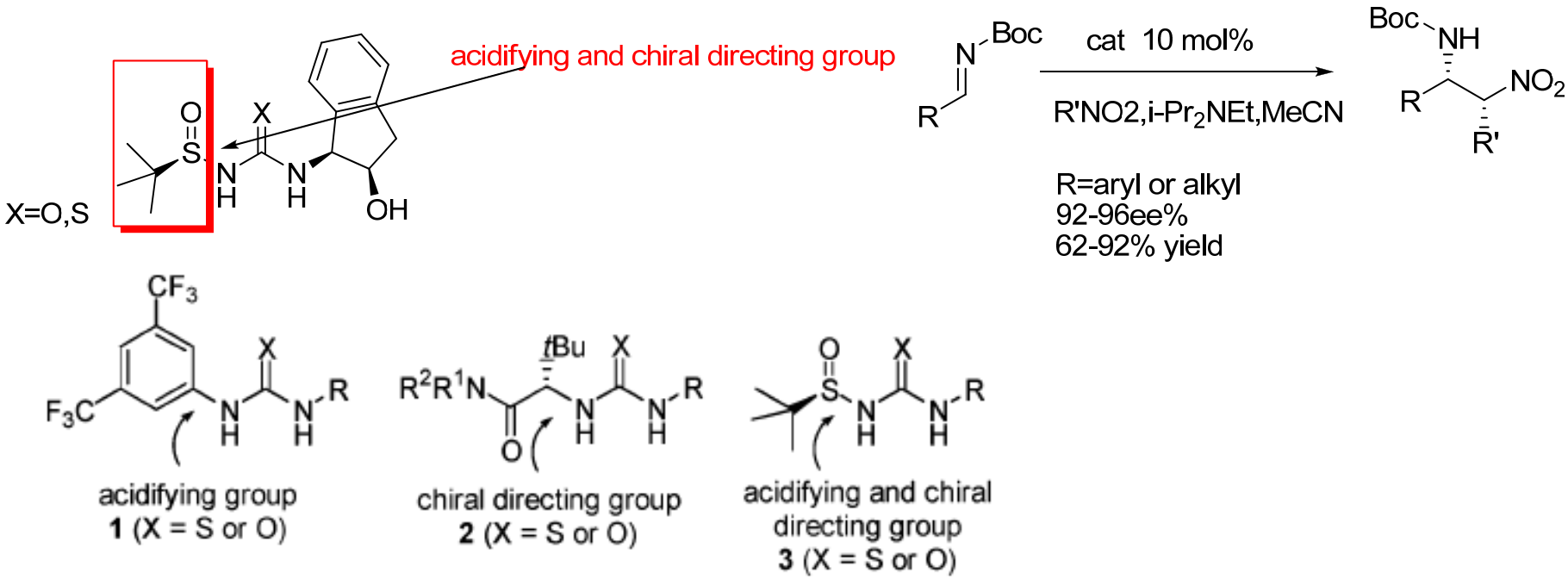
7: 85% *ee*



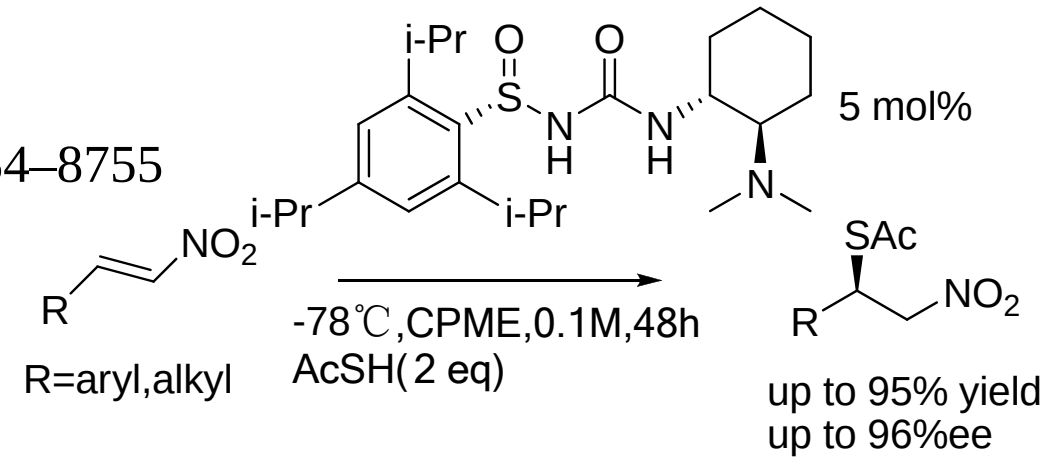


	Yield **4a**	*ee*
1d: R = OH	78%	85%
1f: R = $OSi(CH_3)_3$	18%	39%
1g: R = H	15%	0%

Jonathan A. Ellman, *J. Am. Chem. Soc.* **2007**, 129, 15110-15111



J. Am. Chem. Soc. **2009,** *131*, 8754–8755



4.Application in the total synthesis and industry

Total Synthesis of (+)-Yohimbine

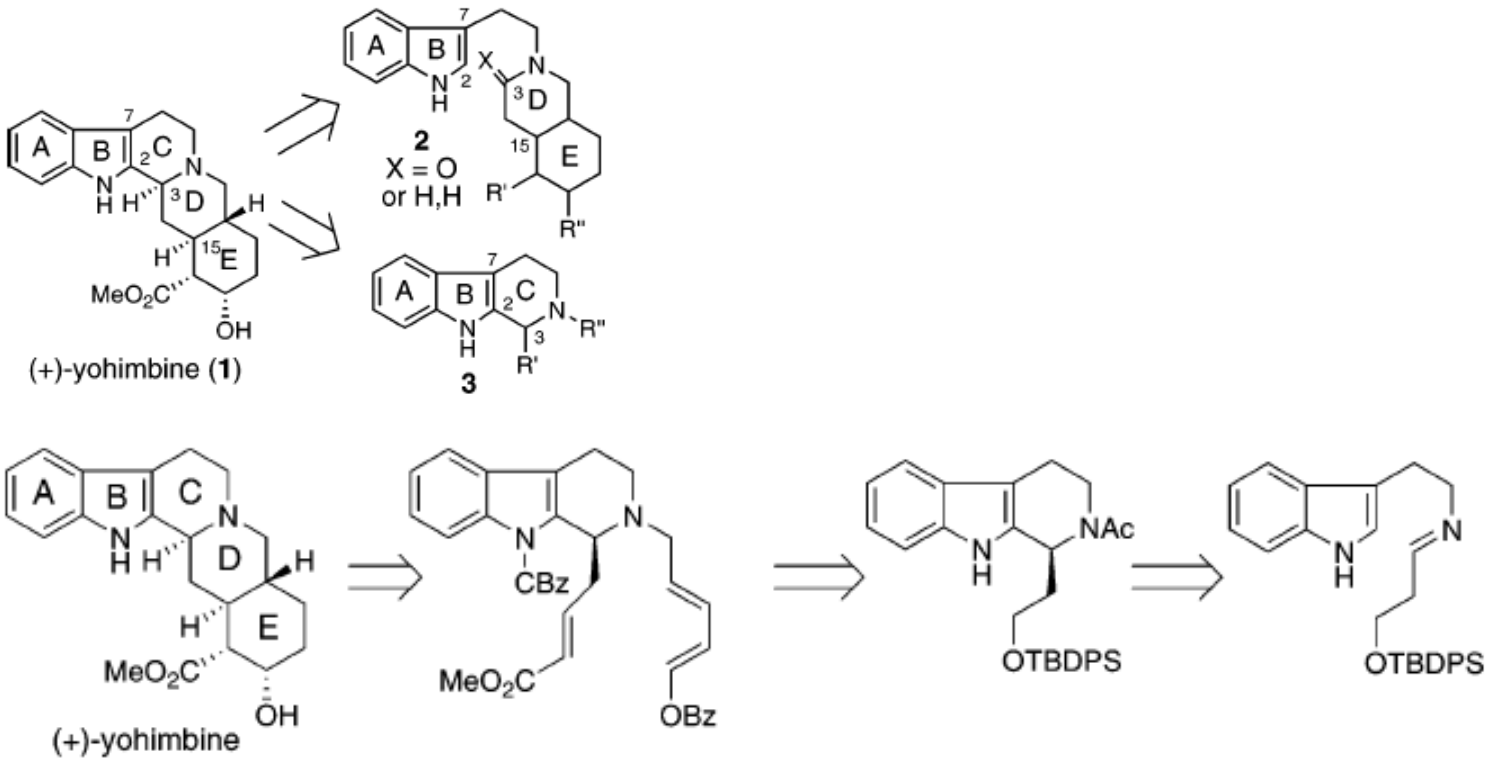
Org. Lett. **2008**, *10*, 1577–1580

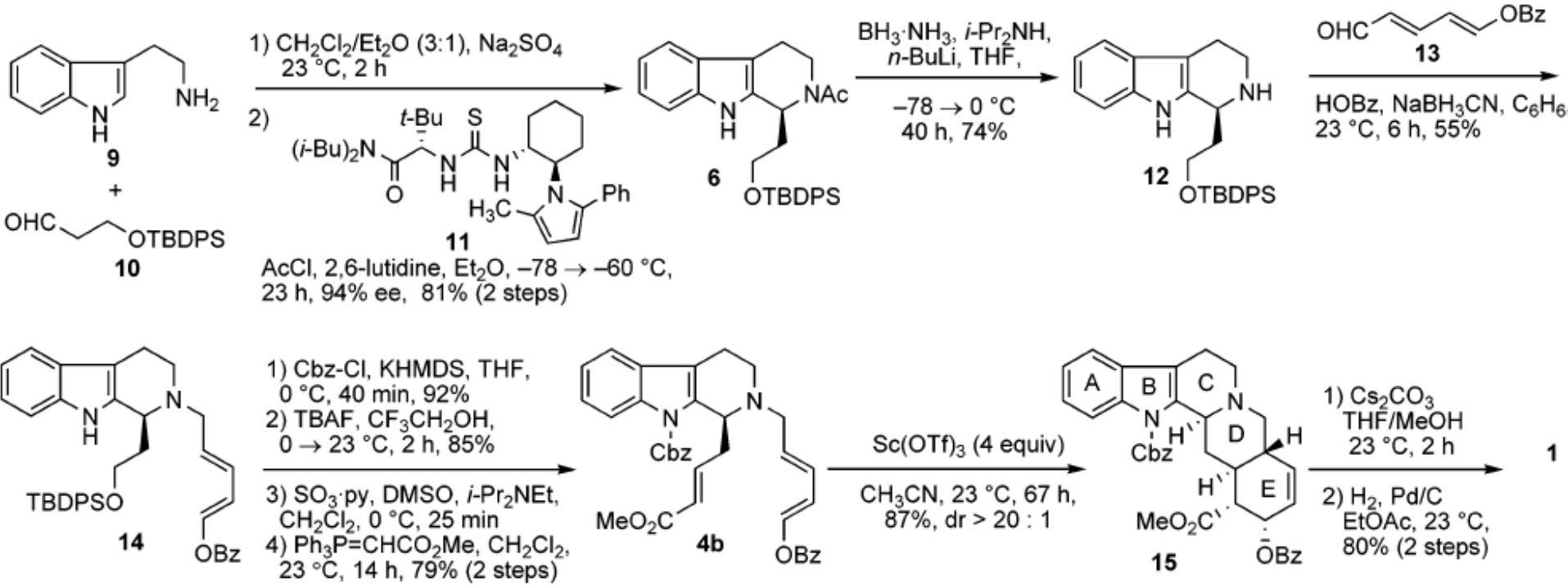
Yohimbine is an important member of the monoterpenoid indole alkaloids, a large class of natural products that features synthetically challenging structures with diverse biological activity

the first total synthesis of yohimbine, see:

van Tamelen, E.E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1958**, *80*, 5006-5007.; *J. Am. Chem. Soc.* **1969**, *91*, 7315-7333.

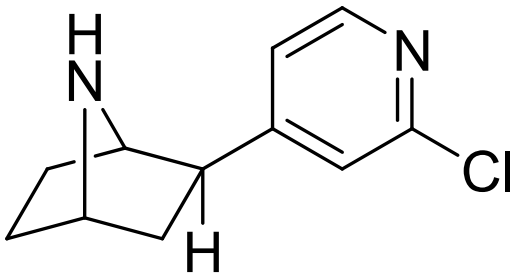
Scheme 1. General Strategies Employed in Previous Syntheses of Yohimbine and Related Alkaloids

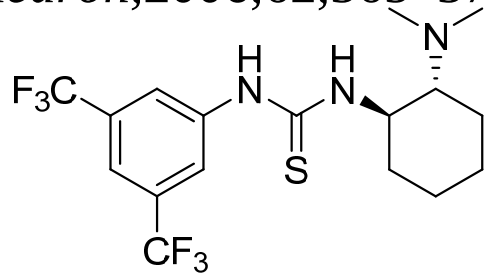



1) CH2Cl2/Et2O (3:1), Na2SO4
23 °C, 2 h
2)
AcCl, 2,6-lutidine, Et2O, –78 → –60 °C,
23 h, 94% ee, 81% (2 steps)
BH3·NH3, i-Pr2NH,
n-BuLi, THF,
–78 → 0 °C
40 h, 74%
HOBz, NaBH3CN, C6H6
23 °C, 6 h, 55%
1) Cbz-Cl, KHMDS, THF,
0 °C, 40 min, 92%
2) TBAF, CF3CH2OH,
0 → 23 °C, 2 h, 85%
3) SO3·py, DMSO, i-Pr2NEt,
CH2Cl2, 0 °C, 25 min
4) Ph3P=CHCO2Me, CH2Cl2,
23 °C, 14 h, 79% (2 steps)
Sc(OTf)3 (4 equiv)
CH3CN, 23 °C, 67 h,
87%, dr > 20 : 1
1) Cs2CO3
THF/MeOH
23 °C, 2 h
2) H2, Pd/C
EtOAc, 23 °C,
80% (2 steps)
9
10
11
6
12
13
14
4b
15
1

Enantioselective tandem Michael reaction to nitroalkene catalyzed by bifunctional thiourea: total synthesis of (-)-epibatidine

Yoshiji Takemoto, *Tetrahedron*,**2006**,62,365–374

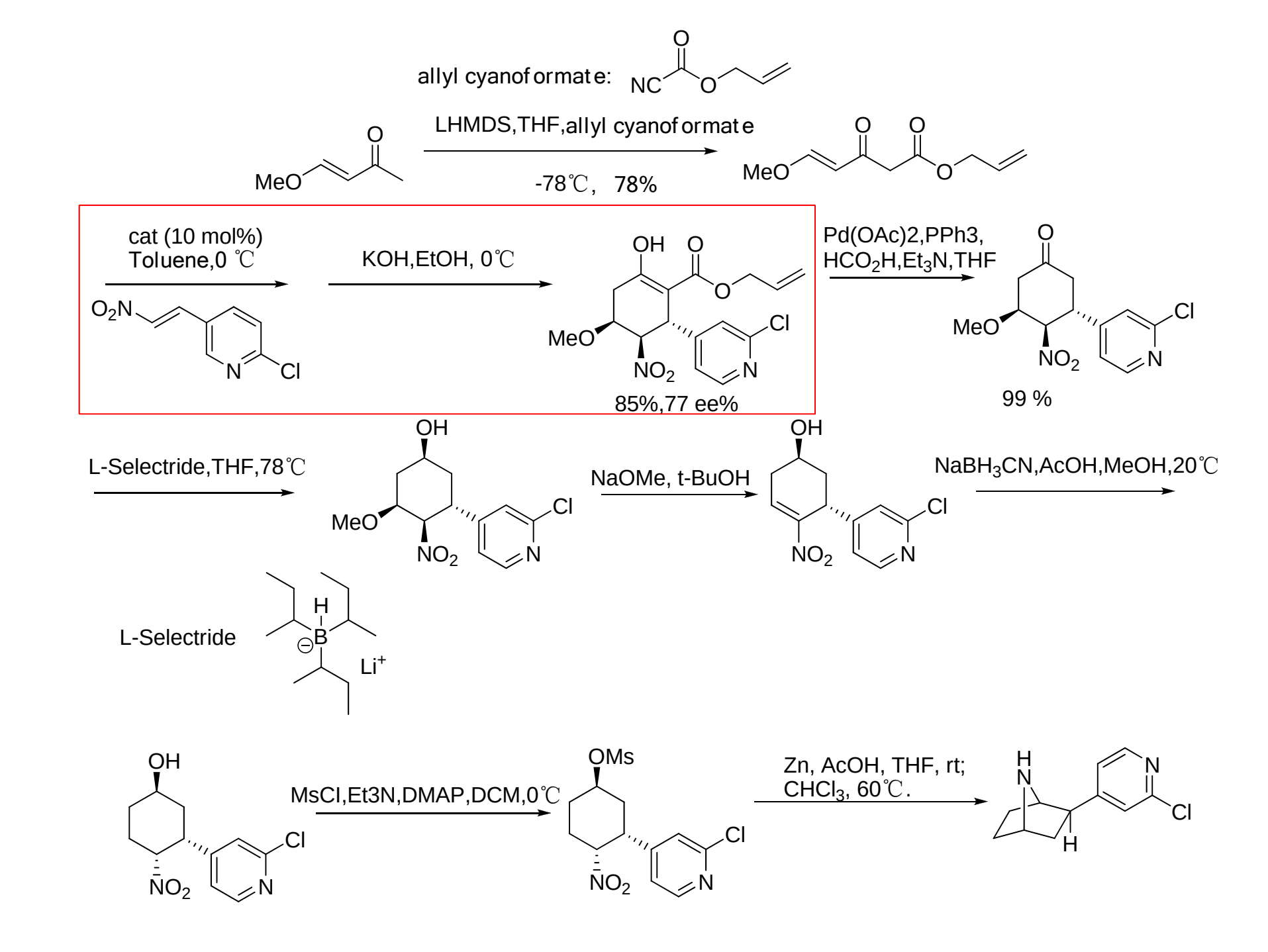


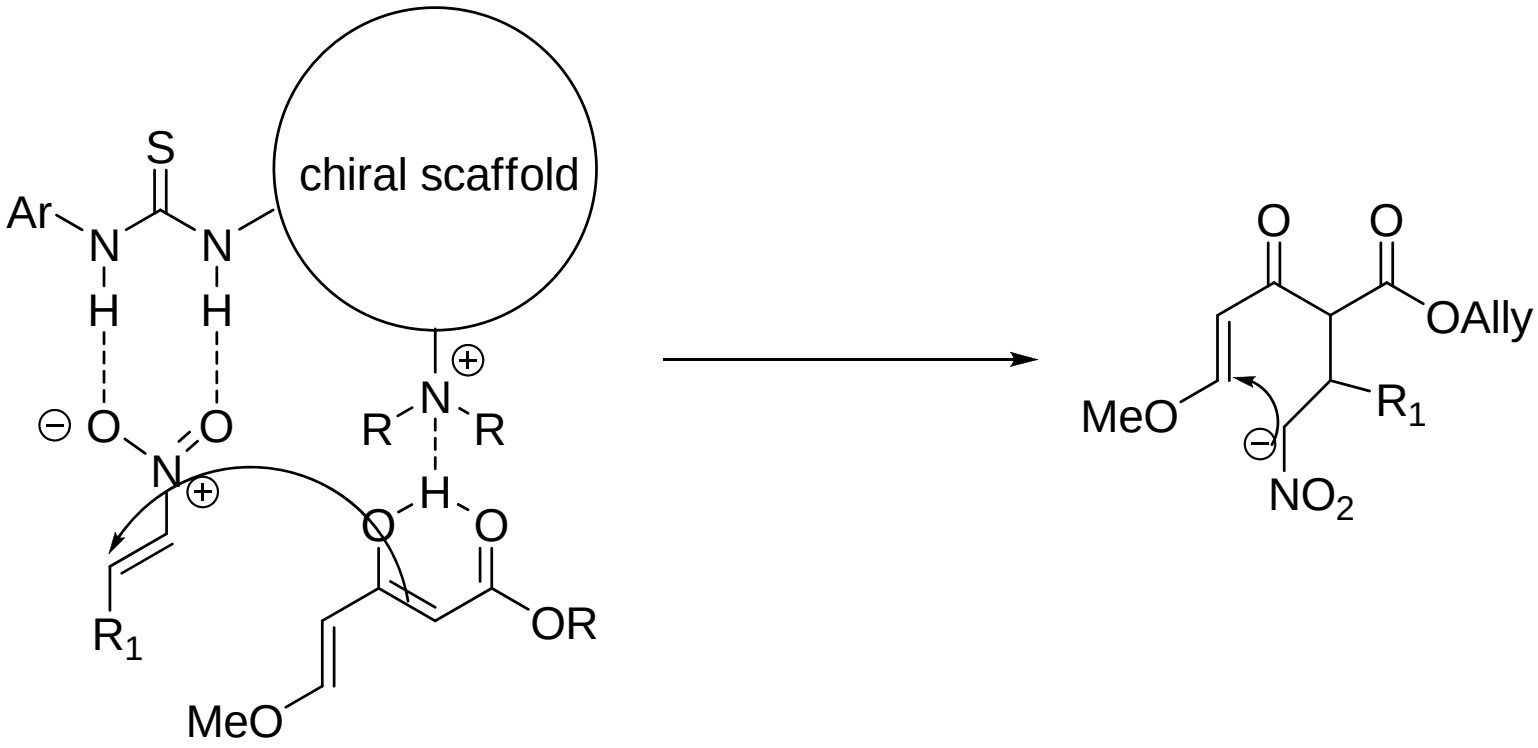


Epibatidine是由Daly等于1992年从厄瓜多尔的一种学名Epipedobates ericolord的毒蛙皮肤萃取液中分离得到的生物碱。他们从750只毒蛙皮肤中萃取得到60mg的生物碱类萃取液，对这些粗萃取液重复进行柱层析及HPLC纯化得到25mg稍纯的样品，最后得到纯化合物仅1mg，通过红外、质谱及核磁氢谱测定并结合它的乙酰化衍生物的核磁氢谱分析，确定该化合物的结构。后由Watt等人通过单晶衍射确定其绝对构型为左旋对映体。

后来发现它的镇痛活性大约为吗啡的200—500倍，并且其作用机制和吗啡及其鸦片类止镇痛作用完全不同：当它与鸦片拮抗剂同时使用时，它的止痛效果并不减弱．由于Epibatidine的这些生物活性，其合成工作引起了人们极大的兴趣．到目前为止，关于Epibatidine全合成的文章已超过了80篇。

Corey在1993年通过先合成它的一对外消旋体再进行拆分的方法首次进行了全合成（*J. Org. Chem*,**1993**,58,5600-5602），其后又有多个小组以易得天然手性化合物为手性源，如薄荷醇等进行了全合成，此文报道的是首例不对称催化合成。


allyl cyanoformate:
LHMDS,THF,allyl cyanoformate
-78℃, 78%
cat (10 mol%)
Toluene,0 ℃
KOH,EtOH, 0℃
85%,77 ee%
Pd(OAc)2,PPh3,
HCO2H,Et3N,THF
99 %
L-Selectride,THF,78℃
NaOMe, t-BuOH
NaBH3CN,AcOH,MeOH,20℃
L-Selectride
MsCl,Et3N,DMAP,DCM,0℃
Zn, AcOH, THF, rt;
CHCl3, 60℃.


chiral scaffold
Ar
S
N
H
N
H
O
O
N
R
N
R
H
O
O
OR
R1
MeO
MeO
O
O
OAlly
R1
NO2

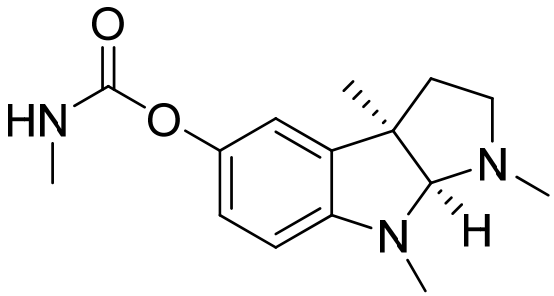
Additions of Oxindoles to Nitroolefins: Application to the Formal Synthesis of (+) -Physostigmine

Carlos F. Barbas III

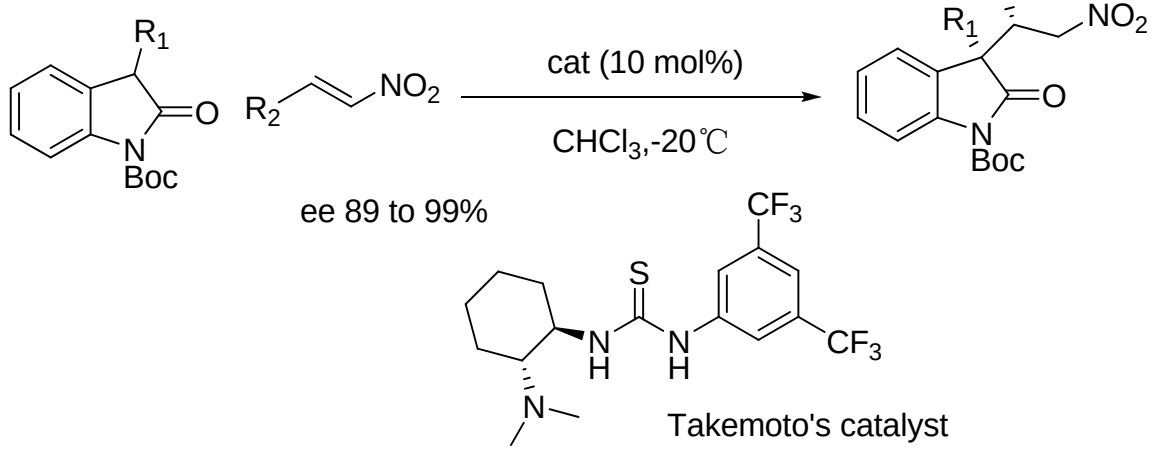
J. Am. Chem. Soc. **2009**, *131*, 8758–8759

(+) – Physostigmine:毒扁豆碱，依色林

有抗胆碱酯酶的作用，使胆碱能神经末梢所释放的乙酰胆碱不致被灭活而积聚，作用于M胆碱受体呈现与其他拟胆碱药类似的作用，即瞳孔缩小、流涎、胃肠蠕动增强、心率减慢等现主要用其0.2％～0.5％溶液点眼，用于青光眼、调节肌麻痹。



(+)-Physostigmine



Takemoto's catalyst

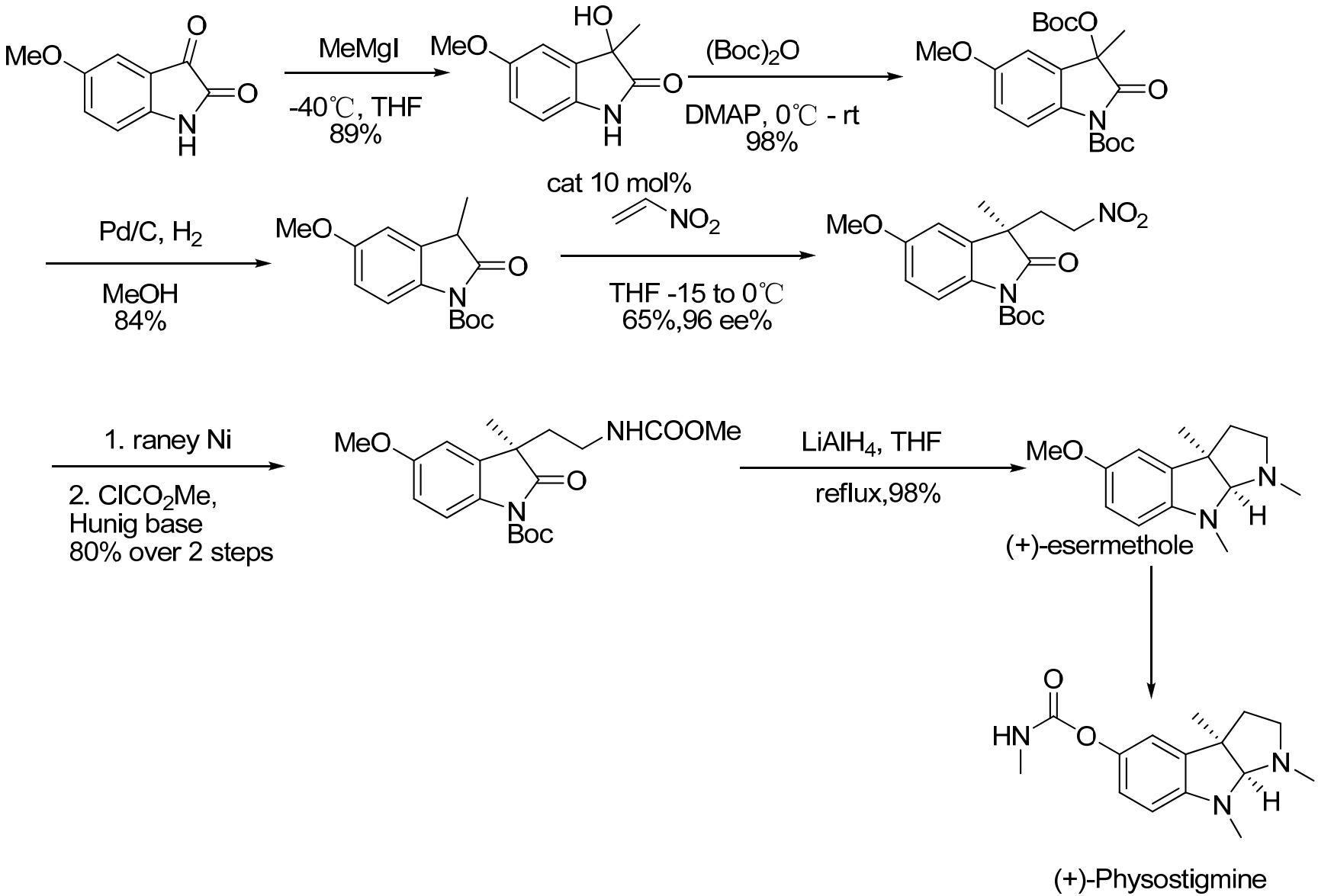

MeO
O
O
N
H
MeMgI
-40℃, THF
89%
HO
MeO
O
N
H
(Boc)2O
DMAP, 0℃ - rt
98%
BocO
MeO
O
N
Boc
Pd/C, H2
MeOH
84%
MeO
O
N
Boc
cat 10 mol%
NO2
THF -15 to 0℃
65%,96 ee%
MeO
NO2
O
N
Boc
1. raney Ni
2. ClCO2Me,
Hunig base
80% over 2 steps
MeO
NHCOOMe
O
N
Boc
LiAlH4, THF
reflux,98%
MeO
N
N
H
(+)-esermethole
O
HN
O
N
N
H
(+)-Physostigmine

Table 1 Organocatalytic processes of industrial relevance

Asymmetric organocatalytic reaction	Company	Developed at	Catalyst
Intramolecular aldol reaction	Schering AG Hoffm.-LaRoche	in house	L-proline
Alkylation of indanone derivative	Merck	in house	alkaloid-deriv. cat.
Alkylation of glycinates	Nagase	Maruoka group	phase-transfer-cat.
Strecker reaction	Rhodia ChiRex	Jacobsen group	(thio-)urea cat.
Protonation	Firmenich	in house	amino alcohol
Epoxidation of chalone and derivatives	Bayer AG Degussa AG	Julia/ Colonna group	poly-/oligo-Leu cat.
Epoxidation of alkenes	DSM	Shi group	chiral ketone

From :Asymmetric Organocatalysis on a Technical Scale: Current Status and Future Challenges by H. Gröger

The technologies developed in Jacobsen's lab have been commercialized by Rhodia ChiRex, a joint venture between Jacobsen and global chemical giant Rhodia.The catalysts have been used in many pharmaceutical syntheses

6. Conclusion

1.Catalyst

a.economy
b.stability and operation
c.synthesis
d.*ee*, conversion and catalyst loading
f. novel reaction

2.Reaction

Michale addition
Mannich Reactions
Transfer hydrogenation
Acyl-Pictet-Spengler Reaction
Cycloaddition
Ring Opening of Aziridine
Claisen Rearrangement
Hydrophosphonylation
Baylis–Hillman reaction
Kinetic Resolution