Asymmetric Hydrogen-Bond catalysis
Topic review

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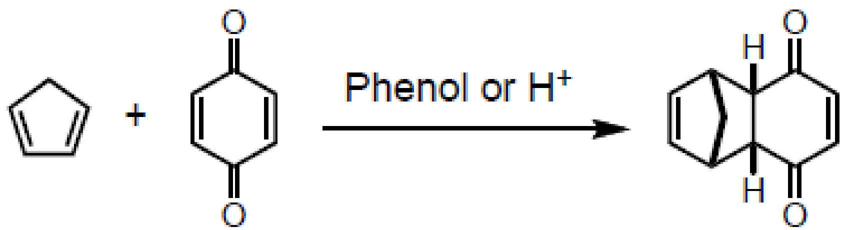
Introduction

Lewis acids *versus* Brønsted acids

- Dominant strategy: Metal-centered Lewis Acid starting with Friedel and Crafts

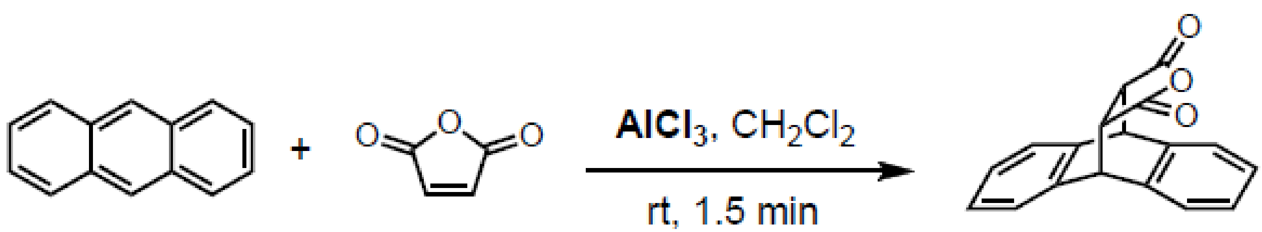
Wasserman, 1942 : cycloaddition of cyclopentadiene with benzoquinone



$H^+ = CH_3CO_2H, ClCH_2CO_2H$
$BrCH_2CO_2H, Cl_3CCO_2H$

yield >90%

Yates and Eaton, 1960: Diels-Alder



Without $AlCl_3$: 200 d, 95% yield

Wassermann, A. *J. Chem. Soc.* **1942,** 618-621
Yates, P.; Eaton P. *J. Am. Chem. Soc.* **1960,** 4436-4437

Lewis acids *versus* Brønsted acids

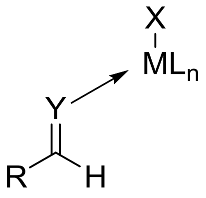
Lewis acid

Advantages

- Highly tunable (M, L*, X)
- Interactions well defined
  - ✓ Strong (LA-LB)
  - ✓ Directional

Disadvantages

- Mostly metals
  - ✓ Toxic
  - ✓ Expensive



usually, Y=O, NR^2
L_n = chiral ligand
X= counterion

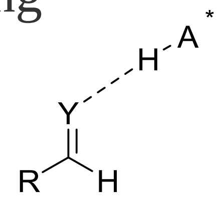
Brønsted acid

Advantages

- Somewhat tunable (A*, pKa)
- Metal free catalyst
  - ✓ Mild reaction conditions
  - ✓ Non toxic (application to pharmaceutical industry) and environment friendly
  - ✓ Inexpensive
  - ✓ Stable (usually to water and O_2)
- Dominant catalysts in biocatalysis

Disadvantages

- Interactions not well defined
- High loading



M.S. Taylor, E. N. Jacobsen, *Ang ew. Chem. Int. Ed*. **2006**, *45*, 1520-1543
Y. Takemoto, *Org. Biomol. Chem*, **2005**, *3*, 4299-4306

Hydrogen-Bond Catalysis or Brønsted-Acid Catalysis?

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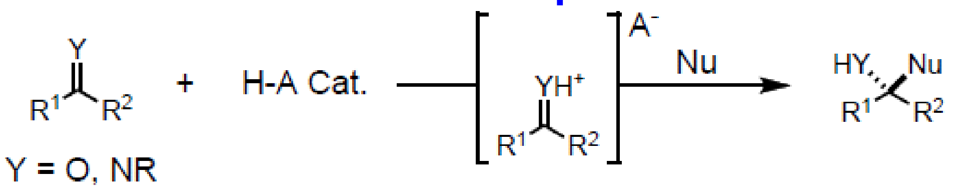
- The terms : Weak/Strong Bronsted acid, General/Specific acid catalysis
- LUMO energy of the carbonyl or imine decreases by lowering the electron density at O or N atoms
- The H^+ or H-bond a crucial role in accelerating the reaction

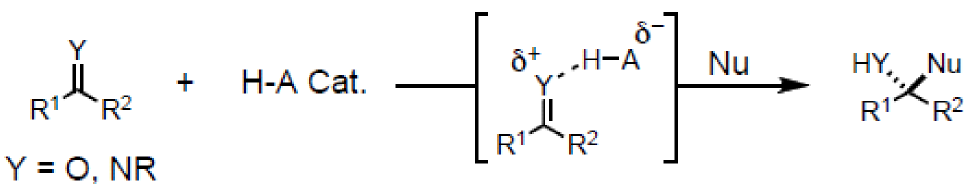
Specific Acid Catalysis: Reversible protonation of the electrophile in a pre-equilibrium step prior to nucleophilic attack.

Ions pair



Bronsted acid catalysis

General acid catalysis or *Hydrogen bond catalysis*: Acid activation of an electrophile, but not full proton transfer.



H-bond catalysis

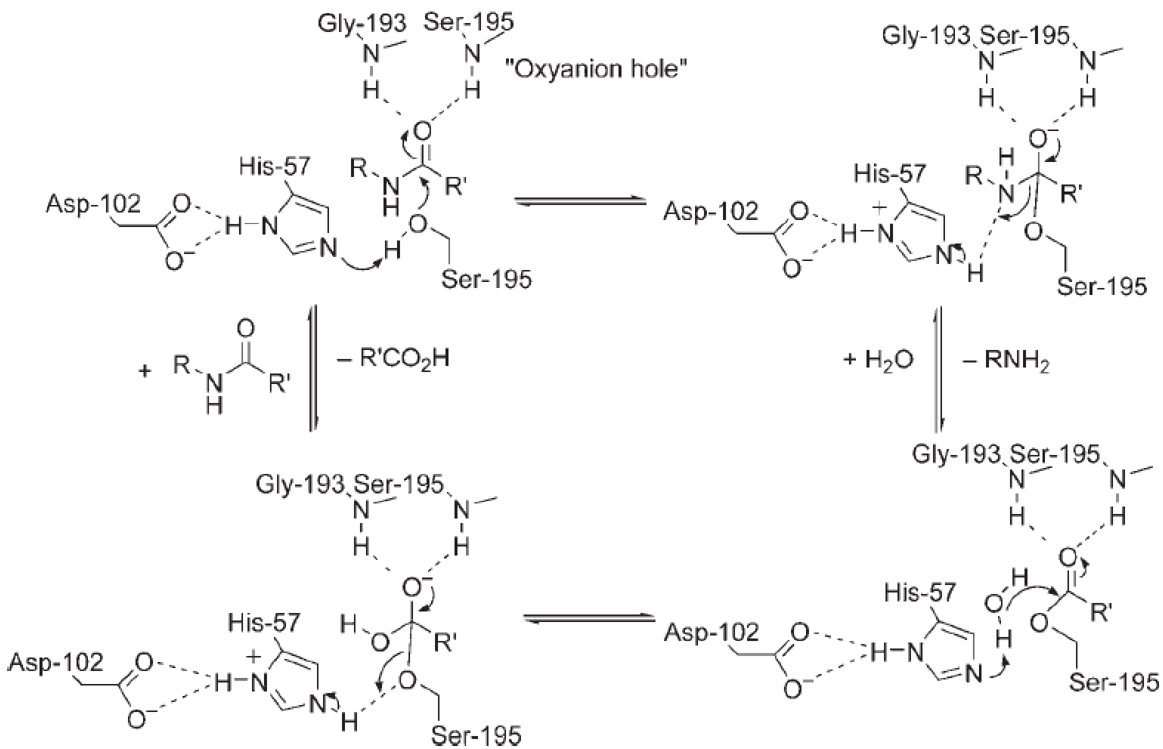
H-bond complex

- A strong Brønsted acid will do Brønsted-acid catalysis
- A weak Brønsted acid (e.g. neutral) will do Hydrogen-bond catalysis

Petri M. Pihko Hydrogen Bonding in Organic Synthesis, **2009**.

H-bond occuring in nature

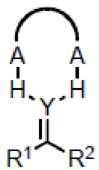
> Serine protease acceleration of amide hydrolysis
  - Double H-bonding: effective method for electrophile activation
  - Multiple non covalent interaction with substrate : organisation of the binding site
  - Bifunctional catalysis : activation of the nucleophile



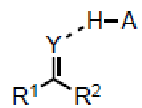
M. S. Taylor, Eric N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543

Modes of H-bond catalysis

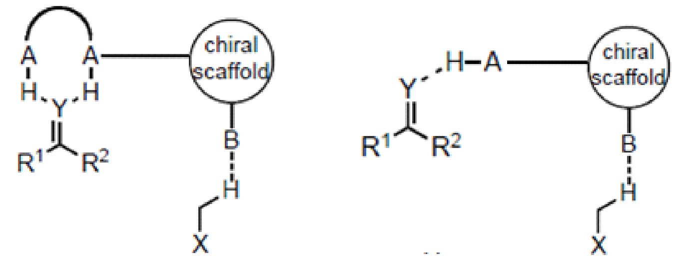
> Three modes of H-bond catalysis are going to be discussed



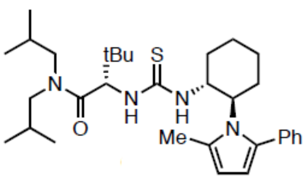
double hydrogen bonding



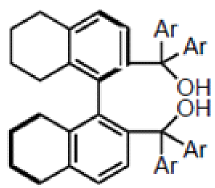
single hydrogen bonding



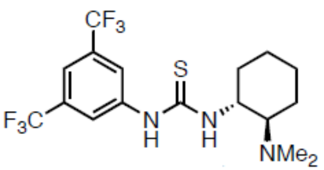
bifunctional catalysis



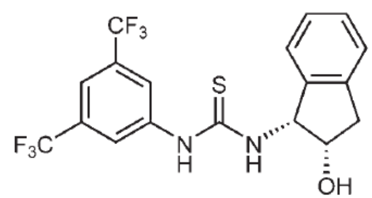
Jacobsen



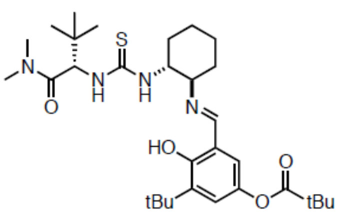
Rawal, Yamamoto



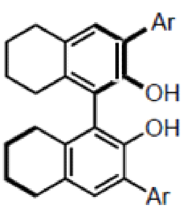
Takemoto



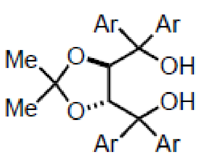
Ricci



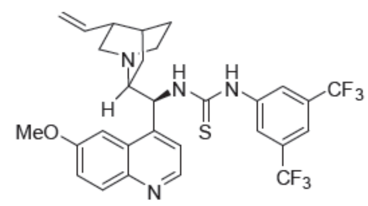
Jacobsen



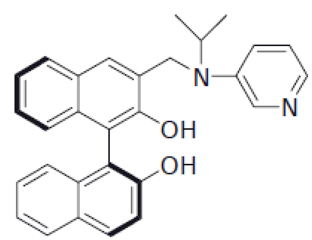
Schaus



Rawal

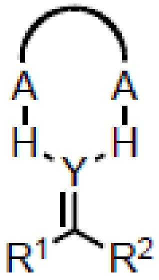


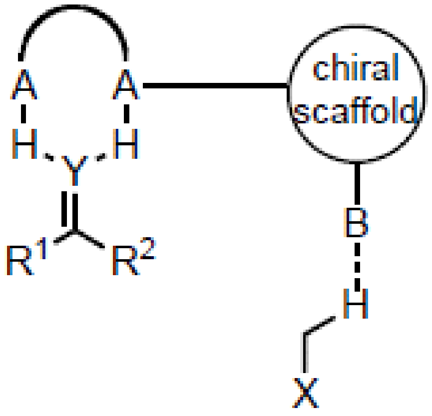
Deng



Sasai

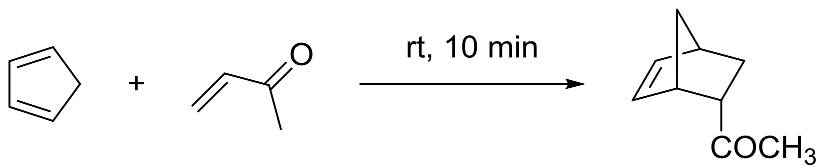
Double H-bond catalysts



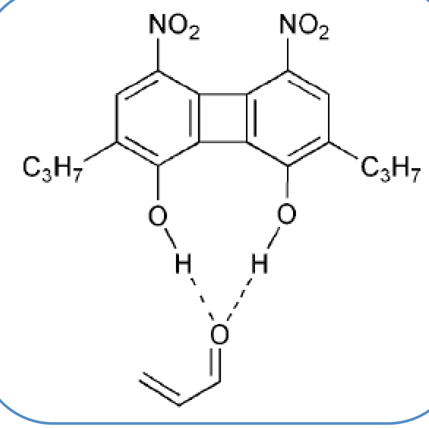


Double H-bond
Pioneering work in achiral synthesis

Kelly, 1990 : Diels Alder reaction



yield without catalyst : 3%
with catalyst : 94%



> Acceleration of the reaction rate (result with or without catalyst) and control outcome

> First proposition of a mechanism *via* double H-bond activation of the dienophile

> Control experiment:
- Presence of a monoprotic acid
- H-bond acceptor on diene decreases effect

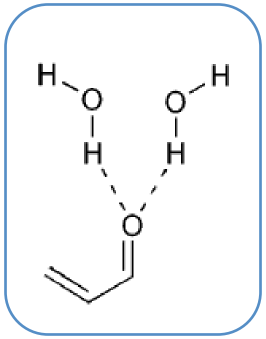
> H-bond used to position (control) and activate (acceleration) the dienophile

T. R. Kelly, P. Meghani and V. S. Ekkundi, *Tetrahedron Lett.*, **1990**, *31*, 3381–3384

Double H-bond
Pioneering work in achiral synthesis

Jorgensen, 1991 : Hydratation model (computationnal studies)

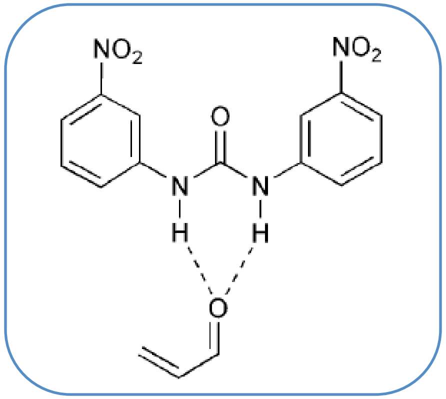
> Accelerating effect of water in Diels Alder: Variation of ΔG and polarization
> Two water molecule "clamp" the carbonyl : solvent effect



Etter, 1991 : Crystallization

> 1: 1 cocrystals e^- poor urea with a wide variety of H-bond acceptors
- With solvents : THF, DMSO …
- With other acceptor : triphenylphosphine oxide, ethylene glycol

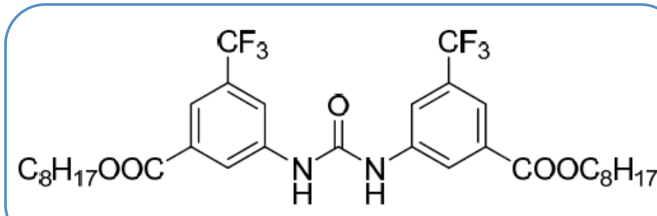
> Proof of Double H-bond with the urea moiety (IR/X-ray)
> Ortho, para EWG, metha EDG : no crystallization
> Meta EWGs → molecules become nearly planar
→ ortho- C-H protons lie as close as possible to the carbonyl group
→ Carbonyl (strong LB) does'nt form any intermolecular H-bond
→ N-H free to bind
→ otherwise, no crystallization



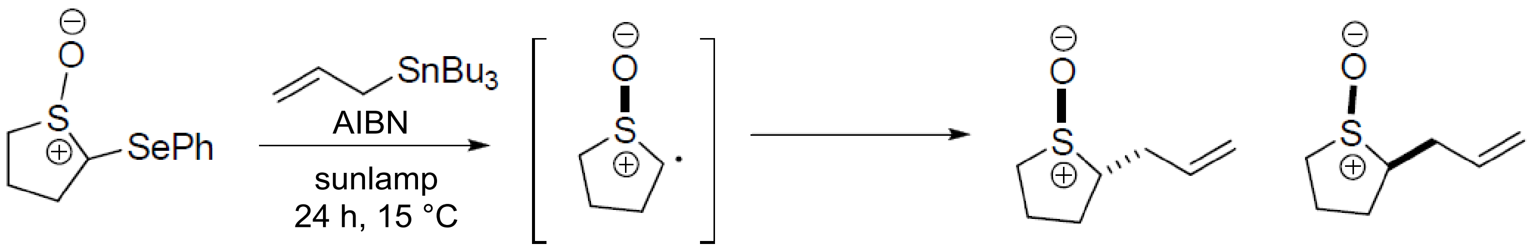
J. F. Blake and W. L. Jorgensen, *J. Am. Chem. Soc.*, **1991**, *113*, 7430–7432
M.C Etter, T. W. Panunto, *J. Am. Chem. Soc.* **1988**, *110*, 5896-5897

Double H-bond
Pioneering work in achiral synthesis

Curran, 1994 : Allylation of α-sulfinyl radical



- > Structure inspired by Kelly (NO_2 replace by CF_3)
- > New "protic Lewis acid" to modify the rate and stereochemical outcome
- > Work of Renaud and Ribezzo : stereoselectivity increase with LA

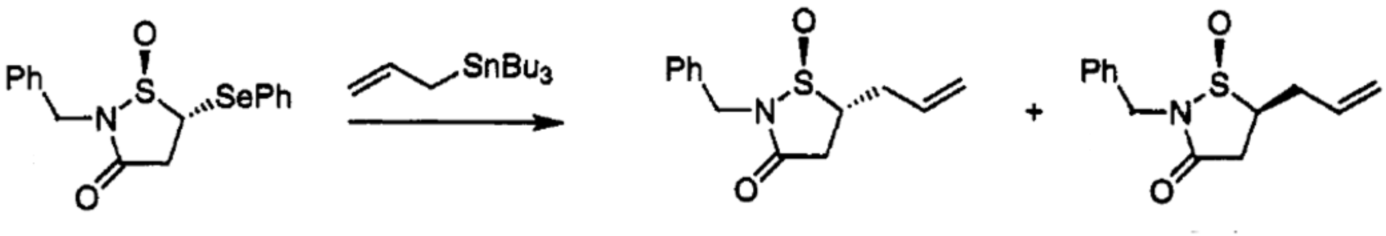


solvent	additive	Trans/cis (yield %)
benzene	none	2.5/1 (60)
CF_3CH_2OH	none	8.1/1 (83)
THF	$ZnBr_2$(0.5 eq)	8/1 (60)
benzene	Cat (1 eq)	7/1 (81)

D. P. Curran, L. H. Kuo, *J. Org. Chem.* **1994**, *59*, 3259.

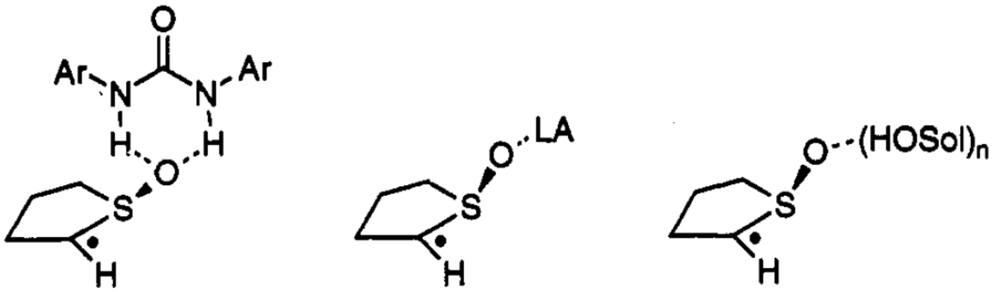
Double H-bond
Pioneering work in achiral synthesis

- Work of Waldner and De Mesmaeker : stereoselectivity increase in H-bond donating solvent



solvent	additive	Trans/cis (yield %)
benzene	none	5.3/1 (59)
EtOH	none	9.8/1 (63)
benzene	TFE (5 eq)	10.3/1 (63)
benzene	Cat (1 eq)	14.1/1 (72)

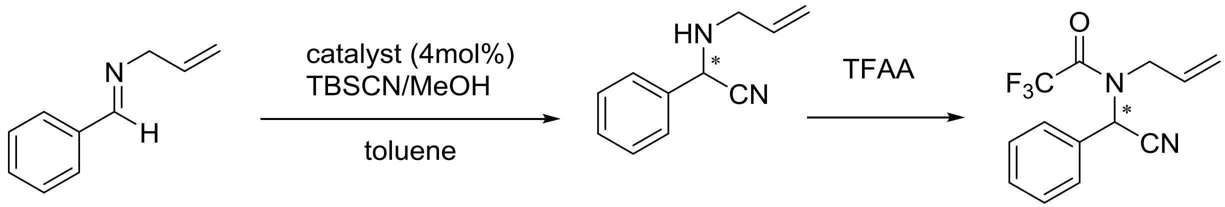
- Stereoselectivity cf model
- Acceleration polar effect



D. P. Curran, L. H. Kuo, *J. Org. Chem.* **1994**, *59*, 3259.

Double H-bond
Monofunctional thiourea

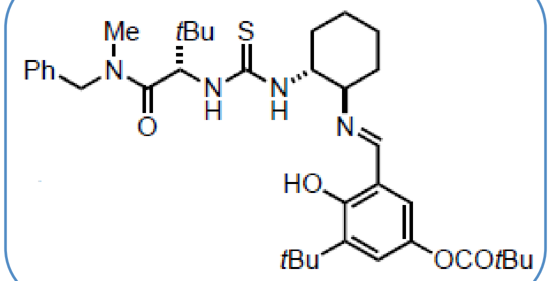
Jacobsen, 1998 : Strecker reaction



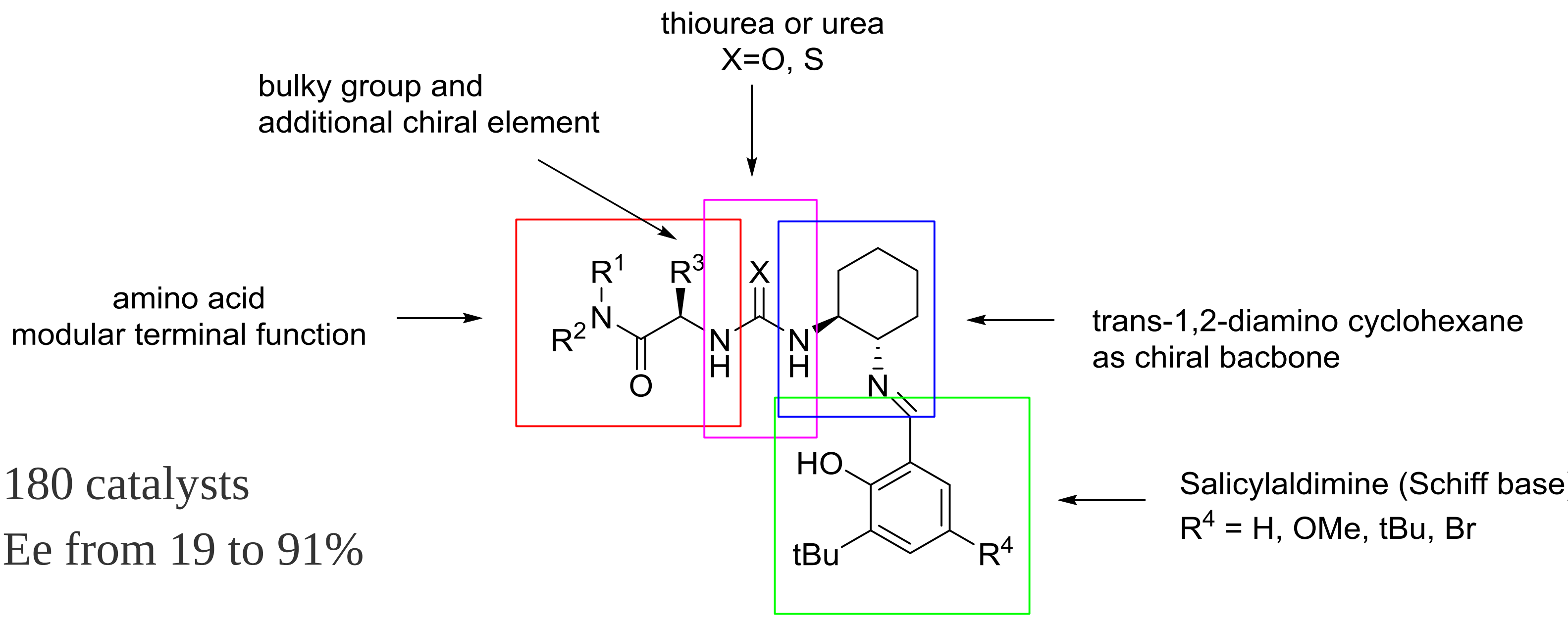
conversion by 1H NMR

ee by chiral GC

78% yield
91% ee



> Optimisation of catalyst (parallel synthetic libraries)

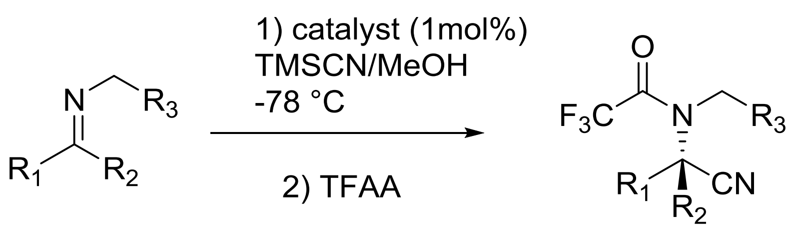


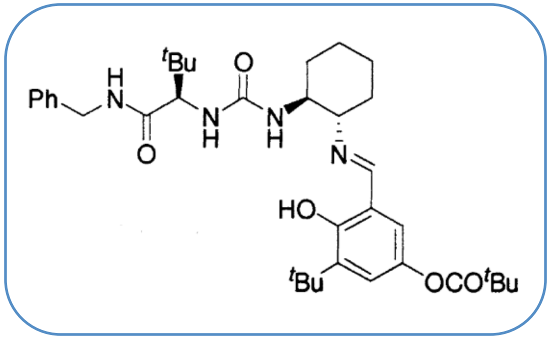
- 180 catalysts
- Ee from 19 to 91%

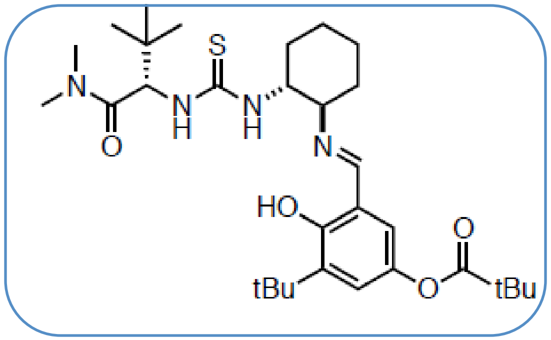
M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998,** *120,* 4901-4902

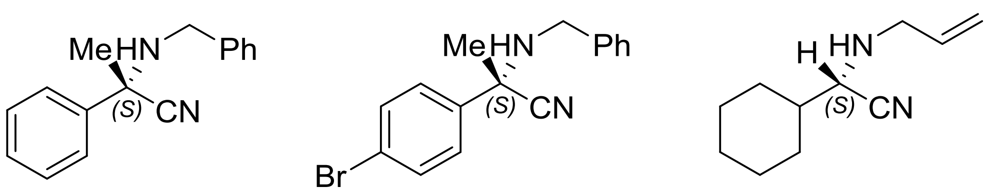
Double H-bond
Monofunctional thiourea

Jacobsen, 2000 : Strecker reaction







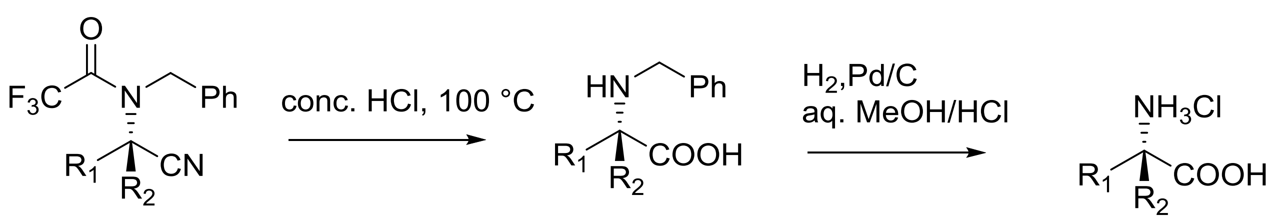


97% yield
90% ee

quant yield
99.9% ee

88% yield
86% ee

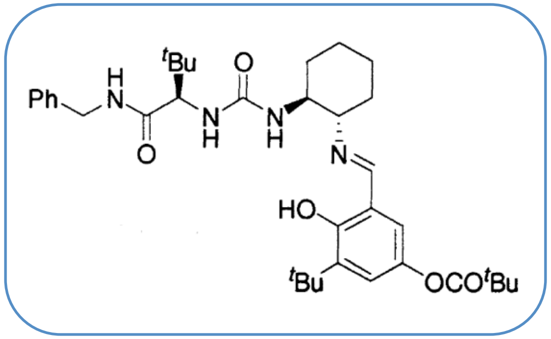
> Further modifications



M. S. Sigman, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2000,** *39,* 1279-1281
Vachal, P.; Jacobsen, E.N. *Org. Lett.* **2000,** *2*, 867-870

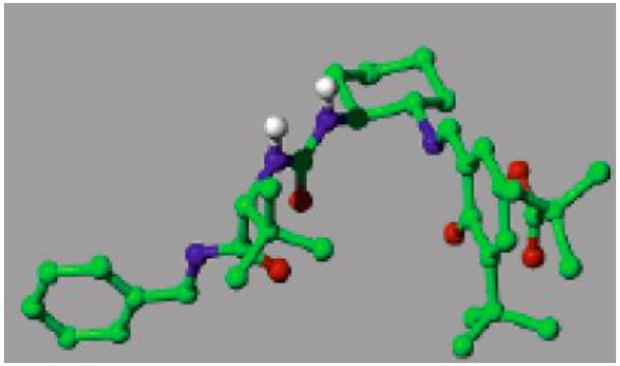
Double H-bond
Monofunctional thiourea

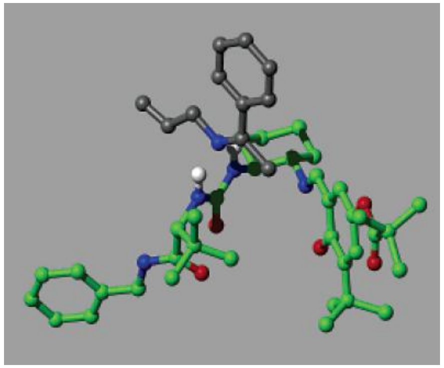
Jacobsen, 2002 : Mechanism ,Strecker reaction



> First studies :

- Conformation of ground state A determined by ROESY/NOE
- Rate-limiting addition of HCN
- Reversible formation of imine-catalyst complex
- Only the 2 urea H are necessary
- Imine in the Z conformation (mixture of E/Z interconvert in solution)
- Conformation of complexe determined by ROESY/NOE





Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002,** *124,* 10012-10014

Double H-bond
Monofunctional thiourea

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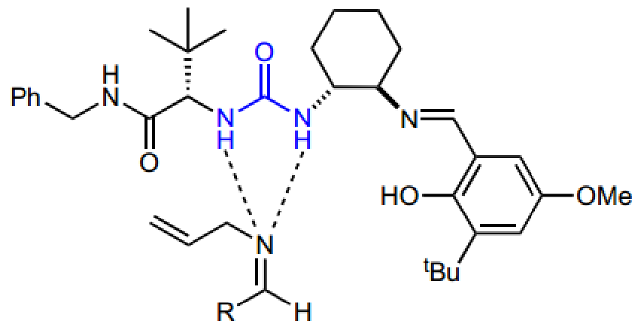
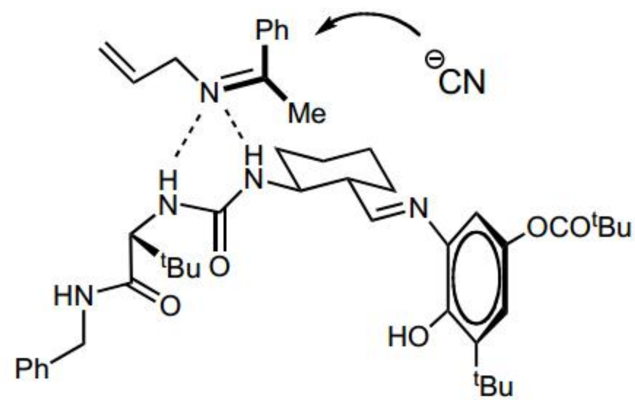
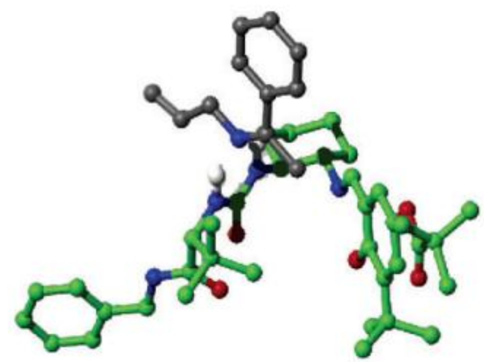
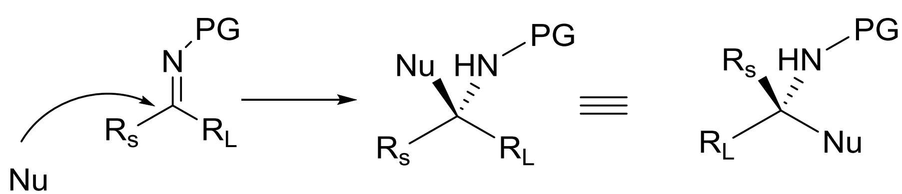
- Model proposed
- Bridging mode





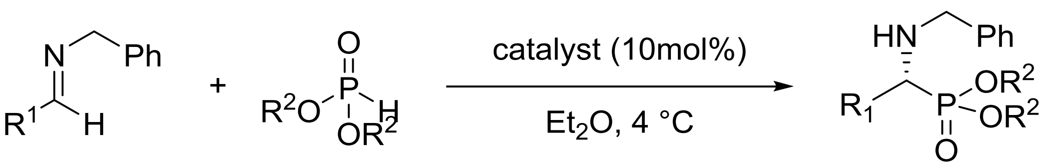




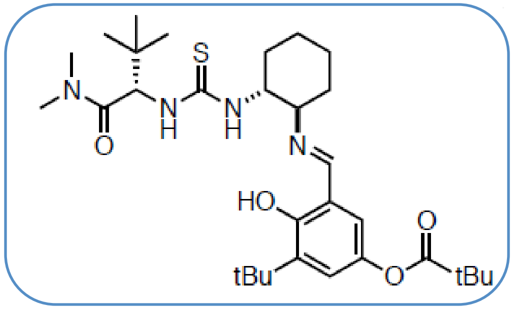
Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002,** *124,* 10012-10014

Double H-bond
Monofunctional thiourea

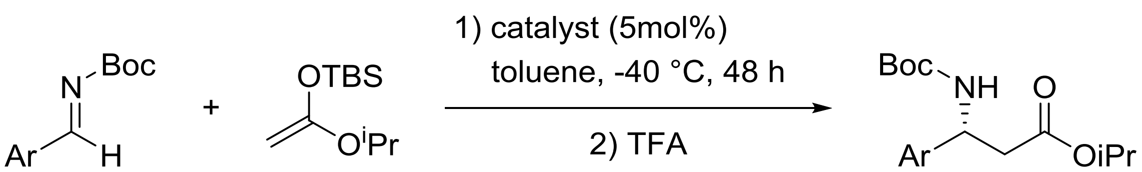
Jacobsen, 2004 : Hydrophosphonylation of benzyl imines



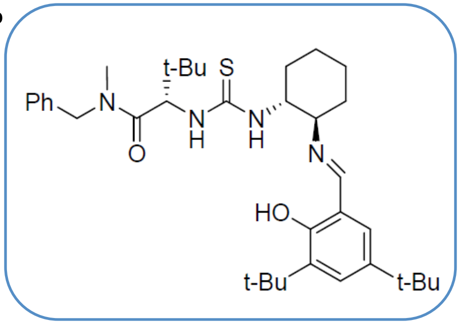
R^1=alkyl, aryl
R^2=Aryl
yield 52-93%
ee 81-98%



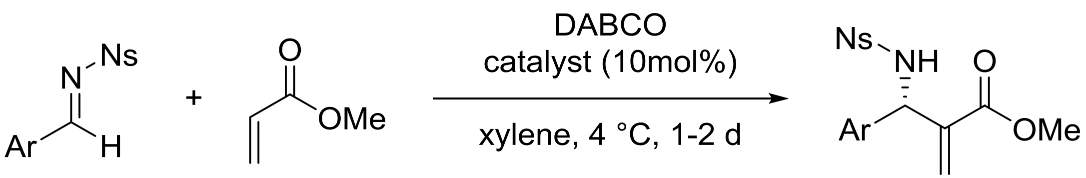
Jacobsen, 2002 : Mannich type reaction



yield 84-98%
ee 86-98%



Jacobsen, 2005 : Baylis-Hillman

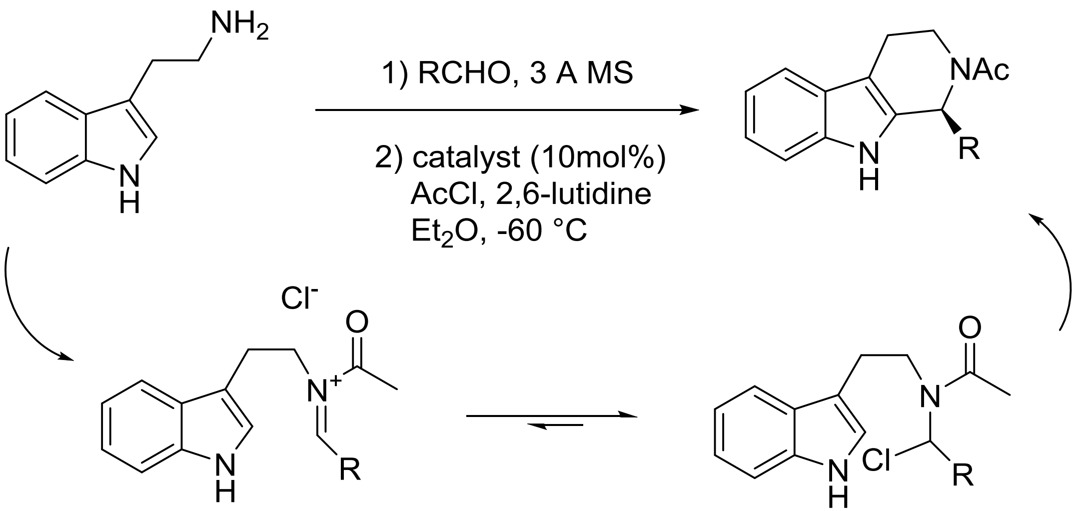


yield 25-49%
ee 87-99%

1) Joly, G.D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004,** *126,* 4102-4103 2) Wenzel, A.G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002,** *124,* 12964-12965 3) I. T. Raheem, E. N. Jacobsen, *Adv. Synth. Catal.* **2005,** *347,* 1701-1708

Double H-bond
Monofunctional thiourea

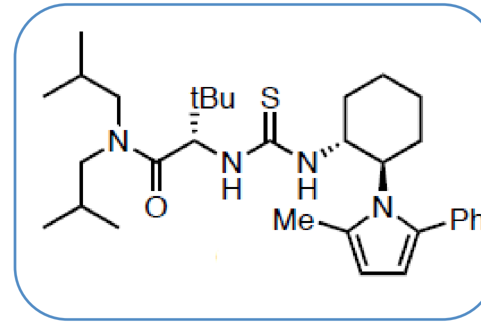
Jacobsen, 2004 : Acyl-Pictet-Spengler



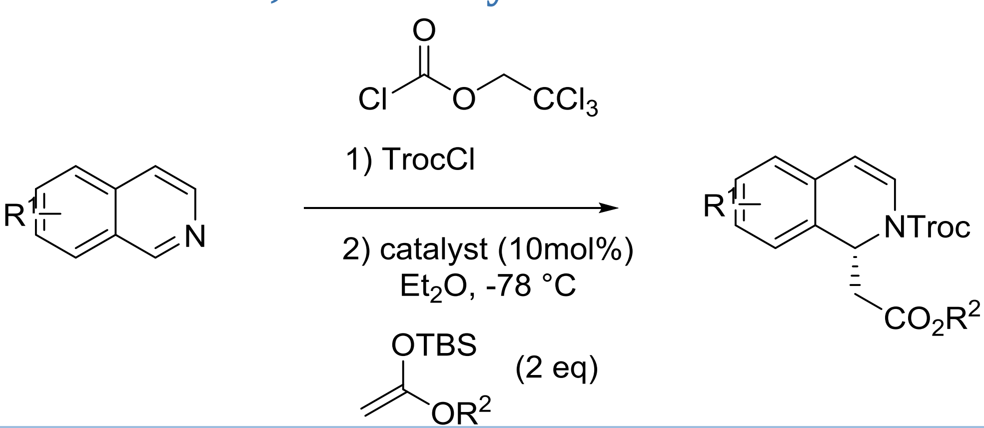
N-acylium ion

chloroamide

R=alkyl
yield 65-80%
ee 85-95%



Jacobsen, 2005 : Acyl-Mannich reaction



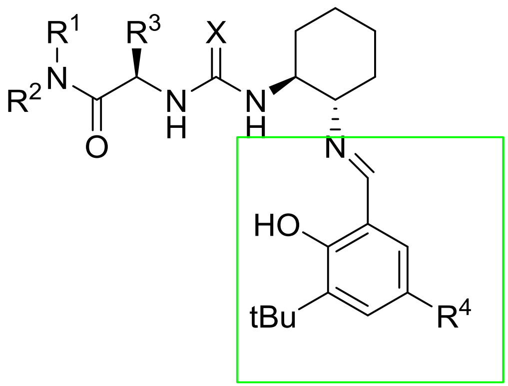
R^1 = H, R^2 = alkyl
yield 65-80%
ee73-86%

R^1 = Hal, Alk, NO_2, R^2 = iPr
yield 67-86%
ee 60-92%

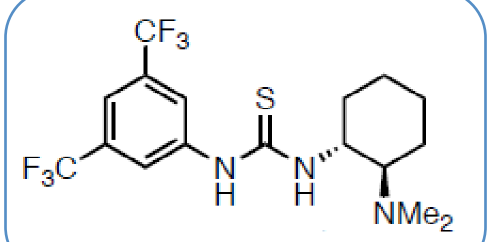
Taylor, M.S.; Jacobsen, E.N.; *J. Am. Chem. Soc.* **2004,** *126,* 10558-10559
Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005,** *44,* 6700-6704

Double H-bond
Bifunctional thiourea

- Substrates used previously, restricted to imines
- But variation of the N-substituents
- Introduction of a functional group to obtain dual activation of both electrophile and nucleophile
- Catalysts usually possess an acidic and basic structural group for dual activation
- Higher yields and enantioselectivities can be obtained

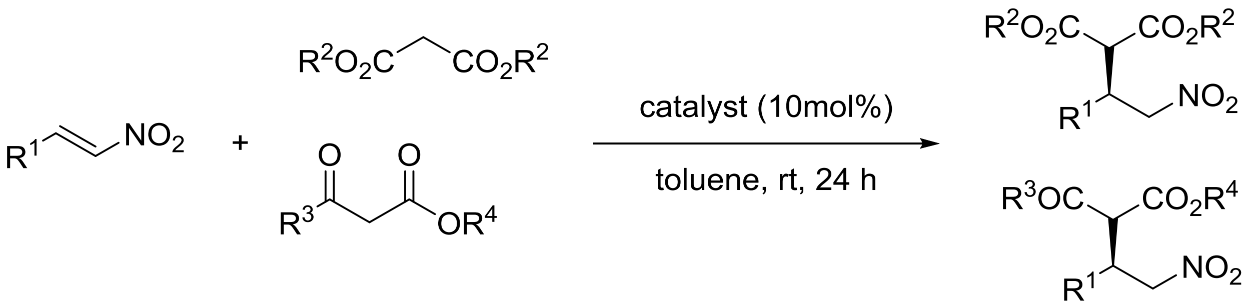


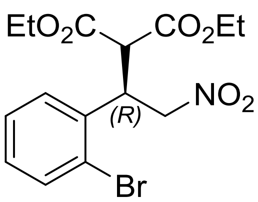
Double H-bond
Bifunctional thiourea



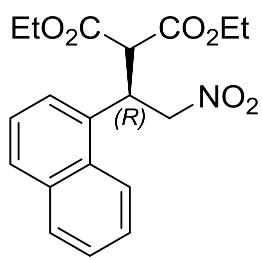
Takemoto, 2004 : Michael reaction

- > Chiral scaffold helps control approach of nucleophile

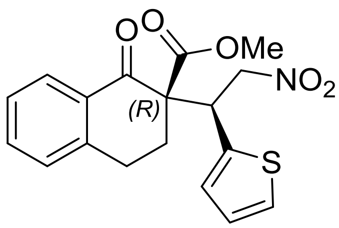




96% yield
94% ee



95% yield
92% ee



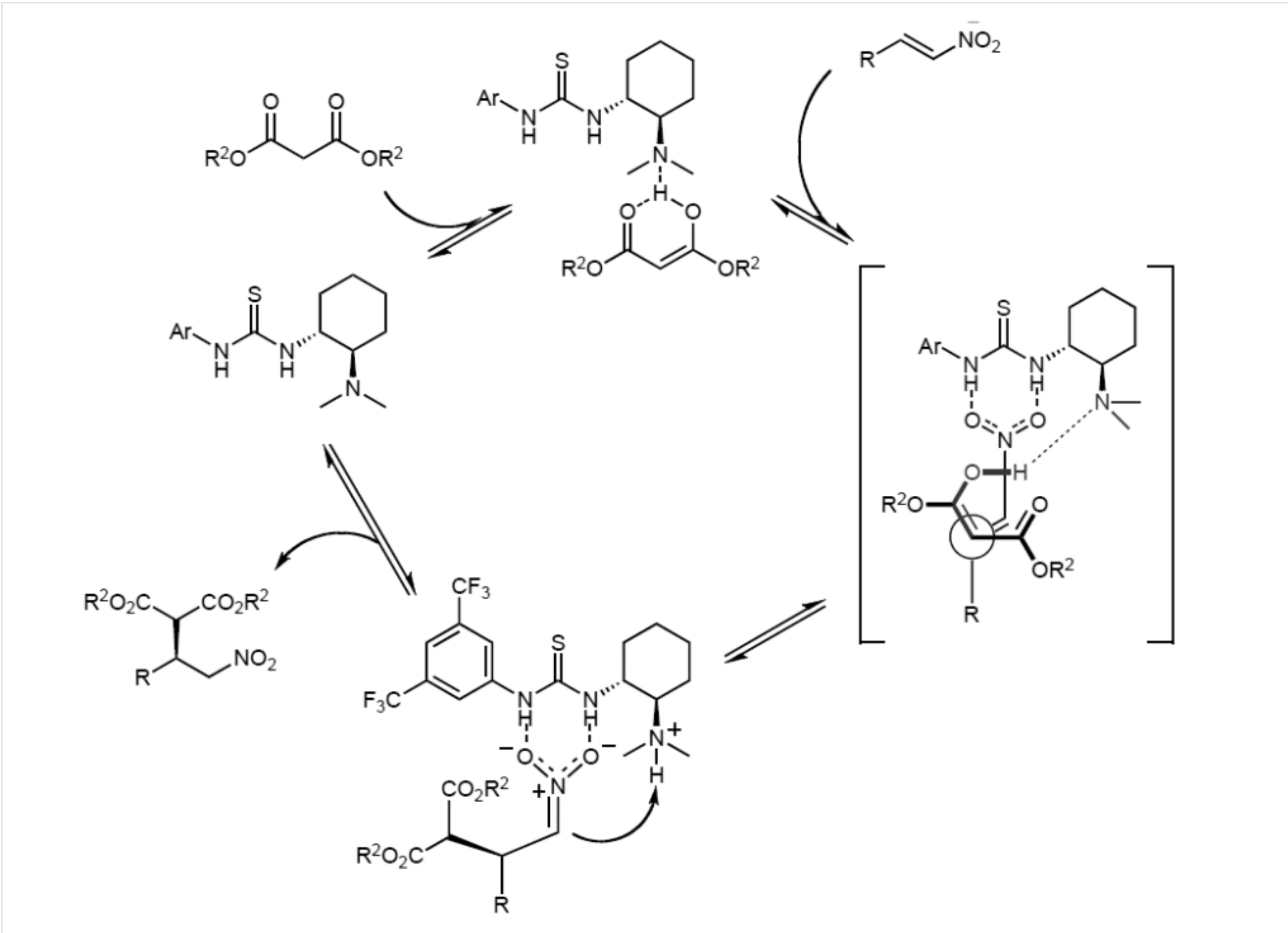
98% yield
syn/anti 99/1
90% ee

- > Acidic thiourea activates nitroolefin
- > Basic tertiary amine enhances the nucleophilicity of the 1,3-dicarbonyl compound

Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005,** *127,* 119-125

Double H-bond
Bifunctional thiourea

> Mechanism proposed (H-bond and orientation identified by NMR and X-ray)

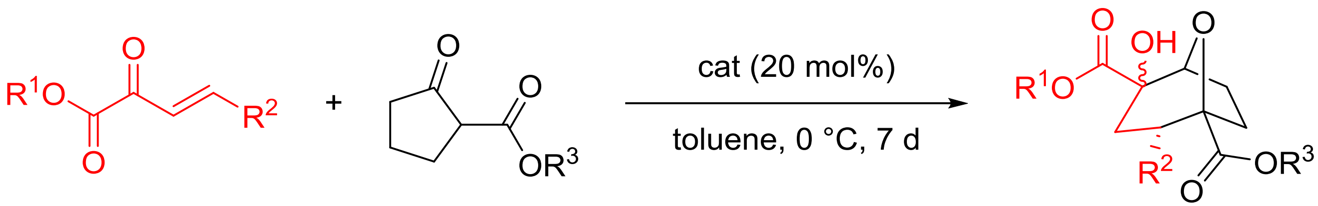


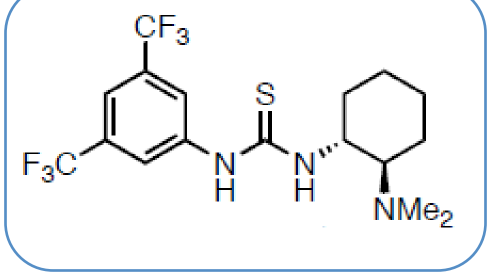
Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005,** *127,* 119-125

Double H-bond
Bifunctional thiourea

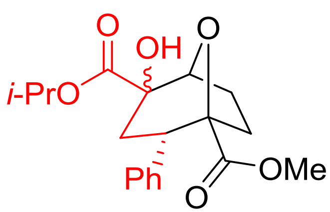
UNIVERSITÄT BERN

Alexakis, 2014 : Domino Michael/Aldol reaction

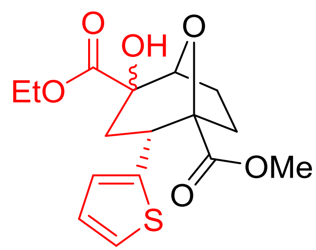




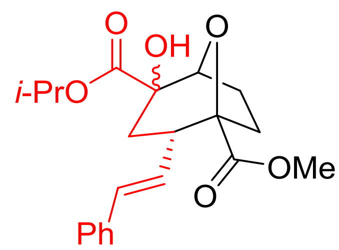
- Bicyclo [3.2.1] octane highly substituted with 4 stereogenic centers (2 quaternary C)
- Only two diastereomers (can be separeted on FC)



97% yield
dr 1.1:1
87:13/85:15



98% yield
dr 1:1
82:18/80:20

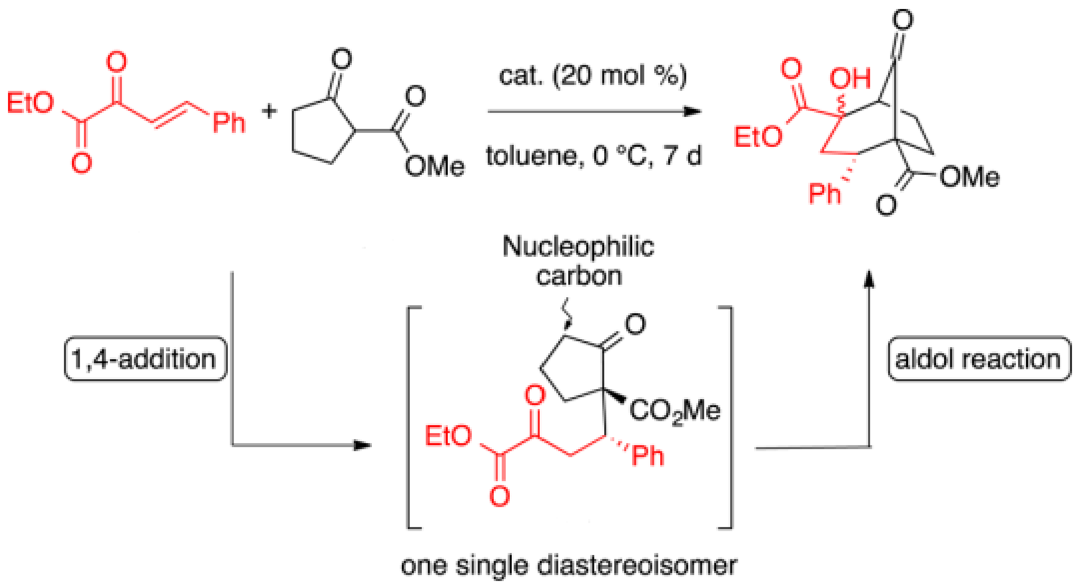


96% yield
dr 1:4
91:9/94:6

A. Lefranc, L. Gremaud, A. Alexakis, *Org. Lett*, ASAP

Double H-bond
Bifunctional thiourea

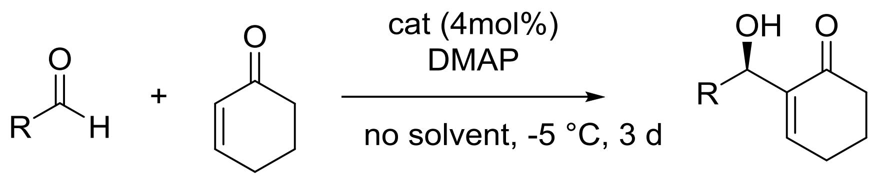
> First insight into mechanism

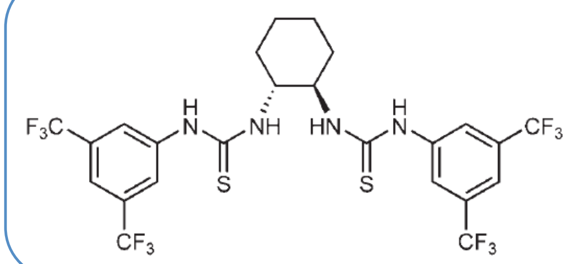


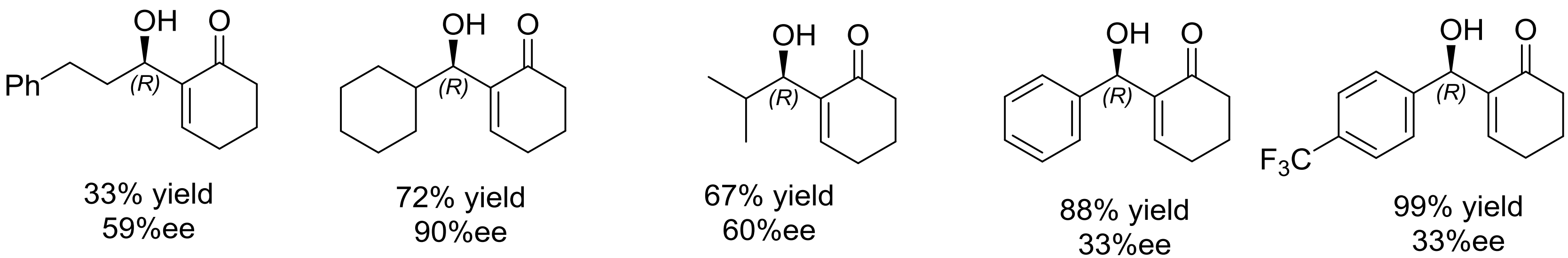
> Diastereoselectivity determined in the aldol reaction

Double H-bond
Bifunctional thiourea

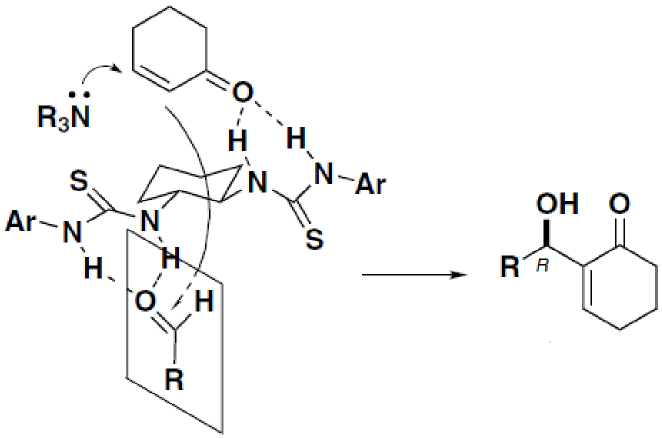
Nagasawa, 2004 : Baylis-Hillman reaction







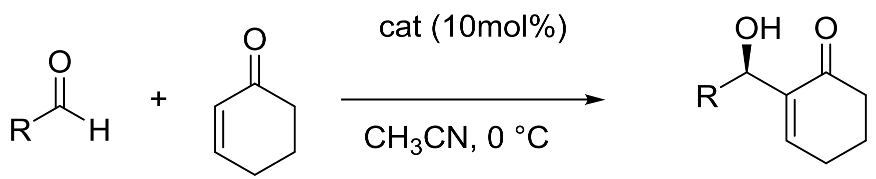
> Model proposed

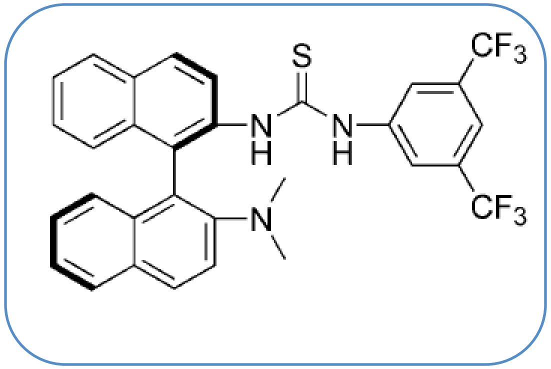


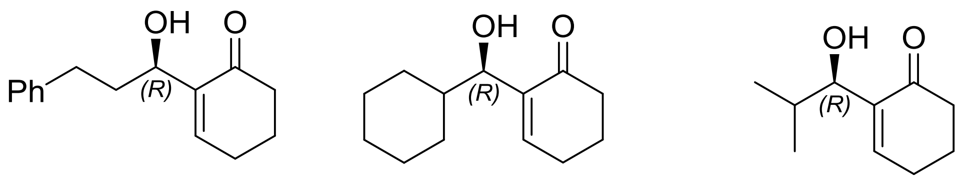
Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett*. **2004**, *45*, 5589

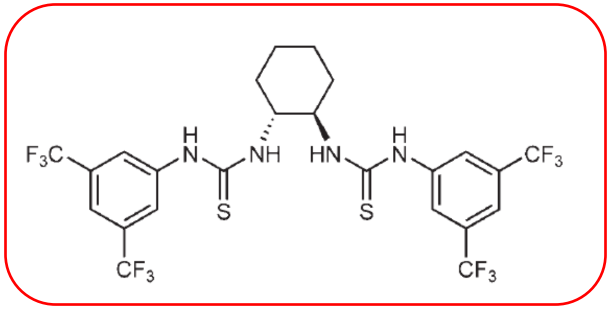
Double H-bond
Bifunctional thiourea

Wang, 2005: Morita-Baylis-Hillman







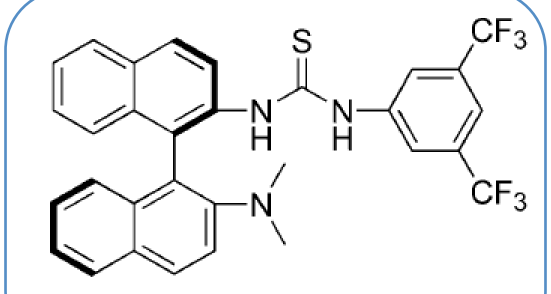


2 d	5 d	3 d
80% yield	67% yield	63% yield
83%ee	92%ee	94%ee
33% yield	72% yield	67% yield
59%ee	90%ee	60%ee

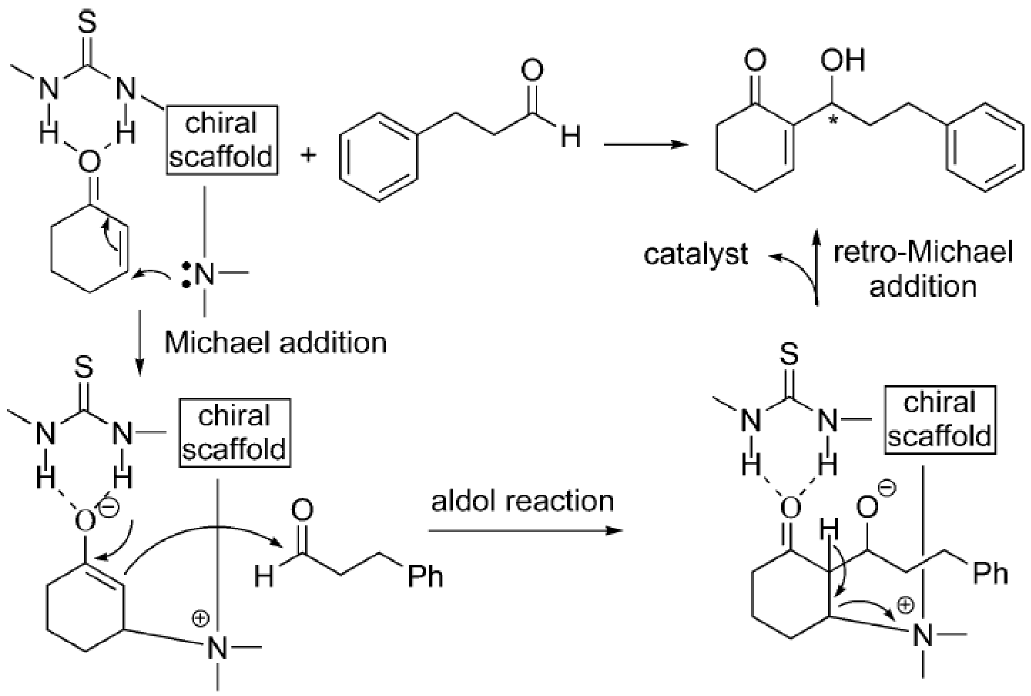
> Amine should not be too bulky to be better nucleophile
> Aromatic part of thiourea bearing EWG give stronger H-bond with carbonyl
> Still long reaction times!

Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, 7, 4293-4296

Double H-bond
Bifunctional thiourea



> Insight into mechanism

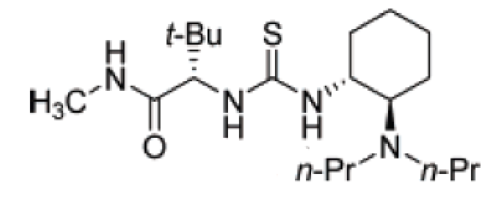


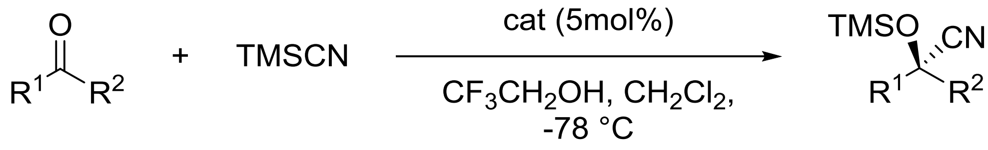
> Low temperature and no H-bond donor solvent

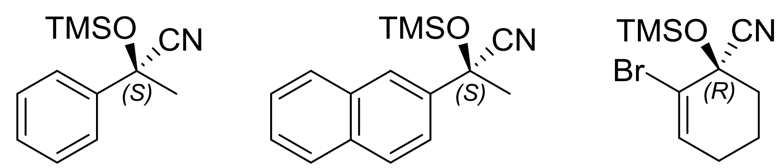
Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293-4296

Double H-bond
Bifunctional thiourea

Jacobsen, 2005: Cyanosilylation of ketones

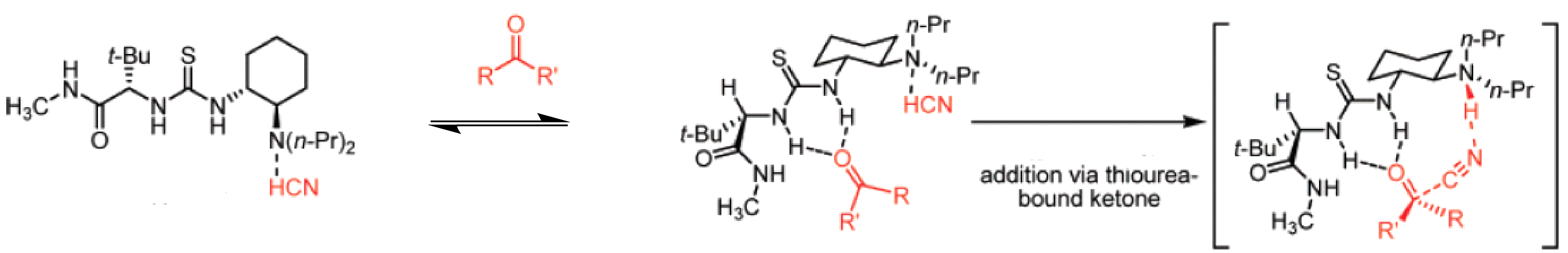






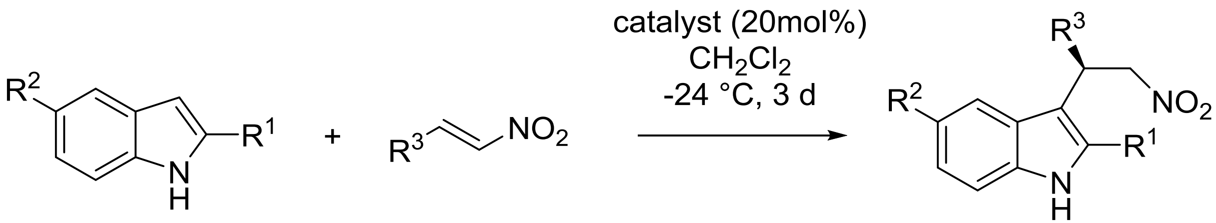
96% yield 97% ee	98% yield 97% ee	95% yield 97% ee

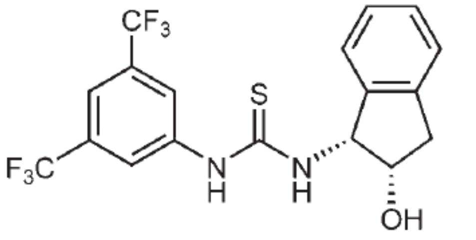
> Mechanism

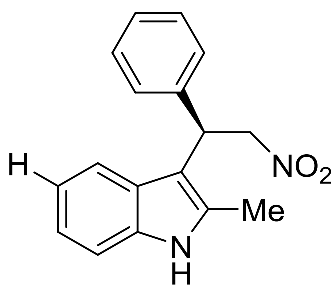


Double H-bond
Bifunctional thiourea

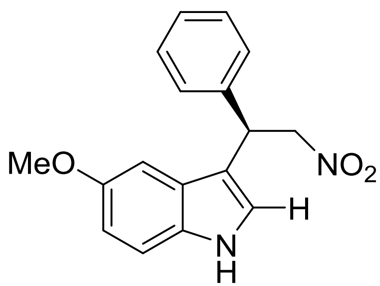
Ricci, 2006: Friedel-Crafts



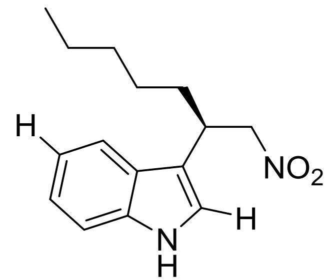




82% yield
74% ee



86% yield
89% ee

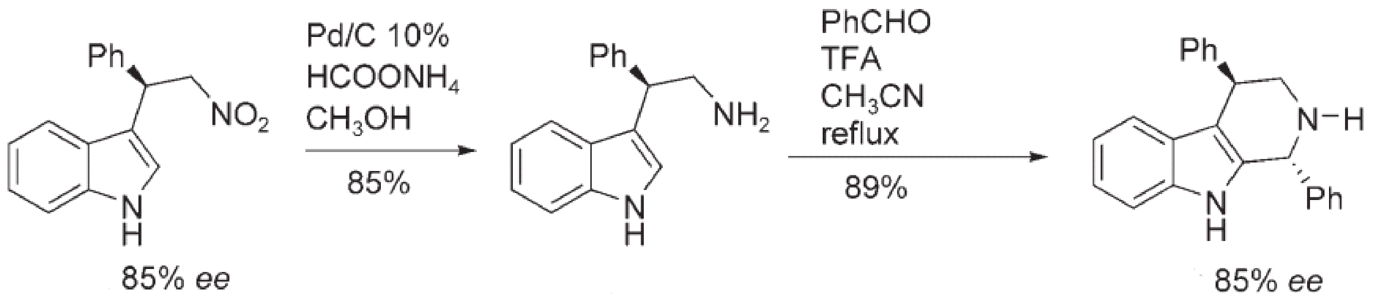


76% yield
83% ee

R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed.* **2005**, *44*, 6576

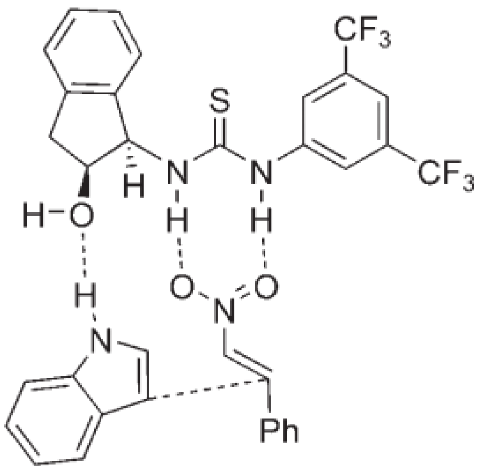
Double H-bond
Bifunctional thiourea

> Further modifications



→ Without loss in ee

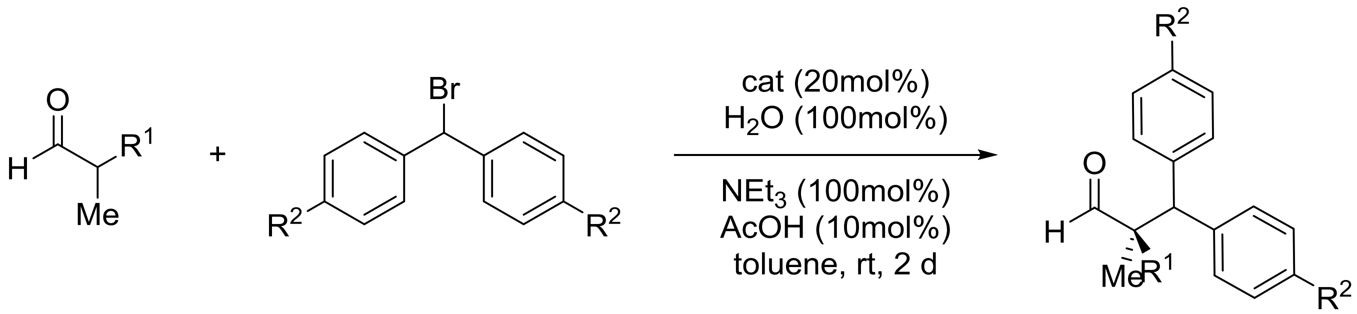
> Model proposed (according to crystal structure)

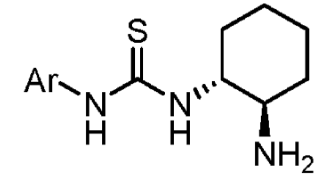


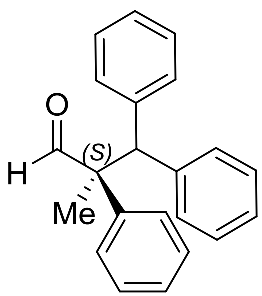
R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed.* **2005**, *44*, 6576.

Double H-bond
Bifunctional thiourea-counteranion effect

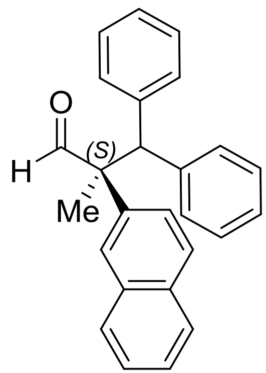
Jacobsen, 2010: α-alkylation of aldehyde



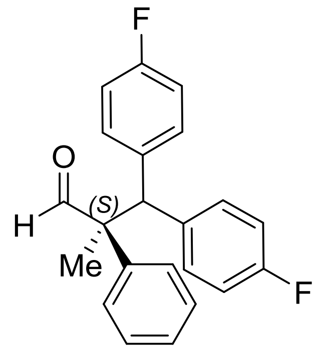




70% yield
91% ee



68% yield
92% ee

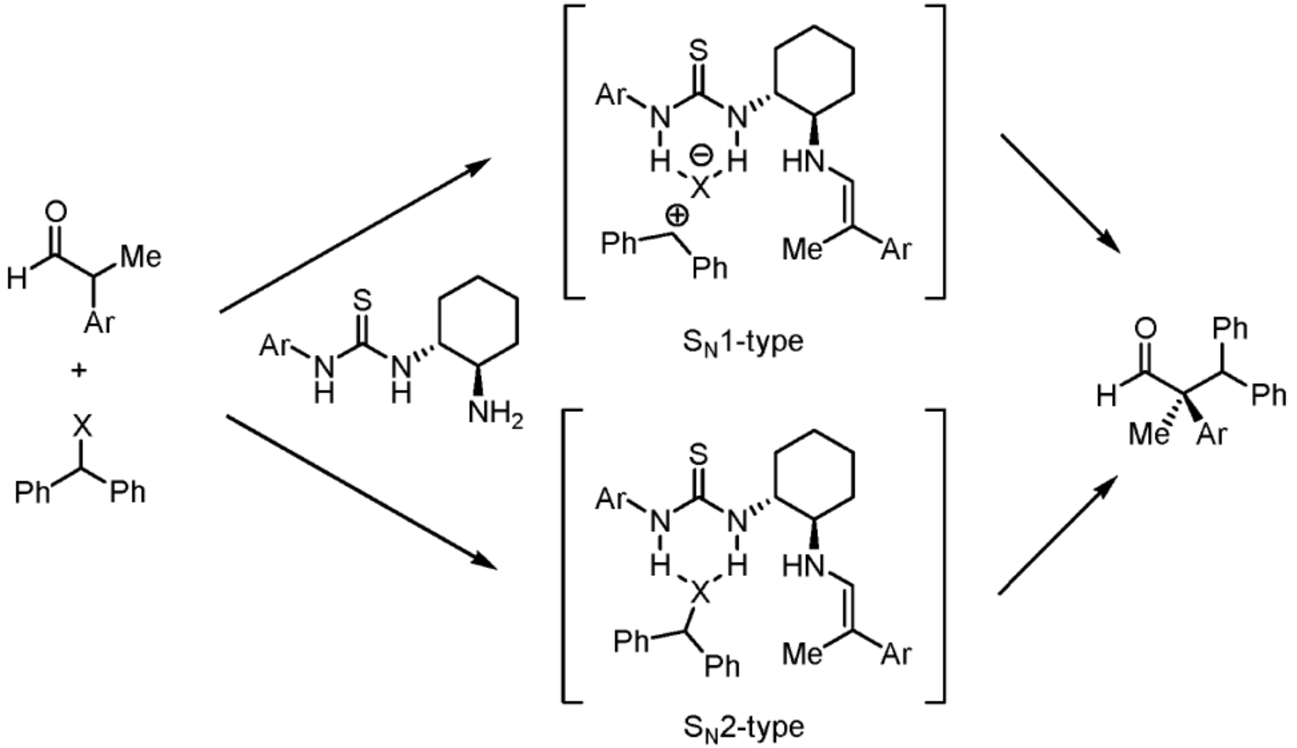


60% yield
90% ee

> General acid catalysis (S_N2) *versus* formation of ion-pair intermediate (S_N1)

Brown, A. R., Kuo, W-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010,** *132,* 9286-9288

Double H-bond
Bifunctional thiourea-counteranion effect



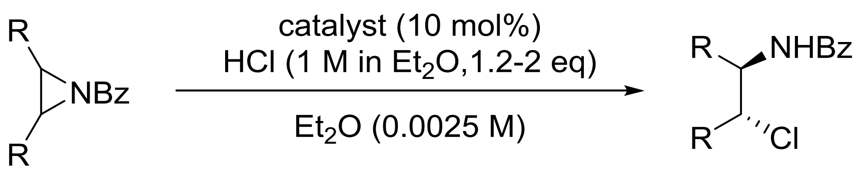
- Secondary kinetic isotope effect : k_H/k_D = 1.12 (transition state = sp3 to sp2)
- Effect of EDG of the electrophile (reaction more rapid)
- Reaction does nt work with primary halide

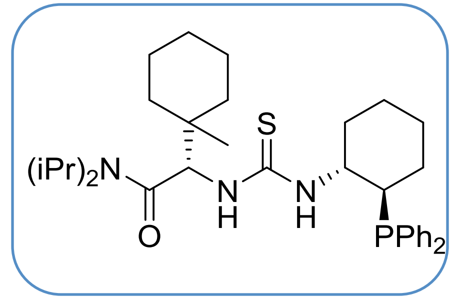
→ S_N1 via carbocation (anion abstraction)

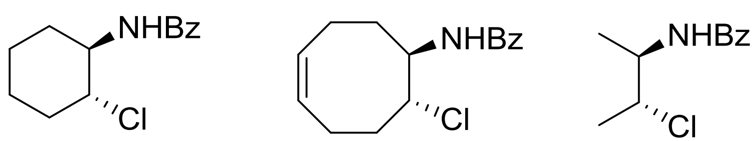
Brown, A. R., Kuo, W-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010,** *132,* 9286-9288

Double H-bond
Bifunctional thiourea-counteranion effect

Jacobsen, 2009: Ring Opening of Aziridines





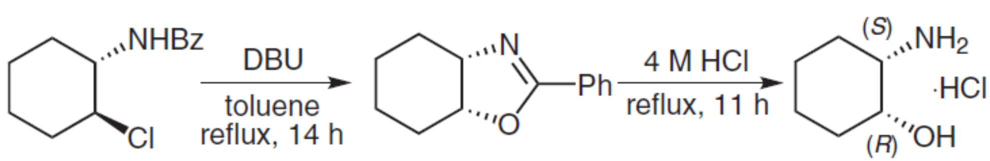


97% yield
83% ee

94% yield
92% ee

96% yield
70% ee

> Further modifications



3a
71% ee

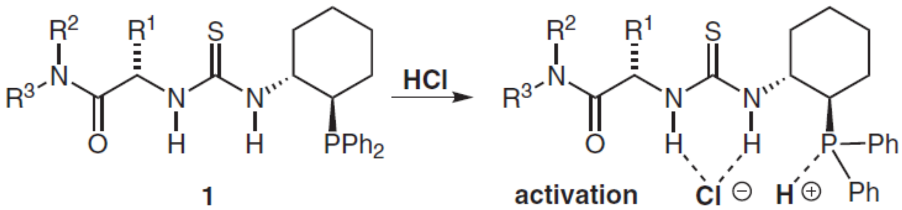
4
72% ee
96% yield

5
71% yield
$[\alpha]_D^{23}$ –18.3
(c = 0.44, EtOH)

Mita T, Jacobsen EN, *Synlett*. **2009,** *10,* 1680-1684

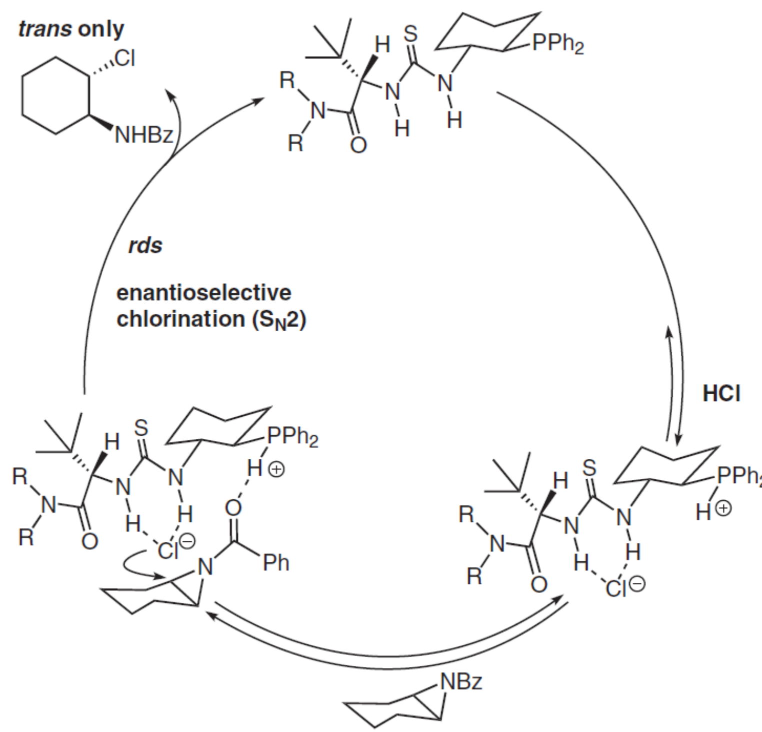
Double H-bond
Bifunctional thiourea-counteranion effect

> Activation HCl confirmed by ^{13}P NMR: phosphonium-Cl complex



> Proposed catalytic cycle
- Diasteroselective: trans product
- Inversion of stereochemistry

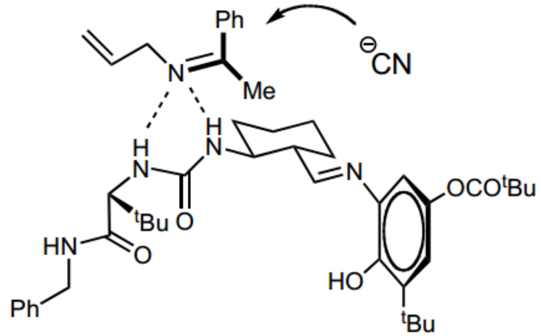
→ S_N2 pathway



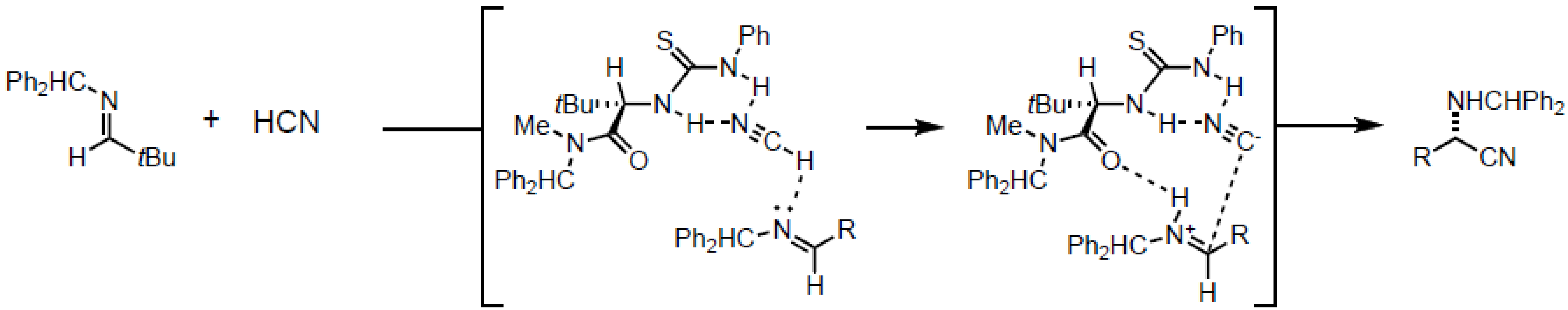
Double H-bond
Bifunctional thiourea-counteranion effect

Jacobsen, 2009 : Strecker reaction

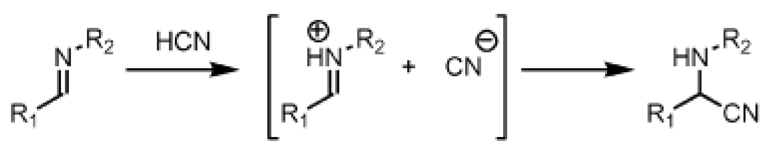
> Previous mechanism



> New mechanism proposed: in accordance with enantioselectivity!



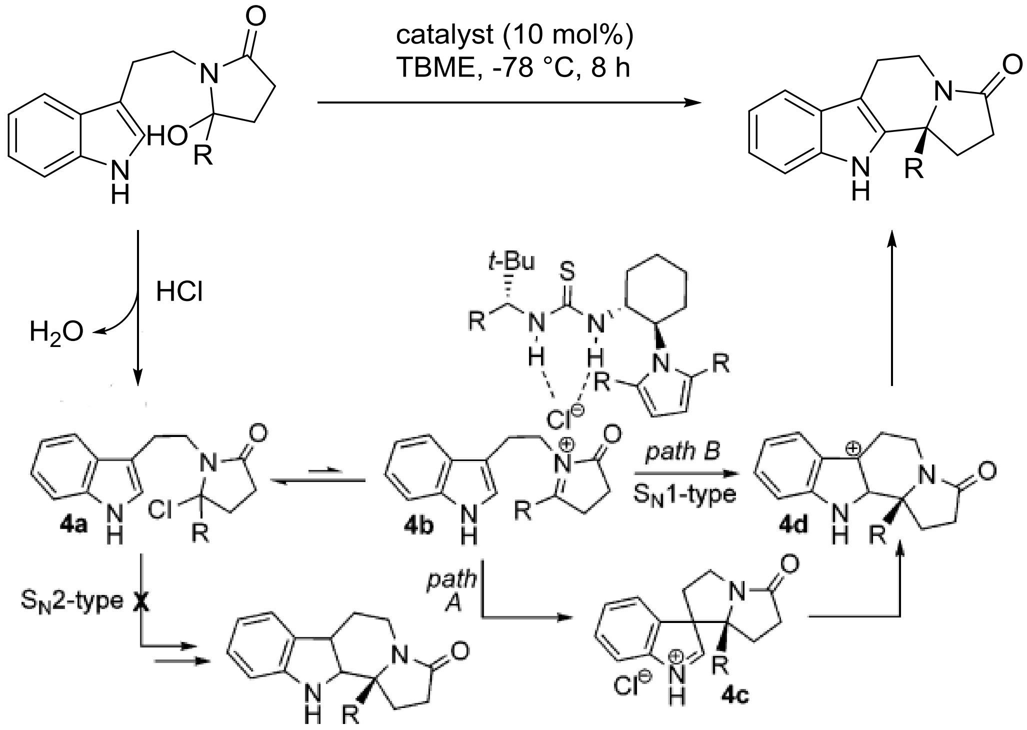
> According to kinetics + computational studies (bond distance)



S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc*. **2009**, *131*, 15358–15374

Double H-bond
Bifunctional thiourea-counteranion effect

Jacobsen, 2007 : Acyl-Pictet-Spengler



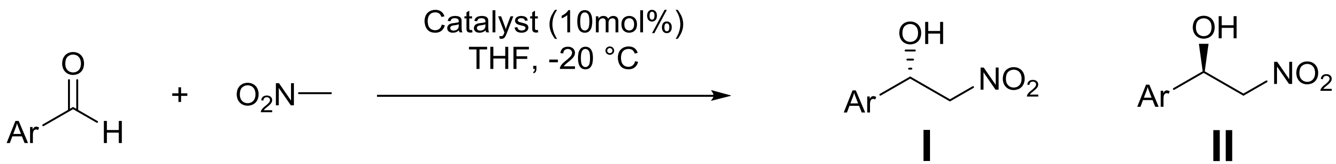
- R group : alkyl *vs* H
- Halide counteranion effect
- Solvent effects

→ S_N1-type mechanism (in accordance with DFT calculation)

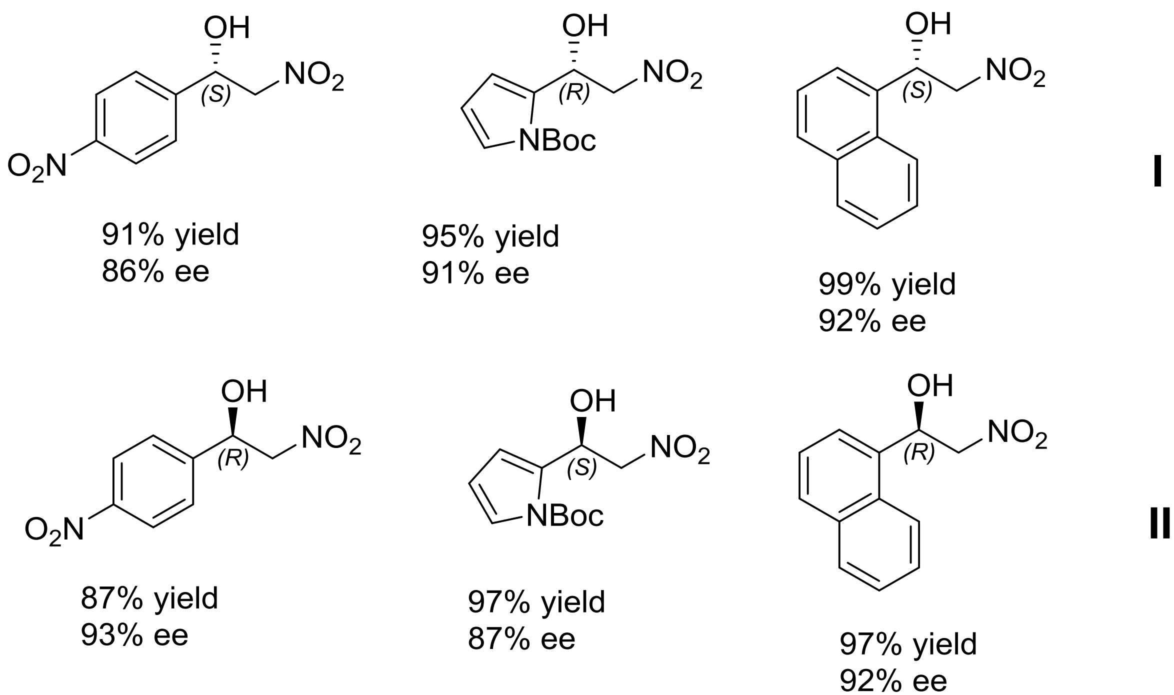
I. T. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen, *J. Am. Chem. Soc*. **2007**, *129*, 13404-13405

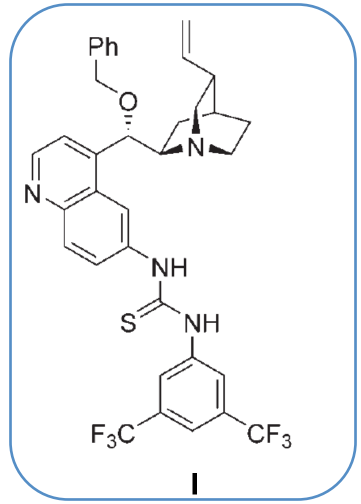
Double H-bond
Bifunctional Cinchona-thiourea

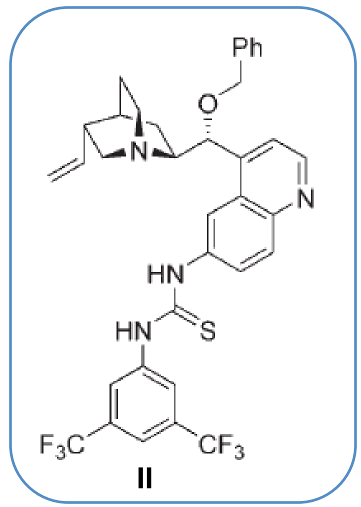
Hiemstra, 2006: Henry reaction



- Metal-free cat: ee<54%
- Cinchona alkaloid: ee<35%







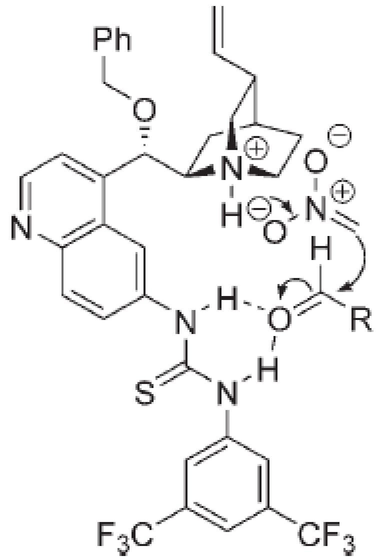
Marcelli, T.; van der Hass, R.N.S.; van Maarseven, J.H.; Hiemstra, H. *Angew.Chem. Int. Ed.* **2006,** *45,* 929-931

Double H-bond
Bifunctional Cinchona-thiourea

> Enantioselectivity observed not clear but
- Aldehyde activated by thiourea
- Nitromethan activated by basic quinuclidine N

> Also acceleration

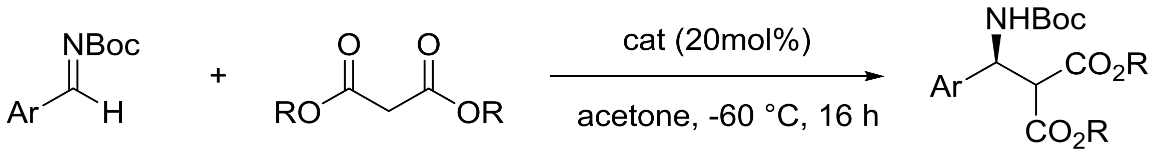
> Model proposed

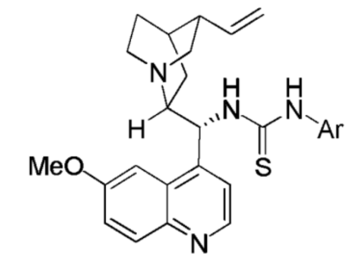


Marcelli, T.; van der Hass, R.N.S.; van Maarseven, J.H.; Hiemstra, H. *Angew.Chem. Int. Ed.* **2006,** *45,* 929-931**.**

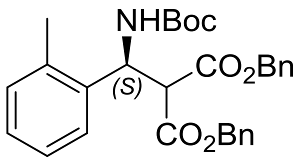
Double H-bond
Bifunctional Cinchona-thiourea

Deng, 2006: Mannich reaction

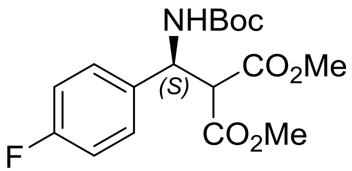




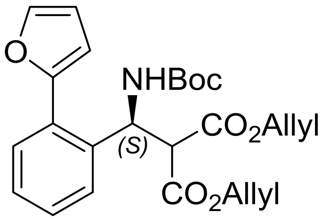
Ar= 3,5-*bis*CF_3Ph



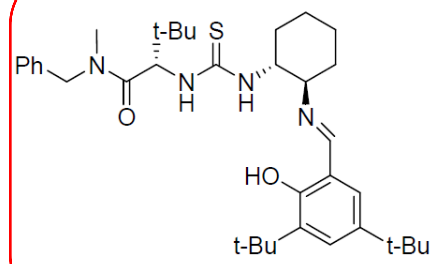
99% yield
99% ee (91)



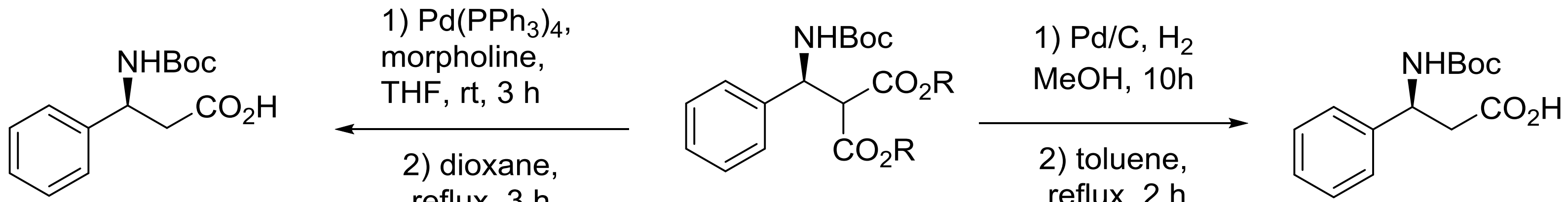
99% yield
99% ee (93)



99% yield
97% ee (91)



> Further modifications



R=allyl, 96% ee
72% yield

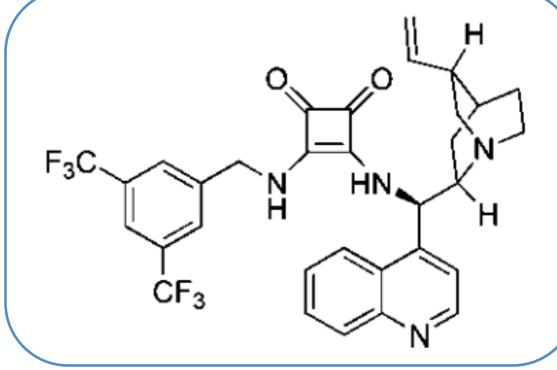
R=Bn 96% ee
R=allyl 96% ee

R=Bn, 94% ee
74% yield

Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc*. **2006,** *128,* 6048-6049

Double H-bond
Bifunctional Squaramide

Rawal, 2008: Michael reaction

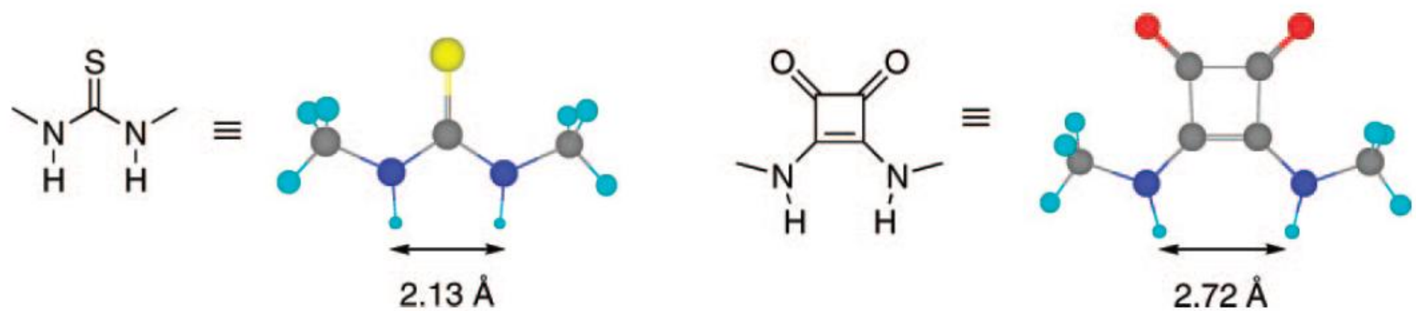


> Scaffold rigidity

> Pseudo-aromatic nature
- polarized nitrogen moiety /N–H acidity enhanced

> Longer hydrogen bond spacing

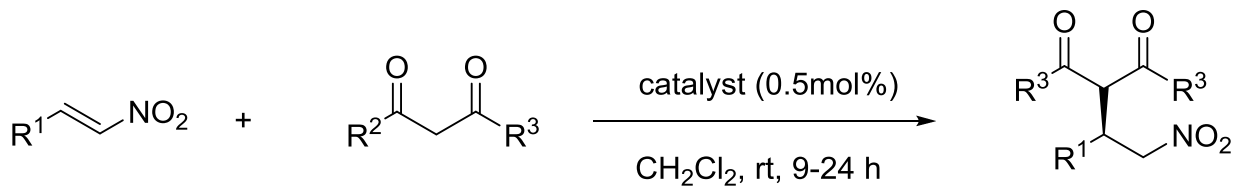
> Inward converging N–H bond vectors

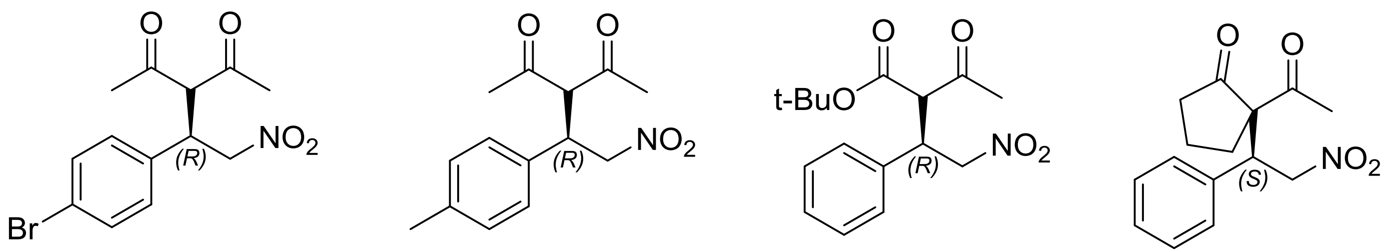


J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc*. **2008**, *130*, 14416–14417

Double H-bond
Bifunctional Squaramide

Rawal, 2008: Michael reaction



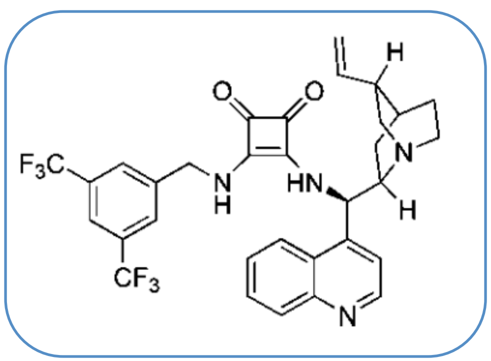


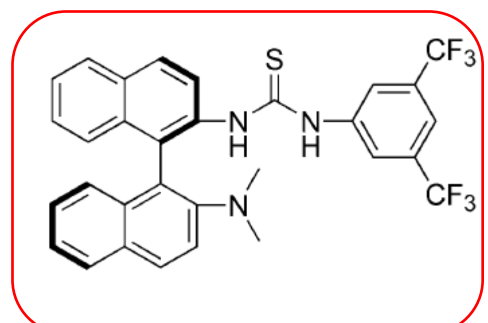
98% yield (89)
98% ee (95)

98% yield (84)
97% ee (93)

95% yield
dr :1.6:1
96% ee

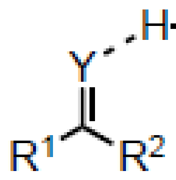
96% yield
dr :18:1
98% ee

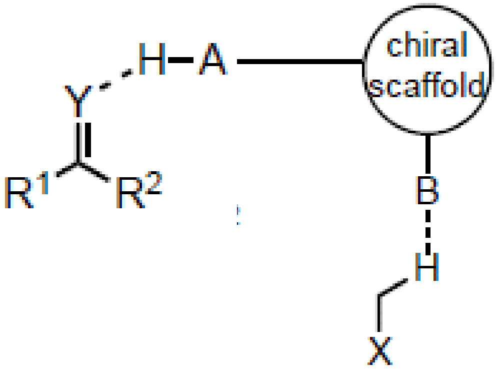




J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc*. **2008**, *130*, 14416–14417
J. Wang , H. Li ,W. Duan , L Zu , W Wang, *Org. Lett*., **2005**, *7*, 4713–4716

Single H-bond catalysts





Single H-bond
Monofunctional diol

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> Challenges with single H-bond :

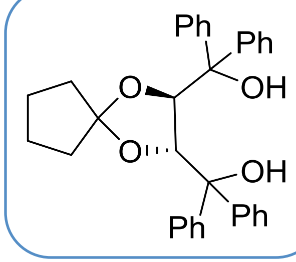
- Less strenght than double H-bond
- Less directionality which reduces the ability to achieve suitably rigid catalyst-substrate complex

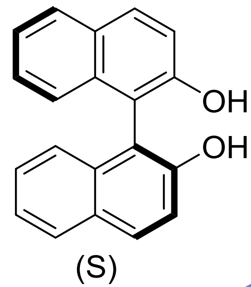
> Goal :

- Good catalytic activity : lowering LUMO level electrophile
- Good enantioselectivity by shielding one face of the electrophile

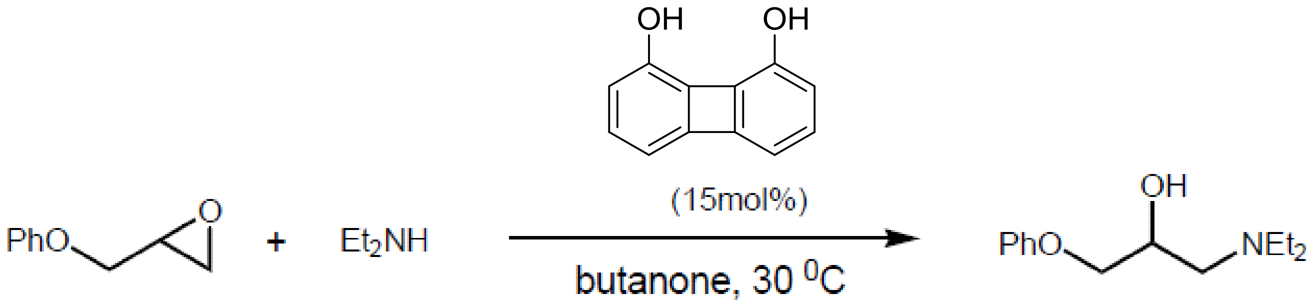
Single H-bond
Monofunctional diol

- TADDOL and BINOL useful ligands for LA mediated processes
- Use in general acid asymetric catalysis recent
- pKa binol ~ 18 / pKa diol ~ 20
- Commercially available (TADDOL 1g, 190 CHF, BINOL, 1g, 43 CHF)



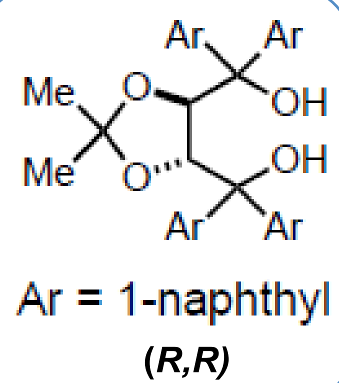


- Previous work done by Hine and co-workers showed that Biphenylenediol can accelerate epoxyde opening probably by double H-bond



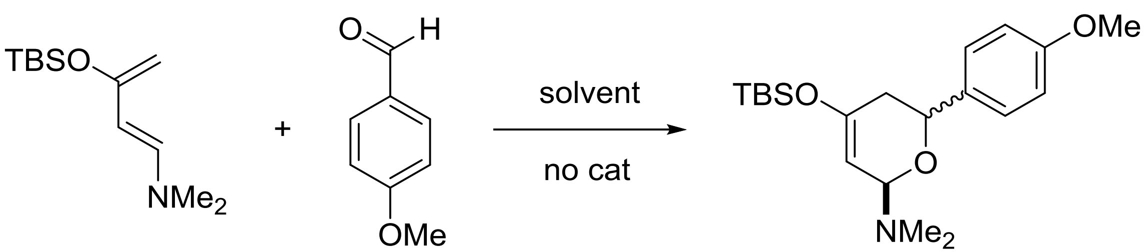
J. Hine, S-M Linden, V. M. Kanagasabapathy , *J. Am. Chem. Soc*, **1985**, *107*, 1082

Single H-bond
Monofunctional diol : TADDOL derivative



Rawal, 2002: Hetero-Diels-Alder reaction (HAD)

> Investigation of solvent effect : acceleration in protic solvents (reaction 630 times faster in isopropyl alcohol than THF)



> Solvent protic with OH not shielded and not implied in solvolys are the best !

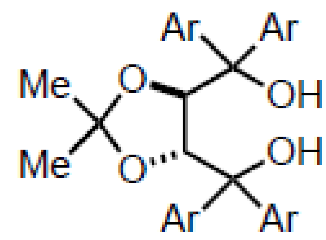
> H-bond between a solvent molecule the aldehyde carbonyl served to lower the carbonyl LUMO

> Extension this new concept to asymmetric catalysis by examination of various chiral alcohols

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

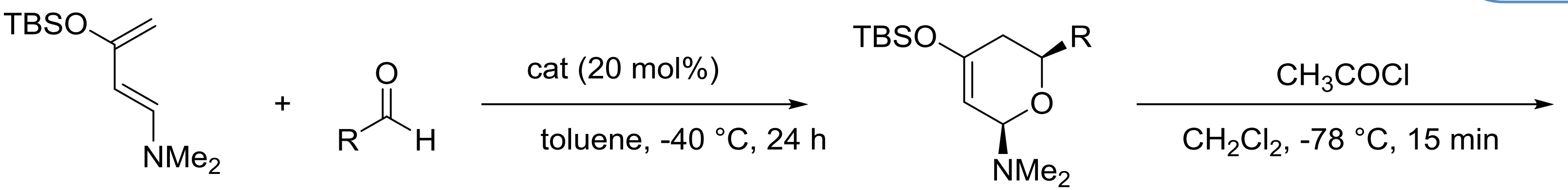
Single H-bond
Monofunctional diol : TADDOL derivative

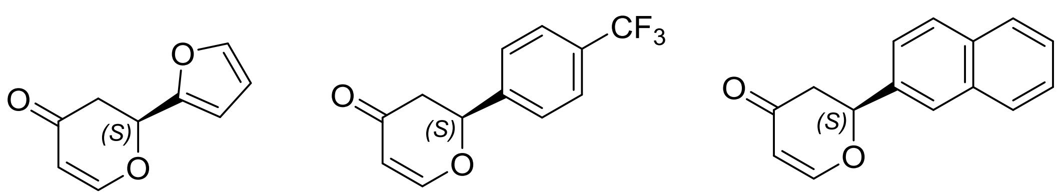
- HAD using chiral catalyst



Ar = 1-naphthyl

(R,R)





77%
96:4 ee

78%
97:3 ee

97%
97:3 ee

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

Single H-bond
Monofunctional diol : TADDOL derivative

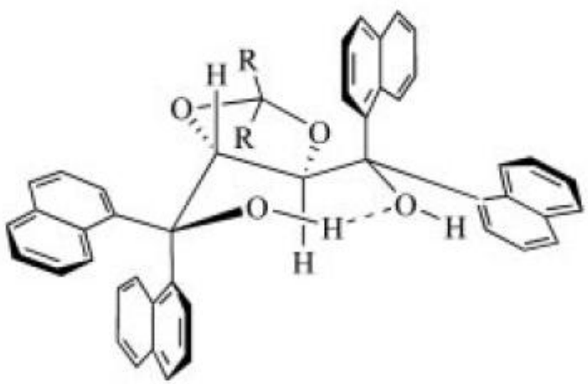
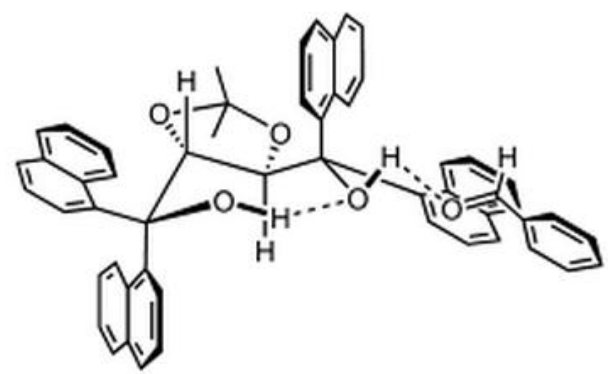
> Evidence for acceleration : without catalyst, no reaction

> Evidence for H-bond : mono-methyl or di-methyl derivativ

> Crystal structure of catalyst

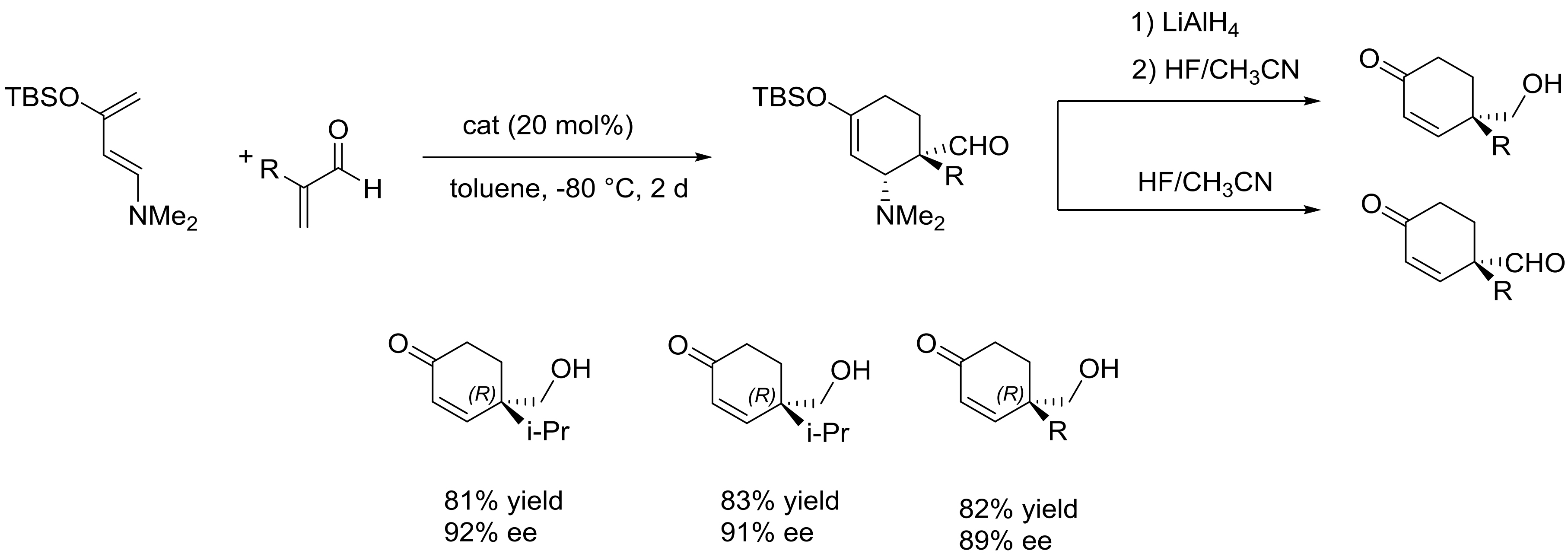
- Intramolecular H-bond between the 2 hydroxyl groups: resulting proton more acidic for intermolecular H-bond and well orientated
- 1-naphtyl group restrict the rotation about C-naphtyl

> Representation of the X - ray structure of a 1 : 1 complex between TADDOL and aldehyde: *Re*-face

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

Single H-bond
Monofunctional diol : TADDOL derivative



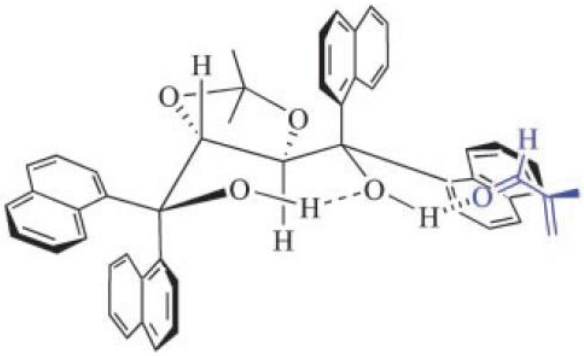
> TADDOL (Ar= Ph, yield=30%, 31% ee)
> Derivativ (Ar=1, naphtyl, yield=83%, 91% ee)

A.N. Thadani,. A.R. Stankovic, V.H. Rawal, *Proc. Natl. Acad. Sci*. **2004**, *101*, 5846-5850

Single H-bond
Monofunctional diol : TADDOL derivative

> Proposed mechanism

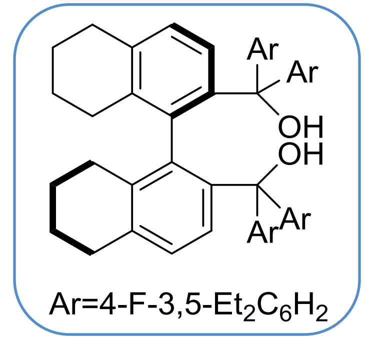
- Free proton forms strong H-bond to the carbonyl (low LUMO level)
- Electron deficient double bond stabilized through π-π
- 1-naphtyl shields one face
- *Si*-face favoured
- At low T, more persisten H-bond, better organisation



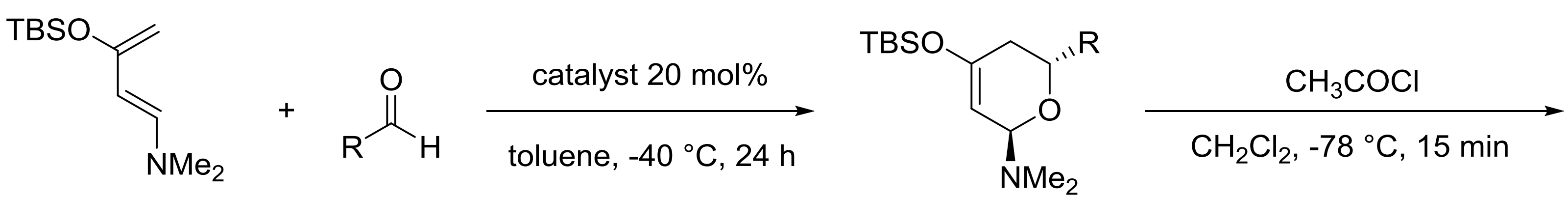
A.N. Thadani,. A.R. Stankovic, V.H. Rawal, *Proc. Natl. Acad. Sci*. **2004**, *101*, 5846-5850

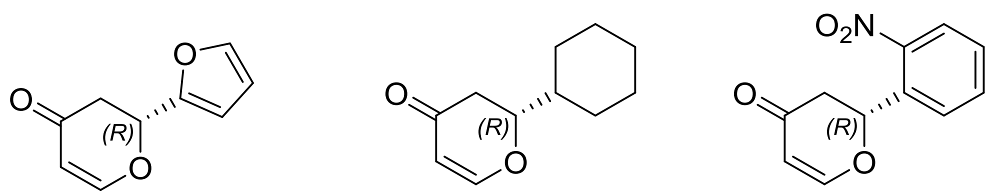
Single H-bond
Monofunctional diol : BAMOL

Rawal and Yamamoto 2005: Hetero-Diels-Alder reaction (HAD)



- Axially chiral BAMOL catalyst proved effective

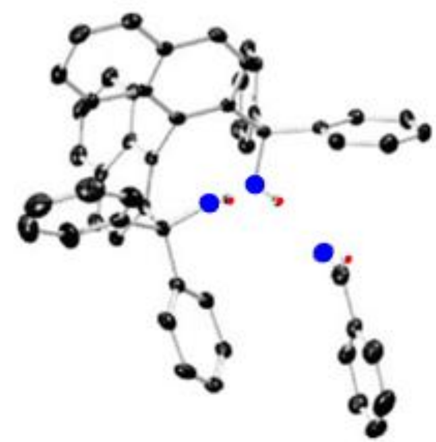




96% yield
99% ee

99% yield
84% ee

93% yield
98% ee

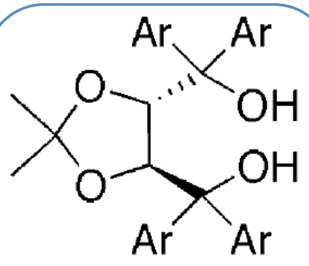


- Evidence of single H-bond donation: X-ray structure catalyst (Ar=Ph)/benzaldehyde.
- Both intra- and inter- molecular H-bonds are observed

A.K. Unni, N. Takenaka, H. Yamamoto, V.H Rawal, *J. Am. Chem. Soc.* **2005**, *127*, 1336-1337.

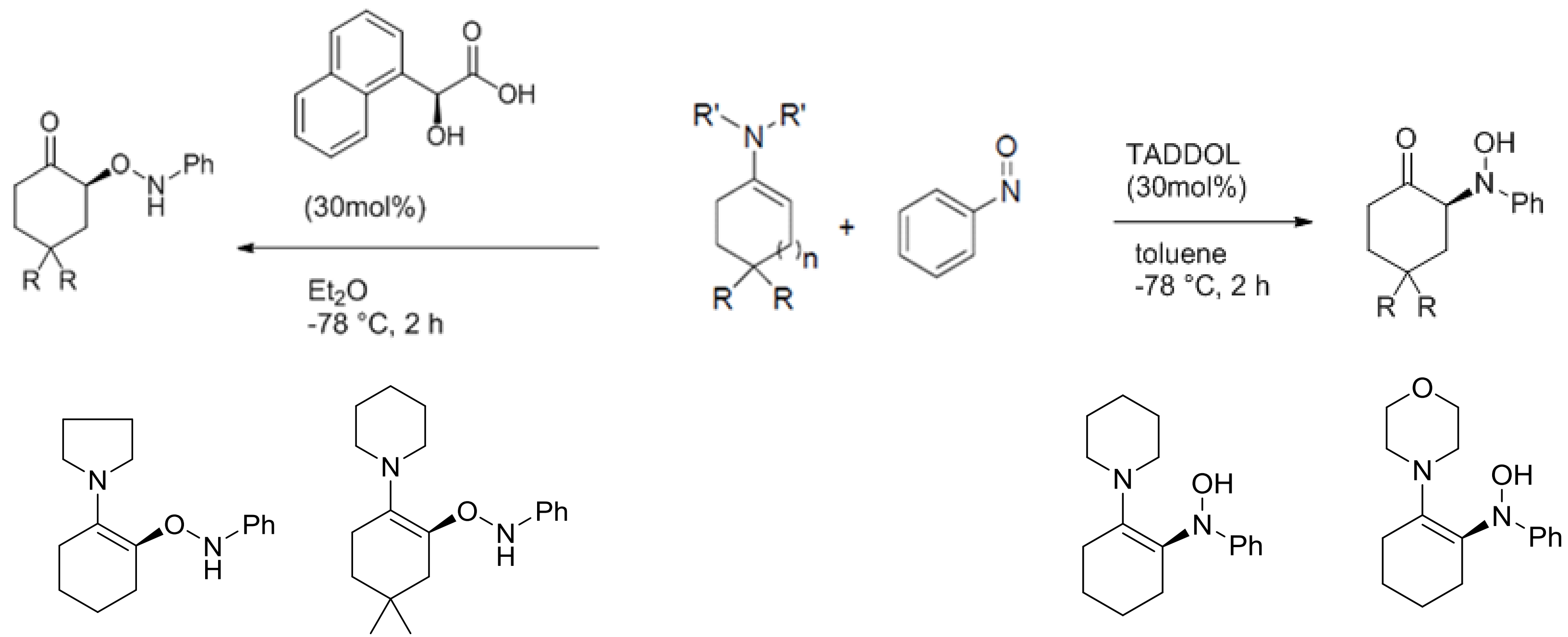
Single H-bond
Monofunctional diol : TADDOL derivative

Yamamoto 2004: Nitroso Aldol Synthesis



Ar=1-napthyl
(S,S)

> *O*-nitroso *versus* *N*-nitroso :*O*-nitroso favored in acetic acid (99:1)
> *N*-nitroso favored in MeOH (99:1)



77% yield
92%ee

91% yield
90%ee

81% yield
83%ee

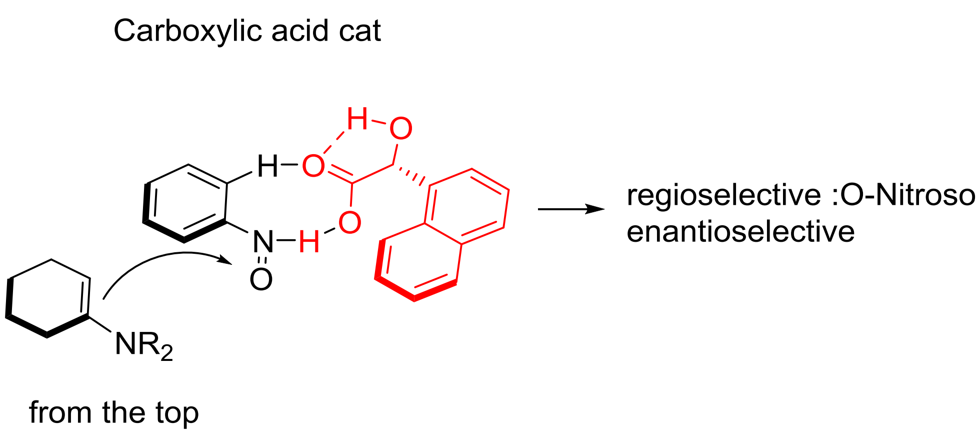
91% yield
79%ee

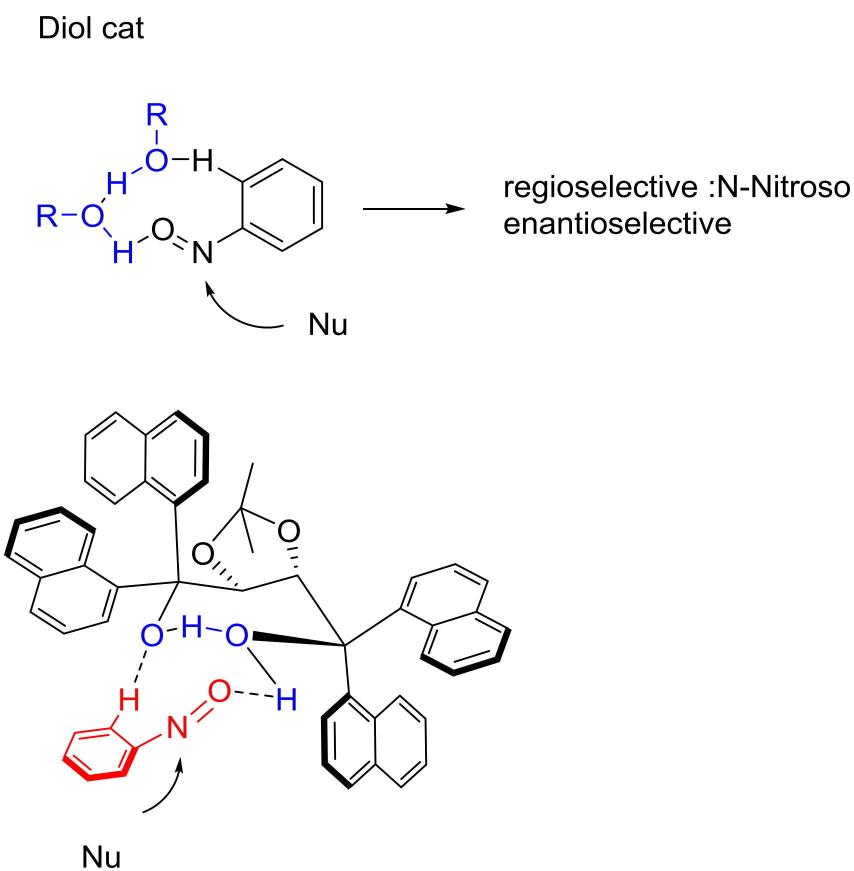
N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2005,** *127,* 1080-1081

Single H-bond
Monofunctional diol : TADDOL derivative

> A single regioisomer can be formed exclusively depending on Brønsted acid and enamine

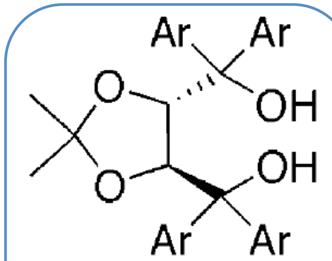
- Pyrrolidine for acidic conditions with (S)-1-naphtyl glycol
- Morpholine for less acidic conditions with TADDOL





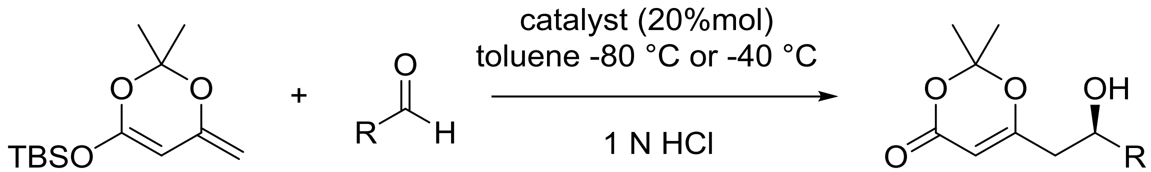
N. Momiyama, H. Yamamoto, J. Am. Chem. Soc. **2005,** *127,* 1080-1081
Yamamoto , H., Kawasaki , M, *Bull. Chem. Soc. Jpn.*. **2007,** *80* , 595 – 607

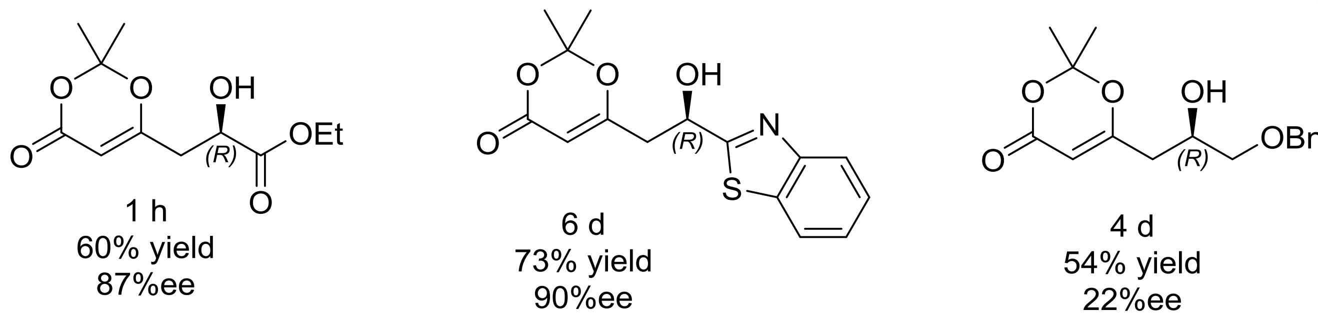
Single H-bond
Monofunctional diol : TADDOL derivative



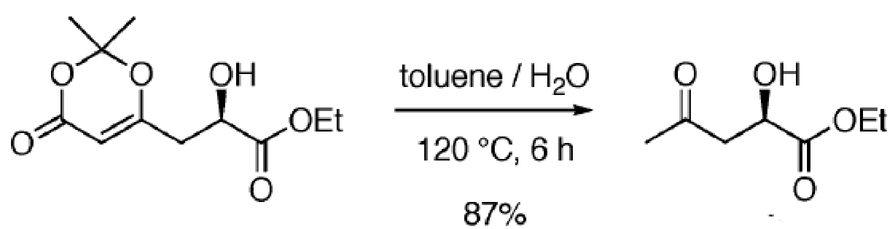
Ar=1-napthyl
(*S*,*S*)

Rawal 2005 : Vinylogous Mukaiyama Aldol reaction





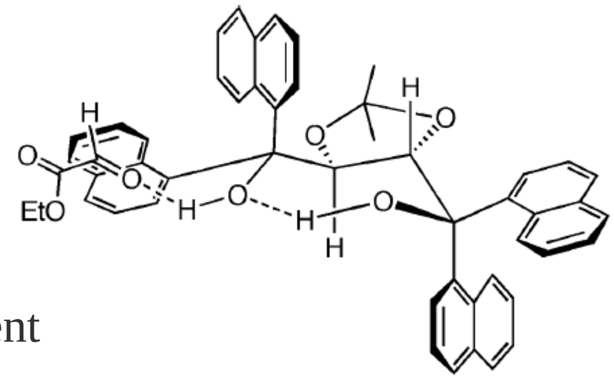
> Only product from attack at the γ position of silyldiene
> Further transformation



V. Bhasker, M. Gravel, V. H. Rawal, *Org. Lett.* **2005**, *7*, 5657-5660

Single H-bond
Monofunctional diol : TADDOL derivative

> Insight into the Mechanism, proposed model



> Internally H-bond arrangement

> Free H atom on the catalyst (expected to be more acidic than a normal OH) can form H-bond with the aldehyde oxygen, and lower its LUMO

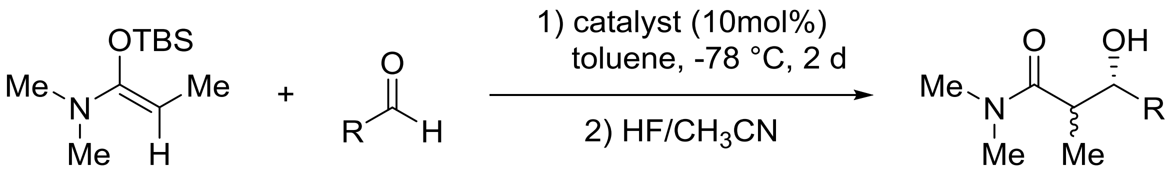
> Stabilization of the H-bonded aldehyde through a postulated π- π

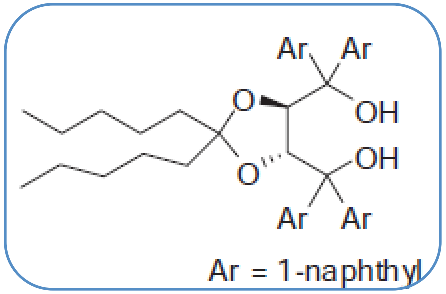
> *Re*-face accessible to attack by the nucleophile

V. Bhasker, M. Gravel, V. H. Rawal, *Org. Lett*. **2005**, *7*, 5657-5660

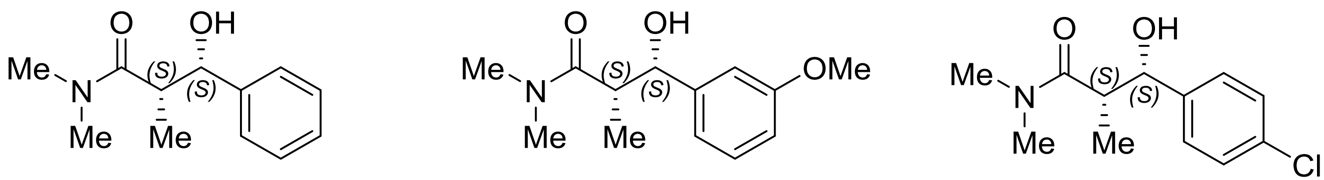
Single H-bond
Monofunctional diol : TADDOL derivative

Rawal 2006 : Mukaiyama Aldol reaction



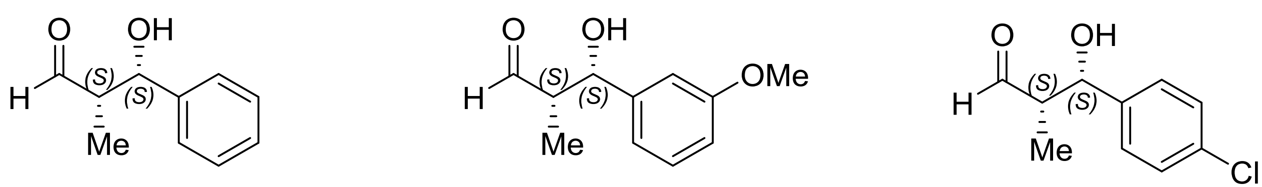


> Enantioselective and Diastereoselective reaction



94% yield	81% yield	86% yield
d.r. : 15:1	d.r. : 13:1	d.r. : 20:1
98%ee	97%ee	97%ee

$[Cp_2Zr(H)Cl]$ Schwartz reagent
CH_2Cl_2, rt, 30 min-]2 h



88% yield | 84% yield | 85% yield

McGilvra, J.D.; Unni, A.K.; Modi, K.; Rawal, V.H. *Angew. Int Chem. Ed.* **2006,** *45,* 6130-6133

Single H-bond
Monofunctional diol : TADDOL derivative

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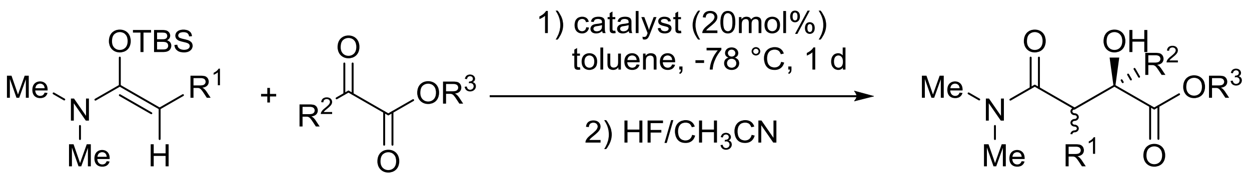
Rawal 2009 : Mukaiyama Aldol reaction

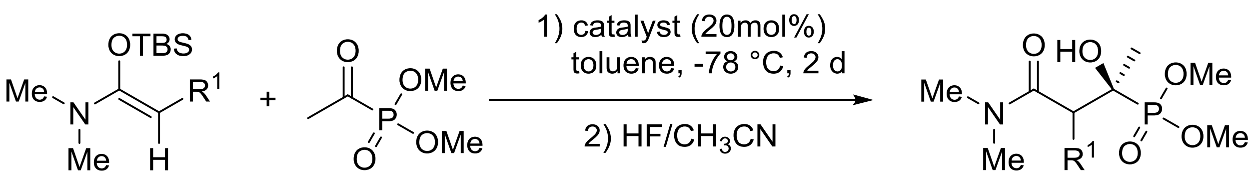
> Aldol reaction of α-ketoester



R^1=alk, O-alk, O-ar, hal
R^2= Me, Ph
R^3=Me, tBu

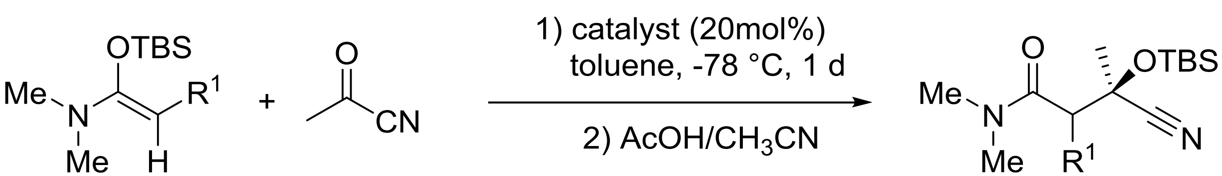
yield 51-85%
dr 15:1-99:1
ee 78-97%

> Aldol reaction with acetyl phosphonate



R^1=alk, O-alk, O-ar, hal..
yield 51-82%
dr 97:3-99:1
ee 89-99%

> Aldol reaction with acyl cyanide

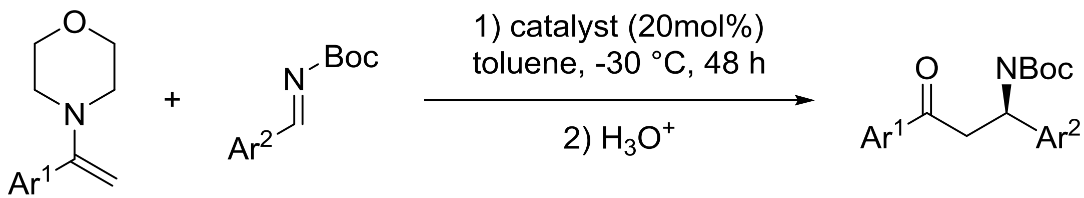


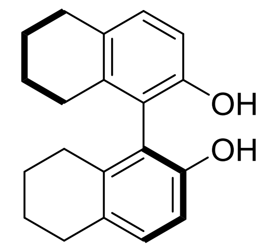
R^1=Me, 78% yield, dr 1:1, 75%ee
R^1=OPh, 85% yield, dr 2:1, 70%ee

V. Bhasker Gondi, K. Hagihara, Rawal, V.H. *Chem. Commun.*, **2010**, *46*, 904–906
V. Bhasker Gondi, K. Hagihara, Rawal, V.H *Angew. Chem. Int. Ed*. **2009**, *48*, 776 –779

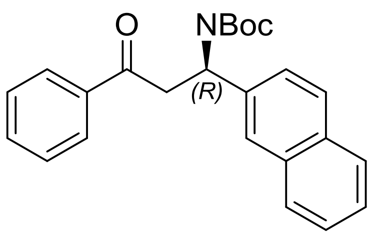
Single H-bond
Monofunctional diol : BINOL derivative

Dixon, 2006 : Enamine Mannich Reaction

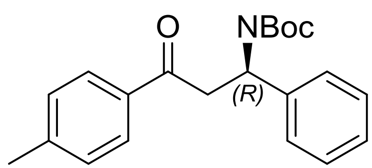




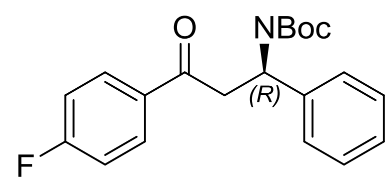
(S)



64% yield
84% ee



98% yield
68% ee



92% yield
80% ee

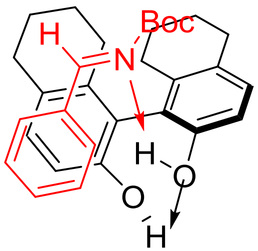
- Extra H- bond, bulky group or EWG at 3,3’ position decrease catalytic activity and ee
- Aprotic apolar solvent and low temperature are optimal conditions
- Mono-methylated: decreased yield and ee : 2 OH involved

→ Double or Single H bond?!

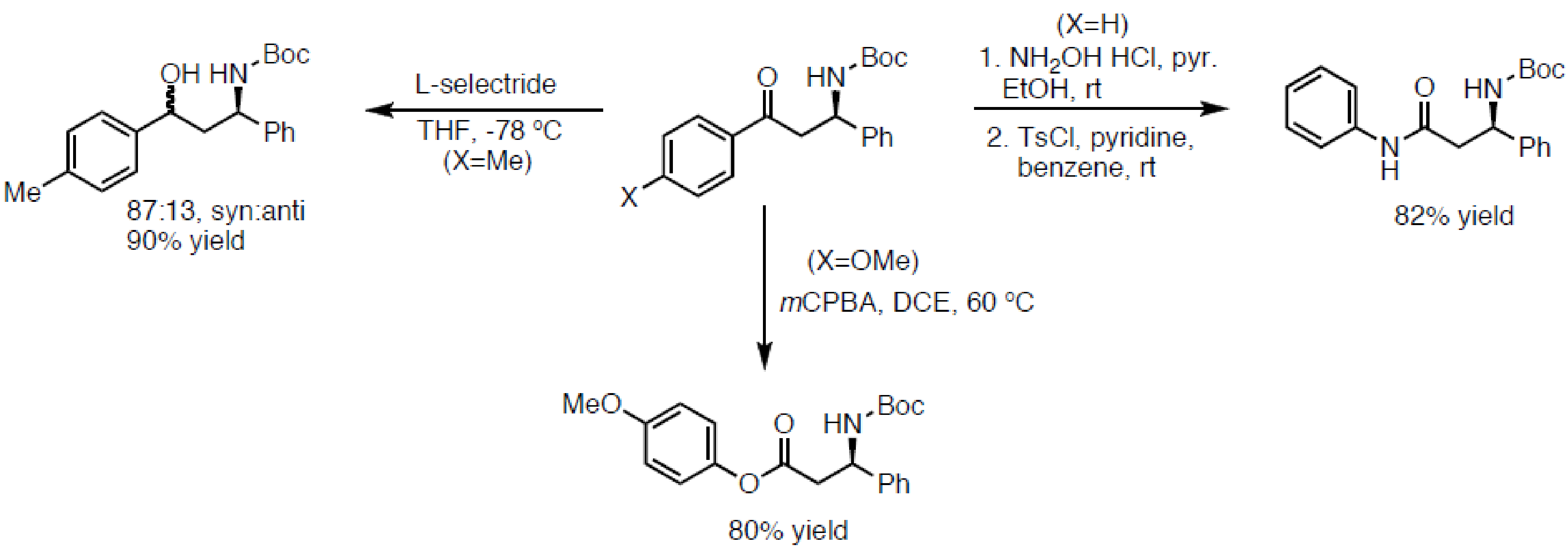
Tillman, A.L.; Dixon, D. *Org. Biomol. Chem.* ***2007***, *5*, 606-609

Single H-bond
Monofunctional diol : BINOL derivative

> Model proposed (by me!) with nucelophilic attack on *Re* face



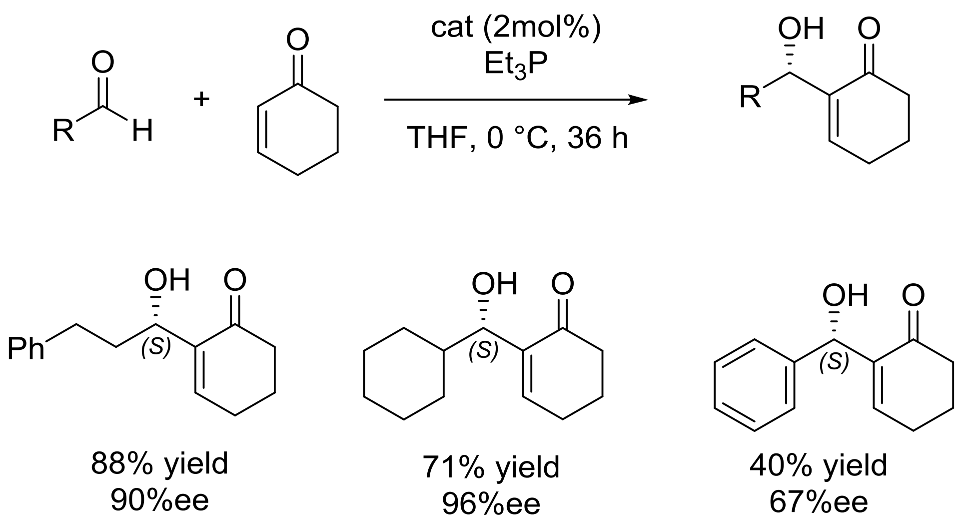
> Conversion into a number of diverse structural motifs without racemization

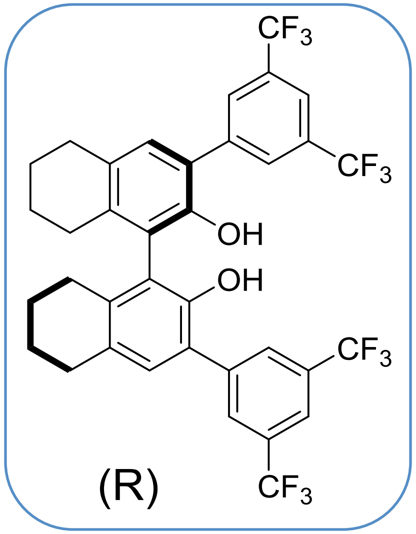


Tillman, A.L.; Dixon, D. *Org. Biomol. Chem.* ***2007***, *5*, 606-609.

Single H-bond
Monofunctional diol : BINOL derivative

Schaus 2003:Morita-Baylis-Hillman





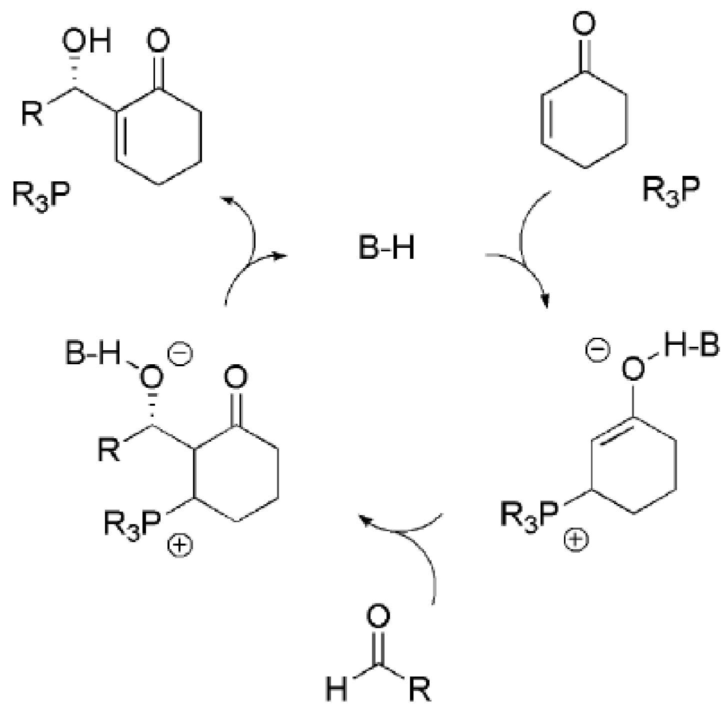
> Optimisation of catalyst show that structural features are needed :

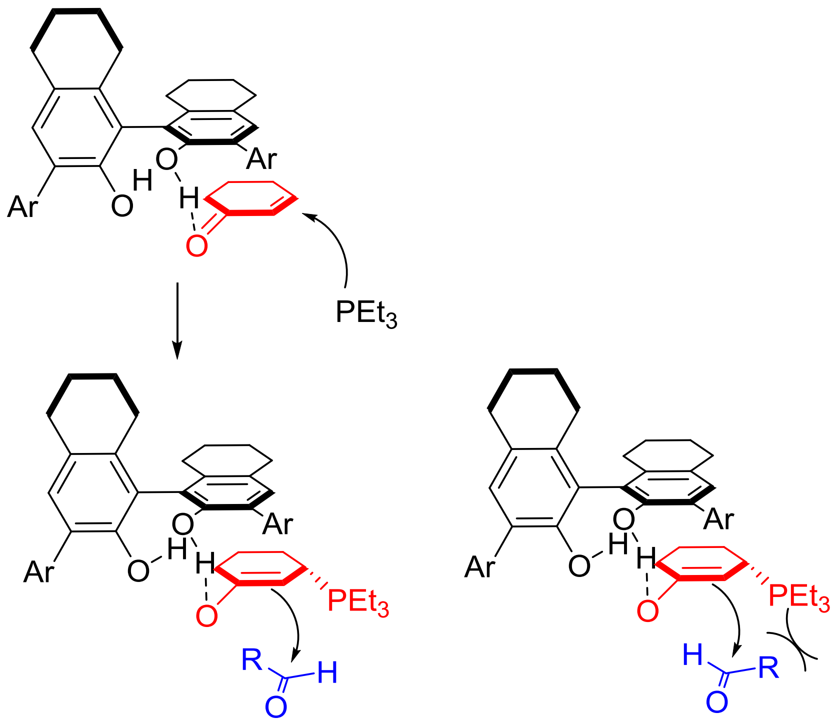
- Saturation of BINOL
- Substitution at the 3,3' positions with bulky groups
- Restricted rotation about the biaryl bound of the 3-substituent
- The 2 OH groups are needed and involved in intramolecular and intermolecular bond

N. T. McDougal, S. E. Schaus, *J. Am. Chem. Soc*. **2003**, *125*, 12094 – 12095

Single H-bond
Monofunctional diol : BINOL derivative

- The phosphonium enolate of cyclohexenone is stabilized via a H-bond with the binaphthol derived Brønsted acid, creating a chiral nucleophile

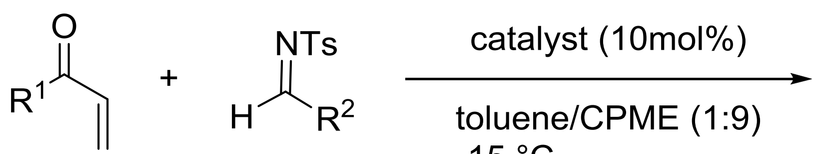


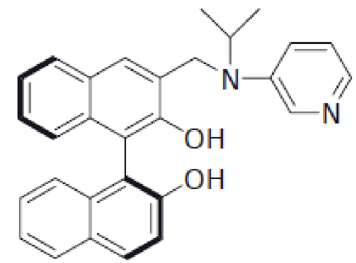


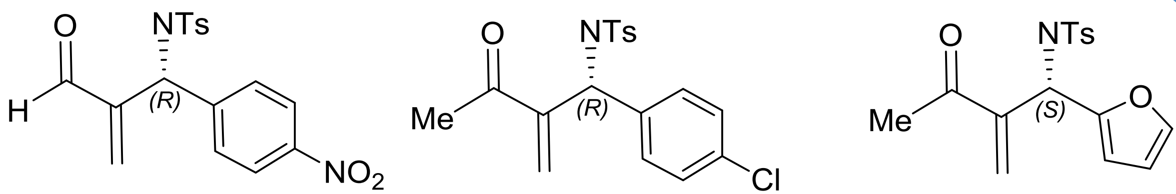
N. T. McDougal, S. E. Schaus, *J. Am. Chem. Soc.* **2003**, *125*, 12094 – 12095

Single H-bond
Bifunctional diol : BINOL derivative

Sasai, 2005:Morita-Baylis-Hillman

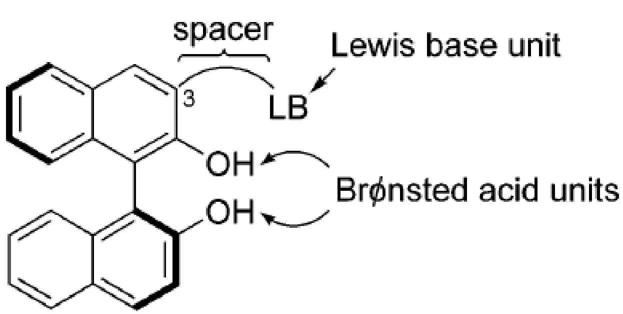






1.5 d	2.5 d	2 d
95% yield	96% yield	quant
94%ee	95%ee	88%ee

> New concept : chiral Brønsted acid unit connected with LB via a spacer

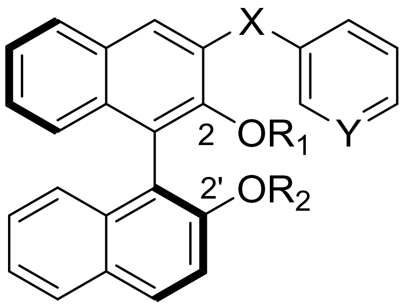


Matsui, K. Takizawa, S. Sasai, H. *J. Am. Chem. Soc*. **2005**, *127*, 3680-3681

Single H-bond
Bifunctional diol : BINOL derivative

- Importance of the phenolic hydroxy group at position 2 and 2'
  - R_1 = Me, R_2= H slightly decrease activity (yield 93% to 85%, ee 87% to 79%)
  - R_1 = H, R_2= H considerably decrease activity (yield 93% to 5%, ee 87% to 24%)

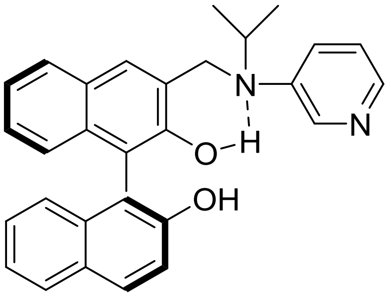
→ only one H-bond implied



- Importance of Nitrogen at Y : without, no reaction occur

- Importance of the chain size and Nitrogen at X to position LB

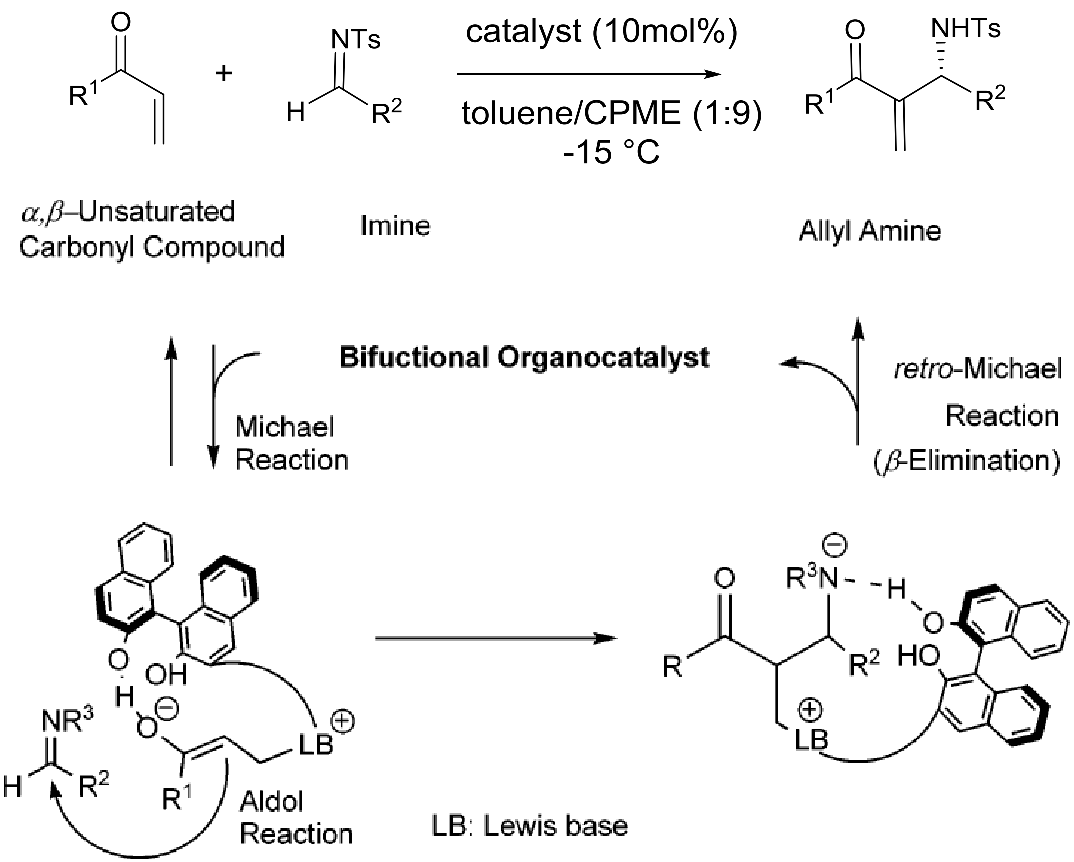
- Two pairs of acid base :
  - One to fixes the conformation
  - One to activate the substrate

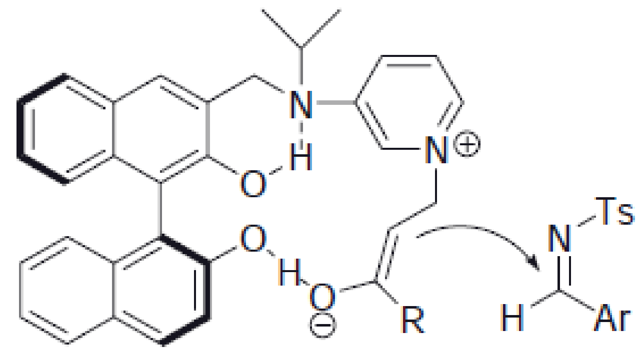


Matsui, K. Takizawa, S. Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680-3681.

Single H-bond
Bifunctional diol : BINOL derivative

> Insight into mechanism

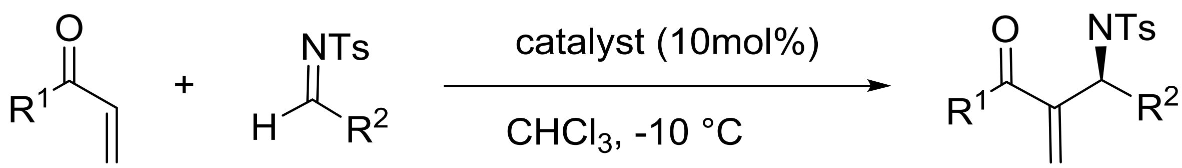


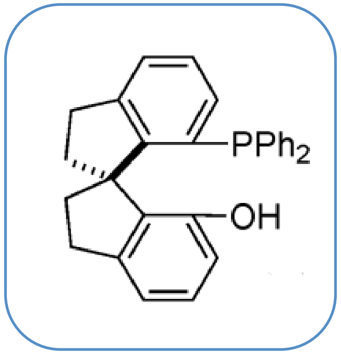


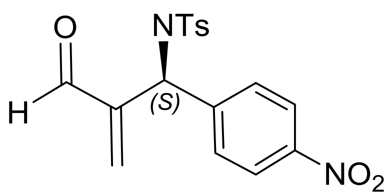
attack from the bottom to the *Si*-face

Single H-bond
Bifunctional diol : BINOL derivative

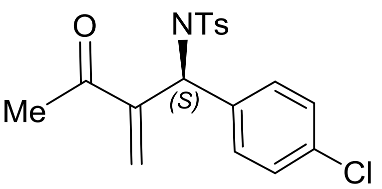
Sasai, 2011: Baylis Hillman



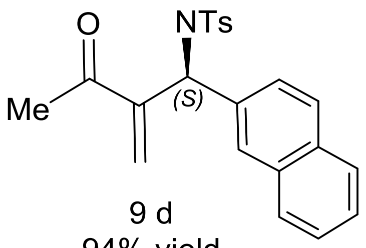




5 d
97% yield
96%ee



4 d
86% yield
94%ee



9 d
94% yield
85%ee

> Spiro catalyst: geometry distinct and more rigid than BINOL

S. Takizawa, K. Kiriyama, K. Ieki, H. Sasai. *Chem. Commun.*, **2011**, *47*, 9227–9229

Conclusion

Conclusion

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> Bad points

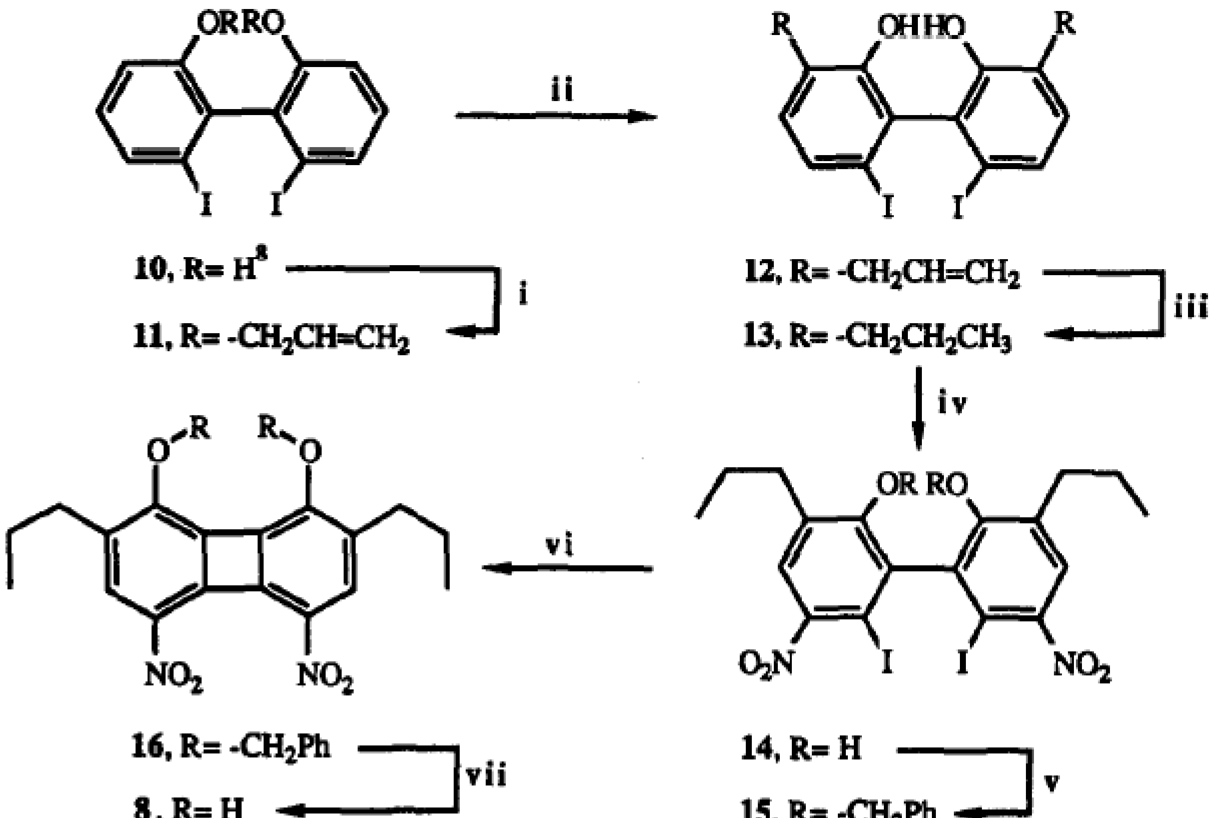
- Time of reaction (from 15 min to 9 days)
- Limited scope of subsrate
- High loading of catalysts
- Mechanisms not always clear

> Good points

- Inexpensive catalyst
- Reusable after column with still same ee
- Catalyst tunable
- Really high yield and ee can be obtained
- Wide scope of reactions
- Development of bifunctionnal catalyst gave improvments
- Improvements are on going

Thank you!

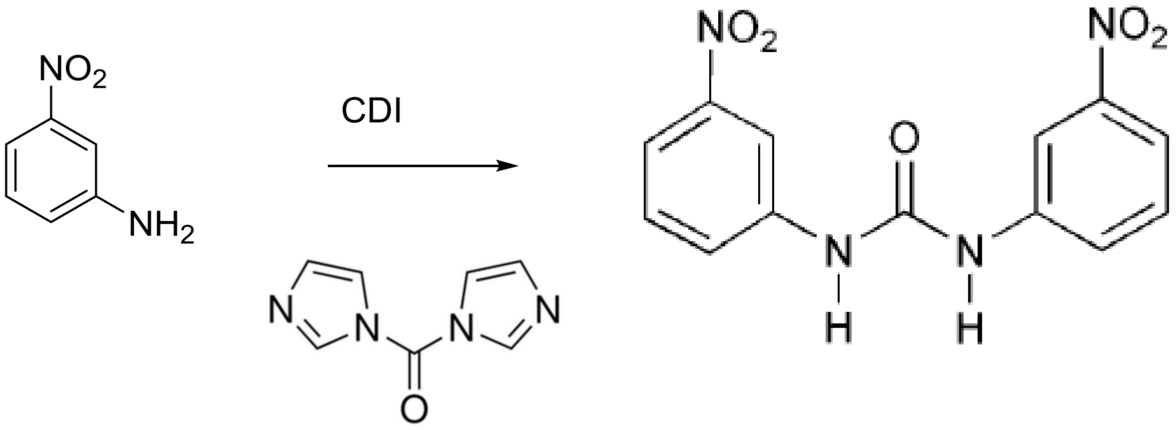
Synthesis thiourea catalyst Kelly



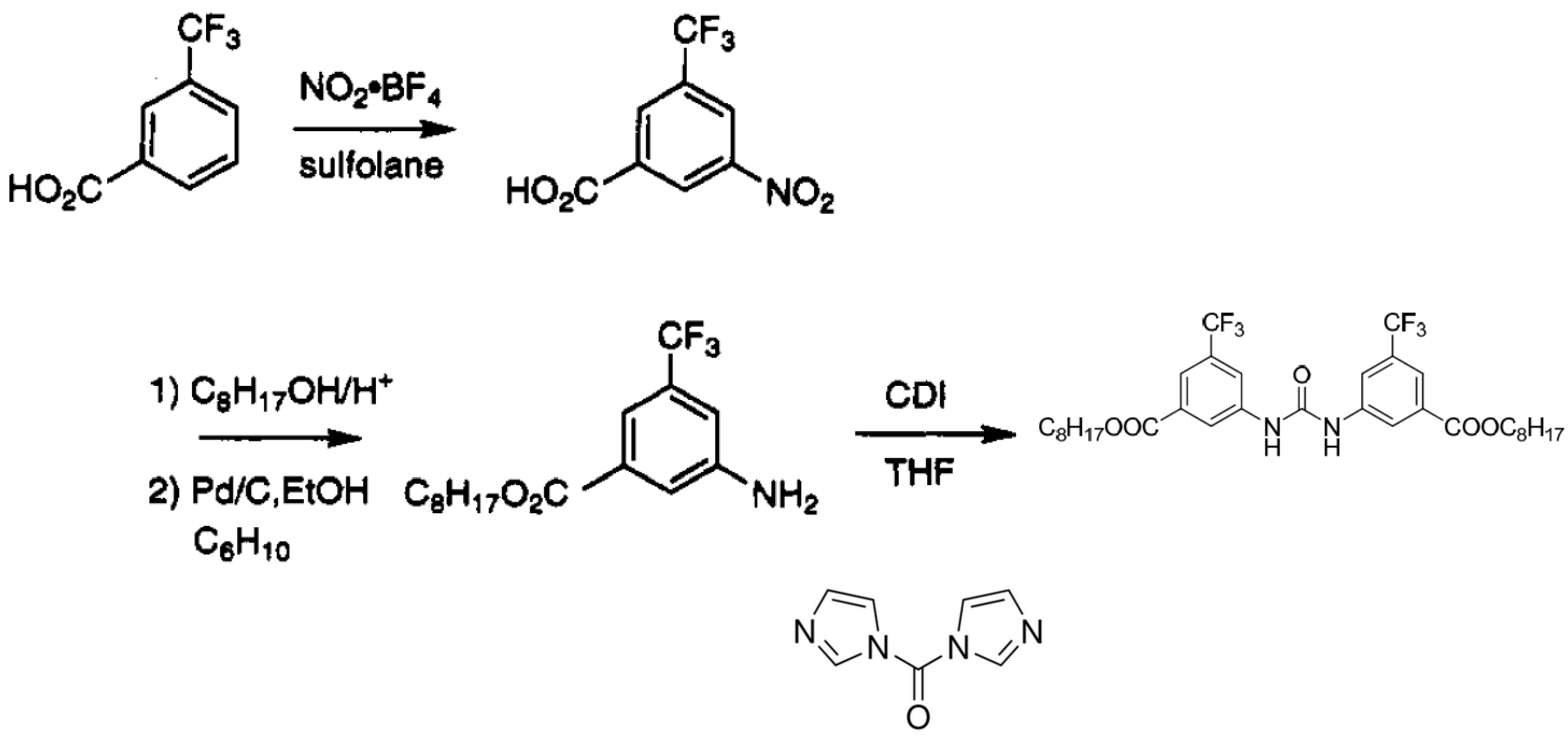
SCHEME:[11] Reagents: (i) CH_2=CH_2CH_2Br, K_2CO_3, acetone, Δ, 2 h; (ii) Double Claisen rearrangement: *N*, *N*-dimethylaniline, 200°C, 23 h; (iii) H_2 (~ 1 atm.), PtO_2, EtOH, 5 min; (iv) NO_2BF_4, AcOH, 2.5 h; (v) $PhCH_2Br$, K_2CO_3, DME-DMF (1:0.3); (vi) Cu-bronze, DMF, Δ, 4 h; (vii) BBr_3, C_6H_6, 3.5 h.

T. R. Kelly, P. Meghani and V. S. Ekkundi, *Tetrahedron Lett.*, **1990**, *31*, 3381–3384

Etter urea

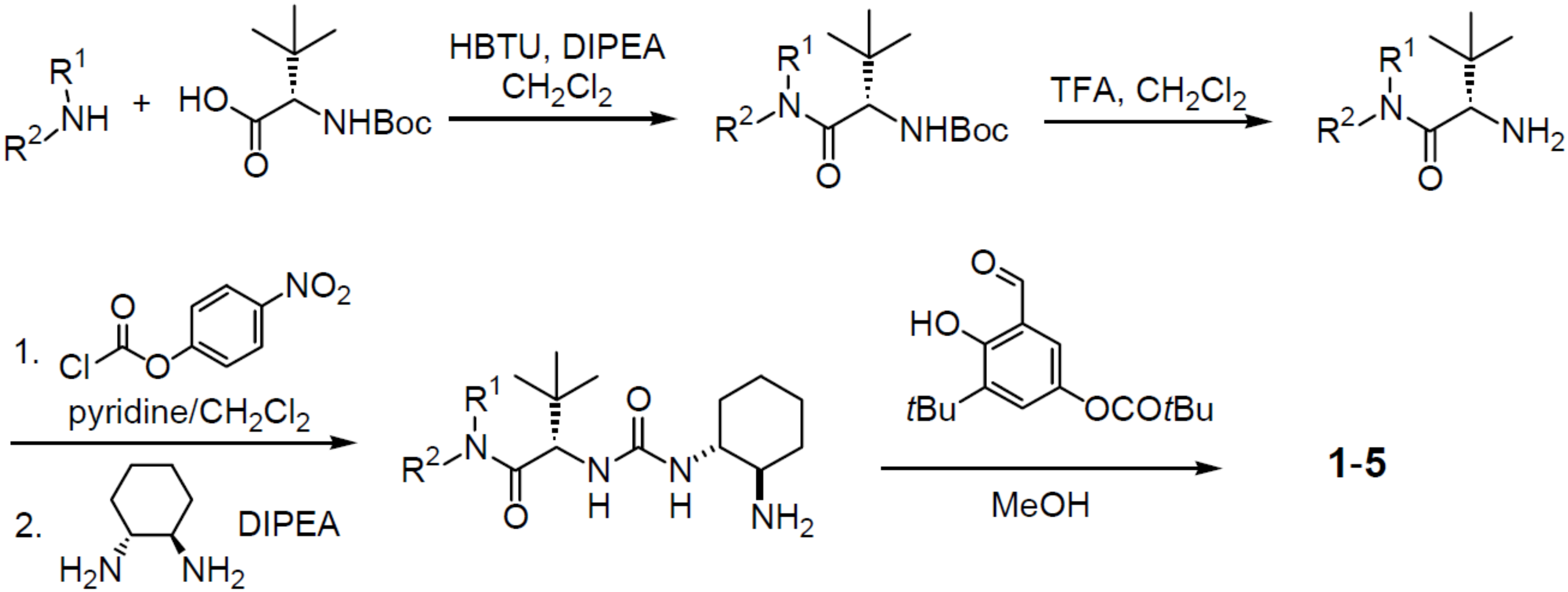


Synthesis thiourea catalyst Curran

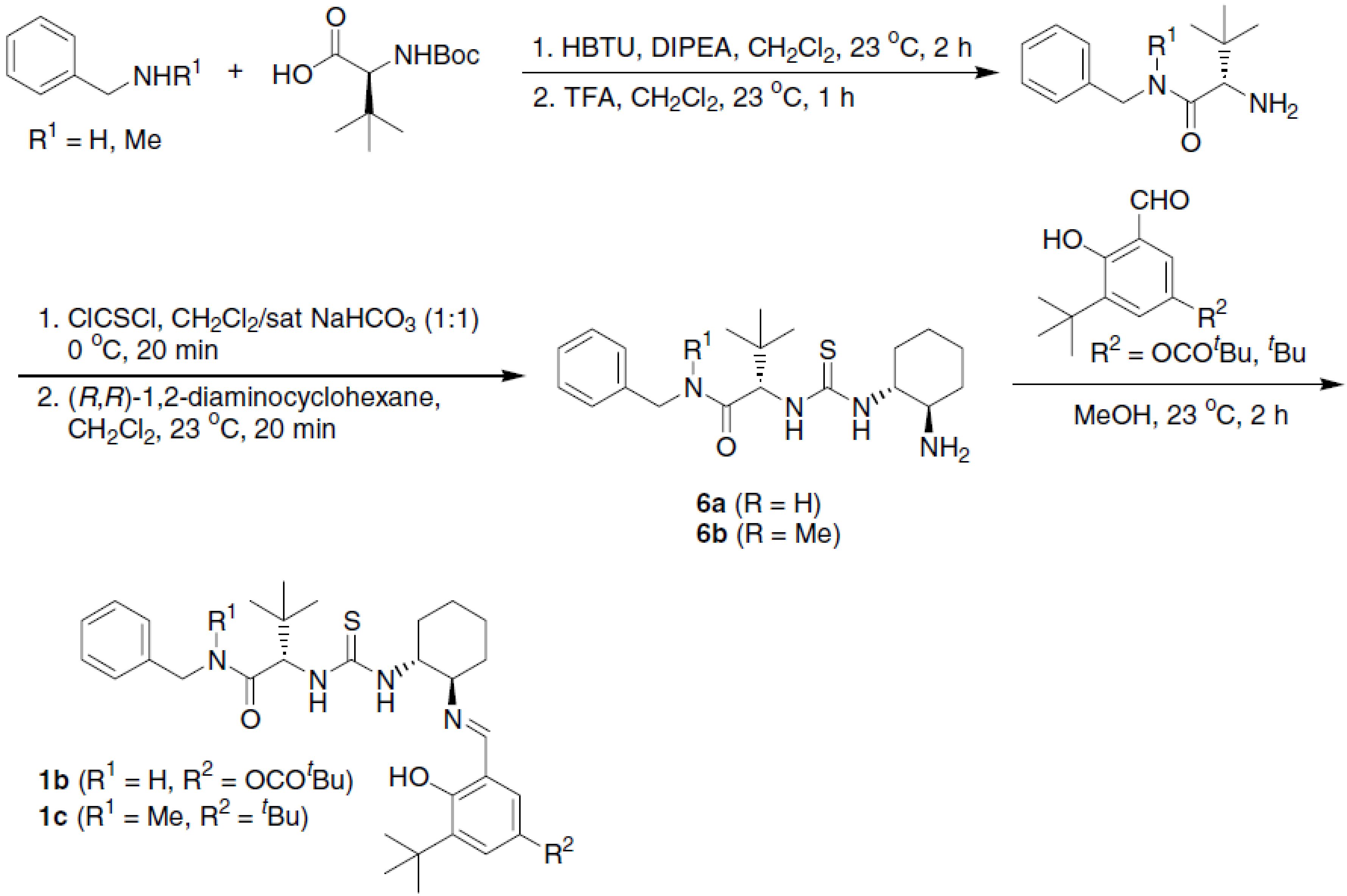


D. P. Curran, L. H. Kuo, *J. Org. Chem*. **1994**, *59*, 3259.

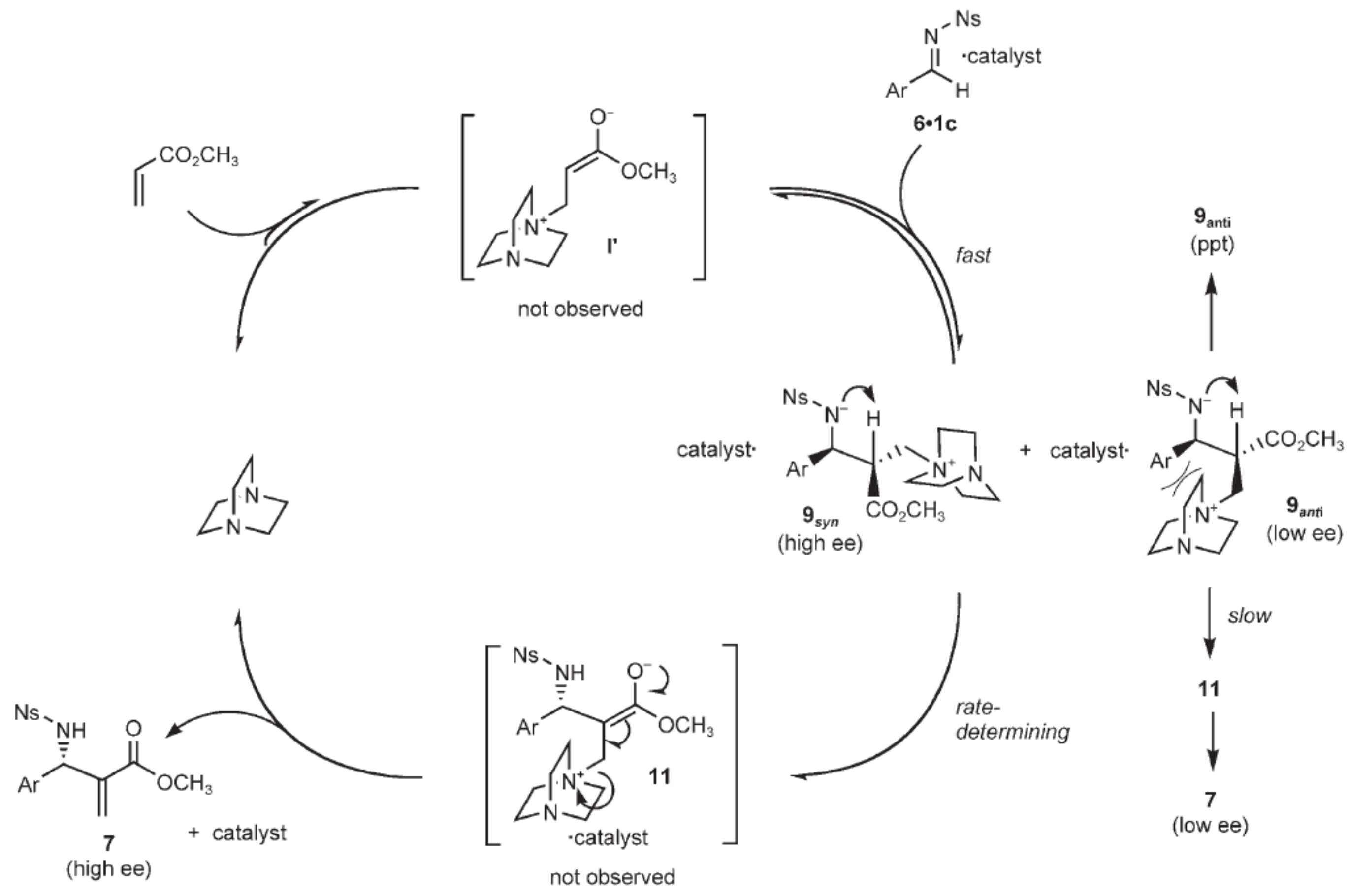
Synthesis Thiourea Jacobsen



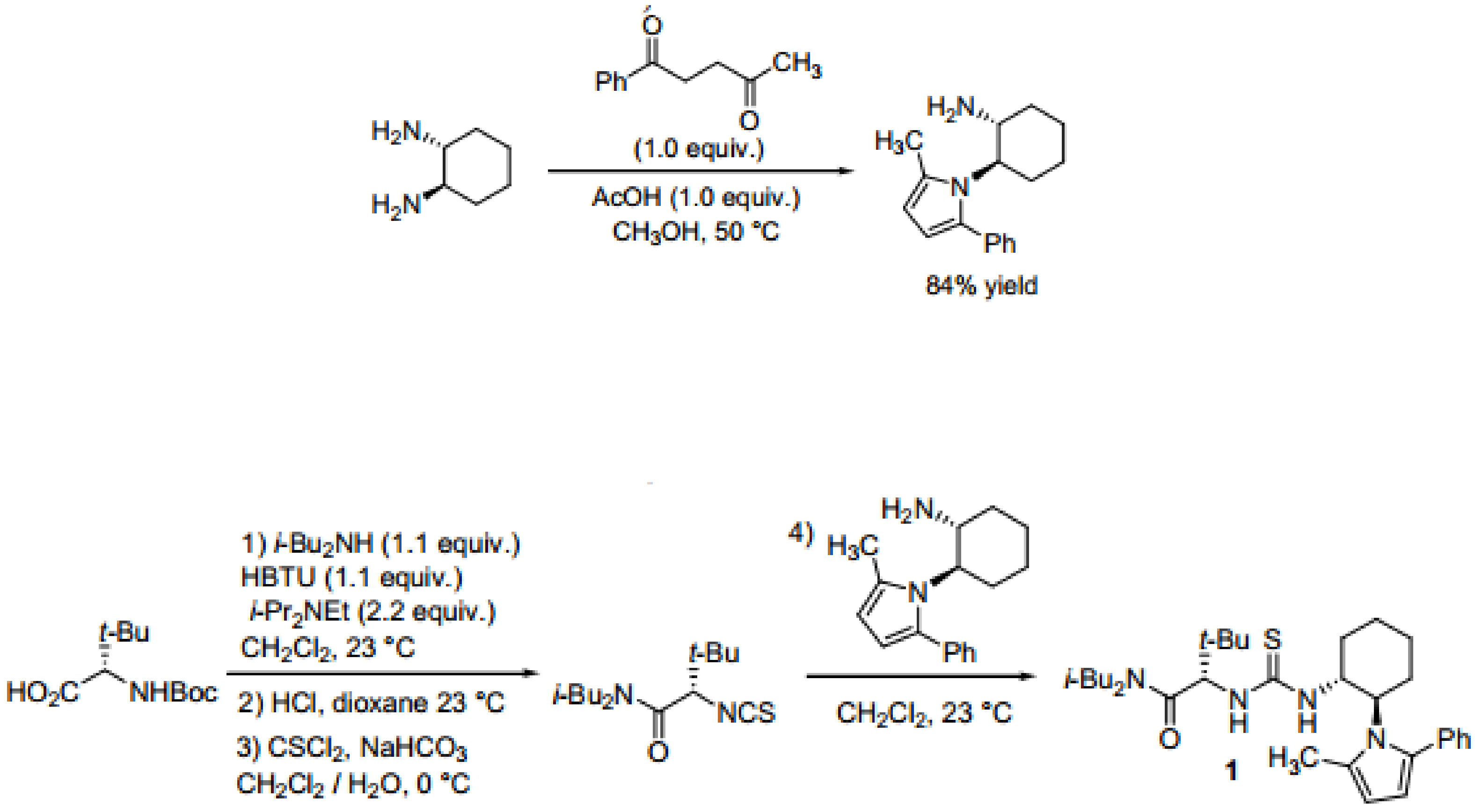
Synthesis Thiourea Jacobsen



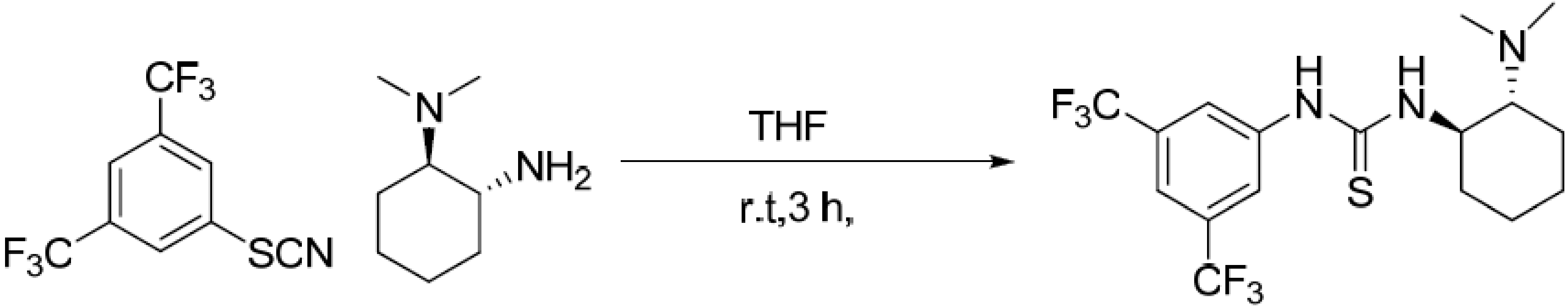
Meca ABH Jacobsen



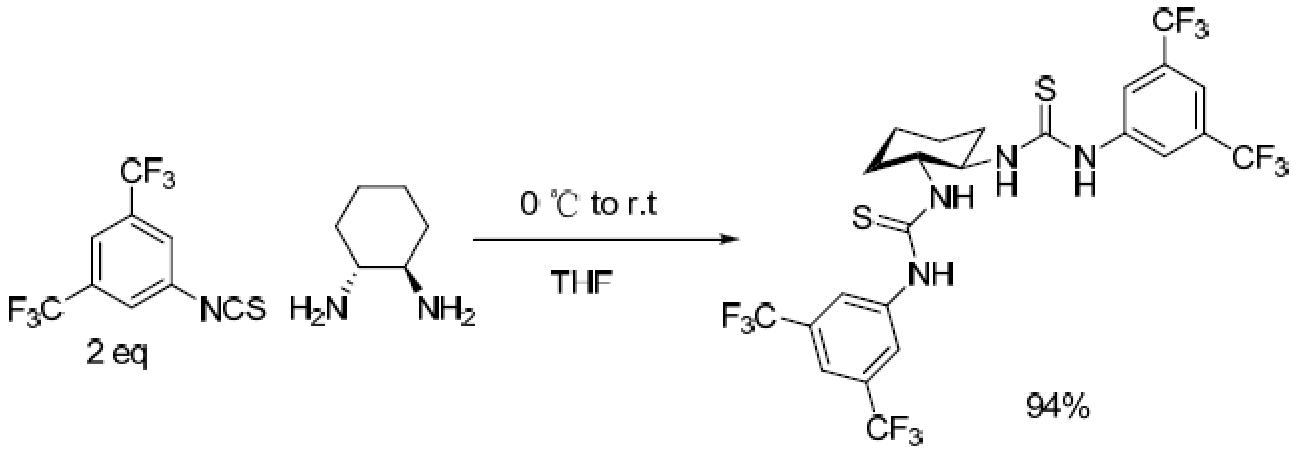
Thiourea pictet-spingler



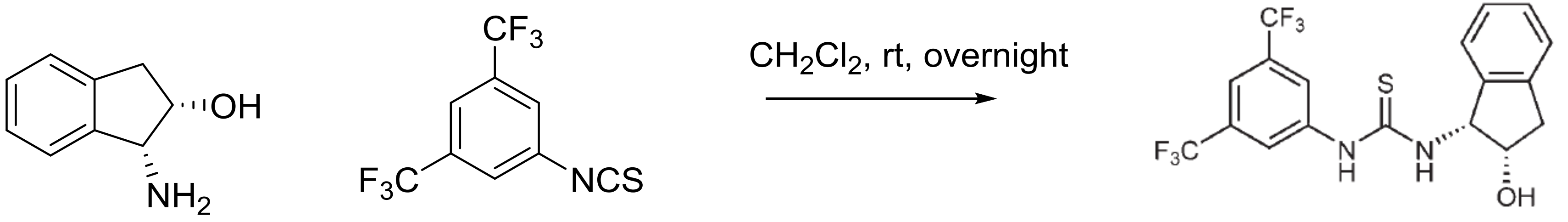
Catalyst Takemoto



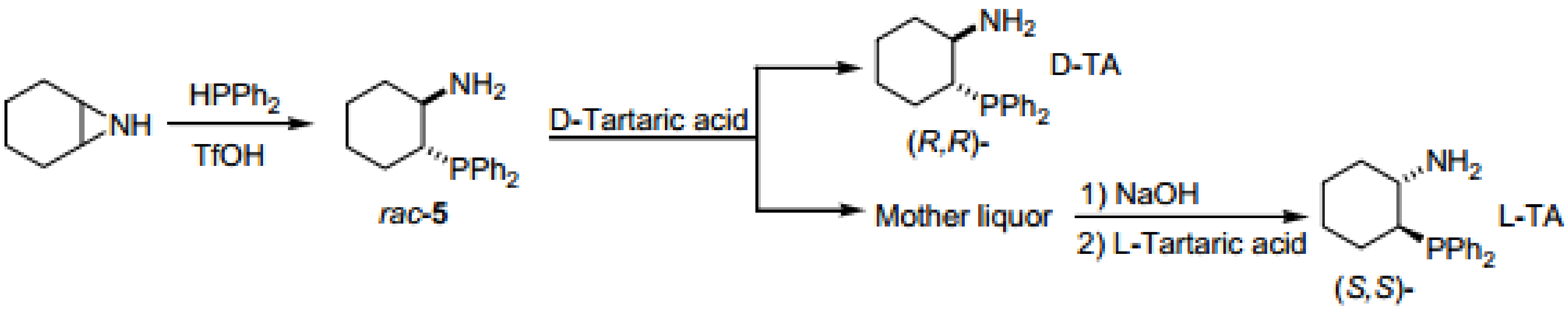
Synthesis bifunctional thiourea nagasawa



Thiourea Ricci



Jacobsen aziridine



Cinchona derivativ Hiemstra

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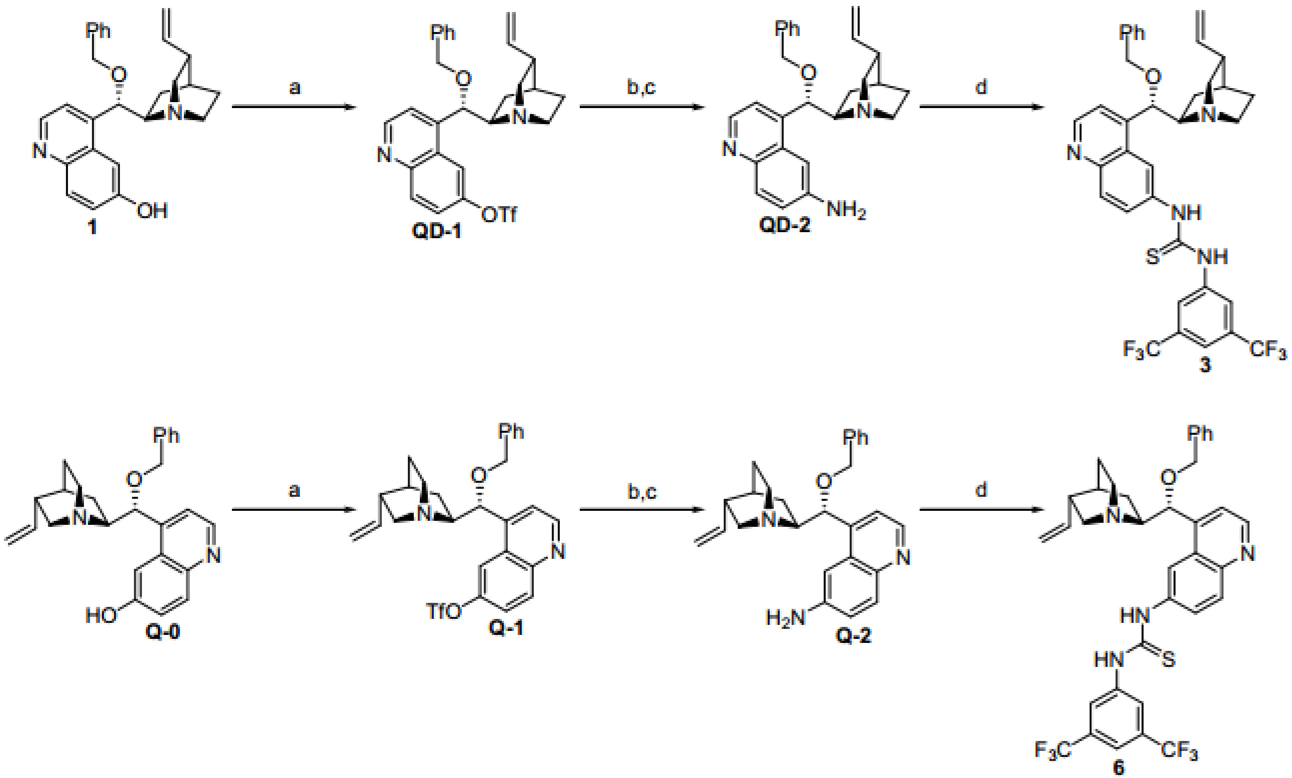
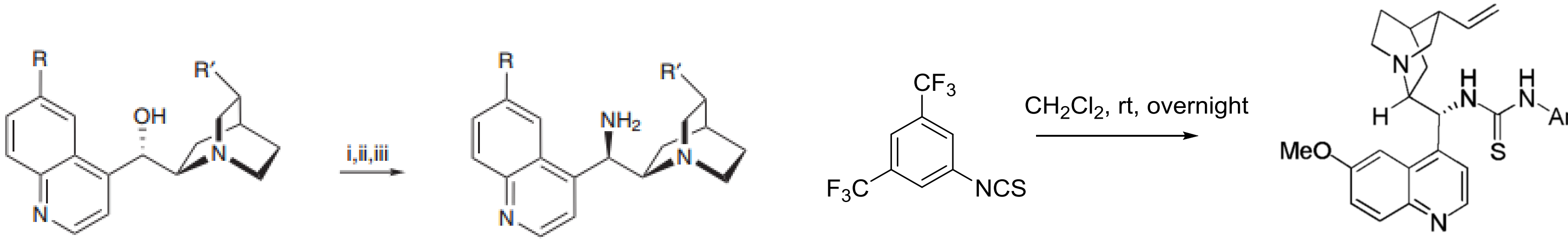


Conditions: a) $PhNTf_2$, DMAP, DCM; b) $Pd(OAc)_2$, BINAP, Cs_2CO_3, THF, $Ph_2C{=}NH$; c) citric acid, THF, H_2O; d) $3,5\text{-}(CF_3)_2PhNCS$, THF.

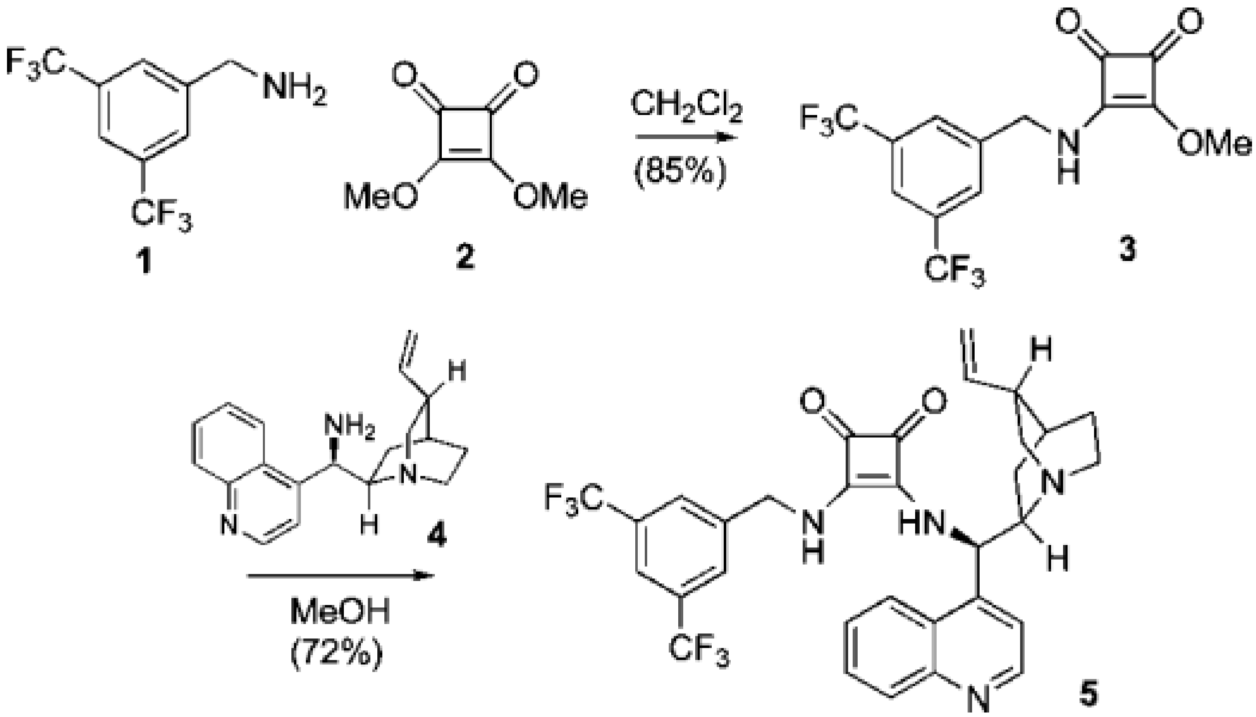
Cinchona derivativ Deng



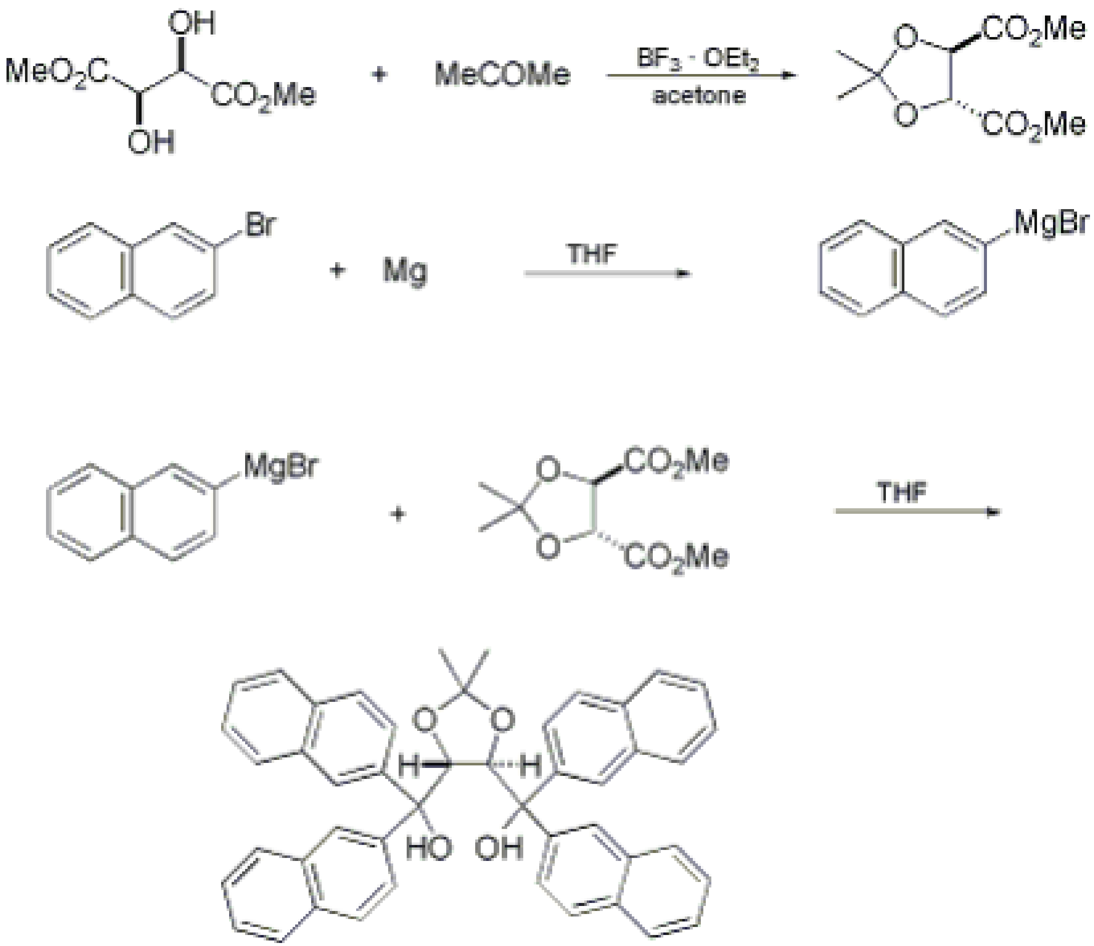
Ar= 3,5-*bis*CF_3Ph

(i) PPh_3, DIAD, DPPA, THF, 0–45 °C; (ii) PPh_3, 45 °C; (iii) H_2O, 45 °C; then HCl_{aq} then NH_4OH;

Rawal squaramides

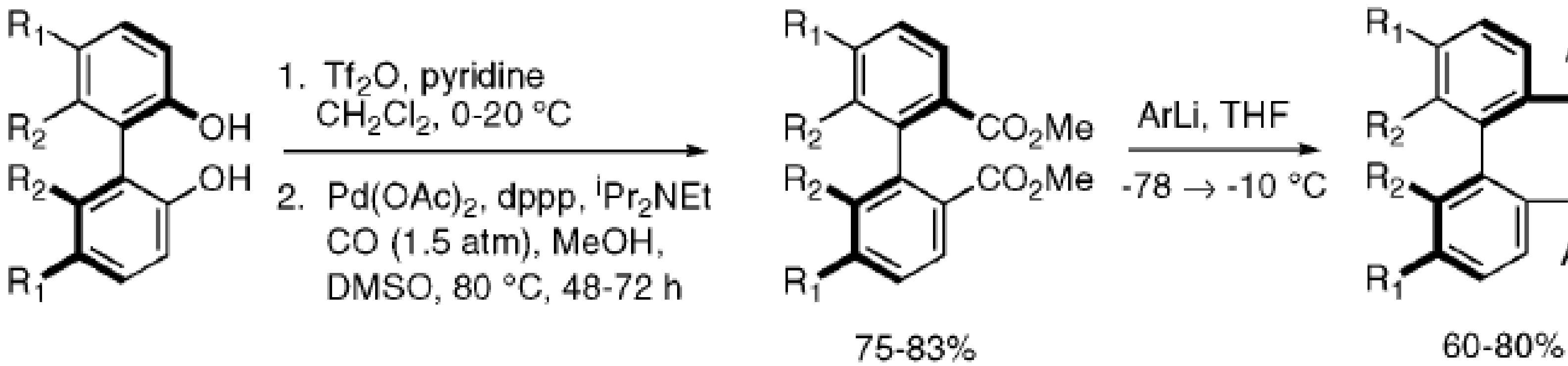


Synthesis Taddol derivativ

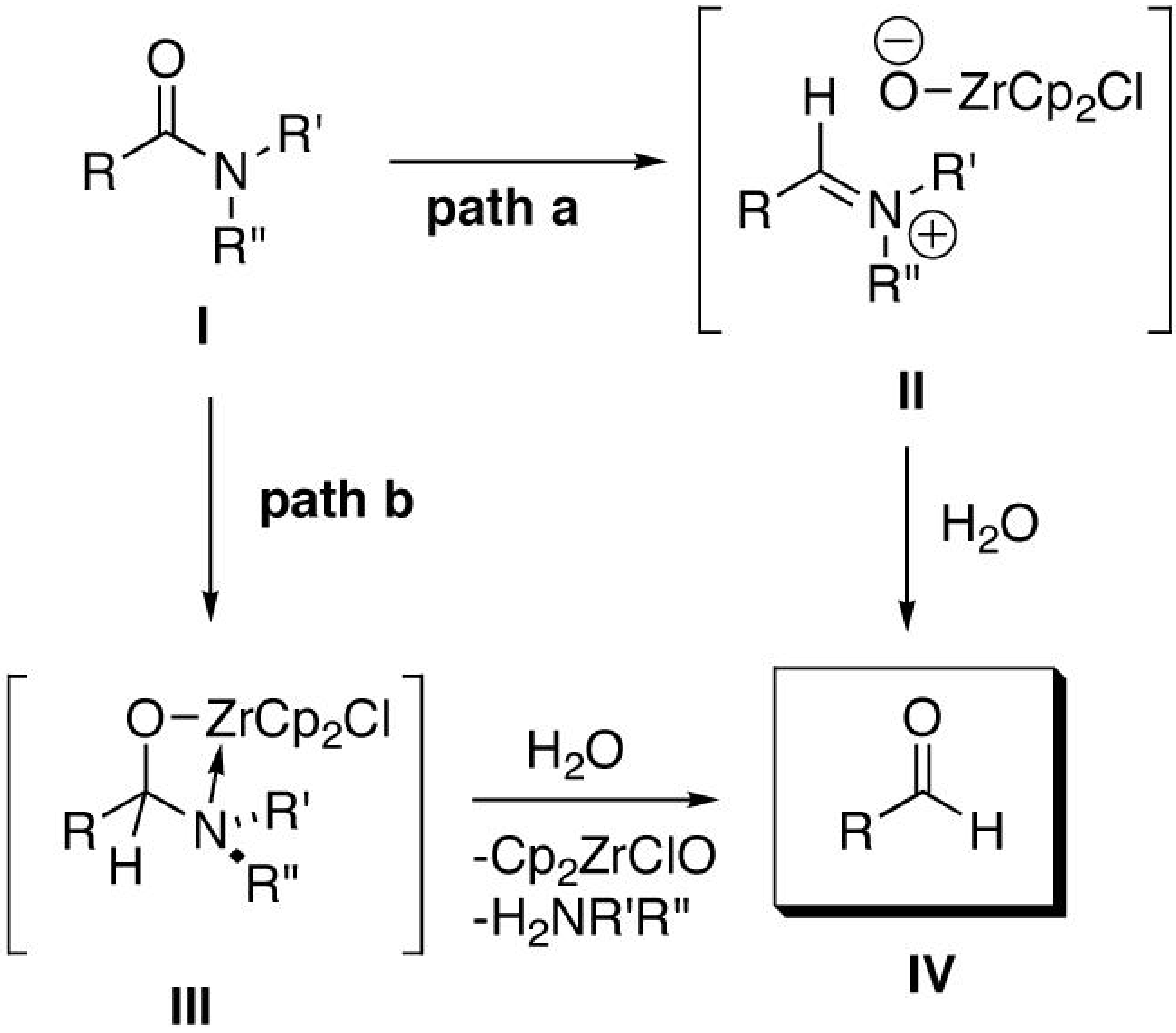


A. K. Beck, P. Gysi, L. La Vecchia, D. Seebach, *Org. Synth*. **1999**, *76*, 12, 22.

Synthesis of BAMOL

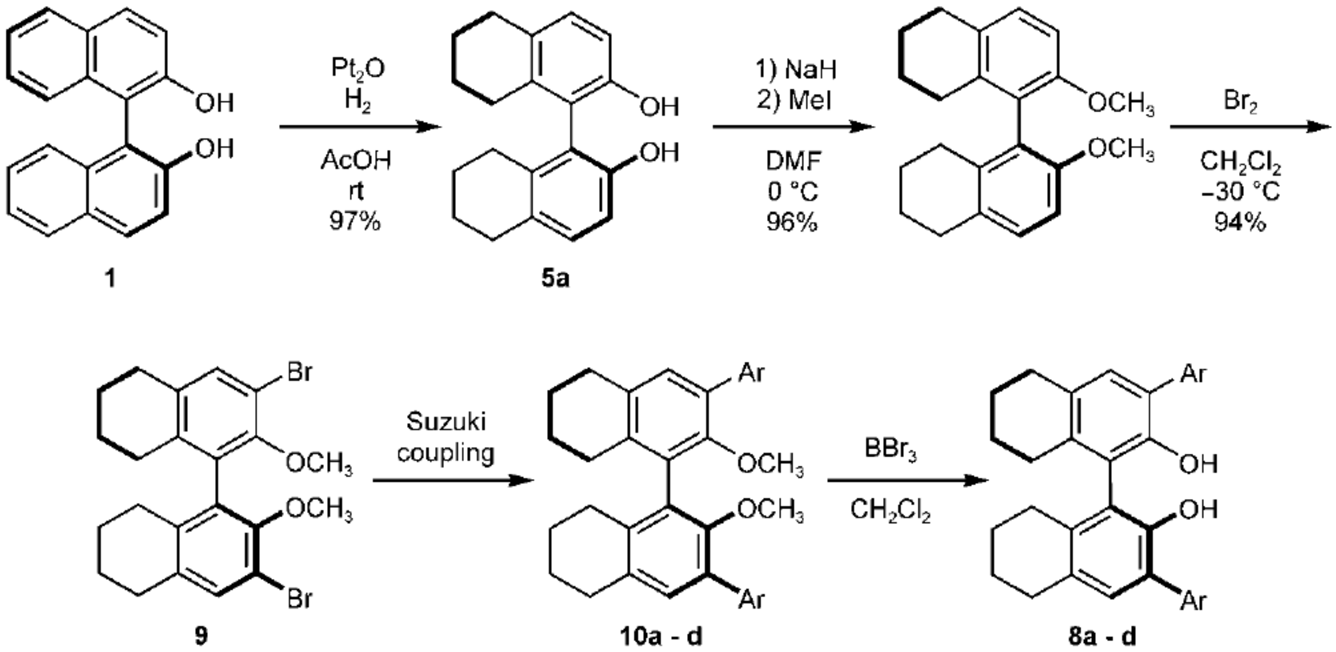


Reduction dimethylamide



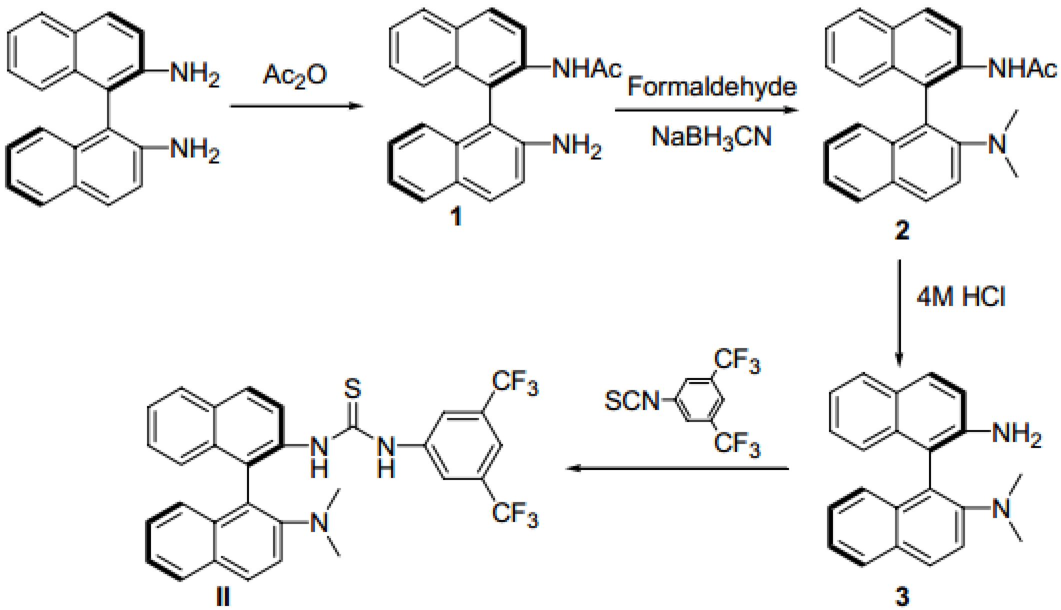
Goerg et *al J Am Chem Soc*. **2007**; 129, 3408–3419.

Synthesis of BINOL derivativ Schaus

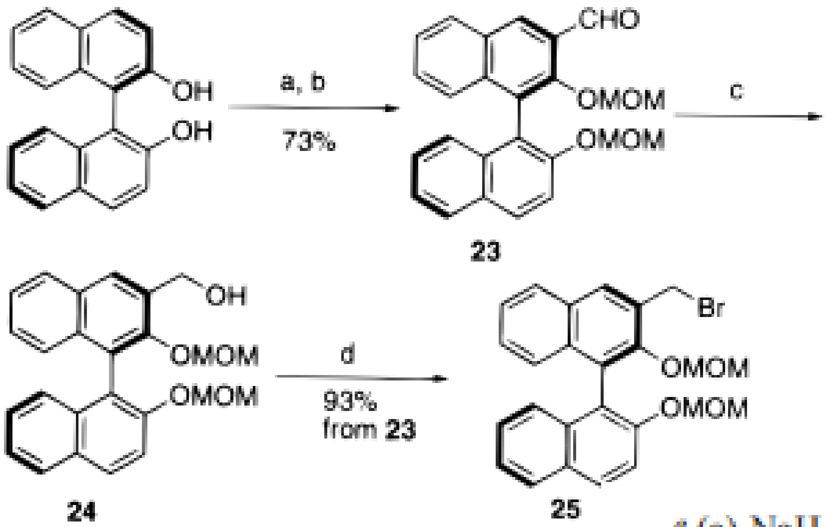


Schaus and co-workers, *Adv. Synth. Catal*. **2004**, *346*, 1231.

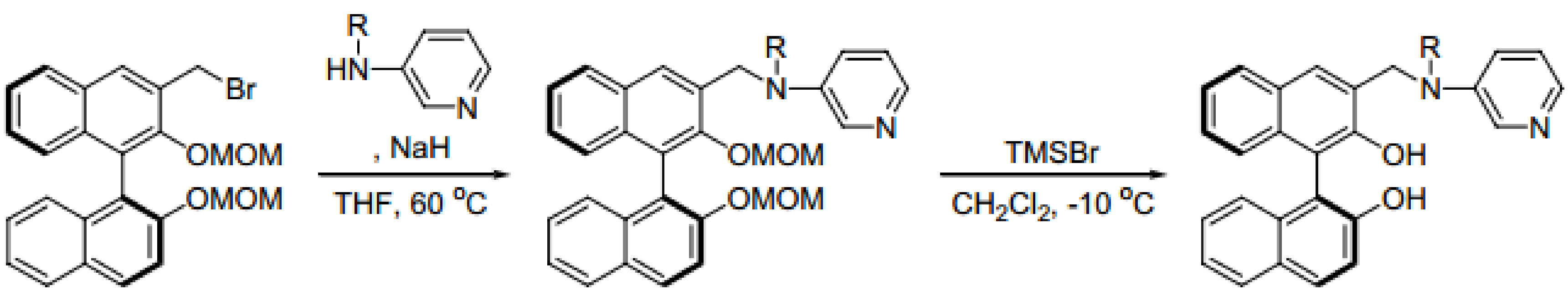
Synthesis of BINOL derivativ Wang



Synthesis of BINOL derivativ Sasai



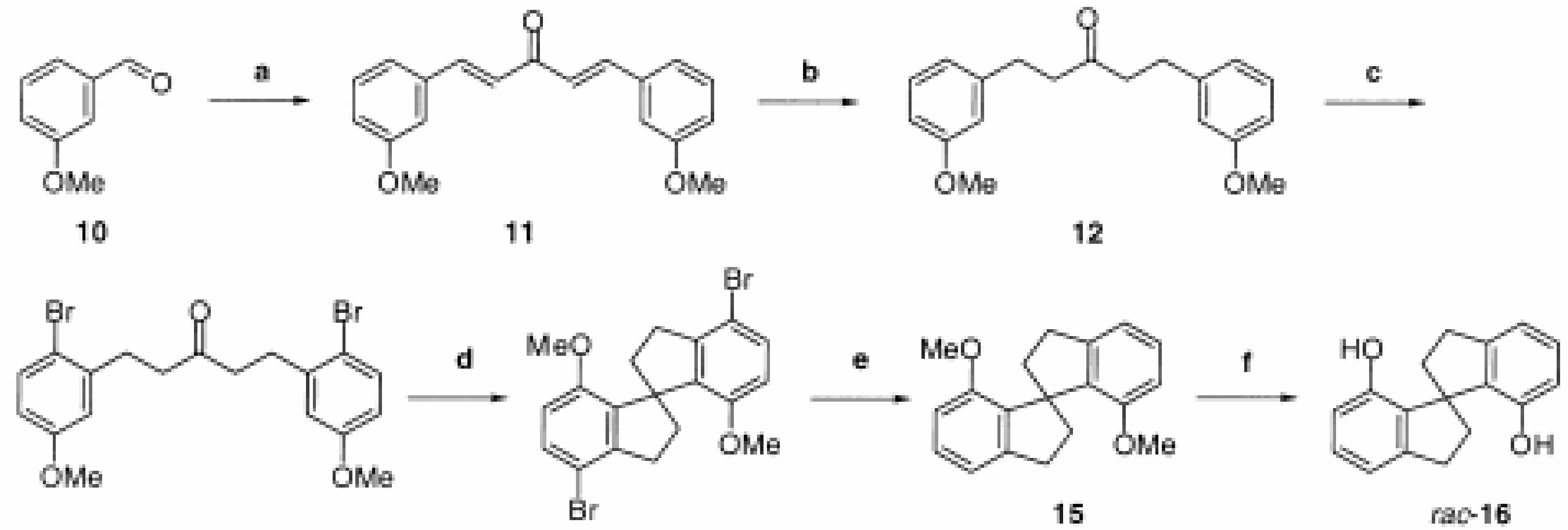
[a] (a) NaH, MOMCl, DMF, 0 °C, 5 h; (b) i) BuLi, TMEDA, THF, −78 to 0 °C; (ii) DMF, −78 to 0 °C; (c) NaBH$_4$, THF, MeOH, 0 °C, 15 min; (d) (i) MsCl, toluene, AcOEt, 0 °C, 90 min; (ii) LiBr, DMF, room temperature, 10 min;



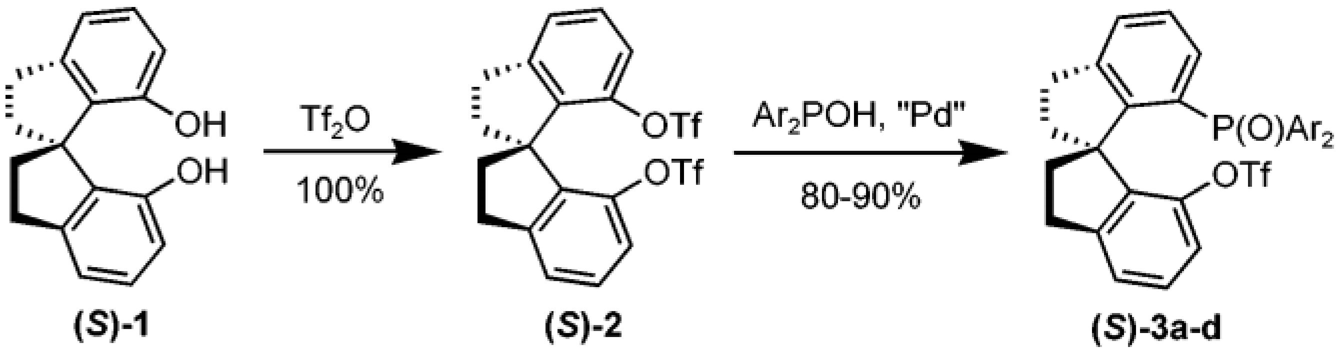
(*S*)-I

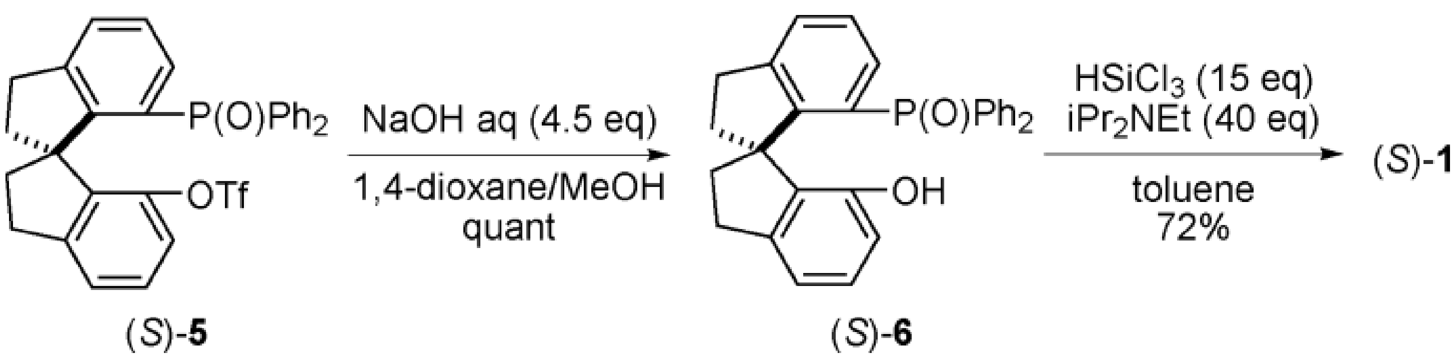
(*S*)-**IIa** (R=Me)
(*S*)-**IIb** (R=*i*-Pr)

(*S*)-**2a** (R=Me)
(*S*)-**6a** (R=*i*-Pr)



Reaction Conditions: (a) 0.5 eq Me_2CO, NaOH, 50% EtOH-H_2O, rt, 2h, 62%;[9] (b) Raney Ni, Me_2CO, rt, 1 atm. H_2, 1 day; (c) 2.5 eq Br_2, 3.5 eq pyridine, CH_2Cl_2; -10 °C to rt, 4h; (d) polyphosphoric acid, 105 °C, 5.5h, 57% for 3 steps;[7d] (e) *n*-BuLi (4 eq), THF, -78 °C, 1h; EtOH, 93%; (f) 2.3 eq BBr_3, CH_2Cl_2, -78 °C to rt overnight, 85%.


OH
OH
Tf2O
100%
OTf
OTf
Ar2POH, "Pd"
80-90%
P(O)Ar2
OTf
(S)-1
(S)-2
(S)-3a-d


P(O)Ph2
OTf
NaOH aq (4.5 eq)
1,4-dioxane/MeOH
quant
P(O)Ph2
OH
HSiCl3 (15 eq)
iPr2NEt (40 eq)
toluene
72%
(S)-1
(S)-5
(S)-6