Thiourea Hydrogen-Bond Donor Catalysts in Asymmetric Synthesis

Outline

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3. **1,4-Additions**
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   b. Applications in Synthesis
4. **Anion-binding Catalysis**
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   b. Glycosylation
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   c. 1,2-Boronate Rearrangement

Not covered:
Racemic thiourea organocatalysis, other hydrogen-bond donor catalysts (squaramide), other chiral organocatalysts

See Also:
Chris Bemis' Topic "Tethered Dimeric Catalysts in Asymmetric Reactions" 5/19/2017
Mikiko's Topic "Non-covalent interactions in TM Catalysis" 9/15/2017

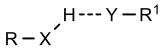
Key References:

Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.
https://doi.org/10.1002/anie.200503132
Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.
https://doi.org/10.1021/cr068373r

1. Introduction

Hydrogen bonding basics

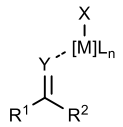
donor acceptor



X,Y = N, O, F

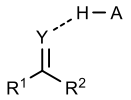
Bond strength ranges from 1-2 kcal/mol to 39 kcal/mol in extreme cases $(HF_2)^-$

Bond characater ranges from electrostatic to mostly covalent



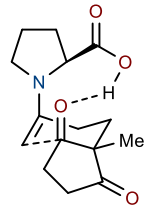
Lewis acid catalysis

-Low catalyst loadings
-Strong Lewis acid/base interactions
-Tunable at ligand, metal
-Water sensitive



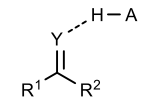
Hydrogen bond catalysis

-Higher catalyst loadings
-Weaker substrate/catalyst interactions
-Tunable catalyst structure
-Water stable

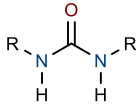


e.g. Hajos-Parrish reaction

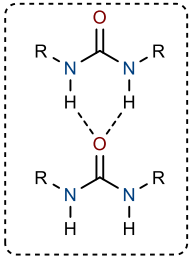
Urea vs. Thiourea

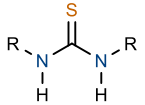


Desired Interaction
- Moderate acidity
- Low dimerization potential
- Induce directionality in substrate



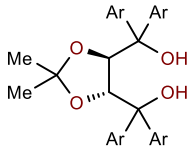
pK_a ~ 26
readily dimerizes, inefficient catalysis



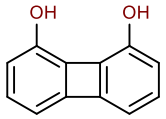


pK_a ~ 20
less prone to dimerize, higher TOF

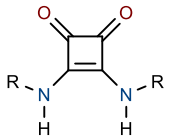
Additional Hydrogen-Bond Donor Catalysts



TADDOL



bisphenol

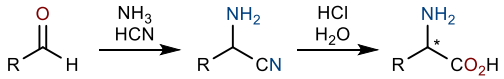


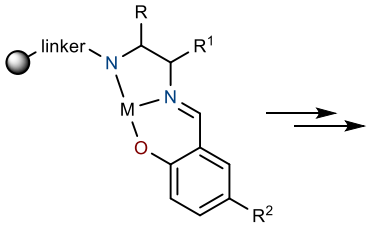
squaramide

Thiourea Hydrogen-Bond Donor Catalysts in Asymmetric Synthesis

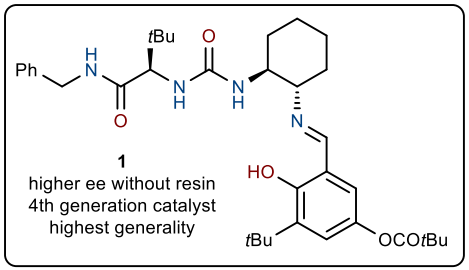
2. 1,2-Additions

2a. Strecker Reaction



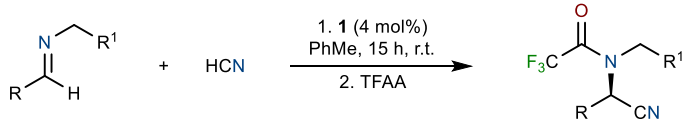


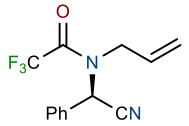
parallel ligand library of solid-phase supported Schiff bases



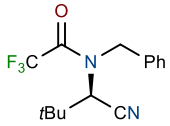
1
higher ee without resin
4th generation catalyst
highest generality

highest ee obtained without metal
optimized amino acid, diamine, and salicylaldehyde fragments

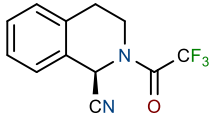




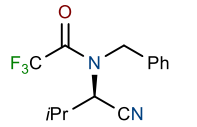
74%, 95% ee



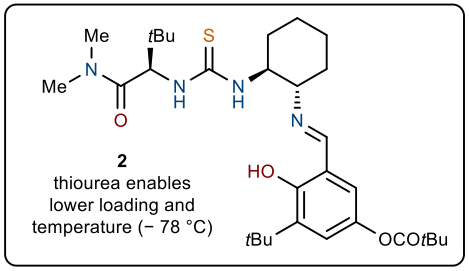
88%, 96% ee



88%, 91% ee

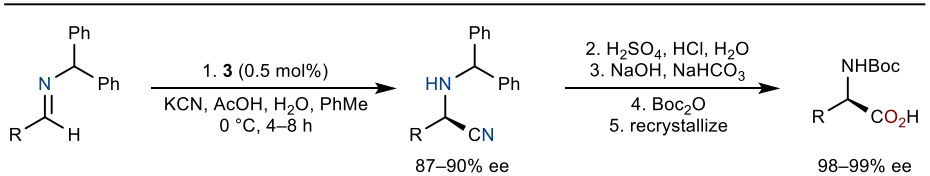


80% ee with **1** (4 mol%)
97% ee with **2** (1 mol%)



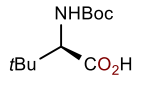
2
thiourea enables
lower loading and
temperature (− 78 °C)

Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. https://doi.org/10.1021/ja980139y.
Sigman, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. https://doi.org/10.1002/(SICI)1521-3773(20000403)39:7<1279::AID-ANIE1279>3.0.CO;2-U
Vachal, P; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012. https://doi.org/10.1021/ja027246j

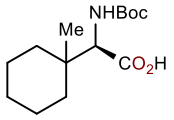


87–90% ee

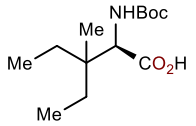
98–99% ee



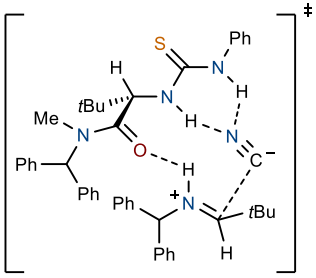
65%
14 g scale



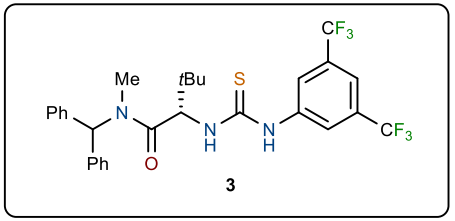
51%
3.5 g scale



51%
4 g scale



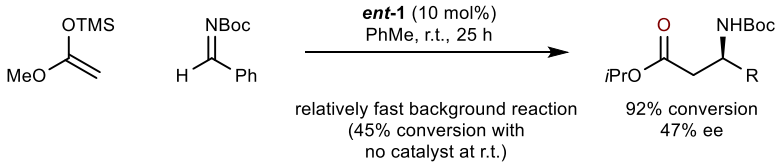
calculated at B3LYP/6-31G(d)



3

Zuend, S.; Jacobsen, E. N. *Nature* **2009**, *461*, 968. https://doi.org/10.1038/nature08484
Zuend, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358. https://doi.org/10.1021/ja9058958

2b. Mannich Reaction



relatively fast background reaction
(45% conversion with
no catalyst at r.t.)

92% conversion
47% ee

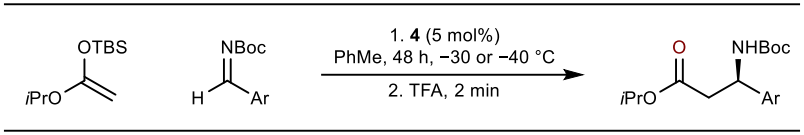
r.t., 5.5 h
54% ee

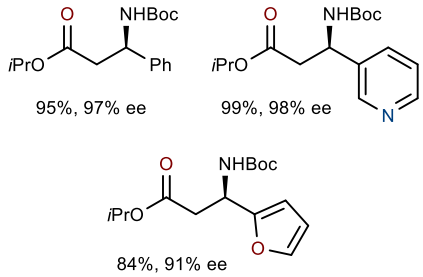
r.t., 3.5 h
63% ee

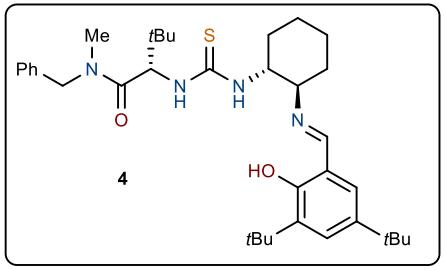
r.t. 2.0 h
68% ee

−40 °C, 48 h
91% ee

Thiourea Hydrogen-Bond Donor Catalysts in Asymmetric Synthesis

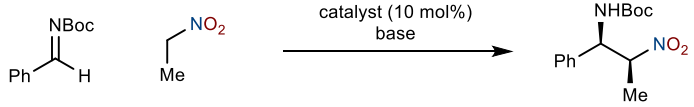


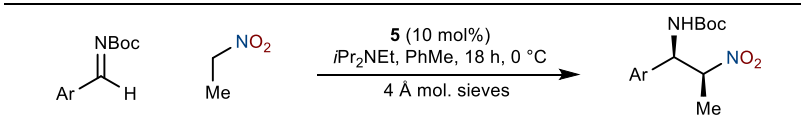


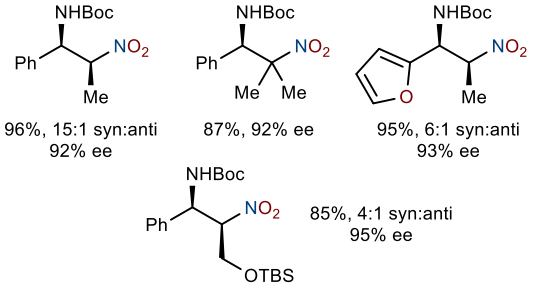


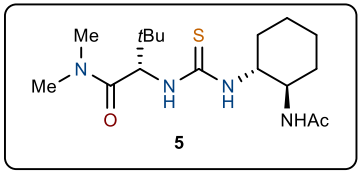
Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. https://doi.org/10.1021/ja028353g

2c. Nitro-Mannich (Aza-Henry)



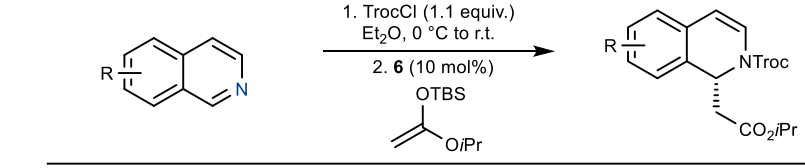


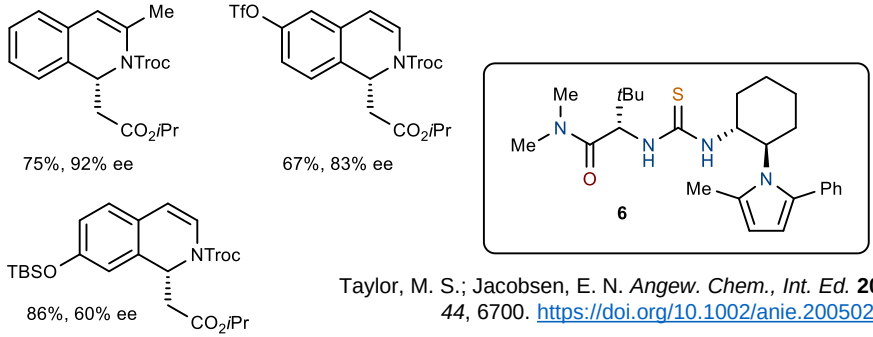




Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2004**, *44*, 466. https://doi.org/10.1002/anie.200461814

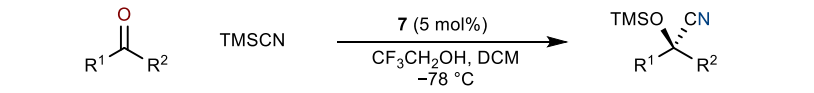
2d. Acyl-Mannich on Isoquinolines

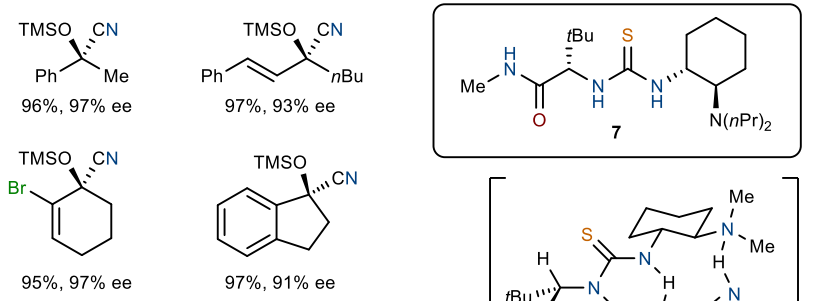


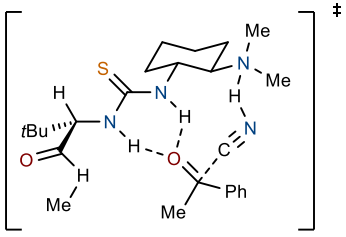


Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700. https://doi.org/10.1002/anie.200502277

2e. Ketone Cyanosilylation

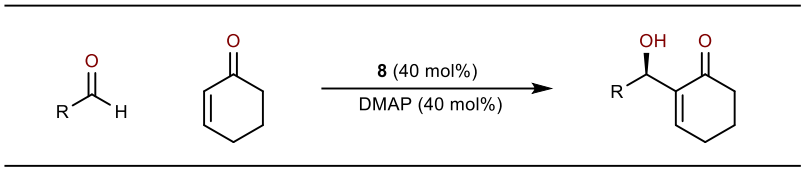


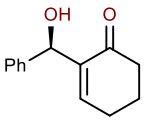


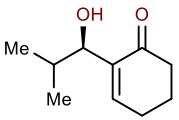


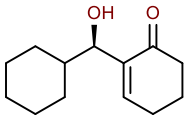
Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964. https://doi.org/10.1021/ja052511x
Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 15872. https://doi.org/10.1021/ja0735352

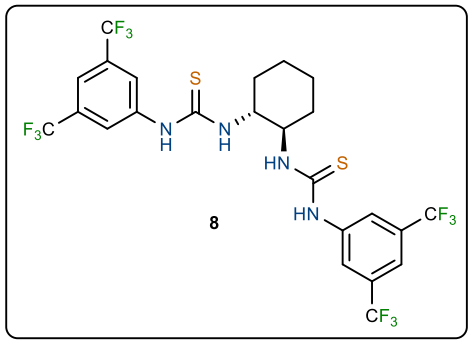
2f. Morita-Baylis-Hillman

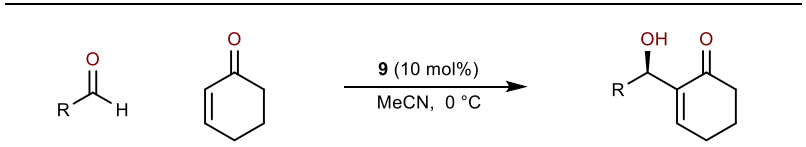


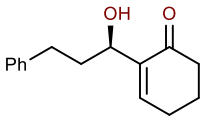

88%, 33% ee

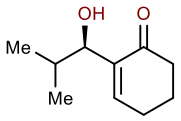

67%, 60% ee

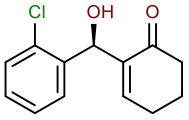

72%, 90% ee

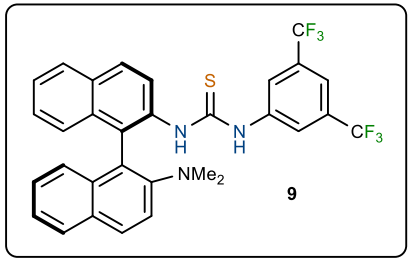




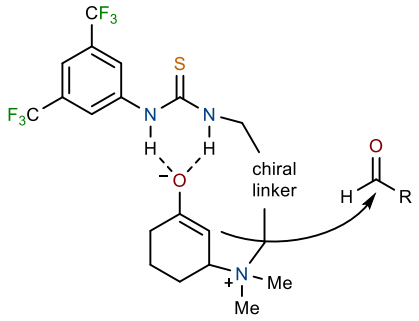

80%, 83% ee


63%, 94% ee


55%, 60% ee



Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589. https://doi.org/10.1016/j.tetlet.2004.05.137
Wang, W. *Org. Lett.* **2005**, *7*, 4293. https://doi.org/10.1021/ol051822

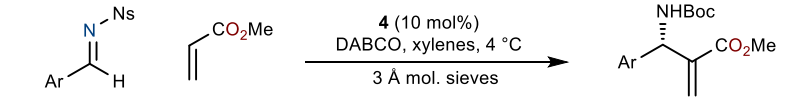


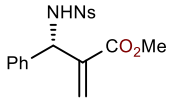
Increased enantioinduction by tethering initial nucleophile to the hydrogen-bond donor

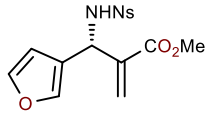
This thiourea serves as a **Bifunctional Catalyst**

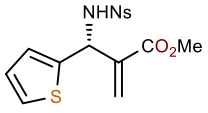
Both methods suffer from a limited scope & generality. Asymmetric Morita-Baylis-Hillman reactions are still an active area of research!

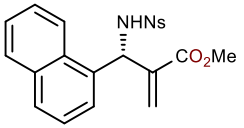
2g. Aza-Morita-Baylis-Hillman

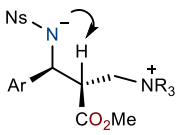



49%, 95% ee

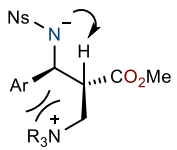

25%, 98% ee


30%, 99% ee


27%, 91% ee


matched, high ee
reacts faster in RDS

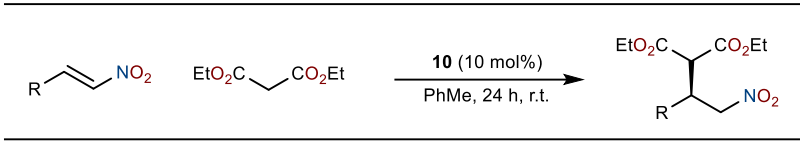
vs.

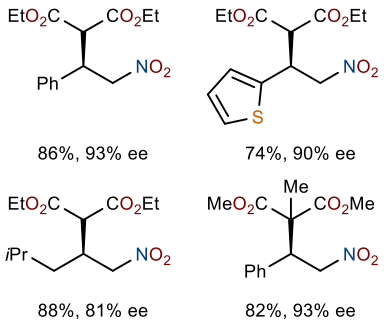

mismatched, low ee
reacts slower, precipitates

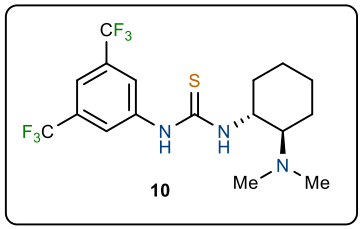
Low yields rationalized by one DABCO-adduct diastereomer, formed in high ee, reacting productively while the other precipitates

Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701. https://doi.org/10.1002/adsc.200505230

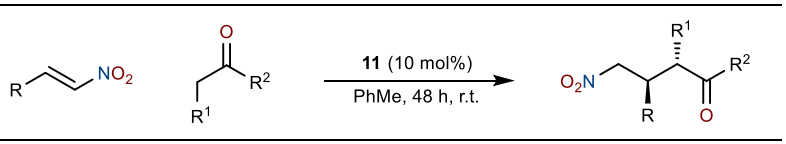
3. 1,4-Addition
3a. Michael Addition

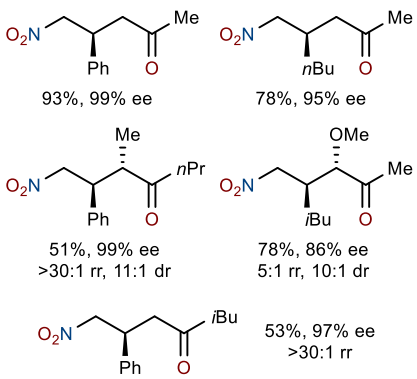


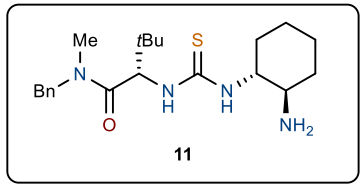


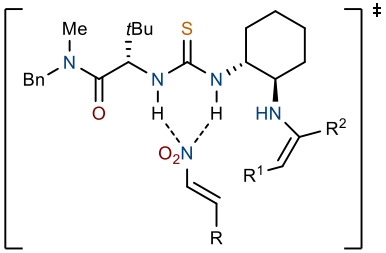


Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. https://doi.org/10.1021/ja036972z

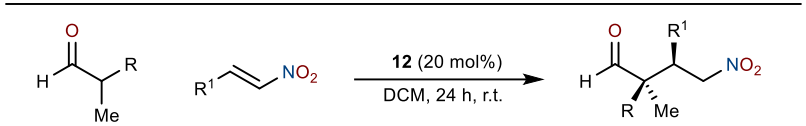


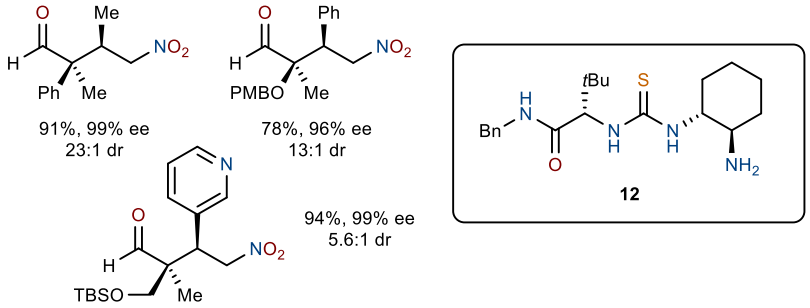




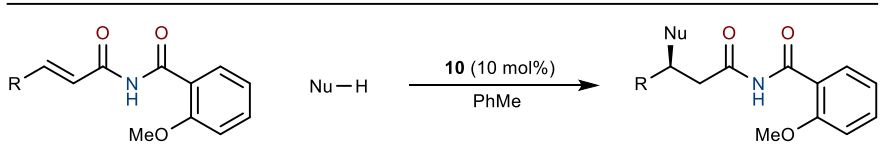


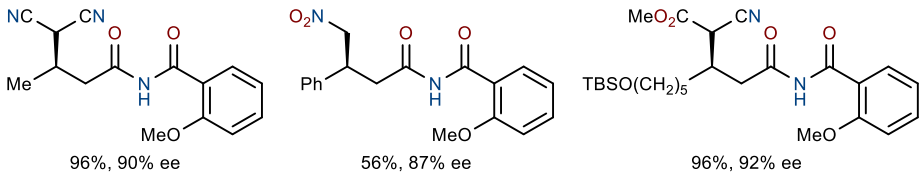
Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. https://doi.org/10.1021/ja0620890





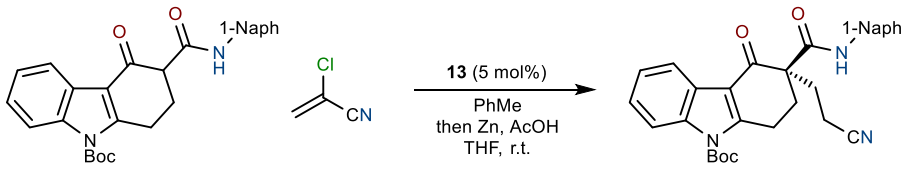
Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. https://doi.org/10.1002/anie.200602221



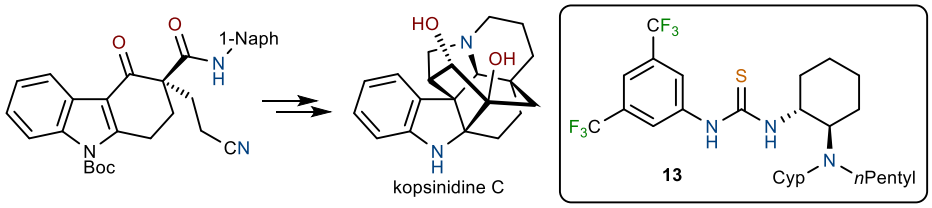


Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413. https://doi.org/10.1021/ja061364f

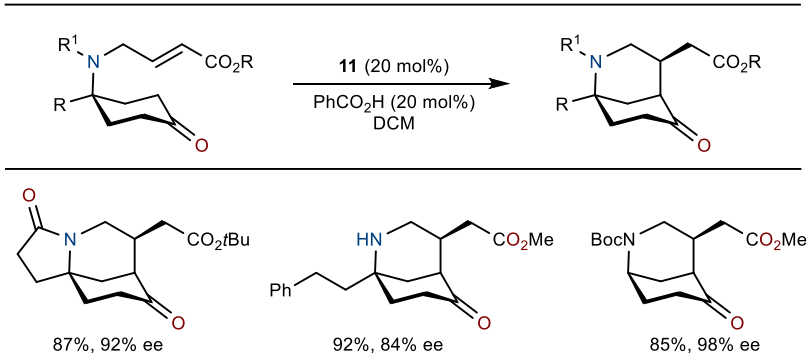
3b. Application in Total Synthesis

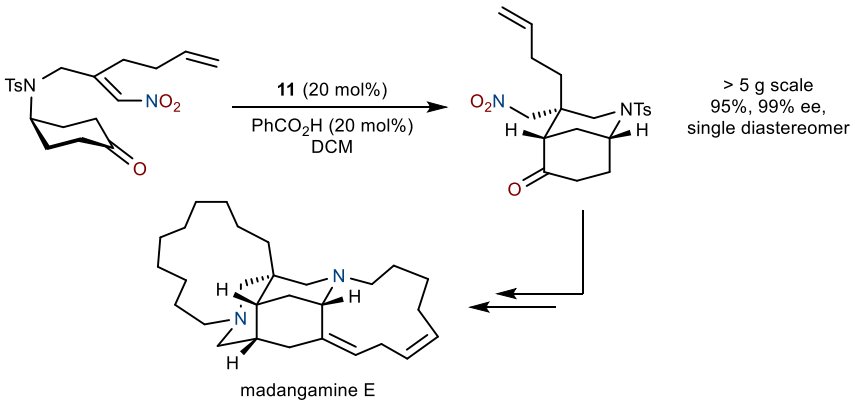


Thiourea Hydrogen-Bond Donor Catalysts in Asymmetric Synthesis



Ma, D. *Angew. Chem., Int. Ed.* **2018**, *57*, 10207. https://doi.org/10.1002/anie.201805905

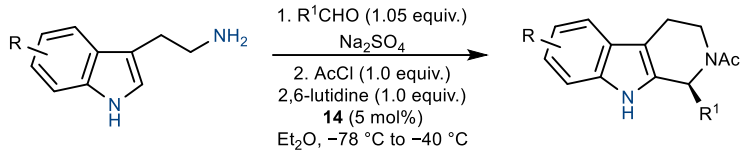


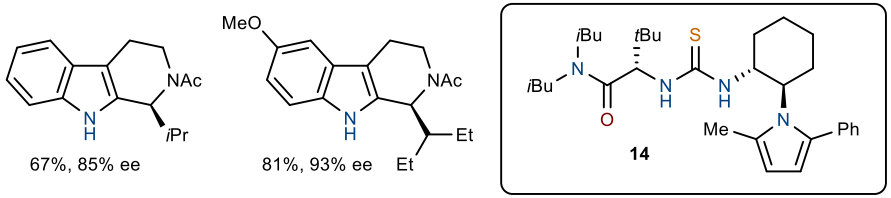


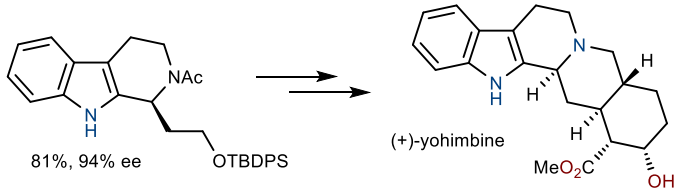
Dixon, D. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 4899. https://doi.org/10.1002/anie.201411924
Dixon, D. J. *J. Am. Chem. Soc.* **2022**, *144*, 1407. https://doi.org/10.1021/jacs.1c12040

4. Anion-Binding Catalysis

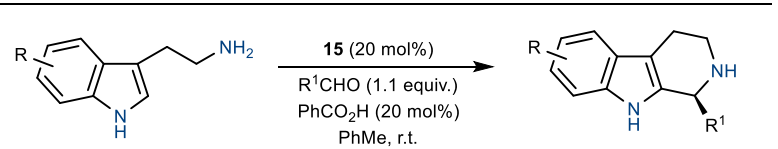
4a. Pictet-Spengler

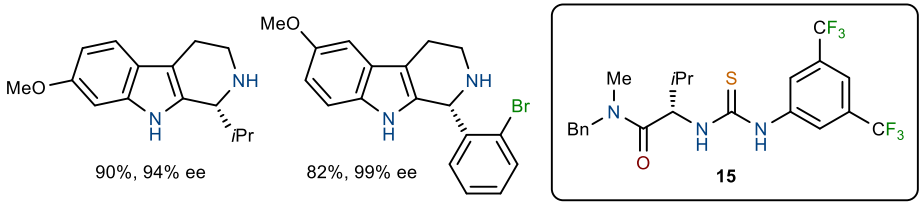




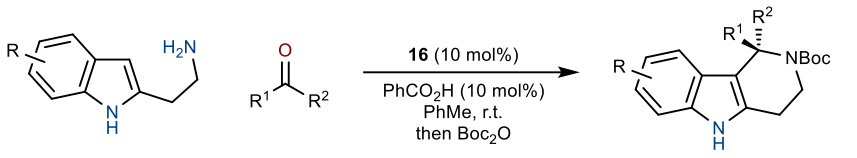


Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. https://doi.org/10.1021/ja046259p
Mergott, D. J.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 745. https://doi.org/10.1021/ol702781q



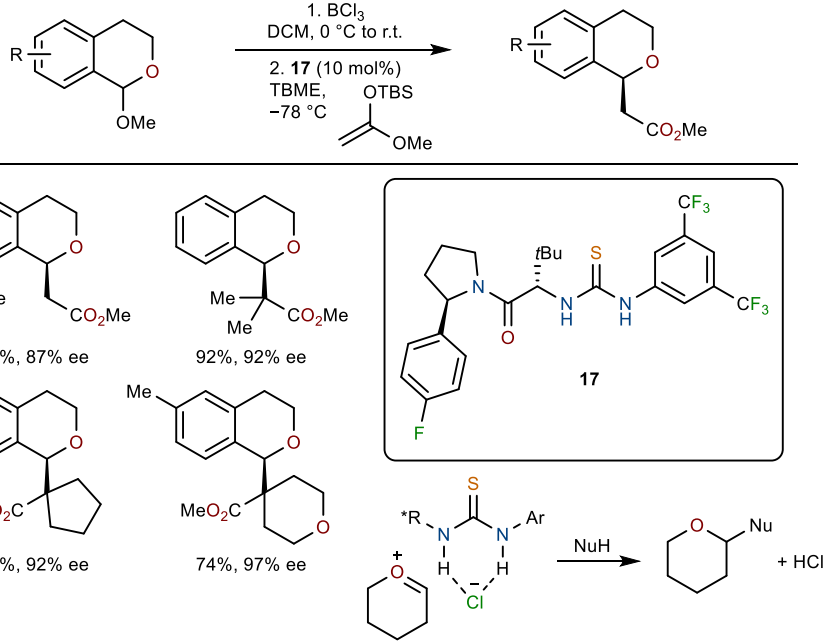


Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887. https://doi.org/10.1021/ol802887h
Klausen, R. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2017**, *139*, 12299. https://doi.org/10.1021/jacs.7b06811

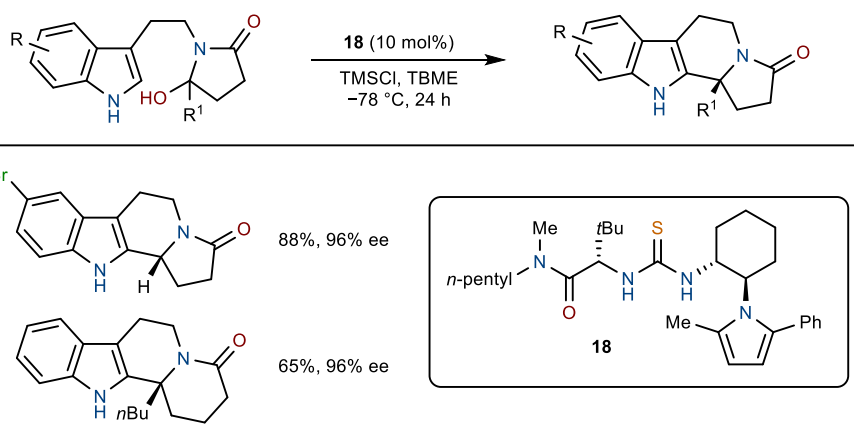


Lee, Y.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 5564. https://doi.org/10.1021/ol202300t

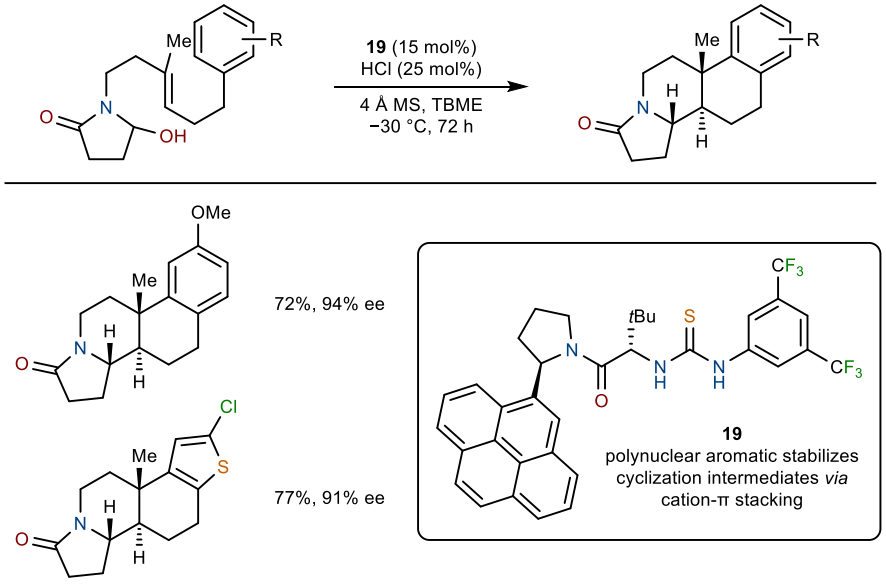
4b. Anion-Binding Catalysis



Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. https://doi.org/10.1021/ja801514m

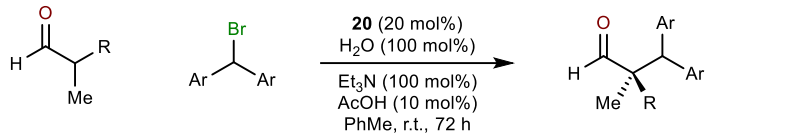


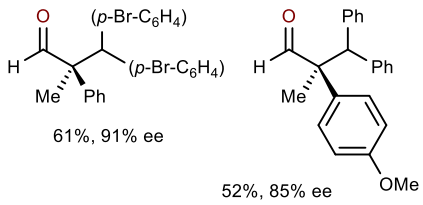
Raheem, I. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. https://doi.org/10.1021/ja076179w

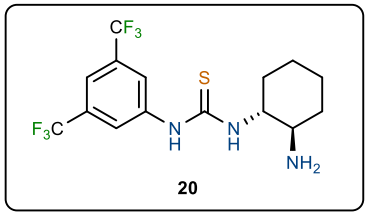


Knowles, R. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030. https://doi.org/10.1021/ja101256v

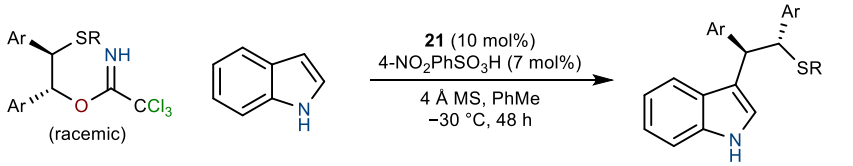
Thiourea Hydrogen-Bond Donor Catalysts in Asymmetric Synthesis

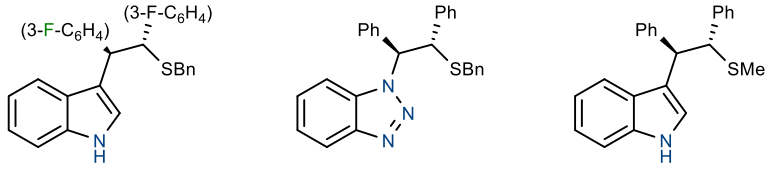


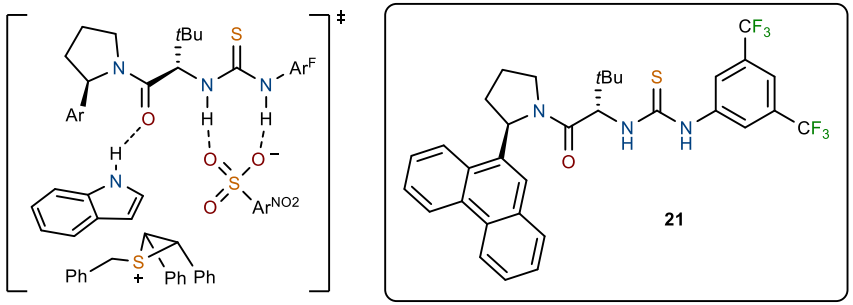




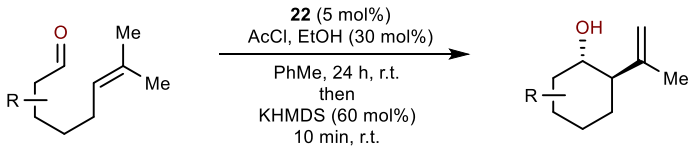
Brown, A. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286. https://doi.org/10.1021/ja103618r

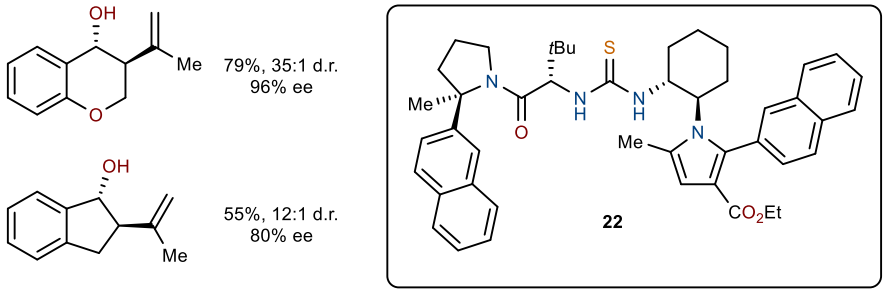


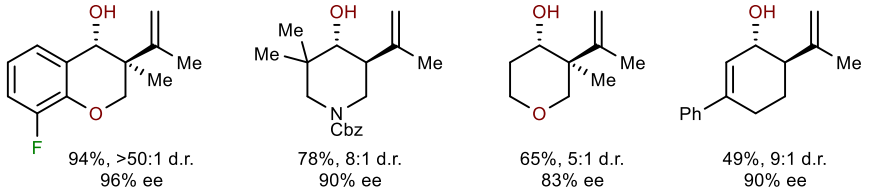


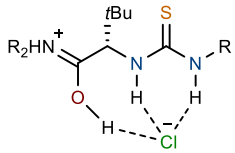


Lin, S.; Jacobsen, E. N. *Nature Chem.* **2012**, *4*, 817. https://doi.org/10.1038/nchem.1450



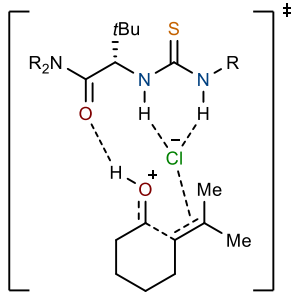






22·HCl is less acidic than HCl, but this complex reacts much faster than the HCl-catalyzed background reaction and provides high enantioselectivity

Computational studies suggest HBD-bound chloride increases alkene nucleophilicity through electrostatic stabilization



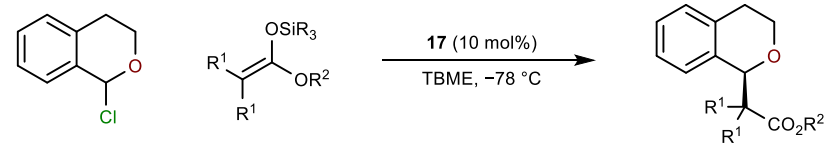
Kutateladze, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2021**, *143*, 20077. https://doi.org/10.1021/jacs.1c10890

Kutateladze, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2022**, *144*, 15812. https://doi.org/10.1021/jacs.2c06688

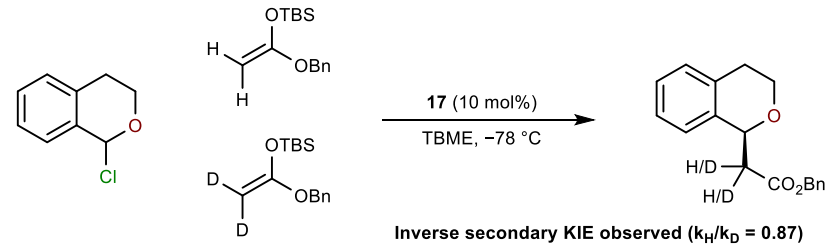
Thiourea Hydrogen-Bond Donor Catalysts in Asymmetric Synthesis

5. Bis-thiourea Catalysis

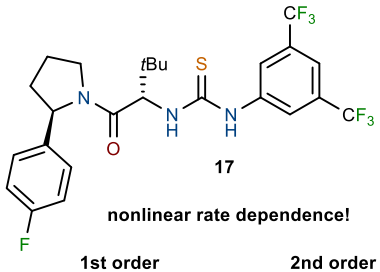
Initial anion-binding catalysts suffer from:
- High catalyst loadings
- Long reaction times
- Dilute reaction conditions



1st order rate dependence | **1st order rate dependence** | **no rate dependence on silyl group**



Inverse secondary KIE observed (k_H/k_D = 0.87) implies rehybridization (sp^2 to sp^3) in RDS



17

nonlinear rate dependence!

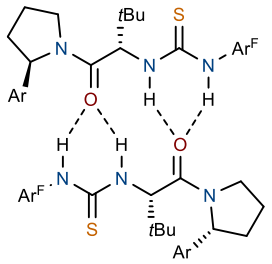
1st order at high concentration | **2nd order at low concentration**

also, nonlinear relationship between catalyst ee and product ee

implies influential catalyst-catalyst interaction during catalysis

5a. Mechanistic Studies

How can reaction efficiency be improved? Detailed mechanistic understanding & rational catalyst design!



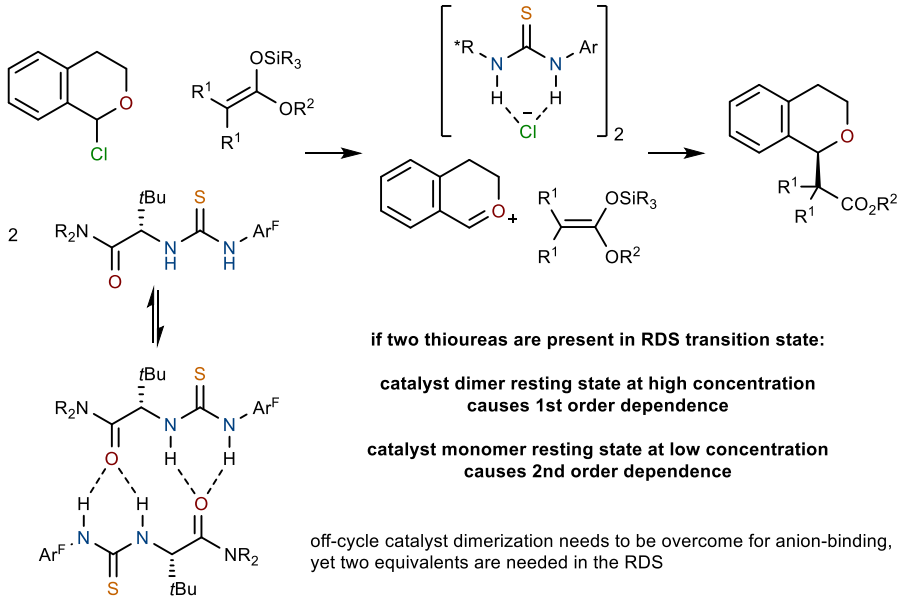
(*Z*)-17

(*E*)-17

catalyst dimers observed in solution by NOE

(*Z*)-(*Z*) and (*E*)-(*E*) also observed in solution

Ford, D. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 7860.
https://doi.org/10.1021/jacs.6b04686

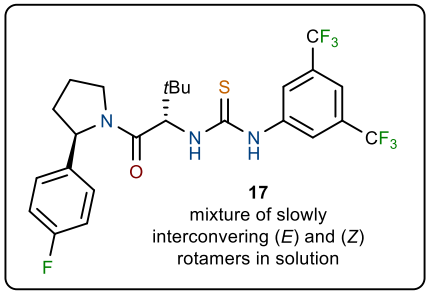


if two thioureas are present in RDS transition state:

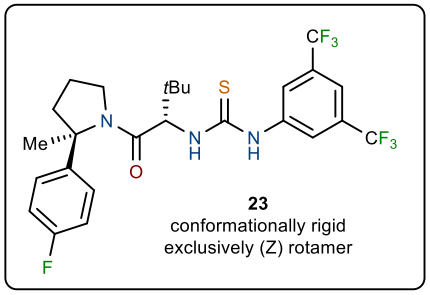
catalyst dimer resting state at high concentration causes 1st order dependence

catalyst monomer resting state at low concentration causes 2nd order dependence

off-cycle catalyst dimerization needs to be overcome for anion-binding, yet two equivalents are needed in the RDS

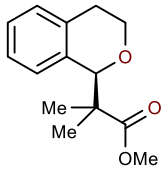


17
mixture of slowly interconverting (*E*) and (*Z*) rotamers in solution



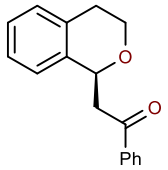
23
conformationally rigid exclusively (Z) rotamer

(Z)-17 dimer computationally predicted to provide higher enantioselectivity



66%, 92% ee with **17**

> 95%, 97% ee with **23**

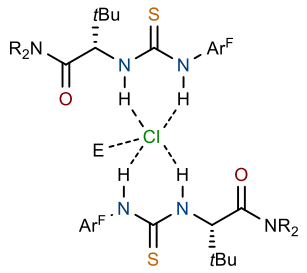


82%, 88% ee with **17**

> 95%, 96% ee with **23**

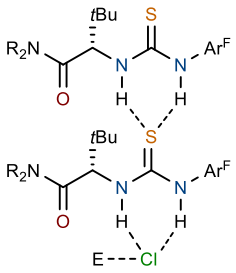
Ford, D. D.; Jacobsen, E. N. *ACS Catal.* **2016**, *6*, 4616.
https://doi.org/10.1021/acscatal.6b01384
Lehnherr, D.; Jacobsen, E. N. *Org. Lett.* **2016**, *18*, 3214.
https://doi.org/10.1021/acs.orglett.6b01435

Thiourea Hydrogen-Bond Donor Catalysts in Asymmetric Synthesis



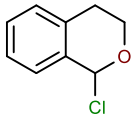
4H Mode Anion Abstraction

or

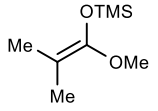


2H Mode Anion Abstraction

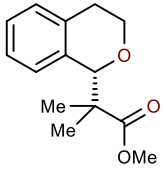
4H mode chloride binding observed in the solid state
(17)$_2$·NMe$_4$Cl



5 mmol scale

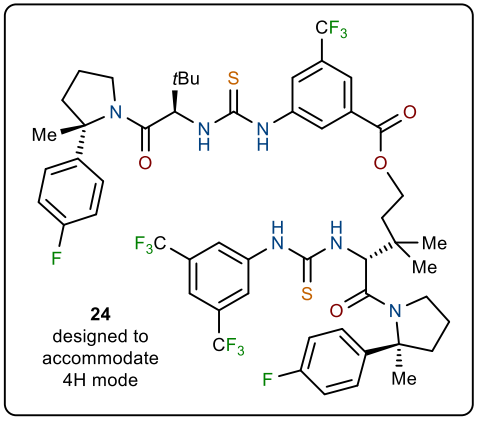


24 (0.1 mol%)
TBME (0.5 M)
3 h, −78 °C



96%, 92% ee

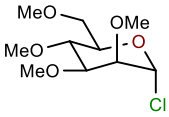
100x lower catalyst loading
8x shorter reaction time
5x more concentrated



24
designed to accommodate 4H mode

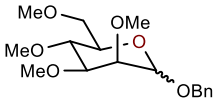
Kennedy, C. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 13525.
https://doi.org/10.1021/jacs.6b09205

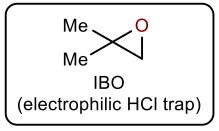
5b. Glycosylation



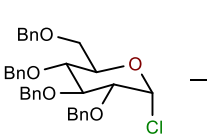
BnOH
(2 equiv.)

catalyst (5 mol%)
IBO (1.1 equiv.)
PhMe, −40 °C

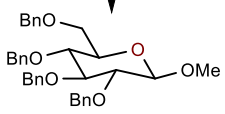




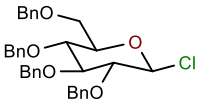
catalyst **17**	1%	52:48 α:β
catalyst **24**	15%	20:80 α:β
catalyst **25**	88%	8:92 α:β



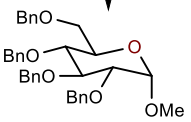
25 (10 mol%)
MeOH (2 equiv.)
IBO (1.1 equiv.)
PhMe, r.t., 24 h



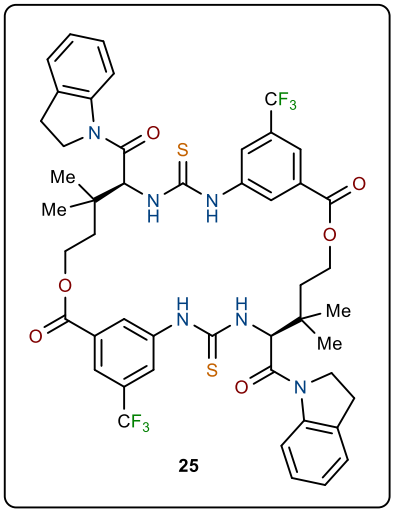
83%, <1:50 α:β



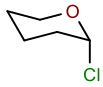
25 (10 mol%)
MeOH (2 equiv.)
IBO (1.1 equiv.)
PhMe, r.t., 24 h



87%, 3:1 α:β

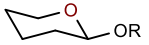


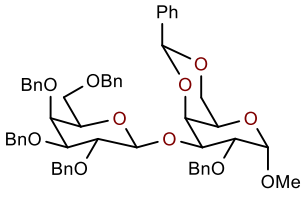
25



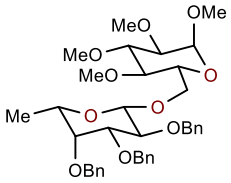
ROH
(2 equiv.)

25 (5 mol%)
IBO (2 equiv.)
o-dichlorobenzene

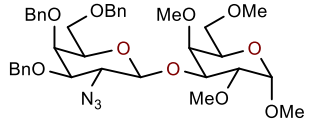




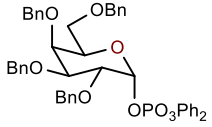
69%, 1:99 α:β



80%, 5:95 α:β

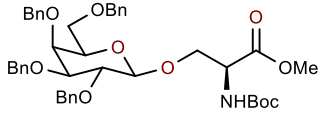


73%, 8:92 α:β



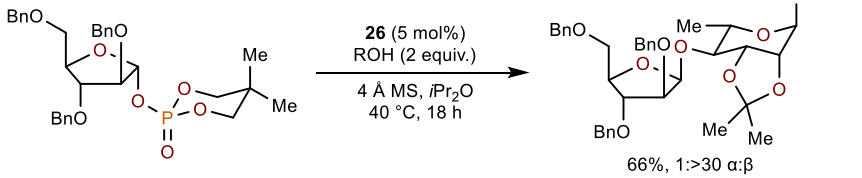
ROH
(2 equiv.)

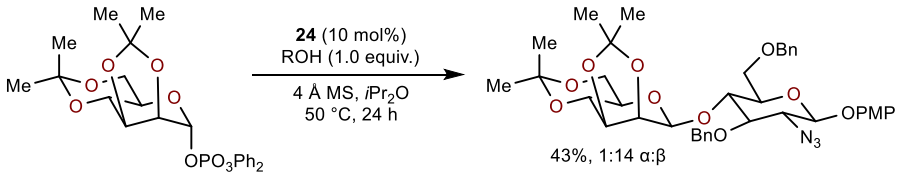
ent-24 (5 mol%)
4 Å MS, *i*Pr$_2$O
19 h

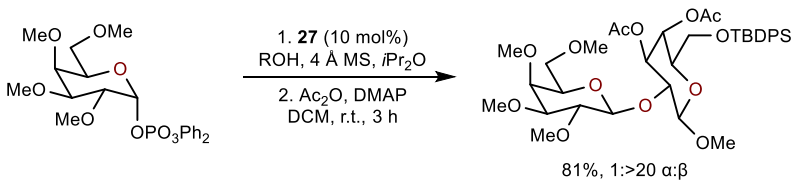


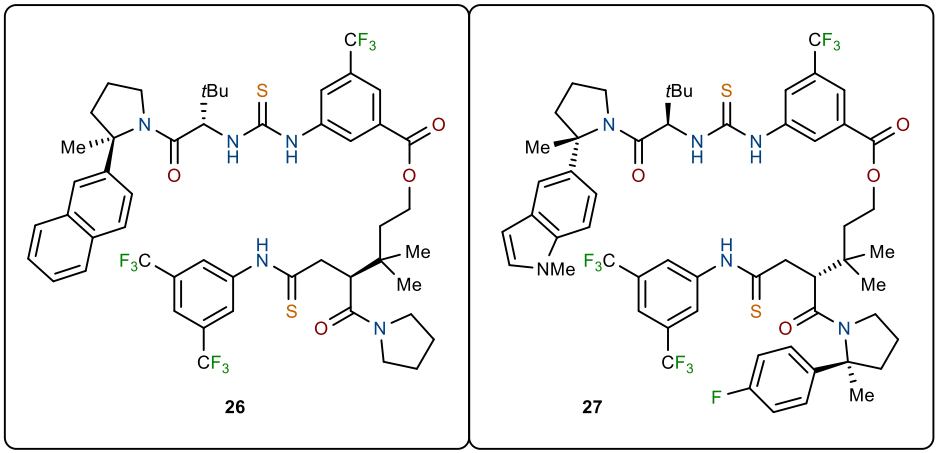
quant., 3:97 α:β

Park, Y.; Jacobsen, E. N. *Science* **2017**, *355*, 162. https://doi.org/10.1126/science.aal1875
Levi, S. M.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2018**, *116*, 35.
https://doi.org/10.1073/pnas.1811186116



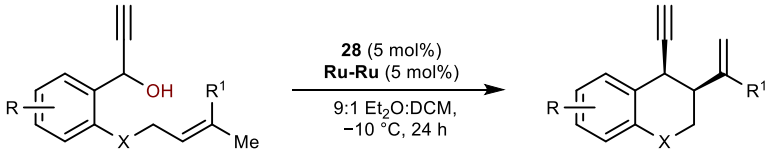


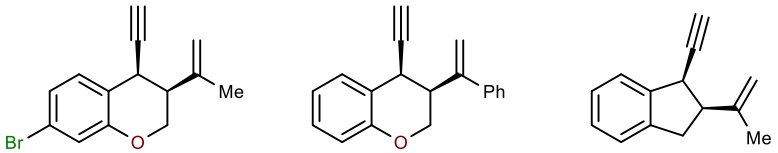


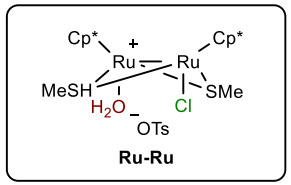


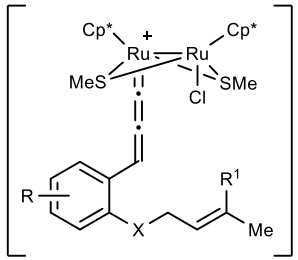
Mayfield, A. B.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2020**, *142*, 4061.
https://doi.org/10.1021/jacs.0c00335
Li, Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2020**, *142*, 11865.
https://doi.org/10.1021/jacs.0c04255
Li, Q.; Jacobsen, E. N. *Nature* **2022**, *608*, 74.
https://doi.org/10.1038/s41586-022-04958-w

5c. Propargylic Substitution

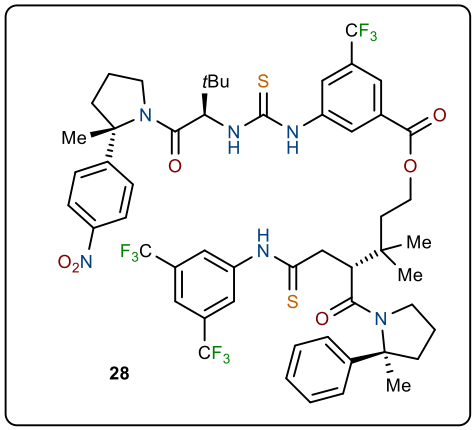


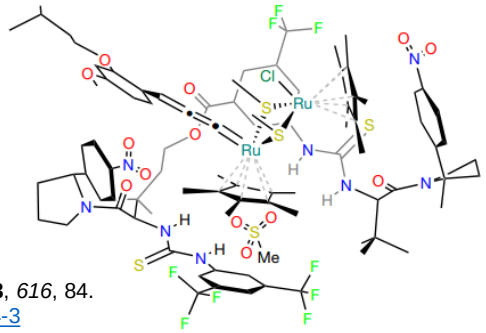






Anion-bound bis-thiourea complex studied using DFT and ROESY correlations

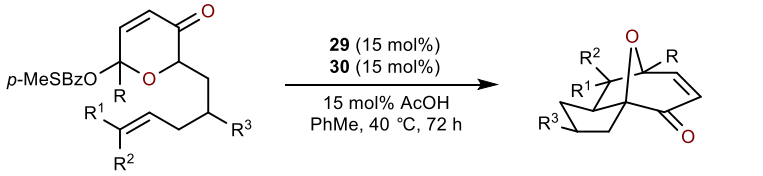


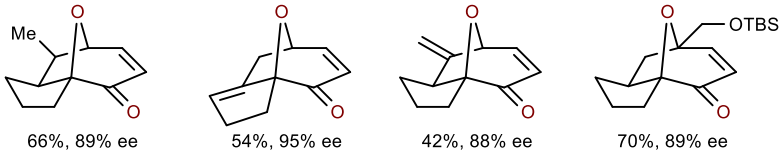


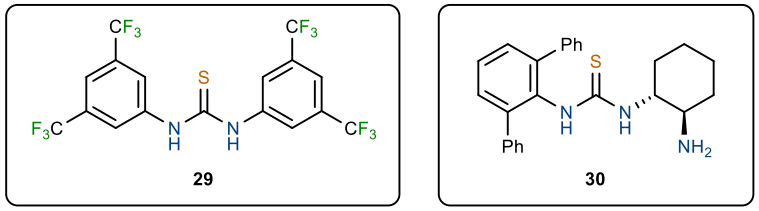
Ovian, J. M.; Jacobsen, E. N. *Nature* **2023**, *616*, 84.
https://doi.org/10.1038/s41586-023-05804-3

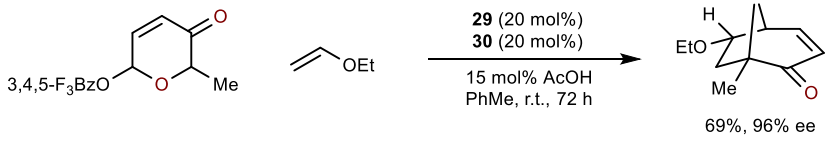
6. Other Bifunctional Catalysts

6a. [5+2] Cycloaddition



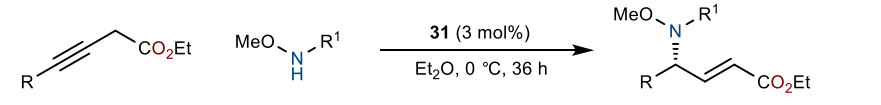


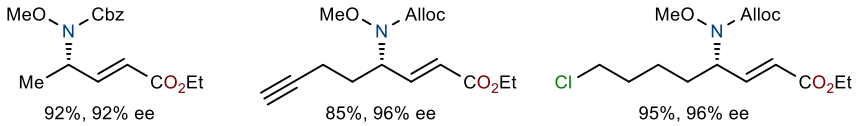


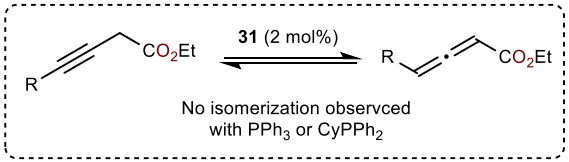


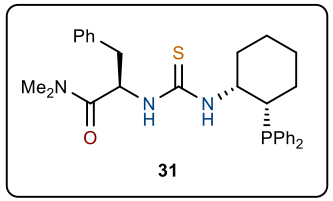
Burns, N. Z.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578.
https://doi.org/10.1021/ja206997e
Witten, M. R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2014**, *53*, 5912.
https://doi.org/10.1002/anie.201402834

6b. Allyl & Homoallyl Amine Synthesis

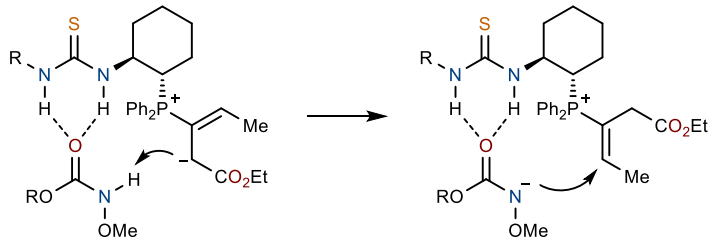


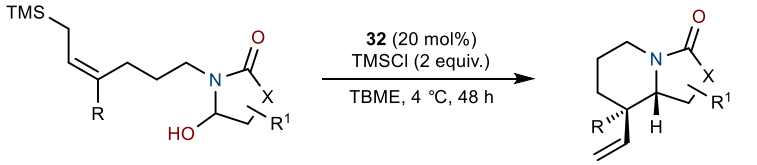


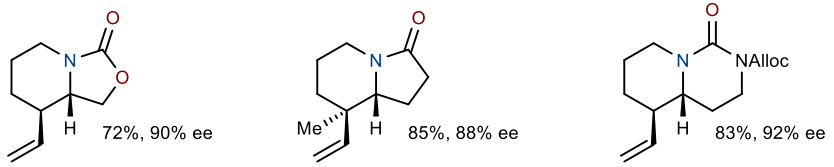




Proposed Mechanism:

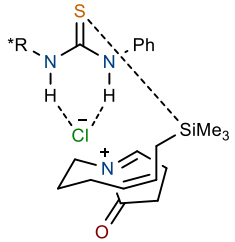


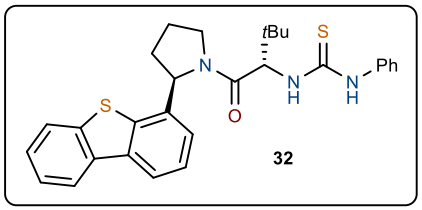




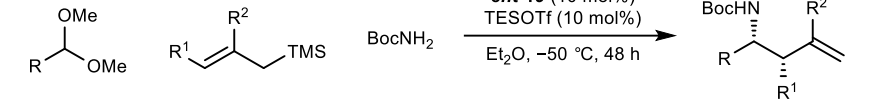
Fang, Y.-Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2014**, *136*, 17966.
https://doi.org/10.1021/ja5117638

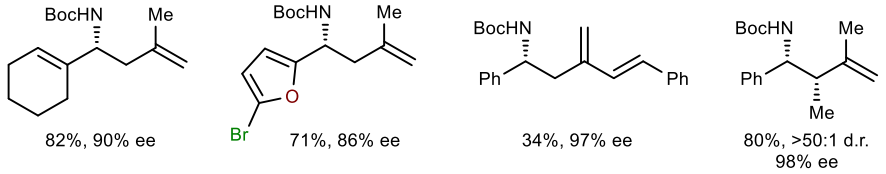
Thiourea Hydrogen-Bond Donor Catalysts in Asymmetric Synthesis





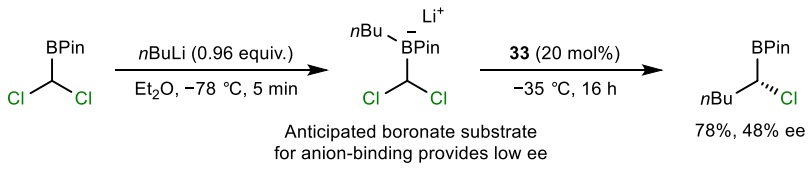
Park, Y.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 14848.
https://doi.org/10.1021/jacs.6b09736

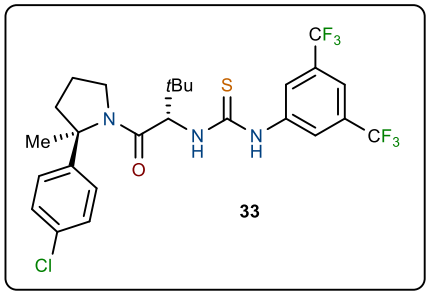


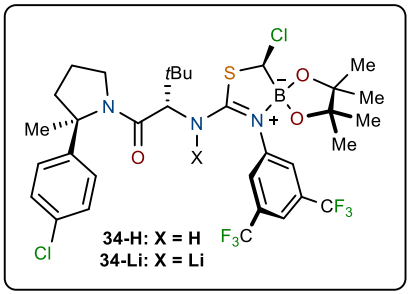


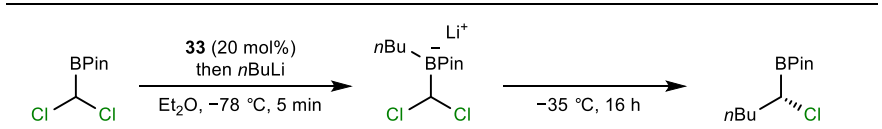
Ronchi, E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2021**, *143*, 7272.
https://doi.org/10.1021/jacs.1c03024

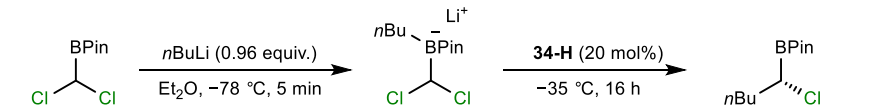
6c. 1,2-Boronate Rearrangement

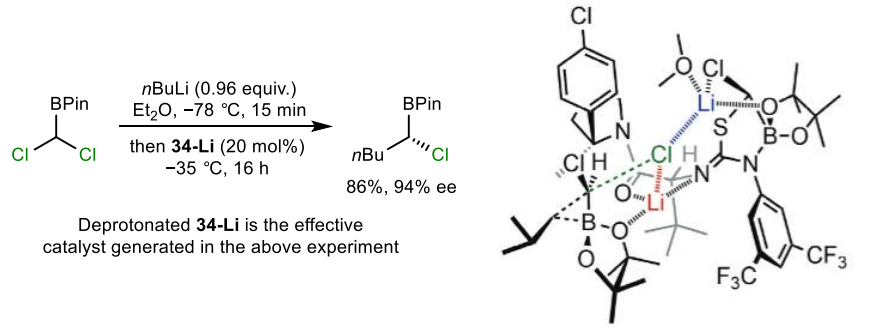


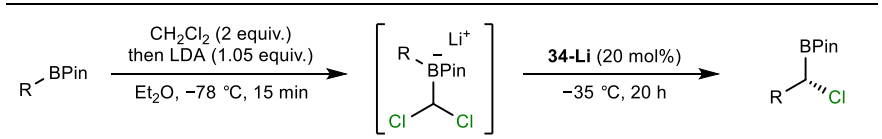


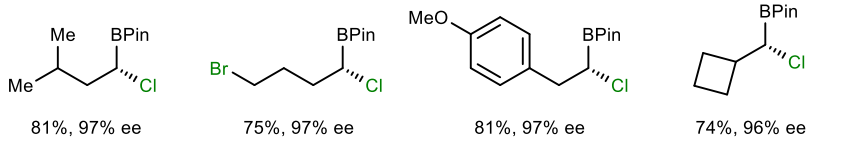












Sharma, H. A.; Jacobsen, E. N. *Science* **2021**, *374*, 752.
https://doi.org/10.1126/science.abm0386