Enantioselective Protonation

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Supervisor: Yong Huang

Date: 2012-12-17

Mohr, J. T., Hong, A. Y. Stoltz, B. M. *Nature Chemistry*, **2009**, *1*, 359

Contents

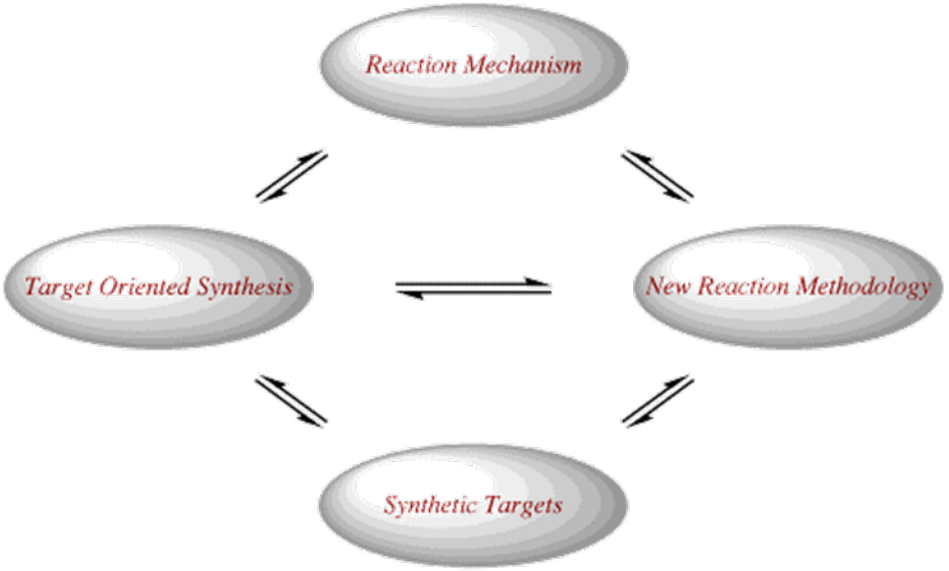
Introduction

Brian M. Stoltz

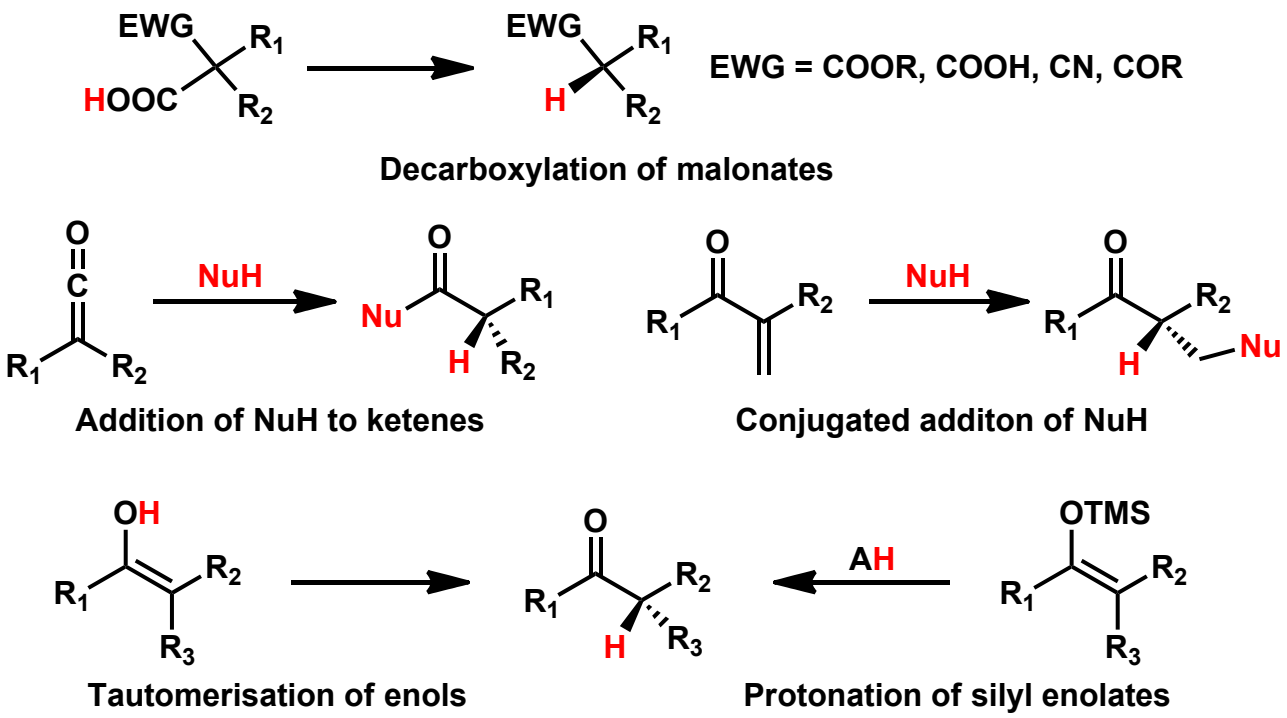
Degrees

- **B.S.** Indiana University of Pennsylvania 1993
- **M.S.** Yale University (John Wood), 1996
- **Ph.D.** Yale University (John Wood), 1997
- **NIH Postdoctoral Fellow** Harvard University (E. J. Corey) 1998-2000

Research Interests



Introduction



Scheme 1: Main strategies investigated in enantioselective protonation

Enantioselective transfer of a proton presents unusual challenges —manipulating a very small atom and avoiding product racemization at a particularly labile stereocentre.

Introduction

Important factors in achieving enantioselective protonation

1. **Kinetic processes**
2. **Match the p*K*a of the proton donor and the product**
3. **Prevent background reaction**
4. **Stereochemistry of the substrate**
5. **Mechanistic details of enantioselective protonations**

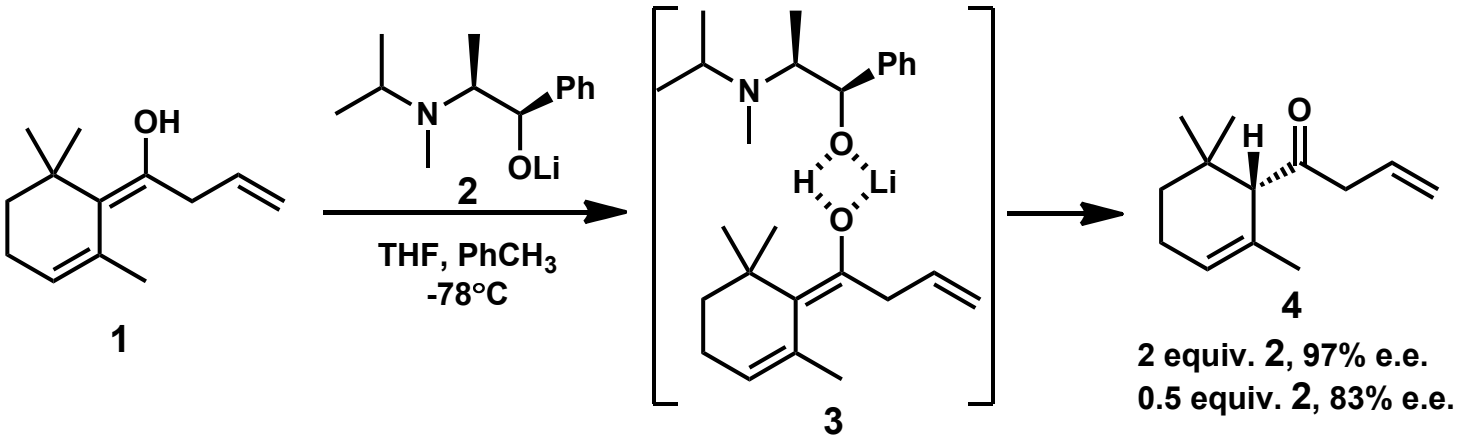


Figure 1: Enantioselective tautomerization of an isolated enol

Fehr, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 7119

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Enantioselective protonation in enzymatic systems

Decarboxylases and esterases have proved to be two popular classes of natural enzymes for the construction of α-stereocentres adjacent to ketones.

Esterases release latent enolates from prochiral substrates whereas decarboxylases generate enolates *in situ* from malonic acid derivatives

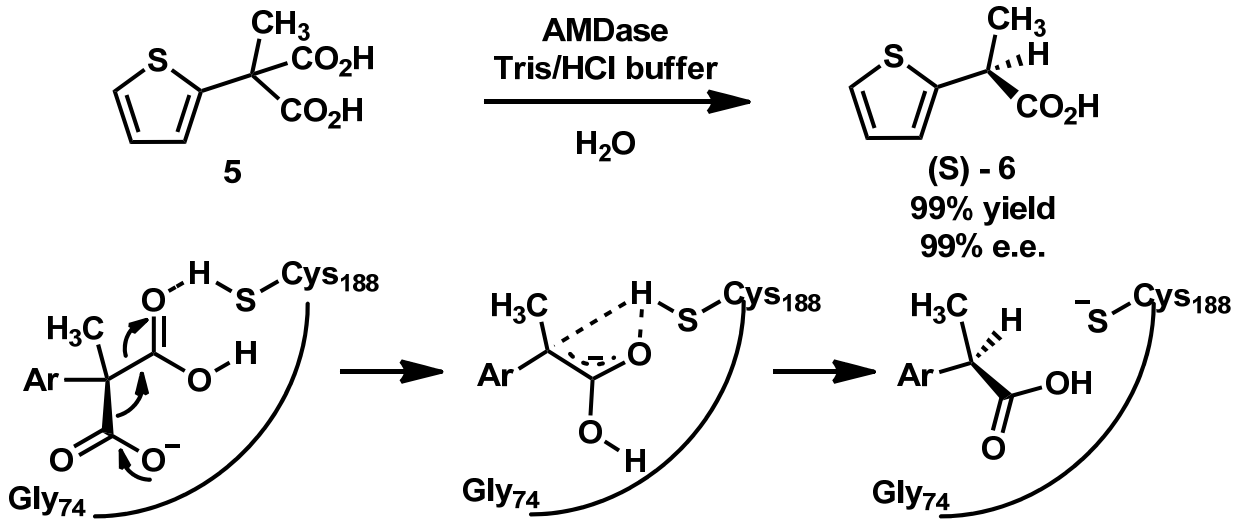


Figure 2: Enzymatic decarboxylative protonation with wild-type decarboxylase

Matoishi, K., Ueda, M., Miyamoto, K., Ohta, H. *J. Mol. Catal. B.* **2004**. *27*, 161

Enantioselective protonation in enzymatic systems

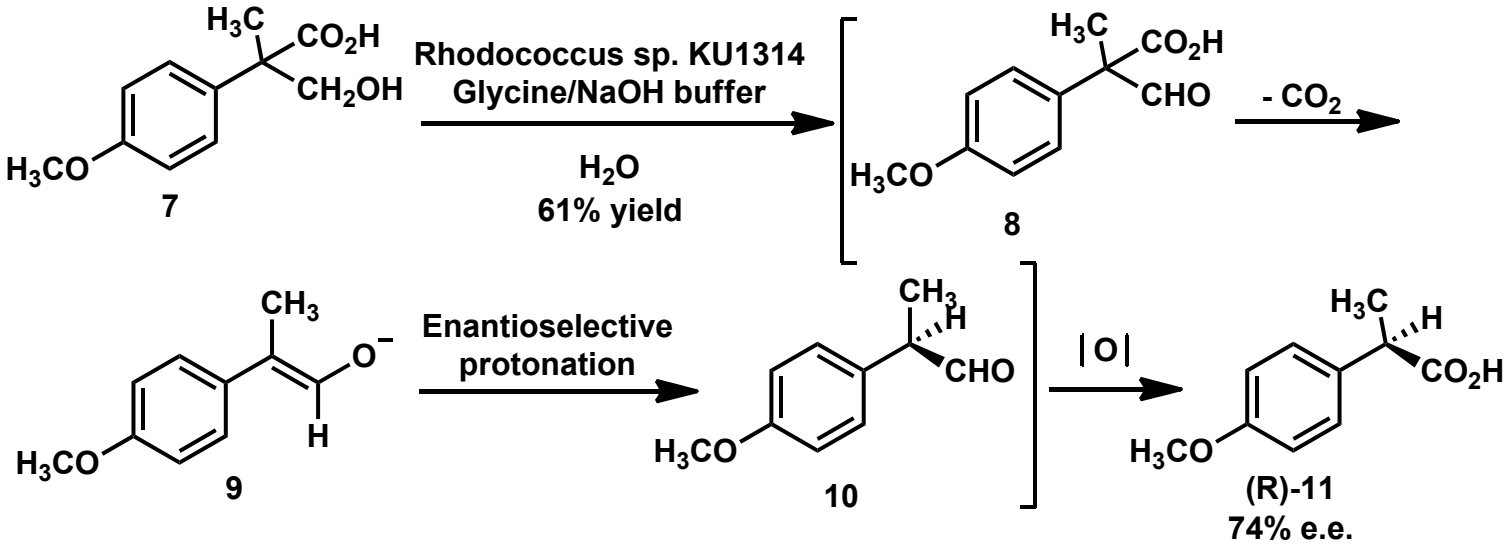
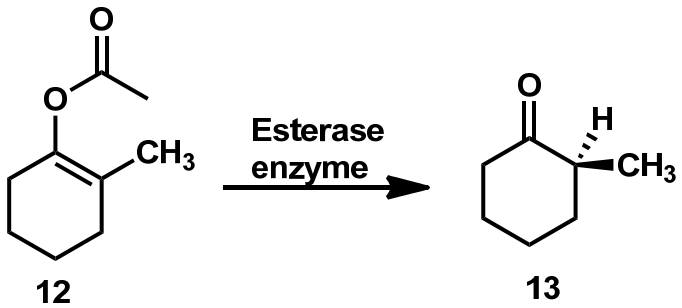


Figure 3: Enzymatic oxidation/decarboxylation/protonation/oxidation cascade



Pichia miso IAM 4682. 99% e.e.
Marchantia polymorpha esterase I, 99% e.e.

Figure 4: Enzymatic hydrolysis of enol acetates

Miyamoto, K., Hirokawa, S., Ohta, H. *J. Mol. Catal. B*: *Enzym.* **2007**, *46*, 14
Matsumoto, K., Tsutsumi, S., Ihori, T., Ohta, H. *J. Am. Chem. Soc.* **1990**, *112*, 9614
Hirata, T., Shimoda, K., Kawano, T. *Tetrahedron* **2000**, *11*, 1063

Enantioselective protonation in enzymatic systems

Advantage of enzymatic enantioselective protonation:

1. Environmental-friendly

2. Also give high yield and high e.e.

3. Demonstrate many of the key controlling elements necessary for successful enantioselective protonation

Shortage of enzymatic enantioselective protonation: Enzymatic reactions can not provide a general solution to the synthesis of enantioenriched protonation products

1. The difficulty of enzyme modification to give the unnatural antipode of product

2. The need for buffers to help stabilize enzymes or cells

3. Substrate scope is limited due to the specificity of substrate recognition

Approaches for non-enzymatic enantioselective protonation

1. The use of a chiral proton donor and/or the generation of a chiral proton acceptor intermediate

2. Catalytic generation of a chiral metal–enolate complex *in situ*

3. Coupling of a catalytic chiral proton donor to a stoichiometric achiral proton source (In this case, a specific order of thermodynamic acidity of the reaction components must be used : stoichiometric proton source > catalytic chiral protonating agent > product)

4. An accompanying balance of kinetic rates of proton transfer between all of these components must also be achieved to allow a reasonable rate of protonation through the catalysed pathway while avoiding undesired background reaction between the prochiral proton acceptor and the stoichiometric achiral proton donor.

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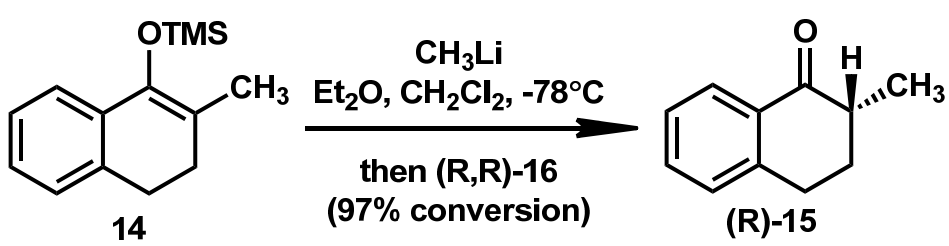
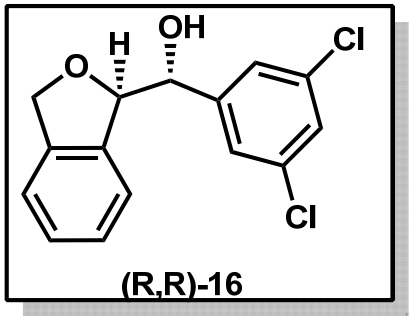
Enantioselective protonation by a chiral proton donor

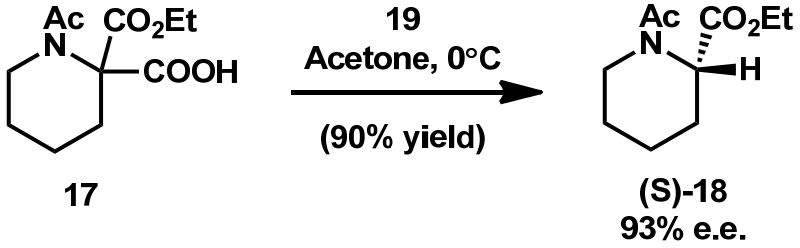
A. Kim's enolate protonation





A π–π-stacking interaction between the substrate and proton source was proposed as the chiral controlling interaction during the protonation event

B. Rouden's decarboxylative protonation



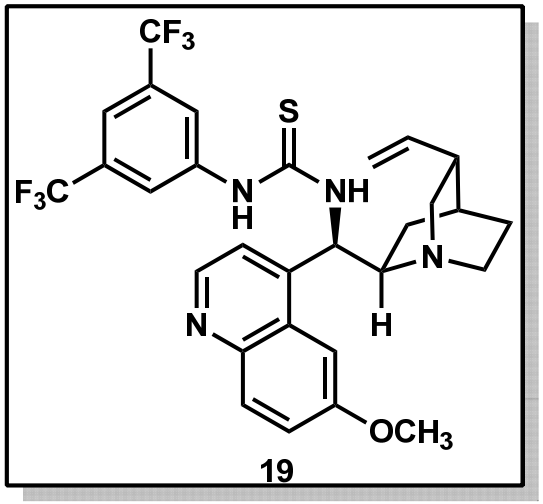


Figure 5: Enantioselective protonations by means of stoichiometric chiral Brønsted acids

Kim, B. M., Kim, H., Kim, W., Im, K. Y., Park, J. K. *J. Org. Chem*. **2004**, *69*, 5104
Amere, M., Lasne, M.-C., Rouden, J. *Org. Lett.* **2007**, *9*, 2621

Enantioselective protonation by a chiral proton donor

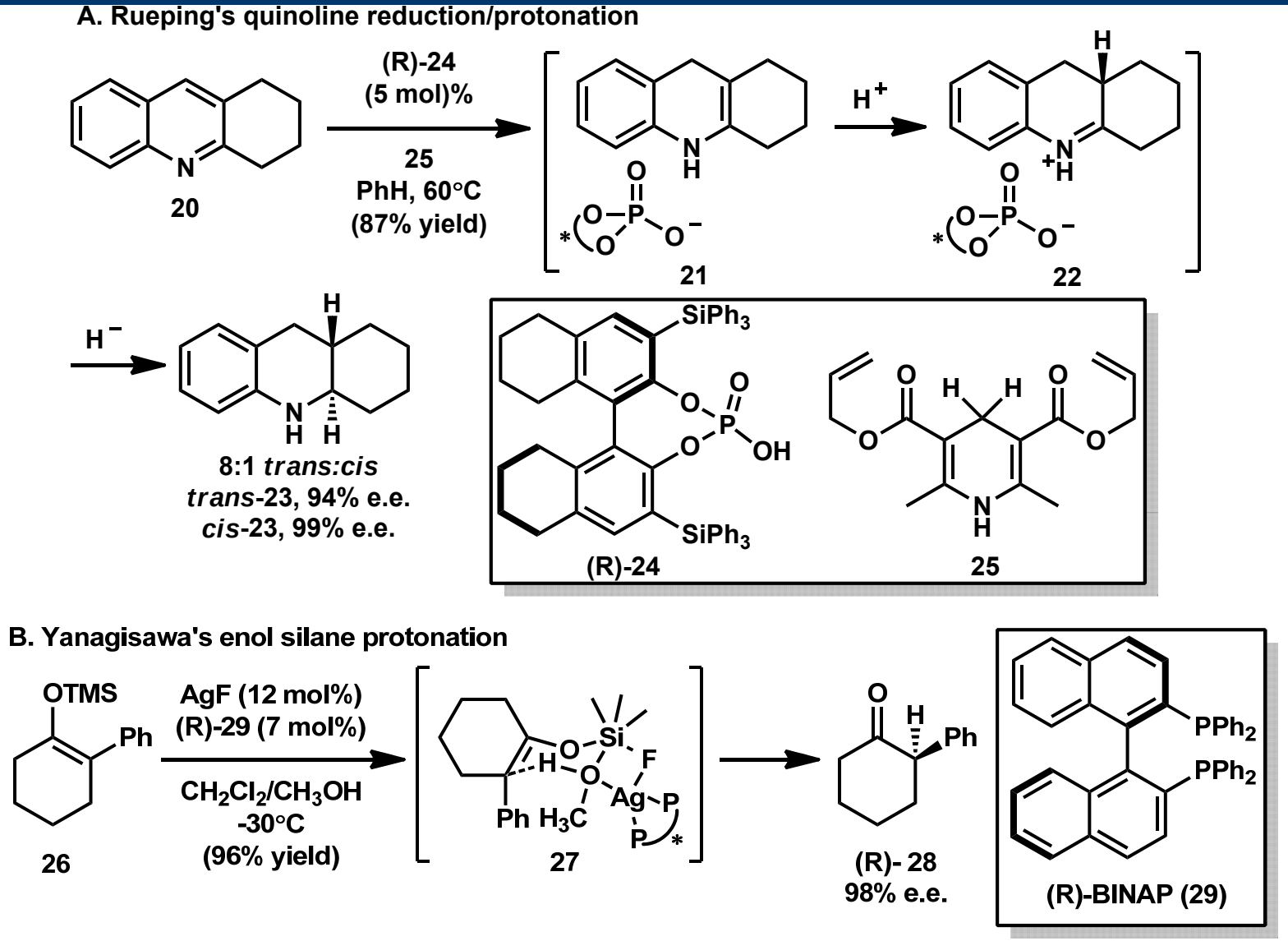


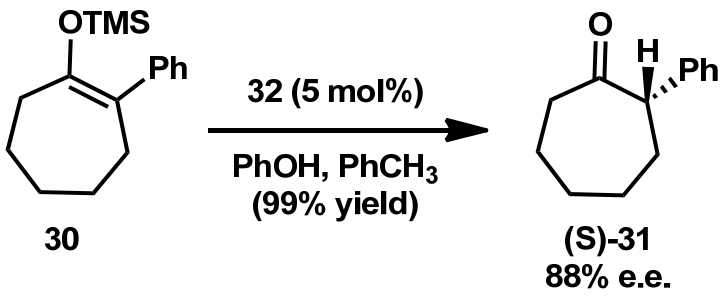
Figure 6: Enantioselective protonations by means of catalytic chiral Brønsted acids

Rueping, M., Theissmann, T., Raja, S., Bats, J. W. *Adv. Synth. Catal*. **2008**, *350*, 1001

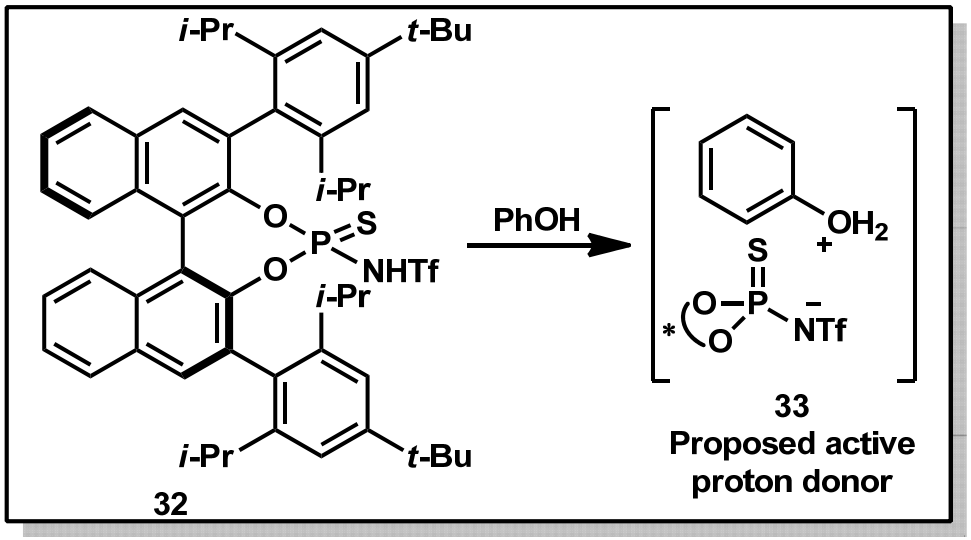
Yanagisawa, A., Touge, T. & Arai, T. *Angew. Chem. Int. Ed*. **2005**, *44*, 1546

Enantioselective protonation by a chiral proton donor

C. Yamamoto's enol silane protonation



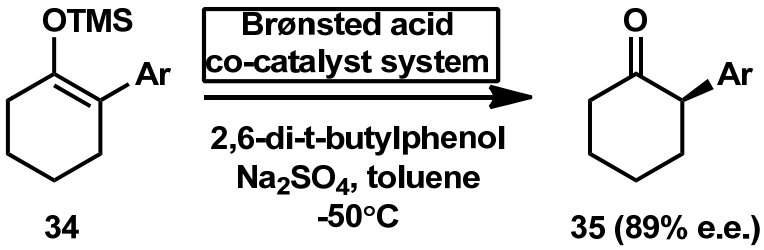
30 (S)-31 88% e.e.



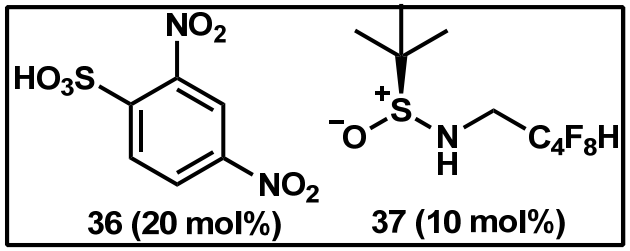
32

33 Proposed active proton donor

D. Jacobsen's enol silane protonation

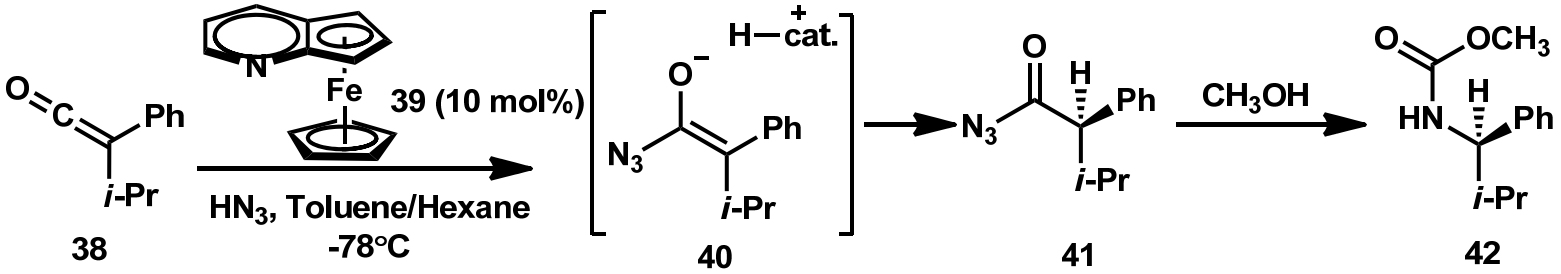


34 35 (89% e.e.)



36 (20 mol%) 37 (10 mol%)

E. Fu's addition of hydrazoic acid to ketenes followed by Curtius rearrangement



38 40 41 42 96% e.e.

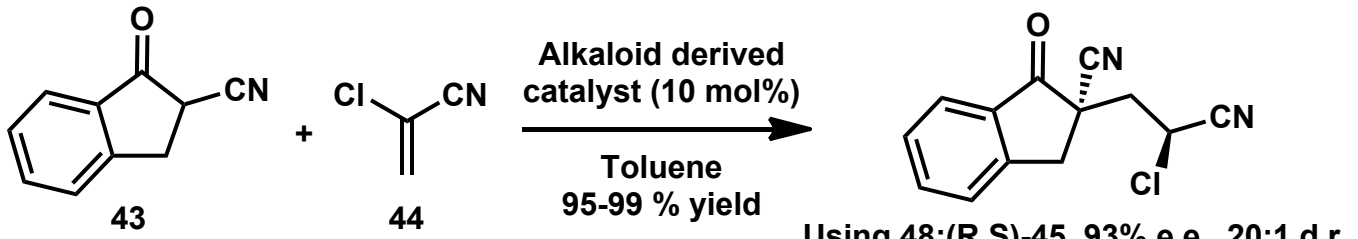
Cheon, C. H., Yamamoto, H. *J. Am. Chem. Soc*. **2008**, *130*, 9246

Beck, E. M., Hyde, A. M., Jacobsen, E. N. *Org. Lett.*, **2011**, *13*, 4260

Dai, X., Nakai, T., Romero, J. A. C., Fu, G. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 4367

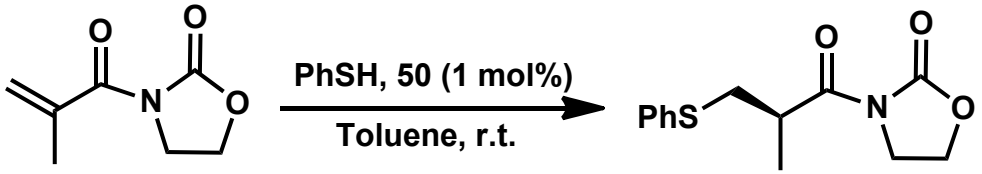
Enantioselective protonation by a chiral proton donor

F. Deng's conjugate addition/protonation

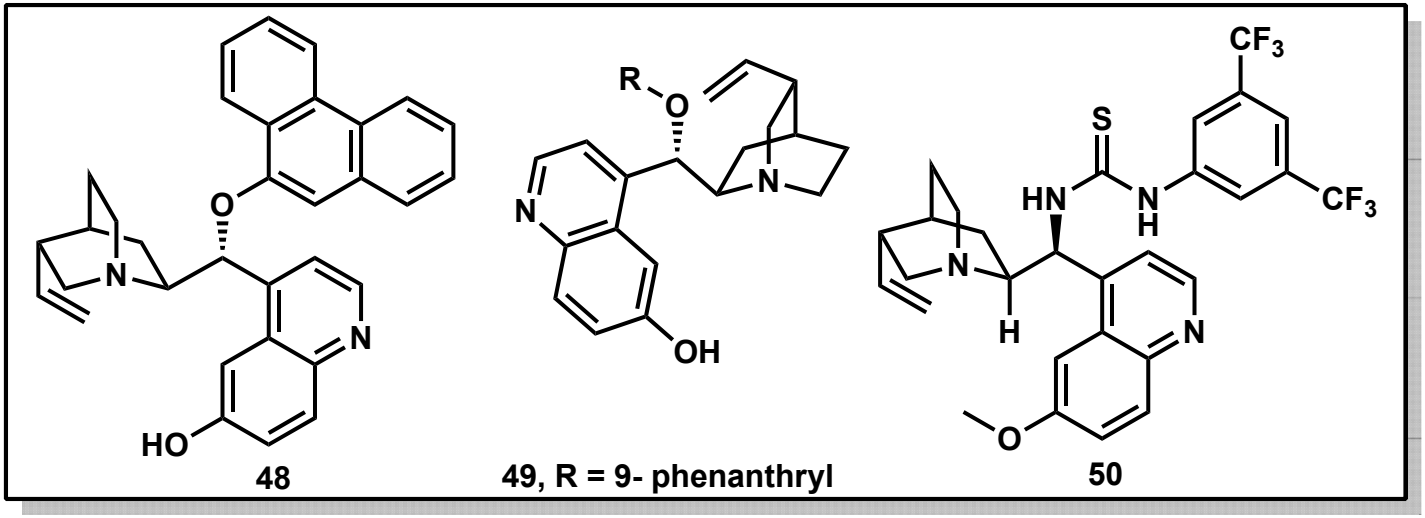


Using 48:(R,S)-45, 93% e.e., 20:1 d.r.
Using 49:(S,R)-45, 96% e.e., 20:1 d.r.
Using 50:(S,S)-45, 93% e.e., 20:1 d.r.

G. Singh's conjugate addition/protonation



90% e.e.



Wang, Y., Liu, X., Deng, L. *J. Am. Chem. Soc*. **2006**, *128*, 3928
Rana, N. K., Singh, V. K. *Org. Lett.* **2011**, *13*, 6520

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Enantioselective protonation by a chiral Brønsted base

The most common form of chiral Brønsted base used in enantioselective protonations is chiral metal enolates.

A variety of techniques for enolate generation have been used including simple deprotonations, pericyclic reactions, decarboxylations and dehalogenations.

To circumvent the challenge of stereoselective generation of acyclic enolates, the majority of methods have focused on cyclic enolate precursors.

Enantioselective protonation by a chiral Brønsted base

Rovis' protonation of chloroenolates

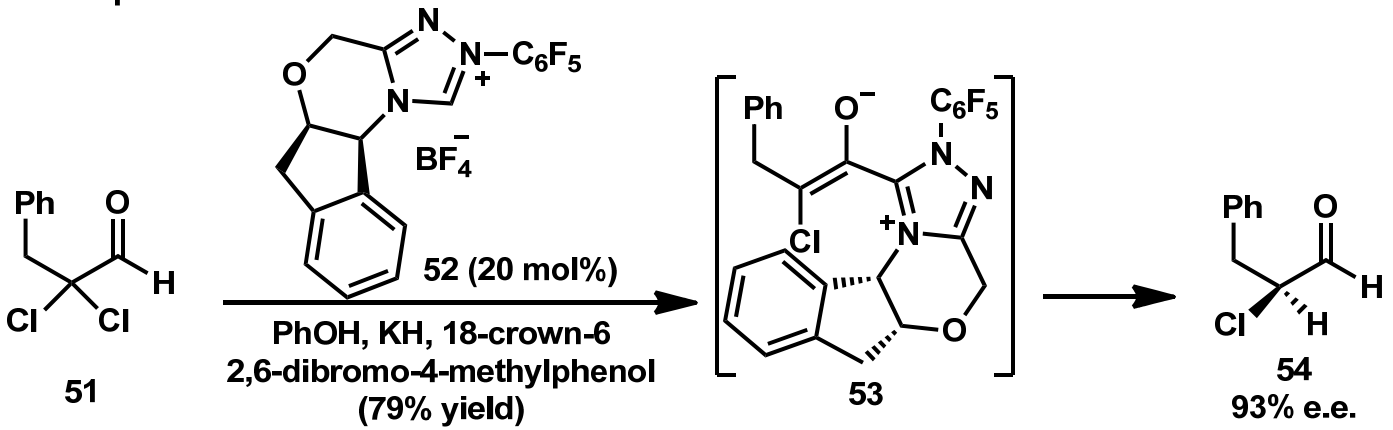

Figure 7: The use of NHC to generate chiral proton acceptors

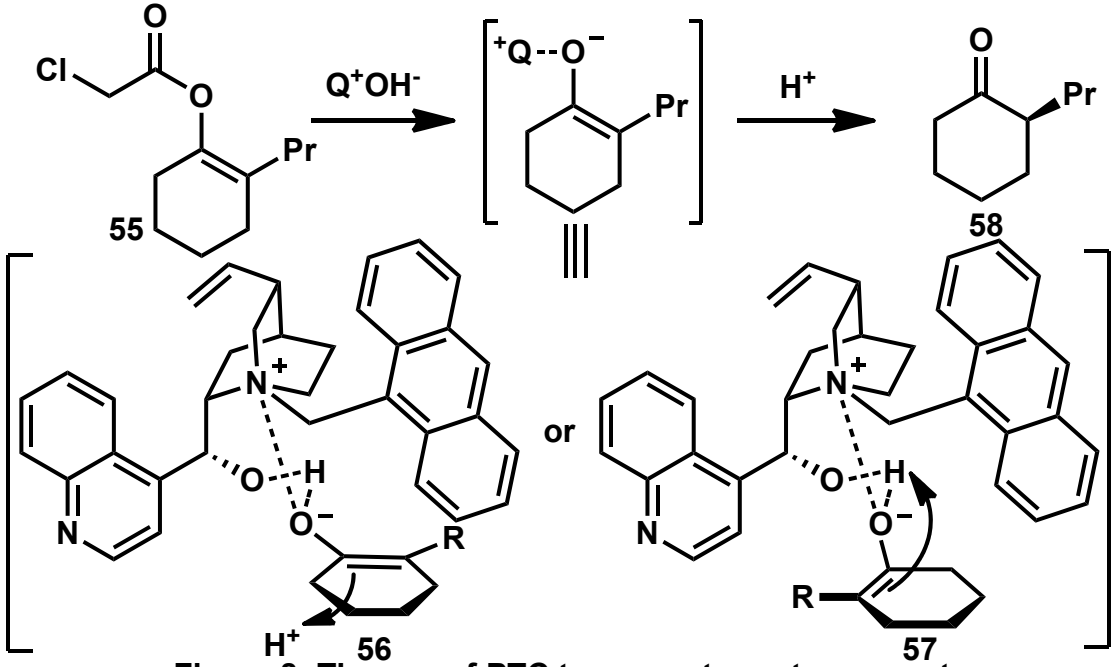

Figure 8: The use of PTC to generate proton accepter

Reynolds, N. T., Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406

Yamamoto, E., Nagai, A., Hamasaki, A., Tokunaga, M. *Chem. Eur. J.* **2011**, *26*, 7178

Enantioselective protonation by a chiral Brønsted base

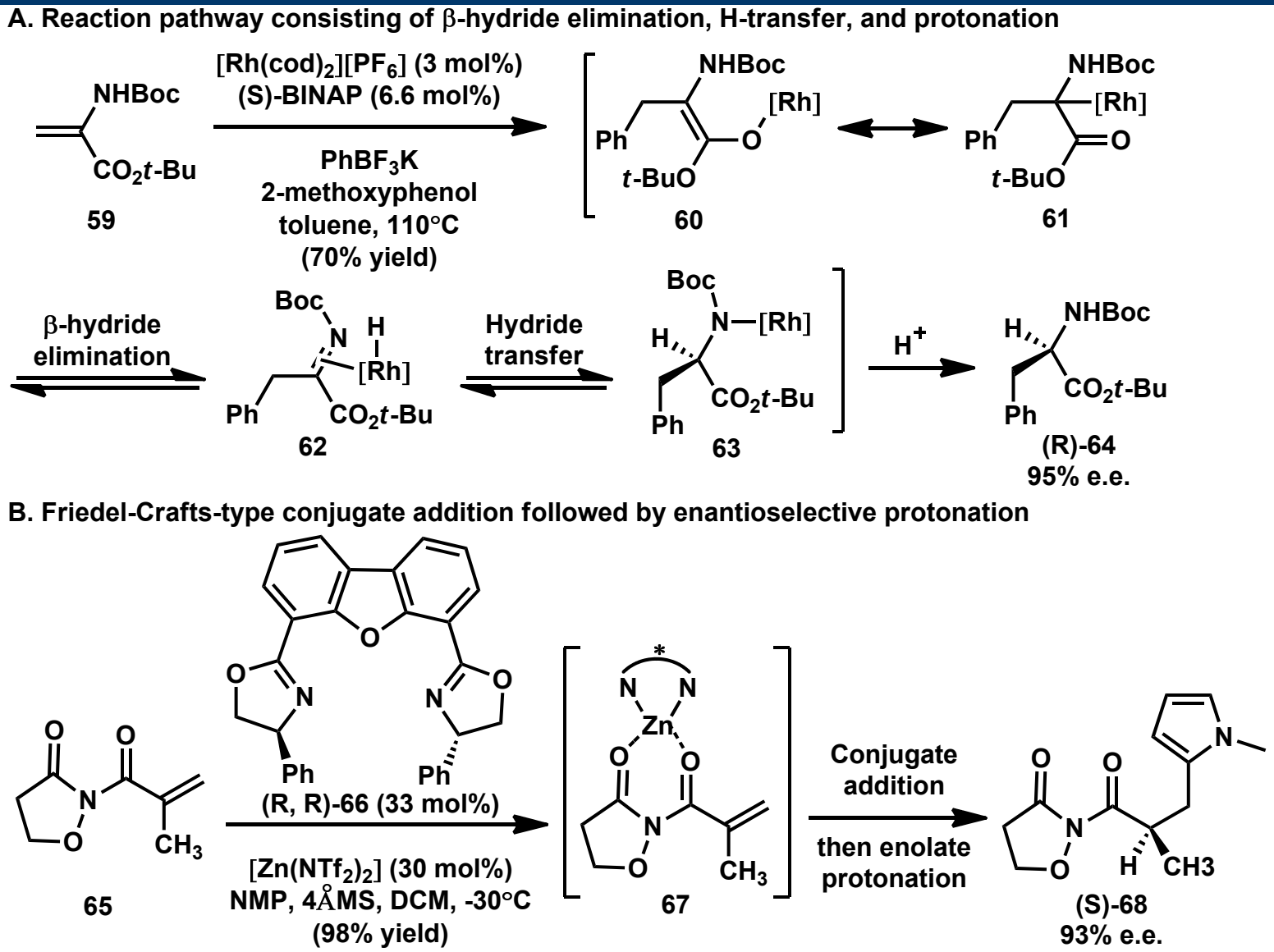

Figure 9: Conjugate addition/protonation sequences catalysed by chiral metal complexes

Navarre, L., Martinez, R., Genet, J.-P., Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159

Sibi, M. P., Coulomb, J., Stanley, L. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 9913

Enantioselective protonation by a chiral Brønsted base

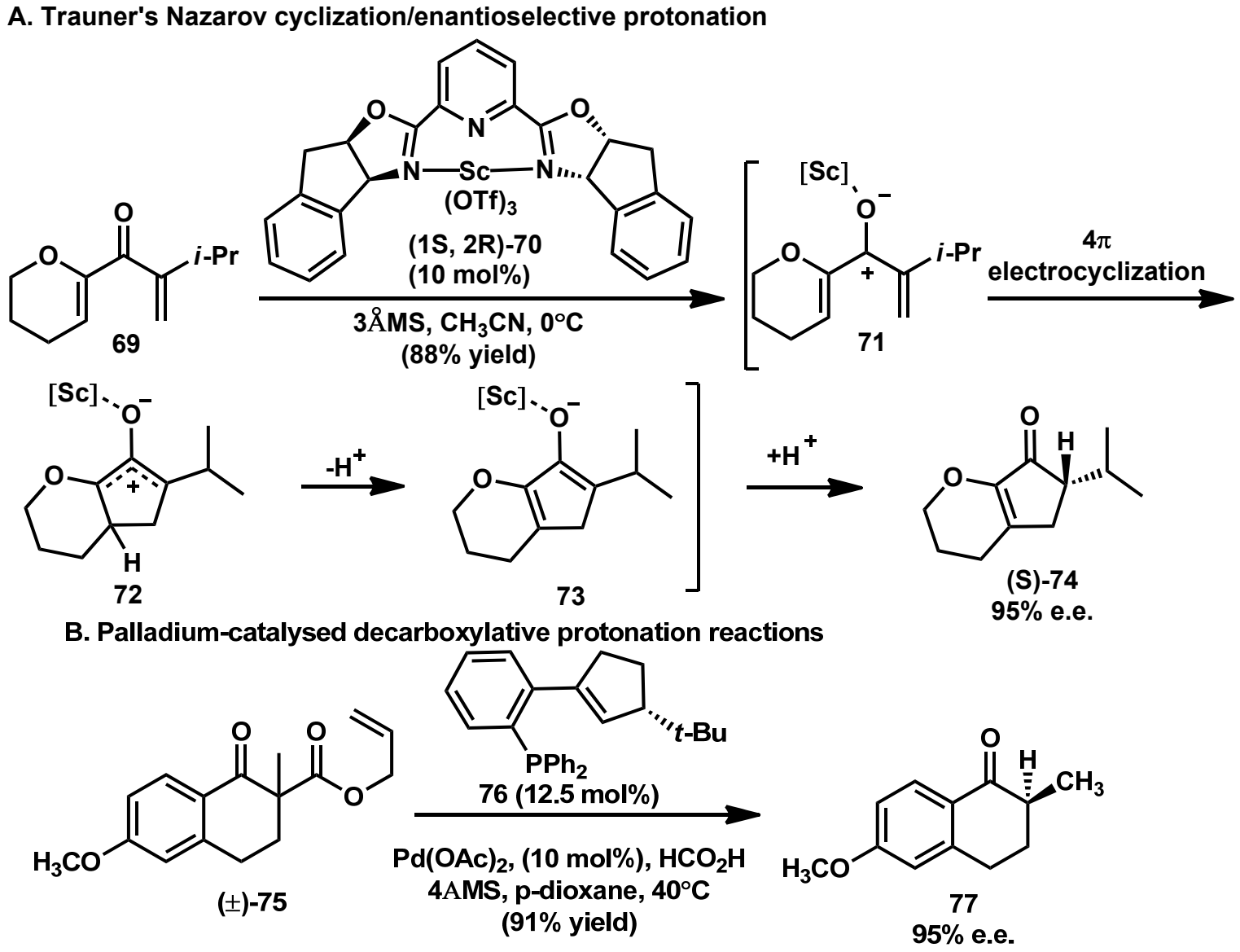

Figure 10: Transition metal-catalysed enantioselective protonation reactions

Liang, G., Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544

Marinescu, S. C., Nishimata, T., Mohr, J. T., Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039

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Enantioselective H-atom transfer

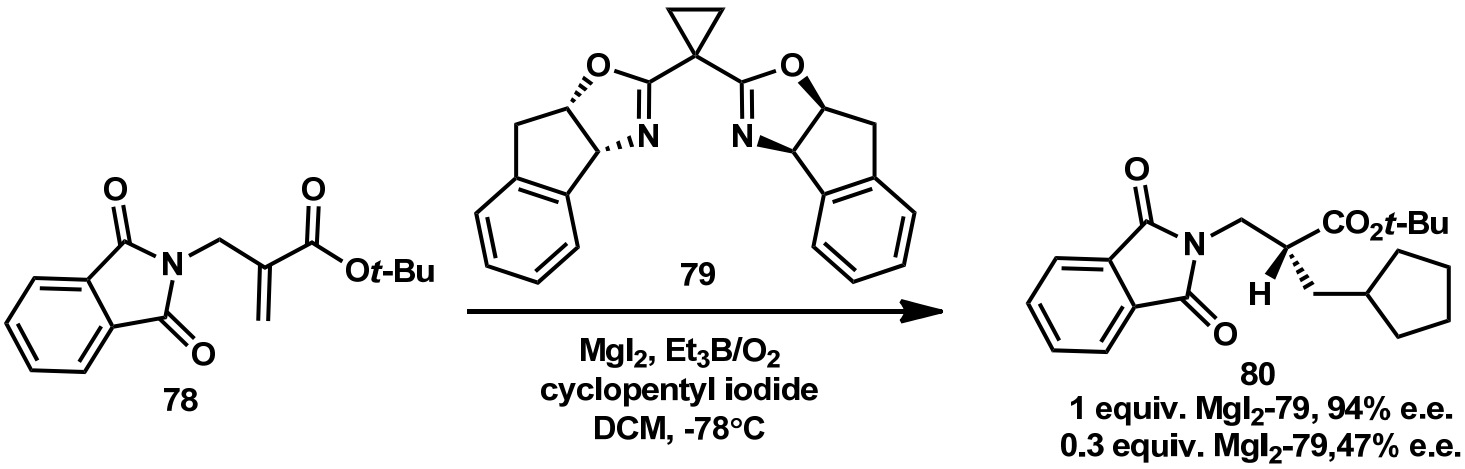

Figure 10: Radical conjugate addition followed by enantioselective H-atom transfer.

Mg·bis(oxazoline) complexes effectively promoted radical conjugate addition to form the enolate followed by enantioselective quenching of the radical intermediate by H-atom transfer

Sibi, M. P., Patil, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1235

Conclusion

Introduced several enantioselective enzymatic protonation reactions and it's advantage and shortage

Introduced a lot of techniques for achieving enantioselective protonation in laboratories

The current level of mechanistic understanding in nearly all of the enantioselective protonation reactions reported to date remains relatively immature.

Thanks for your attention!