

Organocatalysis in Multicatalytic Strategies

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New types of reactivities (unattainable by use of either catalyst alone)



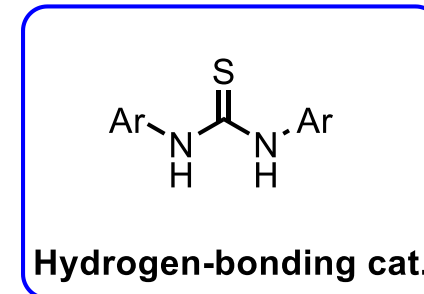
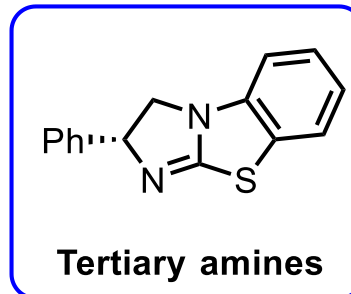
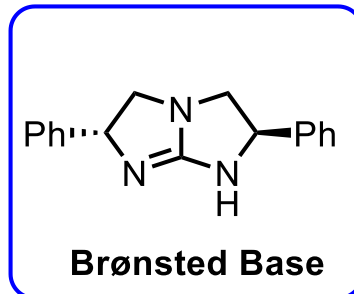
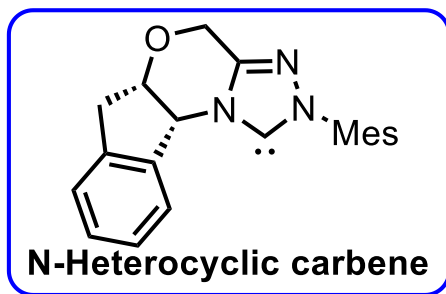
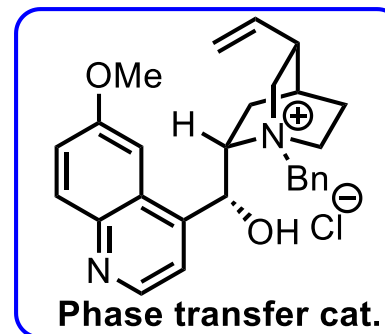
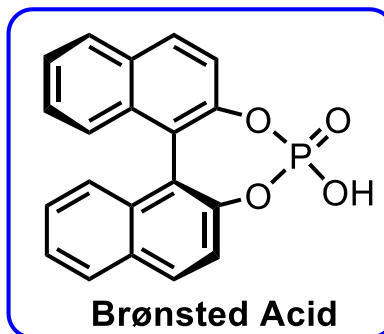
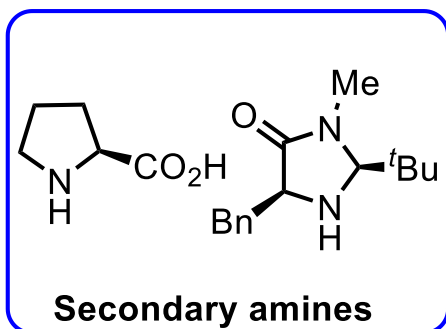
Improvement of stereocontrol



Reaction efficiency and broad substrate scope



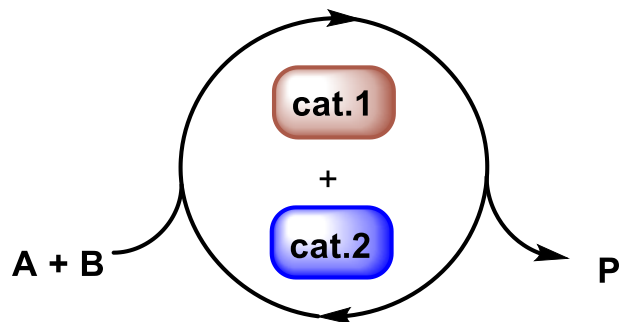
Compatibility of catalysts, substrates, intermediates and solvents



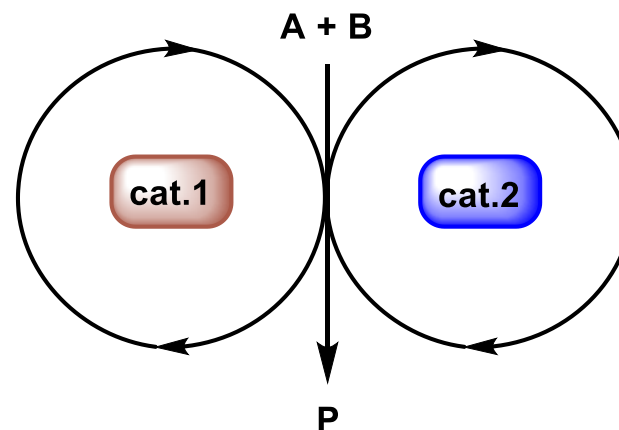
Pd, Rh, Ru, Cu, Ni, Zn, Fe, Ir, Co, Mn, Ti, Y, In, Nb, Au, Ag, Pt, V

Classification of Multicatalytic Strategies

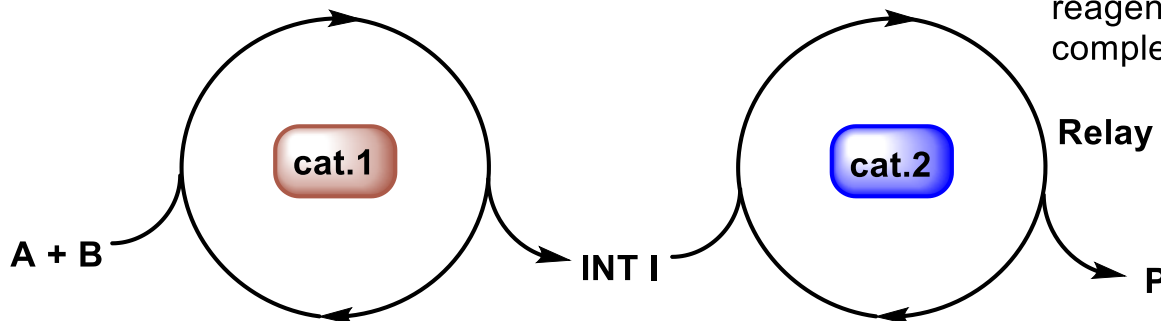
A
Cooperative Catalysis



B
Synergistic Catalysis



C
Sequential or Relay Catalysis

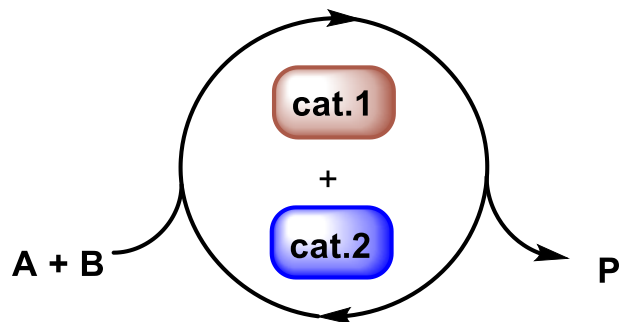


Sequential Catalysis: addition of another catalyst, reagent, or change in reaction conditions after completion of the 1st catalytic cycle

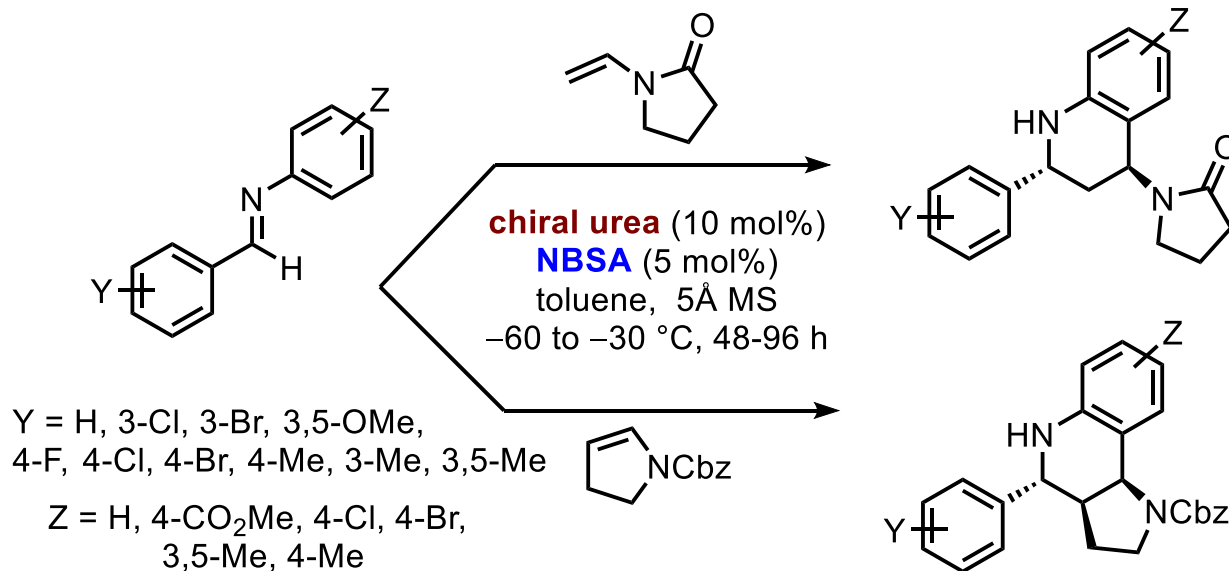
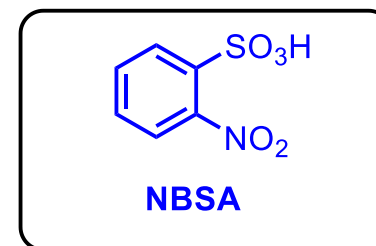
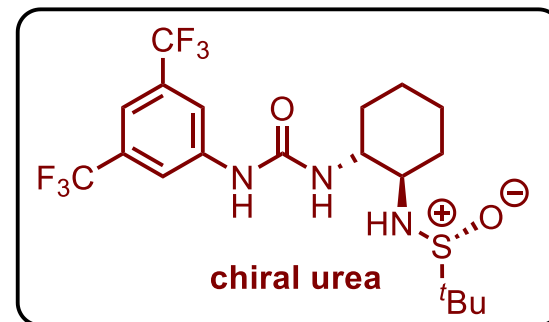
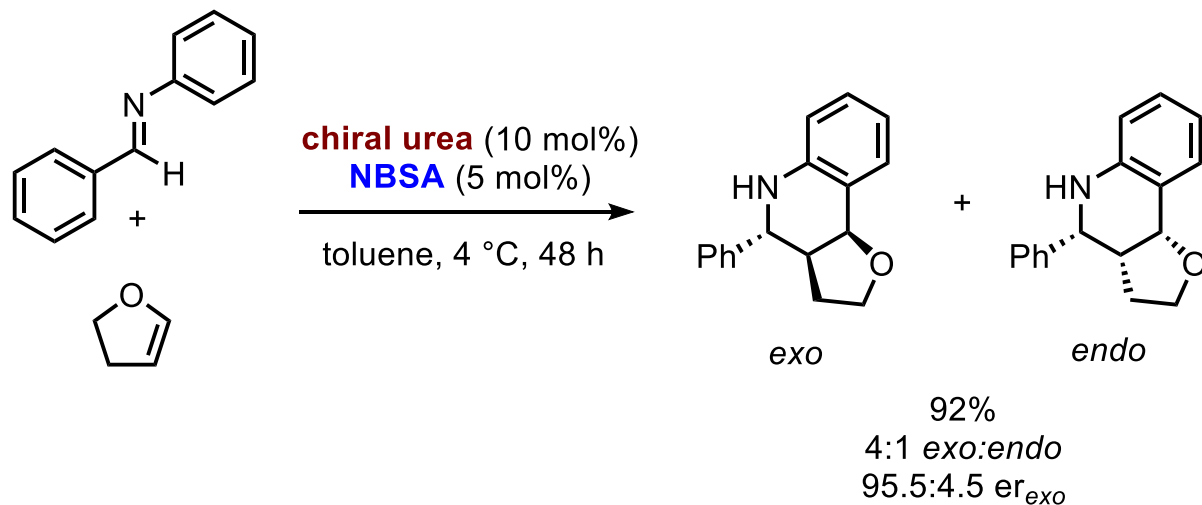
Relay Catalysis: no change in reaction conditions

A

Cooperative Catalysis



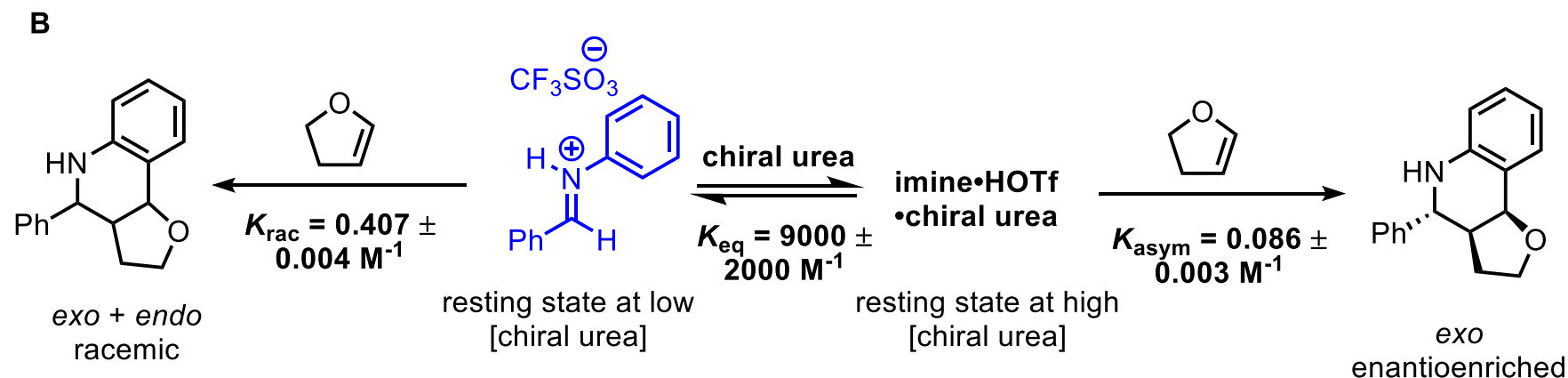
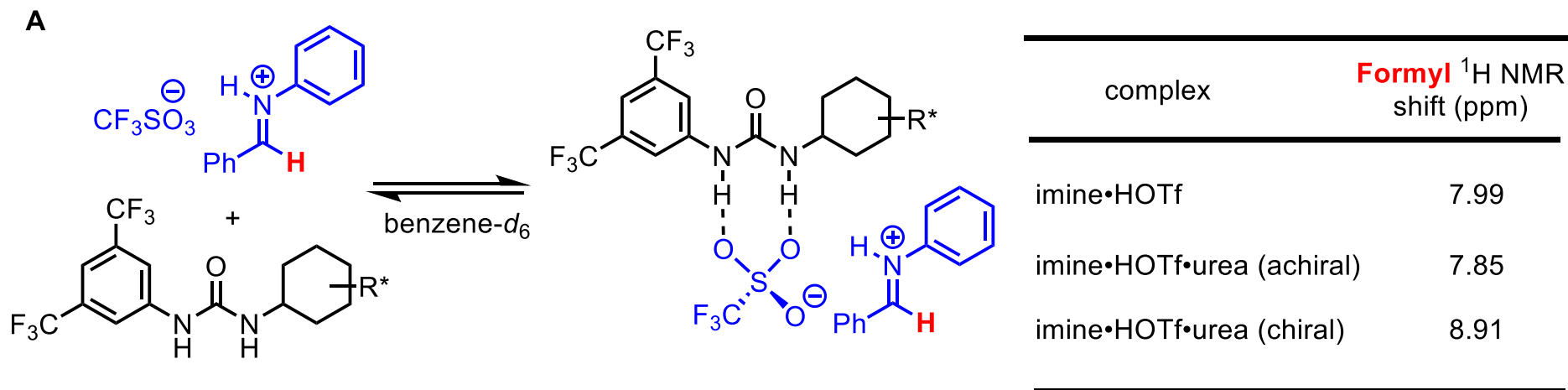
Cooperative Catalysis – Brønsted Acid/Chiral Urea



15 examples
 72-92%
 >20:1 dr
 97.5:2.5 – >99:1 *er*

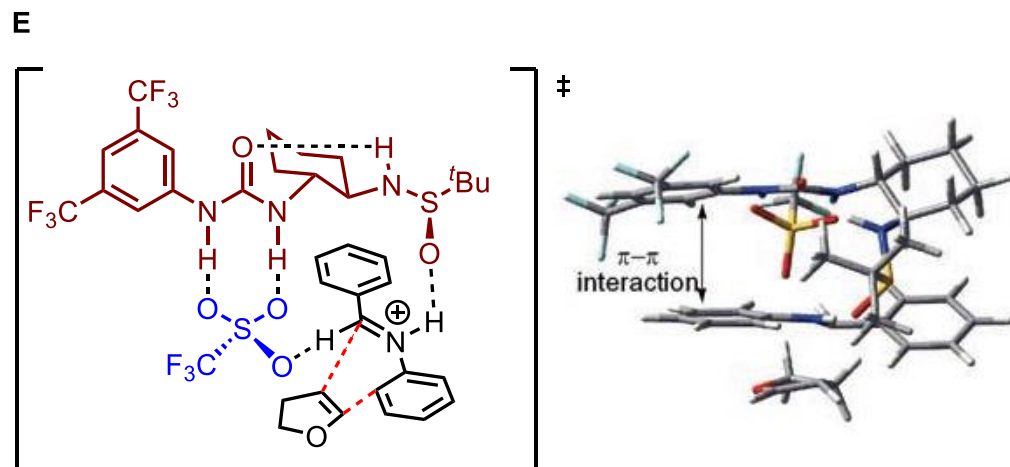
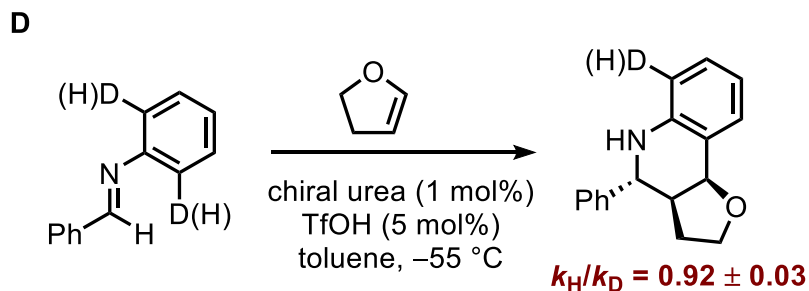
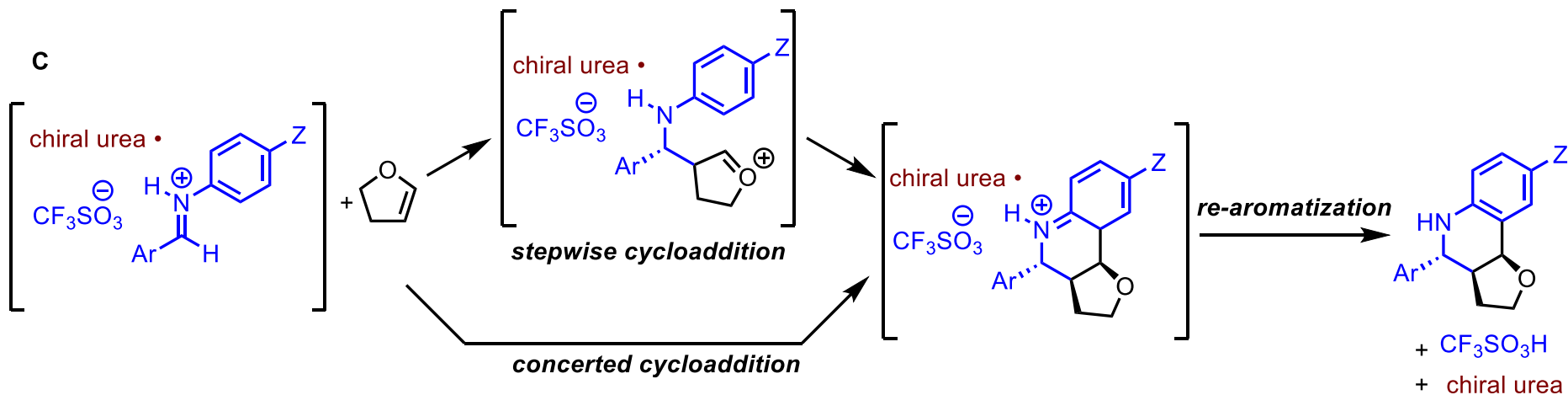
14 examples
 45-73%
 1.4:4.2 dr
 95:5 – 99:1 *er*

Cooperative Catalysis – Brønsted Acid/Chiral Urea



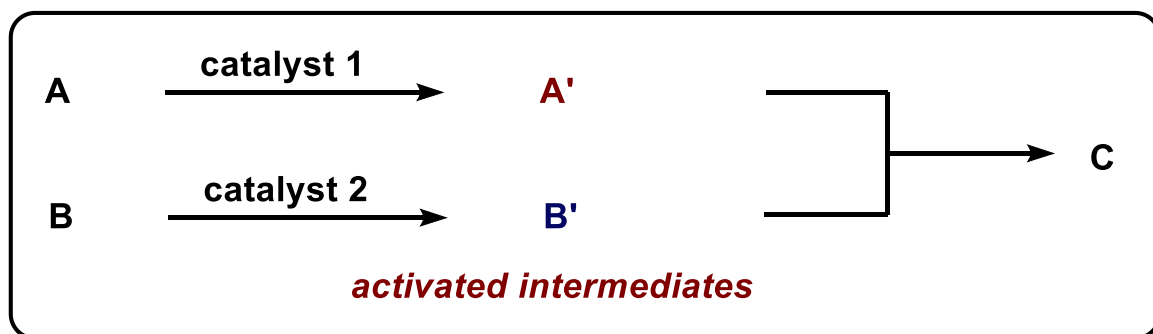
$$\text{Rate} = d[\text{product}]/dt = k_{\text{rac}}[\text{imine}\cdot\text{HOTf}][\text{Nuc}] + k_{\text{asym}}[\text{imine}\cdot\text{HOTf}\cdot\text{chiral urea}][\text{Nuc}]$$

Cooperative Catalysis – Brønsted Acid/Chiral Urea

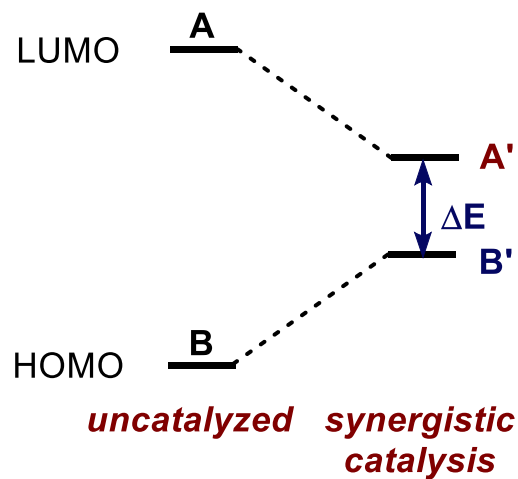
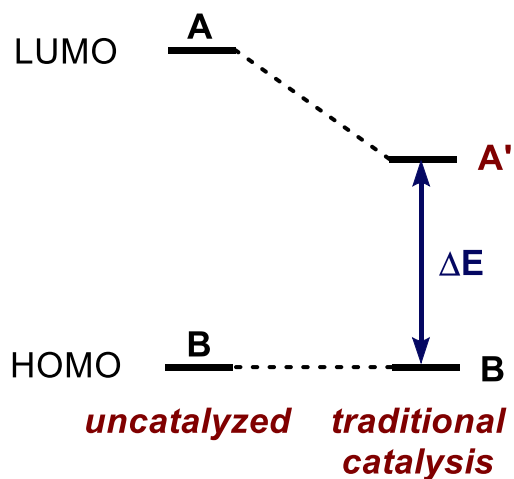
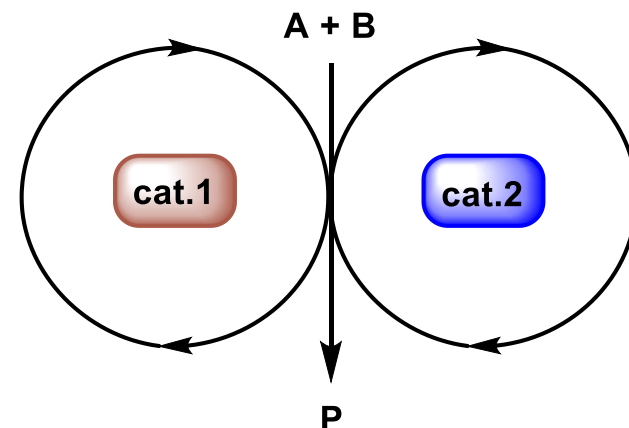


Synergistic Catalysis – Definition

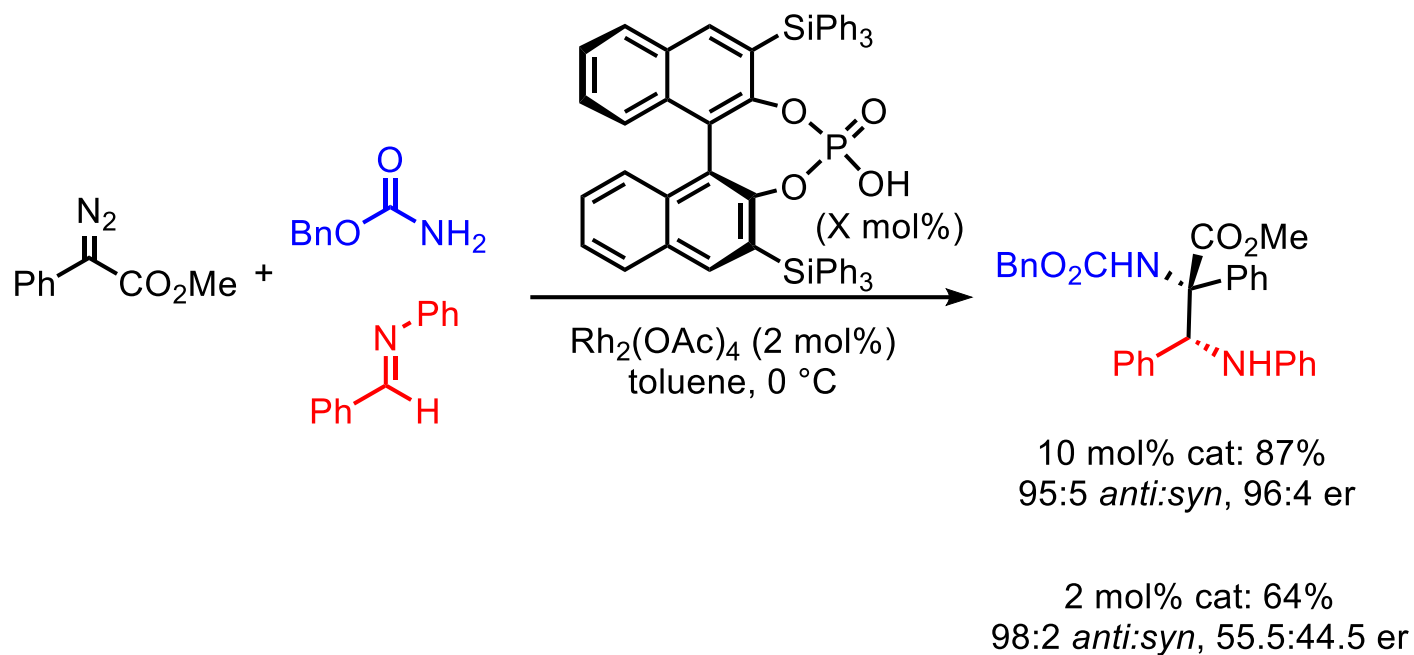
Synergistic Catalysis (MacMillan):



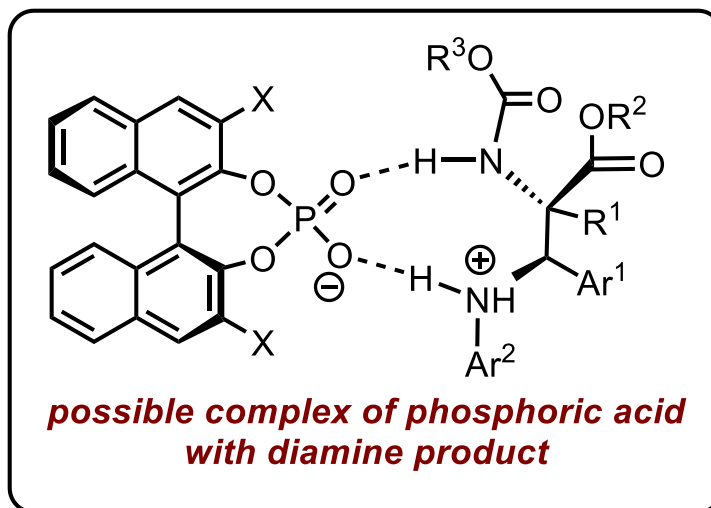
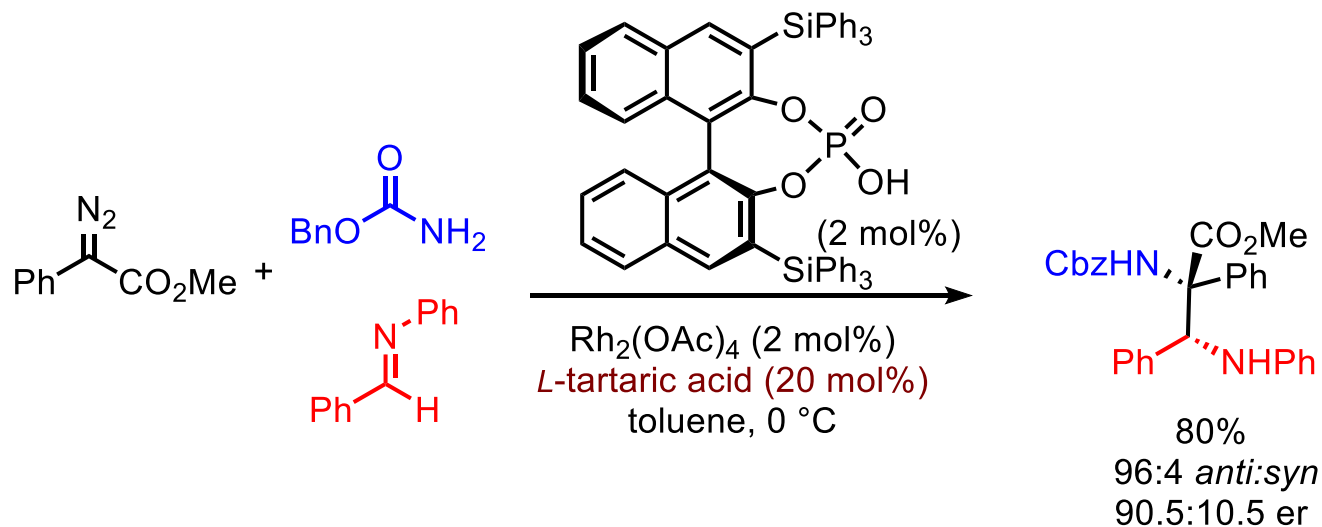
Synergistic Catalysis (Schreiner):



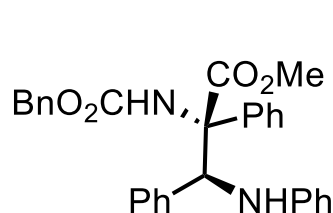
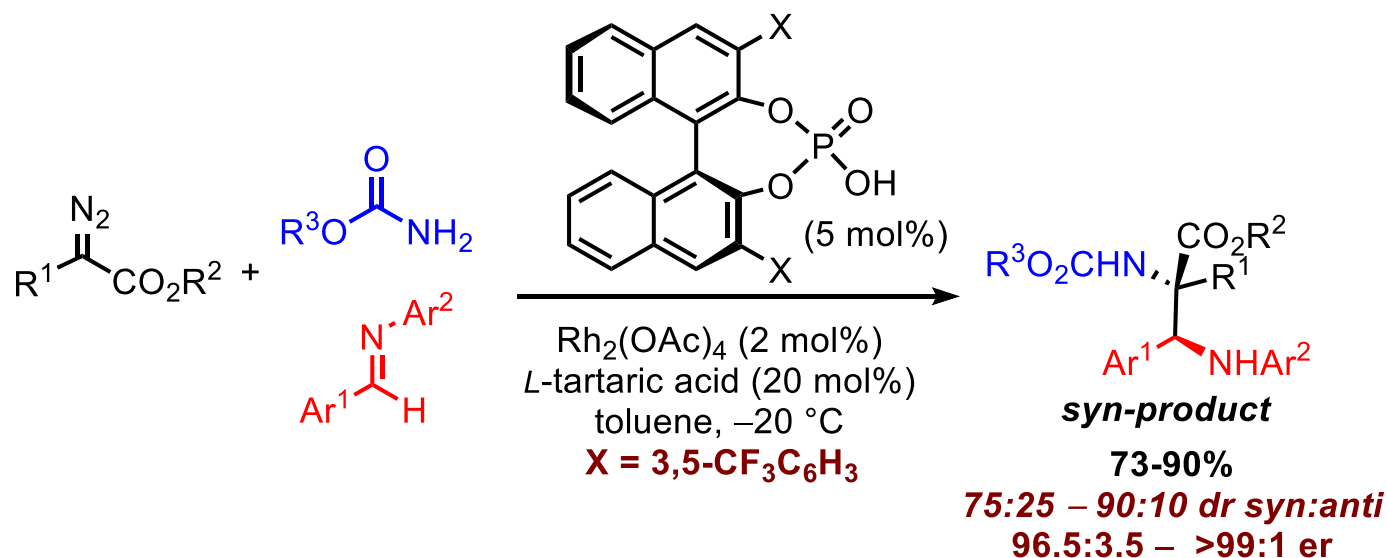
Synergistic Catalysis – Brønsted acid/Rh-Catalysis



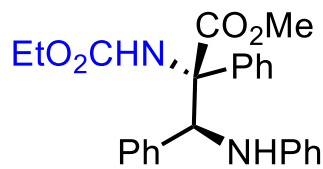
Synergistic Catalysis – Brønsted acid/Rh-Catalysis



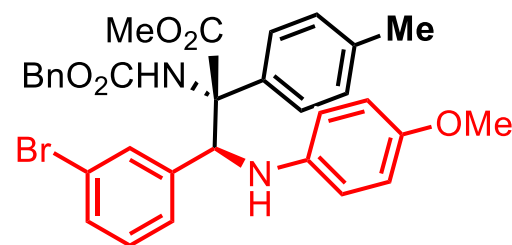
Synergistic Catalysis – Brønsted acid/Rh-Catalysis



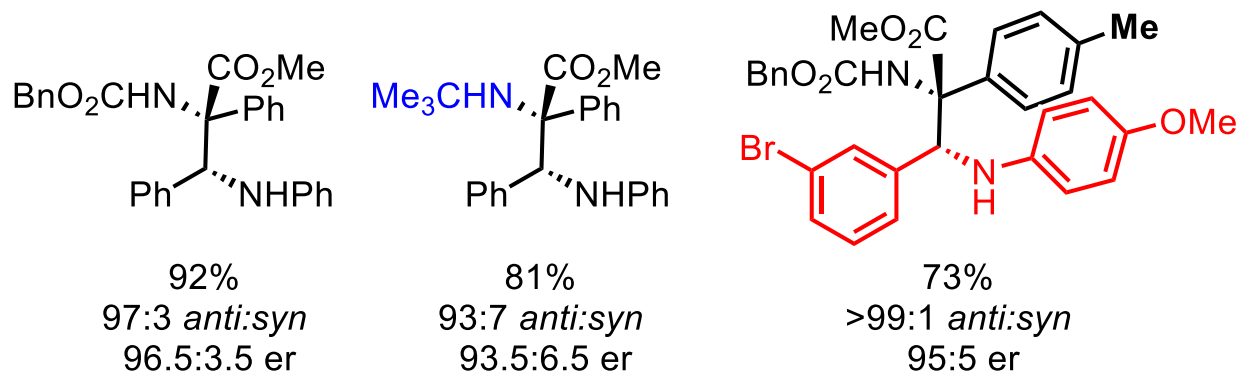
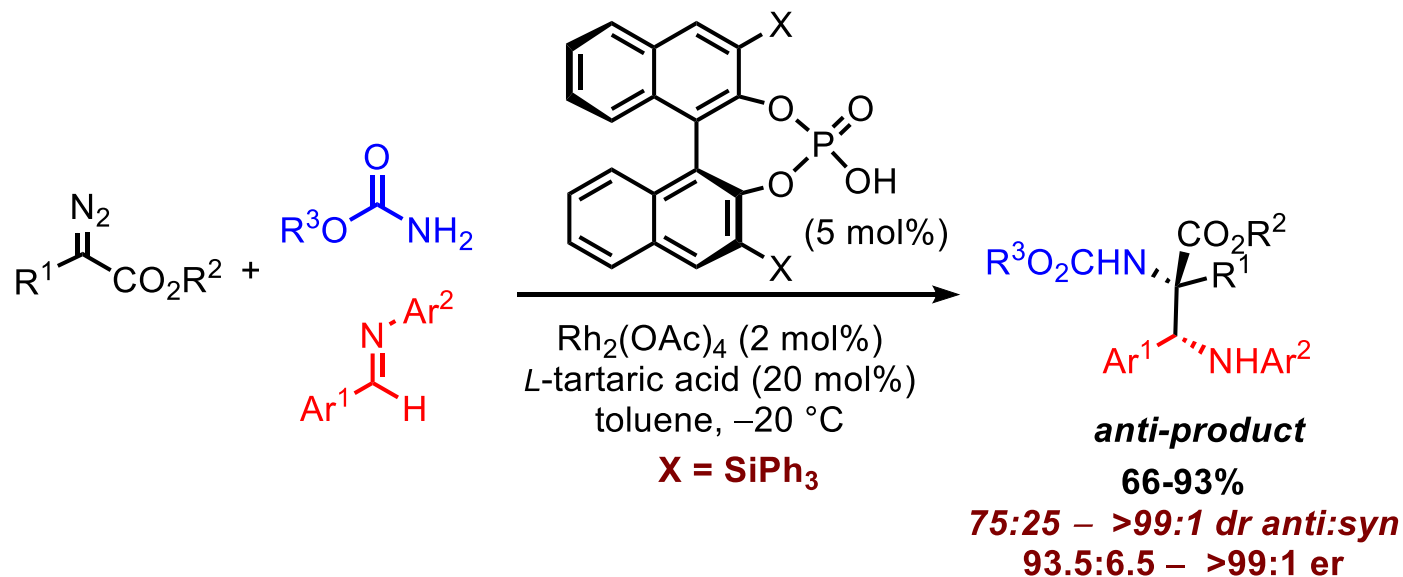
90%
 90:10 *syn:anti*
 98:2 *er*

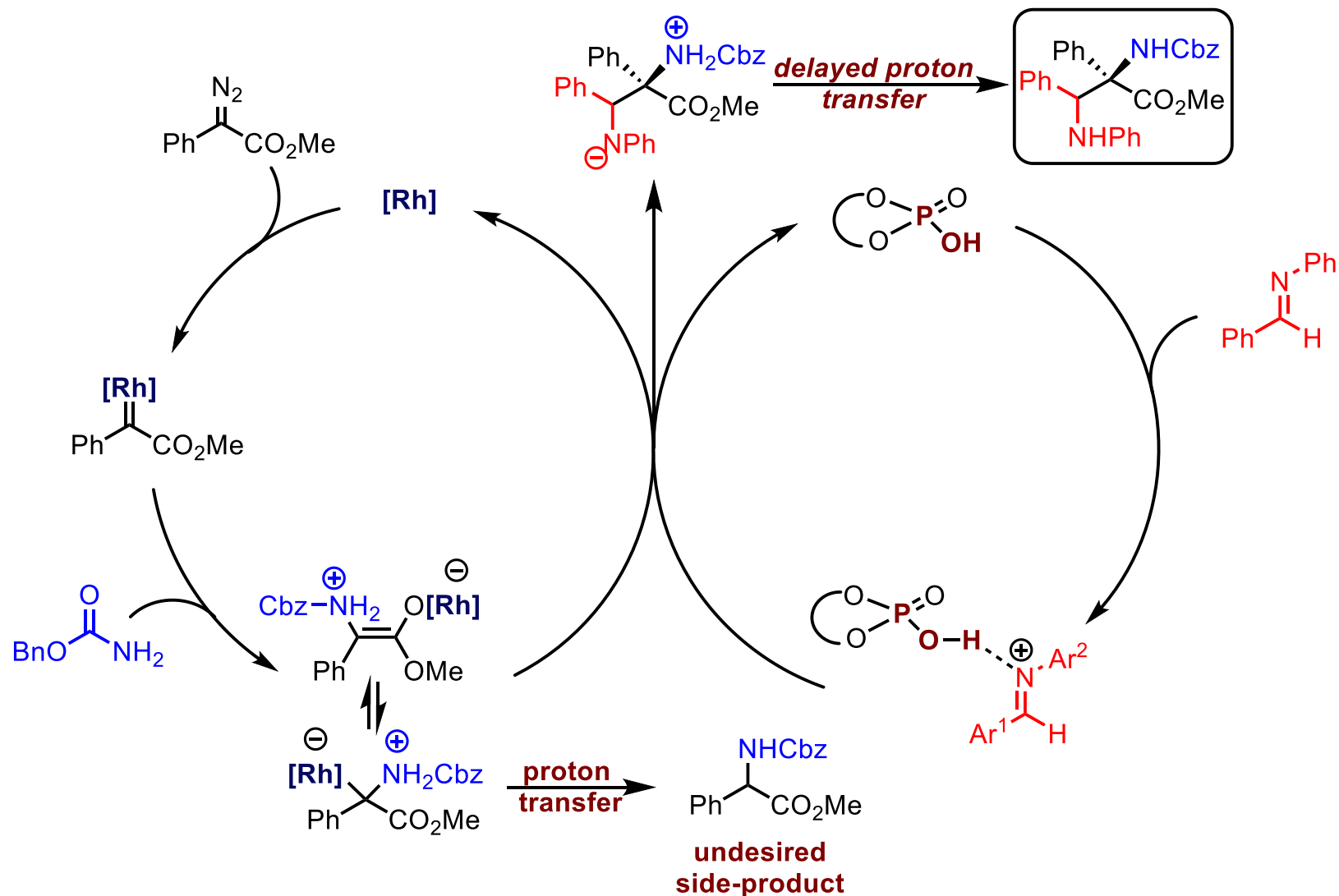


84%
 87:13 *syn:anti*
 98.5:1.5 *er*

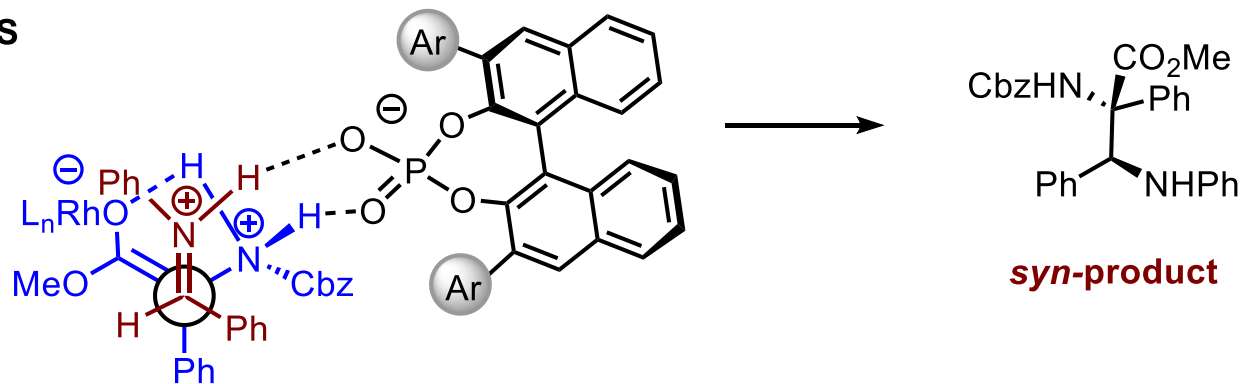


73%
 75:25 *syn:anti*
 >99:1 *er*

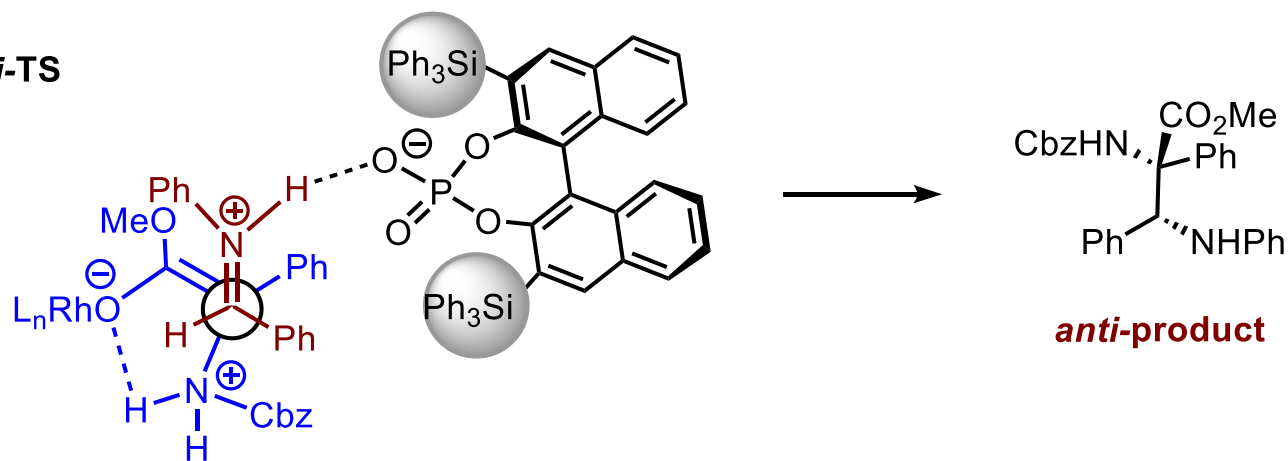




syn-TS

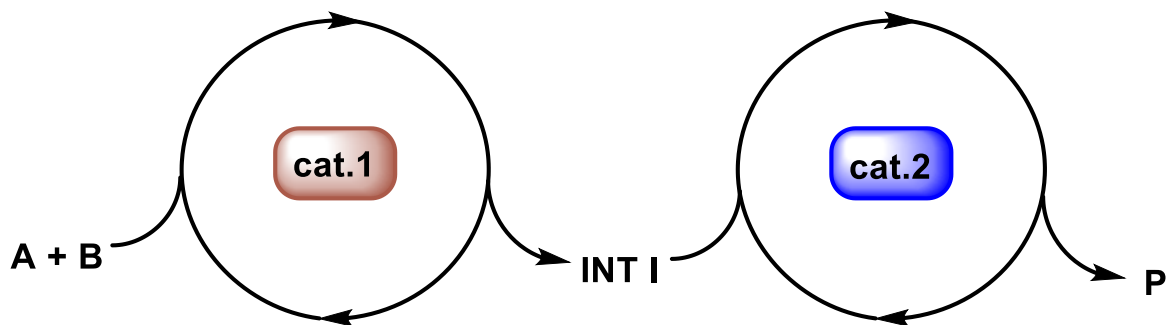


anti-TS



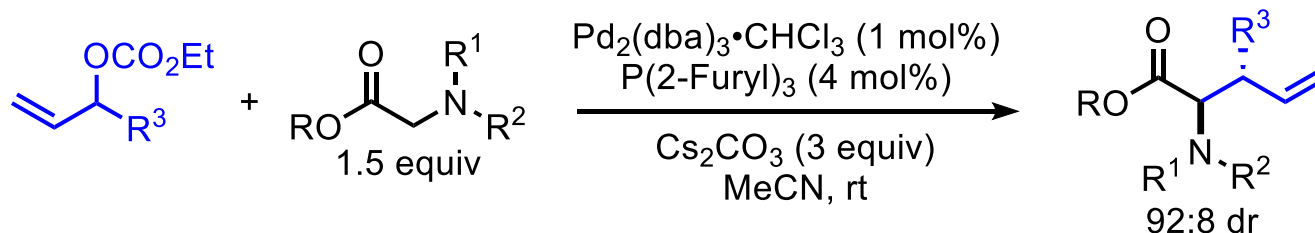
C

Relay Catalysis



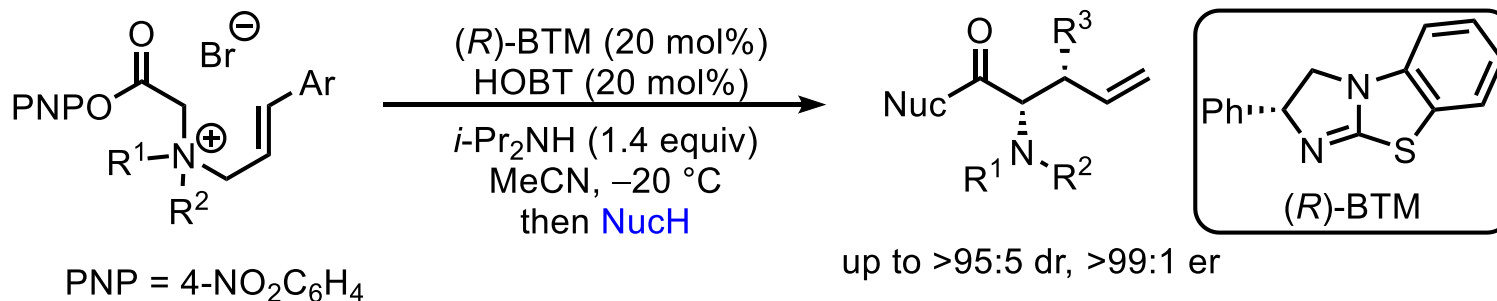
Relay Catalysis – Isothiourea/Pd-Catalysis

a) Tambar, 2011: Pd-catalyzed allylic amination and [2,3]-rearrangement



■ Pd-catalyzed allylic amination ■ [2,3]-Rearrangement gives *anti*-product

b) Smith, 2014: Enantioselective organocatalytic [2,3]-rearrangement



■ Problematic, low yielding salt isolation ■ HOBT additive necessary

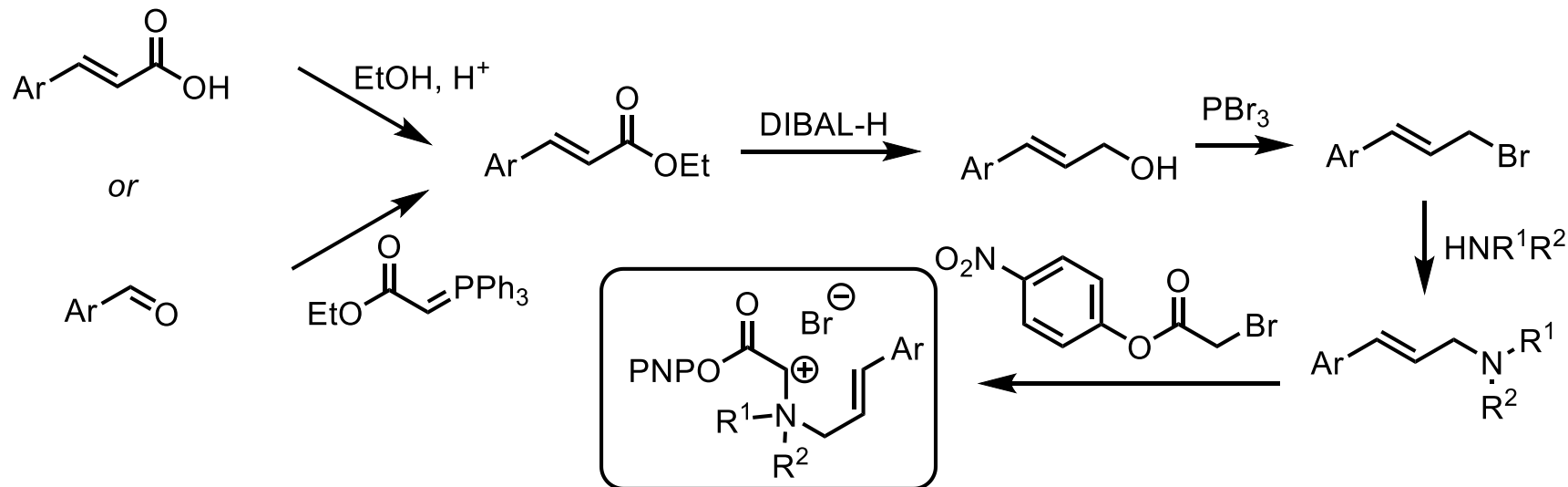
a) A. Soheili, U. K. Tambar, *J. Am. Chem. Soc.* **2011**, *133*, 12956-12959

b) T. H. West, D. S. B. Daniels, A. M. Z. Slawin, A. D. Smith, *J. Am. Chem. Soc.* **2014**, *136*, 4476-4479;

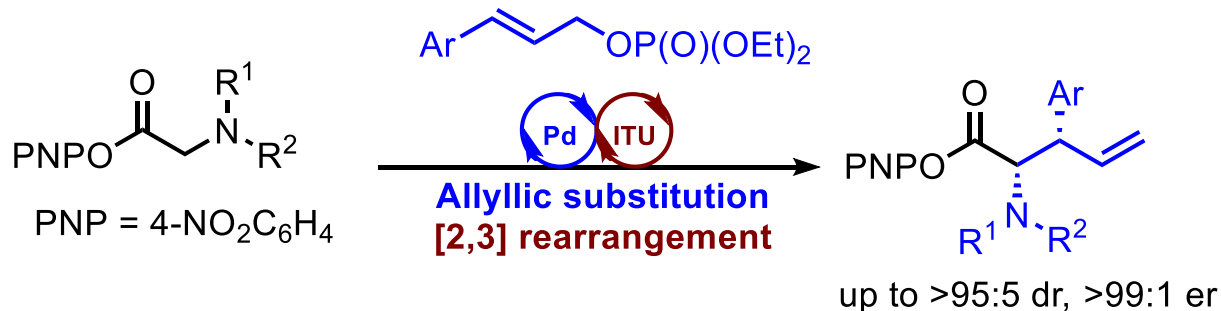
T. H. West, S. S. M. Spoehrle, A. D. Smith, *Tetrahedron* **2017**, *73*, 4138-4149

Relay Catalysis – Isothiourea/Pd-Catalysis

Synthesis of ammonium salts:



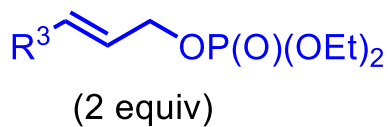
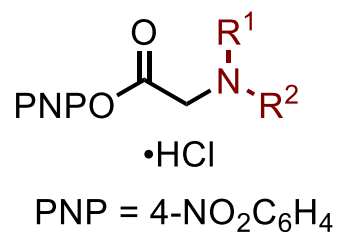
c) Smith, 2017: Enantioselective Pd/Isothiourea relay catalysis



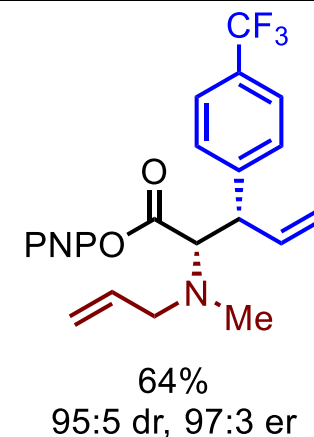
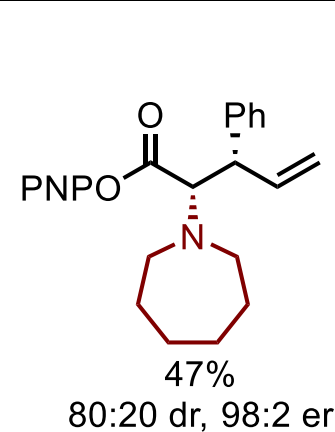
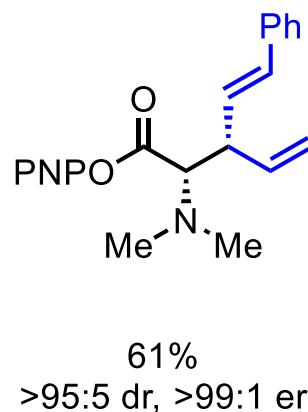
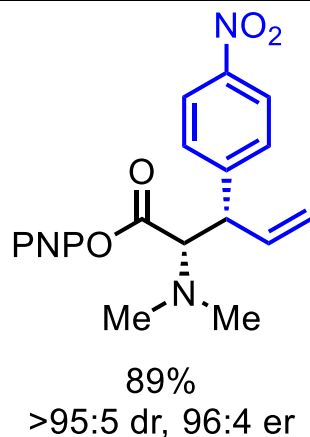
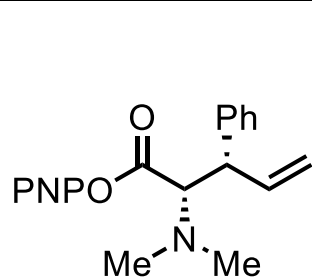
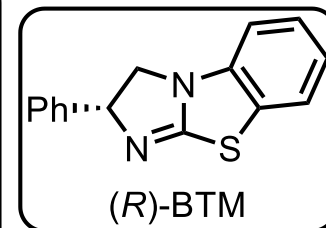
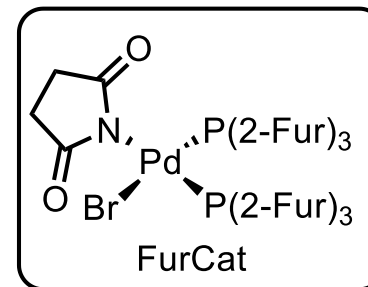
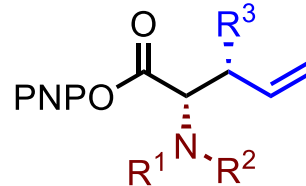
Challenges:

- Compatibility of Lewis Base, Pd, and glycine aryl esters
- Overcoming inherent substrate bias to form *anti*-products

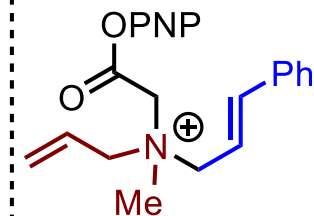
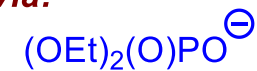
Relay Catalysis – Isothiourea/Pd-Catalysis



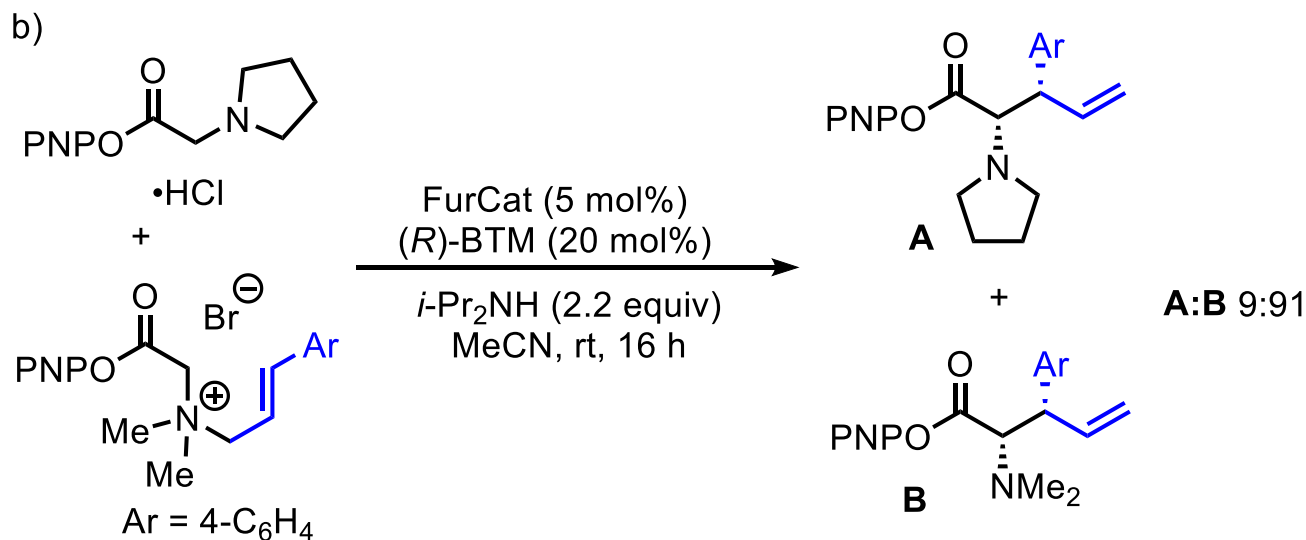
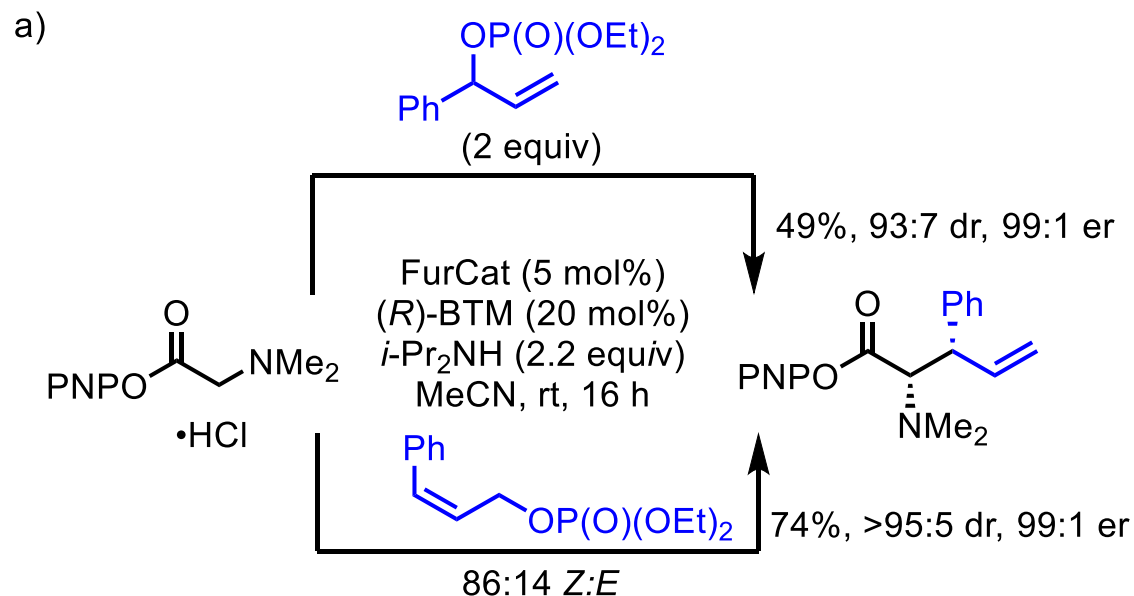
FurCat (5-10 mol%)
 (R)-BTM (20 mol%)
i-Pr₂NH (2.2 equiv)
 MeCN, rt, 16 h



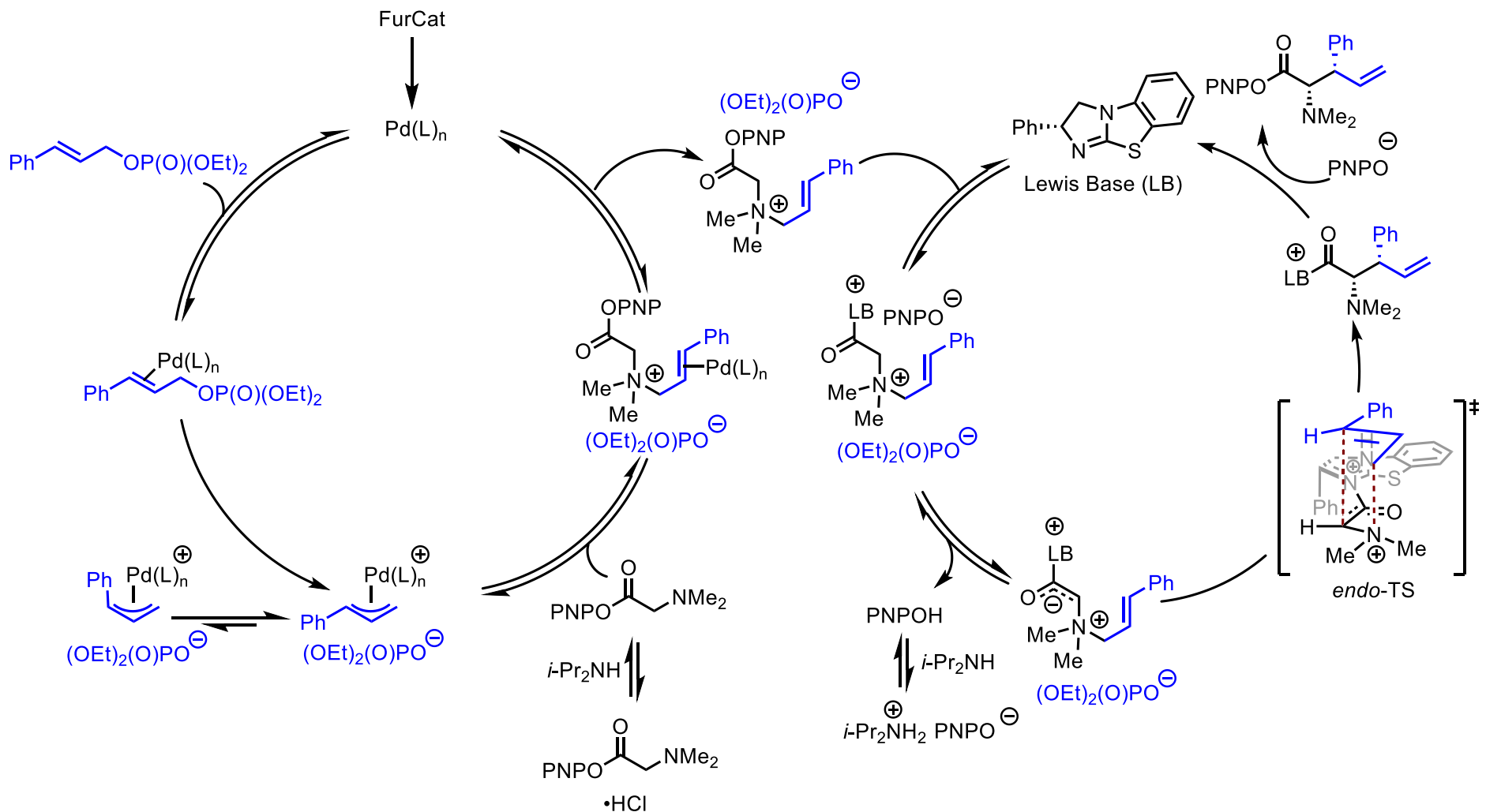
via:



Relay Catalysis – Isothiourea/Pd-Catalysis

Mechanistic
Control Experiments:

Relay Catalysis – Isothiourea/Pd-Catalysis





The area has rapidly developed in the previous decade and continues to expand



Compared to TM and Organocatalysis, it is still limited in number



New types of transformations and catalyst combinations are still to be explored



Application of this concept in total synthesis of natural products is worthy of further investigation

Thank you! Any Questions?



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