

B(C₆F₅)₃-Mediated Iminium Ion Formation - Works by Dr. Wasa -

Literature Seminar

2023/01/21 Koichi Hagiwara

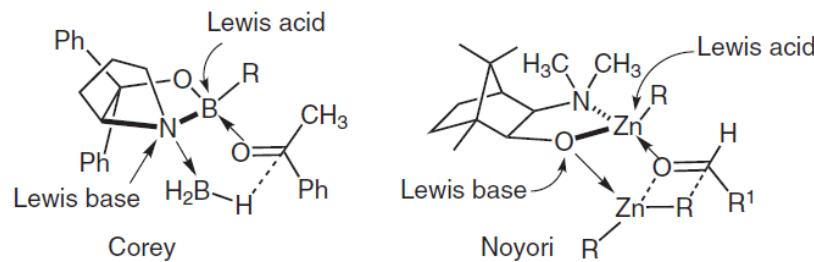
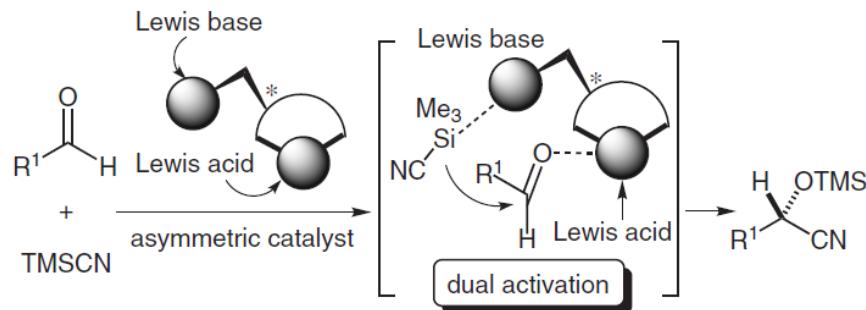
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1. Introduction

2. $B(C_6F_5)_3$ -catalyzed reaction via an iminium ion

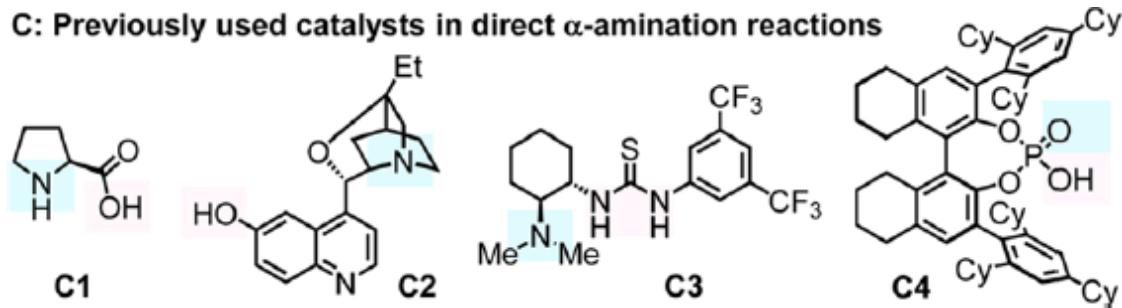
3. $B(C_6F_5)_3$ -catalyzed reaction via an enamine

Cooperative Catalysis



Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491.

C: Previously used catalysts in direct α -amination reactions

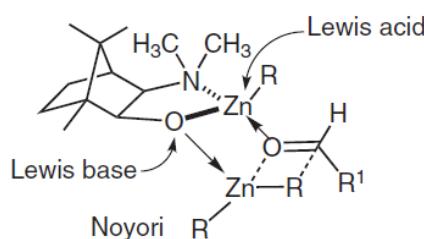
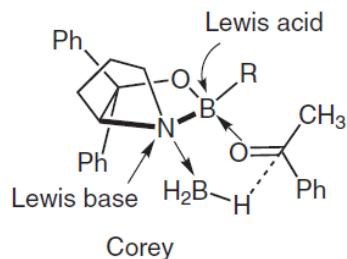
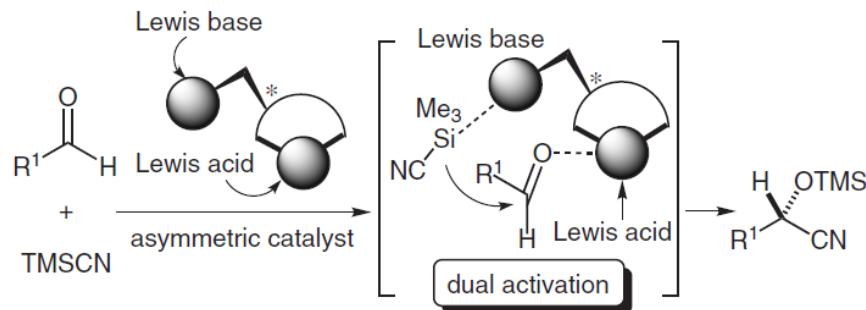


Wasa, M. et al. *J. Am. Chem. Soc.* **2017**, 139, 95.

self-quenching should be avoided

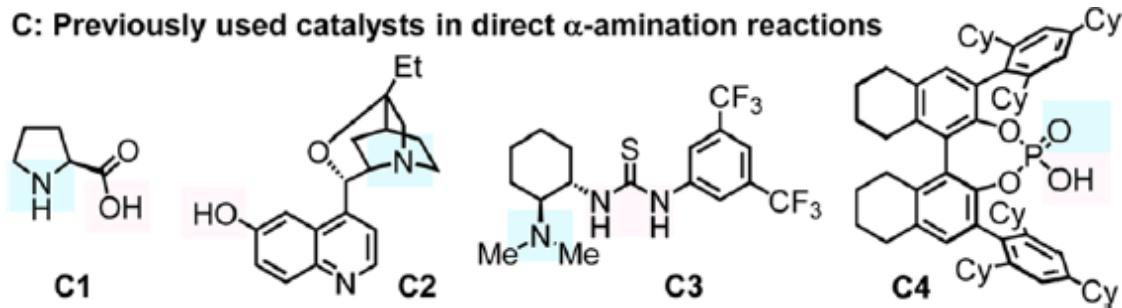
→ strong interactions would not be utilized (hard-hard, soft-soft)
mildly to moderately acidic and basic groups would be used

Cooperative Catalysis



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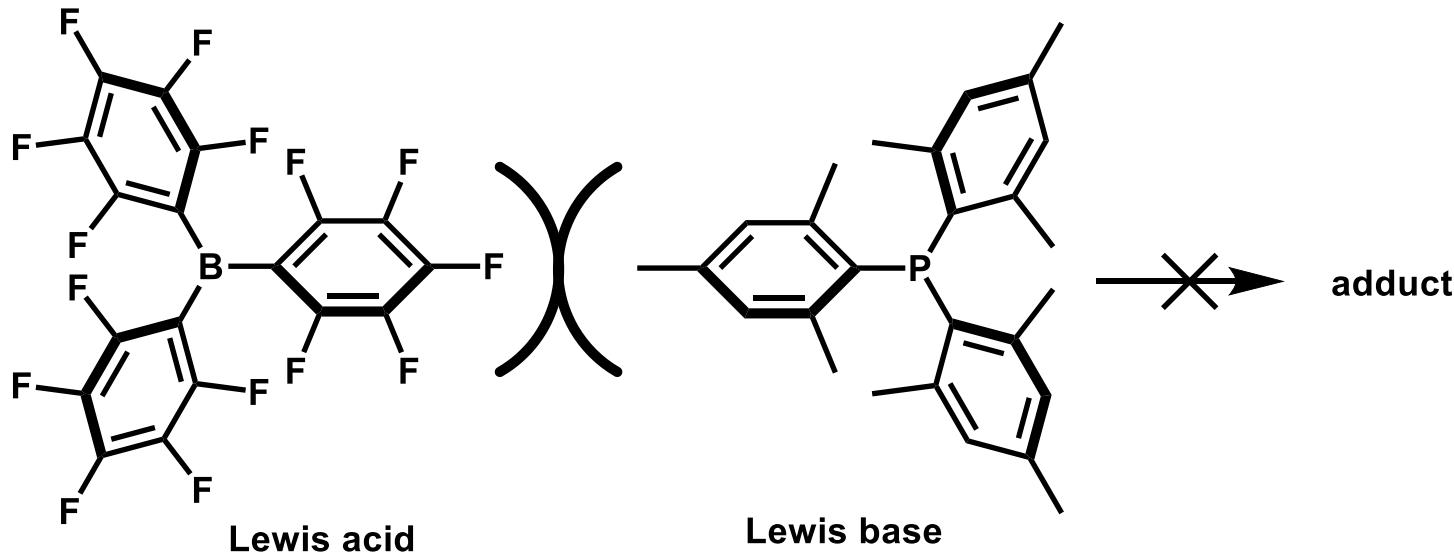
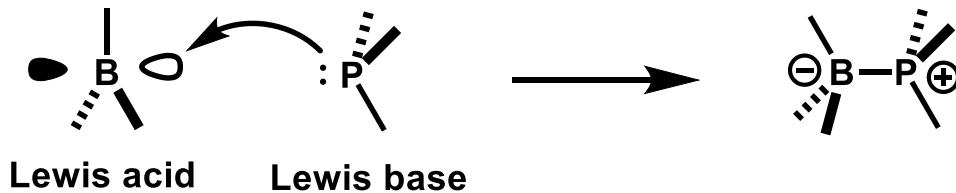


Wasa, M. et al. *J. Am. Chem. Soc.* **2017**, 139, 95.

self-quenching should be avoided

→ strong interactions would not be utilized (hard-hard, soft-soft)
mildly to moderately acidic and basic groups would be used

Frustrated Lewis Pairs



- Combinations of bulky Lewis acid and base
- Sterically prevented from neutralization reaction
- Cooperative activation of small molecules (H_2 , CO_2 , etc.)
- tethering of acidic and basic catalyst component is not necessary
→ facile and independent modification for optimization of reactions

H₂ Activation with Frustrated Lewis Pairs

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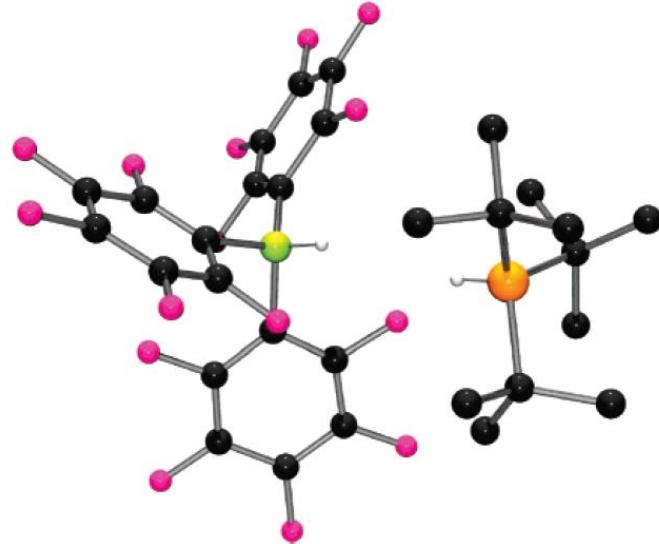
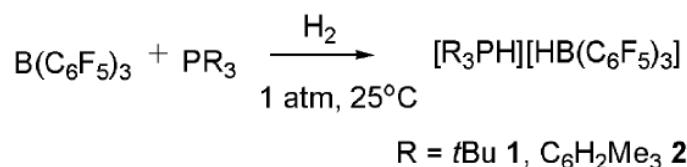
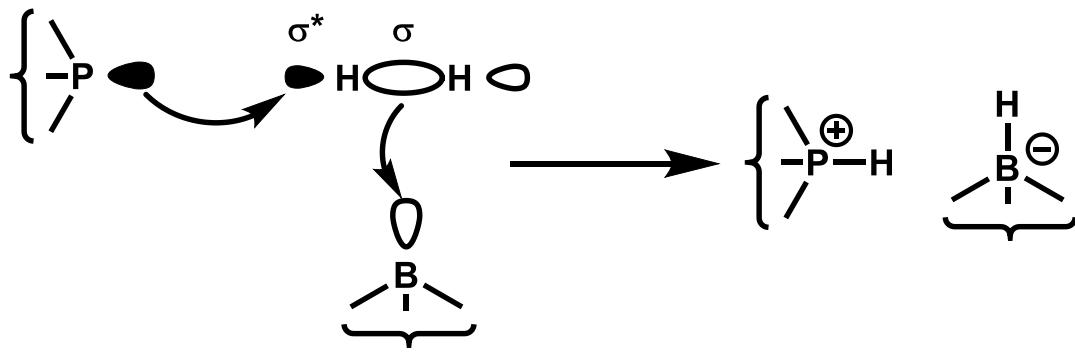
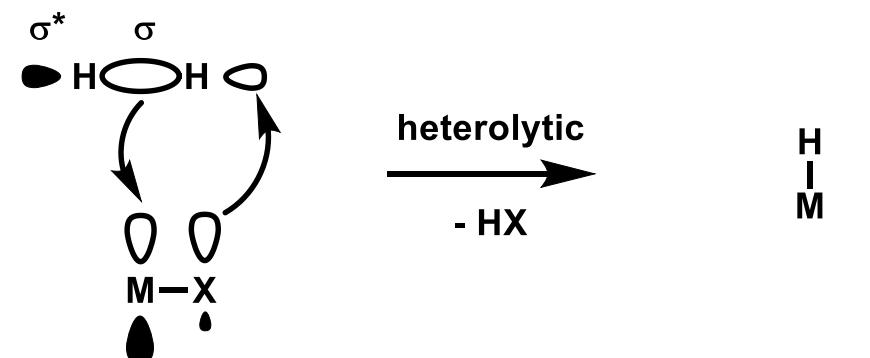
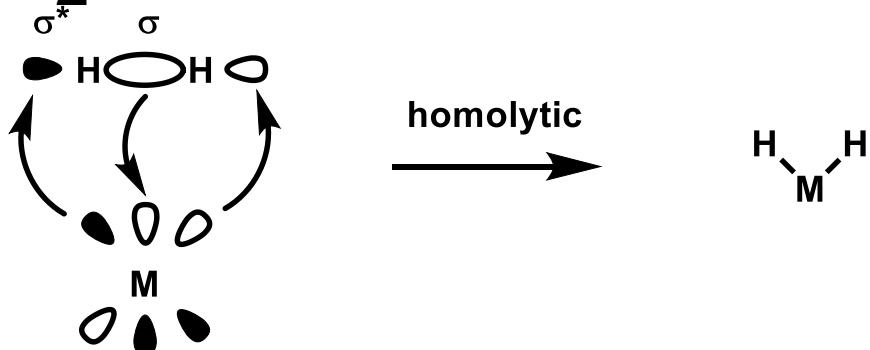


Figure 1. POV-ray drawing of 1. Hydrogen atoms except for BH and PH are omitted for clarity. C, black; P, orange; F, pink; B, yellow-green; H, gray.

Author Information



Dr. Masayuki Wasa

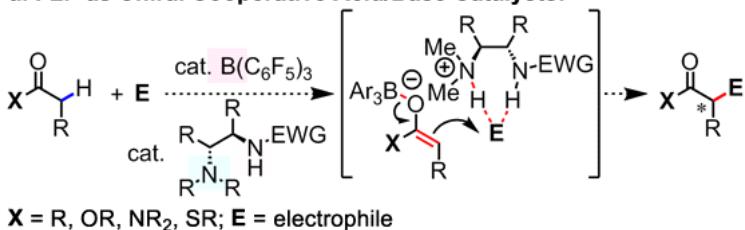
2007-2013 Ph.D., The Scripps Research Institute (with Professor Jin-Quan Yu)

**2013-2015 JSPS Postdoctoral Fellow, Harvard University
(with Professor Eric N. Jacobsen)**

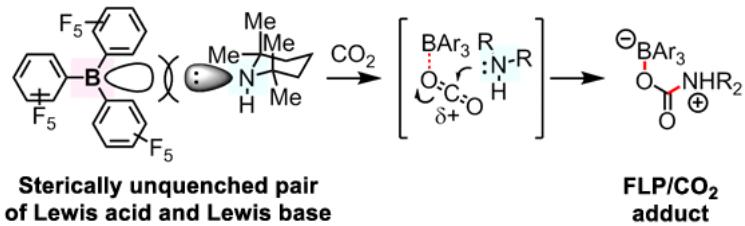
2015- Assistant Professor at Boston College

He develops a series of direct asymmetric C–C and C–heteroatom bond forming reactions that are catalyzed by a “frustrated” acid/base.

a. FLP as Chiral Cooperative Acid/Base Catalysts:



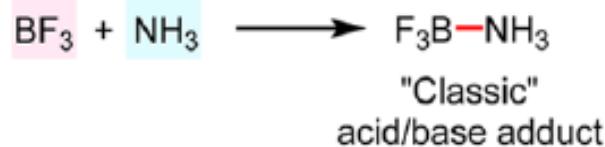
b. Stoichiometric Activation of CO_2 by Frustrated Lewis Pair (FLP):



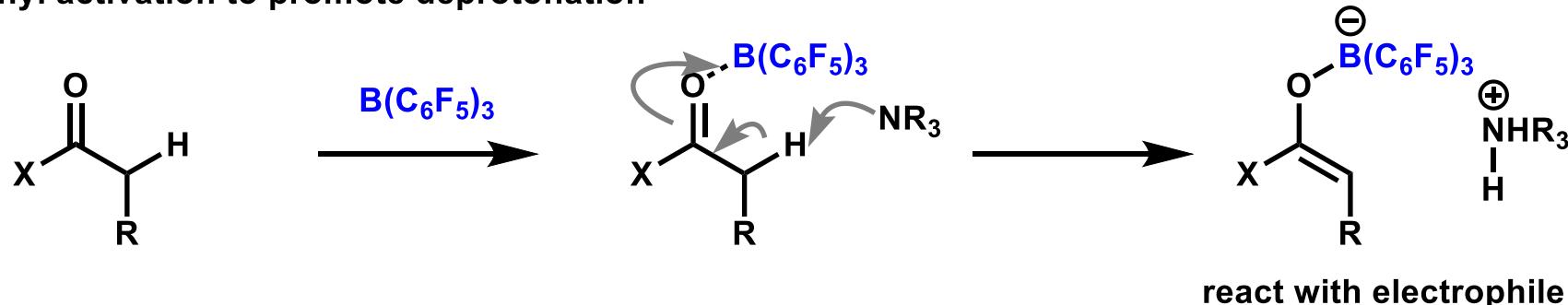
<https://sites.google.com/bc.edu/masayuki-wasa>

Concept of Reactions Using $B(C_6F_5)_3$

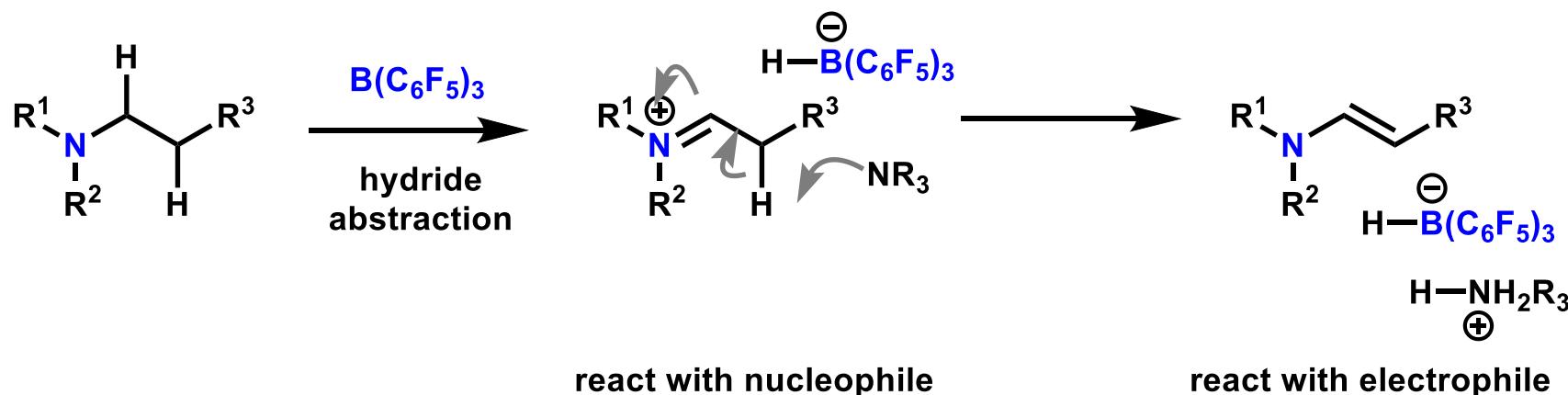
Catalyst design:



- Carbonyl activation to promote deprotonation

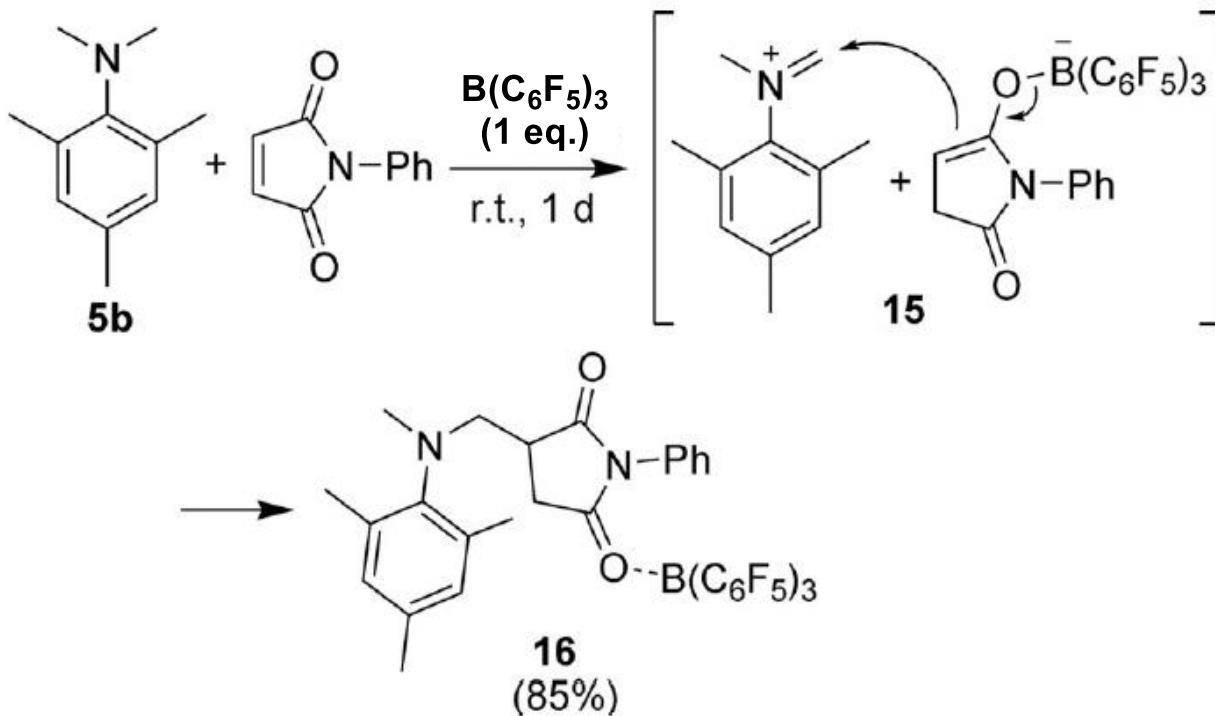


- Iminium ion formation via a hydride abstraction



Precedent Study

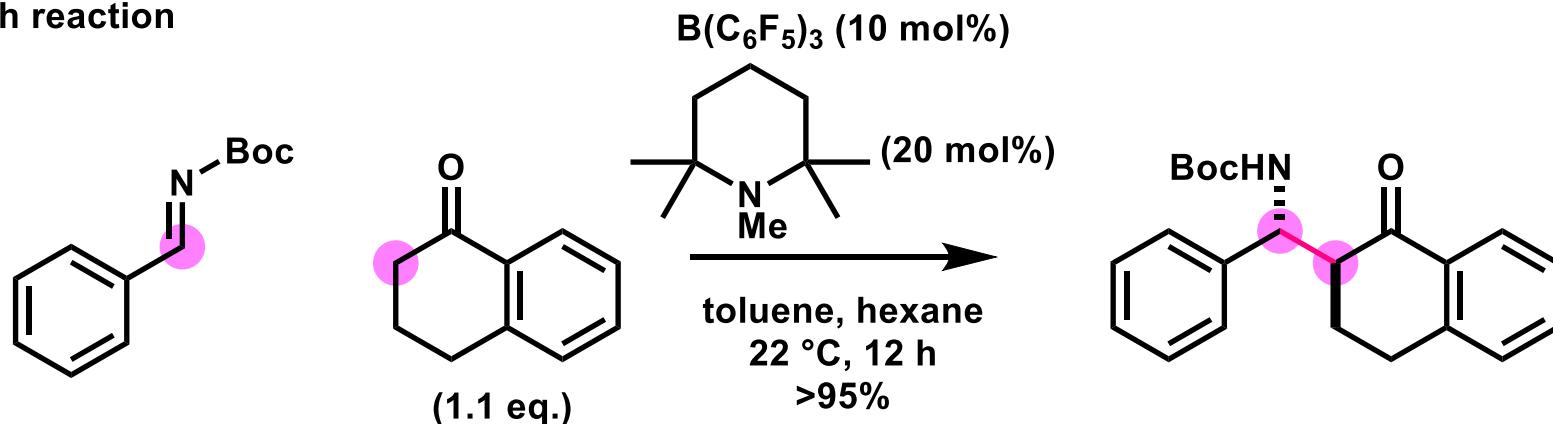
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Reactions through Carbonyl Activation

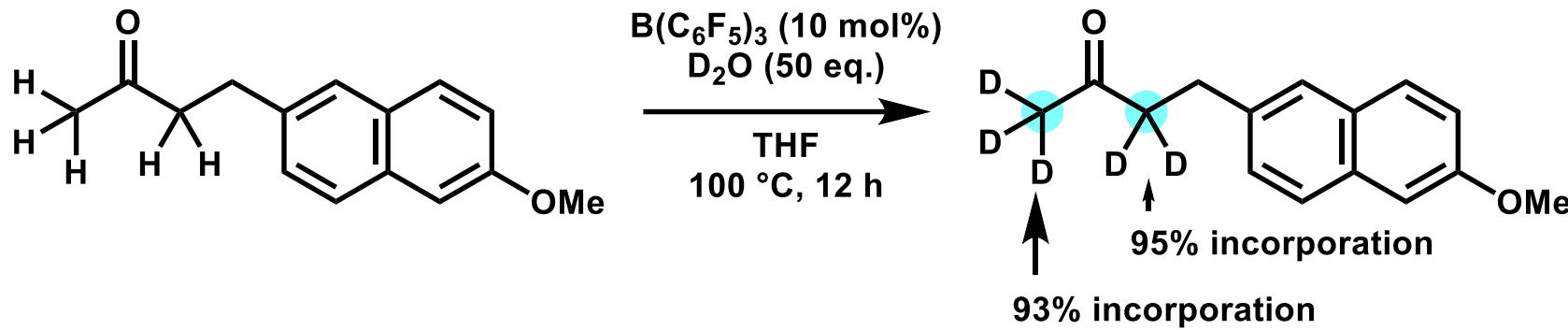
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- Mannich reaction



Angew. Chem. Int. Ed. 2016, 55, 13877.

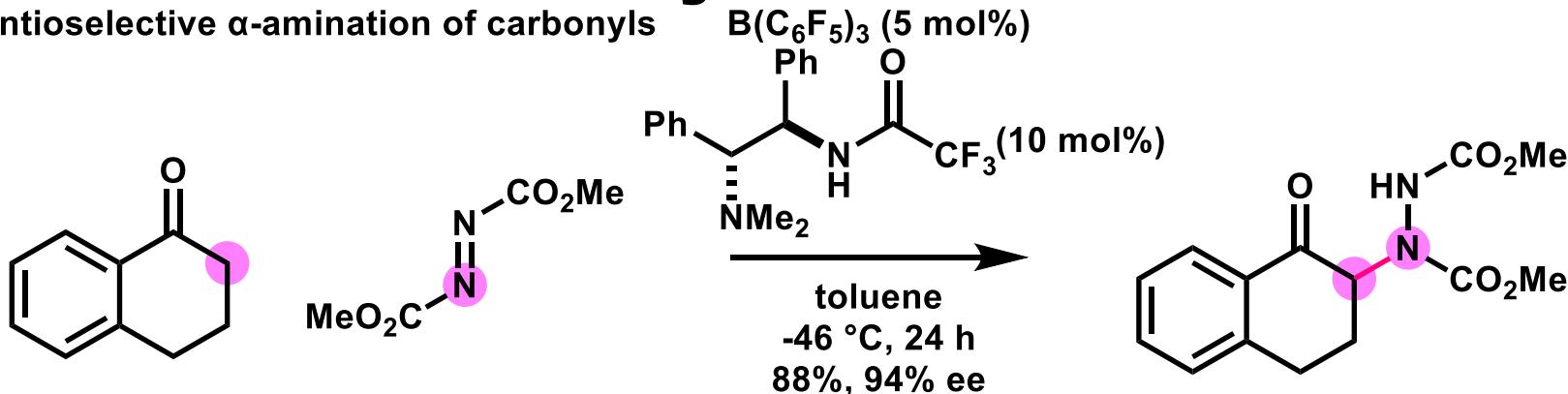
- α -deuteration of ketone



Adv. Synth. Catal. 2020, 362, 360.

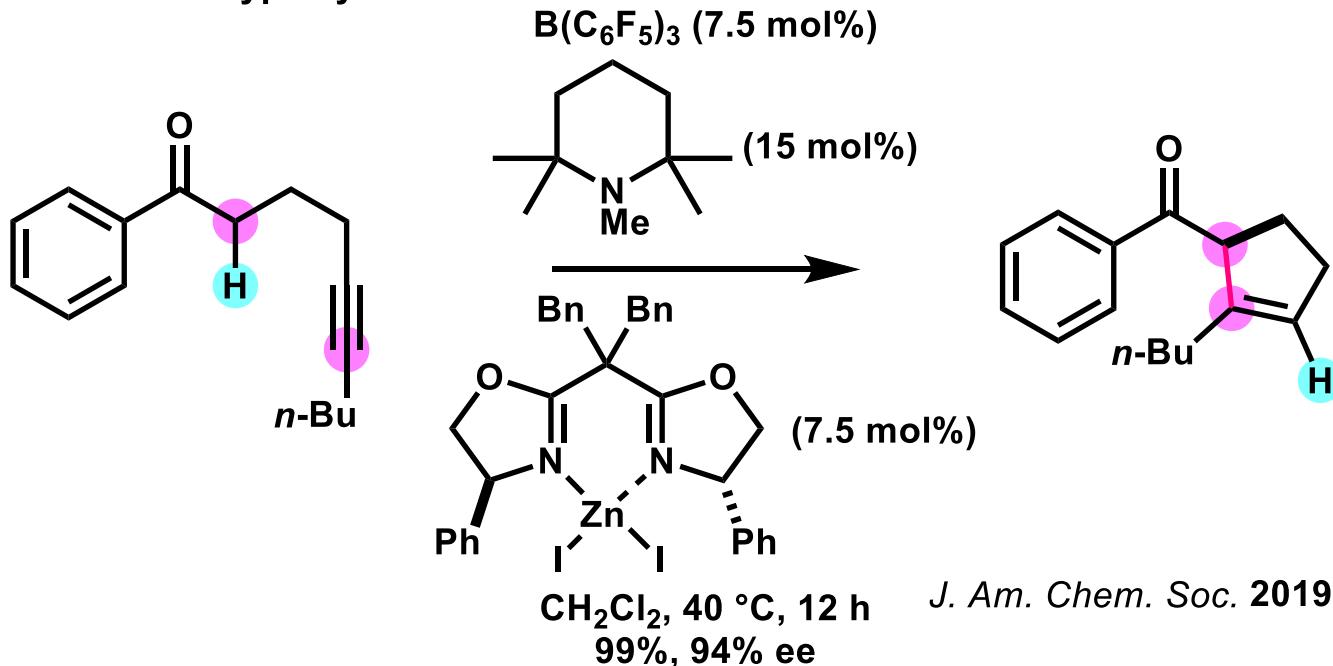
Enantioselective Reactions through Carbonyl Activation

- Enantioselective α -amination of carbonyls

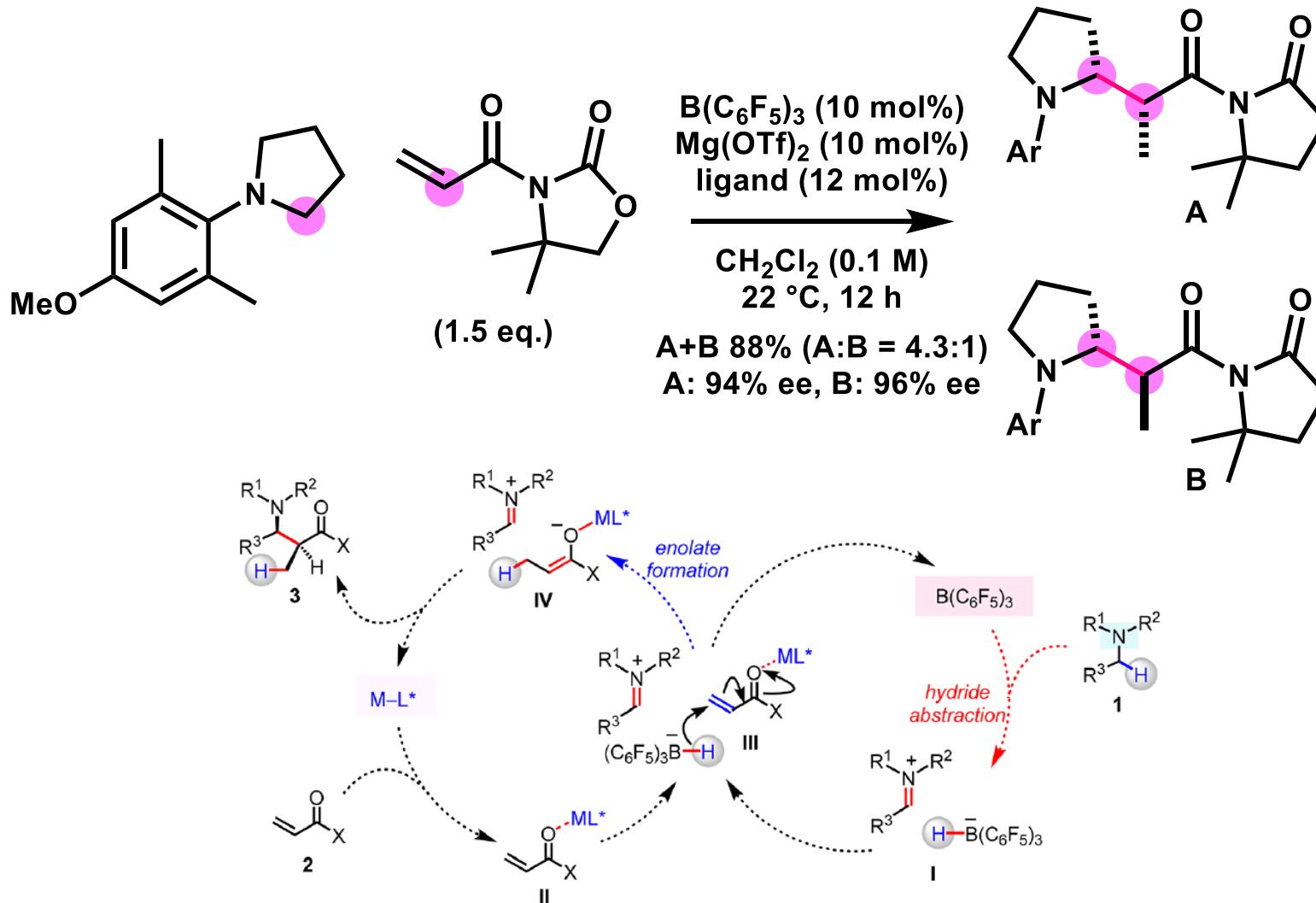


J. Am. Chem. Soc. **2017**, 139, 95.

- Enantioselective Conia-ene-type cyclization



Enantioselective Reactions through Iminium Ion Formation



Contents

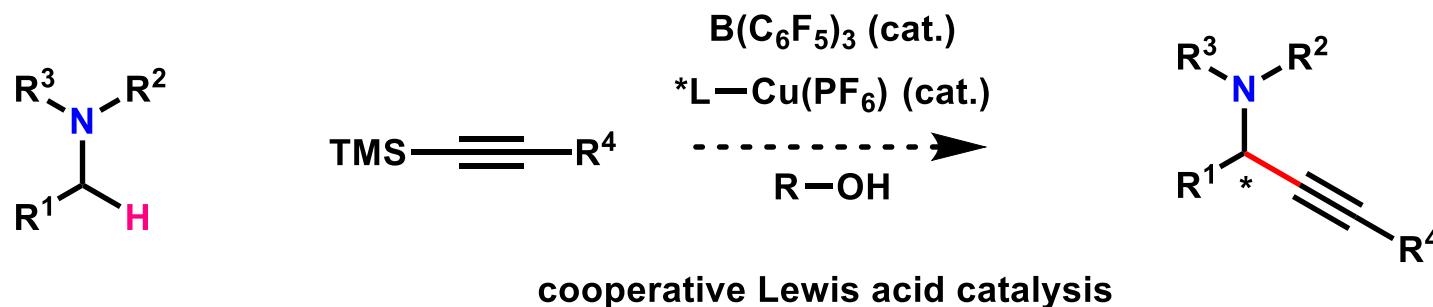
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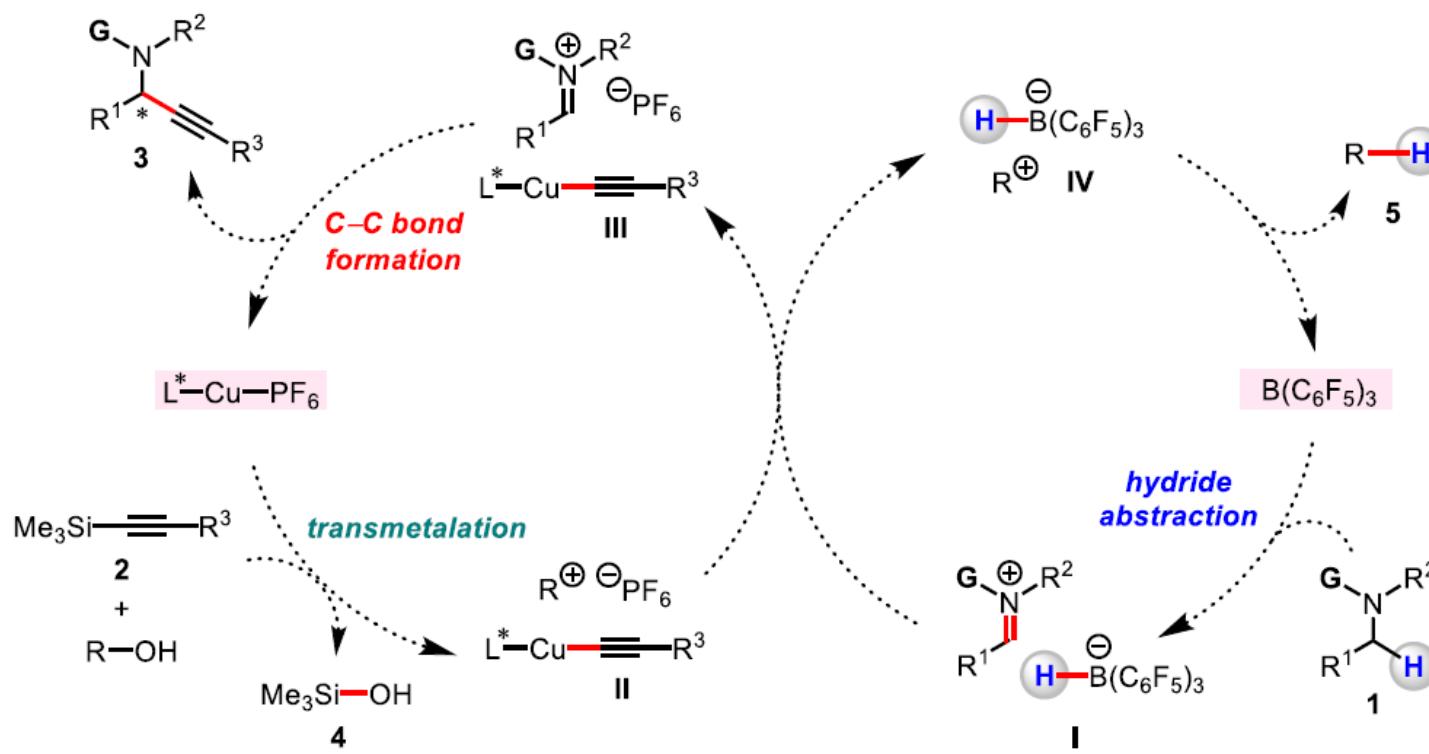
3. $B(C_6F_5)_3$ -catalyzed reaction via an enamine

Conversion of *N*-Alkylamines to *N*-Propargyl Amines - Working Hypothesis -

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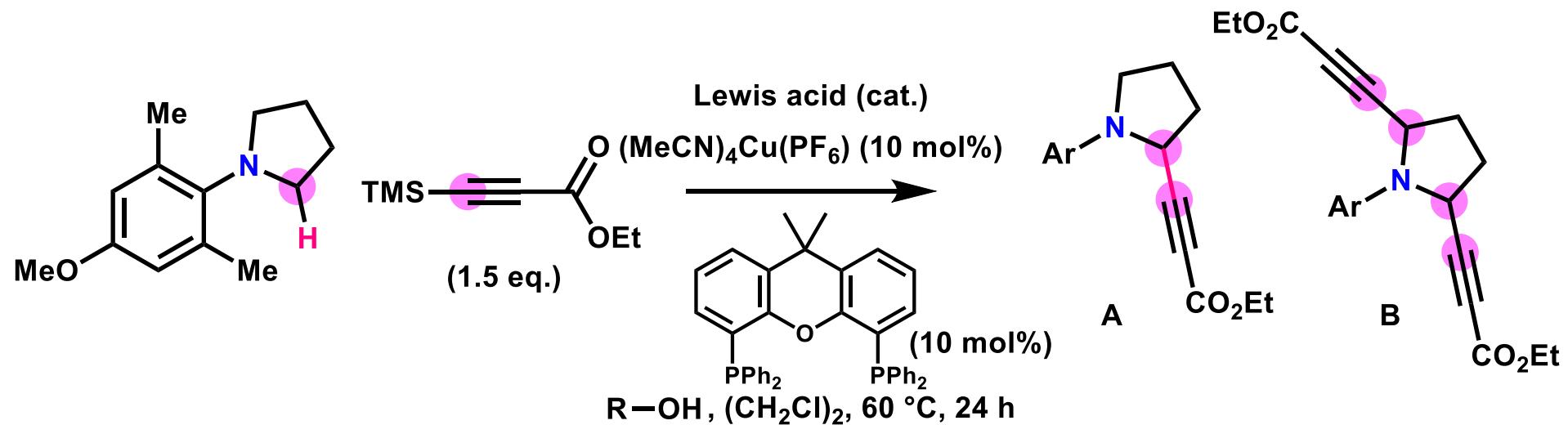


Proposed catalytic cycle:



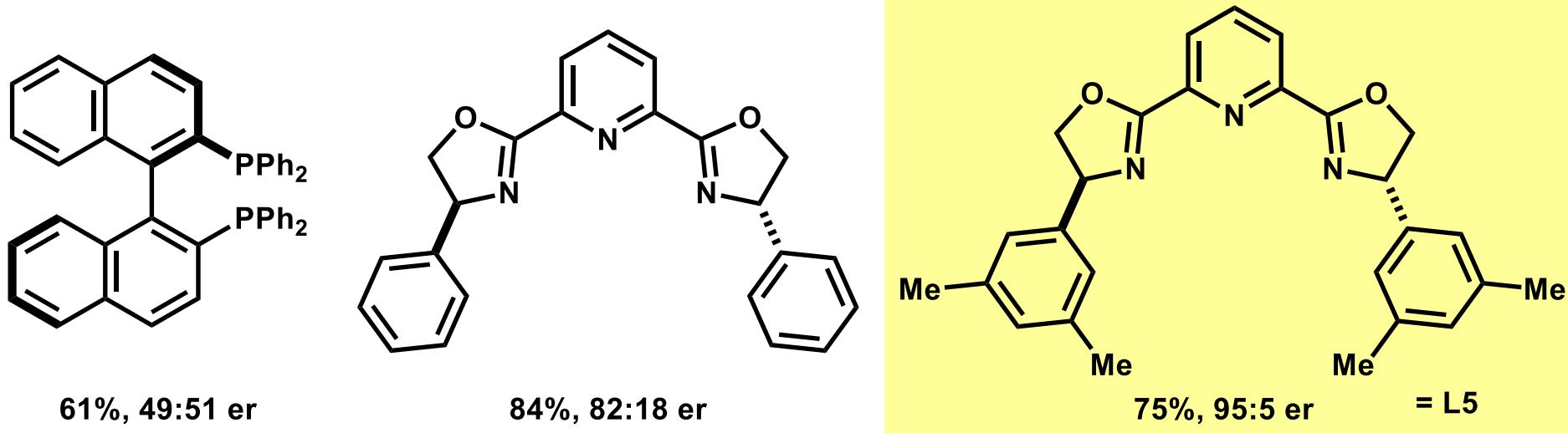
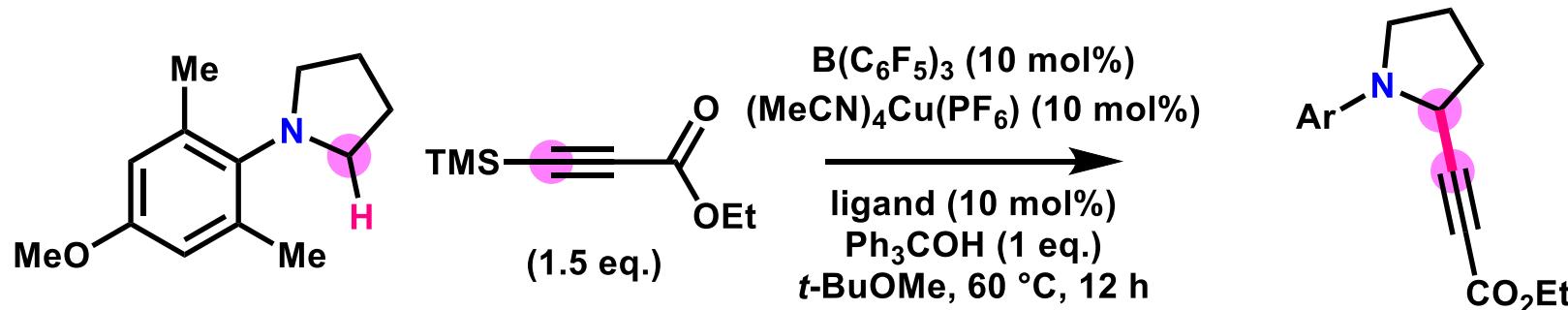
Optimization of Reaction Conditions

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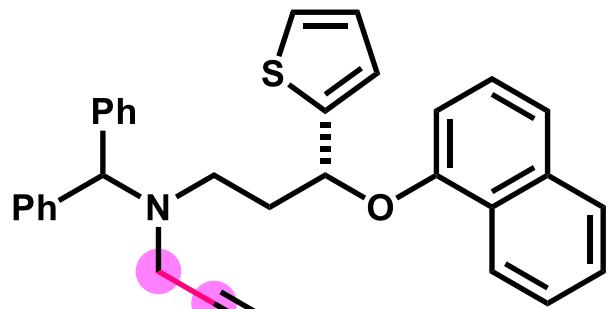
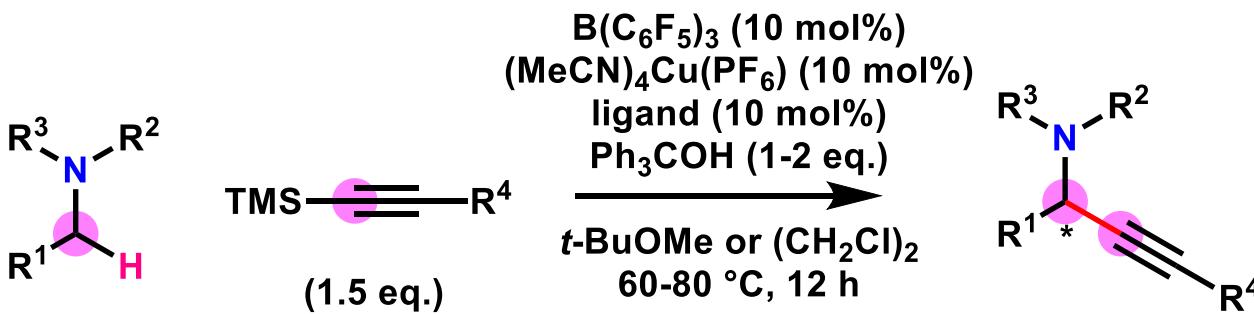


entry	Lewis acid	R-OH	yield		* 12 h
			A	B	
1	$\text{B}(\text{C}_6\text{F}_5)_3$	$i\text{-PrOH}$ (2 eq.)	0%	0%	
2	$\text{B}(\text{C}_6\text{F}_5)_3$	$t\text{-BuOH}$ (2 eq.)	17%	0%	
3	$\text{B}(\text{C}_6\text{F}_5)_3$	Ph_3COH (2 eq.)	52%	34%	
4*	$\text{B}(\text{C}_6\text{F}_5)_3$	Ph_3COH (1 eq.)	90%	<5%	* 12 h
5	$\text{BF}_3 \cdot \text{OEt}_2$	Ph_3COH (1 eq.)	0%	0%	
6	BPh_3	Ph_3COH (1 eq.)	0%	0%	

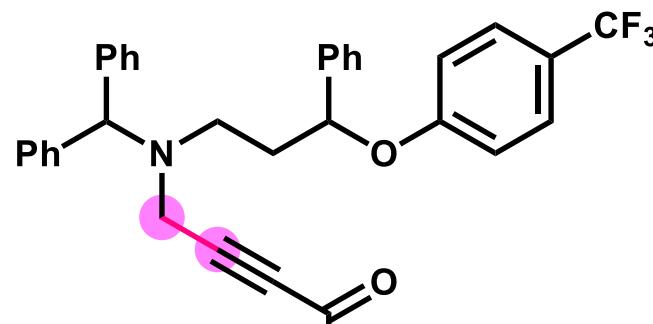
Enantioselective *N*-Propargyl Amine Formation - Ligand Screening -



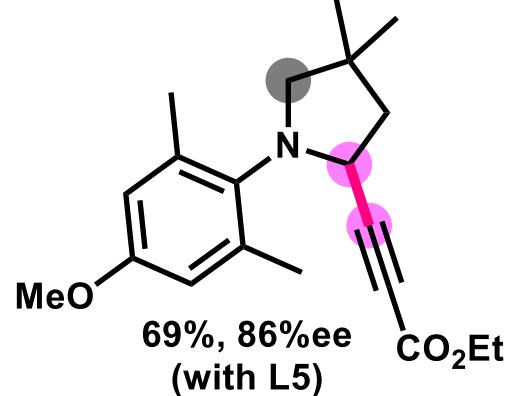
Substrate Scope



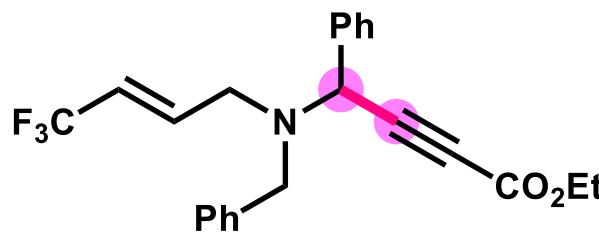
68%
(with dppe)



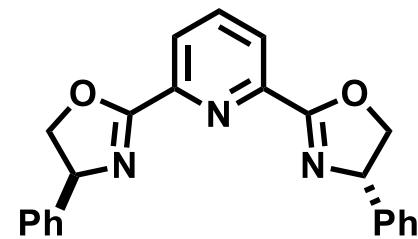
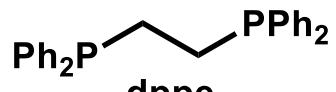
80%
(with (S)-Ph-PyBOX)



69%, 86% ee
(with L5)



45%, 68% ee
(with L5)

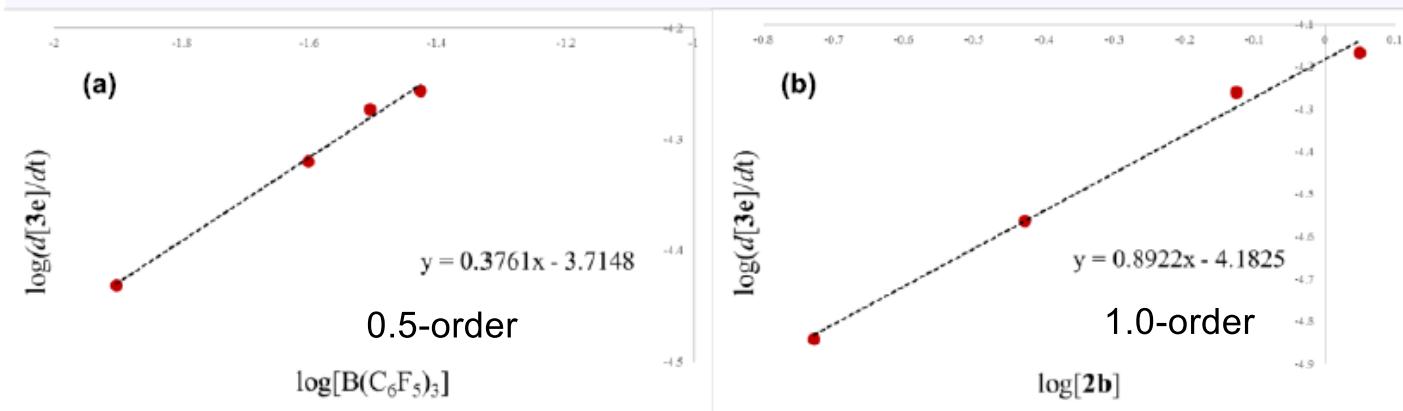
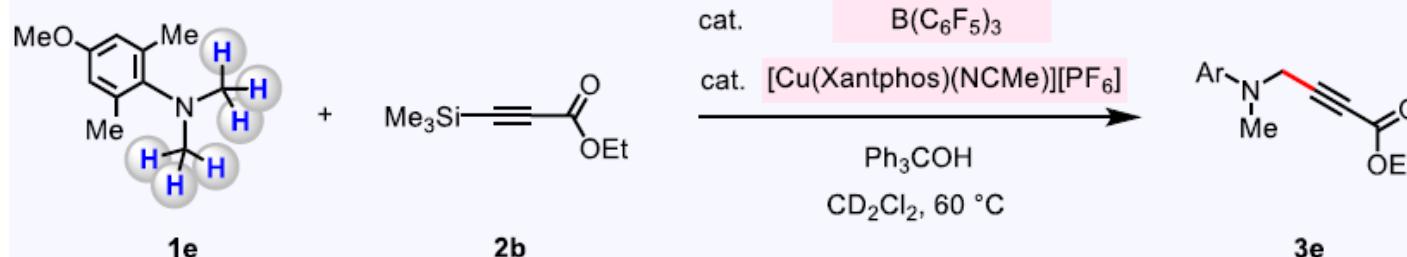


(S)-Ph-PyBOX

Determination of the Reaction Orders

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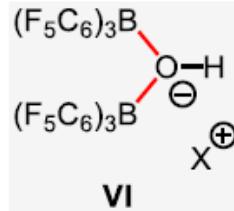
General reaction conditions for the kinetic experiments



Zero-order for 1e, (MeCN)₄CuPF₆/Xantphos complex, and Ph₃COH.

→ Alkyne would be involved in turnover limiting step.

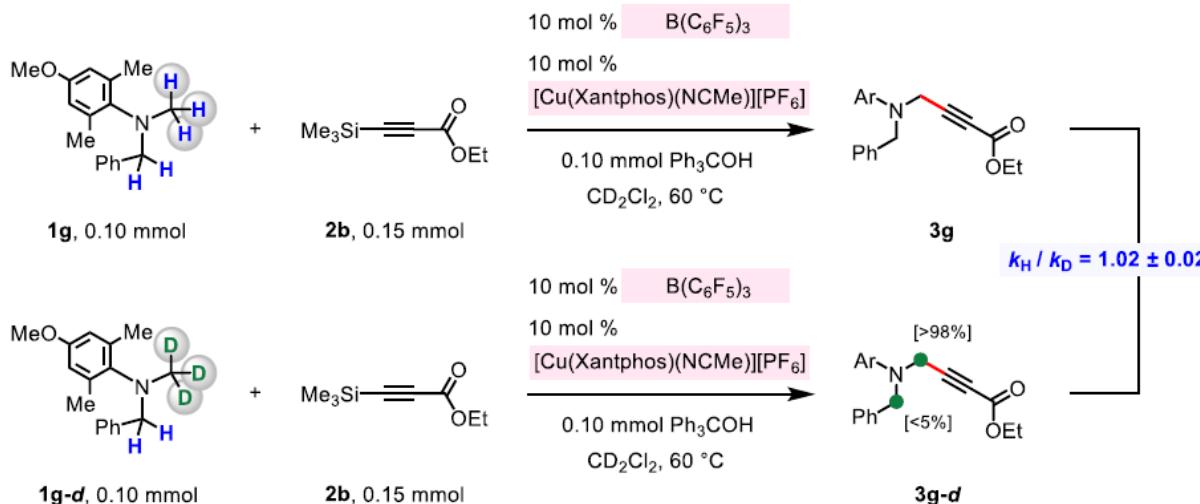
Transformation would have a **resting state** that consists of two $\text{B}(\text{C}_6\text{F}_5)_3$.



confirmed by ¹¹B NMR

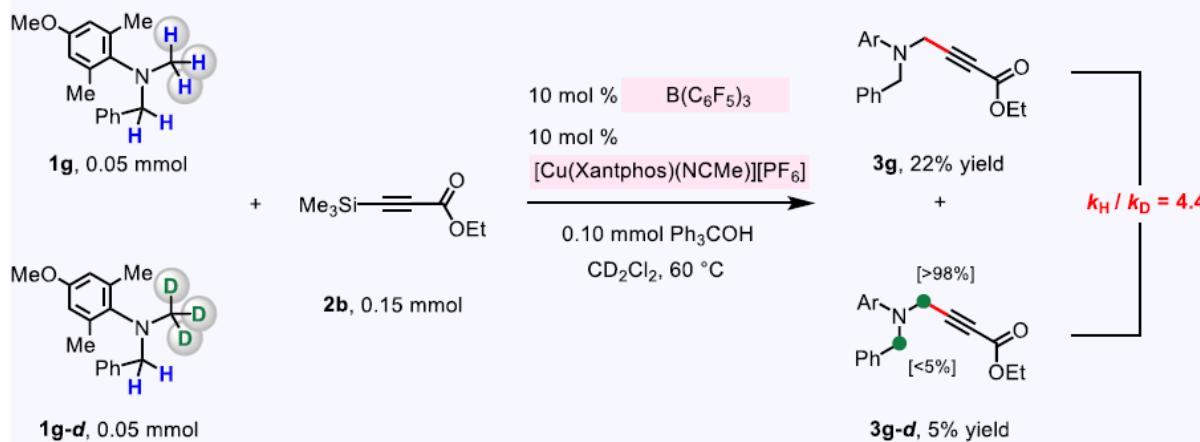
Kinetic Isotope Effect Study

(a) Independent rate measurements with amine isotopologues



Hydride abstraction is not turnover limiting step.

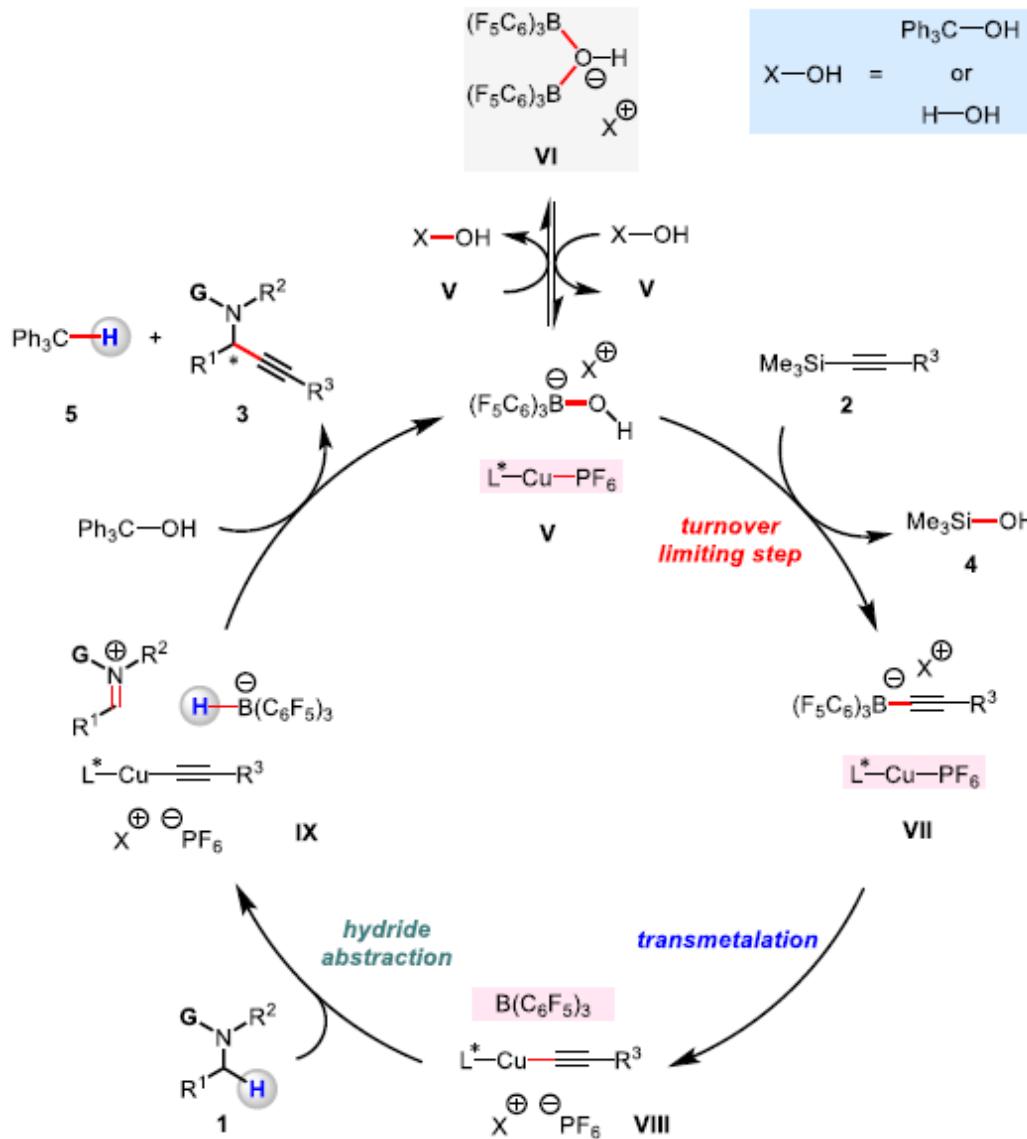
(b) Competition rate measurements with amine isotopologues



KIE is calculated based on the product distribution.
Thus from this experiment, observation of KIE means that step is irreversible.
 →
Hydride abstraction is irreversible.

Plausible Reaction Mechanism

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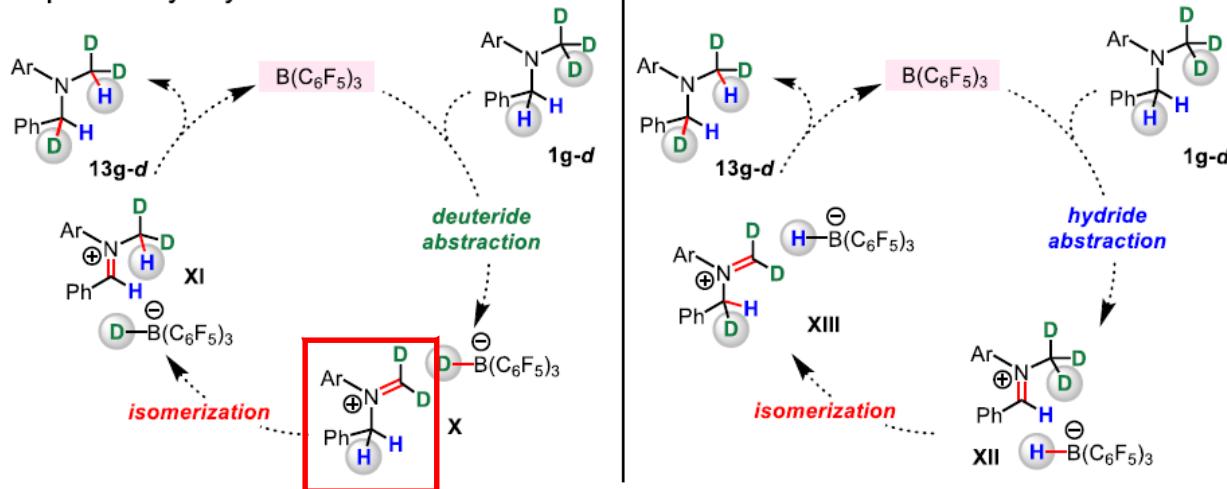


Observation for Regioselectivity

(a)

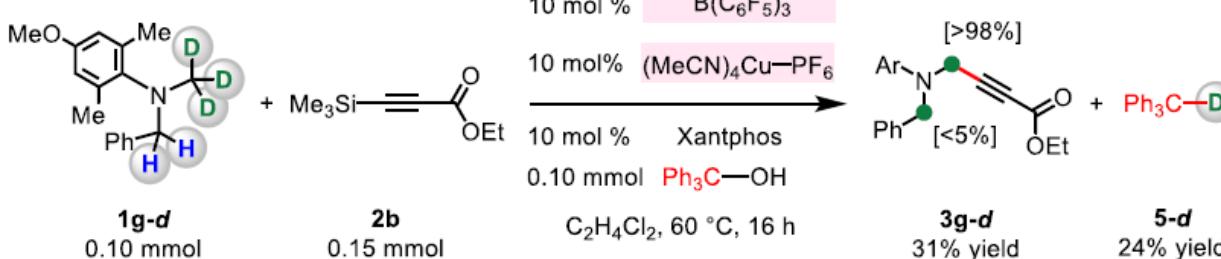


Proposed catalytic cycles:



Cation X would be long-lived without $(MeCN)_4CuPF_6$ /Xantphos to undergo isomerization.

(a)



Cation X would be rapidly consumed by its reaction with $(MeCN)_4CuPF_6$ /Xantphos.

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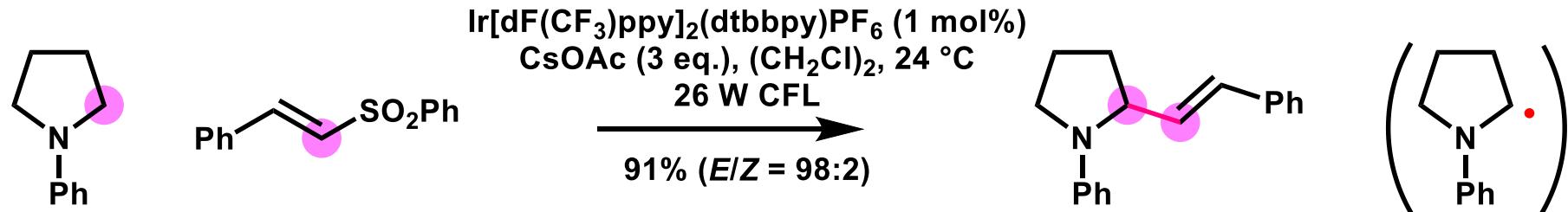
2. $B(C_6F_5)_3$ -catalyzed reaction via an iminium ion

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α - or γ -Amino C-H Functionalization

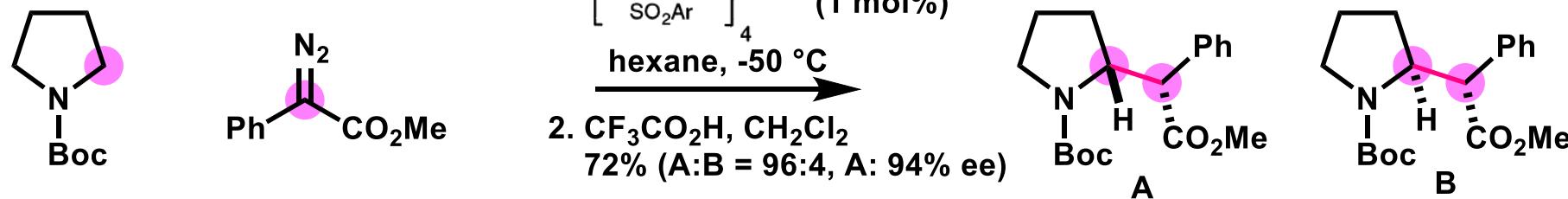
α -amino C-H bond transformation

- via α -amino radical



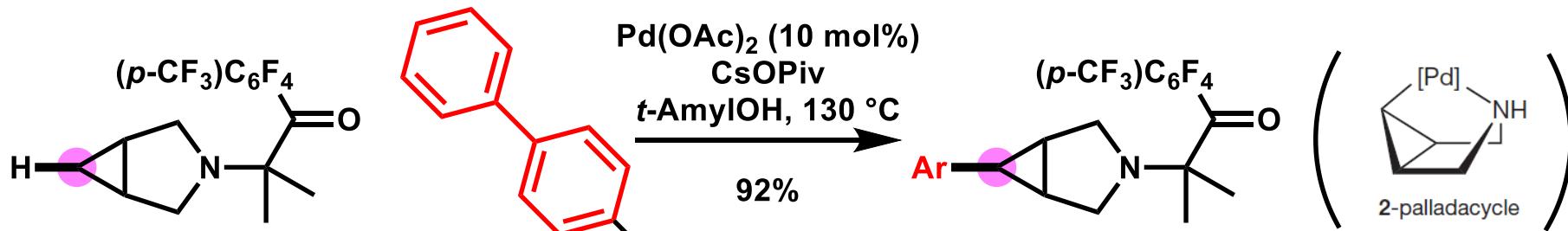
Noble, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 11602.

- via metal carbene insertion



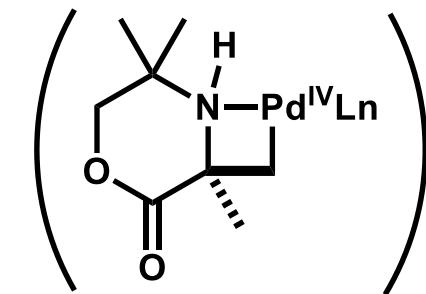
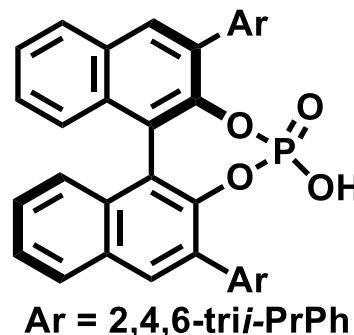
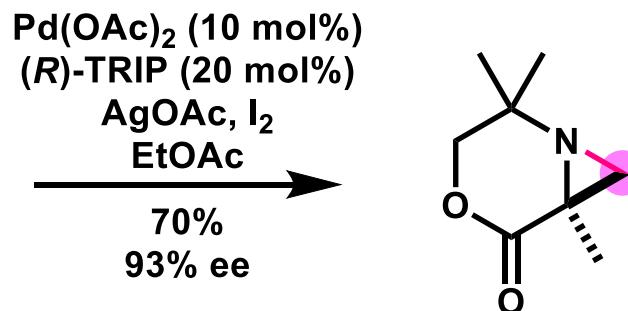
Davies, H. M. L.; Venkataramani, G.; Hansen, T.; Hopper, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 6462.

γ -amino C-H bond transformation

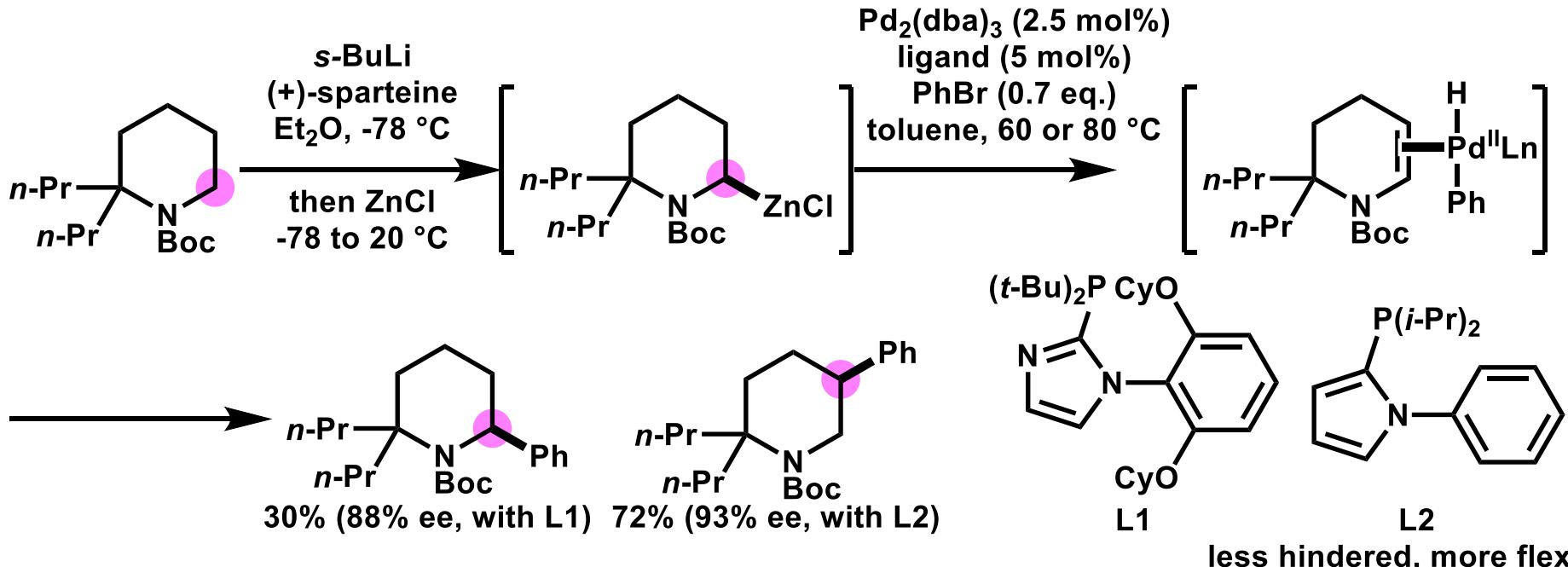


Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. *Nature* **2016**, *531*, 220.

Enantioselective β -Amino C-H Functionalization



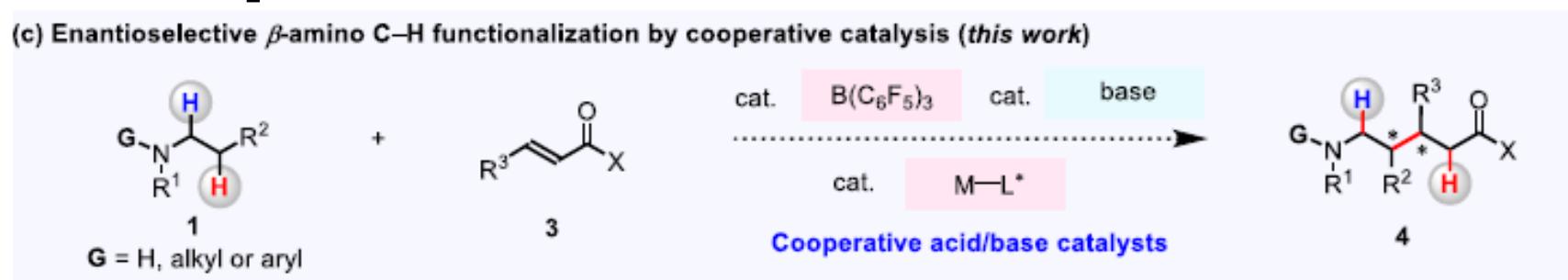
Smalley, A. P.; Cuthbertson, J. D.; Gaunt, M. J. *J. Am. Chem. Soc.* **2017**, *139*, 1412.



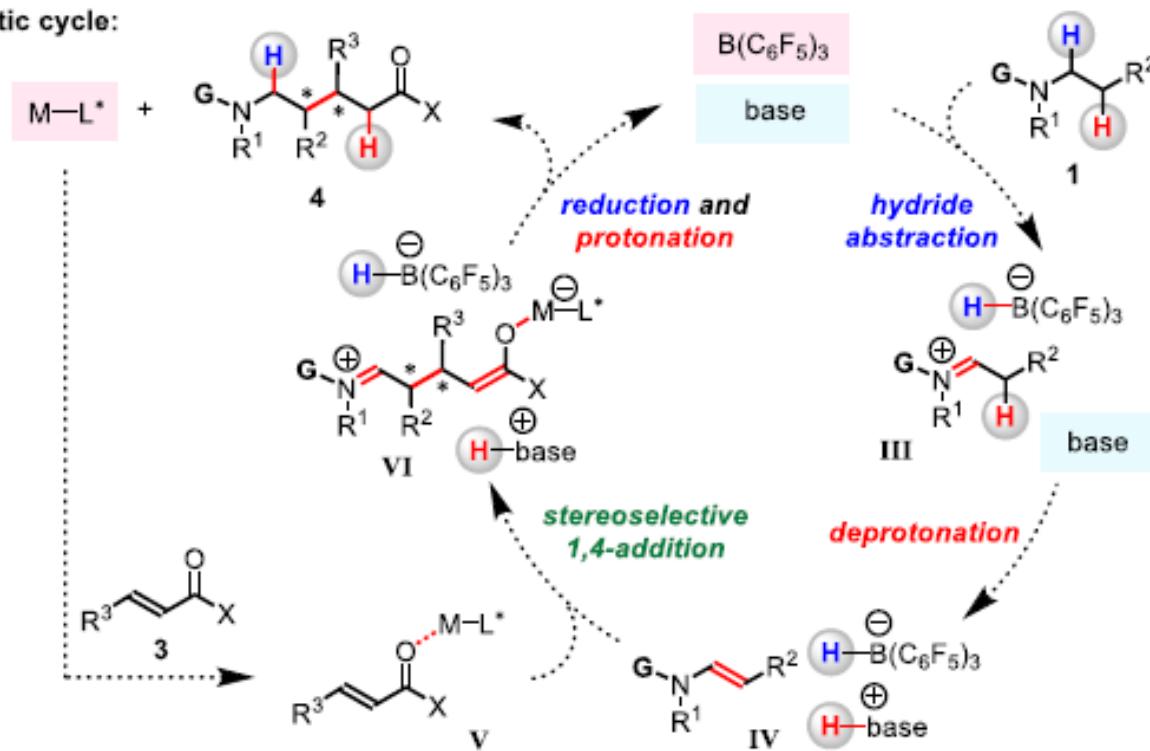
Lin, W.; Zhang, K.-F.; Baudoin, O. *Nat. Catal.* **2019**, *2*, 882.

Initial Design of Enantioselective β -Amino C-H functionalization

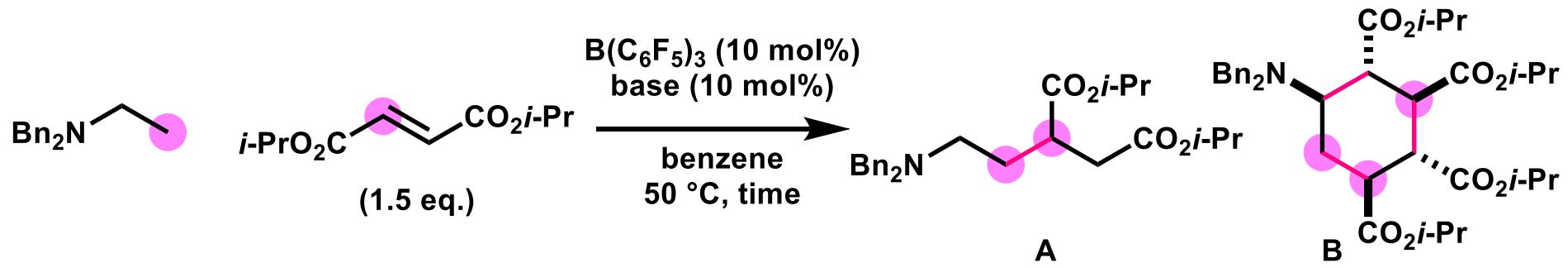
(c) Enantioselective β -amino C-H functionalization by cooperative catalysis (*this work*)



Proposed catalytic cycle:

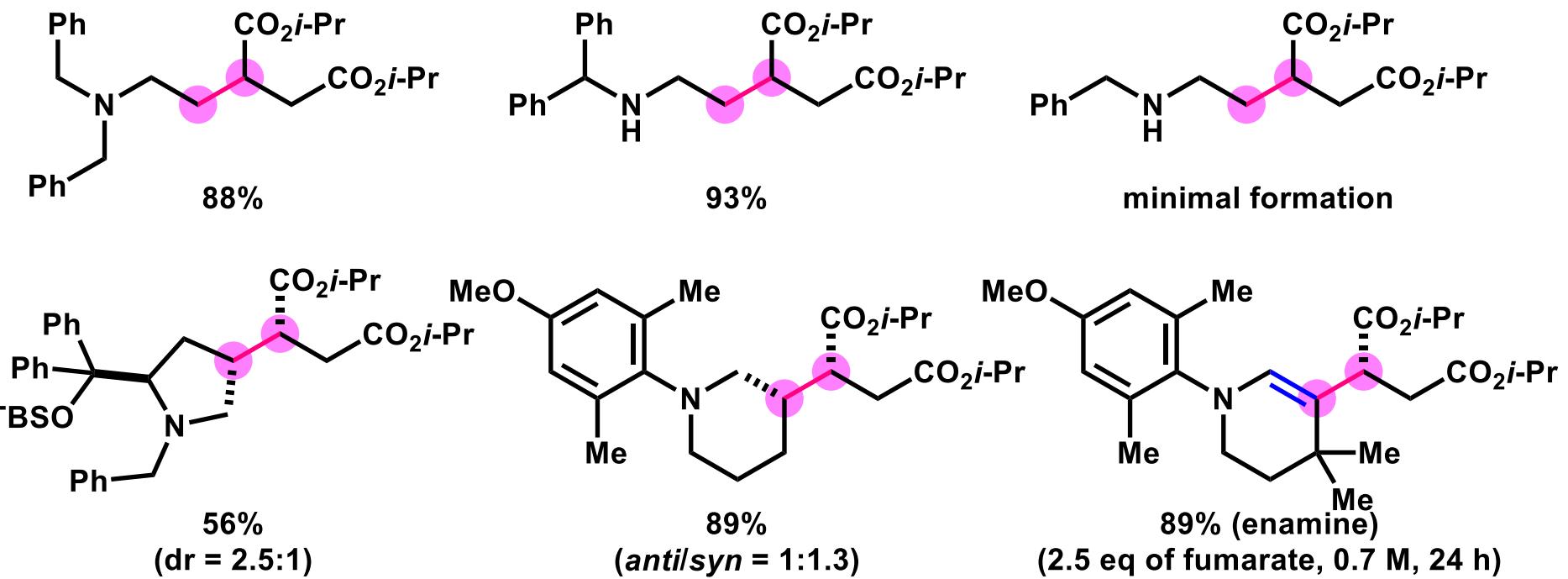
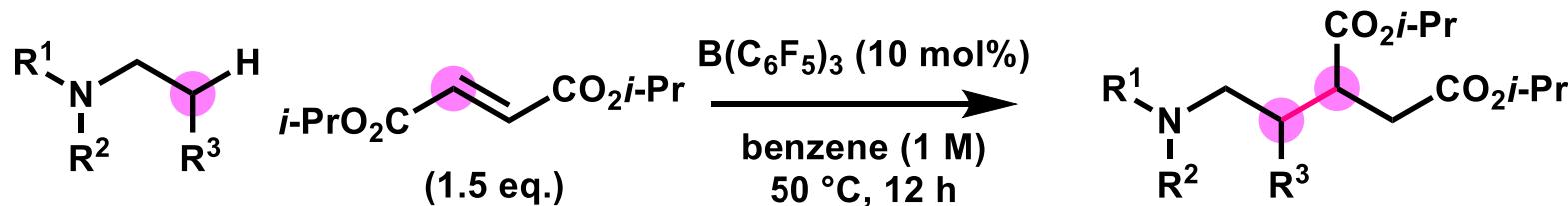


Optimization of Reaction Conditions

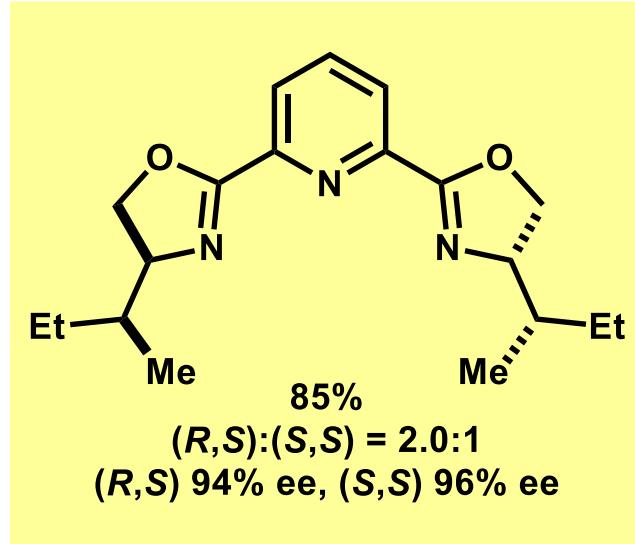
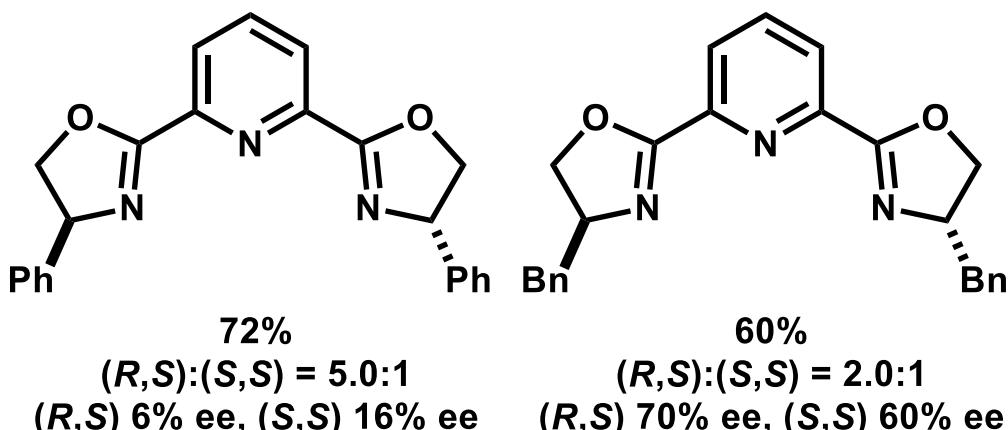
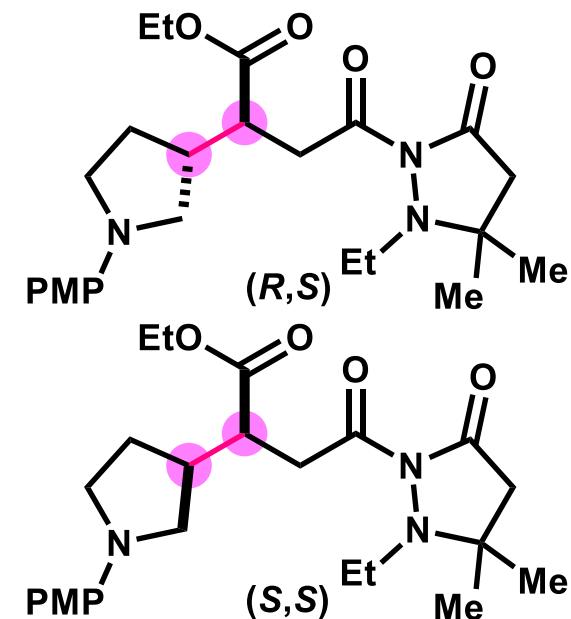
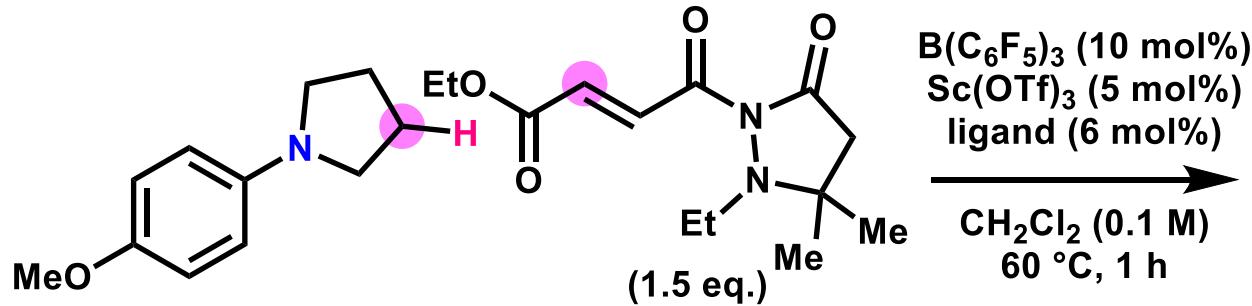


entry	concentration	base	time	yield	
				A	B
1	1 M	Et ₃ N	3 h	50%	23%
2	1 M	2,2,6,6-tetramethylpiperidine	3 h	25%	29%
3	1 M	DBU	3 h	<5%	<5%
4	1 M	none	3 h	73%	25%
5	0.25 M	none	3 h	54%	5%
6	0.25 M	none	12 h	91%	7%

Substrate Scope for Amine



Ligand Screening for Enantioselective Conditions

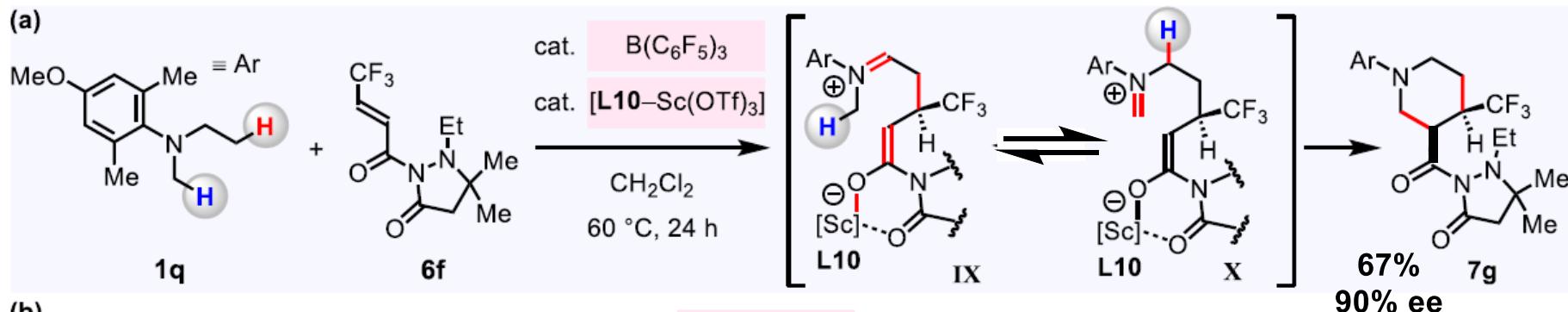


Substrate Scope - Distinctive Reaction -

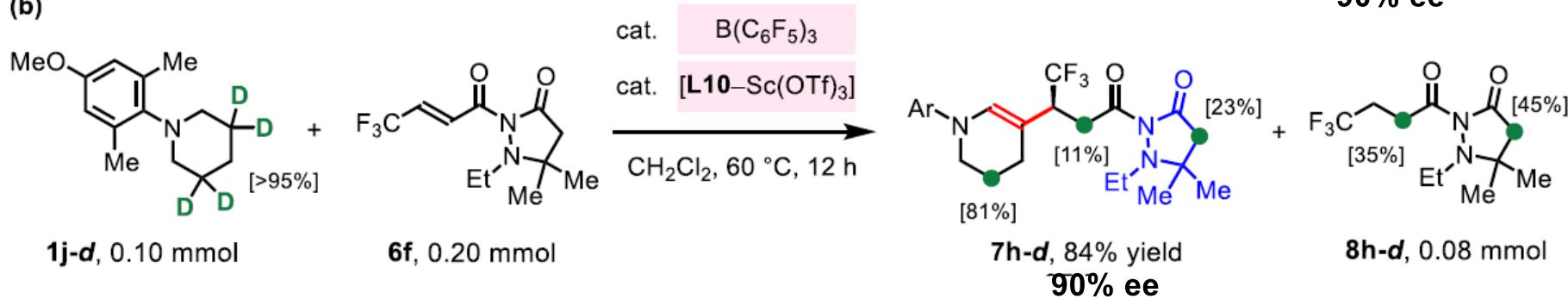
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isomerization of iminium ion

(a)



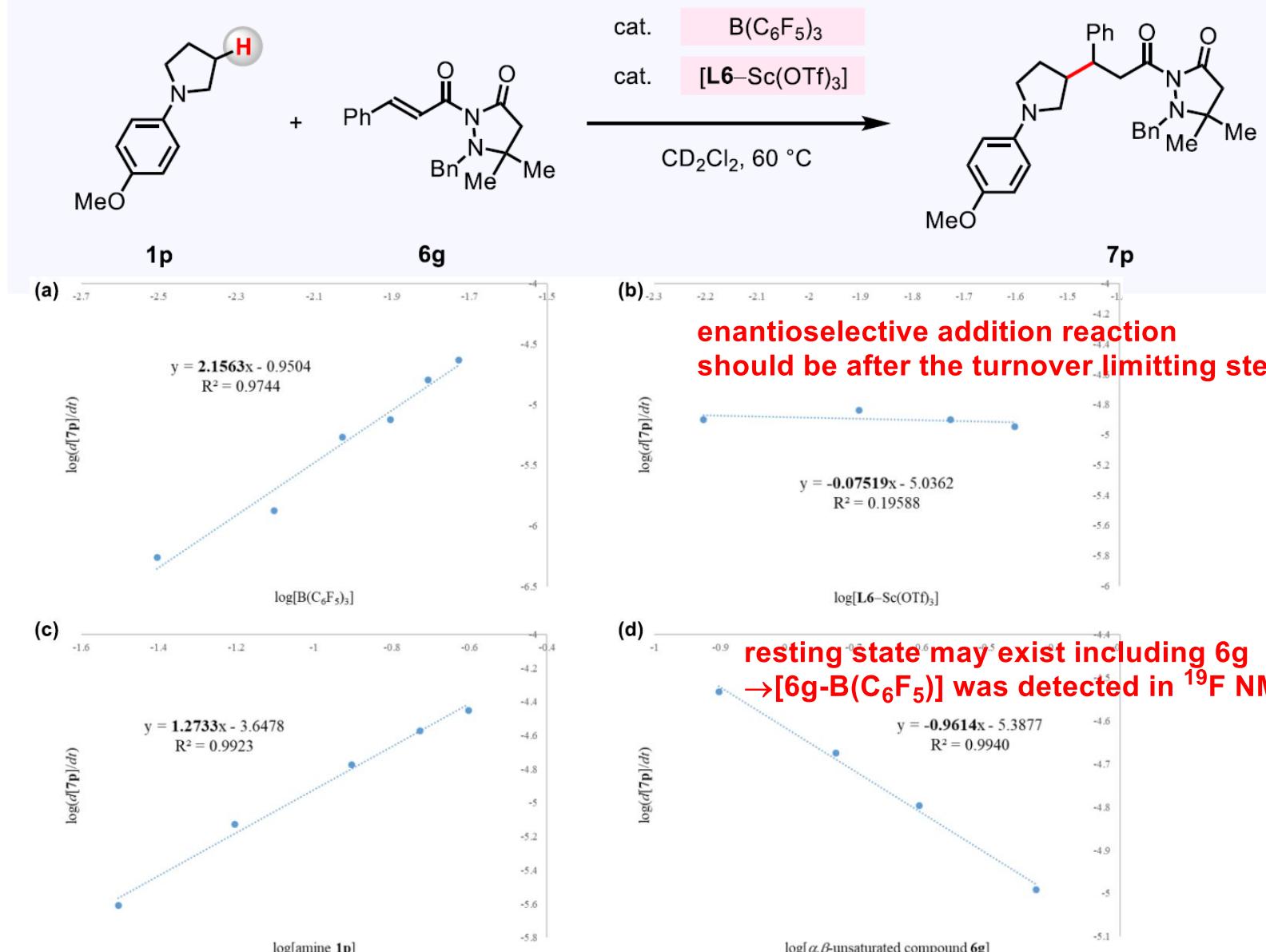
(b)



D was introduced at enolizable positions.

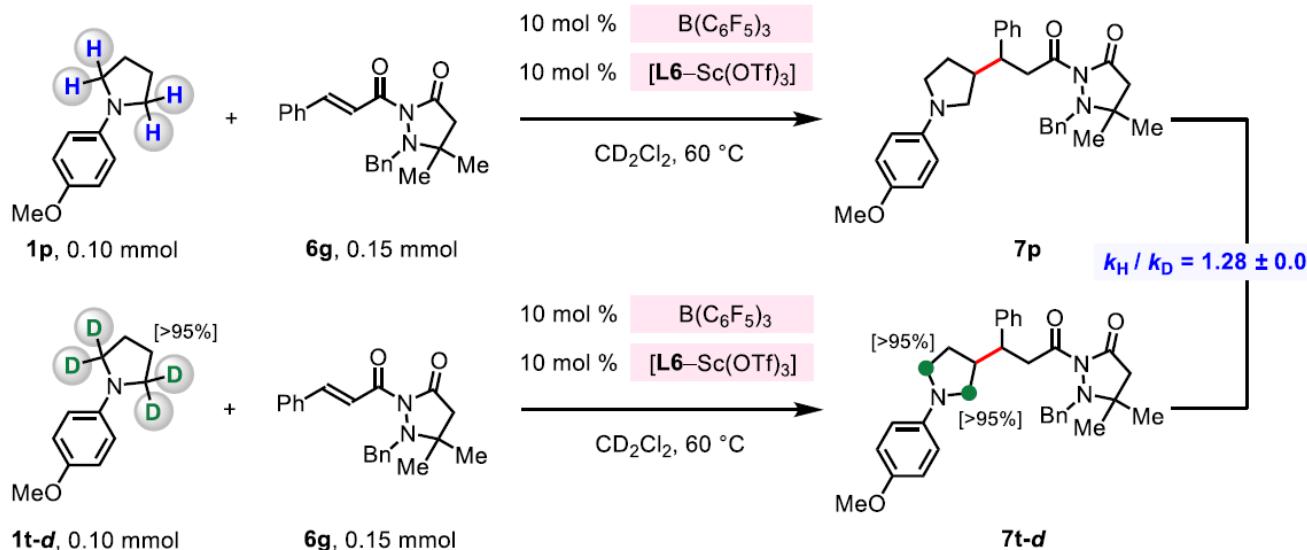
Determination of the Reaction Orders

General reaction conditions for the kinetic experiments



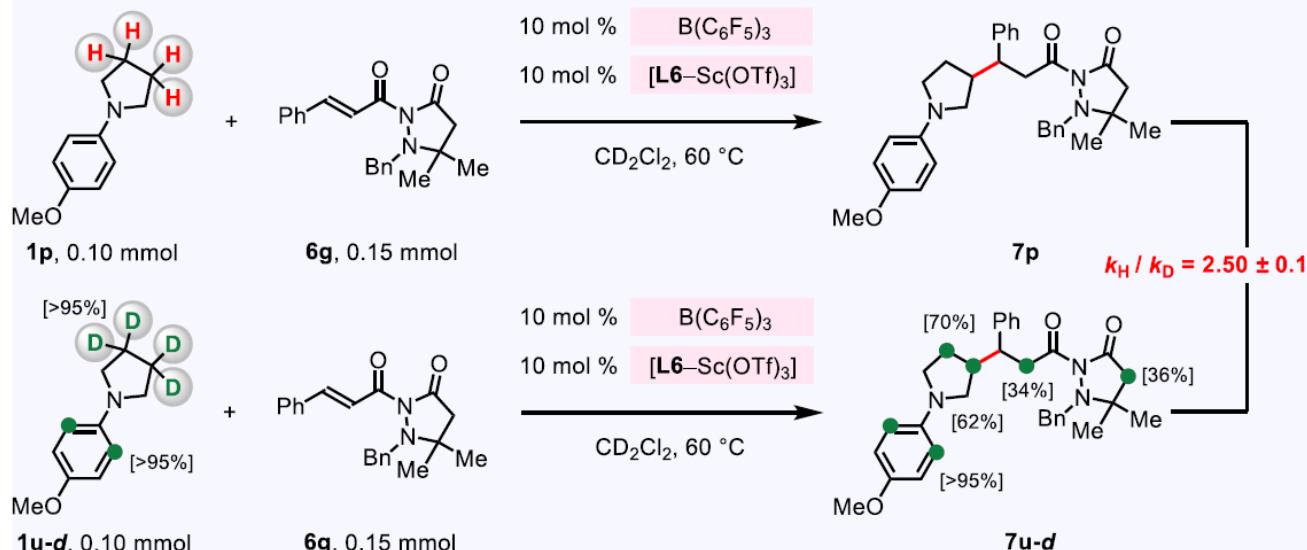
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hydride abstraction is not turnover limiting.

(b) Independent rate measurements with amine isotopologues

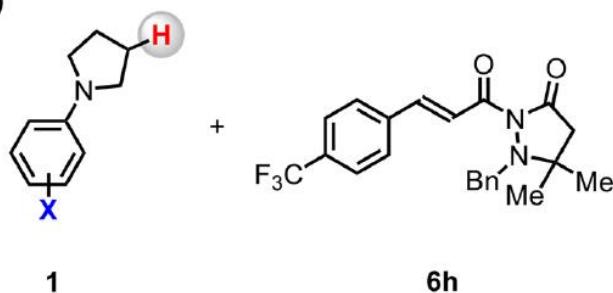


Deprotonation step would be turnover limiting.

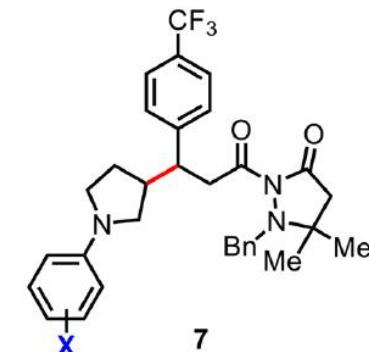
Hammett Studies

Reaction conditions for the Hammett studies

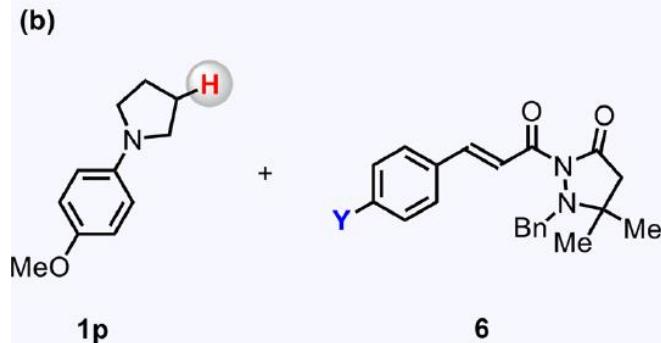
(a)



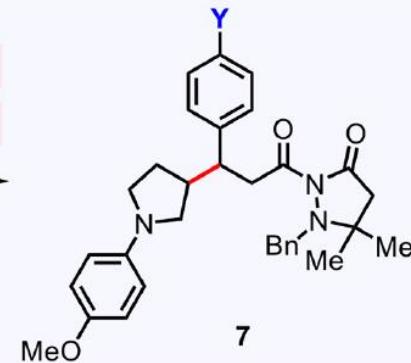
10 mol% $B(C_6F_5)_3$
10 mol% $[L6-Sc(OTf)_3]$
 $\xrightarrow{CD_2Cl_2, 60^\circ C}$
 $= 4.9$



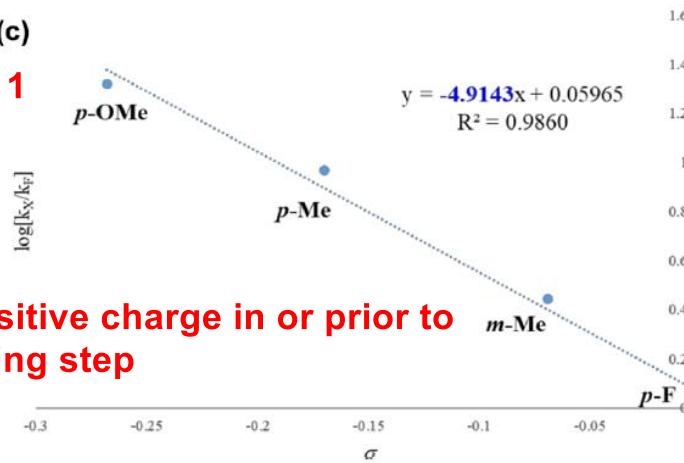
(b)



10 mol% $B(C_6F_5)_3$
10 mol% $[L6-Sc(OTf)_3]$
 $\xrightarrow{CD_2Cl_2, 60^\circ C}$
 $= 0.92$

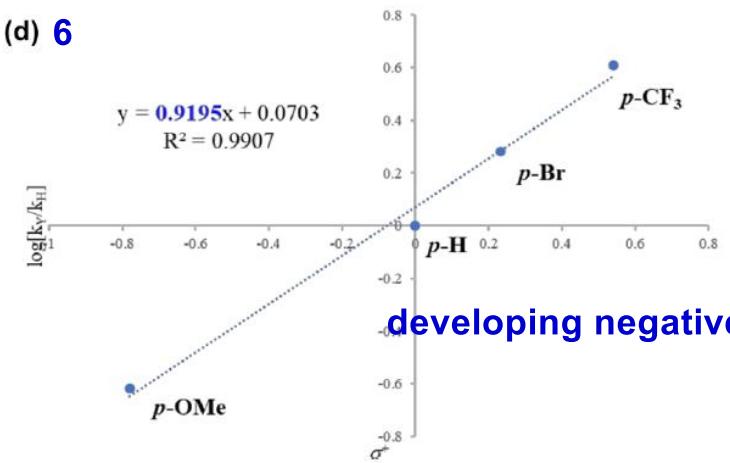


(c)

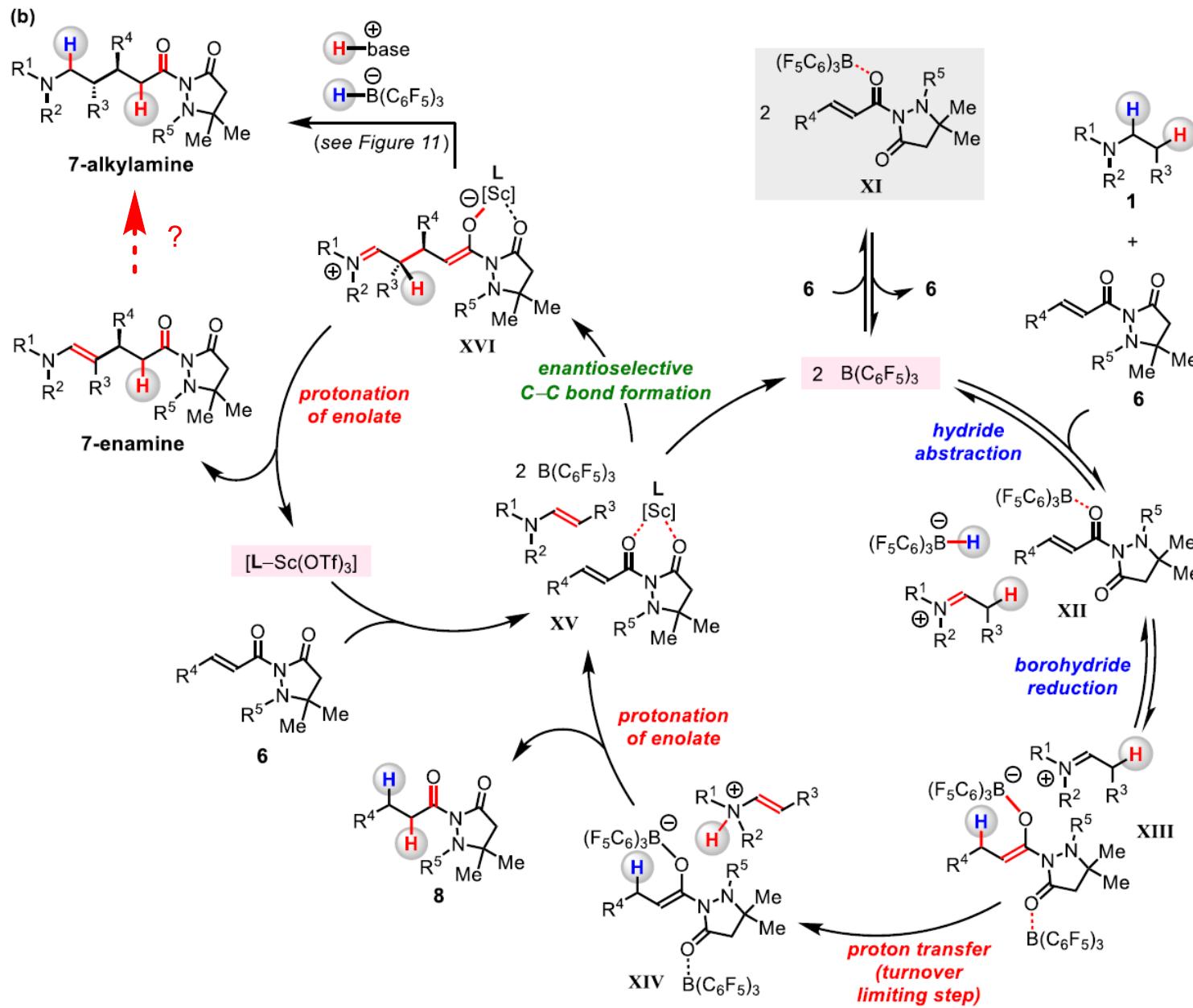


developing positive charge in or prior to
turnover limiting step

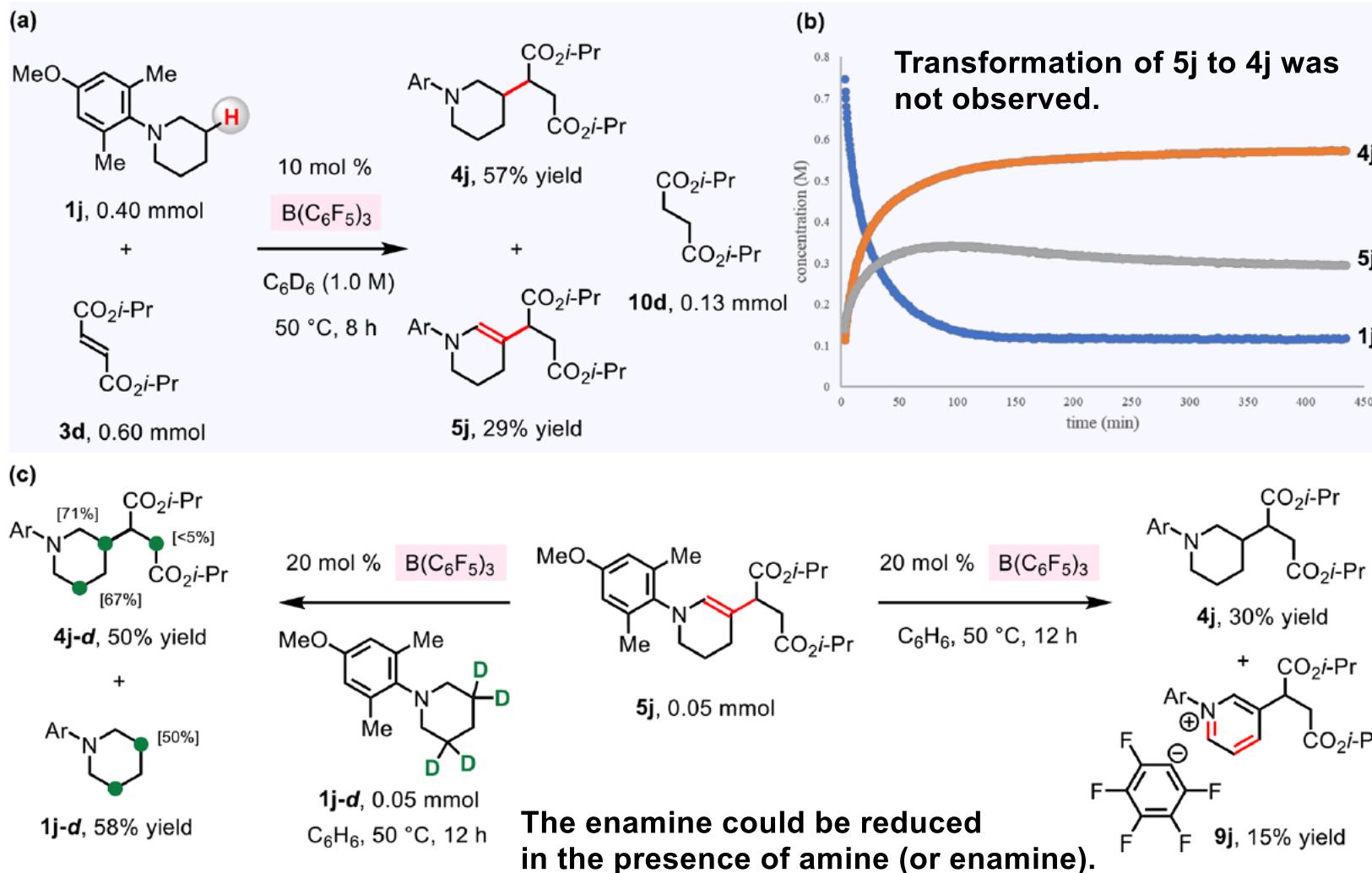
(d) 6



Proposed Reaction Mechanism

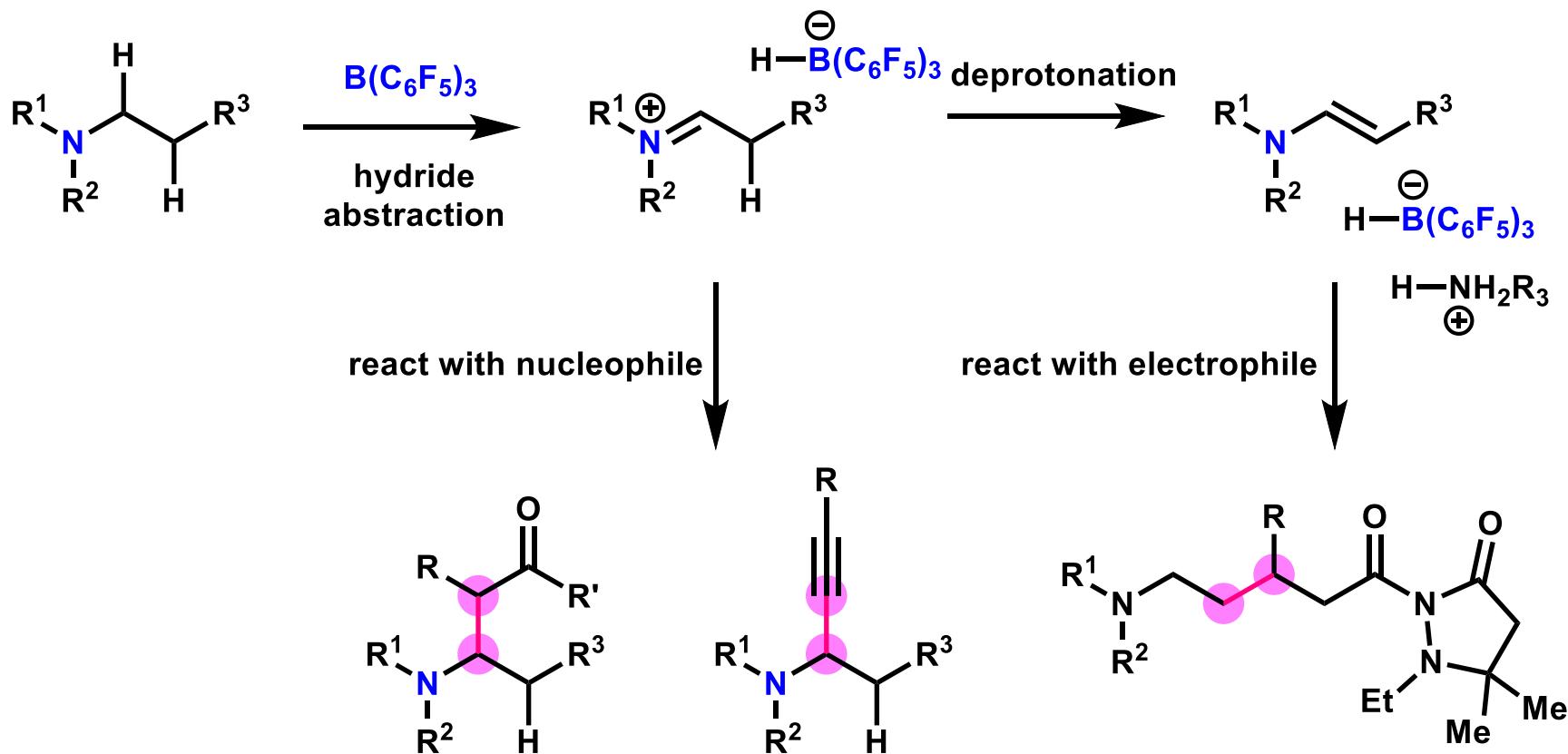


Reduction of Enamines



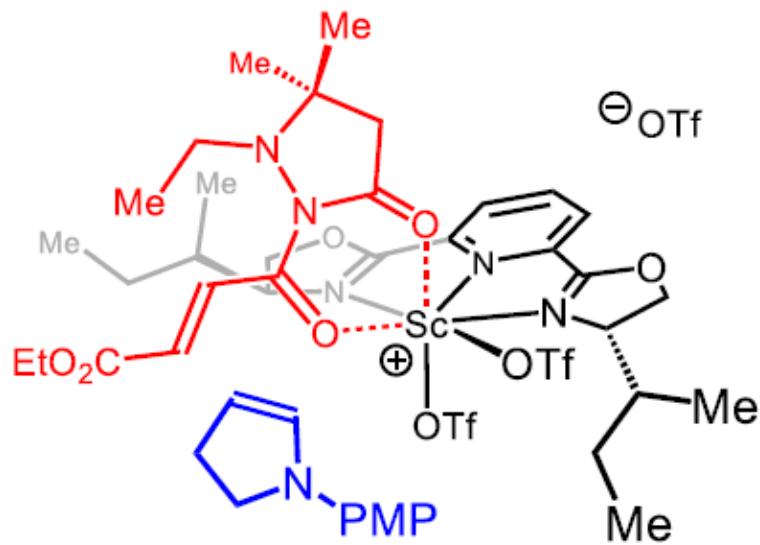
Summary

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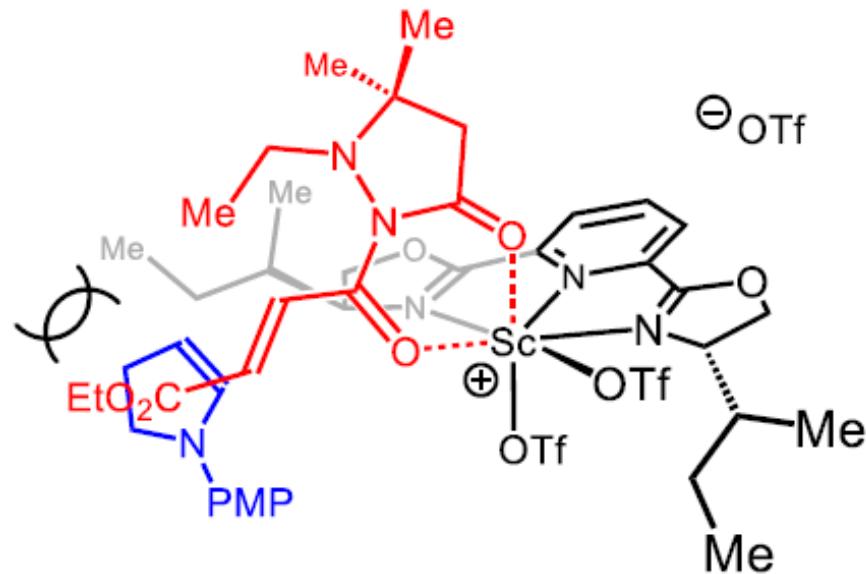


Rationale for the Enantioselectivity

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VII, favored



VIII, disfavored