

## Enantioselective Total Synthesis of (-)-Daphenylline

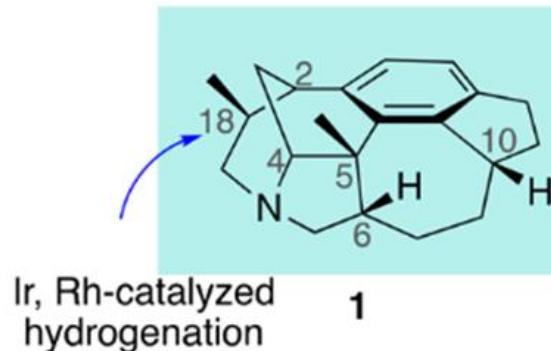
Bing-Lu Wu,<sup>§</sup> Jian-Neng Yao,<sup>§</sup> Xiang-Xi Long, Zong-Qin Tan, Xiao Liang, Li Feng, Kun Wei, and Yu-Rong Yang\*



Cite This: *J. Am. Chem. Soc.* 2024, 146, 1262–1268



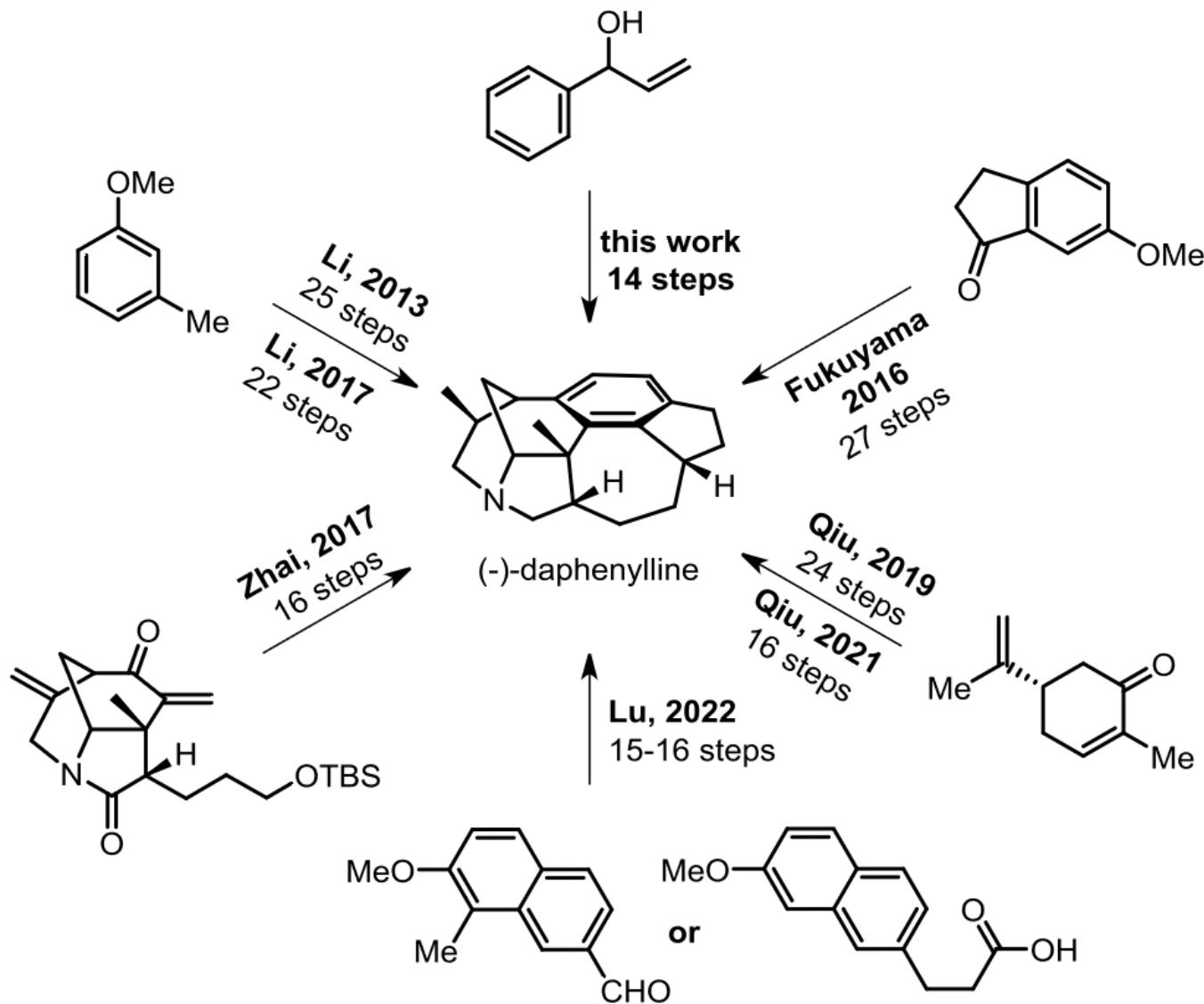
Read Online

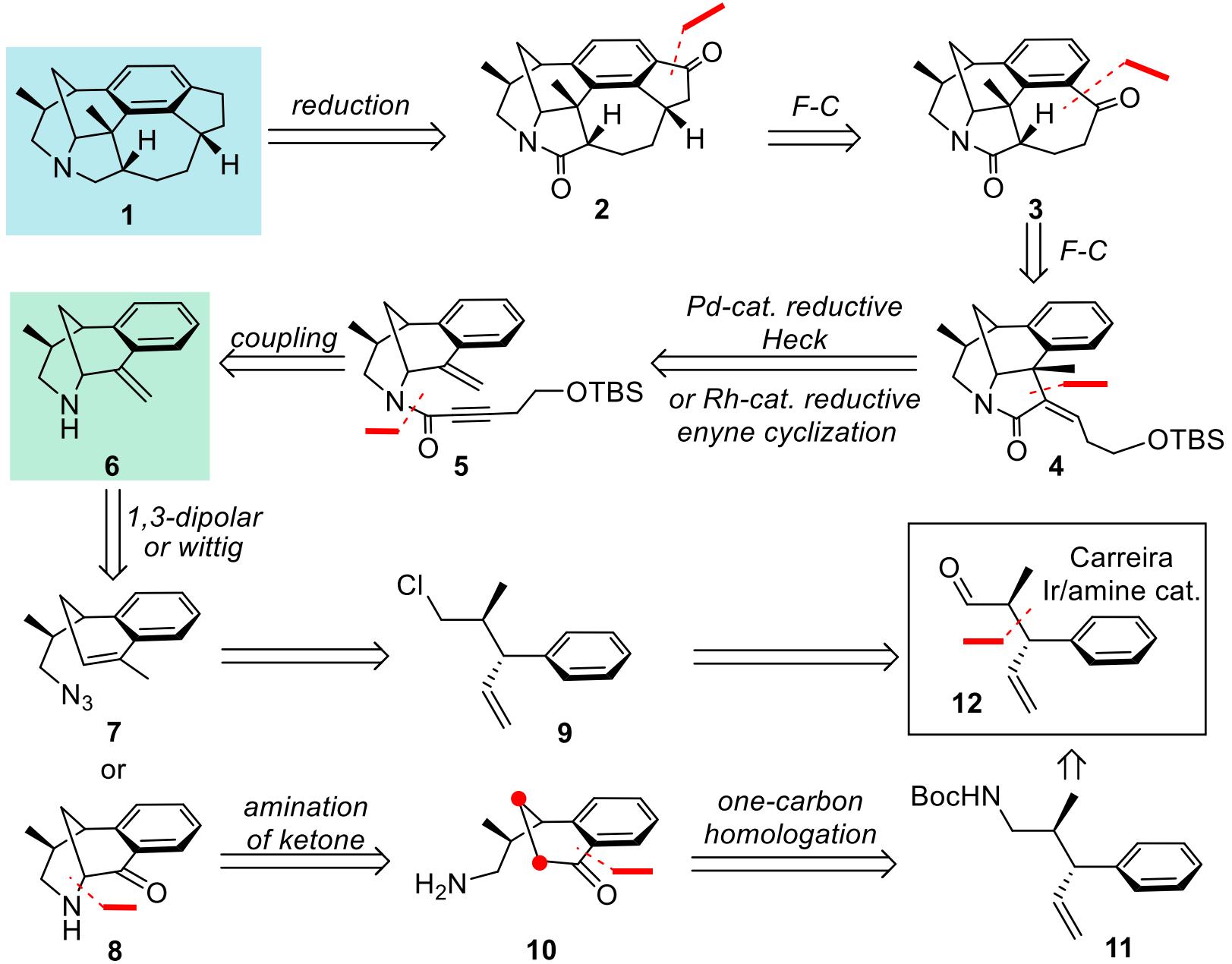


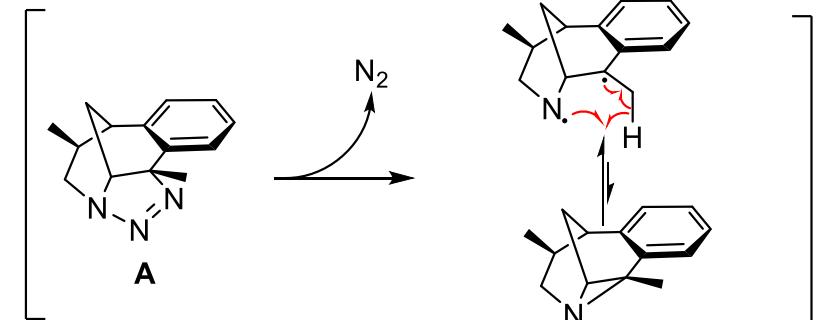
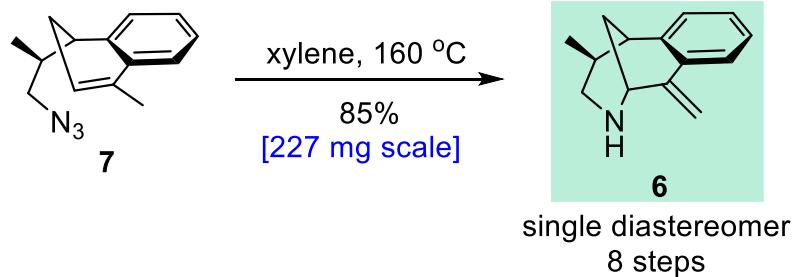
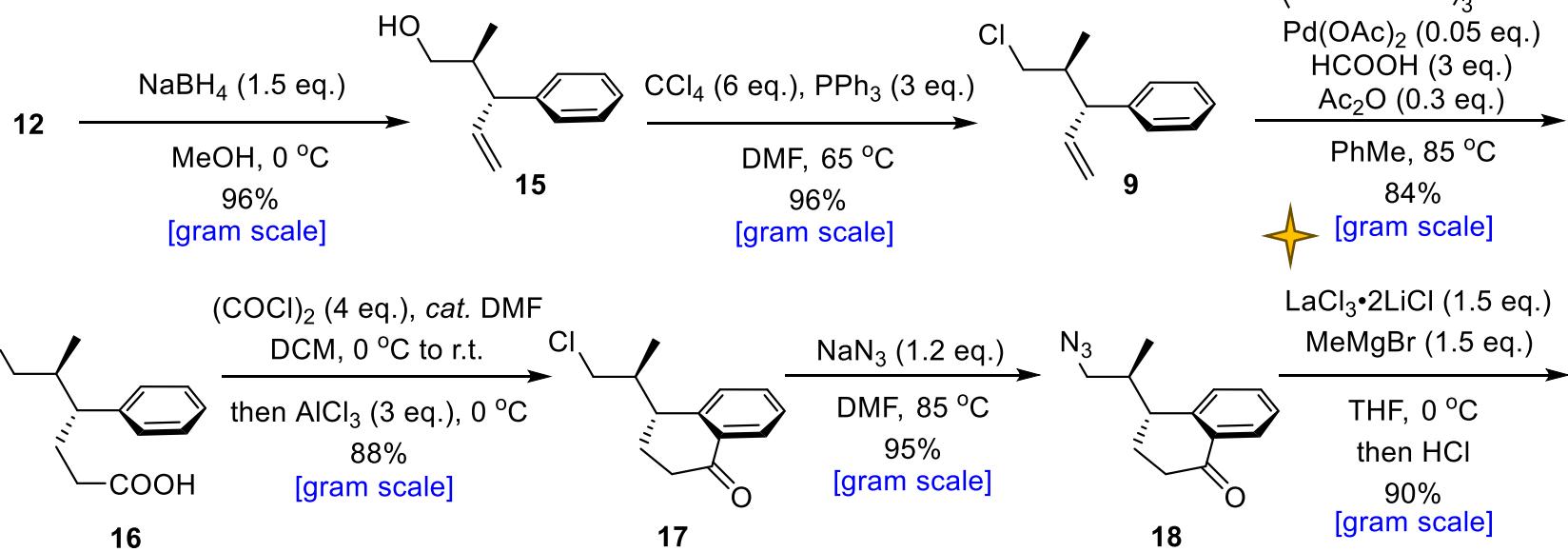
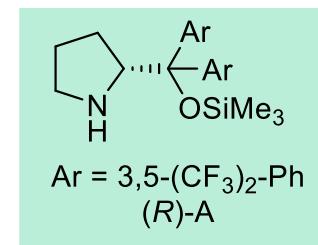
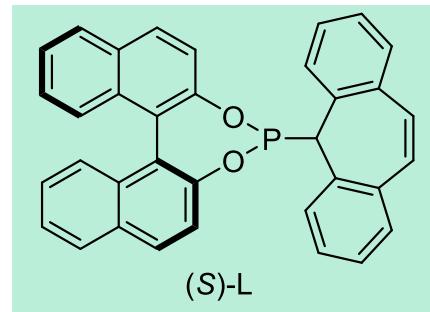
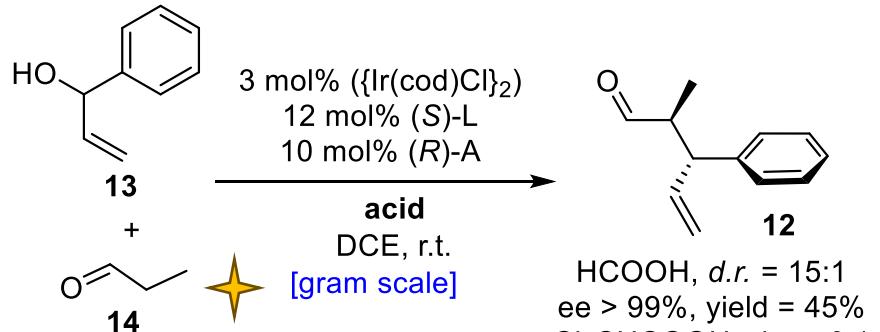
prior asymmetric strategies

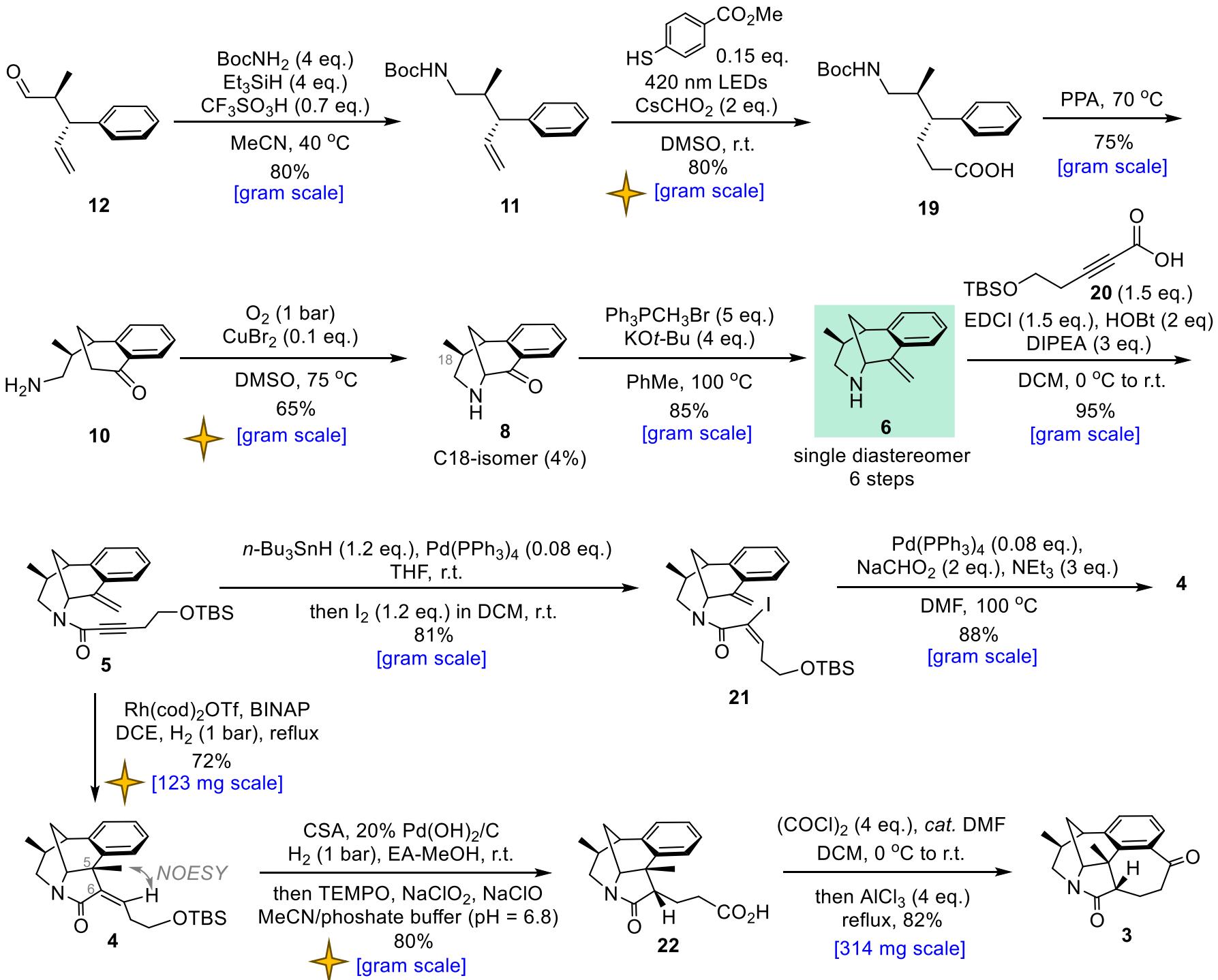
starting with one chiral stereocenter

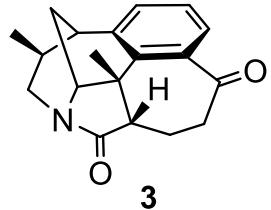
- C4, enzymatic resolution, (A. Li, Zhai)
  - C2, chiral pool, (Qiu)
  - C10, catalytic asymmetric, (Fukuyama, Lu)
- 
- C2 and C18, catalytic asymmetric  
(this work)



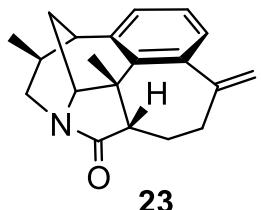




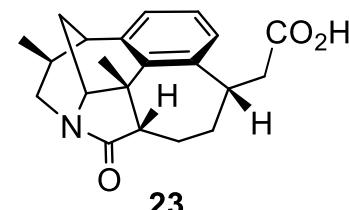




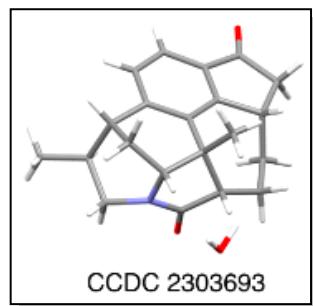
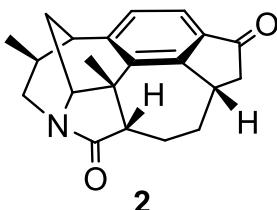
$\text{Ph}_3\text{PCH}_3\text{Br}$  (10 eq.)  
 $\text{KO}t\text{-Bu}$  (8 eq.)  
PhMe, 120 °C  
85%  
[295 mg scale]



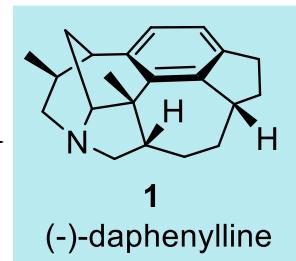
$\text{HS-C}_6\text{H}_4\text{CO}_2\text{Me}$  0.15 eq.  
420 nm LEDs  
 $\text{CsCHO}_2$  (2 eq.)  
DMSO, r.t.  
75%  
[106 gram scale]



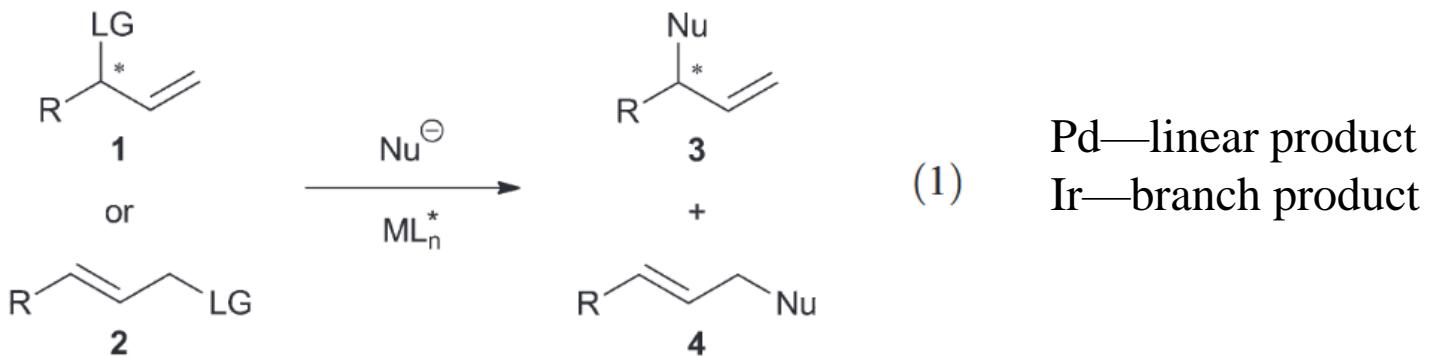
$(\text{COCl})_2$  (4 eq.), cat. DMF  
DCM, 0 °C to r.t.  
then  $\text{AlCl}_3$  (5 eq.)  
reflux, 81%  
[102 mg scale]



Pd/C (0.1 eq.)  
4 Å MS,  $\text{H}_2$  (14 bar)  
DME, 140 °C  
then  $\text{RhH}(\text{CO})(\text{PPh}_3)_3$  (0.15 eq.)  
 $\text{PhSiH}_3$  (3 eq.)  
r.t., 65%

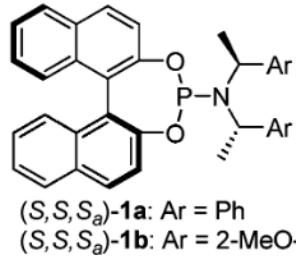
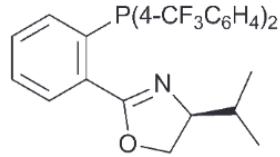


# Iridium-Catalyzed Asymmetric Allylic Substitution Reactions (AAS)

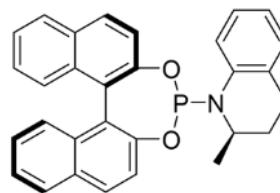


## Development

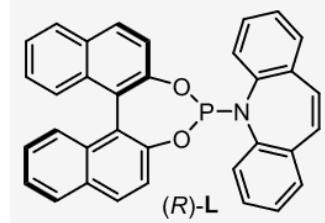
1997 Takeuchi & Kashio  $\longleftrightarrow$  Helmchen & Hartwig  
Ligand  $\longleftrightarrow$  Alexakis-You 2007 Carreira  $\longleftrightarrow$  Krische



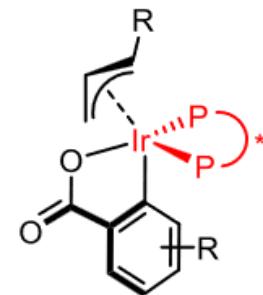
Feringa–Alexakis



You



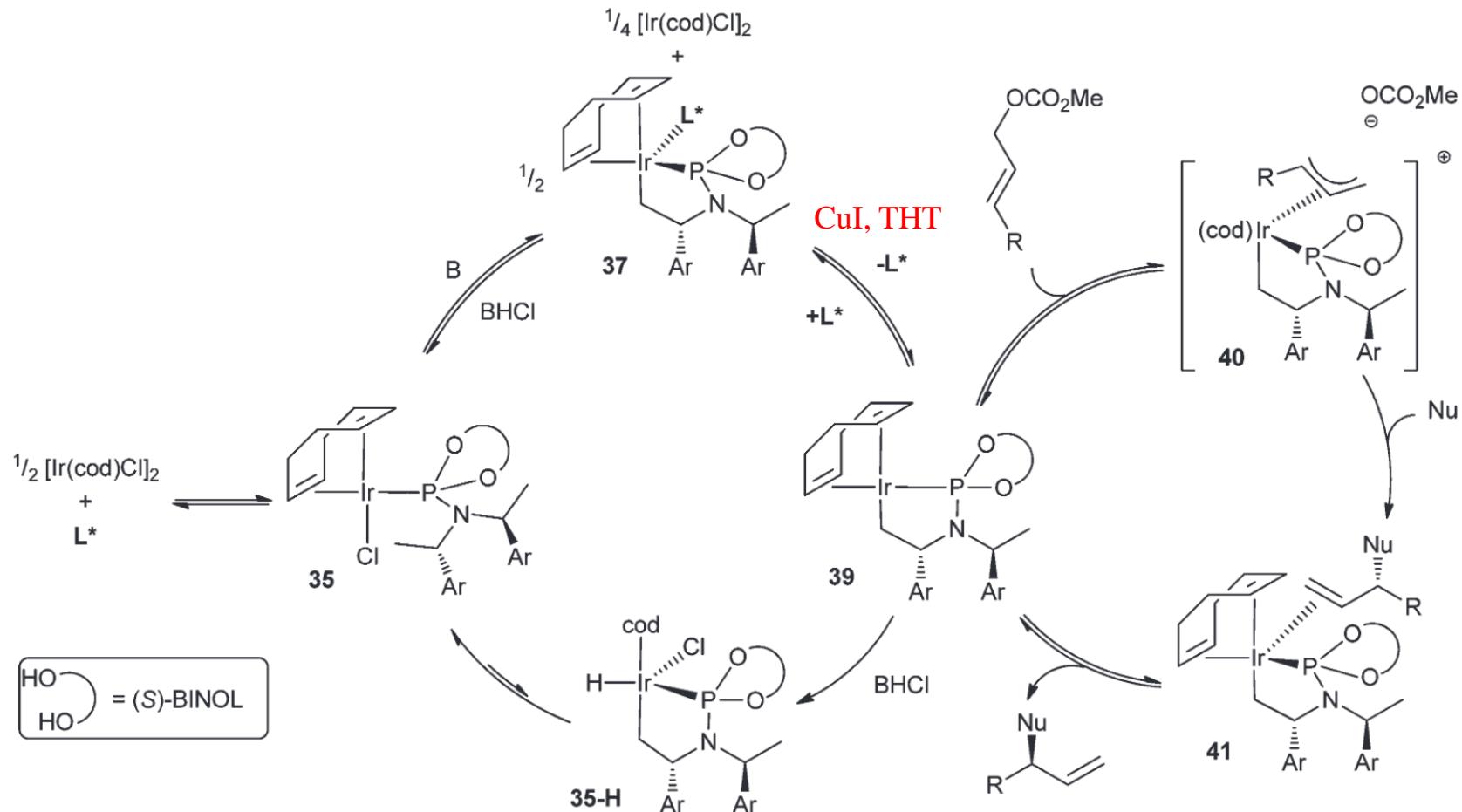
Carreira



Krische

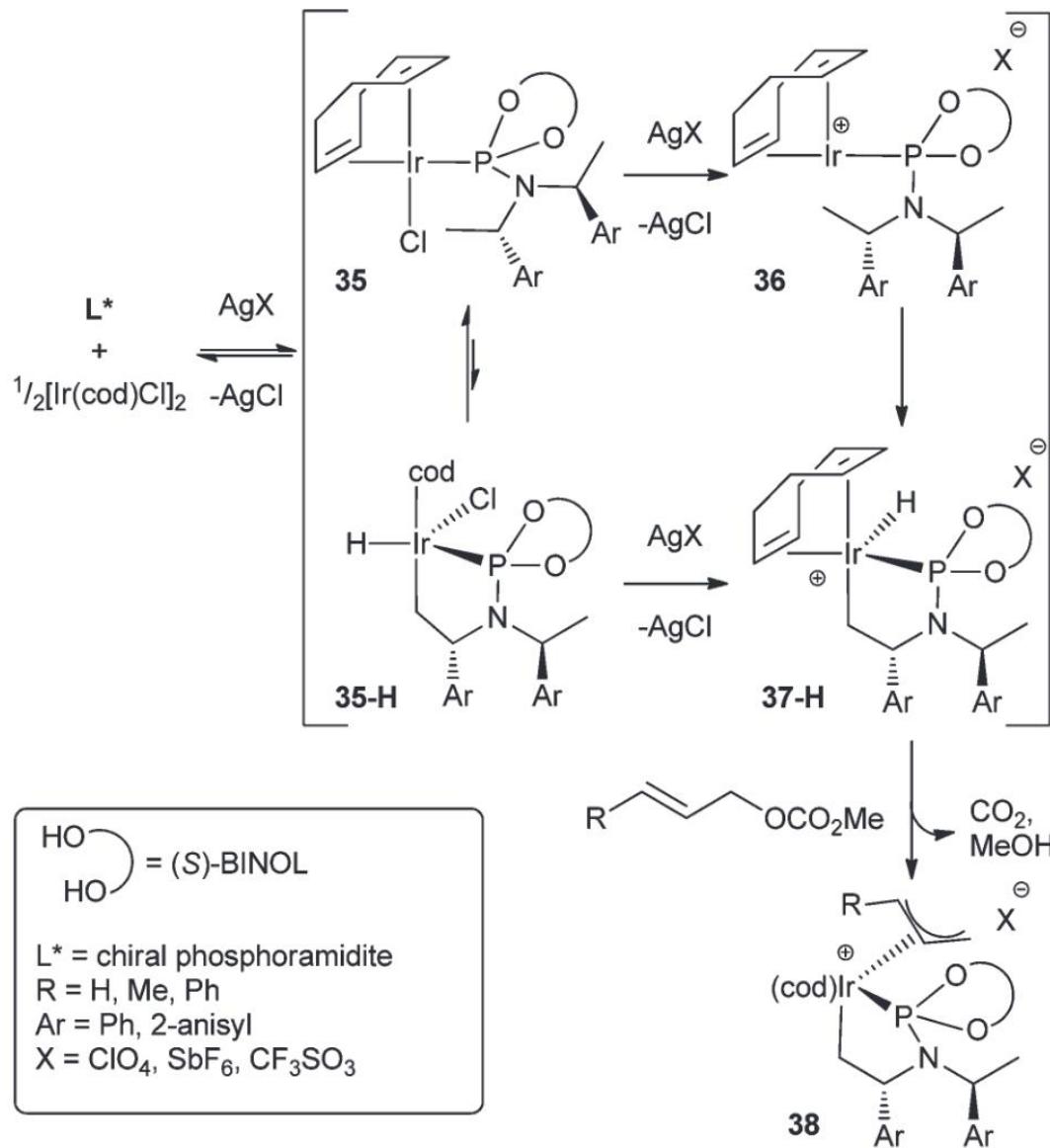
# Iridium-Catalyzed Asymmetric Allylic Substitution Reactions (AAS)

## Mechanism

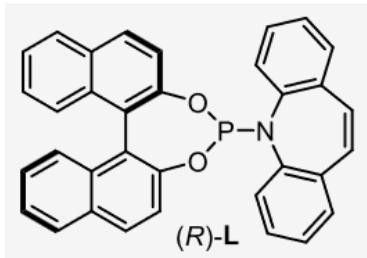


# Iridium-Catalyzed Asymmetric Allylic Substitution Reactions (AAS)

Later



# Iridium-Catalyzed Asymmetric Allylic Substitution Reactions (AAS)

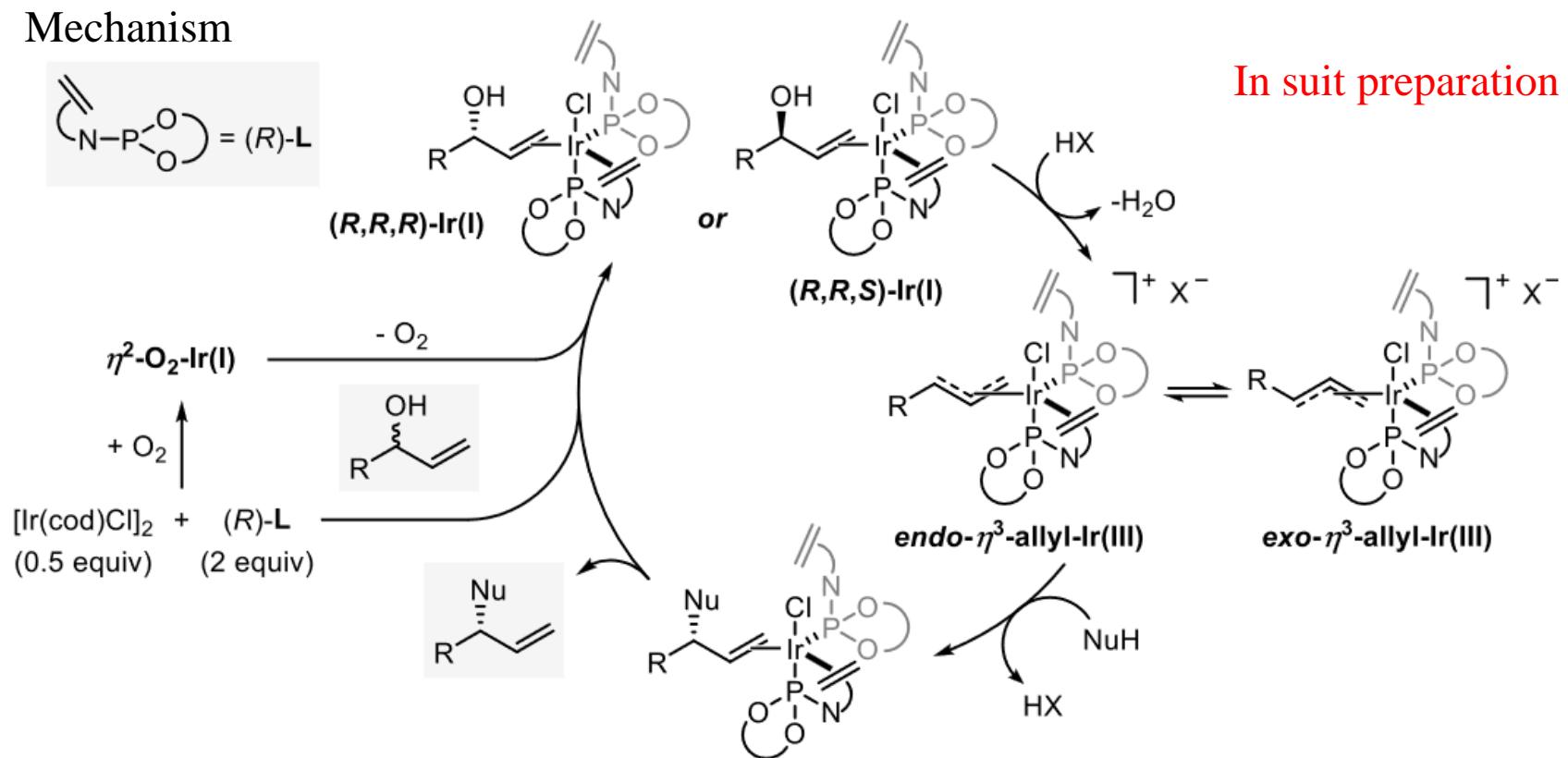


Advantage:

- 1、 excellent tolerance toward acid, air, and moisture
- 2、 unprotected racemic branched allylic alcohols
- 3、 2  $\pi$ -acidic ligands render the metal center more electrophilic

Carreira Ligand

Mechanism

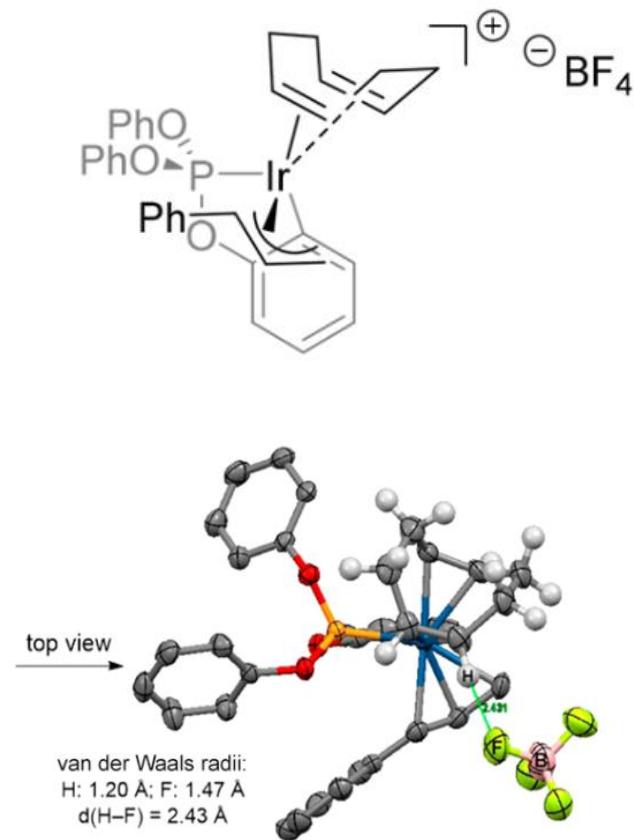
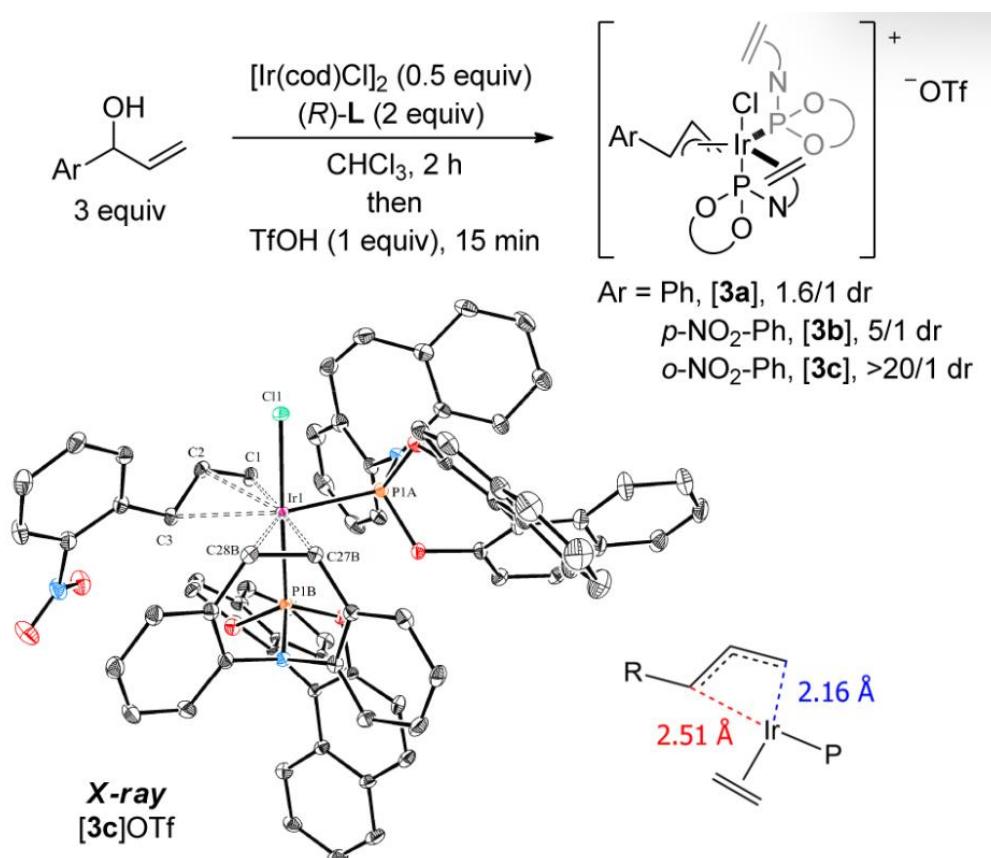


# Iridium-Catalyzed Asymmetric Allylic Substitution Reactions (AAS)

## Regioselectivity

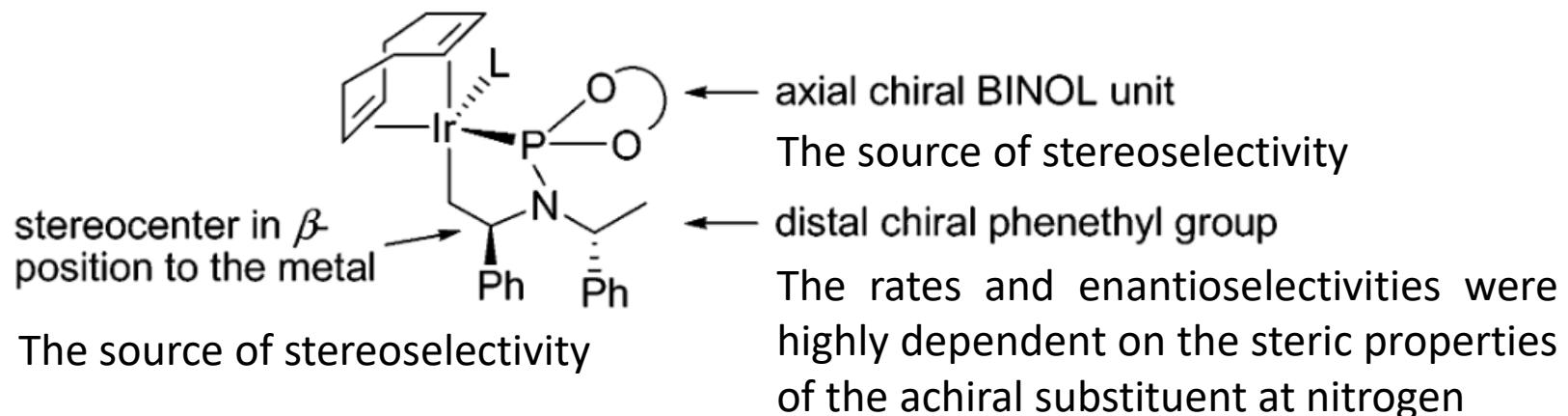
trans-effect & steric

cod ligand's C-H • • • O interactions

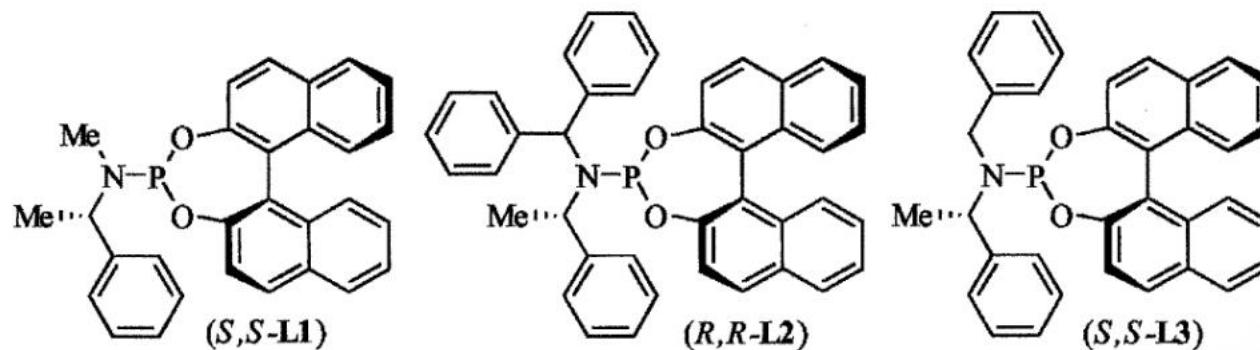


# Iridium-Catalyzed Asymmetric Allylic Substitution Reactions (AAS)

## Stereoselectivity

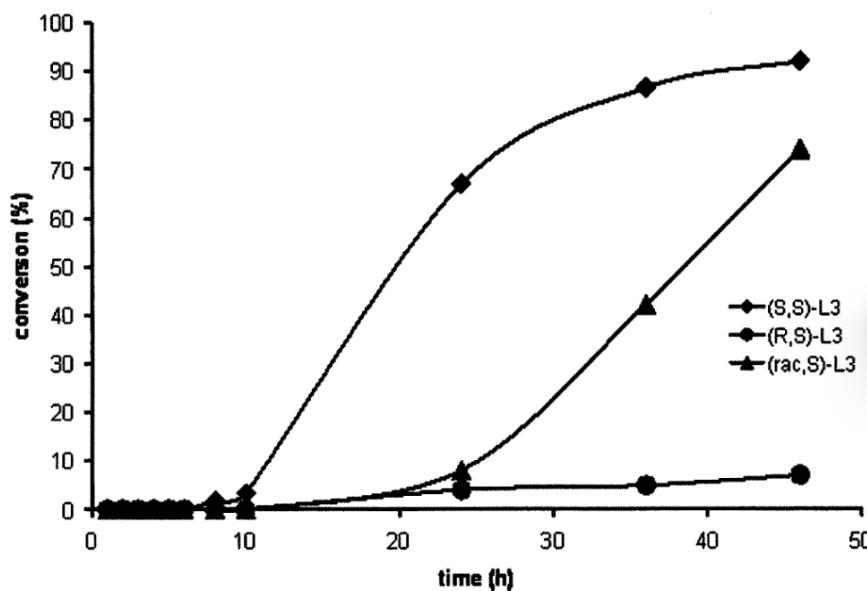


Editing the stereochemical elements in the iridium catalyst

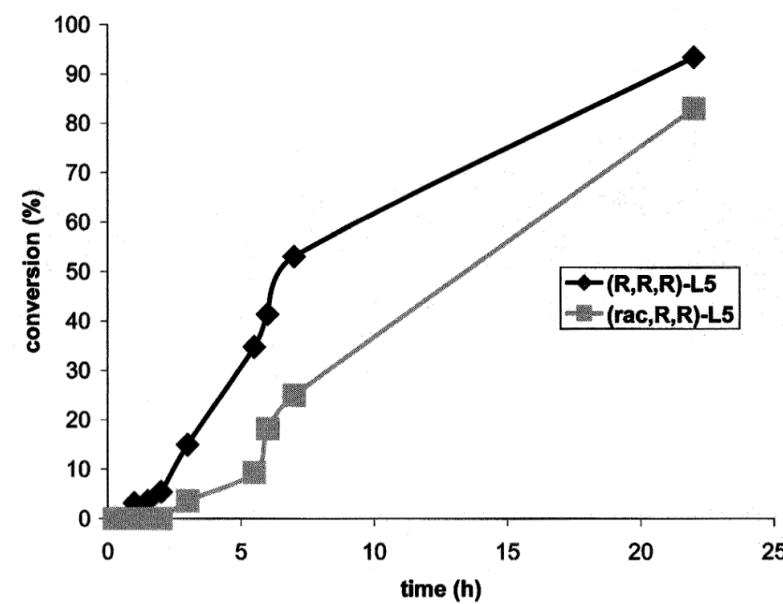
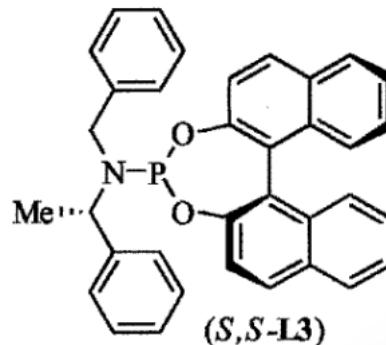


# Iridium-Catalyzed Asymmetric Allylic Substitution Reactions (AAS)

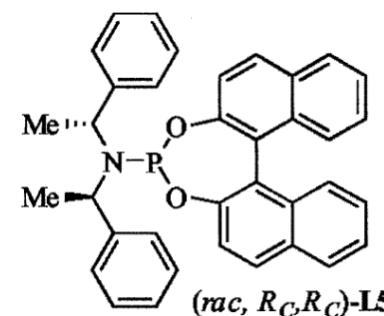
## Stereoselectivity



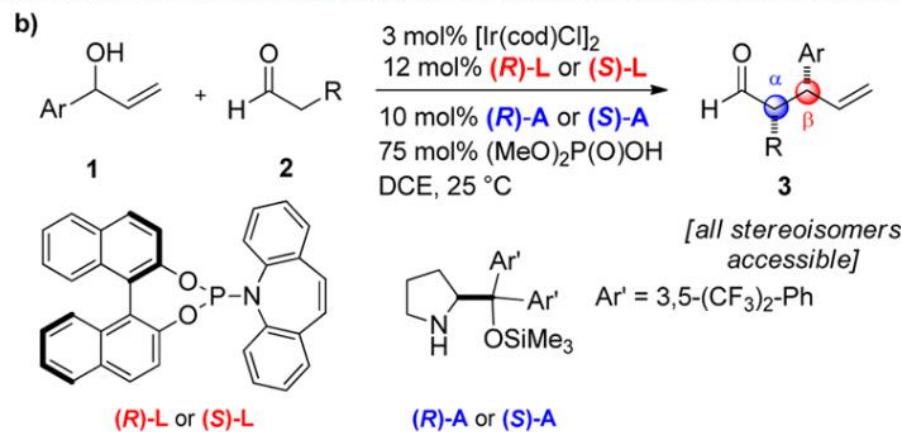
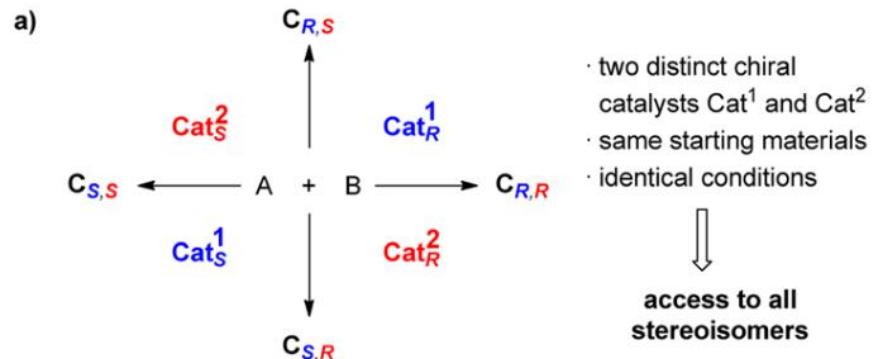
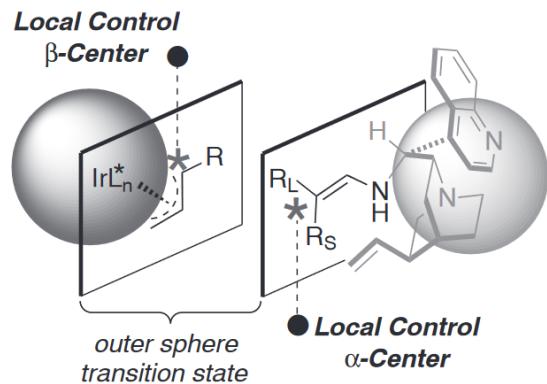
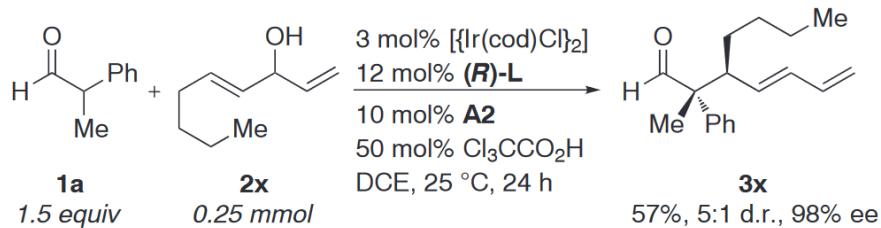
**Fig. 4.** Profile of the reaction of benzylamine with cinnamylcarbonate in the presence of 1 mol % of  $[(\text{COD})\text{IrCl}]_2$  and 2 mol % of the two diastereomeric phosphoramidites from *N*-benzylphenethylamines or the mixture of the two diastereomers together.



**Fig. 5.** Profile of the reaction of allylamine with cinnamylcarbonate in the presence of 0.5 mol % of  $[(\text{COD})\text{IrCl}]_2$  and 1 mol % of the two diastereomeric phosphoramidites from homochiral bis(phenethyl)amine.



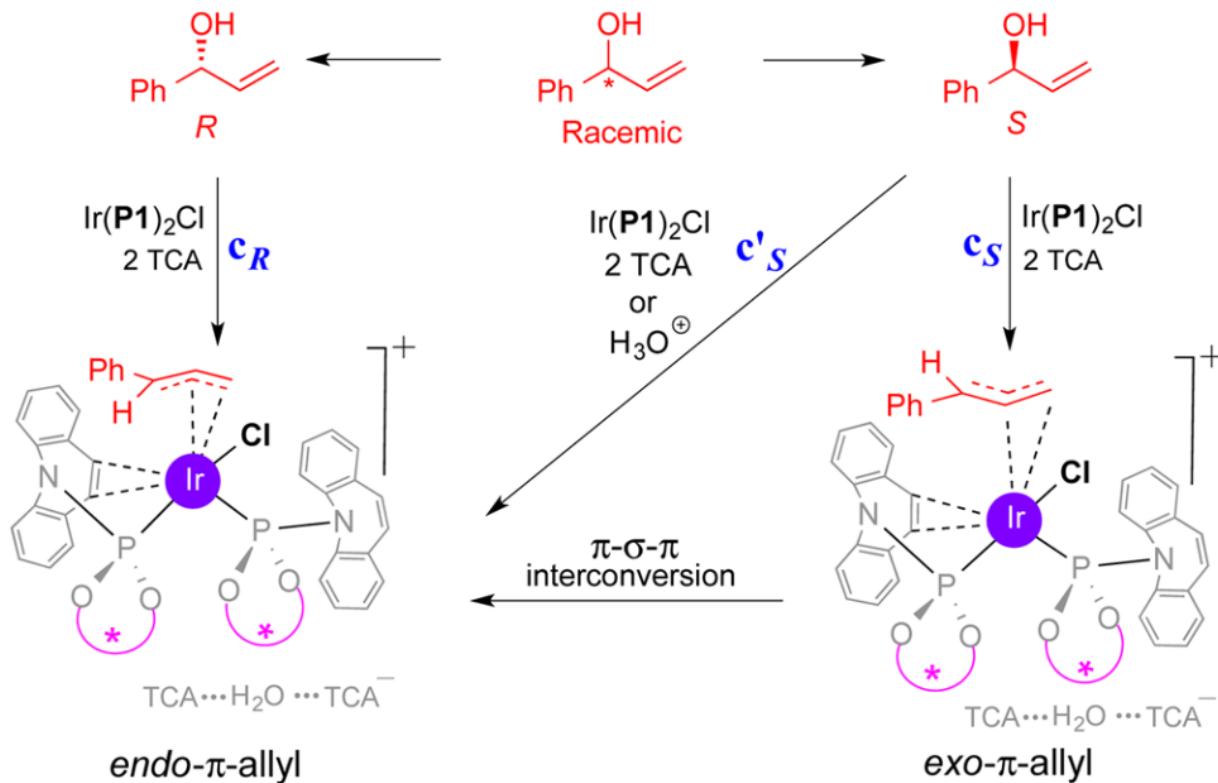
# Stereodivergent $\alpha$ -Allylation of Linear Aldehydes with Dual Iridium and Amine Catalysis



Science, 2013, 340, 1065.

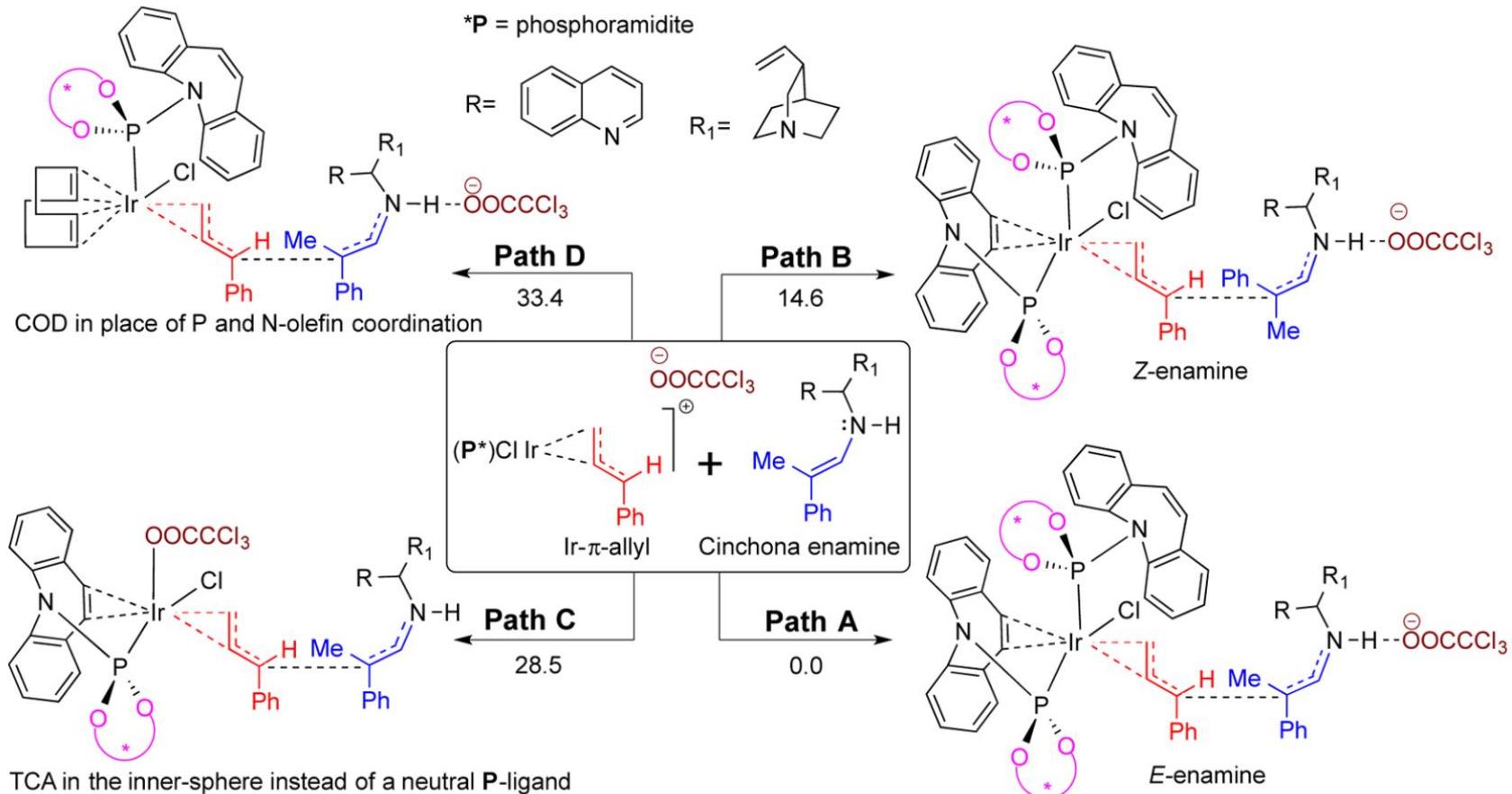
J. Am. Chem. Soc., 2014, 136, 3020.

# Stereodivergent $\alpha$ -Allylation of Linear Aldehydes with Dual Iridium and Amine Catalysis

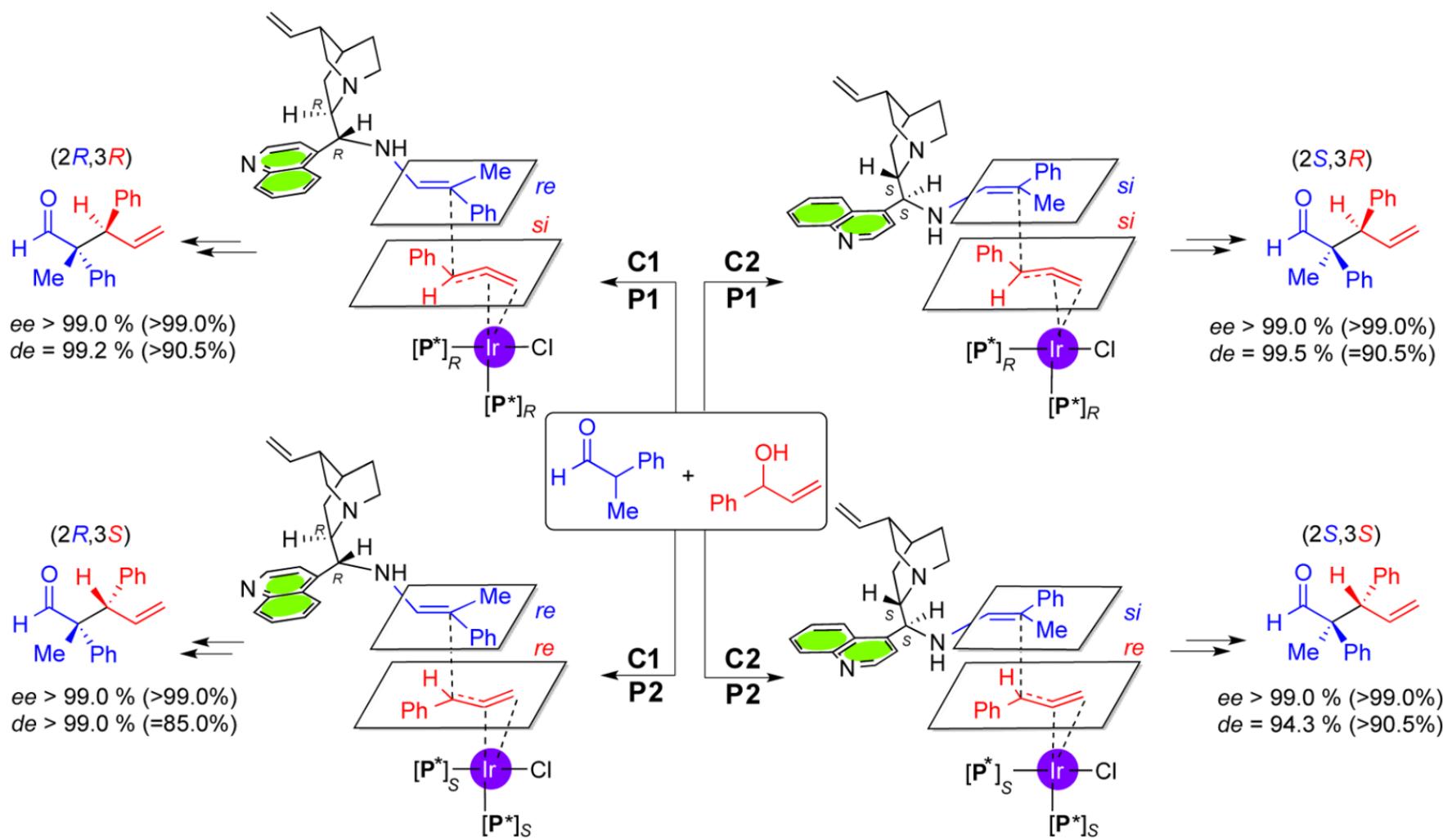


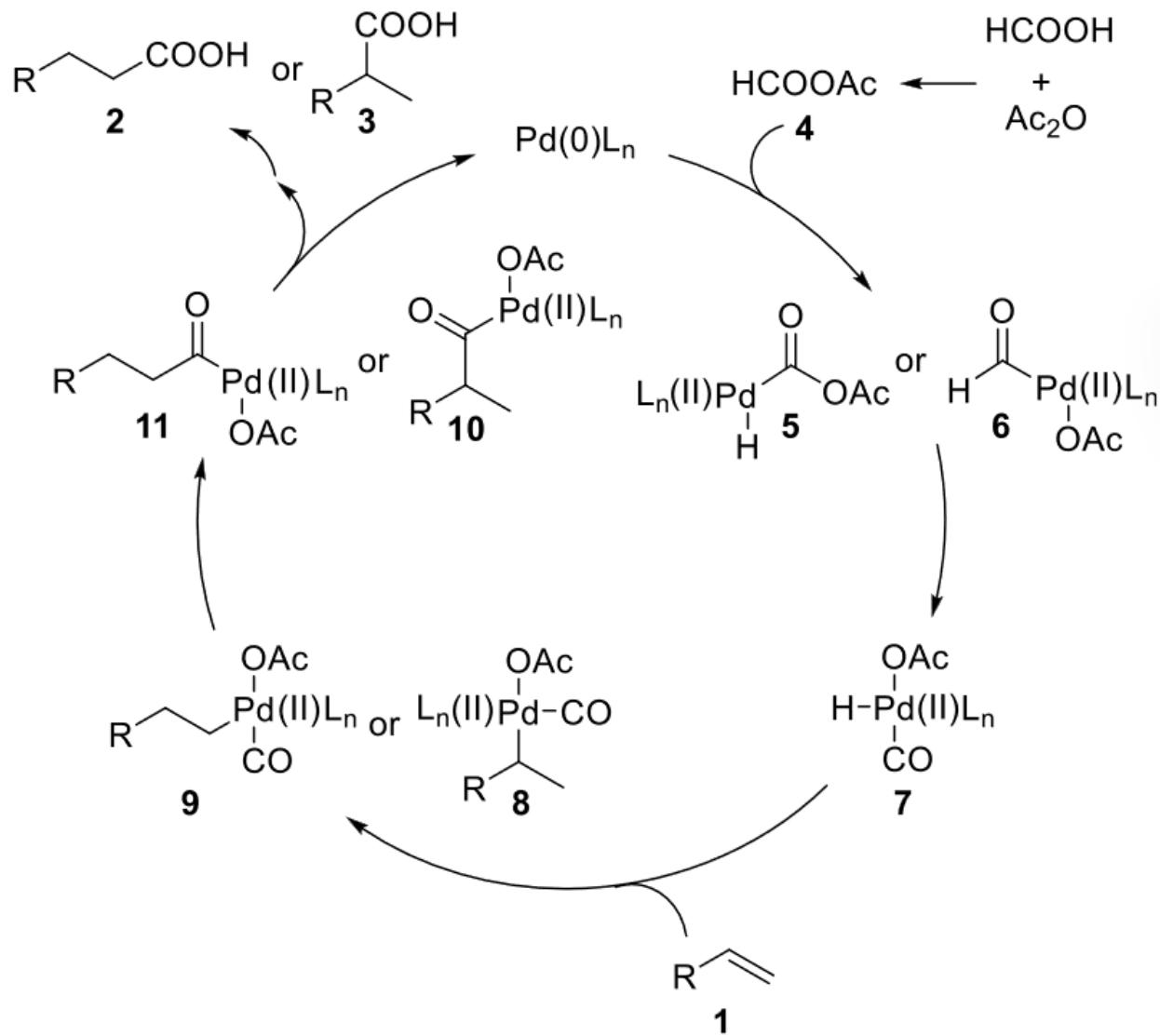
**Figure 3.** Different possibilities for the stereoconvergent formation of the *endo* Ir– $\pi$ -allyl intermediate with *R*-phosphoramidite (**P1**) ligand on iridium.

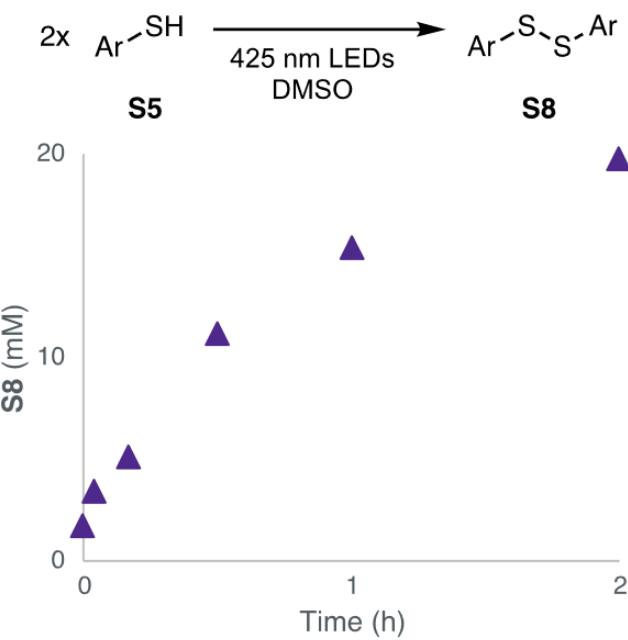
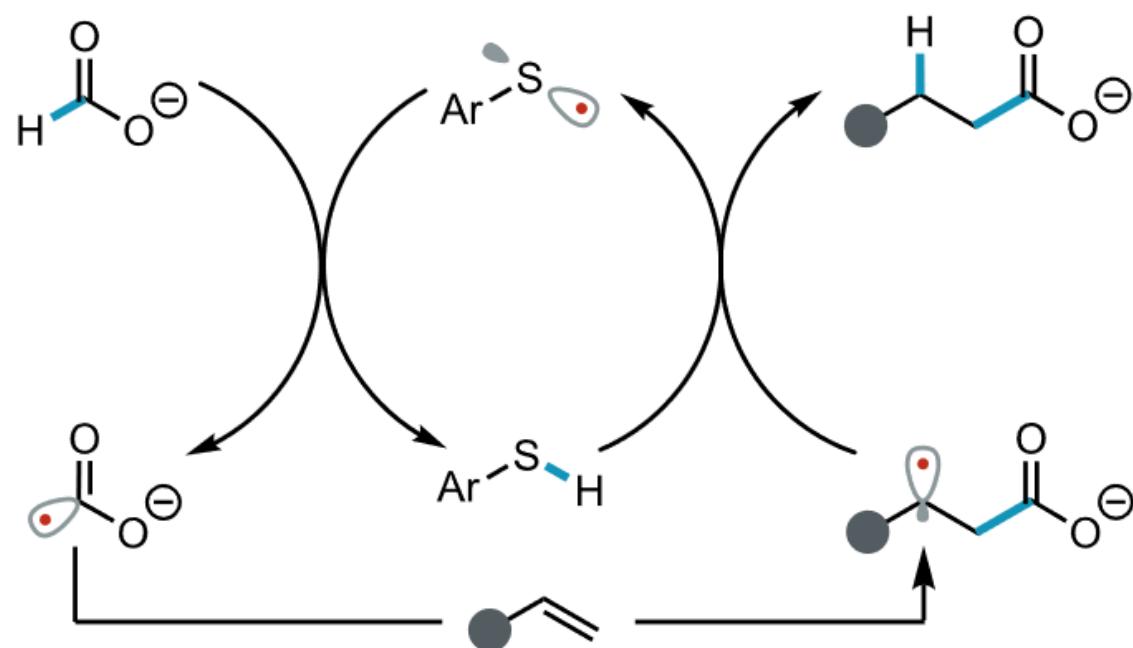
# Stereodivergent $\alpha$ -Allylation of Linear Aldehydes with Dual Iridium and Amine Catalysis

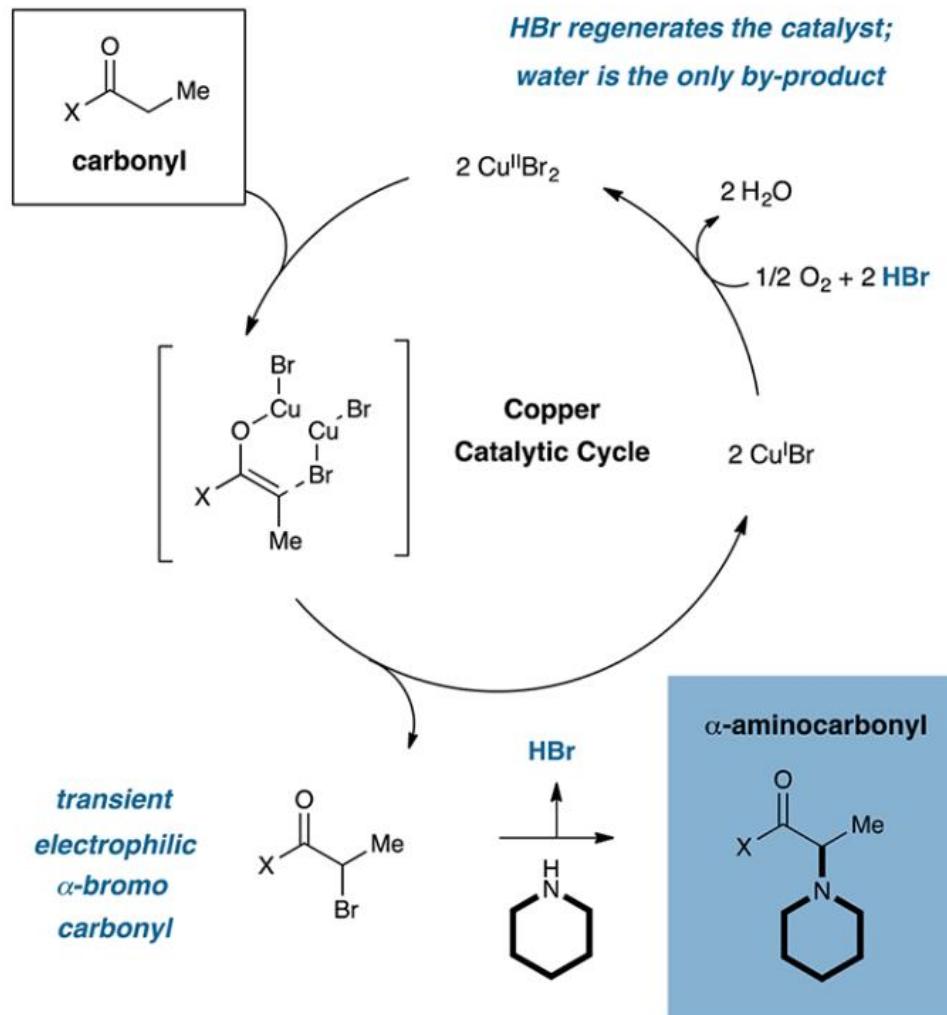


# Stereodivergent $\alpha$ -Allylation of Linear Aldehydes with Dual Iridium and Amine Catalysis







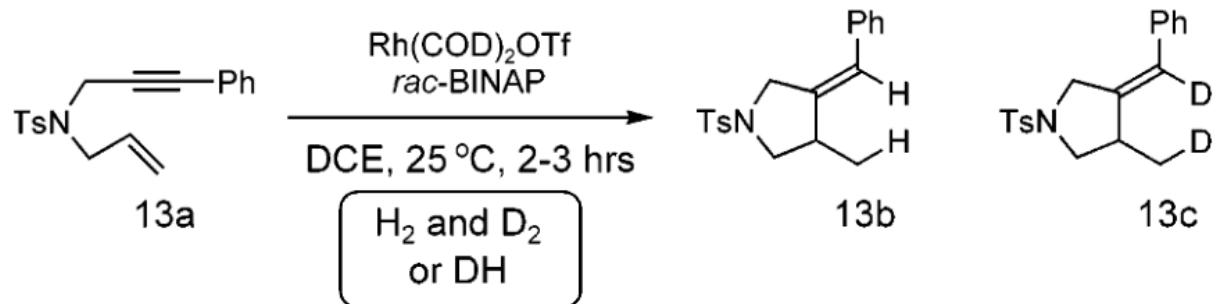


The efficient conversion of electron-deficient ketones was achieved at subambient temperatures to prevent product decomposition, while systems that involve a  $\pi$  rich aryl ring require elevated temperatures.

Efficient  $\alpha$  amination of aliphatic ketones was found to require the introduction of a cocatalyst such as  $NiBr_2$ ,  $ZnBr_2$ , or  $MgI_2$  to facilitate the ketone enolization event.

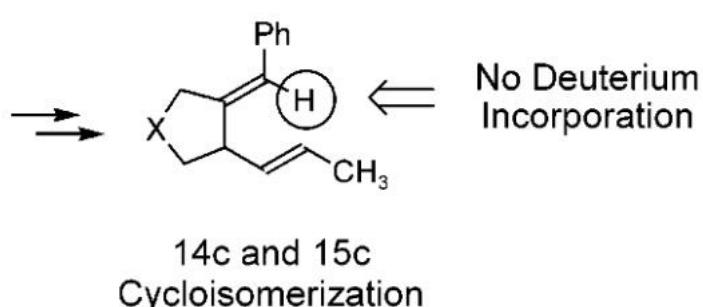
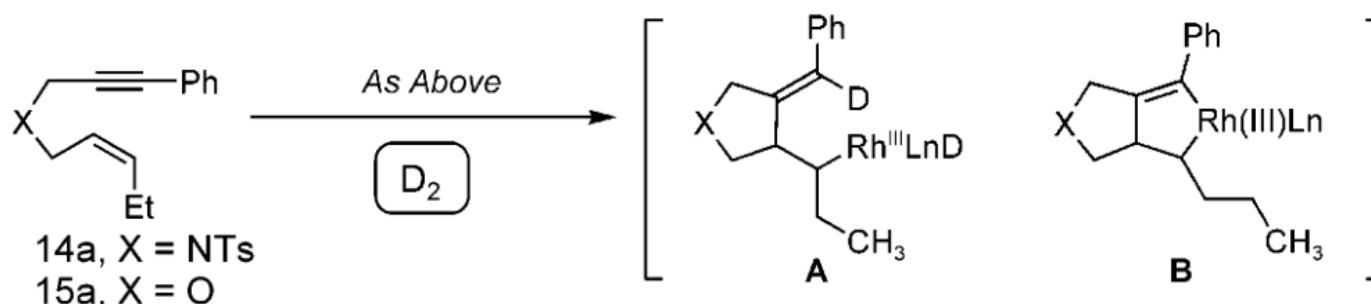
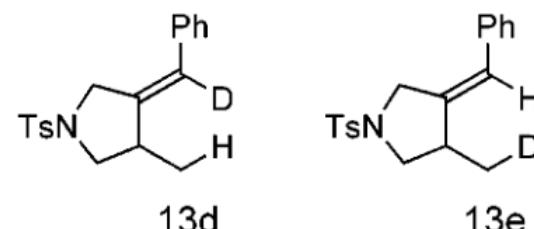
#### Catalyst Regeneration Using Oxygen and Transient HBr





$\text{H}_2/\text{D}_2$ , 95% Yield  
 13b:13c:13d & 13e  
 80.1:19.5:0.4

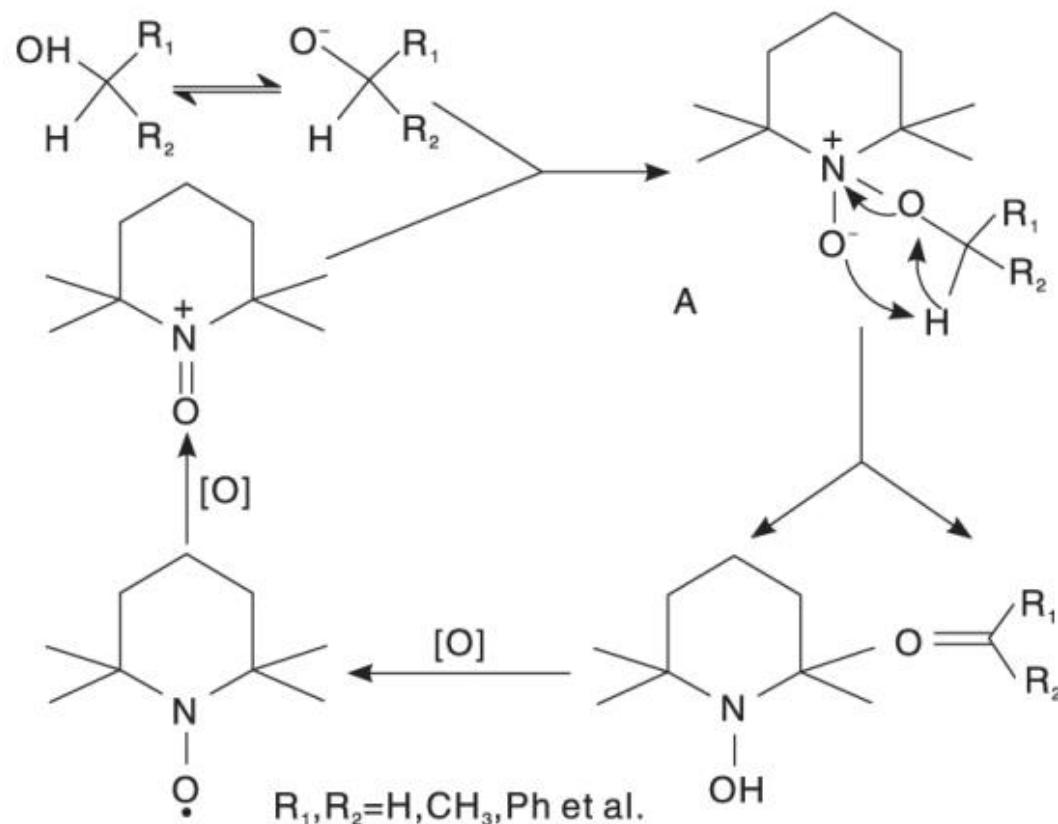
$\text{DH}$ , 88% Yield  
 13b:13c:13d & 13e  
 3.0:0.5:96.5



5 mol% Catalyst Loading  
 14c, 52% Yield  
 (42% Alkyne Reduction)  
 15c, 60% Yield  
100 mol% Catalyst Loading  
 14c, 45% Yield  
 (8% Alkyne Reduction)  
 15c, 71% Yield

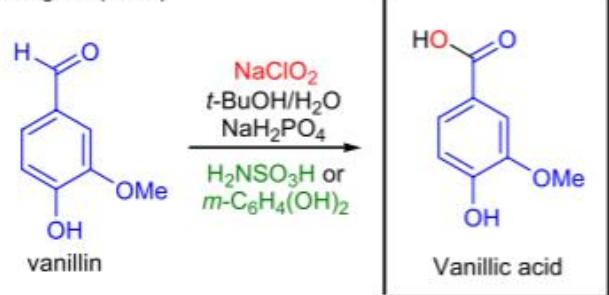
# TEMPO Oxidation

## Proposed Mechanism

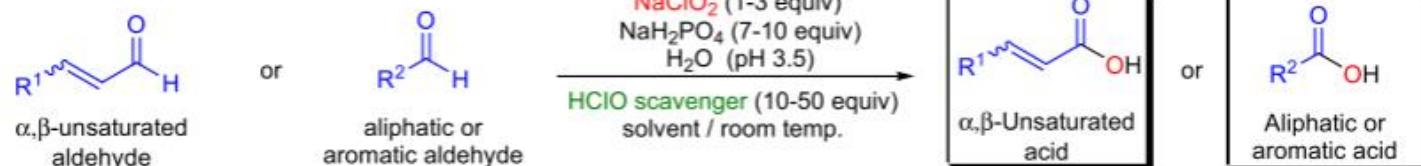
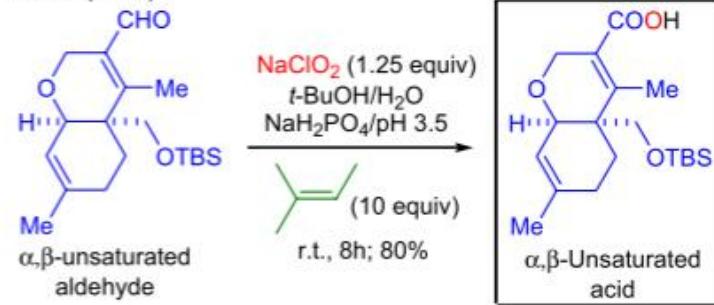


# Pinnick Oxidation

Lindgren (1973):



Kraus (1980):



$\text{R}^1 = \text{H, alkyl, aryl, alkenyl, allyl}; \text{R}^2 = \text{alkyl, aryl, allyl, homoallyl}; \text{scavenger} = 2\text{-methyl-2-butene, H}_2\text{O}_2, \text{H}_2\text{NSO}_3\text{H}, m\text{-C}_6\text{H}_4(\text{OH})_2, \text{DMSO}; \text{solvent} = t\text{-BuOH, } t\text{-BuOH/THF}$

Mechanism:<sup>10,6</sup>

