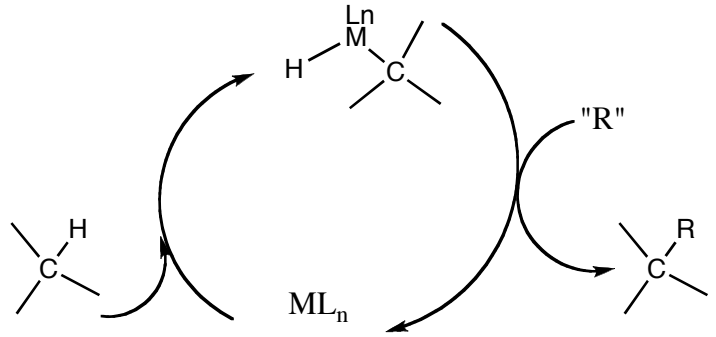
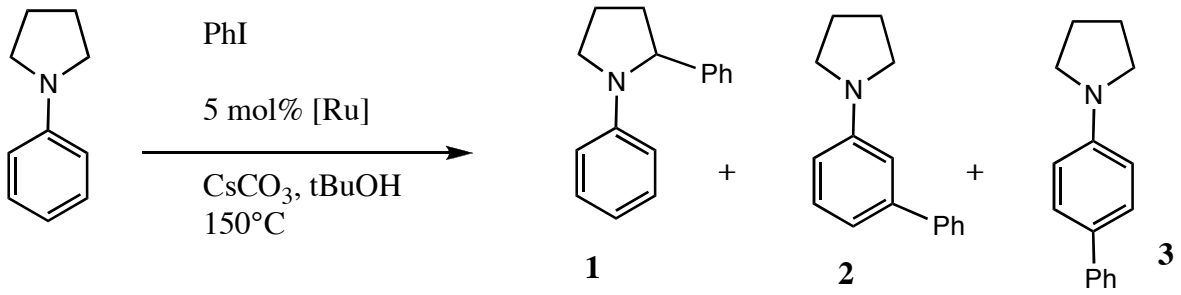
C-H activation for C-C bond formation

Direct C-H activation requires insertion of a transition metal (usually Ru, Ir, Rh or Pd) across a strong C-H bond (90-105 kcal/mol) to form a new, weaker C-M bond (50-80 kcal/mol), followed by generation of a new C-R bond



C-H activation is limited to simple aryl and vinyl sp^2 C-H bonds and C-H bonds adjacent to heteroatoms

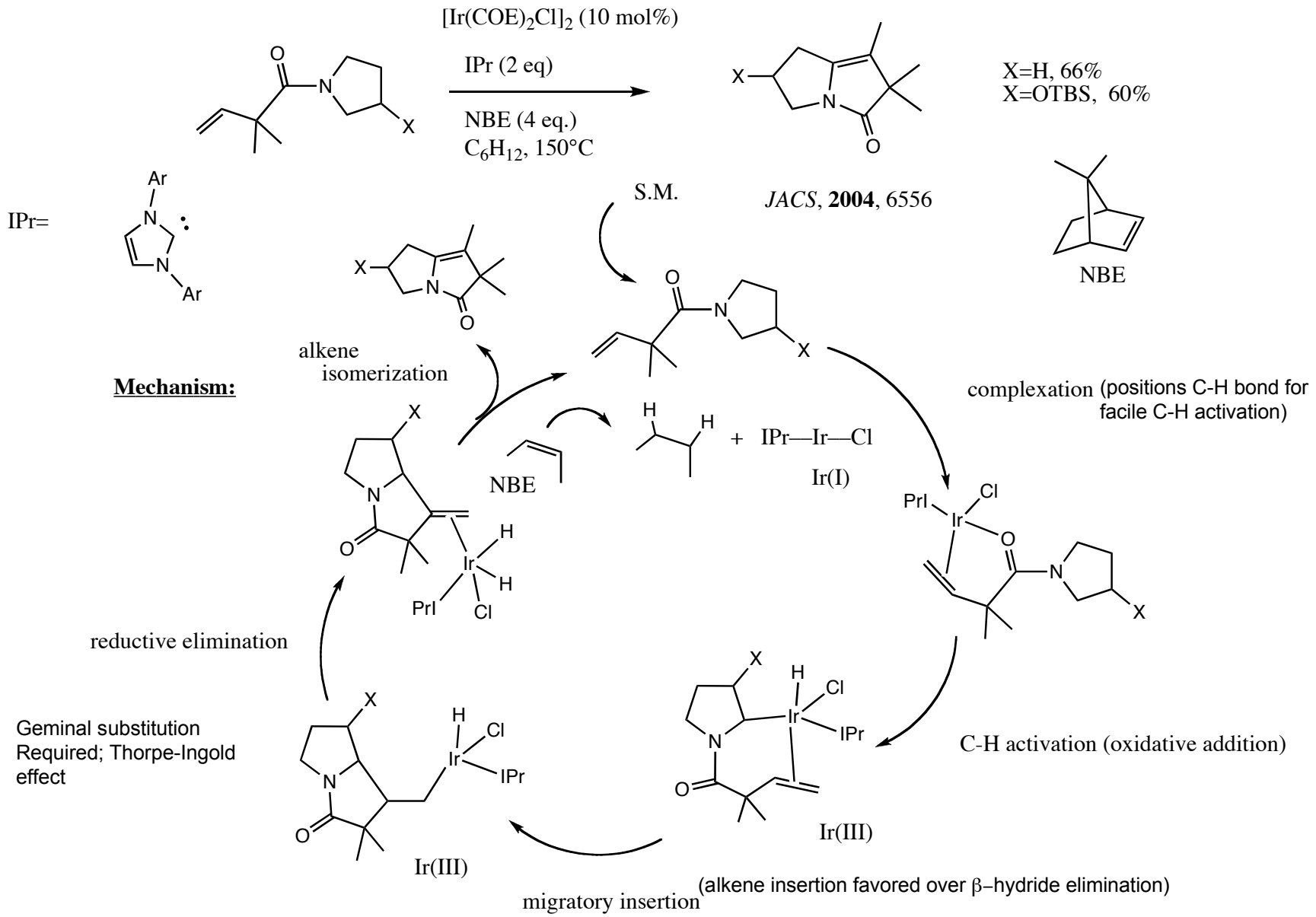


JACS, **2005**, 5284

[Ru]	**1 / 2 / 3 %**
$Ru(H_2)_2(PCy_3)_2$	**40 / 7 / 4**
$Ru(H_2)_2(H)_2(PCy_3)_2$	**59 / 9 / 4**

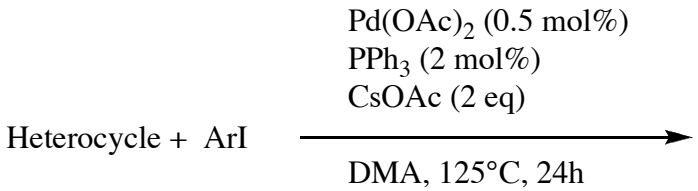
C-H activation for C-C bond formation

Intramolecular sp^3 C-H activation/cyclization

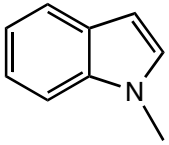
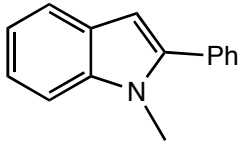
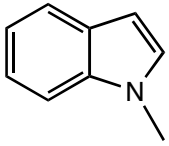
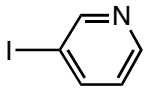
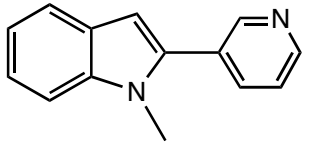
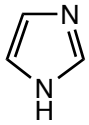
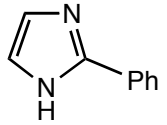
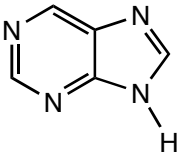
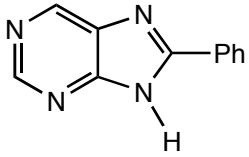


C-H activation for C-C bond formation

Activation of C(sp2)-H bonds α to N:

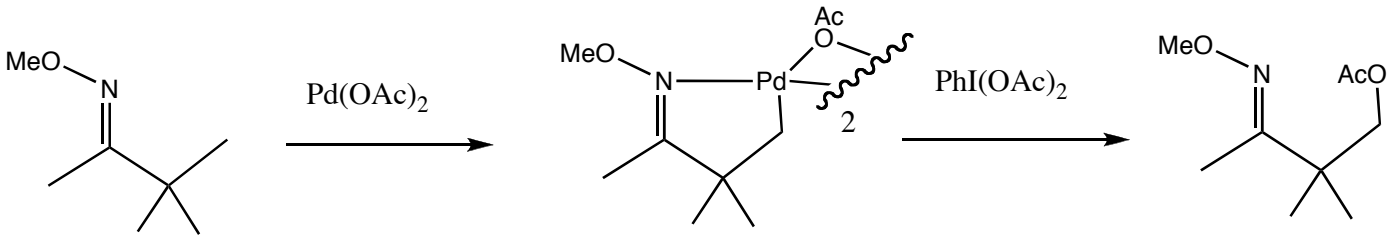


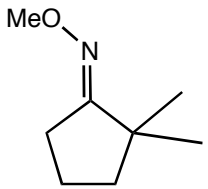
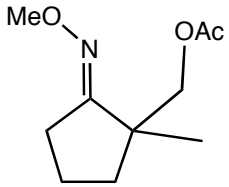
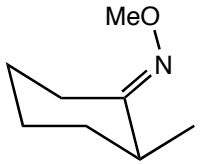
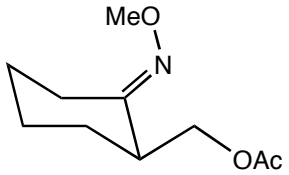
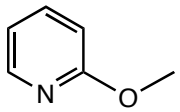
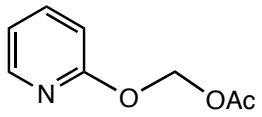
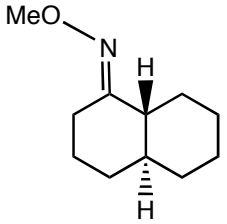
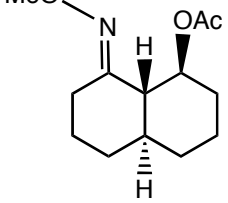
OL, **2004**, 2897

substrate	ArI	products (yield)
	Ph–I	 85%
		 73%
	Ph-I	 52%
	Ph-I	 73%

Palladium-Catalyzed Oxygenation of Unactivated C-H bonds

5-membered palladacycle



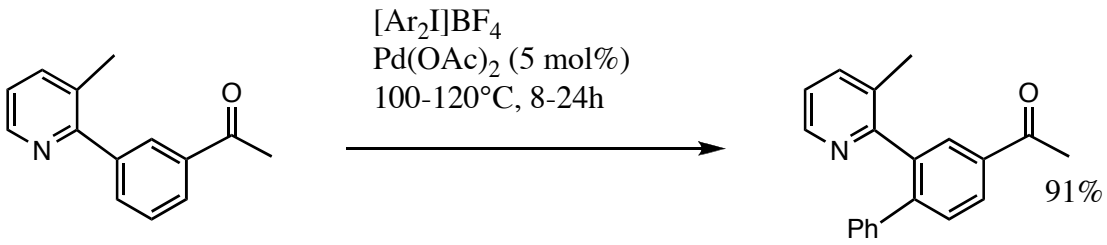
substrate	product	yield
		61%
		81%
		66%
		81%

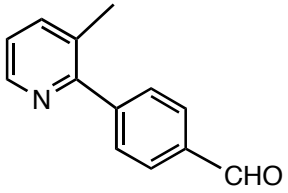
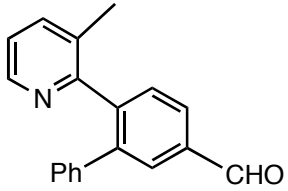
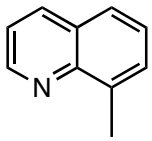
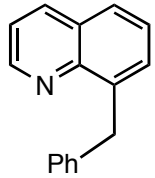
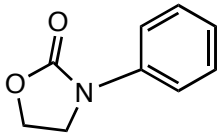
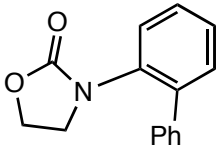
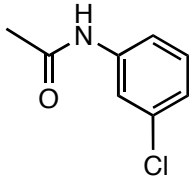
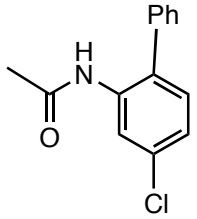
JACS, **2004**, 9542

C-H activation to form a palladacycle intermediate

stoichiometric oxidant accomplishes Pd(II)==>Pd(IV) oxidation, followed by C-O bond-forming reductive elimination

C-H activation for C-C bond formation

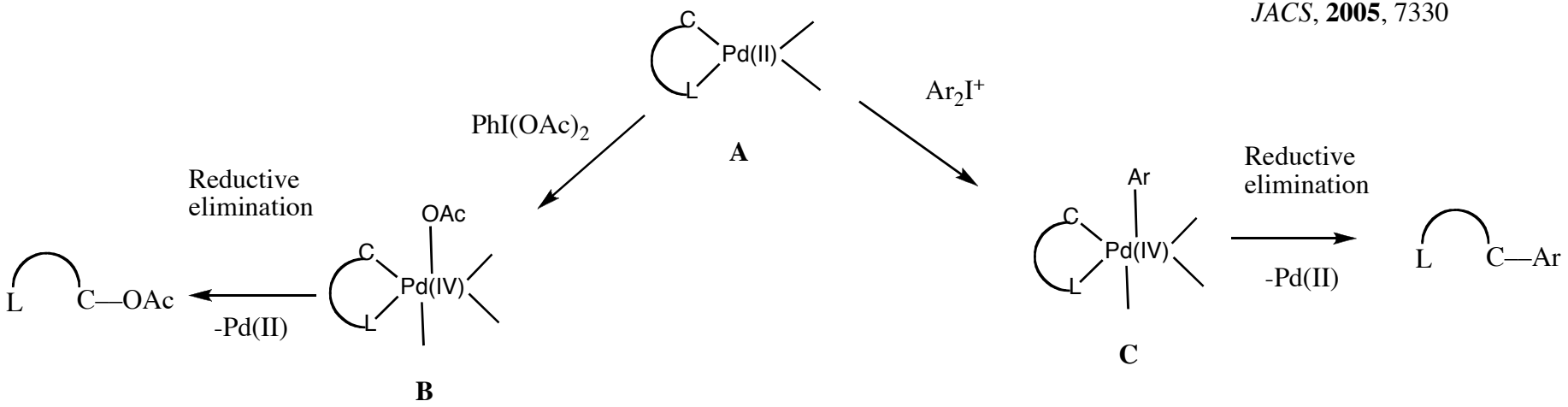


substrate	Product	Yield
		51%
		72%
		83%
		68%

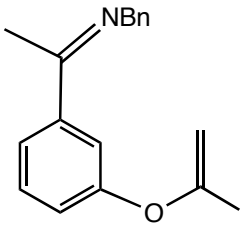
Mechanism of Sanford Arylation/Oxidation: putative Pd(IV) intermediate

L=ligating group; C=carbon of C-H insertion site

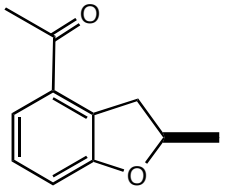
JACS, **2005**, 7330



Imine-directed C-H activation and cyclization: enantioselective C-H activation

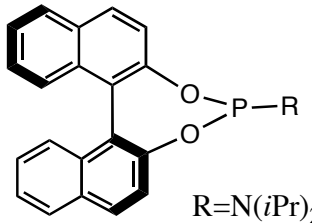


1. 5mol% $[RhCl(coe)_2]_2$
15 mol% L^*
2. aqueous work-up



99%, 96% ee

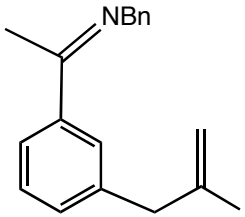
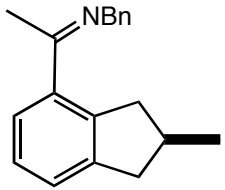
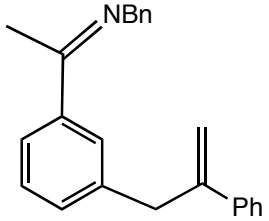
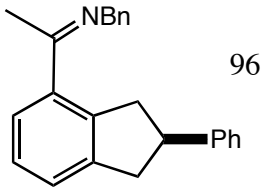
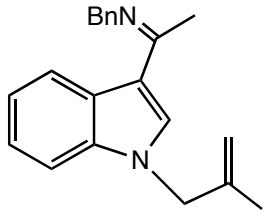
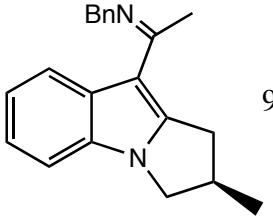
L^*=



$R=N(iPr)_2$

$R=N(CHCH_3Ph)_2$

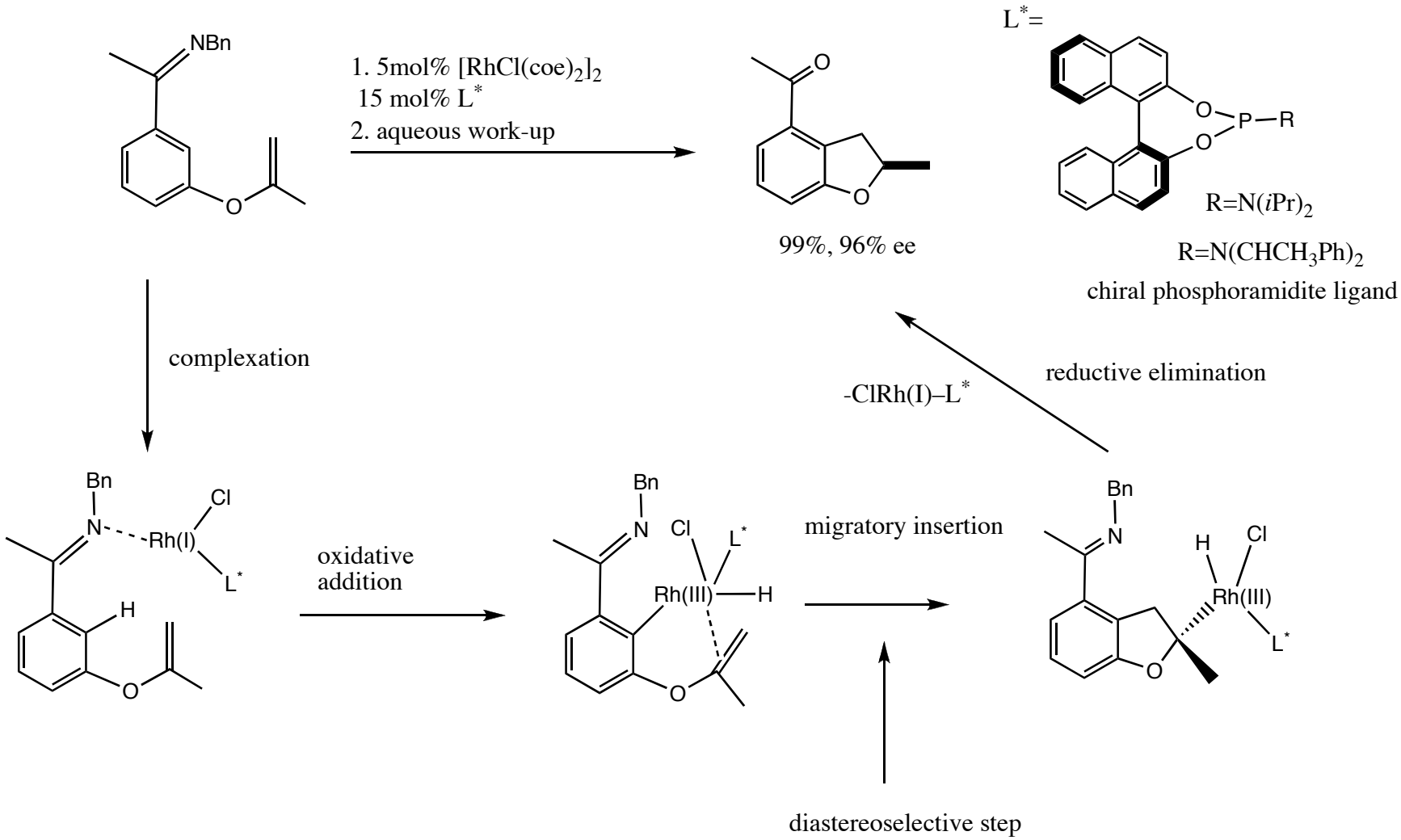
chiral phosphoramidite ligand

substrate	product	yield	ee
		94	95
		96	90
		90	70

- coordination of chiral rhodium to imine
- directed C-H insertion of the α-aryl proton
- migratory insetion of the pendant olefin ligand
- reductive elimination Rh(I)=>Rh(III)=>Rh(I)
- a highly diastereoselective migratory insertion of the olefin into the Rh-H bond is mediated by the chiral ligand framework

JACS, **2004**, 7192

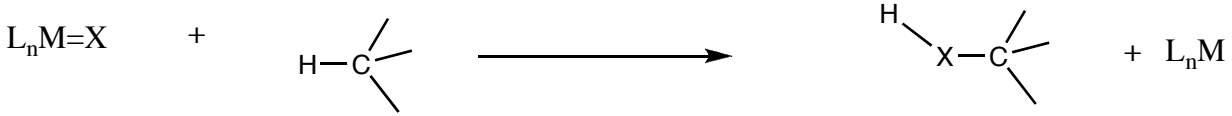
Mechanism of Bergman-Ellman Enantioselective C-H activation

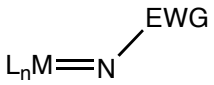


Note the importance of a directing group in all C-H activation processes!

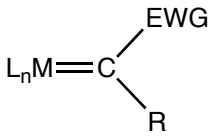
Alternative Approach to C-H activation/ C-H functionalization: use chiral carbenes

C-H insertion:





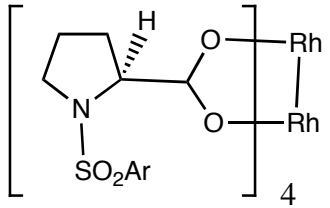
nitrene



carbene

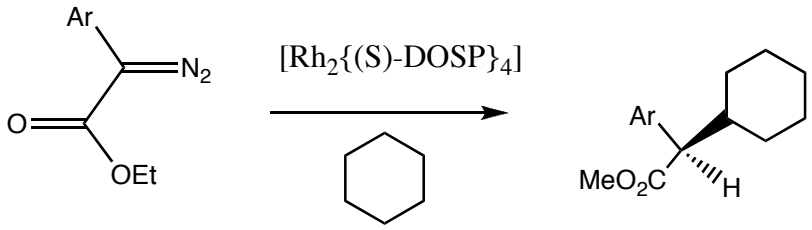
EWG required for sufficient reactivity
R=EDG increases selectivity

common chiral dirhodium for carbenoid formation:



$[Rh_2\{(S)\text{-DOSP}\}_4]$

Consider:



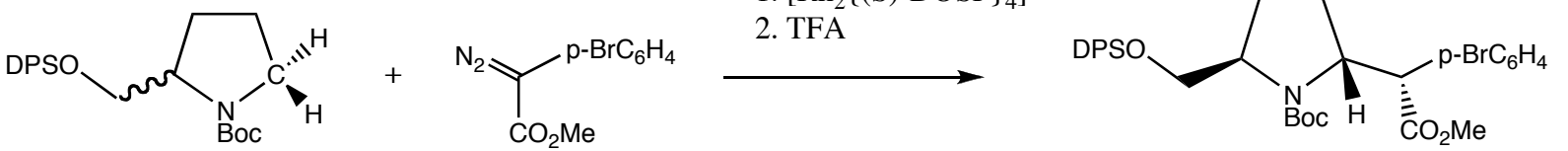
80%, 95%ee

JACS, **2000**, 3063

Alternative Approach to C-H activation/ C-H functionalization: use chiral carbenes

Kinetic Resolution:

racemic

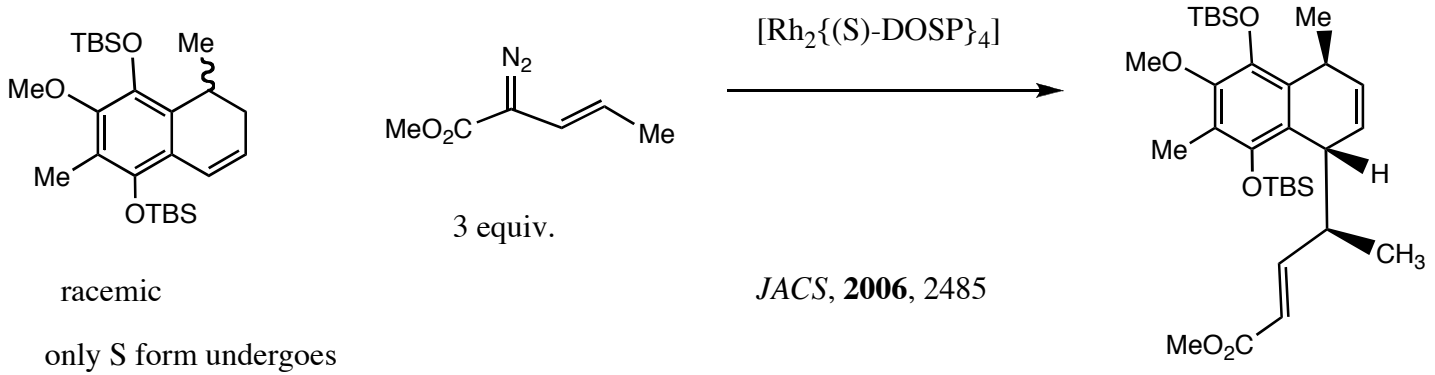


2 equivalents

85% yield, 98%ee, >94% de

JACS, **2003**, 6462

Tandem C-H activation / Cope strategy:



3 equiv.

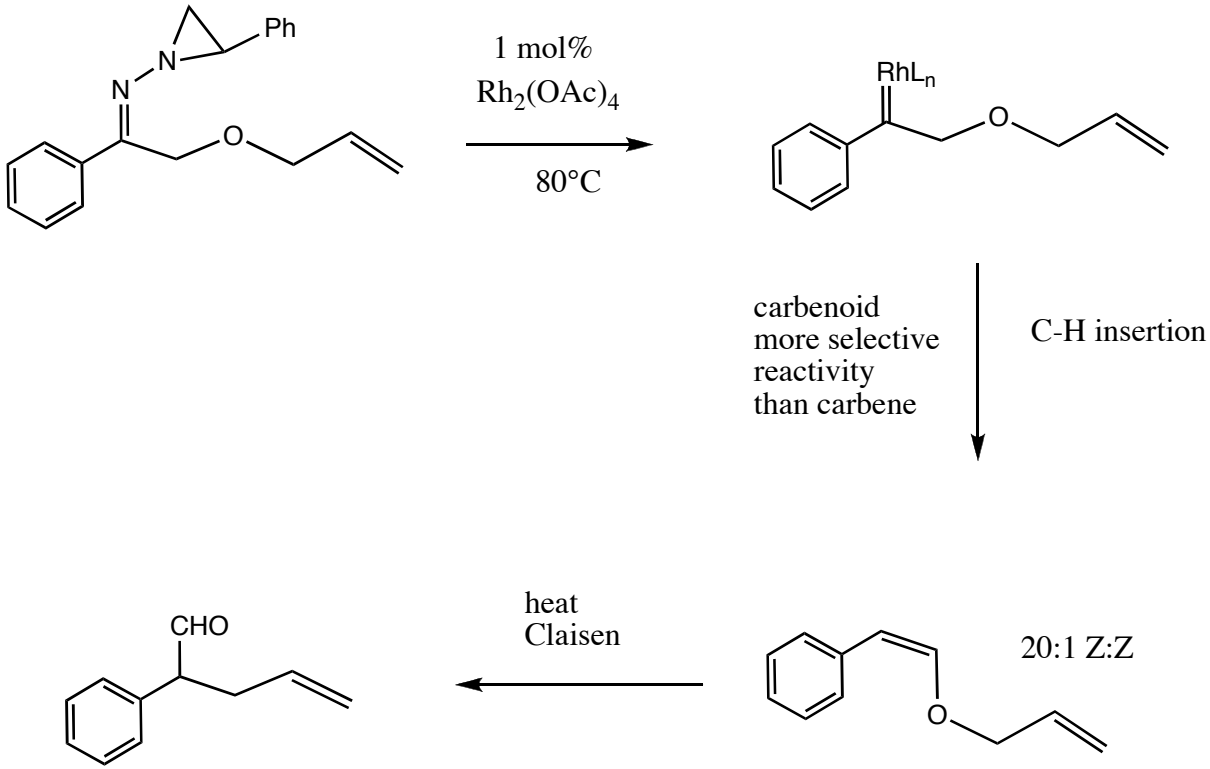
racemic

only S form undergoes C-H activation; R-form undergoes cyclopropanation

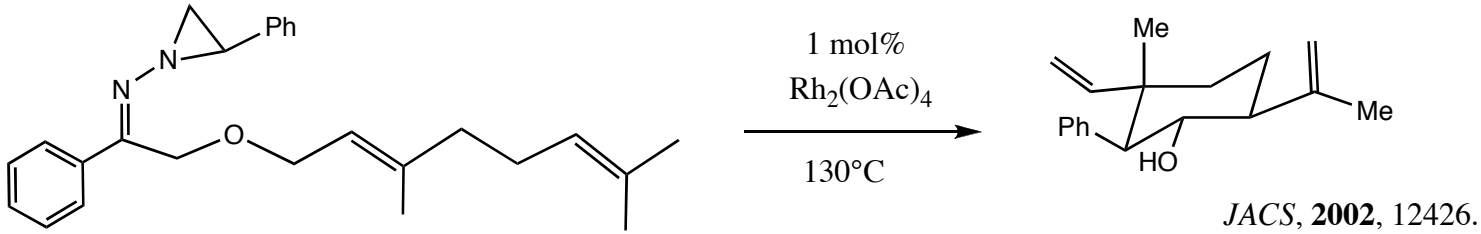
JACS, **2006**, 2485

>95%ee, >94%de

Alternate Carbene/carbenoid processes: Tandem Bamford-Stevens/Claissen sequence



A cascade reaction; explain



JACS, **2002**, 12426.

Tandem carbenoid formation/ carbonyl ylide formation / 3+2 cycloaddition