

Outline

- I. Introduction to C-H Activation and Functionalization
 - Catalytic C-H Functionalization
 - Chelation Assistance
- II. C-H/Olefin coupling
- III. C-H Carbonylation
- IV. Ru/Rh C-H Arylation
- V. Pd C-H Arylation
- VI. C-H Oxygenation
- VII. C-H Iodination

General reviews for C-H activation:
Shilov and Shul'pin, *Chem. Rev.*, **1997**, 97, 2879-2932

General reviews for C-H Functionalization:
Pfeffer, *Chem. Rev.*, **2002**, 102, 1731-1769
Murai and Kakiuchi, *Acc. Chem. Res.*, **2002**, 35, 826-834

Good Book on C-H Activation and Functionalization
Murai, Topics in Organometallic Chemistry, "Activation of Unreactive Bonds and Organic Synthesis", Vol. 3, 1999.

Introduction to C-H Bond Activation and Functionalization

C-H Bond Activation: Cleavage of C-H bond that leads to the formation of a metal-C bond either through oxidative addition to a low valent metal center or electrophilic substitution

Thought difficult due to strengths of C-H bond
Stoichiometric cleavage by transition metals extensively studied since 1960s
Traditionally focused on simple hydrocarbons, such as those found in gas and oil



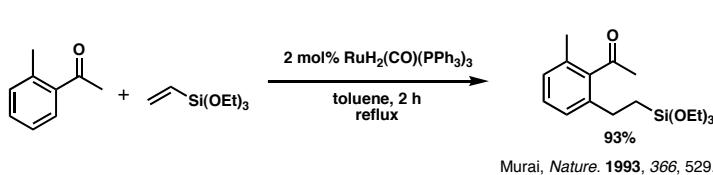
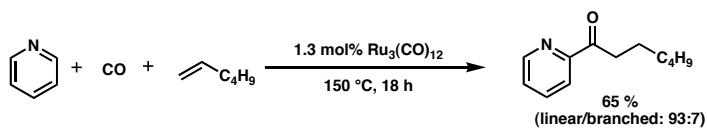
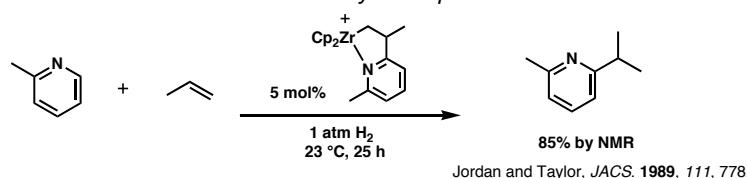
C-H Bond Functionalization: Cleavage of C-H bond that is followed by new bond formation at the carbon center

Catalytic C-H bond functionalization is still in developmental phases (started ~1990s)
Synthetic potential to build complex molecules and construct C-C bond frameworks

C-H Activation: Shilov and Shul'pin, *Chem Rev.*, 1997, 97, 2879-2932.
C-H functionalization: Kakiuchi and Chatani, *Adv. Synth. Catal.* 2003, 345, 1077-1101.

Catalytic C-H Functionalization

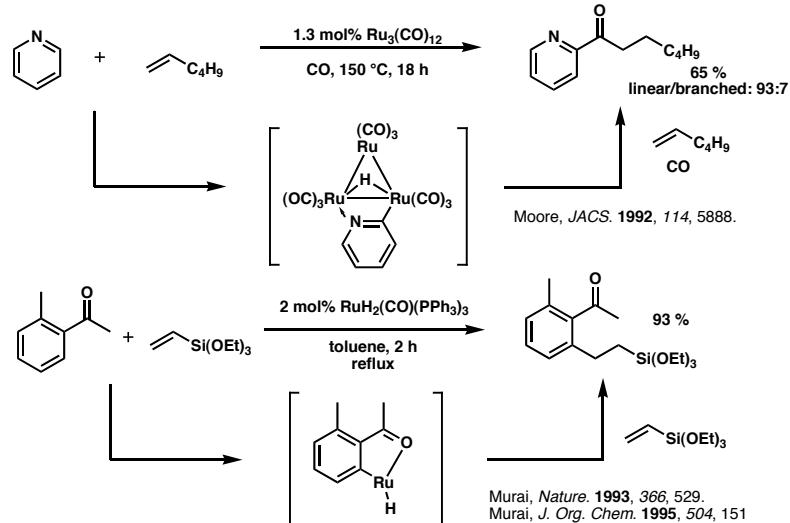
Early Examples



Success of these reactions is attributed to chelation assistance.

Catalytic C-H Functionalization

Chelation Assistance

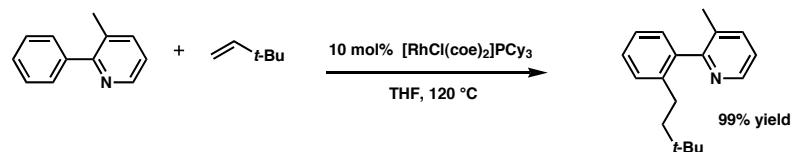


Despite numerous advances in oxygen directed functionalization, this will not be discussed further.

C-H/Olefin Coupling

Aromatic C-H Functionalization

Pyridine as a directing group



Substrate Scope

alkene	yield
pent-1-ene	68%
hex-1-ene	54%
(EtO) ₃ SICH=CH ₂	67%

Cone Angle Dependence

catalyst	cone angle	yield
[RhCl(coe) ₂]PCy ₃	170°	92%
[RhCl(coe) ₂]PPh ₃	145°	80%
[RhCl(coe) ₂]PMe ₃	118°	21%

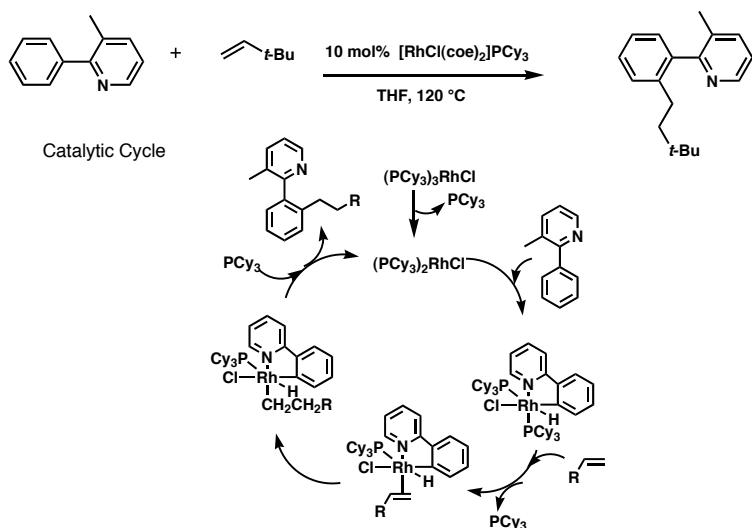
-Methyl group at the 3' position of pyridine ring prevent additional olefin incorporation
-Phosphine cone angle affect reactivity more than electronics

Lim, *J. Chem. Soc., Perkin Trans 1*, 1996, 2201

C-H/Olefin Coupling

Aromatic C-H Functionalization

Pyridine as a directing group

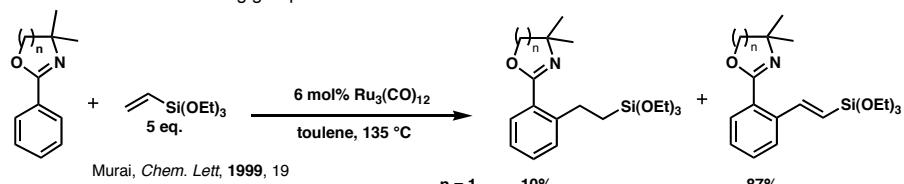


Lim, *J. Chem. Soc., Perkin Trans 1*, 1996, 2201

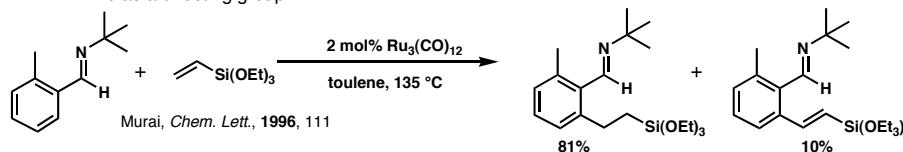
C-H/Olefin Coupling

Aromatic C-H Functionalization

Imidate as a directing group

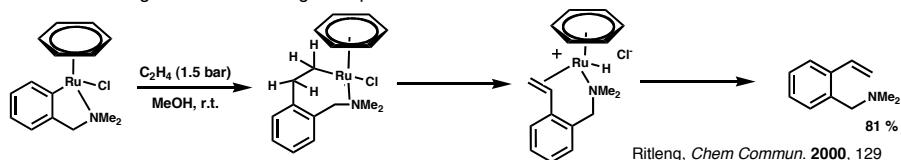


Imine as a directing group



-Unsaturated products are believed to be from β hydride elimination after olefin insertion.

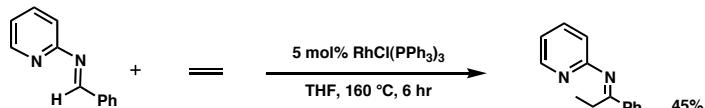
-Analogous to the following example:



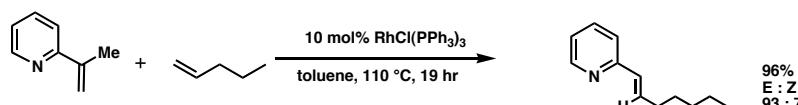
C-H/Olefin Coupling

Olefinic C-H Functionalization

Pyridine as a directing group



Suggs, JACS, 1979, 101, 489



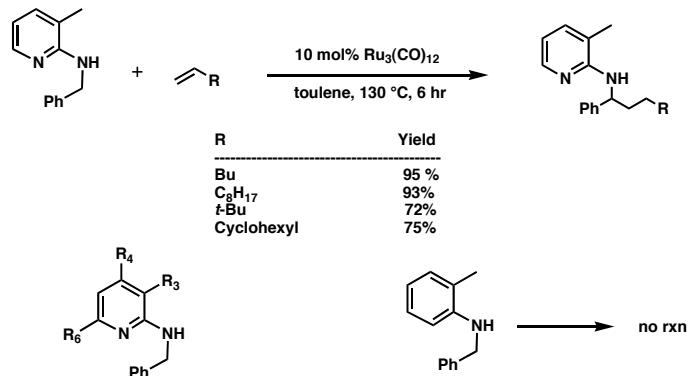
Lim, Chem Commun, 1996, 585.

- No self dimerization products detected
- With propene, bisalkylation products observed

C-H/Olefin Coupling

sp^3 C-H Functionalization

Pyridine as a directing group



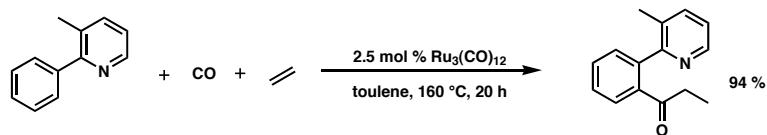
- Substitution at R_4 or R_6 resulted in trace products (same for no substitution)
- Substitution at 3' position of pyridine necessary--may retard the free rotation of the benzyl group around the amine
- Chelation assistance is prerequisite for C-H activation
- Electron donating substituents on phenyl ring increased reactivity--may activate the benzylic CH bond for cleavage

Jun, Chem Commun, 1998, 1405

C-H Carbonylation

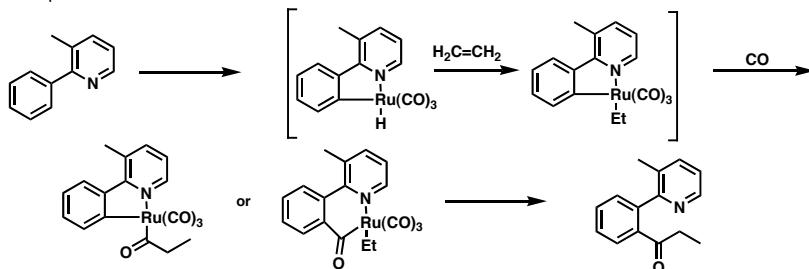
Aromatic C-H Functionalization

Pyridine as directing group



- No substitution on the pyridine ring, some dicarbonylation product observed
- Electron withdrawing substituents on pyridine, no reaction
- m*-substituted phenyl rings, carbonylation determined by sterics

Proposed Mechanism



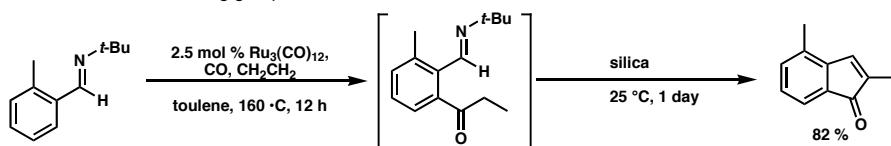
Mononuclear Ru proposed due to isolation of cyclometalated Ru complexes from benzaldehyde imine and $\text{Ru}_3(\text{CO})_{12}$

Murai, J. Org. Chem., 1997, 62, 2604.

C-H Carbonylation

Aromatic C-H Functionalization

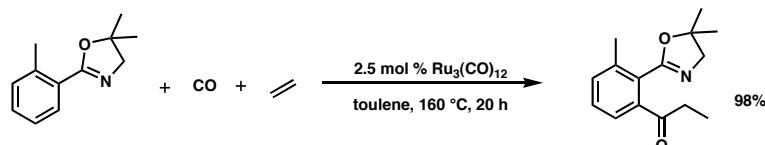
Imine as a directing group



- Products susceptible to aldol type condensation
- Reaction only works with ethylene

Murai, J. Org. Chem., 1997, 62, 5647.

Oxazoline are suitable alternative



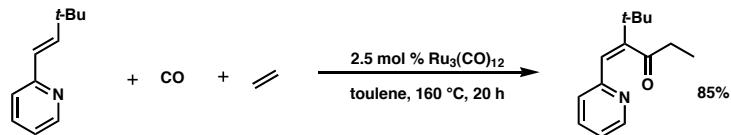
- Gemdimethyl group necessary or aldol type products
- Tolerant to variety of groups but only to Br, CN, and NMe₂ when in *m*-position (*o*-position = no rxn)
- Biscarbonylation products if both *ortho* sites available

Murai, J. Org. Chem., 2000, 65, 1475.

C-H Carbonylation

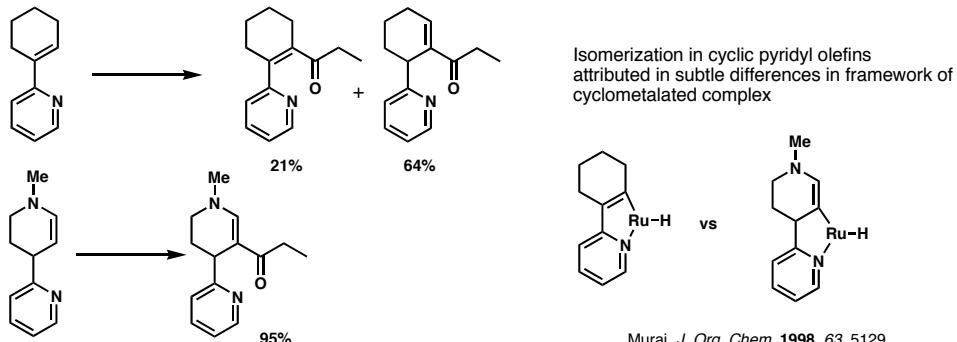
Olefinic C-H Functionalization

Pyridine as a directing group



-No other C-H functionalized products observed
-With groups less bulky than *t*-butyl, complicated mixtures are observed

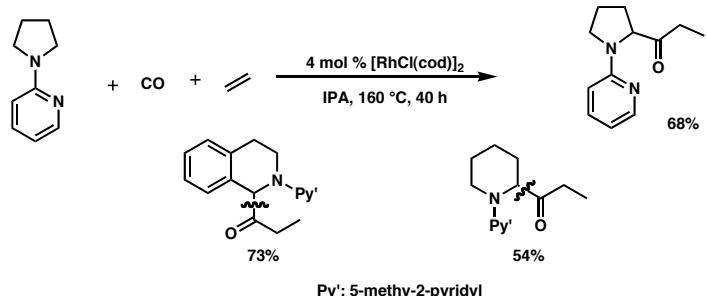
Other substrates for olefin carbonylation



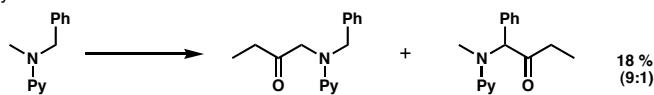
C-H Carbonylation

sp³ C-H Functionalization

Pyridine as a directing group



Acyclic Substrates



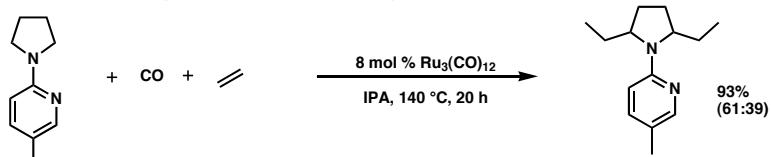
-Trace biscarbonylation products observed
-Steric hindrance around pyridine and electron withdrawing groups on pyridine dramatically dropped yields

Murai, *JACS*, **2000**, *122*, 12882.

C-H Carbonylation

Other Examples

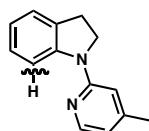
C-H/Olefin coupling observed with metal change



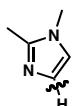
- CO used to keep reaction clean--stop catalyst decomposing
- No explanation why IPA works well with the system
- Can couple with other olefins like hexene and styrene
- Various cyclic amines can be used

Murai, JACS., 2001, 123, 10935.

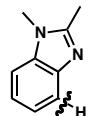
Other carbonylation examples



Murai, J. Org. Chem., 2002, 67, 7557.



Murai, JACS, 1996, 118, 493.

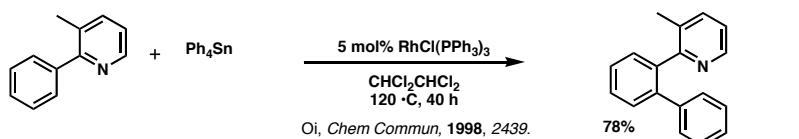


Murai, JACS, 1998, 120, 11522.

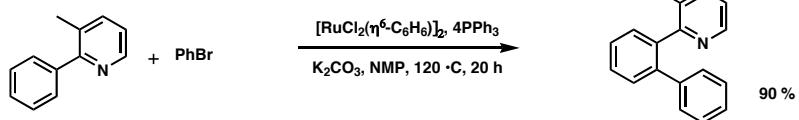
C-H Arylation

Aromatic C-H Functionalization

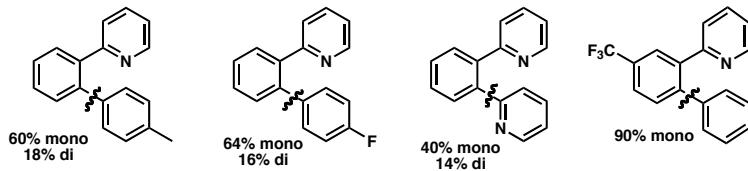
Pyridine as a directing group



Optimized conditions

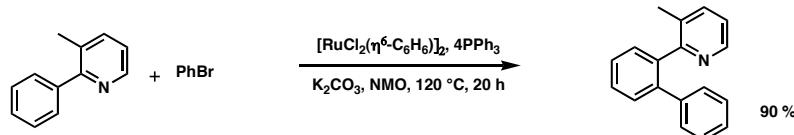


Selected substrate scope

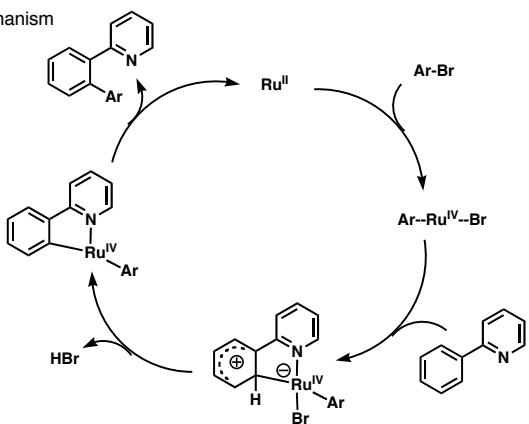


Oi Org Lett, 2001, 3, 2579.

C-H Arylation
Aromatic C-H Functionalization



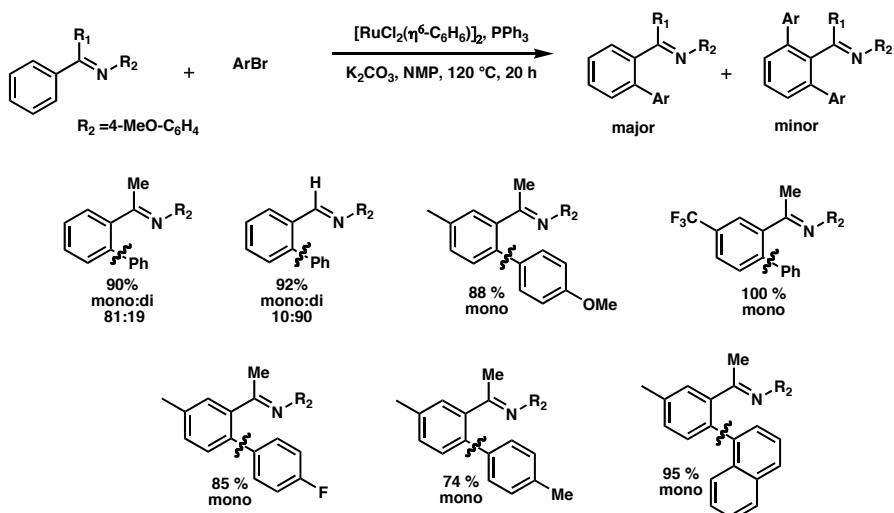
Proposed Mechanism



Oi, Org Lett, 2001, 3, 2579.

C-H Arylation
Aromatic C-H Functionalization

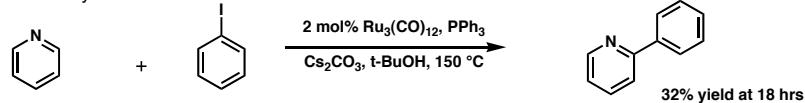
Imine as a directing group



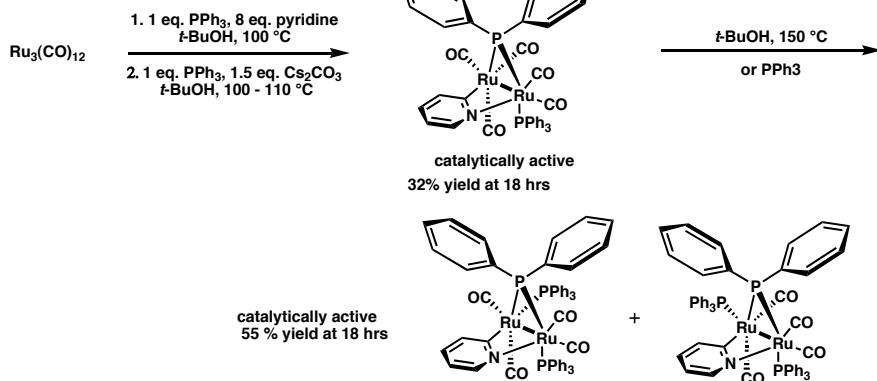
Oi, Org Lett, 2001, 3, 2579.

C-H Arylation
Mechanistic Studies of Ru₃(CO)₁₂

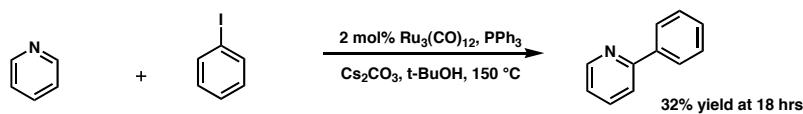
Model System



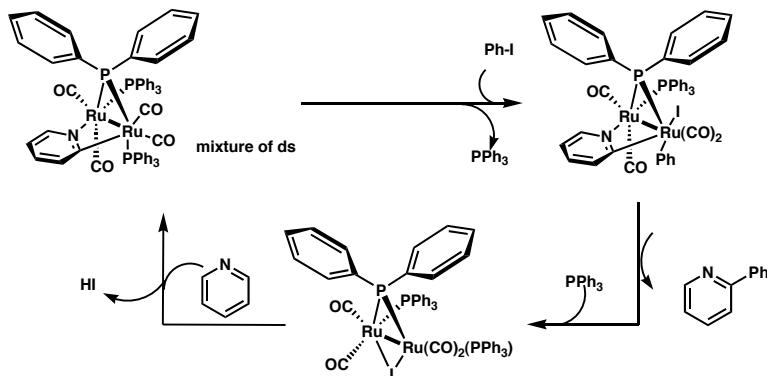
Isolation of Active Catalyst



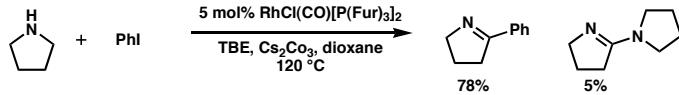
C-H Arylation
Mechanistic Studies of Ru₃(CO)₁₂



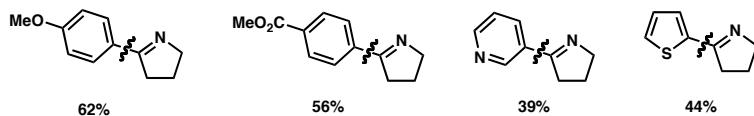
Proposed Catalytic Cycle



C-H Arylation
sp³ C-H Functionalization

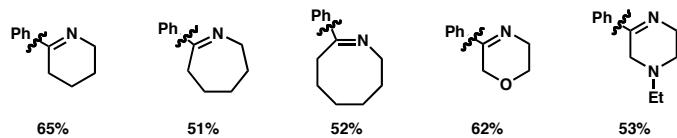


Reaction Scope of Haloarene Donors



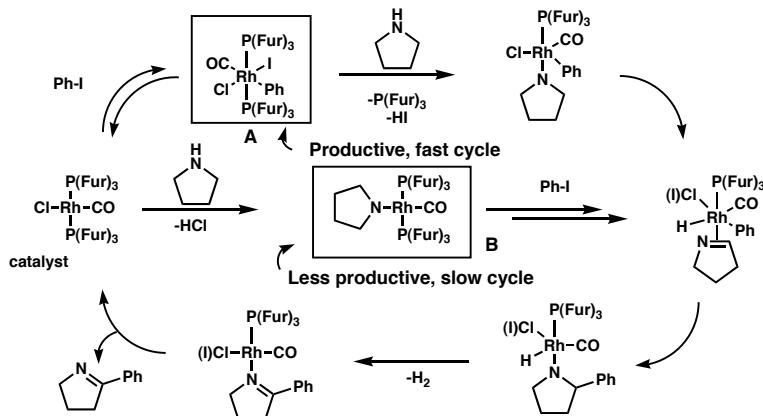
10-30% dehalogenation observed

NH-heterocycle Substrate Scope



Sarnes JACS, 2004, 126, 13244..

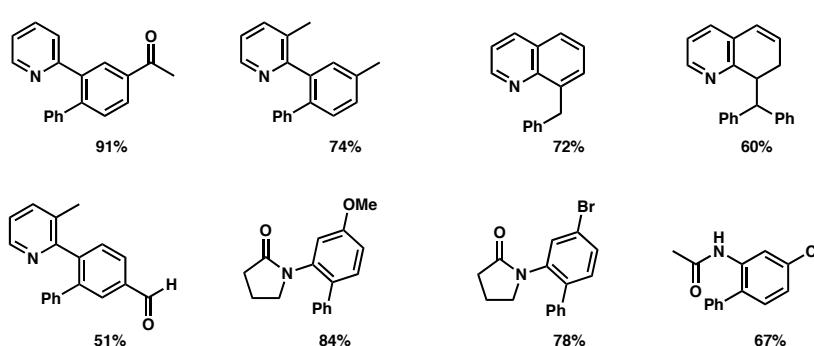
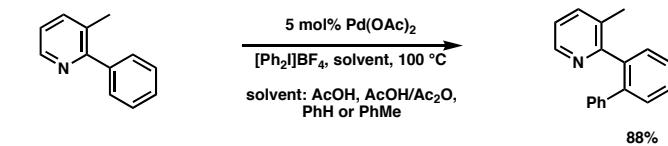
C-H Arylation
sp³ C-H Functionalization



-Both A and B were characterized and isolated from reaction mixture
-A was identical to the catalyst in yield and kinetic profile.
-B reacted at a slower rate and significantly lower efficiency

Sarnes, JACS, 2004, 126, 13244..

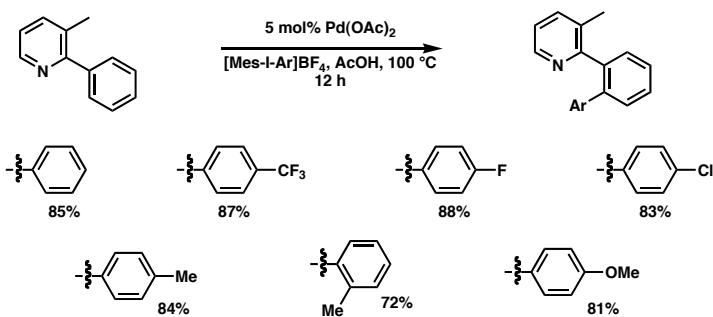
C-H Arylation
Pd Aromatic C-H Functionalization



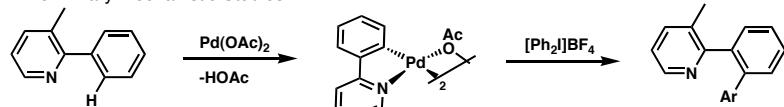
Sanford, JACS, 2005, 127, 7330

C-H Arylation
Pd Aromatic C-H Functionalization

Functionalization with Diverse Aryl Substituents



Preliminary Mechanistic Studies



Reaction believed to involve a Pd(II)/Pd(IV) cycle

-Cyclopalladated complex catalyzes reaction at same rate and yield as Pd(OAc)₂

-Radical inhibitors and heterogeneous catalysis poisons do not affect reaction

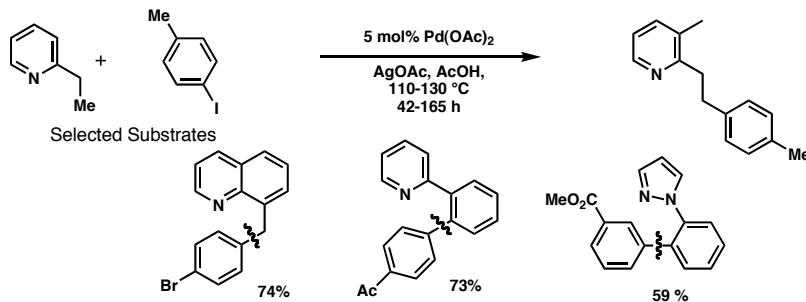
-Replacement of iodine reagent with Ph-I or Ph-OTf, known to generate Pd⁰, gave no product

Sanford, JACS, 2005, 127, 7330

C-H Arylation

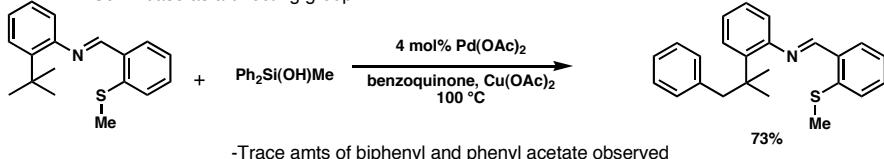
Pd sp³ C-H Functionalization

Pyridine as a directing group



Daugulis, *Org. Lett.*, 2005, 17, 3657

Schiff base as a directing group

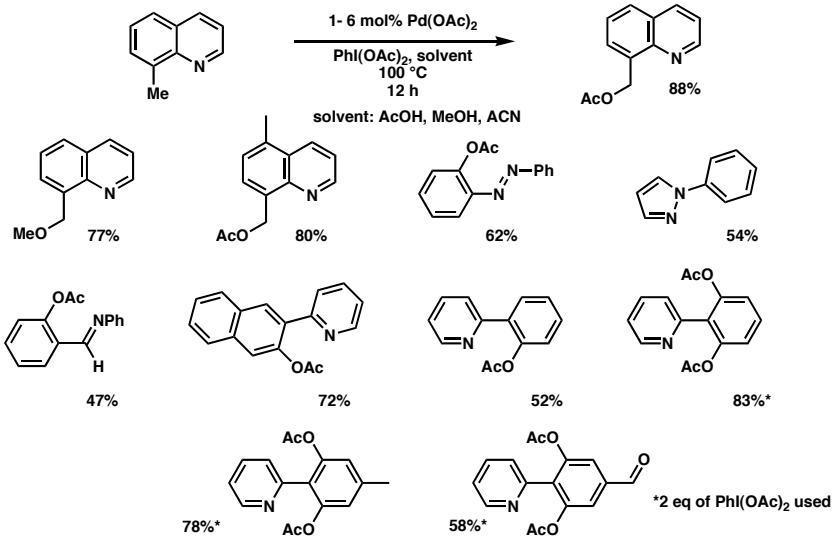


-Trace ams of biphenyl and phenyl acetate observed

Sames, *JACS*, 2002, 124, 13372

C-H Oxygenation

Aromatic C-H Functionalization

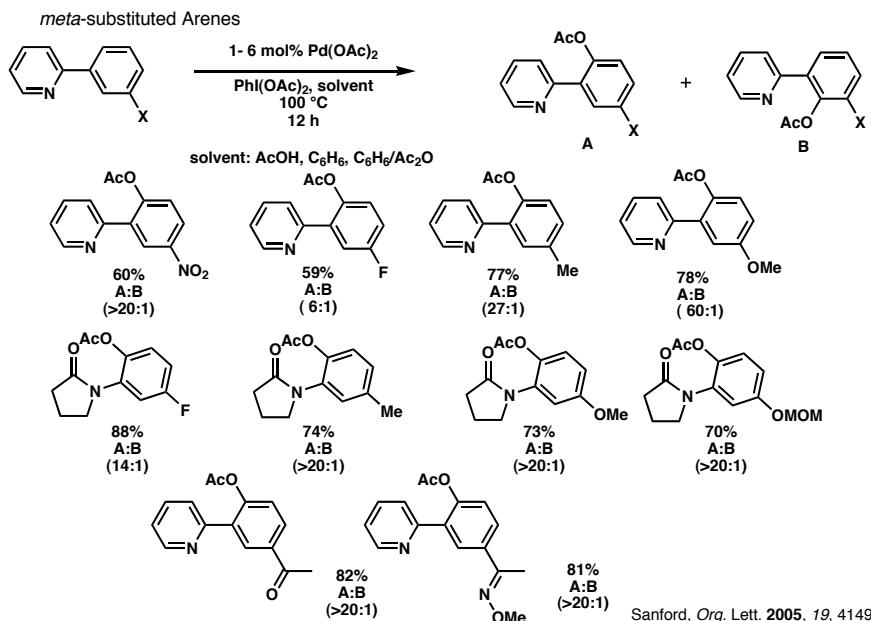


-Good control of mono and di oxidation especially in the presence of two *ortho* C-H sites

Sanford, *JACS*, 2004, 126, 2300

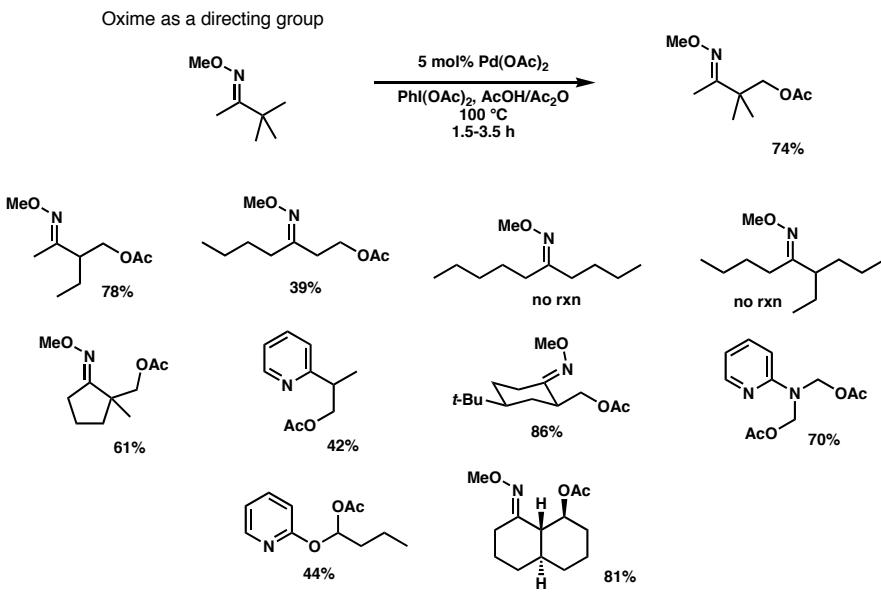
C-H Oxygenation

Aromatic C-H Functionalization



C-H Oxygenation

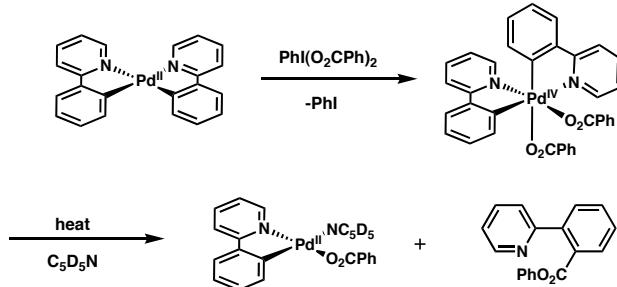
Unactivated sp^3 C-H Functionalization



C-H Oxygenation

Mechanistic Insight

Stable Pd(IV) complex isolated



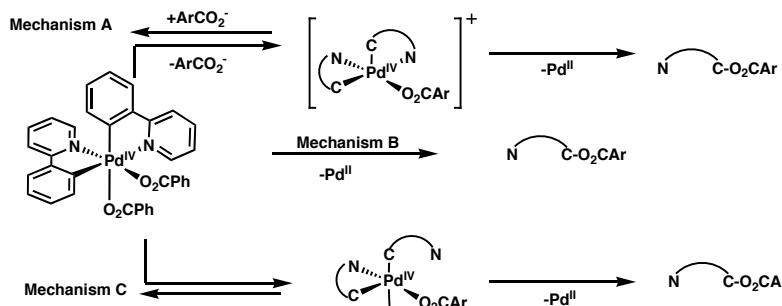
- Rigid cyclometalated pyridine ligands w/ aryl to prevent ligand exchange
- Independent chelating frameworks to prevent C-C bond reductive elimination
- Complex stable for at least a week w/o decomposition

Sanford, JACS 2005, 127, 12790

C-H Oxygenation

Mechanistic Insight

Proposed Mechanisms



Mechanism A is not likely

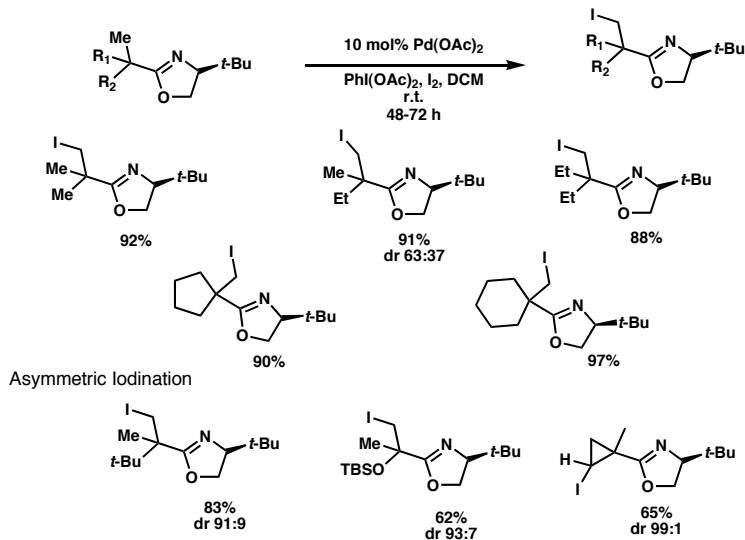
- Rates of reductive elimination are independent of solvent polarity
- Eyring analysis gave ΔS^\ddagger of -1.4 eu in DMSO (ionic R.E. systems usually give -13 to -49 eu due to solvent ordering)
- Electron donating substituents on para position of benzoate increased rate of reductive elimination, suggesting benzoate is a nucleophilic partner
- No crossover products observed with mixtures of two differentially substituted Pd(IV) complexes
- Addition of NBu_4OAc resulted <5% incorporation of OAc in product

Mechanism C is slightly favored

- Rate of reductive elimination decreases with bisbenzoquinoline Pd(IV) complex

Sanford, JACS 2005, 127, 12790

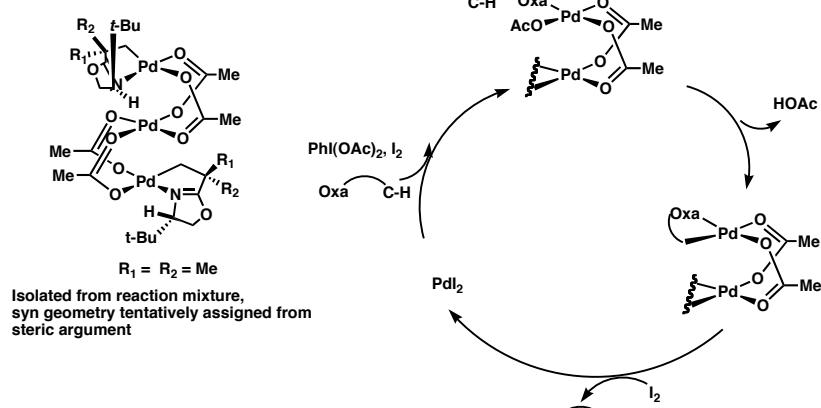
C-H Iodination
Unactivated sp^3 C-H Functionalization



Yu, *Angew. Chem. Int. Ed.* **2005**, *44*, 2112

C-H Iodination
Mechanistic Insight

Proposed catalytic active species



- PdI_2 was unreactive with substrate
- $PhI(OAc)_2$ and I_2 used to regenerate $Pd(OAc)_2$

Yu, *Angew. Chem. Int. Ed.* **2005**, *44*, 2112