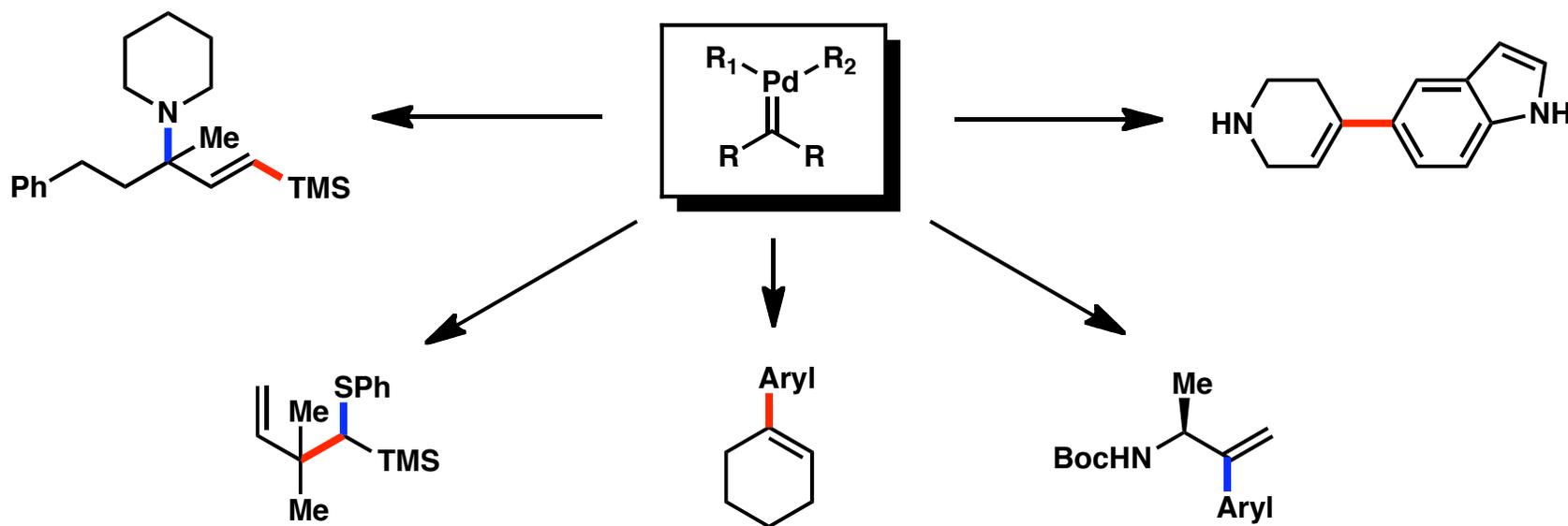


Inspecting Insertions:

Recent Advances in Palladium Carbenoid-Mediated Carbon-Carbon Bond Forming Reactions



17 January 2011
Stoltz/Reisman Literature Group Meeting
Jeffrey C. Holder

Outline of the Proceedings

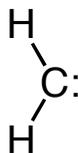
- 1. Brief Overview of Metal Carbenoids in Synthesis**
- 2. Palladium Carbenoids**
- 3. Reactions of Palladium Carbenoids**
 - a. Insertions**
 - b. Cross-Couplings**
 - c. Extensions of Cross-Couplings**
 - d. Outliers and Oddities**

4. Outlook

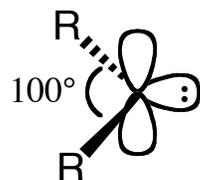


An Overview of Metal Carbenoids in Synthesis: What Is a Carbene? A Brief Review

Carbenes are neutral molecules containing divalent carbon atoms with 2 unshared electrons:

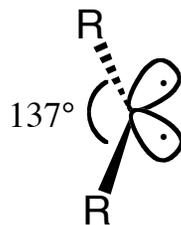


2 possible electronic structures: *singlet* and *triplet*



singlet

- resembles carbocation and carbanion united on same carbon
- "sp²" filled orbital with empty "p" orbital
- many R groups (with unshared electrons) can stabilize singlet more than triplet



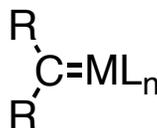
triplet

- resembles diradical
- R groups in "sp" orbital, 2 partially filled orthogonal "p" orbitals
- usually more stable than singlet form (Hund's rule)

An Overview of Metal Carbenoids in Synthesis:

What the hell is a "carbenoid"?

Carbenoid is a vague term used for a molecule in which all carbons are tetravalent but still has properties resembling those of a carbene, typically the carbene-like carbon has multiple bonds with a metal



Carbenoids can be formed by reacting salts of transition metals (eg. Cu, Pd, Rh) with diazo compounds



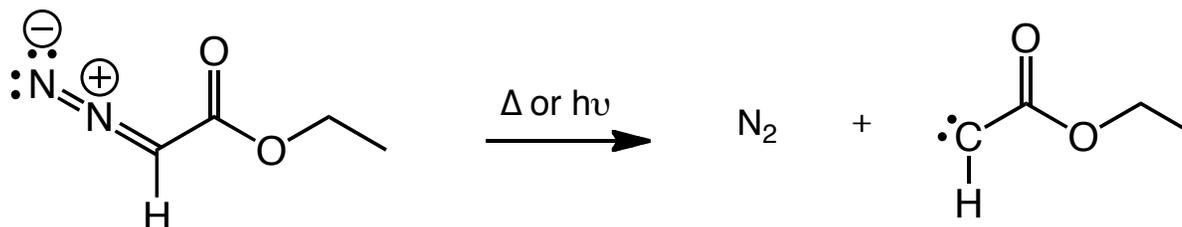
Yates postulated: "reaction of $\text{ROC}:\text{H}$ (or of the $\text{RCOC}:\text{H}$ -copper complex) probably involves an attack by the unshared pair of electrons on oxygen, nitrogen or sulfur at the electron-deficient methine carbon followed by a prototropic shift" (*JACS* **1952**, 74, 5376)

An Overview of Metal Carbenoids in Synthesis:

Carbene Formation via Diazo Decomposition

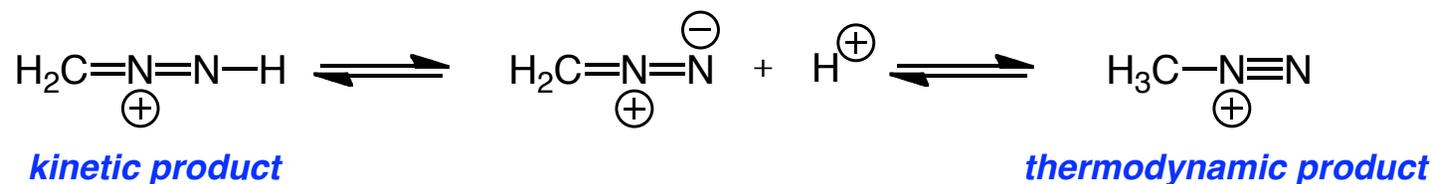
Diazo compounds readily decompose thermally or photochemically

- Activation barrier ca. 30 kcal/mol
- Formation of N₂ bond, liberation of N_{2(g)} serve as driving forces

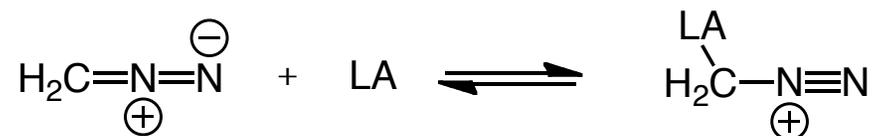


NOTE: it is difficult to know if a "free carbene" reaction in solution actually involves a free carbene or some carbene-like species that reacts in a similar manner

Diazo compounds also readily undergo acid-mediated decomposition



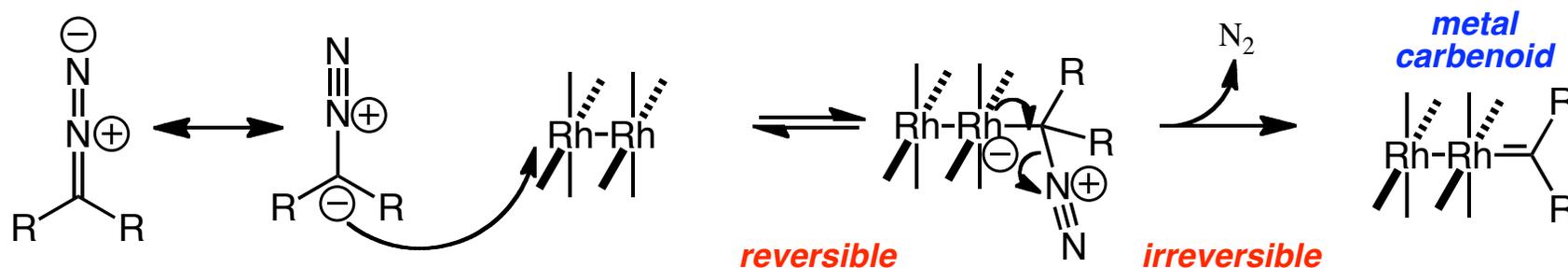
This reactivity is the basis for diazo decomposition catalyzed by Lewis acidic metal complexes



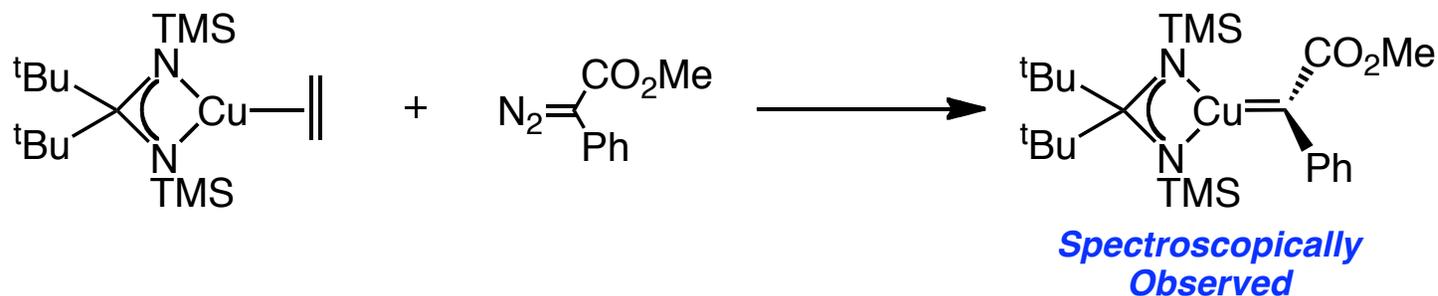
An Overview of Metal Carbenoids in Synthesis:

Metal Carbenoid Formation via Diazo Decomposition

Lewis acidic transition metal complexes are effective means of decomposing a diazo compound to a metal carbenoids. Note that this mechanism requires the metal complex to act as an "electrophile" for the diazo compound and requires coordinative unsaturation at the metal center



There is relatively little data supporting the mechanistic reality of metal carbenoids, but P. Hoffmann and coworkers have observed Cu-carbenoids as intermediates in cyclopropanation



Mechanism: *JACS* **1996**, 118, 8162

Rh(II) Mechanistic evidence: *Science*, **1992**, 256, 1544

Cu carbenoid spectroscopy: *ACIE*, **2001**, 40, 1288

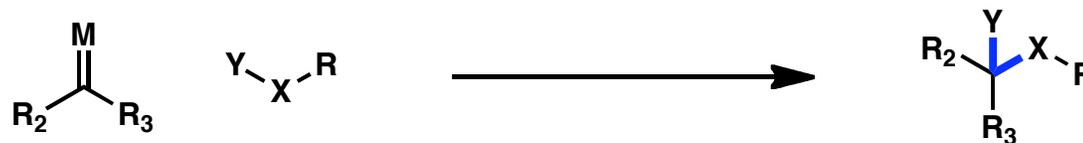
An Overview of Metal Carbenoids in Synthesis:

Common Modes of Reactivity

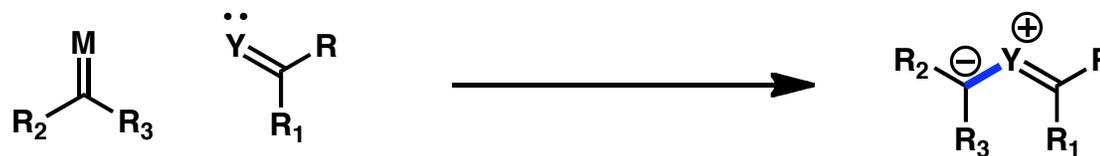
Cyclopropanation



Insertion

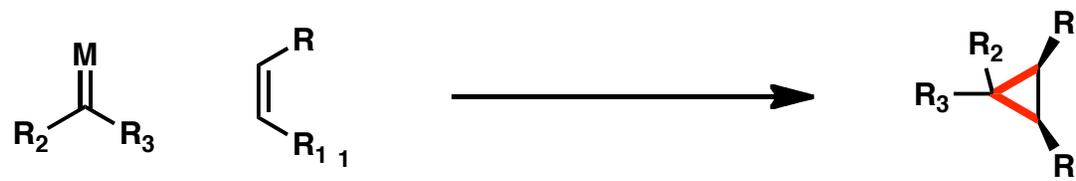


Ylide Formation



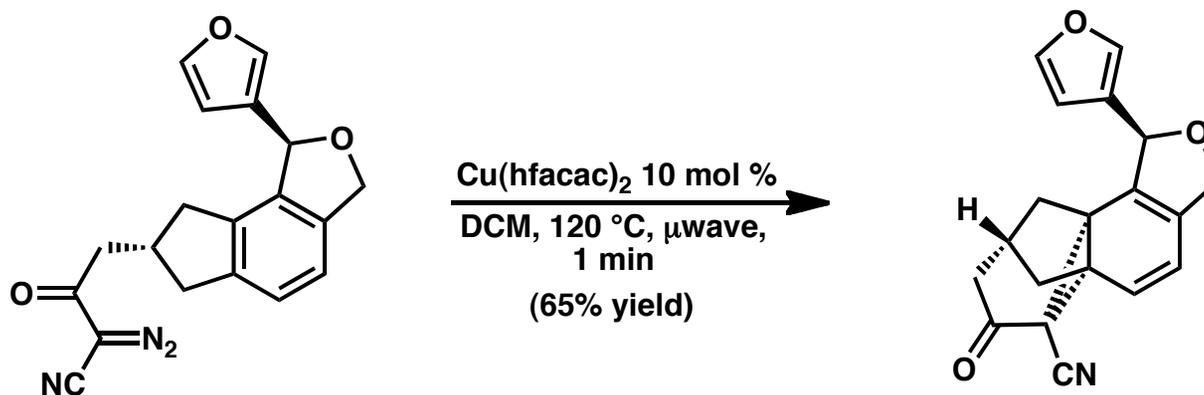
An Overview of Metal Carbenoids in Synthesis

Common Modes of Reactivity: Cyclopropanation



This mode of carbenoid reaction needs little introduction. Many examples of "free" carbene cyclopropanations in addition to Rh and Cu based carbenoid cyclopropanations.

A familiar example:



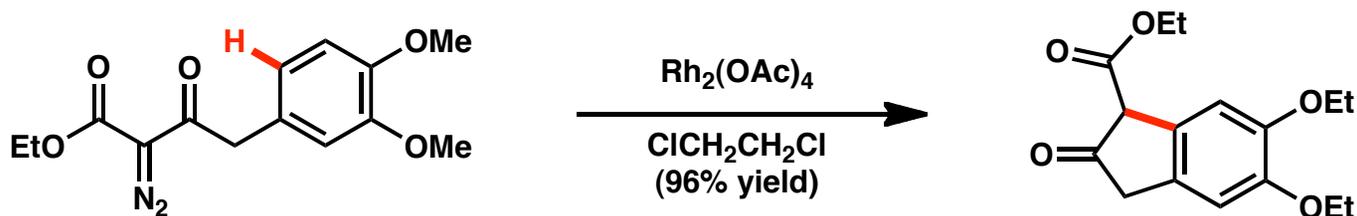
An Overview of Metal Carbenoids in Synthesis:

Common Modes of Reactivity: Insertion Examples



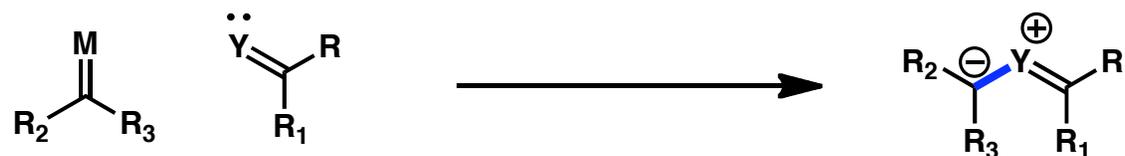
Carbenes are capable of inserting into many sigma bonds, particularly susceptible are X-H bonds where X = C, N, O, S etc. These reactions are useful for quickly building structural complexity.

Another familiar examples:

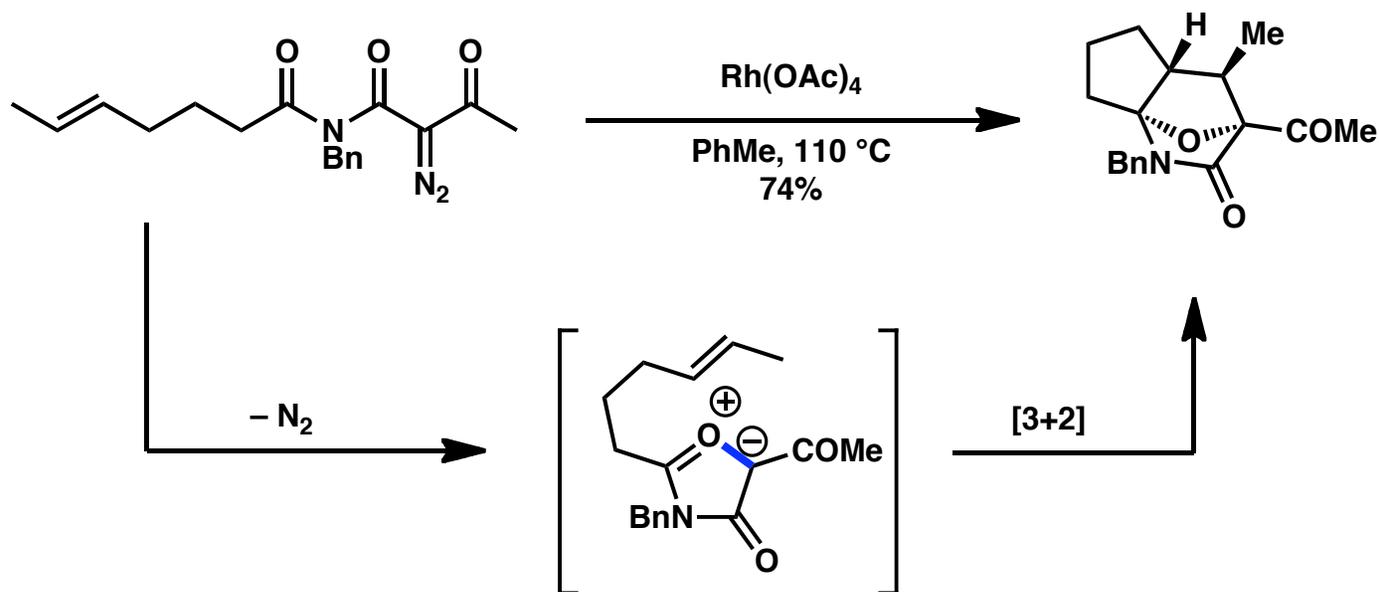


An Overview of Metal Carbenoids in Synthesis:

Common Modes of Reactivity: Ylide Formation



Lewis bases can often react with metal carbenoids to form ylides, which often undergo subsequent reaction in situ. In cases where pendant olefins are present, these ylides often react as dipoles and participate in [3+2] cycloadditions

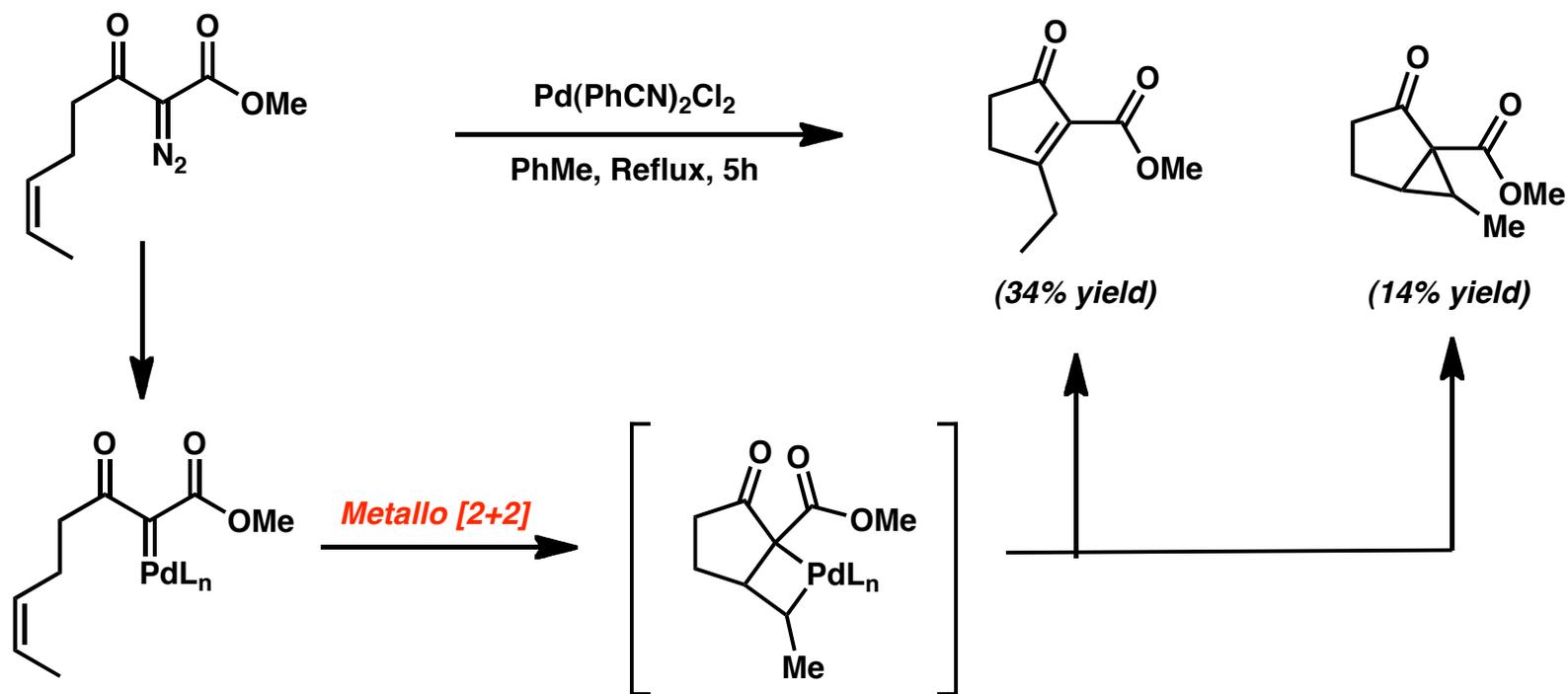


Testing Your Metal:

Palladium Makes an Appearance

Early reports by Taber described a cyclization of diazo ketones with pendant olefins

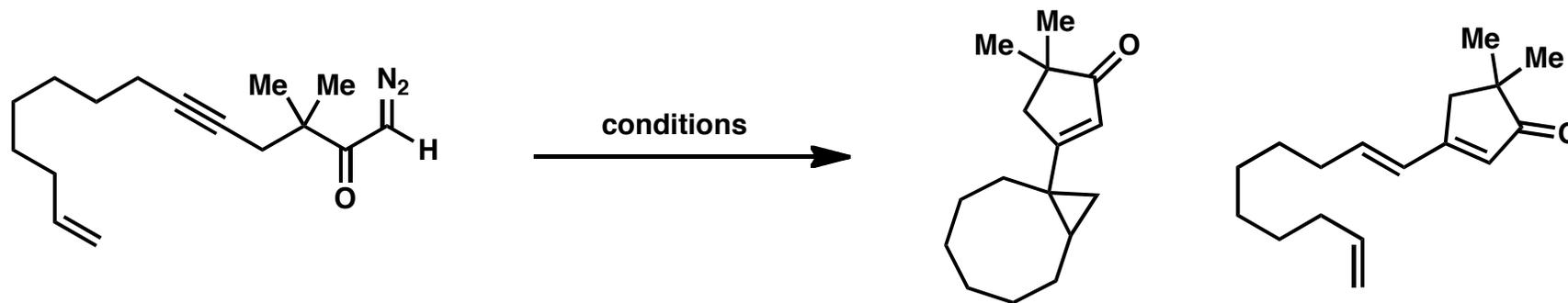
Taber postulated that these reactions proceeded through a metalocyclobutane, presumably *via* Pd-carbenoid



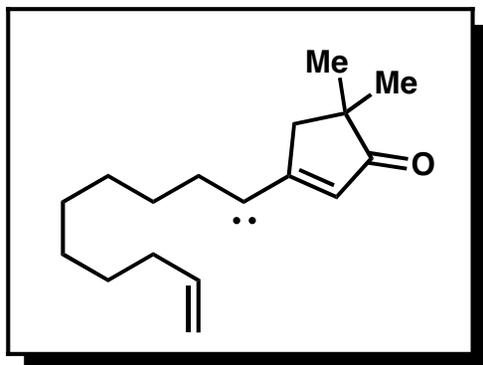
Testing Your Metal:

Palladium Makes an Appearance

– Likewise, work by Hoye demonstrates that various Pd sources are capable of yielding similar products as Rh



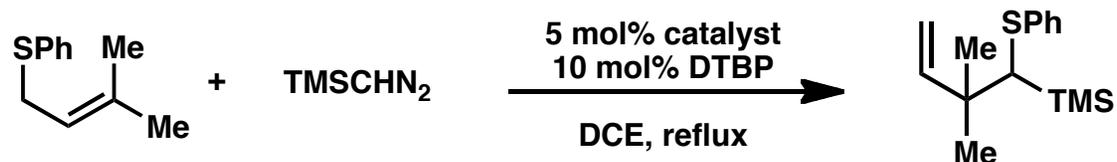
Proposed Intermediate



$\text{Rh}_2(\text{OAc})_4$, 80 °C, 1 h	18% yield	28% yield
$\text{Pd}(\text{acac})_2$, 80 °C, 7 h	87% yield	3% yield
$\text{Pd}(\text{PPh}_3)_4$, 60 °C, 12 h	13% yield	60% yield

Palladium-Catalyzed Insertions: Making the Mental Leap

Van Vranken and coworkers report the Kirmse reaction of phenyl dimethylallyl sulfide with TMSCHN₂

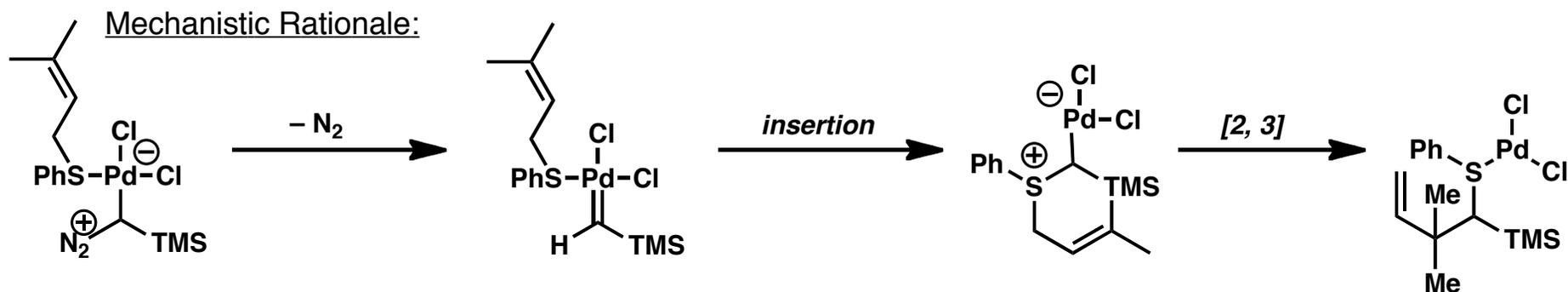


Catalyst	Yield (%)	Recovered SM (%)
Pd(PPh ₃) ₄	0	nd
Pd(OAc) ₂	8	75
Pd(TFA) ₂	22	55
PdCl ₂	83	2

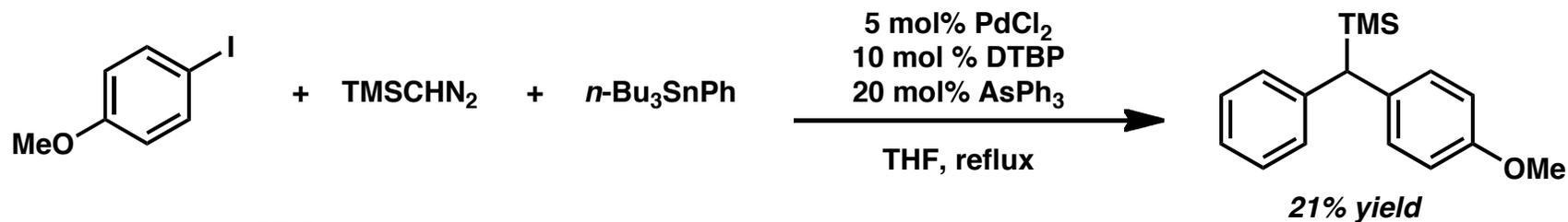
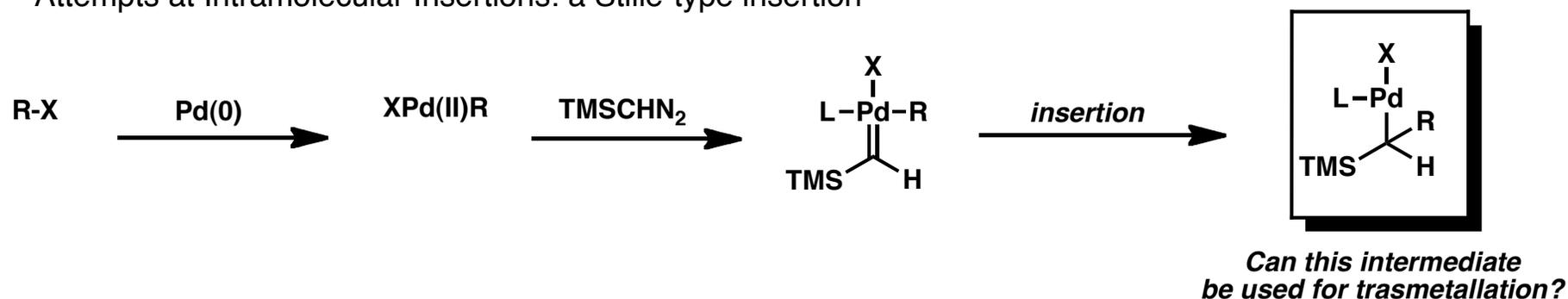
They remark that it is not surprising that tetrakis triphenylphosphine palladium was an insufficient catalyst.

Big Idea: Pd (0) is insufficiently lewis acidic to react with diazo compounds to rapidly form a Pd-carbenoid, so the Pd(II) source can be formed in situ from Pd(0)

Palladium-Catalyzed Insertions: Mechanistic Hypothesis



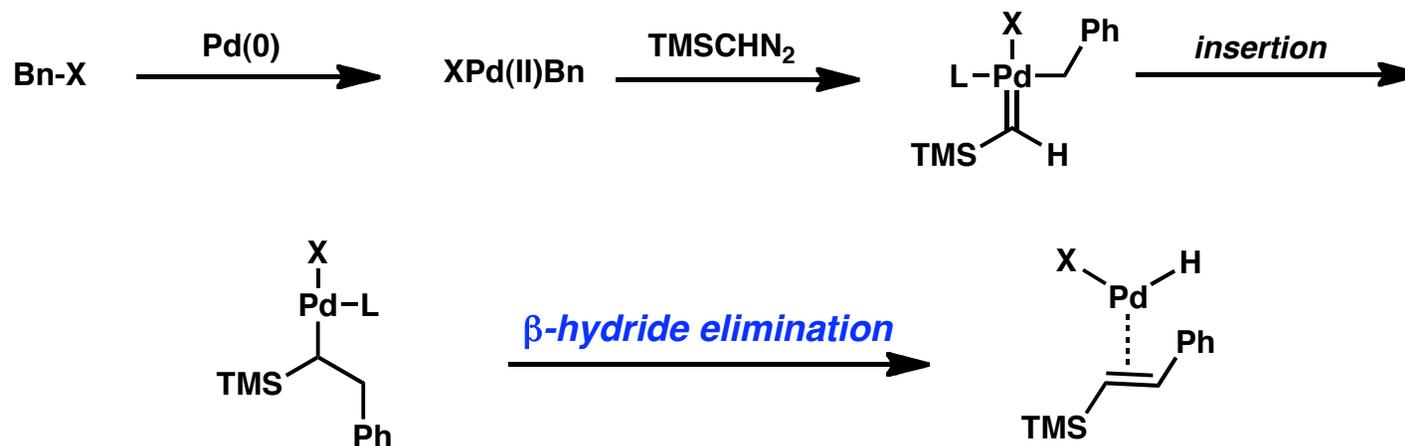
Attempts at Intramolecular Insertions: a Stille-type insertion



Tetrahedron, 2001, 57, 5219

Palladium-Catalyzed Insertions: Homologations

As transmetallation seemed to work poorly, what about β -hydride eliminations?

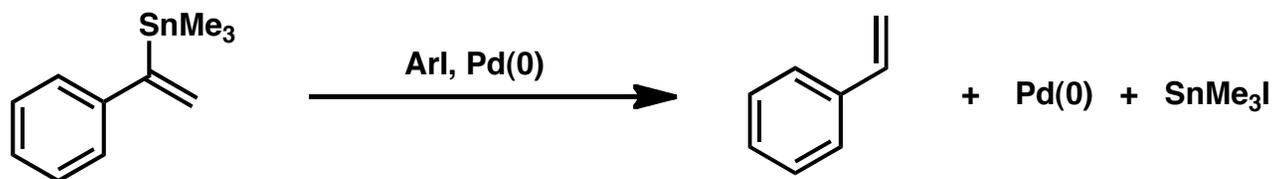


However, a surprising desilylation was observed:



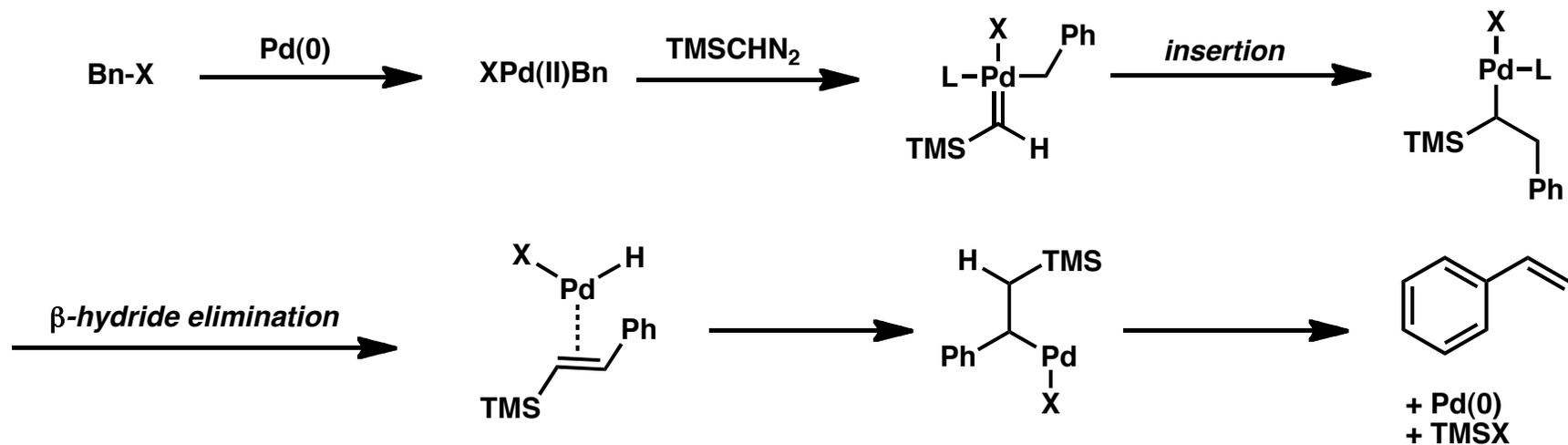
Palladium-Catalyzed Insertions: Benzyl Bromides

Precedent for the observed desilylation:



TL, 1996, 37, 6997

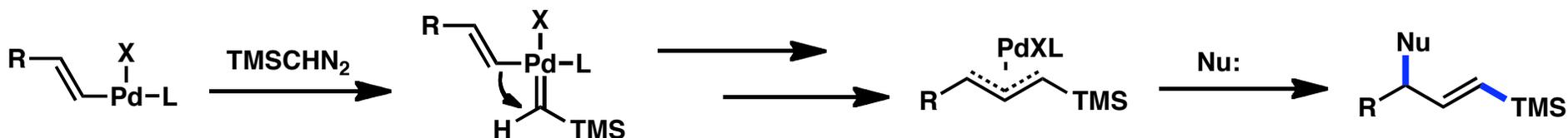
Mechanistic Rationale



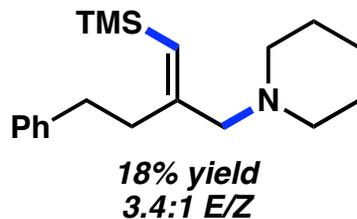
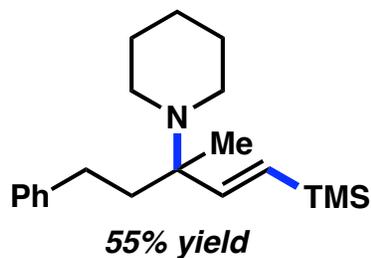
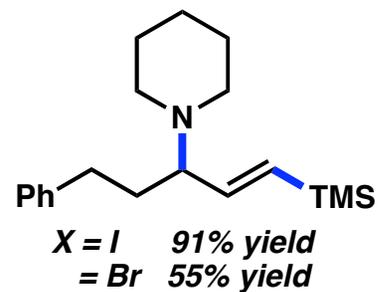
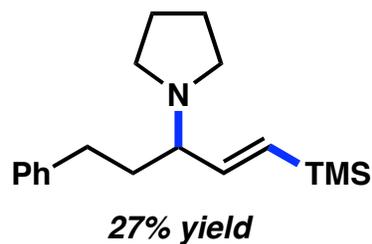
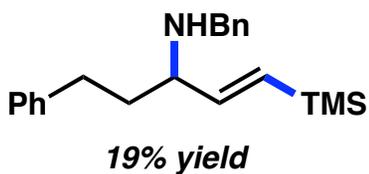
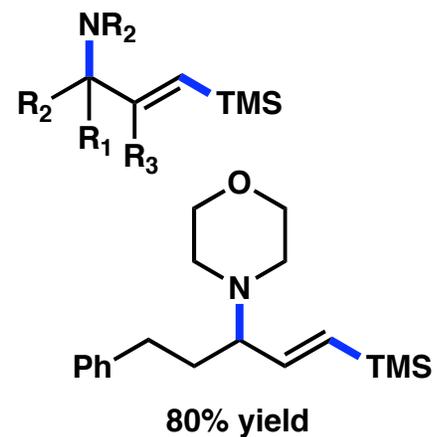
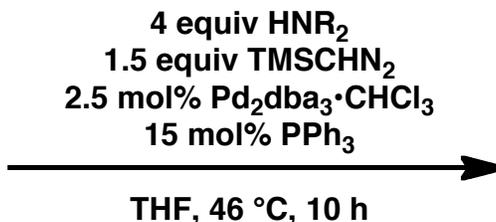
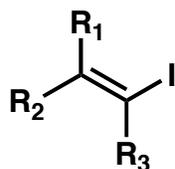
Tetrahedron, 2001, 57, 5219

Palladium-Catalyzed Insertions: External Nucleophiles

Can external nucleophiles be utilized as well?

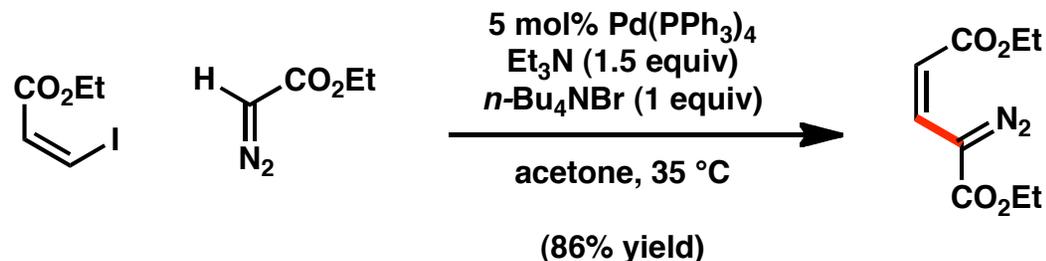


OL, 2007, 9, 2047
Extension with EDA:
ACIE, 2009, 48, 3677

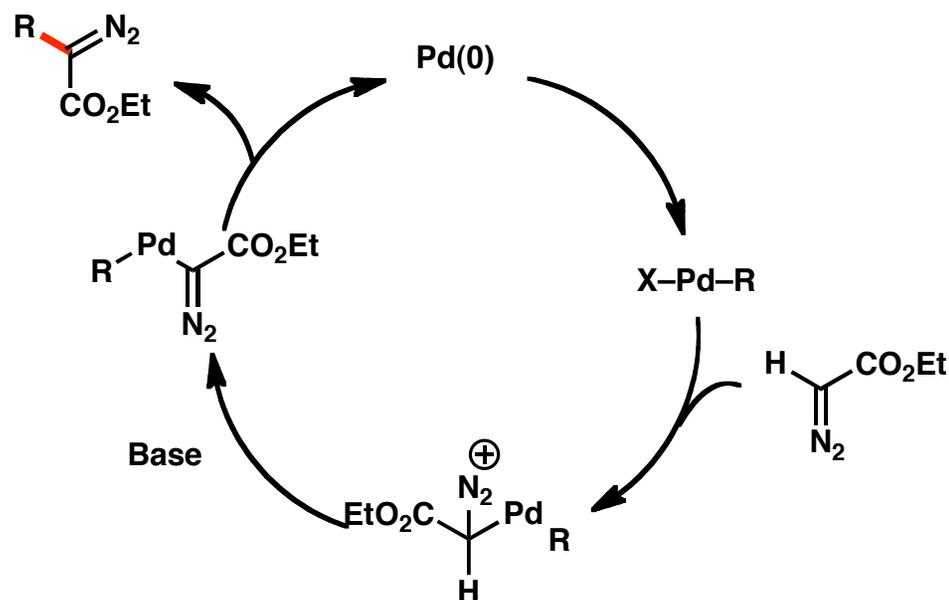


Palladium-Catalyzed Cross-Coupling with Ethyl Diazoacetate

In 2007, J. Wang and coworkers reported the cross-coupling of vinyl halides with ethyl diazoacetate:

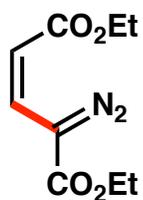


- This formal C-H activation was unexpected, as the insertion of the alkene into the metal carbenoid was the desired product.
- The mechanism is rationalized by the incomplete decomposition of the diazo compound
- Perhaps the lower temperature or lewis basic lone pairs of the ester contribute to diazo stability.

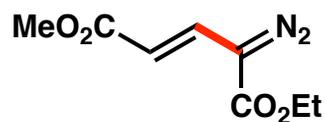


Palladium-Catalyzed Cross-Coupling with Ethyl Diazoacetate

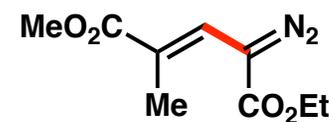
Reaction with corresponding aryl iodide or vinyl iodide



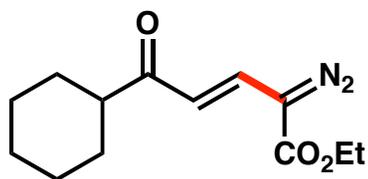
86% yield



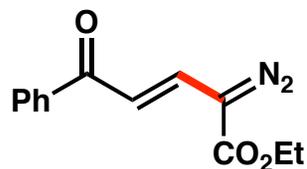
75% yield



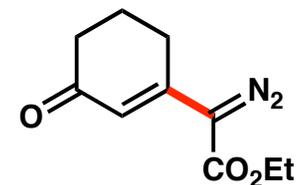
88% yield



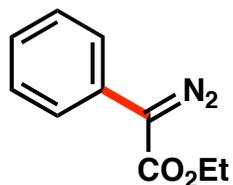
55% yield



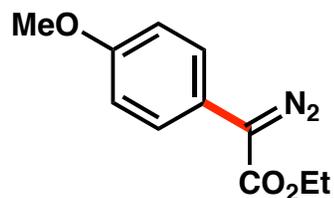
48% yield



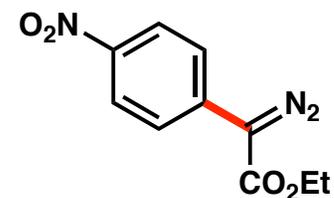
78% yield



96% yield



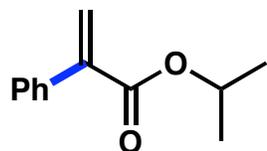
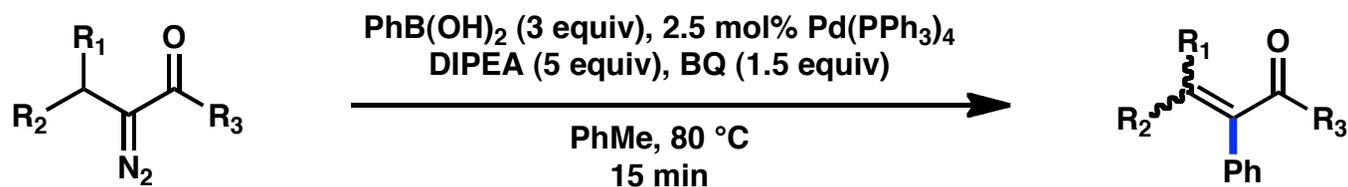
39% yield



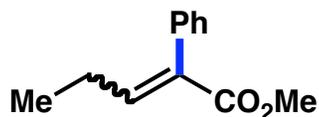
96% yield

Palladium-Carbenoid Catalyzed Cross-Coupling with Arylboronic Acids

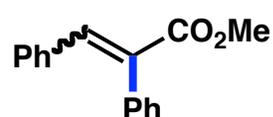
In 2008, J. Wang's group reported the successful cross-coupling of diazo compounds with arylboronic acids, utilizing super-stoichiometric benzoquinone as an oxidant



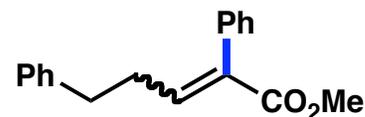
84% yield



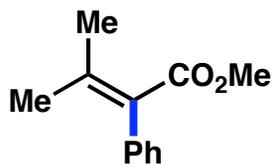
92% yield
Z/E = 1.2/5



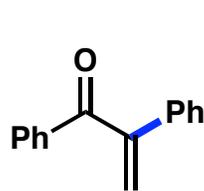
80% yield
Z/E = 1.5/1



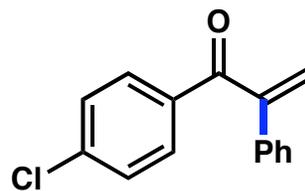
97% yield
Z/E = 1:2.3



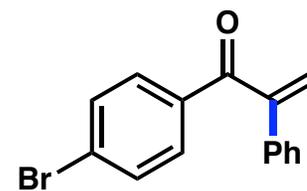
65% yield



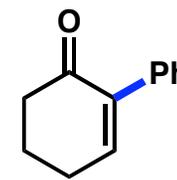
90% yield



87% yield

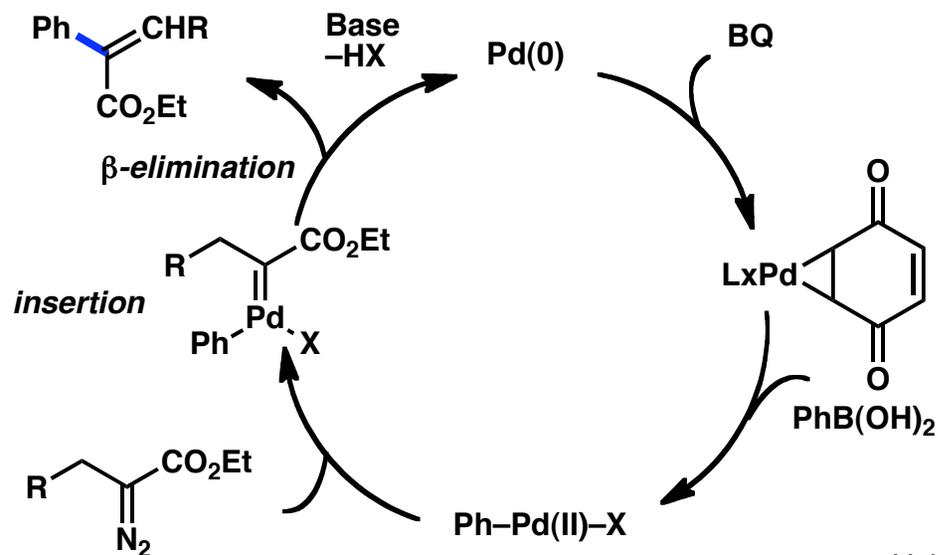


93% yield

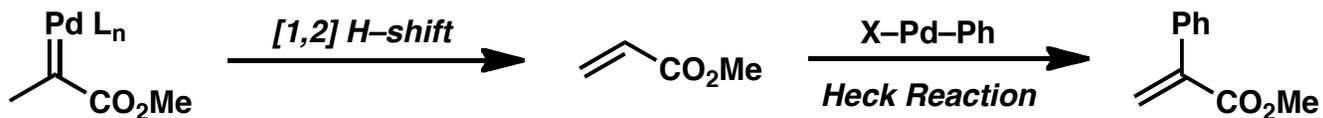


75% yield

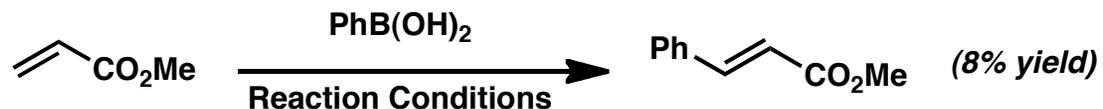
Palladium-Carbenoid Catalyzed Cross-Coupling with Arylboronic Acids: Mechanistic Rationale



Alternative mechanism:

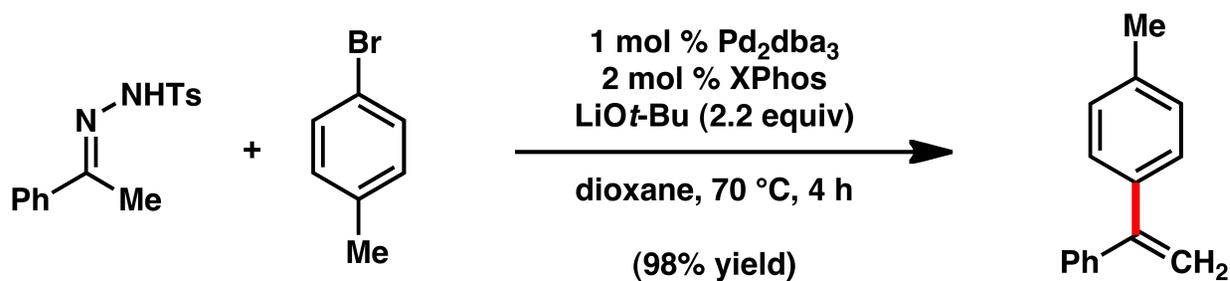


A control experiment:



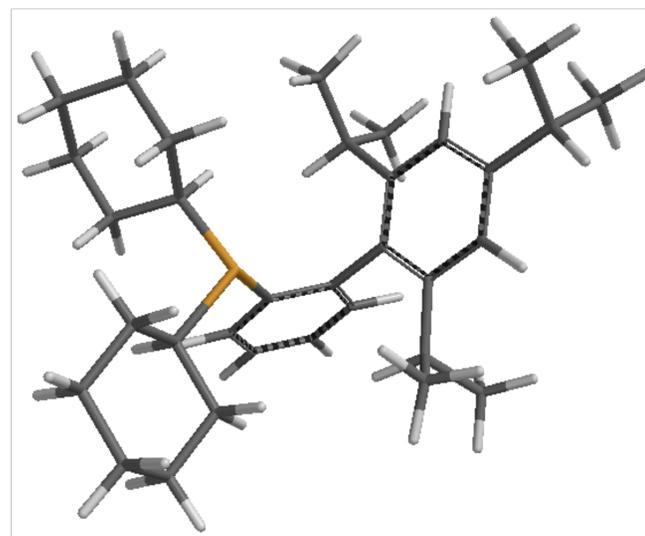
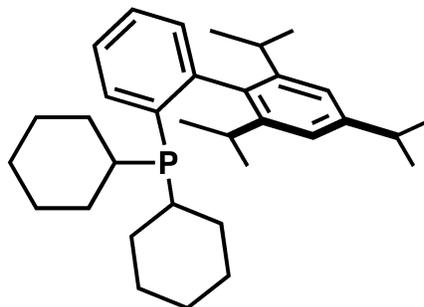
Palladium-Carbenoid Catalyzed Cross-Coupling of N-Tosylhydrazones with Aryl Halides

However, before Wang's report of cross-coupling, Barluenga and coworkers reported the direct cross-coupling of N-tosylhydrazones with aryl halides, utilizing XPhos as a ligand

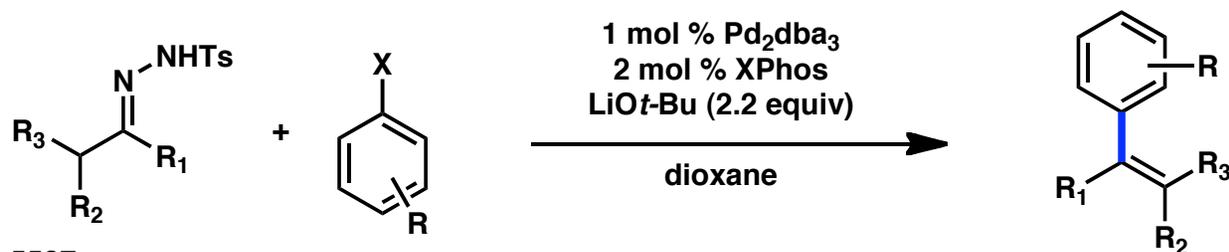


The major advantage of Barluenga's method is the relative ease with which one can access N-tosylhydrazones of many ketones

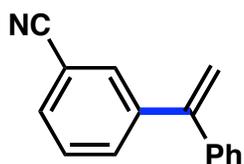
XPhos =



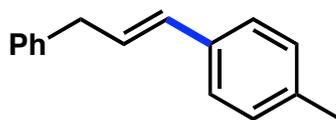
Palladium-Carbenoid Catalyzed Cross-Coupling of N-Tosylhydrazones with Aryl Halides



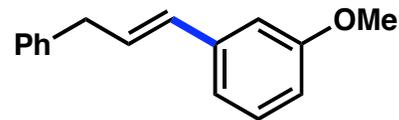
ACIE, 2007, 46, 5587



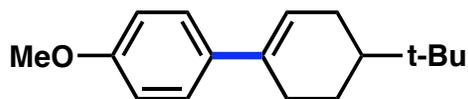
90 °C, 4 h
98% yield



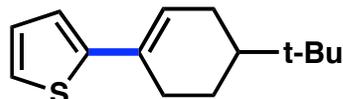
90 °C, 4 h
75% yield



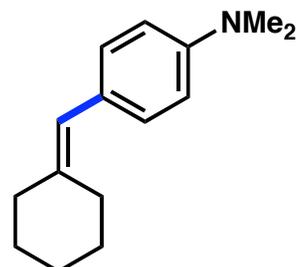
90 °C, 10 h
68% yield



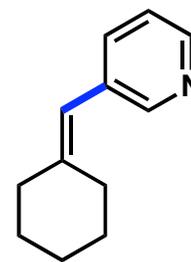
110 °C, 16 h
95% yield



110 °C, 16 h
90% yield



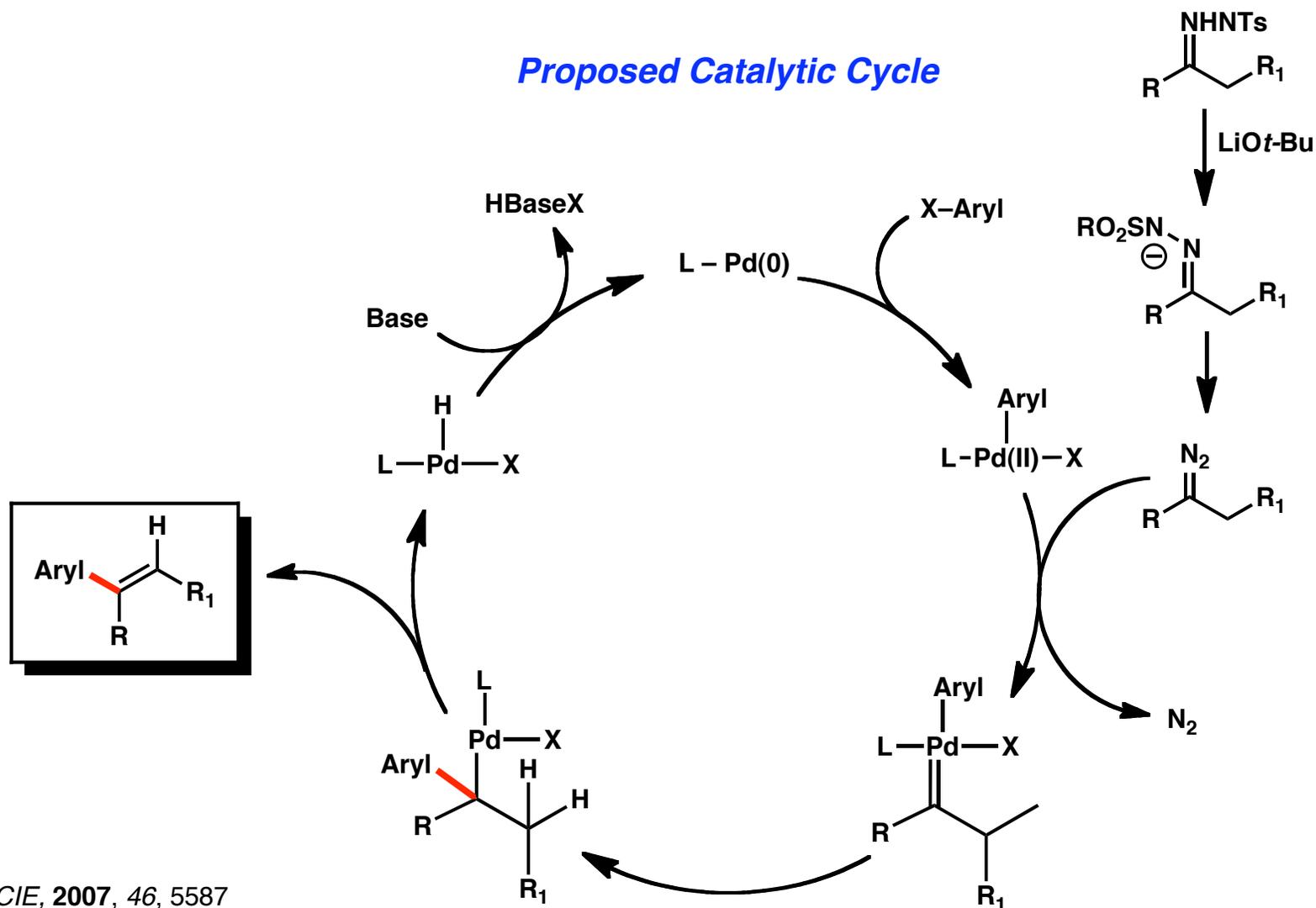
110 °C, 17 h
62% yield
(88% conversion,
2 mol% Pd, 4 mol% XPhos)



90 °C, 17 h
52% yield
(84% conversion)

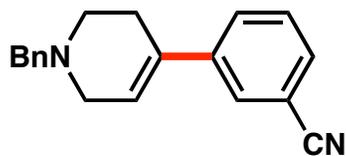
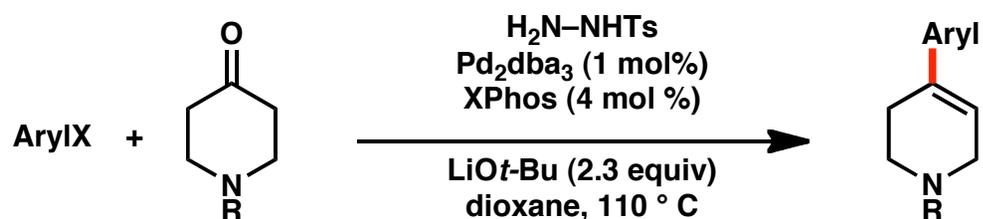
Palladium-Carbenoid Catalyzed Cross-Coupling of N-Tosylhydrazones with Aryl Halides

Proposed Catalytic Cycle

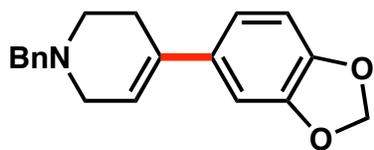


Extensions of the Barluenga Coupling Methodology: Telescoping the Method, Application to Piperidones

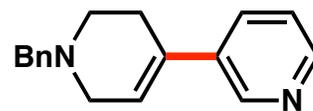
Barluenga and coworkers later determined that their coupling reaction could be telescoped directly from the ketone substrate, i.e. the N-tosylhydrazone could be formed *in situ* and reacted upon formation



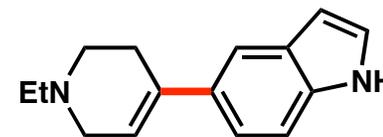
7 h, 98% yield



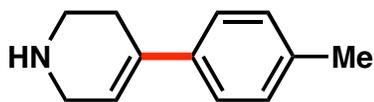
12 h, 97% yield



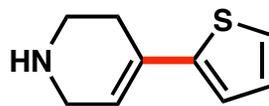
6 h, 99% yield



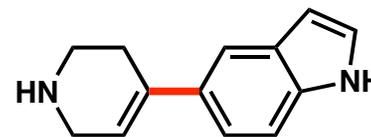
5 h, 83% yield



19 h, 94% yield



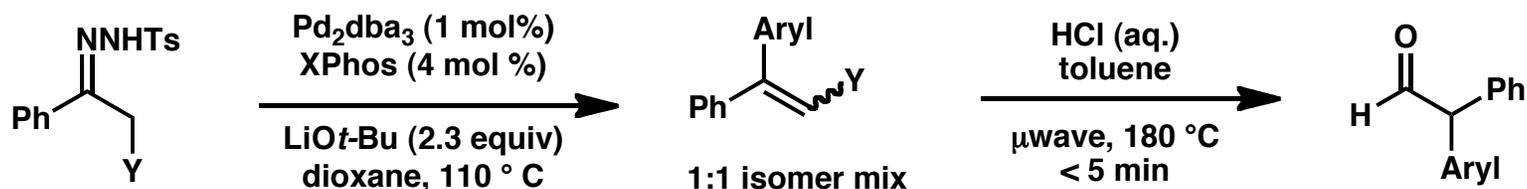
15 h, 70% yield



24 h, 76% yield

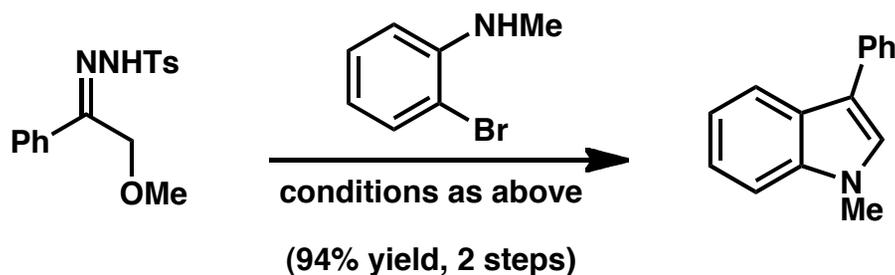
Further Extensions of the Barluenga Coupling Methodology

Synthesis of enol ethers and enamines:



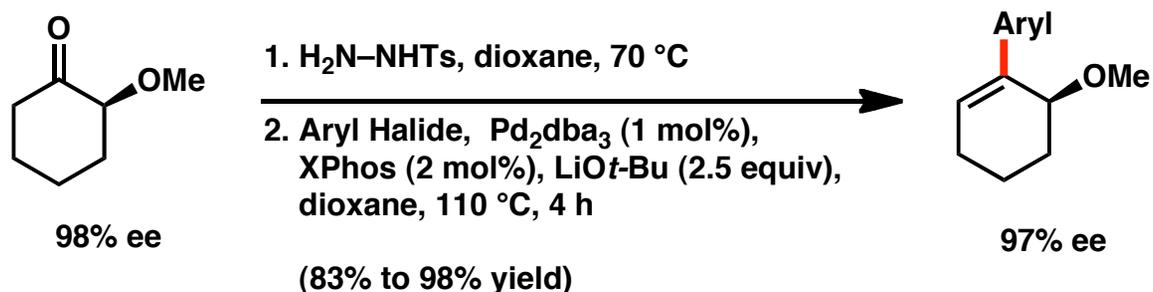
- Y = OMe, OBn, N-morpholine
- Can also start with ketone and use "telescope" method for most substrate, yields 5–10% lower
- The authors note that diaryl aldehydes of the type shown above are very unstable, but are useful intermediates in the synthesis of various heterocycles

Synthesis of 3-phenyl indole as a demonstration of method scope:

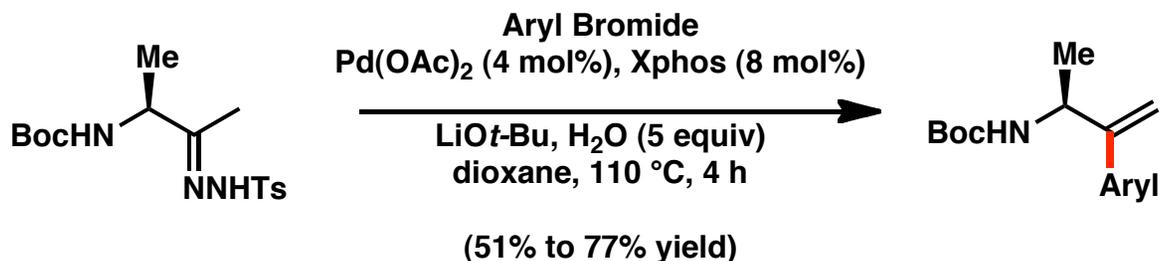


Further Extensions of the Barluenga Coupling Methodology

Stability of α -chiral ketones to coupling conditions: avoiding loss of stereochemical information associated with kinetic deprotonations by strong amide bases:

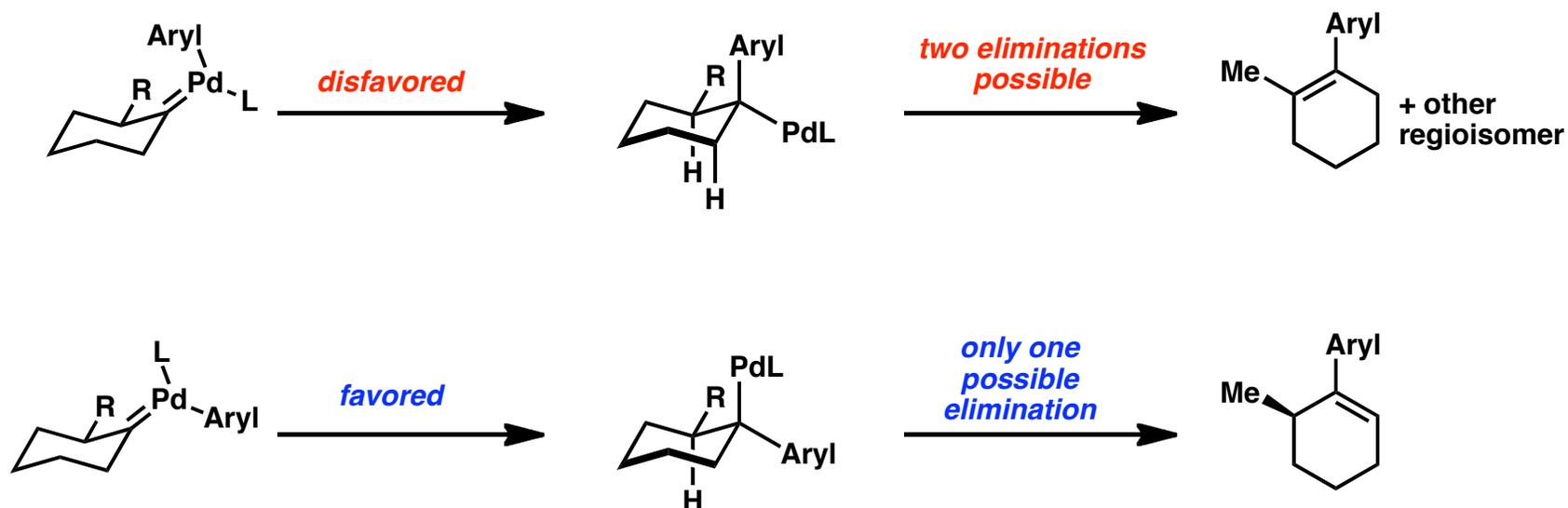


Application to amino ketones, positive effect of H_2O on the reaction:



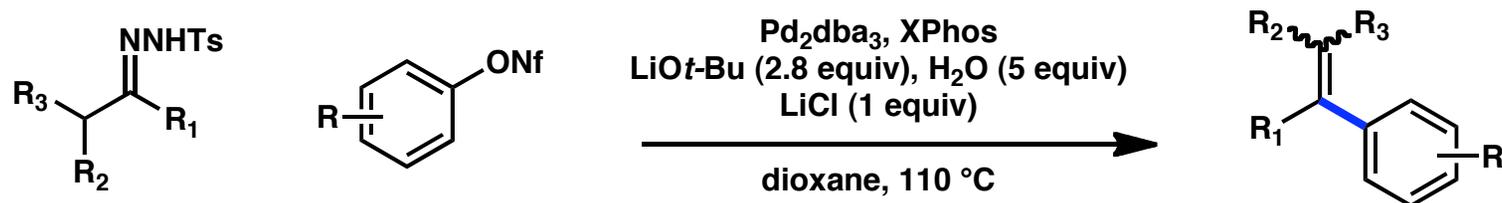
Further Extensions of the Barluenga Coupling Methodology:

Model for High Regioselectivity Observed in Coupling

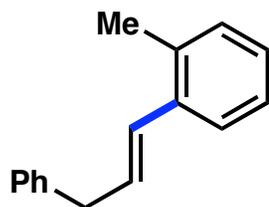


The insertion is favored from the face opposite of the ring substituent, yielding an intermediate Pd species that only has one proton available for β -hydride elimination

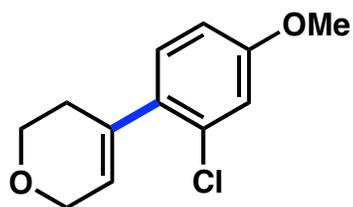
*Further Extensions of the
Barluenga Coupling Methodology:
Aryl Nonaflates Coupled to Make Di-
Tri- and Tetrasubstituted Olefins*



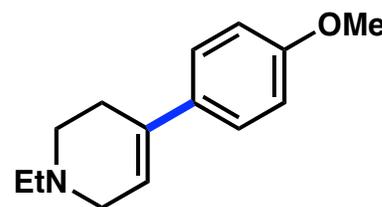
OL, 2011, 13, ASAP



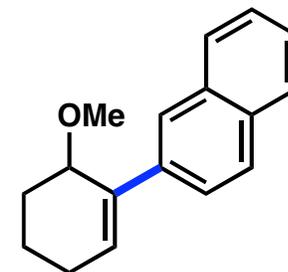
98% yield



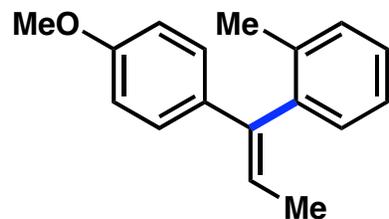
58% yield



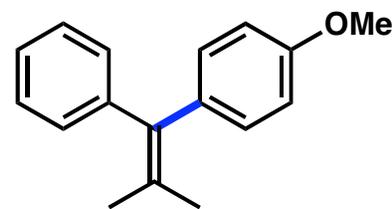
89% yield



83% yield



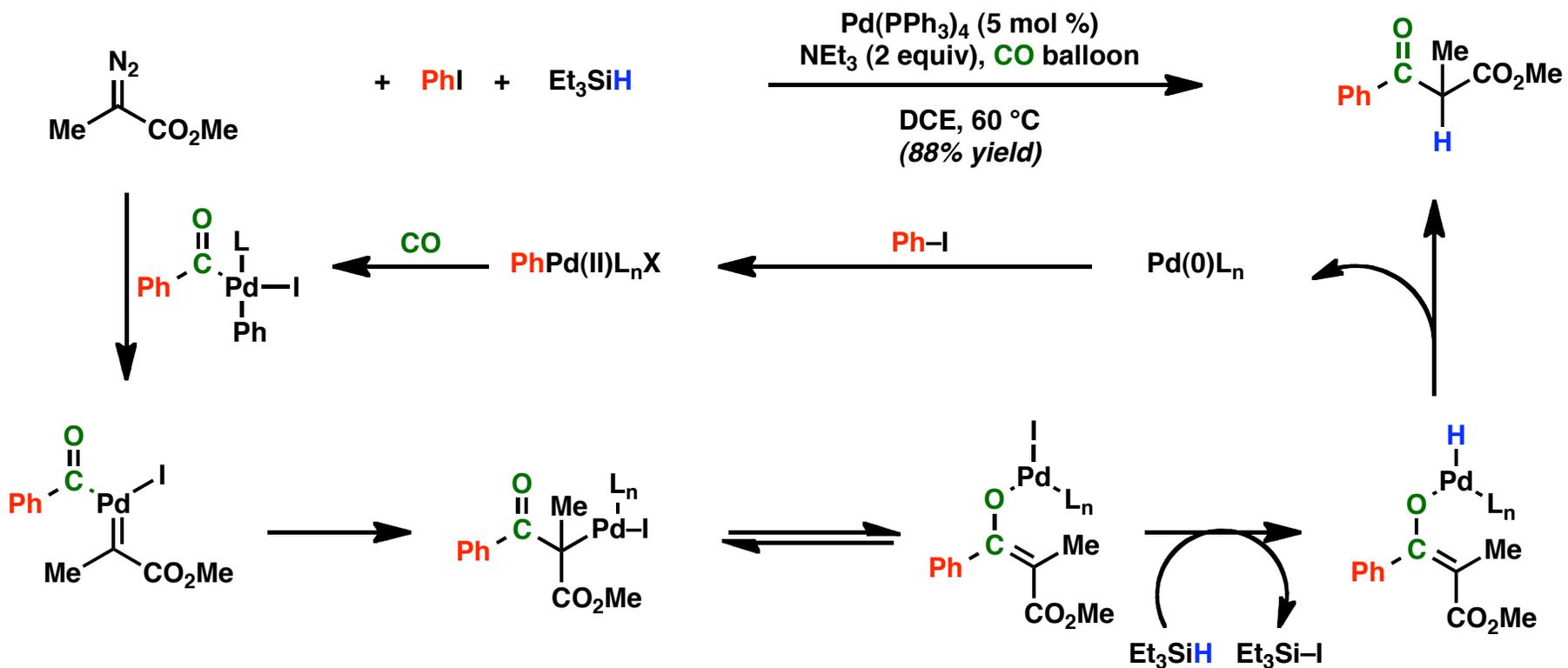
95% yield, single isomer



98% yield

Looking Forward: New Reactivities, Pushing the Boundaries

Wang and coworkers publish the carbonylation/acyl migratory insertion of Palladium carbenoids:

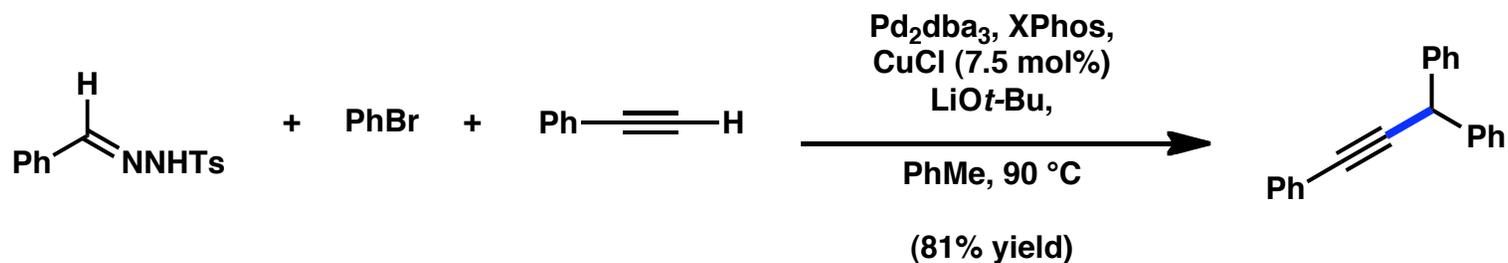


Note: the reaction is also performed with N-tosylhydrazones, utilizing LiOt-Bu at the base

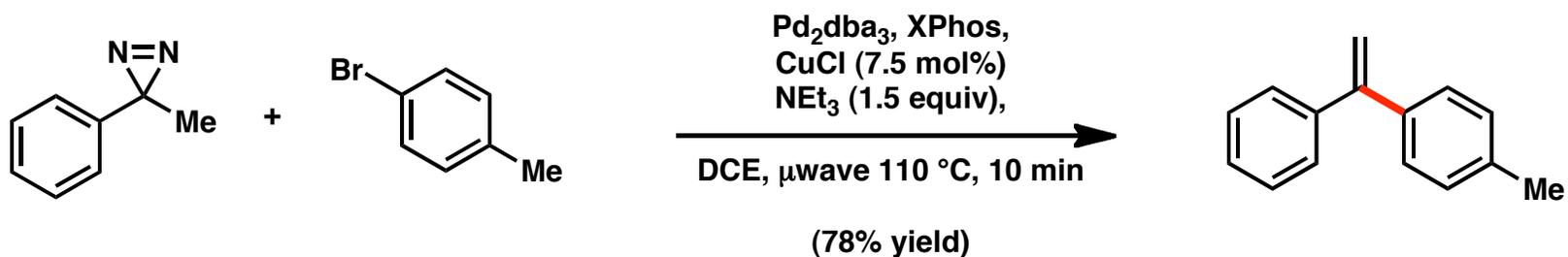
Looking Forward: New Reactivities, Pushing the Boundaries

Recent work from the Wang group:

– Three Component Coupling with alkynes



– Use of diazirines as source of diazo compound



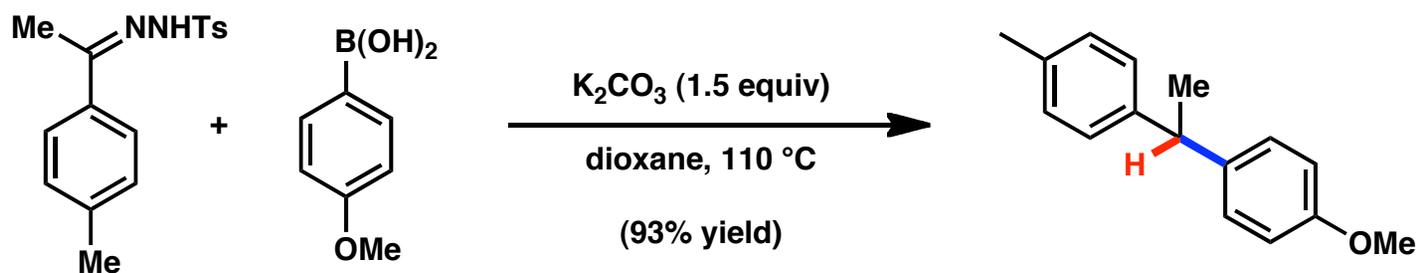
Alkyne coupling: *JACS*, **2010**, *132*, 13590

Diazirine coupling: *OL*, **2010**, *12*, 5580

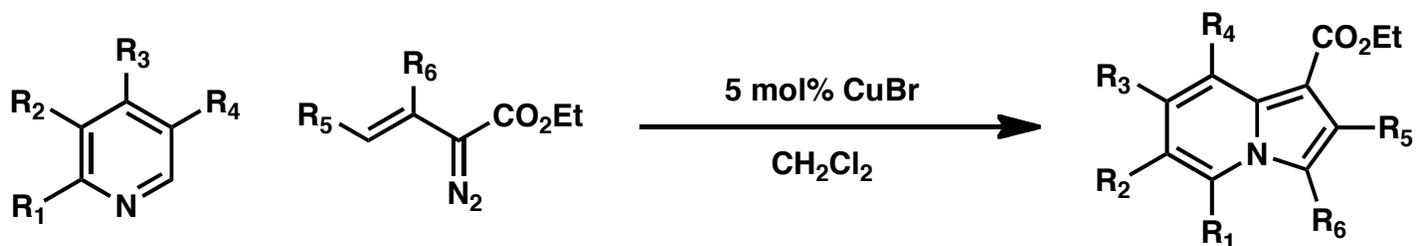
Not Palladium, But Worth Mentioning...

Recently, from the Barluenga group:

- Metal-free reductive coupling of aryl boronic acids and N-tosylhydrazones



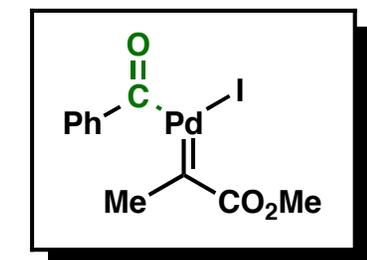
- Work on the synthesis of heterocycles using Cu catalysts



Metal-free coupling: *Nature Chem.* **2009**, *1*, 494

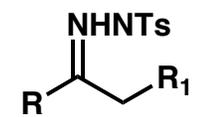
CuBr heterocycles: *JACS*, **2010**, *132*, 13200

Summary and Outlook

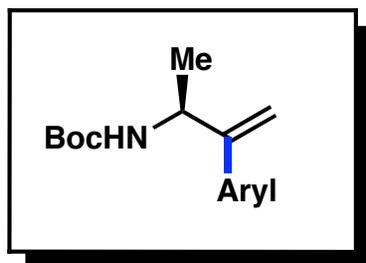
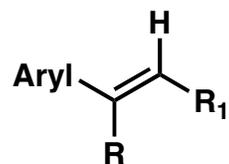
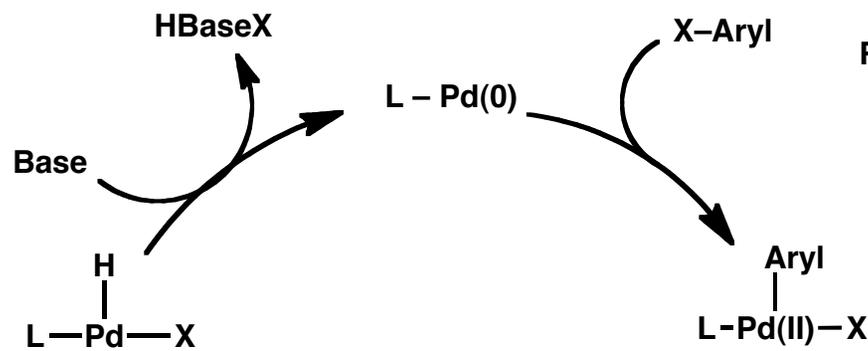
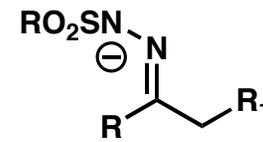


carbonylations
of reactive intermediates

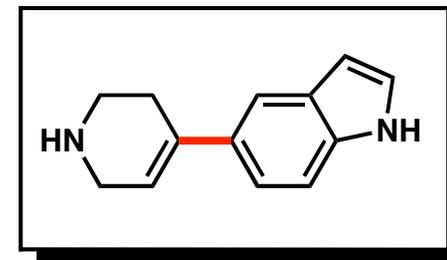
in situ formation of
reactive diazo intermediate



LiOtBu

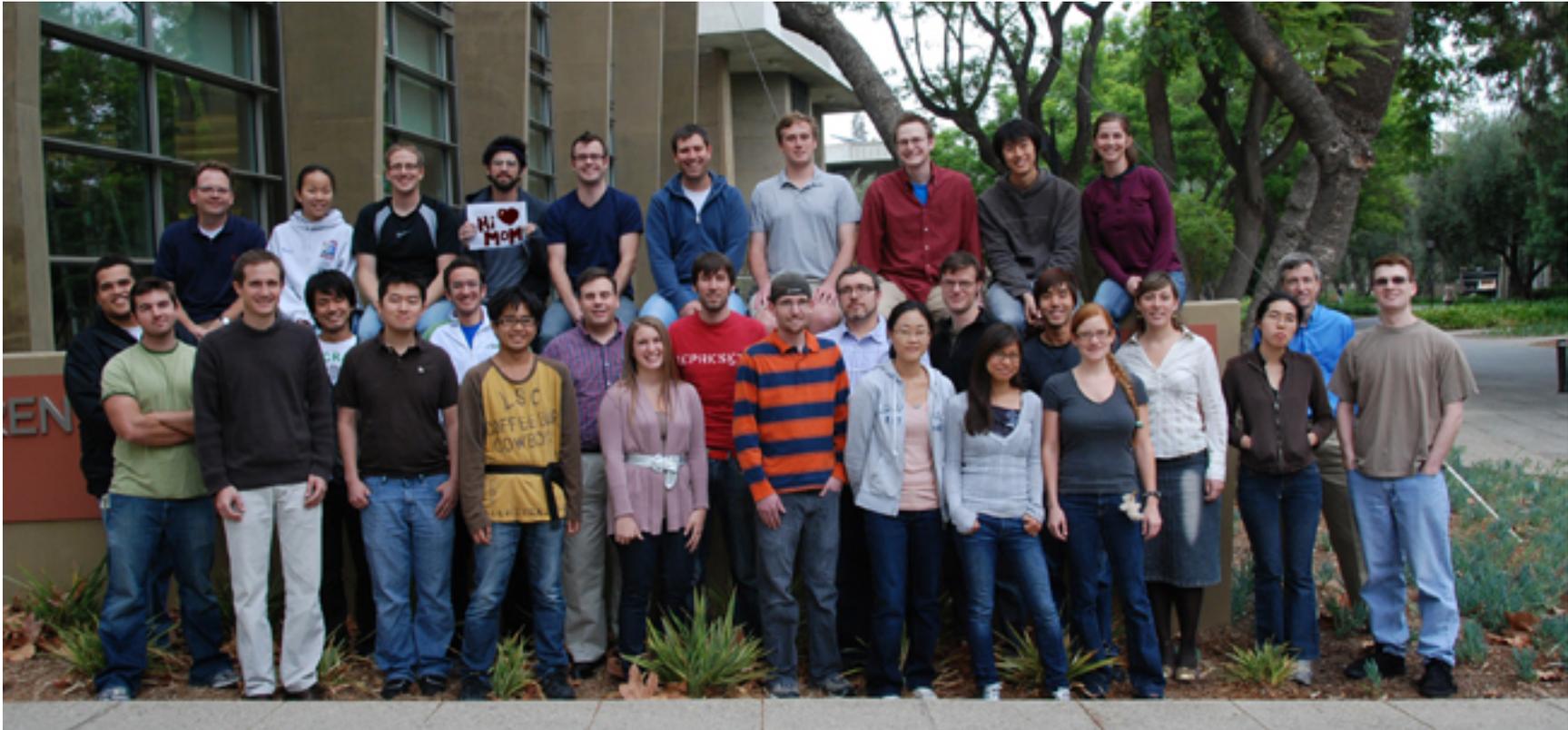


stability of chiral centers to conditions



direct coupling of free N-H fragments

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Rob Craig

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Stoltz Group
Reisman Group

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Uttam Tambar

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Mike, at Tiki-Ti, for fuel
Lil' Wayne for slide-making tunes
Anyone in the audience still awake

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