

High-valent organometallic copper and palladium in organic transformations

Topic Review

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Main sources:

Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177.

Ribas, X. & Casitas, A. in *Ideas in Chemistry and Molecular Sciences: Where Chemistry Meets Life* (ed. Pignataro, B.) 31–57 (Wiley-VCH, 2010).

Muniz, K. *Angew. Chem. Int. Ed.* **2009** *48*, 9412–9423.

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Part I: High-valent copper

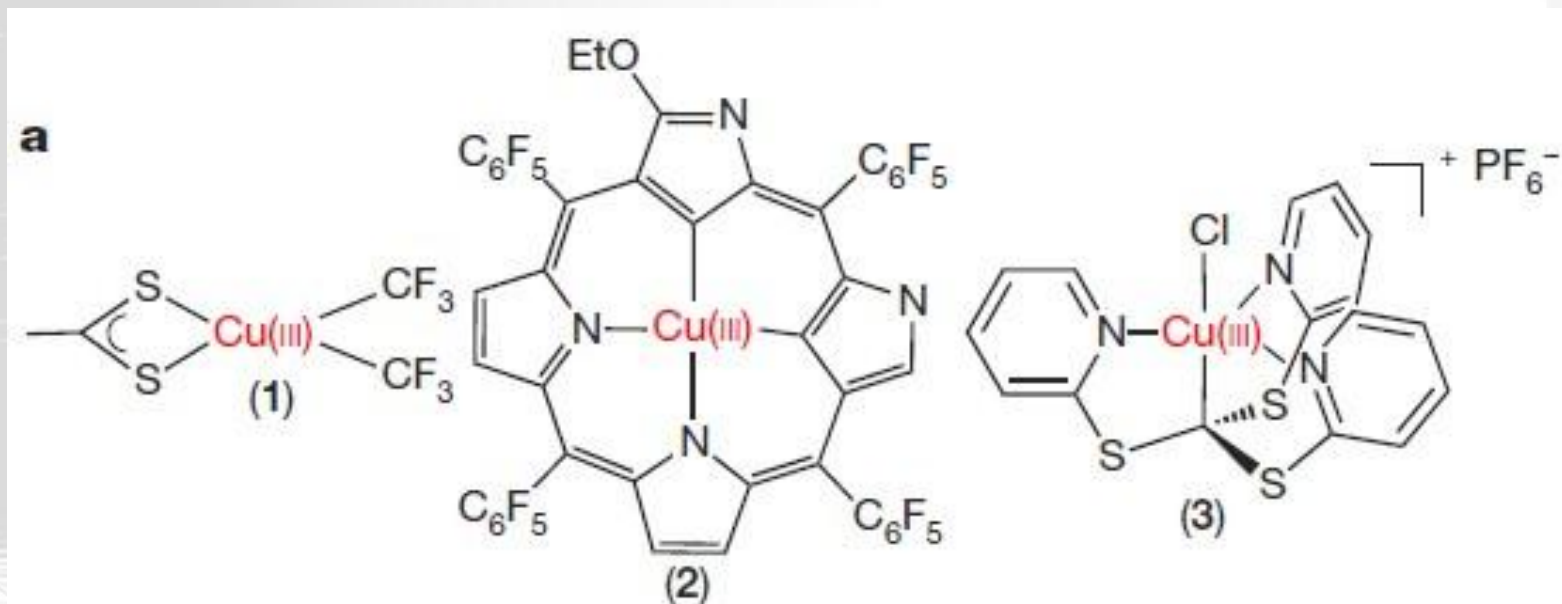
➤ Types of organocopper:

- RCu^{I} -- unreactive species
- $\text{R}_2\text{Cu}^{\text{I}}\text{M}$ (M = Li, MgX);
- $\text{R}_3\text{Cu}^{\text{I}}\text{Li}_2$ species -- lithium cations play a role in the stabilization and reactivity;
- $\text{R}_3\text{Cu}^{\text{III}}$ species – **High-valent copper**, proposed in numerous mechanistic discussions.

General consensus -- the formation of $\text{R-Cu}^{\text{III}}\text{-R}'$ species followed by subsequent reductive elimination.

Part I: High-valent copper

➤ Known isolatable high-valent organometallic copper complexes



Features:

nearly **square planar** in geometry, in consonance with the formal d_8 electronic system;
stabilized by **rigid, chelating and/or perfluorinated ligands**;
structurally interesting, do not have the characteristic reactivity.

Part I: High-valent copper

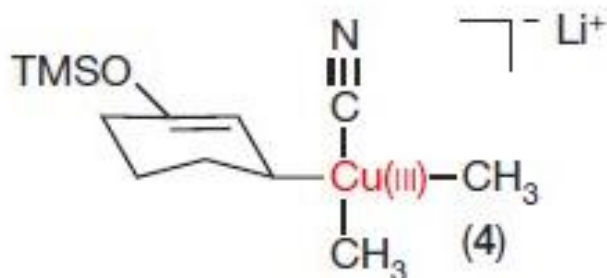
➤ Problem:

- Putative Cu(III) compounds proved too **transient for detection** using standard spectroscopic techniques;
- For many years, **little experimental evidence** was available to support hypothesis.

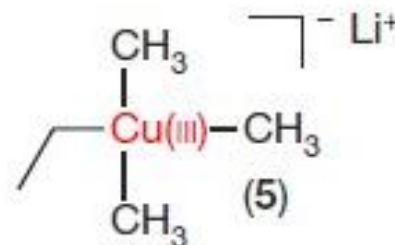
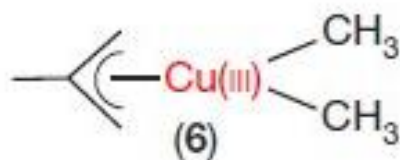
Part I: High-valent copper

➤ Rapid-injection NMR spectroscopy (RI-NMR)

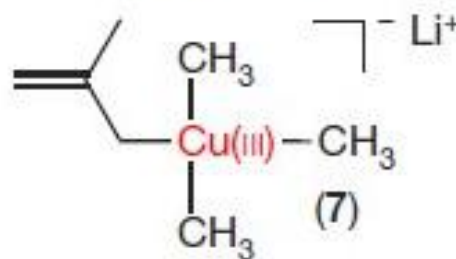
- In 2007, it was introduced as a method to directly observe Cu(III) species in real time, and help to clarify the mechanism.



Conjugate addition



S_N2 alkylation



Part I: High-valent copper

➤ Carbon-Carbon Bond Formation

- Conjugate Addition to α -enones
- Acetylene Carbocupration
- S_N2 and S_N2' Alkylations
- Trifluoroalkylation

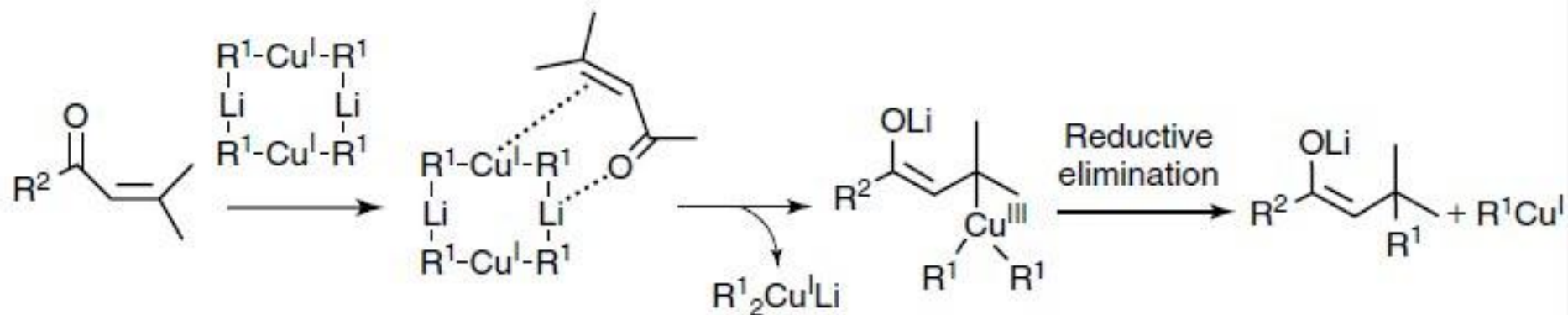
➤ Aryl-Heteroatom Bond Formation

- C-H Bond Organometallic Functionalization

Part I: High-valent copper intermediates

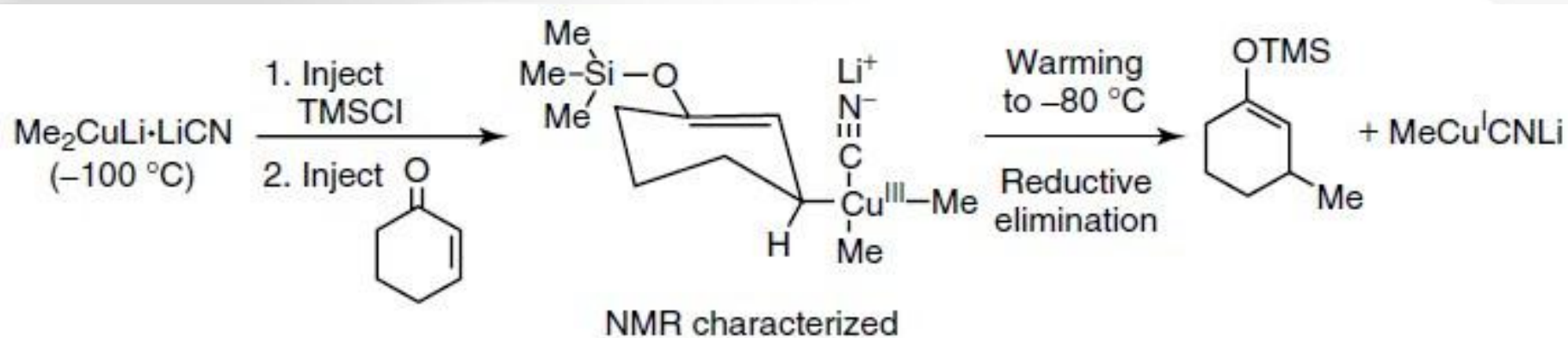
-- in carbon-carbon bond-forming reactions

➤ 1. 1,4-Conjugate addition of $R_2Cu^I Li$ to α -enones



Part I: High-valent copper intermediates

-- in carbon-carbon bond-forming reactions

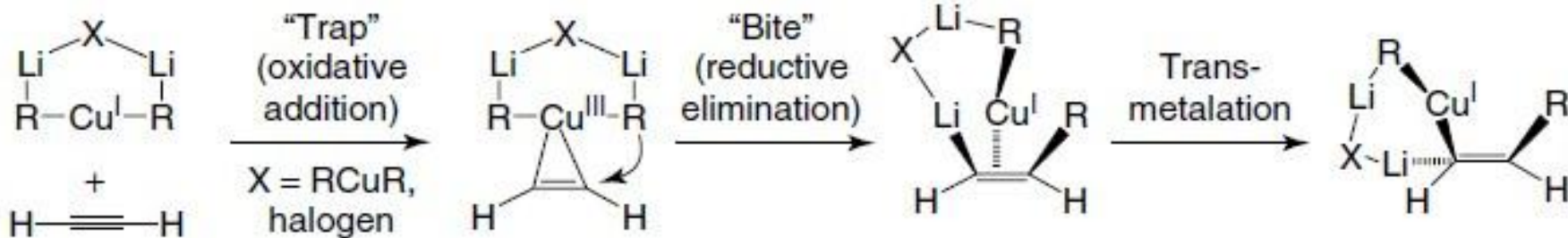


Low-temperature RI-NMR characterization of an $\text{R}_3\text{Cu}^{\text{III}}$ intermediate species in an organocuprate conjugate addition reaction

Part I: High-valent copper intermediates

-- in carbon-carbon bond-forming reactions

➤ 2. Acetylene Carbocupration

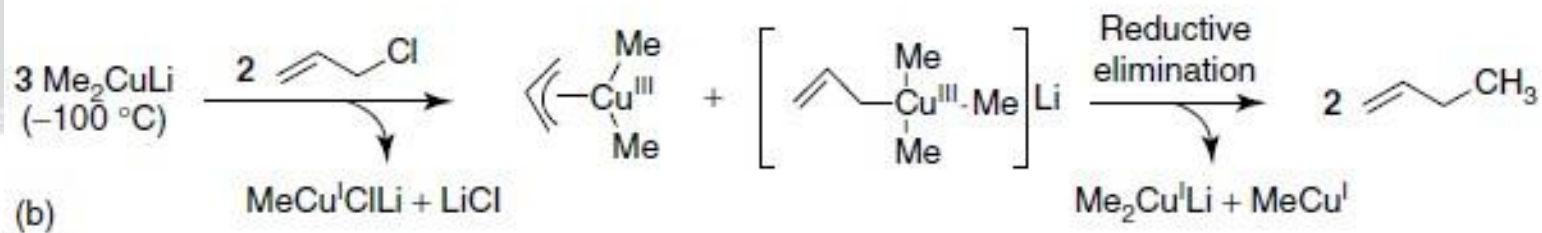
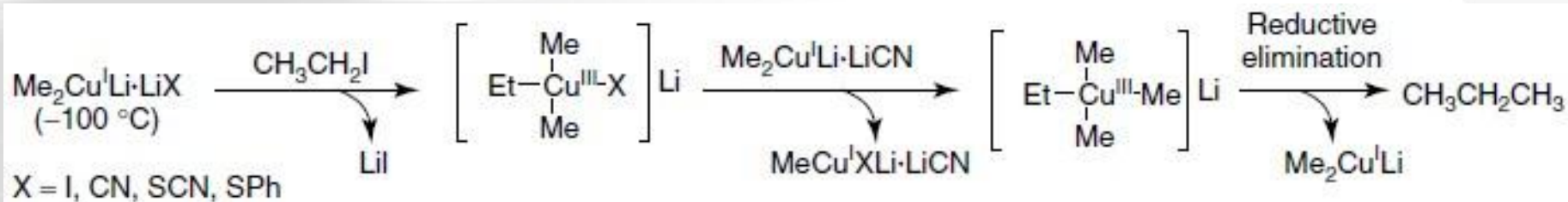


Proposed trap-and-bite mechanism of acetylene carbocupration

Part I: High-valent copper intermediates

-- in carbon-carbon bond-forming reactions

➤ 3. S_N2 and S_N2' Alkylations

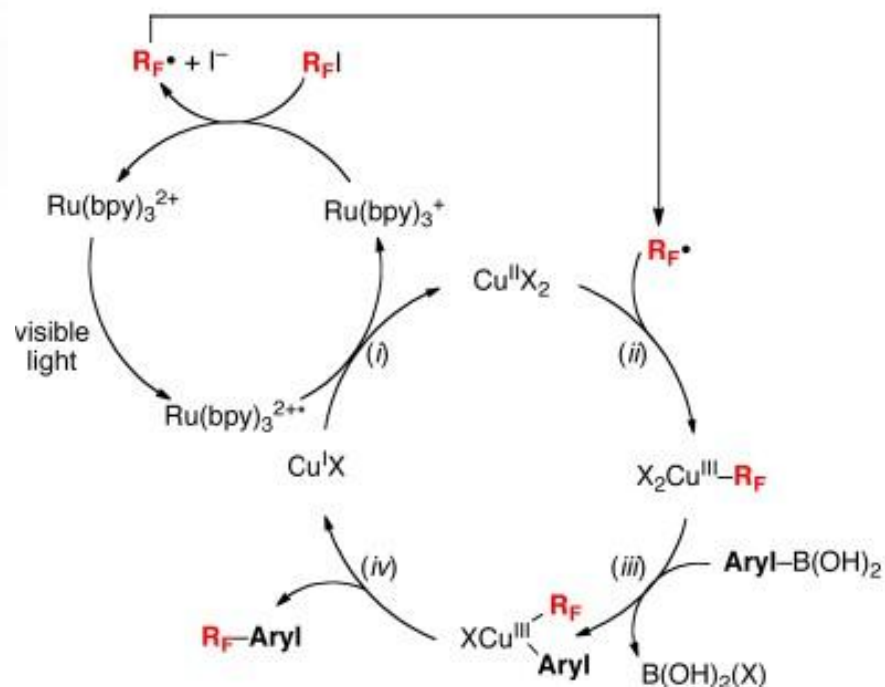
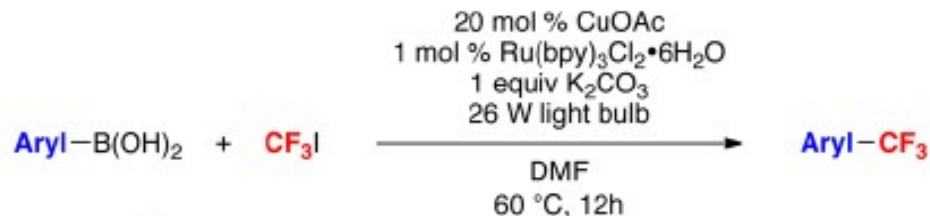


Low-temperature RI-NMR characterization of (a) the first nonfluorinated $\text{R}_4\text{Cu}^{\text{III}}$ intermediate species in an S_N2 alkylation and (b) η^1 σ -allyl and η^3 π -allyl- Cu^{III} species

Part I: High-valent copper intermediates

-- in carbon-carbon bond-forming reactions

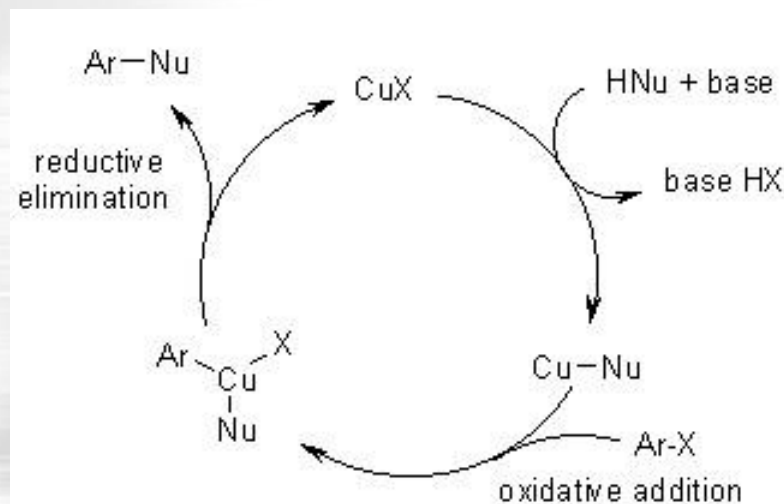
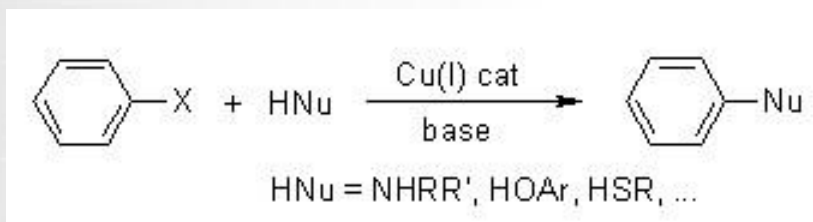
➤ 4. Cu/Ru-Catalyzed Trifluoromethylation of Boronic Acids



Part I: High-valent copper intermediates

-- in carbon-heteroatom bond-forming reactions

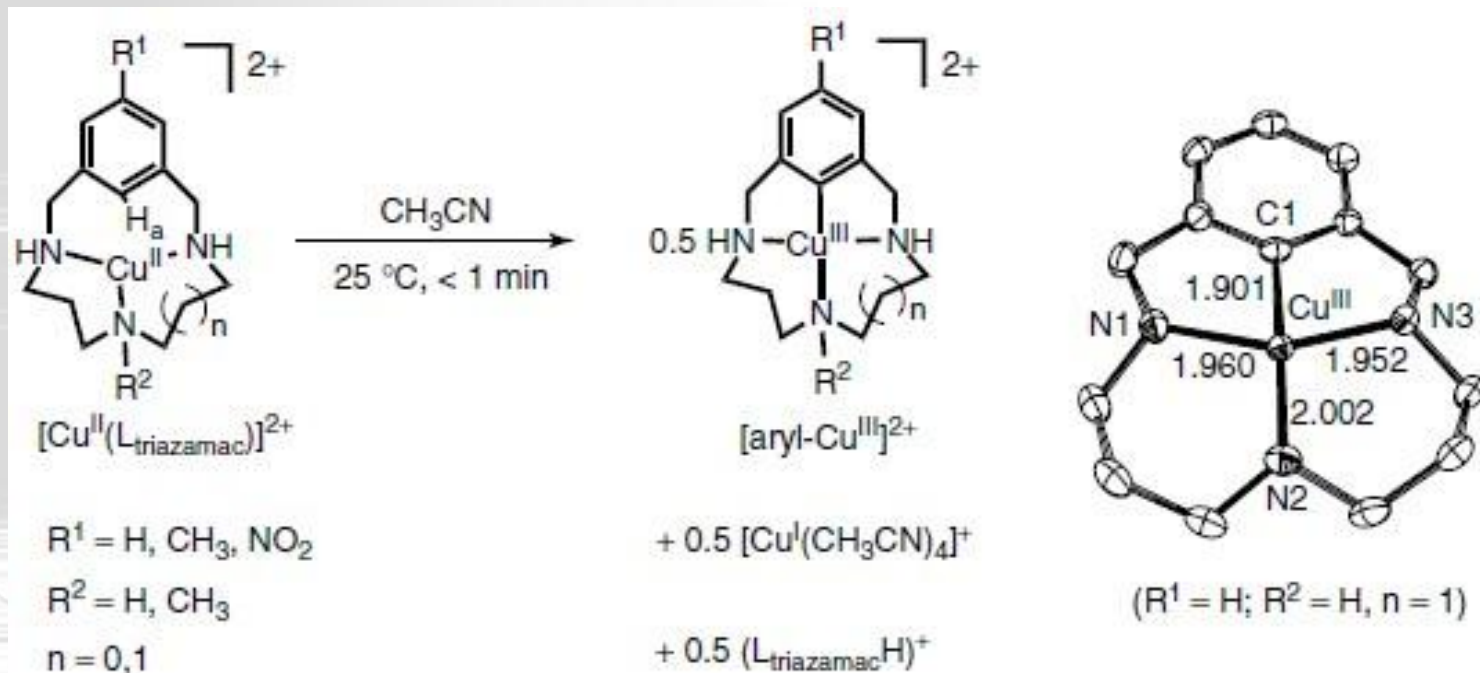
- Century-old **Ullmann chemistry** is thought to proceed by participation of high-valent organometallic aryl-Cu^{III}-Nucleophile.



Part I: High-valent copper intermediates

-- in carbon-heteroatom bond-forming reactions

➤ First isolatable **Cu(III)-monoaryl species**

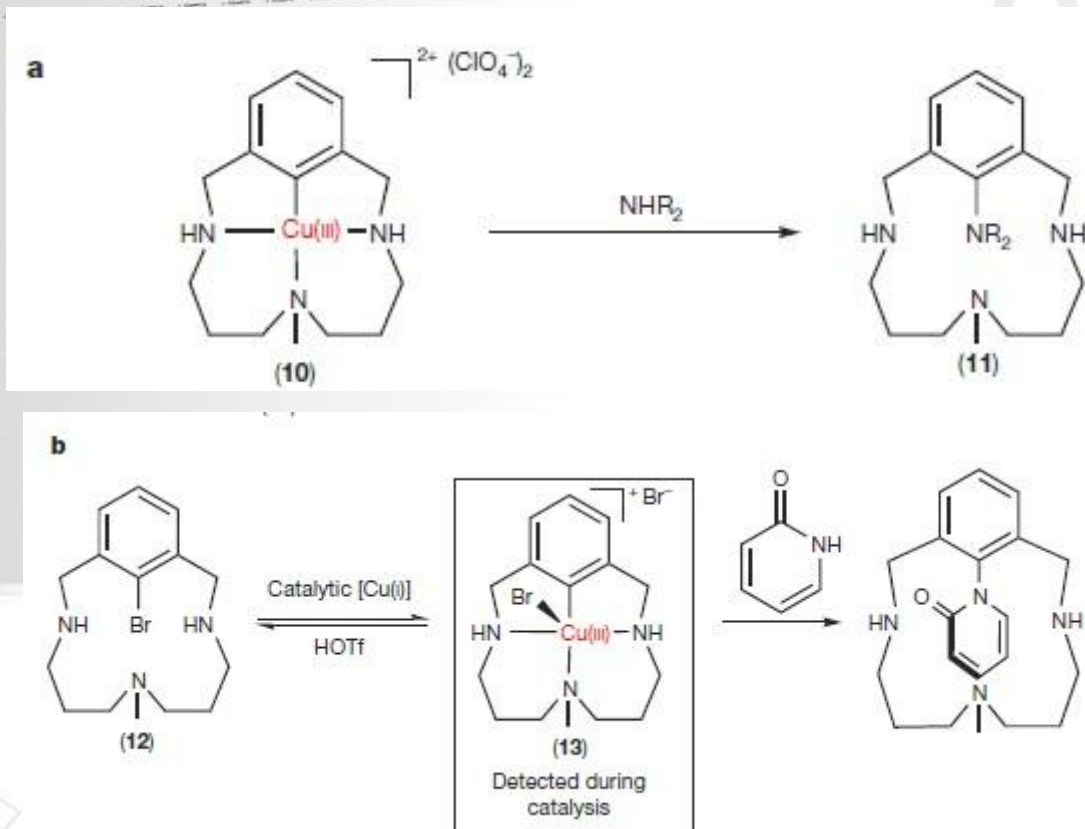


Feature:

stabilized by an electron-donating macrocyclic ligand, but reactive.

Part I: High-valent copper intermediates

-- in carbon-heteroatom bond-forming reactions

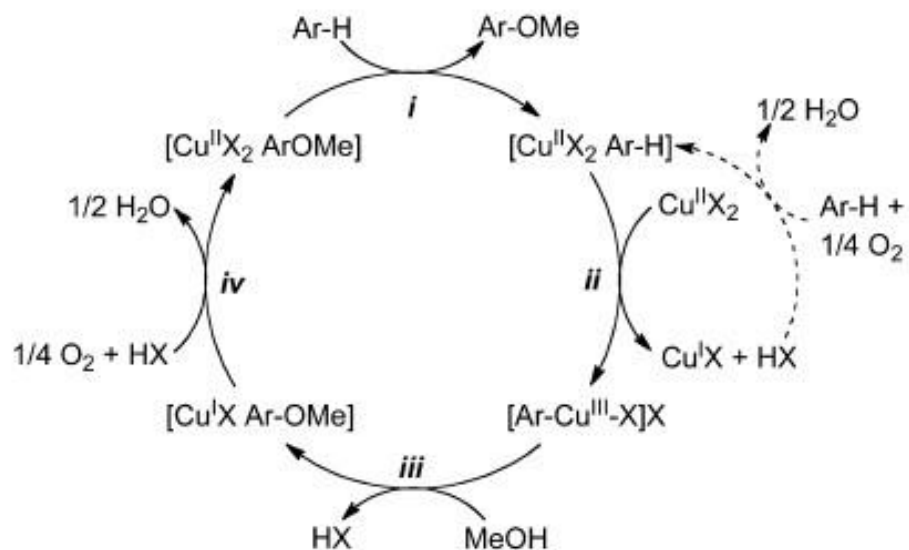
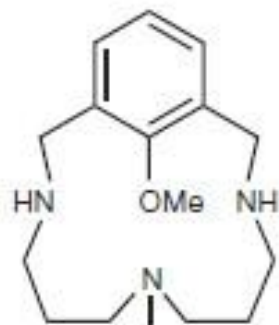
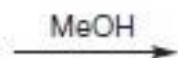
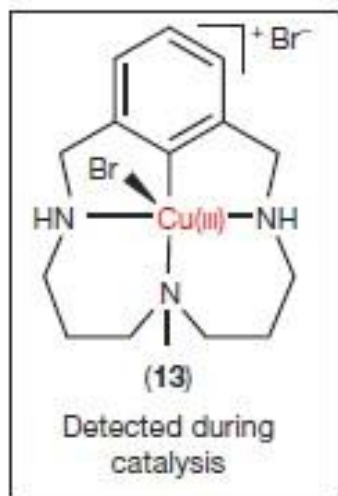


a, Stoichiometric carbon–nitrogen bond formation from an isolated organo-Cu(III). NHR_2 represents **pyridone**, oxazolidinone or acetanilide.

b, In situ observation of an organo-Cu(III) intermediate in the coupling of aryl bromide with pyridone.

Part I: High-valent copper intermediates

-- in carbon-heteroatom bond-forming reactions



In situ observation of an organo-Cu(III) intermediate in the oxygenation of carbon–hydrogen bonds.

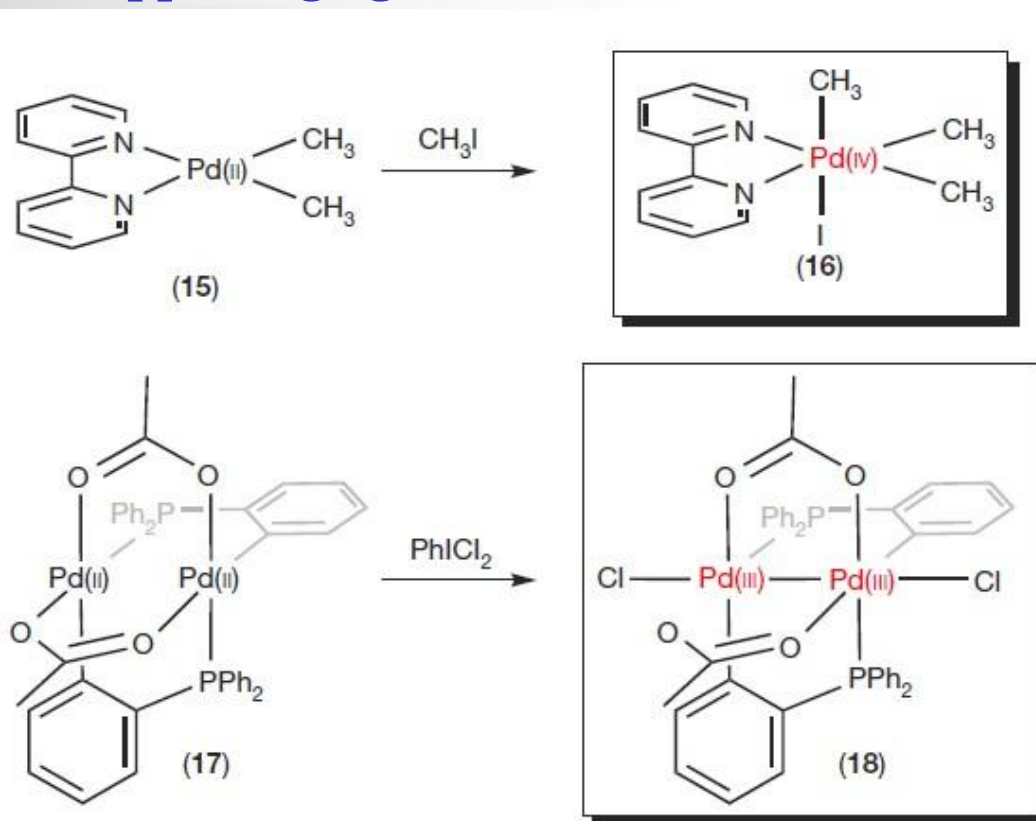
Part I: High-valent copper

➤ Summary

- The mostly proposed or invoked organometallic **Cu^{III} species** for many years are now being **experimentally characterized**.
- Fundamental studies of organo-Cu(III) are beginning to provide greater understanding of mechanism, which in turn should allow the rational development of new synthetic methods.

Part II: High-valent palladium

- High-valent palladium -- in the **+3 or +4 oxidation state** Pd (III) and Pd (IV)
- High-valent palladium products – stabilized by electron-donating, rigid, **multidentate supporting ligands**.



Early examples of Pd(III) and Pd(IV) organometallic complexes

Part II: High-valent palladium

➤ C-C coupling

➤ Aryl-heteroatom coupling

-- C-O and C- X bond formation

-- C-N bond formation

➤ Alkyl-heteroatom coupling

-- Alkyl oxygenation

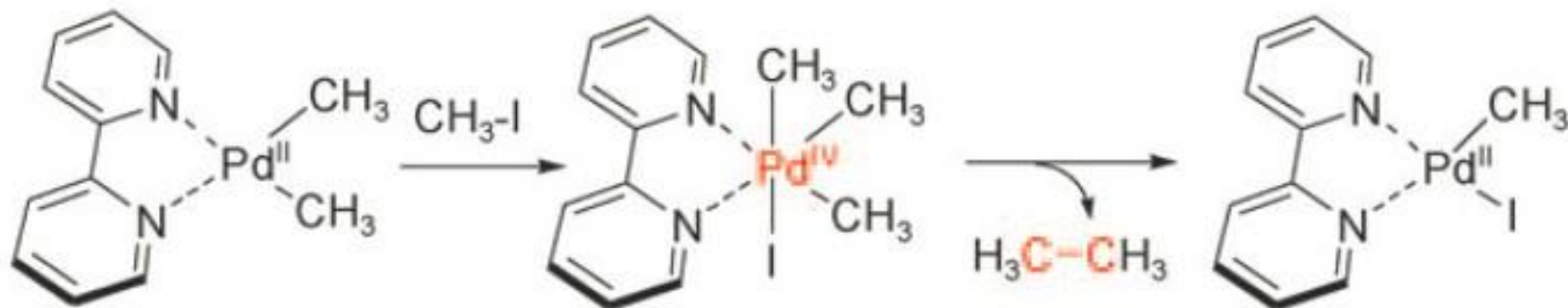
-- 1,2-Difunctionalization of alkenes: dialkoxylation, aminoalkoxylation, and diamination

-- Domino catalysis involving Pd^{IV} catalysts

Part II: High-valent palladium

-- C-C Coupling

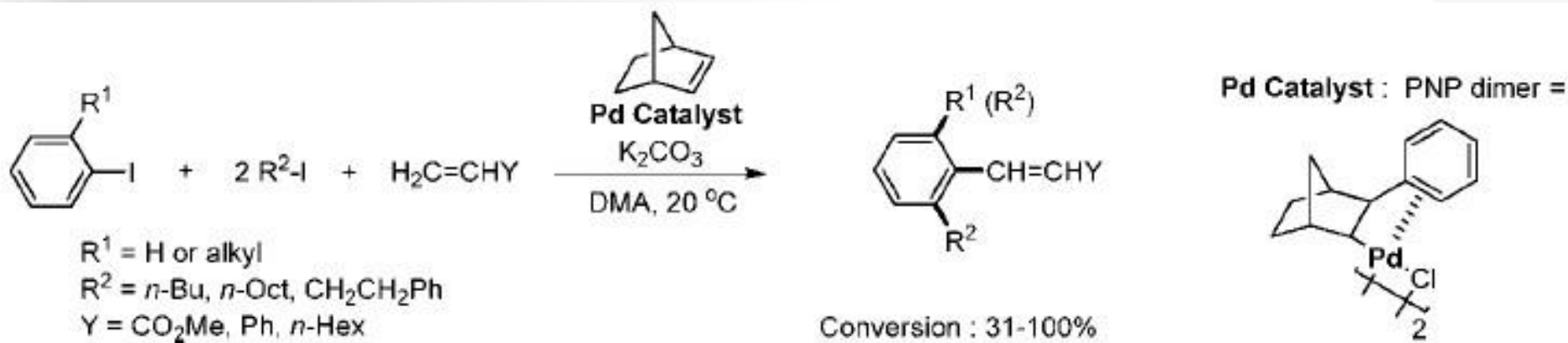
- Involving C(sp³)-C(sp³), C(sp²)-C(sp³), and C(sp²)-C(sp²) coupling.
- The first demonstration reductive elimination to form a C-C bond represents the classical transformation for palladium(IV).



Part II: High-valent palladium

C-C Coupling

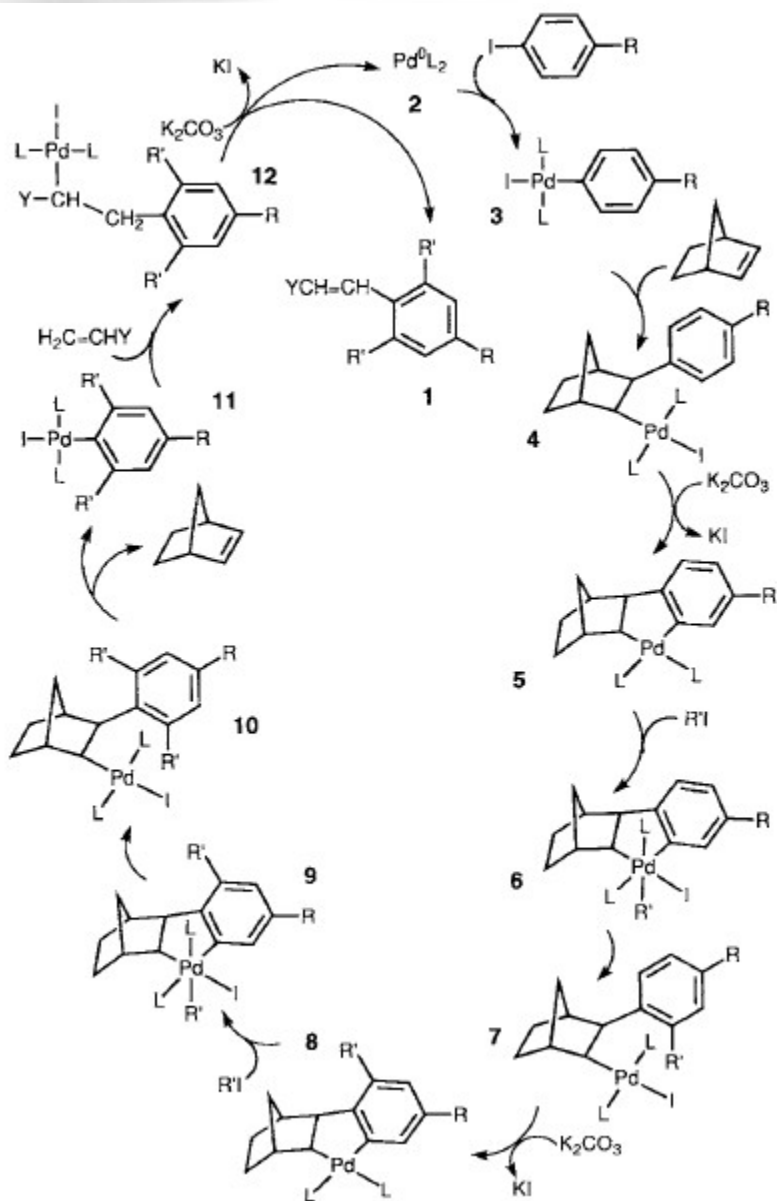
- **Catellani reaction** -- catalyzed by palladium and mediated by **norbornene** to generate up to three carbon-carbon bonds in one pot.



- **General character:**

substituted aromatic iodides, primary aliphatic iodides

and terminal olefins bearing either electron-withdrawing or electron-releasing groups can be used.



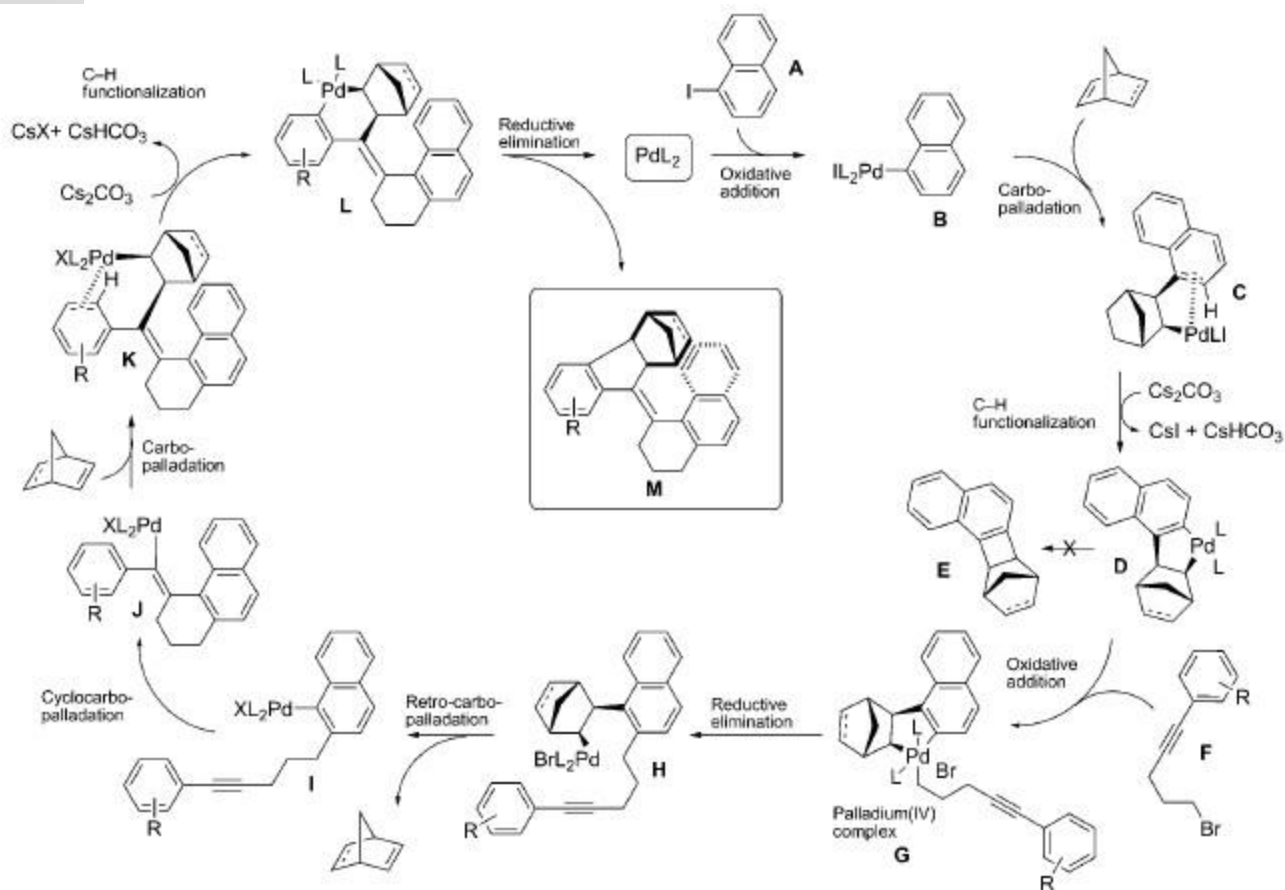
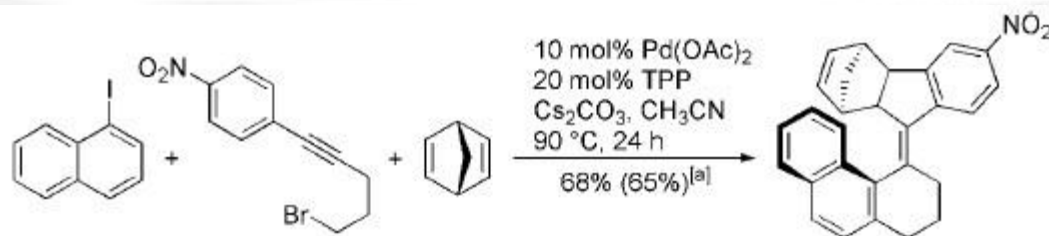
a) Pd⁰ - Pd^{II} (2 - 5)

b) Pd^{II}- Pd^{IV} - Pd^{II} (6 -10)

c) Pd^{II} – Pd⁰ (11 - 12)

Proposed catalytic cycle showing the course of aromatic functionalization through palladium complexes in different oxidation states (L = DMA)

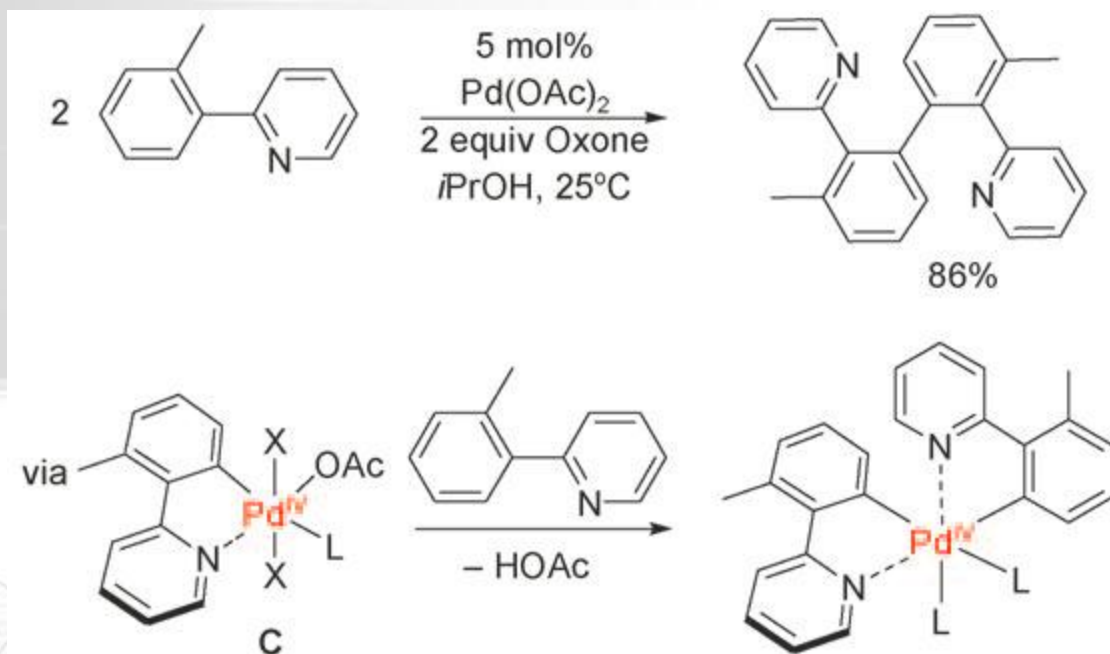
➤ Multicomponent Domino Synthesis of Tetrasubstituted Helical Alkenes through Multiple C-H Functionalization



Part II: High-valent palladium

-- C-C Coupling

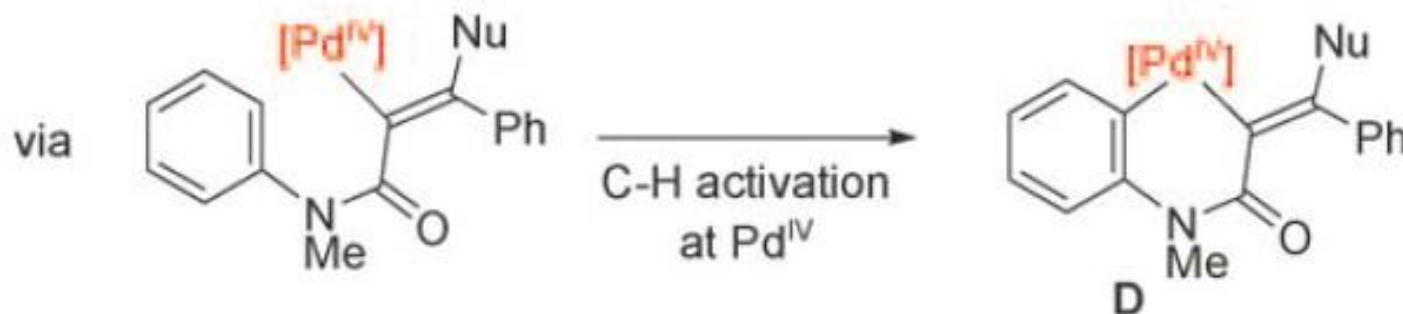
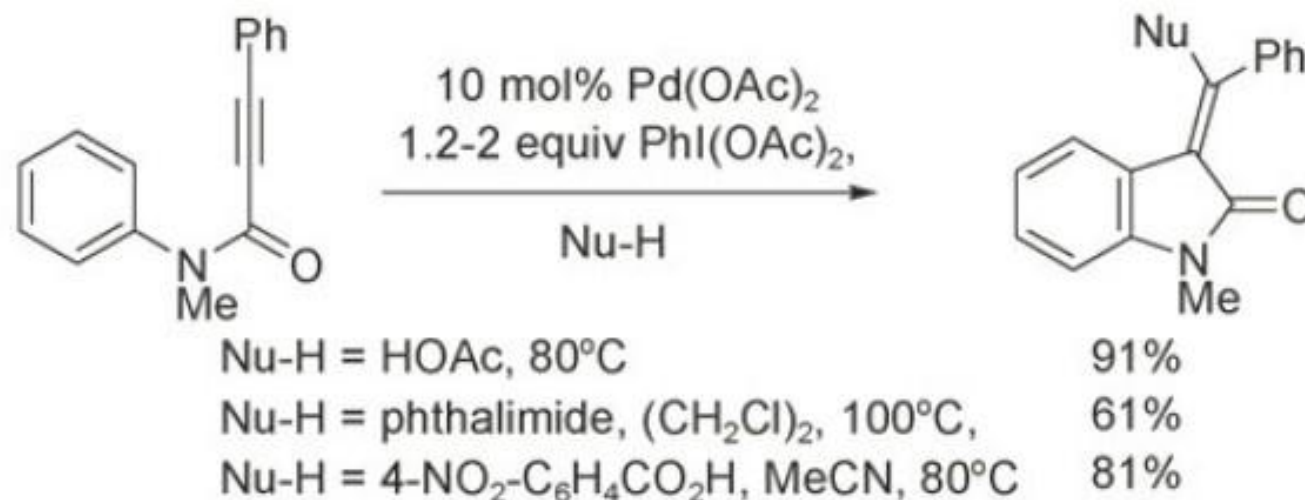
➤ Biaryl synthesis -- Oxone as an oxidant



Part II: High-valent palladium

-- C-C Coupling

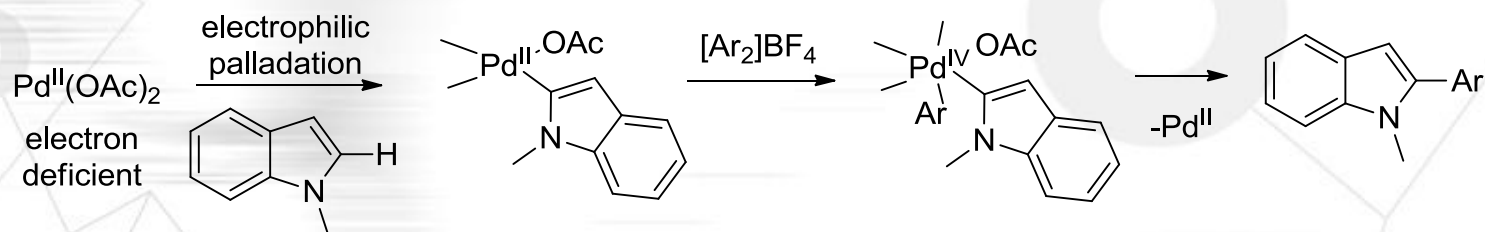
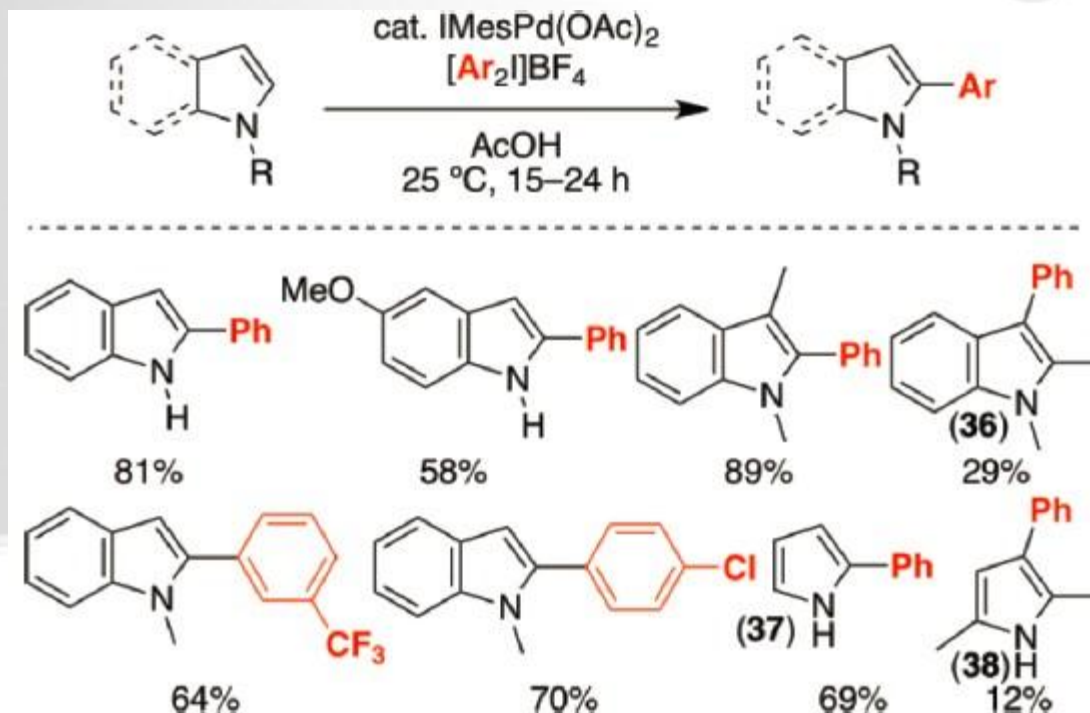
➤ C(sp²)-C(sp²) formation



Part II: High-valent palladium

-- C-C Coupling

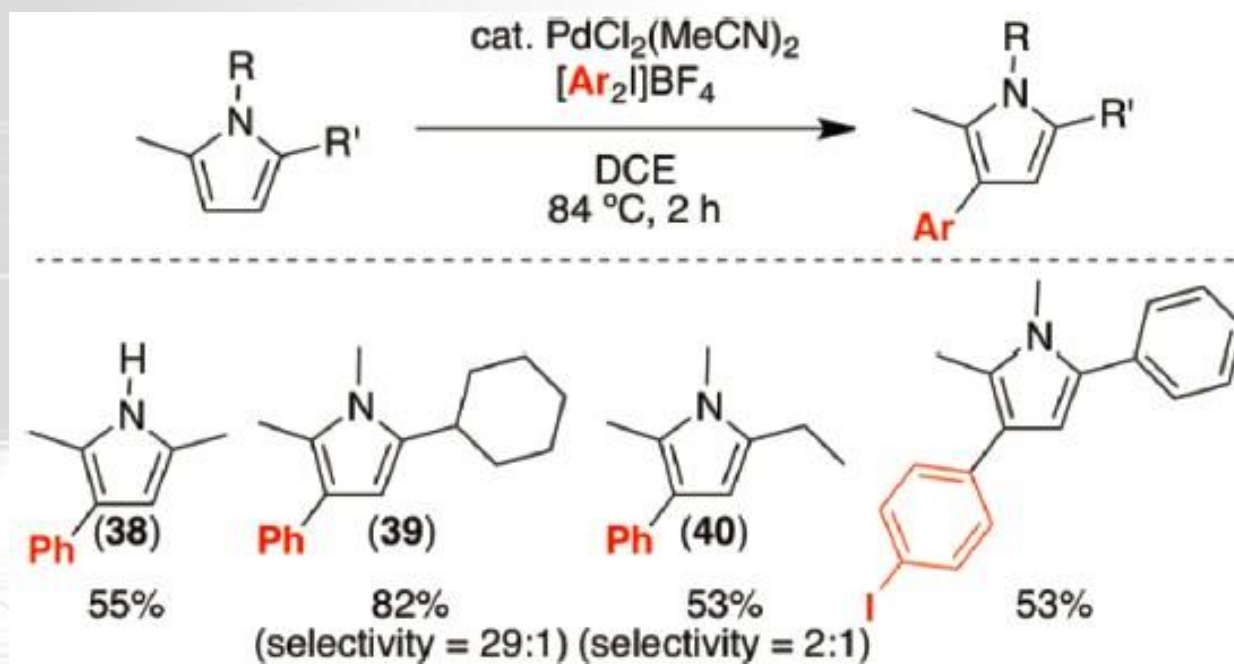
- Pd-Catalyzed **Arylation of Indoles and Pyrroles** with $[\text{Ar}_2\text{I}]\text{BF}_4$



Part II: High-valent palladium

-- C-C Coupling

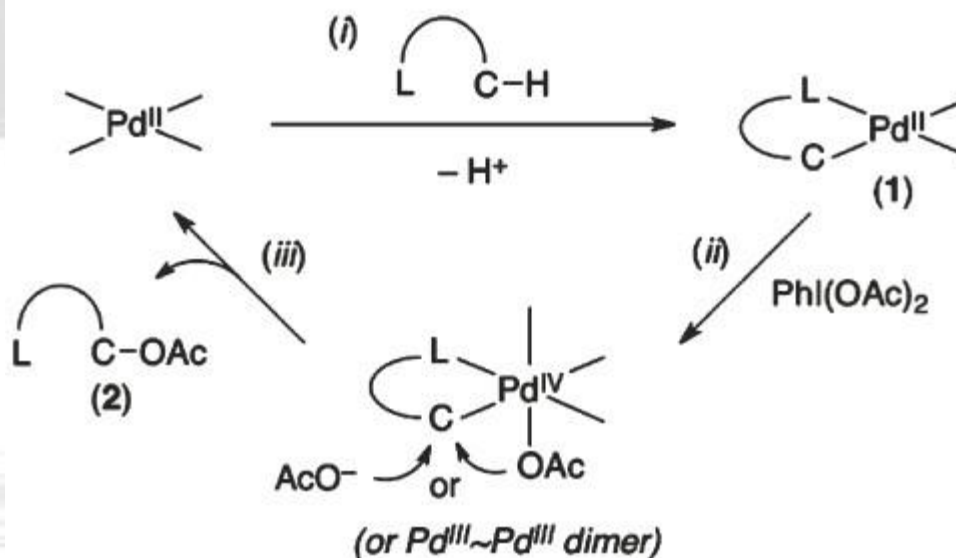
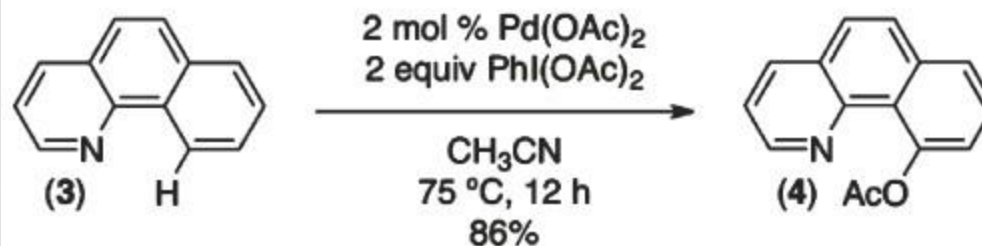
➤ Pd-Catalyzed C-3 Arylation of 2,5-Disubstituted Pyrroles

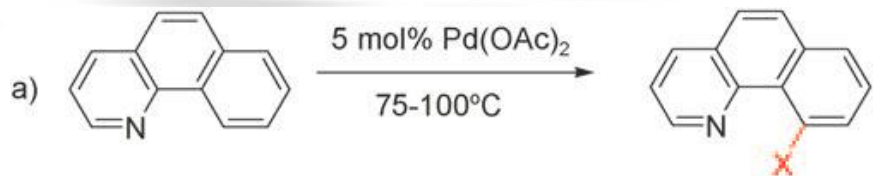


Part II: High-valent palladium

-- Aryl-heteroatom

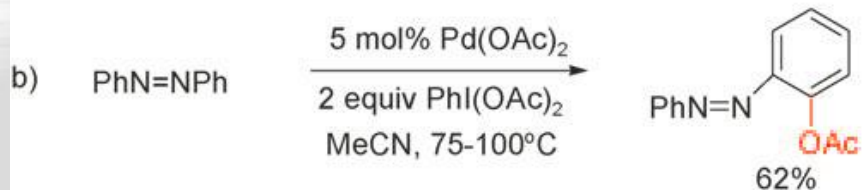
➤ C-O Bond Formation





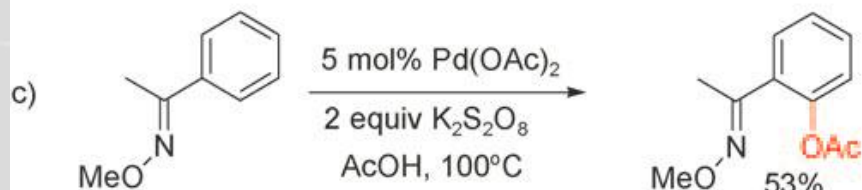
5 mol% Pd(OAc)₂
75-100°C
PhI(OAc)₂, MeCN
PhI(OAc)₂, MeOH
NBS, MeCN
NCS, MeCN

X = OAc, 86%
X = OMe, 95%
X = Br, 93%
X = Cl, 95%



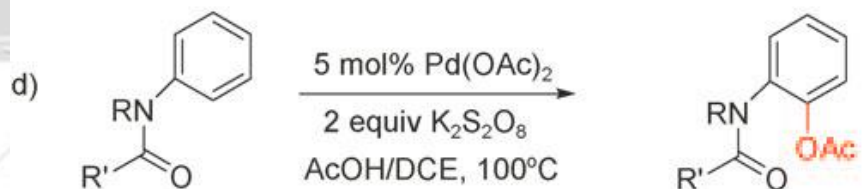
5 mol% Pd(OAc)₂
2 equiv PhI(OAc)₂
MeCN, 75-100°C

62%



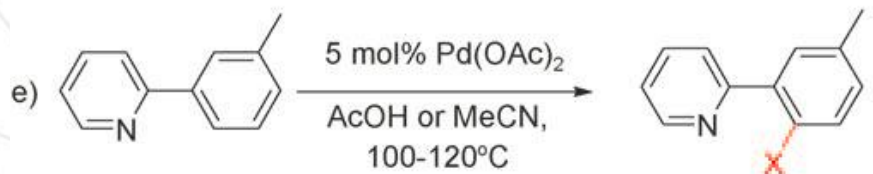
5 mol% Pd(OAc)₂
2 equiv K₂S₂O₈
AcOH, 100°C

53%



5 mol% Pd(OAc)₂
2 equiv K₂S₂O₈
AcOH/DCE, 100°C

12 examples, 22-93%



5 mol% Pd(OAc)₂
AcOH or MeCN,
100-120°C
PhI(OAc)₂
NBS

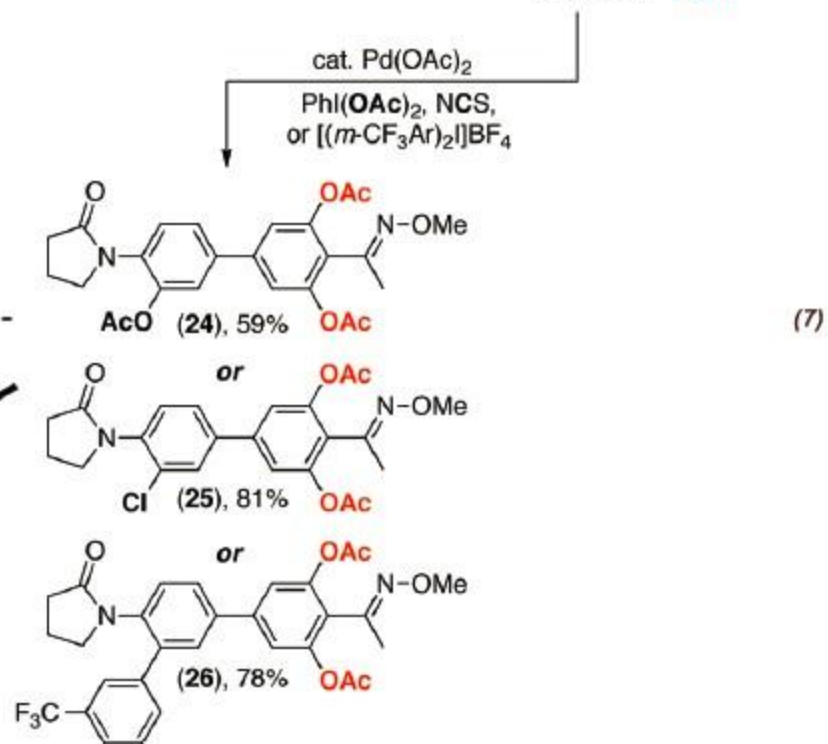
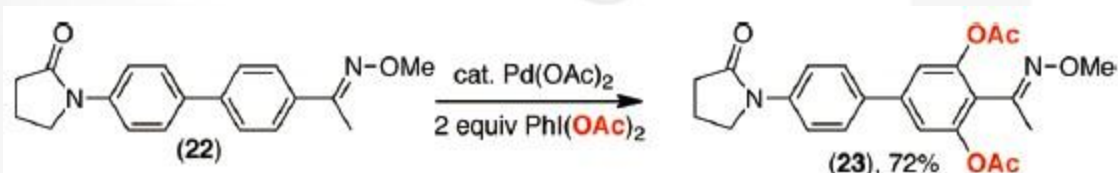
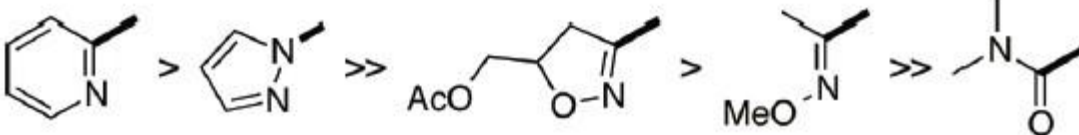
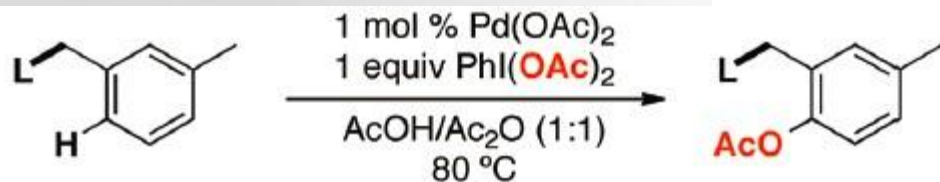
X = OAc, 77%
X = Br, 51%

1. PhI(OAc)₂
Acetoxylation in acetonitrile,
Alkoxylation in alcoholic solvents.
2. selectivity for the **ortho** position.
3. **Oxone and acetic acid** instead of Iodosobenzene diacetate.
4. 3-substituted arenes - complete selectivity in favor of the **1,2,4-tri-substituted** product.
5. introduction of halogen atoms with strong oxidants (NCS, or NBS).

Part II: High-valent palladium

--Aryl--heteroatom

➤ Relative reactivity

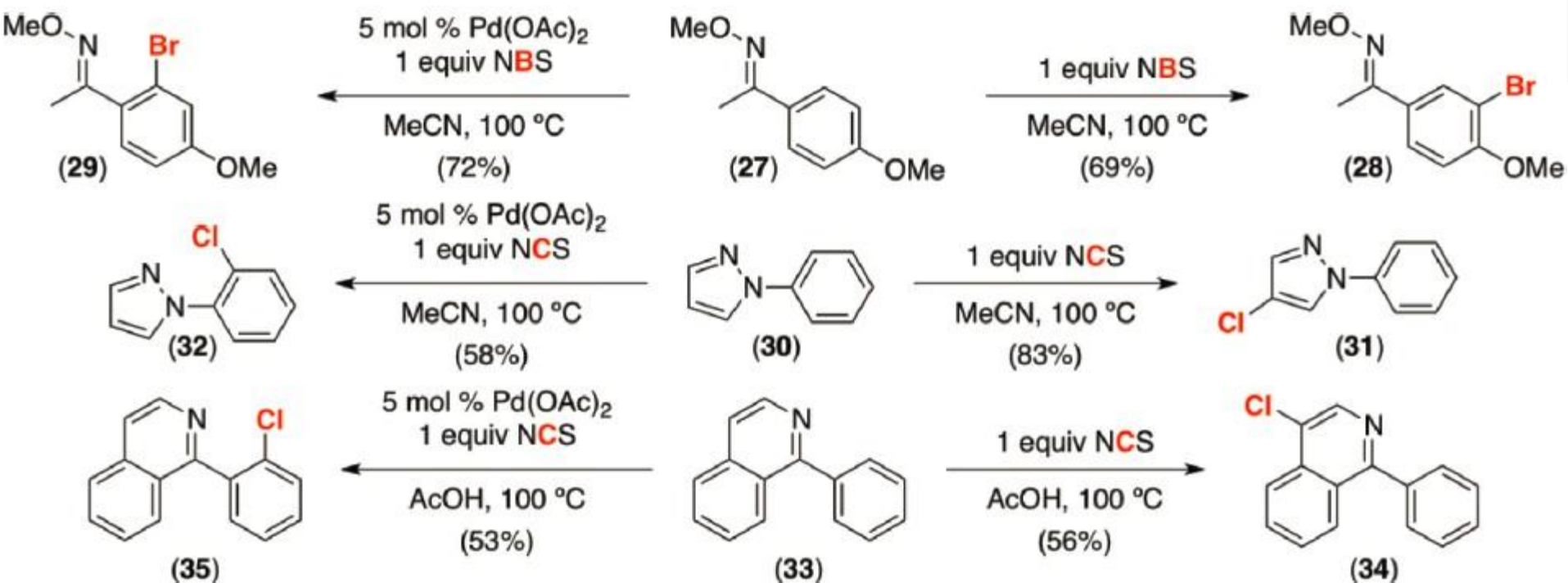


(7)

Part II: High-valent palladium

-- Aryl-heteroatom

- C-X formation



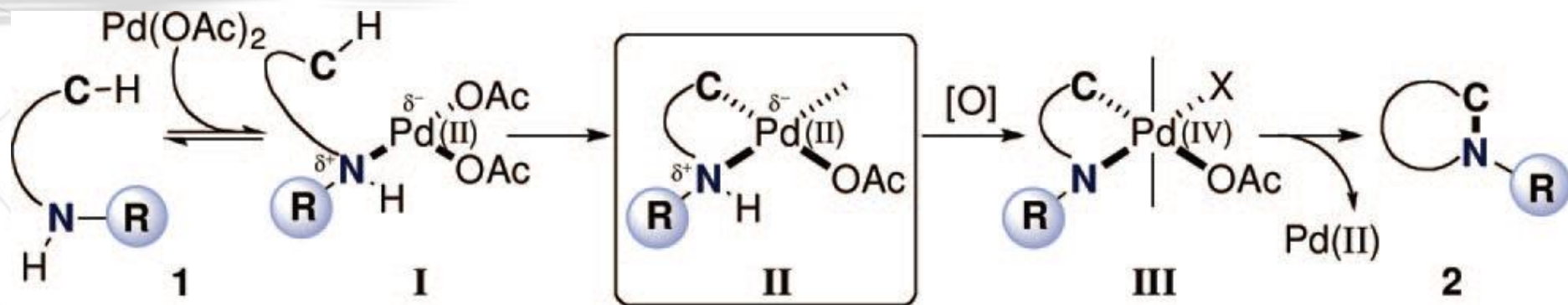
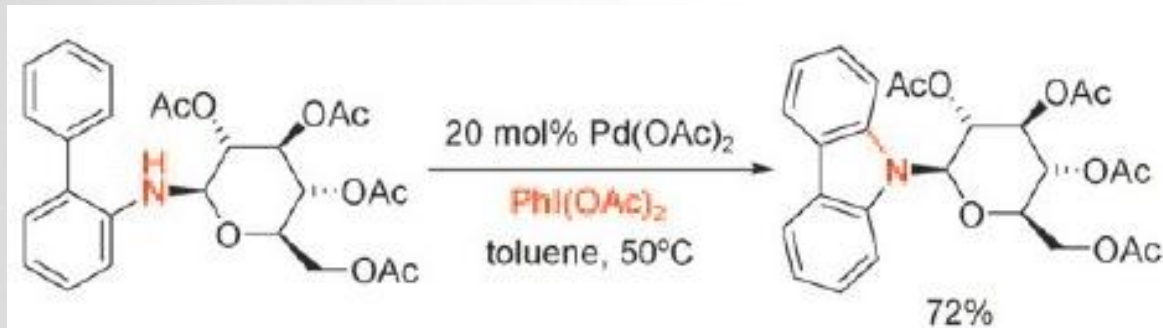
Catalyzed versus Uncatalyzed Selectivity

Part II: High-valent palladium

-- Aryl-heteroatom

➤ C-N Bond Formation

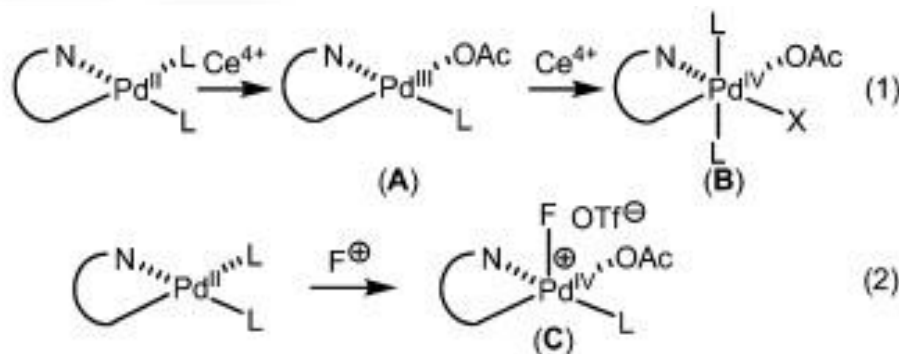
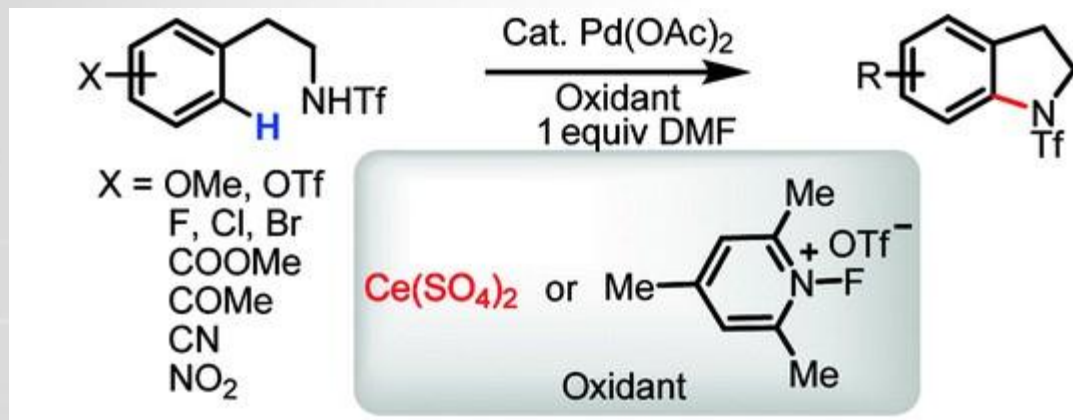
- **carbazole synthesis** from various 2-aminobiphenyls.



Part II: High-valent palladium

-- Aryl-heteroatom

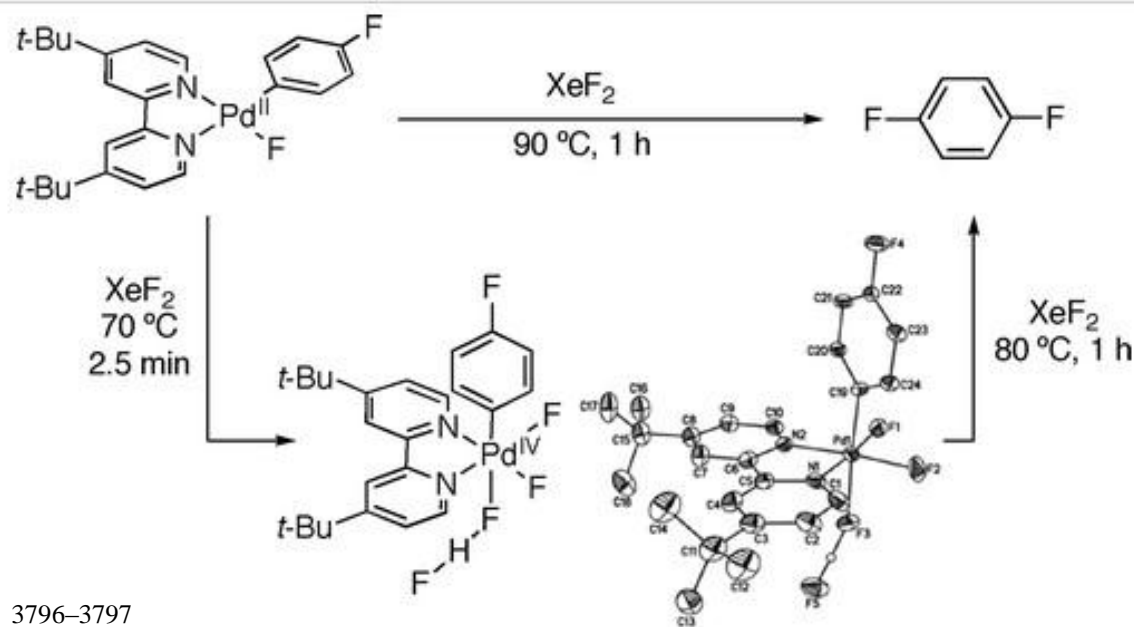
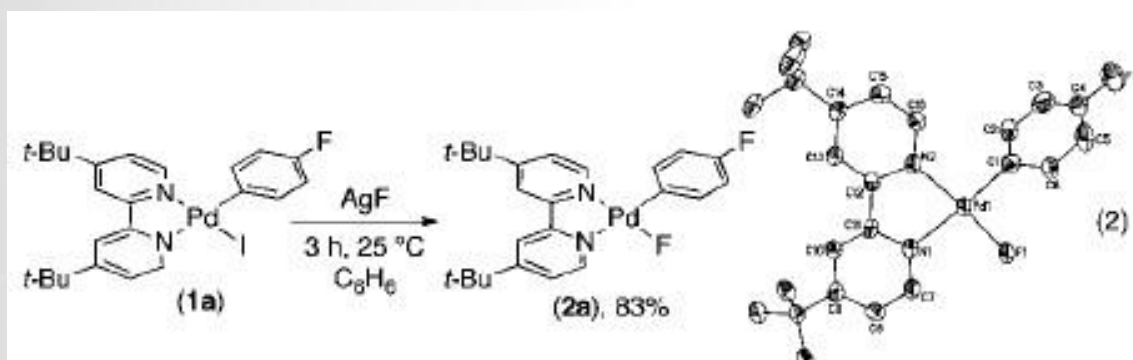
- Amination of C-H Bonds for **synthesis of indolines**.



Part II: High-valent palladium

-- Aryl-heteroatom

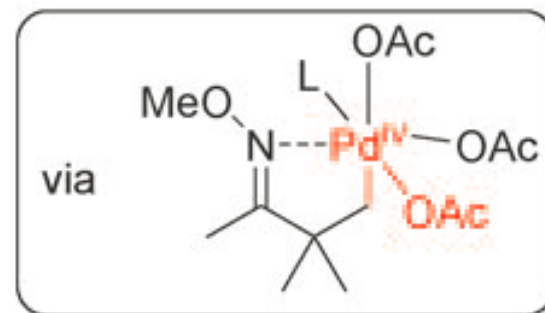
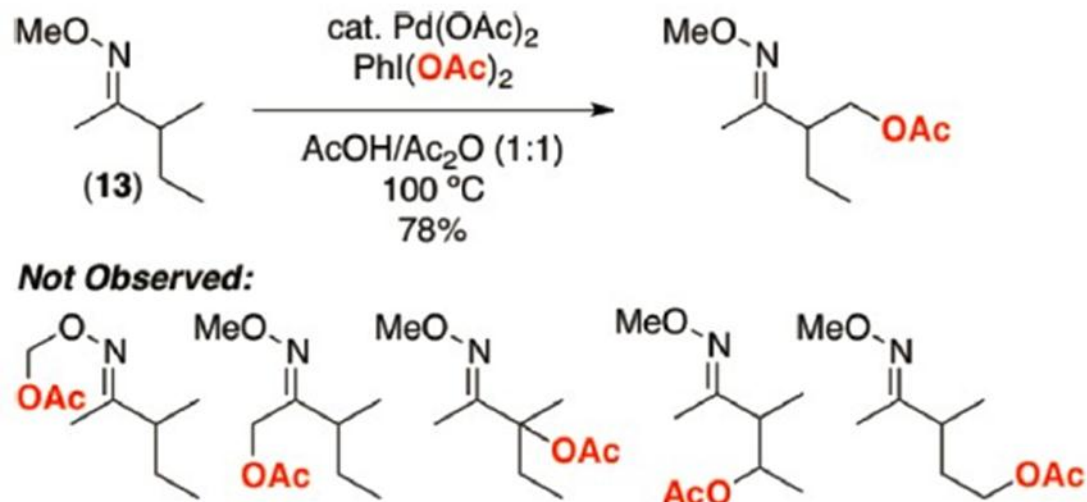
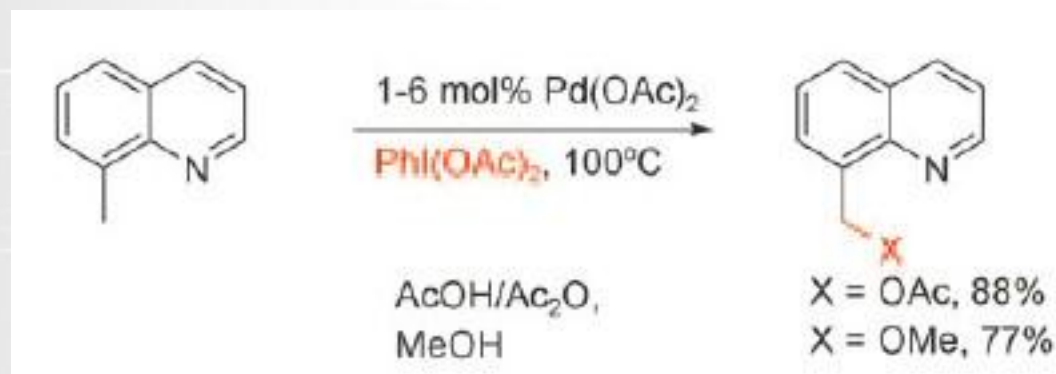
➤ C-F Bond Formation



Part II: High-valent palladium

-- Alkyl-Heteroatom Coupling

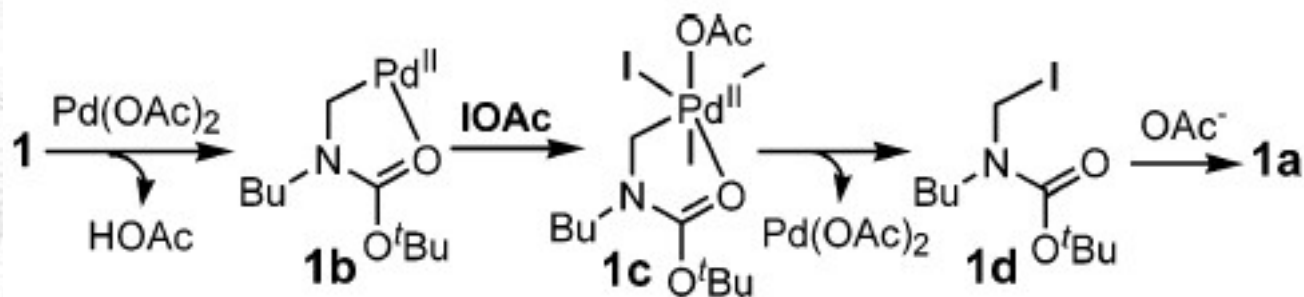
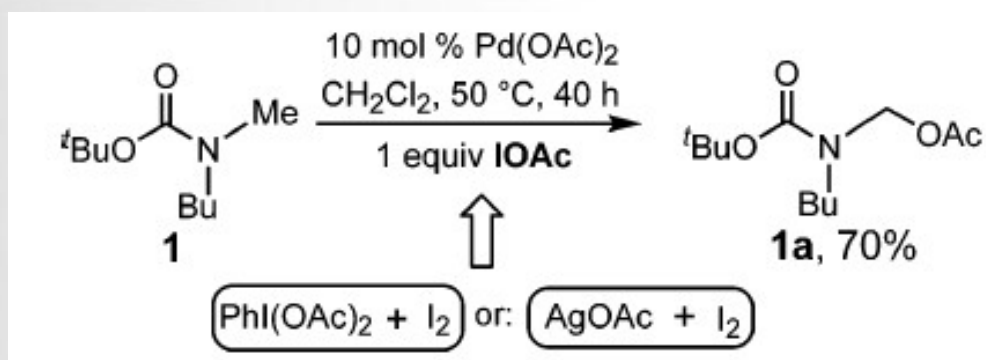
➤ Alkyl oxygenation



Part II: High-valent palladium

-- Alkyl-Heteroatom Coupling

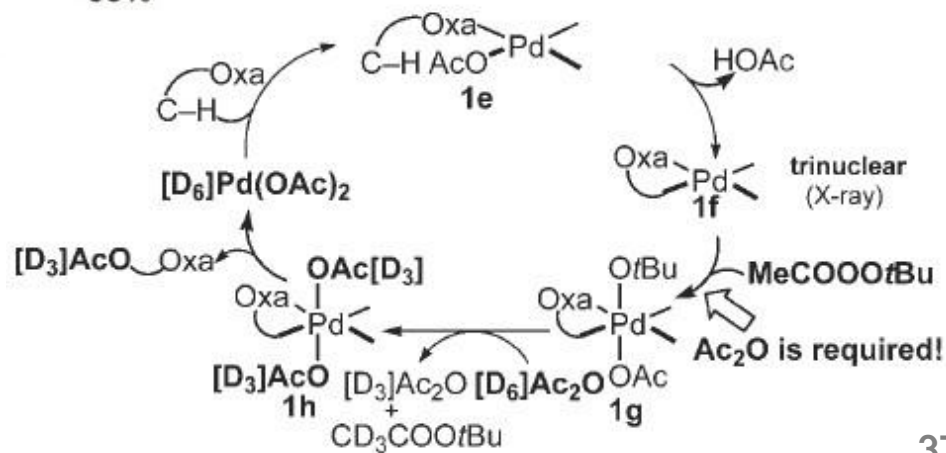
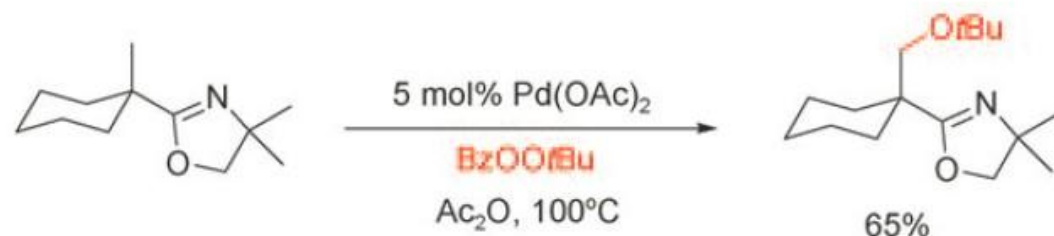
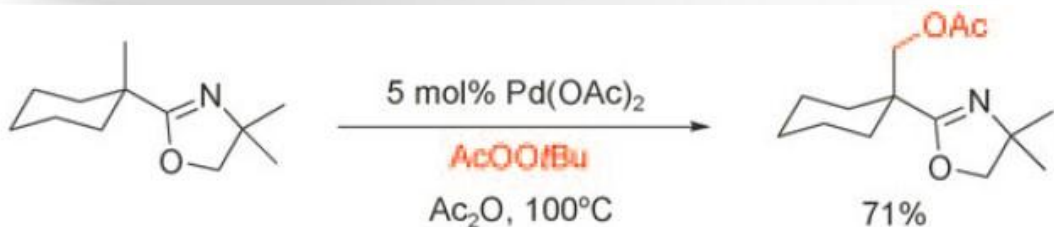
Acetoxylation of **N-Methylcarbamates** with **IOAc** as a Crucial Oxidant



Part II: High-valent palladium

-- Alkyl-Heteroatom Coupling

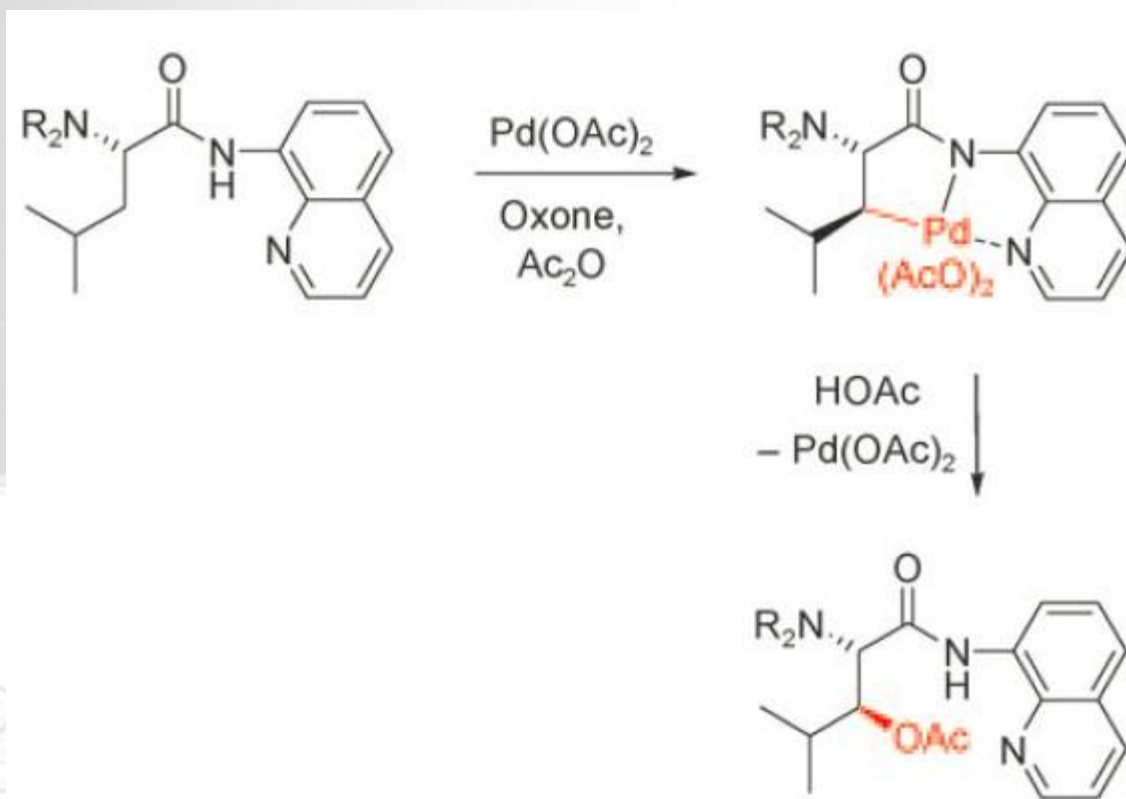
-- acetyl tert-butyl peroxide and benzoyl tert-butyl peroxide for palladium oxidation



Part II: High-valent palladium

-- Alkyl-Heteroatom Coupling

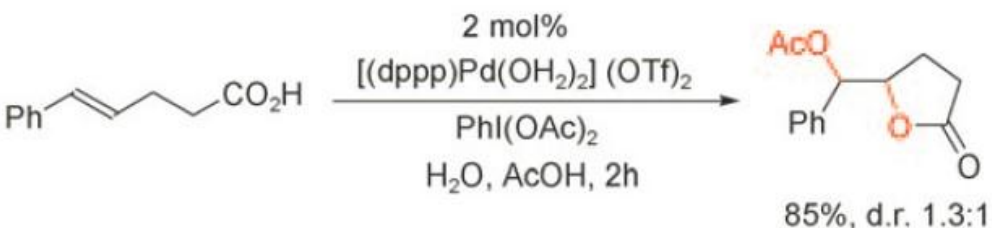
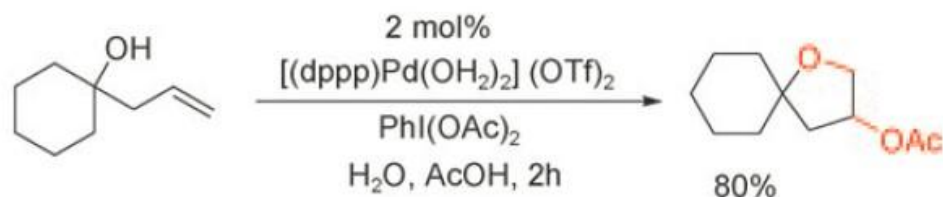
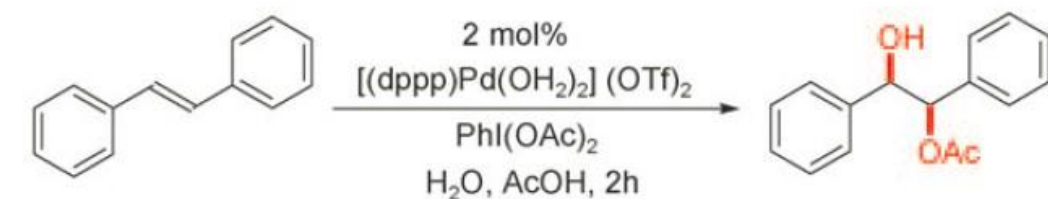
- Palladium(IV)-catalyzed **amino acid functionalization**.



Part II: High-valent palladium

-- Alkyl-Heteroatom Coupling

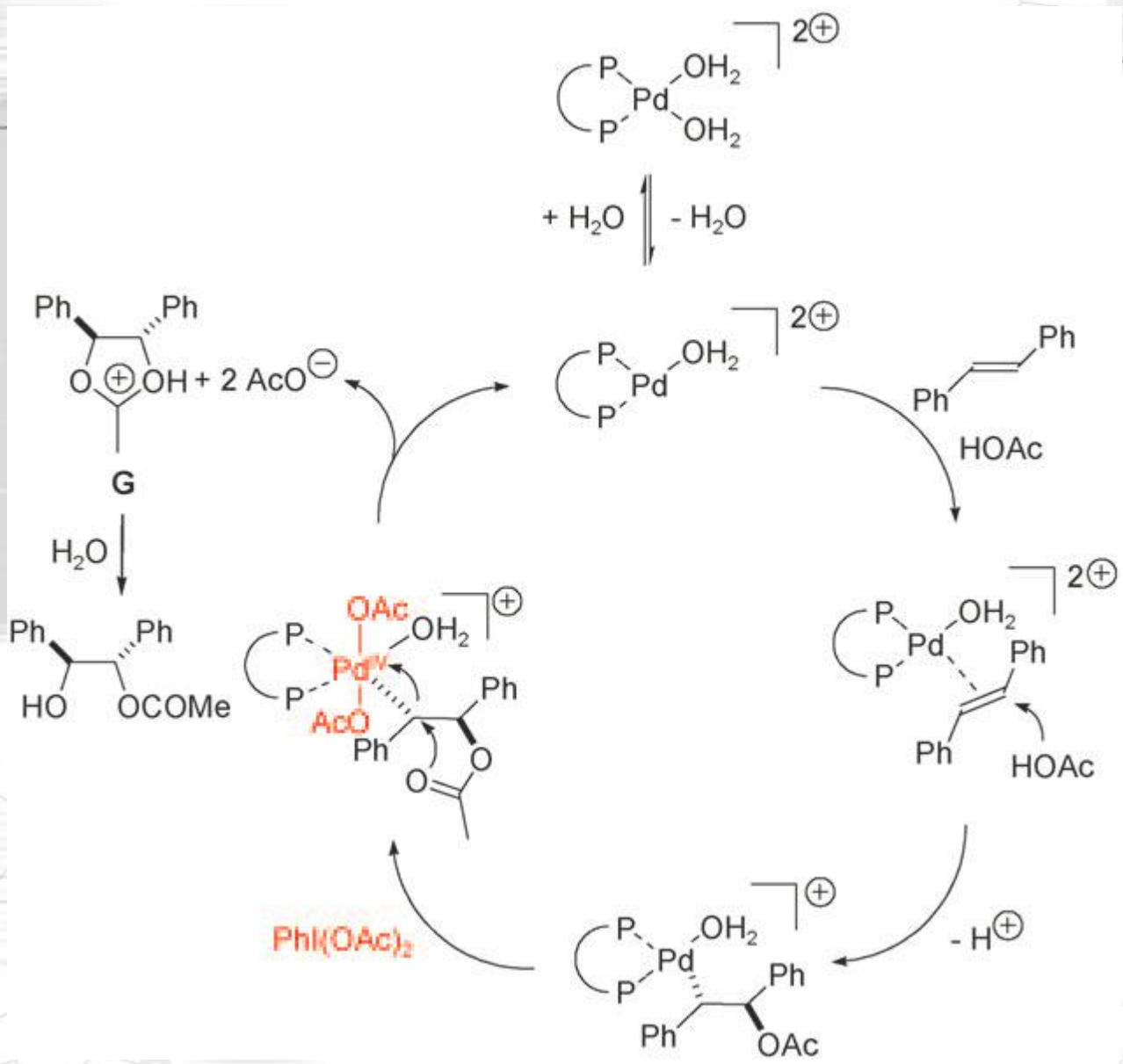
➤ 1,2-Dialkoxylation of Alkenes:



7 examples



Catalytic cycle for the palladium(IV)-catalyzed formation of a vicinal hydroxyacetate from an alkene

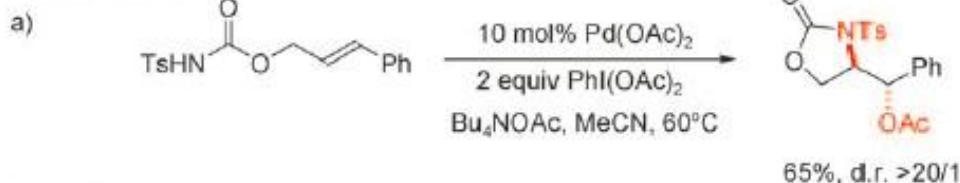


Part II: High-valent palladium

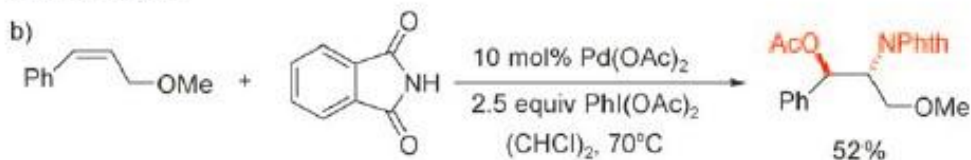
-- Alkyl-Heteroatom Coupling

➤ Aminoalkoxylation

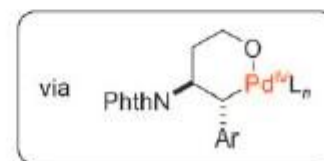
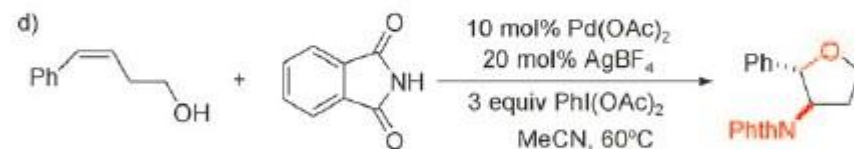
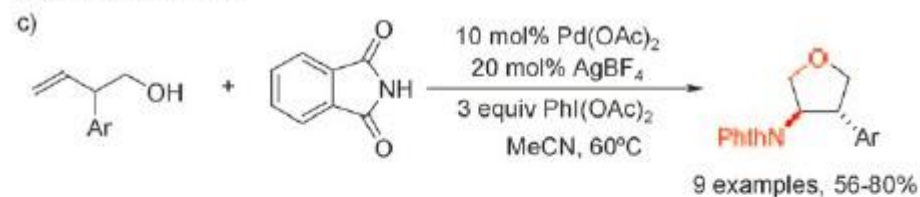
intramolecular:



intermolecular:



inter-/intramolecular:

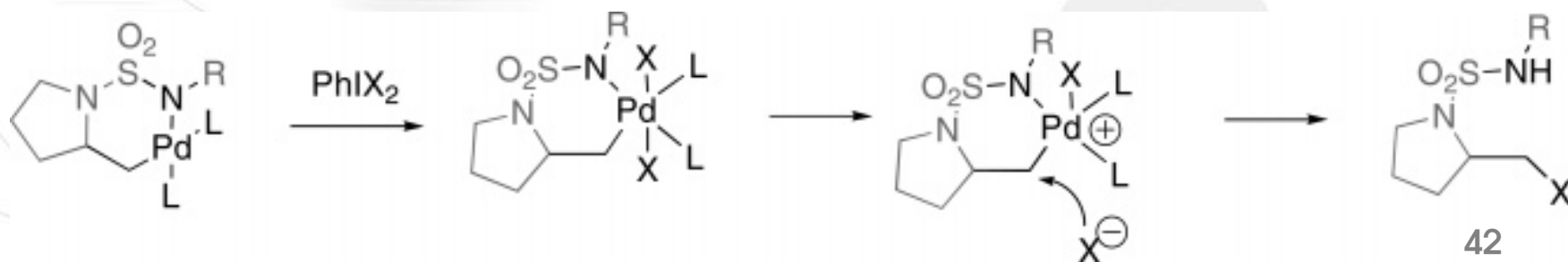
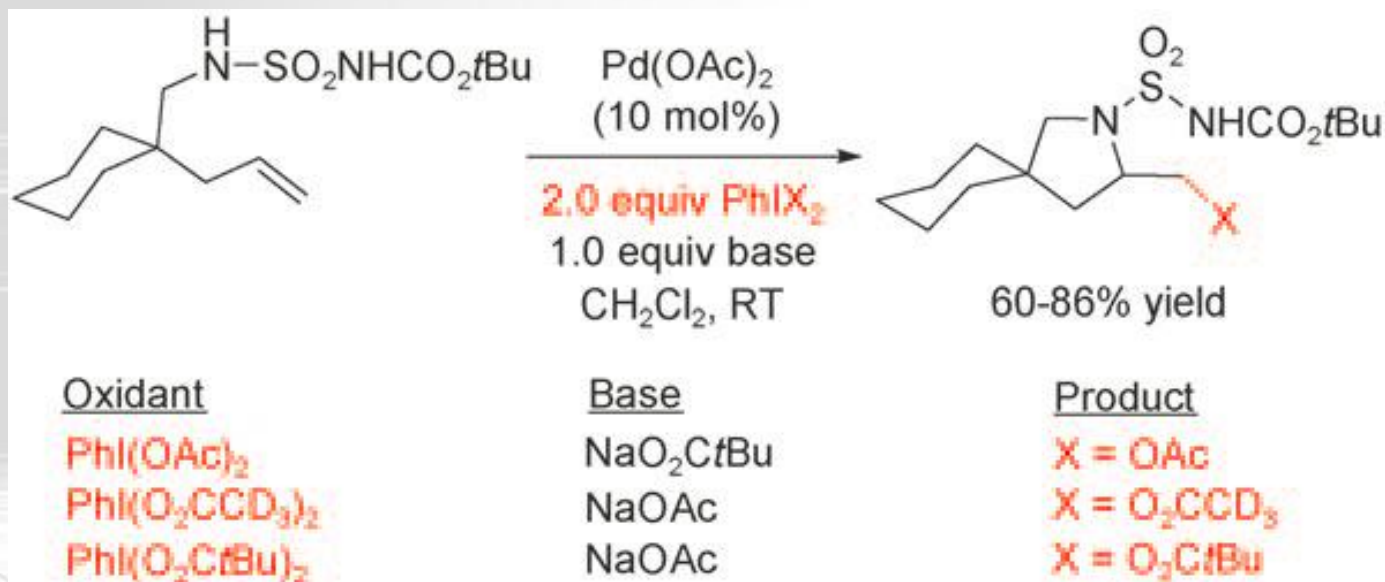


Palladium(IV)-catalyzed aminoacetoxylation and aminoalkoxylation of alkenes.
Phth=phthaloyl

Part II: High-valent palladium

-- Alkyl-Heteroatom Coupling

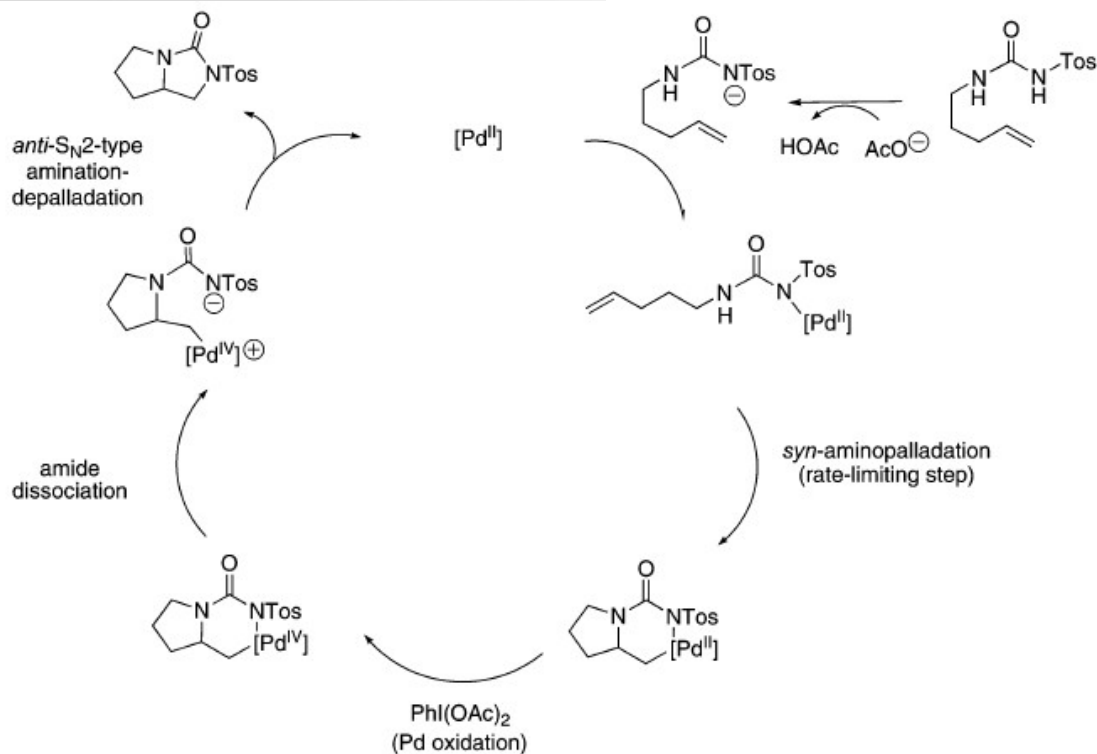
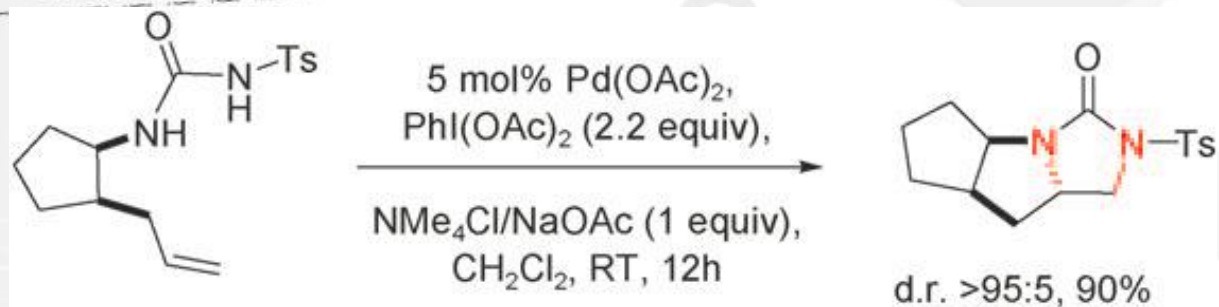
- **Selectivity of anion transfer** for the palladium(IV)-catalyzed aminoalkoxylation of alkenes



Part II: High-valent palladium

-- Alkyl-Heteroatom Coupling

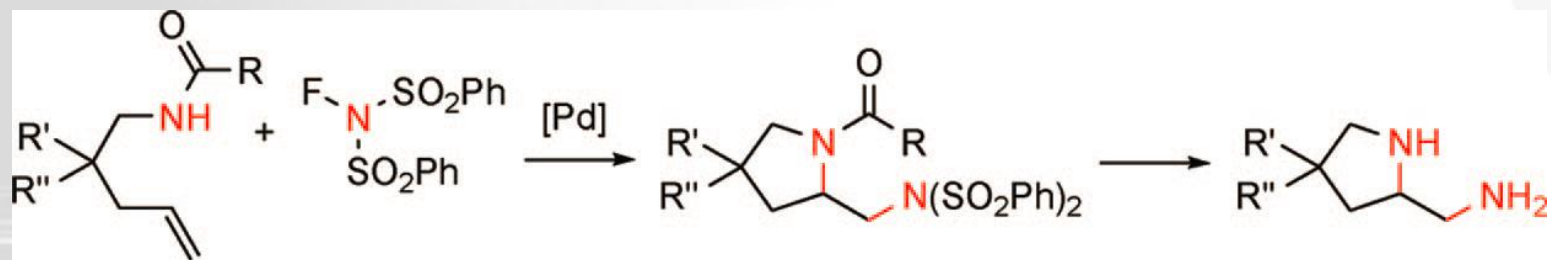
➤ Diamination



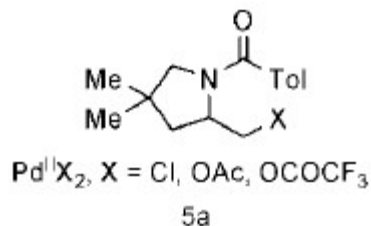
Part II: High-valent palladium

-- Alkyl-Heteroatom Coupling

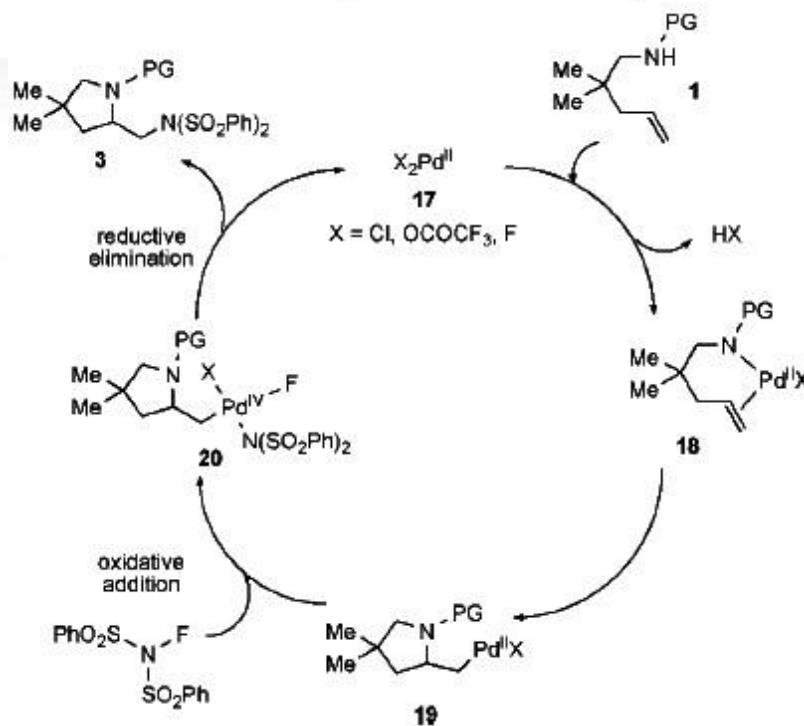
- Palladium-Catalyzed **Diamination of Unactivated Alkenes** Using **N-Fluorobenzenesulfonimide** as Source of Electrophilic Nitrogen



R = *Ot*-Bu, OBn, Me, *p*-Tol



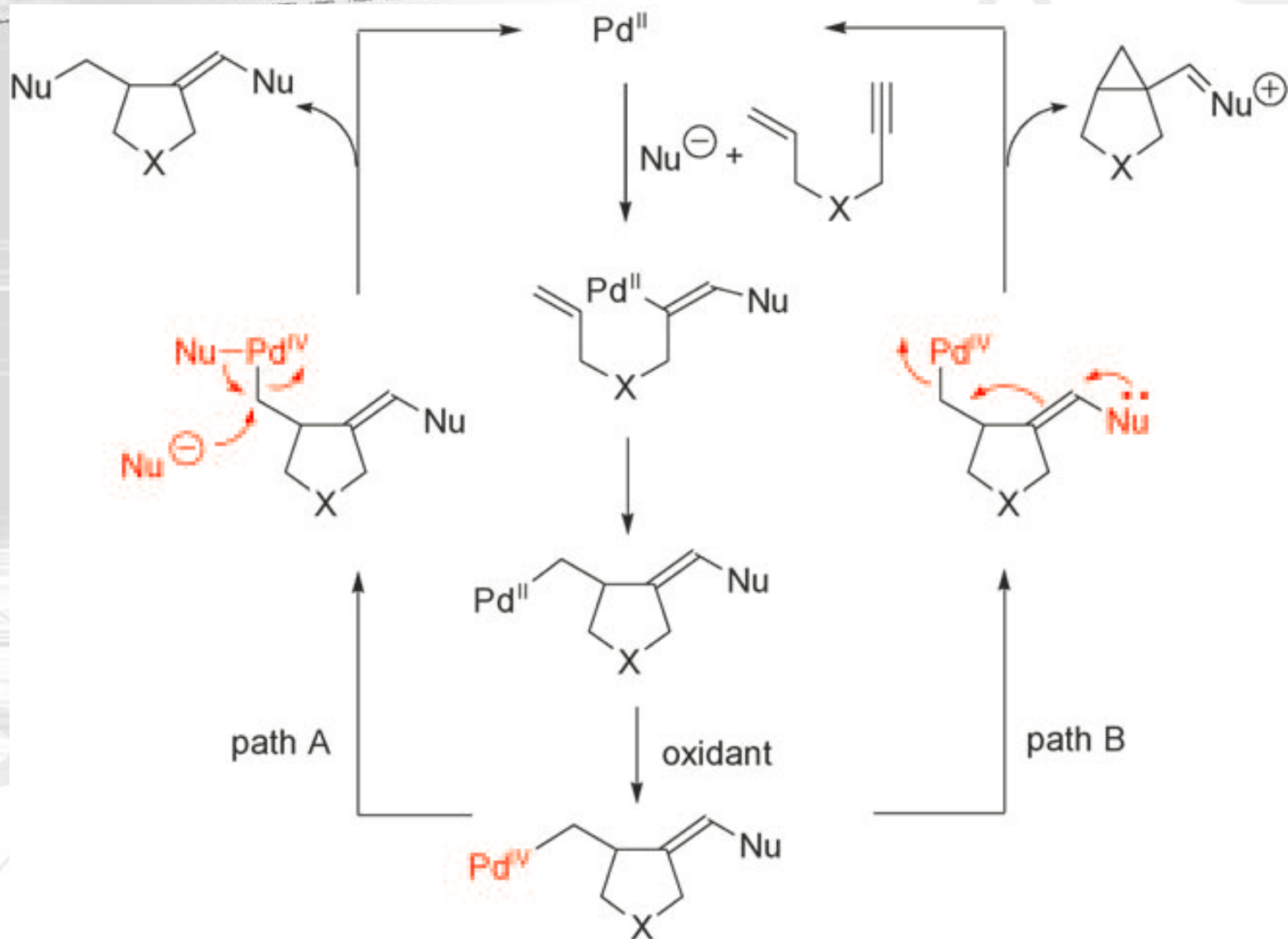
byproducts



Part II: High-valent palladium

-- Domino Catalysis Involving Pd^{IV} Catalysts

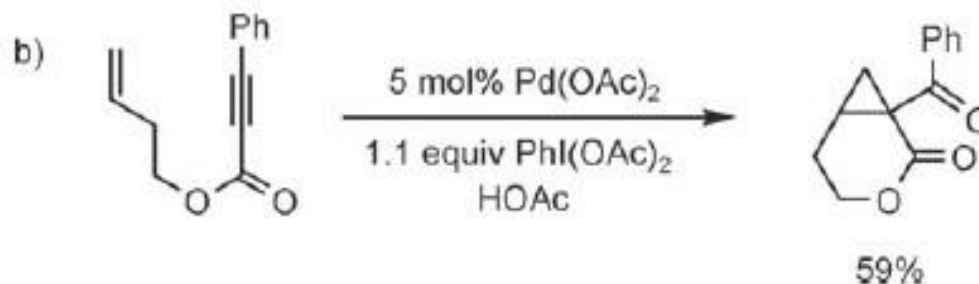
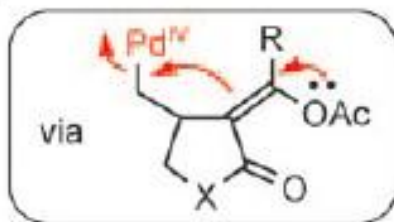
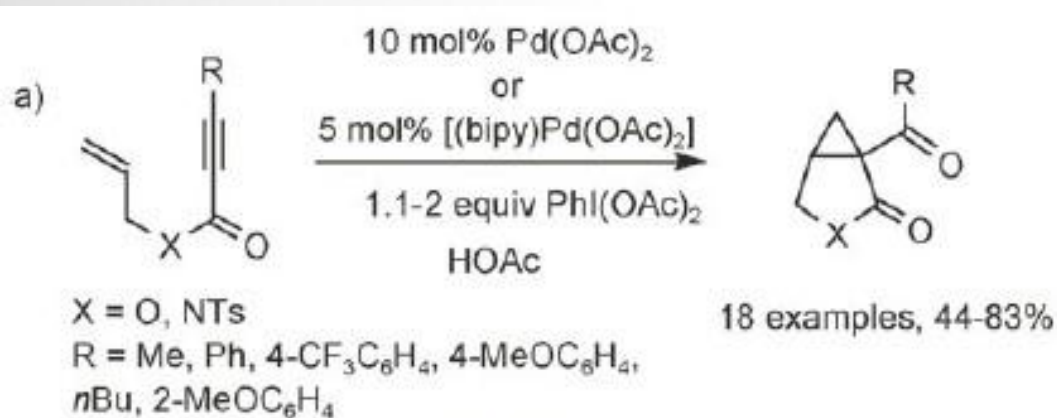
- **Domino reactions of 1,6-enynes** through Pd^{II}/Pd^{IV} sequential catalysis



Part II: High-valent palladium

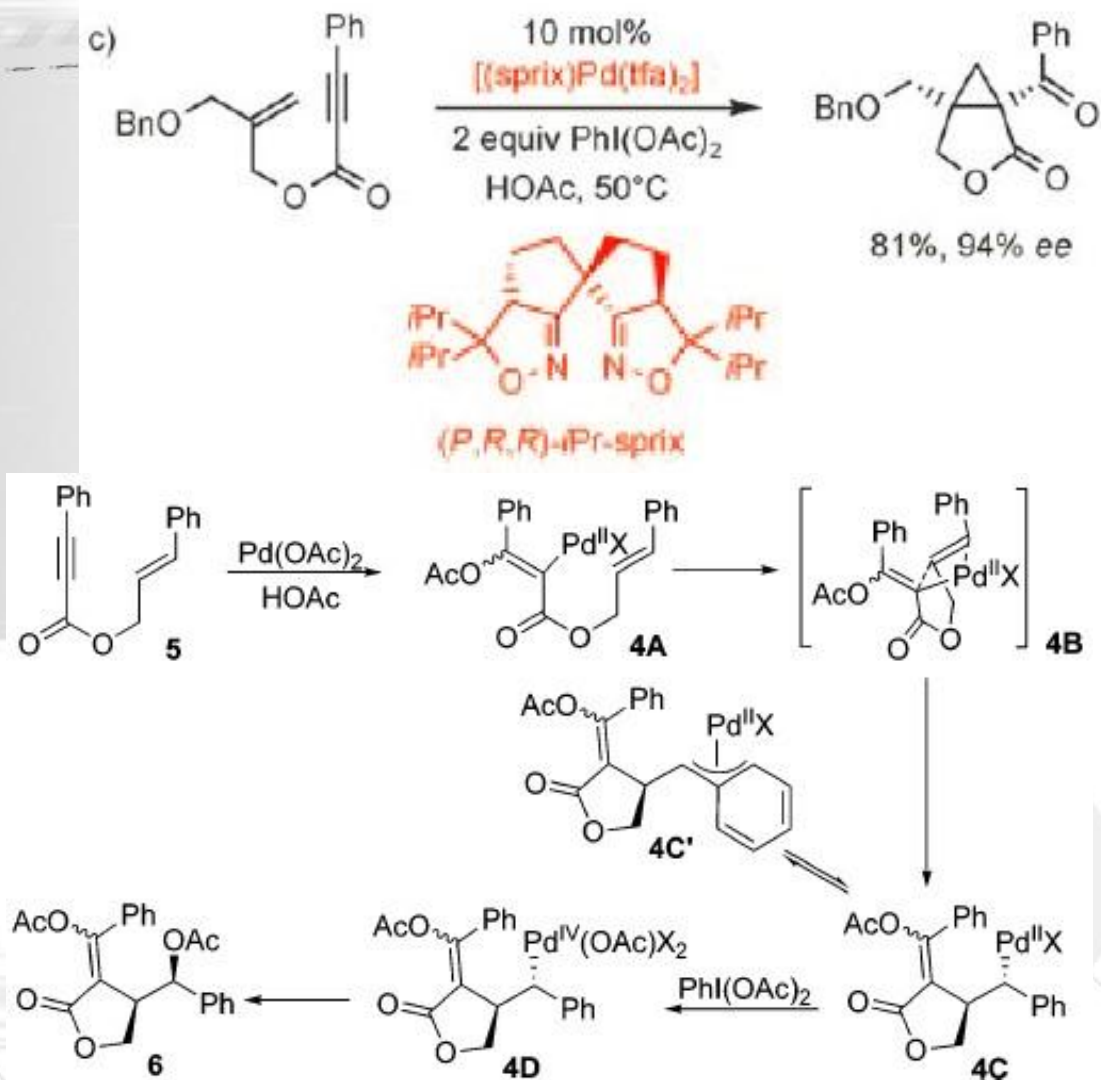
-- Domino Catalysis Involving Pd^{IV} Catalysts

➤ Cyclopropanation from 1,6-enynes



Part II: High-valent palladium

-- Domino Catalysis Involving Pd^{IV} Catalysts



Part II: High-valent palladium

➤ Summary

1. Numerous organometallic Pd(IV) and Pd(III) complexes have been synthesized by **the reaction of Pd(II) starting materials with strong oxidants**.
2. A wide range of **carbon–carbon and carbon–heteroatom bond-forming reductive elimination reactions** can be achieved from these species, and the selectivity, reactivity and mechanisms of these transformations have been studied in detail.
3. Future studies should broaden the spectrum of **aryl palladium(IV) chemistry**, for example, by removing the synthetic requirement for chelation-directed C-H activation in favor of direct C-H activation or transmetalation.

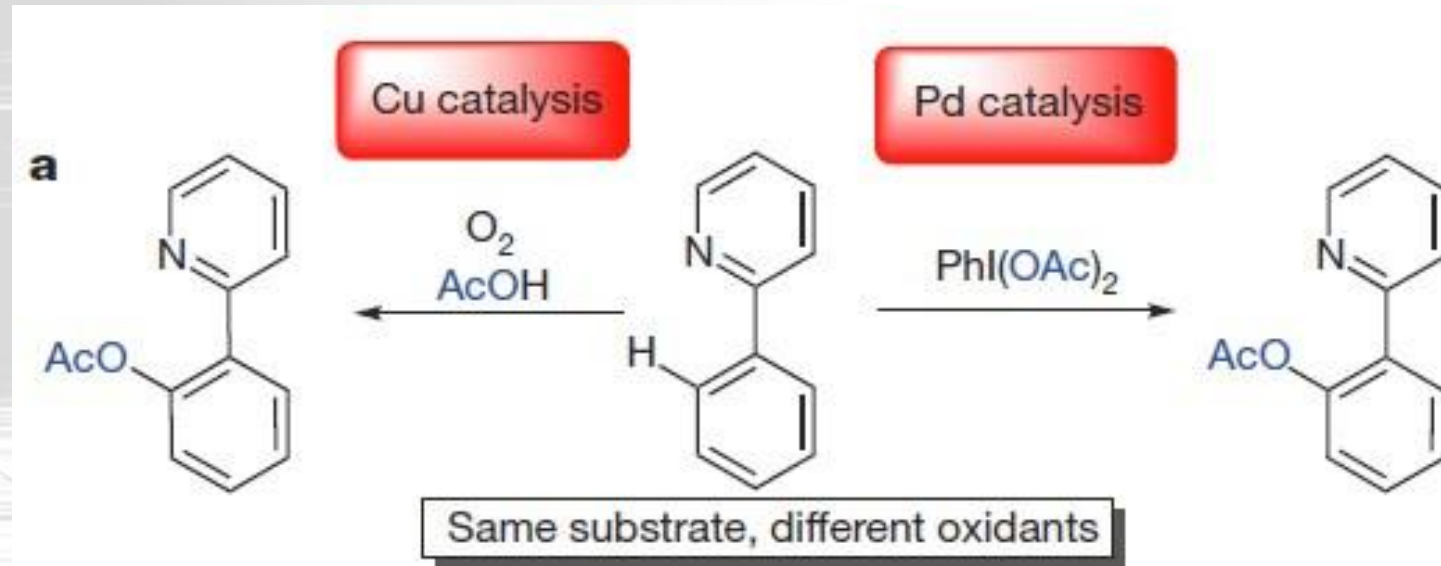
Part III: Comparison and contrast

Similarities:

- Similar **ligand environments** to stabilize high-valent complexes of both metals.
- The presence of multiple highly electron-donating σ -aryl or σ -alkyl ligands facilitate the detection or isolation of high-valent species of both copper and palladium.
- Construction of **similar types of carbon-carbon and carbon-heteroatom bonds.**

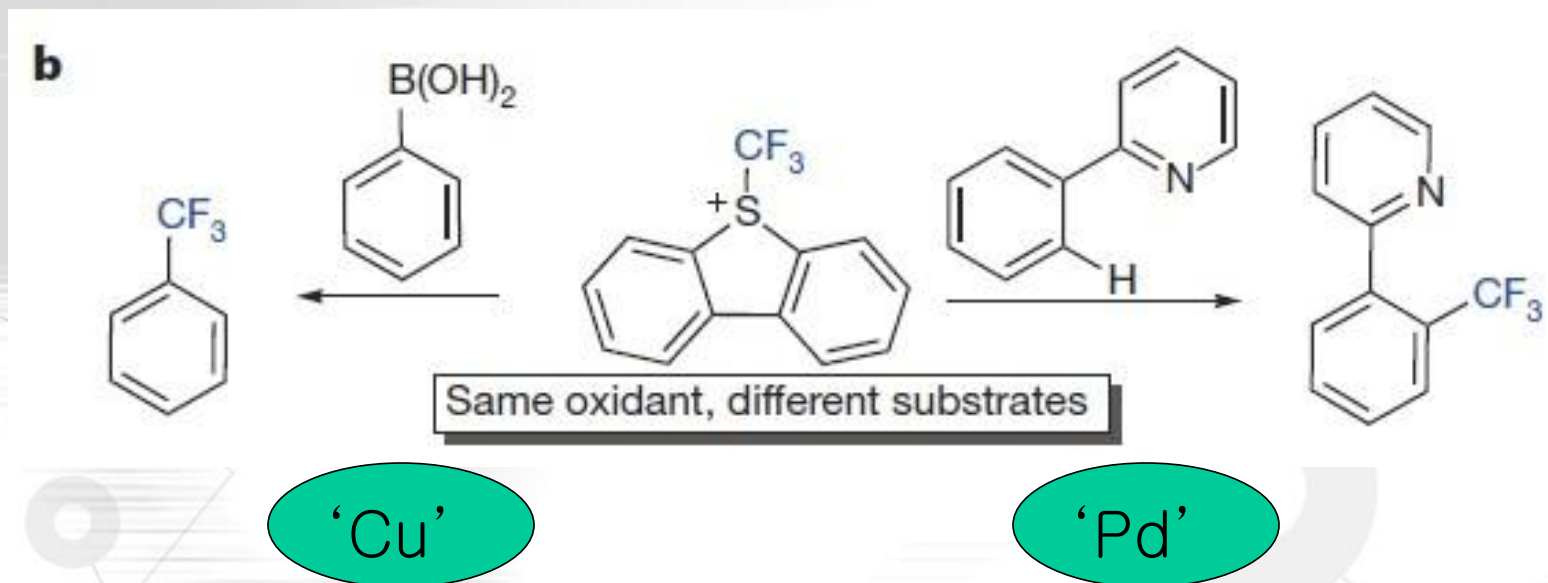
Part III: Comparison and contrast

- Ligand-directed carbon-hydrogen acetoxylation
- Different oxidants



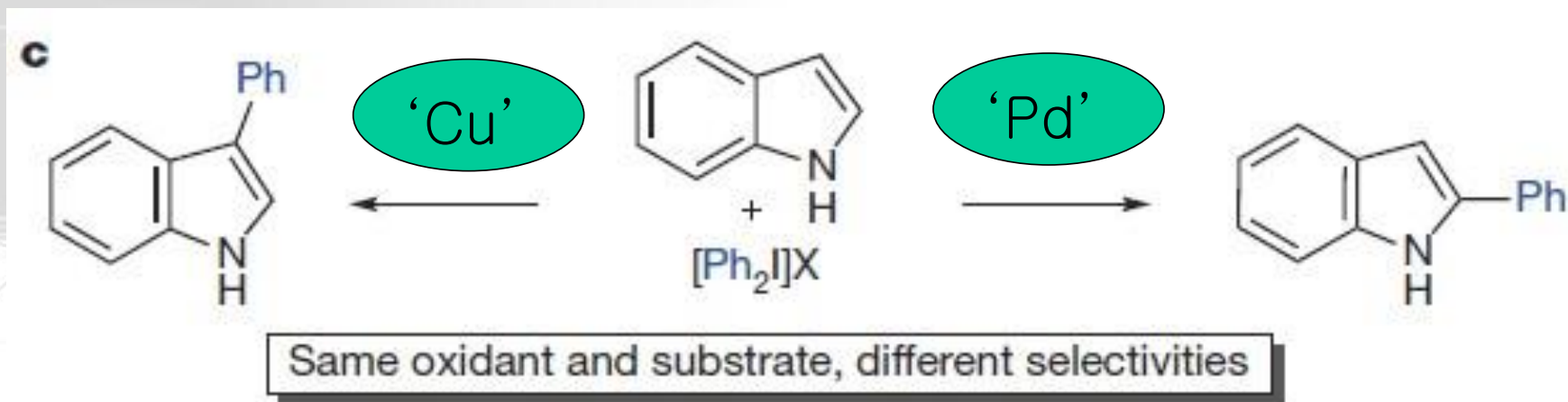
Part III: Comparison and contrast

- The same oxidant (S-(trifluoromethyl) dibenzothiophenium) is used to effect the trifluoromethylation of two different organic substrates.
- Palladium-catalysed -- common, general
- High-valent copper catalysis -- focused on prefunctionalized substrates such as aryl boronic acids and aryl halides



Part III: Comparison and contrast

- Both metals catalyse the carbon–hydrogen arylation of indole with diaryliodonium salts.
- The site selectivities are orthogonal.



Part IV: Conclusion

- The development of copper and palladium catalysis has been inextricably linked because both metals have been used extensively in the construction of **similar types of carbon-carbon and carbon-heteroatom**;
- Future work in this field will focus **on expanding the scope of the fundamental organometallic reactions** that are possible at high-valent copper and palladium centers.
- Finally, a number of recent reports suggest that high-valent organometallic complexes of **other late transition metals** can catalyze reactions similar to those discussed for Cu(III) and Pd(III)/Pd(IV).

The background features a light gray gradient with various geometric elements. A prominent dashed line with a diagonal hatched pattern runs across the upper portion of the slide. In the corners, there are faint, light gray wireframe structures resembling molecular models or complex geometric shapes. Large, semi-transparent circular rings are also scattered throughout the design.

Thank you!