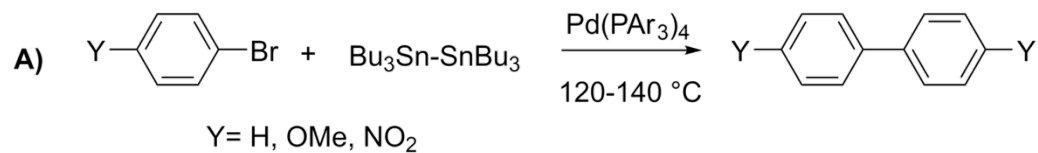# Stille Cross-Coupling

John Kenneth Stille

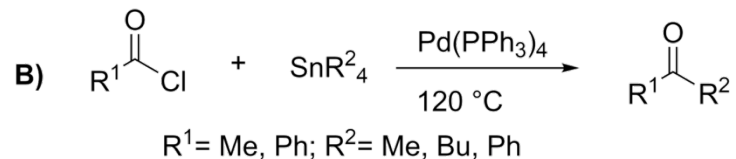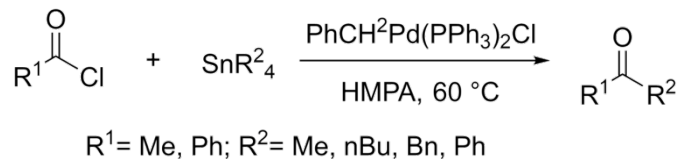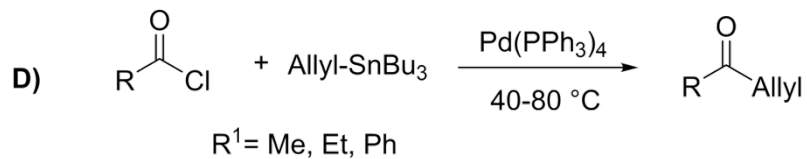|	
Born	May 8, 1930 Tucson, Arizona, United States
Died	July 19, 1989 (aged 59) Sioux City, Iowa, United States
Nationality	American
Known for	Stille reaction
Scientific career	
Institutions	Colorado State University

A)

Y—⟨C₆H₄⟩—Br + Bu₃Sn-SnBu₃ $\xrightarrow[\text{120-140 °C}]{\text{Pd(PAr}_3)_4}$ Y—⟨C₆H₄⟩—⟨C₆H₄⟩—Y

Y= H, OMe, NO₂

Colin Eaborn , 1976

B)

$R^1C(O)Cl$ + SnR^2_4 $\xrightarrow[\text{120 °C}]{\text{Pd(PPh}_3)_4}$ $R^1C(O)R^2$

R¹= Me, Ph; R²= Me, Bu, Ph

C)

Y—⟨C₆H₄⟩—X + Allyl-SnBu₃ $\xrightarrow[\text{80-120 °C}]{\text{PdX}_2}$ Y—⟨C₆H₄⟩—Allyl

Y= H, Me, OMe, Cl, NO₂; X= Cl, Br, I

Migita, 1977

D)

$RC(O)Cl$ + Allyl-SnBu₃ $\xrightarrow[\text{40-80 °C}]{\text{Pd(PPh}_3)_4}$ $RC(O)Allyl$

R¹= Me, Et, Ph

$R^1C(O)Cl$ + SnR^2_4 $\xrightarrow[\text{HMPA, 60 °C}]{\text{PhCH}^2\text{Pd(PPh}_3)_2\text{Cl}}$ $R^1C(O)R^2$

R¹= Me, Ph; R²= Me, nBu, Bn, Ph

Stille, 1978

Y—⟨C₆H₄⟩—Cl + Allyl-SnBu₃ $\xrightarrow[\text{HMPA, 60 °C}]{\text{PhCH}^2\text{Pd(PPh}_3)_2\text{Cl}}$ Y—⟨C₆H₄⟩—Allyl

Y= H, Me, CN, Cl, NO₂

Stille Cross-Coupling

$$R^1-Sn(alkyl)_3 \quad + \quad R^2-X \quad \xrightarrow[\text{ligand}]{Pd^{(0)} \text{ (catalytic)}} \quad \boxed{\begin{array}{c} R^1-R^2 \\ \text{Coupled product} \end{array}} \quad + \quad X-Sn(alkyl)_3$$

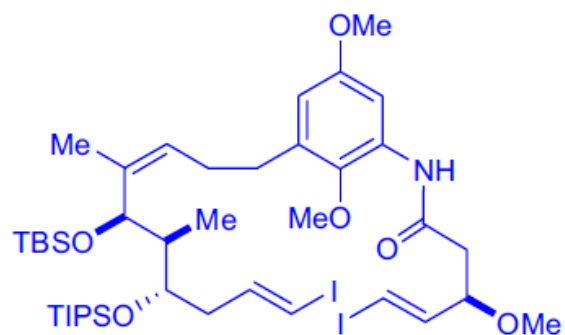R^1 = allyl, alkenyl, aryl; R^2 = alkenyl, aryl, acyl; X = Cl, Br, I, OTf, OPO(OR)$_2$

Reaction features

1. The reaction conditions are compatible with many types of functional groups (carboxylic acid, amide, ester, nitro, ether, amine, hydroxyl, ketone, and formyl groups);

2. The precursor organotin compounds are not sensitive to moisture or oxygen unlike other reactive organometallic compounds;

3. The organotin reagents are easily prepared, isolated, and stored.

4. The main disadvantages are their toxicity and the difficulty to remove the traces of tin by-products from the reaction mixture.

5. High levels of stereochemical complexity can be tolerated by both coupling partners.

Mechanism
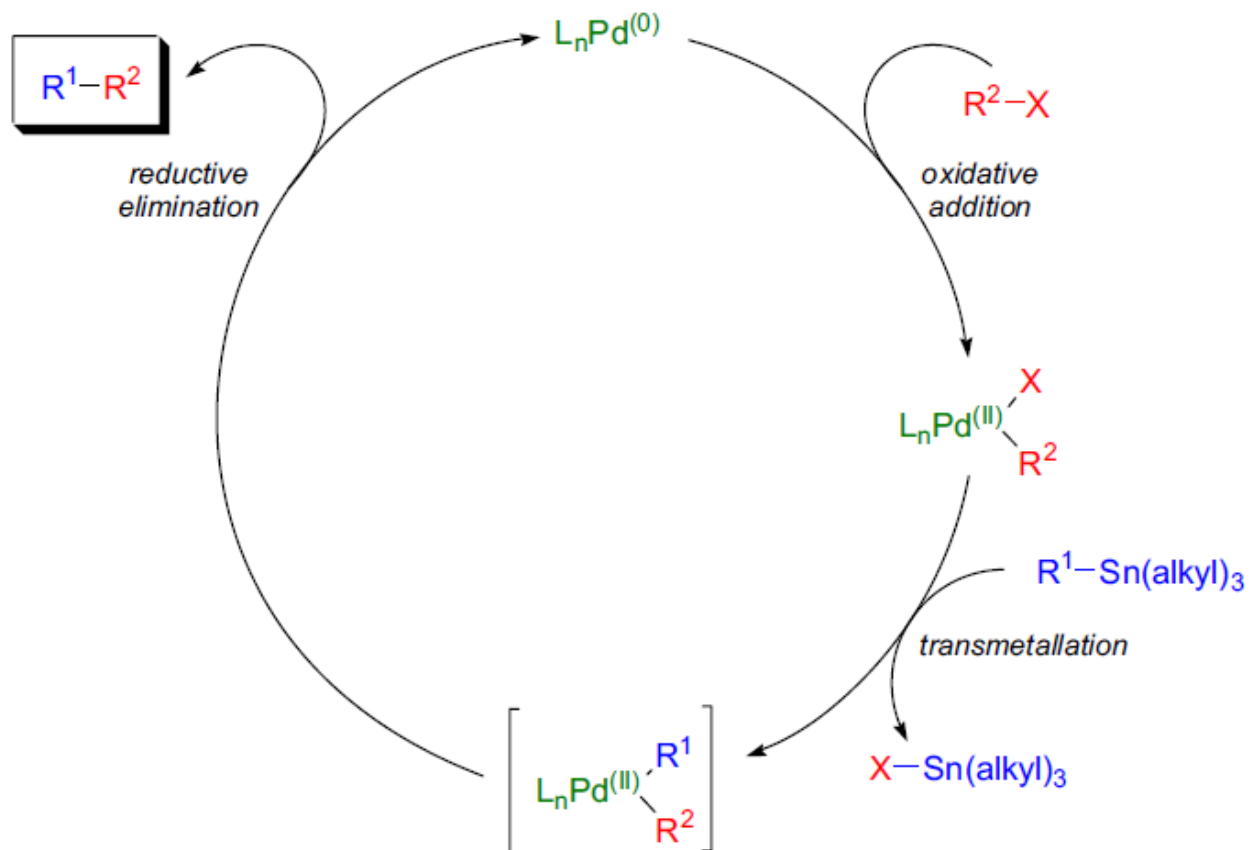
The transcmetallation step is the rate-determining step in the catalytic cycle. Different groups on the tin coupling partner transmetallate to the Pd(II) intermediate at different rates and the order of migration is: alkynyl > vinyl > aryl > allyl - benzyl > alkyl.
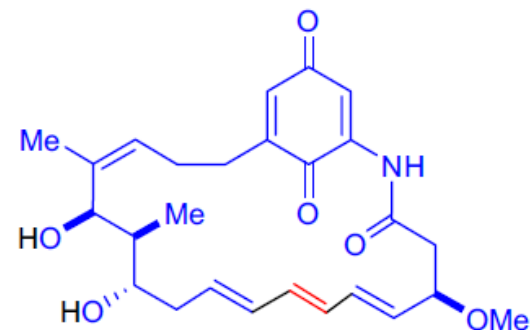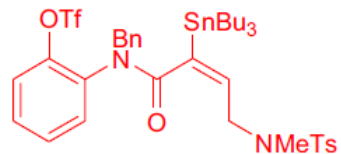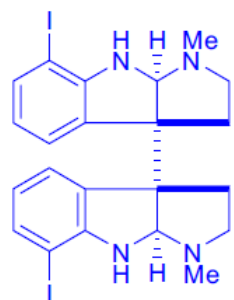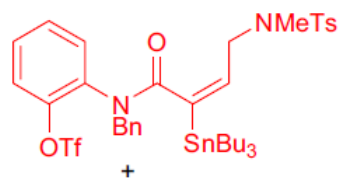
Applications

1. Bu₃Sn⟍⟍SnBu₃
Pd(MeCN)₂Cl₂ (20 mol%)
DMF / THF (1:1), N(i-Pr)₂Et
r.t., 24h

2. CAN, THF / H₂O
3. HF (aq.) / CH₃CN

54% for 3 steps

(+)-Mycotrienol

Pd₂(dba)₃·CHCl₃
P(2-furyl)₃, CuI,
NMP, r.t.
71%
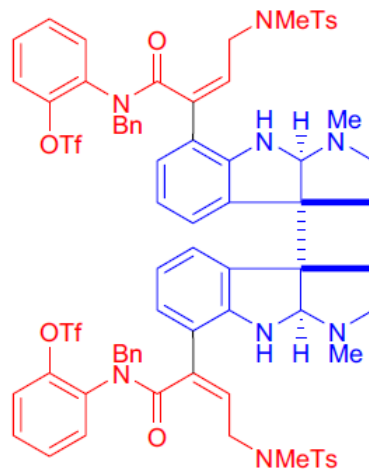
steps
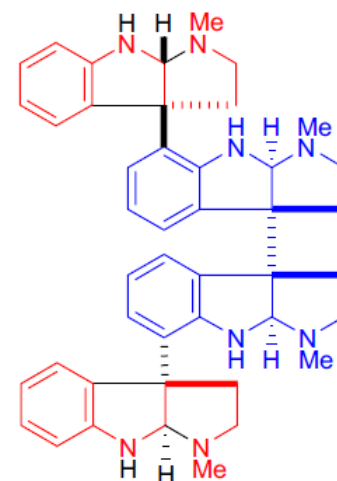
Quadrigemine C

Stille Carbonylative Cross-Coupling

$$R^1-Sn(alkyl)_3 \quad + \quad R^2-X \quad \xrightarrow[\substack{CO \\ ligand}]{Pd^{(0)}\ (catalytic)} \quad \boxed{R^1-\overset{\overset{\displaystyle O}{\|}}{C}-R^2} \quad + \quad X-Sn(alkyl)_3$$
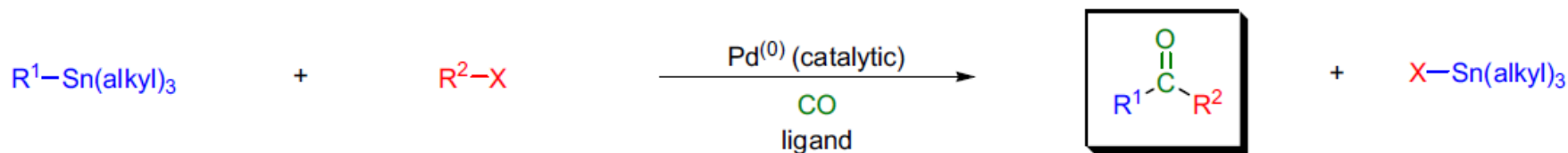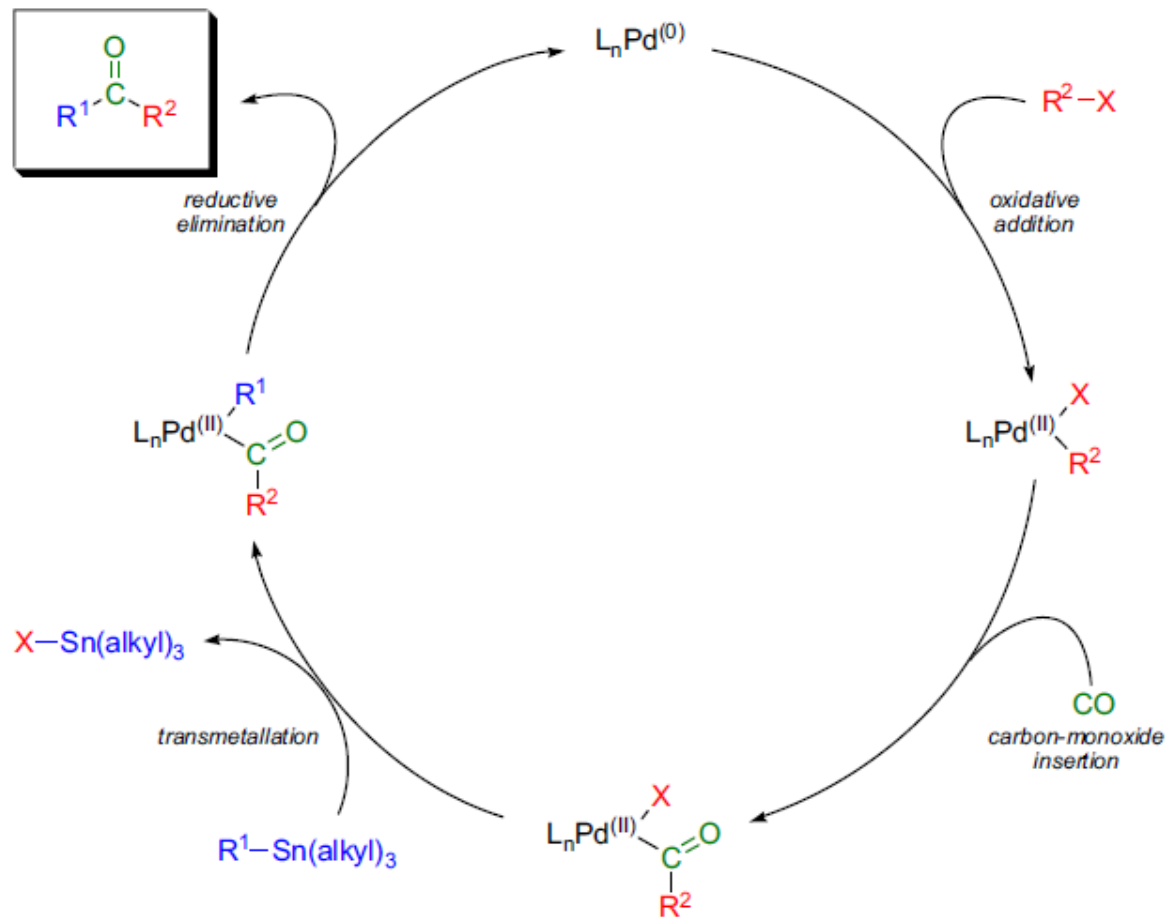
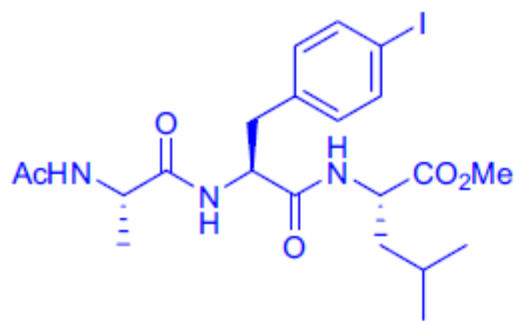R^1 = alkyl, allyl, alkenyl, aryl; R^2 = alkenyl, aryl; X = Cl, Br, I, OTf, $OPO(OR)_2$

Reaction features

1. Many organic halides are commercially available or easily prepared and indefinitely stable;
2. The coupling occurs not only with *chemo- and regioselectivity*, but also with *stereoselectivity*, generally retaining the configuration at the substituted position of both the vinyl/aryl halide and the organostannane;
3. Allyl and benzyl chlorides react, and they give the corresponding ketones with inversion of configuration;
4. The reaction of alkenyl iodides and alkenyltins takes place under neutral and mild conditions;
5. The use of alkoxy, thioalkoxy, and aminostannanes allows the preparation of the corresponding carboxylic acid derivatives.
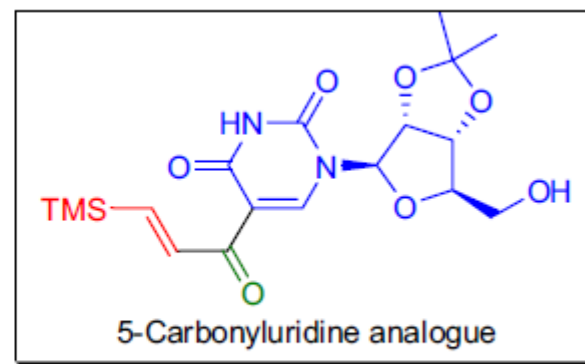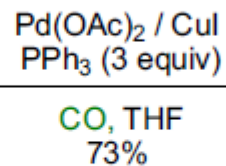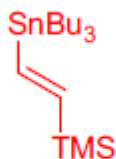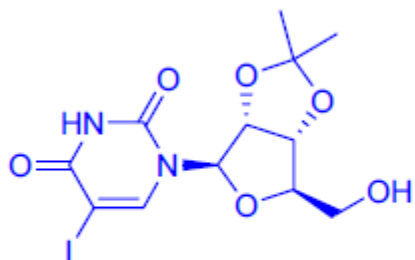
Mechanism

Applications

Ala-4-I-Phe-Leu

PdCl$_2$ (5 mol%)
PPh$_3$ (10 mol%)

1 atm CO
DMF, 90 °C, 5h
96%

Photoactivatable BPA-containing peptide

Pd(OAc)$_2$ / CuI
PPh$_3$ (3 equiv)

CO, THF
73%

5-Carbonyluridine analogue
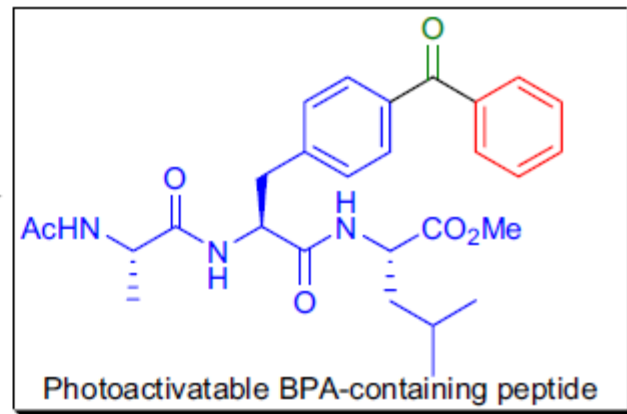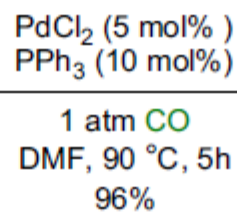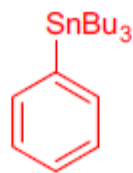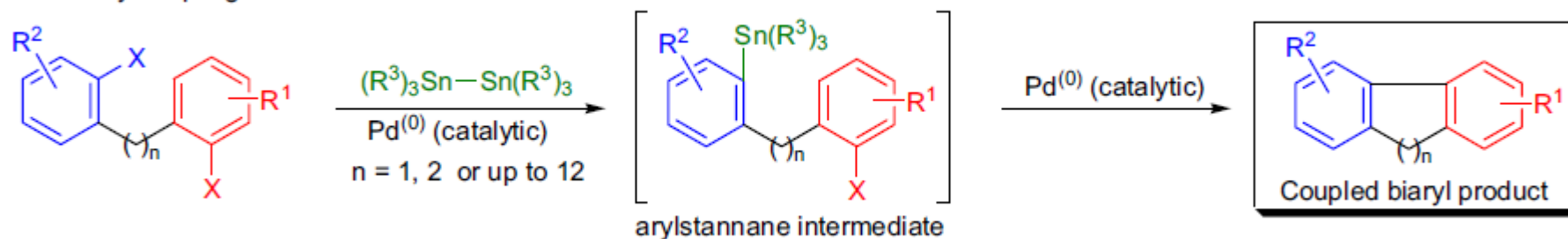
# Stille-Kelly Coupling

Stille-Kelly coupling:

R^1, R^2 = alkyl, aryl, electron-withdrawing or electron-donating; R^3 = Me, n-Bu; X = Br, I, OTf
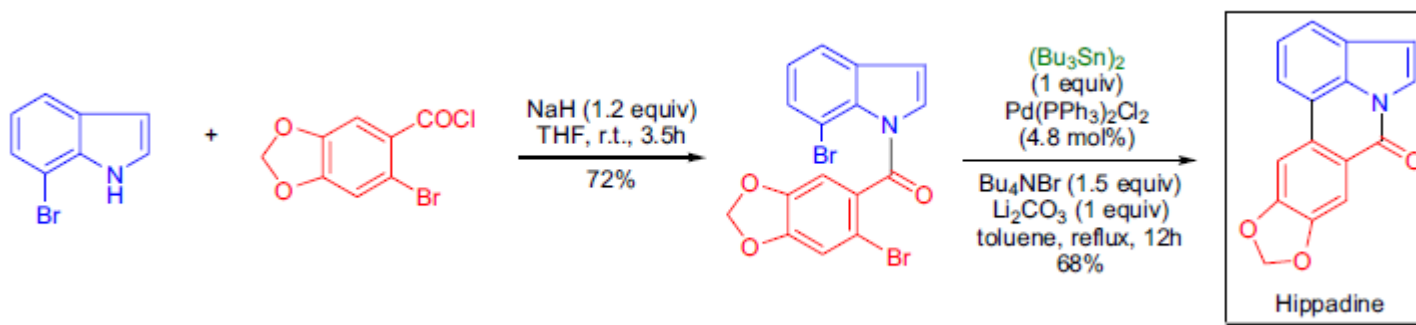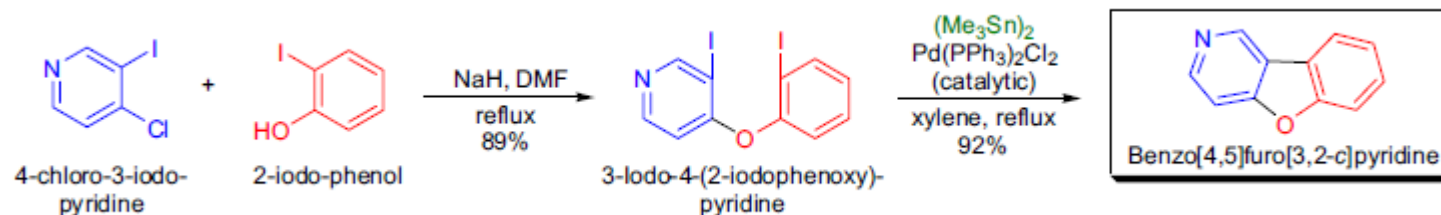
Reaction features

1. Aryl iodides, bromides, and triflates work best, but there are no examples for this coupling with aryl chlorides;

2. Usually the newly formed ring is five or six-membered, but there are cases when the formation of larger rings and even macrocycles is possible.

Mechanism
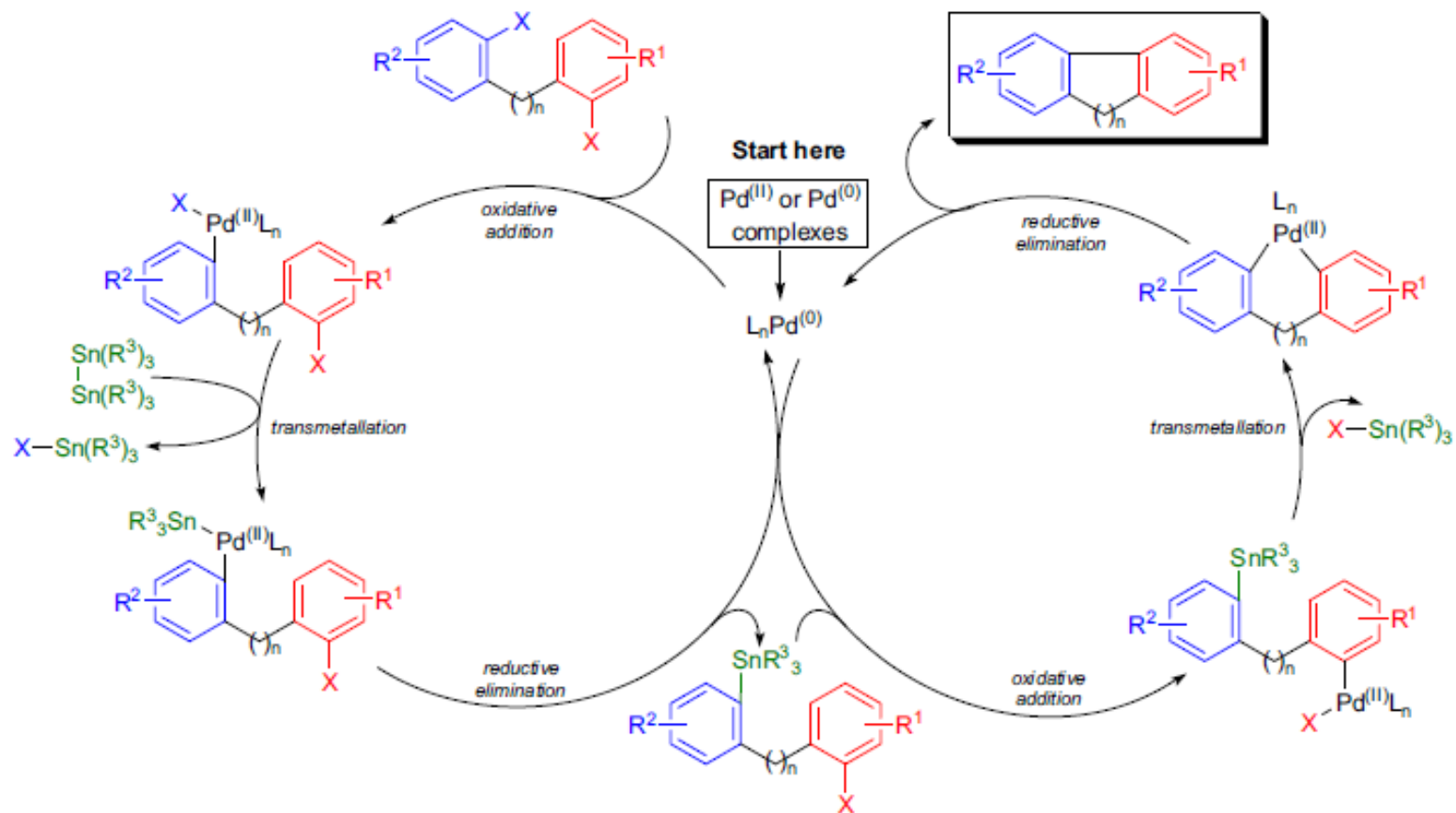
Applications

Thanks for attention!