PRESSMEDDELANDE
Press release

6 October 2010

The Nobel Prize in Chemistry 2010

The Royal Swedish Academy of Sciences has decided to award the Nobel Prize in Chemistry for 2010 to

Richard F. Heck
University of Delaware, Newark, DE, USA,

Ei-ichi Negishi and
Purdue University, West Lafayette, IN, USA

Akira Suzuki
Hokkaido University, Sapporo, Japan

"for palladium-catalyzed cross couplings in organic synthesis".

Transmetallation with palladium

Application of R- Zn-I : **Negishi coupling**

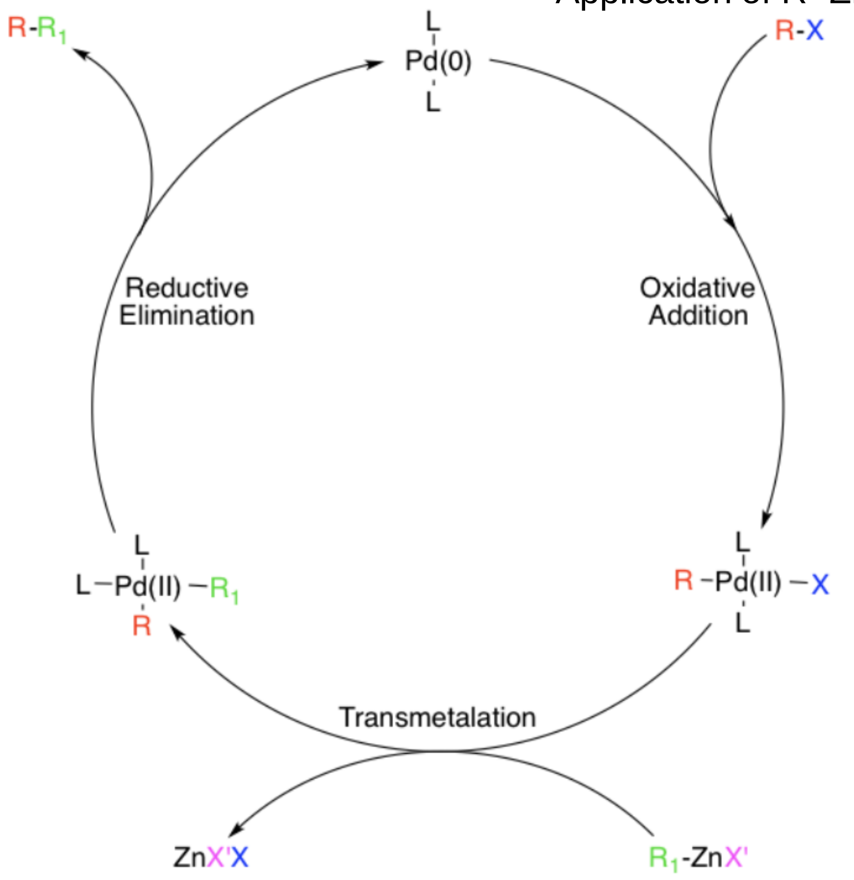
Otherwise similar as Stille coupling, but Zn alkyls are used for transmetallation.

Various Zn-alkyls are obtainable:
1) via a reaction of zinc powder and R-I
2) using Et_2Zn as a starting material
3) via transmetallation (e.g. LiR)

The R-Zn-X compounds are non-isolable and are used without purification.

Transmetallation with palladium

Application of R- Zn-I : **Negishi coupling**



R = aryl, alkenyl, propargyl, acyl
R_1 = aryl, alkenyl, allyl, benzyl, homoallyl, homopropargyl
X = I, Br, Cl, OTf, OAc
X' = I, Br, Cl
L= ligand

Transmetallation with palladium

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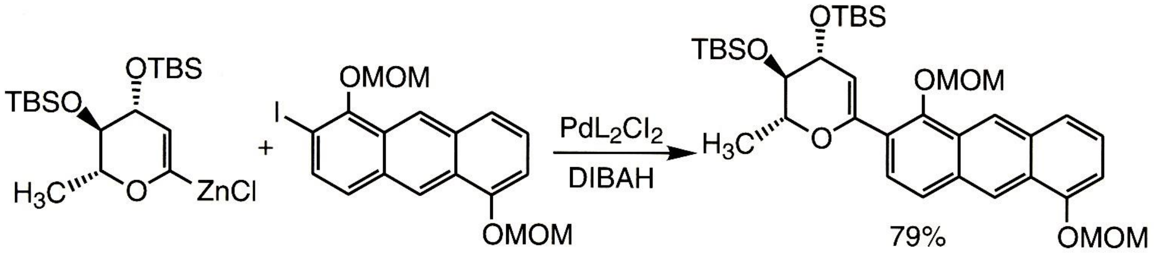
Reaction tolarates a large variety of functional groups



An important intermediate in total synthesis of vineomycinone **B2** methyl ester.

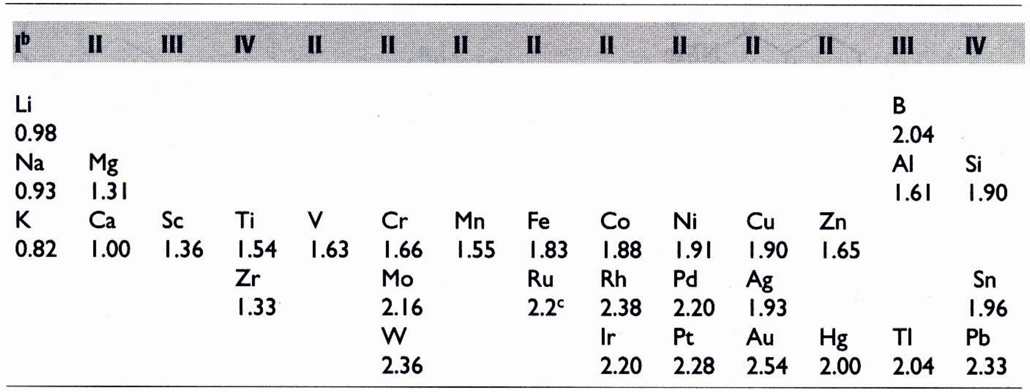
Transmetallation

Application of R- Mg-I : Corriu-Kumada reaction

M’ - R + M - X ↔ M’ - X + M - R

Transmetallation is an excellent way of introducing σ-bonded hydrocarbon ligands into the coordination sphere of transition metals.

If the electronegativity of M is greater than M’, the reaction (left to right) is thermodynamically favored.



I^b	II	III	IV	II	II	II	II	II	II	II	II	III	IV
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If an empty orbital is available on both metals, the reaction is kinetically favorable.

Transmetallation with palladium

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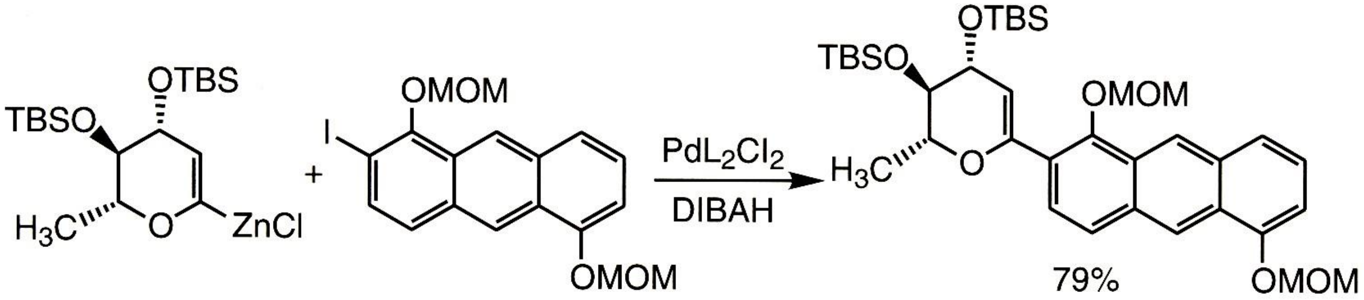
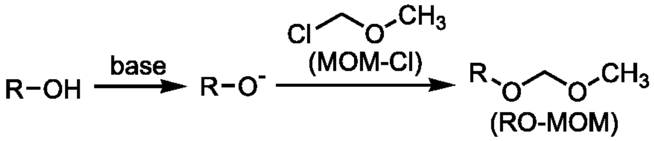


An important intermediate in total synthesis of vineomycinone **B2** methyl ester.



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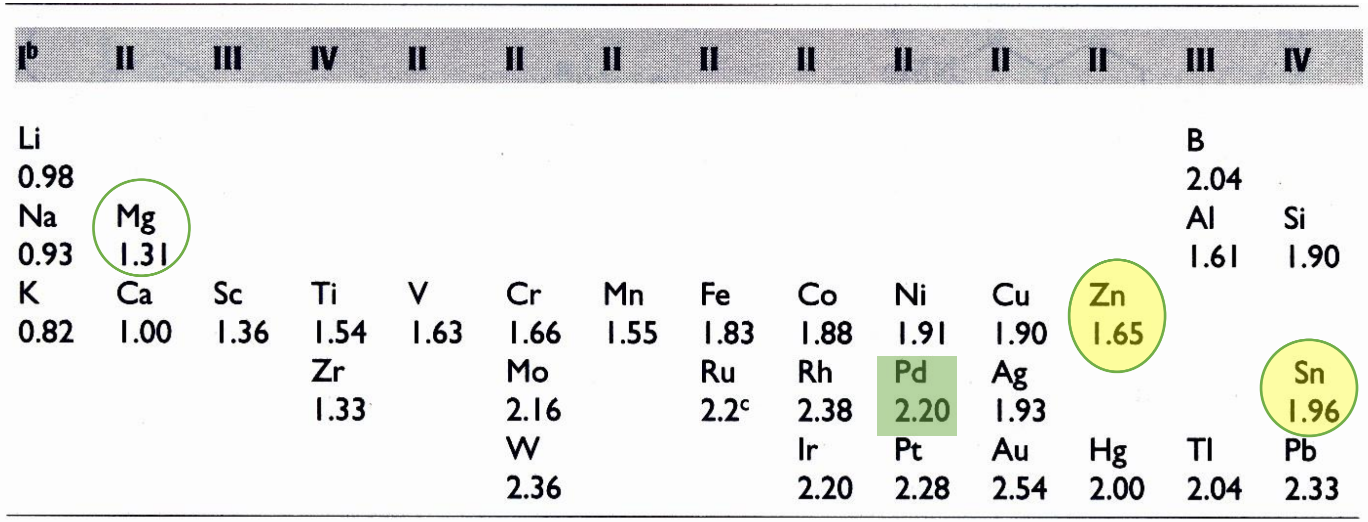

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Transmetallation with palladium

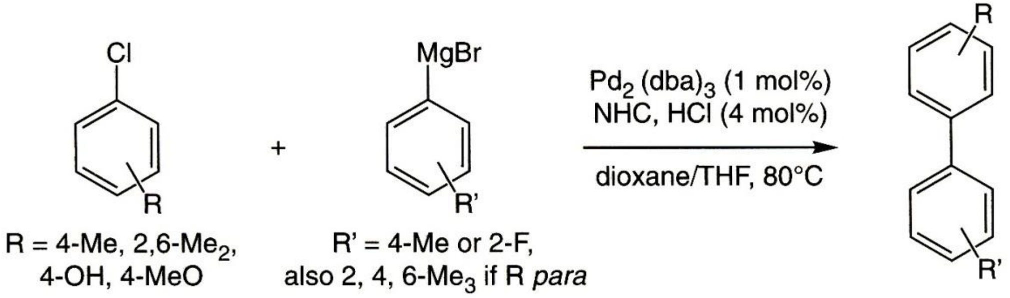
to couple a combination of two alkyl, aryl or vinyl groups.

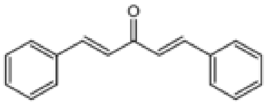
Application of R- Mg-I : Corriu-Kumada reaction - already from 1972

Otherwise similar as Stille and Negishi, but Mg alkyls are used for transmetallation.
Also Ni^{2+} can be used as a catalyst precursor.

R – X + R-Mg-Br → R – R + X -Mg– Br ; R and R = vinyl or aryl, alkyl less common

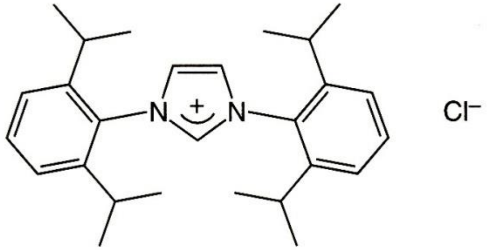
Even unactivated aryl chlorides can be coupled with aryl Grignards
Reaction tolarates a large variety of functional groups, even OH.





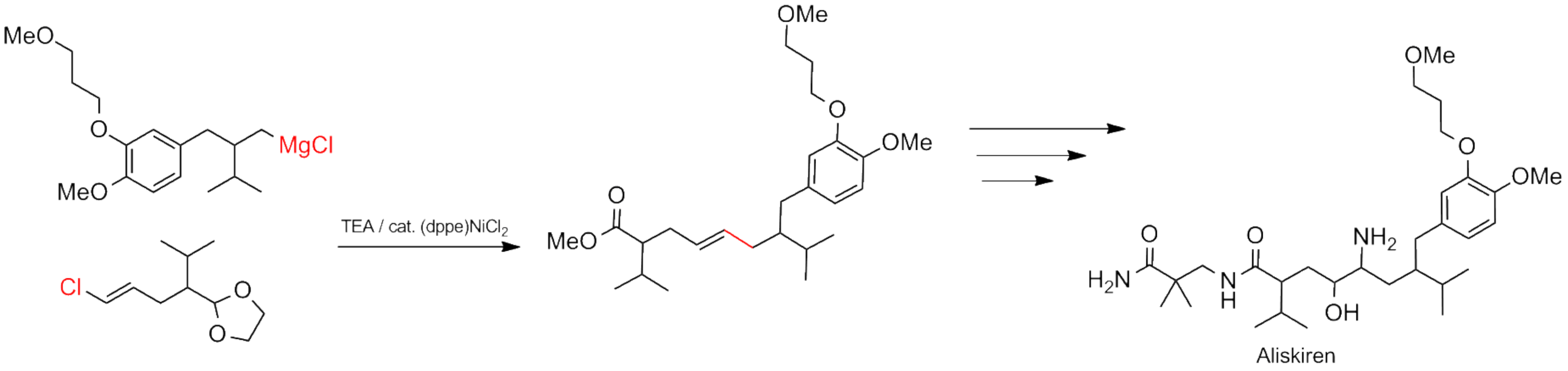
dba = dibenzylideneacetone

NHC, HCl =

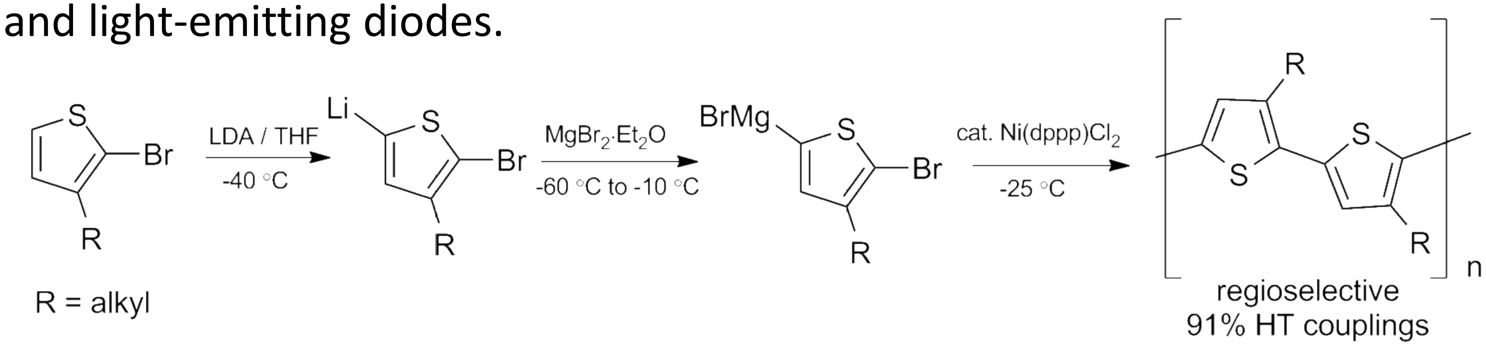


Transmetallation with palladium

The Corriu-Kumada coupling is suitable for large-scale, industrial processes, such as drug synthesis. The reaction is used to construct the carbon skeleton of aliskiren (trade name Tekturna), a treatment for hypertension.

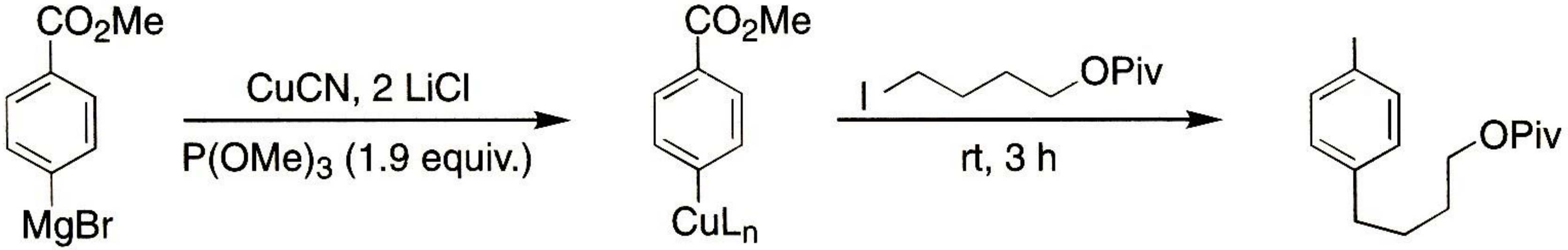


The coupling also shows promise in the synthesis of conjugated polymers, polymers such as polyalkylthiophenes (PAT), which have a variety of potential applications in organic solar cells and light-emitting diodes.



Transmetallation with palladium

An extension for Corriu-Kumada coupling is transmetallation of CuCN/LiCl with Grignard and use of this Cu(I) complex for further coupling

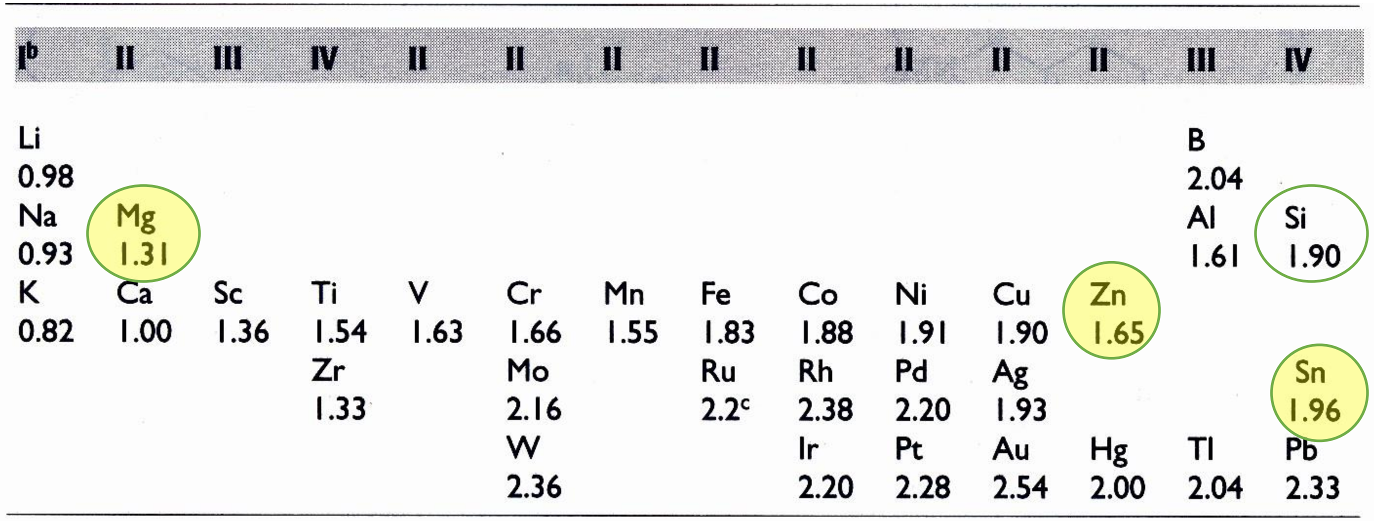


Transmetallation with palladium

Application of trimethoxysilanes : Hiyama reaction

The use of silion-derived compounds for transmetallation is interesting as

1) Silicon compounds have low toxicity
2) Low cost



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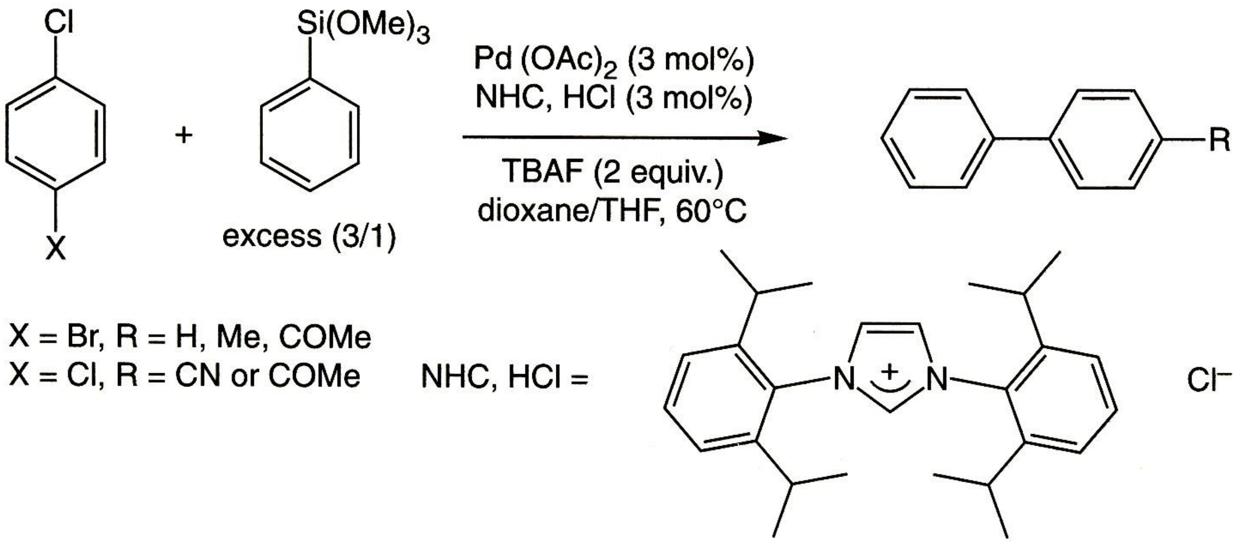


The reaction is known with aryl- and vinyltrimethoxysilanes. Without NHC ligands it requires high catalyst loading and is unselective.

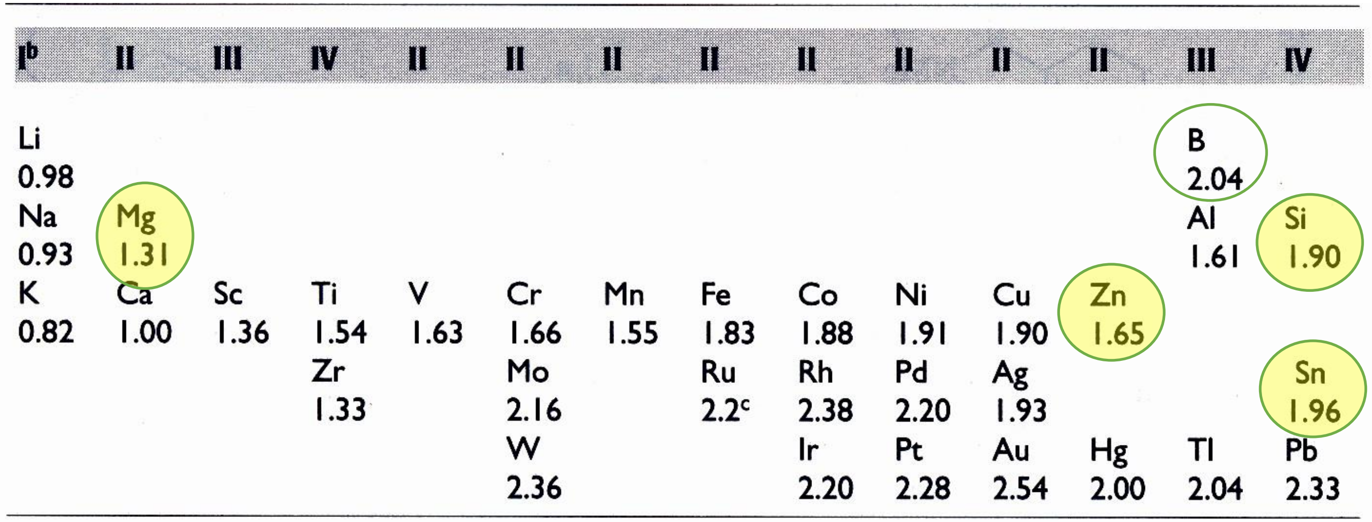
Transmetallation with palladium

Application of Boron : Suzuki reaction

Otherwise similar as Stille and Negishi, but vinyl and arylboranes are used for transmetallation.

R – I + Ar-B-R'$_2$ → R – Ar + I -B– R'$_2$; R=vinyl or aryl
R' = OH, OR''' or alkyl (9-BBN)

The reaction is far-reaching, because wide variety of thermal stable organoboron are commercial available or easily synthesized – extensive use in synthesis of natural products.



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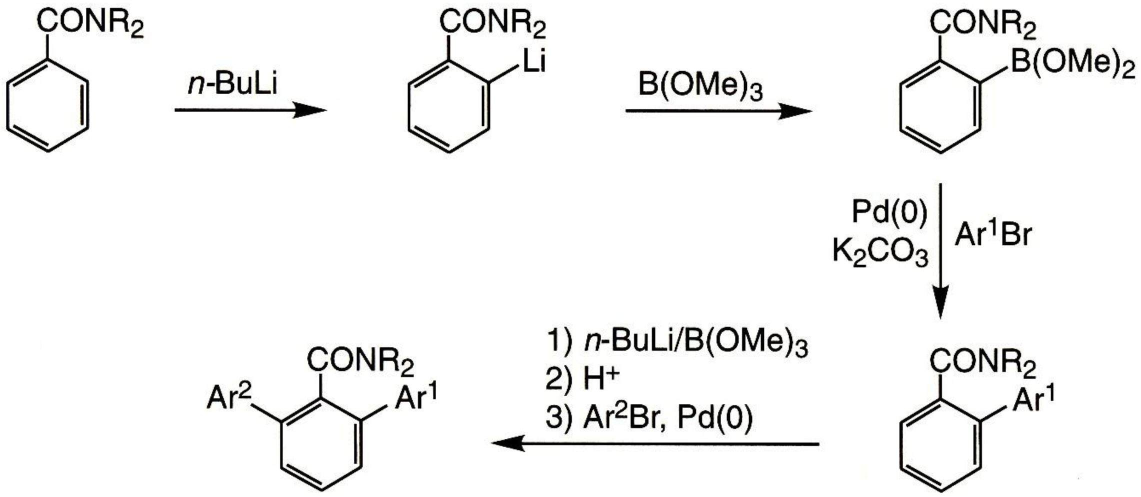
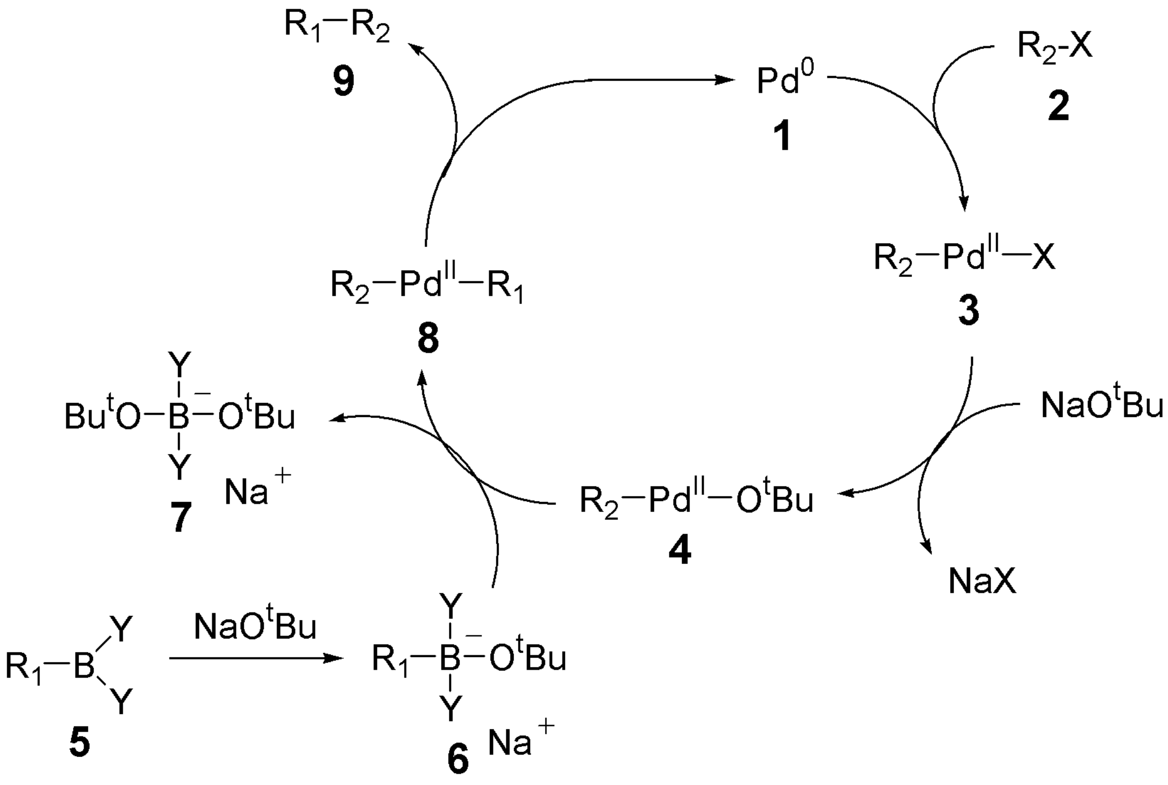


Transmetallation with palladium

Application of Boron : Suzuki reaction

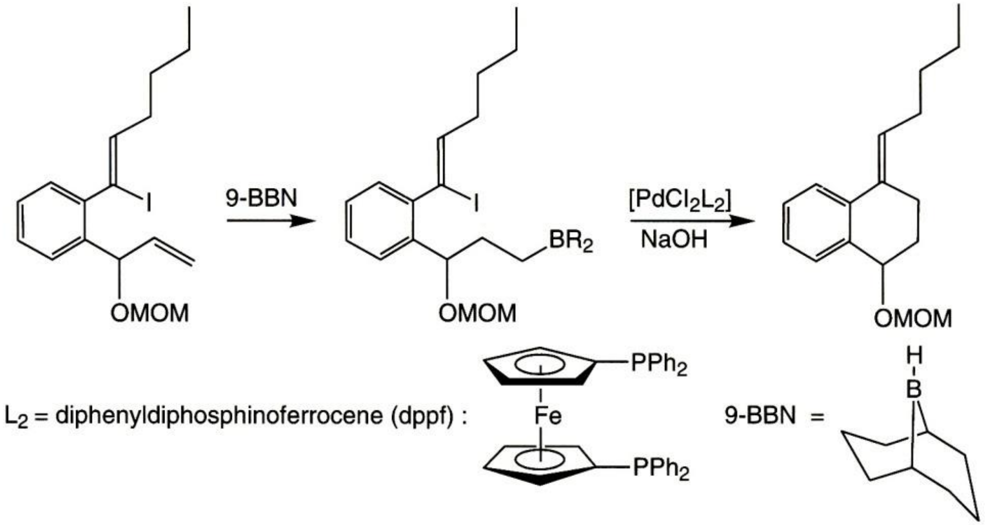


The mechanism of the Suzuki reaction is best viewed from the perspective of the palladium catalyst. The first step is the oxidative addition of palladium to the halide 2 to form the organopalladium species 3. Reaction with base gives intermediate 4, which via transmetalation[7] with the boron-ate complex 6 forms the organopalladium species 8. Reductive elimination of the desired product 9 restores the original palladium catalyst 1.

Transmetallation with palladium

Application of Boron : Suzuki reaction

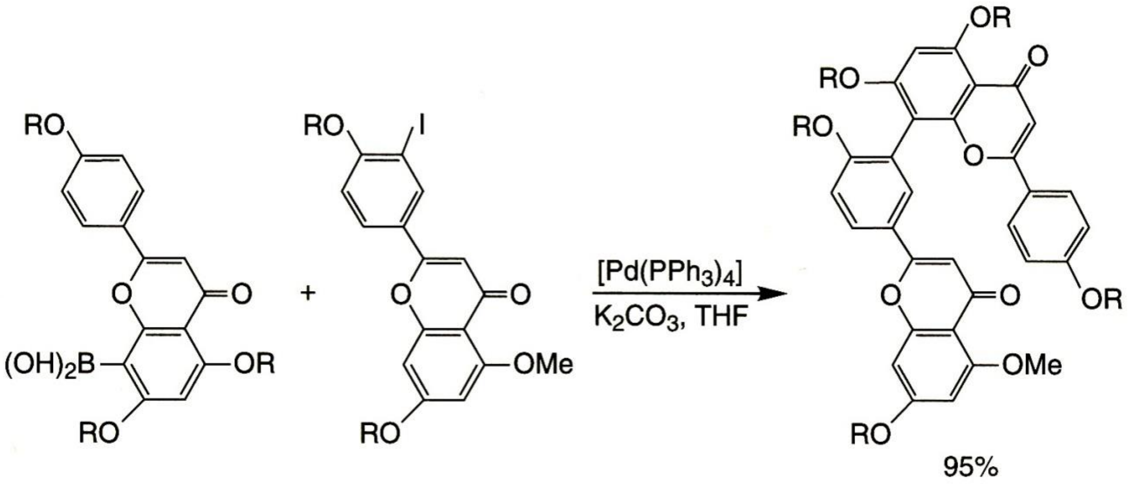
Also hydroboration of alkenes and alkynes is highly useful to generate organoboron compounds

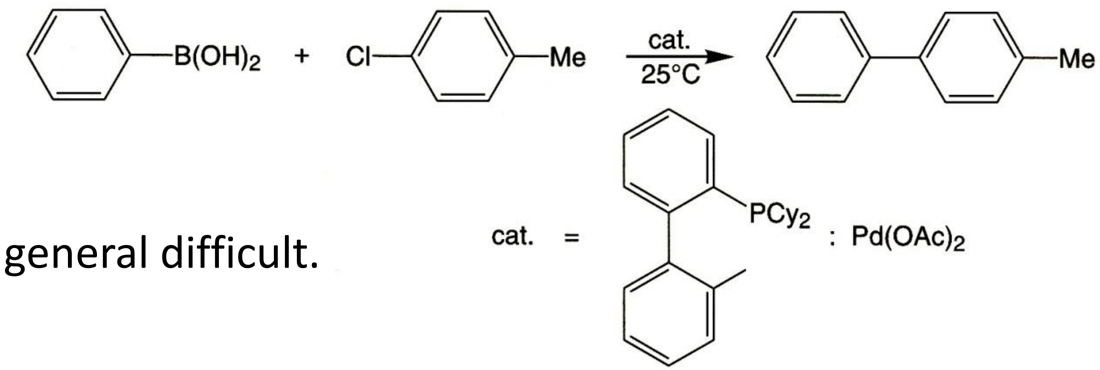


Addition of base activates the borates, BR_3OH^- is the active species.

Transmetallation with palladium

Application of Boron : Suzuki reaction

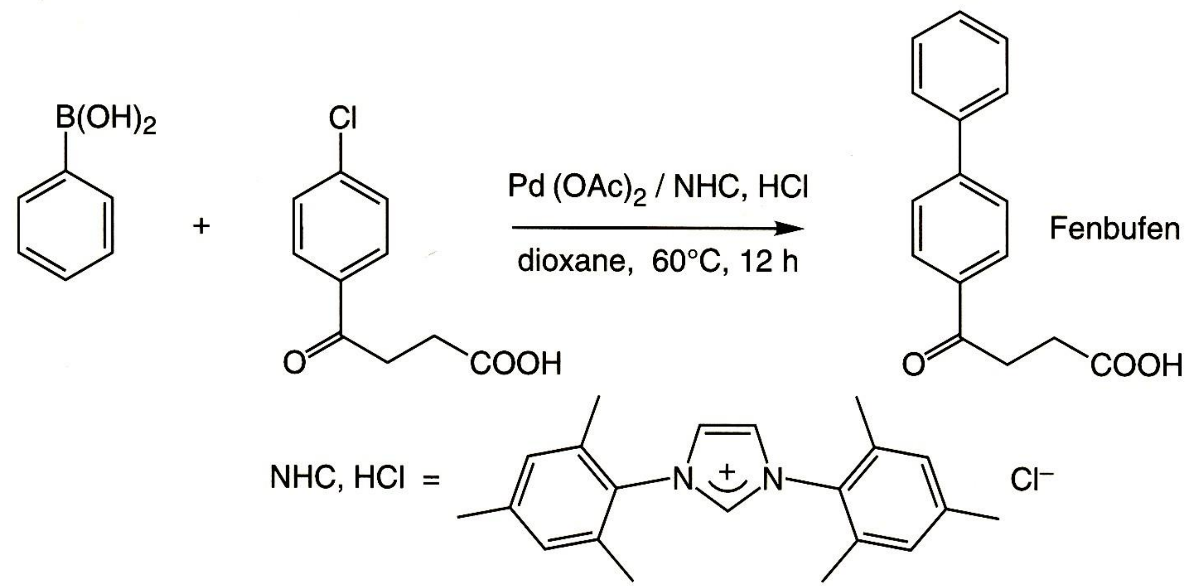




Coupling of aryl chlorides is in general difficult.

Transmetallation with palladium

Application of Boron : Suzuki reaction



Fenbufen is an anti-flamatory drug .

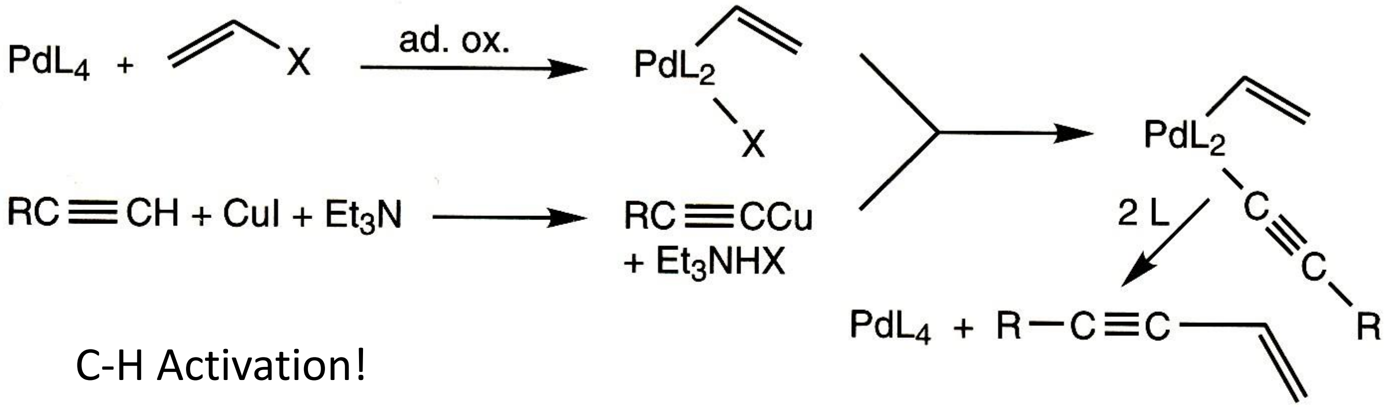
Transmetallation with palladium

Sonogashira reaction: *in situ* metallation with Cu^I

The Sonogashira reaction allows to couple a vinyl or aryl halide with a terminal alkyne.

The benefit of Heck and Sonogashira reactions is that preparation of actual organometallic complex is not needed.

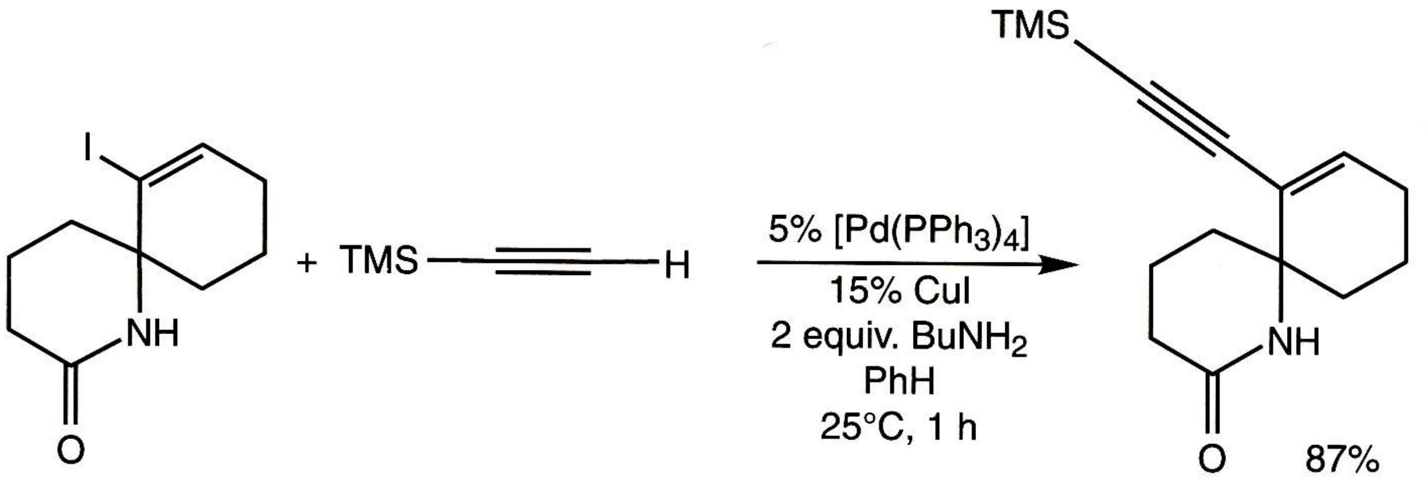
Catalyzed by Cu^I and Pd^0 or Pd^0 alone.



C-H Activation!

Transmetallation with palladium

Sonogashira reaction: in situ metallation



5% [Pd(PPh$_3$)$_4$]

15% CuI

2 equiv. BuNH$_2$

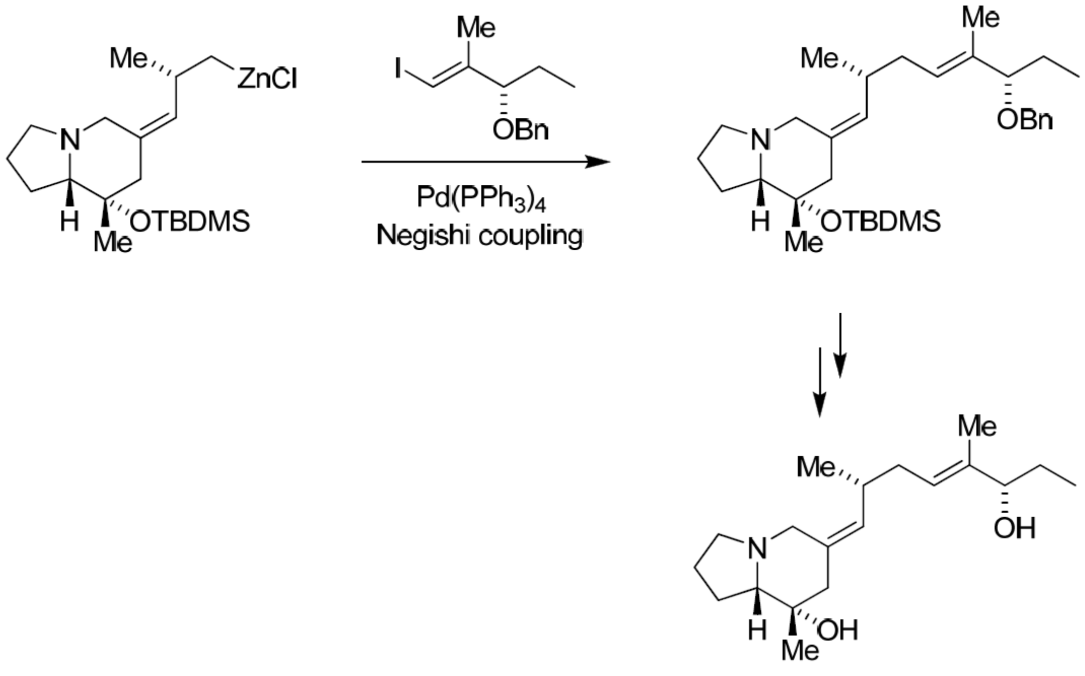
PhH

25°C, 1 h

Transmetallation with palladium

The Negishi and Suzuki reactions have also been frequently employed in natural product synthesis.

Pumiliotoxin A is a toxic alkaloid found in the skin of frogs from the Dendrobatidae family that the frog uses for its defence. The total synthesis of pumiliotoxin A was performed via the use of a Negishi coupling in one of the key steps. It is interesting to note that an alkylzinc compound with β-hydrogens is used in this reaction.



Pumiliotoxin A

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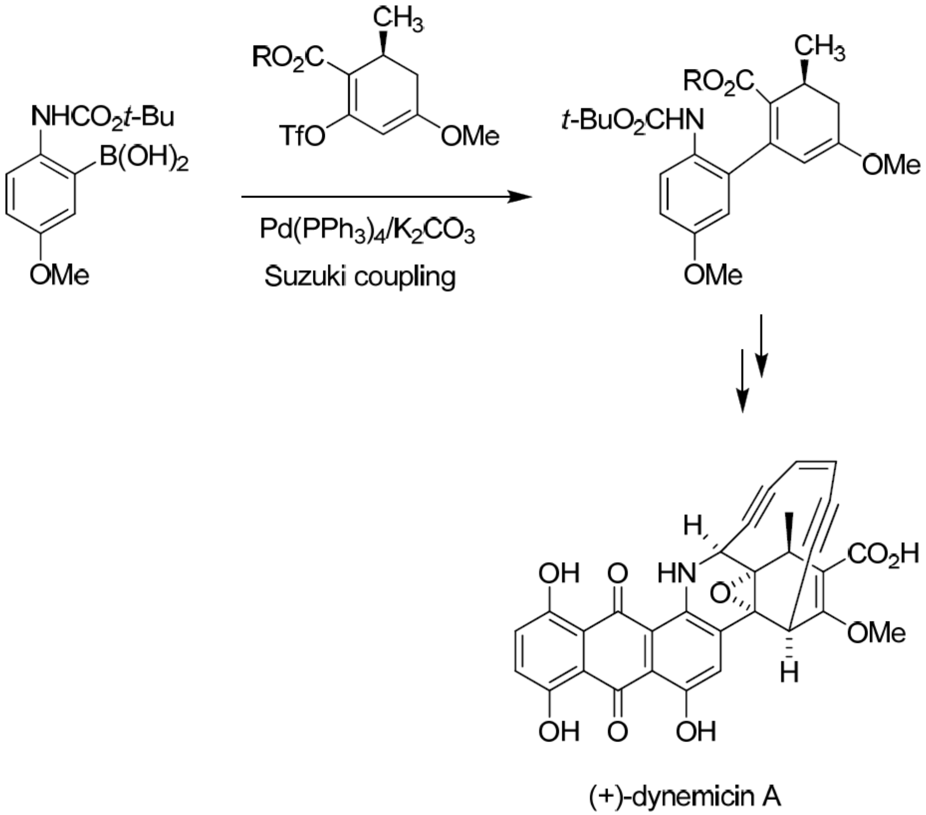
Dynemicin A is an anti-cancer enediyne drug. It displays properties which illustrate promise for cancer treatments, but still requires further research.



Transmetallation with palladium

There are a number of natural product syntheses reported in the literature that rely on the Negishi and Suzuki couplings for carbon-carbon bond formation.

Two more examples: The Negishi coupling was employed in the synthesis of the natural marine antiviral product hennoxazole A and the Suzuki reaction was used for preparing the antiviral bromoindole alkaloid dragmacidin F. At the cross-coupling stage there were several sensitive functional groups present, and therefore mild reagents such as an organoboron or organozinc reagent are required.

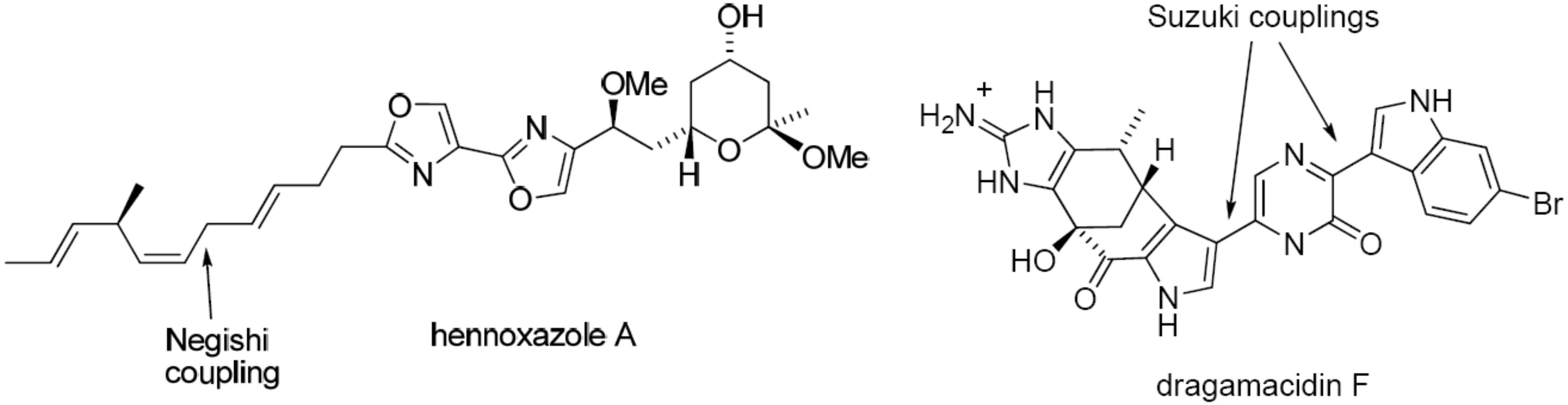
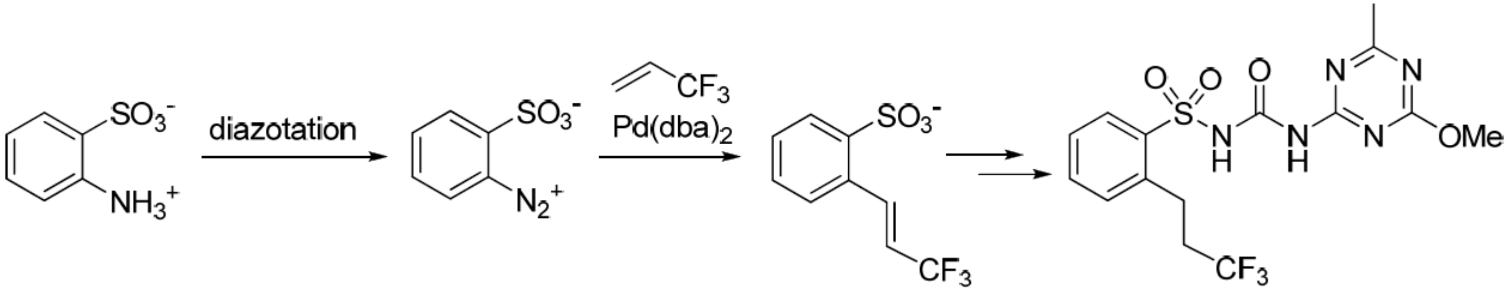


Figure 1. Synthesis of hennoxazole A (ref 34) and dragmacidin F (ref 35) via palladium-catalyzed cross coupling.

Transmetallation with palladium

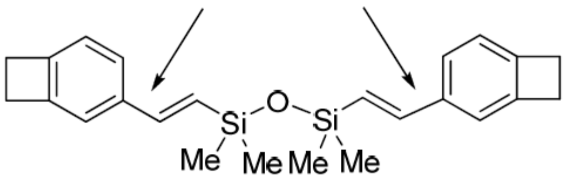
The palladium-catalyzed cross-coupling reactions are suitable for carrying out on a large scale and the Heck reaction has been used for a number of large-scale industrial applications. Several of these processes are run on a multiton scale per year. The sulfonyl urea herbicide Prosulforon® is produced on a large scale with a process developed by Ciba-Geigy. The key step is a Heck reaction, where a diazonium salt generates an arylpalldium intermediate, which couples with the olefin.



Prosulfuron®

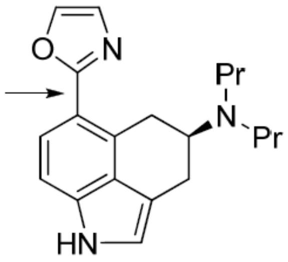
Transmetallation with palladium

The anti-inflammatory drug Naproxen (Albermarle, Hoechst AG, 1994) and the asthma drug Singulair (Merck, 1993) are other examples of industrial manufacturing of pharmaceuticals via the Heck reaction. Some examples of the use of the Heck, Negishi, and Suzuki reactions in the industrial preparation of fine chemicals are given below.



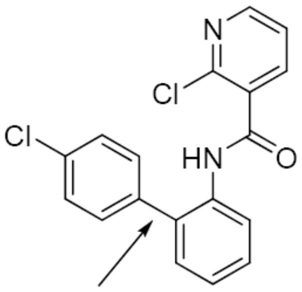
Heck reactions

DVS-bis-BCB
(Monomer for high performance electronic resins (Cyclotene®))
(Dow chemical 1989)



Negishi coupling

5-HT$_{1A}$ Agonist
(Eli Lilly, 1997)



Suzuki coupling

Boscalid (fungicide)
BASF, 1997

Transmetallation with palladium (summary)

$R - X + R''\text{-Sn-}R'_3 \rightarrow R - R'' + X\text{-Sn} - R'_3$; PdL_2

$R - (CO)X + R''\text{-Sn-}R'_3 \rightarrow R\,(CO) - R'' + X\text{-Sn} - R'_3$; PdL_2

$R - X + R''\text{-Sn-}R'_3 \rightarrow R\,(CO) - R'' + X\text{-Sn} - R'_3$; PdL_2 and CO

Stille-coupling

Application of R- Zn-I

Negishi coupling

Application of trimethoxysilanes :

Corriu-Kumada coupling

Application of Boron :

Suzuki coupling

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and

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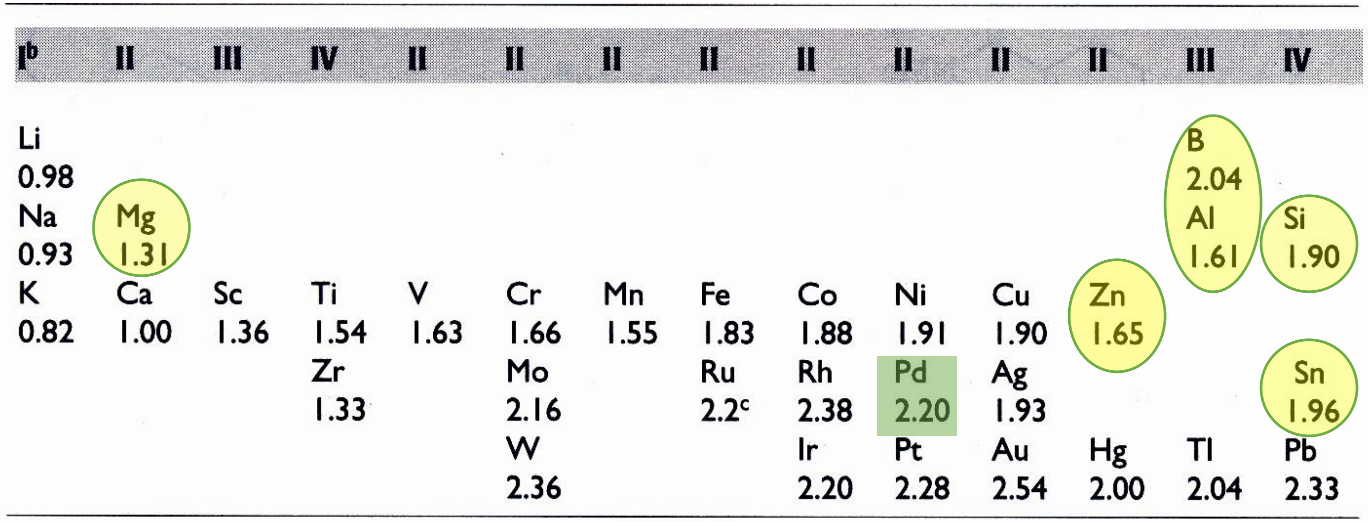

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Transmetallation with palladium

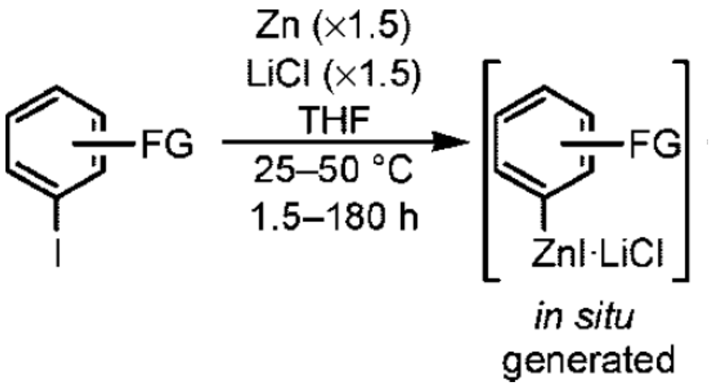
One-pot Negishi reaction: *in situ* metallation

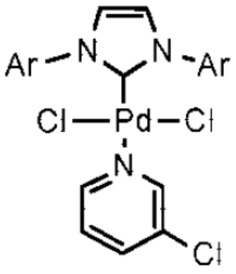
Application of R- Zn-I

One limitation in Negishi reaction is, that the R-Zn-X compounds are non-isolable and are used without purification. In addition, Zn-R reagents are air and moisture sensitive.

In this respect one-pot protocol would be beneficial.

LiCl-mediated direct insertion of zinc into unsaturated halides has been developed.





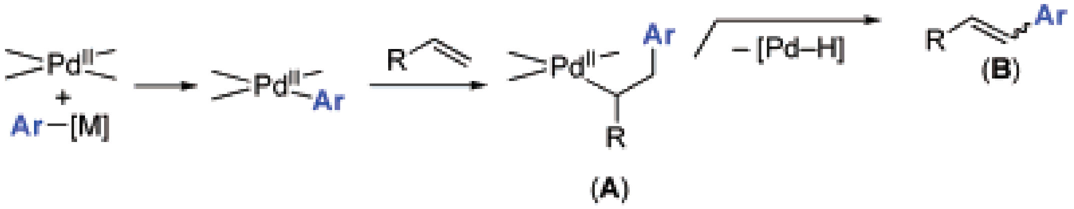
PEPPSI
(Ar = 2,6-diisopropylphenyl)

This procedure suits for large-scale applications

Knochel, JOC, 2008, 7380

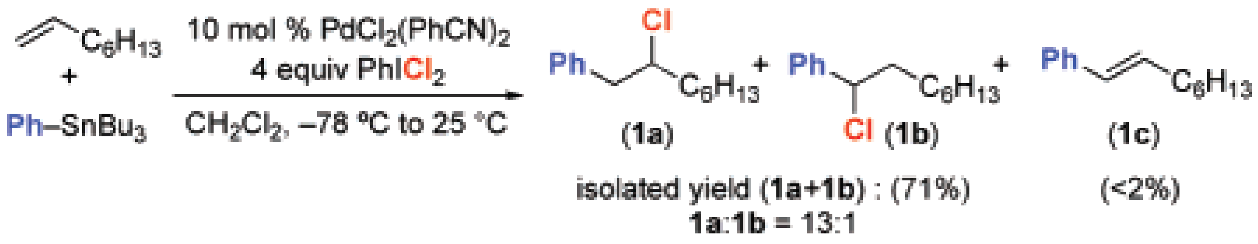
Transmetallation with palladium

Combination of Heck reaction and oxidative functionalization



β-elimination followed by olefin dissociation limits scope severely!

Pd-alkyl species can be oxidatively intercepted with iodine (III) reagents!



(Dichloroiodo)benzene (Willgerodt's reagent)

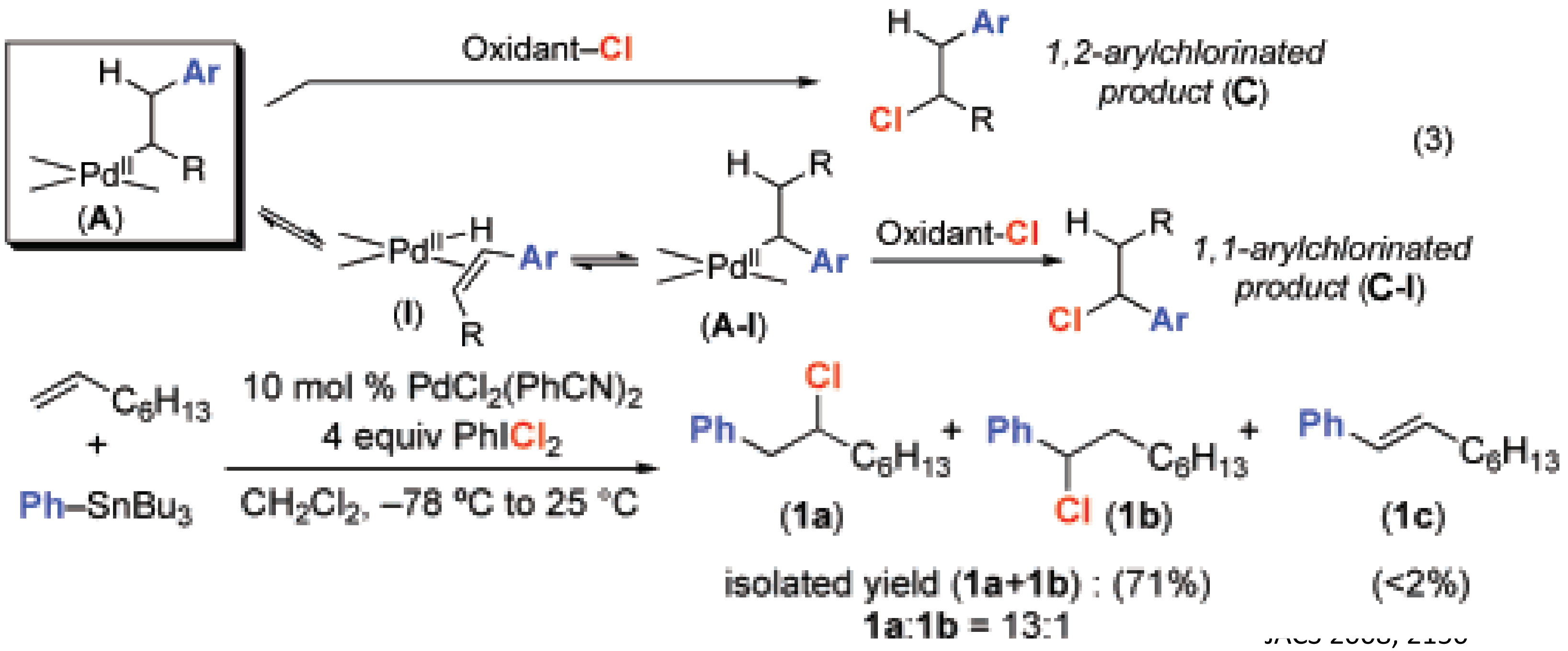
JACS 2008, 2150

Transmetallation with palladium

Combination of Heck reaction and oxidative functionalization

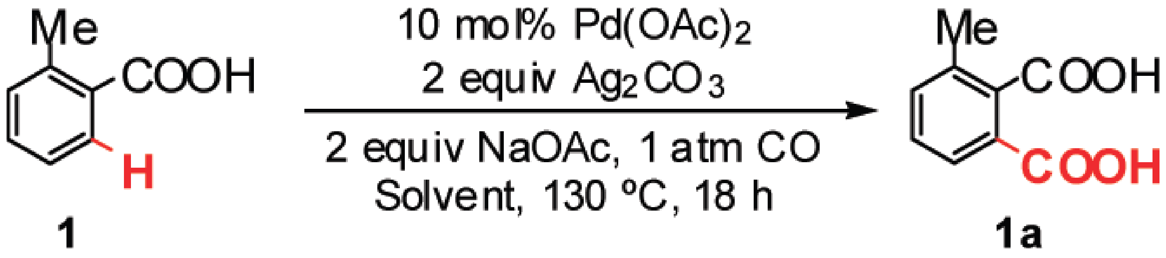
When less reactive electrophilic chlorinating reagents ($CuCl_2$) was used,
1,1 arylchlorinated **1b** was major product.
(solvent was changed from CH_2Cl_2 to EtOH).

How 1,1 arylchlorinated **1b** is formed?



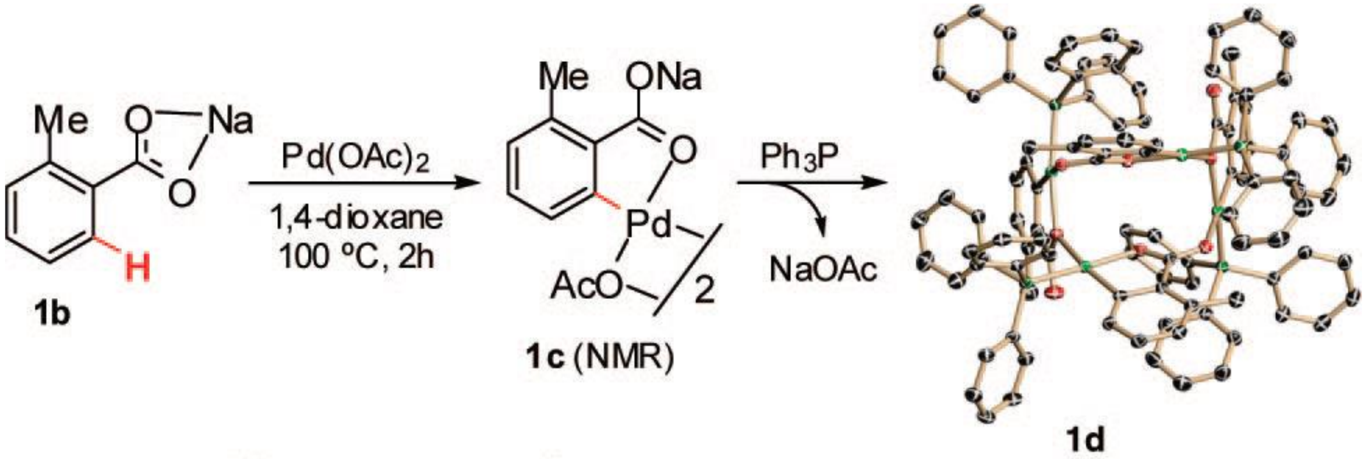
C-C coupling with palladium

Carboxylation of aryl and vinyl C-H bonds



Acid formation includes C-H activation and CO insertion

Ag_2CO_3 is needed to recycle Pd(0) back to Pd(II).



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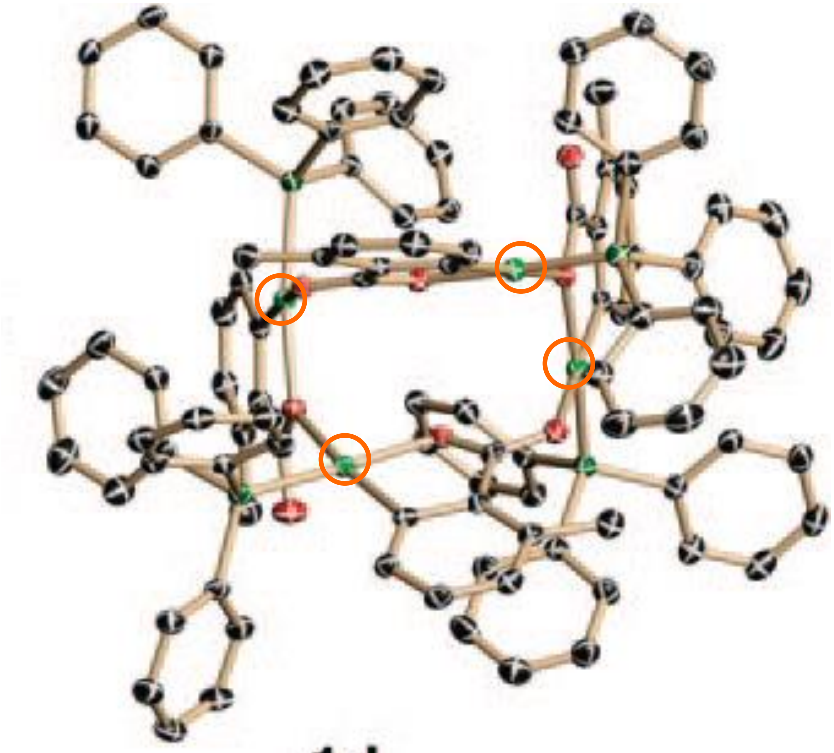
C-C coupling with palladium

Carboxylation of aryl and vinyl C-H bonds



1d

tetrameric palladium cycle

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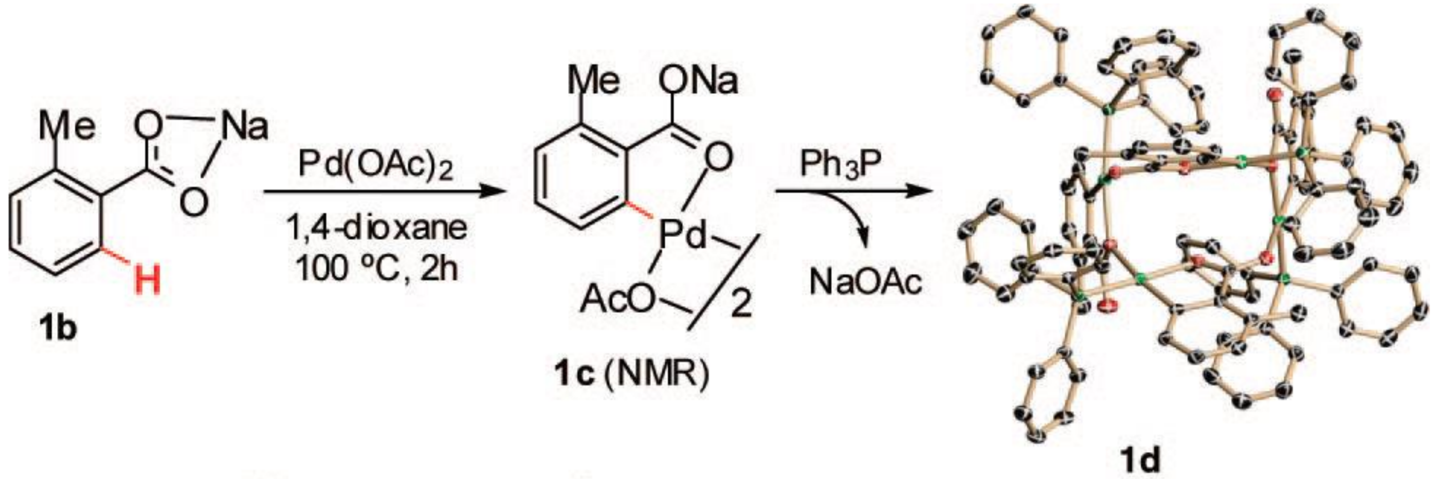
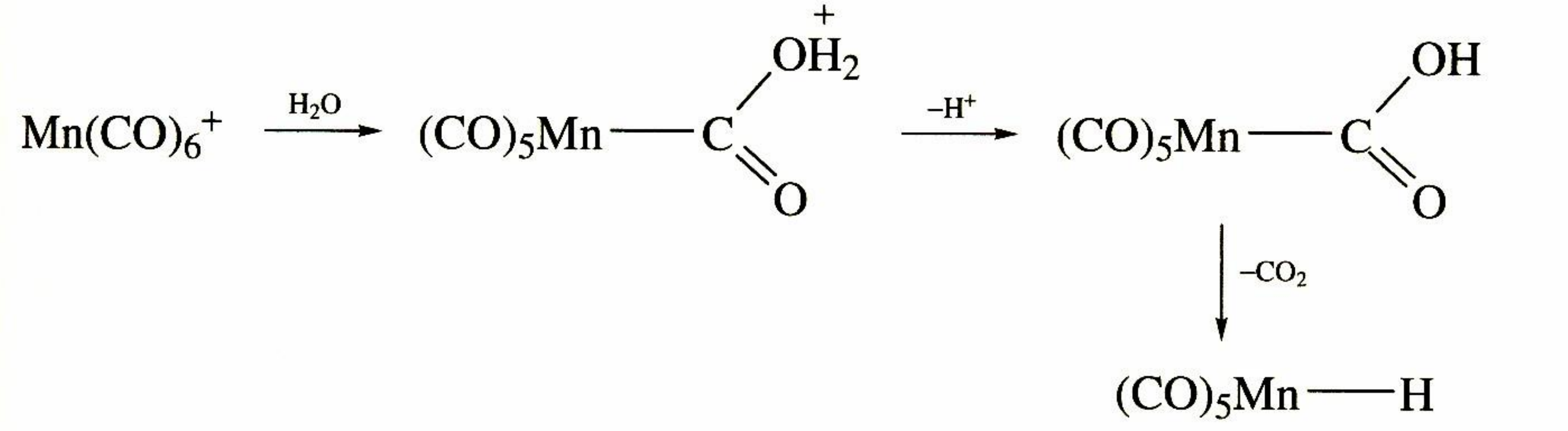
C-C coupling with palladium

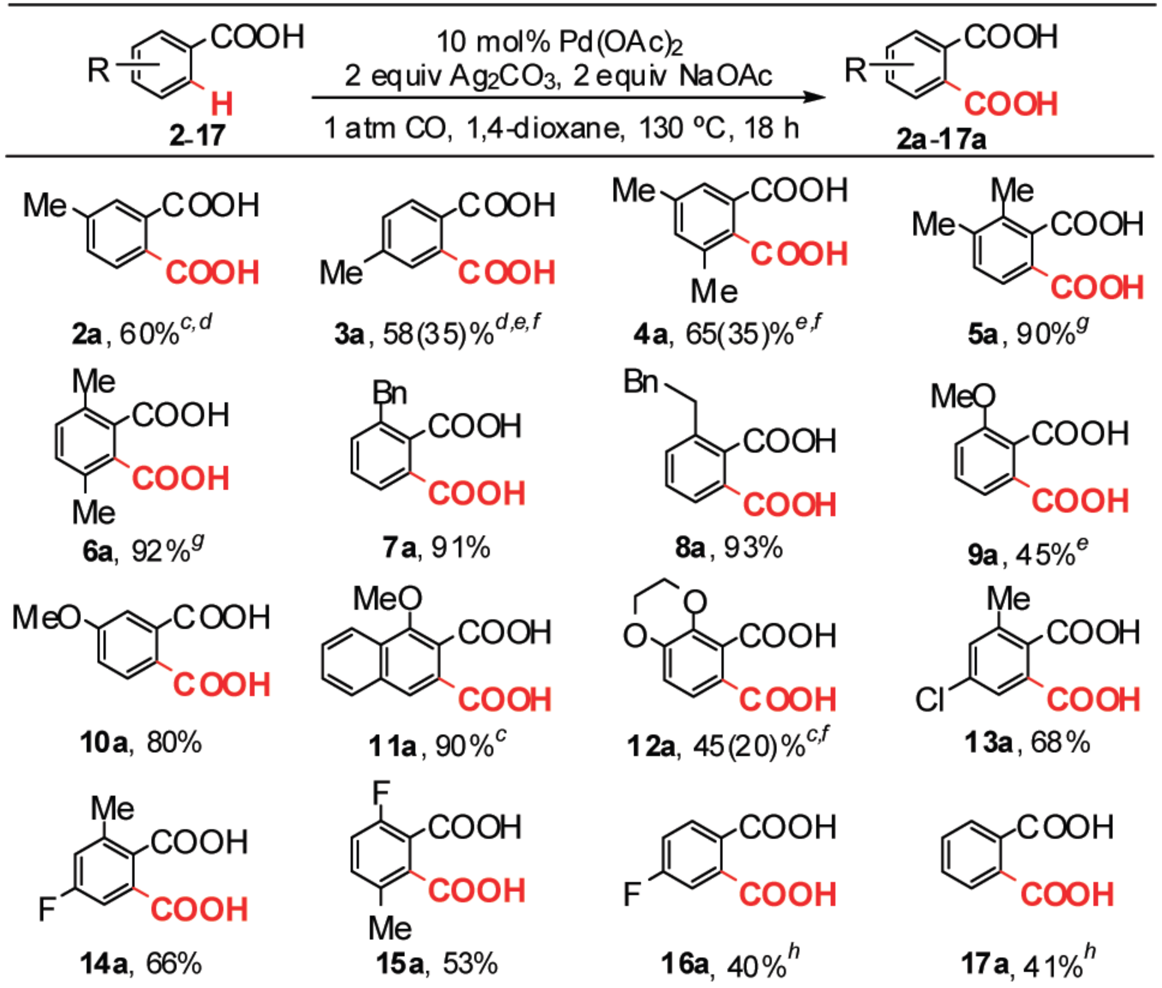
Carboxylation of aryl and vinyl C-H bonds





C-C coupling with palladium

Carboxylation of aryl and vinyl C-H bonds (benzoic acids)



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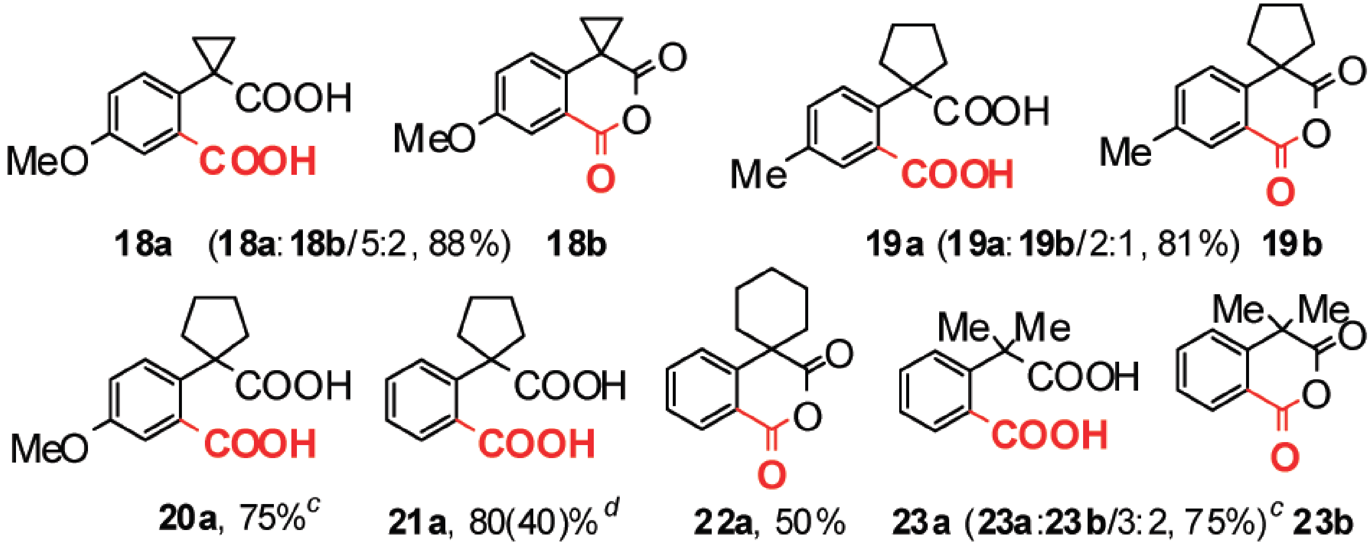
C-C coupling with palladium

Carboxylation of aryl and vinyl C-H bonds (phenylacetic acids)



18a (**18a**: **18b**/5:2, 88%) **18b**

19a (**19a**: **19b**/2:1, 81%) **19b**

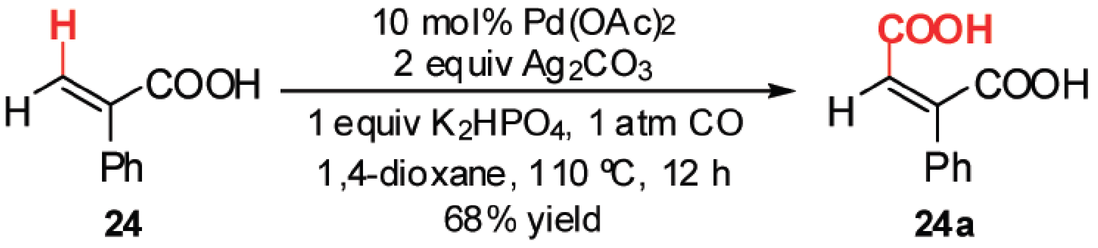
20a, 75%[c]

21a, 80(40)%[d]

22a, 50%

23a (**23a**:**23b**/3:2, 75%)[c] **23b**

Carboxylation of aryl and vinyl C-H bonds (unsaturated carboxylic acids)



10 mol% $Pd(OAc)_2$
2 equiv Ag_2CO_3
1 equiv K_2HPO_4, 1 atm CO
1,4-dioxane, 110 ℃, 12 h
68% yield

24 **24a**

(1)

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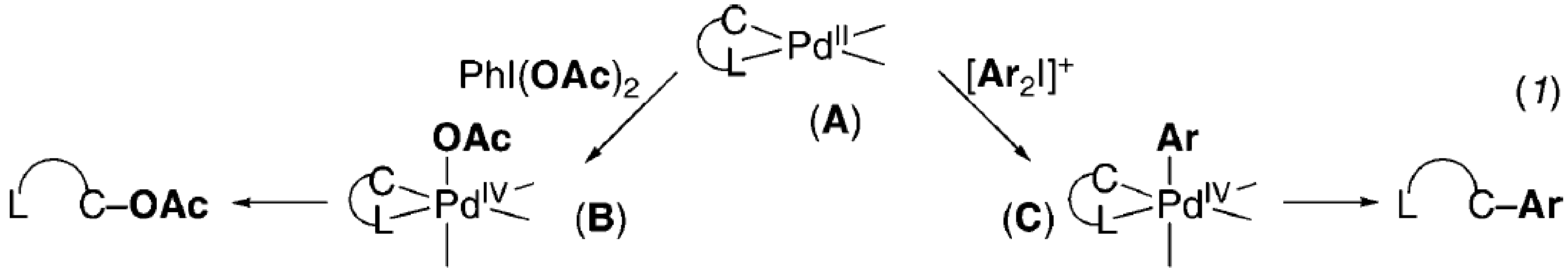
C-C coupling with palladium

Disanvantage of transmetallation reactions is that two functional starting materials are needed.

An alternative strategy for C-C coupling includes C-H activation and ”arylation”

In general, this would facilitate late stage construction of C-C bond in multistep synthesis.



L = pyridine, quinoline, oxazolidinone, pyrrolidinone, amide, etc

Pd (IV)

iodine(III) agents are needed

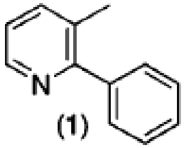
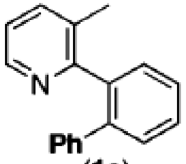
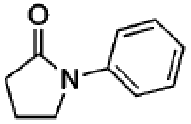
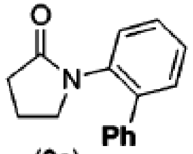
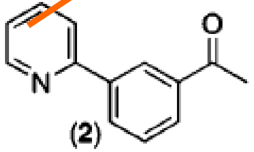
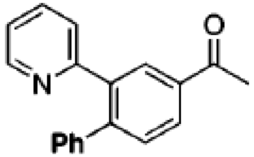
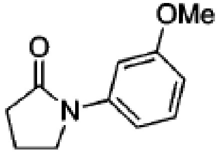
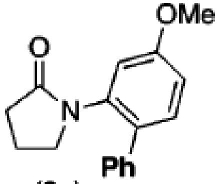
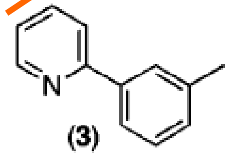
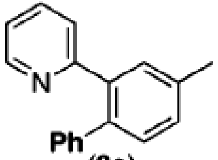
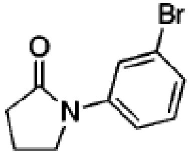
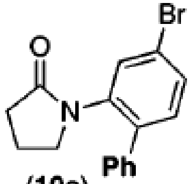
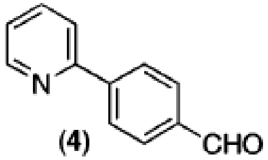
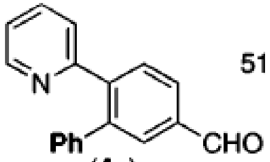
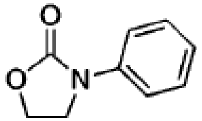
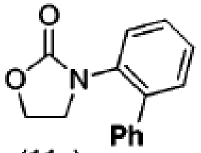
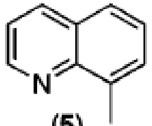
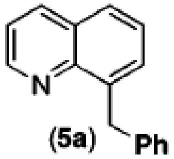
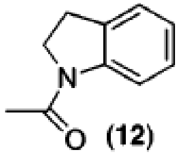
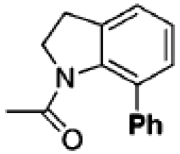
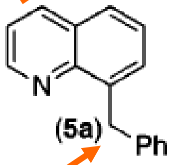
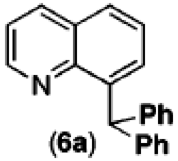
$[Ph_2I]^+ BF_4^-$

Ligand directed C-H activation!

Reductive elimination from **B** proceeds via C-O bond forming

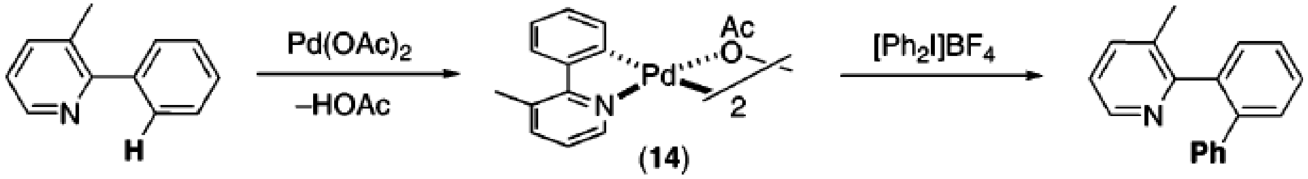
R. E. from **C** generates C-C bond

Table 1. Palladium-Catalyzed Phenylation of C−H Bonds[a]

Entry	Substrate	Product	Yield	Entry	Substrate	Product	Yield
1	 (1)	 (1a)	88%	8	 (8)	 (8a)	75%[c]
2	 (2)	 (2a)	91%	9	 (9)	 (9a)	84%[c]
3	 (3)	 (3a)	74%	10	 (10)	 (10a)	78%
4	 (4)	 (4a)	51%[e]	11	 (11)	 (11a)	83%[c]
5	 (5)	 (5a)	72%[b]	12	 (12)	 (12a)	49%[e]
6	 (5a)	 (6a)	60%[d]				

C-C coupling with palladium

If Pd(0) is applied in the reaction, the yield is <1%.



14 undergoes stoichiometric and rapid reaction with $[Ph_2I]BF_4$

With Ph-I or Ph-OTf the yield is below reaction <1%.

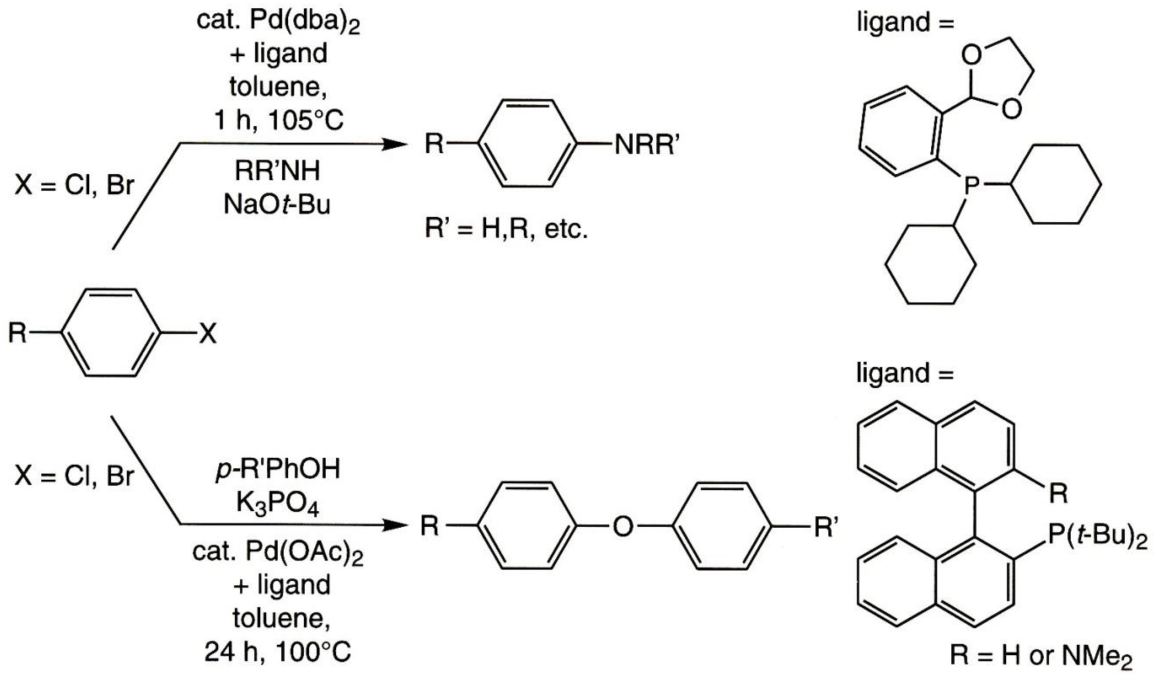
C-O and C-N coupling with palladium

Same principles as applied in C-C coupling starting from organic halides.

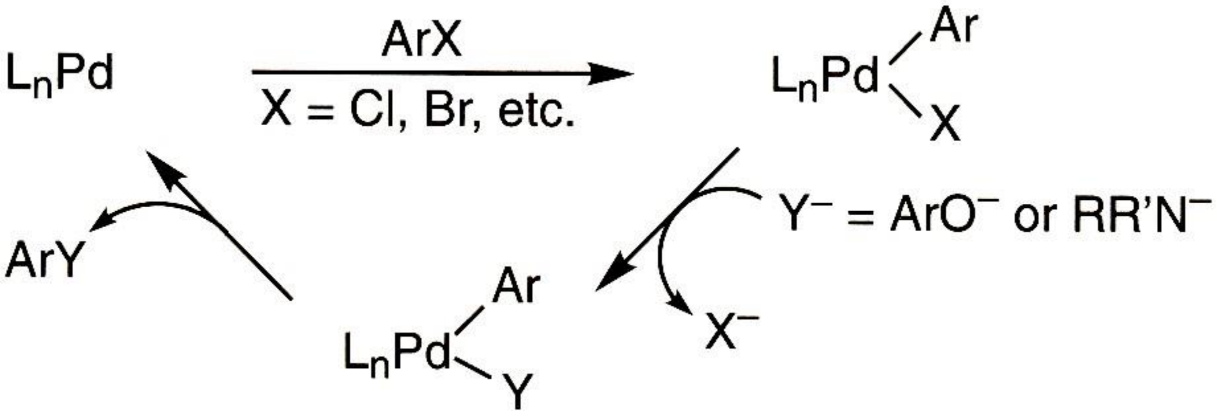
Aryl halides can be coupled to phenols > unsymmetric aryl ethers

Nature of halides in aryls is important: reactivity has order Cl > Br > I

Pd(0) and electron-rich and bulky phosphines are needed

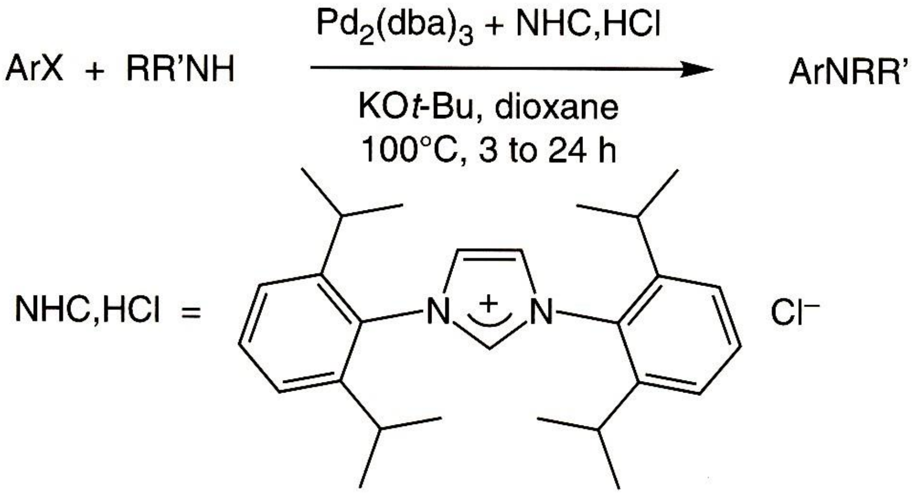


C-O and C-N coupling with palladium

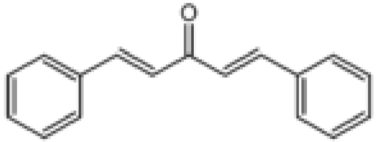


C-O and C-N coupling with palladium

Although phosphine-ligated Pd(0) complexes constitute the active catalysts in many C-N bond-forming cross-coupling methodologies, such complexes are usually difficult to prepare and extremely air sensitive.



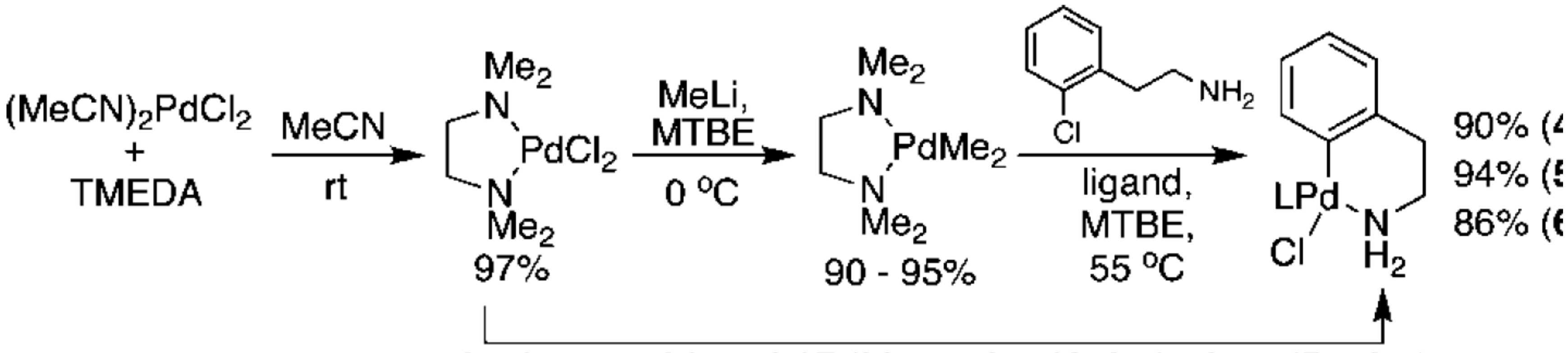
dba = dibenzylideneacetone



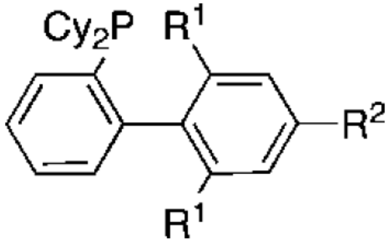
a stable source of Pd(0),

4-chlorotoluene, 4-chloroanisole, *ortho*-substituted aryl halides, and 2-chloropyridine are efficiently aminated with primary and secondary amines or anilines.

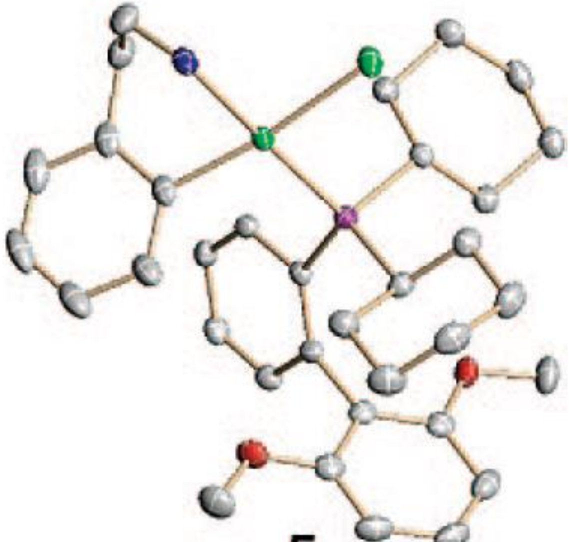
C-O and C-N coupling with palladium



In situ use of (tmeda)$PdMe_2$: 70% (**4**, 8 g); 85% (**5**, 12 g)



XPhos (**1**), R^1, R^2 = *i*-Pr
SPhos (**2**), R^1 = OMe, R^2 = H
RuPhos (**3**), R^1 = O*i*-Pr, R^2 = H



5

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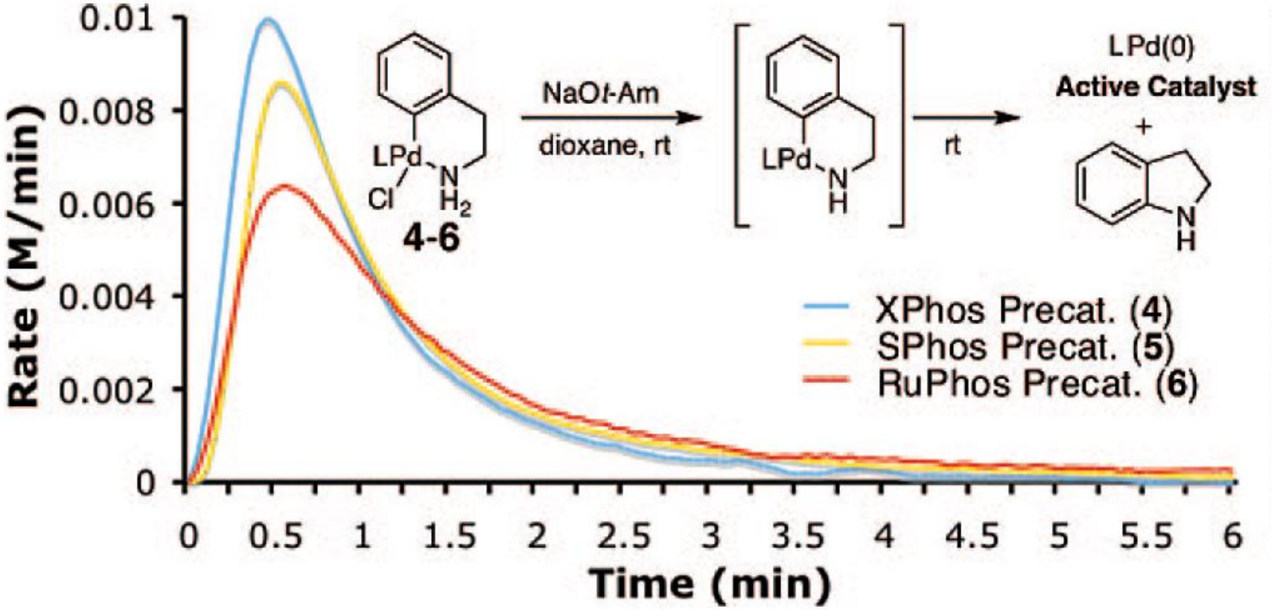
C-O and C-N coupling with palladium



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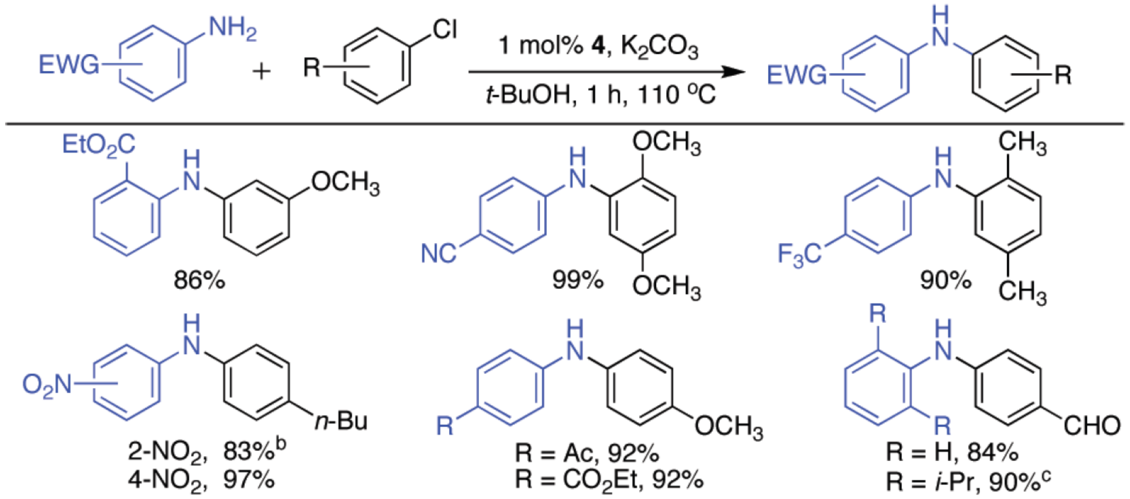
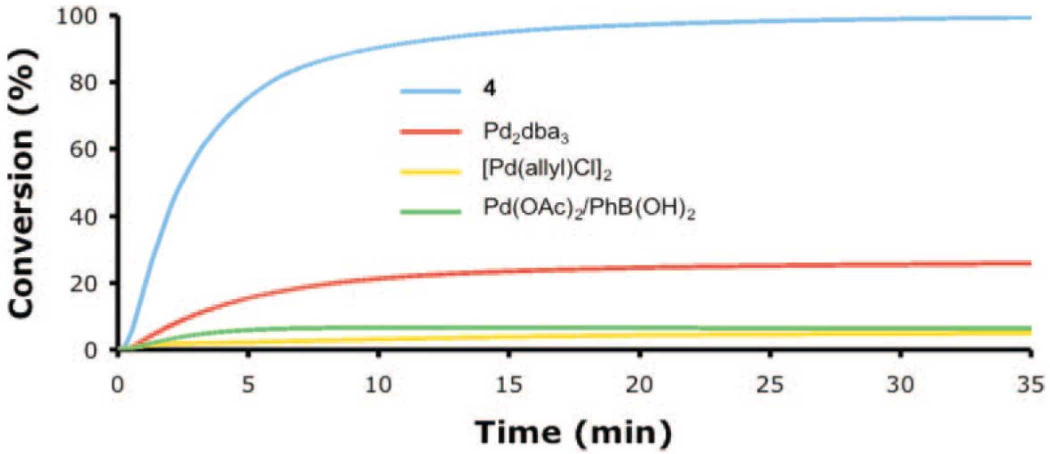
C-O and C-N coupling with palladium

Because of low nucleophilicity, electron deficient anilines are difficult to employ in C-N cross-coupling reactions.





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C-F coupling with palladium

The substitution of hydrogen for fluorine can have a profound effect on the biological activity, metabolism, solubility, hydrophobicity, and bulk properties of organic substances.

Molecules containing carbon-fluorine bonds are extremely important as pharmaceuticals, imaging agents, fine chemicals, and materials.

Relatively few synthetic approaches for the formation of C-F bonds are currently available, and transition metal catalyzed methods for C-F bond construction are particularly rare.

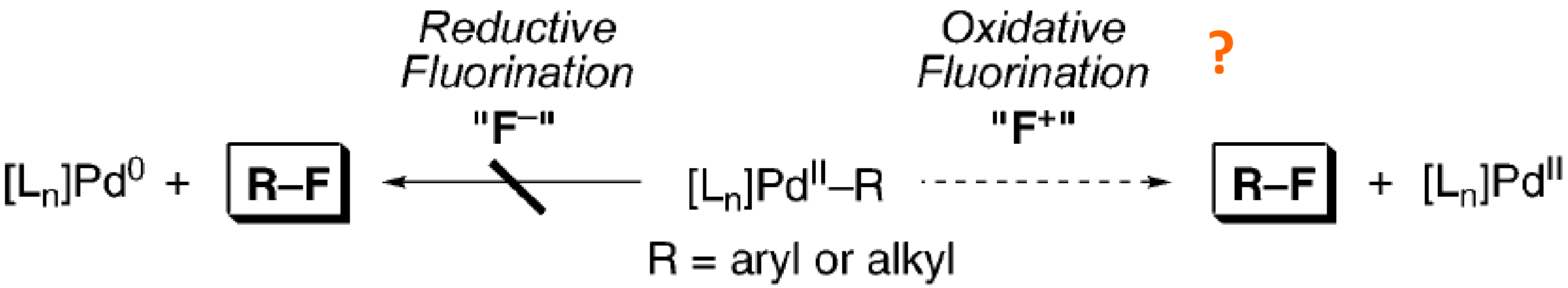
Oxidative addition of an aryl or alkyl halide (R-X) to Pd^0 is known

Metathesis of X- with F- at the resulting *o*-alkyl/aryl PdII complex is known.

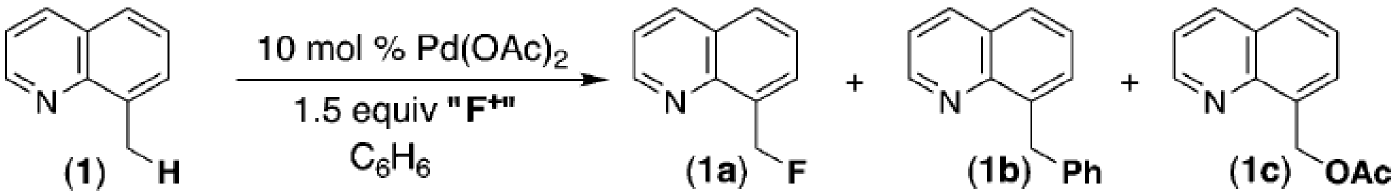
However, C-F bond-forming reductive elimination to release the fluorinated product is not available with Pd(II).

C-F coupling with palladium

What is F^+?

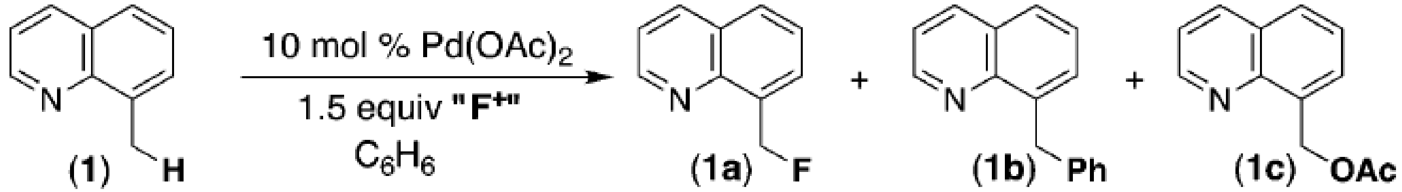


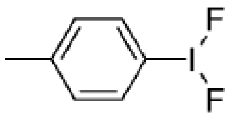
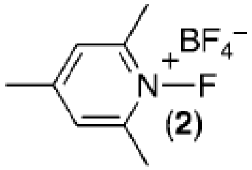
Carbon-fluorine bond formation in these systems could proceed by direct electrophilic attack of F^+ on the Pd^{II}-C bond or via oxidation to Pd^{IV} followed by C-F bond-forming reductive elimination.



8-Methylquinoline

C-F coupling with palladium



	25% (12%)	8% (3%)
	82% (36%)	**97% (75%)**

compare iodine(III) in arylation!

N-fluoro-2,4,6-trimethyl pyridinium tetrafluoro borate (oxidant)

[a] Conditions: 110 °C, 18 h. [b] Conditions: 110 °C, 1 h, 200 W.

8-Methylquinoline undergoes facile quinoline –directed C-H activation (oxidative addition), followed by reductive elimination of acetic acid.

C-F coupling with palladium

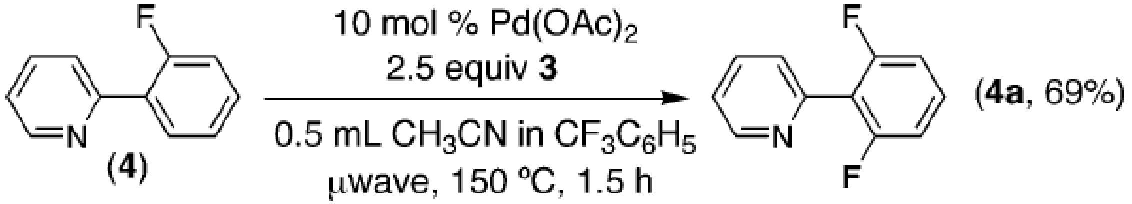
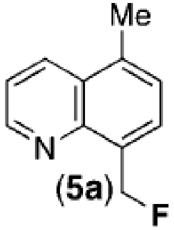
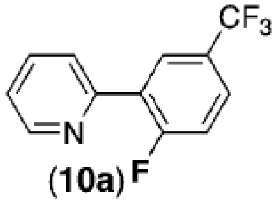
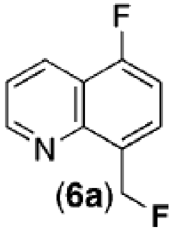
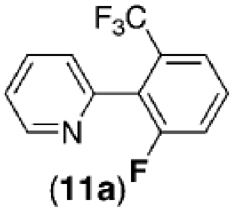
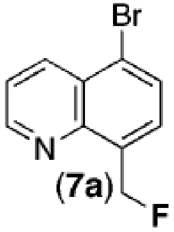
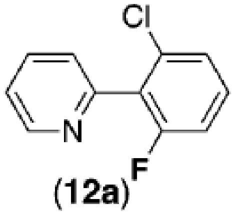


Table 2. Substrate Scope of Pd-Catalyzed C−H Bond Fluorination

entry	oxidant	product	isolated yield	entry	oxidant	product	isolated yield
1	**2**	 **(5a)**	57%^{a}	7	**3**	 **(10a)**	75%^{b}
2	**2**	 **(6a)**	49%^{a}	8	**3**	 **(11a)**	59%^{b}
3	**2**	 **(7a)**	53%^{a}	9	**3**	 **(12a)**	50%^{b}