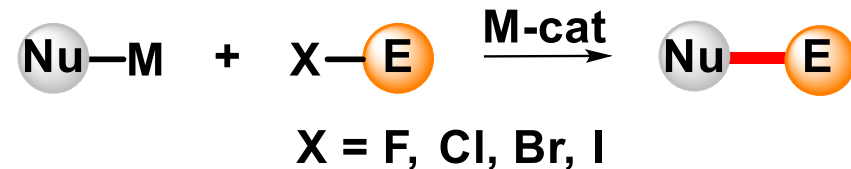
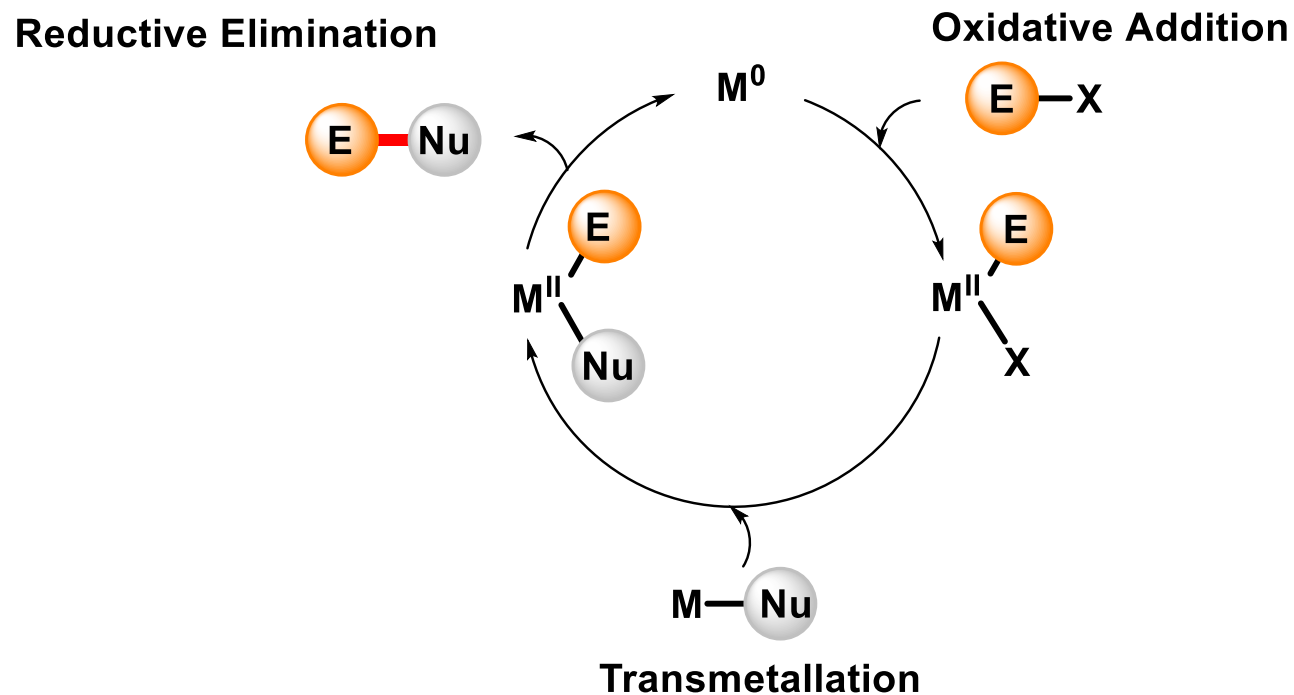


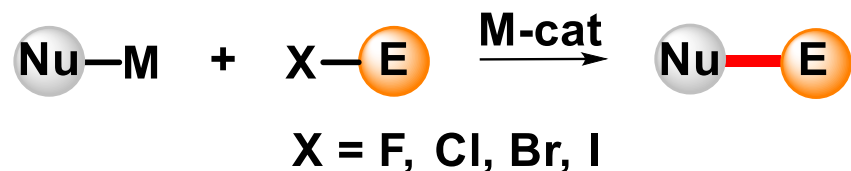
## ➤ General scheme for transition-metal-catalyzed cross-coupling reactions



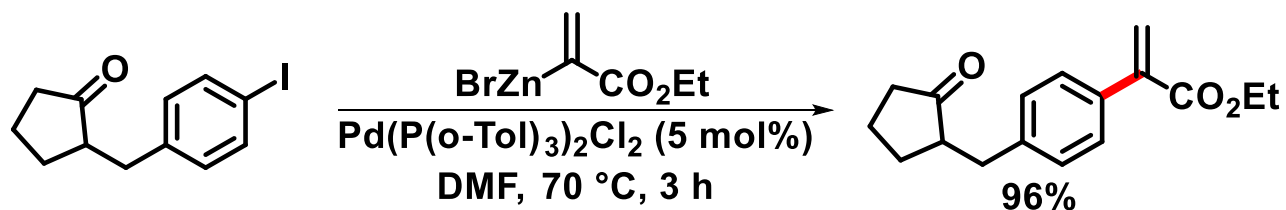
- Simplified mechanism



## ➤ General scheme for transition-metal-catalyzed cross-coupling reactions

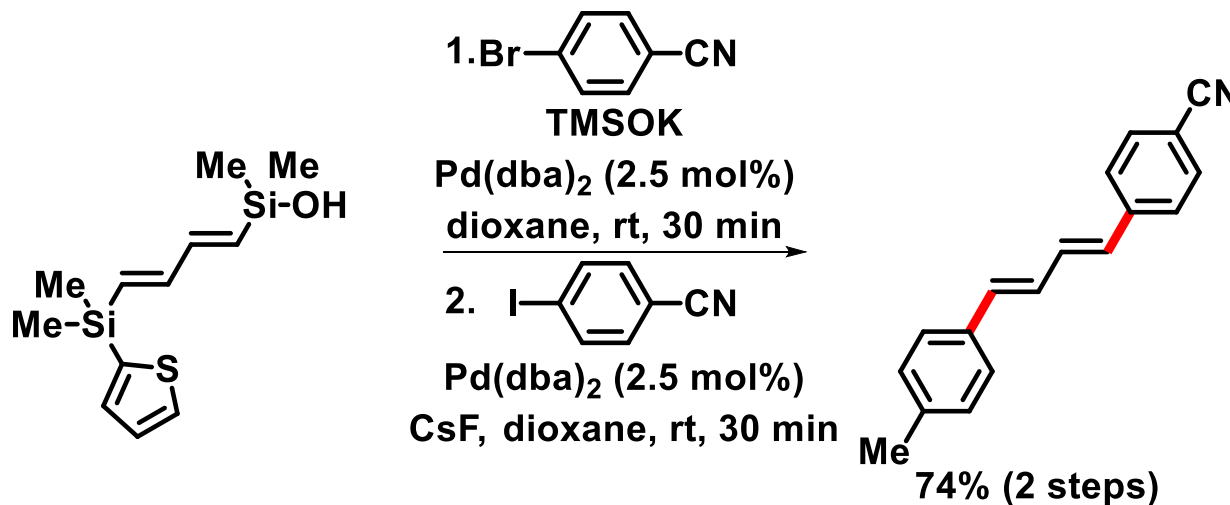


### Negishi reaction



*Synthesis* **2002**, 2681.

### Hiyama reaction



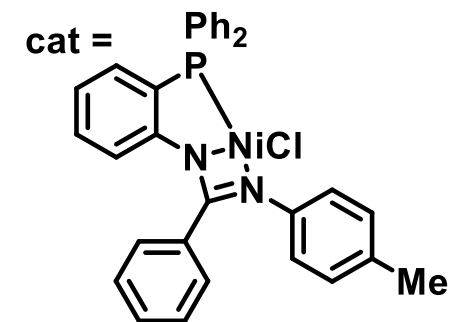
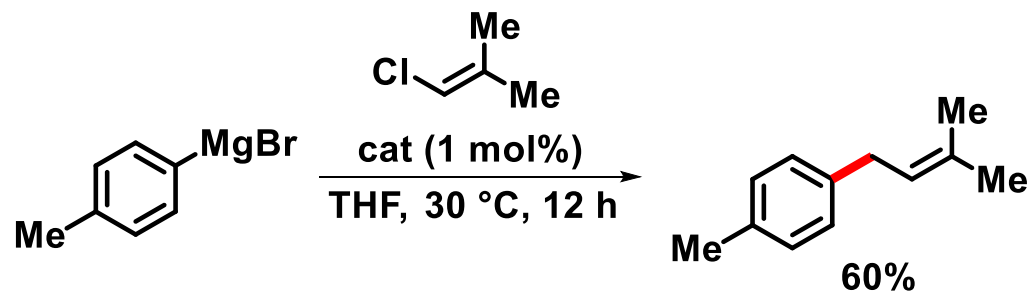
*J. Am. Chem. Soc.* **2005**, *127*, 8004

## ➤ General scheme for transition-metal-catalyzed cross-coupling reactions



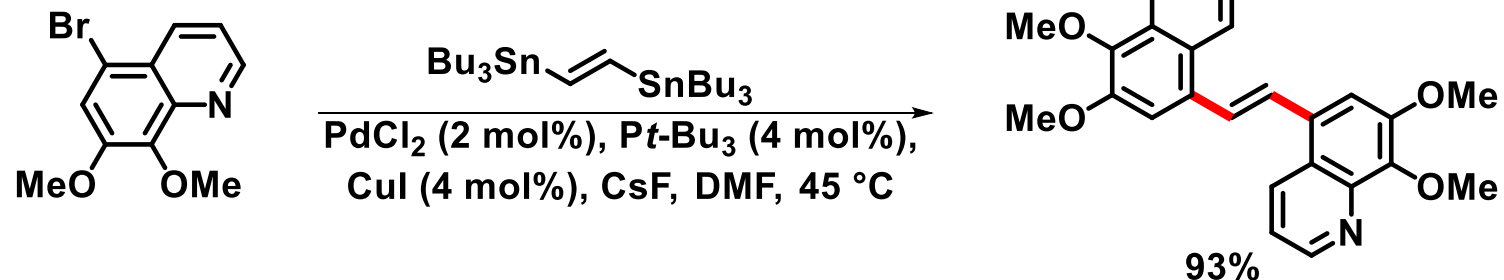
X = F, Cl, Br, I

### Kumada reaction (Kumada–Tamao–Corriu)



*Synlett* 2013, 2081.

### Stille reaction (Migita–Kosugi–Stille)

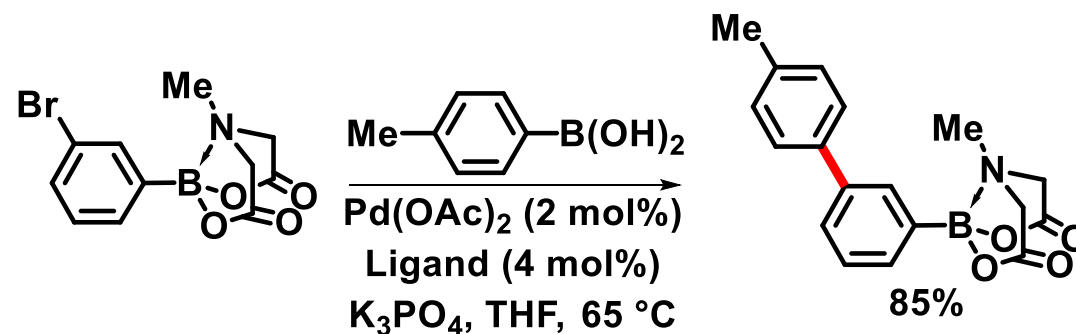


*Angew. Chem. Int. Ed.* 2004, 43, 1132.

## ➤ General scheme for transition-metal-catalyzed cross-coupling reactions

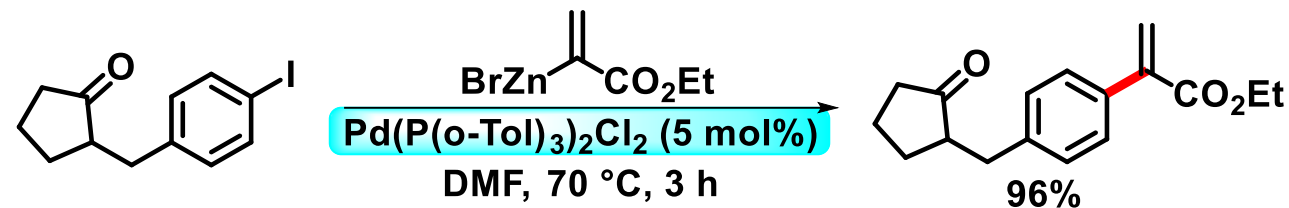


### Suzuki reaction (Suzuki–Miyaura)



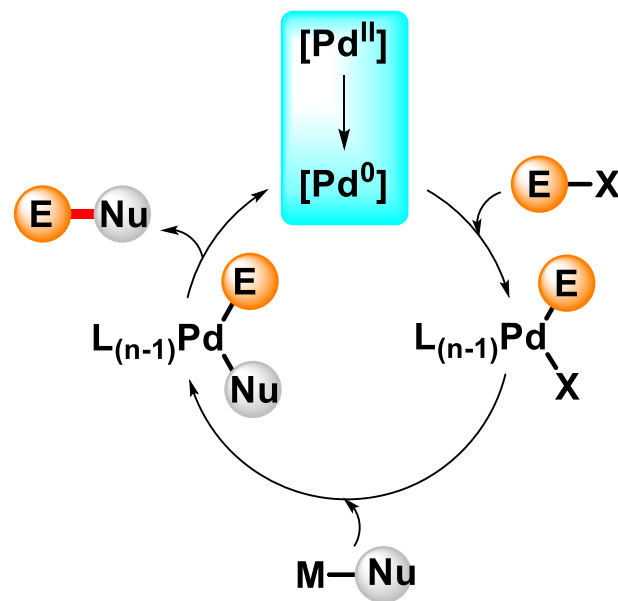
*J. Am. Chem. Soc.* 2007, 129, 6716

## ➤ General scheme for transition-metal-catalyzed cross-coupling reactions



*Synthesis* 2002, 2681.

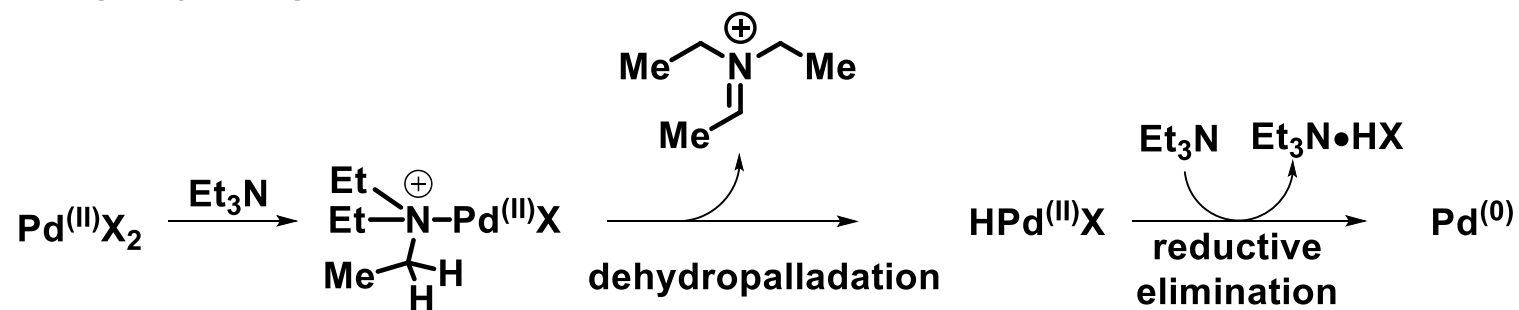
- Simplified mechanism



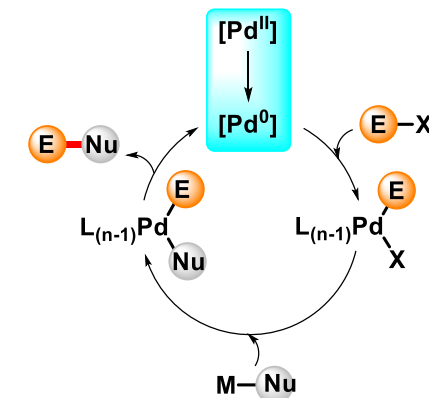
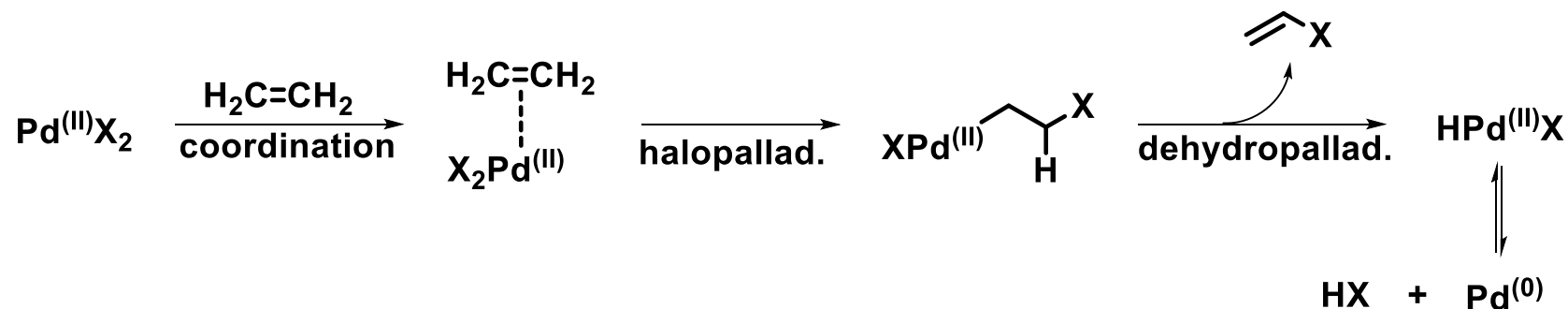
## ➤ Pd<sup>(0)</sup>–Pd<sup>(II)</sup>–Pd<sup>(0)</sup> catalytic cycle

- Generation of Pd<sup>0</sup> from Pd<sup>II</sup>

- From amine

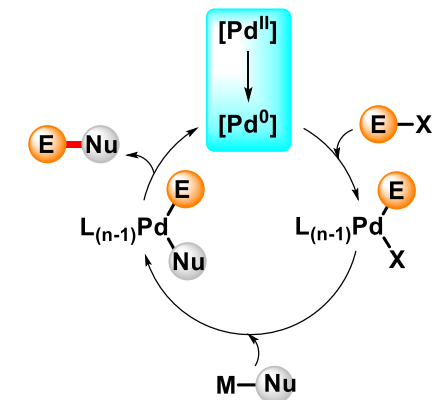
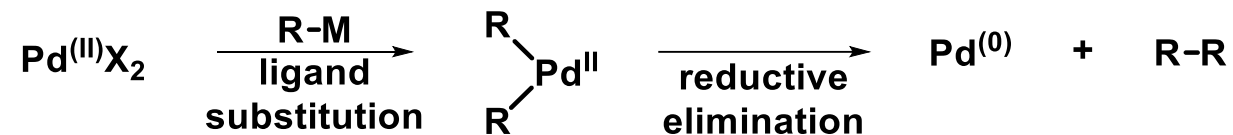


- From alkene



## ➤ Pd<sup>(0)</sup>–Pd<sup>(II)</sup>–Pd<sup>(0)</sup> catalytic cycle

- Generation of Pd<sup>0</sup> from Pd<sup>II</sup>
  - By transmetalation



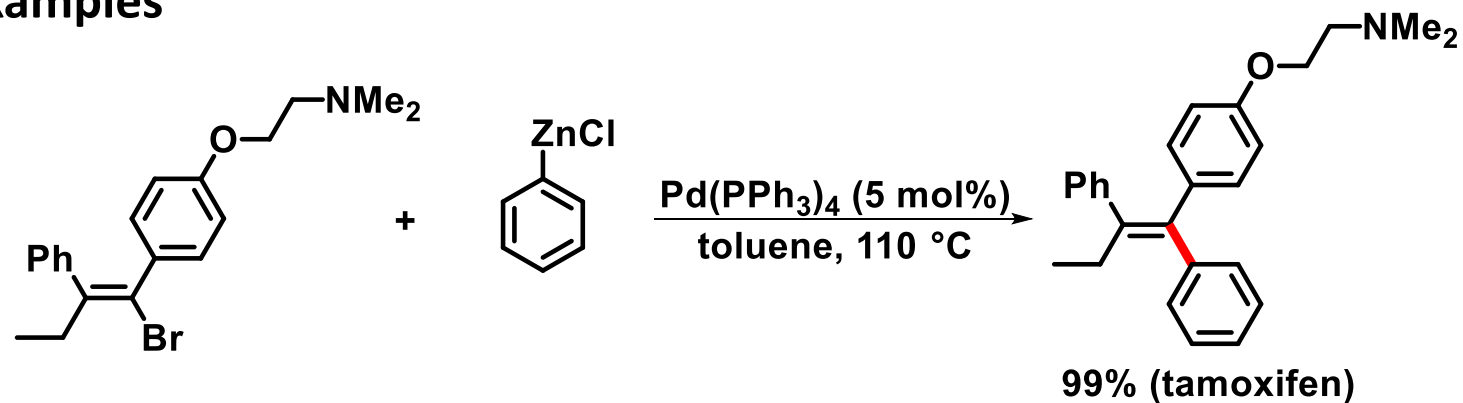
- From phosphine



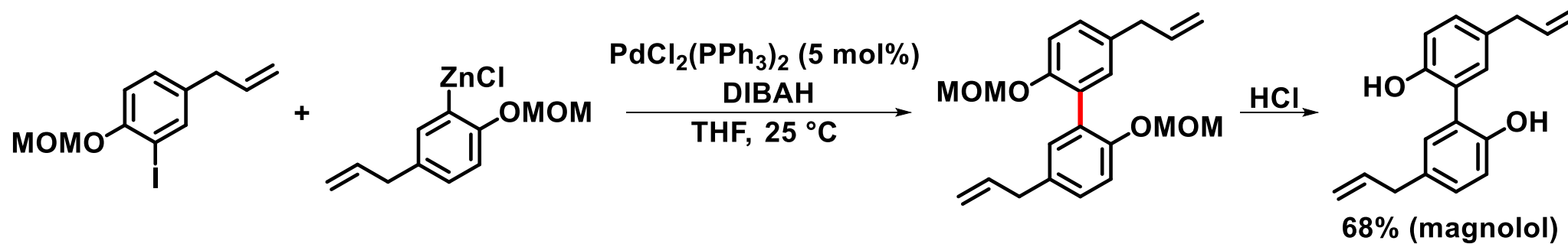
## ➤ Negishi Reaction



- Selected examples



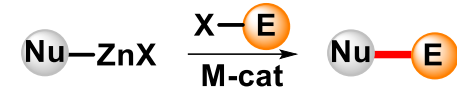
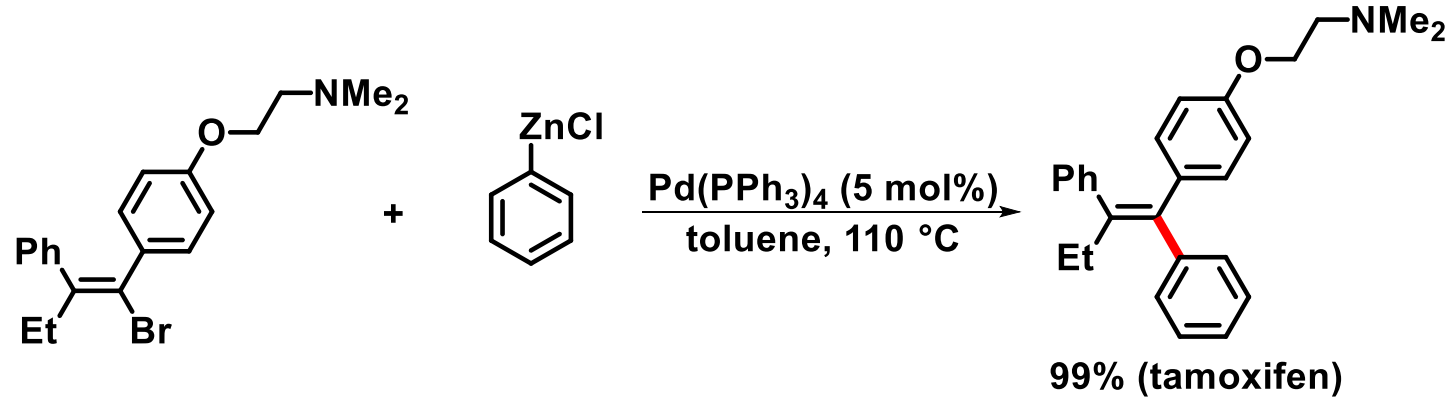
*J. Org. Chem.* **1990**, *55*, 6184



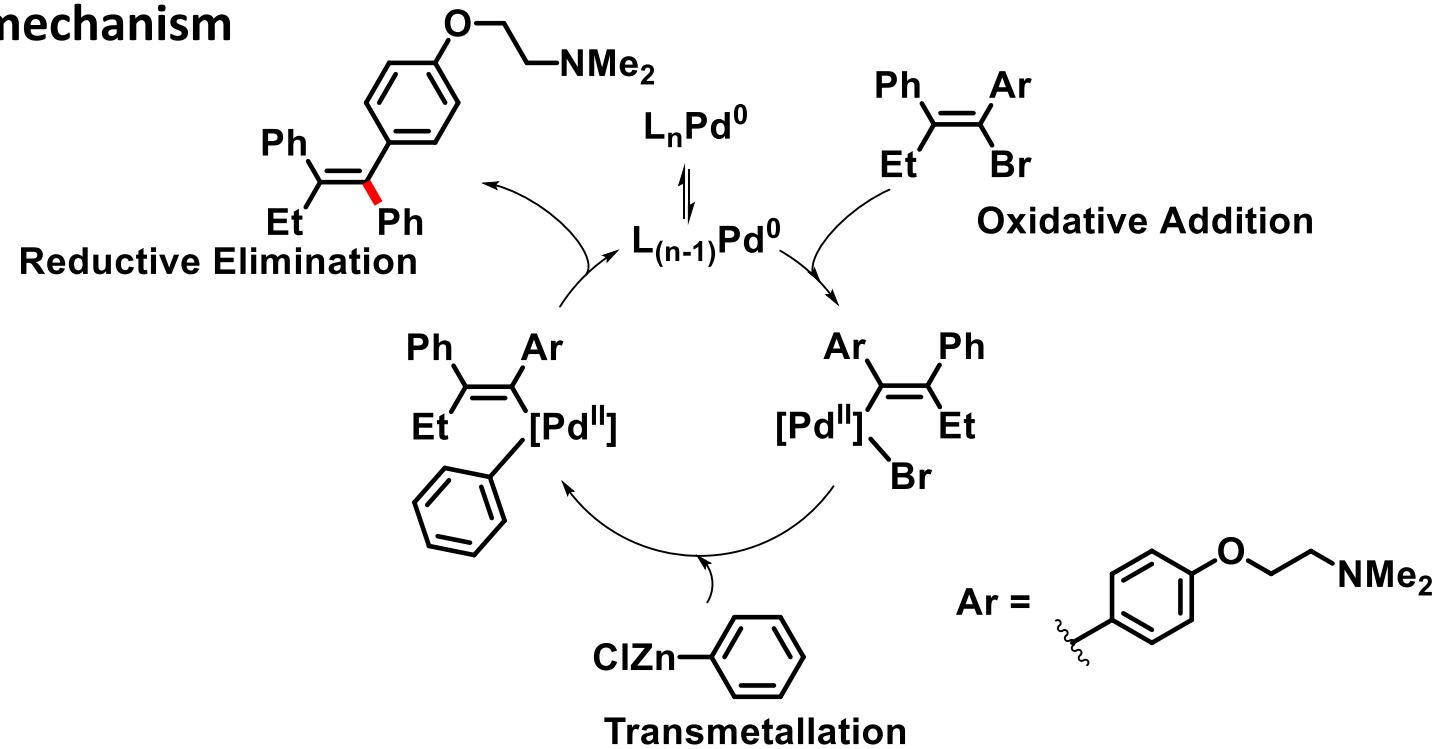
*J. Org. Chem.* **1995**, *60*, 1856



## ➤ Negishi Reaction

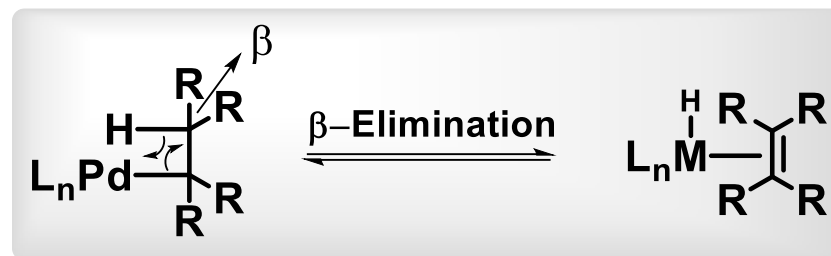
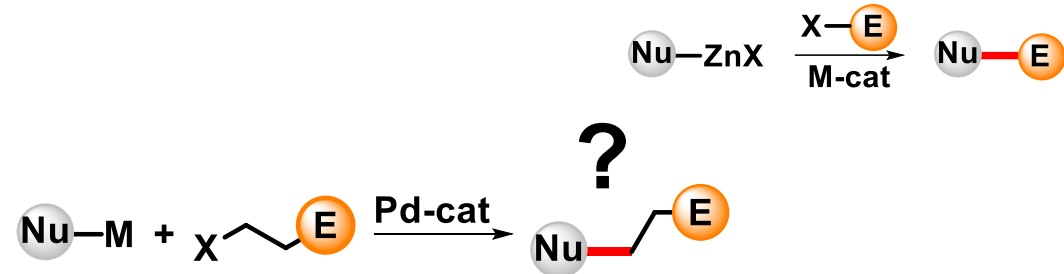


- Generally accepted mechanism



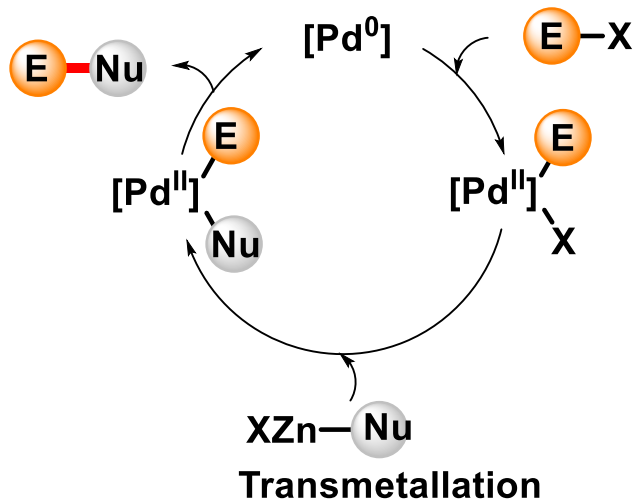
## ➤ Negishi Reaction

- Side reactions –  $\beta$ -elimination

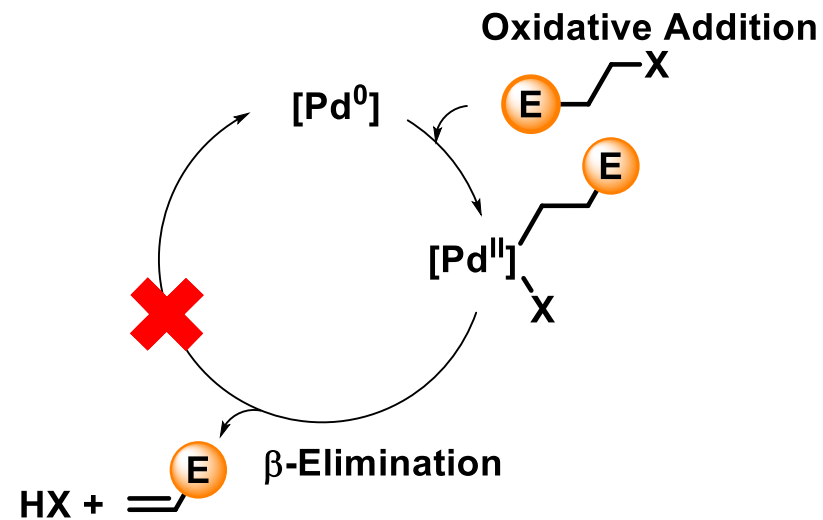


Reductive Elimination

Oxidative Addition



Oxidative Addition

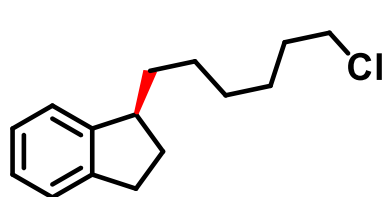


## ➤ Negishi Reaction

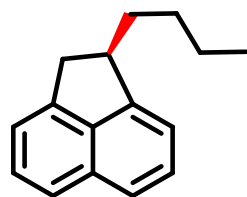
- Side reactions –  $\beta$ -elimination



$\text{NiBr}_2 \cdot \text{diglym}$  (10 mol%)  
 $(\text{S})\text{-}i\text{Pr-PYBOX}$  (13 mol%)  
 DMA, rt

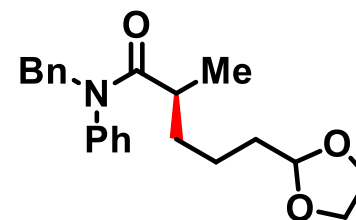


69 %, 94 % ee

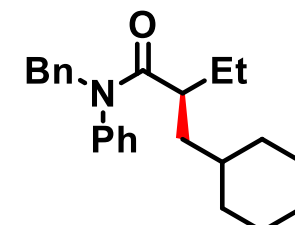


72 %, 98 % ee

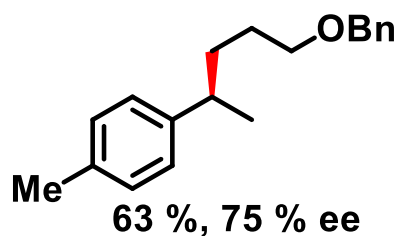
$\text{NiCl}_2 \cdot \text{DME}$  (10 mol%)  
 $(\text{R})\text{-}i\text{Pr-PYBOX}$  (13 mol%)  
 DMI/THF, rt



60 %, 98 % ee

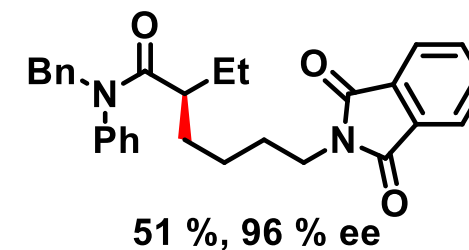
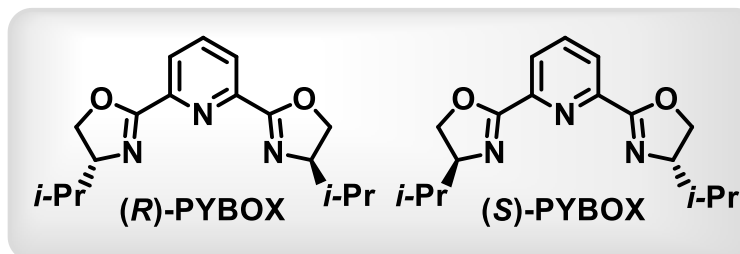


58 %, 92 % ee



63 %, 75 % ee

*J. Am. Chem. Soc.* **2005**, *127*, 10482



51 %, 96 % ee

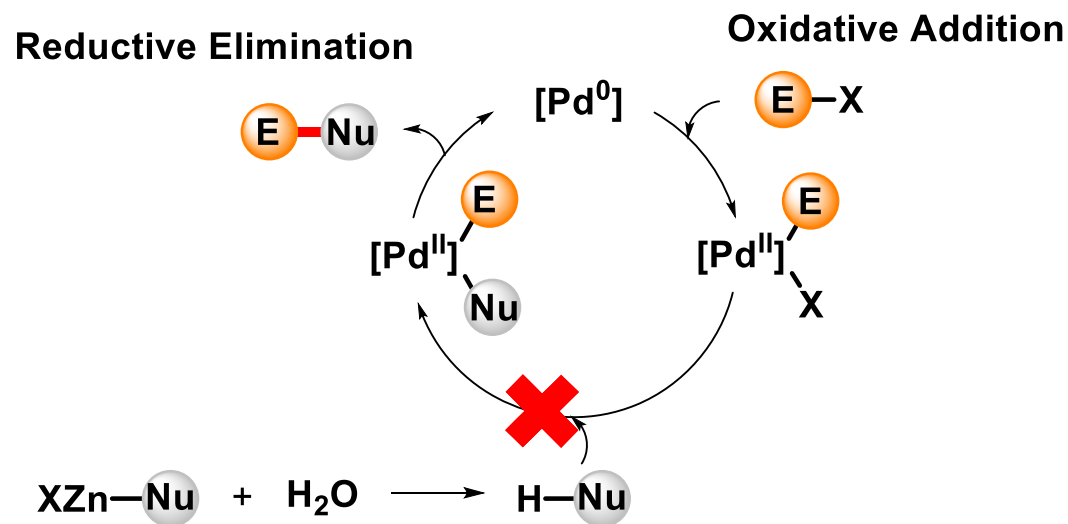
*J. Am. Chem. Soc.* **2005**, *127*, 4594

## ➤ Negishi Reaction

- Side reactions – Acid-base reaction



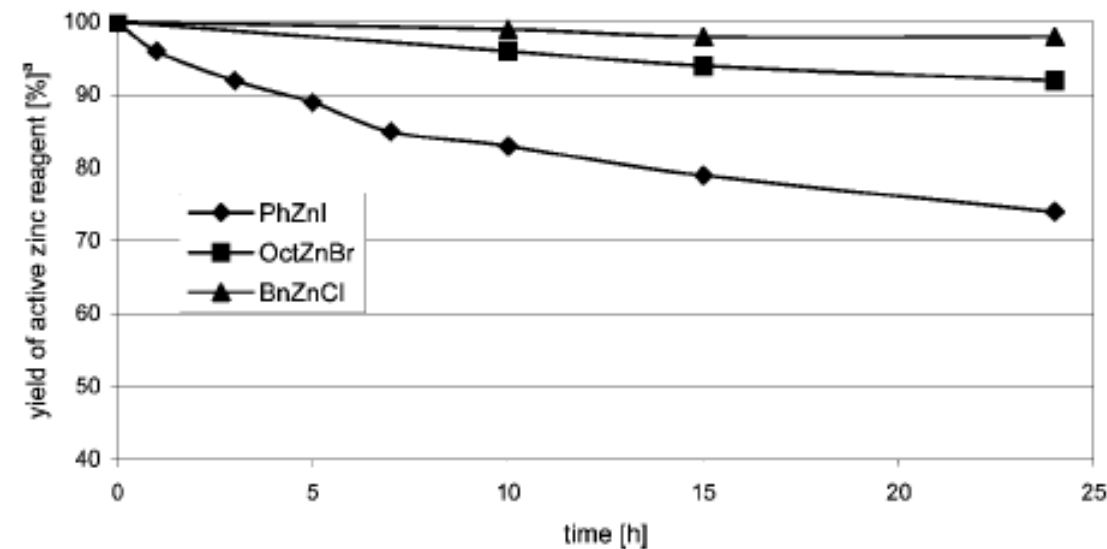
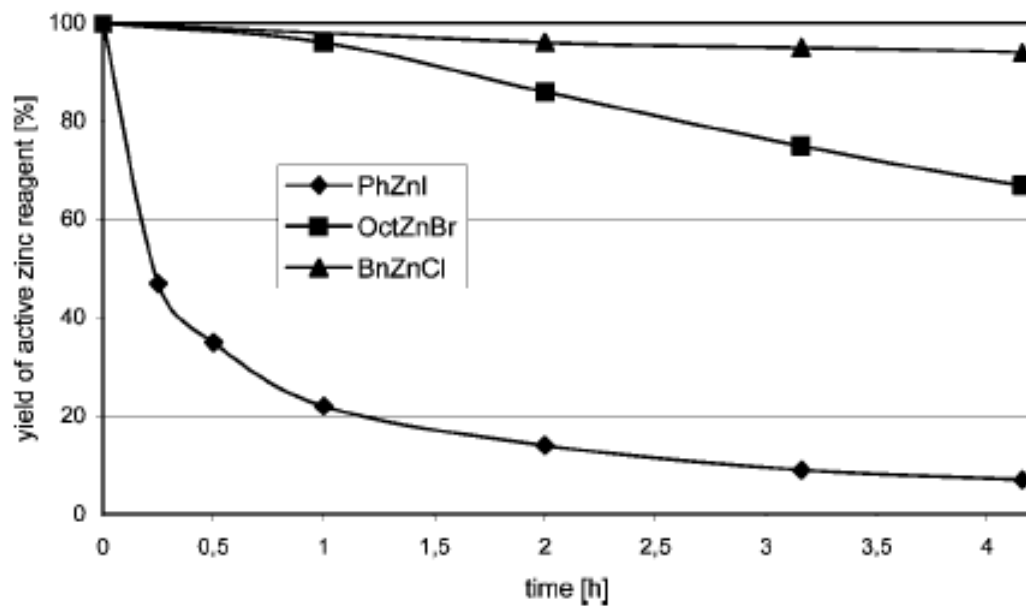
- Dry solvents (THF, Et<sub>2</sub>O, 1,4-dioxane, toluene)





## ➤ Negishi Reaction

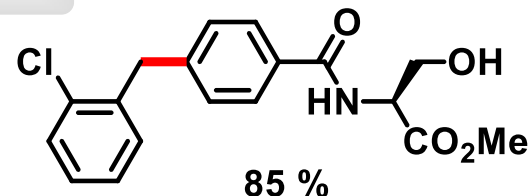
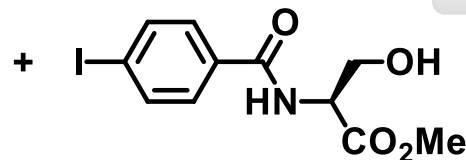
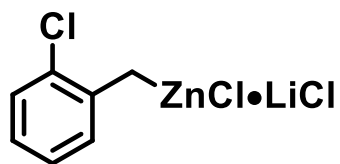
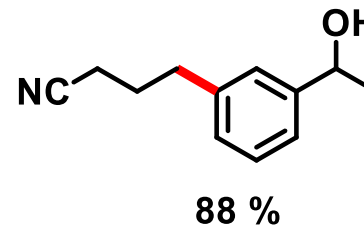
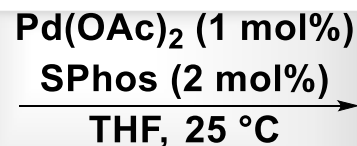
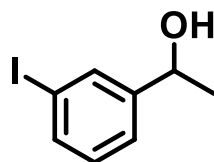
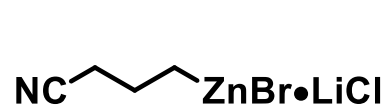
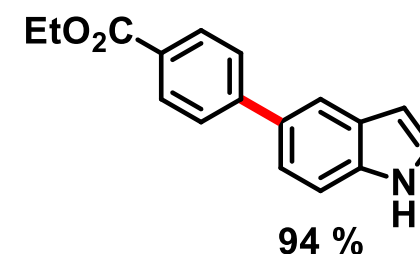
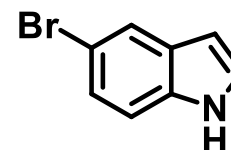
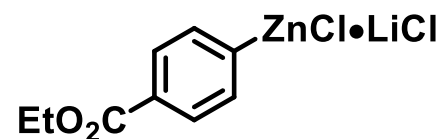
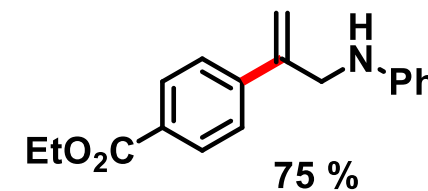
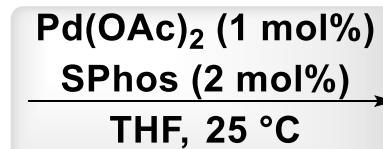
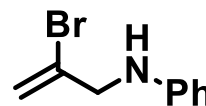
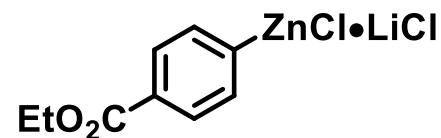
- Negishi reaction of substrates with acidic functional group



*J. Org. Chem.* 2008, 73, 8422

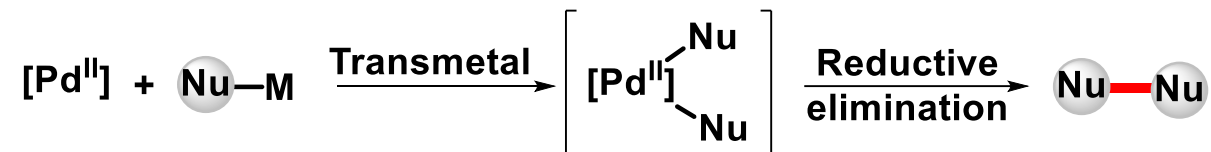
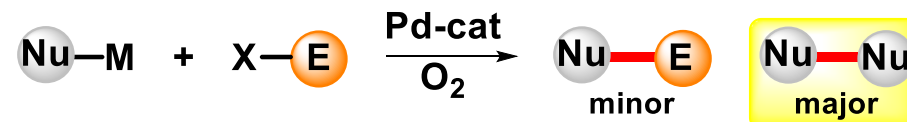
## ➤ Negishi Reaction

- Negishi reaction of substrates with acidic functional groups



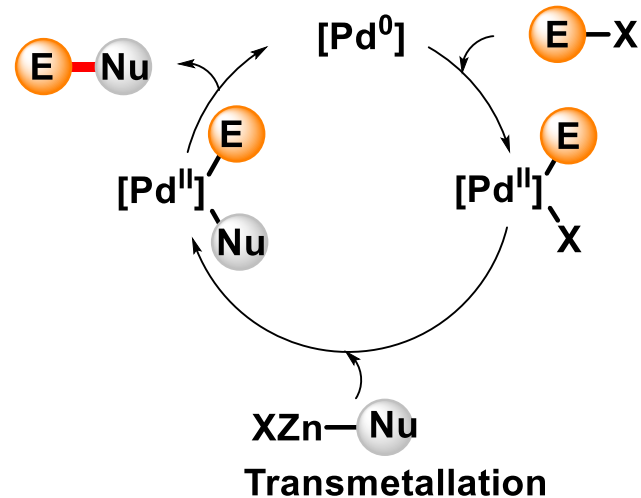
## ➤ Negishi Reaction

- Side reactions – oxidation

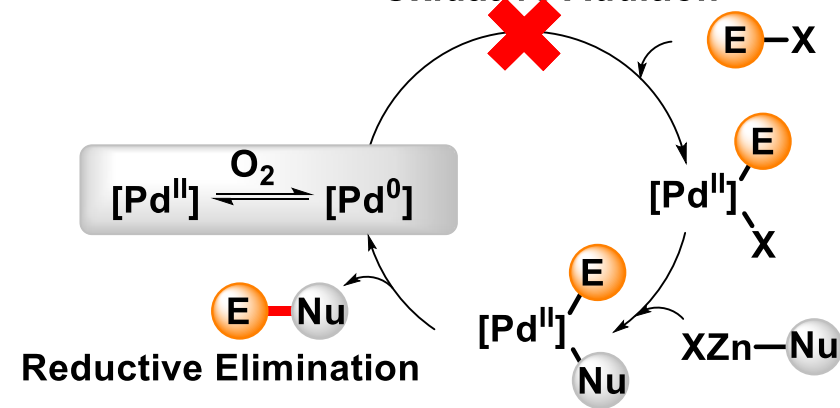


Reductive Elimination

Oxidative Addition



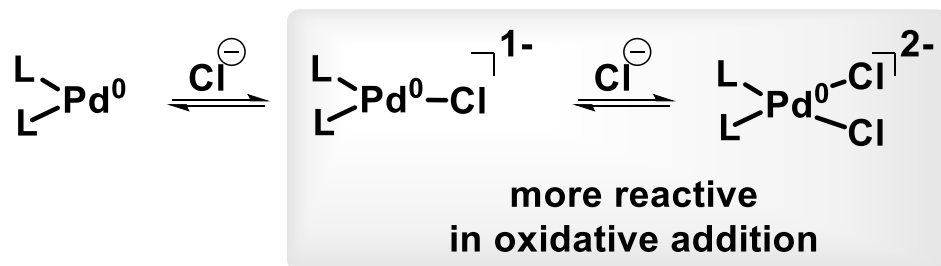
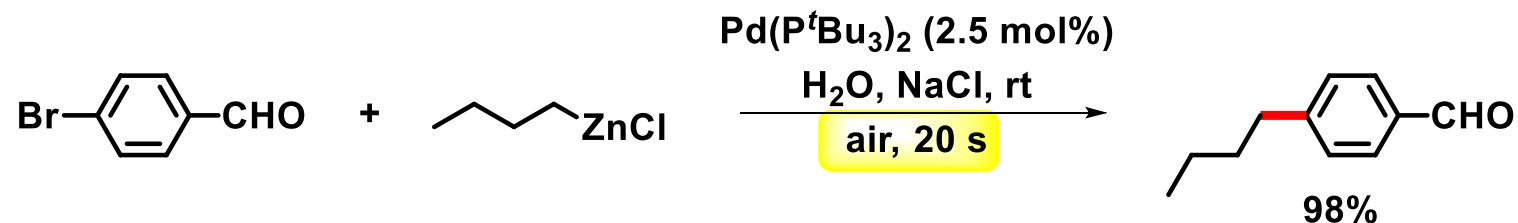
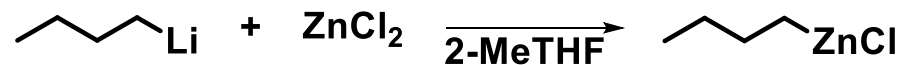
Oxidative Addition





## ➤ Negishi Reaction

- Negishi reaction „on water“ under aerobic conditions



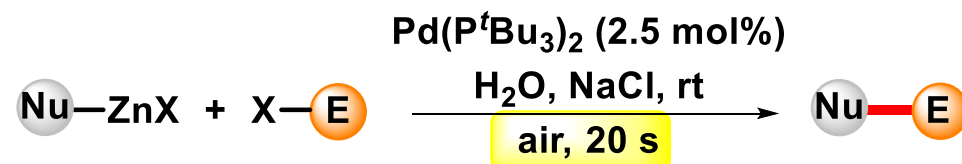
- LiCl maintains the longevity of Pd-phosphine catalyst and speed up the transmetalation step



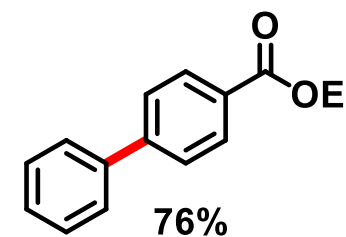
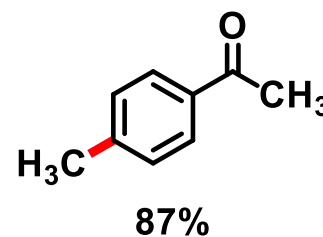
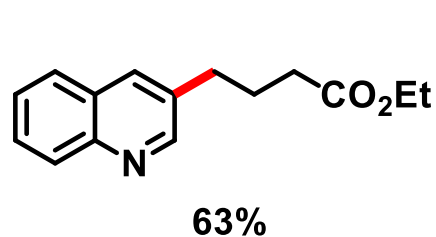
## ➤ Negishi Reaction



- Negishi reaction „on water“ under aerobic conditions



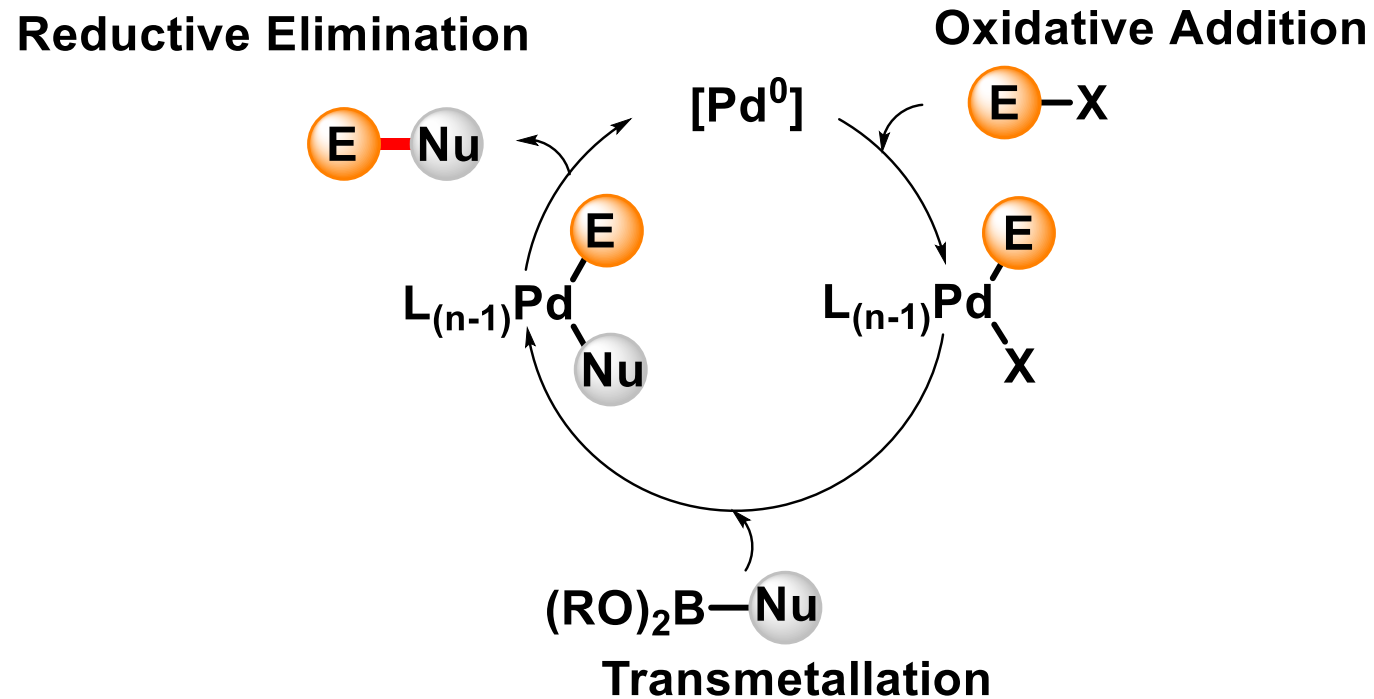
### ○ Selected examples

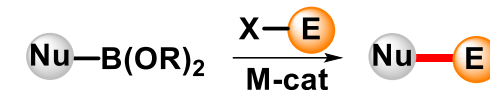


## ➤ Suzuki Reaction (Suzuki–Miyaura reaction)



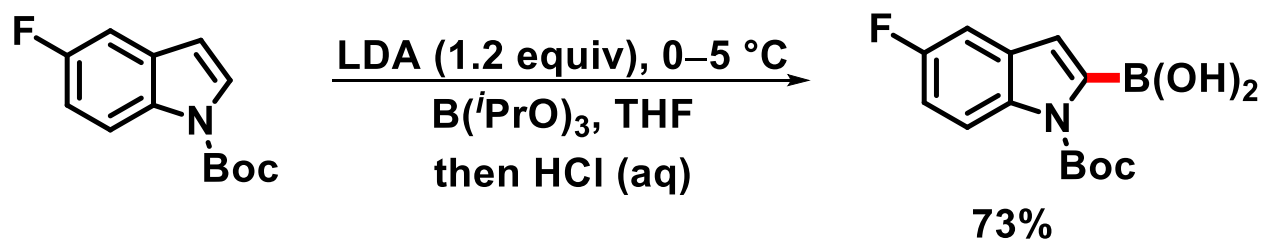
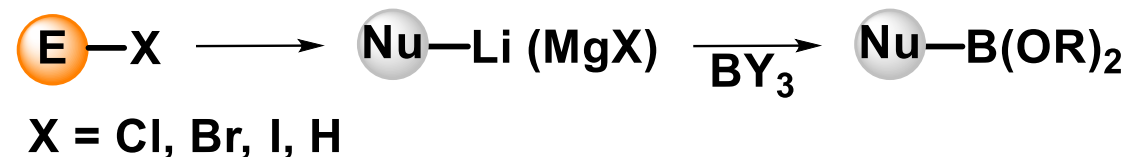
- Simplified mechanism



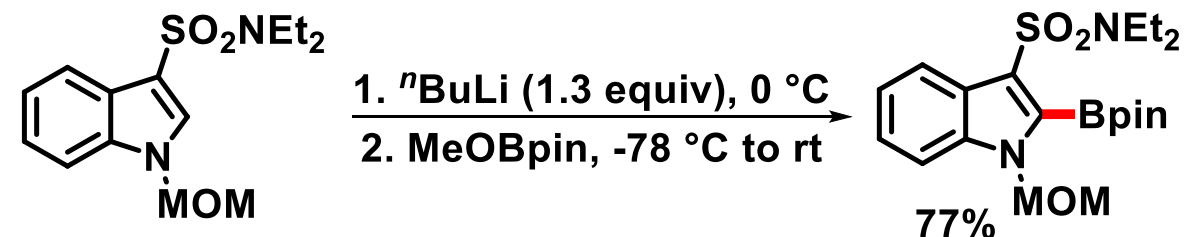


## ➤ Suzuki Reaction (Suzuki–Miyaura reaction)

- Synthesis of boronic acids or boronic acid esters
  - Li (Mg)→B Exchange reaction (suitable for arylboronic acids)



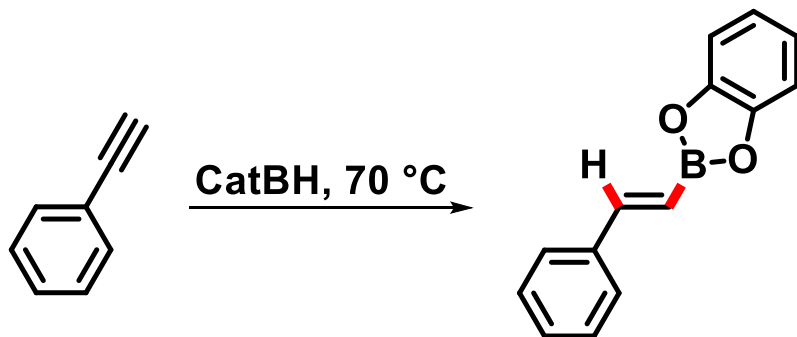
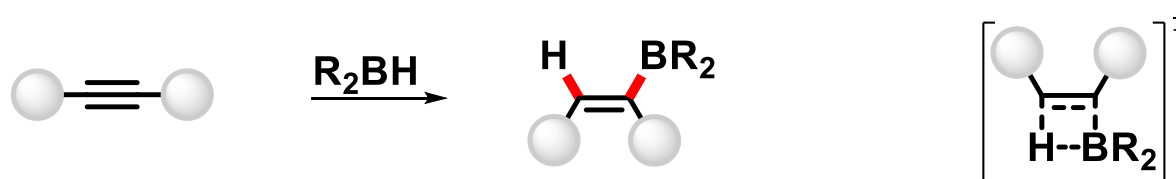
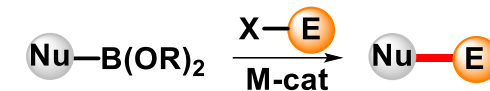
*J. Org. Chem.* 2002, 67, 7551.



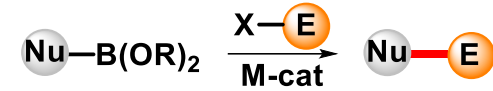
*Org. Lett.* 2011, 13, 3588

## ➤ Suzuki Reaction (Suzuki–Miyaura reaction)

- Synthesis of boronic acids or boronic acid esters
  - Syn hydroboration (suitable for vinylboronic acids)

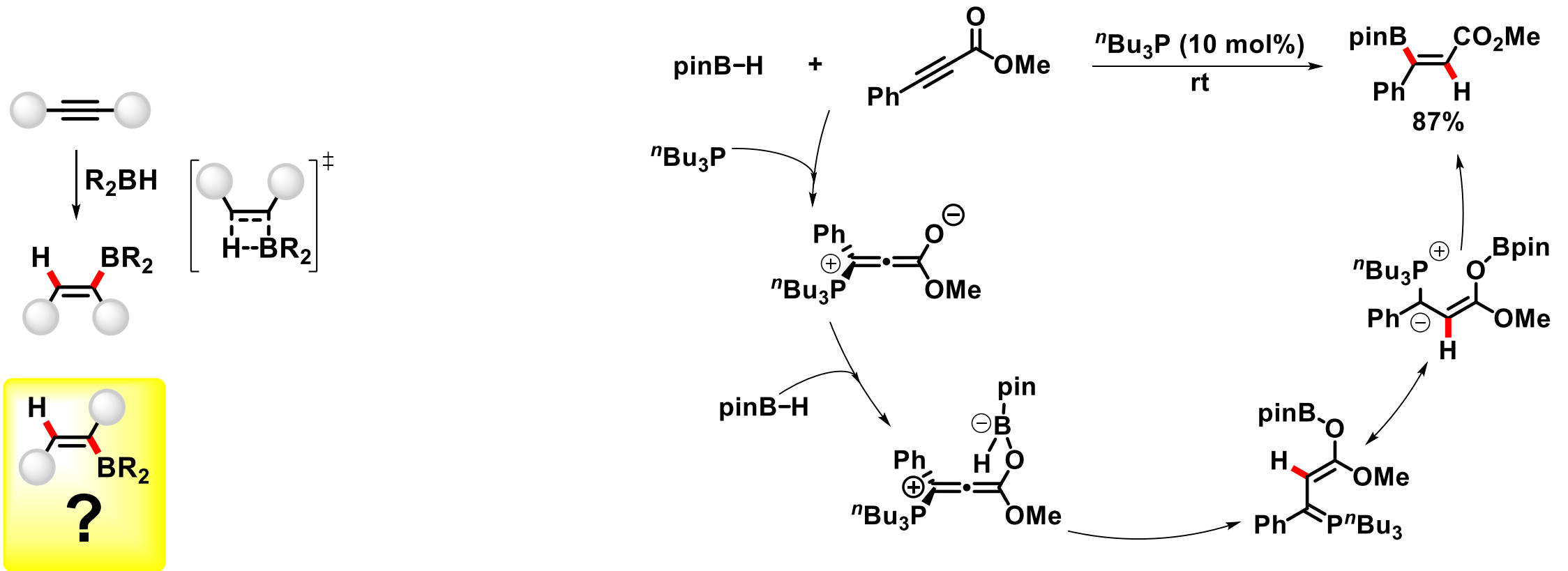


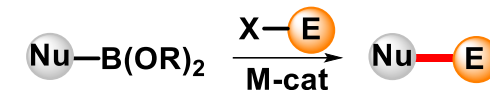
*J. Org. Chem.* 1980, 45, 389



## ➤ Suzuki Reaction (Suzuki–Miyaura reaction)

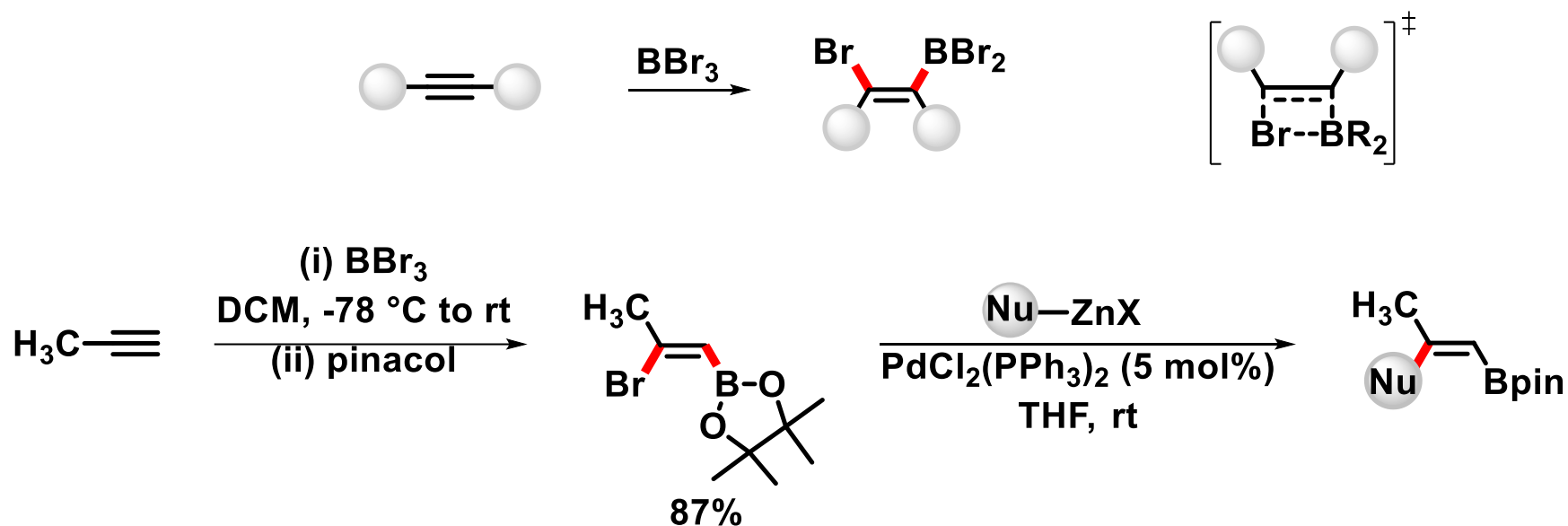
- Synthesis of boronic acids or boronic acid esters
  - Anti hydroboration (suitable for vinylboronic acids)



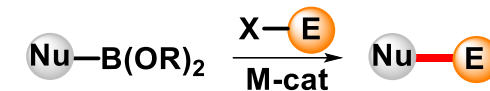


## ➤ Suzuki Reaction (Suzuki–Miyaura reaction)

- Synthesis of boronic acids or boronic acid esters
  - Syn bromoboration (suitable for vinylboronic acids)

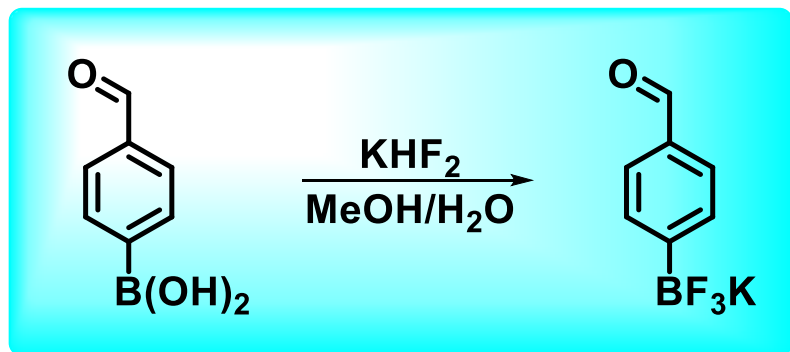


*Org. Lett.* **2009**, *11*, 4092



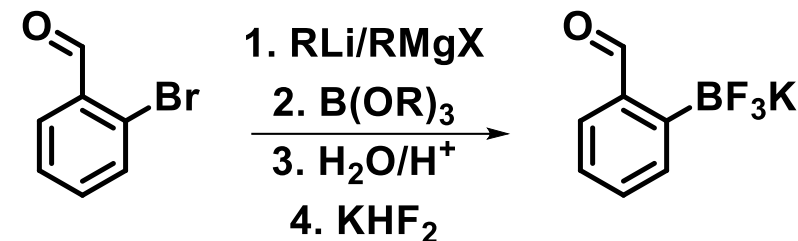
## ➤ Suzuki Reaction (Suzuki–Miyaura reaction)

- Synthesis of boronic acids or boronic acid esters
  - Modification of boronic acids or boronic acid esters sidechain - organotrifluoroborates



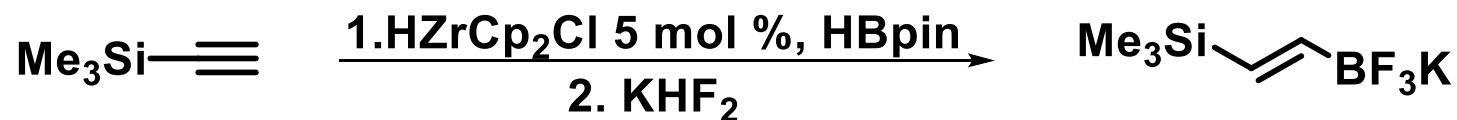
*J. Org. Chem.* 2006, 71, 5743.

## ○ (Transmetallation)

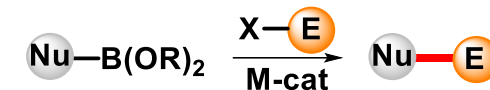


*J. Org. Chem.* 2006, 71, 5743.

## ○ (Hydroboration)

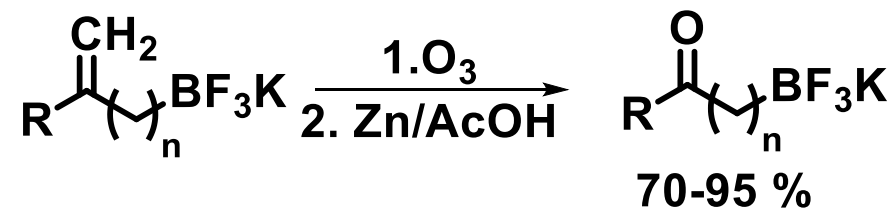


*J. Organomet. Chem.* 2000, 598, 127.

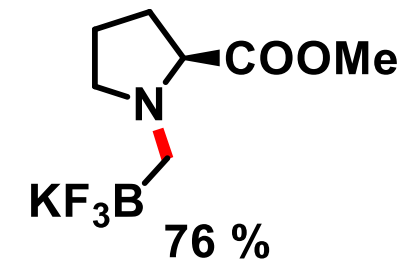
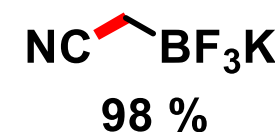
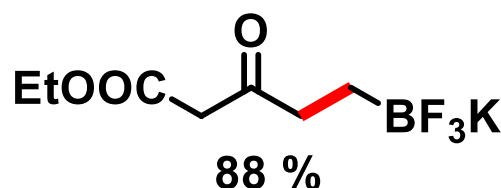


## ➤ Suzuki Reaction (Suzuki–Miyaura reaction)

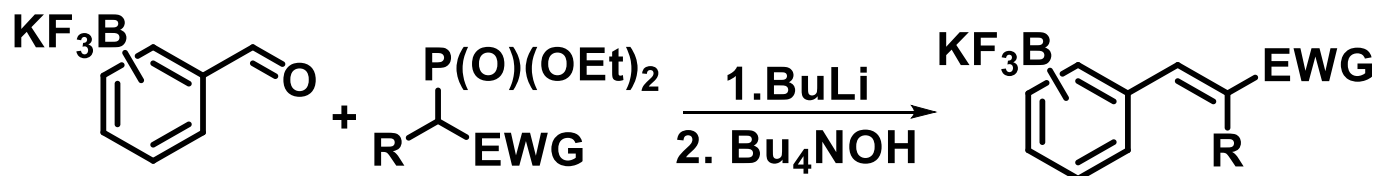
- Synthesis of boronic acids or boronic acid esters
  - Modification of boronic acids or boronic acid esters sidechain - organotrifluoroborates



*J. Org. Chem.* **2007**, *72*, 3558.



*Org. Lett.* **2007**, *9*, 1597; *Org. Lett.* **2006**, *8*, 2031.

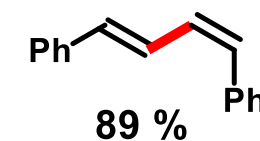
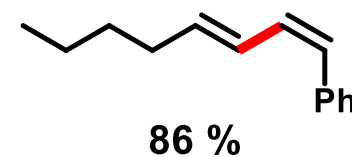
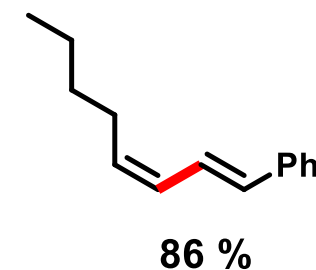
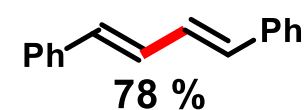
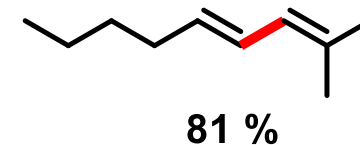
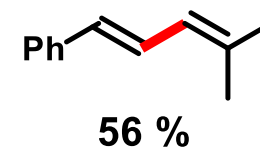
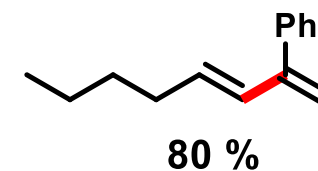
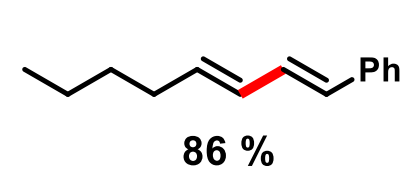
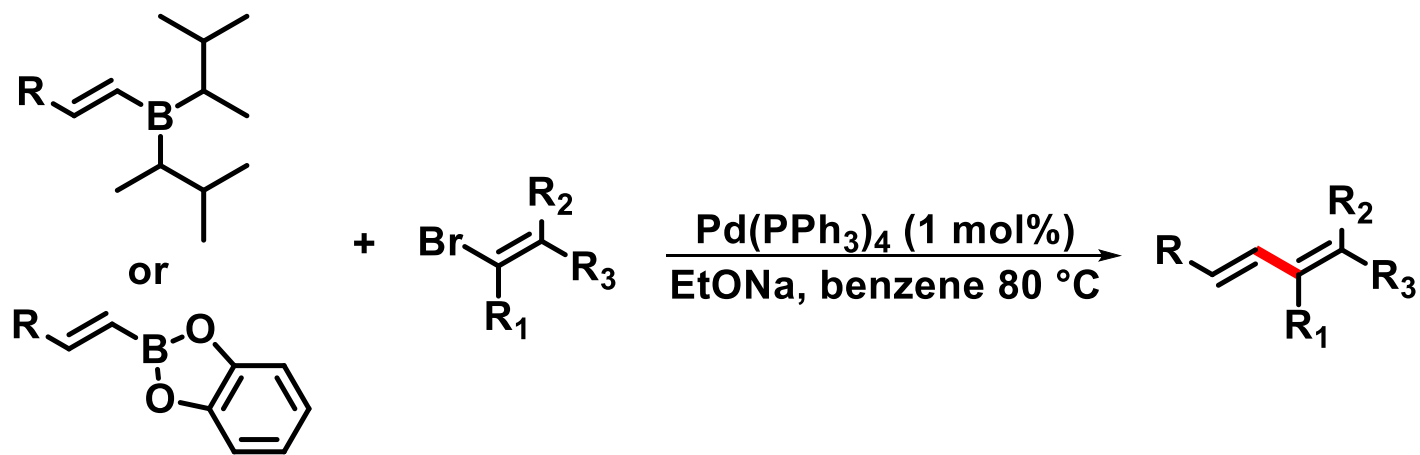


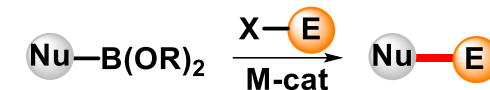
*J. Org. Chem.* **2006**, *71*, 6135.



## ➤ Suzuki Reaction (Suzuki–Miyaura reaction)

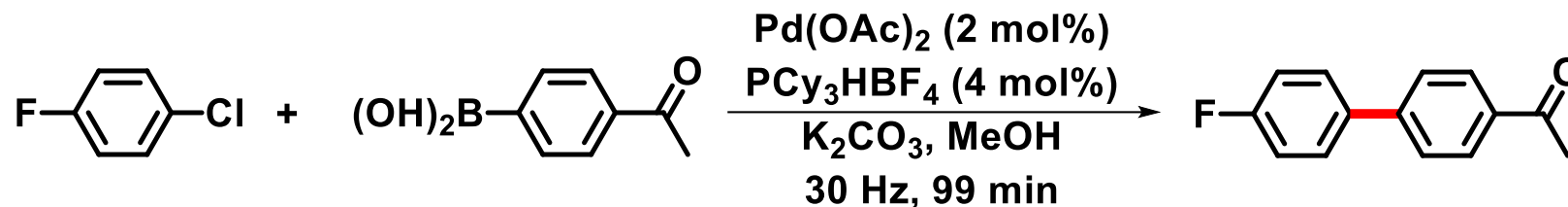
- Earlier results



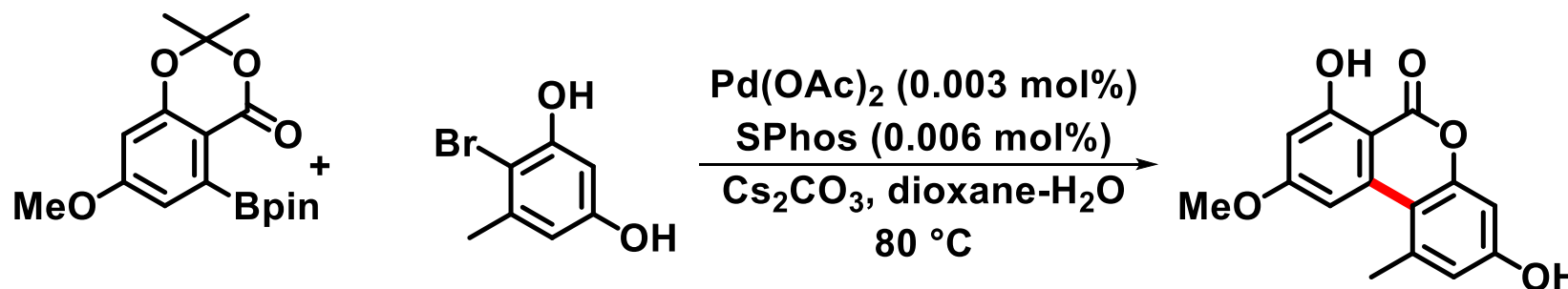


## ➤ Suzuki Reaction (Suzuki–Miyaura reaction)

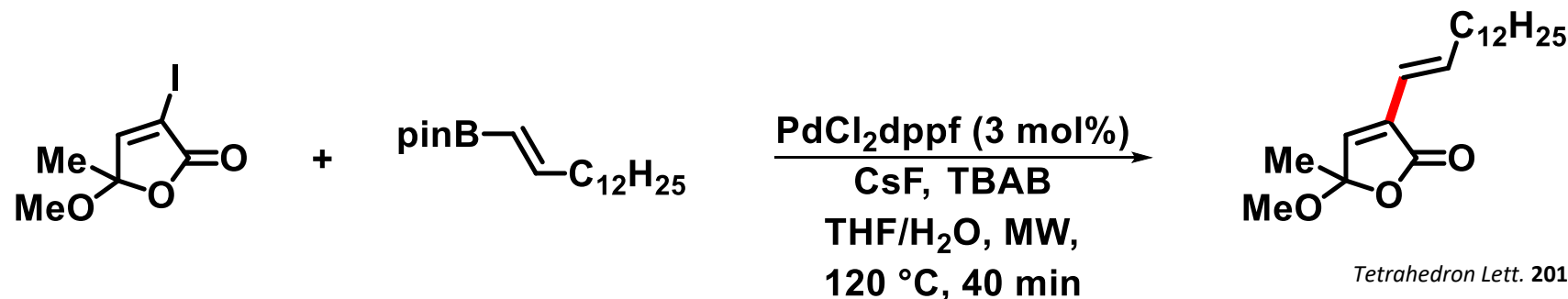
- Suzuki Reaction – Selected examples



*J. Org. Chem.* 2016, 81, 10049



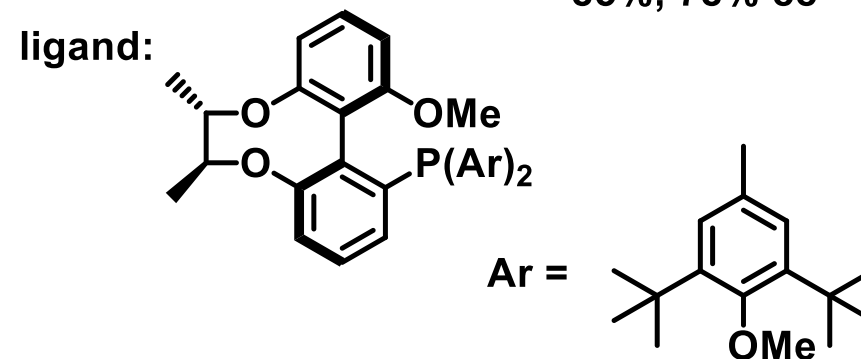
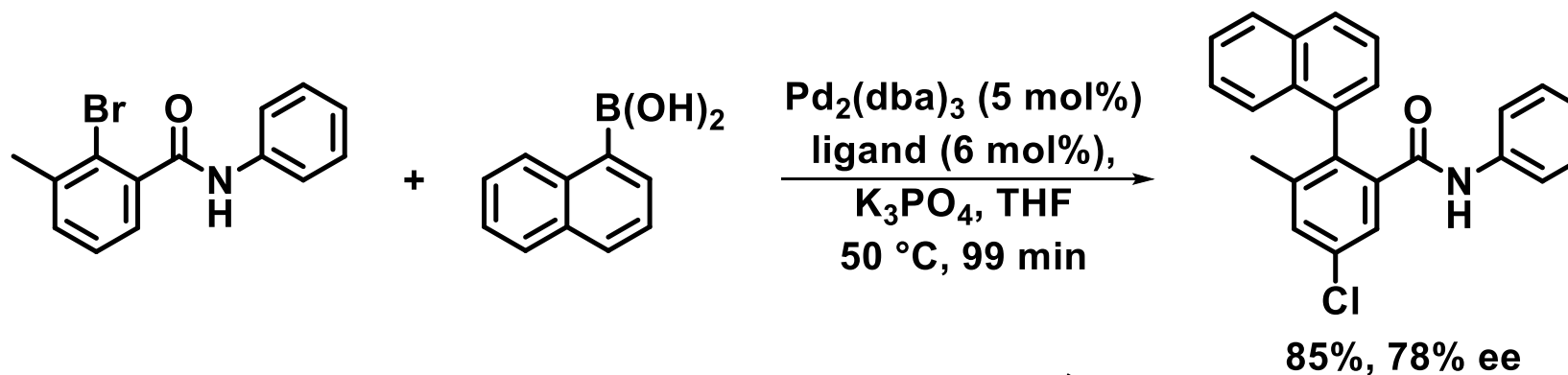
*Tetrahedron* 2013, 69, 2093



*Tetrahedron Lett.* 2013, 54, 3522

## ➤ Suzuki reaction (Suzuki–Miyaura reaction)

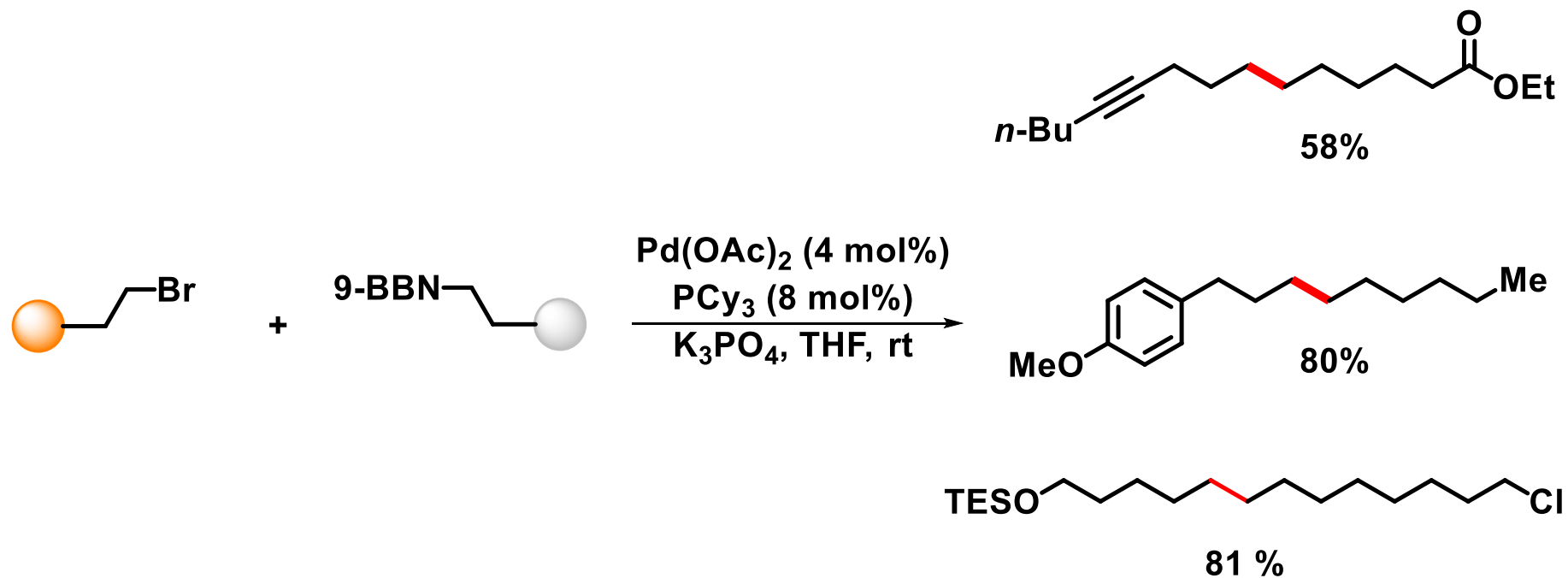
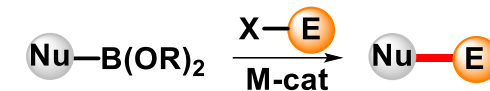
- Asymmetric Suzuki reaction



*Beilstein J. Org. Chem.* **2020**, 16, 966

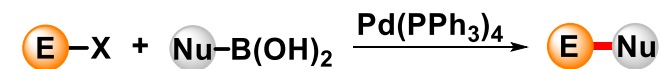
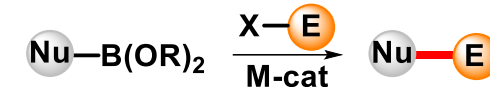
## ➤ Suzuki reaction (Suzuki–Miyaura reaction)

- Alkyl–alkyl Suzuki reaction

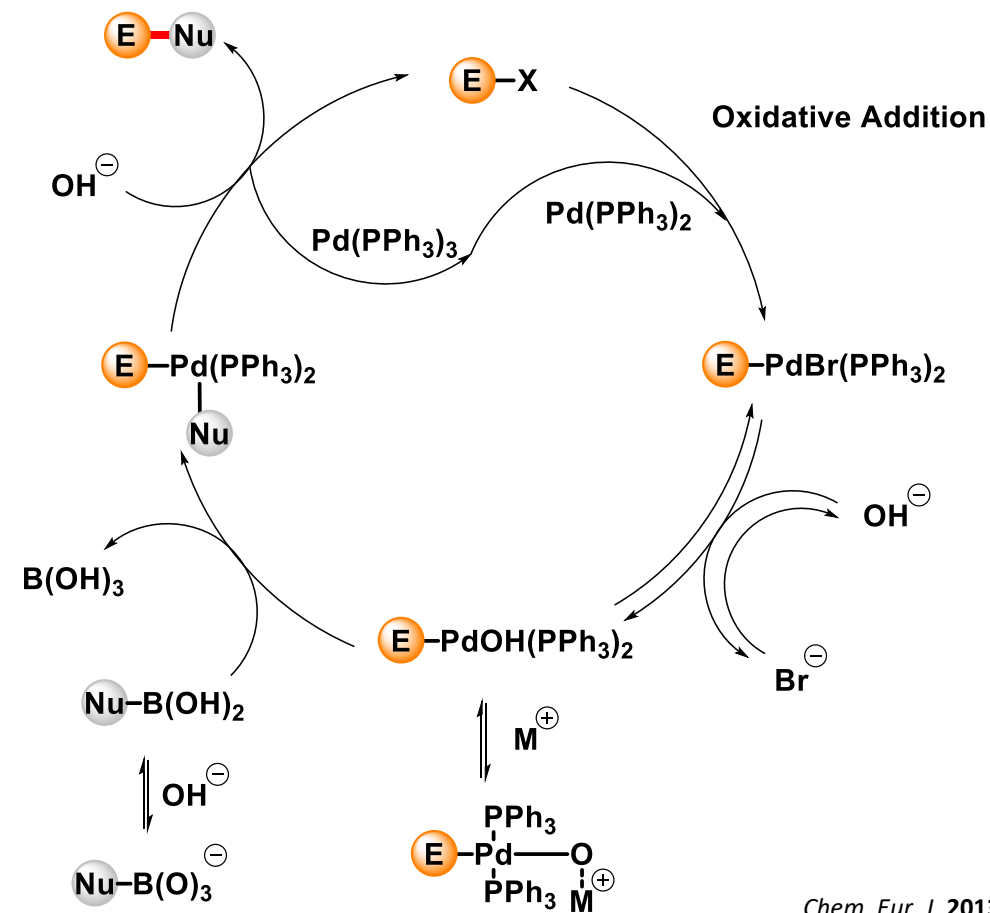
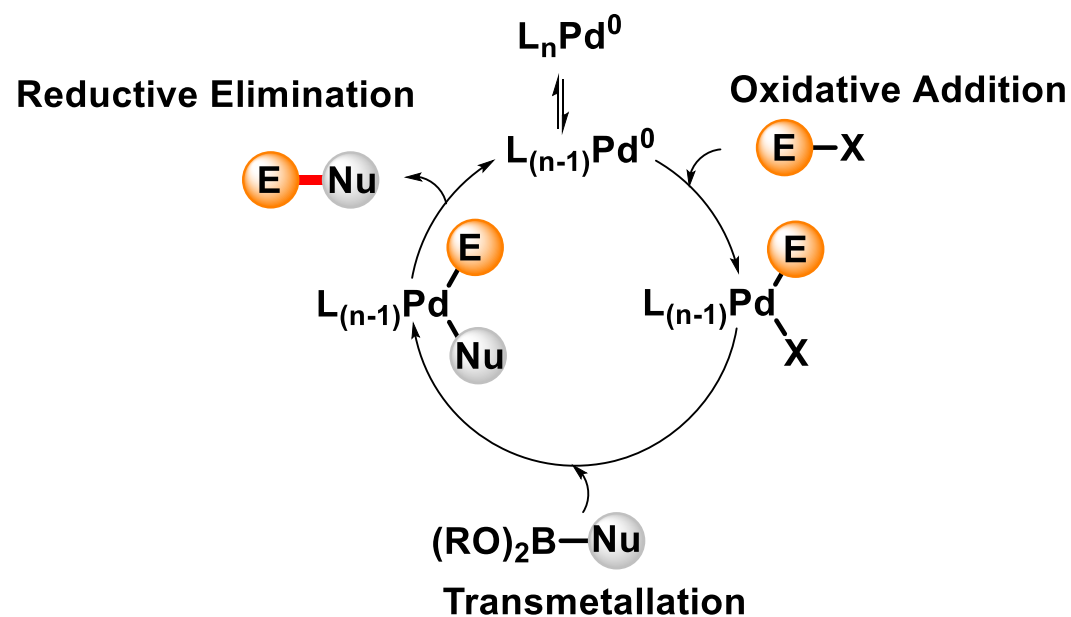


*J. Am. Chem. Soc.* **2001**, *123*, 10099

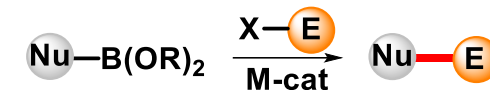
## ➤ Suzuki Reaction (Suzuki–Miyaura reaction) • Advanced mechanism



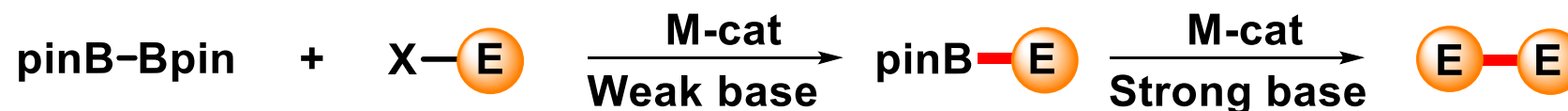
### • Simplified mechanism



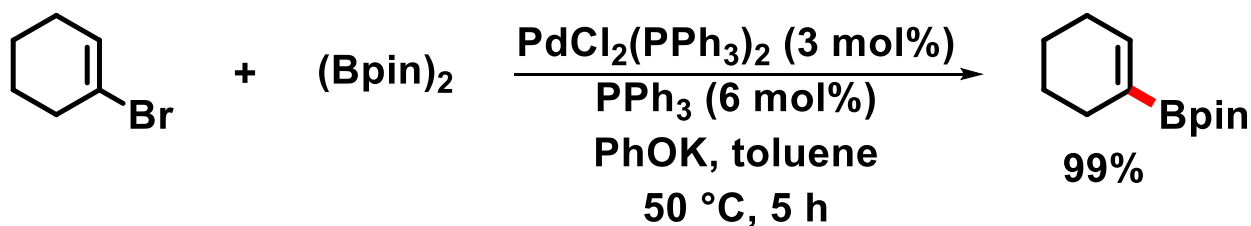
## ➤ Suzuki–Miyaura borylation



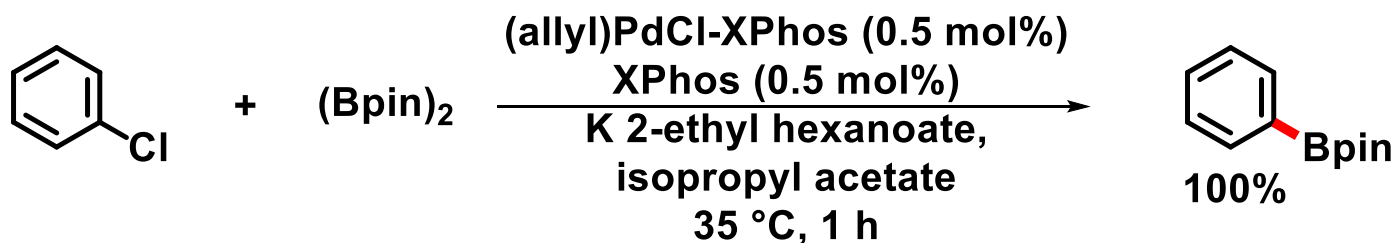
- Typically AcOM or PhOK are used as base



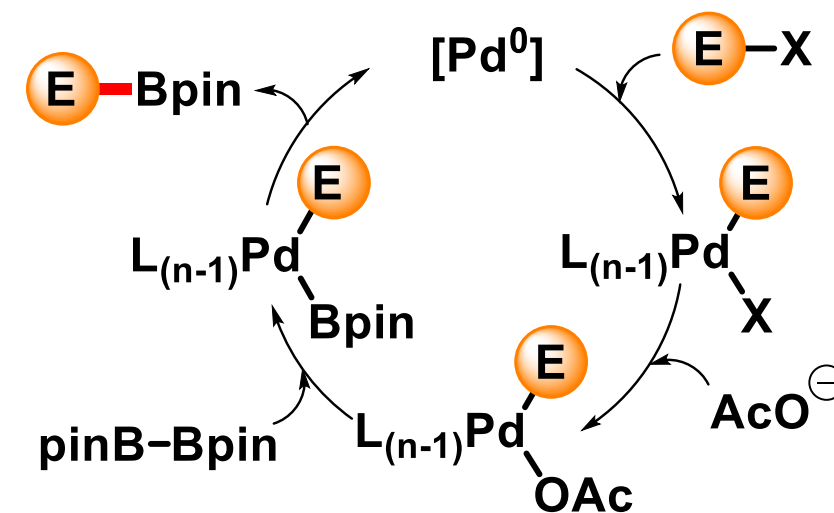
- Mechanism of the Suzuki–Miyaura borylation



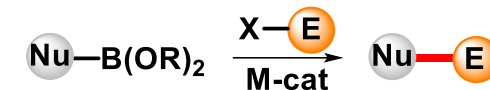
*Chem. Lett.*, 2000, 126



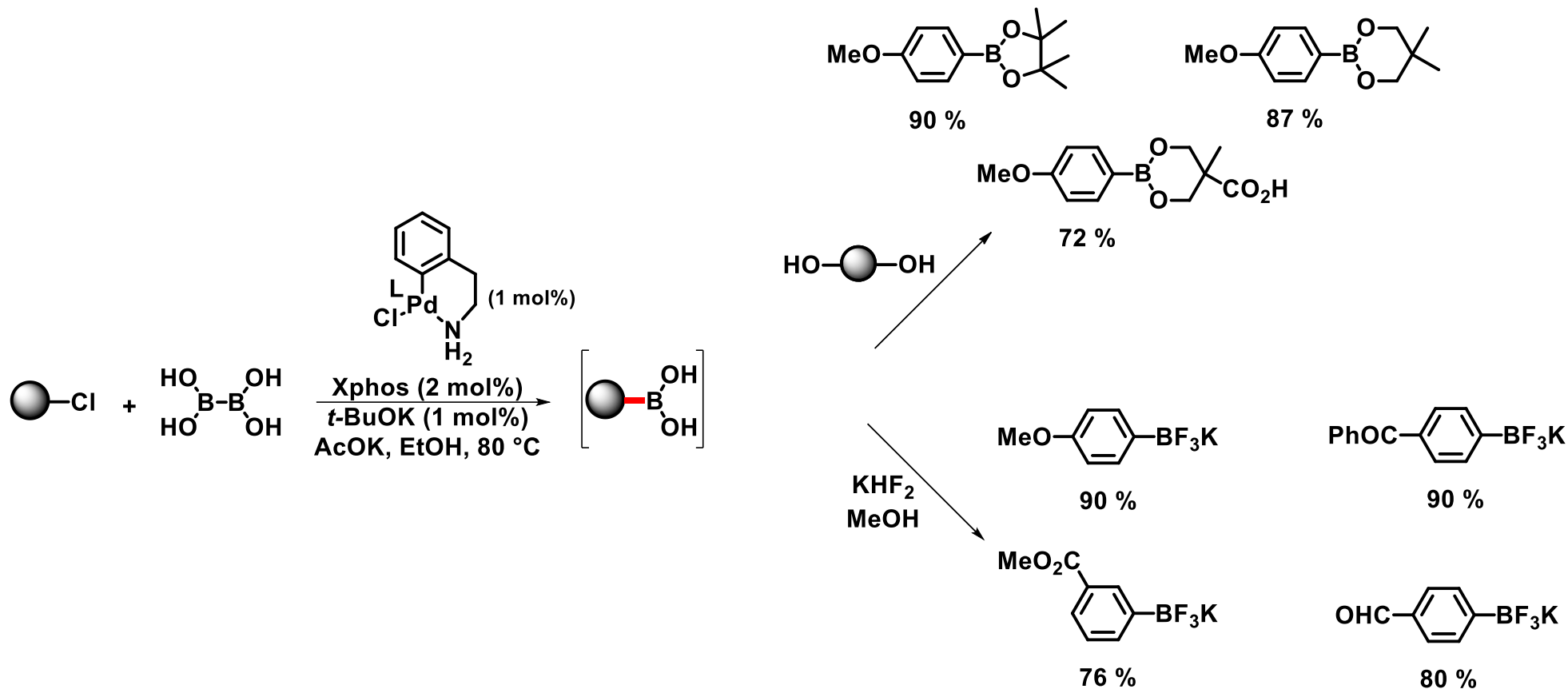
*J. Org. Chem.*, 2021, 86, 103



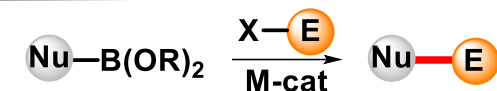
## ➤ Suzuki–Miyaura borylation



- Suzuki–Miyaura borylation for the synthesis of boronic acids



## ➤ Base-catalyzed Suzuki–Miyaura reaction



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<https://doi.org/10.1038/s41929-020-00564-z>

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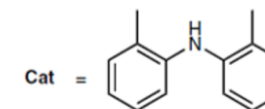
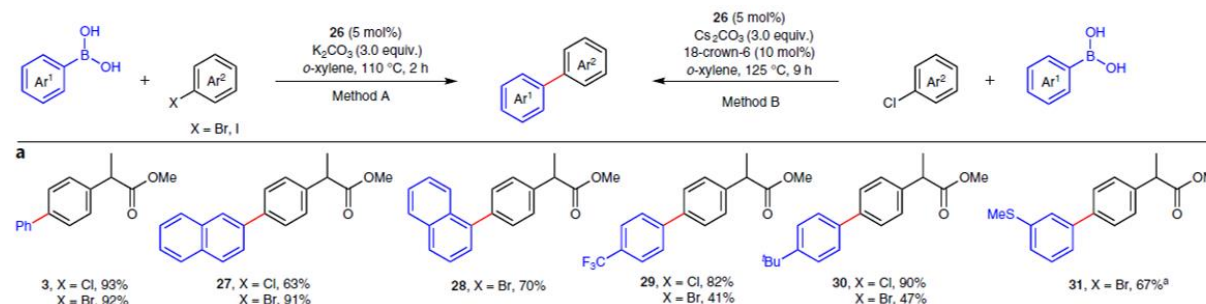
### The amine-catalysed Suzuki–Miyaura-type coupling of aryl halides and arylboronic acids

Lei Xu<sup>1</sup>, Fu-Yue Liu<sup>1</sup>, Qi Zhang<sup>1</sup>, Wei-Jun Chang<sup>1</sup>, Zhong-Lin Liu<sup>1</sup>, Ying Lv<sup>2</sup>, Hai-Zhu Yu<sup>2</sup>, Jun Xu<sup>1</sup>, Jian-Jun Dai<sup>1</sup> and Hua-Jian Xu<sup>1</sup>

Suzuki–Miyaura coupling is a practical and attractive carbon–carbon bond formation reaction due to its high efficiency and wide functional group compatibility, but its industrial applications are limited because it is typically catalysed by expensive palladium-containing transition-metal complexes. Here we show a robust and chemoselective organocatalytic Suzuki–Miyaura-type coupling of aryl halides with arylboronic acids catalysed by amines. The utility and scope of this reaction were demonstrated by the synthesis of several commercially relevant small molecules and a selection of derivatives of pharmaceutical drugs.

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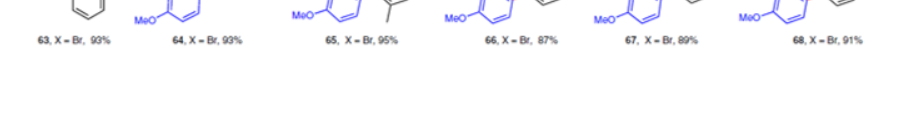
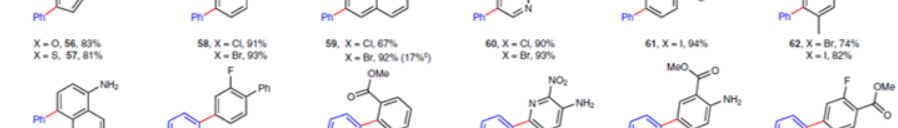
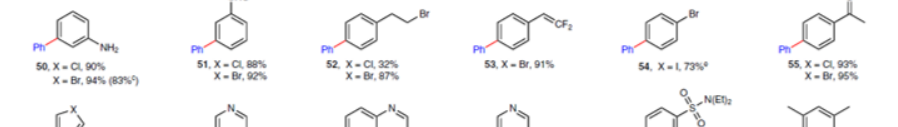
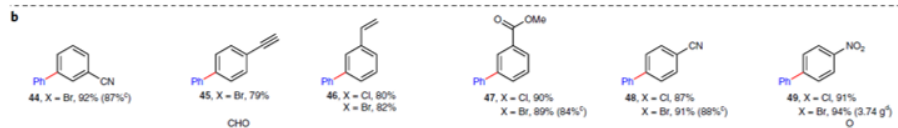
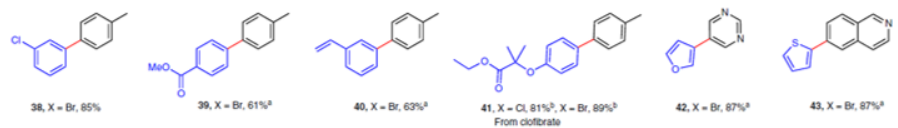
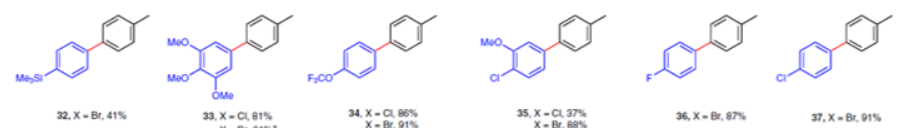
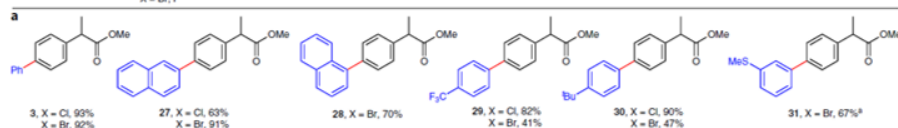
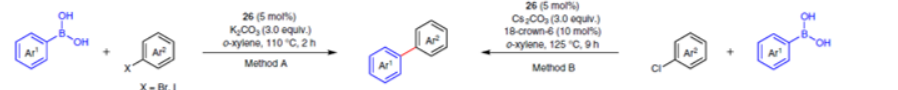
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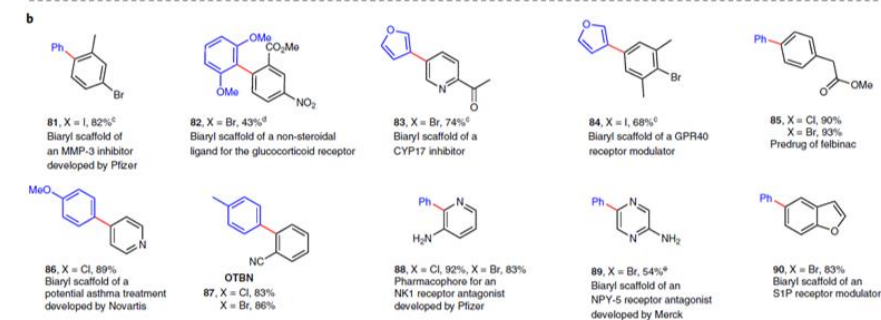
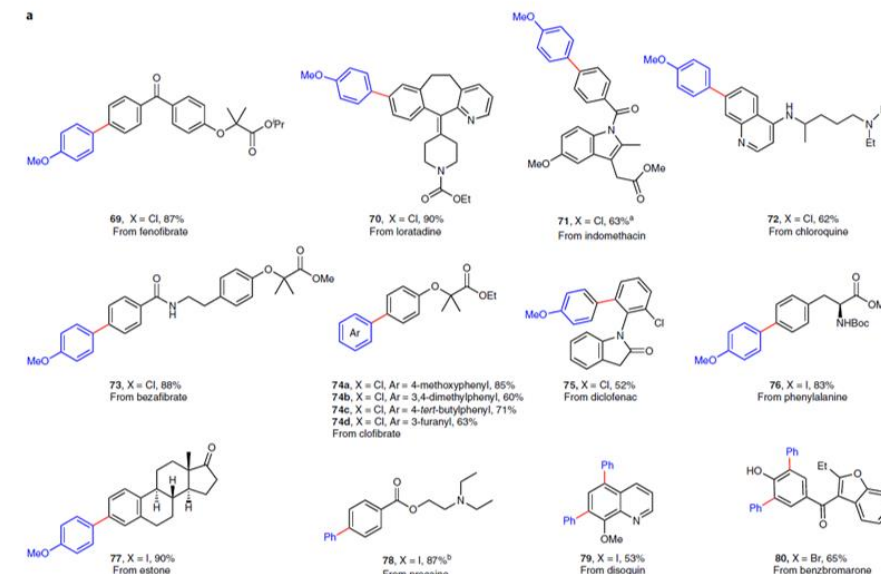
## Base-catalyzed Suzuki–Miyaura reaction

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## ➤ Base-catalyzed Suzuki–Miyaura reaction

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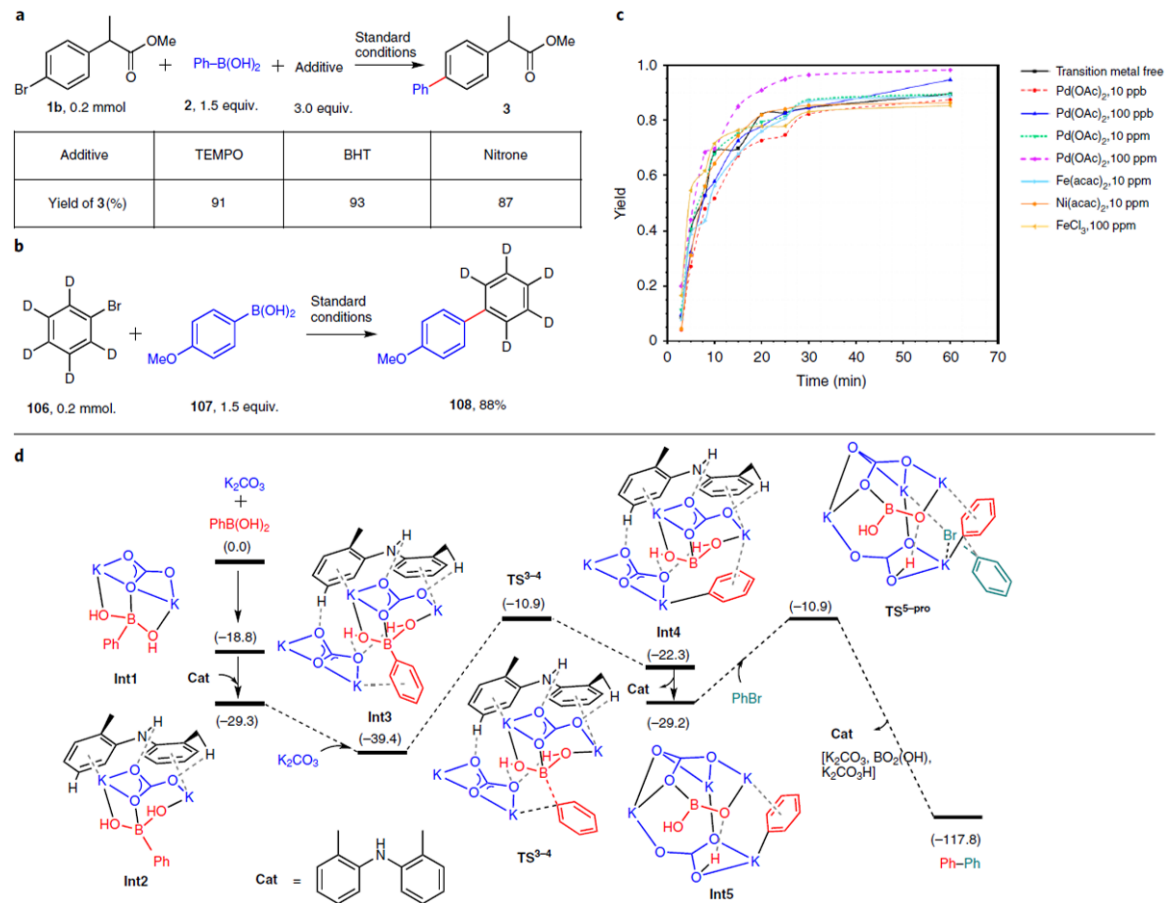


Fig. 6 | Mechanistic probes. **a**, Radical-trapping experiments. **b**, Deuterium-labelling experiments with deuterobromobenzene. **c**, Kinetic data for various transition metal catalysts. **d**, Free energy diagram for the Suzuki–Miyaura reaction mechanism.

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## ➤ Base-catalyzed Suzuki–Miyaura reaction

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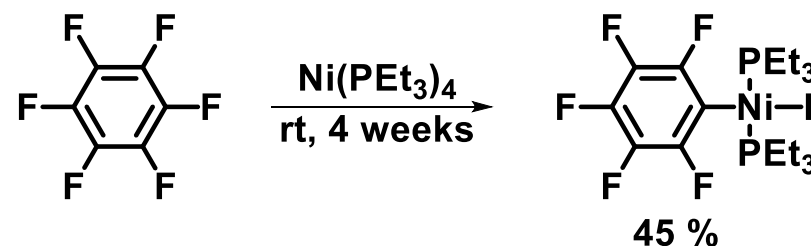
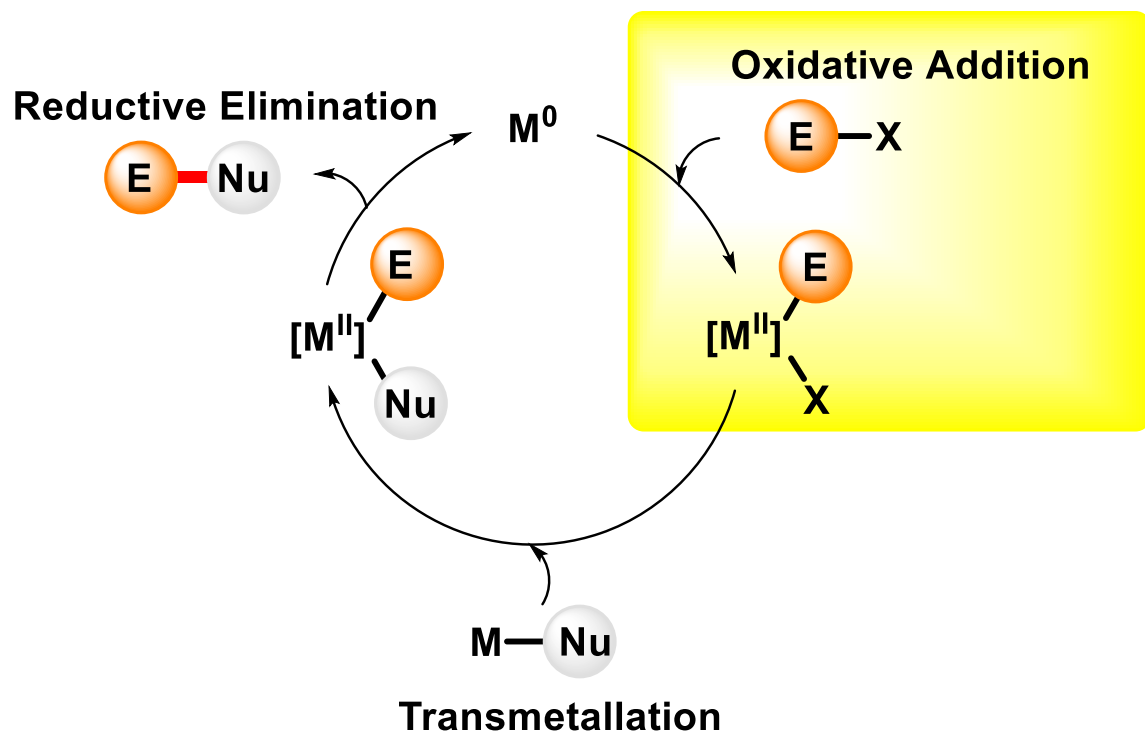
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## ➤ Activation of C–F bond

- Bond dissociation energy of C–Halogen bond (kcal/mol)

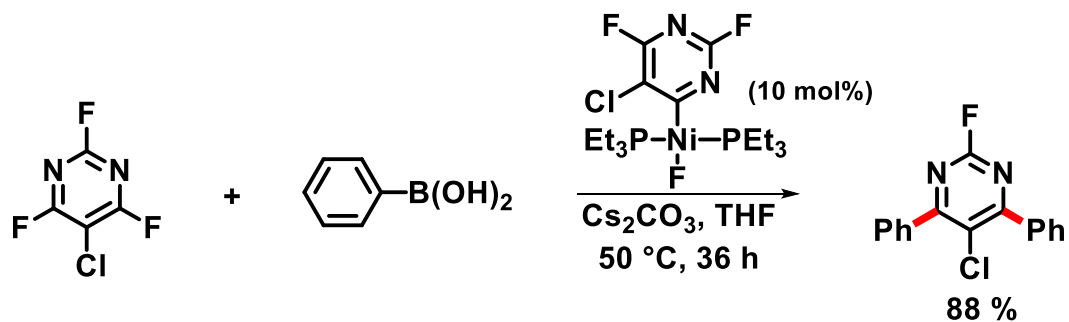
I	Br	Cl	F
272	339	402	645



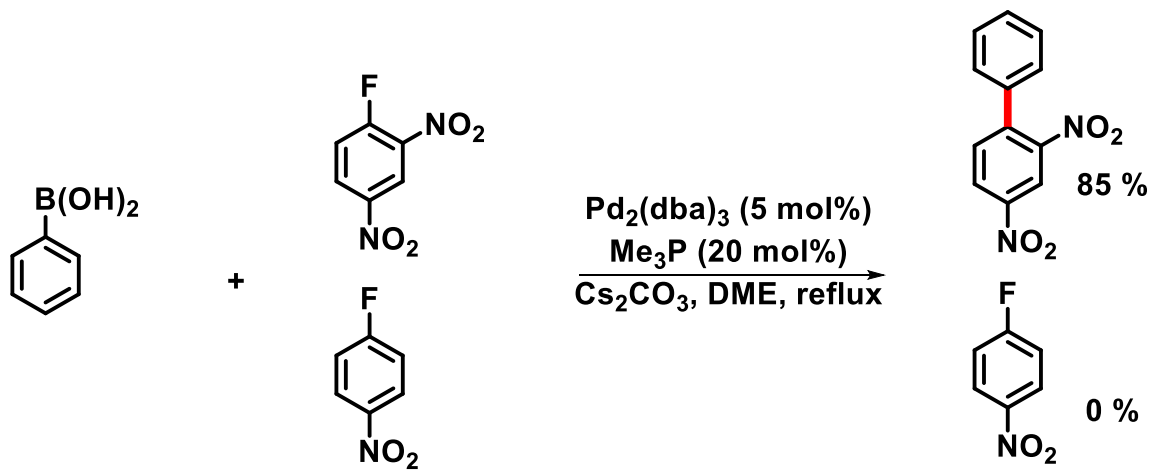
*J. Am. Chem. Soc.* **1977**, *99*, 2501

## ► Activation of C–F bond

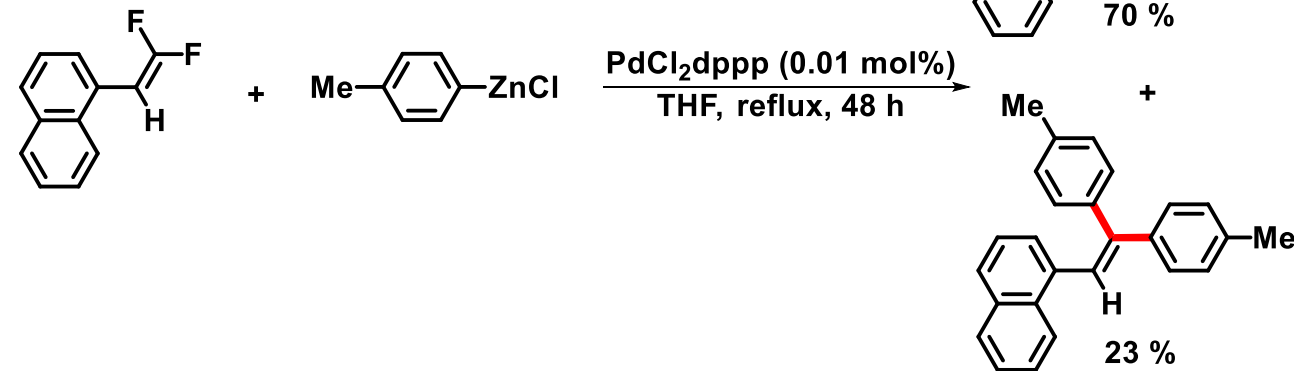
- Selected examples



*Organometallics* **2005**, *25*, 4057

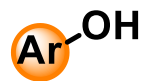
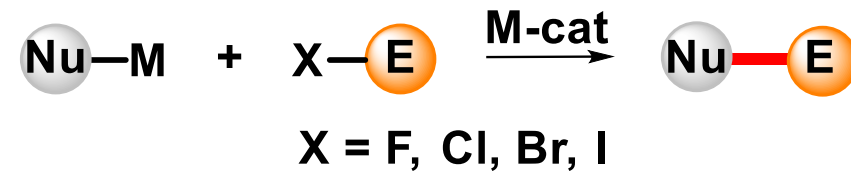


*Chem. Comm.* **2003**, 578

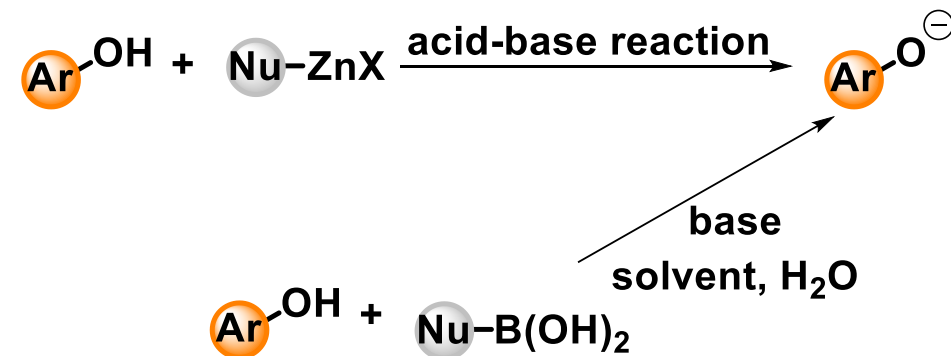


*Synlett* **2005**, 1771

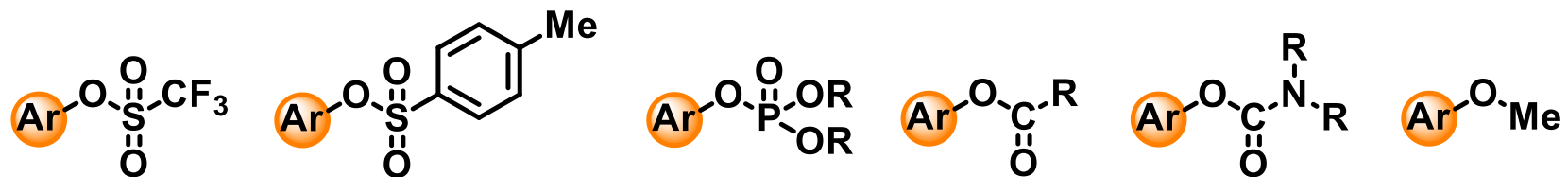
## ➤ Alternative electrophiles for cross-coupling reactions



- The simplest alternative is less suitable

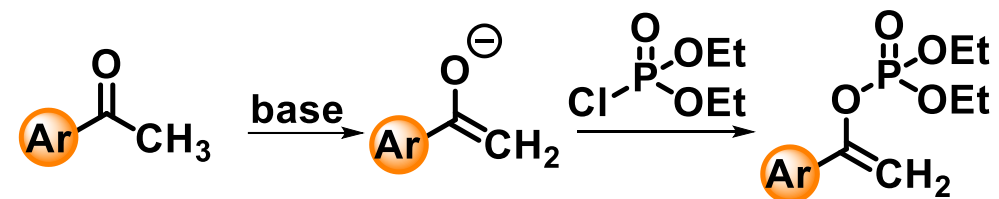
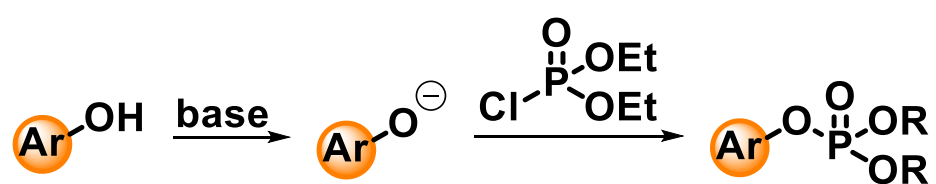


## ➤ Alternative electrophilic templates for the cross-coupling reactions

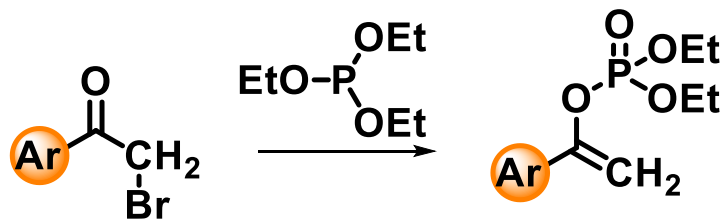


- Easily available from phenols or ketones

### ○ Acid-base reaction

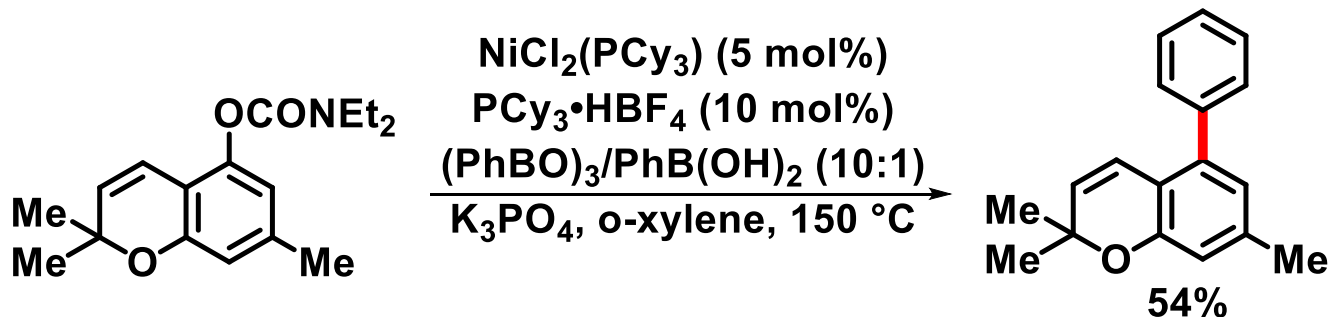


### ○ The Perkow reaction

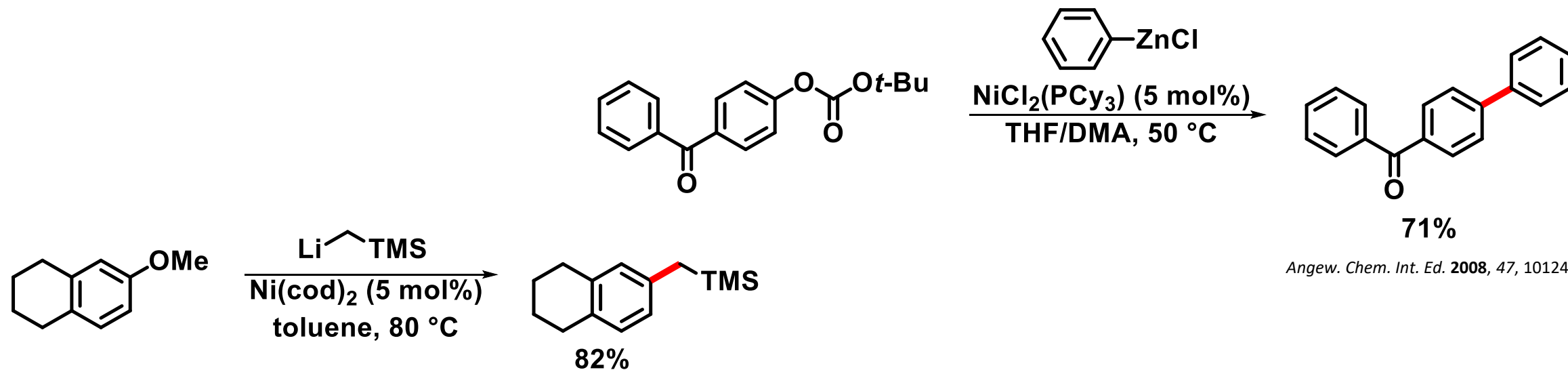


## ➤ Alternative electrophilic templates for the cross-coupling reactions

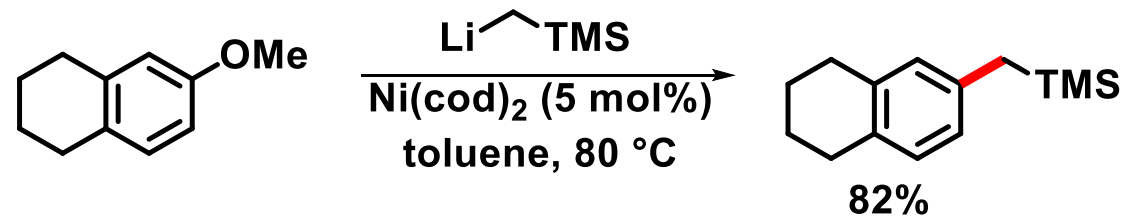
- Selected examples of Ni-catalyzed cross-coupling reactions



*J. Am. Chem. Soc.* **2009**, *131*, 17750



*Angew. Chem. Int. Ed.* **2008**, *47*, 10124

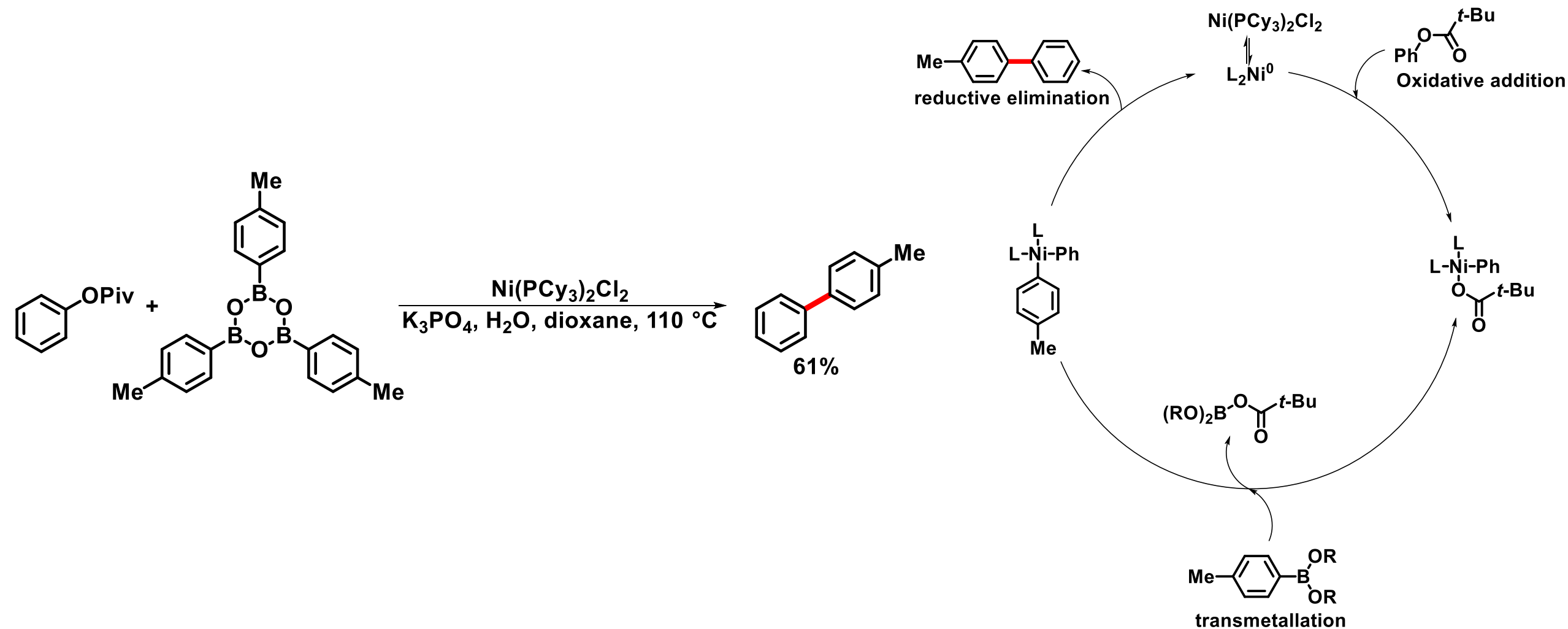


*Angew. Chem. Int. Ed.* **2014**, *53*, 12912



## ➤ Alternative electrophilic templates for the cross-coupling reactions

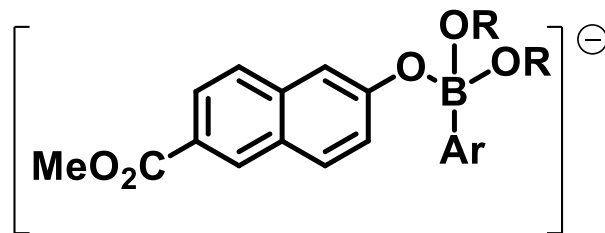
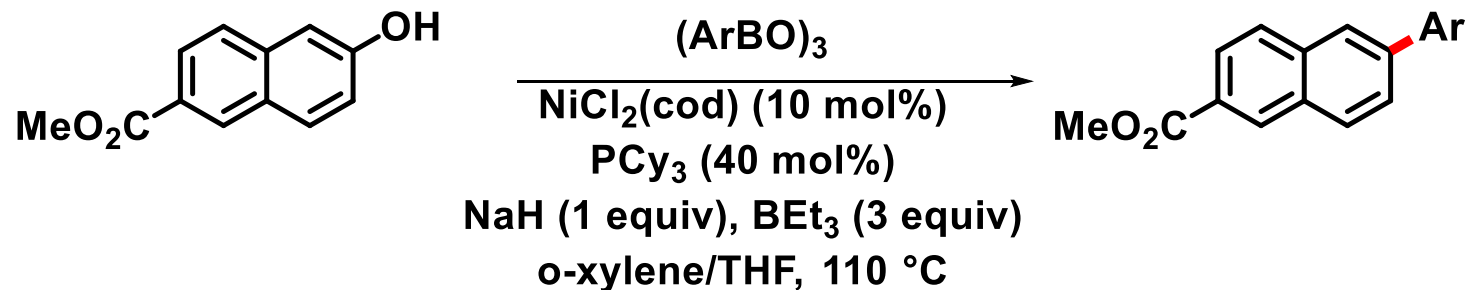
- Simplified general catalytic scheme for the cross-couplings of activated C–O bonds



## ➤ Alternative electrophilic templates for the cross-coupling reactions

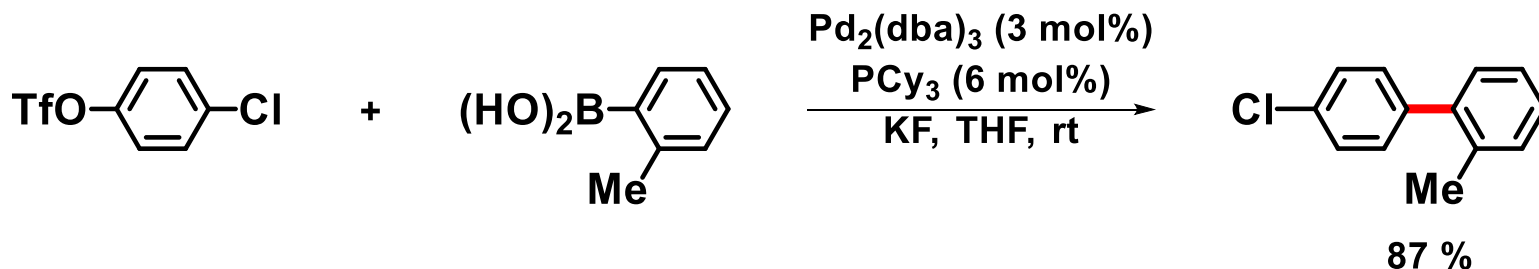
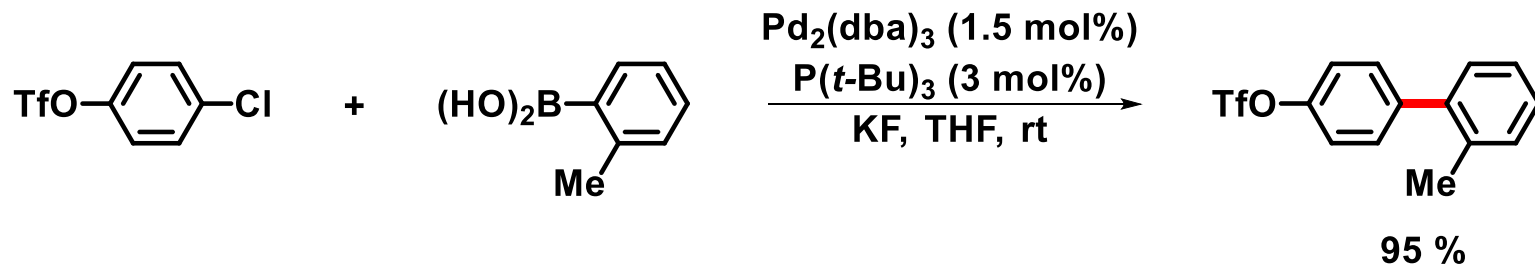
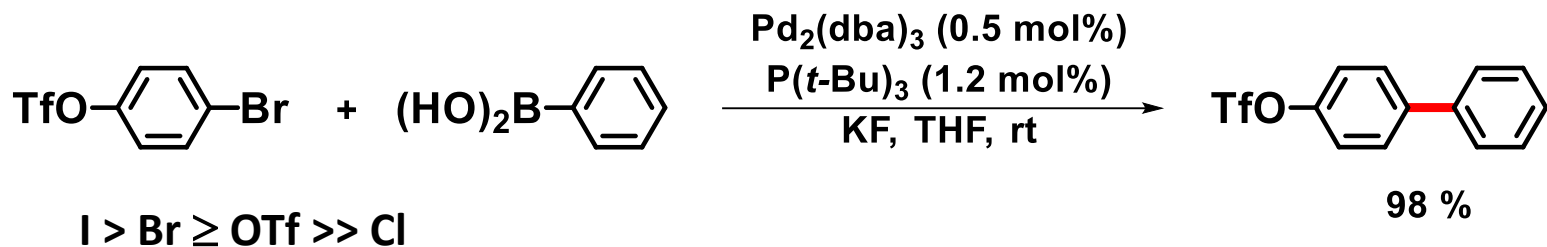
- Cross-coupling reactions of unprotected phenols

- The simplest alternative is less suitable 



## ➤ Alternative electrophilic templates for the cross-coupling reactions

- Chemoselectivity in mixed templates



*J. Am. Chem. Soc.* **2000**, *122*, 4020