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Cross-Coupling Reactions

Mechanisms and Examples

Preface

Cross-coupling reactions have become indispensable tools in organic synthesis, driving innovation across fields such as pharmaceuticals, material science, and natural product synthesis. These reactions have transformed how chemists build complex molecules, offering precision, efficiency, and versatility. This book is designed to serve as a comprehensive resource for understanding these powerful transformations.

Organized by reaction name, this book offers a clear and concise description of each cross-coupling reaction, its catalytic cycle, and key examples from real-world applications. It is designed to be a practical resource for students, researchers, and professionals alike, offering insight into the versatility and importance of these transformations.

My hope is that this book serves as a valuable tool for anyone seeking to deepen their understanding of cross-coupling chemistry and its role in advancing science and industry.

“What the ocean was to the child, the Periodic Table is to the chemist”

−Karl Barry Sharpless

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Introduction

Cross-coupling reactions are foundational in synthetic chemistry, traditionally involving the metal-catalyzed coupling of a sp^2-hybridized aryl halide (electrophile) with an organometallic compound (nucleophile) to form various types of bonds, such as C−C, C−N, and C−O. Developed extensively in the late 20th century, these reactions became crucial for building complex molecular structures efficiently. Palladium, due to its stability and catalytic activity, became the preferred metal catalyst, leading to the creation of widely used reactions such as Suzuki-Miyaura (using organoborane nucleophiles) and Negishi reactions (using organozinc nucleophiles).

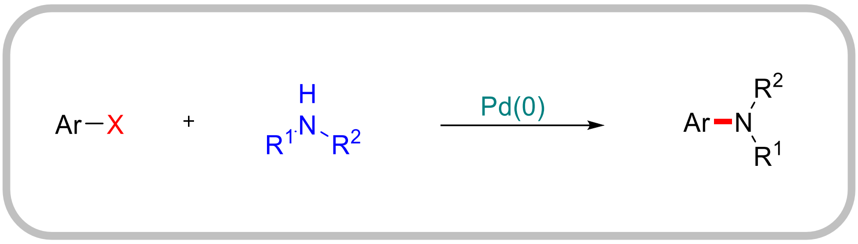
The impact of cross-coupling reactions on synthetic chemistry has been substantial. For example, it enables the efficient synthesis of drug molecules like losartan through late-stage Suzuki-Miyaura reactions. Over time, cross-coupling reactions have expanded molecular design capabilities in medicinal chemistry, shifting many drug structures toward planar geometries.

In recognition of this groundbreaking contribution, Richard Heck, Ei-ichi Negishi, and Akira Suzuki were awarded the 2010 Nobel Prize in Chemistry for developing palladium-catalyzed cross-coupling methods. Their research has inspired further advancements, including using alternative metals like nickel, copper, and iron to enhance reaction sustainability. Additionally, new methods like cross-electrophile and metallaphotoredox couplings are evolving, broadening cross-coupling's applicability and scope.

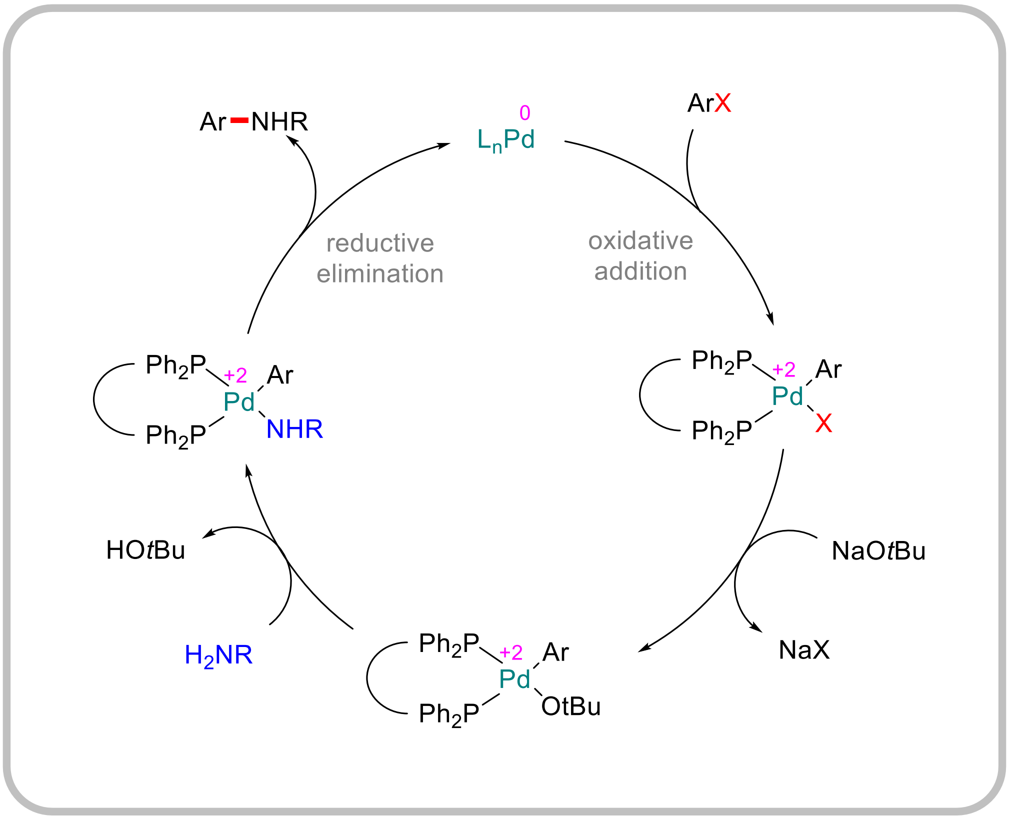
Figure 1. The Nobel prize winners Akira Suzuki, Ei-ichi Negishi and Richard F. Heck.

Buchwald-Hartwig Coupling

The Buchwald-Hartwig coupling is a palladium-catalyzed cross-coupling reaction that forms aryl amines. It can also be applied to the formation of C−O bonds using phenols as nucleophiles. This adaptation has significantly broadened its utility in organic synthesis.



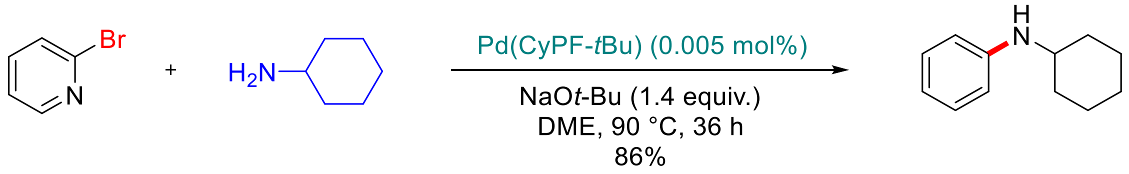
Scheme 1. Buchwald-Hartwig Coupling.



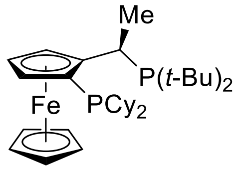
Scheme 2. Buchwald-Hartwig coupling mechanism.

Example 1[1]

Coupling between 2-Pyridine bromide and a secondary aliphatic amine.

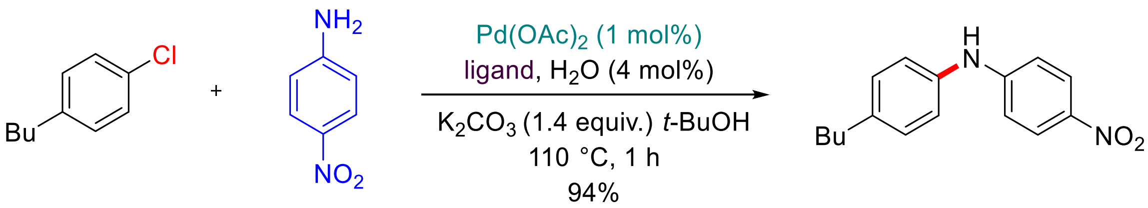


CyPF-*t*Bu =

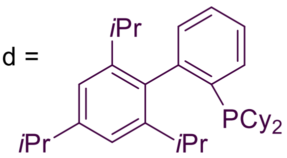


Example 2[2]

Coupling between an aryl chloride and an aniline catalyzed by $Pd(OAc)_2$.

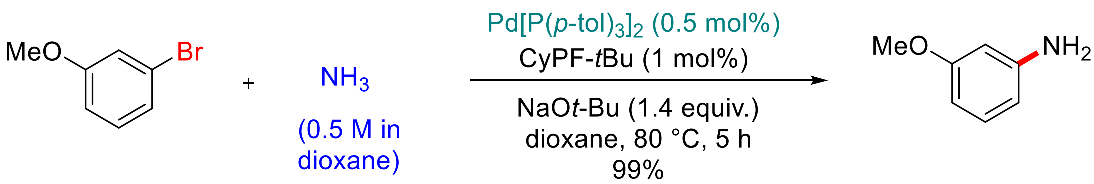


Ligand =

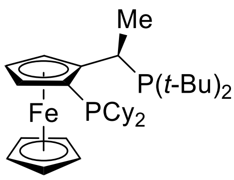


Example 3[3]

Coupling between an aryl bromide and ammonia.

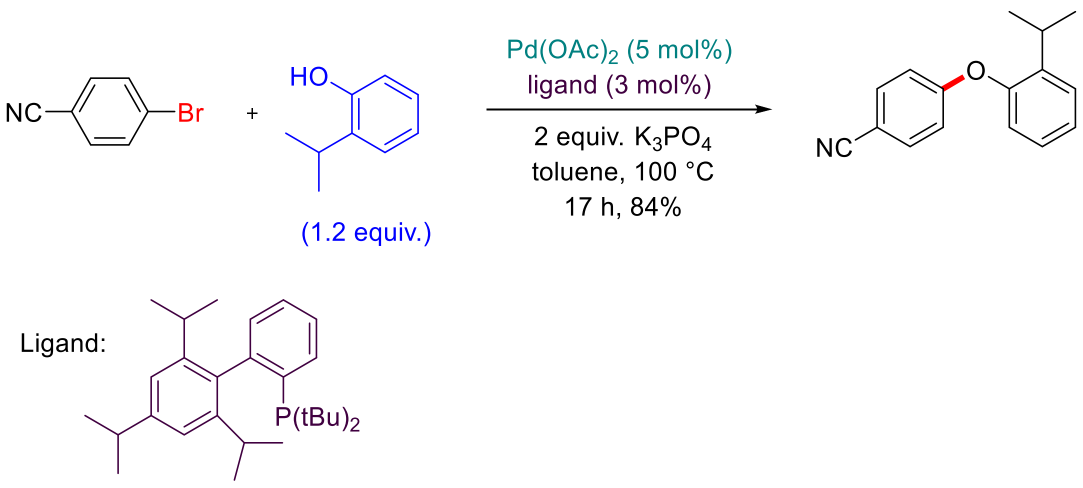


CyPF-*t*Bu =



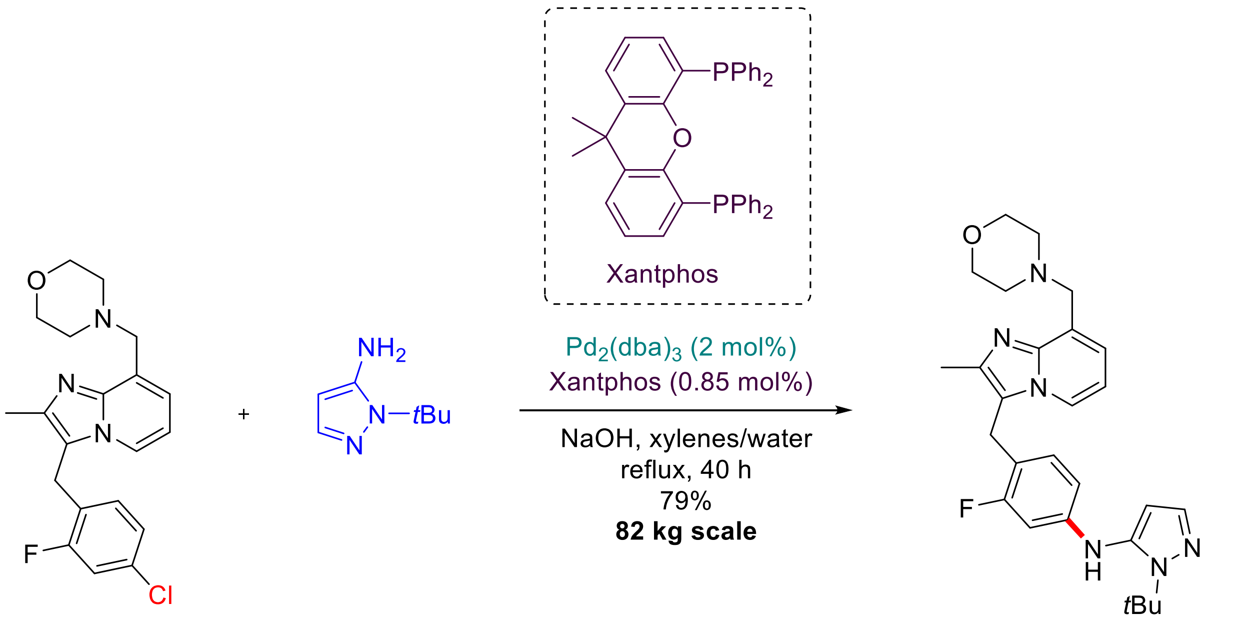
Example 4[4]

Coupling between an aryl bromide and a phenol catalyzed by $Pd(OAc)_2$.



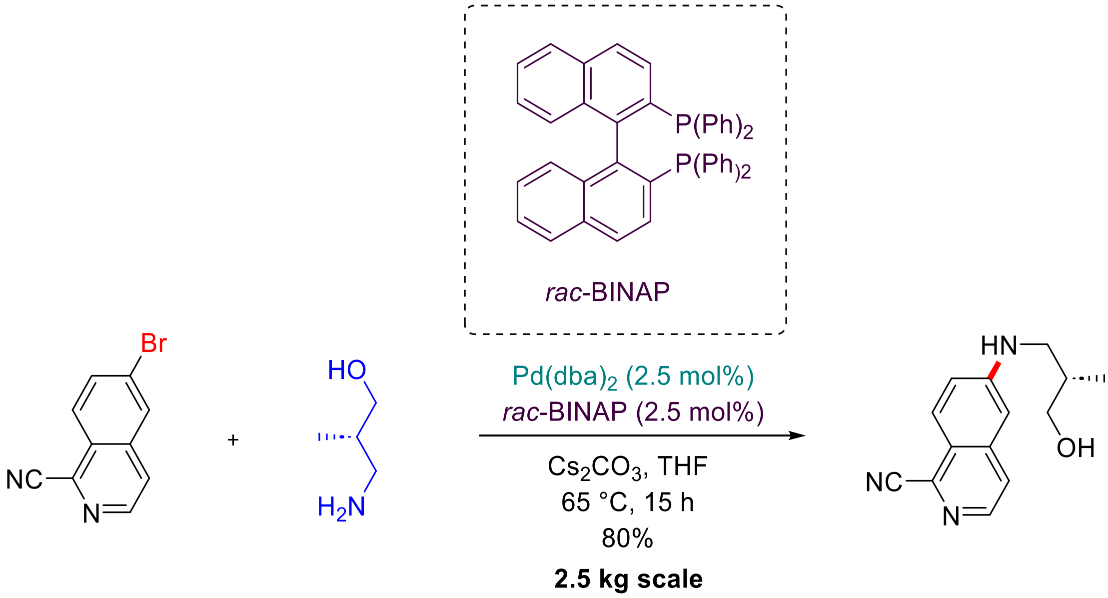
Example 5[5]

Multikilogram scale coupling by Eli Lilly.



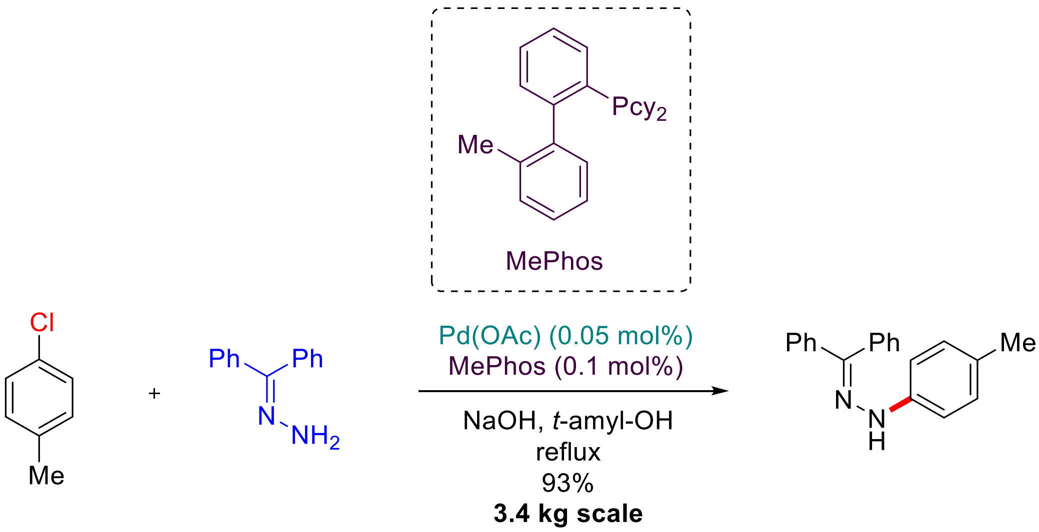
Example 6[6]

2.5 kg scale coupling by Pfizer.



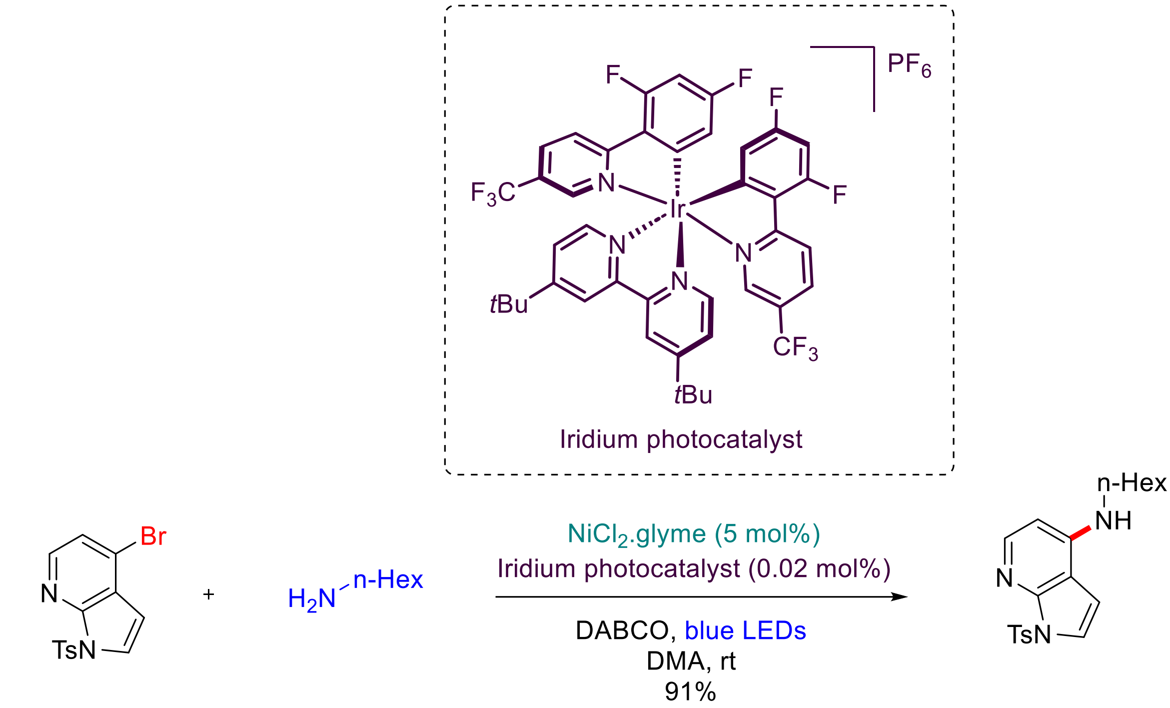
Example 7[7]

Hydrazonation of an aryl chloride at 3.4 kg scale.



Example 8[8]

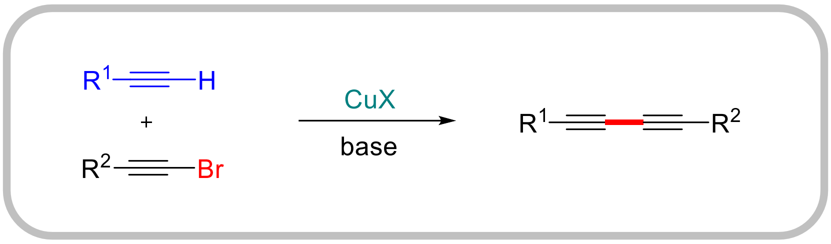
Buchwald-Hartwig coupling under photocatalytic conditions.



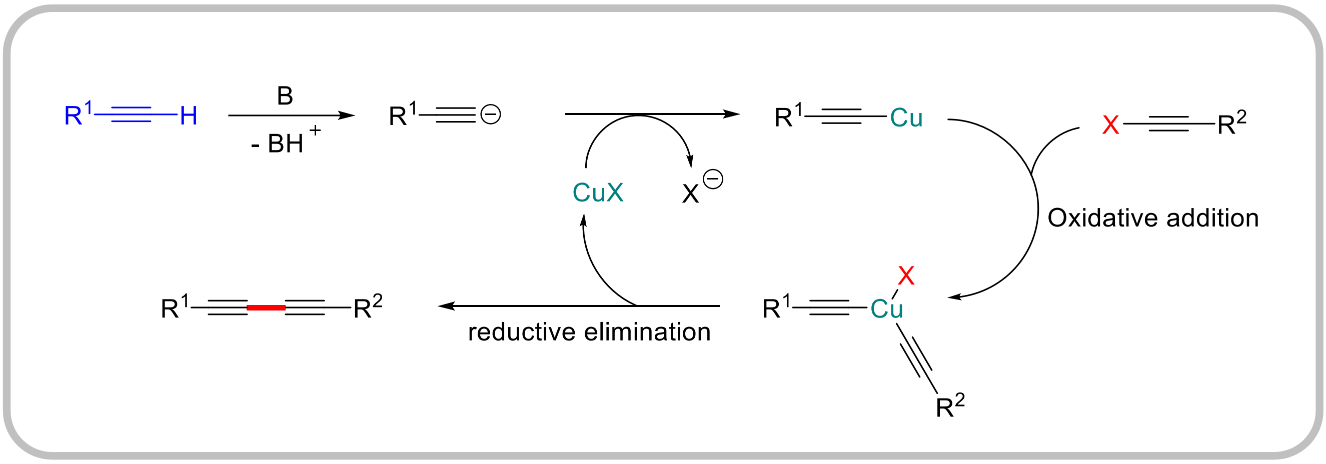
PF6
F
F
F
F
F3C
N
Ir
N
N
N
tBu
tBu
CF3
Iridium photocatalyst
Br
N
TsN
+
H2N
n-Hex
NiCl2.glyme (5 mol%)
Iridium photocatalyst (0.02 mol%)
DABCO, blue LEDs
DMA, rt
91%
n-Hex
NH
N
TsN

Cadiot-Chodkiewicz Coupling

The Cadiot-Chodkiewicz coupling is a copper (I)-catalyzed reaction of a terminal alkyne and an haloalkyne that offers access to unsymmetrical bisacetylenes.

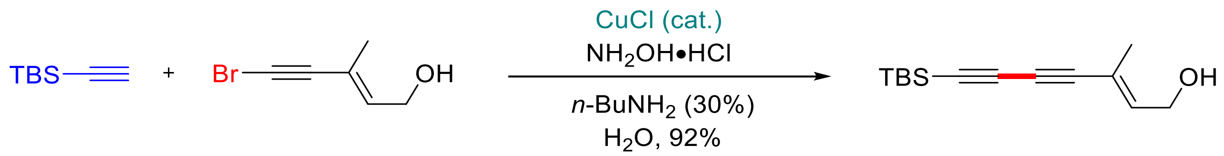


Scheme 3. Cadiot-Chodkiewicz coupling.



Scheme 4. Cadiot-Chodkiewicz coupling mechanism.

Example 1[9]



Example 2[10]