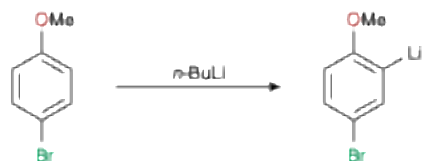


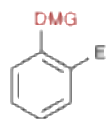
Directed Ortholithiations - Where It All Began

Gilman (1938, 1939)



Formation confirmed via subsequent carbonation reaction and formation of the acid

Ortholithiation has become a powerful way to construct Ar-Elec bonds



Wittig (1940)



Key Challenges Associated With Ortholithiation Chemistry

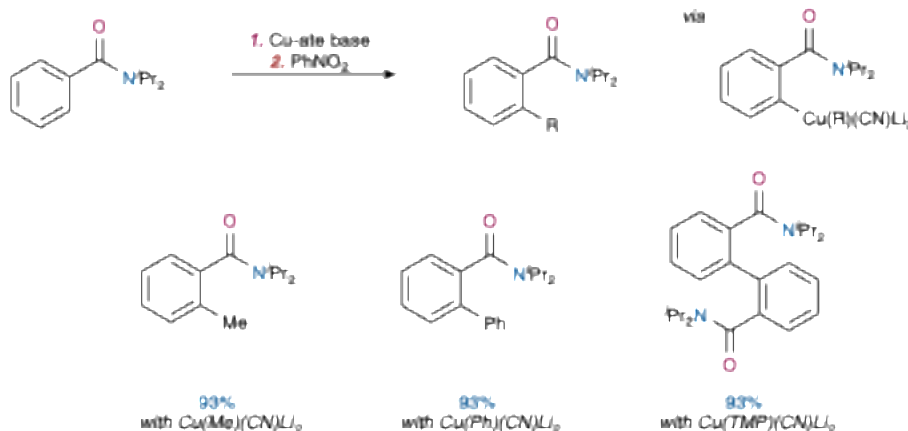
- Highly reactive and not compatible with sensitive functionalities (n-deficient heterocycles, reactive electrophiles, etc.)

- Low reaction temperatures required due to reactivity of aryllithiums

J. Am. Chem. Soc. **1939**, *61*, 106-109.

Ber. Dtsch. Chem. Ges. B., **1940**, *73*, 1197-1218.

Early demonstration of oxidative organocuprate coupling

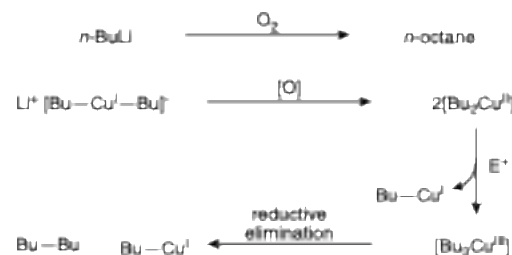


J. Am. Chem. Soc. **2007**, *129*, 48, 15102-103.

General mechanism for TM-free oxidative coupling

Key idea: The high HOMO of organocuprates allow for facile oxidation

Whitesides (1967)

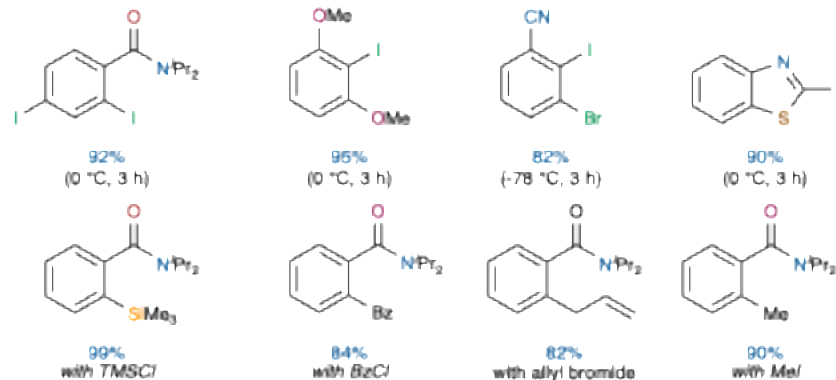
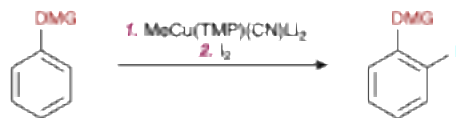


J. Am. Chem. Soc. **1967**, *89*, 5302.

Chem. Soc. Rev. **2008**, *35*, 218-225.

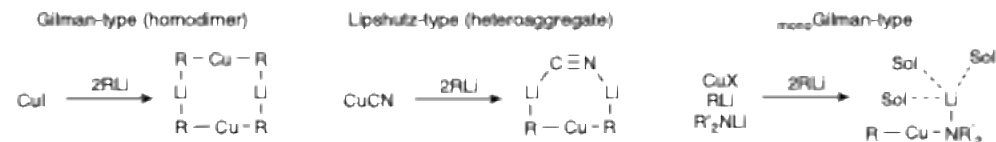
Directed *ortho* Cupration: Trapping With Electrophiles

Seminal Report: Uchiyama (2007) - Regioselective Aromatic Functionalization



Big Question: What is the mechanism of DoC?

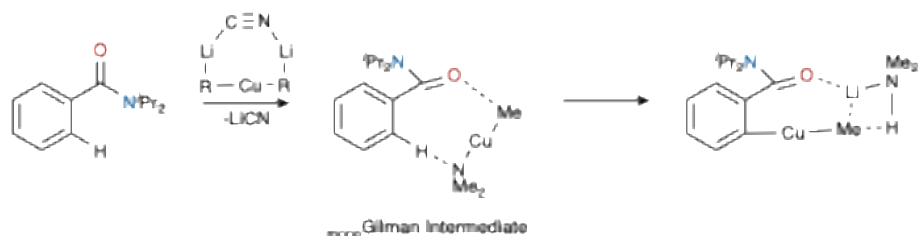
Deprotometalation species: Gilman cuprates vs. Gilman-type cuprates vs. Lipshutz cuprates vs. Lipshutz-type cuprates



Single-step DoC Reaction Proceeds Via *trans*-Gilman Intermediate

Gilman type cuprates saw diminished to no reactivity in DoC reactions while Lipshutz cuprates are competent

Can a Lipshutz-type cuprate interconvert to a Gilman cuprate via exclusion of LIX?

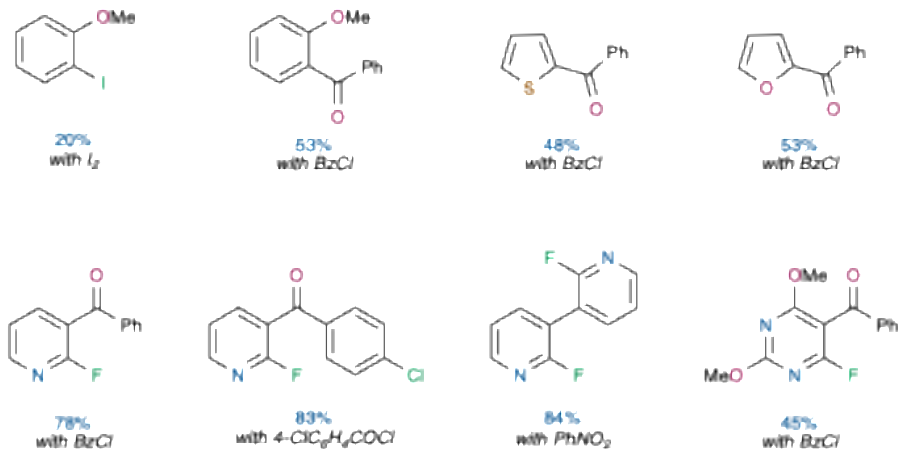


Organometallics 2009, 28, 38-41.
Angew. Chem. Int. Ed. 2012, 51, 12081-85.
Dalton Trans. 2014, 43, 14181-03.

Directed *ortho* Cupration: Expansion of the Methodology To Heterocycles

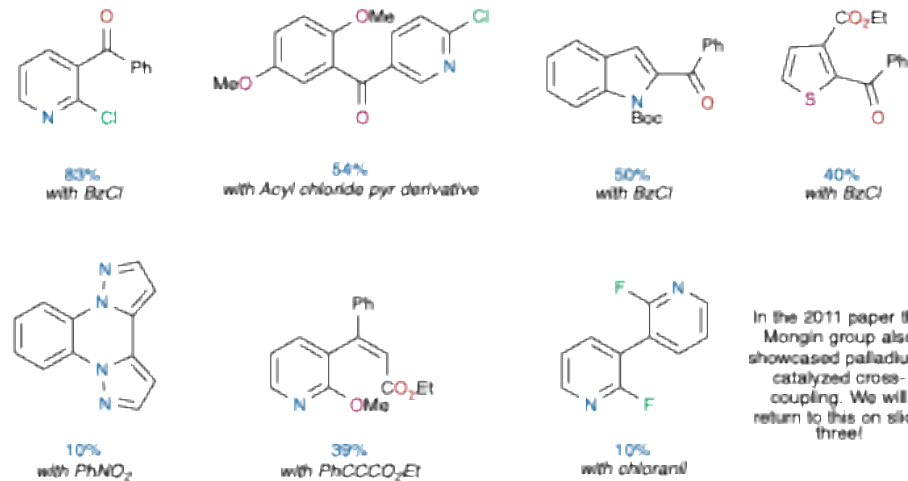
Mongin (2009 and 2011): Anisole, Furan, Thiophene, Pyridine, Pyrimidine, Indole

Gilman-type amido-cuprate postulated $(\text{TMP})_2\text{CuLi} \cdot \text{LiCl}$ is in reaction medium; therefore, it is possible for Lipshutz type cuprate to form (potential evidence in less competent reaction when hexane is the solvent, LiCl less soluble)



Tetrahedron Lett 2009, 50, 49, 6787-90.

Mongin (2009 and 2011): continued

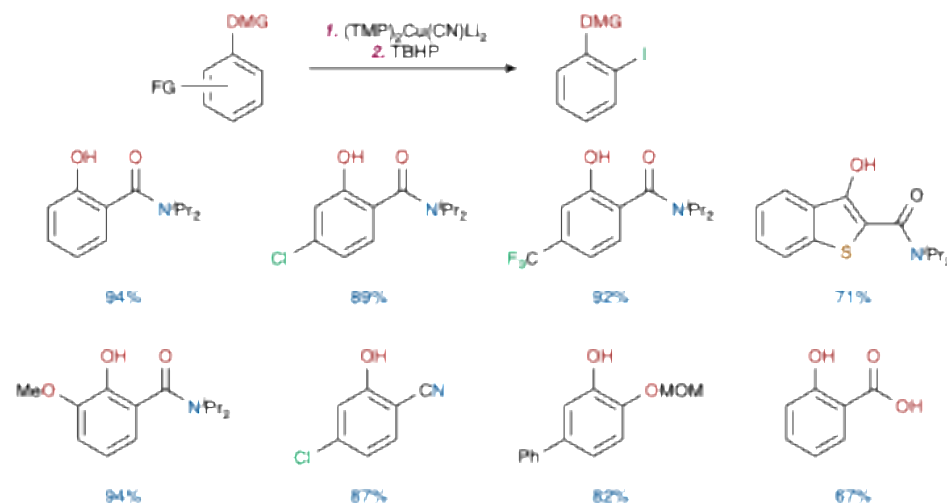


In the 2011 paper the Mongin group also showcased palladium-catalyzed cross-coupling. We will return to this on slide three!

Chem. Eur. J. 211, 17, 10405-16.

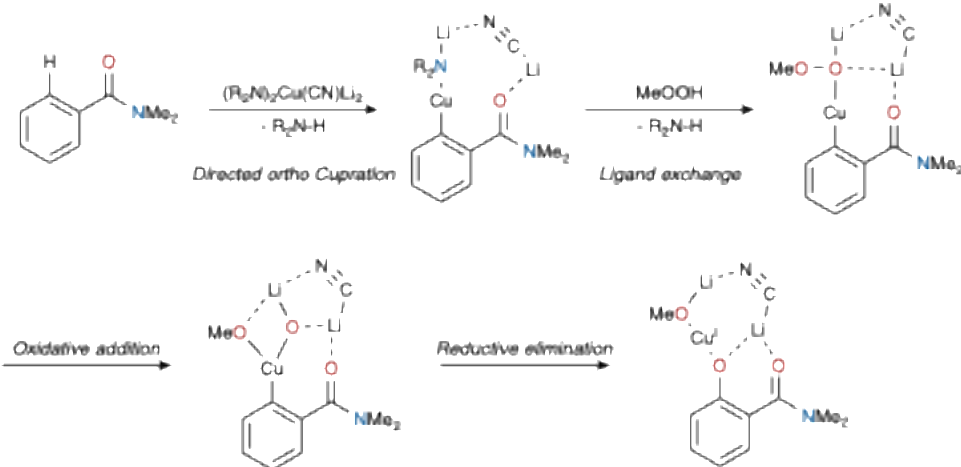
DoC Hydroxylation and Amination of Arenes

Uchiyama (2016): Direct hydroxylation and Amination Via Deprotonative Cupration

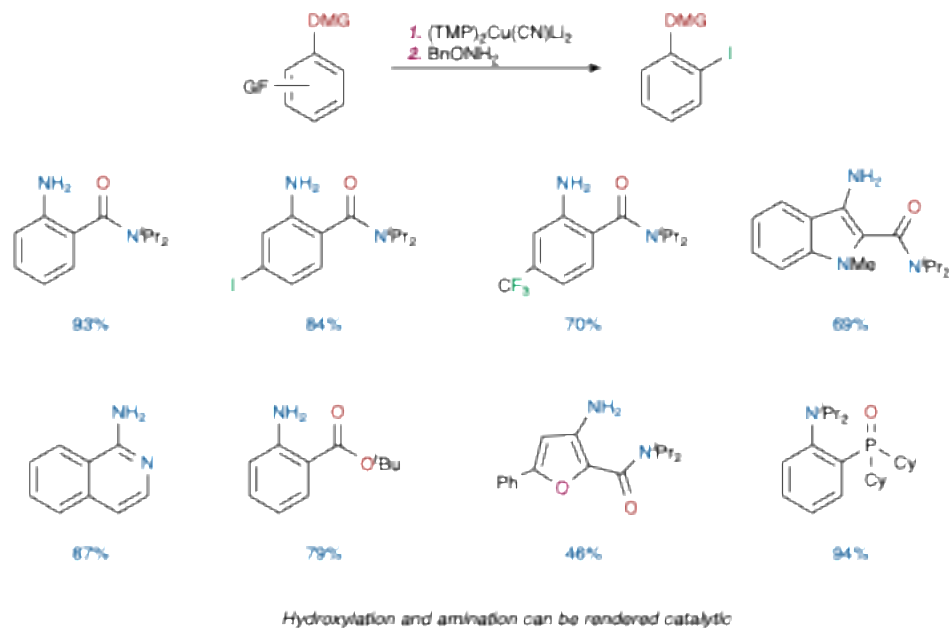


J. Am. Chem. Soc. 2016, 138, 9166-71

Proposed Mechanism For Direct Hydroxylation



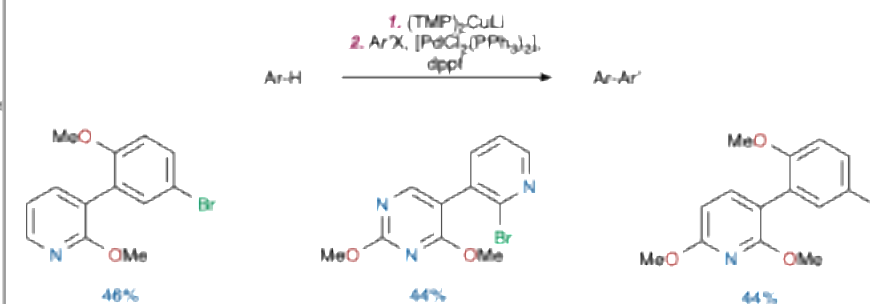
Uchiyama (2016): Amination Continued



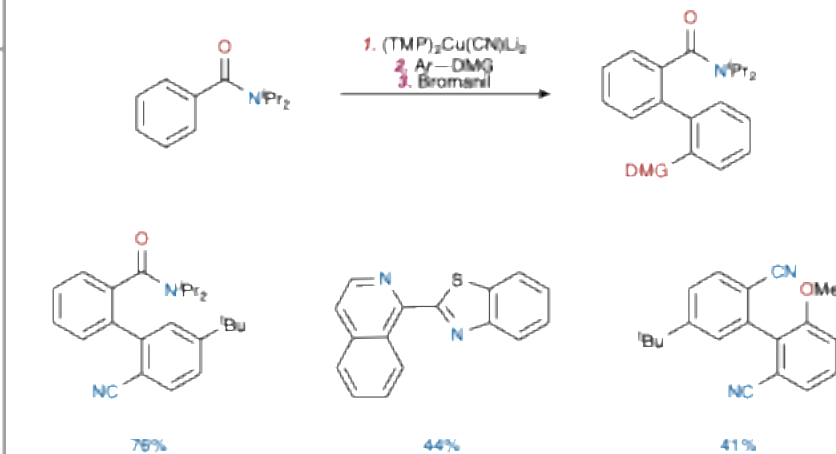
J. Am. Chem. Soc. 2016, 138, 9166-71

Directed *ortho* Cupration: Cross Coupling

Mongin (2011): Palladium-catalyzed Cross Coupling

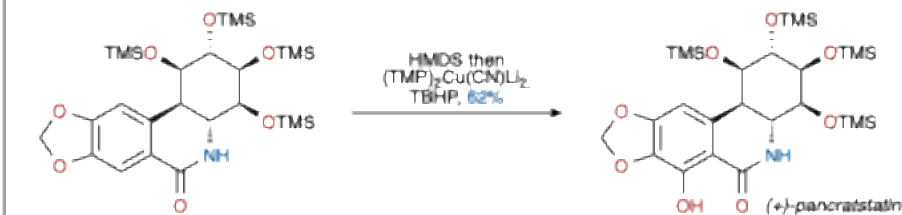


Uchiyama (2019): Oxidative Cross-Coupling



Org. Lett. 2019, 21, 9536-40.

Applications in Synthesis: Sarlah (2018)



J. Am. Chem. Soc. 2019, 141, 657-70