

# **Water-Mediated Catalyst Preactivation: An Efficient Protocol for C-N Cross-Coupling Reactions**

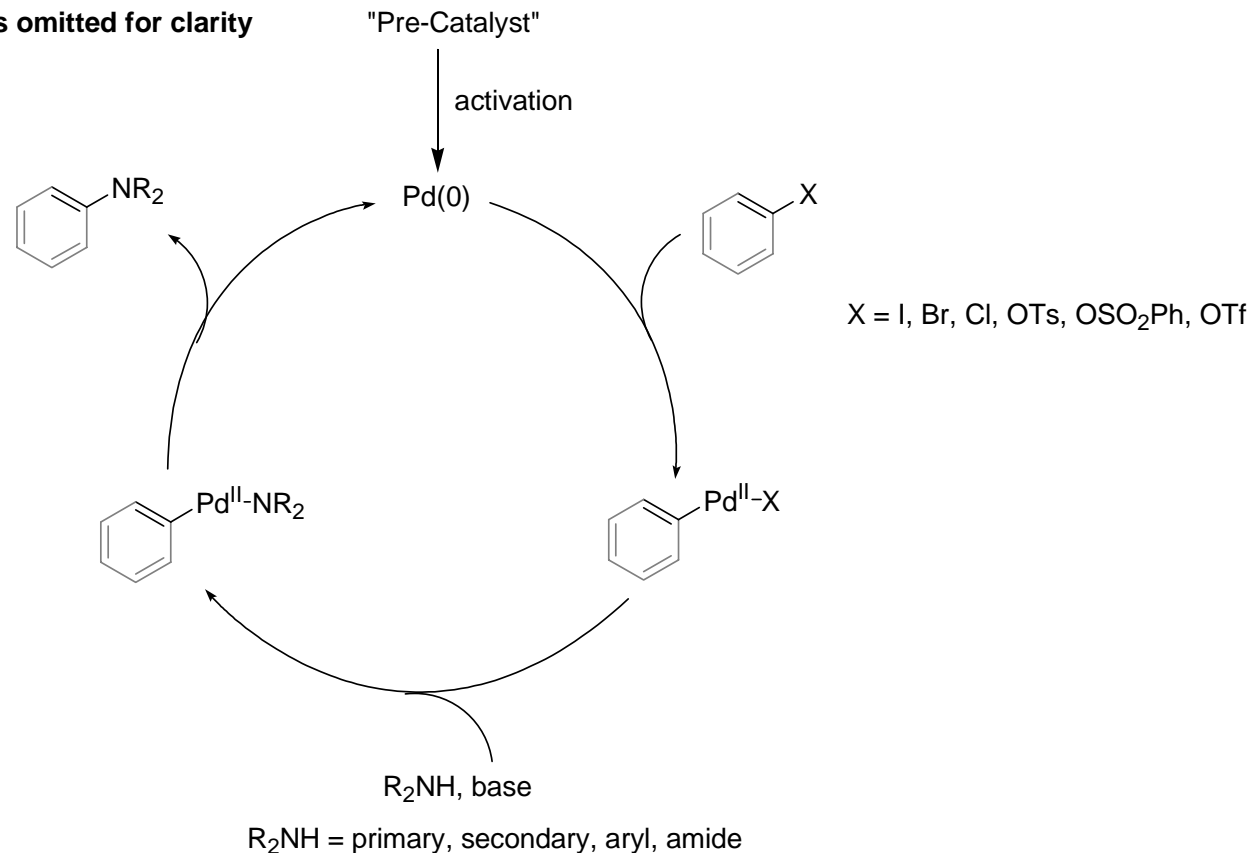
Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L.  
*Org. Lett.* **2008**, *ASAP*.

**Chad Hopkins**  
**Wipf Group Literature Presentation**  
**7-19-08**

# Buchwald-Hartwig Coupling

## General Mechanism

\*Ligands omitted for clarity



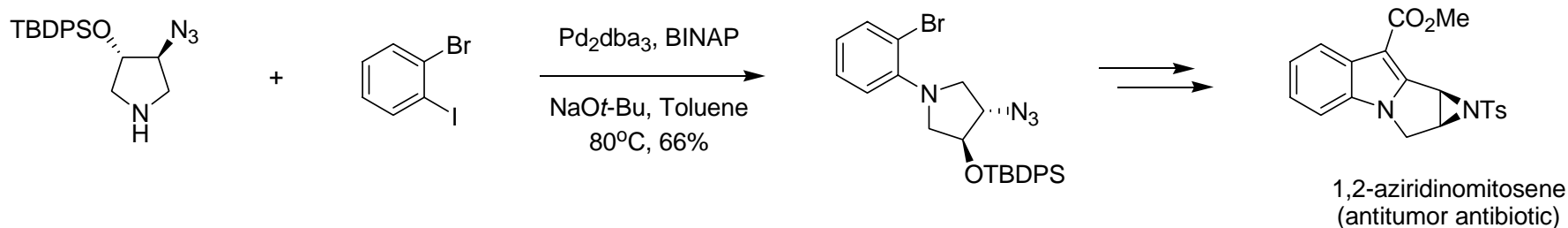
### *Seminal Publications:*

Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

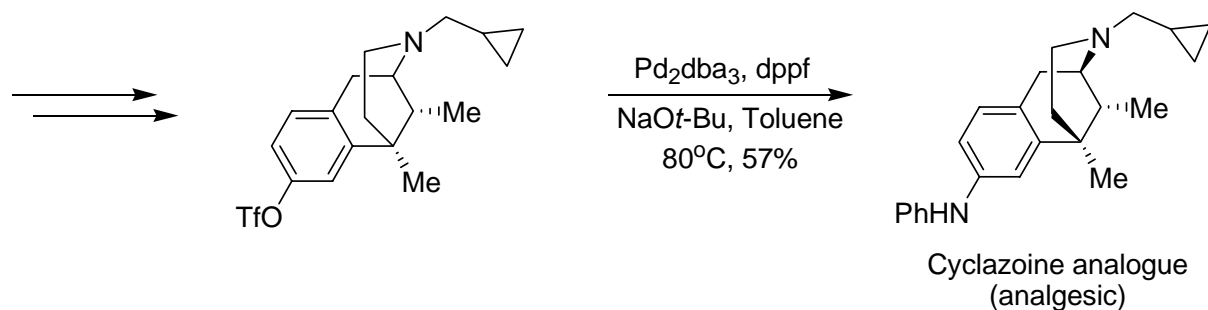
Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (received February 22)

Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (received May 23)

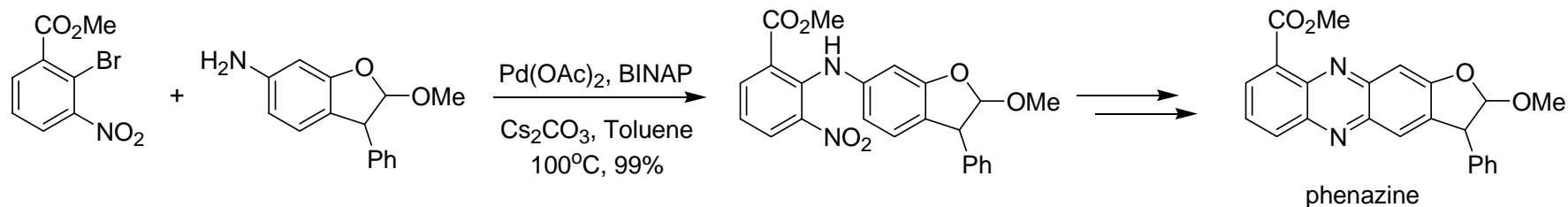
# The Buchwald-Hartwig Reaction as a Tool in Organic Synthesis



Lee, S.; Lee, W.-M.; Sulikowski, G. A. *J. Org. Chem.* **1999**, *64*, 4224.



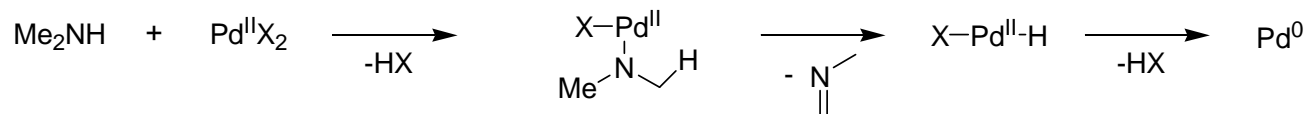
Wentland, M. P.; Xu, G.; Cioffi, C. L.; Ye, Y.; Duan, W.; Cohen, D. J.; Colasurdo, A. M.; Bidlack, J. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 183.



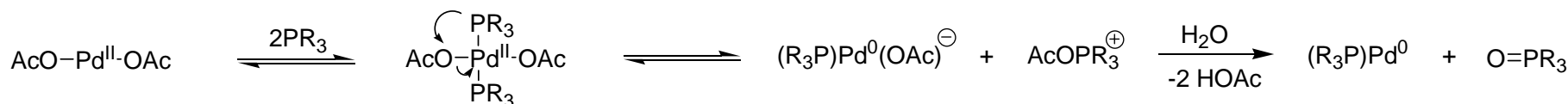
# Activation of Precatalyst



Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.



Trzeciak, A. M.; Ciunik, Z.; Ziolkowski, J. J. *Organometallics*, **2002**, *21*, 132.



Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics*, **1992**, *11*, 3009

Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, ASAP.

# Water-Mediated Preactivation

Catalyst activation: Pd(OAc)<sub>2</sub> (0.01mmol), XPhos (0.03 mmol), H<sub>2</sub>O (0.04 mmol), 1mL 1,4-dioxane, 80°C



0 sec



15 sec



30 sec

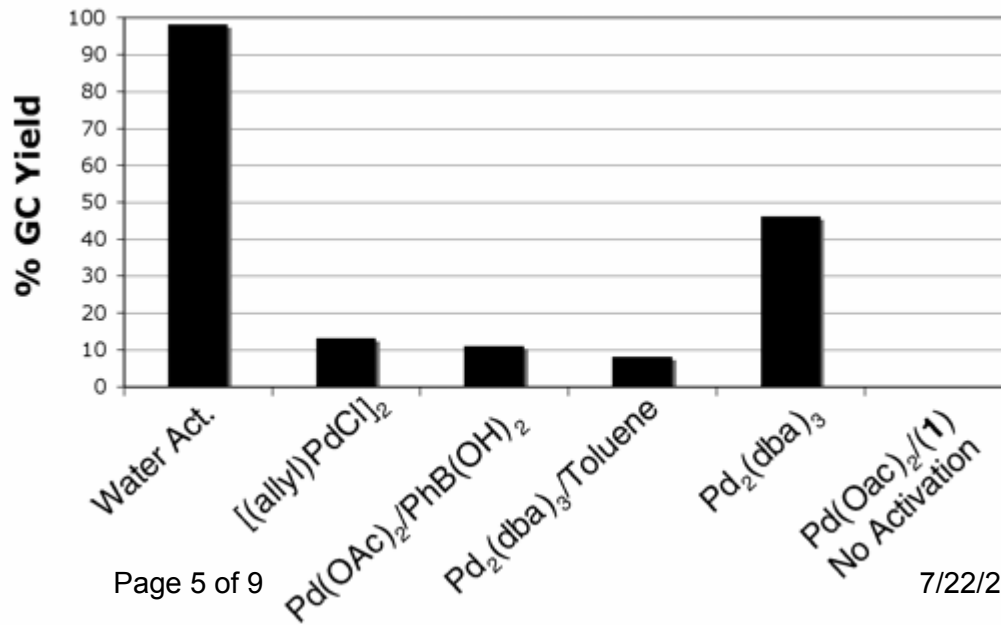
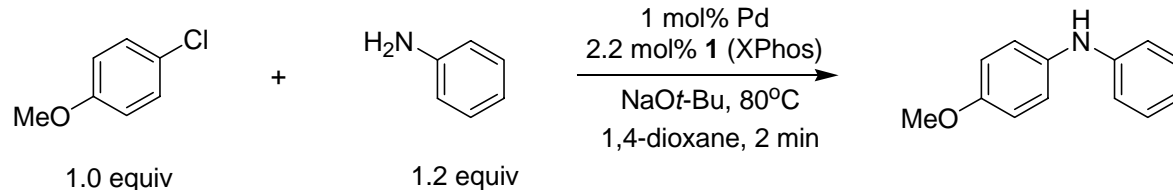


60 sec

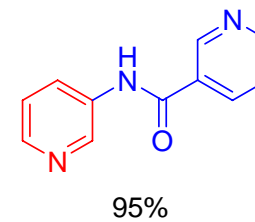
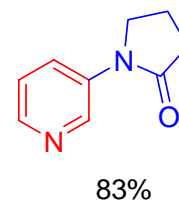
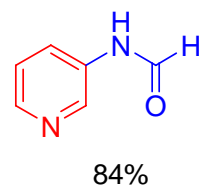
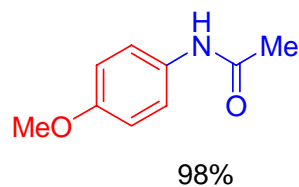
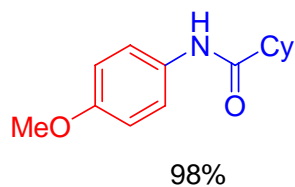
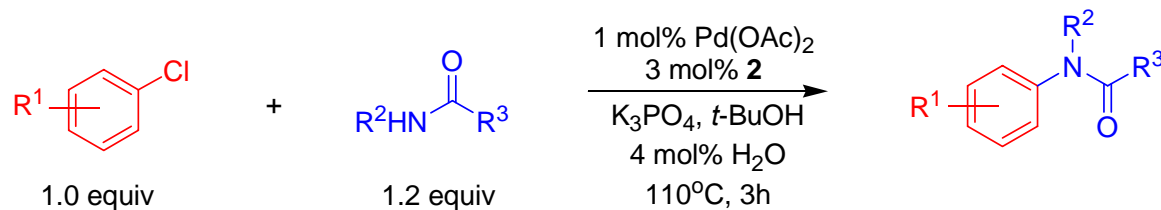
- <sup>31</sup>P NMR was inconclusive as to the structure of active Pd species

- Activated catalyst may be stored under Ar at -25°C for 24h with minimal loss in activity

- **Order of addition is important!!** Catalyst must be activated prior to addition of remaining reactants

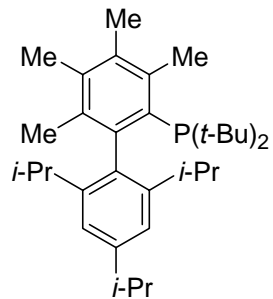


# Improved Amidation of Aryl Chlorides



|     |     |                  |                  |     |
|-----|-----|------------------|------------------|-----|
| 96% | 99% | 82%              | 83%              | 97% |
| 24h | 24h | 4 mol% Pd<br>12h | 2 mol% Pd<br>24h | 24h |

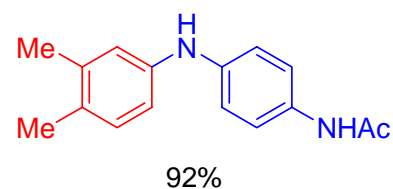
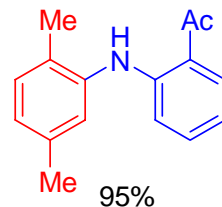
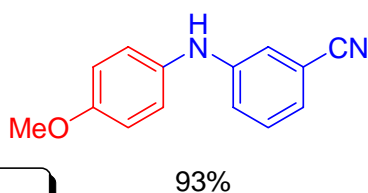
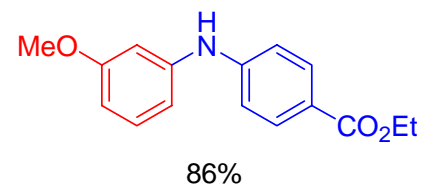
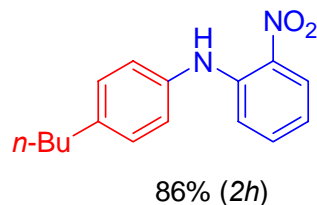
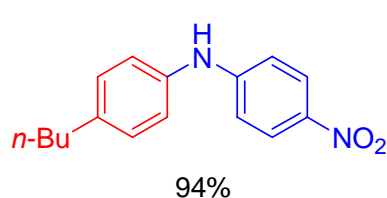
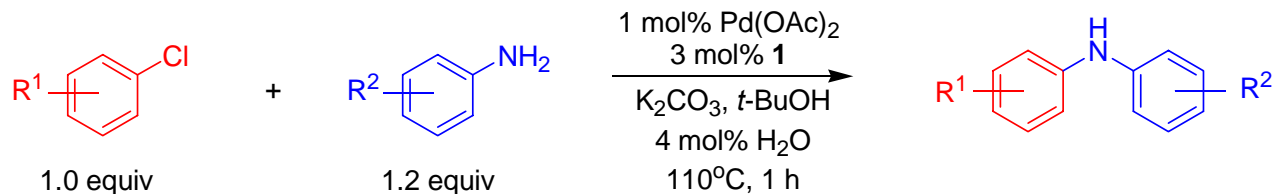
**Previous Results obtained w/ Pd<sub>2</sub>dba<sub>3</sub> or Pd<sub>2</sub>dcb<sub>3</sub>**



Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734-7735.

Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001-13007.

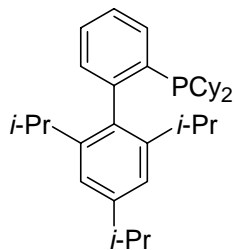
# Efficient Coupling of Electron Deficient Anilines



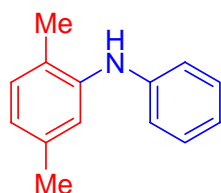
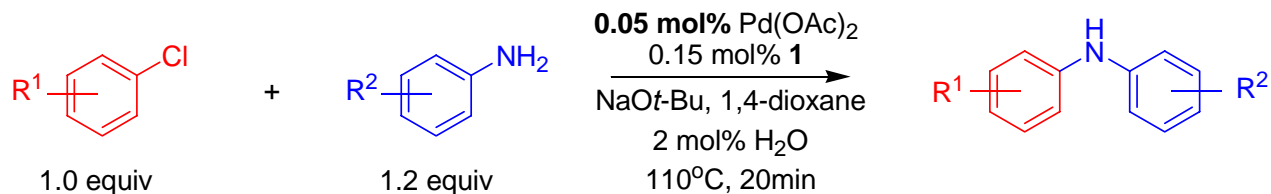
For similar examples, see:

Briscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

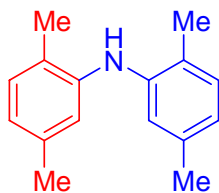
For examples involving  $\alpha$ -arylation of ketones, see:



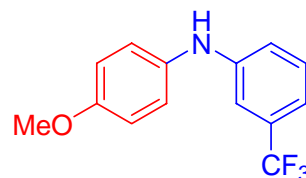
# Coupling of Anilines and Aryl Chlorides with 0.05 mol% Pd Loading



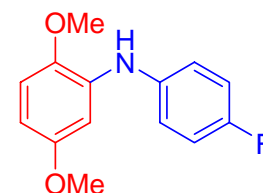
95%



98%



95%



99%

For examples involving coupling of anilines and aryl chlorides using 0.5 mol% Pd see:

Xu, C.; Gong, J.; Wu, Y. *Tetrahedron Lett.* **2007**, 48, 1619.

Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004**, 10, 2983.

Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, 130, 6686.

Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, 128, 4101.



# Conclusions

- Improved Pd-Catalyzed C-N cross-coupling reaction is described
- Preactivation of Pd(OAc)<sub>2</sub> using water in the presence of biaryldialkylphosphine ligands affords a highly active catalyst
- Active catalyst may be stored at low temperature under argon for short periods of time
- Protocol allows for lower catalyst loading and shorter reactions times
- Provides efficient coupling of deactivated aryl chlorides and anilines