Biaryl Ligands for C–N Coupling

**Amination:**

\[
\text{R}^1\text{R}^2\text{Cl} + \text{HN}_2\text{R}^1\text{R}^2 \xrightarrow{\text{Pd(OAc)}_2 (1-2 \text{ mol\%}) \text{ JohnPhos} (2-4 \text{ mol\%})} \text{R}^1\text{N}^1\text{R}^2\text{H} \quad (1.2 \text{ equiv})
\]

\[
\xrightarrow{t\text{-BuONa} (1.4 \text{ equiv}) \text{ PhMe} (1 \text{ M}) \text{ r.t.}} \text{9 examples up to 99\% yield}
\]

- **98\% yield (1 mol\% Pd)**
- **95\% yield* (0.005 mol\% Pd)**
  *used Pd(dba)3 at 100 °C

- **86\% yield (2 mol\% Pd)**
- **99\% yield (1 mol\% Pd)**
- **81\% yield (2 mol\% Pd)**

**Suzuki coupling:**

\[
\text{R}^1\text{Cl} + \text{HO(B)}\text{R}^1 \xrightarrow{\text{Pd(OAc)}_2 (1-1.5 \text{ mol\%}) \text{ JohnPhos} (2-3 \text{ mol\%})} \text{R}^1\text{R}^1\text{B} \quad (1.5 \text{ equiv})
\]

\[
\xrightarrow{KF (3 \text{ equiv}) \text{ THF} (1 \text{ M}) \text{ r.t.}} \text{95\% yield (1 mol\% Pd)}
\]

- **95\% yield (1 mol\% Pd)**
- **92\% yield (1.5 mol\% Pd)**
- **91\% yield (1 mol\% Pd)**

**Significance:** Aryl carbon–nitrogen bonds are ubiquitous in nature and important pharmaceuticals; however, a mild and catalytic method for their formation has been a major hurdle for organic chemistry. In the late 1990s Buchwald described a new series of dialkylbiaryl phosphine ligands that allowed for mild and efficient palladium-catalyzed cross-couplings. Further work led to the development of JohnPhos, which enabled room temperature palladium-catalyzed intermolecular amination. This seminal work set the stage for widespread adoption of Buchwald ligands in both industry and academia. Herein, Buchwald reports the discovery of JohnPhos, a bulky biaryl ligand, for amination and Suzuki coupling under mild conditions.

**Comment:** The reported ligand, JohnPhos, contains bulky tert-butyl groups, which were crucial to facilitate the difficult reductive elimination of the aryl carbon–nitrogen bond. A variety of amines including anilines and alkylamines were tolerated in the reaction. Notably, very low loadings of palladium could be employed for the C–N coupling; however, the reaction required higher temperature. The capability of the new ligand was also explored in Suzuki coupling. The Suzuki coupling could also be run under similarly mild conditions with a variety of aryl halides and aryl boronic acids.