Biaryl Ligands for C–N Coupling

**Amination:**

\[
\text{R}^+\text{Cl} + \text{R}_2\text{N} + \text{Pd(OAc)}_2(1–2\text{ mol%}) + \text{JohnPhos}(2–4\text{ mol%}) \rightarrow \text{R}^1\text{R}^2\text{N}^+ \text{R}^1\text{R}^2 \text{P}((\text{t}-\text{Bu})_2) + \text{t-BuONa}(1.4\text{ equiv}) \text{PhMe}(1\text{ M), r.t.}  
\]

9 examples up to 99% yield

- 98% yield (1 mol% Pd)
- 95% yield* (0.005 mol% Pd)
*used Pd$_2$dba$_3$ at 100 °C

86% yield (2 mol% Pd)

99% yield (1 mol% Pd)

81% yield (2 mol% Pd)

**Suzuki coupling:**

\[
\text{R}^+\text{Cl} + \text{Ph}(\text{HO})_2\text{B}(\text{R}^1) + \text{Pd(OAc)}_2(1–1.5\text{ mol%}) + \text{JohnPhos}(2–3\text{ mol%}) \rightarrow \text{R}^1\text{R}^1\text{BPh}(1.2\text{ equiv}) \text{THF}(1\text{ M), r.t.}  
\]

95% yield (1 mol% Pd)

91% 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.