Biaryl Ligands for C–N Coupling

**Amination:**

\[
\begin{align*}
{R^1} & \quad + \quad H_{N}{R^2} \quad \xrightarrow{\text{Pd(OAc)\textsubscript{2} (1–2 mol\%)} \quad \text{JohnPhos (2–4 mol\%)} \quad \text{t-BuONa (1.4 equiv)} \quad \text{PhMe (1 M), r.t.}} \quad {R^1}_{\text{N}}{R^2} \\
(1.2 \text{ equiv})
\end{align*}
\]

9 examples up to 99% yield

98% yield (1 mol% Pd)
95% yield* (0.005 mol% Pd)
*used Pd\textsubscript{2}dba\textsubscript{3} at 100 °C
96% yield (2 mol% Pd)
99% yield (1 mol% Pd)
81% yield (2 mol% Pd)

**Suzuki coupling:**

\[
\begin{align*}
{R^1} & \quad + \quad (\text{HO})\textsubscript{2}B_{R^1} \quad \xrightarrow{\text{Pd(OAc)\textsubscript{2} (1–1.5 mol\%)} \quad \text{JohnPhos (2–3 mol\%)} \quad \text{KF (3 equiv)} \quad \text{THF (1 M), r.t.}} \quad {R^1}_{\text{N}}{R^2} \\
(1.5 \text{ equiv})
\end{align*}
\]

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.