Biaryl Ligands for C–N Coupling

**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.

**Amination:**

\[
\text{R}_1^+ \text{HN}_2 \text{R}_2^+ \xrightarrow{\text{Pd(OAc)}_2 (1-2 \text{ mol\%}) \text{ JohnPhos (2-4 mol\%)} \text{ tBuONa (1.4 equiv)} \text{ PhMe (1 M), r.t.}} \text{R}_1^1 \text{HN}_2 \text{R}_2^2
\]

- 98% yield (1 mol% Pd)
- 95% yield* (0.005 mol% Pd)

*used Pddba3 at 100 °C

- 86% yield (2 mol% Pd)
- 99% yield (1 mol% Pd)

- 81% yield (2 mol% Pd)

**Suzuki coupling:**

\[
\text{R}_1^+ \text{H} \xrightarrow{\text{Pd(OAc)}_2 (1-1.5 \text{ mol\%}) \text{ JohnPhos (2-3 mol\%)} \text{ KF (3 equiv)} \text{ THF (1 M), r.t.}} \text{R}_1^1
\]

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

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