Copper-Catalyzed Amidation of π-Excessive Heterocycles

Representative examples:

\[
\begin{align*}
\text{S}&: \quad \text{88\% yield} \\
\text{O}&: \quad \text{78\% yield} \\
\text{N}&: \quad \text{89\% yield} \\
\text{Br}&: \quad \text{86\% yield} \\
\text{MeO}_2\text{C}&: \quad \text{85\% yield} \\
\text{NC}&: \quad \text{83\% yield} \\
\text{Ph}&: \quad \text{76\% yield}
\end{align*}
\]

**Significance:** Amino-substituted heterocycles are prevalent as subunits in a large number of pharmaceutical drug targets. As a result, transition-metal-catalyzed aryl C–N bond formation has been studied extensively. Traditionally, these compounds are synthesized by coupling heteroaryl halides with amine surrogates. Pan and co-workers report an efficient method for direct amidation of π-electron-rich heterocycles with N-fluorobenzenesulfonimide (NFSI). Interestingly, even though NFSI is typically used as a fluorinating reagent, no fluorinated byproducts are observed in this reaction. The procedure uses mild conditions to provide the desired functionalized products in high yields.

**Comment:** A variety of electron-deficient and electron-rich thiophenes, furans, and pyrroles undergo regioselective amidation under these reaction conditions. Although the reaction does proceed at ambient temperature, higher yields are obtained at slightly elevated temperature (60 °C). A mechanistic pathway involving copper(I), copper(II), and copper(III) species is proposed, and further studies to investigate the mechanism of this transformation are underway. For a recent method of 2-aminothiophene and other π-excessive heterocycle synthesis, see the copper(II)-catalyzed synthesis of 2-aminothiophenes from alkynoates and thioamides (Org. Biomol. Chem. 2014, 12, 8473; Synfacts 2015, 11, 24).