Palladium/SOX Catalyzed Tertiary Allylic Aryl Amination

Zachary M. Firestein and M. Christina White

Aryl amines are highly represented motifs in medicinal chemistry, present in one-third of pharmaceutical compounds. However, the synthesis of dissymmetric tertiary aryl amines is often plagued by challenges owed to the relatively poor nucleophilicity of the corresponding secondary aryl amine and frequently relies on the use of harsh conditions and stoichiometric excesses of coupling partners. Metal-mediated protocols have made limited headway into forging these types $C(sp^3)$—$N(sp^2)$ bonds, yet even the most recent art fails to capture a method that accesses tertiary *N*-alkyl aryl amines with generality. We hypothesized that a Pd(SOX) catalyzed C—H amination strategy would empower a $C(sp^3)$—$N(sp^2)$ cross-coupling strategy that features high functional group tolerance and excellent reactivity and selectivities. Herein we report the development of such a method that couples secondary aryl amine nucleophiles and terminal olefins via an electrophilic palladium-π-allyl intermediate under fragment coupling conditions. Our comprehensive scope of tertiary *N*-alkyl aryl amine products showcases over 90 examples highlighting broad functional group tolerance, challenging steric and electronic profiles for both coupling partners, an array of complex and drug-fragment couplings, and exceptional reactivity and selectivity under mild conditions. Mechanistic studies provide insight into the nature of the palladium-π-allyl electrophile, the mode of functionalization by the amine nucleophile, and the rate determining step of the reaction.