Boronic Ester Design Enables Rapid, Anhydrous, and Homogenous Suzuki-Miyaura Cross-Coupling of Secondary Alkylboronates

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Within the last few decades, B-alkyl Suzuki-Miyaura cross-coupling (SMCC) has sparked considerable interest as a method for forging C(sp^2)-C(sp^3) bonds. Nonetheless, despite advances made in both ligand and boronate design, these challenging couplings typically lack in generality and suffer from long reaction times, stemming from slow transmetalation of alkylboronates and rapid β-hydride elimination of alkylpalladium(II) complexes. To address these issues, our group recently developed a rapid, anhydrous, and homogenous B-alkyl SMCC of aryl halides and primary boronic esters, employing neopentyl alkylboronic esters as a means of increasing the rate of transmetalation. Unfortunately, these conditions were unsuccessful with secondary alkylboronic esters due to deleterious protodehalogenation arising from the boronic ester backbone.

Here, we present a rapid, anhydrous, and homogenous B-alkyl SMCC of aryl and alkenyl halides enabled by formation of a fully substituted boronate. Investigation of many *sec*-butylboronic esters derived from 1,2 and 1,3 diols indicated that substitution proximal to the oxygens on the boronic ester skeleton was crucial for circumventing protodehalogenation. Subsequently, further experimentation led to the identification of a boronate generated *in situ* from tetramethyl N-methyliminodiacetic acid (TIDA) alkylboronates and potassium trimethylsilanolate, tentatively identified as RB(OTMS)$_3$, that could undergo secondary B-alkyl SMCC. After a brief high-throughput optimization campaign, B-alkyl SMCCs could be performed with both cyclic and acyclic secondary alkylBTIDAs and variety of aryl and alkenyl halides in good to great yields, branched/linear selectivities, and fast reaction times. Furthermore, preliminary studies suggest that this transformation is highly stereospecific with inversion of configuration. Overall, this method not only greatly optimizes known B-alkyl SMCCs but also enables new reactivity with previously unreported electrophiles, positioning this method to be a state-of-the-art approach for direct C(sp^2)-C(sp^3) bond formation.