The Report of Study in Cross-Coupling Reactions Between Boronic Esters and Unhalogenated Coupling Partner

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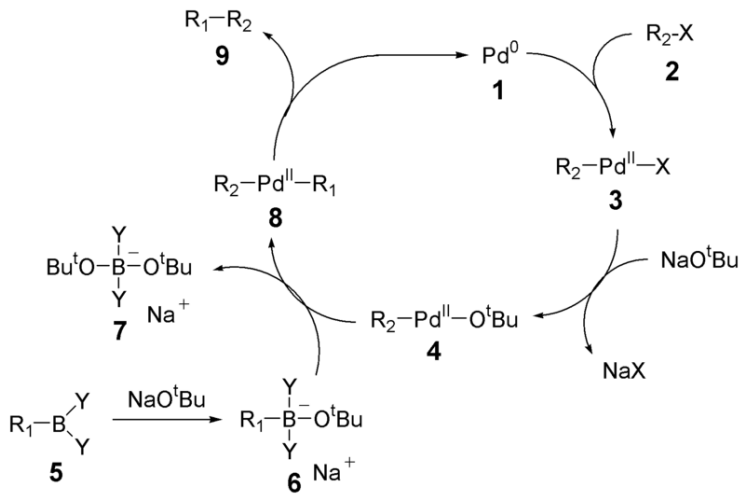
The Suzuki cross-coupling reaction is one of the most common methods for aromatic carbon-carbon bond formation both in industry and academia. It enables transformations which otherwise would be difficult (requiring multiple steps and activating reagents) or even impossible. In brief, two activated aryl groups are joined together through metal catalysis. As you can see from the mechanism (Scheme 1) the first step is oxidative addition of the catalyst (usually palladium) into the halogen-carbon bond of the activated aryl ring followed by the transmetallation (facilitated by base) of the boron- activated second aryl ring. Finally, reductive elimination gives the cross coupled biaryl product, usually in high yield. This reaction is very commonly used despite the fact that a stoichiometric amount of halogenated waste (NaX) is produced during the cycle and subsequently needs to be disposed of. Furthermore the production of the aryl halide starting material also produces halogenated waste in as well as an additional step requiring solvents, reagents and purification. It is clear that changing this coupling species into something which does not produce halogenated waste would be a great improvement: not only would the addition step would be avoided but an enormous amount of energy would be saved from the elimination of the disposal of byproduct step.



Scheme 1: Mechanism of the Suzuki-Myiaura Cross-Coupling Reaction

Shortly before I joined his group, Chatani-sensei had published a procedure to do this: through nickel catalysis they could afford the cross-coupling of a boronic ester and an aryl ether (Scheme 2). This provides industry with a less polluting alternative to the Suzuki-Myiaura cross-coupling as the byproduct formed from the ether is methanol. Unfortunately, the scope of this reaction was limited to extended π system like naphthalene. The

Scheme 2: Cross-Coupling Reaction Conditions Using a Non-Halogenated Aryl Species

goal of my research was to extend the scope to more common aryl substrates in order to make the methodology more widely applicable. Preliminary results showed that a carbonyl group in the meta position of the phenyl ring was a promising route. The first series of compounds scanned possessed this functionality combined to another which ranged from very electron withdrawing to very electron donating.

Figure 1: example of an effective chelating substrate

This initial scan did not show any promising results so we moved on to a different class of substrates with chelating groups in spatial proximity to the C-O bond we were trying to activate (Figure 1). We were very happy to isolate 48 % yield under the reaction conditions. Many other chelating groups in the same position were scanned to get an idea of the scope of this reaction. Amides and amines were unreactive under the reaction conditions (these functional groups are known to bind irreversibly to metals). Extended ethers were also unsuitable coupling partners but *o*-ketones cross-coupled to a small extent (14 %). Based on these results, we decided it would be very difficult to broaden the scope to an applicable extent. We then considered two options; the first was to design a pyridine-based directing group to be used instead of the methyl ether in which the chelating nitrogen would be in a position to aid reactivity but would be eliminated during the course of the reaction and the second, to test various pyridine bases as ligands for the reaction. Given that the second option would avoid an additional chemical step and that the first option produces a pyridine byproduct instead of just methanol, we decided to look into the effect of different ligands. Various pyridines were scanned: pyridine; 2- picolidine; 2,6-lutidine and 2,5-lutidine were scanned an different equivalents. The most promising reaction conditions were done using 2,6-lutidine. We saw a 10 % increase in yield with 2-methoxyacetophenone compared to the reaction without ligand. We are confident that we will see a more pronounced effect with substrates which do not possess a chelating group but due to time constraints I was unable to scan the scope of the reaction conditions with different aryl ether reagents.

The work left to do on this project is straightforward: verify that the increase in yield caused by 2,6-lutidine with 2-methoxyacetophenone is applicable to other substrates. In this case the reaction conditions can be further optimized to increase the yield.