

Boron Facilitated Catalytic Conjunctive Cross Coupling

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The enantiospecific formation of C–C bonds and carbon-heteroatom bonds is an important reaction¹ that has important applications in the synthesis of pharmaceuticals and fine chemicals, as well as other industrial processes.² For example, in the Suzuki-Miyaura cross-coupling reaction, a palladium catalyst is used to form new C–C bonds from organic halides and organoboronic esters.^{2,3} Although traditional cross-coupling reactions have been designed to combine only two molecular fragments, a new reaction known as conjunctive cross-coupling combines three easily accessible starting materials to form two new C–C bonds.⁴ These three reagents are an organoboronic ester, an organolithium (or Grignard) reagent, and an organic electrophile.⁴

Cross coupling reactions take advantage of the electron deficient nature of boron reagents, which have an empty p-orbital. Lewis bases or other electron rich substrates often interact with this empty p-orbital to form 4-coordinate borate or boronate complexes.⁵ These complexes undergo 1,2-metallate rearrangements in the presence of an electrophile, to rid the boron of the negative charge (**Figure 1**).^{5,6}

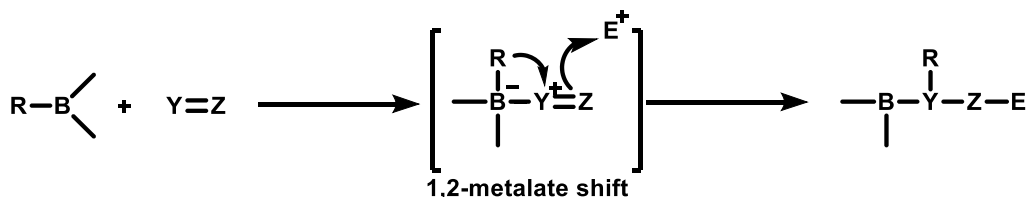


Figure 1: 1,2-metallate shift promoted by presence of an electrophile.

Interestingly, palladium can induce this type of transformation when coordinated to these anionic borate complexes.⁷ Utilizing this reactivity, the Morcken Lab has designed a system to carry out what they term conjunctive cross-coupled products. The word conjunctive describes the ability of the system to combine two nucleophilic reagents during one catalytic cycle, unlike traditional cross-coupling chemistries.⁴ The proposed catalytic cycle, shown in **Figure 2**, begins with oxidative addition of the organic electrophile to palladium(0) to produce a palladium(II) species. It is the following step where the mechanism of the conjunctive cross-coupled reaction diverges from its Suzuki-Miyaura counterpart; instead of undergoing transmetalation with the boronate complex, the boronate complex coordinates to the palladium center through an olefin. This step is followed by the metal induced 1,2-rearrangement to transfer an alkyl/aryl group to the sp^2 carbon, generating the first new C–C bond. The stereoelectronic requirements dictate that the migration must occur in an anti-periplanar fashion, which results in the formation of a stereocenter on the carbon that is receiving the migrating group. This step is followed by reductive elimination to furnish the second the final C–C bond.⁴

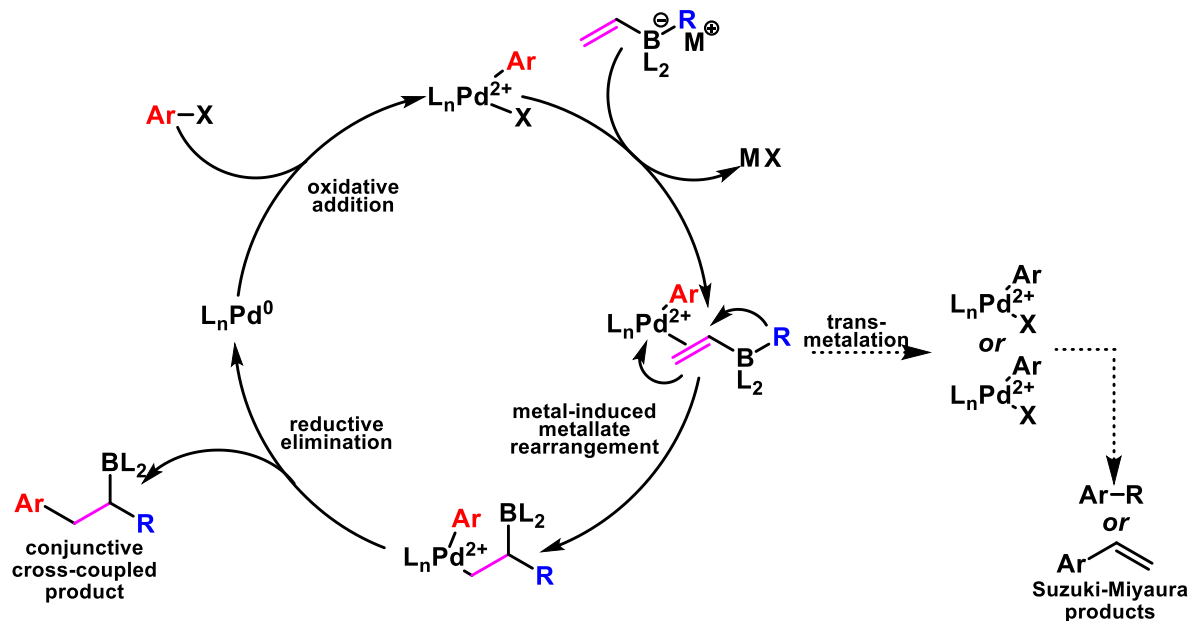


Figure 2: Proposed catalytic cycle for conjunctive cross-coupling.

Mechanistic studies^{4,8,9} have established the role that each component plays in the conjunctive cross-coupling reaction. The bidentate ligand should have a large bite angle so as to promote the reductive elimination step, and this ligand also affects the enantiomeric ratio of the final product.^{4,10} However, the ligand is not solely responsible for this stereochemical outcome, as the boronic ester used also dictates whether one enantiomer is favored over the other.¹¹ The reagent used to activate the boronic ester is also a key factor and must be highly nucleophilic to generate and stabilize the boronate complex. Recent advancements in this area have shown that the organolithium reagents can be replaced with standard Grignard reagents provided that NaOTf is added, which make the latter more nucleophilic, and provided that DMSO is employed as a co-solvent, which aids in the stabilization of the boronate complexes.⁹ Lastly, electron-poor aryl groups on the borate complex are slightly detrimental to this reactivity,⁴ probably because they stabilize the boronate complex and disfavor migration.

In conclusion, by employing three readily accessible components – an organoboronic ester, and organolithium reagent/Grignard reagent, and an organic electrophile – and an appropriate catalyst, it is now possible to form two new C–C bonds, and generate a stereocenter bearing a boronic ester functionality, in a single reaction known as conjunctive cross-coupling. This process is widely adaptable and tolerant of an array of functional groups, and possess a great future for applications in industrial synthesis.

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