

# DEVELOPMENT OF ASYMMETRIC CROSS-COUPLING REACTIONS

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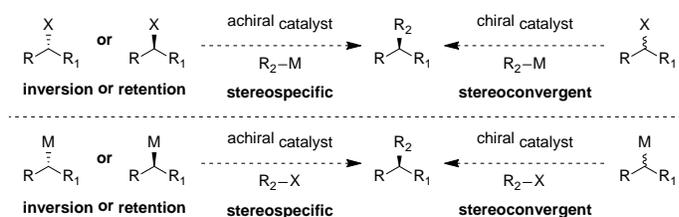
## BACKGROUND

Transition metal-catalyzed cross-coupling reactions have become one of the most powerful methods for the synthesis of diverse and complex organic compounds which is essential for the production of commodities such as pharmaceuticals, agrochemicals and high-performance materials.<sup>1</sup> In a typical cross-coupling reaction, an organic electrophile,  $R^1-X$ , reacts with an organometallic nucleophile,  $R^2-M$ , in the presence of a transition metal catalyst, generating a new  $R^1-R^2$  bond.

Traditional cross-coupling methods are extremely efficient for the cross-coupling of  $C(sp^2)$  or  $C(sp)$  reactants. However, traditional methods for the cross-coupling of  $C(sp^3)$  compounds possess three main challenges.<sup>1</sup> First, alkyl organometallic compounds that possess  $\beta$ -hydrogen atoms can lead to undesired  $\beta$ -hydride elimination. Second, oxidative addition of alkyl halides is slow due to increased steric hindrance and electron density.<sup>2</sup> Finally, when coupling secondary  $sp^3$  carbons up to two stereocenters are formed; to be synthetically useful the process should be either stereospecific or stereoconvergent.

## ASYMMETRIC C-C CROSS-COUPLING

Pioneering work has led to the recent development of a wide-variety of primary  $C(sp^3)$  cross-coupling reactions with a range of electrophiles and organometallic reagents.<sup>3,4</sup> However, little reactivity was observed during cross-coupling of secondary electrophiles which possess the same disadvantages as primary alkyl halides, but oxidative addition is even slower. To increase the rate of oxidative addition, many strategies rely on the use of directing groups or other activated substrates. The nature of the electrophile and nucleophile can lead to useful stereospecific or stereoconvergent reactions (Scheme 1).



**Scheme 1.** Asymmetric Cross-Coupling Strategies

### Stereospecific Cross-Coupling

The majority of asymmetric cross-coupling reactions that have been developed are stereospecific. Pioneering work with chiral tin<sup>5</sup> and boron<sup>6,7</sup> organometallic agents has shown that stereospecific couplings can occur with inversion or retention based on reaction conditions. Recently, Lewis-basic directing groups that contain a carbonyl have been used to coordinate to the empty p-orbital on boron-containing substrates which leads to inversion, because the approach of the metal catalyst is restricted to the back side of the substrate (Scheme 2).<sup>8</sup> It has also been demonstrated that by using a Lewis-acidic

additive, retention of configuration can be achieved with little or no  $\beta$ -hydride elimination or protodeboronation.<sup>9</sup> Although stereospecific reactions can be achieved with high yields and enantioselectivities, they require an additional step to install the chiral organoboron nucleophile.

### Stereoconvergent Cross-Coupling

A more synthetically useful method would be one that uses racemic starting materials and takes advantage of catalyst control of configurationally labile intermediates to achieve stereoconvergent cross-coupling.<sup>10,11</sup> Pioneering work<sup>12</sup> has led to the use homobenzylic halides that are coupled through a Suzuki reaction in high enantioselectivities

using a chiral nickel catalyst (Scheme 3). In this case, a single electron transfer pathway generates a radical on the electrophile, enabling the chiral catalyst to

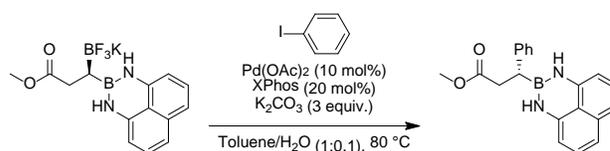
preferentially react with one face of the achiral intermediate. More recently, the scope has expanded to incorporate a wide variety of functional groups beyond homobenzylic halides.<sup>13–15</sup>

### Future Directions

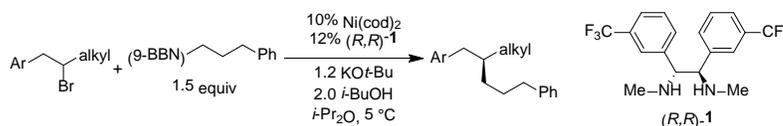
Two challenging future directions for the asymmetric cross-coupling reaction are the use of tertiary electrophiles to generate quaternary stereocenters<sup>3</sup> and the coupling of two secondary  $sp^3$  carbons to allow two adjacent stereocenters to be set simultaneously through a stereoconvergent cross-coupling.

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**Scheme 2.** Stereospecific cross-coupling of 1,1-diboron compounds



**Scheme 3.** The first asymmetric cross-coupling of unactivated substrates