

## Asymmetric Suzuki–Miyaura cross-coupling of aryl chlorides with enhancement of reaction time and catalyst turnover

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The Suzuki–Miyaura cross-coupling reaction is one of the most widely used method for preparing biaryl bonds. The widespread availability of aryl chlorides contributes to the utility of this reaction in synthetic organic chemistry. The asymmetric variant remains an important challenge due to the importance of axially chiral biaryls in synthetic applications, material, and supramolecular chemistry. So far a few examples on catalytic enantioselective versions have been reported.

Recently, Lassaletta<sup>1</sup> and Uozumi<sup>2</sup> reported on highly efficient asymmetric cross-couplings. Lassaletta and co-workers utilized a novel C<sub>2</sub>-symmetric bis-hydrazone ligand, and Uozumi developed a polymer-supported catalyst. While their procedures achieved valuable enantioselectivities there is still room for improvement especially in terms of catalyst loadings and reaction times. In these prior works a minimum of 5 mol % of catalyst and 24 h of reaction time was necessary, though Uozumi was able to reuse their catalyst 4 times.

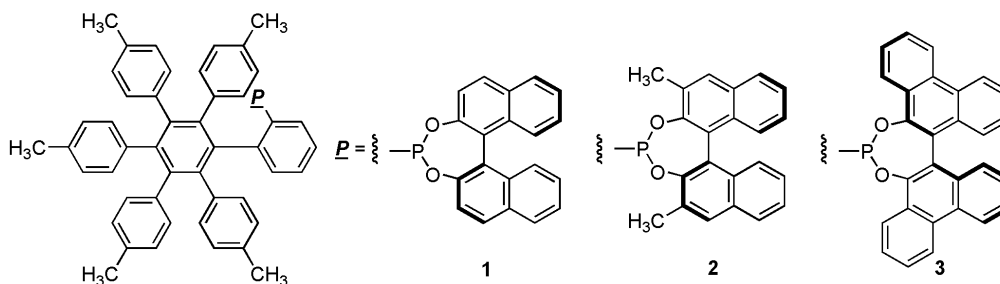
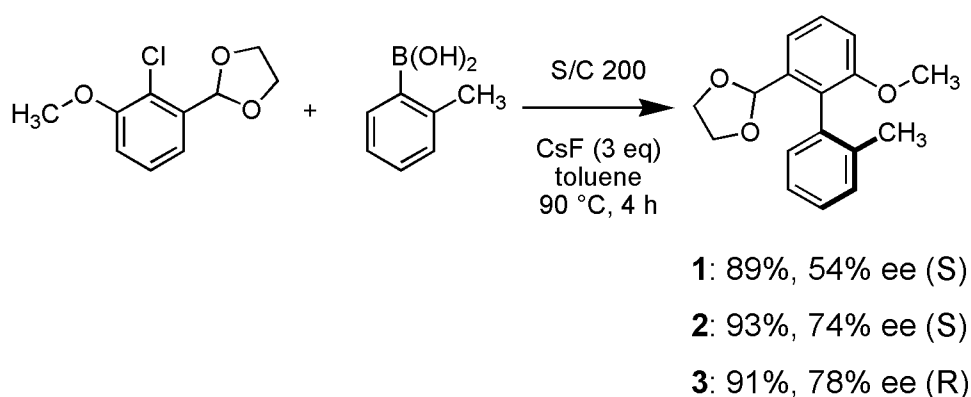


Figure 1 phosphonite **1**, **2** and **3**

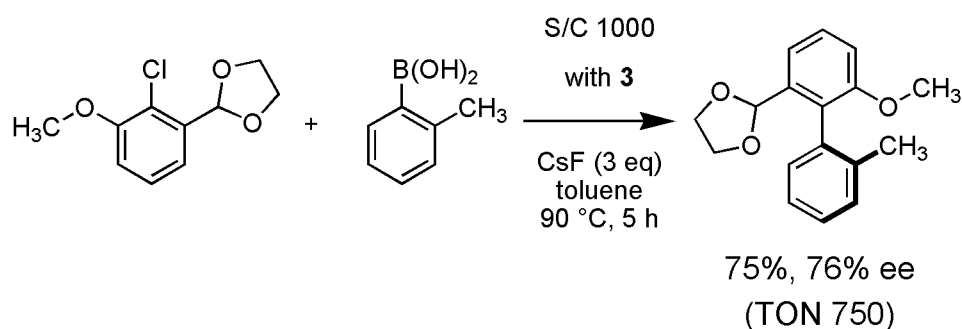
We report here in the three new phosphonites (**1**, **2**, and **3**) that promote the asymmetric cross-coupling of aryl chlorides with low catalyst loading and short reaction time (Fig. 1). Phosphonite **3** was found to give the axially chiral tri-ortho-substituted biaryl in 75% yield and 76% ee with a 0.1 mol % catalyst loading (catalyst turnover = 750) and 5 h reaction time.

At the outset of our study, the readily preparation of **1-3** led us to investigate its performance as a chiral ligand in palladium-catalyzed asymmetric Suzuki–Miyaura reactions. The reactions were carried out in the presence of [Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>] (dba = dibenzylideneacetone) and **1** (Scheme 1). As coupling partners, 2-(2-chloro-3-methoxyphenyl)-1,3-dioxolane **4** and ortho-tolylboronic acid **5** were chosen because of their availability.

The reactions were carried out in toluene with CsF at 90 °C for 4 h. The results in the S/C ratio 200 were summarized in Scheme 1. The ligand **1** gave a desired biaryl of (S) conformer with 89% yield and 54% ee. The phosphonite **2** bearing dimethyl group afforded the biaryl in 93% yield, increasing the stereoselectivity to 74% ee. The biphenanthrol derivative **3** yielded the best ee among ligand **1-3**, 91% yield and 78% ee. When the catalyst loading of Pd/phosphonite **3** system was lowered to 0.1 mol% (S/C = 1000) as shown in Scheme 2, the same reaction in 5 h proceeded in 75% yield (TON 750) and 76% ee.



Scheme 1. Asymmetric Suzuki–Miyaura reaction of **4** with **5**.



Scheme 2. Asymmetric cross-coupling in S/C 1000

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