Oligoarene Strategy for Catalyst Development. Hydroxylated Oligoarene-type Phosphines for Palladium-catalyzed Cross Coupling

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Various oligoarene-type phosphines having a hydroxy group were synthesized based on a two-step repetitive method that we developed, and these phosphines were used as ligands for palladium in catalytic cross coupling with Grignard reagents. The study revealed that a hydroxylated terphenylphosphine accelerated the rate of the cross coupling of *o*-bromophenol and exhibited preference for the ortho-isomer over the meta- and para-isomers.

Development of catalysts that enable highly efficient transformation of organic compounds is a major focus in synthetic chemistry. Here, we describe a new strategy based on oligoarene-type ligands for metal-catalyzed organic reactions.

Oligoarenes, composed of aromatic rings such as benzene rings connected through a single bond, provide a useful framework for functional molecules.[1] We have developed a synthetic method of oligoarenes having various functional groups.[2] The method, involving a two-step repetitive technique, includes triflation of a hydroxy group and subsequent Suzuki–Miyaura coupling[3] of hydroxyphenylboronic acids or their derivatives (Figure 1a). Repetition of these two steps affords oligoarenes containing various functional groups in high yields.

As an application of oligoarenes to catalytic molecules, we designed hydroxylated oligoarene-type phosphines[4] (HOPs, Figure 1b) as ligands for metals, based on biphenylphosphines developed mainly by Buchwald et al.[5] It was expected that a HOP library would be readily prepared by the two-step repetitive method. The OH group of HOP is introduced during the synthesis of the oligoaryl moiety, while it simultaneously functions as an assisting group in a catalytic reaction in which the HOP is used as a ligand for a metal. For example, the metal oxido group (M^2–O in Figure 1c), formed from the OH group, would bind a substrate through a functional group (Y). This binding would place the reactive group (Z) close to the catalytic metal (M^1) coordinated by the phosphino group, leading to acceleration of the catalytic reaction. Optimizing linker length and substitution pattern (ortho-, meta-, para-) of HOPs would give suitable HOPs for specific reactions and also realize high substrate specificity and reaction selectivity.

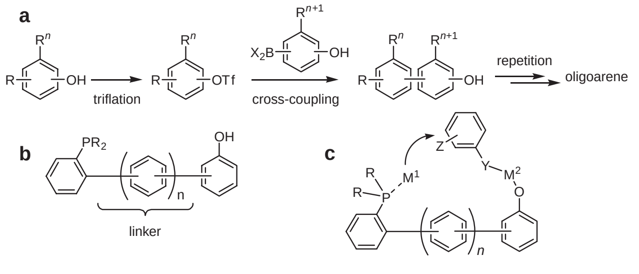


Figure 1. (a) Two-step repetitive method for oligoarene synthesis. (b) HOP. (c) Proposed intermediate of the reaction using an oligoarene-type metal complex as catalyst.

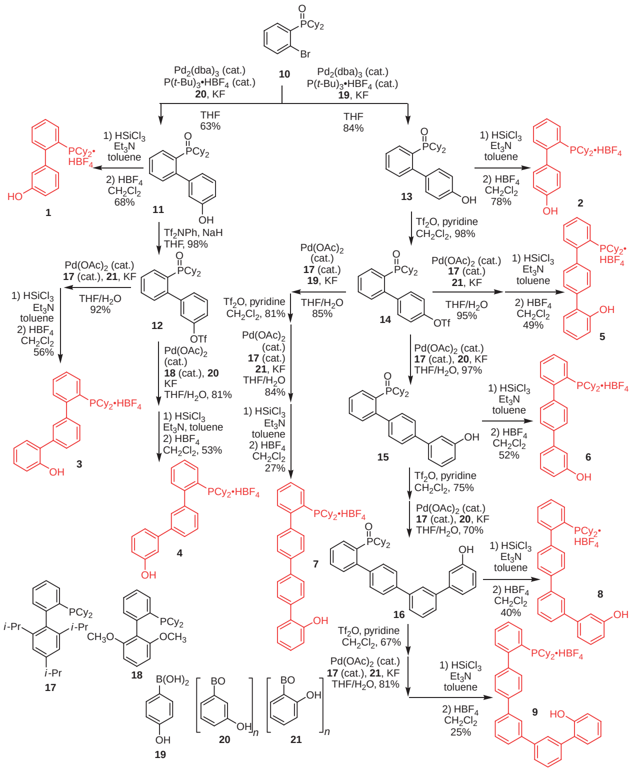


Figure 2. Synthetic scheme of HOPs. Formulas **20** and **21** represent boronic anhydrides.[6] Some HOPs contain solvents of recrystallization.[7]

Figure 2 shows the synthetic scheme of a library of HOPs **1**–**9**.[7] The key features of the synthesis include: (1) The two-step repetitive method mentioned above was used for construction of the oligoarene frameworks. For the synthesis of HOPs having the common 2-dicyclohexylphosphinobiphenyl core structure, this synthetic scheme efficiently produced the HOP library, because intermediates such as **11**–**16** were commonly utilized; (2) Since the PCy_2 group is gradually oxidized in an air atmosphere, the phosphino group was protected as a phosphinyl group throughout the oligoarene elongation. This protection also facilitates the triflation steps, since Tf_2O reacts with the phosphino group to give undesired products. Finally, reduction of the phosphinyl group gave the corresponding phosphines, which were purified and stored as the HBF_4 salts.[8] For convenience, these HBF_4 salts are also called HOPs throughout this paper; (3) Although HOPs synthesized in the present work have only phosphino and OH functional groups, the present synthetic strategy can be applied to the synthesis of HOPs having other types

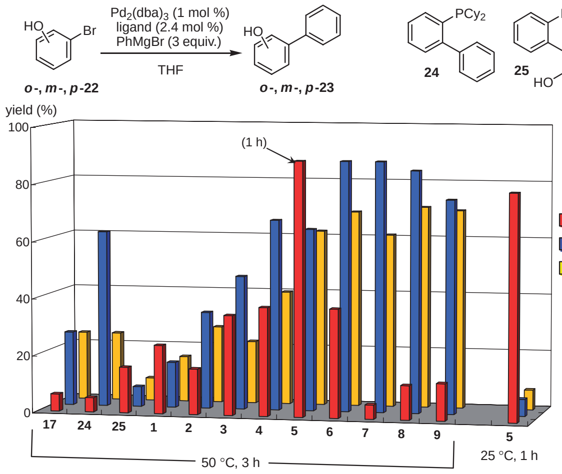
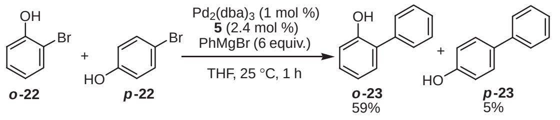


Figure 3. Cross coupling of a bromophenol with PhMgBr.

of functional groups, according to our previous work.[2]

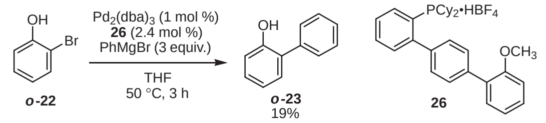
To demonstrate the effectiveness of HOPs **1**–**9**, they were tested in Pd-catalyzed cross coupling of bromoarenes with Grignard reagents.[7,9] Bromophenols as bromoarenes were used, because the phenolic oxygen of the substrates was expected to act as the interacting group (Y) as shown in Figure 1c. Figure 3 shows the results of cross coupling of a bromophenol with PhMgBr in the presence of $Pd_2(dba)_3$ and a phosphine ligand. HBF_4 salts **1**–**9** were directly used for the reaction. As the ligand, commercially available phosphines **17**,[5b] **24**,[5a] and **25**[5e] were also tested. The yields of ***o*-23**, ***m*-23**, and ***p*-23** were significantly affected by the ligands. For each ligand, ***m*-22** gave a higher yield than did ***o*-22** and ***p*-22**, except when ligand **1**, **5**, or **25** was used. In particular, **5** exhibited much greater activity for ***o*-22** than for ***m*-22** and ***p*-22**, and the higher yield of ***o*-23** maintained even with a shorter reaction time (1 h). The reaction of ***o*-22** using **5** proceeded even at 25 °C in good yield (79%), and the preference for ***o*-22** over ***m*-22** and ***p*-22** was further emphasized. This high activity for ***o*-22** was observed only for **5**, indicating that **5** is an optimized ligand for the reaction of ***o*-22**.

Next, a competitive experiment using bromophenols was conducted (eq 1). Under the reaction conditions utilizing HOP **5** and a 1:1:6 mixture of ***o*-22**, ***p*-22**, and PhMgBr, ***o*-23** was afforded preferentially over ***p*-23**. Thus, substrate specificity for ***o*-22** was clearly demonstrated.

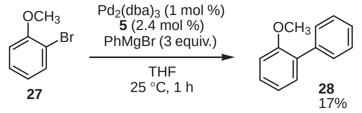


(1)

Although the mechanism that allows HOP **5** to catalyze the reaction of ***o*-22** effectively is unknown, the following experiments strongly suggest that the OH groups of both **5** and ***o*-22** play a major role in the rate acceleration and substrate specificity observed. First, reference ligand **26**[7] resulted in very low yield (eq 2). Second, compound **27** in the presence of **5** gave the product **28** in very low yield (eq 3). From these results, we assume that the reaction proceeds via the intermediate as shown in Figure 1c, in which the Mg oxido group of HOP holds a position ortho to the oxido group of bromophenoxide close to the Pd atom coordinated by the phosphine.



(2)



(3)

In conclusion, we have developed a strategy for the development of useful catalysts based on oligoarene-type phosphine ligands having an OH group. The use of these ligands for Pd-catalyzed cross coupling successfully resulted in identification of one ligand that drastically accelerated the reaction of *o*-bromophenol and exhibited substrate specificity. Although the focus of this study was a specific reaction of the substrate, the concept presented for finding suitable catalysts is applicable to other catalytic reactions using various substrates.[10]

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6 The real aggregation states of the boronic anhydrides are unclear because of the complexity associated with the phenolic OH groups.

7 See Supporting Information for experimental details. The material is available electronically on the CSJ-Journal web site, http://www.csj.jp/journals/chem-lett/.

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