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Improving reactivity and selectivity of aqueous-based Heck reactions by the local hydrophobicity of phosphine ligands

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ABSTRACT

Modification of a triarylphosphine with a cholate moiety affords a new ligand, **1**, which is effective in palladium-catalyzed Heck cross-couplings between acrylates and aryl iodides under mild, aqueous reaction conditions. High yields, up to 99%, were achieved in water at 40 °C. In competition studies, a more hydrophobic substrate (*n*-Bu acrylate) was preferred over the least hydrophobic substrate (methyl acrylate), supportive of a localized hydrophobic microenvironment near the catalytic center. The enhanced reactivity and selectivity for hydrophobic substrates disappeared when the local hydrophobicity was eliminated using a standard water-soluble phosphine or in organic solvents.

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1. Introduction

Transition metal-catalyzed reactions in water have attracted significant research attention.^{1,2} An important motivation comes from the low cost, abundance, nonflammability, and nontoxicity of water as a green solvent. If the reactants are organic and phase-separate from water, while the catalyst stays in the aqueous phase, the product can be easily separated. Traditionally, transition metal catalysts are made water-soluble by installing polar groups such as sulfonate on the metal-coordinating ligands.^{2–4} However, this method is limited to reactants with substantial solubility in water, since highly nonpolar substrates tend to have difficulty accessing catalysts located in the aqueous phase.

Because surfactant micelles can solubilize a wide variety of nonpolar compounds, chemists have also performed transition metal-catalyzed reactions in the micellar phase.^{5–7} The benefit of micelles is that they provide a local hydrophobic microenvironment to transition metal catalysts and may help enhance the local concentration of the substrate near the catalysts. Conversely, the surfactants may contaminate the products and could also hamper the product isolation by emulsion formation.

In this work, we report the synthesis of a cholate-functionalized phosphine ligand and its application in heterogeneous palladiumcatalyzed Heck cross-coupling reactions. The facially amphiphilic cholate group was found to exert a strong influence on the activity and selectivity of the reactions, owing to its ability to create a hydrophobic microenvironment near the catalytic center. This feature resulted in a preference for hydrophobic substrates over less hydrophobic ones by the catalyst. In contrast, the enhanced selectivity and reactivity was not observed in organic solvents or with a homogeneous control in which the catalyst was coordinated to watersoluble phosphines.

2. Results and discussion

2.1. Ligand synthesis

The motivation for designing a cholate-functionalized phosphine ligand was derived from the unusual amphiphilicity and topology of cholic acid. Cholic acid and its associated bile salts (cholates) are formed in the liver and used as a surfactant for emulsifying lipids and cholesterol.⁸ Its rigid ring structure provides unusual facial amphiphilicity derived from the hydrophilic and hydrophobic moieties residing on opposite faces rather than in the conventional head-to-tail arrangement of amphiphiles such as so-dium dodecyl sulfate (SDS).⁹ This unique structure and facial amphiphilicity has been exploited in supramolecular chemistry.^{9–13} According to Small's primary/secondary aggregation model, cholates form primary micelles at low concentrations in water, with 2–10 monomers in the structure stabilized mainly by hydrophobic interactions.¹⁴ As the cholate concentration increases, these primary micelles can aggregate to larger secondary structures





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through hydrogen bonds, leading to increased polydispersity in solution. $^{6,15-18}_{\rm c}$

Phosphine ligand **1** was readily derived from methyl cholate as shown in Scheme 1. Of the three hydroxyl groups, the most reactive hydroxyl resides at the C-3 position.^{19–21} Thus, the 3α -hydroxyl was selectively transformed into an azide by initially forming the β -mesylate (**2**) with methanesulfonic acid under Mitsunobu conditions, and subsequently treating the mesylate with sodium azide.²² The overall stereochemistry of the 3α -hydroxyl was retained in azide compound **3**, thus maintaining the original bifacial topology of the cholate. Azide reduction to amine **4** was achieved with hydrogenation using palladium over carbon as the catalyst, and the phosphine moiety was added via formation of an amide linkage between **4** and activated ester **5**. The methyl ester functionality of **6** was hydrolyzed with 1.0 M NaOH in methanol (MeOH). Isolation of the carboxylic acid (**1**) was achieved by purification on a silica gel

molecule to self-assemble into micellar aggregates, which are soluble in water.^{18,24} For this reason, we employed a precatalyst complexation methodology for our catalysis. Sonication of Pd(OAc)₂ and 3 equiv of ligand **1** in MeOH produced a light yellow, hazy suspension within 30 min at ambient temperature. Removing MeOH under vacuo provided a solid yellow phosphinocholate Pd complex that was insoluble in water but formed an evenly dispersed suspension upon addition of NEt₃. Increased dispersion was likely due to deprotonation of the carboxylic acid moiety of **1**, producing a charged Pd-L complex.

Studies by Jutand and co-workers established that a Pd^0 complex was formed between $Pd(OAc)_2$ and PPh_3 , and the dominate species was directly dependent on the amount of phosphine added to the system.^{25–27} Three equiv of phosphine, in the presence of wet DMF, led to the overall formation of an anionic palladium (0) species (**7**) and phosphine oxide (eq. 1), identified by ³¹P NMR.

$$3 PPh_3 + Pd(OAc)_2 + H_2O \longrightarrow O=PPh_3 + [Pd(PPh_3)_2OAc^-] + AcOH + H^+ (1)$$
7
(1)

column. Similar to cholic acid, **1** was essentially insoluble in water and sparingly to moderately soluble in ethanol, MeOH, chloroform and dichloromethane.^{16,17} The ³¹P NMR spectrum of **1** exhibited a single phosphine signal at -5.0 ppm with triphenylphosphate (-18.0 ppm)²³ as an external standard (CDCl₃/CD₃OD, 1:1).

Under a similar study with ligand **1** and Pd(OAc)₂, analogous ³¹P NMR peaks were observed. A solvent mixture of 1:1 CDCl₃:CD₃OD sufficiently solubilized the yellow phosphinocholate Pd solid isolated from MeOH (1:3, Pd(OAc)₂ to **1**), and three ³¹P NMR signals were observed (-5.0, 16.9, and 32.6 ppm). The signals at -5.0 and



Scheme 1. Synthesis of phosphine ligand 1.

The insolubility of compound **1** in water was not surprising. Even for cholic acid itself, the dominance of hydrophobic groups makes the molecule practically insoluble in water. Only when the carboxylic acid is deprotonated, the ionic carboxylate enables the 32.6 ppm corresponded to free and oxidized ligand **1**, respectively. The peak at 16.9 ppm was assigned to a Pd⁰ complex, **8**, coordinated with 2 equiv of **1**. After 4 h in organic solvents, complex **8** mostly decomposed to palladium black, resulting in an increase in the

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