



Synthesis of 4-sulfonatobenzylphosphines and their application in aqueous-phase palladium-catalyzed cross-coupling



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ABSTRACT

Aqueous-biphasic catalysis offers the potential for safer and more environmentally sustainable synthetic processes. In addition, hydrophilic supporting ligands allow homogeneous catalysts to be readily separated from organic products and potentially reused. The synthesis of two new water-soluble ligand precursors, di-*tert*-butyl(4-sulfonatobenzyl)phosphonium and di-1-adamantyl(4-sulfonatobenzyl)phosphonium, are reported. The air-stable, zwitterionic phosphonium salts were prepared by the reaction of dialkylphosphines with ethyl 4-bromomethylbenzenesulfonate, which results in a one-pot alkylation followed by deprotection of the ethyl sulfonate. This methodology provides an operationally simpler route to sulfonated benzylphosphines than electrophilic sulfonation. The new phosphine ligands were applied to aqueous-phase Suzuki and Sonogashira couplings of aryl bromides.

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Introduction

Water has received significant attention as a reaction medium in metal-catalyzed reactions because of its numerous attractive properties compared to traditional organic solvents [1–4]. Water is nonflammable, nontoxic, renewable, and widely available. Water has also been considered as an environmentally friendly solvent due these many beneficial properties. Reactions run in water are not inherently environmentally friendly, however; as aqueous waste streams with organic contaminants represent their own disposal challenges. For metal-catalyzed reactions, water offers the potential to easily separate hydrophilic precious metal catalysts from organic product streams for potential reuse. Finally, water has been shown to promote organic reactions of hydrophobic substrates in many reactions [5].

Palladium-catalyzed cross-coupling reactions have become widely used tools for construction of carbon–carbon and carbon–heteroatom bonds [6,7]. Significant research effort has identified several highly effective classes of ligands, such as sterically demanding trialkylphosphines (Pt-Bu₃, Ad₂PBu) [8], dialkylbiarylphosphines (X-phos) [9], and *N*-heterocyclic carbenes (IMes, IPr)

[10]. Common features among these ligands are large steric demands and strong σ -electron donating ability. These properties favor low-coordination, electron-rich active species that are highly active towards oxidative addition [11]. The steric bulk can also favor challenging reductive eliminations [12,13].

The use of water-soluble phosphine ligands in palladium-catalyzed cross-coupling reactions dates to Casalnuovo's pioneering report of the use of Pd(TPPMS)₃ (TPPMS = sodium diphenyl(3-sulfonato)phenylphosphine) for Suzuki, Heck, and Sonogashira couplings of aryl halides in water/organic solvent mixtures [14]. Since that initial report, numerous examples of hydrophilic ligands have been disclosed to provide effective cross-coupling catalysts [2,15]. Early hydrophilic ligands, such as TPPTS (Fig. 1) [16], were based on modified triphenylphosphine scaffolds. Catalysts derived from these ligands showed modest activity and were limited to aryl iodides or in some cases aryl bromides at elevated temperatures (>100 °C). Our group reported the first examples of hydrophilic, sterically demanding trialkylphosphine ligands for cross-coupling reactions [17,18]. Since these initial reports, we and others have developed hydrophilic phosphines [19–25] and *N*-heterocyclic carbene precursors [26,27] that provide high activity catalysts capable of coupling aryl bromides and chlorides under mild conditions (Fig. 1).

In designing more effective water-soluble phosphine ligands, we were interested in exploring alkylaryl substituents, such as

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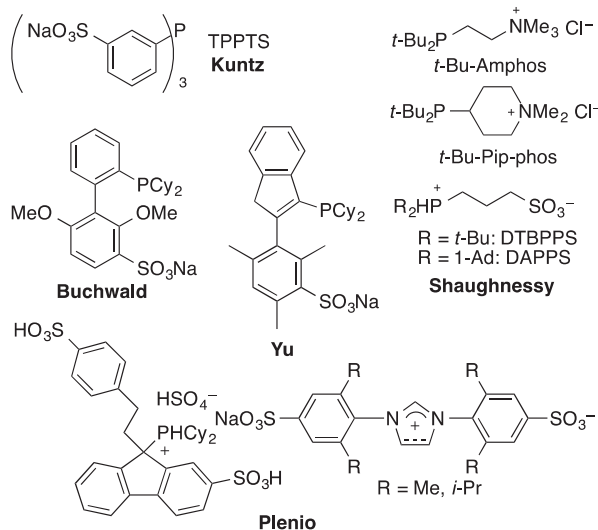


Fig. 1. Examples of water-soluble ligands previously reported.

benzyl or phenethyl. We envisioned that these substituents would be an easily introduced group that would provide the potential for incorporation of hydrophilic substituents through well-established arene functionalization chemistry. Electrophilic sulfonation of benzylphosphines have been previously reported, for example [28,29]. In addition, we hypothesized that the nearby aromatic substituent could provide additional stabilization of the palladium center. This hemilabile coordination is thought to play a key role in the success of the 2-biarylphosphine class of ligands (Fig. 2) [30,31]. Herein, we report a novel synthesis of 4-sulfonatobenzylphosphines and their application in aqueous-phase Suzuki and Sonogashira coupling reactions.

Results and discussion

Synthesis of sulfonated benzylphosphines

Synthesis of the sulfonated benzylphosphines was originally envisioned to involve electrophilic sulfonation of readily available dialkylbenzylphosphonium salts (Scheme 1). Sulfonation of tribenzylphosphine is reported to give the trisulfonated phosphine in good yield as a mixture of *ortho* and *para* isomers, with the all *para*-isomer being the major product [28]. Small amounts of phosphine oxide byproducts were also observed. Homologous tri(*ω*-phenyl-alkyl)phosphines were less prone to competitive oxidation than tribenzylphosphine. The typical sulfonation conditions are strongly oxidizing due to the presence of SO₃. Under the highly acidic reaction conditions, the basic trialkylphosphine is protonated and protected from oxidation. During neutralization with base, it is critical to control the pH in order to consume the remaining SO₃ prior to deprotonation of the phosphorus center in order to avoid oxidation of phosphorus.

Reaction of dialkylphosphines with benzyl bromide in toluene produced the respective dialkylbenzylphosphonium bromides as

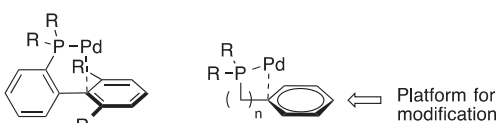
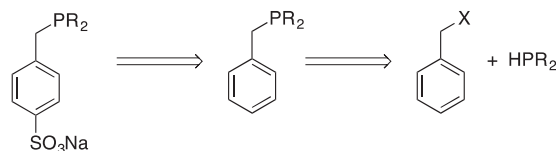
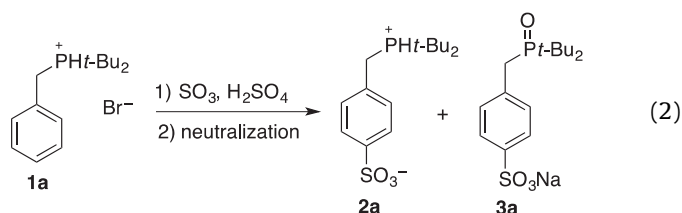
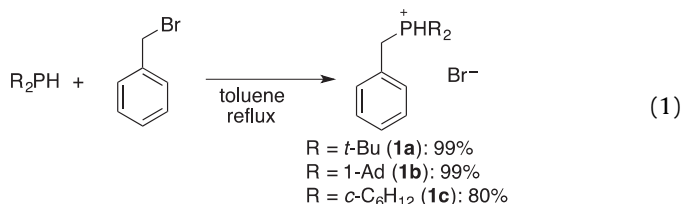


Fig. 2. Potential coordination of pendant aryl groups.

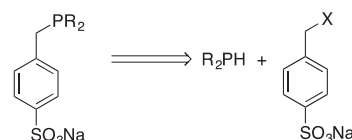


Scheme 1. Retrosynthetic plan to synthesis sulfonated benzylphosphines.

white precipitates (**1a–c**, Eq. (1)). Treatment of phosphonium salt **1a** with concentrated sulfuric acid gave no appreciable sulfonation. Use of 20% fuming sulfuric acid resulted in sulfonation of the aromatic ring predominately at the *para*-position to give **2a** (Eq. (2)). Neutralization of the reaction mixture afforded desired **2a** along with the corresponding oxide (**3a**) and other unknown phosphorus containing byproducts. In order to better control the pH during neutralization, 5 equivalents of KH₂PO₄ were added after completion of the sulfonation reaction followed by careful neutralization to pH 7 with 10% aqueous NaOH. The product was extracted into methanol to give **2a** with no oxide (**3a**) contamination. The product was contaminated with a significant amount of phosphate salts that could not be effectively separated, however. Use of Herrmann's [32] isolation protocol allowed sulfonated phosphine **2a** to be isolated as a pure material, but in low yield (17%). Spectroscopic characterization showed that material was exclusively the *para*-sulfonated isomer. Further attempts to improve the yields from sulfonation reactions were unsuccessful.



With the sulfonation reaction requiring tedious separation and providing poor yields, alternative routes to the desired sulfonated benzylphosphines were explored. Since oxidation of the phosphorus center during workup was a major challenge with **1a**, we considered an alternative synthetic strategy in which the sulfonate would be installed on the benzyl group prior to alkylation of the phosphorus center (Scheme 2). This approach would require synthesis of a 4-bromomethylbenzene sulfonic acid equivalent. The synthesis of sodium 4-bromomethylbenzenesulfonate has been previously reported in three steps starting from *N,N*-dimethylbenzylamine [33]. As an alternative, we envisioned that radical



Scheme 2. Revised approach to sulfonated benzylphosphines.

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