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Amphiphilic Biaryl Monophosphine Ligands by Regioselective Sulfonation

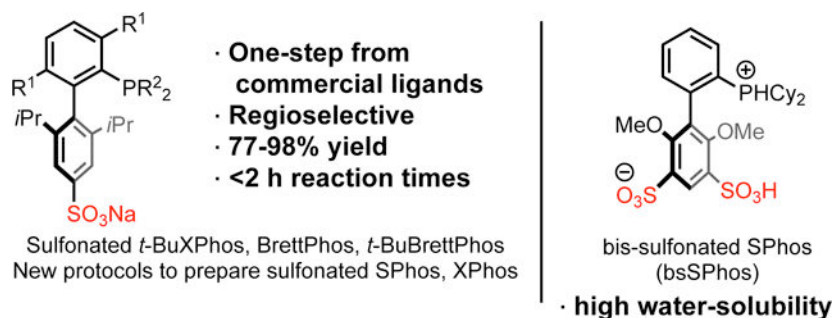
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Abstract

Amphiphilic ligands are valued for their ability to facilitate organometallic reactions in the presence of water. The regioselective sulfonation of a series of commercially available biaryl monophosphines to generate amphiphilic ligands is presented. In this one-step protocol, the temperature and addition of fuming sulfuric acid were carefully controlled to arrive at sulfonated biaryl monophosphine ligands in high yields with >95% regioselectivity without the need for chromatographic purification.

Graphical Abstract



The use of water-soluble organometallic complexes often capitalizes on reaction rate acceleration due to hydrophobic clustering of substrates and lowering of transition state barriers through hydrogen bonding.^{1,2} Conducting reactions in aqueous conditions can also simplify the purification of products and ease recycling of catalytic complexes in biphasic solvent mixtures. However, many organometallic transformations are developed in organic

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data for all compounds (PDF)

The authors declare the following competing financial interest(s): MIT has or has filed patents on the ligands that are described in the paper from which S.L.B. and former coworkers receive royalty payments.

solvents, and the metal-complexes employed are either minimally or completely insoluble in water. To adapt these transformations for use in an aqueous solvent without the need to employ surfactants or micelles, modification of the ancillary ligand is necessary. These changes to the ligand are designed to impart increased hydrophilicity of the resulting organometallic complex allowing for the corresponding organic transformations to be carried out in aqueous solvent.^{3,4}

With regard to palladium-mediated transformations, biaryl monophosphines are a class of ligands that excel in promoting various C–C and C–heteroatom bond forming reactions.⁵ The substituents of each of these ligands has been designed to facilitate key elements of the Pd-mediated cross-coupling catalytic cycle, including oxidative addition and reductive elimination.⁶ However, hydrophilic analogues of this particular class of ligands are largely absent from the literature. Sulfonation of the ancillary ligand imparts increased water solubility to the resulting organopalladium complex, expanding its effective reactivity to hydrophilic substrates. In addition to aqueous solubility considerations, amphiphilic biaryl monophosphine ligands have found utility in electrostatically guided Pd-catalysis.^{7,8} Our interest in these ligands stemmed from our ongoing efforts in the use of organometallic palladium reagents for bioconjugation where biopolymer substrates such as proteins often require the use of water as a solvent to prevent denaturation.⁹

Our group has previously described mild heteroatom-arylation reactions for the conjugation of lysine and cysteine residues utilizing stoichiometric palladium oxidative addition complexes (OACs) of the type [LPd(Ar)X] (L = biaryl monophosphine, X = Cl, Br, OTf).¹⁰ For these reactions, ligand choice was a key parameter that influenced chemoselectivity¹¹ and overall yield.¹² Sulfonated SPhos (sSPhos, **2**), previously prepared via sulfonation of SPhos (**1**)¹³ (Figure 1A), allowed us to carry out *S*-arylation with enhanced efficiency in aqueous solutions presumably due to the increased water solubility imparted onto the OAC reagent.¹⁴ While **2** confers greater water solubility on what would otherwise be a hydrophobic complex, most OACs we prepared were only soluble at micromolar concentrations and, in some cases, still required the use of an organic co-solvent.¹⁵

To improve the water solubility of Pd-OACs derived from biaryl monophosphine ligands known to accommodate *N*-, *O*-, and *S*-nucleophiles, we set out to prepare sulfonated variants of commercially available biaryl monophosphine ligands. Here we disclose new protocols for the preparation of **2** and sXPhos (**5**)¹³ (Figure 1A, B) that is complete within hours or, in most cases, minutes. These improved protocols are further applied for the sulfonation of four commercially available biaryl monophosphine ligands to give the corresponding sulfonated ligands in a single synthetic step, each prepared on a one-gram scale (Figure 1C).

During the preparation of **2** using our literature protocol (Fig. 1A),¹³ monitoring of the reaction by tandem liquid-chromatography mass spectrometry (LC-MS) showed that the conversion of **1** to its sulfonated form **2** was complete at room temperature in less than two hours, not requiring the elevated temperature (40 °C) or 24 h reaction time reported. Isolation and analysis of the product after a one-hour reaction time confirmed its identity as **2** with ¹H, ¹³C and ³¹P NMR spectra comparable to that reported in the literature.

Given the rapid sulfonation we observed for ligand **1**, we investigated whether other commercially available ligands would maintain a similarly high reactivity. The original protocol reported by our lab¹³ and repeated by others⁸ for the sulfonation of **1** also detailed a sulfonation strategy for the selective monosulfonation of XPhos (**3**) via a Friedel-Crafts/retro-Friedel-Crafts reaction (Figure 1B). We therefore examined this approach toward the sulfonation of BrettPhos (**10**, Scheme 1) which has not previously been reported to undergo sulfonation. Unlike **1** or **3**, **10** contains an electron-rich top ring bearing two electron-donating methoxy groups. It was unclear if or where sulfonation would occur, but we hypothesized that protonation of the phosphine under the reaction conditions would deactivate the top ring toward electrophilic aromatic substitution. Thus, we employed conditions analogous to those used in the preparation of **5**. First, **10** was exposed to a mixture of CH₂Cl₂ and H₂SO₄ to protonate the phosphine followed by the addition of fuming sulfuric acid at 0 °C. This gave a monosulfonated form of BrettPhos (sBrettPhos, **7**) in 84% yield and proceeded to completion within minutes, validating the high reactivity of these biaryl systems toward sulfonation.

Next, we attempted an analogous protocol using *t*-BuBrettPhos (**11**, Table 1) as the substrate. Unfortunately, multiple products were observed when monitoring the reaction by LC-MS: two peaks with different retention times and the same *m/z* corresponding to monosulfonated products (523 Da, entry 1). This observation was confirmed by ¹H and ³¹P NMR analysis of the crude reaction mixture and indicated a mixture of isomers **8** and **12** in a ratio of 13:1, respectively.¹⁶ Although separation of the isomers was possible, we sought to optimize the regioselectivity of the sulfonation reaction to avoid any additional purification steps. We note that our initial attempts to prepare **5** and *s*-t-BuXPhos (**6**) also gave mixtures of unassigned products under analogous reaction conditions. We chose to continue optimizing the reaction using **11** as the substrate for our further studies.

From the outset of our optimization, it was unclear which parameters would most influence product distribution. Hypothesizing that the concentration of SO₃ played an important role in the reaction, we reversed the order of addition of the reagents, adding a solution of **11** dropwise into fuming sulfuric acid. From this adjustment, a 48:1 ratio of **8**:**12** (entry 2) was obtained as determined by analysis of the crude reaction mixture by ³¹P NMR. When this protocol was carried out at a measured bath temperature of –10 °C, the ratio of **8**:**12** formed was improved to 82:1 (entry 3).

With an optimized procedure for the selective monosulfonation of **11** on a 50 milligram scale, we extended this protocol to other biarylphosphine ligands and conducted it on a 1.0 gram scale (Scheme 2, **13** to **14**). In each case, the sulfonated products **5**, **6**, and **8** were isolated with >96:4 product distribution as assessed by ³¹P NMR and in good yield (77% – 98%).¹⁷

The high degree of reactivity of these ligands toward sulfonation caused us to then consider the use of fuming sulfuric acid to obtain a bis-sulfonated derivative of the more electron-rich **1** (bsSPhos, **9**, Scheme 3). Thus, sequential treatment of SPhos with H₂SO₄ followed by the addition of fuming sulfuric acid (21–30% SO₃ basis) led to full conversion of **1** to **9**, as determined by LC-MS.

The increased water solubility of the deprotonated form of bsSPhos made extraction with organic solvents difficult. All previous efforts in our group for the preparation of sulfonated ligands showed that the products could be isolated by neutralization of the reaction mixture with aqueous NaOH followed by extraction with dichloromethane. As an alternative, we employed a method reported for the preparation of a bis-sulfonated version of XantPhos.¹⁸ Isolation of **9** was achieved by precipitating it through the addition of a controlled amount of water prior to neutralization, which provided the product in 96% yield as a single regioisomer. The addition of stoichiometric quantities of NaOH to generate the sodium salt of the product followed by lyophilization produced an unstable form of the ligand which decomposed over the course of several weeks when left on the bench, open to air. As a means to circumvent this issue, we have found that we can store the compound in its zwitterionic form. In this form, **9** was stable for six months under ambient conditions as indicated by ¹H NMR and ³¹P NMR.

In summary, we have developed a modified sulfonation protocol for the controlled, regioselective sulfonation of the commercially available ligands SPhos, XPhos, *t*-BuXPhos, BrettPhos, and *t*-BuBrettPhos.¹⁹ Additionally, we have devised a protocol to prepare the bis-sulfonated version of SPhos, bsSPhos. In the case of bsSPhos, we anticipate the ligand to confer increased water solubility to what would otherwise be a hydrophobic complex, thus avoiding the need to modify the hydrophobic aryl halide electrophile for aqueous conjugation, with the ligand operating as a traceless solubility modifier. We expect these ligands will find use in bioconjugation, catalyst separation, and cation-pair directed Pd catalysis.²⁰

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

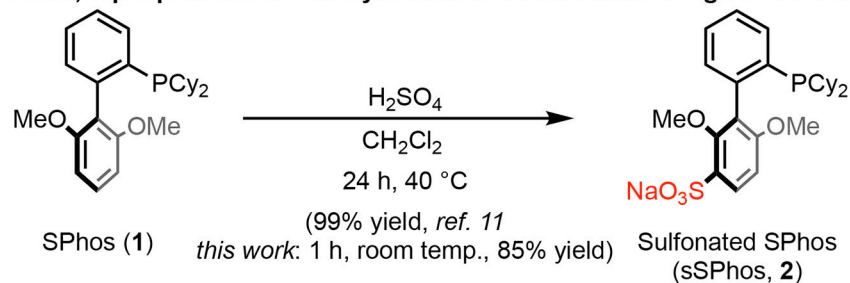
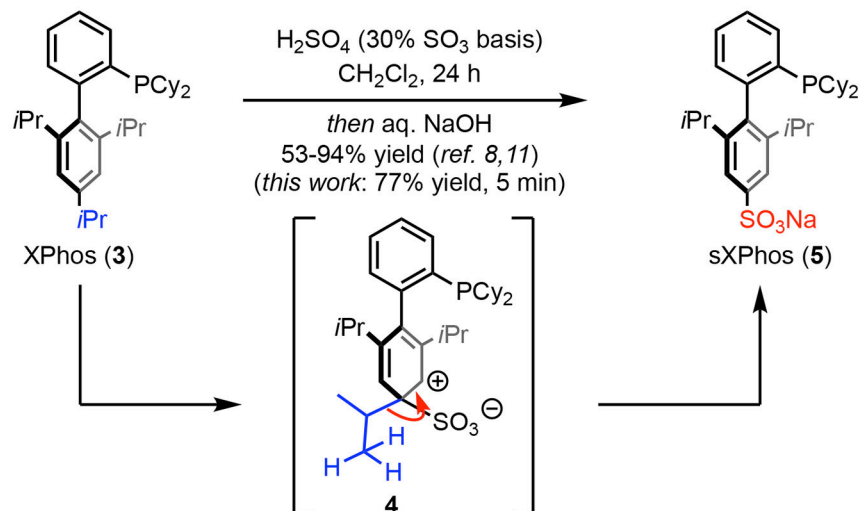
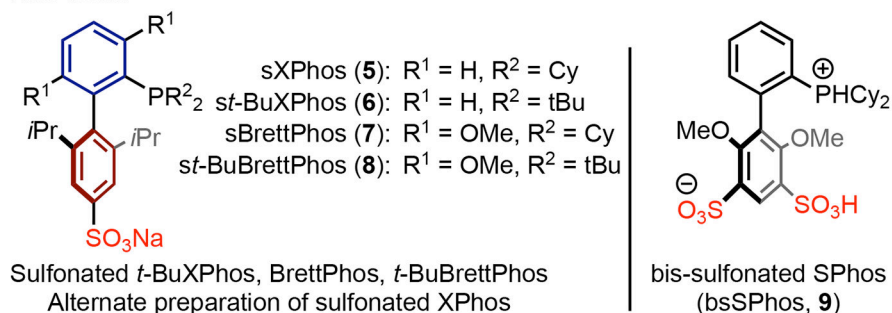
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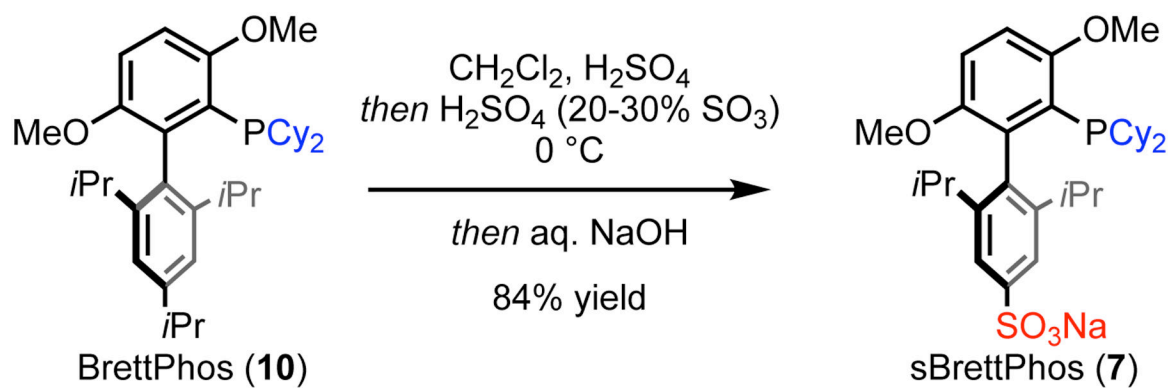
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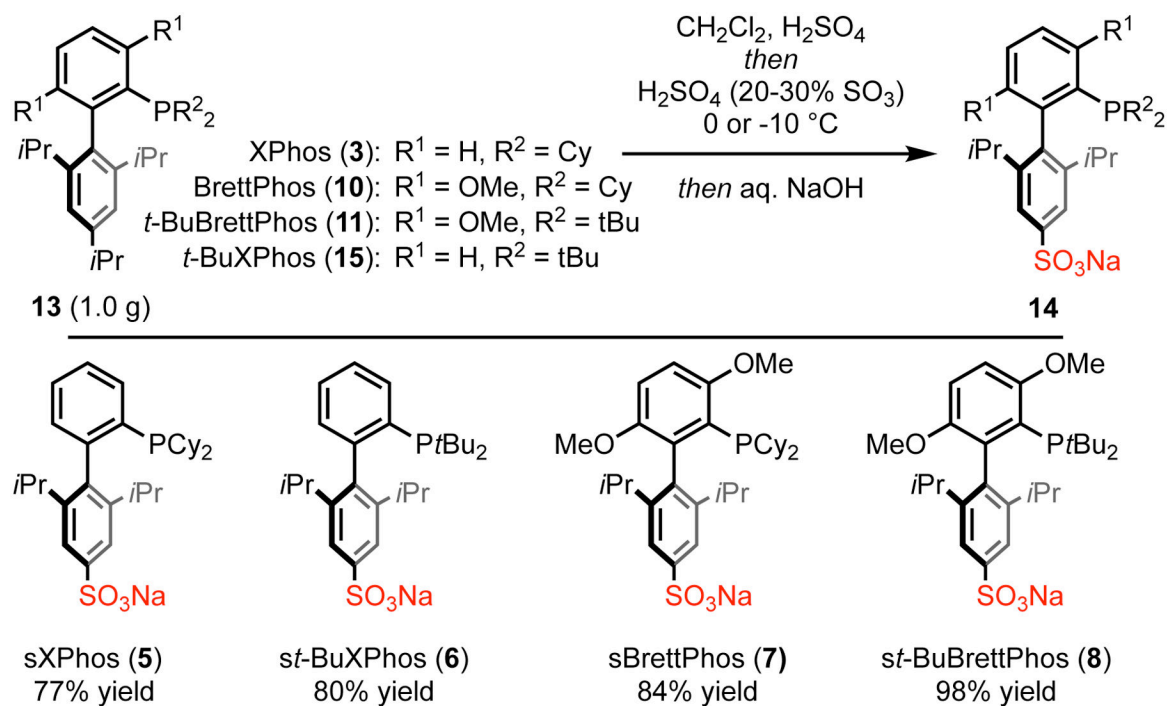
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- (17). To minimize the formation of phosphine oxide it was necessary to ensure that substrates were both: (1) fully dissolved in CH_2Cl_2 when cooled to 0 °C and (2) treated with sulfuric acid to protonate the phosphine and thereby protect it from oxidation prior to exposure to SO_3 . The lone exception to this was **15** where sulfuric acid was avoided; in short, we used a modified protocol to prevent significant (we observed 2–7%) phosphine oxide formation. For more details, see the Supporting Information²²³**15**
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- (20). For a preprint of this paper, see: Rodriguez Jacob; Dhanjee Heemal; Buchwald Stephen L. Amphiphilic Biaryl Monophosphine Ligands by Regioselective Sulfonation. *ChemRxiv* 2020, DOI: 10.26434/chemrxiv.13337471.v1.

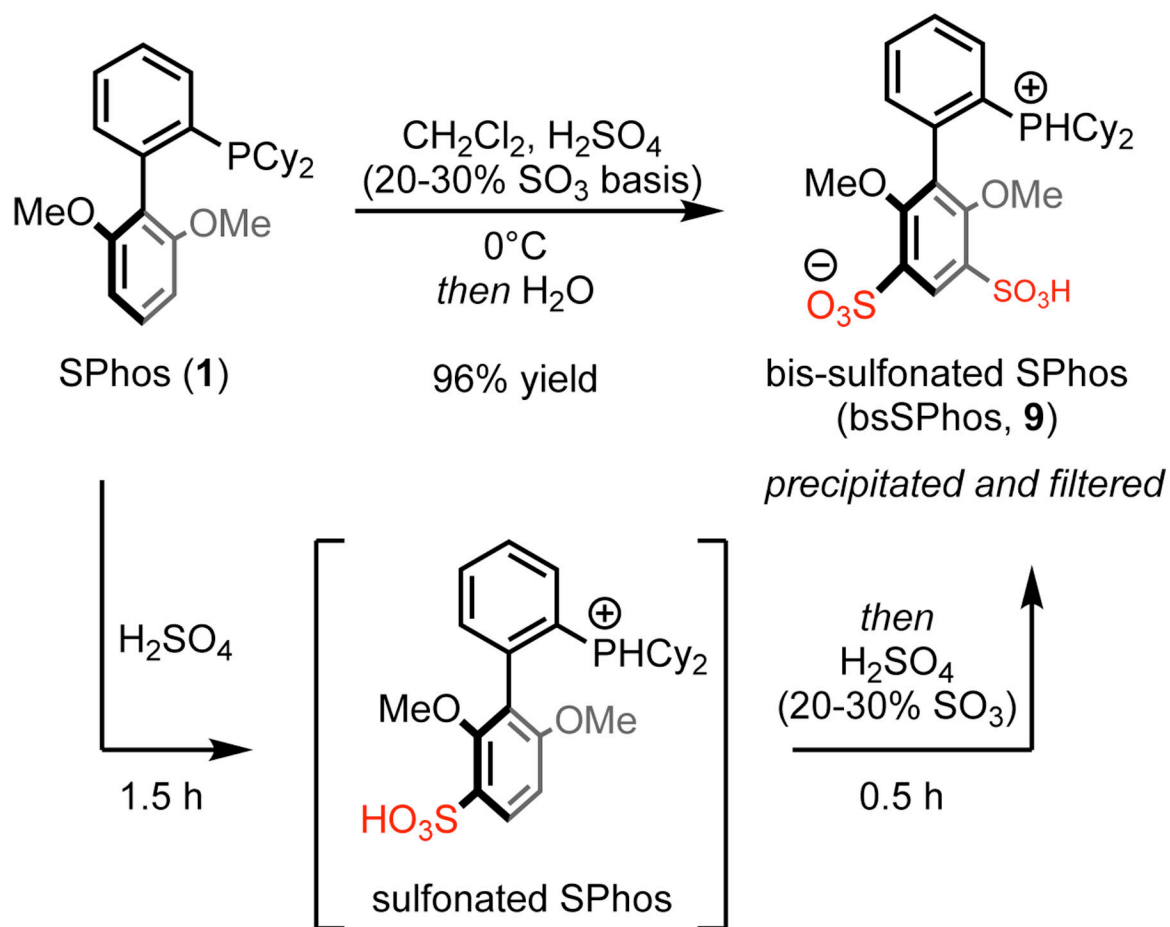
A New, rapid protocol for the synthesis of a water-soluble ligand sSPhos:**B Sulfonation of XPhos via Friedel-Crafts/Retro-Friedel-Crafts:****C This work:****Figure 1.**

Preparation of sulfonated biaryl monophosphine ligands via sulfonation. (A) New protocols for the preparation of sulfonated SPPhos (sSPPhos, 2) and (B) sulfonated XPhos (sXPhos, 5) with reduced reaction times. (C) Synthesis of sulfonated *t*-BuXPhos, BrettPhos, and *t*-BuBrettPhos (*st*-BuXPhos (6), sBrettPhos (7), and *st*-BuBrettPhos (8) respectively).

**Scheme 1.**

Monosulfonation of BrettPhos to provide sBrettPhos.

**Scheme 2.**Gram-scale synthesis of sulfonated XPhos, *t*-BuXPhos, BrettPhos, and *t*-BuBrettPhos



Scheme 3.
Synthesis of bis-sulfonated SPhos (bsSPhos).

Table 1.Optimization for a single regioisomeric product in the sulfonation of *t*-BuBrettPhos

<p><i>t</i>-BuBrettPhos (11) $\xrightarrow[\text{temperature}]{\text{CH}_2\text{Cl}_2, \text{H}_2\text{SO}_4 \text{ then } \text{H}_2\text{SO}_4 (20-30\% \text{SO}_3)}$ <i>st</i>-BuBrettPhos (8) + (minor isomers, 12)</p>			
Entry	Reaction Time	Temperature (°C)	Ratio 8:12
1 ^a	5 min	0	13:1
2 ^b	5 min	0	48:1
3 ^b	5 min	−10	82:1
4 ^b	1 h	−10	84:1 ^c

^aThe reaction was carried out by the addition of fuming sulfuric acid dropwise to a solution of ligand.^bReactions were carried out by the slow addition of a solution of ligand to a solution of fuming sulfuric acid.^cUnder these conditions, an increased number of unidentified by-products were observed.