Amphiphilic Biaryl Monophosphine Ligands by Regioselective Sulfonation

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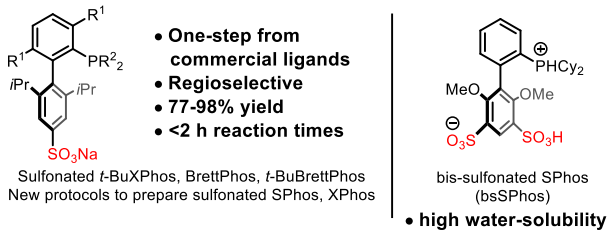
Supporting Information Placeholder



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.

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 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 chemoselectivity[11] 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).

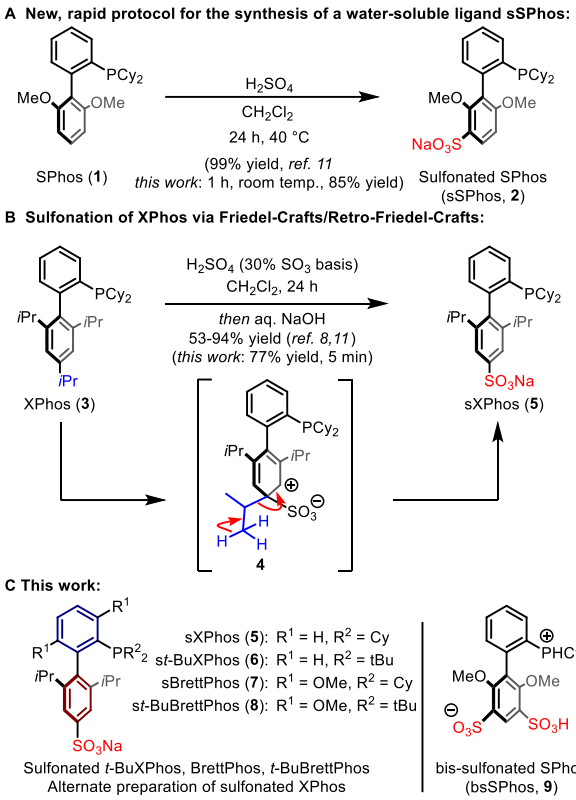
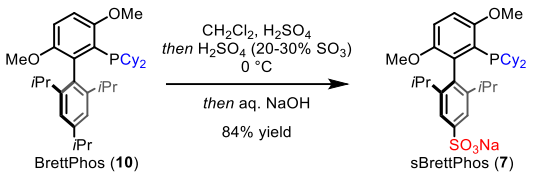


Figure 1. Preparation of sulfonated biaryl monophosphine ligands via sulfonation. (A) New protocols for the preparation of sulfonated SPhos (sSPhos, **2**) and (B) sulfonated XPhos (sXPhos, **5**) with reduced reaction times. (C) Synthesis of sulfonated *t*-BuXPhos, BrettPhos, and *t*-BuBrettPhos (*st*-BuXPhos (**6**), sBrettPhos (**7**), and *st*-BuBrettPhos (**8**) respectively).

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** by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy.

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 lab[13] and repeated by others[8] for the sulfonation of **1** also detailed a sulfonation strategy for the selective monosulfonation of XPhos (**3**) via a Friedel-

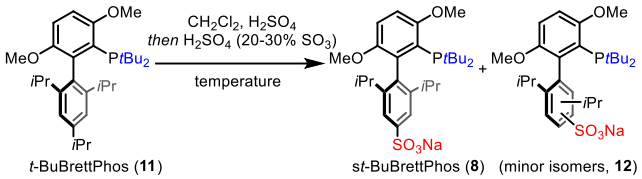
Scheme 1. Monosulfonation of BrettPhos to provide sBrettPhos.



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 CH_2Cl_2 and H_2SO_4 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 ^{1}H and ^{31}P 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 *st*-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.

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



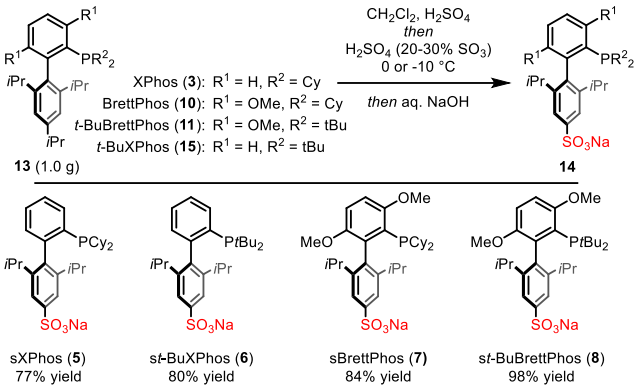
Entry	Reaction Time	Temperature (°C)	Ratio **8**:**12**
1[a]	5 min	0	13:1
2[b]	5 min	0	48:1
3[b]	5 min	-10	82:1
4[b]	1 h	-10	84:1[c]

[a]The reaction was carried out by the addition of fuming sulfuric acid dropwise to a solution of ligand. [b]Reactions were carried out by the slow addition of a solution of ligand to a solution of fuming sulfuric acid. [c]Under these conditions, an increased number of unidentified by-products were observed.

From the outset of our optimization, it was unclear which parameters would most influence product distribution. Hypothesizing that the concentration of SO_3 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 ^{31}P 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 as well as conduct 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 ^{31}P NMR and in good yield (77% - 98%).[17]

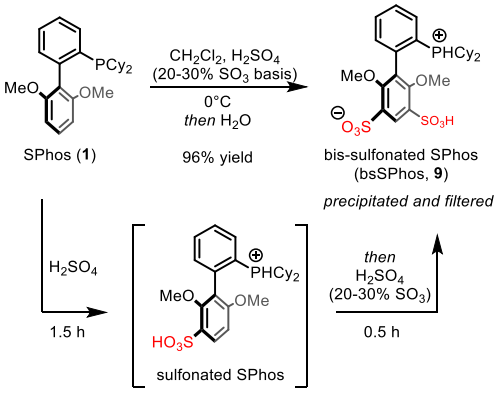
Scheme 2. Gram-scale synthesis of sulfonated XPhos, *t*-BuXPhos, BrettPhos, and *t*-BuBrettPhos



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 H_2SO_4 followed by the addition of fuming sulfuric acid (21-30% SO_3 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,

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



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 ^{1}H NMR and ^{31}P 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.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures and characterization data for all compounds (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

Author Contributions

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.

ACKNOWLEDGMENT

This work was supported by the NIH (Grant No. R35GM122483). We thank MilliporeSigma for the generous donation of all ligands used in this study. We also thank Alexander W. Schuppe and Christine Nguyen for advice and assistance in the preparation of this manuscript. This work was in part supported by an NIH postdoctoral fellowship under Grant No. 1F32GM131592-01A1 (H.H.D.). J. R. gratefully acknowledges support from the National Science Foundation Graduate Research Fellowship under Grant No. 174530 and the MIT Dean of Science Fellowship.

REFERENCES

(1) Shaughnessy, K. H. Beyond TPPTS: New Approaches to the Development of Efficient Palladium-Catalyzed Aqueous-Phase Cross-Coupling Reactions. *Eur. J. Org. Chem.* **2006**, *8*, 1827–1835.
(2) Butler, R. N.; Coyne, A. G. Water: Nature's Reaction Enforcer—Comparative Effects for Organic Synthesis "In-Water" and "On-Water." *Chem. Rev.* **2010**, *110*, 6302-6337.
(3) Cho, J. H.; Prickett, C. D.; Shaughnessy, K. H. Efficient Sonogashira Coupling of Unprotected Halonucleosides in Aqueous Solvents Using Water-Soluble Palladium Catalysts. *Eur. J. Org. Chem.* **2010**, *19*, 3678–3683.
(4) Messina, M. S.; Maynard, H. D. Modification of Proteins Using Olefin Metathesis. *Mater. Chem. Front.* **2020**, *4*, 1040–1051.
(5) Stradiotto, M., Lundgren, R. J., Eds. *Ligand Design in Metal Chemistry: Reactivity and Catalysis,* 1st ed.; John Wiley & Sons, Ltd: Chichester, UK, 2016.
(6) Ingoglia, B. T.; Wagen, C. C.; Buchwald, S. L. Biaryl Monophosphine Ligands in Palladium-Catalyzed C–N Coupling: An Updated User's Guide. *Tetrahedron* **2019**, *75*, 4199–4211.
(7) (a) Golding, W. A.; Phipps, R. J. Electrostatically-Directed Pd-Catalysis in Combination with C–H Activation: Site-Selective Coupling of Remote Chlorides with Fluoroarenes and Fluoroheteroarenes. *Chem. Sci.* **2020**, *11*, 3022–3027. (b) Golding, W. A.; Pearce-Higgins, R.; Phipps, R. J. Site-Selective Cross-Coupling of Remote Chlorides Enabled by Electrostatically Directed Palladium Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 13570–13574.
(8) Thomas, G. T.; Janusson, E.; Zijlstra, H. S.; McIndoe, J. S. Step-by-Step Real Time Monitoring of a Catalytic Amination Reaction. *Chem. Commun.* **2019**, *55*, 11727-11730.
(9) Mattos, C.; Ringe, D. Proteins in Organic Solvents. *Curr. Opin. Struct. Biol.* **2001**, *11*, 761–764.
(10) Vinogradova, E. V.; Zhang, C.; Spokoyny, A. M.; Pentelute, B. L.; Buchwald, S. L. Organometallic Palladium Reagents for Cysteine Bioconjugation. *Nature* **2015**, *526*, 687–691.
(11) Lee, H. G.; Lautrette, G.; Pentelute, B. L.; Buchwald, S. L. Palladium-Mediated Arylation of Lysine in Unprotected Peptides. *Angew. Chem. Int. Ed.* **2017**, *56*, 3177–3181.
(12) Zhao, W.; Lee, H. G.; Buchwald, S. L.; Hooker, J. M. Direct ^{11}CN-Labeling of Unprotected Peptides via Palladium-Mediated Sequential Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2017**, *139*, 7152–7155.
(13) Anderson, K. W.; Buchwald, S. L. General Catalysts for the Suzuki-Miyaura and Sonogashira Coupling Reactions of Aryl Chlorides and for the Coupling of Challenging Substrate Combinations in Water. *Angew. Chem. Int. Ed.* **2005**, *44*, 6173–6177.
(14) Rojas, A. J.; Pentelute, B. L.; Buchwald, S. L. Water-Soluble Palladium Reagents for Cysteine *S*-Arylation under Ambient Aqueous Conditions. *Org. Lett.* **2017**, *19*, 4263–4266.
(15) Dhanjee, H. H.; Saebi, A.; Buslov, I.; Loftis, A. R.; Buchwald, S. L.; Pentelute, B. L. Protein–Protein Cross-Coupling via Palladium–Protein Oxidative Addition Complexes from Cysteine Residues. *J. Am. Chem. Soc.* **2020**, *142*, 9124–9129.
(16) For structural assignment of the isomer **12** by 1-D and 2-D NMR, see the Supporting Information.
(17) Due to the poor solubility of *t*-BuXPhos (**15**) in CH_2Cl_2 at low temperatures, a modified protocol was used. For more details, see the Supporting Information.
(18) Mul, W. P.; Ramkisoensing, K.; Kamer, P. C. J.; Reek, J. N. H.; van der Linden, A. J.; Marson, A.; van Leeuwen, P. W. N. M. New, Highly Efficient Work-Up Protocol for Sulfonated Diphosphines. *Adv. Synth. Catal.* **2002**, *344*, 293–298.
(19) We observed a higher degree of solubility for each of the sulfonated ligands in polar organic solvents. For further details see the Supporting Information.