

Design and Discovery of Water-Soluble Benzooxaphosphole-Based Ligands for Hindered Suzuki–Miyaura Coupling Reactions with Low Catalyst Load

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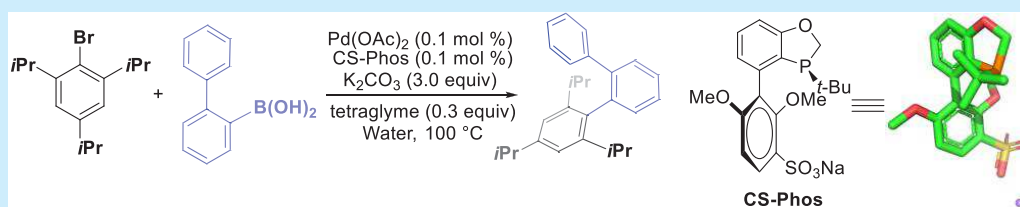
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ABSTRACT: We report a new class of highly effective, benzooxaphosphole-based, water-soluble ligands in the application of Suzuki–Miyaura cross-coupling reactions for sterically hindered substrates in aqueous media. The catalytic activities of the coupling reactions were greatly enhanced by the addition of catalytic amounts of organic phase transfer reagents, such as tetraglyme and tetrabutylammonium bromide. The optimized general protocol can be conducted with a low catalyst load, thereby providing a practical solution for these reactions. The viability of this new Suzuki–Miyaura protocol was demonstrated with various substrates to generate important building blocks, including heterocycles, for the synthesis of biologically active compounds.

Palladium-catalyzed Suzuki–Miyaura cross-coupling reactions have advanced into one of the most powerful carbon–carbon bond-forming reactions.^{1–5} It is one of the catalytic C–C forming transformations that has been applied successfully on commercial scales for synthesizing key intermediates and active ingredients in the pharmaceutical^{6,7} and agricultural arena.¹ As a result, the Suzuki–Miyaura reaction⁸ has garnered immense interest in the synthetic research community to continue investing on identifying sustainable conditions with new and effective catalysts and in alternative solvent systems.^{9–27} The first water-soluble ligand for this reaction was developed from the sulfonation of a monodentate phosphine ligand and has been applied in Pd-catalyzed Suzuki–Miyaura reactions in aqueous media, albeit with a higher catalyst load than in its organic solvent counterpart.^{28–34} Recently, Buchwald and co-workers developed new water-soluble ligands, which have addressed the greenness and sustainability of the Suzuki–Miyaura coupling reactions. These water-soluble ligands have a sulfonyl moiety, which provides a handle to conduct reactions in water and with an enhancement of reactivity in aqueous media.³⁵ Interestingly, the discovery of a suitable, efficient catalyst system to provide effective C–C bond formation between sterically hindered

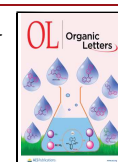
substrates in water is still scarce, especially for the high-yielding reactions using low catalyst load.

In 2010, Senanayake and Tang developed a special Suzuki–Miyaura ligand named **BIDIME** {(R)-3-(*tert*-butyl)-4-(2,6-dimethoxyphenyl)-2,3-dihydrobenzo[d][1,3]oxaphosphole}, which is known to be highly superior for many C–C bond forming reactions,^{4,36–43} including the Suzuki–Miyaura variant, and especially for the sterically hindered substrates. However, the application of these ligands in aqueous media is applicable to limited substrate scope with respect to the steric hindrance.¹⁹ Therefore, the design of a new ligand series is required in order to perform the coupling reactions of highly sterically demanding substrates in water. It was postulated that the sulfonated version of **BIDIME** ligand derivatives might have an advantage in providing a handle to operate the

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reactions in water or water containing an organic solvent. In turn, it can be a practical solution for running the Suzuki–Miyaura reactions in a sustainable manner for active pharmaceutical ingredient (API) development in the pharmaceutical industry. Herein, we disclose the identification and characterization of the new and competent water-soluble ligands **CS-Phos** for conducting highly efficient, palladium-catalyzed Suzuki–Miyaura coupling reactions on sterically hindered substrates in largely aqueous media with a low catalyst load.

We began our journey to identify a general catalyst system for performing Suzuki–Miyaura coupling reactions in water using the reported and known sulfonate sodium salt phosphine ligands, water-soluble variants of XPhos (*s*-XPhos) and SPhos (*s*-SPhos) ligands. The sterically demanding substrates 1-bromo-2,4,6-triisopropylbenzene and biphenyl boronic acid were selected for the Suzuki cross-coupling reaction in water according to the literature conditions.^{35,44} Surprisingly, even with 1 mol % of Pd(OAc)₂ and 2 mol % of ligand, the desired product **3a** was generated in 17% and 9% yields with *s*-SPhos and *s*-XPhos, respectively, after 16 h at 100 °C in water (see the Supporting Information, Table S1). We next turned our attention to the synthesis of a new type of water-soluble sulfonate sodium salt ligand, **CS-Phos**, based on the biaryl oxaphosphole scaffold (Scheme 1, Figure 1). The water-soluble

ligand **CS-Phos** was synthesized by treating (*S*)-3-(*tert*-butyl)-4-(2,6-dimethoxyphenyl)-2,3-dihydrobenzo[d][1,3]-oxaphosphole (**BIDIME**) with 6 equiv of concentrated sulfuric acid in DCM at 0 °C for 2 h followed by quenching the reaction with aqueous NaOH under N₂ to generate the sodium sulfonate ligand **CS-Phos** in 86% yield on a multigram scale.

However, the **Mono-CSPhos** ligand was found to be highly prone to oxidation. Under the same reaction conditions under N₂ after treatment with NaOH, a creamy white solid was isolated, which was confirmed to be the corresponding phosphine oxide. Fortunately, performing the reaction under an argon atmosphere afforded the **Mono-CSPhos** ligand as a white solid. The mono-OMe ligand was treated with neat H₂SO₄ at 0 °C for 2 h, and working up the reaction under argon resulted in the complete formation of a new product whose structure was confirmed by both LC-MS and ³¹P NMR. The reaction was quenched at 0 °C with aqueous NaOH, and the product was extracted with DCM to provide **Mono-CSPhos** as a white solid in 79% yield (see the Supporting Information).

When the reaction progress of the **CS-Phos** ligand was monitored by ³¹P NMR, a major new peak A at $\delta = -6.06$ ppm was observed, along with a small peak B at 10% in the isolated compound. The ratio of the two resonances did not vary with reaction temperature (−20 vs 10 °C). The ratio of the major to minor diastereomer was consistently observed at 9:1 in the isolated ligand. This mixture was directly applied to the Suzuki–Miyaura cross-coupling reactions for the sterically hindered substrates in aqueous media. Extensive 2D NMR studies were performed on the isolated mixture, which confirmed that the two signals emanated from the restricted rotation of the biaryl C–C bond, notably, because of the formation of the two atropodiastereomers. The sulfonation-induced chirality through the atropisomeric axis has been observed for the sulfonated SPhos (*s*-SPhos) ligand.⁴⁵ A clear splitting pattern on the bottom ring of both components shows that sulfonation occurs on the bottom phenyl ring of the ligand. A major atropo-diastereomer resulted from the chirality of the phosphorus center. Variable temperature NMR experiments were conducted, and it was found that the two diastereomeric atropoisomers do not coalesce even when heated to 125 °C in the NMR tube, thereby indicating the high rotational barrier of the two atropoisomers. Furthermore, a torsion scan was performed for the aryl–aryl bond (C7–C6–C8–C13) using Spartan 18 with molecular force field (MMFF) with 10° steps in the gas phase. The calculated energies showed a significant barrier to rotation (relative energies of 30 kcal/mol at 20° and 41 kcal/mol at −170°) with two local minima at −70° (Rel E, 0 kcal/mol) and 120° (Rel E, 2 kcal/mol). Given the calculated difference in energies for the minima, it was deduced that the major isomer would be the one with a torsion angle of −70°, and the minor isomer would be that with a torsion angle of 120°. The results of these calculations were consistent to the data from a NOESY experiment (see the Supporting Information for the ligand structure characterization and confirmation).

The reactivity toward the sterically hindered Suzuki coupling reactions in aqueous solvent systems was explored with the newly developed water-soluble ligand **CS-Phos**. The first trials were performed with 1-bromo-2,4,6-triisopropylbenzene and biphenyl boronic acid in water, as depicted in Table 1.

Contrary to what has been observed for the known water-soluble *s*-SPhos and *s*-XPhos ligands (see Table S1), the

Scheme 1. Synthesis of New CS-Phos and Mono-CSPhos Ligands

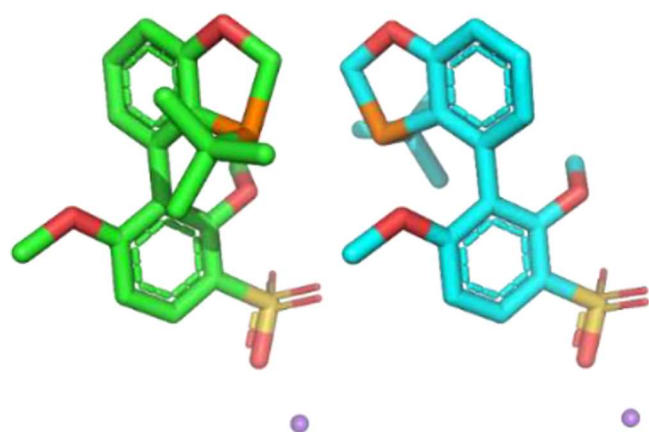
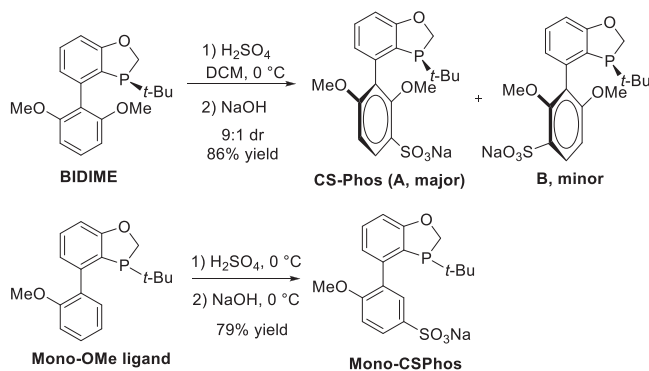
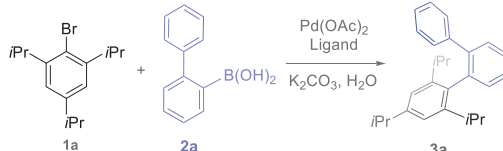


Figure 1. CS-Phos major (left) and minor (right) atropoisomers. These structures were calculated by DFT geometry optimization at the B3LYP/6-31+G(d,p) level. See the Supporting Information for details.

Table 1. Suzuki–Miyaura Coupling of the Hindered Substrate **1a** and **2a** Using Water-Soluble Ligands^a


entry	2a (equiv)	[Pd] (mol %)	ligand	time (h)	additive	amount (equiv)	3a (A %) ^b (yield %)
1	1.5	1.0	CS-Phos	20			55
2	1.5	1.0	CS-Phos	4	1,4 dioxane	2.0	97 (92)
3	1.5	0.1	CS-Phos	5	1,4-dioxane	2.0	85 (78)
4	1.5	1.0	CS-Phos	4	TBAB	0.3	74
5	3	1.0	CS-Phos	4	TBAB	0.3	96
6	3	0.1	CS-Phos	4	TBAB	0.3	87
7	3	0.1	CS-Phos	5	TBAB	0.3	92 (82)
8	3	1.0	Mono-CSPhos	5	TBAB	0.3	84
9	3	1.0	<i>s</i> -SPhos	5	TBAB	0.3	31
10	3	1.0	<i>s</i> -XPhos	5	TBAB	0.3	7

^aReaction conditions: 1.0 equiv of **1a**, 3.0 equiv of K₂CO₃, degassed water (1.5 mL/mmol of **1a**), catalyst/ligand = 1:1 (the 9:1 mixture of CS-Phos was applied for the study), [Pd] = Pd(OAc)₂; 100 °C. ^bArea % (A %) of **3a** is calculated by considering remaining **1a**, des-Br, and product **3a** on HPLC at 210 nm; the isolated yields are in parentheses. For more optimized conditions, refer to the Supporting Information.

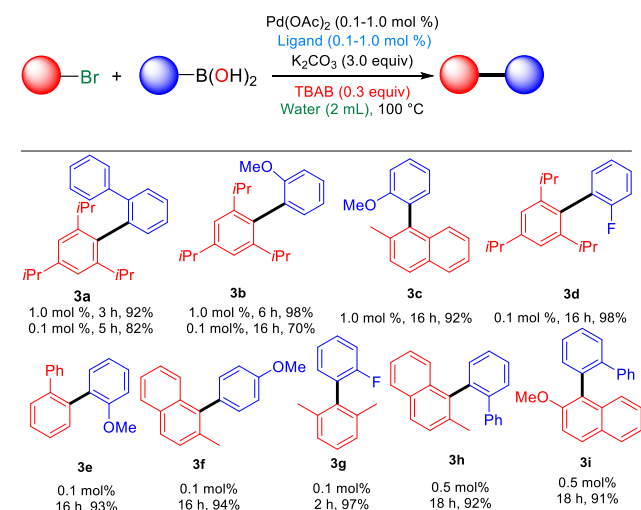
coupling of significantly sterically hindered 1-bromo-2,4,6-triisopropylbenzene **1a** with **2a** in the presence of 1.0 mol % Pd(OAc)₂ and 1.0 mol % CS-Phos resulted in 55% product after 20 h at 100 °C (Table 1, entry 1). The use of additional catalysts (2 mol %) did not improve the conversion; rather, a decreased conversion was observed with a product formation of only 52% because of the complete consumption of boronic acid **2a** resulting from the proto-deboronation side product. This result was confirmed by an increase in the amount of boronic acid to 4 equiv. In this case, 66% of product **3a** was observed after being heated at 100 °C for 4 h (Table S1).

Because of the hydrophobic nature of both starting substrates, we attempted to add a small amount of organic solvent (dioxane, 2.0 equiv) to the reaction mixture to increase the solubility of the coupling partners and facilitate the reaction. Indeed, complete conversion was observed with only 0.1 mol % Pd(OAc)₂ (Table 1, entries 2 and 3) with 97% and 85% product **3a** formation, respectively. Furthermore, we reasoned that a phase transfer catalyst (PTC) would have the same effect of increasing the solubility of hydrophobic substrates in aqueous media. To test the hypothesis, tetra-*N*-butyl ammonium bromide (TBAB) was evaluated for this purpose.⁴⁶ When 0.3 equiv of TBAB was utilized, 74% of the desired product was observed with 1.0 mol % palladium catalyst. The incomplete conversion was once again due to the disappearance of boronic acid (Table 1, entry 4). Doubling the amount of boronic acid resulted in 96% **3a** formation (Table 1, entry 5). When the PTC loading was kept at 0.3 equiv, 87% **3a** resulted, even with 0.1 mol % of Pd(OAc)₂ (Table 1, entry 6). By further extending the reaction time to 5 h with the catalyst load of 0.1 mol % Pd(OAc)₂ with 0.1 mol % CS-Phos ligand, 92% product **2a** was achieved with an isolated yield of 82% (Table 1, entry 7).

With these optimized conditions in hand (Table 1, entry 7), we retested and compared the reactivities of other similar water-soluble ligands. The coupling of hindered 1-bromo-2,4,6-triisopropylbenzene **1a** with **2a** in the presence of 1 mol % Pd(OAc)₂ and 1 mol % *s*-SPhos, together with 0.3 equiv of TBAB, resulted in 31% of **3a** formation and 7% with *s*-XPhos under optimized conditions (Table 1, entries 9 and 10). An

84% product formation was obtained for the Mono-CSPhos ligand (Table 1, entry 8).

With the optimized reaction conditions in hand (Table 1, entry 7), we investigated the substrate scope of the reaction toward sterically hindered aryl bromides (Scheme 2). Excellent yields of cross-coupling products **3a–i** were obtained using TBAB as PTC and in the presence of 0.1 to 1.0 mol % of 1:1 Pd(OAc)₂ and CS-Phos.

Scheme 2. Suzuki–Miyaura Coupling of Aryl Halides Using CS-Phos in the Presence of TBAB as PTC^a

^aReaction conditions: 1.0 equiv of aryl bromide, 3.0 equiv of boronic acid, 3.0 equiv of K₂CO₃, 0.3 equiv of TBAB, degassed water (1.5 mL/mmol alkyl halide), Pd(OAc)₂/CS-Phos (9:1 mixture) = 1:1, 100 °C; isolated yields are provided.

Having established the best catalyst system for the C–C bond-forming reactions, we next focused on identifying a more suitable additive to enable the reaction to proceed without the requirement of using highly excessive amounts of boronic acids. To achieve this goal, we looked beyond the traditional PTC/TBAB system and explored various PTC systems to

probe the reactivity of the CS-Phos ligand. Initially, we tested the micelle as the PTC with the conditions applied in our previous study,¹⁹ and similar reactivity was observed for both CS-Phos and BIDIME ligands when coupling the substrates **1a** with **2a** using 0.05 mol % of Pd(OAc)₂. The product **3a** was produced in about 30% yield with micelle conditions for coupling the extremely hindered substrates. We then continued to identify a preferable PTC to promote the coupling reaction in water. The addition of TDA-1⁴⁷ resulted in 69% of **3a** formation (Table 2, entry 2) under the best conditions (Table

Table 2. Suzuki–Miyaura Coupling of the Hindered Substrate Using Various PTCs as Additives^a

entry	time (h)	2a (equiv)	additive	amount (equiv)	3a ^b (A %)
1	5	3	TBAB	0.3	92
2	5	3	TDA-1	0.3	69
3	5	3	DME	0.3	12
4	5	3	Diglyme	0.3	24
5	5	3	triglyme	0.3	67
6	5	3	tetraglyme	0.3	93
7	7	3	tetraglyme	0.3	96
8	8	1.5	tetraglyme	0.3	90 (85 ^c)

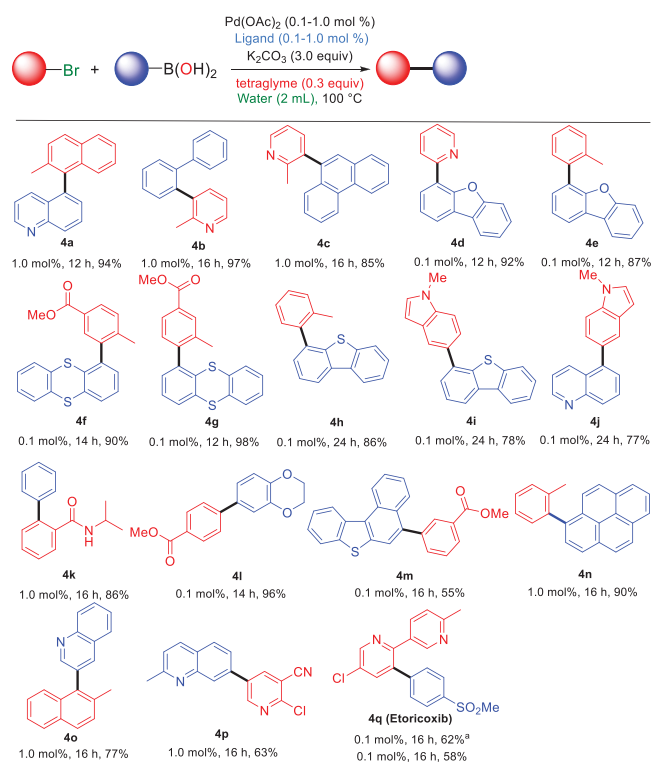
^aReaction conditions: 1.0 equiv of **1a**, 3.0 equiv of **2a**, 3.0 equiv of K₂CO₃, degassed water (1.5 mL/mmol of **1a**), 0.1 mol % catalyst, catalyst Pd(OAc)₂/CS-Phos (9:1 mixture) = 1:1, TBAB = tetrabutyl ammonium bromide, TDA-1 = triethanolamine tris(2-methoxyethyl) ether, DME = dimethoxyethane, triglyme = triethylene glycol dimethyl ether, tetraglyme = tetraethylene glycol dimethyl ether. ^bArea % (A %) of **3a** is calculated by considering remaining **1a**, des-Br, and product **3a** on HPLC at 210 nm. ^cIsolated yield.

1, entry 7). The use of crown ethers did not improve the reactivity, and 14% and 51% of products were observed with 18-Crown-6 and 15-Crown-5, respectively (Table S1). We then employed glyme as the PTC. Monoglyme DME gave 12% of **3a** (Table 2, entry 3). Diglyme delivered 24% of the product (Table 2, entry 4). Triglyme yielded 67% (Table 2, entry 5), and tetraglyme provided 93% product within 5 h (Table 2, entry 6). Product **3a** was observed at 96% when the reaction time was extended for 7 h in the presence of 0.1 mol % Pd(OAc)₂, 0.1 mol % CS-Phos, and 3.0 equiv of K₂CO₃ with 0.3 equiv of tetraglyme in water (Table 2, entry 7).

Interestingly, we observed that when we used tetraglyme as an additive, the excess amount of boronic acid **2a** remained in the system without significant side product proto-deboronation, whereas in the case of TBAB, 3.0 equiv of boronic acid was required to compensate for the proto-deboronation (Table 1, entry 5). On the basis of these results, we attempted the same reaction with 1.5 equiv of boronic acid **2a**. This reaction resulted in the complete conversion of the aryl halide within 8 h at 100 °C. An 85% isolated yield for **3a** was resulted (Table 2, entry 8). The additive tetraglyme as a PTC promotes the coupling reaction of the hindered substrates and mitigates the proto-deboronation of boronic acids.

Besides the excellent reactivity toward the hindered coupling substrate, CS-Phos also performed the coupling on a broad range of challenging substrates, including sterically congested aryl halides, heteroaryl aryl boronic acids, and compounds containing heteroaryl moieties. As shown in Scheme 3, we have demonstrated a variety of heteroatom-substituted aryl bromides and boronic acid couplings in excellent yields using tetraglyme as the PTC (Scheme 3, entries 4a–q). These heteroatom substrates include pyridines (4b–d), indoles (4i,j),

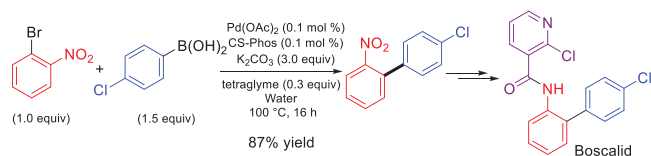
Scheme 3. Suzuki–Miyaura Coupling of Heteroaryl Aryl Boronic Acids Using CS-Phos in the Presence of Tetraglyme as PTC^b



^a1,4-dioxane/water = 0.1:1.4 mL. ^bReaction conditions: 1.0 equiv of aryl bromide (1.0 mmol), 1.5 equiv of boronic acid, 3.0 equiv of K₂CO₃, 0.3 equiv of tetraglyme, degassed water (1.5 mL/mmol of alkyl halide), Pd(OAc)₂/CS-Phos (9:1 mixture) = 1:1. Isolated yields are provided.

quinoline (4a,j), dibenzothiophenes (4h,i), and amines (4k). The coupling of thianthrenylboronic acid with phenyl esters also gave excellent yields (4f,g). With the currently established catalyst system, we have also demonstrated the conditions for the synthesis of the pesticide, boscalid,⁴⁸ using 0.1 mol % catalyst loading (Scheme 4). The key C–C bond-forming

Scheme 4. Synthesis of Boscalid Using Suzuki–Miyaura Coupling of Aryl Halides Using CS-Phos on a Gram Scale



Suzuki coupling step was obtained in 82% yield on a gram scale. The BACE inhibitor precursor, **4p**,^{49,50} was also synthesized in 63% yield using our optimized conditions. Etoricoxib (**4q**), a selective COX-2 inhibitor, was also prepared with 63% yield using the 0.1 mol % Pd(OAc)₂/CS-Phos catalyst system loading (in 1.9:0.1 mL of water/dioxane), an enhanced yield compared with the current commercial synthesis.⁵¹

In summary, we have developed a novel class of water-soluble biaryl benzooxophosphole-based ligands, CS-Phos and Mono-CSPhos, to facilitate the Suzuki–Miyaura coupling reactions of sterically hindered substrates in aqueous media.

These ligands are highly effective compared with the known water-soluble phosphine ligands. The coupling reactions can be accomplished in high yields with a low catalyst load of 0.1 mol % Pd(OAc)₂. Various organic-phase-transfer catalysts were applied to facilitate the coupling reaction in water. Tetraglyme was found to be one of the best PTCs for hindered Suzuki coupling reactions in aqueous media. A variety of sterically congested aryl- and heteroaryl cross-coupling reactions were demonstrated in excellent yields and with a low catalyst load. The purification of the diastereomerically pure **CS-Phos** and the applications of the enantio- and diastereomerically pure **CS-Phos** ligand and its derivatives for many enantioselective catalytic transformations are currently ongoing in TCG GreenChem laboratories.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

■ Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.3c01663>.

Experimental procedures, ¹H NMR and ¹³C NMR of the ligands and coupling products, and calculation confirmation of the major diastereomeric ligand (PDF)

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Notes

The authors declare no competing financial interest.

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