C–C Coupling Reactions

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General Catalysts for the Suzuki–Miyaura and Sonogashira Coupling Reactions of Aryl Chlorides and for the Coupling of Challenging Substrate Combinations in Water**

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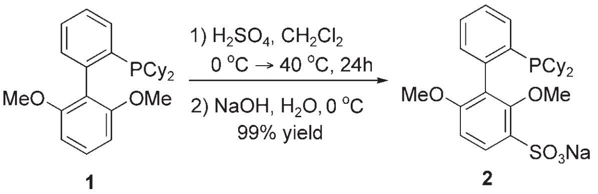
Metal-catalyzed cross-coupling methodology to form carbon–carbon bonds has inarguably advanced organic synthesis.[1] The Suzuki–Miyaura coupling is one of the preeminent methods for formation of carbon–carbon bonds and has been used in numerous synthetic ventures.[2] We recently reported a new catalyst system that manifested high activity paired with extremely broad scope.[3] There remained, however, a need to develop reaction conditions for the coupling of water-soluble aryl chlorides and for the combination of difficult coupling partners in aqueous conditions. Additionally, substrates containing hydrophilic functional groups, which are insoluble in organic solvents and are present in many pharmaceutically interesting compounds, may be transformed, obviating the need for additional protection/deprotection steps. Furthermore, reactions conducted in water are attractive as water is nontoxic, nonflammable, and inexpensive, and is easily separated from organic products.[4]

Very few examples have been reported concerning palladium-catalyzed cross-coupling reactions of hydrophilic aryl chlorides with aryl boronic acids using purely aqueous reaction conditions.[5–9] Several sulfonated phosphine derivatives have been prepared and used in cross-coupling reactions conducted in water or water/organic biphasic solvent systems.[10,11] Shaughnessy and coworkers reported that use of sterically demanding, water-soluble, alkylphosphine salts in the Suzuki–Miyaura, Sonogashira, and Heck coupling reactions of unactivated aryl bromides provided products derived from carbon–carbon bond formation in excellent yields.[12] Limitations to this methodology include a lengthy synthesis and poor thermal and air stability of the ligand. Furthermore, only a single example of a substituted aryl chloride was described. The activated aryl chloride 4-chlorobenzonitrile was combined with phenylboronic acid in a reaction that required 4 mol% of the palladium catalyst. Very recently, a Pd/glucosamine-based dicyclohexylarylphoshine catalyst was reported that displayed modest activity in Suzuki–Miyaura couplings of activated aryl chlorides when conducted in a mixture of water, toluene, and ethanol.[13] This system, as reported, was not general and the ligand was not readily available.

We felt that the electron-rich lower aromatic ring on **1** would be readily amenable to the incorporation of a water-solubilizing sulfonate group. In fact, treatment of **1** with concentrated H_2SO_4 at 40 °C for 24 h gave **2** with exclusive monosulfonation at the 3′-position in 99% yield after treatment with NaOH and workup [Eq. (1)]. With **2**, excellent yields were obtained in Suzuki–Miyaura couplings of highly functionalized aryl chlorides or heterocyclic chlorides/bromides (containing carboxy, amino, hydroxy, sulfonamide, or sulfonate groups) and aryl or alkyl boronic acids in aqueous media.



(1)

Using a catalyst system based on **2**, we investigated the coupling of hydrophobic and hydrophilic substrates (Table 1). The coupling of electronically neutral 1-chloro-3,4-dimethylbenzene and phenylboronic acid at room temperature using water as the solvent provided the corresponding biaryl product in 99% yield (Table 1, entry 1). A temperature of 100 °C was necessary for successful coupling of 3-chlorobenzamide and hindered 2,6-dimethylphenylboronic acid resulting in 99% yield of the biaryl amide (Table 1, entry 2). Using microwave irradiation (150 °C), the same coupling product was obtained in 94% yield in 10 minutes.[14,15] This result indicates that the catalyst system based on **2** exhibits high thermal stability. We found that coupling of 3-chlorobenzoic acid with phenylboronic acid proceeds at room temperature using 0.5% Pd and at 100 °C using 0.1% Pd to provide the coupled product in 97% yield in both cases (Table 1, entry 3). Similar catalytic activity was observed in the coupling of 3-chlorobenzoic acid and 2-methylphenylboronic acid using 0.5% Pd at room temperature and 0.1% Pd at 100 °C to give the desired product in yields of 95% and 96%, respectively (Table 1, entry 4). Using microwave irradiation (150 °C) and 0.1% Pd, the same coupling product was obtained in 98% yield in 10 minutes. The combination of 5-chloro-2-hydroxybenzoic acid and 2-methylphenylboronic acid, while slower, provided an excellent yield of the biaryl product using 2% Pd (room temperature) or 0.1% Pd (100 °C; Table 1, entry 5).

The Suzuki–Miyaura coupling of hydrophobic aryl bromides in aqueous media has been reported to occur with an assortment of catalysts including those that operate without a supporting ligand. Successful application to moderately hindered substrate combinations, however, has not been

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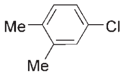
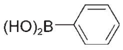
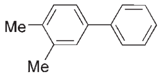
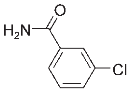
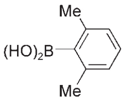
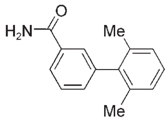
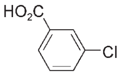
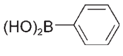
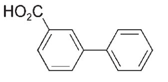
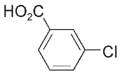
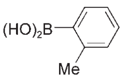
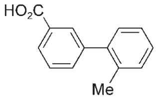
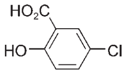
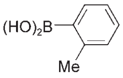
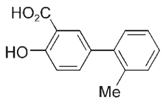
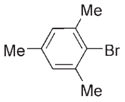
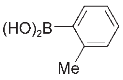
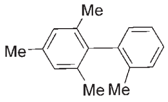
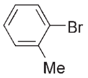
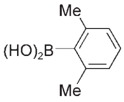
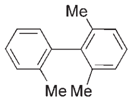
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Suzuki–Miyaura coupling of aryl halides using ligand **2**.[a]

Entry	Halide	Boronic acid	Product	Pd [mol %]	Conditions	Yield [%][b]
1				2	RT, 10 h	99
2				1 1	100 °C, 8 h 150 °C, 10 min	99 94[c]
3				2 0.5 0.1 0.1	RT, 2 h RT, 8 h 100 °C, 5 h 150 °C, 10 min	96 97 97 98[c]
4				0.5 0.1	RT, 8 h 100 °C, 6 h	95 96
5				2 0.1	RT, 12 h 100 °C, 12 h	99[d] 96[d]
6				2	RT, 22 h	94
7				2	RT, 22 h	97

[a] Reaction conditions: 1.0 equiv aryl chloride, 1.2 equiv boronic acid, 3.0 equiv K_2CO_3, degassed water (1.5 mL mmol^{-1}), cat. Pd(OAc)$_2$, ligand **2**, L/Pd = 2:1. [b] Yield of isolated product (average of two runs). [c] Conducted using microwave irradiation with cooling. [d] 4.0 equiv K_2CO_3 was used.

disclosed or possible.[11,12,15] To ascertain whether our Pd(OAc)$_2$/**2** catalyst system could address this limitation, we examined two reasonably hindered substrate combinations using water as the solvent at room temperature: the reactions of 2-bromomesitylene with 2-methylphenylboronic acid and 2-bromotoluene with 2,6-dimethylphenylboronic acid to form biaryl products that contain three substituents *ortho* to the aryl–aryl connection (Table 1, entries 6, 7).[16] To our knowledge, this represents the first successful coupling of a hindered substrate combination conducted using a water or water/organic biphasic solvent at room temperature.

To determine the scope of this process, we examined the reaction of chlorobenzoic acids with 3-carboxyphenylboronic acid, 2-hydroxyphenylboronic acid, 2-aminophenylboronic acid, 2-acetylphenylboronic acid, and 2-formylphenylboronic acid. These coupling processes all proceeded in excellent yields using 1 % catalyst (Table 2, entries 1–3). Using microwave irradiation (150 °C), 4-chlorobenzoic acid and 3-carboxyphenylboronic acid were coupled in 10 minutes with 1 % Pd to provide the product in 95 % yield (Table 2, entry 1), again demonstrating catalyst stability at higher temperatures.

We next turned our attention to Suzuki–Miyaura couplings of functionalized hydrophilic aryl chlorides and substituted arylboronic acids. Chlorobenzoic acids containing hydroxy (Table 2, entry 4) and amino (Table 2, entry 5) groups on the aromatic ring were effectively coupled with substituted arylboronic acids (4-cyanophenylboronic acid and 3-aminophenylboronic acid, respectively) to generate the biaryl products in high yields (92 % and 99 %, respectively). 4-Chlorobenzenesulfonic acid successfully coupled with methylboronic acid to give the sulfonic acid derivative in 96 % yield, (Table 2, entry 6). To the best of our knowledge, this is the first reported Suzuki–Miyaura coupling of an aryl halide bearing an unprotected sulfonic acid.[17]

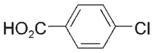
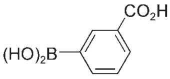
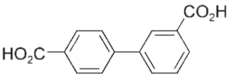
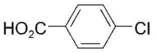
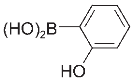
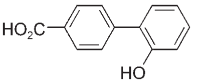
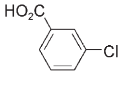
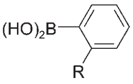
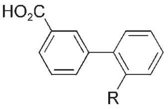
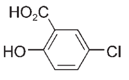
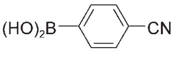
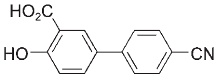
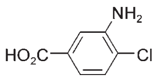
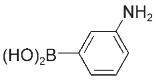
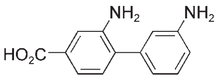
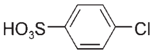
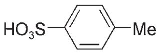
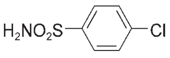
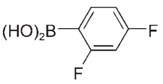
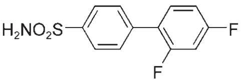
Applications of heterocyclic compounds in cross-coupling processes remain a challenge. To the best of our knowledge, very few examples of aqueous-phase Suzuki couplings of water-soluble heterocyclic halides have been published.[18] We have examined the use of **2** as a supporting ligand in the Suzuki–Miyaura coupling with a variety of challenging hydrophilic heterocyclic halides (Table 3). As is shown, the method worked well for a number of different carboxy-group-containing heterocyclic chlorides and bromides, including indole (with a free N–H bond), pyridine, and thiophene derivatives (Table 3, entries 2, 3, 5). Even 2-amino-5-chloropyridine, which can potentially chelate to metal centers such as Pd^{II}, was successfully coupled with 3-pyridylboronic acid in 93 % yield (Table 3, entry 4).[19]

The Suzuki–Miyaura coupling of 3-chlorobenzoic acid and phenylboronic acid employing **1** provided efficient conversion and yield of the desired product using a water/organic biphasic solvent system at 100 °C (Table 4, entries 3, 4). However, at room temperature this reaction was sluggish (Table 4, entry 5). A dramatic increase in activity was observed when using the amphiphilic ligand **2** in water at room temperature, which provided the biaryl product in 97 % yield (Table 4, entry 7). Although a catalyst system using **1** in a similar biphasic solvent system may work in many instances, this has not yet been explored.

Recently, we disclosed that a catalyst system based on [$PdCl_2(CH_3CN)_2$]/**3** provided excellent reactivity in the copper-free Sonogashira coupling of aryl chlorides or tosylates and terminal alkynes.[20] This catalyst system was successful in coupling aryl alkynes only when the alkyne was added slowly over the course of the reaction. This is presumably due to competing oligomerization of the alkyne at higher concentrations in the presence of the catalyst. We felt that incorporation of a water-solubilizing sulfonate group on **3** would provide an amphiphilic Sonogashira catalyst which might address the limitations that were previously reported and allow for the coupling of hydrophilic substrate combinations.[21] We found that treatment of **3** with fuming sulfuric acid (H_2SO_4/20 % SO_3) at room temperature for 24 h provided **4**, with selective monosulfonation at the 4′-position, in 93 % yield after treatment with NaOH and workup [Eq. (2)].[22]

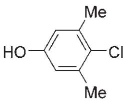
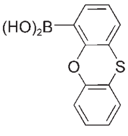
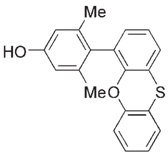
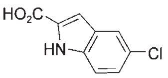
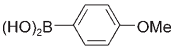
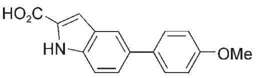
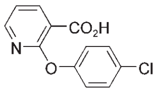
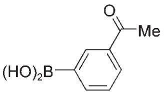
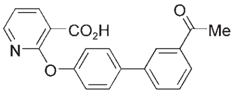
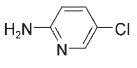
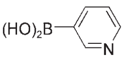
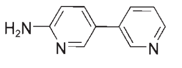
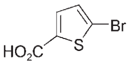
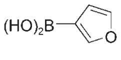
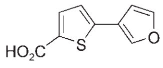
For the first time, by using a catalyst system based on [$PdCl_2(CH_3CN)_2$]/**4** and a water/acetonitrile biphasic solvent system, propiolic acid was successfully coupled with 3-bromoanisole and 3-bromobenzoic acid to provide aryl alkynoic acids in yields of 70 % and 69 %, respectively (Table 5, entries 1, 2). This result represents a significant advancement in Sonogashira coupling reactions, as electron-deficient propiolate esters have been problematic coupling partners due to their increased reactivity towards nucleophilic attack and their propensity to polymerize in the presence of Pd catalysts.[23] Good yields were obtained for the coupling of hydrophilic aryl chlorides bearing carboxy groups (Table 5, entries 3, 5) and an alkyne derived from an aliphatic carboxylic acid (Table 5, entry 4). Interestingly, by using **4** and a water/acetonitrile solvent system, the coupling of aryl chlorides and aryl alkynes

Table 2: Suzuki–Miyaura coupling of aryl chlorides using ligand **2**.[a]

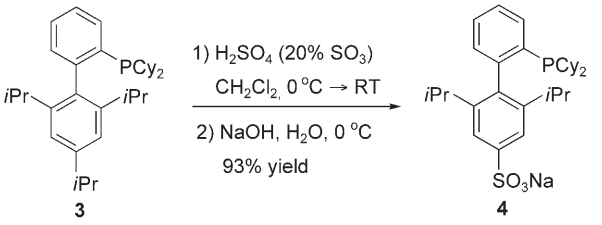
Entry	Halide	Boronic acid	Product	Yield [%][b]
1				99[c] 95[d]
2				99
3				94 (R = NH_2) 97 (R = C(O)Me) 87[e] (R = CHO)
4				92[e]
5				93
6		$(HO)_2BMe$		97
7				96

[a] Reaction conditions: 1.0 equiv aryl chloride, 1.3–1.5 equiv boronic acid, 3.0 equiv K_2CO_3, degassed water (2.0 mL mmol^{-1}), $Pd(OAc)_2$ (1.0 mol %), ligand **2** (2.0 mol %), 100 °C, 2–8 h. Reaction times and temperatures were not optimized. [b] Yield of isolated product (average of two runs). [c] The reaction was conducted at 50 °C. [d] Conducted using microwave irradiation with cooling, 150 °C for 10 min. [e] The reaction was conducted at 80 °C.

Table 3: Suzuki–Miyaura coupling of heterocyclic halides using ligand **2**.[a]

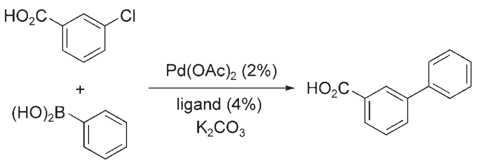
Entry	Halide	Boronic acid	Product	Yield [%][b]
1				93
2				93[c]
3				92[c]
4				93
5				97 95[d]

[a] Reaction conditions: 1.0 equiv aryl halide, 1.3–1.5 equiv boronic acid, 3.0 equiv K_2CO_3, degassed water (4.0 mL mmol^{-1}), $Pd(OAc)_2$ (1.0 mol %), ligand **2** (2.0 mol %), 100 °C, 10–12 h. Reaction times and temperatures were not optimized. [b] Yield of isolated product (average of two runs). [c] The reaction was conducted at 80 °C. [d] The reaction was conducted using microwave irradiation with cooling, 150 °C for 10 min.



(2)

Table 4: Screening of conditions for Suzuki–Miyaura coupling with **1** and **2**.



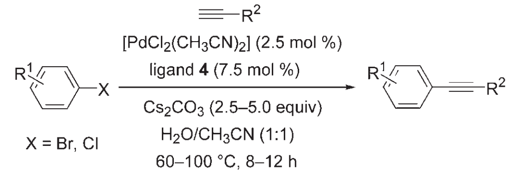
Entry	Ligand	Solvent	*T* [°C]	Conv. [%]	Yield [%][b]
1	**1**	*n*BuOH	100	77	75
2	**1**	*n*BuOH/H_2O (5:1)	100	27	26
3	**1**	CH_3CH_2CN/H_2O (1:1)	100	>99	96
4	**1**	DMF/H_2O (1:1)	100	>99	94
5	**1**	CH_3CN/H_2O(1:1)	RT	17	12
6	**1**	H_2O	100	22	20
7	**2**	H_2O	RT	>99	97[c]

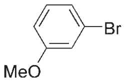
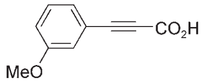
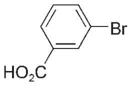
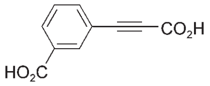
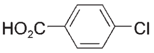
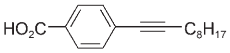
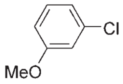
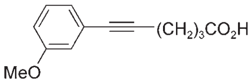
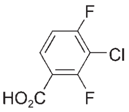
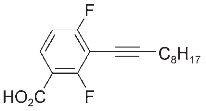
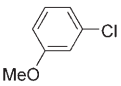
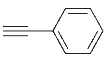
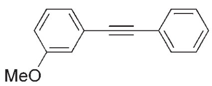
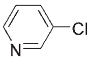
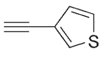
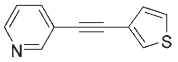
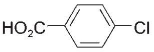
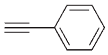
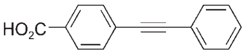
[a] Reaction conditions: 1.0 equiv aryl chloride, 1.2 equiv boronic acid, 3.0 equiv K_2CO_3, solvent (2.0 mL mmol^{-1}), cat. $Pd(OAc)_2$, ligand **1** or **2**, L/Pd = 2:1, 14 h. [b] Yield of product determined by NMR spectroscopy. [c] The reaction was complete in 2 h.

proceeds and obviates the need to employ slow addition of the aryl alkyne (Table 5, entries 6–8). This result may be attributed to the lower effective concentration of the alkyne in proximity to the catalyst, which resides at the water/organic interface.

We have demonstrated that use of sulfonated ligands **2** and **4** provides highly active catalyst systems for Suzuki–Miyaura and Sonogashira cross-coupling reactions, with unprecedented scope, reactivity, and stability for aqueous-phase processes. Further work to apply sulfonated biarylphosphines in other transition-metal-catalyzed processes is underway in our laboratories.

Table 5: Sonogashira coupling of aryl halides using ligand **4**.[a]



Entry	Halide	Alkyne	Product	Yield [%][b]
1		$\equiv\!-CO_2H$		70[c,d]
2		$\equiv\!-CO_2H$		69[c,d]
3		$\equiv\!-C_8H_{17}$		86
4		$\equiv\!-(CH_2)_3CO_2H$		85[d]
5		$\equiv\!-C_8H_{17}$		71
6				88
7				93
8				96[d]

[a] Reaction conditions: 1.0 equiv aryl halide, 1.3–1.5 equiv terminal alkyne, 2.5–5.0 equiv Cs_2CO_3, degassed water (2.0 mL mmol^{-1}), CH_3CN (2.0 mL mmol^{-1}), $[PdCl_2(CH_3CN)_2]$ (2.5 mol%), ligand **4** (7.5 mol%), 100 °C, 8–12 h. Reaction times were not optimized. [b] Yield of isolated product (average of two runs). [c] The alkyne was added to the reaction at 0 °C and the mixture was heated to 60 °C. [d] To ease in purification, the product was converted to the methyl ester using trimethylsilyldiazomethane.

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