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Retraction: Suzuki–Miyaura Coupling of Aryl Tosylates and Mesylates in Water

Jan Pschierer[a] and Herbert Plenio*[a]

Keywords: C-C coupling / Palladium / Water / Suzuki–Miyaura reactions / Phosphanes

The following article from the *European Journal of Organic Chemistry*, "Suzuki–Miyaura Coupling of Aryl Tosylates and Mesylates in Water", published online on April 15, 2010 in Wiley Online Library (www.onlinelibrary.wiley.com, doi: 10.1002/ejoc.201000251) and in print (*Eur. J. Org. Chem.* **2010**, 2934–2937), has been retracted by agreement between the corresponding author, the journal Editor, Dr. Haymo Ross, and Wiley-VCH. The retraction has been agreed because several ^{1}H and ^{13}C NMR spectroscopic data listed in the manuscript are incorrect, and the original mass spectra cannot be located. Attempts to repeat the synthesis of several representative products under the conditions reported in this manuscript have failed.

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Suzuki–Miyaura Coupling of Aryl Tosylates and Mesylates in Water

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Keywords: C-C coupling / Palladium / Water / Suzuki–Miyaura reactions / Phosphanes

The palladium complex (0.5 mol-%) of a water-soluble sulfonated fluorenylphosphane (cataCXium Fsulf) enables the facile Suzuki–Miyaura coupling of various (heterocyclic) aryl tosylates and aryl mesylate with various (heterocyclic) boronic acids in excellent yields (> 95 %) using water as the reaction solvent.

Introduction

Traditionally for organic transformations a large number of different organic solvents are used as the reaction medium. However, the use of volatile organics also has some drawbacks, as these liquids tend to be toxic and flammable. The search for alternative solvents or solvent mixtures with special properties led to the development of numerous advanced solvent concepts involving ionic liquids, supercritical phases or perfluorinated solvents.[1] Water, on the other hand, appears to be less sophisticated.[2] However, the use of water as the reaction solvent for organic transformations has a number of advantages: It is widely available in excellent purity, it is non-flammable, non-toxic and it normally has a low, but nonetheless significant solubility for many organic compounds.[3] The same holds true for chemical transformations catalyzed by late transition metals, such as palladium-catalyzed cross coupling reactions[4] or ruthenium-mediated olefin metathesis.[5] However, apart from a potential benign effect of using water, we have demonstrated recently that water is an excellent solvent for promoting the catalytic activity in Suzuki–Miyaura and Sonogashira coupling reactions as compared to that of the same catalysts in traditional organic solvents.[6] Specifically we have shown that catalysts for Suzuki–Miyaura reactions, especially for heterocyclic substrates are much more efficient in water or aqueous/organic solvent mixtures than in organic solvents. One explanation for the usefulness of water for such transformation, was that the potentially inhibiting (i.e., palladium-coordinating) heterocycles prefer to form hydrogen bonds with water molecules rather than coordinate to palladium.[7] Furthermore formation of less reactive boroxines occurs easily in the absence of water and the formation of aryl boronates intermediates is more facile in water than in less polar solvents.[6]

Up until now our work was focused on cross coupling reactions utilizing aryl chlorides as the substrates.[7–8] The excellent performance of catalysts based on palladium complexes of sulfonated and water soluble fluorenylphosphanes, motivated us to test the activity of such complexes in reactions utilizing much less reactive aryl tosylates and the rarely utilized mesylates in Suzuki–Miyaura coupling.[9]

These substrates, derived from the respective phenols, are much cheaper than triflates or nonaflates. Recently significant progress in the Suzuki transformations of tosylates/mesylate substrates was reported by Kwong et al. utilizing *tert*-butyl alcohol and between 1–2 mol-% of Pd/indolylphosphane complex for aryl mesylate coupling[10] and between 0.5–2 mol-% for tosylates.[11] More recently Buchwald et al. reported Suzuki reactions with the same pseudohalide substrates utilizing ca. 2 mol-% of [Pd] and two equivalents of Brettphos in amyl alcohol solvent.[12] We would like to report here on the Suzuki–Miyaura reactions in water utilizing aryl tosylate and mesylate substrates.

Results and Discussion

We first optimized the catalytic transformation by varying the nature of the base, the Pd source, the Pd/phosphane ratio and the solvent composition (Table 1). As noted before, the nature of the base does not have a strong influence on the coupling reactions in water.[7] The use of water-soluble Na_2PdCl_4 gives much better results than with $PdCl_2$. Despite the fact that a monoligated PdL_1 species is the likely active species, two equivalents of phosphane ligand are required for efficient catalysis.[6] For a few highly water insoluble substrates, the use of *n*-butanol/water mixtures instead of pure water was found to be advantageous.[7] For the test reaction this did not turn out to be the case, since most of the heterocyclic substrates possess a reasonable solubility in hot water. The mono and disulfonated fluorenylphosphane are equally efficient (Scheme 1). We therefore chose cataCXium F sulf since it is commercially available or can be synthesized easily.[13] It is convenient to use K_2CO_3 as the base and water as the reaction solvent.

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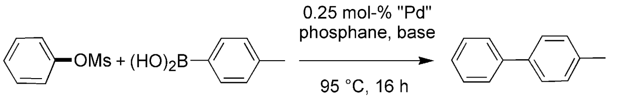
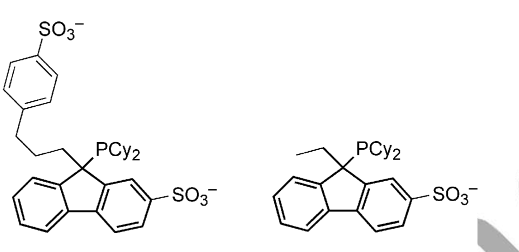
Table 1. Optimization of Suzuki–Miyaura conditions.



Ligand	Pd/ligand	Pd source	Base	Solvent	Conv.[a]
1	1:2	Na_2PdCl_4	K_2CO_3	water	89%
1	1:2	$PdCl_2$	K_2CO_3	water	9%
2	1:2	$PdCl_2$	K_2CO_3	water	7%
2	1:2	Na_2PdCl_4	K_2CO_3	water	80%
1	1:1	Na_2PdCl_4	K_2CO_3	water	10%
2	1:1	Na_2PdCl_4	K_2CO_3	water	13%
–	no ligand	Na_2PdCl_4	K_2CO_3	water	–
2	1:2	Na_2PdCl_4	NaOH	water	78%
2	1:2	Na_2PdCl_4	K_2CO_3	water/*n*-butanol, 1:3	81%
1	1:2	Na_2PdCl_4	NaOH	water	82%

[a] Conversion determined via gas chromatography (heptadecane, internal standard). Average of two runs.



1
cataCXium Fsulf

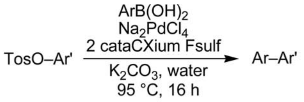
2
ligand

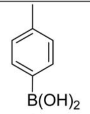
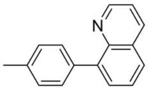
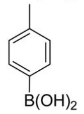
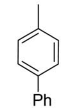
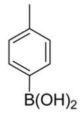
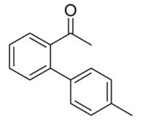
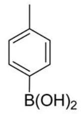
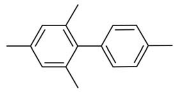
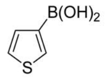
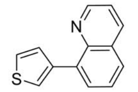
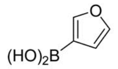
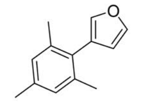
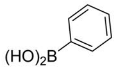
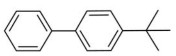
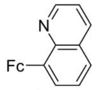
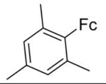
Scheme 1. Sulfonated and water-soluble fluorenylphosphanes.

We first tested a number of aryl tosylates in the Suzuki–Miyaura coupling with aryl boronic acids. In general the conversions are facile at 95 °C for overnight reactions; in water 0.5 mol-% of [Pd] complex are sufficient for excellent substrate conversion with isolated yields in excess of 90%. The only two exceptions are the sterically highly demanding 2,4,6-trimethyl-tosylates with slightly lower yield (Table 2, entry 6 (89%) and entry 9 (87%). It is also remarkable that thiophene boronic acid and furan boronic acid, produce the cross coupling products in water as the solvent in excellent yields – even in combination with a sterically hindered substrate (Table 2, entry 6). Ferrocene boronic acid, a substrate rarely used in Suzuki coupling reactions,[9d,14] also gives the desired coupling products under the normal reaction conditions.

The isolation of the coupling products is facile. For large scale reactions the poorly water-soluble product "swims" on the surface of the water reaction mixture. It can be easily separated in good purity from the water without the use of additional solvents. For small scale reactions during the work-up a second solvent (*n*-butanol) is added to enable isolation of the product following phase separation and evaporation. For both work-up techniques inorganic salts and boron containing species remain in the aqueous phase and consequently the isolated crude products are of good purity since all of the aryl tosylates and mesylates are consumed during the reaction.

Table 2. Suzuki–Miyaura coupling of aryl tosylates.[a]



Entry	Boronic acid	Product	mol-% [Pd]	Yield [%]
1			1.0 0.5 0.25	99 99 61
2			1.0 0.5 0.25	99 99 81
3			1.0 0.5 0.25	99 99 47
4			1.0 0.5 0.25 0.1	99 99 92 69
5			1.0 0.5 0.25	99 99 56
6			1.0 0.5 0.25	99 89 41
7			1.0 0.5 0.25 0.1	99 99 97 66
8	Fc-B(OH)2		1.0 0.5 0.25	99 99 57
9	Fc-B(OH)2		1.0 0.5 0.25	99 87 49

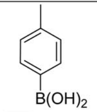
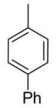
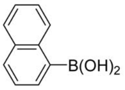
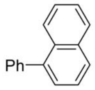
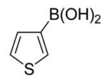
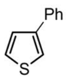
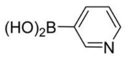
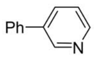
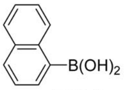
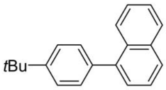
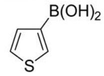
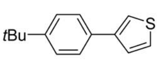
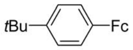
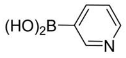
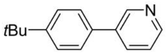
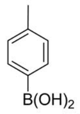
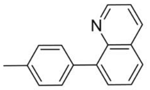
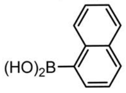
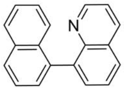
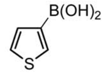
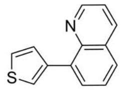
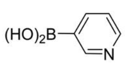
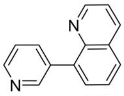
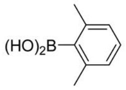
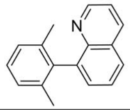
[a] Conditions: 1.0 mmol aryl tosylate, 1.2 mmol boronic acid, 2.5 mmol K_2CO_3, degassed water (5.0 mL), 95 °C, reaction time: 16 h, catalyst stock solution in water, *c*(Pd) = 1.0 mol-%/mL, Na_2PdCl_4/cataCXium Fsulf, 1:2. Yields correspond to isolated material after chromatography (silica), cyclohexane/EtOAc, 4:1.

Somewhat to our surprise the reactions of aryl mesylates, which are considered to be less reactive in cross coupling reactions,[10] turned out to be equally or even slightly more efficient than cross coupling involving the aryl tosylates (Table 3). For all reactions done at a 0.5 mol-% loading, virtually quantitative reactant conversion with isolated yields of 99% are observed for the mesylate reactions. Even at 0.25 mol-% [Pd] loading respectable yields for the mesylate reactions in the range of 59–89% are found, with most transformations providing yields in excess of 70%, which were slightly, but significantly lower for the tosylate conversions.

For the mesylate reactions we screened a few simple substrates (entries 1, 2 and 5, Table 3), several reactions involving heterocyclic substrates (entries 3, 4, 6, 8–13), labile bor-

Table 3. Suzuki–Miyaura coupling of aryl mesylates.[a]

$$\text{MsO–Ar'} \xrightarrow[\text{K}_2\text{CO}_3\text{, water; 95 °C, 16 h}]{\text{ArB(OH)}_2\text{; Na}_2\text{PdCl}_4\text{; 2 cataCXium Fsulf}} \text{Ar–Ar'}$$

Entry	Boronic acid	Product	mol-% [Pd]	Yield [%]
1			1.0 0.5 0.25	99 99 89
2			1.0 0.5 0.25	99 99 74
3			1.0 0.5 0.25	99 99 71
4			1.0 0.5 0.25	90 99 67
5			1.0 0.5 0.25	99 99 82
6			1.0 0.5 0.25	99 99 76
7	Fc-B(OH)$_2$		1.0 0.5 0.25	99 99 70
8			1.0 0.5 0.25	99 99 72
9			1.0 0.5 0.25	99 99 87
10			1.0 0.5 0.25	99 99 81
11			1.0 0.5 0.25	99 99 77
12			1.0 0.5 0.25	99 99 64
13			1.0 0.5 0.25	99 99 59

[a] Conditions: 1.0 mmol aryl mesylate, 1.2 mmol boronic acid, 2.5 mmol K_2CO_3, degassed water (5.0 mL), 95 °C, reaction time: 16 h, catalyst stock solution in water, c(Pd) = 1.0 mol-%/mL, Na_2PdCl_4/cataCXium F sulf, 1:2. Yields correspond to isolated material after chromatography (silica), cyclohexane/EtOAc, 4:1.

onic acids (entries 3, 4, 6, 8), sterically demanding reactants (entry 13). For all reactions 0.5 mol-% [Pd] loading provides excellent yields, typically nearly quantitative.

Conclusions

We have shown that the use of water as the reaction solvent in combination with water-soluble catalysts provides excellent catalytic activity for Suzuki–Miyaura coupling of aryl tosylates and mesylates. Water rather than organic solvents appear to be the better solution.

Experimental Section

Suzuki–Miyaura Coupling of Aryl Tosylates/Mesylates with Pd/cataCXium® F sulf

Preparation of the Catalyst Stock Solution: [Na_2PdCl_4] (14.7 mg, 0.05 mmol), phosphonium salt (0.1 mmol) and K_2CO_3 (56 mg, 0.4 mmol) were placed in a Schlenk tube under argon. Degassed water (5.0 mL) was added and the mixture was stirred at 45 °C for 3 h. This stock solution had a Pd concentration of 0.01 mol L^{-1}.

General Procedure for Suzuki–Miyaura Coupling: Boronic acid (1.2 mmol), aryl tosylate or mesylate (1.0 mmol) and K_2CO_3 (345 mg, 2.5 mmol) were placed in a 25 mL Schlenk tube and evacuated and backfilled with Ar twice. Degassed water (5.0 mL) was added together with the appropriate volume of catalyst stock solution. The reaction mixture was stirred for 16 h at 100 °C and then cooled to room temperature. The reaction mixture was extracted with *n*-butanol (5.0 mL) twice. The combined organic layers were dried with $MgSO_4$, filtered and the volatiles evaporated. The residue normally consists of pure product (>99%), which was further purified by column chromatography (cyclohexane/EtOAc, 4:1) to afford the analytically pure corresponding cross coupling product.

Supporting Information (see also the footnote on the first page of this article): Analytical and spectroscopic data for the cross coupling products.

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