

Palladium-catalyzed Suzuki cross-coupling reactions in a microemulsion

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Received 21 June 2007; revised 19 December 2007; accepted 3 January 2008

Available online 8 January 2008

Abstract

An enhancement of palladium-catalyzed Suzuki cross-coupling reactions between substrates possessing long-chain alkyl or oxyalkyl substituents in two-phase media, in the presence of sodium dodecylsulfate, is shown. Quantitative evaluations of the influence of SDS on the reaction rates were determined.

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Keywords: Cross-coupling; Suzuki reaction; Palladium; Microemulsion

The Suzuki cross-coupling reaction is one of the most powerful tools in the synthesis of biaryls.¹ Initially, the reaction was carried out in a two-phase water–organic solvent medium.² This approach gives good-to-excellent results in many cases, and has consequently become the most widely used methodology. Although the reaction has a wide synthetic utility, the Suzuki cross-coupling reaction has been found to play a particularly important role in the syntheses of thermotropic liquid crystal materials.³ The molecular structures of these compounds are usually composed of 2–3 benzene or heterocyclic rings with long-chain terminal alkyl or alkoxy substituents. Sometimes these structural features prevent effective solubilization of such hydrophobic substrates in the reaction medium, thus leading to modest yields of the desired products.

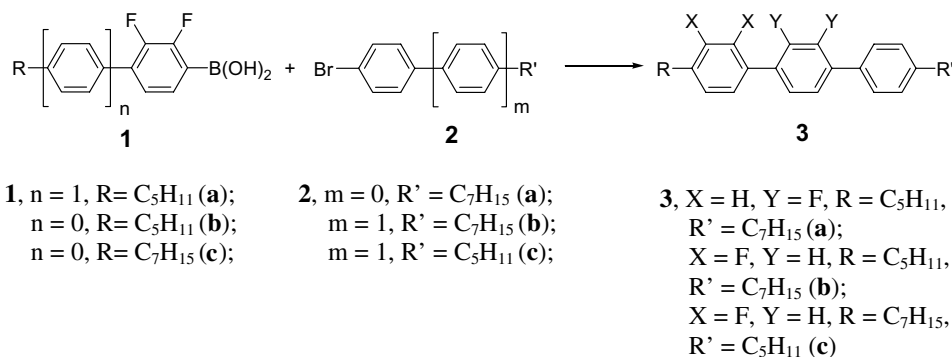
We have modified the traditional protocol of the Suzuki cross-coupling reaction by carrying out the procedure in an oil-in-water microemulsion. This is especially useful in the case of the synthesis of aryl bromides and areneboronic acids, which possess strongly hydrophobic alkyl or alkoxy groups (Scheme 1).^{4,5}

Our initial efforts were aimed at the optimization of the syntheses of the liquid crystal materials **3a–c**⁶ via the Suzuki cross-coupling of areneboronic acids **1a–c** with aryl bromides **2a–c** (Scheme 1).

It has been shown that the yield of compound **3a** ranges from 35% to 55% when carrying out the Suzuki cross-coupling of areneboronic acid **1a** and bromide **2a**.⁶ In our hands, the reaction of **1a** with **2a** according to Ref. 6 in a benzene/water mixture using a catalytic amount of Pd(PPh₃)₄ and Na₂CO₃, as the base, produced **3a** in 50% yield after purification (Table 1, entry 1). Changing the solvent to dimethoxyethane did not improve the yield (entry 2). The reaction performed in a DMSO/water mixture with Pd(OAc)₂ catalysis led predominantly to the product formed by protodeboronation^{1,7} of **1a** (Table 1, entry 3).

Starting from the assumption that low solubility of the substrates in water is the main reason for the low conversion of the starting materials, we tried carrying out the reaction with the addition of a solubilizing agent to enhance the rate of the desired cross-coupling relative to side reactions, which lead to consumption of the areneboronic acid, for example, base-catalyzed protodeboronation,⁷ homocoupling,⁸ and coupling with aryls from

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Scheme 1.

Table 1
Palladium-catalyzed Suzuki cross-coupling of areneboronic acids **1a–e** with aryl halides **2a–d** and **6**

Entry	Areneboronic acid	Aryl halide	Product	Solvent ^a	Catalyst	Base	Surfactant	Reaction time (h)	Yield ^b (%)
1	1a	2a	3a	PhH/H ₂ O	Pd(PPh ₃) ₄	Na ₂ CO ₃	None	15	50
2				DME/H ₂ O	Pd(PPh ₃) ₄	Na ₂ CO ₃	None	29	53
3				DMSO/H ₂ O	Pd(OAc) ₂	K ₂ CO ₃	None	22	— ^c
4				PhH/H ₂ O	Pd(PPh ₃) ₄	NaHCO ₃	SDS/BuOH	14	73
5				DME/H ₂ O	Pd(PPh ₃) ₄	NaHCO ₃	SDS/BuOH	7 (1 ^d)	75
6				DME/H ₂ O	Pd(OAc) ₂	NaHCO ₃	SDS/BuOH	29	43 ^c
7				PhMe/H ₂ O	Pd(PPh ₃) ₄	NaHCO ₃	SDS/BuOH	7 (1 ^d)	72
8				PhMe/H ₂ O	PdCl ₂ (dppf)	NaHCO ₃	SDS/BuOH	7 (4 ^d)	74
9	1b	2b	3b	DME/H ₂ O	Pd(PPh ₃) ₄	Na ₂ CO ₃	None		77
10				DME/H ₂ O	Pd(PPh ₃) ₄	NaHCO ₃	SDS/BuOH	5	91
11				PhMe/H ₂ O	Pd(PPh ₃) ₄	NaHCO ₃	SDS/BuOH	6 (2 ^d)	86
12	1c	2c	3c	DME/H ₂ O	Pd(PPh ₃) ₄	Na ₂ CO ₃	None		77
13				DME/H ₂ O	Pd(PPh ₃) ₄	NaHCO ₃	SDS/BuOH	5	80
14				PhMe/H ₂ O	Pd(PPh ₃) ₄	NaHCO ₃	SDS/BuOH	6 (4 ^d)	91
15	1d	2d	3d	DME/H ₂ O	Pd(PPh ₃) ₄	NaHCO ₃	None	3	— ^c
16 ^f				DMF	Pd(PPh ₃) ₄	K ₃ PO ₄	None	11	— ^g
17				PhMe/H ₂ O	Pd(PPh ₃) ₄	NaHCO ₃	SDS/BuOH	18	59
18	1e	6	3e	DME/H ₂ O	Pd(PPh ₃) ₄	Na ₂ CO ₃	None	16	53 ^h
19				DMSO/H ₂ O	Pd(OAc) ₂	NaHCO ₃	None	0.5	68 ⁱ
20				PhMe/H ₂ O	Pd(PPh ₃) ₄	NaHCO ₃	SDS/H ₂ O	18	70

^a The organic solvent to water volume ratios were 1:1.

^b Yields of purified substances are given.

^c 2,3-Difluoro-4'-pentylbiphenyl (product of protodeboronation) was detected by GC–MS analysis.

^d Time for the completion of the reaction according to HPLC.

^e Compound **4** (Scheme 2) was the only isolated product.

^f Similarly to Ref. 16.

^g Compound **5** (Scheme 2) was the only isolated product.

^h According to Ref. 17.

ⁱ At 0.5 g scale only.

phosphine ligands.⁹ A similar approach has already been applied to several allied transition metal-catalyzed reactions; for example, oxycarbonylation of aryl iodides,¹⁰ reductive homocoupling of aryl halides,¹¹ Heck-type coupling of areneboronic acids with activated alkenes,¹² and for Suzuki coupling with the use of water-soluble phosphine ligands and cationic surfactants.¹³ Since the Suzuki reaction proceeds under basic conditions, in this work we used a more suitable anionic surfactant, that is, sodium dodecylsulfate (SDS).

It has been shown that the Suzuki cross-coupling reaction of sterically hindered substrates is substantially enhanced by using a 3:3:1 mixture of toluene, ethanol,

and water as a solvent.¹⁴ Similar improvement has been made for the case of the oxycarbonylation of aryl iodides in a microemulsion;¹⁰ however, it was shown that even a small amount of *n*-butyl alcohol enhances the reaction. In our case, addition of SDS and a small amount of *n*-butyl alcohol as co-surfactants improved the yield of **3a** in comparison to when the reaction was carried out in benzene/water mixture (Table 1, cf. entries 1 and 4). The effect of SDS when the reaction was performed in DME/water was also pronounced (entries 2 and 5). Use of Pd(OAc)₂ led to a lowering of the yield for **3a** (entry 6), and a substantial amount of protodeboronation was observed by GC/MS analysis. Employing PdCl₂(dppf) as a catalyst,¹⁵

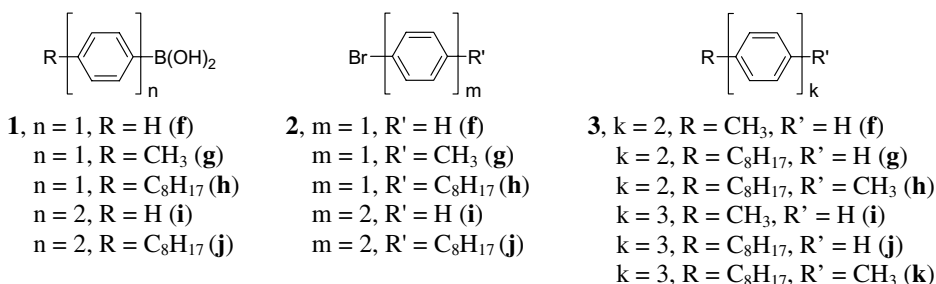
as it is more stable and easier to handle than $\text{Pd}(\text{PPh}_3)_4$, was also quite effective (see entry 8). Further improvement was achieved by using toluene as the organic solvent (entries 7 and 8).

In the case of areneboronic acids **1b,c** and aryl bromides **2b,c**, the use of DME/water and toluene/water mixtures with SDS/BuOH additives also led to good yields of **3b** and **3c** (cf. entries 9 and 12, and 10 and 13, respectively).

NaHCO_3 ¹⁸ was selected as the base for the standard reaction protocol instead of the typically used base Na_2CO_3 .¹ The application of such a weak base in combina-

purification could be achieved by flash-chromatography and/or crystallization.²¹

To investigate the dependency of the relative yields of the Suzuki cross-coupling performed with and without SDS additive, the reaction of a range of areneboronic acids **1f–j** and aryl bromides **2f–j** possessing terminal alkyl substituents of different lengths and different numbers of benzene rings was studied. The yields of products **3f–k**, determined by HPLC analyses 5 min after the reaction had started (see Table 2), reflect the difference in the reaction rates for the various substrates.



tion with SDS in most cases showed similar effectiveness and was especially useful in the reaction of base-sensitive substrates. Thus, in the case of lactonitrile ester **2d**,¹⁹ the use of the combination of SDS and NaHCO_3 was the only suitable method for obtaining **3d** by Suzuki cross-coupling (Scheme 2, Table 1, entry 17), as acids **4** and **5** only were isolated from the reactions in DME/ H_2O and DMF (entries 15 and 16).

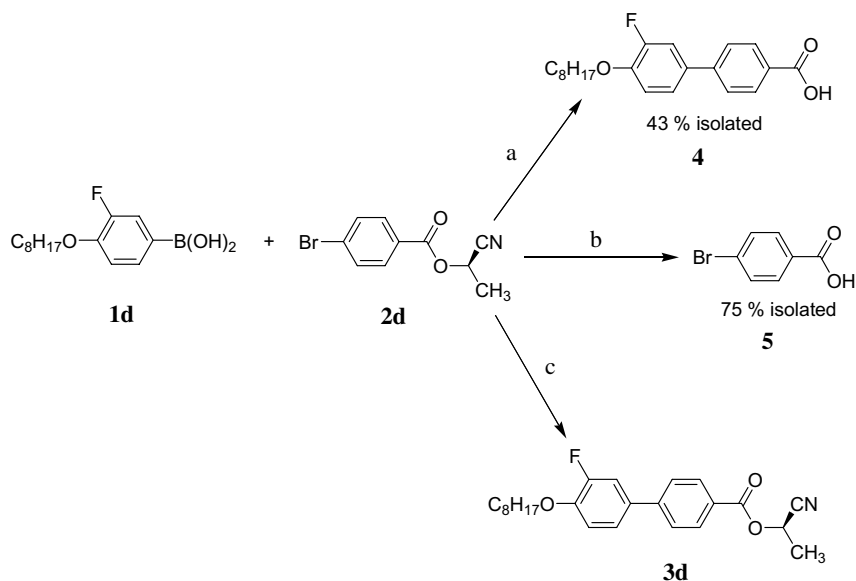
Furthermore, the reaction of 5-bromo-2-iodopyrimidine **6**²⁰ with **1e** gave the useful intermediate **3e** in modest yield only when carried out in DME/water mixture (Scheme 3, Table 1, entry 18).¹⁷ Enhancement of the yield was possible when a DMSO/water mixture was used for the reaction; however, only at the 2 mmol scale or less (entry 19). Use of the microemulsion technique produced **3e** employing larger loadings (i.e., 4–5 mmol) resulting in similar yields (entry 20).

Thus, Suzuki cross-coupling reactions of substrates possessing hydrophobic substituents can be substantially enhanced if the reaction is carried out in an oil-in-water microemulsion. Toluene appeared to be the organic solvent of choice for this purpose. Both the Pd(0) complexes, $\text{Pd}(\text{PPh}_3)_4$ and Pd(II) ($\text{PdCl}_2(\text{dppf})$), were effective as transition-metal catalysts for the reaction. NaHCO_3 was found to be sufficiently effective, and was a gentle basic catalyst. It should be noted that the areneboronic acid should be added to the refluxing reaction mixture dropwise to avoid its consumption in side processes, while the desired reaction was fast at elevated temperatures.

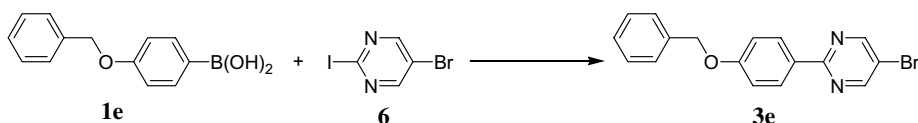
Separation of the products from the surfactant-containing residue could be easily achieved either by acidification of the reaction mixture followed by extraction or by evaporation to dryness with the addition of alcohol (butyl or isopropyl), which acts as a foam suppressor. Subsequent

The stabilities of the substrates and products toward the bases allowed for the use of sodium carbonate instead of NaHCO_3 . The thermal stability of the areneboronic acids in water in the absence of bases allowed for the injection of the aqueous solution of the base directly into the refluxing mixture of the reagents. The reaction started immediately after base addition, and thereby the reaction time could be determined exactly. The reaction in toluene/water mixture, which was shown to be suitable for the preparative syntheses (see above), was completed in minutes (Table 2, entries 5 and 7), and so appeared to be too fast to reveal small differences in the reaction rates. Therefore, benzene was chosen as the organic solvent to slow down the reaction by lowering the solvent reflux temperature.²²

Comparing the results obtained with and without SDS shows that the reaction with the SDS additive leads essentially to a rate enhancement (Table 2). The reaction in the presence of SDS is estimated to be 1.6–6.6 times faster. This fact is consistent with our initial assumption concerning the effect of the solubilization of the hydrophobic reagents in the microemulsion. The highest reaction rates were estimated in cases where a less hydrophobic bromide was used (compare entries 1 and 2; 4 and 6; 8 and 9; 12 and 13; 14 and 15, respectively, except for entries 10 and 11, where the yields are nearly the same). This fact indicates the negative influence of the hydrophobic substituent on the rate of oxidative addition of an aryl bromide to a catalytically active palladium species, which is supposed to be the rate limiting step in the Suzuki catalytic cycle for sterically non-hindered substrates.¹ Therefore, for preparative purposes, it seemed better to use less-alkyl substituted bromide **2** for each coupling product of type **3**. In these cases, the nature of areneboronic acid **1** (phenyl or biphenyl-containing) was less significant (compare entries 1, 4, 8, 12 and 14).



Scheme 2. Reagents and conditions: (a) Pd(PPh₃)₄, NaHCO₃, DME/H₂O (1:1) reflux; (b) Pd(PPh₃)₄, K₃PO₄, DMF, 100 °C; (c) Pd(PPh₃)₄, NaHCO₃, SDS, PhMe/H₂O/BuOH (1:1:0.14), reflux.



Scheme 3.

In conclusion, the palladium-catalyzed Suzuki cross-coupling reaction of aryl bromides and areneboronic acids

Table 2
Quantitative study of the effect of SDS on palladium-catalyzed Suzuki cross-coupling reactions

Entry	Areneboronic acid		Aryl bromide		Product	Yield ^a (%)	
	<i>n</i>	R	<i>m</i>	R'		With SDS	Without SDS
1	1g	1 CH ₃	2f	1 H	3f	48	28
2	1f	1 H	2g	1 CH ₃		28	5
3						—	33 ^b
4	1h	1 C ₈ H ₁₇	2f	1 H	3g	67	19
5						100 ^c	—
6	1f	1 H	2h	1 C ₈ H ₁₇		37	18
7						77 ^c	—
8	1h	1 C ₈ H ₁₇	2g	1 CH ₃	3h	59	19
9	1g	1 CH ₃	2h	1 C ₈ H ₁₇		39	18
10	1i	2 H	2g	1 CH ₃	3i	45	28
11	1g	1 CH ₃	2i	2 H		53	8
12	1j	2 C ₈ H ₁₇	2f	1 H	3j	51	23
13	1f	1 H	2j	2 C ₈ H ₁₇		38	15
14	1j	2 C ₈ H ₁₇	2g	1 CH ₃	3k	58	10
15	1g	1 CH ₃	2j	2 C ₈ H ₁₇		27	10

^a Yields were determined from a sample taken 5 min after the addition of the base unless otherwise noted.

^b A sample was taken 30 min after the addition of the base.

^c Reaction in 1:1 toluene/water mixture.

possessing hydrophobic alkyl or oxyalkyl substituents can be enhanced in toluene or dimethoxyethane/water mixtures by the addition of sodium dodecylsulfate (SDS) and *n*-butyl alcohol as co-surfactants. The use of NaHCO₃ in combination with SDS makes the reaction conditions tolerant to base-sensitive functional groups. Quantitative investigations show that the most pronounced effect of SDS was achieved when each coupling product combination of longer alkyl chain-containing areneboronic acid and shorter alkyl-containing aryl bromide were used.

Acknowledgements

We appreciate Dr. Thomas Gurley for helpful discussions. Financial support of part of the work from the INTAS (Grant 1997-1730) is gratefully acknowledged.

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 - General procedure for the reaction in microemulsion.* A mixture of an aryl halide (2 mmol), NaHCO₃ (500 mg, 6 mmol, 3 equiv), SDS (75 mg), water (5 ml) and toluene (2.5 ml) was degassed and flushed with argon. Then, PdCl₂(dppf) (44 mg, 0.06 mmol, 0.03 equiv) was added under argon and the degassing was repeated. The resultant emulsion was heated to reflux with stirring, and the areneboronic acid (2.4 mmol, 1.2 equiv) in *n*-butyl alcohol (0.7 ml) and toluene (2.5 ml) was added dropwise over 5–10 min. The reaction mixture was stirred at reflux until HPLC revealed that the reaction was complete. The reaction was then allowed to cool. The organic layer was separated, the water layer was extracted with toluene, the extracts were collected, washed with water and dried. In the case of base-insensitive materials, the reaction mixture was cooled, diluted with isopropyl alcohol (100 ml), evaporated to dryness and suspended in dichloromethane (25 ml). The resultant suspension was filtered through a short pad of silica, washed with dichloromethane (30 ml) and evaporated to dryness. The product obtained was purified by crystallization from an appropriate solvent.
 - Procedure for the quantitative experiment.* PdCl₂(dppf) (44 mg, 0.06 mmol, 0.03 equiv) was added to a well-degassed mixture of an areneboronic acid (2.4 mmol, 1.2 equiv) and 75 mg of SDS (if appropriate), in *n*-butyl alcohol (0.7 ml), water (2 ml), and benzene (5 ml) under a flow of argon. Then, the aryl bromide (2 mmol, 1 equiv, neat or as a concentrated benzene solution) was added, followed by an appropriate internal standard (4-substituted biphenyl (C₅H₁₁ or OC₉H₁₉), 1.6 mmol, 0.8 equiv). The reaction mixture was bubbled with argon while the bromide was added through a rubber septum via a syringe. The reaction mixture was then degassed and heated to reflux with stirring. A solution of sodium carbonate decahydrate (1.7 g, 6 mmol, 3 equiv) in water (3 ml) was thoroughly degassed by bubbling with argon and added quickly through the rubber septum into the reaction mixture via a syringe. A sample of the reactants was taken after a period of time measured from the addition of the base (Table 2).