Letter

Suzuki–Miyaura Cross-Coupling Reactions in Acetic Acid Employing Sydnone-Derived Catalyst Systems

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Abstract The catalyst system consisting of lithium *N*-phenylsydnone-4-carboxylate/Pd(PPh₃)₄ has proven to be an effective catalyst for the Suzuki–Miyaura reaction of 2,4-dinitrochlorobenzene with boronic acids in acetic acid at pH 5.7, whereas the *N*-phenylsydnone carbene palladium complex [sydPd(PPh₃)₂Br] required pH 8.0.

Key words catalysis, Suzuki–Miyaura reaction, N-heterocyclic carbenes, sydnones, palladium, pH value

The Suzuki-Miyaura cross-coupling is one of the most important transition-metal-catalyzed C-C coupling reaction in organic chemistry.¹ Mild reaction conditions, the commercial availability of numerous organoboron compounds, and the toleration of a broad variety of functional groups are inestimable advantages of the Suzuki-Miyaura reaction in comparison to other cross-couplings.² The reaction has proven to fail in the absence of bases, however, which sometimes induce side reactions such as racemization of asymmetric carbon atoms or aldol condensations.² In continuation of our interest in mesomeric betaines,³ Nheterocyclic carbenes (NHCs)^{4,5} and their application in catalysis^{6,7} we report here on our preliminary results of Suzuki-Miyaura reactions in the presence of sydnone-derived catalyst systems which give best yields in dependence of the pH of the reaction mixture, covering the range from strongly basic to acidic media. Sydnones 1⁸ are conjugated mesomeric betaines9 which belong to the subclass of mesoionic compounds (Scheme 1).¹⁰ On deprotonation they give unique anionic NHCs 2 which can be regarded as anionic abnormal NHCs or anionic NHCs depending on the favored mesomeric structure.⁵ Sydnone carbenes 2 and their derivatives can be trapped by CO₂ as sydnone carboxylates **3** or



as palladium complexes 4.5 The latter have already proved to be catalytically active.^{5,7} Efficient procedures to prepare 3^{11} and 4^{12} start from 4-halosydnones and lithium bases.

The relationship between mesomeric betaines including mesoionic compounds and NHCs has been summarized in a review article.¹³ In order to test the catalytic properties of sydnone-4-carboxylate **3** and of the sydnone carbene palladium complex **4** we performed a catalyst screening and compared the results with other catalysts for the Suzuki-Miyaura reaction. We chose the cross-coupling of 1-chloro-2,4-dinitrobenzene (**5**) with phenylboronic acid **6a**





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(Scheme 2) as model reaction and examined six different catalyst systems, which are listed in Table 1, under identical conditions.

Table 1 Six Catalyst Systems Tested in a Model Reaction		
Catalyst	system	Ingredients
cat. 1		sydnone carboxylate 3 , Pd(PPh ₃) ₄
cat. 2		sydnon palladium complex 4
cat. 3		sydnone 1 , Pd(PPh ₃) ₄
cat. 4		Pd(PPh ₃) ₄
cat. 5		Pd(OAc) ₂
cat. 6		PdCl ₂ (PPh ₃) ₂

At pH 8.0 the catalyst system consisting of lithium sydnone-4-carboxylate **3** and Pd(PPh₃)₄ (cat. **1**) gave only low yields of 2,4-dinitro-1,1'-biphenyl (**7a**) and 1-(2,4-dinitrophenyl)naphthalene (**7b**, Table 2, entries 1 and 7). In contrast to catalysis systems cat. **3–6** (Table 2, entries 3–6), the catalysis by the sydnone carbene palladium complex **4** (cat. **2**) gave excellent to quantitative yields of **7a** and **7b** at pH 8.0 (Table 2, entries 2 and 8).⁵ 1-(2,4-Dinitrophenyl)phenanthrene (**7c**) was obtained in 80% yield (Table 2, entry 9).⁷ Under these conditions, cat. **2** is among the best catalyst systems for this reaction.¹⁴

Table 2Yields of the Suzuki-Miyaura Reaction of 5 with Boronic Acids6a-cEmploying the Catalyst Systems 1-6 at pH 8.0

Entry	Ar	Reaction conditions ^a	Yield (%) ^b
1	6a Ph	cat. 1	7a 38
2	6a Ph	cat. 2	7a 99
3	6a Ph	cat. 3	7a 78
4	6a Ph	cat. 4	7a 82
5	6a Ph	cat. 5	7a 81
6	6a Ph	cat. 6	7a 60
7	6b 1-naphthyl	cat. 1	7b 32
8	6b 1-naphthyl	cat. 2	7b 95
9	6c 9-phenanthryl	cat. 2	7c 80

^aReaction conditions: catalyst systems (10 mol%), respectively, 1,4-dioxane (8 mL), **5** (0.2 mmol), **6a–c** (2 equiv), respectively, Na₂CO₃ (4.7 mmol), water (2 mL).

^bIsolated yields after chromatography; for conditions, cf. Scheme 2.

In order to find optimized reaction conditions for the reaction in the presence of the sydnone-4-carboxylate-derived catalyst system (cat. 1), we varied the reaction conditions by adjusting the pH value of the reaction mixture by addition of sodium carbonate and acetic acid (Table 3). Addition of neither of these ingredients gave only 37% yield of **7a** (Table 3, entry 1). Performing the reaction in acetic acid without sodium carbonate at pH 4.0 gave considerably decreased yields (Table 3, entry 2). Excellent yields, however, were obtained at pH 5.7 in the presence of acetic acid as well as sodium carbonate (1:1, Table 3, entry 3). By contrast, performing the reaction without sodium carbonate under acidic conditions (Table 3, entries 4, 6) or without water (Table 3, entry 5)¹⁵ gave only low yields of **7a** when the sydnone palladium complex (cat. **2**) was employed, whereas a pH value of 8.0 gave quantitative yields as mentioned before (cf. Table 1, entry 2). The catalyst systems **3–6** either failed or gave low to moderate yields at pH 5.7 (Table 3, entries 7–9 and 12). Palladium acetate in acetic acid at pH 4.0 failed almost completely as catalyst (Table 3, entry 10), whereas its catalysis at pH 6.5 gave moderate yields (Table 3, entry 11) of **7a**.

Table 3Yields of the Model Reaction between 5 and PhenylboronicAcid (6a) to Give 7a Employing Cat. 1–6 at Various pH Values

Entry	Reaction conditions ^a	рН	Yield (%) ^f
1	cat. 1 , H ₂ O ^b	6.5	37
2	cat. 1 , H ₂ O, AcOH ^c	4.0	18
3	cat. 1 , H ₂ O, AcOH, Na ₂ CO ₃ ^d	5.7	91
4	cat. 2 , H ₂ O, AcOH ^c	4.0	15
5	cat. 2 , Na ₂ CO ₃ ^e	-	<10
6	cat. 2 , H ₂ O, AcOH, Na ₂ CO ₃ ^d	5.7	50
7	cat. 3 , H ₂ O, AcOH, Na ₂ CO ₃ ^d	5.7	15
8	cat. 4 , H ₂ O, AcOH, Na ₂ CO ₃ ^d	5.7	0
9	cat. 5 , H ₂ O, AcOH, Na ₂ CO ₃ ^d	5.7	45
10	cat. 5 , H ₂ O, AcOH ^c	4.0	<5
11	cat. 5 , H ₂ O ^b	6.5	61
12	cat. 6 , H ₂ O, AcOH, Na ₂ CO ₃ ^d	5.7	0

^aReaction conditions: catalyst systems (10 mol%), respectively, of 1,4-dioxane (8 mL), **5** (0.2 mmol), **6a** (2 equiv). Variations: ^b2 mL of water.

°17 mmol of AcOH, 2 mL water.

^d4.7 mmol of Na₂CO₃, 17 mmol of AcOH, 2 mL of water.

 $e^{4.7}$ mmol of Na₂CO₃.

flsolated yields after chromatography.

We applied the optimized reaction conditions of the Suzuki–Miyaura reaction in the presence of sydnone carboxylate **3** and Pd(PPh₃)₄ (cat. **1**) in acetic acid at pH 5.7 to other boronic acids which gave new products **7c–h** (Table 4).¹⁶ 1-Naphthyl boronic acid gave a very good yield of **7b** in an acidic medium (Table 4, entry 1). As a comparison, under analogous reaction conditions, the sydnone palladium complexes achieved only 43% of **7b** in acid, whereas 95% were formed under basic conditions at pH 8.0 (cf. Table 2, entry 8). Under acidic conditions the formation of 1-(2,4-dinitrophenyl)phenanthrene **7c** is even more effective with cat. **1** than under basic conditions and cat. **2** (Table 4, entry 3). 3'-Methyl-2,4-dinitro-1,1'-biphenyl (**7d**) was formed in moderate yield under these conditions (Table 4, entry 4). 2-(2,4-

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Dinitrophenyl)thiophene (**7e**), 2,4-dinitro-1,1':4',1"-terphenyl (**7f**), 2',4'-dinitro-(1,1'-biphenyl)-4-thiol (**7g**), and 2,4-dinitro-4'-(trifluoromethoxy)-1,1'-biphenyl (**7h**) were formed in very good yields by Suzuki–Miyaura reaction in acid (Table 4, entries 5–8).

Table 4	Yields of the Model Reaction at pH 5.7
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Entry	Ar	Reaction conditions ^a	Yield (%) ^b
1	6b 1-naphthyl	cat. 1	7b 91
2	6b 1-naphthyl	cat. 2	7b 43
3	6c 9-phenanthryl	cat. 1	7c 91
4	6d <i>m</i> -tolyl	cat. 1	7d 53
5	6e 2-thiophen	cat. 1	7e 94
6	6f 4-biphenyl	cat. 1	7f 91
7	6g 4-(methylthio)phenyl	cat. 1	7g 89
8	6h 4-(trifluoromethoxy)phenyl	cat. 1	7h 86

^aReaction conditions: Cat. **1** or **2** (10 mol%), 1,4-dioxane (8 mL), **5** (0.2 mmol), **6a–h** (2 equiv), Na₂CO₃ (4.7 mmol), AcOH (17 mmol), water (2 mL).

^bIsolated yields after chromatography.

Finally, we examined the role of sodium acetate and carried out a series of reactions of 2,4-dinitrochlorobenzene (**5**) and phenylboronic acid (**6a**) in the presence of the sydnone carbene palladium complex (cat. **2**). As shown in Table 5, the presence of water is necessary, and best results were achieved when sodium acetate, sodium carbonate, and water were present (Table 5, entry 5). These conditions represent an alternative procedure to those shown in Table 2 (entry 2).

 Table 5
 Yields of the Model Reaction of 5 and 6a in the Presence of Cat. 2 (10 mol%) and Sodium Acetate

Entry	Reaction conditions ^a	pH value	Yield (%) ^b
1	NaOAc	-	16
2	NaOAc, Na ₂ CO ₃	-	17
3	NaOAc, Na ₂ CO ₃ , H ₂ O, AcOH	5.9	68
4	NaOAc, H ₂ O	8.3	93
5	NaOAc, Na ₂ CO ₃ , H ₂ O	8.1	>99

^aReaction conditions: NaOAc (6.1 mmol), Na₂CO₃ (4.7 mmol), H₂O (2 mL), AcOH (17 mmol), respectively.

^blsolated yields after chromatography.

Finally, we added *N*-Boc-*O*-benzyl-L-tyrosine as optically pure compound into selected model reactions and measured the optical rotation after isolation from the reaction mixtures. No racemization took place under the reaction conditions applied. Additional investigations along these lines are under way.

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In summary, we demonstrated that the catalyst systems consisting of sydnone carboxylate **3** and Pd(PPh₃)₄ (cat. **1**) required acidic conditions (pH 5.7) to give good to excellent yields of Suzuki–Miyaura cross-couplings, whereas the sydnone carbene palladium complex **4** needed basic conditions (pH 8.0).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589059.

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- (16) General Procedure for the Preparation of Compounds 7a-h Under a nitrogen atmosphere samples of 1-chloro-2,4-dinitrobenzene (1, 0.050 g, 0.2 mmol) were dissolved in anhydrous

1,4-dioxane (8 mL) and treated with the catalyst (cat. **1–6**, 10 mol%). The mixtures were subjected to ultrasound irradiation for 5 min and then stirred at r.t. for additional 25 min. Then, the corresponding boronic acid **6a–h** (2 equiv), sodium carbonate (4.7 mmol), and water (2 mL) were added. The mixtures were heated at 70 °C for 30 min. After cooling to r.t. the mixtures were dried over MgSO₄. The resulting crude products were purified by column chromatography over silica gel (40–60 mesh) using a PE-CH₂Cl₂ (1:3) mixture as eluent. The analytical data and the characterization of each produced compound can be found in the Supporting Information.

2,4-Dinitro-1,1':4',1"-terphenyl (7f)

A sample of 1-(4-biphenyl)-boronic acid (0.098 g, 0.5 mmol), cat. 1 (10 mol%), Na₂CO₃ (4.7 mmol), and AcOH (17 mmol) were used. The reaction was monitored by TLC. The product was isolated as a yellowish solid; yield 91%; mp 154 °C. ¹H NMR (600 MHz, CDCl₃): δ = 7.41–7.42 (m, 3 H, H-2', H-4', H-6'), 7.47–7.49 (m, 2 H, H-3", H-5"), 7.62–7.64 (d, J = 7.7 Hz, 2 H, H-2", H-6"), 7.69-7.72 (m, 3 H, H-3', H-5', H-6'), 8.46-8.48 (dd, J = 7.7 Hz, 1 H, H-5), 8.72 (s, 1 H, H-3) ppm. ¹³C NMR (150 MHz, CDCl₂): δ = 119.7 (+, 1 C, C-3), 126.5 (+, 1 C, C-5), 127.1 (+, 2 C, C-6", C-2"), 127.7 (+, 2 C, C-3', C-5'), 128.0 (+, 1 C, C-4"), 128.1 (+, 2 C, C-6', C-2'), 128.9 (+, 2 C, C-3", C-5"), 133.1 (+, 1 C, C-6), 133.9 (o, 1 C, C-1'), 139.7 (o, 1 C, C-1"), 141.8 (o, 1 C, C-1), 142.4 (o, 1 C, C-4'), 146.8 (o, 1 C, C-4), 149.0 (o, 1 C, C-2) ppm. IR (ATR): v = 666, 833, 1274, 1489, 1598, 3079 cm⁻¹. MS (EI-MS, 70 eV): m/z $(C_{18}H_{12}N_2O_4) = 320.1$. HRMS (EI, 70 eV): m/z calcd for [C₁₈H₁₂N₂O₄]⁺: 320.0797; found: 320.0797.