Efficient catalysis of the Suzuki—Miyaura reaction under mild conditions with cyclopalladated *N*,*N*-dimethylaminomethylferrocene

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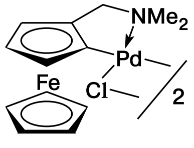
High catalytic activity of *N*,*N*-dimethylaminomethylferrocene cyclopalladated derivative was demonstrated in the the Suzuki—Miyaura cross-coupling of aryl bromides with phenylboronic acid, which allowed us to carry out the reaction under extremely mild conditions.

Key words: *CN*-palladacycle, *N*,*N*-dimethylaminomethylferrocene, homogeneous catalysis, the Suzuki—Miyaura reaction, homocoupling, aryl bromides, aryl chlorides.

In the last decades, cyclopalladated complexes (CPC), possessing high thermal, oxidative, and hydrolytic stability, showed themselves as excellent highly efficient catalysts of the cross-coupling reactions.[1,2] Starting our program for the testing chiral CPC in enantioselective catalysis, we have chosen the Suzuki—Miyaura reaction for the following reasons: 1) with the general practice of thermal (60—160 °C)[1,3,4] activation of this type cross-coupling processes, only several precedents of carrying out such reactions at room temperature are known;[5,6] 2) the only example of moderately successful (up to 49% *ee*) enantioselective catalysis of cross-coupling with palladacycles deals with exactly the Suzuki—Miyaura reaction.[7]

In our search for the complex capable to catalyze reactions of this type under mild conditions, we have chosen the known[8] *CN*-palladacycle based on *N*,*N*-dimethylaminomethylferrocene (**1**), since the ferrocenyl CPC with other *N*-donor groups have proved especially efficient catalysts of achiral Suzuki—Miyaura reactions.[5,6] As far as we know, only one short communication has been published on the application of this CPC in catalysis: the Heck reaction in the high-temperature regime (140—160 °C) and only involving active aryl iodides.[9]



rac-**1**

The present work deals with evaluation of catalytic activity of racemic dimer **1** (*rac*-**1**) in the achiral Suzuki—Miyaura reaction and a possibility to carry out it under the maximum mild conditions necessary for the further accomplishment of asymmetric versions of this process. Preliminary results of this study have been reported earlier.[10]

Results and Discussion

We used a cross-coupling of phenylboronic acid with *para*-tolyl bromide (**2**) as a model version of the Suzuki—Miyaura reaction. The presence of the Me group in the starting substrate simplified monitoring the reaction progress by ^{1}H NMR. In addition, a reduced reactivity of aryl halides with electron-donating substituents[1] in the cross-coupling processes provides higher correctness of such model reaction as a method for the evaluation of a catalyst efficiency.

On catalysis with dimer *rac*-**1**, in the reaction of aryl bromide **2** with phenylboronic acid, carried out at room temperature in air (Scheme 1), the target biaryl **3a** is formed in high yield (94%, Table 1, entry *1*) at moderate loading* of the catalyst in 2.5 mol.%.

Unfortunately, the attempts to decrease amount of the catalyst have proved not very successful: when the concentration of dimer *rac*-**1** was decreased to 0.05 mol.%, the final product **3a** in the same temperature regime is formed only in insignificant yield (7%, entry *2*). The yield is somewhat increased only on heating (20%, entry *3*).

A possibility to carry out the model Suzuki—Miyaura reaction even at negative temperature (−18 °C) upon its catalysis with *CN*-dimer *rac*-**1** is the most important result

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* Here and further, concentration of the catalyst is given in molar percent of the dimeric complex.

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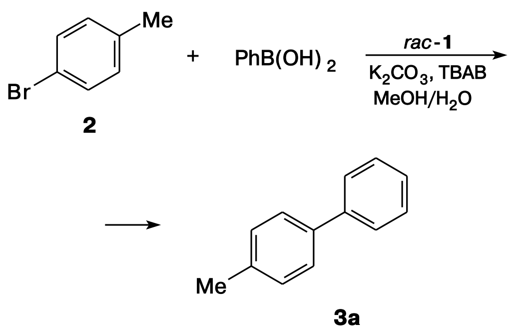
Scheme 1



TBAB is the tetrabutylammonium bromide.

of the study. Under these conditions, biaryl **3a** is formed in satisfactory yield (53%, entry *4*), however, in this case the reaction time is significantly longer (to 18 days). To our knowledge, this is the first example of carrying out the cross-coupling in so low-temperature regime.

Attempted involvement of aryl chlorides with either electron-donating or electron-withdrawing substituents into the Suzuki—Miyaura reaction failed. In the reactions of phenylboronic acid with *p*-chlorotoluene (**4a**) either at room or elevated temperature (55 °C), the formation of unsubstituted biphenyl (**5**) is observed resulting from the homocoupling, chromatographic isolation yielded 10 and 50% of the product, respectively (Scheme 2). In this case, the target biaryl **3a** is formed only in trace amounts (<1%, ^{1}H NMR data).

Even when more reactive aryl chlorides with electron-withdrawing substituents (**4b** and **4c**) are used, the homocoupling with the formation of biphenyl **5** in 33 and 40% yield, respectively, remains the main direction of the reaction. The formation of substituted biaryl **3b** with the minimum yield of 3% was registered spectrally only in the mixture of reaction products of aryl chloride **4b**.

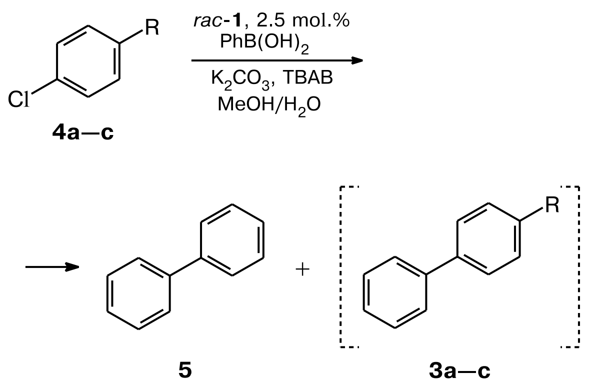
In conclusion, we found unusually mild conditions for the catalysis of the Suzuki—Miyaura cross-coupling of aryl bromides, which is based on the use of cyclopalladated *N*,*N*-dimethylaminomethylferrocene as the catalyst.

Table 1. Results of the Suzuki—Miyaura reaction catalysis with complex *rac*-**1**

Entry	[*rac*-**1**] (mol.%)	Reaction conditions			Yield* of **3a** (%)
		t/°C	τ	Solvent	
1	2.5	20	1 day	MeOH/H$_2$O	94
2	0.05	20	4 day	MeOH/H$_2$O	7
3	0.05	55	20 h	MeOH/H$_2$O	20
4	2.5	−18	18 day	MeOH	53

* The yield is given for the chromatographically isolated 4-methylbiphenyl.

Scheme 2



R = Me (**a**), COOMe (**b**), Ac (**c**)

Development of this catalytic system makes promising further creation of asymmetric versions of the Suzuki—Miyaura reaction with involvement of a wide range of aryl bromide substrates, particularly because the *CN*-palladacycle (*S*)-**1** of high degree of enantiomeric enrichment (96% *ee*) is easily available.[11]

Experimental

^{1}H NMR spectra were recorded on a Bruker Avance-400 spectrometer (400.1 MHz) in CDCl$_3$ at room temperature; chemical shifts were measured relatively to Me$_4$Si (internal standard). Reaction progress and purity of compounds formed were monitored by TLC on silufol UV-254 with visualization under the UV light. Flash-chromatography on Fluka 60 silica gel was used for preparative isolation of compounds obtained. Purification of solvents was performed using standard methods.[12] Dimeric complex *rac*-**1** was synthesized using the known procedure.[8]

Procedure for the Suzuki—Miyaura reaction. *A*. A mixture of *para*-bromotoluene (0.1067 g, 0.6238 mmol), phenylboronic acid (0.1141 g, 0.9357 mmol), TBAB (0.2011 g, 0.6238 mmol), K$_2$CO$_3$ (0.1724 g, 1.2474 mmol), and catalyst *rac*-**1** (0.0120 g, 0.0156 mmol, 2.5 mol.%) was stirred in the methanol—water (3 : 1.5) system at room temperature for 24 h. The reaction mixture was filtered off from Pd^0, extracted with diethyl ether (3×4 mL) and dichloromethane (DCM) (2×4 mL). The organic extracts were washed with water (2×3 mL), combined, concentrated to dryness, and purified by column flash-chromatography (*d* = 1 cm, *h* = 20 cm; hexane) to obtain 4-methyl-1,1´-biphenyl (**3a**) (0.0973 g, 94%) as fine colorless crystals. ^{1}H NMR, δ: 2.45 (s, 3 H, CH$_3$); 7.30 (d, 2 H, C(3)H, C(5)H, ^3J = 7.8 Hz); 7.37 (t, 1 H, C(4´)H, ^3J = 7.5 Hz); 7.47 (t, 2 H, C(3´)H, C(5´)H, ^3J = 7.8 Hz); 7.550 (d, 2 H, C(2)H, C(6)H, ^3J = 7.8 Hz); 7.630 (d, 2 H, C(2´)H, C(6´)H, ^3J = 7.5 Hz).

The other reactions with *p*-bromotoluene **2** were carried out similarly with modification of conditions (see Table 1).

B. Catalyst *rac*-**1** (0.0120 g, 0.0156 mmol, 2.5 mol.%), phenylboronic acid (0.1141 g, 0.9357 mmol), TBAB (0.2011 g, 0.6238 mmol), and K$_2$CO$_3$ (0.1724 g, 1.2474 mmol) were added sequentially to a cooled to −18 °C solution of *p*-bromotoluene **2** (0.1067 g, 0.6238 mmol) in methanol with cooling and the mixture was kept in refrigerator (–18 °C) for 18 days. The work-up of the reaction mixture was performed at –5 °C: Pd^0 was removed by filtration, extraction was made by diethyl ether (3×4 mL) and DCM (2×4 mL). The organic layers were washed with water (2×3 mL), combined, and concentrated to dryness. Purification of the product was performed by chromatography (see above) to obtain 4-methylbiphenyl **3a** (0.0293 g, 53%).

The Suzuki—Miyaura reactions with aryl chlorides were performed using general procedure *A*; modifications of conditions are given in the text. The biphenyl **5** isolated was characterized spectrally. ^{1}H NMR, δ: 7.38 (t, 2 H, *p*-H, ^3J = 7.5 Hz); 7.47 (t, 4 H, *m*-H, ^3J = 7.5 Hz); 7.63 (d, 4 H, *o*-H, ^3J = 7.5 Hz).

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