

Coupling of Boronic Acids with Amines in the Presence of a Supported Copper Catalyst

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Abstract An efficient heterogeneous catalytic method was developed for Chan-Lam reaction, coupling of amines and boronic acid. Copper on 4 Å molecular sieve provided yields comparable to the methods published. The method provides the main advantages of a heterogeneous catalytic procedure, the preparation of the catalyst is easy, the workup of the reaction mixture is simple.

Keywords Chan-Lam reaction · Copper · Molecular sieve · Heterogeneous catalysis

1 Introduction

The metal catalyzed cross-coupling reactions gave valuable synthetic tools in the preparative organic chemistry. Among the methods developed the palladium catalyzed C–C(aryl) bond formation has an outstanding role [1, 2]. However, there are fewer examples for the formation of C(aryl)-heteroatom bond. The traditional Ullmann reaction [3] requires hard reaction conditions, produces large amount of harmful waste and gives variable yields. Recently an efficient method was developed by Buchwald and Hartwig for the arylation of amines using palladium or nickel catalyst [4, 5]. Aryllead, arylbismuth, arylborane and arylsilane compounds were also used as coupling component [6–10].

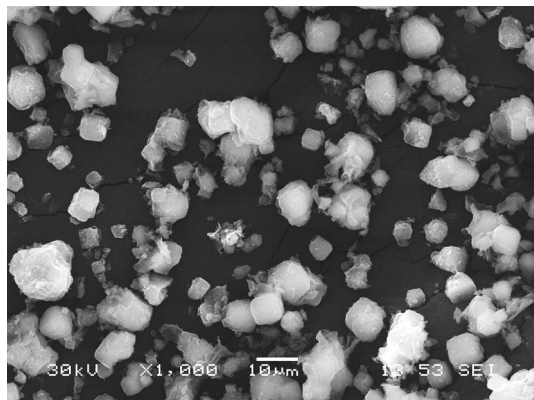
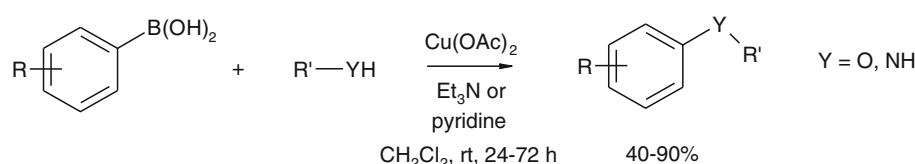
In the method developed by Chan and Lam boronic acids were used as reagents for the arylation of compounds

having NH or OH groups. Among the substrates amines, amides, imides, phenols, carbamides and sulfonamides have been described. The reaction was catalyzed by copper(II)-acetate, and generally pyridine or triethylamine were used as base [11, 12] (Fig. 1).

Numerous modifications of this method has been published. Thus *e.g.* aromatic amines were coupled with methylboronic acid in the presence of copper(II)-acetate and pyridine [13]. Vinyl boronates and allyl alcohols in the presence of copper(II)-acetate gave allyl vinyl ethers [14]. Instead of boronic acids organotrifluoroborate salts were also used for the preparation of aryl, alkenyl or diaryl ethers [15] as well as aryl and diaryl amines [16]. Different catalysts were also tested, thus copper(I) oxide in boiling methanol [17], or copper-exchanged fluorapatite in methanol at room temperature [18] gave also good results. A detailed review has been published recently presenting the scope and limitation of the method, the published reagents, as well as descriptions about the mechanism [19]. Some interesting variations were also presented, thus *e.g.* the arylation of tetrazoles in the presence of copper(I) oxide, oxidative atmosphere and DMSO as solvent. The authors established that copper(I) will oxidize to copper(II), which then forms a complex with both tetrazole and DMSO. A disproportionation of copper(II) yields copper(I) and copper(III) and this copper(III) is the responsible for the catalytic effect [20, 21]. A Ni-catalyzed method was also published [22]. In some cases 4 Å molecular sieve was also added to the reaction mixture [15, 16, 23].

Working on the examination of heterogeneous catalytic methods in the preparative organic chemistry we prepared copper(II) on 4 Å molecular sieve ($\text{Cu}^{2+}/4\text{A}$) by impregnation of finely ground molecular sieve with copper(II) chloride in deionized water. The targeted copper content of this catalyst was 6.3 wt%, the experimental value was

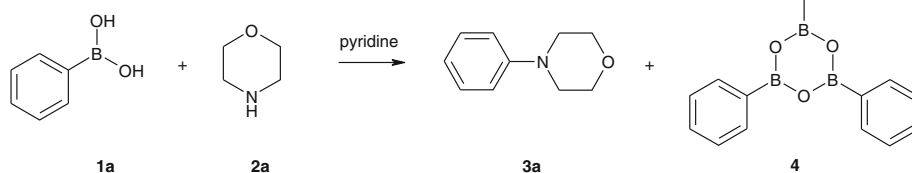
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Fig. 1 General scheme of the Chan-Lam reaction**Fig. 2** SEM image of the Cu²⁺/4A catalyst

5.8 wt% (determined by ICP-OES). The surface analysis by scanning electron microscope (SEM) showed cubic zeolite crystals, most of the particles were in the 2.5–5 µm range (Fig. 2, 1000× magnification). EDS showed that copper covered the support's surface evenly. The surface area of the original molecular sieve (810 m²/g) dropped to 360 m²/g after the impregnation. This catalyst was applied successfully in the A³-coupling [24] as well as in the transformation of oximes into nitriles [25] or nitriles into amides [26]. Cu²⁺/4A was reduced with hydrazine hydrate using the proven method described for the preparation of the supported Pd⁰ catalysts earlier [27, 28]. Copper content of Cu⁰/4A catalyst dropped to 5.5 wt%. There were no remarkable changes in the surface area, the particle size distribution remained practically the same. Copper distribution on the surface was not modified during the reduction. The finely distributed copper made the catalyst sensitive to the atmospheric oxygen.

2 Results and Discussion

We investigated the reactivity of our catalyst in the Chan-Lam reaction. The optimal reaction conditions were

Fig. 3 Model reaction for the determination of the optimal reaction conditions

elaborated in the reaction of phenylboronic acid and morpholine (Fig. 3). The results are summarized in Table 1.

Good results were obtained only in dichloromethane. Methanol, which is also known solvent of the Chan-Lam reaction, gave poor yield. Using Cu(II) on Mg-La mixed oxide support (Cu²⁺/MgLaO) as catalyst the desired product was not observed. Cu²⁺/4A gave moderate yield. In all experiments large amount (20–40 %) of triphenylboroxine (**4**, Fig. 2.) was also formed. Although in the literature mostly pyridine (sometimes triethylamine) has been described as base in this reaction, we checked the possibility of the use of other bases, too. Replacing pyridine with triethylamine the yields decreased appreciably. Use of other bases (sodium hydrogencarbonate or potassium carbonate) gave poor yield probably due to the multiple heterogeneous system.

Replacing Cu²⁺/4A with its reduced form (Cu⁰/4A) the conversion increased significantly, and the amount of **4** decreased below 5 %. As Cu⁰/4A is sensitive to the atmospheric oxygen, the weighing of the catalyst were carried out under argon atmosphere. Increasing drastically the amount of copper on the support's surface the yield of the desired product dropped dramatically while the amount of **4** increased strongly (see Table 1, last entry).

Further experiments were made under these reaction conditions. The results of the reaction of phenylboronic acid with different amines (Fig. 4.) are summarized in Table 2.

The desired products were obtained with moderate to good yield. A slight substituent effect was observed, see compounds **3b-d**. The aliphatic boronic acid **1f** gave similar result than the aromatic derivatives. A few amount (<5 %) of the appropriate boroxine was obtained in all cases, this could be separated easily by column chromatography. XRF study showed that no remarkable amount of copper could be found in the product.

The recyclability of the catalyst was examined in the reaction of phenylboronic acid and morpholine. In this case

Table 1 Optimization of the reaction conditions

Solvent	Catalyst	Temperature (°C)	Reaction time (h)	Yield (%) ^a
Dichloromethane	Cu ²⁺ /4A, 0.2 g	40	24	42
Methanol	Cu ²⁺ /4A, 0.2 g	65	20	7
Toluene	Cu ²⁺ /4A, 0.2 g	110	20	–
Acetonitrile	Cu ²⁺ /4A, 0.2 g	80	35	–
Dichloromethane	Cu ²⁺ /MgLaO, 0.2 g	40	24	–
Dichloromethane	Cu ⁰ /4A, 0.2 g	40	14	35 ^b
Dichloromethane	Cu ⁰ /4A, 0.5 g	40	20	90 ^b
Dichloromethane	Cu ⁰ /4A, 0.5 g	40	20	90 ^b
Dichloromethane	Cu ⁰ /4A, 0.5 g	40	20	82 ^{b,c}
Dichloromethane	5xCu ⁰ /4A ^d , 0.5 g	40	20	40 ^e

2 mmol phenylboronic acid, 1 mmol morpholine, 2 mmol pyridine, 10 ml solvent

^a Based on GC–MS analysis of the reaction mixture

^b In Ar atmosphere

^c Using triethylamine as base

^d 27.8 wt% Cu

^e Biphenyl was formed as main product

the solid material filtered out from the reaction mixture contained not only the catalyst, but the salt formed from the boronic acid—pyridine salt, too. Thus, the pretreatment of the catalyst was necessary before the reusability test. The filtered solid was washed with water and then with alcohol, then dried at 120 °C for 1 h. The yield of the 2nd run dropped to 65 %. When this purification process was not effectuated, only 58 % *N*-phenylmorpholine was obtained. Perhaps, in this case the salts formed in the reaction might precipitate onto the surface of the catalyst, covering and thus blocking the active metal centers.

The Chan-Lam coupling has also been described with phenols [18, 23]. We investigated the reaction of different boronic acids with 4-nitrophenol (**5**, Fig. 5). The results are summarized in Table 3. The desired products were obtained with moderate yield.

In summary, copper(0) on 4 Å molecular sieve support proved to be a suitable catalyst for the arylation of amines

as well as phenols. The yields were comparable with the published ones. The workup of the reaction mixture was very simple, the catalyst was filtered out, then the solvent was evaporated and the residue was purified by column chromatography.

3 Experimental

The commercial starting materials were purchased from Merck-Hungary Ltd.

¹H NMR spectra were made on Bruker Avance 500 spectrometer in CDCl₃ using TMS as internal standard. GC–MS spectra were made on Agilent 6890 N-GC-5973 N-MSD instrument, column: Restek, Rtx-5SILMS, 30 m × 0.25 mm, 25 μm film layer. Temperature program: 45 °C (1 min) → 10 °C/min → 310 °C (17 min). Injector temperature: 250 °C, carrier gas: He. SEM images were made on JEOL JSM-6380LA scanning electron microscope, with 30 kV accelerating voltage, in vacuo.

3.1 Preparation of the Catalyst

Cu²⁺/4A was prepared by treatment of powdered 4 Å molecular sieve with CuCl₂ in deionized water as described in [19]. Thus, 2 g of support and 0.34 g (2 mmol) of CuCl₂·2H₂O in 200 ml deionized water were stirred at room temperature for 12 h. Then the light green solid was filtered out, washed with deionized water and then with acetone, and dried in an oven at 120 °C for 1 h.

1 g of this material in 10 ml ethanol was treated with 1 g hydrazine hydrate at room temperature for 3 h. Then the light reddish-brown solid was filtered out under Ar atmosphere, washed with ethanol and dried under vacuo. As this material is sensitive to the atmospheric oxygen (moderate warming), it was stored under Ar atmosphere.

Targeted copper content of Cu²⁺/4A: 6.3 wt%, measured value: 5.8 wt%, measured value for Cu⁰/4A: 5.5 wt% (ICP-OES).

3.2 Typical Procedure for the Coupling of Boronic Acids

A mixture of boronic acid **1** (2 mmol), amine **2** or 4-nitrophenol **5** (1 mmol), pyridine (2 mmol) and 0.5 g

Fig. 4 Chan-Lam reaction in the presence of Cu⁰/4A catalyst

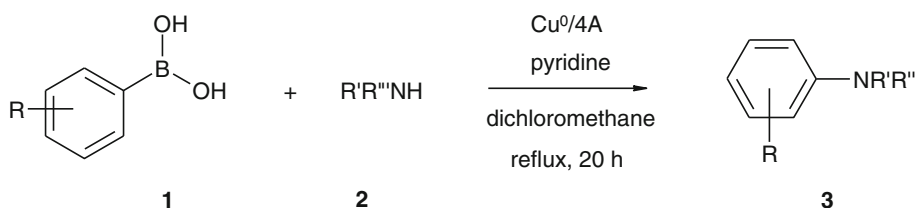
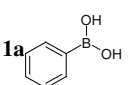

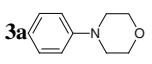
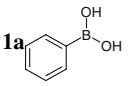
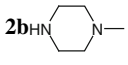
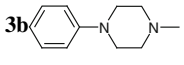
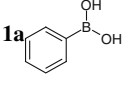
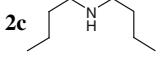
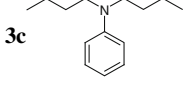
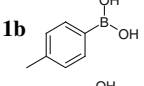

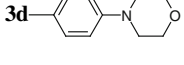
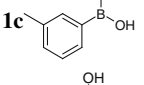

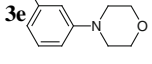
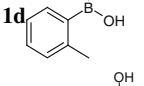

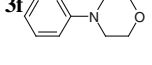
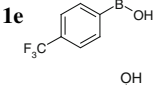

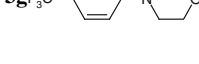
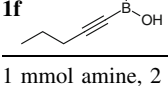

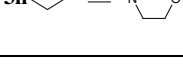


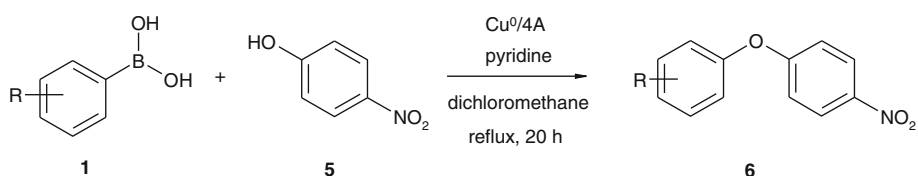
Table 2 Coupling of phenylboronic acids with amines

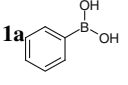
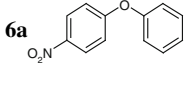
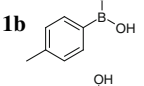
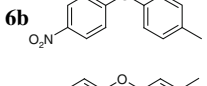
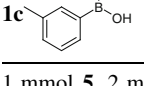
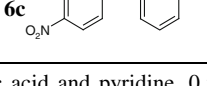
Boronic acid	Amine	Product	Conversion ^a	Yield ^b
			90	77
			80	68
			70	57
			60	53
			60	50
			55	43
			55	50
			n.d.	56

1 mmol amine, 2 mmol boronic acid and pyridine, 0.5 g catalyst, 10 ml dichloromethane

^a Based on the ¹H NMR spectra of the crude product

^b Isolated yield

Fig. 5 Chan-Lam reaction with phenols**Table 3** Coupling of phenylboronic acids with 4-nitrophenol

Boronic acid	Product	Yield ^a
		55
		50
		48

1 mmol **5**, 2 mmol boronic acid and pyridine, 0.5 g catalyst, 10 ml dichloromethane

^a Isolated yield

Cu⁰/4A in boiling dichloromethane (10 ml) was stirred under Ar atmosphere for 20 h. then the mixture was cooled, the solid was filtered, washed with

dichloromethane, the filtrate was evaporated. The residue was purified by column chromatography (Kieselgel, hexane:acetone 4:1 eluent).

All products have satisfactory spectral data (¹H NMR, MS). The spectral data of the known compounds were identical with those reported in the literature.

3.3 Representative Spectroscopical Data of Compounds

3.3.1 *N*-phenylmorpholine, **3a**

¹H NMR (300 MHz, CDCl₃) δ (ppm): d 7.30–7.26 (2H, m), 6.93–6.86 (3H, m), 3.86 (4H, t, J = 4.8 Hz), 3.15 (4H, t, J = 4.8 Hz).

GC: R_t: 22,77 min; MS (m/z): M⁺: 177.

3.3.2 1-Phenyl-4-methylpiperazine, **3b**

¹H NMR (300 MHz, CDCl₃) δ (ppm): d 2.33 (s, 3H), 2.55 (t, J = 4.0 Hz, 4H), 3.19 (t, J = 4.0 Hz, 4H), 6.83–6.91 (m, 3H), 7.24–7.27 (m, 2H).

3.3.3 *N,N*-Dibutylaniline, **3c**

¹H NMR (300 MHz, CDCl₃) δ 7.22 – 7.17 (2H, m), 6.65 – 6.60 (3H, m), 3.25 (4H, t, J = 7.4 Hz), 1.60 – 1.52 (4H, m), 1.40 – 1.30 (4H, m), 0.95 (6H, t, J = 7.3 Hz);

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