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Cu^{II}–β-Cyclodextrin Complex as a Nanocatalyst for the Homo- and Cross-Coupling of Arylboronic Acids under Ligand- and Base-Free Conditions in Air: Chemoselective Cross-Coupling of Arylboronic Acids in Water

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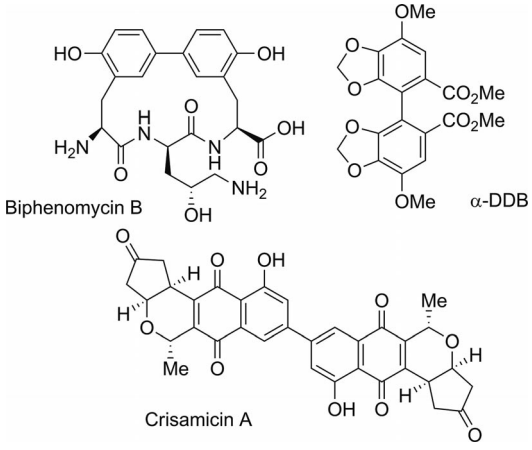
We report here the transition-metal-catalyzed chemoselective cross-coupling of arylbroronic acids in high yields without using ligand or base. We have developed an efficient copper-catalyzed protocol for the homocoupling and cross-coupling of arylboronic acids. The protocol is also suitable for the cross-coupling of aliphatic primary amines with arylboronic acids. Aminophenols and primary amines bearing an alcoholic substituent on the aliphatic chain were coupled with arylboronic acids, and the products were obtained with high C–N coupling selectivity. An effective catalyst was Cu_2–β-cyclodextrin, which is readily available and structurally simple, but has not previously been explored as a catalyst.

Introduction

Symmetrical biaryl compounds are an important class of organic compounds for both synthetic and medicinal chemistry.[1] Several synthetic and naturally occurring symmetrical biaryl scaffolds have been reported to have diverse biological activities (Scheme 1); α-DDB, for example, was used as a leading hepatoprotective agent.[2] Crisamicin A and Biphenomycin B, which were both isolated from natural sources, were found to be active toward Gram-positive and Gram-negative bacteria, respectively.[3] Symmetrical biaryls are traditionally obtained through copper-mediated homocoupling of aryl halides (Ullmann coupling reaction), which has been known for a century.[4] The synthesis of symmetrical biaryl scaffolds has continued to develop over the past decade through the use of metal-assisted homocoupling of aryl halides, boronic acids, aryl Grignard reagents, 1,2-diarylditellanes, and arenediazonium salts.[5]

Among the various biaryl coupling methods, the Suzuki–Miyaura coupling of arylboronic acids has attracted attention due to its compatibility with a variety of functional groups, because of the stability and the lower toxicity of the boronic acids compared with other organometallic reagents, and because of the ease of working up the reaction mixture.[6] Coupling reactions of arylboronic acids is an excellent method for the preparation of numerous important products in biological, pharmaceutical, and material sciences,[7] and the homocoupling of arylboronic acids is a valuable method to obtain symmetrical biaryls.



Scheme 1. Structures of biologically active symmetrical biaryls.

Recently, many studies have reported on the homocoupling of arylboronic acids for the synthesis of symmetrical biaryls; this is mainly due to commercial availability of a wide range of arylboronic acids.[8]

A commonly applied method for the synthesis of symmetrical biaryl compounds relies on palladium catalysis in the presence of different ligands, bases, and solvents.[9] Wong and Zhang reported the synthesis of symmetrical biaryls through the palladium-catalyzed homocoupling of arylboronic acids, but this method requires phosphane ligands and harsh reaction conditions.[1b] In these catalytic methods, metal salts and organic halides or benzoquinone are used as oxidizing agents to restore the catalytically active palladium(II) species.[10] However, researchers have

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recently reported the homocoupling of boronic acids either in air or under an oxygen atmosphere.[11] Although some significant achievements in the palladium-catalyzed homocoupling of arylboronic acids have been made, the drawbacks of the catalyst systems, such as sensitivity to air, high costs, and toxicity, limit their application.

Copper-mediated coupling reactions for the synthesis of biaryls, phenols, aromatic amines, and diaryl ethers is an important transformation that has been developed to include a wide range of substrates.[12] Demir et al. reported that copper(II) acetate is able to mediate the homocoupling of arylboronic acids for the synthesis of biaryls.[13] Recently, Yamamoto et al. reported an efficient method to obtain symmetrical biaryls through the homocoupling of arylboronic acids catalyzed by 1,10-phenanthroline-ligated copper complexes in air, but this method suffers from low yields when substrates with electron-withdrawing functionalities are used as arylboronic acids.[8a] Corma et al. described a supported-gold-catalyzed homocoupling of arylboronic acids that takes place with high conversion and selectivity.[14] With the increasing demand for environmentally friendly methods, we have recently found that the homocoupling of arylboronic acids is mediated by very inexpensive and air-stable copper(II) sulfate in dimethylformamide (DMF).[15]

β-Cyclodextrin (β-CD) is a water-soluble cyclic oligosaccharide that possesses a hydrophobic cavity that can bind substrates selectively and catalyze chemical reactions with high selectivity by involving reversible formation of host–guest complexes with noncovalent bonding, as seen in enzymes. Indeed, β-cyclodextrin has been widely used as a nanoreactor catalyst in organic transformations.[16] Copper(II)–β-cyclodextrin is a dinuclear complex with a good stability constant.[17] For the first time, Messmer reported complexation of Cu^{II} ions with β-cyclodextrin in alkaline solution, and further investigations were undertaken by Matsui et al.[17] Recently, the stability constant and suggested formula of this complex was determined by Norkus et al. (Scheme 2).[17f]

$$2\,Cu^{2+} + \beta\text{-CD} + 6\,OH^- \rightleftharpoons Cu_2\beta\text{-CD}(OH)_2^{2-} + 4\,H_2O$$

Scheme 2. The suggested formula of copper(II)–β-CD complex.

Although this readily available dinuclear supramolecular complex is known, to the best of our knowledge, it has never been employed as a catalyst in organic transformations. We have now found that Cu_2–β-CD complex is an effective dinuclear supramolecular nanoreactor catalyst for the coupling reactions of arylboronic acids under ligand- and base-free conditions in air.

The Cu_2–β-CD complex can be readily prepared by addition of copper sulfate solution (0.04 M) to a mixture of β-cyclodextrin in sodium hydroxide solution (0.5 M).[17b]

Results and Discussion

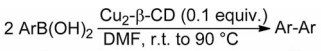
Initially, the homocoupling of phenylboronic acid (**1a**) was chosen as the model reaction. Recently, we reported experimental results for the screening of a range of copper salts in the homocoupling of phenylboronic acids.[15] In a continuation of this screening trial, when the reaction was carried out by using Cu_2–β-CD (0.1 equiv. with respect to 2 equiv. of **1a**) at room temperature in DMF for 14 h, biaryl **2a** was obtained in 83% isolated yield (GC analysis showed 100% conversion, with 92% yield). A control experiment conducted without Cu_2–β-CD showed that the reaction did not occur. When the reaction was carried out by using copper(II) sulfate (0.1 equiv., $CuSO_4$) in the presence of β-CD (0.1 equiv.) at room temperature for 12 h, biaryl **2a** was obtained in a very low yield (less than 5%, detected by GC analysis). It should be noted that the use of common organic solvents, such as tetrahydrofuran (THF) or CH_2Cl_2 as a solvent, did not promote the formation of the biphenyl product. According to these results, the homocoupling of various arylboronic acids was examined by using Cu_2–β-CD in DMF at room temperature in air.

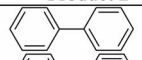
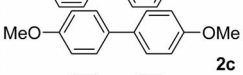
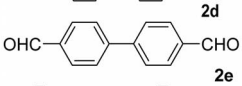
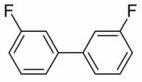
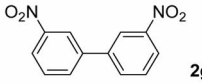
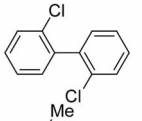
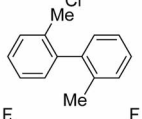
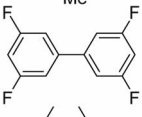
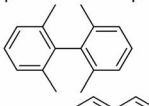
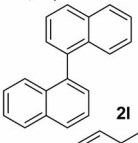
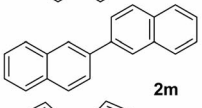
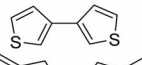
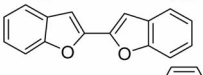
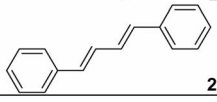
Under the optimized conditions described above, a range of arylboronic acids were employed in the homocoupling reactions; the results are summarized in Table 1. The homocoupling of *para*-substituted arylboronic acids gave the corresponding biaryls in good to excellent yields (Table 1, Entries 2–4). An arylboronic acid bearing an aldehyde group in the *para* position gave the corresponding phenol product (Table 1, Entry 5). *meta*-Substituted arylboronic acids produced the corresponding products **2f** and **2g** in moderate to good yields (Table 1, Entries 6 and 7). An arylboronic acid bearing a weakly coordinating nitro group could also be used to obtain the desired product **2g** in 81% yield (Table 1, Entry 7). It was also possible to carry out this homocoupling with *ortho*-substituted arylboronic acids, which gave the corresponding biaryls in moderate to good yields (Table 1, Entries 8 and 9).

Whereas (3,5-difluorophenyl)boronic acid provided the corresponding biaryl **2j** in 53% yield (Table 1, Entry 10), sterically hindered (2,6-dimethylphenyl)boronic acid gave the corresponding phenol product without formation of the desired biaryl **2k**, presumably due to the steric congestion around the boronic acid (Table 1, Entry 11). This result revealed a degree of substrate-size selectivity in this approach. The method was also applied to the homocoupling of 1- and 2-naphthylboronic acid. The latter substrate gave the corresponding binaphthyl **2m** in 81% yield, however, 1-naphthyl boronic acid produced the corresponding product **2l** in lower yield (31%), which is possibly due to the steric effects (Table 1, Entries 12 and 13).

The homocoupling of (thiophen-3-yl)boronic acid, as an example of a (heteroaryl)boronic acid, gave 83% yield of the desired product **2n** (Table 1, Entry 14), whereas with (benzofuran-2-yl)boronic acid, around 72% yield of the desired product **2o** was obtained (Table 1, Entry 15). Finally, the reaction of [(*E*)-2-phenylvinyl]boronic acid, as an example of a styrylboronic acid, in the presence of Cu_2–β-CD gave **2p** in 70% yield (Table 1, Entry 16). Thus, the conditions reported herein successfully facilitate the homocoupling reaction of a wide variety of arylboronic acids. Of particular note is the homocoupling reaction of (benzofuran-2-yl)boronic acid in good yield.

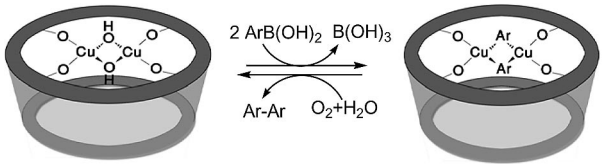
Table 1. Cu_2–β-CD-catalyzed homocoupling reaction of arylboronic acids.



Entry	T [°C]	Product 2	t [h]	Yield [%][a]
1	r.t.	 2a	14	83
2	r.t.	 2b	6	77
3	r.t.	 2c	5	82
4	r.t.	 2d	18	73
5[b]	r.t.	 2e	24	–
6	80	 2f	10	53
7	r.t.	 2g	5	81
8	r.t.	 2h	10	52
9	70	 2i	12	23
10	70	 2j	10	53
11[b]	r.t.	 2k	24	–
12	90	 2l	24	31
13	80	 2m	14	81
14	r.t.	 2n	24	83
15	r.t.	 2o	48	72
16	r.t.	 2p	12	70

[a] Isolated yield. [b] Only the corresponding phenol was detected.

A plausible mechanism is outlined in Scheme 3 for the Cu_2–β-CD-catalyzed homocoupling reaction of arylboronic acids. On the basis of literature precedents[18] and on the structure reported for Cu_2–β-CD,[17] we propose a dimetallic coupling mechanism that yields the biaryl products. We believe that the present process proceeds through attack of the hydroxido ligand to the oxophilic boron center and transmetallation of the arylboronic acids with the (μ-hydroxido)copper(II) complex Cu_2–β-CD to give a dimetallic arylcopper intermediate, which undergoes subsequent reductive elimination to the symmetrical biaryl compound.[18,8a]



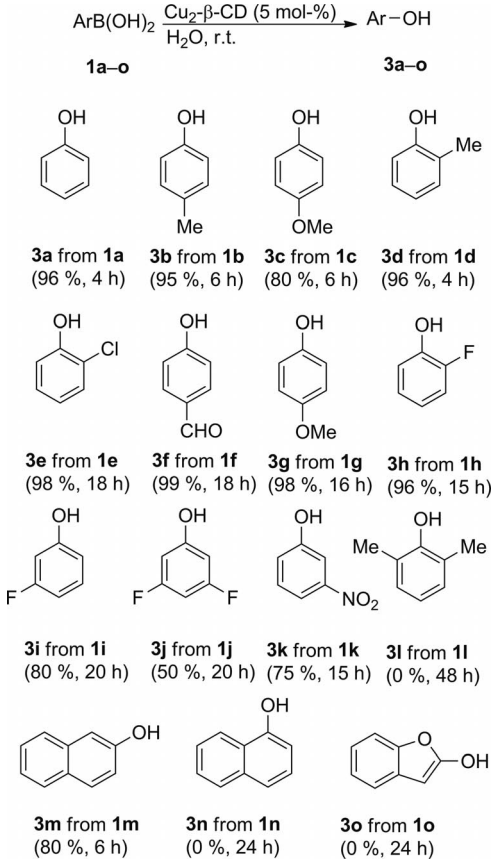
Scheme 3. Suggested mechanism of copper(II)–β-CD-catalyzed homocoupling of arylboronic acids.

We next turned our attention to applying this method to the cross-coupling reaction of arylboronic acids. Phenolic compounds have been found in numerous natural products, and a number of them are pharmaceutically important.[19] Phenols have been observed as byproducts in many metal-catalyzed coupling reactions of arylboronic acids. Recently, Wang and co-workers reported the copper-catalyzed oxidative hydroxylation of arylboronic acids.[20] This method is quite useful; however, it still requires 0.2 equiv. of 1,10-phenanthroline as a ligand. Here, we report a highly efficient and convenient method for the conversion of arylboronic acids into phenols by using Cu_2–β-CD as a catalyst in air at ambient temperature.

As a convenient test case, we targeted the synthesis of phenol (**3a**) and were pleased to find that the reaction of phenylboronic acid with water in the presence of Cu_2–β-CD gave the expected product **3a** in 96% yield (Scheme 4).

As shown in Scheme 4, a range of arylboronic acids were also tested under similar conditions. The method proved to be compatible with a wide variety of substrates, and **1a**–**o** were converted into the corresponding products **3a**–**o** in good to excellent yields. The effect of electron-donating and electron-withdrawing substituents on conversion and yields was studied, and it can be concluded that the method provided superior yields of electron-rich phenols **3a**–**e**, which is in contrast to the traditional nucleophilic substitution of aryl halides. Electron-deficient phenols were also prepared in satisfactory yields, albeit in longer reaction times. Furthermore, significant steric effects were evident for the boronic acids tested. (2,6-Dimethylphenyl)boronic acid gave the protodeboronation product (*m*-xylene) in 96% yield, and (2-naphthyl)boronic acid gave the corresponding phenol **3m** in 98% yield. However, (1-naphthyl)boronic acid produced naphthalene (protodeboronation product) in 90% yield, which is possibly due to steric effects. Finally, the coupling of (benzofuran-2-yl)boronic acid with water at room temperature with Cu_2–β-CD as catalyst, gave 90% yield of the arylboronic acid homocoupling compound **2o** as the exclusive product.

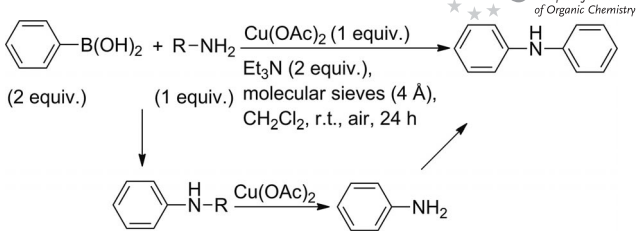
We also examined the heterocoupling of amines with arylboronic acids. Aromatic amines have attracted considerable attention because of their significant biological activity. Uses for aromatic amines can range from pharmaceutical and agrochemical to conducting polymers in material science.[21] Hence, the development of new methods for their



Scheme 4. Synthesis of phenols by using arylboronic acids in the presence of copper(II)–β-CD.

synthesis is still an attractive area of research.[22] The formation of C–N bonds through cross-coupling reactions is an essential methodology for the preparation of nitrogen-containing compounds. Chan et al. reported that copper(II) acetate is able to mediate the heterocoupling of arylboronic acids with amines at room temperature in the presence of a tertiary amine as a promoter.[23] A recent series of developments by Lam and Buchwald and others has shown that the amination of arylboronic acids can be effective in the presence of triethylamine or pyridine when stoichiometric quantities of $Cu(OAc)_2$ were used.[24] However, the approach appears to be limited to aromatic amines and imidazoles, with low yields being obtained with aliphatic amines. Batey and Quach reported that the treatment of aliphatic amines with phenylboronic acid under conditions developed by Chan gave diphenylamine as the sole product through copper-promoted *N*-dealkylation of alkyl(aryl)amine (Scheme 5). They solved this problem by using a catalytic amount of copper acetate in dichloromethane as solvent.[25]

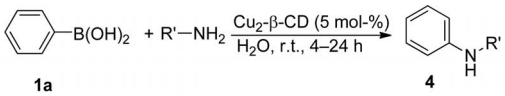
We therefore decided to use Cu_2–β-CD complex as a catalyst in the cross-coupling reaction of arylboronic acids with amines. The cross coupling of phenylboronic acid (**1a**) with aniline (**4a**) was chosen as the model reaction. When the reaction was carried out with Cu_2–β-CD (0.05 equiv. with respect to 1 equiv. of **1a**) at room temperature in DMF



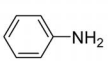
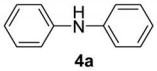
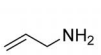
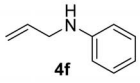
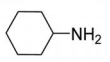
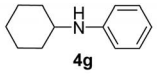
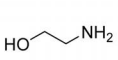
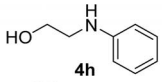
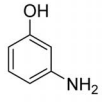
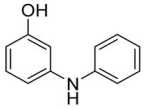
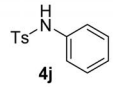
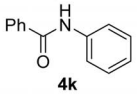
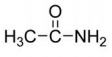
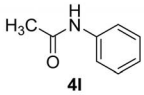
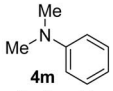
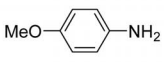
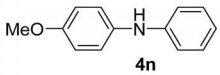
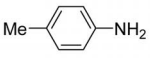
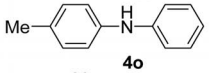
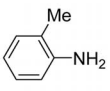
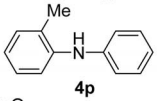
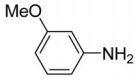
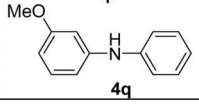
Scheme 5. Diphenylamine formation through *N*-dealkylation of alkyl(aryl)amine.

for 12 h, biphenylamine (**5a**) was obtained in 83% isolated yield. A control experiment showed that without Cu_2–β-CD, the reaction did not occur. It should be noted that the use of common organic solvents, such as THF or CH_2Cl_2 as a solvent did not afford the biphenylamine. According to these results, the cross-coupling of *n*-propylamine as an aliphatic amine with phenylboronic acid was examined by using Cu_2–β-CD in DMF at room temperature in air. The results showed that *n*-propylamine gave low yields of the corresponding amine in DMF. We were pleased to find that when the reaction of boronic acid with *n*-propylamine was carried out in water as solvent, a high yield (97% GC yield, 93% isolated yield) of the corresponding amine was obtained. The cross-coupling reaction of phenylboronic acid with aniline in water gave diphenylamine in 91% isolated yield (GC analysis showed 100% conversion, with 96% yield). According to these results, the cross-coupling reaction of boronic acids with various amines was examined by using Cu_2–β-CD in water at room temperature in air. The scope and limitations of this protocol were examined by using a series of primary and secondary amines and anilines; the results are summarized in Table 2. The cross-coupling of primary aliphatic amines with phenylboronic acid gave the corresponding amines in good to excellent yields (Table 2, Entries 2–5). Aliphatic amines bearing olefin moieties also gave the corresponding amine product in good yield (Table 2, Entry 6). Cyclohexylamine, as an example of a branched amine, was also successfully applied as substrate (Table 2, Entry 7). Interestingly, primary amines bearing an alcoholic substituent on the aliphatic chain gave the corresponding amine in high yield, without any C–O cross-coupling being observed (Table 2, Entries 8 and 9). The application of this reaction to the cross-coupling of 3-aminophenol with phenylboronic acid was also briefly explored (Table 2, Entry 9). To the best of our knowledge, no selectivity has yet been reported between C–N and C–O in the cross-coupling reaction of arylboronic acids. In this reaction, C–N cross-coupling occurred selectively, and the coupling was found to give the desired 3-(phenylamino)phenol product in good yield, without C–O cross-coupling being observed. The cross coupling of toluenesulfonamide with phenylboronic acid, gave *N*-phenyltoluenesulfonamide in good yield (Table 2, Entry 10). We then applied this method to amides, including benzamide and acetamide, and a secondary amine (dimethylamine), but the cross-coupling reaction failed (only phenol product was detected). A range of anilines proved to be suitable cross-coupling partners under

Table 2. Cu_2–β-CD-catalyzed cross-coupling of nitrogen-containing compounds with arylboronic acids.



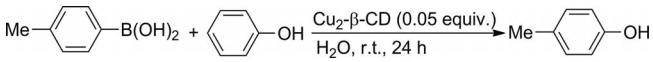
1a 4

Entry	Amine compound	Product **4**	*t* [h]	Yield [%][a]
1		 **4a**	12	91
2	*n*-Pr—NH_2	*n*-Pr—N(H)— **4b**	8	93
3	*n*-Bu—NH_2	*n*-Bu—N(H)— **4c**	8	89
4	*n*-Hex—NH_2	*n*-Hex—N(H)— **4d**	8	86
5	*n*-Oct—NH_2	*n*-Oct—N(H)— **4e**	8	81
6		 **4f**	8	71
7		 **4g**	10	86
8		 **4h**	24	96
9		 **4i**	4	75
10[b]	Ts—NH_2	 **4j**	24	69
11[c]		 **4k**	24	–
12[c]		 **4l**	24	–
13[c]		 **4m**	24	–
14		 **4n**	5	94
15		 **4o**	6	82
16		 **4p**	6	88
17		 **4q**	15	55

[a] Isolated yield. [b] K_2CO_3 (3 equiv.) was used as a base. [c] Only phenol was detected.

these conditions, affording good to excellent yields of the unsymmetrical diarylamine products (Table 2, Entries 14–17).

We next turned our attention to applying this method to the cross-coupling reaction of arylboronic acids with phenols for the synthesis of biaryl ethers. As a convenient test case, we targeted the synthesis of unsymmetrical (4-methylphenyl) phenyl ether. Unfortunately, the reaction of (4-methylphenyl)boronic acid with phenol in the presence of Cu_2–β-CD gave only 4-methylphenol (**3b**) in 96% yield, together with unreacted phenol (Scheme 6).



Scheme 6. Attempted cross-coupling of phenol with (4-methylphenyl)boronic acid.

Conclusions

We have developed an efficient copper-catalyzed protocol for the homocoupling and cross-coupling of arylboronic acids. The transformation can be affected under an aerobic atmosphere without the need for a ligand or base. This new, efficient process offers several advantages over many of the previously published procedures, including high yields and high selectivity. The protocol is suitable for the cross-coupling of aliphatic primary amines with arylboronic acids. Arylation of anilines and amines is more interesting and useful, because it is performed in water instead of the classic dichloromethane. On the other hand, to the best our knowledge, no selectivity has previously been reported between C–N and C–O in the cross-coupling reaction of boronic acids with amines and phenols. We have also achieved chemoselectivity in a copper-catalyzed arylboronic acid C–N cross-coupling reaction by using a protocol similar to the well-documented cross-coupling reaction with primary amines bearing alcoholic substituent on the aliphatic chain and 3-aminophenol.

Experimental Section

General Information: All melting points were measured with a Yanagimoto or a Büchi 510 apparatus and are uncorrected. Mass spectra were recorded with a VG Auto Spec by using electron impact (EI) ionization techniques. NMR spectra were obtained with a Bruker Avance 400 NMR spectrometer (^{1}H NMR: 400 MHz; ^{13}C NMR: 100 MHz). Gas chromatography was performed with a Varian CP 3800 chromatograph. Analytical TLC was carried out with Merck plates precoated with silica gel 60 F_{254} (0.25 mm thickness). Column chromatography was performed with Fluka silica gel 60 (70–230 mesh) in common glass columns. Copper sulfate was recrystallized before use. DMF was dried with CaH_2 for 2 h and filtered. Arylboronic acids and amines were used as received. All solvents were distilled before use.

Preparation of Cu–β-Cyclodextrin Complex: Prepared according to the method described by Matsui.[17b] In a 250 mL beaker containing 0.5 M NaOH (50 mL), β-cyclodextrin (1 mmol) was dissolved with stirring. To this clear solution, $CuSO_4{\cdot}(H_2O)_5$ (0.04 M, 75 mL,

3 mmol) was added. A dark-blue solution was obtained immediately, which was stirred at room temperature. After 6 h, this solution was filtered to remove excess copper salt, which precipitated as a blue solid (copper hydroxide). To this blue solution was added ethanol (ca. 400 mL) until a light-blue suspension was formed, which was filtered, and the residue washed with ethanol and air-dried at room temperature. This complex was ground into a fine powder before use as catalyst.

General Procedure for the Homocoupling of Arylboronic Acids: To a mixture of Cu_2–β-CD (0.01 mmol, 13 mg, in this complex the number of water molecules has not been exactly determined so far, therefore we estimate its molecular weight to be 1300 mg/mmol) in DMF (1 mL), was added arylboronic acid (0.2 mmol), and the resulting mixture was stirred at 25–90 °C for 5–48 h. Water (20 mL) was added to the reaction mixture, which was extracted with CH_2Cl_2 (2 × 20 mL), and the combined extracts dried with Na_2SO_4. The product was purified immediately by flash chromatography (silica gel 60; particle size 230–400 mesh; *n*-hexane/EtOAc) to afford biaryls **2a**–**p** in 31–83% isolated yields. All products are known, and most are commercially available (see the Supporting Information).

General Procedure for the Preparation of Phenols of Arylboronic Acid: To a solution of Cu_2–β-CD (65 mg, 0.05 mmol) in distilled water (3 mL) was added arylboronic acid (1 mmol), and the resulting mixture was stirred at room temperature for 4–20 h (the light-blue color became light-green). The reaction mixture was extracted with dichloromethane (2 × 10), and the combined extracts were dried with Na_2SO_4. The solution was cooled to 0 °C before GC injection. All the phenols are known, and the products correlated with commercially available samples in gas chromatographic analysis (50–96% GC yield).

General Procedure for C–N Coupling of Arylboronic Acid with Amines: To a mixture of Cu_2–β-CD (65 mg, 0.05 mmol) and amine (3 mmol) in distilled water (2 mL) was added arylboronic acid (1 mmol), and the resulting mixture was stirred at room temperature for 8–24 h. The reaction mixture was then diluted with water (20 mL), extracted with dichloromethane (2 × 20), and the combined extracts were dried with Na_2SO_4. The product was purified immediately by flash chromatography (silica gel 60; particle size 230–400 mesh; *n*-hexane/EtOAc) to afford arylamines **4a**–**q** in 69–93% isolated yields (see the Supporting Information).

Supporting Information (see footnote on the first page of this article): Details of analytical data of the products, and ^1H and ^{13}C NMR spectra of the coupling products **4**.

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