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Base-free anaerobic Cu(II) catalysed aryl-nitrogen bond formations

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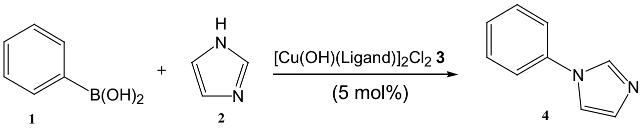
Abstract—The coupling of arylboronic acids with imidazole in the presence of binuclear bis-μ-hydroxy copper(II) complexes is reported. The reactions can be performed in air as well as under nitrogen atmosphere. Reactions are carried out at ambient temperature without the need for base. The presence of water is essential for the reaction to proceed. Ligand effects on the yield and selectivity are reported.

The formation of aryl–aryl bonds and aryl–heteroatom bonds are among the most important transformations in organic synthesis. Copper is the most ancient metal used for the coupling of aryl halides to form biaryls,[1] but in the last decade palladium has gained widespread interest.[1–6] In many cases palladium complexes are more active and selective than copper complexes. Reactions such as the *N*-arylation of imidazole, however, generally proceed only when a copper catalyst is used. Because of the low cost of copper in comparison to palladium, the use of copper in industrial processes is preferred.[7] Copper-catalysed aryl-nitrogen bond formations are typically performed under Ullmann-type conditions.[8–11] Several procedures using copper(I) based catalysts have been reported.[12–14] Typically, these reactions require elevated temperatures and have to be performed under nitrogen atmosphere. Recent developments have shown that the use of stoichiometric quantities of $Cu(OAc)_2$ results in an efficient coupling of amines and arylboronic acids under mild reaction conditions.[15–19] Collman[20] demonstrated that dimeric copper(II) complexes (10 mol%) give moderate to good yields (40–70%) in C–N coupling reactions. Water can be used as a solvent, but in most of the methods described, water is excluded from the reaction mixture to avoid hydrolysis of the boronic acid.[21] Recently it was shown that simple copper salts in protic solvents can efficiently couple arylboronic acids with imidazole.[22] All the procedures described in the literature are performed under dioxygen atmosphere and often in the presence of a base. Dioxygen is proposed to play an important role as oxidant,[19,20,23] whereas the base is used to activate the boronic acid for transmetallation. The mechanisms proposed for Cu(II) catalysed reactions are as yet only reasonable guesses, because none of the intermediates have been isolated or characterised.

As part of our quest for mild catalysts for C_{aryl}–N bond formation and the elucidation of the reaction mechanism we here report on the novel aerobic and anaerobic coupling of phenylboronic acid and imidazole in the absence of base, using catalytic amounts of a copper catalyst (5 mol%) (Scheme 1). The reactions were performed under ambient reaction conditions (air atmosphere and 20 °C) producing moderate to good yields depending on the ligand employed.[24]



Scheme 1.

Keywords: C–N coupling; Catalysts; Cu(II) complexes; Solvent effects; Ligand design.

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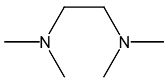
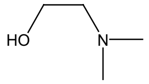
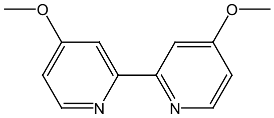
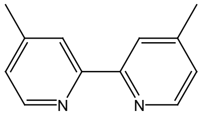
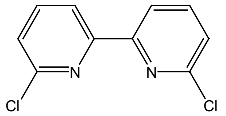
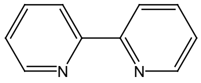
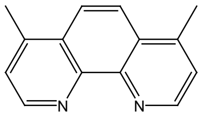
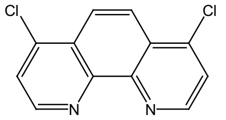
Our first efforts were directed towards the investigation of solvent effects on the phenylation of imidazole, using $[Cu(OH)TMEDA]_2Cl_2$ as a catalyst. After 20 h, no conversion was obtained in anhydrous CH_3CN, CH_2Cl_2 or NMP (*N*-methylpyrrolidone). This can only partly be explained by the poor solubility of the catalyst and/or products in these solvents. In water, in which the catalyst is completely dissolved, a 7% yield (GC) was obtained. Also significant amounts of benzene (~7%) and phenol (<2%) were formed. A mixture of NMP and H_2O (1:1 v/v), however, afforded a yield of 56% of the cross coupled product with high selectivity (less than 5% benzene and no phenol was observed). No significant amounts of homo-coupled biphenyl were observed.

To examine the effect of ligands on the catalyst performance, binuclear Cu(II) complexes **3a**–**h** were synthesised bearing several nitrogen-based bidentate ligands[21,25,26] and tested in the arylation reaction. The results obtained using only 5 mol% of **3a**–**h** in the arylation of imidazole are summarised in Table 1. Reactions performed with the TMEDA–dimer complex **3a** gave excellent yields (99% after 72 h). Increasing the amount of catalyst **3a** from 5 mol% to 7.5 mol% resulted in a yield of 89% after only 48 h. Reactions performed with catalyst **3b** bearing an amino alcohol ligand, resulted in a low yield (10% after 20 h). Changing to an aromatic 2,2-bipyridine ligand **3f** resulted in a decrease of the yield (68%) after a prolonged reaction time (5 days). Using more electron-donating ligands, for example, 4,4-dimethoxy-bipyridine **3c** and 4,4-dimethyl-bipyridine (**3d**) also resulted in a decrease of the yield to, respectively, 44% (5 days) and 32% (4 days). Reactions performed with dimer complexes possessing the more rigid phenanthroline ligands (**3g** and **h**) showed an increase in yield. The 4,7-dichlorophenthroline complex **3h** afforded phenylimidazole in 77% yield after 4 days. Notably, the neocuproine complex **3g** even gave full conversion after 4 days.

The phenylation of imidazole catalysed by complex **3d** was performed at higher temperatures. An increase of the reaction temperature to 60 °C raised the yield from 32% to only 39%. At even higher temperatures, no significant amount of product was formed, which is probably due to catalyst decomposition. With the increase in temperature, there was also an increase in benzene formation.

Most reported Cu(II) catalysed arylations of aza-compounds employ a base, thereby limiting the scope of

Table 1. The effect of different ligands on coupling of $PhB(OH)_2$ and imidazole[a]

Entry	Ligand		Time	Yield **4**[b] (%)
1		**3a**	20 h 72 h	56 99
2		**3b**	20 h	10
3		**3c**	5 d	44
4		**3d**	4 d	32
5		**3e**	5 d	24
6		**3f**	5 d	68
7		**3g**	4 d	99
8		**3h**	4 d	77

[a] Reaction conditions: 5 mol% of Cu(II) dimer (**3a**–**h**), imidazole (68 mg, 1.0 mmol), $PhB(OH)_2$ (121 mg, 1.0 mmol) in NMP/H_2O (1:1 v/v, 5 mL), 20 °C in an air atmosphere.

[b] Determined by GC analysis using dihexyl ether as an internal standard.

the reaction to substrates, which contain base-stable functionalities. The method described here does not require the presence of a base. In our search for efficient methods for the arylation of imidazole, however, we studied the effect of pH on the catalyst performance. To this end different buffered solutions were used in the phenylation of imidazole using 5 mol% of catalyst **3a**. At pH 4 and 6 (citrate buffer) no product was observed. At pH 8 (tricine buffer) no product formation was observed either, probably due to the interference of tricine with the copper complex. The use of a $HCO_3^-/CO_3^{2-}/KOH$ buffer (pH 10), yielded only 14% of coupled product after 20 h at room temperature. Reactions performed in the presence of 2.5 equiv (with respect to phenylboronic acid) of NaOH or 1 equiv of K_2CO_3 yielded only traces of product (4% and less than 1%, respectively). The use of 1 equiv of NaOAc under the same conditions resulted in a somewhat higher yield of 10% after 20 h, still significantly lower than the results obtained in the absence of a base (56%).

To investigate the role of dioxygen in our system, we performed reactions with complex **3d** under pure dioxygen atmosphere, resulting in a similar yield as was obtained under an ambient atmosphere. To our surprise, reaction under nitrogen atmosphere resulted in the same yield as obtained in the presence of dioxygen.

Our mild method proved useful for the coupling of imidazole with a range of different arylboronic acids. The highest yield (75%) was obtained with an electron withdrawing CF_3 substituent at the *meta* position of the boronic acid. The *meta* nitro analogue, however, only resulted in a 21% yield. Introduction of an electron releasing methoxy group at the *para* position resulted in a similar yield of 19%. The presence of a substituent at the *ortho* position decreased the yield dramatically. Obviously the steric hindrance caused by these substituents slows down the reaction considerably. Naphthylboronic acid was coupled to imidazole in 21% yield. Under the conditions employed, attempted use of heteroaryl boronic acids such as benzofuranboronic acid resulted in C–C coupling rather than C–N coupling.

The use of phenylboronic acid in the absence of imidazole results in a fast C–C homocoupling, forming biphenyl. A stoichiometric reaction of the Cu(II) dimer and phenylboronic acid, followed by the addition of imidazole did not result in C–N product formation, while the reverse addition sequence (first imidazole and then phenylboronic acid) resulted in selective formation of the C–N coupled product. We therefore concluded that the Cu complex reacts rapidly with imidazole in the selectivity-determining step, followed by reaction with the boronic acid. Experiments with increasing amounts of imidazole or phenylimidazole product added to the reaction mixture resulted in a decrease of the reaction rate. This suggests inhibition of the reaction by excess imidazole and/or phenylimidazole.

Collman proposed a mechanism for Cu(II) catalysed C–N bond formation in which the binuclear Cu(II) first reacts with phenylboronic acid. This transmetallation step is followed by coordination of imidazole and subsequent oxidation with dioxygen to a transient Cu(III) species. After reductive elimination of the product, a Cu(I) species is formed. This Cu(I) intermediate is then oxidised to the starting dimeric Cu(II) complex, again by dioxygen. Our results, however, suggest that the first step of the reaction involves imidazole. Furthermore, dioxygen is not required as an oxidant under the conditions employed here. Studies to gain further insight into the mechanism of this important reaction are in progress. The implications of these results for the mechanism, together with spectroscopic studies, will be discussed elsewhere.[27]

In conclusion, we have developed a novel, mild method for the *N*-arylation of imidazole. We have demonstrated that this reaction can be selectively performed in an NMP/H_2O mixture, at ambient temperature and atmosphere, using catalytic amounts of the cheap and commercially available $[Cu(OH)TMEDA]_2Cl_2$ dimer as the catalyst. The presence of an NMP/H_2O mixture increases the yield considerably, whereas addition of base and the presence of dioxygen are not needed. Moreover, our results suggest that the first step of the reaction involves imidazole coordination.

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24. Typical experimental conditions: To the appropriate amount of Cu catalyst **3** in 5 mL of solvent was added imidazole **2** (68 mg, 1 mmol) and arylboronic acid **1** (1 mmol). Dihexyl ether (115 μL, 0.5 mmol) was added as an internal standard. Unless otherwise stated no base was added and the reactions were carried out in an air atmosphere. The reaction mixture was stirred according to the given reaction times. Product formation was determined by GC and GC–MS. Samples (0.05 mL) were taken from the reaction mixture at regular time intervals. CH_2Cl_2 and a saturated solution of NH_4Cl were added to the sample. After separation of the layers, the organic layer was filtered through a plug of $MgSO_4$. The retention time of the products (phenylimidazole **4**, biphenyl, phenol and benzene) were confirmed by comparison with authentic samples.
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