Chapter 7a

Base-free Anaerobic Cu(II) Catalyzed Aryl-Nitrogen Bond Formation

Abstract

The coupling of arylboronic acids with imidazole and benzimidazole in the presence of binuclear bis-µ-hydroxy copper(II) complexes is reported. The reactions can be performed in air as well as under a dinitrogen atmosphere. Reactions are carried out at ambient temperature without the need of 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-hetero-atom bonds are among the most important tools in organic synthesis. Copper is the most ancient metal used for the coupling of aryl halides to form biaryls, but in the last decade palladium has gained widespread interest. 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 costs of copper in comparison to palladium, the use of copper in industrial processes is preferred. Copper catalyzed aryl-nitrogen bond formations are usually performed under Ullmann-type conditions. Several procedures using copper(I) based catalysts have been reported. Typically, these reactions require elevated temperatures and have to be performed under a dinitrogen atmosphere. Recent developments by Chan, Lam and others 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. Collman demonstrated that dimeric copper 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 methods described, water is excluded from the reaction mixture to avoid the hydrolysis of boronic acid. Procedures described in literature are often performed under a dioxygen atmosphere and in the presence of a base. Base is used to activate the boronic acid for the transmetallation, whereas dioxygen is proposed to play an important role as oxidant for the copper (II) catalyzed arylation of imidazole.

In this study we report a novel method for the coupling of arylboronic acid and imidazole, using catalytic amounts of a copper catalyst (5 mol %), no base and a NMP/H$_2$O mixture (1:1 v/v) as the solvent. The reactions were performed at ambient reaction conditions producing moderate to good yields depending on the ligand employed.
Results and Discussion

Our first efforts were directed towards the investigation of solvent effects on the phenylation of imidazole, using 5 mol % $[\text{Cu(OH)TMEDA}]_2\text{Cl}_2$ as a catalyst, performed under ambient reaction conditions (Scheme 1).

Scheme 1. Cu(II) catalyzed reaction of imidazole with phenylboronic acid.

After 20 hours, no conversion is obtained in anhydrous $\text{CH}_3\text{CN}$, $\text{CH}_2\text{Cl}_2$ or NMP (N-methylpyrrolidone). This can only partly be explained by the poor solubility of the catalyst in these solvents. In water, in which the catalyst is completely dissolved, a 7% yield (GC) was obtained. Also significant amounts of benzene ($\sim$7%) and phenol (<2%) were formed. A mixture of NMP and $\text{H}_2\text{O}$ (1:1 v/v), however, afforded a yield of 56% of the cross coupled product in high selectivity (less than 5% benzene and no phenol was observed). No significant amounts of homo-coupled biphenyl were observed.

To test the effect of ligands on the catalyst performance, dimeric Cu(II) complexes were synthesized bearing several nitrogen-based bidentate ligands. Reaction of CuCl with ligands a-h in the presence of dioxygen resulted in a 50-94% yield of the hydroxy bridged dimeric complexes $3\text{a-h}$. The results obtained using only 5 mol % of $3\text{a-h}$ in the arylation of imidazole are summarized in Table 2. Reactions performed with the TMEDA-dimer complex $3\text{a}$ gave excellent yields (99% after 72 h). Increasing the amount of catalyst $3\text{a}$ from 5 mol % to 7.5 mol % resulted in a yield of 89% after only 48 hours. Reactions performed with catalyst $3\text{b}$ bearing an amino alcohol ligand, resulted in a low yield (10% after 20 h). Changing to an aromatic 2,2-bipyridine ligand ($3\text{f}$) resulted in a decrease of the yield (68%) after prolonged reaction time (5 days). Using more electron-donating ligands e.g. 4,4-di-MeO-bipyridine ($3\text{c}$) and 4,4-di-Me-bipyridine ($3\text{d}$) 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 phenantroline ligands ($3\text{g}$ and $3\text{h}$) showed an increase in yield. The 4,7-di-Cl-phenantroline complex ($3\text{h}$) yielded 77% after 4 days. The neocuproine complex ($3\text{g}$) even gave full conversion after 4 days.
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Table 1. The effect of different ligands on coupling of PhB(OH)₂ and imidazole[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time</th>
<th>Yield 4 [%][b]</th>
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<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>20 h</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>72 h</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>20 h</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>5 d</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>4 d</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>5 d</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>5 d</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>4 d</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>4 d</td>
<td>77</td>
</tr>
</tbody>
</table>

[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/H₂O (1:1 v/v, 5 ml), 20 °C in an air atmosphere.
[b] Determined by GC analysis using dihexyl ether as an internal standard.

For further optimization of the reaction conditions, the arylation of imidazole catalyzed by complex 3d was performed at higher temperatures. Elevation of the reaction temperature to 60 °C raised the yield from 32% to only 39%. At even higher temperatures (60 °C), no significant amount of product is formed, which is probably due to catalyst decomposition. With the increase of temperature there is also an increase of benzene formation.

To investigate the role of dioxygen in our system, we performed reactions with complex 3d under a pure dioxygen atmosphere, resulting in a similar yield as was obtained at ambient atmosphere. To our surprise, reaction under a dinitrogen atmosphere resulted in the same yield as obtained in the presence of dioxygen. Collman proposed a mechanism for Cu(II) catalyzed C-N bond formations in which the presence of dioxygen is needed for the oxidation of a Cu(II) intermediate to a Cu(III) complex. This Cu(III) complex readily undergoes reductive elimination to form the organic product and a Cu(I) complex. This Cu(I) intermediate is then oxidized to the starting dimeric Cu(II) complex by dioxygen. Lam has shown that different oxidizing agents influence the yield of the arylation of imidazole by Cu(OAc)₂. Our results suggest that dioxygen is not required as an oxidant under the
conditions employed. This opens the possibility to use oxygen sensitive substrates. Furthermore, this result has important implications for the mechanism (vide infra).

Most reported Cu(II) catalyzed arylations of aza-compounds are employed in the presence of a base, limiting the scope of the reaction to substrates which contain base-sensitive functionalities. The method described here does not need 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 hours at room temperature. Reactions performed in the presence of 2.5 equivalents (referring to phenyl boronic acid) of NaOH or 1 equivalent of K$_2$CO$_3$ yields only traces of product (4% and less than 1%, respectively). The use of 1 equivalent NaOAc under the same conditions, resulted in a somewhat higher yield of 10 % after 20 hours. Still significantly lower than the results obtained in the absence of a base (56%).

This systematic study towards an efficient Cu(II) catalyzed phenylation of imidazole has resulted in a mild procedure using cheap [Cu(OH)TMEDA]$_2$Cl$_2$ as a catalyst in NMP/H$_2$O at ambient reaction conditions. Unfortunately, extension of this method to several aza-compounds such as aniline, diethyl amine, morpholine, piperazine and pyrole was not successful. Benzimidazole, however, could be phenylated using this protocol.
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Table 2. Results of Caryl-N coupling using different boronic acids\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic Acid</th>
<th>Yield [%](^{[b]})</th>
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<tbody>
<tr>
<td>1</td>
<td>(\text{B}OH) (\text{O}^3\text{C})</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>(\text{B}OH) (\text{O}^2\text{N})</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>(\text{O}^3\text{B}OH) (\text{OH})</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>(\text{B}OH) (\text{OH}^3\text{CF}) (\text{O}^3\text{C})</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>(\text{B}OH) (\text{OH}) (\text{Cl})</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>(\text{Cl}) (\text{B}OH) (\text{OH})</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>(\text{B}OH) (\text{OH}) (\text{O}^3\text{N})</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>(\text{B}OH) (\text{OH}) (\text{O}^3\text{H})</td>
<td>56</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Reaction conditions: 5 mol % of Cu(II)dimer 3a, imidazole (68 mg, 1.0 mmol), ArB(OH)\(_2\) (1.0 mmol) in NMP/H\(_2\)O (1:1 v/v, 5 ml), 20 °C in an air atmosphere.

\(^{[b]}\) Determined after 20h. by GC analysis using dihexylether as an internal standard.

Applying the method to several substituted arylboronic acids, resulted in product formation after 20 hours (Table 2). The highest yield (75%) was obtained with an electron withdrawing CF\(_3\) substituent at the meta position. The meta nitro analogue, however, only resulted in 21% yield. Introduction of a electron releasing methoxy group at the para position resulted in a similar yield of 19%. The presence of a substituent at the ortho position decreases 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, hetero aryl boronic acids such as benzofuranboronic acid, resulted in C-C coupling rather than C-N coupling.

The absence of dioxygen as an oxidant for this catalytic reaction, implies the involvement of another oxidant since the reaction is necessarily oxidative. A tentative
mechanism for this reaction is shown in figure 1. The binuclear complex [Cu(OH)(N,N)₂]Cl₂ (I) reacts with imidazole to form a mononuclear Cu(II) species of type II. Addition of phenylboronic acid to the starting Cu(II) dimer results in the fast formation of biphenyl. Reaction of this Cu dimer with a stoichiometric amount of phenylboronic acid followed by addition of imidazole does not result in product formation. Addition of stoichiometric amounts of imidazole to the Cu(II) dimer, followed by addition of phenylboronic acid results in the formation of phenylimidazole. From these results we conclude that the first step in the reaction involves imidazole. We propose that imidazole is deprotonated by the hydroxide moiety of the starting complex. The resulting Cu(II)imidazolate complex reacts with the phenylboronic acid reagent to form the product and the starting Cu(II) dimer I again. A possible pathway involves the homolytic splitting of the phenyl boronic acid, resulting in the formation of the a transient Cu(iii) species (III). After reductive elimination of the product, the known Cu(I) compound IV is formed. Next, the boronic species formed (from the phenyl boronic acid) after addition of a phenyl radical to the Cu(II) intermediate II, in combination with water, is involved in the re-oxidation of Cu(I) to the starting Cu(II) dimer. Alternatively, the Cu(II)imidazolate species reacts with the phenylboronic acid to the phenylimidazole product and a Cu(II)-B(OH)_2 species. This species decomposes in water to the starting hydroxo-Cu(II) dimer and HB(OH)₂. Extensive spectroscopic (EPR, NMR, ED-XAFS, UV-Vis, IR), kinetic and structural (X-ray) studies to further elucidate the reaction mechanism are in progress.
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Figure 1. Proposed reaction mechanism for the Cu(II) catalyzed arylation of imidazole under anaerobic conditions.
Conclusion

Establishing efficient methods for constructing Caryl-N bonds is currently an active area in organic synthesis. Caryl-N bond containing structures are not only important in biological systems but also common moieties in pharmaceutical research. We have developed a novel, mild method for the N-arylation of imidazole. We have demonstrated that this reaction can be selectively performed in a NMP/H$_2$O mixture, at ambient temperature and atmosphere, using catalytic amounts of a cheap and commercially available [Cu(OH)TMEDA]$\text{Cl}_2$ dimer as the catalyst. The HSE (Health, Safety and Environmental) acceptable NMP/H$_2$O mixture makes this an interesting industrial procedure. The product can be separated easily from the reaction mixture by diethyl ether, whereas the catalyst remains in the water layer, making this solvent mixture suitable for recycling. The presence of an NMP/H$_2$O mixture increases the yield considerably, whereas addition of base and the presence of dioxygen are not needed. Implication of these results for the mechanism, together with spectroscopic studies, will be discussed elsewhere (Chapter 7b).
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Experimental Section

General Remarks

Unless stated otherwise, all reactions were carried out in an air atmosphere using 20 cm glass tubes. THF, hexane and diethyl ether were distilled from sodium benzophenone ketyl, CH₂Cl₂, acetonitrile and NMP (N-methylpyrrolidone) were distilled from CaH₂ and toluene was distilled from sodium under nitrogen. Reactions in the absence of dioxygen were carried out using standard Schlenk techniques. Reactions under a dioxygen atmosphere were conducted by bubbling dioxygen through the solvent for 15 minutes, followed by presurizing the mixture with 1 bar of dioxygen. Gas chromatographic analyses were run on an Interscience HR GC Mega 2 apparatus (split/splitless injector, J&W Scientific, DB-1 J&W 30 m column, film thickness 3.0 µm, carrier gas 70 kPa He, FID detector) equipped with a Hewlett Packard data system (Chrom-Card). Gas chromatographic mass spectra were run on an Agilent Technologies 6890/5973 GC-MS combined with an Agilent Mass Selective detector. Column type; HP5MS, length 30 m, film thickness 0.25 µm, crosslinked 5% PhMe-siloxane.

All reagents were purchased from commercial suppliers and used without further purification. Ligand e²⁵ and bis-µ-hydroxy copper(II) complexes (3a-h)²¹, ²³, ²⁴ were prepared according to a literature procedure.

General procedure

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. When appropriate a base was added. The reaction was stirred under the given conditions. Product formation was determined by GC and GC-MS. Samples (0.05 ml) were taken from the reaction mixture at regular time intervals. CH₂Cl₂ and a saturated solution of NH₄Cl were added to the sample. After separation of the layers, the organic layer was filtered through a plug of MgSO₄. The retention time of the products (phenylimidazole, biphenyl, phenol and benzene) were confirmed with authentical samples.
References