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Mechanistic Studies on a Cu-Catalyzed Aerobic Oxidative Coupling Reaction with *N*-Phenyl Tetrahydroisoquinoline: Structure of Intermediates and the Role of Methanol As a Solvent

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S *Supporting Information*

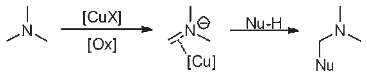
ABSTRACT: The mechanism of an aerobic copper-catalyzed oxidative coupling reaction with *N*-phenyl tetrahydroisoquinoline was investigated. The oxidized species formed from the reaction of the amine with the copper catalyst were analyzed by NMR-spectroscopy. An iminium dichlorocuprate was found to be the reactive intermediate and could be structurally characterized by X-ray crystallography. The effect of methanol to effectively stabilize the iminium ion was investigated and shown to be beneficial in an oxidative allylation reaction.

The functionalization of carbon−hydrogen bonds is a long-standing goal in organic synthesis. Oxidative coupling reactions can form new C−C bonds starting from two C−H bonds and an oxidant.[1] The prospect of using environmentally benign and cheap oxidants like oxygen or hydrogen peroxide under catalytic conditions with water as the only waste product makes these reactions particularly attractive. In recent years, several methods for the oxidative coupling of amines with various nucleophiles[2] using simple copper salts as catalysts have been developed,[3] but other metals like Ru,[4] Fe,[5] Rh,[6] and V[7] or metal-free variants[8] have been used as well. In general, mechanistic studies of oxidative coupling reactions are rare and the lack of a detailed understanding makes further developments difficult. Here, we present mechanistic and synthetic studies on aerobic copper-catalyzed coupling reactions between an amine and silyl nucleophiles which elucidate the structure of the reactive intermediate as well as the stabilizing effect of methanol.

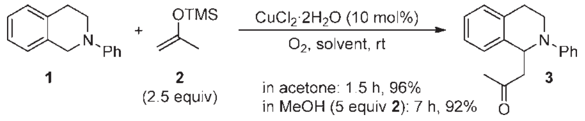
Commonly, metal-catalyzed oxidative coupling reactions with tertiary amines are proposed to proceed via catalyst−iminium ion species[1c,4a] which subsequently react with a nucleophile to form the final product (Scheme 1). Support for this mechanistic proposal comes from a few studies involving the characterization of potential intermediates like methanol and *tert*-butyl peroxide adducts[3e,h,4d,4f,6] or model compounds like preformed iminium bromides.[3e,j] Iminium π-complexes with copper have not yet been structurally characterized but are known for other metals also used in oxidative coupling reactions.[9] Recently, an iminium ion formed in a metal-free oxidative coupling reaction has been characterized by X-ray crystallography.[8f]

For the present mechanistic study, we chose the coupling of *N*-phenyl tetrahydroisoquinoline **1** and the silyl enol ether **2** as a test reaction which was recently developed in our lab and is exemplary in scope for other copper-catalyzed oxidative coupling reactions with amines. The optimized conditions had been established as 10 mol % of $CuCl_2 \cdot 2H_2O$ as the catalyst, acetone or methanol as the solvent, and elemental oxygen as the oxidant (Scheme 2).[3l]

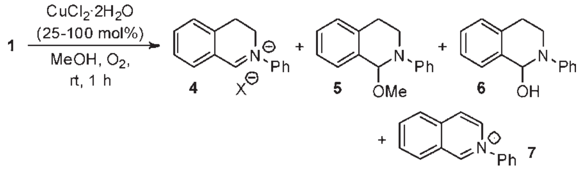
Scheme 1. Common Mechanistic Suggestion for Cu-Catalyzed Oxidative Coupling Reactions with Amines



Scheme 2. Standard Reaction for the Present Study



Scheme 3. Products of the Reaction between Amine 1 and $CuCl_2$



To gain information on potential intermediates, we reacted amine **1** with 50 mol % $CuCl_2 \cdot 2H_2O$ in methanol under oxygen and investigated the resulting products (Scheme 3).

After 1 h, full conversion of **1** was achieved and a green precipitate had formed. After filtration, the solution was directly analyzed by NMR spectroscopy. Two major compounds were found, an iminium ion **4** and a methanol adduct **5** in a ratio of ca. 40:60. Performing the reaction in acetone resulted in a similar amount of **4** and hemiaminal **6** as the major products. To facilitate

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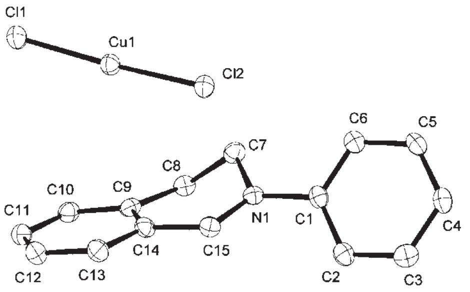


Figure 1. X-ray structure of iminium salt **4a**.

full characterization of the compounds, methanol was exchanged by DMSO-d_6 after filtration in further experiments. Under these conditions, nearly equal amounts of **4**, **5**, and **6** were observed. Repeating the reaction with different ratios of amine and $CuCl_2$ did not significantly alter the outcome of the reaction except for the formation of 3−4% of isoquinolinium salt **7** at higher ratios of amine (see Supporting Information).

The precipitate was shown to be a copper(II) chloride hydroxide by powder X-ray diffraction. Compound **4** could be isolated in 26% yield by crystallization and was analyzed by X-ray crystallography, revealing the counterion as dichlorocuprate (**4a**). The distance between the iminium carbon C15 and copper was found to be 4.15 Å and that between C15 and Cl2 3.34 Å, indicating a purely ionic interaction (Figure 1).

Compound **5** had been observed before in related coupling reactions run in methanol.[3h,4c,6] The existence of dynamic equilibria between the individual species **4**, **5**, **6**, and **7** was investigated by NMR Exchange Spectroscopy (2D EXSY).[10] The presence of exchange cross-peaks between corresponding protons revealed that both the methanol adduct **5** and the hemiaminal **6** were in chemical exchange with the iminium salt **4a**. No other exchange cross-peaks were observed from the isoquinolinium salt (**7**) or between **5** and **6**, indicating very slow or absence of chemical exchange.

Repeating the experiment of Scheme 3 with CuBr, the most common copper catalyst in related reactions,[3a−k] resulted in the same species **4**−**6** as indicated by NMR, only with a lower amount of the iminium ion **4**. X-ray crystallography revealed it to be an ionic compound like **4a**, with $(Cu_2Br_4)^{2-}$ as a counterion (**4b**, Figure 2).

To gain further understanding of the potential role of **4a**−**6**, we studied their reactivity. Adding enolate **2** to the mixture of compounds from the experiment shown in Scheme 3 in acetone resulted in the formation of product **3** in 94% conversion or 87% isolated yield after 2 h (Scheme 4a). Reacting pure **4a** with the enolate gave 85% isolated yield of **3** after 1 h and quantitative yield after 2 h (Scheme 4b). In comparison, the iminium bromide **4c**[11] was significantly less reactive in the same transformation, giving very low yields after 1 h and even after 4 h (Scheme 4c). The bromide in **4c** apparently forms a contact ion pair with the iminium that reduces its reactivity while the dichlorocuprate anion is only weakly coordinating. This is further supported by the difference in chemical shifts of the iminium methine proton in acetone-d_6: it appears at ca. 9.8 ppm for **4a** and at 10.1 ppm for **4c**, which is possibly due to a deshielding effect of the bromide by hydrogen bonding.[12] **4c** had been used as a model compound for the proposed iminium ion reaction intermediate of oxidative coupling reactions before.[3e,j] Our results show that its reactivity is far too low to be a suitable model while the reactivity of **4a** is in

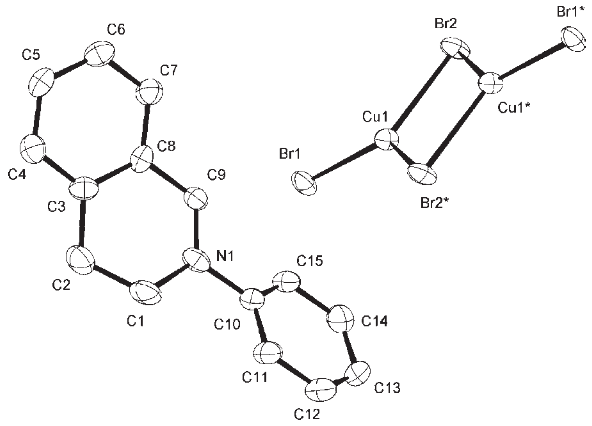
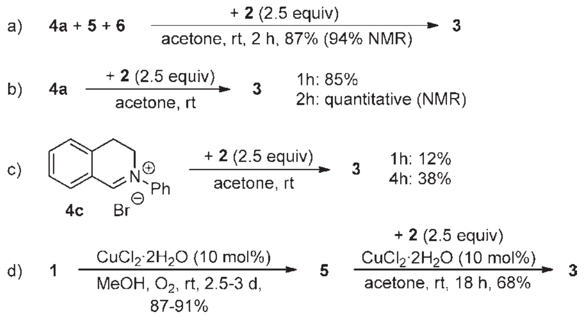


Figure 2. X-ray structure of iminium salt **4b**.

Scheme 4. Reactivity Studies of the Amine-Derived Species



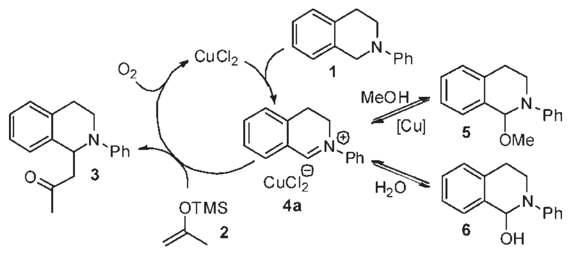
good agreement with the rate of the reaction under study. Moreover, **4a** and **4b** are easily prepared and isolated and should thus find applications in future mechanistic studies.

Methanol adduct **5** was synthesized independently by reacting amine **1** with methanol under reaction conditions in the absence of enolate **2**. Full conversion was achieved only after 60 to 72 h, giving **5** in good yield. For the coupling of **5** with **2**, the presence of $CuCl_2$ as a catalyst was needed. Subjecting **5** to reaction conditions in the presence of **2** gave the product **3** in 68% isolated yield after 18 h (Scheme 4d).

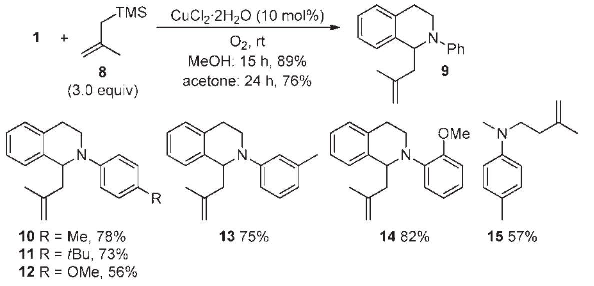
These results indicate several details of the reaction under study: The discovery of a Cu(I) counterion in **4a** and of a CuCl(OH) precipitate suggests that the main oxidation states of copper in the catalytic cycle are (I) and (II). The oxidation of **1** to the iminium ion **4a** requires two electrons to be transferred, thus 2 equiv of $CuCl_2$ would be reduced to Cu(I). One remains as a counterion to the iminium ion while another is reoxidized by oxygen to CuCl(OH), which precipitates. Under catalytic reaction conditions, Cu species are probably kept in solution by complexation due to a larger excess of amine.

The observed species **4a**−**6** derived from amine **1** can all be converted to the product **3** under reaction conditions, i.e. in the presence of a copper salt and enolate **2**. The methanol adduct **5** can be discounted as a true reactive intermediate in the catalytic cycle, as its separate formation and reaction to the product under reaction conditions proceed slower than the oxidative coupling reaction of Scheme 2 itself. Furthermore, it can only be formed in methanol and not in reactions conducted in other solvents. Hemiaminal **6** is unlikely as a true intermediate since an S_N2-type

Scheme 5. Suggested Catalytic Cycle



Scheme 6. Oxidative Allylation in Methanol



reaction with the enolate **2** appears much less facile than an S_N1-type reaction via the stabilized iminium ion **4**.

Both the formation of iminium salt **4a** and its reaction to the product (Scheme 3 and Scheme 4b) proceed at a rate comparable to that of the oxidative coupling reaction of Scheme 2 itself. Accordingly, **4a** appears to be the reactive species in the catalytic cycle which is in off-cycle equilibrium with **5** and **6** in the presence of methanol and water, respectively. The structures of **4a** and **4b** confirm the general nature of the commonly proposed reactive intermediate, a Cu-iminium species, but reveal that copper is in the oxidation state (I) and bound ionically, not covalently. We thus believe that iminium cuprates like **4a** constitute the general structure of the reactive intermediates in aerobic copper-catalyzed oxidative coupling reactions with tertiary amines and possibly in reactions using other oxidants as well.

Based on the above results, a tentative catalytic cycle can be proposed. Oxidation of amine **1** leads to the reactive iminium cuprate species **4a** which can react with methanol or water in an off-cycle equilibrium, the former catalyzed by copper acting as a Lewis acid. Reaction of **4a** with silyl enol ether **2** forms the desired product **3** in an irreversible step. The active Cu^{II} catalyst is then regenerated by reoxidation with oxygen (Scheme 5).

These findings also indicate why methanol is frequently found to be a solvent of choice for oxidative coupling reactions with amines.[3g,h,l,4a,4b,5b−5e,6,7,8e] Hemiaminal methyl ethers like **5** can obviously act as a stable reservoir for the reactive iminium ion intermediate. This could improve the yield and diminish undesired decomposition reactions of the iminium ion if nucleophile addition is significantly slower than oxidative iminium formation. This case has actually been reported for a photoredox reaction.[4e] A similar role is discussed for *tert*-butylperoxide adducts formed by the use of *tert*-butylhydroperoxide.[3h,4d,4f,6] The synthesis of methyl hemiaminal ethers and subsequent employment in metal-catalyzed reactions has also been used as a two-step strategy to generate iminium ions.[13]

As an application of these mechanistic findings and to further investigate the role of methanol as a solvent, we have developed an aerobic oxidative allylation of amines.[5h,14] Allyl silanes are less nucleophilic than silyl enolates;[15] accordingly, methanol should exert a stronger positive influence on the product yield if the model discussed above is correct. Reacting amine **1** with 2-methylallylsilane **8** did indeed give the desired product **9**, taking considerably longer than the reaction with **2**. With the less nucleophilic allyltrimethylsilane,[15] no reaction was observed. The allylation reaction with **8** proved to be general and several allylated *N*-aryl tetrahydroisoquinolines (**10**−**14**) and one allylated *N,N*-dimethyl aniline (**15**) could be synthesized. Of the solvents screened, methanol gave the best results followed by acetone (Scheme 6).

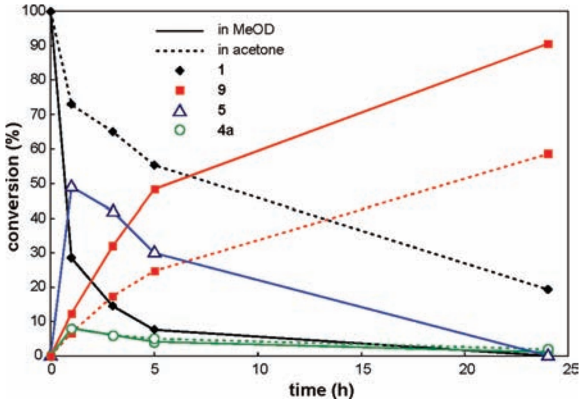


Figure 3. Reaction progress and formation of major intermediates of the oxidative allylation of **1** with **8**, monitored by ^{1}H NMR spectroscopy. Reaction conditions as given in Scheme 6.

To gain further information on the potential intermediates of this reaction as proposed in Scheme 5, we compared the oxidative coupling reactions of Schemes 2 and 6 in methanol-d_4 and acetone-d_6 by NMR spectroscopy. The coupling of **1** with **2** proceeded faster in acetone than in methanol, without intermediates **4**, **5**, or **6** being clearly visible in samples taken during the reaction. In contrast, in the allylation with **8** all intermediates were visible by ^{1}H NMR spectroscopy (**4** and **5** in methanol-d_4 and **4** and **6** in acetone-d_6) and the reaction proceeded faster in methanol than in acetone (Figure 3). At the beginning of the reaction in methanol, amine **1** is consumed quickly while the final coupling product **9** is formed at a much slower rate. **5** is formed as an intermediate product with nearly 50% yield at the beginning of the reaction and is then fully consumed over 24 h. The amount of iminium salt **4** is relatively constant throughout most of the reaction at 4−8% and nearly vanishes at the end. The reaction is relatively clean with an estimated product yield of 91% and the sum of identifiable species accounting for over 90% of the signals in the NMR after 24 h. In acetone, amine **1** is consumed at a considerably slower rate, its conversion reaching ca. 80% after 24 h. **9** is formed as the major product, giving an estimated yield of 60% after 24 h. The amount of **4** is again relatively constant throughout most of the reaction at 5−8% and nearly vanished at the end. Hemiaminal **6** was initially formed with ca. 4% but was consumed after 5 h. The reaction appeared less clean with the sum of identifiable species accounting for only 80% of the signals in the NMR after 24 h.

These results support a mechanism as depicted in Scheme 5. With less nucleophilic substrates like **8**, methanol can effectively compete in the reaction with **4a**, forming larger amounts of **5** in an off-cycle equilibrium and liberating the catalyst. Over time, **5** acts as a reservoir to **4a** and is finally converted to the product. In acetone, **5** cannot be formed and thus the conversion of amine **1** is much slower as the catalyst is only liberated upon reaction with a nucleophile. The reservoir effect in methanol could also be responsible for the higher purity observed as compared to the reaction in acetone: without the off-cycle equilibrium, unwanted side reactions of **4a** could compete with nucleophile addition if the latter step is slow. In the case of good nucleophiles like **2**, the formation of iminium salt **4a** is slower than nucleophile addition. Accordingly, conversion of **4a** to **3** is fast and intermediates **5** and **6** are not observable. Using methanol or acetone as solvent does not have a significant effect on the product yield. The slower reaction rate in methanol could be due to more subtle solvent effects, e.g. different stabilization energies of the reactants. Solubility of the catalyst cannot explain the different performances, as $CuCl_2 \cdot 2H_2O$ dissolves well in both methanol and acetone.

In summary, we have investigated the mechanism of the aerobic copper-catalyzed oxidative coupling reaction of *N*-phenyl-tetrahydroisoquinoline **1** with silyl enolate **2**. Studies of the products formed by reaction of the amine with the copper catalyst indicated iminium dichlorocuprate **4a** as the reactive intermediate in the catalytic cycle. X-ray crystallography showed an ionic bond between the iminium cation and cuprate in **4a**. The beneficial role of methanol in oxidative coupling reactions with amines could be explained by an off-cycle equilibrium forming hemiaminal ethers, which act as a reservoir for the more reactive iminium ions. This stabilizing effect could be demonstrated to be effective in reactions with less nucleophilic coupling partners like allyl silanes. We hope that this study will help in the development of new and improved oxidative coupling methods and in the mechanistic investigation of related reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. General experimental procedures, spectroscopic and analytical data for new compounds, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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