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# Mechanistic Aspects of Submol% Copper-Catalyzed C–N Cross-Coupling

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Carbon-nitrogen bond formation can be catalyzed by copper in very low concentrations ( $\approx$  100 ppm), with mechanistic features that are distinct from those in the high-concentration regime. The reaction was studied by initial rate kinetics, competitive Hammett studies, and DFT calculations. The deprotonation of the model nucleophile, pyrrole, is limited by mass transfer with the heterogeneous base. The positive reaction

#### Introduction

Since the 1970s, the area of cross-coupling reactions has been dominated by palladium and nickel catalysts.<sup>[1]</sup> However, environmental concerns together with economic factors have shifted the scientific focus to alternative catalytic systems able to perform these transformations with comparable or even higher efficiency. These efforts have resulted in the development of several improved procedures based on catalysts with beneficial characteristics. Among these, copper-based systems have proven effective for heteroatom (C-N, C-O, and C-S) cross-coupling reactions.<sup>[2-6]</sup> The early Ullmann chemistry is in general known for being ineffective because of the limited substrate scope and the necessity of using high catalytic loadings and high temperatures.<sup>[2]</sup> Since the revival of the Ullmann chemistry by Buchwald<sup>[7-22]</sup> and others<sup>[23-43]</sup> during the late 90's and early 00's, the field of cross-coupling catalysis centered on C-heteroatom bond formation has grown tremendously.[44-73] Although much progress has been made, there are still unresolved issues related to the inherent properties of copper. Turnover numbers and frequencies can be small, resulting in slow reaction rates and/or the requirement of using high catalyst loadings.

Recently, in a collaborative effort our research group and the Bolm group found that if using dimethylethylenediamine

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order in dimethylethylenediamine was explained by this reagent working not only as a ligand to Cu, but also as a facilitator for mass transfer. The selectivity-determining step in the competitive Hammett study is oxidative addition. Alternative mechanisms for this step, such as single-electron transfer, atom transfer, or  $\sigma$ -bond metathesis, can be excluded based on the observed Hammett behavior and DFT calculations.

(DMEDA) as an additive, originally developed as a ligand in Cu catalysis by Buchwald and co-workers,<sup>[9,11]</sup> C–N couplings can be performed with ppm levels of Cu.<sup>[74,75]</sup> The role of diamines in formation of the Cu–Nuc (Nuc = nucleophile) complex has been studied with both experimental and computational methods.<sup>[40,76-82]</sup> The main conclusion from these studies is that the diamines at high concentration prevent copper from forming multiligated species that could otherwise hamper the catalytic activity. Even though the concentration effect of the diamines have been addressed partly, the details of the mechanism for copper-catalyzed cross-coupling reactions is still not understood to a satisfactory extent.<sup>[83]</sup>

Several proposals can be found in the literature, supported by both experimental and computational investigations. A recent study by Houk, Buchwald, and co-workers concluded that the reacting species in C-N coupling reactions between aryl iodides and primary amines is a complex between ligand, Cu, and the deprotonated nucleophile.<sup>[81]</sup> Depending on ligand and nucleophile, the rate-determining step can be either a single electron transfer or atom transfer between the L-Cu-Nuc (L=ligand) complex and the aryl iodide, forming an aryl radical that couples with the Cu-bound nucleophile (Figure 1). However, Fu and co-workers revisited these specific calculations and could conclude that a polar mechanism involving a classical oxidative addition/reductive elimination process governed by a coordinative activation of the nucleophile actually is a viable mechanism.<sup>[84]</sup> In addition, Jutand, Ciofini, and co-workers have shown that the coupling between primary amines and aryl halides can be influenced by halogen bonding (ArX-N) between the aryl halide and the L-Cu-Nuc complex.<sup>[78,82]</sup> Most relevant to the present work is perhaps the conclusion drawn from a theoretical study by Zhang et al., in which the authors convincingly showed that diamine-ligated Cu<sup>1</sup> complexes catalyze the coupling between aryl bromides and amides through a three-centered oxidative addition/reductive elimination mechanism.<sup>[78]</sup> Clearly, the operating mecha-



Figure 1. a) Present reaction studied. b) Intermediates achieved through different mechanisms proposed for various constellations of ligands and nucleophiles.

nism or competing mechanisms for Cu-catalyzed C–N cross coupling are highly dependent on the nature of both ligand and nucleophile. All mechanistic rationales are compatible with the reaction orders measured for most reactants and reagents in the low-Cu regime,<sup>[75]</sup> but they do not explain the reaction order observed for DMEDA. It is also difficult to reconcile the proposed single-electron-transfer (SET) and atom-transfer (AT) mechanisms with the failure of radical clocks to detect radical intermediates.<sup>[85]</sup>

We present herein a kinetic investigation that together with a computational study reveals additional functions of the diamine additive. Also, the investigation clearly suggests that the activation energies for the proposed traditional nonradical mechanism are surprisingly low.

#### **Results and Discussion**

#### **Kinetic experiments**

To broaden the understanding for the role of DMEDA and the formation of the copper-amide complex, the initial rates for the cross-coupling of pyrrole with iodobenzene was followed by systematically excluding one essential reaction component, then starting the pre-equilibrated reaction mixture (at 135 °C) by adding the missing reagent (Figure 2). Starting the reaction with either CuCl<sub>2</sub> or DMEDA gave curvatures similar to what had previously been observed with pyrazole.<sup>[75]</sup> In fact, initiating the reaction using the Cu<sup>II</sup> solution gave the highest initial rate. The difference between starting with CuCl<sub>2</sub> or DMEDA may not be significant, but at least demonstrates that formation of the presumed Cu<sup>1</sup> catalyst must be a very fast process. In contrast, starting the reaction with pyrrole clearly had a lag phase of approximately 60 min before the catalyst activated, a qualitative difference from the curves for the other three reactions.

The most probable explanation for this lag phase is masstransfer limitation for the deprotonation of pyrrole by the heterogeneous base ( $K_3PO_4$ ). For all cases in which these two components had a chance to equilibrate, the catalyst was immediately activated upon addition of the last reaction component.



Figure 2. Copper-catalyzed coupling of pyrrole with iodobenzene together with initial rates measured for initiation of the reaction using different reactants.



Scheme 1. Mass transfer for copper-catalyzed C-N cross-coupling reactions.

This observation also points to a possible additional role of DMEDA: as a mass-transfer catalyst assisting in solubilizing the heterogeneous base (Scheme 1). This mechanism is further supported by the observation that if DMEDA is used as a solvent,<sup>[75]</sup> the base is fully dissolved at the end of the reaction, in contrast to reactions run in aromatic hydrocarbons such as toluene. Moreover, Buchwald and co-workers have shown that with the high-[Cu] regime conditions, the corresponding coupling displays zero-order kinetics with regards to the [diamine] if the diamine/Cu ratio is 14:1 or higher. At lower ratios, the reaction displays a first-order rate dependence on the [diamine]. A mechanistic model including a catalytically inactive resting state of the catalyst was used to rationalize the observation.<sup>[80]</sup> The present low-[Cu] conditions displays a positive non-zero reaction order with regards to [diamine] at a diamine/Cu ratio up to 1000:1.<sup>[75]</sup> Clearly, the role of diamine is, in part, different in the submol% Cu-catalyzed coupling from that in the high-[Cu]-regime conditions. A mass-transfer-facilitating rational does corroborate well with these differences.

To further gain insight into the mechanism behind the submol% copper catalyzed cross-coupling reaction, a competitive Hammett study was performed. The competitive conditions have the distinct advantage that only the portion of the

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reaction path from the entry of aryl iodide up to the selectivity-determining transition state is probed. Thus, complications from the unknown activity of the heterogeneous base and the possible mass-transfer limitations affecting the deprotonation are effectively avoided in this setup. The cross-coupling of pyrazole with iodobenzene was chosen as the standard reaction (Figure 3). As can be seen in Figure 4, there is a good correlation with the standard  $\sigma$  values. The results are in close agreement with a similar study by Taillefer in the high-[Cu]



Figure 3. Competitive Hammett study using aryl iodide derivatives and pyrazole as nucleophiles.

regime,<sup>[40]</sup> but with an even lower  $\rho$  value. We note that there is no correlation at all with  $\sigma$ . This, together with the low  $\rho$  value, clearly shows that the reaction does not follow an SET mechanism. It also casts doubt on the AT mechanism proposal, because a rate limiting formation of an aryl radical would be expected to have some correlation with  $\sigma$ , that is, both electron withdrawing and electron donating groups would be expected to stabilize a radical intermediate and increase the rate of its formation. We note that the  $\sigma$  scale was developed for benzylic radicals,<sup>[86]</sup> and thus may not correlate well with formation of a phenyl radical, but the observed survival of radical clocks also argue against a radical intermediate.<sup>[85]</sup>

During the course of the experimental work, using pyrazole as a nucleophile, we encountered issues with reproduction of a zero yield in "blank" reactions, that is, reactions missing only the Cu catalyst. The issue was traced back to leaching from the magnetic stirring bars used in the reaction. By peeling off the protective Teflon cover of the stirring bars and running the reaction under standard conditions without added copper salt, full conversion to the cross-coupling product was observed. This proves the great sensitivity of the system towards metal



Figure 4. Competitive Hammett correlation for  $\sigma$  and  $\sigma$ .

contaminations. Janiak and co-workers recently showed that nanoparticles are easily deposited onto Teflon-coated magnetic stirring bars.<sup>[87]</sup> This could be a potential source for trace metal contaminations in many catalytic systems. However, in our case, we were able to reproduce zero yields for the standard reaction by using magnetic stirring bars with thicker Teflon coating. To exclude the possibility of catalysis by palladium traces in the submol%-copper-catalyzed reaction, PdOAc ( $20 \mu$ L, 1 mm in dry THF, final loading 0.001 mol%) was added instead of CuCl<sub>2</sub>. The reaction was run under standard reaction conditions for 24 h without any product formation.

#### **DFT calculations**

The reaction mechanism was also investigated by computational methods, focusing on the fate of the already formed DMEDA-Cu-pyrrolide complex reacting with PhI (Figure 5). The results discussed above indicate that the rate-limiting step may well be formation of this complex. Following the work of





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Buchwald, Houk, and coworkers,<sup>[81]</sup> we first investigated the possibility for SET and AT mechanisms, but also evaluated alternatives that would better rationalize the observed Hammett behavior as well as the survival of radical clocks (see below). The reaction paths were derived by calculation of free energies by using dispersion-corrected DFT calculations as described in the following.

In nonpolar solvents such as toluene, charge separation is generally disfavored. Accordingly, we find the formation of expected intermediates resulting from a SET mechanism, a cationic Cu<sup>II</sup> complex, and a PhI anion radical, to be associated with a highly endergonic reaction (291 kJ mol<sup>-1</sup>). Thus, an SET mechanism was discarded as a possible pathway. The direct iodine atom transfer (AT, in Figure 1) results in a neutral Cu<sup>II</sup> complex and a phenyl radical, a process that is less dramatically uphill, endergonic by 102 kJ mol<sup>-1</sup>. Recombination of the two intermediates ultimately provide the new C-N bond, a process that is monotonously downhill on the potential energy surface and, therefore, diffusion-controlled. Bimolecular diffusion-controlled processes in general have a free-energy barrier of approximately 20 kJ mol<sup>-1.[88]</sup> The reverse reaction, from intermediates to starting materials, is also diffusion-controlled and thus has also a barrier of approximately 20 kJ mol<sup>-1</sup>. Both transition states of the AT process can therefore be estimated to have energies of  $> 120 \text{ kJ mol}^{-1}$ .

Interestingly, employing unrestricted open-shell singlet calculations, we could identify a transition state (TS) for the direct transfer of the phenyl group via a four-centered TS that electronically can by characterized as a concerted AT recombination or, alternatively, a "biradical  $\sigma$ -bond metathesis". The free energy barrier of this process is higher than that of the AT, 144 kJ mol<sup>-1</sup>, in part owing to the high entropic penalty associated with the more ordered TS. The more common closedshell  $\sigma$ -bond metathesis has been excluded as a viable pathway in the Buchwald-Houk study,<sup>[81]</sup> but for comparison, we also calculated this more compact TS, which had an energy barrier of 152 kJ mol<sup>-1</sup>. However, a detailed comparison of these paths became irrelevant when we next turned to investigate the "standard" path of oxidative addition/reductive elimination. The oxidative addition of PhI to the DMEDA-Cu-pyrrolide complex proceeds with a low barrier of 68 kJ mol<sup>-1</sup>. This step was found to be effectively irreversible, with the reductive elimination TS (in which the C-N bond is formed) lying approximately 30 kJ mol<sup>-1</sup> lower on the free-energy surface. This is a significant difference from the results in the Buchwald-Houk study,<sup>[81]</sup> but in agreement with the work of Zhang et al.,<sup>[78]</sup> as well as Lefèvre et al.<sup>[82]</sup>

The low calculated barrier obtained for the oxidative addition pathway is rather unexpected from an experimental viewpoint. With such a low barrier, the reaction should proceed rapidly even below room temperature, whereas the standard protocol calls for a temperature of 135 °C, and even our most reactive system (in neat DMEDA) requires 65 °C.<sup>[75]</sup> To reconcile the temperature requirement with our current computational results, it is reasonable to assume that formation of the DMEDA–Cu–pyrrolide complex constitute an unfavorable equilibrium that necessitates both the high reaction temperatures and the high DMEDA concentration. The alternative, that formation of the reactive complex in itself is rate-limiting, can be excluded by the positive reaction order observed for the aryl iodide.<sup>[75]</sup> We can thus conclude that the reactive complex depicted in Figure 5 partakes in an equilibrium with a resting state, and that this equilibrium is facilitated by DMEDA even if in 2000-fold excess. In addition to acting as a mass-transfer mediator in this equilibrium process, we cannot exclude other roles of DMEDA, such as promoting the displacement of deactivating ligands on Cu (e.g., iodide or excess nucleophile).

#### Conclusions

Cu-catalyzed C-N cross coupling utilizing "trace amounts" of catalyst are to date restricted to aryl iodides and sp<sup>2</sup>-hybridized N-containing substrates, such as pyrrols and amides. By careful exclusion of contaminants, it was possible to show that the reaction does not run in the complete absence of copper, but is highly effective with only ppm levels of Cu salts. At these very low loadings, it is highly unlikely that any other metal could be present in amounts high enough to allow the observed catalysis. One of the few metals that has been shown to work at ppb levels is Pd,<sup>[89,90]</sup> which, however, was found to be incompetent under the present conditions in which Cu is hyperactive. The specific reaction studied was found to be limited by mass transfer of the heterogeneous base, possibly in combination with inadequate mass transfer of the potassium salt of the deprotonated heteroaromatic substrate. The diamine additive dimethylethylenediamine (DMEDA) is believed to act as a mass-transfer promoter, accelerating the reaction rate even at a 2000-fold excess. Liu and co-workers have shown that using soluble organic bases and more polar solvents promotes the reaction efficiently at room temperature utilizing high-[Cu] regime conditions.<sup>[55]</sup> This observation not only lends support to the conclusions presented here, but it also provides a starting point for further development of the submol% Cu catalyzed C-N cross-coupling methodology.

From the Hammett study, we can exclude a single-electrontransfer (SET) mechanism, and also cast severe doubts on the atomic-transfer (AT) mechanism. The DFT results gives further evidence against these proposals as well as the  $\sigma$ -bond metathesis mechanism, but instead supports a classical oxidative addition/reductive elimination mechanism. The collective results indicate that the rate-limiting step of the reaction includes both the formation of the apparent reactive intermediate, a DMEDA-Cu<sup>I</sup>-nucleophile complex, and the subsequent oxidative addition, also found in previously published works by Zhang et al.,<sup>[78]</sup> as well as Lefèvre et al.<sup>[82]</sup> As a final remark, it is evident from this study, and in light of previous published works by several research groups, that the reaction mechanism is highly dependent on ligand, aryl halide, and nucleophile. Most probably, the mechanism of these reactions does not involve radical intermediates or biradical-type transition states.

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#### **Experimental Section**

#### General

All the experiments were performed under inert atmosphere (nitrogen). CuCl<sub>2</sub> (Aldrich, purity of 99.999% metal basis), K<sub>3</sub>PO<sub>4</sub> (98%), and pyrazole (98%) were stored under air- and moister-free conditions. DMEDA, iodobenzene, and dodecane were distilled over calcium hydride. The toluene was dried over calcium and stored under nitrogen. A gas chromatograph with flame ionization detector and a 30 m–0.25 mm EQUITY-5 fused-silica capillary column was used, with hydrogen as a carrier gas. General temperature program: 100 °C for 14 min, then up to 300 °C at 50 °C min<sup>-1</sup> for 4 min. Dodecane was used as an internal standard.

# Procedure for starting the reaction with the reaction components

The general reaction were as follows; pyrrole (140  $\mu$ L, 2 mmol, 1 equiv.), K<sub>3</sub>PO<sub>4</sub> (849 mg, 4 mmol, 2 equiv.), CuCl<sub>2</sub> (40  $\mu$ L, 5 mM in dry THF, 0.01 mol%), toluene (2 mL), DMEDA (21.5  $\mu$ L, 0.20 mmol, 10 mol%), iodobenzene (334  $\mu$ L, 3 mmol, 1.5 equiv), and dodecane (50  $\mu$ L, 0.22 mmol). Starting with pyrrole: a microwave vial was charged with K<sub>3</sub>PO<sub>4</sub>. The vial was sealed and the CuCl<sub>2</sub> solution was added. The THF was removed by three cycles of vacuum followed by nitrogen, whereupon toluene, DMEDA, iodobenzene, and dodecane were added. The vial was placed in a preheated aluminum block at 135 °C and pre-equilibrated for 30 min. After 30 min, the pyrrole was added. Samples (50  $\mu$ L) were collected at certain time intervals, filtered through a small silica plug, and analyzed by GC. The GC yield was determined by using dodecane as an internal standard. The same starting procedure was repeated for iodobenzene, DMEDA, and CuCl<sub>2</sub>.

#### Procedure for the competitive Hammett study

Pyrazole (136 mg, 2 mmol, 1 equiv.),  $K_3PO_4$  (849 mg, 4 mmol, 2 equiv.), and, if solid, *para*-substituted iodobenzene (1.5 mmol, 0.75 equiv.) were added to a microwave vial. The sealed vial was charged with CuCl<sub>2</sub> (40 µL, 5 mM in dry THF, 0.01 mol%). The THF was removed by three cycles of vacuum followed by nitrogen. Subsequently, toluene (2 mL), DMEDA (43 µL, 0.40 mmol, 20 mol%), iodobenzene (167 µL, 1.5 mmol, 0.75 equiv.), if liquid, *para*-substituted iodobenzene (1.5 mmol, 0.75 equiv.), and dodecane (50 µL, 0.22 mmol) were added. The vial was placed in a preheated aluminum block at 135 °C. Samples were collected (50 µL) on certain time intervals (30, 60, 90, 120, 240, 360, and 480 min), filtered through a small plug of silica, and analyzed by GC. Dodecane was used as internal standard.

#### **Computational details**

All geometries were optimized by using the dispersion-corrected DFT functional B3LYP-D3<sup>[91-94]</sup> together with the LACVP\* basis set in Jaguar.<sup>[95]</sup> LACVP\* uses 6-31G\* for the light atoms, and the Hay–Wadt ECPs with accompanying basis sets for copper<sup>[96]</sup> and iodine.<sup>[97]</sup> Frequency calculations were used for verifying the nature of stationary points, as well as for calculating free energy corrections. Solvation contributions to the free energy were calculated at the final geometries using the PBF continuum method<sup>[98,99]</sup> with parameters for benzene. Unless otherwise stated, all energies reported herein are free energies.

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**Keywords:** copper · cross-coupling · density functional calculations · kinetics · N ligands

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## **FULL PAPERS**

A dash of copper: The submol% copper catalyzed C–N bond formation has been studied by kinetic and DFT methods. DMEDA acts as a facilitator for mass transfer, as well as a ligand. Oxidative addition leads to a Cu<sup>III</sup> intermediate undergoing facile reductive elimination.



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Mechanistic Aspects of Submol%