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Effect of steric hindrance of N-heterocyclic carbene in a copper complex on the efficiency of the Chan–Evans–Lam reaction proceeding

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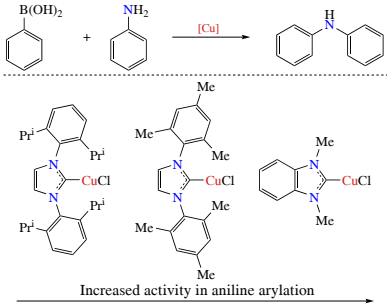
This work investigates the effect of the steric hindrance of the NHC ligand in the NHC–CuCl complex on the Chan–Evans–Lam reaction between $PhB(OH)_2$ and $PhNH_2$ affording Ph_2NH. The primary reaction products of $PhB(OH)_2$ with NHC ligands such as BIMe, IMes, and IPr were obtained for the first time, showing that reducing steric hindrance improves the yield of Ph_2NH and decreases side reactions. However, complete absence of steric shielding around copper prevents product formation.



Keywords: NHC carbene, Chan–Evans–Lam reaction, cross-coupling, arylation, steric hindrance.

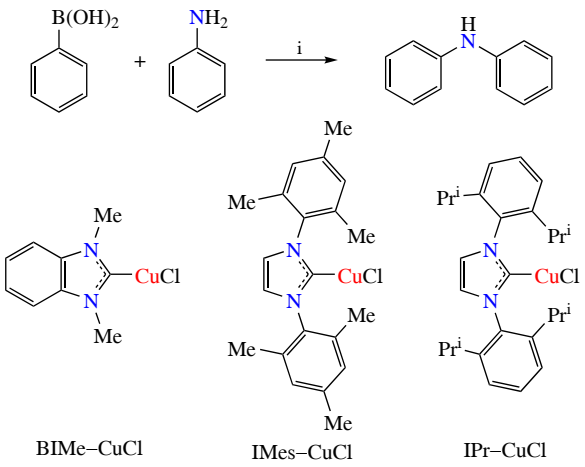
N-Heterocyclic carbenes (NHCs) have found widespread use in metal complex catalysis.[1–4] The stability in air, high binding energy to metals, ease of preparation, and structural variability allow the ligand to be precisely tuned for specific catalytic systems.[5,6] Palladium and nickel complexes are notable examples of metals with NHC ligands, although there are numerous other examples across the Mendeleev Periodic Table.[7] Due to the high strength of the metal–NHC (M–NHC) bond, which ranges from about 50 to 80 kcal mol^{-1} depending on the metal and ligand,[8–10] it is generally assumed that this bond is preserved in catalytic systems and that species containing the NHC–M moiety are catalytically active. However, recent mechanistic studies have questioned the stability of the M–NHC bond as the sole determining factor for catalytic activity. In 2017, the dynamic interplay between homogeneous and nanoscale pathways was demonstrated, providing insights into the origins of high catalytic performance.[11]

Studies of M/NHC catalytic systems have revealed two operational modes: NHC-connected and NHC-disconnected catalysis.[12] In the NHC-connected catalysis, the catalytically active species contains a covalently bound NHC–M fragment.[13,14] In contrast, NHC-disconnected catalysis involves the initial breaking of this bond resulting in the formation of ionic NHC compounds, followed by dynamic rearrangements.[15] These dynamic transformations proceed through various pathways, including the formation of new metal complexes, clusters, and nanoparticles, as well as the leaching and dissolution of metal clusters and nanoparticles through interactions with reactants and solvents.[11]

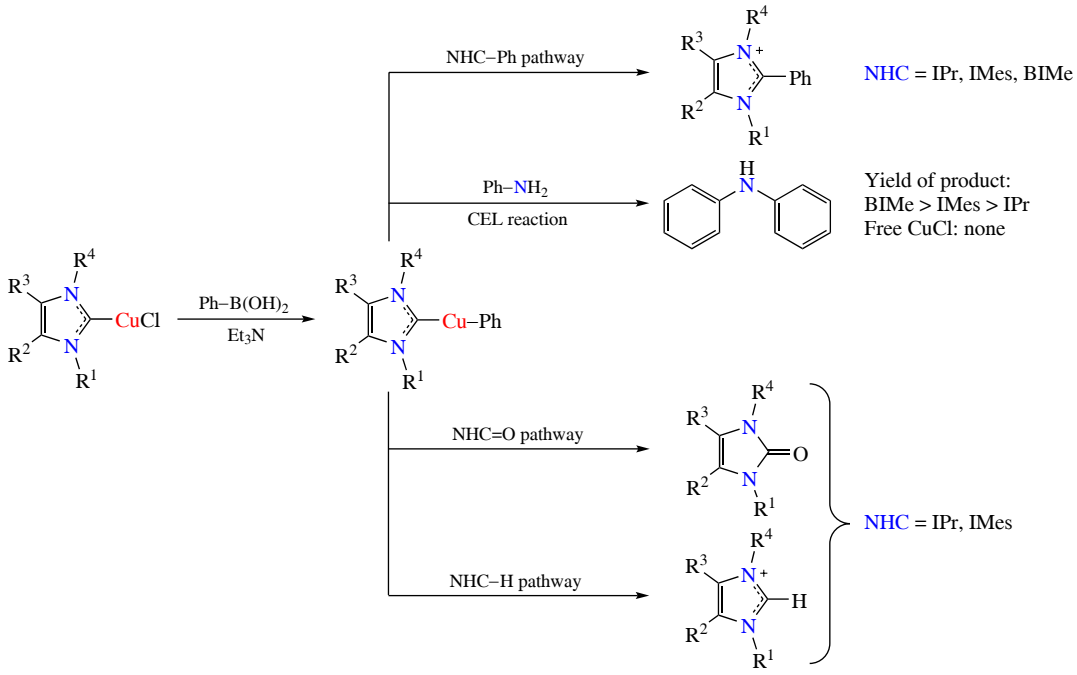
The phenomenon of cocktail-type catalysis in dynamic system was discovered and formulated in 2012[16] and conceptualized to several catalytic systems.[11,17] The cocktail-type behavior was also found in the metal/NHC systems[12] with a great influence on the reaction mechanism. Previously, we have shown the dynamic nature of the catalytic system of the Chan–Evans–Lam reaction (CEL reaction) in the arylation of aniline with the use of Cu/NHC complexes.[18] Copper-containing intermediates of the catalytic reaction were recorded by mass spectrometry, and Cu nanoparticles were detected by electron microscopy. In this work, we have deepened our understanding of the mechanism of this reaction and demonstrated the balance between the steric loading of the NHC ligand in the Cu/NHC complex and the activity of this complex.

We compared the catalytic activity of three complexes of the NHC–CuCl species on the example of the reaction between phenylboronic acid and aniline affording diphenylamine (Scheme 1).

Despite literature reports on the catalytic role of NHC–Cu species in the CEL reactions, our results indicate that under the examined conditions these complexes exhibit only limited efficiency, with product yields ranging from 1.5% (IPr) to 7.5% (IMes), and near-equimolar conversion for BIMe. We discuss potential reasons for this discrepancy, including alternative



Scheme 1 *Reagents and conditions*: i, Cu/NHC (0.1 equiv.), Et_3N, CH_2Cl_2, room temperature, 12 h.



Scheme 2

pathways for NHC ligand degradation, the competitive formation of NHC–Ph species, and the possibility of different mechanistic routes depending on reaction conditions. Copper-catalyzed arylation of anilines in some cases requires copper loading above one equivalent for preparative synthesis,[19] but such amounts are not required to study the mechanism; in addition, excess metal may adversely affect the performance of contact methods such as HRMS used in this work. Therefore, we limited ourselves to 10 : 1 ratio of reactant/Cu with parallel registration of the product by ^{1}H NMR to prove the catalytic activity of the system. It turned out that the catalytic activity strongly depended on the type of NHC-ligand and decreased as its steric loading increased. Based on the reactant/complex ratio, it is obvious that Cu/NHC is a reagent rather than a catalyst. At the same time, completely free CuCl showed no activity under the same conditions, which was in good agreement with earlier works.[20] This fact seemed significant to us, and we set about analyzing the phenomena occurring in the system to describe their influence on the activity in the reaction.

Mass spectrometry (ESI-HRMS) confirms the presence of NHC–Ph ions, supporting the hypothesis that phenylboronic acid participates in an unexpected side reaction with the NHC ligand. This raises questions about the stability and reactivity of NHC–Cu species in cross-coupling chemistry. Furthermore, we re-evaluate the possible formation of the NHC–Cu–Ph intermediate, originally proposed based on prior studies. While reference[21] suggests its formation *via* an NHC–Cu–OBu^t pathway, our experimental results do not confirm its direct appearance under the current conditions, necessitating further investigation into alternative mechanistic possibilities. Indeed, analysis of the reaction system by ESI-HRMS showed that ions of the NHC–Ph species were present in the system, which meant that phenylboronic acid also acted as an arylating agent for the NHC-ligand, which negatively affected the outcome of the target reaction. In addition to NHC–Ph coupling products, azolones IMes=O and IPr=O were detected. Interestingly, ligand BIMe which showed the highest activity did not form azolones, and only in this case no NHC–H ions were detected. We may hypothesize several competing pathways for the reaction (Scheme 2). Our findings underscore the need for optimized reaction conditions and a deeper understanding of NHC–Cu-mediated transformations. By refining experimental parameters and elucidating mechanistic pathways, we aim to clarify the role of these complexes in the CEL chemistry and related catalytic processes.

The first step involves the rapid substitution of chlorine for phenyl, after which the resulting intermediate is consumed through four major transformation pathways. This step is likely accomplished *via* the NHC–Cu–OH intermediate, where the complex has reacted with water that may have originated from phenylboronic acid. The first pathway is the passage of the NHC–Ph combination, which is observed for all NHC ligands. The pathway of degradation of the Cu/NHC complex by the action of phenylboronic acid through the formation of the NHC–Ph product has not been previously described in the literature. It is probably responsible for the degradation of the strong NHC–Cu bond under mild conditions at room temperature, since the high energetic cost of bond breaking is compensated by the strength of the formed C–C bond. The second pathway is the CEL reaction with aniline. The third pathway is the formation of azolone in the case of the most sterically crowded NHC-ligands, IPr and BIMe, as well as the fourth pathway for the same ligands is the formation of the product NHC–H. From the experimental observations, it can be concluded that pathway *1* is common to all systems. Pathways *2*, *3*, and *4* compete with each other, and blocking the NHC=O and NHC–H pathways should promote the accumulation of the target product of the CEL reaction in the system, as can be seen from the data analysis for BIMe. Despite the equimolar Cu/NHC loadings required to produce the product, which does not allow us to call this reaction catalytic, it can be concluded that the influence of the NHC ligand nature is important. The activation reaction itself is NHC-unbound, but the use of free CuCl without ligand does not result in product formation, making NHC participation necessary for the activation of the reaction.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7700.

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