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Well-Defined Copper(I) Amido Complex and Aryl Iodides Reacting to Form Aryl Amines

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Summary: The Cu^{I} complex (IPr)Cu(NHPh) {IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene} reacts with aryl iodides to form diaryl amine products and (IPr)Cu(I), which was confirmed by independent synthesis and characterization. For the reaction with iodobenzene, the products are diphenylamine and aniline. Protection of the hydrogen para to the iodo functionality with ortho-methyl groups results in quantitative conversion to diaryl amine. Combined computational and experimental studies suggest that C−N bond formation most likely occurs via an oxidative addition/reductive elimination sequence.

Copper-mediated Ullmann-type reactions are among the oldest and most widely utilized catalytic processes available to organic chemists. In recent years, there has been a resurgence of interest in such reactions, and several groups have developed methods for aryl amination using Cu salts as catalysts.[1−10] In contrast to the well-defined and tunable Pd catalysts,[11−13] many systems for Cu catalysis involve mixtures of Cu salts and ligands. Thus, studies based on the reaction of isolable and well-defined Cu−amido complexes with aryl halides have not been possible. By analogy with Pd-based reactions, copper amido intermediates are possible; however, catalytic cycles analogous to Pd that involve C−halide oxidative addition would form rarely observed Cu^{III} intermediates.[14−17] Taillefer et al. have recently studied the role of a tetradentate nitrogen-based ligand on arylation reactions;[18] however, these studies did not identify Cu intermediates in the catalytic cycle. In addition, Paine disclosed a detailed comparison of homogeneous and heterogeneous copper catalysts for transformations of Li amides that suggests the formation of an unobserved "cuprous nucleophile species, Ph_2NCu" that reacts with iodobenzene,[19] but observation of Cu amido systems was not reported. A kinetic and spectroscopic study of Cu-catalyzed amidation of aryl iodides, a reaction that is potentially related to aryl amination, indicated a Cu^{I} amidate as an intermediate. In these studies, the Cu^{I} amidate was observed by NMR spectroscopy but not isolated.[20] Hartwig et al. have studied a range of Cu amidate systems and concluded that amidation of aryl halides likely occurs through C−X oxidative addition,[21] and more recently Giri and Hartwig have reported a mechanistic study of Cu^{I} amido complexes reacting with iodoarenes.[22]

Although Cu amido complexes have been implicated in Cu-catalyzed C−N bond formation, to our knowledge a well-defined monomeric Cu amido complex has not been previously demonstrated to react with an aryl halide to give an amine product. In fact, isolation of monomeric Cu complexes with a terminal amido ligand (i.e., amido is not part of a chelate and is not bridging) is rare, with only three examples of such systems.[23−26] Herein, we report the conversion

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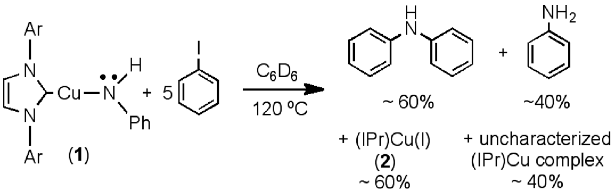
of a fully characterized monomeric Cu^I−anilido complex and aryl iodides to amine products.

We recently reported the preparation, isolation, and full characterization (including solid-state structure) of the monomeric anilido complex (IPr)Cu(NHPh) (**1**) [IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene].[27] The stoichiometric reaction of **1** with 5 equiv of PhI in C_6D_6 (120 °C, 4 h) leads to the formation of diphenylamine (~60%), aniline (~40%), (IPr)Cu(I) (**2**) (60%), and a second uncharacterized (IPr)Cu system in ~40% yield (eq 1). Performing this reaction with PhI-d_5 produces Ph_2NH-d_5 (determined by GC/MS analysis). Multiple attempts to characterize the second Cu complex from the reaction of (IPr)Cu(NHPh) (**1**) and PhI were unsuccessful. We independently prepared and fully characterized complex **2**, including a solid-state X-ray structure (Supporting Information), by reaction of free IPr and Cu^I iodide. In contrast to the reaction with iodobenzene, heating complex **1** and PhOTs (OTs = tosylate) to 120 °C in C_6D_6 for 20 h results in no apparent formation of diphenylamine. Complex **1** can be heated in C_6D_6 at 120 °C for at least 24 h without evidence of aniline production. Thus, the production of aniline from **1** and PhI is not likely due to thermal decomposition.

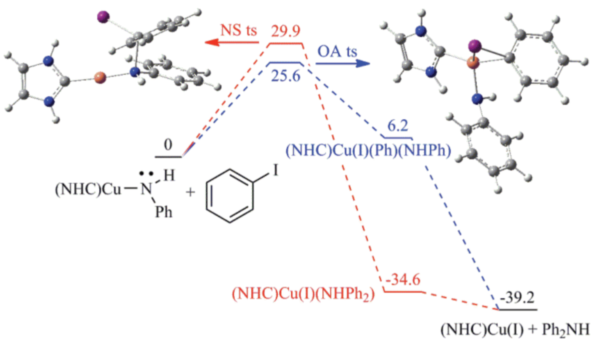


(1)

We posit that an initial Cu−N_{amido} bond homolysis to give aniline radical is unlikely for formation of aniline from the reaction of **1** with iodobenzene. No evidence of diphenylhydrazine is observed, which forms with a rate constant of $1.5 \times 10^9\ M^{-1}\ s^{-1}$ from the aminyl radical in water.[28] In addition, previous computational studies of complex **1** reveal that the Cu−N_{amido} BDE is 87 kcal/mol, and experimental studies support the calculated strong Cu−N bond.[24] Furthermore, if Cu−N bond homolysis were responsible for aniline production, we anticipate that reaction of **1** with 1-iodo-3,5-dimethylbenzene would produce some aniline; however, aniline is not observed in this reaction (see below). Finally, we attempted to trap the putative aniline radical. Given the N−H BDE of aniline of 92 kcal/mol and the C−H BDE of 1,4-cyclohexadiene (CHD) of 76.5 kcal/mol,[29] the formation of aniline radical in the presence of CHD should give aniline and benzene. Heating **1** in C_6D_6 to 120 °C in the presence of 5 equiv of CHD does not produce free aniline or additional protio benzene after 4 h.

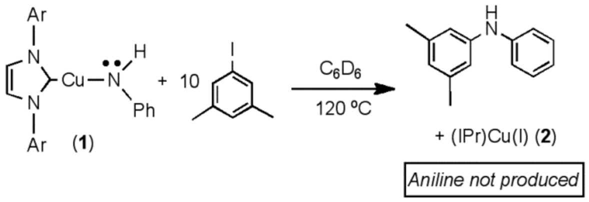
The production of aniline (40%) from the reaction of **1** and PhI suggests the possibility that an aromatic C−H bond is cleaved (regardless of the specific mechanism).[30] We suspected that the iodide functionality might be providing electronic activation for the *para*-C−H bond of iodobenzene. To test this possibility, we reacted complex **1** with 10 equiv of 1-iodo-3,5-dimethylbenzene, for which the C−H bond *para* to the iodide functionality is sterically protected by the methyl groups. This stoichiometric reaction cleanly produces (IPr)Cu(I) (**2**) and the corresponding aryl amine *without production of aniline* (eq 2).

Scheme 1. DFT-calculated ΔG's (kcal/mol, 298 K)[a]

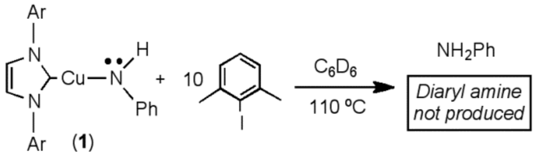


[a] OA = oxidative addition, NS = nucleophilic substitution, ts = transition state.

The reaction of complex **1** and 1-iodo-3,5-dimethylbenzene to produce only diaryl amine (and no aniline) suggests that steric protection of the *iodo* functionality should increase the production of aniline. Indeed, the reaction of (IPr)Cu(NHPh) (**1**) and 10 equiv of 1-iodo-2,6-dimethylbenzene produces aniline without observation of diaryl amine (eq 3).



(2)



(3)

Of primary interest is the mechanism for (IPr)Cu(NHPh) + ArI → (IPr)Cu(I) + diarylamine. As a probe of possible pathways, we studied the conversion of **1** and PhI using DFT with the parent NHC ligand at 298 K. Several different pathways were studied (see Supporting Information), with two emerging as most likely from calculated energetics (Scheme 1). Utilizing a benzene solvation model, calculations indicate that PhI coordination to complex (NHC)Cu^I(NHPh) is endergonic by 0.7 kcal/mol. An oxidative addition (OA) to form (NHC)Cu^{III}(I)(Ph)(NHPh) was calculated to occur with $\Delta G_{OA}^{\ddagger} = 25.6$ kcal/mol relative to separated PhI and (NHC)Cu^I(NHPh), which is similar to the calculated $\Delta G^{\ddagger}$ of 25 kcal/mol for a Cu amidate system.[21] This leads to an *endergonic* Cu^{III} product with $\Delta G_{OA} = 6.2$ kcal/mol for the most stable geometric isomer. Reductive elimination of Ph_2NH from (NHC)Cu^{III}(I)(Ph)(NHPh) to give (NHC)Cu(I) and free Ph_2NH is calculated to have a small $\Delta G^{\ddagger}$ of 11 kcal/mol.

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A second plausible mechanism that involves a nucleophilic substitution (NS) of iodide by the anilido ligand has a calculated $\Delta G_{NS}^{\ddagger}$ in benzene of 29.9 kcal/mol relative to separated PhI and (NHC)Cu^{I}(NHPh). The NS transition state leads to a product (NHC)Cu^{I}(I)($NHPh_2$) whose formation is *exergonic* by 34.6 kcal/mol. The (NHC)Cu^{I}(I)($NHPh_2$) intermediate easily rearranges (calculated $\Delta G^{\ddagger} = 0.7$ kcal/mol) to place the iodo ligand *trans* to the NHC ligand and dissociate $NHPh_2$, which is calculated to be a further 4.6 kcal/mol exergonic. Variations of this NS pathway were calculated to be higher energy transformations (see Supporting Information).[19]

The calculated $\Delta G^{\ddagger}$ for conversion of (NHC)Cu(NHPh) and PhI to (NHC)Cu(I) and Ph_2NH by an OA pathway is 25.6 kcal/mol. While the calculated activation barrier for the NS route is not substantially greater than the OA route, a $\Delta\Delta G^{\ddagger}$ of 4.3 kcal/mol is sufficiently large to *suggest* the OA pathway. Also, given that OTs is typically a good leaving group for nucleophilic substitutions, the failure of complex **1** to react with PhOTs provides further evidence against the NS mechanism. Although formation of a byproduct in the transformation of **1** and PhI to **2** and Ph_2NH complicates a detailed experimental kinetic analysis of this stoichiometric reaction, we can estimate the half-life for formation of Ph_2NH and **2** at 40 min (120 °C).

An initial electron transfer from **1** to aryl iodide to generate Cu^{II} and a radical anion, followed by iodide elimination and combination of phenyl radical with $[(IPr)Cu(NHPh)]^{+}$, cannot at this point be definitively eliminated from consideration.[31] However, the reaction of **1** with AgOTf rapidly produces diphenylhydrazine and (IPr)Cu(OTf). Thus, the combination of phenyl radical with Cu^{II} would need to occur via a rapid recombination event.

The fully characterized Cu complex **1** reacts with aryl iodides to give aryl amine products, which provides direct evidence that a Cu amido can react with aryl halide to produce arylamine. Although more detailed experiments are required to provide complete details, our preliminary experimental/computational studies suggest a pathway that involves oxidative addition to form a Cu(III) intermediate to be the most reasonable route.

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Supporting Information Available: Details of experiments and calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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