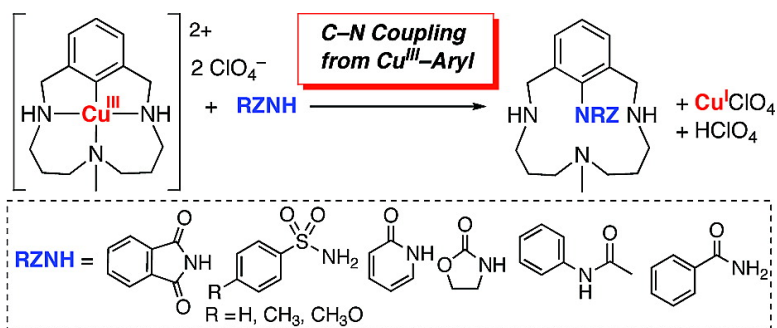


Carbon#Nitrogen Bond Formation Involving Well-Defined Aryl#Copper(III) Complexes

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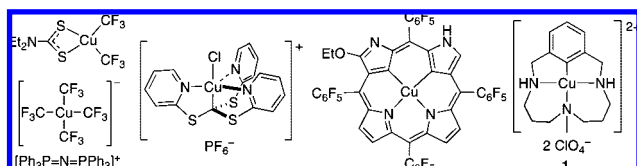
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Copper-mediated carbon–carbon and carbon–heteroatom coupling reactions have been known for more than 100 years;^{1,2} however, these reactions have been overshadowed by the scope and versatility of analogous Pd-catalyzed coupling methods. The dramatic success of Pd catalysis can be attributed, in part, to the availability of sophisticated insights into the fundamental organometallic chemistry of palladium, including knowledge of the reactivity of organopalladium complexes in oxidation states ranging from Pd⁰ to Pd^{IV}. Fundamental studies of organocopper chemistry could play a similar role in Cu catalysis, yet the organometallic chemistry of copper in oxidation states higher than +1 is almost completely unexplored.³ Only a small number of structurally characterized organo-copper(III) complexes are known (Chart 1),⁴ and no studies of their reactivity toward C–C or C–X bond formation have been reported. Here, we present the first reactions of this type and provide preliminary mechanistic insights into C–N bond-forming reactions that arise from the reaction of arylcopper(III) complexes with neutral carboxamides and related nucleophiles. These observations complement recent in situ spectroscopic studies that provide evidence for alkylcopper(III) intermediates in reactions of organocuprates,⁵ and they provide an important starting point for characterization of the fundamental organometallic chemistry of copper(III).

Chart 1. Examples of Well-Defined Organometallic Cu^{III} Complexes



Aryl amination reactions are among the most widely used Cu-catalyzed coupling reactions,^{2,6,7} and arylcopper(III) species are commonly speculated as intermediates in these reactions.² Cu^{III}–aryl complex **1**, originally reported by Llobet, Stack, and co-workers,^{4d} drew our attention because it features a Cu–C_{aryl} bond within a square-planar Cu^{III} coordination environment that resembles the proposed intermediates in C–N coupling reactions.^{2c} This recognition prompted us to investigate whether **1** could react with nitrogen nucleophiles commonly employed in copper-catalyzed aryl–amination reactions.

Reactions between **1** and amide-type nitrogen nucleophiles proved to be very facile. Addition of pyridone (**2a**) to a solution of **1** in acetonitrile resulted in a color change of the solution from orange to colorless within minutes at ambient temperature. Conversion of **1** to a single ligand-derived product was evident from the ¹H NMR spectrum of the crude reaction mixture (Figure 1), and full characterization of the product by NMR spectroscopy (¹H, ¹³C, 2D NOESY), mass spectrometry (ESI-MS), and X-ray crystallography established the product as the *N*-aryl pyridone C–N coupling product **3a**. The Cu^I byproduct, [Cu(NCMe)₄]ClO₄, was also isolated from the reaction mixture.

The reaction of phthalimide (**2b**) with **1** (eq 1) proceeded at a rate somewhat slower than that with pyridone, enabling the reaction kinetics to be monitored conveniently by ¹H NMR and UV–visible spectroscopy.

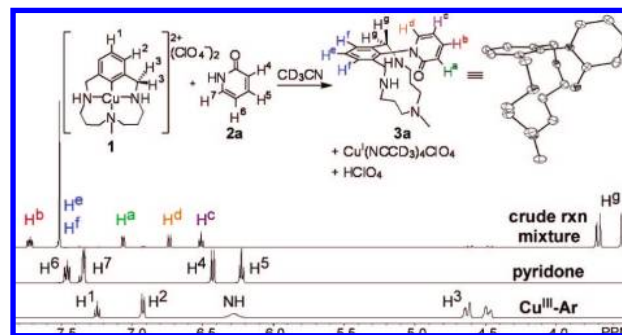


Figure 1. ¹H NMR spectra of the Cu^{III}–aryl complex **1** (bottom), pyridone (middle), and the crude product mixture obtained upon mixing **1** and pyridone in a 1:1 ratio (top).

The rate exhibited a first-order dependence on both [**1**] and [phthalimide] (Figure 2). No evidence was obtained for kinetic saturation in [phthalimide] up to 50 equiv of the nucleophile, and no intermediate was detected in the reaction. Activation parameters for the reaction were obtained by monitoring the rate at different temperatures (20–60 °C): $\Delta H^\ddagger = 13.3 \pm 0.3 \text{ kcal} \cdot \text{mol}^{-1}$ and $\Delta S^\ddagger = -17 \pm 2 \text{ cal} \cdot \text{mol}^{-1} \cdot \text{K}^{-1}$.

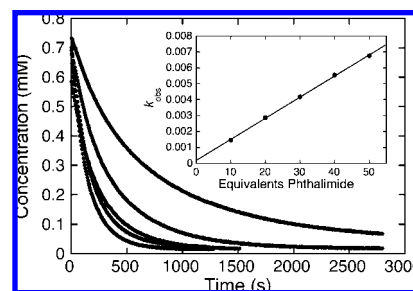
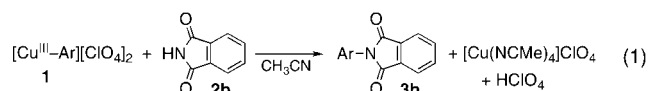
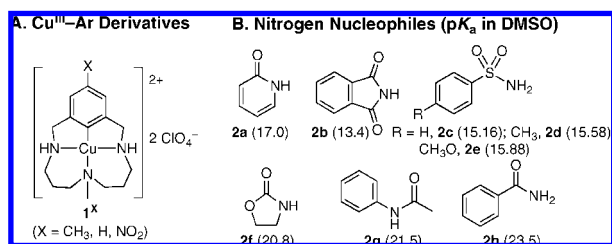


Figure 2. Kinetic study of the reaction of Cu^{III}–aryl complex **1** with phthalimide. Reaction conditions: [**1**] = 0.8 mM, [nucleophile] = 8.0–40 mM, CH₃CN, 30 °C.

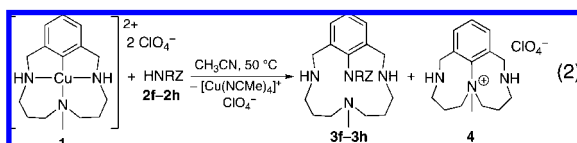
Cu^{III}–aryl derivatives **1^X** (X = CH₃, H, NO₂; Chart 2A),⁸ were used to evaluate electronic effects on the relative rates of the net C–N bond-forming reaction. All three analogues reacted cleanly with phthalimide to yield the C–N coupling product, and the reaction of the electron-deficient derivative **1^{NO2}** proceeded significantly more rapidly than the reactions of **1^H** and **1^{CH3}**: *t*_{1/2} = 5 min (**1^{NO2}**) versus 82 and 115 min (**1^H** and **1^{CH3}**, respectively).⁹ Although the precise mechanism of the C–N bond-forming step is not yet known, these results are consistent with the expectation that more-electrophilic Cu^{III}–aryl species should react more rapidly with nitrogen nucleophiles.

Electronic effects associated with the nitrogen nucleophile were examined by monitoring the reaction of **1** with nucleophiles that vary

Chart 2. Substrates Used to Probe Electronic Effects



with respect to the acidity of the N–H bond, $pK_a(\text{DMSO}) = 13.4\text{--}23.3$ (Chart 2B). Reactions with each of the substrates **2a–h** exhibited pseudo-first-order kinetic behavior over >4 half-lives in the presence of excess nucleophile (≥ 10 equiv). Nucleophiles **2a–e** produced the corresponding C–N coupling products **3a–e** in quantitative yield. The remaining nucleophiles **2f–h**, which have less-acidic N–H bonds, reacted more slowly, and yielded two different products: the intermolecular C–N coupling products **3f–h** together with an intramolecular C–N coupling product **4**, arising from an unusual trans C–N reductive elimination reaction (eq 2). The latter product formed quantitatively upon heating a solution of the arylcopper(III) complex **1** in the absence of added nucleophile.¹⁰



A rough correlation is evident between the logarithm of the pseudo-first-order rate constant for intermolecular C–N coupling and the pK_a of the nitrogen nucleophile (not including pyridone; Figure 3). The negative slope evident in this plot indicates that more-acidic substrates (those with lower pK_a values) react more rapidly. This correlation is opposite to that expected if the bimolecular rate law (see above) arises from a reaction of the neutral amide with the Cu^{III} –aryl species. Substrates with lower pK_a values should be less coordinating and/or nucleophilic and, therefore, react more slowly. Instead, the trend suggests that the nitrogen nucleophile undergoes deprotonation before (or in) the rate-limiting step of the reaction. The anomalously rapid rate observed with pyridone may reflect the fact that pyridone has a readily accessible tautomer, 2-hydroxypyridine (eq 3),¹¹ which may be capable of reacting without prior substrate deprotonation.

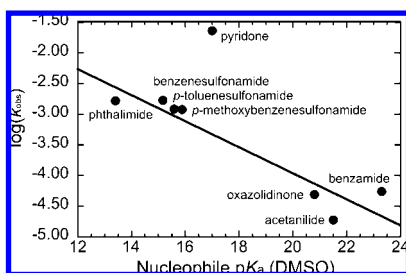
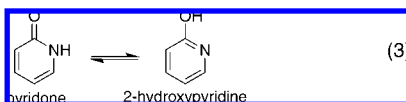


Figure 3. Correlation between the rate of intermolecular C–N bond formation and the acidity of the nitrogen nucleophile. Reaction conditions: $[1] = 0.8$ mM, $[\text{nucleophile}] = 8.0$ mM, CH_3CN , 50 °C.



The kinetic data and electronic effects obtained for these reactions are consistent with at least two different mechanisms for C–N bond formation:

(1) a three-centered C–N reductive elimination from an (unobserved) Cu^{III} (aryl)(amidate) intermediate or (2) bimolecular nucleophilic attack of an amidate on the ipso carbon of the aryl ligand.¹² Further studies will be necessary to distinguish between these possibilities and to address other open mechanistic questions, including the identity of the base that participates in amide deprotonation and the origin of deviations from linearity in the Brønsted plot (Figure 3).¹³

The results of this study reveal the extraordinary reactivity of the Cu^{III} –aryl fragment: C–N bond formation is facile despite stabilization of the Cu–aryl ligand within a macrocyclic chelate and the use of neutral amide-type substrates that are only weakly nucleophilic. That reactions of this type have not been described previously, despite the century-long history of Cu-mediated coupling reactions, highlights the dearth of fundamental insights into the organometallic chemistry of copper. Further characterization of the reactivity of high-valent organocopper species should play an important role in the ongoing discovery and development of copper-catalyzed reactions.

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Supporting Information Available: Experimental procedures and kinetic and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- See section 1 of the Supporting Information for further details.
- In acetonitrile at 25 °C, the pyridone tautomer is more stable than 2-hydroxypyridine by approx 3 kcal/mol: Frank, J.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1428–1431.
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- The deviations do not appear to reflect a major change in the reaction mechanism. The reaction of benzamide, a slow nucleophile, exhibits bimolecular reaction kinetics and a negative ΔS^\ddagger (-9.4 ± 2.5 eu), similar to that observed with phthalimide, and more-acidic benzamide derivatives (i.e., 4-Br and 4- NO_2) react more rapidly than benzamide (see section 2 of the Supporting Information for details).

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