

HIGH-VALENT COPPER CATALYSIS

Reported by Hannah M. S. Haley

December 6, 2012

INTRODUCTION

Copper reagents have been widely utilized for over a century, mainly in the construction of carbon-carbon and carbon heteroatom bonds.¹ Despite a long history of application, the fundamental organometallic chemistry of copper remains largely ambiguous or unexplored. A dearth of knowledge concerning the basic mechanistic details of Cu-mediated reactions, such as the oxidation state of the metal throughout the process, has rendered reaction optimization and the development of novel Cu-catalyzed transformations difficult. High-valent Cu(III) species have been hypothesized as viable intermediates in cross-coupling and organocuprate reactions, yet the isolation or definitive characterization of such complexes has remained elusive. Recent advances in the field have begun to offer evidence for the intermediacy of such high valent species. Furthermore, a host of new methodologies invoking Cu(III) complexes have emerged, validating the continued synthetic utility of copper catalysis and indicating that continued mechanistic insight may play a key role in reaction development.

EARLY CHARACTERIZATION OF COPPER(III) COMPLEXES

The isolation and characterization of a small set of high-valent copper complexes confirmed the viability of the metal in its second highest oxidation state.² While theoretically interesting, these species contain rigid, chelating, and/or electron-donating ligands capable of stabilizing the metal center, and more importantly, were not reported to have reactivity toward bond formation. The application of rapid-injection NMR (RI-NMR) proved instrumental in the direct observation of transient Cu(III) intermediates in reactions of organocuprates with enones, alkyl halides, and allylic electrophiles.³ The capacity of RI-NMR to monitor the reactivity of high-valent organocopper species has allowed for mechanistic interrogation of these systems. It was empirically known that Lewis basic additives increase the yield and/or rate of alkylation reactions. While it was speculated that the additives may function only to increase the solubility of the starting materials or intermediates, others suggested that they may perform a more integral role, binding to the copper to tune the metal's reactive properties. Observation via RI-NMR of Lewis base-bound Cu(III) complexes which displayed disparate stabilities dependent upon the electron-donating ability of the base confirmed the role of the additive in modulating reactivity.⁴

CARBON-CARBON AND CARBON-HETEROATOM BOND FORMATION

The synthesis and characterization of the first isolable Cu(III)-monoaryl species,⁵ later shown competent to undergo C-halide and C-N bond formation,⁶ represented a key advance in the field. The triazamacrocyclic ligand **1** was activated by a copper reagent to generate a square pyramidal Cu(III)-centered species **2** (Figure 1). Intriguingly, the complex displayed the ability to repeatedly interconvert between the oxidative addition and reductive elimination products upon treatment with acid and base, respectively.⁷

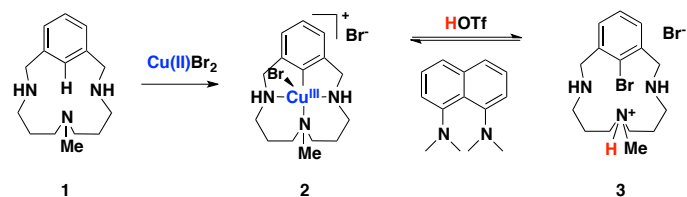


Figure 1: Redox active high-valent copper complex

A recent innovative application of copper catalysis involves electrophilic metalation of a diverse range of substrates using Cu-activated iodonium reagents.⁸ This process is suggested to proceed through a highly electrophilic copper(III) intermediate. In one example, this strategy has been applied for the C-3 selective arylation of indole substrates.^{8a} Perhaps more compelling than the transformation itself is the

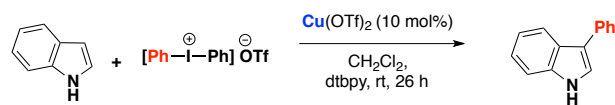


Figure 2: C-3 selective indole arylation

completely divergent C-2 site selectivity seen upon application of a palladium catalyst but otherwise almost identical conditions, suggesting the possibility for similar Cu-Pd site-selective complementarity in other systems.⁹

SUMMARY

Recent mechanistic investigations have confirmed the existence and reactivity of high-valent copper complexes, yet transformations involving such species remain not well understood. Continued study of these species will allow for the rational optimization of known processes and the development of novel reactions involving Cu(III).

REFERENCES

- (1) Krause, N. *Modern Organocopper Chemistry*; Wiley-VCH: Weinheim, Germany, 2002.
- (2) (a) Willert-Porada, M. A.; Burton, D. J.; Baenziger, N. C. *J. Chem. Soc. Chem. Commun.* **1989**, 1633. (b) Furuta, H.; Maeda, H.; Osuka, A. *J. Am. Chem. Soc.* **2000**, *122*, 803 (c) Santo, R. et al. *Angew. Chem. Int. Ed.* **2006**, *45*, 7611.
- (3) (a) Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A.; Taylor, B. J. *J. Am. Chem. Soc.* **2007**, *129*, 7208. (b) Gartner, T.; Henze, W.; Gschwind, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 11362. (c) Bartholomew, E. R.; Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A. *J. Am. Chem. Soc.* **2008**, *130*, 11244.
- (4) Bartholomew, E. R.; Bertz, S. H.; Cope, S.; Dorton, D. C.; Murphy, M.; Ogle, C. A. *Chem. Commun.* **2008**, 1177.
- (5) Ribas, X.; Jackson, D. A.; Donnadiou, B.; Mahia, J.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. P. *Angew. Chem. Int. Ed.* **2002**, *41*, 2991
- (6) Huffmann, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196.
- (7) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. *Chem. Sci.* **2010**, *1*, 326.
- (8) (a) Phipps, R. J.; Grimseter, N. P. Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (b) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (c) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260 (d) Bigot, A.; Williamson, A. E.; Gaunt, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13778 (e) Harvey, J. S.; Simonovich, S. P.; Jamison, C. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 13782
- (9) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972.