

Cu-MEDIATED C-N AND C-O CROSS-COUPLING REACTIONS

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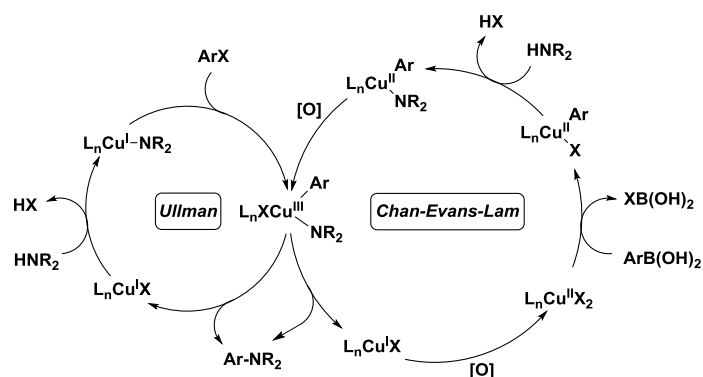
INTRODUCTION

Classical approaches to forming aryl C-N and C-O bonds include nucleophilic aromatic substitution and the copper-mediated Ullman coupling in which a nucleophile is coupled with an aryl halide. However, these reactions require notoriously harsh conditions which lead to greatly limited substrate scope. Despite being some of the oldest known transition-metal mediated reactions, the development of copper-mediated cross-coupling reactions have far lagged behind their palladium counterparts. One likely explanation for this is the relative dearth of fundamental mechanistic understanding of the organometallic chemistry of copper in this context. Recent work¹ has led to copper based methods which proceed under much milder and functional group tolerant conditions, but more importantly, has also inspired a renaissance in efforts to understand the underpinnings of this chemistry and the unique reactivity copper has to offer.

MODERN ULLMAN-TYPE COUPLING

Traditional Ullman coupling is performed in polar solvents (DMF, DMSO), at high temperatures (>150 °C), and without added ligands. The use of ancillary bidentate N and O chelating ligands allows access to a much wider substrate scope and the use of much softer reaction conditions; however, no useful trends in the structural or electronic factors dominating the use of these ligands have emerged. Unlike the frequently rational design of sophisticated phosphine ligands for use in palladium-mediated methods, these systems are usually discovered on an empirical, *ad hoc* basis.

Studies by Buchwald, Hartwig, and Stahl² have begun to elucidate the fundamental steps and chemical species involved in these updated Ullman couplings. Unlike palladium, copper is known to readily undergo one-electron processes; however, all current experimental evidence suggests two-electron chemistry is the dominant process in catalytically relevant systems. While the catalytic cycle of these reactions proceeds through a Cu(I)/Cu(III) redox cycle, akin to the well-known Pd(0)/Pd(II) cycle, the order of steps is actually reversed. First, a ligated Cu(I)X species undergoes ligand exchange with the nucleophilic coupling reagent. This species then undergoes oxidative addition with an aryl halide to generate a Cu(III) species which rapidly reductively eliminates, producing product and Cu(I). While subtle differences in the mechanism have been noted depending upon the nucleophilic species, the general scheme holds for amines, amides, imides, and phenoxides.



Scheme 1. Catalytic cycles of the Ullman and CEL cross couplings.

CHAN-LAM AND RELATED CROSS COUPLINGS

In 1998, Chan, Evans, and Lam simultaneously reported the $\text{Cu}(\text{OAc})_2$ -mediated coupling of anilines, phenols, and N-heterocycles with aryl boronic acids.^{3a-c} In stark contrast to even the most modern Ullman couplings, the Chan-Evans-Lam (CEL) coupling proceeds under extremely mild conditions—room temperature and open to the air. This mildness represents a reactivity that is complimentary to that of palladium based methods, and suggests a mechanism that is distinct from that of Ullman couplings. Indeed, the mechanism of this reaction has been shown to proceed through a catalytic cycle encompassing both one- and two-electron processes $[\text{Cu}(\text{II})/\text{Cu}(\text{III})/\text{Cu}(\text{I})]$. Transmetalation of the aryl boronic acid to $\text{Cu}(\text{II})$ has been shown to likely be the rate determining step. Additionally, these reactions have thus far not required the use of external ligands, relying primarily on simple $\text{Cu}(\text{II})$ salts. Oxidation of the resulting $\text{Cu}(\text{I})$ back to the active $\text{Cu}(\text{II})$ species by oxygen has rendered the system catalytic in copper. Despite the dangers associated with the use of oxygen gas, this chemistry has also been used in industry through the safety-conscious optimization of reaction conditions.

Recently, Lalic⁴ and coworkers have demonstrated the utility of $\text{Cu}(\text{I})$ -NHC and $\text{Cu}(\text{I})$ -phosphine complexes in the coupling of aryl and alkyl organoborons with electrophilic aminating reagents. This is distinct from both the Ullman and CEL coupling reactions in both scope and mechanism. These methods allow access to highly hindered aniline and alkyl amine products in good yields. These are motifs which have been very rarely accessed by other methods, and in much lower efficiency. This work also demonstrates the potential for sophisticated ligand scaffolds to control and tune the reactivity of copper, an area of research that will surely be pursued in coming years.

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