

RAPID, ROOM-TEMPERATURE ULLMANN-TYPE COUPLINGS AND AMMONOLYSES OF ACTIVATED ARYL
HALIDES IN HOMOGENEOUS SOLUTIONS CONTAINING COPPER(I) IONS¹

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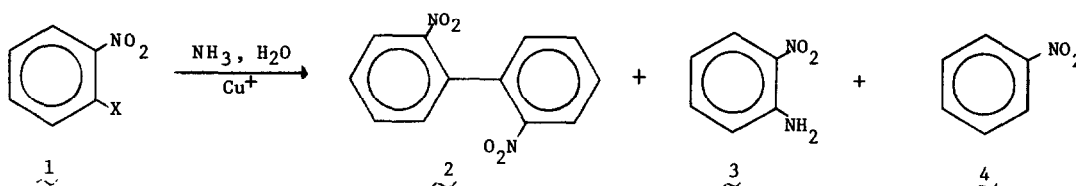
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We have recently provided evidence that the displacement of aromatic halogens by benzoate², halide³, or cyanide³ by use of the corresponding cuprous salts proceeds by arylcopper intermediates. The latter are believed to include arylcopper(III) species formed by oxidative addition of the aryl halide to copper(I)³. The substituent effects reported for such exchanges⁴ are remarkably similar to those reported for the Ullmann biaryl coupling which is usually performed by heating the aryl halide, with or without solvent, to a high temperature in the presence of copper metal.⁵ Furthermore, both reactions proceed via arylcopper intermediates,^{6,7} both occur stereospecifically with retention of configuration when applied to vinyl halides^{7,8} and both can occur without the intervention of radicals.^{3,7,9} It is therefore tempting to suggest that the first step in the Ullmann coupling also involves oxidative addition to copper(I) on the surface of the metal; indeed, pretreatment of the copper with various complexing agents, a process believed to expose the copper(I) on the metal surface, considerably increases the activity of the copper in the Ullmann coupling¹⁰ and solid cuprous oxide is sometimes used successfully in place of the metal^{5,11}

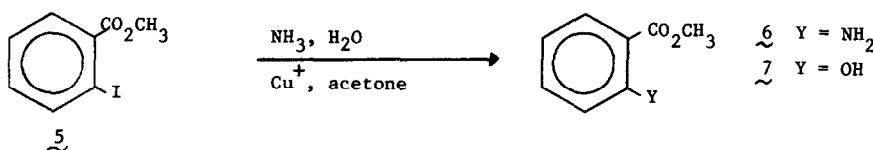
These considerations suggest that Ullmann couplings may be possible in homogeneous media containing copper(I) ions. Copper(I) trifluoromethanesulfonate¹² (triflate) was prepared, undoubtedly as an acetonitrile complex, by heating under nitrogen 1.24 g (2.70 mmol) of the hydrated¹³ copper(II) salt¹² and 2.50 mg atom of copper powder at reflux for one hour in the reaction solvent (25 ml) and enough acetonitrile (1.25 ml) to allow the redox reaction to proceed to completion. There was no perceptible reaction after 24 hours between o-iodonitrobenzene (1; X=I, 0.25 mmol)

and the copper(I) triflate in the following solvents at reflux: acetonitrile, sulfolane, 2-propanol, and acetone. However, when the latter reaction mixture was stirred with 25 ml. of 5% aqueous ammonia, the aryl iodide coupled in less than 5 minutes¹⁴ at room temperature (nitrogen atmosphere) to produce a 92% yield (glpc) of 2,2'-dinitrobiphenyl (2)¹⁵ 1-Iodo-2,4-dinitrobenzene behaved in a similar fashion. With o-iodonitrobenzene isopropyl alcohol or acetonitrile could be used in place of acetone but the reaction was somewhat slower; tetrakisacetonitrilecopper(I) perchlorate¹⁶ was found to be as effective as copper(I) triflate.¹⁷ No reaction occurred during one hour when cuprous oxide was used in place of cuprous triflate or when 1 (X=I) was stirred for one hour in acetone with copper powder at ambient temperature.



o-Bromonitrobenzene (1; X=Br), under the successful conditions described above, was not quite completely used up after 24 hours and only 15% of 2 was produced; the other major product was o-nitroaniline (3). Under reflux conditions, the mixture produced a black precipitate, the yield of biaryl(2) remained the same, and o-nitrophenol (1; X=OH) became the major product. At room temperature, using 20% rather than 5% ammonia, o-nitroaniline was the major product, followed by nitrobenzene (4); very little biaryl was produced.

When methyl o-iodobenzoate (5) was treated at room temperature with cuprous triflate in acetone and 5% aqueous ammonia, the substrate was almost used up after 24 hours and about 80% of methyl anthranilate (6) was produced; the only other product was methyl salicylate (7). The following aryl iodides failed to react at room temperature: p-iodonitrobenzene, o-iodofluorobenzene, o-iodoanisole, iodobenzene.



The reactivity order is identical to that of conventional Ullmann biaryl couplings.⁵ The mildest conditions ever reported for such a reaction are those of o-iodonitrobenzene (1; X=I); a

near quantitative yield of biaryl was produced after 60 hours at 60°. ¹⁸ The present conditions are by far the mildest and the reaction time the shortest for any reported Ullmann coupling; the practical advantage of this procedure is obvious. It is not yet known whether, as in the conventional Ullmann coupling, ⁵ high yields of cross-coupled product can be obtained from a mixture of an activated and an unactivated aryl halide. The coupling reaction nicely complements that of Semmelhack and co-workers ¹⁹ who have found that aryl halides which lack nitro groups can be coupled in good yield by the use of a nickel(0) complex at 33-60° for 11-90 hours. Finally, it should now be possible for the first time to perform kinetic measurements on Ullmann-type couplings in homogeneous solution and thus to probe the mechanism by a more direct technique than methods heretofore available.

The rapidity of oxidative additions is thought to be related to the nucleophilicity of the metal. ²⁰ The relative ineffectiveness of copper(I) when complexed with acetonitrile and its great effectiveness when complexed to ammonia becomes understandable on the basis that the latter ligand is a strong sigma donor while not being capable of accepting d electrons from the metal, whereas acetonitrile is a weak sigma donor and an acceptor of d electrons by backbonding. The apparent catalysis by *n*-octylamine and phenylhydrazine of the coupling of *o*-nitrobromobenzene induced by cuprous oxide in pyridine ¹¹ can possibly be explained in the same way.

The formal nucleophilic displacement of halide in 5 by ammonia at room temperature in one hour is also unprecedented. Copper induced ammonolyses at much higher temperatures are well known; ²¹ these are undoubtedly related to the above mentioned displacement reactions involving cuprous salts. The competition between coupling and ligand exchange (ammonolysis) may be largely controlled by the fact that coupling is of a higher order in aryl species than is the exchange. The coupling may occur between two arylcopper molecules or between one such species and an aryl halide; ⁵⁻⁷ in either case coupling would be favored by more reactive aryl halides and that is what is found here.

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13. The light blue salt obtained after drying in an evacuated desiccator at ambient temperature for one hour analyzed for $C_2O_6S_2F_6Cu \cdot 5.5 H_2O$.
14. The reaction is 85% complete at the end of one minute.
15. A scale-up involving 4.96 g (10.8 mmol) of cupric triflate, 10 mg atoms of copper, 100 ml of acetone, 5 ml of acetonitrile, 10 mmol of aryl iodide, and 100 ml of 5% ammonia led to an 80% isolated yield of biaryl.
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17. With both copper(I) triflate and perchlorate, a small amount of sediment was present during the reaction but did not appear to influence the rate or yield. A completely homogeneous reaction solution could be attained only in the case of the triflate by filtering the acetone mixture of the cuprous triflate in a glove bag under nitrogen, diluting the filtrate with 20 ml of acetone and proceeding in the usual manner.
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