J. Am. Chem. Soc. 1987, 109, 1496–1502

Mechanisms and Models for Copper Mediated Nucleophilic Aromatic Substitution. 2. A Single Catalytic Species from Three Different Oxidation States of Copper in an Ullmann Synthesis of Triarylamines[1]

Anthony James Paine

Contribution from the Xerox Research Centre of Canada, Mississauga, Ontario, Canada L5K 2L1. *Received June 5, 1986*

Abstract: Ullmann condensation of diarylamines with iodobenzenes has been investigated under homogeneous and heterogeneous catalytic conditions with cuprous and curpic salts, as well as powdered copper metal. Copper catalyzed condensation of diarylamines with iodoaromatics is relatively insensitive to substituent (for substituted iodobenzenes $\rho = -0.25$; for substituted diphenylamines $\rho = 1.09$) but quite sensitive to halogen ($k_I/k_{Br} > 200$). The first direct evidence for solution catalysis after filtration of a metal catalyzed reaction was obtained. Quantitative analysis of reaction rates, product yields, and catalyst characteristics leads to a comprehensive picture of the formation of soluble cuprous ion as the single active catalytic species under all conditions investigated. This hypothesis rationalizes many of the perplexing results which typify the literature associated with copper catalyzed nucleophilic aromatic substitution.

Catalysis by metals or organometallic complexes is a forum of considerable interest,[2] particularly with respect to the structure and role of intermediates in these processes.[3] Much fundamental investigation has focussed on neoclassical surface spectroscopy (for example, Auger, EXAFS, LEED, PES, reflectance, SEW, etc.).[4] Even though the extension from clean single crystal surfaces with well-characterized chemisorbed layers to typical condensed phase organic reactions is decidedly tenuous,[5] there still exists a strong bias to believe that organic reactions involving solid metal catalysts either occur on the surface or proceed via electron transfer with the surface. Such assumptions are particularly seductive when the reaction rate and product yield or purity are critically dependent on factors such as the stirring rate and unexpected catalyst variables like the supplier, the particle size and shape, and/or the catalyst history. Seductive, but not necessarily correct.

Ullmann condensations (loosely defined here as copper catalyzed nucleophilic aromatic substitutions on unactivated aryl halides) are classic examples:[6]

$$\mathrm{NUH} + \mathrm{ArX} \xrightarrow{\text{“Cu”/base}} \mathrm{ArNu} + \mathrm{HX} \qquad (1)$$

$$\mathrm{NuH} = \mathrm{ArNH_2},\ \mathrm{Ar_2NH},\ \mathrm{ArOH},\ \mathrm{ArSH},\ \mathrm{ArCO_2H},\ \mathrm{ArC{\equiv}CH},\ \mathrm{ROH},\ \mathrm{RSH},\ \mathrm{H_2O},\ \mathrm{HX},\ \mathrm{HCN},\ \text{etc.}$$

$$\mathrm{X} = \mathrm{Cl},\ \mathrm{Br},\ \mathrm{I}$$

$$\text{“Cu”} = \text{Cu metal, oxides, salts, alloys, complexes, etc.}$$

$$\text{base} = \mathrm{K_2CO_3},\ \mathrm{KOH},\ \mathrm{NaH},\ \text{etc., or preformed } \mathrm{Nu^-}$$

These reactions have been catalyzed by a variety of forms of copper, including the metal itself (in various forms: copper, bronze, freshly precipitated, "activated", etc.[6]), salts or complexes of cuprous or cupric ion, and insoluble oxides. For reasons which have not been well understood, one form of catalyst good for a certain reaction will be poor for another,[7] and in general there is a wide variability in the rate and yield of Ullmann condensations using copper metal from different sources.

In this paper we report results for homogeneous and heterogeneous catalysis by three different oxidation states of copper in an Ullmann synthesis of triarylamines which rationalize these perplexing catalyst features.

Experimental Section

1. Homogeneous Reaction of Ph_2NLi. General Procedure. Under a nitrogen atmosphere in a glovebox, Ph_2NLi was generated in the reaction solvent (triglyme or sulfolane) by the action of *n*-BuLi, using Ph_3CH as indicator. Usually 1–2 equiv were required to achieve a colored end point at 20 °C. Cuprous halide and aromatic halide were added and the solution stirred at 40–50 °C for 30 min to dissolve the catalyst. Sometimes PhPh was added as an internal standard for HPLC mass balance. The resulting yellow solution was filtered through glass wool and divided into 10–20 aliquots of 0.3–1.0 mL and sealed in clear glass tubes. These tubes were removed from the glovebox and placed in a temperature-controlled oil bath for kinetics. At appropriate intervals, individual tubes were withdrawn and quenched with water. The organics were extracted into cyclohexane and analyzed by response-factor-corrected reverse-phase HPLC.

Reaction profiles obtained with use of the internal standard (e.g., Figure 1) established a material balance of 95–100% throughout the reaction and for long periods of time thereafter. In less thoroughly deoxygenated solutions, a small amount (<5%) of Ph_2NNPh_2 was detected by HPLC. PhPh was often omitted from the reaction mixture. In those cases, the chromatograms confirmed the absence of PhPh from possible Ullmann coupling as a side reaction (<0.1%). The final percent conversion was seldom quantitative because Ph_2NLi slowly abstracted protons from the solvent, ultimately forming a solvent polymer gel in extreme cases. Table I summarizes the homogeneous experiments. The rate of formation of triarylamine product was first order in haloaromatic and catalyst, but zero order in Ph_2NLi, so that experiments performed with a large excess of haloaromatic were pseudo-zero order (Figure 1).

Cupric Ion Oxidation of Ph_2NLi. $CuBr_2$ (0.401 g; 1.8 mmol) was added to a 25-mL sulfolane solution of Ph_2NLi (prepared as above from

---

(1) For the preceding paper see: Couture, C.; Paine, A. J. *Can. J. Chem.* **1985**, *63*, 111–120.

(2) For recent reviews see: (a) Somorjai, G. A. *Science* **1985**, *227*, 902–908. (b) Kemball, C. *Chem. Soc. Rev.* **1984**, *13*, 375–392. (c) *The Chemical Physics of Solid Surfaces and Heterogeneous Catalysis Volume 4: Fundamental Studies of Heterogeneous Catalysis*; King, D. A., Woodruff, D. P., Eds.; *Elsevier: Amsterdam, Netherlands*, 1982. (d) Sleight, A. W. *Science* **1980**, *208*, 895–900 (which contains the following statement: "Heterogeneous catalysis has traditionally been a largely empirical science. Many obviously critical experiments have never been performed. This has encouraged speculation on mechanisms to run rampant.").

(3) (a) Kochi, J. K. *Organometallic Mechanisms and Catalysis: The Role of Reactive Intermediates in Organic Processes*; Academic Press: New York, 1978. (b) Henrici-Olive, G.; Olive, S. *Coordination and Catalysis*; Verlag Chemie: Weinheim, Germany, 1977.

(4) (a) Ertl, G.; Kuppers, J. *Low Energy Electrons and Surface Chemistry*; Verlag Chemie: Weinheim, Germany, 1974. (b) Bell, R. J.; Alexander, R. W., Jr.; Ward, C. A.; Tyler, I. L. *Surf. Sci.* **1975**, *48*, 253–287. (c) Somorjai, G. A. *Chimia* **1981**, *35*, 1–9. (d) Lagarde, P.; Dexpert, H. *Adv. Phys.* **1984**, *33*, 567–594.

(5) *The Physical Basis for Heterogeneous Catalysis*; Drauglis, E., Jaffee, R. I., Eds.; Plenum: New York, 1974.

(6) For general reviews of Ullmann condensation and related Ullmann biaryl coupling, see: (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456. (b) Fanta, P. E. *Synthesis* **1974**, *9*, 1–21. (c) Goshaev, M.; Otroshchenko, O. S.; Sadykov, A. S. *Russ. Chem. Rev.* **1972**, *41*, 1046–1059. (d) Bacon, R. G. R.; Hill, H. A. O. *Q. Rev.* **1965**, *19*, 95–125.

(7) Lewin, A. H.; Zovko, M. J.; Rosewater, W. H.; Cohen, T. *J. Chem. Soc., Chem. Commun.* **1967**, 80–81.

0002-7863/87/1509-1496$01.50/0

Table I. Summary of Results from Homogeneous Ullmann Condensation of Halobenzenes with Ph_2NLi^a

solvent[b]	$[\text{haloaromatic}]_0$ (mol L^{-1})			$[Ph_2NH]_0$ (mol L^{-1})	$[\text{catalyst}]_0$ (mmol L^{-1})			conversion (%)[c]	10^4k_2 (L mol^{-1} s^{-1})
triglyme A	[PhI]	=	0.812	0.095	[CuI]	=	6.67	36.2 ± 2.0	3.6 ± 0.2
	[PhBr]	=	1.055	0.093			6.52	1.8	0.065 ± 0.006
	[PhF]	=	2.478	0.080			5.63	≤0.07	≤0.0011
	$[PhOCH_3]$	=	2.140	0.080			5.63	≤0.01	≤0.00013
triglyme A	[PhI]	=	0.993	0.089	[CuI]	=	25.93	80	4.8 ± 1.9
			0.110	0.099			8.38	27	3.4 ± 0.8
			0.323	0.097			8.18	45	3.2 ± 0.2
			1.787	0.080			6.79	62.5 ± 4	2.9 ± 0.3
triglyme A	[PhI]	=	1.277	0.092	[CuI]	=	1.15	18.3 ± 0.5	4.1 ± 0.4
			1.277	0.092			3.05	30.7 ± 1.5	4.1 ± 0.4
			0.687	0.100			6.70	40.5 ± 3.5	5.4 ± 1.2
			0.687	0.100			11.52	49.0 ± 3.0	4.8 ± 0.3
triglyme B	[PhI]	=	0.812	0.076	[CuBr]	=	27.2	~14	0.64
			0.812	0.076	[CuCl]	=	13.5	>15	0.57
triglyme B[d]	[PhI]	=	1.489	0.088	[CuI]	=	3.35	42.7	4.19
			1.233	0.091			3.47	38.8	4.55
			0.972	0.094			3.58	37.6 ± 1.0	4.64
			1.489	0.088	[CuCl]	=	21.8	85 ± 3	4.05
			1.489	0.088	$[CuSO_4]$	=	25.0	16.8 ± 0.4	0.11[e]
			1.051	0.093	[Cu][f]	=	(272)	>10	0.006
sulfolane[d]	[PhI]	=	0.812	0.099	[CuI]	=	11.0	39.7 ± 0.9	≥3.4
			0.812	0.099	$[Cu(acac)_2]$	=	53.1	40 ± 2	1.4[g]
	[PhBr]	=	2.713	0.078			53.1	20	too much scatter[h]
			2.713	0.078	[CuI]	=	25.1	31 ± 1	≤0.18[i]
	[PhCl]	=	2.807	0.078			25.1	2.1 ± 0.1	0.07

[a] Temperature 130 °C, except where noted. Runs are grouped to include all those from the same batch of Ph_2NLi. [b] Triglyme batch A was distilled from $CaSO_4$ and batch B from CaH_2, after $CaCl_2$ treatment. Sulfolane was distilled from $CaSO_4$. [c] Standard deviations are included for cases where a number of points indicate that the reaction is over. Some reactions were not monitored to completion. [d] Reaction temperature was 140 °C. [e] Accompanied by about 5% Ph_2NNPh_2. [f] This is a heterogeneous catalyst. Concentration given assumes all the copper is soluble. [g] Accompanied by 13% Ph_2NNPh_2. [h] Accompanied by 2–10% Ph_2NNPh_2. [i] Halogen exchange (PhBr + CuI → PhI + CuBr) was not observed in the HPLC chromatogram until after the condensation was over. Even so, the detection limit for PhI was ~10% in this experiment, so it is possible that this measured rate corresponds to rate-determining PhI formation (and PhI + Ph_2NCu → Ph_3N was a faster second step).

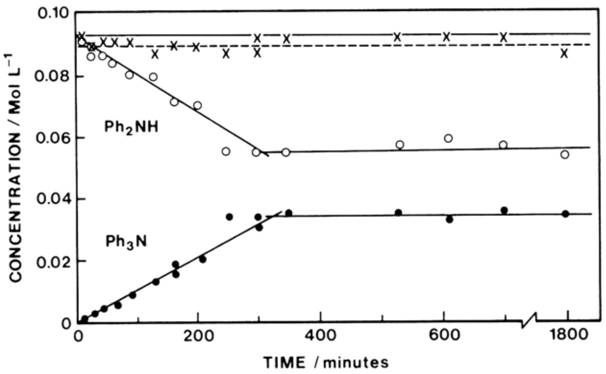


Figure 1. Reaction profile for condensation of Ph_2NLi (0.095 M) with PhI (0.812 M) catalyzed by CuI (0.0067 M) in triglyme A at 130 °C. The ×'s represent the sum of $[Ph_2NH]$ and $[Ph_3N]$ and their average (dashed line) accounts for 95% of the original material (horizontal solid line). Under pseudo-zero order conditions, the slope = $k_2[CuI]_0[PhI]_0$ = $1.9 \pm 0.1 \times 10^{-6}$ mol L^{-1} s^{-1}, so $k_2 = 3.6 \pm 0.2 \times 10^{-4}$ L mol^{-1} s^{-1}.

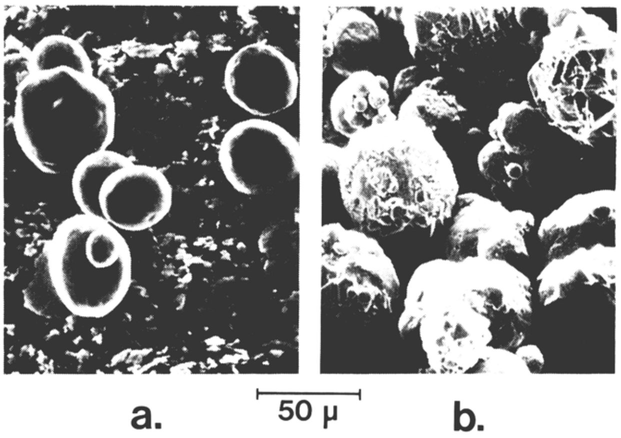


Figure 2. SEM micrographs of (a) virgin copper powder and (b) recovered catalyst. TEM diffraction and X-ray powder diffraction identified the crystallites in part b as Cu_2O and the surface of part a to be 360 ± 50 Å of Cu_2O.

3.0 mmol of Ph_2NH) at room temperature. The reaction was over in less than 60 s (HPLC chromatograms contained large amounts of Ph_2NNPh_2), and the black, homogeneous solution was stirred for 30 min and then poured into water/CH_2Cl_2. After the solution was left to stand for 3 days, the resulting precipitate was isolated by filtration and washed with water and THF to give a black solid (0.153 g). Quantitative X-ray powder diffraction analysis: 52% amorphous material plus 48% of a mixture of crystalline cuprous and cupric oxides in the mole ratio $Cu^+/Cu^{2+} = 3.3$ (43% yield of crystalline Cu_2O; 13% recovery of crystalline CuO).

2. Heterogeneous Reactions. General Synthesis of Substituted Triphenylamines. Ph_2NH (10 mmol), KOH (75 mmol), powdered copper metal (J. T. Baker Chemical Co.; 94.4 mmol), and hexadecane (6 mL) were brought to 160 °C under an argon atmosphere with vigorous magnetic stirring in a stoppered 22-mL flask designed to minimize catalyst creep (Figure 3 in ref 8). PhI (18 mmol) was added and the reaction monitored by HPLC analysis of aliquots quenched into water/CH_2Cl_2. At the end of the reaction it was worked up into water/CH_2Cl_2 and the crude product chromatographed on silica gel with hexane elution and recrystallized. The heterogeneous reactions were insensitive to atmospheric oxygen, particularly when copper metal catalyst was employed.

Table II summarizes the yield and measured physical properties of the triarylamines synthesized by this method. Generally, the reactions were very clean, with little detectable hydrodehalogenation or Ullmann biaryl coupling. One exception was the slow conversion of the product 2-iodotriphenylamine to Ph_3N, which occurred over long reaction times.

Competitive Reactions. Example. With use of a procedure similar to the above, PhI and $4\text{-}CF_3C_6H_4I$ (5 mmol each) were reacted with a limiting amount of Ph_2NH (1 mmol). The reaction was sampled several times and the HPLC product ratio $4\text{-}CF_3C_6H_4NPh_2/Ph_3N$ used to calculate the relative reactivity, k_{rel}, by standard means.[9] The relative

---

(8) Rogers, H. R.; Hill, C. L.; Fujiwara, Y.; Rogers, R. J.; Mitchell, H. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 217–226.

(9) See, for example, competitive experiments applied to the Grignard reaction (ref 8).

Table II. Summary of Triarylamine Syntheses in This Study[a]

amine used (mmol)[b]	substituent on PhI (mmol)	product	reaction time (h)	HPLC yield (%)	isolated yield (%)[c]	mp (or bp) (°C)	mp (°C) (lit. ref)
$C_{10}H_7NHPh$ (10.4)[d]	H (13.4)	$C_{10}H_7NPh_2$[e]	24	67[f]	23	140.5–141	140–141 (35)
	H (17.9)	Ph_3N	8	96	88	126–127	126–127 (36)
	4-MeO (11.2)	$4\text{-}MeOC_6H_4NPh_2$	5	96	79	103	104–105 (36)
	$3\text{-}CF_3$ (7.1)	$3\text{-}CF_3C_6H_4NPh_2$	24	70	64	(150 (0.1 mmHg))	new compound[g]
	$4\text{-}CF_3$ (7.1)	$4\text{-}CF_3C_6H_4NPh_2$	24	60	56	105	104–105 (36)
	4-I (3.2)	$4\text{-}Ph_2NC_6H_4NPh_2$	24	96	62	188–193[h]	199–200 (37a)
(5.2)	4-I (10.1)[i]	$4\text{-}IC_6H_4NPh_2$	16		41	107	107 (38)
	2-Cl (10.0)[j]	$2\text{-}ClC_6H_4NPh_2$	27	61	55	52–52.5	(200 (1 mmHg)) (12, 39)[k]
	2-I (10.0)	$2\text{-}IC_6H_4NPh_2$	27	36[l]	18	95.5–96	83 (12)[m]
$3\text{-}ClC_6H_4NHPh$	H (17.9)[j]	$3\text{-}ClC_6H_4NPh_2$	27		88	87–87.5	new compound[n]
	$3\text{-}CH_3$ (23.4)[j]	$3\text{-}CH_3C_6H_4NPh_2$	24	96	82	68–69.5	69–70 (37b)
	$2\text{-}CH_3$ (23.6)[j]	$2\text{-}CH_3C_6H_4NPh_2$	24	93	81	60–60.5	56–58 (39)
	3-Cl (13.8)[o]	$3\text{-}ClC_6H_4NPh_2$	24[p]	86	82		
$3\text{-}CF_3C_6H_4NHPh$	H (36.4)[q]	$3\text{-}CF_3C_6H_4NPh_2$	24[p]	80	77		
$3\text{-}CF_3C_6H_4NHPh$	H (44.7)[r]	$3\text{-}CF_3C_6H_4NPh_2$	24[p]	80			
	$C_{10}H_7I$[s] (15.7)[t]	$C_{10}H_7NPh_2$[e]	24[p]	83[u]	59		

[a] All runs with 6 mL hexadecane solvent at 160 °C. Catalyst was Cu (94.3 mmol)/KOH (80–95 mmol) except where noted. [b] Ph_2NH; 10.0 mmol, except where noted. [c] After column chromatography and recrystallization (or distillation). Note that yields could be slightly higher if aliquots had not been removed to monitor the reaction. Note also that these syntheses are not optimized—each line represents a single reaction. [d] *N*-Phenyl-1-naphthylamine. [e] *N*,*N*-Diphenyl-1-naphthylamine. [f] Assuming equal HPLC response factors at 254 nm for product and reactant amines. [g] Consistent UV, IR, ^1H NMR, ^{13}C NMR spectra, and Anal. ($C_{19}H_{14}F_3N$) C, H, N. [h] Could not be crystallized to >93% purity. [i] Catalyst was Cu_2O (2.0 mmol)/KI (6.2 mmol)/KOH (89 mmol). [j] Catalyst was Cu (78.7 mmol)/KOH (76 mmol). [k] Consistent UV, IR, ^1H NMR, ^{13}C NMR spectra, and Anal. ($C_{18}H_{14}ClN$) C, H, N; Cl: calcd, 12.67; found, 12.25. [l] 54% at 7 h. Product hydrodehalogenates slowly to form Ph_3N. [m] Consistent UV, IR, ^1H NMR, ^{13}C NMR spectra, and Anal. ($C_{18}H_{14}IN$) C, H, N; I: calcd, 34.19; found, 35.26. [n] Consistent UV, IR, ^1H NMR, ^{13}C NMR spectra, and Anal. ($C_{18}H_{14}ClN$) C, H, N, Cl. [o] Catalyst was CuI (0.52 mmol). [p] Longer reaction times did not improve the yield. [q] Catalyst was CuO (2.83 mmol). [r] Catalyst was CuO (4.3 mmol)/KOH (125 mmol). Temperature was 175 °C. [s] 1-Iodonaphthalene. [t] Catalyst was CuI (0.68 mmol)/NaH (15 mmol). Temperature was 175 °C. [u] Significant yield of naphthalene as a byproduct.

Table III. Relative Reactivity of $4\text{-}CF_3C_6H_4I$ and PhI toward Ph_2NH in the System Catalyst/KOH/160 °C, as Determined by Competitive Experiments

catalyst type	mol ratio of catalyst/Ph_2NH	k_{rel}[a] ($k_{4\text{-}CF_3}/k_H$)
Cu	22	0.88
	22	0.71
Cu_2O	0.7	0.84
CuI	0.3	0.61
CuO[b]	1.2	0.70
	0.3	0.79
$CuBr_2$[b]	0.1	0.67
	0.5	1.06
average		0.8 ± 0.15

[a] The uncertainty in a given value of k_{rel} is about ±10%. [b] The amount of cupric catalyst reduced to cuprous ion (as determined by the yield of Ph_2NNPh_2) was 3–6% of the amine.

Table IV. Relative Reactivities of Substituted PhI toward Ph_2NH Determined from Competitive Experiments Using Cu/KOH/160 °C

substituent in PhI	σ[a]	mol ratio of catalyst/Ph_2NH	k_{rel}[b] (k_{sub}/k_H)
$4\text{-}NPh_2$	−0.66[c]	22	1.8 ± 0.3
$4\text{-}OCH_3$	−0.27	33	1.05 ± 0.15
$4\text{-}CH_3$	−0.17	32	1.24 ± 0.06
4-I	0.18	33	0.86 ± 0.04[d]
$4\text{-}CF_3$	0.54	22	0.8 ± 0.1[e]
2-I		38	1.5 ± 0.1[d]
$2\text{-}CH_3$		25	1.04 ± 0.03

[a] From ref 40. [b] Error limits are one standard deviation of the mean in a single experiment. [c] Assumed $\sigma(NPh_2) \sim \sigma(NH_2)$ because of $\sigma(Ph) = 0.01 \sim \sigma(H)$. [d] After division by a statistical factor of 2. [e] Average of two runs in Table III.

Table V. Relative Reactivities of Substituted Ph_2NH toward PhI Determined from Competitive Experiments Using Cu_2O/KOH/160 °C

substituent in Ph_2NH	σ[a]	mol ratio of Cu^+/amines	k_{rel}[b] ($k_{3\text{-sub}}/k_H$)
$3\text{-}CH_3$	−0.07	22	0.96 ± 0.04
3-Cl	0.37	33	2.81 ± 0.20
$3\text{-}CF_3$	0.43	32	2.89 ± 0.16

[a] From ref 40. [b] Error limits are one standard deviation of the mean in a single experiment.

reactivity was independent of the percent conversion, from 5 to 100% of the limiting reagent in all cases, except where an additional iodine atom gave one of the products subsequent reactivity (i.e., *o*- and *p*-diiodobenzene). In those cases, k_{rel} was extrapolated to time zero, or else second generation products were incorporated into the product ratio. The values of k_{rel} cited in Tables III–V are the averages of 4–7 aliquots removed over 10–80% conversion.

Characterization of the Baker Copper Metal Catalyst. "J. T. Baker purified copper" is manufactured by spraying molten copper into an "oxidizing atmosphere" at about 1400 °C.[10] This produces a powder of spherical particles (Figure 2a) varying from 1 to 100 μm in diameter. Scanning electron microscopy (SEM) was used to determine the size and size distribution of this material: wt average diameter = 19 μm; GSD = 2.0. Assuming perfect spheres, the total surface area was calculated to be 5×10^{-3}% of the atoms (100% × atomic length × total area/total volume). Electron diffraction patterns obtained by transmission electron microscopy (TEM) positively identified Cu_2O in the surface oxide layer, and powder diffraction X-ray analysis of particles >45 μm found 1.2 ± 0.1% Cu_2O in the top 20 μm (i.e., the X-ray penetration depth).[11] Particles of <45 μm contained 1.5% Cu_2O. Assuming the thickness of the oxide layer is independent of the particle diameter and that the solid material is composed of cubes, the density and MW data for Cu and Cu_2O permit calculation of the following quantities:

$$\text{depth per monolayer of } Cu^+ = (MW_{Cu_2O}/(2 \times \rho_{Cu_2O} \times N_A))^{1/3} = (143/(2 \times 6.0 \times 6.02 \times 10^{23}))^{1/3} \times 10^8 = 2.7 \text{ Å} \quad (2)$$

$$\text{oxide layer depth} = \text{X-ray pen. depth} \times \text{wt \% } Cu_2O \times \rho_{Cu}/(\rho_{Cu_2O} \times 100) = 360 \text{ Å} \quad (3)$$

$$\text{no. of monolayers of } Cu^+ = \text{thickness of oxide layer/depth per monolayer} = 360/2.7 = 130 \text{ layers} \quad (4)$$

Direct Evidence for Solution Catalysis. Reference Reaction. A 250-mL 3-necked flask fitted with mechanical stirrer, condensor, drying tube, and nitrogen inlet was preheated in a large oil bath to 190 °C. Ph_2NH (50 mmol), copper bronze (BDH Chemicals Ltd; 118 mmol), iodobenzene (89 mmol), K_2CO_3 (100 mmol), and Soltrol 170 (a hydrocarbon

---

(10) Meinhofer, F. L., private communication from J. T. Baker Chemical Co.

(11) Klug, H. P.; Alexander, L. E. *X-Ray Diffraction Procedures for Polycrystalline and Amorphous Materials*, 2nd ed.; Wiley: New York, 1974; p 94.

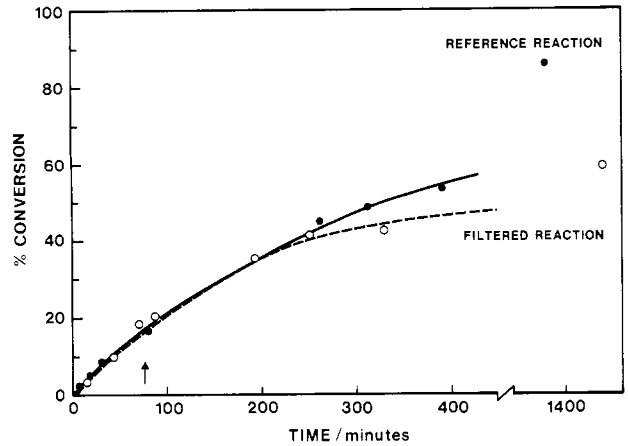


Figure 3. Reaction profiles for $Ph_2NH + PhI \rightarrow Ph_3N$ at 190 °C, catalyzed by copper bronze/K_2CO_3. The solid curve corresponds to a reference reaction, while the dashed curve corresponds to a similar reaction filtered from the catalyst after 75 min (18% conversion).

solvent from Phillips Chemical Co.; 25.0 mL) were added to the flask and stirring commenced. The reaction was monitored by HPLC with a two channel response-factor-corrected UV detector at 254 and 290 nm. The results from both channels were in good agreement, but only the results at 290 nm are shown in Figure 3.

Filtered Reaction. A reaction employing reagent, catalyst, and solvent quantities the same as in the reference reaction was begun. After 75 min, the stirrer was stropped and ca. 8 mL of the reaction mixture was withdrawn through a 1 cm glass wool filter in 5 mm Teflon tubing into a 10-mL graduated pipet. The filtered mixture was slightly milky (possibly due to some precipitation on cooling) but contained no visible copper bronze. The filter was discarded and the filtrate added to a regular 22-mL catalysis flask containing additional K_2CO_3 (29 mmol), where it was stirred magnetically at 190 °C, under nitrogen for the balance of the experiment. About 2 h after filtration, the mixture developed a light brown color which persisted until the end of the run. HPLC data are summarized in Figure 3.

Results and Discussion

We have investigated the Ullmann synthesis of triarylamines from condensation of diphenylamines with halobenzenes with a view to relating mechanisms for heterogeneous catalysis by copper metal to those for homogeneous catalysis by soluble copper salts. Two main types of reaction conditions were investigated: a homogeneous system employing preformed Ph_2NLi in triglyme or sulfolane solvent at 130 or 140 °C and a heterogeneous mixture using hexadecane solvent with an insoluble base at 160 °C (designated by the notation "catalyst/base/temperature"). Reaction kinetics were monitored by analytical HPLC. Mass balances of 95–100% were obtained, and there was no (<0.1%) evidence for competing hydrodehalogenation or Ullmann coupling to give biaryls. The overall yields of triphenylamines under homogeneous conditions averaged only 40% because of competing irreversible proton transfer from solvent to Ph_2NLi. Under heterogeneous conditions with hexadecane, HPLC yields up to 95+% and isolated yields, after column chromatography, averaging 70+% were obtained in under 24 h reaction time. This compares quite favorably to the typical literature synthesis conditions—Cu/K_2CO_3/180 °C—where the yields are typically 55% in 72 h.[12]

Homogeneous Catalysis. Rate Equation. Attempts to force uncatalyzed reaction between Ph_2NLi and PhI or PhF were unsuccessful up to 220 °C. A few mole percent of any form of copper (metal, Cu^+, or Cu^{2+}) catalyzed the reaction, giving a reasonable rate at 130 °C. Under homogeneous cuprous ion catalysis, the rate expression was zero order in nucleophile (see Figure 1: $dP/dt = k_2[PhI][Cu^+]_0$ until $[Ph_2N^-] < [Cu^+]_0$). Second-order rate constant k_2 (Table I) was reproducible to ±10% and was relatively independent of the use of CuI, CuBr, or CuCl as catalyst.

This rate equation parallels that for cuprous ion catalyzed condensation of phenoxides with aryl bromides to form diaryl ethers:[13] the reaction rate is zero order in nucleophile, but, since it responds to substituents in the aromatic nucleophile ring, the nucleophile is clearly present in the transition state. This suggests irreversible formation of a cuprous nucleophile species, "Ph_2NCu", which reacts with iodobenzene in the slow step:

$$Ph_2N^- + CuI_{(insol)} \xrightarrow{\text{fast; irreversible}} Ph_2NCu + I^- \tag{5}$$

$$Ph_2NCu + PhI \xrightarrow{\text{slow; } k_2} Ph_3N + CuI \tag{6}$$

Cuprous nucleophiles are well-known species—for example, PhSCu (which can be purchased from Alfa Ventron Corp.) and PhOCu react with haloaromatics to give thioethers and ethers, respectively.[14,15] Cuprous halides, and cuprous nucleophiles, in general, undergo the same types of reactions.[1]

Figure 1 shows the reaction profile from a typical homogeneous experiment, and Table I summarizes the measured rate constants. Most were obtained from pseudo-zero order experiments with excess PhI. That the reaction is zero order in nucleophile was indeed fortunate, because Ph_2NLi can be readily oxidized to Ph_2NNPh_2 and react with solvent.[16] These processes consumed Ph_2NLi, and were obviously detrimental to the *yield* of the experiment (which averaged only 40%) but had no impact on the zero-order *kinetics*. Thus, while the homogeneous experiments were mechanistically useful, they were not synthetically practical. (On the other hand, the heterogeneous conditions were synthetically useful, but kinetically complex.)

Solvent and Solvent Purity Effects. The measured rate constants are quite sensitive to both solvent and solvent purity. For example, batch B of triglyme, distilled from CaH_2, gave rates at 130 °C a factor of 8 lower than batch A, distilled from $CaSO_4$. Rates in sulfolane were 10 times greater than in the "faster" batch of triglyme. These observations are consistent with literature results. Weingarten used diglyme as solvent and found that diesters present as impurities seemed to be necessary to better solubilize the cuprous ion.[18] In fact, he deliberately added ethylene diacetate to his reactions to enhance the solubility of the catalyst. The nature of reaction of solvent impurities with the nucleophiles PhO^- or Ph_2NLi is unknown, but presumably the products of any such reactions are equally effective as cuprous ion solubilizers.

In their investigation of copper mediated halogen exchange reactions, Bacon and Hill found that the rates varied by a factor of 200 in 13 solvents.[14d] Generally, they found that better cation complexing solvents, such as pyridines and benzonitrile, or added anions (e.g. Cl^-, PhS^-) lowered the rates, while more polar, aprotic media (dimethylacetamide, DMF, Me_2SO, and HMPA) gave similar rates, about 100–200 times faster than the others. There is no correlation of this kind of data with any solvent polarity parameter, so it is not clear at this time whether good copper complexing agents accelerate or retard reaction and what, if any, effect "pure" solvent polarity has.

In spite of the problem of solvent purity effect on the reaction, a number of useful generalizations were drawn from the kinetic results in Table I. The runs were usually conducted in groups, so a single solution of Ph_2NLi was split among 2–6 runs to ensure that most variables were held constant, and rates determined from

---

(12) Grimley, E.; Collum, D. H.; Alley, E. G.; Layton, B. *Org. Magn. Reson.* **1981**, *15*, 296–302.

(13) (a) Litvak, V. V.; Gavrilova, N. M.; Shein, S. M. *Zh. Org. Khim.* **1975**, *11*, 1652–1656. (b) Litvak, V. V.; Shein, S. M. *Ibid.* **1975**, *11*, 92–96. (c) Litvak, V. V.; Shein, S. M. *Ibid.* **1974**, *10*, 2360–2364. (d) Litvak, V. V.; Shein, S. M. *Ibid.* **1974**, *10*, 1478–1482. (e) Litvak, V. V.; Shein, S. M. *Ibid.* **1974**, *10*, 550–554.

(14) (a) Campbell, J. R. *J. Org. Chem.* **1962**, *27*, 2207–2209. (b) Bacon, R. G. R.; Hill, H. A. O. *J. Chem. Soc.* **1964**, 1097–1107.

(15) (a) Kawaki, T.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1499–1500. (b) Camus, A.; Marsich, N.; Nardin, G.; Randaccio, L. *J. Organomet. Chem.* **1979**, *174*, 121–128.

(16) Air or cupric ion oxidation of Ph_2NLi produces Ph_2NNPh_2, but oxidation of Ph_2NH produces diphenylbenzidine and other poorly characterized products (ref 17).

(17) Cserfalvi, T.; Meisel, T.; Erdey, L. In *Proc. 3rd Anal. Chem. Conf.* **1970**, *2*, 93 (Buzas, I., Ed.).

(18) Weingarten, H. *J. Org. Chem.* **1964**, *29*, 977–978 and 3624–3626.

the same batch of solvent on different days were reproducible to ±10%.

Element Effect. In the case of catalysis by CuI of the reaction $Ph_2NLi + PhX \rightarrow Ph_3N + LiX$, the following element effects were observed: $k_I \sim 55k_{Br} \sim 480k_{Cl} \sim 3300k_F \sim 28000k_{OCH_3}$ (from Table I), quite typical of copper mediated reactions,[1,6] and in the opposite sense to the element effect in uncatalyzed nucleophilic aromatic substitutions,[19] which proceed via an addition elimination mechanism through an intermediate Meisenheimer complex. In the uncatalyzed reaction, the halide effect is consistent with rate limiting *addition*, whereas the element effect in the copper-catalyzed reactions is more consistent with rate limiting halide *elimination*. This may suggest that copper exerts its catalytic action by preferentially lowering the addition barrier to the point where elimination becomes rate limiting.

Cupric Ion Catalysis. Cupric ion, if at all catalytically active, must be much less so than cuprous ion. The catalytic activity of cupric ion solutions can be ascribed to Cu^+ only. When catalysis of the homogeneous reaction was attempted with soluble cupric salts ($CuBr_2$ or $Cu(acac)_2$), cupric ion was first reduced to cuprous (by the nucleophile) before catalysis occurred. Evidence for this conclusion includes the following: (a) high yields of instantaneously formed tetraphenylhydrazine ($Cu^{2+} + Ph_2N^- \rightarrow Cu^+ + {}^1/_2Ph_2NNPh_2$) which correlate quantitatively with (b) slower reaction kinetics due to incomplete nucleophile reduction and (c) the yield of cuprous salts in quenched reaction mixtures. For example, in an experiment using $Cu(acac)_2$, an instantaneous yield of 13% Ph_2NNPh_2 (based on Ph_2NH) became 32% when based on Cu^{2+}, and the rate constant in that run was about 40% of the rate constant in a parallel run with CuI catalyst (footnote *g* in Table I). The lowered rate quantitatively reflects the fractional conversion of cupric ion to cuprous. In another experiment catalyzed by $CuSO_4$ (not all soluble), the rate constant was 5% of that for cuprous ion, and a correspondingly smaller yield of amine oxidation product was detected (footnote *e* in Table I). In a control experiment analogous to the earlier investigation of phenoxides,[18] cupric bromide rapidly oxidized Ph_2NLi to Ph_2NNPh_2, even at room temperature.

Copper Metal Catalysis. The (so-called) homogeneous reaction could also be catalyzed by powdered copper metal, albeit very slowly. On a total moles basis, the metal powder was about 700 times less effective than cuprous ion. SEM sizing analysis suggested that about 5×10^{-3}% of the atoms were on the surface of this regularly spherical powder, making a hypothetical surface atom some 30 times more active than cuprous ion ($100\%/(700 \times 5 \times 10^{-3}\%)$). In actual fact, copper metals are covered with a thin oxide layer[20] which would have to be removed for clean metal surface catalysis to occur. Copper oxides are insoluble in organic solvents and water but can dissolve in strong acids or bases.[21] Of course, amines are excellent cuprous ion ligands,[22] and may assist this process. Quantitative X-ray powder diffraction analysis of the Baker catalyst employed indicated that the oxide layer was 360 ± 50 Å (130 monolayers) of Cu_2O. Therefore, the amount of cuprous oxide which must be removed to expose the Cu surface was 300% more than adequate to carry the reaction in solution. Providing that the oxide was dissolved by Ph_2NLi, there is no need to propose even a minor surface catalyzed component to the already established soluble cuprous ion mechanism.

A Single Catalytic Species from Three Oxidation States of Copper. The hypothesis that dissolved curpous oxide from the metal surface actually carries the reaction was further corroborated by a number of additional experiments performed under our heterogeneous reaction conditions. These were very complex reactions consisting of a solid copper metal catalyst, a molten KOH phase, and one or two organic phases, so it was not possible to determine the rate equation (although the reactions were quite reproducible). Competitive experiments were employed to probe the mechanism.[9] Qualitatively, the reaction rate was increased by increases in the amount of any reagent (catalyst, base, amine, or iodoaromatic) and decreased by dilution with solvent. Substituting NaH for KOH had little impact on the rate, and sometimes lowered the yield (Table II). Note also that these conditions were, in contrast to the homogeneous conditions, highly suitable for organic synthesis and gave very good yields of the target compounds.

The evidence for a single catalytic species includes the following: first, the substituent effect of a 4-trifluoromethyl group in iodobenzene was small, and apparently independent of the catalyst used (within experimental error; Table III); second, the element effect, k_I/k_{Br}, was the same for Cu/KOH/160 °C and Cu_2O/KOH/160 °C (220 ± 50 and 250 ± 50, respectively); third, workup of runs employing copper metal or cupric salts gave crystalline Cu_2O in 40–60% of the yield necessary to carry the reaction; and fourth, electron microscopy of recovered copper metal catalyst shows the surface to be covered by large crystallites of Cu_2O not present on the original catalyst (Figure 2b). Clearly, some of the soluble oxide was reprecipitated on the metal upon workup. Thus, the weight of evidence arising from all the conditions and catalysts employed in both the homogeneous and heterogeneous experiments point to cuprous ion as the single catalytic species. In sufficiently basic media, the oxide layer on copper metals may dissolve, forming active Ph_2NCu.

Depending on their preparation or history, different copper metals have slightly different oxide structures.[20] X-ray diffraction analysis was used to examine several other commercial copper catalysts, with the following results: Alfa Ventron 1 μm copper powder (20% Cu_2O); BDH electrolytic copper (50–500 μm; no detectable Cu_2O or CuO); BDH "copper reduced by hydrogen" (1.5% Cu_2O + 5.5% CuO); SPEX 99.9999% copper (10–15 μm; 1.0% Cu_2O + 1.0% CuO). Clearly, a wide range of these materials have sufficient surface oxide to carry soluble catalysis under conditions where the oxide can dissolve. In this regard, preformed Ph_2NLi or KOH is adequately basic, but K_2CO_3 (a literature standard[6,12]) is a borderline case. In fact, with weaker bases, catalyst dissolution from Cu, Cu_2O, CuO, CuX, Cu_2X, etc., may well be partially or completely rate limiting, so consistent results have been difficult to achieve with a weak base. Copper metal effects are much reduced with stronger bases, and cleaner reactions are the rule.[23]

Direct Evidence for Solution Catalysis. Unfortunately, the evidence cited above is both indirect and subject to significant experimental uncertainties, particularly in the measurement of rate constants. Unambiguous direct evidence for solution catalysis by metals requires demonstration of substantial catalytic activity in the filtrate after removal of the solid catalyst.

Our results from a number of Cu/KOH experiments were not satisfying in this regard, for a variety of reasons. First, in Cu/KOH systems there are two liquid phases: molten KOH and an organic phase. It is not clear which phase contains the active form of the catalyst. The organic phase can be filtered and treated with ArI or ArI/KOH. In these cases, conversions of 1–2% Ph_3N (accuracy 0.05%) were observed in a pseudo-zero order process whose rate increased with the amount of KOH added after filtration. The main products, however, corresponded to oxidation of Ph_2NH. Second, the molten KOH phase could not be successfully filtered through either a medium porosity Teflon or glass fibre filter heated to 200 °C, so we have no information on the activity of that layer. Third, CuI/KOH/160 °C runs were equally difficult to filter, and, once filtered, they gave low conversions comparable to filtered Cu/KOH/160 °C runs. This appears to reflect the inherent difficulty of the filtration step when KOH is involved, and the main conclusion drawn from the KOH runs was that not much persistent catalytic activity resided in the organic layer.

---

[19] Bunnett, J. F.; Garbisch, E. W., Jr.; Pruitt, K. M. *J. Am. Chem. Soc.* **1957**, *79*, 385–391.

[20] Rhodin, T. N., Jr. *J. Am. Chem. Soc.* **1951**, *73*, 3143–3146.

[21] Linke, W. F.; Seidell, A. *Solubilities of Inorganic and Metal-Organic Compounds*, 4th ed.; American Chemical Society: Washington, 1958; Vol. 1, pp 958–963.

[22] Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1972; pp 903–911.

[23] Turner, S. R.; Yanus, J., unpublished Xerox internal literature.

The KOH problems were eliminated by shifting the experimental focus to a different catalyst/base system: copper bronze/K_2CO_3/190 °C. Although these conditions are less useful synthetically (due to the generally lower yields, higher temperatures, and longer reaction times than for Cu/KOH), they proved highly suitable to the filtration experiment. In this case the potassium carbonate remained with the copper as a largely insoluble powder, from which the organic phase could be readily filtered. Figure 3 presents reaction profiles from two runs—one without filtration (solid line) and one filtered after 75 min (i.e., at 18% conversion; dashed line). In the former (reference) reaction, conversion proceeded smoothly to an 86% yield over 22 h. The filtered reaction continued to track the reference reaction for several hours, although the 24-h conversion (60%) was somewhat less. This later loss of yield may reflect diversion of some of the soluble catalyst to inactive forms which could not be replaced in the absence of the original copper bronze metal. Nevertheless, the increase in yield from 18 to 60% after filtration clearly establishes that the condensation reaction continued substantially unimpeded in the absence of the metal form of the catalyst. This experiment provides the first direct evidence for solution catalysis as the primary reaction mechanism, verifying our hypothesis of soluble catalysis, most probably by cuprous ion.

Substituent Effects. Competition experiments were also employed to probe the effect of substituent under conditions of heterogeneous catalysis. Table IV shows that the effect of substituent in positions 2 or 4 of iodobenzene is uniformly small. Weighted least-squares analysis of these data gives $\rho = -0.25 \pm 0.05$ ($r = 0.933$; $\sigma = 0.046$). This result differs somewhat from the generally positive ρ values typical of other Ullmann condensations, such as the following: 0.61 for CuBr catalyzed condensation of PhO^-K^+ with substituted bromobenzenes at 170 °C;[13e] 0.52 for halogen exchange between CuCl and aryl bromides at 110 °C;[24] and 1.0 for CuCl catalyzed iodine exchange in aryl iodides at 77 °C.[25] The reason for this discrepancy in sign is not clear. It may be a solvent effect (hexadecane vs pyridine/phenol, pyridine, and DMSO, respectively), but all four of these values are considerably attenuated when compared to typical ρ values of 3–7 for *uncatalyzed* nucleophilic aromatic substitution.[13e,26,27]

In a similar series of competitive experiments, the effect of substitution in the 3 position of diphenylamine was probed with use of the system Cu_2O/KOH/160 °C and iodobenzene (Table V). Here the substituent effect is larger than in the iodoaromatic: $\rho = 1.09 \pm 0.06$ ($r = 0.990$; $\sigma = 0.045$). This, too, is in the opposite sense to the value of −0.86 for CuI catalyzed condensation of substituted cesium phenolates with bromobenzene at 170 °C,[13a] but the difference here is due to the fact that the amine requires deprotonation in the KOH medium, while the phenolate anion was preformed. This is consistent with our previous deduction that Ph_2NLi forms Ph_2NCu irreversibly. Here again, ρ values for catalyzed processes implicate much less charge development than in uncatalyzed nucleophilic aromatic substitution, where, for example, ρ values for substituted anilines as nucleophile are in the range −3 to −3.5.[28]

Reaction Mechanism. A priori, the range of possible mechanisms and intermediates for copper catalyzed nucleophilic aromatic substitution includes those already established for the uncatalyzed process[29] and any additional ones imaginable for catalysis. The intervention of Ph_2NCu as a cuprous nucleophile (CuNu) in copper *catalyzed* Ullmann condensation reactions confirms the mechanistic generalization to copper *mediated* nucleophilic aromatic substitutions (eq 7). These may include Ullmann biaryl coupling (via CuNu = CuPh),[30] halogen exchange reactions,[1,6] and possibly even the Sandmeyer reaction[31] ($X = N_2$) under some conditions.

$$\mathrm{CuNu} + \mathrm{PhX} \rightleftharpoons \mathrm{PhNu} + \mathrm{CuX} \tag{7}$$

The large element effect may be indicative of either cuprous–halogen complexation (a polarizability effect) or of rate limiting CX rupture (a leaving group effect). The low ρ values obtained here and elsewhere have often been interpreted as favoring either a radical or 4-center mechanism via a halogen-complexed organocuprate intermediate.[6,13,25] However, there are no well-established precedents for concerted 4-center processes in aromatic substitutions, and the intervention of radicals or radical anions, however briefly, is contradicted by a number of experiments by ourselves and others.[6,32]

Our evidence includes the fact that *o*- and *p*-diiodobenzenes initially gave monosubstituted products which underwent subsequent reaction at similar rates. On the other hand, radical anion intermediates anticipated for $S_{RN}1$[33] or electron exchange mechanisms would be expected[33c] not to undergo bimolecular electron transfer to give monosubstituted product, but rather to favor rapid, unimolecular loss of the second halide ion. We also found no effect (within 10% experimental error) on the macroscopic reaction rate of heterogeneous catalysis upon addition of 28 mol % of 1,1-diphenylethylene. In addition, the effect of aromatic nucleus is negligible (k_{rel} (PhI vs. 1-iodonaphthalene) = 0.99 ± 0.02), also suggesting little involvement of the aromatic ring electrons. Finally, absolute and relative rate constants are in as much qualitative agreement as is possible in the heterogeneous systems. For all these reasons, the intervention of free radicals *on the path to product* seems unlikely, although they could be involved in hydrodehalogenation or other competing reactions.

Benzyne mechanisms are inconsistent with the well-known conservation of substitution site in these reactions. CX insertion mechanisms and/or phenyl copper intermediates (PhCu) are likely involved in Ullmann biaryl *coupling* reactions,[6] but they are phenyl anion or phenyl radical equivalents, and ought not to be susceptible to ipso attack by nucleophiles in Ullmann *condensation* processes. The negligible ortho effects of bulky methyl or iodo substituents (Table IV), and even the *tert*-butyl group,[1] are more consistent with rate limiting halide loss than with concerted CX insertion mechanisms, which are expected to have crowded transition states.

It is difficult to say anything new about the detailed reaction mechanism for these copper mediated nucleophilic aromatic substitutions. Very little is known about the nature of the interaction of cuprous ion with either the halogen or the aromatic ring, yet this is the key to the mechanism. Many authors have drawn their conclusions from limited data sets. In a detailed mechanistic study of copper mediated ligand exchange reactions, we recently developed two working hypothesis mechanisms: intimate electron transfer (in which the radical intermediates never escape the solvent cage) and π-complexed organocuprate intermediates (eq 8).[1] As discussed in the previous paper, the intimate mechanism is unusual in that it requires electron transfer to the higher energy σ^* CX orbital, rather than the π^* aromatic orbital (the latter is the case in the $S_{RN}1$ mechanism). Furthermore, the intimate mechanism is operationally indistinguishable from a concerted mechanism.

On the other hand, the π-complexed mechanism appeared attractive on the basis of parallels with aromatic substitutions on

---

(24) Calculated from the data in ref 14b.

(25) Stanko, V. I.; Iroshnikova, N. G. *Zh. Obsh. Khim.* **1979**, *49*, 2076–2082.

(26) Bartoli, G.; Ciminale, F.; Todesco, P. E. *J. Org. Chem.* **1975**, *40*, 872–874.

(27) Pinholster, D. F., Jr. Ph.D. Thesis. Georgia Institute of Technology, 1970.

(28) (a) Brewis, D. M.; Chapman, N. B.; Paine, J. S.; Shorter, J. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1802–1805. (b) Chapman, N. B.; Chaudhury, D. K.; Shorter, J. *J. Chem. Soc.* **1962**, 1975–1986.

(29) For recent reviews of uncatalyzed nucleophilic aromatic substitution see: (a) Crampton, M. R. *Org. React. Mech.* **1982–1983**, 241–261. (b) Bernasconi, C. F. *Chimia* **1980**, *34*, 1–11.

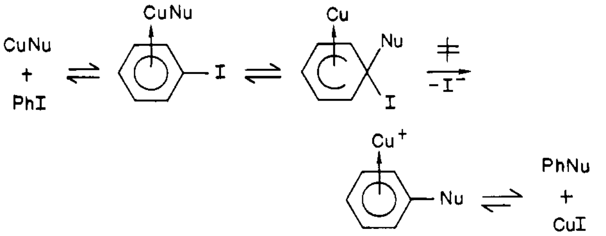
(30) Note that in the case of Ullmann biaryl coupling, we do not know whether formation of PhCu or loss of X^- might be rate limiting (or, indeed, what oxidation state of copper forms PhCu), only that once PhCu is formed, it may give the biaryl product by the same mechanism.

(31) Cowdrey, W. A.; Davies, D. S. *Q. Rev.* **1952**, *6*, 358–379.

(32) (a) Cohen, T.; Wood, J.; Dietz, A. G., Jr. *Tetrahedron Lett.* **1974**, 3555–3558. (b) Mugnier, Y.; Laviron, E. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1264–1266.

(33) (a) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413–420. (b) Rossi, R. A. *Ibid.* **1982**, *15*, 164–170. (c) Bunnett, J. F.; Creary, X. *J. Org. Chem.* **1974**, *39*, 3611–3614.

other, stable transition metal arene carbonyl complexes,[34] but it suffered two disadvantages. First, the element effect of the model arene carbonyl substitutions is the same order as in uncatalyzed nucleophilic aromatic substitution[34c]—i.e., in the reverse order of the copper mediated reactions. Second, the π-complexed intermediates cannot easily rationalize the well-known strong *o*-carboxylate accelerating effect when *p*-carboxylate has no effect.[1]



(8)

Thus, neither of the working hypotheses is completely satisfactory. Another unresolved issue is whether CuNu is monomeric or aggregated in solution, and what the role of the various species might be. Given the plethora of demonstrated mechanisms for uncatalyzed nucleophilic aromatic substitution (including benzyne, $S_{RN}1$, S_N(ANRORC), S_NAr, S_N1, etc.[29] it is not unreasonable to expect that several mechanisms may also exist for transition metal catalyzed nucleophilic aromatic substitution. Fortunately, the synthetic scope and industrial utility of these reactions guarantees continued interest in the details of the reaction mechanism.

Conclusions

The weight of evidence from all the conditions and catalysts employed in these experiments points to a single catalytic species in Ullmann condensation reactions, which (on the basis of the homogeneous experiments) must be cuprous ion. Our direct evidence for solution catalysis in a filtered metal catalyzed reaction forces us to reject the seductive appeal of metal surface catalysis in this case. Wide variations in catalytic activity and yield commonly associated with various copper catalyzed condensations appear to be due to variations in the availability of surface cuprous ion, and the ease with which it may be dissolved for homogeneous catalysis. Where copper salts are to be used, it is important to employ the nucleophile anion to solubilize cuprous ion, so, for example, CuI/K_2CO_3 is an ineffective catalyst for triarylamine synthesis.[23] Cupric ion is less suitable a catalyst than cuprous ion because it must first be reduced to cuprous by the nucleophile, and use of large mole ratios of cupric catalyst often leads to undesirable oxidative side reactions.

Acknowledgment. We thank Dr. T. Bluhm for X-ray powder diffraction analyses and Dr. A. Perovic for transmission electron microscopy.

Registry No. PhI, 591-50-4; Ph_2NLi, 5856-89-3; CuI, 7681-65-4; CuBr, 7787-70-4; CuCl, 7758-89-6; $CuSO_4$, 7758-98-7; Cu, 7440-50-8; $Cu(acac)_2$, 13395-16-9; $C_{10}H_7NHPh$, 90-30-2; $3\text{-}ClC_6H_4NHPh$, 101-17-7; $3\text{-}CF_3C_6H_4NHPh$, 101-23-5; $4\text{-}MeOC_6H_4I$, 696-62-8; $3\text{-}CF_3C_6H_4I$, 401-81-0; $4\text{-}CF_3C_6H_4I$, 455-13-0; $4\text{-}IC_6H_4I$, 624-38-4; $2\text{-}ClC_6H_4I$, 615-41-8; $2\text{-}IC_6H_4I$, 615-42-9; $3\text{-}CH_3C_6H_4I$, 625-95-6; $2\text{-}CH_3C_6H_4I$, 615-37-2; $3\text{-}ClC_6H_4I$, 625-99-0; $C_{10}H_7NPh_2$, 61231-45-6; Ph_3N, 603-34-9; $4\text{-}MeOC_6H_4NPh_2$, 4316-51-2; $3\text{-}CF_3C_6H_4NPh_2$, 106336-12-3; $4\text{-}CF_3C_6H_4NPh_2$, 36809-32-2; $4\text{-}Ph_2NC_6H_4NPh_2$, 14118-16-2; $4\text{-}IC_6H_4NPh_2$, 38257-52-2; $2\text{-}ClC_6H_4NPh_2$, 20441-02-5; $2\text{-}IC_6H_4NPh_2$, 78600-32-5; $3\text{-}ClC_6H_4NPh_2$, 106336-13-4; $3\text{-}CH_3C_6H_4NPh_2$, 4316-54-5; $2\text{-}CH_3C_6H_4NPh_2$, 4316-55-6; CuO, 1317-38-0; $C_{10}H_7I$, 90-14-2.

---

(34) (a) Knipe, A. C.; McGuinness, S. J.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1979**, 842–843. (b) Semmelhack, M. F.; Hall, H. T., Jr.; Farina, R.; Yoshifuji, M.; Clark, G.; Bargar, T.; Hirotsu, K.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 3535–3544. (c) Walker, P. J. C.; Mawby, R. J. *Inorg. Chim. Acta* **1973**, *7*, 621–625. (d) Litvak, V. V.; Filatova, L. S.; Selivanova, G. A.; Shteingarts, V. D. *J. Org. Chem. USSR* **1978**, *16*, 303. (e) Alemagna, A.; Buttero, P. D.; Gorini, C.; Landini, D.; Licandro, E.; Maiorana, S. *J. Org. Chem.* **1983**, *48*, 605–607. (f) Kane-Maguire, L. A. P.; Honig, E. D.; Sweigart, D. A. *Chem. Rev.* **1984**, *84*, 525–543.

(35) Wittig, G.; Reidel, B. *Chem. Ber.* **1963**, *96*, 2851.

(36) Creason, S. C.; Wheeler, J.; Nelson, R. F. *J. Org. Chem.* **1972**, *37*, 4440–4446.

(37) *Dictionary of Organic Compounds*, 4th ed.; Eyre and Spottiswoode Ltd: London, UK, 1965; (a) p 2686, (b) p 1299.

(38) Bacon, R. G. R.; Hamilton, S. D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2391.

(39) Nelson, R. F.; Adams, R. N. *J. Am. Chem. Soc.* **1968**, *90*, 3925–3930.

(40) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper and Row: New York, 1976; p 62.