

COPPER(1) CATALYSED AROMATIC NUCLEOPHILIC SUBSTITUTION: A MECHANISTIC
 AND SYNTHETIC COMPARISON WITH THE $S_{RN}1$ REACTION

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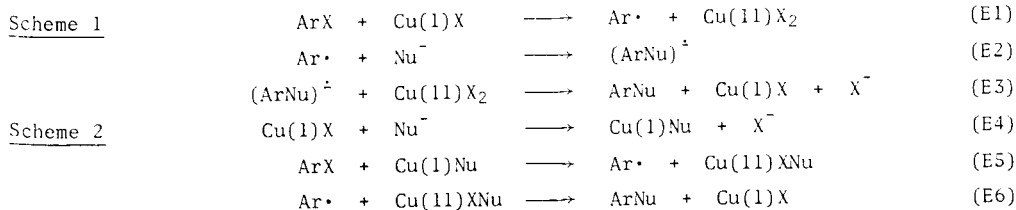
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Summary: Evidence is provided to support a mechanism for Cu(1) catalysed aromatic nucleophilic substitution via inner-sphere electron-transfer and a Cu(111) intermediate, and to show the synthetic potential for Cu(1) catalysis relative to the $S_{RN}1$ reaction.

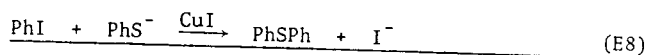
Substitution in non-activated aromatic compounds can be achieved by de-diazonation, $S_{RN}1$, and metal-catalysed reactions. The scope of the $S_{RN}1$ reaction continues to grow rapidly.¹ Increasing interest has been shown in the use of Cu(1) catalysis for nucleophilic substitution² in synthesis. It is therefore surprising that relatively little comment²⁻⁷ has been made regarding the mechanism of Cu(1) catalysis.

We initially reported⁶ that 2-phenyl- and 2-methyl-1,3-benzothiazole could be synthesised from *o*-halothiobenzanilides by $S_{RN}1$ with entrainment or by the use of catalytic amounts of Cu(1). These Cu(1) catalysed reactions were not inhibited by strong electron-acceptors [O_2 , *p*-dinitrobenzene (*p*DNB)] or radical-scavengers [O_2 , di-*t*-butylnitroxide (DTBN)]. In this communication we present the results of our studies of Cu(1) catalysed nucleophilic substitution.

The close similarity with $S_{RN}1$ reactions suggested a $S_{RN}1$ type mechanism⁵ (Scheme 1). In this chain mechanism Cu(1) acts in catalytic manner, as we previously observed.⁶ The first step (E1) involves inner-sphere electron-transfer with atom-transfer.⁷ The electron available for transfer in Cu(1) is in an inner-sphere and is only able to transfer via atom-transfer. The effectiveness of halogens as bridging atoms in this process is $I > Br > Cl$, which supports earlier observations^{2,6} on relative rates of Cu(1) catalysed nucleophilic substitutions. Steps (E2) and (E3) are similar to the $S_{RN}1$ mechanism, with intermediate aryl radicals and radical-anions.



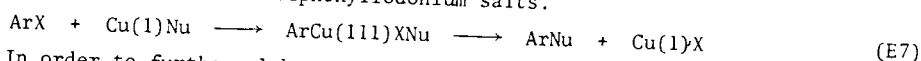
J.K. Kochi⁷ has, however, shown that free radicals react rapidly with Cu(11) species with atom-transfer (E6), e.g. in the Sandmeyer reaction. A chain mechanism (Scheme 2), also with Cu(1) as the chain carrier, involving inner-sphere electron-transfer with atom-transfer (E5), and atom-transfer (E6), is therefore also possible. A third mechanism with a Cu(111) inter-



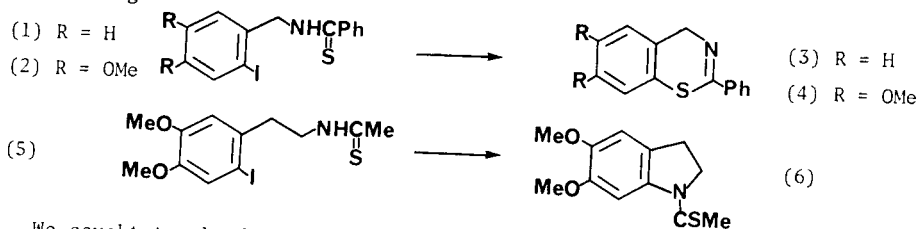
Equiv. CuI	Conditions*	% Recovery PhI	% Yield PhSPH
0	Dark; hv	63; 35	4; 20
1.0	90°; 6.5 h; 2.75 h (2 equiv. PhI); 1 h	Near quant.; 59; 44	Trace; 59; 23
	Standard conditions*	14, 14, 24	73, 67, 52
	Dark; dark + 20 mol % pDNB	8; 12	42; 61
	Dark + 20 mol % DTBN	12	52
0.2	Standard Conditions*	27, 43, 56, 20	32, 16, 21, 14
	Dark; 20 mol % pDNB and DTBN	44, 44; 37; 35	16, 11; 10; 19

* PhI (1.225 mmol), PhSH (1.2 equiv.), NaH (1.4 equiv.), N₂, 100-110°C, 4 h, hv (12 x 25 W at 350 nm), HMPA. - Unless otherwise stated.

mediate (E7) which undergoes reductive elimination⁷ (E7) has been proposed for aryl halogen exchange³ and reactions of diphenyliodonium salts.⁴



In order to further elaborate the mechanism and synthetic potential of Cu(1) we studied several systems related to the *o*-halothiobenzanilides. When *N*-thiobenzoyl-*o*-iodobenzylamine (1) was reacted under S_{RN}1 conditions,⁶ even with entraining anions, no cyclised product was obtained. A low yield was obtained by prolonged heating at 75°C. The use of one equiv. of CuI gave good yields (61-78%) of the cyclised 2-phenylbenzo-1,3-thiazine (3) (DMF, 75°C, t-BuOK 2-3 h) while a catalytic amount of CuI (0.2 equiv.) gave a 39% yield. The addition of 20 molar % of pDNB to the former reaction gave no inhibition (75% yield). The dimethoxy analogue (2) and its phenylethylamine analogue (5) were similarly unreactive by S_{RN}1 but with Cu(1) gave cyclised products, (4) (48%) and (6) (35%) resp. The latter thioamide (5) cyclised via the *N*-centred nucleophile (not observed in S_{RN}1 reactions¹) rather than via sulphur to a seven-membered ring.



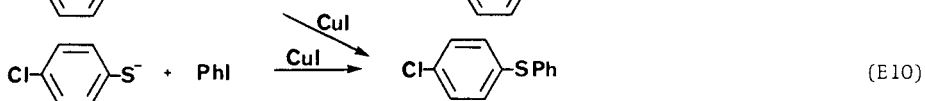
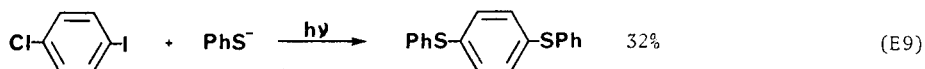
We sought to obtain further evidence on the mechanism of Cu(1) catalysis and therefore carried out a study of a well-established aromatic nucleophilic substitution. The reaction between iodobenzene and phenylthiolate (E8) has been reported to proceed by both S_{RN}1¹ and by Cu(1)⁸ catalysis. The results of our studies are shown in the table. The reaction was studied at 100-110°C for 4 h so as to observe maximum possible inhibition effects (*i.e.* near completion). In the absence of Cu(1) and light a very low yield of Ph₂S was obtained, indicating a slight thermal S_{RN}1 reaction.¹ With light catalysis the yield increased to 20% indicating a significant S_{RN}1 contribution. The use of a catalytic amount of CuI (0.2 equiv.) gave lower yields suggesting that Cu(1) is not completely catalytic.

Addition of pDNB, O₂, or DTBN gave lower yields of Ph₂S with both 0.2 and 1.0 equivs. of CuI, which corresponded approximately to the inhibition of the S_{RN}1 contribution; *e.g.* the yield of Ph₂S with CuI (1.0 equiv.) in the dark (S_{RN}1 largely excluded) was 47% and with added

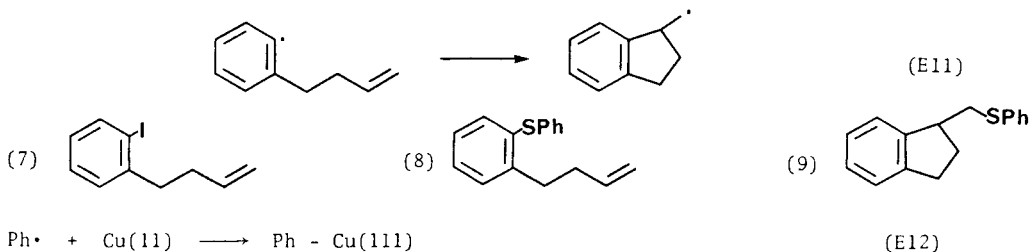
DNB or DTBN was 61 and 52% resp. These results suggest that the yield of Ph₂S due to CuI catalysis (0.2 or 1.0 equivs.) is unaffected by these inhibitors.

Inhibition is certainly not significant in any of our reactions, but the results do vary and do not give clear-cut evidence for the absence of intermediate radical-anions and aryl radicals and, therefore, can only be used as a guide. In order to obtain better evidence for the lack of S_{RN}1-type mechanism two important diagnostic methods were used.

The use of dihalobenzenes has been reported^{1,9} as an excellent test for the intermediacy of aryl radical-anions and the S_{RN}1 mechanism. Reaction between phenylthiolate and chloroiodobenzenes yield exclusively di-substitution under S_{RN}1 conditions whereas chlorobenzene is unreactive. 1-Chloro-4-iodobenzene was reacted with PhS⁻ under S_{RN}1 conditions to yield exclusively the disubstituted product (E9). When the reaction was repeated with CuI (0.2 or 1.0 equivs.) a quantitative yield of mono-substitution was obtained (E9/10). Similarly, the reaction between *p*-chlorophenylthiolate and iodobenzene (E10) gave only mono-substitution (92%) but under S_{RN}1 conditions gave polymeric material. These results conclusively eliminate halo-aryl radical-anions in the mechanisms.

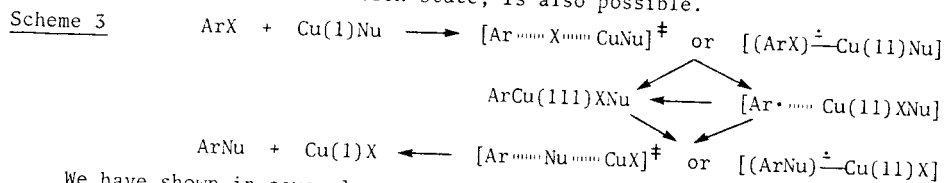


The second diagnostic technique used was the potential intramolecular ring closure between an olefin and an aryl radical (E11) to prove the intermediacy of aryl radicals.¹⁰ Prof. Glen Russell (Iowa State University) has kindly allowed us to use some of his preliminary results: the reaction between 4-(2-iodophenyl)-1-butene (7) and PhS⁻ with CuI (HMPA, 100°C, 1.5 h) gave the diarylsulphide (8) (76%) with unreacted starting material (7) (20%) and no ring-closed product, while the reaction between (7) and PhS⁻ under S_{RN}1 conditions (DMSO, 45°C, hν) gave considerable amounts of the ring-closed sulphide (9). The S_{RN}1 reactions of aryl halides are well known to proceed via aryl radicals as borne out by the above result.



The absence of ring closure in the Cu(I) reaction suggests that aryl-radicals are not intermediates unless the reaction between aryl-radical and Cu(I) (E12) is much faster than the ring closure. The rate for ring closure¹¹ and for the reaction between Cu(I) and phenyl (Ph·)¹² (E12) have been reported to be $\approx 10^6 \text{ s}^{-1}$ and $1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ resp. The rates are not strictly comparable and no definite conclusion can be drawn but the difference in actual rate is unlikely to be large enough to exclude ring-closure completely as has been reported for some aliphatic reactions.¹²

The results reported indicate that neither aryl-radicals or halo-aryl radical-anions are free intermediates in Cu(I) catalysed aromatic substitution reactions. Mechanisms as shown in Schemes 1 and 2 are therefore unlikely. We propose that Scheme 3 is a likely explanation for the mechanism. Evidence for the reductive elimination (E7) from Cu(III) species by intramolecular migration has been elaborated.^{3,4,7} The first step in (E7) could therefore be formulated as the reverse reaction, *i.e.* oxidative addition of Cu(I) to the aryl halide. A nucleophilic displacement by Cu(I) on the aryl-carbon cannot be ruled out but is unlikely due to the inner-sphere nature of the Cu(I) bonding electrons. Our conclusions are summarised in Scheme 3 : inner-sphere electron-transfer from Cu(I) to ArX to give a transition-state (or a distinct radical-anion/Cu(III) complex) which leads to a Cu(III) intermediate, followed by the reverse movement of the electrons and atoms to ArNu and Cu(I)X. An 'undissociated complex' of the aryl-radical and Cu(III), tightly held in a solvent cage, leading either to Cu(III) species or to the next transition state, is also possible.



We have shown in several systems that Cu(I) catalysis gives good yields of substituted products when $S_{\text{RN}}1$ conditions have failed. We therefore recommend that Cu(I) catalysis can be used in syntheses which could be predicted to proceed by the $S_{\text{RN}}1$ mechanism and are unsuccessful, and should be regarded as a standard procedure in organic synthesis for aromatic nucleophilic substitution.

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