# The Reaction of Phenyllithium and the Halotoluenes. Competing Aryne, Displacement, and Halogen–Metal Exchange Processes

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Abstract: The reaction of phenyllithium with the halotoluenes in benzene and benzene–ether has been studied in refluxing solvent and at 20°. The catalytic effect of piperidine and N,N,N′,N′-tetramethylethylenediamine (TMEDA) was also examined. Aryne formation was found to be the exclusive mechanism leading to biaryl generation for the fluoro, chloro, and bromo compounds while competition from an alternative process, apparently displacement, was observed for the iodotoluenes. Extensive halogen–metal exchange was observed only for the bromo and iodo compounds. Depletion of the concentration of the initial reagents by this process as well as the subsequent reaction of these exchange products prevents determination of an order of aryne-forming ability for the halide series. The relative rates of the various processes, as well as the over-all biaryl yield, were found to depend on the particular solvent–catalyst system employed. The possibility of synthetic application of dimethyl sulfate quenching of reaction mixtures was also examined.

The reaction of aryl halides with strong bases (*e.g.*, OH^-, NH_2^-, $C_6H_5^-$) has been extensively investigated.[2a] The appearance of "rearrangement" product, wherein the nucleophile appears *ortho* to the site of displaced halogen, in addition to the expected displacement product (eq 1) is characteristic of these reactions.[3] This unusual result led to numerous synthetic applications and a reasonable amount of confusion regarding the mechanism of the reaction[3] which has been re-

$$(1)$$

<center>displacement   rearrangement</center>
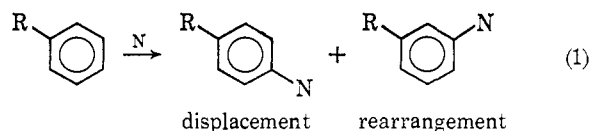
solved by the conclusive demonstration that the aryne intermediate is the major reaction pathway to products (both "rearrangement" and "displacement") in a number of reaction systems: the amination of chlorobenzene with potassamide in liquid ammonia,[4] the reaction of aryl fluorides with phenyllithium in ether,[5] and the hydrolysis of the halotoluenes at 340°.[6]

Aryne formation occurs *via* a two-step process, proton abstraction to generate the *o*-halo aryl carbanion which subsequently eliminates halide to form the aryne.[2b] The aryne can then undergo nucleophilic attack at either site to yield product carbanions corresponding to "rearrangement" and "displacement" (eq 2). Depending on the nucleophile–solvent system employed, proton abstraction,[4,7] and/or halide elimination[8,9] can be reversible. The relative rates at which these two steps

occur is also dependent on the system and either may be rate determining.[10]

$$(2)$$
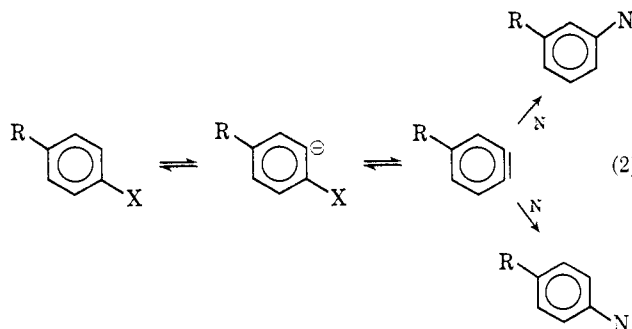
For a given halo arene the rate of reaction depends on the particular halide employed, regardless of which step is rate determining. If proton loss is rate determining, the halides should react in the order $F > Cl > Br > I$, paralleling the decreasing electronegativity of the halogen[11] and consequently the acidity of the adjacent proton. If the second step is rate determining, the rate should depend on the leaving-group ability of the halogen. Experimental evidence indicates that the order with regard to this property is $I > Br > Cl > F$.[2c,9]

Previous studies on the reaction of the unsubstituted aryl halides with phenyllithium have yielded an order of halide reactivity which is not compatible with either of the above predictions, *i.e.*, $F > Br > Cl > I$.[10,12] Other systems in which a "scrambled" order of reactivity exists have been reported.[10,13] A detailed explanation of such observations involves the reversibility of proton abstraction as an important process.[10] However, this would not be expected to be significant in the

(1) (a) National Science Foundation Graduate Trainee; (b) taken in part from the Ph.D. dissertation of J. F. C., Case Western Reserve University, 1969.

(2) R. W. Hoffman, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967: (a) pp 9–60, 133–150; (b) p 15; (c) pp 44, 46; (d) pp 136, 140; (e) p 148.

(3) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 49, 273 (1951).

(4) J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith, and C. W. Vaughan, *J. Am. Chem. Soc.*, 75, 3290 (1953).

(5) R. Huisgen and H. Rist, *Naturwissenschaften*, 41, 348 (1954).

(6) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, 79, 1458 (1957).

(7) G. E. Dunn, P. G. Krueger, and W. Rodewald, *Can. J. Chem.*, 39, 180 (1961).

(8) G. Wittig and R. W. Hoffman, *Chem. Ber.*, 95, 2729 (1962).

(9) R. W. Hoffman, *ibid.*, 98, 222 (1965).

(10) R. Huisgen and J. Sauer, *ibid.*, 92, 192 (1959). For a comprehensive review of the reactions of aryl halides with phenyllithium and lithium piperidide see R. Huisgen in "The Kekulé Symposium," Butterworth & Co. (Publishers), Ltd., London, 1959, p 158, and "Organometallic Chemistry," H. Zeiss, Ed., American Chemical Society Monograph Series No. 147, Reinhold Publishing Corp., New York, N. Y., 1960, p 36.

(11) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, p 90.

(12) G. Wittig, G. Pieper, and G. Fuhrmann, *Ber.*, 73, 1193 (1940).

(13) F. W. Bergstrom, R. E. Wright, C. Chandler, and W. A. Gilkey, *J. Org. Chem.*, 1, 170 (1936).

aryllithium–aryl halide systems since benzene, the conjugate acid of the proton abstracting agent, is extremely insensitive to deprotonation in the absence of amine catalysts. An alternative explanation of the "scrambling" is the inclusion of a competing displacement process in the reaction scheme. Under these circumstances any order of halide reactivity would be possible.

The high relative reactivity of the fluoro arenes suggests that proton abstraction is the rate-determining step for the aryne-forming process. Displacement of halide via a bimolecular process depends on the leaving-group ability of halogen and has been observed: for example, the reaction of lithium diphenylphosphide with aryl bromides[14] and the reaction of aryl fluorides with potassium t-butoxide in dimethyl sulfoxide.[15] Thus, inclusion of the displacement process in the over-all reaction scheme could provide a reasonable explanation of the scrambled order of reactivity. Unfortunately, the products of the aryne and displacement reactions are indistinguishable for the halobenzenes. In the present study the reaction of phenyllithium with the halotoluenes was examined since the site of attack by the nucleophile could be detected and determination of the extent of reaction via distinct pathways might be possible.

As a corollary to this investigation, the effect of amine catalysis was also examined. Enhancement of both metalation and substitution reactions of alkyl- and aryllithium compounds in the presence of secondary and tertiary amines has been reported.[16-18] Therefore, in the phenyllithium–halotoluene system, where both processes might occur, the effect of such catalysis was expected to be of theoretical and possible synthetic value.

The results of reaction of the halotoluenes with phenyllithium in benzene[19] at reflux are given in Table I.[20] Interpretation of these data in terms of competing processes demands that a standard isomer composition for reaction occurring via the aryne route be established. Reference to reports of nucleophilic addition to the 3- and 4-methylbenzyne (1 and 2) is confusing. The meta/ortho product ratio (products derived from addition to 1) ranges from 0.8 to exclusive meta attack; the para/meta ratio (addition to 2) varies between 0.54 and 1.0.[2d] In view of this inconsistency, the biaryl distribution observed from reaction of the fluoro compounds was chosen as the internal standard for aryne-derived product composition.

The validity of this choice is based primarily on the constant isomer composition obtained from both the isomeric fluoro- and chlorotoluenes under normal reaction conditions and in the presence of the amine catalyst N,N,N',N'-tetramethylethylenediamine

(14) A. M. Anguiar, H. J. Greenberg, and K. E. Rubenstein, J. Org. Chem., 28, 2091 (1963).

(15) D. J. Cram, B. Rickborn, and G. R. Knox, J. Am. Chem. Soc., 82, 6412 (1960).

(16) M. D. Rausch and D. J. Ciapenelli, J. Organomet. Chem. (Amsterdam), 10, 127 (1967).

(17) A. J. Chalk and T. J. Hoogeboom, ibid., 11, 615 (1968).

(18) R. J. Honour, unpublished data.

(19) The phenyllithium used in these experiments was obtained from Lithium Corporation of America as a benzene solution which contains about 20% ether by volume.

(20) Less than the stoichiometric amount of phenyllithium necessary for complete consumption of halotoluene was used (1.65 mol of phenyllithium per mol of halotoluene vs. 2.00 mol of phenyllithium per mol of halotoluene demanded by the stoichiometry). This was done to allow observation of secondary processes which would have escaped detection in the presence of an excess of phenyllithium.

Table I. Methylbiphenyl Product Composition from Reaction of Halotoluenes with Phenyllithium in Benzene–Ether[a]

| $CH_3C_6H_4X$ X	% yield[b,c]	% composition of methylbiphenyls		
		ortho	meta	para
Uncatalyzed Reactions				
o-F	45	33	67	
m-F	53	12	55	33
p-F	72		50	50
o-Cl	19	34	66	
m-Cl	27	9	54	37
p-Cl	51		51	49
o-Br	6	56	44	
m-Br	14	5	73	22
p-Br	17		26	74
o-I	21	94	6	
m-I	28	2	91	7
p-I	24		2	98
TMEDA-Catalyzed Reactions				
o-F	53	34	66	
m-F	73	14	54	32
p-F	77		50	50
o-Cl	53	33	67	
m-Cl	63	14	53	33
p-Cl	71		51	49
o-Br	27	46	54	
m-Br	30	10	64	26
p-Br	30		39	61
o-I	23	88	12	
m-I	36	3	85	12
p-I	20		12	88

[a] Relative reagent concentration $CH_3C_6H_4X$–C_6H_5Li–TMEDA (where used): 1 (0.3 M):1.6:0.02. Reactive conditions: 5 hr at reflux (~75°); solvent system: cf. Experimental Section and ref 19. [b] Based on starting halotoluene. [c] The balance of reaction products can be accounted for as recovered starting material and (where applicable) exchange-derived products. For example, the total product composition from p-bromotoluene is: p-bromotoluene 14%, bromobenzene 20%, biphenyl 33%, methylbiaryls 17%, dimethylbiaryls 3%, material balance 87%.

(TMEDA). If more than one mechanism were operative, one would expect drastic variations in isomer composition on enhancing the base strength and nucleophilicity of the anionic reagent via addition of amine. It would be remarkably fortuitous that such a change should have the same effect (or lack of effect) on different aryl halides were not a single mechanism operative for both compounds.

Additional evidence that these compounds react exclusively via the aryne route is the statistical substitution observed on reaction of the p-halotoluenes, that is, equal attack at both positions of the aryne bond. The selectivity observed on reaction of the ortho compounds (meta substitution is favored by a factor of 2 over attack at the ortho position of 3-methylbenzyne) is also compatible with a scheme implicating solely the aryne as intermediate. The meta/ortho ratio is within the range of values observed previously (vide supra). Furthermore, the observed product composition obtained from reaction of the fluoro and chloro meta compounds which afford both 3-methyl and 4-methylbenzyne (eq 3) as intermediates is consistent with the assumption that all products are derived from aryne intermediates. That is, the per cent composition of ortho- and para-substituted product can be used as an index of the amount of 1 and 2 formed, yielding a predicted meta-product composition consistent with that observed.[21]

(21) Calculation of the predicted meta product composition (for the fluoro- and chlorotoluenes) is based on the assumption that all

(3)
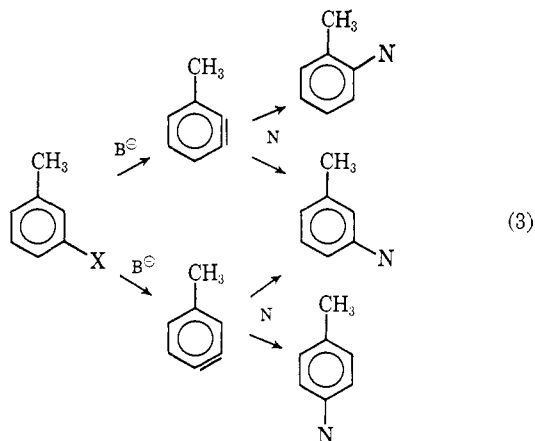
The selectivity noted above for nucleophilic attack on 1 can be explained on the basis of either kinetic or thermodynamic control. That is, product orientation can be determined by either electronic[22] and/or steric effects[2e] of substituents on the aryne (kinetic control) or by the relative stabilities of the product anions (thermodynamic control).[4,23] Thermodynamic control can be discounted on the basis of the stabilizing power of the phenyl substituent which is *ortho* to the anion in both products. The presence of the phenyl substituent would be expected to make differences in carbanion stability attributed to the inductive effect of the methyl group insignificant.[24]

A distinction between steric and electronic effects of the methyl group on the intermediate aryne can be made by referring to the analogous selectivity observed in systems where distinguishable arynes can be formed. The *m*-halotoluenes give 1 and 2 arising from abstraction of proton *ortho* and *para* to the methyl group, respectively, with subsequent halide loss. The ratio of 2 to 1 calculated[25] from the observed isomer distribution indicates a preference for formation of 2 from *all* *m*-halides (Table II). This can be explained in terms of

Table II. Ratio of 4-Methylbenzyne to 3-Methylbenzyne Formed from the *m*-Halotoluenes

m-CH₃C₆H₄X X	4-Methylbenzyne/3-methylbenzyne[a,25] No catalyst	TMEDA catalyst
F	1.8	1.5
Cl	2.7	1.5
Br	2.9	1.7
I	2.3	2.7

a Calculated from data in Table I.

product is formed from aryne intermediates and that the total biaryl yield from the *m*-halotoluenes is related to the amount of *ortho-* and *para*-substituted product by: total biaryl = 3(*o*-methylbiphenyl) + 2(*p*-methylbiaryl) as derived from the selectivity observed from reaction of the *o*- and *p*-fluorotoluenes. Thus the composition of the *meta*-substituted product is given by the relation: % *m*-biaryl = 2(% *o*-biaryl) + % *p*-biaryl. For example, the predicted *meta* composition from the reaction of *m*-fluorotoluene in the absence of catalysis is 57 % [2(12 % *ortho*) + 33 % *para*] compared to the observed composition, 55 %.

(22) R. Huisgen and J. Sauer, *Angew. Chem.*, **72**, 91 (1960).
(23) R. Huisgen and H. Rist, *Ann. Chem.*, **594**, 137 (1955).
(24) R. Huisgen, W. Mack, K. Herbig, N. Ott, and E. Anneser, *Chem. Ber.*, **93**, 412 (1960).
(25) Calculation of the ratio of 2 to 1 is based on the following assumptions: (1) all *ortho* and *para* product is aryne derived and (2) the substituted patterns observed for the assumed "standard" aryne reactions are valid. The ratio can then be obtained from the expression

$$2/1 = \frac{2(para\text{-substituted biaryl})}{3(ortho\text{-substituted biaryl})}$$

the stability of the product carbanion or the acidity and/or steric hindrance to removal of the proton. Relative carbanion stability can again be discounted since the inductive contribution of the methyl group affecting carbanion stability would be expected to be minor in comparison to the effect of the halogens which are powerfully electron-withdrawing, stabilizing groups. This is substantiated by the results; in general the selectivity of proton removal decreases as the electron-withdrawing power of the halogen increases. In the presence of catalyst the same effect is observed although a leveling effect due to the increased strength of the proton-abstracting agent is apparent. Significantly, a selectivity factor of 1.5 remains (favoring *para* abstraction) when the discriminating ability of the base is the same for reaction with the fluoro and chloro compounds. Thus, steric inhibition by methyl and halide (the order of decreasing halogen size also parallels decreasing selectivity) appears to be the best explanation for the *residual* selectivity.

Since the selectivity for proton removal is of the same magnitude and in the same direction as that observed for selectivity of nucleophilic attack on the aryne, the same explanation can be applied. That is, the steric effect of the methyl group, rather than its inductive contribution to polarization of the aryne, best explains the preference for *meta*, rather than *ortho*, attack.

The wide variation in yield of methylbiaryls from the reaction of the halotoluenes with phenyllithium is a result of the following factors: (1) the relative reactivity of the halotoluene which in turn limits the extent of reaction completed at quenching, (2) the stability of tolyllithium as a function of time, and (3) the effect of catalyst on factors 1 and 2. In the uncatalyzed reactions the increase in yield of methylbiphenyls from the *o*-, *m*-, and *p*-fluoro and -chloro isomers can be explained as follows. The low yields from the *ortho* isomer can be attributed to a statistical effect, *i.e.*, only one hydrogen is available. In the case of the *meta* isomer, while there are two available hydrogens, one is sterically hindered. In the catalyzed reaction these differences are compressed.

If aryne formation and a competing displacement reaction were the only reactions occurring in the system, one could interpret deviations from the "aryne distribution" as characteristic of the SN2 process, and a numerical estimate of the extent to which each process occurs could be formulated. However, an alternate route which does not involve displacement reaction can be postulated. If halogen–metal exchange occurs in these systems, the products of exchange, phenyl halide and tolyllithium, are capable of reacting *via* a benzyne route, as substrate and nucleophile respectively, to generate products which on quenching would be identical with those attributed to displacement (eq 4).

(4)
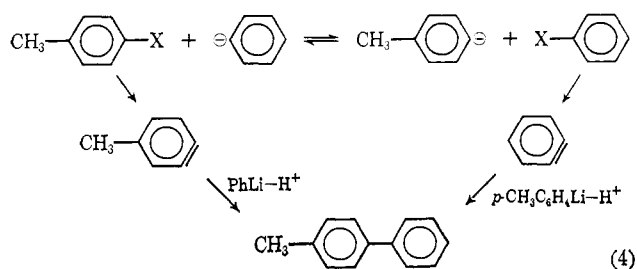
Halogen–metal exchange has been suggested as an important side reaction for *all* the halotoluenes reacted under similar conditions.[26] However, dimethylbiaryls, which implicate the lithiotoluenes as intermediates, were detected only from reaction of the bromides and iodides (Table III). Moreover, when the reactions

Table III. Dimethylbiphenyl as a Function of *p*-Halotoluene Precursor[a]

p-CH₃C₆H₄X X	Methylbiphenyls *meta*	Methylbiphenyls *para*	Dimethylbiphenyls 3′,4	Dimethylbiphenyls 4,4′
F	36	36	0	0
Cl	25	26	0	0
Br	6	24	2	3
I	tr	35	0	6

[a] Halotoluene:phenyllithium 1:1.65; benzene–ether solvent.

were analyzed for halobenzene and toluene (the expected products of exchange) they were not detected in the product mixtures obtained from the fluoro and chloro isomers.[27] On the basis of these observations, it is apparent that the exchange reaction is important as a competitive process only for the bromo- and iodotoluenes.

The exchange reaction of the bromo-[28] and iodotoluenes[29] has been studied in some detail and has been shown to be an equilibrium system governed by the stoichiometry depicted above (eq 4). This observation was confirmed under the conditions of this study by quenching reaction mixtures with dimethyl sulfate, thus allowing direct determination of all the components of the exchange equilibrium. Thus, phenyllithium and *p*-tolyllithium were detected as toluene and *p*-xylene, respectively.[30a] The values of the equilibrium relationship obtained at 5 and 60 hr correspond to those reported (Table IV).

In view of these observations, the mechanism leading to "unrearranged" product in excess of that attributed to nucleophilic attack on aryne cannot be immediately determined. Product compositions which may arise *via* the displacement reaction are observed only in those systems wherein exchange occurs, and can be followed by an aryne process.

(26) H. J. S. Winkler and H. Winkler, *J. Am. Chem. Soc.*, **88**, 969 (1966).

(27) Small amounts (*ca.* 1%) of dimethylbiaryl can be observed in the early stages of the reaction of the chlorotoluenes. However, the fact that there is no increase in these products after 10 min suggests that these spurious results may be attributed to reagent impurity. Regardless of the source of these products, participation of the halogen–metal exchange for the chlorotoluenes is a negligible process.

(28) H. J. S. Winkler and H. Winkler, *J. Am. Chem. Soc.*, **88**, 964 (1966).

(29) H. Gilman and R. G. Jones, *ibid.*, **63**, 1441 (1941).

(30) (a) Determination of the amounts of aryl anions present by this method was complicated by the reaction of these anions with proton source in the system. That is, a fraction of the toluene derived on quenching phenyllithium with dimethyl sulfate was the product of reaction of *p*-tolyllithium with a proton source prior to quenching. This was allowed for in these determinations by referring to the normal reactions to obtain the amount of internally quenched material. (b) Analysis of the biaryl products of these reactions was complicated by residual biaryl formed in the preparation of the *p*-tolyllithium. Although care was taken (see Experimental Section) to remove contaminants (both *m*- and *p*-methylbiphenyl and bromotoluene) from the organometallic, oxidative coupling, resulting in the formation of 4,4′-dimethylbiphenyl, could not be excluded. Therefore, in all these reactions, the amount of contaminant was determined and subtracted from the observed product distribution.

Table IV. Evaluation of the Equilibrium Relation, K_{eq},[a] as a Function of Time

Solvent	Temp, °C	Time, hr	K_{eq}
Benzene–ether	20	5	0.17
		60	0.64
Ether	25	18	0.36[b]
		48	0.60[b]

[a] $K_{eq} = (p\text{-}CH_3C_6H_4^-Li^+)(C_6H_5Br)/(C_6H_5^-Li^+)(p\text{-}CH_3C_6H_4Br)$.
[b] Data taken from ref 28.

Clarification of this ambiguity is possible by examination of the reaction of *p*-tolyllithium with the *p*-halotoluenes. In this system, halogen–metal exchange does not alter the composition of the reaction mixture, since the process results in regeneration of the initial reagents. Thus, "unrearranged" product in excess of that expected from aryne reaction can only result from a competing, nonaryne process. Limited participation of the *p*-tolyllithium–*p*-halotoluene couple had been observed in reactions of phenyllithium with the *p*-halotoluenes (Table II). However, although the composition of dimethylbiaryl products were distinct from the methylbiaryl composition, indicating a greater degree of aryne participation, the yields were low and the data were not sufficient to clarify the problem.

The results of direct reaction of *p*-tolyllithium with the *p*-halotoluenes (Table V)[30b] exclude participa-

Table V. Dimethylbiaryl Composition from Reaction of *p*-Tolyllithium and *p*-Halotoluene

p-CH₃C₆H₄X X	% yield[a,b]	Dimethylbiaryls —% composition— 3,4′	Dimethylbiaryls —% composition— 4,4′
F	80	51	49
Cl	28	50	50
Br	28	53	47
I	26 (18)[c]	35	65

[a] Based on *p*-tolyllithium (solvent: ether). [b] Reaction quenched (EtOH) after 5 hr (reflux). [c] Corrected for displacement reaction.

tion of the displacement process for the fluoro-, chloro-, and bromotoluenes where the statistical substitution pattern is observed, but do indicate that at least a fraction of the product obtained from the iodo compounds arises from a nonaryne process, presumably displacement.

It is apparent that the mechanistic pathways for reaction of phenyllithium with the halotoluenes cannot be generalized, but vary with the halogen. The overall scheme for the reaction of the *p*-halotoluenes, incorporating all *possible* modes of reaction, is depicted in Scheme I. The fluoro and chloro compounds react *only via* the sequence of steps 1 (proton abstraction from halotoluene), 3 (halide elimination), and 4 (nucleophilic attack on aryne by phenyllithium). The bromotoluenes, in addition to this sequence, readily undergo halogen–metal exchange (2) and then the series of steps leading to benzyne formation, (1′) and (3′), followed by nucleophilic attack by both phenyl and tolyllithium (4′ and 5′, respectively). In addition, methylbenzyne is trapped by tolyllithium (5) formed in the exchange process. The iodo compounds undergo reaction *via* all the indicated paths, including displacement (7).

Scheme I[a]
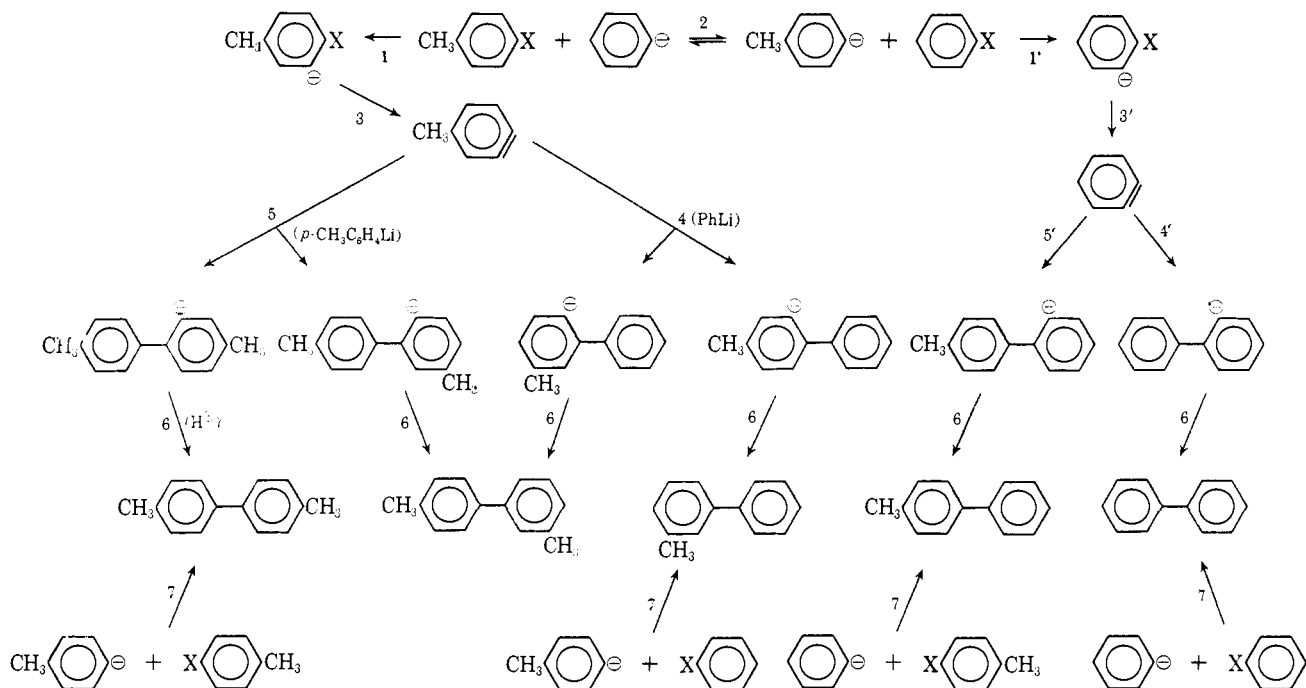
[a] 1 and 1', proton abstraction from halotoluenes and phenyl halide, respectively; 2, halogen–metal exchange; 3 and 3', halide elimination yielding methylbenzyne and benzyne, respectively; 4 and 4', nucleophilic attack of phenyllithium on methylbenzyne and benzyne, respectively; 5 and 5', nucleophilic attack of tolyllithium on methylbenzyne and benzyne, respectively; 6, proton quenching of carbanion; 7, displacement reaction.

The relative and absolute rates at which the various processes occur are quite sensitive to changes in the solvent system and the presence of amine catalyst. When TMEDA is present, in catalytic amounts, the relative rates for aryne formation from the fluoro and chloro compounds, as indicated from the yield data, are tremendously compressed. In the reaction of the bromo- and iodotoluenes, where exchange and displacement are implicated as pathways[31] competing with aryne formation, the increased fraction of "rearrangement" product formed indicates that the rate of aryne formation relative to the exchange process has been accelerated (Table I).

This is not to imply that amine catalysis or alteration of the solvent system affects only one branch of this system. Indeed, the complete product distributions obtained for the p-halotoluenes at 20° in a variety of solvent–catalyst systems indicate that the exchange process as well as the aryne-forming sequence is quite sensitive to changes in the medium (Table VI). A gross measure of the extent to which the halogen–metal exchange equilibrium has been established can be obtained if it is assumed that the total amount of aryl anion remains constant.[32] With this assumption a value for

the equilibrium relationship can be calculated and these results are tabulated in Table VI. The extent of exchange of phenyllithium with p-bromotoluene increases with variation in the solvent system in the order benzene < benzene–TMEDA < ether < ether–TMEDA < benzene–piperidine < ether–piperidine. This is in accord with previous reports in which the rate of attaining, but not the final value of the equilibrium, was found to vary with the medium.[28] The variation in extent of aryne participation measured by the change in methylbiaryl yield roughly parallels the solvent effect observed for the exchange reaction, biaryl yield increasing in the order benzene < ether < benzene–piperidine < ether–TMEDA < benzene–TMEDA < ether–piperidine (Table VII). The ability of TMEDA, ether, and piperidine to enhance biaryl formation is readily explained although the relative magnitude of these effects is not predictable. Ether, which acts as a specific complexing agent for aryllithium compounds,[33] is a polar solvent in contrast to benzene. The effect of assisting the break-up of aryllithium aggregates and providing a medium capable of charge stabilization would be expected to promote formation of intermediates leading to the aryne. TMEDA acts as a complexing agent of lithium, promoting aggregate break-up and/or enhancing the base strength of the aryllithium species. Piperidine is immediately converted to lithium piperidide on mixing with phenyllithium.[10,23] Thus the possibility of catalysis via amine–lithium complexing similar to that for TMEDA is minimized. However, lithium piperidide is a powerful proton-abstracting agent relative to

(31) Detailed mechanisms (one-electron transfer processes) have been postulated for both exchange and displacement reactions of alkyllithium compounds with alkyl and aryl bromides and iodides. Evidence for this has been observed "spectroscopically" [nmr dynamic nuclear polarization; cf. H. R. Ward, R. G. Lawler, and H. T. Loken, J. Am. Chem. Soc., 90, 7360 (1968); A. R. Lepley, ibid., 91, 749 (1969), and references contained therein] and from product isolation (rearrangement products from neophyl bromide and iodide and organolithium reagents: L. Friedman, R. J. Honour, unpublished data). While mechanistic details cannot be inferred from this study, it is apparent that uncaged free radicals are not intermediates in the reaction of p-bromotoluene and p-tolyllithium. They may, however, be present in the reactions of p-iodotoluene (Table V).

(32) Calculations of the value of the equilibrium relation were performed on the basis of the following assumptions: (1) total amount of aryl anion is the same in all systems at the quenching point; that is,

anion depletion by biaryl formation is neglected; and (2) the amount of phenyllithium and tolyllithium observed in the direct determinations is equal to the total aryl anion in these systems (variations in internal quenching are ignored).

(33) G. Wittig, F. W. Meyer, and G. Lange, Ann. Chem., 571, 167 (1951).

p-CH₃-C₆H₄X X	Diluent/catalyst	% yield[b,c] CH₃-C₆H₅	C₆H₅X	CH₃-C₆H₄X	D_{eq}[c,d]
F	Benzene/no catalyst	0	0	65	
Cl		0	0	95	
Br		23	28	75	0.09
I		38	46	42	0.45
F	Ether/no catalyst	0	0	53	
Cl		0	0	95	
Br		32	35	49	0.23
I		33	37	57	0.24
F	Benzene/TMEDA	0	0	18	
Cl		0	0	80	
Br		24	30	56	0.12
I		39	43	47	0.41
F	Ether/TMEDA	0	0	27	
Cl		0	0	84	
Br		29	36	39	0.24
I		43	48	42	0.58
F	Benzene/piperidine	0	0	55	
Cl		0	0	99	
Br		34	41	44	0.34
I		41	49	36	0.62
F	Ether/piperidine	0	0	5	
Cl		0	0	80	
Br		38	34	33	0.35
I		34	42	34	0.42

[a] Relative reagent concentration CH₃C₆H₄X–C₆H₅Li–catalyst (where used) 1 (0.3 M):1.6:0.02. [b] Based on starting halotoluenes; thus for 100% halogen–metal exchange the total yield would be 200%. See Table VII for biaryl products. [c] Determined at 5-hr reaction. [d] $D_{eq} = (CH_3C_6H_4^-Li^+)(C_6H_5X)/(CH_3C_6H_4X)(C_6H_5^-Li^+)$ (for calculation of D_{eq} see ref 32).

Table VII. Biaryl Yield from Reaction at 20°, Media Variation

p-CH₃-C₆H₄ X	Diluent/catalyst	Methylbiphenyls % yield	% composition meta	para
F	Benzene/no catalyst	20	49	51
Cl		22	48	52
Br		2	20	80
I		4	0	100
F	Ether/no catalyst	40	48	52
Cl		3	46	54
Br		2	35	65
I		1	0	100
F	Benzene/TMEDA	75	49	51
Cl		11	48	52
Br		9	48	52
I		7	12	88
F	Ether/TMEDA	64	50	50
Cl		10	49	51
Br		9	46	54
I		5	14	86
F	Benzene/piperidine	46	49	51
Cl		3	44	56
Br		3	36	64
I		5	10	90
F	Ether/piperidine	82	48	52
Cl		21	48	52
Br		14	38	42
I		7	16	84

[a] Relative reagent concentration CH₃C₆H₄X–C₆H₅Li–catalyst (where used) 1 (0.3 M):1.6:0.02.

phenyllithium, accelerating the aryne-forming sequence.[34] The effect of changes in media on the halogen–metal exchange phenomenon can be related to the increase in concentration of reactive anion or enhancement of the solvating power of the solvent and/or catalyst. Further rationalization of these results is not possible, since the mechanism of this process has not been delineated.

In addition to these processes two other reactions have been observed in similar systems: product carbanions (e.g., biaryl anion) act (1) as nucleophiles reacting with aryne in competition with reagent anion,[35] or (2) as bases abstracting labile protons (step 6, Scheme I). Under the conditions used in this study, nucleophilic reaction of the product carbanions was not observed. This implied a relatively high rate of "internal quenching" and, since adaptation of the reaction to general synthetic utility (providing a route to complex aryl compounds via quenching of the carbanion with a carboxylating or methylating agent)[36] depended on the possibility of trapping the carbanion, a more detailed examination of this process was undertaken.

The extent to which aryl carbanion survived the reaction period was determined (Table VIII) by quench-

Table VIII. Anion Survival-Control Reactions and Normal Reaction Mixtures

Temp, °C/catalyst	% aryl anion (at 5 hr)[c] C₆H₅Li	CH₃C₆H₄Li
Control Reactions[a,b]		
75/no catalyst	114	
75 TMEDA	80	
75/piperidine	30	
Normal Reaction Mixtures[b,d]		
75/no catalyst	18	20
75/TMEDA	1	1
75/piperidine	1	0.1
20/no catalyst	96	29

[a] Relative reagent concentration C₆H₅Li–catalyst (where used) 1.6 (0.5 M):0.02. [b] Based on 165% aryl anion at start of reaction. [c] All mixtures from reaction of p-bromotoluene. [d] Relative reagent concentration CH₃C₆H₄Br–C₆H₅Li–catalyst (where used) 1 (0.3 M):1.6:0.02.

ing typical reaction mixtures and control samples with dimethyl sulfate. Carbanion survival is markedly dependent on the temperature, catalyst, and solvent employed. The near total quenching observed when either TMEDA or piperidine is present is best attributed to catalytic enhancement of carbanion base strength and/or the ability of the respective amines to act as proton sources.[37]

Examination of the relative rates of biaryl formation and the quenching reaction showed that both processes occur at almost identical rates under conditions practical for synthetic use. Thus, product carbanion reaches a maximum yield of only 25%, and is internally

(34) Nucleophilic attack on aryne intermediates by piperidide would be expected to be unimportant under these conditions. Phenyllithium has been shown to a much more reactive species for this reaction (cf. ref 9).

(35) R. Huisgen and J. Sauer, Chem. Ber., 91, 1453 (1958).

(36) Preparative quenching reactions of this type are by no means a novel suggestion (cf. ref 4). However, reported methods entail exacting reaction and work-up procedures which would be avoided using the conditions employed in this study.

(37) G. C. Eberhardt and W. A. Butte, J. Org. Chem., 29, 2928 (1964).

quenched so rapidly that capture of this fraction of the biaryl product with an externally added quenching agent is impractical.

As a result of the manifold reactions which occur, to varying degrees, in the phenyllithium–halotoluene system, conclusive resolution of the initial problem (the anomalous relative rates observed for generation of aryne from the halobenzenes, *i.e.*, F > Br > Cl > I) is not possible.

Use of either methylbiaryl product composition or over-all methylbiaryl yield as a measure of the relative reactivities of the halotoluenes is precluded by the occurrence of the exchange reaction (altering the relative concentration of aryne precursor in these systems) and further reaction of the products of the exchange reaction (resulting in facile benzyne formation, occurring at a rate which cannot be related to that for aryne formation). The effect of the exchange reaction is perhaps best illustrated by comparing the effect of the relative reagent ratios in the reaction of the *p*-bromo- and -chlorotoluenes (Table IX).

Table IX. Biaryl Yields as a Function of Phenyllithium–*o*-Halotoluene Ratio

| | $C_6H_5^-Li^+/p$-CH_3- | | | % yield | |
X	$C_6H_4X^a$	$C_6H_5C_6H_5$	m-$CH_3C_6H_4$-C_6H_5	p-$CH_3C_6H_4$-C_6H_5
Cl	0.9	0	12	12
Cl	1.6	0	26	25
Cl	2.7	0	45	45
Br	1.8	38	5.1	18
Br	2.4	47	4.9	18
Br	3.6	45	3.9	13

^{a} 0.3 M.

The only reliable measure of the relative rates for aryne formation can be obtained by correlating the yields of dimethylbiaryls corrected for displacement product from reaction for the *p*-halotoluenes with *p*-tolyllithium. The relative reactivity is F > Cl ≈ Br > I, paralleling that observed from the reaction of phenyllithium with the halobenzenes.[10]

It is apparent, from the results detailed above, that variation of halogen has a profound and complex effect on the reactions of the aryl halide–aryllithium system. The accepted correlations of halogen electronegativity and leaving-group ability with reactivity are not sufficient to explain the participation (or lack of participation) of the manifold reaction pathways and the relative rates at which they occur. Interpretation of the data obtained is further complicated by the dramatic effect of variation of the solvent–catalyst medium. Not only are the relative rates of the various reactions altered, but, in some cases, solvent or "catalyst" may participate directly in the reaction scheme as nucleophile or proton source.

The extent, in some cases, of halogen–metal exchange and apparent displacement demands that all side reactions be rigorously investigated before the product-forming process can be simply described as an aryne reaction. The mechanism of the alternative processes and their ability to compete with aryne formation must be further detailed before a clear understanding of organometallic–aryl halide systems can be obtained.

Experimental Section

Materials. All materials used in this study, with the following exceptions, were reagent grade compounds purchased from commercial suppliers used without further purification.

o-, *m*-, and *p*-iodotoluenes were prepared *via* aqueous diazotization of the appropriate toluidine in the presence of potassium iodide, a modification of the method of Lucas and Kennedy.[38]

Phenyllithium, purchased in benzene–ether solution, was titrated to determine its true molarity using an adaptation of the method of Eppley and Dixon.[39]

p-Tolyllithium was prepared according to the following procedure: 50 ml of a 2.2 M solution of *n*-butyllithium (0.11 M) in hexane was placed in a 500-ml, three-necked, round-bottomed flask. Benzene (150 ml) was added as a diluent, and the flask, fitted with a reflux condenser, stirrer, and addition funnel, was gently warmed. A nitrogen atmosphere was maintained over the solution throughout the reaction. *p*-Bromotoluene (0.10 mol) in 50 ml of benzene was then added dropwise to the solution. *p*-Tolyllithium, precipitating from solution as a white solid, was gradually formed as addition proceeded over 30 min. The solution was allowed to stir for an additional 15 min to allow complete reaction.

Aliquots (50 ml) of the resultant slurry were then transferred to centrifuge tubes, flushed with nitrogen, and capped with a rubber septum. The samples were centrifuged; the supernatant benzene was removed with a syringe, and the remaining solid was washed with fresh benzene to remove organic contaminants. The centrifuging process was repeated several times and the solid tolyllithium was then dissolved in anhydrous ether.

Reactions of Aryllithium and Halotoluene at Solution Reflux. The appropriate halotoluene (0.01 mol) was weighed into a 50-ml, round-bottomed flask. Benzene (15 ml) and 15 ml of a 1.1 M solution of phenyllithium (0.016 mol) were then added. For reactions of *p*-tolyllithium, 30-ml portions of an ether solution of the organometallic compound (each solution was individually titrated) replaced the benzene–phenyllithium solution mixture. Where used, the catalyst, TMEDA (0.002 mol), was weighed out separately and rinsed into the flask with benzene. The flask, fitted with a stirrer and reflux condenser, was placed in an oil bath which was then heated to 100°. At all times the reaction mixture was maintained under a nitrogen blanket to limit decomposition of aryllithium compounds by reaction with air. After a 5-hr period, the flask was removed from the oil bath, allowed to cool for a short period, and then quenched by addition of 10 ml of absolute ethanol. Internal standard was added and the mixture was analyzed *via* glpc.

Reaction of Phenyllithium and Halotoluene at 20°. The procedure followed was that described above with the following modifications. Both TMEDA and piperidine were employed as catalysts and benzene and diethyl ether as diluents. After the reagents were mixed, the reaction flask was immersed in a water bath maintained at 20 ± 1° by use of a Wilkens–Anderson Lo-Temp Bath.

Study of Reaction Rate by Product Yield. The appropriate halotoluene (0.02 mol) and a suitable amount of naphthalene (used as internal standard) were mixed in 45 ml of benzene and poured into a 250-ml, three-necked flask. The flask was fitted with a stirrer, reflux condenser, and an adaptor fitted with a rubber septum. Phenyllithium solution (0.032 mol) was added, the flask was placed in an oil bath, and reaction proceeded as described above. At suitable time intervals, aliquots were drawn from the mixture with a syringe and quenched by injection into ethanol or a solution of dimethyl sulfate in benzene. The quenched samples were then analyzed by glpc.

Analyses. Analyses were carried out *via* glpc of the samples on two instruments, a thermal conductivity detector machine constructed at Case Western Reserve fitted with a 12 ft × 0.25 in. copper column packed with 15% Apiezon L on Chromosorb P operated at 155° with 15 lb of He inlet pressure, and a Varian Hy-Fi machine fitted with a 15 ft × 1/8 in. aluminum column packed with 15% Apiezon L on Chromosorb P operated at 276° with 23 lb of N₂ inlet pressure.

The products were identified by the correspondence of their retention times to those of authentic materials. Determination of product yields was made by comparing peak areas with that of an internal standard. Adjustment was made for differences in ther-

(38) H. J. Lucas and E. R. Kennedy, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 351.

(39) R. L. Eppley and J. A. Dixon, *J. Organomet. Chem.* (Amsterdam), **8**, 176 (1967).

mal conductivity or heat of combustion and applied to correct the observed areas.

The relative retention times of materials analyzed are as follows: low-boiling compounds (analyzed on 12 ft × 0.25 in. column), toluene, 1.00; p-fluorotoluene, 1.00; p-xylene, 1.95; bromobenzene;

3.17; p-chlorotoluene, 3.38; p-bromotoluene, 6.08; iodobenzene 6.60; p-iodotoluene, 12.50; high-boiling compounds (analyzed on 15 ft × ⅛ in. column), naphthalene, 1.00; o-methylbiphenyl, 1.54; biphenyl, 1.65; m-methylbiphenyl, 2.20; p-methylbiphenyl, 2.42; 3,4′-dimethylbiphenyl, 3.06; 4,4′-dimethylbiphenyl, 3.22.
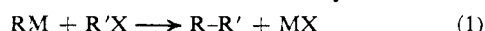
Reaction of Lithium Dialkyl- and Diarylcuprates with Organic Halides[1,2]

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Abstract: Lithium dialkyl- or diarylcuprates (R_2CuLi) react with aryl iodides in ether solution by competing metal–halogen exchange and coupling reactions. Using appropriate reagents, high yields of the coupled product R–Ar can be obtained by allowing the metal–halogen exchange to proceed to completion in the presence of an excess of R_2CuLi, and oxidizing the resulting mixture of organometallic species present in solution with nitrobenzene or oxygen. This reaction sequence works well with lithium di-n-alkyl- and diarylcuprates; it fails with di-sec-alkyl- and di-t-alkylcuprates. Although most alkyllithium reagents react with aryl iodides only by metal–halogen exchange, methyllithium, uncomplexed with copper, smoothly converts aryl iodides to arylmethanes. Coupling of lithium dialkyl- and diarylcuprates with *alkyl* halides appears to take place without significant metal–halogen exchange. The reaction of lithium diphenylcuprate with (−)-(R)-2-bromobutane occurs with the predominant *inversion* of configuration (84–92% stereoselectivity) expected of an S$_N$2-like displacement. Coupling reactions involving an n-alkyl halide as one reaction partner proceed in high yield; those involving t-alkyl halides fail. Lithium di-n-alkyl-, di-sec-alkyl-, and di-t-alkylcopper reagents all couple with n-alkyl halides. A number of preparations for representative copper(I) ate complexes are described, and the sensitivity of the coupling reactions to the method of preparation of the ate complex, to the nature of the solvent, and to the presence of lithium halides, trialkylphosphines, and dialkyl sulfides in solution are discussed.

A broadly applicable procedure for coupling the organic moiety of an organometallic reagent with that of an organic halide would be a useful member of the class of reactions available for the synthesis of carbon–carbon σ bonds. Unfortunately the commonly encountered organometallic derivatives of the

$$RM + R'X \longrightarrow R-R' + MX \qquad (1)$$

main group metals appear to be unsatisfactory as reagents for effecting the formation of carbon–carbon bonds by nucleophilic displacement at a carbon–halogen bond. Although organolithium reagents are strongly basic, they appear to be only weakly nucleophilic toward carbon: reaction of an organolithium compound with an alkyl or aryl halide in hydrocarbon or ether solutions usually leads to mixtures of products derived from competing metal–halogen exchange,[4] α metalation,[5] β elimination, and coupling, with the last reaction apparently proceeding, at least in part, through a complex free-radical mechanism.[6] Organomagne-

sium reagents are relatively unreactive toward simple alkyl and aryl halides; their reaction with activated halides again leads to mixtures of products.[7,8] Organozinc and organoaluminum compounds exhibit low reactivity toward, e.g., n-alkyl halides. At present, the structural factors responsible for low nucleophilicity of these organometallic reagents toward carbon are not entirely evident.

In contrast, organometallic compounds containing carbon–copper(I) bonds provide a class of reagents whose usefulness in coupling reactions with organic halides has been amply demonstrated in certain specialized circumstances. Thus reaction of copper(I) acetylides with acetylenic,[9] aromatic,[10] vinyl,[11a,b] and acyl[11c] ha-

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