THE BENZYNE AND RELATED INTERMEDIATES

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I. INTRODUCTION

The rearrangements of nonactivated aryl halides which are initiated by strong nucleophiles have been known for more than sixty years. The most widely studied examples have been the amination reactions using metallic amides. The first reports of such reactions gave low yields at high temperatures (40, 41, 42, 77). These rearrangements were not studied extensively until it was found (13) that aryl halides gave, with excess sodium or potassium amide in liquid ammonia or with lithium piperidide in diethyl ether, fair to good yields of the corresponding amines.

It is only recently, however, that these results have been interpreted in terms of a logical mechanism which involves benzyne-type intermediates (61, 99). An essentially similar mechanism has been postulated (111) in order to account for the abnormal reactions of certain aryl halides with metallating agents and *o*-dihaloaromatic compounds with metals and organolithium compounds.

Although the majority of the reactions now interpreted in terms of the benzyne intermediate involve the presence of a halogen atom, such an atom is not essential to the mechanism. Any other group which is sufficiently electronegative can give rise to benzyne. Thus reactions of perchloroylaromatic compounds with strong nucleophiles (106) and the conversion of aryl sulfonates to phenates have been interpreted in terms of a benzyne-type intermediate.

Cine-substitution (defined as substitution in which the entering group takes a position other than that vacated by the leaving group (18, 24)) characteristically accompanies many of the reactions proceeding by the benzyne mechanism; this may be checked by using a substituent or an isotopic label as a reference point. Not all reactions involving cine-substitution proceed by the benzyne mechanism (for example, the von Richter reaction), but if nitro groups are absent cine-substitution may be taken as good evidence of such a mechanism.

Any mechanism which tries to explain the observed results must be in accord with certain well-established facts. First, the reactions frequently are rapid at temperatures as low as $-33°$ in the case of aminations in liquid ammonia and $-50°$ in the case of coupling reactions of *o*-halophenyllithiums. Second, the entering group never has been found more than one carbon atom away from the leaving halogen. Third, the reactants and products are not isomerized under the reaction conditions used. Fourth, reaction only occurs (except with *o*-dihalo compounds) where there is a hydrogen

atom attached to the position adjacent to that occupied by the leaving halogen. Finally, when cine-substitution occurs and a mixture of products is obtained, the product ratio is almost constant and independent of the nature of the leaving group.

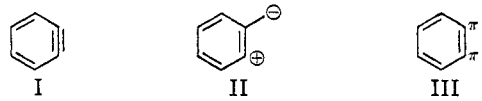
Most of the work discussed in this review has been published since 1953, but some mention is made of reactions investigated previously and which are now known to proceed by way of a benzyne-type intermediate. The literature is covered up to the end of 1960.

A. NOMENCLATURE

The benzyne intermediate also has been called dehydrobenzene, *o*-phenylene, and cyclohexadieneyne and a general term "aryne" has also been applied in the case of substituted benzynes.

B. FORMULATION

The intermediate has been written in a variety of ways



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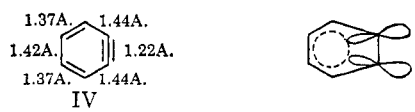
each of which has certain advantages over the others.

C. THE STRUCTURE OF THE INTERMEDIATE

It is generally agreed that the aromatic character of the cyclic system in the aryne intermediates is undisturbed (53). Models of the electronic structure show that the ring strain is not excessively high and can be compared with that in the cyclopropene ring (74). The existence of a bent, excited acetylene has been quoted in favor of the existence of the benzyne intermediate (71, 72).

Evidence for gaseous benzyne has been adduced from the flash photolysis of the diazonium salt obtained from anthranilic acid, which results in the formation of biphenylene and triphenylene (14).

Simplified calculations (26) indicate the bond lengths shown (IV), except that those indicated as 1.44 Å. should perhaps be smaller by 0.03 Å.



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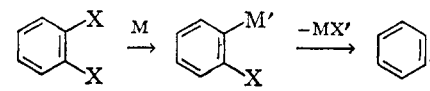
II. MECHANISM OF FORMATION

A. FROM DIHALOGEN COMPOUNDS

The participation of the benzyne intermediate in the reactions of *o*-dihalo aromatic compounds with metals and organolithium compounds is necessary in order to explain the enhanced reactivity of *o*-haloaryl-lithium compounds and *o*-haloaryl Grignard reagents as compared with other haloaryl-lithium and haloaryl Grignard reagents. Thus, although *p*-chlorobromobenzene gives a 90 per cent yield of *p*-chlorophenyllithium with *n*-butyllithium at ambient temperatures (37), attempts to prepare *o*-chlorophenyllithium at 0° and −30° were unsuccessful. Comparable yields were only obtained by carrying out the reaction at −90° (35).

Similar results have been obtained with Grignard reagents. Whereas *m*-bromophenylmagnesium bromide can be obtained in 70 per cent yield (73) from *m*-dibromobenzene, *o*-bromophenylmagnesium bromide can only be obtained in 30 per cent yield from *o*-dibromobenzene (46). In addition, complex products are obtained in the reactions of *o*-dihalo compounds which are not obtained with other isomers. All the *o*-halo organometallic compounds are highly labile; for a given metal the order is Br > Cl > F (90), and for a given halogen the ease of elimination of metal halide is in the order Na > Li > MgBr (120).

The benzyne intermediate must arise in the above cases by elimination of metal halide from the organo-monometallic compound, since the organo-dimetallic compounds are known to be stable (118, 120).



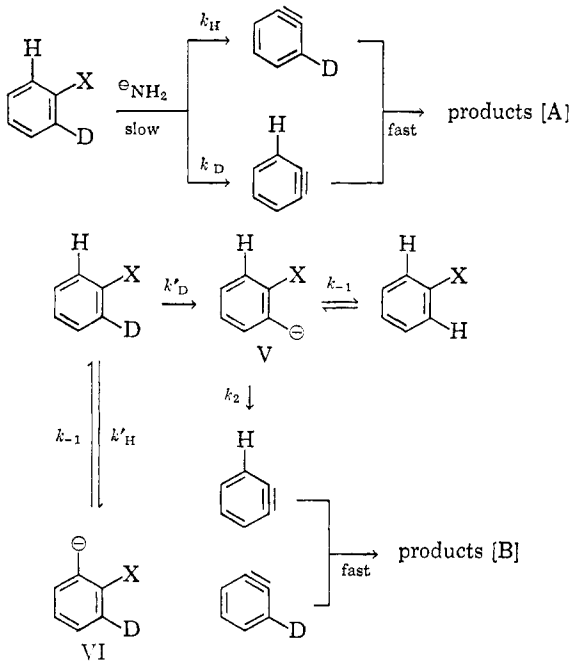
X = halogen; M = Mg or Li; M' = Li or MgX; MX' = LiX or MgX_2

B. FROM ARYL HALIDES WITH NUCLEOPHILES

The benzyne intermediate can explain the cine-substitution products which arise in the reactions of aryl halides with strong nucleophiles but, whereas in the case of *o*-dihalo aryl compounds the benzyne intermediate can only arise by one mechanism, in the present case there are two possible mechanisms which could operate. The two mechanisms may be formulated either as a concerted process [A] or as a stepwise process [B]. The penetrating studies using deuterated aryl halides (98) have thrown considerable light on this problem.

In more conventional eliminations these mechanisms have been distinguished conclusively by using deuterium as a tracer for the hydrogen adjacent to the leaving halogen (27, 49, 108).

If the hydrogen is removed in the rate-determining step as in process [A], the relative rates of the *o*-deuterated and *o*-protonated halobenzenes should correspond to an isotope effect k_H/k_D of $\sim$ 6–7. If, however, the stepwise mechanism, [B], operates the carbanions V and VI may either form benzyne by loss of halide ion or revert to aryl halide at a specific rate k_{-1} by abstraction of a proton from the solvent. If k_{-1} is not detectably large, then the two mechanisms are indistinguishable. The apparent isotope effect will be smaller in mechanism [B] than in mechanism [A] and will depend on the ratio k_2/k_{-1}.

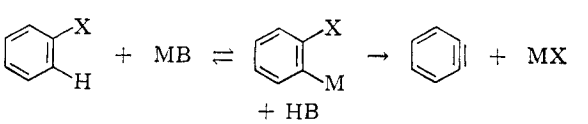


In the reactions of aryl halides with potassium amide in liquid ammonia it is found that the nature of the halogen determines not only which mechanism operates but also the specific rate constants.

Fluorobenzene-2-^{2}H, fluorobenzene-2,4,6-$^2H_3$, and 4-fluorotoluene-3,5-$^2H_2$ were found to exchange deuterium ortho to the fluorine extremely rapidly, although amination products were not formed at a significant rate. Chlorobenzene-2-^{2}H is aminated by the stepwise mechanism, while for bromobenzene-2-^{2}H the k_H/k_D value is 5.5, which is close to the 6–7 range expected for a concerted E2 dehydrobromination.

The changeover in mechanism from a stepwise process to a concerted process enables one to explain the order of reactivity of phenyl halides in the amination reactions in liquid ammonia (Br > I > Cl ≫ F) (13). Two influences are relevant. First, the ortho hydrogen atom is removed as a proton and the rate of this process is expected to follow the order F > Cl > Br > I. Second, halide ion must depart, the expected rate sequence for this process being I > Br > Cl > F. This suggests that the change in mechanism from [B] to [A] occurs when loss of halide ion becomes easier than the removal of a proton; the two steps then become synchronous.

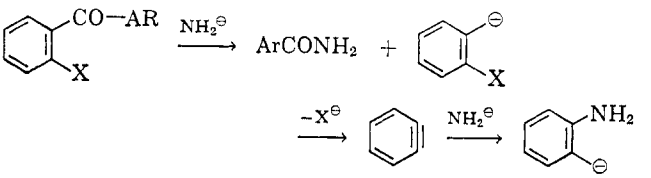
Studies using chlorobenzene-2-^{2}H and bromobenzene-2-^{2}H in the reaction with lithium diethylamide in ether suggest that benzyne arises in these cases by the concerted mechanism (98). However, there is no general agreement that there are two mechanisms



operating; some authors prefer to explain all the reactions in terms of the stepwise mechanism (53).

C. FROM HALOBENZOPHENONES WITH POTASSIUM AMIDE IN LIQUID AMMONIA

The cleavage of *o*-halobenzophenones by potassium amide in liquid ammonia has given certain interesting results (51). 2-Chloro-2′,5′-dimethylbenzophenone is cleaved with the formation of aniline and 2,5-dimethylbenzamide. *o*-Fluorobenzophenone gives fluorobenzene but no aniline. These results suggest the mechanism:



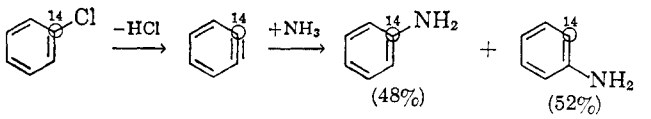
The formation of benzyne by a stepwise mechanism was proved in the case of 2-chloro-4-methylbenzophenone by analysis of the toluidines produced. A concerted cleavage with direct formation of benzyne would give 4-methylbenzyne, which can yield only *m*- and *p*-toluidines. However, the 2-chloro-4-methylphenyl anion which results from a stepwise cleavage may lose chloride ion to form 4-methylbenzyne or it may react with solvent to form *m*-chlorotoluene, which then can yield either 3- or 4-methylbenzyne which mixture would give *o*-, *m*-, and *p*-toluidines, under the reaction conditions. As an appreciable amount of *o*-toluidine was identified, the stepwise mechanism is proved in this case.

III. AMINATION REACTIONS

Amination reactions of aryl halides which involve cine-substitution have been reviewed up to 1950 (24).

A. WITH ALKALI DERIVATIVES OF AMMONIA

When a solution of chlorobenzene, bromobenzene, or iodobenzene in liquid ammonia is treated with potassium amide, elimination of hydrogen halide occurs followed by the addition of amide ion (13). This results in the formation of aniline. Fluorides are less reactive than chlorides, which are less reactive than bromides (12). Using 1-^{14}C-labeled halobenzene, an almost 1:1 mixture of aniline-1-^{14}C and aniline-2-^{14}C is obtained (96, 99).



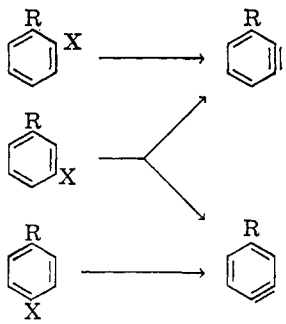
Alternative mechanisms, for example, involving direct replacement and simultaneous rearrangement at identical rates are unlikely, since the two halides would not be expected to have the same ratio of direct to abnormal reaction. This dual mechanism is also ex-

cluded by the fact that bromodurene and bromomesitylene are not aminated by sodium amide in liquid ammonia. Iodobenzene-1-^{14}C-2,4,6-$^{2}H_3$ was found to give results almost identical with those obtained with iodobenzene-1-^{14}C; these results also are in accord with the exclusive operation of a benzyne mechanism.

Perchloroylbenzene reacts vigorously with amide ion in liquid ammonia (106). The major product obtained is triphenylamine, together with a high yield of chlorate ion. Competition reactions between perchlorobenzene and fluorobenzene show that chlorate ion is eliminated preferentially; similar results were obtained when bromobenzene was used in place of fluorobenzene.

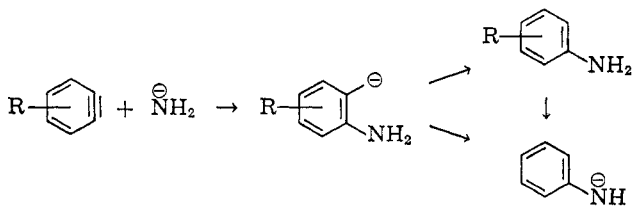
The degree of rearrangement in aminations of substituted halobenzenes with alkali amides is influenced by the position of the substituent relative to the halogen. Two factors must be considered: (*1*) factors governing the formation of particular benzyne isomers; (*2*) the effect of substituents on the direction of addition to the aryne.

Whereas ortho- and para-substituted aryl halides can give rise to only 3- or 4-substituted arynes, respectively, *m*-substituted aryl halides can give rise to either or both isomers.

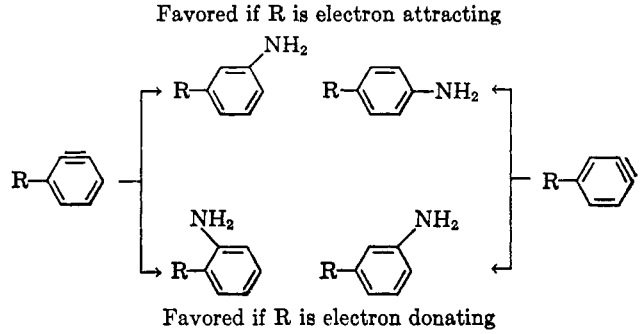


The direction of elimination for a meta-substituted halide is predictable on the basis of which hydrogen is more acidic; this is governed largely by the inductive effects of substituents (43). In the case of electron-attracting groups the acidity order is $o > m > p$; this order is reversed in the case of electron-donating groups.

The amination of an aryne seems most likely to occur in two steps, the first being a slow addition of amide ion and the second being either a fast abstraction of a proton from solvent or an intramolecular proton shift.



The direction of addition may be predicted by considering the amide ion to add in such a way as to provide the more favorable location of the negative charge with respect to the inductive effect of the R group (100).



The amide ion almost certainly attacks the aryne in the plane of the ring; therefore the π electron system is not primarily involved; conjugation effects do not therefore apply. There is some evidence that steric hindrance to the formation of the ortho-substituted aniline may operate.

Some of the results obtained before it was realized that these reactions proceed by a benzyne mechanism may be inaccurate, owing to the fact that crude reaction mixtures were not always analyzed for isomers present in small quantity.

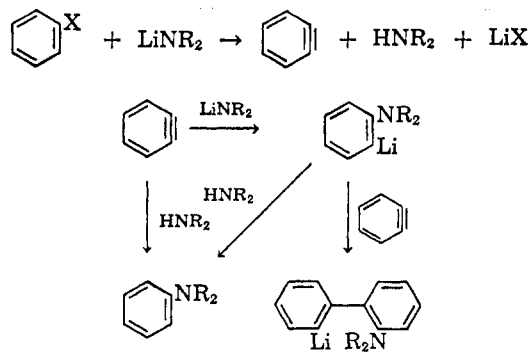
TABLE 1

Reactions of amide ions with aryl halides in liquid ammonia

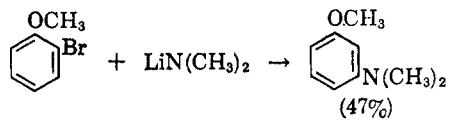
Aryl Halide	Amide	Yield	Product Ratios, %			Reference
			o	*m*	*p*	
		per cent				
2-Bromo-6-methylanisole	$NaNH_2$	30		100		(7)
2-Bromo-4-methylanisole	$NaNH_2$	50		100		(7)
2-Bromo-5-(trifluoromethyl)anisole	$NaNH_2$	71		100		(7)
2-Bromo-4-(trifluoromethyl)anisole	$NaNH_2$	14–20	100			(7)
o-Chloroanisole	$NaNH_2$	57		100		(36)
o-Chloroanisole	KNH_2	60		100		(36)
o-Bromoanisole	$LiNH_2$	22		100		(36)
o-Bromothioanisole	$NaNH_2$	46		100		(38)
Methyl *o*-bromobenzenesulfinate	$NaNH_2$	15		100		(38)
o-Chlorothioanisole	KNH_2	35		100		(38)
2,6-Dibromoanisole	$NaNH_2$	92		100		(10)
2,5-Dichloroanisole	$NaNH_2$	78		100		(10)
2,4-Dichloroanisole	$NaNH_2$					(10)
o-Bromotoluene	$NaNH_2$	64	48.5	51.5		(100)
o-Chlorotoluene	KNH_2	66	45	55		(100)
o-Chlorobenzotrifluoride	$NaNH_2$	28		100		(100)
m-Bromoanisole	$NaNH_2$	59		100		(100)
m-Bromotoluene	KNH_2	61	22	56	22	(100)
m-Chlorotoluene	KNH_2	66	40	52	8	(100)
m-Chlorobenzotrifluoride	$NaNH_2$	16		100		(100)
p-Bromoanisole	KNH_2	31		49	51	(100)
p-Chlorotoluene	KNH_2	35		62	38	(100)
p-Chlorobenzotrifluoride	$NaNH_2$	25		50	50	(100)
p-Bromofluorobenzene	KNH_2	30		20	80	(100)

B. WITH ALKALI DERIVATIVES OF ALIPHATIC SECONDARY AMINES

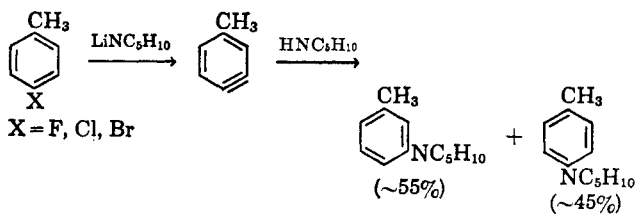
Many papers have been published on the reactions of alkali derivatives of aliphatic secondary amines with aryl halides in ethereal solution. These include kinetic investigations of partial rate factors (59) and also competition reactions with alkali derivatives of arylamines (84). Interestingly, it is found that whereas in the system alkali amide in liquid ammonia fluorobenzene is inert, in the systems using organolithium compounds fluorobenzene is highly reactive. This reversal of reactivity does not, however, apply to perchloroyl aromatic compounds. The same reagent which brings about the elimination of hydrogen halide subsequently adds to the aryne. In many cases secondary reactions have been suppressed by including the free secondary amine in the reaction system as a proton donor.



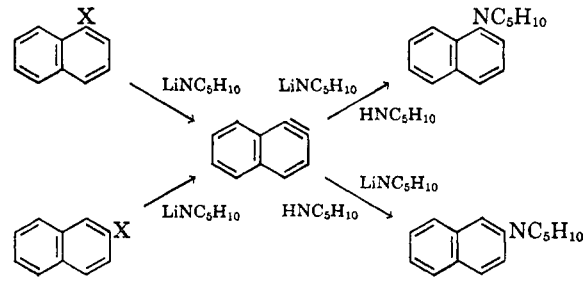
Cine-substitution has been observed in these systems, thus indicating a benzyne type mechanism; *e.g.*, *o*-bromoanisole produces *N*,*N*-dialkyl-*m*-anisidines (8).



p-Halotoluenes react with lithium piperidide in boiling ether in the presence of free piperidine to produce a mixture of *m*- and *p*-*N*,*N*-disubstituted toluidines, in approximately constant ratio; these results are indicative of a benzyne type mechanism (64).

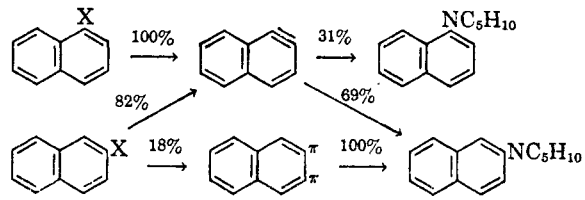


The reactions of 1- and 2-chloro-, 1- and 2-bromo-, or 1- and 2-iodonaphthalenes with lithium piperidide in ether give good yields (~90%) of *N*-naphthylpiperidines. Infrared analysis of the product shows it to be a mixture of 31% *N*-(1-naphthyl)piperidine and 69% *N*-(2-naphthyl)piperidine, independent of the position of the halogen (63, 101, 102). Since both 1- and 2-substituted naphthalenes give the same product ratio it follows that the intermediate involved in all cases is α-naphthalyne; if some β-naphthalyne was involved in the reactions of 2-halonaphthalenes, the product ratio would not be the same as that found with 1-halonaphthalenes.



It is suggested that the preferred formation of α-naphthalyne results from the greater acidity of the α-hydrogen. Steric factors in the addition of nucleophiles to α-naphthalyne have been investigated; it is found (70) that, although the 1-position is hindered, only in the case of very bulky nucleophiles such as diisopropylamide and dicyclohexylamide do steric effects have any great importance.

In the case of 2-halonaphthalenes in piperidine solution elimination occurs to give both α- and β-naphthalyne in the ratio 82:18.



One of the interesting problems that has been solved recently is the apparent discrepancy in the results published on aminations of α-fluoronaphthalene. It was originally reported (109) that when α-fluoronaphthalene is aminated by potassium amide in liquid ammonia only α-naphthylamine is obtained. It also was found that the same substance reacts with lithium diethylamide in ether to produce only *N*,*N*-diethyl-β-naphthylamine (34).

In the amination of α-fluoronaphthalene with lithium piperidide it has been found that mixtures are obtained; the composition of these mixtures depends on the concentration of free piperidine—the more piperidine the less rearrangement.

This behavior can be explained by the stepwise mechanism for the production of α-naphthalyne, the first stage being the production of the 1-fluoro-2-naphthyl anion. This can either gain a proton from the piperidine or lose fluoride ion to give α-naphthalyne. If α-fluoronaphthalene can undergo a slow direct

TABLE 2

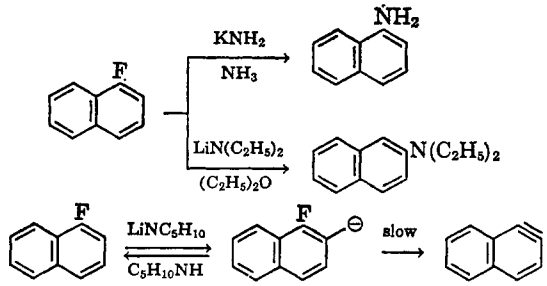
Reactions of aryl halides with alkali derivatives of aliphatic secondary amines

Aryl halide	Amide	Solvent	Yield	Product/Ratio	Reference
			per cent		
o-Fluoroanisole	$LiNEt_2$	Et_2O	26	100% *m*	(36)
o-Chloroanisole	$LiNEt_2$	Et_2O	26	100% *m*	(36)
o-Bromoanisole	$LiNEt_2$	Et_2O	33	100% *m*	(36)
o-Iodoanisole	$LiNEt_2$	Et_2O	5	100% *m*	(36)
m-Chloroanisole	$LiNEt_2$	Et_2O	48	100% *m*	(36)
o-Bromophenol	$LiNEt_2$	Et_2O	15	100% *m*	(36)
o-Chloroanisole	$LiN(Bu\text{-}n)_2$	Et_2O	42	100% *m*	(36)
o-Chlorophenetole	$LiNEt_2$	Et_2O	30	100% *m*	(36)
o-Bromoanisole	$LiNC_5H_{10}$	Et_2O	28	100% *m*	(36)
o-Bromoanisole	Li morpholide	Et_2O	9	100% *m*	(36)
p-Dibromobenzene	$LiNEt_2$	Et_2O	23	100% *p*-$BrC_6H_4NEt_2$	(36)
o-Bromoanisole	$LiNMe_2$	Me_2NH	35	100% *m*	(8)
o-Bromoanisole	$LiNMe_2$	*o*-BrC_6H_4OMe	47	100% *m*	(8)
o-Bromoanisole	$LiNMeCH_2C_6H_5$	Et_2O	26	100% *m*	(8)
o-Bromoanisole	$LiN(CH_2C_6H_5)_2$	Et_2O	8	100% *m*	(8)
2-Bromo-5-methylanisole	$LiNMe_2$	Et_2O	63	100% *m*	(9)
2-Bromo-4-methylanisole	$LiNMe_2$	Et_2O	81	100% *m*	(9)
o-Bromoanisole	$LiNMe_2$	Et_2O	39	*o*:*m* = 20:80	(9)
Bromobenzene	$NaNH_2$	HNC_5H_{10}	99	N-Phenylpiperidine	(21)
Bromobenzene	$NaNH_2$	$HNEt_2$	64	N,N-Diethylaniline	(21)
Bromobenzene	$NaNH_2$	$HN(i\text{-}Pr)_2$	22	N,N-Di-isopropylaniline	(21)
Bromobenzene	$NaNH_2$	$HN(n\text{-}Bu)_2$	67	N,N-Di-*n*-butylaniline	(21)
Bromobenzene	$NaNH_2$	Morpholine	46	N-Phenylmorpholine	(21)
Fluorobenzene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	84	N-Phenylpiperidine	(64)
Chlorobenzene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	86	N-Phenylpiperidine	(64)
Bromobenzene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	90	N-Phenylpiperidine	(64)
Iodobenzene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	86	N-Phenylpiperidine	(64)
Fluorobenzene	$LiNEt_2$	$HNEt_2/Et_2O$	83	N,N-Diethylaniline	(64)
Chlorobenzene	$LiNEt_2$	$HNEt_2/Et_2O$	71	N,N-Diethylaniline	(64)
Bromobenzene	$LiNEt_2$	$HNEt_2/Et_2O$	82	N,N-Diethylaniline	(64)
Bromobenzene	$LiNC_4H_8$	HNC_4H_8/Et_2O	84	N-Phenylpyrrolidine	(64)
p-Fluorotoluene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	74	N-Tolylpiperidine *m*:*p* = 53:47	(64)
p-Chlorotoluene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	73	N-Tolylpiperidine *m*:*p* = 55:45	(64)
p-Bromotoluene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	88	N-Tolylpiperidine *m*:*p* = 56:44	(64)
1-Bromonaphthalene	$NaNH_2$	HNC_5H_{10}	92	1:2 = 32:68	(19)
2-Bromonaphthalene	$NaNH_2$	HNC_5H_{10}	94	1:2 = 26:74	(19)
1-Fluoronaphthalene	$NaNH_2$	HNC_5H_{10}	57	1:2 = 60:40	(20)
1-Chloronaphthalene	$NaNH_2$	HNC_5H_{10}	84	1:2 = 32:68	(20)
1-Iodonaphthalene	$NaNH_2$	HNC_5H_{10}	54	1:2 = 35:65	(20)
2-Fluoronaphthalene	$NaNH_2$	HNC_5H_{10}	54	1:2 = 26:74	(20)
2-Chloronaphthalene	$NaNH_2$	HNC_5H_{10}	44	1:2 = 26:74	(20)
2-Iodonaphthalene	$NaNH_2$	HNC_5H_{10}	48	1:2 = 22:78	(20)
1-Fluoronaphthalene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	93	1:2 = 52:48	(101)
1-Chloronaphthalene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	92	1:2 = 31.5:68.5	(101)
1-Bromonaphthalene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	93	1:2 = 30:70	(101)
1-Iodonaphthalene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	83	1:2 = 34:66	(101)
2-Fluoronaphthalene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	93	1:2 = 21:79	(101)
2-Chloronaphthalene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	92	1:2 = 31:69	(101)
2-Bromonaphthalene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	79	1:2 = 31:69	(101)
2-Iodonaphthalene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	54	1:2 = 31.5:68.5	(101)
1-Fluoro-4-methylnaphthalene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	88	1:2 = 34.5:65.5	(101)
1-Chloro-4-methylnaphthalene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	88	1:2 = 26.5:73.5	(101)
2-Chloro-4-methylnaphthalene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	91	1:2 = 28:72	(101)
1-Bromo-4-methylnaphthalene	$LiNC_5H_{10}$	HNC_5H_{10}/Et_2O	92	1:2 = 28:72	(101)
1-Fluoronaphthalene	$LiNEt_2$	Et_2O	82	1:2 = 56.5:43.5	(101)
1-Chloronaphthalene	$LiNEt_2$	Et_2O	77	1:2 = 39.5:60.5	(101)
2-Fluoronaphthalene	$LiNEt_2$	Et_2O	90	1:2 = 38:62	(101)
2-Chloronaphthalene	$LiNEt_2$	Et_2O	84	1:2 = 38.5:61.5	(101)
1-Chlornaphthalene	$LiN(i\text{-}Bu)_2$	Et_2O	53	1:2 = 36:64	(70)
1-Chloronaphthalene	$LiN(i\text{-}Pr)_2$	Et_2O	46	1:2 = 36:64	(70)
1-Chloronaphthalene	$LiN(cyclohexyl)_2$	Et_2O	59	1:2 = 8:92	(70)
3-Bromo-thianaphthene		HNC_5H_{10}		2-Piperidinothianaphthene	(17)

reaction with lithium piperidide to give α-naphthyl piperidine, then the degree of rearrangement observed is dependent on the mass-action lowering of the concentration of 1-fluoro-2-naphthyl anion by piperidine, which acts as an acid (63, 66, 101).

With potassium amide in liquid ammonia the large excess of solvent keeps the anion concentration low and therefore favors the direct attack of the α-position.

The possibility of a 1,4-naphthalyne is excluded by



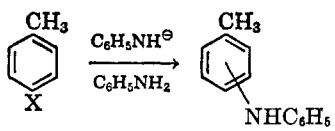
the fact that 4-methyl-1-halo- and 4-methyl-2-halonaphthalenes give identical mixtures of 28 per cent 1- and 72 per cent 2-piperidine-4-methylnaphthalene.

Similar results have been obtained using the system halonaphthalene–sodium amide–piperidine; seven of the eight monohalonaphthalenes appear, from product composition, to react entirely by way of naphthalyne intermediates. α-Fluoronaphthalene is again exceptional, and the direct replacement of fluorine is confirmed by the reaction of 1-fluoro-2-methylnaphthalene, which cannot give a naphthalyne derivative (20).

C. WITH ALKALI DERIVATIVES OF ARYLAMINES

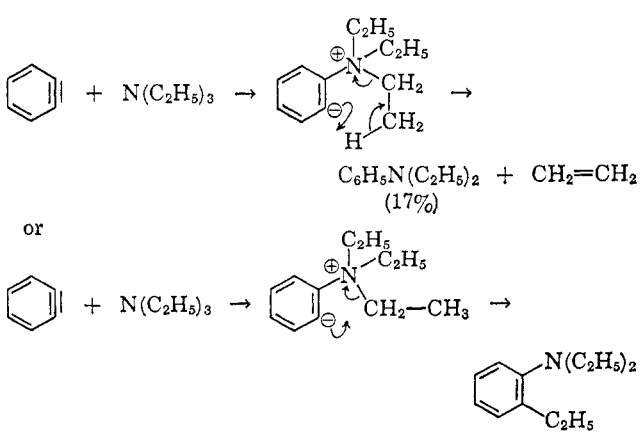
The first example of a reaction in which rearrangement occurs during amination was reported in 1894 (77). *p*-Dibromobenzene was treated with the potassium salt of *p*-toluidine, the product being a mixture of the expected *N*,*N*′-di-*p*-tolyl-*p*-phenylenediamine and *N*,*N*¹-di-*p*-tolyl-*m*-phenylenediamine. Sodium and potassium anilides do not react with aryl halides in liquid ammonia, but potassium anilide and diphenylamide react with bromobenzene at elevated temperatures (88).

Information about the mechanism of such reactions has been obtained by treating potassium anilide with *p*-halotoluenes in refluxing aniline (105). The mixtures of *p*- and *m*-tolylphenylamines were found to have the same isomer ratios irrespective of the nature of the halogen. This is taken as strong evidence that such reactions proceed exclusively by way of an aryne intermediate.



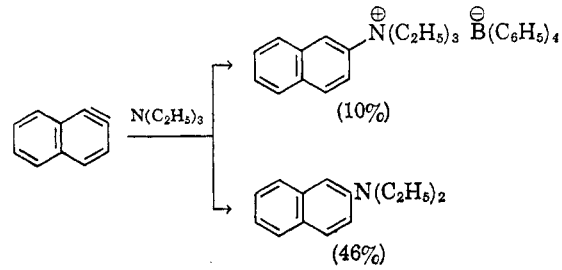
D. WITH ALIPHATIC TERTIARY AMINES

A few cases have been reported in the literature where tertiary aliphatic amines have reacted with systems which can give rise to arynes; interesting results have been obtained as a result of careful investigations.



Fluorobenzene reacts with phenyllithium in the presence of triethylamine to give diethylaniline and *o*-ethyldiethylaniline; these results can be explained in terms of the benzyne intermediate (116, 129).

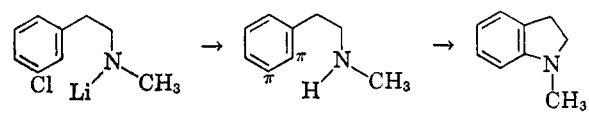
Similar results have been obtained in the reactions of 1-bromo-2-fluoronaphthalene and 2-bromo-1-fluoronaphthalene with *n*-butyllithium in the presence of triethylamine.



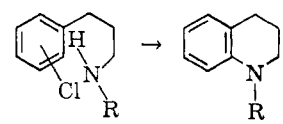
IV. RING CLOSURE REACTIONS

The intramolecular addition of nucleophiles to benzyne intermediates has provided a new general method for the synthesis of cyclic systems.

Thus methyl-[2-(*m*-chlorophenyl)ethyl]amine gave *N*-methylindoline with ethereal phenyllithium; the same product was obtained using the *o*-chloro compound, but in this case the yield was lower (54). The optimum yield of *N*-methylindoline (88 per cent) was obtained when phenyllithium was used together with lithium diethylamide (55).

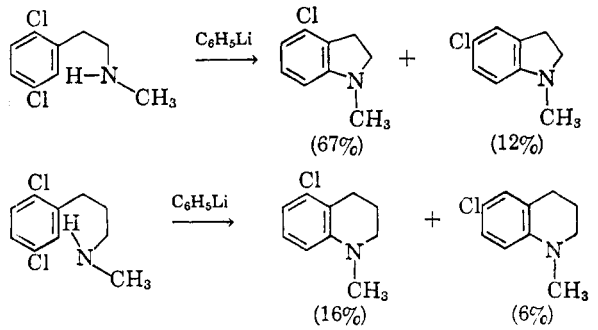


N-Substituted-tetrahydroquinolines can be made by an analogous route, the *m*-chloro compounds again giving the best yields (54, 55, 76).



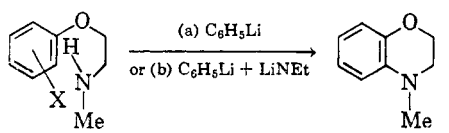
R = CH_3:	*o*-Cl	→	24 per cent
	m-Cl	→	49 per cent
R = C_6H_5:	*o*-Cl	→	26 per cent
	m-Cl	→	28 per cent

These results suggest that the formation of this type of aryne intermediate is more difficult from *o*-chloro compounds because of steric effects. This has been proved by carrying out cyclizations using compounds containing two chlorine atoms, one *ortho* and the other *meta* to the side chain (57).



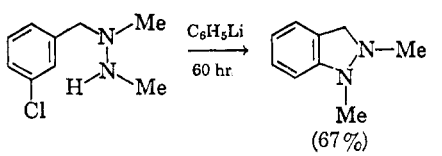
Other examples of the intramolecular reaction of secondary amines with arynes (76) include:

N-Methylbenzmorpholine

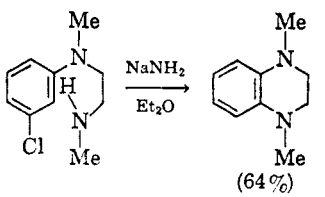


X = *M*-Cl	(a) 27%	(b) 10%
= *M*-Br	(a) 44%	(b) 48%
= *o*-Cl	(a) 0%	(b) 0%

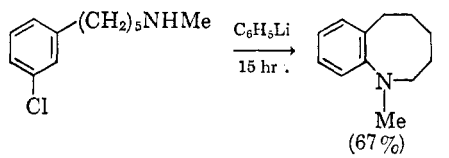
N,N'-Dimethylindazoline

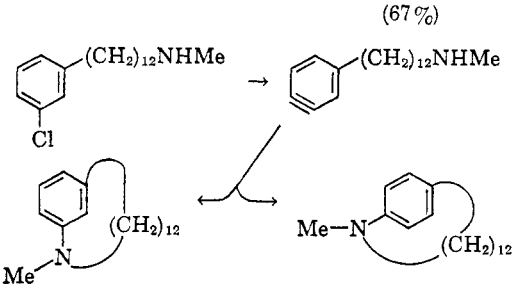


N,N'-Dimethyltetrahydroquinoxaline



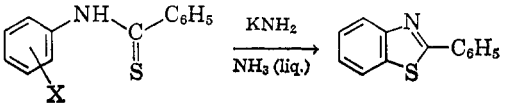
Large ring compounds also have been made by this method, having eight, sixteen, and seventeen atoms in the ring.





$NaNH_2/C_6H_5CH_3$	38%	4%
$NaNH_2/C_6H_6$	51%	6%
C_6H_5Li/Et_2O	35%	3%

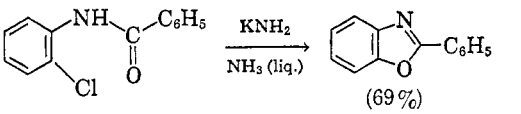
The ring closure by means of nucleophiles other than secondary amides also has been published. Thus thiobenz-*o*-bromoaniline is converted into 2-phenylbenzothiazole by the action of potassium amide in liquid ammonia. The *m*-bromo-isomer gives the same product, but in reduced yield (52).



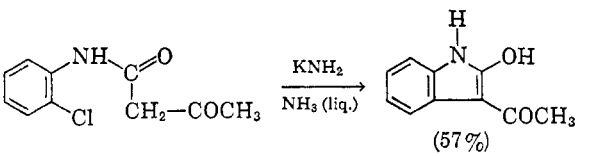
X = *o*-Br → 90%
m-Br → 68%

The same authors also have carried out these syntheses:

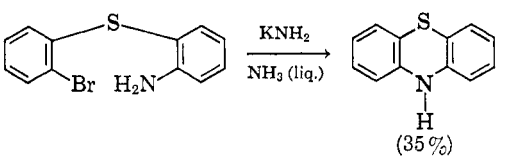
2-Phenylbenzoxazole



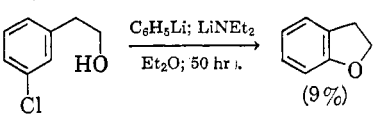
3-Acetyloxindole (23)



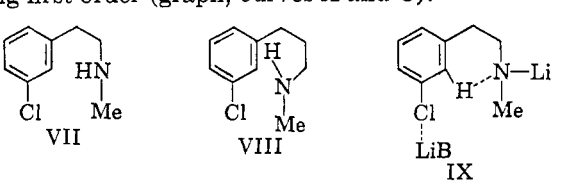
Phenothiazine



The intramolecular addition of alcoholate also has been studied (57).



The kinetics of the ring closure reaction resulting in the formation of *N*-methylindoline and *N*-methyltetrahydroquinoline have been investigated (56) in order to determine whether the aryne is formed intramolecularly or intermolecularly. Excess of lithium diethylamide improves the yield of *N*-methylindoline without forming the isomeric "wrong" aryne. The rate of the reaction is increased by the addition of lithium diethylamide but the increase is found to be the same for one, two, or five equivalents; further, the lithium diethylamide does not appear in the rate equation, the kinetics being first order (graph, curves A and C).



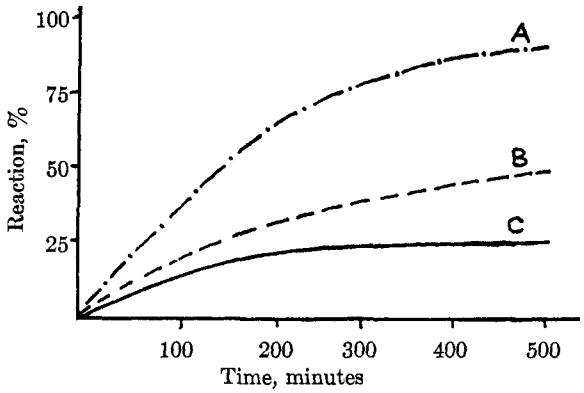


FIG. 1.—Kinetics of aryne formation from VII and VIII in ether at 20°; influence of added lithium diethylamide [A, 1, 2 or 5 equivalents of Et_2NLi added; C, no Et_2NLi added; B, 0 or 5 equivalents of Et_2NLi added].

It has been suggested that lithium diethylamide assists by pulling the *m*-bound chlorine IX. It is surprising that the rate constant of the aryne formation of the next higher homolog (from VIII, Curve B) is unaffected by added lithium diethylamide, in this case the steric situation presumably is such that elimination of hydrogen chloride can occur intramolecularly without any assistance from lithium diethylamide. The assumed complexing of lithium amides has been proved by the retardation found in the kinetics of the reaction of lithium piperidide with bromobenzene, where lithium bromide effectively blocks a second mole of lithium piperidide by formation of an ineffective 1:1 complex (58). In addition auto-complexes of organolithium compounds are well known (119, 127).

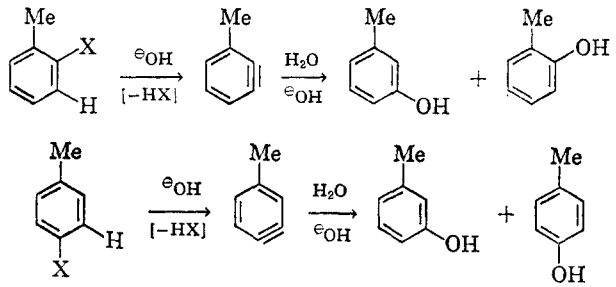
V. HYDROLYTIC REACTIONS

The preferred formation of resorcinol by alkali fusion of the isomeric benzene disulfonates has been known for many years (5, 6). Similarly the alkaline hydrolysis of the isomeric halotoluenes long has been known as invariably yielding some *m*-cresol (87, 89). 3-Bromobenzothiophene gives some 2-hydroxybenzothiophene on hydrolysis with ethanolic potassium hydroxide at 200–220° (75).

The high temperature liquid phase hydrolyses of the halotoluenes have been investigated in detail (15), the results indicating that the hydrolyses involve either the benzyne mechanism, which gives both rearranged and unrearranged products, or an SN2 type mechanism.

The SN2 mechanism is favored by lower temperatures in the presence of weaker bases and with the more easily ionizable halogens. By carefully controlling the conditions one mechanism or the other could be made to operate almost exclusively. Chlorobenzene-1-^{14}C gave with 4 *M* sodium hydroxide at 340° 58 ± 1% phenol-1-^{14}C and 42 ± 1% phenol-2-^{14}C, which indicates that under these conditions the benzyne mechanism, although not exclusive, predominates.

In the reactions of the halotoluenes no *o*-cresol was detected in the hydrolyses of *p*-halotoluenes and no *p*-cresol was detected from *o*-halotoluenes. These results establish that the cresolates are not isomerized under the reaction conditions. At 340° the *o*-halotoluenes gave essentially similar mixtures of *o*- and *m*-cresols and the *p*-halotoluenes behaved similarly. The amount of direct substitution probably accounts for no more than 2–3% of the cresols formed.



Considerable direct substitution was observed at 250° with the halotoluenes; the iodotoluenes consistently gave more direct substitution than the corresponding bromotoluenes. Direct substitution proved to be the main route using 4 *M* sodium acetate at 340°. The amount of rearrangement at 250° for the iodo- and bromotoluenes was found to decrease with increasing distance of the halogen from the methyl group. This indicates that the direct substitution proceeds by an SN2 mechanism; the inductive effect of the methyl group would be expected to retard an SN2 reaction, the effect decreasing with increasing distance between the groups. The possibility of an SN1 mechanism for the direct reaction appears to be ruled out by the fact that *p*-iodotoluene failed to yield any cresols with 4 *M* sodium iodide at 340°.

This duality in mechanism satisfactorily accounts for the different behavior of the chlorobiphenyls with different bases. Thus with sodium carbonate no re-

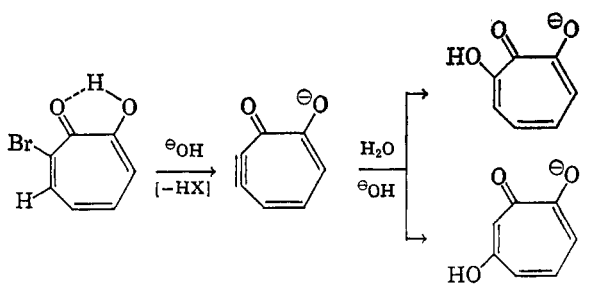
TABLE 3

Hydrolysis of halotoluenes with 4 M aqueous sodium hydroxide

Halide	Temperature	Yield	Product Ratios, %		
			o-	*m*-	*p*-
	°C.	*per cent*			
o-Cl	340	68	48.2	51.8	
m-Cl	340	56	21.4	63.6	15.0
p-Cl	340	59		50.4	49.6
p-Cl	250	12		14.4	85.6
o-Br	250	15	53.6	47.4	
o-Br	340	63	45.4	54.6	
m-Br	340	60	23.9	60.2	15.9
p-Br	250	17		25.8	74.2
p-Br	340	55		54.6	45.4
o-I	340	50	41.7	58.3	
m-I	250	38	5.7	88.9	5.4
m-I	340	47	19.8	66.1	14.1
p-I	250	45	3	3	97
p-I	340	43		48.7	51.3

arrangement was observed (16), while with sodium hydroxide rearrangement was observed (92).

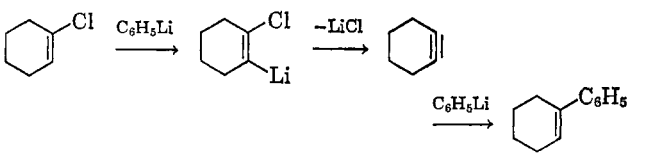
The hydrolysis of 3-bromotropolone with aqueous alkali gives both rearranged and unrearranged products (95). A repetition of previous work (1) showed that hydrolysis with 50% aqueous sodium hydroxide gave largely 4-hydroxytropolone. 3-Bromotropolone when heated at 130–140° with 75% potassium hydroxide gave a mixture of 3-hydroxy- and 4-hydroxytropolone. This reaction presumably proceeds by way of a "tropolonyne" intermediate.



VI. Reactions Involving Aliphatic Analogs of Benzyne

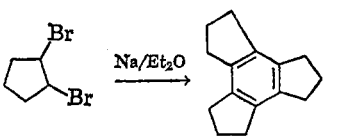
Elimination–addition mechanisms which are essentially similar to the benzyne mechanism have been postulated in order to account for the results obtained in some reactions of alkyl and alkenyl halides with metals and organo metallic compounds.

Low yields of 1-phenylcyclohexene were reported (122) in the reaction of phenyllithium with 1-chlorocyclohexene. Using labeled 1-chlorocyclohexene and a modified technique improved yields have been obtained. Degradation to benzoic acid then gave results in reasonable accord with those predicted assuming a cyclohexyne intermediate (103).

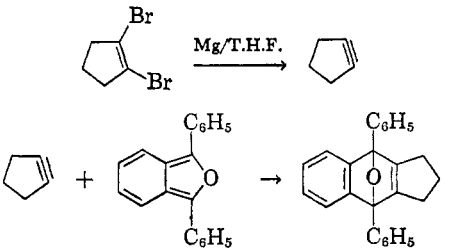


A cyclohexyne trimer is formed in the reaction of 1,2-dibromocyclohexene with sodium (32), and this reaction may also involve cyclohexyne.

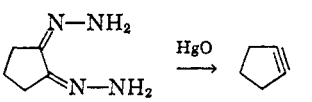
Experiments designed to determine the minimum ring size for the operation of an elimination–addition mechanism show that an intermediate with the symmetry properties of cyclopentyne can be produced. Such an intermediate can explain the formation of tris-trimethylenebenzene from 1,2-dibromocyclopentane by reaction with sodium in ether (31).



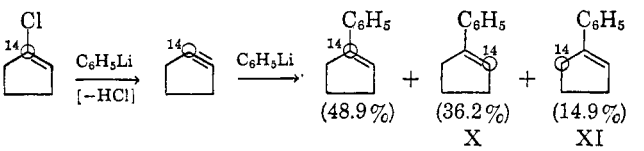
1,2-Dibromocyclopentene reacts with magnesium in tetrahydrofuran containing some 1,3-diphenylisobenzofuran to produce a Diels–Alder adduct in low yield, presumably involving cyclopentyne (125).



Similar evidence also has been obtained for cyclohexyne and cycloheptyne, the adducts being isolated in 25 and 35% yields, respectively. The same intermediate has been detected in the oxidation of cyclopentan-1,2-dione dihydrazone (30).

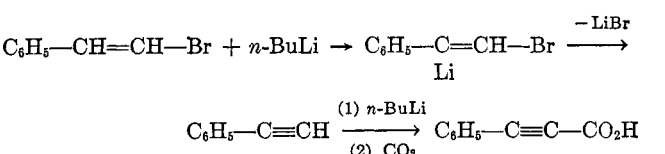


Experiments using 1-chlorocyclopentene-1-^{14}C and phenyllithium produce 1-phenylcyclopentene in which the ^{14}C distribution can be interpreted in terms of the cyclopentyne intermediate (91).



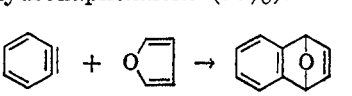
The presence of 14.9% of XI has been suggested as being due to an allylic rearrangement of X, induced by phenyllithium.

The elimination of lithium halide also has been noted in acyclic systems, resulting in the isolation of acetylenic derivatives (134). Thus *n*-butyllithium reacts with ω-bromostyrene to produce phenylpropiolic acid after carboxylation (37).



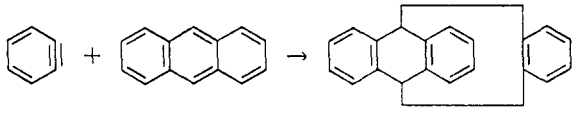
VII. Reactions with Dienes

The first example of the reaction of benzyne as a dienophile was reported in 1955 when *o*-fluorobromobenzene was treated with lithium amalgam in the presence of furan (131), the major product being 1,4-epoxy-1,4-dihydronaphthalene (76%).

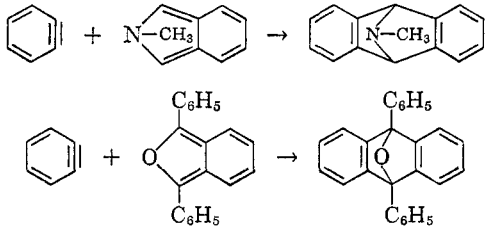


The reaction was formulated in this way by analogy with the well-known reaction of acetylenedicarboxylic ester as a dienophile (2, 28). The production of 1,4-epoxy-1,4-dihydronaphthalene in high yield from other dihalobenzenes with lithium amalgam in the presence of furan (132) and from *o*-dibromobenzene or *o*-dichlorobenzene and tetraphenylethylene disodium in the presence of furan (93) indicates that the mechanism must involve some common intermediate and that the intermediate is highly reactive toward dienes.

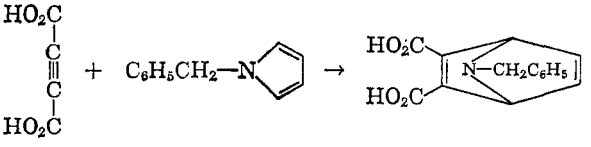
The production of triptycene by addition of benzyne to anthracene has given a new synthesis of this otherwise rather inaccessible hydrocarbon. *o*-Fluorobromobenzene reacts with magnesium in the presence of anthracene to produce triptycene in 28% yield (113, 126). Fluorobenzene reacts with *n*-butyllithium in the presence of anthracene to give triptycene (10%) (115). A good yield (23%) of triptycene can be obtained using fluorobenzene and lithium hexaphenyl antimonide in the presence of anthracene (117). The lithium hexaphenyl antimonide dissociates reversibly to a small extent into pentaphenylantimony and phenyllithium; thus phenyllithium can be used at extremely high dilution.



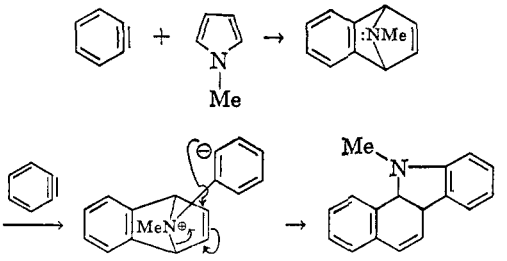
The benzyne intermediate reacts with other dienes to produce adducts in good yield (112). Thus cyclopentadiene reacts to produce 1,4-endomethylene-1,4-dihydronaphthalene in 65% yield (124); also with *N*-methylisoindole and 1,3-diphenylisobenzofuran to produce 9,10 - endo - *N* - methylamine - 9,10 - dihydroanthracene (54%) and 9,10-epoxy-9,10-diphenyl-9,10-dihydroanthracene (85%), respectively (133).



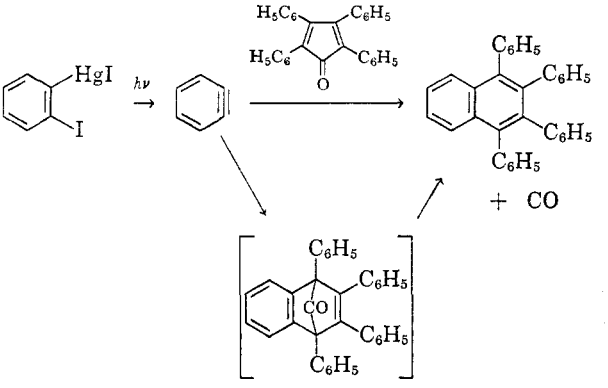
N-Benzylpyrrole forms a Diels–Alder adduct with acetylene dicarboxylic acid (85, 86).



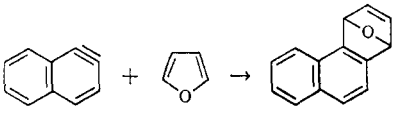
Benzyne, produced from *o*-fluorophenylmagnesium bromide, reacts with *N*-methylpyrrole, the initial Diels–Alder adduct reacting with more benzyne to produce *N*-methyl-10,11-dihydro-1,2-benzocarbazole (114).



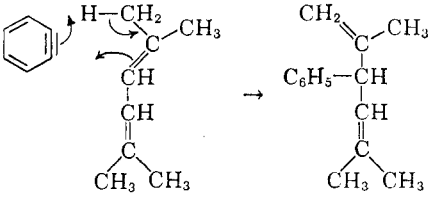
The benzyne intermediate may be produced by ultraviolet irradiation of *o*-iodophenylmercuric iodide or bis-(*o*-iodophenyl)-mercury, and has been trapped by reaction with tetraphenylcyclopentadieneone (121).



Furan has been used to detect the production of α-naphthalyne in the reaction of either 1-bromo-2-fluoronaphthalene or 2-bromo-1-fluoronaphthalene with *n*-butyllithium (116).



Not all dienes react with benzyne to produce a Diels–Alder adduct. 2,5-Dimethyl-2,4-hexadiene reacts with benzyne to produce 2,5-dimethyl-3-phenyl-1,4-hexadiene (3).

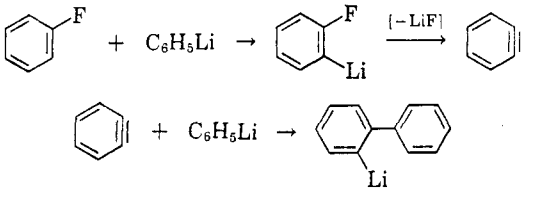


Models of the diene show that it cannot be forced into the conformation required for ring closure; the isobutylene groups assume positions *trans* to each other and only one of them is in the correct position for addition to benzyne.

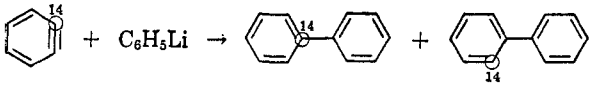
VIII. Reactions in Which Polynuclear Compounds Are Produced

A. ISOLATED SYSTEMS

The first suggestion that reactions in which polynuclear hydrocarbons are produced may proceed by an elimination–addition mechanism was put forward to account for the isolation of biphenyl from the reaction of fluorobenzene with phenyllithium (111, 128, 130).

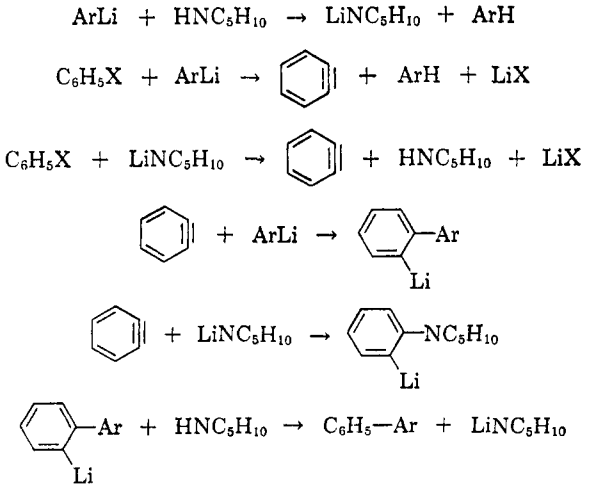


This reaction has been repeated using fluorobenzene-1-^{14}C (74), and the isotope distribution in the resulting biphenyl found to be as expected if the benzyne mechanism operates.



Biphenyl is produced in the reaction of all the halobenzenes with phenyllithium, the highest yield being obtained from fluorobenzene.

The arylation of aryl halides is catalyzed by the addition of piperidine or pyrrolidine (67). These results indicate that the elimination of hydrogen halides to form aryne intermediates is effected much more rapidly by lithium piperidide or pyrrolidide than by aryl lithiums even though they are weaker bases. The reactions were carried out by adding piperidine or pyrrolidine to excess ethereal aryllithium in the presence of the aryl halide. Although the secondary amide can compete with the aryllithium for the liberated aryne, since the aryllithium is present in excess, the yield of biaryl always exceeds that of tertiary amine.



The catalytic effect of the addition of secondary aliphatic amines also is shown in the arylation of chlorobiphenyls, chloronaphthalenes and 9-chlorophenanthrene.

In fact lithium piperidide at 20° is 27 times more efficient in the formation of benzyne from fluorobenzene, and 70 times more efficient with chlorobenzene than is phenyllithium (60). Competition reactions show that phenyllithium adds to benzyne 4.4 times as readily as does lithium piperidide. The competition constants for α-naphthyne and 9,10-phenanthryne are 5.8 and 12.8, respectively. It should also be noted that the nature of the halogen does not influence the product composition.

TABLE 4

Catalytic arylation of aryl halides with aryllithium by secondary aliphatic amines

ArX	Ar'Li	Time	Yield Ar–Ar', %		Yield *tert* amine
			With amine	Without amine	
		hr.			*per cent*
Chlorobenzene	Phenyl-	9	61	17	13
Bromobenzene	Phenyl-	9	64		13
Iodobenzene	Phenyl-	9	46		10
Chlorobenzene	*o*-Tolyl	2	23	6	2
Chlorobenzene	*o*-Tolyl	9	51		14
p-Chlorobiphenyl	Phenyl	6	65[a]	18[b]	
9-Chlorophenanthrene	Phenyl	9	77	13	
9-Chlorophenanthrene	*o*-Tolyl	8	70	14	
9-Chlorophenanthrene	Mesityl	40	36	9	
1-Chloronaphthalene	Phenyl	9	66[c]	22[d]	
2-Chloronaphthalene	Phenyl	9	72[e]	37[f]	

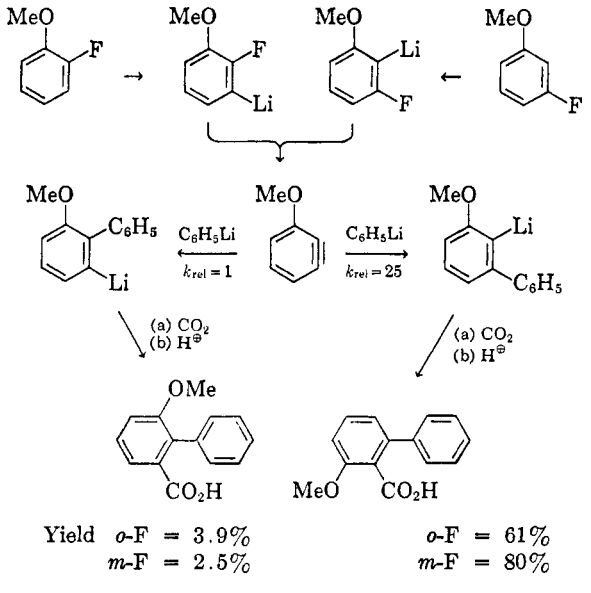
[a] Ratio of *p*:*m* = 45:55. [b] Ratio of *p*:*m* = 48:52. [c] Ratio of 1:2 = 35:65. [d] Ratio of 1:2 = 33:67. [e] Ratio of 1:2 = 30:70. [f] Ratio of 1:2 = 24:76.

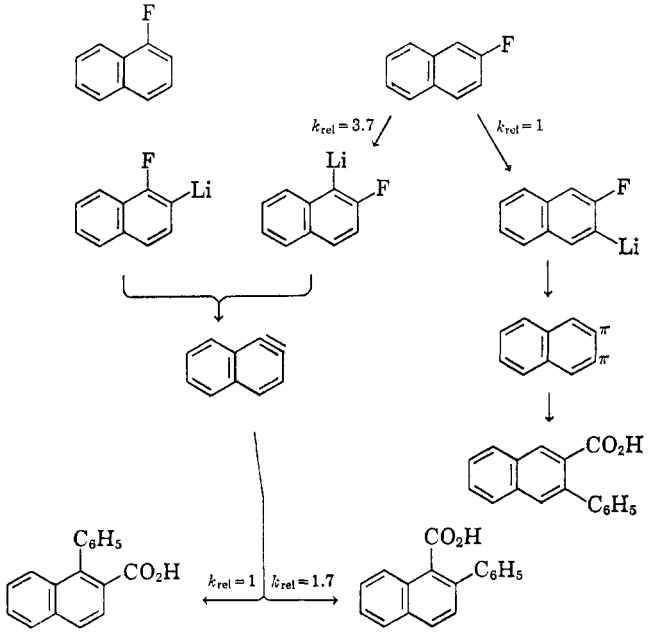
The removal of an *o*-hydrogen by an organometallic compound in the metalation of aryl halides is dependent on the acidity of the *o*-hydrogen. The inductive effect of the halogen facilitates this removal, decreasing in the order F > Cl > Br.

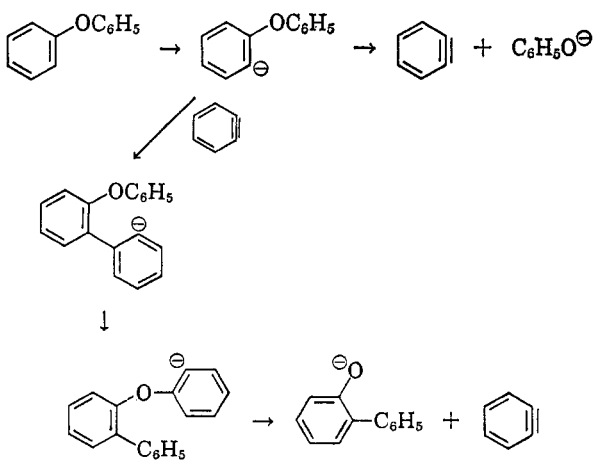
The carboxylation of the reaction mixture, in place of hydrolysis, has been used in certain cases (61, 62, 69). The pattern shown was observed with *o*- and *m*-fluoroanisole in the presence of four equivalents of phenyllithium.

The direction of addition of the phenyl anion to the aryne is in accord with the inductive effect of the methoxyl group. Similar results were obtained on treatment of the fluoronaphthalenes with excess phenyllithium, carboxylation giving mixtures of isomeric phenylnaphthoic acids.

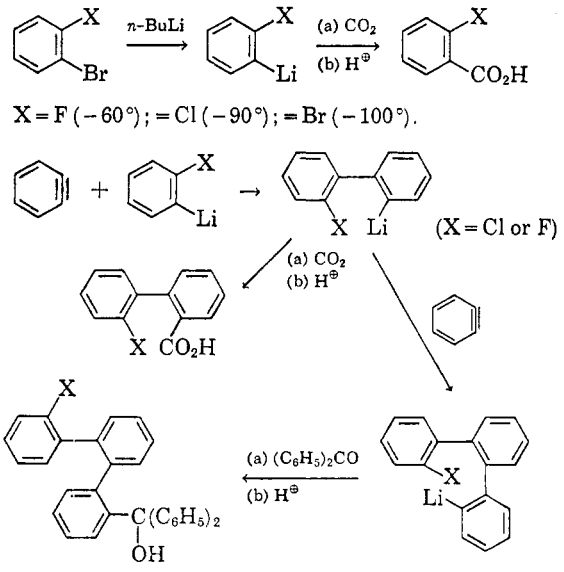
Phenylsodium reacts with diphenyl ether to produce 2-hydroxybiphenyl (46%) and 2-phenoxybiphenyl (9%) (82, 83). This isomerization is envisioned as proceeding by a benzyne mechanism as a result of initial *o*-metallation.



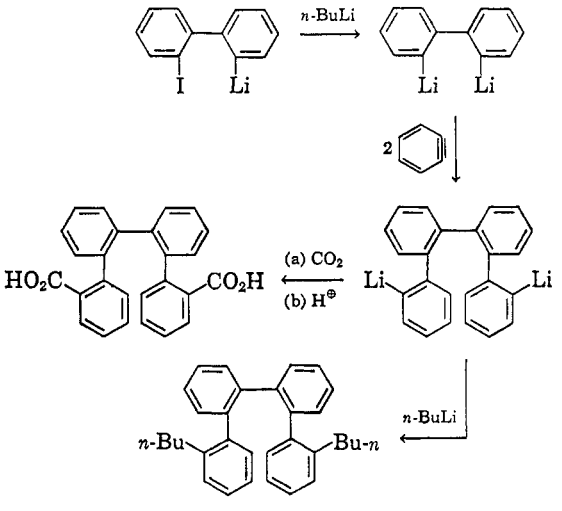




The reactions of *o*-dihalobenzenes with metals and metallating agents have also resulted in the production of polynuclear compounds. The *o*-halobromobenzenes can be converted into the corresponding *o*-halophenyllithium by reaction with *n*-butyllithium in ether at temperatures below −60° (35). If the reactions are carried out at slightly more elevated temperatures these compounds lose metal halide, the resulting benzyne intermediate giving rise to more complex products.



o-Di-iodobenzene reacts with *n*-butyllithium in benzene–petroleum ether solution, *o*-quaterphenyl derivatives being isolated (45, 47). In this case both halogen atoms can undergo halogen–metal transfer and a modification of the above scheme may operate:



Alternatively the same products could arise by reaction of *o*-phenylenedilithium with three molecules of benzyne.

B. CONDENSED SYSTEMS

Biphenylene and triphenylene frequently are isolated

in reactions which proceed by a benzyne mechanism. Other arynes can give rise to substituted biphenylenes and triphenylenes. Although dimerization and trimerization of benzyne has been suggested (82), to account for the formation of biphenylene and triphenylene, respectively, there are strong arguments against this route in the case of triphenylene formation.

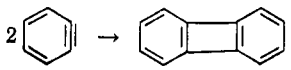
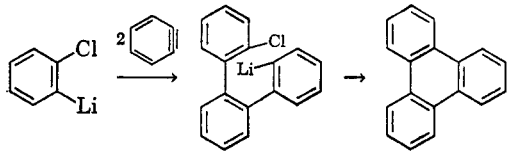


TABLE 5

Formation of biphenylene and substituted biphenylenes

Dihalide	Reagent	Product	Yield	Reference
			per cent	
o-Dibromobenzene	Li/Hg	Biphenylene	9	(132)
o-Bromofluorobenzene	Li/Hg	Biphenylene	24	(132)
o-Bromoiodobenzene	Mg	Biphenylene	3.5	(47)
3-Bromo-4-iodotoluene	Mg	2,6-Dimethylbiphenylene	0.5	(50)
3-Bromo-4-fluoro-1,3,5-trimethylbenzene	Li/Hg	1,3,4,5,6,8-Hexamethylbiphenylene	16	(123)
1-Bromo-2-iodonaphthalene	Mg	1,2,5,6-Dibenzobiphenylene		(110)
2,3-Dibromonaphthalene	Li/Hg	2,3,6,7-Dibenzobiphenylene		(97)
2-Bromo-3-iodonaphthalene	Cu	2,3,6,7-Dibenzobiphenylene		(97)

Two pieces of evidence favor a stepwise mechanism for the formation of triphenylene in the reaction between *o*-chlorobromobenzene and *n*-butyllithium (35).



XII

Triphenylene and derivatives of the intermediate (XII) are never isolated together. At room temperature only triphenylene is isolated whereas at −65° only the benzophenone adduct of XII is isolated. Further, the yield of triphenylene is comparable to that of the benzophenone adduct.

IX. Reactions Involving Carbanions

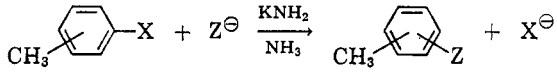
A large number of compounds containing active hydrogen atoms can be phenylated with chlorobenzene and bromobenzene in the presence of potassium amide or sodium amide in liquid ammonia. In all of these reactions aniline, diphenylamine and triphenylamine can be formed as side-products. The fact that these reactions do proceed by a benzyne mechanism has been checked by making use of the known rearrangement of the tolyl halides in aryne type reactions (103).

The carbanions generally are made by reaction with

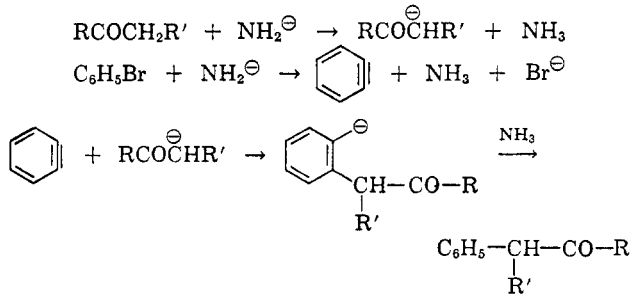
TABLE 6

Formation of triphenylene and substituted triphenylenes

Dihalide	Reagent	Product	Yield	Ref.
			per cent	
Fluorobenzene	*n*-BuLi	Triphenylene		(39)
o-Fluorobromobenzene	Li/Hg	Triphenylene	3	(132)
o-Chloroiodobenzene	Cu	Triphenylene		(94)
o-Chlorobromobenzene	*n*-BuLi	Triphenylene	7	(35)
o-Fluorobromobenzene	Mg	Triphenylene	20	(124)
o-Diiodobenzene	Li	Triphenylene	30	(45)
o-Bromoiodobenzene	Li	Triphenylene	54	(48)
3-Bromo-4-iodotoluene	Li	2,6,11-Trimethyltriphenylene	11	(50)
9,10-Dichlorophenanthrene	Mg	Hexabenzotriphenylene	60	(25)



excess amide ion which then can produce the aryne from the aryl halide. The type of compounds which have been phenylated by this method range from ketones and esters to heterocyclic derivatives such as quinaldine and lepidine. The direct phenylation of ketones has been carried out using bromobenzene and the ketone in the presence of a strong nucleophile (usually sodium amide). No reaction occurs in the absence of a base strong enough to liberate benzyne. The reaction is envisioned as proceeding by the steps (78):



Although chlorobenzene was found to give yields almost as good as bromobenzene, fluorobenzene was found not to react (79).

The existence of a γ-pyridyne intermediate has been postulated to account for the product obtained when 3-bromopyridine and sodioacetophenone react with sodamide in liquid ammonia (81).

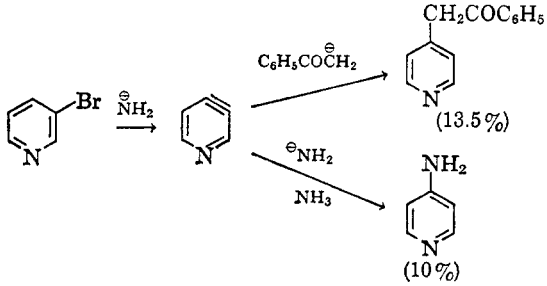


TABLE 7

Reaction of bromobenzene with carbanions in the presence of alkali amides

Amide	Active Hydrogen Compound	Product	Yield	By-products	Yield	Reference
			per cent		*per cent*	
$NaNH_2$	$MeCOCH_3$	$MeCOCH_2C_6H_5$	35	$C_6H_5NH_2$	18	(79)
$NaNH_2$	$MeCOCH_2Me$	$MeCOCH(Me)C_6H_5$	75	$C_6H_5NH_2$	5	(79)
$NaNH_2$	$MeCOCH_2Et$	$MeCOCH(Et)C_6H_5$	65	$C_6H_5NH_2$	9	(79)
$NaNH_2$	$EtCOCH_2Me$	$EtCOCH(Me)C_6H_5$	62	$C_6H_5NH_2$	9	(79)
$NaNH_2$	*n*-$PrCOCH_2Et$	*n*-$PrCOCH(Et)C_6H_5$	35	$(C_6H_5)_2NH$	14	(79)
KNH_2	*n*-$PrCOCH_2Et$	*n*-$PrCOCH(Et)C_6H_5$	56	$C_6H_5NH_2$	15	(79)
$NaNH_2$	$C_6H_5COCH_3$	$C_6H_5COCH_2C_6H_5$	28	$C_6H_5NH_2$	4	(79)
$NaNH_2$	CH_3CO_2Et	$C_6H_5CH_2CO_2Et$	42	$C_6H_5NH_2$	21	
		$(C_6H_5)_2CHCO_2Et$	14	$CH_3CONHC_6H_5$	15	(80)
$NaNH_2$	$CH_3CO_2C_4H_9$	$C_6H_5CH_2CO_2C_4H_9$-*t*	40	$CH_3CONHC_6H_5$	27	(80)
		$(C_6H_5)_2CHCO_2C_4H_9$-*t*	16			
$NaNH_2$	$MeCH_2CO_2Et$	$MeCH(C_6H_5)CO_2Et$	73	$CH_3CH_2CONHC_6H_5$	28	(80)
$NaNH_2$	$MeCH_2CO_2Bu$	$MeCH(C_6H_5)CO_2Bu$	38	$CH_3CH_2CONHC_6H_5$	39	(80)
$NaNH_2$	$C_6H_5CH_2CO_2Et$	$(C_6H_5)_2CHCO_2Et$	63	$C_6H_5NH_2$	11	(80)
$NaNH_2$	$CH_3(CO_2Et)_2$	$C_6H_5CH(CO_2Et)_2$	51	$C_6H_5NH_2$	18	(80)
$NaNH_2$	$EtCH(CO_2Et)_2$	$C_6H_5EtC(CO_2Et)_2$	22	$C_6H_5NH_2$	9	(80)
$NaNH_2$	$CH_2(CO_2Me)_2$	$C_6H_5CH(CO_2Me)_2$	37	$C_6H_5NH_2$	17	(80)
$NaNH_2$	$C_6H_5C{\equiv}CH$	$C_6H_5C{\equiv}CC_6H_5$	26			(104)
KNH_2	$(C_6H_5)_3CH$	$(C_6H_5)_4C$	31			(104)
KNH_2	Fluorene	9-Phenylfluorene	40			
		9,9-Diphenylfluorene	18			(104)
$NaNH_2$	$(CH_3)_2CHCN$	$Me_2C(C_6H_5)CN$	23	$C_6H_5NH_2$	29	(22)

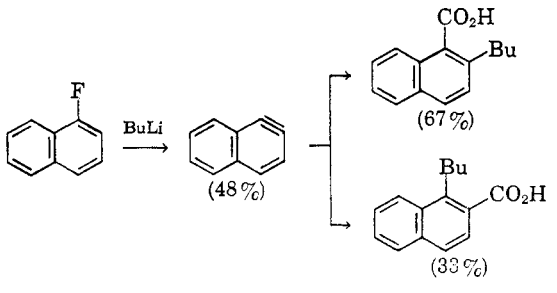
Certain esters including malonic and substituted malonic esters have been phenylated in fair to good yields by reaction with bromobenzene and excess sodium amide in liquid ammonia. This reaction is particularly useful in the case of malonic esters for the synthesis of barbituric acid derivatives (80). Anilides are produced as by-products in this reaction, presumably due to attack of the anilide ion at the carbonyl carbon of some ester which has not been converted into its anion.

$$RCO_2R' + C_6H_5{}^{\ominus}NH \rightarrow RCONHC_6H_5 + R'O^{\ominus}$$

Diethyl α-ethyl-α-phenylmalonate has been prepared in 39% yield from diethyl malonate without the isolation of intermediate phenylated product.

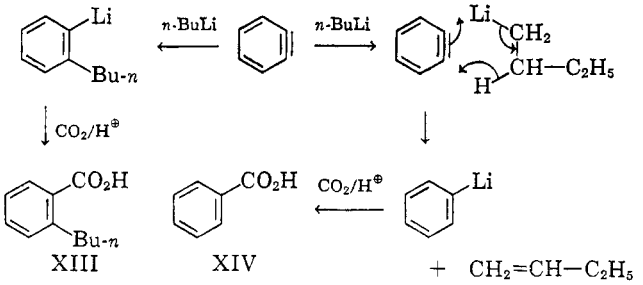
Potassium diphenylmethide is phenylated very slowly by chlorobenzene in liquid ammonia; the rate of this reaction is, however, increased markedly by the addition of potassium amide (135). The phenylation of quinaldine, lepidine, α-picoline, *o*-tolunitrile and acetonitrile also can be achieved with chlorobenzene or bromobenzene in the presence of potassium amide in liquid ammonia (11, 29, 107).

The butylation of arynes has been noted in several instances. Thus *n*-butyllithium and *t*-butyllithium react with 1-fluoronaphthalene to give mixtures of



butylnaphthoic acids subsequent to carboxylation (69).

Benzyne, produced by the reaction of *n*-butyllithium on *o*-bromochlorobenzene at −60° gives a mixture of acids on carboxylation, the product ratio depending on the temperature at which the carboxylation is carried out (33).

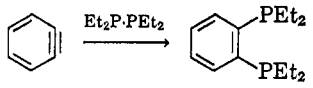


Ratio of XIII:XIV 2:1 at −80°
40:1 at −20°

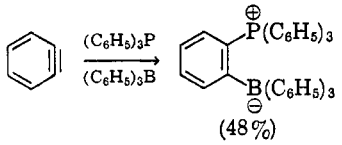
X. Reactions with Other Nucleophiles and Electrophiles

Reactions of benzyne with a variety of nucleophiles in competition with amide ions show that benzyne displays a considerable lack of selectivity in its addition reactions. Further, base strength is not the only factor of importance in determining the attack of a nucleophile on benzyne. Triphenylmethide, anilide, fluorenyl and thiophenate although having widely different pK_a values give comparable yields of products (22, 104).

It has been suggested that *o*-phenylenebis-(diethyl phosphine) is produced by the attack of tetraethyldiphosphine on benzyne (44).



The simultaneous attack of a nucleophile in the presence of an electrophile has been studied (116), quite high yields being obtained.



(48%)

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