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COMPETITION STUDIES ON ARYNE GENERATION FROM HALOPHENYL TRIFLATES

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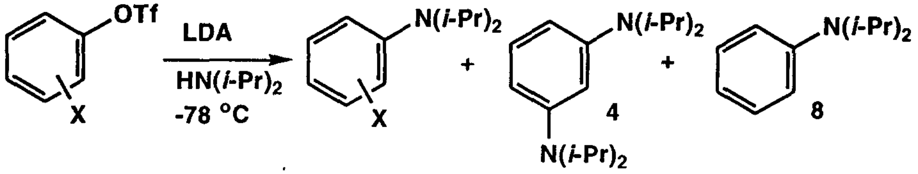
Summary: Reaction of halophenyl triflates with LDA in diisopropylamine at -78 °C affords isomeric mixtures of halo-*N,N*-diisopropylanilines, occasionally accompanied by variable amounts of *m*-bis(*N,N*-diisopropylamino)benzene and/or small amounts of *N,N*-diisopropylaniline. Use of *ortho*- or *meta*-halophenyl triflates gives largely the *m*-haloaniline, while the *p*-haloaniline predominates in reactions of the *para*- isomer. The magnitude of the directing effects varies with the halide (Cl>Br>I).

The ability to utilize aryl electrophiles as aryne precursors has become increasingly important to the synthetic chemist.[3,4] Classically, benzyne has been generated by the decomposition of diazocarboxylate salts,[5] by the oxidation of 1-aminobenzotriazole,[6] or by the base-catalyzed elimination of hydrogen halide from a halobenzene.[7] We have demonstrated that aryl triflates undergo *ortho*-deprotonation followed by rapid elimination to form the corresponding aryne, which can then be trapped *in situ* with nucleophiles.[8,9]

Dihaloarenes have been employed in both metallation/elimination[10] and deprotonation/ elimination mediated aryne forming reactions.[3] When the two halogens on the arene differ, the initial products of deprotonation/elimination are governed by the relative rates of deprotonation, which are determined by the inductive effects of both of the halogens, and by the relative rates of elimination.[3,11] The rate of benzyne formation from monohalobenzenes (Br > I > Cl >> F) reflects this combination of factors.[11] The reaction of a 3- or 4-halobenzyne intermediate with nucleophiles can lead to isomeric mixtures of products. The few studies on nucleophilic addition to 3-halobenzynes report preponderant or exclusive formation of the meta-substituted haloaryne, though examples appear to exist only for Cl and F.[12] 4-Halo-benzynes lead to mixtures of the para- and meta-products, with the para isomer predominating.[12a,13] Wotiz and Huba showed that treatment of *p*-dichlorobenzene with $NaNH_2$ in liquid NH_3 gave *p*-chloroaniline, while the meta- and ortho-analogues afforded *m*-chloroaniline, however isolated yields were low with diamines observed, but not isolated.[14] Biehl later reported that *o*-dichlorobenzene reacts with $NaNH_2$ in primary amine solvents to give the *N*-substituted *m*-chloroanilines in good yield.[15] Because little selectivity among halides is normally afforded by the conditions required for aryne formation,[12b,14,16] tandem aryne formation is commonly observed for *o*- and *m*-dihaloarynes. Perhaps the most spectacular examples of rational synthesis via tandem aryne formation are due to Hart and coworkers.[17]

Having developed a novel leaving group for deprotonation/elimination based aryne formation,[8,9] it was of interest to determine the relative rates of elimination of aryl triflates versus aryl halides. Furthermore, studies on the selective elimination of one leaving group might offer access to aryne-based chemistry while maintaining a leaving group for further elaboration of the aryne. Finally, it was believed that a comprehensive study might provide additional insight into haloaryne directing effects. Herein we report the results of the reaction of haloaryl triflates with LDA using *N,N*-diisopropylamine as solvent.

Treatment of halophenyl triflates with 2 equiv of LDA in diisopropylamine at -78 °C for 1 h, followed by warming to room temp and quenching with water afforded a mixture of products which typically could be separated by radial chromatography (Table). *o*-Bromophenyl triflate required the use of additional base (4 equiv LDA) in order to completely consume the starting material. Mass balances were typically in the 55-75% range based on isolated yields and product ratios corresponded well with GC analyses of crude reaction mixtures. In most cases, no attempt was made to isolate any phenol which may have formed from hydrolysis of the triflate.[8,9] In those reactions studied (entries 1,3,7) no halophenol was observed.



In general, three types of products were obtained. With two exceptions (entries 2 and 4), the major products isolated were the isomeric halo-*N*,*N*-diisopropylanilines obtained from selective loss of the elements of triflic acid followed by addition of diisopropylamine to the resulting halobenzyne. The *o*-halophenyl triflates can only generate 3-halobenzyne. Thus, the product ratios from these cases reflect the directing effects of the respective halogens, less any haloaniline which might have undergone further reaction to form diamine **4** or aniline **8**. As reported previously,[12,14,15] 3-chlorobenzyne was found tostrongly direct nucleophilic addition to the meta position (entry 1). This electronic effect drops off as the

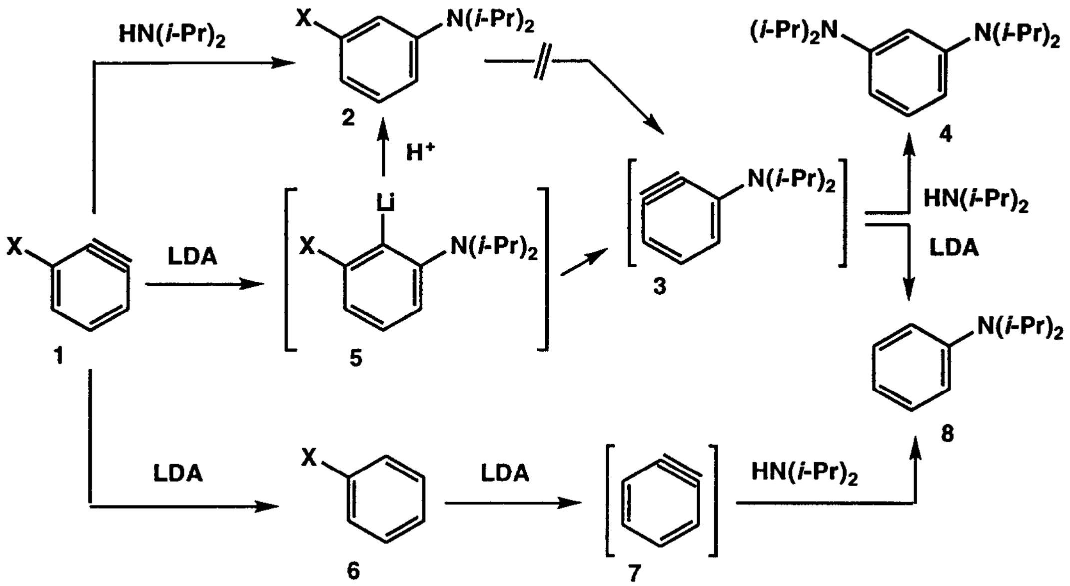
Table. Reaction of Haloaryl Triflates with Lithium Diisopropylamide (LDA)[a]

Entry	Triflate	$C_6H_5N(iPr)_2$ % Yield	$XC_6H_4N(iPr)_2$ % Yield (o:m:p)	$C_6H_4[N(iPr)_2]_2$ % Yield (m:p)
	Chlorophenyl			
1	ortho	0	51 (3:97:--)	26
2	meta	0	28 (8:83: 9)	35
3	para	0	56 (--:28:72)	0
	Bromophenyl			
4	ortho[b]	6	26 (20:80:--)	23
5	meta	tr	52 (6: 82:12)	25
6	para	0	55 (--: 23:77)	tr
	Iodophenyl			
7	ortho[c]	19	45 (33:67:--)	8
8	meta	11	53 (00:80:20)	18
9	para	0	69 (--:45:55)	0

a.) Reaction of 0.4 g of haloaryl triflate with 2.0 equiv LDA in 25 mL of diisopropylamine as solvent at -78 °C for 1 h followed by warming to room temp over 10 min and immediately quenching by the addition of water. Yields refer to isolated yields. Numbers in parentheses refer to isomer ratios. tr refers to trace amounts (>1%) observed or isolated.

b.) 4.0 equiv of LDA used.

c.) An unidentified side-product was also isolated from the *o*-iodophenyl triflate reaction.



Scheme. Proposed mechanisms for the formation of mono- and *m*-bis(*N*,*N*-diisopropylamino)benzene

halide is changed from chloride (30:1 meta:ortho) to bromide (4:1) to iodide (2:1). 4-Chloro- and 4-bromobenzyne direct nucleophilic addition to the para position (3:1 para:meta; entries 3 and 6). Again, the level of discrimination falls off for the iodo case (1:1). The *m*-halophenyl triflates can generate either halobenzyne. 4-Halo-*N*,*N*-diisopropyl-aniline formation increases on varying the halide from Cl to I with concomittant decreases in the amount of 2-halo-*N*,*N*-diisopropylaniline. This suggests that the 3-halobenzyne/4-halobenzyne formation is dependent on the halogen with Cl>Br>I. It is noteworthy that in no case was phenyl triflate, or an *N*,*N*-diisopropylaminophenyl triflate observed. This attests to the rapid elimination of the elements of triflic acid relative to any of the hydrogen halides under the reaction conditions.

The second commonly observed product is *m*-bis(*N*,*N*-diisopropylamino)benzene (**4**). Diamines are commonly observed in the reactions of dihaloarenes with amide anions.[12b,18] Typically, the *meta*-isomer has been the sole or predominant product observed from *o*-dihalobenzenes and a meta/para mixture is obtained from *p*-dihalobenzenes.[12b,18] The diamine obtained in the present study was always >99% meta. *p*-Halophenyl triflates did not afford significant amounts of the diamines. *m*-Haloaniline (**2**) is formed from *para*-halo triflates through the intermediacy of the 4-lithio-3-(diisopropyl-amino)phenyl halide. The lack of diamine formation from *p*-halophenyl triflates suggests that only the 2-lithio intermediate (**5**), and not the *m*-haloaniline (**2**), undergoes elimination to aryne **3** and further reaction. Diamine formation was also found to vary with the halide with Cl>Br>I. This then must reflect the relative tendency for elimination vs protonation of the 2-lithio-3-(diisopropylamino)phenyl halide intermediates.

The final product typically observed in these reactions is *N,N*-diisopropylaniline (**8**). This reduction product may be envisioned as arising from an amination/reduction scheme via arynes **1** and **3**, or from a reduction/amination scheme via arynes **1** and **7**. Inspection of the Table shows that the amount of aniline **8** varied with the halide (I>Br>>Cl) and that only the *o*- and *m*-iodophenyl triflates led to appreciable amounts of diisopropylaniline. Though either amination of benzyne (**7**) or reduction of aryne **3** could lead to the observed product, we prefer the latter pathway both because aryne **3** has already been shown to be present during the reaction, and because we have not observed any halobenzene (**6**) in crude reaction mixtures.

In conclusion, we have demonstrated that haloaryl triflates can be utilized in aryne-mediated reactions. Exclusive elimination of the elements of triflic acid affords haloarynes, amination of which occurs with regioselectivities similar to those observed previously.

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