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Formation of 3-Halobenzyne: Solvent Effects and Cycloaddition Adducts

Jotham W. Coe,* Michael C. Wirtz, Crystal G. Bashore, and John Candler

*Pfizer Global Research and Development, Groton Laboratories, Pfizer, Inc.,
Groton, Connecticut 06340*

coejw@groton.pfizer.com

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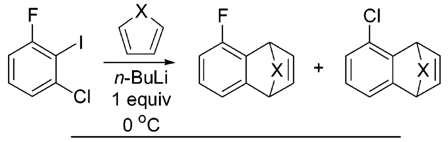
ABSTRACT

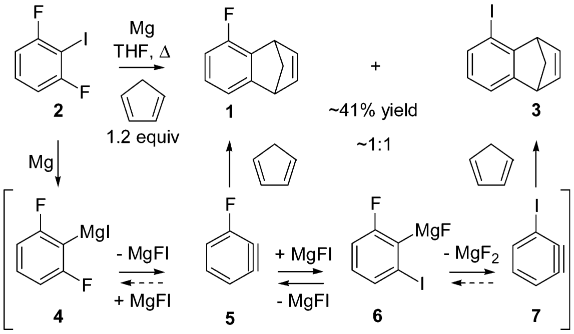


X	THF	pentane
CH$_2$	N.R.	<1:10
1,1-cyclopropane	97:3	3:97

Noncoordinating solvents permit the halogen–metal exchange-induced formation of benzyne (aryne) from di- and trihalobenzene precursors in the presence of cyclopentadiene to give 1,4-dihydro-1,4-methano-naphthalenes. Studies with mixed halide precursors and nonacidic Diels–Alder diene traps reveal that ethereal and hydrocarbon solvents influence the halide leaving group facility, resulting in a reversal of 3-halobenzyne regioselectivity.

Benzynes (arynes) are highly reactive chemical intermediates that continue to fascinate synthetic and mechanistic chemists.[1] As transient species, they are often studied indirectly through chemical reactions, some of which generate structures inaccessible by other pathways.[2] One early example, the Diels−Alder cycloaddition of benzyne and cyclopentadiene, remains the only direct approach to 1,4-methano-1,4-dihydronaphthalenes. We became interested in their corresponding 5-halo-derivatives as pharmaceutical intermediates (e.g., **1**). The known preparation of **1** involves the potentially hazardous nitroanthranilic acid benzyne route (three steps, 18% yield).[3] We sought a more controllable, scalable, and direct synthesis. To our surprise, the reaction of **2**[4] with cyclopentadiene under halogen−magnesium exchange conditions[5] afforded a mixture of fluoride **1** and unwanted iodide **3**, the latter of which presumably formed by exchange of iodide via intermediate 3-fluorobenzyne **5** (Scheme 1; see Supporting Information [SI]).[6]

Scheme 1



We reasoned that *n*-BuLi would sequester iodide (as *n*-BuI) in the halogen−metal exchange step and avoid the formation of **3**. Earlier studies by Hart et al. demonstrated the successful generation of benzyne by this approach with highly substituted 1,2-dibromobenzenes in cycloaddition

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[1] For recent developments and leading references in benzyne chemistry, see: Kitamura, T.; Yamane, M.; Inoue, K.; Todaka, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11674−11679. Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701−730.

[2] Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502−528.

[3] (a) Snow, R. A.; Cottrell D. M.; Paquette L. A. *J. Am. Chem. Soc.* **1977**, *99*, 3734−3744. (b) For methods of generation from other relevant anthranilic acids, see: Seltzman, H. H.; Berrang, B. D. *Tetrahedron Lett.* **1993**, *34*, 3083−3086.

[4] Rausis, T.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, *19*, 3351−3358.

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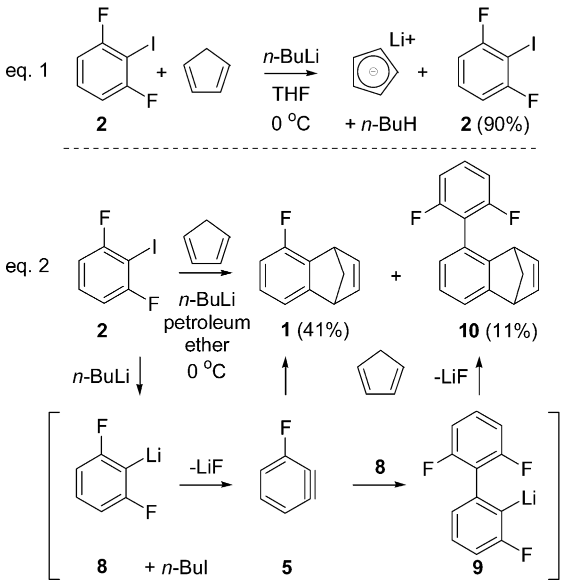
reactions.[7] However, only three examples with cyclopentadiene are known.[8,9] Herein we reveal that *n*-BuLi-induced halogen−metal exchange in the presence of cyclopentadiene *in noncoordinating solvents* effects the formation of the desired benzyne-derived products. Moreover, in addition to circumventing the iodide exchange reaction and affording acceptable cycloaddition yields, hydrocarbon solvents also profoundly shift the lithium halide leaving group facility.

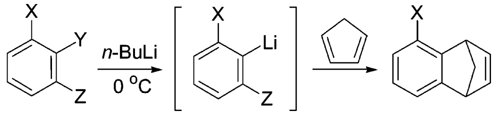
When a mixture of 2,6-difluoroiodobenzene (**2**, 1 equiv) and cyclopentadiene (1.5 equiv) in THF (0.2 M) was treated with *n*-BuLi (1 equiv) at 0 °C, starting iodide **2** was recovered unchanged (>90%, Scheme 2, eq 1). Proton transfer from cyclopentadiene was more rapid than halogen−metal exchange with **2** in THF.[9,10] However, under otherwise identical conditions in petroleum ether, **1** was produced as the only halo-1,4-dihydro-1,4-methano-naphthalene in 35−41% yield (eq 2, Scheme 2).[11] Starting iodide **2** was completely consumed, and the 5-aryl-1,4-dihydro-1,4-methano-naphthalene byproduct **10** was readily separated (~11% yield, GC-MS).[12]

Scheme 2



In petroleum ether and other hydrocarbon solvents (pentane, hexane, heptane, and cyclohexane), a precipitate, presumably LiF, forms upon *n*-BuLi addition. The reaction mixtures thicken considerably and require mechanical stirring on a larger scale. In contrast, toluene better dissolves all trihalobenzene precursors and affords readily stirred reaction mixtures.[13] In toluene, however, substrate **2** gave lower isolated yields of **1** (28%, Table 1) than did the corresponding chloro- and bromo-substrates **11**[14] and **12**,[15] respectively (entries 3−5). Similar conversions of 1,2-dihalobenzenes afforded the parent 1,4-dihydro-1,4-methano-naphthalene **18**. As with the trihalogenated precursors **2**, **11**, and **12**, the isolated yields of **18** improve in the sequence from **15**, **16**, and **17** (entries 6−8). This trend correlates well with literature precedent regarding the relative reactivity of lithiated *o*-haloaryllithium intermediates (Br > Cl > F).[16]

Table 1. 1,4-Dihydro-1,4-methano-naphthalenes



entry	substrate	X	Y	Z	solvent	product	yield
1	**2**	F	I	F	THF	**1**	0
2	**2**	F	I	F	hydrocarbons	**1**	41%
3	**2**	F	I	F	toluene	**1**	28%
4	**11**	Cl	I	Cl	toluene	**13**	42%
5	**12**	Br	I	Br	toluene	**14**	69%
6	**15**	H	Br	F	toluene	**18**	27%
7	**16**	H	I	Cl	toluene	**18**	56%
8	**17**	H	Br	Br	toluene	**18**	89%

Although acceptable yields under mild, convenient conditions were in hand, the conversion of **17** to **18** illustrated the high efficiency possible: equimolar **17**, cyclopentadiene, and *n*-BuLi gave **18** in 89% of theory on a 100 g scale. Indeed, the results in Table 1 and the literature precedent[16] suggested that by judicious choice of halogens, more reactive *o*-haloaryllithium species should more efficiently form 3-fluorobenzyne **5** and its cycloaddition products.[17] We

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(5) (a) Wittig, G.; Knauss, E. *Chem. Ber.* **1958**, *91*, 895−907. (b) Muir, D. J.; Stothers, J. B. *Can. J. Chem.* **1993**, *71*, 1290−1296.

(6) (a) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334−5341. (b) Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178−7184. (c) Wang, A.; Maguire, J. A.; Biehl, E. *J. Org. Chem.* **1998**, *63*, 2451−2455. (d) Okano, M.; Amano, M.; Tagaki, K. *Tetrahedron Lett.* **1998**, *39*, 3001−3004.

(7) (a) Hart, H.; Lai, C.-Y.; Nwokogu, G. C.; Shamouilian, S.; Teuerstein, A.; Zlotogorski, C. *J. Am. Chem. Soc.* **1980**, *102*, 6651−6652. (b) Hart, H.; Shamouilian, S. *J. Org. Chem.* **1981**, *46*, 4874−4876. (c) Nwokogu, G. C.; Hart, H. *Tetrahedron Lett.* **1983**, *24*, 5725−5726. (d) Hart, H.; Nwokogu, G. C. *Tetrahedron Lett.* **1983**, *24*, 5721−5724. (e) Blatter, K.; Schlüter, A.-D. *Chem. Ber.* **1989**, *122*, 1351−1356.

(8) (a) Hart, H.; Lai, C.; Nwokogu, G. C.; Shamouilian, S. *Tetrahedron* **1987**, *43*, 5203−5224. (b) Koenig, B.; Knieriem, B.; Rauch, K.; de Meijere, A. *Chem. Ber.* **1993**, *126*, 2531−2534.

(9) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300−305. Beak, P.; Musick, T. J.; Chen, C.-W. *J. Am. Chem. Soc.* **1988**, *110*, 3538−3542.

(10) We chose to study this process at 0 °C, expecting that the formation of benzyne from lithiated species would be more rapid than proton transfer processes. The formation of benzyne from *meta*-dihalolithiobenzenes in isolated systems is known to proceed rapidly above −15 °C; see: Saednya, A.; Hart, H. *Synthesis* **1996**, 1455−1458.

(11) These yields are comparable to those in previously reported Grignard approaches to unsubstituted products. See ref 5.

(12) This common byproduct in benzyne reactions is derived by addition of 2,6-difluorophenyllithium (**8**) to 3-fluorobenzyne (**5**) to form biaryllithium species **9**, from which elimination of LiF and Diels−Alder cycloaddition form **10**.

(13) 1,2-Difluoro-3-iodo-benzene is immiscible in hydrocarbons. See SI.

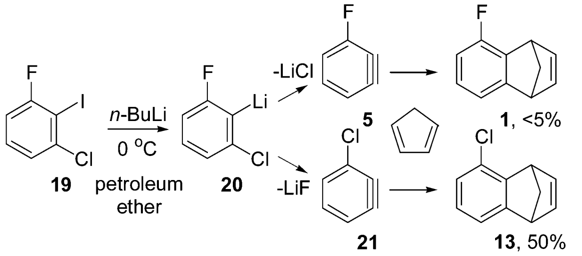
(14) See SI and: Bennetau, B.; Rajarison, F.; Dunogues, J.; Babin, P. *Tetrahedron* **1993**, *49*, 10843−10854.

(15) Du, C. J. F.; Hart, H.; Ng, K. K. D. *J. Org. Chem.* **1986**, *51*, 3162−3165.

(16) (a) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1956**, *78*, 2217−2222. (b) Bunnett, J. F.; Kearley, Jr. F. J. *J. Org. Chem.* **1971**, *36*, 184−186. (c) Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Organomet. Chem.* **1980**, *193*, 283−292.

therefore explored mixed halide precursors of 3-fluorobenzyne such as **19** (Scheme 3).

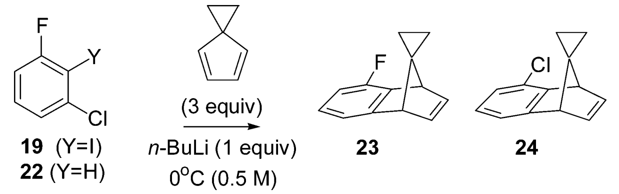
Scheme 3



A solution of **19**[18] and cyclopentadiene (1.5 equiv) in petroleum ether at 0 °C treated with *n*-BuLi gave **13** in 50% yield with less than 5% of the expected adduct **1** (Scheme 3). Fluoride instead of chloride elimination was entirely unexpected[16,19] and stimulated our interest as to the role of solvents in the formation of 3-halobenzyne. To investigate this question we used a nonacidic dienophile that would be inert to halogen−metal exchange in THF (vide infra).

Spiro[2.4]hepta-4,6-diene (1,1-cyclopropylcyclopenta-diene, or CPCP) was chosen as the Diels−Alder trap.[20] As shown in Scheme 4, intermediate 2-chloro-6-fluorophenyllithium (**20**) was generated in the presence of CPCP (3 equiv) by either halogen−metal exchange with **19** or by direct metalation of 3-fluorochlorobenzene (**22**). These reactions were induced by treatment with *n*-BuLi (1 equiv) in the indicated solvent (0.5 M) at 0 °C. In THF, adduct **23** (derived from **5**) was formed with high selectivity (Scheme 4, entries 1, 3), whereas in toluene, adduct **24** (derived from **21**) was obtained (Scheme 4, entries 2, 4).[21] Isolated and GC yields of the major product were independent of the method of entry to lithiated intermediate **20** from both **19** and **22**.

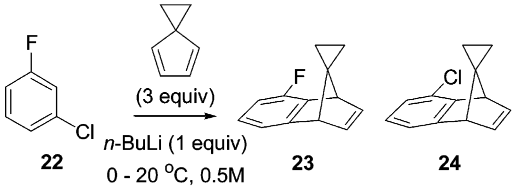
Scheme 4



entry	Y	solvent	**23**/**24** (GC)	yield
1	H	THF	> 97:3	46%
2	H	toluene	> 3:97	41%
3	I	THF	> 97:3	43%
4	I	toluene	> 3:97	64%

The effects of other ethereal and hydrocarbon solvents on regioselectivity are summarized in Table 2. Polar solvents favor the 3-fluorobenzyne-derived adduct **23**. Dimethoxyethane (DME) differs little from THF. 2,2,5,5-Tetramethyl-THF (Me_4THF), which has a dielectric constant comparable to that of THF but is sterically hindered, gives product ratios similar to those obtained in Et_2O and methyl *tert*-butyl ether (MTBE). Toluene and pentane favor the 3-chlorobenzyne-derived product **24**.

Table 2. Product Ratio (GC) as a Function of Solvent



	23	24
THF	95	5
DME	94	6
Me_4THF	35	65
MTBE	29	71
Et_2O	27	73
toluene	16	84
pentane	3	94

The effects of THF/pentane solvent mixtures appear in Figure 1. A shift to chloride elimination was observed with increasing THF concentration (see Figure 1 and SI). A maximum ratio of 98:2 (**23**:**24**) was obtained at dilute substrate concentration in neat THF (0.05 M).[22] In related experiments, 3-fluorobenzyne-derived products were not favored beyond 35% as Me_4THF/pentane concentration was

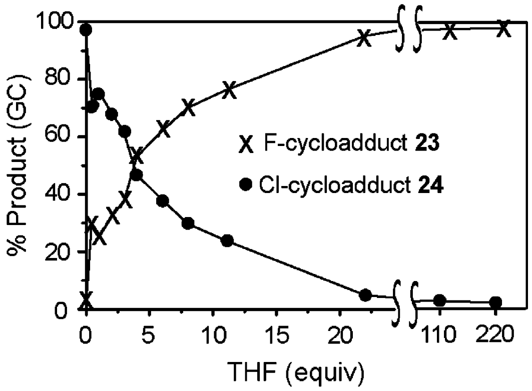


Figure 1. Effects of increasing THF concentration in pentane (0.5 M) with **22** and *n*-BuLi.

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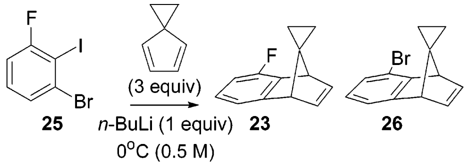
[17] More reactive (unstable) benzyne precursors lacking the 3-halogen substituent give high yields with other dienophiles (e.g., furan). See refs 6 and 7 and: Caster, K. C.; Keck, C. G.; Walls, R. D. *J. Org. Chem.* **2001**, *66*, 2932−2936.

[18] 1-Chloro-3-fluoro-2-iodobenzene (**19**) was prepared by metalation of 3-fluoro-chlorobenzene and reaction with iodine: Bennetau, B.; Rajarison, F.; Dunoguès, J.; Babin, P. *Tetrahedron* **1993**, *49*, 10843−10854.

[19] For a discussion of the stability of 2,6-dihalophenyllithium, see ref 16b. For halide selectivity in related *o*-halo-zincate benzyne precursors, see: Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Kondo, Y.; Otani, Y.; Ohwada, T. *J. Am. Chem. Soc.* **2002**, *124*, 8514−8515.

[20] Dienes such as furan or N-substituted pyrroles were considered; however, CPCP ensures minimal diene involvement as a solvent additive.

Scheme 5



entry	solvent	**23**/**26** (GC)	yield
1	THF	>97:3	75%
2	pentane	>5:95	75%

increased, suggesting that polar solvent effects are attenuated by steric influences (see Table 2 and SI).

The solvent effect extends to competitive fluoride versus bromide elimination. Reactions of iodo-arene **25** under halogen−metal exchange conditions (*n*-BuLi, 1.05 equiv, Scheme 5) produced fluoro adduct **23** in THF, derived by LiBr departure. In pentane, LiF departs to give **26**. Experiments with 2-chloro-6-bromophenyllithium revealed that a slight preference for the expulsion of LiBr versus LiCl in THF was eroded only slightly when the reaction was performed in pentane (see SI).

Our efforts to optimize yields of 3-fluorobenzyne-derived products showed that the solvent alters the product distribution in systems with available competing elimination pathways. Mixed halide substrates exhibit a dramatic ∼200:1 selectivity shift in hydrocarbons versus THF, suggesting a solvent-dependent change in product-determining steps.[23] We suspect that solvent association with intermediates and the departing lithium halide greatly impacts the reaction course. Related effects have been observed in cycloaddition reactions of LiBr-free and complexed forms of cyclopentyne.[24]

In conclusion, solvent and halide influence the generation and reactions of 3-halogen-substituted benzyne. In THF, proton transfer from cyclopentadiene to *n*-BuLi occurs faster than halogen−metal exchange with **2**. Noncoordinating solvents permit a straightforward preparation of 1,4-methano-1,4-dihydronaphthalenes[25] and 5-substituted derivatives from symmetrical 2,6-dihaloaryliodides. Initial probes with mixed halide precursors reveal a solvent-dependent regioselectivity.

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Supporting Information Available: Tables, figures, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The same product ratios were observed when the experiments were carried out at −78 °C (metalation by *n*-BuLi for 2 h in the presence of CPCP (3 equiv)) followed by slow warming to 20 °C.

(22) Butyl adducts resulting from nucleophilic addition of *n*-BuLi to 3-halobenzyne followed by elimination of lithium halide and subsequent Diels−Alder trap of 3-butylbenzyne with CPCP were observed in high dilution experiments. GC yields of these side products can be as much as 10−20% with increasing dilution.

(23) Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 4008−4009.

(24) Gilbert, J. C.; Hou, D.-R. *J. Org. Chem.* **2003**, *68*, 10067−10072. Wang, X.; Rabbat, P.; O'Shea, P.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2001**, *41*, 4335−4338.

(25) Representative procedure for benzyne Diels−Alder cycloaddition with cyclopentadiene: 1,2-Dibromobenzene (**17**, 100 g, 429 mmol) and cyclopentadiene (28.4 g, 429 mmol) were stirred in toluene (510 mL) at 0 °C under N_2. To this solution was added *n*-BuLi (241 mL, 1.78 M in hexanes, 429 mmol) dropwise over 30 min during which the reaction solution became first yellow then cloudy white. After an additional 10 min at 0 °C, the mixture was allowed to warm to room temperature, stirred overnight, and treated with H_2O (200 mL) and extracted with hexanes (3 × 150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to an oil that was purified by chromatography on silica gel eluting with hexanes to provide a clear, colorless oil (54.3 g, 89%).