Synthesis of Benzonorbornadienes: Regioselective Benzyne Formation

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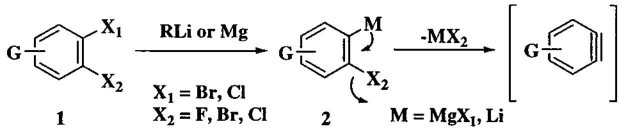
This report details the synthesis of several benzonorbornadienes by Diels−Alder cycloaddition of cyclopentadiene derivatives with substituted benzyne intermediates, which were generated by low-temperature metal−halogen exchange of halobenzenes. General conditions were developed, allowing synthesis of most benzonorbornadienes described herein at the multigram scale with isolated yields approaching 90% in some cases. Cycloaddition of the benzyne produced by substitution of a chlorodifluorobenzene for a bromodifluorobenzene in the metal−halogen exchange reaction unexpectedly gave a different benzonorbornadiene. The benzyne, which resulted by a deprotonation pathway rather than by metal−halogen exchange, formed in a highly regioselective elimination step.

Introduction

Several years ago, we began a program to prepare polymers with designed, controlled properties using ring-opening metathesis polymerization (ROMP). Structurally, ROMP monomers require a disubstituted olefin to be part of a strained ring system such as a norbornene, norbornadiene, benzonorbornadiene, or cyclooctene.[1] Many synthetic routes to the benzonorbornadiene ring system may be imagined with a primary method involving Diels−Alder [4 + 2] cycloaddition of cyclopentadiene derivatives with benzyne intermediates. Although the rich chemistry of these intermediates has been investigated in great detail, they are short-lived, fleeting species that must be generated and trapped in situ; many different approaches to their generation have been reported.[2] Only recently have they been isolated and spectroscopically characterized in an argon matrix[3] and in solution.[4] Through these intermediates, we have prepared the substrates for our study (Figure 1). It was during the preparation of halogenated benzonorbornadienes that we encountered an unusual regioselective elimination during benzyne generation.

Metal−Halogen Exchange Reactions. Metalation of 1,2-dihalogenated benzenes either through Grignard or aryllithium formation is an extremely useful method to generate benzynes: metal−halogen exchange is followed by elimination of a stable MX compound (M = metal, X = halogen) with simultaneous formation of the benzyne. Grignard chemistry usually requires elevated temperatures for both metalation and elimination steps, and solvent choice depends on the halogen being exchanged[5] (Scheme 1).

Scheme 1



In contrast to arylmagnesium formation, lithium−halogen exchange occurs at low temperature. Monohalogenated benzenes undergo metalation, but regiocontrol may be lost during the elimination step. 1,2-Disubstituted dihalogens **1** provide the best regiocontrol in the elimination step (Scheme 1). When different halogens are present on the ring, two opportunities for lithium−halogen exchange exist. In general, the more electropositive halogen exchanges first.[2,5] Once formed, several pathways are available for the aryllithium to react. Side-reactions are known, but these can be controlled by proper reagent choice, reaction stoichiometry, and solvent.[5,6] At low temperature, the aryllithium **2** is stable to elimination. This temperature is highly dependent on what group is being eliminated (e.g., triflates, tosylates, mesylates)[7] and on the overall electronic effects in the ring induced by other substitution. For example (G = H), the relative stability of halogenated aryllithium **2** toward elimination of LiX follows the order LiBr (−100 °C) < LiCl (−90 °C) < LiF (−60 °C).[8] It is expected that substitution will greatly affect these elimination temperatures. Many reactions can occur once the benzyne has been generated. For example, biphenylenes readily form by dimerization while nucleophilic alkyllithium reagents can add to give new aryllithium reagents.[9] In the presence of a suitable diene, cycloaddition can give a benzonorbornadiene derivative.[2]

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(1) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic: New York, 1997.

(2) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic: New York, 1967.

(3) Moriyama, M.; Ohana, T.; Yabe, A. *J. Am. Chem. Soc.* **1997**, *119*, 10229.

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(6) Negishi, E.-I. *Organometallics in Organic Synthesis*; John Wiley: New York, 1980; p 116.

(7) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735.

(8) Reference 5, pp 43−44.

(9) Cava, M. P.; Mitchell, M. J. *Cyclobutadiene and Related Compounds*; Academic: New York, 1967; Chapter 10.

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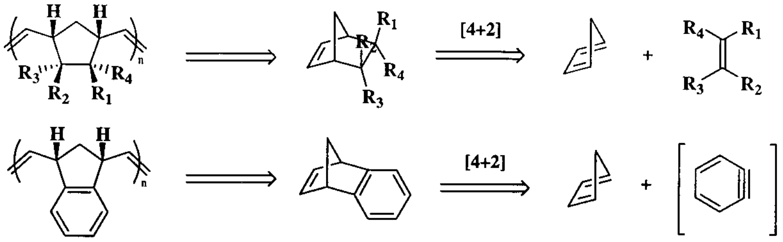
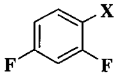


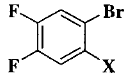
Figure 1. Stereochemistry between norbornene monomer and ROMP polymer. Substituent control in the Diels–Alder cycloaddition reaction.

Results and Discussion

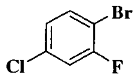
Of the two dienes used in this work, furan actively participated in cycloaddition reactions, whereas *N*-methylpyrrole was more sluggish as a result of its increased aromaticity.[10,11] Six different halogenated benzenes (**3**–**8**) were used as starting materials. Compounds **3**, **4** and **5**, **6** should give mono- and difluoro-benzonorbornadienes, respectively, and were chosen to understand reactivity differences between Cl–F, Br–F, and Br–Br substitution patterns. It is with compounds **3** and **4** that regioselective benzyne formation was observed. The parent 7-oxabenzonorbornadiene **9** (1,4-diepoxy-1,4-dihydronaphthylene[12]) was commercially available and was used to aid in NMR analysis of products **10**–**15**.



3, X=Br
4, X=Cl



5, X=F
6, X=Br



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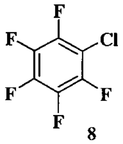

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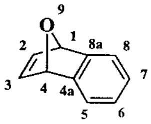

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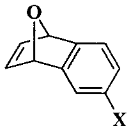
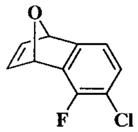
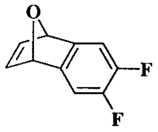


10, X=F
13, X=Cl



11



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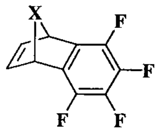

14, X=O
15, X=NMe

Benzonorbornadiene Synthesis by Metal–Halogen Exchange. A variety of reactions were examined while identifying the best conditions for metal–halogen exchange and trapping of the intermediate benzyne. The synthesis of benzonorbornadienes via lithium-induced benzyne formation has been examined by Coe. They reported on the strong solvent effects associated with the metal–halogen exchange reaction and concluded that THF was a poor solvent for this chemistry and that more highly selective reactions resulted when performed in diethyl ether.[13] Our results support their findings. Lithiation of 1-bromo-2,4-difluorobenzene **3** with *n*-BuLi (1.2 equiv) in THF at low temperature and trapping of the generated benzyne **18** on warming with furan (1.6 equiv) yielded a product mixture containing benzonorbornadiene **10** and many impurities as determined by analysis of the crude ^{1}H NMR spectrum and by thin-layer chromatography (nine spots). Identifiable from the NMR spectrum was *n*-butylbenzene **17**. This side-product arises by alkylation of the aryllithium **16** with *n*-butyl bromide, which is formed as a byproduct of the initial metal–halogen exchange.[6] As primary alkyl bromides are good alkylating agents, this process is competitive with cycloaddition to give norbornadiene **10** or dimerization to give biphenylene **19** (Scheme 2). While no direct evidence was obtained for **19**, it is a likely side-product, as biphenylenes are known to be produced by benzyne dimerization.[9] Butylbenzene **17** was minimized by using an excess of *n*-BuLi (2 equiv). However, while benzonorbornadiene **10** formed, so were other impurities as revealed by ^{1}H NMR.

By changing the reaction solvent to diethyl ether and trapping fluorobenzyne **18** with 10 equiv of furan, reaction yield and product selectivity to **10** were dramatically increased giving isolated yields ranging from 85 to 95%. Even on the 25 g scale, the isolated yield was 94%, which compared favorably with lower scale runs. This improvement is clearly the result of a strong solvent effect. We wondered if this same effect was operable when chlorobenzene **4** was substituted for bromobenzene **3**. *This substitution, which will be described below, gave very different results.*

Again, with chlorobenzene **4** we saw mixed results when performing the metal–halogen exchange with *n*-BuLi in THF. At least five compounds, with a primary one, were observed by TLC and ^{1}H NMR spectroscopy. As described above, changing the reaction solvent to diethyl ether and increasing the number of equivalents of diene to 10 yielded a pure compound as an oily, clear-yellow liquid in 90% crude yield. Kugelrohr distillation yielded it as a waxy, white, low-melting solid which displayed very clean ^{1}H and ^{13}C NMR spectra and was determined to be another benzonorbornadiene **11** (Scheme 2). This reaction was easily scaled-up to yield larger quantities of **11** in 86% (5.3 g) and 97% (30.4 g) yields.

Significant differences in metalation between bromobenzene **3** and chlorobenzene **4** resulted in *different benzonorbornadienes*. Specifically, norbornadiene **10** was the primary product isolated from the bromobenzene whereas norbornadiene **11** was derived from the chlorobenzene. Potential deprotonation pathways leading to this other benzonorbornadiene were envisioned as shown

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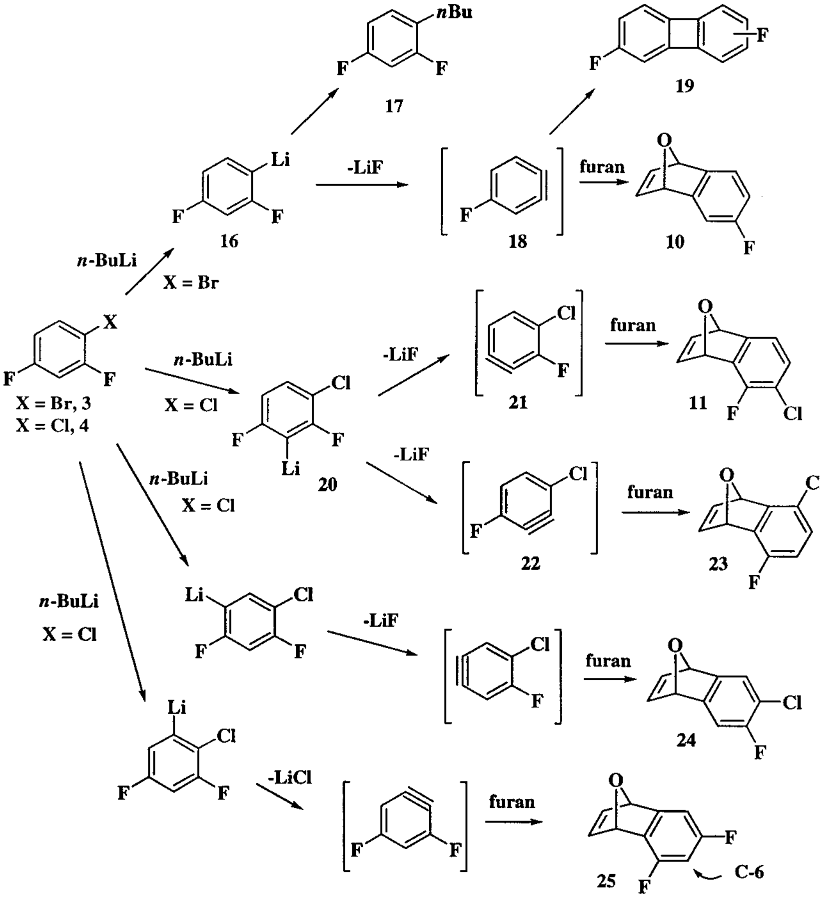
[10] Acheson, R. M. *An Introduction to the Chemistry of Heterocyclic Compounds*; 3rd ed.; John Wiley: New York, 1976; p 174.

[11] Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon: New York, 1985; p 76.

[12] Stiles, M.; Miller, R. G.; Burckhardt, U. *J. Am. Chem. Soc.* **1963**, *85*, 1792.

[13] Coe, P. L.; Waring, A. J.; Yarwood, T. D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2729.

Scheme 2



in Scheme 2. Formation of benzonorbornadiene **10** involves metal–halogen exchange of bromobenzene **3** to give aryllithium **16** followed by elimination of LiF to give benzyne **18** which then undergoes cycloaddition with furan. Benzonorbornadienes **11** and **23** are formed by deprotonation of chlorobenzene **4** to give the common aryllithium intermediate **20** which on elimination of LiF gives either benzyne **21** or **22** followed by cycloaddition with furan. Benzonorbornadienes **24** and **25** would be produced by metalation at C-5 and C-6, respectively, subsequent loss of LiF or LiCl, and cycloaddition to furan. That elemental analysis of the crude product isolated from reaction of **4** showed it to be analytically pure (>99.7%), and that the NMR showed other benzonorbornadienes in addition to the main product **11**, suggests that isomers **23** and **24** were generated in the reaction. C-13 NMR data obtained on a component isolated by column chromatography during one of the THF solvated reactions showed characteristic doublet-of-doublet carbon–fluorine coupling patterns associated with an 1,3-difluoro substitution on the aromatic ring, as shown in norbornadiene **25**. This differential reactivity was unanticipated.

In an attempt to understand and explain these unusual results, literature on metalation of halogen-containing benzene derivatives was critically evaluated. Aryl bromides are known to undergo metal–halogen exchange at much lower temperatures than the corresponding aryl chloride. Besides metal–halogen exchange, alkyllithium reagents can deprotonate appropriately substituted benzene derivatives. For example, 1,3-difluorobenzene is deprotonated at the relatively acidic 2-position.[14] Many similar examples have been reported in the literature.[2,13,15,16]

The ^{1}H NMR data allow assignment of the correct fluoro- and chloro-regiochemistry in the primary benzonorbornadiene reaction product. Bridgehead proton resonances were key to determining the structure of **11** over its isomer **23**, and substituent effects from the aromatic ring on these resonances are clearly observed by comparison of differently substituted halogenated benzonorbornadienes. Halogen substitution in the aromatic ring at C-5,8 deshields C-4,1 protons, respectively, whereas substitution at C-6,7 has no affect on them. Benzonorbornadienes **24** and **25**, while present in small quantities in the reaction mixture, are easily eliminated as the primary reaction product based on their expected NMR spectral data and on the low probability of metalation at C-5 and C-6 positions of the chlorobenzene.

Most puzzling was the high regioselectivity observed in the elimination step to generate benzyne **21** over **22**. This result may be explained by considering that aryne reactivity and stability are determined by substituent inductive rather than resonance effects.[17] As fluoride is eliminated from the aromatic ring, chlorine proximity to the developing positive charge on the eliminated C–F

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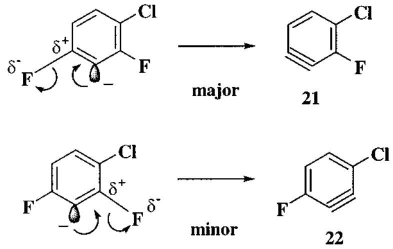
[14] Tamborski, C.; Soloski, E. J. *J. Org. Chem.* **1966**, *31*, 746.

[15] Büker, H. H.; Nibbering, N. M. M.; Espinosa, D.; Mongin, F.; Schlosser, M. *Tetrahedron Lett.* **1997**, *38*, 8519.

[16] Schlosser, M. *Angew. Chem., Int. Ed.* **1998**, *110*, 1496.

[17] Modena, G.; Scorrano, G. Directing, Activating and Deactivating Effects. In *The Chemistry of the Carbon–Halogen Bond*; Patai, S. Ed.; John Wiley: New York, 1973; Part 1, Chapter 6, pp 355–361, 366–374.

Scheme 3



bond determines relative transition state stability. Hence, chlorine substitution destabilizes positive charge formation at C-2 more than at C-4 and leads to selective formation of **21** (Scheme 3).

Other Benzonorbornadienes. The knowledge gained as a result of the syntheses of benzonorbornadienes **10** and **11** allowed the straightforward synthesis of several heterocyclic benzonorbornadiene derivatives. On examination of its ^{1}H and ^{13}C NMR spectra, benzonorbornadiene **12** appeared cleaner when prepared from dibromodifluorobenzene **6** (65−85%) than from bromotrifluorobenzene **5** (60%). Benzonorbornadiene **13** (52−65%) was prepared from bromochlorobenzene **7**. NMR analysis showed one primary product and a small amount of an isomeric benzonorbornadiene side-product. Heavily fluorinated benzonorbornadienes **14**[18] (28−70%) and **15**[19] (36−64%) were also prepared. The benzonorbornadienes prepared in this study are stable oils or crystalline solids and are readily isolated by column chromatography. While undistillable using short-path distillation (i.e., they tend to decompose), high mass balances were obtained by Kugelrohr distillation, which left only small amounts of resinous products in distillation pot. Full physical property and combustion data and ^{1}H and ^{13}C NMR and IR spectra including analysis and assignment are available in Supporting Information.

Summary

A series of benzonorbornadienes were prepared by trapping in situ generated benzynes with furan and *N*-methylpyrrole. Benzynes were generated by metal−halogen exchange of substituted halobenzenes followed by elimination of a lithium salt. High product yields and selectivities were obtained when (a) bromoaromatics were used as starting materials, (b) diethyl ether was used as the reaction solvent, (c) low temperatures (←70 °C) were used in the metal−halogen exchange step, and (d) excess diene (10 equiv) was used to trap the intermediate benzyne. In some cases, reactions were performed on up to 50 g of starting halobenzene and could easily be done on a larger scale. We expect this procedure to be general and should be applicable to other halogen-containing benzene derivatives.

Cycloaddition of the benzyne produced by substitution of 1-chloro-2,4-difluorobenzene for its 1-bromo analogue in the metal−halogen exchange reaction unexpectedly gave benzonorbornadiene **11** instead of **10**. The benzyne, which resulted by a deprotonation pathway rather than by metal−halogen exchange, formed in a highly regioselective elimination step. We expect this surprisingly efficient pathway to occur for other appropriately substituted aromatic and heteroaromatic compounds.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 250 MHz NMR at 250.13 and 62.9 MHz, respectively. All chemical shifts (δ) are positive and referenced downfield from tetramethylsilane (TMS); coupling constants (J) are recorded in Hz unless otherwise noted.

All reagents and solvents were ordinary commercial grade and obtained from either Aldrich, Acros, Fluka, or PCR, Inc. Furan, *N*-methylpyrrole, 1-bromo-2,4-difluorobenzene **3** (P_2O_5), 1-chloro-2,4-difluorobenzene **4** (P_2O_5), 1-bromo-4-chloro-2-fluorobenzene **7** (P_2O_5), and 1-chloro-2,3,4,5,6-pentafluorobenzene **8** ($CaSO_4$) were purified by distillation at reduced pressure from the drying agent shown. 1-Bromo-2,4,5-trifluorobenzene **5**, 1,2-dibromo-4,5-difluorobenzene **6**, and 9-oxabenzonorbornadiene **9** were used as received. THF and diethyl ether were freshly distilled from benzophenone ketyl before use. *n*-BuLi (2.5 M solution in hexanes) was purchased from Aldrich and used without analysis. All handling of air-sensitive materials was done under an argon or nitrogen atmosphere using standard syringe and cannula techniques.

Thin-layer chromatography (TLC) was performed on glass-backed silica gel plates (0.25 mm thickness, E. Merck). Spots were visualized under UV light (254 nm) and then stained with an ethanolic solution (5%) of phosphomolybdic acid and charred with a heat gun. Flash column chromatography was performed using Merck grade 9385, 230−400 mesh, 60 Å silica gel (available from Aldrich, 22,719−6). Compounds were diluted to 25% solution with hexanes and applied to the top of the adsorbent bed. Elution began with 100% hexanes followed by hexanes/EtOAc (75%:25%) and finally with 100% EtOAc. Melting points and boiling points are uncorrected. Kugelrohr distillation temperatures are oven temperatures. Combustion elemental analyses were performed by Galbraith Laboratories (Knoxville, TN).

Typical Procedure: 9-Oxa-6-fluorobenzonorbornadiene (10).[13] To a 1000 mL, 4-neck, round-bottom flask, which was equipped with an overhead stirrer, condenser, thermometer, rubber septum, gas adapter, and stirring bar and flame-dried under Ar, were charged 400 mL of diethyl ether and 17.6 mL of bromobenzene **3** (0.156 mol). To the solution, which was cooled to −78 °C in an acetone/dry ice bath, was added via gastight syringe 72 mL of a 2.5 M solution of *n*-BuLi in hexanes (0.180 mol) over a 1 h period at such a rate to keep the reaction mixture below −70 °C. The reaction mixture was then stirred for 35 min at −78 °C before 120 mL of furan (1.650 mol) was added over 20 min at such a rate to keep the reaction temperature below −73 °C. It was then allowed to warm slowly to room-temperature overnight. The cloudy-orange reaction mixture was poured into 600 mL of stirring deionized water, vacuum filtered, separated, and the aqueous phase was washed (2 × 75 mL) with ether. The combined organic phases were dried over $MgSO_4$, vacuum filtered, and concentrated by rotoevaporation and high vacuum to give 23.76 gm of clear-gold **10** (94% yield) which was purified by Kugelrohr distillation to give a clear-yellow, liquid: bp 100 °C/0.25 Torr; R_f 0.36 (95:5 hexane/EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.648 (pt, J = 1.6, 1.6 Hz, 2H), 6.597 (ddd, J = 9.8, 7.5, 2.0 Hz, 1H), 6.968 (d, J = 1.5 Hz), 6.985 (d, J = 1.7 Hz), 6.94−7.01 (m), 7.100 (dd, J = 7.9, 4.7 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 81.77, 82.09, 109.37 (d, J = 24.9 Hz), 110.10 (d, J = 22.5 Hz), 120.47 (d, J = 8.8 Hz), 142.34, 143.33, 144.14 (d, J = 2.4), 151.85 (d, J = 8.8 Hz), 160.27 (d, J = 244.6 Hz); IR (neat, NaCl) ν 3016, 1608 (s), 1459 (s), 1350, 1281 (s), 1217 (s), 1185, 1083, 993 (s), 966, 928, 852 (s), 834 (s), 816 (s), 740 (s), 698 (s), 645 (s), 603 (s), 576 (s) cm^{-1}. Anal. Calcd for $C_{10}H_7FO$: C 74.06; H 4.36; F 11.72. Found: C 74.25; H 4.75; F 11.36; Br 123 ppm; Li <0.03%.

9-Oxa-5-fluoro-6-chlorobenzonorbornadiene (11). The reaction was carried out according to the typical procedure using 50 mL of ether and 2.2 mL of chlorobenzene **4** (0.022

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[18] Gribble, G. W.; LeHoullier, C. S.; Sibi, M. P.; Allen, R. W. *J. Org. Chem.* **1985**, *50*, 1611.

[19] Gribble, G. W.; Allen, R. W.; LeHoullier, C. S.; Eaton, J. T.; Easton, N. R.; Slayton, R. I.; Sibi, M. P. *J. Org. Chem.* **1981**, *46*, 1025.

mol), 9 mL of a 2.5 M solution of *n*-BuLi in hexanes (0.022 mol), and 14.5 mL of furan (0.200 mol). This gave 2.915 g of **11** as a clear-orange, oily liquid (90% yield), which on Kugelrohr distillation yielded a waxy, white solid.

9-Oxa-6,7-difluorobenzonorbornadiene (12).[13] The reaction was carried out according to the typical procedure using 15.318 g of dibromobenzene **6** (0.056 mol), 250 mL of ether, 29.0 mL of 2.5 M *n*-BuLi (0.072 mol) in hexanes, and 41.0 mL of furan (0.564 mol). Workup gave 8.63 g of crude product (85% yield) which on purification by Kugelrohr distillation gave 5.282 g of **12** (52% yield) as a clear, light-yellow liquid. Compound **12** was also prepared according to the typical procedure using 4.128 g of bromobenzene **5** (0.020 mol), 50 mL of ether, 9.0 mL of 2.5 M *n*-BuLi in hexanes (0.022 mol), and 14.5 mL of furan (0.199 mol). Workup gave 2.12 g of crude compound **12** (60% yield).

9-Oxa-6-chlorobenzonorbornadiene (13). The reaction was carried out according to the typical procedure using 4.327 g of freshly distilled chlorobenzene **7** (20.66 mmol) in 30 mL of dry diethyl ether, 8.4 mL of 2.5M *n*-BuLi in hexanes (21.00 mmol), and 1.5 g of freshly distilled furan (22.00 mmol). Workup gave 2.25 g of crude **13** (61%) as a cloudy orange liquid. Purification by Kugelrohr distillation gave 1.93 g (52%) of **13** as a clear liquid.

9-Oxa-5,6,7,8-tetrafluorobenzonorbornadiene (14).[18] The reaction was carried out according to the typical procedure using 2.04 g of freshly distilled **8** (10.07 mmol) in 30 mL of dry diethyl ether, 3.9 mL of 2.6 M *n*-BuLi in hexanes (10.14 mmol), and 0.84 g of freshly distilled furan (12.37 mmol). Workup gave 1.635 gms of crude **14** as an orange crystalline solid which was sublimed (80 °C/1 Torr) to give 0.613 g (28%) as near white crystals.

9-Methyl-9-aza-5,6,7,8-tetrafluorobenzonorbornadiene (15).[19] The reaction was carried out according to typical procedure A using 5.396 g of freshly distilled **8** (26.65 mmol) in 30 mL of dry diethyl ether, 10.8 mL of 2.6 M *n*-BuLi in hexanes (27 mmol), and 8.70 g of freshly distilled *N*-methylpyrrole (107.22 mmol). The combined ether layers were concentrated by rotoevaporation to give 5.435 g of crude product. ^{1}H NMR showed this to be contaminated with unreacted *N*-methylpyrrole (42%). The crude product was purified by staged Kugelrohr distillation (rt/5 Torr) to remove the pyrrole. The receiving flask was changed, and the product was sublimed (125 °C/5 Torr) in the Kugelrohr apparatus. This gave 2.56 g of yellow-white crystals which on sublimation a second time (75 °C/10 Torr) gave 2.073 g of **15** as white crystals (32% yield).

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Supporting Information Available: Physical property data, combustion analysis data, and ^{1}H and ^{13}C NMR assignments for most compounds are available. Copies of spectra for **3**, **4**, **5**, **7**, **9**, **10**, **11**, **12**, **13**, **14**, **15** (^{1}H NMR); **3**, **4**, **7**, **9**, **10**, **11**, **12**, **13**, **14**, **15** (^{13}C NMR); and **9**, **10**, **11**, **13**, **15** (IR). This material is available free of charge via the Internet at http://pubs.acs.org.

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