Ortho-Directed Lithiation of 3,4-(Alkylenedioxy)halobenzenes with LDA and LiTMP. The First Ortho Lithiation of an Iodobenzene

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Introduction

In comparison to other groups, the 1,2-methylenedioxy and -ethylenedioxy groups are poor ortho-directed metalation groups. Early attempts to ortho-lithiate 1,3-benzodioxole failed,[1] while later attempts with 1,3-benzodioxole and 2,2-dimethyl-1,3-benzodioxole demonstrated that the cleavage of the methylenedioxy ring competes with ortho lithiation.[2] Similarly, the attempted lithiation of 1,4-benzodioxane gave only the ring-opened product, catechol monovinyl ether.[3] More recent work successfully lithiated 2,2-dimethyl-1,3-benzodioxole using butyllithium in ether, although the reaction was slow, requiring 32 h at room temperature.[4a] 2,2-Difluoro-1,3-benzodioxole was also lithiated at −10 °C using butyllithium/TMEDA in ether.[4b] While the ortho metalation of unsubstituted (alkylenedioxy)benzenes is problematic, the ortho lithiation of some substituted examples has been reported,[5] and the related benzyne has been generated from 5-bromo-1,3-benzodioxole and sodium amide.[6] The ortho lithiation of 3,4-(alkylenedioxy)halobenzenes, however, has not been investigated.

There are many examples in the literature of the ortho lithiation of fluoro- and chlorobenzenes, but there are fewer examples of the ortho lithiation of bromo-aromatics with LiTMP and LDA.[7] Even more rare are iodine-directed ortho lithiations, which have been described for iodothiophenes,[8] iodoisothiazoles,[9] and iodopyridines.[10] We are unaware, however, of any examples of the ortho lithiation of iodobenzenes.

Results and Discussion

Since 1,2-(alkylenedioxy)benzenes readily halogenate at the 4-position, we investigated whether the additional halogen atom would increase the thermodynamic acidity[11] of the ortho hydrogen and shift the reaction with lithium bases from ring-opening to ortho lithiation. Schlosser's ortho lithiation of 3-bromobenzotrifluoride[7a] required 2 h at −100 °C and gave better yields with 2 equiv of LiTMP. In contrast, each of the 3,4-(alkylenedioxy)chlorobenzenes and -bromobenzenes used in the present study (Table 1) underwent rapid deprotonation with 1.1 equiv of either LDA or LiTMP in THF at −78 °C. Subsequent quenching of the aryllithiums with DMF gave the expected benzaldehyde products, **1**−**6**, in yields of 68−81% for the chloro- and bromo-aromatics. Yields did not significantly increase using LiTMP rather than LDA. To investigate whether these aryllithium reagents would efficiently trap other electrophiles, 5-bromobenzodioxole was metalated with LDA under the general conditions and then treated with methyl iodide, TMS-Cl, benzaldehyde, acetaldehyde, and acetone to give the expected products, **7**−**11**. The aryllithium was efficiently trapped with even the enolizable electrophiles, acetaldehyde, and acetone.

The facile lithiation of the bromo- and chloro(alkylenedioxy)benzenes led us to attempt the lithiation of an iodo case. Reaction of 5-iodobenzodioxole with LDA for 15 min and quenching with DMF gave a 12.5% yield of **12**, while LiTMP (15 min) gave a 50% yield. Longer lithiation times with LiTMP (40 min) gave only a slight increase in yield (55%). Thus, even in the iodo case, lithiation is rapid and the *o*-iodo aryllithium species appears to be stable at −78 °C for at least 40 min. 5-Iodobenzodioxole was also metalated in a similar manner and treated with TMS-Cl and with iodine to give the expected products, **13** and **14**. Since we believe this to be the first example of an iodine-directed ortho lithiation of a benzene ring, the structure of **12** was confirmed by single-crystal X-ray analysis. As further structural proof, catalytic hydrogenation of **12** gave benzodioxole-4-carboxaldehyde that was identical with the commercially available material by ^{1}H NMR and MS spectra.

In one reaction of 5-iodobenzodioxole with LDA and DMF, the temperature was allowed to go above −70 °C.

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§ Analytical Research and Development.

|| Discovery Analytical/Core Chemistry.

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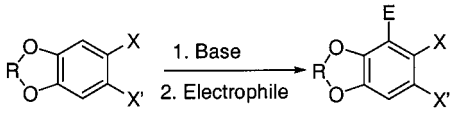
Table 1. Ortho-Directed Lithiations of 3,4-(Alkylenedioxy)halobenzenes



R	base	X	X′	electrophile	product	E	% yield
$-CH_2-$	LDA	Cl	H	DMF	**1**	−CHO	76
$-CH_2-$	LDA	Br	H	DMF	**2**	−CHO	72
$-CH_2-$	LiTMP	Br	H	DMF	**2**	−CHO	75
$-CH_2-$	LDA	Br	Br	DMF	**3**	−CHO	69
$-(CH_2)_2-$	LDA	Br	H	DMF	**4**	−CHO	68
$-(CH_2)_2-$	LiTMP	Br	H	DMF	**4**	−CHO	77
$-(CH_2)_3-$	LDA	Br	H	DMF	**5**	−CHO	77
$-C(CH_3)_2-$	LDA	Br	H	DMF	**6**	−CHO	81
$-CH_2-$	LDA	Br	H	MeI	**7**	$-CH_3$	94
$-CH_2-$	LDA	Br	H	TMS−Cl	**8**	−TMS	83
$-CH_2-$	LDA	Br	H	PhCHO	**9**	−CHOHPh	89
$-CH_2-$	LDA	Br	H	CH_3CHO	**10**	$-CH(CH_3)OH$	78
$-CH_2-$	LDA	Br	H	CH_3COCH_3	**11**	$-C(CH_3)_2OH$	78
$-CH_2-$	LDA	I	H	DMF	**12**	−CHO	12.5
$-CH_2-$	LiTMP	I	H	DMF	**12**	−CHO	50[a]
$-CH_2-$	LiTMP	I	H	DMF	**12**	−CHO	56[b]
$-CH_2-$	LDA	I	H	TMS−Cl	**13**	−TMS	57
$-CH_2-$	LiTMP	I	H	I_2	**14**	−I	85

[a] Metalated for 15 min. [b] Metalated for 40 min.

Scheme 1

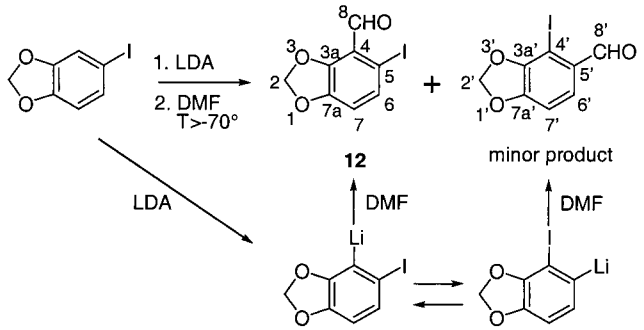
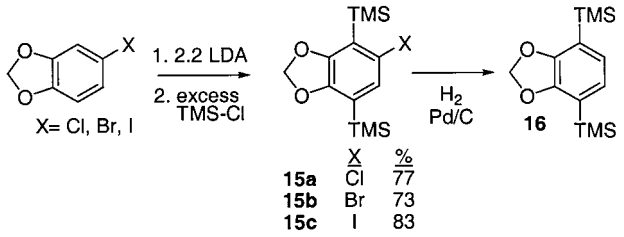


Table 2. Chemical Shifts of 12 and the Minor Product (ppm) in $CDCl_3$ (500 MHz)

major component (**12**)			minor component		
assignt	carbon	proton	assignt	carbon	proton
C2	103.10	6.13	C2′	103.70	6.22
C3a	149.20		C3a′	149.60	
C4	118.30		C4′	118.40	
C5	86.10		C5′	131.60	
C6	133.40	7.38	C6′	129.20	7.51
C7	114.30	6.70	C7′	111.40	7.06
C7a	149.90		C7a′	155.10	
C8	193.80	10.03	C8′	189.10	10.20

Before recrystallization of product **12,** a minor component (about 9%) was seen. While we were not able to separate the minor component, the structure was characterized by 1D and 2D NMR spectroscopic techniques. The observed NMR data, including H-1, C-13, HMQC, and HMBC spectra indicated that the structural difference between the minor component and the major component was in the position of the substituents. On the basis of an interpretation of the NMR data, the minor component is the isomeric 4-iodobenzodioxole-5-carboxaldehyde (Scheme 1). This structure is supported by the observation of a C−H three-bond long-range correlation: from the C-6′ proton (7.51 ppm) to the C8′ carbon (189.1 ppm) and from the C-8′ proton (10.20 ppm) to the C-4′ carbon (118.4 ppm). The total spectral assignments (Table 2) on both components have also been made and are consistent with the assigned structures. In his ortho lithiation of

Scheme 2



	X	%
15a	Cl	77
15b	Br	73
15c	I	83

3-iodopyridines, Quéguiner observed a similar rearrangement, isolating only 4-iodopyridine products.[10] This shift may occur through an elimination of lithium iodide, and subsequent readdition[12] in opposite regiochemistry, to the intermediate benzyne. A more likely mechanism proposed by Bunnett for this "halogen dance" involves the involvement of trace amounts of a diiodo contaminant to give scrambling of the regiochemistry.[13]

The in situ trapping of the 5-iodo-4-lithiobenzodioxole with TMS-Cl gave the expected product, **13** (57%), along with a small amount of a bis(trimethylsilyl) product resulting from the excess LDA and TMS-Cl performing a further deprotonation and trapping of **13**. To further investigate the position of this second subsequent lithiation, the chloro-, bromo-, and iodobenzodioxoles were metalated with 2.2 equiv of LDA and treated with excess TMS-Cl to give high yields of the bis(trimethylsilyl) products. The structure of **15c** was confirmed both by single-crystal X-ray analysis and by removal of the iodo substituent by catalytic reduction to give a product that showed a singlet in the ^1H NMR for two equivalent aromatic protons. Thus, the second lithiation occurs adjacent to the methylenedioxy group to give **15c**, which upon catalytic hydrogenation gives the symmetrical product **16** (Scheme 2).

The chloro-, bromo-, iodo-, and dibromo substrates were all metalated efficiently, and no evidence of ring opening

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was seen. Unlike previous studies, no significant differences in yields or purity of products from the chloro- and bromo-aromatics were seen in the present study using LiTMP rather than LDA as the base. Only in the iodo case were significantly better yields obtained with LiTMP. These *o*-halo aryllithiums are easily generated at −78 °C using only a slight excess of LDA or LiTMP, and they can be reacted with a variety of electrophiles to form 2,3-(alkylenedioxy)phenyl compounds in quite good yields. Moreover, the halogen substituents on these products are useful for further synthetic manipulation, or they can be removed by mild catalytic hydrogenation. This provides a facile route to the products that would result from a formal ortho lithiation of the unsubstituted (alkylenedioxy)benzenes.

Experimental Section

General Considerations. The NMR spectra were determined using $CDCl_3$ as a solvent and TMS as an internal standard. All yields are of analytically pure material, and all compounds had NMR, IR, and MS spectra and elemental analyses (±0.4%) consistent with the assigned structures. Several of the products were highly crystalline, and the structures of **2**,[14] **12**, and **14c** were confirmed by single-crystal X-ray analyses (enclosed as Supporting Information). The THF was freshly distilled from Na−benzophenone ketyl under N_2. The lithium bases were prepared immediately before use from the appropriate amine (distilled from calcium hydride) and *n*-butyllithium (titrated[15] with the tosyl hydrazone of benzophenone). Commercially available 5-chloro-, 5-bromo-, and 5-iodobenzodioxoles were used without purification. 6-Bromobenzodioxane, 5-bromo-2,2-dimethylbenzodioxole, and 7-bromo-3,4-dihydro-2*H*-1,5-benzodioxepine were prepared by literature methods.[16,17]

General Procedure for 2-Substituted 3,4-(Alkylenedioxy)halobenzene. The 3,4-(alkylenedioxy)halobenzene (10 mmol) was added dropwise under dry nitrogen to a −78 °C solution of the lithium dialkylamide (11 mmol) in THF (30 mL) at a rate such that the temperature remained less than −70 °C. The resulting solution was stirred for 15 min at −78 °C, and then the electrophile (12.5 mmol) was added. The solution was stirred for 15 min, and the −78 °C cooling bath was removed. The reaction was warmed to room temperature over a 30 min period, quenched with water, and diluted with ethyl acetate (30 mL). The organic layer was separated, washed twice with 1 N HCl, twice with saturated sodium carbonate, and then dried with brine. The organic layer was concentrated in vacuo to give the crude products, which were purified by recrystallization or column chromatography.

5-Chloro-1,3-benzodioxole-4-carboxaldehyde (1): pale yellow needles from cyclohexane; mp 129.5−131.5 °C. ^{1}H NMR: δ 6.16 (s, 2H), 6.90 (s, 2H), 10.40 (s, 1H). IR: 1678, 1459, 1246 cm^{-1}. Anal. Calcd for $C_8H_5ClO_3$: C, 52.06; H, 2.73; N, 0.00. Found: C, 51.80; H, 2.65; N, <0.02.

5-Bromo-1,3-benzodioxole-4-carboxaldehyde (2): pale yellow needles from isopropyl acetate; mp 160−162 °C. ^{1}H NMR: δ 6.16 (s, 2H), 6.85 (d, 1H, J = 8.2 Hz), 7.10 (d, 1H, J = 8.2 Hz), 10.28 (s, 1H). IR: 1681, 1454, 1244 cm^{-1}. Anal. Calcd for $C_8H_5BrO_3$: C, 41.95; H, 2.20; N, 0.00. Found: C, 41.99; H, 2.16; N, <0.02.

5,6-Dibromo-1,3-benzodioxole-4-carboxaldehyde (3): pale yellow powder from isopropyl acetate; mp 200−202 °C. ^{1}H NMR: δ 6.18 (s, 2H), 7.25 (s, 1H), 10.28 (s, 1H). IR: 1681, 1462, 1238, 1202 cm^{-1}. Anal. Calcd for $C_8H_4Br_2O_3$: C, 31.20; H, 1.31; N, 0.00. Found: C, 31.36; H, 1.33; N, <0.02.

6-Bromo-2,3-dihydro-1,4-benzodioxane-5-carboxaldehyde (4): pale orange needles from cyclohexane/ethyl acetate; mp 105−107 °C. ^{1}H NMR: δ 4.28−4.31 (m, 2H), 4.35−4.38 (m, 2H), 6.92 (d, 1H, J = 8.7 Hz), 7.11 (d, 1H, J = 8.7 Hz), 10.34 (s, 1H). IR: 1689, 1291, 1255, 1221 cm^{-1}. Anal. Calcd for $C_9H_7BrO_3$: C, 44.47; H, 2.90; N, 0.00. Found: C, 44.57; H, 2.87; N, <0.02.

7-Bromo-3,4-dihydro-2*H*-1,5-benzodioxepine-6-carboxaldehyde (5): pale yellow oil that solidified on standing (chromatographed on silica gel using 10−30% ethyl acetate/hexanes); mp 63−66 °C. ^{1}H NMR: δ 2.28−2.31 (m, 2H), 4.26 (t, 2H, J = 5.7 Hz), 4.36 (t, 2H, J = 5.7 Hz), 7.02 (d, 1H, J = 8.7 Hz), 7.20 (d, 1H, J = 8.7 Hz), 10.34 (s, 1H). IR: 1700, 1472, 1455, 1265 cm^{-1}. Anal. Calcd for $C_{10}H_9BrO_3 \cdot 0.1C_6H_{12}$: C, 47.95; H, 3.87; N, 0.00. Found: C, 47.94; H, 3.79; N, <0.02.

5-Bromo-2,2-dimethyl-1,3-benzodioxole-4-carboxaldehyde (6): pale yellow needles from cyclohexane; mp 91−92.5 °C. ^{1}H NMR: δ 1.74 (s, 6H), 6.75 (d, 1H, J = 8.2 Hz), 7.04 (d, 1H, J = 8.2 Hz), 10.27 (s, 1H). IR: 1694, 1686, 1458, 1241 cm^{-1}. Anal. Calcd for $C_{10}H_9BrO_3$: C, 46.72; H, 3.53; N, 0.00. Found: C, 46.83; H, 3.53; N, <0.02.

5-Bromo-4-methyl-1,3-benzodioxole (7): white solid (Kügelrohr distilled); mp 131−133 °C. ^{1}H NMR: δ 2.24 (s, 3H), 5.95 (s, 2H), 6.55 (d 1H, J = 8.3 Hz), 7.00 (d, 1H, J = 8.3 Hz). IR: 1458, 1254, 1057, 800 cm^{-1}. Anal. Calcd for $C_8H_7BrO_2$: C, 44.69; H, 3.28; N, 0.00. Found: C, 44.79; H, 3.19; N, <0.02.

5-Bromo-4-(trimethylsilyl)-1,3-benzodioxole (8): pale yellow viscous oil (chromatographed on silica gel using 10−20% ethyl acetate/hexanes). ^{1}H NMR: δ 0.42 (s, 9H), 5.90 (s, 2H), 6.63 (d, 1H, J = 8.2 Hz), 6.99 (d, 1H, J = 8.2 Hz). IR: 1411, 1229, 1045, 853 cm^{-1}. Anal. Calcd for $C_{10}H_{13}BrO_2Si$: C, 43.96; H, 4.80; N, 0.00. Found: C, 43.70; H, 4.73; N, <0.02.

1-(5-Bromo-1,3-benzodioxol-4-yl)-1-phenylmethanol (9): pale yellow viscous oil (chromatographed on silica gel using 20% ethyl acetate/hexanes). ^{1}H NMR: δ 3.11 (d, 1H, J = 9.6 Hz), 5.95 (d, 1H, J = 1.3 Hz), 6.00 (d, 1H, J = 1.3 Hz), 6.18 (d, 1H, J = 9.6 Hz), 6.66 (d, 1H, J = 8.3 Hz), 7.06 (d, 1H, J = 8.3 Hz), 7.25−7.43 (m, 5H). IR: 1454, 1241, 1052, 738 cm^{-1}. Anal. Calcd for $C_{14}H_{11}BrO_3$: C, 54.75; H, 3.61; N, 0.00. Found: C, 55.12; H, 3.67; N, <0.02.

1-(5-Bromo-1,3-benzodioxol-4-yl)ethanol (10): pale yellow viscous oil (chromatographed on silica gel using 20% ethyl acetate/hexanes). ^{1}H NMR: δ 1.54 (d, 3H, J = 6.7 Hz), 5.17 (q, 1H, J = 6.7 Hz), 6.00 (s, 2H), 6.60 (d, 1H, J = 8.3 Hz), 6.99 (d, 1H, J = 8.3 Hz). IR: 1453, 1241, 1058, 1035 cm^{-1}. Anal. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70; N, 0.00. Found: C, 43.89; H, 3.53; N, <0.02.

1-(5-Bromo-1,3-benzodioxol-4-yl)-1-methylethanol (11): white solid (chromatographed on silica gel using 20% ethyl acetate/hexanes); mp 41 °C. ^{1}H NMR: δ 1.75 (s, 6H), 3.62 (br s, 1H), 5.93 (s, 2H), 6.58 (d, 1H, J = 8.3 Hz), 7.08 (d, 1H, J = 8.3 Hz). IR: 1427, 1327, 1234, 1041 cm^{-1}. Anal. Calcd for $C_{10}H_{11}BrO_3$: C, 46.36; H, 4.28; N, 0.00. Found: C, 46.42; H, 4.07; N, <0.02.

5-Iodo-1,3-benzodioxole-4-carboxaldehyde (12): pale yellow needles from cyclohexane; mp 162−165 °C. ^{1}H NMR: δ 6.13 (s, 2H), 6.70 (d, 1H, J = 8.2 Hz), 7.38 (d, 1H, J = 8.2 Hz), 10.03 (s, 1H). IR: 1674, 1582, 1451, 1242 cm^{-1}. Anal. Calcd for $C_8H_5IO_3 \cdot 0.12\ C_6H_{12}$: C, 36.60; H, 2.27; N, 0.00. Found: C, 36.82; H, 2.00; N, <0.02.

5-Iodo-4-(trimethylsilyl)-1,3-benzodioxole (13): clear oil (chromatographed on silica gel using 0−5% ethyl acetate/hexanes). ^{1}H NMR: δ 0.44 (s, 9H), 5.89 (s, 2H), 6.49 (d, 1H, J = 8.1 Hz), 7.33 (d, 1H, J = 8.1 Hz). IR: 1408, 1394, 1228, 846 cm^{-1}. Anal. Calcd for $C_{10}H_{13}IO_2Si$: C, 37.51; H, 4.09; N, 0.00. Found: C, 37.60; H, 4.09; N, <0.02.

4,5-Diiodo-1,3-benzodioxole (14): pale yellow oil that solidified on cooling (purified by Kügelrohr distillation). ^{1}H NMR: δ 6.05 (s, 2H), 6.60 (d, 1H, J = 8.0 Hz), 7.38 (d, 1H, J = 8.0 Hz). IR: 1445, 1234, 1033, 934 cm^{-1}. Anal. Calcd for $C_7H_4I_2O_2$: C, 22.49; H, 1.08; N, 0.00. Found: C, 22.62; H, 1.26; N, <0.02.

General Procedure for 4,7-Bis(trimethylsilyl)-5-halo-1,3-benzodioxoles. The 3,4-(alkylenedioxy)halobenzene (4 mmol) was added dropwise under dry nitrogen to a −78 °C solution of

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the lithium dialkylamide (8.8 mmol) and TMS-Cl (2 mL) in THF (30 mL) at a rate such that the temperature remained less than −70 °C. The solution was stirred for 15 min, and the −78 °C cooling bath was removed. The reaction mixture was warmed to room temperature over a 30 min period, quenched with water, and diluted with ethyl acetate (30 mL). The organic layer was separated, washed twice with water, and then dried with brine. The organic layer was concentrated in vacuo to give the crude products, which were purified by column chromatography.

4,7-Bis(trimethylsilyl)-5-chloro-1,3-benzodioxole (15a): clear oil that solidified on standing (chromatographed on silica gel using hexanes); mp 44−47 °C. ^{1}H NMR: δ 0.27 (s, 9H), 0.38 (s, 9H), 5.89, (s, 2H), 6.79 (s, 1H). IR: 1374, 1249, 1056, 841 cm^{-1}. Anal. Calcd for $C_{13}H_{21}ClO_2Si_2$: C, 51.89; H, 7.03; N, 0.00. Found: C, 52.08; H, 7.08; N, <0.02.

4,7-Bis(trimethylsilyl)-5-bromo-1,3-benzodioxole (15b): clear oil that solidified on standing (chromatographed on silica gel using hexanes); mp 36−39 °C. ^{1}H NMR: δ 0.26 (s, 9H), 0.39 (s, 9H), 5.88, (s, 2H), 6.98 (s, 1H). IR: 1368, 1250, 1052, 840 cm^{-1}. Anal. Calcd for $C_{13}H_{21}BrO_2Si_2$: C, 45.21; H, 6.13; N, 0.00. Found: C, 45.48; H, 6.12; N, <0.02.

4,7-Bis(trimethylsilyl)-5-iodo-1,3-benzodioxole (15c): clear oil that solidified on standing (chromatographed on silica gel using hexanes); mp 66−68 °C. ^{1}H NMR: δ 0.20 (s, 9H), 0.38 (s, 9H), 5.81 (s, 2H), 7.26 (s, 1H). IR: 1364, 1249, 1048, 839 cm^{-1}. Anal. Calcd for $C_{13}H_{21}IO_2Si_2$: C, 39.79; H, 5.39; N, 0.00. Found: C, 39.65; H, 5.43; N, <0.02.

Hydrogenation of 5-Iodo-1,3-benzodioxole-4-carboxaldehyde (12). An ethanol solution of **12** (50 mg) was stirred with 10% Pd/C (50 mg) and potassium carbonate (50 mg) under hydrogen (balloon pressure) for 3 h. The mixture was filtered and the filtrate concentrated in vacuo to give 1,3-benzodioxole-4-carboxaldehyde (25 mg, 92%) by ^{1}H NMR and MS spectra.

4,6-Bis(trimethylsilyl)-1,3-benzodioxole (16). An ethanol solution of **15c** (100 mg) was hydrogenated (60 psi) over 10% Pd/C (100 mg) for 2 h. The mixture was filtered and concentrated in vacuo to give 4,6-bis(trimethylsilyl)-1,3-benzodioxole (**16**) as a clear oil that solidified on standing (60 mg, 88%). ^{1}H NMR: δ 0.32 (s, 18H), 5.94 (s, 2H), 6.90 (s, 2H). IR: 1370, 1249, 1197, 839 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_2Si_2$: C, 58.59; H, 8.32; N, 0.00. Found: C, 58.30; H, 8.15; N, <0.02.

Supporting Information Available: Tables giving details of the single-crystal X-ray analyses of **2**, **12**, and **14c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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