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Hydride-promoted Demethylation of Methyl Phenyl Ethers

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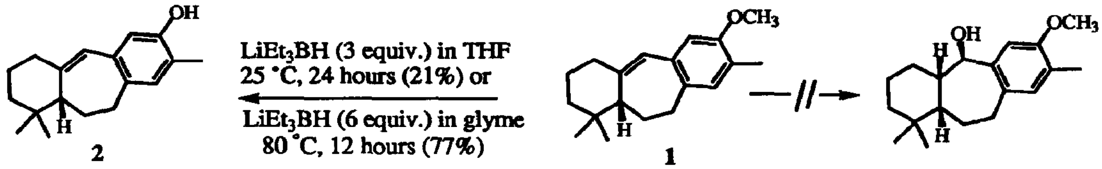
Abstract: Solutions of L-Selectride or SuperHydride in refluxing THF efficiently deprotect methyl phenyl ethers. L-Selectride is the more effective reagent, while electron-poor arenes work best. Unlike other hydride sources, these reagents permit ether cleavage without the reduction of aryl halides.

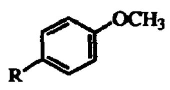
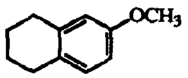
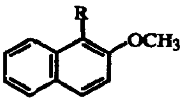
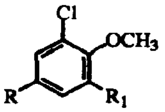
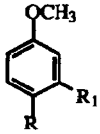
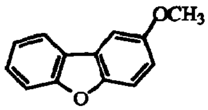
In 1977 Brown and Kim found that lithium triethylborohydride [SuperHydride] permits the hydroboration of substituted styrenes under mild conditions.[1] However, we found that treatment of alkene **1** with SuperHydride in tetrahydrofuran at room temperature for twenty-four hours gave deoxyfaveline (**2**) in 21% yield, with the balance of the material being unreacted **1**.[2] Using glyme as the solvent at 80 °C, or increasing the number of equivalents of SuperHydride, improved the production of **2** to 77% (100% conversion) and reduced the reaction time to twelve hours.



Methyl ethers are popular protecting groups for phenols because they are easy to prepare and easy to remove using a variety of acidic conditions.[3a] The use of nucleophilic conditions for demethylation, however, is limited to hot (~200 °C) ethanolic potassium hydroxide,[3b] hot solutions of NaSR,[3c] or, for aryl methyl ethers with neighboring ether functions, lithium aluminium hydride ($LiAlH_4$) in either a hydrocarbon solvent[3d] or THF.[3e] Here, we report the scope and limitations using either L-Selectride or SuperHydride in the demethylation of aryl methyl ethers.[4]

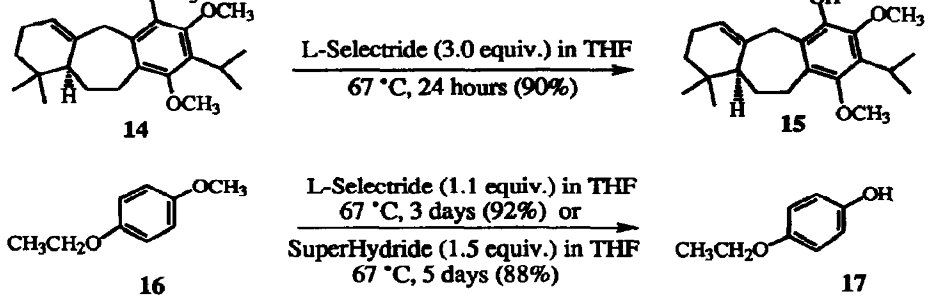
The deprotections shown in Table 1 were all accomplished more rapidly using the more powerful reagent L-Selectride, and gave only the phenol along with unreacted ether.[5] In general, reaction workup required only the addition of water,[6] although the use of basic hydrogen peroxide was needed to free the phenol of **13** from a boron-containing complex. When the aryl ring has an electron-withdrawing substituent, the reaction yield generally increases and the reaction time decreases; cf. **3** versus **4**, or **6** versus **7**, or **8** versus

9 versus **10**. Although less rapid than other procedures, this method is also useful for removing the methyl ethers of hydroquinone (cf. **11**) and resorcinol (cf. **12**).[3a] Note that these deprotections proceed without cleavage of C-Br or C-Cl bonds, which are easily reduced using LiAlH$_4$ (cf. **7**, **8**, **9** and **10**).[7]

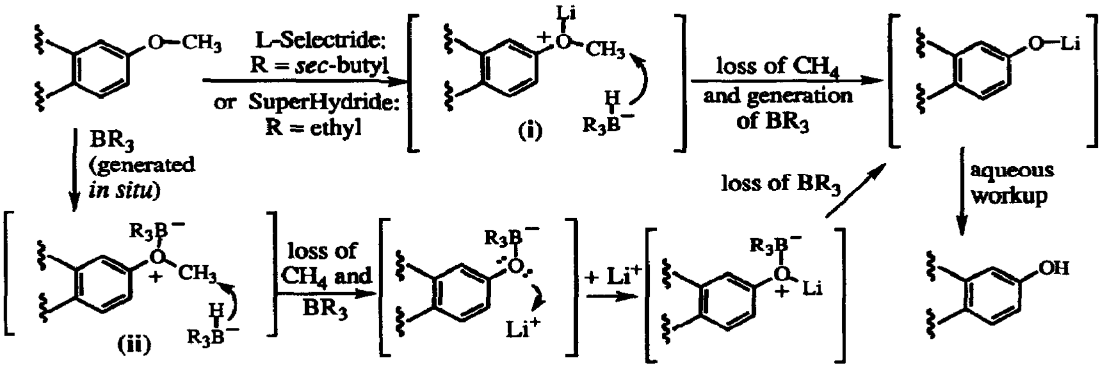
Table 1	Methyl Phenyl Ethers	L-Selectride	SuperHydride
	R = H (3)	67 °C, 3.0 equiv. 3 days (91%)	67 °C, 3.0 equiv. 6 days (33%)
	R = Br (4)	67 °C, 1.5 equiv. 12 hours (94%)	67 °C, 1.5 equiv. 3 days (76%)
	(5)	67 °C, 2.0 equiv. 2 days (97%)	67 °C, 3.0 equiv. 5 days (96%)
	R = H (6)	67 °C, 2.0 equiv. 2 days (98%)	67 °C, 2.0 equiv. 5 days (98%)
	R = Br (7)	67 °C, 2.0 equiv. 12 hours (69%)	67 °C, 2.0 equiv. 24 hours (68%)
	R = R$_1$ = H (8)	67 °C, 1.1 equiv. 24 hours (83%)	67 °C, 2.0 equiv. 3 days (73%)
	R = Cl; R$_1$ = H (9)	67 °C, 1.1 equiv. 24 hours (93%)	67 °C, 2.0 equiv. 2 days (77%)
	R = R$_1$ = Cl (10)	25 °C, 1.1 equiv. 12 hours (100%)	25 °C, 1.1 equiv. 12 hours (96%)
	R = OCH$_3$; R$_1$ = H (11)	67 °C, 3.0 equiv. 2 days (71%)	67 °C, 5.0 equiv. 7 days (90%)
	R = H; R$_1$ = OCH$_3$ (12)	67 °C, 3.0 equiv. 4 days (93%)	67 °C, 3.0 equiv. 5 days (15%)
	(13)	67 °C, 1.5 equiv. 2 days (98%)	67 °C, 3.0 equiv. 3 days (92%)

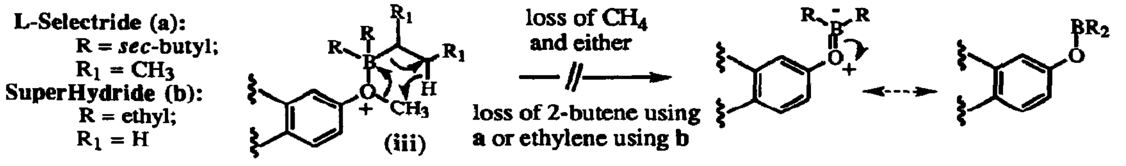
Because these hydride reagents are sterically bulky, these demethylations can be selective (Scheme 1). Treatment of trimethoxy ether **14** with excess L-Selectride results in only the deprotection of the least sterically congested ether (cf. **15**). In the case of substrate **16**, which contains both methyl and ethyl ethers, only the methyl ether undergoes deprotection.[8]

Scheme 1



Both inter- and intramolecular mechanisms can be postulated for demethylation. In the intermolecular process, a lithium cation-activated complex (cf. i) is formed first. This intermediate facilitates nucleophilic attack by hydride on the methyl group to irreversibly generate methane and a tri-alkylborane, which, being a stronger Lewis acid, can accelerate further intermolecular displacements via ii. Either process leads to the build up of lithium phenoxide, which affords the phenol upon aqueous workup. Alternatively, one can explain demethylation by means of an intramolecular transfer of a hydride from complex iii to the methyl group via a pericyclic rearrangement.[9]





Support for the intermolecular mechanism can be found in the work of Brown and co-workers with catalytic triethylborane and lithium tri-*tert*-butoxyaluminohydride.[10] Although these reagents cleave cyclic ethers via an intermolecular process,[10a] the deprotection of methyl phenyl ethers was not observed.[10b]

Moreover, demethylation was not observed when ethers **6**, **10** and **13** were treated with either tri-*sec*-butylborane or triethylborane (cf. L-Selectride or SuperHydride) and refluxed in either THF or toluene for three days. We can therefore discount the intramolecular mechanism.

In summary, we have shown that L-Selectride and SuperHydride are useful agents for the nucleophilic deprotection of methyl phenyl ethers. The presence of other reducible groups in a molecule is an obvious limitation of this method, but one that can be exploited.[11]

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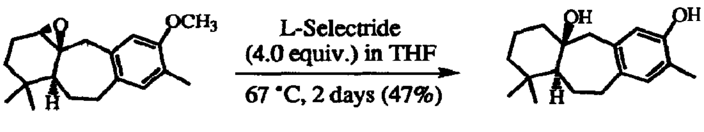
1. Brown, H. C.; Kim, S. C. J. Org. Chem. **1977**, *42*, 1482.
2. For a synthesis of **2**, see: Majetich, G.; Zhang, Y.; Hicks, R.; Feltman, T. L.; Gratale, D.; Duncan, S. G., Jr. "The Use of Conjugated Dienones in Cyclialkylations: The Total Synthesis of (±)-Barbatusol, (±)-Deoxyfaveline and (±)-Faveline." Manuscript submitted for publication.
3. a) Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis," 2nd ed. Wiley, **1991**, 145-149. b) Kharasch, M. S.; Kleiman, M. J. Am. Chem. Soc. **1943**, *65*, 11. c) Feutrill, G. I.; Mirrington, R. N. Tetrahedron Lett. **1970**, 1327. d) Carroll, J. F.; Kulkowit, S.; McKervey, M. A. J. Chem. Soc. Chem. Commun. **1980**, 507. e) Czech, A.; Czech, B. P.; Desai, D. H.; Hallman, J. L.; Phillips, J. B.; Bartsch, R. A. Heterocyc. Chem **1986**, *23*, 1355.
4. In 1976, reduction of 17α-ethinyl-3-methoxy-1,3,5(10)-ostratrien-17β-ol with DIBAL in toluene was reported to produce 17β-ethyl-1,3,5(10)-ostratrien-3-ol in 71% yield. In this reaction, the propargylic alcohol moiety is reduced and demethylation of the C(3) methoxy ether occurs. See: Hilscher, J.-C. Chem Ber. **1976**, *109*, 1208.
5. a) Spectroscopic data obtained for all new compounds were fully consistent with the assigned structures. b) All yields are isolated yields. c) Reaction conditions have not been optimized.
6. *A typical experiment follows:* To 751 mg of **5** (5.00 mmol) was added 10 mL of either L-Selectride (1.0 M, 10.00 mmol) or SuperHydride (1.0 M, 10.00 mmol) and the resulting mixture was refluxed until TLC analysis indicated that the reaction was complete. The reaction mixture was cooled to 0 °C, diluted with 100 mL of ether and the resulting mixture was quenched slowly with water. The ethereal solution was washed with aqueous 5% HCl and brine. The organic phase was dried over anhydrous magnesium sulfate, concentrated, and chromatographed (silica gel, hexanes:ether, 4:1) to give 705 mg (96%) of β-naphthol.
7. a) Karabatsos, G. J.; Shone, R. L. J. Org. Chem. **1968**, *33*, 619. b) Han, B. H.; Boudjouk, P. Tetrahedron Lett. **1982**, *23*, 1643.
8. The ethyl ether of 2,3,5-trichlorophenol also undergoes deprotection in 92% yield using L-Selectride (1.1 equiv.) in glyme at 110 °C after only 12 hours.
9. a) Meerwein, H.; Hintz, G.; Majert, H.; Sonke, H. J. Prakt. Chem. **1936**, *147*, 226. b) Mikhailov, B. M.; Kiselev, V. G.; Bubnov, Y. N.; Izv. Akad. Nauk. USSR. Ser. Khim. **1965**, 898. c) Okushi, T.; Manabe, O.; Hiyaman, H.; Yoshida, Z. J. Chem. Soc. Japan **1969**, *72*, 1702.
10. a) Brown, H. C.; Krishnamurthy, S.; Coleman, R. A. J. Am. Chem. Soc. **1972**, *94*, 1750. b) Krishnamurthy, S.; Brown, H. C. J. Org. Chem. **1979**, *44*, 3678.
11. For example:[2]



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