Sodium Bis(trimethylsilyl)amide and Lithium Diisopropylamide in Deprotection of Alkyl Aryl Ethers: α-Effect of Silicon

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Received June 24, 1996 (Revised Manuscript Received February 18, 1997[⊗])

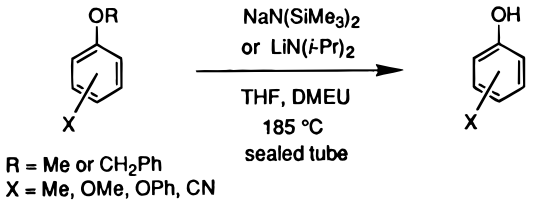
Removal of methyl, benzyl, and methylene groups from alkyl aryl ethers is among the most popular deprotecting methods in organic synthesis. Alkali organoamides $NaN(SiMe_3)_2$ and $LiN(i\text{-}Pr)_2$, often used as organic bases, have been developed as efficient deprotecting agents. Treatment of aryl methyl ethers with 1.5 equiv of $NaN(SiMe_3)_2$ or $LiN(i\text{-}Pr)_2$ in THF and 1,3-dimethyl-2-imidazolidinone in a sealed tube at 185 °C produced the corresponding phenol derivatives in good to excellent yields (80−97%). Removal of the methylene unit from benzodioxole derivatives was also accomplished by use of 2.5 equiv of these alkali organoamides. The corresponding catechols were obtained in 93−99% yields. The activity of $NaN(SiMe_3)_2$ was proven lower than that of $LiN(i\text{-}Pr)_2$; it is due to the steric congestion and the α-stabilizing effect of the silyl groups. Thus selective mono-*O*-demethylation of *o*-dimethoxybenzenes can be achieved by the use of $NaN(SiMe_3)_2$ but not $LiN(i\text{-}Pr)_2$. *O*-Debenzylation of aryl benzyl ethers, however, can be accomplished by the use of $LiN(i\text{-}Pr)_2$.

Introduction

Sodium bis(trimethylsilyl)amide ($NaN(SiMe_3)_2$) and lithium diisopropylamide ($LiN(i\text{-}Pr)_2$) are hindered bases used frequently in the deprotonation of organic compounds.[1,2] During the development of new methods for protection and deprotection of organic functional groups,[3−11] we found that these two commercially available reagents functioned as efficient nucleophiles for the cleavage of alkyl aryl ethers. This opened the possibility for them to be developed as deprotecting agents for methyl, benzyl, and methylene ethers.

Alkali amides often react with aryl methyl ethers to give aniline derivatives.[12] Several alkali organoamides, however, have been developed as demethylating or debenzylating agents.[13] Examples include sodium *N*-methylanilide and piperidide, as well as sodium and potassium amide. All of these are unhindered species. Herein we report our findings on the application of $NaN(SiMe_3)_2$ and $LiN(i\text{-}Pr)_2$ as efficient agents for demethylation, debenzylation, or demethylenation (Schemes 1 and 3). The silicon-containing agent $NaN(SiMe_3)_2$ exhibited selective monodemethylating ability in some dimethoxybenzene derivatives.

Scheme 1



Results

To search for optimum conditions and to establish a reproducible procedure for dealkylations of alkyl aryl ethers by hindered organoamides, we carried out reactions in which we varied the solvent and the temperature between 65 and 200 °C. A reliable procedure for giving the deprotected products involved treatment of a substrate with various amounts of $NaN(SiMe_3)_2$ or $LiN(i\text{-}Pr)_2$ in a mixture of THF and 1,3-dimethyl-2-imidazolidinone (DMEU) in a sealed tube at 185 °C for 12 h.

The substrates included aryl and heteroaryl methyl ethers, dimethoxyarenes, aryl benzyl ethers, and benzodioxoles. The desired product was generated in good to excellent yields as shown in Tables 1−7. The nitrogen-containing coproducts, benzylbis(trimethylsilyl)amine and benzyldiisopropylamine, generated in debenzylations were detected and characterized by GC and GC−mass spectrometry.

Discussion

Generality of Deprotections. Regarded as hindered bases, $NaN(SiMe_3)_2$ and $LiN(i\text{-}Pr)_2$ can also act as efficient nucleophiles in *O*-demethylations. This synthetic strategy is applicable to methoxyarenes including benzenes, naphthalene, anthracene, biphenyl, and pyridine that bear either an electron-withdrawing or an electron-donating group (see Tables 1−3). Both reagents can also

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⊗ Abstract published in *Advance ACS Abstracts,* May 15, 1997.

(1) Fieser, F.; Fieser, L. F. *Reagents for Organic Synthesis*; John Wiley: New York, 1974; Vol. 4, p 298.
(2) Fieser, F.; Fieser, L. F. *Reagents for Organic Synthesis*; John Wiley: New York, 1967; Vol. 1, p 1046.
(3) Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1985**, *50*, 3946.
(4) Hwu, J. R.; Chua, V.; Schroeder, J. E.; Barrans, R. E., Jr.; Khoudary, K. P.; Wang, N.; Wetzel, J. M. *J. Org. Chem.* **1986**, *51*, 4731.
(5) Hwu, J. R.; Leu, L.-C.; Robl, J. A.; Anderson, D. A.; Wetzel, J. M. *J. Org. Chem.* **1987**, *52*, 188.
(6) Hwu, J. R.; Robl, J. A.; Wang, N.; Anderson, D. A.; Ku, J.; Chen, E. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1823.
(7) Hwu, J. R.; Anderson, D. A.; Wang, N.; Buchner, M. M.; Gani, P.; Tsay, S.-C. *Chem. Ber.* **1990**, *123*, 1667.
(8) Hwu, J. R.; Tsay, S.-C. *J. Org. Chem.* **1990**, *55*, 5987.
(9) Shiao, M.-J.; Ku, W.-S.; Hwu, J. R. *Heterocycles* **1993**, *36*, 323.
(10) Hwu, J. R.; Jain, M. L.; Tsay, S.-C.; Hakimelahi, G. H. *J. Chem. Soc., Chem. Commun.* **1996**, 545.
(11) Hwu, J. R.; Jain, M. L.; Tsay, S.-C.; Hakimelahi, G. H. *Tetrahedron Lett.* **1996**, *37*, 2035.
(12) Cuvigny, T.; Normant, H. *J. Organomet. Chem.* **1973**, *55*, 41.
(13) Bhatt, M. V.; Kulkarni, S. U. *Chem. Rev.* **1983**, *83*, 249.

S0022-3263(96)01191-7 CCC: $14.00

Table 1. *O*-Demethylation of Aryl or Heteroaryl Methyl Ethers with 1.5 Equiv of $NaN(SiMe_3)_2$ or $LiN(i\text{-}Pr)_2$ in THF and DMEU at 185 °C

substrate	product	yield (%) $NaN(SiMe_3)_2$	yield (%) $LiN(i\text{-}Pr)_2$
2,6-dimethylanisole (**1**)	2,6-dimethylphenol (**12**)	82	91
3-methylanisole (**2**)	*m*-cresol (**13**)	87	85
4-methylanisole (**3**)	*p*-cresol (**14**)	94	97
4-phenoxyanisole (**4**)	4-phenoxyphenol (**15**)	80	84
2-methoxybenzonitrile (**5**)	2-cyanophenol (**16**)	90	91
2-methoxypyridine (**45**)	2-pyridone (**49**)	81	83

be used in demethylenation of various benzodioxoles to give the corresponding catechols in excellent yields.

We chose DMEU as the solvent because of its high boiling point (221−223 °C) and dipolar aprotic characteristics.[14] It is stable toward strong bases and has been applied to many nucleophilic displacement reactions that originally were only possible in solution of hexamethylphosphoramide.[15] The toxicity of DMEU is, however, much lower than that of hexamethylphosphoramide.[14] Moreover, use of the "sealed tube" technique allowed us to prevent intrusion of moisture and vaporization of solvents.

***O*-Demethylation by Sodium Bis(trimethylsilyl)-amide and Lithium Diisopropylamide.** The methyl group is one of the most popular protecting units for phenols.[16a] By applying the standard procedure involving 1.5 equiv of alkali amides, we efficiently *O*-demethylated anisole derivatives **1**−**3**, in which the methoxy group is ortho, meta, or para to a methyl substituent in a benzene ring (Table 1). The corresponding cresols **12**−**14** were produced in 82−94% yields by use of $NaN(SiMe_3)_2$ and 85−97% yields by $LiN(i\text{-}Pr)_2$.

To investigate the temperature effect, we performed the *O*-demethylation of anisole **3** with 1.5 equiv of $NaN(SiMe_3)_2$ or $LiN(i\text{-}Pr)_2$ at 65, 100, 125, 155, and 185 °C (Table 2). We found that use of a lower temperature provided the product *p*-cresol (**14**) in a lower yield.

Under the newly developed conditions at 185 °C, *O*-demethylation also proceeded smoothly in anisoles bearing an electron-donating group, such as −OPh in **4**, and an electron-withdrawing group, such as −CN in **5** (Table 1). Thus 4-phenoxyphenol (**15**) was obtained in 80−84% yields and 2-cyanophenol (**16**) in 90−91% yields. Furthermore, we successfully extended this new method for *O*-demethylation of a heteroaryl methyl ether (**45**) to give 2-pyridone (**49**) in 81−83% yields.

For a substrate having an acidic proton, such as *o*-aminoanisole, use of 1.5 or 2.5 equiv of $NaN(SiMe_3)_2$ or $LiN(i\text{-}Pr)_2$ gave *o*-aminophenol in 19−24% yields only. We also explored the possibility of removing the methyl group from β-methoxystyrene, in which the methoxy unit is connected to a C−C double bond that is conjugated to a benzene ring. *O*-Demethylation, however, did not take place, and β-methoxystyrene remained intact.

Mono- versus Bis-*O*-demethylations. We applied the standard procedure to aryl dimethoxy ethers by using 2.5 equiv of $NaN(SiMe_3)_2$ or $LiN(i\text{-}Pr)_2$. Monodemethylation occurred with compounds **7**−**10** and **40** to give products **19**−**22** and **41**, respectively, in excellent yields (87−98%, see Table 3). Although the reaction of 1,2-dimethoxybenzene (**6**) with $NaN(SiMe_3)_2$ also gave an excellent yield (98%) of the monodemethylated product **17**, use of $LiN(i\text{-}Pr)_2$ to replace $NaN(SiMe_3)_2$ afforded a mixture of **17** (44%) and bis-*O*-demethylated compound **18** (51%).

When applying $NaN(SiMe_3)_2$ and $LiN(i\text{-}Pr)_2$ under the same conditions to 3,4-dimethoxybenzonitrile (**11**), we obtained both mono- and bis-*O*-demethylated products **23** and **24** (Table 3). The stabilizing effect on the phenoxide intermediate resulting from an electron-withdrawing cyano group may facilitate the second *O*-demethylation process. Similarly, 9,10-dimethoxyanthracene (**42**) was converted to a mixture of **43** and **44** through mono- and bis-*O*-demethylations. Anthraquinone (**44**) was generated by air oxidation of the corresponding diol.[17] Furthermore, demethylations of 4,4′-dimethoxybiphenyl (**46**) by use of $NaN(SiMe_3)_2$ or $LiN(i\text{-}Pr)_2$ produced mono-*O*-demethylated phenol **47** as the major product in 68−70% yields; the bis-*O*-demethylated byproduct **48** was obtained in 18−22% yields. For the bis-*O*-demethylation of dimethoxybenzenes **6**, **11**, and **25**−**27** (Table 4), we were able to improve the yields of diols **18**, **24**, and **28**−**30** to 93−97% by using 5.0 equiv of $LiN(i\text{-}Pr)_2$.

During the study of the conversion of **6** to **17** and **18**, we learned that highly selective mono-*O*-demethylation of aryl dimethoxy ethers could be accomplished by $NaN(SiMe_3)_2$ but not by $LiN(i\text{-}Pr)_2$. To confirm our new findings, we applied the standard conditions to dimethoxybenzenes **25**−**27**, which bear a methyl, ethyl, or *tert*-butyl group. Treatment of these dimethoxybenzenes with 2.5 equiv of $NaN(SiMe_3)_2$ at 185 °C gave, in each reaction, mono-*O*-demethylated products **31**−**36** in good to excellent overall yields (83−98%, Table 5). In each of the deprotecting reactions, however, a pair of regioisomers was generated as determined by the GC or NMR technique. Comparable results were also obtained by use of 1.5 equiv of $NaN(SiMe_3)_2$ under the same reaction conditions.

To investigate the counterion effect on *O*-demethylation, we replaced the sodium ion in $NaN(SiMe_3)_2$ with the lithium ion. When $LiN(SiMe_3)_2$ was used to react with aryl methyl ethers **6**−**8** in THF and DMEU at 185 °C for 12 h, we obtained only mono-*O*-demethylated products **17** (75%), **19** (72%), and **20** (82%), respectively. These results indicate that $LiN(SiMe_3)_2$ functioned similarly to $NaN(SiMe_3)_2$, although the former was less efficient.

***O*-Debenzylation and Selective Deprotection by Lithium Diisopropylamide.** Loubinoux et al.[18] reported a method for dealkylations of alkyl aryl ethers by using NaNMePh. They found that both methyl and

(14) For the properties of DMEU, see: (a) Fieser, F.; Fieser, L. F. *Reagents for Organic Synthesis*; John Wiley: New York, 1984; Vol. 11, p 202. (b) Barker, B. J.; Rosenfarb, J.; Caruso, J. A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 503.

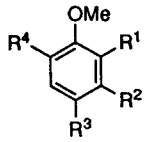
(15) Oi, R.; Shimakawa, C.; Takenaka, S. *Chem. Lett.* **1988**, 899.

(16) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley: New York, 1991; (a) pp 145−149; (b) pp 156−158; (c) pp 170−172 and references cited therein.

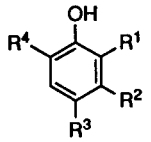
(17) Blankespoor, R. L.; Smart, R. P.; Batts, E. P.; Kiste, A. A.; Lew, R. E.; Vliet, M. E. V. *J. Org. Chem.* **1995**, *60*, 6852.

(18) Loubinoux, B.; Coudert, G.; Guillaumet, G. *Synthesis* **1980**, 638.

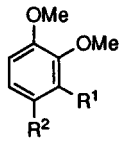
Chart 1



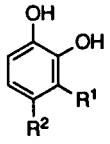
1. $R^1 = R^4 = Me$, $R^2 = R^3 = H$
2. $R^1 = R^3 = R^4 = H$, $R^2 = Me$
3. $R^1 = R^2 = R^4 = H$, $R^3 = Me$
4. $R^1 = R^2 = R^4 = H$, $R^3 = OPh$
5. $R^1 = CN$, $R^2 = R^3 = R^4 = H$
6. $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
7. $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
8. $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
9. $R^1 = R^4 = H$, $R^2 = OMe$, $R^3 = CN$
10. $R^1 = CN$, $R^2 = OMe$, $R^3 = R^4 = H$
11. $R^1 = R^2 = H$, $R^3 = CN$, $R^4 = OMe$



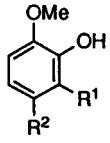
12. $R^1 = R^4 = Me$, $R^2 = R^3 = H$
13. $R^1 = R^3 = R^4 = H$, $R^2 = Me$
14. $R^1 = R^2 = R^4 = H$, $R^3 = Me$
15. $R^1 = R^2 = R^4 = H$, $R^3 = OPh$
16. $R^1 = CN$, $R^2 = R^3 = R^4 = H$
17. $R^1 = OMe$, $R^2 = R^3 = R^4 = H$
18. $R^1 = OH$, $R^2 = R^3 = R^4 = H$
19. $R^1 = R^3 = R^4 = H$, $R^2 = OMe$
20. $R^1 = R^2 = R^4 = H$, $R^3 = OMe$
21. $R^1 = R^4 = H$, $R^2 = OMe$, $R^3 = CN$
22. $R^1 = CN$, $R^2 = OMe$, $R^3 = R^4 = H$
23. $R^1 = R^2 = H$, $R^3 = CN$, $R^4 = OMe$
24. $R^1 = R^2 = H$, $R^3 = CN$, $R^4 = OH$



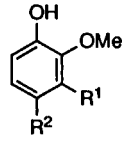
25. $R^1 = Me$, $R^2 = H$
26. $R^1 = H$, $R^2 = Et$
27. $R^1 = H$, $R^2 = Bu^t$



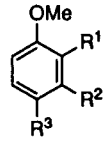
28. $R^1 = Me$, $R^2 = H$
29. $R^1 = H$, $R^2 = Et$
30. $R^1 = H$, $R^2 = Bu^t$



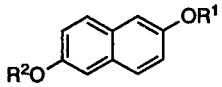
31. $R^1 = Me$, $R^2 = H$
32. $R^1 = H$, $R^2 = Et$
33. $R^1 = H$, $R^2 = Bu^t$



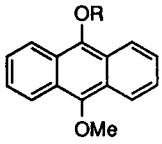
34. $R^1 = Me$, $R^2 = H$
35. $R^1 = H$, $R^2 = Et$
36. $R^1 = H$, $R^2 = Bu^t$



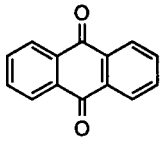
37. $R^1 = R^2 = H$, $R^3 = OCH_2Ph$
38. $R^1 = R^3 = H$, $R^2 = OCH_2Ph$
39. $R^1 = OCH_2Ph$, $R^2 = R^3 = H$



40. $R^1 = R^2 = Me$
41. $R^1 = H$, $R^2 = Me$



42. R = Me
43. R = H



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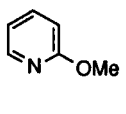

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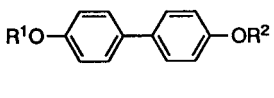
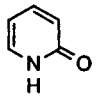


46. $R^1 = R^2 = Me$
47. $R^1 = H$, $R^2 = Me$
48. $R^1 = R^2 = H$



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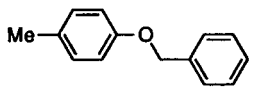

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benzyl ethers are cleaved but methyl ethers are cleaved more easily. Contrasting sharply with NaNMePh,[18] LiN(*i*-Pr)$_2$ was found to attack preferentially the benzyl moiety in 4-, 3-, and 2-(benzyloxy)anisoles (i.e., **37**−**39**).

Table 2. *O*-Demethylation of 4-Methylanisole (3) with 1.5 Equiv of NaN(SiMe$_3$)$_2$ or LiN(*i*-Pr)$_2$ To Give *p*-Cresol (14) in THF and DMEU at Various Temperatures for 12 h

	yield (%)	
temperature (°C)	NaN(SiMe$_3$)$_2$	LiN(*i*-Pr)$_2$
65	9	34
100	25	45
125	48	65
155	65	78
185	94	97

The selectively debenzylated products **17**−**20** were generated in 61−91% yields (Table 6). These results represent the first examples of selective *O*-debenzylation[13,16b,19,20] of (benzyloxy)arenes bearing a methoxy group by LiN(*i*-Pr)$_2$.

Although NaN(SiMe$_3$)$_2$ and LiN(*i*-Pr)$_2$ exhibited a similar ability for *O*-demethylation, these two hindered amides showed different reactivities toward aryl benzyl ethers. Upon treatment of aryl benzyl ethers **50** and **37** with NaN(SiMe$_3$)$_2$ at 185 °C, we did not detect any debenzylated products; instead, the starting materials were recovered. To clarify this puzzle, we worked up the reaction mixture involving **37** by adding D_2O (Scheme 2). Analysis of the proton integration of the reaction products in their ^{1}H NMR spectrum indicates that 66% of **37** was deuterated (i.e., **51**). Thus we conclude that NaN(SiMe$_3$)$_2$ functioned as a base, instead of a nucleophile, toward aryl benzyl ethers.

To rationalize the difference between these two bulky reagents, we performed AM1 calculations to obtain the conformation with the lowest heat of formation for $^-$N(*i*-Pr)$_2$, $^-$N(SiMe$_3$)$_2$, and 4-(benzyloxy)anisole (**37**, ΔH = −23.3702 kcal/mol). Their CPK space-filling spheres are shown in Figure 1.

The steric congestion created by the two Me$_3$Si groups hindered the amide center in $^-$N(SiMe$_3$)$_2$ to a greater extent than did the two isopropyl groups in $^-$N(*i*-Pr)$_2$. Thus the amide center of $^-$N(SiMe$_3$)$_2$, as shown in Figure 1b, is less able to attack nucleophilically the "buried" benzylic carbon of 4-(benzyloxy)anisole (**37**). Instead, it attacked a benzylic proton. On the other hand, the amide center in $^-$N(*i*-Pr)$_2$ (i.e., Figure 1a) exposes itself enough to function as a nucleophile for the benzylic carbon.

Demethylenation by Sodium Bis(trimethylsilyl)-amide and Lithium Diisopropylamide. The moiety of methylene acetal of catechol exists in many natural products.[21] Methods for removal of the methylene unit therein have been investigated extensively.[13,16c,20] Having succeeded in the *O*-demethylations of anisoles by the use of NaN(SiMe$_3$)$_2$ and LiN(*i*-Pr)$_2$, we further established their applicability to demethylenation of benzodioxoles (Scheme 3). The yields were 93−99% in the demethylenations of **52**−**55** (see Table 7).

α-Effect of Silicon in *O*-Demethylation. A silyl group can stabilize α-carbanion by 14−20 kcal/mol[22] through "p−d homoconjugation"[23] or "σ^*−n hyperconjugation"[24−26] or both.[27] This property has been used in control of organic reactions involving the generation of

(19) Haslam, E. In *Protective Groups in Organic Synthesis*; McOmie, J. F. W., Ed.; Plenum: New York, 1973; p 157 and references cited therein.
(20) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart, 1994.
(21) Haslam, E.; Haworth, R. D. *J. Chem. Soc.* **1955**, 827.
(22) Brinkman, E. A.; Berger, S.; Brauman, J. I. *J. Am. Chem. Soc.* **1994**, *116*, 8304.
(23) Kawamura, T.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 648.
(24) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworth: London, 1981; p 12.

Table 3. *O*-Demethylation of Dimethoxyarenes with 2.5 Equiv of $NaN(SiMe_3)_2$ or $LiN(i\text{-}Pr)_2$ in THF and DMEU at 185 °C

substrate	product	yield (%) $NaN(SiMe_3)_2$	yield (%) $LiN(i\text{-}Pr)_2$
1,2-dimethoxybenzene (**6**)	2-methoxyphenol (**17**) +	98	44
	catechol (**18**)	0	51
1,3-dimethoxybenzene (**7**)	3-methoxyphenol (**19**)	98	96
1,4-dimethoxybenzene (**8**)	4-methoxyphenol (**20**)	96	93
2,4-dimethoxybenzonitrile (**9**)	4-hydroxy-2-methoxybenzonitrile (**21**)	87	91
2,6-dimethoxybenzonitrile (**10**)	2-hydroxy-6-methoxybenzonitrile (**22**)	89	93
3,4-dimethoxybenzonitrile (**11**)	4-hydroxy-3-methoxybenzonitrile (**23**) +	28	20
	3,4-dihydroxybenzonitrile (**24**)	53	62
2,6-dimethoxynaphthalene (**40**)	6-methoxy-2-naphthol (**41**)	96	95
9,10-dimethoxyanthracene (**42**)	10-methoxyanthracen-9-ol (**43**) +	32	27
	anthraquinone (**44**)	57	59
4,4′-dimethoxybiphenyl (**46**)	4-hydroxy-4′-methoxybiphenyl (**47**) +	70	68
	4,4′-biphenol (**48**)	18	22

Table 4. Bis-*O*-demethylation of Dimethoxybenzenes with 5.0 Equiv of $LiN(i\text{-}Pr)_2$ in THF and DMEU at 185 °C

substrate	product	yield (%)
1,2-dimethoxybenzene (**6**)	catechol (**18**)	97
3,4-dimethoxybenzonitrile (**11**)	3,4-dihydroxybenzonitrile (**24**)	94
1,2-dimethoxy-3-methylbenzene (**25**)	3-methylcatechol (**28**)	94
4-ethyl-1,2-dimethoxybenzene (**26**)	4-ethylcatechol (**29**)	95
4-*tert*-butyl-1,2-dimethoxybenzene (**27**)	4-*tert*-butylcatechol (**30**)	93

Table 5. Mono-*O*-demethylation of Substituted Dimethoxybenzenes with 2.5 Equiv of $NaN(SiMe_3)_2$ in THF and DMEU at 185 °C

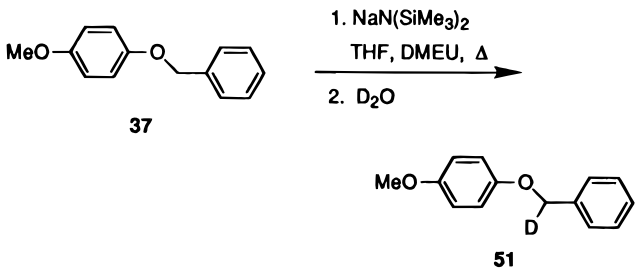
substrate	product	yield (%)	yield (%) overall
1,2-dimethoxy-3-methylbenzene (**25**)	2-methoxy-6-methylphenol (**31**) +	25	83
	2-methoxy-3-methylphenol (**34**)	58	
4-ethyl-1,2-dimethoxybenzene (**26**)	5-ethyl-2-methoxyphenol (**32**) +	36	87
	4-ethyl-2-methoxyphenol (**35**)	51	
4-*tert*-butyl-1,2-dimethoxybenzene (**27**)	5-*tert*-butyl-2-methoxyphenol (**33**) +	*a*	98
	4-*tert*-butyl-2-methoxyphenol (**36**)	*a*	

[a] Compounds **33** and **36** could not be separated by chromatography.

Table 6. *O*-Debenzylation of Aryl Benzyl Ethers with 1.5 or 2.5 Equiv of $LiN(i\text{-}Pr)_2$ in THF and DMEU at 185 °C

substrate	equiv of $LiN(i\text{-}Pr)_2$	product	yield (%)
4-(benzyloxy)toluene (**50**)	1.5	*p*-cresol (**14**)	83
4-(benzyloxy)anisole (**37**)	2.5	4-methoxyphenol (**20**)	87
3-(benzyloxy)anisole (**38**)	2.5	3-methoxyphenol (**19**)	91
2-(benzyloxy)anisole (**39**)	2.5	2-methoxyphenol (**17**) +	61
		catechol (**18**)	27

Scheme 2



α-silylcarbanions.[28–32] The α-stabilizing effect of silicon on anions also exists in a nitrogen center. Thus hexamethyldisilazane is >9 pK_aS (in DMSO) units stronger as an acid than dialkylamines, such as diisopropylamine.[33] This stabilizing effect made a difference in *O*-demethylation of 1,2-dimethoxybenzene (**6**) between the use of $NaN(SiMe_3)_2$ and $LiN(i\text{-}Pr)_2$: highly selective mono-*O*-demethylation can be achieved by the former reagent but not the latter one, despite that both are efficient demethylating agents. The selectivity offered by $NaN(SiMe_3)_2$ can be attributed to its lower activity as compared with that of $LiN(i\text{-}Pr)_2$.

Conclusions

Hindered bases $NaN(SiMe_3)_2$ and $LiN(i\text{-}Pr)_2$ were developed as efficient deprotecting agents for aryl methyl ethers and benzodioxoles. Debenzylation of aryl benzyl ethers can also be accomplished by use of $LiN(i\text{-}Pr)_2$, which showed greater nucleophilicity than $NaN(SiMe_3)_2$. A steric effect and the α-anion-stabilizing effect of the silyl group decreased the activity of $NaN(SiMe_3)_2$ and thus increased its selectivity. Evidence was obtained on its ability of selective mono-*O*-demethylation of 1,2-dimethoxybenzenes.

(25) Yukio, N.; Teiji, T.; Tsuneo, H. *Makromol. Chem.* **1989**, *190*, 1855.
(26) Takahashi, O.; Morihashi, K.; Kikuchi, O. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1178.
(27) Bassindale, A. R.; Taylor, P. G. In *The Chemistry of Functional Groups: The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley: Chichester, 1989; Part 2, p 893 and references cited therein.
(28) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983; Chapter 6, p 59.
(29) Colvin, E. W. *Chem. Soc. Rev.* **1978**, *7*, 15.
(30) Paquette, L. A. *Science* **1982**, *217*, 793.
(31) Fleming, I. *Chem. Soc. Rev.* **1981**, *10*, 83.
(32) Krief, A. *Tetrahedron* **1980**, *36*, 2531.
(33) Grimm, D. T.; Bartmess, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 1227 and references cited therein.

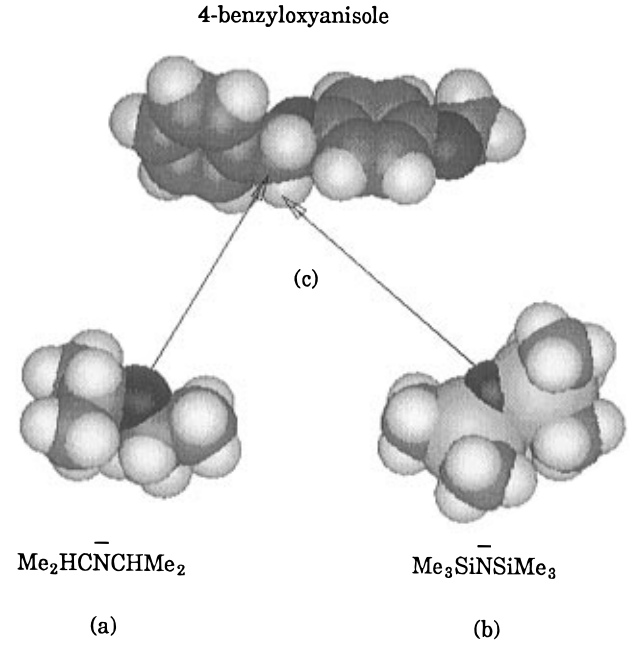
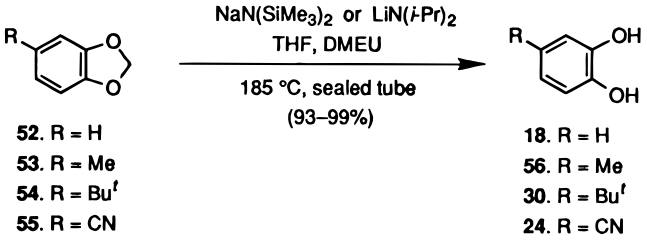


Figure 1. Use of CPK space-filling molecular model to present the results obtained from AM1 calculations. The conformation with the lowest energy is shown in (a) for $^-N(i\text{-}Pr)_2$, (b) for $^-N(SiMe_3)_2$, and (c) for 4-(benzyloxy)anisole (**37**). The species $^-N(i\text{-}Pr)_2$ and $^-N(SiMe_3)_2$ prefer to attack **37** at its benzylic carbon and proton, respectively.

Scheme 3



52. R = H
53. R = Me
54. R = Bu^t
55. R = CN

18. R = H
56. R = Me
30. R = Bu^t
24. R = CN

Table 7. Deprotection of Benzodioxoles by Use of 2.5 Equiv of $NaN(SiMe_3)_2$ or $LiN(i\text{-}Pr)_2$ in THF and DMEU at 185 °C

		yield (%)	
benzodioxole	product	$NaN(SiMe_3)_2$	$LiN(i\text{-}Pr)_2$
52	**18**	99	98
53	**56**	98	96
54	**30**	93	94
55	**24**	95	96

Experimental Section

General Procedure. Ethyl acetate and hexanes, purchased from Mallinckrodt Chemical Co., were dried and distilled from CaH_2. 1,3-Dimethyl-2-imidazolidinone (DMEU) from Aldrich was dried by distillation from CaH_2 under reduced pressure and then stored in serum-capped bottles over molecular sieves (4A) under argon. The following reagents were purchased from Aldrich Chemical Co.: 1,3-benzodioxole, 4-*tert*-butylcatechol, 4-*tert*-butyl-1,2-(methylenedioxy)benzene, 2,4- and 3,4-dimethoxybenzaldehydes, 1,2-, 1,3-, and 1,4-dimethoxybenzenes, 2,4-, 2,6-, and 3,4-dimethoxybenzonitriles, 4,4′-dimethoxybiphenyl, 2,6-dimethoxynaphthalene, 1,2-dimethoxy-4-nitrobenzene, 3,5-dimethoxyphenol, 2,6-dimethylanisole, lithium diisopropylamide (LDA), 2-methoxyaniline, 2-methoxybenzonitrile, 4-methoxyphenol, 2-methoxypyridine, β-methoxystyrene, 3- and 4-methylanisoles, 3-methylcatechol, 3,4-(methylenedioxy)toluene, 4-methylphenol, 2- and 4-nitroanisoles, 4-phenoxyphenol, piperonylonitrile, and sodium bis(trimethylsilyl)amide. Compounds prepared by literature methods[34,35] include 2-, 3-, and 4-(benzyloxy)anisoles, 4-(benzyloxy)toluene, 4-*tert*-butyl-1,2-dimethoxybenzene, 1,2-dimethoxy-3-methylbenzene, 4-ethyl-1,2-dimethoxybenzene, and 4-phenoxyanisole.

An explosion-proof oven from Blue M. Electric Co. and Pyrex combustion tubes (8 × 10 × 200 mm) from Tung Kuang Glassware Industrial Corp. were used for performance of experiments that required high temperature (e.g., 185 °C). Analytical thin layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254), purchased from Merck Inc. Mixtures of ethyl acetate and hexanes were used as eluants. Purification by gravity column chromatography was carried out by use of Merck reagent silica gel 60 (particle size 0.063−0.200 mm, 70−230 mesh ASTM). Gas chromatographic analyses were performed on a Hewlett-Packard 5890 Series II instrument equipped with a 25-m cross-linked methylsilicone gum capillary column (0.32 mm i.d.). Nitrogen gas was used as a carrier gas, and the flow rate was kept constant at 14.0 mL/min. The retention time t_R was measured under the following conditions: injector temperature 260 °C, initial temperature for column 70 °C, duration 2.00 min, increment rate 10 °C/min, and final temperature for column 250 °C.

The computations were performed on a Silicon Graphics IRIS CRIMSON/Elan workstation by use of *Builder* and *AMPAC/MOPAC* modules of Insight II (Biosym Technologies, versions 2.3.0 and 6.0.0 individually) for model building and energy minimization, respectively.

Standard Procedure for *O*-Demethylation, *O*-Debenzylation, and *O*-Demethylenation. A solution containing an alkyl aryl ether, aryl benzyl ether, or benzodioxole (1.0 equiv) in DMEU (0.50 mL) was transferred into a Pyrex combustion tube under argon. Lithium diisopropylamide (2.0 M in a mixture of heptane, THF, and ethylbenzene) or $NaN(SiMe_3)_2$ (1.0 M in THF) was injected into the tube, which was then sealed. The sealed tube was heated in an oven at 185 °C for 12 h. The reaction mixture was diluted with water at room temperature, neutralized with 10% HCl, and extracted with Et_2O (4 × 25 mL). The combined ethereal solutions were washed with water and saturated aqueous NaCl. The combined organic extracts were dried over $MgSO_4$(s), filtered, and concentrated under reduced pressure. The residue was purified by gravity column chromatography (2.2 cm × 16 cm column) packed with silica gel to provide the desired product.

2,6-Dimethylphenol (12). Method 1. The standard procedure was followed by use of 2,6-dimethylanisole (**1**; 116 mg, 0.848 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 1.3 mL, 1.3 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **12** (84.7 mg, 0.693 mmol) as a yellow solid[36a] in 82% yield: mp 46−47 °C (lit.[36b] mp 46−48 °C).

Method 2. The standard procedure was followed by use of 2,6-dimethylanisole (**1**; 96.2 mg, 0.706 mmol, 1.0 equiv), LDA (2.0 M, 0.55 mL, 1.1 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **12** (78.7 mg, 0.644 mmol) as a yellow solid in 91% yield.

***m*-Cresol (13). Method 1.** The standard procedure was followed by use of 3-methylanisole (**2**; 96.9 mg, 0.794 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 1.2 mL, 1.2 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **13** (75.0 mg, 0.694 mmol) as a red liquid[36a] in 87% yield.

Method 2. The standard procedure was followed by use of 3-methylanisole (**2**; 96.5 mg, 0.790 mmol, 1.0 equiv), LDA (2.0 M, 0.60 mL, 1.2 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified

(34) Rao, K. V.; Chattopadhyay, S. K. *J. Org. Chem.* **1990**, *55*, 1427.
(35) Kozuka, S.; Kikuchi, A.; Yamaguchi, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 307.
(36) (a) Its physical properties and spectroscopic characteristics are consistent with those of authentic samples available from Aldrich Chemical Co. (b) *Aldrich Catalog Handbook of Fine Chemicals 1996−1997*; Aldrich Chemical Co: Milwaukee, WI, 1996.

by chromatography (30% EtOAc in hexanes as eluant) to give pure **13** (72.8 mg, 0.673 mmol) as a red liquid in 85% yield.

***p*-Cresol (14). Method 1.** The standard procedure was followed by use of 4-methylanisole (**3**; 97.1 mg, 0.795 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 1.2 mL, 1.2 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **14** (80.8 mg, 0.747 mmol) as a light yellow liquid[36a] in 94% yield.

Method 2. The standard procedure was followed by use of 4-methylanisole (**3**; 94.6 mg, 0.774 mmol, 1.0 equiv), LDA (2.0 M, 0.60 mL, 1.2 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **14** (81.3 mg, 0.752 mmol) as a light yellow liquid in 97% yield.

Method 3. The standard procedure was followed by use of 4-(benzyloxy)toluene (**50**; 111 mg, 0.561 mmol, 1.0 equiv), LDA (2.0 M, 0.42 mL, 0.84 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **14** (50.3 mg, 0.465 mmol) as a light yellow liquid in 83% yield.

4-Phenoxyphenol (15). Method 1. The standard procedure was followed by use of 4-phenoxyanisole (**4**; 113 mg, 0.566 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 0.85 mL, 0.85 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **15** (84.5 mg, 0.454 mmol) as a white solid[36a] in 80% yield: mp 84−85 °C (lit.[36b] mp 83−85 °C).

Method 2. The standard procedure was followed by use of 4-phenoxyanisole (**4**; 137 mg, 0.684 mmol, 1.0 equiv), LDA (2.0 M, 0.50 mL, 1.0 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **15** (107 mg, 0.575 mmol) as a white solid in 84% yield.

2-Cyanophenol (16). Method 1. The standard procedure was followed by use of 2-methoxybenzonitrile (**5**; 131 mg, 0.985 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 1.5 mL, 1.5 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **16** (106 mg, 0.890 mmol) as a white solid[36a] in 90% yield: mp 94−95 °C (lit.[36b] mp 92−95 °C).

Method 2. The standard procedure was followed by use of 2-methoxybenzonitrile (**5**; 109 mg, 0.819 mmol, 1.0 equiv), LDA (2.0 M, 0.60 mL, 1.2 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **16** (88.9 mg, 0.746 mmol) as a white solid in 91% yield.

2-Methoxyphenol (17). Method 1. The standard procedure was followed by use of 1,2-dimethoxybenzene (**6**; 134 mg, 0.969 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 2.4 mL, 2.4 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **17** (118 mg, 0.951 mmol) as a yellow liquid[36a] in 98% yield.

Method 2. The standard procedure was followed by use of 1,2-dimethoxybenzene (**6**; 108 mg, 0.783 mmol, 1.0 equiv), LDA (2.0 M, 1.0 mL, 2.0 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **17** (42.6 mg, 0.343 mmol) as a yellow liquid in 44% yield and pure **18** (43.7 mg, 0.397 mmol) as a white solid in 51% yield.

Method 3. The standard procedure was followed by use of 2-(benzyloxy)anisole (**39**; 85.2 mg, 0.398 mmol, 1.0 equiv), LDA (2.0 M, 0.50 mL, 1.0 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **17** (30.2 mg, 0.243 mmol) as a yellow liquid in 61% yield and pure **18** (11.8 mg, 0.107 mmol) as a white solid in 27% yield.

Catechol (18). Method 1. The standard procedure was followed by use of 1,2-dimethoxybenzene (**6**; 108 mg, 0.784 mmol, 1.0 equiv), LDA (2.0 M, 2.0 mL, 3.9 mmol, 5.0 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **18** (83.7 mg, 0.760 mmol) as a white solid[36a] in 97% yield: mp 104−106 °C (lit.[36b] mp 104−106 °C).

Method 2. The standard procedure was followed by use of 1,3-benzodioxole (**52**; 106 mg, 0.871 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 2.2 mL, 2.2 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **18** (94.9 mg, 0.862 mmol) as a white solid in 99% yield.

Method 3. The standard procedure was followed by use of 1,3-benzodioxole (**52**; 97.1 mg, 0.796 mmol, 1.0 equiv), LDA (2.0 M, 1.0 mL, 2.0 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **18** (85.7 mg, 0.778 mmol) as a white solid in 98% yield.

3-Methoxyphenol (19). Method 1. The standard procedure was followed by use of 1,3-dimethoxybenzene (**7**; 127 mg, 0.916 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 2.3 mL, 2.3 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **19** (111 mg, 0.894 mmol) as a yellow liquid[36a] in 98% yield.

Method 2. The standard procedure was followed by use of 1,3-dimethoxybenzene (**7**; 106 mg, 0.764 mmol, 1.0 equiv), LDA (2.0 M, 0.96 mL, 1.9 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **19** (91.1 mg, 0.734 mmol) as a yellow liquid in 96% yield.

Method 3. The standard procedure was followed by use of 3-(benzyloxy)anisole (**38**; 53.2 mg, 0.249 mmol, 1.0 equiv), LDA (2.0 M, 0.31 mL, 0.62 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **19** (28.2 mg, 0.227 mmol) as a yellow liquid in 91% yield.

4-Methoxyphenol (20). Method 1. The standard procedure was followed by use of 1,4-dimethoxybenzene (**8**; 131 mg, 0.946 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 2.4 mL, 2.4 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **20** (113 mg, 0.910 mmol) as a white solid[36a] in 96% yield: mp 54−55 °C (lit.[36b] mp 55−57 °C).

Method 2. The standard procedure was followed by use of 1,4-dimethoxybenzene (**8**; 103 mg, 0.747 mmol, 1.0 equiv), LDA (2.0 M, 0.93 mL, 1.9 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **20** (85.9 mg, 0.692 mmol) as a white solid in 93% yield.

Method 3. The standard procedure was followed by use of 4-(benzyloxy)anisole (**37**, 117 mg, 0.547 mmol, 1.0 equiv), LDA (2.0 M, 0.70 mL, 1.4 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **20** (58.8 mg, 0.474 mmol) as a white solid in 87% yield.

4-Hydroxy-2-methoxybenzonitrile (21).[37] **Method 1.** The standard procedure was followed by use of 2,4-dimethoxybenzonitrile (**9**; 144 mg, 0.881 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 2.2 mL, 2.2 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **21** (114 mg, 0.764 mmol) as a yellow solid in 87% yield: mp 164−165 °C; GC t_R 12.37 min; TLC R_f 0.45 (50% EtOAc in hexanes); ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 400 MHz) δ 3.87 (s, 3 H), 6.42 (d, J = 8.8 Hz, 1 H), 6.52 (s, 1 H), 7.35 (d, J = 8.8 Hz, 1 H); ^{13}C NMR (DMSO-d_6 + $CDCl_3$, 100 MHz) δ

(37) Otto, D.; Helmut, C.; Helmut, G. *Liebigs Ann. Chem.* **1982**, 1836.

55.3, 92.0, 101.4, 106.7, 117.3, 133.9, 161.6, 164.2; IR (neat) 3267 (br s), 2942 (s), 2218 (s), 1607 (m) cm^{-1}; MS *m/z* (relative intensity) 149 (M^+, 100), 134 (10), 119 (16), 106 (57), 91 (38), 79 (14), 69 (12), 63 (19), 51 (20).

Method 2. The standard procedure was followed by use of 2,4-dimethoxybenzonitrile (**9**; 154 mg, 0.942 mmol, 1.0 equiv), LDA (2.0 M, 1.2 mL, 2.4 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **21** (128 mg, 0.858 mmol) as a yellow solid in 91% yield.

2-Hydroxy-6-methoxybenzonitrile (22).[38] **Method 1.** The standard procedure was followed by use of 2,6-dimethoxybenzonitrile (**10**; 106 mg, 0.648 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 1.6 mL, 1.6 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **22** (85.9 mg, 0.576 mmol) as a white solid in 89% yield: mp 164−165 °C (lit.[38] mp 163−166 °C); GC t_R 11.94 min; TLC R_f 0.30 (50% EtOAc in hexanes); ^1H NMR (DMSO-d_6 + $CDCl_3$, 400 MHz) δ 3.88 (s, 3 H), 6.39 (d, J = 8.4 Hz, 1 H), 6.57 (d, J = 8.4 Hz, 1 H), 7.28 (dd, J = 8.4, 8.4 Hz, 1 H); IR (neat) 3245 (br s), 2231 (s), 1525 (m), 1478 (m) cm^{-1}; MS *m/z* (relative intensity) 149 (M^+, 100), 134 (1), 122 (15), 106 (53), 93 (14), 91 (12), 78 (16), 63 (12), 51 (12).

Method 2. The standard procedure was followed by use of 2,6-dimethoxybenzonitrile (**10**; 154 mg, 0.946 mmol, 1.0 equiv), LDA (2.0 M, 1.2 mL, 2.4 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **22** (131 mg, 0.878 mmol) as a white solid in 93% yield.

4-Hydroxy-3-methoxybenzonitrile (23). Method 1. The standard procedure was followed by use of 3,4-dimethoxybenzonitrile (**11**; 154 mg, 0.941 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 2.4 mL, 2.4 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **23** (39.5 mg, 0.265 mmol) as a yellow solid[36a] in 28% yield and **24** (66.8 mg, 0.494 mmol) as a yellow solid in 53% yield. For **23**: mp 87−88 °C (lit.[36b] mp 85−87 °C).

Method 2. The standard procedure was followed by use of 3,4-dimethoxybenzonitrile (**11**; 247 mg, 1.49 mmol, 1.0 equiv), LDA (2.0 M, 1.8 mL, 3.7 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **23** (44.9 mg, 0.301 mmol) as a yellow solid in 20% yield and **24** (125 mg, 0.925 mmol) as a yellow solid in 62% yield.

3,4-Dihydroxybenzonitrile (24).[39] **Method 1.** The standard procedure was followed by use of 3,4-dimethoxybenzonitrile (**11**; 87.8 mg, 0.538 mmol, 1.0 equiv), LDA (2.0 M, 1.4 mL, 2.7 mmol, 5.0 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **24** (68.3 mg, 0.505 mmol) as a yellow solid in 94% yield: mp 127−129 °C (lit.[39] mp 128−130 °C); TLC R_f 0.30 (50% EtOAc in hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.89 (d, J = 8.8 Hz, 1 H), 7.05 (d, J = 8.8 Hz, 1 H), 7.13 (s, 1 H); IR (neat) 3291 (br s), 2233 (s), 1605 (m) cm^{-1}; MS *m/z* (relative intensity) 135 (M^+, 100), 117 (12), 106 (11), 89 (38), 79 (10), 62 (28), 52 (25), 51 (22).

Method 2. The standard procedure was followed by use of piperonylonitrile (**55**; 141 mg, 0.955 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 2.4 mL, 2.4 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **24** (122 mg, 0.903 mmol) as a yellow solid in 95% yield.

Method 3. The standard procedure was followed by use of piperonylonitrile (**55**; 70.6 mg, 0.479 mmol, 1.0 equiv), LDA (2.0 M, 0.60 mL, 1.2 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **24** (61.9 mg, 0.458 mmol) as a yellow solid in 96% yield.

3-Methylcatechol (28). The standard procedure was followed by use of 1,2-dimethoxy-3-methylbenzene (**25**; 102 mg, 0.671 mmol, 1.0 equiv), LDA (2.0 M, 1.7 mL, 3.4 mmol, 5.0 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **28** (78.0 mg, 0.628 mmol) as a light yellow solid[36a] in 94% yield: mp 66−67 °C (lit.[36b] mp 65−68 °C).

4-Ethylcatechol (29). The standard procedure was followed by use of 4-ethyl-1,2-dimethoxybenzene (**26**; 103 mg, 0.617 mmol, 1.0 equiv), LDA (2.0 M, 1.6 mL, 3.1 mmol, 5.0 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **29** (81.2 mg, 0.588 mmol) as a light yellow solid in 95% yield.

4-*tert*-Butylcatechol (30). Method 1. The standard procedure was followed by use of 4-*tert*-butyl-1,2-dimethoxybenzene (**27**; 99.5 mg, 0.512 mmol, 1.0 equiv), LDA (2.0 M, 1.3 mL, 2.6 mmol, 5.0 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **30** (79.0 mg, 0.475 mmol) as a yellow solid[36a] in 93% yield: mp 55−56 °C (lit.[36b] mp 52−55 °C).

Method 2. The standard procedure was followed by use of 4-*tert*-butyl-1,2-(methylenedioxy)benzene (**54**; 115 mg, 0.646 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 1.6 mL, 1.6 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give pure **30** (100 mg, 0.602 mmol) as a yellow solid in 93% yield.

Method 3. The standard procedure was followed by use of 4-*tert*-butyl-1,2-(methylenedioxy)benzene (**54**; 105 mg, 0.587 mmol, 1.0 equiv), LDA (2.0 M, 0.75 mL, 1.5 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **30** (91.9 mg, 0.553 mmol) as a yellow solid in 94% yield.

2-Methoxy-6-methylphenol (31) and 2-Methoxy-3-methylphenol (34).[40] The standard procedure was followed by use of 1,2-dimethoxy-3-methylbenzene (**25**; 155 mg, 1.02 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 2.6 mL, 2.6 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (10% EtOAc in hexanes as eluant) to give pure **31** (34.8 mg, 0.252 mmol) as a light yellow solid in 25% yield and **34** (81.6 mg, 0.591 mmol) as a light yellow liquid in 58% yield. For **31**: mp 40−41 °C (lit.[40] mp 41−42 °C); GC t_R 6.91 min; TLC R_f 0.28 (10% EtOAc in hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3 H), 3.81 (s, 3 H), 5.87 (br s, 1 H), 6.71 (d, J = 7.5 Hz, 1 H), 6.82 (d, J = 7.5 Hz, 1 H), 6.93 (dd, J = 7.5, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.8, 60.5, 113.2, 122.5, 124.6, 130.8, 145.5, 148.9; IR (neat) 3427 (br s), 2946 (s), 1597 (m), 1467 (m), 1279 (m) cm^{-1}; MS *m/z* (relative intensity) 138 (M^+, 57), 123 (100), 95 (18), 77 (27), 67 (16), 65 (11), 51 (10).

For **34**:[41] GC t_R 7.62 min; TLC R_f 0.45 (10% EtOAc in hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3 H), 3.87 (s, 3 H), 5.70 (br s, 1 H), 6.71−6.75 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.3, 55.9, 108.2, 119.1, 123.1, 123.9, 143.7, 146.2; IR (neat) 3499 (br s), 2942 (s), 1619 (m), 1473 (m), 1355 (w), 1273 (m) cm^{-1}; MS *m/z* (relative intensity) 138 (M^+, 65), 123 (100), 105 (4), 95 (25), 77 (31), 67 (17), 65 (13), 51 (11).

5-Ethyl-2-methoxyphenol (32)[42] **and 4-Ethyl-2-methoxyphenol (35).** The standard procedure was followed by use of 4-ethyl-1,2-dimethoxybenzene (**26**; 123 mg, 0.739 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 1.8 mL, 1.8 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (10% EtOAc in

(38) Loic, R.; Simone, R.; Pierre, D.; Rene, R.; Raymond, C. *Eur. J. Med. Chem. Chim. Ther.* **1979**, *14*, 281.

(39) Pelizzetti, E.; Mentasti, E.; Pramauro, E. *J. Chem. Soc., Perkin Trans. 2* **1978**, 620.

(40) Carvalho, C. F.; Sargent, M. V. *J. Chem. Soc., Chem. Commun.* **1984**, 227.

(41) Maissant, J. M.; Bouchoule, C.; Blanchard, M. *J. Mol. Catal.* **1982**, *14*, 333.

(42) Nolte, D. J. *J. Insect. Physiol.* **1976**, *22*, 833; *Chem. Abstr.* **1976**, *85*, 156902m.

hexanes as eluant) to give pure **32** (40.3 mg, 0.265 mmol) as a light yellow liquid in 36% yield and **35** (57.8 mg, 0.380 mmol) as a brown liquid in 51% yield. For **32**: GC t_R 10.54 min; TLC R_f 0.30 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7.5 Hz, 3 H), 2.58 (q, J = 7.5 Hz, 2 H), 3.79 (s, 3 H), 6.41 (d, J = 2.5 Hz, 1 H), 6.47 (dd, J = 8.3, 2.5 Hz, 1 H), 7.05 (d, J = 8.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 22.5, 55.3, 98.8, 106.4, 124.9, 129.2, 154.7, 158.1; IR (neat) 3356 (br s), 2954 (s), 1607 (m), 1507 (m), 1462 (m), 1196 (m) cm^{-1}; MS m/z (relative intensity) 152 (M^+, 30), 137 (100), 121 (3), 107 (40), 77 (20), 65 (10).

5-*tert*-Butyl-2-methoxyphenol (33) and 4-*tert*-Butyl-2-methoxyphenol (36). The standard procedure was followed by use of 4-*tert*-butyl-1,2-dimethoxybenzene (**27**; 119 mg, 0.615 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 1.5 mL, 1.5 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (30% EtOAc in hexanes as eluant) to give a mixture of **33** and **36** (109 mg, 0.605 mmol) as a yellow liquid[36a] in 98% overall yield. These regioisomers were not separable by chromatography.

6-Methoxy-2-naphthol (41).[43] **Method 1.** The standard procedure was followed by use of 2,6-dimethoxynaphthalene (**40**; 122 mg, 0.648 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 1.6 mL, 1.6 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **41** (108 mg, 0.620 mmol) as a white solid in 96% yield: mp 148−149 °C (lit.[43] mp 148−150 °C); TLC R_f 0.45 (40% EtOAc in hexanes); ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 400 MHz) δ 3.88 (s, 3 H), 7.06−7.13 (m, 4 H), 7.54−7.60 (m, 2 H), 8.59 (br s, 1 H); IR (neat) 3256 (br s), 1606 (m) cm^{-1}; MS m/z (relative intensity) 174 (M^+, 100), 159 (26), 131 (31), 103 (6).

Method 2. The standard procedure was followed by use of 2,6-dimethoxynaphthalene (**40**; 160 mg, 0.847 mmol, 1.0 equiv), LDA (2.0 M, 1.1 mL, 2.1 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **41** (140 mg, 0.804 mmol) as a white solid in 95% yield.

10-Methoxyanthracen-9-ol (43) and Anthraquinone (44). Method 1. The standard procedure was followed by use of 9,10-dimethoxyanthracene (**42**; 122 mg, 0.514 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 1.3 mL, 1.3 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **43** (36.9 mg, 0.165 mmol) as a light yellow solid[36a] in 32% yield and **44** (60.9 mg, 0.293 mmol) as a light yellow solid[36a] in 57% yield. For **43**: mp 156−158 °C (lit.[36b] mp 156−158 °C).

Method 2. The standard procedure was followed by use of 9,10-dimethoxyanthracene (**42**; 152 mg, 0.637 mmol, 1.0 equiv), LDA (2.0 M, 0.80 mL, 1.6 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **43** (38.8 mg, 0.173 mmol) as a light yellow solid in 27% yield and **44** (77.8 mg, 0.374 mmol) as a light yellow solid in 59% yield.

4-Hydroxy-4′-methoxybiphenyl (47)[44] **and 4,4′-Biphenol (48). Method 1.** The standard procedure was followed by use of 4,4′-dimethoxybiphenyl (**46**; 124 mg, 0.578 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 1.4 mL, 1.4 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **47** (80.6 mg, 0.403 mmol) as a white solid in 70% yield and **48** (19.7 mg, 0.106 mmol) as a white solid[36a] in 18% yield. For **47**: mp 174−176 °C (lit.[44] mp 175−177 °C); GC t_R 19.02 min; TLC R_f 0.45 (40% EtOAc in hexanes); ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 400 MHz) δ 3.83 (s, 3 H), 6.90−6.95 (m, 4 H), 7.39 (d, J = 6.6 Hz, 2 H), 7.46 (d, J = 6.6 Hz, 2 H), 8.23 (br s, 1 H); IR (neat) 3355 (br s), 2919 (m), 1608 (m) cm^{-1}; MS m/z (relative intensity) 200 (M^+, 100), 185 (69), 171 (3), 157 (27), 128 (14).

For **48**: mp 283−285 °C (lit.[36b] mp 282−284 °C).

Method 2. The standard procedure was followed by use of 4,4′-dimethoxybiphenyl (**46**; 28.0 mg, 0.131 mmol, 1.0 equiv), LDA (2.0 M, 0.16 mL, 0.33 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (40% EtOAc in hexanes as eluant) to give pure **47** (17.9 mg, 0.089 mmol) as a white solid in 68% yield and **48** (5.4 mg, 0.029 mmol) as a white solid in 22% yield.

2-Pyridone (49). Method 1. The standard procedure was followed by use of 2-methoxypyridine (**45**; 125 mg, 1.14 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 1.7 mL, 1.7 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **49** (88.1 mg, 0.926 mmol) as a white solid[36a] in 81% yield: mp 106−107 °C (lit.[36b] mp 105−107 °C).

Method 2. The standard procedure was followed by use of 2-methoxypyridine (**45**; 104 mg, 0.951 mmol, 1.0 equiv), LDA (2.0 M, 0.70 mL, 1.4 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (EtOAc as eluant) to give pure **49** (74.7 mg, 0.785 mmol) as a white solid in 83% yield.

4-(α-*d*-Benzyloxy)anisole (51). The standard procedure was followed by use of 4-(benzyloxy)anisole (**37**; 125 mg, 0.584 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 0.88 mL, 0.88 mmol, 1.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up by addition of D_2O, and the residue was purified by recrystallization from hexanes to give a mixture of **37** and **51** as a white solid (113 mg): ^{1}H NMR (DMSO-d_6 + $CDCl_3$, 400 MHz) δ 3.78 (s, 3 H), 5.01 (s, 1.34 H), 6.83−6.94 (m, 4 H), 7.33−7.45 (m, 5 H).

4-Methylcatechol (56). Method 1. The standard procedure was followed by use of 3,4-(methylenedioxy)toluene (**53**; 136 mg, 1.00 mmol, 1.0 equiv), $NaN(SiMe_3)_2$ (1.0 M, 2.5 mL, 2.5 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **56** (122 mg, 0.983 mmol) as a yellow solid[36a] in 98% yield: mp 67−68 °C (lit.[36b] mp 67−69 °C).

Method 2. The standard procedure was followed by use of 3,4-(methylenedioxy)toluene (**53**; 114 mg, 0.838 mmol, 1.0 equiv), LDA (2.0 M, 1.1 mL, 2.1 mmol, 2.5 equiv), and DMEU (0.50 mL). The reaction mixture was worked up, and the residue was purified by chromatography (50% EtOAc in hexanes as eluant) to give pure **56** (99.8 mg, 0.804 mmol) as a yellow solid in 96% yield.

Benzylbis(trimethylsilyl)amine (57) and Benzyldiisopropylamine (58). Both were detected by GC and GC−MS spectrometry. For **57**: GC t_R 12.71 min; MS m/z (relative intensity) 251 (M^+, 12), 236 (66), 162 (66), 148 (22), 135 (44), 91 (45), 73 (100), 59 (36).

For **58**: GC t_R 11.15 min; MS m/z (relative intensity) 191 (M^+, 6), 176 (59), 134 (8), 100 (45), 91(100).

Acknowledgment. For financial support, we thank the National Science Council of the Republic of China (Grant NSC 86-2113-M007-028) and Academia Sinica.

JO961191K

(43) Kidwell, R. L.; Murphy, M.; Darling, S. D. *Org. Synth.* **1969**, *49*, 90.

(44) Abramovitch, R. A.; Alvernhe, G.; Bartnik, R.; Dassanayake, N. L.; Inbasekaran, M. N.; Kato, S. *J. Am. Chem. Soc.* **1981**, *103*, 4558.