8, 103-30-0; 9, 3195-78-6; 10, 96-33-3; 11, 614-47-1; 12, 19522-25-9; 13, 1754-62-7; (+)-I, 115270-40-1; (−)-I, 115270-41-2; $Pd(OAc)_2$, 3375-31-3; $PdCl_2$, 7647-10-1; $Pd(PhCN)_2Cl_2$, 14220-64-5; Pd, 7440-05-3; (*E,X*)-$H_2NCONHN$=C(Ph)CH=CHOBu, 115270-34-3; MeO-*m*-C_6H_4COCl, 1711-05-3; MeO-*p*-C_6H_4COCl, 100-07-2; Cl-*p*-C_6H_4COCl, 122-01-0; Br-*p*-C_6H_4COCl, 586-75-4; (*E*)-H_3CC(Ph)=CHOBu, 109125-24-8; (*Z*)-H_3CC(Ph)=CHOBu, 109125-26-0; O_2N-*p*-C_6H_4COCl, 122-04-3; (*E*)-O_2N-*p*-C_6H_4COCH=CDOBu, 115270-43-4; (*E*)-O_2N-*p*-C_6H_4CH=CDOBu, 115288-63-6; (*E*)-O_2N-*p*-C_6H_4CD=CHOBu, 115270-44-5; (*Z*)-O_2N-*p*-C_6H_4CH=CDOBu, 115270-45-6; (*Z*)-O_2N-*p*-C_6H_4CD=CHOBu, 115270-46-7; (*Z*)-O_2N-*p*-C_6H_4C(OBu)=CHD, 115270-47-8; (*E*)-O_2N-*p*-C_6H_4C(OBu)=CHD, 115270-48-9; benzoyl chloride, 98-88-4; 3,4,5-trimethoxybenzoyl chloride, 4521-61-3; 3-thiophenecarbonyl chloride, 41507-35-1; 3-furancarboxylic acid chloride, 26214-65-3; 2-naphthalenecarboxylic acid chloride, 2243-83-6; 4-nitrobenzoic acid, 62-23-7; butyl α-deuteriovinyl ether, 115270-42-3.

Metalation of Phenols. Synthesis of Benzoquinones by the Oxidative Degradation Approach

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In an effort to explore the potential of the so-called oxidative degradation approach for the synthesis of quinones, we have investigated the direct metalation of a number of simple phenols such as *o*- and *p*-hydroxybenzyl alcohols, benzyl methyl ethers and *N,N*-dimethylbenzylamines. Apparently, only those phenolic substrates having available both a coordinating group for chelation and an electron-withdrawing group in a 1,3-relationship are efficiently lithiated, by the action of *n*-BuLi, in a regioselective manner. Those positions on the aromatic nucleus just flanked by a coordinating, or an acid–base, group could be metalated by the action of the *t*-BuLi/THP system, in favorable cases.

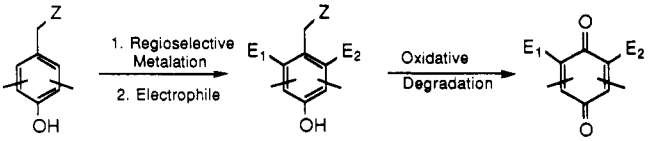
The search for new synthetic approaches for the widespread quinone functionality is a continuously growing area of investigation.[1] In regard to an ongoing research project, we have recently developed a novel route to quinones based on the very simple strategy outlined in Scheme I.[2]

As depicted (Scheme I), there were two main objectives to be reached throughout the work: first, it was essential to develop a novel degradative oxidation of substituted phenols; and second, it was also of prime importance to achieve metalation of substituted phenols in a direct manner.

In a series of recent publications[3] we have shown that several para-substituted phenols, namely *p*-hydroxybenzyl alcohols and *p*-hydroxybenzylamines, as well as some *p*-hydroxybenzoic acids and *p*-hydroxybenzamides, undergo Fremy's salt promoted oxidative degradation to the corresponding quinones. Obviously, the above type of substrates appeared as the most immediate highly promising quinone synthons for our planned synthetic endeavors, provided that our expectations of finding a working protocol for the regioselective functionalization of phenols (via metalation followed by trapping with electrophiles) could be established.

In spite of the outstanding growth of aromatic organolithium chemistry[4] witnessed during the past few years,

Scheme I



organolithium derivatives of phenols, or rather lithium phenolates, have remained largely unexplored. Possibly, the lack of success of Gilman et al.[5] in their pioneering studies on the lithiation of simple phenols convinced researchers to resort to the well-established protection/deprotection strategy, whenever a regioselective metalation—and subsequent functionalization—of a phenol were needed. In fact, only very recently[6] the regioselective ortho metalation (*t*-BuLi/THP) of phenol itself has been described.

Therefore we embarked upon a systematic study of the direct metalation of phenols,[7] the results of which are reported herein. We will demonstrate that the direct metalation of phenols is a powerful tactic for the regioselective functionalization of phenolic substrates, thus giving support, at least in part, to the unwritten though nevertheless very familiar synthetic principle: "the best way of protecting a (phenolic) functional group is no protection at all".

Results

At the outset of our work, the metalation of a series of simple *p*-hydroxybenzyl alcohols was attempted in order to find the appropriate conditions not only for achieving ring metalation but also for avoiding undesirable benzylic

(1) For some recent developments in the area, see: Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759. Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821. Wulff, W. D.; Tang, P.-C.; Chan, K.-S.; McCallum, J. S.; Yang, D. C.; Gilberton, S. R. *Tetrahedron* **1985**, *24*, 5813. Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W.; Zask, A. *Tetrahedron* **1985**, *24*, 5803.

(2) Saá, J. M.; Morey, J.; Costa, A. *Tetrahedron Lett.* **1986**, *27*, 5125.

(3) Saá, J. M.; Morey, J.; Rubido, C. *J. Org. Chem.* **1986**, *51*, 4471. See ref 2 and 20.

(4) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1. Omae, I. *Chem. Rev.* **1979**, *79*, 287. Snieckus, V. *Heterocycles* **1980**, *14*, 1649. Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957.

(5) Gilman, H.; Morton, J. W., Jr. *Org. React. (N.Y.)* **1954**, *8*, 258. Santucci, L.; Gilman, H. *J. Am. Chem. Soc.* **1958**, *80*, 4537.

(6) Posner, G. H.; Canella, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 2571. Talley, J. J.; Evans, I. A. *J. Org. Chem.* **1984**, *49*, 5267.

(7) For preliminary results, see ref 2 and 3.

0022-3263/88/1953-4263$01.50/0

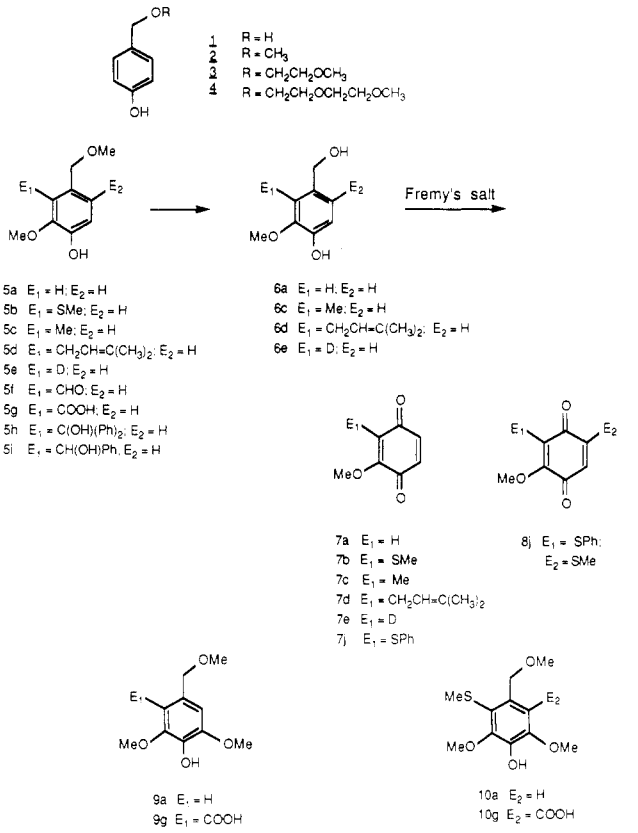


Figure 1.

metalations.[8] On the other hand, we were confident that ring metalation would occur at an ortho position with respect to a directing group other than the weakly directing OLi.[9,6]

Our first efforts concerned the metalation of *p*-hydroxybenzyl alcohols (or easily available derivatives thereof) since these types of substrates had already been proven to be efficiently converted into the corresponding 1,4-benzoquinones, through the recently developed Fremy's salt promoted oxidative degradation approach.[2,3]

Not unexpectedly,[10] however, the direct metalation of **6a** (Figure 1) with *n*-BuLi (THF, room temperature, 4 h) or *n*-BuLi/TMEDA (under otherwise identical conditions) was unsuccessful, the starting phenolic alcohol being recovered completely unchanged upon treatment with $(MeS)_2$. We believe that this behavior is a consequence of the insolubility of the substrate's dilithium salt, which precipitates immediately after addition of 2 mol of *n*-BuLi. Further addition of excess *n*-BuLi did not alter the above reaction mixture appearance.

Hence, our attention was focused on the direct ring metalation of lithium phenolates, which, we hoped, would be less insoluble than the above dilithium salt and, therefore, amenable to further metalation to the desired dianions. However, *p*-hydroxy methyl ether **2** could not be successfully lithiated under our set of standard conditions (THF, room temperature, 4 h), as evidenced by the recovery of starting material after quenching of the reaction mixture with typical electrophiles such as D_2O, Me_2S_2, and MeI.

Moreover, no improvement in ring metalation was observed by increasing the chelating capacity of the phenol "arm" at C-4,[11] as demonstrated by the recovery of the starting material when phenolic glymes **3** and **4** were submitted to the standard conditions of deprotonation (ca. 5% metalation was detected by ^1H NMR spectroscopy for **3** under long reaction times). No further improvement was, however, reached by operating at higher temperatures or in the presence of TMEDA. In spite of these negative results, it was encouraging to see that no benzylic metalation took place in competition with the desired ring metalation.

With the aim to accomplish direct regioselective metalations of phenolic substrates, it was decided then to look at guaiacol derivatives such as the easily available benzyl methyl ether **5a**.[12] To our delight, a clean and regioselective ring metalation was observed in this case after quenching with dimethyl disulfide. The ^1H NMR spectra of both the crude and purified product clearly showed (clean AB system, J = 8 Hz) that metalation had occurred exclusively at the most encumbered position to give the highly substituted phenol **5b** in 72% isolated yield. Analogously, by using MeI, $BrCH_2CH{=}C(CH_3)_2$, D_2O, DMF, CO_2, $(C_6H_5)_2CO$, and C_6H_5CHO as electrophiles, the corresponding 2,3,4-trisubstituted phenols **5c–i** were obtained in consistently high isolated yields. On the other hand, we did not detect, in the above examples, any competitive benzylic metalation[13] when working under the reported standard conditions. However, longer reaction times and higher temperatures clearly induced side reactions to compete. We have not investigated in detail the constitution of these byproducts, though the presence of a doublet (J = 6.5 Hz) at 1.45 ppm apparently suggests that a Wittig rearrangement[13] may have taken place to some extent, ca. 0–5%, in competition with ring metalation.

All attempts to introduce a further OH group onto the aromatic ring by the use of appropriate electrophiles ended in failure. In particular, the reaction of the metalated lithium phenolate of **5a** with nitrobenzene[14] or with the recently developed bis(trimethylsilyl)peroxide[15] both returned starting material, while the reaction of the metalated **5a** with trimethyl borate followed by hydrogen peroxide oxidation[16] furnished a complex mixture, which was not further investigated.

Consistent with our initial observations (vide supra), all attempts of metalating a 2,3,4-trisubstituted phenol such as **5c** also failed.

In contrast with the above result, the stepwise introduction of two electrophiles was achieved in a clean and efficient manner on the aromatic nucleus of a syringyl

(8) Bates, R. B.; Siahan, T. J. *J. Org. Chem.* **1986**, *51*, 1432. See also Kende, A. S.; Ebetino, F. H.; Ohta, T. *Tetrahedron Lett.* **1985**, *26*, 3063.

(9) Wakefield, B. J. *The Chemistry of the Organolithium Compounds*; Pergamon: New York, 1974. See also ref 4 and 6.

(10) Several authors have reported failure in their attempts of formation of trianions. See: Sibi, M. P.; Chattopadhyay, S.; Dankwardt, J. W.; Snieckus, V. *J. Am. Chem. Soc.* **1985**, *107*, 6312 and references therein. See, however: Bhide, B. H.; Narasimhan, N. S. *Chem. Ind.* **1974**, *75*, for a case where a trianion has presumably been generated. See also ref 8 for additional cases.

(11) See, for example: Ronald, R. C.; Winkle, M. R. *Tetrahedron* **1983**, *39*, 2031. Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1983**, *24*, 5465 and references therein.

(12) *p*-Hydroxybenzyl alkyl ethers were best prepared by stirring the *p*-hydroxybenzyl alcohol with excess alcohol and *p*-toluenesulfonic acid (catalyst). For an alternative preparation, see: De Jonge, J.; Bibo, B. H. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 1448. This later method was the method of choice for the preparation of *o*-hydroxybenzyl methyl ethers like **22**.

(13) Benzyl methyl ethers are generally considered unsuitable coordinating groups in metalation reactions. See ref 4 and Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *38*, 3324. Keay, B. A.; Rodrigo, R. *Tetrahedron* **1984**, *40*, 4597. Christensen, H. *Synth. Commun.* **1974**, *4*, 1. Gilman, H.; Meikle, W. J.; Morton, J. W., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 6282.

(14) Cava, M. P.; Wiriyachitra, P. *J. Org. Chem.* **1977**, *42*, 2274 and references therein.

(15) Taddei, M.; Ricci, A. *Synthesis* **1986**, 633.

(16) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.

derivative, 3,5-dimethoxy-4-hydroxybenzyl methyl ether (**9a**). Thus, highly substituted phenols **9g** and **10g** were easily obtained in 90 and 47% isolated yields (not optimized) (Figure 1).

On the basis of the above results it appeared that the presence of both a coordinating and an electron-withdrawing group appropriately disposed in a 1,3-relationship would be required for successful metalation.[17]

Since *p*-hydroxybenzyl methyl ethers do not undergo the Fremy's salt promoted oxidative degradation,[3] a hydrolytic step was required to give utility to the synthesized systems. Not unexpectedly, the conversion of the *p*-hydroxybenzyl methyl ethers to the corresponding benzyl alcohol was a difficult problem to overcome.[18] Under careful controlled conditions, hydrolysis of **5c–e** to the desired benzyl alcohols **6c–e** was achieved in moderate yield (40–60%). We were unable, however, to carry out the hydrolysis of **5b** cleanly. Oxidative degradation of **6c–e** then provided *p*-benzoquinones **7c–e** in high yield (63–87%).[2]

Since we had already discovered that *p*-hydroxybenzylamines were also excellent precursors of the corresponding *p*-benzoquinones,[19] we pursued metalation of these substrates.

As expected from our previous observations with *p*-hydroxybenzyl methyl ethers, attempted metalation with *n*-BuLi of **11** and **12**, followed by quenching with dimethyl disulfide, gave unchanged starting material. Apparently the presence of the CH_2NMe_2 directing group was not sufficient for bringing about the desired ortho metalation. This was also supported by the fact that even the ethylenediamine derivative **13** could not be metalated under several experimental conditions, thus confirming the inability of *n*-BuLi to metalate phenols at aromatic positions not activated by the presence of a neighbor withdrawing group.

Fortunately, however, metalation of *N,N*-dimethylvanillylamine **14a** or analogues **15a**, **17a**, and **18a** occurred cleanly in the expected regioselective manner[20] when submitted to our standard conditions for lithiation. Quenching the reaction mixture with typical electrophiles such as Me_2S_2, D_2O, Ph_2CO, MeI, PhCHO, and $CH_3COCH_2CH_2CH{=}C(CH_3)_2$ yielded the corresponding 2,3,4-trisubstituted phenols: **14b**, **14e**, **14j**, **15b**, **15c**, **15e**, **15i**, **17b**, **17k**, and **18b**. Carefully controlled conditions were needed for the preparation of **15c** and **18k** (see the Experimental Section).

On the other hand, metalation of vanillin derivatives **14b** and **18b** were unsuccessful under the standard conditions.

In striking contrast with the above, we found that two different (or identical) electrophiles could be introduced onto a phenolic benzylamine having two positions available for deprotonation, provided that both were flanked by a coordinating (CH_2NMe_2) and an acid–base group[4] (OMe). Thus, *N,N*-dimethylsyringylamine **15a** was easily converted into the highly substituted phenolic benzylamines **16b**, **16e**, and **16i**, in good overall yields (Figure 2a).

Fremy's salt promoted oxidative degradation of tertiary *p*-hydroxybenzylamines **14**, **15**, and **17** worked well in all cases, including those of highly congested substrates **16b** and **16i**, to give benzoquinones **7a**, **7b**, **7e**, **7j**, **19a**, **19c**, **19e**, **20b**, **20i**, **21a** and **21k** in high yield (Figure 2b).

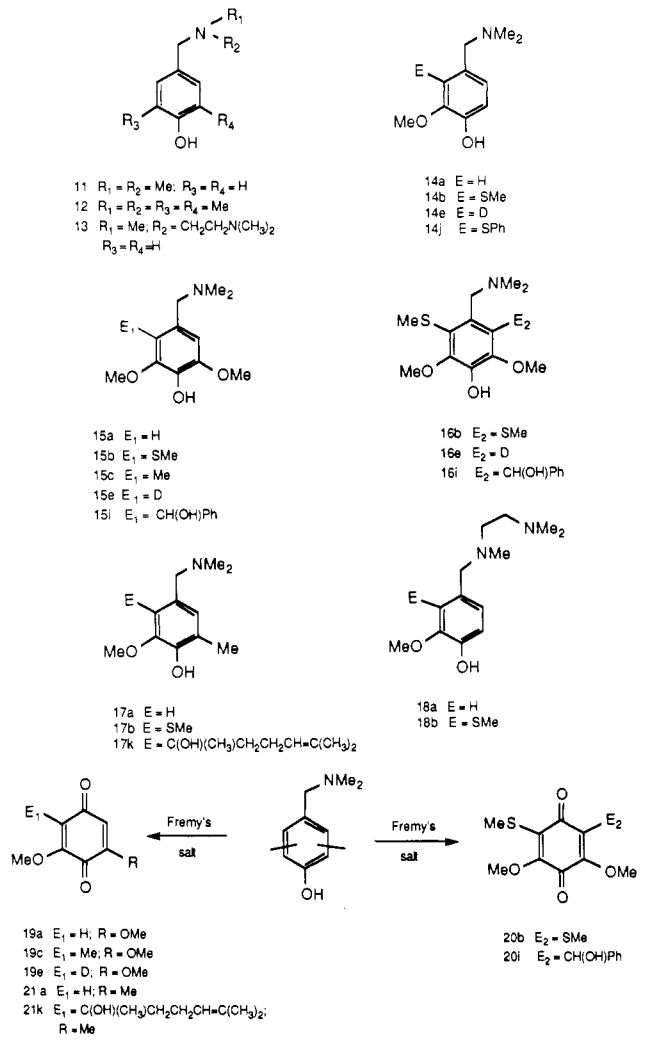
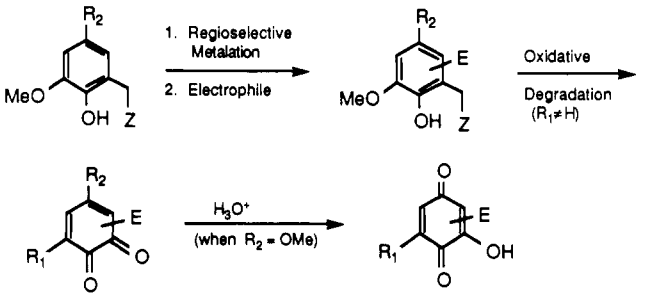


Figure 2.

Scheme II



Having found an efficient route for the synthesis of 1,4-benzoquinones, we then turned our attention to the possible application of this protocol[21] for the preparation of *o*-quinones[22] and such interesting derivatives as 2-hydroxy-1,4-benzoquinones[22] (Scheme II).

To achieve these goals, metalation of benzyl methyl ether **22**, easily available from *o*-vanillyl alcohol,[12] was initially attempted. In sharp contrast to the para hydroxy series, the Wittig rearrangement product **23** was the only

(17) Narasimhan, N. S.; Mali, R. S.; Bulkarni, B. K. *Tetrahedron* **1983**, *39*, 1975.

(18) Presumably, the intermediate formation of quinone methides gives rise to competitive reactions. See: *Methoden der organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1979; Band 7, Teil 3b, p 395.

(19) Saá, J. M.; Llobera, A.; Deyá, P. M. *Chem. Lett.* **1987**, 771.

(20) After this work was completed, we became aware of the results of Hlasta et al., which corroborated our own. See: Hlasta, D. J.; Bell, M. R. *Tetrahedron Lett.* **1985**, *26*, 2151.

(21) Some 4-unsubstituted phenols having hydroxymethyl or (dimethylamino)methyl groups at C-2 (and/or C-6) undergo oxidative degradation by the action of Fremy's salt, thus providing the corresponding 1,2-benzoquinones. See: Deyá, P. M.; Dopico, M.; García-Raso, A.; Morey, J.; Saá, J. M. *Tetrahedron* **1987**, *43*, 3523.

(22) *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1979; Band 7, Teil 3b.

component isolated (40%) other than starting material **22**. Careful examination (^{1}H NMR) of the crude reaction mixture did not provide evidence of ring metalation.

No satisfactory explanation for the puzzling benzylic metalation of phenolic substrates can be advanced for the moment, though similar observations have been reported.[23,45]

We therefore turned our attention to metalation reactions of *o*-hydroxybenzylamines (Scheme II, Z = NMe_2). However, metalation of the easily available *N,N*-dimethyl-*o*-vanillylamine **24a** lead to recovered starting material. We reasoned that the amino group in *o*-hydroxybenzylamines was likely involved in coordinating the lithium atom of the neighbor phenolate group, which could prevent its coordination with an incoming lithium base. This, together with the decreased acidity of the aromatic hydrogens of the lithium phenolate, led us to propose that deprotonation of *N,N*-dimethyl-*o*-hydroxybenzylamines would require either the use of a stronger lithium base or the existance of appropriately located electron-withdrawing groups, thereby making adjacent aromatic hydrogens more acidic and, hence, amenable for deprotonation.

In this regard, the reported enhanced activity of organolithium bases in the presence of potassium alkoxides[24] convinced us to submit **24a** to the action of the so-called Lickor reagent (*n*-BuLi/KO-*t*-Bu). Unfortunately, neither the use of the standard reagent nor the employment of modified reagents containing variable amounts of KO-*t*-Bu led to any improvement, the starting material **24a** being recovered (ca. 90%).

However, the change to a strong base such as *t*-BuLi gave somewhat more encouraging results. Thus, treatment of a concentrated (ca. 1 M) tetrahydropyran solution[25] of *N,N*-dimethyl-*o*-vanillylamine **24a** with *t*-BuLi in pentane (see the Experimental Section for the appropriate working conditions), followed by quenching with benzophenone, afforded the triarylmethanol **24h** in very low isolated yield together with some other unidentified minor byproducts. The structure of **24h** was firmly secured on the basis of its ^{1}H–^{1}H COSY spectrum, which showed a proton centered at 6.50 (d, 1 H, J = 7.9 Hz) coupled with the CH_2NR_2, while the other aromatic proton appeared as a clean doublet (1 H, d, J = 7.9 Hz) not coupled to any other hydrogen nucleus.

In further examining these reaction conditions, the metalation (*t*-BuLi) of 5-methoxy- and 4-methoxy-2-[(dimethylamino)methyl]phenols **25a** and **26a** was carried out to give, after quenching with benzophenone, compounds **25h** and **26h**, respectively (Figure 3). Their structures have been elucidated on the basis of the characteristic shielding caused by the aromatic rings on appropriately disposed hydrogen nucleus. Thus, compound **25h** showed a high field methoxy group at 3.58 ppm and aromatic singlets at 6.46 and 6.03 ppm. Much the same effect was present in the ^{1}H NMR of compound **26h**, which showed high field signals at 3.59, 6.55, and 6.07 ppm, in support of the proposed structure. Conclusive evidence for these structures came from the analysis of their ^{1}H–^{1}H NMR COSY and/or NOESY spectra. Thus, for **25h** it became clear that the proton signal at 6.46 (s, 1 H) was close to the OMe group and the one at 6.03 (s, 1 H) was

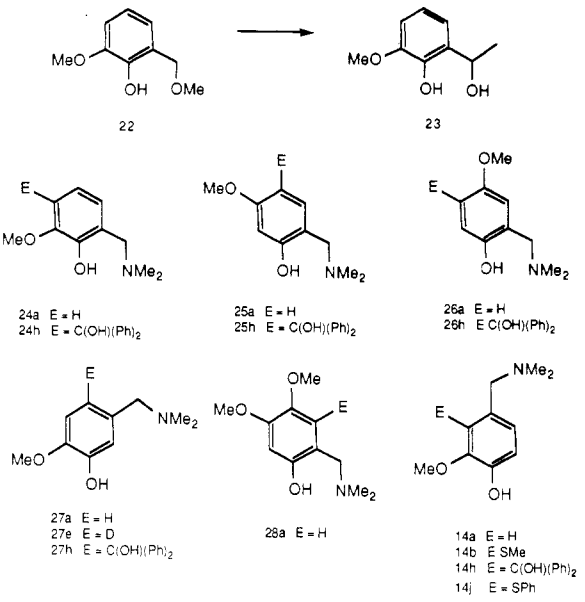


Figure 3.

proximate to the CH_2NR_2, while for the case of **26h** both the OMe and CH_2NR_2 groups must be flanking the hydrogen appearing at 6.55 (s, 1 H) and further away from the hydrogen at 6.07 ppm.

The regioselectivity found strongly suggests that the nitrogen atom does not play a significant role during hydrogen abstraction by the incoming *t*-BuLi molecules. In other words, its electron pair must be involved in chelating the adjacent lithium atom (Ar OLi), and, consequently, it is the other directing group present in the molecule (OMe) that is the one which coordinates with the *t*-BuLi prior to the actual deprotonation step.[26] Deprotonation at the less sterically hindered position of the resulting complex would explain the formation of the observed products.

Poor results were obtained when only a sterically hindered hydrogen was left available for deprotonation in *o*-hydroxybenzylamines. Thus, in an attempted synthesis of maesanine[27] and related compounds,[28] treatment of 2-[(dimethylamino)methyl]-4,5-dimethoxyphenol **28a** with *t*-BuLi as above gave rise to a complex mixture of products and decomposition. This is to be remarked in light of the fact that metalation of a *p*-hydroxybenzylamine such as **14a**, either with *n*-BuLi[20] or with *t*-BuLi, followed by treatment with benzophenone, gives rise to **14h**.

Therefore, due to the difficutly in introducing side chains at hindered positions of substituted *o*-hydroxybenzylamines, the planned synthesis of *o*-benzoquinones and hydroxy *p*-benzoquinones (Scheme II) was abandoned.

On the basis of the above results, we reasoned that compound **27** should be metalated by *t*-BuLi (but not *n*-BuLi) at C-4, as a consequence of this being a less encumbered position than the alternative C-6.

The validity of both predictions has been shown. Thus, **27a** was recovered unchanged after treatment with *n*-BuLi followed by quenching with Ph_2CO, while its deprotonation with *t*-BuLi/THP, followed by treatment with Ph_2CO, afforded the expected triaryl methanol **27h**. Its structure was assigned on the basis of the ^{1}H NMR spectrum, which featured a high field benzylic group (2.85 ppm) as well as

(23) See, for example: Ronald, R. C.; Winkle, M. R. *Tetrahedron* **1983**, *39*, 2031.
(24) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9. See also: Schlosser, M.; Strunck, S. *Tetrahedron Lett.* **1984**, *25*, 741.
(25) Significantly improved metalations have been observed when using THP as solvent. See: Einhorn, J.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 1793. See also ref 6.
(26) See: Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356 and also ref 17.
(27) Kubo, I.; Tamikawa, T.; Miura, I. *Tetrahedron Lett.* **1983**, *24*, 3825.
(28) Thomson, R. H. *Naturally Occurring Quinones*; Academic: New York, 1971.

a shielded aromatic hydrogen (6.21 ppm). Conclusive evidence for this assignment came from two independent experiments. In one, quenching of the lithiated material with D_2O gave rise to the monodeuteriated compound **27e** (87% yield; above 90% deuterium incorporation) having the expected ^1H and ^{13}C NMR spectra. Moreover, the ^1H–^1H COSY and NOESY spectra of **27h** were in total agreement with the proposed structure. Thus, the aromatic hydrogen at 6.21 ppm was in close proximity to the OMe group, while the one at 6.74 ppm was shown to be nearby the CH_2NR_2 group.

Thus, the regioselective stepwise introduction of different electrophiles (Scheme I) into phenolic substrates such as **14a** appears within reach.[29] We were conscious of the difficulties of the second lithiation (*t*-BuLi) of substrates having acidic hydrogens close to the directing gorup (CH_2NMe_2). In order to test this hypothesis, trisubstituted phenol **14b** was treated with *t*-BuLi under the standard conditions, followed by quenching with dimethyl disulfide. Not unexpectedly, a very complex mixture of products was obtained, possibly due to competitive metalation at the methylthio group.[30] Finally, the desired metalation was observed when **14j** was treated with *t*-BuLi, followed by quenching with Ph_2CO. This furnished a crude mixture (30%), which on oxidation with Fremy's salt provided an unseparable 1:1 mixture of quinones tentatively identified (^1H NMR, GC/EIMS) as **7j** and **8j**.

Discussion

The work described above clearly proves that phenols can be regioselectively lithiated in a direct manner. More precisely, *n*-BuLi efficiently metalates phenols having a coordinating and an electron-withdrawing (acid–base) group attached to the ring in a 1,3-relationship. However, if only one group for coordination (apart of the OLi group) is available, efficient metalation can be achieved only by using the *t*-BuLi/THP system.

Moreover, both types of phenol metalation appear to be highly regioselective. Thus, on the one hand, *n*-BuLi metalates phenols at the position flanked by both the coordinating and the acid–base groups. On the other hand, *t*-BuLi metalates phenols (having only one coordinating group) at the less hindered position.

In summary, we hope to have shown that the so-called oxidative degradation approach may be useful for the rational synthesis of simple quinones.

Further developments regarding the use of metalated phenolates are presently being studied.

Experimental Section

General methods. All melting points are uncorrected and were taken on a Büchi capillary melting point apparatus. IR spectra were recorded with a Hitachi 260-10 spectrometer. Proton and carbon NMR spectra were obtained on a Varian FT-80A, Brucker WP-200SY and WM-250 instruments, with $CDCl_3$ as solvent and tetramethylsilane as internal standard, unless otherwise stated. Electron-impact mass spectra were recorded with a Kratos MS-25 or Hewlett-Packard 5985B instruments, operating at 70 eV ionizing energy.

Packing materials for column chromatography was Merck silica gel 60 (70–230 mesh) or alumina. Solvents used for metalations were thoroughly dried prior to use. Thus, diethyl ether, tetrahydrofuran, and tetrahydropyran were distilled from sodium benzophenone ketyl.

Organolithium reagents, purchased from Chemetall (Frankfurt, FRG) were used as received, once titrated. All operations involving carbanionic species were carried out under argon atmosphere.

The boiling points given refer to those observed on bulb-to-bulb distillations, conducted in a Büchi GKR-50 apparatus.

Elemental analysis were obtained at the Servei de Microanalisi del CSIC (Barcelona).

4-Hydroxybenzyl Methyl Ether (2). To a stirred suspension of commercial 4-hydroxybenzyl alcohol (3 g, 24.1 mmol) in methanol (75 mL) was added a catalytic amount of *p*-toluenesulfonic acid (0.3 g). Stirring was maintained for 6 h at room temperature. Standard extractive workup gave a crude oil, which on distillation (bp 140 °C/2 mmHg; lit.[31] bp 147–153 °C/11 mmHg) yielded analytically pure **2** (66%), which solidified on standing, mp 80–81 °C (hexane/ether) (lit.[31] mp 82–83 °C).

4-Hydroxybenzyl 2-Methoxyethyl Ether (3). Phenolic ether **3** was obtained as for the case of **2**, from 4-hydroxybenzyl alcohol (4 g, 31.4 mmol) and ethyleneglycol monomethyl ether (2-methoxyethanol, 35 mL), in 73% isolated yield, after bulb-to-bulb distillation (bp 140 °C/0.05 Hg). ^1H NMR: 3.38 (s, 3 H), 3.60 (s, 4 H), 4.45 (s, 2 H), 6.50 (br s, 1 H), 6.72 (d, 2 H, J = 8.5 Hz), 7.14 (d, 2 H, J = 8.5 Hz) ppm. IR (neat): 3350, 2930, 1620, 1600, 1510, 1440, 1350, 1220, 1080, 840, 820 cm^{-1}. EIMS, *m/e* (percent relative abundance): 182 (M^+, 8), 123 (17), 107 (100), 78 (10), 77 (24). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.93; H, 7.69. Found, C, 65.73; H, 8.04.

4-Hydroxybenzyl 2-(2-Methoxyethoxy)ethyl Ether (4). This compound was prepared from 4-hydroxybenzyl alcohol (2.5 g, 20 mmol) and 2-(2-methoxyethoxy)ethanol (15 mL) by the method described above for the preparation of **2**. Bulb-to-bulb distillation of the crude product yielded pure **4** in 42% isolated yield (bp 190–200 °C/0.05 mmHg). ^1H NMR: 3.36 (s, 3 H), 3.63 (br s, 8 H), 4.45 (s, 2 H), 6.40 (br s, 1 H), 6.74 (d, 2 H, J = 8.4 Hz), 7.15 (d, 2 H, J = 8.4 Hz) ppm. IR (neat): 3320, 2900, 1620, 1600, 1580, 1510, 1450, 1360, 1240, 1105, 860, 830, cm^{-1}. EIMS, *m/e* (percent, relative abundance): 226 (M^+, 5), 123 (78), 107 (100), 77 (34). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.72; H, 7.96. Found, C, 63.62; H, 8.24.

4-Hydroxy-3-methoxybenzyl Methyl Ether (5a). This compound was obtained as a viscous oil (solidifies on standing, mp 34–5 °C (hexane/ether)) in 88% yield from commercial 4-hydroxy-3-methoxybenzyl alcohol (vanillyl alcohol, 8 g, 51.9 mmol) and methanol (350 mL), as described above for the preparation of **2**. Bp 150–5 °C/2 mmHg. ^1H NMR: 3.35 (s, 3 H), 3.86 (s, 3 H), 4.37 (s, 2 H), 5.75 (br s, 1 H), 6.85 (br s, 3 H) ppm. IR (neat): 3380, 2940, 1605, 1505, 1460, 1430, 1270, 1240, 1150, 1090, 1030 cm^{-1}. EIMS, *m/e* (percent relative abundance): 168 (M^+, 97), 167 (32), 138 (26), 137 (100), 122 (36), 77 (31), 66 (39), 65 (81), 51 (67). Anal. Calcd for $C_9H_{12}O_3$: C, 64.28; H, 7.14. Found, C, 64.03; H, 7.33.

4-Hydroxy-3,5-dimethoxybenzyl Methyl Ether (9a). The titled compound was prepared from the corresponding benzyl alcohol (5 g, 25.2 mmol) and methanol (100 mL) as described previously for the case of **2**. Bulb-to-bulb distillation of the crude material furnished pure **9a** in 72% yield, bp 175–180 °C/2 mmHg, which solidified on standing. Mp 33–5 °C (hexane/ether). ^1H NMR: 3.36 (s, 3 H), 3.86 (s, 6 H), 4.37 (s, 2 H), 6.05 (br s, 1 H), 6.57 (s, 2 H) ppm. IR (neat): 3420, 2950, 1615, 1508, 1465, 1430, 1390, 1335, 1220, 1120, 840 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 198 (M^+, 61), 168 (22), 167 (100), 123 (18), 95 (12), 77 (11). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.61; H, 7.07. Found: C, 60.17; H, 6.95.

General Procedure for the Direct Metalation of Phenolic Substrates with *n*-BuLi. An oven-dried three-necked flask was charged with the phenolic substrate (typically 2 mmol) and purged with argon for 15 min. Freshly distilled ether or THF (ca. 5 mL/mmol) was introduced into the flask with a syringe. To the stirred solution, at room temperature, a commercial solution of *n*-BuLi in hexanes (6 mmol) was added dropwise via syringe. The resulting yellowish solution was stirred at room temperature for an additional 2–4 h. To the final brownish mixture cooled to −40 °C was added the appropriate electrophile. Stirring was continued for an additional 2 to 4 h, and the temperature was slowly increased to 0 °C. The mixture was quenched with cold water, the solvent was removed in vacuo, and the remaining aqueous phase

(29) Highly substituted aromatics have been obtained by sequential deprotonation of aromatic tertiary amides. See: Mills, R. J.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1565.

(30) Cabiddu, S.; Floris, C.; Melis, S. *Tetrahedron Lett* **1986**, *27*, 4625.

(31) DeJonge, J.; Bibo, B. H. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 1449.

was extracted twice with hexane. The basic aqueous solution was acidified with cold HCl and extracted with methylene chloride or ether. The extracts were washed successively with brine and water and dried over anhydrous sodium sulfate. Removal of the solvent yielded a crude material, which was chromatographed and/or bulb-to-bulb distilled.

Attempted Lithiation of Phenols 2–4 and 6a. The titled phenols (2 mmol) dissolved in dry THF were treated with *n*-BuLi (6 mmol) as described in the general procedure. This was followed by quenching with excess methyl iodide or DMF, and the mixture was stirred for 2–4 h. Standard workup gave the following results: 4-hydroxy-3-methoxybenzyl alcohol (**6a**) was recovered unchanged after being submitted to the above reaction conditions (*n*-BuLi/MeI). 4-Hydroxybenzyl methyl ether (**2**) on treatment *n*-BuLi/MeI as described above gave unchanged starting material (95%). 4-Hydroxybenzyl 2-methoxyethyl ether (**3**) was recovered unaltered (85%) after its reaction with *n*-BuLi/DMF in THF. When the reaction was carried out in ether, the crude mixture obtained (55%) showed signals in its ^{1}H NMR corresponding to a formyl derivative (ca. 3–5% yield). Forcing the reaction conditions (12 h reflux prior to the addition of the electrophile) produced extensive decomposition. Metalation of a hexane suspension of **3** (2 mmol) with *n*-BuLi (6 mmol) in the presence of TMEDA (6 mmol) led—after 12 h of stirring at room temperature followed by quenching with dry DMF—to the recovery of starting material (60%). 4-Hydroxybenzyl 2-(2-methoxyethoxy)ethyl ether (**4**) was recovered unaltered in 80% yield after its reaction with *n*-BuLi/DMF, as described above.

Preparation of 4-Hydroxy-3-methoxy-2-(methylthio)benzyl Methyl Ether (5b). A THF (30 mL) solution of **5a** (1.01 g, 6 mmol) was treated with *n*-BuLi (1.5 M, 12 mL, 18 mmol) as shown in the general procedure and then quenched with dimethyl disulfide (1.5 mL). Standard workup gave rise to a crude product, which, on bulb-to-bulb distillation (bp 105–110 °C/0.2 mmHg), afforded pure **5b** as an oil in 72% yield. ^{1}H NMR: 2.39 (s, 3 H), 3.40 (s, 3 H), 3.96 (s, 3 H), 4.56 (s, 2 H), 6.87 (d, 1 H, J = 8.4 Hz), 7.08 (d, 1 H, J = 8.4 Hz) ppm. IR (neat): 3420, 2950, 1580, 1480, 1420, 1290, 1270, 1220, 1100, 1040, 830 cm^{-1}. EIMS, m/e (percent, relative abundance): 214 (M^+, 62), 199 (100), 168 (51), 167 (42), 137 (99). Anal. Calcd for $C_{10}H_{14}O_3S$: C, 56.05; H, 6.58. Found: C, 56.03; H, 6.30.

Preparation of 4-Hydroxy-3-methoxy-2-methylbenzyl Alcohol (6c). The dianion solution of **5a**—prepared as illustrated for the case of **5b**—was quenched with methyl iodide (6 mL). Standard workup furnished a crude product, which was purified by chromatography on silica gel with $CHCl_3$–CH_3OH (100:1, v/v) as eluent. Final bulb-to-bulb distillation provided 4-hydroxy-3-methoxy-2-methylbenzyl methyl ether (**5c**) (bp 100 °C/0.01 mmHg) in 82% yield. ^{1}H NMR: 2.28 (s, 3 H), 3.35 (s, 3 H), 3.75 (s, 3 H), 4.35 (s, 2 H), 6.76 (d, 1 H, J = 8.4 Hz), 6.95 (d, 1 H, J = 8.4 Hz).

Hydrolysis of **5c** was best carried out by vigorously stirring a 200-mL solution of **5c** (1.7 g, 0.1 mol) in H_2O/THF (10:1, v/v) acidified with concentrated HCl (final pH 1.5). Stirring was continued for several hours until no starting material was present (TLC monitoring). Extractive workup gave crude material, which was purified by chromatography on silica gel ($CHCl_3$/CH_3OH, 100:2, v/v), thus furnishing pure **6c** in 63% yield, mp 134–5 °C (chloroform/hexane). ^{1}H NMR ($CDCl_3$/$(CD_3)_2CO$): 2.27 (s, 3 H), 3.57 (t, 1 H, J = 5.4 Hz, OH), 3.74 (s, 3 H), 4.55 (d, 2 H, J = 5.4 Hz), 6.68 (d, 1 H, J = 8.3 Hz), 6.95 (d, 1 H, J = 8.3 Hz) ppm. IR (KBr): 3490, 3290, 1600, 1510, 1490, 1350, 1305, 1290, 1285, 1005, 835 cm^{-1}. EIMS, m/e (percent, relative abundance): 168 (M^+, 100), 151 (36), 135 (30), 107 (64), 77 (36). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.18; H, 7.12.

Preparation of 4-Hydroxy-3-methoxy-2-(3-methyl-2-buten-1-yl)benzyl Alcohol (6d). As indicated previously, **5a** (0.68 g, 4 mmol) was converted into its dianion by the action of *n*-BuLi. Quenching the resulting mixture with 1-chloro-3-methyl-2-butene (1.7 g, 16 mmol), followed by the usual workup, provided **5d** in 72% yield. ^{1}H NMR: 1.69 (br s, 3 H), 1.78 (br s, 3 H), 3.35 (s, 3 H), 3.37 (d, 2 H, J = 6.5 Hz), 3.76 (s, 3 H), 4.34 (s, 2 H), 5.19 (br t, 1 H, J = 6.5 Hz), 6.78 (d, 1 H, J = 8.3 Hz), 6.99 (d, 1 H, J = 8.3 Hz). Hydrolysis of **5d** was carried out as described for the case of **5c**. Standard workup yielded the corresponding benzyl alcohol **6d** (55% isolated yield), mp 93–4 °C (methylene chloride/hexane). ^{1}H NMR: 1.69 (br s, 3 H), 1.78 (br s, 3 H), 3.44 (d, 2 H, J = 6.5 Hz), 3.74 (s, 3 H), 4.55 (s, 2 H), 5.11 (br t, 1 H, J = 6.5 Hz), 6.75 (d, 1 H, J = 8.3 Hz), 7.00 (d, 1 H, J = 8.3 Hz). IR (KBr): 3460, 3260, 1600, 1490, 1450, 1430, 1300, 1220, 1190, 1160, 1000 cm^{-1}. EIMS, m/e (percent, relative abundance): 222 (M^+, 58), 204 (43), 189 (73), 166 (79), 157 (100), 151 (83), 137 (37), 129 (66). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.99; H, 8.19.

Preparation of 2-Deuterio-4-hydroxy-3-methoxybenzyl Alcohol (6e). Treatment of a solution of the dianion of **5a** with deuterium oxide, followed by the usual workup procedure, provided a crude mixture of **5e** and **5a** (ca. 9:1) in 88% isolated yield, as revealed by integration of its ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$/$(CD_3)_2CO$): 3.36 (s, 3 H), 3.86 (s, 3 H), 4.37 (s, 2 H), 6.85 (s, 1 H), 7.37 (s, 1 H).

Hydrolysis of the above mixture, as illustrated for the case of **5c**, afforded **6e** (ca. 90% deuteriated), mp 114–5 °C. ^{1}H NMR: 3.90 (s, 3 H), 4.60 (s, 2 H), 6.86 (s, 2 H) ppm. IR (KBr): 3460, 3200, 1590, 1490, 1430, 1260, 1235, 1200, 1125, 1060, 1000, 840 cm^{-1}. EIMS, m/e (percent, relative abundance): 155 (M^+, 100), 154 (19), 138 (34), 126 (25), 94 (48), 66 (38). Anal. Calcd for $C_8H_9DO_3$: C, 61.92; H + D, 7.15. Found: C, 61.99; H + D, 6.85.

Preparation of 3-Hydroxy-2-methoxy-6-(methoxymethyl)benzaldehyde (5f). A solution of the dianion of **5a**—generated as above from **5a** (1.01 g, 6 mmol)—was treated with excess DMF (dry). Workup as usual furnished crude **5f** (75% yield), which was distilled (bulb-to-bulb) at 175 °C/2 mmHg, thus providing analytically pure **5f** (60% yield), which solidified on standing, mp 92–5 °C. ^{1}H NMR: 3.39 (s, 3 H), 3.44 (s, 3 H), 3.92 (s, 3 H), 4.71 (s, 2 H), 7.17 (d, 1 H, J = 8.2 Hz), 7.25 (d, 1 H, J = 8.2 Hz), 10.45 (s, 1 H) ppm. IR (KBr): 3200, 1655, 1570, 1370, 1300, 1240, 1230, 1115, 1060, 1000, 980, 820 cm^{-1}. EIMS, m/e (percent, relative abundance): 196 (M^+, 100), 181 (61), 164 (46), 163 (40), 149 (99), 137 (28), 135 (54), 121 (75), 107 (14). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.34; H, 6.23.

Preparation of 3-Hydroxy-2-methoxy-6-(methoxymethyl)benzoic Acid (5g). A solution of the dianion of **5a**, generated from **5a** (1.68 g, 10 mmol) and *n*-BuLi (1.5 M, 20 mL, 30 mmol) as shown previously, was quenched with solid carbon dioxide (excess). Standard extractive workup provided an acidic fraction containing **5g**, which crystallized from chloroform as needles (76% yield), mp 68–70 °C. ^{1}H NMR: 3.37 (s, 3 H), 3.91 (s, 3 H), 4.54 (s, 2 H), 6.63 (br s, 2 H), 7.02 (s, 2 H). IR (KBr): 3550, 3520–2200, 1700, 1330, 1290, 1270, 1245, 1070, 830 cm^{-1}. EIMS, m/e (percent, relative abundance): 212 (M^+, 35), 194 (28), 179 (100), 165 (39), 137 (27), 136 (27). Anal. Calcd for $C_{10}H_{12}O_5 \cdot H_2O$: C, 52.17; H, 6.10. Found: C, 51.99; H, 6.41.

3-Hydroxy-2-methoxy-6-(methoxymethyl)-α,α-diphenylbenzyl Alcohol (5h). The dianion of **5a** (1.01 g, 6 mmol), generated with *n*-BuLi (1.5 M, 12 mL, 18 mmol) as indicated above, was quenched with benzophenone, followed by the usual workup, thus providing crude **5h**, which crystallized from methylene chloride/hexane, mp 117–8 °C (50% isolated yield). ^{1}H NMR: 3.01 (s, 6 H), 3.67 (s, 2 H), 6.31 (s, 1 H), 6.92 (d, 1 H, J = 8.3 Hz), 7.09 (d, 1 H, J = 8.3 Hz), 7.31 (m, 10 H) ppm. IR (KBr): 3250, 1490, 1440, 1330, 1300, 1080, 1060, 1000, 980, 810 cm^{-1}. EIMS, m/e (percent, relative abundance): 350 (M^+, 3), 332 (100), 301 (29), 300 (29), 241 (21), 226 (22), 152 (24), 105 (65), 75 (95). Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.40; H, 6.28. Found: C, 74.92; H, 6.15.

Preparation of 3-Hydroxy-2-methoxy-6-(methoxymethyl)-α-phenylbenzyl Alcohol (5i). Treatment of the dianion of **5a** (from 0.67 g (4 mmol) of **5a** and 12 mmol of 1.5 M *n*-BuLi) with freshly distilled benzaldehyde (10 mmol), followed by the standard workup, furnished crude **5i**. Analytically pure **5i** was obtained by bulb-to-bulb distillation (bp 180 °C/0.03 mmHg) followed by crystallization (methylene chloride/hexane). ^{1}H NMR (CD_3OD): 3.21 (s, 3 H), 3.65 (s, 3 H), 4.05 (d, 1 H, J = 11.4 Hz), 4.27 (d, 1 H, J = 11.4 Hz), 6.30 (s, 1 H), 6.81 (d, 1 H, J = 8.3 Hz), 6.96 (d, 1 H, J = 8.3 Hz), 7.28 (m, 5 H) ppm. IR (KBr): 3200, 1300, 1180, 1160, 1140, 820 cm^{-1}. EIMS, m/e (percent, relative abundance): 247 (M^+, 2), 242 (68), 241 (100), 226 (25), 165 (19). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.19; H, 6.68.

Preparation of 3-Hydroxy-2,4-dimethoxy-6-(methoxymethyl)benzoic Acid (9g). A cooled (0 °C) solution of **9a** (1.2 g, 6 mmol) in dry THF was metalated with *n*-BuLi as described

previously. The resulting mixture was quenched, at −78 °C, with excess carbon dioxide. Standard extractive workup gave crude **9g** (80% yield), which crystallized from chloroform, mp 137–8 °C. ^{1}H NMR: 3.47 (s, 3 H), 4.04 (s, 3 H), 4.74 (s, 2 H), 7.03 (s, 1 H). IR (KBr): 3410, 3550–2400, 1725, 1610, 1395, 1305, 1260, 1230, 1180, 1105, 1080 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 242 (M^+, 27), 224 (15), 210 (16), 209 (100), 194 (11). Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.08; H, 5.78.

Preparation of 3-Hydroxy-2,4-dimethoxy-6-(methoxymethyl)-5-(methylthio)benzoic Acid (10g). Phenol **9a** (0.59 g, 3 mmol) was metalated with *n*-BuLi (1.5 M, 6 mL, 9 mmol) as above and then treated (at 0 °C) with dimethyl disulfide (0.9 mL). The standard workup provided crude **10a** in 89% yield (90% pure as revealed by ^{1}H NMR), which was used without further purification (bulb-to-bulb distillation produced extensive decomposition) for the subsequent metalation step. Thus, addition of *n*-BuLi (1.5 M, 6 mL, 9 mmol) to a cooled (0 °C) solution of crude **10a** (0.73 g, 3 mmol) in THF was followed by quenching (at −78 °C) with excess solid carbon dioxide. Standard workup provided crude **10g** in 47% yield. ^{1}H NMR: 2.33 (s, 3 H), 3.38 (s, 3 H), 3.94 (s, 3 H), 3.97 (s, 3 H), 4.80 (s, 2 H) ppm. EIMS, *m/e* (percent, relative abundance): 228 (M^+, 12), 270 (25), 255 (36), 241 (22), 237 (21), 227 (20), 209 (100), 181 (40). Since an analytically pure sample of **10g** could not be obtained, this compound was converted into the corresponding phthalide by treatment with trifluoroacetic anhydride in methylene chloride.[32] The so-formed phthalide,[32] mp 107–8 °C (methylene chloride/hexane), gave correct analytical and spectroscopic data. ^{1}H NMR: 2.40 (s, 3 H), 4.10 (s, 3 H), 4.24 (s, 3 H), 5.20 (s, 2 H), 5.96 (s, 1 H) ppm. IR (KBr): 3390, 1745, 1595, 1470, 1320 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 256 (M^+, 100), 241 (22), 227 (16), 223 (55). Anal. Calcd for $C_{11}H_{12}SO_5$: C, 51.55; H, 4.72. Found: C, 52.35; H, 4.54.

Fremy's Salt Promoted Oxidative Degradation of *p*-Hydroxybenzyl Alcohols and *p*-Hydroxybenzylamines. General Procedure.[2,3] A chloroform or ether solution of the phenolic substrate was treated with a PO_4HNa_2/PO_4H_2Na buffered solution (pH 6) of Fremy's salt (3 M excess) with stirring for the required period of time (TLC monitoring). Typical workup involved separation of the organic phase and further extraction of the aqueous solution. The combined extracts were then washed with water and dried over sodium sulfate. Evaporation of the solvent yielded yellow-orange residues, which were eventually crystallized or distilled (bulb-to-bulb).

2-Methoxy-3-methyl-1,4-benzoquinone (7c). This compound was prepared by oxidation of **6c** (0.1 g, 0.59 mmol) with Fremy's salt (0.5 g) as described above. Standard workup provided **7c** as an oil (89% yield), bp 90–5 °C (0.06 mmHg) (lit.[33] bp 55–60 °C/0.04 mmHg). ^{1}H NMR: 1.95 (s, 3 H), 4.02 (s, 3 H), 6.60 (d, 1 H, J = 8.2 Hz), 6.67 (d, 1 H, J = 8.2 Hz) ppm. IR (neat): 2950, 1660, 1450, 1380, 1310, 1210, 1160, 1090, 1020, 840 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 152 (M^+, 100), 140 (20), 139 (32), 125 (25), 122 (36), 111 (27), 109 (32), 85 (31), 83 (50), 81 (25).

2-Methoxy-3-(3-methyl-2-buten-1-yl)-1,4-benzoquinone (7d). Compound **7d** was obtained as an oil, bp 80–5 °C (0.09 mmHg), by oxidation of **6d** (0.066 g, 0.32 mmol). ^{1}H NMR: 1.67 (s, 3 H), 1.73 (s, 3 H), 3.14 (d, 2 H, J = 7.4 Hz), 4.02 (s, 3 H), 5.05 (br t, 1 H, J = 7.4 Hz), 6.60 (d, 1 H, J = 8.1 Hz), 6.64 (d, 1 H, J = 8.1 Hz) ppm. IR (neat): 3030, 1670, 1650, 1595, 1320, 1240, 1210, 1150, 1060, 845 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 206 (M^+, 34), 191 (83), 176 (62), 163 (100), 151 (21), 149 (22), 117 (24). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.94; H, 6.84.

3-Deuterio-2-methoxy-1,4-benzoquinone (7e). The titled compound was prepared in 90% yield from **6e** (0.06 g, 0.43 mmol) by treatment with Fremy's salt (0.35 g) according to the general procedure. Compound **7e** crystallized as yellow needles, mp 135–7 °C. ^{1}H NMR: 3.82 (s, 3 H), 6.71 (s, 2 H) ppm. IR (film): 2940, 1670, 1630, 1570, 1250, 1210, 1110, 800 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 139 (M^+, 83), 138 (6), 111 (33), 109 (74), 82 (40), 70 (100).

4-[(Dimethylamino)methyl]phenol (11). A mixture of 3.2 g (39.2 mmol) of dimethylamine hydrochloride, 2.6 g (31.6 mmol) of sodium acetate, and 2 g (28.6 mmol) of sodium cyanoborohydride (90–95% pure, Sigma) was dissolved in methanol (200 mL). The pH was adjusted to 7–8 (glacial HOAc). To a stirred solution was added 2.44 g (20 mmol) of *p*-hydroxybenzaldehyde. Stirring of the resulting mixture was maintained for 22 h at room temperature. Acetone was added, and the solution acidified (pH 1) with 2 N HCl. The organic solvent was removed in vacuo, and water (15 mL) was added. The mixture was extracted with ether, and the aqueous solution was made slightly basic (pH 8–9) and extracted with ether. Typically the pH of the aqueous solution had to be adjusted after every extraction with ether. Evaporation of the solvent furnished a pale yellow oil, which solidified (1.61 g, 53%). The hydrochloride crystallized from absolute ethanol, mp 194–5 °C (lit.[34] mp 194 °C). ^{1}H NMR: 2.25 (s, 6 H), 3.38 (s, 2 H), 6.64 (d, 2 H, J = 8.5 Hz), 7.10 (d, 2 H, J = 8.5 Hz) ppm. EIMS, *m/e* (percent, relative abundance): 151 (M^+, 84), 108 (10), 107 (55), 44 (41), 42 (100).

4-[(Dimethylamino)methyl]-2,6-dimethylphenol (12). A solution of 12.22 g (0.1 mol) of 2,6-dimethylphenol in 22.5 mL of 40% aqueous dimethylamine was stirred as formalin (10 mL, 0.125 mol) was added dropwise during 35 min. The solution was heated on a steam bath for 3 h. The resulting two-phase mixture was then separated with the aid of a small amount of ether. On evaporation, the organic phase solidified. The solid was filtered and washed with cold water. Recrystallization from methanol yielded **12**, mp 114–5 °C (lit.[35] mp 108–110 °C), in 70% yield. ^{1}H NMR: 2.20 (s, 12 H), 3.28 (s, 2 H), 6.88 (s, 2 H) ppm. IR (CCl_4): 3610, 2960, 2930, 2800, 1530, 1460, 1245, 1200, 1000, 965 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 179 (M^+, 41), 178 (20), 136 (28), 135 (100), 91 (36).

4-[[[2-(Dimethylamino)ethyl]methylamino]methyl]phenol (13). 4-Hydroxybenzaldehyde (3.66 g, 30 mmol) was added to a mixture of commercial *N,N,N'*-trimethylethylenediamine (6.12 g, 60 mmol), sodium acetate (3.9 g, 47.4 mmol), and sodium cyanoborohydride (3.15 g, 51 mmol) in methanol (120 mL). The mixture was stirred at 25 °C for 22 h, while the pH was adjusted with concentrated HCl to 7–8. Acetone was then added to the mixture and then 6 N HCl till pH 2–3 was reached. The solvent was removed in vacuo, and the residue was dissolved in water (50 mL) and extracted with ether (3 × 30 mL). The organic phase on evaporation yielded back 0.86 g of 4-hydroxybenzaldehyde. The remaining aqueous phase was made alkaline (pH 9–10) with 10% NaOH and extracted repeatedly with chloroform. The chloroform extracts were washed several times with 2% NaOH. The remaining chloroform phase yielded 2.5 g of the starting *N,N,N'*-trimethylethylenediamine on evaporation. The above 2% NaOH extracts were then treated with saturated ammonium chloride solution, and the resulting solution (pH 8–9) was extracted with chloroform (5 × 20 mL). The organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed in vacuo, thus yielding **13** as an oil (4.49 g). The picrate crystallized from absolute EtOH, mp 160–1 °C. ^{1}H NMR: 2.26 (s, 9 H), 2.52 (s, 4 H), 3.41 (s, 2 H), 6.56 (d, 2 H, J = 8.5 Hz), 7.05 (d, 2 H, J = 8.5 Hz) ppm. IR (CH_2Cl_2): 3680, 2960, 1605, 1590, 1505, 1420, 1250, 1020, 890 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 208 (M^+, 4), 150 (32), 108 (9), 107 (100). Anal. Calcd for $C_{24}H_{26}N_8O_{15}\cdot H_2O$: C, 42.10; H, 4.09; N, 16.37. Found: C, 41.88; H, 3.95; N, 16.49.

2-Methoxy-4-[(dimethylamino)methyl]phenol (14a, *N,N*-Dimethylvanillylamine). This compound was prepared as described.[36] Analytically pure material was obtained by bulb-to-bulb distillation (bp 120–130 °C/2 mmHg). ^{1}H NMR: 2.23 (s, 6 H), 3.36 (s, 2 H), 3.79 (s, 3 H), 6.75 (s, 2 H), 6.87 (s, 1 H) ppm. EIMS, *m/e* (percent, relative abundance): 181 (M^+, 100), 138 (34), 137 (69), 58 (30), 44 (22), 42 (60).

2,6-Dimethoxy-4-[(dimethylamino)methyl]phenol (15a, *N,N*-Dimethylsyringylamine). The titled compound was

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obtained from commercial 2,6-dimethoxyphenol as described by Short et al.,[36] mp 84–5 °C (lit.[36] mp 82–4 °C). ^{1}H NMR: 2.23 (s, 6 H), 3.34 (s, 2 H), 3.85 (s, 6 H), 6.54 (s, 2 H) ppm. EIMS, *m/e* (percent, relative abundance): 211 (M^+, 76), 168 (75), 167 (100).

4-[(Dimethylamino)methyl]-2-methoxy-6-methylphenol (17a). A solution of 1.38 g (10 mmol) of 2-methoxy-6-methylphenol[37] in 2.2 mL of 40% aqueous dimethylamine was stirred as formalin (1 mL, 12.5 mmol) was added dropwise. The solution was heated in a steam bath during 3 h. Extractive workup yielded **17a** (1.81 g, 93%), which crystallized from ether, mp 99–100 °C. ^{1}H NMR: 2.22 (s, 9 H), 3.34 (s, 2 H), 3.85 (s, 3 H), 6.65–6.69 (m, 2 H) ppm. EIMS, *m/e* (percent, relative abundance): 195 (M^+, 30), 152 (34), 151 (100). Anal. Calcd for $C_{11}H_{17}O_2N$: C, 67.66; H, 8.77; N, 7.17. Found: C, 67.51; H, 8.71; N, 6.88.

4-[[[2-(Dimethylamino)ethyl]methylamino]methyl]-2-methoxyphenol (18a). 4-Hydroxy-3-methoxybenzaldehyde (vanillin, 3.04 g, 20 mmol) was added to a mixture of *N,N,N'*-trimethylethylenediamine (4.08 g, 40 mmol), sodium acetate (2.6 g, 31.6 mmol), and sodium cyanoborohydride (3.01 g, 48.3 mmol) in 40 mL of methanol. The pH of the mixture was adjusted to neutrality (7–8) with concentrated HCl and then stirred at room temperature for 24 h. Acetone was added to the mixture and then 6 N HCl till pH 2–3 was reached. The solvent was removed under reduced pressure, and the residue taken up in water (30 mL) and extracted with methylene chloride. The organic phase on evaporation yielded back 0.5 g of unaltered vanillin. The remaining aqueous phase was made basic (pH 9–10) with 10% NaOH and extracted repeatedly with methylene chloride. These extracts were then extracted with 2% NaOH several times. The remaining organic phase yielded on evaporation 0.97 g of unchanged *N,N,N'*-trimethylethylenediamine. The above 2% NaOH extracts were treated with saturated ammonium chloride solution and then (pH 8–9) extracted with methylene chloride (6 × 25 mL). The organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed in vacuo, thus yielding **18a** as an oil (3.75 g), which slowly solidified, mp 65–6 °C. ^{1}H NMR: 2.35 (s, 9 H), 2.60 (s, 4 H), 3.55 (s, 2 H), 3.94 (s, 3 H), 6.86 (s, 2 H), 7.00 (s, 1 H) ppm. IR (CCl_4): 3560, 2940, 2820, 2770, 1540, 1250, 1235, 1005, 980 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 238 (M^+, 4), 180 (20), 137 (100), 122 (6), 94 (5), 58 (23). Anal. Calcd for $C_{13}H_{22}O_2N_2$: C, 65.52; H, 9.30; N, 11.75. Found: C, 65.52; H, 9.57; N, 11.45.

Attempted Lithiation of Phenolic Benzylamines 11–13. The titled phenolic benzylamines (typically 2 mmol) dissolved in THF were treated with *n*-BuLi (6 mmol) as described in the general procedure. The resulting mixtures were then quenched with dimethyl disulfide (6 mmol). The mixture was stirred for 2–4 h and finally worked up as usual. 4-[(Dimethylamino)-methyl]phenol (**11**) was recovered unchanged (61%) after its reaction with *n*-BuLi/Me_2S_2, as illustrated above. 4-[(Dimethylamino)methyl]-2,6-dimethylphenol (**12**) yielded unaltered starting material **12** (80%) on treatment with *n*-BuLi/Me_2S_2 as described above. 4-[[[2-(Dimethylamino)ethyl]methylamino]-methyl]phenol (**13**) was recovered unaltered (70%) after its reaction with *n*-BuLi/DMF, as described above.

4-[(Dimethylamino)methyl]-2-methoxy-3-(methylthio)-phenol (14b). A cooled (0 °C) solution of *N,N*-dimethylvanillylamine (**14a**) (0.54 g, 3 mmol) was treated with *n*-BuLi (1.5 M, 6 mL, 9 mmol) as illustrated in the general procedure and then quenched with dimethyl disulfide (1 mL). The standard extractive workup provided **14b** in 86% yield as a viscous oil, bp 110 °C (0.001 mmHg). ^{1}H NMR: 2.24 (s, 6 H), 2.37 (s, 3 H), 3.58 (s, 2 H), 3.93 (s, 3 H), 6.79 (d, 1 H, J = 8 Hz), 7.00 (d, 1 H, J = 8 Hz). IR (film): 3200 (br), 2960, 2930, 2850, 2820, 2770, 1580, 1560, 1460, 1280, 1040, 1020 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 227 (M^+, 28), 212 (69), 183 (10), 168 (24), 167 (21), 137 (27), 58 (100). Anal. Calcd for $C_{11}H_{17}O_2SN$: C, 58.14; H, 7.48; N, 6.16. Found: C, 58.05; H, 7.21; N, 6.08.

3-Deuterio-4-[(dimethylamino)methyl]-2-methoxyphenol (14e). Lithiated *N,N*-dimethylvanillylamine **14a** (0.54 g, 3 mmol) was treated, as shown in the general procedure, with deuterium oxide (1 mL). The usual workup provided **14e** in 93% yield (over 90% deuterium incorporation). ^{1}H NMR: 2.23 (s, 6 H), 3.37 (s, 2 H), 3.81 (s, 3 H), 6.77 (d, 1 H, J = 8 Hz), 6.87 (d, 1 H, J = 8 Hz) ppm. IR (film): 3300 (br), 2975, 2930, 2880, 2845, 2810, 1590, 1580, 1485, 1455, 1260, 1185, 1110, 1050 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 182 (M^+, 27), 181 (14), 139 (24), 138 (82), 137 (15), 123 (16), 95 (19), 58 (100).

4-[(Dimethylamino)methyl]-2-methoxy-3-(phenylthio)-phenol (14j). The dilithio derivative of **14a**—generated as shown in the general procedure—was treated with excess diphenyl disulfide. Standard extractive workup yielded crude **14j** in good yield (77%). A pure sample was obtained by bulb-to-bulb distillation at 210–5 °C (0.02 mmHg) (extensive decomposition). ^{1}H NMR: 2.20 (s, 6 H), 3.50 (s, 2 H), 3.81 (s, 3 H), 6.90–7.24 (m, 7 H) ppm. EIMS, *m/e* (percent, relative abundance): 289 (M^+, 74), 274 (100), 243 (35), 229 (31), 178 (17), 137 (10), 121 (20), 77 (18). Exact mass: calcd for $C_{16}H_{19}O_2SN$ 289.1136, obsd 289.1153.

4-[(Dimethylamino)methyl]-2,6-dimethoxy-3-(methylthio)phenol (15b). The dilithio derivative of **15a**—generated by direct lithiation of **15a** (0.63 g, 3 mmol)—was quenched with dimethyl disulfide (0.8 mL). Standard workup provided **15b** in high yield (98%), which crystallized from ether, mp 112–3 °C. ^{1}H NMR: 2.26 (s, 6 H), 2.30 (s, 3 H), 3.66 (s, 2 H), 3.87 (s, 3 H), 3.96 (s, 3 H), 6.82 (s, 1 H) ppm. IR (CCl_4): 3550, 2960, 2930, 2845, 2810, 2765, 1595, 1485, 1300, 1100 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 257 (M^+, 20), 242 (100), 212 (12), 198 (24), 197 (58), 151 (26). Anal. Calcd for $C_{12}H_{19}O_3SN$: C, 56.00; H, 7.44; N, 5.44. Found: C, 55.89; H, 7.58; N, 5.35.

4-[(Dimethylamino)methyl]-2,6-dimethoxy-3-methylphenol (15c). To the cooled (−30 °C) mixture obtained by standard metalation of 0.42 g (2 mmol) of **15a** was added methyl iodide (1 mL). The mixture rapidly became transparent and homogeneous. After 7 min (no precipitate was formed at this point) water was added, followed by the usual workup. The resulting crude material (0.4 g) was chromatographed on alumina (Merck grade I; ether), thus yielding crystalline **15c**, mp 115–6 °C (ether). ^{1}H NMR: 2.20 (s, 3 H), 2.24 (s, 6 H), 3.32 (s, 2 H), 3.81 (s, 3 H), 3.86 (s, 3 H), 6.66 (s, 1 H) ppm. IR (CCl_4): 3550, 2940, 2845, 2810, 2760, 1610, 1300, 1120 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 225 (M^+, 29), 182 (9), 181 (57), 180 (100), 165 (48), 58 (53). Anal. Calcd for $C_{12}H_{19}O_3N$: C, 63.97; H, 8.50; N, 6.21. Found: C, 64.06; H, 8.45; N, 6.09.

When the reaction was run at higher temperatures (0 °C) for longer reaction times, symmetrical diarylmethane was obtained as the major product.

3-Deuterio-4-[(dimethylamino)methyl]-2,6-dimethoxyphenol (15e). A solution of the dianion of **15a**—generated from **15a** (0.42 g, 2 mmol) as shown previously—was quenched with deuterium oxide (1 mL). The standard workup provided **15e** in 95% yield (over 90% deuterium incorporation). ^{1}H NMR: 2.24 (s, 6 H), 3.36 (s, 2 H), 3.86 (s, 6 H), 6.56 (s, 1 H) ppm. EIMS, *m/e* (percent, relative abundance): 212 (M^+, 39), 211 (15), 169 (61), 168 (100), 154 (8), 58 (24). Anal. Calcd for $C_{11}H_{16}DO_3N$: C, 53.11; H, 7.69; N, 5.63. Found: C, 53.13; H, 7.70; N, 5.52.

3-Hydroxy-6-[(dimethylamino)methyl]-2,4-dimethoxy-α-phenylbenzyl Alcohol (15i). Recently distilled benzaldehyde (1 mL) was added to a cooled solution of the dianion of **15a**, prepared from 3 mmol of phenol **15a** and 9 mmol of *n*-BuLi as indicated above. Standard workup provided crude **15i** (0.85 g), which was chromatographed on silica gel 60 (Merck), with ethyl acetate as eluent, thus yielding **15i** as crystals, mp 173–4 °C (absolute ethanol). ^{1}H NMR: 2.09 (s, 6 H), 2.45 (d, 1 H, J = 12.5 Hz), 3.23 (d, 1 H, J = 12.5 Hz), 3.87 (s, 3 H), 3.94 (s, 3 H), 6.31 (s, 1 H), 6.46 (s, 1 H), 7.20–7.37 (m, 5 H) ppm. IR (KBr): 3150 (br), 2955, 2820, 2780, 1600, 1580, 1260, 1240, 1130 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 317 (M^+, 1), 272 (61), 271 (100), 256 (13), 195 (12), 77 (11). Anal. Calcd for $C_{18}H_{23}O_4N$: C, 68.11; H, 7.30; N, 4.41. Found: C, 67.42; H, 7.49; N, 4.52.

4-[(Dimethylamino)methyl]-2-methoxy-6-methyl-3-(methylthio)phenol (17b). The cloudy ether solution of dilithiated **17a**, prepared from 0.39 g (2 mmol) of **17a** as illustrated in the general procedure, was quenched at 0 °C with dimethyl disulfide (0.6 mL). After the usual workup, crude **17b** (0.32 g) was chromatographed on alumina (Merck grade I, ether), thus furnishing **17b** as an oil, which slowly solidified. The hydrochloride of **17b** crystallized from absolute ethanol, mp 199–200 °C. ^{1}H NMR: 2.25 (s, 9 H), 2.34 (s, 3 H), 3.55 (s, 2 H), 3.96 (s, 3 H), 6.93

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(s, 1 H) ppm. IR (CCl_4): 3530, 2960, 2920, 2840, 2805, 2760, 1530, 1265, 1100 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 241 (M^+, 6), 226 (80), 182 (22), 181 (50), 85 (22), 83 (42), 44 (100). Anal. Calcd for $C_{12}H_{19}O_2SN$: C, 51.88; H, 7.25; N, 5.04. Found: C, 51.12; H, 7.16; N, 4.77.

6-[(Dimethylamino)methyl]-3-hydroxy-2-methoxy-4,α-dimethyl-α-(4-methyl-3-penten-1-yl)benzyl Alcohol (17k). To a cooled suspension of **17a** (0.39 g, 2 mmol) in 40 mL of anhydrous ether was added 6 mmol of *n*-BuLi (1.0 M), and the stirring at 0 °C was maintained for 30 min. The ice bath was removed, and the mixture was stirred overnight, recooled to −60 °C, and quenched with commercial 6-methyl-5-hepten-2-one (0.9 mL). The mixture was kept at −60 °C for 48 h and then worked up as usual. This provided **17k** (0.41 g, 64%) as a solid, which sublimed, mp 125–6 °C, together with unreacted starting material **17a** (25%). ^1H NMR: 1.50 (s, 3 H), 1.59 (s, 3 H), 1.6 (s, 3 H), 2.20 (s, 9 H), 3.49 (d, 1 H, J = 12 Hz), 3.64 (d, 1 H, J = 12 Hz), 3.76 (s, 3 H), 5.02 (m, 1 H), 6.62 (s, 1 H) ppm. IR (CCl_4): 3560, 3150, 2970, 2920, 2880, 2820, 2780, 1450, 1400, 1360, 1270, 1205, 1040 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 321 (M^+, 4), 306 (4), 290 (6), 276 (7), 238 (51), 194 (55), 193 (100), 179 (32), 178 (34), 135 (8), 91 (10). Anal. Calcd for $C_{19}H_{31}O_3N$: C, 70.99; H, 9.72; N, 4.35. Found: C, 70.85; H, 9.48; N, 4.05.

Working at higher temperatures led to poorer results as the metalated **17a** was rapidly protonated by the ketone. Best results were obtained by working with ether rather than THF.

4-[[[2-(Dimethylamino)ethyl]methylamino]methyl]-2-methoxy-3-(methylthio)phenol (18b). The dilithio derivative of **18a**, prepared as previously shown from **18a** (0.95 g, 4 mmol), was treated at 0 °C with dimethyl disulfide (0.117 g, 12 mmol). The usual workup provided 0.94 g of **18b** as a tan oil. Neither bulb-to-bulb distillation in vacuo—which produced extensive decomposition—nor crystallization of the free base or hydrochloride allowed us to have analytically pure samples of **18b**. ^1H NMR: 2.24 (s, 9 H), 2.36 (s, 3 H), 2.52 (s, 4 H), 3.63 (s, 2 H), 6.79 (d, 1 H, J = 8.3 Hz), 7.00 (d, 1 H, J = 8.3 Hz) ppm. EIMS, *m/e* (percent, relative abundance): 284 (M^+, 4), 237 (2), 226 (18), 183 (100), 168 (37), 137 (47), 93 (9), 58 (33).

4-[(Dimethylamino)methyl]-2,6-dimethoxy-3,5-bis(methylthio)phenol (16b). Phenol **15b** (0.77 g, 3 mmol) was lithiated as illustrated in the general procedure and then quenched with dimethyl disulfide (0.81 mL). The standard workup yielded crude **16b**, which was chromatographed on a silica gel column with ether as eluent. This provided 0.76 g (83% yield) of oily **15b**, which could not be induced to crystallize (either as free base, hydrochloride, or oxalate), whereas attempted bulb-to-bulb distillation in vacuo gave rise to extensive decomposition. Their spectroscopic properties are, however, in accordance with structure **15b**. ^1H NMR: 2.24 (s, 6 H), 2.35 (s, 6 H), 3.91 (s, 2 H), 3.98 (s, 6 H) ppm. IR (CCl_4): 3530, 2960, 2925, 2850, 2760, 1540, 1480, 1295, 1080 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 303 (M^+, 26), 288 (71), 258 (56), 243 (77), 228 (100), 167 (34), 149 (63).

5-Deuterio-4-[(dimethylamino)methyl]-2,6-dimethoxy-3-(methylthio)phenol (16e). The dilithio derivative of **15b**, prepared as shown in the general procedure from 0.68 g (2.64 mmol) of **15b**, was quenched with deuterium oxide (1 mL) and then worked up as usual. This provided 0.58 g of crude **16e**, which crystallized from ether, mp 112–3 °C. ^1H NMR: 2.26 (s, 6 H), 2.30 (s, 3 H), 3.65 (s, 2 H), 3.87 (s, 3 H), 3.96 (s, 3 H) ppm. IR (CCl_4): 3545, 2960, 2930, 2840, 2810, 2765, 1590, 1470, 1295, 1100 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 258 (M^+, 29), 257 (6), 244 (15), 243 (100), 213 (15), 199 (30), 198 (43), 152 (15). Anal. Calcd for $C_{12}H_{18}DO_3SN$: C, 55.78; H, 7.80; N, 5.42. Found: C, 55.65; H, 7.53; N, 5.08.

6-[(Dimethylamino)methyl]-3-hydroxy-2,4-dimethoxy-5-(methylthio)-α-phenylbenzyl Alcohol (16i). Freshly distilled benzaldehyde (1 mL) was added to a cooled (−78 °C) solution of the dianion of **15b**, generated from **15b** (0.77 g, 3 mmol) as indicated in the general procedure. The bath was removed, and the stirring was continued for 1 h. The usual workup yielded a crude material, which was chromatographed on a silica gel column with ether as eluent. This provided **16i** in 80% yield, which crystallized as the hydrochloride (EtOH), mp 181–2 °C. ^1H NMR: 2.16 (s, 6 H), 2.26 (s, 3 H), 2.98 (d, 1 H, J = 12.7 Hz), 3.98 (d, 1 H, J = 12.7 Hz), 3.91 (s, 3 H), 3.96 (s, 3 H), 6.43 (s, 1 H), 7.18–7.44 (m, 5 H) ppm. IR (CCl_4): 3520, 3100, 2950, 2920, 2840, 2760, 1635, 1605, 1425, 1400, 1275, 1270, 1090, 1065 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 363 (M^+, 7), 319 (19), 318 (82), 317 (100), 303 (14), 287 (15), 271 (11), 242 (11). Anal. Calcd for $C_{19}H_{25}O_4NS{\cdot}HCl{\cdot}H_2O$: C, 54.61; H, 6.70; N, 3.35. Found: C, 54.65; H, 6.70; N, 3.09.

2-Methoxy-1,4-benzoquinone (7a). This compound was obtained in 80% yield by Fremy's salt oxidation of **14a** (0.18 g, 1 mmol) as described in the general procedure, mp 138–9 °C (lit.[38] mp 140 °C). ^1H NMR: 3.83 (s, 3 H), 5.94 (s, 1 H), 6.71 (s, 3 H) ppm.

3-(Methylthio)-2-methoxy-1,4-benzoquinone (7b). This compound, prepared by oxidation of **14b** (0.23 g, 1 mmol) as illustrated in the general procedure, was isolated in 65% yield as an oil, bp 80–3 °C (0.005 mmHg). ^1H NMR: 2.54 (s, 3 H), 4.07 (s, 3 H), 6.58 (d, 1 H, J = 10 Hz), 6.74 (d, 1 H, J = 10 Hz) ppm. IR (film): 2950, 2850, 1640, 1550, 1440, 1325, 1310, 1265, 1210, 1160, 1040, 940, 840 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 186 (M^+ + 2, 23), 184 (M^+, 81), 169 (100), 141 (10), 139 (13), 137 (13), 123 (21), 113 (17), 87 (26), 85 (28). Anal. Calcd for $C_8H_8O_3S$: C, 52.16; H, 4.38. Found: C, 52.23; H, 4.53.

3-Deuterio-2-methoxy-1,4-benzoquinone (7e). The titled compound was obtained by Fremy's salt oxidation of **14e** (0.18 g, 1 mmol) as a yellow solid in 71% yield (over 90% deuterium incorporation as measured by ^1H NMR), having spectroscopic properties identical with those of **7e** obtained from **6e** (vide supra).

2,6-Dimethoxy-1,4-benzoquinone (19a). This compound was obtained by Fremy's salt oxidation of **15a** (0.21 g, 1 mmol) as yellow crystals, mp 250–2 °C (lit.[39] mp 249 °C). ^1H NMR: 3.83 (s, 6 H), 5.85 (s, 2 H) ppm.

2,6-Dimethoxy-3-methyl-1,4-benzoquinone (19c). The titled compound was obtained by standard Fremy's salt oxidation of crude **15c** (0.4 g, 1.73 mmol)—derived from lithiation/methylation of 2 mmol of **15a**—in an overall 69% yield, mp 125–6 °C (lit.[40] mp 125 °C). ^1H NMR: 1.96 (s, 3 H), 3.80 (s, 3 H), 3.96 (s, 3 H), 5.84 (s, 1 H) ppm. IR (CCl_4): 2930, 2840, 1680, 1640, 1600, 1540, 1285, 1240, 1110, 1000, 975 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 182 (M^+, 48), 167 (10), 149 (14), 139 (76), 111 (40), 83 (100).

3-Deuterio-2,6-dimethoxy-1,4-benzoquinone (19e). This compound was isolated in 90% yield from the Fremy's salt oxidation of **15e** (0.21 g, 1 mmol), mp 254–5 °C. ^1H NMR: 3.81 (s, 6 H), 5.85 (s, 1 H) ppm. IR (KBr): 1690, 1630, 1580, 1290, 1245, 1200, 1110 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 169 (M^+, 49), 141 (8), 139 (14), 126 (13), 98 (13), 70 (100). Anal. Calcd for $C_8H_7DO_4$: C, 56.85; H, 5.10. Found: C, 56.81; H, 5.35.

2,6-Dimethoxy-3,5-bis(methylthio)-1,4-benzoquinone (20b). This compound was obtained by oxidation of **16b** (0.09 g, 0.3 mmol) as an oil (90% yield), which distilled at 115–120 °C (0.02 mmHg) with partial decomposition. ^1H NMR: 2.52 (s, 6 H), 4.03 (s, 6 H) ppm. IR (CCl_4): 1690, 1660, 1260, 1080 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 260 (M^+, 100), 245 (34), 227 (10), 211 (12), 199 (14), 189 (23), 161 (34). Exact mass: calcd for $C_{10}H_{12}O_4S_2$ 260.0177, obsd 260.0164.

2,6-Dimethoxy-3-(methylthio)-5-(α-hydroxy-α-phenylmethyl)-1,4-benzoquinone (20i). This compound was obtained (87% yield) by Fremy's salt oxidation of **16i** in a very slow reaction (6 h). Quinone **20i** distilled (with extensive decomposition) at 170–180 °C (0.03 mmHg). ^1H NMR: 2.50 (s, 3 H), 3.99 (s, 3 H), 5.95 (s, 1 H), 7.20–7.59 (m, 5 H) ppm. IR (CCl_4): 3540, 1680, 1635, 1250, 1080 cm^{-1}. EIMS, *m/e* (percent, relative abundance): 320 (M^+, 100), 305 (22), 302 (36), 259 (37), 227 (24), 199 (43), 165 (32), 105 (73), 77 (81). ^{13}C NMR: 16.21, 60.74, 61.20, 68.45, 125.14, 127.06, 128.41, 130.17, 142.0, 153.51, 176.80, 185.53 ppm. Exact mass: calcd for $C_{16}H_{16}O_5S$ 320.0718, obsd 320.0743.

2-Methoxy-6-methyl-1,4-benzoquinone (21a). Quinone **21a**, prepared in 95% yield by Fremy's salt oxidation of **17a** (0.19 g, 1 mmol), was isolated as a solid, mp 148–9 °C (lit.[41] mp 151 °C). ^1H NMR: 2.06 (d, 3 H, J = 1.6 Hz), 3.81 (s, 3 H), 5.86 (s, 1 H), 6.52 (d, 1 H, J = 1.6 Hz) ppm.

3-(2-Hydroxy-6-methyl-5-hepten-2-yl)-2-methoxy-6-

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methyl-1,4-benzoquinone (21k). The titled compound was obtained by oxidation of **17k** (45 mg, 0.14 mmol) as described in the general procedure. The crude material obtained was chromatographed on a silica gel column with ether as eluent, thus yielding **21k** in 75% yield. ^{1}H NMR: 1.52 (s, 3 H), 1.55 (s, 3 H), 1.62 (s, 3 H), 2.02 (d, 3 H, J = 1.5 Hz), 3.99 (s, 3 H), 5.05 (m, 1 H), 6.47 (q, 1 H, J = 1.5 Hz) ppm. IR (CCl_4): 3460, 2950, 2920, 2850, 1715, 1670, 1650, 1620, 1270, 1070 cm^{-1}. EIMS, m/e (percent, relative abundance): 278 (M^+, 21), 260 (29), 245 (12), 220 (34), 217 (13), 205 (27), 196 (75), 195 (100), 181 (48), 178 (42), 149 (22), 83 (33), 69 (52), 43 (87). ^{13}C NMR: 14.68, 17.47, 22.89, 25.48, 28.52, 42.26, 61.24, 72.58, 124.30, 131.44, 134.51, 134.78, 143.10, 155.09, 181.61, 183.80. Exact mass: calcd for $C_{16}H_{22}O_4$ 278.1518, obsd 278.1508.

2-Methoxy-6-(methoxymethyl)phenol (22). The titled compound was prepared by the general method of DeJonge et al.[31] and was isolated as an oil, bp 160 °C (2 mmHg) [lit.[42] bp 128–130 °C (0.18 mmHg)]. ^{1}H NMR: 3.41 (s, 3 H), 3.87 (s, 3 H), 4.56 (s, 2 H), 6.83 (m, 3 H) ppm.

Attempted Lithiation of 2-Methoxy-6-(methoxymethyl)-phenol (22). A cooled (0 °C) THF solution of **22** (0.31 g, 2 mmol) was treated with 1 M n-BuLi (6 mL, 6 mmol) as illustrated in the general procedure, followed by quenching with methyl iodide (0.56 g). Extractive workup furnished crude material (0.2 g, which, on chromatography (silica gel, chloroform/ether (95:5)), yielded unchanged **22** (40 mg) and the Wittig rearrangement product **23** (0.1 g, 32% yield). ^{1}H NMR: 1.52 (d, 3 H, J = 6.6 Hz), 3.78 (s, 3 H), 5.10 (q, 1 H, J = 6.6 Hz), 6.81 (s, 3 H) ppm. EIMS, m/e (percent, relative abundance): 168 (M^+, 14), 152 (7), 151 (49), 150 (100), 135 (32), 107 (67), 91 (19), 79 (26), 78 (15), 77 (46). IR (film): 3500–3300 (br), 1610, 1590, 1475, 1440, 1270, 1220, 1060, 1010 cm^{-1}.

6-[(Dimethylamino)methyl]-2-methoxyphenol (24a, *N,N*-Dimethyl-*o*-vanillylamine). A solution of 2-hydroxy-3-methoxybenzaldehyde (*o*-vanillin, 3.04 g, 20 mmol) in methanol (40 mL) was added to a mixture of 3.48 g (42.7 mmol) of dimethylamine hydrochloride, sodium acetate (2.73 g, 33.3 mmol), and 1.46 g (23.2 mmol) of sodium cyanoborohydride in methanol (100 mL). The pH of the solution was maintained throughout the reaction in the range 7–8, if necessary by the addition of concentrated HCl. The solution was stirred at room temperature during 24 h. Acetone was then added, followed by 6 N HCl (until pH 2–3 was reached). The solvent was removed in vacuo, and the residue was dissolved in water (50 mL) and extracted with ether (4 × 15 mL). The organic phase on evaporation of the solvent yielded a mixture of starting aldehyde and the corresponding alcohol (0.5 g). The remaining aqueous phase was made basic (pH 8–9) and extracted with ether (10 × 25 mL). The organic extracts were dried, and the solvent was removed in vacuo, thus yielding an amber oil residue (2.85 g, 78%), which on distillation (bp 180–5 °C/2 mmHg) yielded pure **24a** (2.56 g, 71% yield) as an oil, which slowly solidified. Recrystallization from hexane gave needles mp 48–50 °C (lit.[43] mp 50–1 °C). ^{1}H NMR: 2.31 (s, 6 H), 3.63 (s, 2 H), 3.86 (s, 3 H), 6.61–6.76 (m, 3 H) ppm.

2-[(Dimethylamino)methyl]-5-methoxyphenol (25a). The titled compound was obtained from 2-hydroxy-4-methoxybenzaldehyde (1 g, 6.6 mmol) as described above for the case of **24a**. Bulb-to-bulb distillation (bp 175–180 °C/2 mmHg) of crude **25a** afforded pure **25a** in 77% yield as a yellowish oil. ^{1}H NMR: 2.29 (s, 6 H), 3.55 (s, 2 H), 3.74 (s, 3 H), 6.32 (d, 1 H, J = 8 Hz), 6.37 (s, 1 H), 6.81 (d, 1 H, J = 8 Hz) ppm. EIMS, m/e (percent, relative abundance): 181 (M^+, 57), 166 (1), 138 (35), 137 (97), 136 (15), 108 (10), 91 (19). Anal. Calcd for $C_{10}H_{15}O_2N$: C, 66.29; H, 8.28; N, 7.73. Found: C, 66.35; H, 8.30; N, 7.73.

2-[(Dimethylamino)methyl]-4-methoxyphenol (26a). This compound was prepared, as illustrated for the cases of **24a** and **25a**, by treatment of 2-hydroxy-5-methoxybenzaldehyde (3.04 g, 20 mmol) with dimethylamine hydrochloride (3.48 g, 42.7 mmol) and sodium cyanoborohydride (1.46 g, 23.2 mmol) in methanol (140 mL) containing 2.73 g (33.3 mmol) of sodium acetate. The usual workup furnished crude **26a** as an oil, which, on distillation (bp 160–5 °C/2 mmHg), afforded 2.4 g (63%) of pure **26a**, mp 49–51 °C (hexane) (lit.[44] mp 47 °C). ^{1}H NMR: 2.30 (s, 6 H), 3.54 (s, 2 H), 3.73 (s, 3 H), 6.53 (s, 1 H), 6.73 (s, 2 H) ppm. EIMS, m/e (percent, relative abundance): 181 (M^+, 93), 166 (12), 138 (47), 137 (33), 136 (76), 108 (33), 91 (20).

5-[(Dimethylamino)methyl]-2-methoxyphenol (27a, *N,N*-Dimethylisovanillylamine). Isovanillin (4 g, 26.3 mmol) was reacted, as illustrated for the previous cases, with dimethylamine hydrochloride (4.64 g, 56.9 mmol) and sodium cyanoborohydride (2.88 g, 45.7 mmol) in methanol (200 mL) containing sodium acetate (3.64 g, 44.4 mmol). Standard workup yielded crude **27a** as an oil, which, on distillation, afforded pure **27a** (87% yield),[20] mp 71–3 °C (hexane). ^{1}H NMR (C_5D_5N): 2.18 (s, 6 H), 3.35 (s, 2 H), 3.72 (s, 3 H), 6.91 (s, 2 H), 7.28 (s, 1 H). EIMS, m/e (percent, relative abundance): 181 (M^+, 25), 180 (14), 138 (31), 137 (100), 122 (15), 94 (13). Anal. Calcd for $C_{10}H_{15}O_2N$: C, 66.29; H, 8.28; N, 7.73. Found: C, 66.32; H, 8.48; N, 8.02.

2-[(Dimethylamino)methyl]-4,5-dimethoxyphenol (28a). A solution of 2.31 g (15 mmol) of 3,4-dimethoxyphenol in 3.3 mL of 40% aqueous dimethylamine was stirred with 0.6 g (20 mmol) of paraformaldehyde in 7.5 mL of ethanol. The solution, after being heated on a steam bath for 3 h, was treated with water, and the volatiles were removed in vacuo. Extractive workup yielded a crude residue, which solidified on standing (2.53 g, 79%). An analytically pure sample was obtained by bulb-to-bulb distillation at 160 °C (1.5 mmHg), mp 50–2 °C (hexane). ^{1}H NMR: 2.31 (s, 6 H), 3.55 (s, 2 H), 3.79 (s, 3 H), 3.83 (s, 3 H), 6.44 (s, 1 H), 6.48 (s, 1 H) ppm. EIMS, m/e (percent, relative abundance): 211 (M^+, 63), 196 (21), 168 (14), 167 (86), 166 (80), 151 (25), 139 (32), 138 (100), 123 (46), 109 (29), 95 (65). Anal. Calcd for $C_{11}H_{17}O_3N$: C, 62.55; H, 8.05; N, 6.63. Found: C, 62.41; H, 8.15; N, 6.70.

General Procedure for the Direct Metalation of Phenolic Substrates with *t*-BuLi. An oven-dried three-necked flask was charged with the phenolic substrate (typically 2 mmol) and purged with argon for 15 min. Dry THP (2 mL) was then introduced into the flask with a syringe. The resulting solution was cooled to −15 °C. To the stirred solution was added 1.3 M t-BuLi (6 mmol) dropwise via syringe. The bath was then removed while a slow stream of argon was maintained during 75–90 min, thus giving rise to a orange solid paste to which the appropriate electrophile was eventually added. Workup involved treatment with water, removal of volatiles in vacuo, and final extraction with ether, both at pH 12 and pH 9. The extracts were then dried over anhydrous sodium sulfate and evaporated to dryness, thus providing a crude material, which was then chromatographed or bulb-to-bulb distilled. The use of less concentrated THP solutions led to significantly lower yields.

4-[(Dimethylamino)methyl]-3-hydroxy-2-methoxy-α,α-diphenylbenzyl Alcohol (24h). Treatment of 0.4 g (2.21 mmol) of **24a** with t-BuLi as indicated above furnished a red-orange paste, which was reacted with 0.85 g (4.68 mmol) of benzophenone. The standard extractive workup provided two fractions: fraction B (pH 8) was proven (^{1}H NMR) to be mostly starting phenol **24a** (0.06 g), while fraction A (pH 12) was a mixture of several products. Preparative thin-layer chromatography of fraction A (silica gel plates, ether) gave 0.12 g (15%) of **24h**, mp 130–1 °C. ^{1}H NMR: 2.31 (s, 6 H), 3.26 (s, 3 H), 3.62 (s, 2 H), 5.93 (d, 1 H, J = 7.9 Hz), 6.50 (d, 1 H, J = 7.9 Hz), 7.29 (s, 10 H). EIMS, m/e (percent, relative abundance): 363 (M^+, 36), 286 (12), 285 (14), 258 (8), 241 (7), 227 (29), 105 (100), 77 (50). Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.03; H, 6.89; N, 3.86. Found: C, 76.39; H, 7.14; N, 3.78.

5-[(Dimethylamino)methyl]-4-hydroxy-2-methoxy-α,α-diphenylbenzyl Alcohol (25h). A solution of 0.4 g (2.21 mmol) of **25a** in 2 mL of THP was treated with t-BuLi (4.68 mmol) as illustrated in the general procedure and then reacted with benzophenone (0.85 g, 4.68 mmol). Extractive workup (pH 12) yielded a crude mixture (1.1 g), which was chromatographed on a silica gel column with hexane/ether as eluent. This furnished pure **25h**, mp 170–2 °C, in 37% isolated yield. ^{1}H NMR: 2.25 (s, 6 H), 3.39 (s, 2 H), 3.58 (s, 3 H), 6.03 (s, 1 H), 6.46 (s, 1 H), 7.23 (s, 10 H). EIMS, m/e (percent, relative abundance): 363 (M^+, 100), 320 (13), 319 (56), 302 (15), 287 (14), 243 (14), 241 (34), 213 (33), 105

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4-[(Dimethylamino)methyl]-3-hydroxy-6-methoxy-α,α-diphenylbenzyl Alcohol (26h). A solution of 0.4 g (2.21 mmol) of **26a** in 2 mL of THP was treated with *t*-BuLi (4.68 mmol) as shown in the general procedure and then reacted with benzophenone (0.85 g, 4.68 mmol). Standard extractive workup furnished fractions A and B (1.1 and 0.07 g, respectively). Column chromatography (silica gel, hexane/ether) of fraction A afforded pure **26h** in 40% yield, mp 169–170 °C (ether). ^{1}H NMR: 2.31 (s, 6 H), 3.50 (s, 3 H), 3.59 (s, 2 H), 6.07 (s, 1 H), 6.55 (s, 1 H), 7.25 (s, 10 H) ppm. EIMS, *m/e* (percent, relative abundance): 363 (M^+, 63), 348 (6), 302 (12), 301 (6), 257 (5), 213 (20), 183 (21), 152 (10), 105 (100), 77 (50). Anal. Calcd for $C_{23}H_{25}O_3N$: C, 76.03; H, 6.89; N, 3.86. Found: C, 76.08; H, 7.00; N, 3.90.

2-[(Dimethylamino)methyl]-4-hydroxy-5-methoxy-α,α-diphenylbenzyl Alcohol (27h). Treatment, as illustrated in the general procedure, of a solution of **27a** (0.4 g, 2.21 mmol) with *t*-BuLi (4.68 mmol) was followed by treatment with benzophenone (4.68 mmol). The standard workup furnished two fractions containing 1.3 g (pH 12) and 0.04 g (pH 8–9). Column chromatography (silica gel; chloroform/methanol, 95:5) of the major fraction yielded 0.43 g (53%) of pure **27h**, mp 207–9 °C (lit.[20] mp 208–210 °C). ^{1}H NMR: 2.08 (s, 6 H), 2.85 (s, 2 H), 3.50 (s, 3 H), 6.21 (s, 1 H), 6.74 (s, 1 H), 7.21–7.43 (m, 10 H) ppm. EIMS, *m/e* (percent, relative abundance): 363 (M^+, 24), 345 (19), 330 (16), 318 (55), 286 (39), 270 (32), 242 (41), 241 (73), 210 (24), 181 (50), 165 (55), 105 (100). Anal. Calcd for $C_{23}H_{25}O_3N$: C, 76.03; H, 6.89; N, 3.86. Found: C, 75.95; H, 6.80; N, 3.83.

4-Deuterio-5-[(dimethylamino)methyl]-2-methoxyphenol (27e). The dilithio derivative of **27a** (generated as shown above from 0.4 g of **27a**) was treated with deuterium oxide (0.5 mL). Standard workup afforded 0.35 g (87%) of **27e** (90% deuteriated). ^{1}H NMR (C_5D_5N): 2.18 (s, 6 H), 3.25 (s, 2 H), 3.72 (s, 3 H), 6.91 (s, 1 H), 7.28 (s, 1 H) ppm. EIMS, *m/e* (percent, relative abundance): 182 (M^+, 27), 181 (22), 139 (32), 138 (100), 137 (22), 123 (16), 95 (9).

6-[(Dimethylamino)methyl]-3-hydroxy-2-methoxy-α,α-diphenylbenzyl Alcohol (14h). Treatment of 0.8 g (4.4 mmol) of **14a** with *t*-BuLi as shown in the general procedure was followed by quenching with benzophenone (9.3 mmol). The standard extractive workup furnished a major fraction (2.04 g; extraction at pH 12), which was purified by chromatography (silica gel plates, hexane/ether), thus yielding pure **14h** (0.8 g, 50%). Its acetate crystallized from ether/ethanol (6:1, v/v), mp 172–7 °C (lit.[20] mp 173–9 °C). ^{1}H NMR (C_5D_5N): 1.97 (s, 6 H), 2.99 (s, 3 H), 3.26 (s, 2 H), 6.79 (d, 1 H, J = 8 Hz), 6.96 (d, 1 H, J = 8.1 Hz), 7.10–7.70 (m, 10 H) ppm. EIMS, *m/e* (percent, relative abundance): 363 (M^+, 76), 345 (27), 344 (12), 330 (30), 318 (19), 317 (44), 270 (50), 241 (96), 165 (44), 152 (38), 105 (62), 77 (100).

2-Methoxy-5-(methylthio)-3-(phenylthio)-1,4-benzoquinone (8j). A solution of **14j** (0.29 g, 1 mmol) was treated with *t*-BuLi (2.2 mmol) as indicated in the general procedure and then quenched with dimethyl disulfide (3 mmol). The standard extractive workup yielded 0.22 g (extraction at pH 12) of a crude shown to be (^{1}H NMR) a complex mixture. Extraction at pH 8–9 provided 0.09 g of an oil, which without purification was submitted to Fremy's salt oxidation under the usual reaction conditions. This yielded a crude quinone mixture, which was chromatographed on a short path silica gel column with chloroform/hexane (9:1, v/v) as eluent. An unseparable (1:1) mixture (0.056 g) of **7j** and **8j** was obtained as an oil. ^{1}H NMR 2.30 (s, SMe), 3.90 (s, OMe), 4.02 (s, OMe), 6.21 (s, quinone H of **8j**), 6.65 (d, J = 10 Hz, quinone H of **8j**), 6.76 (d, J = 10 Hz, quinone H of **7j**), 7.25 (br s, C_6H_5) ppm. GC EIMS of **8j**, *m/e* 292 (M^+, 100), 277 (11), 259 (21), 231 (5), 178 (9), 121 (20), 109 (21), 91 (52). GC EIMS of **7j**, *m/e* 246 (M^+, 100), 215 (6), 187 (8), 147 (21), 121 (27), 109 (15), 91 (60).

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Supplementary Material Available: ^{1}H–^{1}H COSY spectra for compounds **24h–27h**, and NOESY spectra for compounds **25h–27h** (4 pages). Ordering information is given on any current masthead page.