by comparing their GC-MS and NMR spectra with those of authentic samples.

The authentic sample of 3-methyl-2,3-dihydrobenzofuran (**19**) was prepared according to the literature;[19b] ^{1}H NMR δ 1.26 (d, J = 7 Hz, 3 H), 3.1-3.6 (m, H), 3.90 (t, J = 8 Hz, H), 4.50 (t, J = 9 Hz, H), 6.5-7.3 (m, 4 H). Authentic samples of phenyl (*Z*)-1-propenyl ether (**21**) and 2-chlorophenyl (*Z*)-1-propenyl ether (**22**)[37] were prepared according to the literature method.[34] ^{1}H NMR of **21**: δ 1.65 (q, J = 5 and ~1.5 Hz, 3 H), 4.4-4.9 (m, H), 6.0-6.3 (m, H), 6.5-7.3 (m, 5 H). ^{1}H NMR of **22**: δ 1.73 (q, J = 6 and ~1.5 Hz, 3 H), 4.8-5.1 (m, H), 6.2-6.4 (m, H), 6.9-7.4 (m, 4 H).

The deuterium incorporation from the reaction in the presence of D_2O was monitored by GC-MS analyses of products. The D contents were determined from molecular ions of the products, i.e., by subtracting the natural abundance from observed values of M + 1, M + 2, and M + 3. The D contents in the phenyl ring are easily calculated from the fragment ions of the phenoxy group.

(37) Yamamoto, K.; Higashimura, T. *J. Polym. Sci.* **1974**, *12*, 613.

Direct Lithiation of Alkoxyphenols: Metalation vs Demethylation. An Experimental and Theoretical (MNDO) Study

Jeroni Morey, Antoni Costa, Pere M. Deyà, Guillem Suñer, and Josè M. Saá*

Departament de Química, Universitat de les Illes Balears, 07071 Palma de Mallorca, Spain

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The direct lithiation of simple alkoxyphenols has been studied both from a theoretical and an experimental viewpoint. Efficient lithiations were achieved by using a 2:1 tBuLi-tBuOLi mixture (LICLIOR) in THF at room temperature. In most cases alkoxy groups are responsible for the regioselectivity observed, although for the case of 2-methoxyphenol both the OMe and OLi groups actually act as ortho-directing groups during lithiation. Demethylation has been shown to be a common side reaction of lithiation of phenolic or nonphenolic alkoxy aromatics. MNDO calculations provide good support for all the experimental observations. Thus, lithiation and demethylation are shown to be competing pathways, the former being kinetically favored whereas the latter leads to the thermodynamically more stable compounds. Calculations also show that the so-called geminal demethylations are more favored processes than the alternative vicinal demethylations. Moreover, MNDO allows the measurement of the extent of agostic activation of the ortho hydrogens with respect to the OMe and OLi groups involved in lithiation. Finally, MNDO nicely predicts the important role of reaction temperature in successful direct lithiation of simple alkoxyphenols.

The direct ring metalation of phenolic compounds[1] and closely related substances[2] has gained recent attention as a potentially useful methodology for the direct introduction of functional groups and alkyl side chains into monphenolic compounds and related systems. However, apart from the lithiation of phenol[1] itself and naphthols,[3] only a handful of other cases have been reported in the literature.[4] Therefore, it seemed worthwhile to study the direct metalation of relevant phenols in more detail, so as to determine the real scope and limitations of this potentially powerful synthetic method.

Our plan was to avoid the rigidly controlled conditions required for achieving direct metalation of simple hydroxy aromatics[1,3,4] since, mainly as a result of the difficulty in stirring a highly viscous mass, a number of problems arise when these reactions are scaled-up. Thus, on the one hand, large amounts of starting materials are usually recovered unchanged,[4d,e] and, on the other, important side reactions show up as a consequence of high local concentration of reactants and/or the uncontrolled increase of temperature.

Being aware of these experimental difficulties we focused our attention on using complex bases such as tBuLi-tBuOK and related systems, usually referred to as LIC-KOR reagents.[5] Actually we were driven to employ the easy-to-prepare tBuLi-tBuOLi (LICLIOR) mixture instead of the more commonly used tBuLi-tBuOK. The ultimate reason behind this choice was the fact, noticed both by Posner and ourselves during the tBuLi-THP promoted lithiation of hydroxy aromatics,[1,3,4] that the solvent used (tetrahydropyran, THP) was being partially cleaved to the corresponding alkoxide (6,6-dimethylheptan-1-ol lithium salt) by the action of tBuLi.

Though the role played by the alkoxide in this reaction has yet to be properly defined, we speculated that its action might significantly determine two very distinct though intimately related questions, namely, the structure of the lithiated reagents and products and, last but not least, the solubility of these compounds in the reaction medium. In very recent disclosures MacGarrity et al.[6,7] have provided convincing evidence not only in regard with the actual constitution of the mixed complexes co-occurring in RLi-ROLi mixtures, but also on the expected reactivity,

(1) Posner, G. H.; Canella, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 2571.
(2) (a) Figuly, G. D.; Loop, C. K.; Martin, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 654. (b) Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. *Ibid.* **1989**, *111*, 658. (c) Smith, K.; Lindsay, C. M.; Pritchard, G. J. *Ibid.* **1989**, *111*, 665.
(3) Coll, G.; Morey, J.; Costa, A.; Saá, J. M. *J. Org. Chem.* **1988**, *53*, 5345.
(4) (a) Saá, J. M.; Llobera, A.; García-Raso, A.; Costa, A.; Deyà, P. M. *J. Org. Chem.* **1988**, *53*, 4263. (b) Costa, A.; Saá, J. M. *Tetrahedron Lett.* **1987**, *28*, 5551. (c) Saá, J. M.; Llobera, A. *Tetrahedron Lett.* **1987**, *28*, 5045. (d) Santucci, L.; Gilman, H. *J. Am. Chem. Soc.* **1958**, *80*, 4537. (e) See: Gilman, H.; Morton, J. W., Jr. *Organic Reactions*; Wiley: New York, 1954; Vol. 8 and references therein.
(5) (a) Lochmann, L.; Pospisil, J.; Lim, D. *Tetrahedron Lett.* **1966**, 257. (b) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9. (c) Lochmann, L.; Trekoval, J. *Ibid.* **1987**, *326*, 1. (d) Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741. (e) For a closely related system, see: Screttas, C. G.; Steele, B. R. *J. Org. Chem.* **1989**, *54*, 1013 and references therein.
(6) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805.
(7) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H. R. *J. Am. Chem. Soc.* **1985**, *107*, 1810. See also: Al-Aseer, M. A.; Allison, B. D.; Smith, S. G. *J. Org. Chem.* **1985**, *50*, 2715. Baryshnikov, Yu. N.; Kaloshina, N. N.; Vernovskaya, G. I. *J. Gen. Chem. USSR* **1977**, *47*, 2535.

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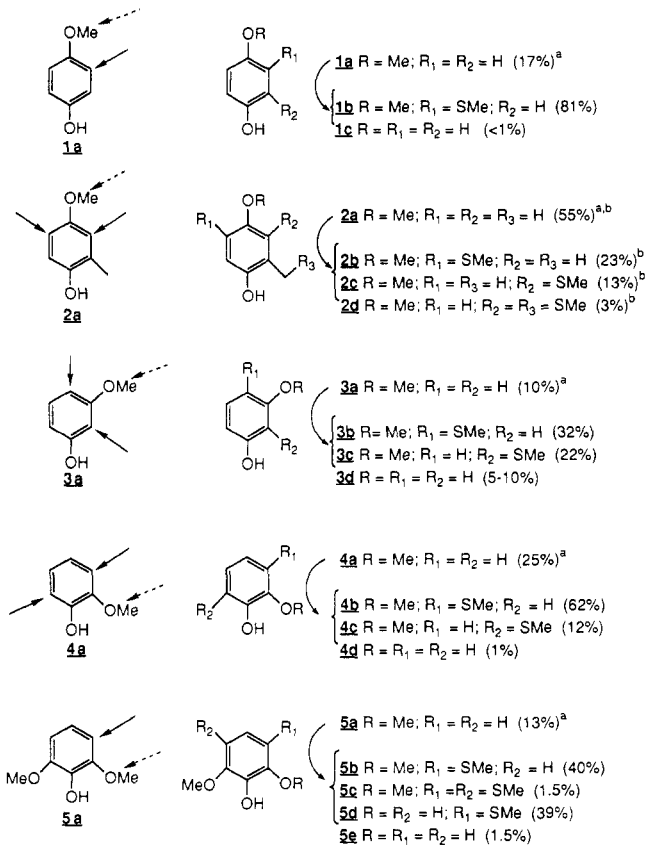
Scheme I



[a] Recovered starting material. [b] Unoptimized.

i.e., the increased basicity and nucleophilicity of these mixed aggregates.[7]

Initial trials with different alcohols (octanol, ethylene glycol, and *tert*-butyl alcohol) and solvents (THF, THP, and ether) were carried out in order to define the optimal conditions of operation. Eventually it was decided to work with a 2:1 tBuLi–tBuOLi mixture. Under these conditions we learned that THF was much less reluctant to undergo base-promoted ring opening[8] than with plain tBuLi (no alkoxide added), and, most important, the resulting lithiating mixtures were found to be easy-to-stir viscous solutions, therefore amenable for scale-up.

Simple alkoxyphenols were studied first (Scheme I). In agreement with Posner's observations,[1] we found that the direct metalation of **1a** carried out with the above-described LICLIOR reagent in THF at 25 °C yielded, after quenching with dimethyl disulfide, **1b** as the major component together with some unreacted starting material. Gas chromatographic examination (GC/MS) of the crude reaction mixture revealed, however, the presence of three very minor products (total yield <2%) having mass spectra (molecular ions at 110, 202, and 248) which might correspond to hydroquinone itself: **1c** and bis(methylthio)- and tris(methylthio)-substituted hydroquinones, i.e., the result of demethylation and polylithiation reactions.

Treatment of phenol **2a** with LICLIOR reagent followed by quenching with dimethyl disulfide gave rise to a complex mixture of at least six products. Open-column chromatography furnished unaltered starting material **2a** (55%), (methylthio)phenols **2b** (23%) and **2c** (13%), and 4-methoxy-2-[(methylthio)methyl]-3-(methylthio)phenol (**2d**) as a very minor byproduct. Several other minor components, presumably diphenolic, were also detected (GC) though not properly identified.

Lithiation of 3-methoxyphenol (**3a**), followed by quenching with dimethyl disulfide as above, yielded a mixture of **3b** (32%) and **3c** (22%), together with unreacted starting material (10%) and several minor products, namely, resorcinol (**3d**) (ca. 5–10%) and trace amounts (<3%) of unidentified compounds, presumably mono- and poly(methylthio) derivatives showing molecular ions at 170, 216, and 260 (GC/MS).

Thus, as for the cases of **1a** and **2a**, there appears to be a kinetic preference for lithiation taking place at a position ortho to the methoxy group. In our view this ought to be due to the nature of the mixed complex [$ArOCH_3$–RLi] involved in the ortho metalation of alkyl aryl ethers[9] (see below for data from MNDO calculations). Unexpectedly, however, treatment of 2-methoxyphenol (**4a**) as above yielded a mixture of **4b** and **4c** in 62 and 12% yield, respectively, together with some unreacted starting material (25%), minor amounts of catechol (**4d**) (1%), and an unidentified (methylthio)catechol (EIMS, GC/MS, M^+ 156). The formation of **4c** represents clear-cut evidence for the competitiveness of both lithiation pathways, ortho to the OMe and to the OLi groups. At this point we speculated on the possibility that lithiation ortho to the OLi group could be somewhat facilitated by the steric compression caused by the ortho substituent. In other words, the adjacent OMe group might be forcing the mixed dimer [ArOLi–RLi] to be spacially closer to the ortho hydrogen, thus facilitating its removal (see MNDO calculations below).

Moreover, reaction of 2,6-dimethoxyphenol (**5a**) yielded a 1:1 mixture of monophenolic and diphenolic products, as determined by gas chromatographic analysis. Chromatographic separation of the complex mixture provided the expected phenol derivative **5b** as the major compound (40%), together with doubly functionalized **5c** (1.5%), diphenols **5d** (39%) and **5e** (1.5%), unreacted starting materials (13.2%), and other unidentified minor byproducts.

The appearance of demethylated compounds as minor byproducts in the above reactions was thought to be a consequence of competition between metalation and demethylation reactions undergone by these aggregates or mixed complexes.[9] Definitive proof for the involvement of the lithium base in the previously described demethylation processes came from the observation that treatment of **5a** (the choice of **5a** as a model was marked by the fact that this phenol, as shown above, tends to undergo substantial demethylation) with our lithiating reagent at 25 °C, under otherwise identical conditions, followed by quenching with water gave a mixture of **5a** and **5e** in 35 and 65% yield, respectively, as determined by GC. Furthermore, as expected, longer reaction times (17 h instead of 6) led to a significant increase in demethylation (15% of **5a**, 85% of **5e**, as determined by GC). Analogous treatment of **4a** with our lithiating reagent for 17 h, followed by quenching with water also yielded increasing amounts of **4d** (9% yield) together with unreacted starting material (91%).

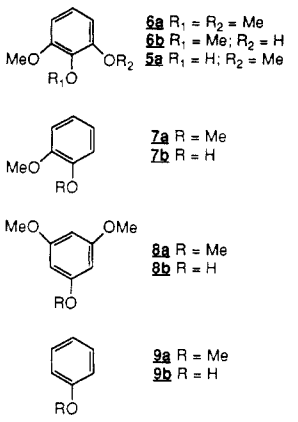
The picture that evolves from the above experimental evidence is that, at the temperature of operation, deprotonation[10] and demethylation[11] are actually competing

(8) This behavior has been recently reported for other mixed complexes; see ref 5e.

(9) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191.

(10) Gschwend, H. W., Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. Wakefield, B. J. *The Chemistry of the Organolithium Compounds*; Pergamon Press: New York, 1974. Beak, P., Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. Beak, P.; Meyers, A. I. *Ibid* **1986**, *19*, 356. Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957.

Scheme II



processes. Furthermore, since the new lithiation diphenolates originating from demethylations are, in principle, capable of undergoing further metalation, the reactions should give rise to complex mixtures of products.[12]

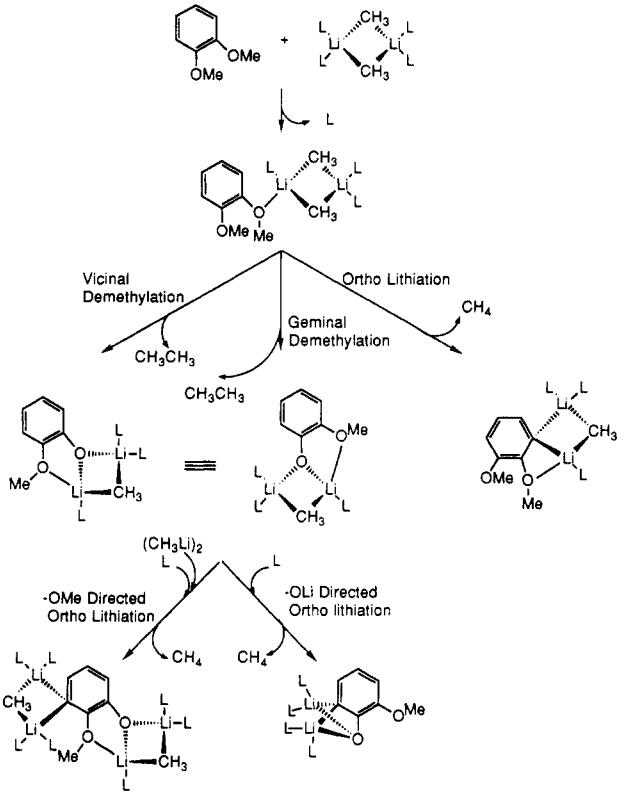
In summary, it can be safely concluded that the value of the OMe-directed lithiation of complex phenols is limited in part by competitive demethylations. In this regard it is worth remarking that no demethylation was ever detected during our previous work with *N,N*-dimethylvanillylamine and related substrates in which a much better coordinating group such as the $-NMe_2$ in the side chain was available.[4] In other words, we envisaged demethylation reactions as CIPE processes[13] restricted, therefore, to those metalations directed by an alkoxy group of either phenolic or nonphenolic alkyl aryl ethers.

In a rapid survey of the literature we found that several authors had observed demethylation reactions during their metalation of alkyl aryl ethers. However, the reported evidence for the formation of phenols was, for most cases, only circumstantial (odor, mass balance),[15] except for a very few number of examples where phenols have been actually isolated.[14] Consequently, we turned our attention to briefly studying demethylation of very simple nonphenolic alkyl aryl ethers by the action of the most commonly used lithiating agents. Our plan was to approach this study concurrently from a theoretical and experimental point of view.

Our first concern in regard with this new objective was to make clear that the alkyllithium reagent was actually the agent responsible for the demethylation of alkyl aryl ethers. This was demonstrated by examining the reaction of (3-phenylpropyl)lithium with **6a** (ether, 4 h), followed by quenching with water. GC/MS analysis of the extracts (neutral fraction) showed the existence of propylbenzene in the reaction mixture.

A number of simple alkyl aryl ethers (**6a**, **7a**, **8a**, and **9a**, Scheme II) were then submitted to the action of nBuLi. After some experimentation we found that optimal conditions for achieving demethylation of the above methyl aryl ethers involved treatment of an ether solution of the substrate with commercial 1.6 M nBuLi at room temperature for up to 48 h. Most interesting, in striking contrast with the acid-promoted dealkylation of alkyl aryl ether **6a**, which cleanly produced phenol **5a**,[16] treatment with nBuLi/ether yielded (78%) a mixture of phenols **6b** and **5a** in a 3:1 ratio, respectively, as determined by ^1H NMR. The analogous reactions on compounds **7a**, **8a**, and **9a** gave rise in low yield to the expected demethylation products **7b** (60%), **8b** (25%), and **9b** (<10%), respectively.[11,14]

Scheme III. Manifold Mechanism for the Reaction of 1,2-Dimethoxybenzene (Veratrol) with Methyllithium Dimer in Donor Solvents (L)



As mentioned previously, in an effort to obtain a good overall picture of the competitive routes available for a reaction of the type ROAr + R′Li (R being hydrogen or methyl), we decided to undertake a theoretical study for which veratrol (1,2-dimethoxybenzene, **7a**) was chosen as a model. Calculations were performed according to a mechanistic scheme involving[9,17] (1) complexation of the lithiating species with the aromatic substrate; (2) intramolecular demethylation and/or hydrogen abstraction, followed by (3) subsequent demethylation or metalation (both ortho to the OMe or OLi groups) on the mixed dimer resulting from demethylation of **7a**. A fully comprehensive diagram of the different processes studied appears illustrated in Scheme III. In particular, we envisaged demethylation of veratrol taking place on an intermediate complex either by attack at the geminal or vicinal OMe groups. Either one of them should give rise to a unique mixed dimer (ArOLi–RLi), itself capable of undergoing subsequent demethylation or deprotonation reactions, thus providing a good explanation for the experimentally observed results.

(11) Bahtt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249. Tiecco, M. *Synthesis* **1988**, 749. Burwell, R. L., Jr. *Chem. Rev.* **1954**, *54*, 615. *Methoden der Organischen Chemie* (Houben-Weyl), 4th ed.; Müller, E. Ed.; Georg Thieme Verlag: Stuttgart 1965; Vol. 6/3. Staude, E.; Patai, F. In *The Chemistry of the Ether Linkage*; Patai, S., Ed.; Interscience: New York.

(12) See: Crowther, G. P.; Sundberg, R. J.; Sarpeshkar, A. M. *J. Org. Chem.* **1984**, *49*, 4657 and references therein.

(13) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

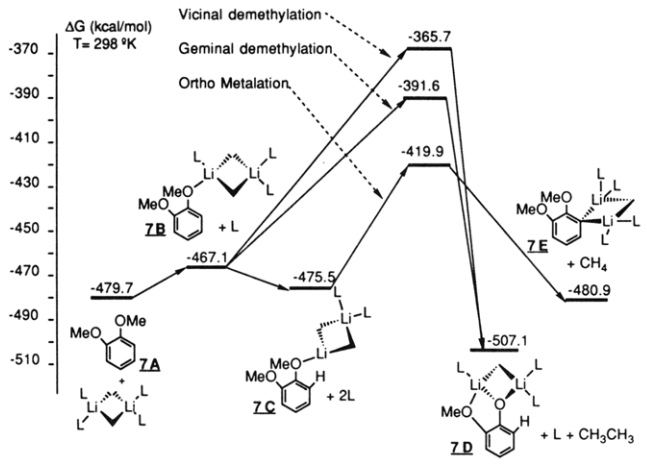
(14) (a) Schill, G.; Logemann, E. *Chem. Ber.* **1973**, *106*, 2910. (b) Kun, K. A.; Cassidy, H. G. *J. Org. Chem.* **1962**, *27*, 841. (c) Byck, J. S.; Dawson, C. R. *J. Org. Chem.* **1967**, *32*, 1084. (d) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653. (e) See, however: Furlano, D. C.; Calderón, S. N.; Chen, G.; Kirk, K. L. *J. Org. Chem.* **1988**, *53*, 3145.

(15) Narasimhan, N. S.; Bhide, B. H. *Tetrahedron Lett.* **1968**, 4159. See also ref 12.

(16) Basler Chemiske Fabrik. German Patent 162,658; *Chem. Zentr.* **1905**, *11*, 1961. See also ref 11.

(17) Suñer, G. A.; Deyá, P. M.; Saá, J. M. *J. Am. Chem. Soc.*, **1990**, *112*, 1467.

Scheme IV. Schematic Representation of the Minimum-Energy Pathways for Lithiation and Demethylation of 1,2-Dimethoxybenzene (Veratrol)



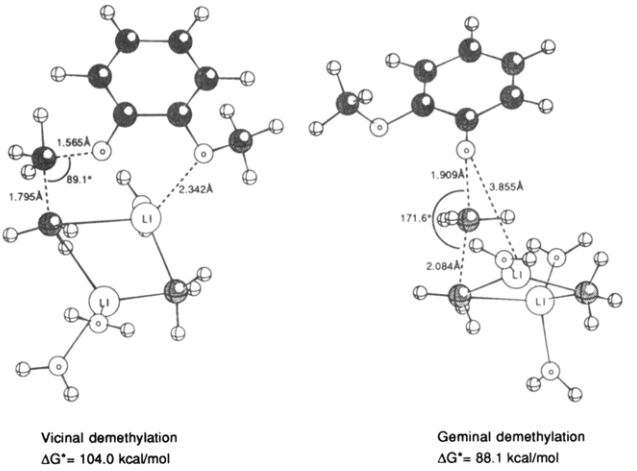
The extremely large nature of the structures of the lithio derivatives demanded the use of a semiempirical method such as MNDO for our theoretical study. As in our recent work on the lithiation of 1- and 2-naphthol,[17] several assumptions were made in order to be able to perform our theoretical calculations using a reasonable amount of computer time. Specifically, dimeric CH_3Li solvated with two H_2O molecules (per lithium) was selected as our working model.[18] This model has been frequently employed in computational chemistry,[19] and, most important, it has proved to be useful for qualitatively describing important mechanistic features regarding lithium coordination in organolithium compounds.[18]

Theoretical calculations were carried out at the restricted Hartree–Fock (RHF) level using the MNDO[20] semiempirical SCF–MO method as implemented in a modified version[21] of the MOPAC program.[22] Although the energy of the C–Li bond is overestimated by MNDO,[23] it is undoubtedly the method of choice for the study of large organolithium species.

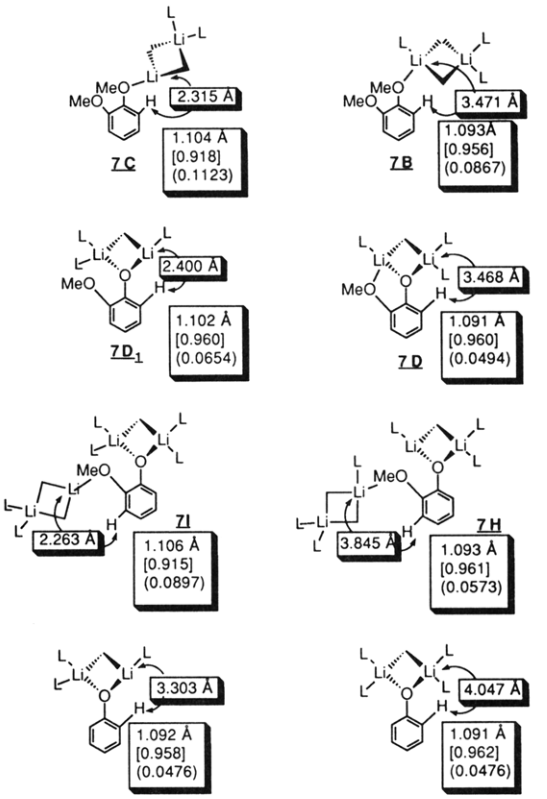
All geometric parameters were optimized without symmetry constraints. All stationary points on the potential energy surfaces were characterized by calculating and diagonalizing the Hessian matrix and checking the number of negative eigenvalues.[24]

As illustrated in Scheme IV, two intramolecular demethylation routes (geminal and vicinal) were studied for the mixed complex **7b** derived from 1,2-dimethoxybenzene (**7A**) (**7a** in Scheme II) and methyllithium dimer. Our calculations show that geminal demethylation (**7B** → **7D**), which formally involves a distorted four-membered ring transition state, is kinetically preferred (75.5 vs 101.4 kcal/mol) over the so-called vicinal demethylation (**7B** → **7D**) involving, in a formal sense, a seven-membered ring transition state.

Scheme V. MNDO-Calculated Energies (T = 298 K) and Optimized Geometries (Distances in Å, Angles in Degrees) for the Transition States of Vicinal and Geminal Demethylation of 1,2-Dimethoxybenzene (Veratrol)



Scheme VI. MNDO-Calculated Values for Agostic Activation Indicators: Li–H Distance (Å, Small Box), C–H Distance (Å, Large Box), C–H Bond Order (in Brackets), Net Atomic Charge in H Atom (in Parentheses)



Remarkably, the four-membered ring transition structure for geminal demethylation is almost that of the idealized S_N2 reaction,[25] i.e., the course of the bond-forming and bond-breaking operations being almost equally advanced and, in addition, taking place at an C–C–O angle (171.6°) very close to the optimum value (180°) for a symmetrical trigonal bipyramid (Scheme V). In striking contrast, the seven-membered ring transition structure for vicinal demethylation involves a highly deviated C–C–O angle (89.1°). In other words, it looks like an S_N2 transition

(18) Bauer, W.; Feigel, M.; Müller, G.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1988**, *110*, 6033.

(19) Monomeric unsolvated LiH has been used as model for alkyl lithiums and their aggregates. See: (a) Kaufmann, E.; Sieber, S.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 121. (b) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y. D. *Ibid.* **1985**, *107*, 5560. (c) Houk, K. N.; Rondan, N. G.; Schleyer, P. v. R.; Kaufmann, E.; Clark, T. *Ibid.* **1985**, *107*, 2821.

(20) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

(21) Olivella, S. *QCPE Program No. 486.*

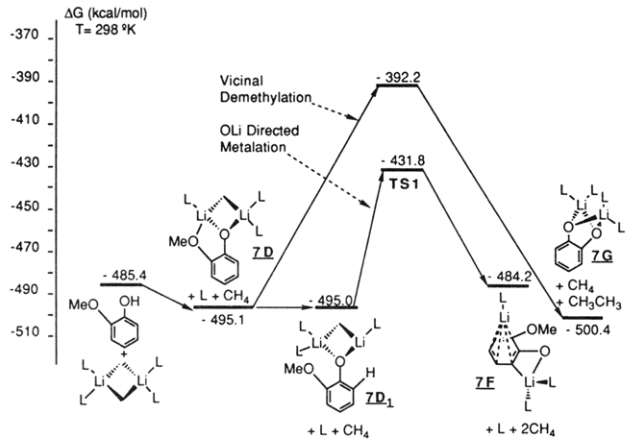
(22) VAX Version: Stewart, J. J. P. *QCPE Bull.* **1983**, *3*, 101. Lithium parametrization: Thiel, W.; Clark, T. Unpublished work (Thiel, W. Personal communication to S. Olivella, Jan 1982).

(23) Schleyer, P. v. R. *Pure Appl. Chem.* **1983**, *55*, 355.

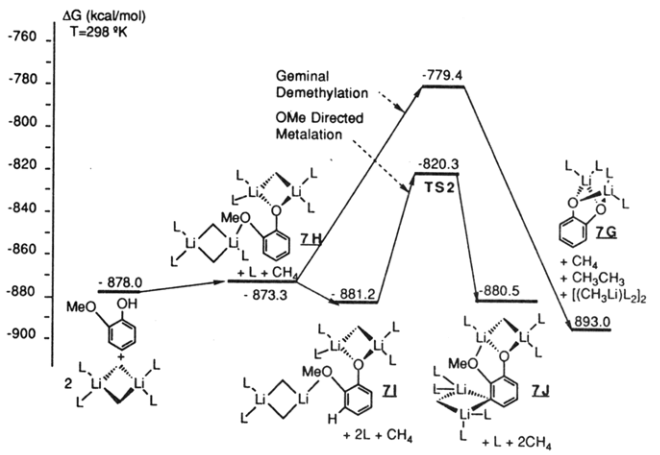
(24) McIver, J. W.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625.

(25) Carrion, F.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 3531.

Scheme VII. Schematic Representation of the Minimum-Energy Pathways for Lithiation and Demethylation of 2-Methoxyphenol (Guaiacol)



Scheme VIII. Schematic Representation of the Minimum-Energy Pathways for Lithiation and Demethylation of 2-Methoxyphenol (Guaiacol)



state with retention of configuration, and, accordingly, it is of much higher energy.

Furthermore, in accordance with the recent results reported both by Bauer and Schleyer[9] (for the lithiation of anisole) and ourselves[17] (for the lithiation of 1- and 2-naphthol), we can conclude that lithiation of alkoxy aromatics (and presumably related compounds) must take place not on the fully coordinated complex **7B** (or the like), but at an stage such as **7C** where a non-fully-coordinated lithium atom is capable of "recognizing" an adjacent hydrogen atom.[26] Actually, at this point of the reaction coordinate a clear-cut agostic activation[27] of the vicinal ortho hydrogen atom is evident, as determined by the following four indicators: (a) larger C–H bond, (b) reduced bond order of the C–H bond, (c) larger positive charge at the hydrogen atom, and (d) shorter Li–H distance. The calculated values for **7B** and **7C** are shown in Scheme VI for comparison.

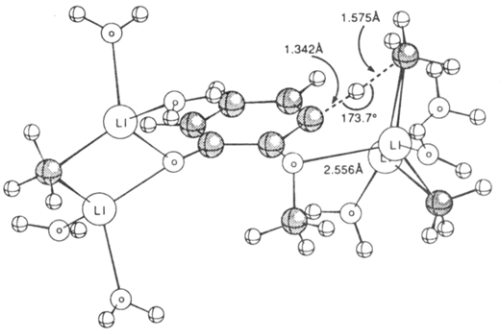
As expected, the transition structure for ortho metalation (**7C** → **7E**) was calculated to lie 55.6 kcal/mol above the starting mixed complex **7C**, whereas for demethylation (**7B** → **7D**) the corresponding transition structure lies at 75.5 kcal/mol. It follows that metalation leading to **7E** is the kinetic process whereas demethylation to mixed dimer **7D** is the thermodynamic one (Scheme IV). These results are not only in good agreement with experience but also with the recent calculations reported by Bauer and Schleyer[9] for the lithiation of anisole.

Calculations were then performed on **7D**, the expected mixed dimer from treatment of 2-methoxyphenol with lithium base (Scheme VII). Vicinal demethylation (**7D** → **7G**) was found to have a high energy barrier to surmount (ΔG^* = 102.9 kcal/mol), whereas that for the competitive ortho metalation with respect to the OLi group (**7D**$_1$ → **7F**) was calculated to lie at only 63.2 kcal/mol.

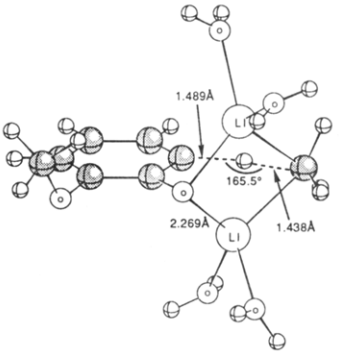
To examine the competitive ortho metalation (with respect to the OMe) and the geminal demethylation of **7D**, further complexation with lithium base was required. MNDO calculations (Scheme VIII) on the resulting very large complex **7H** showed that lithiation of 2-methoxyphenol (ortho to the OMe) is thermodynamically feasible at room temperature (ΔG = −2.5 kcal/mol at 25 °C; Scheme VIII). This is in contrast with results obtained for ortho lithiation with respect to the OLi group, which was found to be strongly dependent on operating conditions. Thus, formation of **7F** from 2-methoxyphenol (Scheme VII) is slightly endergonic (ΔG = +1.2 kcal/mol) at 25 °C, but exergonic at temperatures higher than 55 °C (ΔG = 0 kcal/mol at 55 °C).

On the other hand, geminal demethylation of **7H** was calculated to require the surmounting of an energy barrier of 93.9 kcal/mol (compare with the 102.9 kcal/mol required for vicinal demethylation of **7D**). Thus, in line with the results found for **7B**, the so-called geminal demethylation of alkoxy aromatics appears to be the demethylation route of choice, since it will always be kinetically

Scheme IX. MNDO-Calculated Energies (T = 298 K) and Optimized Geometries (Distances in Å, Angles in Degrees) for the Transition States of 2-Methoxyphenol (Guaiacol) Dilithiation.



TS2 (-OMe Directed Ortho Lithiation)
ΔG^*= 60.9 kcal/mol.



TS1 (-OLi Directed Ortho Lithiation)
ΔG^*= 63.2 kcal/mol.

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(27) Brookhart, M.; Green, M. L. H. *J. Organomet. Chem.* **1983**, *250*, 395. The original term introduced by Green et al. was first applied to organolithium compounds by Schleyer et al. See ref 18, 9, and Kaufmann, E.; Raghavachari, K.; Reed, A. E.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 1597.

preferred over vicinal demethylation.

In addition, interesting trends in regard to the lithiation step were revealed by comparing the transition structures corresponding to the lithiation of 2-methoxyphenol ortho to the OMe and OLi groups (**TS2** and **TS1**, respectively, Scheme IX). The former transition structure **TS2** is kinetically preferred by virtue of the fact that it involves an angle (C–H–C) for proton abstraction much closer to linearity (173.7°) than in **TS1** (165.6°), in accordance with the hypothesis that angle deviations of the key proton-transfer process should give rise to a considerable energy cost.[28] In our view the ultimate reason for this lies in the fact that the O–Li bond of the actual lithiating species, namely, the conformationally flexible mixed complex ArOMe–RLi (**7H**), is large (2.65 Å) whereas that for the more rigid mixed dimer ArOLi–RLi (**7D**) is much shorter (2.12 Å).

As indicated above for the case of **7C** significant levels of agostic activation were also noticed for the lithiation of $\mathbf{7D}_1$ and **7I**, both having a non-fully-coordinated lithium atom. In other words, as shown in Scheme VI, the uncoordinated lithium atom is capable of "recognizing" the vicinal hydrogen atom. As demonstrated by all four indicators mentioned above, "recognition", though quite advanced in both cases, is slightly more pronounced in the case of **7I** than in $\mathbf{7D}_1$. This is quite remarkable as it points out that, contrary to common view, deprotonation ortho to the OLi should take place (and it actually does) in competition with deprotonation ortho to the OMe.

Moreover, since no agostic activation of the adjacent hydrogen atoms is detected at the analogous mixed dimer derived from simple phenol (Scheme VI), we suggest that the ortho methoxy group in $\mathbf{7D}_1$ must be strongly pushing the adjacent mixed dimer ($ArOLi–CH_3Li$) group toward the vicinal hydrogen atom, thereby facilitating its removal. According with this reasoning, we believe that selective lithiation of phenols (ortho to the OH group) might be achieved even in the presence of other better directing groups provided that a very large group is available at the ortho position.

Also noteworthy is that, in accordance with our recent results on the lithiation of 1- and 2-naphthol,[17] MNDO calculations show that the most stable structure for phenol dilithio derivative **7F** is of the π type. Unfortunately though, no experimental proof for this is available yet.

In summary, alkoxyphenols undergo lithiation by the action of tBuLi–tBuOLi in THF at room temperature, the alkoxy group being the exclusive or main group involved in directing the incoming base for ortho metalation. The case of *o*-methoxyphenol is particularly noteworthy in this regard because the OMe and OLi groups actually compete for directing the incoming lithium base to their corresponding ortho sites.

In all cases studied a minor byproduct was detected or isolated from the reaction mixture, namely, the corresponding demethylated compound. We have demonstrated that this byproduct is the result of a competing demethylation reaction in which the lithium base must intervene.[29] Accordingly, demethylation has been proved not to be a unique reaction for the lithiation of phenols but, more on the contrary, it must be regarded as a general reaction of alkoxy aromatics, its relative importance being enhanced when no other better group for coordination to the lithium base is available. Indeed, simple alkoxybenzenes undergo demethylation (to differing extents) by the action of common lithium bases at room temperature. Furthermore, demethylations appear to be facilitated by the presence of adjacent groups which force the active complex to lie closer to the geminal OMe.[11]

In addition, MNDO calculations provide good support for all these experimental observations. Thus, on the one hand, the demethylation profile of our models, 1,2-dimethoxybenzene (veratrol) and 2-methoxyphenol (guaiacol), clearly shows that both are thermodynamically favored processes, although a high-energy barrier must be surpassed for them to occur. On the other hand, our calculations also make clear that the so-called geminal demethylation is kinetically preferred over the alternative vicinal demethylation. In other words, MNDO predicts demethylation to compete with high-temperature metalation.

Emphasis is also drawn to the fact that MNDO allows the measurement of the extent of agostic activation of the adjacent hydrogens ortho to the OMe and OLi groups. Since these values can be taken as indicative of the proximity of the transition state for lithiation, it follows that they provide valuable information with regard to the ease of going of the exothermic lithiation reactions (Hammond postulate).

Finally, MNDO calculations also give a good explanation for the fact that phenol lithiations are highly dependent on the reaction conditions. Actually only when entropy changes are taken into consideration do the calculated ΔG values make sense. In other words, MNDO nicely predicts that the temperature of operation is of fundamental importance for success in the direct metalation of simple alkoxyphenols. However, it must be kept in mind that demethylation might become an important competitive reaction at this temperature of operation.

Experimental Section

General Methods. All melting points are uncorrected and were taken on a Büchi capillary melting point apparatus. The boiling points given refer to those observed on bulb-to-bulb distillations, conducted in a Büchi GKR-50 apparatus. IR spectra were recorded with a Hitachi 260-10 spectrometer. Proton NMR spectra were obtained on a Varian FT-80A and Bruker WM-250 instruments, with $CDCl_3$ as solvent and tetramethylsilane as internal standard, unless otherwise stated. Electron impact mass spectra (EIMS) were recorded with a Hewlett-Packard 5985B instrument, operating at 70-eV ionizing energy. Elemental analyses were obtained at the Servei de Microanalisi del CSIC (Barcelona). The purity of new compounds (**2d** and **5c**) for which combustion analysis could not be obtained owing to the scarcity of material, was judged to be ≥85% on the basis of its ^1H NMR spectrum.

A 3% SE-30 on 80-100 Supelcoport column was used for gas chromatographic analysis. Packing material for column chromatography was Merck silica gel 60 (70–230 mesh). 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. All operations involving organolithium compounds were carried out under argon atmosphere.

General Procedure for the Direct Lithiation of Phenols. An oven-dried, round-bottom flask protected from the atmosphere by rubber septa, under argon, was charged with *t*-BuOH (0.32 g, 4.3 mmol), the appropriate phenol (4 mmol), and dry THF (4 mL). To this stirred solution, at room temperature (23 °C), *t*-BuLi in pentane (6.8 mL, 13.2 mmol) was added dropwise via syringe. The mixture was stirred for 6 h, cooled to 0 °C, and finally quenched with an excess of dimethyl disulfide (0.94 g, 10 mmol) in dry THF (4 mL). Stirring was continued for 17 h at room temperature. The standard workup involved treatment with 20%

(28) Liotta, D.; Saindane, Waykole, L.; Stephens, J.; Grossman, J. *J. Am. Chem. Soc.* **1988**, *110*, 2667.

(29) Nucleophilic ether fissions promoted by alkyllithium derivatives have been reported by: Köbrich, G.; Baumann, A. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 856. See also ref 11, 14, 15.

NaOH, the basic solution being washed with hexane (4 × 20 mL) and ether (4 × 20 mL), acidification of the aqueous phase with HCl, and extraction with ether (4 × 20 mL). The extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness, the resulting oily residue being chromatographed on silica gel.

Lithiation of 4-Methoxyphenol (1a). Preparation of 4-Methoxy-3-(methylthio)phenol (1b). Treatment of 0.5 g (4 mmol) of **1a** as indicated above provided 0.66 g of a crude mixture, gas chromatographic analysis of which revealed the presence of starting material (17%), a major compound **1b** (81%) and three minor byproducts (2%). Column chromatography on silica gel (hexane–ether 8:2) yielded the following.

1b: pale yellow oil, bp 145 °C (0.1 mmHg), which solidifed on standing. White crystals were obtained by recrystallization from CH_2Cl_2–hexane, mp 61–2 °C; IR (film) 3400, 1580, 1480, 1425, 1210, 1070, 1030, 840, 805, 750 cm^{-1}; ^1H NMR 6.65 (m, 3 H), 4.8 (bs, 1 H), 3.82 (s, 3 H), 2.73 (s, 3 H) ppm; EIMS *m/e* (%) 170 (100, M^+), 155 (76), 137 (28), 111 (26), 109 (20), 99 (12), 94 (11), 85 (17), 65 (18). Anal. Calcd for $C_8H_{10}O_2S$: 56.45; H, 5.92. Found: C, 56.76; H, 5.91.

Examination of the crude reaction mixture by GC/MS revealed the following mass spectra for the minor byproducts.

1c: EIMS *m/e* (%) 110 (M^+ 100), 108 (17), 95 (9), 81 (23), 79 (9), 63 (12). The structure of **1c** was confirmed by comparison with an authentic sample of hydroquinone.

1d: EIMS *m/e* (%) 204 (7), 203 (14), 202 (M^+ 100), 189 (11), 187 (92), 170 (59), 159 (50), 155 (32).

1e: EIMS *m/e* (%) 249 (7), 248 (M^+ 100), 234 (14), 233 (33), 218 (15), 199 (13), 186 (19), 185 (23), 157 (11).

Lithiation of 4-Methoxy-2-methylphenol (2a). Preparation of 4-Methoxy-2-methyl-5-(methylthio)phenol (2b), 4-Methoxy-2-methyl-3-(methylthio)phenol (2c), and 4-Methoxy-2-[(methylthio)methyl]-3-(methylthio)phenol (2d). Chromatographic analysis of the crude reaction mixture (0.76 g) obtained by treatment of 0.54 g (4 mmol) of **2a** as shown in the general procedure, revealed the presence of starting material (55%) together with two major compounds **2b** (23%) and **2c** (13%), a minor compound **2d** (3%), and several other not properly identified byproducts. Chromatographic separation (silica gel, hexane–ether) provided the following products.

2b: white solid, mp 92–3 °C (CH_2Cl_2–hexane); IR (KBr) 3370, 1605, 1590, 1500, 1270, 1195, 1140, 1070, 820 cm^{-1}; ^1H NMR 7.04 (s, 1 H), 6.38 (s, 1 H), 5.07 (s, 1 H), 3.78 (s, 3 H), 2.25 (s, 3 H), 2.16 (s, 3 H) ppm; EIMS *m/e* (%) 186 (5), 185 (10), 184 (100, M^+), 169 (28), 141 (7), 125 (19), 123 (12), 97 (12), 79 (11), 77 (11). Anal. Calcd for $C_9H_{12}SO_2$: C, 58.67; H, 6.56. Found: C, 57.89; H, 6.48.

2c: colorless oil, bp 65 °C (0.3 mmHg); IR (film) 3380, 2815, 1605, 1490, 1410, 1300, 1265, 1200, 1170, 1140, 1085, 790 cm^{-1}; ^1H NMR 7.15 (s, 1 H), 7.04 (d, 1 H, J = 8.4 Hz), 6.36 (d, 1 H, J = 8.4 Hz), 3.86 (s, 3 H), 2.25 (s, 3 H), 2.20 (s, 3 H) ppm; EIMS *m/e* (%) 186 (5), 185 (10), 184 (100, M^+) 169 (31), 141 (9), 125 (21), 123 (13), 97 (12), 79 (13), 77 (12). Anal. Calcd for $C_9H_{12}SO_2$: C, 58.67; H, 6.56. Found: C, 57.74; H, 6.48.

2d: pale yellow oil; ^1H NMR 7.27 (s, 1 H), 7.17 (d, 1 H, J = 8.5 Hz), 6.43 (d, 1 H, J = 8.4 Hz), 3.89 (s, 3 H), 3.71 (s, 2 H), 2.26 (s, 3 H), 2.06 (s, 3 H) ppm; EIMS *m/e* (%) 232 (3), 231 (5), 230 (35, M^+) 184 (14), 183 (100), 182 (55), 167 (10), 149 (25), 135 (20). HREIMS: Calcd for $C_{10}H_{14}S_2O_2$: 230.0434. Found: 230.0401.

Lithiation of 3-Methoxyphenol (3a). Preparation of 3-Methoxy-4-(methylthio)phenol (3b), 3-Methoxy-2-(methylthio)phenol (3c), and Resorcinol (3d). Gas chromatographic examination of the crude reaction mixture (0.62 g) obtained by treatment of **3a** (0.5 g, 4 mmol), as indicated in the general procedure, showed the presence of starting material (30%), together with two major compounds **3b** (32%) and **3c** (22%), resorcinol (**3d**) (ca. 5–10%), and several minor compounds (3%). Chromatographic separation on silica gel (hexane–ether 8:2) afforded the following.

3b: white crystals (benzene–hexane), mp 92–3 °C; IR (KBr) 3350, 1590, 1480, 1465, 1450, 1425, 1280, 1195, 1160, 1070, 1025, 950, 830 cm^{-1}; ^1H NMR 7.05 (d, 1 H, J = 9 Hz), 6.33 (m, 2 H), 4.90 (bs, 1 H), 3.76 (s, 3 H), 2.27 (s, 3 H) ppm; EIMS *m/e* (%) 172 (5), 171 (9), 170 (M^+ 100), 155 (28), 127 (14), 111 (31), 109 (10), 99 (14), 85 (17), 81 (15), 69 (30), 65 (19). Anal. Calcd for $C_8H_{10}SO_2$: C, 56.45; H, 5.92. Found: C, 56.72; H, 5.93.

3c: pale yellow oil, bp 80 °C (0.5 mmHg): IR (film) 3380, 1590, 1465, 1450, 1260, 1215, 1175, 1080, 780 cm^{-1}; ^1H NMR 7.19 (t, 1 H, J = 8.2 Hz), 6.64 (dd, 1 H, J = 8.2 and 1.2 Hz), 6.45 (dd, 1 H, J = 8.2 and 1.2 Hz), 7.01 (bs, 1 H), 3.88 (s, 3 H), 2.24 (s, 3 H) ppm; EIMS *m/e* (%) 172 (4), 171 (9), 170 (M^+ 100), 155 (30), 127 (19), 111 (37), 99 (10), 97 (14), 65 (20). Anal. Calcd for $C_8H_{10}SO_2$: C, 56.45; H, 5.92. Found: C, 56.44; H, 6.14.

3d was found to be identical with an authentic sample. Examination of the crude reaction mixture by GC/MS revealed the following mass spectra for the minor byproducts.

3e: EIMS *m/e* (%) 171 (14), 170 (M^+ 100), 155 (38), 127 (26), 111 (39), 109 (11).

3f: EIMS *m/e* 216 (5), 215 (11), 260 (M^+ 100), 245 (56), 230 (27), 202 (26), 198 (20), 187 (13).

3g: EIMS *m/e* (%) 262 (9), 261 (11), 260 (M^+ 100), 245 (56), 230 (27), 202 (26), 198 (20), 187 (13), 169 (16).

Lithiation of 2-Methoxyphenol (4a). Preparation of 2-Methoxy-3-(methylthio)phenol (4b), 2-Methoxy-6-(methylthio)phenol (4c), and Catechol (4d). Gas chromatographic analysis of the crude reaction mixture (0.62 g) obtained by treatment of **4a** (0.5 g, 4 mmol), as indicated in the general procedure, showed the presence of starting material (25%), together with two major compounds **4b** (62%) and **4c** (12%), catechol (**4d**) (<1%), and several minor compounds (1%). Chromatographic separation on silica gel (benzene) afforded the following.

4b was obtained as a clear oil which solidified on standing. Crystallization (benzene–hexane) yielded a white solid, mp 52–3 °C: IR (film) 3500, 1600, 1480, 1465, 1440, 1275, 1220, 1050, 765, 730 cm^{-1}; ^1H NMR 6.89 (m, 3 H), 6.18 (bs, 1 H), 3.88 (s, 3 H) ppm; EIMS *m/e* (%) 172 (5), 171 (10), 170 (M^+ 100), 155 (26), 111 (19), 109 (20), 93 (23), 65 (21). Anal. Calcd for $C_8H_{10}SO_2$: C, 56.45; H, 5.92. Found: C, 56.28; H, 5.66.

4c: colorless oil, bp 105 °C (1 mmHg); IR (film) 3400, 1580, 1465, 1430, 1280, 1225, 990, 910, 770 cm^{-1}; ^1H NMR 6.80 (m, 3 H), 5.82 (bs, 1 H), 3.87 (s, 3 H), 2.42 (s, 3 H) ppm; EIMS *m/e* (%) 172 (5), 171 (10), 170 (M^+ 100), 155 (67), 111 (30), 109 (18), 93 (42), 65 (33). Anal. Calcd for $C_8H_{10}SO_2$: C, 56.45; H, 5.92. Found: C, 56.37; H, 5.93.

4d was identified by comparison with an authentic sample. Examination of the crude reaction mixture by GC/MS revealed the following mass spectra for the minor byproduct.

4e: EIMS *m/e* (%) 216 (M^+ 100), 201 (15), 187 (10), 157 (10), 139 (36), 125 (52), 124 (21), 111 (96).

Lithiation of 2,6-Dimethoxyphenol (5a). Preparation of 2,6-Dimethoxy-3-(methylthio)phenol (5b), 2,6-Dimethoxy-3,5-bis(methylthio)phenol (5c), 3-Methoxy-6-(methylthio)-catechol (5d), and 3-Methoxycatechol (5e). Treatment of 0.31 g (2 mmol) of **5a** as indicated in the general procedure provided 0.35 g of a crude mixture, gas chromatographic analysis of which revealed the presence of starting material (13%), two major compounds **5b** and **5d** (40 and 39%, respectively), and two minor byproducts **5c** and **5e**, both in 1.5% yield. Column chromatography on silica gel (hexane–ether, 8:2) furnished the following.

5b: colorless oil, bp 105 °C (0.1 mmHg); IR (film) 3420, 1580, 1480, 1465, 1285, 1215, 1085, 890 cm^{-1}; ^1H NMR 6.74 (d, 1 H, J = 8.7 Hz), 6.60 (d, 1 H, J = 8.7 Hz), 5.57 (bs, 1 H), 3.93 (s, 3 H), 3.86 (s, 3 H), 2.39 (s, 3 H) ppm; EIMS *m/e* (%) (silyl derivative) 272 (M^+ 58), 243 (16), 242 (100), 227 (18), 73 (21). Anal. Calcd for $C_9H_{12}SO_3$: C, 53.98; H, 6.04. Found: C, 53.90; H, 6.07.

5c: colorless oil, bp 95 °C (0.1 mmHg); ^1H NMR 6.61 (s, 2 H), 5.63 (s, 1 H), 3.91 (s, 6 H), 2.43 (s, 6 H) ppm; EIMS *m/e* (%) (silyl derivative) 320 (15), 319 (21), 318 (M^+ 100), 303 (22), 290 (15), 289 (18), 288 (96), 273 (13), 258 (12), 73 (53). HREIMS of **5c**: Calcd for $C_{10}H_{14}S_2O_3$: 246.0383. Found: 246.0361.

5d: colorless oil, bp 115 °C (0.1 mmHg); IR (film) 3400, 1610, 1490, 1285, 1205, 1080, 890, 780 cm^{-1}; ^1H NMR 6.99 (d, 1 H, J = 8.7 Hz), 6.48 (d, 1 H, J = 8.7 Hz), 6.31 (s, 1 H), 5.37 (bs, 1 H), 3.88 (s, 3 H), 2.30 (s, 3 H) ppm; EIMS *m/e* (%) (disiyl derivative) 332 (12), 331 (23), 330 (M^+ 84), 315 (34), 302 (13), 301 (24), 300 (100), 270 (13), 227 (10), 73 (58). Anal. Calcd for $C_8H_{10}SO_3$: C, 51.60; H, 5.41. Found: C, 51.90; H, 5.60.

5e was identified by comparison with an authentic sample.

General Procedure for the *n*-BuLi Promoted Demethylation of Phenolic and Nonphenolic Alkyl Aryl Ethers. An oven-dried round-bottom flask protected from the atmosphere

by rubber septa, under argon, was charged with the appropriate phenol (3 mmol) and dry ether (6 mL). To this stirred solution, at room temperature (23 °C), 1.5 M *n*-BuLi (6 mL, 9 mmol) was added dropwise (4 min) via syringe. The mixture was magnetically stirred for up to 48 h, cooled to 0 °C, and finally carefully quenched with water. The standard workup yielded a residue which was then examined by gas chromatographic analysis against authentic samples. Quantitative results are given in the text.

Acknowledgment. Financial support by the DGICYT (PB87-0019) is gratefully acknowledged. We are indebted to Professor S. Olivella (University of Barcelona, Spain) for helpful discussions and also for making available to us his modified version of MOPAC. Time allocation for calculations, performed with VAX 11/750 and VAX 8820 computers, was generously provided by the Centre de Càlcul de la Universitat de les Illes Balears. Thanks are also due to Dr. G. Tojo (University of Santiago de Compostela) for obtaining our high-resolution mass spectra.

Registry No. **1a**, 150-76-5; **1b**, 127087-14-3; **1c**, 123-31-9; **1d**, 127087-15-4; **1e**, 127087-16-5; **2a**, 5307-05-1; **2b**, 127087-17-6; **2c**, 127087-18-7; **2d**, 127087-19-8; **3a**, 150-19-6; **3b**, 19555-09-0; **3c**, 33617-66-2; **3d**, 108-46-3; **3e**, 127087-20-1; **3f**, 127087-21-2; **3g**, 127087-22-3; **4a**, 90-05-1; **4b**, 127087-23-4; **4c**, 38377-31-0; **4d**, 120-80-9; **4e**, 127087-24-5; **5a**, 91-10-1; **5b**, 127087-25-6; **5c**, 127087-26-7; **5d**, 127087-27-8; **5e**, 87-66-1; **6a**, 634-36-6; **6b**, 5150-42-5; **7a**, 91-16-7; **7b**, 90-05-1; **8a**, 100-66-3; **8b**, 500-99-2; **9b**, 108-95-2.

Supplementary Material Available: Listing of Cartesian coordinates of the optimized molecular structures (16 pages). Ordering information is given on any current masthead page.

Electrochemical Hydrotrifluoromethylation of Fumaronitrile

Kenji Uneyama* and Shunsuke Watanabe

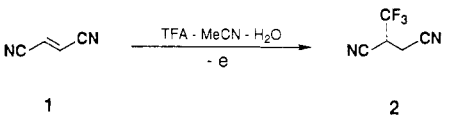
Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700, Japan

Received January 19, 1990

Electrooxidation of trifluoroacetic acid in the presence of fumaronitrile (1) in an MeCN–H_2O–(Pt) system provides 2-(trifluoromethyl)succinonitrile (2) in a 65% yield. The electrochemical reaction is remarkably affected by the reaction temperature. That is, at the ice-cooling temperature, a simple hydrogenation of 1 predominates, while at 50–55 °C, the desired hydrotrifluoromethylation proceeds exclusively. The anodically generated trifluoromethyl radicals recombine with the succinonitrile radicals produced at the cathode, leading to the formation of 2.

Because of the increasing attention to trifluoromethyl compounds for medicines and material science,[1,2] trifluoromethyl metal complexes have been extensively employed for trifluoromethylation of carbonyl compounds[3-5] and aryl halides.[6-8] Perfluoroalkanoyl peroxide,[9-11] *N*-(trifluoromethyl)-*N*-nitrosotrifluoromethanesulfonamide-,[12,13] and xenon difluoride–trifluoroacetic acid[14] can trifluoromethylate aromatic compounds. Recently, electrochemical trifluoromethylation of olefins has been recognized as a useful method for the preparation of aliphatic trifluoromethylated compounds since electrochemical oxidation of trifluoroacetic acid (TFA) in an MeCN–H_2O–(Pt) system generates trifluoromethyl radicals almost quantitatively[15] and TFA is one of the economically feasible trifluoromethyl sources. Renaud,[17,18] Brookes,[19,20]

Scheme I



1 2

Muller,[21,22,24] and our group[15,16] have demonstrated the usefulness of electrochemical trifluoromethylation. Trifluoromethyl–dimerization of methyl acrylate,[15] bistrifluoromethylation of acrylamide,[16] diethyl fumarate, and maleimide,[18] and trifluoromethyl–acetamidation of methyl methacrylate[23] are typical examples which are not realized by conventional chemical reactions. On the other hand, hydrotrifluoromethylation of olefins sometimes occurs as a side reaction[17-20] but does not predominate in most electrochemical trifluoromethylations. Judging from the reported results so far, the electronic and steric features of the substituents attached to the carbon–carbon double bond of the reactant olefins are intensively influential toward the chemical and electrochemical fate of the initially formed trifluoromethylated radical intermediates and thus to the final products. Among the nitrogen-containing functional groups, both carbamoyl groups of acrylamide[16] and maleimide[18] enhance bistrifluoromethylation while the cyano group in acrylonitrile promotes trifluoromethyl–dimerization.[20] Generalization on the substituent effect of the electrochemical trifluoromethylation of olefins re-

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