Deoxygenation of Highly Hindered Phenols

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Received May 2, 1989

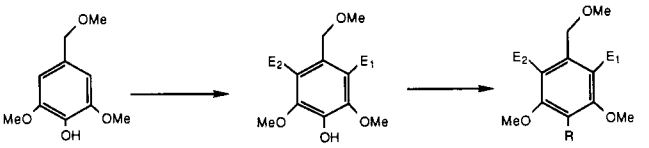
Highly hindered phenolic compounds can be efficiently deoxygenated by reduction of the corresponding triflates under homogeneous [RCOOH, Bu_3N, $PdCl_2(PPh_3)_2$, $Ph_2PCH_2CH_2CH_2PPh_2$, DMF] or heterogeneous (Pd/C) conditions. Reductive deoxygenation under homogeneous conditions has been shown to occur both in the presence of acid (HCOOH, CH_3COOH, $(CH_3)_3CCOOH$, $PhCH_2COOH$) or in its absence. The concomitant formation of dibutylformamide apparently derives from aminolysis of DMF by dibutylamine, the Pd(0)-catalyzed hydrolysis product of tributylamine. Deuteration experiments suggest that several hydrogen (or deuterium) sources operate in the hydrogenolysis processes studied.

Due to the synthetic importance of having appropriate methodology for the conversion of shikimic acid metabolites into polyketide metabolites,[1] we planned to demonstrate the versatility of the following conceptually simple design (Scheme I). The first part of the plan was based in our recent work on the direct lithiation of phenols, which allowed us to introduce, with great ease, a variety of electrophiles (E_1 and E_2 in Scheme I) onto highly substituted phenols.[2] As an added bonus, the symmetric nature of the starting material required for our purposes (4-hydroxy-3,5-dimethoxybenzyl methyl ether) clearly simplified the regioselectivity problems foreseen in the metalation step of nonsymmetric phenols.

On the other hand, the second part of the plan called for developing appropriate conditions for the removal of the phenolic group in highly hindered electron-rich substrates and the simultaneous introduction of different groups such as hydrogen, alkyl, alkenyl, alkynyl, carbaldehyde, carboxyl, etc.[3] This, we expected, would provide derivatives of potential interest as advanced intermediates for the synthesis of complex polyketide metabolites. According to the currently accepted mechanism for these and related processes,[4a] serious problems were expected as a consequence of the strong (negative) influence of both steric hindrance and (the presence of) electron-donating substituents on the reaction rate of the oxidative addition[4b] and reductive elimination[4c] steps.

The deoxygenation of hindered phenols, the matter of the present report, was planned the first target, the remaining objectives being allocated for future development. Actually, the deoxygenation (COH → CH) of a variety of phenol derivatives such as esters, ethers, urethanes, ureas, etc., has been the target issue of an abundant number of

Scheme I



recent publications,[3,5] each one of them claiming the usefulness of the cleavage reagent employed. For the most part these reactions belong to the three following types: (a) hydrogenolysis under heterogeneous conditions (Pd/C, Ni Raney); (b) Pd(0)-catalyzed reduction under homogeneous conditions; (c) reduction induced by alkali (Na, K, Li) or other zero-valent (Ti) metals.

In spite of these recent developments and of the tremendous activity witnessed in the field of palladium-catalyzed C–H (and C–C) bond formation while this work was still in progress,[3,6,15] it is our belief that the reported methodology is not useful for the highly encumbered and functionalized substrates required in our objectives[6] (vide infra). Actually, most papers either deal with unhindered phenol derivatives or describe reduction problems when sterically hindered ones are used. Only zerovalent metal reductions, as expected, are effective for the reduction of phenol derivatives when severe steric hindrance exists.[7]

(1) *Secondary metabolism*; Mann, J., Ed.; Oxford University Press: London, 1980.

(2) Saá, J. M.; Llobera, A.; García-Raso, A.; Costa, A.; Deyá, P. M. *J. Org. Chem.* **1988**, *53*, 4263. Saá, J. M.; Morey, J.; Costa, A. *Tetrahedron Lett.* **1986**, *27*, 5125.

(3) For a recent account on the subject, see: Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. For more recent developments, see: Echevarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478. Echevarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557. Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296. Dolle, R. V.; Schmidt, S. J.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1987**, 904. Petrakis, K. S. Nagabhushan, T. L. *J. Am. Chem. Soc.* **1987**, *109*, 2831. Lu, X.; Zhun, J. *Synthesis* **1987**, 726. Chen, Q.-Y.; He, Y.-B. *Synthesis* **1988**, 897. Chen, Q.-Y.; He, Y.-B. *Tetrahedron Lett.* **1987**, *28*, 2387. Cachi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931. Chen, Q.-Y.; Yang, Z.-Y. *Tetrahedron Lett.* **1986**, *27*, 1171. García Martínez, A.; Martínez, R.; Arranz, J.; Subramanian, K. R. *J. Chem. Soc., Perkin Trans. 1*, **1986**, 1595.

(4) (a) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson G., Ed.; Pergamon Press: New York, 1982; Vol. 8, p 799. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992. Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287. (c) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933. Widowsson, D. A.; Zhang, Y.-Z. *Tetrahedron* **1986**, *42*, 2111.

(5) *Methoden der Organischen Chemie (Houben Weyl)*, Band 6/1c, Teil 2; Georg Thieme Verlag: Stuttgart, 1976.

(6) To our knowledge, very few hindered phenols (2,6-dimethylphenol and some 1-naphthol derivatives) have been the subject of Pd(0)-catalyzed deoxygenation studies. See ref 3, 15, and Chen, Q. Y.; He, Y.-B.; Yang, Z.-Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1452. C–C bond formation has been achieved in hindered bromoaniline derivatives. See: Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1988**, *53*, 1170.

(7) Welch, S. C.; Walters, M. E. *J. Org. Chem.* **1978**, *43*, 4797. See also ref 8 and 12.

(8) For deoxygenation procedures leading to simple resorcinol dimethyl ethers, see: Bailey, K. *Can. J. Chem.* **1974**, *52*, 2136. Azzena, U.; Denurra, T.; Melloni, G.; Rassu, G. *J. Chem. Soc., Chem. Commun.* **1987**, 1549.

(9) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.

(10) Care must be taken to ensure that no sulfur impurities accompany the desired triflates, as they apparently poisson the catalyst, thus precluding the reaction to take place. Typically, crude triflates (>95% pure by ^1H NMR) need to be chromatographed (silica gel, methylene choride) prior to be submitted to Pd/C-catalyzed hydrogenolysis.

(11) Phenol phosphates were prepared as described by Rossi, R. A.; Bunnett, J. F. *J. Org. Chem.* **1973**, *38*, 2314.

(12) Dominianni, S. J.; Ryan, C. W.; DeArmitt, C. W. *J. Org. Chem.* **1977**, *42*, 344. See also ref 11.

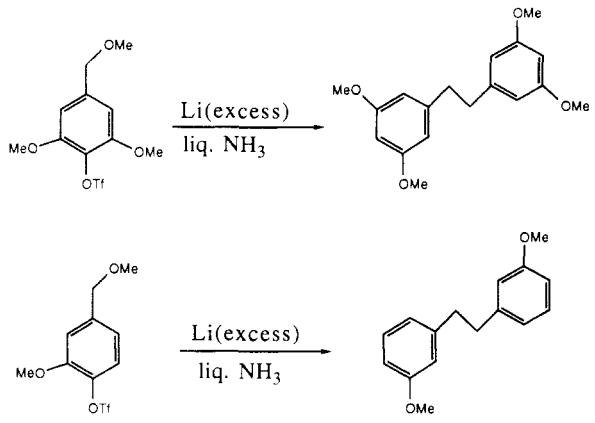
(13) Cachi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541.

(14) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

(15) Peterson, G. A.; Kunnung, F. A.; McCallum, J. S.; Wulff, W. D. *Tetrahedron Lett.* **1987**, *28*, 1381.

0022-3263/90/1955-0991$02.50/0

Scheme II



Unfortunately, the reaction conditions needed are not compatible with numerous functionalities and, therefore, its applicability is considered to be narrow.

The purpose of the present report is to communicate the results of our studies which demonstrate that highly substituted phenol triflates can be reduced either under homogeneous or heterogeneous conditions, the former being the method of choice for the efficient preparation of a variety of functionalized resorcinol dimethyl ethers.[8] Furthermore, it was quite clear to us at the beginning that a major goal to be achieved by any methodology in the field of phenol deoxygenation should be its high chemoselectivity, i.e., the survival of other functional groups present in the molecule was considered a high priority objective for the wide applicability of the plan.

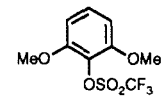
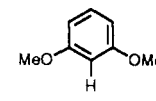
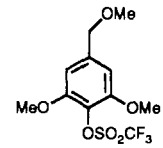
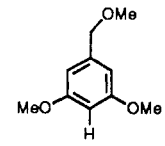
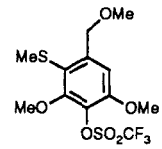
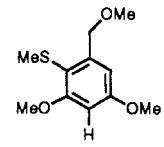
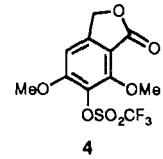
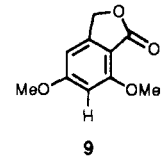
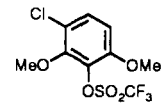
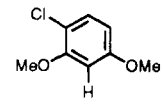
The starting phenols, prepared as described previously,[2] were easily converted, under the reported conditions,[9] into the corresponding triflates **1–5**. In particular, the synthesis of triflyl lactone **4** is worthy of note as it was best obtained by a two-step one-pot procedure involving first lactonization (overnight) of 3-hydroxy-2,4-dimethoxy-6-(methoxymethyl)benzoic acid[2] with triflic anhydride in the absence of base, followed by further treatment with triflic anhydride and base (2,4,6-collidine), for the final phenol triflation.

We soon learned that heterogeneous hydrogenolysis of phenol triflates **1**, **2**, and **4**[10] to the corresponding resorcinol dimethyl ethers **6**, **7**, and **9** could be achieved in high yield (Table I, method A) by working under somewhat harsh conditions (H_2, 65 psi, Et_3N, 10% Pd/C, 4–6 h), though poisoning problems were immediately encountered (Table I, entry 3).

On the other hand, attempts at reducing phenol phosphates[11] under the usual conditions[12] (excess lithium was employed) unexpectedly led to the corresponding deoxygenated 1,2-arylethane derivatives in good yields. As illustrated in Scheme II, this deoxygenative reductive dimerization was shown to be applicable to other closely related substrates. Due to this unwanted, though quite efficient, reductive dimerization no further exploration into the use of phenol phosphates for the original plan (Scheme I) was attempted. Moreover, efforts at reducing phenol phosphates by the method of Cachi et al.[13] invariably led to extensive hydrolysis (up to 85% phenol recovered).

Therefore we turned our attention to the Pd(0)-catalyzed reduction of phenol triflates (method B). In spite of the fact that the reduction of model compound 1-naphthyl triflate was achieved in the reported yield,[13] our initial attempts at reducing **1** under otherwise identical conditions were disappointing, the starting material being recovered unchanged, after heating at 80–90 °C for 5 h. The use of

Table I. Deoxygenation of Highly Hindered Phenols

entry	substrate	product	method (yield, %)
1	 **1**	 **6**	A (90) B (89) C (70) D (82)
2	 **2**	 **7**	A (81) B (79) C (70)
3	 **3**	 **8**	A (0)[a] B (60)
4	 **4**	 **9**	A (75) B (76)
5	 **5**	 **10**	B (78)

[a] Starting material **3** was recovered in 72% yield.

$Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ as catalysts (no phosphine added[6]) did not significantly improve the above results with **1**.

Cachi[13] and Wulff,[15] on the basis of the well-known[14] accelerating effect induced by 1,1′-bis(diphenylphosphino)ferrocene (dppf) in Pd(0)-catalyzed C–C coupling reactions (presumably by facilitating the reductive elimination step), have recently explored, with some success, its use for the reduction of somewhat encumbered phenol triflates. Unfortunately, in our hands, the recourse to the dppf bidentate ligand, under the conditions described by Cachi, led to very slight improvement as only small amounts (<30%) of the reduced product were observed in the crude reaction mixture (^1H NMR), the remaining being unreacted starting material. To our delight, however, we found that by using 1,3-bis(diphenylphosphino)propane (dppp) as bidentate ligand good yields of the desired arenes were obtained,[16] not only for model compound **1** but also for a series of functionalized phenol triflates, as shown in Table I (method B). Entries 2–5 are worthy of note as they illustrate the chemoselectivity of the present methodology. As expected, further hydrogenolysis of benzyl methyl ethers in neutral conditions (H_2, 33 psi, 10% Pd/C, MeOH) gave the corresponding toluene derivatives (**7** → orcinol dimethyl ether, 100% yield).

In principle one would be prone to accept that the latter method for deoxygenating hindered phenols (method B) is just a simple exploitation of previous developments by other workers.[3,13,15] However, a pair of remarkable observations have led us to think that the hydrogenolysis of

(16) Similar observations in regard with the use of the bidentate ligand dppp have been reported by other authors. See: Murahashi, S.-I.; Imada, Y.; Nishimura, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1578.

hindered phenol triflates[17] may take place through different mechanistic pathways, depending on the experimental conditions employed. The first observation refers to the fact that reduction of hindered phenol triflates occurs even when formic acid (the well-established[13] hydrogen donor for the reductive deoxygenation of simple phenol triflates) was replaced by acetic, pivalic acid, or phenylacetic acid, under otherwise identical conditions. The yields (not optimized; Table I (method C)), however, were somewhat lower, i.e., 70% (**1** → **6**) and 70% (**2** → **7**). Interestingly, under these conditions, *N*,*N*-dibutylformamide was formed (23% yield, based on the amine employed), as well as a very minor byproduct identified (GC/MS) as *N*,*N*-dibutylacetamide.

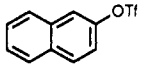
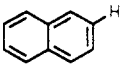
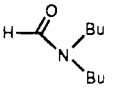
That the formation of dibutylformamide in the above reactions is not a Pd-catalyzed process was eventually proved by reacting Bu_2NH with DMF (100 °C, 28 h), with and without palladium catalyst ($(Ph_3P)_2PdCl_2$/dppp). In both cases dibutylformamide was formed in yields (ca. 9%) similar to those found in those reduction of hindered phenol triflates carried out either by method B or method D (vide infra).

As a preliminary working idea, we hypothesized that tributylamine was acting as a reducing agent[18] in those reductions involving $(Ph_3P)_2PdCl_2$/dppp/Bu_3N/AcOH/DMF, as well as those which employ pivalic or phenylacetic acid instead of acetic acid. According to the proposed mechanism,[18] tributylamine may undergo oxidation to a palladium hydride–imminium complex, in equilibrium with the corresponding enamine complex, whose hydrolysis would provide dibutylamine which on subsequent reaction with dimethylformamide should give rise to dibutylformamide. Seemingly, one would expect that tributylamine might also be doing a similar job (at least in part) as a reducing agent in those hydrogenolysis which employ the $(Ph_3P)_2PdCl_2$/dppp/Bu_3N/HCOOH/DMF system (method B) and, in fact, in a model reaction (**1** → **6**) we did observe that *N*,*N*-dibutylformamide was being formed, through in lower yield (9%, based on the amine employed) than in the case of method C above.

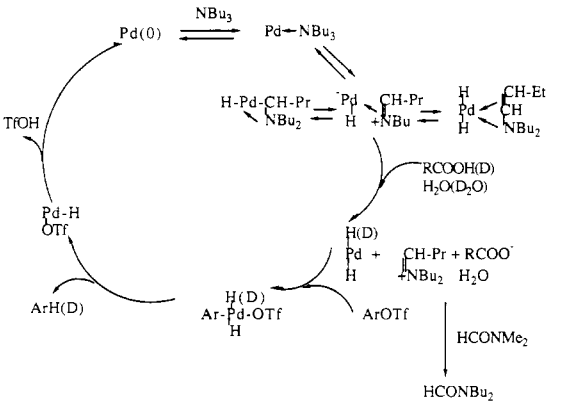
Yet, we have now demonstrated that the reduction of hindered phenol triflates works well (**1** → **6**, 11 h, 100 °C, 82% isolated yield) even when no acid is present [$(Ph_3P)_2PdCl_2$/dppp/Bu_3N/DMF] (method D), dibutylformamide being also isolated (ca. 7%) from the reaction mixture. This observation can also be understood on the basis of the reported mechanism for the Pd(0)-catalyzed hydrolysis of tertiary amines,[18] provided that residual water (or other oxygen nucleophiles) were operating as the hydrolytical agent. The use of dry commercial DMF (maximum 100 ppm of H_2O) did not led to a significant increase in reaction time (11 h, 100 °C, 70% isolated yield).

In order to shed more light into the mechanism of the above reactions, several deuteration experiments were launched. In particular, we were curious to see whether or not a common mechanism was applicable to those reductions carried out with HCOOH/Bu_3N (method B), CH_3COOH/Bu_3N (method C), or Bu_3N (method D). Furthermore it was also of interest to learn if the accepted mechanism for the reduction of simple phenol triflates[13] was the one operating in the case of hindered phenols (method B).

Table II. Deoxygenation of Unhindered Phenols

substrate	products	method (isoalted yield, %)
		B (72) C (70) D (77)
		B (6) C (19) D (3)

Scheme III



In the event, hydrogenolysis of **1** and **2** in the presence of CD_3COOD yielded partially deuterated **6** and **7** (20 and 30%, respectively, as measured by EIMS). A similar level of deuteration was realized (20%) when hydrogenolysis of **1** was treated with CH_3COOH/D_2O. In contrast with these results, hydrogenolysis of **1** with D_2O-dopped DMF as deuterium source (0.1 mL of D_2O added to 3 mL of commercial dry DMF) led to very low (ca. 5%) deuteration, both when the reaction was carried out with HCOOH or without acid.

Thus, in striking difference with Cachi's finding that simple phenol triflates incorporate 100% deuterium from (the deuterium–carbon bond of) DCOOD, our results for the hydrogenolysis of hindered phenol triflates provide indirect evidence for the existance of several hydrogen sources in the reaction medium. Thus, in accordance with the mechanistic proposal of Murahashi[18] for the palladium-catalyzed hydrolysis of tertiary amines, we believe that the ultimate hydrogen (or deuterium) donors for method C reductive deoxygenations must be tributylamine (through protons on the α- and β-carbons) and acetic acid (through its hydroxyl hydrogen). On the other hand, for those reductions involving Bu_3N alone (method D) the only hydrogen donor available is tributylamine itself (through its α- and β-hydrogens). Moreover, since (method B) reductions carried out with HCOOH/Bu_3N and HCOOH/Bu_3N/D_2O gave only a marginal level of deuteration, we conclude that a different mechanism must be operating in these cases, possibly that generally accepted for the reduction of simple phenol triflates which involves: (a) complexation of palladium(0) with formate ion, (b) β-elimination of palladium hydride, (c) oxidative addition of ArOTf, and (d) reductive elimination.

Finally, deoxygenation of a nonhindered phenol triflate (2-naphthyl triflate) was studied under all set of conditions for comparison purposes. As shown in Table II the results obtained are in complete agreement with those shown above for hindered substrates, thus supporting our view

(17) Partial hydrogenolysis of hindered aryl bromides has been noticed during attempted Heck (and related) reactions. See, for example: Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941. Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 1206.

(18) Clark, F. R. S.; Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1975**, 121. Murahashi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348. Murahashi, S.-I.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7429. Murahashi, S.-I.; Yano, T. *J. Am. Chem. Soc.* **1980**, *102*, 2456. McCrindle, R.; Ferguson, G.; Arsenault, G. J.; McAlees, A. J.; Stephenson, D. K. *J. Chem. Res. (S)* **1984**, 360.

regarding the existance of several mechanistic pathways common for both the Pd(0)-catalyzed deoxygenation of hindered and unhindered phenol triflates.

Though it is clearly premature to provide clear-cut evidence for the mechanistic details in regard of the so-called methods C and D just described, in our view the above experimental observations are consistent with the following working hypothesis (Scheme III).

In conclusion, indirect evidence for the intervention of tributylamine as reducing agent in some Pd(0)-catalyzed reductions of phenol triflates has been presented. Several (unexplained) examples of abnormal hydrogenolysis found in the literature[17] may be related to the above observations.

In summary, two methods for the reduction of highly hindered phenol triflates are now at hand. Work is being done toward the development of analogous methodology for the formation of C–C bonds, as illustrated in Scheme I.

Experimental Section

General Methods. All melting points are uncorrected and were taken on a capillary melting point apparatus. The boiling points given refer to those observed on bulb-to-bulb distillation (Büchi GKR-50 apparatus). Proton NMR spectra were obtained on a Varian FT-80A spectrometer in $CDCl_3$ with Me_4Si as internal standard. Electron impact mass spectra were recorded on a Hewlett-Packard 5988A GC/MS operating at 70 eV ionizing energy. Infrared spectra were recorded on a Hitachi 260-10 infrared spectrophotometer. Elemental analyses were obtained at the Servei de Microanalisi del CSIC (Barcelona). Column chromatographies were performed on Merck silica gel (Kieselgel 40). Commercial dry DMF was used as received. Dry Bu_3N was prepared according to known procedures.[19]

General Procedure for the Preparation of Phenol Triflates. Typically, a chilled (0 °C) solution of phenol (3 mmol) and 2,4,6-trimethylpyridine (12.12 mmol) in anhydrous methylene chloride (15 mL) was treated, under argon, with triflic anhydride (3.6 mmol), and then stirred overnight. Workup was carried out by adding diethyl ether (50 mL), followed by washing with water (2 × 10 mL), and then with a saturated aqueous solution of $CuSO_4$ (8 × 20 mL). Evaporation of the solvent in vacuo usually furnished a crude material which was first purified by chromatography on a silica gel column (methylene chloride) and finally bulb-to-bulb distilled.

2,6-Dimethoxyphenyl triflate (1) was obtained in 76% yield as a clear oil: bp 145–150 °C (0.5 mmHg); IR (film)[20] 1610, 1490, 1420, 1310, 1260, 1240, 1200, 1140, 1120, 890, 780 cm^{-1}; ^1H NMR[20] 7.23 (d, J = 8.4 Hz), 6.67 (d, J = 8.4 Hz), 3.88 (s, 6 H) ppm; ^{13}C NMR 152.37, 128.45, 128.02, 118.59 (q, J = 321 Hz), 104.77, 55.89 ppm; EIMS m/e (%) 286 (M^+, 29), 153 (100), 125 (37), 110 (53), 95 (45), 93 (43), 69 (33), 65 (25).

2,6-Dimethoxy-4-(methoxymethyl)phenyl triflate (2) was obtained from the corresponding phenol[2] as a white solid, mp 60–61 °C (CH_2Cl_2), in 71% yield: IR (KBr) 1610, 1460, 1400, 1230, 1215, 1200, 1190, 1120, 880, 810 cm^{-1}; ^1H NMR 6.60 (s, 2 H), 4.42 (s, 2 H), 3.88 (s, 6 H), 3.42 (s, 3 H) ppm; ^{13}C NMR 152.16, 139.46, 126.87, 118.51 (q, J = 320 Hz), 103.42, 73.94, 58.14, 55.99 ppm; EIMS m/e (%) 330 (M^+, 21), 197 (100), 169 (35), 167 (17), 154 (17), 139 (18), 138 (27), 111 (12), 69 (18). Anal. Calcd for $C_{11}H_{13}F_3O_6S$: C, 40.00; H, 3.94. Found: C, 39.97; H, 3.94.

2,6-Dimethoxy-4-(methoxymethyl)-3-(methylthio)phenyl triflate (3) (oil, bp 135–140 °C (0.02 mmHg)) was synthesized in 51% yield (isolated) starting from the corresponding phenol:[2] IR (film) 1600, 1470, 1425, 1335, 1210, 1130, 900, 800 cm^{-1}; ^1H NMR 6.97 (s, 1 H), 4.66 (s, 2 H), 3.96 (s, 3 H), 3.91 (s, 3 H), 3.49 (s, 3 H), 2.33 (s, 3 H) ppm; ^{13}C NMR 154.34, 152.00, 143.09, 131.58, 120.50, 118.48 (q, J = 320 Hz), 107.03, 72.17, 61.04, 58.25, 55.95, 18.42 ppm; EIMS m/e (%) 378 (M^+ + 2, 8), 377 (M^+ + 1, 12), 376 (M^+, 82), 244 (13), 243 (100), 228 (10), 227 (11), 213 (16), 198 (15), 197 (20), 185 (11), 168 (20), 153 (16), 69 (28).

1*H*,3*H*-5,7-Dimethoxy-6-((trifluormethyl)sulfonyl)isobenzofuran-1-one (4) was prepared in 75% overall yield in a two-step one-pot reaction. Lactonization of 3-hydroxy-2,4-dimethoxy-6-(methoxymethyl)benzoic acid[2] was first achieved by overnight treatment with a 2.5 molar excess of triflic anhydride (no base added). This was followed by triflation of the resulting phenolic lactone[2c] by further stirring (15 h) with triflic anhydride (1.1 molar excess) and 2,4,6-trimethylpyridine (4 molar excess). The usual workup furnished 4 as a crystalline solid; mp 119–121 °C (methylene chloride or ether): IR (KBr) 1750, 1600, 1420, 1360, 1345, 1250, 1215, 1130, 1085, 1020, 940, 885, 800 cm^{-1}; ^1H NMR 6.79 (s, 1 H), 5.22 (s, 2 H), 4.27 (s, 3 H), 3.99 (s, 3 H) ppm; ^{13}C NMR 184.67, 167.23, 157.41, 149.12, 120.16, 118.50 (q, J = 321 Hz), 109.51, 99.60, 68.60, 63.37, 56.76 ppm; EIMS m/e (%) 342 (M^+, 10), 210 (11), 209 (100), 181 (12), 151 (15), 69 (20). Anal. Calcd for $C_{11}H_9F_3O_7S$: C, 38.60; H, 2.63. Found: C, 38.72; H, 2.73.

3-Chloro-2,6-dimethoxyphenyl triflate (5) was obtained in 75% yield by triflation of the corresponding phenol[21] as a clear oil: bp 130–140 °C (0.001 mmHg); IR (film) 1605, 1480, 1425, 1305, 1275, 1220, 1135, 1100, 1010, 935, 910, 860, 800, 760, 740 cm^{-1}; ^1H NMR 7.28 (d, 1 H, J = 9.1 Hz), 6.71 (d, 1 H, J = 9.1 Hz), 3.93 (s, 3 H), 3.86 (s, 3 H) ppm; ^{13}C NMR 151.23, 149.49, 129.04, 119.61, 118.53 (q, J = 320 Hz), 108.14, 105.58, 61.10, 56.04 ppm. Anal. Calcd for $C_9H_8ClF_3O_5S$: C, 33.70; H, 2.50. Found C, 33.78; H, 2.53.

General Procedures for the Deoxygenation of Hindered Phenol Triflates 1–5. Method A. The heterogeneous mixture resulting from mixing a methanolic solution (15 mL) of purified[10] triflate 1–4 (2.0 mmol), triethylamine (0.51 g, 5.05 mmol), and 10% Pd/C (equal weight to that of triflate) was hydrogenated (H_2, 65 psi) for 4–6 h. The standard workup usually provided crude materials which were then bulb-to-bulb distilled (see Table I for yields).

Method B. A round-bottom flask charged with 1.0 mmol of triflate 1–5, tributylamine (1 mL, 4.2 mmol), 1,3-bis(diphenylphoshino)propane (0.062 g, 0.15 mmol), $PdCl_2(PPh_3)_2$ (0.037 g, 0.06 mmol) suspended in DMF (3 mL), and formic acid (0.1 mL) was heated, under an inert atmosphere, at 80–90 °C during 18–24 h (unoptimized). Water and ether (25 mL) were added. The organic phase after being washed with 1.5 N HCl (6 × 20 mL) and dried over anhydrous sodium sulfate yielded on evaporation a crude material which, bulb-to-bulb distillation furnished pure resorcinol dimethyl ethers 6–10 in the yields given (Table I). A single experiment recently carried out (1 → 6) has shown that the reaction time can be substantially reduced (3 h) by just increasing the reaction temperature at 100 °C.

Method C. Identical to method B except that acetic acid (0.15 mL) was employed instead of formic acid. Yields given in Table I refer to those obtained on heating at 100 °C during 11 h. Identical results were obtained when pivalic acid or phenyl acetic were used instead of acetic acid.

Method D. Identical to method B except that no acid was added to the reaction mixture. Yields given (Table I) refer to those obtained by heating at 100 °C during 11 h. 1,3-Dimethoxybenzene (resorcinol dimethyl ether) (6) was obtained, in the yields given in Table I, as a clear oil: bp 85–90 °C (0.4 mmHg) (lit.[22] bp 85–7 °C (7 mmHg)); IR (film) 1590, 1490, 1250, 1200, 1160, 1050, 795 cm^{-1}; ^1H NMR 7.17 (m, 1 H), 6.49 (dd, 2 H, J = 8.0 and 2.1 Hz), 6.46 (s, 1 H), 3.78 (s, 6 H) ppm; EIMS m/e (%) 140 (1), 139 (8), 138 (M^+, 100), 137 (4), 109 (38), 108 (12), 95 (20), 78 (32).

α,3,5-Trimethoxytoluene (7) was obtained in the yields given in Table I; oil; bp 105–110 °C (0.4 mmHg); IR (film) 1600, 1465, 1430, 1380, 1200, 1155, 1100, 1070, 840 cm^{-1}; ^1H NMR 6.49 (d, 2 H, J = 2.0 Hz), 6.39 (d, 1 H, J = 2.0 Hz), 4.40 (s, 2 H), 3.78 (s, 6 H), 3.38 (s, 3 H) ppm; ^{13}C NMR 160.67, 140.45, 105.02, 99.50,

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74.31, 57.75, 54.95 ppm; EIMS m/e (%) 182 (M^+, 53), 153 (10), 152 (100), 151 (21), 121 (11), 91 (12), 77 (17), 65 (13). Anal. Calcd for $C_{10}H_{14}O_3$; C, 65.93; H, 7.69. Found: C, 65.80; H, 7.75. Hydrogenolysis (H_2, 10% Pd/C, 33 psi, 0.5 h) of a methanolic solution of **7** yielded 3,5-dimethoxytoluene (orcinol dimethyl ether) in 98%: bp 100–105 °C (0.5 mmHg); mp 243–4 °C (lit.[22] bp 112–3 °C (13 mmHg), mp 244 °C); IR (film) 1590, 1450, 1305, 1190, 1135, 1055, 815 cm^{-1}; ^1H NMR 6.31 (s, 3 H), 3.76 (s, 6 H), 2.29 (s, 3 H) ppm; EIMS m/e (%) 152 (M^+, 100), 123 (53), 122 (18), 109 (24), 91 (22), 77 (21).

α,3,5-Trimethoxy-2-(methylthio)toluene (**8**) was obtained in the yields given in Table I: oil; bp 115–120 °C (0.01 mmHg); IR (film) 1595, 1460, 1325, 1200, 1160, 1075, 840 cm^{-1}, ^1H NMR 6.67 (d, 1 H, J = 2.5 Hz), 6.41 (d, 1 H, J = 2.5 Hz), 4.70 (s, 2 H), 3.88 (s, 3 H), 3.82 (s, 3 H), 3.45 (s, 3 H) ppm; ^{13}C NMR 160.87, 160.67, 143.73, 113.56, 103.84, 97.91, 72.68, 58.06, 55.63, 55.02, 18.19 ppm; EIMS m/e (%) 230 (M^+ + 2, 7), 229 (M^+ + 1, 12), 228 (M^+, 100), 213 (60), 198 (14), 182 (10), 181 (21). Anal. Calcd for $C_{11}H_{16}O_3S$: C, 57.89; H, 7.02. Found: C, 57.81; H, 6.99.

1*H*,3*H*-5,7-Dimethoxyisobenzofuran-1-one (**9**) was prepared in the yields given in Table I: mp 151–3 °C (chloroform–methanol, 9:1) (lit.[24] mp 151–3 °C); IR (KBr) 1750, 1600, 1460, 1345, 1225, 1195, 1160, 1050, 1010, 840 cm^{-1}; ^1H NMR 6.48 (s, 1 H), 6.43 (s, 1 H), 5.16 (s, 2 H), 3.95 (s, 3 H), 3.89 (s, 3 H) ppm; EIMS m/e (%) 194 (M^+, 84), 176 (50), 165 (39), 148 (100), 135 (26), 120 (11).

1,3-Dimethoxy-4-chlorobenzene (**10**) was isolated in the yields given in Table I: oil; bp 115–120 °C (0.2 mmHg) (lit.[25] bp 238–240 °C (760 mmHg)); IR (film) 1590, 1490, 1460, 1435, 1310, 1200, 1160, 1070, 1030, 835, 790 cm^{-1}; ^1H NMR 7.23 (d, 1 H, J = 8.3 Hz), 6.48 (s, 1 H), 6.43 (d, 1 H, J = 8.3 Hz), 3.86 (s, 3 H), 3.78 (s, 3 H) ppm; EIMS m/e (%) 174 (M^+ + 2, 35), 172 (M^+, 100), 131 (11), 129 (35), 79 (14), 65 (13).

Deoxygenation of 2-Naphthyl Triflate. Method B. 2-Naphthyl triflate (0.276 g, 1 mmol) was reacted as indicated in the general procedure at 100 °C during 2.5 h. The usual workup provided naphthalene and dibutylformamide in 72% and 6% isolated yields, respectively.

Method C. 2-Naphthyl triflate (0.276 g, 1 mmol) was reacted as shown in the general procedure at 100 °C during 5.5 h. The usual workup yielded naphthalene and dibutylformamide in 70% and 19% isolated yields, respectively.

Method D. 2-Naphthyl triflate (0.276 g, 1 mmol) was reacted as indicated in the general procedure at 100 °C during 8 h. The usual workup yielded naphthalene and dibutylformamide in 77% at 3% isolated yields, respectively.

Deuteration Experiments. Method B. A mixture of triflate **1** (1.0 mmol), tributylamine (1 mL, 4.2 mmol), 1,3-bis(diphenylphosphino)propane (0.062 g, 0.15 mmol), $PdCl_2(PPh_3)_2$ (0.037 g, 0.06 mmol), formic acid (0.1 mL), and D_2O (0.1 mL), in DMF (3 mL), was heated, under an inert atmosphere, at 100 °C during 24 h (unoptimized). The usual workup yielded partially deuterated **6**: EIMS m/e (%) 137 (4), 138 (100), 139 (14), 140 (1).

Method C. (a) A mixture of triflate **1** (1.0 mmol), tributylamine (1 mL, 4.2 mmol), 1,3-bis(diphenylphosphino)propane (0.062 g, 0.15 mmol), $PdCl_2(PPh_3)_2$ (0.037 g, 0.06 mmol), and CD_3COOD (0.16 mL), in DMF (3 mL), was heated, under an inert atmosphere, at 100 °C during 24 h (unoptimized). The usual workup yielded partially deuterated **6**: EIMS m/e (%) 137 (4), 138 (100), 139 (32), 140 (3).

(b) Identical to (a) above except that CD_3COOD was replaced by CH_3COOH (0.15 mL) and D_2O (0.1 mL). The usual workup provided partially deuterated **6**: EIMS m/e (%) 137 (4), 138 (100), 139 (30), 140 (3).

Method D. A mixture of triflate **1** (1.0 mmol), tributylamine (1 mL, 4.2 mmol), 1,3-bis(diphenylphoshino)propane (0.062 g, 0.15 mmol), $PdCl_2(PPh_3)_2$ (0.037 g, 0.06 mmol), and D_2O (0.1 mL), in DMF (3 mL), was heated, under an inert atmosphere, at 100 °C during 24 h (unoptimized). The usual workup yielded partially deuterated **6**: EIMS m/e (%) 137 (5), 138 (100), 139 (14), 140 (1).

Preparation of Aryl Diethyl Phosphates. Triethylamine (11.7 mmol) was added dropwise, with stirring, to a chilled (0 °C) solution of phenol (10 mmol) in Cl_4C (5 mL) and diethyl phosphonate (11.7 mmol). The mixture was stirred at 0 °C for 1 h and then left at room temperature for another 16 h. Methylene chloride (25 mL) was added, and the resulting mixture was washed with 4 N NaOH, water, diluted HCl, water, and brine. The organic phase was then dried and evaporated to dryness. The oil residue yielded pure aryl diethyl phosphates on bulb-to-bulb distillation.

Diethyl 2,6-dimethoxy-4-(methoxymethyl)phenyl phosphate was obtained in 75% yield as an oily substance: bp 160–5 °C (0.001 mmHg); IR (film) 1600, 1510, 1460, 1420, 1335, 1280, 1130, 1030, 980, 960, 930 cm^{-1}; ^1H NMR 6.57 (s, 2 H), 4.39 (s, 2 H), 4.25 (q, 4 H, J = 7 Hz), 3.85 (s, 6 H), 3.38 (s, 3 H), 1.38 (t, 6 H, J = 7 Hz) ppm; EIMS m/e (%) 334 (M^+, 100), 303 (20), 259 (64), 229 (30), 167 (63), 155 (57), 150 (95), 127 (58), 99 (57), 81 (34). Anal. Calcd for $C_{14}H_{23}O_7P$: C, 50.30; H, 6.89. Found: C, 50.43; H, 6.81.

Diethyl 2-methoxy-4-(methoxymethyl)phenyl phosphate was prepared in 82% yield as an oily substance: mp 170–5 °C (0.2 mmHg); IR (film) 1590, 1510, 1275, 1210, 1155, 1095, 1050, 1030, 960, 820 cm^{-1}; ^1H NMR 7.23 (d, 1 H, J = 6.1 Hz), 6.94 (s, 1 H), 6.83 (d, 1 H, J = 6.1 Hz), 4.40 (s, 2 H), 4.23 (q, 4 H, J = 7.0 Hz), 3.86 (s, 3 H), 3.37 (s, 3 H), 1.34 (t, 6 H, J = 7.0 Hz) ppm; EIMS m/e (%) 304 (M^+, 45), 273 (18), 257 (17), 229 (36), 215 (16), 199 (16), 185 (23), 155 (100), 137 (88), 127 (78), 99 (80), 81 (67). Anal. Calcd for $C_{13}H_{21}O_6P$; C, 51.32; H, 6.91. Found: C, 51.50; H, 6.87.

Lithium–Ammonia Reduction of Aryl Diethyl Phosphates. A THF (40 mL) solution of 4 mmol of the above aryl diethyl phosphates was added to liquid ammonia (ca. 50 mL). Small pieces of lithium (56 mmol) were then added. The resulting dark blue mixture was left to stir for one additional hour. The excess of lithium was destroyed by carefully adding solid ammonium chloride. After evaporation the residue was dissolved in water and extracted with ether. The organic extracts were washed with 4 N NaOH, water, and brine, dried over anhydrous sodium sulfate, and evaporated to dryness, and, finally, the residue was bulb-to-bulb distilled.

1,2-Bis(3′-methoxyphenyl)ethane was obtained in 74% isolated yield; bp 235–250 °C (0.8 mmHg);[26] ^1H NMR 7.15 (m, 2 H), 6.72 (m, 6 H), 3.74 (s, 6 H), 2.88 (s, 4 H) ppm; EIMS m/e (%) 242 (M^+, 36), 121 (100), 91 (19), 78 (11), 77 (10). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.34; H, 7.44. Found: C, 79.21; H, 7.39.

1,2-Bis(3′,5′-dimethoxyphenyl)ethane was obtained in 67% isolated yield: mp 212 °C (ethyl acetate); ^1H NMR 6.32 (s, 6 H), 3.75 (s, 12 H), 2.83 (s, 4 H) ppm; EIMS m/e (%) 302 (M^+, 55), 151 (100), 121 (4), 91 (8), 77 (5). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.52; H, 7.28. Found: C, 71.45; H, 7.34.

Acknowledgment. Financial support by the DGICYT (PB87-0019) is gratefully acknowledged. M. Dopico thanks the Ministry of Education for a fellowship. G. Martorell thanks the Conselleria de Sanitat i Seguretat Social del Govern de les Illes Balears for a fellowship.

Registry No. **1**, 60319-07-5; **2**, 124200-73-3; **3**, 124200-74-4; **4**, 124200-75-5; **5**, 124200-76-6; **6**, 150-78-7; **7**, 73569-69-4; **8**, 124200-77-7; **9**, 3465-69-8; **10**, 7051-13-0; CD_3COOD, 1186-52-3; $PhCl_2(PPh_3)_2$, 13965-03-2; palladium, 7440-05-3; naphthalene, 91-20-3; acetic acid, 64-19-7; formic acid, 64-18-6; tributylamine, 102-82-9; 2-deuterio-1,3-dimethoxybenzene, 49771-99-5; dibutylformamide, 761-65-9; diethyl phosphonate, 762-04-9; 2,6-dimethoxyphenol, 91-10-1; 2,6-dimethoxy-4-(methoxymethyl)-phenol, 60824-64-8; 2,6-dimethoxy-4-(methoxymethyl)-3-(methylthio)phenol, 115319-83-0; 3-hydroxy-2,4-dimethoxy-6-(methoxymethyl)benzoic acid, 115319-82-9; 3-chloro-2,6-dimethoxyphenol, 18113-22-9; 1*H*,*H*-5,7-dimethoxy-6-hydroxysiobenzofuran-1-one, 58137-86-3; triflic anhydride, 358-23-6; 2-naphthyl triflate, 3857-83-8; 3,5-dimethoxytoluene, 4179-19-5; diethyl 2,6-dimethoxy-4-(methoxymethyl)phenyl phosphate, 124200-78-8; diethyl 2-methoxy-4-(methoxymethyl)phenyl phosphate, 124200-79-9; 1,2-bis(3′-methoxyphenyl)ethane, 36707-27-4; 1,3-bis(diphenylphosphino)propane, 6737-42-4; 2-methoxy-4-(methoxymethyl)phenol, 5533-03-9; 1,2-bis(3′,5′-dimethoxyphenyl)-ethane, 22976-41-6.

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