Mechanism of the Unusual Ether Cleavage of (2-Methoxy-1,3-xylylene)-15-crown-4 by Organomagnesium Reagents

Gert-Jan M. Gruter, Gerard P. M. van Klink, Otto S. Akkerman, and
Friedrich Bickelhaupt*

Department of Chemistry, Vrije Universiteit, De Boelelaan 1083,
NL-1081 HV Amsterdam, The Netherlands

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The surprisingly easy ether cleavage reaction of (2-methoxy-1,3-xylylene)-15-crown-4 (**7**) and organomagnesium reagents in diethyl ether solution was investigated. Facile alkyl ether cleavage was found to take place only with **7**. (2-Ethoxy-1,3-xylylene)-15-crown-4 (**17**) was cleaved at a considerably lower rate, while the (2-isopropoxy-1,3-xylylene)-15-crown-4 (**18**) did not show ether cleavage at all. The sulfur analogues [2-(methylthio)-1,3-xylylene]- (**21**) and [2-(ethylthio)-1,3-xylylene]-15-crown-4 (**22**) are unreactive at ambient temperature. The reactivity of the cleaving reagent decreases in the order diphenylmagnesium > phenylmagnesium bromide > magnesium dibromide. The reaction is proposed to proceed via an initially formed 1:1 "side-on" complex (**13**), in which the organomagnesium compound is coordinated to the two central crown ether oxygens. When the solvent is coordinating more strongly to the organomagnesium compound than the crown ether, such as THF, the reaction does not take place because the side-on complex (**13**) is not formed. As in previously reported metalation reactions, it was found that the 1,3-xylylene-15-crown-4 derivatives react faster than the larger 1,3-xylylene-18-crown-5 derivatives.

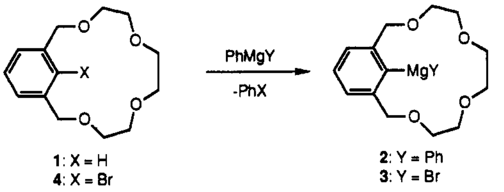
Introduction

Recently, we reported the surprising exchange reactions of 1,3-xylylene crown ethers with diphenylmagnesium and phenylmagnesium bromide.[1,2] Metalation, which is uncommon for organomagnesium compounds but reminiscent of the behavior of organolithium compounds, was found for 1,3-xylylene-15-crown-4 (**1**) as a substrate, under the formation of [2-(phenylmagnesio)-1,3-xylylene]-15-crown-4 (**2**) and [2-(bromomagnesio)-1,3-xylylene]-15-crown-4 (**3**), respectively (Scheme I).

Analogous halogen–metal exchange reactions occurred even more easily with (2-bromo-1,3-xylylene)-15-crown-4 (**4**); with diphenylmagnesium at room temperature, within a few minutes, the same product **2** was obtained. Phenylmagnesium bromide reacted somewhat slower than diphenylmagnesium in these reactions. Reaction of the larger macrocycle 1,3-xylylene-18-crown-5 (**5**) with diphenylmagnesium did not lead to a chemical transformation, but instead a 1:1 complex was formed which was characterized as a rotaxane complex by an X-ray crystal structure determination.[3] With the bromine-substituted larger crown ether (2-bromo-1,3-xylylene)-18-crown-5 (**6**), a halogen–metal exchange reaction was observed, but at a much lower rate than with **4**, probably as a consequence of the less symmetrical orientation of the organomagnesium reagent in the transition state.[1,2]

In a preliminary paper[4] we reported the reaction of (2-methoxy-1,3-xylylene)-15-crown-4 (**7**) with diphenylmagnesium and phenylmagnesium bromide as another example of the increased reactivity induced by crown ethers. This choice of **7** was based on the following considerations. In the first place, an anisyl ether function is notoriously inert against organometallic compounds; if a reaction did occur, it would demonstrate an extraordinary reactivity indeed. Second, **7**, unlike **1**, **4**, and **6**, is not expected to undergo nucleophilic attack by the phenyl "anion" at the atom directly bonded to the ipso-carbon because, in this case, this atom is oxygen; instead, electrophilic attack of magnesium on this oxygen might go along with two different modes of cleavage: that of the oxygen–aryl bond (S_N2(Ar) at the ipso-carbon) leading to **8**, or of the oxygen–methyl bond (S_N2 at the methyl carbon) leading to **9** (Scheme II); it is the latter reaction which was actually observed. In diethyl ether, the reaction of **7** with either diphenylmagnesium or phenylmagnesium bromide showed cleavage of the methyl–oxygen bond with unprecedented ease, leading, after hydrolytic workup, to (2-hydroxy-1,3-xylylene)-15-crown-4 (**10**) and toluene. One of the currently used methods[5] for the synthesis of **10** is the attack of lithium iodide on **7**,[6d,e] which requires heating for several hours to 115 °C; it should be pointed out that under the same conditions anisole does not react at all!

Scheme I



1: X = H
4: X = Br

2: Y = Ph
3: Y = Br

Recently, a study was published which showed that alkali metal ions strongly enhance the rate of demethylation of crown ether anisols by toluenethiolates.[6g] The mechanism postulated by the authors is nearly identical to that proposed in our preliminary paper.[4]

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[1] Markies, P. R.; Nomoto, T.; Akkerman, O. S.; Bickelhaupt, F.; Smeets, W. J. J.; Spek, A. L. *Angew. Chem.* **1988**, *100*, 1143.

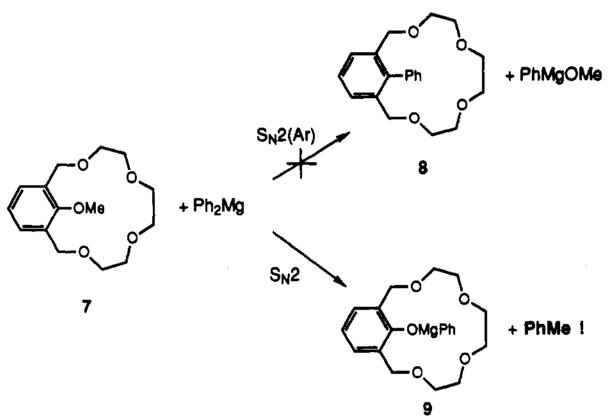
[2] Markies, P. R.; Nomoto, T.; Schat, G.; Akkerman, O. S.; Bickelhaupt, F.; Smeets, W. J. J.; Spek, A. L. *Organometallics* **1991**, *10*, 3826.

[3] Markies, P. R.; Nomoto, T.; Akkerman, O. S.; Bickelhaupt, F.; Smeets, W. J. J.; Spek, A. L. *J. Am. Chem. Soc.* **1988**, *110*, 4845.

[4] Gruter, G. J. M.; van Klink, G. P. M.; Heropoulos, G. A.; Akkerman, O. S.; Bickelhaupt, F. *Organometallics* **1991**, *10*, 2535.

0276-7333/93/2312-1180$04.00/0

Scheme II



Cleavage of alkyl aryl ethers[7] by Grignard reagents has been reported but requires drastic conditions.[8] The reactions can be represented as a second-order displacement reaction (eq 1). In order for the Lewis acid/base complex 11 to be formed, all diethyl ether used in the Grignard formation reaction must be completely removed.[8d] For satisfactory yields of the ether cleavage reaction, temperatures higher than 200 °C are needed.[9,10] Under these conditions, pyrolysis of the Grignard reagents occurs to a major extent.[11] Other frequently encountered side products are unsaturated hydrocarbons formed in an E2-type cleavage reaction (eq 2).

$$\mathrm{PhOR + R'MgX \rightarrow \underset{11}{Ph(R)OMg(R')X} \rightarrow PhOMgX + RR'} \quad (1)$$

With anisole as a substrate, simultaneous ortho-metalation (12–20%) has been reported.[12] The reactivity of alkylmagnesium iodide was found to be higher than that of the corresponding bromide in analogous cleavage reactions.[13] Magnesium iodide as such has also been reported to cleave alkyl aryl ethers under drastic conditions,[13,14] while results with magnesium dibromide were poor.[14]

$$\mathrm{PhOEt + R'MgX \rightarrow Ph(Et)OMg(R')X \rightarrow PhOMgX + CH_2{=}CH_2 + R'H} \quad (2)$$

More recently, Richey et al. observed the ring cleavage of 2,1,1-cryptand when heating it with dineopentylmagnesium in diethyl ether/benzene.[15] One of the arms of the cryptand containing a single oxygen was cleaved by an E2 mechanism.

Cleavage of the *aryl–oxygen* bond of substituted anisols by alkyl Grignard compounds has only been reported when a strongly electron-withdrawing ortho group such as a nitrile or an oxazoline was present, which obviously activates the system for an $S_N2(Ar)$ reaction (Scheme III).[16]

Alkyl benzyl ethers have been reported to react more easily with Grignard compounds (eq 3).[17]

$$\mathrm{PhCH_2OR + R'MgBr \rightarrow PhCH_2R' + ROMgBr} \quad (3)$$

Of the alkyl phenyl ether cleavage reactions described so far, none is comparable in ease and selectivity with that of (2-methoxy-1,3-xylylene)-15-crown-4.

Kharasch[8a] proposed two possible mechanistic routes for ether cleavage reactions by Grignard reagents, which are depicted in his notation in Schemes IV and V. After formation of a complex between the two reagents, cleavage can take place through thermal rearrangement of such a complex or through attack of a second molecule of the Grignard reagent on the complex. In view of the relatively high stability of most ethereal carbon-to-oxygen bonds, Kharasch regarded the latter possibility as favored because it affords an opportunity for a concerted "push–pull" mechanism which he presumed to have a relatively low energy of activation. A mechanism for the Grignard cleavage reaction was formulated in terms of a quasi six-membered ring transition state (Scheme IV).

Kharasch also postulated a second possible mechanism as indicated in Scheme V.

The latter mechanism, although not necessarily very different from that of Scheme IV, is more concurrent with our proposition (vide infra).

In the present investigation the scope and mechanism of the ether cleavage reaction has been studied more extensively.

Results and Discussion

Metalation. For the exchange reactions it has previously been established[2] that the activation of organomagnesium compounds depends strongly on the 1,3-xylylene crown ether system. Attempts with other substrates failed: a crown ether functionality incorporated into the substrate next to the site of the reaction was not a sufficient

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(5) Various syntheses of 2-hydroxy-1,3-xylylene crown ethers have been reported previously. Most routes involve protection/deprotection of the hydroxyl function; a major concern of this approach is that deprotection can also lead to cleavage of the benzylic ether bonds. In the reported syntheses of 2-hydroxy-1,3-xylylene crown ethers, methoxymethyl,[6a,b] allyl,[6c] and methyl[6d,e] groups were used for protection of the hydroxy group. In the case of methyl protection, deprotection was accomplished by anhydrous LiI in pyridine at 100 °C and later also by $LiAlH_4$.[6f] Recently, Reinhoudt et al. reported a new, alternative route to 2-hydroxy-1,3-xylylene crown ethers, without a protection/deprotection step:[26b] lithiation of 2-bromo-1,3-xylylene crown ethers followed by reaction with trimethyl borate, hydrolysis, and oxidation by H_2O_2.

(6) (a) Koenig, K. E.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1976**, *98*, 4018. (b) Koenig, K. E.; Lein, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553. (c) van der Leij, M.; Oosterink, H. J.; Hall, R. H.; Reinhoudt, D. N. *Tetrahedron* **1981**, *37*, 3661. (d) McKervey, M. A.; Mulholland, D. L. *J. Chem. Soc., Chem. Commun.* 1977, 438. (e) Browne, C. M.; Ferguson, G.; McKervey, M. A.; Mulholland, D. L.; O'Connor, T.; Parvez, M. *J. Am. Chem. Soc.* **1985**, *107*, 2703. (f) Czech, A.; Czech, B. P.; Desai, D. H.; Hallman, J. L.; Phillips, J. B.; Bartsch, R. A. *J. Heterocycl. Chem.* **1986**, *23*, 1355. (g) Cacciapaglia, R.; Mandolini, L.; Romolo, F. S. *J. Phys. Org. Chem.* **1992**, *5*, 457.

(7) For an overview of aryl methyl ether cleavage reagents see: (a) Larock, R. C. In *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; VCH: New York, 1989; p 501–4. (b) March, J. *Advanced Organic Chemistry*, 3rd ed.; J. Wiley & Sons: New York, 1985; p 384.

(8) For an overview of ether cleavage reactions by organomagnesium compounds see: (a) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: New York, 1954; p 1013. (b) Nützel, K. In *Methoden der Organischen Chemie (Houben Weyl)*, 4th ed.; Müller, E.; Ed.; Thieme Verlag: Stuttgart, FRG, 1973; Vol. XIII/2a, p 336. (c) Burwell, R. L., Jr. *Chem. Rev.* **1954**, *54*, 615, 668. (d) Meerwein, H. In *Methoden der Organischen Chemie (Houben Weyl)*, 4th ed.; Thieme Verlag: Stuttgart, FRG, 1965; Vol. VI/3, p 160. (e) Staude, E.; Patat, F. In *The Chemistry of the ether linkage*; Patai, S., Ed.; Wiley & Sons: New York, 1967; pp 62–5.

(9) Simonis, H.; Remmert, P. *Ber.* **1914**, *47*, 269.

(10) Späth, E. *Monatsh. Chem.* **1914**, *35*, 319.

(11) See ref 8b, pp 220, 336.

(12) Challenger, F.; Miller, S. A. *J. Chem. Soc.* **1938**, 894.

(13) Grignard, V.; Ritz, J. *Bull. Soc. Chim. Fr.* **1936**, *3*, 1181.

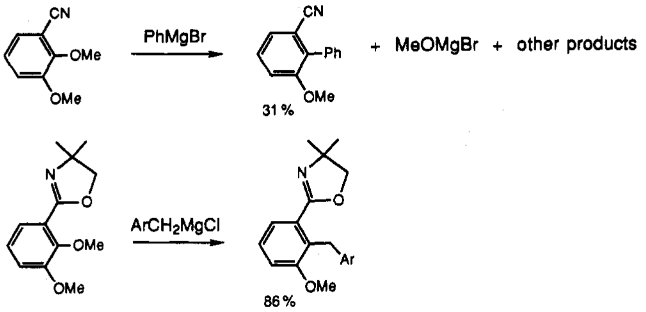
(14) Schönberg, A.; Moubasher, R. *J. Chem. Soc.* **1944**, 462.

(15) Squiller, E. P.; Whittle, R. R.; Richey, H. G., Jr. *Organometallics* **1985**, *4*, 1154.

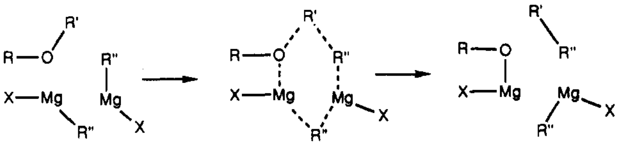
(16) (a) Richtzenhain, H. *Ber.* **1948**, *81*, 92. (b) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *7*, 1372. (c) Nicoletti, T. M.; Raston, C. L.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1990**, 133.

(17) Tschelinzew, W.; Pawlow, *Ber.* **1913**, *45*, 289; *J. Chem. Soc.* **1913**, *1*, 1962.

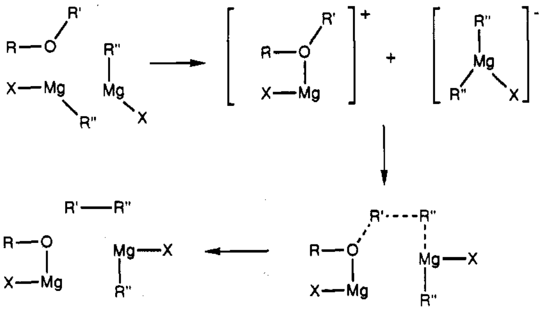
Scheme III



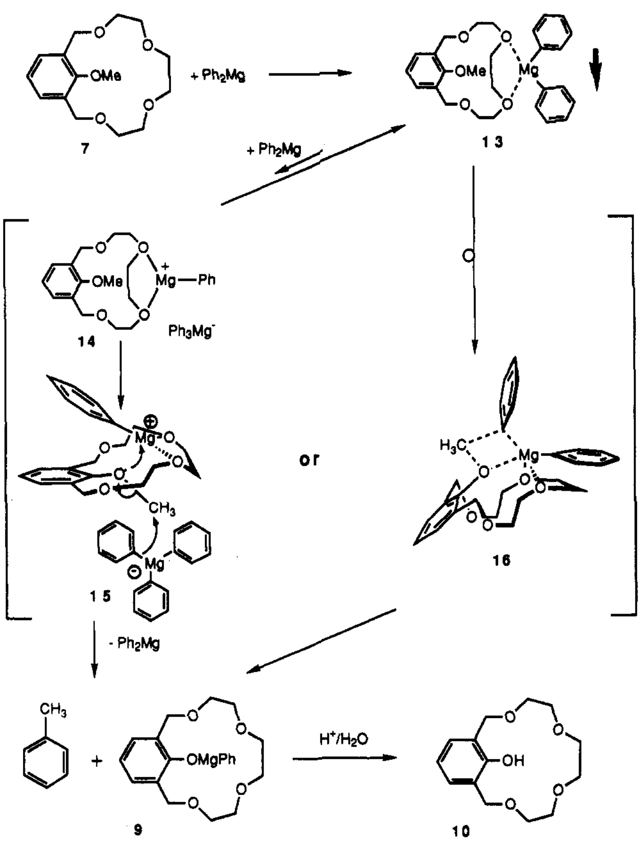
Scheme IV



Scheme V



Scheme VI



condition for the halogen–metal exchange reaction to occur. The extreme reversal of the "natural" reactivity order was provided by the *metalation* of (5-bromo-1,3-xylylene)-15-crown-4 (**12**) at the intraannular position 2,[2] instead of the "normal" bromine–metal exchange at position 5, which occurs with *n*-butyllithium.

For the exchange reactions, preorganization must be important: an initial side-on complex is formed (analogous to **13** in Scheme VI). Subsequently the reaction clearly has an "intramolecular" component. The cationic magnesium (analogous to that in **14**), stabilized by the coordinating power of the crown ether ring, is involved in an electrophilic attack on the aromatic xylylene 2-carbon; it is directed by coordination with the crown ether ring. A magnesiate counterion attacks the intraannular substituent (H or Br) in a nucleophilic substitution process.

Ether Cleavage. It was of interest to investigate the reaction conditions (solvent, temperature, concentration of the reactants) and the reactivity of a variety of intraannular, ether-substituted derivatives of 1,3-xylylene crown ethers.

When (2-methoxy-1,3-xylylene)-15-crown-4 (**7**) was added to a solution of 1 molar equiv of diphenylmagnesium in diethyl ether solution, a white precipitate formed instantaneously. This is almost certainly the "side-on" complex **13** (Scheme VI). Immediate quenching of this reaction mixture with dilute hydrochloric acid showed the formation of 6% of (2-hydroxy-1,3-xylylene)-15-crown-4 (**10**) and 94% of unreacted **7** (^{1}H NMR); 3% of toluene was observed (GC and/or GC/MS). In other experiments, after 1 h at room temperature, the supernatant was separated from the solid by decantation and analyzed by GC after addition of *m*-xylene as an internal standard. In this supernatant, up to 50% of toluene was detected by gas chromatography. Sometimes small amounts of crown ether **7** (but never **10**) were found. In an experiment performed in diethyl-d_{10} ether in a system sealed under high vacuum, ^{1}H NMR spectroscopy indicated practically quantitative formation of toluene.

The solid residue, from which the ether layer had been decanted, was hydrolyzed with dilute hydrochloric acid and gave the phenolic crown ether **10** (^{1}H NMR) in >95% yield; the presence of benzene was shown by gas chromatography. The yield of **10** follows from the ratio **7**:**10**, which can easily be determined by using ^{1}H-NMR spectroscopy, as the benzylic protons of these crown ethers appear as an AB-system in **7** and as a singlet in **10**.

Similarly, reaction of **7** with bis(*p*-*tert*-butylphenyl)magnesium gave, after hydrolysis, *p*-*tert*-butyltoluene and **10** (93%). With phenylmagnesium bromide, **7** reacted analogously to furnish toluene and (presumably) the bromomagnesium salt of **10** (analogous to **9**), but the reaction was much slower: at 50 °C, the conversion of **7** was 59% after 1 day, and (in another experiment) complete after 2 days.

The S_N2 attack of a (formal) phenyl anion on an aliphatic carbon, with a phenoxide anion as a relatively poor leaving group is, to our knowledge, without precedent; it comes down to the alkylation of an organomagnesium compound by an anisole!

A $S_{RN}1$ mechanism (eq 4–6),[18] initiated by a single electron transfer (SET) is a priori a serious alternative to the S_N2 mechanism, but in our case, it is unlikely for several reasons. In the first place, aromatic ethers are, in contrast to aryl halides, poor electron acceptors; secondly, analogous SET reactions do not occur with organolithium com-

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[18] Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.

pounds, which are better electron donors than organomagnesium compounds.

$$\mathbf{13} \rightarrow Ph^{\bullet} + [PhMg^{+}]\cdot\mathbf{7}^{\bullet -} \quad (4)$$

$$Ph^{\bullet} + \mathbf{7}^{\bullet -} \rightarrow PhMe + RO^{-} \quad (5)$$

$$RO^{-} + [PhMg^{+}] \rightarrow \mathbf{9} \quad (6)$$

Most convincingly, however, a $S_{RN}1$ mechanism is excluded by the observation that **17**, the ethoxy analogue of **7**, reacted very slowly (36 h at 45 °C; 11% conversion) to give **9** and ethylbenzene, while the isopropoxy analogue **18** gave no reaction at all (72 h at 45 °C). If a SET step was involved and presumably rate limiting, the reaction should not depend dramatically on the nature of the alkyl substituent (and if so, probably in the opposite direction), whereas the observed reactivity order **7** > **17** ≫ **18** is exactly as expected for a S_N2 attack at the alkyl carbon atom.

In analogy to the metalation and halogen–metal exchange reactions,[1,2] we propose initial coordination to give the side-on complex **13**, which is confirmed by several earlier results:

(1) Previously, the X-ray crystal structures of the 1:1 complexes of **4**, **5**, and **6** with diphenylzinc[19] served as model compounds for the intermediate "side-on" complexes in the earlier mentioned metalation reactions.

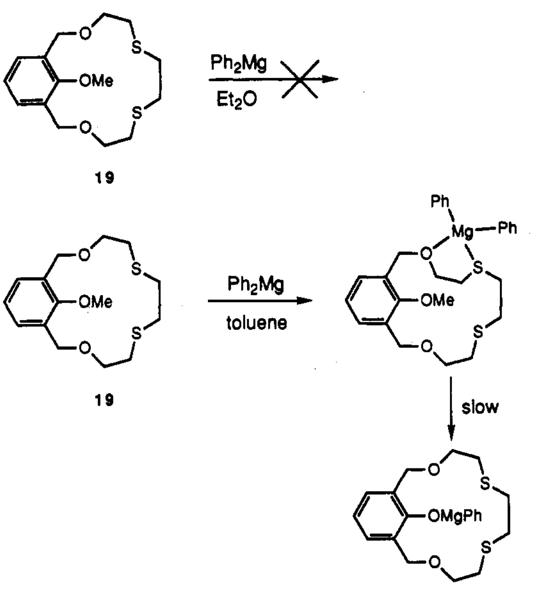
(2) Recently, further proof for the existence of the "side-on" complex as an intermediate in reactions with diphenylmagnesium became available from the X-ray crystal structure of the 1:1 complex between diphenylmagnesium and (2-chloro-1,3-xylylene)-15-crown-4 which shows the expected coordination of magnesium to oxygens 2 and 3 (cf. **16**) of the crown ether ring. A paper which includes this result is in preparation.

(3) Immediate quenching of the white precipitate (side-on complex **13**) after mixing of the two reagents furnished 94% of unreacted starting material.

(4) THF, being a stronger coordinating solvent than **7**, prevents the formation of **13** (a precipitate is not formed; no change in the ^1H NMR spectrum of **7** in THF-d_8 is observed); consequently, no reaction occurs.

(5) Because sulfur is a weaker coordinating donor atom toward magnesium than oxygen, **19**, the dithio analogue of **7**, was prepared. With diphenylmagnesium in diethyl ether, no reaction took place, not even after prolonged heating, presumably because the side-on complex is not formed or is not strong enough to initiate further reaction. When diethyl ether was replaced by the noncoordinating toluene, ^1H NMR spectroscopy showed that a complex was formed. However, the reaction did not proceed beyond formation of this initially formed complex, which is probably a side-on complex in which diphenylmagnesium is coordinated to one of the oxygens and one of the sulfur atoms of the crown ether as indicated in Scheme VII. We feel that this unsymmetrical orientation of diphenylmagnesium is unfavorable for attack on the methoxy group, but, as pointed out by a reviewer, it cannot be fully excluded that geometrical changes in the crown ether bridge due to replacements of oxygen by sulfur are responsible for the lack of reactivity. In the ^1H NMR spectrum, the two benzylic CH_2 groups appear as a simple AB system, even at −80 °C; however, we assume that the apparent C_s symmetry is due to fast exchange rather than to bonding to the two sulfur atoms. The latter mode of bonding would be required for a linear attack at the methyl group. As this does not occur, ether cleavage does not take place easily (Scheme VII). Long reaction times at elevated temperature in toluene resulted in extensive decomposition of the crown ether ring.

Scheme VII



Absolute proof for the intermediacy of a discrete 1:1 side-on complex **13** would be found by a crystal structure of **17**·Ph_2Mg or of **18**·Ph_2Mg. Unfortunately, we have not been able to grow crystals suitable for X-ray crystal structure determinations so far.

After the formation of **13**, the electrophilic part of the reaction proceeds via an intramolecular pathway (Scheme VI): the magnesium binds to the oxygen atom of the methoxy group; simultaneously, the methyl group combines with a phenyl group of the organomagnesium reagent to form toluene. Initially, the coordinating power of the crown ether ring helps the heterolytic cleavage of one of the phenylmagnesium bonds by stabilizing the phenylmagnesium cation in **14**, probably via all of the four crown ether oxygens. This heterolytic cleavage is further facilitated by a second molecule of diphenylmagnesium,[20] which stabilizes the phenyl "anion" as a magnesiate counterion. A similar interaction has been postulated for the crown ether metalation reactions;[1,2] it was also indispensable to explain the rotaxane formation between 1,3-xylylene-18-crown-5 (**5**) and diphenylmagnesium because the phenyl group is too large to penetrate the crown ether ring.[3] The formation of magnesiate species from diorganylmagnesium compounds and crown ethers has been observed spectroscopically and was confirmed by a crystal structure.[21,22] The possible concomitant increase of positive charge on

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[19] Markies, P. R.; Schat, G.; Akkerman, O. S.; Bickelhaupt, F.; Smeets, W. J. J.; Spek, A. L. *Organometallics* **1991**, *10*, 3538.

[20] Richey et al. observed that interaction of dialkylmagnesium compounds with chelating crown ethers did not generate solvation-separated ion pairs.[21] Therefore, the magnesiate species **14** must be present in a very low steady-state concentration only. The additional molecule of diphenylmagnesium needed for its formation may arise either from another **13** or from the equilibrium between **13** and $Ph_2Mg\cdot(Et_2O)_2$.

[21] (a) Pajerski, A. D.; Parvez, M.; Richey, H. G., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 2660. (b) Pajerski, A. D.; BergStresser, G. L.; Parvez, M.; Richey, H. G., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 4844. (c) Richey, H. G., Jr.; Kushlan, D. M. *J. Am. Chem. Soc.* **1987**, *109*, 2510.

[22] Magnesiate complexes from dialkylmagnesium compounds with 2,1,1-cryptand were characterized by their crystal structures: Squiller, E. P.; Whittle, R. R.; Richey, H. G., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 432.

magnesium by crown ether coordination will result in increasing electrophilicity of this center; simultaneously, the nucleophilic character of the R group will increase. The combination of both comes down to the push–pull attack often invoked for organomagnesium compounds.[8a,23] The process can take place in a S_N2-like fashion when the magnesium center of the intermediate phenylmagnesium cation is involved in an electrophilic attack on the methoxy oxygen, directed by the coordination with the crown ether ring. The magnesiate counterion attacks the methyl in a nucleophilic substitution process. Both components of the substitution reaction probably take place simultaneously, but the nucleophilic component is probably the most important because $MgBr_2$ does not react under similarly mild conditions with 7 (vide supra). Elimination of toluene and diphenylmagnesium completes the process leading to [2-[(phenylmagnesio)oxo]-1,3-xylylene]-15-crown-4 (9).

In the absence of kinetic data, which are difficult to obtain because of the heterogeneous nature of the reaction mixture, an intramolecular alternative route via 16 cannot be fully excluded. A cyclic intermediate could be formed as suggested for many reactions at a polarized $X^{\delta-}–X^{\delta+}$ bond.[23] In this intermediate, bond formation and bond cleavage is a concerted process (Scheme VI); however, in 16 both the cationic character of magnesium and the anionic activation of the phenyl group is less pronounced and less obvious than in 15; more importantly, the linear orientation of ArO···Me···Ph as a condition for a S_N2 reaction is not likely to be attained in 16. In any case, both reaction pathways finally lead to the formation of [2-[(phenylmagnesio)oxo]-1,3-xylylene]-15-crown-4 (9), which after quenching with dilute hydrochloric acid affords (2-hydroxy-1,3-xylylene)-15-crown-4 (10).

As with crown ethers 1, 4, 5, and 6, reactions involving diphenylmagnesium were much faster than those with phenylmagnesium bromide, which in turn were considerably faster than the reactions with (anhydrous) magnesium dibromide: 60% cleavage of 7 after heating at 60 °C for 11 days. This might be attributed to the formation of a less reactive, halide-containing, magnesiate species Ar_2MgBr^- or $MgBr_3^-$, respectively, instead of the Ar_3Mg^- anions present in 14. In addition, unreactive and hardly soluble [crown ether]·$[MgBr_2]_n$ complexes may be formed via the Schlenk equilibrium. Similar to the metalation reactions, the larger macrocycles react at a considerably lower rate than their crown-4 analogues. (2-Methoxy-1,3-xylylene)-18-crown-5 (20) was cleaved for 45% after heating for 3 days at 60 °C.

In view of the unexpected ether cleavage reactions of phenylmagnesium compounds with the crown ethers mentioned, it was of interest to investigate the behavior of compounds of other metals. The most obvious candidate was zinc, an element whose organometallic chemistry is often related to that of magnesium. However, as was shown already for the metalation reactions, with diphenylzinc only "simple" 1:1 complexation occurred.[19] Even after prolonged heating of diphenylzinc with the most reactive crown ether (2-methoxy-1,3-xylylene)-15-crown-4 (7) in toluene, the ^1H NMR spectrum showed no signs of dynamic processes or chemical reactions. A reference spectrum of pure 7 in the same solvent showed evidence for complexation; the crown ether signals are generally deshielded (0.1–0.3 ppm shift downfield) and the coupling patterns of the C_2H_4 units and the benzylic CH_2 groups (AA′BB′ and AB multiplets, respectively) broadened due to a diminished flexibility of the crown ether. Obviously, the activating power of the crown ether moieties is sufficient for organomagnesium compounds to cleave 7, but insufficient for weaker Lewis acidic organozinc compounds.

Chart I

21
22

The literature contains few reports on the rates of cleavage of ethers and their thio analogues. Data for cleavage by organometallics are practically absent. Qualitatively, thioethers are more difficult to cleave than their oxygen analogues both with acidic and with basic reagents.[24] With $AlCl_3$ at 200 °C, anisole was cleaved in 2 h, while thioanisole was cleaved only 20%. Similarly, anisole was cleaved by MgI_2 (200 °C, 1 h, 58%) and by KOH/EtOH (200 °C, 7 h, 7%), but thioanisole was unreactive under these conditions.[25] This is ascribed to the less basic character of thioethers.

The thio crown ethers [2-(methylthio)-1,3-xylylene]-15-crown-4 (21) and [2-(ethylthio)-1,3-xylylene]-15-crown-4 (22) were synthesized by a procedure analogous to one described in the literature for 21.[26] After metalation of the corresponding (2-bromo-1,3-xylylene) crown ether with *n*-butyllithium at low temperature, addition of dialkyl disulfide yielded the 2-(alkylthio)-1,3-xylylene crown ethers in high yields.

The reaction of 21 with diphenylmagnesium was extremely slow, even at elevated temperature. After 4 days in diethyl ether at 60 °C, only 4% reaction was observed (^1H NMR, GC/MS). With the ethylthio analogue 22, no reaction took place in diethyl ether after several weeks at 60 °C (Chart I). Although the crown ether functionality greatly enhances the reactivity at the 2-position (between the bridge), this is apparently not sufficient for an easy thioether cleavage to take place.

In the context of analyzing the relative importance of the nucleophilic and electrophilic components of these ether cleavage reactions, the reduced reactivity of 21 as compared to 7 tells us that the electrophilic component of the reaction is important. If the reactions were strongly dominated by the nucleophilic attack of the phenyl anion (as discussed for the cleavage of 7, vide supra), 21 would be expected to react faster than 7 as it has the better leaving group thiophenolate.

Conclusions

Except for special S_NAr reactions[16]; ethers are generally notoriously inert toward organomagnesium compounds, but (2-methoxy-1,3-xylylene)-15-crown-4 (7) undergoes,

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[23] Lindsell, W. E. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: New York, 1982; Vol. 1, p 193.

[24] See ref 8c, p 677.

[25] Hughes, G. K.; Thompson, E. O. P. *J. Proc. R. Soc. N. S. Wales* **1950**, *83*, 269.

[26] (a) Skowronska-Ptasinska, M.; Telleman, P.; Aarts, V. M. L. J.; Grootenhuis, P. D. J.; Van Eerden, J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron Lett.* **1987**, *28*, 1937. (b) Skowronska-Ptasinska, M.; Telleman, P.; Aarts, V. M. L. J.; Grootenhuis, P. D. J.; Van Eerden, J.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1988**, *53*, 5484.

with extraordinary ease, ether cleavage of its intraannular methoxy group. The reaction is quantitative within 1 h at room temperature. The reaction proceeds via an initially formed "side-on" complex **13** if the solvent is *not* stronger coordinating to the organomagnesium species than the crown ether. In stronger coordinating solvents, the side-on complex is not formed, and consequently, further reaction does not take place.

The mechanism of the ether cleavage has some features similar to those of the earlier reported metalation and halogen–metal exchange reactions.[2] By binding to the crown ether ring, the electrophilicity of the organomagnesium species is increased, leading to an intermediate cationic magnesium species which is stabilized by polycoordination to the crown ether oxygens. The favorable spacial arrangement of this cationic intermediate directs and facilitates electrophilic attack of the magnesium on the methoxy oxygen, while at the same time, in a "push–pull" fashion, an anionic phenyl species attacks the methyl group in a S_N2-like process. A radical mechanism (SET) can be excluded.

The following reactivity orders were observed for (a) the electrophiles, $Ph_2Mg \gg PhMgBr > MeMgBr > MgBr_2 > Ph_2Zn = 0$; (b) the intraannular ether group, OMe ≫ OEt > SMe > SEt = O-*i*-Pr = 0; and (c) the crown ether skeleton, 15-crown-4 > 18-crown-5.

Experimental Section

All manipulations involving organomagnesium and organozinc compounds were carried out in fully sealed glassware using standard high vacuum techniques. Solvents were dried by distillation from liquid Na/K alloy after predrying on NaOH. Amounts of "total base" and Mg^{2+} in organomagnesium samples were determined after hydrolysis of a sample by titration with HCl and EDTA, respectively. NMR spectra were measured on a Bruker AC 200 spectrometer (^1H NMR (200 MHz), ^{13}C NMR (50.29 MHz)) and on a Bruker MSL 400 spectrometer (^1H NMR (400.1 MHz)). GS/MS analyses were performed on a HP 5890 GC/5970 MS combination, operating at 70 eV and equipped with a Chrompack BP1 (QSGE) 50-m/0.25-mm column. HRMS measurements were performed on a Finnigan MAT 90 mass spectrometer (direct inlet). The starting materials 1-bromo-4-*tert*-butylbenzene (Aldrich), diphenylmercury (Merck), 2,6-dimethylaniline (Janssen), 2,6-dimethylphenol (Aldrich), triethylene glycol (Merck), tetraethylene glycol (Aldrich), 3,6-dithia-1,8-octanediol (Janssen), sodium hydride (Janssen), potassium hydride (Janssen), *N*-bromosuccinimide (Janssen), dimethyl disulfide (Aldrich), and diethyl disulfide (Aldrich) were commercially available. Column chromatography was performed with Al_2O_3-90 (Merck, activity II–III, 70–230 mesh). The THF needed for the crown ether synthesis was dried by distillation from $LiAlH_4$ before use. All melting points are uncorrected. Elemental analyses were carried out at the Mikroanalytisches Labor Pascher, Remagen, Germany.

Synthesis of Phenylmagnesium Bromide. In a fully sealed glass apparatus, bromobenzene (3.1 g, 20 mmol, dried on molecular sieve 4 Å) was added dropwise to diethyl ether (200 mL) and double sublimed magnesium (2.4 g, 100 mmol) under stirring. After being stirred for another 24 h and settling of the magnesium dust, the solution was decanted into a second vessel and a sample was hydrolyzed and titrated (total base and Mg^{2+}) to verify a quantitative conversion of the starting bromide.

Synthesis of Diarylmagnesium Compounds. Diphenylmagnesium and bis(*p*-*tert*-butylphenyl)magnesium were prepared from diphenylmercury and bis(*p*-*tert*-butylphenyl)mercury, respectively. In a fully sealed glass apparatus, the diarylmercury compound (18 mmol) was stirred with magnesium (2.2 g, 90 mmol) in diethyl ether (180 mL) for 3 weeks. After settling of the magnesium amalgam, the clear solution was decanted into a second vessel and a sample was hydrolyzed and titrated (total base and Mg^{2+}) to verify quantitative conversion of the starting material.

Synthesis of Diphenylzinc. Diphenylzinc was prepared from diphenylmercury as described for diphenylmagnesium.

Synthesis of 1,3-Xylylene Crown Ethers. The 1,3-xylylene crown ethers were synthesized from the appropriate oligoethylene glycol and substituted 1,3-bis(bromomethyl)benzenes, using sodium hydride (for the 15-crown-4 derivatives) or potassium hydride (for the 18-crown-5 derivatives) in THF. The mineral oil in which the hydrides are stored was removed by washing several times with THF. All functionalized 2,6-bis(bromomethyl)benzenes were synthesized from the corresponding functionalized 2,6-dimethylbenzenes by light-induced radical bromination with 2 equiv of NBS in refluxing CCl_4.

To optimize the yield of monomeric crown ether, high dilution conditions were applied to avoid dimer and polymer formation. In a typical crown ether synthesis, 40 mmol of the functionalized dibromide and 40 mmol of the oligoethylene glycol were dissolved in 0.5 L of THF and dropped under stirring during 3 days into a flask containing 100 mmol of the alkali hydride in 3 L of THF. After settling of the salts and the excess of hydride, the THF solution containing the crown ether was decanted and the solvent was evaporated. Unless stated otherwise, further purification was accomplished by column chromatography (Al_2O_3) to separate the monomeric crown ether from dimeric and polymeric material. During the elution, the eluent was gradually changed in 10% increments from pure petroleum ether (40–60) to pure THF. The fractions containing the pure crown ether were combined, and if possible, the crown ethers were recrystallized. The purified product was characterized by ^1H and ^{13}C NMR and GC/MS. For the new crown ethers **17**, **18**, **19**, and **22**, an additional elemental analysis and high-resolution mass spectroscopy (HRMS) measurements were carried out.

(2-Methoxy-1,3-xylylene)-15-crown-4 (7). Crown ether **7** was obtained from 2-methoxy-1,3-bis(bromomethyl)benzene and triethylene glycol with NaH in THF. The obtained spectral data were in accordance with those reported.[6e]

2-Ethoxy-1,3-bis(bromomethyl)benzene (23) was prepared from 2-ethoxy-1,3-dimethylbenzene by light-induced radical bromination with 2 equiv of *N*-bromosuccinimide. The dibromide was purified by high-vacuum distillation, bp 102–106 °C (10^{-4} mmHg), as a white solid which turned purple-red upon standing, mp 55–58 °C (35% yield): ^1H NMR ($CDCl_3$, 200 MHz, ref $CHCl_3$ = 7.27 ppm), δ 1.54 (t, ^3J = 7.0 Hz, 3 H, CH_3), 4.20 (q, ^3J = 7.0 Hz, 2 H, OCH_2), 4.57 (s, 4 H, xylyl-CH_2), 7.12 (t, ^3J = 7.5 Hz, 1 H, H5), 7.39 (d, ^3J = 7.5 Hz, 2 H, H4 and H6); ^{13}C NMR ($CDCl_3$, 50.29 MHz, ref $CDCl_3$ = 77.00 ppm) δ 15.70 (qt, ^1J = 126.68 Hz, ^2J = 4.43 Hz, CH_3), 27.72 (td, ^1J = 154.31 Hz, ^3J = 5.84 Hz, CH_2Br), 70.45 (tq, ^1J = 144.70 Hz, ^2J = 4.43 Hz, OCH_2), 124.80 (s, *J* not resolved, C1 and C3), 132.09 (dt, ^1J = 160.12 Hz, ^2J = 8.55 Hz, $^3J_{CH_2Br}$ = 5.48 Hz, C4 and C6), 155.63 (s, C1); GC/MS *m/z* (rel intensity) 306 (M^+, $C_{10}H_{12}Br_2O$, 12), 227 ($M^+ - Br$, 100), 147 (50), 119 (95), 91 (48), 65 (17); HRMS calcd for $C_{10}H_{12}{}^{81}Br_2O$ 309.9215, obsd 309.922 ± 0.001.

18-Ethoxy-3,6,9,12-tetraoxabicyclo[12.3.1]octadeca-1(18),14,16-triene ((2-ethoxy-1,3-xylylene)-15-crown-4) (17) was prepared analogously to **7**. After preparative column chromatography (silica gel) using gradual elution (PE–THF), the fractions containing pure **17** were combined and the solvent was removed to give a white solid, mp 70–72 °C (30% yield relative to 2-ethoxy-1,3-bis(bromomethyl)benzene): ^1H NMR ($CDCl_3$, 200 MHz, ref $CHCl_3$ = 7.27 ppm) δ 1.43 (t, ^3J = 7.0 Hz, 3 H, CH_3), 3.12–3.22 (m, 4 H, $O(2)CH_2CH_2O(3)$), 3.27–3.75 (m, 8 H, CH_2), 4.12 (q, ^3J = 7.0 Hz, 2 H, OCH_2), 4.26, 4.96 (dd, AB, ^2J = 12.3 Hz, 4 H, xylyl-CH_2), 7.03–7.31 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$, 50.29 MHz, ref $CDCl_3$ = 77.00 ppm) δ 15.67 (q, ^1J = 126.00 Hz, ^2J = 2.5 Hz, CH_3), 68.11 (tt, ^1J = 148.7 Hz, ^2J = 4.1 Hz, $O(1)CH_2\mathit{C}H_2O(2)$), 68.74 (t, ^1J = 143.2 Hz, $O(2)\mathit{C}H_2\mathit{C}H_2O(3)$), 69.88 (tt, ^1J = 140.9 Hz, ^2J = 3.5 Hz, $O(1)\mathit{C}H_2CH_2O(2)$), 70.33 (t, ^1J = 141.1 Hz, xylyl-CH_2), 71.10 (tq, ^1J = 147.2 Hz, ^2J = 4.4

Hz, OCH_2CH_3), 122.67 (d, ^1J = 161.4 Hz, C5), 131.40 (ddt, ^1J = 158.1 Hz, ^2J = 8.6 Hz, ^3J = 4.6 Hz, C4 and C6), 157.77 (bs, C2), 132.03 (bs, C1 and C3); GC/MS 296 (M^+, $C_{16}H_{24}O_5$, 14), 179 (5), 164 (37), 147 (100), 133 (98), 91 (41), 45 (37); HRMS calcd for $C_{16}H_{24}O_5$ 296.1624, obsd 296.161 ± 0.001. Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.17. Found: C, 64.50; H, 8.13.

2-Isopropoxy-1,3-bis(bromomethyl)benzene (24) was prepared from 2-isopropoxy-1,3-dimethylbenzene by light-induced radical bromination with 2 equiv of *N*-bromosuccinimide. The dibromide was purified as a light yellow oil by high vacuum distillation, bp 110 °C (2 × 10^{-4} mmHg): ^{1}H NMR ($CDCl_3$, 200 MHz, ref $CHCl_3$ = 7.27 ppm) δ 1.40 (d, ^3J = 6.1 Hz, 6 H, CH_3), 4.20 (pt, ^3J = 6.1 Hz, 1 H, OCH), 4.58 (s, 4 H, xylyl-CH_2), 7.11 (t, ^3J = 7.6 Hz, 1 H, H5), 7.41 (d, ^3J = 7.6 Hz, 2 H, H4 and H6); ^{13}C NMR (50.29 MHz, ref $CDCl_3$ = 77.00 ppm) δ 22.53 (qd, ^1J = 127.00 Hz, ^2J = 5.63 Hz, $2CH_3$), 28.56 (td, ^1J = 154.14 Hz, ^3J = 5.88 Hz, CH_2Br), 76.81 (dspt, ^1J = 144.58 Hz, ^2J = 4.07 Hz, OCH), 124.45 (dd, ^1J = 163.74 Hz, ^2J = 0.96 Hz, C5), 131.95 (dt, ^3J = 8.10 Hz, $^2J_{CH_2Br}$ = 3.42 Hz, C1 and C3), 132.27 (dt, ^1J = 160.07 Hz, ^3J = 8.75 Hz, $^3J_{CH_2Br}$ = 5.48 Hz, C4 and C6), 155.34 (bs, C2); GC/MS *m/z* (rel intensity) 320 (M^+, $C_{11}H_{14}OBr_2$, 0.2), 278 ($M^+ - C_3H_6$, 2.5), 241 (M^+ − Br, 3.0), 199 (39), 119 (100), 91 (96), 65 (49), 51 (20); HRMS calcd for $C_{11}H_{14}O^{81}Br_2$ 323.9372, obsd 323.937 ± 0.001.

18-Isopropoxy-3,6,9,12-tetraoxabicyclo[12.3.1]octadeca-1(18),14,16-triene ((2-isopropoxy-1,3-xylylene)-15-crown-4) (18) was prepared analogously to **7**. After preparative column chromatography (silica gel) using gradual elution (PE–THF), the fractions containing pure **18** were combined and the solvent was removed to give a pale yellow oil (37%): ^{1}H NMR ($CDCl_3$, 200 MHz, ref $CHCl_3$ = 7.27 ppm) δ 1.27 (d, ^3J = 6.1 Hz, 6 H, CH_3), 3.14–3.67 (m, 12 H, CH_2), 4.01 (spt, ^3J = 6.1 Hz, 1 H, OCH), 4.35/4.87 (dd, AB, ^2J = 12.4 Hz, 4 H, xylyl-CH_2), 7.01–7.31 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$, 50.29 MHz, ref $CDCl_3$ = 77.00 ppm) δ 22.16 (qd, ^1J = 125.9 Hz, ^2J = 4.7 Hz, CH_3), 68.50 (tt, ^1J = 143.1 Hz, ^2J = 4.1 Hz, O(1)CH_2CH_2O(2)), 68.74 (t, ^1J = 143.2 Hz, O(2)CH_2CH_2O(3)), 69.88 (tt, ^1J = 140.9 Hz, ^2J = 3.5 Hz, O(1)CH_2CH_2O(2)), 70.45 (t, ^1J = 142.1 Hz, xylyl-CH_2), 76.71 (dspt, ^1J = 142.8 Hz, ^2J = 4.1 Hz, $OCH(CH_3)_2$), 122.93 (d, ^1J = 161.5 Hz, C5), 131.16 (ddt, ^1J = 154.7 Hz, ^2J = 8.5 Hz, ^3J = 4.6 Hz, C4 and C6), 132.97 (bs, C1 and C3), 155.34 (bs, C2); GC/MS *m/z* (rel intensity) 310 (M^+, $C_{17}H_{26}O_5$, 0.3), 268 (2.5), 133 (9), 119 (11), 91 (28), 89 (24), 65 (11), 45 (100); HRMS calcd for $C_{17}H_{26}O_5$ 310.1780, obsd 310.178 ± 0.001. Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.45. Found: C, 65.68; H, 8.45.

18-Methoxy-3,12-dioxa-6,9-dithiabicyclo[12.3.1]octadeca-1(18),14,16-triene ((2-methoxy-1,3-xylylene)-6,9-dithia-15-crown-4) (19) was prepared analogously to **7** from 2-methoxy-1,3-bis(bromomethyl)benzene and 3,6-dithia-1,8-octanediol. The monomeric crown ether was separated from its oligomers by preparative column chromatography (silica gel) using gradual elution (PE–THF). The fractions containing pure **19** were combined, and the solvent was removed to give **19** as a white solid (mp 82–83 °C) in 25% yield: ^{1}H NMR ($CDCl_3$, 200 MHz, ref $CHCl_3$ = 7.27 ppm) δ 2.29–2.66 (m, 8 H, SCH_2), 3.27–3.52 (m, 4 H, OCH_2), 3.73 (s, 3 H, OCH_3), 4.36/4.78 (dd, AB, ^2J = 11.7 Hz, 4 H, xylyl-CH_2), 7.11–7.37 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$, 50.32 MHz, ref $CDCl_3$ = 77.00 ppm) δ 15.67 (q, ^1J = 126.00 Hz, ^2J = 2.5 Hz, CH_3), 68.11 (tt, ^1J = 148.7 Hz, ^2J = 4.1 Hz, O(1)CH_2CH_2O(2)), 68.74 (t, ^1J = 143.2 Hz, O(2)CH_2CH_2O(3)), 69.88 (tt, ^1J = 140.9 Hz, ^2J = 3.5 Hz, O(1)CH_2CH_2O(2)), 70.33 (t, ^1J = 141.1 Hz, xylyl-CH_2), 71.10 (tq, ^1J = 147.2 Hz, ^2J = 4.4 Hz, OCH_2CH_3), 122.67 (d, ^1J = 161.4 Hz, C5), 131.40 (ddt, ^1J = 158.1 Hz, ^2J = 8.6 Hz, ^3J = 4.6 Hz, C4 and C6), 132.03 (bs, C1 and C3), 157.77 (bs, C2); GC/MS *m/z* (rel intensity) 314 (M^+, $C_{15}H_{22}O_3S_2$, 8), 211 (15), 165 (50), 151 (23), 133 (25), 121 (25), 105 (100), 91 (58); HRMS calcd for $C_{15}H_{22}O_3S_2$ 314.1010, obsd 314.101 ± 0.001. Anal. Calcd for $C_{15}H_{22}O_3S_2$: C, 57.29; H, 7.06. Found: C, 57.25; H, 7.08.

21-Methoxy-3,6,9,12,15-pentaoxabicyclo[15.3.1]heneicosa-1(21),17,19-triene ((2-methoxy-1,3-xylylene)-18-crown-5) (20) was prepared analogously to **7** as a white crystalline solid after recrystallization from Et_2O (50%). The obtained spectral data were in accordance with those reported.[6c]

18-(Methylthio)-3,6,9,12-tetraoxabicyclo[12.3.1]octadeca-1(18),14,16-triene ([2-(methylthio)-1,3-xylylene]-15-crown-4) (21) is known.[27a] It was prepared by reaction of (2-lithio-1,3-xylylene)-15-crown-4 with dimethyl disulfide at −70 °C. (2-Lithio-1,3-xylylene)-15-crown-4 was prepared in situ from (2-bromo-1,3-xylylene)-15-crown-4 (**4**) and *n*-butyllithium. After standard workup the product was crystallized from ethanol at −20 °C as white crystals (57%). The obtained spectral data were in accordance with those reported.[27b]

18-(Ethylthio)-3,6,9,12-tetraoxabicyclo[12.3.1]octadeca-1(18),14,16-triene ([2-(ethylthio)-1,3-xylylene]-15-crown-4) (22) was prepared analogously to **21**. The in situ prepared (2-lithio-1,3-xylylene)-15-crown-4 was reacted with a slight excess of diethyl disulfide at −70 °C. After standard workup the product was crystallized from ethanol at −20 °C as white crystals (42%, mp 66 °C): ^{1}H NMR ($CDCl_3$, 200 MHz, ref $CHCl_3$ = 7.27 ppm) δ 1.16 (t, ^3J = 7.4 Hz, 3 H, CH_3), 2.69 (q, ^3J = 7.4 Hz, 2 H, SCH_2), 3.18–3.72 (m, 12 H, CH_2), 4.33, 5.36 (dd, AB, ^2J(AB) = 12.4 Hz, 4 H, xylyl-CH_2), 7.27–7.40 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$, 50.29 MHz, ref $CHCl_3$ = 77.00 ppm) δ 14.78 (qt, ^1J = 127.3 Hz, ^2J = 3.4 Hz, 1 C, CH_3), 31.43 (tq, ^1J = 139.8 Hz, ^2J = 4.7 Hz, 1 C, SCH_2), 68.61 (t, ^1J = 137.8 Hz, 2 C, xylyl-CH_2OCH_2), 70.37 (t, ^1J = 140.8 Hz, 4 C, O(1)CH_2CH_2O(2)CH_2CH_2O(3)CH_2CH_2O(4)), 72.01 (t, ^1J = 142.9 Hz, 2 C, xylyl-CH_2), 127.29 (d, ^1J = 161.0 Hz, 1 C, Ar-C5), 130.36 (d, ^1J = 168.1 Hz, 2 C, Ar-C4 and Ar-C6), 136.35 (s, 1 C, Ar-C2), 143.22 (s, 2 C, Ar-C1 and Ar-C3); GC/MS *m/z* (rel intensity) 312 (M^+, $C_{16}H_{24}O_4S$, 1.2), 251 (M^+ − SMe, 3.2), 162 (51), 149 (25), 135 (25), 89 (20), 45 (100); HRMS calcd for $C_{16}H_{24}O_4S$ 312.1395, obsd 312.139 ± 0.001. Anal. Calcd for $C_{16}H_{24}O_4S$: C, 61.51; H, 7.75. Found: C, 61.47; H, 7.75.

Reaction of (2-Methoxy-1,3-xylylene)-15-crown-4 (7) with Diphenylmagnesium. In a fully sealed glass apparatus were combined **7** (1 mmol, 0.282 g) and diphenylmagnesium (1 mmol in 8 mL of Et_2O) to give immediately a white precipitate. After 1 h, the reaction mixture was quenched with dilute hydrochloric acid, extracted (Et_2O), dried ($MgSO_4$), and filtered. GC/MS analysis showed only toluene as a reaction product. After removal of the solvent by using a rotary evaporator the residue (colorless oil, 0.20 g) was identified by ^{1}H NMR as the crown ether 2-hydroxy-1,3-xylylene-15-crown-4 (**10**), which could not be analyzed by GC/MS as it does not pass the column. The ^{1}H NMR spectrum showed that only a few percent (<5%) of the starting material (**7**) remained after the reaction. The product **10** could be extracted from CH_2Cl_2 into an alkaline solution and after acidification back into $CHCl_3$. The NMR signals of the few percent of starting crown **7** had now disappeared.

10: ^{1}H NMR ($CDCl_3$, 200 MHz, ref $CHCl_3$ = 7.27 ppm) δ 3.60–3.73 (m, 12 H, CH_2), 4.65 (s, 4 H, xylyl-CH_2), 6.77–7.12 (m, 3 H, ArH).

Reaction of 7 with Diphenylmagnesium in Et_2O-d_{10}. In a fully sealed glass apparatus were combined **7** (0.29 mmol, 0.0819 g) and diphenylmagnesium (0.29 mmol in 2 mL of Et_2O-d_{10}). Almost immediately a white suspension was formed, which was stirred for 3 h at room temperature. After settling of the solid material, the ether solution was filtered and all volatile components were distilled into the ether layer by cooling with liquid nitrogen for 1 h. The solid residue was warmed moderately (hot air). The part of the system that contained the (frozen) ether layer was sealed off. After it was warmed to room temperature, the ether layer was homogenized and divided equally into two sealed-on NMR tubes. After being cooled with liquid nitrogen, the NMR tubes were sealed off. ^{1}H NMR (200 MHz, Et_2O-d_{10}) showed that only starting material **7** and toluene were present. From the known amount of starting material **7**, from the ratio toluene/**7** (^{1}H NMR) after the reaction, and from the weighed amount of **7** after the reaction, determination of the amount of toluene formed during the reaction was possible. This amount

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(27) Program PANIC, Bruker program Library.

was almost the same as the amount of **10** that could be extracted from the solid material. In the NMR spectra no methane or ethane could be detected.

Reaction of 7 with Diphenylmagnesium Followed by H_2O Quench after 3 min. In a fully sealed glass apparatus were combined **7** (0.75 mmol, 0.213 g) and diphenylmagnesium (0.75 mmol in 9 mL of Et_2O) to give almost immediately a white precipitate. After 3 min, the reaction mixture was quenched with dilute hydrochloric acid, extracted (Et_2O), dried ($MgSO_4$), and filtered. GC/MS analysis showed some toluene as a reaction product (toluene:**7** = 3:97). After removal of the solvent by using a rotary evaporator, the residue (0.164 g) was identified by ^1H NMR (200 MHz, $CDCl_3$): 6.4% of the crown ether (2-hydroxy-1,3-xylylene)-15-crown-4 (**10**) had been formed, while 93.6% of the starting material (**7**) remained after the reaction.

Reaction of 7 with 2 Equiv of Diphenylmagnesium. In a fully sealed glass apparatus were combined **7** (0.38 mmol, 0.108 g) and diphenylmagnesium (0.75 mmol in 8 mL of Et_2O) to give almost immediately a white precipitate which was heated at 75 °C for 4 h. After settling of the solid material, the ether layer was decanted and sealed off. Analysis of this ether layer showed that there was no compound in solution: no toluene or starting material was found (GC and GC/MS), no Ph_2Mg or other base was found (HCl and EDTA titrations), and finally no crown ethers were present (^1H NMR). The solid residue was suspended in toluene and heated for 3 h at 80 °C. Some of the precipitate dissolved during this heating. Subsequently, this reaction mixture was quenched with dilute hydrochloric acid, extracted (Et_2O), dried ($MgSO_4$), and filtered. After removal of the solvent, the residue (0.092 g) was identified by ^1H NMR (200 MHz, $CDCl_3$) to be (2-hydroxy-1,3-xylylene)-15-crown-4 (**10**) exclusively.

Reaction of 7 with Bis(*p-tert*-butylphenyl)magnesium. This reaction was carried out analogously to the reaction of **7** with diphenylmagnesium. GC/MS analysis of the organic layer after quenching with dilute hydrochloric acid showed only *p-tert*-butyltoluene as a reaction product. ^1H NMR (200 MHz, $CDCl_3$) showed the presence of **10** (93%) and the starting material **7** (7%) after quenching and evaporation of the solvent.

Reaction of 7 with Diphenylzinc. In a fully sealed glass apparatus were combined **7** (1.01 mmol, 0.289 g) and diphenylzinc (1.0 mmol in 10 mL of Et_2O). Slowly, a gray precipitate was formed. After a few hours the diethyl ether was distilled off, and the residue was sealed off. After removing the last traces of diethyl ether, the solid material was dissolved into toluene-d_8 and transferred into a NMR tube, which was sealed off. A ^1H NMR spectrum revealed the formation of a solvent-free 1:1 complex (200 MHz, toluene-d_8, ref $C_6D_5CD_2H$ = 2.03 ppm); δ 2.95–3.40 (m, 12 H, CH_2), 3.72 (s, 3 H, OMe), 3.76, 4.93 (dd, AB, $^2J(AB)$ = 12.3 Hz, 4 H, xylyl-CH_2), 6.79–6.95 (m, 3 H, xylyl-H), 7.22–7.27 (m, 6 H, phenyl-H3, 4 and 5), 7.39–7.44 (m, 4 H, phenyl-H2 and 6). To quantify the effects of complexation on the crown ether shifts, a reference spectrum of pure **7** was measured under the same conditions: δ 2.72–3.46 (m, 12 H, CH_2), 4.00 (s, 3 H, OMe), 3.89, 5.03 (dd, AB, $^2J(AB)$ = 12.2 Hz, 4 H, xylyl-CH_2), 6.75–6.99 (m, 3 H, xylyl-H). Prolonged heating at 60 °C of the NMR tube with the complex did not change the ^1H NMR spectrum. Finally, the contents of the NMR tube was quenched and after workup the residual oil was found to be pure **7** (^1H NMR, 200 MHz, $CDCl_3$); **10** was not detected.

Reaction of 7 with Phenylmagnesium Bromide. In a fully sealed glass apparatus were combined **7** (0.69 mmol, 0.196 g) and phenylmagnesium bromide (0.68 mmol in 5 mL of Et_2O) to give almost immediately a white precipitate. After 1 day at 50 °C, the reaction mixture was quenched with dilute hydrochloric acid, extracted (Et_2O), dried ($MgSO_4$), and filtered. GC/MS analysis showed only toluene as a reaction product. After removal of the solvent by using a rotary evaporator the residue (colorless oil, 0.144 g) was identified by ^1H NMR (200 MHz, $CDCl_3$). Only two crown ethers were present: starting material crown **7** (41%) and the product **10** (59%).

In another experiment **7** (0.89 mmol, 0.251 g) and phenylmagnesium bromide (0.9 mmol in 7 mL of Et_2O) were reacted for 2 days at 50 °C. After workup only two crown ethers were present in the residual oil (0.194 g): starting material crown **7** (10%) and the product **10** (90%).

Reaction of 7 with Methylmagnesium Bromide. In a fully sealed glass apparatus were combined **7** (0.79 mmol, 0.223 g) and methylmagnesium bromide (0.8 mmol in 10 mL of Et_2O) to give almost immediately a white precipitate. After 5 days at 60 °C, the reaction mixture was quenched with dilute hydrochloric acid, extracted (Et_2O), dried ($MgSO_4$), and filtered. After removal of the solvent the residue (colorless oil, 0.179 g) was identified by ^1H NMR (200 MHz, $CDCl_3$). Only two crown ethers were present: starting material crown **7** (56%) and the product **10** (44%).

Reaction of 7 with Magnesium Dibromide, $MgBr_2$. In a fully sealed glass apparatus were combined **7** (0.81 mmol, 0.229 g) and magnesium dibromide (0.81 mmol, 0.149 g) in 8 mL of Et_2O to give almost immediately a white precipitate. After 11 days at 60 °C, the reaction mixture was quenched with dilute hydrochloric acid, extracted (Et_2O), dried ($MgSO_4$), and filtered. After removal of the solvent the residue (colorless oil, 0.194 g) was identified by ^1H NMR (200 MHz, $CDCl_3$). Only two crown ethers were present: starting material crown **7** (40%) and the product **10** (60%).

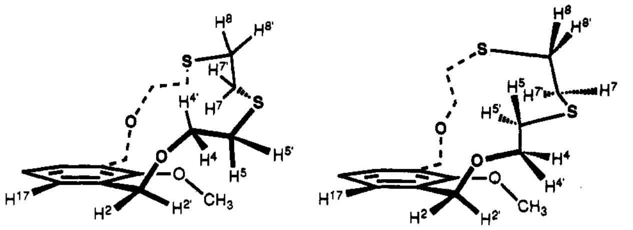
Reaction of (2-Ethoxy-1,3-xylylene)-15-crown-4 (17) with Diphenylmagnesium. In a fully sealed glass apparatus **17** (0.74 mmol, 0.220 g) and phenylmagnesium bromide (0.9 mmol in 7 mL of Et_2O) were combined to give almost immediately a white precipitate. After 5 days at 50 °C, the reaction mixture was quenched with dilute hydrochloric acid, extracted (Et_2O), dried ($MgSO_4$), and filtered. GC/MS analysis showed only ethylbenzene as a reaction product. After removal of the solvent by using a rotary evaporator, the residue (colorless oil, 0.187 g) was identified by ^1H NMR (200 MHz, $CDCl_3$). Only two crown ethers were present: starting material crown **17** (89%) and the product **10** (11%).

Reaction of (2-Isopropoxy-1,3-xylylene)-15-crown-4 (18) with Diphenylmagnesium. In a fully sealed glass apparatus were combined **18** (0.80 mmol, 0.249 g) and diphenylmagnesium (0.75 mmol in 7 mL of Et_2O) to give almost immediately a white precipitate. After 5 days at 50 °C, the reaction mixture was quenched with dilute hydrochloric acid, extracted (Et_2O), dried ($MgSO_4$), and filtered. GC/MS analysis showed only starting crown **18**. After removal of the solvent by using a rotary evaporator the residue (colorless oil, 0.190 g) was identified by ^1H NMR (200 MHz, $CDCl_3$) to be only starting material crown ether **18**.

Reaction of (2-Methoxy-1,3-xylylene)-6,9-dithia-15-crown-4 (19) with Diphenylmagnesium in Et_2O. In a fully sealed glass apparatus were combined **19** (0.75 mmol, 0.237 g) and diphenylmagnesium (0.75 mmol in 9 mL of Et_2O) to give a pale yellow solution. After 3 days at room temperature, the clear solution was heated at 60 °C for 1 week, after which the reaction mixture was quenched with diluted hydrochloric acid. The residue (0.203 g) was identified by ^1H NMR (200 MHz, $CDCl_3$) as pure starting material, crown ether **19**.

Reaction of 19 with Diphenylmagnesium in Toluene. In a fully sealed glass apparatus were combined **19** (0.75 mmol, 0.237 g) and diphenylmagnesium (0.75 mmol in 9 mL of Et_2O) to give a pale yellow solution. The ether solvent was distilled off, and the last traces were removed by high vacuum pumping. The solid residue was dissolved in 8 mL of toluene. From this toluene solution 0.5 mL was separated for NMR investigation. The toluene was removed by high vacuum pumping, and the solid residue was dissolved in 0.5 mL of toluene-d_8. A ^1H NMR spectrum revealed the formation of a 1:1 complex (400 MHz, toluene-d_8, ref $C_6D_5CD_2H$ = 2.03 ppm): δ 2.105–2.431 (m, 8 H, SCH_2), 3.12 (s, 3 H, OMe), 3.351 (t, ^3J = 7.6 Hz, 4 H, OCH_2), 4.168, 4.502 (dd, AB, $^2J(AB)$ = 11.7 Hz, 4 H, xylyl-CH_2), 6.758 (t, ^3J = 7.5 Hz, xylyl-H(5)), 7.032 (d, ^3J = 7.5 Hz, 2 H, xylyl-H(4,6), 7.19–7.36 (m, 6 H, phenyl-H(3, 4, and 5)), 8.05–8.15 (m, 4 H, phenyl-H2 and 6). To quantify the effects of complexation on the crown ether shifts, a reference spectrum of pure **19** was

Chart II



measured under the same conditions. The spectral analysis was performed with the program PANIC[27] (a version of the LAOCOON type programs[28]) on a Bruker Aspect 3000 computer: ^{1}H NMR (for numbering, see Chart II) (toluene-d_8, 400 MHz, ref $C_6D_5CD_2H$ = 2.03 ppm) 2.249, 2.302 ((AA′BB′ ($H^7,H^8,H^{7'},H^{8'}$)), $^2J_{AB} = {}^2J_{A'B'} = -13.31$ Hz, $^3J_{AB'}$, $^3J_{A'B} = 4.73$ Hz, $^3J_{AA'} = 12.83$ Hz, $^3J_{BB'} = 12.84$ Hz, 4 H, $H^7,H^8,H^{7'},H^{8'}$), 3.349, 3.317, 2.411, 2.187 ((ABCD ($H^4,H^{4'},H^5,H^{5'}$)), $^2J_{AB} = -10.37$ Hz, $^2J_{CD} = -13.84$ Hz, $^3J_{AC} = 5.29$ Hz, $^3J_{BD} = 6.19$ Hz, $^3J_{AD} = 9.46$ Hz, $^3J_{BC} = 9.44$ Hz, 8 H, $H^4,H^{4'},H^5,H^{5'}$ and $H^{12},H^{12'},H^{11},H^{11'}$), 3.213 (s, 3 H, OCH_3), 4.078, 4.525 (dd, AB, $^2J = 11.7$ Hz, 4 H, xylyl-CH_2), 6.790 (t, $^3J = 7.5$ Hz, 1 H, xylyl-H(5), 7.062 (d, $^3J = 7.5$ Hz, 2 H, xylyl-H(4,6)). NOESY interactions: OCH_3–$H^{2'}$, H^2–$H^{2'}$, $H^{2'}$–H^5, H^5–$H^{5'}$, $H^{2'}$–H^4 and/or $H^{4'}$, H^2–H^{17}, H^5–H^4 and/or $H^{4'}$, $H^{5'}$–H^4 and/or $H^{4'}$. The $H^{2'}$–H^5, $H^{2'}$–H^4 and/or $H^{4'}$ NOESY interactions suggest the presence of at least two conformers in solution, between which rapid interchange takes place (see Chart II).

The rest of the toluene solution was heated for 14 days at 60 °C; a clear yellow solution and some slimy brown precipitate was obtained. The toluene was removed by distillation and high vacuum pumping; from the solid residue, as much as possible was dissolved in 0.5 mL of toluene-d_8. The ^{1}H NMR spectrum showed that many different products were present and that all of the starting material had disappeared. GC/MS analysis of this solution showed that more than 15 products were present, most of which could not be identified. The resulting solid material (not dissolved in the toluene-d_8) was quenched with diluted hydrochloric acid and analyzed by ^{1}H NMR and GC/MS spectroscopy. Again, more than 15 products were present, most of which could not be identified.

Reaction of (2-Methoxy-1,3-xylylene)-18-crown-5 (20) with Diphenylmagnesium in Et_2O. In a fully sealed glass apparatus were combined **20** (0.77 mmol, 0.250 g) and diphenylmagnesium (0.75 mmol in 9 mL of Et_2O) to give a gray precipitate almost immediately. After 3 days at 60 °C, the reaction mixture was quenched with dilute hydrochloric acid, extracted (Et_2O), dried ($MgSO_4$), and filtered. After removal of the solvent by using a rotary evaporator, the residue (colorless oil, 0.171 g) was identified by ^{1}H NMR (200 MHz, $CDCl_3$): only two crown ethers were present: starting material crown **20** (55%) and the product (2-hydroxy-1,3-xylylene)-18-crown-5 (45%).

Reaction of [2-(Methylthio)-1,3-xylylene]-15-crown-4 (21) with Diphenylmagnesium. In a fully sealed glass apparatus were combined **21** (0.75 mmol, 0.223 g) and diphenylmagnesium (0.75 mmol in 10 mL of Et_2O) to give a pale yellow solution. After 1 h a precipitate was formed. The reaction mixture was heated at 60 °C for 4 days, during which period the solid material did not dissolve. After settling of the solid material, the ether layer was decanted and sealed off. GC/MS analysis showed only a trace of toluene (1%) as only reaction product. After removal of the ether solvent the residue of this ether layer (0.058 g) was identified by ^{1}H NMR (200 MHz, $CDCl_3$): a crown ether, probably (2-mercapto-1,3-xylylene)-15-crown-4 (**25**), has been formed in 4% yield relative to the starting material **21**, which could not be analyzed by GC/MS as it does not pass the column. (4% out of 0.058 g is approximately 1% of the starting material). For definite identification of the crown ether product a reference spectrum of **25** would be necessary, but independent synthesis of **25** is difficult. The solid residue of the reaction mixture which was separated from the ether layer was quenched separately, and after workup ^{1}H NMR revealed that only starting material **21** was present. Strangely enough, cleavage product **25** was only found in the ether layer, while **10** (cleavage product of **7**) was always obtained only from the solid residue.

Reaction of [2-(Ethylthio)-1,3-xylylene]-15-crown-4 (22) with Diphenylmagnesium. In a fully sealed glass apparatus were combined **22** (0.75 mmol, 0.267 g) and diphenylmagnesium (0.75 mmol in 10 mL Et_2O) to give a pale yellow solution. After some time a precipitate was formed. The reaction mixture was heated at 60 °C for 2 weeks, during which period the solid material did not dissolve. The reaction mixture was quenched with dilute hydrochloric acid, extracted (Et_2O), dried ($MgSO_4$), and filtered. GC analysis of the ether layer showed that ethylbenzene had not been formed. After workup of the aqueous layer, the combined organic fractions were concentrated to give 0.225 g of starting material **22** (^{1}H NMR) as a yellow oil.

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(28) Castellano, S.; Bothner-By, A. A. *J. Chem. Phys.* **1964**, *41*, 3863.