# Direct metalation of methoxymethyl arylmethyl ethers: A tin-free approach to the generation of α-alkoxyalkoxy-substituted aryllithiums

Ugo Azzena *, Luisa Pisano, Sarah Mocci

*Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy*

### ABSTRACT

The generation of a series of α-methoxymethoxy-substituted arylmethyllithiums was achieved by direct metalation of the corresponding arylmethyl methoxymethyl ethers. While the effect of substituents at the benzylic position is straightforward, substituents located on the aromatic ring promote the set up of a competition between lateral and aromatic metalation, strongly affected by the position and relative *ortho* directing properties of the new substituent. The proposed methodology allows a simple approach to the generation of a wide array of functionalized organolithium reagents.

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## 1. Introduction

Directed *ortho* (DoM) and benzylic metalation of aromatic compounds are widely employed synthetic procedures allowing the regioselective generation of funtionalized organometals, although, with appropriate substrates, competition between the two reaction pathways could lead to the formation of isomeric reaction products [1,2].

From this point of view, acetals of arylmethyl alcohols are usually considered as weak *ortho* directing metalation groups (DMGs) [3]. Indeed, benzyl methoxymethyl or 1-ethoxyethyl ethers substituted at C3 with a methoxy group [4,5], or with a fluorine [6], undergo regioselective metalation at C2 under various reaction conditions.

Despite the known possibility to generate α-methoxy-substituted benzyllithiums by the metalation of arylmethyl methyl ethers [7,8], only a single example concerns the application of this procedure to the generation of an *O*-alkoxyalkyl-substituted benzyllithium [9].

Indeed, the most widely employed procedure for the generation of these organometals involves condensation of lithium tributylstannane with an aromatic aldehyde, followed by protection of the resulting α-tributylstannyl-substituted benzyl alcohol, and final tin–lithium exchange (Scheme 1) [9–17].

Planning to develop an alternative approach to the generation of this interesting class of functionalized organometallic reagents,

to shorten the reaction sequence, and to avoid the manipulation of toxic organotin reagents, we undertook an investigation aimed to establish the reactivity of a series of arylmethyl methoxymethyl [18] ethers, **1a–l**, under metalation reaction conditions (Scheme 2).

## 2. Results and discussion

### 2.1. Synthesis of methoxymethyl ethers

Arylmethyl methoxymethyl ethers were synthesized by the reaction of the corresponding arylmethyl alcohol with $CH_3OCH_2Cl$ according to known procedures, either under basic (**1a** and **1c–l**, NaH, THF) [19] or acidic (**1b**, Na–Y zeolite, $CH_2Cl_2$) [20] reaction conditions.

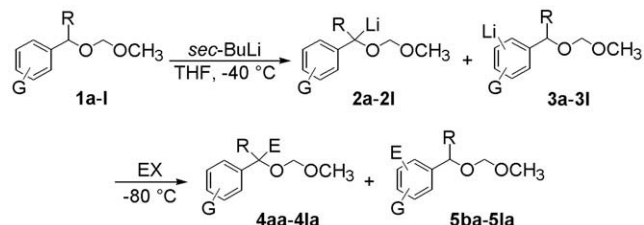### 2.2. Metalation of benzyl methoxymethyl ether, 1a

Metalation reactions were carried out under dry Ar in the presence of an excess (2 equiv) of *sec*-BuLi. Metalation of benzyl methoxymethyl ether, **1a**, taken as a model compound, was investigated in some detail; the results are reported in Table 1 (Scheme 2). Reaction of **1a** with *sec*-BuLi in THF at −80 °C, followed by quenching with $D_2O$, showed a not quantitative formation of the desired intermediate organometal within 3 h (Table 1, entry 1). A somewhat better result was obtained running the reaction at −40 °C under otherwise identical reaction conditions (Table 1, entry 2), and similar results were obtained employing *n*-BuLi as a base (not reported in Table 1). These results underline the thermal stability of organolithium **2a**, in contrast with the recent hypothe-
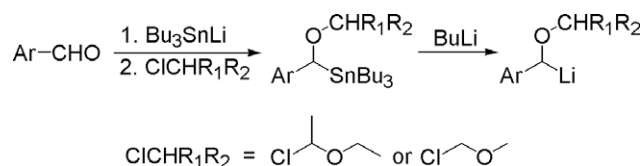
**Scheme 1.** Generation of alkoxyalkoxyl-substituted benzyllithiums, according to Ref. [9–15].



**Scheme 2.** Metalation of arylmethyl methoxymethyl ethers, and reaction with electrophiles. **1a–5a**: G = R = H; **1b–5b**: G = 4-OCON(CH$_3$)$_2$, R = H; **1c–5c**: G = 4-F, R = H; **1d–5d**: G = 3-F, R = H; **1e–5e**: G = 4-OCH$_3$, R = H; **1f–5f**: G = 4-OCH(CH$_3$)$_2$, R = H; **1g–5g**: G = 3-OCH$_3$, R = H; **1h–5h**: G = 4-Cl, R = H; **1i–5i**: G = 4-CH$_3$, R = H; **1j–5j**: G = H, R = C$_6$H$_5$; **1k–5k**, G = H, R = CH$_3$; **1l–5l**, G = 4-OCH$_3$, R = CH$_3$; EX, E, see text and tables.

**Table 1**
Metalation of benzyl methoxymethyl ether, **1a**, and reaction with electrophiles.[a]

| | T (°C) | EX | Product, E | Yield (%)[b] |
|---|---|---|---|---|
| 1 | −80 | D$_2$O | **4aa**, D | 81 |
| 2 | −40 | D$_2$O | **4aa**, D | 88 |
| 3 | −40[c] | D$_2$O | **4aa**, D | –[d] |
| 4 | −10[c] | D$_2$O | **4aa**, D | –[d] |
| 5 | 0[c] | D$_2$O | **4aa**, D | –[e] |
| 6 | −40 | n-BuBr | **4ab**, n-Bu | 74[f] |
| 7 | −40 | i-PrI | **4ac**, i-Pr | 80[f] |
| 8 | −40 | Cl(CH$_2$)$_4$Cl | **4ad**, (CH$_2$)$_4$Cl | 76[f] |
| 9 | −40 | PhCH$_2$O(CH$_2$)$_3$Cl | **4ae**, PhCH$_2$O(CH$_2$)$_3$ | 63[f] |
| 10 | −40 | (CH$_3$)$_2$CO | **4af**, (CH$_3$)$_2$COH | 40[f] |
| 11 | −40 | (CH$_2$)$_5$CO | **4ag**, (CH$_2$)$_5$COH | 56[f] |

[a] All metalations were run in THF, in the presence of 2 equiv of sec-BuLi during 3 h, unless otherwise indicated; 1.1 equiv of the EX was added at −80 °C.
[b] As determined by $^1$H NMR spectroscopy of crude reaction mixtures, unless otherwise indicated.
[c] Reaction run in hexane.
[d] Starting material was quantitatively recovered.
[e] Extended decomposition.
[f] Yield calculated on the isolated product.

sis of an easy Wittig rearrangement of similar organometals [6]. Finally, it is worth noting that, besides several attempts (Table 1, entries 3–5), we were unable to generate stable solutions of the same organometal in hexane.

To evaluate the reactivity of organometal **2a**, and in agreement with the above reported results, additional metalations were run at −40 °C, in dry THF, employing sec-BuLi as a base; the resulting mixtures were quenched by slow dropwise addition of a THF solution of an electrophile. Satisfactory results were obtained employing either alkyl halides (Table 1, entries 6–9) or ketones (Table 1, entries 10 and 11) as electrophilic reagents. Careful inspection of $^1$H NMR of crude reaction mixtures showed that metalation reactions occurred regioselectively at the benzylic position of the starting material, with no evidences of substitution on the aromatic ring.

To check the versatility of the proposed methodology, few reaction products were submitted to acidic hydrolysis to remove the MOM-protecting group (Scheme 3).
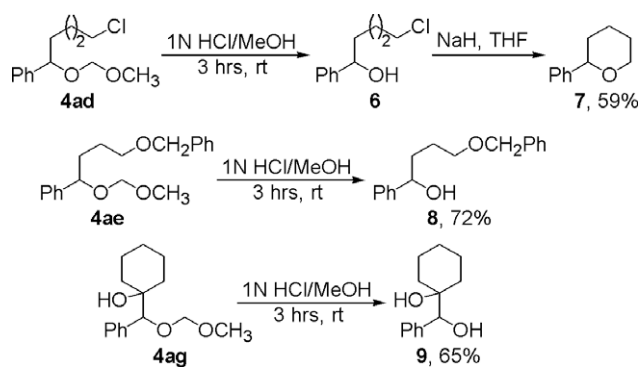


**Scheme 3.** Deprotection of methoxymethyl benzyl ethers.

Accordingly, chloroether **4ad** was hydrolyzed by reacting it with 1 N HCl in MeOH during 3 h at r.t., and the resulting chloroalcohol **6** was reacted with NaH in dry THF to afford the corresponding tetrahyropyran **7** in 59% overall yield. Under similar hydrolytic conditions, acetal **4ae** afforded the monoprotected diol **8**, and hydroxyether **4ag** was hydrolyzed to the corresponding diol, **9**.

### 2.3. Metalation of Arylmethyl Methoxymethyl Ethers, 1b–l

To obtain more information on the ability of the O-methoxymethyl substituent to direct α-metalation, we extended our study to the metalation of several arylmethyl methoxymethyl ethers bearing an additional substituent, located either on the benzylic carbon or on the aromatic ring including, in the last series, groups known for their ability to direct the metalation reaction at their ortho position (DMGs) [1–3].

Metalation reactions were run as described in the above paragraph, followed by quenching with an electrophilic reagent, aqueous work up, and $^1$H NMR analyses of crude mixtures to determine the distribution of reaction products (benzylic versus ring hydrogen abstraction). Selected results, as reported in Table 2, show that the prevalence of one of these reaction pathways depends on the nature and the relative position of the new substituent; a (minor) effect of reaction temperature was also observed in few instances (Table 2, entries 2, 5 and 7 versus entries 3, 6 and 8).

Metalation of carbamate **1b** followed by quenching with TMSCl, afforded the corresponding 1,2,4-trisubstituted benzene **5bb**, with no evidences for the formation of an intermediate arylmethyllithium derivative (Table 2, entry 1). Clearly, the strong ortho-directing properties of the carboxyamido group overwhelm the ability of the methoxymethyl ether to direct benzylic metalation.

At variance with this result, lithiation of para-substituted fluoride **1c** (Table 2, entries 2–4) afforded mixtures of ortho-fluoro- and benzylic-metalated organometals [21], and similar results were obtained with the corresponding meta-isomer **1d** (Table 2, entries 5 and 6). Interestingly, aromatic metalation of fluoride **1d** regioselectively afforded the corresponding 2,6-disubstituted organolithium, thus highlighting the already known ortho-directing properties of the acetal moiety [4–6].

More complex results were obtained with the alkoxy-substituted acetals **1e–g**. Indeed, while metalation of the 4-methoxy-substituted derivative **1e** afforded a mixture of ortho-methoxy- and benzylic-metalated regioisomers (Table 2, entries 7 and 8), steric hindrance at the aromatic oxygen promoted the highly regioselective benzylic deprotonation of the corresponding 4-isopropoxy derivative **1f** (Table 2, entry 9). Furthermore, the meta-methoxy-substituted acetal **1g** underwent exclusive benzylic hydrogen–metal exchange (Table 2, entry 10). The last example shows a major solvent effect on the regioselectivity of metalation

**Table 2**
Metalation of arylmethyl methoxymethyl ethers, **1b–l**, and reaction with electrophiles.[a]

| Entry | Substrate, G, R | EX | E | Product distribution (%)[b] | |
|---|---|---|---|---|---|
| | | | | 4 | 5 |
| 1 | **1b**, 4-OCONEt$_2$, H | (CH$_3$)$_3$SiCl | (CH$_3$)$_3$Si | **4ba**, – | **5ba**, >90 (85)[c] |
| 2 | **1c**, 4-F, H | (CH$_3$)$_3$SiCl | (CH$_3$)$_3$Si | **4ca**, 27 (20)[c] | **5ca**, 73 (54)[c] |
| 3 | **1c**, 4-F, H | (CH$_3$)$_3$SiCl | (CH$_3$)$_3$Si | **4ca**, 12[d] | **5ca**, 88 (65)[c,d] |
| 4 | **1c**, 4-F, H | (CH$_3$)$_3$CCHO | (CH$_3$)$_3$CCHOH | **4cb**, 29 (23)[c,e] | **5cb**, 71 (52)[c] |
| 5 | **1d**, 3-F, H | (CH$_3$)$_3$SiCl | (CH$_3$)$_3$Si | **4da**, 45 (33)[c] | **5da**, 55 (41)[c] |
| 6 | **1d**, 3-F, H | (CH$_3$)$_3$SiCl | (CH$_3$)$_3$Si | **4da**, 69[d] | **5da**, 31[d] |
| 7 | **1e**, 4-OCH$_3$, H | (CH$_3$)$_3$SiCl | (CH$_3$)$_3$Si | **4ea**, 54 (32)[c] | **5ea**, 46 (27)[c] |
| 8 | **1e**, 4-OCH$_3$, H | (CH$_3$)$_3$SiCl | (CH$_3$)$_3$Si | **4ea**, 43[d] | **5ea**, 57[d] |
| 9 | **1f**, 4-OCH(CH$_3$)$_2$, H | (CH$_3$)$_3$SiCl | (CH$_3$)$_3$Si | **4fa**, >90 (86) | **5ba**, – |
| 10 | **1g**, 3-OCH$_3$, H | (CH$_3$)$_3$SiCl | (CH$_3$)$_3$Si | **4ga**, >90 (82)[c] | **5ga**, – |
| 11 | **1h**, 4-Cl, H | D$_2$O | D | **4ha**, >90 | **5ha**, – |
| 12 | **1h**, 4-Cl, H | (CH$_3$)$_3$SiCl | (CH$_3$)$_3$Si | **4hb**, >90 (78)[c] | **5hb**, – |
| 13 | **1i**, 4-CH$_3$, H | D$_2$O | D | **4ia**, >90 | **5ia**, – |
| 14 | **1i**, 4-CH$_3$, H | (CH$_3$)$_3$SiCl | (CH$_3$)$_3$Si | **4ib**, >90 (81)[c] | **5ib**, – |
| 15 | **1j**, H, C$_6$H$_5$ | D$_2$O | D | **4ja**, >90 | **5ja**, – |
| 16 | **1j**, H, C$_6$H$_5$ | *n*-BuBr | *n*-Bu | **4jb**, >90 (78)[c] | **5jb**, – |
| 17 | **1k**, H, CH$_3$ | D$_2$O | D | **4ka**, 34 | **5ka**, – |
| 18 | **1l**, 4-OCH$_3$, CH$_3$ | (CH$_3$)$_3$SiCl | (CH$_3$)$_3$Si | **4lb**, – | **5lb**, >90 (84)[c] |

[a] All metalations were run in THF at −40 °C, in the presence of 2 equiv of *sec*-BuLi, during 3 h, unless otherwise indicated; 1.1 equiv of the EX was added at −80 °C.
[b] As determined by $^1$H NMR spectroscopy of crude reaction mixtures, unless otherwise indicated.
[c] Yield calculated on the isolated product.
[d] Metalation run at −80 °C, during 6 h.
[e] A diastereoisomeric mixture (75:25) was obtained.

reactions; indeed, it was reported that metalation of acetal **1g**, run in hexane, occurred exclusively at C2 [5].

Finally, with substituents endowed with poor or no directing metalation properties, i.e., aryl chloride **1h** and toluene derivative **1i**, respectively, we observed clean benzylic metalation (Table 2, entries 11–14). It is however worth noting that chloride **1h** was metalated at −80 °C; indeed, reactions run at −40 °C led to the formation of complex reaction mixtures (not reported in Table 2), thus suggesting competitive metalation *ortho* to the clorine atom, followed by LiCl elimination and aryne formation [22].

The effect of α-substitution on the α-lithiation of arylmethyl methoxymethyl ethers is straightforward. Indeed, we obtained quantitative α-metalation of benzydrylic derivative **1j** under standard conditions, and the corresponding intermediate organolithium was efficiently trapped with electrophilic reagents (Table 2, entries 15 and 16).

On the other side, under similar conditions, lithiation of (1-methoxymethoxy)ethylbenzene, **1k**, led to extensive decomposition of the starting material (not reported in Table 2), while only a minor amount of deuterium incorporation was evidenced when the metalation reaction, run at −80 °C, was quenched with D$_2$O (Table 2, entry 17). We were unable to improve this result on running a similar reaction in the presence of 2 equiv of TMEDA (not reported in Table 2). According to these findings, reaction of *sec*-BuLi with 1-methoxy-4-(1-methoxymethoxy)ethylbenzene, **1l**, run at −40 °C, led to regioselective deprotonation at C2 (Table 2, entry 18).

## 2.4. Concluding remarks

In conclusion, we have shown that direct α-metalation of arylmethyl methoxymethyl ethers is a feasible reaction allowing the generation of a wide array of α-methoxymethoxy-substituted arylmethyl organoliths, thus avoiding manipulation of tin derivatives. Although in the presence of a strong DMG, i.e., an *O*-carbamate, the MOM group acts as an effective protective group of the alcoholic moiety, this acetal is able to promote the formation of arylmethyl organoliths in the presence of substituents endowed with moderate to low *ortho*-directing properties, including

chlorine, alkoxy (depending upon the relative position and/or steric hindrance) and alkyl groups. From this point of view, it is worth noting that THF appears as the solvent of choice to promote α-lithiation of our acetals, as also evidenced by a comparison with literature reports concerning similar reactions run in hydrocarbon solvents [4,5]. On the other side, the strong acidifying effect of fluorine competes well with the methoxymethoxy group, leading to the formation of mixtures of regioisomers, easily separated by simple column chromatography.

## 3. Experimental

### 3.1. General

All air sensitive reactions were carried out under dry Ar. THF was distilled from Na/K alloy under N$_2$ immediately prior to use. $^1$H NMR spectra were recorded at 300 MHz and $^{13}$C NMR spectra were recorded at 75 MHz in CDCl$_3$ on a Varian VXR 300 spectrometer. Deuterium incorporation was calculated by monitoring the $^1$H NMR spectra of crude reaction mixtures, and comparing the integration of the signal corresponding to protons in the arylmethyl position with that of known signals. Resonances of arylmethyl CHD protons appear as unresolved broad triplets shifted 0.02–0.05 ppm ($\delta$) upfield relatively to the corresponding arylmethyl CH$_2$ protons; the resonances of the arylmethyl CHD carbons appear as triplets ($J$ = 19–21 Hz) shifted 0.3–0.4 ppm ($\delta$) upfield relatively to the corresponding arylmethyl CH$_2$ carbons. IR spectra were recorded on a FT-IR Jacso 480 P. Flash chromatography was performed on Merck silica gel 60 (40–63 μm), and TLC analyses on Macherey-Nagel silica gel pre-coated plastic sheets (0.20 mm). Elemental analyses were performed by the microanalytical laboratory of the Dipartimento di Chimica, Università di Sassari.

### 3.2. Starting materials

Acetals **1a** [19], **1b** [20] and **1c–k** [19] were synthesized according to general procedures, and purified either by fractional distillation or flash chromatography. Typical yields range from 70% to 85%. Acetals **1a** [19], **1c** [6,19], **1d** [6], **1j** [23], and **1k** [24], were

characterized according to the literature. Other products were purified and characterized as follows.

### 3.2.1. 4-Methoxymethoxymethylphenyl ester of N,N-diethylcarbamic acid (1b)

Oil, purified by flash chromatography (CH$_2$Cl$_2$/EtOAc/Et$_3$N = 7:3:0.5; R$_f$: 0.80). Bp 126/1 (°C/Torr). IR (neat): 1716 cm$^{-1}$ (CO). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.16–1.28 (m, 6H, 2 × CH$_3$), 3.35–3.47 (m, 4H, 2 × CH$_2$N), 3.41 (s, 3H, OCH$_3$), 4.58 (s, 2H, ArCH$_2$), 4.69 (s, 2H, OCH$_2$O), 7.08–7.14 (m, 2H, 2 × ArH), 7.31–7.37 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 13.3, 14.2, 41.8, 42.1, 55.2, 68.4, 95.4, 121.6, 128.6, 134.5, 150.9, 154.1. Anal. Calcd. for C$_{14}$H$_{21}$NO$_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.78; H, 8.06; N, 5.36%.

### 3.2.2. 1-Methoxy-4-methoxymethoxymethylbenzene (1e)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 8:2:0.5; R$_f$: 0.52). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.41 (s, 3H, CH$_3$O), 3.81 (s, 3H, CH$_3$OAr), 4.53 (s, 2H, ArCH$_2$), 4.69 (s, 2H, OCH$_2$O), 6.86–6.92 (m, 2H, 2 × ArH), 7.26–7.31 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 55.2, 68.8, 71.6, 95.4, 113.8, 129.5, 129.9, 159.2. Anal. Calcd. for C$_{10}$H$_{14}$O$_3$: C, 65.91; H, 7.74. Found: C, 65.76; H, 7.94%.

### 3.2.3. 1-Isopropoxy-4-methoxymethoxymethylbenzene (1f)

Oil, purified flash chromatography (petroleum ether/EtOAc/Et$_3$N = 7:3:1; R$_f$: 0.79). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.33 (d, 6H, J = 6.0 Hz, 2 × CH$_3$), 3.41 (s, 3H, OCH$_3$), 4.52 (s, 2H, ArCH$_2$), 4.55 (hept, J = 6.0 Hz, CH), 4.69 (s, 2H, OCH$_2$O), 6.84–6.90 (m, 2H, 2 × ArH), 7.24–7.30 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 22.0, 55.2, 68.8, 69.8, 95.4, 115.8, 129.6, 129.6, 157.5. Anal. Calcd. for C$_{12}$H$_{18}$O$_3$: C, 68.54; H, 8.63. Found: C, 68.37; H, 8.81%.

### 3.2.4. 1-Methoxy-3-methoxymethoxymethylbenzene, (1g)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 9:1:0.5; R$_f$: 0.43). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.42 (s, 3H, CH$_3$O), 3.82 (s, 3H, CH$_3$OAr), 4.58 (s, 2H, ArCH$_2$), 4.72 (s, 2H, OCH$_2$O), 6.81–6.86 (m, 1H, ArH), 6.90–6.96 (m, 2H, 2 × ArH), 7.23–7.29 (m, 1H, ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 55.1, 55.3, 68.9, 95.6, 113.1, 113.3, 120.0, 129.4, 139.4, 159.7. Anal. Calcd. For C$_{10}$H$_{14}$O$_3$: C, 65.91; H, 7.74. Found: C, 66.10; H, 7.84%.

### 3.2.5. 1-Chloro-4-methoxymethoxymethylbenzene (1h)

Oil, purified by flash chromatography (petroleum ether/EtOAc = 9:1; R$_f$: 0.52). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.41 (s, 3H, OCH$_3$), 4.56 (s, 2H, ArCH$_2$), 4.70 (s, 2H, OCH$_2$O), 7.27–7.35 (m, 4H, 4 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 55.3, 68.3, 95.6, 128.5, 129.1, 133.4, 136.3. Anal. Calcd. for C$_9$H$_{11}$ClO$_2$: C, 57.92; H, 5.94. Found: C, 57.78; H, 6.11%.

### 3.2.6. 4-Methoxymethoxymethyltoluene, (1i)

Oil, purified by flash chromatography (petroleum ether/EtOAc = 9:1; R$_f$: 0.34). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.35 (s, 3H, CH$_3$Ar), 3.41 (s, 3H, CH$_3$O), 4.56 (s, 2H, ArCH$_2$), 4.70 (s, 2H, OCH$_2$O), 7.14–7.19 (m, 2H, 2 × ArH), 7.23–7.27 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 21.0, 55.2, 68.9, 95.4, 127.9, 129.0, 134.7, 137.3. Anal. Calcd. for C$_{10}$H$_{14}$O$_2$: C, 72.26; H, 8.49. Found: C, 72.13; H, 8.56%.

### 3.2.7. 1-Methoxy-4-(1-methoxymethoxyethyl)benzene (1l)

Oil, purified by distillation or flash chromatography (petroleum ether/EtOAc/Et$_3$N = 8:2:0.5; R$_f$: 0.52. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.46 (d, J = 6.6 Hz, 3H, CH$_3$CH), 3.37 (s, 3H, CH$_3$OCH$_2$), 3.81 (s, 3H, CH$_3$OAr), 4.52 (d, J = 6.6 Hz, 1H, OCHO), 4.55 (d, J = 6.6, Hz, 1H, OCHO), 4.71 (q, J = 6.6 Hz, 1H, ArCH), 6.85–6.91 (m, 2H, 2 × ArH), 7.22–7.29 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$):

$\delta$ = 23.5, 55.2, 55.2, 73.1, 93.8, 113.7, 127.6, 135.2, 159.0. Anal. Calcd. for C$_{11}$H$_{16}$O$_3$: C, 67.32; H, 8.22. Found: C, 67.14; H, 8.39%.

### 3.3. General procedure for lithiation methoxymethyl arylmethyl ethers, and reaction with electrophiles

To a cooled (see tables) solution of the appropriate acetal (3.0 mmol) in 10 mL of dry THF, sec-butyllithium (6.0 mmol; 3.8 mL of a 1.6 M solution in cyclohexane) was added dropwise with stirring. Stirring was continued for 3–6 h (see tables) and then the appropriate electrophile (1.1 equiv), dissolved in 5 mL of THF was added to the reaction mixture chilled at −80 °C. After the addition, the reaction mixture was allowed to warm to r.t. overnight, then quenched by dropwise addition of 20 mL of H$_2$O. The resulting mixture was extracted with Et$_2$O (3 × 40 mL), washed with brine (20 mL), and the organic phase dried (K$_2$CO$_3$) and evaporated. Crude products were purified and characterized as follows.

### 3.3.1. 1-Methoxymethoxy-1-phenylpentane (4ab)

Oil, purified by flash chromatography (hexane/EtOAc = 9:1; R$_f$: 0.53). Bp 95/1 (°C/Torr). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.88 (t, J = 7.2 Hz, t, 3H, CH$_3$), 1.20–1.48 (m, 4H, 2 × CH$_2$), 1.58–1.74 (m, 1H, CH), 1.78–1.92 (m, 1H, CH), 3.37 (s, 3H, CH$_3$O), 4.52 (s, 2H, OCH$_2$O), 4.55 (dd, J = 7.8, 6.0 Hz, 1 H CHPh), 7.23–7.37 (m, 5H, 5 × PhH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 14.0, 22.6, 28.1, 37.7, 55.5, 78.0, 94.0, 126.9, 127.5, 128.3, 142.3. Anal. Calcd. for C$_{13}$H$_{20}$O$_2$: C, 74.96; H, 9.68. Found: C, 74.75; H, 9.83%.

### 3.3.2. 1-Methoxymethoxy-1-phenyl-2-methylpropane (4ac)

Oil, purified by flash chromatography (petroleum ether/Et$_3$N = 9:1; R$_f$: 0.35). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.75 (d, J = 6.9 Hz, 3H, CH$_3$), 1.04 (d, J = 6.9 Hz, 3H, CH$_3$), 1.90–2.03 (m, 1H, CH), 3.37 (s, 3H, CH$_3$), 4.22 (d, J = 7.5 Hz, 1H, PhCH), 4.50 (s, 2H, OCH$_2$O), 7.23–7.33 (m, 5H, 5 × PhH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 19.0, 19.1, 34.6, 55.5, 83.5, 94.2, 127.4, 127.6, 128.0, 140.9. Anal. Calcd. for C$_{12}$H$_{18}$O$_2$: C, 74.19; H, 9.34. Found: C, 73.91; H, 9.52.

### 3.3.3. 1-Methoxymethoxy-1-phenyl-5-chloropentane (4ad)

Oil, purified by flash chromatography (hexane/EtOAc = 9:1; R$_f$: 056;). Bp 160/1 (°C/Torr). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.37–1.96 (m, 6H, 3 × CH$_2$), 3.37 (s, 3H, CH$_3$O), 3.52 (t, J = 6.6 Hz, 2H, CH$_2$Cl), 4.52 (s, 2H, OCH$_2$O), 4.57 (dd, J = 7.8, 5.1 Hz, 1H, CHPh), 7.24–7.38 (m, 5H, 5 × PhH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 23.3, 32.5, 37.2, 44.9, 55.6, 77.7, 94.1, 126.8, 127.7, 128.3, 141.9. Anal. Calcd. For C$_{13}$H$_{19}$ClO$_2$: C, 64.32; H, 7.89. Found: C, 64.21; H, 7.96.

### 3.3.4. 4-Methoxymethoxy-4-phenylbutyl benzyl ether (4ae)

Oil, purified by flash chromatography (hexane/EtOAc = 9.5:0.5; R$_f$: 0.53;). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.52–1.98 (m, 4H, 2 × CH$_2$), 3.35 (s, 3H, CH$_3$O), 3.44–3.51 (m, 2H, CH$_2$O), 4.48 (s, 2H, CH$_2$Ph), 4.52 (s, 2H, OCH$_2$O), 4.57 (dd, J = 7.8, 5.1 Hz, 1H, CHPh), 7.23–7.37 (m, 10H, 10 × PhH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 26.3, 34.6, 55.6, 70.1, 72.9, 77.8, 94.0, 126.9, 127.5, 127.6, 127.6, 128.3, 138.5, 142.0. Anal. Calcd. for C$_{19}$H$_{24}$O$_3$: C, 75.97; H, 8.05. Found: C, 75.84; H, 8.26%.

### 3.3.5. 1-Methoxymethoxy-1-phenyl-2-methylpropan-2-ol (4af)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 8:2:0.5); R$_f$: 0.40. IR (neat): 3463 cm$^{-1}$ (OH). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.12 (s, 3H, CH$_3$), 1.23 (s, 3H, CH$_3$), 3.40 (s, 3H, CH$_3$O), 4.45 (s, 1H, PhCH), 4.55 (d, J = 6.6 Hz, 1H, OCHO), 4.60 (d, J = 6.6 Hz, 1H, OCHO), 7.28–7.35 (m, 5H, 5 × PhH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 24.8, 26.3, 56.0, 7.1.6, 84.7, 94.7, 127.9, 127.9, 128.5, 137.9. Anal. Calcd. for C$_{12}$H$_{18}$O$_3$: C, 68.54; H, 8.63. Found: C, 68.38; H, 8.81%.

### 3.3.6. 1-(Methoxymethoxyphenyl)methylcyclohexanol (4ag)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 8:2:0.5; R$_f$: 0.56). IR (neat): 3481 cm$^{-1}$ (OH). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.10–2.05 (m, 11H, 5 × CH$_2$ + OH), 3.39 (s, 3H, CH$_3$O), 4.43 (s, 1H, PhCH), 4.52 (d, J = 6.6 Hz, 1H, OCHO), 4.56 (d, J = 6.6 Hz, 1H, OCHO), 7.30–7.35 (m, 5H, 5 × PhH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 21.3, 21.5, 25.8, 33.0, 34.5, 55.9, 73.1, 84.0, 94.4, 127.8, 127.8, 128.8, 137.5. Anal. Calcd. for C$_{15}$H$_{22}$O$_3$: C, 71.97; H, 8.86. Found: C, 72.18; H, 8.64%.

### 3.3.7. 2-Trimethylsilyl-4-methoxymethoxymethylphenyl ester of N,N-diethylcarbamic acid (5ba)

Oil, purified by flash chromatography (CH$_2$Cl$_2$/EtOAc/Et$_3$N = 7:3:1; R$_f$: 0.56). IR (neat): 1718 cm$^{-1}$ (CO). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.28 (s, 9H, 3 × CH$_3$Si), 1.16–1.28 (m, 6H, 2 × CH$_3$), 3.35–3.52 (m, 4H, 2 × CH$_2$N), 3.42 (s, 3H, OCH$_3$), 4.57 (s, 2H, ArCH$_2$), 4.71 (s, 2H, OCH$_2$O), 7.01–7.05 (m, 1H, 1 × ArH), 7.24–7.38 (m, 1H, 1 × ArH), 7.40–7.42 (m, 1H, 1 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = −1.0, 13.2, 14.1, 41.5, 41.8, 55.3, 68.7, 95.5, 122.2, 130.1, 131.5, 133.9, 134.4, 154.3, 155.9. Anal. Calcd. for C$_{17}$H$_{29}$NO$_4$Si: C, 60.14; H, 8.61; N, 4.13. Found: C, 59.87; H, 8.79; N, 4.02%.

### 3.3.8. (4-Fluorophenyl)methoxymethoxymethyltrimethylsilane (4ca)

Oil, purified by flash chromatography (petroleum ether/EtOAc = 9:1; R$_f$: 0.54). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = −0.01 (s, 9H, 3 × CH$_3$Si), 3.36 (s, 3H, CH$_3$O), 4.44 (s, 1H, ArCH), 4.50 (d, J = 6.3 Hz, 1H, OCHO), 4.53 (d, J = 6.3 Hz, 1H, OCHO), 6.92–7.01 (m, 2H, 2 × ArH), 7.06–7.13 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = −4.0, 55.5, 72.1, 94.9, 114.9 (d, J = 21 Hz), 127.5 (d, J = 8 Hz), 136.4 (d, J = 3 Hz), 161.3 (d, J = 242 Hz). Anal. Calcd. for C$_{12}$H$_{19}$FO$_2$Si: C, 59.47; H, 7.90. Found: C, 59.24; H, 8.12%.

### 3.3.9. 2-Trimethylsilyl-4-methoxymethoxymethylfluorobenzene (5ca)

Oil, purified by flash chromatography (petroleum ether/EtOAc = 9:1; R$_f$: 0.43). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.31 (d, J = 0.6 Hz, 9H, CH$_3$Si), 3.42 (s, 3H, CH$_3$O), 4.55 (s, 2H, ArCH$_2$), 4.70 (s, 2H, OCH$_2$O), 6.93–7.01 (m, 1H, ArH), 7.30–7.38 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = −1.12, 55.3, 68.8, 95.7, 114.6 (d, J = 26 Hz), 126.2 (d, J = 31 Hz), 131.1 (d, J = 9, Hz), 133.1 (d, J = 3 Hz), 134.8 (d, J = 10 Hz), 167.0 (d, J = 239 Hz). Anal. Calcd. for C$_{12}$H$_{19}$FO$_2$Si: C, 59.47; H, 7.90. Found: C, 59.21; H, 8.18%.

### 3.3.10. 1-(4-Fluorophenyl)-2-hydroxy-3,3-dimethylbutyl methoxymethyl ether (4cb)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 8:2:0.5; R$_f$: 0.24). IR (neat): 3484 cm$^{-1}$ (OH). Major Diastereoisomer: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.91 (s, 9H, 3 × CH$_3$C), 2.86 (1H, d, J = 6.0 Hz, OH), 3.36 (s, 3H, OCH$_3$), 3.36 (1H, d, J = 6.0, 4.5 Hz, CHOH), 4.49 (1H, d, J = 6.6 Hz, OCHO), 4.54 (1H, d, J = 6.6 Hz, OCHO), 4.67 (1H, d, J = 4.5 Hz, ArCH), 6.99–7.08 (m, 2H, 2 × ArH), 7.30–7.36 (m, 2, 2 × ArH); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 26.5, 34.8, 56.4, 76.5, 81.8, 94.0, 115.3 (d, J = 21 Hz), 129.4 (d, J = 8 Hz), 136.3 (d, J = 3 Hz), 162.4 (d, J = 245 Hz). Minor diastereoisomer: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.87 (s, 9H, ×CH$_3$C), 1.9 (1H, d, J = 3.6 Hz, OH), 3.34 (s, 3H, OCH$_3$), 3.65 (1H, dd, J = 4.5, 3.6 Hz, CHOH), 4.44 (1H, d, J = 6.6 Hz, OCHO), 4.49 (1H, d, J = 6.6 Hz, OCHO), 4.63 (1H, d, J = 4.5 Hz, ArCH), 6.99–7.08 (m, 2H, 2 × ArH), 7.38–7.44 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 26.5, 34.3, 55.9, 77.7, 81.1, 93.7, 115.1 (d, J = 21 Hz), 130.8 (d, J = 8 Hz), 134.5 (d, J = 3 Hz), 162.4 (d, J = 245 Hz). Anal. Calcd. for C$_{14}$H$_{21}$FO$_3$: C, 65.60; H, 8.26. Found: C, 65.76; H, 8.01%.

### 3.3.11. 1-(2-Fluoro-5-methoxymethoxymethyl)phenyl-2,2-dimethylpropan-1-ol (5cb)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N, 8:2:0.5; R$_f$: 0.37). IR (neat): 3465 cm$^{-1}$ (OH). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.95 (d, 9H, J = 1.2 Hz, 3 × CH$_3$Si), 3.41 (s, 3H, CH$_3$O), 4.56 (s, 2H, ArCH$_2$), 4.70 (s, 2H, OCH$_2$O), 4.80 (d, 1H, J = 4.2 Hz, CHO), 6.90 (dd, J = 8.4, 1.8 Hz, 1H, ArH), 7.21–7.28 (m, 1H, ArH), 7.43 (dd, J = 4.8, 2.1 Hz, 1H, ArH). $^{13}$C NMR (CDCl$_3$, $\delta$/ppm): 25.5, 36.2, 55.3, 68.7, 74.5, 95.6, 114.8 (d, J = 23 Hz), 128.3 (d, J = 9 Hz), 128.8 (d, J = 5 Hz), 129.3 (d, J = 14 Hz), 133.1 (d, J = 3 Hz), 159.5 (d, J = 244 Hz). Anal. Calcd. for C$_{14}$H$_{21}$FO$_3$: C, 65.60; H, 8.26. Found: C, 65.48; H, 8.39%.

### 3.3.12. (3-Fluorophenyl)methoxymethoxymethyltrimethylsilane (4da)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 9.7:0.3:0.2; R$_f$: 0.49). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.02 (s, 9H, 3 × CH$_3$Si), 3.38 (s, 3H, CH$_3$O), 4.48 (s, 1H, CHAr), 4.53 (d, J = 6.3 Hz, 1H, OCHO), 4.56 (d, J = 6.3 Hz, 1H, OCHO), 6.81–6.92 (m, 3H, 3 × ArH), 7.18–7.27 (m, 1H, ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = −4.0, 55.5, 72.5, 95.2, 112.5 (d, J = 3 Hz), 112.8 (d, J = 3 Hz), 121.6 (d, J = 3 Hz), 129.4 (d, J = 8 Hz) 144.0 (d, J = 7 Hz), 163.0 (d, J = 243 Hz). Anal. Calcd. for C$_{12}$H$_{19}$FO$_2$Si: C, 59.47; H, 7.90. Found: C, 59.38; H, 7.96%.

### 3.3.13. (2-Trimethylsilyl-3-methoxymethoxymethylfluorobenzene (5da)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 9.7:0.3:0.2; R$_f$: 0.39). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.39 (d, J = 2.1 Hz, 9H, 3 × CH$_3$Si), 3.40 (s, 3H, CH$_3$O), 4.63 (s, 2H, ArCH$_2$), 4.68 (s, 2H, OCH$_2$O), 6.89–6.95 (m, 1H, ArH), 7.22 (dd, 1H, J = 7.5, 0.3 Hz, ArH), 7.32 (td, 1H, J = 7.8, 6.0 Hz, ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 1.4 (d, J = 4 Hz), 55.5, 68.7 (d, J = 2 Hz), 95.5, 114.4 (d, J = 28 Hz), 124.7 (d, J = 2 Hz), 124.8 (d, J = 27 Hz), 130.8 (d, J = 10 Hz), 145.0 (d, J = 10 Hz), 169.2 (d, J = 239 Hz). Anal. Calcd. for C$_{12}$H$_{19}$FO$_2$Si: C, 59.47; H, 7.90. Found: C, 59.63; H, 7.95%.

### 3.3.14. (4-Methoxyphenyl)methoxymethoxymethyltrimethylsilane (4ea)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 9:1:0.5; R$_f$: 0.42). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.00 (s, 9H, 3 × CH$_3$Si), 3.37 (s, 3H, CH$_3$O), 3.79 (s, 3H, CH$_3$OAr), 4.41 (s, 1H, ArCH), 4.50 (d, 1H, J = 6.6 Hz, OCHO), 4.55 (d, 1H, J = 6.6 Hz, OCHO), 6.81–6.87 (m, 2H, 2 × ArH), 7.04–7.10 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = −3.9, 55.1, 55.3, 72.1, 94.6, 113.5, 127.4, 132.6, 157.9. Anal. Calcd. for C$_{13}$H$_{22}$O$_3$Si: C, 61.38; H, 8.72. Found: C, 61.13; H, 8.92%.

### 3.3.15. 2-Trimethylsilyl-4-methoxymethoxymethylanisole (5ea)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 9:1:0.5; R$_f$: 0.28). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.26 (s, 9H, 3 × CH$_3$Si), 3.42 (s, 3H, CH$_3$O), 3.80 (s, 3H, CH$_3$OAr), 4.52 (s, 2H, ArCH$_2$), 4.70 (s, 2H, OCH$_2$O), 6.70–6.85 (m, 1 H, ArH), 7.30–7.34 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = −1.0, 55.1, 55.3, 69.1, 95.5, 109.4, 128.1, 129.3, 130.9, 135.2, 164.1. Anal. Calcd. for C$_{13}$H$_{22}$O$_3$Si: C, 61.38; H, 8.72. Found: C, 61.17; H, 8.89%.

### 3.3.16. (4-Isoproxyphenyl)methoxymethoxymethyltrimethylsilane (4fa)

Oil, purified by flash chromatography (CH$_2$Cl$_2$/EtOAc/Et$_3$N = 7:3:1; R$_f$: 0.56). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.00 (s, 9H, 3 × CH$_3$Si), 1.32 (d, 6H, J = 6.0 Hz, 2 × CH$_3$), 3.37 (s, 3H, CH$_3$O), 4.39 (s, 2H, OCH$_2$O), 4.49 (d, J = 6.3, Hz, 1H, OCHO), 4.51 (hept, J = 6.0 Hz, 1H, ArCH), 4.56 (d, J = 6.3, Hz, 1H, OCHO), 6.79–6.83 (m, 2H, 2 × ArH), 7.01–7.07 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = −3.9, 22.1, 55.4, 69.8, 72.2, 94.6, 115.5, 127.4, 132.4,

156.2. Anal. Calcd. for $C_{15}H_{26}O_3Si$: C, 63.78; H, 9.28. Found: C, 63.68; H, 9.41%.

### 3.3.17. (3-Methoxyphenyl)methoxymethoxymethyltrimethylsilane (4ga)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 9:1:0.5; R$_f$: 0.38). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.01 (s, 9H, 3 × CH$_3$Si), 3.38 (s, 3H, CH$_3$), 3.79 (s, 3H, CH$_3$OAr), 4.46 (s, 1H, ArCH), 4.53 (d, $J$ = 6.3, Hz, 1H, OCHO), 4.58 (d, $J$ = 6.3, Hz, 1H, OCHO), 6.68–6.75 (m, 3H, 3 × ArH), 7.15–7.22 (m, 1H, ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = −3.9, 55.0, 55.5, 72.8, 95.1, 111.2, 111.5, 118.7, 129.0, 142.6, 159.5. Anal. Calcd. for $C_{13}H_{22}O_3Si$: C, 61.38; H, 8.72. Found: C, 61.25; H, 8.95%.

### 3.3.18. (4-Chlorophenyl)methoxymethoxymethyltrimethylsilane (4hb)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 9:1:0.5; R$_f$: 0.60). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.00 (s, 9H, 3 × CH$_3$Si), 3.36 (s, 3H, CH$_3$O), 4.45 (s, 1H, ArCH), 4.52 (s, 2H, OCH$_2$O), 7.05–7.10 (m, 2H, 2 × ArH), 7.23–7.28 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = −4.0, 55.5, 72.2, 95.0, 127.3, 128.2, 131.4, 139.5. Anal. Calcd. for $C_{12}H_{19}ClO_2Si$: C, 55.69; H, 7.40. Found: C, 55.42; H, 7.58%.

### 3.3.19. (4-Methylphenyl)methoxymethoxymethyltrimethylsilane (4ib)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 9.5:0.5:0.5; R$_f$: 0.60). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.00 (s, 9H, 3 × CH$_3$Si), 2.32 (s, 3H, CH$_3$), 3.38 (s, 3H, CH$_3$O), 4.44 (s, 1H, ArCH), 4.51 (d, $J$ = 6.3, Hz, 1H, OCHO), 4.56 (d, $J$ = 6.3, Hz, 1H, OCHO), 7.01–7.12 (m, 4H, 4 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = −3.9, 21.0, 55.3, 72.6, 94.8, 126.1, 128.8, 135.3, 137.6. Anal. Calcd. for $C_{13}H_{22}O_2Si$: C, 65.50; H, 9.30. Found: C, 65.36; H, 9.49%.

### 3.3.20. 1,1-Diphenyl-1-methoxymethoxypentane (4jb)

Oil, purified by flash chromatography (hexane/EtOAc, 9:1; R$_f$: 0.61). Bp 120/1 (°C/Torr). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.84 (t, $J$ = 7.2 Hz, 3H, CH$_3$), 1.04–1.20 (m, 2H, CH$_2$), 1.21–1.30 (m, 2H, CH$_2$), 2.29–2.35 (m, 2H, CH$_2$), 3.42 (s, 3H, CH$_3$O), 4.52 (s, 2H, OCH$_2$O), 7.17–7.23 (m, 2H, 2 × PhH), 7.24–7.31 (m, 4H, 4 × PhH), 7.34–7.38 (m, 4H, 4 × PhH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 14.1, 23.0, 25.5, 37.2, 56.3, 83.1, 92.0, 126.7, 127.0, 127.8, 145.8. Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.11; H, 8.69%.

### 3.3.21. 2-Trimethylsilyl-4-(1-methoxymethoxy)ethylanisole (5lb)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 8:2:0.5; R$_f$: 0.59). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.26 (s, 9H, 3 × CH$_3$Si), 1.47 (d, $J$ = 6.6 Hz, 3H, CH$_3$Ar), 3.38 (s, 3H, CH$_3$), 3.80 (s, 3H, CH$_3$OAr), 4.55 (s, 1H, OCH$_2$O), 4.71 (q, $J$ = 6.6 Hz, 1H, CH), 6.78–6.82 (m, 1H, ArH), 7.27–7.33 (m, 2H, 2 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = −1.0, 23.5, 55.1, 55.2, 73.4, 93.8, 109.3, 127.9, 128.8, 133.2, 134.5, 163.9. Anal. Calcd. for $C_{14}H_{24}O_3Si$: C 62.64; H, 9.01. Found: C, 62.47; H, 9.14%.

### 3.4. Acidic hydrolysis of methoxymethyl ethers; general procedures

Acidic hydrolysis of acetals was performed according to a general procedure described in Ref. [25]. Reaction products 8 and 9 were purified and characterized as follows:

### 3.4.1. 4-Benzyloxy-1-phenylbutan-1-ol (8)

Oil, purified by flash chromatography (petroleum ether/EtOAc = 8:2; R$_f$: 0.43). Bp 175/1 (°C/Torr). IR (neat): 3353 cm$^{-1}$ (OH). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.60–1.90 (m, 4H, 2 × CH$_2$), 2.47 (1H, br s, OH), 3.51 (t, $J$ = 6.3 Hz, 2H, CH$_2$), 4.51 (s, 2H, CH$_2$Ph), 4.70 (t, $J$ = 6.3 Hz, 1H, CHPh), 7.24–7.35 (m, 10H, 10 × ArH). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 26.2, 36.5, 70.3, 73.0, 74.1, 125.8,

127.3, 127.6, 127.7, 128.3, 128.4, 138.1, 144.8. Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.49; H, 8.04%.

### 3.4.2. (Hydroxyphenylmethyl) cyclohexanol (9)

Oil, purified by flash chromatography (petroleum ether/EtOAc/Et$_3$N = 8:2:0.5; R$_f$: 0.26). IR (nujol): 3346 cm$^{-1}$ (OH). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.19–1.64 (m, 11H, 5 × CH$_2$+OH), 2.48 (d, 1H, $J$ = 4.2 Hz, OH), 4.48 (d, 1H, $J$ = 4.2 Hz, CH), 7.30–7.38 (m, 5H, 5 × PhH); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 21.3, 21.5, 25.7, 32.1, 34.2, 73.7, 80.7, 127.6, 127.9, 140.4. Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.78; H, 8.98%.

### 3.4.3. Synthesis of 2-phenyltetrahydro-2H-pyran (7)

Acetal 4ad (1.10 g, 4.5 mmol), hydrolyzed according to the general procedure described above, afforded 0.8 g (4.0 mmol, 89%) of crude 1-phenyl-5-chloropentan-1-ol, 6. The crude material was dissolved in dry THF (5 mL) and dropwise added to a suspension of NaH (0.12 g, 5.04 mmol) in dry THF (5 mL), chilled at 0 °C. The reaction mixture was stirred overnight at r.t., then quenched by slow dropwise addition of H$_2$O (10 mL). The resulting mixture was extracted with Et$_2$O (3 × 10 mL), washed with brine (10 mL), and the organic phase dried (Na$_2$SO$_4$) and evaporated. The reaction product was purified by flash chromatography (petroleum ether/EtOAc = 9:1, R$_f$: 0.61); yield: 0.43 g (2.7 mmol, 59% from 4ad); colorless oil; compound 7 was characterized by comparison with literature data [26].

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