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[1,2]-Wittig rearrangement from chloromethyl ethers

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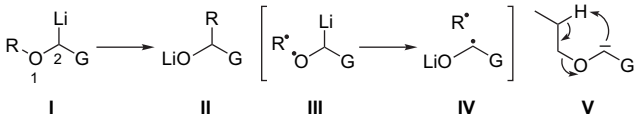
This paper is dedicated in the memory of Professor Pierre Potier

Abstract—The reaction of different chloromethyl ethers **1** with an excess of lithium powder and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (2.5 mol %) in THF at 0 °C leads to the corresponding α-lithiomethyl ether intermediates, through a chlorine–lithium exchange, which spontaneously undergo a clean [1,2]-Wittig rearrangement affording the expected homobenzylic alcohols **2**. This is the first version of this rearrangement starting from easily available chloromethyl ethers.

1. Introduction

The [1,2]-Wittig rearrangement, originally called 'cationotropic isomerization',[1] is the transformation of an α-lithiated ether **I** into a lithium alkoxide **II** by migration of an R group from the oxygen to the α-carbon atom, which initially bore the lithium atom (Scheme 1).[2] Among the different possible mechanistic proposals for this rearrangement, nowadays the most commonly accepted one involves an intramolecular radical process through the species **III** and **IV** (Scheme 1).[3]



I II III IV V

Scheme 1.

Apart from some problems concerning a possible β-elimination from the α-carbanion (see **V**)[4] or stereochemical connotations of the process (mainly retention at the migrating carbon atom and inversion at the carbon terminus),[2] two limitations are associated with the [1,2]-Wittig rearrangement: (a) probably the most simple way to access intermediates of type **I** would be the corresponding deprotonation using a lithium base (LDA or an alkyllithium reagent), but this method only works when the group G can stabilise the negative charge at its α-position (such as a vinyl, phenyl or alkynyl group)[5] and (b) the difficulty of carrying out the migration of the group R when G=H (for lithiomethyl ethers).[6]

In order to avoid the above mentioned problems other alternatives to the deprotonation methodology have been reported including: (a) a tin–lithium transmetallation using *n*-butyllithium as the lithiation agent,[7] (b) a sulfur–lithium exchange using lithium-4,4′-di-*tert*-butylbiphenyl (DTBB) in the lithiation step[8] and (c) selenium–lithium exchange with lithium-naphthalene.[9] However, to our best knowledge the corresponding chlorine–lithium exchange has never been described to perform the [1,2]-Wittig rearrangement.

In the course of our investigations using an arene-catalysed lithiation[10] as a procedure to carry out lithiation reactions under very mild reaction conditions,[11] we recently studied the [2,3]-Wittig rearrangement generating the corresponding lithium intermediate by a chlorine–lithium exchange.[12] In only one case, for benzyl chloromethyl ether, the same methodology afforded 2-phenylethanol as a consequence of a [1,2]-Wittig rearrangement. This result prompted us to study the scope of this reaction using different arylmethyl chloromethyl ethers and the mentioned arene-catalysed lithiation methodology.

2. Results and discussion

Starting materials **1** were prepared according to the procedures described in the literature. Although for compounds **1a–f**,**m**,**n** the reaction of the corresponding benzylic alcohol

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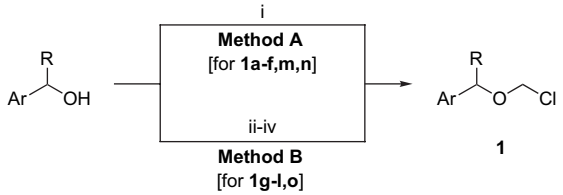
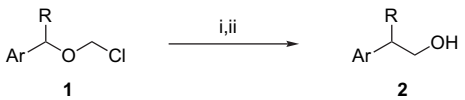
with paraformaldehyde and chlorotrimethylsilane was efficient,[13] for starting chloroethers **2g–l,o** it was necessary to use the reaction of the alkoxides derived from the same alcohols with chloromethyl methyl thioether followed by chlorination with sulfuryl chloride[14] in order to get good results (Scheme 2).



Scheme 2. Reagents and conditions: (i) paraformaldehyde, Me_3SiCl, CCl_4, rt; (ii) NaI, NaH, THF, rt; (iii) $ClCH_2SMe$, THF, 0 °C; (iv) $SOCl_2$, CH_2Cl_2, −78 °C or rt.

The reaction of different arylmethyl chloromethyl ethers **1** with an excess of lithium powder (1:7 molar ratio; theoretical 1:2) and a catalytic amount of DTBB (1:0.05 molar ratio; 2.5 mol %) in THF at 0 °C for 1 h led, after hydrolysis with water, to the expected homobenzylic alcohols resulting from a [1,2]-Wittig rearrangement (Scheme 3 and Table 1). The reaction worked nicely for chloromethyl ethers without (Table 1, entries 1–12) or with substituents (Table 1, entries 13–15) at the benzylic position. In the case of methoxy substituted starting materials **1h–j**, the reaction at 0 °C (standard conditions) led mainly to a benzylic cleavage[15] giving, after hydrolysis, the corresponding methylanisole as the major reaction product. On the other hand, at lower temperatures (−78 °C) the chlorine–lithium exchange took place cleanly, but the expected rearrangement did not occur and the only reaction product isolated after hydrolysis was the corresponding methyl (methoxy)benzyl ether resulting from a chlorine–hydrogen exchange (the undesirable 'reduced' product). Modest but reproducible results were obtained working at −40 °C (Table 1, entries 8–10 and footnote d), the electronic effects of the methoxy substituent having been invoked in order to explain the behaviour observed for compounds **1h–j**. For compounds **1g** and **1l** it is also necessary to work at −40 °C in order to avoid the formation of the corresponding methylarene (benzylic cleavage[15]) at 0 °C or the dimer bis(arylmethyl) (coupling of the corresponding benzylic radicals), at −78 °C, as the major products (Table 1, entries 7 and 12, respectively). Also here the electronic effect of the extra aryl group should be guilty of the obtained results. A special mention merits the results obtained using aryl chloromethyl ethers **1** bearing electron withdrawing groups. Thus, when the reaction shown in Scheme 1 was carried out using *o*-, *m*- or *p*-(trifluoromethyl)phenylmethyl chloroethers, the undesirable benzylic cleavage was the only process observed, so the corresponding trifluoromethylbenzyl alcohols were the only reaction products detected. In addition, the use of fluorophenyl derivatives as starting materials was also problematic: as an example, 4-fluorobenzyl chloromethyl ether (**1k**) gave only 21% yield of the expected alcohol **2k**, making it necessary to work in this case at −78 °C (Table 1, entry 11 and footnote e). Finally, we studied the possibility of scaling up the reaction shown in Scheme 3, mainly with the purpose of investigating the reduction of the amount of lithium used in the process. Thus, starting from 5 mmol of the chloroether **1a**, and using the same protocol but using only 11 mmol of lithium powder (1:2.2 molar ratio; theoretical: 1:2 molar ratio) we obtained reproducible yields in the range of 65–70%, indicating that at higher scale it is not necessary to use a large excess of lithium powder.[16]



Scheme 3. Reagents and conditions: (i) Li, DTBB (2.5 mol %), THF, −78, −40 or 0 °C; (ii) H_2O, rt.

3. Conclusion

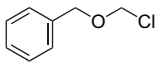
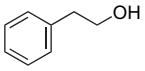
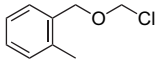
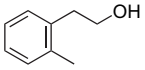
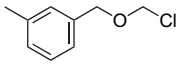
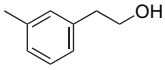
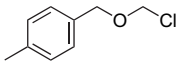
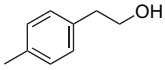
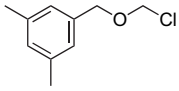
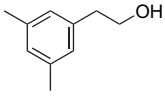
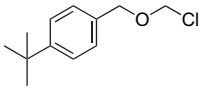
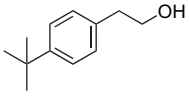
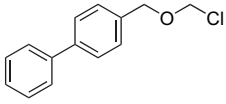
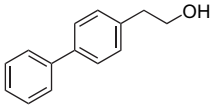
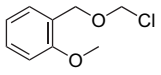
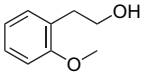
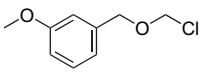
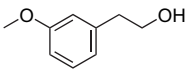
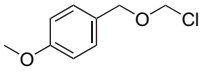
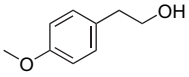
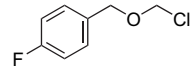
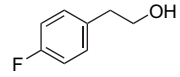
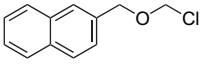
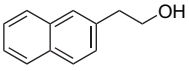
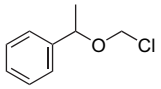
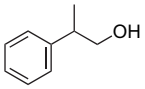
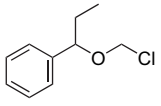
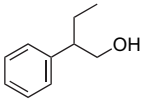
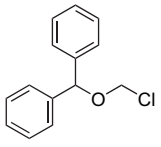
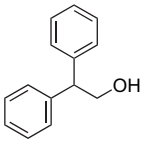
In conclusion, we have described in this paper for the first time the [1,2]-Wittig rearrangement of representative benzylic chloromethyl ethers by a DTBB-catalysed chlorine–lithium exchange. This new process is of interest not only due to the easy access of the starting materials, but also for enabling the migration of the benzylic moiety to a methyl group, a process that can be problematic using other methodologies.

4. Experimental

4.1. General

For general information see Ref. 17. All lithiation reactions were carried out under argon atmosphere in oven-dried glassware. All commercially available reagents (Acros, Aldrich, Fluka) were used without further purification except benzyl chloromethyl ether (**1a**) (Aldrich, purity 60%) that was purified by distillation (Kugelrohr, ca. 70 °C) before use. Commercially available anhydrous THF (99.9%, water content≤0.006%, Acros) was used as solvent in all the lithiation reactions. IR spectra were measured with a Nicolet Impact 400 D-FT spectrometer. NMR spectra were recorded in the Technical Services of the University of Alicante with a Bruker AC-300 or AC-400 using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are given in parts per million and coupling constants (J) are given in hertz. ^{13}C NMR assignments were made on the basis of DEPT experiments. LRMS were measured with Shimadzu GC/HS QP-5000 and Hewlett–Packard EM/CG-5973A spectrometers, and HRMS were measured in the Technical Services of the University of Alicante with a Finingan MAT95 S spectrometer, fragment ions in m/z with relative intensities (%) in parentheses. The purity of volatile products and the chromatographic analyses (GLC) were determined with a Hewlett–Packard HP-4890 instrument equipped with a flame ionisation detector and a 30 m capillary column (0.32 mm diameter, 0.25 μm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{injector}$=275 °C, $T_{detector}$=300 °C, T_{column}= 60 °C (3 min) and 60–270 °C (15 °C/min), P=40 Kpa; retention times (t_R) are given under these conditions. Thin layer chromatography (TLC) was carried out on Merck plastic sheets coated with silica gel 60 F_{254}. Lithium powder, which can be prepared from commercially available lithium granules (99%, high sodium content, Aldrich) as it was already reported by us,[18] was supplied by MEDALCHEMY.

Table 1. Preparation of homobenzylic alcohols **2**

Entry	Starting material		Product[a]		
	Structure	No.	Structure	No.	Yield (%)[b]
1		**1a**		**2a**	70[c]
2		**1b**		**2b**	60
3		**1c**		**2c**	72
4		**1d**		**2d**	84
5		**1e**		**2e**	69
6		**1f**		**2f**	84
7		**1g**		**2g**	42[d]
8		**1h**		**2h**	32[d]
9		**1i**		**2i**	52[d]
10		**1j**		**2j**	22[d]
11		**1k**		**2k**	21[e]
12		**1l**		**2l**	57[d]
13		**1m**		**2m**	70
14		**1n**		**2n**	81
15		**1o**		**2o**	86

[a] All compounds **2** were >95% pure (GLC and/or 300 or 400 MHz ^{1}H NMR).
[b] Isolated yield after distillation in vacuo (ca. 0.01 Torr; for **2a–f**,**h–j**,**m**,**n**) or column chromatography (silica gel, hexane/ethyl acetate; for **2g**,**k**,**l**,**o**) based on the starting material **1**.
[c] See Ref. 12.
[d] Reaction performed at −40 °C.
[e] Reaction performed at −78 °C.

4.2. Preparation of chloromethyl ethers 1b–f,m,n (Method A). General procedure[13]

A solution of the corresponding alcohol (3 mmol), paraformaldehyde (120 mg, 3.75 mmol) and chlorotrimethylsilane (380 μL, 3 mmol) in dry carbon tetrachloride (9 mL) was stirred under argon for 2.5 h at ambient temperature. The solution was filtered and the solvent was evaporated (15 Torr). The residue was distilled under reduced pressure (ca. 0.01 Torr) in a Kugelrohr apparatus to provide the pure chloromethyl ethers.[19] Yields, physical, analytical spectroscopic data, as well as literature references for known compounds, follow.

4.2.1. 1-(Chloromethoxymethyl)-2-methylbenzene (1b).[14] Yield: 55%. Colourless liquid; t_R=10.1 min; ν (film) 3067, 3023 (=CH), 1115 (C–O) cm^{-1}; δ_H (300 MHz) 2.35 (3H, s, CH_3), 4.74 (2H, s, ArCH_2), 5.51 (2H, s, CH_2Cl), 7.18–7.32 (4H, m, 4×ArH); δ_C (75 MHz) 18.8 (CH_3), 69.8 (ArCH_2), 81.8 (CH_2Cl), 125.9, 128.7, 129.5, 130.4 (ArCH), 133.5, 137.3 (ArC); *m/z* 172 (M^++2, 4%), 170 (M^+, 12%), 106 (10), 105 (100), 104 (50), 103 (15), 91 (12), 79 (11), 77 (17).

4.2.2. 1-(Chloromethoxymethyl)-3-methylbenzene (1c).[20] Yield: 50%. Colourless liquid; t_R=10.2 min; ν (film) 3025 (=CH), 1124 (C–O) cm^{-1}; δ_H (400 MHz) 2.34 (3H, s, CH_3), 4.68 (2H, s, ArCH_2), 5.49 (2H, s, CH_2Cl), 7.12–7.15 (3H, m, 3×ArH), 7.22–7.26 (1H, m, ArH); δ_C (100 MHz) 21.2 (CH_3), 71.3 (ArCH_2), 81.7 (CH_2Cl), 125.4, 128.4, 129.1 (ArCH), 135.4, 138.2 (ArC); *m/z* 172 (M^++2, 5%), 170 (M^+, 15%), 140 (10), 106 (16), 105 (100), 103 (10), 91 (11), 77 (14).

4.2.3. 1-(Chloromethoxymethyl)-4-methylbenzene (1d).[20] Yield: 51%. Colourless liquid; t_R=10.1 min; ν (film) 3024 (=CH), 1120 (C–O) cm^{-1}; δ_H (300 MHz) 2.35 (3H, s, CH_3), 4.70 (2H, s, ArCH_2), 5.51 (2H, s, CH_2Cl), 7.18 (2H, d, *J*=7.7, 2×ArH), 7.25 (2H, d, *J*=7.7, 2×ArH); δ_C (75 MHz) 21.2 (CH_3), 71.1 (ArCH_2), 81.6 (CH_2Cl), 128.6, 129.3 (ArCH), 132.4, 138.2 (ArC); *m/z* 172 (M^++2, 6%), 170 (M^+, 18%), 106 (11), 105 (100), 77 (11); HRMS calcd for $C_9H_{11}OCl$ 170.0498, found 170.0504.

4.2.4. 1-(Chloromethoxymethyl)-3,5-dimethylbenzene (1e).[22] Yield: 49%. Colourless liquid; t_R=11.0 min; ν (film) 3017 (=CH), 1121 (C–O) cm^{-1}; δ_H (300 MHz) 2.32 (6H, s, 2×CH_3), 4.67 (2H, s, ArCH_2), 5.52 (2H, s, CH_2Cl), 6.97 (3H, br s, 3×ArH); δ_C (75 MHz) 21.1 (CH_3), 71.3 (ArCH_2), 81.6 (CH_2Cl), 126.2, 129.9 (ArCH), 135.3, 138.1 (ArC); *m/z* 186 (M^++2, 5%), 184 (M^+, 16%), 120 (21), 119 (100), 105 (11), 91 (15); HRMS calcd for $C_{10}H_{13}OCl$ 184.0655, found 184.0674.

4.2.5. 4-*tert*-Butyl-1-(chloromethoxymethyl)benzene (1f). Yield: 42%. Colourless liquid; t_R=12.3 min; ν (film) 3058, 3028 (=CH), 1120 (C–O) cm^{-1}; δ_H (300 MHz) 1.32 (9H, s, 3×CH_3), 4.72 (2H, s, ArCH_2), 5.51 (2H, s, CH_2Cl), 7.30 (2H, d, *J*=8.1, 2×ArH), 7.40 (2H, d, *J*=8.1, 2×ArH); δ_C (75 MHz) 31.3 (CH_3), 34.6 [$C(CH_3)_3$], 71.1 (ArCH_2), 81.7 (CH_2Cl), 125.5, 128.3 (ArCH), 132.4, 151.5 (ArC); *m/z* 214 (M^++2, 6%), 212 (M^+, 18%), 199 (34), 198 (13), 197 (100), 147 (29), 132 (13), 131 (24), 117 (16), 115 (10), 91 (14); HRMS calcd for $C_{12}H_{17}OCl$ 212.0968, found 212.0962.

4.2.6. (1-Chloromethoxyethyl)benzene (1m).[14] Yield: 51%. Colourless liquid; t_R=9.1 min; ν (film) 3064, 3031 (=CH), 1132 (C–O) cm^{-1}; δ_H (300 MHz) 1.51 (3H, d, *J*=6.5, CH_3), 4.93 (1H, q, *J*=6.5, CH), 5.17, 5.51 (2H, 2d, *J*=5.6, CH_2Cl), 7.29–7.34 (5H, m, 5×ArH); δ_C (75 MHz) 22.8 (CH_3), 76.1 (CH), 80.3 (CH_2Cl), 126.4, 126.8, 128.2, 128.6 (ArCH), 140.8 (ArC); *m/z* 172 (M^++2, 2%), 170 (M^+, 6%), 156 (11), 155 (35), 140 (15), 106 (10), 105 (100), 103 (14), 91 (23), 79 (11), 77 (20).

4.2.7. (1-Chloromethoxypropyl)benzene (1n). Yield: 47%. Colourless liquid; t_R=9.8 min; ν (film) 3063, 3030 (=CH), 1111 (C–O) cm^{-1}; δ_H (400 MHz) 0.90 (3H, t, *J*=7.4, CH_3), 1.74, 1.88 (2H, m, CH_2Me), 4.67 (1H, t, *J*=6.8, CH), 5.16, 5.54 (2H, 2d, *J*=5.5, CH_2Cl), 7.28–7.39 (5H, m, 5×ArH); δ_C (100 MHz) 10.1 (CH_3), 30.0 (*C*H_2Me), 80.5 (CH_2Cl), 81.7 (CH), 127.3, 128.2, 128.6 (ArCH), 139.7 (ArC); *m/z* 186 (M^++2, 2%), 184 (M^+, 6%), 157 (34), 155 (100), 119 (26), 91 (75), 77 (12); HRMS calcd for $C_{10}H_{13}OCl$ 184.0655, found 184.0639.

4.3. Preparation of chloromethyl ethers 1g–l,o (Method B). General procedure[14]

4.3.1. Preparation of the precursor thioacetals. The corresponding alcohol (3 mmol) was carefully added dropwise to a mixture of sodium iodide (450 mg, 3 mmol) and sodium hydride (144 mg, 0.6 mmol) in dry THF (3.3 mL) under argon at room temperature. When hydrogen evolution had ceased, the solution was cooled at 0 °C and chloromethyl methyl sulfide (3 mmol, 260 μL) was added dropwise over 10 min. The mixture was stirred at 0 °C for 2 h and then warmed to room temperature and stirred for 6 h. Water (8 mL) was carefully added dropwise to the solution and then ethyl acetate (2.5 mL) was added. The organic phase was separated and the aqueous layer was extracted with ethyl acetate (2×2.5 mL). Extracts were dried ($MgSO_4$) and the solvents were evaporated (15 Torr). The residue was filtered through silica gel, eluting with hexane/ethyl acetate, to give the corresponding *O*,*S*-acetal. Yields, physical, analytical spectroscopic data, as well as literature references for known compounds, follow.

4.3.1.1. 1-(Methylsulfanylmethoxymethyl)-4-phenylbenzene. Yield: 84%. Yellow oil; t_R=17.0 min; ν (film) 3055, 3028 (=CH), 1063 (C–O) cm^{-1}; δ_H (400 MHz) 2.21 (3H, s, CH_3), 4.66 (2H, s, CH_2S), 4.72 (2H, s, ArCH_2), 7.35 (1H, m, ArH), 7.44 (4H, m, 4×ArH), 7.59 (4H, m, 4×ArH); δ_C (100 MHz) 13.9 (CH_3), 69.1 (ArCH_2), 74.4 (CH_2S), 127.1, 127.2, 127.3, 128.6, 128.8 (ArCH), 136.5, 140.8 (ArC); *m/z* (M^+, 6%), 196 (38), 168 (16), 167 (100), 165 (25), 152 (14); HRMS calcd for $C_{15}H_{16}OS$ 244.0922, found 244.0909.

4.3.1.2. 1-Methoxy-2-(methylsulfanylmethoxymethyl)benzene. Yield: 77%. Yellow oil; t_R=12.8 min; ν (film) 1067 (C–O) cm^{-1}; δ_H (400 MHz) 2.18 (2H, s, SCH_3), 3.83 (2H, s, OCH_3), 4.66, 4.71 (2×2H, s, ArCH_2, CH_2S), 6.87–6.88 (1H, d, *J*=8.2, ArH), 6.94 (1H, t, *J*=7.5, ArH), 7.25–7.29 (1H, m, ArH), 7.38 (1H, d, *J*=7.5, ArH); δ_C (100 MHz) 13.7 (SCH_3), 55.3 (OCH_3), 64.5 (ArCH_2), 74.5 (CH_2S), 110.2, 120.3, 128.9, 129.5 (ArCH), 125.7, 157.4 (ArC); *m/z* 198 (M^+, 5%), 150 (33), 137 (15), 122 (10), 121 (100), 93

(10), 91 (72); HRMS: M^+, found 198.0726. $C_{10}H_{14}O_2S$ requires 198.0715.

4.3.1.3. 1-Methoxy-3-(methylsulfanylmethoxymethyl)-benzene. Yield: 78%. Yellow oil; t_R=13.0 min; ν (film) 1051 (C–O) cm^{-1}; δ_H (400 MHz) 2.18 (2H, s, SCH_3), 3.80 (2H, s, OCH_3), 4.59, 4.68 (2×2H, 2s, ArCH_2, CH_2S), 6.81–6.85 (1H, m, ArH), 6.90–6.94 (2H, m, 2×ArH), 7.24–7.28 (1H, m, ArH); δ_C (100 MHz) 13.9 (SCH_3), 55.1 (OCH_3), 69.2 (ArCH_2), 74.3 (CH_2S), 113.3, 120.3, 129.4 (ArCH), 139.0, 159.7 (ArC); *m/z* 198 (M^+, 9%), 150 (20), 122 (23), 121 (100), 91 (20), 78 (10); HRMS: M^+, found 198.0720. $C_{10}H_{14}O_2S$ requires 198.0715.

4.3.1.4. 1-Methoxy-4-(methylsulfanylmethoxymethyl)-benzene.[14] Yield: 80%. Yellow oil; t_R=13.0 min; ν (film) 3033 (=CH), 1063 (C–O) cm^{-1}; δ_H (300 MHz) 2.17 (3H, s, SCH_3), 3.80 (3H, s, OCH_3), 4.55 (2H, s, CH_2S), 4.65 (2H, s, ArCH_2), 6.88 (2H, d, J=8.4, 2×ArH), 7.28 (2H, d, J=8.4, 2×ArH); δ_C (75 MHz) 13.8 (SCH_3), 55.2 (OCH_3), 68.9 (ArCH_2), 73.9 (CH_2S), 113.8, 129.7 (ArCH), 159.2 (ArC); *m/z* 198 (M^+, 5%), 150 (28), 122 (10), 121 (100).

4.3.1.5. 1-Fluoro-4-(methylsulfanylmethoxymethyl)-benzene. Yield: 79%. Yellow liquid; t_R=10.6 min; ν (film) 3043 (=CH), 1063 (C–O) cm^{-1}; δ_H (300 MHz) 2.18 (CH_3), 4.57, 4.67 (2×2H, 2s, ArCH_2, CH_2S), 7.00–7.06 (2H, m, 2×ArH), 7.29–7.34 (2H, m, 2×ArH); δ_C (75 MHz) 13.8 (CH_3), 68.6 (ArCH_2), 74.3 (CH_2S), 115.1, 115.4, 129.8, 129.9 (ArCH), 133.2, 133.3, 160.7, 164.0 (ArC); *m/z* 186 (M^+, 7%), 138 (36), 109 (100), 83 (11); HRMS: M^+, found 186.0518. $C_9H_{11}FOS$ requires 186.0515.

4.3.1.6. (1-Methylsulfanylmethoxymethyl)naphthalene.[20] Yield: 95%. Yellow oil; t_R=15.3 min; ν (film) 3048 (=CH), 1116 (C–O) cm^{-1}; δ_H (400 MHz) 2.23 (3H, s, CH_3), 4.74 (2H, s, CH_2S), 5.07 (2H, s, ArCH_2), 7.42–7.57 (4H, m, 4×ArH), 7.82 (1H, d, J=8.1, 2×ArH), 7.87 (1H, d, J=8.6, ArH), 8.17 (1H, d, J=8.3, ArH); δ_C (100 MHz) 14.1 (CH_3), 67.8 (CH_2), 74.5 (CH), 123.9, 125.2, 125.8, 126.3, 127.2, 128.5, 128.9 (ArCH), 131.8, 132.8, 133.8 (ArC); *m/z* 218 (M^+, 14%), 170 (21), 142 (18), 141 (100), 115 (22).

4.3.1.7. [Methylsulfanylmethoxy(phenyl)methyl]-benzene. Yield: 79%. Yellow oil; t_R=15.4 min; ν (film) 3061, 3028 (=CH), 1051 (C–O) cm^{-1}; δ_H (400 MHz) 2.18 (3H, s, CH_3), 4.64 (2H, s, CH_2), 5.90 (1H, s, CH), 7.22–7.36 (10H, m, 10×ArH); δ_C (100 MHz) 13.9 (CH_3), 72.5 (CH_2), 78.7 (CH), 127.4, 127.5, 128.4 (ArCH), 141.2 (ArC); *m/z* 244 (M^+, 1%), 196 (55), 195 (22), 168 (15), 167 (100), 166 (20), 165 (49), 152 (22); HRMS calcd for $C_{15}H_{16}OS$ 244.0922, found 244.0877.

4.3.2. Preparation of chloromethyl ethers 1g–l,o. To a stirred solution of the corresponding *O*,*S*-acetal (2 mmol) in dry dichloromethane (5 mL) under argon was added dropwise sulfuryl chloride (160 μL, 2 mmol) over 10 min at room temperature (or at −78 °C for the thioacetal precursors of compounds **1h–j**). The mixture was stirred for 30 min and then the solvent and the methanesulfenyl chloride were evaporated (15 Torr) to provide the expected title chloromethyl ethers, which were rather unstable and could not be purified by distillation or column chromatography, so they were used in crude form (purity>85% from ^1H NMR). Yields, physical, analytical spectroscopic data, as well as literature references for known compounds, follow.

4.3.2.1. 1-(Chloromethoxymethyl)-4-phenylbenzene (1g). Yield: 91%. Orange solid; mp 37 °C; t_R=15.8 min; ν (KBr) 3056, 3031 (=CH), 1106 (C–O) cm^{-1}; δ_H (400 MHz) 4.79 (2H, s, ArCH_2), 5.55 (2H, s, CH_2Cl), 7.34–7.37 (1H, m, ArH), 7.42–7.46 (4H, m, 4×ArH), 7.58–7.61 (4H, m, 4×ArH); δ_C (100 MHz) 71.1 (ArCH_2), 81.7 (CH_2Cl), 127.1, 127.3, 127.5, 128.8, 128.9 (ArCH), 134.5, 140.6, 141.4 (ArC); *m/z* 234 (M^++2, 7%), 232 (M^+, 21%), 168 (16), 167 (100), 165 (24), 152 (14); HRMS calcd for $C_{14}H_{13}OCl$ 232.0655, found 232.0668.

4.3.2.2. 1-(Chloromethoxymethyl)-2-methoxybenzene (1h). Yield: 89%. Orange liquid; t_R=11.4 min; ν (film) 1109 (C–O) cm^{-1}; δ_H (400 MHz) 3.83 (2H, s, CH_3), 4.79 (2H, s, ArCH_2), 5.56 (2H, s, CH_2Cl), 6.88 (1H, d, J=8.0, ArH), 6.95 (1H, t, J=7.3, ArH), 7.28–7.34 (2H, m, 2×ArH); δ_C (100 MHz) 55.4 (CH_3), 66.9 (ArCH_2), 82.3 (CH_2Cl), 110.4, 120.4, 129.7, 129.9 (ArCH), 124.0, 157.5 (ArC); *m/z* 188 (M^++2, 10%), 186 (M^+, 30%), 122 (11), 121 (100), 91 (60); HRMS: M^+, found 186.0434. $C_9H_{11}ClO_2$ requires 186.0448.

4.3.2.3. 1-(Chloromethoxymethyl)-3-methoxybenzene (1i).[23a] Yield: 75%. Orange liquid; t_R=11.5 min; ν (film) 1121 (C–O) cm^{-1}; δ_H (400 MHz) 3.80 (2H, s, CH_3), 4.71 (2H, s, ArCH_2), 5.51 (2H, s, CH_2Cl), 6.85–6.94 (3H, m, 3×ArH), 7.25–7.28 (1H, m, ArH); δ_C (100 MHz) 55.1 (CH_3), 71.1 (ArCH_2), 81.6 (CH_2Cl), 113.5, 113.9, 120.4, 129.6 (ArCH), 137.0, 159.7 (ArC); *m/z* 188 (M^++2, 8%), 186 (M^+, 24%), 122 (39), 121 (100), 91 (22), 78 (13), 77 (13).

4.3.2.4. 1-(Chloromethoxymethyl)-4-methoxybenzene (1j).[14] Yield: 90%. Yellow liquid; t_R=11.6 min; ν (film) 3040 (=CH), 1119 (C–O) cm^{-1}; δ_H (400 MHz) 3.80 (3H, s, CH_3), 4.67 (2H, s, ArCH_2), 5.49 (2H, s, CH_2Cl), 6.89 (2H, d, J=8.6, 2×ArH), 7.29 (2H, d, J=8.6, 2×ArH); δ_C (100 MHz) 55.2 (CH_3), 70.9 (ArCH_2), 81.4 (CH_2Cl), 113.9, 130.2 (ArCH), 127.4, 159.7 (ArC); *m/z* 188 (M^++2, 6%), 186 (M^+, 18%), 122 (10), 121 (100).

4.3.2.5. 1-(Chloromethoxymethyl)-4-fluorobenzene (1k).[23b] Yield: 95%. Yellowish liquid; t_R=9.1 min; ν (film) 3045 (=CH), 1121 (C–O) cm^{-1}; δ_H (400 MHz) 4.70 (2H, s, ArCH_2), 5.50 (2H, s, CH_2Cl), 7.03–7.07 (2H, m, 2×ArH), 7.31–7.35 (2H, m, 2×ArH); δ_C (100 MHz) 70.6 (ArCH_2), 81.5 (CH_2Cl), 115.4, 115.6, 130.2, 130.3 (ArCH), 131.3, 131.4, 161.4, 163.9 (ArC); *m/z* 176 (M^++2, 4%), 174 (M^+, 12%), 109 (100), 83 (11).

4.3.2.6. (Chloromethoxymethyl)naphthalene (1l).[24] Yield: 76%. Brownish oil; t_R=14.2 min; ν (film) 3048 (=CH), 1116 (C–O) cm^{-1}; δ_H (400 MHz) 5.20 (2H, s, ArCH_2), 5.54 (2H, s, CH_2Cl), 7.43–7.58 (4H, m, 4×ArH), 7.87 (2H, m, 2×ArH), 8.10 (1H, d, J=8.3, ArH); δ_C (100 MHz) 69.6 (ArCH_2), 81.5 (CH_2Cl), 123.9, 125.1, 126.0, 126.6, 127.9, 128.6, 129.6 (ArCH), 131.7, 133.8 (ArC); *m/z* 208 (M^++2, 8%), 206 (M^+, 24%), 142 (17), 141 (100), 139 (12), 115 (21).

4.3.2.7. [Chloromethoxy(phenyl)methyl]benzene (1o). Yield: 88%. Yellowish oil; t_R=14.3 min; ν (film) 3062, 3030 (=CH), 1109 (C–O) cm^{-1}; δ_H (400 MHz) 5.48 (2H, s, CH_2), 5.92 (1H, s, CH), 7.29–7.35 (10H, m, 10×ArH); δ_C (100 MHz) 80.0 (CH_2), 80.8 (CH), 127.5, 128.1, 128.5 (ArCH), 139.7 (ArC); *m/z* 234 (M^++2, 4%), 232 (M^+, 12%), 168 (16), 167 (100), 166 (13), 165 (35), 152 (16); HRMS calcd for $C_{14}H_{13}OCl$ 232.0655, found 232.0660.

4.4. DTBB-catalysed lithiation of chloromethyl ethers 1. Preparation of compounds 2. General procedure

To a cooled green suspension of lithium (49 mg, 7 mmol) and DTBB (13 mg, 0.05 mmol) in THF (2 mL) at 0 °C (or at −40 °C for **1g–j**,**l** and −78 °C for **1k**) was added the corresponding chloromethyl ether (1 mmol). The resulting mixture was stirred for 1 h at the same temperature and then it was hydrolysed with water (5 mL) allowing the temperature to rise to 20 °C. The resulting mixture was extracted with ethyl acetate (3×5 mL), and the organic layer was dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was then purified by vacuum distillation in a Kugelrohr apparatus (ca. 0.01 Torr for **2a–f**,**h–j**,**m**,**n**) or after column chromatography (silica gel, hexane/ethyl acetate for **2g**,**k**,**l**,**o**) to give the title compounds. Compound **2a** was characterised by comparison of its spectroscopic and chromatographic data with those of the commercially available (Aldrich) authentic sample. Yields are given in Table 1; physical, analytical spectroscopic data, as well as literature references for the known compounds, follow.

4.4.1. 2-(2-Methylphenyl)ethanol (2b).[25] Colourless liquid; t_R=9.3 min; ν (film) 3354 (OH), 3063, 3017 (=CH) cm^{-1}; δ_H (300 MHz) 2.32 (3H, s, CH_3), 2.87 (2H, t, *J*=6.9, ArCH_2), 3.80 (2H, t, *J*=6.9, CH_2O), 7.12–7.18 (4H, m, 4×ArH); δ_C (75 MHz) 19.4 (CH_3), 36.3 (Ar*C*H_2), 62.5 (CH_2O), 126.0, 126.5, 129.6, 130.4 (ArCH), 136.5, 140.1 (ArC); *m/z* 136 (M^+, 39%), 118 (10), 117 (13), 106 (33), 105 (100), 103 (13), 91 (23), 79 (14), 77 (15).

4.4.2. 2-(3-Methylphenyl)ethanol (2c).[26] Colourless liquid; t_R=9.0 min; ν (film) 3346 (OH), 3023 (=CH) cm^{-1}; δ_H (400 MHz) 2.33 (3H, s, CH_3), 2.81 (2H, t, *J*=6.6, ArCH_2), 3.82 (2H, t, *J*=6.6, CH_2O), 7.00–7.03 (3H, m, 3×ArH), 7.17–7.21 (1H, m, ArH); δ_C (100 MHz) 21.3 (CH_3), 39.0 (Ar*C*H_2), 63.6 (CH_2O), 126.0, 127.1, 128.4, 129.8 (ArCH), 138.1, 138.3 (ArC); *m/z* 136 (M^+, 49%), 106 (52), 103 (13), 105 (100), 91 (33), 79 (14), 77 (16).

4.4.3. 2-(4-Methylphenyl)ethanol (2d).[21] Colourless liquid; t_R=8.9 min; ν (film) 3345 (OH), 3048, 3020 (=CH) cm^{-1}; δ_H (300 MHz) 2.39 (3H, s, CH_3), 2.88 (2H, t, *J*=6.6, ArCH_2), 3.87 (2H, t, *J*=6.6, CH_2O), 7.16–7.19 (4H, m, 4×ArH); δ_C (75 MHz) 20.9 (CH_3), 38.6 (Ar*C*H_2), 63.7 (CH_2O), 128.8, 129.2, (ArCH), 135.3, 135.9 (ArC); *m/z* 136 (M^+, 34%), 106 (24), 105 (100), 91 (13), 79 (11), 77 (12).

4.4.4. 2-(3,5-Dimethylphenyl)ethanol (2e).[27] Colourless liquid; t_R=10.0 min; ν (film) 3354 (OH), 3013 (=CH) cm^{-1}; δ_H (300 MHz) 2.25 (6H, s, 2×CH_3), 2.76 (2H, t, *J*=6.7, ArCH_2), 3.78 (2H, t, *J*=6.7, CH_2O), 6.83 (2H, s, ArCH), 6.85 (1H, s, ArCH); δ_C (75 MHz) 21.1 (CH_3), 38.9 (Ar*C*H_2), 63.5 (CH_2O), 126.7, 128.0 (ArCH), 137.9, 138.2 (ArC); *m/z* 150 (M^+, 45%), 120 (41), 119 (100), 106 (10), 105 (27), 91 (21), 77 (10).

4.4.5. 2-(4-*tert*-Butylphenyl)ethanol (2f).[28] Colourless liquid; t_R=11.3 min; ν (film) 3346 (OH), 3055 (=CH) cm^{-1}; δ_H (300 MHz) 1.31 (9H, s, 3×CH_3), 2.83 (2H, t, *J*=6.6, ArCH_2), 3.84 (2H, t, *J*=6.6, CH_2O), 7.16 (2H, d, *J*=8.2, 2×ArH), 7.34 (2H, d, *J*=8.2, 2×ArH); δ_C (75 MHz) 31.3 (CH_3), 34.4 [*C*(CH_3)$_3$], 38.6 (Ar*C*H_2), 63.6 (CH_2O), 125.4, 128.7 (ArCH), 135.3, 149.2 (ArC); *m/z* 178 (M^+, 21%), 164 (21), 163 (100), 149 (41), 147 (15), 117 (18), 105 (12), 91 (20).

4.4.6. 2-(4-Phenylphenyl)ethanol (2g).[29] White solid; mp 91 °C (hexane/ethyl acetate); t_R=15.1 min; ν (KBr) 3249 (OH), 3030 (=CH) cm^{-1}; δ_H (400 MHz) 2.92 (2H, t, *J*=6.5, ArCH_2), 3.92 (2H, m, CH_2O), 7.30–7.36 (3H, m, 2×ArH), 7.41–7.46 (2H, m, 2×ArH), 7.54–7.59 (4H, m, 2×ArH); δ_C (100 MHz) 38.8 (Ar*C*H_2), 63.6 (CH_2O), 127.0, 127.3, 128.7, 129.4 (ArCH), 139.5, 140.9 (ArC); *m/z* 198 (M^+, 36%), 168 (19), 167 (100), 165 (24), 152 (13).

4.4.7. 2-(2-Methoxyphenyl)ethanol (2h).[30] Colourless oil; t_R=10.4 min; ν (film) 3384 (OH) cm^{-1}; δ_H (300 MHz) 2.90 (2H, t, *J*=6.5, ArCH_2), 3.79–3.85 (5H, m, CH_2O, CH_3), 6.85–6.93 (2H, m, 2×ArH), 7.14–7.27 (2H, m, 2×ArH); δ_C (75 MHz) 34.0 (Ar*C*H_2), 55.2 (CH_3), 62.8 (CH_2O), 110.4, 120.6, 127.7, 130.8 (ArCH), 127.0, 157.6 (ArC); *m/z* 152 (M^+, 58%), 122 (31), 121 (100), 92 (10), 91 (98), 77 (12), 65 (13).

4.4.8. 2-(3-Methoxyphenyl)ethanol (2i).[30] Colourless oil; t_R=10.7 min; ν (film) 3384 (OH) cm^{-1}; δ_H (300 MHz) 2.83 (2H, t, *J*=6.6, ArCH_2), 3.79 (3H, s, CH_3), 3.84 (2H, t, *J*=6.6, CH_2O), 6.76–6.82 (3H, m, 3×ArH), 7.20–7.25 (1H, m, ArH); δ_C (75 MHz) 39.2 (Ar*C*H_2), 55.1 (CH_3), 63.5 (CH_2O), 111.7, 114.7, 121.3, 129.5 (ArCH), 140.1, 159.7 (ArC); *m/z* 152 (M^+, 82%), 122 (65), 121 (100), 109 (15), 108 (11), 107 (16), 91 (47), 78 (16), 77 (21), 65 (11).

4.4.9. 2-(4-Methoxyphenyl)ethanol (2j).[21] Colourless liquid; t_R=10.7 min; ν (film) 3373 (OH), 3040 (=CH) cm^{-1}; δ_H (400 MHz) 2.81 (2H, t, *J*=6.5, ArCH_2), 3.79 (3H, s, CH_3), 3.82 (2H, t, *J*=6.6, CH_2O), 6.86 (2H, d, *J*=8.5, 2×ArH), 7.15 (2H, d, *J*=8.5, 2×ArH); δ_C (75 MHz) 38.2 (Ar*C*H_2), 55.2 (CH_3), 63.8 (CH_2O), 114.0, 129.9 (ArCH), 158.2 (ArC); *m/z* 152 (M^+, 22%), 121 (100).

4.4.10. 2-(4-Fluorophenyl)ethanol (2k).[31] Colourless liquid; t_R=8.1 min; ν (film) 3355 (OH), 3040 (=CH) cm^{-1}; δ_H (300 MHz) 2.84 (2H, t, *J*=6.6, ArCH_2), 3.84 (2H, t, *J*=6.6, CH_2O), 7.00 (2H, t, *J*=8.6, 2×ArH), 7.16–7.26 (2H, m, 2×ArH); δ_C (75 MHz) 38.3 (Ar*C*H_2), 63.6 (CH_2O), 115.2, 115.5, 130.3, 130.4 (ArCH), 134.1, 134.2, 160.1, 163.3 (ArC); *m/z* 140 (M^+, 22%), 110 (29), 109 (100), 83 (14).

4.4.11. 2-(1-Naphthyl)ethanol (2l).[32] White solid; mp 59 °C (hexane/ethyl acetate); t_R=13.5 min; ν (KBr) 3290 (OH), 3046 (=CH) cm^{-1}; δ_H (300 MHz) 3.34 (2H, t, *J*=6.6, ArCH_2), 3.98 (2H, t, *J*=6.6, CH_2O), 7.36–7.54 (4H, m, 2×ArH), 7.75 (1H, d, *J*=8.0, ArH), 7.85–7.88 (1H, m, ArH), 8.05 (1H, d, *J*=8.6, ArH); δ_C (75 MHz)

36.1 (Ar*C*H_2), 63.0 (CH_2O), 123.6, 125.4, 125.6, 126.0, 127.1, 128.8 (ArCH), 132.0, 133.9, 134.3 (ArC); *m/z* 172 (M^+, 23%), 156 (14), 155 (14), 143 (10), 142 (24), 141 (100), 129 (23), 128 (34), 115 (27).

4.4.12. 2-Phenylpropanol (2m).[21] Colourless liquid; t_R=8.4 min; ν (film) 3354 (OH), 3061, 3027 (=CH) cm^{-1}; δ_H (300 MHz) 1.31 (3H, d, *J*=7.0, CH_3), 2.96 (1H, m, CH), 3.70 (2H, d, *J*=7.2, CH_2), 7.26–7.40 (5H, m, 5×ArH); δ_C (75 MHz) 17.5 (CH_3), 42.3 (CH), 68.5 (CH_2), 126.5, 127.4, 127.7, 128.2, 128.5 (ArCH), 143.7 (ArC); *m/z* 136 (M^+, 15%), 106 (26), 105 (100), 103 (14), 91 (12), 79 (16), 77 (16).

4.4.13. 2-Phenylbutanol (2n).[33] Colourless liquid; t_R=9.4 min; ν (film) 3356 (OH), 3061, 3027 (=CH) cm^{-1}; δ_H (400 MHz) 0.85 (3H, t, *J*=7.3, CH_3), 1.59, 1.75 (2H, m, CH_2Me), 2.68 (1H, m, CH), 3.74 (2H, m, CH_2O), 7.19–7.35 (5H, m, 5×ArH); δ_C (100 MHz) 11.9 (CH_3), 24.9 (*C*H_2Me), 50.5 (CH), 67.3 (CH_2O), 126.7, 128.1, 128.6 (ArCH), 142.2 (ArC); *m/z* 150 (M^+, 17%), 120 (21), 119 (36), 103 (10), 91 (100).

4.4.14. 2,2-Diphenylethanol (2o).[34] White solid; mp 50 °C (hexane/ethyl acetate); t_R=14.0 min; ν (KBr) 3281 (OH), 3060, 3025 (=CH) cm^{-1}; δ_H (400 MHz) 4.15–4.23 (3H, m, Ph_2CH, CH_2), 7.23–7.34 (10H, m, 10×ArH); δ_C (100 MHz) 53.6 (Ph_2CH), 66.1 (CH_2), 126.8, 128.3, 128.7 (ArCH), 141.3 (ArC); *m/z* 198 (M^+, 5%), 168 (28), 167 (100), 166 (14), 165 (39), 152 (20).

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