

Regioselectivity in arene-catalyzed reductive lithiation of acetals of chlorobenzaldehydes

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Abstract—The regioselectivity of arene-catalyzed reductive lithiation of acetals of chlorobenzaldehydes strongly depends on the form of lithium metal employed as a reducing agent. According to previous findings, naphthalene catalyzed reductions run in the presence of lithium powder (high Na content) led to competitive metalations of both aromatic carbon–chlorine and benzylic carbon–oxygen bonds. At variance with these results, naphthalene catalyzed reductions run in the presence of lithium wire (either high or low Na content) led to highly regioselective metalation of aromatic carbon–chlorine bonds. These results disclose new possibilities of selective applications of arene-catalyzed reductive lithiation reactions.

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1. Introduction

Arene-catalyzed reductive lithiation of carbon-heteroatom bonds is a powerful approach to the generation of a wide array of functionalized and non-functionalized organolithium compounds.^{1,2} Application of this procedure to arylmethyl alkyl ethers results in highly regioselective cleavage of benzylic carbon–oxygen bonds, thus affording access to a wide array of arylalkyl organolithium derivatives, some of which are not easily accessible by other methodologies.^{3–5} Interestingly, reductive lithiation of aromatic ethylene,⁶ dimethyl⁷ and bis-(2-methoxyethyl)⁸ acetals is a useful approach to the generation of α -alkoxy-substituted benzyllithium derivatives, a procedure successfully extended to arenetricarbonylchromium acetals.⁹

The last finding highlights a potential limitation in applying the reductive metalation procedure to the generation of aromatic organolithium derivatives bearing a masked carbonyl group.

Indeed, Yus et al.¹⁰ reported that reductions of 2-(chlorophenyl)-1,3-dioxolanes, run in the presence of lithium powder and a catalytic amount of naphthalene (C₁₀H₈), occurs with regioselective cleavage of the aromatic carbon–chlorine bond.

However, these reactions have to be carried out under Barbier conditions, to avoid decomposition of intermediate organometals, due to competitive cleavage of benzylic carbon–oxygen bonds. Besides affording the desired products in moderate yields, this approach limits the number of electrophiles that can be added to carbanionic intermediates to aldehydes and ketones. Interestingly, an even lower selectivity was observed employing 4,4'-di-*tert*-butylbiphenyl (DTBB) as a catalyst.¹⁰

As an alternative approach, Azzena et al. investigated the reductive metalation of 1,3-dimethyl-2-(4-chlorophenyl)imidazolidine,¹¹ taking advantage of the relatively high stability of carbon–nitrogen bonds to reductive metalation.⁴ This procedure allows the generation of stable solutions of a synthetic equivalent of 4-formylphenyllithium, efficiently trapped with a variety of electrophilic reagents; however, resulting 2-(4-substituted)aryl-1,3-dimethylloxazolidines are not completely stable to purification by flash chromatography, thus precluding the recovery of protected benzaldehydes as reaction products.¹¹

Looking for a more efficient approach to the generation of synthetic analogues of formylphenyllithiums, we investigated the effect of different types of lithium metal (lithium wire vs lithium dispersion,¹² as well as lithium with a high sodium content vs lithium with a low sodium content¹³) on the selectivity of the reductive metalation of several acetals of chlorobenzaldehydes, and wish now to report that the regioselectivity of this reaction strongly depends on the form of lithium metal employed as a reducing agent.

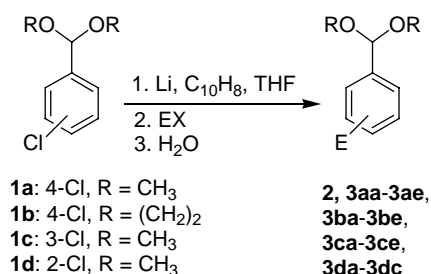
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2. Results and discussion

Dimethyl acetals **1a**, **1c** and **1d** were prepared by heating the corresponding aldehydes in MeOH at reflux in the presence of $\text{HC}(\text{OCH}_3)_3$ and a catalytic amount of NH_4Cl . Ethylene acetal **1b** was prepared by heating 4-chlorobenzaldehyde with 1,2-ethanediol in dry toluene at reflux, in the presence of a catalytic amount of *p*-toluenesulfonic acid.

Reductive metalations were carried out under Ar, with an excess of Li metal, either in the form of Li wire (0.32 mm, low or high Na content) or Li powder (high Na content). All reductions were run in the presence of a catalytic amount of naphthalene (C_{10}H_8), at temperature ranging from -40 to -80 °C, followed by addition of an electrophilic reagent and, finally, aqueous work up (Scheme 1).



Scheme 1. Reductive lithiation of acetals **1a–d**, and reaction with electrophiles. **2:** E=H, R=CH₃; **3aa:** E=4-CH₃, R=CH₃; **3ab:** E=4-PhCHOH, R=CH₃; **3ac:** E=4-(CH₃)₃CCHOH, R=CH₃; **3ad:** E=4-PhCOHAr, R=CH₃; **3ae:** E=4-CHO, R=CH₃; **3ba:** E=H, R=(CH₂)₂; **3bb:** E=4-CH₃, R=(CH₂)₂; **3bc:** E=4-(CH₂)₅COH, R=(CH₂)₂; **3bd:** E=4-Et₂COH, R=(CH₂)₂; **3be:** E=4-PhCHOH, R=(CH₂)₂; **3ca:** E=3-CH₃, R=CH₃; **3cb:** E=3-PhCHOH, R=CH₃; **3cc:** E=3-[(CH₃)₂CH]₂-COH, R=CH₃; **3cd:** E=3-CHO, R=CH₃; **3ce:** E=3-ArCHOH, R=CH₃; **3da:** E=2-CH₃, R=CH₃; **3db:** E=2-PhCHOH, R=CH₃; **3dc:** E=2-[(CH₃)₂CH]₂COH, R=CH₃.

Reductive lithiation and reaction with electrophiles of dimethyl acetal **1a**, taken as a model compound, was investigated in detail.

Reduction with 6 equiv of Li wire (low Na content) and 5 mol% of C_{10}H_8 led, after 4.5 h stirring at -40 °C and aqueous quenching, to the recovery of benzaldehyde dimethyl acetal, **2**, as the only reaction product, with no evidence of formation of products of cleavage of the benzylic carbon–oxygen bonds (Table 1, entry 1).

Intermediate formation of a protected, stable, 4-formyl-substituted aryllithium was evidenced quenching the reduction mixture with CH_3I : under these conditions, we recovered a reaction mixture containing, besides a relatively small amount of dimethyl acetal **2**, the dimethyl acetal of 4-methylbenzaldehyde, **3aa**, in 91% yield, as determined by ^1H NMR spectroscopy of the crude reaction mixture (Table 1, entry 2).

Similar results were obtained reacting dimethyl acetal **1a** with 6 equiv of Li wire containing a high percentage of Na, in the presence of 5 mol% of C_{10}H_8 (Table 1, entries 3 and 4).

Table 1. Reductive lithiation and reaction with electrophiles of dimethyl acetal of 4-chlorobenzaldehyde, **1a**^a

Entry	EX (<i>T</i> (°C)) ^b	Product, E=	Yield (%) ^c
1	H ₂ O (-40)	2 , H	>95 ^d
2	CH ₃ I (-40)	3aa , 4-CH ₃	91 ^d
3	H ₂ O (-40)	2 , H	>95 ^{d,e}
4	CH ₃ I (-40)	3aa , 4-CH ₃	84 ^{d,e}
5	PhCHO (-40)	3ab , 4-PhCHOH	63
6	<i>t</i> -BuCHO (-40)	3ac , 4- <i>t</i> -BuCHOH	71
7	PhCOCl (-80)	3ad , 4-PhCOHAr ^f	58
8	HCOOCH ₃ (-80) ^g	3ae , 4-CHO	55

^a All reactions were run at -40 °C, during 4.5 h, in the presence of 6 equiv of Li wire (low Na content, unless otherwise indicated) and a catalytic amount of C_{10}H_8 (5 mol%).

^b Temperature of addition of EX (2 equiv, if not otherwise indicated).

^c Determined on isolated products, if not otherwise indicated.

^d Determined by ^1H NMR analysis of crude reaction mixture.

^e High Na content Li metal was employed.

^f EX (0.45 equiv) were employed; Ar=4-(CH₃)₂CHC₆H₄.

^g Inverse addition.

It is worth noting that using a higher amount of C_{10}H_8 (10 mol%) did not significantly affect these results, whatever kind of Li wire was employed as a reducing agent (not reported in Table 1).

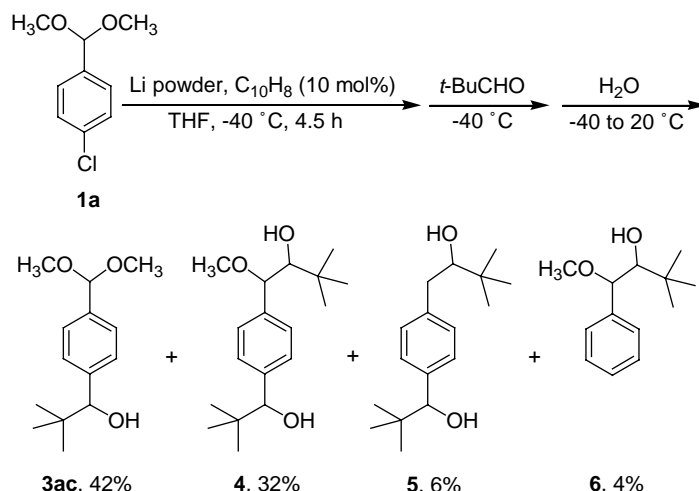
Trapping the intermediate organometal, generated as reported in entries 1 and 2, with PhCHO, *t*-BuCHO, and PhCOCl allowed the synthesis of the corresponding carbinols **3ab**, **3ac** and **3ad**, respectively, in satisfactory yields (Table 1, entries 5–7). Finally, reaction of the same intermediate with HCOOCH₃, under inverse addition reaction conditions, led to the recovery of the monoprotected terephthalaldehyde **3ae**, in 55% yield (Table 1, entry 8).

Different results were obtained performing the reductive lithiation of dimethyl acetal **1a** with Li powder, in the presence of 10 mol% of C_{10}H_8 , at -40 °C. Indeed, quenching this reduction mixture with *t*-BuCHO, followed by aqueous work up, afforded a complex reaction mixture (Scheme 2).

Chromatographic fractionation, followed by tandem GC/MS and ^1H NMR analysis of the different fractions, allowed us to identify, besides the expected carbinol **3ac** (42%), significant amounts of products derived from competitive reductive lithiation of the benzylic carbon–oxygen bonds, that is, alcohols **4–6**. It is interesting to observe that this result is in good qualitative agreement with what is already reported for the arene-catalyzed reductive metalation of aromatic ethylene acetals with lithium powder,¹⁰ thus underlining the major role played by the form of the metal on the regioselectivity of these reactions.

To shed more light on the role of the different forms of the metal on regioselectivity, we investigated the reduction with Li wire of the ethylene acetal of 4-chlorobenzaldehyde, **1b**. To get a better comparison with literature data,¹⁰ we carried out these reactions with 13 equiv of Li wire, in the presence of 10 mol% of C_{10}H_8 , at -80 °C (Table 2).

Contrary to what was observed in the presence of lithium powder,¹⁰ results reported in Table 2 show that employment of Li wire (low Na content) allowed highly regioselective



Scheme 2. Reductive metalation of dimethyl acetal **1a** with Li powder and 10 mol% of $C_{10}H_8$, followed by reaction with *t*-BuCHO and aqueous work up.

Table 2. Reductive lithiation and reaction with electrophiles of ethylene acetal of 4-chlorobenzaldehyde, **1b^a**

Entry	EX (T (°C)) ^b	Product, E=	Yield (%) ^b
1	H ₂ O	3ba , H	>95 ^c
2	CH ₃ I	3bb , 4-CH ₃	93 ^c
3	H ₂ O	3ba , H	86 ^{d,e}
4	CH ₃ I	3bb , 4-CH ₃	84 ^{c,d}
5	(CH ₂) ₅ CO	3bc , 4-(CH ₂) ₅ COH	61
6	Et ₂ CO	3bd , 4-Et ₂ COH	67
7	PhCHO	3be , 4-PhCHOH	67

^a All reactions were run at -80 °C, during 3 h, in the presence of 13 equiv of Li wire (low Na content, unless otherwise indicated) and a catalytic amount of $C_{10}H_8$ (10 mol%).

^b Determined on isolated products, if not otherwise indicated.

^c Determined by ¹H NMR analysis of crude reaction mixture.

^d High Na content Li metal was employed.

^e Ca. 5% of 2-benzyloxyethanol was also recovered.

cleavage of the aromatic carbon–chlorine bond (Table 2, entry 1), via intermediate formation of a stable aromatic organometal, as evidenced by quenching the reduction mixture with CH₃I (Table 2, entry 2).

Similar results were obtained employing Li wire with a high Na content as the reducing agent, although a minor amount ($\leq 5\%$) of 2-benzyloxyethanol, **7**, was recovered when quenching the reduction mixture with H₂O (Table 2, entry 3). It is worth noting that alcohol **7** is the product of cleavage of both the aromatic carbon–chlorine and a benzylic carbon–oxygen bond. However, no product of cleavage of a benzylic carbon–oxygen bond was evidenced quenching a similar reduction mixture with CH₃I (Table 2, entry 4).

Satisfactory results were obtained trapping the intermediate organometal, generated as reported in entries 1 and 2, with enolizable and non-enolizable carbonyl compounds (Table 2, entries 5–7). Interestingly, besides showing higher selectivity, the two-pot procedure led to an improvement of those results obtained under Barbier-type reaction conditions¹⁰ (Table 2, entries 5 and 6).

Finally, to get a wider picture on the versatility of the proposed methodology, we investigated the reductive lithiation of *meta*- and *ortho*-chloro-substituted dimethyl acetals of benzaldehydes, that is, compounds **1c** and **1d**. These reactions were carried out in the presence of 6 equiv of Li wire (low Na content), and in the presence of 5 mol% of $C_{10}H_8$ during 4.5 h at -40 °C. Selected results are reported in Table 3.

Table 3. Reductive lithiation and reaction with electrophiles of acetals **1c** and **1d^a**

Entry	Substrate	EX (T (°C)) ^b	Product, E=	Yield (%) ^c
1	1c	H ₂ O (-40)	2 , H	>95 ^d
2	1c	CH ₃ I (-40)	3ca , 3-CH ₃	82 ^d
3	1c	PhCHO (-80)	3cb , 3-PhCHOH	55
4	1c	[(CH ₃) ₂ CH] ₂ CO (-80)	3cc , 3-[(CH ₃) ₂ CH] ₂ COH	45
5	1c	HCOOCH ₃ (-80) ^e	3cd , 3-CHO	56
6	1c	HCOOCH ₃ (-80) ^f	3ce , 3-ArCHOH ^g	62
7	1d	H ₂ O (-40)	2 , H	>95 ^d
8	1d	CH ₃ I (-40)	3da , 2-CH ₃	83 ^d
9	1d	PhCHO (-80)	3db , 2-PhCHOH	56
10	1d	[(CH ₃) ₂ CH] ₂ CO (-80)	3dc , 2-[(CH ₃) ₂ CH] ₂ COH	80 ^d (52) ^h

^a All reactions were run at -40 °C, during 4.5 h, in the presence of 6 equiv of Li (low Na content) and a catalytic amount of $C_{10}H_8$ (5 mol%).

^b Temperature of addition of EX (2 equiv, if not otherwise indicated).

^c Determined on isolated products, if not otherwise indicated.

^d Determined by ¹H NMR analysis of crude reaction mixture.

^e Inverse addition.

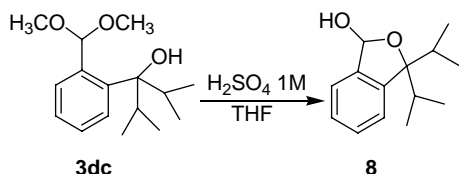
^f EX (0.45 equiv) were employed.

^g Ar = 3-(CH₃O)₂CHC₆H₄.

^h Determined on the corresponding cyclic hemiacetal, **8**, obtained by acidic hydrolysis of alcohol **3dc**.

Under the above mentioned reaction conditions, cleavage of *meta*-substituted acetal **1c** afforded, after aqueous work up, the dimethyl acetal of benzaldehyde, **2**, as the only reaction product (Table 3, entry 1). Furthermore, intermediate formation of 3-dimethoxymethylphenyllithium was evidenced quenching the reduction mixture with CH₃I (Table 3, entry 2), with carbonyl compounds (Table 3, entries 3 and 4), and with HCOOCH₃, either under inverse or conventional addition of the electrophile to the reduction mixture (Table 3, entries 5 and 6, respectively).

Comparable results were obtained in the reductive lithiation of the *ortho*-derivative **1d**. Indeed, under identical reaction conditions, its reductive lithiation allowed the generation of stable solutions of 2-dimethoxymethylphenyllithium; reaction of this intermediate with H₂O, CH₃I and PhCHO, afforded the expected derivatives **2**, **3da–3db** in good to satisfactory yields (Table 3, entries 7–9). Finally, reaction of the same organometals with [(CH₃)₂CH]₂CO led to the formation of alcohol **3dc** (Table 3, entry 10); although it was not possible to purify the latter by flash chromatography, its structure was established by acidic hydrolysis to hemiacetal **8** (Scheme 3).



Scheme 3. Synthesis of hemiacetal **8**, by acidic hydrolysis of alcohol **3dc**.

3. Conclusions

Our results clearly show that regioselective reductive lithiation of acetals of chlorobenzaldehydes strongly depends on the form of the lithium metal. Indeed, the actual form of a metal is known to affect, to various degree, its reactivity, and the higher reactivity of powders towards massive metals is well documented.¹⁴

Reductions carried out with Li wire (either with a high or low Na content) led to the generation of stable solutions of *ortho*-, *meta*- or *para*-substituted protected formylphenyllithium, independent from the nature of the protective group (dimethyl or ethylene acetal), via a highly regioselective cleavage of the aromatic carbon–chlorine bond. Accordingly, it is possible to trap these organometals with a range of electrophilic reagents, as well as to enhance the versatility of this methodology by applying an inverse addition technique.

A relatively lower regioselectivity was observed in a single experiment, that is, in the reaction of ethylene acetal **1b** with Li wire containing a high Na content, followed by aqueous work up (Table 2, entry 3). Under these conditions, competitive cleavage of the benzylic carbon–oxygen bond, although limited to a very low percentage, was also observed.

Completely different results were obtained employing lithium powder (high Na content) as a reducing agent. Indeed, under these conditions, dimethyl acetal **1a** underwent competitive benzylic carbon–oxygen bond(s) cleavage leading, as a consequence, to the formation of significant amounts of disubstituted reaction products, as already reported for several aromatic ethylene acetals.¹⁰

In conclusion, we have shown that aromatic acetals are effective protective groups in the reductive lithiation of chlorine-substituted aromatic carbonyls, provided that lithium

wire (in the presence of C₁₀H₈) is employed as a reducing agent.

In a broader sense, however, our results underline the very powerful reducing power of lithium powder (either in the presence of C₁₀H₈ or DTBB).

4. Experimental

4.1. General

Boiling and melting points are uncorrected; the air bath temperature on bulb-to-bulb distillation are given as boiling points. Commercially available Li wire (Ø 3.2 mm) was 99.9% purity (low Na content) or 99% purity (high Na content). Li powder (high Na content) was prepared as described in Ref. 12. Other starting materials were of the highest commercial quality and were purified by distillation or recrystallization immediately before use. THF was distilled from Na/K alloy under N₂ immediately before use. ¹H NMR spectra were recorded at 300 MHz and ¹³C NMR spectra were recorded at 75 MHz with a Bruker AC-300, or with a Varian VXR 300, in CDCl₃ with SiMe₄ as internal standard. CDCl₃ for recording spectra of acetals was stored over K₂CO₃ in the refrigerator. IR spectra were measured with a Nicolet Impact 400 D-FT Spectrometer, or with a Jasco FT/IR-480 Plus. LRMS and HRMS were measured with a Shimadzu GC/HS QP-5000 and with a Finigan MAT95 S spectrometers, respectively. Elemental analysis were performed by the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari. Flash chromatography was performed on silica gel 60 (40–63 µm), and TLC analyses on silica gel pre-coated plastic sheets (0.20 mm).

4.2. Starting materials

Dimethyl acetals **1a** (88% yield),¹⁵ **1c** (81% yield),¹⁶ and **1d** (80% yield),¹⁶ were prepared by heating the corresponding chlorobenzaldehyde (0.07 mol, 10 g) in a mixture of 50 mL of CH₃OH and 20 mL of HC(OCH₃)₃ at reflux overnight, in the presence of a catalytic amount of NH₄Cl (0.1 g, 1.9 mmol). Reaction mixtures were chilled to 0 °C, made basic by slow dropwise addition of Et₃N (2 mL), evaporated, then diluted with Et₂O (20 mL) and NaHCO₃ (20 mL) and worked up as usual.

Ethylene acetal **1b** (72% yield)¹⁰ was prepared distilling with fractionation a solution of 2-chlorobenzaldehyde (0.036 mol, 5 g) and 1,2-ethanediol (2.46 g, 0.04 mol) in 50 mL of dry toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid (0.53 mmol, 100 mg), until the azeotrope toluene–H₂O was distilled away, followed by work up as described above.

All acetals were purified by vacuum distillation and characterized by comparison with literature data.

4.3. Reductive cleavage of acetals, and reactions with electrophiles. General procedure

Li (6–13 equiv) was placed under Ar in a 50 mL two-necked flask equipped with reflux condenser and magnetic stirrer, and suspended in dry THF (5 mL). A catalytic amount of $C_{10}H_8$ (5–10 mol%) was added to the suspended metal. When using Li wire, each metal piece was cut into 2–3 smaller pieces with a spatula. The resulting mixture was stirred at rt until a dark green colour appeared. The mixture was chilled to the reported temperature (Tables 1–3) and a solution of the appropriate acetal (2.7 mmol) dissolved in THF (2.5 mL) was added dropwise. Reaction mixtures were stirred for the reported time (Tables 1–3), and a solution of the appropriate electrophile (2 equiv), dissolved in THF (2 mL), was added dropwise. After stirring at the reported temperature until an evident chromatic variation occurred, the mixture was quenched by slow dropwise addition of H_2O (5 mL) dissolved in THF (5 mL) (caution!), the cold bath removed, and the resulting mixture extracted with Et_2O (3×10 mL). Organic phases were collected, washed with saturated $NaHCO_3$ (20 mL), dried (K_2CO_3) and the solvent evaporated.

Compounds **2**, **3aa**,¹⁵ **3ba**, **3bb**,¹⁷ **3bc**,¹⁰ **3bd**,¹⁰ **3ca**,¹⁵ **3cd**,¹⁸ **3da**,¹² **3db**,¹⁹ **5**²⁰ and **7** were purified by flash chromatography (petroleum ether/ $AcOEt/Et_3N$) and characterized by comparison with commercially available samples (compounds **2**, **3ba** and **7**) or literature data.

Other products were purified and characterized as follows.

4.3.1. (4-Dimethoxymethylphenyl)phenylmethanol (3ab). Purified by flash chromatography (petroleum ether/ $AcOEt/Et_3N=8:2:1$), colourless oil; [Found: C, 74.2; H, 7.2. $C_{16}H_{18}O_3$ requires C, 74.39; H, 7.02]; R_f 0.64 (petroleum ether/ $AcOEt/Et_3N=8:2:1$); ν_{max} (liquid film) 3467 cm^{-1} ; δ_H 7.45–7.27 (9H, m, $9 \times ArH$), 5.86 (1H, s, OCHO), 5.36 (1H, s, OCHAr), 3.12 (6H, s, $2 \times CH_3$); δ_C 144.0, 143.7, 137.3, 128.5, 127.6, 126.8, 126.5, 126.4, 103.0, 76.0, 52.7.

4.3.2. 1-(4-Dimethoxymethylphenyl)-2,2-dimethylpropan-1-ol (3ac). Purified by flash chromatography (petroleum ether/ $AcOEt/Et_3N=8:2.5:1$), colourless oil; [Found: C, 70.4; H, 9.5. $C_{14}H_{22}O_3$ requires C, 70.56; H, 9.30]; R_f 0.44 (petroleum ether/ $AcOEt/Et_3N=8:2.5:1$); ν_{max} (liquid film) 3465 cm^{-1} ; δ_H 7.43–7.37 (2H, m, $2 \times ArH$), 7.35–7.29 (2H, m, $2 \times ArH$), 5.38 (1H, s, CHAr), 4.41 (1H, d, $J=3.0$ Hz, OCHO), 3.33 (6H, s, $2 \times CH_3$), 1.87 (1H, d, $J=3.0$ Hz, OH), 0.92 (9H, s, $3 \times CH_3$); δ_C 143.4, 137.2, 127.4, 126.8, 103.2, 82.6, 52.6, 35.8, 25.8.

4.3.3. Bis-(4-dimethoxymethylphenyl)phenylmethanol (3ad). Purified by flash chromatography (petroleum ether/ $AcOEt/Et_3N=8:2:1$), colourless oil; [Found: C, 73.4; H, 6.7. $C_{25}H_{28}O_5$ requires C, 73.51; H, 6.91]; R_f 0.42 (petroleum ether/ $AcOEt/Et_3N=8:2:1$); ν_{max} (liquid film) 3426 cm^{-1} ; δ_H 7.42–7.36 (4H, m, $4 \times ArH$), 7.32–7.23 (9H, m, $9 \times ArH$), 5.38 (2H, s, $2 \times OCHO$), 3.34 (12H, s, $4 \times CH_3$); δ_C 147.0, 146.7, 137.0, 127.9, 127.9, 127.8, 127.3, 126.2, 103.1, 81.7, 52.9.

4.3.4. 4-Dimethoxymethylbenzaldehyde (3ae). Purified by flash chromatography (petroleum ether/ $Et_3N=10:1$), colourless oil; [Found: C, 66.5; H, 6.9. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71]; R_f 0.48 (petroleum ether/ $Et_3N=10:1$); ν_{max} (liquid film) 1703 cm^{-1} ; δ_H 10.04 (1H, s, CHO), 7.93–7.87 (1H, m, ArH), 7.67–7.61 (2H, m, $2 \times ArH$), 5.46 (1H, s, CHAr), 3.34 (6H, s, $2 \times CH_3$); δ_C 192.0, 144.5, 136.3, 129.6, 127.4, 102.1, 52.7.

4.3.5. [4-(1,3-Dioxolan-2-ylphenyl)phenylmethanol (3be). Purified by flash chromatography (petroleum ether/ $AcOEt/Et_3N=5:5:1$), colourless oil, which solidifies upon standing; [Found: C, 75.1; H, 6.5. $C_{16}H_{16}O_3$ requires C, 74.98; H, 6.29]; R_f 0.58 (petroleum ether/ $AcOEt/Et_3N=5:5:1$); ν_{max} (Nujol) 3401 cm^{-1} ; δ_H 7.47–7.25 (m, 9H, $9 \times ArH$), 5.85 (br s, 1H, CH), 5.79 (s, 1H, CH), 4.15–3.99 (m, 4H, $2 \times CH_2$), 2.23 (1H, br s, OH); δ_C 144.8, 143.6, 137.0, 128.4, 127.6, 126.6, 126.5, 126.5, 103.5, 75.9, 65.2.

4.3.6. (3-Dimethoxymethylphenyl)phenylmethanol (3cb). Purified by flash chromatography (petroleum ether/ $AcOEt/Et_3N=8:2.5:1.5$), colourless oil; [Found: C, 74.2; H, 7.3. $C_{16}H_{18}O_3$ requires C, 74.39; H, 7.02]; R_f 0.46 (petroleum ether/ $AcOEt/Et_3N=8:2.5:1.5$); ν_{max} (liquid film) 3422 cm^{-1} ; δ_H 7.52–7.48 (1H, m, ArH), 7.40–7.26 (8H, m, $8 \times ArH$), 5.85 (1H, s, CHO), 5.37 (1H, s, CHAr), 3.30 (6H, s, $2 \times CH_3$); δ_C 143.8, 143.7, 138.3, 128.5, 128.4, 127.6, 126.6, 126.5, 125.9, 124.8, 103.0, 76.2, 52.7.

4.3.7. 3-(3-Dimethoxymethylphenyl)-2,4-dimethylpentan-3-ol (3cc). Purified by flash chromatography (petroleum ether/ $AcOEt/Et_3N=10:1$), colourless oil; [Found: C, 71.9; H, 10.1. $C_{16}H_{26}O_3$ requires C, 72.14; H, 9.84]; R_f 0.32 (petroleum ether/ $Et_3N=10:1$); ν_{max} (liquid film) 3502 cm^{-1} ; δ_H 7.48–7.43 (1H, s, ArH), 7.37–7.29 (3H, m, $3 \times ArH$), 5.41 (1H, s, CHAr), 3.32 (6H, s, $2 \times CH_3$), 2.32 (2H, hept, $J=6.9$ Hz, $2 \times CH$), 1.55 (1H, s, OH), 0.85–0.80 (6H, d, $J=6$ Hz, $2 \times CH_3$), 0.65–0.80 (6H, d, $J=6$ Hz, $2 \times CH_3$); δ_C 143.0, 137.0, 127.2, 126.9, 125.0, 124.7, 103.3, 81.0, 52.6, 33.8, 17.5, 16.5.

4.3.8. Bis-(3-dimethoxymethylphenyl)methanol (3ce). Purified by flash chromatography (petroleum ether/ $AcOEt/Et_3N=9:1:1$), colourless oil; [Found: C, 68.5; H, 7.4. $C_{19}H_{24}O_5$ requires C, 68.66; H, 7.28]; R_f 0.18 (petroleum ether/ $AcOEt/Et_3N=9:1:1$); ν_{max} (liquid film) 3425 cm^{-1} ; δ_H 7.51–7.47 (2H, m, $2 \times ArH$), 7.38–7.32 (6H, m, $6 \times ArH$), 5.88 (1H, s, CH), 5.37 (2H, s, $2 \times CHAr$), 3.31 (12H, s, $4 \times CH_3$); δ_C 143.8, 138.3, 128.4, 126.7, 126.0, 125.0, 103.0, 76.2, 52.7.

4.3.9. 1-[4-(1-Hydroxy-2,2-dimethylpropyl)phenyl]-1-methoxy-3,3-dimethylbutan-2-ol (4). Diastereomeric mixture, purified by column chromatography (hexane/ $AcOEt=20:1$), colourless oil; first diastereomer, R_f 0.20 (hexane/ $AcOEt=5:1$); second diastereomer, R_f 0.19 (hexane/ $AcOEt=5:1$); ν_{max} (liquid film) 3474, 3048, 2953, 2908, 2868, 1396, 1361, 1270, 1105, 1065, 1010, 745 cm^{-1} ; first diastereomer, δ_H 7.32–7.26 (4H, m, ArH), 4.41 (1H, s, ArCHOH), 4.17 (1H, d, $J=3.9$ Hz, $CHOCH_3$), 3.35 (1H, m, CHO), 3.22 (3H, s, OCH_3), 2.91 (1H, d, $J=5.7$ Hz, OH), 0.92 (9H, s, $3 \times CH_3$), 0.89

(9H, s, 3×CH₃); second diastereomer, δ_{H} 7.32–7.24 (4H, m, ArH), 4.41 (1H, s, ArCHOH), 4.13 (1H, d, $J=6.0$ Hz, CHOCH₃), 3.52 (1H, d, $J=6.0$ Hz, CHOH), 3.14 (3H, s, OCH₃), 2.85 (1H, br s, OH), 0.92 (9H, s, 3×CH₃), 0.91 (9H, s, 3×CH₃); diastereomeric mixture, δ_{C} 141.2, 141.8, 139.7, 138.1, 127.8, 127.6, 126.5, 82.2, 82.1, 80.7, 56.2, 56.0, 35.6, 34.8, 34.5, 26.5, 25.9; diastereomeric mixture, MS (E.I., 70 eV) m/z 237 ($M^+ - t\text{-Bu}$, 2), 208 (31), 207 (100), 190 (56), 175 (20), 151 (89), 122 (37), 91 (16), 57 (31%); HRMS: found 237.1488. C₁₄H₂₁O₃ requires 238.1491.

4.3.10. 1-Methoxy-3,3-dimethyl-1-phenylbutan-2-ol (6).

Diastereomeric mixture, purified by column chromatography (hexane/AcOEt=40:1), colourless oil; first diastereomer, R_{f} 0.39 (hexane/AcOEt=10:1); second diastereomer, R_{f} 0.38 (hexane/AcOEt=10:1); ν_{max} (liquid film) 3514, 3088, 3063, 3033, 2958, 2903, 1481, 1451, 1401, 1371, 1075, 1015 cm⁻¹; first diastereomer, δ_{H} 7.37–7.24 (5H, m, ArH), 4.17 (1H, d, $J=3.9$ Hz, CHOCH₃), 3.30 (1H, dd, $J=5.8, 3.9$ Hz, CHOH), 3.22 (3H, s, OCH₃), 2.92 (1H, d, $J=5.8$ Hz, OH), 0.90 (9H, s, 3×CH₃); second diastereomer, δ_{H} 7.37–7.24 (5H, m, ArH), 4.11 (1H, d, $J=6.2$ Hz, CHOCH₃), 3.57–3.51 (1H, m, CHOH) 3.14 (3H, s, OCH₃), 2.84 (1H, br s, OH), 0.93 (9H, s, 3×CH₃); diastereomeric mixture, δ_{C} 140.7, 139.9, 128.6, 128.5, 128.4, 127.8, 127.3, 82.3, 82.0, 80.6, 80.5, 56.2, 56.0, 34.8, 34.5, 26.5; first diastereomer, MS (E.I., 70 eV) m/z 176 ($M^+ - \text{MeOH}$, 0.5%), 122 (74), 121 (100), 91 (27), 77 (13%); second diastereomer, MS (E.I., 70 eV) m/z 176 ($M^+ - \text{MeOH}$, 0.5%), 122 (75), 121 (100), 91 (29), 77 (13%); first diastereomer, HRMS: found 176.1183. C₁₂H₁₆O requires 176.1201; second diastereomer, HRMS: found 176.1201. C₁₂H₁₆O requires 176.1201.

4.3.11. 3,3-Diisopropyl-1,3-dihydro-isobenzofuran-1-ol (8).

Acetal **1d** (500 mg, 2.7 mmol) was lithiated as described in the Section 4.3. To this mixture, chilled to -80 °C, a solution of 2,4-dimethylpentan-3-one (620 mg, 5.4 mmol) dissolved in THF (2 mL) was added dropwise. After stirring at the same temperature until almost complete decolouration, the reaction mixture was quenched and elaborated as described in the Section 4.3. The crude reaction product was dissolved in a mixture of THF/1 M H₂SO₄=1:1 (5 mL) and stirred at rt for 8 h. The resulting mixture was extracted with Et₂O (3×10 mL), the organic phases were collected, washed with saturated NaHCO₃ (20 mL), dried (K₂CO₃) and the solvent evaporated. Purification by flash chromatography (petroleum ether/AcOEt/Et₃N=7:3:1), afforded a colourless oil (310 mg, 1.4 mmol, 52%), which solidifies upon standing, and was characterized as following: [Found: C, 76.1; H, 9.5. C₁₄H₂₀O₂ requires C, 76.33; H, 9.15]; R_{f} 0.66 (petroleum ether/AcOEt/Et₃N=7:3:1); ν_{max} (liquid film) 3342 cm⁻¹; δ_{H} 7.30–7.12 (3H, m, 3×ArH), 7.17–7.09 (1H, m, ArH), 6.44 (1H, s, OCHO), 3.10 (1H, br s, OH), 2.38–2.16 (2H, m, 2×CH), 0.95 (3H, d, $J=6.9$ Hz, CH₃), 0.82 (3H, d, $J=6.9$ Hz, CH₃), 0.82 (3H, d, $J=6.9$ Hz, CH₃), 0.73 (3H, d, $J=6.9$ Hz, CH₃); δ_{C} 142.6, 140.5, 129.0, 127.9, 122.8, 121.7, 100.5, 96.7, 34.2, 32.6, 18.1, 17.2.

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