Highly Chemoselective Lithium Metal Reductions of Benzaldehyde Bis(2-Methoxyethyl) Acetals

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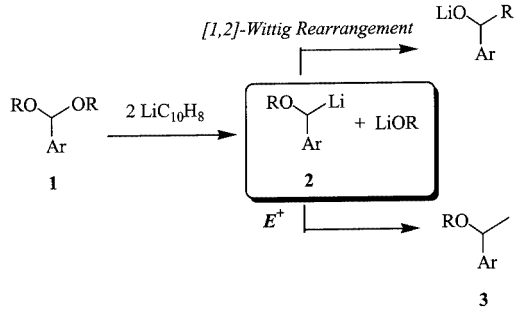
Naphthalene-catalysed reductions of $PhCH(OR)_2$ (R = Me, CH_2CH_2OMe) acetals by lithium metal, followed by reactions with electrophiles (H^+, TMSCl, *n*BuBr, $CH_2{=}CHCH_2Br$), proceed with high chemoselectivity when the reductions are carried out at –90 °C especially for R = CH_2CH_2OMe.

Introduction

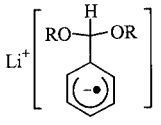
Lithium naphthalenide ($LiC_{10}H_8$) is a well-known, extremely potent, stoichiometric reagent ($E^0 = -2.50$ V vs. SCE) that participates in many single- and multiple-electron reductions.[1] In recent years there has been an upturn in the interest in equivalent reactions using *catalytic* amounts of naphthalene (and related electron-transfer catalysts) in the presence of lithium powder as the terminal reductant.[1] Naphthalenide-promoted cleavages of C–O bonds with stoichiometric $MC_{10}H_8$ (M = Li, Na) were first described in the 1960s.[1a] This paper is concerned with catalytic C–O cleavage reactions of acetals and related species (derived from benzaldehyde), chemistry first developed by Yus, Azzena and co-workers.[2–4] Typical behaviour for these reactions is shown in Scheme 1. Stepwise addition of two electrons to **1** results in organolithium compound **2** with concomitant formation of 1 equiv. of LiOR. The presence of these alkoxide by-products has been proposed[3] to stabilise **2** against [1,2]-Wittig rearrangement[5] allowing interception of **1** with suitable electrophiles (HX, TMSCl, RX, etc.) at relatively high temperatures (typically –40 °C to room temperature). In general, however, while these reactions do provide the desired target molecules the chemistry is rather prone to by-product formation or double reduction.[3]

Additionally, there are interesting stereochemical issues in this reduction chemistry. The organolithium compounds **2** contain a chiral centre but as a consequence of the achiral $LiC_{10}H_8$ reduction is, of course, obtained as a racemic mixture. The configurational stability of such organolithium species is known to be a function of its method of preparation, the solvent and any ligands coordinating the lithium



Scheme 1. Reduction of aromatic acetals

ion.[6] Subsequent reaction with electrophiles (E^+) are also known to proceed with either retention or inversion depending on E^+.[7] If appropriate conditions could be identified whereby the organolithium compounds **2** could be attained with high enantiomeric purity, and subsequently trapped in a controlled manner with E^+, then useful new methodology would result. This major challenge requires selective enantiotopic C–OR cleavage on addition of the second electron to radical anion **A** or subsequent kinetic resolution of the species **2**. Some success has been attained in the reduction of the arenetricarbonylchromium acetal **4** with a stoichiometric amount of lithium 4,4′-di(*tert*-butyl)-biphenyl, followed by TMSCl addition, where an 88% *de* is attained.[8] However, equivalent catalytic approaches remain quite undeveloped.[9] As an initial goal towards this challenging ideal we have focused on identifying reliable conditions whereby aromatic acetals **1** undergo both reductive cleavage and subsequent reaction with electrophiles with very high chemoselectivity.



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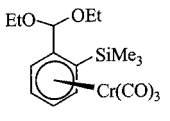

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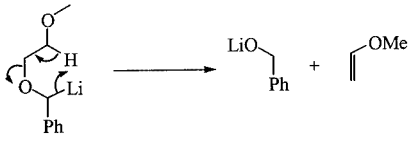
Results and Discussion

In our hands, reduction of THF solutions of (dimethoxymethyl)benzene (**1a**) (R = Me) with 2.8 equiv. of lithium powder, under literature conditions,[3] under argon at −40 °C using 10 mol % $C_{10}H_8$ followed by alkylation with *n*BuBr resulted in only partial consumption of **1a** and the formation of a product mixture. Aside from the desired product **3a** (E = Bu) and small amounts of **3a** (E = H), resulting from adventitious reaction of **2a** with protons, traces of [1,2]-Wittig rearrangement products and benzyl alcohol were detected. In reductions of **1b** (R = CH_2CH_2OMe), at −40 °C, employing either extended reaction times or increased equivalents of lithium gave, after quenching with water, benzyl alcohol as the major product. The latter behaviour implies a rapid intramolecular "complex-induced proximity effect" (CIPE)[10] via **5**. Consistent with this suggestion attempts to intercept **5**, under these conditions, with TMSCl or D_2O were unsuccessful and use of [D_8]THF as solvent did not lead to deuterium incorporation into the product benzyl alcohol. However, in no case was overreduction to toluene observed.



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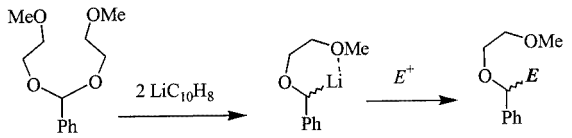
The difficulties of attaining clean reactions under such conditions are hinted at in the literature where low or NMR-estimated yields are frequently reported.[2−4] We considered that by lowering the reaction temperature would significantly improve the stability of the reduction intermediates and thus improve the chemoselectivity. Typical results are shown in Table 1.

Although cleaner, these reductions proceeded rather slowly even though a significant excess of terminal lithium was used (Runs 1−3). Attempts to further promote the reaction by (−)-sparteine as a polar additive (200 mol %) were unsuccessful − the reaction slowed and only racemic **3a** (E = allyl) was attained in reduced yield (Run 3). No reduction was observed in diethyl ether (− 40 °C); difficulty in generating lithium naphthalenide in the absence of THF is known. We believed that the efficiency of the reaction at low temperature could be improved by use of suitable chelate groups built into the acetal substrate **1**. 6-Phenyl-2,5,7,10-tetraoxaundecane (**1b**) was found to be the best. For example, when **1b** was exposed to 7 mol % naphthalene at −90 °C, in the presence of 4−4.5 equiv. of lithium powder extremely clean reduction in just 4−6 h was realised, as evidenced by quenching with water. At these low temperatures no CIPE-induced elimination occurs and **5** may be intercepted by a range of electrophiles (Table 2).

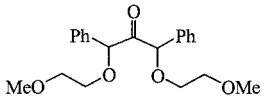
Table 2. $C_{10}H_8$-catalysed reduction of 6-phenyl-2,5,7,10-tetraoxaundecane (**1b**) at −90 °C with lithium followed by reaction with electrophiles



1b **2b** **3b**

Run	E+	Equiv.	Conditions	Yield **3b**/%[a]
1	$H_2C{=}CHCH_2Br$	1.6	40 min, −90 °C	66
2	$H_2C{=}CHCH_2Br$	2	20 min, −90 °C	75
3	NBuBr	1.6	40 min, −90 °C	72
4	NBuBr	2	20 min, −90 °C	89
5	TMSCl	3	20 min, −90 °C	90
6	*t*BuCHO	2	20 min, −90 °C	78 (*syn*/*anti* = 2:1)
7	PhCHO	2	20 min, −90 °C	62 (*syn*/*anti* = 3:1)
8	cyclohexanone	2	20 min, −90 °C	86
9	H_2O	> 5	20 min, −90 °C	90
10	[D_3]MeOD	> 5	20 min, −90 °C	91
11	MeOC(=O)Cl	5	20 min, −90 °C	17 (with 57% **6**)

[a] Isolated yield. Reduction conditions: **1b** (0.17 M in THF), 4−4.5 equiv. Li, 7−8 mol % naphthalene (−90 °C, 6 h). After reaction with the electrophile, the mixture was quenched with water and warmed up.



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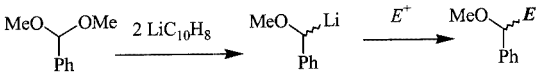
Proton NMR spectra of the crude reaction products (Runs 1−10) revealed only the presence of the desired product **3b**, residual electrophile and traces of naphthalene in all cases except methyl chloroformate (Run 11). For the latter, double addition of the anion leads to the formation of **6** as the major product even when excess chloroformate is used.

Table 1. $C_{10}H_8$-catalysed reduction of (dimethoxymethyl)benzene (**1a**) at −90 °C with lithium followed by reaction with electrophiles



1a **2a** **3a**

Run	Solvent	Conc. **1a**/M (equiv. Li)	$C_{10}H_8$/mol % (time/h)	*E*+ (conditions)	Yield/%[a]
1	THF	0.17 (4.7)	8 (23)	$H_2C{=}CHCH_2Br$ (20 min, −90 °)	69
2	THF	0.17 (5.1)	7 (23)	BuBr (20 min, −90 °)	81
3	THF	0.23 (4.7)	7 (23)[b]	$H_2C{=}CHCH_2Br$ (20 min, −90 °)	53[c]

[a] Isolated yield, sole product by ^{1}H NMR on crude material. [b] 200 mol % (−)-sparteine added. [c] < 2% *ee*.

In condensation of **2b** with aldehydes some modest diastereoselectivity was realised (Runs 6−7).

Potentially, the chelating nature of **2b** and the very low temperatures used in these preparations should increase the configurational stability of the stereogenic centre. Such approaches have proved highly successful in the preparations of chiral organolithium compounds by deprotonation strategies in the presence of chiral additives.[11] However, these deprotonations are normally carried out in diethyl ether or other low-polarity solvents and these are known to strongly inhibit naphthalene-catalysed reductions by lithium. Using naphthalene (15 mol %) as the sole catalyst and an increasing volume fraction of diethyl ether in an Et_2O/THF mixture for the reduction of **1b** with lithium (6 equiv.) leads to a gradual reduction in the reaction efficiency. At a 5:1 Et_2O/THF mixture no reduction is observed. Similar effects are noted for DME/Et_2O mixtures. Because of the very mild conditions associated with this route some chiral additives (binaphthalenes, chiral diamides and oxazolines) bearing pendent naphthalene units were screened, but no significant asymmetric induction was realised.

Conclusion

Approaches to improving the chemoselectivity in naphthalene-catalysed reduction of aromatic acetals have been developed. Both the use of low temperature reduction conditions and employing substrates containing chelate functions improve the utility of the reaction and together these fashion final alkylated products cleanly.

Experimental Section

General: Infrared spectra were recorded using a Nicolet Avatar 320 FT-IR infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with Bruker (AM, 400, AV 400) and JEOL 270 spectrometers at ambient temperature using tetramethylsilane as standard; *J* values are given in Hz. Mass spectra were obtained with a VG Autospec or Micromass 70 E (electron impact, EI, 70 eV) mass spectrometer. CI (NH_3) and ES spectra were measured at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea. Melting points were recorded using a Mel-Temp II and are not corrected. Tetrahydrofuran (THF) and diethyl ether were distilled from Na/benzophenone under argon. Catalytic reactions were carried out under argon using standard Schlenk techniques. Column chromatography and TLC analyses were performed on silica gel Prola 60, 35−75 μm (200−400 mesh) and Merck aluminium sheets 60 F_{254}, respectively. Lithium powder (Merck Eurolab) and all other reagents were used as supplied. Compound **1a** is commercial (Lancaster Synthesis).

Substrate Preparations

6-Phenyl-2,5,7,10-tetraoxaundecane (1b): This compound was prepared using standard techniques (Dean−Stark trap); 5 mL (49.3 mmol) of benzaldehyde and 20 mL of methoxyethanol were solved in 70 mL of benzene and a catalytic amount (300 mg) of *para*-toluenesulfonic acid was added. After usual workup, the crude product was purified by bulb-to-bulb distillation (150−160 °C)$_{0.7}$. Yield 10.0 g, 85%. ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.39 (s, 6 H, 2 × OMe), 3.55−3.57 (m, 4 H, 2 × OCH_2), 3.58−3.72 (m, 4 H, 2 × OCH_2), 5.69 (s, 1 H, PhC*H*), 7.29−7. 38 (m, 3 H, CH-arom.), 7.50−7.52 (m, 2 H, CH-arom.). ^{13}C NMR ($CDCl_3$, 67.8 MHz): δ = 58.5 (OMe), 63.7 (OCH_2), 71.4 (OCH_2), 101.0 (Ph*C*H), 126.4 (CH), 127.7 (CH), 127.9 (CH), 137.8 (C_q) ppm. IR (thin film): $\tilde{\nu}$ = 2926 s, 2877 s, 1451 m, 1104 s, 1063 s cm^{-1}. MS (EI): *m*/*z* (%) = 240 (1.5) [M^+], 165 (100), 59 (98). HRMS, EI: calcd. for $C_{13}H_{20}O_4$ [M^+] 240.1361; found 240.1359.

General Procedure for the Reductions: To a stirred suspension of Li (4−4.5 equiv.) in 3 mL of THF was added naphthalene (10 mg, 7 mol %) at room temp. After obtaining a dark green colour, the mixture was diluted with 3 mL of THF and cooled to −90 °C. The acetal (1 mmol) was added dropwise and stirring was continued for 6 h (**1b**) or 23 h (**1a**). The corresponding electrophiles (2−5 equiv.) were added and the mixture was stirred for 20 min at the same temperature. The reaction mixture was quenched with half-saturated NH_4Cl, warmed up to room temperature and worked up as usual. The resulting crude products were purified by flash chromatography [petroleum ether (b.p. 40−60 °C)/diethyl ether, 3:1−2:1].

(1-Methoxybut-3-enyl)benzene (3a, E = $CH_2CH{=}CH_2$):[12] Yield 115 mg, 69%. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.44 (dddt, *J* = 14, 8, 6, 1.5 Hz, 1 H), 2.58 (dddt, *J* = 14, 7, 6, 1.5 Hz, 1 H), 3.25 (s, 3 H, OMe), 4.17 (dd, *J* = 8, 7 Hz, 1 H, PhC*H*), 5.04 (ddt, *J* = 11, 2, 1.5 Hz, 1 H, =CH_2), 5.08 (ddt, *J* = 17, 2, 1.5 Hz, 1 H, =CH_2), 5.70 (ddt, *J* = 17, 11, 6 Hz, 1 H, =CH), 7.27−7.41 (m, 5 H, CH-arom.) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 42.4 (CH_2), 56.6 (OMe), 83.6 (Ph*C*H), 116.8 (=CH_2), 126.7 (CH), 127.5 (CH), 128.3 (CH), 134.7 (=CH), 141.6 (C_q) ppm. IR (thin film): $\tilde{\nu}$ = 2979 m, 2935 m, 2820 m, 1454 m, 1100 s, 701 s cm^{-1}.

(1-Methoxypentyl)benzene (3a, E = *n*Bu):[12] Yield 144 mg, 81%. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (t, *J* = 7 Hz, 3 H, CH_2*Me*), 1.20−1.43 (m, 4 H), 1.58−1.68 (m, 1 H), 1.77−1.87 (m, 1 H), 3.22 (s, 3 H, OMe), 4.10 (dd, *J* = 7, 6 Hz, 1 H, PhC*H*), 7.27−7.38 (m, 5 H, CH-arom.) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 13.9 (CH_2*Me*), 22.6 (CH_2), 27.9 (CH_2), 37.8 (CH_2), 56.5 (OMe), 84.1 (Ph*C*H), 126.6 (CH), 127.3 (CH), 128.2 (CH), 142.5 (C_q) ppm. IR (thin film): $\tilde{\nu}$ = 2956 s, 2932 s, 2859 m, 1453 m, 1097 s cm^{-1}.

[(2-Methoxyethoxy)phenylmethyl]trimethylsilane (3b, E = TMS): Yield 215 mg, 90%. ^1H NMR ($CDCl_3$, 400 MHz): δ = −0.57 (s, 9 H, $SiMe_3$), 3.34−3.39 (m, 1 H, OCH_2), 3.38 (s, 3 H, OMe), 3.50−3.60 (m, 2 H, OCH_2), 3.68−3.73 (m, 1 H, OCH_2), 4.11 (s, 1 H, PhC*H*), 7.14−7.18 (m, 3 H, CH-arom.), 7.26−7.31 (m, 2 H, CH-arom.) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = −4.0 ($SiMe_3$), 59.0 (OMe), 70.4 (OCH_2), 72.1 (OCH_2), 78.8 (CH), 125.5 (CH), 125.7 (CH), 141.5 (C_q) ppm. IR (thin film): $\tilde{\nu}$ = 2955 m, 2898 m, 1247 s, 1088 s, 869 s, 840 s cm^{-1}. MS (CI): *m*/*z* (%) = 256 (52) [$M^+ + NH_4$], 179 (100). HRMS, ES: calcd. for $C_{13}H_{26}NO_2Si$ [$M + NH_4^+$] 256.1733, found 256.1735.

1-(2-Methoxyethoxy)-3,3-dimethyl-1-phenylbutan-2-ol (3b, E = Me_3CCHOH): Yield 197 mg, 78% (*syn*/*anti* = 2:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.90 (s, 9 H, *t*Bu, syn), 0.94 (s, 9 H, *t*Bu, anti), 3.34 (s, 3 H, OMe), 3.38−3.59 (m, 5 H), 4.30 (d, *J* = 7 Hz, 1 H, PhC*H*), 4.35 (d, *J* = 4 Hz, 1 H, PhC*H*), 7.27−7.41 (m, 5 H, CH-arom.) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) = 26.5 (*t*Bu), [34.4, 34.7] (*C*Me_3), 58.6 (OMe) [67.3, 67.4] (OCH_2), [71.6, 71.7] (OCH_2), [80.3, 81.3] (OCH), [81.9, 83.4] (OCH), 127.2 (CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), [139.4, 140.7] (C_q) ppm. IR (thin film): $\tilde{\nu}$ = 3457 (OH), 2952 s, 2871 s, 1453 m, 1094 s cm^{-1}. MS (CI): *m*/*z* (%) = 270 (80) [$M^+ + NH_4$], 193 (100). HRMS, ES: calcd. for $C_{15}H_{28}NO_3$ [$M^+ + NH_4$] 270.2069, found 270.2067.

1-[(2-Methoxyethoxy)phenylmethyl]cyclohexanol [3b, E = C(CH$_2$)$_5$(OH)]: Yield 227 mg, 86%. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.0−1.8 (m, 11 H), 2.46 (br. s, 1 H), 3.37 (s, 3 H, OMe), 3.4−3.63 (m, 4 H, 2 × OCH$_2$) 4.11 (s, 1 H, PhC*H*), 7.28−7.40 (m, 5 H, CH-arom.) ppm. ^{13}C NMR (CDCl$_3$, 67.8 MHz): δ = 21.2 (CH$_2$), 21.4 (CH$_2$), 25.7 (CH$_2$), 31.8 (CH$_2$), 34.0 (CH$_2$), 58.7 (OMe), 68.5 (OCH$_2$), 71.7 (OCH$_2$), 73.2 (C$_q$), 89.2 (CH), 127.5 (CH), 127.7 (CH), 128.3 (CH), 138.0 (C$_q$) ppm. IR (thin film): $\tilde{\nu}$ = 3453 (OH), 2930 s, 2859 s, 1450 s, 1093 s cm^{-1}. MS (EI): *m*/*z* (%) = 264 (10) [M$^+$], 247 (100). HRMS, EI: calcd. for C$_{16}$H$_{24}$O$_3$ [M$^+$] 264.1725, found 264.1726.

2-(2-Methoxyethoxy)-1,2-diphenylethanol [3b, E = CHC$_6$H$_4$(OH)]: Yield 169 mg, 62% (*syn*/*anti* = 3:1). ^{1}H NMR (CDCl$_3$, 400 MHz): *syn*: δ = 2.85 (d, *J* = 4 Hz, 1 H, OH), 3.34 (s, 3 H, OMe), 3.40−3.70 (m, 4 H, 2 × OCH$_2$), 4.54 (d, *J* = 5 Hz, 1 H, PhC*H*), 4.96 (dd, *J* = 5, 4 Hz, 1 H, PhC*H*), 7.11−7.27 (m, 10 H, CH-arom.) ppm. *anti*: 3.41 (s, 3 H, OMe), 3.49−3.86 (m, 4 H, 2 × OCH$_2$) 3.86 (s, 1 H, OH), 4.25 (d, *J* = 9 Hz, PhC*H*), 4.69 (d, *J* = 9 Hz, PhC*H*), 6.99−7.05 (m, 4 H, CH-arom.), 7.15−7.22 (m, 6 H, CH-arom.) ppm. ^{13}C NMR (CDCl$_3$, 100.6 MHz): *syn*: δ = 58.7 (OMe), 68.3 (OCH$_2$), 71.7 (OCH$_2$), 76.6 (CH), 86.2 (CH), 126.9 (CH), 127.1 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 137.4 (C$_q$), 140.1 (C$_q$) ppm. *anti*: ^{13}C NMR (CDCl$_3$, 67.8 MHz): δ = 58.9 (OMe), 68.4 (OCH$_2$), 71.7 (OCH$_2$), 78.6 (CH), 88.3 (CH), 127.3 (CH), 127.60 (CH), 127.65 (CH), 127.7 (CH), 127.9 (CH), 137.0 (C$_q$), 139.1 (C$_q$) ppm. IR (thin film): $\tilde{\nu}$ = 3431 (OH), 3030 m, 2877 s, 1452 s, 1092 s cm^{-1}. MS (CI): *m*/*z* (%) = 290 (100) [M$^+$ + NH$_4$], 272 (35) [M$^+$], 255 (36), 213 (22). HRMS, ES: calcd. for C$_{17}$H$_{24}$NO$_3$ [M$^+$ + NH$_4$] 290.1756, found 290.1754.

[(2-Methoxyethoxy)methyl]benzene (3b, E = H):[13] Yield 149 mg, 90%. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 3.40 (s, 3 H, OMe), 3.57−3.64 (m, 4 H, 2 × OCH$_2$), 4.58 (s, 2 H, PhC*H*$_2$), 7.28−7.36 (m, 5 H, CH-arom.) ppm. ^{13}C NMR (CDCl$_3$, 67.8 MHz): δ = 58.8 (OMe), 69.1 (OCH$_2$), 71.8 (OCH$_2$), 73.1 (Ph*C*H$_2$), 127.4 (CH), 127.6 (CH), 128.1 (CH), 138.0 (C$_q$) ppm. IR (thin film): $\tilde{\nu}$ = 2873 m, 1453 m, 1102 s cm^{-1}.

[α-D][2-(Methoxyethoxy)methyl]benzene (3b, E = D): Yield 152 mg, 91%. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 3.41 (s, 3 H, OMe), 3.57−3.65 (m, 4 H, 2 × OCH$_2$), 4.56 (t, *J* = 1.6 Hz, 1 H, PhC*H*D), 7.28−7.36 (m, 5 H, CH-arom.) ppm. ^{13}C NMR (CDCl$_3$, 100.6 MHz): δ = 58.9 (OMe), 69.1 (OCH$_2$), 71.8 (OCH$_2$), [72.5, 72.8, 73.0] (Ph*C*HD), 127.4 (CH), 127.6 (CH), 128.2 (CH), 138.0 (C$_q$) ppm. IR (thin film): $\tilde{\nu}$ = 2874 m, 1451 m, 1108 s cm^{-1}. MS (EI): *m*/*z* (%) = 167 (41) [M$^+$], 108 (30), 92 (100). HRMS, EI: calcd. for C$_{10}$H$_{13}$DO$_2$ [M$^+$] 167.1056, found 167.1056.

[1-(2-Methoxyethoxy)but-3-enyl]benzene (3b, E = CH$_2$CH=CH$_2$): Yield 156 mg, 75%. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 2.42 (dddt, *J* = 14, 7, 6, 1.5 Hz, 1 H), 2.64 (dddt, *J* = 14, 7, 7, 1.5 Hz, 1 H), 3.37 (s, 3 H, OMe), 3.40−3.60 (m, 4 H, 2 × OCH$_2$), 4.30 (dd, *J* = 7, 6 Hz, 1 H, PhC*H*), 5.01 (ddt, *J* = 10, 2, 1.5 Hz, 1 H, =CH$_2$), 5.04 (ddt, *J* = 17, 2, 1.5 Hz, 1 H, =CH$_2$), 5.77 (ddt, *J* = 17, 10, 7 Hz, 1 H, =CH), 7.25−7.38 (m, 5 H, CH-arom.) ppm. ^{13}C NMR (CDCl$_3$, 67.8 MHz): δ = 42.4 (CH$_2$), 58.8 (OMe), 67.8 (OCH$_2$), 71.8 (OCH$_2$), 82.4 (Ph*C*H), 116.7 (=CH$_2$), 126.6 (CH), 127.4 (CH), 128.2 (CH), 134.6 (=CH), 141.7 (C$_q$) ppm. IR (thin film): $\tilde{\nu}$ = 2873 m, 1452 m, 1100 s cm^{-1}. MS (CI): *m*/*z* (%) = 224 (65) [M$^+$ + NH$_4$], 147.9 (22), 130 (100). HRMS, ES: calcd. for C$_{13}$H$_{22}$NO$_2$ [M$^+$ + NH$_4$] 224.1651, found 224.1658.

[1-(2-Methoxyethoxy)pentyl]benzene (3b, E = *n*Bu): Yield 198 mg, 89%. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.87 (t, *J* = 7 Hz, 3 H, CH$_2$*Me*), 1.15−1.45 (m, 4 H), 1.58−1.68 (m, 1 H), 1.81−1.92 (m, 1 H), 3.37 (s, 3 H, OMe), 3.38−3.55 (m, 4 H, 2 × OCH$_2$), 4.20 (dd, *J* = 7, 6 Hz, PhC*H*), 7.25 −7.38 (m, 5 H, CH-arom.) ppm. ^{13}C NMR (CDCl$_3$, 67.8 MHz): δ = 13.9 (CH$_2$*Me*), 22.5 (CH$_2$), 27.9 (CH$_2$), 37.9 (CH$_2$), 58.8 (OMe), 67.8 (OCH$_2$), 71.9 (OCH$_2$), 82.8 (Ph*C*H), 126.6 (CH), 127.2 (CH), 128.2 (CH), 142.7 (C$_q$) ppm. IR (thin film): $\tilde{\nu}$ = 2930 s, 2886 s, 1452 m, 1099 s cm^{-1}. MS (EI): *m*/*z* (%) = 222 (3) [M$^+$], 165 (100), 91 (39), 59 (59). HRMS, EI: calcd. for C$_{14}$H$_{22}$O$_2$ [M$^+$] 222.1620, found 222.1627.

Methyl 2-(2-Methoxyethoxy)-2-phenylacetate (3b, E = CO$_2$Me): Yield 38 mg, 17%. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 3.37 (s, 3 H, OMe), 3.59−3.71 (m, 4 H, 2 × OCH$_2$), 3.72 (s, 3 H, COOMe), 4.99 (s, 1 H, PhC*H*), 7.33−7.38 (m, 3 H, CH-arom.), 7.45−7.47 (m, 2 H, CH-arom.) ppm. ^{13}C NMR (CDCl$_3$, 100.6 MHz): δ = 52.1 (CO-O*Me*), 58.9 (OMe), 68.9 (OCH$_2$), 71.8 (OCH$_2$), 81.3 (Ph*C*H), 127.2 (CH), 128.5 (CH), 128.6 (CH), 136.3 (C$_q$), 171.2 (*C*OOMe) ppm. IR (thin film): $\tilde{\nu}$ = 2926 m, 2880 m, 1751 s (C=O), 1113 s cm^{-1}. MS (EI): *m*/*z* (%) = 224 (4) [M$^+$], 165 (100), 59 (96). HRMS, EI: calcd. for C$_{12}$H$_{16}$O$_4$ [M$^+$] 224.1048, found 224.1043.

6,8-Diphenyl-2,5,9,12-tetraoxatridecan-7-one (6): Yield 204 mg, 57%. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 3.30 (s, 3 H, OMe), 3.32 (s, 3 H, OMe), 3.35−3.58 (m, 8 H, 4 × OCH$_2$), 5.15 (s, 2 H, 2 × PhC*H*), 7.17−7.42 (m, 10 H, CH-arom.) ppm. ^{13}C NMR (CDCl$_3$, 100.6 MHz): δ = 58.8 (OMe), [68.4, 68.5] (OCH$_2$), [71.6, 71.7] (OCH$_2$), 84.7 (Ph*C*H), 128.03 (CH), 128.09 (CH), 128.4 (CH), [135.3, 135.6] (C$_q$), [203.9, 204.3] (C=O) ppm. IR (thin film): $\tilde{\nu}$ = 2924 m, 2876 m, 1731 s (C=O), 1453 m, 1109 s cm^{-1}. MS (CI): *m*/*z* (%) = 376 (100) [M$^+$ + NH$_4$], 302 (78), 228 (25), 164 (40). HRMS, ES: calcd. for C$_{21}$H$_{30}$NO$_5$ [M$^+$ + NH$_4$] 376.2124, found 376.2123.

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[1] Reviews: [1a] N. L. Holy, *Chem. Rev.* **1974**, *74*, 243−277. [1b] D. J. Ramón, M. Yus, *Eur. J. Org. Chem.* **2000**, 225−237.
[2] J. F. Gil, D. J. Ramón, M. Yus, *Tetrahedron* **1993**, *49*, 9535−9546.
[3] U. Azzena, G. Melloni, L. Pisano, B. Sechi, *Tetrahedron Lett.* **1994**, *35*, 6759−6762.
[4] U. Azzena, L. Pilo, E. Piras, *Tetrahedron* **2000**, *56*, 3775−3780.
[5] U. Schöllkopf, *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 763−773.
[6] Reviews: D. Hoppe, T. Hense, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282−2316.
[7] F. Hammerschmidt, A. Hanninger, B. P. Simov, H. Völlenkle, A. Werner, *Eur. J. Org. Chem.* **1999**, 3511−3518.
[8] M. J. Siwek, J. R. Green, *Synlett* **1996**, 560−562.
[9] For an alternative approach using BF$_3$·OEt$_2$ activation of acetals in the presence of chiral lithium reagents, see: P. Müller, P. Nury, *Org. Lett.* **2000**, *2*, 2845−2847.
[10] P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356−353.
[11] For recent examples see: [11a] D. J. Pippel, G. A. Weisenburger, N. C. Faibish, P. Beak, *J. Am. Chem. Soc.* **2001**, *123*, 4919−4927. [11b] X. Li, L. B. Schenkel, M. C. Kozlowski, *Org. Lett.* **2000**, *2*, 875−878. [11c] E.-U. Würthwein, K. Behrens, D. Hoppe, *Chem. Eur. J.* **1999**, *5*, 3459−3463. [11d] Y. S. Park, M. L. Boys, P. Beak, *J. Am. Chem. Soc.* **1996**, *118*, 3757−3758.
[12] J. J. Gajewski, W. Bocian, N. J. Harris, L. P. Olson, J. P. Gajewski, *J. Am. Chem. Soc.* **1999**, *121*, 326−334.
[13] M. Sheehan, R. J. Spangler, C. Djerassi, *J. Org. Chem.* **1971**, *36*, 3526−3532.

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