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Reductive lithiation of alkoxy-substituted benzyl methyl ethers and connection with cross-coupling reactions

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Abstract—2-and 4-Ethoxymethoxybenzyl methyl ethers were employied as useful starting materials for the synthesis of 1,2- or 1,4-dicarbo-substituted benzenes. The proposed reaction sequence involves connection between the reductive lithiation of benzyl alkyl ethers and the metal-catalyzed cross-coupling reaction of aromatic triflates.

1. Introduction

The arene-catalyzed reductive lithiation of benzyl alkyl ethers is a highly regioselective reaction finding application in the generation of a wide array of benzyllithium organometals.[1–5] Interestingly, the presence of strong electron donor substituents on the aromatic ring does not affect the efficiency of this procedure.[1,4] Indeed, this reaction shows unique features in the generation of stable solutions of methoxy-substituted benzyllithium derivatives both in terms of regioselectivity and mildness of reaction conditions.[6–8]

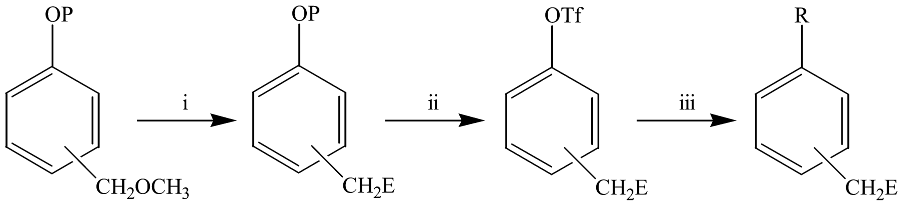
With the aim to expand the synthetic utility of this reaction, and following our interest in the development of highly regioselective strategies for the synthesis of polysubstituted aromatic compounds, we developed a synthetic protocol leading to the synthesis of dicarbo-substituted benzenes by a reaction sequence connecting our reductive lithiation procedure to well known and versatile reactions, i.e. metal-catalyzed cross-coupling reactions of aromatic triflates.[9–14]

To achieve this result, we investigated the reductive lithiation of acetals of 2- and 4-hydroxy-substituted benzyl ethers, planning to complete the reaction sequence through successive hydrolysis of the acetal group and transformation of the resulting phenols into the corresponding triflates, followed by metal-catalyzed cross-coupling reaction of the last compounds (Scheme 1).

2. Results and discussion

2.1. Synthesis of starting materials

The stability of acetal-type phenolic protecting groups, like the methoxymethyl (MOM), towards reduction with alkali metals, has been seldom investigated. We already reported[15] that this type of protecting groups are stable towards reduction with Na metal in aprotic solvents, whilst it was previously reported that, under similar conditions, phenolic acetals cleave with relatively ease, e.g. more easily than the corresponding methyl ethers.[16] In the present work, we investigated the stability, under arene-catalyzed lithiation conditions, of the ethoxymethyl (EOM) group. This protecting group shows distinct advantages over the above mentioned MOM group. Indeed, phenolic ethoxymethyl



Scheme 1. (i) Reductive lithiation and reaction with an electrophile; (ii) acidic hydrolysis and reaction with $(Tf)_2O$; (iii) metal catalyzed cross-coupling reaction.

Keywords: Ethers; Reduction; Lithiation; Cross-coupling.

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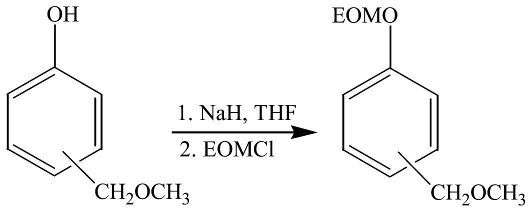
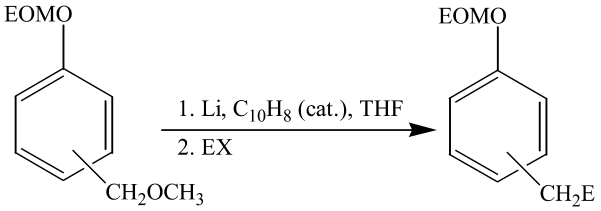
ethers can be easily synthesized reacting phenolates with chloromethyl ethyl ether, which is a cheaper, and much less toxic reagent, than the corresponding chloromethyl methyl ether.

Accordingly, deprotonation of easily available 2- and 4-hydroxybenzyl methyl ether[17] with NaH in dry THF, followed by reaction with chloromethyl ethyl ether, afforded 2- and 4-ethoxymethoxybenzyl methyl ether, **1** and **2**, respectively, in good isolated yields (Scheme 2).



1, 2-CH_2OCH_3, 77%
2, 4-CH_2OCH_3, 85%

Scheme 2. Synthesis of ethoxymethyl ethers of 2-and 4-hydroxybenzyl methyl ether. EOM=$CH_3CH_2OCH_2$.



1, 2-CH_2OCH_3
2, 4-CH_2OCH_3

3-8, 2-CH_2E
9-12, 4-CH_2E

Scheme 3. Reductive lithiation and reaction with electrophiles of ethers **1** and **2**. **3**, **9**: E=H or D; **4**: E=$(CH_3)_2COH$; **5**, **10**: E=PhCHOH; **6**: E=n-C_4H_9; 7: E=n-$C_{12}H_{25}$; **8**, **12**: E=$(CH_3)_2CH$; **11**, E=n-$C_{10}H_{21}$.

Table 1. Reductive lithiation of ethers **1** and **2**, and reaction with electrophiles[a]

Entry	Compoud	T (°C)	t (h)	EX	Product, E=	Yield (%)[b]
1	**1**	0	1.2	H_2O	**3**, H	>95[c]
2	**1**	0	1.2	D_2O	**3**$_d$, D	>95[c]
3	**1**	0	1.2	$(CH_3)_2CO$[d]	**4**, $(CH_3)_2COH$	56
4	**1**	0	1.2	PhCHO	**5**, PhCHOH	67
5	**1**	0	1.2	n-BuBr	**6**, n-BuBr	61[e]
6	**1**	0	1.2	n-$C_{12}H_{25}$Br	**7**, n-$C_{12}H_{25}$	68[e]
7	**1**	0	1.2	i-PrBr	**8**, i-Pr	56[e]
8	**2**	−10	2.0	H_2O	**9**, H	>95[c]
9	**2**	−10	2.0	D_2O	**9**$_d$, D	92[c]
10	**2**	−10	2.0	PhCHO	**10**, PhCHOH	70
11	**2**	−10	2.0	n-$C_{10}H_{21}$Br	**11**, n-$C_{10}H_{21}$	85
12	**2**	−10	2.0	i-PrBr	**12**, i-Pr	72[e]

[a] All reactions were run in the presence of 5 equiv. of Li metal and a catalytic amount of naphthalene (10 mol%).
[b] Isolated yield, unless otherwise indicated.
[c] As determined by ^{1}H NMR spectroscopy.
[d] The electrophile was added at −80 °C.
[e] Yield determined on the corresponding phenol, after acidic hydrolysis of the acetal moiety.

2.2. Reductive metalation reactions

Reductive metalations of ethers **1** and **2** were carried out under Ar with an excess of Li wire in the presence of a catalytic amount of naphthalene in tetrahydrofuran (THF); the results are reported in Table 1 (Scheme 3).

Reaction of a 0.15 M THF solution of ether **1** with 5 equiv. of Li metal in the presence of a catalytic amount of naphthalene (10 mol%) at 0 °C during 1.2 h, furnished a deep red reaction mixture which, upon aqueous work-up, afforded 1-ethoxymethoxy-2-methylbenzene, **3**, in quantitative yield. It is worth noting that we did not observe formation of products of cleavage of the acetal-protecting group, thus showing the stability of the EOM group under reductive electron transfer conditions (Table 1, entry 1). Under these conditions, quantitative formation of an intermediate benzyllithium derivative was evidenced as quenching the reduction mixtures with D_2O (Table 1, entry 2). Similar results were obtained employing di-*tert*-butylbiphenyl (DBB), instead of naphthalene, as an homogeneous electron transfer carrier (not reported in the Table).

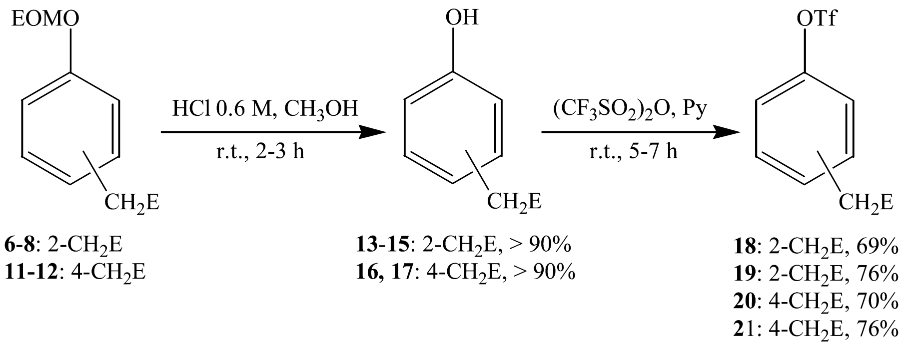
Trapping of this intermediate with acetone or benzaldehyde afforded the corresponding 2-substituted homobenzylic alcohols,[18] **4** and **5**, in satisfactory isolated yields (Table 1, entries 3 and 4).

Furthermore, the organometallic intermediate was successfully trapped with primary or secondary alkyl halides, affording the corresponding 2-alkylated ethoxymethoxybenzenes **6–8** in good yields (Table 1, entries 5–7); these compounds were not isolated, but directly hydrolysed to the corresponding phenols (see below).

Similar results were obtained in the reductive lithiation of ether **2**: reduction of a 0.15 M solution of this substrate with 5 equiv. of Li metal and a 10 mol% of naphtahlene was accomplished within 2.0 h at −10 °C, affording 1-ethoxymethoxy-4-methylbenzene, **9**, in quantitative yield (Table 1, entry 8). It is worth noting that reductive cleavage of ether **2** at 0 °C, under otherwise identical reaction conditions, afforded minor amounts (5–10%) of unindefied by products. Intermediate formation of an organolithium reagent was evidenced by quenching the reduction mixture with D_2O (Table 1, entry 9), and this reactive intermediate was efficiently trapped with benzaldehyde, decylbromide, and 2-bromopropane, to afford the corresponding 4-substituted ethoxymethoxybenzenes **10–12** in good yields (Table 1, entries 10–12); ether **12** was not isolated, but directly hydrolysed to the corresponding phenol (see below).

2.3. Synthesis of triflates

Mild acidic hydrolysis of compounds **6–8** and **11–12** (0.6 M HCl in MeOH, rt) allowed the removal of the protecting group, and the corresponding phenols **13–17** were obtained in almost quantitative yield. According to a known procedure,[14] reaction of phenols **13–17** with trifluoromethanesulfonic anhydride in pyridine afforded triflates **18** (69%), **19** (76%), **20** (70%), **21** (76%), respectively, in good isolated yields (Scheme 4).

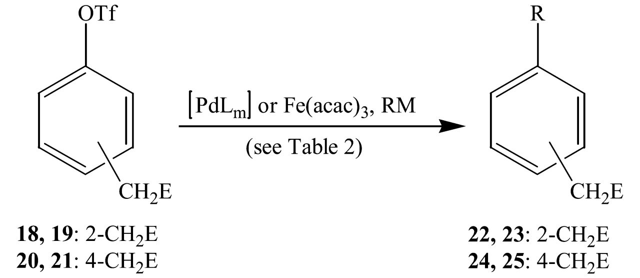


Scheme 4. Synthesis of phenols **13–17**, and triflates **18–21**. **6**, **13**: E=*n*-C_4H_9; **7**, **14**, **18**: E=*n*-$C_{12}H_{25}$; **8**, **12**, **15**, **17**, **19**, **21**: E=$CH(CH_3)_2$; **11**, **16**, **20**: E=*n*-$C_{10}H_{21}$.

Table 2. Cross-coupling reactions

Entry	Compound	Catalyst (mol%)	RM	Solvent	*T* (°C)	*t* (h)	Product [yield (%)][a]
1	**18**	$PdCl_2(PPh_3)_2$ (5)[b]	PhCCH	DMF	90	16	**22**, 70
2	**19**	$Fe(acac)_3$ (10)	$C_6H_{13}MgBr$	THF/NMP	20	16	**23**, 54
3	**20**	$Pd(PPh_3)_4$ (5)[b]	$PhB(OH)_2$	DME	85	5	**24**, 75
4	**21**	$PdCl_2(PPh_3)_2$ (5)[b]	PhCCH	DMF	90	16	**25**, 79

[a] Isolated yield.
[b] The catalyst was added in two portions (see Section 4).



Scheme 5. Cross-coupling reactions. **18**: E=*n*-$C_{12}H_{25}$; **19**, **21**: E=$CH(CH_3)_2$; **20**: E=*n*-$C_{10}H_{21}$; **22**: E=*n*-$C_{12}H_{25}$, R=PhCC, 70%; **23**: E=$CH(CH_3)_2$, R=*n*-C_6H_{13}, 54%; **24**: E=*n*-$C_{10}H_{21}$, R=Ph, 75%; **25**: E=$CH(CH_3)_2$; R=PhCC, 79%.

2.4. Cross-coupling reactions

To test the flexibility of the proposed methodology, triflates **18–21** were allowed to react with different coupling reagents in the presence of a Pd or a Fe catalyst. Reaction conditions and yields are reported in Table 2 (Scheme 5).

Good yields were obtained in cross-coupling reactions involving Pd-catalysed coupling reaction of triflates **18** and **21** with phenylacetylene,[19] as well as of triflate **20** with phenyl boronic acid[20] according to known procedures (Table 2, entries 1, 3 and 4, respectively); as a variation, however, we found that adding the catalyst to the reaction mixtures in two successive portions (see Section 4), significantly improved the yields of these reactions.

Furthermore, a satisfactory yield was obtained coupling triflate 19 with $C_6H_{13}MgBr$ in the presence of 10 mol% of $Fe(acac)_3$ in THF/NMP (Table 2, entry 2), under reaction conditions recently described by Fürstner and co-workers.[9]

3. Conclusions

Our results clearly show that reductive metalation of benzyl alkyl ethers is a particularly mild and practical approach to the generation of stable solutions of alkoxy-substituted benzyllithium derivatives. The observed stability of the EOM group under reductive electron transfer conditions, allowed to develop a synthetic protocol connecting our reductive metalation procedure with metal-catalyzed cross-coupling reactions, thus leading to the regioselective synthesis of 1,2- and 1,4-dicarbo-substituted aromatics, with satisfactory overall yields.

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. Starting materials were of the highest commercial quality and were purified by distillation or recrystallization immediately prior to use. D_2O was 99.8% isotopic purity. THF was distilled from Na/K alloy under N_2 immediately prior to use. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ (unless otherwise indicated) with $SiMe_4$ as internal standard. $CDCl_3$ for recording spectra of EOM-derivatives was stored over K_2CO_3 in the refrigerator. Deuterium incorporation was calculated by monitoring the ^1H NMR spectra of crude reaction mixtures, and comparing the integration of the signal corresponding to protons in the arylmethyl position with that of known signals. Resonances of the CHD protons are usually shifted 0.02–0.04 ppm (δ) upfield relative to the resonances of the corresponding CH_2 protons; the resonances of the arylmethyl CHD carbons appear as triplet (J=18–20 Hz) shifted 0.3–0.5 ppm (δ) upfield relatively to the corresponding arylmethyl CH_2 carbons. IR spectra were recorded on pure samples. Flash chromatography was performed on Merck silica gel 60 (40–63 μm), and TLC analyses on Macherey–Nagel silica gel pre-coated plastic sheets (0.20 mm). Elemental analyses were performed by the microanalytical laboratory of the Dipartimento di Chimica, Università di Sassari.

4.2. Preparation of ethers 1 and 2. General procedure

NaH (1.96 g of a 60% dispersion in mineral oil, 49 mmol) was placed under dry N_2 in a 100 mL two-necked flask equipped with reflux condenser and magnetic stirrer, washed with dry THF (3×10 mL), and suspended in dry THF (30 mL). The mixture was chilled to 0 °C and a solution of the appropriate methyl benzyl ether (5.7 g, 41 mmol) dissolved in THF (15 mL) was added dropwise. The resulting mixture was stirred for 4 h at rt. To this reaction mixture, chilled to 0 °C, a solution of $CH_3CH_2OCH_2Cl$ (4.6 g, 4.5 mL, 49 mmol), dissolved in 10 mL of THF, was slowly added. After stirring overnight at rt, the mixture was quenched by slow dropwise addition of H_2O (20 mL), and the resulting mixture was extracted with Et_2O (3×20 mL). The organic phase was washed brine (10 mL), dried (K_2CO_3) and evaporated. Crude products were purified by distillation, and were characterized as follows.

4.2.1. 1-Ethoxymethoxy-2-methoxymethylbenzene, 1. 6.2 g, 32 mmol, 77%. Colourless oil, bp 125–128 °C/1 mm Hg. (Found: C, 67.12; H, 8.47; $C_{11}H_{16}O_3$ requires C, 67.31; H, 8.23); δ_H (CD_3OD) 1.23 (3H, t, J=7.2 Hz, CH_3), 3.42 (3H, s, OCH_3), 3.76 (2H, q, J=7.2 Hz, OCH_2), 4.53 (2H, s, $ArCH_2$), 5.29 (2H, s, OCH_2O), 7.01 (1H, td, J=7.5, 1.2 Hz, ArH), 7.16 (1H, dd, J=7.5, 1.2 Hz, ArH), 7.27 (1H, td, J=7.5, 1.5 Hz, ArH), 7.37 (1H, dd, J=7.5, 1.5 Hz, ArH); δ_C (DMSO) 6.0, 48.9, 55.8, 61.1, 84.8, 105.7, 113.0, 118.7, 120.4, 120.9, 147.1.

4.2.2. 1-Ethoxymethoxy-4-methoxymethylbenzene, 2. 6.8 g, 35 mmol, 85%. Colourless oil, bp 110–113 °C/1 mm Hg. (Found: C, 67.09; H, 8.50; $C_{11}H_{16}O_3$ requires C, 67.31; H, 8.23); δ_H121(3H, t, J=7.2 Hz, CH_3), 3.36 (3H, s, OCH_3), 3.72 (2H, q, J=7.2 Hz, OCH_2), 4.39 (2H, s, $ArCH_2$), 5.22 (2H, s, OCH_2O), 6.98–7.05 (2H, m, 2×ArH), 7.23–7.28 (2H, m, 2×ArH); δ_C 14.7, 53.3, 60.1, 77.7, 97.8, 114.1, 128.6, 129.5, 161.3.

4.3. Reductive cleavage of ethers 1 and 2, and reaction with electrophiles. General procedure

150 mg of Li wire (22 mg atom, 10 equiv.) was placed under Ar in a 50 mL two-necked flask equipped with reflux condenser and magnetic stirrer, and suspended in THF (5 mL). A catalytic amount of naphthalene (28 mg, 0.22 mmol, 10 mol%) was added to the suspended metal, each metal piece was cut into 2–3 smaller pieces with a spatula, and the mixture stirred until a dark green colour appeared. The mixture was chilled to the reported temperature (Table 1) and a solution of the appropriate ether (0.43 g, 2.2 mmol), dissolved in 5 mL of dry THF, was added dropwise. The mixture was stirred for the reported time (Table 1), and a solution of the appropriate electrophile (1.2 equiv.) in THF (2 mL) was slowly added. After stirring for 30 min, the mixture was quenched by slow dropwise addition of H_2O (10 mL, caution), the cold bath removed, and the resulting mixture extracted with Et_2O (3×10 mL). The organic phase was washed with brine (10 mL), dried (K_2CO_3) and the solvent evaporated.

D_2O quenching was performed by slow dropwise addition of 1 mL of the electrophile, followed by aqueous work-up as described above.

Compounds **6–8** and **12** were not characterized but directly hydrolysed to the corresponding phenols. Other products were characterized as follows.

4.3.1. 1-Ethoxymethoxy-2-methylbenzene, 3. Purified by flash-chromatography (petroleum ether/AcOEt/Et_3N=7:3:1), colourless oil; R_f=0.75 (petroleum ether/AcOEt/Et_3N=7:3:1); bp 55 °C/1 mm Hg (lit.[21] bp 86–87 °C/8 mm Hg); δ_H122 (3H, t, J=6.9 Hz, CH_3), 2.23 (3H, s, $ArCH_3$), 3.72 (2H, q, J=6.9 Hz, CH_2), 5.24 (2H, s, CH_2), 6.90 (1H, td, J=7.5, 1.5 Hz, ArH), 7.03–7.12 (1H, m, ArH), 7.12–7.16 (2H, m, 2×ArH); δ_C 15.1, 16.3, 64.1, 93.2, 113.9, 121.4, 126.8, 130.7, 157.9.

4.3.2. 1-(2-Ethoxymethoxyphenyl)-2-methylpropan-2-ol, 4. Purified by flash-chromatography (CH_2Cl_2/AcOEt/Et_3N=9.8:0.2:0.1), colourless oil. (Found: C, 69.43; H, 9.12; $C_{13}H_{20}O_3$ requires C, 69.60; H, 9.00); R_f=0.30 (CH_2Cl_2/AcOEt/Et_3N=9.8:0.2:0.1); bp 105 °C/1 mm Hg; ν_{max} 3420 cm^{-1}; δ_H 1.23 (6H, s, 2×CH_3), 1.23 (3H, t, J=7.2 Hz, CH_3), 2.39 (1H, bs, OH), 2.87 (2H, s, $ArCH_2$), 3.72 (2H, q, J=7.2 Hz, CH_2), 5.25 (2H, s, OCH_2O), 6.93–6.99 (1H, m, ArH), 7.13–7.23 (3H, m, 3×ArH); δ_C 15.1, 29.4, 43.7, 64.5, 71.6, 93.5, 114.3, 121.6, 127.1, 127.9, 132.5, 155.8.

4.3.3. 2-(2-Ethoxymethoxyphenyl)-1-phenylethanol, 5. Purified by flash-chromatography (CH_2Cl_2/AcOEt/Et_3N=9:1:0.1), colourless oil. (Found: C, 74.76; H, 7.63; $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40); R_f=0.73 (CH_2Cl_2/AcOEt/Et_3N=9:1:0.1); bp 160 °C/1 mm Hg; ν_{max} 3410 cm^{-1}; δ_H 1.26 (3H, t, J=6.9 Hz, CH_3), 2.43 (1H, bs, OH), 3.01 (1H, dd, J=13.7, 8.4 Hz, ArCH), 3.14 (1H, dd, J=13.7, 4.2 Hz, ArCH), 3.75 (2H, q, J=6.9 Hz, CH_2), 4.98 (1H, dd, J=8.4, 4.2 Hz, ArCHO), 5.24 (1H, d, J=6.9 Hz, OCHO), 5.27 (1H, d, J=6.9 Hz, OCHO), 6.94 (1H, td, J=7.5, 1.5 Hz, ArH), 7.09–7.16 (2H, m, 2×ArH), 7.19–7.40 (6H, m, 6×ArH); δ_C 15.1, 41.0, 64.4, 74.3, 93.3, 114.1, 121.7, 125.7, 127.2, 127.3, 128.0, 128.2, 131.5, 144.4, 155.6.

4.3.4. 1-Ethoxymethoxy-4-methylbenzene, 9. Purified by flash-chromatography (petroleum ether/AcOEt/Et_3N=8:2:1), colourless oil; R_f=0.69 (petroleum ether/AcOEt/Et_3N=8:2:1); bp 70 °C/1 mm Hg (lit.[22] bp 78 °C/4.5 mm Hg); δ_H121(3H, t, J=6.8 Hz, CH_3), 2.29 (3H, s, $ArCH_3$), 3.72 (2H, q, J=6.8 Hz, CH_2), 5.18 (2H, s, OCH_2O), 6.92–6.96 (2H, m, 2×ArH), 7.06–7.10 (2H, m, 2×ArH).

4.3.5. 2-(4-Ethoxymethoxyphenyl)-1-phenylethanol, 10. Purified by flash-chromatography (petroleum ether/CH_2Cl_2/Et_3N=8:2:0.1), colourless oil. (Found: C, 74.81; H, 7.68; $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40); R_f=0.68 (petroleum ether/CH_2Cl_2/Et_3N=8:2:0.1); ν_{max} 3450 cm^{-1}; δ_H 1.23 (3H, t, *J*=6.8 Hz, CH_3), 2.03 (1H, bs, OH), 2.92 (1H, dd, *J*=13.6, 8.4 Hz, ArCH), 2.99 (1H, dd, *J*=13.6, 4.8 Hz, ArCH), 3.73 (2H, q, *J*=6.8 Hz, CH_2), 4.82–4.89 (1H, m, CHO), 5.20 (2H, s, OCH_2O), 6.96–7.01 (2H, m, 2xArH), 7.09–7.14 (2H, m, 2×ArH), 7.26–7.36 (5H, m, 5×ArH); δ_C 15.1, 45.2, 64.1, 75.3, 93.2, 116.3, 125.9, 127.5, 128.4, 130.4, 131.2, 143.8, 156.2.

4.3.6. 1-Ethoxymethoxy-4-undecylbenzene, 11. Purified by flash-chromatography (petroleum ether/Et_3N=10:0.1), colourless oil. (Found: C, 78.12; H, 11.46; $C_{20}H_{34}O_2$ requires C, 78.36; H, 11.20); R_f=0.27 (petroleum ether/ Et_3N=10:0.1); δ_H 0.89 (3H, t, *J*=6.6 Hz, CH_3), 1.23 (3H, t, *J*=7.2 Hz, CH_3), 1.24–1.36 (16H, m, 8×CH_2), 1.52–1.64 (2H, m, CH_2), 2.55 (2H, t, *J*=8.1 Hz, ArCH_2), 3.74 (2H, q, *J*=7.2 Hz, CH_2O), 5.20 (2H, s, OCH_2O), 6.94–6.99 (2H, m, 2×ArH), 7.06–7.13 (2H, m, 2×ArH); δ_C 14.1, 15.1, 22.7, 29.3, 29.3, 29.5, 29.6, 29.6, 29.7, 31.7, 31.9, 35.1, 64.1, 93.3, 116.1, 129.2, 136.3, 155.4.

4.4. Acidic hydrolysis of acetals 6–8 and 11–12. General procedure

The appropriate acetal (2–5 mmol) was added under Ar to a stirred 0.6 M solution of HCl in MeOH [obtained by adding AcCl (1 mL) to MeOH (20 mL)] chilled to 0 °C. The mixture was stirred at rt for 2–3 h, until complete disappearence of the starting material, as determined by TLC. The mixture was diluted with H_2O (20 mL), and the MeOH evaporated under reduced pressure. The resulting mixture was extracted with Et_2O (4×20 mL), and the organic phase dried ($CaCl_2$) and evaporated. Crude products were purified by flash chromatography and characterized as follows.

4.4.1. 2-Pentylphenol, 13. Purified by flash-chromatography (petroleum ether/AcOEt/AcOH=9:1:0.2), colourless oil. (Found: C, 80.27; H, 10.06; $C_{11}H_{16}O$ requires C, 80.42; H, 9.82); R_f=0.34 (petroleum ether/AcOEt/AcOH= 9:1:0.2); ν_{max} 3410 cm^{-1}; δ_H 0.89 (3H, t, *J*=6.9 Hz, CH_3), 1.24–1.44 (4H, m, 2×CH_2), 1.56–1.70 (2H, m, CH_2), 2.59 (2H, t, *J*=8.1 Hz, ArCH_2), 4.67 (bs, 1H, OH), 6.75 (1H, dd, *J*=7.8, 1.2 Hz, ArH), 6.86 (1H, td, *J*=7.5, 1.2 Hz, ArH), 7.04–7.15 (2H, m, 2×ArH); δ_C 14.0, 22.5, 29.4, 29.8, 31.7, 115.1, 120.7, 126.9, 128.5, 130.1, 153.3.

4.4.2. 2-Tridecylphenol, 14. Purified by flash-chromatography (petroleum ether/AcOEt/AcOH=9:1:0.2), colourless oil, which solidifies upon standing; R_f=0.41 (petroleum ether/AcOEt/AcOH=9:1:0.2); mp 43–46 °C (lit.[23] 42.5–43 °C); ν_{max} 3380 cm^{-1}; δ_H 0.87 (3H, t, *J*=6.9 Hz, CH_3), 1.18–1.40 (20H, m, 10×CH_2), 1.60 (2H, quint, *J*=7.5 Hz, CH_2), 2.59 (2H, t, *J*=7.5 Hz, ArCH_2), 4.67 (1H, bs, OH), 6.75 (1H, dd, *J*=8.1, 0.9 Hz, ArH), 6.86 (1H, td, *J*=7.2, 0.9 Hz, ArH), 7.02–7.14 (2H, m, 2×ArH); δ_C 14.1, 22.7, 29.4, 29.6, 29.6, 29.7, 29.8, 29.9, 31.9, 115.1, 120.7, 127.0, 128.5, 130.1, 153.3.

4.4.3. 2-(2-Methyl)propylphenol, 15. Purified by flash-chromatography (petroleum ether/AcOEt=9.5:0.5), colourless oil, bp 45–50 °C/1 mm Hg (lit.[24] bp 57 °C/10 mm Hg). (Found: C, 80.12; H, 9.76; $C_{10}H_{14}O$ requires C, 79.94; H, 9.41); R_f=0.28 (petroleum ether/AcOEt=9.5:0.5); ν_{max} 3380 cm^{-1}; δ_H 0.92 (6H, d, *J*=6.8 Hz, 2×CH_3), 1.26 (1H, bs, OH), 1.92 (1H, n, *J*=6.8 Hz, CH), 2.47 (2H, d, *J*= 6.8 Hz, CH_2), 6.74–6.76 (1H, dd, *J*=8.0, 1.2 Hz, ArH), 6.85 (1H, td, *J*=7.6, 1.2 Hz, ArH), 7.05–7.09 (2H, m, ArH).

4.4.4. 4-Undecylphenol, 16. Purified by flash-chromatography (petroleum ether/AcOEt/AcOH=9:1:0.2), colourless oil which solidifies upon standing, mp 52–54 °C (lit.[23] mp 56.5–57 °C); R_f=0.34 (petroleum ether/AcOEt/AcOH= 9:1:0.2); ν_{max} 3350 cm^{-1}; δ_H 0.89 (3H, *J*=6.8 Hz, CH_3), 1.22–1.34 (16H, m, 8×CH_2), 1.53–1.62 (2H, m, CH_2), 2.53 (2H, t, *J*=8.0 Hz, ArCH_2), 4.48 (1H, bs, OH), 6.72–6.78 (2H, m, 2×ArH), 7.02–7.07 (2H, m, 2×ArH); δ_C 14.1, 22.7, 29.2, 29.3, 29.5, 29.6, 29.6, 29.7, 31.7, 31.9, 35.0, 115.0, 129.4, 135.2, 153.3.

4.4.5. 4-(2-Methyl)propylphenol, 17. Purified by flash-chromatography (petroleum ether/AcOEt=9:1), colourless oil, which solidifies upon standing; bp 70–75 °C/1 mm Hg (lit.[25] bp 131 °C/20 mm Hg) R_f=0.28 (petroleum ether/ AcOEt=9:1); ν_{max} 3420 cm^{-1}; δ_H 0.87 (6H, d, *J*=7.2 Hz, 2×CH_3), 1.25 (1H, bs, OH), 1.79 (1H, n, *J*=7.2 Hz, CH), 2.39 (2H, d, *J*=7.2 Hz, ArCH_2), 6.72–6.77 (2H, m, 2×ArH), 6.98–7.24 (2H, m, 2×ArH).

4.5. Synthesis of trifluoromethanesulfonates 18–21. General procedure

These compounds were synthesized according to a general procedure described in Ref. 14. Crude products were purified by flash chromatography and characterized as follows.

4.5.1. 2-Trydecylphenyl trifluoromethanesulfonate, 18. Purified by flash-chromatography (petroleum ether), colourless oil, bp >150 °C/1 mm Hg. (Found: C, 58.57; H, 7.93; $C_{20}H_{31}F_3O_3S$ requires C, 58.79; H, 7.66); R_f=0.48 (petroleum ether); δ_H 0.90 (3H, t, *J*=6.6 Hz, CH_3), 1.21–1.39 (20H, m, 10×CH_2), 1.58–1.65 (2H, m, CH_2), 2.71 (2H, t, *J*=8.1 Hz, ArCH_2), 7.23–7.36 (4H, m, 4×ArH); δ_C 14.1, 22.7, 29.3, 29.5, 29.6, 29.6, 29.7, 29.9, 30.0, 31.9, 118.6 (q, *J*=318 Hz), 121.2, 127.6, 128.2, 131.2, 135.5, 148.0.

4.5.2. 2-(2-Methylpropyl)phenyl trifluoromethanesulfonate, 19. Purified by flash-chromatography (petroleum ether), colourless oil, bp 80–85 °C/1 mm Hg. (Found: C, 46.61; H, 4.91; $C_{11}H_{13}F_3O_3S$ requires C, 46.80; H, 4.65); R_f=0.48 (petroleum ether); δ_H 0.92 (6H, d, *J*=6.6 Hz, 2×CH_3), 1.93 (1H, n, *J*=6.6 Hz, CH), 2.58 (2H, d, *J*= 6.6 Hz, ArCH_2), 7.21–7.32 (4H, m, 4×ArH); δ_C 22.3, 29.1, 39.3, 119.0 (q, *J*=318 Hz), 121.2, 127.7, 128.0, 132.1, 134.3, 148.3.

4.5.3. 4-Undecylphenyl trifluoromethanesulfonate, 20. Purified by flash-chromatography (petroleum ether), colourless oil, bp 125–130 °C/1 mm Hg. (Found: C, 56.64; H, 7.32; $C_{18}H_{27}F_3O_3S$ requires C, 56.81; H, 7.17); R_f=0.48 (petroleum ether); δ_H 0.90 (3H, t, *J*=6.6 Hz, CH_3), 1.21–1.39 (16H, m, 8×CH_2), 1.58–1.65 (2H, m, CH_2), 2.71 (2H, t, *J*=8.1 Hz, ArCH_2), 7.23–7.36 (4H, m, 4×ArH); δ_C 14.1, 22.7, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 31.3, 31.9, 35.3, 116.8 (q, *J*=318 Hz), 120.9, 130.0, 143.5, 147.6.

4.5.4. 4-(2-Methylpropyl)phenyl trifluoromethanesulfonate, 21. Purified by flash-chromatography (petroleum ether), colourless oil, bp 85–90 °C/1 mm Hg. (Found: C, 46.67; H, 4.73; $C_{11}H_{13}F_3O_3S$ requires C, 46.80; H, 4.65); R_f=0.37 (petroleum ether); δ_H 0.90 (6H, d, J=6.4 Hz, 2×CH_3), 1.85 (1H, n, J=6.4 Hz, CH), 2.49 (2H, d, J=6.4 Hz, $ArCH_2$), 7.14–7.23 (4H, m, 4×ArH); δ_C 22.2, 30.2, 44.6, 118.7 (q, J=318 Hz), 120.8, 130.7, 142.3, 147.7; although this triflate was already described,[26] its characterization was not reported.

4.6. Cross-coupling reactions

4.6.1. 1-Phenylethynyl-2-tridecylbenzene, 22. The reaction was run according to a general procedure described in Ref. 18, starting with 0.16 g (0.38 mmol) of **18** and 58 mg (0.57 mmol) of phenyl acetylene in 1.2 mL of dry DMF, in the presence of 0.25 mL (1.7 mmol) of Et_3N and 13 mg (0.019 mmol) of $PdCl_2(PPh)_3$, at 90 °C for 16 h. However, as a variation to the literature procedure, the catalyst was divided in two portions, and the second one was added to the reaction mixtures after 2 h stirring at the reported temperature. The reaction was worked-up as described in the literature, and the crude product purified by flash chromatography (petroleum ether), to afford 97 mg (0.27 mmol, 70%) of 22, as a colourless oil. (Found: C, 90.08; H, 10.36; $C_{27}H_{36}$ requires C, 89.92; H, 10.08); R_f=0.54 (petroleum ether); δ_H 0.90 (3H, t, J=6.9 Hz, CH_3), 1.18–1.42 (20H, m, 10×CH_2), 1.62–1.76 (2H, m, CH_2), 2.86 (2H, t, J= 7.8 Hz, $ArCH_2$), 7.15–7.26 (3H, m, 3×ArH), 7.30–7.40 (3H, m, 3×ArH), 7.47–7.55 (3H, m, 3×ArH); δ_C 14.1, 22.7, 29.4, 29.6, 29.6, 29.7, 29.7, 30.8, 31.9, 34.8, 88.4, 92.7, 122.5, 123.6, 125.6, 128.1, 128.3, 128.8, 131.4, 132.1, 145.1.

4.6.2. 1-Hexyl-2-(2′-methyl)propylbenzene, 23. The described procedure is a variation of a general one described in Ref. 9. A carefully dried two-necked flask is charged under Ar with 0.20 g (0.71 mmol) of **19**, 12 mg (0.035 mmol) of $Fe(acac)_3$, 5 mL of THF and 0.4 mL of NMP. The red reaction mixture was chilled to 0 °C and 0.43 mL (0.86 mmol) of a 2 M solution of $C_6H_{13}MgBr$ in Et_2O were added dropwise, causing an immediate change from red to dark brown. The reaction was allowed to warm to rt under vigorous stirring, whilst monitored by tlc. After 3 h stirring, 12 mg (0.035 mmol) of $Fe(acac)_3$ and 0.43 mL (0.86 mmol) of a 2 M solution of $C_6H_{13}MgBr$ in Et_2O were successively added, and the resulting mixture was stirred overnight at rt. The mixture was diluted with Et_2O (10 mL), chilled to 0 °C and quenched by dropwise addition of 1 M HCl (10 mL). The resulting mixture was extracted with Et_2O (3×10 mL), and the collected organic phases were washed with H_2O (20 mL), dried ($CaCl_2$) and the solvent evaporated. The residue was purified by flash chromatography (petroleum ether), to afford 84 mg (0.38 mmol, 54%) of **23**, as a colourless oil. (Found: C, 87.67; H, 12.31; $C_{16}H_{26}$ requires C, 87.98; H, 12.02); R_f=0.78 (petroleum ether); δ_H 0.89 (3H, t, J=6.0 Hz), 0.92 (6H, d, J=7.2 Hz, 2×CH_3), 1.20–1.42 (6H, m, 3×CH_2), 1.52–1.60 (2H, m, CH_2), 1.84 (1H, n, J=7.2 Hz, CH), 2.48 (2H, d, J=7.2 Hz, $ArCH_2$), 2.56–2.61 (2H, m, $ArCH_2$), 7.08–7.16 (4H, m, 4×ArH); δ_C 14.1, 22.6, 29.5, 29.7, 29.8, 31.3, 31.8, 32.7, 41.9, 125.3, 125.7, 129.0, 130.1, 139.2, 141.0.

4.6.3. 4-Undecylbiphenyl, 24. The reaction was run according to a general procedure described in Ref. 19, starting with 0.396 g (1.04 mmol) of **20** and 0.254 g (2.1 mmol) of phenylboronic acid in 25 mL of DME, in the presence of 5 mL of 2 M aqueous Na_2CO_3, 0.132 g (3.1 mmol) of LiCl, and 60 mg (0.05 mmol) of $Pd(PPh_3)_4$, at 85 °C for 5 h. However, as a variation to the literature procedure, the catalyst was divided in two portions, and the second one was added to the reaction mixtures after 2 h stirring at the reported temperature. The reaction was worked-up as described in the literature, and the crude product was recrystallized from EtOH, to afford 0.240 g (0.78 mmol, 75%) of **24**, mp 45–47 °C. (Found: C, 89.21; H, 10.68; $C_{23}H_{32}$ requires C, 89.53; H, 10.47); δ_H 0.88 (3H, t, J=6.8 Hz, CH_3), 1.24–1.42 (16H, m, 8×CH_2), 1.64 (2H, quint, J=7.6 Hz), 2.64 (2H, t, J=7.6 Hz, $ArCH_2$), 7.22–7.27 (2H, m, 2×ArH), 7.31 (1H, td, J=7.2, 1.6 Hz, ArH), 7.37–7.44 (2H, m, 2×ArH), 7.49–7.53 (2H, m, 2×ArH), 7.56–7.60 (2H, m, 2×ArH); δ_C 14.1, 22.7, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 31.5, 31.9, 35.6, 126.9, 127.0, 128.7, 128.8, 138.5, 141.2, 142.1.

4.6.4. 1-Phenylethynyl-4-(2′-methyl)propylbenzene, 25. The reaction was run according to a general procedure described in Ref. 18, starting with 0.217 g (0.77 mmol) of **21** and 0.118 g (1.16 mmol) of phenyl acetylene in 2.5 mL of dry DMF, in the presence of 0.50 mL (3.5 mmol) of Et_3N and 27 mg (0.038 mmol) of $PdCl_2(PPh)_3$, at 90 °C for 16 h. However, as a variation to the literature procedure, the catalyst was divided in two portions, and the second one was added to the reaction mixtures after 2 h stirring at the reported temperature. The reaction was worked-up as described in the literature, and the crude product purified by flash chromatography (petroleum ether), to afford 0.142 g (0.61 mmol, 79%) of 25, as a colourless oil. (Found: C, 91.97; H, 7.89; $C_{18}H_{18}$ requires C, 92.24; H, 7.76); R_f=0.43 (petroleum ether); δ_H 0.90 (6H, d, J=6.8 Hz, 2×CH_3), 1.86 (1H, n, J=6.8 Hz, CH), 2.47 (2H, d, J=6.8 Hz, CH_2), 7.10–7.14 (2H, m, 2×ArH), 7.30–7.36 (3H, m, 3×ArH), 7.42–7.46 (2H, m, 2×ArH), 7.50–7.55 (2H, m, 2×ArH); δ_C 22.3, 30.2, 45.3, 88.8, 89.6, 120.4, 123.5, 128.0, 128.3, 129.1, 131.4, 131.5, 142.2.

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