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New stabilising groups for lateral lithiation of *ortho*-cresol derivatives and a new route to 2-substituted chromans

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ABSTRACT

2-(2-Methoxyethoxy)-toluene and 2-(2-dimethylaminoethoxy)-toluene have been lithiated using *sec*-BuLi under a variety of conditions and the laterally lithiated species trapped with electrophiles, including but-1-ene oxide, leading to a new synthesis of 2-ethylchroman.

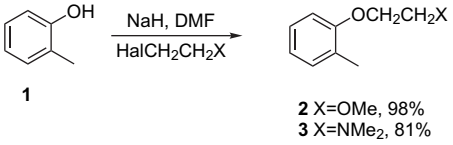
1. Introduction

Lateral lithiation is an important methodology in organic synthesis.[1] Lateral lithiation of benzenoid aromatics requires a stabilising group capable of either delocalising negative charge or stabilising an organolithium by coordination.[2] Oxygen-based stabilising groups placed in the *ortho*-position have been used for a number of lateral lithiations but are problematic in the case of simple *ortho*-cresol derivatives. The methoxy group requires superbase conditions to effect deprotonation and the methoxymethyl group gives exclusive *ortho*-lithiation (Scheme 1).[3]

In a previous work on diarylmethane derivatives we have used the methoxyethoxy group in efficient lateral lithiations.[4] This led us to investigate the use of the same group as a potentially more efficient stabiliser for lateral lithiation of *ortho*-cresol derivatives. We have recently reported lateral lithiation reactions of *ortho*-cresol derivatives using both the methoxyethoxy and dimethylaminoethoxy stabilising groups.[5] Here, we report in full the results of these investigations.

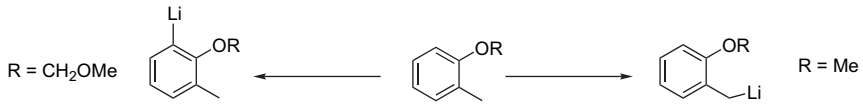
2. Results and discussion

Starting materials **2** and **3** were easily prepared by alkylation of *ortho*-cresol **1** using sodium hydride in DMF (Scheme 2).



Scheme 2.

The results of alkylations of **2** are shown in Table 1. Optimum conditions for alkylation of **2** involved generating the lithio species at −30 °C for 2 h using 1.3 equiv of *sec*-BuLi before quenching (entry 2). Generating the lithio species at −78 °C for 2 h led to isolation of starting material only, while stirring for a 4 h period before quenching or warming to −20 °C led to lower conversions. Our assumption was that the organolithium was slowly quenched by solvent, which would explain the large amounts of starting



Scheme 1.

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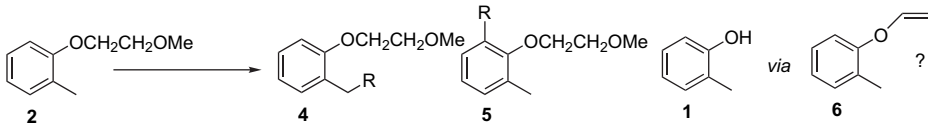
Table 1
Reactions of **2**



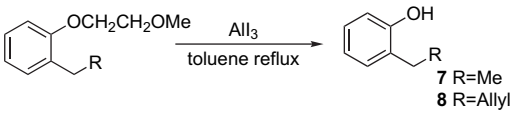
Entry	R–X	Solvent, concentration, additive	Product	4	5	1	2
1	Me–I	Diethyl ether, 0.06 M	**a**	71	15	14	0
2	Me–I	Diethyl ether, 0.03 M	**a**	76	4	0	20
3	Me–I	TBME	**a**	77	23	0	0
4	Me–I	Diethyl ether, 0.03 M, TMEDA	**a**	0	65	15	20
5	Allyl–Br	Diethyl ether, 0.03 M	**b**	25	0	0	75
6	Allyl–Br	Diethyl ether, 0.03 M, Bu_4NI	**b**	50 (47)	0	0	50
7	TMS–Cl	Diethyl ether, 0.03 M	**c**	74 (70)	0	0	26
8.	Benzophenone	Diethyl ether, 0.03 M	**d**	62 (59)	0	0	38

Notes and conditions: Solution of **2** and *sec*-BuLi (1.3 equiv) in ether stirred at −30 °C for 2 h followed by addition of electrophile (1.5 equiv) and warming to rt. Numbers in brackets refer to isolated yields.

material recovered when addition of the electrophile was delayed longer. Methylation could be carried out cleanly with 76% conversion to compound **4a**. Separation of the desired product **4a** from the *ortho*-product **5a** and **2** proved impossible by flash chromatography or HPLC, hence the conversions are based on NMR spectra of the crude products. There was an optimum concentration for this reaction with formation of *ortho*-cresol (as well as **5a**) accompanying product formation above 0.05 M in **2**. Use of *tert*-butyl methyl ether as solvent (entry 3) led to increased methylation at the *ortho*-position. Use of TMEDA as an additive (entry 4), common in the preparation of organolithium compounds, shifted the reaction from lateral to *ortho*-lithiation products completely, again accompanied by some of the deprotected compound **1**. The vinyl ether **6** could be identified in the crude product if a deuteration reaction was run in THF, which led us to believe that the predominant pathway for deprotection was via lithiation adjacent to the aryl oxygen followed by elimination of methoxide and cleavage to **1** in the work-up. The wide variations in product distribution with solvent, concentration and electrophile suggested that the degree of aggregation of the organolithium is crucial. The complete change of regioselectivity when TMEDA was added would seem to support this.[6]

With optimal conditions established, other electrophiles were investigated. Allylation (entry 5) gave a clean reaction at the lateral position but with only 25% conversion to product **4c**. This could be improved to 50% by the addition of tetrabutylammonium iodide (entry 6). Silylation with TMSCl (entry 7) was also clean and gave somewhat better conversion to product as was the case with benzophenone (entry 8). It is not clear why electrophiles other than iodomethane did not give rise to deprotected *ortho*-cresol. Our overall conclusion was that the methoxyethoxy group did stabilise lateral lithiation in preference to *ortho*-, when TMEDA was not added, but that the laterally lithiated species was problematic to work with and underwent a number of side-reactions.

Removal of the methoxyethyl group was carried out on compounds **4a** and **4b** using aluminium triiodide in refluxing toluene giving the known compounds **7** and **8** in 62 and 65% yields, respectively (Scheme 3).[7]



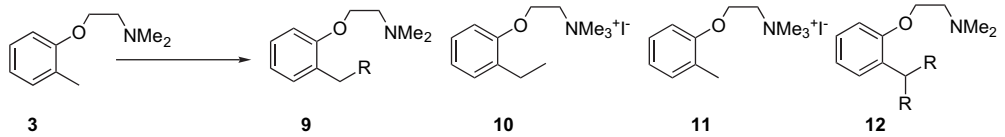
Scheme 3. Conditions: AlI_3, toluene, reflux, 12 h.

The dimethylaminoethoxy group had not been used in our research on asymmetric alkylation since it would make removal of our basic ligands much more inconvenient but it was considered here as a possible way to make the organolithium more stable. A similar range of electrophiles was investigated with compound **3** as had been used with **2** (Table 2). While optimum solvent, time and temperature were similar to those required for reactions of **2**, the stoichiometry was different. In all cases, more than 2 equiv of *sec*-BuLi were needed; no lithiation products were formed and no colour change was observed at less than 2 equiv. A significant excess of electrophile was also required, at least 2.5 equiv suggesting that the first equivalent of *sec*-BuLi was being coordinated by **3** in such a way that rendered it less able to deprotonate the molecule, rather than being quenched entirely. While methylation with 2.5 equiv of iodomethane (entry 1) produced only starting material, 10 equiv (entry 2) gave good conversion to the quaternized **10b**. The degree of quaternization was reduced in TBME (entry 3) but methylated products were impossible to isolate pure due to the presence of quaternised starting material **11** in the mixture. With allyl bromide (entry 4) and TMSCl (entry 5), 2.5 equiv of electrophile was sufficient and reaction at nitrogen was not observed, although TMSCl gave rise to a di-substituted product **12c**.[8] Benzophenone (entry 6) gave adequate conversion to product. Generally, reactions of **3** gave cleaner conversion to lateral lithiation products than those of **2**. Neither deprotection to *ortho*-cresol nor products of *ortho*-lithiation were observed in any of the reactions though starting material was never completely absent from the crude mixtures.

A method was developed for removal of the dimethylaminoethoxy group, which involved quaternisation of the nitrogen using iodomethane, treatment with KO^tBu in DMSO to eliminate trimethylammonium iodide and acidic work-up to cleave the vinyl ether to the cresol derivative. This was used to prepare compounds **7** and **8** from **3** in 64 and 62% overall yields, respectively (Scheme 4).

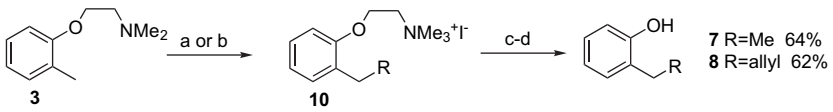
Our work on inhibitors of HGF/SF activation of MET led us to require an efficient synthesis of chroman derivatives substituted at the 2-position.[9] It was felt that the reaction of a laterally lithiated species derived from **2** or **3** with an epoxide, followed by cyclisation to form an ether would be a valuable approach. Laterally lithiated species have only rarely been reacted with epoxides in the past but there is some literature precedent.[10] The reaction of the organolithium derived from **2** with but-1-ene oxide **13** under our established conditions led to a 38% yield of the desired product **14**. Attempts to transmetallate to a copper species, an approach used with great success by other groups, failed to improve the conversion.[11] Lewis acids were able to promote the reaction, boron trifluoride etherate and iron(III) chloride giving confusing mixtures of products but diethylaluminium chloride gave a clean reaction and a good recovery of **14** (Table 3).

Table 2
Reactions of **3**



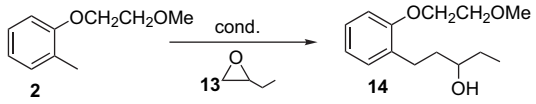
Entry	R–X (equiv)	Solvent, additive	Product	9	10	3	11	12
1	Me–I (2.5)	Diethyl ether	**a**	0	0	100	0	0
2	Me–I (10.0)	Diethyl ether	**a**	0	80	0	20	0
3	Me–I (10.0)	TBME	**a**	31	63	6	0	0
4	Allyl–Br (2.5)	Diethyl ether	**b**	75[a]	0	25	0	0
5	TMS–Cl (2.5)	Diethyl ether	**c**	0	0	14	0	86[b]
6	Benzophenone	Diethyl ether	**d**	72[c]	0	28	0	0

Notes and conditions: solution of **3** and *sec*-BuLi (2.3 equiv) in ether stirred at −30 °C for 2 h followed by addition of electrophile and warming to rt.
[a] Isolated yield of **9b** (59%).
[b] Isolated yield of **12c** (62%).
[c] Isolated yield of **9d** (48%).



Scheme 4. Conditions: (a) (R=Me) solution of **3** and *sec*-BuLi (2.5 equiv) in ether stirred at −30 °C for 2 h followed by addition of MeI (10.0 equiv) and warming to rt; (b) (R=allyl) (i) solution of **3** and *sec*-BuLi (2.5 equiv) in ether stirred at −30 °C for 2 h followed by addition of allyl bromide (2.5 equiv) and warming to rt; (ii) MeI (10.0 equiv), rt, 12 h; (c) KO^{t}Bu, DMSO, rt, 2 h; (d) acidic work-up.

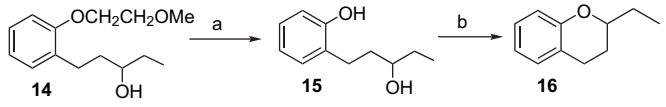
Table 3
Reactions of **2** with epoxide **13**



Entry	Additive (equiv)	Conditions	Yield of **14** (%)
1	$FeCl_3$ (1.33)	2 h, −30 °C, warm up to rt	17
2	BF_3 (1.33)	3 h, −78 °C, warm up to rt	35
3	CuCN·2LiCl (2.00)	2 h, −30 °C, warm up to rt	40
4	Et_2AlCl (1.33)	2 h, −30 °C, warm up to rt	63

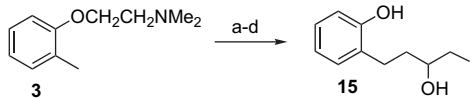
Conditions: 1.25 equiv *sec*-BuLi, 1.25 equiv but-1-ene oxide.

The product **14** was deprotected to **15** in acceptable yield (Scheme 5) and Mitsonobu conditions effected efficient cyclisation to the chroman **16** in an overall yield of 33% from **2**.



Scheme 5. Conditions: (a) AlI_3, toluene, reflux, 12 h, 56%; (b) Ph_3P, DEAD, 93%.

The organolithium derived from **3** also reacted well with **13** under these conditions but the product was impossible to purify at that stage, apparently due to the amino group coordinating to the Lewis acid. For this reason, a direct synthesis of **15** from **3** was developed (Scheme 6), with reaction with **13** followed by treatment with excess iodomethane in situ, elimination with base and acid work-up to give **15** in 38% yield from **3**.



Scheme 6. Conditions: (a) solution of **3** and *sec*-BuLi (2.3 equiv) in ether stirred at −30 °C for 2 h followed by addition of Et_2AlCl and but-1-ene oxide (2.4 equiv), stirring for 2 h; (b) MeI (10.0 equiv) rt, 12 h; (c) KO^{t}Bu, DMSO, rt, 2 h; (d) acidic work-up.

This represents two short and fairly high-yielding syntheses of 2-ethylchroman from *ortho*-cresol.

Overall we have demonstrated the utility of organolithium species derived from **2** and **3** in reactions with a good range of electrophiles.

3. Experimental

3.1. General

Melting points were determined on a Gallenkamp electrothermal apparatus. Infrared absorption spectra were recorded on a Bruker VECTOR-200 instrument, as liquid films or solutions in chloroform. NMR spectra (^{1}H and ^{13}C) were recorded on a Bruker AC-400 instrument, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C NMR. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra (MS) were measured on a JEOL JMS-DX303 or JEOL JMN-SX-102A instruments, chemical ionisation with methane was used throughout. Unless otherwise stated, all new compounds were determined to be >95% pure by signal/noise ratio in the ^{13}C NMR. Flash chromatography was carried out with silica gel, Merck Type 60 (70–325 mesh ASTM) or Merck Type 60 (230–400 mesh ASTM).

3.2. 2-(2-Methoxyethoxy)-toluene (2)[12]

To a well-stirred mixture of sodium hydride (60% dispersion) (6.2 g, 0.15 mol) in anhydrous DMF (150 mL) was added *ortho*-cresol **1** (5.4 g, 0.05 mol) in anhydrous DMF (50 mL). The reaction mixture was stirred at rt for 1 h. 2-Methoxy-bromoethane (8.3 g, 0.06 mol) was added and after stirring overnight, the reaction was quenched with satd ammonium chloride (150 mL). After extraction into ethyl acetate (200 mL), the organic layer was washed with 2 M sodium hydroxide (50 mL), water (5×200 mL), brine (200 mL), dried over $MgSO_4$ and purified by flash chromatography (cyclohexane/ethyl acetate 9:1) to afford the 2-(2-methoxyethoxy)-toluene **2** as a yellow oil (8.1 g, 98%). All data corresponded to literature values.

3.3. 2-(2-Dimethylaminoethoxy)-toluene (3)

To a well-stirred mixture of sodium hydride (60% dispersion) (6.2 g, 0.15 mol) in anhydrous DMF (150 mL) was added *ortho*-cresol **1** (5.4 g, 0.05 mol) in anhydrous DMF (50 mL). The reaction mixture was stirred at rt for 1 h. 2-Dimethylaminoethylchloride (6.5 g, 0.06 mol) was added and after stirring overnight, the reaction was quenched with satd ammonium chloride (150 mL). After extraction into ethyl acetate (200 mL), the organic layer was washed with 2 M sodium hydroxide (50 mL), water (5×200 mL), brine (200 mL), dried over $MgSO_4$ and purified by flash chromatography (ethyl acetate) to afford dimethylaminoethoxy-toluene as a yellow oil (7.2 g, 81%). ν_{max} (cm^{-1}) 3020, 2927, 2820, 1246, 1033. ^1H NMR (400 MHz, $CDCl_3$) δ 7.12–7.14 (2H, m, Ar–*H*), 6.81–6.86 (2H, m, Ar–*H*), 4.09 (2H, t, *J*=5.7 Hz, CH_2O), 2.78 (2H, t, *J*=5.7 Hz, CH_2N), 2.37 (6H, s, CH_3N), 2.23 (3H, s, CH_3). ^1H NMR (100 MHz, $CDCl_3$) δ 157.4, 131.0, 127.2, 127.1, 120.8, 111.4, 67.2, 58.8, 46.7, 16.7. MS (CI) *m*/*z* 180 (M+1, 100). HRMS (ES): $[M+H]^+$ $C_{11}H_{18}NO$ required 180.1383, found 180.1381.

3.4. General procedure 1 for lithiation reactions of 2 (Table 1)

Under an argon atmosphere was added dropwise at −30 °C *sec*-BuLi (2.5 M in cyclohexane) (0.28 mL, 0.6 mmol) to a solution of 1-(2-methoxyethoxy)-2-methyl-benzene **2** (0.05 g, 0.3 mmol) in diethyl ether (5 mL). The reaction mixture was stirred at −30 °C for 2 h followed by addition of the electrophile (0.45 mmol). The reaction mixture was allowed to warm to rt over 2 h. Dilution with ether (5 mL) was followed by washing with 2 M HCl (5 mL), water (3×5 mL) and brine (5 mL). Drying over $MgSO_4$, concentration in vacuo and purification by column chromatography afforded the desired product.

3.4.1. 2-(2-Methoxyethoxy)-ethylbenzene (**4a**)

2-(2-Methoxyethoxy)-ethylbenzene was prepared using iodomethane as alkylating agent according to general procedure 1 as an oil, contaminated with starting material **2**. Discernible data: ν_{max} (cm^{-1}) 3023, 2966, 2930, 1244, 1127. ^1H NMR (400 MHz, $CDCl_3$) δ 7.15–7.19 (2H, m, Ar–*H*), 6.92 (1H, dt, *J*=7.5, 1.0 Hz, Ar–*H*), 6.85–6.87 (1H, m, Ar–*H*), 4.15 (2H, t, *J*=4.9 Hz, CH_2OC$_{ar}$), 3.79 (2H, t, *J*=4.9 Hz, CH_2O), 3.49 (3H, s, CH_3O), 2.70 (2H, q, *J*=7.5 Hz, CH_2CH$_3$), 1.24 (3H, t, *J*=7.5 Hz, CH$_2$CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 133.4, 129.6, 127.4, 121.4, 111.8, 71.7, 68.3, 59.6, 27.3, 14.5. MS (CI) *m*/*z* 198 (M+18, 100), 181 (M+1, 60), 59 (20). HRMS (ES): $[M+NH_4]^+$ $C_{11}H_{20}NO_2$ requires 198.1489, found 198.1488.

3.4.2. 2-(2-Methoxyethoxy)-but-3-enylbenzene (**4b**)

2-(2-Methoxyethoxy)-but-3-enylbenzene was prepared using allyl bromide as alkylating agent according to general procedure 1 as a colourless oil (29 mg, 47%). ν_{max} (cm^{-1}) 3023, 2956, 2925, 1288, 1127. ^1H NMR (400 MHz, $CDCl_3$) δ 7.12–7.18 (2H, m, Ar–*H*), 6.81–6.91 (2H, m, Ar–*H*), 5.84–5.94 (1H, m, C$H_{vinylic}$), 5.06–5.01 (2H, m, CH_2=), 4.13 (2H, t, *J*=4.7 Hz, C$_{ar}$OCH_2), 3.78 (2H, t, *J*=4.7 Hz, CH_2O), 3.47 (3H, s, CH_3O), 2.96–2.95 (2H, m, C$_{ar}$CH_2), 2.73–2.71 (2H, m, CH_2CH=). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 139.2, 138.9, 130.1, 127.5, 121.2, 114.8, 111.6, 71.7, 68.8, 68.0, 64.4, 30.5. MS (EI) *m*/*z* 206 (M^+, 10), 133 (60), 39 (100). HRMS (ES) $[M+NH_4]^+$ $C_{13}H_{22}NO_2$ requires 224.1645, found 224.1643.

3.4.3. 2-(2-Methoxyethoxy)-benzyltrimethylsilane (**4c**)

2-(2-Methoxyethoxy)-benzyltrimethylsilane was prepared using trimethylsilyl chloride as electrophile according to general procedure 1 as a colourless oil (50 mg, 70%). ν_{max} (cm^{-1}) 3021, 2934, 2893, 1244, 1130. ^1H NMR (400 MHz, $CDCl_3$) δ 7.14–7.19 (2H, m, Ar–*H*), 6.80–6.82 (2H, m, Ar–*H*), 4.08 (2H, t, *J*=3.8 Hz, CH_2OC$_{ar}$), 3.75 (2H, t, *J*=3.8 Hz, CH_2O), 3.43 (3H, s, CH_3O), 2.12 (2H, s, CH_2Si), 0.0 (9H, s, Si(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 133.6, 129.3, 125.3, 120.8, 111.2, 72.2, 67.2, 60.0, 27.3, 0.0. MS (CI) *m*/*z* 256 (M+NH_4, 100), 239 (40), 90 (80). HRMS (ES): $[M+NH_4]^+$ $C_{13}H_{26}NO_2Si$ requires 256.1727, found 256.1727.

3.4.4. 2-[2-(2-Methoxyethoxy)-phenyl]-1,1-diphenylethanol (**4d**)

2-[2-(2-Methoxyethoxy)-phenyl]-1,1-diphenylethanol was prepared using benzophenone as electrophile according to general procedure 1 as a yellow oil (62 mg, 59%). ν_{max} (cm^{-1}) 3447, 3059, 2927, 1246. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.32 (4H, m, Ar–*H*), 7.19–7.28 (1H, m, Ar–*H*), 7.11–7.14 (4H, m, Ar–*H*), 7.03–7.09 (1H, m, Ar–*H*), 7.00 (1H, dt, *J*=7.5, 1.7 Hz, Ar–*H*), 6.71 (1H, dd, *J*=8.2, 1.0 Hz, Ar–*H*), 6.52 (1H, dt, *J*=7.5, 1.2 Hz, Ar–*H*), 6.23 (1H, dd, *J*=7.5, 1.7 Hz, Ar–*H*), 4.18 (1H, s, O*H*), 4.01 (2H, t, *J*=4.5 Hz, CH_2OC$_{ar}$), 3.57 (2H, s, CH_2C$_{ar}$), 3.56–3.59 (2H, m, CH_2O), 3.15 (3H, s, CH_3O). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 148.0, 144.2, 132.6, 128.9, 128.6, 128.4, 128.0, 127.9, 127.5, 127.0, 126.9, 126.8, 126.7, 126.3, 123.4, 121.0, 112.3, 71.3, 68.0, 59.3, 42.6. MS (EI) *m*/*z* 348 (M^+, 40), 331 (100), 183 (40). HRMS (EI): $[M^+]$ $C_{23}H_{24}O_3$ requires 348.1720, found 348.1715.

3.5. General procedure 2 for removal of the methoxyethoxy group

Aluminium powder (19.0 mg, 0.7 mmol) and iodine (122 mg, 0.5 mmol) were heated at reflux in acetonitrile (1.0 mL) for 15 min. Starting material (0.3 mmol) in acetonitrile (0.2 mL) was added and the reaction mixture was heated at reflux for a further 18 h. The solvent was removed in vacuo and the crude product was dissolved in ethyl acetate (5 mL). The organic layer was washed with water (3×5 mL), brine (5 mL) and dried over magnesium sulfate. Purification by column chromatography afforded 2-ethyl-phenol **7** (23 mg, 62%) or 2-but-3-enyl-phenol **8** (30 mg, 67%) as yellow oils. Spectral data were in accordance with literature values.[6]

3.6. General procedure 3 for lithiation reactions of 3 (Table 2)

Under an argon atmosphere was added dropwise at −30 °C *sec*-BuLi (2.5 M in cyclohexane) (0.23 mL, 0.5 mmol) to a solution of 2-(2-dimethylaminoethoxy)-toluene (36 mg, 0.2 mmol) in diethyl ether (5 mL). The reaction mixture was stirred at −30 °C for 2 h. This was followed by addition of the electrophile (0.5 mmol). The reaction mixture was allowed to warm to rt over 2 h. The solvent was removed in vacuo and purification by flash chromatography afforded the desired product.

3.6.1. 4-[2-(2-Dimethylaminoethoxy)-phenyl]-but-1-ene (**9b**)

4-[2-(-Dimethylaminoethoxy)-phenyl]-but-1-ene was prepared using allyl bromide as electrophile according to general procedure 3 as a colourless oil (26 mg, 59%). ν_{max} (cm^{-1}) 3024, 2940, 2826, 1242, 1043. ^1H NMR (400 MHz, $CDCl_3$) δ 7.11–7.18 (2H, m, Ar–*H*), 6.83–6.90 (2H, m, Ar–*H*), 5.83–5.93 (1H, m, C$H_{vinylic}$), 5.05–5.00 (2H, m, CH_2=), 4.09 (2H, t, *J*=5.9 Hz, CH_2O), 2.77 (2H, t, *J*=5.7 Hz, CH_2N), 2.73 (2H, t, *J*=7.5 Hz, CH_2C$_{ar}$), 2.70 (2H, m, CH_2CH=), 2.36 (6H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 139.1, 130.8, 130.2, 127.4, 120.8, 116.7, 114.8, 111.6, 67.4, 58.3, 46.6, 30.6. MS (CI) *m*/*z* 219 (M^+, 10), 56 (100). HRMS (ES): $[M+H]^+$ $C_{14}H_{22}NO$ requires 220.1696, found 220.1697.

3.6.2. 2-[2-(2-Dimethylaminoethoxy)-phenyl]-1,1-diphenylethanol (**9d**)

2-[2-(2-Dimethylaminoethoxy)-phenyl]-1,1-diphenylethanol was prepared using benzophenone as electrophile according to general procedure 3 as a yellow oil (48 mg, 67%). ν_{max} (cm^{-1}) 3020, 2947, 2826, 1248, 1057. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.74 (4H, m, Ar–*H*), 7.54–7.56 (4H, m, Ar–*H*), 7.39–7.48 (3H, m, Ar–*H*), 7.13 (1H, dd, *J*=8.2, 1.0 Hz, Ar–*H*), 6.91 (1H, dt, *J*=7.5, 1.2 Hz, Ar–*H*), 6.54 (1H, dd, *J*=7.5, 1.7 Hz, Ar–*H*), 4.35 (2H, t, *J*=5.5 Hz, CH_2O), 3.96 (2H, s, CH_2), 2.92 (2H, t, *J*=5.5 Hz, CH_2N), 2.38 (6H, s, CH_3N). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 148.9, 132.1, 128.3, 128.1, 127.9, 127.7, 127.3, 126.8, 126.6, 126.5, 120.6, 112.2,

64.4, 59.1, 45.9, 42.3. MS (CI) *m/z* 362 (M+1, 45), 344 (40), 56 (100). HRMS (ES): $[M+H]^+$ $C_{24}H_{28}NO_2$ requires 362.2115, found 362.2116.

*3.6.3. 2-(2-Dimethylaminoethoxy)-phenyl-bis-trimethylsilylmethane (**12c**)*

2-(2-Dimethylaminoethoxy)-phenyl-bis-trimethylsilylmethane was prepared using trimethylsilyl chloride as electrophile according to general procedure 3 as a colourless oil (40 mg, 62%). ν_{max} (cm^{-1}) 3046, 2952, 2820, 1247, 1047. ^1H NMR (400 MHz, $CDCl_3$) δ 6.95–7.01 (2H, m, Ar–*H*), 6.78–6.85 (2H, m, Ar–*H*), 4.04 (2H, t, *J*=6.1 Hz, CH_2O), 2.76 (2H, t, *J*=6.1 Hz, CH_2N), 2.36 (6H, s, CH_3N), 0.3 (1H, s, C*H*), 0.0 (18H, s, CH_3Si). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 133.6, 132.3, 139.4, 120.5, 111.5, 66.6, 58.1, 45.9, 18.0, 0.0. MS (CI) *m/z* 324 (M+1, 5), 70 (100), 56 (58). HRMS (ES): $[M+H]^+$ $C_{17}H_{34}NOSi$ requires 324.2173, found 324.2172.

3.7. General procedure 4 for removal of dimethylaminoethoxy group

Starting material (0.4 mmol) was dissolved in iodomethane (4 mmol) and the reaction mixture was stirred at rt for 12 h. The remaining iodomethane was removed in vacuo and the crude product was dissolved in anhydrous DMSO (1 mL). Potassium *tert*-butoxide (68 mg, 0.6 mmol) was added and the reaction mixture was stirred at rt for 1 h. Ethyl acetate (5 mL) was added and the organic layer was washed with water (5×10 mL), brine (5 mL) and dried over magnesium sulfate. Concentration in vacuo and purification by column chromatography afforded the desired compounds **7** (33 mg, 68%) or **8** (37 mg, 62%).

3.8. 1-[2-(2-Methoxyethoxy)-phenyl]-pentan-3-ol (14)

Under an argon atmosphere was added dropwise at −30 °C *sec*-BuLi (2.5 M in cyclohexane) (1.12 mL, 1.5 mmol) to a solution of 2-methoxyethoxy-toluene **2** (0.20 g, 1.2 mmol) in diethyl ether (20 mL). The reaction mixture was stirred at −30 °C for 2 h. This was followed by addition of diethylaluminium chloride (0.19 mL, 1.6 mmol). After stirring for 1 min, but-1-ene oxide **13** (0.13 mL, 1.5 mmol) was added. The reaction mixture was allowed to warm to rt over 2 h. Dilution with ether (10 mL) was followed by washing with satd ammonium chloride (10 mL), water (3×20 mL) and brine (20 mL). Drying over $MgSO_4$, concentration in vacuo and purification by flash chromatography (cyclohexane/ethyl acetate 8:2) afforded the 1-[2-(2-methoxyethoxy)-phenyl]-pentan-3-ol **14** as a colourless oil (180 mg, 63%). ν_{max} (cm^{-1}) 3420, 2926, 1243, 1126. ^1H NMR (400 MHz, $CDCl_3$) δ 7.15–7.17 (2H, m, Ar–*H*), 6.82–6.80 (2H, m, Ar–*H*), 4.09 (2H, t, *J*=3.8 Hz, CH_2OC_{ar}), 3.74 (2H, t, *J*=3.8 Hz, CH_2O), 3.51–3.46 (1H, m, C*H*OH), 3.44 (3H, s, CH_3O), 2.94–2.86 (2H, m, C_{ar}CH_2), 2.70–2.64 (2H, m, C_{ar}CH_2CH_2), 1.79–1.75 (2H, m, CH_2CH_3), 1.19 (3H, t, *J*=7.5 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 134.6, 129.3, 126.3, 126.0, 120.6, 73.2, 72.2, 67.0, 60.8, 37.4, 30.8, 27.3, 10.5. MS (CI) *m/z* 239 (M+1, 40), 221 (100), 59 (30). HRMS (ES): $[M+NH_4]^+$ $C_{14}H_{26}NO_3$ requires 256.1907, found 256.1904.

3.9. 2-(3-Hydroxypentyl)-phenol (15)

3.9.1. Method A

2-(3-Hydroxypentyl)-phenol (**15**) was prepared from **14** according to general procedure 2 as a pale yellow oil (71 mg, 56%). ν_{max} (cm^{-1}) 3435, 2984, 2929. ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.15 (2H, m, Ar–*H*), 6.90–6.82 (2H, m, Ar–*H*), 3.52–3.48 (1H, m, C*H*OH), 2.98–2.95 (2H, m, C_{ar}CH_2), 2.72–2.68 (2H, m, C_{ar}CH_2CH_2), 1.80–1.78 (2H, m, CH_2CH_3), 1.19 (3H, t, *J*=7.4 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 136.8, 130.9, 127.9, 121.0, 116.8, 72.2, 37.3, 31.4, 26.5, 10.2. MS (EI) *m/z* 180 (M^+, 10), 163 (55), 107 (100). HRMS (ES): $[M+NH_4]^+$ $C_{11}H_{20}NO_2$ requires 198.1489, found 198.1487.

3.9.2. Method B

Under an argon atmosphere was added dropwise at −30 °C *sec*-BuLi (2.5 M in cyclohexane) (1.00 mL, 2.5 mmol) to a solution of 2-dimethylaminoethoxy-toluene **3** (0.21 g, 1.2 mmol) in diethyl ether (20 mL). The reaction mixture was stirred at −30 °C for 2 h. This was followed by addition of diethylaluminium chloride (0.28 mL, 2.5 mmol). After stirring for 1 min, but-1-ene oxide **13** (0.21 mL, 2.5 mmol) was added. The reaction mixture was allowed to warm to rt over 2 h. Dilution with ether (10 mL) was followed by washing with satd ammonium chloride (10 mL), water (3×20 mL) and brine (20 mL). Drying over $MgSO_4$ and concentration in vacuo was followed by dissolving the crude product in boiling acetonitrile (10 mL) and hot filtration to remove aluminium salts. Concentration afforded a crude product, which was subjected to general procedure 4 to give 1-[2-(2-methoxyethoxy)-phenyl]-pentan-3-ol **15** as a colourless oil (52 mg, 38%).

All spectral data were identical to those above for method A.

3.10. 2-Ethylchroman[13] (16)

2-(3-Hydroxypentyl)-phenol **15** (62 mg, 0.34 mmol) and triphenylphosphine (0.18 g, 0.7 mmol) were dissolved in freshly distilled THF (1 mL). Diethyl azodicarboxylate (40% in toluene) (0.22 mL, 0.7 mmol) was added dropwise and the mixture was stirred for 3 h at rt. After removing the solvent in vacuo, the crude product was purified by flash chromatography (cyclohexane/ethyl acetate 9:1) to afford 2-ethylchroman **16** as a yellow oil (51 mg, 93%). All data accorded with literature values.

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References and notes

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