

A Dispensable Methoxy Group? Phenyl Fencholate as a Chiral Modifier of *n*-Butyllithium

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Dedicated to Professor Dr. Paul von Ragué Schleyer on the occasion of his 75th birthday

Abstract: Phenyl fenchol forms a 3:1 aggregate with *n*-butyllithium (3-BuLi), showing unique lithium–HC agostic interactions both in toluene solution (¹H,⁷Li-HOESY) and in the solid state (X-ray analysis). Although methoxy–lithium coordination is characteristic for many mixed aggregates of anisyl fencholates with *n*-butyllithium, *endo*-methyl coordination to lithium ions compensates for the missing methoxy groups in 3-BuLi. This gives rise to a different orientation of the fenchane moiety, encapsulating and chirally modifying the butylide unit.

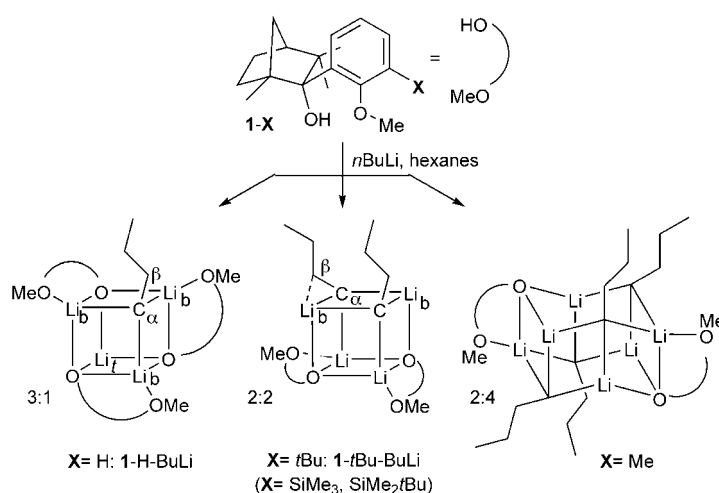
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Introduction

Organolithiums are among the most versatile and widely used reagents in organic chemistry.^[1] Their use in enantioselective alkylations^[2] and lithiations^[3] is of special interest. Structural elucidations of chiral *n*BuLi complexes in the solid state^[4] and in solution^[5] provide the basis for more rational developments of new and efficient, chirally modified organolithium compounds for asymmetric synthesis.^[6] We have recently shown that modular fenchols^[7] are efficiently accessible and applicable in both organozinc^[8] and organopalladium^[9] catalysts for the purpose of exploring the origins of enantioselectivities. Mixtures of anisyl fenchols (**1**) with *n*-butyllithium in hexanes generate enantiopure *n*BuLi aggregates. Such species are unique in terms of their variable

stoichiometries, binding modes and enantioselectivities in C–C couplings with benzaldehyde, because all of these properties can be tuned by modification of the anisyl *ortho*-substituents **X** (Scheme 1).^[10]

The anisyl methoxy unit appears to be essential for the formation of such unusual mixed *n*BuLi aggregates: With the strong chelating side-arm in *N,N*-dimethylaminobenzyl fenchol (**2**), only a simple, organolithium-free, pure lithium fencholate (**2-Li**)₂ is created with *n*BuLi (Scheme 2).^[11]



Scheme 1. Anisyl fenchols (**1-X**) form a variety of *n*BuLi aggregates (**1-X-BuLi**), depending on the *ortho*-substituent **X**, with 3:1, 2:2 or 2:4 compositions.^[10]

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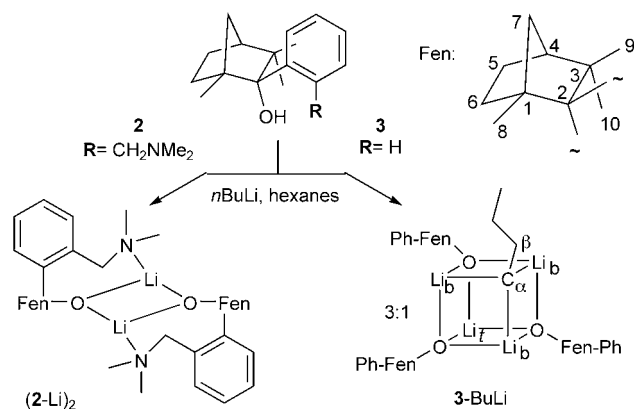
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[⁺] NMR analysis.

[⁺⁺] X-ray analysis.



Scheme 2. Instead of an *n*BuLi aggregate, a simple lithium fencolate (**2-Li**)₂ is formed with **2** and *n*BuLi.^[11] However, the new 3:1 aggregate **3-BuLi** originates from methoxy-free phenyl fenchol (**3**). Butylide-binding and *trans*-lithium ions are denoted as Li_b and Li_t, respectively.

Here, we report the formation and structural characterisation, both in solution and in the solid state, of the methoxy-free aggregate **3-BuLi** (Scheme 2), which demonstrates that methoxy groups are indeed dispensable for chiral modifications of *n*BuLi with aryl fencolates.

Results and Discussion

The aggregate **3-BuLi** crystallises with a 3:1 composition from mixtures of phenyl fenchol **3** and *n*-butyllithium in hexanes (Figure 1), and hence shows the same stoichiometry as the parent anisyl fencolate **1-H-BuLi** (Scheme 1).^[10d] Both **3-BuLi** and **1-H-BuLi**^[10d] exhibit a distorted cubic [Li₄O₃C] core in which three lithium ions bind to the butylide unit (Li_b, Figure 1). Although in **1-H-BuLi**, methoxy groups coordinate to these butylide-binding lithium ions (Li_b, Scheme 1),^[10d] in methoxy-free **3-BuLi**, *endo*-methyl groups (C₁₀, Me_{endo}) of the bicyclic [2.2.1]heptane moieties develop close contacts to the Li_b ions, and hence compensate for the missing methoxy coordination (Li–H: 2.1 Å, Table 1, Figure 1). Agostic Li–C_(β) contacts with butylide units appear in some 2:2 aggregates with “naked” Li_b cations, for example, in **1-SiMe₃-BuLi** (Scheme 1, Li_b–C_(β): 2.38 Å).^[10b,c,12] Apparently due to rather strong C₁₀–Me_{endo} coordination, no close agostic Li_b–C_(β) butylide contact is formed in **3-BuLi** (Figure 1, Li_b–C_(β): 2.73 Å). In the case of **1-H-BuLi**, the lithium cation *trans* to the butylide unit (Li_t) tends to be contacted by C₍₈₎H₃

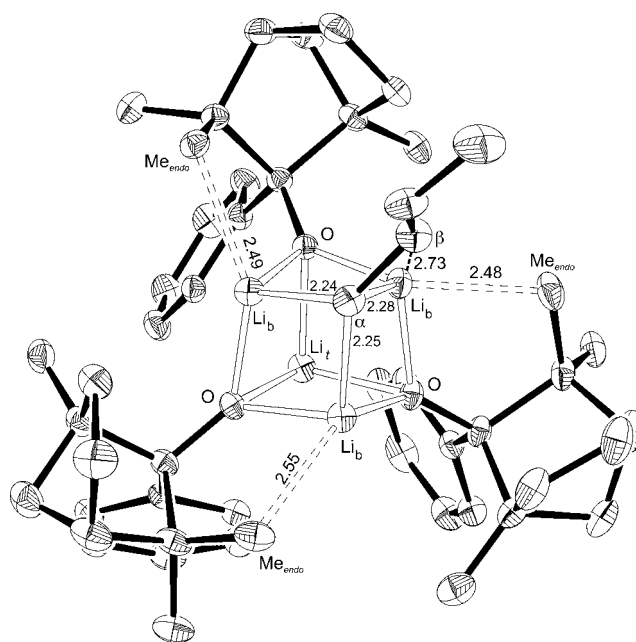


Figure 1. X-ray crystal structure of **3-BuLi**. *Endo*-methyl groups (C₁₀, Me_{endo}) exhibit close contacts to butylide-binding lithium ions (Li_b, distances in Å, for Li–H distances see Table 1) and compensate the missing lithium coordination of methoxy groups.

Table 1. Li–H distances [Å] in the X-ray crystal structure of phenyl fencolate **3-BuLi** (Scheme 2, Figure 1).^[a]

	Ph–H _m	Ph–H _o	C ₍₈₎ H ₃	C ₍₁₀₎ H ₃	C ₍₆₎ H _{endo}	C _(β) HH	C _(β) HH	C _(α) HH	C _(α) HH
Li _b	–	2.9	2.9	2.2	2.4	3.6	4.0	2.1	2.8
Li _b	–	3.0	3.2	2.1	2.3	2.6	2.8	2.9	3.0
Li _b	–	2.9	2.9	2.1	2.3	3.4	4.0	2.1	2.9
Li _t	3.8 ^[b]	2.1 ^[b]	– ^[c]	– ^[c]	– ^[c]	– ^[c]	– ^[c]	– ^[c]	– ^[c]

[a] Hydrogen atoms at butylide C_(α) are refined, other hydrogen atoms are constructed with a C–H bond length of 0.990 Å. [b] Mean value. [c] Distances longer than 4.50 Å.

Table 2. Li–H distances [Å] in the parent anisyl fencolate **1-H-BuLi** due to X-ray structure analysis (Schemes 1 and 2)^[a] and to cross-peaks (+) of ¹H,⁷Li-HOESY experiments (in [D₈]toluene at –10 °C).^[b]

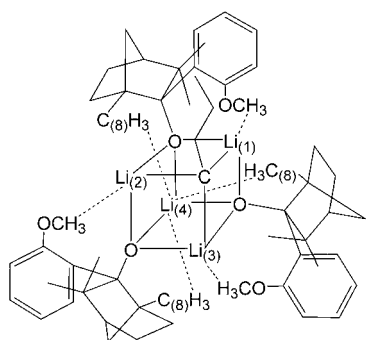
	OCH ₃ (δ=3.76 ppm)	C ₍₈₎ H ₃ (δ=0.98 ppm)	C _(α) HH (δ=–0.39 ppm)	C _(α) HH (δ=–0.63 ppm)
Li _b (δ = 1.06 ppm)	3.1, 3.3, 3.2 (+) ^[c]	4.3, 4.4, 4.2 (+) ^[c]	2.3, 2.6, 3.1 (+) ^[c]	2.6, 3.1, 2.2 (+) ^[c]
Li _t (δ = 0.73 ppm)	– ^[c]	2.7 ^[d] (+) ^[c]	– ^[c]	– ^[c]

[a] The X-ray crystal structure is reported in reference [10d]. [b] Hydrogen atoms at butylide C_(α) are derived from a Fourier-map, other hydrogen atoms are constructed with a C–H bond length of 0.990 Å. [c] (+)-NOE-effect indicating short ¹H–⁷Li distances in solution. [d] Mean value. [e] Distances longer than 4.50 Å, no NOE-effects (–) were detected.

methyl groups (Li–H: 2.7 Å, Table 2).^[10d] However, in **3-BuLi**, this Li_t cation experiences significant *ortho*-hydrogen coordination by phenyl C–H_{ortho} units (mean value: Li–H_o 2.1 Å, Table 1). Hence, in contrast to anisyl fencolates (Scheme 1), **3-BuLi** encapsulates its butylide with the fenchane moiety rather than with the methoxy-free aryl units (Figure 1).

To complement the solid-state structural analyses of *n*BuLi fencolates and to gain additional information about

aggregation and coordination in solution, $^1\text{H}, ^7\text{Li}$ -HOESY experiments were performed in $[\text{D}_8]\text{toluene}$ at -10°C .^[13] A toluene solution of the parent anisyl fenolate aggregate **1**-H-BuLi shows a ^1H NMR singlet at $\delta = 3.76$ ppm for the methoxy group (Table 2). Two triplets at $\delta = -0.39$ and -0.63 ppm can be assigned to the diastereotopic α - CH_2 protons of the butylide unit, which couple to β - CH_2 protons. This diastereotopy of the α - CH_2 butylide protons indicates a significant chiral butylide modification and rigidity induced by the anisyl fenolate. The 9:1:1 intensities of the methoxy proton and the two α - CH_2 protons agree with the 3:1 composition of **1**-H-BuLi found in the solid state (Scheme 1).^[10d] Two ^7Li NMR signals at $\delta = 0.73$ and 1.06 ppm show intensities in the ratio of 1:3. The results of $^1\text{H}, ^7\text{Li}$ -HOESY experiments reveal that short contacts due to NOE correlations are apparent in **1**-H-BuLi between the three lithium ions at $\delta = 1.06$ ppm and the methoxy groups at $\delta = 3.76$ ppm (Table 2). In contrast, no such methoxy contacts are found for the lithium ion at $\delta = 0.73$ ppm, which is rather close to the $\text{C}_{(8)}$ -methyl groups ($\delta = 0.98$ ppm) of the bicyclic [2.2.1]heptane fragments (Table 2). This suggests a methoxy-coordination of three Li_b cations and a non-coordinated Li_t cation, in agreement with the X-ray crystal structure of **1**-H-



Scheme 3. $^1\text{H}, ^7\text{Li}$ -HOESY experiments of the parent anisyl fenolate aggregate **1**-H-BuLi in toluene solution (-10°C) reveal a structure similar to that found from X-ray analysis (Scheme 1, Table 2).^[10d]

BuLi (Scheme 3).^[10d]

The *t*-butyl-substituted anisyl fenolate **1**-*t*Bu-BuLi (Scheme 1) shows a ^1H NMR singlet at $\delta = 3.71$ ppm, which again can be assigned to the methoxy group of the anisyl moiety (Figure 2). The butylide group in **1**-*t*Bu-BuLi gives rise to two triplets of doublets at $\delta = -0.74$ and -0.85 ppm ($^2J = 4.2$, $^3J = 12.8$ Hz), which originate from diastereotopic α - CH_2 protons by coupling with non-equivalent β - CH_2 protons (multiplets at $\delta = 0.70$ and 1.04 ppm). The 3:1:1 intensities of the methoxy and α - CH_2 signals, as well as the same intensities of two ^7Li signals at $\delta = 1.03$ and 2.15 ppm, reveal **1**-*t*Bu-BuLi to be a 1:1 aggregate in solution, as it was also found in the solid state (Scheme 1).^[10b] From the $^1\text{H}, ^7\text{Li}$ -HOESY cross-peaks between the methoxy group ($\delta = 3.71$ ppm) and the ^7Li signal at $\delta = 1.03$ ppm, but not the signal at $\delta = 2.15$ ppm (Figure 2), methoxy coordination corresponding to that exhibited by the X-ray structure of **1**-

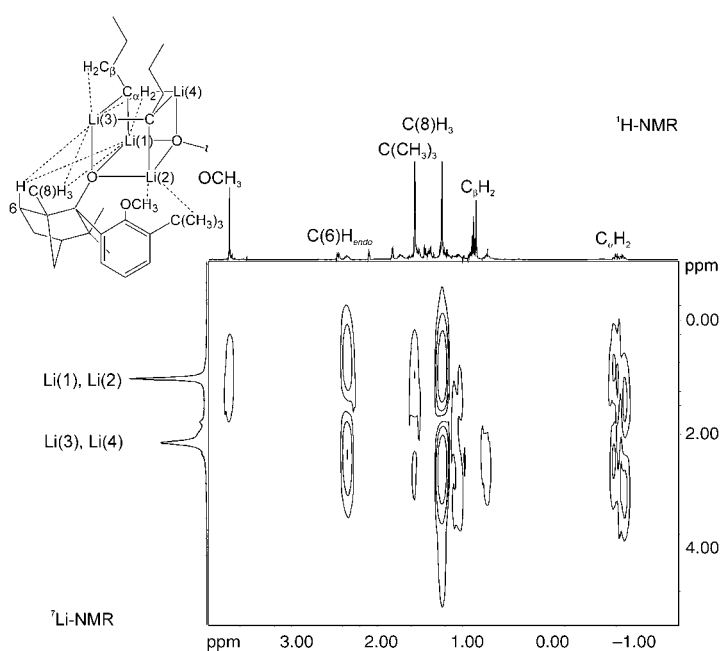


Figure 2. Two-dimensional $^1\text{H}, ^7\text{Li}$ -HOESY contour plot of complex **1**-*t*Bu-BuLi (-10°C , $[\text{D}_8]\text{toluene}$, 500 MHz). Dashed lines indicate the selected correlations. Only one fenolate and one *n*-butylide unit are shown for clarity.

*t*Bu-BuLi can be derived.^[10b] From this X-ray structure, short Li-H distances between non-methoxy-coordinated lithiums and $\text{C}_{(8)}\text{H}_3$ groups, as well as butylide β - CH_2 groups, are apparent (Table 3).^[10b] $^1\text{H}, ^7\text{Li}$ -HOESY cross-peaks indicate analogous short contacts in solution (Figure 2) and signify the close similarity between the solid-state and solution structures of **1**-*t*Bu-BuLi.

Table 3. Li-H distances [\AA] in the X-ray crystal structure of the anisyl fenolate **1**-*t*Bu-BuLi (Scheme 1).^[a]

	OCH ₃	C ₍₆₎ H _{endo}	C(CH ₃) ₃	C ₍₈₎ H ₃	C _(β) HH	C _(β) HH
Li(1)	3.2	2.3	3.1	3.8	— ^[b]	— ^[b]
Li(2)	3.1	3.2	3.4	3.3	— ^[b]	— ^[b]
Li(3)	— ^[b]	2.6	— ^[b]	2.1	2.6	2.5
Li(4)	— ^[b]	2.9	— ^[b]	2.0	2.8	2.5

[a] The X-ray crystal structure is reported in reference [10b]. Hydrogen atoms are constructed with a C-H bond length of 0.990 \AA . [b] Distances longer than 4.50 \AA .

The new phenyl fenolate **3**-BuLi exhibits ^1H -multiplets at $\delta = -0.21$ ppm for the butylide α - CH_2 group, with intensities of 2:15 relative to phenyl protons (Figure 3). This is in agreement with a 3:1 composition (Figure 1). In analogy to the solid-state structure of **3**-BuLi, ^7Li signals ($\delta = 0.48$ ppm, one lithium and $\delta = 2.15$ ppm, three lithium nuclei) indicate $\text{Li}_{b(1,2,3)}$ and $\text{Li}_{t(4)}$ differentiations (Figure 3). The unique agostic interactions of Li_b ions with the *endo*- $\text{C}_{(10)}\text{H}_3$ methyl groups (^1H $\delta = 1.29$ ppm) are not only apparent from the X-ray crystal structure of **3**-BuLi (Figure 1, Table 1), but also from $^1\text{H}, ^7\text{Li}$ -HOESY cross-peaks (Figure 3). In addition, Li_b ions have close contacts to $\text{C}_{(6)}\text{H}_{endo}$ (^1H $\delta = 2.37$ ppm) of the

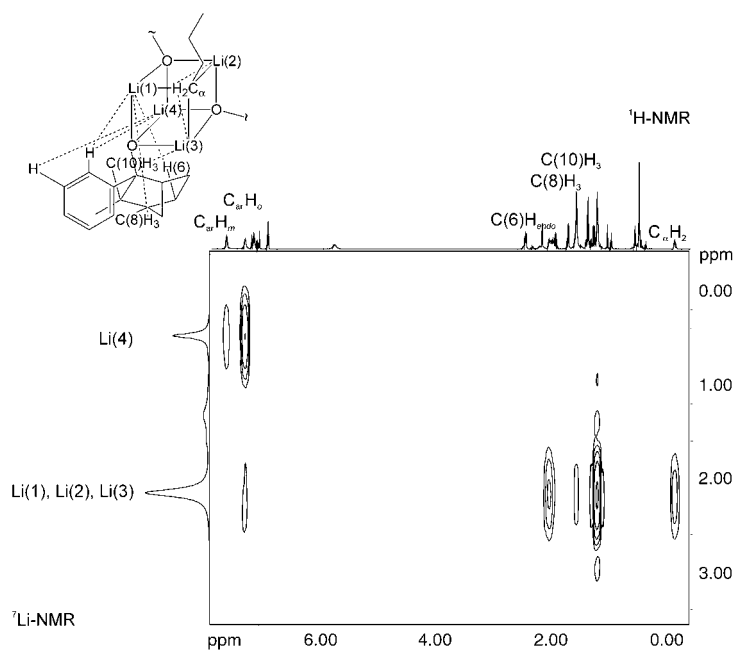


Figure 3. ^1H , ^7Li -HOESY contour plot of **3**-BuLi (-10°C , $[\text{D}_8]$ toluene, 500 MHz). Dashed lines indicate the selected correlations. Only one fencholate unit is shown for clarity.

bicyclic [2.2.1]heptane unit. In agreement with the solid state structure (Table 1, Figure 1), the Li⁺ ion exhibits agostic interactions mainly with *ortho*-hydrogen atoms of phenyl groups (Figure 3).

Conclusion

The new *n*-butyllithium phenyl fencholate **3**-BuLi demonstrates that methoxy groups are indeed dispensable for the formation of mixed organolithium aggregates with fenchols, although the manifold of *n*BuLi anisyl fencholates was hitherto ascribed to methoxy coordination. In methoxy-free **3**-BuLi, agostic *endo*-methyl coordination to the lithium ions compensates for the lack of missing Li–OMe contacts. In contrast to “classical” *n*BuLi anisyl fencholates, the aryl group orients towards the lithium ion *trans* to butylide (Li₁), and the chiral fenchane unit encapsulates the *n*-butylide unit to a greater extent. This might give rise to altered enantioselectivities in C–C couplings or lithiations. In non-polar toluene solutions and in the solid state, basically the same structures are apparent, as revealed by the results of NMR spectroscopic analysis. Hence, with **3**-BuLi, an even broader range of aryl fencholates becomes available for the design of new chiral *n*-butyllithium modifiers.

Experimental Section

General: Reactions were conducted under argon atmosphere (by using Schlenk and needle-septum techniques) with dried and degassed solvents.

X-ray crystal analyses were performed by using a Bruker Smart CCD diffractometer with a $\text{MoK}\alpha$ radiation at 200 K. Data sets corresponding to a complete sphere of data were collected by using 0.3° ω -scans. The structure was solved by using direct methods, least-squares refinement and Fourier techniques. Most hydrogen atoms were taken into account at geometrically calculated positions, C(α) hydrogen atoms were refined isotropically. NMR spectra were recorded by using a Bruker Ac 300 and DRX 500 spectrometer (^1H chemical shifts refer to toluene, ^7Li to LiBr). CCDC 192453 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

^1H , ^7Li -HOESY NMR spectroscopy experiments: All measurements were performed by using $[\text{D}_8]$ toluene at -10°C and a Bruker DRX 500 spectrometer. All 2D spectra were acquired by using non-spinning 5 mm tube diameter samples with deuterium field-frequency locking. Spectra were processed in phase-sensitive mode with square sinebell weighting both in F_1 and F_2 . The following parameters were used:^[12e] spectral window of 1000 Hz ($F_1 = ^7\text{Li}$) and 6000 Hz ($F_2 = ^1\text{H}$); 128 increments and 16 scans per increment in t_1 ; sinebell weighting in F_1 and F_2 for the phase-sensitive spectra; 10.1 μs proton 90° decoupler pulse, in inverse mode with gradient selection.

Synthesis and characterisation of **3:** *n*-Butyllithium (50.3 mL, 0.08 mol, 1.6 M solution in hexane) was added to a solution of 2-bromobenzene (12.6 g, 0.08 mol) in 20 mL THF at -78°C over 30 min. A white precipitate was formed after stirring for 20 min at -78°C . An amount of (–)-fenchone (12.9 mL, 0.08 mol) was added slowly to this suspension at -78°C , and the mixture was stirred for 12 h at room temperature. Hydrolytic workup, drying and concentration of the organic layer and distillation yielded colourless **3** (17.1 g, 93%). B.p. 106°C (1.0×10^{-2} mbar). $[\alpha]_{\text{Na}}^{20} = -31.5$ (*n*-hexane); ^1H NMR (CDCl_3 , 300 MHz): $\delta = 0.45$ (s, 3H; CH_3), 1.05 (s, 3H; CH_3), 1.14 (s, 3H; CH_3), 1.22 (m, 1H; CH_2), 1.41 (m, 1H; CH_2), 1.50 (m, 1H; CH_2), 1.61 (s, 1H; OH), 1.81 (m, 1H; CH_2), 2.21 (m, 1H; CH_2), 2.34 (m, 1H; CH_2), 7.17 (m, 1H; H_{ar}), 7.28 (m, 2H; H_{ar}), 7.56 ppm (m, 2H; H_{ar}); ^{13}C NMR (CDCl_3 , 75.5 MHz): $\delta = 17.4$, 21.3, 24.1, 30.1, 33.7, 41.9, 45.7, 49.0, 52.8, 84.1, 126.0, 127.2, 127.6, 145.1 ppm; MS(EI): 230.0 [M^+], 213.0 [$M^+ - \text{OH}$], 153.0 [$M^+ - \text{C}_6\text{H}_5$]; IR (neat): $\tilde{\nu} = 3494$ (s, OH), 3091 (w, aryl), 2990–2874 cm^{-1} (s, alkyl); elemental analysis calcd (%): C 83.43, H 9.63; found: C 83.16, H 9.60.

Synthesis and characterisation of **3-BuLi:** A solution of *n*BuLi in hexanes (1.60 M, 0.42 mL, 0.66 mmol) was added to phenyl fenchol **3** (0.115 g, 0.5 mmol) at RT. Maintaining the reaction mixture at -60°C for some days yielded **3**-BuLi as colourless crystals. Yield 54%. M.p. 160°C bubbly, 165°C gelatinous; ^1H NMR (500 MHz, $[\text{D}_8]$ toluene, -10°C): $\delta = -0.16$ (m, 2H; $\text{C}_\alpha\text{H}_2$, BuLi), 0.45 (s, 9H; 3 CH_3), 0.96 (m, 2H; CH_2 , BuLi), 1.18 (s, 9H; 3 CH_3), 1.23 (m, 2H; CH_2 , BuLi), 1.31 (m, 3H; CH_3 , BuLi; m, 2H; CH_2), 1.53 (s, 9H; 3 CH_3 ; m, 2H; CH_2), 1.67 (s, 3H; CH), 1.93 (m, 6H; CH_2 ; m, 2H; CH_2 , BuLi), 2.41 (m, 3H; CH_2), 6.88 (t, $J = 7.3$ Hz, 3H; H_{ar}), 7.09 (m, 6H; H_{ar}), 7.28 (d, $J = 7.0$ Hz, 3H; H_{ar}), 7.59 ppm (d, $J = 7.7$ Hz, 3H; H_{ar}); ^{13}C NMR (125 MHz, $[\text{D}_8]$ toluene, -10°C): $\delta = 10.1$ ($\text{C}(\alpha)\text{H}_2$ -BuLi), 14.0 (CH_3 -BuLi), 19.2 (CH_3), 23.3 (CH_3), 26.0 (CH_2), 30.9 (CH_3), 33.5 (CH_2 -BuLi), 34.7 (CH_2 -BuLi), 35.2 (CH_2), 42.0 (CH_2), 46.5 (C_q), 49.5 (CH), 53.7 (C_q), 84.1 (C_q), 124.9 (C_{ar}), 125.0 (C_{ar}), 125.1 (C_{ar}), 127.0 (C_{ar}), 127.1 (C_{ar}), 152.0 ppm (C_{ar}); ^7Li NMR (194 MHz, $[\text{D}_8]$ toluene, -10°C): $\delta = 0.48$, 2.15 ppm; X-ray crystal analysis of **3**-BuLi: $\text{C}_{52}\text{H}_{72}\text{Li}_4\text{O}_3$, $M_r = 772.86$, $T = 200(2)$ K, $\lambda = 0.71073$ Å, monoclinic crystal system, space group $P2_1$, $Z = 4$, $a = 12.6737(3)$, $b = 22.5085(5)$, $c = 16.1657(3)$ Å, $\beta = 94.045(1)^\circ$, $V = 4600.04(17)$ Å³, ρ_{calcd} : 1.116 g cm^{-3} , reflections collected: 34814, independent reflections: 14599, observed reflections: 10711 [$I > 2\sigma(I)$], absorption coefficient μ : 0.065 mm^{-1} , Flack parameter: 0.2(8), R -values [$I > 2\sigma(I)$]: $R1 = 0.046$, $wR2 = 0.093$, largest diff. peak and hole: 0.17, -0.18 $\text{e} \text{Å}^{-3}$; goodness-of-fit: 0.98.

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