Lithium Naphthalenide-Induced Reductive Alkylation and Addition of Aryl- and Heteroaryl- Substituted Dialkylacetonitriles

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Abstract: Lithium naphthalenide (LN)-induced reductive alkylation/addition reactions of aryl-, pyridyl-, and 2-thienyl-substituted dialkylacetonitriles have been investigated. Upon treatment with LN in THF at –40 °C, both aryl and pyridyl precursors could undergo the reductive decyanation smoothly, and the in situ generated carbanions could be readily trapped by alkyl halides, ketones, aldehydes, or even oxygen to afford a wide range of functionalized aromatic derivatives bearing a newly established quaternary carbon. To effect the desired reductive alkylation of 2-thienyldialkylacetonitriles, a much lower temperature such as –100 °C was required. Also with these substrates, an interesting ring-opening/S-alkylation process was observed when the reductive alkylation were performed at –78 °C to give 1-alkylsulfanyl-1,3,4-trienes. A mechanistic discussion is given for this observation.

Key words: reductive alkylation, reductive addition, reductive decyanation, nitriles, lithium naphthalenide, aryl derivatives, heteroaryl derivatives, substituted 1,3,4-trienes

The controlled creation of highly substituted quaternary carbon centers presents an interesting challenge for organic chemists.[1]The synthetic sequence involving the reductive decyanation of tertiary nitriles, followed by trapping the resulting anionic intermediates with electrophiles has served as an attractive option for this purpose. This combined operation first requires that the initial cleavage of the cyano group should be achieved in a convenient and efficient manner. Among the numerous procedures reported for decyanation, dissolving metal (Na or Li) in liquid ammonia solution has shown to be the most widely employed reagent system.[2,3] Moreover, it is essential that the anionic intermediates thus generated should maintain certain stability in order to react with an electrophile such as an alkyl halide, rather than being quickly destroyed by proton sources. In this context, the introduction of an electron-withdrawing functionality or an electronegative atom[4] to the α-carbon of the cyano group appears to be a reasonable strategy to facilitate the process. On the basis of this concept, we have developed several useful methodologies based on lithium naphthalenide (LN)-induced reductive alkylation of α-cyano derivatives during the past years.[5]

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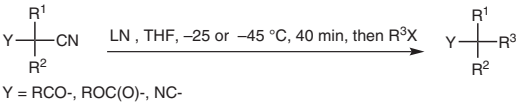
Our investigation began with the reductive alkylation of α-cyano esters[5a] and ketones [Scheme 1, Y = RO(CO), RCO].[5b] It was found that upon treatment with LN, these compounds could readily undergo the reductive decyanation, and the in situ generated enolates could then be trapped by alkyl halides (RX) to ensure the regiocontrolled introduction of various alkyl groups to the α-position of the carbonyl group. Following this, the reductive alkylation operation was further extended to the fused bicyclic α-cyano ketone[5c,d] and γ-cyano α,β-unsaturated ketone systems[5e] possessing an angular cyano group at the ring-junction positions, and the resulting alkylated products were used as the key intermediates to accomplish the total syntheses of a few clerodane diterpenoid[5f,g] and sesquiterpenoid[5e] natural products. Recently, the reductive alkylation and addition on dialkylmalononitriles (Scheme 1, Y = CN) were also attempted to allow the generation of a series of highly substituted nitriles in good yields.[5h] As expected, the above-mentioned reactions were all dependent on the efficient generation of the lithium enolates or lithiated nitriles via decyanation. The LN reagent used by us displayed a compatible C–CN bond cleaving capability as the commonly employed dissolving metals agents,[6] but it has several advantages in terms of easy preparation and handling[5a] as well as broad functional group compatibility.



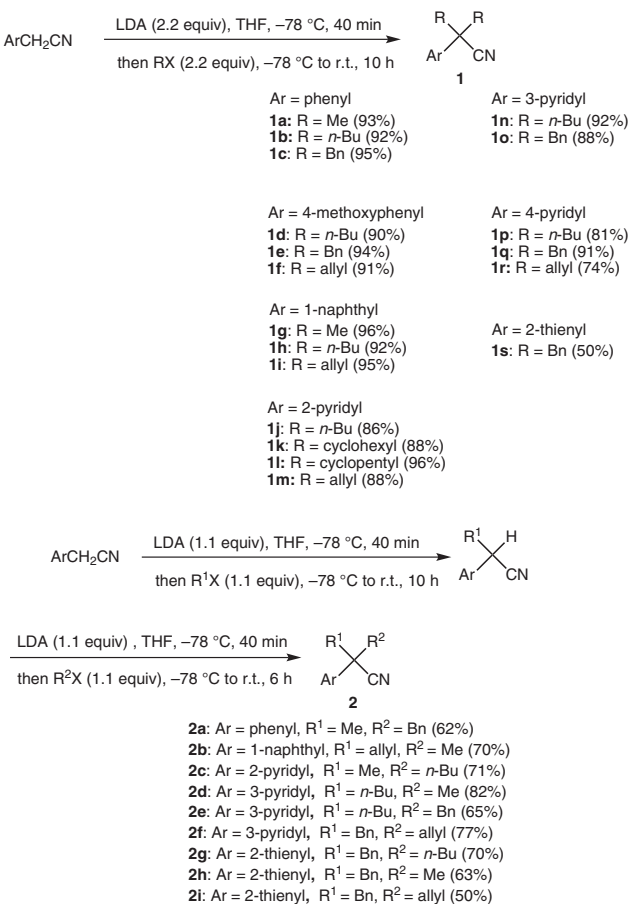
Scheme 1 Reductive alkylation of α-cyano esters, α-cyano ketones and dialkylmalononitriles

It is well known that carbanions can be stabilized by the connected aromatic functionalities.[7] In practice, these anions are usually generated by the α deprotonation of aromatic compounds using strong lithium or potassium bases.[8] Based on this, it was envisioned that such anionic intermediates could also be formed through the decyanation, and decided to study the reductive alkylation/addition reactions of α-aryl and -heteroaryl substituted nitriles, which, to our knowledge, have never been reported before. Through this investigation, we wished to develop an efficient route to highly functionalized aromatic and het-

eroaromatic compounds, which are of considerable importance in synthetic and pharmaceutical chemistry.[8b,9,10] To this end, various substrates including phenyl-, naphthyl-, 2-, 3- and 4-pyridyl- and 2-thienyldialkylacetonitriles were synthesized and evaluated for the operation. During the investigation it was found that most of the substrates could undergo the desired reactions smoothly to yield a wide range of functionalized aryl and heteroaryl derivatives in good to high yields. Herein, we wish to report these results as well as the markedly different outcomes obtained from 2-thienylacetonitriles.

The substrates used for the current study were all readily prepared from commercially available phenyl-, 4-methoxyphenyl-, 1-naphthyl-, 2-, 3- and 4-pyridyl-, and 2-thienylacetonitriles following the known procedure.[10] As outlined in Scheme 2, the alkylation of these compounds by using 2.2 equivalents of each LDA and alkylating reagents (RX), including iodomethane, 1-bromobutane, benzyl bromide, allyl bromide, 1,5-dibromopentane, and 1,4-dibromobutane, afforded precursors **1a–s** possessing two identical alkyl groups. Besides, several unsymmetrical precursors ($R^1 \neq R^2$) were also synthesized via two alkylation steps, which involved the first alkylation with 1.1 equivalents of an alkylating reagent (R^1X) and LDA, followed by the reaction of the resulting monoalkylated intermediate with another alkylating reagent (R^2X). In such a manner, compounds **2a–i** were obtained in 50–82% yields over two steps.

The reductive alkylation/addition reactions of aromatic acetonitriles **1a–i**, **2a**, and **2b** were initially examined. It was found that the decyanation of these substrates could be readily achieved within 40 minutes by treating with LN (3 equiv)[11] in THF at –40 °C. The subsequent addition of electrophiles (4 equiv) to the reaction mixtures, followed by continuous reaction at room temperature for a period of time allowed the formation of products **3a–x**[12] as shown in Table 1. Among which, the addition reactions with the carbonyl electrophiles including acetone, benzaldehyde, and 2-furancarbaldehyde could be completed in two hours to afford the corresponding aromatic alcohols in good to high yields (62–90%). On the other hand, much longer reaction time was required (16 h) for the reductive alkylation reactions with the use of iodomethane, 1-bromobutane, 4-bromobut-1-ene, benzyl bromide, allyl bromide, and ethyl bromoacetate as the alkylating agents. The alkylated products were generally formed in moderate to good yields (52–71%), except for **3m** (entry 13) from the reaction of **1e** with ethyl bromoacetate. The formation of **3m** in 30% yield along with a significant amount of unidentified by-products presumably resulted from the competitive deprotonation of the alkylating reagent. For some alkylation reactions, 15–25% of decyanated by-products were isolated together with the major alkylated products (entries 3, 10, 15, 16, 18–20, and 22), and this could not be circumvented by prolonged reaction time. For a given substrate, it was observed that the yield(s) of reductive addition reaction(s) with ketone and/or aldehyde was unexceptionally higher than that of the



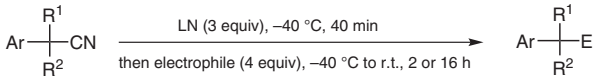
Scheme 2 Preparation of aryl- and heteroaryldialkylacetonitrile substrates

reductive alkylation reaction(s). Taking **1f** as an example, its reductive alkylation with iodomethane and 1-bromobutane afforded **3o** and **3p** in 52% and 58% yield, respectively (entries 15 and 16), while a much higher yield (71%, entry 17) was obtained from its addition reaction with acetone. Apart from the inherent strong electrophilicity of the carbonyl electrophiles, the higher yields of the addition reactions might be associated with the activation of the carbonyl groups by coordination with lithium ion.

In addition to aromatic dialkylacetonitriles, the above-mentioned reaction conditions are also compatible with pyridyl substrates. As shown in Table 2, the reactions of 2-pyridyl precursors **1j–m**, **2c** with LN and various alkylating reagents yielded products **4a–i** in 71–94% yields (entries 1–9), generally higher than those of the alkylation reactions listed in Table 1. The higher yields should be attributed to the relatively strong anion-stabilizing capability of the 2-pyridyl moiety. Besides, the reductive alkylation and addition of 3-pyridyl substrates **1n**, **1o**, and **2d** with alkyl halides and aldehydes also proceeded smoothly to afford compounds **4j–o** in 60–80% yields (entries 10–15). More interestingly, it was discovered that after the decyanation of **2e** and **2f** was completed, purging oxygen to the reaction mixtures at –78 °C could result in the formation of alcohols **4p** and **4q** with the cyano group being directly replaced by a hydroxy group (entries 16 and

17). The excess of LN reagent might be responsible for the cleavage of oxygen–oxygen bond of the peroxide intermediates in these cases. Finally, the reductive alkylations of 4-pyridyl precursors **1p**, **1q**, and **1r** were performed respectively with three different alkylating reagents, to afford **4r**–**t** in the yields of 48–78% (entries 18–20). Combined with the reactions shown in Table 1, we have thus developed an efficient route to highly functionalized aryl and pyridyl derivatives bearing a controllable quaternary carbon center.

Table 1 LN-Induced Reductive Alkylation and Addition of Aromatic Dialkylacetonitriles



Ar = phenyl, 4-methoxyphenyl, 1-naphthyl

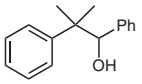
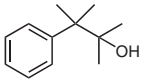
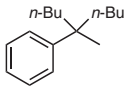
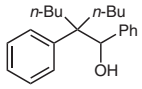
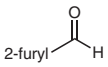
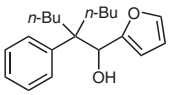
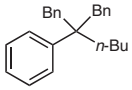
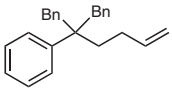
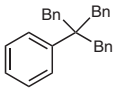
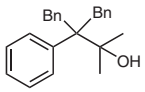
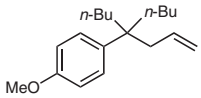
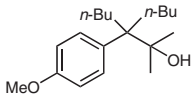
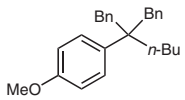
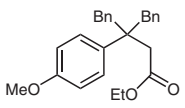
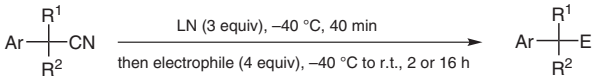
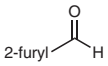
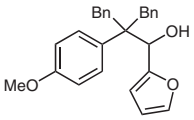
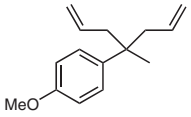
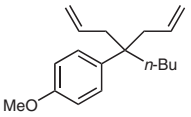
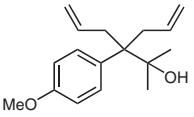
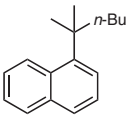
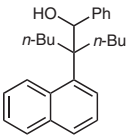
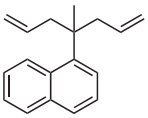
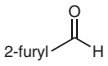
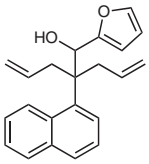
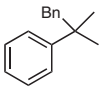
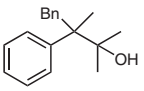
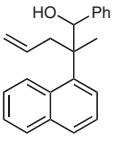
Entry[a]	Substrate	Electrophile	Product	Yield (%)[b]
1	**1a**		**3a** 	82
2	**1a**		**3b** 	75
3[c]	**1b**	MeI	**3c** 	53
4	**1b**		**3d** 	90
5	**1b**		**3e** 	77
6	**1c**	*n*-BuBr	**3f** 	68
7	**1c**	CH_2=$CHCH_2CH_2Br$	**3g** 	71
8	**1c**	BnBr	**3h** 	70
9	**1c**		**3i** 	83
10[c]	**1d**	CH_2=$CHCH_2Br$	**3j** 	56
11	**1d**		**3k** 	75
12	**1e**	*n*-BuBr	**3l** 	66
13	**1e**	$BrCH_2CO_2Et$	**3m** 	30

Table 1 LN-Induced Reductive Alkylation and Addition of Aromatic Dialkylacetonitriles (continued)

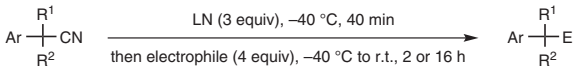


Ar = phenyl, 4-methoxyphenyl, 1-naphthyl

Entry[a]	Substrate	Electrophile	Product	Yield (%)[b]
14	**1e**		**3n**		83
15[c]	**1f**	MeI	**3o**		52
16[c]	**1f**	*n*-BuBr	**3p**		58
17	**1f**		**3q**		72
18[c]	**1g**	*n*-BuBr	**3r**		48
19[c]	**1h**		**3s**		86
20[c]	**1i**	MeI	**3t**		53
21	**1i**		**3u**		74
22[c]	**2a**	MeI	**3v**		54
23	**2a**		**3w**		62
24	**2b**		**3x**		75

[a] Additions reactions were all performed for 2 h at r.t., while alkylation reactions were all carried out for 16 h at r.t.
[b] Isolated yield.
[c] Decyanated by-product was isolated.

Table 2 LN-Induced Reductive Alkylation and Addition of Pyridyldialkylacetonitriles



Ar = 2-pyridyl, 3-pyridyl, 4-pyridyl

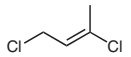
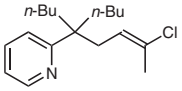
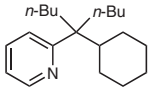
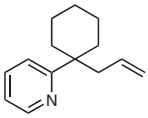
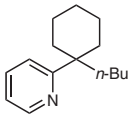
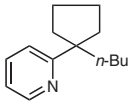
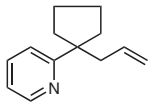
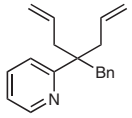
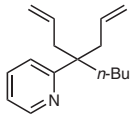
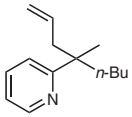
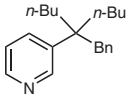
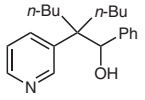
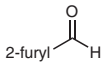
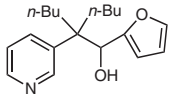
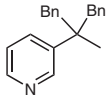
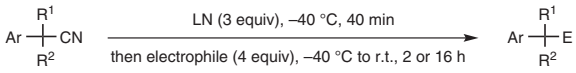
Entry[a]	Substrate	Electrophile	Product	Yield (%)[b]
1	**1j**		**4a**		92
2	**1j**		**4b**		78
3	**1k**	CH_2=$CHCH_2Br$	**4c**		84
4	**1k**	*n*-BuBr	**4d**		87
5	**1l**	*n*-BuBr	**4e**		75
6	**1l**	CH_2=$CHCH_2Br$	**4f**		71
7	**1m**	BnBr	**4g**		94
8	**1m**	*n*-BuBr	**4h**		92
9	**2c**	*n*-BuBr	**4i**		86
10	**1n**	BnBr	**4j**		62
11[c]	**1n**		**4k**		77
12[c]	**1n**		**4l**		75
13	**1o**	MeI	**4m**		70

Table 2 LN-Induced Reductive Alkylation and Addition of Pyridyldialkylacetonitriles (continued)



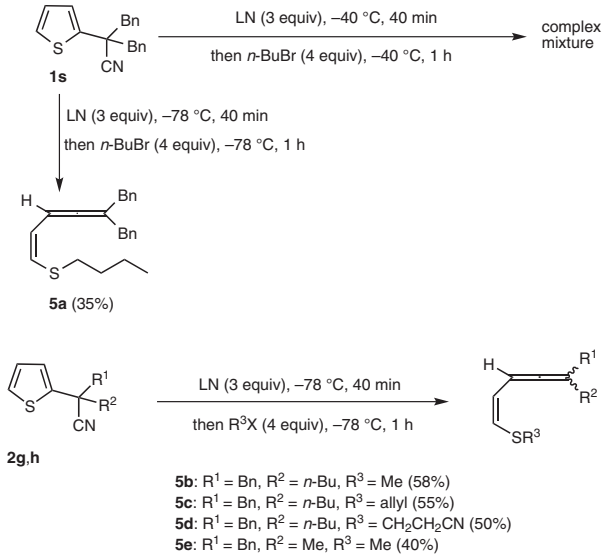
Ar = 2-pyridyl, 3-pyridyl, 4-pyridyl

Entry[a]	Substrate	Electrophile	Product	Yield (%)[b]
14	**1o**	*n*-BuBr	**4n**	60
15	**2d**	BnBr	**4o**	80
16[d]	**2e**	O_2	**4p**	48
17[d]	**2f**	O_2	**4q**	60
18	**1p**	MeI	**4r**	78
19	**1q**	*n*-BuBr	**4s**	48
20	**1r**	BnBr	**4t**	52

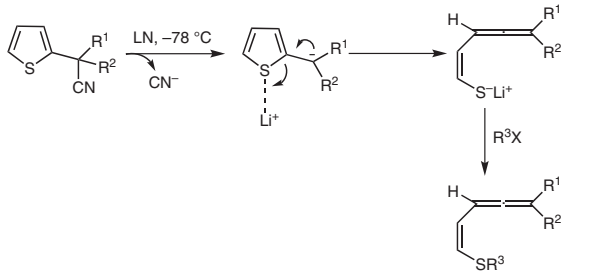
[a] Alkylation reactions were all carried out for 16 h at r.t.
[b] Isolated yield.
[c] Addition reaction with aldehyde was performed for 2 h at r.t.
[d] Addition reaction with oxygen was conducted at –78 °C for 2 h.

Significantly different results were obtained when the aforementioned reaction conditions were applied to 2-thienyldialkylacetonitriles. As illustrated in Scheme 3, the reaction of **1s** with LN and 1-bromobutane at –40 °C merely gave a complex mixture rather than the desired alkylated product. When carried out at –78 °C, the reaction unexpectedly afforded 5-(benzyl-6-phenylhexa-1,3,4-trienyl)butylsulfane (**5a**) in 35% yield. Under the same reaction conditions, the formation of trienes **5b–e** was also observed for the unsymmetrical precursors **2g** and **2h** by using iodomethane, allyl bromide, and 3-bromopropionitrile as the alkylating agents. The generation of the trienes apparently resulted from the opening of the thiophene ring. At this stage, however, it was unclear for us whether the ring-opening happened before or after the addition of alkylting agent. To address this question, an experiment was subsequently conducted by treating **1s** with LN at –78 °C for 40 minutes, and then quenching the reaction with saturated NH_4Cl aqueous solution. The reaction gave only a mixture of several unidentified by-products with the cyano carbon signal disappearing on the ^{13}C NMR spectrum, but without any trace of the decyanated thiophene. Therefore, it can be proposed that the 2-thienyl group has poor anion-stabilizing capability, and once the reductive decyanation occurred, the initially formed anionic intermediate would be prone to undergo the ring-opening and transfer the negative charge to the sulfur atom. The addition of an alkyl halide thereafter would cause the formation of the S-alkylated triene. In the event, the coordination between sulfur atom and a lithium ion might assist the cleavage of sulfur–carbon bond (Scheme 4). It should be noted that **5b–e** were all produced as the single isomers in *E*- or *Z*-form.[13] Moreover, regarding several potential nucleophilic sites of the sulfide intermediate, it would not be surprising for us to see the formation of complex by-products.

It was assumed that the initially formed anionic intermediates might be stable at lower temperatures,[14] and thus attempted the reaction of **1s** with 1-bromobutane at –100 °C. To our delight, the alkylated product **6a** could be produced in 70% yield under the conditions, suggesting that temperature-control indeed played an essential role in maintaining the stability of the anion. Further application

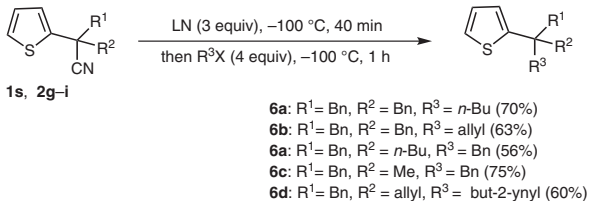


Scheme 3 Preparation of **5**



Scheme 4 Proposed mechanism for the formation of 1-alkylsulfanyl-1,3,4-trienes

of the reaction conditions to **1s** with allyl bromide, **2g**, **2h** with benzyl bromide, and **2i** with 1-bromobut-2-yne also resulted in the formation of desired alkylated products **6a–d** in 56–75% yields (Scheme 5). Our original goal of bringing about the reductive alkylation to the 2-thienyl substrates has therefore been fulfilled.



Scheme 5 Reductive alkylation of 2-thienyldialkylacetonitriles

In summary, we have developed an efficient and general procedure for preparing highly substituted aromatic and heteroaromatic derivatives, which are otherwise difficult to synthesize. Among the substrates investigated, both aryl and pyridyl substituted acetonitriles underwent the reductive decyanation readily at –40 °C, and the resulting anionic intermediates could be easily trapped by various electrophiles to afford a range of aromatic and heteroaromatic derivatives with variable functionalities. On the other hand, the unique reactivity was observed for 2-thienyldialkylacetonitriles. The designed reductive alkylation of these substrates was achieved at a much lower temperature (–100 °C) due to the weaker anion-stabilizing ability of the thiophene group. Also with these compounds, an interesting and novel reductive ring-opening/S-alkylation process was observed when the reactions were performed at –78 °C. This finding has potentially led to a new approach to synthesize thiotriene compounds. Currently, the investigation on the detailed correlation between temperatures and the reactivity of 2-thienyl substrates is ongoing in our group.

All starting materials were obtained from commercial suppliers and used without further purification. All reactions were performed under an atmosphere of argon. THF was distilled from sodium benzophenone, and *i*-Pr_2NH was distilled from CaH_2 before use. Lithium naphthalenide reagent was freshly prepared as a 0.50 M THF solution[11] before each use. TLC analyses were performed on Merck 25 DC-Alufolien Kieselgel 60F254 aluminum-backed plates and visualized by UV or permanganate treatment. All products were purified by flash chromatography using Merck Art. 9385 Kieselgel 60 silica gel (230–400 mesh), and characterized by IR, ^1H and ^{13}C NMR, DEPT 90 and 135, and HRMS. IR spectra were recorded on a JASCO FT/IR 410 spectrometer. ^1H, ^{13}C NMR, DEPT 90 and 135 spectra were recorded on a Varian Unity-400, a Varian Mercury-400 or a Bruker DMX-600 spectrometer using $CDCl_3$ as solvent. High resolution mass spectra (HRMS) were determined by using a JEOL JMS-HX110 high-resolution mass spectrometer in an electron impact (EI, 70 eV) mode. Melting points were determined on noncalibrated Büchi B-540 melting point apparatus.

Reductive Addition of Aryl- and Pyridyldialkylacetonitriles; 2-Butyl-1,2-diphenylhexan-1-ol (3d); Typical Procedure

To a stirred solution of **1b** (200 mg, 0.87 mmol) in THF (10 mL) precooled at –40 °C was slowly added lithium naphthalenide in THF (0.5 M, 5.3 mL, 2.65 mmol) in 5 min via a syringe under an argon atmosphere. The resulting dark green solution was stirred at –40 C for 40 min and treated with benzaldehyde (0.4 mL, 3.48 mmol). The reaction mixture was warmed to r.t. within 1 h and stirred at r.t. for 1 h. The mixture was then poured into sat. aq NH_4Cl (10 mL), and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL) and concentrated. Chromatographic purification on silica gel (hexane–EtOAc, 18:1) afforded **3d** as a colorless oil (243 mg, 90%).

IR (neat): 3479, 3014, 1602, 1210 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.11 (m, 8 H), 6.68 (d, *J* = 7.2 Hz, 2 H), 4.75 (s, 1 H), 2.14–1.96 (m, 2 H), 1.85 (br, OH), 1.72–1.59 (m, 2 H), 1.45–1.17 (m, 8 H), 0.96 (t, *J* = 7.2 Hz, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.2 (C), 141.4 (C), 128.5 (2 × CH), 127.7 (2 × CH), 127.3 (2 × CH), 127.1 (CH), 127.0 (2 × CH), 125.1 (CH), 79.6 (CH), 48.5 (C), 32.9 (CH_2), 32.8 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 23.6 (CH_2), 23.5 (CH_2), 14.1 (CH_3), 14.0 (CH_3)

HRMS-EI: *m/z* $[M]^+$ calcd for $C_{22}H_{30}O$: 310.2297; found: 310.2293.

Reductive Alkylation of Aryl- and Pyridyldialkylacetonitriles; 2-Benzyl-1,2-diphenylhexane (3f); Typical Procedure

To a stirred solution of **1c** (200 mg, 0.67mmol) in THF (8 mL) precooled at –40 °C was slowly added lithium naphthalenide in THF (0.5 M, 4.1 mL, 2.05 mmol) in 5 min via a syringe under an argon atmosphere. The resulting dark green solution was stirred at –40 °C for 40 min and treated with 1-bromobutane (0.29 mL, 2.68 mmol). The reaction mixture was warmed to r.t. within 1 h and stirred at r.t.

for 16 h, then quenched with sat. aq NH_4Cl (8 mL), and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL) and concentrated. The crude product was subjected to chromatographic purification on silica gel (hexane–EtOAc, 50:1) to give **3f** as a white solid (150 mg, 68%); mp 76–77 °C.

IR (neat): 2934, 1600, 1496 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 6 H), 3.87–6.83 (m, 3 H), 7.14–7.12 (m, 6 H), 3.17 (d, *J* = 13.6 Hz, 2 H), 3.10 (d, *J* = 13.6 Hz, 2 H), 1.64–1.60 (m, 2 H), 1.50–1.42 (m, 2 H), 1.30 (tq, *J* = 7.0, 7.6 Hz, 2 H), 0.91 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9 (C), 138.4 (2 × C), 130.4 (4 × CH), 127.8 (2 × CH), 127.5 (4 × CH), 127.4 (2 × CH), 125.8 (2 × CH), 125.6 (CH), 45.7 (C), 44.9 (2 × CH_2), 33.5 (CH_2), 26.0 (CH_2), 23.1 (CH_2), 14.1 (CH_3).

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{25}H_{28}$: 328.2191; found: 328.2184.

Reductive Addition with Oxygen to Pyridyldialkylacetonitriles; 1-Phenyl-2-pyridin-3-ylhexan-2-ol (4p); Typical Procedure

To a stirred solution of **2e** (200 mg, 0.76 mmol) in THF (10 mL) precooled at –40 °C was slowly added lithium naphthalenide in THF (0.5 M, 4.6 mL, 2.30 mmol) in 5 min via a syringe under an argon atmosphere. The resulting dark green solution was stirred at –40 °C for 40 min, then cooled to –78 °C and purged with O_2 for 1 h. The reaction mixture was then quenched with sat. aq NH_4Cl (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (15 mL) and concentrated. Chromatographic purification on silica gel (hexane–EtOAc, 3:1) yielded **4p** as a yellowish oil (93 mg, 48%).

IR (neat): 3231, 2955, 1590, 1576 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 1.6 Hz, 1 H), 8.42 (d, *J* = 4.4 Hz, 1 H), 7.63 (dt, *J* = 8.0, 1.6 Hz, 1 H), 7.22 (dd, *J* = 8.0, 4.4 Hz, 1 H), 7.18-7.13 (m, 3 H), 6.95–6.91 (m, 2 H), 3.10 (d, *J* = 13.6 Hz, 1 H), 3.05 (d, *J* = 13.6 Hz, 1 H), 1.93 (dt, *J* = 12, 3.6 Hz, 1 H), 1.79 (dt, *J* = 12, 3.6 Hz, 1 H), 1.32–1.16 (m, 3 H), 1.01–0.91 (m, 1 H), 0.79 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.1 (CH), 147.0 (CH), 141.4 (C), 135.6 (C), 133.8 (CH), 130.6 (CH), 128.2 (CH), 126.8 (CH), 122.9 (CH), 75.5 (C), 49.5 (CH_2), 41.5 (CH_2), 25.5 (CH_2), 22.9 (CH_2), 13.9 (CH_3).

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{17}H_{21}NO$: 255.1623; found: 255.1613.

Generation of 1-Alkylsulfanyl-1,3,4-triene from 2-Thienyldialkylacetonitriles; (5-Benzyl-6-phenylhexa-1,3,4-trienyl)(butyl)sulfane (5a); Typical Procedure

To a stirred solution of **1s** (100 mg, 0.33 mmol) in THF (5 mL) precooled at –78 °C was slowly added lithium naphthalenide in THF (0.5 M, 1.98 mL, 0.99 mmol) in 5 min via a syringe under an argon atmosphere. The resulting dark green solution was stirred at –78 °C for 40 min and treated with 1-bromobutane (0.14 mL, 1.32 mmol). The reaction mixture was stirred at –78 °C for 1 h, quenched with sat. aq NH_4Cl (4 mL) and extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with brine (5 mL) and concentrated. The purification of the crude products on silica gel (hexane–EtOAc, 20:1) provided **5a** as a yellowish oil (39 mg, 35%).

IR (neat): 3027, 2956, 2929, 1942, 1602 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.10 (m, 10 H), 6.10–5.89 (m, 3 H), 3.28 (s, 4 H), 2.68 (t, *J* = 7.2 Hz, 2 H), 1.62–1.36 (m, 4 H), 0.91 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.2 (C), 139.1 (C), 129.0 (3 × CH), 128.2 (3 × CH), 126.2 (2 × CH), 125.8 (CH), 123.1 (CH), 104.4 (C), 90.3 (CH), 38.5 (CH_2), 34.1 (CH_2), 32.3 (CH_2), 21.6 (CH_2), 13.6 (CH_3).

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{23}H_{26}S$: 334.1755; found: 334.1748.

Reductive Alkylation of 2-Thienyldialkylacetonitriles; 2-(1,1-Dibenzylpentyl)thiophene (6a); Typical Procedure

To a stirred solution of **1s** (200 mg, 0.66 mmol) in THF (8 mL) precooled at –100 °C was slowly added lithium naphthalenide in THF (0.5 M, 3.95 mL, 1.98 mmol) in 5 min via a syringe under an argon atmosphere. The resulting dark green solution was stirred at –100 °C for 40 min and treated with 1-bromobutane (0.28 mL, 2.64 mmol). The reaction mixture was stirred at –100 °C for 1 h, quenched with sat. aq NH_4Cl (8 mL) and extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (10 mL) and concentrated. Chromatographic purification on silica gel (hexane–EtOAc, 30:1) gave **6a** as a white solid (154 mg, 70%); mp 61–63 °C.

IR (neat): 3028, 2934, 1602, 1495, 1455 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.20 (m, 7 H), 7.07–6.91 (m, 5 H), 6.55 (d, *J* = 3.6 Hz, 1 H), 3.14 (d, *J* = 13.6 Hz, 2 H), 3.02 (d, *J* = 13.6 Hz, 2 H), 1.62–1.25 (m, 6 H), 0.91 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3 (C), 137.8 (2 × C), 130.3 (4 × CH), 127.5 (4 × CH), 126.2 (CH), 126.1 (2 × CH), 124.5 (CH), 122.9 (CH), 46.8 (CH_2), 45.8 (C), 35.1 (CH_2), 25.9 (CH_2), 23.0 (CH_2), 14.1 (CH_3).

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{23}H_{26}S$: 334.1755; found: 334.1755.

Following the same procedure, **6a** was also prepared from **2g** and benzyl bromide in 56% yield.

Acknowledgment

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