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Reductive Cleavage of Benzannelated Cyclic Ethers and Amines: Synthetic Applications

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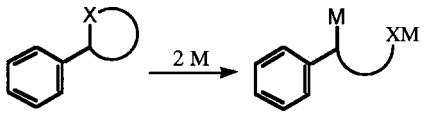
Abstract—Reduction of symmetrical intramolecular diarylmethyl ethers (**3a** and **8a**) and amines (**3b** and **8b**) with alkali metals in THF allows the generation of unsymmetrical oxy- or amino-functionalised arylmethyl organometallics. Such intermediates were successfully trapped with various electrophiles, allowing a new access to unsymmetrically 2,2′-disubstituted-1,1′-biaryls (**5aa**–**5bf**) and 1,8-disubstituted naphthalenes (**10aa**–**10be**).

Introduction

Reductive cleavage of the arylalkyl carbon–heteroatom bond of 2-aryl-substituted oxygen or nitrogen heterocycles by electron transfer from alkali metals in ethereal solvents is a useful approach to the generation of 1-arylalkyl organometallics which are functionalised with an oxyanionic or an aminoanionic group, suitable for further elaboration (Scheme 1). Interesting results on this topic include: the reductive cleavage of styrene oxide,[1] 1,3-dihydroisobenzofurans (phthalans),[2,3] *N*-phenylisoindoline,[4] 4-phenyl-1,3-dioxanes,[5] 2-aryl-1,3-oxazolidines.[6] Due to these satisfactory results and to the current interest in electron-transfer reactions mediated by alkali metals,[7–11] we further investigated the synthetic exploitation of this approach.

As already observed with phthalan[2,3] and *N*-phenylisoindoline,[4] reductive metalation of symmetrical oxygen and nitrogen heterocycles allows the generation of unsymmetrical organometallics. Accordingly, we wish to present here applications of this procedure to suitable six- and seven-membered dibenzo-oxygen and -nitrogen heterocycles leading to the synthesis of unsymmetrically disubstituted biaryls and naphthalenes.



Scheme 1. X=O, NCH_3; M=alkali metal

Keywords: amines; ethers; carbanions; lithium and compounds; reduction.
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Results and Discussion

Synthesis of unsymmetrically 2,2′-disubstituted-1,1′-biaryls

Unsymmetrically disubstituted biaryls are an important class of organic compounds which find useful application in the synthesis of pharmaceuticals, ligands, polymers, and liquid crystals. Most approaches to their synthesis rely on the cross-coupling of aromatic halides or triflates with suitable partners.[12,13]

We investigated an alternative approach to 2,2′-disubstituted-1,1′-biaryls having 6,7-dihydro-5*H*-dibenz[*c*,*e*]oxepine (diphenane), **3a**, or 6,7-dihydro-6-methyl-5*H*-dibenz[*c*,*e*]azepine (*N*-methyldibenzazepine), **3b**, as key intermediates (Scheme 2). Commercially available anhydride **1** was reduced with $LiAlH_4$ in THF, affording 2,2′-hydroxymethyl-1,1′-diphenyl, **2**, in 80% yield; diol **2** was cyclised with 85% H_3PO_4 to give ether **3a** in 82% isolated yield.

Alternatively, reaction of diol **2** with 48% HBr, followed by aminolysis of the crude dibromide with 40% aqueous CH_3NH_2, afforded amine **3b** in 85% overall yield.

Reductive cleavage of ether **3a** by electron transfer from alkali metals in ethereal solvents should generate the corresponding unsymmetrical dianion **4a**. Further reaction of such an intermediate with electrophilic reagents should lead to the synthesis of 2-hydroxymethyl-2′-substituted-1,1′-biaryls **5a**. Application of a similar reaction sequence to amine **3b** should allow the synthesis of 2-*N*-methylaminomethyl-2′-substituted-1,1′-biaryls **5b** via the intermediate formation of the corresponding dianion **4b**.

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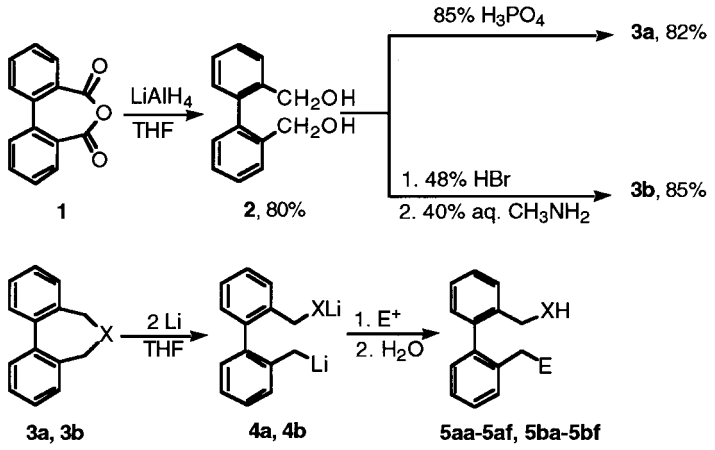


Scheme 2. X=O, NCH_3

Reductive lithiation of ether 3a

Reductive cleavage reactions were carried out under Ar in THF with an excess of Li dispersion. Selected results are reported in Table 1. The results of D_2O quenching experiments, carried out to check the formation of intermediate organometallic derivatives are also reported.

Effective reductive cleavage of **3a** was accomplished with Li metal (5 equiv.) in the presence of a catalytic amount of naphthalene (10 mol%) in THF at rt during 2 h. Under these conditions we observed exclusive formation of 2-hydroxymethyl-2′-methyl-1,1′-biphenyl, **5aa**; quenching the reaction mixture with D_2O resulted in 70% deuteration at the arylmethyl position, as evidenced by ^1H NMR spectroscopic analysis of the crude reaction mixture (Table 1, entries 1 and 2).

A similar result was obtained when the reaction was performed at 0°C (not reported in Table 1), whilst performing the reaction at −15°C and quenching it with D_2O showed quantitative intermediate formation of the corresponding arylmethyllithium derivative (Table 1, entry 3).

Due to the above reported results, reductive eletrophilic substitution reactions of **3a** were performed at −15°C. The dilithium derivative **4a** was efficiently trapped with primary and secondary alkyl halides, chlorotrimethylsilane and acetone, affording the corresponding 2-hydroxymethyl-2′-substituted-1,1′-biphenyl derivatives **5ac**–**5af**, respectively, in satisfactory yields (Table 1, entries 4–7).

Reductive lithiation of amine 3b

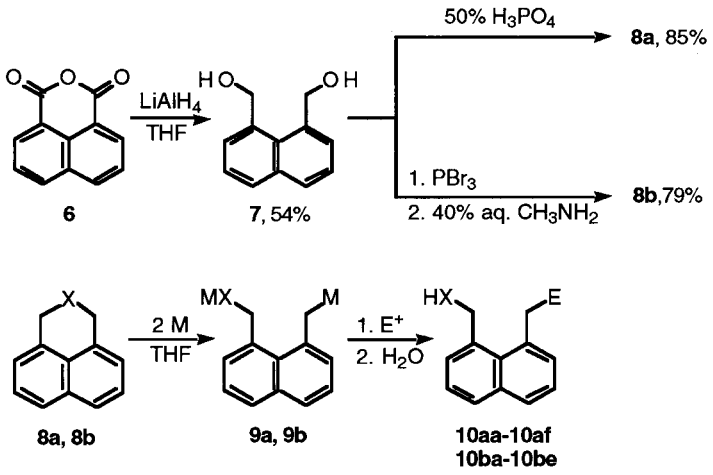
Reductive lithiation of amine **3b** was efficiently obtained at 0°C in the presence of 5 equiv. of Li metal and a catalytic amount of naphthalene (10 mol%) after 6 h. Under these conditions 2-methyl-2′-*N*-methylaminomethyl-1,1′-biphenyl, **5ba**, was obtained in quantitative yield via quantitative intermediate formation of the corresponding dilithium derivative **4b** (Table 1, entries 8 and 9).

Under these conditions, quenching the intermediate **4b** with $(CH_3)_2CHBr$ and chlorotrimethylsilane afforded compounds **5bc** and **5bd**, respectively, in satisfactory yields (Table 1, entries 10 and 11). At variance with these results, quenching the intermediate **4b** with *n*-BuBr at 0°C afforded an intractable reaction mixture (not reported in Table 1). However, addition of the electrophile to a suspension of the organolithium reagent at −40°C afforded compound **5be** in 75%

Table 1. Reductive cleavage and electrophilic substitution of compounds **3a** and **3b**

Entry	Compound, X=	*T* (°C)	*t* (h)	EX	Product, E=	Yield (%)[a,b]
1	**3a**, O	20	2	H_2O	**5aa**, H	>95
2	**3a**, O	20	2	D_2O	**5ab**, D	70[c]
3	**3a**, O	−15	3	D_2O	**5ab**, D	>95[c]
4	**3a**, O	−15	3	BuBr	**5ac**, Bu	85
5	**3a**, O	−15	3	$(CH_3)_2CHBr$	**5ad**, $(CH_3)_2CH$	56
6	**3a**, O	−15	3	$(CH_3)_3SiCl$	**5ae**, $(CH_3)_3Si$	72
7	**3a**, O	−15	3	Acetone	**5af**, $(CH_3)_2COH$	57
8	**3b**, NCH_3	0	6	H_2O	**5ba**, H	>95
9	**3b**, NCH_3	0	6	D_2O	**5bb**, D	>95[c]
10	**3b**, NCH_3	0	6	$(CH_3)_2CHBr$	**5bc**, $(CH_3)_2CH$	47
11	**3b**, NCH_3	0	6	$(CH_3)_3SiCl$	**5bd**, $(CH_3)_3Si$	68
12	**3b**, NCH_3	0	6	BuBr[d]	**5be**, Bu	75
13	**3b**, NCH_3	0	6	Acetone[e]	**5bf**, $(CH_3)_2COH$	75

[a] All reactions run in the presence of 5 equiv. of Li and 10 mol% of naphthalene; reaction time with the electrophile (1.1 equiv.)=15 min.
[b] Isolated yield, unless otherwise indicated.
[c] As determined by ^1H NMR spectroscopy, unless otherwise indicated.
[d] Added at −40°C.
[e] Added at −80°C.



Scheme 3. X=O, NCH_3; M=Li, K

isolated yield (Table 1, entry 12). A related procedure allowed us to obtain aminoalcohol **5bf** in good isolated yield (Table 1, entry 13).

Synthesis of unsymmetrically 1,8-disubstituted naphthalenes

Regioselective synthesis and functionalization of the naphthalene core skeleton is an attractive topic in organic synthesis: indeed, this skeleton is present in several biologically active compounds.[14,15]

Unsymmetrically 1,8-disubstituted naphthalenes can be synthesised by perilithiation of suitable 1-substituted naphthalenes[16–20] or via elaboration of symmetrically 1,8-disubstituted naphthalenes.[17]

However, perilithiation suffers competing ortholithiation and is restricted to *N*,*N*-dimethylaminonaphthalene or *N*,*N*-dimethylaminomethylnaphthalene; furthermore, as recently pointed out,[17] several difficulties can be encountered in the unsymmetrical elaboration of commercially available 1,8-disubstituted naphthalenes, like acenaphthenequinone or 1,8-naphthalic anhydride. As an alternative to these procedures, we investigated the synthetic route depicted in Scheme 3.

Reduction of 1,8-naphthalic anhydride **6** with $LiAlH_4$ in THF afforded the corresponding diol **7** in 54% isolated yield. Diol **7** was cyclised with 50% H_3PO_4 to give 1*H*,3*H*-benzo[*de*]isochromene (1,8-naphthalan), **8a**, in 85% isolated yield.

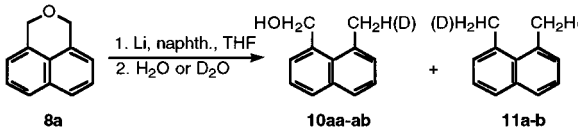
Alternatively, reaction of diol **7** with PBr_3, followed by aminolysis of the crude dibromide with 40% aqueous CH_3NH_2, afforded 2-methyl-2,3-dihydro-1*H*-benzo[*de*]isoquinoline, **8b**, in 79% overall yield.

Application of the reductive eletrophilic substitution procedure to compounds **8** should result in a new synthesis of 1,8-unsymmetrically disubstituted naphthalenes **10** via intermediate organometallics **9**.

Reductive metallation of ether 8a

Reductive cleavage reactions were carried out under Ar in dry THF using Li dispersion or K sand as reducing agents; selected results are reported in Table 2.

Depending upon the reaction conditions, reductive cleavage of **8a** afforded, besides the expected 1-hydroxymethyl-8-methylnaphthalene, **10aa**, variable amounts of 1,8-dimethylnaphthalene, **11a**, i.e. the product of a double reductive cleavage reaction (Eq. (1)).



(1)

Indeed, reaction of **8a** with 5 equiv. of Li and 10 mol% of naphthalene at 0°C led to the formation of alcohol **10aa** as the main reaction product (Table 2, entry 1). Decreasing the reaction temperature led to low conversion of the substrate and did not result in complete suppression of the second cleavage reaction (Table 2, entries 2 and 3). We ran several other experiments (not reported in Table 2) with different amounts of Li and different reaction times and temperatures, but were unable to avoid the second cleavage reaction under practical reaction conditions. Furthermore, D_2O quenching experiments (not reported in Table 2) suggested that formation of **11** occurred via an intermediate dicarbanion. These observations strongly suggest formation of the hydrocarbon via two successive reductive cleavage reactions, as already observed in the reductive cleavage of 1,3-dihydronaphtho[2,3-*c*]furan (2,3-naphthalan);[2] lithium oxide probably acts as a leaving group in the second cleavage step.

Looking for a practical and selective access to alcohol **10aa**, we investigated the reductive cleavage of ether **8a** with 5 equiv. of K metal and 10 mol% of naphthalene at −30°C; under these reaction conditions, aqueous work up of the reaction mixture afforded alcohol **10aa** as the only reaction product (Table 2, entry 4); quenching the reaction

Table 2. Reductive cleavage and electrophilic substitution of compounds **8a** and **8b**

Entry	Compound, X=	M (equiv.)	T (°C)	t (h)	EX	Product, E=	Yield (%)[a,b]
1	**8a**, O	Li (5)	0	2	H_2O	**10aa**, H	42[c,d]
2	**8a**, O	Li (5)	−15	7	H_2O	**10aa**, H	55[c,e]
3	**8a**, O	Li (5)	−65	7	H_2O	**10aa**, H	28[c,f]
4	**8a**, O	K (5)	−30	5	H_2O	**10aa**, H	>95
5	**8a**, O	K (5)	−30	5	D_2O	**10ab**, D	45[c]
6	**8a**, O	K (5)	−45	5	D_2O	**10ab**, D	83[c]
7	**8a**, O	K (5)	−45	5	BuBr	**10ac**, Bu	63
8	**8a**, O	K (5)	−45	5	$(CH_3)_2CHBr$	**10ad**, $(CH_3)_2CH$	61
9	**8a**, O	K (5)	−45	5	CO_2	**10ae**, CO_2[g]	35
10	**8a**, O	K (5)	−45	5	Acetone	**10af**, $(CH_3)_2COH$	35
11	**8b**, NCH_3	Li (5)	−15	4	H_2O	**10ba**, H	70[c]
12	**8b**, NCH_3	Li (10)	−15	4	H_2O	**10ba**, H	>95
13	**8b**, NCH_3	Li (10)	−15	4	D_2O	**10bb**, D	83[c]
14	**8b**, NCH_3	Li (10)	−15	4	BuBr	**10bc**, Bu	24
15	**8b**, NCH_3	Li (10)	−15	4	BuBr[h]	**10bc**, Bu	53
16	**8b**, NCH_3	Li (10)	−15	4	$(CH_3)_2CHBr$[h]	**10bd**, $(CH_3)_2CH$	38[c]
17	**8b**, NCH_3	Li (10)	−15	4	$(CH_3)_2CHBr$[h,i]	**10bd**, $(CH_3)_2CH$	66
18	**8b**, NCH_3	Li (10)	−15	4	Acetone[h,i]	**10be**, $(CH_3)_2COH$	38

[a] All reactions run in the presence of 10 mol% of naphthalene; reaction mixtures were quenched with 1.1 equiv. of the electrophile, unless otherwise indicated; reaction time with the electrophile=15 min.
[b] Isolated yield, unless otherwise indicated.
[c] As determined by ^1H NMR spectroscopy.
[d] 47% of **8a** and 11% of **11** were also detected.
[e] 11% of **8a** and 34% of **11** were also detected.
[f] 70% of **8a** and 2% of **11** were also detected.
[g] Lactonization occured during acidic workup.
[h] Added at −80°C.
[i] In the presence of 3 equiv. of the electrophile.

mixture with D_2O resulted in low deuteriation at the arylmethyl position (Table 2, entry 5). A better result was obtained performing the reaction at −45°C: under these conditions the corresponding organometallic was obtained in 83% yield, as evidenced by D_2O quenching (Table 2, entry 6).

Due to the above results, reductive electrophilic substitution reactions of ether **8a** were performed using K metal as the reducing agent at −45° C. The intermediate dipotassium derivative **9a** was trapped with primary and secondary alkyl halides, CO_2 and acetone, affording the corresponding 1,8-disubstituted naphthalenes **10ac**–**10af** in satisfactory yields (Table 2, entries 7–10; Scheme 3, M=K).

Reductive lithiation of amine 8b

Reductive and selective cleavage of amine **8b** was accomplished with Li metal. Reduction at −15°C in the presence of 5 equiv. of Li metal and a catalytic amount of naphthalene was somewhat sluggish, resulting in non-complete conversion of the starting amine after 4 h (Table 2, entry 11). Quantitative cleavage was obtained increasing the relative amount of the reducing agent to 10 equiv.; under these conditions, the corresponding intermediate dilithium derivative **9b** was obtained in 84% yield (Table 2, entries 12 and 13). At variance with the reductive lithiation of ether **8a**, we did not observe a second cleavage reaction.

Reductive electrophilic substitution reactions of the amine **8b** were performed with 10 equiv. of Li metal at −15°C. Under these conditions, quenching the reaction mixture with *n*-BuBr afforded a complex reaction mixture; careful flash chromatography allowed the recovery of amine **10bc** in 23% yield (Table 2, entry 14). A better result was obtained adding the electrophile to the organometallic intermediate **9b** at −80°C: under these conditions, amine **10bc** was obtained in 53% isolated yield (Table 2, entry 15). Reaction of organometallic **9b** at −80°C with an excess of $(CH_3)_2CHBr$ or acetone afforded compounds **10bd**–**10be**, respectively, in satisfactory yields (Table 2, entries 16–18).

Concluding Remarks

The results obtained in the present work provide further evidence of the synthetic usefulness of the reductive metallation of arylalkyl ethers and amines. This procedure allows the transformation of symmetrically substituted starting materials into unsymetrically substituted reaction intermediates, affording new synthetic routes to unsymmetrically 2,2′-disubstituted-1,1′-biphenyls and 1,8-disubstitued naphthalenes.

Reductive cleavage of naphthalene derivatives deserves some comment. In particular, the different reactivities evidenced in the lithium- and potassium-mediated reductive cleavages of ether **8a** can be attributed to several factors: (i) different redox potentials of the metals; (ii) different solubilities (and reactivities) of the intermediates **9a** with M=Li or K; (iii) different leaving group abilities of lithium and potassium oxides. The results obtained with the amino intermediate **9b** (M=Li) suggest that the nature of the leaving group is important in determining whether the (un)stability of intermediates **9** leads to a second reductive cleavage step.

Experimental

General

Boiling and melting points are uncorrected; the air bath temperature on bulb-to-bulb distillations are given as boiling points. Starting materials were of the highest commercial quality and were used without further purification. 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 on a Varian VXR 300 at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ with $SiMe_4$ as internal standard. Deuterium incorporation was calculated by monitoring the ^1H NMR spectra of the crude mixtures and comparing the integration of the signal corresponding to the protons in the arylmethyl position with that of known signals. IR spectra were recorded on thin films, unless otherwise indicated. Elemental analyses were performed by the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari.

Preparation of starting materials

2,2′-Dihydroxymethyl-1,1′-biphenyl (2). Diphenic anhydride (10.0 g, 0.045 mol) was added in 1 g portion to a mechanically stirred suspension of $LiAlH_4$ (3.4 g, 0.09 mol) in 250 mL of dry THF over 2 h. The mixture was heated at reflux temperature for 16 h. Excess hydride was decomposed by slow dropwise addition of H_2O (80 mL, *Caution*), followed by 1 M H_2SO_4 (100 mL) and 1:1 H_2SO_4 (ca. 50 mL) until complete dissolution of a white precipitate. The organic phase was separated, washed with 2 M NaOH (2×50 mL), H_2O (50 mL), and dried (Na_2SO_4). Evaporation of the solvent afforded a light yellow solid, which was recrystallised from benzene to give 8.0 g (0.037 mol, 83%) of compound **2**. White solid; mp 109–111°C (benzene, lit.[21] mp 110.5–111.5°C).

6,7-Dihydro-5*H*-dibenz[*c*,*e*]oxepine (3a). Diol **2** (8.0 g, 0.037 mol) was suspended in 50 mL of 85% H_3PO_4 and heated at reflux temperature for 1 h. The mixture was cooled to rt and extracted with Et_2O (3×20 mL), washed with H_2O (20 mL), $NaHCO_3$ (20 mL), and dried (Na_2SO_4). Evaporation of the solvent afforded a white solid, which was recrystallised from hexane to give 5.9 g (0.030 mol, 82%) of compound **3a**. White solid; mp 70–72°C (hexane, lit.[21] mp 71.5–72°C).

6,7-Dihydro-6-methyl-5*H*-dibenz[*c*,*e*]azepine (3b). According to Cohen et al.,[22] reaction of diol **2** (5.2 g, 0.024 mol) with boiling 48% aqueous HBr (100 mL) over 0.5 h afforded the corresponding crude dibromide (8.1 g, 0.024 mol, quantitative). Without further purification, the dibromide was dissolved in benzene (80 mL) and added dropwise at rt to a vigorously stirred suspension of 40% aqueous solution of CH_3NH_2 (10.3 mL, 0.120 mol) in benzene (15 mL). After 4 h at rt, the mixture was heated at 40°C for 12 h, then cooled to rt, the organic phase separated, washed with 2 M NaOH (2×50 mL) and H_2O (50 mL), dried (K_2CO_3) and the solvent evaporated. Vacuum distillation afforded azepine **3b** (4.3 g, 0.020 mol, 83%). Light yellow viscous oil; bp 155–158°C/8 mmHg (lit.[23] bp 175–178°C/10 mmHg).

1,8-Dihydroxymethylnaphthalene (7). 1,8-Naphthalic anhydride (10.0 g, 0.050 mol) was added in 1 g portions to a mechanically stirred suspension of $LiAlH_4$ (3.8 g, 0.10 mol) in 250 mL of dry THF over 2 h. The mixture was stirred at rt for 16 h. Excess hydride was decomposed by slow dropwise addition of H_2O (80 mL, *Caution*), followed by 1 M H_2SO_4 (100 mL) and 1:1 H_2SO_4 (ca. 50 mL) until complete dissolution of a white precipitate. The organic phase was separated, washed with 2 M NaOH (2×50 mL), H_2O (50 mL), and dried (Na_2SO_4). Evaporation of the solvent afforded a white solid, which was recrystallised from EtOH to give 5.2 g (0.028 mol, 55%) of compound **7**. White solid; mp 155–156°C (EtOH, lit.[21] mp 154–154.5°C).

1*H*,3*H*-Benzo[*de*]isochromene (8a). Diol **7** (10.0 g, 0.053 mol) was suspended in 75 mL of 50% H_3PO_4 and heated at reflux temperature for 1 h. The mixture was cooled to rt and extracted with Et_2O (3×20 mL), washed with H_2O (20 mL), $NaHCO_3$ (20 mL), and dried (Na_2SO_4). Evaporation of the solvent afforded a white solid, which was recrystallised from hexane to give 7.7 g (0.045 mol, 85%) of compound **3a**. White solid; mp 83–84°C (hexane, lit.[21] mp 83.0–83.5°C).

2-Methyl-2,3-dihydro-1*H*-benzo[*de*]isoquinoline (8b). Following the procedure of Carpino,[24] reaction of diol **7** (4.1 g, 0.022 mol) in CH_2Cl_2 (60 mL) with PBr_3 (11.7 g, 0.043 mol) at rt over 5 h afforded the corresponding crude dibromide (5.9 g, 0.019 mol, 88%). Without further purification, the dibromide was dissolved in benzene (120 mL) and mechanically stirred at rt, whilst a 40% aqueous solution of CH_3NH_2 (8.3 mL, 0.095 mol) was slowly added dropwise. After 4 h at rt, the mixture was heated at 40°C for 12 h, then cooled to rt, the organic phase separated, washed with 2 M NaOH (2×50 mL) and H_2O (50 mL), and dried (K_2CO_3). Evaporation of the solvent afforded a light yellow solid, which was recrystallised from hexane to give 3.2 g of compound **8b** (0.017 mol, 79%). White solid; mp 58–60°C (hexane, lit.[25] mp 60–61°C).

Reductive cleavage of compounds 3 and 8 and reaction with electrophiles—general procedure

Li metal (5–10 equiv. of a 30% wt. dispersion in mineral oil) was placed under Ar in a two-necked flask equipped with a reflux condenser and magnetic stirrer, washed with THF (3×10 mL), and suspended in THF (30 mL). Alternatively, K dispersion was prepared in a similar apparatus by vigorously stirring the freshly cut metal (5 equiv.) in THF (30 mL) at reflux temperature for 10 min; the metal suspension was then allowed to cool to rt without stirring. A catalytic amount of naphthalene (10 mol%) was added to the suspension of the metal, and the mixture was stirred until a dark green colour appeared. The mixture was chilled to the reported temperature (Tables 1 and 2) and a solution of the substrate (5 mmol) in THF (2 mL) was added dropwise. After stirring for the reported time (Tables 1 and 2), a solution of the appropriate electrophile (1.1–3 equiv.) in THF (5 mL) was slowly added. After stirring for 15 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 (3×20 mL). The

organic phase was washed with brine (10 mL), dried (Na_2SO_4 or 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.

CO_2 quenching was performed by bubbling gaseous CO_2 into the reaction vessel for 10 min; the mixture was quenched by slow dropwise addition of H_2O (10 mL, *Caution*), the cold bath removed, and the resulting mixture acidified to pH 1 with conc. HCl, stirred at rt for 1 h, and worked up as described above.

Crude products were purified by flash chromatography (petroleum ether/AcOEt or petroleum ether/AcOEt/Et_3N); compounds **5aa**[26] and **10aa**[27] are already known.

Deuterated compounds **5ab**, **5bb**, **10ab** and **10bb** were characterised by ^1H- and ^{13}C NMR spectroscopy: the resonances of the arylmethyl CHD protons appear as unresolved broad triplets shifted 0.02–0.04 ppm (δ) upfield relatively to the corresponding arylmethyl CH_2 protons; the resonances of the arylmethyl CHD carbons appear as triplets (J=19–21 Hz) shifted 0.3–0.4 ppm (δ) upfield relatively to the corresponding arylmethyl CH_2 carbons.

Other products were characterised as follows.

2-Hydroxymethyl-2′-pentyl-1,1′-biphenyl (5ac). Purified by flash chromatography (petroleum ether/AcOEt=7:3), colourless oil; (Found: C, 84.86; H, 8.90; $C_{18}H_{22}O$ requires C, 84.98; H, 8.73); R_f (petroleum ether/AcOEt=7:3) 0.48; bp 195°C/1 mmHg; ν_{max} 3615, 3451, 3059, 2927, 1621, 1473, 1006 cm^{-1}; δ_H 0.78 (3H, t, J=6.6 Hz, CH_3), 1.07–1.22 (4H, m, 2×CH_2), 1.34–1.46 (2H, m, CH_2), 1.59 (1H, b s, OH), 2.22–2.45 (2H, m, CH_2Ar), 4.39 (2H, s, CH_2O), 7.08–7.24 (3H, m, ArH), 7.27–7.42 (4H, m, ArH), 7.51–7.56 (1H, m, ArH); δ_C 13.9, 22.3, 30.5, 31.5, 33.0, 53.1, 125.5, 127.1, 127.4, 127.6, 127.7, 129.0, 129.5, 129.9, 138.5, 139.6, 140.1, 140.6.

2-Hydroxymethyl-2′-(2-methyl)propyl-1,1′-biphenyl (5ad). Purified by flash chromatography (petroleum ether/AcOEt=7:3), colourless oil; (Found: C, 85.08; H, 8.32; $C_{17}H_{20}O$ requires C, 84.94; H, 8.40); R_f (petroleum ether/AcOEt=7:3) 0.40; bp 135°C/1 mmHg; ν_{max} 3321, 3017, 2949, 1595, 1462, 1006 cm^{-1}; δ_H 0.68 (3H, d, J=7.0 Hz, CH_3), 0.76 (3H, d, J=7.0 Hz, CH_3), 1.59 (1H, b s, OH), 1.67 (1H, n, J=7.0 Hz, CH), 2.16 (1H, dd, J=13.5, 7.0 Hz, ArCH), 2.34 (1H, dd, J=13.5, 7.0 Hz, ArCH), 4.38 (2H, s, CH_2O), 7.09–7.16 (2H, m, ArH), 7.20–7.42 (5H, m, ArH), 7.51–7.57 (1H, m, ArH); δ_C 19.2, 19.5, 26.2, 39.1, 60.1, 122.5, 124.0, 124.3, 124.3, 124.5, 126.5, 126.7, 127.0, 135.4, 136.3, 136.9, 137.1.

2-Hydroxymethyl-2′-trimethylsilyl-1,1′-biphenyl (5ae). Purified by flash chromatography (petroleum ether/AcOEt=7:3), colourless oil; (Found: C, 75.53; H, 8.10; $C_{17}H_{22}OSi$ requires C, 75.48; H, 8.22); R_f (petroleum ether/AcOEt=7:3) 0.37; bp 140°C/1 mmHg; ν_{max} 3335, 3055, 2949, 1625, 1470, 1244, 1036 cm^{-1}; δ_H −0,17 (9H, s, 3×CH_3Si), 1.52 (1H, b s, OH), 1.78 (1H, d, J=13.5 Hz, ArCH), 2.00 (1H, d, J=13.5 Hz, ArCH), 4.40 (2H, s, CH_2O), 7.03–7.15 (4H, m, ArH), 7.18–7.25 (1H, m, ArH), 7.27–7.40 (2H, m, ArH), 7.48–7.54 (1H, m, ArH); δ_C −1.1, 23.5, 63.2, 124.1, 127.2, 127.3, 127.5, 127.5, 129.1, 129.9, 130.5, 138.5, 138.5, 138.5, 140.5.

2-Hydroxymethyl-2′-(2-methyl-2-hydroxy)propyl-1,1′-biphenyl (5af). Purified by flash chromatography (petroleum ether/AcOEt=1:1), colourless oil; (Found: C, 79.80; H, 8.01; $C_{17}H_{20}O_2$ requires C, 79.64; H, 7.88); R_f (petroleum ether/AcOEt=1:1) 0.26; bp 210°C/1 mmHg; ν_{max} 3420, 3080, 1600, 1480, 1380, 1150 cm^{-1}; δ_H 1.01 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.15 (2H, b s, 2×OH), 2.53 (1H, d, J=13.5 Hz, ArCH), 2.89 (1H, d, J=13.5 Hz, ArCH), 4.32 (1H, d, J=12.6 Hz, CHO), 4.50 (1H, d, J=12.6 Hz, CHO), 7.11–7.19 (2H, m, ArH), 7.23–7.41 (5H, m, ArH), 7.49–7.56 (1H, m, ArH); δ_C 28.5, 30.7, 45.6, 62.8, 71.9, 126.2, 127.1, 127.2, 127.6, 128.7, 130.2, 130.4, 131.6, 135.8, 138.9, 140.6, 141.0.

2-*N*-Methylaminomethyl-2′-methyl-1,1′-biphenyl (5ba). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=3:7:1), colourless oil; (Found: C, 85.10; H, 8.24; $C_{15}H_{17}N$ requires C, 85.25; H, 8.12); R_f (petroleum ether/AcOEt/Et_3N=3:7:1) 0.60; bp 145–150°C/1 mmHg; ν_{max} 3320, 2930, 1595, 1470, 1440, 760 cm^{-1}; δ_H 1.35 (1H, b s, NH), 2.06 (3H, s, CH_3Ar), 2.27 (3H, s, CH_3N), 3.45 (1H, d, J=14.0 Hz, CHAr), 3.51 (1H, d, J=14.0 Hz, CHAr), 7.08–7.15 (2H, m, ArH), 7.18–7.38 (5H, m, ArH), 7.47 (1H, dd, J=7.4, 1.5 Hz, ArH); δ_C 20.0, 35.9, 53.2, 125.5, 126.7, 127.3, 127.4, 128.5, 129.3, 129.6, 129.9, 135.8, 137.7, 140.6, 141.1.

2-*N*-Methylaminomethyl-2′-pentyl-1,1′-biphenyl (5bc). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=8:2:1), colourless oil; (Found: C, 85.44; H, 9.51; $C_{19}H_{25}N$ requires C, 85.32; H, 9.44); R_f (petroleum ether/AcOEt/Et_3N=8:2:1) 0.37; bp 165°C/1 mmHg; ν_{max} 3350, 3060, 2980, 2940, 1590, 1480, 1440, 760 cm^{-1}; δ_H 0.78 (3H, t, J=7.0 Hz, CH_3), 1.04–1.24 (5H, m, 2×CH_2, NH), 1.32–1.50 (2H, m, CH_2), 2.20–2.44 (2H, m, CH_2Ar), 2.28 (3H, s, CH_3N), 3.47 (2H, s, CH_2N), 7.07–7.15 (2H, m, ArH), 7.17–7.40 (5H, m, ArH), 7.47 (1H, dd, J=7.4, 1.5 Hz, ArH); δ_C 13.9, 22.3, 30.5, 31.6, 33.0, 36.0, 53.3, 125.3, 126.4, 127.3, 127.4, 128.2, 128.9, 129.5, 129.9, 137.9, 140.2, 140.6, 140.8.

2-*N*-Methylaminomethyl-2′-(2-methyl)propyl-1,1′-biphenyl (5bd). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=8:2:1), colourless oil; (Found: C, 85.19; H, 9.10; $C_{18}H_{23}N$ requires C, 85.31; H, 9.17); R_f (petroleum ether/AcOEt/Et_3N=8:2:1) 0.25; bp 165–170°C/1 mmHg; ν_{max} 3300, 3080, 2980, 1590, 1455, 755 cm^{-1}; δ_H 0.68 (3H, d, J=7.0 Hz, CH_3), 0.77 (3H, d, J=7.0 Hz, CH_3), 1.43 (1H, bs, NH), 1.68 (1H, n, J=7.0 Hz, CH), 2.17 (1H, dd, J=13.5, 7.0 Hz, CHAr), 2.27 (3H, s, CH_3), 2.33 (1H, dd, J=13.5, 7.0 Hz, CH_2), 3.45 (2H, s, CH_2), 7.08–7.15 (2H, m, ArH), 7.18–7.38 (5H, m, ArH), 7.46 (1H, dd, J=7.4, 1.2 Hz, ArH); δ_C 22.3, 22.5, 29.2, 36.0, 42.2, 53.3, 125.4, 126.3, 127.2, 127.3, 128.1, 129.5, 129.6, 130.1, 137.8, 139.4, 140.6, 140.9.

2-*N*-Methylaminomethyl-2′-trimethylsilyl-1,1′-biphenyl (5be). Purified by flash chromatography (petroleum ether/

AcOEt/Et_3N=7:3:1), colourless oil; (Found: C, 76.37; H, 9.01; $C_{18}H_{25}NSi$ requires C, 76.25; H, 8.91); R_f (petroleum ether/AcOEt/Et_3N=7:3:1) 0.45; bp 165–170°C/1 mmHg; ν_{max} 3350, 3080, 2980, 1590, 1480, 1450, 1250, 860 cm^{-1}; δ_H −0.14 (9H, s, 3×CH_3Si), 1.26 (1H, b s, NH), 1.81 (1H, d, J=14.0 Hz, CHSi), 2.00 (1H, d, J=14.0 Hz, CHSi), 2.27 (3H, s, CH_3N), 3.49 (2H, s, CH_2N), 7.04–7.14 (3H, m, ArH), 7.18–7.40 (3H, m, ArH), 7.45 (1H, dd, J=7.8, 1.2 Hz, ArH); δ_C −1.1, 23.5, 36.0, 53.4, 124.0, 126.5, 127.1, 127.3, 128.3, 128.9, 129.8, 130.5, 137.9, 138.5, 139.2, 141.2.

2-*N*-Methylaminomethyl-2′-(2-methyl-2-hydroxy)propyl-1,1′-biphenyl (5bf). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=5:5:1), white solid; (Found: C, 80.07; H, 8.78; $C_{18}H_{23}N$ requires C, 80.23; H, 8.62); R_f (petroleum ether/AcOEt/Et_3N=5:5:1) 0.25; mp 85–87°C (petroleum ether); ν_{max} (nujol) 3280, 3150, 1560, 1350, 1220, 1150, 750 cm^{-1}; δ_H 1.03 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.12 (2H, b s, OH, NH), 2.22 (3H, s, CH_3N), 2.55 (1H, d, J=14.0 Hz, CHAr), 2.91 (1H, d, J=14.0 Hz, CHAr), 3.43 (1H, d, J=13.0 Hz, CHN), 3.65 (1H, d, J=13.0 Hz, CHN), 7.12–7.20 (2H, m, ArH), 7.23–7.44 (6H, m, ArH); δ_C 29.1, 30.8, 36.0, 45.8, 53.4, 70.9, 126.1, 126.7, 127.0, 127.4, 129.0, 130.1, 130.6, 131.6, 136.4, 137.7, 141.4, 145.1.

1-Hydroxymethyl-8-pentylnaphthalene (10ac). Purified by flash chromatography (Petroleum ether/AcOEt=8:2), colourless oil; (Found: C, 84.23; H 8.57; $C_{16}H_{20}O$ requires C, 84.15; H, 8.85); R_f (Petroleum ether/AcOEt=8:2) 0.52; bp 185–190°C/1 mmHg; ν_{max} 3337, 2951, 2921, 1600, 1462, 1001 cm^{-1}; δ_H 0.90 (3H, t, J=7.2 Hz, CH_3), 1.30–1.49 (4H, m, 2×CH_2), 1.57–1.68 (2H, m, CH_2), 1.76 (1H, b s, OH), 3.25 (2H, t, J=8.0 Hz, CH_2Ar), 5.11 (2H, s, CH_2O), 7.35–7.43 (3H, m, ArH), 7.52 (1H, dd, J=6.9, 0.9 Hz, ArH), 7.69–7.76 (1H, m, ArH), 7.82 (1H, dd, J=8.1, 1.5 Hz, ArH); δ_C 14.1, 22.6, 31.9, 33.1, 36.2, 66.5, 124.7, 125.4, 128.0, 129.0, 129.6, 130.5, 130.7, 135.9, 136.7, 139.7.

1-Hydroxymethyl-8-(2′-methyl)propylnaphthalene (10ad). Purified by flash chromatography (Petroleum ether/AcOEt=1:1), colourless oil; (Found: C, 84.31; H 8.62; $C_{16}H_{20}O$ requires C, 84.05; H, 8.48); R_f (Petroleum ether/AcOEt=1:1) 0.59; bp 175–180°C/1 mmHg; ν_{max} 3350, 3060, 2980, 1600, 1460, 1390 cm^{-1}; δ_H 0.92 (6H, d, J=6.6 Hz, 2×CH_3), 1.60 (1H, bs, OH), 1.77 (1H, n, J=6.6 Hz, CH), 3.12 (2H, d, J=6.6 Hz, CH_2), 5.12 (2H, s, CH_2O), 7.31 (1H, dd, J=5.1, 1.5 Hz, ArH), 7.37–7.43 (2H, m, ArH), 7.54 (1H, dd, J=6.1, 1.5 Hz, ArH), 7.75 (1H, dd, J=8.1, 1.5 Hz, ArH), 7.84 (1H, dd, J=8.1, 1.5 Hz, ArH); δ_C 22.4, 30.7, 45.5, 66.6, 124.7, 125.0, 128.3, 129.1, 130.5, 130.8, 131.0, 136.0, 136.8, 137.9.

1*H*,4*H*-Naphth(1,8-cd)oxepin-3-one (10ae). Purified by flash chromatography (Petroleum ether/AcOEt=6:4), white solid; (Found: C, 78.53; H 5.31; $C_{13}H_{10}O$ requires C, 78.76; H, 5.10); R_f (Petroleum ether/AcOEt=6:4) 0.35; mp 160–161°C (isopropanol); ν_{max} (nujol) 3025, 1944, 1738, 1596, 1583, 1378 cm^{-1}; δ_H 4.45 (2H, b s, CH_2), 5.60 (2H, b s, CH_2), 7.35–7.48 (4H, m, ArH), 7.81 (1H, d, J=8.1 Hz, ArH), 7.87 (1H, d, J=8.1 Hz, ArH); δ_C 42.3, 71.7, 125.4, 126.3, 127.3, 127.7, 128.5, 128.7, 130.4, 130.5, 131.1, 134.7, 171.9.

1-Hydroxymethyl-8-(2′-hydroxy-2′-methyl)propylnaphthalene (10af). Purified by flash chromatography (Petroleum ether/AcOEt=3:7), white solid; (Found: C, 78.07; H 7.73; $C_{15}H_{18}0_2$ requires C, 78.21; H, 7.89); R_f (Petroleum ether/AcOEt=3:7) 0.26; mp 109–111°C (petroleum ether); ν_{max} (nujol) 3380, 1580, 1420, 1350, 1190, 900 cm^{-1}; δ_H 1.25 (6H, s, 2×CH_3), 1.53 (1H, b s, OH), 3.57 (2H, s, CH_2), 3.95 (1H, b s, OH), 5.17 (2H, s, CH_2O), 7.34 (1H, dd, J=7.2, 1.5 Hz, ArH), 7.40 (1H, t, J=7.2 Hz, ArH), 7.42 (1H, t, J=7.2 Hz, ArH), 7.53 (1H, dd, J=7.2, 1.5 Hz, ArH), 7.79 (1H, dd, J=7.2, 1.5 Hz, ArH), 7.81 (1H, dd, J=7.2, 1.5 Hz, ArH); δ_C 29.4, 47.7, 66.4, 72.7, 124.6, 125.0, 129.2, 130.5, 131.5, 132.4, 132.6, 133.6, 135.7, 136.9.

1-*N*-Methylaminomethyl-8-methylnaphthalene (10ba). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=5:5:1), colourless oil; (Found: C, 84.36; H 8.26; $C_{13}H_{15}N$ requires C, 84.26; H, 8.18); R_f (petroleum ether/AcOEt/Et_3N=5:5:1) 0.54; bp 115–120°C/1 mmHg; ν_{max} 3300, 3020, 2920, 1580, 1450 cm^{-1}; δ_H 1.42 (1H, b s, NH), 2.54 (3H, s, CH_3), 3.01 (3H, s, CH_3N), 4.23 (2H, s, CH_2N), 7.32 (1H, d, J=6 Hz, ArH), 7.37 (1H, d, J=8.1 Hz, ArH), 7.43 (1H, dd, J=6.9, 1.4 Hz, ArH), 7.66–7.74 (2H, m, ArH), 7.77 (1H, dd, J=9.0, 1.8 Hz, ArH); δ_C 24.3, 36.1, 57.1, 124.7, 125.1, 127.9, 129.4, 129.6, 130.1, 132.0, 134.7, 135.7, 136.6.

1-*N*-Methylaminomethyl-8-pentylnaphthalene (10bc). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=7:3:1), colourless oil; (Found: C, 84.42; H, 9.75; $C_{16}H_{21}N$ requires C, 84.57; H, 9.62); R_f (petroleum ether/AcOEt/Et_3N=7:3:1) 0.50; bp 145–150°C/1 mmHg; ν_{max} 3320, 3040, 2900, 1560, 1450; δ_H 0.92 (3H, t, J=7.2 Hz, CH_3), 1.26 (1H, b s, NH), 1.32–1.51 (4H, m, 2×CH_2, 1.59–1.72 (2H, m, CH_2), 2.52 (3H, s, CH_3N), 3.23 (2H, t, J=7.8 Hz, CH_2), 4.14 (2H, s, CH_2N), 7.33–7.40 (3H, m, ArH), 7.44 (1H, dd, J=7.2, 1.5 Hz, ArH), 7.68–7.74 (1H, m, ArH), 7.78 (1H, dd, J=8.4, 1.5 Hz, ArH); δ_C 14.1, 22.6, 32.0, 33.3, 36.3, 36.6, 57.5, 124.5, 125.1, 128.1, 129.6, 129.8, 129.9, 130.9, 136.1, 136.1, 139.7.

1-*N*-Methylaminomethyl-8-(2′-methyl)propylnaphthalene (10bd). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=7:3:1), colourless oil; (Found: C, 84.74; H, 9.20; $C_{16}H_{21}N$ requires C, 84.51; H, 9.33); R_f (petroleum ether/AcOEt/Et_3N=7:3:1) 0.54; bp 115–120°C/1 mmHg; ν_{max} 3320, 3060, 2960, 1590, 1470; δ_H 0.91 (6H, d, J=6.6 Hz, 2×CH_3), 1.47 (1H, b s, NH), 1.80 (1H, n, J=6.6 Hz, CH), 2.51 (3H, s, CH_3N), 3.07 (2H, d, J=6.6 Hz, CH_2), 4.14 (2H, s, CH_2N), 7.27 (1H, dd, J=6.9, 1.5 Hz, ArH), 7.35 (2H, t, J=7.7 Hz, ArH), 7.43 (1H, dd, J=7.7, 1.5 Hz, ArH), 7.72 (1H, dd, J=7.7, 1.5 Hz, ArH), 7.78 (1H, dd, J=7.7, 1.5 Hz, ArH); δ_C 22.4, 30.6, 36.2, 45.8, 57.6, 124.5, 124.7, 128.4, 129.9, 129.9, 130.9, 131.0, 136.2, 136.2, 137.9

1-*N*-Methylaminomethyl-8-(2′-hydroxy)propylnaphthalene (10be). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=5:5:1), white solid which decomposes when exposed to air (we were unable to obtain a satisfactory

elemental analysis); bp 145–150°C/1 mmHg; R_f (petroleum ether/AcOEt/Et_3N=5:5:1) 0.29; ν_{max} (nujol) 3400, 3260, 1640, 1370;; δ_H 1.21 (6H, s, 2×CH_3), 1.93 (2H, b s, OH, NH), 2.60 (3H, s, CH_3N), 3.44 (2H, s, CH_2), 4.22 (2H, s, CH_2N), 7.28–7.34 (3H, m, ArH), 7.39 (1H, t, J=7.5 Hz, ArH), 7.72–7.82 (m, 2H, ArH); δ_C 30.1, 35.9, 48.3, 57.3, 70.4, 124.2, 124.2, 129.0, 130.6, 131.7, 132.6, 133.1, 134.5, 134.8, 135.9.

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