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Research Article

Investigations into the *C*-deuteriation of aryl alkyl ketones using urea as a pro-base in the presence of a deuterium donor

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Summary

Results are reported on the regioselective *C*-deuteriation of a series of enolates derived from the deprotonation of aryl alkyl ketones using dilithiated urea as the *pro*-base in the presence of a suitable deuterium donor. Copyright © 2006 John Wiley & Sons, Ltd.

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Key Words: alkyl aryl ketones; *D*-enols; deuterium; enolates and internal deuterium transfer

Introduction

Thermodynamic deuteriation of enolates has been shown to be a reliable and efficient method for the synthesis of deuterium-labelled carbonyl derivatives.[1] By comparison, kinetic deuteriation[2] is known to be problematic and has been shown to be dependent on the method used for enolate formation,[3] the structural nature of the enolate,[4] *D*-source[5] and potential additives.[6]

Kinetic formation of enolates through *C*-deprotonation of carbonyl derivatives is well known,[7] whereas, efficient *C*-deuteriation has proved to be far more challenging.[8,†]

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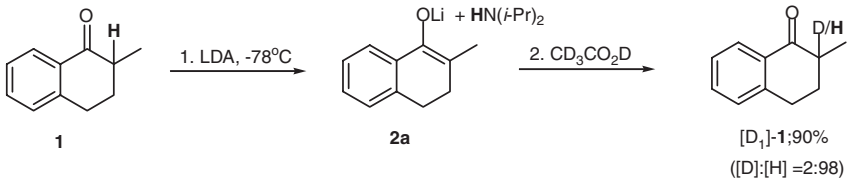
[†] For enantioselective protonation of lithium enolates with reduced deuterium incorporation: see Yanagisawa A, Kikuchi T, Kuribayashi T, Yamamoto H. *Tetrahedron* 1998; **54**: 10253–10264.



Scheme 1.

This is in-part due to the use of lithium amides[9] (e.g. lithium diisopropylamide, LDA) as Brønsted bases to form the required lithium enolate, such as **2a**,[3] through simple deprotonation of the corresponding ketone derivative **1** at *C*(2) (Scheme 1). Addition of a suitable deuterium source, such as [D_4]-acetic acid, to a preformed solution of lithium enolate **2a** in THF invariably gave a mixture of the required *D*-labelled and unwanted unlabelled ketones [D_1]-**1** and **1** ([D]:[H] = 2:98), respectively (Scheme 1).[3] This is primarily due to the presence of a competitive base, diisopropylamine (in **2a**), formed by deprotonation of the parent ketone **1** with lithium diisopropylamide (LDA) (Scheme 1); this phenomenon has previously been reported by Seebach and co-workers,[10] and has led to the concept of *internal proton return*. This is where the original hydrogen atom, **H**, present in the ketone **1** can be re-delivered back to re-form the parent substrate **1** via the residual diisopropylamine on addition of [D_4]-acetic acid, thus leading to the partially deuteriated ketone [D_1]-**1** (Scheme 1). Removal of the problematic[11,‡] NH proton from the enolate complex **2a** (by sequential addition of MeLi) to give the corresponding lithium enolate–lithium amide complex **3** (Scheme 2), or by ensuring the residual amine was less basic[12] has been shown to increase the levels of deuterium incorporation. By comparison, deuteriation of 'base-free' enolates (e.g. **2b**) in the absence of the unwanted residual amine can lead to higher levels of deuteriation (Scheme 2).[13,§] However, the obviously drawback for this methodology is the requirement for the formation of the corresponding silyl enol ether **4** (by trapping the original lithium enolate **2a** with trimethylsilyl chloride) (Scheme 2). The required 'base-free' enolate **2b** can be liberated from parent enol equivalent **4** using Stork's methodology[14] by simple addition of methyl lithium (Scheme 2).

Results and discussion

We were interested in extending this methodology by developing a lithium amide base which disfavoured internal proton return.[10] For our study, we chose to use urea **5** as our pro-base due to its non-basic nature ($pK_{HA} \sim 0$),[15]

‡For further information see References.[8,10]
§For further information see reference.[3]

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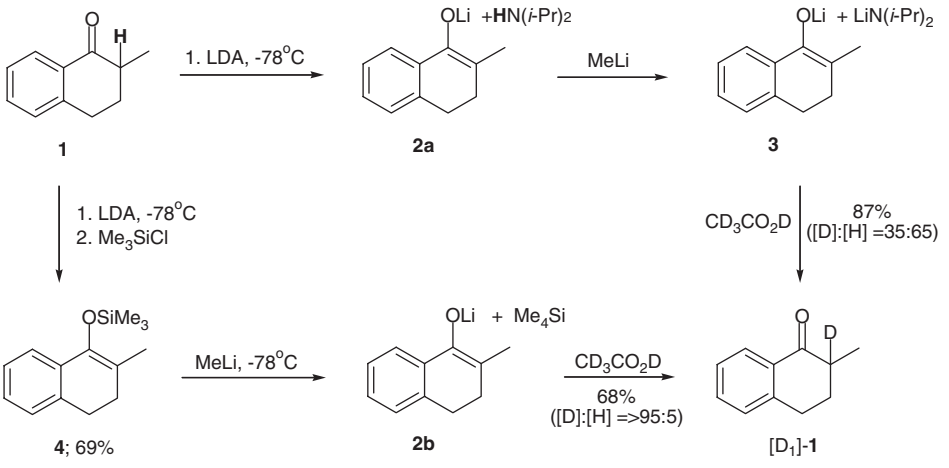

Scheme 2.

and to ensure its conjugate base was sufficiently basic enough to deprotonate an aryl alkyl ketone[¶] the corresponding dilithiated urea **7** was used as the parent base [**5**; pK_A = 26.9].[16] We first investigated the suitability of dilithium amide **7** as a potential Brønsted base for efficient enolate formation by probing the deprotonation of tetralone **8** and 2-methyl-tetralone **1** (Scheme 4). The required dilithiated urea **7** was formed by addition of *n*-BuLi (two equivalents) to a stirred solution of urea **5** in THF at -78°C as illustrated in Scheme 3. Sequential addition of tetralone **8**, followed by trimethylsilylacetate (Me_3SiOAc)[‖] gave the corresponding silyl enol ether **9** in good yield (52%). By comparison, addition of methyl iodide to the lithium enolate formed by deprotonation of 2-methyl-tetralone **1**, gave the corresponding 2,2-dimethyl-tetralone **10** in 70% yield (Scheme 4). From these results, it appears lithium enolate formation (for **8** and **1**, respectively) occurs efficiently giving directly the *O*-silylated enol and *C*-alkylated derivatives **9** and **10**, respectively (Scheme 4). We next probed the de-deuteriation of 2-deuterio-2-methyl-tetralone [D_1]-**1** using dilithiated urea **7** to ensure that potential internal deuterium return was negligible (Scheme 5). Addition of 2-deuterio-2-methyl-tetralone [D_1]-**1** to a solution of preformed **7** in THF at -78°C, followed an acetic acid quench gave the required 2-methyl-tetralone **1** with virtually no deuterium remaining ([D]:[H] = $<2:>98$) (Scheme 5). From these experiments, it appears that dilithiated urea **7** is a suitable Brønsted base for enolate formation and versatile enough for a wide range of potential electrophiles (e.g. Me_3SiOAc and MeI) and acids (e.g. acetic acid) (Schemes 4 and 5).

[¶] For a related ketone, e.g., acetophenone; p*K*a (enol OH) = 7.9 and p*K*a (carbonyl CH) = 18.2.
[‖] Using a more electrophilic Me_3Si source (e.g. Me_3SiCl) the yield was reduced to 33%; Weerasooriya N. *PhD Thesis*, University of London, 2003.

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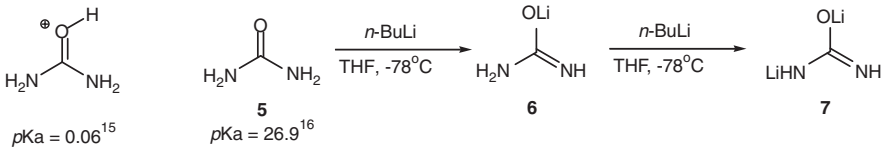
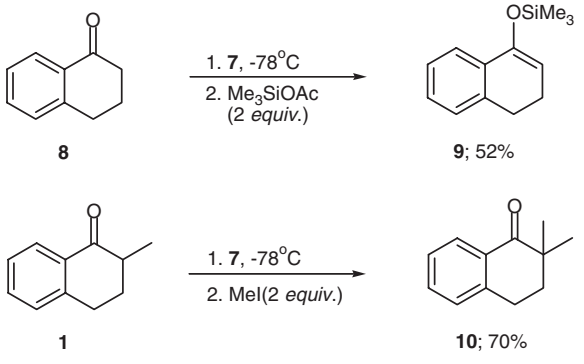
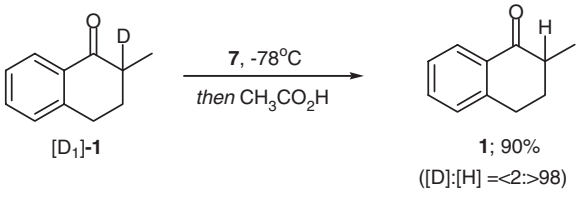


Scheme 3.



Scheme 4.



Scheme 5.

With this information in hand, we next investigated the deuteriation of the lithium enolate **2c** (formed by deprotonation of 2-methyl-tetralone **1** using **7**) with a variety of deuterium sources (Scheme 6: Entry 4). From these regioselective *C*-deuteriations, it appears the structural nature of the deuterium donor was particularly important for controlling the regioselective *C*-deuteriation of enolate **2c** to give 2-deuterio-2-methyl-tetralone [D_1]-**1** (Scheme 6). For weakly *D*-acidic sources, like D_2O and [D_4]-MeOH these gave moderately higher levels of *D*-incorporation than mildly *D*-acidic [D_4]-acetic acid (Scheme 6: Entry 4). Whereas, a more *D*-acidic source like DCl gave little or no *D*-incorporation (Scheme 6: Entry 4). This effect is expected as an increase in *D*-acidity has been shown to favour *D*-enol formation [D_1]-**11** by promoting regioselective *O*-deuteriation (as illustrated in Scheme 7) which leads to loss of the deuterium label through tautomerization during aqueous work-up.[3,4] It is interesting to note, the use of dilithiated urea **7** appears to be

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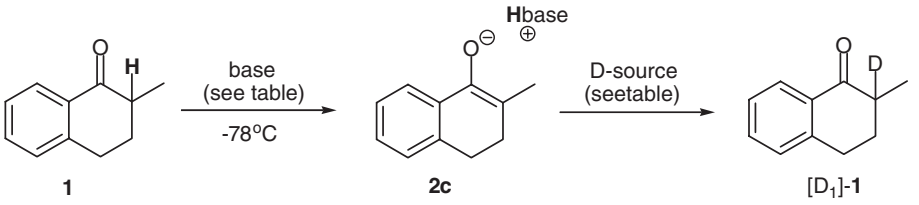
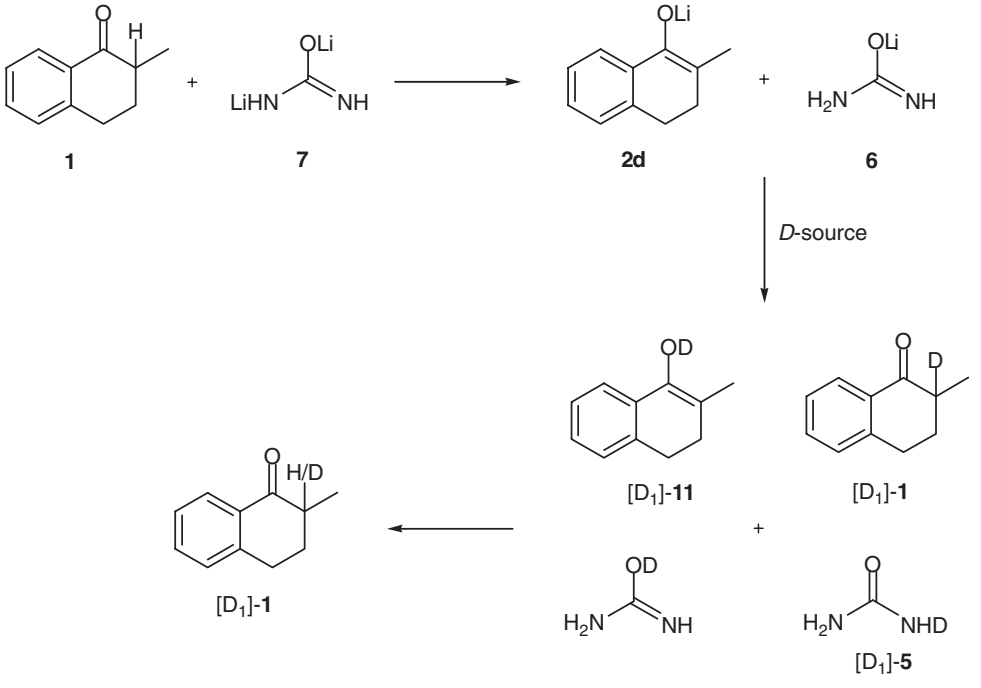


Entry	Base	D-source [D4]-MeOH	D2O	[D4]-acetic acid	DCl
1	LDA	55:45[a] (67%)	52:48[a] (72%)	<2:>98[a] (90%)	72:28[a] (78%)
2	LDA.MeLi	58:42[a] (81%)	62:38[a] (78%)	35:65[a] (87%)	83:17[a] (72%)
3	under "base-free" conditions *via* **2b**	>98:2[a] (60%)	>98:2[a] (72%)	>95:5[a] (68%)	84:16[a] (70%)
4	di-lithiated urea **7**	73:27[a] (65%)	78:22[a] (66%)	46:65[a] (64%)	1:99[a] (62%)

[a]isotopic[D]:[H]ratio.

Scheme 6.



Scheme 7.

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more efficient at aiding regioselective *C*-deuteriation than lithium diisopropylamide (LDA), with and without addition of methyl lithium (Scheme 6: Entries 2 and 1, respectively). For 'residual base-free' enolates, such as **2b**, which do not contain an additional competitive amine base, kinetic *C*-deuteriation with D_2O, [D_4]-MeOH and [D_4]-acetic acid is particularly efficient leading to the required 2-deuterio-2-methyl-tetralone [D_1]-**1** in good yield with high *D*-incorporation (Scheme 6: Entry 3). Efficient *D*-incorporation appears to occur when using DCl with 'base-free' enolates in the presence and absence of diisopropylamine (see Scheme 6: Entries 1 and 3), and this is may be due to a combination of *D*-enol formation [D_1]-**11**, and competitive thermodynamic tautomerization.

We next turned our attention to the deuteriation of a wide variety of structurally related aryl alkyl ketones **1**, **8** and **12-15** using our developed methodology (Scheme 8). In line with our preliminary study, the relative order of deuterium incorporation was found to be: D_2O > [D_4]-MeOH > [D_4]-acetic acid > DCl (Scheme 8). However, it appears that selective deuteriation under kinetic control, in particular for D_2O had not occurred during the lifetime of these reactions. This presumably was due to proton-deuterium exchange under basic conditions involving the byproduct lithium deuteroxide (LiOD), the mono-deuteriated ketone and an excess of deuterium donor to give dideuteriated ketones. However, it is surprising to find that the level of deuterium incorporation were not complete for ketones like **1** (to give [D_1]-**1**) which cannot under go this type of proton-deuterium exchange. Whereas, for *D*-acidic deuterium donors, which contain intrinsically weaker conjugate bases (e.g. [D_4]-acetic acid) further deuterium incorporation appears not to be a problem.

We next turned our attention to the deuteriation of a series of sterically demanding phenyl alkyl and phenyl cycloalkyl ketones **16** and **17–19**, respectively as these were known to be difficult to deuteriate under kinetic control (Scheme 9).[4,19] Addition of these ketones **16–19** to a stirred solution of preformed **7** in THF at −78°C, followed by the addition of a suitable deuterium source (e.g. D_2O, [D_4]-MeOH and [D_4]-acetic acid), gave the partially deuteriated ketones [D_1]-**16–19** in good yield (Scheme 9). The overall levels of regioselective *C*-deuteriation were found to be similar[4] to those obtained using Stork's[14] 'base-free' enolate methodology and in fact near their natural regioselectivity. By comparison, these levels of *D*-incorporation and the yields were higher than those obtained using lithium diisopropylamide (LDA) (See footnote ¶).[3,4] It is particularly interesting to note that competitive β-hydride reduction of ketones **17–19** does occur with the use of LDA, thus lowering the overall yield of [D_1]-**17–19** through diminished enolate formation (by approximately 7, 10 and 25%, respectively),[4] whereas, using the dilithiated urea **7** this does not occur.

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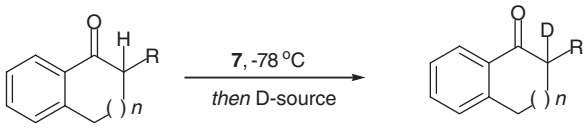
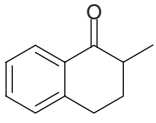
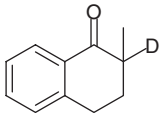
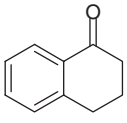
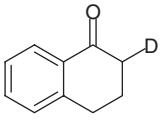
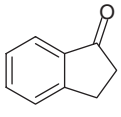
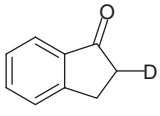
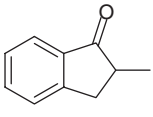
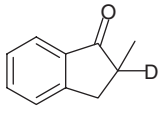
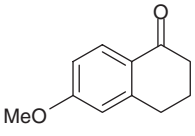
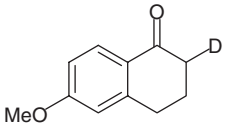
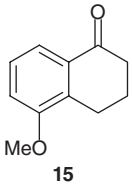
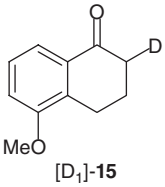


Ketone	Product	D-source [D_4]-MeOH	D_2O	[D_4]-aceticacid	DCl
 **1**	 [D_1]-**1**	73:27[a] (65%)	78:22[a] (66%)	46:54[a] (64%)	1:99[a] (62%)
 **8**	 [D_1]-**8**	80:20[a] (65%)	78:22[b] (66%)	20:80[a] (69%)	1:99[a] (71%)
 **12**	 [D_1]-**12**	78:22[a] (62%)	86:14[b] (65%)	26:74[a] (66%)	4:96[a] (67%)
 **13**	 [D_1]-**13**	68:32[a] (58%)	71:29[a] (55%)	20:80[a] (59%)	5:95[a] (63%)
 **14**	 [D_1]-**14**	64:36[b] (70%)	70:30[b] (70%)	22:78[a] (61%)	5:95[a] (67%)
 **15**	 [D_1]-**15**	55:45[b] (62%)	70:30[b] (70%)	42:58[a] (60%)	1:99[a] (69%)

[a]isotopic [D]:[H] ratio; [b]isotopic [D_1]:[D_2] ratio.

Scheme 8.

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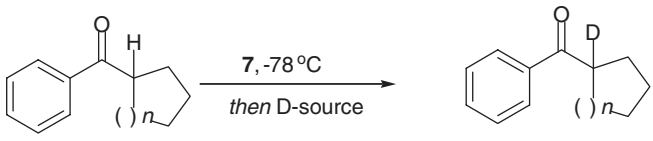
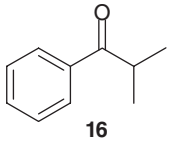
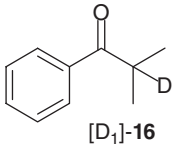
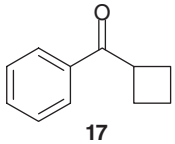
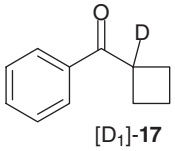
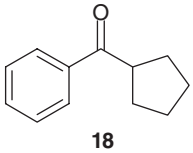
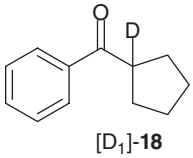
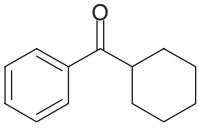
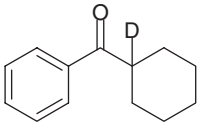


Ketone	Product	D-source [D_4]-MeOH	D-source D_2O	D-source [D_4]-acetic acid
 **16**	 [D_1]-**16**	65:35[a] (60%)	69:31[a] (60%)	14:86[a] (59%)
 **17**	 [D_1]-**17**	60:40[a] (62%)	65:35[a] (58%)	30:70[a] (57%)
 **18**	 [D_1]-**18**	59:41[a] (53%)	67:33[b] (59%)	22:78[a] (52%)
 **19**	 [D_1]-**19**	60:40[a] (62%)	65:35[a] (58%)	25:77[a] (60%)

[a]isotopic [D]:[H] ratio.

Scheme 9.

In an attempt to find a suitable method for the formation of 2-deuterio-2-methyl-tetralone [D_1]-**1**, we next probed the thermodynamic deuteriation of 2-methyl-tetralone **1** under basic conditions (Scheme 10). Excellent levels of deuterium incorporation ([D]:[H]: $>98:<2$) were achieved by using lithium hydroxide monohydrate (1 equivalent) as the base and [D_4]-MeOH as the deuterium donor and solvent (Scheme 10). It is important to note, using an excess of lithium hydroxide monohydrate (e.g. three equivalents) lowered the yield of 2-deuterio-2-methyl-tetralone [D_1]-**1** (from 99 to 28%) through competitive aldol addition, and using D_2O can lead to lower overall *D*-incorporation due to reduced solubility of the substrate. This same level of deuterium incorporation could be achieved by using its silyl enol ether

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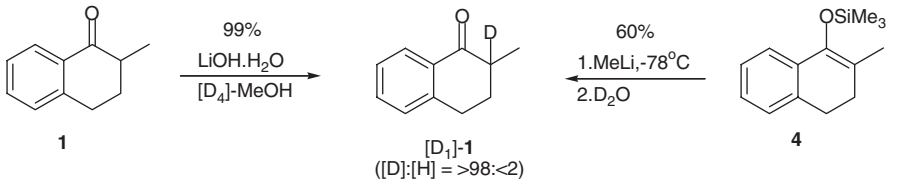

Scheme 10.

precursor **4** under Stork's[14] 'base-free' conditions, but the yield is generally lower (Scheme 10).[2,3]

Experimental

General

All solvents were distilled before use. Tetrahydrofuran (THF) and ether were freshly distilled from sodium wire. Benzophenone was used as the indicator for THF. All reactions were carried out under nitrogen using oven-dried glassware. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel $60F_{254}$ silica). Proton and carbon NMR spectra were recorded on a Bruker AM 250 Fourier transform spectrometer using an internal deuterium lock. Chemical shifts are quoted in parts per million downfield from tetramethylsilane. Carbon NMR spectra were recorded with broad proton decoupling. Infrared spectra were recorded on a Shimadzu 8300 FTIR spectrometer and mass spectra were recorded on a Kratos 50MSTC spectrometer using a DS503 data system for high-resolution analysis. The levels of *D*-incorporation were determined by a combination of mass, proton and carbon NMR spectra.

Representative procedure for deuteriation of 2-methyl-tetralone 1 to give 2-deuterio-2-methyl-tetralone [D_1]-1 using the dilithium amide **7**

n-BuLi (0.25 ml, 2.5 M in hexane, 0.62 mmol) was added dropwise to a solution of urea **5** (0.37 mg, 0.62 mmol) in THF at room temperature and stirred for 1 h. The resulting solution was cooled to -78°C. 2-Methyl-tetralone **1** (0.1 g, 0.62 mmol) in THF (1 ml), was slowly added and the reaction mixture was stirred for 30 min. The chosen deuterium donor (e.g. [D_4]-acetic acid (0.79 mg, 71 µl, 1.24 mmol)) in THF (1 ml) was added dropwise and the resulting mixture was stirred for a further 30 min. The reaction was quenched by the addition of water (10 ml). The solution was extracted with diethyl ether (3×20 ml), dried (over $MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with light

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petroleum (40–60°C):diethyl ether (9:1) to give 2-methyl-tetralone-[D_1]-**1** (63 mg, 63%) as an oil; R_F (light petroleum (40–60°C):diethyl ether (9:1)] 0.5; ν_{max} (film); cm^{-1} 2106 (C–D) and 1683 (CO); d_H (250 MHz, $CDCl_3$) 8.00 (1 H, d, $J = 7.7$, CH; Ar), 7.47 (1 H, d, $J = 7.7$, CH; Ar), 7.25 (1 H, t, $J = 7.7$, CH; Ar), 7.22 (1 H, d, $J = 7.7$, CH; Ar), 3.00 (2 H, m, $CH_2C{=}CH$), 2.20 (1 H, dt, $J = 13.2$ and 4.4, CH_AH_B), 1.87 (1 H, m, CH_AH_B) and 1.28 (3 H, s, CH_3CD); δ_C (62.5 MHz, $CDCl_3$) 200.8 (C=O), 144.2 (*i*-C; Ar), 133.1 (*i*-C; Ar), 132.4, 128.7, 127.4 and 126.6 (4 × CH; Ar), 42.0 (1 C, t [1:1:1], $^1J_{C,D}$ = 19.0, CDMe), 31.3 and 28.8 (2 × CH_2) and 15.3 (CH_3) (Found MH^+, 162.1034. $C_{11}H_{12}DO$ requires MH^+, 162.1029); *m/z* 162 (100%, MH^+). The isotopic shift was 0.5 ppm (75.4 Hz at 150 MHz).

Representative procedure for silylation of tetralone 8 to give silyl enol ether 9 using the dilithium amide **7**

n-BuLi (0.25 ml, 2.5 M in hexane, 0.62 mmol) was added dropwise to a solution of urea 5 (0.37 mg, 0.62 mmol) in THF at room temperature and stirred for 1 h. The resulting solution was cooled to −78°C. Tetralone **8** (90 mg, 0.62 mmol) in THF (1 ml), was slowly added and the reaction mixture was stirred for 30 min. Trimethylsilylacetate (0.17 g, 1.24 mmol) was added dropwise and the resulting mixture was stirred for a further 2 h. The reaction was quenched by the addition of water (10 ml). The solution was extracted with diethyl ether (3 × 20 ml), dried (over $MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with light petroleum (40–60°C):diethyl ether (9:1) to give 1-trimethylsilyloxy-tetral-1-ene **9** (70 mg, 52%) as an oil; R_F ((light petroleum (40–60°C):diethyl ether (9:1)) 0.93; ν_{max}(film); cm^{-1} 1687 (C=C); δ_H(270 MHz, $CDCl_3$) 7.38 (1 H, d, $J = 7.7$, CH; Ar), 7.10 (3 H, m, 3 × CH; Ar), 5.19 (1 H, t, $J = 4.5$, C=CH), 2.78 (2 H, t, $J = 7.7$, $CH_2C{=}CH$), 2.31 (2 H, m, CH_2) and 0.21 (9 H, s, Si−$(CH_3)_3$); δ_C(100 MHz, $CDCl_3$) 147.8 (*i*-C; Ar), 136.8 (C=*C*O), 133.4 (*i*-C; Ar), 127.2, 126.9, 126.2 and 121.8 (4 × CH; Ar), 105.2 (*C*=CO), 39.1, 28.2 and 22.2 (3 × CH_2) and 0.2 (Si−$(CH_3)_3$); *m/z* 145 (30%, M − $SiMe_3$) and 219.1 (100, MH^+).

Representative procedure for methylation of 2-methyl-tetralone 1 to form 2,2-dimethyl-tetralone 10 using the dilithium amide **7**

n-BuLi (0.25 ml, 2.5 M in hexane, 0.62 mmol) was added dropwise to a solution of urea **5** (0.37 mg, 0.62 mmol) in THF at room temperature and stirred for 1 h. The resulting solution was cooled to −78°C. 2-Methyl-tetralone **1** (0.1 g, 0.62 mmol) in THF (1 ml), was slowly added and the reaction mixture was stirred for 30 minutes. Methyl iodide (0.18 g, 1.24 mmol) in THF (1 ml) was added dropwise and the resulting mixture was stirred for 12 h. The reaction was quenched by the addition of water (10 ml). The solution was

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extracted with diethyl ether (3×20 ml), dried (over $MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with light petroleum (40–60°C):diethyl ether (9:1) to give 2,2-dimethyl-tetralone-**10** (76 mg, 70%) as an oil; R_F (light petroleum (40–60°C):ether (9:1)) 0.6; ν_{max} (film); cm^{-1} 1680 (C=O); δ_H(250 MHz, $CDCl_3$) 8.05 (1 H, d, $J=7.5$, CH; Ar), 7.45 (1 H, t, $J=7.5$, CH; Ar), 7.29 (1 H, t, $J=7.5$, CH; Ar), 7.20 (1 H, d, $J=7.5$, CH; Ar), 2.98 (2 H, t, $J=6.5$, $CH_2C=CH$), and 1.99 (2 H, t, $J=6.5$, CH_2) and 1.20 (6 H, s, $2 \times CH_3$); δ_C (62.5 MHz, $CDCl_3$) 203.2 (C=O), 143.8 (*i*-C; Ar), 133.4 (*i*-C; Ar), 131.8, 129.1 128.4 and 127.0 ($4 \times$ CH; Ar), 42.0 (CMe_2), 37.1 and 26.1 ($2 \times CH_2$), and 24.8 ($2 \times CH_3$) (Found MH^+, 175.1120. $C_{12}H_{15}O$ requires MH, 175.1123).

2-deuterio-2-methyl-3,4-dihydronaphthlene-1-one [d_1]-1

$LiOH \cdot H_2O$ (21 mg, 0.5 mmol) was added to a stirred solution of 2-methyltetralone **3** (80 mg, 0.5 mmol) in [D_4]-MeOH (1.6 ml). The mixture was stirred for 24 h, extracted into diethyl ether (2×10 ml) and concentrated to give 2-deuterio-2-methyltetralone [D_1]-1 (80 mg, 99%) ([D]:[H] = >98:<2) as an oil, which was spectroscopically identical to that previously obtained.[3]

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