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**Research Article**

# Investigations into the regioselective *C*-deuteriation of enolates using a diisopropylammonium salt

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## Summary

Results are reported on the regioselective *C*-deuteriation of 2-methyl tetralone using a series of diisopropylamine derived *D*-sources. The results presented further aid the understanding of kinetic deuteriation of both 'base-containing' and 'base-free' enolates. Copyright © 2002 John Wiley & Sons, Ltd.

**Key Words:** ammonium salts; *D*-enols; deuterium; enolates; internal deuterium transfer; 2-methyl tetralone

## Introduction

The understanding of proton transfer in chemical and biological systems is an increasingly important area.[1] The absolute and relative rates of many individual chemical proton transfer processes have been well documented,[2] but their chemical consequence has been less

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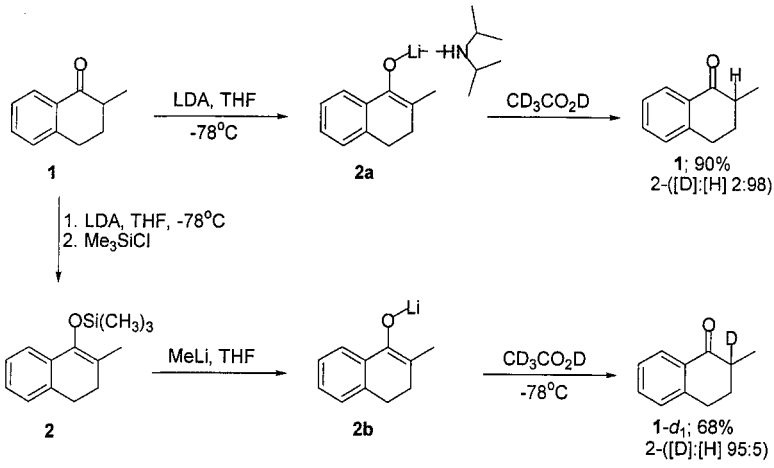
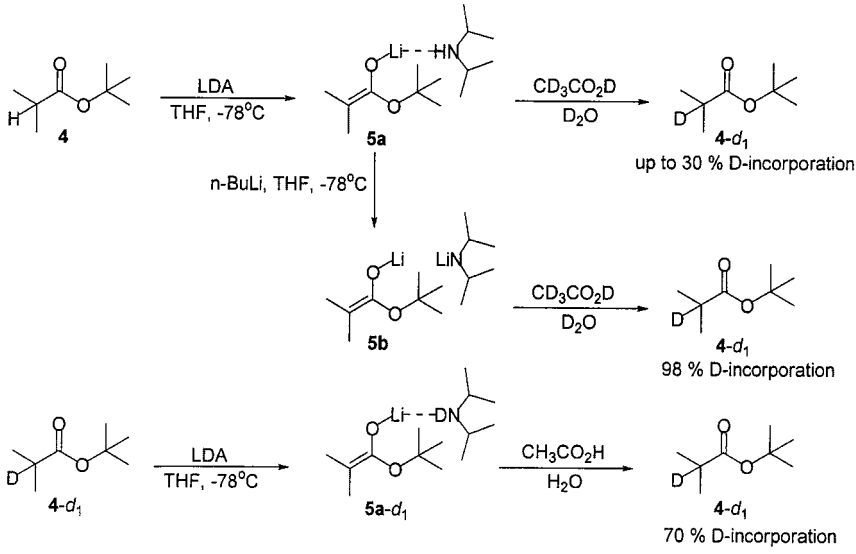



**Scheme 1.**

studied.[3] Over the last decade,[4] numerous research groups have focused their attention on the enantioselective protonation of enol(ates) derivatives with some success.[5] Of these reports, many have used the commercially available racemic ketone, 2-methyl tetralone **1** as their preferred carbonyl substrate.[6] Over the last few years,[7] we have been interested in the mechanistic pathway of such processes, and recently, we have reported[8] the deuteriation of related 'base-free' enolates to aid the understanding of these proton transfer processes. For example, deprotonation of 2-methyl tetralone **1** with lithium diisopropylamide (LDA) and attempted deuteriation of the corresponding enolate **2a** with acetic acid-$d_4$ gave the original tetralone **1** in 90% yield with virtually no incorporation ([D]:[H] = 2:98) determined by $^1$H NMR spectroscopy (Scheme 1).[†] It has been found that deuteriation of the related 'base-free' enolate **2b** – formed by the addition of MeLi to the silyl enol ether **2** – with acetic acid-$d_4$ gave exclusively the required 2-deuterio-2-methyl tetralone **1**-$d_1$ with near perfect *D*-incorporation ([D]:[H] = 95:5).[8] Clearly, the presence of the residual diisopropylamine in **2a** – formed by deprotonation of 2-methyl tetralone **1** with LDA has a dramatic effect on the overall deuterium transfer process. Previous studies into this *residual base* effect have been documented by Seebach and co-workers;[9] they have shown that deprotonation of the ester **4** with LDA, followed by the addition of a solution of acetic acid-$d_4$ (in $D_2O$) gave only moderate *D*-incorporation (of up to 30%) (Scheme 2). However,

[†]Determined by integration of the $^1$H NMR spectrum of the corresponding methyl doublet at 1.28 ppm in **1** versus the methyl singlet at 1.28 ppm in **1**–$d_1$.

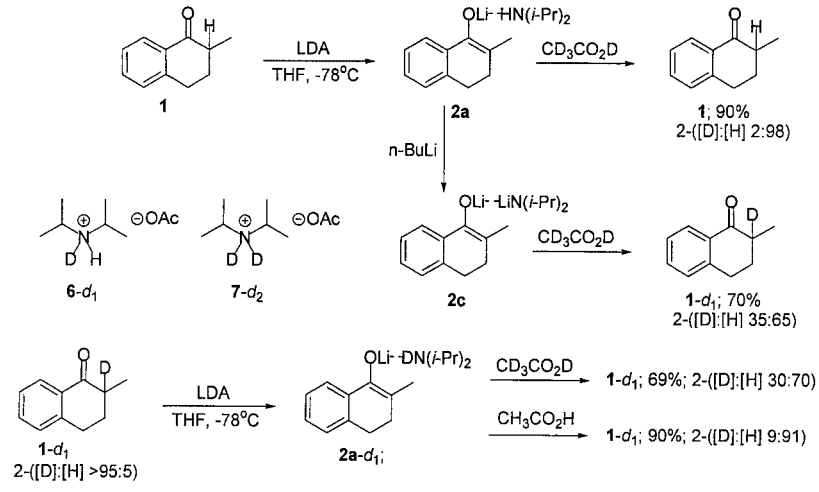



**Scheme 2.**

by removing the *unwanted* NH proton by the sequential addition of *n*-BuLi to form the amide–enolate complex **5b**, and repeating the same deuterium quench gave significantly higher levels of *D*-incorporation (98%). This has led to the idea of *internal proton return*,[9] in which the NH proton of the intermediate amine is re-supplied to the enolate (during the *D*-quench) to give back the recovered starting ester **4**. Further evidence of this proton return has come from a complementary *internal deuterium return*; de-deuteriation of the related ester **4**-$d_1$ with LDA, followed by attempted protonation with acetic acid (in $H_2O$) simply re-formed the original ester **4**-$d_1$ with moderately high levels of *D*-incorporation (70%). This reaction must proceed *via* the intermediate diisopropylamine–enolate complex **5a**-$d_1$, which must evidently allow efficient internal deuterium return (back to the enolate) in the presence of acetic acid.[10]

In an attempt to increase the level of *D*-incorporation, we removed the problematic NH protonation from the intermediate 'base'-enolate **2a** using *n*-BuLi. Deuteriation of the performed amide-enolate **2c** with acetic acid-$d_4$ gave slightly better *D*-incorporation (increasing from 2 to 35%) (Scheme 3). However, this level of *D*-incorporation was significantly lower than expected. This may be attributed to the reduced *C*-basicity of the tetralone enolate **2** thus lowering the amount of *C*-deuteriation than that of the corresponding ester **4** (Scheme 2). This

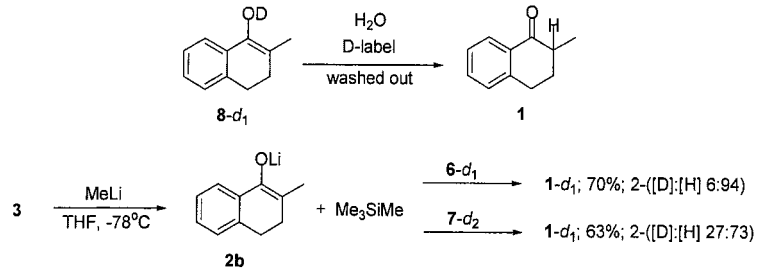



**Scheme 3.**

level of *D*-incorporation was found to be similar to that obtained by direct formation of the 'base'–enolate complex **2a**-$d_1$ – through de-deuteriation of 2-methyl tetralone **1**-$d_1$ using LDA – followed by the addition of acetic acid-$d_4$ ([D]:[H] = 30:70), which suggests that both reactions proceed *via* the formation of diisopropylamine in **6**-$d_1$. Alternatively, addition of non-labelled acetic acid to the 'base'-enolate **2a**-$d_1$ gave lower *D*-incorporation ([D]:[H] = 9:91), which presumably suggests that *internal proton/deuterium return* is not a dominant reaction pathway under these reaction conditions, using 2-methyl tetralone as the carbonyl component.

The required 2-deuterio-2-methyl tetralone **1**-$d_1$ could in principle be formed through regioselective *C*-deuteriation of the enolate **2a** with acetic acid-$d_4$ or by deuterium transfer using the *D*-acidic ammonium acetates **6**-$d_1$/**7**-$d_2$. To probe the effect of such ammonium salts as potential *D*-sources, we chose to synthesise them *in situ* by adding an appropriate amount of acetic acid-$d_4$ to a stirred solution of preformed LDA in THF at $-78^{\circ}$C. Of these ammonium salts, the ammonium acetate **7**-$d_2$ gave much better *C*-regioselectivity than the corresponding ammonium acetate **6**-$d_1$ ([D]:[H] = 27:73 for **7**-$d_2$ versus [D]:[H] = 6:94 for **6**-$d_1$). This lack of *D*-incorporation was presumably due to competitive protonation involving the NH of the ammonium acetate **6**-$d_1$. However, this mechanism does not account for the formation of the unlabelled 2-methyl tetralone **1**, when using the ammonium acetate **7**-$d_2$ as the *D*-source. This presumably

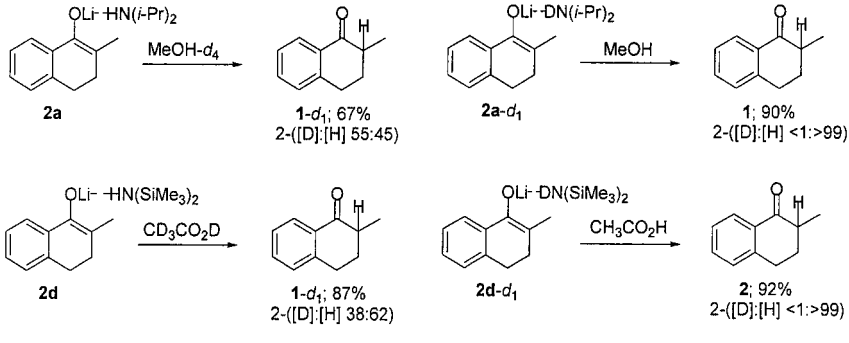
 




**Scheme 4.**

occurs *via* regioselective *O*-protonation/deuteriation of the enolate **2** to give the corresponding *H*/*D*-enol **8**-$d_1$, followed by thermodynamic tautomerisation under aqueous work-up ($H_2O$) to give the unlabelled tetralone **1** (Scheme 4). This washing out of a deuterium label (from a *D*-enol) to give an unlabelled carbonyl derivative has previously been responsible for the lack of deuteriation for sterically hindered enolates.[10] Furthermore, these positively charged ammonium slats may slightly favour *O*-protonation/deuteriation more so than similarly acidic but neutral organic-based acids due to their electrostatic attraction.

The amount of deuterium transfer between the *D*-source and the residual base can be controlled by the *in-situ* formation of a less basic residual amine, such as hexamethyldisilazane [by using lithium hexamethyldisilazide (LHMDS) as the lithium amide] or by using a less *D*-acidic source like MeOH-$d_4$. Treatment of the 'base'-enolate **2a** (formed by the addition of 2-methyl tetralone **1** to a stirred solution of LDA in THF at $-78°C$) with MeOH-$d_4$ gave significantly better *D*-incorporation ([D]:[H] = 55:45) (Scheme 5). However, by repeating

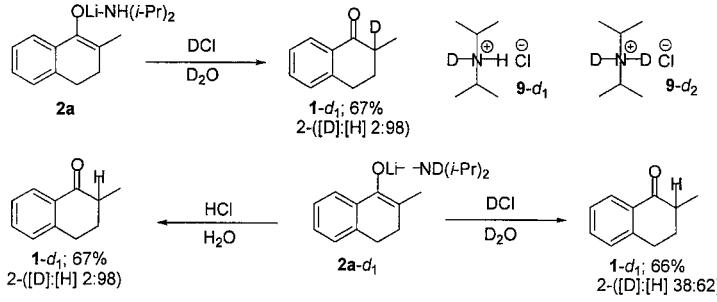



**Scheme 5.**

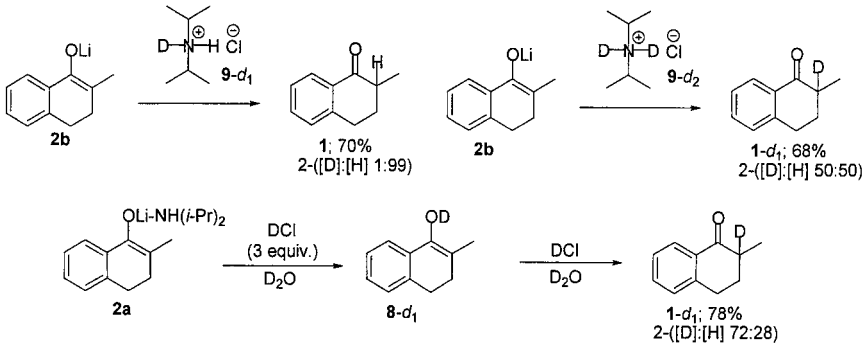
this reaction using complementary isotopic reagents: addition of MeOH to the 'base'-enolate **2a**-$d_1$ gave virtually no *D*-incorporation ([D]:[H] = < 1: > 99). On the other hand, by using a less basic residual amine, hexamethyldisilazane (HMDS) [formed by deprotonation of 2-methyl tetralone **1** using lithium hexamethyldisilazide (LiHMDS)] gave a slight improvement in *D*-incorporation when using acetic acid-$d_4$ (from 2 to 38% – [D]:[H] = 38:62). Under the related isotopic conditions: addition of unlabelled acetic acid to the *D*-labelled residual base–enolate complex **2d**-$d_1$ gave no *D*-incorporation. From this series of experiments, it appears that use of a less *D*-acidic reagent, like MeOH-$d_4$, and formation of a less basic residual base such as hexamethyldisilazide does prevent *internal deuterium return* under these reaction conditions.

Deuteriation of the more common residual base, diisopropylamine can be promoted further using a strongly *D*-acidic reagent like concentrated DCl (37% solution in $D_2O$) (Scheme 6). Addition of one equivalent of DCl to the 'base'–enolate **2a** gave no *D*-incorporation ([D]:[H] = 2:98). Attempts at promoting an internal deuterium return by protonation of the 'base'–enolate **2a**-$d_1$ with HCl (1 equivalent) also gave no *D*-incorporation ([D]:[H] = 2:98). This suggests that the major reaction pathway in both reactions proceed *via* formation of the ammonium salt **9**-$d_1$, which appears to subsequently favour proton transfer rather than deuterium transfer. However, this could be prevented by ensuring the ammonium chloride **9**-$d_2$ was doubly deuteriated; addition of DCl (1 equivalent) to the deuteriated 'base'–enolate **9**-$d_1$ gave the required 2-deuterio-2-methyl tetralone **1**-$d_1$ with moderate incorporation ([D]:[H] = 38:62) (Scheme 6). The level of *D*-incorporation was found to be similar to that obtained by the direct addition of the ammonium chloride **9**-$d_2$[11] to the 'base-free' enolate **2b**




**Scheme 6.**




**Scheme 7.**

(Scheme 7). This level of *D*-incorporation can be increased further (to 72% – [D]:[H] = 72:28) by conducting the reaction under thermodynamic control – by the addition of an excess of DCl (3 equivalents) to the 'base'–enolate **2a**. This reaction presumably proceeds *via* initial formation of the ammonium salt **9**-$d_1$, followed by *O*-deuteriation of the enolate (using DCl) to give the *D*-enol **8**-$d_1$, tautomerisation of which in the presence of DCl forms the required 2-deuterio-2-methyl tetralone **1**-$d_1$ ([D]:[H] = 72:28) in 78% yield.

In conclusion, we have shown that efficient *C*-deuteriation of a given enolate was dependent on the structural nature of the deuterium donor (*D*-acidity and charge) and the structural nature of the residual base. *C*-Deuteriation in the presence of a residual amine can be improved by disfavouring competitive deuteriation using either a weakly *D*-acidic deuterium source or a by formation of a weakly *D*-basic amine to prevent internal proton return. The deuterium donor must naturally favour *C*-deuteriation to give directly the required 2-deuterio-carbonyl derivative rather than *O*-deuteriation to give the related *D*-enol. This can be partially controlled by ensuring that the deuterium donor is weakly *D*-acidic (to prevent *D*-enol formation) and by using a *C*-directing deuterium donor. The effect of *O*-deuteriation can be particularly problematic since this can lead to the unlabelled carbonyl derivative by 'washing-out' the deuterium label (from the *D*-enol) through tautomerisation under aqueous work-up.

### *Typical deuteriation procedure for a 'base-free' enolate*

A solution of MeLi (0.32 ml, 1.6 M in ether, 0.48 mmol) was added dropwise to the silyl enol ether **2** (0.1 g, 0.43 mmol) at room

temperature. This resulting solution was stirred for 1 h at room temperature and then cooled at −78°C. The deuterium donor [e.g. ammonium chloride **9**-$d_2$ (0.12 g, 0.86 mmol)] in THF (1 ml) was added dropwise to this solution and the mixture stirred for a further 30 min. The reaction was quenched by the addition of water (10 ml). The solution was extracted with ether (3 × 20 ml), dried ($MgSO_4$) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum (40–60°C):ether (9:1) to give the tetralone **1**-$d_1$ (48 mg, 70%) as an oil; ([D]:[H] = 50:50); $R_F$ [light petroleum (40–60°C):ether (9:1)] 0.5; $\upsilon_{max}$ (film)/cm 2106 (C–D) and 1683 (CO); $\delta_H$ (250 MHz, $CDCl_3$) 8.00 (1 H, d, *J*7.7, CH; Ar), 7.47 (1 H, dd, *J*7.7 and 7.6, CH; Ar), 7.25 (1 H, t, *J*7.7, CH; Ar), 7.22 (1 H, d, *J*7.6, CH; Ar), 3.00 (2 H, m, $CH_2CH=C$), 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, MeCD); $\delta_C$(62.5 MHz, $CDCl_3$) 200.8, 144.2, 133.1, 132.4, 128.7, 127.4, 126.6, 42.0 (1 C, t, *J*19.0, CDMe), 31.3, 28.8 and 15.3 (Found $MH^+$, 162.1034. $C_{11}H_{12}DO$ requires MH, 162.1029); *m/z* 162 (100%, M). The isotopic shift was 0.75 ppm (75.4 Hz at 100 MHz).

*Typical deuteriation procedure for a 'base' enolate*

A solution of LDA (0.46 ml, 1.5 M in THF, 0.69 mmol) was added dropwise to a stirred solution of tetralone 1 (0.1 g, 0.62 mmol) and stirred for 1 h at −78°C. The deuterium donor [e.g. DCl (32 mg, 87 µl, 37% solution in $D_2O$, 0.86 mmol)] in THF (1 ml) was added dropwise to this solution and the mixture stirred for a further 30 min. The reaction was quenched by the addition of water (10 ml). The solution was extracted with ether (3 × 20 ml), dried ($MgSO_4$) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum (40–60°C):ether (9:1) to give the tetralone **1**-$d_1$ (78 mg, 78%) as an oil, [D]:[H] = 72:28).

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