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Investigations into the mechanism of regioselective C-deuteration of enolates under ‘base-free’ conditions

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Abstract

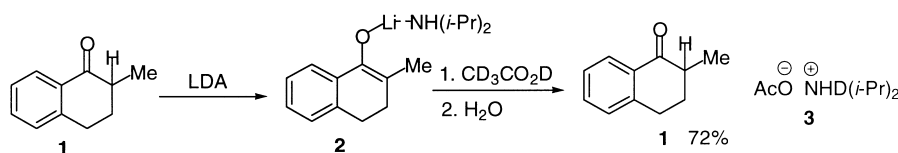
Regioselective C-deuteration of enolates was efficiently achieved by quenching the corresponding base-free enolate in the presence of a carbonyl chelating deuterium source. We comment on factors (such as the presence of base and the structural nature of the deuterium reagent) that are responsible for this observed regioselectivity and comment on the role of the deuterium source. © 2000 Elsevier Science Ltd. All rights reserved.

The continuing development of novel synthetic methodology for direct incorporation of non-radioactive isotopic labels within organic molecules for both chemical and biological mechanistic studies is paramount.¹ Some of this attention has been concerned with deuterium incorporation involving simple carbon–hydrogen bond exchange reactions,² many of which have relied on a deprotonation–deuteration strategy involving relatively acidic centres,³ most notably adjacent to a carbonyl group.⁴ For synthetic ease, most H–D exchange reactions are usually performed under thermodynamic control⁵ by using an excess of the deuterium source, which is generally used as the solvent, to drive the reaction to completion.⁶ However, there are some problems associated with this protocol, such as overall D-efficiency, cost and the difficulty associated with product separation (due to incomplete substitution or over incorporation). We believe that deuteration under kinetic control⁷ would solve many of these problems, such as single incorporation of deuterium, but this type of methodology has been studied far less. Indeed in some cases direct incorporation has been shown to be rather problematic due to a number of factors.⁸ Firstly, the method of enolate generation is particularly important since many have additional competing bases present, such as diisopropylamine (derived from the original lithium amide base, e.g. LDA), which can cause contamination via internal proton return in the deuteration step.⁹ This has partially been solved by further deprotonation to form enolate-amide complexes,^{4,10,11} or by ensuring the formation of a less basic amine.⁴ Of similar importance is the less obvious concept of

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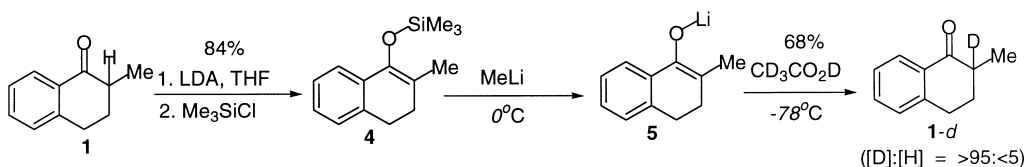
regioselective *C*-deuteration which potentially leads directly to the α -deuteriated carbonyl functionality rather than the corresponding reaction proceeding via the enol by *O*-deuteration, tautomerisation of which under aqueous work-up can result in the loss of the deuterium label.

Ideally, the method of choice would involve the use of enolates in the absence of additional bases, coupled with the use of an efficient *C*-deuterating reagent. It is rather surprising that such methodology has not been studied to date. We have previously shown that carbonyl chelating proton donors, such as acetoacetate and acetic acid are an efficient method for regioselective *C*-protonation of enolates under the required 'base-free' conditions.¹² We now wish to report our studies into regioselective *C*-deuteration of such 'base-free' enolates using an analogous carbonyl chelating deuterium donor such as acetic acid-*d*₄ under kinetic control. We comment on factors (such as the presence of base and the structural nature of the deuterating agent) on the observed regioselectivity and discuss the role of such deuterium sources.



Scheme 1.

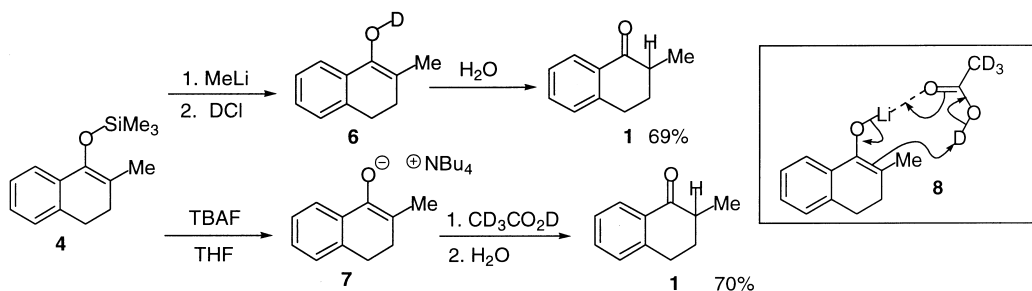
We first established the need for such a process by attempting to synthesise the tetralone **1-d** under traditional base-enolate conditions. Formation of the tetralone enolate **2** by the addition of LDA to **1** and attempted deuteration with acetic acid-*d*₄ gave only recovered tetralone **1** with no deuterium incorporation (Scheme 1).¹³ This was unexpected since it is well documented¹¹ that deuteration of the residual diisopropylamine in **2** and the formation of the mixed ammonium salt **3** is more than likely responsible for this internal proton return. By using less acidic D-sources, such as D₂O and MeOH-*d*₄, where deuterium transfer to the amine is no longer kinetically favourable, it is still rather surprising that complete incorporation does not occur. However, the deuterium enriched tetralone **1** ([D]:[H] = 52:48; 72% and [D]:[H] = 55:45; 67%) was isolated using D₂O and MeOH-*d*₄, respectively, but similar effects have been reported.¹⁴



Scheme 2.

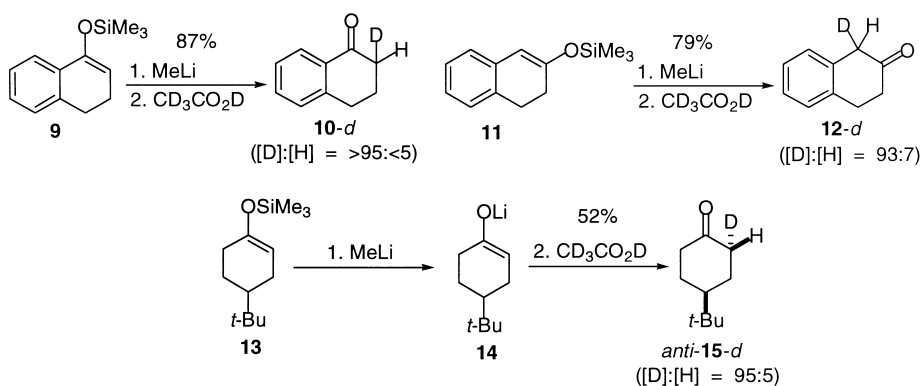
Repeating this reaction under Koga's 'base-free' lithium enolate¹⁵ procedure—by the addition of MeLi to the preformed silyl enol ether **4** (derived from 2-methyl tetralone **1**)—generates the 'base-free' enolate **5** of the parent tetralone **1** (Scheme 2).¹⁵ Simple addition of acetic acid-*d*₄ (1 equiv.) to this stirred solution at -78°C gave the tetralone **1-d** in acceptable yield (68%) with near complete incorporation (determined by ¹H NMR).¹³ This regiocontrol is even more remarkable, when considering that addition of a non-chelating deuterium source such as DCl gave no incorporation, presumably due to *O*-deuteration,^{11,16} to give the enol **6**, tautomerisation of which, in the presence of water (on aqueous work-up), leads to the non-deuterium incorporated tetralone **1**. In

contrast, using D_2O gave the required tetralone **1-d** with near perfect isotopic incorporation ($[D]:[H] > 98:2$) in 61% yield, presumably due to *O*-deuteration being no longer favoured.¹⁷ $MeOH-d_4$ behaved similarly, giving identical incorporation, but in a slightly improved yield (66%). This reaction was also shown to be sensitive to the presence of the lithium counter-ion; without it, in the case of the naked enolate **7**, no incorporation was observed using acetic acid- d_4 , whereas using D_2O gave the tetralone **1-d** in 72% yield ($[D]:[H] = 89:11$). The presence of the lithium cation is clearly important in both cases, but more so for acetic acid- d_4 which presumably requires carbonyl chelation¹⁸ to aid regioselective *C*-deuteration as illustrated in **8** (Scheme 3).¹²



Scheme 3.

We next investigated the versatility of this procedure by synthesising the more challenging single deuteriated ketones **10-d** and **12-d**. The simple addition of MeLi to their corresponding silyl enol ethers **9** and **11**, followed by the external addition of acetic acid- d_4 gave the required ketones **10-d** and **12-d** with no over d_2 incorporation, in excellent yield (Scheme 4). To probe the effect of stereochemistry, we also chose to quench the chiral 'base-free' enolate of 4-*tert* butylcyclohexane **14** with acetic acid- d_4 which gave the 4-*tert* butylcyclohexane *anti*-**15-d** directly as a single diastereoisomer in a moderate 52% yield.¹⁹ This diastereoselectivity was particularly good due to the complementarity of both reagent¹² and substrate control.



Scheme 4.

In conclusion, we have shown²⁰ that efficient regioselective *C*-deuteration of enolates can occur under kinetic control by using either D_2O , $MeOH-d_4$ and acetic acid- d_4 under 'base-free' conditions. Furthermore, we believe that there are three factors which are responsible for such efficient *C*-deuteration: (a) the absence of diisopropylamine to prevent internal proton return; (b)

for non-chelating D-sources, *O*-deuteration can be avoided by ensuring that the analogous non-isotopic acid has a $pK_a > 10^{17}$ (e.g. D₂O and MeOH-*d*₄); and (c) for chelating proton donors, the presence of a Lewis acidic lithium cation is essential to regioselectively direct *C*-deuteration.

Acknowledgements

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