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**The synthesis of compounds containing partially deuterated groups such as CD<sub>2</sub>H lacks general methods. These compounds could be important for fine control of metabolic processes in drug discovery, or in the development of multifunctional probes for analysis by complementary spectroscopic techniques. Here, a convenient route to CD<sub>2</sub>H-methyl ketones is reported through coupling of esters with bis[(pinacolato)boryl]methane and trapping with D<sub>2</sub>O.**

Recent approvals of the first two deuterated drugs Austedo (deutetabenazine)<sup>1</sup> and Sotyktu (deucravacitinib)<sup>2</sup> by the US-FDA have cemented the merits of deuterium incorporation in medicinal chemistry.<sup>3</sup> The kinetic isotope effect of the carbon-deuterium bond as compared to the carbon-hydrogen bond offers lower rates of metabolism and so longer half-life for deuterated drug candidates.<sup>4</sup> Aside from their application in drug discovery, deuterated molecules have long been used as isotopic labels to elucidate reaction mechanisms<sup>5</sup> and tracers to disclose metabolic pathways.<sup>6</sup> Deuterium is an important probe atom in Raman spectroscopy,<sup>7</sup> as well as in mass spectrometry.<sup>8</sup>

There is an important and growing need for molecules containing site-selective deuteration.<sup>9</sup> The majority of methods for deuteration fall into 3 categories: (i) H/D exchange,<sup>10</sup> (ii) addition of deuterium to unsaturated functionality,<sup>11</sup> and (iii) coupling of reagents with pre-incorporated deuterium.<sup>12</sup>

Ketones are some of the most common substrates for deuteration. H/D exchange using acid-, base- or transition-metal-catalysis *via* enolate or enol intermediates is the most common approach to access  $\alpha$ -deuterated ketones (Scheme 1(a)).<sup>13</sup>

It is extremely difficult to control the level of deuteration at the  $\alpha$ -position of a ketone. Protocols that afford deuterated ketones give an all-or-nothing outcome, transforming a CH<sub>3</sub> to a CD<sub>3</sub> substituent and it is not possible to obtain products

containing intermediate degrees of deuteration such as CDH<sub>2</sub> or CD<sub>2</sub>H with control. There is therefore a demand to discover methods that would allow partial deuteration of methyl groups labelled with both <sup>1</sup>H and <sup>2</sup>H.

This would be important for a couple of reasons. Firstly, partial deuteration would allow fine-tuned control of metabolic processes. In cases where metabolism of a CH<sub>3</sub> group was too fast and a CD<sub>3</sub> group metabolized too slow, intermediate levels of deuteration could give ideal rates of metabolism. A second application of molecules containing CD<sub>2</sub>H and CDH<sub>2</sub> groups could be as mechanistic probes containing both <sup>1</sup>H and <sup>2</sup>H, allowing the deuterated site to be simultaneously studied by multiple complementary techniques including <sup>1</sup>H NMR and Raman spectroscopy (<sup>2</sup>H), as well as mass spectrometry.

However, approaches to achieve the synthesis of partially-deuterated methyl groups are extremely rare. Silicates derived from CDH<sub>2</sub>I and CD<sub>2</sub>HI allow the addition of deuterated methyl groups to (hetero)arenes.<sup>14</sup> However, CDH<sub>2</sub>I and CD<sub>2</sub>HI are both extremely costly and difficult to access. Another approach to access ketones containing partially-deuterated methyl groups would be from the hydration of terminal alkynes using a source of deuterium (Scheme 1(a)). Isolated examples of the synthesis of CD<sub>2</sub>H ketones have been reported using this approach, but the majority of cases suffer over-deuteration, with CD<sub>3</sub>-ketones formed commonly, particularly under acid catalysis.<sup>15</sup>

Our goal at the outset of this project was the development of an efficient and selective methodology for the synthesis of ketones containing a partially-deuterated CD<sub>2</sub>H methyl substituent. Our group and others have demonstrated the reaction of lithiated geminal bis(boron) compounds<sup>16</sup> with esters and related derivatives to generate  $\alpha,\alpha$ -bis(enolate) equivalents that can be trapped with a variety of electrophiles to afford geminally difunctionalized ketones.<sup>17</sup> Each boron atom could be trapped successively with an electrophilic deuterium source to construct a di-deuterated methyl ketone (Scheme 1(b)). D<sub>2</sub>O would be our ideal source of deuterium due to its low cost and ready availability.

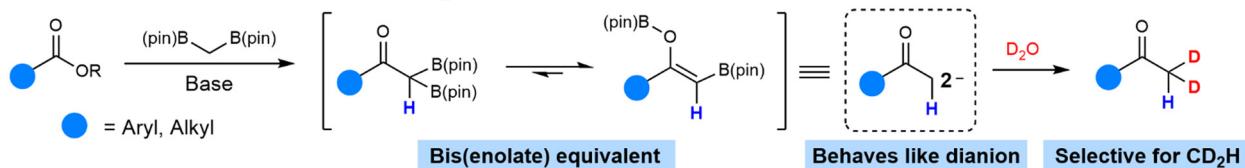
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## a) Partially-deuterated methyl groups are difficult to access

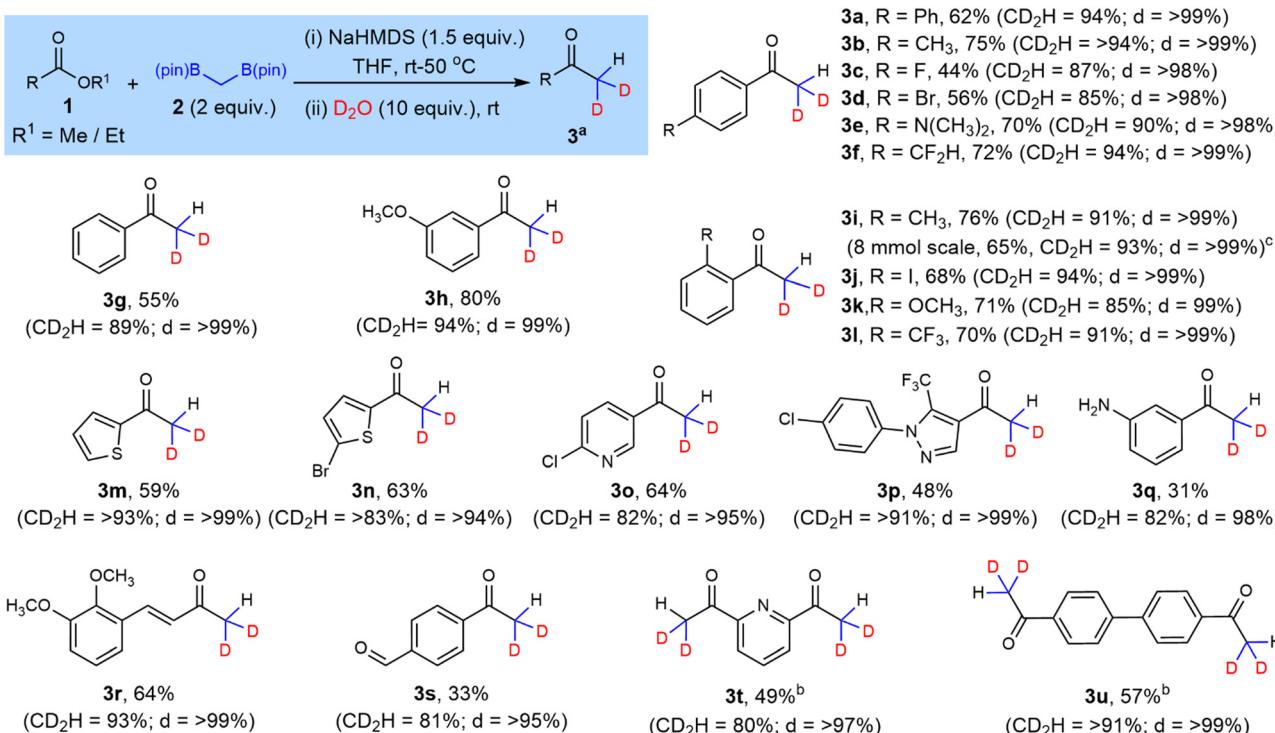
b) This study: Bis(boron) enolates for  $\text{CD}_2\text{H}$ -methyl ketones

Scheme 1 Challenges in partial deuteration of ketones and our approach.

The biggest challenge we anticipated would be control over the degree of deuteration. In our previous chemistry<sup>17a</sup> we trapped bis(boron)-enolate intermediates with either NFSI or iodomethane to provide *gem*-difluoro and *gem*-dimethyl ketones respectively.<sup>17a</sup> In those cases, further reaction to give a trifluoromethyl or *tert*-butyl ketone might be difficult. Fluorination lowers the reactivity of enolates due to its electron-withdrawing effect,<sup>18</sup> and electrophilic fluorination of a  $\text{CF}_2\text{H}$ -ketone to give a  $\text{CF}_3$ -ketone is not a known reliable transformation. Further alkylation of a  $\text{CH}(\text{CH}_3)_2$ -ketone to give a  $\text{C}(\text{CH}_3)_3$ -ketone is likely to be slow due to steric hindrance. However, in a di-deuteration process, exchange of hydrogen for deuterium could be facile and controlling the degree of deuteration

may prove to be a challenge under the basic conditions used to generate bis(boron) enolates.

Here we report our protocol for the synthesis of  $\text{CD}_2\text{H}$ -substituted ketones. We used similar conditions to our recently reported difluorination and dimethylation methods, but found that reducing the amount of solvent used and increasing the amount of  $\text{D}_2\text{O}$  for trapping was required for high selectivity towards the di-deuterated compound over other isotopomers. After optimization,<sup>19</sup> we standardized the reaction conditions to those with the highest combination of both conversion and selectivity towards the di-deuterated product, *i.e.*, 1.5 eq. NaHMDS, 2.0 eq. bis[(pinacolato)boryl]methane in 0.3 mL

Scheme 2 Substrate scope for di-deuteration of non-enolizable esters (a)  $\text{CD}_2\text{H}$  = % dideuteration; d = overall% deuteration (mono + di); (b) reaction performed with 4 equiv. 2, 3 equiv. NaHMDS and 20 equiv.  $\text{D}_2\text{O}$ ; (c) reaction performed with 8 mmol 1i.

anhydrous THF and 10 eq. of  $D_2O$ . We then examined the generality of this protocol with non-enolizable esters.

Ratios of deuterated products were measured by  $^1H$  NMR and validated by mass spectrometry. No  $CD_3$ -ketone product was ever observed in  $^{13}C$  NMR, and could only be observed in trace amounts (<5%) in a high resolution mass spectrum.

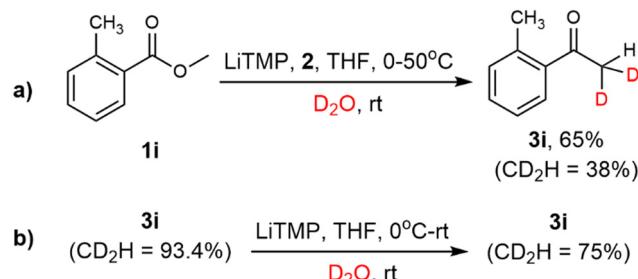
*para*-Substituted benzoates (Scheme 2, **1a–f**) reacted smoothly under the optimized conditions affording the desired ketone (**3a–f**) in moderate to good yields (44–75%) and high selectivity for di-deuteration (85–94%). The reaction was equally successful when unsubstituted (**3g**), as well as *meta*- and *ortho*-substituted benzoate esters were used (**3h–l**). The strategy also excelled with heteroaromatic derivatives, with systems containing thiophene, pyridine and pyrazole rings (**3m–p**). An 8 mmol scale reaction giving **3i** proceeded with comparable yield and isotopic selectivity to its smaller scale performance.

Next, we tested the tolerance of the protocol towards some reactive functional groups. Methyl 3-aminobenzoate resulted in a mixture of products with the di-deuterated ketone **3q** as the major product in 31% isolated yield and 82% di-deuteration. Methyl 4-hydroxybenzoate proved unreactive likely due to the interaction of the acidic phenol with NaHMDS. A cinnamate ester derivative (**1r**) showed highly selective reaction at the ester rather than the  $\beta$ -position of the alkene to furnish **3r**. Interestingly, the strategy could also tolerate to some extent an aldehyde, giving **3s** in 33% isolated yield. The boron-Wittig olefination product<sup>16a,d</sup> was also obtained *via* reaction at the aldehyde but this by-product was fully separable from the desired acetophenone.

Symmetric aromatic diesters when subjected to double the standard stoichiometry produced tetra-deuterated diketones **3t** and **3u** with moderate yields (Scheme 2). The slightly lower yields of these tetra-deuterated diketones was attributed to small amounts of reaction at only one of the ester sites.

We were interested in the stability of the products we had prepared, particularly with regard to scrambling of deuterium. Pleasingly, the di-deuterated compounds showed no signs of change in deuteration ratios even after a year of storage at room temperature. However, compound **3q**, containing an amine did show deterioration over time in the ratio of deuterated products when stored in solution. We also carried out exchange experiments in buffers of different pH which showed that the ketones showed little deuterium exchange at acidic or neutral pH after 24 hours, but showed a small amount of exchange at pH 10 and significant exchange at pH 12.<sup>19</sup>

Once the substrate scope with non-enolizable esters was established, we then explored the behaviour of enolizable esters. Unfortunately, using the same conditions as in Scheme 2 gave poor yields due to self-Claisen and competing processes. In our previous work we found LiTMP to be a useful base to avoid self-Claisen byproducts.<sup>17a</sup> As a stronger base than NaHMDS<sup>20</sup> it allowed complete lithiation of the geminal bis(boron) compound before addition to the ester, meaning formation of the bis(boron) enolate occurred before any self-Claisen processes as the reagents were added sequentially. However, in this case whilst the use of LiTMP



Scheme 3 Mechanistic studies on exchange processes using LiTMP.

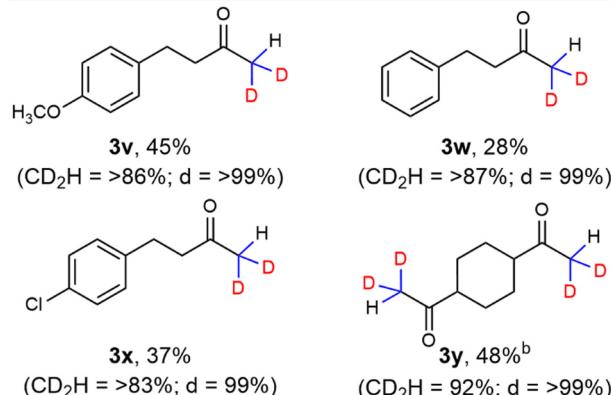
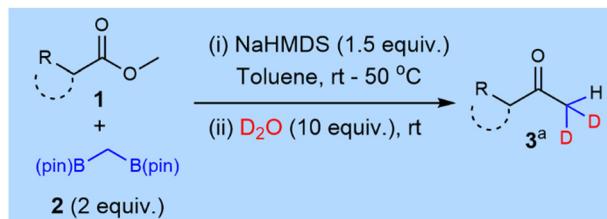
did improve the yield, it gave very poor selectivity for di-deuteration.<sup>19</sup>

This failure to improve selectivity with LiTMP prompted us to carry out some mechanistic work to examine the effects of LiTMP on di-deuteration. We began by looking at the use of LiTMP with non-enolizable esters, which had proved very successful with NaHMDS. Methyl 2-methylbenzoate (**1i**) was subjected to dideuteration coupling in the presence of 2 equivalents of LiTMP, which resulted in the synthesis of **3i** (65%) with 38% di-deuteration and 75% overall deuteration. This was much less selective than when NaHMDS was used (Scheme 3(a)). For further evidence, we treated pre-prepared selectively di-deuterated **3i** (93.4%  $CD_2H$ ) with 2 equivalent LiTMP for 45 minutes which was then quenched with  $D_2O$ . This led to a decrease in di-deuteration to 75% (Scheme 3(b)). Evidently, the use of LiTMP allowed us to avoid any self-Claisen reaction, but gave significant scrambling and low selectivity in deuteration.

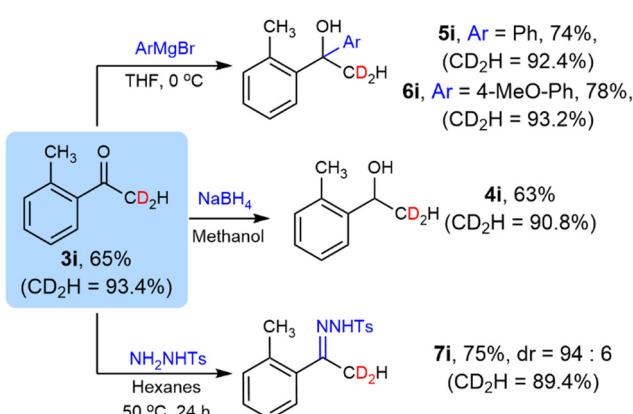
We therefore returned to NaHMDS as our base of choice. A change of solvent to anhydrous toluene combined with delayed addition of ester gave some improvement in yield and deuteration selectivity.<sup>19</sup> As our priority was selectivity for di-deuteration rather than isolated yield these conditions were selected to further explore the substrate scope of the reaction with enolizable esters (Scheme 4). A series of 3-phenylpropionate esters were transformed to the  $CD_2H$ -ketones in low to moderate yield (28–45%), but with very good purity and selectivity for the di-deuterated product (83–87%, Scheme 4, **3v–3x**). Dimethyl cyclohexane-1,4-dicarboxylate **1y** with double the quantities of reagents, gave the symmetric tetra-deuterated diketone **3y**. No deuterium was introduced at the non-methyl  $\alpha$ -position, confirming the high selectivity of this process, and any self-Claisen by-product was separable.

We next wanted to test our products in some standard carbonyl transformations to see if the deuteration was retained. Reactions that involved nucleophilic addition to the carbonyl group, including reduction with  $NaBH_4$  (**4i**), Grignard addition (**5i**, **6i**) and tosyl-hydrazone formation (**7i**) all proceeded in good yield and with very high levels of retention of deuteration (Scheme 5). However, reactions involving enolate formation perhaps predictably led to significant erosion of deuteration.

To summarize, a protocol has been developed to access partially deuterated methyl ketones through coupling of an ester with bis[(pinacolato)boryl]methane in the presence of base. The strategy gives moderate to good yields of the di-deuterated methyl ketones with deuteration only at the



**Scheme 4** Synthesis of CD<sub>2</sub>H-ketones from enolizable esters; (a) CD<sub>2</sub>H = % dideuteration; d = overall % deuteration (mono + di); (b) reaction performed with 4 equiv. **2**, 3 equiv. NaHMDS and 20 equiv. D<sub>2</sub>O.



**Scheme 5** Transformations of CD<sub>2</sub>H ketones with retention of deuterium.

positions where boron was present in the bis(boron) enolate intermediate. Gram-scale synthesis and further transformations of the di-deuterated methyl ketones with retention of deuterium validates the method for use in future pharmaceutical and industrial explorations.

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## Data availability

The data supporting this article have been included as part of the ESI.<sup>†</sup>

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

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