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# Lithium triethylborohydride-promoted generation of $\alpha,\alpha$ -difluoroenolates from 2-iodo-2,2-difluoroacetophenones: an unprecedented utilization of lithium triethylborohydride†

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Lithium triethylborohydride was found to promote the generation of  $\alpha,\alpha$ -difluoroenolates from 2-iodo-2,2-difluoroacetophenones, and applied to the synthesis of polyfluorinated  $\beta$ -hydroxy ketones via self-condensation or aldol reaction. The reaction indicates an unprecedented utilization of lithium triethylborohydride and provides novel access to the generation of  $\alpha,\alpha$ -difluoroenolates.

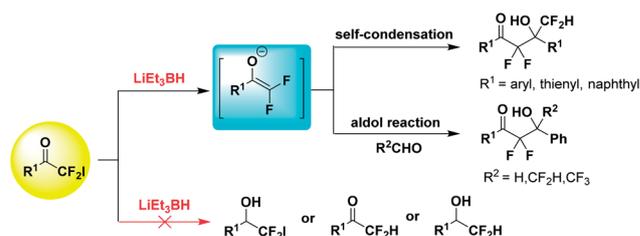
Difluoroenolates are useful fluorinated synthons for preparing difluoromethylene compounds,<sup>1</sup> with significant application in medicinal chemistry.<sup>2</sup> Accordingly, the protocols to generate difluoroenolates have attracted much attention. Colby firstly reported that compounds trifluoromethyl- $\alpha,\alpha$ -difluoro- $\beta$ -keto gem-diols could be used to give difluoroenolates by the release of trifluoroacetate.<sup>3</sup> Additionally, more difluorinated compounds have been developed as valuable precursors of difluoroenolates, such as  $\alpha,\alpha$ -difluoroketones,<sup>4</sup>  $\alpha,\alpha$ -difluoro- $\alpha$ -(trimethylsilylacet)amides,<sup>5</sup>  $\alpha,\alpha$ -difluoro- $\beta$ -ketoesters,<sup>6</sup>  $\alpha,\alpha,\alpha$ -trifluoroketones,<sup>7</sup> and 2,2-difluoro-1,3-diketones.<sup>8</sup> Furthermore, difluoroenoxyasilanes or difluoroenol *O*-Boc esters were often served as difluoroenolates in different difluoromethylenation reactions,<sup>9</sup> as well as transition-metal difluoroenolates.<sup>10</sup>

2-Iodo-2,2-difluoroacetophenones are one of the important building blocks to introduce  $\alpha,\alpha$ -difluoromethyl ketone fragment into molecules.<sup>11</sup> Our group has reported several reactions with 2-iodo-2,2-difluoroacetophenones to construct structurally diverse difluoromethylene compounds.<sup>11d-f</sup> As part of our continued research, further structure modification of 2-iodo-2,2-difluoroacetophenones was investigated. Lithium triethylborohydride (LiEt<sub>3</sub>BH, a superhydride, 1 M in THF) is a powerful reducing agent and can efficiently reduce a wide range of functional groups, especially halogen atoms.<sup>12</sup> However, the reaction with 2-iodo-2,2-difluoroacetophenones and LiEt<sub>3</sub>BH result in the generation of difluoroenolates instead of reduction products. Herein, we disclosed the

LiEt<sub>3</sub>BH-promoted *in situ* generation of difluoroenolates from 2-iodo-2,2-difluoroacetophenones and their application in aldol-type self-condensation and aldol reactions to give various  $\alpha,\alpha$ -difluoro- $\beta$ -hydroxy ketones (Scheme 1).

Initially, we chose LiEt<sub>3</sub>BH as one of the reducing agents to selectively reduce the carbonyl group or iodine atom of 2-iodo-2,2-difluoroacetophenones. Surprisingly, our initial attempt to perform the reaction between 2,2-difluoro-2-iodo-1-phenylethanone **1a** and LiEt<sub>3</sub>BH at -78 °C did not furnish any reduction product, instead leading to a self-adduct  $\alpha,\alpha,\gamma,\gamma$ -tetrafluoro- $\beta$ -hydroxy ketone **2a** with high yield (Table 1, entry 1). Raising the temperature of LiEt<sub>3</sub>BH only led to a little increasing of the yield of reduction product **3a** and **4a** (entries 2 and 3). It was speculated that a difluoroenolate **5** was generated from 2,2-difluoro-2-iodo-1-phenylethanone with LiEt<sub>3</sub>BH, then the difluoroenolate **5** went through protonation process to form  $\alpha,\alpha$ -difluoroacetophenone **6**. The aldol reaction between **5** and **6** gave the  $\alpha,\alpha,\gamma,\gamma$ -tetrafluoro- $\beta$ -hydroxy ketone **2a** (Scheme 2).

We wonder that whether the fluorine atom in 2-iodo-2,2-difluoroacetophenone play an important role in the fortuitous reaction. Therefore, the reaction of 2-halo-acetophenone or 2-chloro(bromo, fluoro)-2,2-difluoroacetophenone or 2,2-



Scheme 1 The novel utilization of LiEt<sub>3</sub>BH for the generation of  $\alpha,\alpha$ -difluoroenolates from 2-iodo-2,2-difluoroacetophenones.

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**Table 1** The influence of temperature to reaction of 2,2-difluoro-2-iodo-1-phenylethanone with LiEt<sub>3</sub>BH<sup>a</sup>

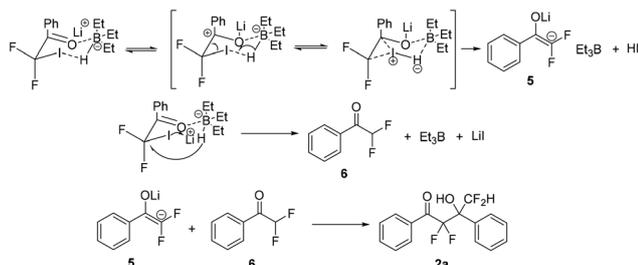
Entry	Temp.	Yield <sup>b</sup> (%)		
		2a	3a	4a
1	−78 °C	98.9	0.8	0.3
2	0 °C	43.9	6.9	49.2
3	rt	42.3	7.9	49.8

<sup>a</sup> Reaction conditions: **1a** (1 mmol), LiEt<sub>3</sub>BH (1.2 mmol, 1.2 equiv.), THF (dry), N<sub>2</sub>, 4 h. <sup>b</sup> Yield based on GC.

difluoroacetophenone with LiEt<sub>3</sub>BH were also performed in THF at −78 °C. The results showed that all these reduction reactions proceeded well leading to the formation of different reduction products (see Scheme 1 in ESI<sup>†</sup>), which demonstrates the specific characteristic of substrate 2-iodo-2,2-difluoroacetophenone owing to the adjacent fluorine atoms of carbonyl group.

Then, other reducing agents were also investigated using 2,2-difluoro-2-iodo-1-phenylethanone **1a** as substrate, only led to the formation of different reduction products (Scheme 3). It was noteworthy that the reducing agents sodium borohydride and Zn power show high selectivity, affording 2,2-difluoro-2-iodo-1-phenylethanol-1-ol **3a** and 2,2-difluoro-1-phenylethanol **6** as major products separately.

Next, the scope of 2,2-difluoro-2-iodo-1-phenylethanone **1** was explored through the LiEt<sub>3</sub>BH promoted self-condensation (Table 2). The 2-iodo-2,2-difluoroacetophenones **1b–f** bearing electron-donating groups, electron-withdrawing group or halogen atoms, 2,2-difluoro-2-iodo-1-(thiophen-2-yl)ethanone **1g** and 2,2-difluoro-2-iodo-1-(naphthalen-2-yl)ethanone **1h** were subjected to the self-condensation reaction and all were found applicable to the reaction, giving the corresponding  $\alpha,\alpha,\gamma,\gamma$ -tetrafluoro- $\beta$ -hydroxy ketones **2a–h** in good yields. Few of the reduction products **4d**, **4f**, **4g** were still observed in low yields. The results indicated that 2-iodo-2,2-difluoroacetophenone derivatives bearing different aryl or heterocyclic ring could be served as difluoroenolates precursors

**Scheme 2** Proposed mechanism of LiEt<sub>3</sub>BH-promoted aldol-type self-condensation.**Scheme 3** The reduction reactions of 2-iodo-2,2-difluoroacetophenone **1a**. <sup>a</sup>Yield based on GC.

through the reaction with LiEt<sub>3</sub>BH, which provided a novel and efficient access to difluoromethylation reactions.

$\alpha,\alpha$ -Difluoro- $\beta$ -hydroxy ketones are an important class of substructure in medicinal chemistry,<sup>13</sup> which could be obtained *via* aldol reaction with difluoroenolates.<sup>14</sup> Accordingly, to further demonstrate the utility of LiEt<sub>3</sub>BH, aldol reaction of 2-iodo-2,2-difluoroacetophenones with aldehydes promoted by LiEt<sub>3</sub>BH were conducted. 2-Iodo-2,2-difluoro-1-phenylethanone **1a** and benzaldehyde **7** was selected as model reaction substrates to optimize the reaction condition (Table 3). The corresponding aldol product **8** was produced in the presence of LiEt<sub>3</sub>BH (1.2 equiv. to compound **1a**) at −78 °C in THF (entry 1). The results showed that raising the temperature led to an increased yield of reduction product **4a** (entries 2–4) and the conversion decreased with the decreasing of the amount of LiEt<sub>3</sub>BH (entry 5).

Hence, more aldol reactions were carried out under the optimized condition (Scheme 4). To our delight, the aldol products polyfluorinated  $\beta$ -hydroxy ketones were obtained in high yields by employing the fluorinated aldehydes such as 2,2-

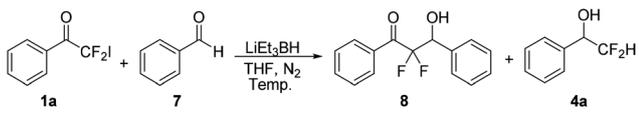
**Table 2** LiEt<sub>3</sub>BH-promoted self-condensation of 2,2-difluoro-2-iodo-1-phenylethanones<sup>a</sup>

Entry	R	Yield <sup>a</sup> (%)	
		2	4
1	Ph	<b>2a</b> , 86	<b>4a</b> , —
2	4-MeC <sub>6</sub> H <sub>4</sub>	<b>2b</b> , 83	<b>4b</b> , —
3	4-BrC <sub>6</sub> H <sub>4</sub>	<b>2c</b> , 85	<b>4c</b> , —
4	3-FC <sub>6</sub> H <sub>4</sub>	<b>2d</b> , 72	<b>4d</b> , 20
5	4-ClC <sub>6</sub> H <sub>4</sub>	<b>2e</b> , 87	<b>4e</b> , —
6	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>2f</b> , 71	<b>4f</b> , 14
7	Thienyl	<b>2g</b> , 70	<b>4g</b> , 15
8	Naphthyl	<b>2h</b> , 84	<b>4h</b> , —

<sup>a</sup> Isolated yields.



**Table 3** The optimization of aldol reaction of 2-iodo-2,2-difluoroacetophenone **1a** and benzaldehyde **7**<sup>a</sup>



Entry	LiEt <sub>3</sub> BH (equiv.)	Temp.	Conv.( <b>1a</b> ) <sup>b</sup> (%)	Yield <sup>b</sup> (%)	
				<b>8</b>	<b>4a</b>
1	1.2	-78 °C	100	95.2	4.8
2	1.2	-40 °C	100	85.2	14.8
3	1.2	0 °C	100	79.6	20.4
4	1.2	rt	100	74.7	25.3
5	1.0	-78 °C	91.6	90.1	9.9

<sup>a</sup> Reaction conditions: **1a** (1.0 mmol), **7** (1.0 mmol), THF (dry), N<sub>2</sub>, 4 h.

<sup>b</sup> Yield based on GC.

difluoro-1-phenylethanone or 2,2,2-trifluoro-1-phenylethanone (Scheme 4a and b). The substrate 1-(4-bromophenyl)-2,2-difluoro-2-iodoethan-1-one **1c** was also suitable for the aldol reaction (Scheme 4c). Furthermore, 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-phenylbutan-1-one **12** was also used to react with benzaldehyde in the present of LiEt<sub>3</sub>BH. The reaction gave the aldol product 2,2-difluoro-3-hydroxy-1,3-diphenylpropan-1-one **8** and self-condensation product 2,2,4,4-tetrafluoro-3-hydroxy-1,3-diphenylbutan-1-one **2a** with 4 : 1 ratio (Scheme 4d), which indicated that difluoroenolate can be generated from 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-phenylbutan-1-one with LiEt<sub>3</sub>BH either.

In summary, we have demonstrated an unprecedented utilization of LiEt<sub>3</sub>BH for the generation of  $\alpha,\alpha$ -difluoroenolates from 2-iodo-2,2-difluoroacetophenones in THF. Applications of the protocol led to the synthesis of polyfluorinated  $\beta$ -hydroxy ketones *via* self-condensation reaction and aldol reaction. The effectiveness of LiEt<sub>3</sub>BH was discussed by the variation of  $\alpha$ -halogen acetophenones and reducing agents in the reduction reaction. It turned out that LiEt<sub>3</sub>BH was served as a reducing agent with most  $\alpha$ -halogen acetophenones, resulting in the formation of different reduction products. The result disclosed

the specific property of 2-iodo-2,2-difluoroacetophenones, which might due to that the fluorine atoms of 2-iodo-2,2-difluoroacetophenones have significant impact and change the property of the adjacent C-I bond. Further study to apply the protocol for the preparation of diverse difluoromethylene compounds are in progress in our laboratory.

## Conflicts of interest

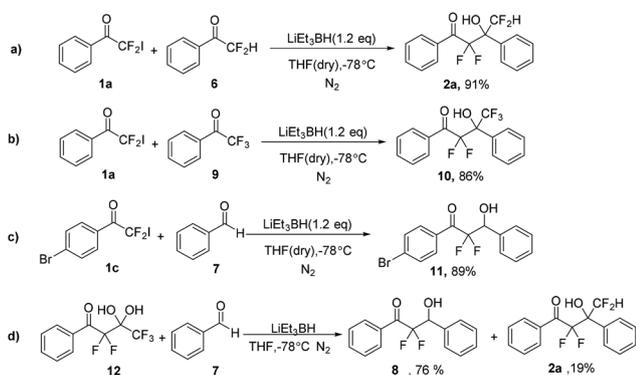
There are no conflicts to declare.

## Acknowledgements

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**Scheme 4** The aldol reactions promoted by LiEt<sub>3</sub>BH.



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