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Lithium triethylborohydride-promoted generation of α,α -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 α,α -difluoroenolates from 2-iodo-2,2-difluoroacetophenones, and applied to the synthesis of polyfluorinated β -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 α,α -difluoroenolates.

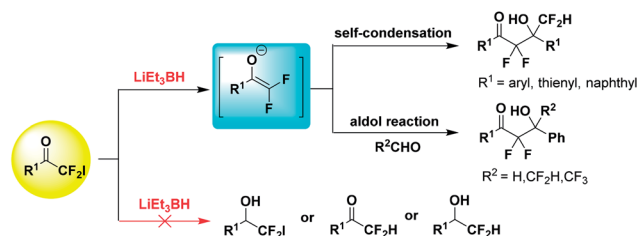
Difluoroenolates are useful fluorinated synthons for preparing difluoromethylene compounds,¹ with significant application in medicinal chemistry.² Accordingly, the protocols to generate difluoroenolates have attracted much attention. Colby firstly reported that compounds trifluoromethyl- α,α -difluoro-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

2-Iodo-2,2-difluoroacetophenones are one of the important building blocks to introduce α,α -difluoromethyl ketone fragment into molecules.¹¹ Our group has reported several reactions with 2-iodo-2,2-difluoroacetophenones to construct structurally diverse difluoromethylene compounds.^{11d-f} As part of our continued research, further structure modification of 2-iodo-2,2-difluoroacetophenones was investigated. Lithium triethylborohydride (LiEt₃BH, a superhydride, 1 M in THF) is a powerful reducing agent and can efficiently reduce a wide range of functional groups, especially halogen atoms.¹² However, the reaction with 2-iodo-2,2-difluoroacetophenones and LiEt₃BH result in the generation of difluoroenolates instead of reduction products. Herein, we disclosed the

LiEt₃BH-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 α,α -difluoro- β -hydroxy ketones (Scheme 1).

Initially, we chose LiEt₃BH 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 LiEt₃BH at -78 °C did not furnish any reduction product, instead leading to a self-adduct $\alpha,\alpha,\gamma,\gamma$ -tetrafluoro- β -hydroxy ketone **2a** with high yield (Table 1, entry 1). Raising the temperature of LiEt₃BH 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 LiEt₃BH, then the difluoroenolate **5** went through protonation process to form α,α -difluoroacetophenone **6**. The aldol reaction between **5** and **6** gave the $\alpha,\alpha,\gamma,\gamma$ -tetrafluoro- β -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 LiEt₃BH for the generation of α,α -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 LiEt₃BH^a

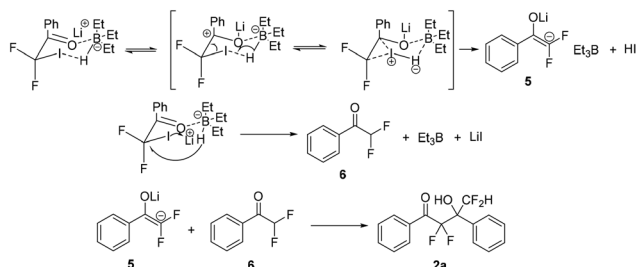
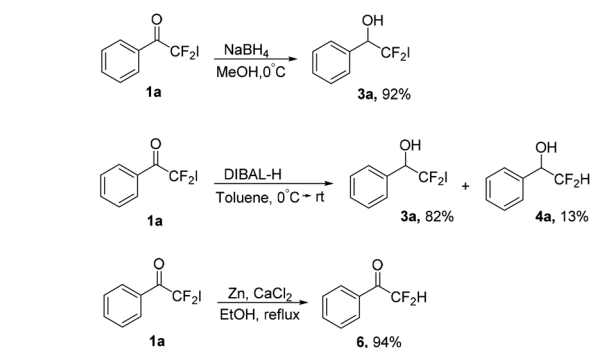
Entry	Temp.	Yield ^b (%)		
		2a	3a	4a
1	−78 °C	98.9	0.8	0.3
2	0 °C	43.9	6.9	49.2
3	rt	42.3	7.9	49.8

^a Reaction conditions: **1a** (1 mmol), LiEt₃BH (1.2 mmol, 1.2 equiv.), THF (dry), N₂, 4 h. ^b Yield based on GC.

difluoroacetophenone with LiEt₃BH 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[†]), 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 **3a** and 2,2-difluoro-1-phenylethanone **6** as major products separately.

Next, the scope of 2,2-difluoro-2-iodo-1-phenylethanone **1** was explored through the LiEt₃BH 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- β -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 LiEt₃BH-promoted aldol-type self-condensation.**Scheme 3** The reduction reactions of 2-iodo-2,2-difluoroacetophenone **1a**. ^aYield based on GC.

through the reaction with LiEt₃BH, which provided a novel and efficient access to difluoromethylation reactions.

α,α -Difluoro- β -hydroxy ketones are an important class of substructure in medicinal chemistry,¹³ which could be obtained *via* aldol reaction with difluoroenolates.¹⁴ Accordingly, to further demonstrate the utility of LiEt₃BH, aldol reaction of 2-iodo-2,2-difluoroacetophenones with aldehydes promoted by LiEt₃BH 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 LiEt₃BH (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 LiEt₃BH (entry 5).

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

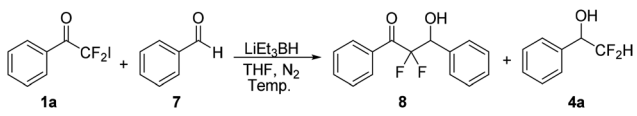
Table 2 LiEt₃BH-promoted self-condensation of 2,2-difluoro-2-iodo-1-phenylethanones^a

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

^a Isolated yields.



Table 3 The optimization of aldol reaction of 2-iodo-2,2-difluoroacetophenone **1a** and benzaldehyde **7**^a



Entry	LiEt ₃ BH (equiv.)	Temp.	Conv.(1a) ^b (%)	Yield ^b (%)	
				8	4a
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

^a Reaction conditions: **1a** (1.0 mmol), **7** (1.0 mmol), THF (dry), N₂, 4 h.
^b 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 LiEt₃BH. 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 LiEt₃BH either.

In summary, we have demonstrated an unprecedented utilization of LiEt₃BH for the generation of α,α -difluoroenolates from 2-iodo-2,2-difluoroacetophenones in THF. Applications of the protocol led to the synthesis of polyfluorinated β -hydroxy ketones *via* self-condensation reaction and aldol reaction. The effectiveness of LiEt₃BH was discussed by the variation of α -halogen acetophenones and reducing agents in the reduction reaction. It turned out that LiEt₃BH was served as a reducing agent with most α -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

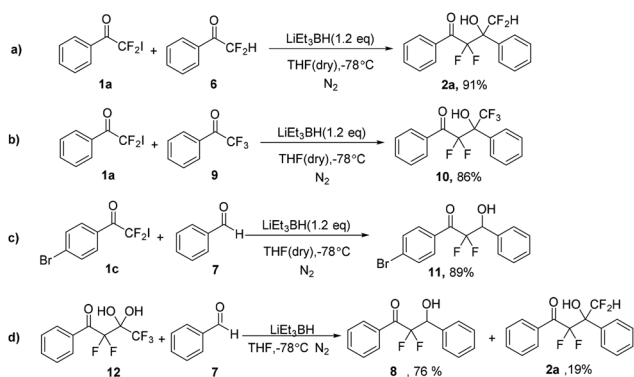
There are no conflicts to declare.

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References

- (a) D. Stolz and U. Kazmaier, in *Chemistry of Metal Enolates*, ed. J. Zabicky, Wiley, London, 2009, p. 355; (b) B. M. Stoltz, N. B. Bennett, D. C. Duquette, A. F. G. Goldberg, Y. Liu, M. B. Loewinger and C. M. Reeve, in *Comprehensive Organic Synthesis II*, ed. P. Knochel and G. A. Molander, Elsevier, Oxford, 2014, vol. 3, p. 1.
- (a) J. Wang, M. Sánchezroselló, J. L. Aceña, P. C. Del, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (b) J. O. Link, J. G. Taylor, L. Xu, M. Mitchell, H. Guo, H. Liu, D. Kato, T. Kirschberg, J. Sun, N. Squires, J. Parrish, T. Keller, Z.-Y. Yang, C. Yang, M. Matles, Y. Wang, K. Wang, G. Cheng, Y. Tian, E. Mogalian, E. Mondou, M. Cornpropst, J. Perry and M. C. Desai, *J. Med. Chem.*, 2014, **57**, 2033; (c) F. Xue, H. Li, S. L. Delker, J. Fang, P. Martíásek, L. J. Roman, T. L. Poulos and R. B. Silverman, *J. Am. Chem. Soc.*, 2010, **132**, 14229; (d) M. O. Anderson, J. Zhang, Y. Liu, C. Yao, P.-W. Phuan and A. S. Verkman, *J. Med. Chem.*, 2012, **55**, 5942.
- (a) C.-H. Han, E. H. Kim and D. A. Colby, *J. Am. Chem. Soc.*, 2011, **133**, 5802; (b) C.-H. Han, A. E. Salyer, E. H. Kim, X.-Y. Jiang, R. E. Jarrard, M. S. Powers, A. M. Kirchoff, T. K. Salvador, J. A. Chester, G. H. Hockerman and D. A. Colby, *J. Med. Chem.*, 2013, **56**, 2456; (c) R. A. Hazlitt, Q.-L. Tran, M. F. Sowaileh and D. A. Colby, *J. Org. Chem.*, 2017, **82**, 2231; (d) R. A. Hazlitt, J. P. John, Q.-L. Tran and D. A. Colby, *Tetrahedron Lett.*, 2016, **57**, 1906.
- S. Ge, W. Chaladaj and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 4149.
- Q. Chen, J. Zhou, Y. Wang, C. Wang, X. Liu, Z. Xu, L. Lin and R. Wang, *Org. Lett.*, 2015, **17**, 4212.
- M. Yang, D. L. Orsi and R. A. Altman, *Angew. Chem., Int. Ed.*, 2015, **54**, 2361.
- R. Doi, M. Ohashi and S. Ogoshi, *Angew. Chem., Int. Ed.*, 2016, **55**, 341.
- J.-L. Qian, W.-B. Yi, X. Huang, J. P. Jasinski and W. Zhang, *Adv. Synth. Catal.*, 2016, **358**, 2811.
- (a) Y.-L. Liu and J. Zhou, *Chem. Commun.*, 2012, **48**, 1919; (b) Y.-L. Liu, X.-P. Zeng and J. Zhou, *Chem.-Asian J.*, 2012, **7**, 1759; (c) J.-S. Yu, Y.-L. Liu, J. Tang, X. Wang and J. Zhou,



Scheme 4 The aldol reactions promoted by LiEt₃BH.



- Angew. Chem., Int. Ed.*, 2014, **53**, 9512; (d) S. Sasaki, T. Suzuki, T. Uchiya, S. Toyota, A. Hirano, M. Tanemura, H. Teramoto, T. Yamauchi and K. Higashiyama, *J. Fluorine Chem.*, 2016, **192**, 78.
- 10 (a) R. Doi, M. Ohashi and S. Ogoshi, *Angew. Chem., Int. Ed.*, 2016, **55**, 341; (b) R. Doi, K. Kikushima, M. Ohashi and S. Ogoshi, *J. Am. Chem. Soc.*, 2015, **137**, 3276; (c) P. V. Ramachandran and A. Chatterjee, *Org. Lett.*, 2008, **10**, 1195.
- 11 (a) Z.-M. Qiu and D. J. Burton, *Tetrahedron Lett.*, 1993, **34**, 3239; (b) K. C. Kwak, H. Oh, Y. G. Yun, B. H. Kim, Y. H. Lee and K. Y. Chai, *Bull. Korean Chem. Soc.*, 2002, **23**, 157; (c) Z.-M. Qiu and D. J. Burton, *J. Org. Chem.*, 1995, **60**, 6798; (d) J.-X. Wang, J.-J. Wu, H. Chen, S.-W. Zhang and F.-H. Wu, *Chin. Chem. Lett.*, 2015, **26**, 1381; (e) D.-F. Wang, J.-J. Wu, J.-W. Huang, J.-Q. Liang, P. Peng, H. Chen and F.-H. Wu, *Tetrahedron*, 2017, **73**, 3478; (f) H. Chen, J.-X. Wang, J.-J. Wu, Y.-J. Kuang and F.-H. Wu, *J. Fluorine Chem.*, 2017, **200**, 41.
- 12 (a) S. Krishnamurthy, R. M. Schubert and H. C. Brown, *J. Am. Chem. Soc.*, 1973, **75**, 8486; (b) S. Krishnamurthy and H. C. Brown, *J. Am. Chem. Soc.*, 1973, **95**, 1669; (c) F.-P. Liang, H. W. Schmalle and H. Berke, *Eur. J. Inorg. Chem.*, 2006, 5081; (d) J.-J. Wu and S. Cao, *ChemCatChem*, 2011, **3**, 1582; (e) S. Chowdhury and R. F. Standaert, *J. Org. Chem.*, 2016, **81**, 9957; (f) L. Silva, R. F. Affeldt and D. S. Lüdtkke, *J. Org. Chem.*, 2016, **81**, 5464; (g) B. Denolf, E. Leemans and N. De Kimpe, *J. Org. Chem.*, 2007, **72**, 3211; (h) H. Tanaka and K. Ogasawara, *Tetrahedron Lett.*, 2002, **43**, 4417.
- 13 (a) C.-H. Han, A. E. Salyer, E. H. Kim, X.-Y. Jiang, R. E. Jarrard, M. S. Powers, A. M. Kirchoff, T. K. Salvador, J. A. Chester, G. H. Hockerman and D. A. Colby, *J. Med. Chem.*, 2013, **56**, 2456; (b) M.-H. Yang, J. R. Hunt, N. Sharifi and R. A. Altman, *Angew. Chem., Int. Ed.*, 2016, **55**, 9080; (c) A. M. Doherty, I. Sircar, B. E. Kornberg, J. Quinlll, R. Thomas Winters, J. S. Kaltenbronn, M. D. Taylor, B. L. Batley and S. R. Rapundalo, *J. Med. Chem.*, 1992, **35**, 2.
- 14 (a) P. Zhang and C. Wolf, *J. Org. Chem.*, 2012, **77**, 8840; (b) P. Zhang and C. Wolf, *Angew. Chem., Int. Ed.*, 2013, **52**, 7869; (c) C. Xie, L.-M. Wu, H.-B. Mei, V. A. Soloshonok, J.-L. Han and Y. Pan, *Tetrahedron Lett.*, 2014, **55**, 5908; (d) H.-B. Mei, C. Xie, J. L. Aceña, V. A. Soloshonok, G.-L. Röscenthaler and J.-L. Han, *Eur. J. Org. Chem.*, 2015, 6401.

