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An expedient synthesis of α,α-difluoro-β-hydroxy ketones *via* decarboxylative aldol reaction of α,α-difluoro-β-keto acids with aldehydes

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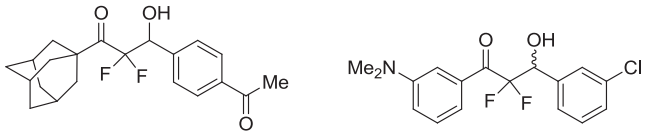
ABSTRACT

A novel decarboxylative aldol reaction of α,α-difluoro-β-keto acids with aldehydes in the absence of any base and metal catalysts has been developed. This reaction provides a highly convenient and efficient method for the synthesis of structurally diverse α,α-difluoro-β-hydroxy ketones in good to excellent yields.

Introduction

During the past decades, fluorine-containing compounds have attracted an increasing interest in the fields of agrochemistry, pharmaceutical industry, and materials science.[1] In part, this is due to the introduction of a fluoroalkyl group into organic compounds that may result in profound changes to physical, chemical, and biological properties. Among various fluorine-containing compounds, α,α-difluoro-β-hydroxy ketones have been the focus of the scientific community since this compound class represents a critical and widely found substructure unit in bioactive compounds and pharmaceuticals (Fig. 1).[2] Based on the high significance in drug industry, a variety of synthetic methods have been developed for this compound species, including the Mukaiyama-Aldol reaction of difluoroenoxysilanes or difluoroenol O-Boc esters (Scheme 1, eq. a),[3] the metal-mediated Reformatsky reaction of halodifluoromethyl ketones (Scheme 1, eq. b),[4] the detrifluoroacetylative aldol reaction of trifluoromethyl α,α-difluoro-β-keto *gem*-diols (Scheme 1, eq. c),[5] etc.[6] However, most of these reactions exhibit various practical drawbacks, including the use of preformed difluoroenoxysilanes or difluoroenol O-Boc esters which renders the reaction process more tedious and often results in the production of metal waste. Furthermore, these reactions generally lack of atomic economy. Therefore, the development of new, simple and efficient methods for the rapid synthesis of α,α-difluoro-β-hydroxy ketones still remains a critical, albeit unmet, scientific goal.



GABA$_B$ agonist — potential analgesic agent

Fig. 1. α,α-Difluoro-β-hydroxy ketone motifs in bioactive molecules.

In recent years, the decarboxylative aldol reaction has emerged as a powerful tool for the generation of carbon-carbon bonds due to its mild reaction conditions.[7] Although great progress has been made for the development of advanced decarboxylative aldol reactions of malonic acid half thioesters (MAHT) and malonic acid half oxyesters (MAHO),[8] the decarboxylative aldol reaction of β-ketoacids remains far less explored.[9] To the best of our knowledge, no report on the decarboxylative aldol reaction of fluorinated β-ketoacids can be found in the literature to date.[10] In an effort to continue our studies in the field of fluorinated ketones and imines,[11] herein, we report the first decarboxylative aldol reaction of α,α-difluoro-β-keto acids with aldehydes. This reaction provides a convenient, yet

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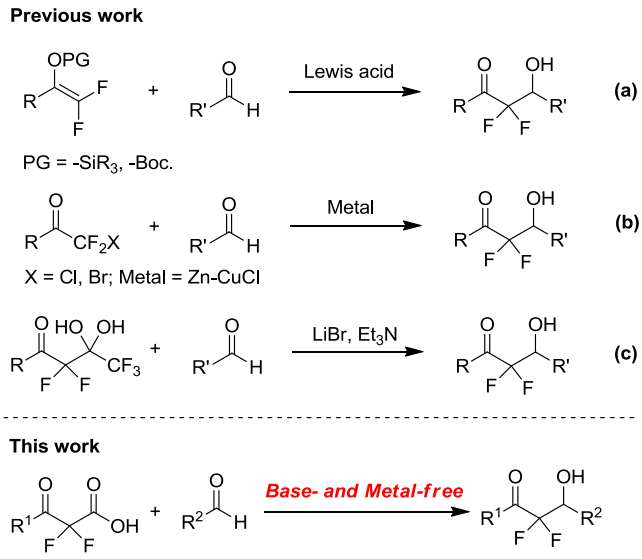


Scheme 1. Methods for the synthesis of α,α-difluoro-β-hydroxy ketones.

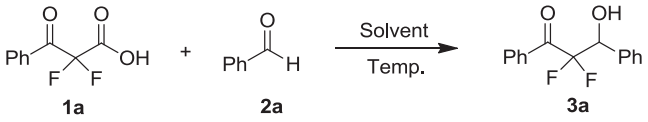
efficient base- and metal-free process for the synthesis of α,α-difluoro-β-hydroxy ketones in high yields.

Results and discussion

The precursor α,α-difluoro-β-keto acid **1a** was selected as a model substrate to investigate the feasibility of this decarboxylative aldol reaction with benzaldehyde **2a**. The results are summarized in Table 1. In order to improve the efficacy of the decarboxylation and to inhibit the formation of the decarboxylative protonation side product, α,α-difluoroacetophenone,[5b–e] inorganic bases such as Na_2CO_3 and Cs_2CO_3 were used initially. However, lower yields (9–13%) of the desired product **3a** were obtained (Table 1, entries 1–2). The decarboxylative aldol reaction proceeded smoothly, without the need for any further addition of base or metal catalyst (Table 1, entries 3–15). Among the solvents tested, toluene demonstrated to be the best solvent for this reaction, resulting in the formation of the corresponding aldol adduct **3a** in moderate to high yield (Table 1, entries 3–19). Further screening of the reaction conditions revealed that the reaction could be completed in 12 h at 100 °C, providing the aldol product in 95% yield (Table 1, entry 10). Decreasing the amount of α,α-difluoro-β-keto acid **1a** or performing the reaction in an open flask resulted in a significant yield reduction (Table 1, entries 14–15). Thus, the optimized reaction conditions for this novel decarboxylative aldol reaction were as follows: α,α-difluoro-β-keto acid **1a** (3.0 equiv.) and benzaldehyde **2a** (1.0 equiv.) in toluene at 100 °C for 12 h.

With the optimized reaction conditions in hand, the substrate scope and generality of this decarboxylative aldol reaction was investigated through variations of both α,α-difluoro-β-keto acids and aldehydes. As is shown in Table 2, all reactions proceeded readily and furnished the corresponding α,α-difluoro-β-hydroxy ketones in good to high yields. Aromatic aldehydes were demonstrated to be excellent substrates for the reaction (Table 2, entries 1–8). The electronic properties and positions of the substituents on the phenyl ring of the aromatic aldehydes exhibited a negligible effect on the yields of the reaction (Table 2, entries 2–7). However, worth noting in this context is the finding that in the case of

Table 1
The decarboxylative aldol reaction of α,α-difluoro-β-keto acid **1a** with benzaldehyde under different conditions.[a]

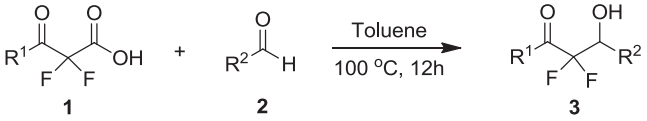


1a **2a** **3a**

Entry	Base (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	Na_2CO_3 (1)	THF	70	24	13
2	Cs_2CO_3 (1)	Toluene	80	24	9
3	–	THF	70	24	21
4	–	Toluene	70	24	59
5	–	Toluene	80	24	89
6		Toluene	90	24	94
7	–	Toluene	100	24	95
8	–	Toluene	110	24	89
9	–	Toluene	100	16	95
10	–	Toluene	100	12	95
11	–	Toluene	100	10	94
12	–	Toluene	100	8	91
13	–	Toluene	100	6	86
14[c]	–	Toluene	100	12	65
15[d]	–	Toluene	100	12	64
16	–	NMP	100	12	NR[e]
17	–	DMF	100	12	NR[e]
18	–	DMSO	100	12	NR[e]
19	–	Dioxane	100	12	NR[e]

[a] Reaction conditions: α,α-difluoro-β-keto acid **1a** (0.6 mmol), benzaldehyde **2a** (0.2 mmol), solvent (1.5 mL).
[b] Yields of products isolated after column chromatography.
[c] 0.4 mmol of α,α-difluoro-β-ketoacid **1a** was used.
[d] The reaction was performed in an open flask.
[e] NR = No reaction.

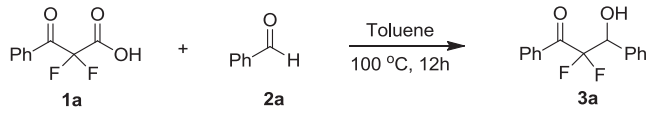
Table 2
Scope of the decarboxylative aldol reaction of α,α-difluoro-β-keto acids **1** with aldehydes **2**.[a]



1 2 3

Entry	R^1	R^2	Product	Yield (%)[b]
1	Ph (**1a**)	Ph (**2a**)	**3a**	95
2	Ph (**1a**)	4-MeC_6H_4 (**2b**)	**3b**	99
3	Ph (**1a**)	4-$MeOC_6H_4$ (**2c**)	**3c**	88
4	Ph (**1a**)	4-ClC_6H_4 (**2d**)	**3d**	>99
5	Ph (**1a**)	4-$NO_2C_6H_4$ (**2e**)	**3e**	83
6	Ph (**1a**)	3-MeC_6H_4 (**2f**)	**3f**	>99
7	Ph (**1a**)	2-MeC_6H_4 (**2g**)	**3g**	77
8	Ph (**1a**)	2-naphthyl (**2h**)	**3h**	90
9	Ph (**1a**)	PhCH=CH (**2i**)	**3i**	92
10	Ph (**1a**)	$Ph(CH_2)_2$ (**2j**)	**3j**	55[c]
11	4-MeC_6H_4 (**1b**)	Ph (**2a**)	**3k**	88
12	4-$MeOC_6H_4$ (**1c**)	Ph (**2a**)	**3l**	>99
13	4-ClC_6H_4 (**1d**)	Ph (**2a**)	**3m**	>99
14	2-Furyl (**1e**)	Ph (**2a**)	**3n**	89

[a] Reaction conditions: α,α-difluoro-β-keto acids **1** (0.9 mmol) and aldehydes **2** (0.3 mmol) in toluene (1.5 mL) at 100 °C for 12 h under N_2.
[b] Yields of products isolated after column chromatography.
[c] The reaction was run at 110 °C for 16 h.

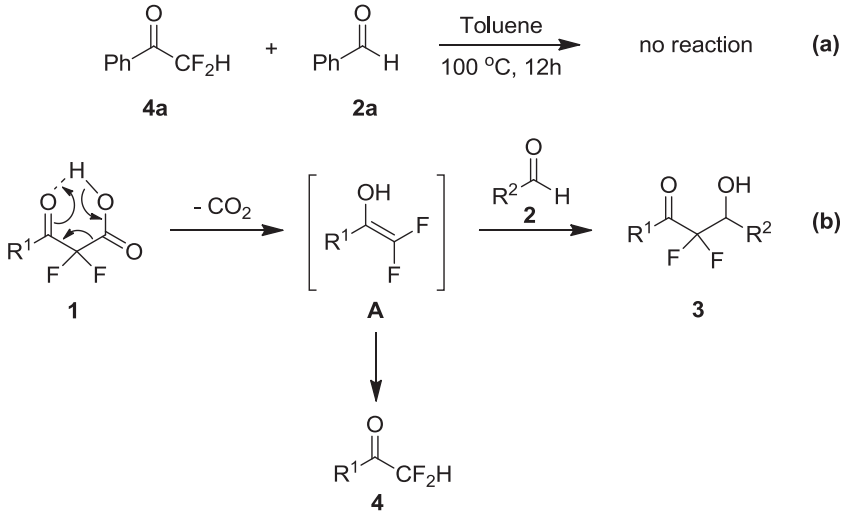


1a **2a** **3a**
1.0g, 5.0mmol **0.21g, 2.0mmol** **0.51g, 97.6%**

Scheme 2. Scaled-up version of the decarboxylative aldol reaction.

cinnamaldehyde **2i** employed as the electrophilic partner, the reaction proceeded regiospecifically in a 1,2-addition fashion, providing the 1,2-adduct in high yield (92%, Table 2, entry 9). Moreover, enolizable aliphatic aldehyde **2j** was also found to be tolerated, affording the corresponding aldol product in moderate yield (Table 2, entry 10). Heteroaromatic aldehydes such as 2-furylaldehyde and 2-pyridylaldehyde were also evaluated for this reaction, but only traces of the desired aldol products were found. In addition, different aryl- and heteroaryl-substituted α,α-difluoro-β-keto acid species **1b–e** could also be used in this reaction and high yields were obtained (Table 2, entries 11–14). However, alkyl-substituted α,α-difluoro-β-keto acid was found to be unsuitable for this transformation and no product formation could be observed. Furthermore, the model reaction could be scaled up to gram quantities, and excellent yields could be obtained (Scheme 2), indicating the potential industrial applicability of this reaction.

To gain further insights into the reaction pathway, a control experiment was carried out using α,α-difluoroacetophenone **4a** instead of α,α-difluoro-β-keto acid **1a** under the optimized reaction conditions described above (Scheme 3, eq. a). However, via ^{19}F NMR monitoring of the crude reaction mixture, we determined that no desired product **3a** was formed. On the basis of our research results and other published literature procedures,[5b–e,9a–c,f] a preliminary reaction mechanism for this decarboxylative aldol reaction could be proposed as shown in Scheme 3, eq. b. Upon heating above 70 °C, the α,α-difluoro-β-keto acids **1** first decarboxylate to form the difluoro enol intermediate



4a **2a** **1** **A** **2** **3** **4**

Scheme 3. Plausible reaction mechanism.

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A along with one equivalent of gaseous carbon dioxide. The difluoro enol intermediate **A** may then react with the aldehydes **2** to afford the corresponding α,α-difluoro-β-hydroxy ketones **3**. From the optimized reaction results, we assume that the addition rate of intermediate **A** to aldehydes **2** was significantly faster than the isomerization of the intermediate **A** to form the decarboxylative protonation product **4**. However, all attempts to capture and detect the difluoro enol intermediate **A** using TMSCl or TBDMSCl proved to be unsuccessful. Therefore, sufficient experimental evidence to draw a fully conclusive reaction mechanism still remains to be obtained.

Conclusions

In summary, we have successfully developed the first decarboxylative aldol reaction of α,α-difluoro-β-keto acids with aldehydes in the absence of any base or metal catalysts. The reaction is very mild and a variety of structurally diverse α,α-difluoro-β-hydroxy ketones could be obtained in good to excellent yields. These α,α-difluoro-β-hydroxy ketones represent useful structural motifs for the synthesis of a variety of natural products and bioactive compounds. Further studies are currently underway in our laboratory to evaluate mechanistic details and to develop an asymmetric type of the title reaction.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.07.060.

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