


# Cleavage of Carbon–Carbon Bonds through the Mild Release of Trifluoroacetate: Generation of $\alpha,\alpha$ -Difluoroenolates for Aldol Reactions

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 Supporting Information

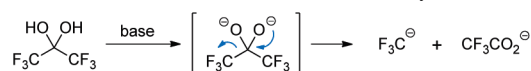
**ABSTRACT:** The selective cleavage of carbon–carbon bonds is a significant challenge in synthetic chemistry, yet this strategy can be a powerful way to generate reactive intermediates. We have discovered that, through the facile release of trifluoroacetate which occurs by C–C bond scission, difluoroenolates can be generated under very mild reaction conditions. Unlike existing reactions, this method is not limited to a small group of fluorinated building blocks. We have applied this process to the aldol reaction to install difluoromethylene groups.

The rapid and efficient synthesis of complex structures has been a clear goal of synthetic organic and medicinal chemistry, and accordingly, many processes to form new chemical bonds have been developed. However, the inverse process of selectively cleaving bonds poses a significant synthetic challenge. In the case of cleaving a C–C bond, very few procedures are available.<sup>1–4</sup> One of the most useful of these methods is decarboxylation, because it is a powerful, yet mild process for generating a reactive intermediates.<sup>4–8</sup> Recent reports by Shibasaki,<sup>5</sup> Trost,<sup>6</sup> Stoltz,<sup>7</sup> Tunge,<sup>8</sup> and others<sup>9</sup> have demonstrated the power of decarboxylation. Despite the tremendous synthetic utility of these bond-cleaving processes, they are powerful, underdeveloped methods for generating reactive precursors by releasing labile groups under mild reaction conditions.

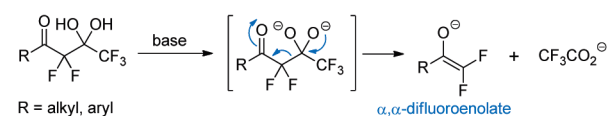
Trifluoroacetate is a ubiquitous counterion in many reactions, and we hypothesized that a release of trifluoroacetate would be analogous to decarboxylation; however, a gem-diol of a trifluoromethyl ketone would be the requisite precursor. Indeed, a mild and rapid C–C bond fragmentation of hexafluoroacetone hydrate has been observed after the addition of 2 equiv of base; trifluoroacetate is released from this hydrate fragmentation process (Scheme 1).<sup>10</sup> We are unaware of any synthetic methods that exploit this potentially powerful fragmentation.<sup>11</sup> Thus, we envisioned that this trifluoroacetate-release strategy could be readily adapted to generate  $\alpha,\alpha$ -difluoroenolates by replacing one fluorine atom on hexafluoroacetone hydrate with a carbonyl group to stabilize the anion as an enolate (Scheme 1). The generation of  $\alpha,\alpha$ -difluoroenolates has attracted significant attention,<sup>12</sup> because it is a reliable method to install difluoromethylene groups.<sup>13</sup> The usual synthetic protocols to prepare  $\alpha,\alpha$ -difluoroenolates rely on the few available fluorinated building

## Scheme 1

Release of Trifluoroacetate from Hexafluoroacetone Hydrate<sup>10</sup>



Release of Trifluoroacetate to Generate  $\alpha,\alpha$ -Difluoroenolates (*this work*)



blocks (e.g., ethyl bromodifluoroacetate) and/or harsh reaction conditions, which further limit the scope of the substrates for the process.<sup>12</sup> Herein, we describe the application of the trifluoroacetate-release strategy to cleave a C–C bond and generate an  $\alpha,\alpha$ -difluoroenolate. This method uses exceedingly mild reaction conditions, is not limited to a small group of fluorinated building blocks, and is compatible with many substrates.

To implement this strategy, our initial studies were designed to find a versatile route to gem-diols with  $\alpha$ -fluorination to test the trifluoroacetate-release strategy. We found that the requisite substrates can be easily prepared under neutral conditions using Selectfluor and 1,1,1-trifluoro-2,4-diones **1–9** (Table 1).<sup>14</sup> Some 1,1,1-trifluoro-2,4-diones are commercially available, and others are readily accessed by trifluoroacetylation of methyl ketones.<sup>15</sup> The 1,1,1-trifluoro-2,4-diones **1–9** exist exclusively in the enol form;<sup>16</sup> therefore this transformation is markedly efficient and is devoid of byproduct from partial fluorination.<sup>17</sup> Additionally, silica chromatography was not necessary for the purification of products **10–12**, **14**, and **15**. The crystalline compound **14** provided further structural data following X-ray analysis, and the data supported the assignment of a gem-diol rather than a ketone with a molecule of water.<sup>18</sup>

With substrates **10–18** in hand, trifluoroacetate release was found to be promoted rapidly using LiBr and Et<sub>3</sub>N. Specifically, treatment of substrate **10** with LiBr/Et<sub>3</sub>N at room temperature produced almost instantaneously the difluorinated compound **19** as well as the self-adduct **20** (eq 1). This example provided evidence that trifluoroacetate release occurs rapidly and that the difluoroenolate can react with electrophiles. Also, this selective

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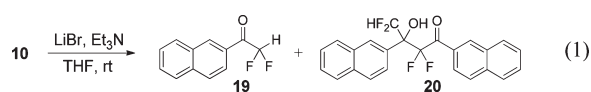
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Table 1. Syntheses of Highly  $\alpha$ -Fluorinated gem-Diols<sup>a</sup>

$\text{R}-\text{C}(\text{OH})=\text{CH}-\text{CF}_3 \xrightarrow[\text{CH}_3\text{CN, rt, 24 h}]{\text{Selectfluor}^\text{®}} \text{R}-\text{C}(\text{OH})_2-\text{CF}_3$			
entry	substrate	product	yield <sup>b</sup>
1			99%
2			97%
3			88%
4			99%
5			93%
6			91%
7			88% <sup>c</sup>
8			61% <sup>c</sup>
9			82% <sup>c</sup>

<sup>a</sup> Unless otherwise noted, reactions were performed with 2.5 equiv of Selectfluor. <sup>b</sup> Isolated yields. <sup>c</sup> Two-step yield from the parent methyl ketone.

C–C bond cleavage to release trifluoroacetate is a striking contrast to previous data.<sup>19</sup>



Next, we explored aldol reactions with substrates **10–18** and aldehydes **21–31** using the trifluoroacetate-release strategy (Table 2). The significance of developing new mild enolization protocols for aldol reactions has been recently demonstrated by Coltart and co-workers.<sup>20</sup> For trifluoroacetate release, the scope was equally impressive for the highly fluorinated substrates **10–18**, because each readily participated in the process. Also, trifluoroacetate release is extremely fast, and the reactions were typically completed after 3 min at room temperature or 30 min at  $-78^\circ\text{C}$ . Good to excellent yields (64–95%) of the aldol adduct(s) were routinely isolated. Both aryl and alkyl aldehydes, as well as the  $\alpha,\beta$ -unsaturated aldehyde **22** and the sensitive dienal **23**, were fully compatible with this process. Other sensitive aldehydes also smoothly reacted with the  $\alpha,\alpha$ -difluoroenolates;  $\beta$ -elimination was not observed with **25**, and little  $\alpha$ -epimerization (i.e., 5%) was observed with **31** after  $^{19}\text{F}$  NMR analysis of the crude reaction mixture. Also, the reaction with **31** displayed the unique tendency of product **47** to form a hemiacetal with an

Table 2. Aldol Reactions with  $\alpha,\alpha$ -Difluoroenolates from Trifluoroacetate Release<sup>a</sup>

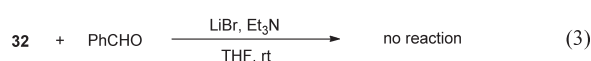
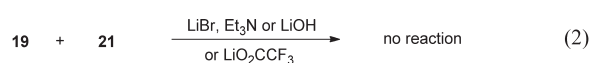
$\text{R}-\text{C}(\text{OH})_2-\text{CF}_3 + \text{H}-\text{C}(=\text{O})-\text{R}' \xrightarrow[\text{THF}]{\text{LiBr, Et}_3\text{N}} \text{R}-\text{C}(\text{OH})(\text{CF}_3)-\text{CH}(\text{OH})-\text{R}'$				
entry	substrate	aldehyde	major product	yield <sup>b</sup>
1	<b>10</b>			84%
2	<b>10</b>			85%
3	<b>10</b>			89%
4	<b>10</b>			74%
5	<b>11</b>	<b>22</b>		79%
6	<b>12</b>			74% (1.2:1)
7	<b>12</b>			95% (1.5:1)
8	<b>13</b>	<b>23</b>		78%
9	<b>14</b>	<b>23</b>		89%
10	<b>15</b>	<b>22</b>		64%
11	<b>15</b>			72%
12	<b>16</b>			89%
13	<b>16</b>			84%
14	<b>17</b>			89% (6.8:5.6:1.1:1) <sup>g</sup>
15	<b>18</b>	<b>30</b>		78% (1.1:1)
16	<b>18</b>			69% <sup>f</sup> (9:1:0.5) <sup>g</sup>

<sup>a</sup> Reactions were typically performed with 3 equiv of LiBr and 1 equiv of Et<sub>3</sub>N; see Supporting Information for details. <sup>b</sup> Isolated yields and diastereomeric ratios (dr) based on  $^{19}\text{F}$  NMR analysis of unpurified reaction products. <sup>c</sup> Absolute stereochemistry determined after desilylation and cyclization. <sup>d</sup> Absolute stereochemistry determined after MPA analysis. <sup>e</sup> Ratio of diastereomers is **45:45:46:46**. <sup>f</sup> Yield determined after acid-promoted hydrolysis of hemiacetal; see Supporting Information for details. <sup>g</sup> Diastereomeric ratio is (*R,R*)-isomer/(*S,R*)-isomer/(*S,S*)-isomer.

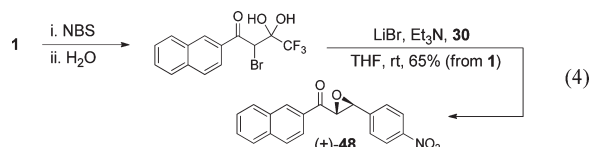
additional aldehyde (this side product was readily hydrolyzed with aqueous acid).<sup>18</sup> In the case of the highly sensitive

*cis*-myrtenol-derived substrate **17** (the *trans*-myrtenol derivative **18** is not susceptible to  $\alpha$ -epimerization but provided adduct **46** to contrast with **45**),<sup>21</sup> 15% of the product mixture was the *trans*-isomer. Even though  $\alpha$ -deprotonation was observed with ketone **17**, the two fluorines adjacent to the ketone significantly enhance the irreversible tendency for the *cis*-myrtenol to convert to the *trans*-myrtenol. Therefore, our conditions were compatible with this highly sensitive substrate. This strategy is quite chemoselective for aldehydes, because the keto-aldehyde **28** provided only the product **43** from aldehyde addition. Also, all of the products **32**–**47** have a ketone that is additionally activated by two  $\alpha$ -fluorines, yet these aldol-adducts do not out-compete the aldehydes. Further evidence of the mild reaction conditions is available from the triene **39** that was isolated in good yield (78%) from the unsaturated starting material **13**. Assignment of the absolute stereochemical configuration of **47** using the traditional Mosher method (i.e., with MTPA esters) was not clear. Existing literature precedents suggest such an analysis on some fluorinated substrates is not straightforward.<sup>22</sup> However, using the recent comparisons of Hoyer and co-workers,<sup>23</sup> preparation of the MPA-derivatives of **47** allowed assignment of the absolute configuration.<sup>18</sup>

To probe the mechanism of the trifluoroacetate-release strategy, we performed a series of control reactions to verify that the aldol reaction is not a stepwise process in which trifluoroacetate release occurs, followed by deprotonation of the  $\alpha,\alpha$ -difluoroketone, and addition to the aldehyde. Indeed, the  $\alpha,\alpha$ -difluoroketone **19** did not react with aldehyde **21** using the trifluoroacetate-release conditions (LiBr/Et<sub>3</sub>N) or other combinations of reagents (eq 2). Also, we tested if a retro-aldol process occurs under the reaction conditions and the aldol adduct **32** was recovered without the presence of any products from a retro-aldol reaction with benzaldehyde (eq 3). These mechanistic data further highlight the powerful, yet mild process of trifluoroacetate release to generate reactive intermediates.



As a demonstration of the potential broad compatibility of this trifluoroacetate-release process to other substrates, we monobrominated<sup>24</sup> the trifluoroacetylated ketone **1**, stirred over water, and then immediately treated the crude reaction mixture with LiBr and Et<sub>3</sub>N in the presence of aldehyde **30** (eq 4). The reaction was completed in 10 min at room temperature, and the Darzens product **48** was isolated in good 65% yield (from **1**) as a single diastereomer.<sup>25</sup> The implication of this finding is that this process is not limited to the generation of  $\alpha,\alpha$ -difluoroenolates and the production of  $\alpha,\alpha$ -difluoroketones but presents additional synthetic opportunities.



In summary, we have discovered a novel trifluoroacetate-release strategy to generate reactive intermediates using mild conditions to cleave a C–C bond and concurrently provided a

solution to the existing synthetic limitations of preparing  $\alpha,\alpha$ -difluoroenolates. We demonstrated the broad scope of substrates and aldehydes that participate in this mild process and provided key mechanistic details. Studies to apply our trifluoroacetate-release strategy to generate reactive intermediates for other processes are currently underway as well as additional mechanistic studies.

## ■ ASSOCIATED CONTENT

**S Supporting Information.** Full experimental details, spectroscopic data, and X-ray data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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