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Cleavage of Carbon−Carbon Bonds through the Mild Release of Trifluoroacetate: Generation of α,α-Difluoroenolates for Aldol Reactions

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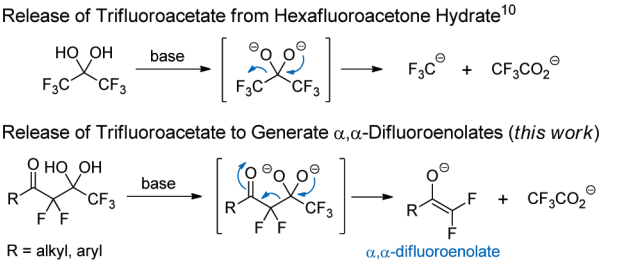
Supporting Information

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.[1−4] One of the most useful of these methods is decarboxylation, because it is a powerful, yet mild process for generating a reactive intermediates.[4−8] Recent reports by Shibasaki,[5] Trost,[6] Stoltz,[7] Tunge,[8] and others[9] 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).[10] We are unaware of any synthetic methods that exploit this potentially powerful fragmentation.[11] Thus, we envisioned that this trifluoroacetate-release strategy could be readily adapted to generate α,α-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 α,α-difluoroenolates has attracted significant attention,[12] because it is a reliable method to install difluoromethylene groups.[13] The usual synthetic protocols to prepare α,α-difluoroenolates rely on the few available fluorinated building blocks (e.g., ethyl bromodifluoroacetate) and/or harsh reaction conditions, which further limit the scope of the substrates for the process.[12] Herein, we describe the application of the trifluoroacetate-release strategy to cleave a C−C bond and generate an α,α-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.

Scheme 1



To implement this strategy, our initial studies were designed to find a versatile route to gem-diols with α-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).[14] Some 1,1,1-trifluoro-2,4-diones are commercially available, and others are readily accessed by trifluoroacetylation of methyl ketones.[15] The 1,1,1-trifluoro-2,4-diones **1**−**9** exist exclusively in the enol form;[16] therefore this transformation is markedly efficient and is devoid of byproduct from partial fluorination.[17] 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.[18]

With substrates **10**−**18** in hand, trifluoroacetate release was found to be promoted rapidly using LiBr and Et_3N. Specifically, treatment of substrate **10** with LiBr/Et_3N 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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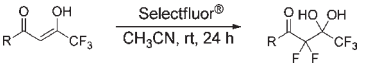
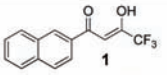
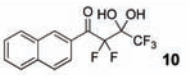
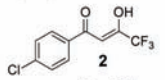
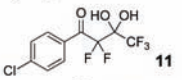
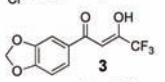
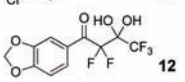
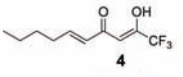
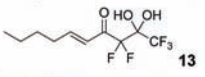
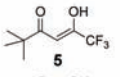
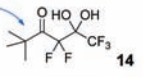
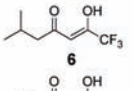
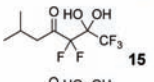
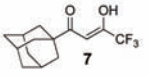
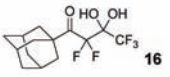
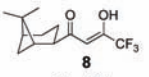
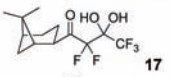
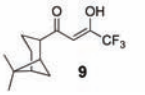
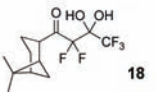
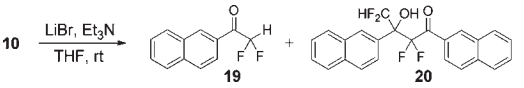
Table 1. Syntheses of Highly α-Fluorinated gem-Diols[a]



entry	substrate	product	yield[b]
1	 1	 10	99%
2	 2	 11	97%
3	 3	 12	88%
4	 4	 13	99%
5	 5	X-ray  14	93%
6	 6	 15	91%
7	 7	 16	88%[c]
8	 8	 17	61%[c]
9	 9	 18	82%[c]

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

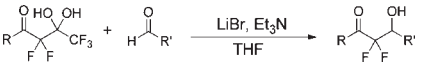
C−C bond cleavage to release trifluoroacetate is a striking contrast to previous data.[19]

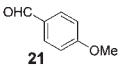
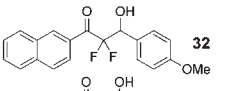
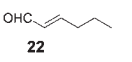
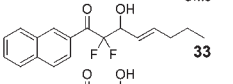
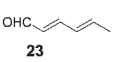
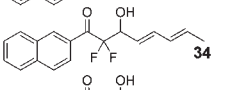
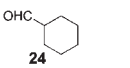
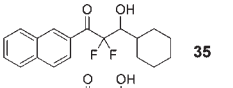
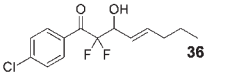
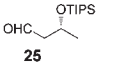
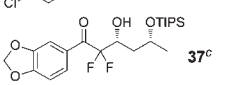
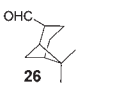
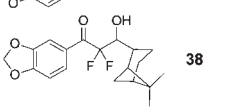
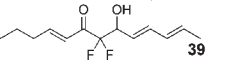
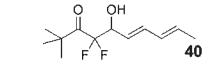
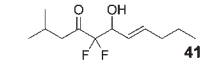
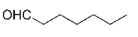
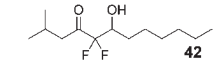
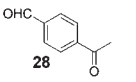


(1)

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.[20] 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* °C. Good to excellent yields (64−95%) of the aldol adduct(s) were routinely isolated. Both aryl and alkyl aldehydes, as well as the α,β-unsaturated aldehyde **22** and the sensitive dienal **23**, were fully compatible with this process. Other sensitive aldehydes also smoothly reacted with the α,α-difluoroenolates; β-elimination was not observed with **25**, and little α-epimerization (i.e., 5%) was observed with **31** after ^{19}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 additional aldehyde (this side product was readily hydrolyzed with aqueous acid).[18] In the case of the highly sensitive

Table 2. Aldol Reactions with α,α-Difluoroenolates from Trifluoroacetate Release[a]



entry	substrate	aldehyde	major product	yield[b]
1	10	 21	 32	84%
2	10	 22	 33	85%
3	10	 23	 34	89%
4	10	 24	 35	74%
5	11	22	 36	79%
6	12	 25	 37[c]	74% (1.2:1)
7	12	 26	 38	95% (1.5:1)
8	13	23	 39	78%
9	14	23	 40	89%
10	15	22	 41	64%
11	15	 27	 42	72%
12	16	 28	43	89%
13	16	29	44	84%
14	17	30	45	89% (6.8:5.6: 1.1:1)[e]
15	18	30	46	78% (1.1:1)
16	18	31	47[d]	69%[f] (9:1: 0.5)[g]

[a] Reactions were typically performed with 3 equiv of LiBr and 1 equiv of Et_3N; see Supporting Information for details. [b] Isolated yields and diastereomeric ratios (dr) based on ^{19}F NMR analysis of unpurified reaction products. [c] Absolute stereochemistry determined after desilylation and cyclization. [d] Absolute stereochemistry determined after MPA analysis. [e] Ratio of diastereomers is **45**:**45**:**46**:**46**. [f] Yield determined after acid-promoted hydrolysis of hemiacetal; see Supporting Information for details. [g] Diastereomeric ratio is (*R*,*R*)-isomer/(*S*,*R*)-isomer/(*S*,*S*)-isomer.

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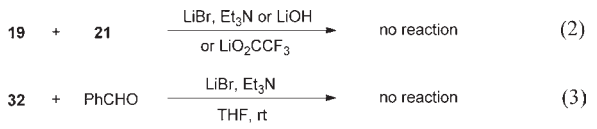
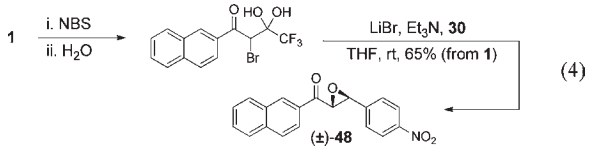
cis-myrtenol-derived substrate **17** (the *trans*-myrtenol derivative **18** is not susceptible to α-epimerization but provided adduct **46** to contrast with **45**),[21] 15% of the product mixture was the *trans*-isomer. Even though α-deprotonation was observed with ketone **17**, the two fluorines 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 α-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.[22] However, using the recent comparisons of Hoye and co-workers,[23] preparation of the MPA-derivatives of **47** allowed assignment of the absolute configuration.[18]

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 α,α-difluoroketone, and addition to the aldehyde. Indeed, the α,α-difluoroketone **19** did not react with aldehyde **21** using the trifluoroacetate-release conditions (LiBr/Et_3N) 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 trifluoroacatete-release process to other substrates, we *mono*-brominated[24] the trifluoroacetylated ketone **1**, stirred over water, and then immediately treated the crude reaction mixture with LiBr and Et_3N 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.[25] The implication of this finding is that this process is not limited to the generation of α,α-difluoroenolates and the production of α,α-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 α,α-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

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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