

Nucleophilic 5-*endo-trig* Cyclization of 3,3-Difluoroallylic Ketone Enolates: Synthesis of 5-Fluorinated 2-Alkylidene-2,3-dihydrofurans

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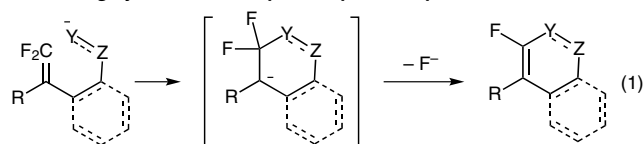
Abstract: 3,3-Difluoroallylic ketones readily undergo nucleophilic 5-*endo-trig* cyclization through their metal enolates to afford 5-fluorinated 2-alkylidene-2,3-dihydrofurans. O-Cyclization exclusively occurred via intramolecular substitution of the vinylic fluorines.

Key words: cyclization, fluorine, alkenes, furans, 5-*endo-trig*, ketone enolates, vinylic substitution

gem-Difluoroalkenes (1,1-difluoro-1-alkenes) have unique reactivities toward nucleophiles, which are based on their electron-deficient and highly polarized nature. They facilitate extraordinary substitution reactions, which hardly proceed in normal alkenes.¹ Difluoroalkenes readily undergo vinylic nucleophilic substitution (S_NV) via addition to electrophilic difluoromethylene carbons and subsequent fluoride elimination. We have already reported syntheses of ring-fluorinated heterocycles by conducting the S_NV reaction of difluoroalkenes in an intramolecular fashion.² As well as sp³ heteroatom and carbon nucleophiles,³ sp² nucleophiles⁴ have also participated in the 6-*endo-trig* cyclization to afford six-membered heterocycles (Scheme 1, eq 1). Furthermore, the high reactivity of 1,1-difluoro-1-alkenes has even allowed normally ‘disfavored’ 5-*endo-trig* cyclization,^{5–9} which provides scaffolds for 2-fluoro-4,5-dihydroheteroles and 2-fluorobenzoheteroles (Scheme 1, eq 2).¹⁰ Addressing the next challenge to the ‘disfavored’ process, we herein demonstrate the 5-*endo-trig* cyclization with the metal enolates of 3,3-difluoroallylic ketones, which are sp² atom-based ambident nucleophiles and rotationally restricted around the anionic centers (Scheme 1, eq 3). This process efficiently provides 2-alkylidene-2,3-dihydrofurans¹¹ by (i) constructing the heterocyclic ring and (ii) introducing a fluorine substituent and an alkylidene group onto the prescribed ring carbon.

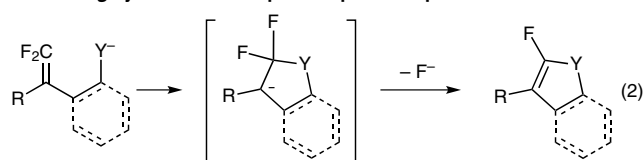
The starting 3,3-difluoroallylic ketones are readily accessible through the following chemoselective difluoromethylation protocol. 1,3-Ketoaldehydes **1**, the precursors of 3,3-difluoroallylic ketones **2**, were synthesized by the acylation of either morpholine enamines **3** or metal *N*-*tert*-butyl enamides prepared by deprotonation of imines **4**, followed by hydrolysis (Scheme 2).¹² Finally, difluoroal-

6-*endo-trig* cyclization with sp³ and sp² nucleophiles



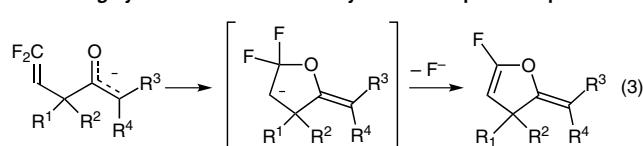
Y=Z: TsN-CH₂, N=CR', O-CH₂, S-CH₂, CR'=N

5-*endo-trig* cyclization with sp³ and sp² nucleophiles



Y: NTs, O, S

5-*endo-trig* cyclization with rotationally restricted sp² nucleophiles



Scheme 1 Intramolecular cyclization of *gem*-difluoroalkenes

lylic ketones **2** were obtained in moderate to high yield (27–86%) via difluoromethylation of ketoaldehydes **1** by a triaminophosphonium difluoromethylide, generated in situ from dibromodifluoromethane and tris(dimethylamino)phosphine (Scheme 2).¹³ Success of the exclusively selective difluoromethylation of **1** was due to the much higher reactivity of formyl groups compared to ketone carbonyl groups.

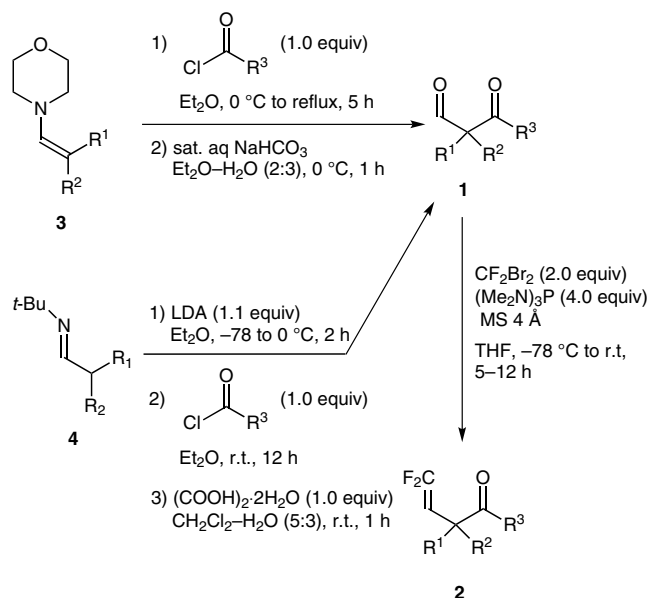
First, we sought bases suitable for the enolate formation and the subsequent 5-*endo-trig* cyclization by using difluoroallylic ketone **2a** as a model substrate (Table 1). Lithium diisopropylamide (LDA) afforded the O-cyclization product **5a** as a single isomer, albeit in low yield, while the C-cyclization product **6a** was not detected at all (Table 1, entry 1).¹⁴ Two-fold increase in the amount of LDA (2 equiv) turned out to be effective for the cyclization (Table 1, entry 2). Also, potassium hydride (1 equiv) exclusively gave **5a** and drastically improved its yield up to 79% (Table 1, entry 3). As in the case of LDA, use of doubled amounts of potassium hydride (2 equiv) was highly effective, leading to a 91% yield of the desired dihydrofuran **5a** (Table 1, entry 4). Thus, the nucleophilic 5-*endo-trig* cy-

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Scheme 2 Synthesis of 3,3-difluoroallylic ketones **2**

cyclization successfully proceeded even with rotationally restricted sp^2 nucleophiles in **2a**. This is likely due to the large polarization of the $CF_2=C$ moiety.^{10a}

Table 1 Screening of Bases Suitable for 5-*endo-trig* Cyclization of **2a**

Entry	Base (equiv)	Time	Yield of 5a (%)	Yield of 6a (%)
1	LDA (1.0)	5 h	29	— ^a
2	LDA (2.0)	4 h	42	— ^a
3	KH (1.0)	2 h	79	— ^a
4	KH (2.0)	2 h	91	— ^a

^a Not detected.

The optimized conditions obtained above for **2a** were successfully applied to the cyclizations of a variety of difluoroallylic ketones **2** (Table 2).^{15,16} Ketones **2b–g**, which are dimethylated at the allylic position, gave corresponding fluorine-containing dihydrofurans **5b–g** in good to excellent yield. Difluoroallylic benzylic ketones **2e** and **2f** gave 2-benzylidene dihydrofurans **5e** and **5f**, respectively. Reactions of difluoroallylic ketones **2h–j**, which possess a cyclohexane ring at the allylic position, constructed a spirocyclic structure in **5h–j**. The reactions of $\alpha,\alpha,\alpha',\alpha'$ -tetra-substituted ketones **2g** and **2j** were sluggish under the same conditions. However, the longer reaction time or the

Table 2 5-*endo-trig* Cyclization of 3,3-Difluoroallylic Ketones **2**

Entry	Time (h)	Product	Yield of 5 (%)
1	2		5a 91
2	2		5b 97
3	2		5c 83
4	2		5d 75
5	2		5e 98
6	2		5f 97
7	21		5g 91
8	5		5h 91
9	2		5i 94
10 ^a	3		5j 97

^a Pyridine was used as the solvent instead of THF.

use of pyridine as the solvent instead of THF improved the yields of **5g** or **5j**, respectively. Intriguingly, dihydrofuran derivatives **5a–f** and **5i** were obtained as single isomers about the *exo* double bond, judging from ¹H NMR and ¹³C NMR studies. The configurations of **5a–f** and **5i** were assigned as *Z*-isomers by a NOESY experiment of **5b**.¹⁷ This *Z*-selectivity in the formation of dihydrofurans **5a–f** and **5i** is interpreted as follows: the *Z*-enolates seem to be generated predominantly by deprotonation of difluoroallylic ketones **2** because of steric repulsion between substituents at both of the α positions of the carbonyl groups in **2**. The subsequent cyclization presumably proceeds through the *Z*-enolates with retention of stereochemistry.

Difluoroallylic ketones **2**, as shown in Table 2, underwent 5-endo-trig O-cyclization via their enolate forms. The reaction afforded the corresponding 2-alkylidene-5-fluoro-2,3-dihydrofurans **5** without the formation of C-cyclization products, 3-fluorocyclopent-3-en-1-ones **6**. Although 5-endo-trig cyclization is assigned as disfavored in Baldwin's rules,⁵ the reactivity of 1,1-difluoro-1-alkenes allows the substrates to undergo such an extraordinary cyclization.

In summary, we have demonstrated that 3,3-difluoroallylic ketone enolates exclusively underwent intramolecular O-alkenylation to afford fluorinated dihydrofurans **5** bearing a *Z*-*exo*-alkylidene unit. The cyclization proceeded in a 5-endo-trig fashion, which is disfavored according to Baldwin's rules. In this process, a fluorine substituent was introduced selectively onto the 5-position of the 2,3-dihydrofuran scaffold. Furthermore, since fluorinated 2-alkylidene-2,3-dihydrofurans are unprecedented and highly functionalized, it is expected that these compounds would serve as parts of bioactive molecules and versatile intermediates.¹⁸

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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To a suspension of KH (oil free, 46 mg, 1.2 mmol) in THF (11 mL) was added 6,6-difluoro-4,4-dimethyl-1-phenylhex-5-en-3-one (**2b**, 138 mg, 0.58 mmol), and the mixture was heated to reflux for 2 h. After cooling to r.t., the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with Et₂O three times. The combined extracts

were washed with brine and dried over MgSO_4 . After removal of the solvent under reduced pressure, the residue was purified by TLC on silica gel (EtOAc–hexane, 1:5) to give **5b** (122 mg, 97%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ = 1.26 (d, J_{HF} = 1.1 Hz, 6 H), 3.45 (d, J = 7.5 Hz, 2 H), 4.20 (d, J_{HF} = 5.4 Hz, 1 H), 4.73 (td, J = 7.5 Hz, J_{HF} = 3.4 Hz, 1 H), 7.18–7.22 (m, 3 H), 7.27–7.30 (m, 2 H). ^{13}C NMR (126 MHz, CDCl_3): δ = 30.1 (d, J_{CF} = 2 Hz), 30.9, 44.2 (d, J_{CF} = 2 Hz), 79.7 (d, J_{CF} = 8 Hz), 99.4, 125.9, 128.2, 128.4, 141.0, 157.5 (d, J_{CF} = 276 Hz), 160.6 (d, J_{CF} = 3 Hz). ^{19}F NMR (470 MHz, CDCl_3): δ = 46.2 (s). IR (neat): 3028, 2970, 2931, 1801, 1726, 1703, 1454, 1279, 1219, 1126, 1088, 993, 976, 748, 698 cm^{-1} . Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{FO}$: C, 77.04; H, 6.93. Found: C, 76.80; H, 7.16%.

- (16) 3,3-Disubstituted 5-fluoro-2-alkylidene-2,3-dihydrofurans **5** are air- and heat-stable.

- (17) In the NOESY experiment of dihydrofuran **5b**, substantial correlation between the methyl protons and the vinylic proton H^a was observed. No NOE correlation was detected between the methyl protons and the allylic protons H^b (Figure 1).

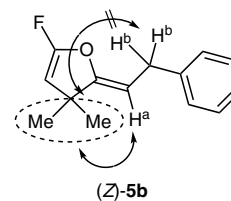


Figure 1 NOE correlation between protons in dihydrofuran **5b**

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