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

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

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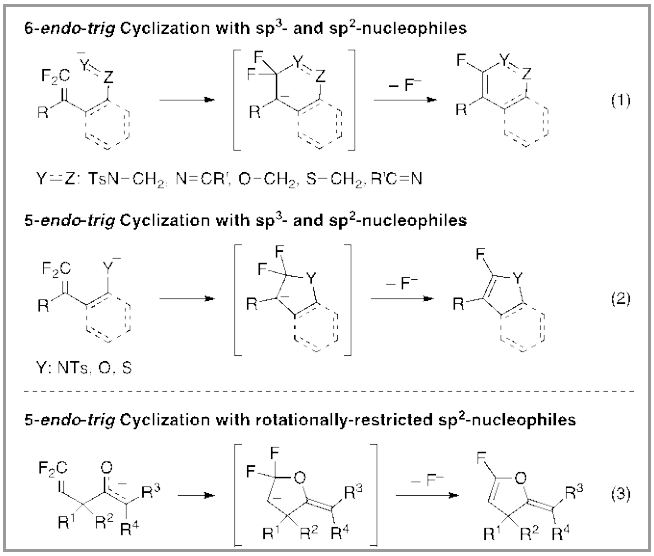
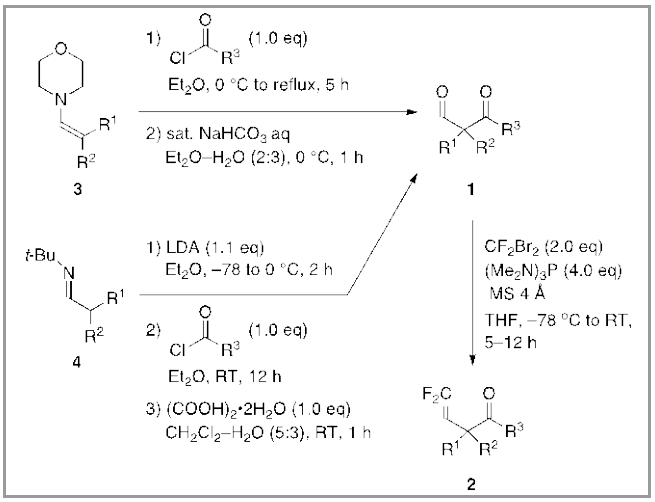
Abstract: 3,3-Difluoroallylic ketones readily undergo nucleophilic 5-*endo-trig* cyclization through their metal enolates to afford 5-fluorinated 2-alkylidene-2,3-dihydrofurans. *O*-Cyclization exclusively occurred via intramolecular substitution of the vinylic fluorines.

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 sp^3-heteroatom and carbon nucleophiles,[3] sp^2-nucleophiles[4] have also participated in the 6-*endo-trig* cyclization to afford 6-membered heterocycles (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 (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 sp^2-atom-based ambident nucleophiles and rotationally-restricted around the anionic centers (eq 3). This process efficiently provides 2-alkylidene-2,3-dihydrofurans[11] by (i) constructing the heterocyclic ring and (ii) introducing a fluorine substituent and an alkylidene group onto the prescribed ring carbon.



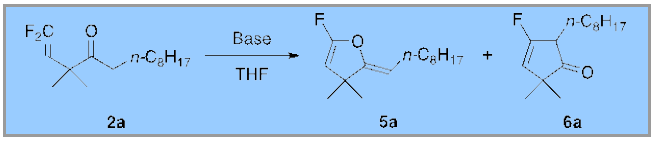
The starting 3,3-difluoroallylic ketones are readily accessible through the following chemoselective difluoromethylenation protocol. 1,3-Ketoaldehydes **1**, the precursors of 3,3-difluoroallylic ketones **2**, were synthesized by the acylation of either morpholine enamines **3** or metal *N*-*tert*-butyl enamides prepared by deprotonation of imines **4**, followed by hydrolysis (Scheme 1).[12] Finally, difluoroallylic ketones **2** were obtained in moderate to high yield (27–86%) via difluoromethylenation of ketoaldehydes **1** by a triaminophosphonium difluoromethylide, generated in situ from dibromodifluoromethane and tris(dimethylamino)phosphine (Scheme 1).[13] Success of the exclusively selective difluoromethylenation of **1** was due to the much higher reactivity of formyl groups compared to ketone carbonyl groups.



Scheme 1 Synthesis of 3,3-difluoroallylic ketones **2**

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 (Entry 1).[14] Two-fold increase in the amount of LDA (2 equiv) turned out to be effective for the cyclization (Entry 2). Also, potassium hydride (1 equiv) exclusively gave **5a** and drastically improved its yield up to 79% (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** (Entry 4). Thus, the nucleophilic 5-*endo-trig* 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**



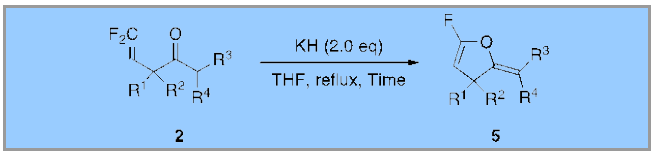
Entry	Base (eq)	Conditions	**5a** (%)	**6a** (%)
1	LDA (1.0)	reflux, 5 h	29	–[a]
2	LDA (2.0)	reflux, 4 h	42	–[a]
3	KH (1.0)	reflux, 2 h	79	–[a]
4	KH (2.0)	reflux, 2 h	91	–[a]

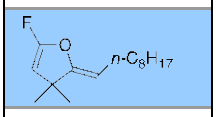
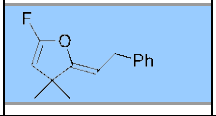
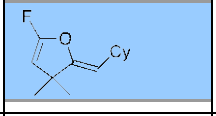
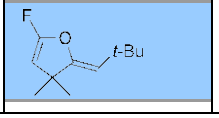
[a] Not detected.

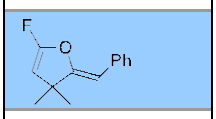
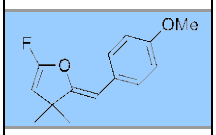
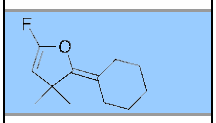
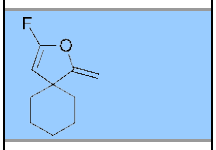
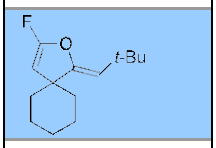
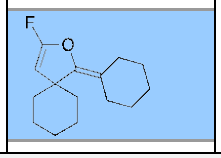
The optimized conditions obtained above for **2a** were successfully applied to the cyclizations of a variety of difluoroallylic ketones **2** (Table 2).[15,16] Ketones **2b**–**g**, which are dimethylated at the allylic position, gave corresponding fluorine-containing dihydrofurans **5b**–**g** in good 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 $\alpha,\alpha,\alpha',\alpha'$-tetrasubstituted ketones **2g** and **2j** were sluggish under the same conditions. However, the longer reaction time or the 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 ^{1}H and ^{13}C 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.

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



Entry	Time	Product		Yield (%)
1	2 h		**5a**	91
2	2 h		**5b**	97
3	2 h		**5c**	83
4	2 h		**5d**	75

5	2 h		**5e**	98
6	2 h		**5f**	97
7	21 h		**5g**	91
8	5 h		**5h**	91
9	2 h		**5i**	94
10[a]	3 h		**5j**	97

[a] Pyridine was used as the solvent instead of THF.

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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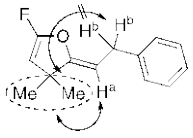
cyclization would be preferable because of an in-plane approach to enolates. The chemoselectivity in our case could be partially explained by a similar reasoning, albeit with the sp^2-CF_2 electrophile instead of sp^3-C electrophiles. See: Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1977**, 233.

(15) **(*Z*)-5-Fluoro-3,3-dimethyl-2-(2-pheylethylidene)-2,3-dihydrofuran (5b)**
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-on (**2b**, 138 mg, 0.58 mmol), and the mixture was heated to reflux for 2 h. After cooling to room temperature, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with Et_2O 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 thin layer chromatography on silica gel (AcOEt–hexane 1 : 5) to give **5b** (122 mg, 97%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (d, J_{HF} = 1.1 Hz, 6H), 3.45 (d, J = 7.5 Hz, 2H), 4.20 (d, J_{HF} = 5.4 Hz, 1H), 4.73 (td, J = 7.5, J_{HF} = 3.4 Hz, 1H), 7.18–7.22 (m, 3H), 7.27–7.30 (m, 2H). ^{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 $C_{14}H_{15}FO$: 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 thermally-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.



Z-5b

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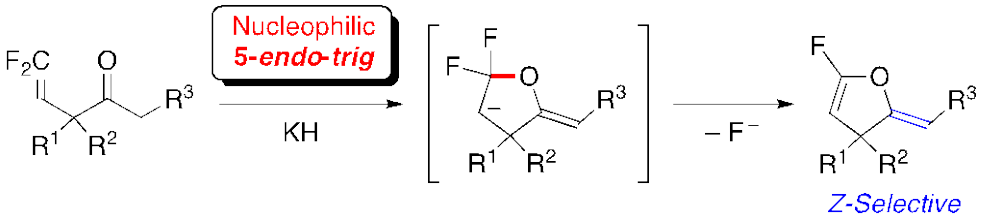

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