

The 5-*endo-trig* Cyclization of *gem*-Difluoroolefins with sp^3 Carbon Nucleophiles: Synthesis of 1-Fluorocyclopentenes

Junji Ichikawa*, Kotaro Sakoda, and Yukinori Wada

Department of Chemistry, Graduate School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033

(Received November 9, 2001; CL-011128)

A disfavored 5-*endo-trig* cyclization is accomplished in *gem*-difluoroolefins with sp^3 carbon nucleophiles, generated via the lithium–iodine exchange reaction of 1,1-difluoro-5-iodo-1-pentenes with *tert*-butyllithium, to afford 1-fluorocyclopentenes.

The 5-*endo-trig* cyclization is well known, according to Baldwin's rules, to be a disfavored process for the construction of five-membered rings.¹ This is considered to be due to the severe distortions required in the reaction geometry. Although successful examples of radical-initiated² and electrophile-driven³ ring closures of this type have been reported in recent years, nucleophile-driven 5-*endo-trig* cyclizations are still rarely observed in synthetic chemistry.^{4–6}

Most nucleophilic 5-*endo-trig* ring closures that have been reported are effected by heteronucleophiles. Carbocyclizations, which would have great potential as effective C–C bond-forming reactions, are mostly limited to a few examples of addition of stabilized sp^2 carbanions (anions α to cyano or carbonyl groups) to electrophilic double bonds such as (1) olefins activated by sulfonyl, cyano, nitro, or carbonyl groups, (2) imines, and (3) a π -allylpalladium system.^{4c–h,6d} One exception to our knowledge is the cyclization of a 2-cyclohexenone bearing an alkyl anion generated by electrochemical reduction, which is remarkably facilitated in microemulsions.⁴ⁱ

In our recent publications, we have reported the nucleophilic 5-*endo-trig* cyclizations of *gem*-difluoroolefins bearing *N*-, *O*-, and *S*-nucleophiles, providing ring-fluorinated heterocycles such as indoles, pyrrolines, furans, and thiophenes in high yields.⁵ This five-membered ring formation proceeds *via* intramolecular vinylic substitution of fluorine,^{7,8} based on our concept of *gem*-difluoroolefins: (i) the highly polarized C–C double bond which allows disfavored 5-*endo* addition and (ii) the successive elimination of fluoride ion which suppresses the reverse ring opening.⁶

Thus, we turned our attention to 5-*endo-trig* cyclization of *gem*-difluoroolefins with an sp^3 carbon nucleophile to broaden the scope of this cyclization. For the generation of sp^3 carbanion, metal–halogen exchange was adopted. The substrates were designed to be *gem*-difluoroolefins bearing an iodine substituent and subjected to the ring-forming reaction. Herein we wish to report the results of our studies on the synthesis of 1-fluorocyclopentenes by this cyclization.⁹

The starting materials **4** were easily prepared as outlined below by using the one-pot sequence that we have previously established for a wide range of *gem*-difluoroolefins.¹⁰ 2,2-Difluorovinylboranes **2** were prepared *in situ* from 2,2,2-trifluoroethyl *p*-toluenesulfonate **1** and trialkylboranes generated by hydroboration of MOM ethers of allyl and metallyl alcohols. The coupling reactions of **2** with aryl iodides were achieved in the

presence of a palladium catalyst and CuI, followed by deprotection of the MOM group to afford **3a–e**.¹¹ Thus obtained alcohols **3** were transformed into the desired iodides **4a–e**¹¹ *via* their mesylates (Table 1).

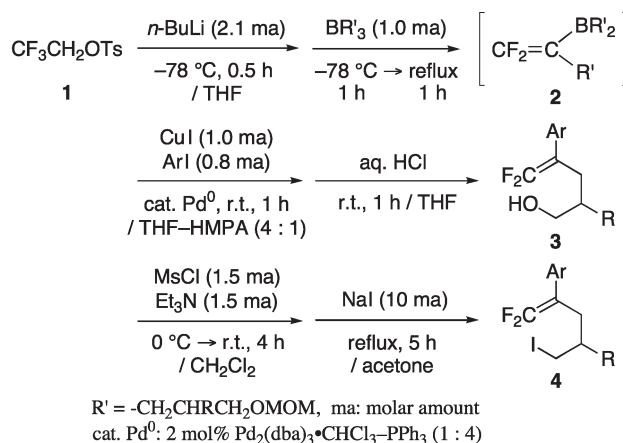


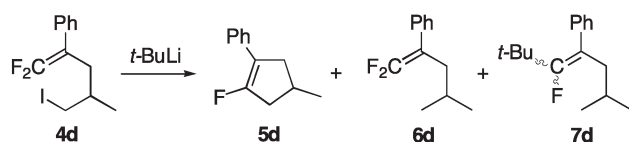
Table 1. Preparation of the substrates **4**

Entry	Ar	R	Yield of 3 /%	Yield of 4 /%
1	C ₆ H ₅	H	43 (3a)	83 (4a)
2	<i>p</i> -CF ₃ -C ₆ H ₄	H	54 (3b)	77 (4b)
3 ^a	<i>p</i> -MeO-C ₆ H ₄	H	47 (3c)	72 (4c)
4	C ₆ H ₅	Me	75 (3d)	68 (4d)
5 ^a	<i>p</i> -MeO-C ₆ H ₄	Me	58 (3e)	90 (4e)

^aBR'₃ (1.1 mol. amt.), 2 mol% Pd₂(dba)₃·CHCl₃·PPh₃ (1:8).

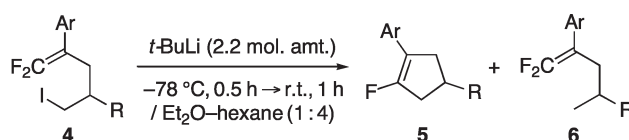
According to the reported procedure for lithium–halogen exchange of primary alkyl iodides,¹² 1,1-difluoro-5-iodo-4-methyl-2-phenyl-1-pentene **4d** was treated with 2.2 molar amount of *tert*-butyllithium (1.4 mol dm^{−3} in pentane) in diethyl ether–hexane at −78 °C. The reaction was quenched at −78 °C to give the cyclized product, 1-fluorocyclopentene **5d**¹¹ in 28% yield along with a 28% yield of the reduced product **6d**, which confirmed the generation of the carbanion (Entry 1, Table 2). The cyclization was effectively promoted by allowing the reaction mixture to stand at room temperature for 1 h, improving the yield up to 69% (Entry 2).¹³ Some other solvent systems were examined, however in vain (Entries 3–5). In diethyl ether direct replacement of the fluorine by *tert*-butyllithium occurred to give **7d** in 10% yield (Entry 4). Addition of HMPA (2 molar amount) after the lithiation of **4d** decreased the yield of **5d** (Entry 5).

Having obtained the optimum conditions as shown above, the cyclization of several other 1,1-difluoro-5-iodo-1-pentenes **4** was examined and the results are shown in Table 3.¹¹ The substrates

**Table 2.** Effect of reaction conditions^a

Entry	Conditions	Solvent	Yield / %		
			5d	6d	7d
1	-78 °C, 3 h	Et ₂ O-hexane (1 : 4)	28	28	0
2	-78 °C, 0.5 h → r.t., 1 h	Et ₂ O-hexane (1 : 4)	69	7	0
3	-78 °C, 0.5 h → r.t., 1 h	hexane	43	21	0
4	-78 °C, 0.5 h → r.t., 1 h	Et ₂ O	55	0	10
5	-78 °C, 0.5 h → r.t., 1 h	Et ₂ O-hexane (1 : 4) ^b	48	0	3

^a*t*-BuLi (2.2 mol. amt.). [4d] = 0.04 mol dm⁻³. ^bAfter addition of *t*-BuLi and stirring at -78 °C for 0.5 h, HMPA (2 mol. amt.) was added.

**Table 3.** Synthesis of 1-fluorocyclopentenes **5**^a

Entry	Ar	R	Yield of 5 / %	δ _F ^b	Yield of 6 / %
1	C ₆ H ₅	H	76 (5a)	45.0	0 (6a)
2	<i>p</i> -CF ₃ -C ₆ H ₄	H	65 (5b)	48.5	0 (6b)
3	<i>p</i> -MeO-C ₆ H ₄	H	74 (5c)	42.2	0 (6c)
4	C ₆ H ₅	Me	69 (5d)	46.1	7 (6d)
5	<i>p</i> -MeO-C ₆ H ₄	Me	69 (5e)	43.3	7 (6e)

^a[4d] = 0.04 mol dm⁻³. ^bVinylc ¹⁹F NMR of **5** (254 MHz, CDCl₃/C₆F₆).

bearing no substituents on the 4-position gave better results (Entries 1 vs 4 and 3 vs 5). Concerning *para*-substituents on the 2-phenyl group, electron-withdrawing and electron-donating groups caused little effect on the cyclization (Entries 2, 3, and 5).¹⁴

In conclusion, 5-*endo-trig* cyclizations of *gem*-difluoroolefins are successfully achieved by not only intramolecular heteronucleophiles but also sp³ carbon nucleophiles, to which much less attention has been paid in such ring closure. By this carbocyclization, the scope of the intramolecular substitution of *gem*-difluoroolefins has been expanded in terms of five-membered ring formation.

We dedicate this article to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

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- When 1,1-difluoro-2-phenyl-1-hexene was treated with butyllithium (1.1 mol. amt.) under the same reaction conditions as those for **4**, the intermolecular substitution of the butyl group for the vinylic fluorine occurred to give the *E/Z* mixture (*E/Z* = 70/30) of products in 69% yield.⁷
- 1,1-Difluoro-2-(3-iodopropyl)-4-phenyl-1-pentene underwent no cyclization on treatment with *tert*-butyllithium (2.2 mol. amt.) under the same reaction conditions as those for **4**.