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

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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.

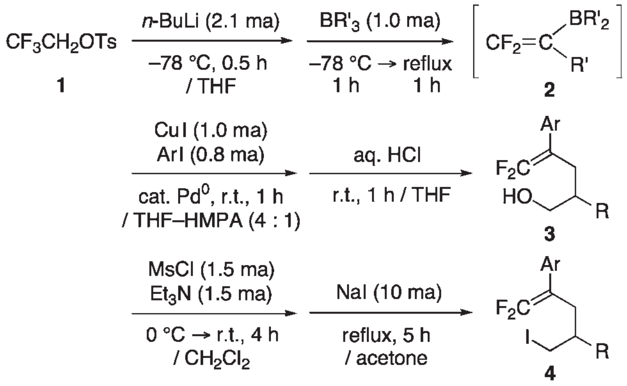
The 5-*endo-trig* cyclization is well known, according to Baldwin's rules, to be a disfavored process for the construction of five-membered rings.[1] This is considered to be due to the severe distortions required in the reaction geometry. Although successful examples of radical-initiated[2] and electrophile-driven[3] 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).



R' = $-CH_2CHRCH_2OMOM$, ma: molar amount
cat. Pd^0: 2 mol% $Pd_2(dba)_3$•$CHCl_3$–PPh_3 (1 : 4)

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

Entry	Ar	R	Yield of **3**/%	Yield of **4**/%
1	C_6H_5	H	43 (**3a**)	83 (**4a**)
2	*p*-CF_3-C_6H_4	H	54 (**3b**)	77 (**4b**)
3[a]	*p*-MeO-C_6H_4	H	47 (**3c**)	72 (**4c**)
4	C_6H_5	Me	75 (**3d**)	68 (**4d**)
5[a]	*p*-MeO-C_6H_4	Me	58 (**3e**)	90 (**4e**)

[a] BR'_3 (1.1 mol. amt.), 2 mol% $Pd_2(dba)_3$•$CHCl_3$–PPh_3 (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

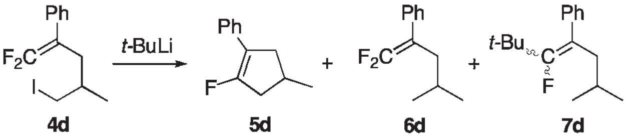


Table 2. Effect of reaction conditions^a

Entry	Conditions	Solvent	Yield / %		
			5d	**6d**	**7d**
1	–78 °C, 3 h	Et_2O–hexane (1 : 4)	28	28	0
2	–78 °C, 0.5 h → r.t., 1 h	Et_2O–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_2O	55	0	10
5	–78 °C, 0.5 h → r.t., 1 h	Et_2O–hexane (1 : 4)^b	48	0	3

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

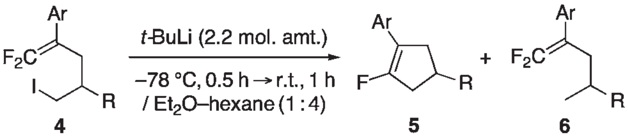


Table 3. Synthesis of 1-fluorocyclopentenes **5**^{a}

Entry	Ar	R	Yield of **5**/%	δ_F^{b}	Yield of **6**/%
1	C_6H_5	H	76 (**5a**)	45.0	0 (**6a**)
2	*p*-CF_3-C_6H_4	H	65 (**5b**)	48.5	0 (**6b**)
3	*p*-MeO-C_6H_4	H	74 (**5c**)	42.2	0 (**6c**)
4	C_6H_5	Me	69 (**5d**)	46.1	7 (**6d**)
5	*p*-MeO-C_6H_4	Me	69 (**5e**)	43.3	7 (**6e**)

^{a}[**4d**] = 0.04 mol dm^{-3}. ^{b}Vinylic ^{19}F NMR of **5** (254 MHz, $CDCl_3/C_6F_6$).

bearing no subutituents 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 sp^3 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.

References and Notes

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13 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]

14 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**.